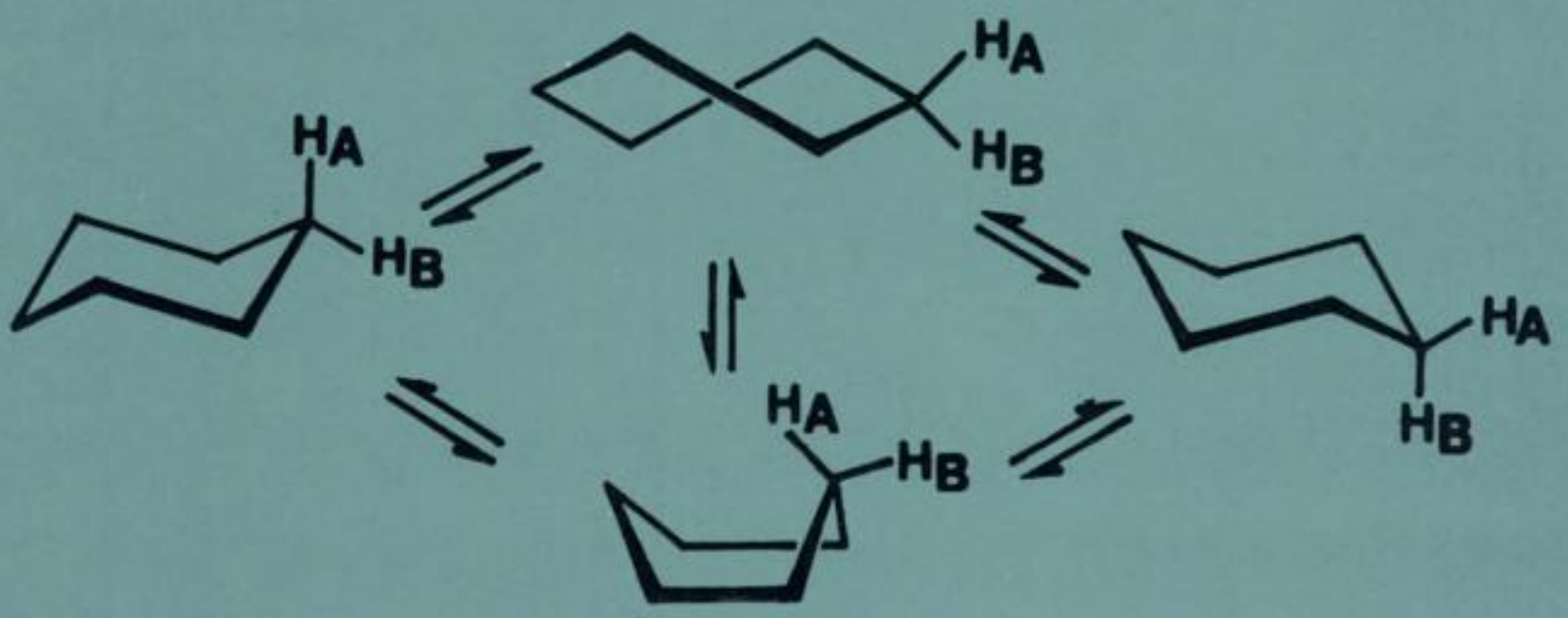
SECOND EDITION

Stereochemistry of Organic Compounds

Principles and Applications



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Stereochemistry of Organic Compounds

Principles and Applications

Second Edition

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hand, deformation of bond angles is relatively easy requiring approximately 0.04 kJ mol^{-1} for a change of 1° and may be sizeable thus causing substantial deviation in the molecular geometry from the *idealised* model based on the equilibrium values of bond lengths and bond angles. These deviations are, however, not sufficiently high to invalidate the usefulness of describing molecules in their idealised forms (see Chapter 9).

1.2.2 Covalent radii and van der Waals atomic radii

A useful concept has been introduced to express the bond length between two atoms, as in A—B, in terms of the hypothetical radii r_A and r_B, known as covalent radii of atoms A and B respectively, so that $r_A + r_B$ is equal to the equilibrium bond length. The covalent radius of an atom is independent of the nature of the other atom to which it is bonded. The bond lengths and the covalent radii of a few common elements are given in Table 1.1.

Bond energy is another very important parameter of a bond but we are not concerned with it at the moment.

Table 1.1 Bond lengths and covalent radii

Bond	Bond lengths (nm)	Element	Coordination number	Covalent radii (nm)
C –C	0.154	C	4	0.077
C = C	0.133	C	3	0.0665
C≡C	0.121	C	2	0.0605
C –H	0.110	H	1	0.033
C –O	0.143	O	2	0.074
C = O	0.121	O	1	0.062
C –N	0.147	N	3	0.074
C = N	0.127	N	2	0.062
C≡N	0.115	N	1	0.055
C –Cl	0.177	Cl	1	0.100
C –Br	0.191	Br	1	0.114
C –I	0.210	I	1	0.133

To each atom or neutral grouping corresponds a definite distance within which it resists penetration by other atoms. Pauling has estimated this distance, known as van der Waals atomic or group radius for a number of atoms and groups (Table 1.2). When two non-bonded atoms approach each other, weak attractive forces, known as van der Waals attraction (or London forces) operate until at a certain distance (r), an energy minimum is reached. Beyond this, the attractive forces are replaced by a very strong repulsive force (van der Waals repulsion or Born force). The sum of the attractive and repulsive forces is known as non-bonded interaction and the distance r is the sum of the van der Waals radii of the two atoms. It corresponds to the optimal approach between two non-bonding atoms or groups and plays an important role in determining steric strain in a molecule. The values given in Table 1.2 are from crystallographers' data which are slightly lower (by approximately 0.03 nm) than the more realistic values applied to isolated atoms (Allinger 1976) in which, unlike in crystals, intermolecular packing forces are absent.

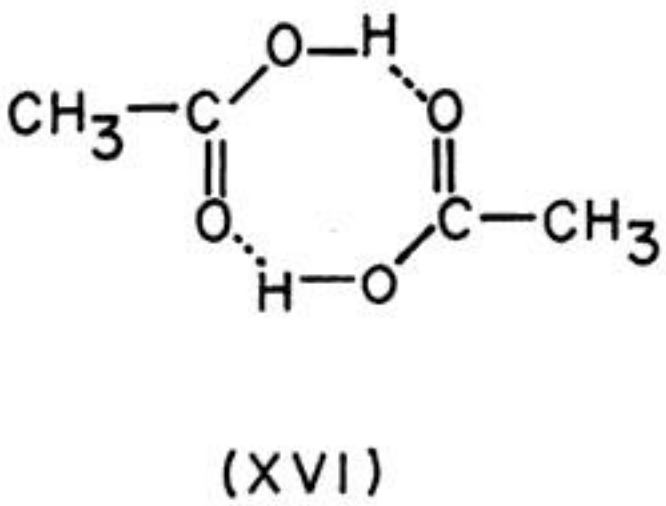
because of higher electronegativity of oxygen. The order of the repulsive interaction between pairs of electrons is: lone pair-lone pair > lone pair-bond pair > bond pair-bond pair. The H—N—H angle in ammonia (XIV) is 107.3° and may be ascribed to the interaction between lone pair and bond pair electrons.

1.3.2 Bond angle deformation in small ring compounds

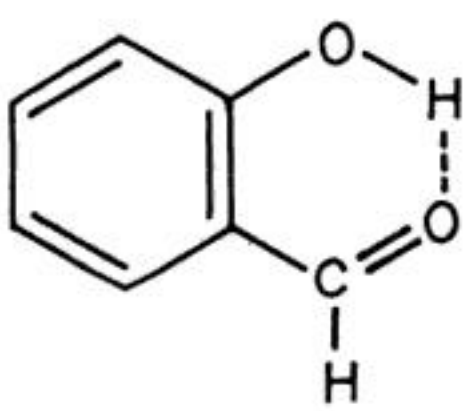
Bond angle deformation plays a more important part in cyclic compounds. Thus in cyclopropane, the internuclear angle is, by necessity, 60° much smaller than the ideal interorbital angle, 109.5°. This gives rise to serious angle strain (Baeyer strain) in the molecule which can be partially relieved by rehybridising the endo ring orbitals (increasing the p component) so that the *ideal interorbital angle* is reduced to 106° or even less. The orbitals forming C—C bonds overlap partly along the axial and partly in the lateral direction. This type of bond is known as a *banana* or *bent* or τ bond and is intermediate between a pure σ and a pure π bond. The region of maximum overlap (see XV in Figure 1.3) does not correspond to the internuclear axis and cyclopropane behaves like an unsaturated compound in certain respects (e.g., addition of bromine). In cyclobutane, the internuclear and interorbital angles are 90° and 109.5° respectively and the angle strain is considerably less. The different strains in other ring systems will be discussed in a later chapter.

1.4 Hydrogen bonding

No discussion of chemical bonding can be complete without the consideration of hydrogen bonding. When a proton donor group (A—H, A being an electronegative element) interacts with an electron donor (:B) having a lone pair of electrons or a π bond, a weak bond is formed represented by A-H $\cdots$ B known as hydrogen-bond (H-bond). If the two groups belong to two different molecules, the H-bond is called intermolecular and association between the two molecules occurs. If they form part of the same molecule, the H-bond is called intramolecular and, by default, opposes association. Examples are shown in acetic acid dimer (XVI) and salicylaldehyde (XVII) respectively (Figure 1.4). The molecules of



(XVI)



(XVII)

Figure 1.4 Hydrogen bonding

water and alcohols are highly associated due to intermolecular H-bonds. The bond angle in A-H $\cdots$ B is preferably 180° (linear) but may vary (especially in crystals or when the bond is intramolecular) depending on the requirements of the

by the π bond cannot be maintained in the rigid ring system. On the other hand, the bicyclononene (XXVI) with a bridgehead double bond is stable. Here the planarity of the π bond is accommodated by the puckering of the large ring. Many exceptions to Bredt's rule are now known*.

1.5.3 Restricted rotation around intermediate (hybrid) bonds

There are molecules in which a particular bond is neither a purely single nor a purely double bond but a hybrid between the two. A common example is 1,3-butadiene (XXVII) (Figure 1.7) in which the bond connecting the second and the third carbon develops some double bond character due to resonance between the two canonical forms (XXVIIa) and (XXVIIb). An alternative explanation based on delocalisation of the four π electrons over the σ framework of the molecule (π-orbital overlap) may be given. Two conformations, cisoid (XXVIII) and transoid† (XXVII) are possible and are separated by an energy barrier of approximately 25 kJ mol^{-1} which is much higher than in ethane but not high enough to permit

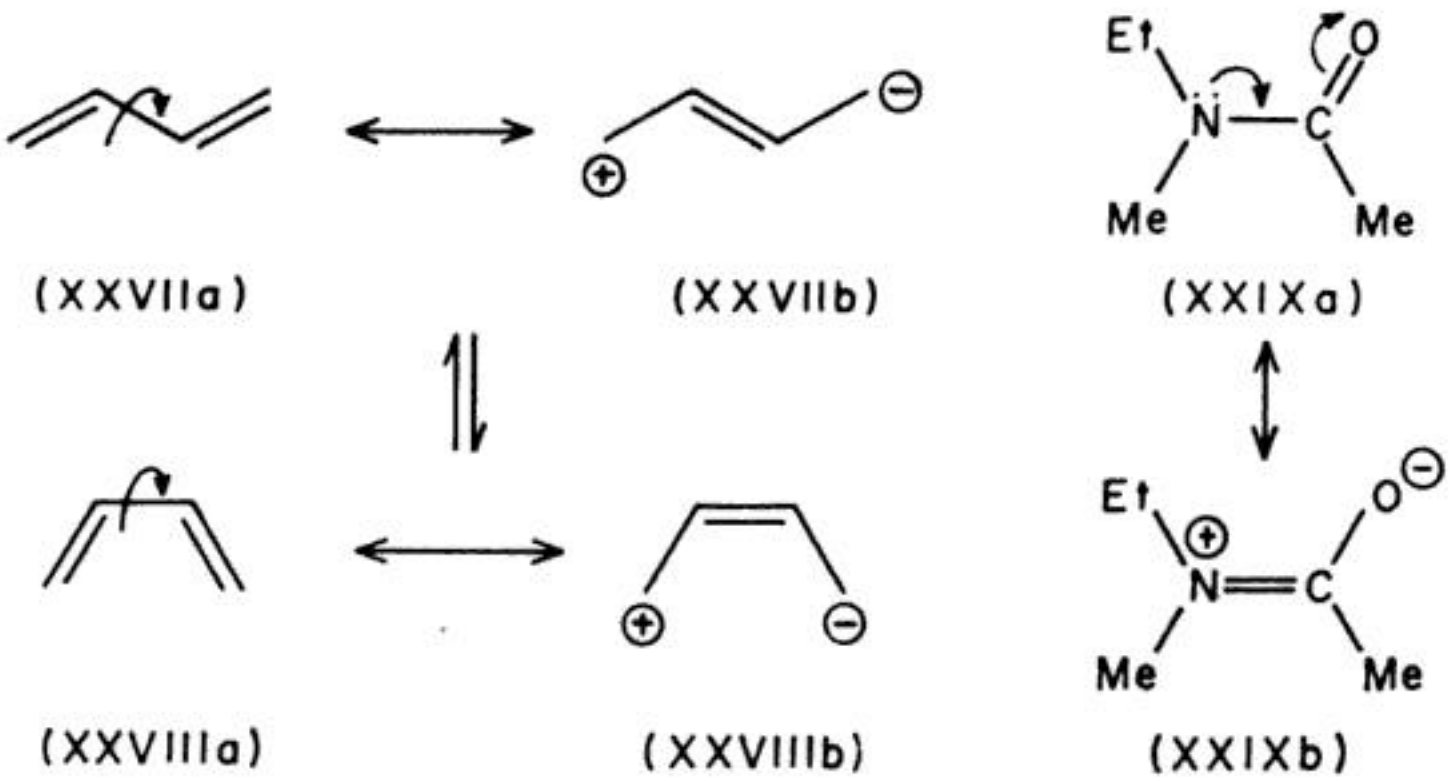


Figure 1.7 Restricted rotation around partial double bond

isolation under ordinary conditions‡. A still higher energy barrier (about 75 kJ mol^{-1}) is encountered in the rotation around C—N bond in N-methyl, N-ethylacetamide (XXIX), the double bond character of the amide bond arising out of delocalisation of the nitrogen lone pair of electrons. Here also, restricted rotation leads to two distinct isomers; however, the rotation is too fast to permit their isolation although they can be distinguished by low temperature NMR. It may be noted that any two species in equilibrium cannot ordinarily be separated at room temperature unless they are separated by a minimum energy barrier of 100

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* See Buchanan (1974) for a review of Bredt's rule and Keese (1975) for a review on bridgehead olefins.

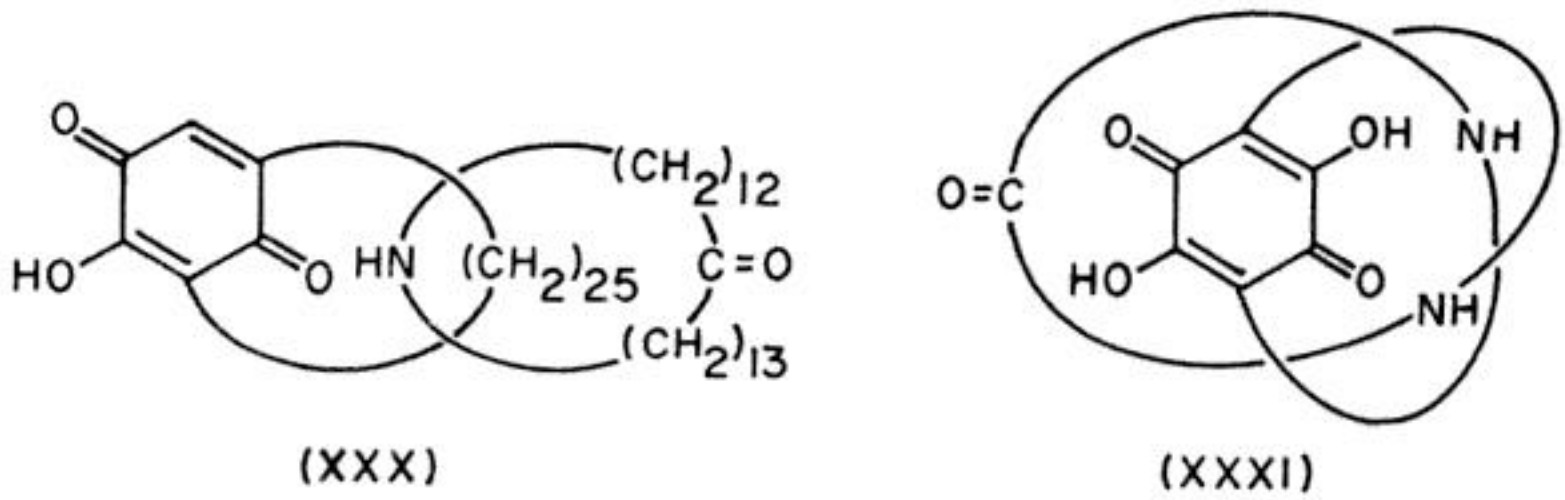
† Also called *s*-cis and *s*-trans respectively (*s* stands for single bond).

‡ The *s*-cis form has been trapped on CsI plate and studied by UV and IR (Squillacote et al 1979) by suddenly cooling a hot vapour (400-900°C) of butadiene to 30 K (matrix separation): λ_{max} of *s*-cis and *s*-trans is 226 and 220 nm respectively.

kJ mol^{-1}. Below that, they can be detected by various physical measurements (IR, NMR etc.) depending on the time-scale of observation, instrument frequency, and the average lifetime of the species in equilibrium.

1.6 Catenanes

An interesting class of compounds in which two or more rings are held together not by any chemical bond but through interlock between rings (Figure 1.8) is known as *catenanes*. One of the earliest catenane synthesised is represented by structure (XXX). Some DNA's provide examples of naturally occurring catenanes, the two closed strands being interlocked with each other. A catenane may be called a *topological isomer* of the two isolated composite rings. The catenanes pose certain intriguing problems regarding their physicochemical properties (Dmitriev 1981). The trefoils are another interesting type of molecules in which a single chain is knotted, e.g., XXXI. They are topological isomers of the corresponding unknotted molecules (Schill 1971). Topological stereochemistry has been recently reviewed (Walba 1985, Sauvage and Dietrich 1991).



(XXX) (XXXI)

Figure 1.8 Catenane and trefoil

1.7 Summary

1. Three basic parameters, namely, bond length, bond angle, and dihedral angle which affect the molecular geometry have been defined. Deformation of a bond length is a high energy process but change of bond angle is relatively easy and of general occurrence. Fairly drastic change in bond angles is seen in small ring compounds like cyclopropane and cyclobutane in which the internuclear and interorbital bond angles are widely different. This leads to angle strain also known as Baeyer strain.

2. Bond length can be expressed as the sum of the covalent radii (a hypothetical parameter) of the two atoms forming the bond. Each atom and group has a definite radius within which it resists penetration by other atoms and groups. These radii are known as van der Waals atomic or group radii and define the optimal approach that two non-bonding atoms or groups can make. They determine the intra- and intermolecular non-bonded interactions which are responsible for steric effects in stereochemistry.

3. The formation of covalent bonds (single, double and triple) in carbon compounds has been rationalised using the concept of hybridisation of bonding

orbitals. The geometry and other characteristic properties of bonds formed by overlap of sp^3, sp^2, and sp hybrid orbitals have been discussed with particular reference to stereochemistry. Deviations of bond angles from the mean or equilibrium values expected from bond hybridisation (*idealised* values) have been explained on the basis of steric (Thorpe-Ingold effect) and electronic factors. Alternative explanation based on the change of hybridisation of bonding orbitals to accommodate steric and electronic factors is also thought to be important. The sp^3, sp^2 and sp hybridised carbons are called tetrahedral, trigonal, and linear with bond angles of 109.5°, 120°, and 180° respectively.

4. When a proton donor group (A—H) and electron donor group (:B) interact, a weak bond known as H-bond, A-H···B is formed with an average energy of 8-40 kJ mol^{-1} and a typical bond length of 0.3 nm. In view of its directional property and its ability to join two groups many bonds apart, this bond plays an important part in stereochemistry. Depending on whether the two groups, A—H and :B belong to the same molecule or to different molecules, the H-bond is called intramolecular or intermolecular. The two types affect molecular properties differently.

5. When two atoms in a molecule are joined by a single bond, the molecule behaves as a dynamic system in which a few species with different geometries (conformers) exist in equilibrium. They are usually separated by low energy barrier. Nevertheless, this affects the physical and chemical behaviour of the molecule. If the energy barrier separating the conformers is sufficiently high (>100 kJ mol^{-1}), stable stereoisomers may be expected. Rotations around single, double, and intermediate bonds have been discussed with the help of energy diagrams.

6. The different strains and interactions encountered during the discussion are weak attractive van der Waals forces (London forces), non-bonded interaction (van der Waals repulsion), angle or Baeyer strain, coulombic or electrostatic interactions, torsional strain, and interaction due to H-bond. Other interactions such as dipole-dipole and dipole-induced dipole are not separately discussed but may be collectively considered along with the H-bond, under the general term, electrostatic interactions.

7. A class of compounds in which two or more rings are interlocked without any chemical bonds between them is called catenanes.

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2.5 Point groups and symmetry number

Another symmetry parameter, namely, symmetry number (σ) is defined as the number of equivalent positions a molecule can be turned into through simple rotation around an axis or axes. The symmetry number is important since it is related to the entropy of a molecule, the entropy contribution due to symmetry being $-R\ln\sigma$. The benzene molecule has a symmetry number twelve calculated as follows. The six carbons are numbered as in the structure (XV) (Figure 2.4). During the rotation of the molecule around the C_6 axis through 360°, six equivalent arrangements result counting the original to which it returns. This operation thus contributes six to the symmetry number. Next, the molecule is rotated around a C_2 axis passing through carbons marked 1 and 4 by an angle of 180°. A new arrangement (XVI) is reached as evident from the positions of the numerals. A second rotation of 180° around the axis, however, leads to an arrangement identical with the original (XV) which has been counted already. Thus each of the six horizontal C_2 axes contributes one to the symmetry number making the total twelve.

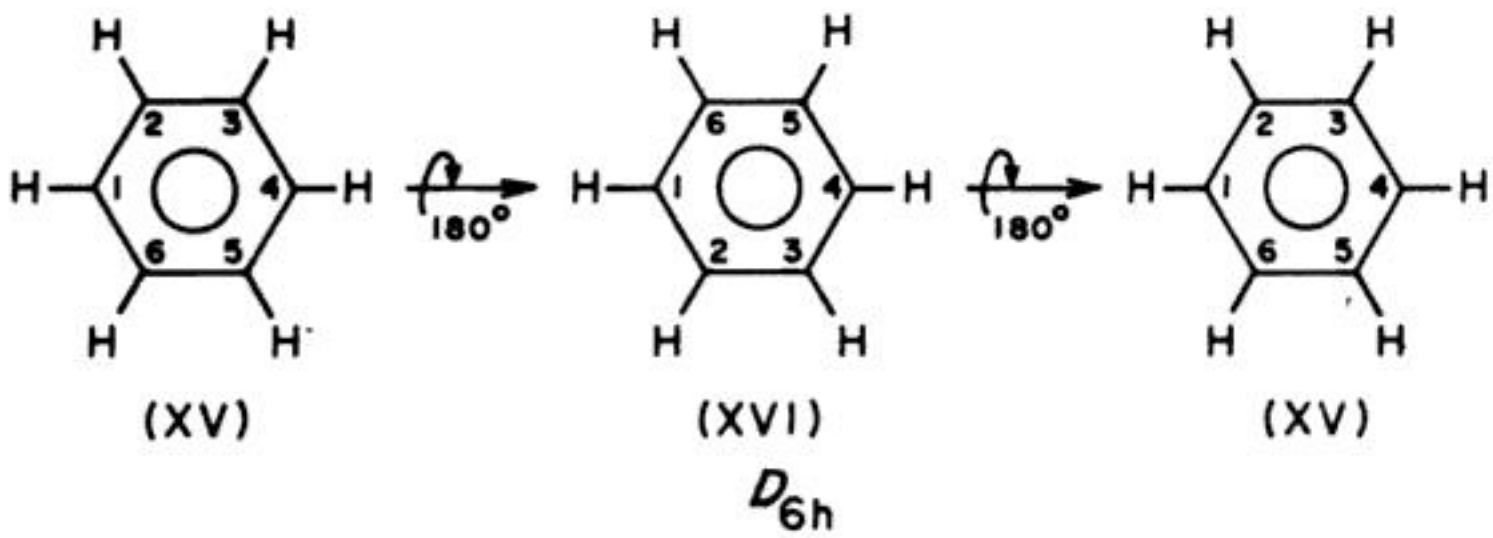

Figure 2.4 Symmetry number of benzene

The symmetry number is related to the point groups to which the molecule belongs in the manner shown below:

Point groups	*Symmetry No.*	*Point groups*	*Symmetry No.*
$C_{\infty v}$, C_1, C_s, and C_i	1	$D_{\infty h}$	2
C_n, C_{nh}, and C_{nv} ($n \neq \infty$)	n	T_d	12
D_n, D_{nd}, and D_{nh} ($n \neq \infty$)	$2n$	O_h	24
		I_h	48

2.6 Summary

(*i*) Four symmetry operations, namely, rotation, reflection, inversion, and rotation-reflection are described through which similar atoms and groups in a molecule can be interchanged to give arrangements indistinguishable from the original.

(*ii*) Four symmetry elements have been defined in terms of the above symmetry

operations which are: a simple (proper) axis of symmetry (C_n), a plane of symmetry (σ), an inversion centre (i), and an alternating (improper) axis of symmetry (S_n). The same symbols are used for the symmetry operations and the symmetry elements.

(*iii*) The molecules have been classified into a number of symmetry point groups based on the symmetry operations that can be performed on them. Schemes for classification as well as flow-sheet diagrams are given.

(*iv*) Molecules which are not superposable with their mirror images are called chiral and those which are superposable are called achiral. Chiral molecules exhibit a type of stereoisomerism known as enantiomerism and belong to point groups C_1, C_n or D_n; they can be recognised by the absence of an S_n axis of any order. The common method of ascertaining the chirality of a molecule is to look for a plane of symmetry (S_1) and an inversion centre ($i = S_2$) and if the situation warrants, for an S_n axis of order higher than two. In general, the absence of a σ plane and an inversion centre (i) is sufficient to ensure chirality in a molecule.

(v) The symmetry number (σ)* of a molecule is defined by the number of equivalent orientations that a molecule can assume through rotations around axis or axes. The symmetry number is relevant for the calculation of the entropy of a molecule and can be inferred directly from the symmetry point group by a character table.

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*It is unfortunate that the plane of symmetry and symmetry number are both designated σ.

Chapter 2

Molecular Symmetry and Chirality

2.1 Introduction

Stereochemistry is primarily concerned with molecular geometry and molecular geometry is best described in terms of symmetry. Molecules consist of atoms held together by more or less well defined bonds and may usually be treated as rigid bodies (see Chapter 1). The multitude of molecular structures can be brought into some sort of order by classifying them into several categories based on the symmetry operations that can be performed on them. The classification not only helps to understand the stereochemical behaviour of the molecules but finds significant applications in other branches of chemistry as well. For non-rigid molecules, the symmetry is considered either for a particular conformation or for a time-average one. An elementary treatment of symmetry classification is presented here as being useful in several aspects of organic stereochemistry.

2.2 Symmetry operations and symmetry elements

In order to study the symmetry of a molecule, certain operations such as rotation and reflection are performed and if by so doing, an arrangement is obtained which is indistinguishable from (superposable on) the original one, the operation is called a symmetry operation and the molecule is said to possess an element of symmetry defined by the operation performed. The symmetry operation and symmetry element are thus inseparably linked* and often represented by the same symbols. There are basically only two symmetry operations, namely, rotation and reflection (and a combination thereof). Symmetry based solely on simple rotation is often called symmetry of the first kind whereas symmetry based on reflection or rotation-reflection is known as symmetry of the second kind. It is customary to describe the symmetry of a molecule in terms of four symmetry operations and four corresponding elements of symmetry.

2.2.1 Simple or proper axis of symmetry

If a molecule is rotated around an appropriate imaginary axis by an angle of $360°/n$ and arrives at an arrangement indistinguishable from the original, the axis is called an n-fold simple or proper axis of symmetry or a simple axis of order n. The axis is designated C_n and the operation is called a C_n operation. The operation

* A symmetry element is a geometrical entity, e.g., a point, a line, or a plane with respect to which symmetry operations are carried out.

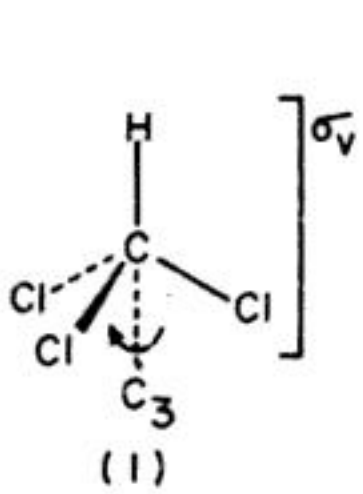
if repeated n times leads to an orientation identical* with the original. The molecule of water has one two-fold simple axis of symmetry (C_2) bisecting the H—O—H angle, chloroform (I) (as also NH_3 and NR_3) has one C_3 axis along the C—H bond, benzene (II) has one perpendicular C_6 axis and in addition, six C_2 axes lying in the molecular plane (three passing through opposite atoms and three bisecting the opposite C—C bonds), *cis*- and *trans*-1,3-dimethylcyclobutanes (III) and (IV) have one C_2 axis (vertical in III, horizontal in IV), *trans*-dichloroethylene (V) has one C_2 axis perpendicular to the molecular plane, and cyclopropane (VI) has one vertical C_3 and three horizontal C_2 axes (Figure 2.1). A C_1 axis is trivial since rotation of any molecule around any axis by 360° leads to the original arrangement (an identity operation). On the other extreme, linear molecules like H—C≡C—H and H—C≡N possess a C_∞ axis coincident with the internuclear axis since rotation around it by any angle gives an equivalent structure. Acetylene (VII) in addition possesses an infinite number of C_2 axes perpendicular to the centre of the C_∞ axis.

It is customary to write a molecule so that the axis of the highest order known as the principal axis is placed vertically, i.e., along the z-axis shown in the diagram (Figure 2.1) and thus provides a good reference for describing other axes and planes. In the case where a molecule has several symmetry axes of the same order, the one passing through the greatest number of atoms is taken as the principal axis, see, for example, naphthalene (VIII), ethylene (IX) and allene (X). All of them contain several C_2 axes but those shown vertically pass through more than one atom. It is also to be noted that during the operations, one poin in the molecule (the centre of gravity) remains unchanged in space. Symmetry of this kind is called point symmetry to distinguish it from translational symmetry which involves displacement in space.

2.2.2 **Plane of symmetry**

A plane of symmetry is a plane which divides the molecule (or an object) into two halves which are mirror images of each other. In other words, reflection of the two halves of the molecule across the plane (a reflection plane) gives a structure indistinguishable from the original. The plane is called a σ plane and the operation a σ operation. Two σ operations are equivalent to an identity operation since they turn the molecule into the original. It is important to note that the two halves themselves may not be superposable. The molecule of water has two mutually perpendicular σ planes, chloroform (I) has three, each containing a H—C—Cl grouping, benzene (II) has one horizontal (the molecular plane) and six vertical (a set of three passing through opposite atoms and another set of three passing through the opposite bonds), *cis*-1,3-dimethylcyclobutane (III) has two vertical (one passing through the methyl-bearing carbons and the other passing through the two methylene carbons), the trans isomer (IV) has one vertical (passing through

*The terms *indistinguishable* and *identical* have different connotations in the present context. The former refers to any equivalent arrangement arrived at by exchanging similar atoms or groups while the latter refers strictly to the original. The operation which leaves the molecule unchanged, i.e., as if nothing had been done to it, is called an identity operation, denoted by E or I, equivalent to C_1, C_2^2, C_n^n, σ^2 etc. (the superscripts represent the number of times the operation is performed.).



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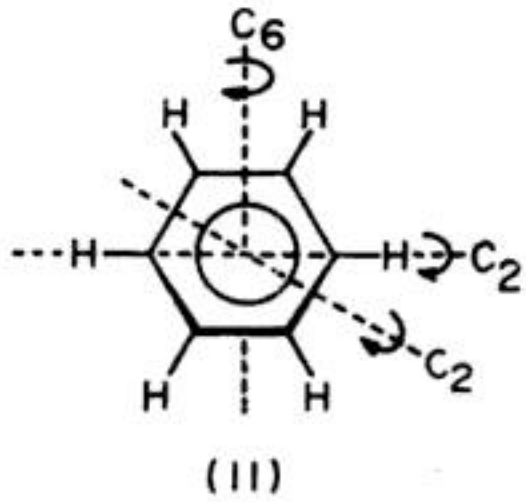

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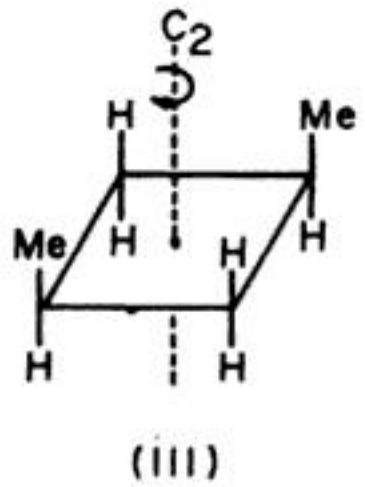

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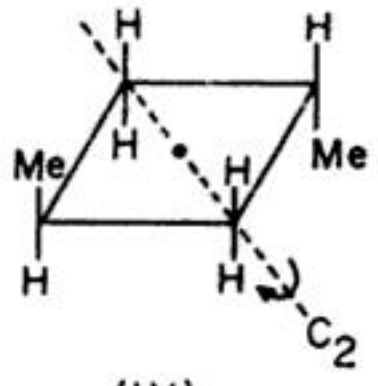

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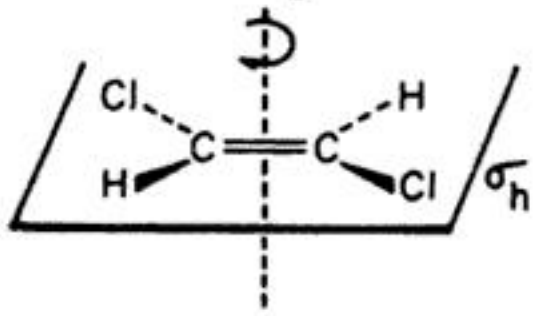

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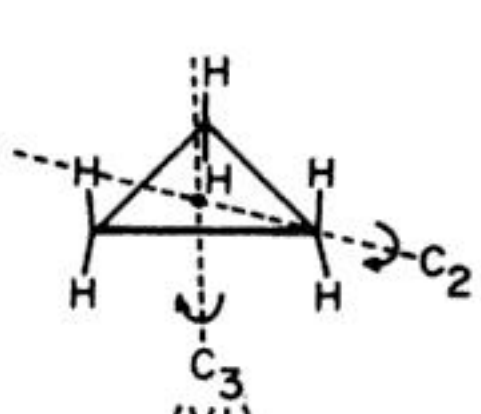
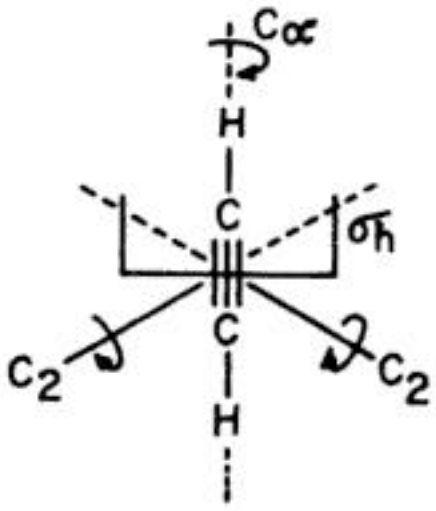
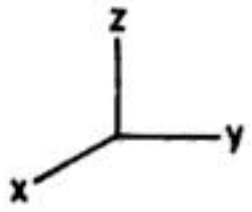
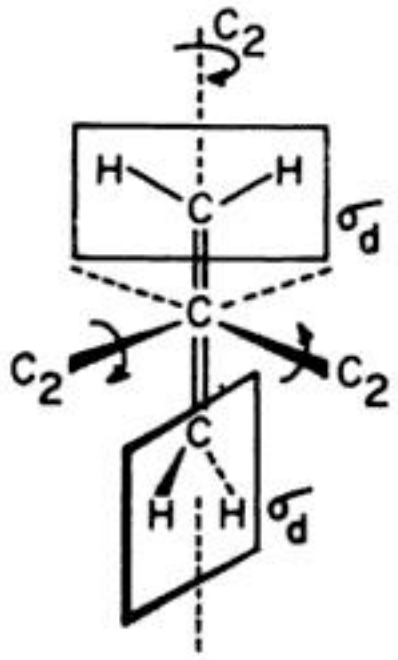


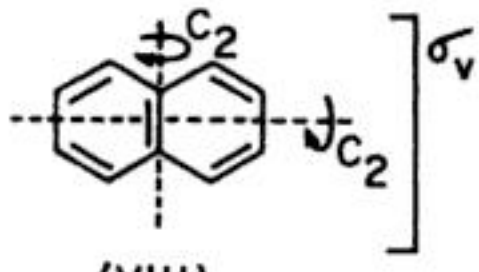
(VI)



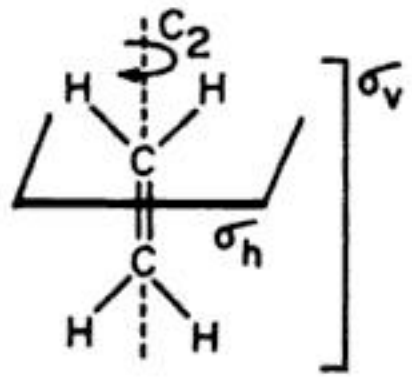
(VII)







(VIII)



(IX)

(X)

Figure 2.1 Examples of C_n, σ_h, σ_v, and σ_d (dotted lines represent axes)

the methyl-bearing carbons), *trans*-dichloroethylene (V) has one coincident with the molecular plane, cyclopropane (VI) has one horizontal and three vertical (each passing through an apex of the ring and bisecting the opposite side), acetylene (VII) has one horizontal at the centre and an infinite number passing through the internuclear axis (C_∞), naphthalene (VIII) has one horizontal and two vertical, ethylene (IX) has two vertical and one horizontal, and allene (X) has two vertical

mutually perpendicular. They are easy to comprehend even without the help of models.

σ Planes and C_n axes often occur together. Since a convention has been set up by placing the principal axis vertically (along the z-axis), the σ planes may be designated in relation to it. Thus σ_h refers to a (horizontal) plane perpendicular to the principal axis and is unique; σ_v, stands for a (vertical) plane containing the principal axis, and σ_d, represents a (diagonal) plane bisecting the angle between two C_2 axes. The three types of planes are exemplified in Figure 2.1. The number of σ_v and σ_d planes may be and usually is greater than one.

2.2.3 Centre of symmetry or inversion centre

A centre of symmetry or an inversion centre (i) is a point within a molecule such that if an atom (or point) is joined to it and the line extrapolated to an equal distance beyond, it encounters an equivalent atom (or point). In other words, inversion of all atoms (or points) in the molecule through the point gives an arrangement indistinguishable from the original. Mathematically, for every atom with coordinates x, y, z there must be a similar atom with coordinates $-x$, $-y$, $-z$, the inversion centre being the origin of the coordinates. There can be only one inversion centre in a molecule. *trans*-1,3-Dimethylcyclobutane (IV) has one at the centre of the ring, *trans*-dichloroethylene (V) has one at the mid-point of the C = C bond; α-truxillic acid (XI) and the anti conformation of *meso*-tartaric acid (XII) have one each marked by a heavy dot (Figure 2.2). The presence or absence of an inversion centre in any molecule can be easily ascertained by an inspection of the molecule.

2.2.4 Improper or alternating or rotation-reflection axis

An improper or an alternating or a rotation-reflection axis of symmetry of order n (S_n) is an (n-fold) axis such that a rotation of $360°/n$ around it followed by reflection in a plane perpendicular to the axis generates a structure indistinguishable from the original. The order of the two operations may be reversed without change in the result. The vertical axis in α-truxillic acid (XI) is an S_2 axis since a rotation of 180° around it leads to the structure (XIa) which on being reflected across the plane of the ring, gives a structure superposable on the original (XI). Conformation (XII) of *meso*-tartaric acid on being similarly reflected in a plane placed at the centre of the C—C axis and at right angles to it (Figure 2.2) gives an orientation (XIIa) which on being rotated around the axis by 180° becomes superposable with the original (XII). The conformation (XII), therefore, contains an S_2 axis. Sometimes, it is more convenient to imagine a mirror (a mirror plane) placed perpendicular to the axis but outside the molecule followed or preceded by rotation. In this case, a translational operation is necessary in order to superpose the image on the original and the centre of gravity of the molecule is displaced during the operation which contravenes the definition of point symmetry. The same conclusion, however, is reached and this procedure is recommended for molecules in which a reflection plane is not easily visualised. The S_n axis is called an alternating axis of symmetry because the equivalent atoms or groups exchanged by the operation lie alternately above and below the reflection plane.

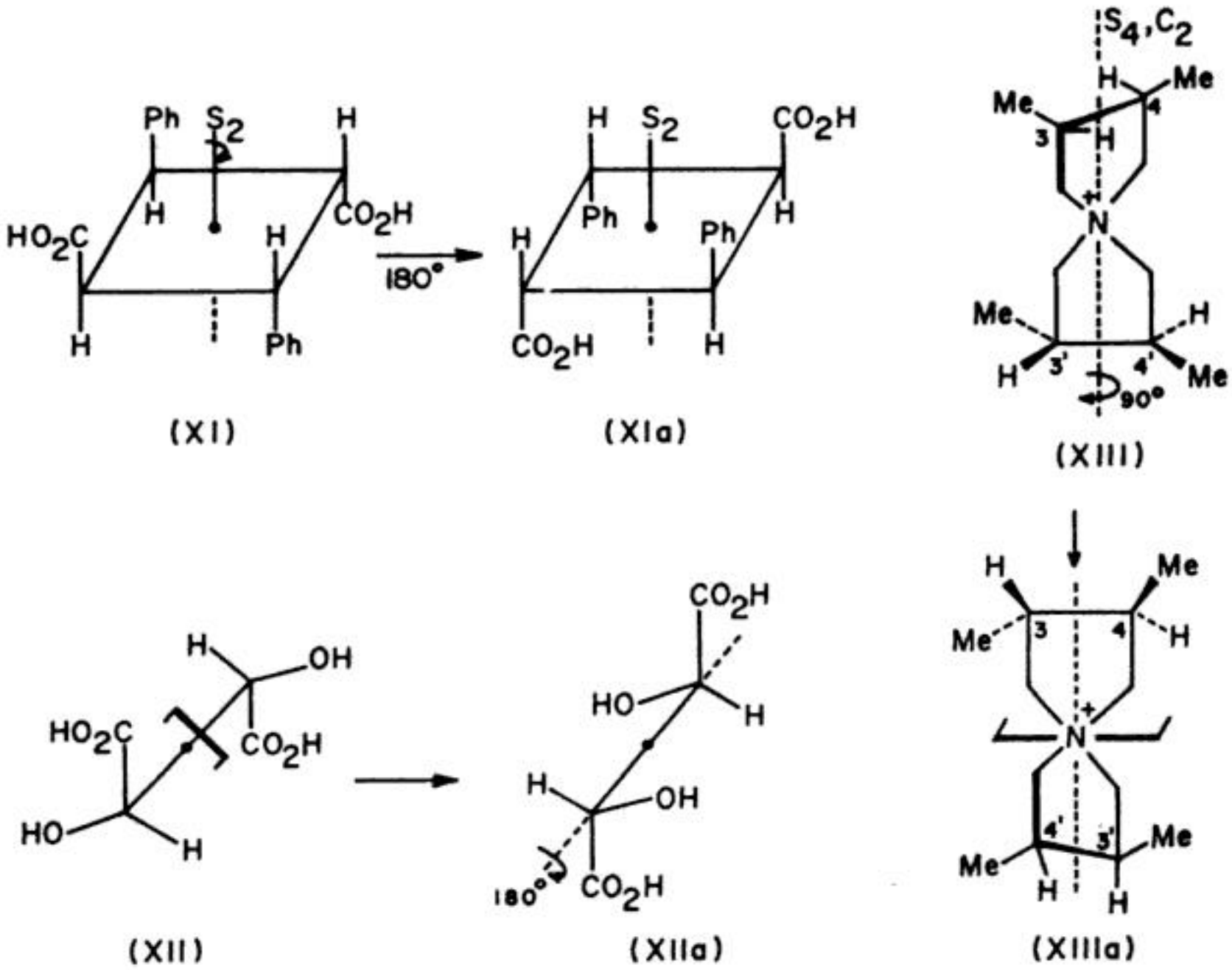


Figure 2.2 Examples of inversion centre, S_2, and S_4 axes

It may be observed that an S_2 operation brings about the exchange of like pairs of atoms or groups which are equidistant but in opposite directions from a centre, i.e., their coordinates change from x, y, z to −x, −y, −z with respect to the centre. This is precisely what an inversion operation (*i*) does. Thus an S_2 axis is equivalent to an inversion centre (*i*). In fact, *any* axis passing through an inversion centre present in a molecule is an S_2 axis. The readers may confirm this with the help of models.

An S_1 operation consists of two operations, namely, a C_1 and a σ. Since the C_1 operation leaves the molecule unchanged (i.e., an identity operation), the S_1 operation can be equated to a σ operation (the axis and the plane are not the same though the operations are). Therefore, instead of looking for S_1 and S_2 axes in a molecule, one may look for a σ plane and an inversion centre respectively.

There are few known molecules which do not have a σ plane (S_1) or an inversion centre (S_2) but have an S_n ($n > 2$) axis as the only element of reflection symmetry*. An example is found in 3,4,3′,4′-tetramethyl-spiro-(1,1′)-dipyrrolidinium ion (XIII) (Figure 2.2) which has been specially prepared (as salt) to study this type of symmetry. The structure does not have a σ plane nor an inversion

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An S_n axis without a σ plane must have *n* even and always encompasses a $C_{n/2}$ axis ($S_n = C_{n/2}$) but not necessarily the reverse).

centre but possesses a four-fold alternating axis of symmetry (S_4). A 90° rotation around the molecular axis transforms it into the structure (XIIIa) which when reflected across the horizontal plane shown, gives a structure indistinguishable from the original (XIII). During the process of reflection, the upper half of XIIIa coincides with the lower half of XIII and the lower half of XIIIa with the upper half of XIII. It may be noticed that carbons marked 3 and 4 in the structure (XIII) have *R*-configuration (to be discussed later) while the carbons marked 3′ and 4′ have the opposite ***S*-configuration** (*R* and *S* are mirror images of each other). The different symmetry operations and the corresponding elements of symmetry are summarised below:

Symmetry operations	*Symmetry elements*
1. Rotation	Simple or proper axis of symmetry, C_n
2. Reflection	Plane of symmetry, σ
3. Inversion through a point	Centre of symmetry or inversion centre, i
4. Rotation-reflection	Alternating or improper or rotation-reflection axis of symmetry, S_n

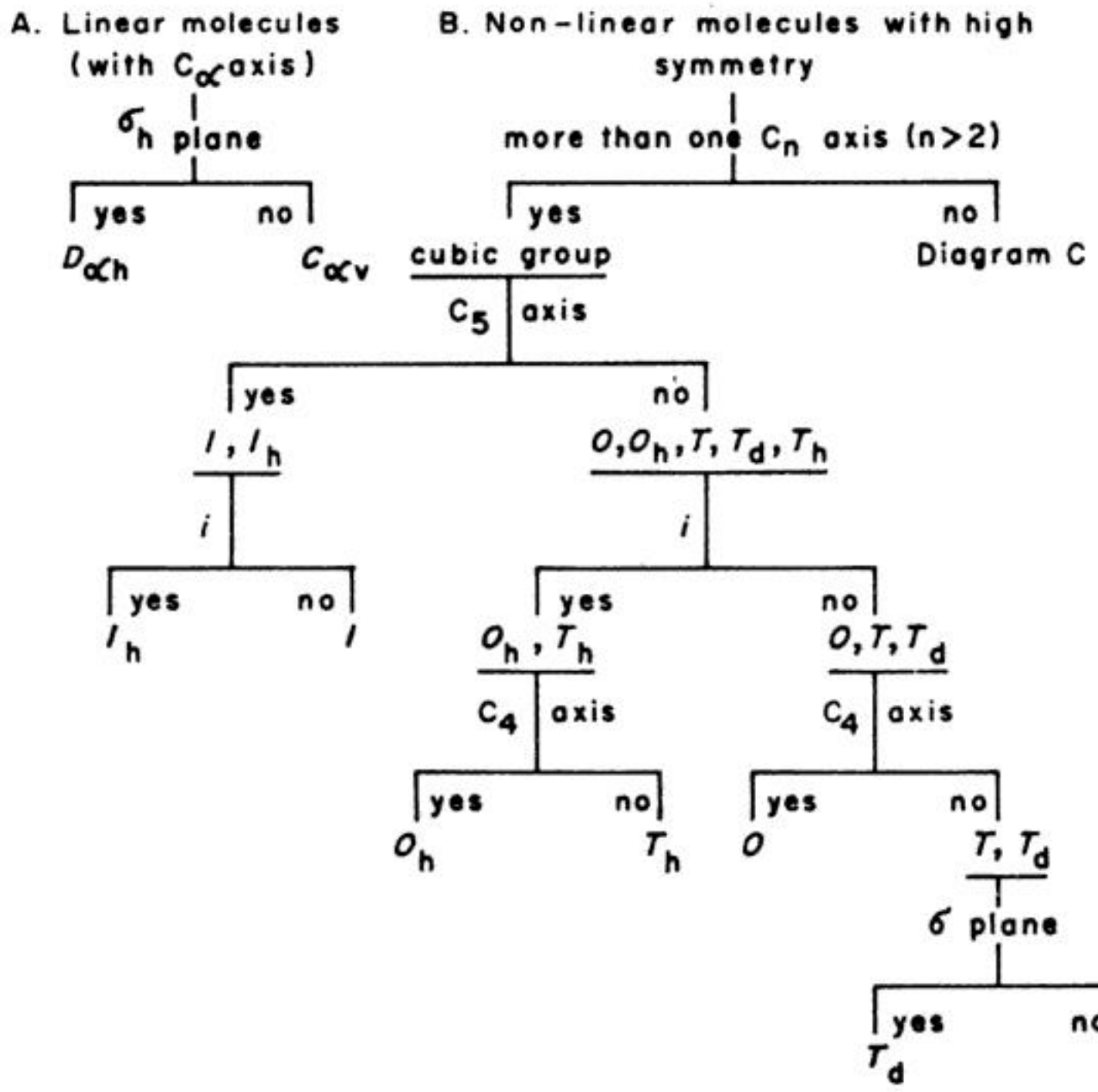
2.3 Point group classification

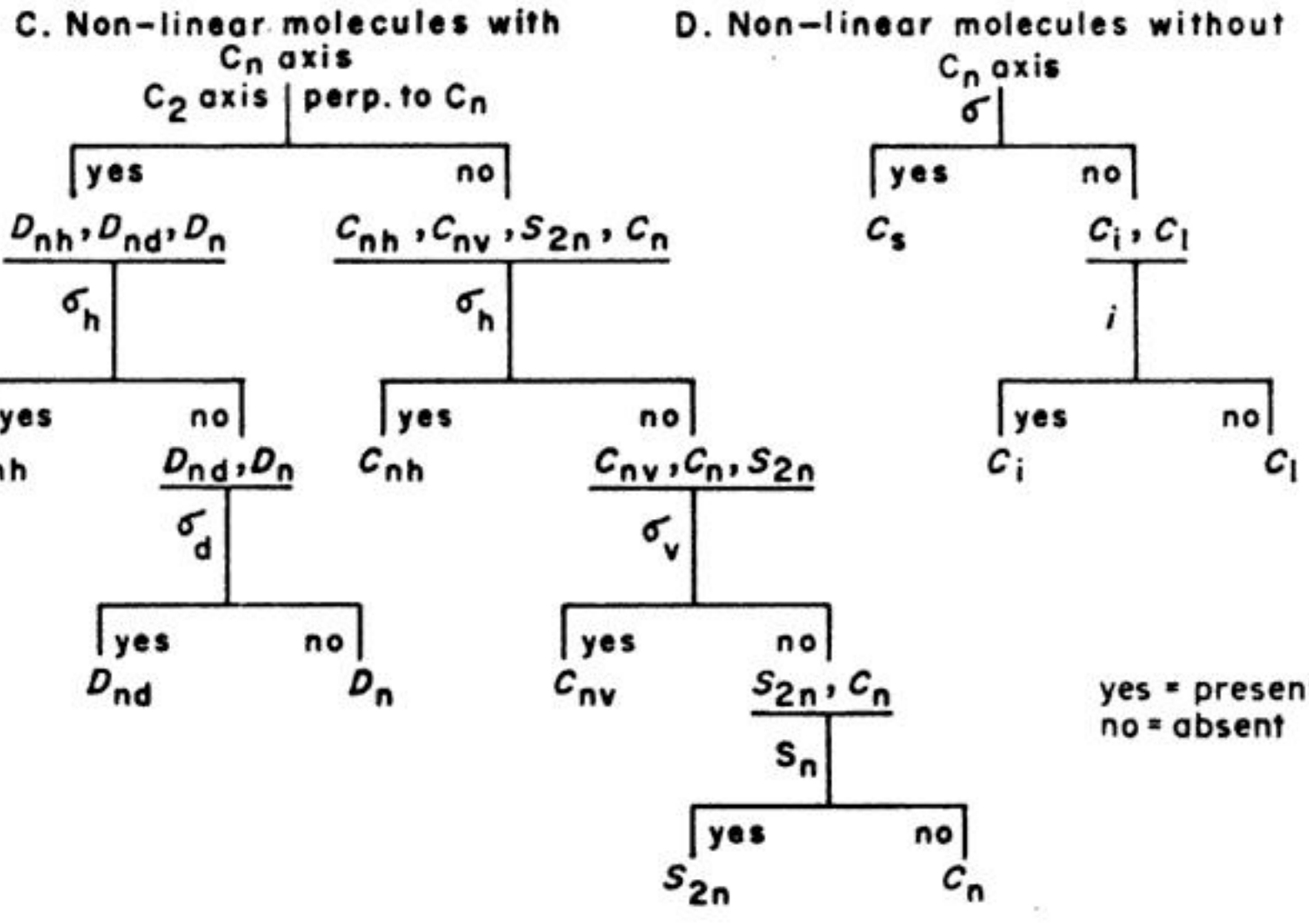
The molecular structures are almost infinitely varied; nevertheless they can be classified into a limited number of symmetry-related categories known as symmetry point groups (or simply point groups) on the basis of the symmetry operations that can be performed on them. These symmetry operations (or symmetry elements) combinedly form a group and since each of the operations leaves the centre of gravity of the molecule unchanged, the group is called a *point group*. There are some mathematical requirements for a set of symmetry operations to constitute a group, the most important one being the existence of certain binary relationship among them. Thus when two operations in the group are multiplied, i.e., carried out one after the other, the result should correspond to a third operation in the same group. For further details, the readers are referred to the textbooks cited at the end of the chapter. The scheme for classification into point groups is summarised below :

1. Linear molecules with a C_∞ axis and a σ_h plane, e.g., HC≡CH, O=C=O, belong to the point group $D_{\infty h}$. Those with a C_∞ axis but no σ_h plane, e.g., H—C≡N, belong to the point group $C_{\infty v}$ (see diagram A).

2. Non-linear molecules of high symmetry are classified under point groups T_d (tetrahedral symmetry), O_h (octahedral symmetry), and I_h (icosahedral symmetry). Methane and carbon tetrachloride having four C_3 axes, three C_2 axes (which are also S_4 axes), and six σ planes belong to the T_d point group and octahedral species like SiF_6 having a still higher number of symmetry elements belong to the O_h point group. Molecules containing a C_5 axis (actually several) belong to I_h point group and are the most highly symmetrical molecules (see dodecahedrane in Chapter 11). The classification is shown in diagram B. The K_h point group contains infinite number of C's and σ's and does not apply to molecules.

Flow-sheet diagrams for classification of molecules into point groups





3. Non-linear molecules with lesser symmetry may have a principal simple axis of symmetry (C_n, $n > 1$). If in addition to C_n, they possess n C_2 axes perpendicular to C_n, they belong to the point groups D_{nh}, D_{nd} or D_n (D stands for dihedral symmetry). In order to differentiate them, one looks for a σ_h plane. If it exists (along with n σ_v planes), point group D_{nh} is indicated. If there is no σ_h but only σ_d planes, the molecule belongs to the point group D_{nd}. In the absence of both, the point group is D_n. This is shown on the left hand side of the flow-sheet diagram C.

4. In the case where C_n is the only axis with no C_2 axis perpendicular to it, four point groups, C_{nh}, C_{nv}, C_n, and S_{2n} are to be considered. The presence of a σ_h plane indicates point group C_{nh}; if it is absent but σ_v's are present, the molecule belongs to point group C_{nv}. Both of them being simultaneously absent, the point group is either S_{2n} or C_n which can be readily distinguished by the presence (S_{2n} point group) and absence (C_n point group) of an S_{2n} axis (the order must be even and hence $2n$ is used). This is shown on the right hand side of the diagram C.

5. For molecules which do not have any C_n ($n > 1$) axis, only three point groups C_s, C_i, C_1 are to be considered. If a σ plane is present, the molecule belongs to the point group C_s; if it is absent but an inversion centre is present, the point group is C_i. In the absence of both, the molecule belongs to the point group C_1 which does not have any element of symmetry except for the trivial C_1 axis and is truly asymmetric. The assignments are shown in the diagram D. For organic molecules, point groups under diagrams C and D are more pertinent.

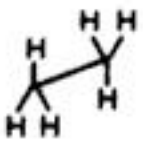
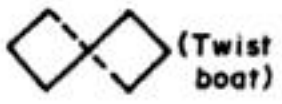
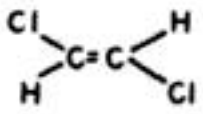
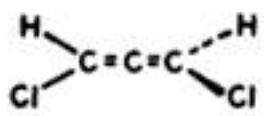
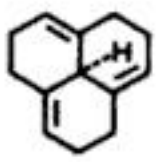
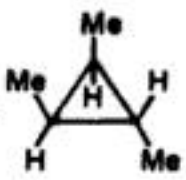
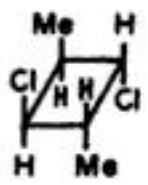
In Table 2.1, a few representative molecules, their elements of symmetry and point group classification are given. The readers are advised to verify the assignment of the point groups with the help of the flow-sheet diagrams. More examples will follow in subsequent chapters.

2.4 Molecular symmetry and chirality

A molecule (or an object) can have only one mirror image. If the image is superposable on the original, the molecule is called achiral. On the other hand, if it is not superposable, the molecule and its mirror image form two distinct species called enantiomers (see Chapter 3) giving rise to a type of stereoisomerism known as enantiomerism. Such molecules are called chiral and the two enantiomers are said to differ in their sense of chirality or handedness in the same way as a right hand differs from a left. A case in hand is the two forms of lactic acid (XIV) and (XIV′) (Figure 2.3) which are mirror images of each other but non-superposable. The former is dextrorotatory, i.e., it turns the plane of the polarised light to the right when the light beam is viewed end on and the other is levorotatory, i.e., it turns the plane of the polarised light to the left. Chirality is a necessary and sufficient condition for the occurrence of enantiomerism and is determined by the absence of rotation-reflection symmetry (S_n axis of any order) in the molecule. All molecules belonging to the point groups C_1, C_n and D_n (shown in the flow-sheet diagrams) lack reflection symmetry and are chiral while molecules belonging to the rest of the point groups shown in the diagrams* are achiral. For example, lactic

*In principle, molecules with tetrahedral, octahedral, and icosahedral symmetry but lacking plane of symmetry or inversion centre (point groups *T*, *O*, and *I*) are also chiral. But they are almost non-existent.

Table 2.1 Some molecules with their symmetry elements and point group classification

Molecules[a]	Symmetry elements[b]	Point group	Instruction
1. $CHCl_3$ (I)	C_3 (C_n), $3 \times \sigma_v$ no C_2 and σ_h	C_{3v}	Follow right hand side of Chart C
2. 	C_6 (C_n), $6 \times C_2$, σ_h	D_{6h}	Follow left hand side of Chart C
3. 	C_3 (C_n), $3 \times C_2$, $3\ \sigma_d$	D_{3d}	"
4.  (Twist boat)	C_2 (C_n), $2 \times C_2$ no σ_n and σ_d	D_2	"
5. 	C_2 (C_n), σ_h	C_{2h}	Follow right hand side of Chart C
6. 	C_2 (C_n) no C_2, σ_v, σ_h and S_n	C_2	"
7. 	C_3 (C_n) no C_2, σ_v, σ_h and S_n	C_3	"
8. 	σ no C_n	C_s	Follow Chart D
9. 	i no C_n and σ	C_i	"
10. XIII	C_2 (C_n), S_4 no C_2, σ_h, and σ_v	S_4	Follow right hand side of Chart C
11. Allene (X)	C_2 (C_n), $2 \times C_2$, $2 \times \sigma_d$	D_{2d}	Follow left hand side of Chart C
12. Lactic acid (XIV)	No C_n, C_i and σ	C_1	Follow Chart D

[a] Some of the molecular structures will be better understood after going through later chapters.
[b] C_n in parenthesis indicates the principal axis, other C_2 axes are perpendicular to it.

acid (Figure 2.3) belonging to point group C_1 and 1,3-dichloroallene belonging to point group C_2 (see Table 2.1) are chiral. Since chiral molecules may contain C_2 **axis, it is not proper to equate chiral with 'asymmetric' or achiral* with 'symmetric'.**

There are two practical ways to determine the chirality of a molecule without first classifying it into a point group. One is to construct the mirror image of the molecule and see whether it is superposable on the original. With complex molecules, this is often not an easy task, particularly because the molecules are usually represented in two dimensions following some conventions which impose

* It is better to call achiral molecule as non-dissymmetric.

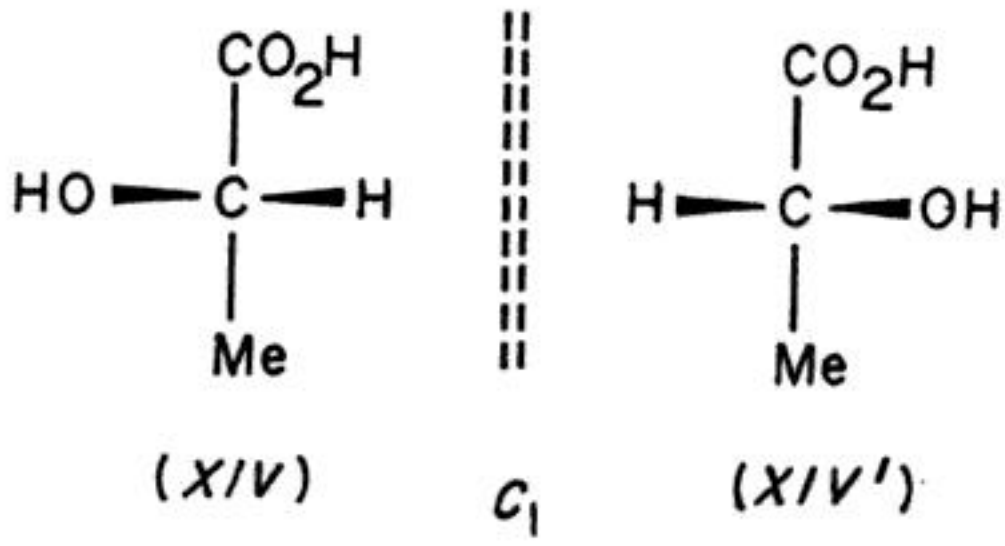
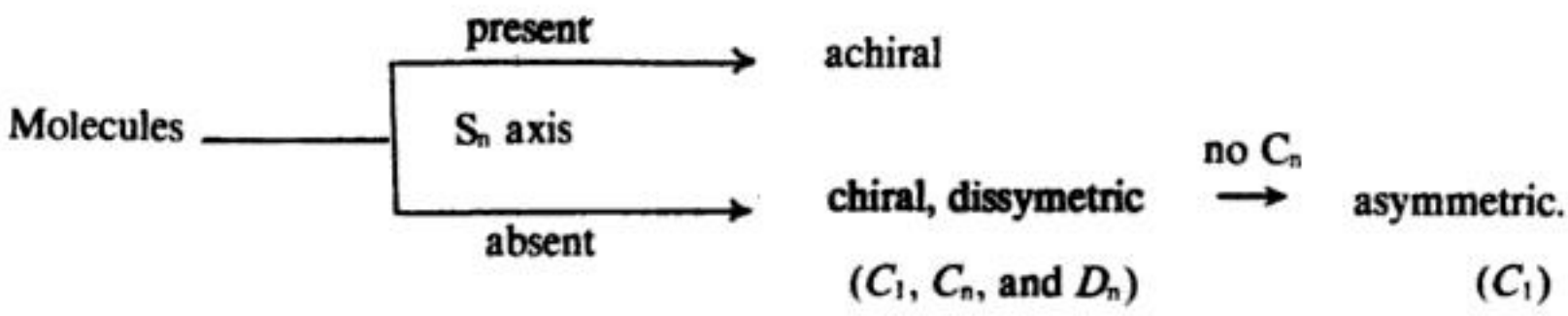


Figure 2.3 Enantiomers of lactic acid

certain restrictions on their movement in the plane of the paper. Thus it is preferable to take recourse to molecular models*. The second way is to look for the absence of reflection symmetry in a molecule. The presence of a σ plane (S_1) is *sufficient* to make a molecule achiral. However, it is not a *necessary* condition since even in its absence, a molecule may be achiral due to the presence of an S_n axis of higher order, see, for example, molecules (XI) and (XIII). One should, therefore, ascertain the absence of an S axis of any order before proclaiming a molecule chiral. In practice, it is advisable to look for a σ plane (S_1) and an inversion centre (S_2) in the first place and then for an S_n axis of higher order if the situation warrants. The σ plane and inversion centre are easy to locate and except for a few molecules specially prepared to prove a point (as XIII), a molecule is achiral due to the presence of either of these two elements of symmetry.

The presence of one or more C_n axes does not interfere with a molecule being chiral and existing as two enantiomers; thus molecules belonging to point groups D_n and C_n are chiral. Three terms have almost been interchangeably used to describe molecules which show enantiomerism : asymmetric, dissymmetric, and chiral. The term *chiral* (whence *chirality*) is synonymous with *dissymmetric* (Eliel and Wheland 1962) although the former is now getting wider currency. The term *asymmetric* (or asymmetry) has a slightly different connotation in the sense that while an asymmetric molecule is a chiral molecule, it lacks C_n axis also; i.e., all symmetry elements are absent except for the trivial C_1 axis. The following diagram clarifies the situation.



*The readers are advised to make use of molecular models throughout the reading of the book.

Chapter 3

Stereoisomerism : Definitions and Classification

3.1 Introduction

In the light of the bonding geometry (Chapter 1) and symmetry properties (Chapter 2) of molecules, it may be appropriate to examine the nature of the different molecular species that a given set of atoms specified by a molecular formula can furnish. Except for a few simple molecules, e.g., H_2O, CH_4, CH_3X, CH_2X_2, CHX_3 etc., the molecular formula alone cannot describe uniquely the structure of a molecule. Two additional pieces of information, namely, the nature of linkages among atoms regardless of direction in space (bonding connectivity) and the relative orientation of atoms and groups in space (configuration) are necessary. Depending on these two parameters, a certain combination of atoms can give rise to a number of molecular species, known as *isomers* which are separated by energy barrier and differ in their chemical and physical properties. Molecules with the same molecular formula but differing in bonding connectivities are called *constitutional isomers**. They may differ in the nature of the functional group, e.g., CH_3CH_2OH and CH_3OCH_3, or in the position of an atom or a group, e.g., 1-propanol and 2-propanol, or in the nature of the skeletal structure, e.g., *n*-butane and *i*-butane and are further subdivided into functional group isomers, tautomers, positional isomers, ring chain isomers etc. which are discussed in all texts on organic chemistry. When molecules differ only in the relative orientation of atoms and groups in space, *stereoisomerism* results. Stereoisomers thus have the same bonding connectivity but differ in their configurations and are often called *configurational isomers*. Stereoisomers resemble one another only in the general properties of the functional group(s) common to them but may otherwise differ substantially in chemical, physical, physicochemical, and biochemical properties including chemical reactivities. These differences which form the basis of stereochemistry are manifest in the various stereodifferentiating reactions so useful in organic syntheses and in biochemical reactions so vital for life processes. Most of the natural products and biologically important molecules occur in specific stereoisomeric forms and their chemical and biochemical behaviours are regulated by their molecular architecture.

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*They are also called structural isomers in many textbooks. However, the term *structure* is now used in a broader sense comprising constitution, configuration, and conformation.

3.2 Molecular representation

Since stereochemistry refers to molecules in three dimensions, appropriate modes of representations of three-dimensional molecules on two-dimensional paper is essential. Two systems of representation commonly used, namely, sawhorse and Newman projection have already been introduced in Chapter 1. A tetrahedral carbon containing four different groups, e.g., Cabcd (see lactic acid in Chapter 1) known as asymmetric (chiral) carbon is represented by the structures (I) and (II) (Figure 3.1a) which are non-superposable mirror images of each other. When

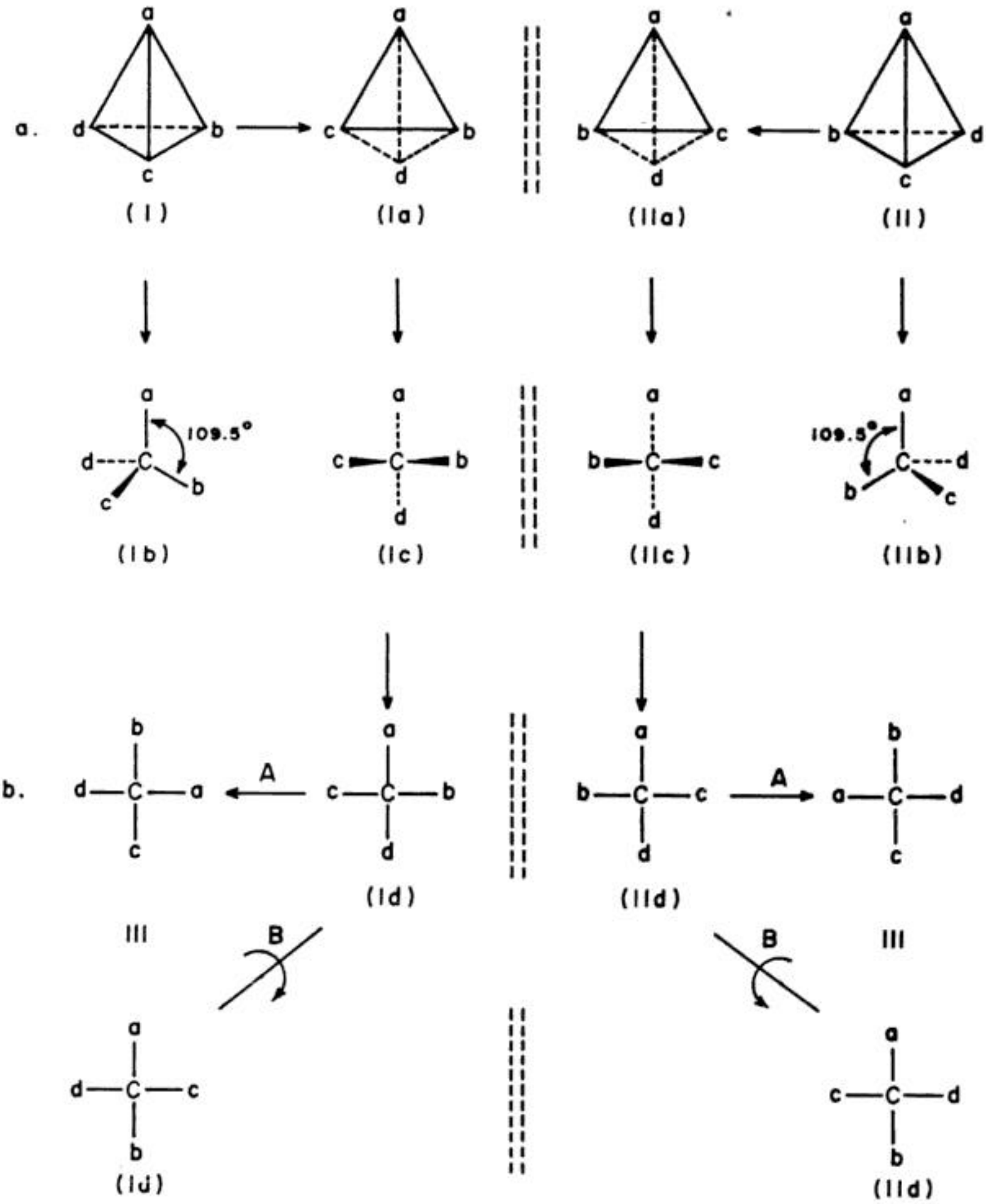


Figure 3.1 Molecular representation : I_b and II_b are flying wedges and I_c $(=I_d)$ and II_c $(=II_d)$ are Fischer projection (dotted double lines represent mirrors)

in this connection: The Fischer projection formula actually represents a molecule in eclipsed conformation (III = IIIa = IIId; IV = IVa = IVd) which is energetically unfavourable and thus gives an improper perspective of the molecule. Secondly, for each of the stereoisomers (III) and (IV), three staggered Newman and sawhorse formulae can be drawn (by successive 120° rotations of the front carbon) each corresponding to a distinct conformer. Care should be taken so that during the above interconversions, the order (clockwise or anticlockwise) of the groups in space around a chiral centre is not disturbed. Sawhorse and Newman projection formulae can likewise be converted into Fischer projection formulae by reversing the procedure.

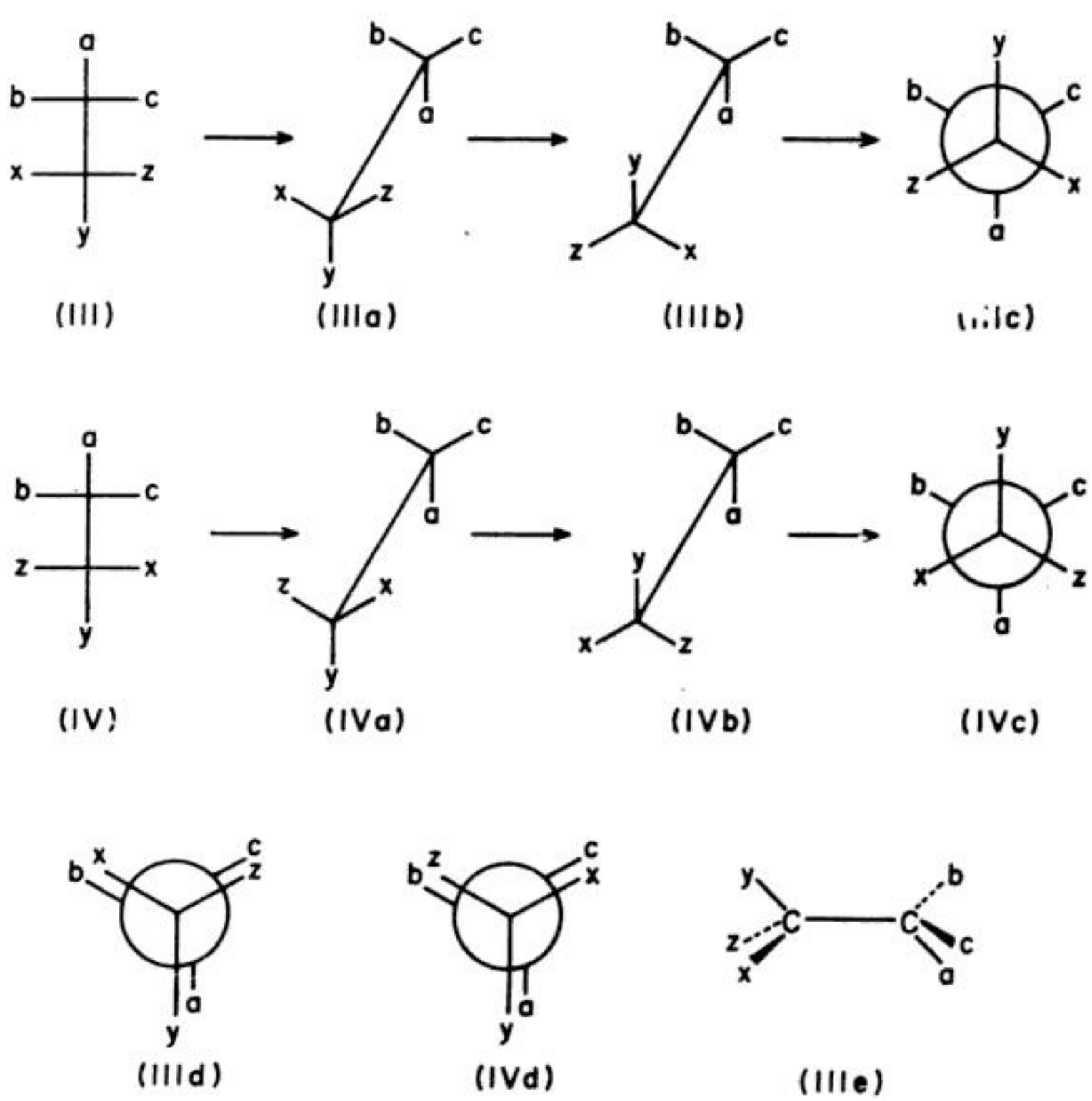


Figure 3.2 Interconversion of Fischer projection, saw-horse, and Newman projection formula.

The structures can also be represented by flying-wedge notation in which the molecule is viewed *side on*. Thus the sawhorse formula (IIIb) in flying wedge notation would appear as IIIe. The only advantage of this system is that it shows the valency angles in their proper magnitude. In the present text, this notation will not be used except to denote a single chiral centre.

3.3 Classification of stereoisomers

In classical stereochemistry (see Eliel 1962), stereoisomers were divided into three classes: optical isomers, diastereomers, and geometrical (or cis-trans) isomers. Mislow (1965) has suggested a new system of classification based on symmetry and energy criteria which is now generally adopted and is discussed below.

3.3.1 Classification based on symmetry criterion

The classification of stereoisomers based on symmetry criterion is simple and straightforward. Only two types are recognised: enantiomers and diastereomers.

If two stereoisomers are related to each other as object and mirror image which are not superposable, (like a left hand and a right hand) they are called *enantiomers* and said to exhibit an *enantiomeric relationship*. As discussed in Chapter 2, such molecules are necessarily chiral and belong to point groups C_1, C_n, and D_n only. Since enantiomers are usually optically active, i.e., they turn the plane of a polarised light to an equal degree but in opposite directions, they are also called *optical isomers* or *optical antipodes*. These terms, however, are losing popularity and better be abandoned since some enantiomers, e.g., *R*- and *S*-*n*-butyl ethyl-*n*-hexyl-*n*-propylmethane do not show any detectable optical rotation. On the other hand, many optically active compounds display diastereomerism (see below).

Stereoisomers which are not related to each other as object and mirror image, i.e., which are not enantiomers, are called *diastereomers* and said to exhibit a *diastereomeric relationship*. A broad range of molecules falls under this category. Some typical examples of enantiomers and diastereomers are shown in Figure 3.3. The classification is summarised in the flow sheet chart 3.1. which also includes constitutional isomers. The following points serve to highlight some of the distinctive features of enantiomers and diastereomers.

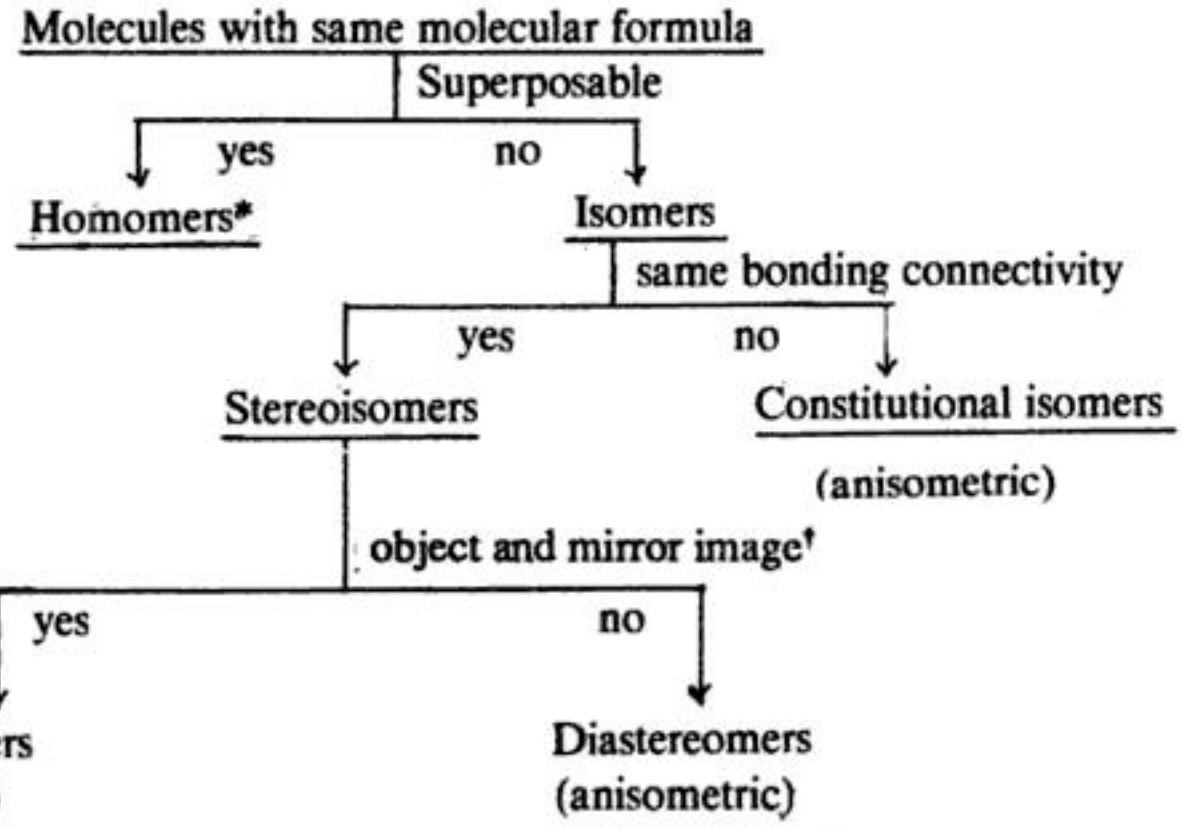


Chart 3.1 Symmetry-based classification of stereoisomers

*At first sight, it appears superfluous to represent homomers as a class, since they are in essence identical. However, the concept of homomers as opposed to isomers is useful as will be seen later.

† Necessarily non-superposable.

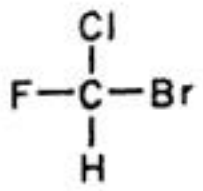
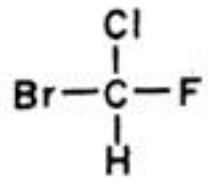
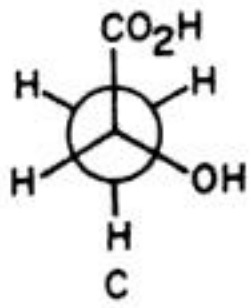
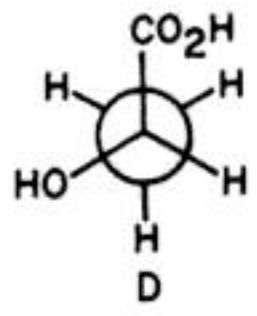
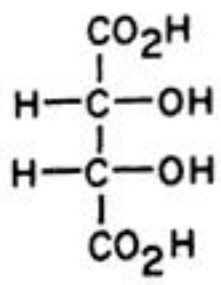
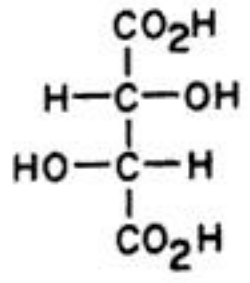
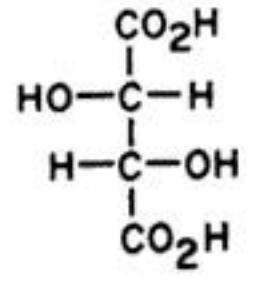
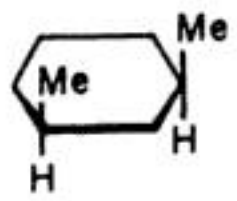
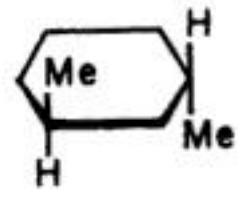
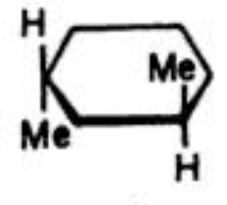
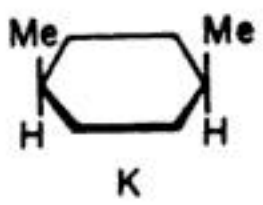
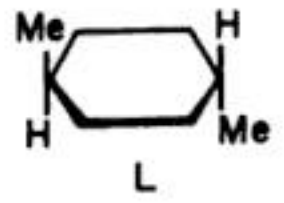
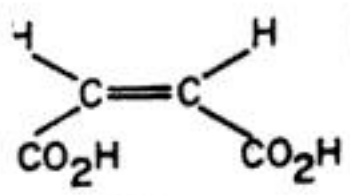
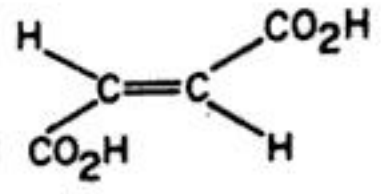
Entry	Compounds	Enantiomers	Diastereomers
1.	 A  B	A,B	—
2.	 C  D	C,D	—
3.	 E  F  G	F,G	E,F E,G
4.	 H  I  J	I,J	H,I H,J
5.	 K  L	—	K,L
6.	 M  N	—	M,N

Figure 3.3 Examples of configurational enantiomers and diastereomers

(*i*) Enantiomers being mirror images of each other are related by symmetry elements of the second kind, i.e., σ plane, i, and S_n axis but diastereomers are not related by any such symmetry element.

(*ii*) Since a molecule (or an object) can have only one mirror image, enantiomers can exist only in pairs. On the other hand, structural conditions permitting, a molecule can have any number of diastereomers.

(*iii*) No two stereoisomers can be enantiomers and diastereomers at the same time, i.e., enantiomeric and diastereomeric relationships are mutually exclusive.

(*iv*) Diastereomers may be (but do not have to be) chiral in which case each of them in turn would exhibit enantiomerism. Thus cholesterol is one stereoisomer of a set of one hundred twenty eight diastereomers each of which has an enantiomer. It is, therefore, diastereomeric with two hundred fifty four molecules and enantiomeric with one.

(*v*) Diastereomers in the new definition include all stereoisomers (except enantiomers) such as optically active diastereomers, geometrical isomers, and cis-trans isomers of classical stereochemistry. Thus 1,3-dimethylcyclohexane containing two chiral centres in previous nomenclature was said to exist in two diastereomers (cis and trans) one of which (trans) is resolvable into enantiomers (I and J in Figure 3.3) while similarly constituted but achiral 1,4-dimethylcyclohexane was said to exist in two geometrical or cis-trans isomers (K and L) none of which is resolvable. In the present system, this dichotomy is removed and both of them are said to exhibit diastereomerism. Like optical isomerism, the term geometrical isomerism has thus become redundant although the analogous term cis-trans isomerism still finds application as a subclass of diastereomerism.

(*vi*) In a chiral molecule, the atoms have exactly the same relative positions with respect to interatomic distances and interactions as they have in its enantiomer. The two enantiomers are thus *isometric* to each other and in achiral media, behave in identical fashion, as if they were homomers (any two structures which are superposable are called *homomers*). Thus enantiomers have the same melting points, boiling points, densities, solubilities, refractive indices, dipole momemts, etc., and the same thermodynamic and spectroscopic properties. They also show the same reactivity towards achiral reagents. In contrast, the diastereomers differ in the spatial relationship of atoms and groups and are, therefore, *anisometric* relative to one another (Coxeter 1969). They differ, in principle, in all the above mentioned properties, however small the difference may be.

(*vii*) Two enantiomers have all their geometrical parameters identical as mentioned above. They differ only in terms of absolute direction in space (algebraic sign of the coordinates of atoms)—a vector rather than a scalar quantity described by the science of topography which individualises each point and deals with the properties of each separately (Klein 1968). It is thus appropriate to say that enantiomers are geometrically equivalent (molecules or structures are called geometrically equivalent if they can be made superposable by any of the symmetry operations mentioned in Chapter 2) but differ in their topography (in the sense of chirality). In contrast, diastereomers differ both in geometry and in topography.

(*viii*) Chirality or enantiomeric relationship cannot be specified without comparison with an external reference which itself must be chiral. Thus when one says

right-handed chirality (or *R* and *S* configuration), one refers it to a right hand (which, too, is a right hand only by convention). Chirality can be recognised only through the diastereomeric relationship a chiral object establishes either with its own kind or with another chiral object. Two enantiomers behave differently toward a plane-polarised light because a plane-polarised light is composed of two dissymmetric components, a right-handed and a left-handed circularly polarised light beam (see Chapter 15) and thus constitutes a chiral environment. The well known enzyme stereospecificity is another example of chiral recognition of a chiral substrate by a dissymmetric system or reagent (here the enzyme).

Diastereomers and diastereomeric relationship, on the other hand, can be specified and recognised without any external reference.

(*ix*) As a corrolary of the above, a single stereoisomer cannot be designated an enantiomer or a diastereomer since such terms refer to relationship within a set of two or more stereoisomers. A molecule is either an enantiomer of (or a diastereomer of) or enantiomeric with (or diastereomeric with) another molecule.

(*x*) Both constitutional isomers and diastereomers containing the same functional group(s) usually differ in scalar properties, e.g., boiling points, melting points, density, refractive index, thermodynamical and spectroscopic properties, and even in their reactivities. In fact, two diastereomers may differ in their properties as much as (in some cases, even more than) two constitutional isomers. From an operational point of view, therefore, distinction between these two classes appear to lose their significance (Mislow 1965).

3.3.2 Classification based on energy criterion

It has already been stated that isomers are separated by energy barrier and their kinetic stabilities depend on the barrier height. Stereoisomers separated by *high energy barrier* ($>$ 100 kJ mol^{-1}) are quite stable and at room temperature are isolable. They are called configurational isomers. Stereoisomers separated by relatively *low energy barrier* ($<$ 60 kJ mol^{-1}) are easily interconvertible at ambient temperature and are known as conformational isomers or conformers. The difficulty arises when one goes to define *high* and *low* (the use of 100 and 60 kJ mol^{-1} as above is quite arbitrary) since it is almost impossible to set a standard acceptable to all. For a synthetic chemist who is interested in isolating stable stereoisomers, the desired barrier is high ($>$ 100 kJ mol^{-1}). For a spectroscopist who is interested in identifying the different stereoisomers in equilibrium, a low energy barrier is sufficient as long as the physical technique (e.g., infrared, nuclear magnetic resonance, microwave spectroscopy etc.) used has a time scale of measurement which is short in comparison to the rate of interconversion of the isomers. If the rate of interconversion is fast compared to the time scale of measurement, only an average picture of the species in equilibrium is obtained. According to Eliel (1976), it is appropriate that we accept an energy barrier of RT (2.58 kJ mol^{-1} at room temperature) as the standard below which two species may be considered as homomers. From energy criterion, the stereoisomers are thus classified into three categories. Stereoisomers which are separated by high energy barrier are known as configurational isomers. Stereoisomers which are separated by low energy barrier are known as conformational isomers. Finally, stereoisomers which are separated by energy barrier of intermediate magnitude (falling within

gray area) may be called configurational isomers at low temperature and conformational isomers at ambient temperature.

The two classifications (based on symmetry and on energetics) are not mutually exclusive. Enantiomers or diastereomers may be configurational enantiomers or configurational diastereomers if the energy barriers are high. Similarly, one can have conformational enantiomers and conformational diastereomers when the energy barriers are relatively low. Examples are given in Figure 3.4*. The combined classification is shown in the flow sheet Chart 3.2.

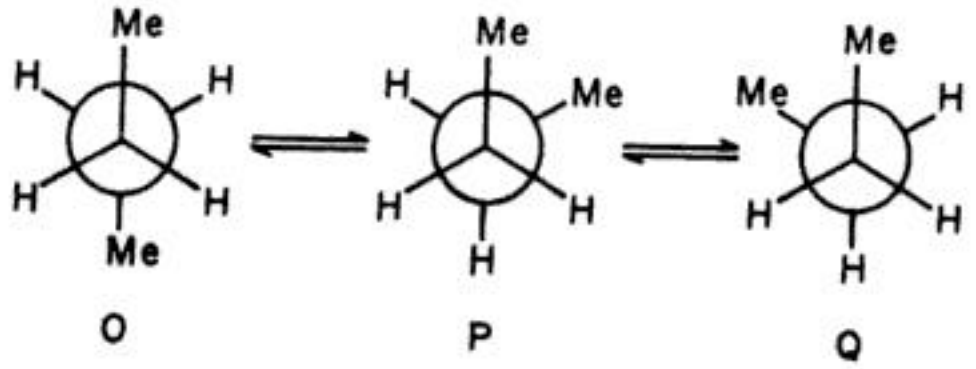
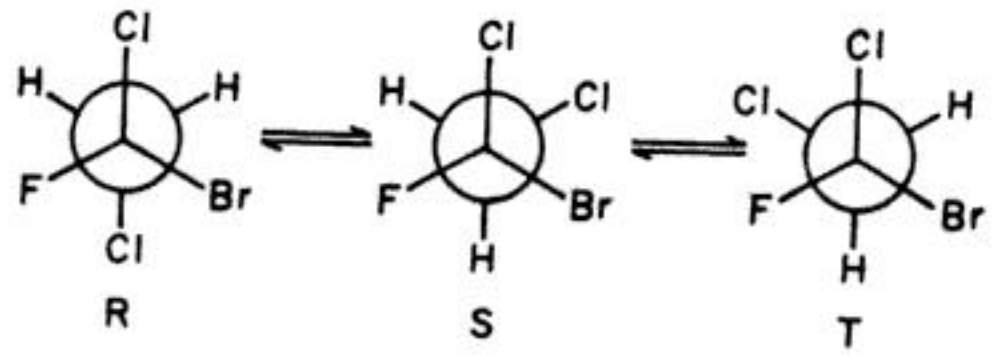
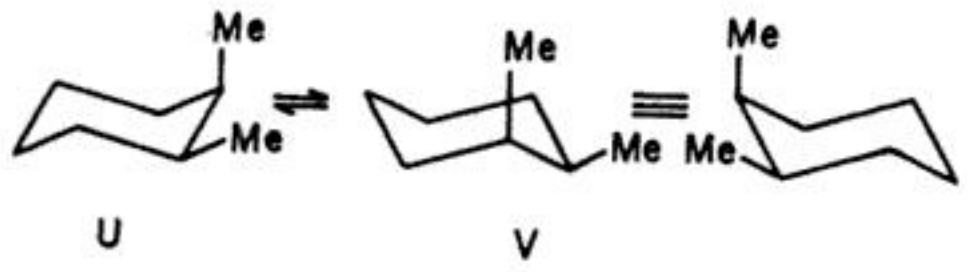
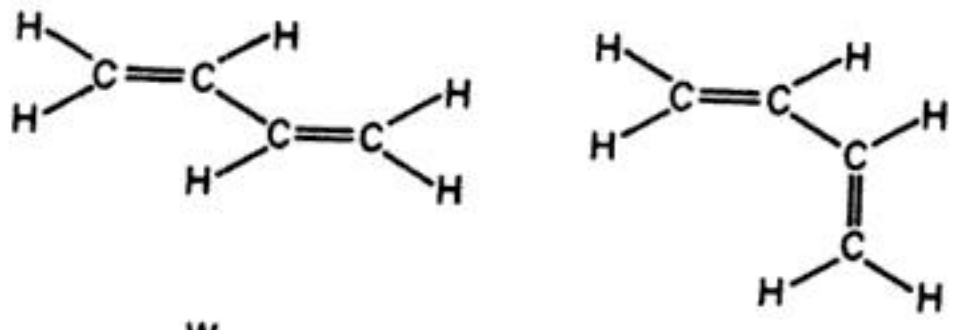
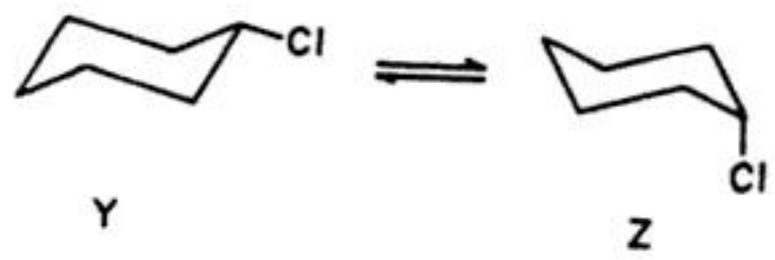
Entry	Conformations	Enantiomers	Diastereomers
1.	 O, P, Q	P, Q	O, P O, Q
2.	 R, S, T	—	R, S, T
3.	 U, V	U, V	—
4.	 W, X	—	W, X
5	 Y, Z	—	Y, Z

Figure 3.4 Examples of conformational enantiomers and diastereomers

*Some of the examples will be better understood later.

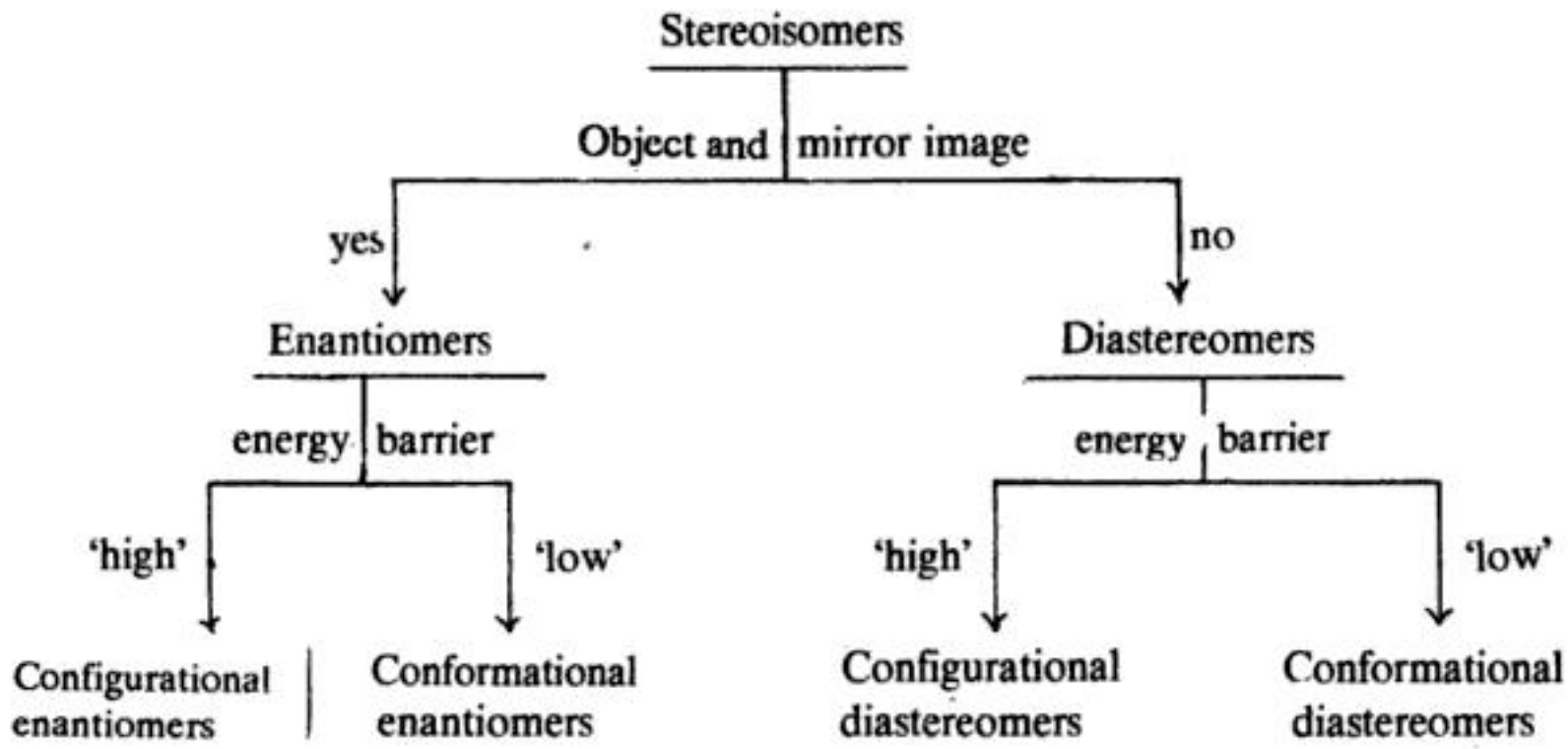


Chart 3.2 Classification of stereoisomers based on joint criteria of symmetry and energy.

The energy barrier separating any two stereoisomers depends on the mechanism of interconversion. The two enantiomers of lactic acids are separated by high energy barrier since their interconversion involves a σ bond breaking. They represent configurational enantiomers. In the isomerisation of *cis*- and *trans*-2-butene (Chapter 1), a π bond is disrupted which requires an appreciable amount of energy; they are also configurational diastereomers. Ethylenic compounds of the type, $RR'C=C(OR)(OR')$, on the other hand. have relatively low (60-70 kJ mol^{-1}) torsional energy and give conformational diastereomers at ambient temperature in spite of the double bond (Kalinowski and Kessler 1973).

Rotation around a single bond is in general easy and leads to conformational isomers as in *n*-butane (entry 1, Figure 3.4) and in dichlorobromofluoroethane (entry 2, Figure 3.4). Rotational energies about sp^2-sp^2 single bonds are in comparison higher, e.g., 25 kJ mol^{-1} for 1,3-butadiene (see Chapter 1) but not high enough to permit isolation of stereoisomers at ambient temperature and thus leads to conformational isomers (entry 4, Figure 3.4). In some crowded molecules, however, rotation about a single bond may be sufficiently restricted to give stable and isolable conformers known as atropisomers (Chapter 5) which are configurational isomers. Inversion in nitrogen compounds is normally facile and give conformers known as invertomers. The barrier height, however, depends on a number of factors and can vary enormously (see Chapter 10), the average value being of the order of 25 kJ mol^{-1} (Lehn 1970). In comparison, inversion in phosphorus compounds is associated with high energy (of the order of 150 kJ mol^{-1}) and configurational isomers are encountered.

Ring inversion (also pseudorotation) is a facile process and leads to conformational isomers (entries 3 and 5, Figure 3.4). These will be discussed in Chapter 10.

3.4 Stereoisomerism, conformation, and chirality

The concept of conformation has widened the definition of stereoisomerism and introduced a time-dependent element in the molecular structures. The molecule in

most cases cannot be treated as a static system of fixed geometry but as a dynamic system consisting of a number of species in equilibrium continuously changing their geometries. Molecules containing a single bond between two sp^3 hybridised carbons reside in three conformers which can be homomeric, enantiomeric, or diastereomeric with one another. Compounds containing two such bonds can have as many as nine conformers of which only a few are preferred on energy ground. Thus the number of conformers increases in geometric progression with chain length*. Ethane (Chapter 1) exists in three conformers all of which are homomeric. *n*-Butane, an achiral molecule has three distinct conformers based on rotation around C_2—C_3 bond, two of which are enantiomeric and the third is diastereomeric with both (entry 1 in Figure 3.4). The other conformers arising out of rotations around C_1—C_2 and C_3—C_4 bonds are homomeric with one or other of the above three. In the case of a chiral molecule, the three conformers of a particular enantiomer can either be all homomeric or all diastereomeric (see 1,2-dichlorofluorobromoethane, entry 2, Figure 3.4). No two conformers of a given enantiomer can have enantiomeric relationship although all the conformers must be necessarily chiral.

From the above discussion, it is quite clear that if a particular conformer of a molecule is chiral, the molecule is not necessarily chiral. There are two simple rules to determine the chirality or achirality of a molecule from its conformers:

(*i*) If during a 360° rotation about one or more single bonds, a conformer passes through a conformation (may be with an energy maximum) which is achiral, the molecule is achiral. If there is no achiral conformation or conformer, then the molecule is chiral. This rule is specially useful in deciding the chirality of an acyclic molecule. The optically inactive meso form of tartaric acid (E in Figure 3.3.) possesses a plane of symmetry in the eclipsed conformation (C_s point group), as in the Fischer projection formula and a centre of symmetry in one of the staggered conformers (C_i point group) and so the meso form is achiral. On the other hand, all the conformers of optically active tartaric acid (F and G, Figure 3.3) are chiral.

(*ii*) The second rule is to see whether any two conformers of a molecule are mirror images of each other, i.e., enantiomeric. If they are, the molecule is achiral (see two conformational enantiomers in *n*-butane). This rule is specially useful for cyclic compounds in which conformers originate through ring inversion or pseudorotation and in the case of invertomers which originate through inversion at a centre. The two rules should be used simultaneously. An achiral species with two chiral conformers does not show any chiral manifestation because the two are equally populated by virtue of their identical free energy content. Thus the species is a racemic mixture of too rapidly interconverting enantiomeric conformers. An example is *cis*-1,2-dimethylcyclohexane (entry 3, Figure 3.4).

3.5 Racemic modifications

When equimolecular quantities of two enantiomers of a chiral molecule are mixed

*This is true in principle but actually because of homomerism (degeneracy), improbability of high energy conformations, and excluded volume problems there are not all that many. Homomers are not usually counted more than once.

together or formed in a reaction, the resultant mixture is called a racemic modification, or a racemic mixture, or a racemate, or simply a (±)-pair. Since the differentiation of stereoisomers is made at the molecular level, racemic modifications do not really represent a separate class of stereoisomers although they differ from the corresponding pure enantiomers in certain physical properties, especially in the solid state. In addition, they do not show any optical rotation, the rotation due to one enantiomer being exactly cancelled by an equal and opposite rotation of the other enantiomer (external compensation). The difference in properties between a racemic modification and the corresponding pure enantiomer arises from the difference in the intermolecular interactions which govern the molecular packing in the crystal lattice and the intermolecular association in the liquid state or in concentrated solution. The situation may be compared to two boxes one holding only right-handed or left-handed gloves and the other holding an equal mixture of both. The stacking of the gloves in the two boxes would be different which at the molecular level is equivalent to packing enantiomers of the same chirality, e.g., (++) or (−−) and of opposite chirality, e.g., (+−) in two crystal lattices. The two crystals are thus diastereomerically related and behave so as long as the intermolecular interactions are appreciable. Under this condition, they will have different physical and spectroscopic properties. In dilute solutions or in the gaseous form, the molecular species are usually well segregated i.e., the intermolecular interactions become negligible and as a result, the differences in physical and spectroscopic properties between a racemate and the corresponding pure enantiomers are minimised (except for optical activity) (Mislow 1965). What happens is that the diastereomeric relationship between them disappears.

3.5.1 **Racemic modifications and thermodynamic properties**

A racemic modification being a mixture of two molecular species possesses an entropy of mixing (ΔS) which can be calculated (assuming the mixture to be an ideal one) as follows:

$$\Delta S = -Rx_1 \ln x_1 - Rx_2 \ln x_2; (x_1 \text{ and } x_2 \text{ are the mole fractions}).$$
$$= -R\ln\tfrac{1}{2} = R\ln 2 \approx 6 \text{ J mol}^{-1} \text{ degree}^{-1}, (x_1 = x_2 = \tfrac{1}{2})$$

The entropy of mixing is thus a positive quantity. Conceptually, a racemic modification consisting of two molecular species corresponds to a more random or less orderly system than the enantiomeric form which consists of a single molecular species. Entropy which is a measure of randomness is, therefore, expected to be higher in racemic modification.

The changes of free energy (ΔG), enthalpy (ΔH), and entropy (ΔS) are related by the equation :

$$\Delta G = \Delta H - T\Delta S$$

At room temperature (300 K), the change of free energy due to mixing is 300×6 J or 1.8 kJ mol^{-1} assuming that the enthalpy remains constant. This means that the conversion of pure enantiomers into the racemic modification—a process known as racemisation—is thermodynamically favourable and a spontaneous process.

3.5.2 Classification of racemic modifications

On the basis of the difference in the nature of packing in the crystal lattice, racemic modifications are divided into three classes (Jaques et al 1981).

(*i*) **Racemic conglomerate** (A). If the crystal lattices are formed entirely from enantiomers of like chirality (see diagram A in Figure 3.5), the racemic modification is called a conglomerate (A) (previously also called a racemic mixture). Two crystals containing enantiomers of opposite chirality are enantiomorphous* and under favourable conditions may be separated mechanically.

(*ii*) **Racemic compound** (B). If, on the other hand, each unit crystal contains an equal number of (+) and (−) enantiomers, the racemic form is called a racemic compound (B) (see diagram B) (previously called a racemate) which in the solid state behaves as a separate entity distinct from either of the enantiomeric form.

(*iii*) **Pseudoracemate** (C). Finally, in some rare cases, the lattice energy becomes almost independent of the configuration of the constituent enantiomers and the unit crystals are formed indiscriminately from both the enantiomers (see diagram C). Such form is known as a pseudoracemate, a racemic solid solution, or mixed crystals (C).

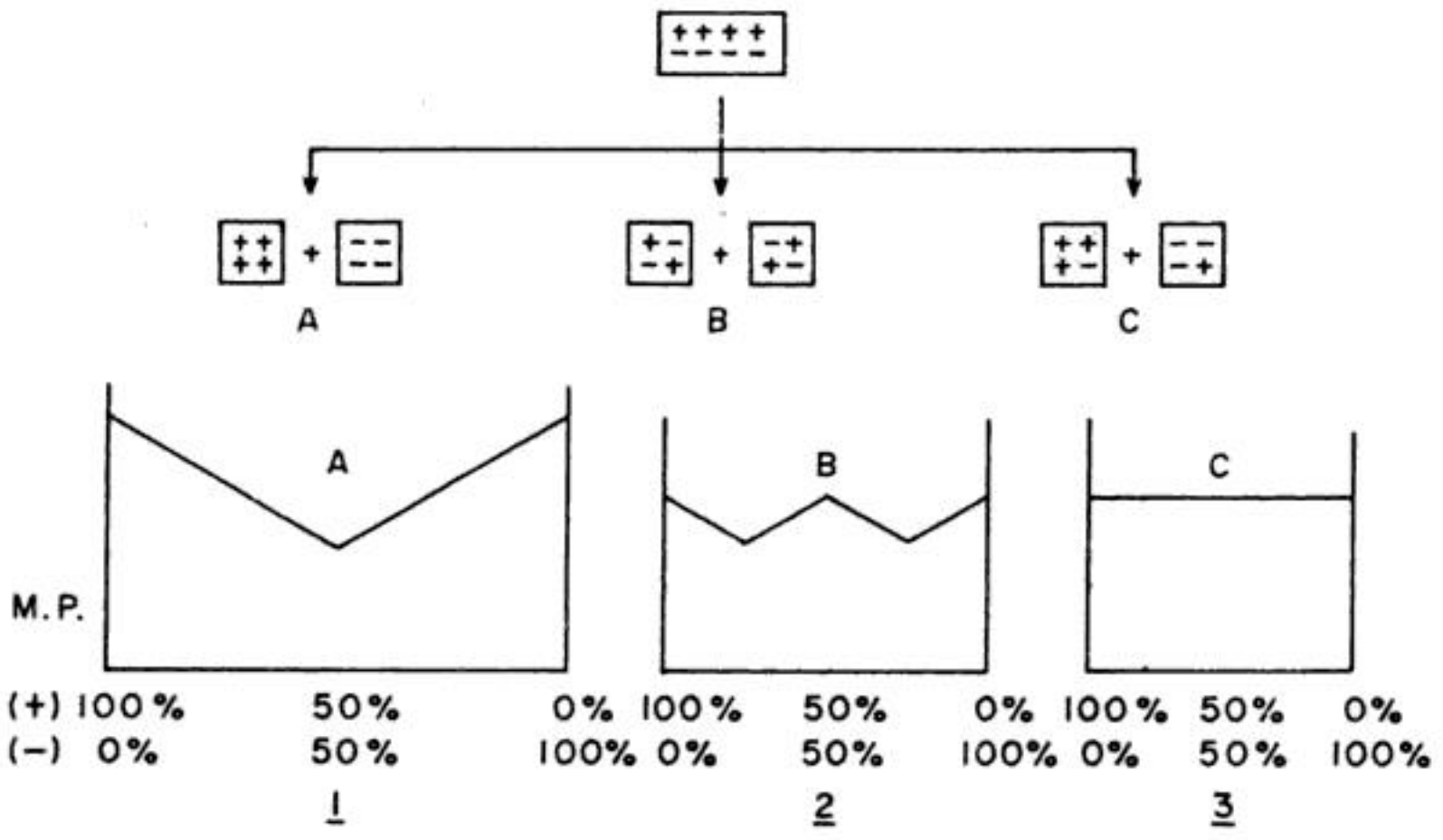


Figure 3.5 Racemic modifications and their melting point diagrams (Diagrams 1, 2 and 3 are idealised).

The above-mentioned three types of racemic modifications can be distinguished by their solid phase behaviour and in the case of the racemic compounds also by infrared spectra in the solid state and by X-ray diffraction pattern. The conglomerate (A) is a true eutectic mixture and corresponds to the lowest temperature in the melting point diagrams drawn for different mixtures of enantiomers

*The terms 'enantiomer' and 'diastereomer' (and the corresponding adjectives) generally refer to molecules and compounds while the terms 'enantiomorph' and 'diastereomorph' refer to macroscopic objects and models.

(diagram 1, Figure 3.5). It is exemplified by (±) sodium ammonium tartrate crystallised from an aqueous solution at a temperature below 27°C (first observed by Pasteur and used for the resolution of tartaric acid). The solid solutions or pseudoracemates (C) do not change melting points appreciably with changes in composition of the mixture (diagram 3). An example is found in (±)- camphor oxime crystallised above 103°C.The racemic conglomerate (A) and the racemic solid solution (C) both give infrared spectra and X-ray power diagram identical with those of their enantiomers.

In contrast, a racemic compound (B) retains the diastereomeric relation with respect to the enantiomeric form even in the unit crystals and gives an infrared spectrum (in the solid state) and an X-ray diffraction pattern quite different from those of the enantiomers. It has a lower enthalpy than the enantiomers and its melting point is usually higher (although it can also be lower) than that of the pure enantiomers (diagram 2). As expected of a new compound, the melting point diagram shows two depressions. Racemic compounds are more commonly encountered than the other two racemic modifications (conglomerates and pseudoracemates).

The solubility behaviour of the three racemic modifications is also different but is less reliable as a guide in distinguishing them (see Eliel 1962).

3.5.3 **Quasi-racemates**

Sometimes, analogous compounds of the same constitution and relative configuration and having similar geometry and charge distribution can replace each other in the crystal lattice. In that case, they are called isomorphous. If two such compounds with opposite configurations* are mixed in equimolecular proportion, quasi-racemic modifications may result. Like true racemic modifications, they may also form quasi-racemic compounds or quasi-racemic solid solutions. Of these, quasi-racemic compounds (or more properly, quasi-racemates) are important because they are used for configurational correlation. Thus (+)-chlorosuccinic acid and (−)-bromosuccinic acid form a quasi-racemic compound as recognised by their mixed melting point diagram similar to the diagram 2 (Figure 3.5) but dissymmetrical in appearance—a fact which indicates that they are of opposite configurations. They may be called heterochiral or said to be heterochirally related like two almost equal and similar right and left hands which are of opposite-chirality but are never *perfect* mirror images of each other. Conversely, (+)-chloro- and (+)-bromosuccinic acids are homochiral (like two almost equal and similar right hands) having the same gross chirality† (Mislow and Bickart 1967-77).

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*Such pairs of opposite chirality may be called quasi-enantiomers (also heterochiral, see below).

†The terms 'homochiral' and 'heterochiral' have been used here in the sense first used by Lord Kelvin, *Baltimore Lectures* (1904), referred to by Mislow and Bickart (1976-77). The two terms have been later elaborated by Ruch (1977) by analogy with shoes and screws. Thus an assorted number of shoes may be sorted out in two sets : right-footed and left-footed. Members of each set may be called homochiral while members of different sets are heterochiral. The terms have also found application in segmentation of an achiral object such as an apple (or a sphere of K_h symmetry) into two homochiral halves, a French parlour trick known as '*la coupe du roi*' (the royal cut). Two vertical half-cuts perpendicular to each other, one from the top to the equator and the

3.6 Summary

1. A particular molecular formula may correspond to several molecular species, known as isomers, differing in bonding connectivity (nature of linkage among the constituent atoms) and in configuration (relative orientation of atoms and groups). Isomers differing in bonding connectivity are called constitutional isomers and isomers of the same constitution but with different configurations are called stereoisomers.

2. The different modes of representation of three dimensional molecular structures on two dimensional paper, namely, Fischer projection, sawhorse, and Newman projection formulae are discussed. Mention has also been made of the flying wedge notation which is important in denoting a single chiral centre. The interconversion of the various projection formulae is illustrated.

3. Stereoisomers have been classified into enantiomers and diastereomers based on symmetry criteria. Two stereoisomers which are related as an object and a mirror image but are non-superposable are called enantiomers. If not so related, they are called diastereomers which include compounds containing more than one chiral centre, cyclic compounds, and compounds containing double bonds. The distinctive features of enantiomers and diastereomers have been highlighted.

4. Enantiomers are isometric with each other, i.e., all the intramolecular interactions are similar in the two enantiomers. On the other hand, diastereomers as also constitutional isomers are anisometric with one another, i.e., intramolecular interactions in them are different.

5. Stereoisomers are also classified on the basis of the energy barrier separating them. Stereoisomers separated by a high energy barrier are called configurational isomers and those separated by comparatively low energy barrier so that interconversion is easy under ordinary conditions are called conformational isomers. The two methods of classification, one based on symmetry criterion and the other on energy criterion are not mutually exclusive. One can have, for example, configurational enantiomers, configurational diastereomers, conformational enantiomers, and conformational diastereomers. All of them have been illustrated with examples.

6. The inter-relationship between conformers and the molecules representing the conformers has been discussed and certain rules have been formulated which permit one to deduce the chirality (or otherwise) of a compound from one or more of its conformers.

7. The racemic modifications arising out of mixing equimolecular quantities of enantiomers have been subdivided into three classes, namely, a conglomerate, a racemic compound, and a solid solution (pseudoracemate). A racemic form in the

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other from the bottom to the equator, followed by two non-adjacent horizontal quarter-cuts along the equator give two homochiral halves of an apple. Homochiral halves of opposite chirality are obtained by reversing the direction of the horizontal quarter-cuts (see Anet et al 1983 and also Cinquini et al 1988 for such bisection of an achiral molecule). The interesting thing is that only the combination of two homochiral segments gives the original achiral apple.

Recently, Masamune et al (1985) have used the term homochiral to mean enantiomerically pure substance, i.e., either all (+)- or all (−)-forms of chiral molecules. This terminology has gained wide currency.

Chapter 4

Stereoisomerism and Centre of Chirality

4.1 Introduction

Organic stereochemistry is based mainly on the tetrahedral geometry of carbon and a few other atoms such as N, P, Si, and S and to a lesser extent on the trigonal geometry of sp^2 hybrid carbon and nitrogen (and of course on the unique catenating property of carbon). The regular tetrahedron provides an achiral three-dimensional framework of T_d symmetry having four topologically equivalent vertices. If they are occupied with four different achiral atoms (or groups) so that the four vertices become distinguishable, all elements of symmetry disappear, and the tetrahedron turns into a three-dimensional four-point chiral simplex of C_1 symmetry which is non-superposable with its mirror image (see Figure 3.1a in Chapter 3). Actually a fifth point, a tetracovalent atom (e.g., C) is also necessary at the centre of the tetrahedron to which the four ligands are bonded giving what is known as an asymmetric or a chiral centre (e.g. Cabcd). The presence of a chiral centre usually leads to molecular chirality*. One unique feature of this chiral tetrahedral model is that transposition (exchange or permutation) of any two ligands reverses the chirality of the centre giving a new stereoisomer. If all the ligands are achiral, the transposition leads to an enantiomer; on the other hand, if one or more of the ligands are chiral, a diastereomer results (e.g., *meso*-tartaric acid to optically active tartaric acid and vice versa). The chiral centre is, therefore, a stereogenic centre, or in short a stereocentre.† The number of stereoisomers (enantiomers and diastereomers) goes on increasing with the number of chiral centres. For tricoordinate atoms such as N, P, and S, (in sulphoxides), the three ligands form the base of a trigonal pyramid with the ligating atom placed at an

*The centre of chirality is only one source of molecular chirality. According to Cahn, Ingold, and Prelog (1966), 'three-dimensional space can, in principle, be occupied asymmetrically about the zero-, one-, or two-dimensional elements of symmetry, that is, the point (centre), the line (axis), and the plane'. Molecular chirality is thus factorised into central, axial, and planar chirality, collectively known as elements of chirality (see Chapter 5). Recently, Mislow and Siegel (1984) have pointed out some apparent arbitrariness in the process of factorisation and opined that these elements of chirality are related more properly to stereogenicity than to molecular chirality. Prelog and Helmchen (1982) have also designated these elements as stereogenic units following a suggestion of McCasland (1953).

†A special name, *chirogen* (whence *chirogenic* and *chirogenicity*) has been suggested (Brewster 1986, Mezey 1986) for a tetrahedral chiral centre which is reflection variant, i.e., on reflection gives a stereoisomer (e.g., an enantiomer).

4.2.3 Molecules with a tricoordinate chiral centre

Molecules with a tricoordinate chiral atom (e.g., :Xabc)* may be treated in the same way as the tetracoordinate compounds with the lone pair acting as the fourth substituent. They can, however, often undergo racemisation through inversion at the centre. Examples are tertiary amines (IX), phosphines (X), sulphonium salts (XI), sulphoxides (XII), carbanions (XIII), C-radicals (XIIIa) (Figure 4.3.), arsines, stilbines etc. The stability of the pyramidal configuration increases with increasing

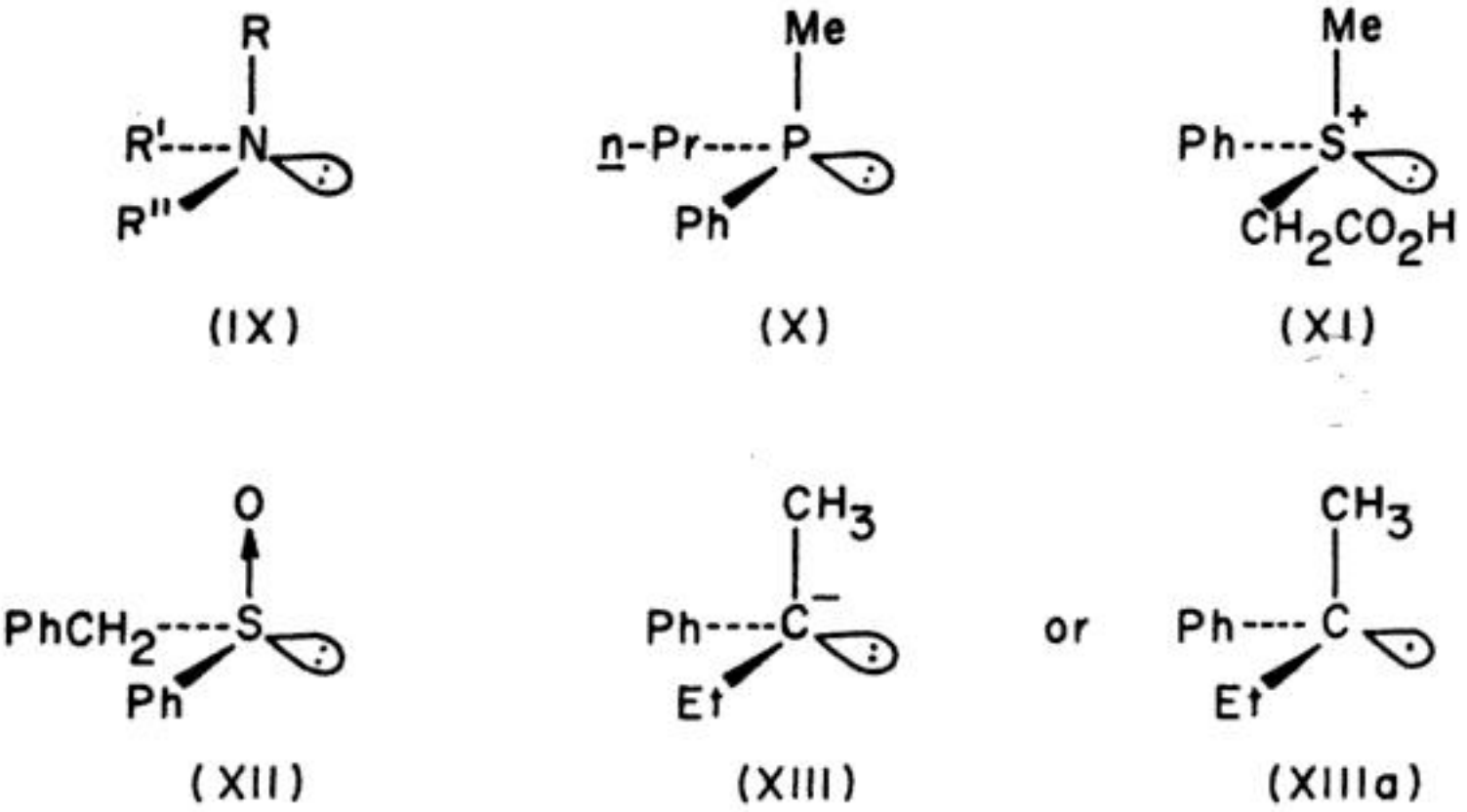

Figure 4.3 Molecules with tricoordinate chiral centres

atomic number. Thus tricoordinate derivatives of carbon, nitrogen, and oxygen (first row atoms of the periodic table) undergo fast inversion and give only conformational enantiomers or diastereomers (if there is a second chiral centre). When a nitrogen atom forms part of a ring, the barrier to inversion increases substantially. It is more so in aziridine derivatives (see Chapter 10). Thus 2-methyl-3,3-diphenyloxaziridine (XIV) has been obtained in stable optically active form (levo) by asymmetric epoxidation of diphenylmethylenemethylamine with (+)–peroxycamphoric acid (Figure 4.4a)

In Tröger's base (XV) (Figure 4.4b), nitrogen is placed on a bridgehead and

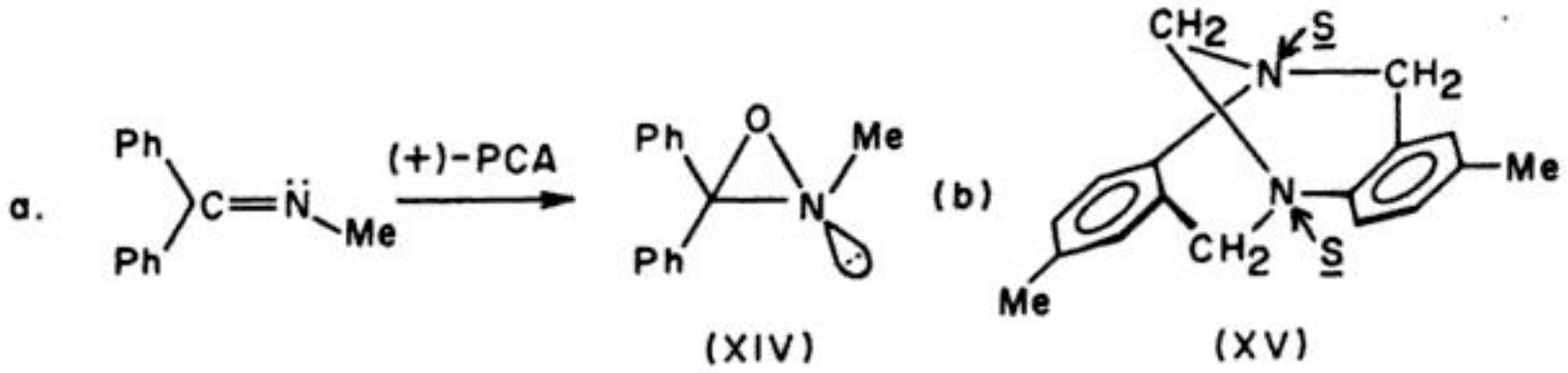

Figure 4.4 (a) Chiral oxaziridine and (b) Tröger's base : 2,8-dimethyl-6 *H*, 12 *H*-5, 11-methanodibenzo[b,f][1,5]diazocine

*In the absence of a lone pair, the molecule tends to be planar such as trialkylboranes (Babc).

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Fischer projection (it does not matter whether it is at the top or at the bottom), the sequence gives the correct descriptor*; if on the other hand, 'd' is on the horizontal line, the sequence gives the wrong answer and the descriptor assigned on this basis should be reversed. The procedure is illustrated with (+)-tartaric acid (XXI), D-(−)-arabinose (XXII), and 3-bromobutan-2-ol (XXIII) (Figure 4.10). In the first two cases, H is on the horizontal line in all the chiral centres and so the descriptors arrived at from the sequence a → b → c have to be reversed. In the third case, H is on the vertical line in both the chiral centres and the sequence a → b → c gives the correct descriptor.

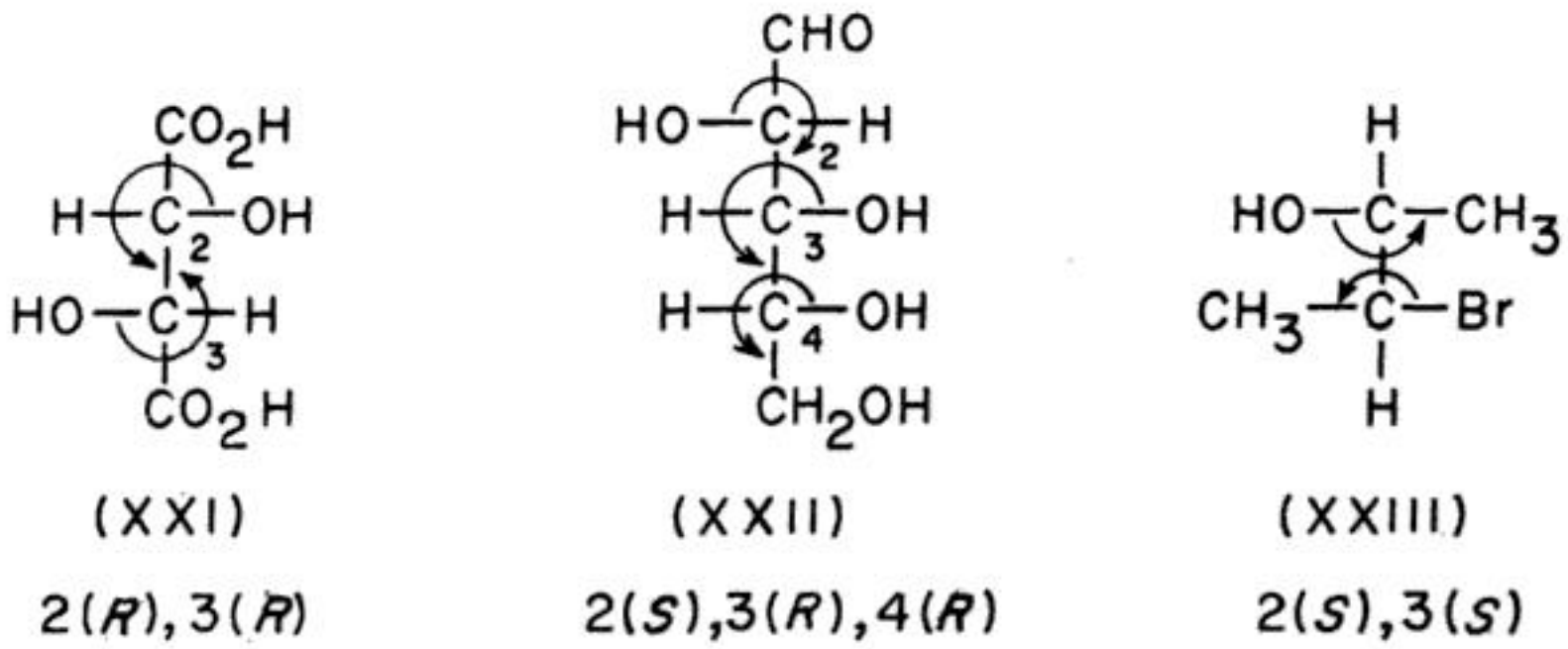
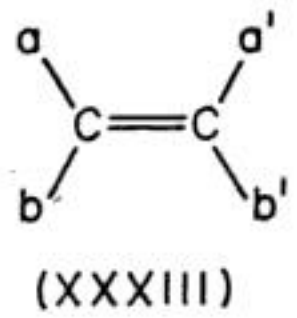


Figure 4.10 Examples of the 'very good' mnemonic

Cyclic molecules such as steroids and terpenes are usually projected on the plane of the paper and hydrogens (or substituents) located below and above the plane are assigned α and β descriptors respectively (α represented by dotted and β by thick lines as shown in 3-cholestanol XXIV in Figure 4.11)—a system recommended by the Chemical Abstract Service (*Pure and Applied Chem.*, 1972, **31**, 283). These descriptors relate to relative configuration and are meaningful if the cyclic system is drawn in an accepted way as in steroids and terpenes. For absolute configuration, each of the chiral centre in the cyclic molecule must be defined by *RS* descriptors following CIP nomenclature. A convenient method has been suggested by Eliel (1985) which is as follows. At any particular chiral centre, one ligand must be clearly in the front (F) or clearly in the back (B). This would be regarded as the reference ligand. The order (clockwise or anticlockwise) of the remaining three can be very easily determined, all three being in the plane of the paper. If this reference ligand is 4/B (lowest locant and in the back), the sequence of the remaining three ligands would give the correct descriptor. So 4/B(+) may be used as a mnemonic [(+) stands for correct]. For other combinations, the numbers will alternate with signs, e.g., 4/B (+), 3/B(−), 2/B(+), 1/B(−) and 4/F(−), 3/F(+), 2/F(−), 1/F(+). For example, the C-10 chiral centre of cholestanol (XXIV) corresponds to 4/F and so although the order 1 → 2 → 3 is

*The method is simply an extension of Eliel's since a Fischer projection is permitted 180° rotation and it is immaterial whether d is put at the bottom or at the top of the projection.

configuration is seq-trans (CIP 1966). Thus if a precedes b and a′ precedes b′, the configuration of the compounds (XXXIII) and (XXXIV) (Figure 4.15) are seq-cis and seq-trans respectively. Later, the system has been modified (Blackwood et al 1968), the two terms being replaced by two shorter symbols, *Z* (from the German *zusammen* meaning 'together') and *E* (from the German *entgegen* meaning 'across') which are used as prefixes to the olefins. According to this system, β-methylcinnamic acid (XXXV) is called *E*-3-phenylbut-2-enoic acid (here Ph and CO_2H groups are fiducial*). The previously called *cis*-1,2-dichlorobromoethene (XXXVI) is now known as *E*-1-bromo-1,2-dichloroethene which goes to prove that *E* and *Z* do not always correspond to trans and cis.



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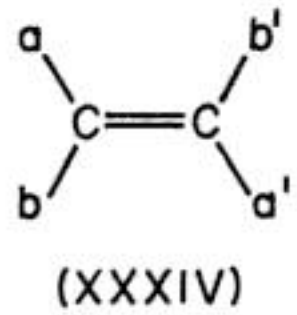

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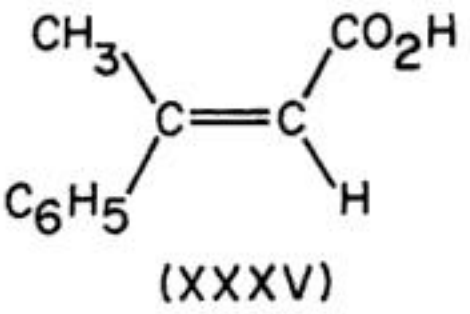

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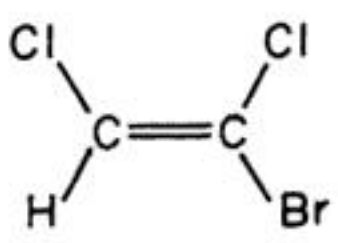

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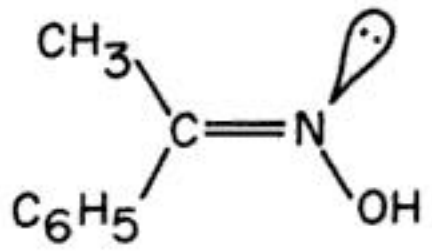

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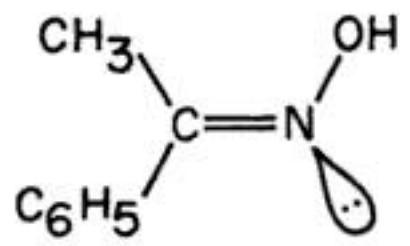

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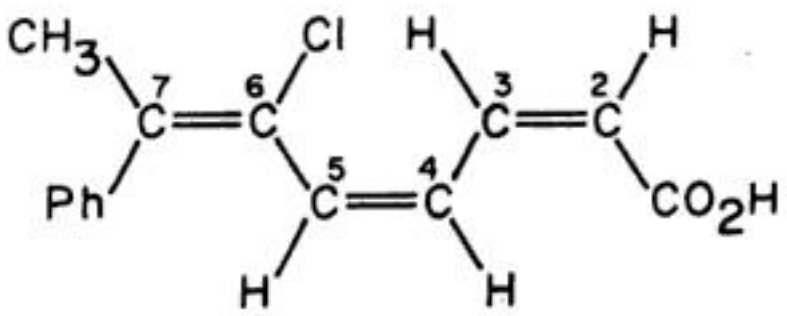

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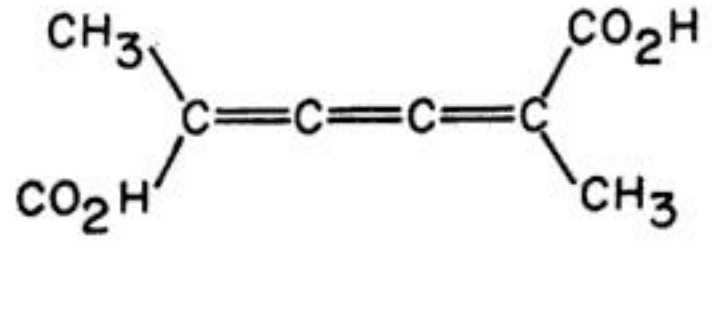

(XL)

Figure 4.15 Examples of *E* and *Z* nomenclature

This system leads to a great simplification in the nomenclature of the diastereomeric oximes for which the (often ambiguous) terms 'syn' and 'anti' were previously coined. Thus the syn (XXXVII) and the anti (XXXVIII) oximes of acetophenone are now called *Z*- and *E*-isomers respectively.

In the case of compounds, containing more than one non-cumulated (belonging to different carbon atoms) double bonds, the number of π-diastereomers (2^n where n is the number of non-equivalent double bonds) increases. The descriptors *Z* and *E* can be applied to each diastereogenic unit. Thus the triene (XXXIX) is 6-chloro-7-phenylocta-2*Z*, 4*Z*, 6*E*-trienoic acid. Cumulenes with an odd number of cumulated (consecutive) double bonds with two $=Cab$ as terminal groups display

*The word 'fiducial' means 'fixed basis of reference'.

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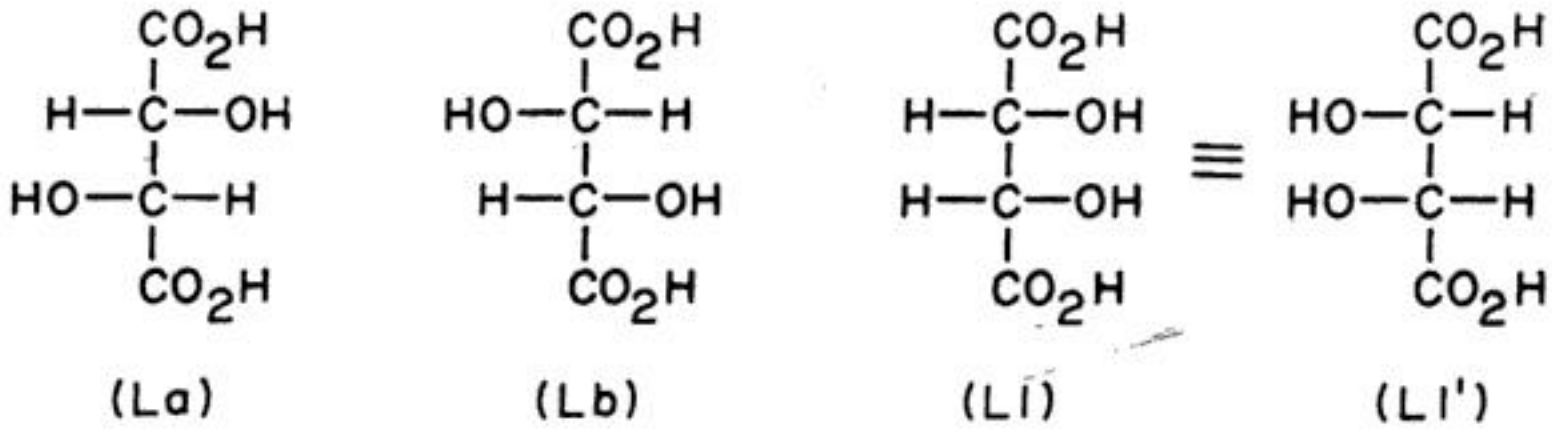

Figure 4.21 2,3-Dihydroxysuccinic acid

number of stereoisomers being three $[2^{(2-1)} + 2^{(2-2)/2}]$. The dextro form has the *R,R*, the levo form the *S,S*, and the meso form the *R,S* or *S,R* configuration. The dextro and the levo forms are diastereomeric with the meso form and differ substantially from it in physical and chemical properties. The meso form (LI) is superposable with its mirror image (LI′). A rotation of 180° makes the two structures indistinguishable. The meso form may be desymmetrised by preferentially esterifying one of the carboxylic groups. All the conformations of the two enantiomers are chiral. On the other hand, the meso form (LI) has an achiral conformer with a centre of inversion and two chiral conformers with *P* and *M* helicity respectively (see Chapter 5). Because the last two are equally populated, the molecule possesses statistical symmetry, and hence is optically inactive.

It is worth noting that the dextro and the levo isomers in the Fischer projection have their horizontal groups so disposed that equivalent groups are on opposite sides and in that respect, may be regarded as the counterparts of threo isomers encountered in constitutionally unsymmetrical molecules. The meso form has all the equivalent groups eclipsed (i.e., on the same side) and thus bears analogy with the erythro isomers.

(*b*) **2,3,4-Trihydroxyglutaric acid.** 2,3,4-Trihydroxyglutaric acid, a constitutionally symmetrical molecule has three chiral centres and exists as four $[2^{(3-1)}]$ stereoisomers. Two of them (LIIa) and (LIIb) (Figure 4.22) are enantiomers and the remaining two (LIII) and (LIV) are meso forms being diastereomeric with each other and also with the two enantiomers. The meso forms can be desymmetrised by esterifying any of the two equivalent carboxyl groups thus giving two pairs of enantiomers. The two carboxylic groups in the two active compounds (LIIa) and (LIIb) are non-equivalent and so monoesterification of each gives two (±)-pairs of diastereomers. Thus the total number of half esters of trihydroxyglutaric acid is eight (2^3) corresponding to a constitutionally unsymmetrical structure with three chiral centres. There are some long-standing ambiguities regarding the status of the C-3 centre in these molecules which are discussed below in the context of a recent observation of Mislow and Siegel (1984).

The two enantiomeric structures (LIIa) and (LIIb) are considered first. The chiral grouping, $-CH(OH)CO_2H$ can be designated by either *R* or *S* and accordingly, the enantiomers (LIIa) and (LIIb) are abbreviated as A and B shown at the bottom of Figure 4.22. The C-3 centre is thus achiral, two of the ligands, *R,R* in LIIa and *S,S,* in LIIb being identical, and no configurational assignment (*R* and *S*) can be given to C-3. Moreover, C-3 is also non-stereogenic; the interchange

Finally, a completely different type of stereoisomerism is exhibited by bridged ring compounds in which the two bridgehead atoms are joined through three large rings as shown for bicyclo[8.8.8]hexacosan (for nomenclature, see Chapter 11). The compound can exist in three diastereomeric forms (LXV), (LXVI), and (LXVII) (Figure 4.26). In the isomers, the two bridgehead H's are both 'in' (LXV),

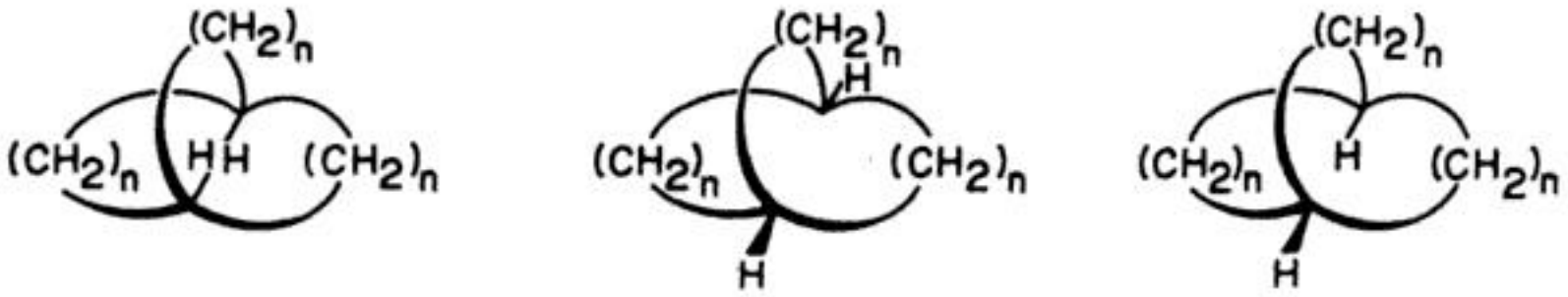

Figure 4.26 'Out-in' isomerism

both 'out' (LXVI), or one 'in' and the other 'out' (LXVII). This type of stereoisomerism is called 'out-in' isomerism (Park and Simmons 1972). Here also, the stereogenicity of the two bridgehead atoms (which are achirotopic) is interlinked and together they form a stereogenic dyad. Depending on the nature of the rings, the two bridgehead atoms may be chiral and so may lead to enantiomerism

4.7 Summary

1. When four different achiral ligands are bonded to a central atom making a regular tetrahedral arrangement, a five-centre chiral simplex is produced which belongs to C_1 point group and exhibits enantiomerism. The central atom is called a chiral centre. Exchange of a pair of groups reverses the chiral sense of the centre and gives new stereoisomer: an enantiomer if there is no other chiral centre and a diastereomer if there is a second chiral centre. Chirotopicity and stereogenicity are two distinct aspects of an asymmetric centre; the former is defined by its local symmetry and the latter by disposition of its bonds. Examples have been given (in later sections) showing that a compound can be chirotopic but non-stereogenic; alternatively, a compound can be achirotopic but stereogenic. In the majority of cases, however, these two properties are closely linked together in organic stereochemistry.

2. In addition to tetrahedral carbon, various tetracoordinate atoms such as nitrogen, silicon, phosphorus, and arsenic may provide tetrahedral chiral centres with varying degree of configurational stability. Molecules with tricoordinate chiral atoms such as trivalent nitrogen, phosphorus, and sulphur are also well known. A lone pair of electrons on the atom serves as the fourth substituent. Racemisation can occur through inversion at the chiral centre which is relatively easy for the first row of elements but is increasingly difficult for elements in the second and third rows of the periodic table.

3. A chiral compound can be recognised only by establishing a diastereomeric relationship with another chiral substrate or environment. The usual method is to determine the optical rotation, an observable property of a chiral compound, by a polarimeter. The plane-polarised light being constituted of two oppositely circularly

an elongated tetrahedron (D_{2d} point group with $3C_2$ axes and 2σ planes) has lesser symmetry than a regular tetrahedron (T_d) and the condition for its desymmetrisation is less stringent. Instead of all the four vertices being distinguishable, only pairs of vertices around the two ends of the axis need to be distinguished (i.e., a ≠ b). The structure (II) thus becomes three-dimensionally chiral and is enantiomorphous with its mirror image (II′). The axis along which the tetrahedron is elongated (shown by the dotted lines) is called the chiral axis or the stereoaxis (exchange of ligands at either of the terminal atoms across the axis reverses the chirality)*. Actually, the elongated tetrahedron II (C_2) is a *desymmetrised* tetrahedron of type Caabb (C_{2v}).

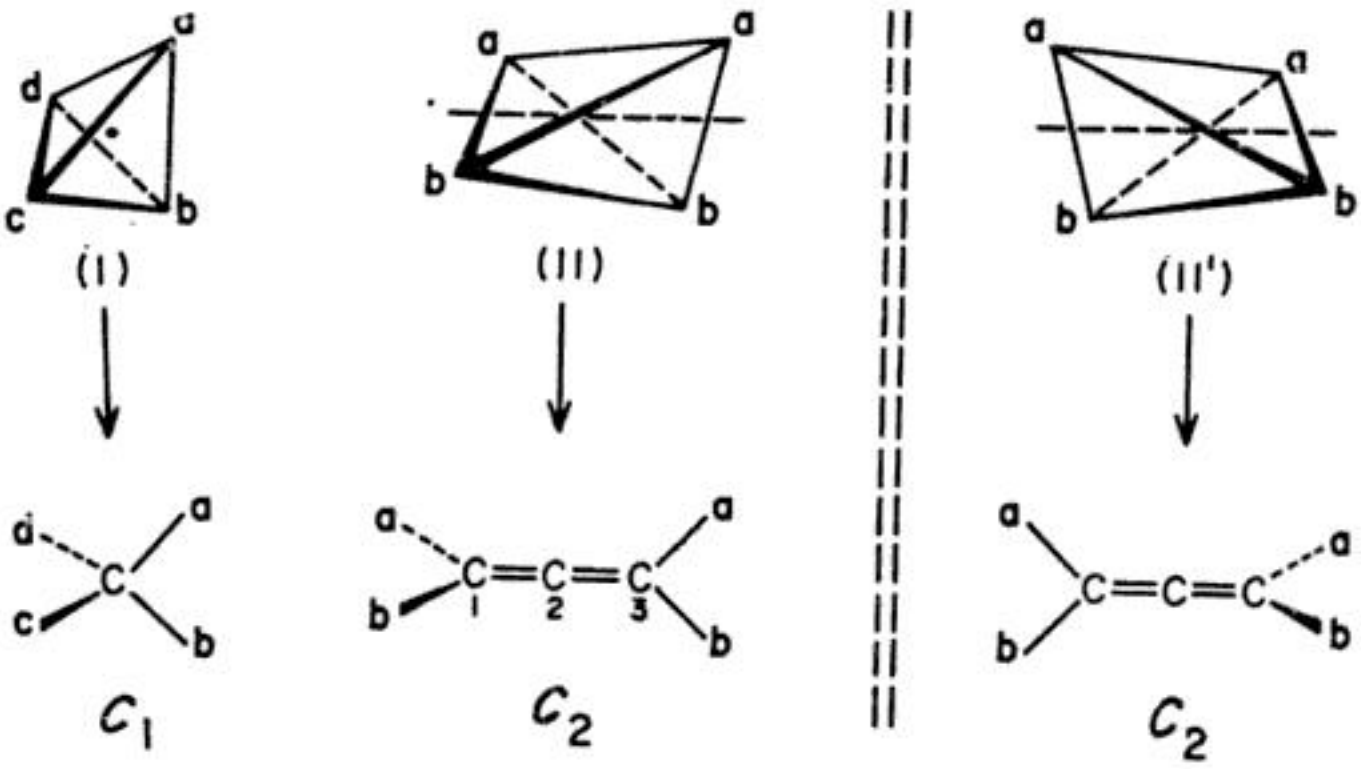

Figure 5.1 Elongated pyramid and chiral axis.

5.2.2 Approach based on two-dimensional chiral simplex

Some aspects of stereochemistry can be conveniently explained on the basis of two-dimensional chiral simplex. An equilateral triangle with three distinguishable vertices is a two-dimensional chiral simplex, i.e., chiral in two dimensions. In the molecular level, a substituted trigonal tricoordinate carbon (as III) (Figure 5.2) represents a two-dimensional chiral simplex (the double bond may be ignored). Two such groupings can combine together either to give (*i*) a composite molecule in which the two planes are brought to coincide (planar combination) or to give (*ii*) a composite molecule in which the two planes are perpendicular to each other (non-planar combination). The planar combination affords two diastereomers, e.g., cis (IV) and trans (V) whereas the non-planar combination affords a three-dimensionally chiral structure (VI) which exists in two enantiomorphic forms similar to structures II and II′. The allene (II) with the two terminal planes at right angle to each other thus has a chiral axis (along C = C = C) which is stereogenic. The biphenyl derivative (VII) in which the two substituted phenyl groups (a ≠ b) are non-planar due to steric reason provides another example, the pivotal bond coinciding with the chiral axis.

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*According to Brewster (Chapter 4), the stereogenicity rests on both C-1 and C-3 interdependently, i.e., C-1 is stereogenic because C-3 is and vice versa. Together they form a stereogenic dyad.

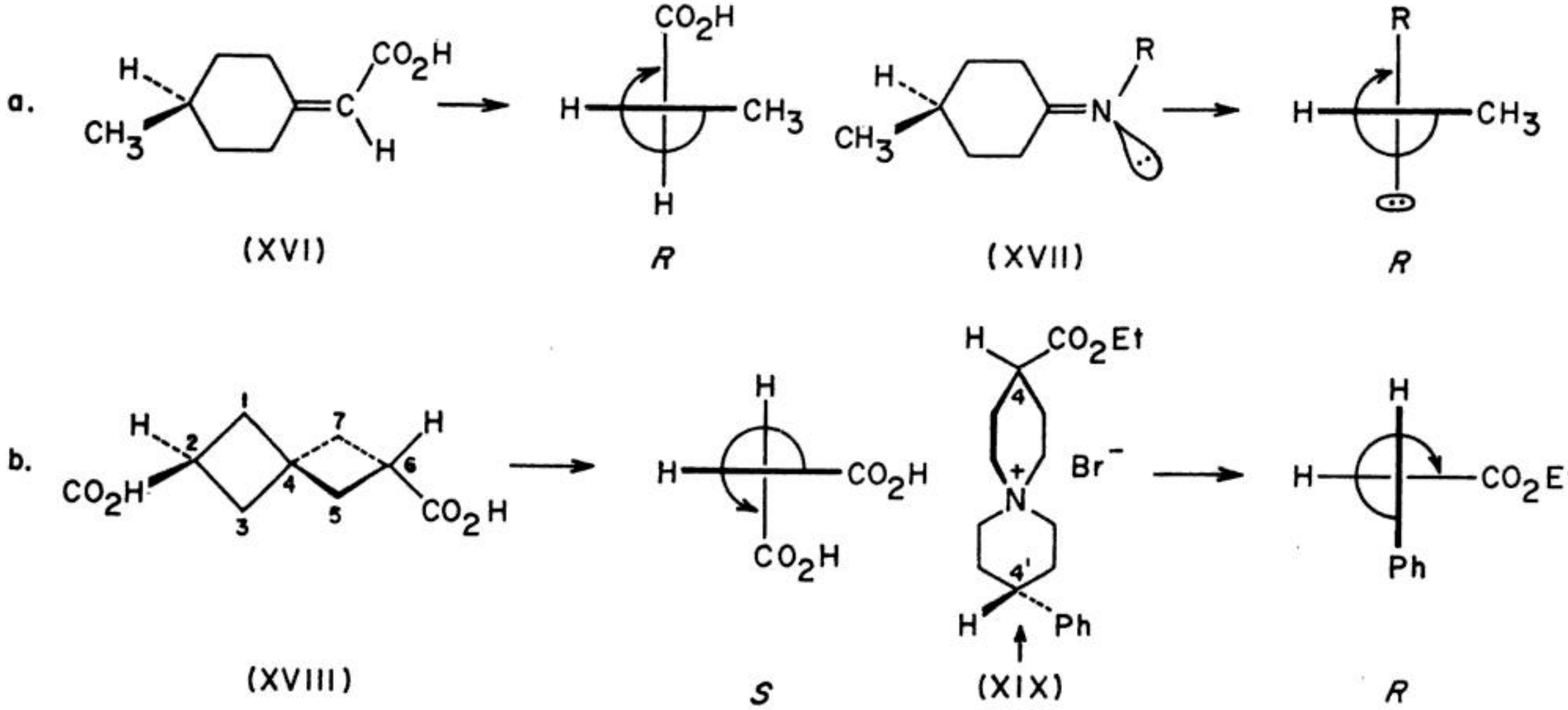


Figure 5.5 (a) Alkylidenecycloalkanes and oximes
(b) Spiranes

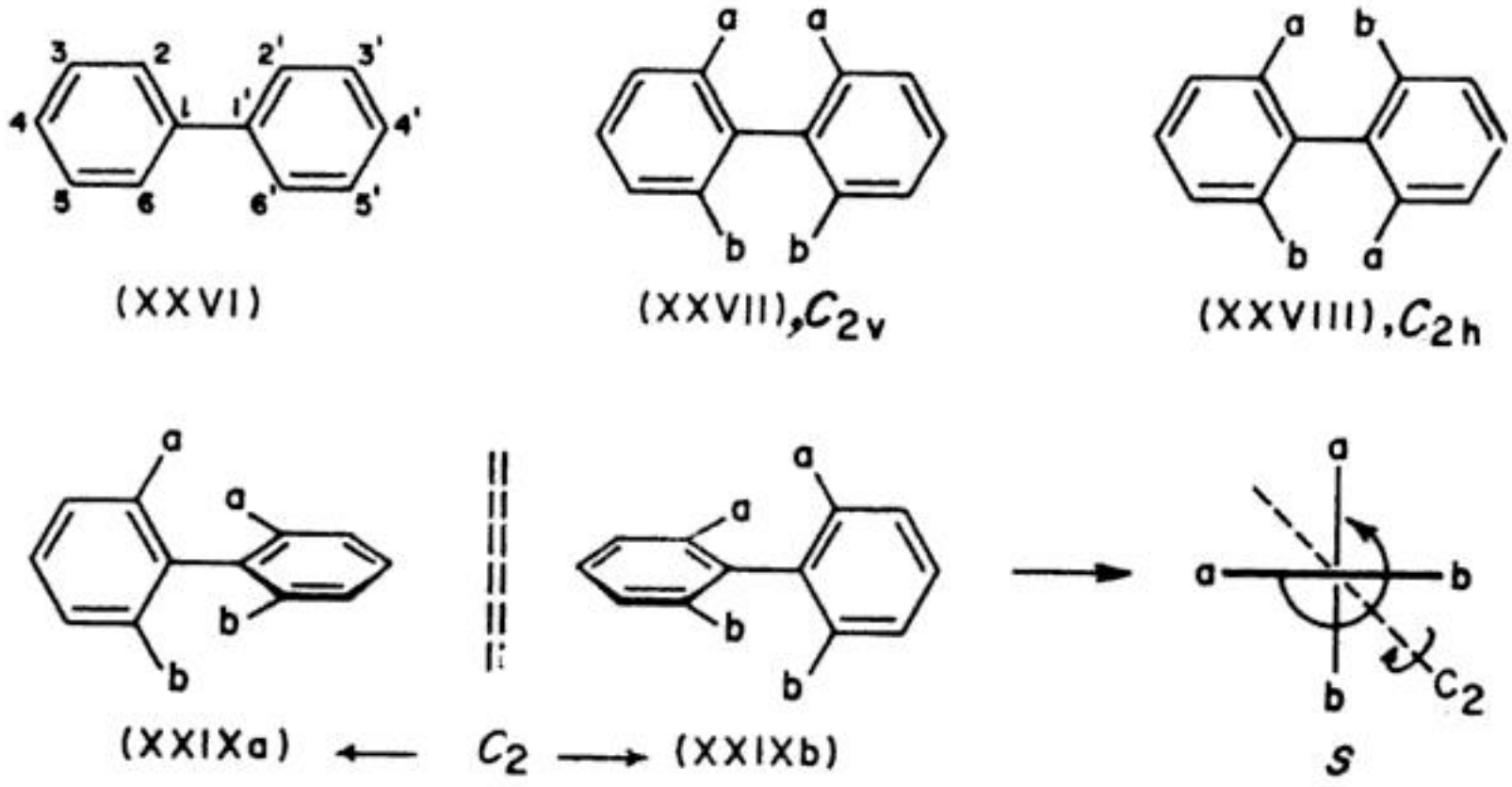


Figure 5.9 Principle of optically active biphenyls

introducing bulky groups in the ortho positions so that the planar conformations are destabilised due to steric repulsion. An approximate energy profile diagram* is shown in Figure 5.10 for a 360° (θ) rotation around the pivotal bond. Since inter-ring resonance is minimum at 90°, the true situation may be that of a double minimum when θ is around 90° and 270° as shown so that the preferred conformations of the enantiomers are those in which the two phenyl planes are approximately but not *exactly* perpendicular to each other.

It may be noted that the two diastereomeric planar conformations (XXVII) and (XXVIII) represent the energy maxima, the one with similar groups on the same side (cisoid) having higher energy than the other with similar groups on opposite sides (transoid). Racemisation, therefore, takes place with greater ease through the transoid configuration. The bulkier the ortho substituents are, the higher is the energy barrier separating the enantiomers and when it exceeds 80-100 kJ mol^{-1}, the stereoisomers may be separable at room temperature. This type of isomerism which owes its existence to restricted rotation around a single bond is known as *atropisomerism* and the isomers are called *atropisomers*. They are actually torsional isomers about single bonds.

The characteristic of atropisomers is that they cannot be represented by any type formula (e.g., XXVII) as in the case of allenes, spiranes, and centrally chiral compounds since the stereochemistry depends on the bulks of the ortho substituents which restrict the rotation about the single bond. Thus even a 2,2′,6,6′-tetrasubstituted biphenyl may be non-resolvable: an example is difluoro-dimethoxy derivative (XXX). On the other hand, biphenyl-2,2′-disulphonic acid (XXXI) with only

*The exact conformation of biphenyl itself is still controversial. X-ray analysis shows the molecule to be almost planar which is expected because of inter-ring resonance and very little of steric repulsion among the inter-ring ortho H's. Electron diffraction in the gas phase shows the two rings at an angle with each other (close to 45°).

the presence of electron-attracting and electron-donating groups (capto-dative groups, e.g., NO_2 and OMe) at 4- and 4′-positions helps interannular resonance so that the pivotal bond assumes more double bond character and the transition state energy is lowered. However, this effect is found to be very small (Oki et al 1971, Nasipuri et al 1977).

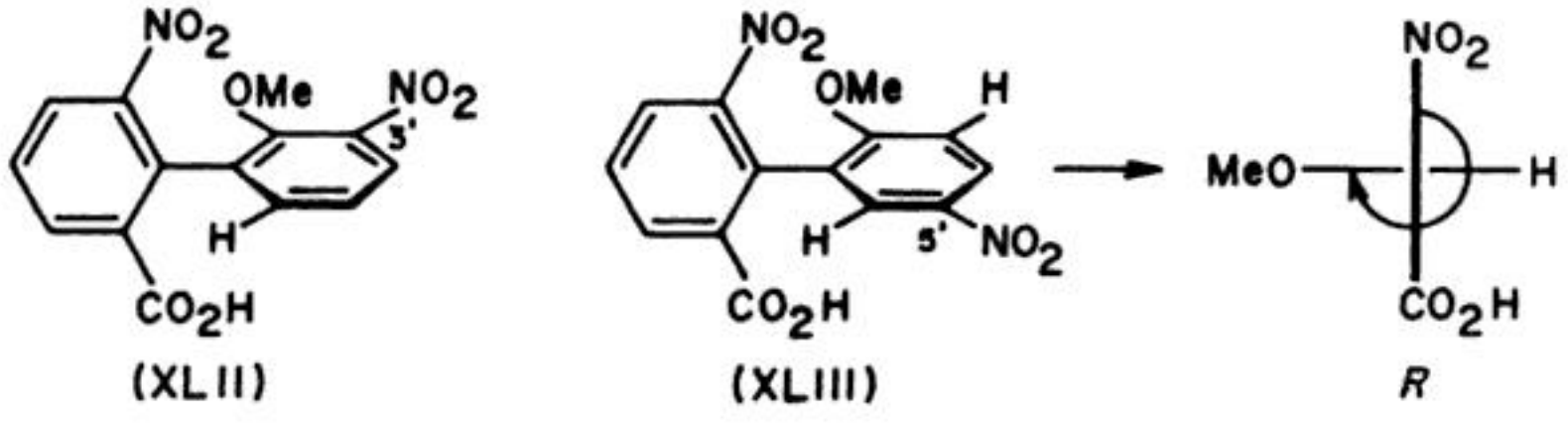


Figure 5.15 Buttressing effect on configurational stability of biphenyls

5.5.2 Bridged biphenyls

A large number of biphenyls are known in which the 2- and 2′-positions are bridged with rings of different sizes as XLIV (Figure 5.16). When n is 1, the

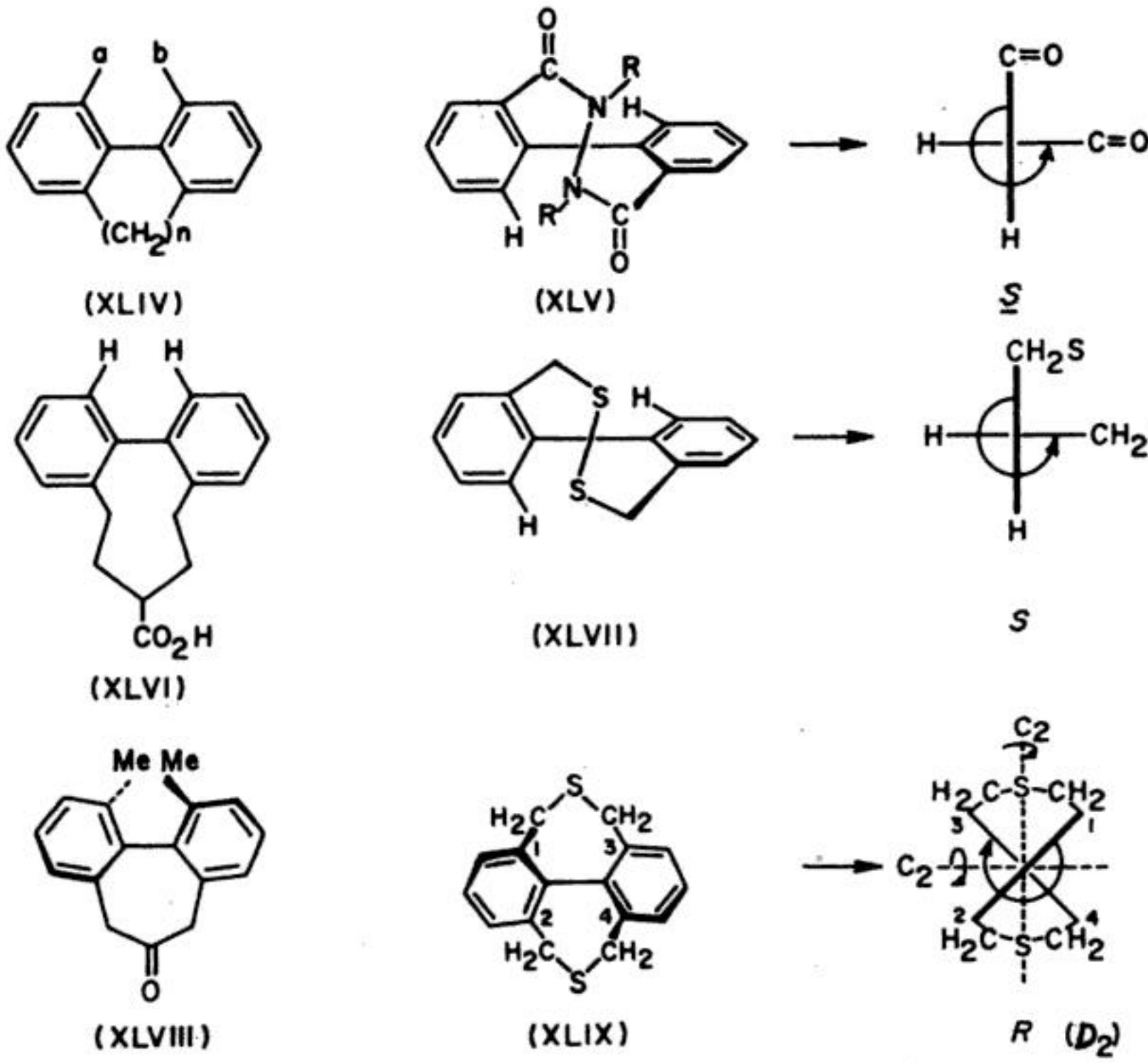
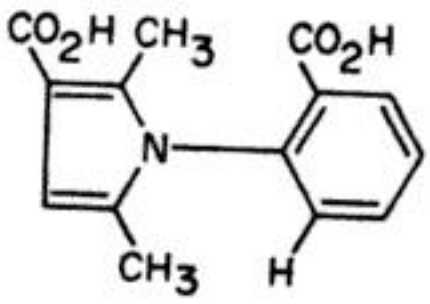
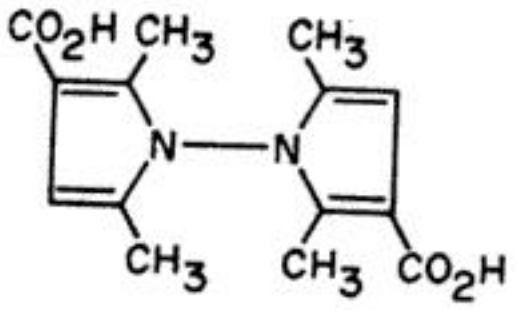


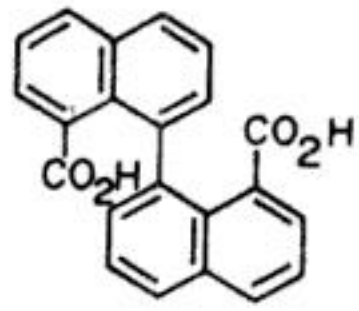
Figure 5.16 Bridged biphenyls and their configurational nomenclature



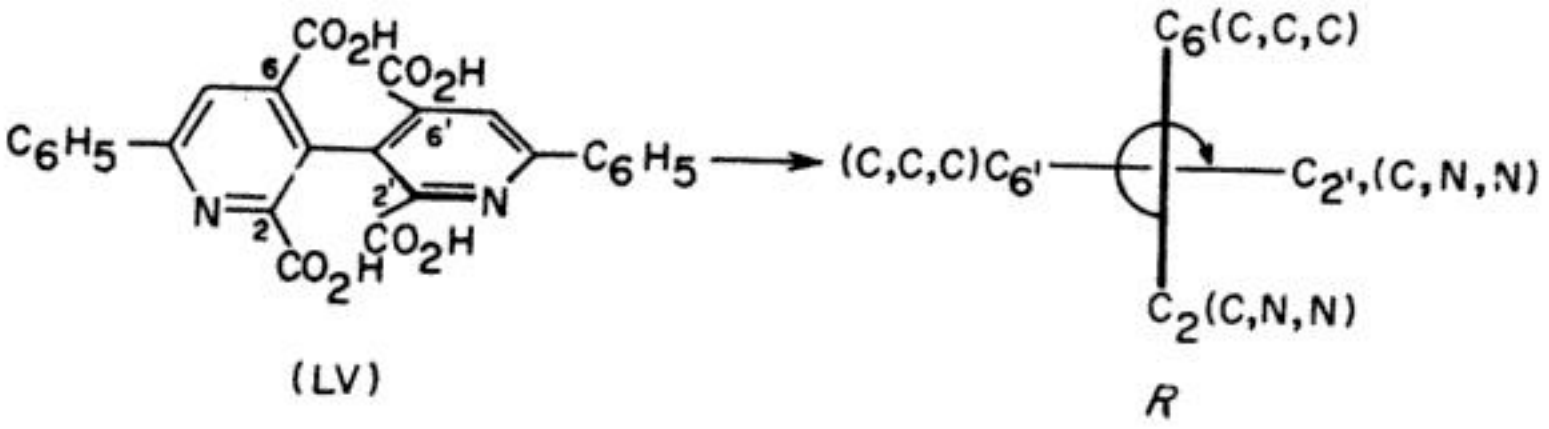
(LII)



(LIII)

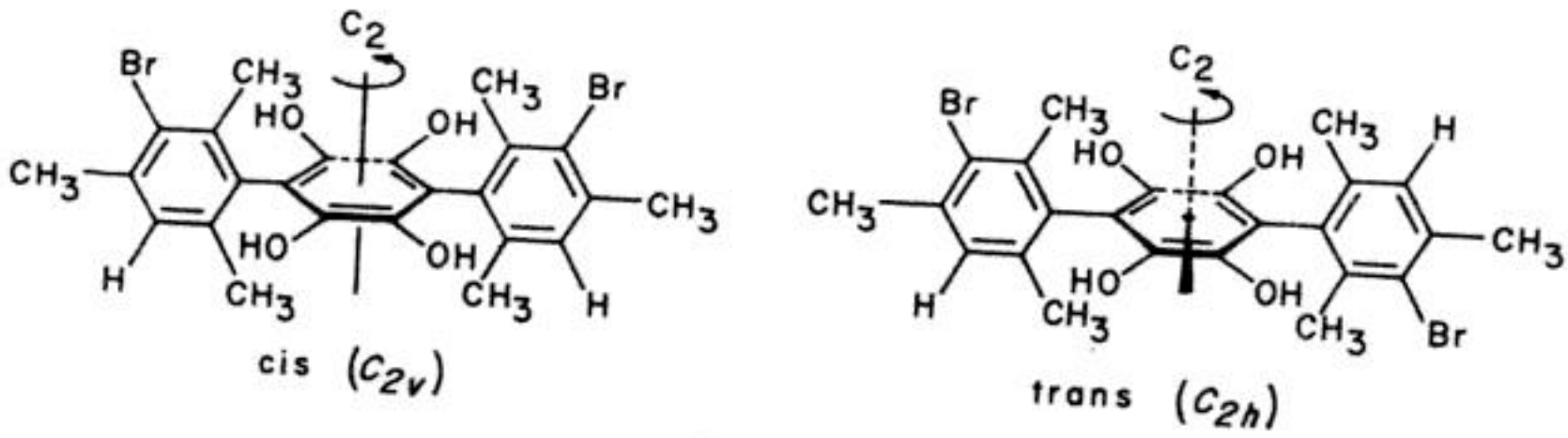


(LIV)

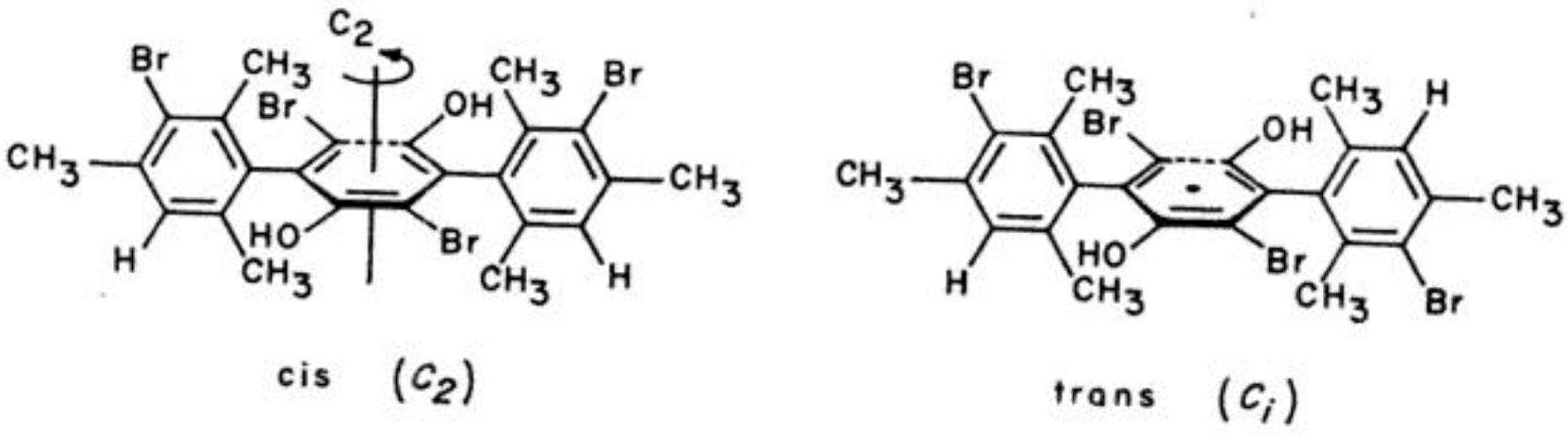


(LV)

Figure 5.19 Atropisomerism in biphenyl analogues



(LVI)



(LVII)

Figure 5.20 Stereoisomerism in terphenyl derivatives

addition, has a centre of symmetry, the mid-point of the central ring (denoted by a dot). They belong to point groups C_{2v} and C_{2h} respectively. In the analogous compound (LVII), the central ring is dissymmetrically substituted which eliminates the σ plane. The cis isomer (C_2) is resolvable but the trans isomer still retains the centre of symmetry and is a meso compound. The molecule (LVII) thus behaves as if it has two equivalent elements of chirality like tartaric acid.

(*iii*) One of the planar rings is replaced by an acyclic grouping which is two-dimensionally chiral usually due to a dissymmetrically substituted trigonal atom. Molecules of this type may give atropisomers if sufficient steric hindrance is

is a simple paracyclophane with one aromatic ring only (resembling an ansa compound) which has been resolved. The pilot atom is the methylene carbon (underlined) on the side of the carboxyl group and the structure (LXIX) has *R* configuration. In more complex paracyclophanes (e.g., LXX), the two benzene rings are arranged one above the other (parallel) and the one with the substituent (CO_2H) cannot make a full turn if the chains are small.

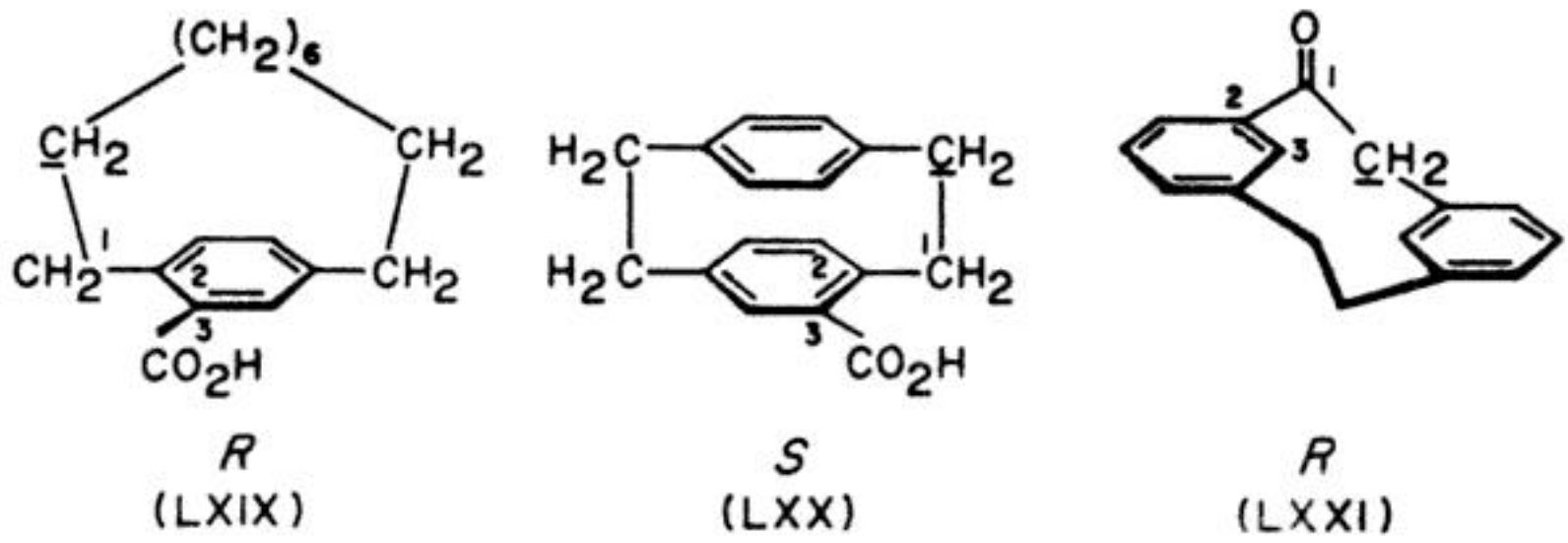


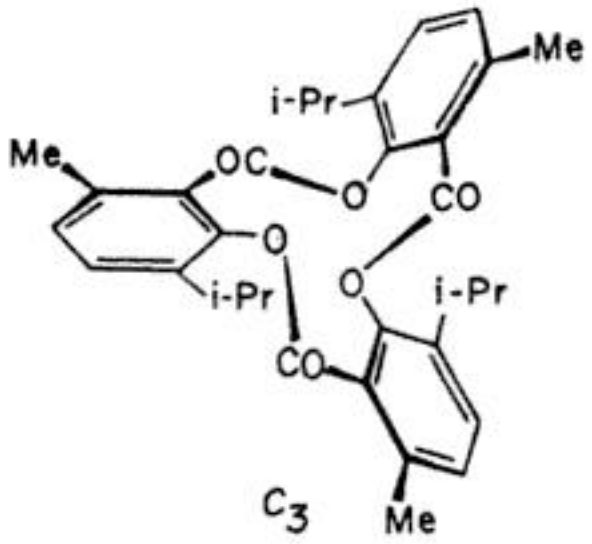
Figure 5.25 Cyclophanes: simple, para, and meta

To have enantiomerism, at least one of the ring must be dissymmetrically substituted or, in the case of the metacyclophanes, the two chains must be non-equivalent as in the structure (LXXI). For the assignment of configuration, the same procedure is adopted. The pilot atoms are underlined and the molecules (LXX) and (LXXI) have configurations *S* and *R* respectively. Paracyclophanes have been reviewed by Cram and Cram (1971) and metacyclophanes by Vögtle and Neumann (1974). The two parallel aromatic π electronic systems interact with each other (π-π transannular interaction) which is exhibited in many of their physical properties particularly in the electronic spectrum.

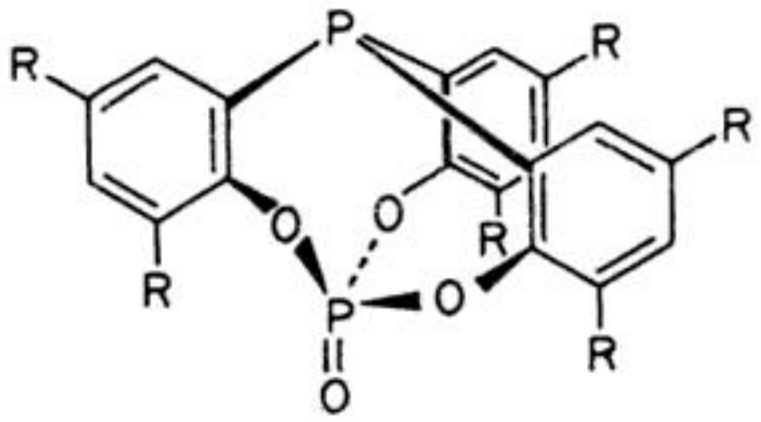
5.6.3 *trans*-Cycloalkenes

trans-Cycloalkenes provide another type of molecules with planar chirality. The two trigonal carbons and the atoms directly attached to them are in a plane and the polymethylene bridge is skewed in the third dimension. Cyclooctene is the smallest ring* which can accommodate a trans double bond and two conformations (LXXIIa) and (LXXIIb) (Figure 5.26) are possible which are mirror images of each other. The interconversion of the two enantiomers which requires the swinging of the tetramethylene chain over and below the plane of the trigonal atoms (chiral plane) is opposed by ring strain (angle strain) and the two enantiomers have been separated (Cope et al 1963). The molecule has a C_2 axis (passing through the centre of the double bond and bisecting 5-6 bond) and therefore belongs to point group C_2. In passing to higher homologues, the mobility of the polymethylene chain increases and the rotational barrier decreases. *trans*-

**trans*-Cycloheptene has been seen as a fleeting intermediate; the case of *trans*-cyclohexene is more controversial.



(LXXIX) C_3

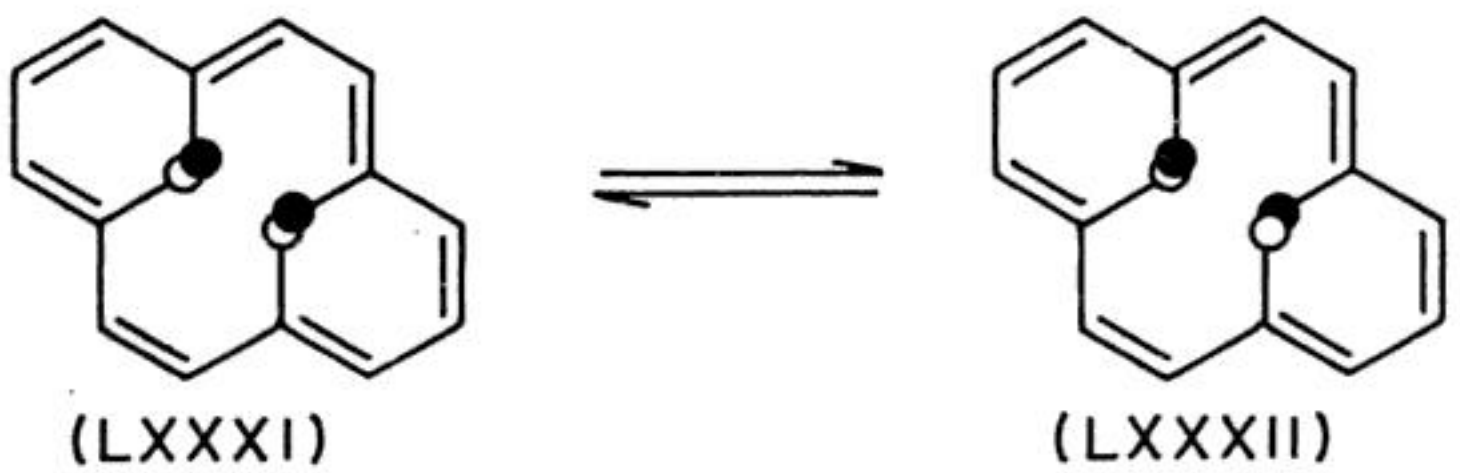


(LXXX) C_3

Figure 5.30 Chiral molecules of C_3 point group

Very recently, Sharpless (Bolm et al 1988) synthesised an interesting type of chiral monophosphanes of C_3 symmetry represented by the structure (LXXX, R = H, *t*-Bu) which are chiral also for a similar reason. The C_3 axis passes through the two phosphorus atoms and is tilted by about 27° with respect to the planes of the aromatic rings which eliminates the σ planes.

Annulenes are large ring compounds with conjugated (alternate) double bonds which may exist both in cis and trans configuration. Thus the [14]annulenes shown in structures LXXXI and LXXXII (Figure 5.31) have four trans and three cis double bonds (Gaoni and Sondheimer 1964). In each of the structures, four transannular hydrogens overlap with each other leading to two conformational diastereomers which differ in the mode of overlapping. The two forms although separable (on silica gel column impregnated with silver nitrate) are easily interconvertible.



(LXXXI) (LXXXII)

Figure 5.31 Stereoisomers of annulenes differing in the mode of overlap of intraannular H atoms

5.9 Cyclostereoisomerism

A new type of stereoisomerism has been described first by Prelog et al (1964) and later extended by Mislow et al (1986-87) which is based on *cyclic directionality* and is known as cyclostereoisomerism. Compounds exhibiting such stereoisomerism are generally cyclic and contain more than one chiral centre either as a part of the

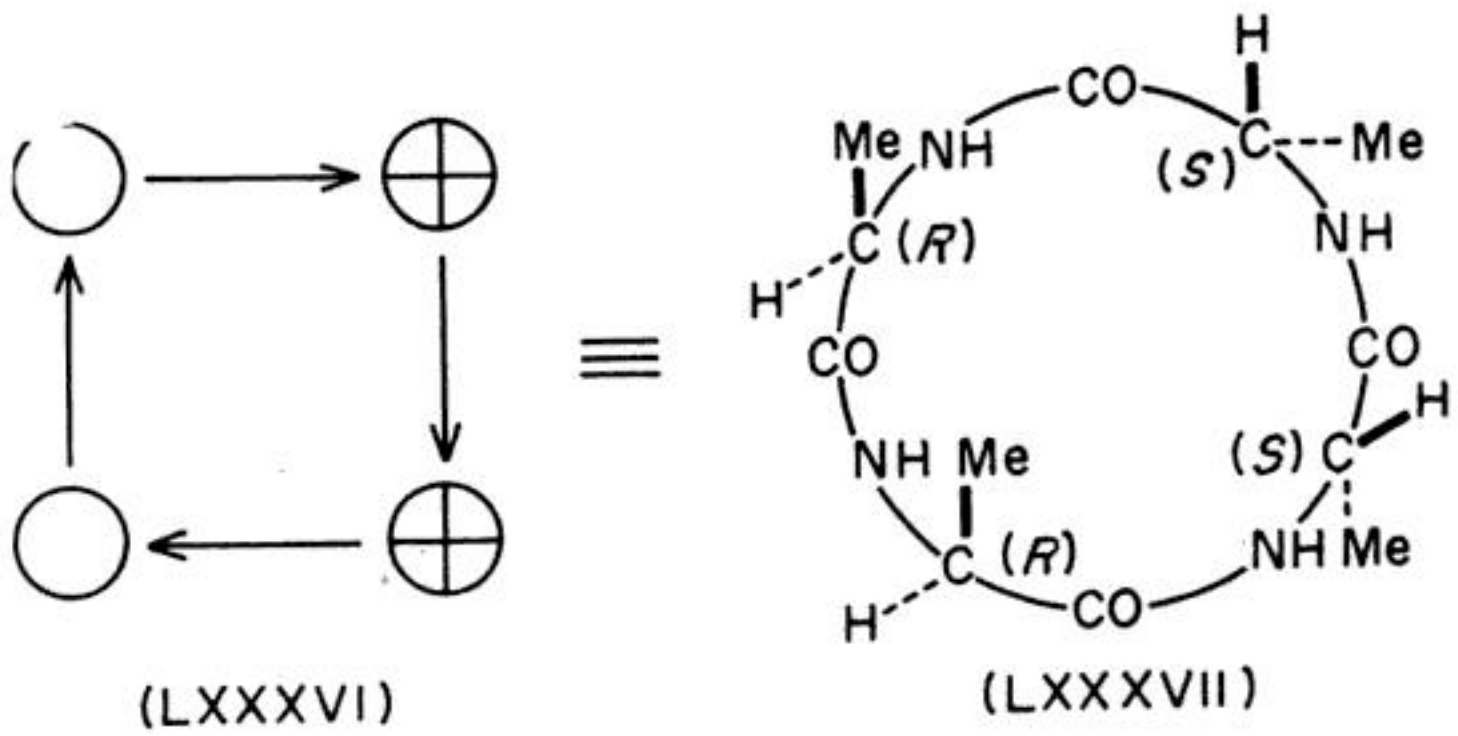


Figure 5.33 Cyclotetraalanyls: two meso isomers

When $2n = 6$, three different arrangements of the chiral centres are possible. The one in which three *R* and three *S* centres are placed consecutively has an S_2 axis and is a meso isomer (structure not shown). The second one with *R* and *S* placed alternately (XC) (Figure 5.34) is also a meso compound (presence of an S_6 axis); its mirror image (XCI) apparently differing in ring directionality* is superposable with the original when rotated by 180° around a horizontal axis. The third one (XCII) does not have any S_n axis and is chiral (point group C_1). Its mirror image (XCIII) shows an unusual structural feature, all the *R* and *S* units are arranged exactly as in the original (XCII); only the ring directionality is different which prevents the two from being superposable (a 180° rotation of XCIII around the horizontal axis makes the ring directionality the same but now the chiral framework is different). The two structures are called *cycloenantiomers* (the stereoisomerism is called *cycloenantiomerism*). Like true enantiomers, they possess identical properties and differ only in optical rotation which is equal but opposite.

* Cyclic directionality and ring directionality are used here synonymously.

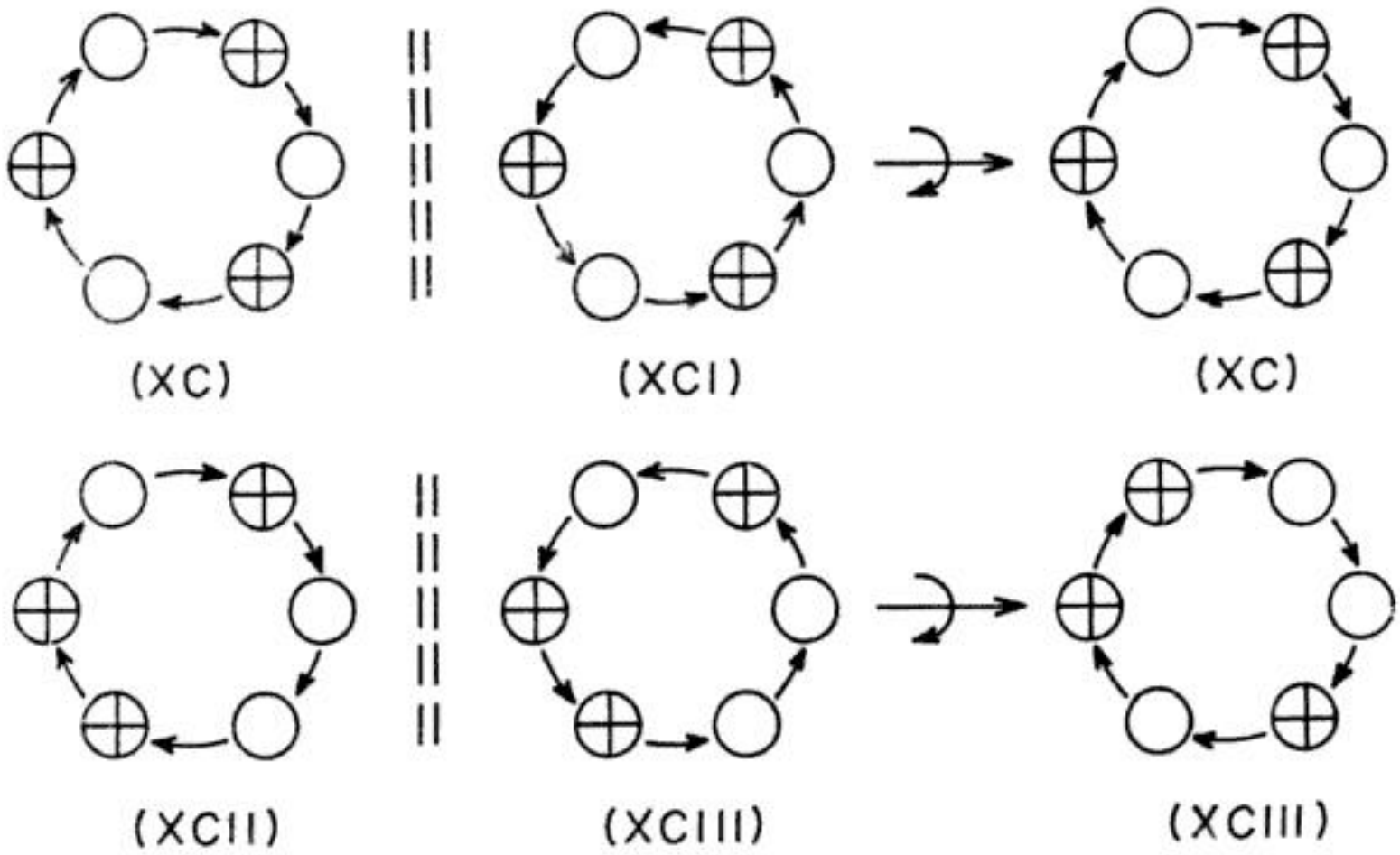


Figure 5.34 Cycloenantiomers

Thus the cyclohexaalanine (XCII) with a clockwise directionality has α_D^{23} of $-25.5°$ while its cycloenantiomer (XCIII) with an anticlockwise directionality has α_D^{23} of $+22.2°$ (the small difference is due to imperfect purification).

With the increase of 2n, the number of stereoisomers also increases and when $2n = 10$, there occur four meso forms, six pairs of cycloenantiomers, and five pairs of enantiomers (a total of 26 stereoisomers). The structures (XCIV) and (XCV) (Figure 5.35) represent a normal enantiomeric pair while the structure (XCVI) represents a member of another enantiomeric pair. Inspection of XCIV and XCVI reveals an interesting fact : their chiral frameworks are identical, only the ring directionality is different. They cannot be cycloenantiomers since they are not mirror images of each other. They are, therefore, called *cyclodiastereomers* and like normal diastereomers, they differ in all their properties. The enantiomer of XCVI is in turn cyclodiastereomeric with XCV. Characterisation of a pair of cyclostereoisomers is thus made on the basis of three criteria : the identity or non-identity of the chiral framework, ring directionality, and mirror image relation, as summarised in Table 1.

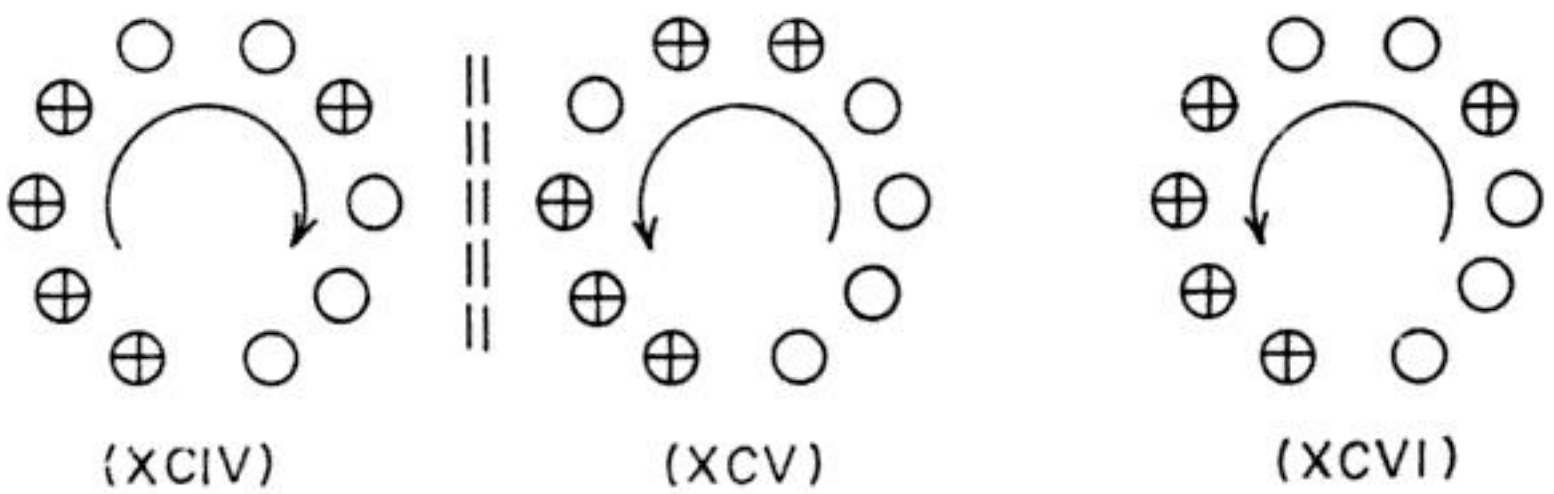


Figure 5.35 Cyclodiastereomers

Table 5.1 Criteria for cyclostereoisomers

Stereoisomers	*Chiral frame*	*Directionality*	*Mirror image*	*Example*
Enantiomers	different	opposite	yes	XCIV & XCV
Cycloenantiomers	same	opposite	yes	XCII & XCIII
Cyclodiastereomers	same	opposite	no	XCIV & XCVI

Since ring directionality can be changed at will by simply turning over the ring, the nature of cyclostereoisomers is best determined by keeping the ring directionality of any two structures opposite and then applying the other two criteria. Compounds which are neither enantiomers, nor cycloenantiomers, nor cyclodiastereomers are normal diastereomers by default, e.g., XCV and XCVI.

5.9.2. Cyclic directionality of conformational origin

Recently, Mislow and coworkers (1987) have shown that cyclic directionality may also originate from several conformationally mobile groups arranged around the periphery of an undirected ring and rendered immobile by steric factors. This is best illustrated by examples. 1,2-Diethyl-3,4,5,6-tetraisopropylbenzene (XCVII) (Figure 5.36) on photobromination affords two diastereomers (the two ethyl side chains are converted into two stereogenic α-bromoethyl groups). One of the diastereomers (*R,S*) is shown in its two enantiomeric forms (XCVIII) and (XCIX). In the structures, the white circles stand for Me and the black circles for Br; the tertiary H's are indicated by short lines. It may be noted that the six side chains are interlocked in such a way that the tertiary H's are all arranged in a clockwise or in an anticlockwise fashion giving cyclic directionality. The two enantiomers (XCVIII) and (XCIX) have the same chiral framework (*R,S*) but differ in cyclic directionality and may, therefore, be called *conformational cycloenantiomers*. The second diastereomer (not shown) also exists in two enantiomeric forms, *R,R* and *S,S* which are normal enantiomers. Under condition of rapid rotation of the side chains around aryl-C bonds, the enantiomers of the first diastereomer interconvert into each other; the diastereomer thus becomes a meso isomer similar to *meso*-tartaric acid

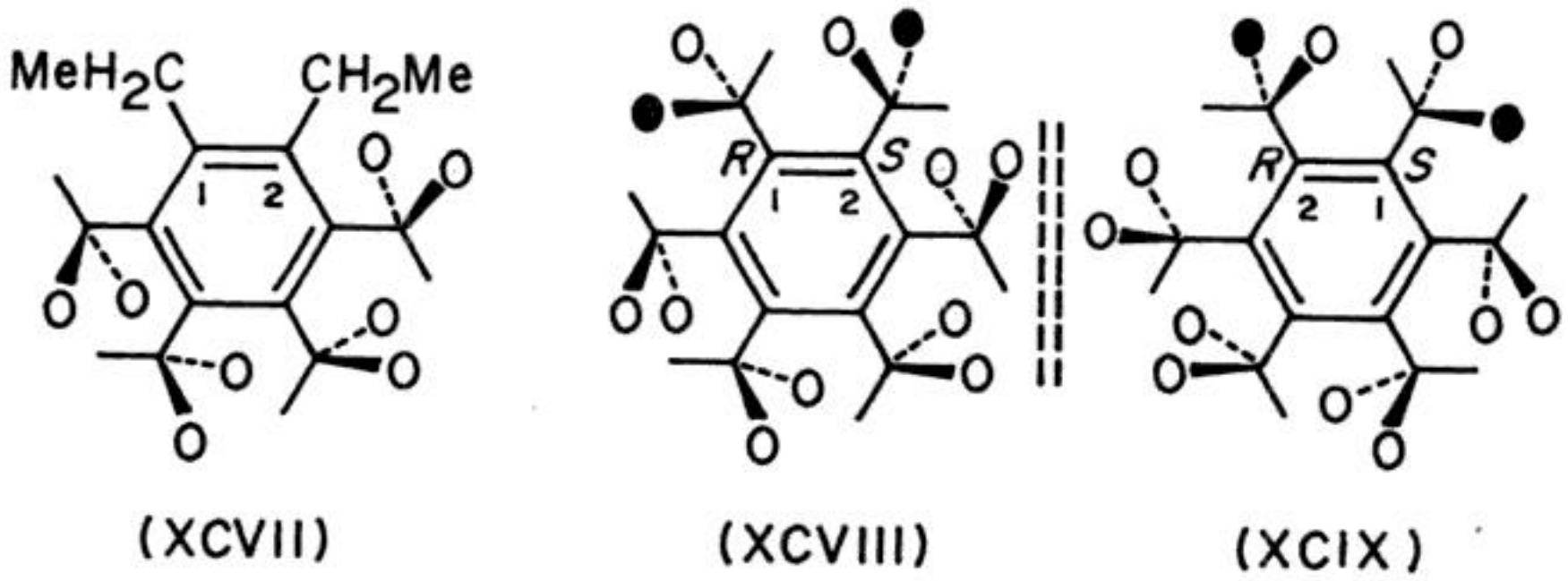


Figure 5.36 Conformational cycloenantiomers

which also exists in two chiral conformers, *P* and *M*. The enantiomers of the second diastereomer, on the other hand, retain their configurational integrity under condition of rapid internal rotation similar to (+)- and (−)- tartaric acid.

5.9.3 **Retro-enantio isomers**

Yet another interesting type of cyclostereoisomerism is encountered in cyclooligopeptides and analogues consisting of two or more different chiral centres (polytonic). If the configuration of each chiral unit and the ring direction are both reversed for a structure, a new structure results which is essentially a constitutional isomer of the original since the sequence C_1-NH-CO-C_2 has now been replaced by the sequence C_1-CO-NH-C_2, C_1 and C_2 representing two different chiral centres. Two such tripeptides (C) and (CI) are shown in Figure 5.37. The circles of different radii refer to different amino acid residues. Such pairs of compounds are called 'retro-enantio' isomers. They are of biological interest because one can effectively replace the other in a biological (enzymatic) reaction (see Nogradi 1981). This is due to the fact that both of them have the same relative disposition of the side chains and the same conformation of the peptide chain but differ in the ring direction as evident in the two structures (CII) and (CIII). Thus the antimicrobial activities of enniatin, an antibiotic cyclohexapeptide are almost identical with those of its retro-enantio isomer (Shemjakin et al 1969).

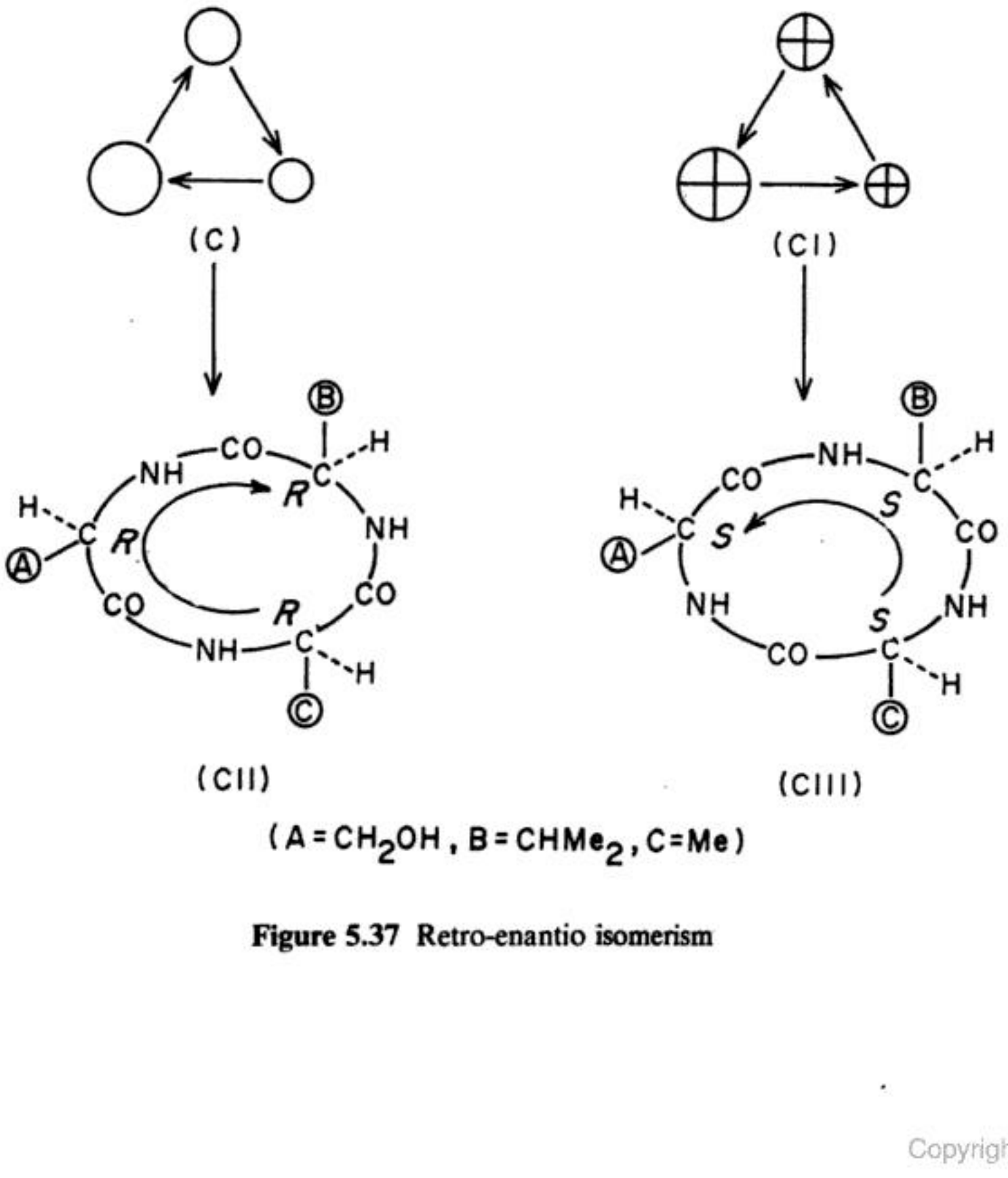


Figure 5.37 Retro-enantio isomerism

5.10 Summary

1. A molecule may be chiral even in the absence of a centre of chirality due to the presence of other elements of chirality such as axes, planes, and helices. The principle of axial chirality is explained on the basis of an elongated tetrahedron, the two adjacent pairs of vertices of which are distinguishable from each other. Such a tetrahedron serves as the model of axial chirality and the line along which the tetrahedron is elongated acts as the chiral axis. At the molecular level, a large number of molecules such as appropriately substituted allenes, hemispiranes, spiranes, adamantoids, biphenyls, and their analogues conform to this model and show enantiomerism due to axial chirality.

2. The three-dimensional stereoisomers based on axial and planar chirality can be conveniently analysed in terms of two-dimensional chiral simplexes as structural units. When two such units undergo planar combination, they lead to planar diastereomers such as cis and trans olefins but when they combine in a non-planar way, three-dimensional structures result which correspond to an elongated tetrahedron previously mentioned and the resulting molecules show enantiomerism.

A two-dimensionally chiral plane divides the three-dimensional space into two distinguishable half-spaces. An atom or a group may be attached to a centre in the chiral plane from either half-space giving two enantiomers. Molecules belonging to this category are said to be chiral due to the presence of a chiral plane.

3. A number of allenes, hemispiranes, spiranes, and adamantoids which are chiral according to the above principles, are discussed. In order to assign configurational symbols to axially chiral molecules, the standard subrule (0) is applied first which states that near groups precede far groups. The molecule is viewed from any end of the axis and the groups near to the observer are numbered 1 and 2 whereas the groups at the far end are numbered 3 and 4 following the priority rule. The order $1 \rightarrow 2 \rightarrow 3$ (clockwise or anticlockwise) gives the configuration as *R* and *S*.

4. Stereoisomerism in biphenyls requires a new principle, namely, hindered rotation around the pivotal bond (the bond connecting the two phenyl groups) and is known as atropisomerism. The two aryl rings must be dissymmetrically substituted (so that they conform to two-dimensional chiral units) and there should be sufficient bulky ortho substituents to prevent them from being planar. A large number of biphenyls of this type have been discussed which exhibit different extent of configurational stability including a few which are singly or doubly bridged (through ortho positions). Terphenyl derivatives with suitable substituents may show both cis-trans isomerism as well as enantiomerism.

5. The assignment of configurational symbol to biphenyls and analogues is done following the same general procedure as recommended for axially chiral molecules. Unlike in the previous practice, however, the fiducial groups are not the ortho substituents *per se* but the four ortho carbons properly complemented to quadriligancy according to the sequence rule.

6. Atropisomerism is also known to occur in compounds with restricted rotation around single bond joining two sp^3 hybridised carbons atoms. Thus a few triptycene type molecules are known which have been isolated in enantiomeric as well as in diastereomeric forms.

7. Molecules with planar chirality include ansa compounds, paracyclophanes, metacyclophanes (in which remote atoms of a phenyl ring are joined by chain or chains), and a few *trans*-cycloalkenes. The enantiomeric forms result due to the position of the methylene chain on either side of the aryl ring or C = C bond, the interconversion between the isomers being prevented by the inability of the chain to swing from one side to the other of the aryl or olefinic plane.

The assignment of configurational descriptors to these compounds is done by first selecting a pilot atom (spectator point) which is the first out-of-plane atom linked to the sequence-preferred end of the chiral plane. The sequencing starts with the first in-plane atom and continues through atoms in the plane along the preferred path. These atoms are numbered respectively 1, 2 and 3 and the order in which they appear when seen from the pilot atom determines the configuration; i.e., *R* for clockwise and *S* for anticlockwise.

8. The α-helix represents a secondary structure of protein molecules arising out of coiling of polypeptide chain and is thus conformational in origin. Certain polycyclic aromatic compounds known as helicenes also assume helical structure due to molecular overcrowding. As a helix is traversed, it describes either a clockwise or an anticlockwise direction and accordingly it is called a *P* (plus) or an *M* (minus) helix. Polypeptide chains formed from L-amino-acids give mostly *P* helices which are held rigidly through intramolecular H-bonding.

Sometimes, it is more convenient to specify the chirality of conformers of acyclic molecules and biphenyl derivatives (having axial chirality) by helical nomenclature. A few illustrations are given.

9. Finally, a new type of stereoisomerism, namely, cyclostereoisomerism based on cyclic directionality (of constitutional or conformational origin) has been discussed.

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Chapter 6

Topicity and Prostereoisomerism

6.1 Introduction

Ligands (atoms or groups in a molecule)* are called homomorphic (Greek *homos* means same and *morphe* means form) if they are indistinguishable when considered in isolation. In the case of atoms, they must be of the same element, e.g., two H or two Br atoms and in the case of groups, they must have the same constitution and configuration, e.g., two Me or two Ph groups or two secondary butyl groups of the same chirality *R* or *S*. Such homomorphic ligands may, however, be distinguishable in an intact molecule if they are bonded to constitutionally different ligating centres in the molecule or if they have different spatial relation with the rest of the molecule. In the former case, the ligands are called *constitutionally heterotopic* (Greek 'topos' means place), as for example, H's at C-2 compared to H's at C-3 in *n*-pentane (Figure 6.1). This type of heterotopicity has no stereochemical relevance and will not be discussed any further. When their spatial relation with the rest of the molecule is different, the ligands are called *stereoheterotopic* as for example, the geminal H's at C-2 (designated H_A and H_B) of *n*-pentane. The Me-C-Pr plane (Me and Pr may be regarded as two distinguishable points) forms a two-dimensional chiral simplex dividing the three-dimensional space into two half-spaces (right and left) which are stereochemically distinguishable (they are enantio-

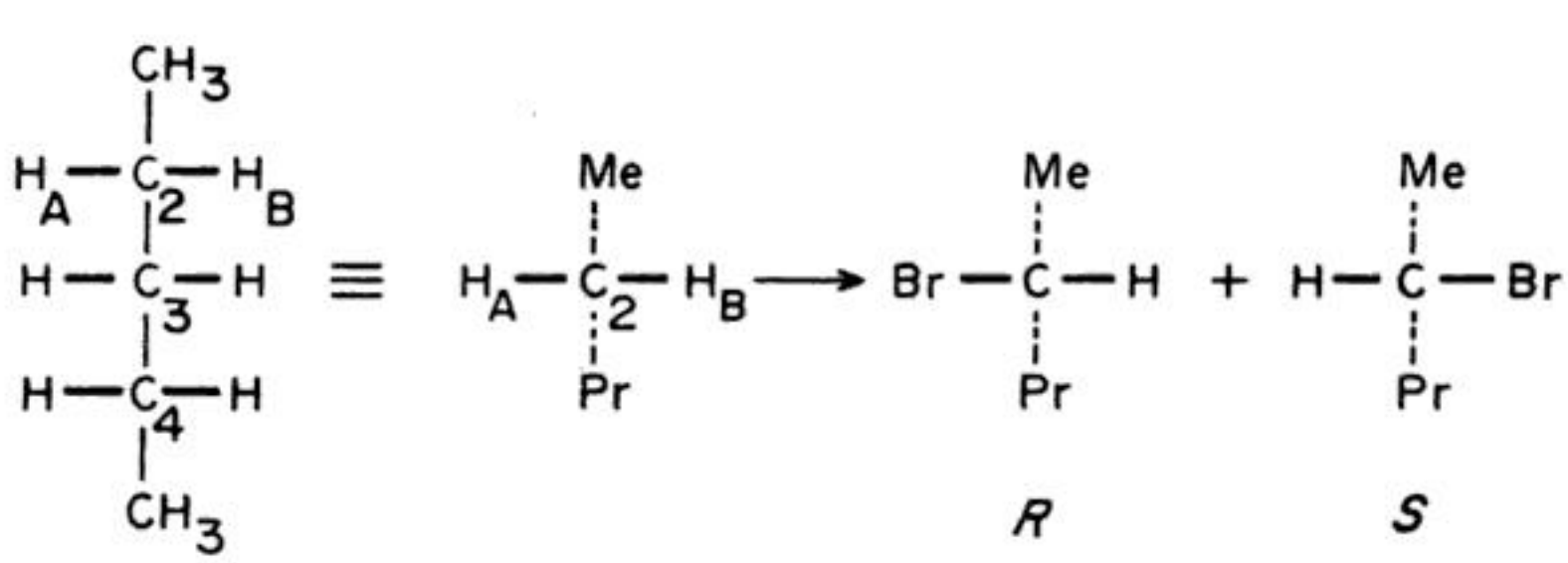

Figure 6.1 Homotopic and heterotopic ligands

*Actually, ligands may be considered as subunits of a molecule.

morphic in the present case) which makes the two H's residing in them stereochemically non-equivalent; i.e., *stereoheterotopic* (actually enantiotopic). The difference becomes more obvious when the two H's are replaced, hypothetically and one at a time, say by Br, giving two enantiomers (as shown). Similar replacement of constitutionally heterotopic ligands would lead to constitutional isomers. If Me or Pr is replaced by a chiral group, the two half-spaces as defined above become diastereomorphous with respect to the plane and bromination at C-2 leads to two diastereomers which also makes the two H's stereoheterotopic (actually diastereotopic). The geminal H's at C-3, on the other hand, are *homotopic*, there being no distinction between the two half-spaces they reside in (Et-C-Et plane is two-dimensionally achiral). Replacement of either of the two H's by Br gives identical product.

A few points emerge from the above illustrations. Molecules having stereoheterotopic ligands exhibit *prostereoisomerism* (provided the ligands can be reacted on) which proves that stereoheterotopicity and prostereoisomerism are two associated phenomena. Prostereoisomerism, in the present case, is attributed to C-2 (or C-4) of *n*-pentane which may be described as a prostereogenic centre. Just as stereoisomerism is discussed in terms of stereogenic elements (centres, axes, and planes), prostereoisomerism may also be described in terms of analogous prostereogenic elements, i.e., prostereocentres, prostereoaxes, and prostereoplanes. The term *chirality* in stereoisomerism should similarly be replaced by the term *prochirality* in prostereoisomerism which would mean that if two homomorphic ligands at a prochiral centre (or axis or plane) be made different, a chiral centre (or axis or plane) would result. A tetrahedrally bonded atom of the general formula Xaabc (where none of the groups a,b, or c is the enantiomer of another) illustrates a typical prochiral centre, e.g., C-2 in *n*-pentane. Just as a stereogenic centre may not necessarily be a chiral centre, a prostereogenic centre may not necessarily be a prochiral centre, i.e., a centre may be prostereogenic without being prochiral (examples will follow). Two faces of appropriate molecules may also be stereoheterotopic and reactions on either face would lead to different stereoisomers.

Stereoheterotopic ligands (or faces) can, in principle, be differentiated by chemical, biochemical, and spectroscopical (particularly, NMR) methods. The principle of stereoselective synthesis (Chapter 13) is based on the differential behaviour of heterotopic groups and faces towards chemical reactions. The concept of stereoheterotopicity has been discussed by Mislow and Raban (1967) and that of prochirality by Hanson (1966). The topic has been recently reviewed (Eliel 1982).

6.2 Topicity of ligands and faces

It may be pointed out that topicity as defined above describes the relationships of two or more homomorphic ligands (or faces) which together constitute a set. Hence, a ligand cannot by itself be called homotopic or heterotopic; in order to use this terminology, a comparison with other homomorphic ligand or ligands present either in the same molecule (internal comparison) or in a different molecule (external comparison) is necessary. These terms are thus similar to the

terms *enantiomeric* and *diastereomeric* used in reference to stereoisomers (Chapter 3).

6.2.1 **Homotopic ligands and faces**

Two criteria, namely, a substitution (or addition) criterion and (or) a symmetry criterion are employed to determine the topic relationships of homomorphic ligands and faces (only one test suffices).

(A) **Substitution-addition criterion**: Two homomorphic ligands are homotopic if substitution (replacement) of first one and then the other by an atom or a group which is not already attached to the ligating centre gives identical product. By this token, all hydrogen atoms in methylene dichloride, methyl chloride, ethylene, and allene (Figure 6.2a) are homotopic. (Substitution of hydrogen atoms in each set gives a single product). The two methine hydrogens in (+)-tartaric acid (I) [as also in the (−)-enanatiomer] are also homotopic since their respective replacement by deuterium leads to identical product (II) (Figure 6.2b). The last example proves that molecular asymmetry is no bar in having homotopic ligands.

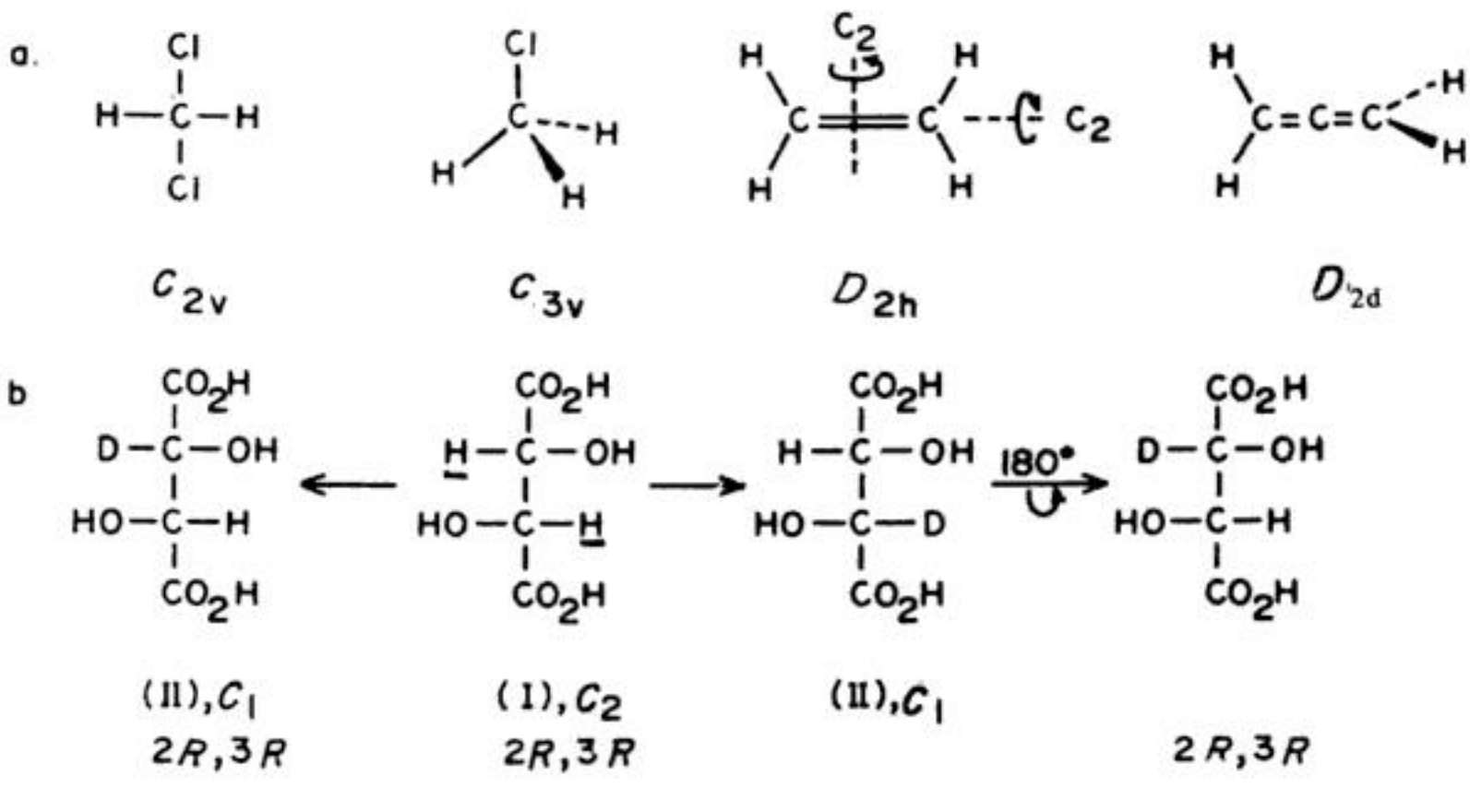

Figure 6.2 Homotopic ligands

For conformationally mobile molecules like cyclohexane (which undergoes ring inversion), the topicity of ligands depends on the time scale of experimental observation. Thus cyclohexane at low temperature is immobilised in the two equivalent chair conformations (IIIa) and (IIIb) in which two types of protons (H_a and H_e are discernible (by low temperature NMR). The twelve hydrogen atoms form two sets of homotopic hydrogens ($6H_a$ and $6H_e$). Replacement of any hydrogen of the same set by deuterium gives identical product. Members of the two sets, H_a and H_e are, however, heterotopic since their replacement gives different products (axial and equatorial isomers).* On the other hand, at room

*See Chapter 10.

temperature, the ring inversion is rapid on the experimental time scale and all the twelve H's become homotopic as in the planar structure (IIIc). Replacement of any one of them, say by Cl, gives a single monochlorocyclohexane.

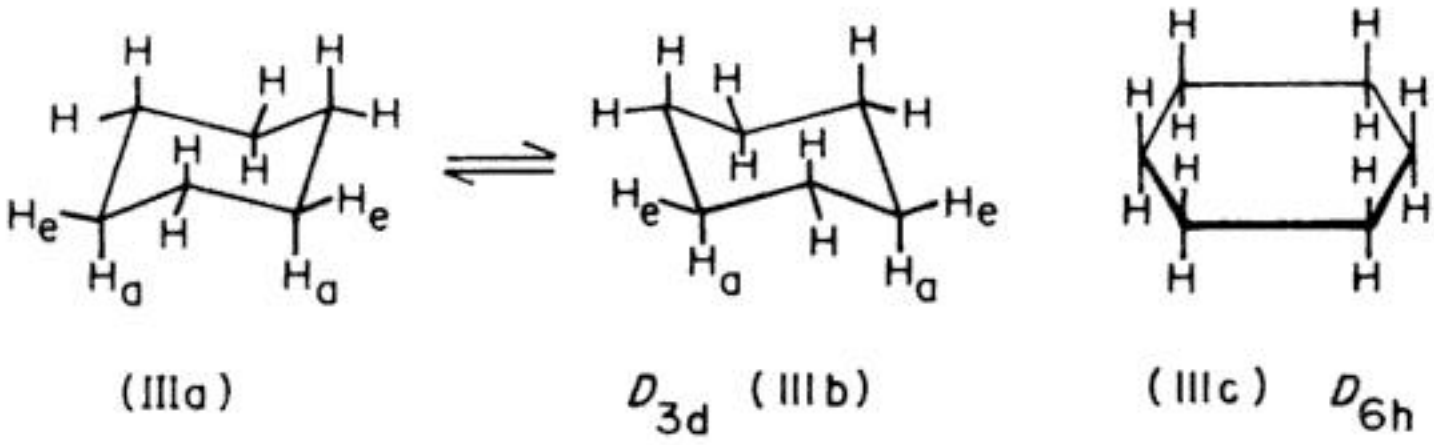

Figure 6.3 Conformation and topicity in cyclohexane

Two faces of a double bond are homotopic if addition to either face gives identical product, e.g., formation of ethanol by addition of MeMgI to either face of formaldehyde (Figure 6.4a). The two faces of the dialkyl sulphide (IV) are homotopic by the same token (oxidation to sulphoxide may be taken as a test reaction here). Alternatively, the two lone pairs may be considered to be homotopic. Things become more complicated when addition takes place at both ends of a double bond as in ethylene, 1,1 -dimethylethylene, and *cis*-2-butene (Figure 6.4b); these molecules all contain two homotopic faces. Confusion may be avoided by using epoxidation as the test reaction as demonstrated for *cis*-2-butene which gives the same epoxide on reaction at either face as shown.

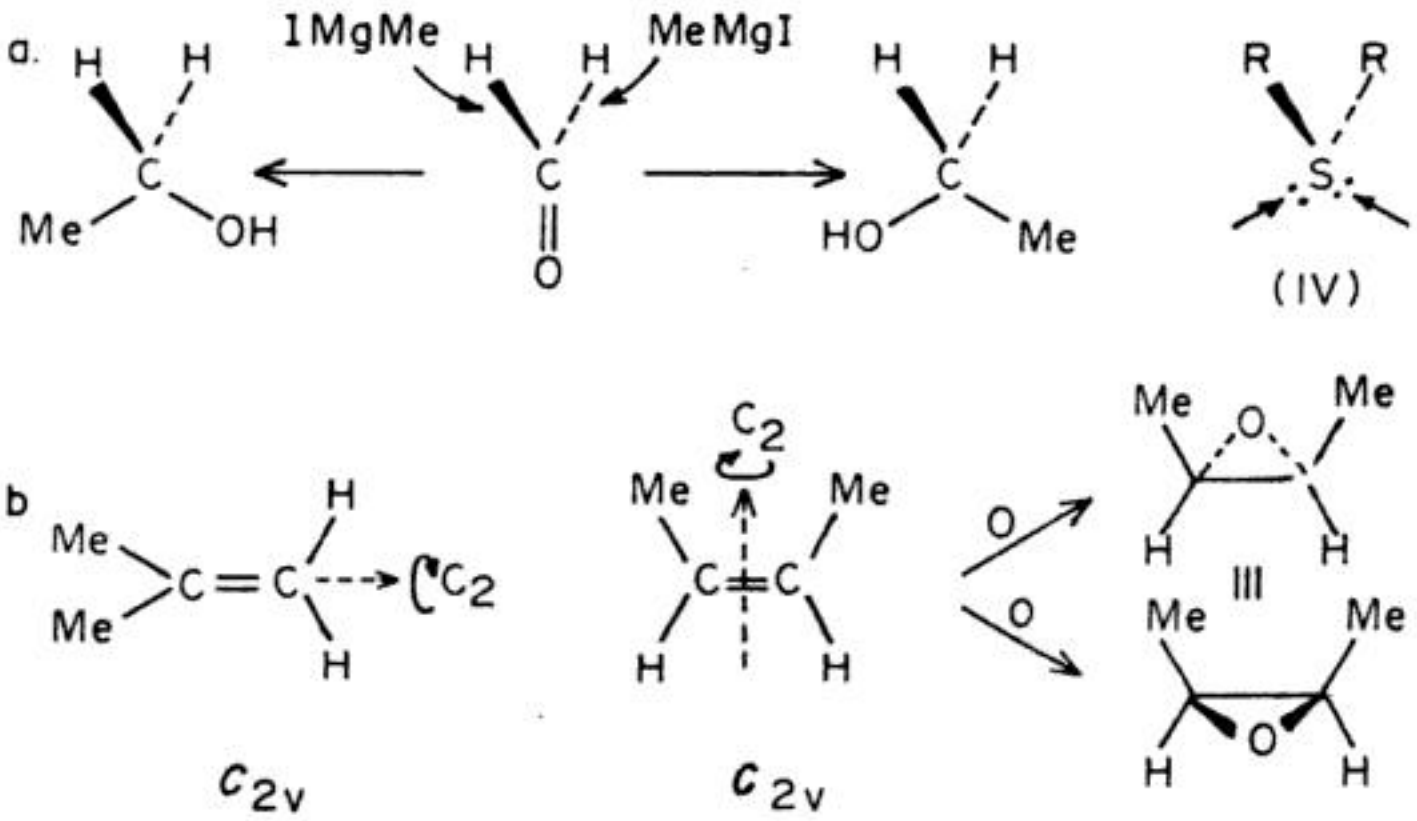

Figure 6.4 Homotopic faces

(B) Symmetry criterion. Ligands are homotopic (by internal comparison) if they can interchange positions by rotation around a simple axis C_n ($\infty > n > 1$). Thus the two hydrogens in methylene dichloride (see Figure 6.2; the point group is shown under each structure), the three hydrogens of methyl chloride, and the four

hydrogens of ethylene can interchange positions through rotations around C_2, C_3, and C_2 axes respectively. In allene, the geminal hydrogens are interchangeable in pairs by rotation around the molecular axis (C_2 axis) while the non-geminal hydrogens are interchangeable through rotation around the two C_2 axes perpendicular to the former. All the four hydrogen atoms are thus homotopic. This proves that if ligands A and B are found homotopic through rotation around one C_n axis and ligands B and C through rotation around another C_n axis, all three (A,B, and C) form a set of homotopic ligands. The two methine protons (as also the two OH and the two CO_2H groups) of (+)-tartaric acid (I) are interchangeable through rotation around a C_2 axis either in the eclipsed conformation or in a staggered conformation (the reader may verify this). These pairs of ligands are, therefore, homotopic.

In the chair conformations (IIIa,b) of cyclohexane (Figure 6.3), the two sets of homotopic ligands H_a and H_e can interchange positions through rotations around the C_3 axis and C_2 axes. All twelve homotopic hydrogens in the planar cyclohexane (IIIc) can interchange positions through rotations around the C_6 axis and C_2 axes.

The following points may be noted:

(*i*) Any achiral or chiral molecule with a C_n axis ($\infty > n > 1$) must contain at least one set (usually two) of homotopic ligands. The presence of a C_n axis in a molecule itself does not ensure that any two ligands are homotopic. The ligands in question must interchange positions by the operation of the C_n symmetry element.

(*ii*) Molecules belonging to non-axial point groups. such as C_1, C_s and C_i (and also $C_{\infty v}$ for a different reason) which do not possess any C_n axis cannot have homotopic ligands.

(*iii*) For conformationally mobile systems, if the structural change is rapid on the time scale of observation, homomorphic ligands (interchanged under condition of fast rotation) are homotopic (e.g., H's in cyclohexane). The same is true for homomorphic ligands which undergo rapid exchange of sites by torsion around a single bond as in CH_3, NR_2, PO_3 etc. (groups which possess rotational symmetry). The three methyl hydrogens in acetic acid are homotopic by the same token although any conformation of CH_3CO_2H belongs to point group C_s which does not allow any homotopic ligands (vide supra).

(*iv*) In a rigid molecule, the number of homotopic ligands belonging to a set cannot be greater than (although it may be equal to) its symmetry number (σ).* The symmetry number of molecules belonging to C_1, C_s, C_i, and $C_{\infty v}$ point groups is 1 and so they cannot have homotopic ligands.

Faces of double bonds, carbonium ions, and molecules with disubstituted atoms capable of accepting a third ligand (e.g., R-S-R) are homotopic if they interchange through a C_2 axis.

6.2.2 Enantiotopic ligands and faces

The origin of stereoheterotopicity of ligands has already been discussed in Section 6.1. The stereoheterotopic ligands are of two types: *enantiotopic* if their positions

*See Chapter 2.

in the molecule are related in mirror-image fashion and *diastereotopic* if their positions do not bear a mirror-image relationship. While the difference between diastereotopic ligands is self evident, that between two enantiotopic ligands is more subtle. Two identical windows symmetrically placed in a symmetrical house front may apparently look the same. But to a person approaching the house, one of them is always at his right and the other always at his left. The two windows may be likened to two enantiotopic ligands attached to the house. A chiral *discriminator* (here a man whose right and left sides are distinguishable) is necessary to differentiate enantiotopic ligands (as in the case of two enantiomers).

Enantiotopic ligands and faces may be recognised by the application of the substitution-addition and symmetry criteria as follows:

(A) Substitution-addition criterion. Two heterotopic ligands are enantiotopic if replacement of first one and then the other by a different achiral ligand gives rise to two enantiomers*. The same goes for addition to enantiotopic faces. Substitution or addition with a chiral group leads to diastereomers and will not be discussed at present. The principle is illustrated by examples (see Figure 6.5a,b).

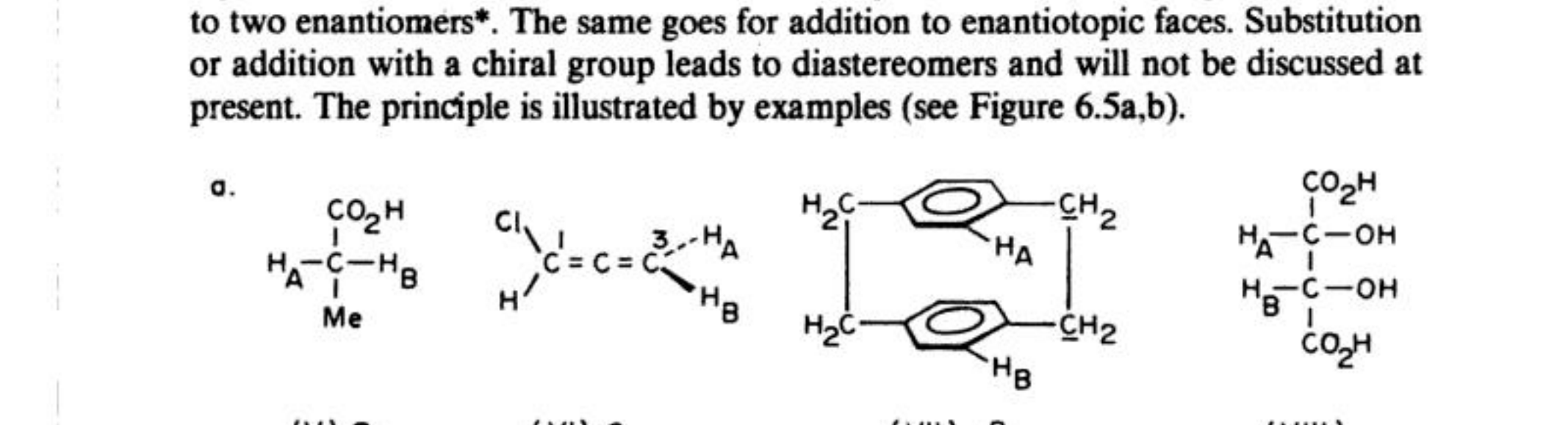

Figure 6.5 Enantiotopic ligands

The cases of propionic acid (V), monochloroallene (VI), and paracyclophane (VII) (only one pair of enantiotopic H's is shown) are easy to understand; replacement of H_A and H_B one at a time with D leads to enantiomers. Molecular chirality of the products is due to the presence of a centre, an axis, and a plane of chirality respectively (see Chapter 5); the molecules (V)—(VII) thus provide examples of a prochiral centre, a prochiral axis and a prochiral plane respectively.

*The test ligand must differ from all other ligands attached to the ligating centre (or axis or plane). Such a prostereogenic element is called a prochiral centre, axis, or plane as the case may be (vide infra).

Substitution of H_A and H_B in *meso*-tartaric acid (VIII, Fischer projection) by D similarly gives rise to two enantiomeric structures. Monoesterification of CO_2H groups and mono-acetylation of OH groups likewise lead to enantiomeric products. The two H's, CO_2H groups, and OH groups are, therefore, enantiotopic. In cyclobutanone (IX), H_A and H_D are homotopic as are H_B and H_C since their substitution by deuterium gives identical products: 2*R* by replacement of H_A or H_D and 2*S* by replacement of H_B or H_C. H_A is, however, enantiotopic with both H_B and H_C while H_D is enantiotopic with both H_B and H_C, since their replacement gives enantiomeric products. This shows that unlike enantiomers, enantiotopic ligands may be more than 2 in number.

Addition of a hydride ion to the right face of acetophenone (X) (Figure 6.6) gives *S*- while addition to the left face gives *R*-phenylmethylcarbinol indicating that the two faces are enantiotopic. Addition of oxygen to the two faces of ethyl methyl sulphide (XI) gives two enantiomeric sulphoxides (shown by the arrows) and hence the two faces of sulphur are enantiotopic. In fact, the two lone electron pairs on sulphur may be regarded as enantiotopic.

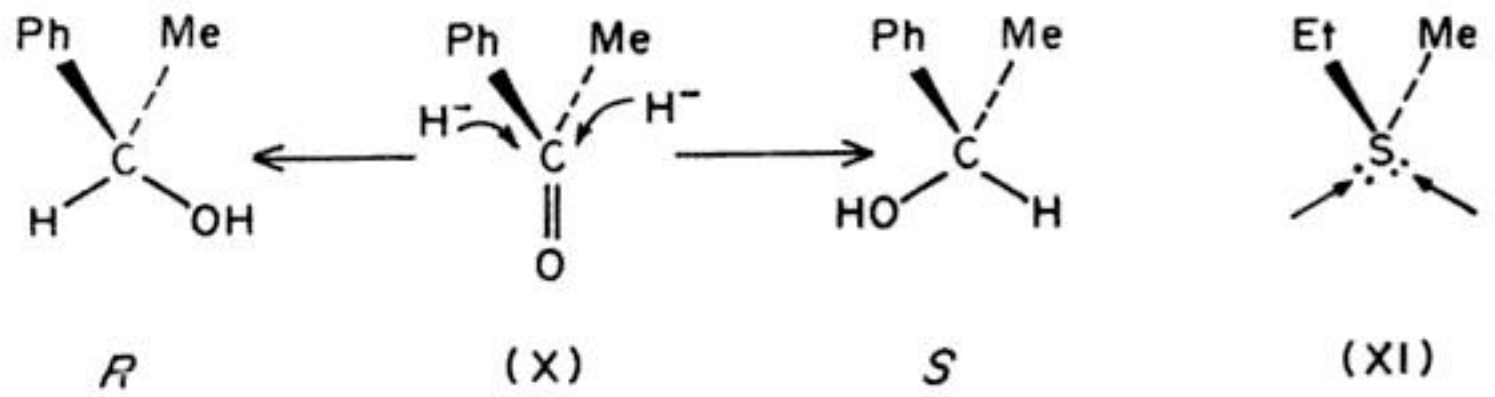

Figure 6.6 Enantiotopic faces

(B) Symmetry criterion. Heterotopic ligands or faces are enantiotopic if they are interchangeable through operation of symmetry of the second kind, i.e., σ planes and S_n axes. Thus H_A and H_B in V, VI, and VII (Figure 6.5) exchange positions through a σ plane, so also the two H's, two OH groups, and two CO_2H groups in VIII. These ligands are, therefore, enantiotopic. In cyclobutanone (IX), H_A and H_B as also H_C and H_D are interchangeable through a σ plane coincident with the molecular plane while H_A and H_C as also H_B and H_D are interchangeable through a σ plane perpendicular to it. Thus each of the four H's in the molecule is enantiotopic with two other H's. On the other hand, H_A and H_D, H_B and H_C as also the two unlabeled H's at C-3 are homotopic since they are interchangeable through the operation of a C_2 axis.*

Enantiotopic ligands may also be interchangeable through the operation of a centre of symmetry (if present). Thus H_A and H_C, H_B and H_D, the two Ph groups, and the two CO_2H groups in α-truxillic acid (XII) are related through a centre of symmetry (*i*) (Figure 6.7). Each pair of ligands is, therefore, enantiotopic. *meso*-Tartaric acid (VIII, Figure 6.5a) in its stable staggered conformation also contains a centre of symmetry the operation of which makes enantiotopic pairs of ligands

*Homotopicity and heterotocicity are mutually exclusive.

(two H's two OH groups, and two CO_2H groups) interchangeable. Compounds with the general formula (XIII) in which F and ℶ represent two enantiomeric ligands* have an S_4 axis (a rotation of 90° around the vertical axis leads to XIIIa which on reflection across the molecular plane gives the original molecule). Each of the four hydrogens is interchangeable with two adjacent hydrogens through S_4 operation. Thus H_A is enantiotopic with H_B and H_D, H_B with H_A and H_C and so on. At the same time, alternate pairs of hydrogens (H_A and H_C; H_B and H_D) are homotopic due to the presence of a C_2 ($S_{n/2}$) axis.

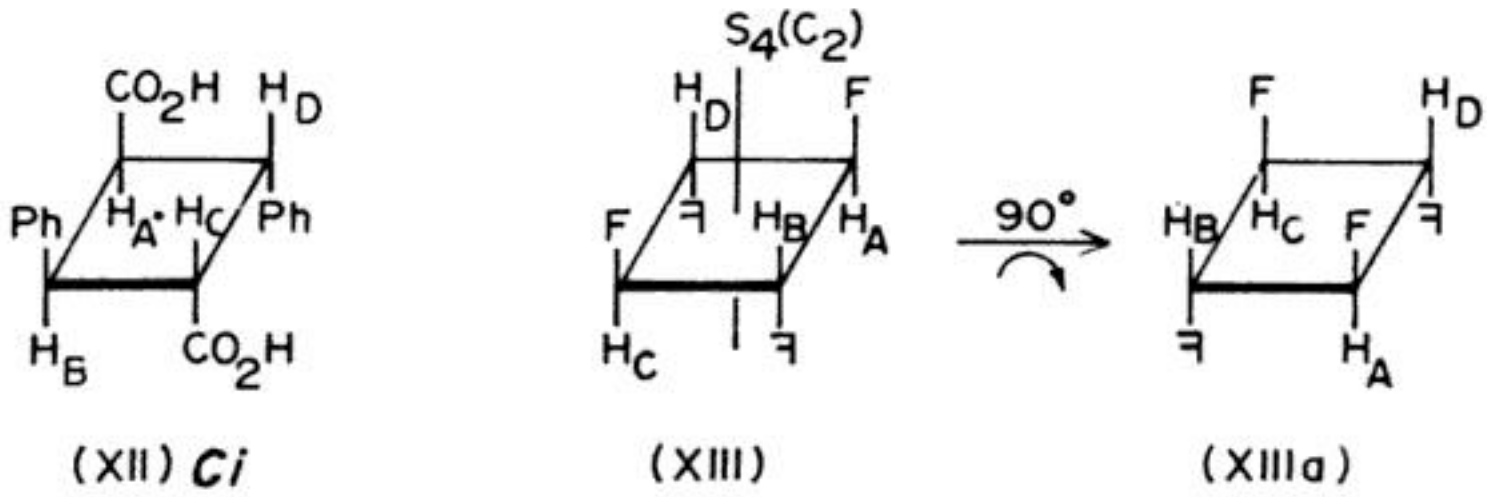

Figure 6.7 Enantiotopic ligands exchangeable through S_n axis

The enantiotopic faces of acetophenone (X) and of ethyl methyl sulphide (XI) (Figure 6.6) are likewise interchangeable through a σ plane coinciding with the plane of the molecules.

The following points are to be noted in connection with enantiotopicity of ligands:

(*i*) Only achiral molecules can have internally enantiotopic ligands (or faces) since the presence of a symmetry element of the second kind is necessary for interchange. This excludes all molecules belonging to chiral point groups C_n and D_n (and also $C_{\infty v}$ and $D_{\infty h}$ for a different reason).

(*ii*) Molecules with enantiotopic ligands may belong to non-axial point groups, e.g., C_i and C_s (in contrast to molecules containing only homotopic ligands) as well as to axial point groups. Since molecules of axial point groups contain C_n (often C_2) axis, enantiotopic and homotopic ligands may coexist in them (e.g., IX).

(*iii*) Molecules with enantiotopic ligands (and faces) are not only prostereogenic but also prochiral.†

(*iv*) Unlike enantiomers which occur only in pairs, a ligand can be enantiotopic with more than one other ligand.

(*v*) Like enantiomers, enantiotopic ligands or faces cannot be distinguished by achiral reagents or in achiral media but are distinguishable by chiral reagents notably by enzymes and by NMR in chiral media.

(*vi*) Corresponding atoms and groups in enantiomers are enantiotopic by external comparison. Thus the two methyl groups in D- and L-alanine or in (+)-

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* They are not homomorphic and therefore cannot be topically related.

† These two adjectives should better be used to qualify centres, axes, and planes (Hanson 1966) rather than molecules, although they often are.

and (−)-lactic acid are enantiotopic because they show mirror-image relationship.

6.2.3 **Diastereotopic ligands and faces**

Diastereotopic ligands and faces reside in diastereomeric environments and can be distinguished very often simply by an inspection of the molecular structure. However, application of the substitution-addition and symmetry criteria often makes the task easy.

(A) Substitution-addition criterion. The hydrogen atoms H_A and H_B in propene (XIV) and bromocyclobutane (XV)* (Figure 6.8) on substitution (as specified before) give two diastereomeric products in each case and are, therefore, diastereotopic. Even in the original molecules, they can be distinguished, H_A being cis and H_B trans to Me and Br respectively. Two geminal methylene protons (or other homomorphic groups, e.g., Me) adjacent to a chiral centre are usually diastereotopic as in the molecules represented by the general formula (XVI). The replacement criterion leads to two chiral diastereomers differing in the configuration at C-2 which correspond to erythro and threo isomers. The methylene protons H_A and H_B in *trans*-1,2-dibromocyclopropane (XVII) containing two chiral centres are, however, homotopic (in spite of the presence of two chiral centres) since substitution of either of them gives identical products.

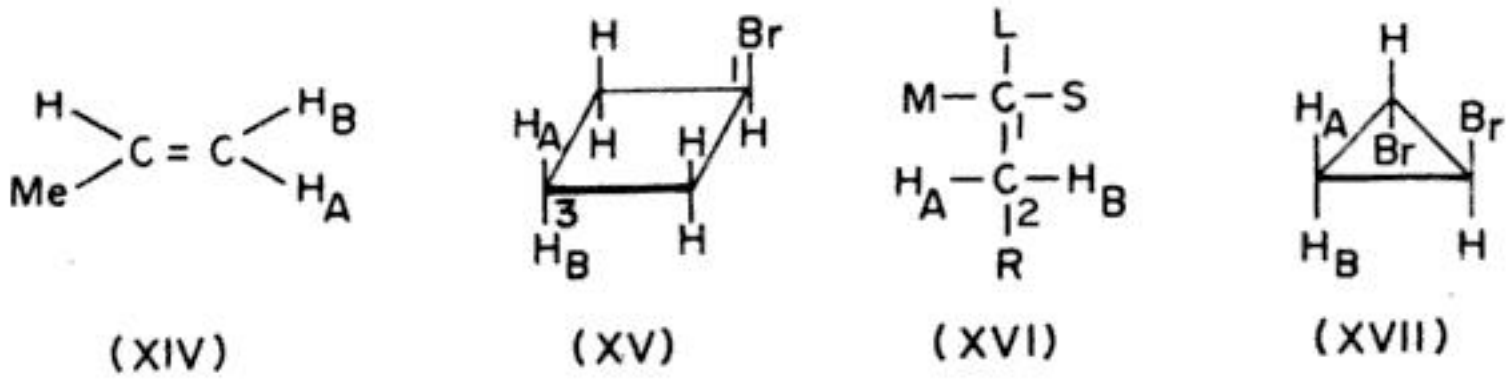


Figure 6.8 Diastereotopic ligands

The two faces of the carbonyl group in a molecule of the general formula (XVIII) (Figure 6.9) containing a chiral centre are diastereotopic since addition of a hydride to the two faces gives different diastereomers: XIX when addition takes place to the left face and XX when addition takes place to the right face. 4-*t*-Butylcyclohexanone (XXI) is an example of an achiral molecule in which the two faces of the carbonyl group are diastereotopic since addition of hydride to the two faces (one at a time) gives two diastereomeric (achiral) products, *trans*-(XXII) and *cis*-(XXIII) 4-*t*-butylcyclohexanol.

(B) Symmetry criterion. Diastereotopic ligands are not related by any symmetry operation and are, therefore, relatively easy to spot. Since the application of the

*The C-3 atom in XV is an example of a prostereogenic centre which is not prochiral while the C-2 atom in XVI is prostereogenic as well as prochiral.

(*vi*) Ligands may be diastereotopic by external comparison as well. Just as two corresponding ligands in enantiomers are enantiotopic, two corresponding ligands in any two diastereomers are diastereotopic. The distinction of diastereotopic ligands by external comparison is a mere formality but the concept may be useful in some cases, e.g., ^{13}C-NMR (see Eliel 1982).

6.2.4 Summary of topic relationships

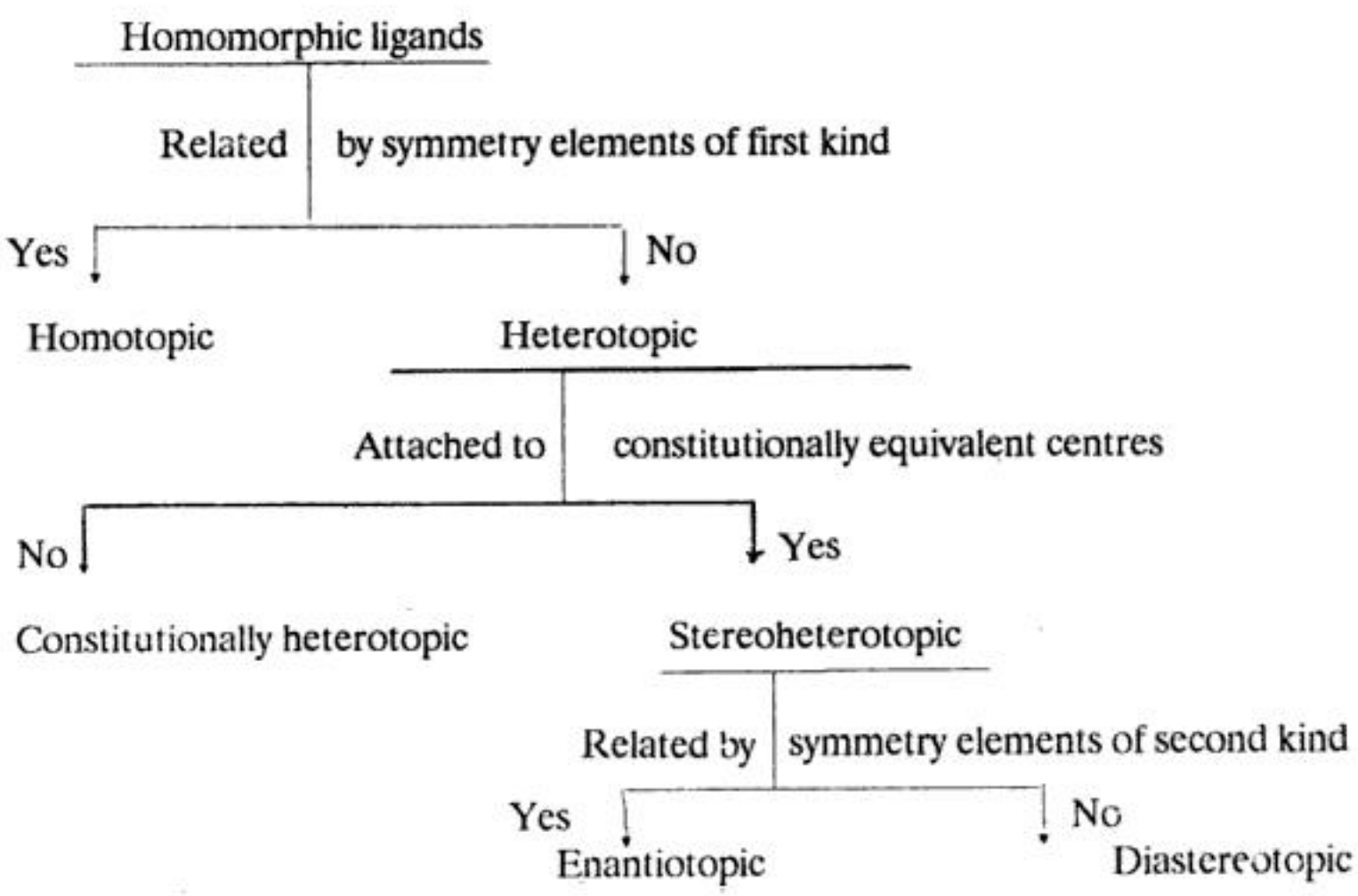
The points so far discussed are summarised in Table 6.1. The table has much in common with that given by Mislow and Raban (1967) and by Eliel (1980).

Table 6.1 Topic relationship of ligands and faces

Topicity	Substitution-addition criterion*	Symmetry criterion	Difference
Homotopic	Identical product	Ligands related through C_n and faces by C_2 axis.	No difference by any method
Enantiotopic	Enantiomeric products	Ligands (faces) related through σ, i, or S_n	Distinguishable, in principle, in chiral media (NMR), by chiral reagents, and enzymes
Diastereotopic	Diastereomeric products	Ligands and faces not related by any symmetry element	Distinguishable, in principle, by all methods

*Substition-addition by achiral groups only is considered.

In view of the interrelationship between topicity of ligands and isomerism in general, it may be instructive to draw a classification diagram for topicity and to compare it with that drawn for isomerism (Chapter 3).



6.3 Nomenclature of stereoheterotopic ligands and faces

Stereoheterotopic ligands differ in their spatial relationships in the same way as stereoisomers differ in the spatial arrangements of their constituent atoms and groups. It is, therefore, desirable that like stereoisomers, such ligands should be given appropriate descriptors. Configurational descriptors such as *R, S, Z, E, cis,* and *trans* which are used to describe stereogenic units may be prefixed with *pro* and used to describe the heterotopic ligands attached to analogous prostereogenic units. Such a system was first introduced by Hanson (1966) and since then has gained wide currency among chemists and especially among biochemists.

6.3.1 Symbols for stereoheterotopic ligands

Since enantiotopic and diastereotopic ligands often coexist and their labeling systems are correlated, the assignment of descriptors to both kinds of stereoheterotopic ligands is discussed under the same headings.

1. Molecules with one prochiral centre. Molecules with a single prochiral centre are represented by the general formula CabXX and depicted by Fischer plane projection in two perspectives (A) and (B) (Figure 6.10). It is assumed that ligand 'a' has a higher priority than ligand 'b' as determined by the sequence rules (Chapter 4) while ligand X may have any priority lower, higher, or in between with respect to 'a' and 'b'. For the present discussion, it is assumed that X has the lowest priority. In order to assign a descriptor to any of the paired ligands, say X_A, it is arbitrarily given a higher priority than X_B without disturbing the priorities of 'a' and 'b' (the unpaired ligands). The chirality rule is now applied to the hypothetical chiral centre which happens to have *R* configuration (viewed from the side remote from X_B, the lowest ranking group, a→b→X_A describes a clockwise direction). The ligand X_A is called *pro-R* and may be denoted by adding a subscript R, as X_R. The other ligand X_B is *pro-S* (denoted by X_S) by default—a conclusion which is alternatively arrived at by adopting the above procedure but

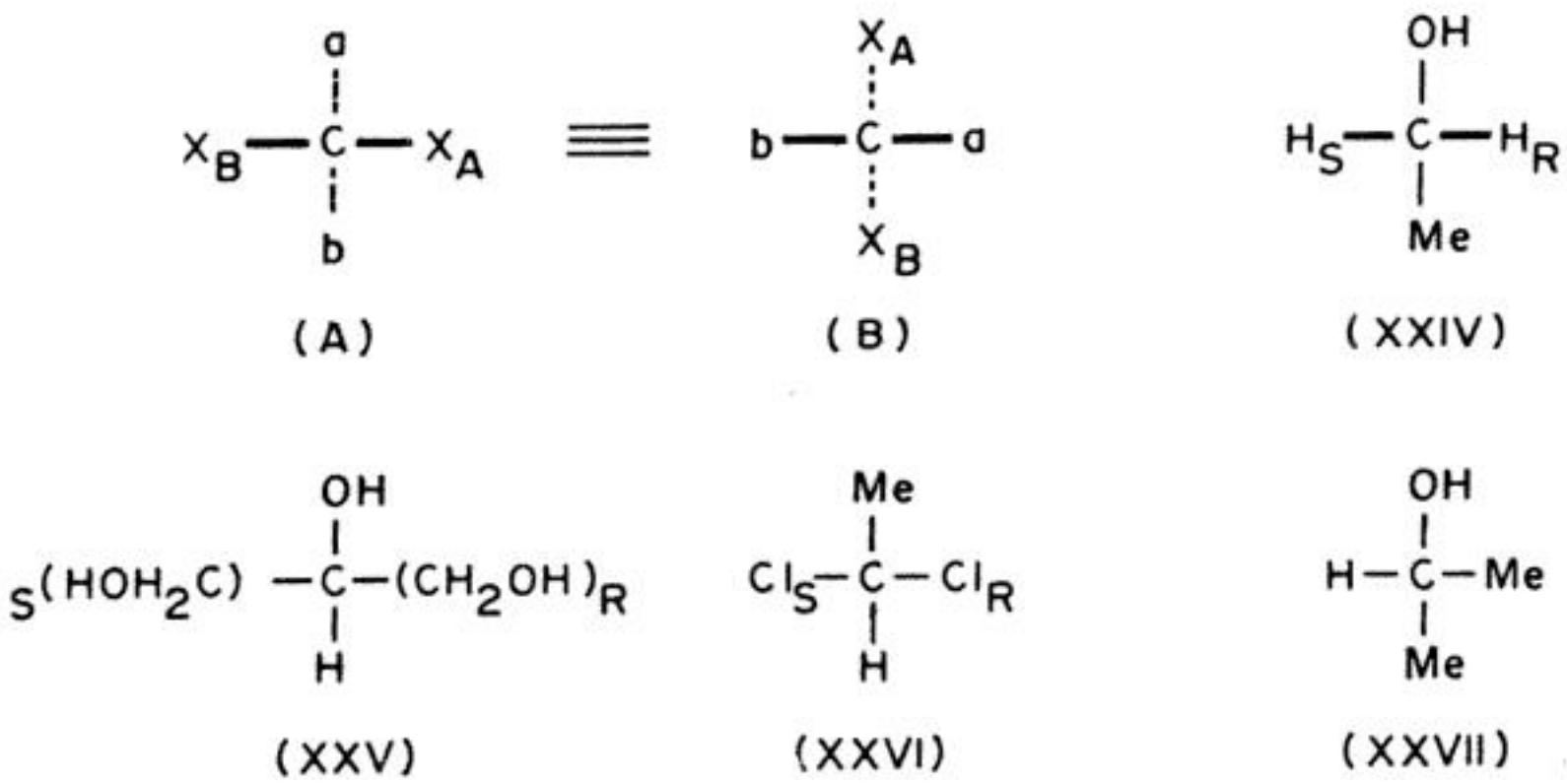


Figure 6.10 A mnemonic for pro-R and pro-S descriptors

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neither they are enantiotopic since they are not interchangeable by the symmetry of any kind (homomorphic pairs of ligands at C-2 and C-4 are, however, enantiotopic as in *meso*-tartaric acid). They must, therefore, be diastereotopic and indeed the substitution criterion (replacement of H_A and H_B by D) gives two diastereomers (XXIX) and (XXX) in which C-3 is pseudoasymmetric centre with *r* and *s* configuration respectively (see Chapter 4). The C-3 centre in XXVIII may, therefore, be called a *pro*-pseudoasymmetric centre or perhaps more logically (Mislow and Siegel 1984) a prostereogenic but proachirotopic centre. H_A is *pro-r* (denoted by H_r) and H_B is *pro-s* (denoted by H_S): a conclusion which can also be reached by the application the 'Top-right' mnemonic (C-2 has *R* configuration and so precedes C-4 which has *S* configuration and becomes the fiducial ligand 'a' and H_A which is on the right side is thus *pro-r*).

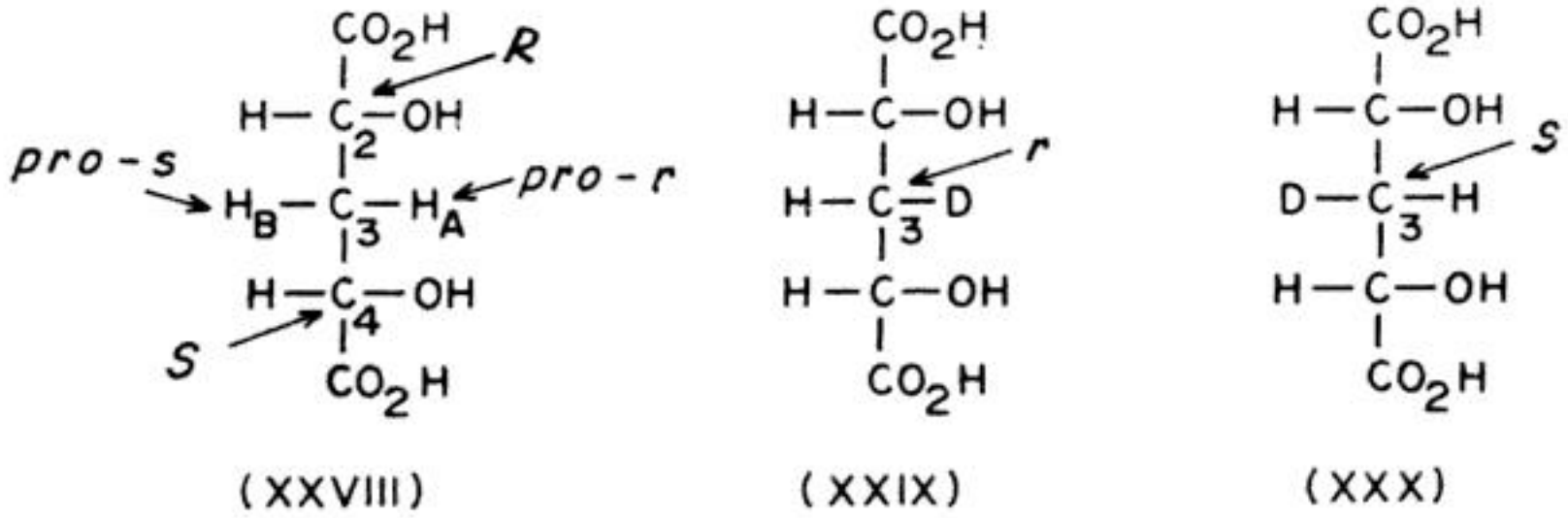


Figure 6.12 A molecule with pro-pseudoasymmetric centre

3. Molecules with more than one prochiral centre. Citric acid with three prochiral centres provides an interesting example in which enantiotopic and diastereotopic H's coexist. All the four methylene H's (see structure XXXIa) (Figure 6.13), designated H_A, H_B, H_C, and H_D are distinguishable (by enzymes as well as by NMR under appropriate conditions). The topic descriptors to each of the H's can be assigned very easily with the help of the 'Top-right' mnemonic. The CO_2H group evidently corresponds to the fiducial ligand 'a' both at C-2 and C-4. The top-right and bottom-left mnemonics label the four H's directly or by default, as *pro-S* (H_A), *pro-R* (H_B), *pro-R* (H_C), and *pro-S* (H_D), denoted by the first

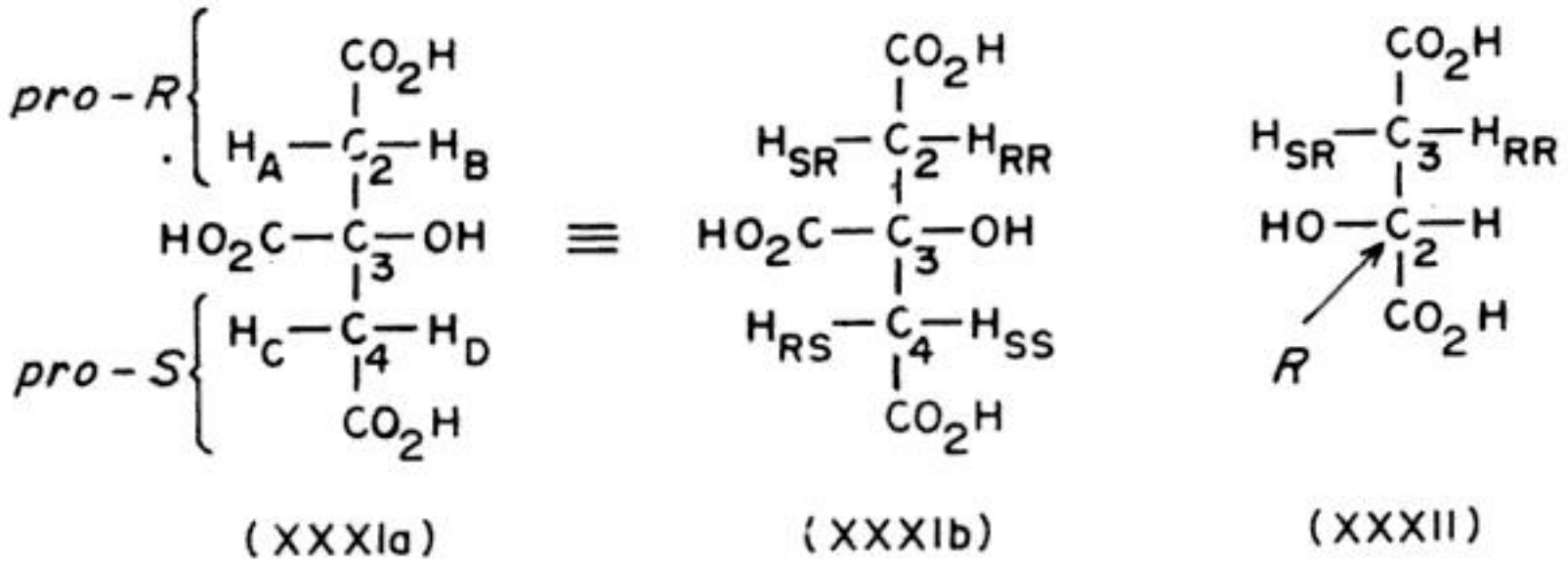
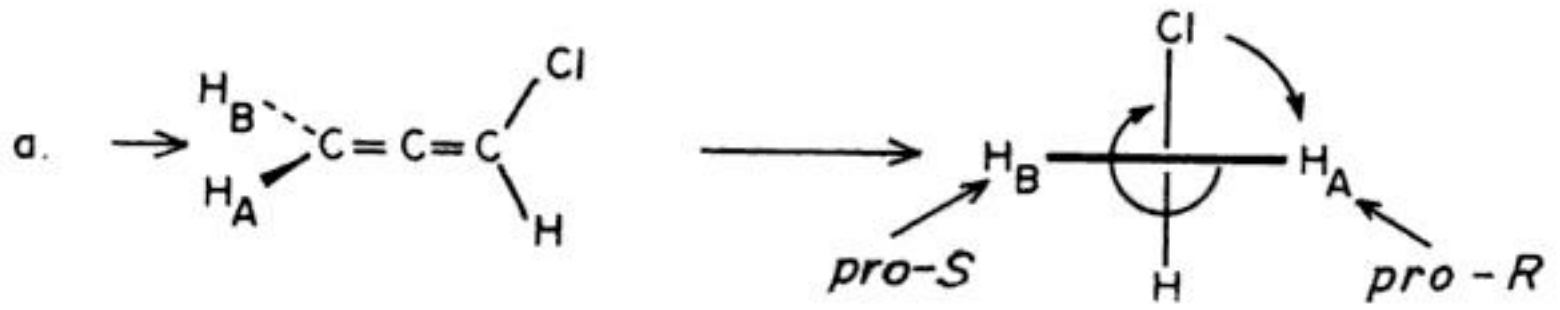


Figure 6.13 Methylene protons in citric acid and malic acid

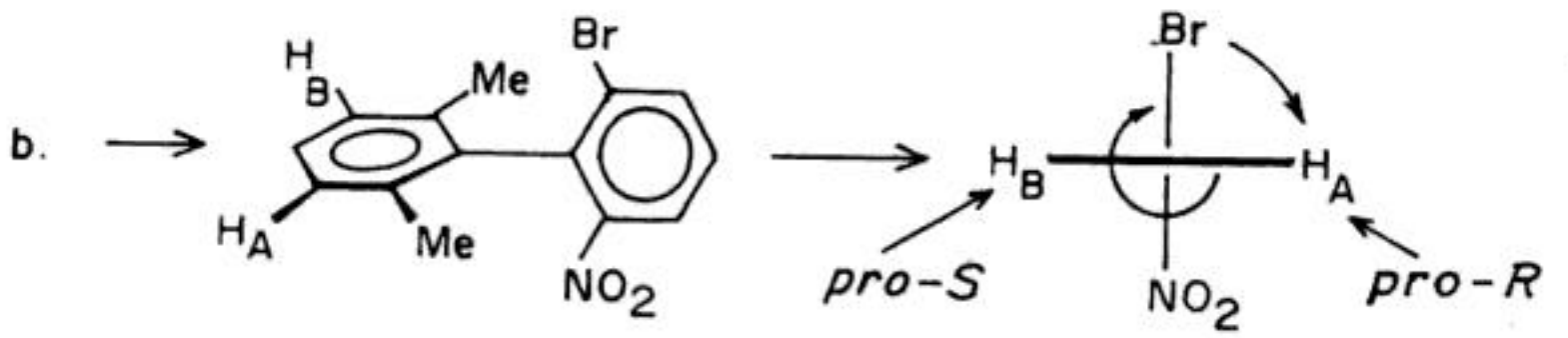
subscripts of the H's as shown in XXXIb. The C-3 atom is also prochiral, the two CH_2CO_2H being enantiotopic. The OH group at C-3 is the fiducial ligand 'a' and according to right-top mnemonic, the upper CH_2CO_2H is *pro-R* and the lower one is *pro-S*. The subscripts of the groups are now added to the individual subscripts of H's which are thus labeled H_{SR}, H_{RR}, H_{RS}, and H_{SS} (as in XXXIb) respectively. The double indexing system first used by Retey and Robinson (1982) in a somewhat modified form has the advantage that it makes the topic relationship (enantiotopic and diastereotopic) immediately obvious; thus H_{SR} is diastereotopic with H_{SS} and H_{RR} but enantiotopic with H_{RS}.

4. Molecules with a chiral as well as a prochiral centre. A prochiral centre in a molecule containing one or more chiral elements usually contains diastereotopic ligands which may also be specified by topic descriptors. They are first labeled with appropriate *R* and *S* subscripts following the top-right mnemonic and to these is added the configurational descriptor (*R* and *S*) of the nearest chiral centre with the proviso that when two nearest chiral centres are equidistant, the one in the higher priority branch at the prochiral centre is chosen. The two diastereotopic H's at C-3 of *R*-malic acid (XXXII in Figure 6.13) are thus denoted by paired subscripts as H_{SR} and H_{RR}. It may be noted that the second subscripts of the citric acid H's and the malic acid H's have different connotations the former referring to group prochirality and the latter to central chirality. The two situations are, however, mutually exclusive since a chiral molecule (e.g., malic acid) cannot have enantiotopic ligands (prochiral groupings), there being no reflection symmetry.

5. Molecules with a prochiral axis. Molecules like allenes, biphenyls, and analogues when suitably substituted may have a pair of stereoheterotopic ligands. The usual way to assign topic descriptors to such ligands is to project the molecule on to a plane in the way it is done for determining *R* and *S* chirality (shown for monochloroallene and for a biphenyl in Figure 6.14), preferably with the enantiotopic ligands in the front. To assign topic descriptor to H_A, its priority is elevated



(XXXIII)



(XXXIV)

Figure 6.14 Enantiotopic ligands at prochiral axis

over that of H_B (alternatively, H_A may be hypothetically replaced by D). If the configuration of the hypothetical chiral axis is *R* as in XXXIII, then H_A is *pro-R* and is denoted by H_R and so on. Similar procedure is adopted for the biphenyls and illustrated in XXXIV. One may use the top-right mnemonic in these cases as shown by short arrows but it does not offer any advantage. To make the mnemonic operative, the front ligands (be they paired or unpaired) must be placed on the horizontal line so that the arrangement resembles a Fischer projection of a tetrahedral centre. Under this condition, the projection may not be needed since one can immediately see which of the enantiotopic ligands is on the right or on the left of the fiducial ligand (Cl in XXXIII and Br in XXXIV).

6. Molecules with a prochiral plane. The assignment of descriptors to heterotopic ligands in molecules with a prochiral plane is best illustrated with an example, the paracyclophane (VII) in Figure 6.5a. There are several pairs of enantiotopic H's; only one pair, H_A and H_B is shown (they are not interchangeable by a C_n axis but by a σ plane). To give a descriptor to H_A, it must be given priority over H_B (alternatively, it may be replaced by D) so that the bottom methylene C (underlined) becomes the pilot atom (Chapter 5) and the hypothetical chiral plane has *R* configuration; so H_A is *pro-K* (H_R). Similarly, when H_B is considered, the top methylene C (underlined) becomes the pilot atom and H_B becomes *pro-S* (H_S).

7. Molecules with prostereogenic but proachiral centres. A variety of prostereogenic molecules contain diastereotopic ligands which on substitution give achiral diastereomers, i.e., they do not have prochiral centre or centres. Such ligands may be called *pro-Z, pro-E, pro-cis, pro-trans, pro-endo, pro-exo* etc. depending on the nature of the diastereomers formed on their substitution. The nomenclature is self-evident and need not be discussed further.

8. Re and Si system of nomenclature for ligands. A different system of nomenclature for stereoheterotopic ligands has been proposed by Prelog and Helmchen (1972), somewhat similar to that used to differentiate heterotopic faces by Hanson (vide infra). The tetrahedron represented by CabXX (A in Figure 6.10) is divided into two enantiomorphous halves along the a-C-b vertical plane (a two-dimensional chiral simplex). Each half-space contains three ligands, a, b, and X (in addition to the ligating C atom) which when seen in their priority sequence describe a clockwise or an anticlockwise direction. The half-space in which they are clockwise (the observer must be in the same half-space) is designated *Re* and the other is designated *Si*. The ligands are given the designations of the half-spaces they reside in. Thus X_A in the structure (A) falls in the *Re* half-space (a>b>X) and is designated *Re* (X_{Re}) and so on. When X has the lowest or the highest priority, both Hanson's and Prelog's methods give concordant results. But when X has a priority in between those of the unpaired ligands, disconcordant results are obtained as in glycerol (XXV). Now the half-spaces are to be designated by the direction a → X →b (since a>X>b) rather than a→ b → X (or X→a→b) and the right half-space becomes *Si* in A and X_A is designated *Si*. Hanson's method is already extensively used in the literature and a change of terminology at this stage is undesirable particularly since the correspondence between *pro-R* (or *pro-S*) ligands and products of isotopic substitution of *R* (or *S*) configuration is very convenient in biochemical studies.

6.3.2 Symbols for stereoheterotopic faces

(A) Enantiotopic faces. Enantiotopic faces of molecules are two-dimensionally chiral. Hanson's method for specification of such faces is exremely simple. If the three ligands arranged in priority order appear clockwise in a face, the face is *Re* and if they appear anticlockwise, the face is *Si* as shown in the case of acetaldehyde (XXXV) (Figure 6.15). If the double bond contains two specifiable trigonal atoms, a face may be uniquely defined by two symbols one for each specifiable atom. This is illustrated with maleic acid (XXXVI) (here the two faces are homotopic) and fumaric acid (XXXVII) (the two faces are enantiotopic). Olefins of the type (XXXVIII) in which one terminal contains two equivalent ligands require,* however, only one symbol *Re* or Si depending on the priority

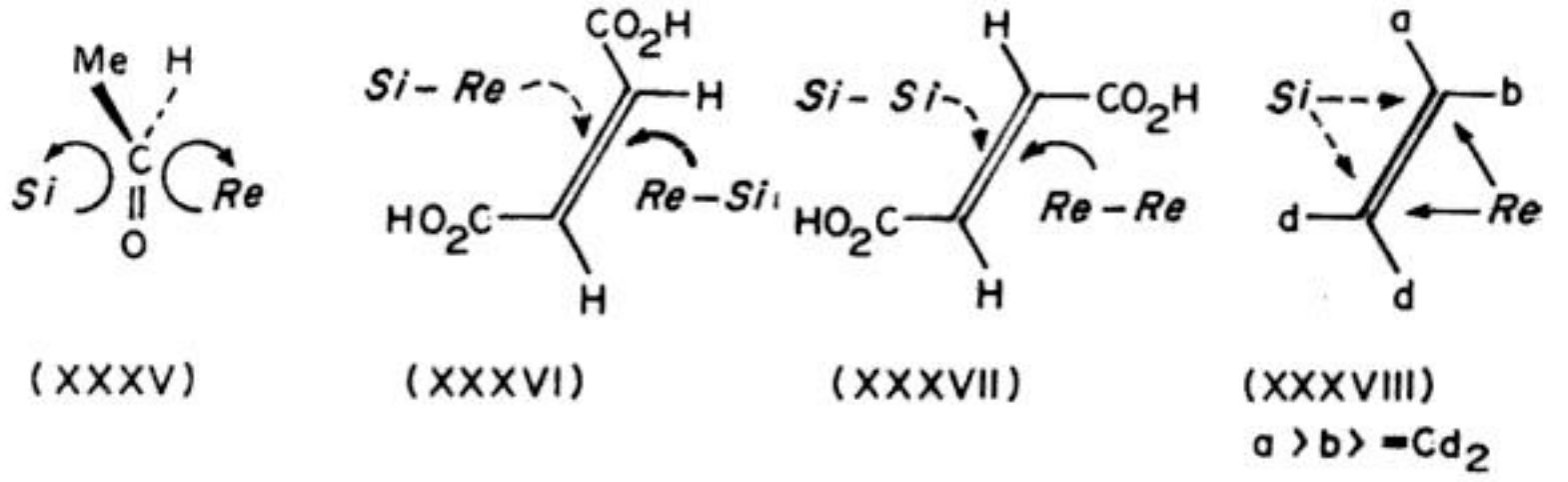


Figure 6.15 Nomenclature of heterotopic faces in achiral molecules

order of a, b, and $= Cd_2$ (in the Figure, the priority order is $a > b > = Cd_2$): see also Kaloustian and Kaloustian 1975.

In the case of molecules containing prochiral bivalent atoms such as the dialkyl sulphide (XI) (Figure 6.6), the lone electron pair is regarded as a phantom ligand having the least priority so that the right face of the molecule is *Re* and the left face *Si*.

(B) Diastereotopic faces. The two carbonyl faces of 3-hydroxybutanal (XXXIX) (Figure 6.16) are diastereotopic (presence of a chiral centre). The right face is *Re*

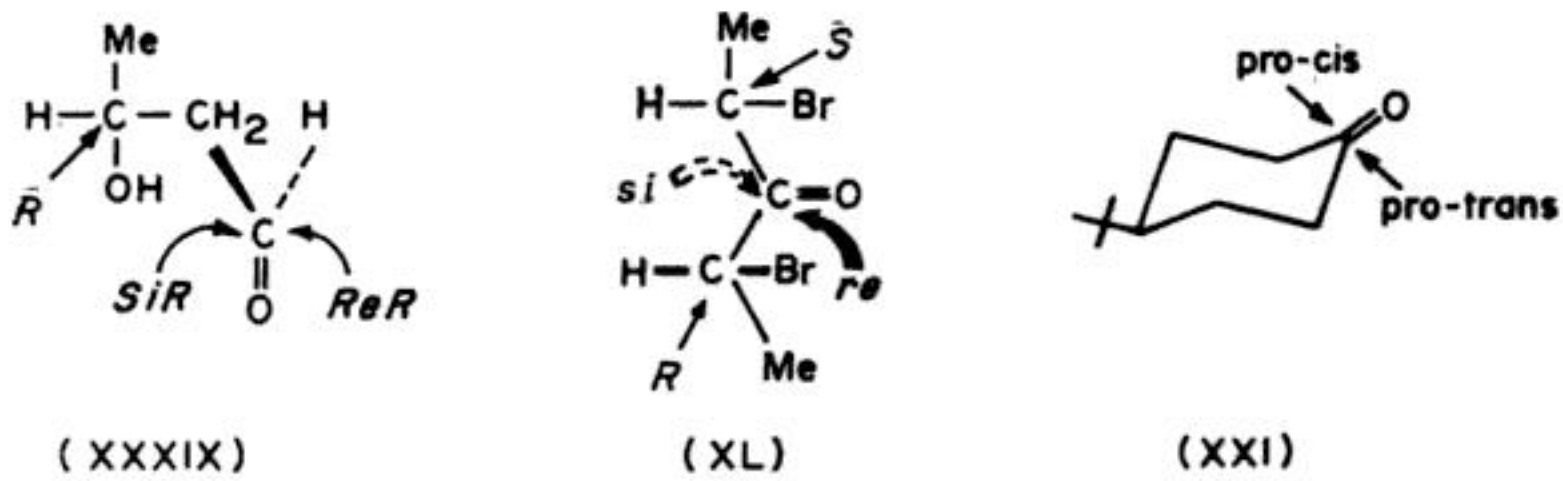


Figure 6.16 Nomenclature of heterotopic faces (continued)

*A double bond is important in assigning two-dimensional chirality to a plane.

and the left face is *Si* according to the above procedure to which a further subscript *R* (the chirality descriptor of C-3) may be added so that the double-lettered subscripts *ReR* and *SiR* are truly diastereotopic.

If the trigonal atom is *pro*-pseudoasymmetric as in the general formula G_R-CO-G_S (G_R and G_S are enantiomeric groups), the two diastereotopic faces as in XL may be designated by *re* (upper face) and *si* (lower face): the *R* group gets precedence over *S*. The lower case alphabets are used to indicate reflection-invariance.

The two diastereotopic faces (axial and equatorial) of 4-*t*-butylcyclohexanone (XXI) are designated *pro-cis* and *pro-trans* (upper and lower faces respectively) on the basis that a substituent when added to the upper face becomes cis and when added to the lower face becomes trans with respect to the *t*-butyl group. The actual products of addition may, however, have opposite designations, e.g., trans instead of cis and so on (compare the alcohols obtained on reduction of XXI with hydrides in Figure 6.9).

6.4 Stereoheterotopic ligands and NMR spectroscopy

NMR spectrosocopy can distinguish between nuclei which reside in different environments so that they are shielded or deshielded to different extents. Such nuclei differ in their chemical shifts and are called chemical shift non-equivalent or *anisochronous*. Homotopic ligands reside in identical environments and cannot be distinguished by NMR; they show chemical shift equivalence and are called *isochronous*. Enantiotopic nuclei are also isochronous since they reside in environments which are geometrically equivalent and differ only in topography. NMR is an achiral probe and cannot in itself make topographical (chiral) discrimination. Enantiotopic nuclei can be distinguished by NMR only if a diastereomeric relationship be established by using a chiral solvent or a chiral additive with which the substrate forms an *associate* (solvate, complex etc.). Diastereotopic ligands (or nuclei) reside in different environments and are, in principle, always anisochronous. The difference in chemical shifts (anisochrony) is, however, often very small (1 ppm or less) and may even be undetectable in which case, one speaks of chance or accidental isochrony. Use of higher fields or of ^{13}C-NMR instead of ^{1}H-NMR can be helpful in increasing anisochrony, as, especially in ^{1}H-NMR, can a change of solvents.

6.4.1 Diastereotopic ligands and NMR spectroscopy

Different types of diastereotopic nuclei (mostly protons) and their spectral behaviour are discussed under different headings.

1. Geminal ligands adjacent to a chiral centre. Nair and Roberts (1957) first showed that methylene protons adjacent to a chiral centre are chemically non-equivalent. A typical example is the methyl ester of 2,3-dibromo-2-methylpropionic acid (XLI) (Figure 6.17) in which H_A and H_B are anisochronous and appear in the NMR spectrum as an AB-quartet ($J_{AB} = 10$ Hz) (see diagram). Although the fact

that they are not symmetry related (diastereotopic) is itself a sufficient cause for anisochrony, a conformational factor is also involved (vide infra).

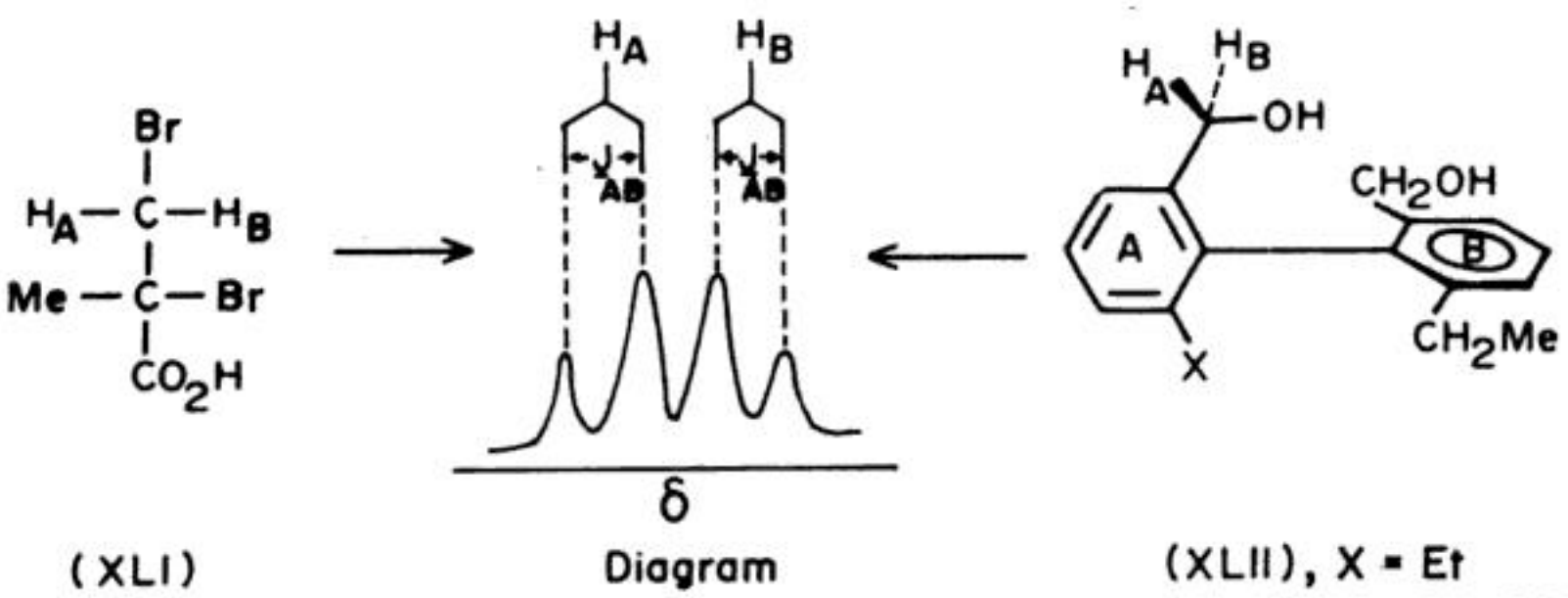


Figure 6.17 Non-equivalence of geminal protons

2. Geminal nuclei adjacent to a chiral axis. Appropriately substituted biphenyls possess a chiral axis (Chapter 5) and suitably placed geminal ligands therein may be diastereotopic and anisochronous. Thus the methylene protons in each of the CH_2OH group in the biphenyl (XLII) are diastereotopic (no σ plane bisecting the H_A-C-H_B angle) and so anisochronous. They appear as an AB-quartet (with δ_A and δ_B at 4.05 and 4.20 ppm respectively and $J_{AB} = 12$ Hz) (Meyer and Meyer. 1963). The biphenyls need not be necessarily chiral since chirality is not a necessary condition for diastereotopicity. In the achiral biphenyl (XLIII), the geminal hydrogens in each CH_2OH group in ring A are diastereotopic (absence of σ plane bisecting H_A-C-H_B angle)* and so appear as an AB-quartet. The geminal hydrogens in CH_2OH attached to ring B in XLIII, on the other hand, are enantiotopic (related by a σ plane) and thus isochronous.

3. Diastereotopic ligands in cis-trans isomers. The cis and trans isomers of N-benzyl-2,6-dimethylpiperidine (XLIV and (XLV) (Figure 6.18) are classical examples of molecules which are distinguished by NMR. In the cis isomer, the

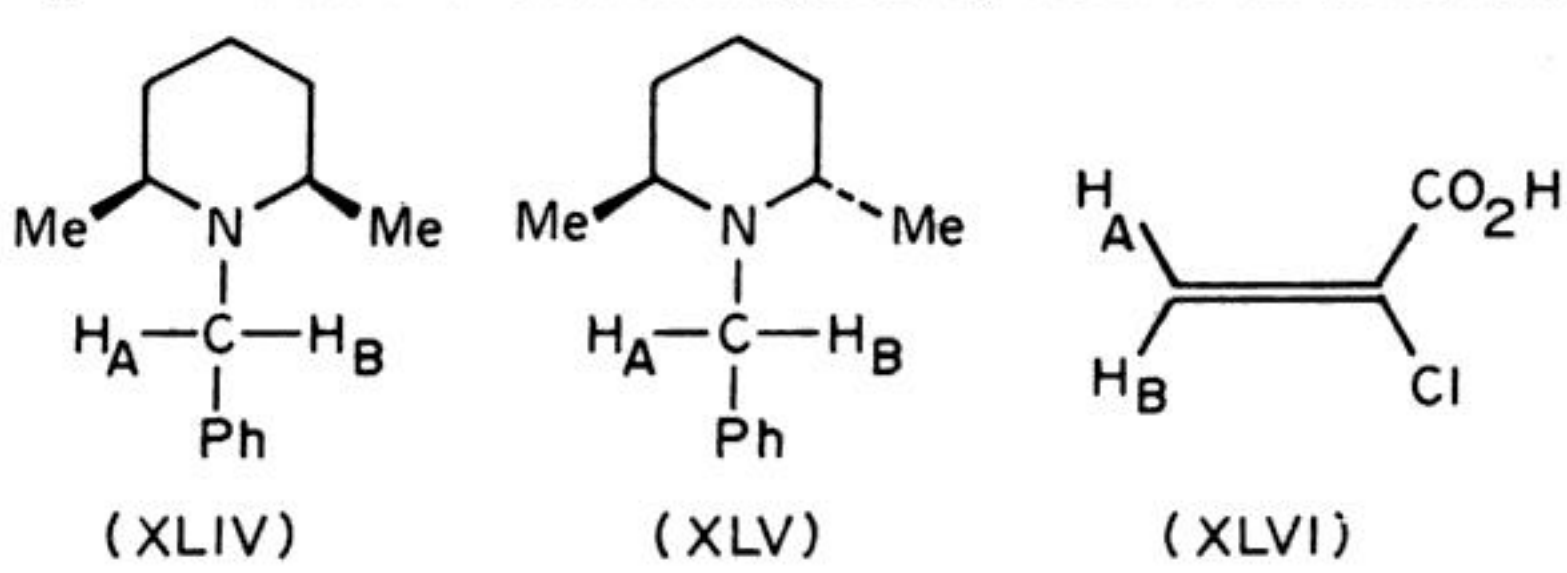


Figure 6.18 Non-equivalence of geminal protons in cis and trans isomers

*See Jennings (1975).

benzylic protons H_A and H_B are enantiotopic and so isochronous appearing as a sharp singlet at δ 3.70 ppm (isochronous nuclei do not visibly couple with each other). On the other hand. H_A and H_B in the trans isomer are diastereotopic and so anisochronous. They form an AB-quartet centred at δ 3.63 ppm ($J_{AB} = 14$ Hz). (Hill and Chan, 1965).

Another simple example showing geminal anisochrony of this type is 2-chloropropenic acid (XLVI) in which the two terminal hydrogens form an AB-quartet with an appreciable chemical shift difference (0.85 ppm).

4. Diastereotopic ligands in molecules devoid of stereogenic centres. Citric acid (XXXI) (Figure 6.13) and analogous compounds, e.g., $PhCH(OCH_2CH_3)_2$ contain two enantiotopic pairs of hydrogens. H_A & H_C and H_B & H_D (labels as in citric acid). Each pair being isochronous exhibits identical chemical shifts. A member of an isochronous pair (say H_A) is, however, diastereotopic and so anisochronous with a member of the other pair (say H_B) and the NMR spectrum shows them as an AB-quartet (of two protons each) similar to the diagram (Figure 6.17). In the case of $PhCH(OCH_2CH_3)$, the methylene protons are further split by the adjacent methyl hydrogens. The two methyl groups, on the other hand, are enantiotopic and isochronous.

6.4.2 Diastereotopic faces and NMR spectroscopy

The case of (−)-menthyl esters of maleic and fumaric acids (XLVII) and (XLVIII) (Schurig 1977) is a very instructive one. The two faces of the maleate are homotopic (related by a C_2 axis) while those of the fumarate are diastereotopic. The two olefinic protons in each are, however, homotopic (interchangeable through C_2 axes). The esters form complexes with iron tetracarbonyl, $Fe(CO)_4$. The faces of the maleate being homotopic, a single complex is formed (cf. epoxidation). The two olefinic protons are now diastereotopic (by internal comparison) due to the absence of C_2 axis and σ plane. They are thus anisochronous and give rise to an AB-quartet in NMR.

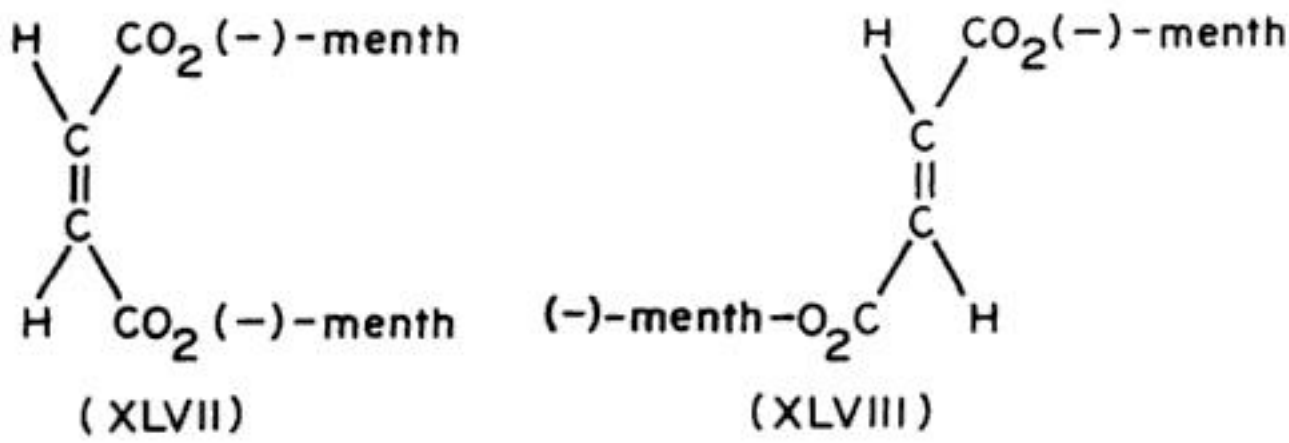


Figure 6.19 Anisochrony arising out of stereoheterotopic faces

The fumarate (XLVIII), on the other hand, gives two diastereomeric complexes in each of which the olefinic protons are homotopic (related by a C_2 axis) and so isochronous. The two olefinic protons in one distereomer are, however, diastereo-

topic with the two olefinic protons of the other diastereomer (by external comparison). The diastereomeric complexes thus give two singlets resulting in two peaks (not necessarily of equal intensity) for the olefinic protons (see Eliel 1982). Thus the two original esters are distinguished by NMR through complexation with faces of different topicity.

6.4.3 Diastereotopic nuclei in conformationally mobile systems

If two diastereotopic nuclei interchange sites at a rate faster than the NMR time scale (determined by the chemical shift difference of the two nuclei)*, they become isochronous due to averaging of the environments around each. Thus the ^{19}F-NMR of 1,1-difluorocyclohexane (XLIX) (Figure 6.20) shows a sharp singlet for the two diastereotopic fluorines because of rapid exchange between the conformers (XLIXa) and (XLIXb). However, at a temperature below −50°C, the rate of exchange becomes appreciably slow on the NMR time scale and they show the expected AB-quartet. On the other hand, in the conformationally rigid molecule (L), the two fluorine atoms are always anisochronous.

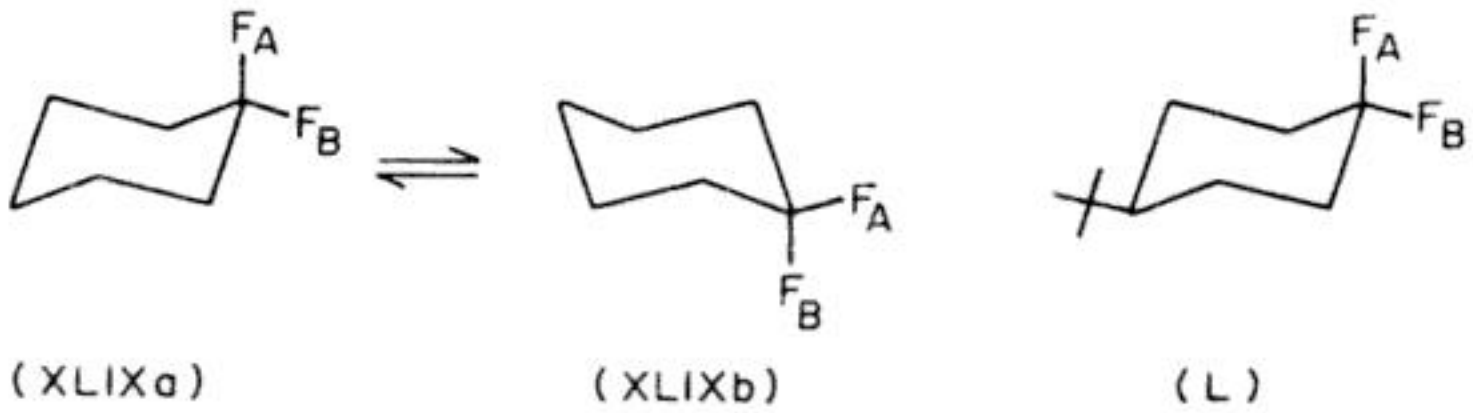


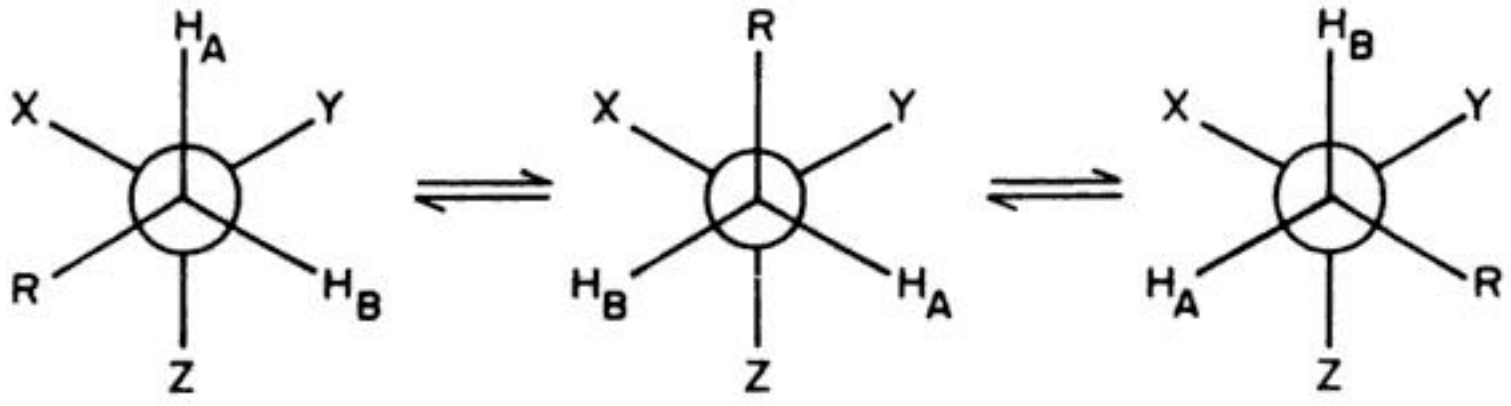
Figure 6.20 Diastereotopic ligands in conformationally mobile system

6.4.4 Intrinsic anisochrony and conformational anisochrony

A conformationally mobile chiral molecule of the type, RCH_AH_B-CXYZ exists usually in three distinct conformations (M), (N), and (O) (Figure 6.21). The effective chemical shift of H_A is given by equation (1) and that of H_B by equation (2) in which n_M, n_N and n_O represent the fractional populations of the respective conformers at a particular temperature and δ_{XY}, δ_{YZ}, and δ_{ZX} the chemical shifts† in conformers with the proton concerned placed between X and Y, Y and Z, and Z and X respectively. Assuming that δ_{XY} for H_A equals δ'_{XY} for H_B and so on (which may not be exactly true) and that the chemical shifts are the weighted average shifts of the contributing conformers (which is possibly true), the difference of the chemical shifts of H_A and H_B can be obtained as the difference between expressions (1) and (2) which primarily depends on the relative populations

*The rate (k) of a process is fast on the NMR scale if $k >> \frac{1}{2}\sqrt{2\pi\Delta\nu}$ where $\Delta\nu$ is the difference in chemical shifts (in Hz) of the exchanging nuclei (see also Chapter 9).

†Actually, these values will vary slightly for the two protons and hence those for H_B are denoted with primes in equation (2).

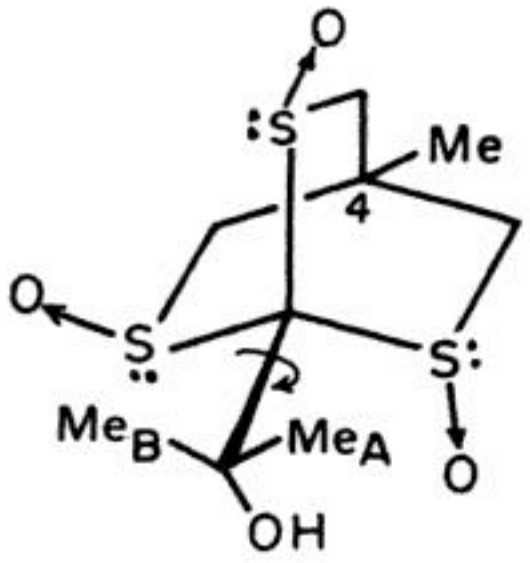


$$\delta_{H_A} = n_M \delta_{XY} + n_N \delta_{YZ} + n_O \delta_{ZX} \quad \text{.....(1)}$$

$$\delta'_{H_B} = n_O \delta'_{XY} + n_M \delta'_{YZ} + n_n \delta'_{XZ} \quad \text{.....(2)}$$

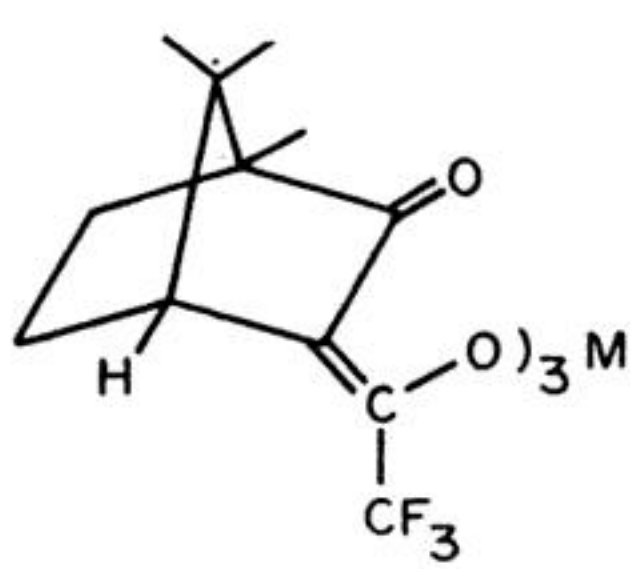
Figure 6.21 Intrinsic anisochrony in conformationally mobile system

(n_M, n_N, n_O) of the conformers. Now at a high temperature, the three conformers should be almost equally populated and the chemical shift difference ($\delta_A - \delta_B$) should tend to be zero: however, this is not observed in practice. The reason is that the environment of H_A in the conformer (M) with H_A flanked by X and Y is not exactly the same as that of H_B in the conformer (O) with H_B flanked by X and Y since in the former, R is anti to Y while in the latter, R is anti to X. The residual anisochrony at high temperature which is independent of population (also of temperature) is known as '*intrinsic anisochrony*' in contrast to the other component known as *conformational anisochrony* which originates from the difference in conformer populations and is temperature dependent (see Jackman and Sternhell 1969). Intrinsic anisochrony freed from conformational anisochrony at room temperature has been demonstrated using substrates like the bicyclic trisulphoxide (LI) (Figure 6.22) in which the three conformers arising out of rotation around C-C bond (as shown) are equivalent due to the presence of a C_3 axis (passing



δ_{AB} = 0.038 ppm

(LI)



M = Eu, Yb, Pr

(LII)

Figure 6.22 (a) Intrinsic anisochrony. (b) chiral shift reagents

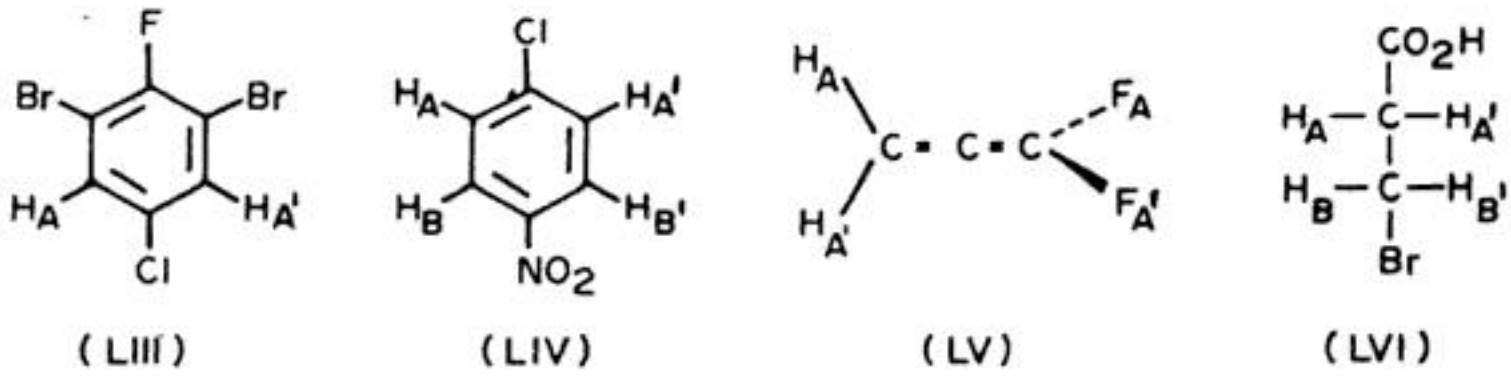


Figure 6.23 Isogamous and anisogamous nuclei

anisogamy of isochronous nuclei is expected must therefore correspond to A_2B_2 or, more precisely, AA′BB′ type such as LIV. In this molecule J_{AB} is not equal to $J_{A'B}$ (nor J_{BA} to $J_{B'A}$) and H_A and H_A', as also H_B and H_B' are thus anisogamous. Even this cannot be generalised since 1,1-difluoroallene (LV) or CH_2F_2 which corresponds to AA′BB′ type has a pair of H's and a pair of F's which are isochronous as well as isogamous. Some symmetry restriction has to be imposed on such molecules in order to have anisogamy in isochronous nuclei. According to Mislow (cited by Eliel 1982), if in a spin system of the type AA′BB′, substitution of one of the B's by a different nucleus Z leads to a system A_2BZ in which the two nuclei A and A′ are no longer interchangeable by symmetry operation of any kind (C_n or S_n), then B and B′ are anisogamous as in LIV; if, on the other hand, in A_2BZ, two A's are interchangeable by a symmetry operation, then the two B's are isogamous as in LV*. The methylene protons in 3-bromopropionic acid (LVI) are examples of enantiotopic nuclei which are isochronous and anisogamous (the molecule conforms to the above symmetry criterion).

6.5 Prostereoisomerism and stereoisomerism

Molecules with stereoheterotopic ligands and faces are prostereogenic and an appropriate chemical (or biochemical) reaction transforms them into stereoisomers. The stereochemical outcome and the relative rates of reactions depend on the topic relationship of the ligands (or faces), the nature of the reagents (chiral and achiral), and the reaction conditions in general. In reactions with heterotopic ligands or faces, one or the other of the stereoisomers is formed in excess leading to what is known as stereoselective synthesis. The reactions may be discussed under two broad headings: chemical reactions using laboratory reagents and biochemical reactions mediated through enzymes.

6.5.1 Chemical transformations of heterotopic ligands and faces

The differential behaviour of stereoheterotopic ligands and faces provides the basis of many stereoselective reactions which will be discussed in chapters on dynamic

*Replacement of one H_B in LIV by Z makes the two H_A's constitutionally heterotopic and so H_B and H_B' are anisogamous (which also holds for H_A and H_A'). Replacement of either a H or a F atom in LV by Z gives an allene in which the two homomorphic nuclei (F's or H's) are enantiotopic (isochronous) and so both H's and F's in LV are isogamous.

stereochemistry. Here only a few general observations which almost parallel those under NMR spectroscopy are made.

(*i*) Homotopic ligands and faces are identical in all respects and hence any reaction (substitution or addition) involving them, whether it is carried out with chiral or achiral reagents (including environments), gives identical product. In case two or more products are formed, they are obtained in the same ratio from the two ligands or faces. Thus chlorocarbene (:CHCl) adds to either of the two homotopic faces of *cis*-2-butene giving two diastereomeric products; a cyclopropane with all the three substituents cis and a cyclopropane with Cl trans to the two cis Me groups. The ratio of the two is the same for the reaction on either side.*

(*ii*) Enantiotopic ligands or faces with achiral reagents or in achiral environments give rise to two enantiomers via enantiomeric transition states which are of equal energy. The two enantiomeric products are, therefore, formed in equal amounts. If the reagent is chiral or if the reaction is carried out in a chiral medium, two diastereomeric transition states may be formed leading either to two enantiomers or to two diastereomers (under kinetical control) in unequal amounts (see Chapter 13 for details).

(*iii*) Diastereotopic ligands and faces undergo reactions, either with achiral or chiral reagents, through diastereomeric transition states which differ in all their thermodynamical properties and two or more diastereomeric products are formed at different rates and thus in different amounts. Such reactions whether carried out under kinetical or under thermodynamical control are stereoselective to a greater or lesser extent. By changing the reaction conditions and the nature of the reagents, stereoselectivity may be improved even to the extent of 100%.

6.5.2 **Biochemical transformations of heterotopic ligands and faces**

Biochemical transformations are carried out through the agency of enzymes (as catalysts). Enzymes are protein molecules constituted of a large number of optically active amino acids and represent a class of most efficient chiral reagents.† As such they are capable of discriminating between two ligands and faces which are enantiotopic by external comparison (as in enantiomers) or by internal comparison (as in prochiral molecules). Like a true catalyst, an enzyme adsorbs the substrate molecules on its surface and orients them in such a fashion that the reacting group is brought in juxtaposition to the active site present in the enzyme itself (known as a prosthetic group) or in a suitably bound coenzyme. The interactions between the enzyme and substrate are highly specific so that only one out of the two diastereomeric transition states is favoured, the other being almost non-existent due to large difference in free energies of activation. Thus the enzymes usually act on only one of the two enantiomers—a property known as stereospecificity—and in the case of prochiral molecules with only one of the enantiotopic ligands or faces—a property known as stereoselectivity (see Chapter 13 for

*No experimental proof can, however, be given.

†It is usually the secondary and tertiary structures (e.g., right- or left-handed helices) of proteins (rather than the chiral centres) which give rise to the active sites in enzymes and are ultimately responsible for stereospecificity.

terminology). The first kind of reactions is illustrated by the enzymatic hydrolysis of the N-acetyl derivatives of a D,L-pair of amino acids when one of the enantiomer (usually the derivative of the naturally occurring L-isomer) is hydrolysed much faster (sometimes by a factor of 10^4) than the other. The second kind is illustrated by the phosphorylation of glycerol when the *pro*-R hydroxymethylene group is esterified exclusively by adenosine triphosphate (ATP) in the presence of an enzyme (glycerol kinase).

Enzymatic discrimination between enantiomers and between enantiotopic ligands is, in most cases, almost total. For detailed study, the reader is referred to two textbooks (Bentley 1970; Alworth 1982) and many reviews (see Eliel 1982). Two examples of enzymatic discrimination of stereoheterotopic ligands (in addition to the above) are discussed below.

(A) Enzyme mediated reduction of acetaldehyde to ethanol.* Acetaldehyde is reduced to ethanol with yeast alcohol dehydrogenase (YAD) in the presence of the hydride donating coenzyme NADH (reduced form of nicotinamide adenine dinucleotide). In the reverse reaction, ethanol is oxidised to acetaldehyde by the oxidised form of the coenzyme (NAD^+) (Figure 6.24). Several stereochemical possibilities exist in this apparently simple oxidation-reduction sequence. Acetaldehyde has two enantiotopic faces and hydride may be transferred to either face. Ethanol has two enantiotopic hydrogens (H_R and H_S) and either of them may be transferred to NAD^+. NAD^+ has two faces (*Re* and *Si*) and either of them can accept a hydride. Finally, NADH has two enantiotopic hydrogens (H_R and H_S) and either of them may be transferred in the reduction step. The facts which have been established are: (i) Only the *Re* faces of both acetaldehyde and NAD^+ are involved and (ii) only H_R of both ethanol and NADH participates in the reactions. (H or D which are transferred are circled in the Figure). The proofs are as follows (consult the Figure) :

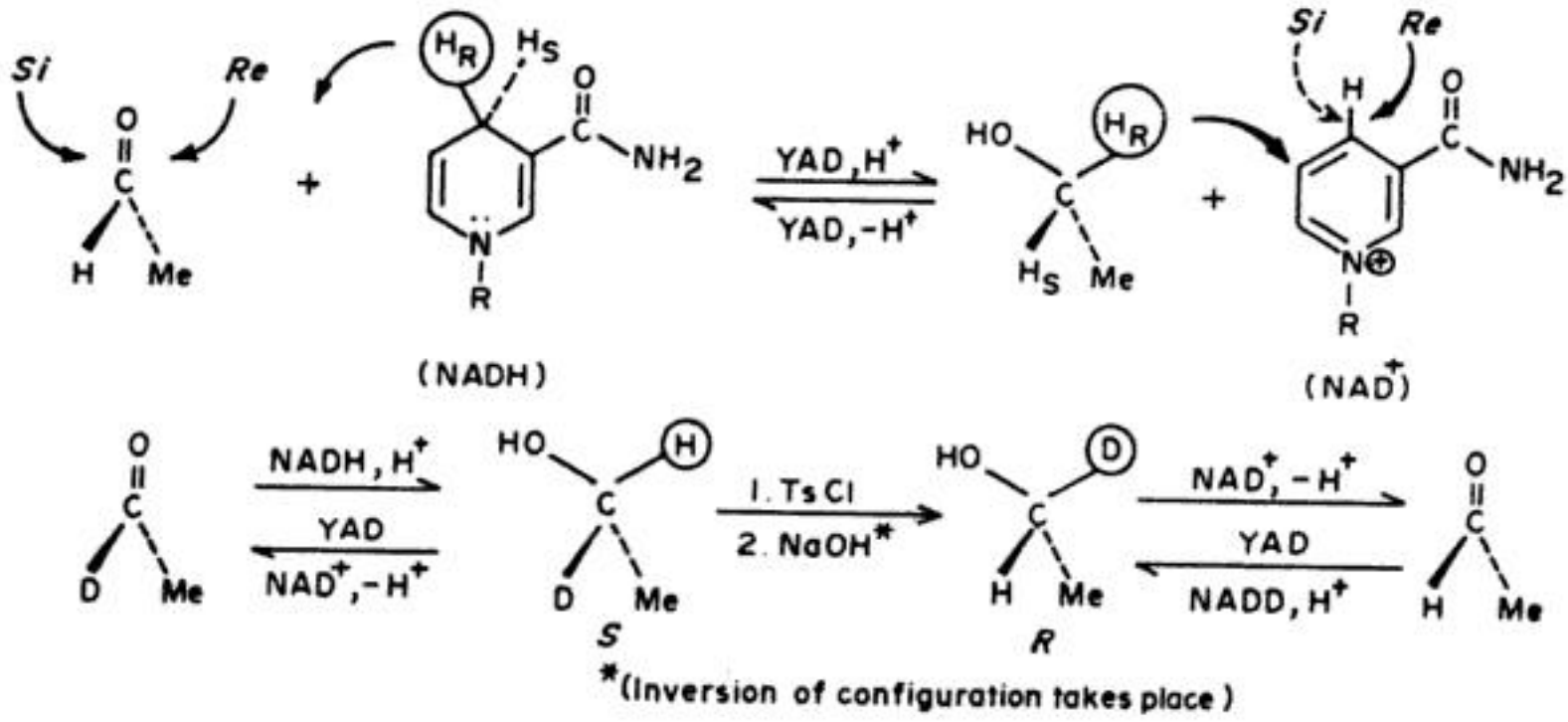


Figure 6.24 Enzymatic transformation of CH_3CHO-CH_3CH_2OH
(R stands for the rest of the molecule)

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* See also Eliel (1980).

(*i*) When acetaldehyde-1-*d* is reduced, *S*-ethanol-1-*d* is formed exclusively which proves that the *Re* face of acetaldehyde is attacked.

(*ii*) In the reverse reaction, *S*-ethanol-1-*d* gives back the original deuterated acetaldehyde which means that the circled H (H_R in ethanol) is transferred.

(*iii*) Both the above points have been further confirmed by converting *S*-ethanol-1-*d* into *R*-ethanol-1-*d* and submitting it to NAD^+—YAD oxidation. Acetaldehyde devoid of deuterium is obtained meaning that D (circled) which occupies the position of H_R in ethanol is transferred.

The complete stereoselectivity of this oxidation- reduction process means that the orientations of the substrates, the enzyme's binding sites, and the coenzyme associated with it are such that one of the two diastereomeric transition states for a particular reaction (oxidation or reduction) is favoured greatly over the other so that only one ligand or face is involved in the hydride transfer.

(B) Citric acid cycle (part). Citric acid (XXXI) (Figure 6.25) is a suggested intermediate in the enzymatic conversion of pyruvic acid into 2-oxoglutaric acid (LVIII). On carbonylation of pyruvic acid with labeled C^*O_2, oxaloacetic acid with C* at the top CO_2H group (LVII) is obtained. Acetylcoenzyme-A ($CH_3COSCoA$) converts it into citric acid with the labeled C* in one of the two CH_2CO_2H groups (that this is the *pro-R* group as shown in the Figure has been proved by experiments with tritiated citric acid). 2-Oxoglutaric acid (LVIII) obtained as an isolable product is found to be labeled only at one of the carboxyl group, the one placed at the top of the structure which means that the enzyme has converted only one of the CH_2CO_2H groups, the *pro-S* one (derived from acetylcoenzyme-A) into $COCO_2H$. This is further confirmed when the other carboxyl group is labeled by using CH_3C^*OSCoA in the second step: the 2-oxoglutaric acid now has C* in the bottom carboxyl group in the structure (LVIII). This once again proves that an enzyme can discriminate between two enantiotopic ligands (Before this was recognised, doubt had been raised regarding citric acid

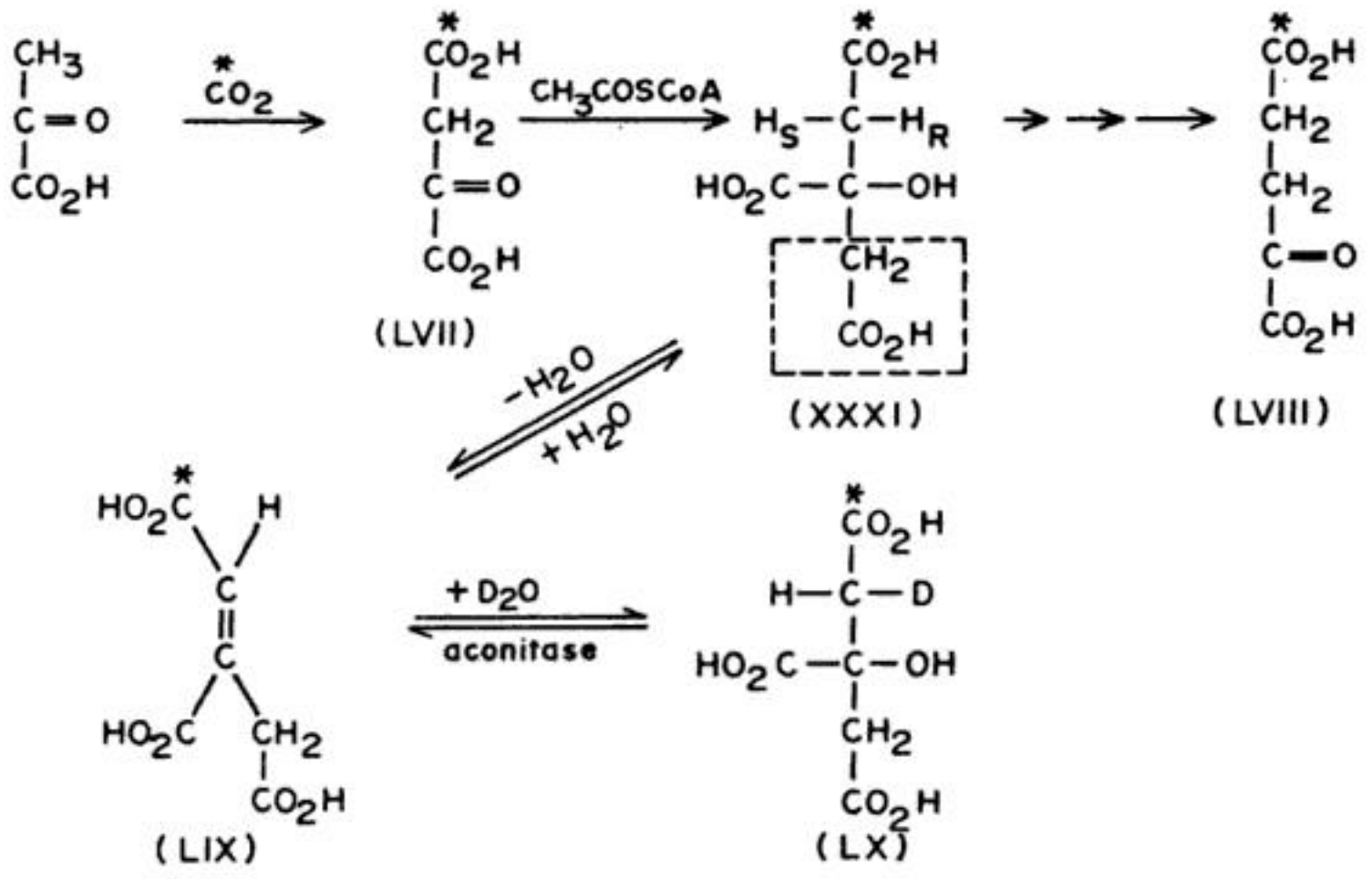

Figure 6.25 Citric acid cycle (a part only)

being an intermediate because of isolation of a singly labeled 2-oxoglutaric acid).

It has been mentioned earlier that the four hydrogens of citric acid are different and so can be distinguished by enzymes. Citric acid is dehydrated reversibly by the enzyme aconitase giving *cis*-aconitic acid (LIX). It has been proved by labeling experiments that it is the *pro-R* hydrogen of the *pro-R* CH_2CO_2H group, i.e., H_{RR} (for nomenclature, see Figure 6.13) which takes part in dehydration (for details, see Arigoni and Eliel 1969). During the enzymatic hydrolysis of *cis*-aconitic acid in D_2O, only one deuterium atom is introduced at the site of H_{RR} to give monodeuterated citric acid (LX).

Before the symmetry criterion was applied to enantiotopic ligands, a mechanistic rationale was given by Ogston (1948) for the ability of enzymes to distinguish between two paired ligands in molecules of the type Cabdd on the basis of three-point contact model (see any biochemistry text). The model, however, while providing a viable kinetic picture, may obscure the intrinsic, symmetry-based difference between heterotopic groups.

6.6 Summary

1. Prostereoisomerism is a property of certain molecules by virtue of which they are capable of giving rise to stereoisomers (enantiomers or diastereomers). Such molecules contain either non-equivalent homomorphic ligands or faces replacement of, or addition to, first one and then the other of which gives stereoisomeric products.

2. Such homomorphic non-equivalent ligands or faces are known as stereoheterotopic; they are further subdivided into enantiotopic and diastereotopic ligands and faces. The former reside in geometrically equivalent molecular environments having mirror-image relationship and replacement or addition gives enantiomeric products. In contrast, diastereotopic ligands or faces reside in diastereomeric environments and on substitution or addition give diastereomers. By default, when ligands or faces reside in completely identical environments, replacement or addition gives rise to a single product; such (equivalent) ligands or faces are called homotopic.

3. The three types of ligands can be distinguished by symmetry criteria also. Homotopic ligands or faces interchange their positions by the operation of symmetry elements of the first kind, i.e., C_n axis. Enantiotopic ligands or faces interchange their positions only by operation of symmetry elements of the second kind, i.e., σ plane, i, and S_n. Molecules with enantiotopic ligands or faces are capable of giving two enantiomers and are known as prochiral. In analogy with chiral or stereogenic elements, the prochiral or prostereogenic elements can be factorised into prostereocentres, prostereoaxes, and prostereoplanes.

4. Descriptors for stereoheterotopic ligands and faces have been devised in close analogy with those used for chiral molecules (*R* and *S*). A ligand is thus called *pro-R* or *pro-S* (and denoted by L_R and L_S respectively) following a certain convention which is consistent with CIP nomenclature and has been explained in the text. A mnemonic has been worked out for the assignment of *pro-R* and *pro-S* symbols to stereoheterotopic ligands.

5. Homotopic nuclei, because of their identical environments have the same chemical shift in NMR and are called isochronous. They are incapable of being distinguished by any physical or chemical method. Enantiotopic ligands are also isochronous by virture of their geometrically equivalent environments. However, their isochrony may be destroyed by creating diastereomeric environments either by taking the spectrum in a chiral medium (solvent) or in the presence of a chiral additive. Ligands in enantiomers (enantiotopic by external comparison) or in prochiral molecules (enantiotopic by internal comparison) may form transient and fast-exchanging associates or complexes with chiral solvents or additives and thereby become anisochronous, i.e., have different chemical shifts. Diastereotopic ligands like diastereomers are always distinguishable in principle and very often in practice. Such nuclei, barring accidental isochrony, are anisochronous.

6. Enzymes can effectively discriminate between enantiomers as well as between enantiotopic ligands and faces. They often react with one of a pair of enantiomers with 100% stereospecificity and with one of the enantiotopic ligands or faces with 100% stereoselectivity. Several examples of enzymatic reactions have been given.

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Chapter 7

Racemisation and Methods of Resolution

7.1 Introduction

Chiral compounds are usually available either in enantiomerically pure (optically active) form, e.g., most of the natural products with one or more chiral centres, or in racemic modification, e.g., those synthesised in the laboratory using achiral substrates, reagents, and media. When an enantiomer is converted into a racemic modification (usually through chemical reactions), the process is known as *racemisation*. Conversely, when a racemic modification is separated into its constituent enantiomers, the process is known as *resolution*. In the latter process, optical rotation is enhanced (a phenomenon called *optical activation*) and equals to that of a pure enantiomer in the case of complete resolution. Racemisation and resolution are thus complementary to each other.

Racemisation is a thermodynamically favourable process (it leads to an increase of entropy, see Chapter 3) and would proceed spontaneously if a convenient pathway is available for the interconversion of the enantiomers. Any mechanism of racemisation, in principle, must operate from either of the enantiomers. Racemisation (in the sense of enantiomerisation) is, therefore, a reversible process, $(+) \rightleftharpoons (-)$, and may formally be regarded as a reaction in which half of one enantiomer undergoes inversion of configuration and the other half retains its configuration, although in fact the two forms remain in dynamic equilibrium in the reaction medium with 50 : 50 population ($\Delta G^\circ = 0$ and so $K = 1$).

If a molecule contains more than one chiral centre and configurational inversion takes place, say reversibly, at one centre only, the product formed is not the enantiomer of the original but a diastereomer, more specifically, an epimer and the process is called *epimerisation*. The two epimers exist in unequal amounts in equilibrium since they differ in their free energies. Epimerisation may be carried out on an enantiomerically pure diastereomer, or on its racemic modification, or on a meso isomer. Racemisation is usually monitored by observing the gradual zeroing of optical rotation. In epimerisation, if rotations of both the epimers are known, the change in optical rotation of the reacting mixture may be used to follow the progress of epimerisation. However, nowadays NMR, particularly ^{13}C-NMR, provides a good probe for monitoring epimerisation of both optically active and inactive stereoisomers.

Resolution of a racemic modification is an altogether different proposition. Since two enantiomers behave identically in achiral environments, they cannot be

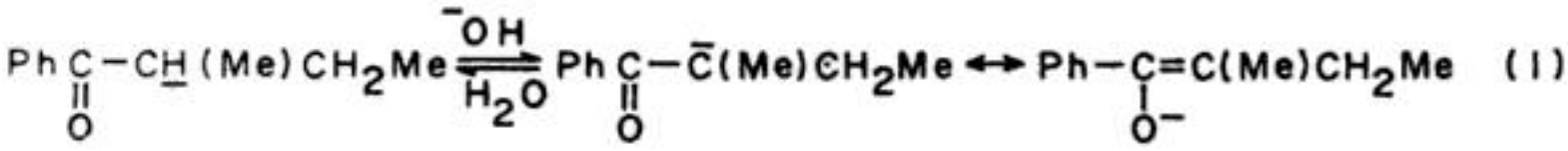
distinguished unless a diastereomeric relationship is established by using chiral reagents, solvents, media etc. Resolution of a racemic modification, therefore, requires a chiral agency in one form or other.

7.2 Mechanisms of racemisation

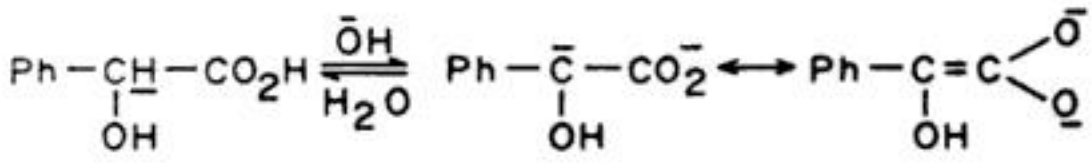
When racemisation is carried out by a chemical reaction, the enantiomer usually has to pass through a symmetrical species*, be it a transition state or an intermediate so that when the molecule is reformed, the two enantiomers are produced with equal facility and in equal amounts. The ease of racemisation depends on the mechanism involved which in turn depends on the nature of the substrates and the reagents employed.

7.2.1 Mechanism involving carbanions

If a ligand at a tetrahedral chiral centre is removed by heterolytic cleavage leaving behind an anionic species, e.g., a carbanion, the latter undergoes rapid inversion so that when the ligand recombines, it can do so either from the same side it left (a homofacial reaction accompanied with retention of configuration) or from the opposite side (a heterofacial reaction accompanied with inversion of configuration). The two approaches are enantiomorphic and so equally facile giving a product which is racemic. Generally, an acidic proton is removed using mild to strong bases such as sodium hydroxide and sodium alkoxides (in appropriate solvents). Two examples are given in equations (1) and (2).



(1)



(2)

The derived anion in each case is stabilised by resonance which facilitates their formation under basic condition. Phenyl *s*-butyl ketone (in eqn. 1) undergoes easy racemisation (with aqueous NaOH), mandelic acid (in eqn. 2) and lactic acid do so much less readily, and atrolactic acid, $PhC(Me)(OH)CO_2H$ with no enolisable H does not racemise at all. The mechanism is the same as that for keto-enol tautomerism, halogenation, and deuterium exchange in enolisable carbonyl compounds.

When the concerned proton is very acidic as in the disulphone (eqn. 3), the

*A tetrahedral chiral centre can change its chirality if two of its ligands are interchanged through chemical transformations. If the interconversion is carried out to 50%, a racemic mixture is obtained without involving an achiral transition state or intermediate.

carbanion may form in appropriate solvents without any base and racemisation takes place spontaneously:

$$(\underline{p})\ MeO-C_6H_4-SO_2-C\underline{H}(Me)-SO_2Ph \underset{H_3O^+}{\overset{H_2O}{\rightleftharpoons}} (\underline{p})\ MeO-C_6H_4-SO_2-\bar{C}(Me)-SO_2Ph \quad (3)$$

A mineral acid may also effect racemisation of a ketone containing an α-H through the intermediate enol (eqn.4).

$$-\underset{|}{CH}-\underset{|}{C}=O + H^+ \rightleftharpoons -\underset{|}{CH}-\underset{|}{C}=\overset{+}{O}H \rightleftharpoons -\underset{|}{C}=\underset{|}{C}-OH + H^+ \quad (4)$$

7.2.2 Mechanism involving carbonium ions

A group (electron-withdrawing) may be detached from a chiral centre with an electron pair leaving behind a cationic species. e.g.. a carbocation which because of its planar structure is achiral. Recombination of the anion, therefore, leads to racemisation. The mechanism operates when the substrate is capable of giving rise to a stable carbocation (benzylic. allylic. or tertiary). The reagents used are Lewis acids such as antimony pentachloride (eqn. 5), aluminium trichloride. and zinc chloride and sometimes a mineral acid (eqn. 6).

$$(+)\ Ph\underset{|}{\underset{Cl}{CH}}-Me + SbCl_5 \rightleftharpoons Ph\underset{|}{\overset{+}{C}}-Me + SbCl_6^- \rightleftharpoons (-)\ Ph\overset{Cl}{\overset{|}{CH}}-Me + SbCl_5 \quad (5)$$

$$R_1R_2R_3CH + 2H_2SO_4 \rightarrow R_1R_2R_3C^+ + HSO_4^- + SO_2 + 2H_2O$$

$$R_1R_2R_3C^+ + R_1R_2R_3CH \rightleftharpoons R_1R_2R_3CH + R_1R_2R_3C^+ \text{ etc.} \quad (6)$$

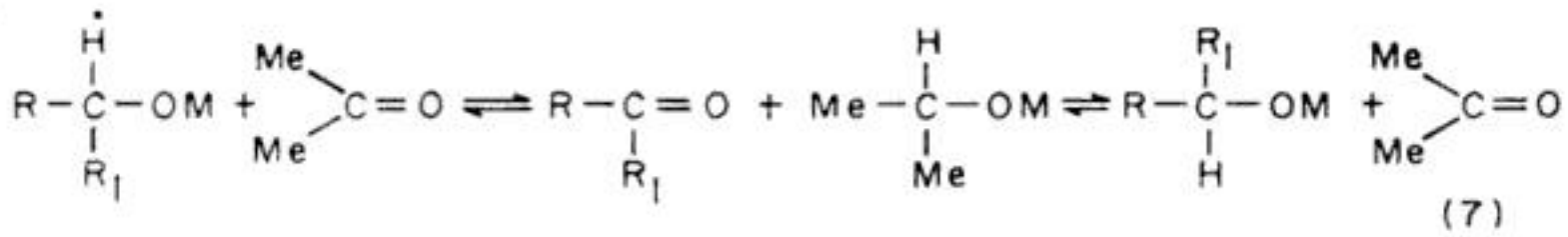
7.2.3 Mechanism involving free radicals

A free radical has a near planar structure (Chapter 4) and if a chiral centre is converted into a free radical pair by homolytic cleavage of a bond, the recombination of the pair would lead to a racemic product. Substrates which produce relatively stable radicals (benzylic. allylic. tertiary) may undergo racemisation through this mechanism under the influence of heat or light. Thus α-chloroethylbenzene (in eqn. 5) in enantiomerically pure form when distilled under normal pressure. undergoes extensive racemisation. Hydrogenation-dehydrogenation catalysts. e.g., Pd-C can racemise a chiral centre containing a H atom through radical mechanism.

7.2.4 Mechanism involving stable symmetrical intermediate

In certain cases. the enantiomers (or diastereomers) are interconverted through stable (isolable) achiral intermediates and get racemised (or epimerised). A classical example is provided by Meerwein-Ponndorf-Verley/Oppenauer reduction-oxidation procedure (M-P-V) in which a secondary alcohol in the form of its aluminium

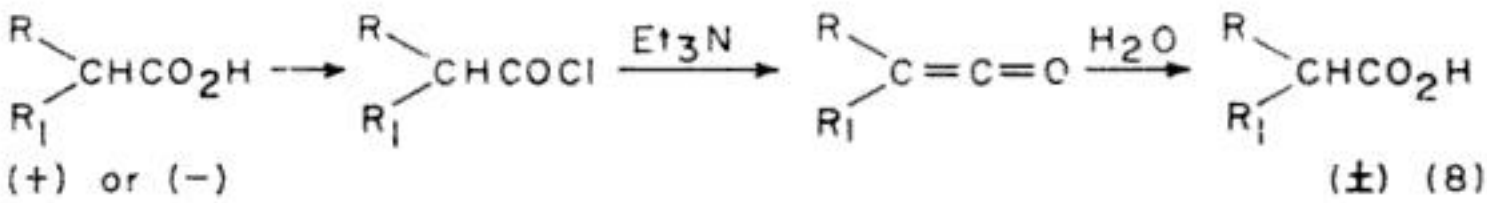
derivative is heated with a trace of a ketone (e.g., acetone). The ketone initiates a reversible oxidation-reduction sequence (eqn. 7) and an equilibrium is established between enantiomers (leading to racemisation) or between diastereomers (leading to epimerisation).



(7)

The method is particularly suitable for equilibration of cyclic secondary alcohols. In the above equation, M stands for dialkoxyaluminium. Sodium, potassium, and lithium alkoxides derived from secondary alcohols (M = Na,K,Li) on prolonged heating in the presence of a trace of a ketone may also establish equilibrium between enantiomeric or epimeric alcohols through an analogous mechanism. A primary alcohol of the type RR_1CHCH_2OH also gets racemised by heating with sodium since the intermediate aldehyde, RR_1CHCHO forms the enolate anion, $RR_1C{=}CHO^-$ before it is converted back into the alcohol.

Sometimes, the acid chloride of an optically active carboxylic acid, during reaction in the presence of a tertiary amine, undergoes racemisation through a ketene (eqn. 8).



(±) (8)

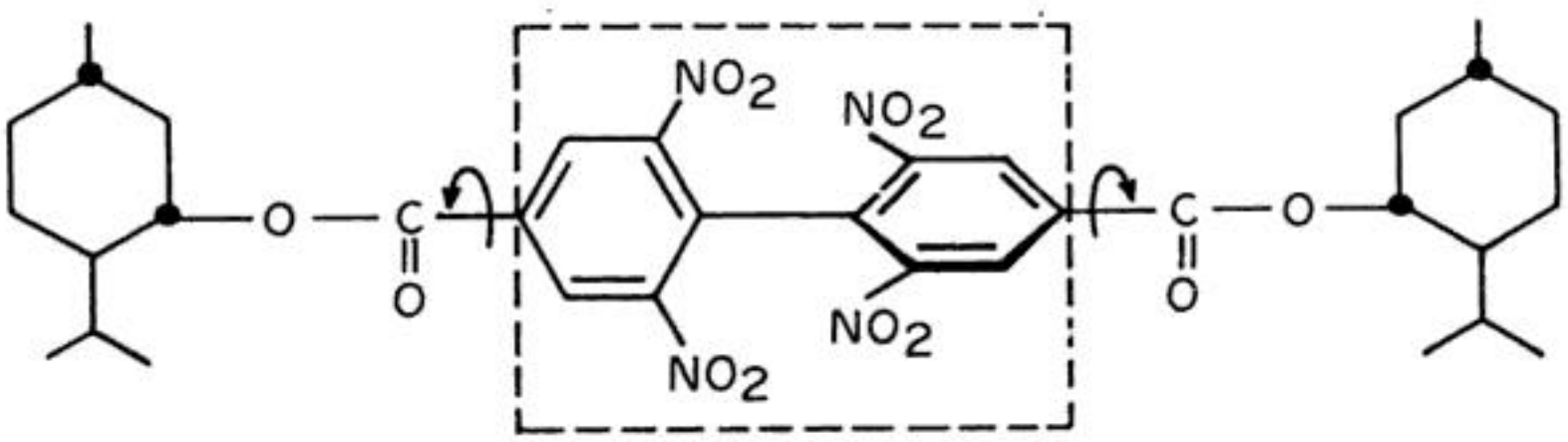
7.2.5 **Racemisation through rotation around bonds**

In the case of conformational enantiomers (Chapter 3), racemisation takes place through rotation around a single bond or bonds and the interconversion usually takes place readily via an achiral conformation. This has been already illustrated for atropisomers, e.g., optically active biphenyls (Chapter 5) in which the configurational stability depends on the steric bulk of appropriately placed substituents. Most of these enantiomeric atropisomers racemise by application of heat which leads to bond stretching and (or) bond bending and helps the non-planar enantiomers to cross the planar transition state.

Cyclic compounds which exist in enantiomeric conformations, e.g., *cis*-1,2-dimethylcyclohexane and *cis*-decalin undergo racemisation through ring inversion (see Chapter 10) apparently without passing through any achiral intermediate or transition state.

Mislow and Bolstad (1955) (see Eliel 1962) have prepared a biphenyl derivative, namely, (+)-menthyl (−)-menthyl 2,6,2′,6′-tetranitrobiphenyl-4,4′-dicarboxylate

(I) (Figure 7.1) which has some interesting structural features. (*i*) The two phenyl rings are prevented from being coplanar by the ortho nitro groups; (*ii*) the two terminals of the molecular axis are attached to two chiral moieties which are mirror images of each other; (*iii*) the non-planar biphenyl unit with its four nitro groups forming the vertices of a tetrahedron (elongated along the molecular axis) eliminates the possibility of the σ plane passing through the centre of the molecule. The net result is that the molecule does not have any element of symmetry (it belongs to C_1 point group) and is thus non-superposable with its mirror image. There is, however, a fourth structural feature: (*iv*) The biphenyl unit (put in a box) as a whole can rotate around two relatively unhindered single bonds joining the phenyl and carboxylate groups. A rotation of 90° converts one enantiomer into the other leading to spontaneous racemisation. The two enantiomers are thus conformational in origin similar to the two gauche conformers of *n*-butane (Chapter 9) with the difference that they do not have to pass through any achiral conformation during enantiomerisation.



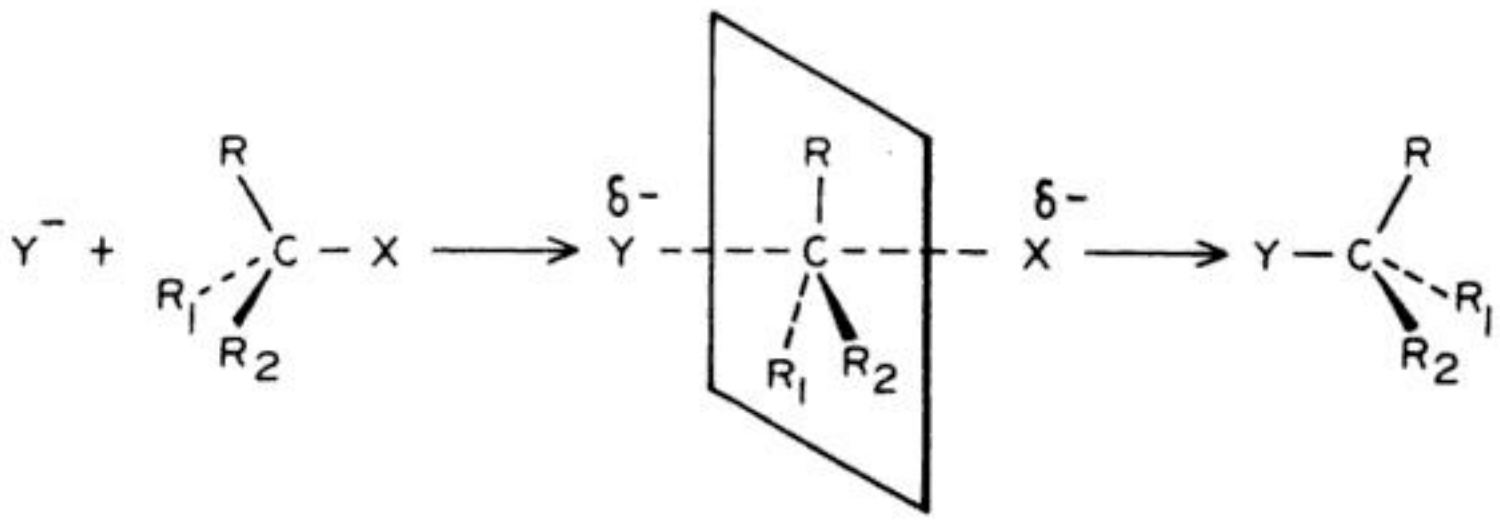
(I)

Figure 7.1 Racemisation through rotation around single bonds

7.2.6 Configurational change in substitution reactions

In a nucleophilic substitution reaction, if substitution takes place at a chiral centre, e.g., when Y^- displaces X in $RR_1R_2C\text{-}X$ to give $RR_1R_2C\text{-}Y$, configurational change occurs the nature of which depends on the mechanism. The case is. however, quite distinct from racemisation since a different chiral centre is formed in the place of the original (unless X = Y). Three things may happen: the product may be racemic even though the starting material is optically active: the product may retain the configuration of the original molecule (Y in place of X): or it may undergo an inversion of configuration at the chiral centre. In S_N1 reactions, X^- departs first in a rate-determining step leaving behind a carbonium ion which, as has already been noted, has a planar structure and so extensive racemisation occurs in the product. In S_N2 reactions, the incoming nucleophile (Y^-) initiates the reaction from the back while X^- leaves the molecule from the front (a heterofacial reaction) in a concerted process as shown in Figure 7.2.* The chiral centre thus

*Orbital picture is given in Chapter 12.



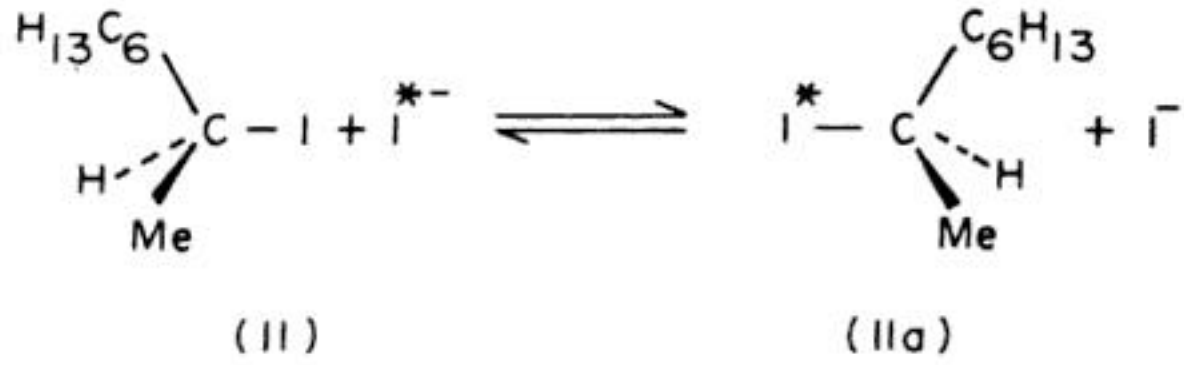


Figure 7.2 Configurational inversion in S_N2 reaction

undergoes an inversion of configuration with respect to the substrate stereochemistry. If X = Y as in the reaction of optically active 2-iodooctane (II) with sodium iodide, the reaction becomes reversible and an equilibrium is set up between the two enantiomers (II) and (IIa) leading to racemisation. The mechanism has been proved by using sodium iodide with radioactive iodine (I*). The rate of incorporation of I* is monitored by radioactivity of the substrate and the rate of racemisation by optical rotation. In the case of S_N2 mechanism, the rate of inversion will be equal to the rate of incorporation of I* which in turn will be half of the rate of racemisation (each inverted molecule forms a racemic pair with an uninverted one). This is found to be true within experimental error.

If the incoming nucleophile forms a part of the outgoing group, as Cl in the chlorosulphite (III) (Figure 7.3), it reacts with the chiral centre from the same side of the leaving group (a homofacial reaction known as S_Ni) and the configuration is retained*. Even before the mechanisms were known, Walden demonstrated the

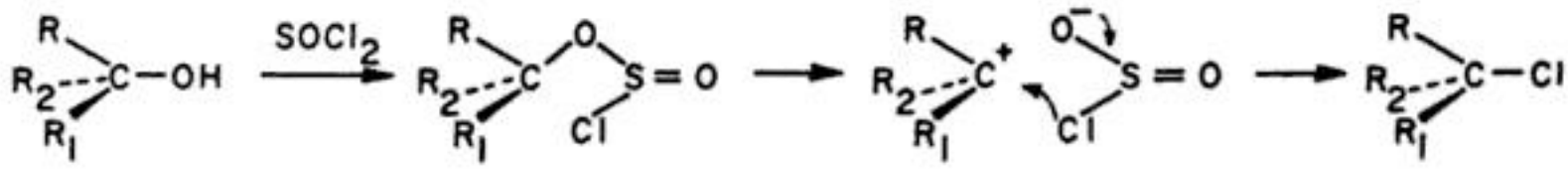


Figure 7.3 Retention of configuration: S_N1 mechanism

* Nucleophilic reaction through neighbouring group participation also leads to retention of configuration (as a result of two successive inversions) which is discussed in Chapter12.

phenomenon of inversion with the help of a few reaction sequences (see Kryger and Rasmussen 1972), one of which is shown in Figure 7.4. (−)-Malic acid on treatment with phosphorus pentachloride gives (+)-chlorosuccinic acid while on treatment with thionyl chloride gives (−)-chlorosuccinic acid. Obviously. in one of the reactions, inversion of configuration has occurred. It is now known that the first reaction goes with inversion (S_N2) and the second with retention (S_Ni) but at

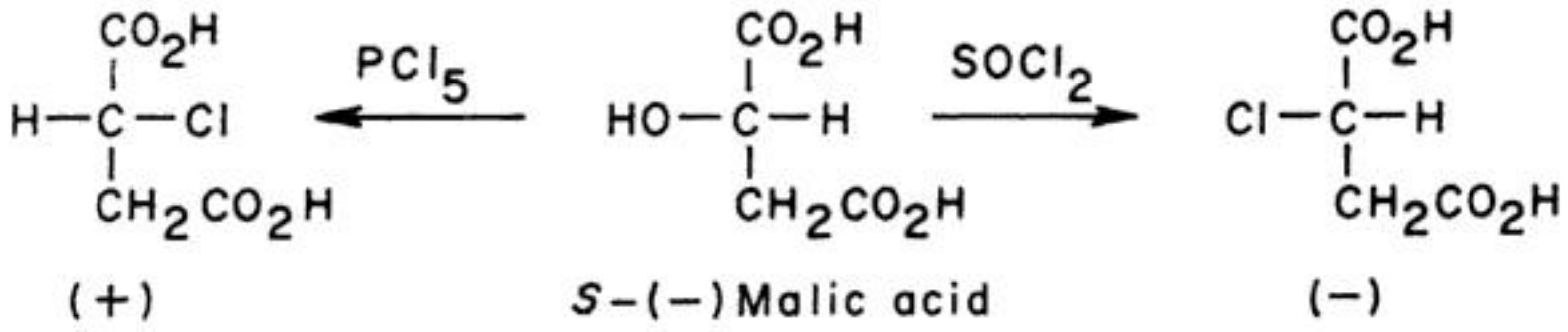


Figure 7.4 An example of Walden inversion

that time it could not be known (sign of rotation is no guide for configuration). A more pertinent example which definitely proves that inversion of configuration accompanies an S_N2 reaction is provided by the sequence of reactions given in Figure 7.5. The (+)-enantiomer of the alcohol (IV) is converted in three steps into the (−)-enantiomer (IVa). Tosylation and hydrolysis of acetate (first and the third steps) do not involve the chiral centre and inversion (designated by a loop), therefore, must have occurred at the second step in which the acetate replaces the tosylate group by S_N2 mechanism.

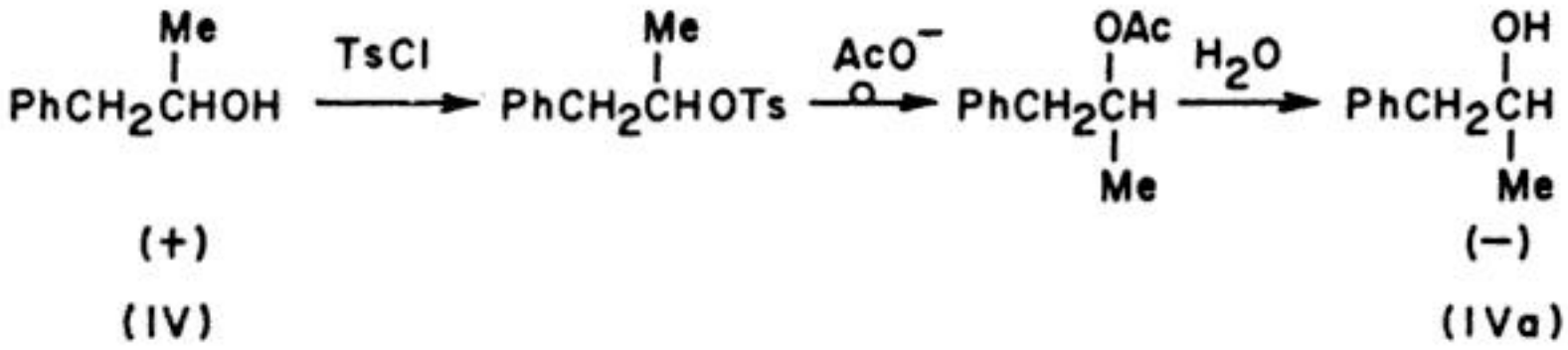


Figure 7.5 Interconversion of enantiomers through Walden inversion

7.3 Asymmetric transformation and mutarotation

A compound with a labile chiral centre can undergo configurational change in solution through any of the mechanisms discussed before and eventually lead to equilibrium. If that is the only chiral centre in the molecule, all that happens under achiral conditions is complete racemisation. If, on the other hand, there exists a chiral element in the environment, one or the other of the enantiomers would predominate in equilibrium leading to what is known as 'asymmetric transformation'. The second chiral element may arise from a chiral solvent, a chiral counter ion, or a covalently linked chiral grouping present either in the molecule itself (in which case, it is purely an epimerisation process) or in another molecule used as an additive. What matters is that the chiral element of the environment must interact with (or form a part of) the chiral substrate giving rise to two diastereomeric associates (or complexes) formed in unequal amounts. For example, if a confi-

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mechanism involves protonation of the oxide ring, deprotonation of 1-OH by base followed by ring opening to the aldehyde form, and its subsequent ring-closure to the original hemiacetal or its epimer by acid catalysis. In consonance with the mechanism, an amphoteric solvent or a combination of acid and base is necessary for mutarotation. Thus in tetramethyl glucose, mutarotation can be arrested by using cresol (a weak acid) or pyridine (a weak base) alone as solvent but goes twenty times faster in the mixture of the two than in water. Hydroxypyridine containing both acidic and basic nuclei is an effective catalyst for mutarotation in sugars.

Mutarotation due to a structural change may be illustrated with gluconolactones a solution of which in water establishes equilibrium between δ-glucono- and γ-gluconolactone through the intermediate gluconic acid (Figure 7.7). In this case, no asymmetric transformation is involved (two compounds in equilibrium are structural isomers).

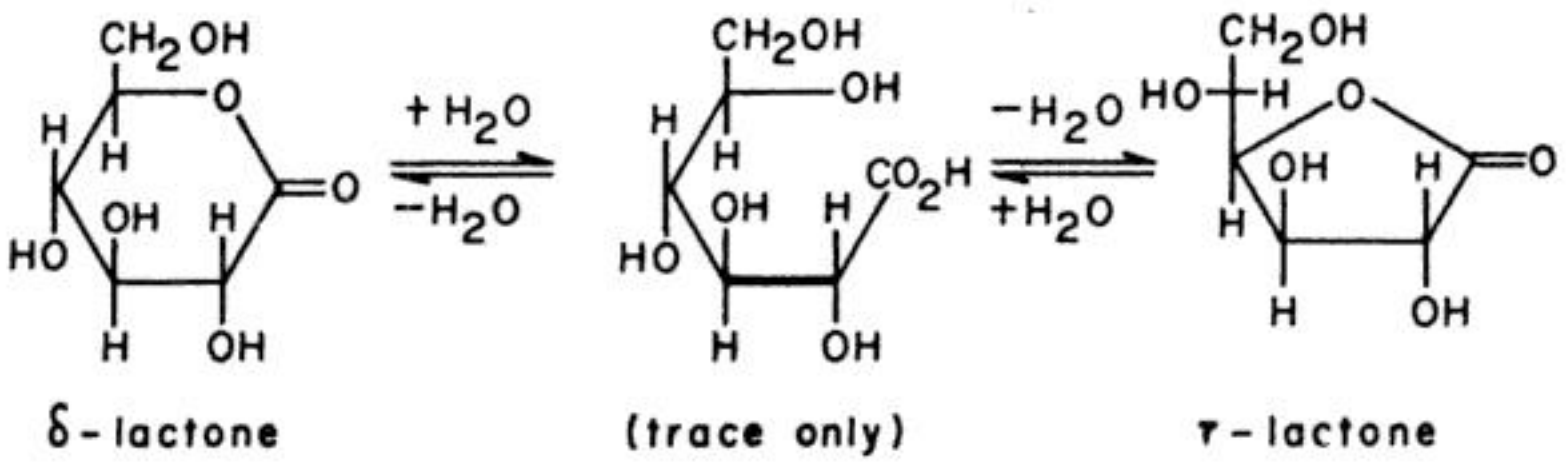

Figure 7.7 Mutarotation due to structural change

First order asymmetric transformation accompanied by mutarotation is exhibited by many biphenyl derivatives and analogues (Chapter 5) in which rotation around the pivotal single bond is moderately restricted so that interconversion between two enantiomeric atropisomers takes place in solution. Such compounds are not resolvable under ordinary conditions but when admixed with appropriate chiral additives, show mutarotation because of first order asymmetric transformation. Thus 3′-bromobiphenyl-2-trimethylarsonium iodide (V) (Figure 7.8) when mixed with (+)-camphorsulphonate (as a salt) in solution shows mutaro-

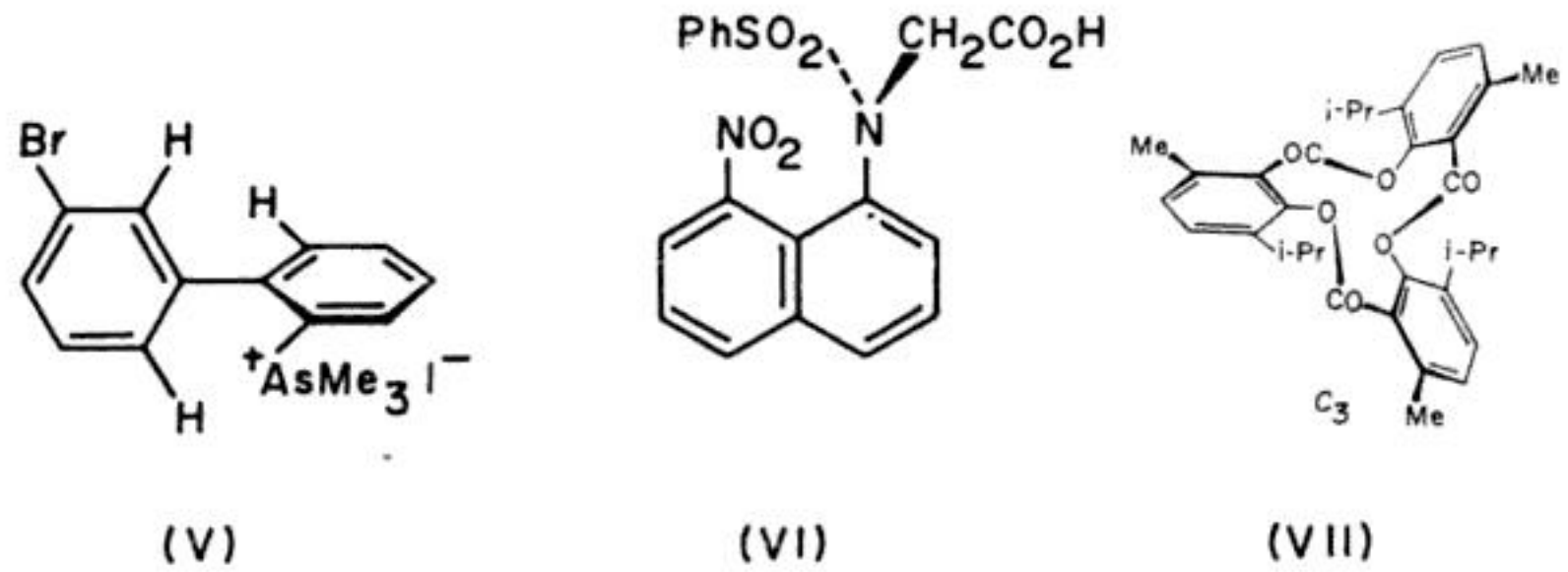

Figure 7.8 Substrates for first and second order asymmetric transformations

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is esterified with an insufficient amount of (−)-menthol, (−)-menthyl (+)-mandelate (n-diastereomer) is formed in higher proportion leaving behind the unreacted mandelic acid enriched in the (−)-isomer.

The biphenyl ketone (XXVIII)) (Figure 7.14) provides another interesting example of kinetic method of resolution. When the (±)-ketone is partially reduced with *S*-2-octanol (in the presence of aluminium *t*-butoxide), the (+)-ketone is reduced at a faster rate and the unreacted ketone becomes enriched in the (−)-enantiomer (XXIX) (Mislow 1965). The resultant alcohol, in turn, becomes

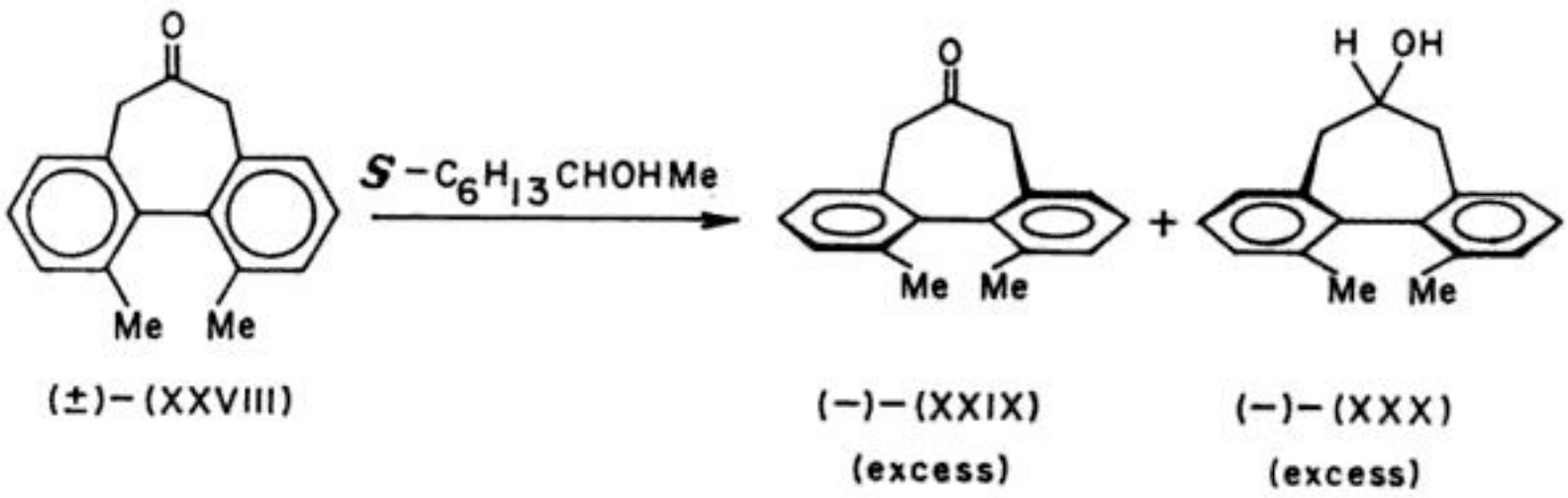

Figure 7.14 Kinetic resolution of a bridged biphenyl ketone

enriched in the (−)-enantiomer (XXX) which is also obtained by the reduction of (+)-XXIX with an achiral reagent, e.g., lithium aluminium hydride. In a somewhat reverse situation, when two moles of (±)-isobornyloxyaluminium dichloride (XXXI) are allowed to react with one mole of (−)-menthone (Figure 7.15), one enantiomer of the reagent is oxidised faster and the product consists of 90% of (+)-camphor (XXXII) (Nasipuri and Mukherjee 1974).

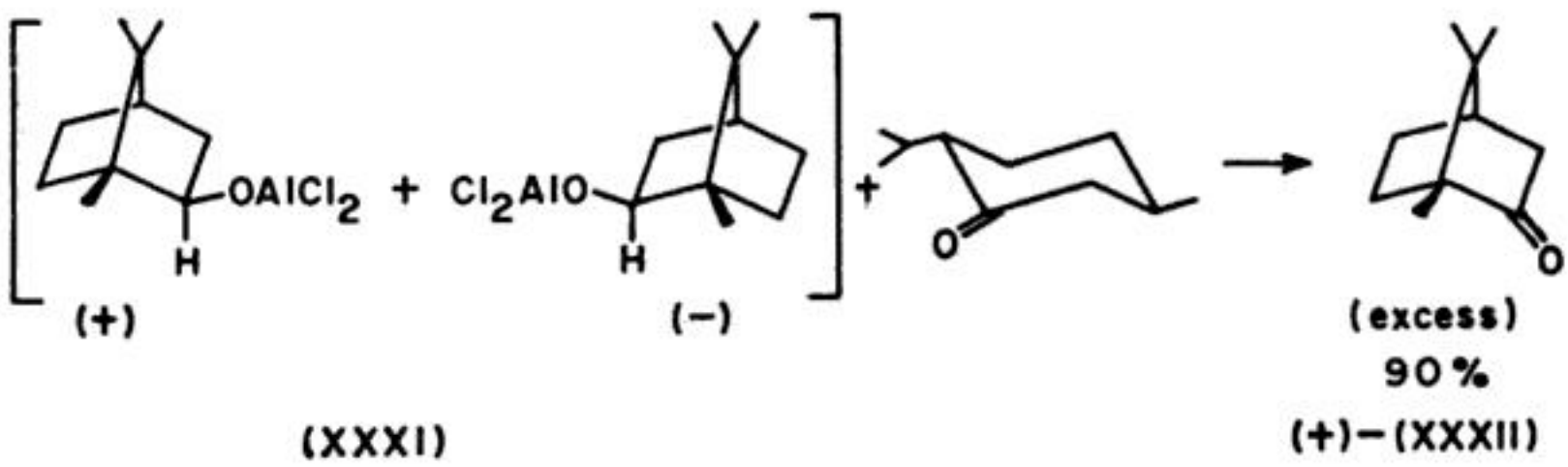

Figure 7.15 Kinetic method of resolution of camphor

These reactions may also be considered as asymmetric synthesis, in the first case, of the alcohol (XXX) and in the second case, of camphor (XXXII). Furthermore, since the difference in the reactivities of the two enantiomers with chiral reagents may ultimately be traced to the difference in the topologies of the reacting molecules (in terms of secondary interactions: steric and electronic), such reactions also provide information regarding the relative configuration of the reacting species (see Chapter 8). In fact, any method of optical activation (which is based on the difference in diastereomeric interactions), is, in principle, capable of establishing

relative configuration provided a precise knowledge of the mechanism of the process is available.

(*ii*) **Kinetic method using diastereomeric substrates**: Instead of using a racemate substrate, a mixture of diastereomers can be used in a reaction with an achiral reagent. The two diastereomers would react at different rates and a partial separation of diastereomers may be effected. Thus the mixed esters derived from (±)-mandelic acid and (−)-menthol on incomplete hydrolysis afford a partial resolution ot the mandelic acid in the hydrolysed product and a partial separation of the diastereomeric esters in the unhydrolysed residue.

(*iii*) **Other variations**: Sometimes a reaction may be carried out in the presence of an optically active catalyst. Thus racemic ethyl phenylchloroacetate on incomplete hydrolysis in the presence of cyclodextrin produces (+)-$C_6H_5CH(Cl)CO_2H$. Another variation is the preferential destruction of a chiral centre in a diastereomer. The most common method is to carry out dehydration or dehydrogenation using chiral catalyst. A simple example is the incomplete dehydration of (±)-phenylmethyl carbinol with (+)- or (−)-camphorsulphonic acid when one or the other of the enantiomeric alcohol predominates in the undecomposed substrate. An asymmetric dehydration has already been referred to in Chapter 5 in the synthesis of an optically active allene.

Asymmetric decomposition of appropriate substrate by circularly polarised light is also well known. As early as 1930, Kuhn and Knopf decomposed (±)-α-azidopropionic dimethylamide $MeCHN_3CONMe_2$, with right and left circularly polarised light to obtain a residue of the azide with weakly dextro- and levorotatory azide respectively.

Like asymmetric destruction, asymmetric synthesis may also be used for getting chiral compounds of high optical purity which will be discussed in a later chapter.

7.4.7 Resolution by biochemical transformation

In the kinetic method of resolution discussed above, the chiral reagents may be replaced by microorganisms or enzymes which are often highly stereoselective in their reactions. Pasteur first observed (his third method) that when a solution of the ammonium salt of (±)-tartaric acid is fermented by yeast or a mold (Penicillium glaucum), the natural (+)-form is completely consumed leaving behind the ammonium salt of (−)-tartaric acid.

The biochemical method has found important application in the resolution of (±)-amino acids. Thus an acetylated (±)-amino acid is treated with an enzyme 'acylase I' (hog-kidney acylase) until half the acetyl groups are hydrolysed away. The unhydrolysed acetyl derivative is that of the D-amino acid while the hydrolysed product consists of L-amino acid.

The shortcomings of the biochemical transformation are as follows. (*i*) Very dilute, usually aqueous solutions have to be used for fermentation, thus the product may be hard to isolate; (*ii*) most of the time, that enantiomer is selectively consumed which is biologically important; so frequently, only the unnatural enantiomer is available; (*iii*) it is not always possible to find an appropriate enzyme or microorganism for a particular substrate. In contrast, enzymatic asymmetric synthesis has found much wider application.

7.4.8 **Resolution through inclusion compounds**

Some compounds crystallise in such a way that a hole is formed inside the crystal which can accommodate another guest molecule without forming any chemical bond. These complexes are known as *inclusion* or *clathrate* compounds. The inclusion of the guest molecule depends on the steric fit inside the crystal lattice and is often very selective. Desoxycholic acid, a steroidal compound forms such crystals in which a particular enantiomer of selected molecules can be included. It has been used for the resolution of camphor.

An interesting case is the crystals of tri-*o*-thymotide (VII in Figure 7.8) which not only separate out from solvents in one particular enantiomorphous form but also sometimes include chiral solvent molecules such as 2-bromobutane in one enanatiomeric variety only, thus effecting partial resolution. Urea, although achiral, forms helical crystals and depending on the helicity can give inclusion compound with either enantiomer of a chiral solvent such as 2-chlorooctane thus causing partial resolution. Chiral crown ethers, previously discussed, can similarly be used to trap enantiomeric cations. These methods, however, are of little practical use.

7.5 **Optical purity and enantiomeric excess**

The specific rotation, $[\alpha]$, is highest for an enantiomerically pure compound and any contamination with the optical antipode lowers it, usually, proportionately. The optical purity (O_p) of a chiral compound is expressed as the percentage ratio of the rotation observed and the maximum rotation (rotation of a pure enantiomer) and is usually equal to the enantiomeric excess, *ee* (excess of one enantiomer over the other). The following equation (10) shows the relationship :

$$O_p = \frac{[\alpha]_{obsd}}{[\alpha]_{max}} \times 100 = ee = \frac{|\ [R] - [S]\ |}{[R] + [S]} \times 100 \qquad (10)$$

where $[R]$ and $[S]$ represent the mole fractions of the R and S enantiomers so that $[R] + [S] = 1$. The percentages of R and S enantiomers can be calculated from the above equation as follows:

$$\begin{aligned} \%\text{ of } R \text{ (or } S) &= ee + \%\text{ of } S \text{ (or } R) \\ &= ee + 100 - \%\text{ of } R \text{ (or } S) \\ &= \frac{ee + 100}{2} \quad \text{(for the major enantiomer)} \qquad (11) \end{aligned}$$

$$\text{Similarly, } \%\text{ of } S \text{ (or } R) = \frac{100 - ee}{2} \quad \text{(for the minor one)} \qquad (12)$$

Determination of O_p or *ee* of a chiral compound is an essential part of any resolution method or asymmetric synthesis since it gives the composition of the product. In the majority of cases, polarimetric measurement gives the true values of O_p and *ee* (Lyle and Lyle 1983). However, difficulty arises when the rotation of a pure enantiomer is not known and in the few cases where the rotation is not

linearly related to the concentration as for some compounds which undergo association through H-bonding or otherwise. Moreover, a polarimetric determination of rotation requires the compounds to be chemically pure, e.g., free of solvent and by-product.

One of the simplest way to know whether a compound is enantiomerically pure or not is to crystallise it (if solid) several times and check the constancy of the melting point and optical rotation. Even this method may not be fully reliable since some racemic modifications form solid solutions; also the crystals incorporate unknown quantities of solvent. A second alternative is to procure the optical antipode—preferably by another route—and to see whether it has exactly equal and opposite rotation. Other methods exist and they are mainly based on enantiomeric recognition through establishment of a diastereomeric relationship between a chiral reagent and the enantiomeric pair (Mislow and Raban 1967).

7.5.1 **Isotopic dilution method**

In isotopic dilution method, a known weight of the sample under examination is mixed in solution with a known weight of the racemic modification of the same compound uniformly labeled with an isotope. The racemic form is then separated out, recrystallised, and its isotope content determined. If the original sample was enantiomerically pure, the isotope dilution factor can be calculated from the known relative amounts of the two specimens mixed. If the factor turns out to be less than the calculated value, the compound was not enantiomerically pure. Instead of a racemic form, an optically active mixture may separate out. In either case, appropriate calculation gives the enantiomeric purity of the original sample (Anderson et al 1983).

7.5.2 **Enzymatic method**

Enzymes are usually highly enantiospecific, i.e., they react often with one enantiomer only and are completely inert to the other. If the test sample is treated with an appropriate enzyme and no reaction occurs as indicated by the absence of any change in optical rotation, the sample is enantiomerically pure (incomplete consumption of the enantiomerically pure substrate would also keep the rotation unchanged). Any enhancement or reduction of the original rotation would mean optical impurity. Thus the oxidase of amino acids which oxidises the L-amino acids 1000 times faster than the D-amino acids may be used to test the optical purity of an amino acid sample.

In a non-enzymatic variation, the enzyme may be replaced by an insufficient amount of optically pure reagent. The two enantiomers of the substrate would react with different rates and at the end, the unreacted substrate would be enriched in the less reactive enantiomer accompanied with a change of rotation (see kinetic method of resolution).

7.5.3 **Methods based on gas chromatography**

An analytical gas chromatography (using capillary columns for better resolution) is

conveniently used for determining the enantiomeric purity of a variety of compounds. The compound is first converted into a diastereomeric mixture by allowing it to react with an optically pure reagent, e.g., esterification of an alcohol or acetylation of an amine with an optically pure acid. The composition as determined by gas chromatography using achiral stationary phase gives the enantiomeric ratio of the original sample. High performance liquid chromatography (HPLC) may be used for unstable compounds. Precautions to be taken are: the derivatising reagents should be enantiomerically pure; no racemisation should take place on the column; and finally, the two diastereomers should be separable on the column under the condition of chromatogram. Diastereomeric esters prepared from N-acetyl (or N-trifluoroacetyl) amino acids and (−)-menthol are conveniently separated by gas chromatography.

Alternatively, an optically active stationary phase may also be used and the enantiomers directly separated (see the resolution method) on the column without derivatisation. Here, it is not necessary for the stationary phase to be enantiomerically pure though the degree of separation increases with the optical purity of the stationary phase.

7.5.4 Methods based on NMR spectroscopy

NMR spectroscopy is extensively used for the determination of enantiomeric purity. Several variations of the method are known.

1. Use of diastereomers: Since any two corresponding ligands (or nuclei) in two enantiomers are enantiotopic by external comparison, they are isochronous and cannot be distinguished in NMR working under achiral condition. But if the enantiomers are first derivatised with an optically pure reagent (as in the case of gas chromatography), two such ligands will be diastereotopic by external comparison and will have different chemical shifts. One has to select one or more groups in the compound which are clearly discernible in the spectrum. Thus phenylmethylcarbinol whose enantiomeric excess is to be determined is esterified with the acid chloride of optically pure *O*-methylmandelic acid (Figure 7.16). The resultant ester (XXXIII) may be a mixture of diastereomers depending on the optical purity of the original alcohol. The methoxyl peaks of the mandelate moiety can be easily detected in ^{1}H-NMR—one for each of the diastereomers—and their relative intensities would indicate the percentage ratio of enantiomers in the original alcohol.

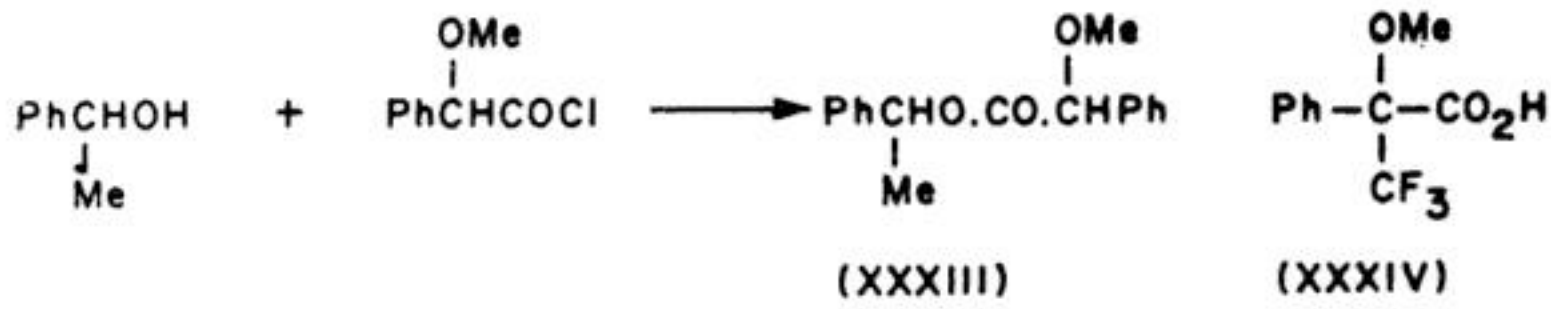

Figure 7.16 NMR method of determination of enantiomeric excess

Optically active α-methoxy-α-trifluoromethyl-α-phenylacetic acid (XXXIV) is a very useful acid for esterification (or acylation) since the products can be

investigated by ^{1}H-, ^{13}C-, and ^{19}F-NMR spectroscopy simultaneously. Mereover, the absence of α-H eliminates the possibility of racemisation. For the method to work satisfactorily, two conditions must be satisfied: the two anisochronous signals be well separated and the derivatising agents be optically pure (see Yamaguchi 1983).

2. Use of Shift reagents. Chiral shift reagents, e.g., XXXV in Figure 7.17 (see also Chapter 6) are also extensively used to determine the enantiomeric excess by NMR. They form diastereomeric complexes with chiral substrates having a variety of functional groups and at the same time, induce increased anisochrony (larger separation of chemical shifts) in the two diastereotopic groups of protons. Here, enantiomeric purity of the shift reagent is not essential; but calibration of the method with racemic material is necessary (see Fraser 1983, Sullivan 1978).

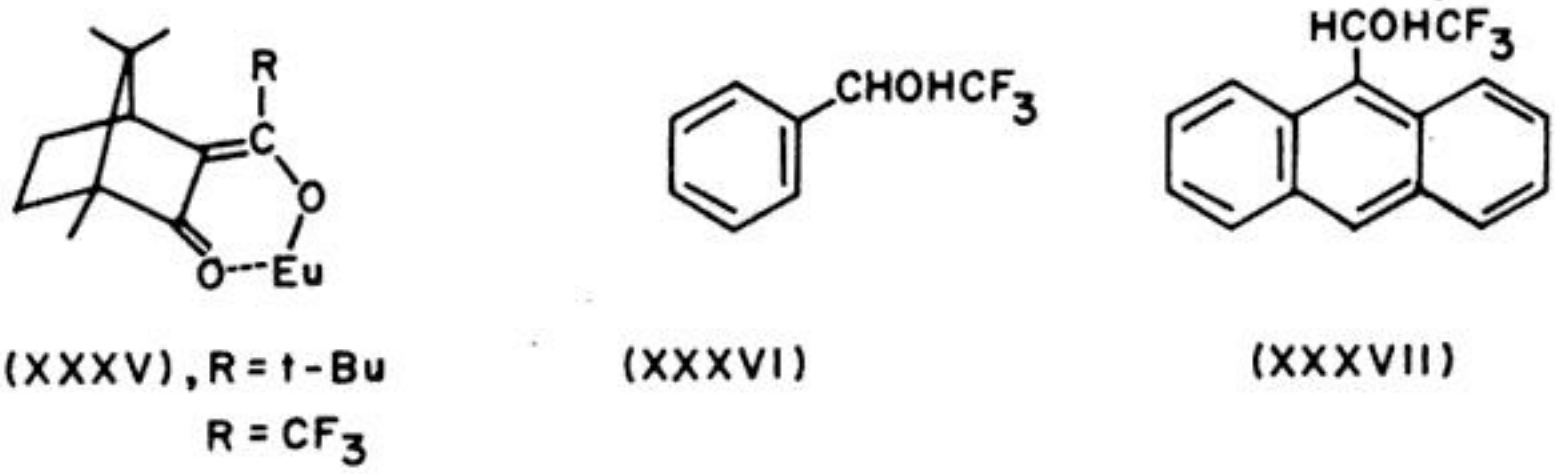

Figure 7.17 Chiral shift reagents and chiral solvating agents (CSA)

3. Use of chiral solvating agents. In yet another variation of NMR method, a 'chiral solvating agent' (CSA) is used which forms diastereomeric solvates with the substrate through weak solvent-solute interaction. The CSA may be either a solvent, or a cosolvent, or even a solid auxiliary (for reason of cost). Two most common CSA's are 2,2,2-trifluoro-1-phenylethanol (XXXVI) and the corresponding anthracyl derivative (XXXVII). The former is available by asymmetric reduction of $PhCOCF_3$ with bornyloxyaluminium dichloride in 68% *ee* (Nasipuri and Bhattacharya 1975) and the latter is available commercially. They interact with a variety of chiral compounds such as alcohols, amines, sulphoxides, phosphines, amine oxides, and epoxides giving diastereomeric solvates (Pirkle et al 1971, 1982) linked through H-bonds (shift reagents also work on the same principle). The association-complexes are unstable (most of the substrate remains uncomplexed at any time) and are in rapid equilibrium exchanging sites constantly. The situation is shown in Figure 7.18 for a racemic sulphoxide and a chiral CSA (XXXVI). Since

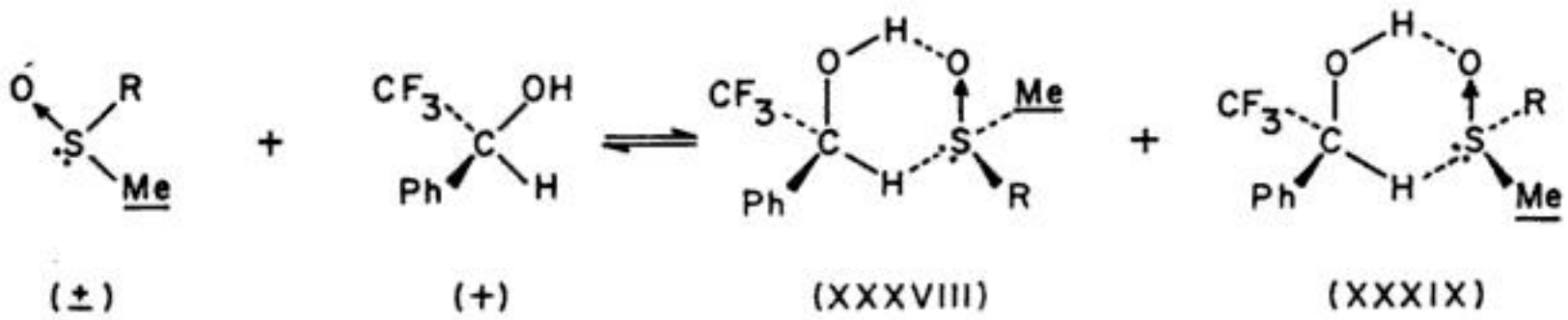

Figure 7.18 Diastereomeric associates with CSA through H-bonding

the site exchange is fast on NMR time scale, the chemical shift of the methyl group for (+)-S (S stands for the substrate) is a weighted average of that in the free (+)-S and that in the association-complex, say XXXVIII. Similarly, the chemical shift of the methyl group in (−)-S is the weighted average of that in the free (−)-S and that in the association-complex (XXXIX). The complexes being diastereomeric will have different values for the chemical shift. The enantiomeric purity of S may thus be determined from the relative intensities of the two peaks.

Here again, it is not necessary that the chiral solvating agent be optically pure; however, the separation of the chemical shifts of the anisochronous group is directly proportional to its optical purity.* With racemic CSA, no separation of peaks is possible because of averaging out of the diastereomeric associates through rapid exchange of enantiomeric ligands.

7.6 Summary

1. Racemisation is a process in which an optically active compound is converted into a mixture containing equal amounts of the two enantiomers with no resultant optical activity. It usually involves a reversible change of configuration at a chiral centre. If the molecule undergoing the change contains more than one chiral centre, a new diastereomer (an epimer) is formed instead of the enantiomer and the process is known as epimerisation. Epimerisation, in principle, always leads to unequal amounts of two epimers.

Depending on the nature of the substrates and the reaction conditions, racemisation may take place through carbanions, carbonium ions, free radicals, or even stable intermediates such as olefins and ketones. A chiral centre which contains an acidic hydrogen, e.g., an α-H in a ketone, racemises easily through the intermediate enol or enolate ion depending on whether it is acid-catalysed or base-catalysed. Atropisomers racemise on heating usually via achiral but occasionally via chiral transition states.

2. Resolution is a process in which pure enantiomers are separated out of the racemic modifications. It leads to optical activation and can be effected only through enantiomeric discrimination which in turn arises out of diastereomeric interaction between a chiral resolving agent and the two enantiomers of the substrate.

3. A compound containing a labile chiral centre may undergo spontaneous configurational change in solution. If there is a second chiral element in the environment such as chiral solvents, chiral additives (auxiliaries), or even other chiral centre (centres) in the molecule itself, one or the other of the enantiomers (or diastereomers) predominates in equilibrium. This is known as first order (or

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* The chiral sample itself can serve as its own reference under certain conditions (Vigneron et al 1973). If the substrate forms homochiral, (+ , +) or (− ,−) and heterochiral, (+ , −) dimeric associates either directly or through an achiral component, e.g., (+)-A-(+) and (+)-A-(−) (where A represents the achiral component) and if fast scrambling of monomeric units among the aggregates occurs, the situation becomes the same as the one for CSA method (Figure 7.18), the two aggregates serving as the two diastereomeric associates (Feringa et al 1985; Pasquier and Marty 1985).

first kind) asymmetric transformation and is accompanied with a change of optical rotation to a steady equilibrium value—a phenomenon known as mutarotation. Mutarotation is exhibited by most of the reducing sugars and their derivatives. It may also be due to a structural change of a chiral compound brought about in solution. Configurationally labile biphenyls and related atropisomers provide interesting examples of first order asymmetric transformation and mutarotation.

If in an asymmetric transformation, one of the diastereomeric species precipitates out of the solution, the equilibrium shifts so as to produce more of the precipitating isomer with the result that the entire amount of the substrate may come out as a single diastereomer. This process is known as second order asymmetric transformation.

4. A large number of methods for resolutions have been known since the time of Pasteur. They include (*i*) mechanical separation and preferential crystallisation, (*ii*) formation of diastereomeric compounds with optically pure reagents and their subsequent separation, (*iii*) formation of molecular complexes with chiral complexing agents, (*iv*) methods based on equilibrium and kinetic asymmetric transformations, (*v*) chromatographic methods using achiral stationary phase and diastereomeric substrates or chiral stationary phase and racemic substrates, and (*vi*) biochemical asymmetric transformation using enzymes and microorganisms. The selection of the most appropriate method depends on the nature of the substrates and the reagents available.

5. The optical purity of a sample (O_p) is defined by the percentage ratio of its specific rotation and that of a pure enantiomer while the enantiomeric excess (*ee*) is the percentage excess of one enantiomer over the other. The conventional method of determining the optical purity (and hence *ee*) of a sample by polarimetric method has now largely been superseded by other methods especially by those based on analytical gas chromatography and NMR spectroscopy. The different variations of these methods have been discussed.

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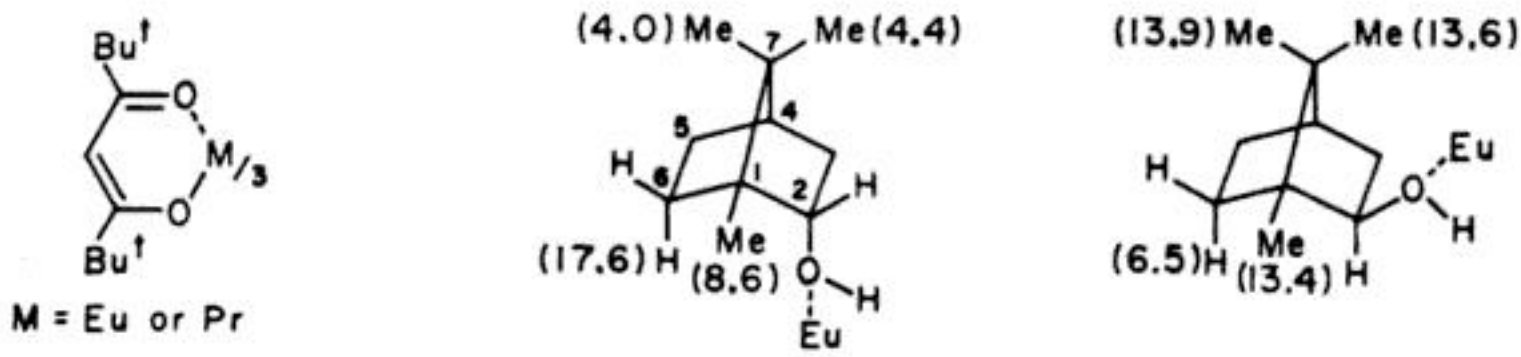
the erythro and threo isomers of LXXV on treatment with methyl iodide followed by heat are converted into LXXVI and LXXVII respectively in which H_A and H_B have different steric disposition distinguishable by J_{AB}.

3. Nuclear Overhauser effect. If two nuclei have different chemical shifts and are close in space e.g.. H_A and H_B in LXXVI (but not in LXXVII) and if the molecule is simultaneously irradiated with the radio frequency ν_A (the resonance frequency of H_A) while recording the NMR spectrum. two things happen : The peak of H_A disappears due to saturation and the peak of H_B (now an uncoupled singlet) is enhanced in intensity (10-50%) due to increased spin-spin relaxation. The technique is called double irradiation and the effect is called *nuclear Overhauser effect* (NOE). The NOE decreases rapidly with increasing distance between the two interacting nuclei and may be used to determine the relative stereochemistry in suitable compounds (Bell 1973). Thus the two chromans (LXXVI) and (LXXVII) may be distinguished by double irradiation with ν_A which would increase the peak intensity of H_B in LXXVI but not in LXXVII (H_B would be decoupled in both the cases).

4. Use of shift reagents. Some paramagnetic reagents like hexacoordinated chelate complexes of europium and praseodymium form labile molecular associates with electron-donating polar groups such as OH. C=O. and NH_2 and bring about large changes in the chemical shifts (downfield for ΔEu and upfield for ΔPr) of protons (or carbons in ^{13}C-NMR) (Hofer 1976). The shifts known as lanthanide-induced shifts (LIS) are inversely proportional to the third power of the distance of the nuclei from the lanthanide and provide a sensitive method of ascertaining the relative distance of various groups and atoms from the complexation site. One such common reagent is the dipivaloylmethanato complex (Figure 8.42). Thus when the reagent (M = Eu) is added to borneol and isoborneol respectively.



(LXXVIII) (LXXIX)

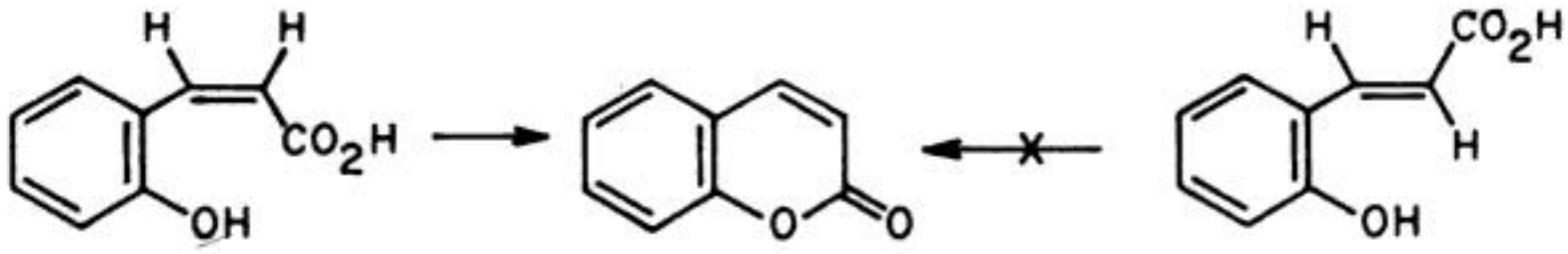
Figure 8.42 Shift reagents and lanthanide-induced shifts

downfield shifts are induced practically to all the protons in the molecules but more so to those near to OH. Shifts (in ppm) induced on 1-Me, 6-H, and 7-Me are shown in the Figure (for 1 : 1 molar complex) which may be used to determine the configuration. Chiral shift reagents and their uses have been discussed elsewhere.

8.5.3 Chemical methods

Two classical methods for the determination of relative configuration are based on ring-closure and ring-opening. Ring closure involving two functional groups which

are on the same side of a double bond or a ring is always more facile than when they are on opposite sides (the ring formation may not take place at all in the latter case). Ring opening always gives a product in which the two newly released functional groups are on the same side (cis) of a double bond or a second ring. The classical examples for the ring-closure method are the formation of an anhydride from maleic acid and not from fumaric acid (on drastic condition, it does form an anhydride but not of its own but of maleic acid) and the spontaneous cyclisation of coumaric acid (LXXX) to coumarin. The isomeric coumarinic acid (LXXXI) does not cyclise without first being isomerised (Figure 8.43). The conclusions are obvious.

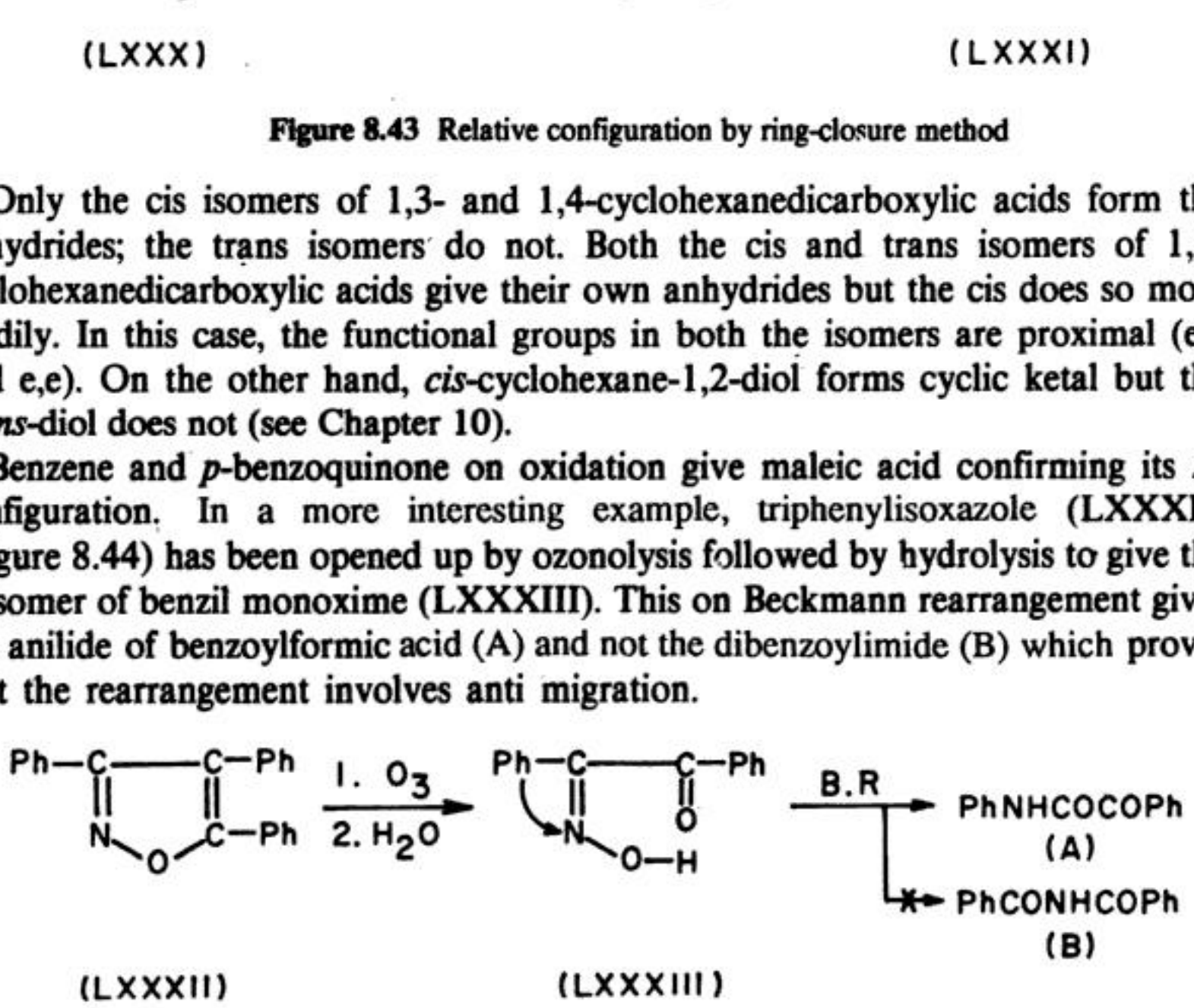


(LXXX) (LXXXI)

Figure 8.43 Relative configuration by ring-closure method

Only the cis isomers of 1,3- and 1,4-cyclohexanedicarboxylic acids form the anhydrides; the trans isomers do not. Both the cis and trans isomers of 1,2-cyclohexanedicarboxylic acids give their own anhydrides but the cis does so more readily. In this case, the functional groups in both the isomers are proximal (e,a and e,e). On the other hand, *cis*-cyclohexane-1,2-diol forms cyclic ketal but the *trans*-diol does not (see Chapter 10).

Benzene and *p*-benzoquinone on oxidation give maleic acid confirming its *Z*-configuration. In a more interesting example, triphenylisoxazole (LXXXII) (Figure 8.44) has been opened up by ozonolysis followed by hydrolysis to give the *Z* isomer of benzil monoxime (LXXXIII). This on Beckmann rearrangement gives the anilide of benzoylformic acid (A) and not the dibenzoylimide (B) which proves that the rearrangement involves anti migration.



(LXXXII) (LXXXIII)

Figure 8.44 Relative configuration by ring opening method

Chemical transformations which distinguish two diastereomers will be discussed in Chapter 12.

8.5.4 Symmetry consideration

One or more members of a set of diastereomers may be meso due to the presence of reflection symmetry. In such cases, the methods of resolution may be adopted to

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temperatures (K_1 and K_2 being the equilibrium constants at T_1 and T_2 in Kelvin respectively). A graphical method can also be employed using data at several temperatures.

Intramolecular H-bonding plays a very important part in conformational preference. Since the average energy of a H-bond is around 8.0-20.0 kJ mol^{-1} (Chapter 1), it frequently dominates over the other factors when it occurs. IR spectroscopy can clearly distinguish between the H-bonded O-H and non-H-bonded O-H frequencies. Thus the intramolecularly H-bonded O-H frequency appears at lower region around 3590 cm^{-1} and the non-H-bonded O-H frequency, around 3630 cm^{-1} ($\Delta\nu \simeq 40$ cm^{-1}). If a compound contains two conformers one capable of forming H-bond (-O-H··X) and the other not, they can be distinguished by IR. The strength of the H-bond is indicated by $\Delta\nu$; the higher the value, the stronger is the H-bond. This value provides additional information as regards the structure of the conformers and will be illustrated in due course.

5. Microwave spectroscopy. Microwave spectroscopy (range $\nu = 10 - 10^{-1}$ cm^{-1}) is concerned with the transitions between rotational states arising out of molecular collisions. The spectrum of a compound consisting of two or more conformers gives torsional frequencies of each individual conformer the analysis of which gives information regarding the structures, the torsion angle, dipole moment, barrier to internal rotation etc. (Wilson 1972). The barrier heights are measured by two techniques: a frequency method applicable to low-energy barriers but extremely sensitive and an intensity method less accurate but applicable to relatively high energy barrier. The two techniques are thus complementary to each other.

Microwave spectroscopy gives complete structural data but is applicable only for simple molecules with relatively high vapour pressure. The compounds must have some dipole moment even if it is as low as in propane. The barrier energies to internal rotation of some typical molecules as determined by microwave spectroscopy are listed in Table 9.4 (see also Lowe 1968). A few data available from thermodynamic methods are also incorporated for comparison.

6. Ultraviolet spectroscopy. Ultraviolet (UV) absorption spectroscopy may be used for conformational analysis in cases where the compound under consideration contains a chromophore capable of interacting electronically with an adjacent group in a particular conformation. This happens in cyclohexanone derivatives with an α-substituted halogen (or a similar electron acceptor group) in axial disposition where the antibonding π^* carbon orbital of the carbonyl function containing an electron in the excited state overlaps with a vacant orbital (usually 3s) of the electronegative group (see Chapter 10). This leads to a bathochromic shift in the axial conformer.

The n-π^* transition (leading to weak absorption) in a carbonyl moiety or other similar chromophore in a chiral molecule is asymmetrically perturbed and used in optical rotatory dispersion and circular dichroism measurement for configurational correlation (Chapter 15).

In conjugated systems such as biphenyls and analogues, both the absorption maxima and extinction coefficients are affected in a predictable fashion as the molecules are twisted around the pivotal bonds (Chapter 5) from a planar to a

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boat configuration. In 1925, Hückel indeed isolated the two isomers of decalin, although, as well be seen later, both isomers contain only chair forms. Boeseken (1921) realised the necessity for the chair conformation of cyclohexane ring from the results of his investigations with *cis*-cyclohexane-1,2-diol. The chair conformation of cyclohexane was finally confirmed by Hassel (1947) with his electron diffraction experiments and by Barton (1950) with his conformational analysis setting a land-mark in organic stereochemistry.

10.2 Conformations of cyclohexane

X-ray and electron diffraction experiments clearly prove that cyclohexane exists almost exclusively in the chair conformation. An examination of the model (Dreiding, Fieser, or Prentice-Hall) of the cyclohexane chair shows that it is devoid of any kind of strain. In an ideal chair, the bond angles are 109°28′, i.e., $E_\alpha = 0$; there is no bond length distortion, i.e., $E_l = 0$; all the bonds are staggered ($\theta = 60°$), i.e., $E_\theta = 0$, and there is no non-bonded interaction. In fact, the chair form lies at the bottom of a deep energy well and any deviation therefrom is strongly resisted by internal forces. The structure is rigid and the rigidity can be felt even in the model which unlike that of *n*-butane resists easy rotation around single bonds.

10.2.1 Characteristics of the chair conformation

The characteristics of the cyclohexane chair are best described under the following headings:

1. Geometry. The electron diffraction experiments of cyclohexane in the gaseous phase (Geise et al 1971) show the following geometric parameters:

C—C bond length = 0.1528 nm (152.8 pm)
C—H bond length = 0.1119 nm (111.9 pm)
C—C—C bond angle = 111°05′ (instead of 109°28′)
Dihedral angle (as shown in Ia) = 56° (instead of 60°)

The increased C—C—C bond angle makes the chair conformation slightly flattened* so that the dihedral angles between adjacent C—C bonds are 56° and the vertical C—H bonds (axial) are not exactly parallel to the C_3 axis but lean outwards from it by 7°. The chair form is drawn in three different perspectives (Figure 10.1). The structure (I) shows the conventional drawing of the chair with the C_3 axis vertical and the six carbon atoms distributed in two parallel horizontal planes, 1-3-5 in one and 2-4-6 in the other separated by a distance of 0.05 nm. Any consecutive four carbon atoms form a gauche butane unit and since there are six such units (1-2-3-4, 2-3-4-5, 3-4-5-6 etc.), the enthalphy of cyclohexane chair may be computed as 3.3×6 or 19.8 kJ mol^{-1} with respect to a hypothetical all-anti chair conformation†

In the structure (Ia), two pairs of *n*-butane units (2-3-4-5 and 2-1-6-5) are seen in Newman projection with dihedral angle of 56° in each. The structure (Ib) shows

*The flattening brings a balance between angle and torsional strains thus minimising the energy of the system.

†For various reasons, the calculation may be spurious as well as hypothetical (see Schleyer et al 1970).

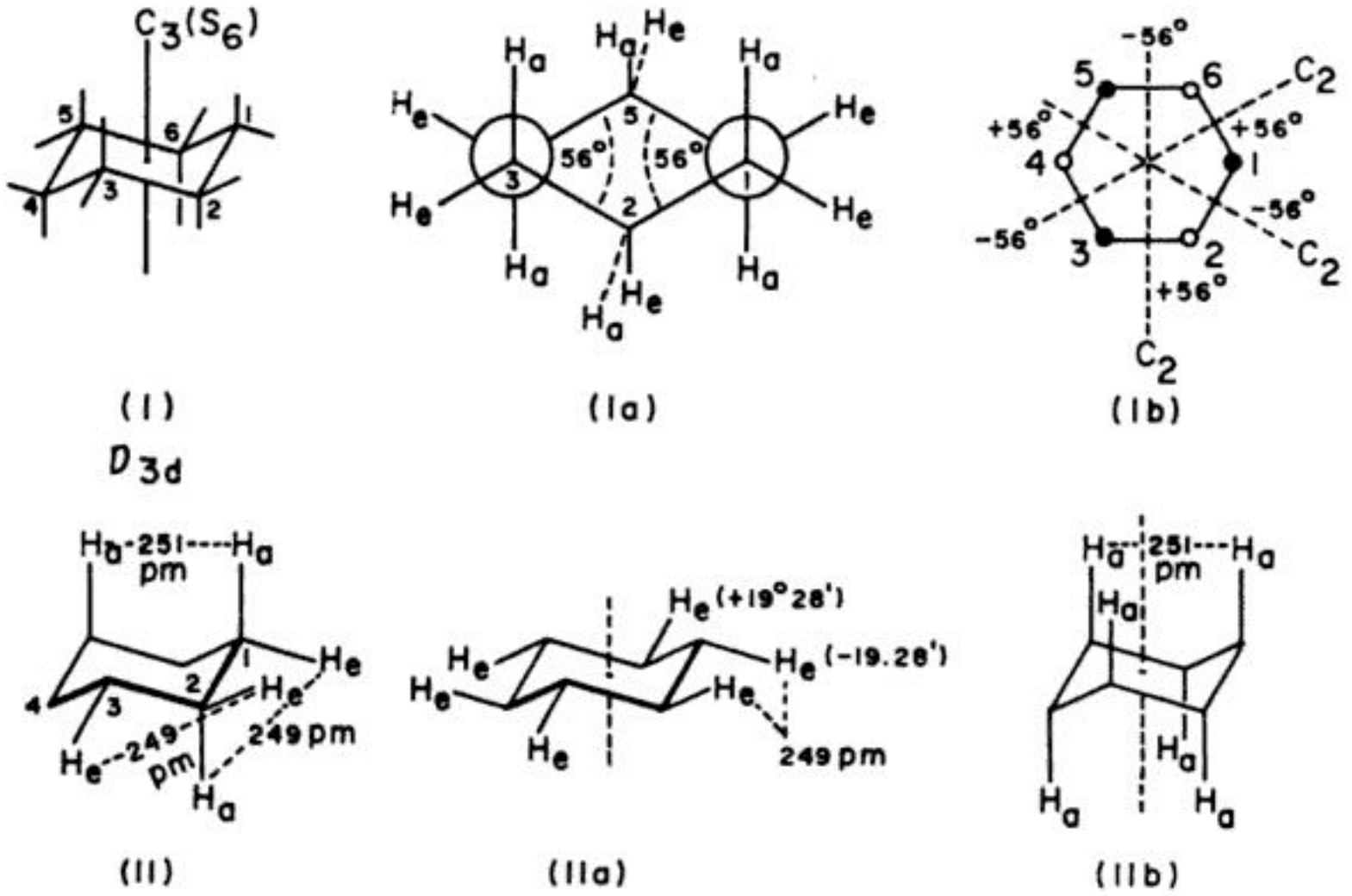

Figure 10.1 Geometry of cyclohexane chair

the six carbon atoms alternately up (●) and down (o) with signs of torsion angles* between pairs of adjacent carbon atoms according to Klyne-Prelog convention.

2. Symmetry. The vertical axis passing through the centre of the chair is a C_3 as well as an S_6 axis. In addition, there are three C_2 axes bisecting pairs of opposite sides and also a centre of symmetry. Then there are three vertical σ planes passing through diagonal carbon atoms. The cyclohexane chair thus belongs to point group D_{3d}.

The symmetry number (σ) is 6 counted thrice for 120° rotation around C_3 and once each for 180° rotation around the three C_2 axis (see Chapter 2).

3. Equatorial and axial bonds. Two types of C-H bonds are discernible in the cyclohexane chair: six are distributed around the periphery of the ring making alternately $+19°28'$ and $-19°28'$ angle with the horizontal plane of the molecule and the remaining six are approximately parallel with the vertical C_3 axis again alternatively up and down as shown separately in the two structures (IIa) and (IIb). The former are called equatorial (e) and the latter axial (a) bonds (Barton et al 1953). The approximate distances between different pairs of adjacent hydrogens are shown which are within 249-251 pm, greater than twice the van der Waals radius of hydrogen (120 pm). Thus there is no non-bonded interaction in the cyclohexane chair and since these distances occur twenty four times in the molecule, the stability of the chair conformation is readily understood.

The interaction between 1e,2e and 1e,2a substituents is known as 1,2-interaction while that between 1a,3a is known as 1,3-interaction or synaxial interaction. One significant difference between the two types of interactions is that while the 1e,2e

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*To designate a torsion angle, three bonds in succession involving four connected atoms have to be considered (Bucourt 1974), e.g., $\phi_{a,\,b,\,c}$ where a, b. and c are bonds. Ordinarily, the position of the central bond, i.e., b is indicated. Models will be helpful to understand the diagram (Ib).

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twisted in the directions shown by the arrows to get the transition state (III). There occurs extensive bond angle deformation accompanied by increased torsional strain and the energy of the transition state is computed as 46.0 kJ mol^{-1} which agrees fairly well with that (42-43 kJ mol^{-1}) found experimentally (see later). The transition state conformation (III) has a C_2 axis but no σ plane and belongs to point group C_2 (chiral). Further change along the direction of the arrows leads to the 'twist-boat' conformation (IV) which does not have any angle strain but suffers from some residual torsional strain. Lying in a high energy valley, it corresponds to an energy minimum (23 kJ mol^{-1} with respect to the chair) and is actually a conformer. Three such indistinguishable twist-boats are possible; they are inter-converted into one another by pseudorotation. The conformer (IV) can either go back to the original chair through the transition state (III) or be converted into the inverted chair (a topomer of the original) equally well through the enantiomeric transition state (III'). This is shown in the energy diagram (A) in Figure 10.3 and is called the C_2 pathway, since the C_2 axis of the ground state chair form is retained along this pathway.

An alternative pathway (B in figure 10.2) is also possible in which the chair is twisted to an envelope-like transition state (V) with five of the carbon atoms in a plane and the sixth one either above or below it. According to calculation, its energy is only slightly higher (ca 47.3 kJ mol^{-1}) than the transition state (III) (ca 46.0 kJ mol^{-1}) and so this pathway cannot be entirely ruled out. Conformation (V) has a σ plane and so is achiral and leads directly to an energy minimum conformation (VI) which is the classical boat. The latter has a slightly higher energy (by ca 3.7 kJ mol^{-1}) more than the twist-boat and exists in three interconvertible homomeric forms. The boat intermediate in its turn can go back to the original chair or its topomer—through two equivalent transition states (V) and (Va) respectively—with equal facility. Pathway B may be called a σ pathway, since both V and VI retain the symmetry plane of the chair ground state. The energy diagram is shown in Figure 10.3 by the dotted lines.

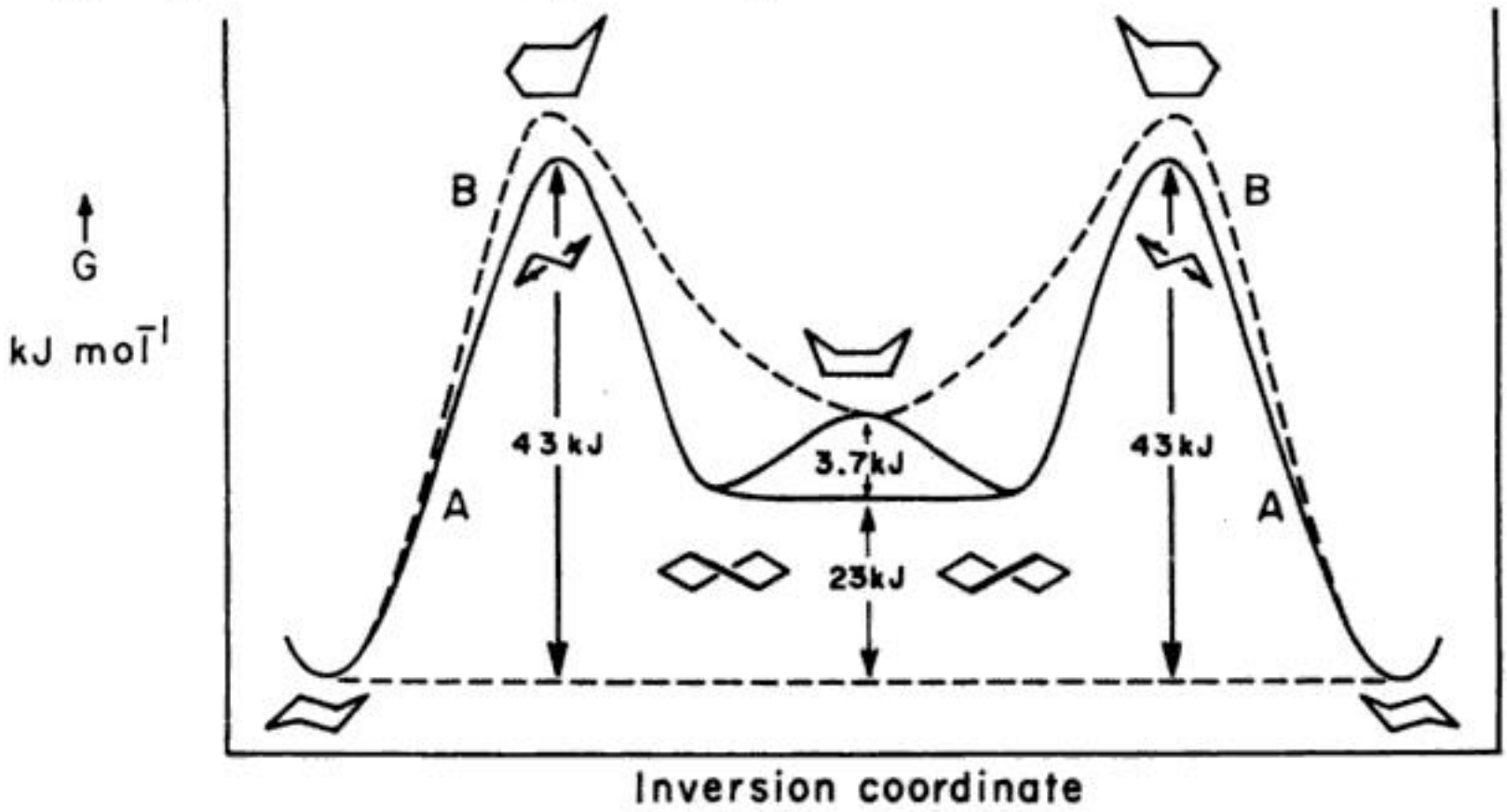
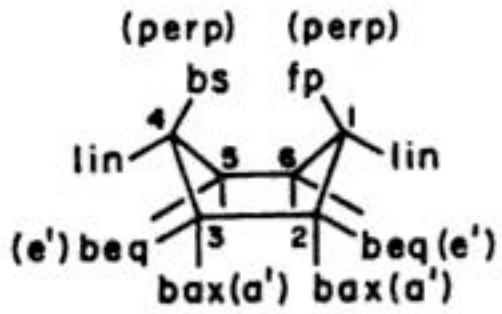


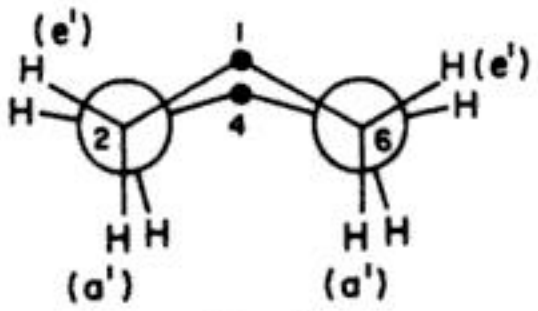
Figure 10.3 Energy profile of ring inversion

In principle, the two pathways (A and B) are mutually exclusive, i.e., the ring inversion takes place either through a twist-boat or through a true boat. However, once a twist-boat or a true boat is formed, they undergo interconversion through pseudorotation* before they are converted back into the chair forms. The entire range of conformations between a true boat and a twist-boat are called *flexible forms* and depending on the nature of substituents, one or the other may be stabilised. The boat form is of slightly higher energy and may be regarded as the transition state of the pseudorotation process. The twist-boat is of lowest energy and the term *flexible* form generally refers to it (in contrast, the chair forms are *rigid* conformers of cyclohexane not interconvertible by pseudorotation). The transition state in path A, i.e., III is a half-chair while that in path B, i.e., V is a half-boat which also suggests ·that path A is energetically preferred.

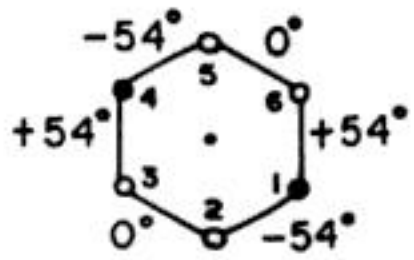
2. The flexible conformers. The boat (B) and the twist-boat (TB) are the two extremes of the flexible forms of cyclohexane. The boat conformation is shown in three different perspectives in Figure 10.4. The conventional boat (VI) with a C_2 axis and two σ planes (point group C_{2v})† shows the following types of bonds: normal equatorial and axial at C-1 and C-4, designated linear (lin) and perpendicular (perp) respectively (one of the perp bonds is also designated flagpole, abbreviated as fp and the other bowsprit abbreviated as bs), four boat-equatorial



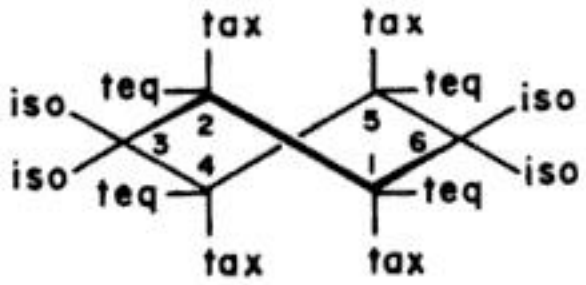
(VI) C_{2v}



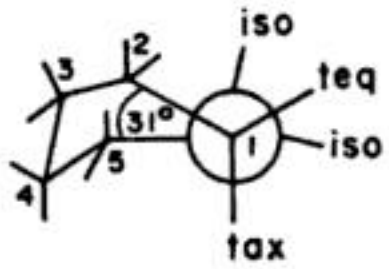
(VIa)



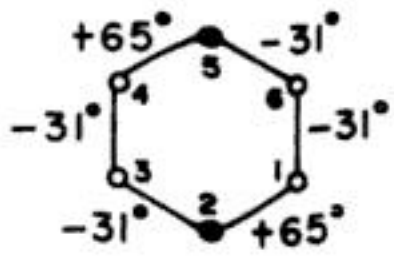
(VIb)



(VII), D_2



(VIIa)



(VIIb)

Figure 10.4 Geometry of flexible forms

*The term *pseudorotation* was originally adopted by Pitzer to describe the rotation of the out-of-plane displacements in a puckered cyclopentane ring. It is now used to describe a variety of conformational changes in cyclic systems which are low-energy processes and do not involve bond angle variations but only changes in torsional strain and other non-bonded interactions, as in transformations of the flexible forms of cyclohexanes (but not the chair-chair interconversion) and interconversions of mobile forms of higher cycloalkanes. The rotation is limited to an oscillation of dihedral angles within certain limits without ever making a complete turn (180°).

†It may be noted that symmetry has been reduced relative to the chair both in the boat and in the twist boat.

(beq, or ψ-e, or e′) on C-2, C-3, C-5, and C-6 which are eclipsed in pairs, and four boat -axial (bax, or ψ-a, or a′) on the same four carbon atoms also eclipsed in pairs. The boat consists of four gauche butane and two eclipsed butane units and the strain may be computed as $4\times3.3+2\times18.0=49.2$ kJ mol^{-1} (minimum) or $4\times3.3+2\times26.0=65.2$ kJ mol^{-1} (maximum). The difference in enthalpies between the chair and boat forms is thus 29.4 kJ mol^{-1} (minimum) or 45.4 kJ mol^{-1} (maximum), the enthalpy of the chair being 19.8 kJ mol.$^{-1}$. In addition, the two perpendicular H's at C-1 and C-4 is only 183 pm away giving rise to a non-bonded interaction, known as flagpole-bowsprit interaction. Structure VIa shows the two eclipsed butane units in Newman projection and structure VIb shows the torsion angles according to Klyne-Prelog convention.

If the fp and bs H's are pulled a little apart, the twist-boat results in which the fp-bs interaction is minimised and the conformation becomes more stable. It belongs to point group D_2 ($3\times C_2$) and is chiral. The different bonds are shown in the structure (VII) in which tax. teq, and iso stand for twist-axial, twist-equatorial, and isoclinal (the two geminal bonds are equivalent) respectively. The structure (VIIa) shows one butane unit in Newman projection and the structure (VIIb) shows the torsion angles according to Klyne-Prelog convention. Although the boats and twist-boats (flexible forms) are of high energy, they have favourable entropy due to more degrees of freedom than the chair and the population of the flexible form is approximately 1 in 1000 at ambient temperature quite insufficient for detection by physical methods.

3. Determination of barrier energy. The axial and equatorial protons of cyclohexane form two broad and complex (due to spin-spin coupling) bands in NMR at -100°C and below separated approximately by 0.45 ppm which coalesce to a broad singlet at –66.7°C (at 60 MHz). The free energy of activation ($\Delta G^{\ddagger}$) as determined by the coalescence temperature (Chapter 9) is found to be $42.2+0.4$ kJ mol^{-1} (Jensen et al 1962). In order to avoid complexity due to spin-spin coupling, cyclohexane-d_{11} (C_6HD_{11}) has been used for variable temperature NMR with deuterium-decoupling so that two sharp signals one due to the axial and the other due to the equatorial proton are obtained (Figure 10.5a) at low temperature (Anet et al 1967). The coalescence temperature is found to be –61.4°C (at 60 MHz) corresponding to the free energy of activation of 43.2 kJ mol^{-1}. A complete line shape analysis (which requires measurements of line-widths at different temperatures) gives the values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ as 45.1 kJ mol^{-1} and 11.7 JK^{-1} mol^{-1} respectively. The large entropy of activation arises from the fact that the transition state (as III) can adopt as many as six (three for simple cyclohexane) conformations giving considerable amount of entropy of mixing. Substituents in the ring do not substantially raise the barrier energy and the usual range of barrier height is 42—50 kJ mol^{-1}.

Anet et al (1975) heated cyclohexane to 800°C when the population of twist-boat form rose to 25% and then suddenly cooled the sample to -253°C on a cesium iodide plate so that all the conformers were frozen*. From the study of kinetics of twist-boat-chair interconversion by IR, the free energy of activation is found to be

*The procedure is known as matrix separation (see butadiene).

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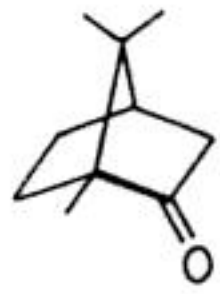

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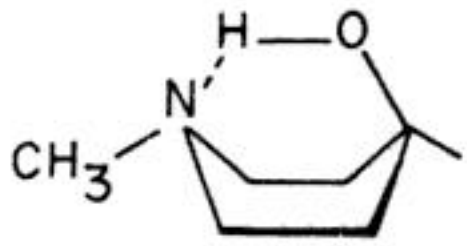

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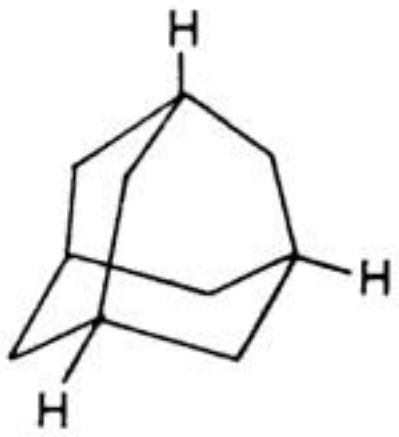

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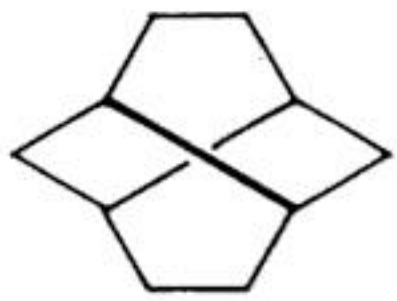

(XV)

Figure 10.6 Rigid molecules from cyclohexane conformers

10.3 Conformations of monosubstituted cyclohexanes

Monosubstituted cyclohexanes exist in two non-equivalent diastereomeric chair conformations, one with the substituent in the equatorial position (conformer E) and the other with the substituent in the axial position (conformer A), shown for methylcyclohexane by the structures (XVIa) and (XVIb) or (XVIc) (Figure 10.7) respectively. The following points are to be considered in connection with monosubstituted cyclohexanes.

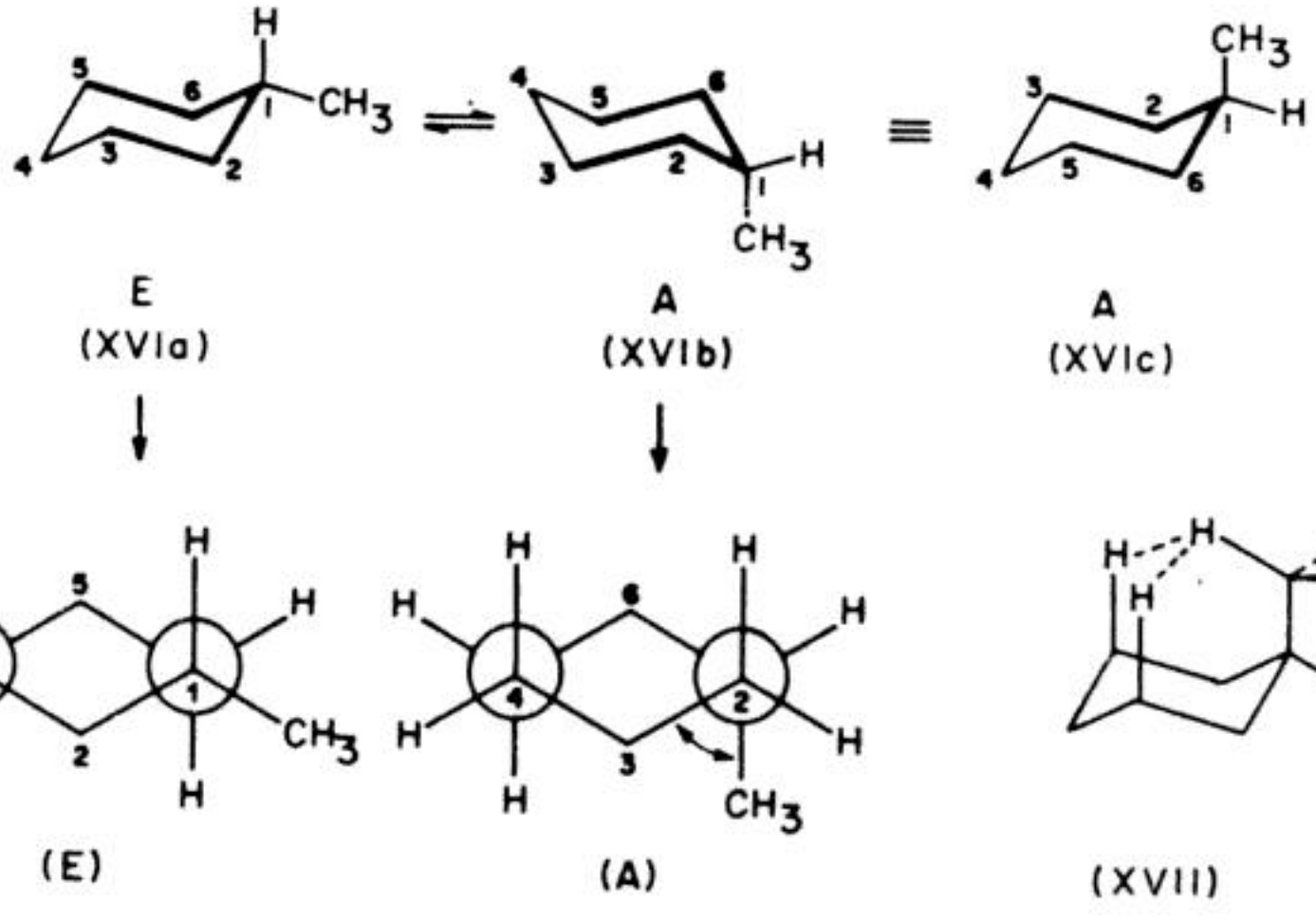

Figure 10.7 Conformers of methylcyclohexane

10.3.1 **Transition states and intermediates**

Energy barrier of ring inversion in substituted cyclohexanes remains practically unaffected. The number of possible transition states and the flexible forms (there are six different carbon atoms to which the substituent can be attached), however, increases because of the loss of symmetry in the molecule. The energy profile diagram is similar to that of cyclohexane ring inversion (Figure 10.3) except for the fact that the two chair conformers have different enthalpies and free energies and the rates of interconversion are different from the two sides.

10.3.2 **Conformational free energy**

The most significant fact from the point of view of conformational analysis is that the two diastereomeric chair forms are of unequal free energy and so are differently populated, the equilibrium constant K being given by the equation :

$$\Delta G^\circ = -RT \ln K \qquad \text{where } K = \frac{[E]}{[A]} \tag{1}$$

ΔG° which is usually negative is the difference of free energy between the equatorial and axial conformers and $-\Delta G^\circ$ is known as conformational free energy of the substituent (sometimes known as A-value). It determines the equatorial preference of the substituent in the substituted cyclohexane which is based on steric ground as explained before* (in some cases, electronic factor may also operate) and is best exemplified by methylcyclohexane. Thus the equatorial conformer (XVIa) does not have any additional gauche butane interaction, the two new butane units, e.g., Me-C_1-C_2-C_3 and Me-C_1-C_6-C_5 (shown by thick lines) having anti orientation. On the other hand, the axial conformer (XVIb) has two additional gauche interactions involving Me-C_1-C_2-C_3 and Me-C_1-C_6-C_5. In the partial Newman projection (E) (Figure 10.7) for the equatorial conformer, no extra gauche interaction is seen whereas in the one (A) for the axial conformer, an extra gauche interaction is observed (the second gauche can be seen in the projection along 1-6 bond). The overall steric interactions may also be evident from the inspection of the structure (XVII) in which the axial methyl protons are very near (183 pm) to the synaxial protons. When the methyl group is equatorially placed, no such interaction exists. Based on the number of additional gauche interactions, the difference in enthalpy of the two conformers is 6.6 (2×3.3) kJ mol^{-1}. If ΔH is equated to ΔG ($\Delta S \approx 0$), the value corresponds to a population of equatorial conformer over 90% (actually 95% as found by NMR) at ambient temperature. The conformational free energies ($-\Delta G^\circ$ values) of a number of

---

*According to a suggestion of Allinger (Wertz and Allinger 1974), it is the tertiary hydrogen which has a preference for the axial position which leaves the substituent in the equatorial position by default (equatorial hydrogen effect). The arguments—which are based on the assumption that while a gauche methyl interaction can be substantially relieved by ring flattening and deformation of bond angles, the gauche H-H interaction cannot get any such relief and this ultimately becomes the deciding factor—are too much involved and since there has been dispute over them, are not discussed here (see also Chapter 9).

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the methine proton of chlorocyclohexane resolves into two sets of signals, the one at δ4.50 ppm (broad singlet) being due to the equatorial and the other (multiplets) at δ3.80 ppm being due to the axial proton (Figure 10.8). The equatorial proton is coupled with adjacent methylene protons which are all gauche (with low coupling constants) (see Chapter 9) and so gives a broad signal while the axial proton is coupled with both equatorial and axial protons (with high coupling constants) and gives well resolved multiplets (Jensen et al 1966, 1969). Their relative intensity provides the conformational free energy at —115°C. At $-$ 150°C, the equatorial conformer crystallises out and the mother liquor can be decanted off thus effecting a separation of the two conformers. The solid when redissolved in a better solvent at very low temperature gives the NMR spectrum of the equatorial conformer (δ3.80 ppm) while the mother liquor gives largely the NMR spectrum of the axial conformer (δ4.50 ppm) recorded for the C*H*Cl proton.*

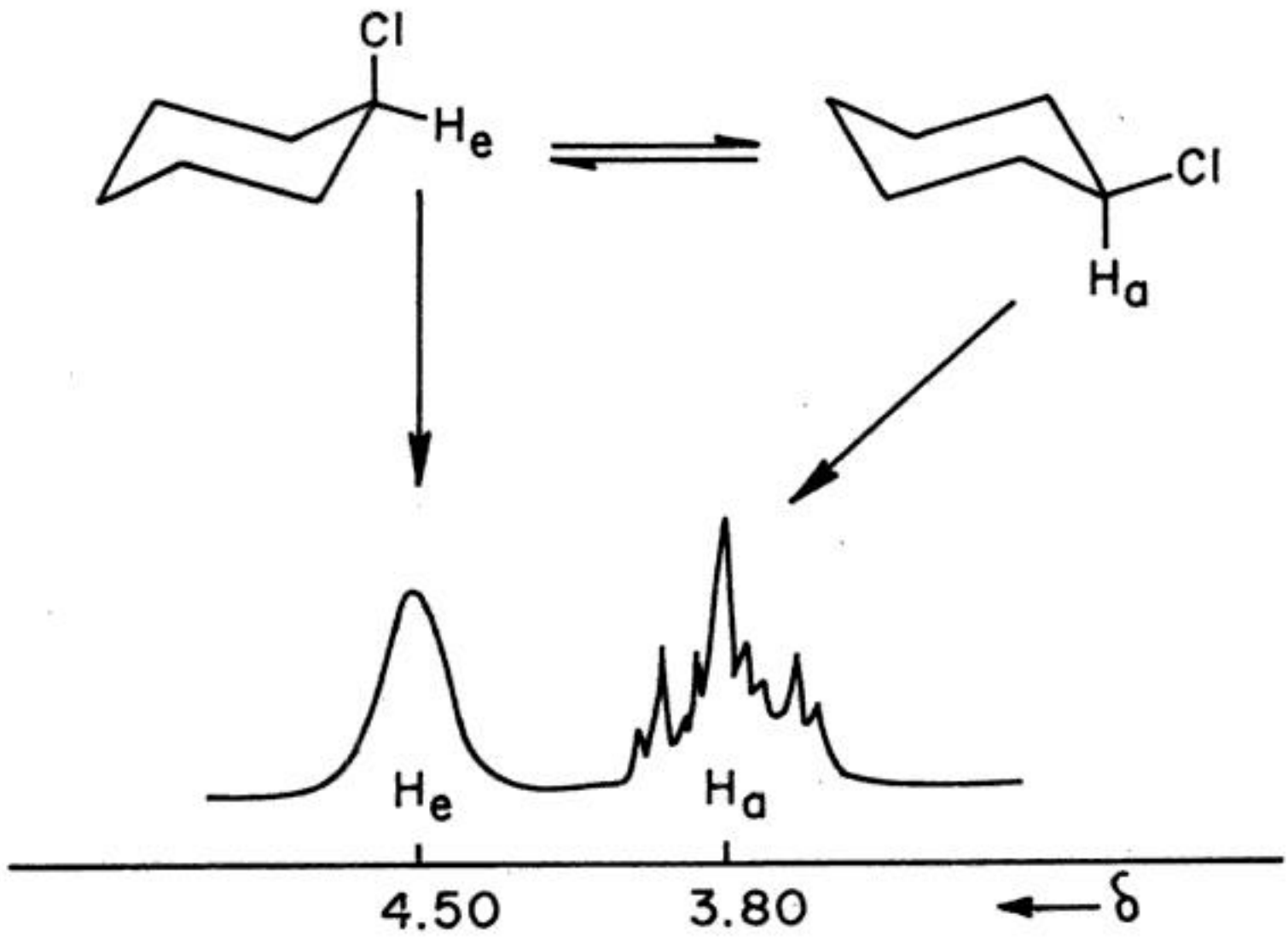

Figure 10.8 Low temperature NMR spectrum of conformers of chlorocyclohexane

Even though separation of two conformers is not always possible, their relative population, rate of interconversion, and the thermodynamic parameters of the exchange process may be studied by NMR. It has been computed (Jensen et al 1969) that equatorial chlorocyclohexane has a half-life of 22 years at $-$ 160°, 23 minutes at $-$ 120°, 0.25 second at $-$ 60°, and 10^{-5} second at 25°C.

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*In IR, even at ambient temperature, the two C-Cl bonds can be distinguished. Thus liquid chlorocyclohexane exhibits two C-Cl stretching frequencies, 684.5 and 731 cm^{-1} for the axial and equatorial bonds respectively. Crystalline chlorocyclohexane gives only the 731 cm^{-1} band characteristic of the equatorial bond.

10.3.4 **Determination of conformational free energy**

The principle of conformational analysis by physical methods including different spectroscopic techniques has already been discussed in a previous chapter. Because of conformational simplicity, its application in cyclohexane system is more straightforward. A particular property, be it physical or chemical, is determined by some suitable means for each of the two conformers and the same property is measured for the conformationally mobile system at a given temperature. Three values, P_a (for axial), P_e (for equatorial), and P (for the mobile) are thus obtained and the equilibrium constant K may be determined by the relation :

$$K = \frac{P_a - P}{P - P_e} = \frac{[E]}{[A]} \qquad (2)$$

This is direct method (it does not require any reference compound) and P may be chemical shifts (δ) in NMR or stretching frequencies (cm^{-1}) in IR. The case of chlorocyclohexane discussed above is a typical example in which δ_a and δ_e are determined directly. The conformational free energies of most of the substituents have been determined by NMR using the low-temperature method.

In certain cases P_a and P_e may be determined from appropriate model compounds (see Chapter 12). Thus *cis*- and *trans*-4-*t*-butylcyclohexyl bromides (XVIIIa) and (XVIIIb) which are conformationally biased (Figure 10.9) show chemical shifts of 198 and 160.5 Hz (at 60 MHz) respectively for α-H while bromocyclohexane shows a chemical shift of 191.5 Hz (Eliel 1959). Putting the values in the equation (2) and assuming that the presence of the *t*-butyl group does not affect the chemical shifts, K is found to be 4.8 corresponding to 83% of equatorial population ($-\Delta G°_{Br} = 3.8$ kJ mol^{-1}).*

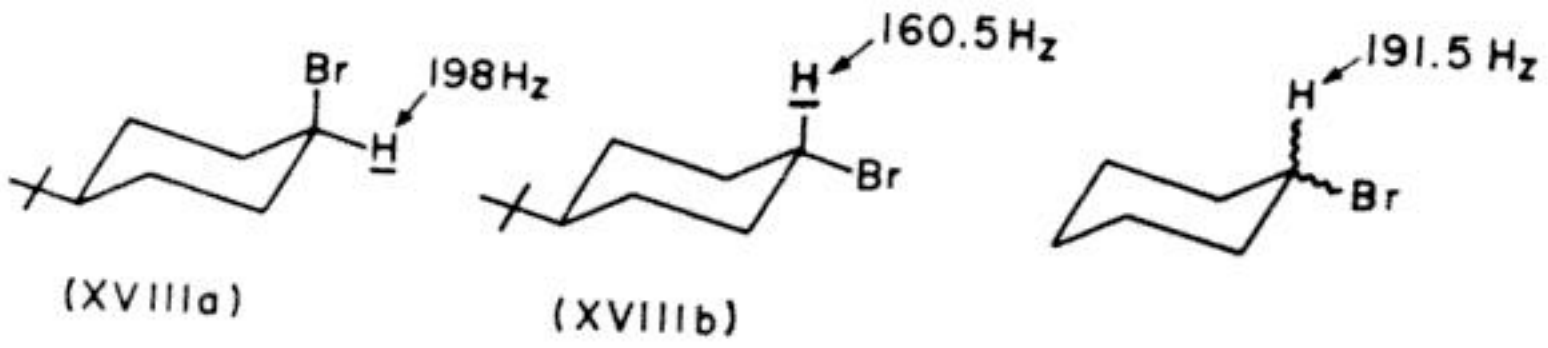

Figure 10.9 Determination of K from conformationally biased molecules

A similar kinetic method substituting P by rate constants in equation (2) will be discussed in Chapter 12.

A chemical method is often used in which two diastereomers are equilibrated and the equilibrium concentration of each is determined. If during equilibration, one of the groups remains unaltered in position, then the conformational free energy of the second group can be calculated from the equilibrium constant. Thus the *cis*- and *trans*-4-*t*-butylcyclohexanols (XIXa) and (XIXb) (Figure 10.10) are

*$-\Delta G°$ values depend very much on the method used and in the case of polar compounds, also on solvent (see Eliel et al 1965).

equilibrated by heating with Raney nickel in refluxing benzene. In the product which is analysed by gas chromatography, the *t*-butyl group always remains in the equatorial position. The equilibrium constant for the reaction (28% of XIXa and 72% of XIXb) gives a value of $-\Delta G°_{OH}$ of 2.9 kJ mol^{-1} (Eliel and Schroeter 1965) in benzene solution.

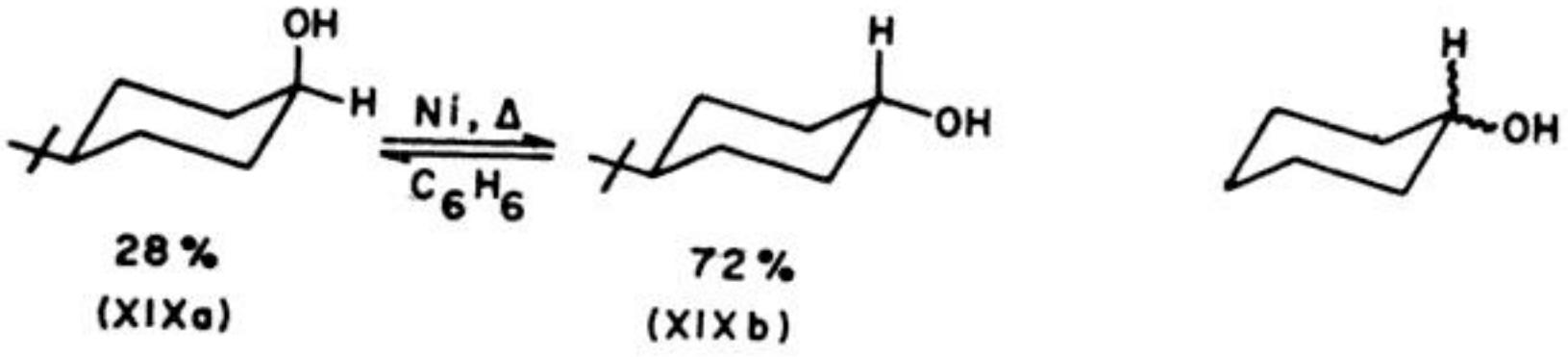

Figure 10.10 Equilibration of 4-*t*-butylcyclohexanols

The various methods used for determining the conformational energies have been reviewed (Jensen and Bushweller 1971).

10.4 Conformations of di- and polysubstituted cyclohexanes

The principle of conformational analysis as applied to monosubstituted cyclohexanes may be extended to di- and polysubstituted cyclohexanes. Two additional points, however, have to be considered. These compounds generally exist in two or more diastereomeric forms and each of them is capable of existing in two (sometimes even more) conformers. It is desirable to examine each pair of conformers of a diastereomer in terms of symmetry, enthalpy, entropy, and free energy and to ascertain the preferred conformation. Comparison is then made between the diastereomers through the preferred conformer or conformers of each. Secondly, the substituents may interact among themselves sterically or otherwise and these interactions must be included in the analysis.

10.4.1 1,1-Disubstituted cyclohexanes

The case of 1,1-disubstituted (geminally substituted) cyclohexanes is relatively simple. They do not exhibit any configurational isomerism but exist in two interconvertible conformers (XXa) and (XXb) (Figures 10.11) separated by an energy barrier usually of the same order of magnitude as the cyclohexane ring inversion. When X and Y are the same as in 1,1-dimethylcyclohexane, the two conformers are identical (topomers). When X and Y are different as in 1-methylcyclohexanol, the two conformers are diastereomers and present in unequal amounts. In principle, the ratio of the two conformers should correspond to the difference in the conformational free energies of the two substituents. However, in reality, this seldom happens; although the conformer with the bulkier substituent in the equatorial position often predominates, there is a levelling effect, the preferred conformer being considerably less populated than expected. Thus 1-methylcyclohexanol exists as a 70 : 30 mixture of axial (XXIa) and equatorial (XXIb) conformers in dimethyl sulphoxide at 35°C corresponding to a free energy difference

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Table 10.3 Conformations, interactions, enthalpies, entropies, and free energies of non-geminal dimethylcyclohexanes[a]

Isomers	Prefd. confn.	No. of gauche (difference)	ΔH_{calcd} (kJ mol^{-1})	ΔH_{exptl} (kJ mol^{-1})	Entropy (JK^{-1}mol^{-1}) contribution from: Rlnσ	(±)	e·e+a·a	Total	ΔS_{exptl} (ΔS_{calcd})	ΔG^{b}_{exptl} (25°C) (ΔG^{b}_{calcd}) (kJ mol^{-1})
cis—1,2	e,a	3			0	5.8	0	5.8		
		(2)	7.5	7.80					3.00[c]	6.9
trans—1,2	e,e	1			−5.8	5.8	0.46	0.46	(5.34)	(5.78)
cis—1,3	e,e	0			0	0	0	0		
		(−2)	−7.5	−8.20					−5.19	−6.65
trans—1,3	e,a	2			0	5.8	0	5.8	(−5.8)	(−5.64)
cis—1,4	e,a	2			0	0	0	0		
		(2)	7.5	7.95					5.00	6.50
trans—1,4	e,e	0			−5.8	0	0.13	−5.6	(5.6)	(5.70)

[a] The numerical values indicate the difference between cis and trans isomers (for sources of information, see Eliel 1962).
[b] ΔG has been calculated from ΔH and ΔS.
[c] The large deviation is probably due to interference with methyl rotation (cog-wheeling) which has not been taken care of.

Table 10.4 Relative population of a,a- and e,e-conformers in *trans*-1,2-dibromocyclohexane

State of aggregation	% of a,a-conformer	% of e,e-conformer
Liquid	65	35
Gaseous	95	5
In CCl_4	84	16
In C_6H_6	52	48

In solution, the relative population of the two conformers depends on the solvent polarity, the diequatorial form being more stabilised by increasing solvent polarity. The dipole moment of the trans isomer changes with solvents but that of the cis isomer remains reasonably constant. *trans*-1,2-Dichlorocyclohexane exists exclusively in the e,e-conformation in crystal, shows some a,a-conformer in the liquid, but in the gaseous state, the a,a-form predominates. The ring inversion parameters (a,a⇌e,e) in dihalides are $\Delta H^{\ddagger} = 42.0$ kJ mol^{-1} and $\Delta S^{\ddagger} = -12.0 \pm 8$ JK^{-1} (Ehrhardt and Vaughan 1981).

2. Effect of H-bond. The effect of intramolecular H-bonding in stabilising the diaxial conformation of *cis*-cyclohexane-1,3-diol has already been mentioned. Both the *cis* and *trans*-cyclohexane-1,2-diols show intramolecular H-bonding which is slightly stronger in the cis than in the trans isomer (the shift of OH stretching frequency from that of free OH being 38 and 33 cm^{-1} respectively). In the *trans*-2-halocyclohexanol, the diequatorial conformer (XXIXa) is stabilised through intramolecular H-bonding and the diaxial conformer (XXIXb) has the advantage of the absence of electrostatic repulsion between the two dipoles (Figure 10.13b). A compromise is reached and the two conformers are almost equally populated.

3. Cis preference for 1,2-disubstituted cyclohexane. A rare example of cis-preference is recorded (Pasto and Rao 1969) for 2-*t*-butylcyclohexanols which on equilibration with Raney Ni give a preponderance of the cis (XXX) over the trans (XXXI) isomer corresponding to $\Delta G_{296}°$ of 2.3 kJ mol^{-1}, ΔH of 3.3 kJ mol^{-1} and ΔS of 3.6 JK^{-1} mol^{-1} (from cis to trans). The relatively low ΔS precludes the existence of any flexible form. This is probably due to the interaction of a Me in the *t*-butyl group with OH although it is not clear why this is less in the cis isomer.

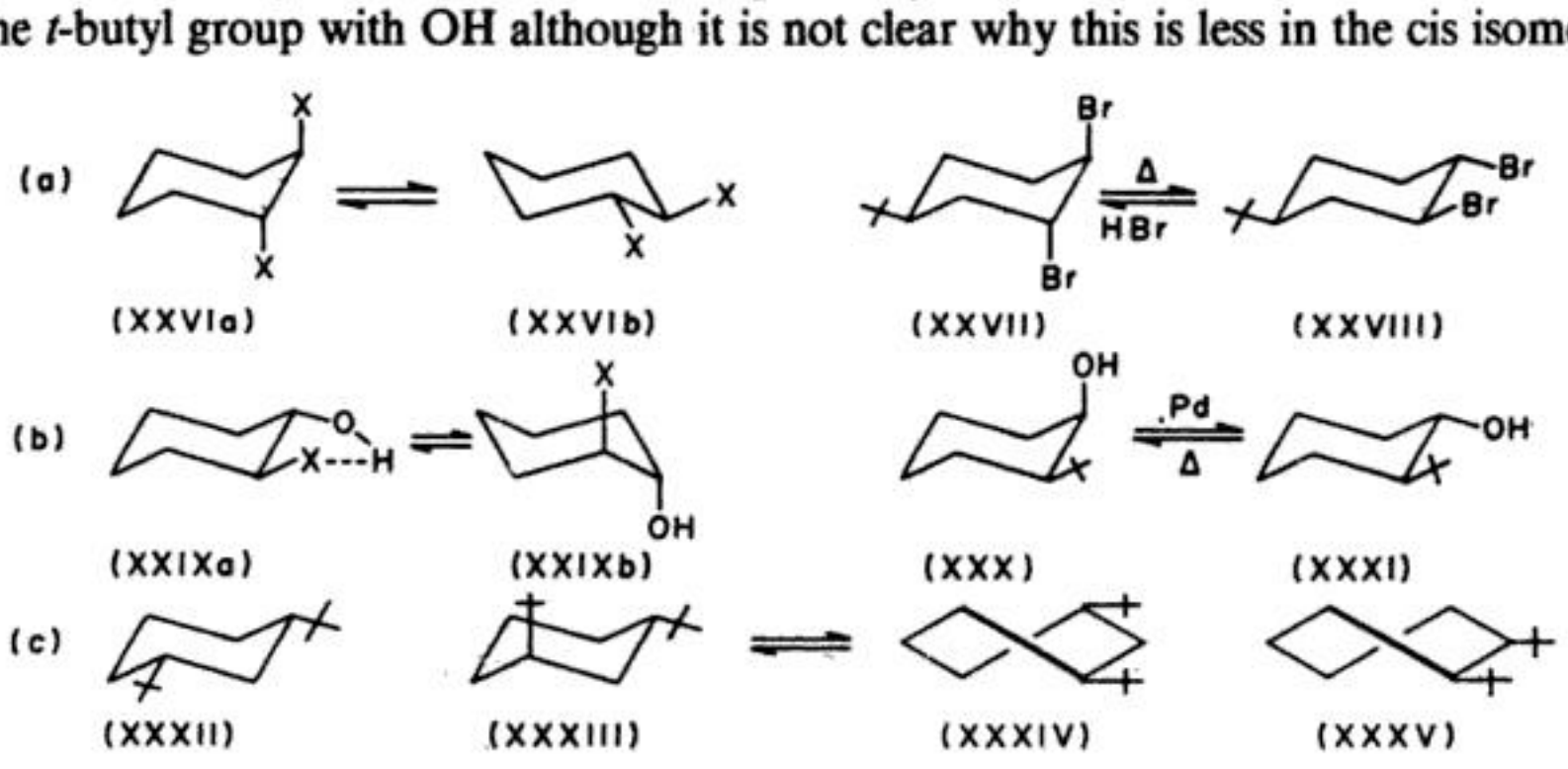


Figure 10.13 Effect of dipole moment, H-bonding, and bulky substituents on conformation

4. Twist-boat conformers. In some cases, the presence of two or more bulky groups like *t*-butyl may destabilise the normal chair and one or more of the flexible forms predominate. Thus the cis isomer of 1,3-di-*t*-butylcyclohexane exists in chair conformation (XXXII) with both the *t*-butyl groups placed in equatorial positions. But in the trans isomer, one of the *t*-butyl groups has to be placed in an axial position which would make the chair conformer (XXXIII) highly strained (Figure 10.13c). The steric interaction can be substantially reduced in the flexible conformation (XXXIV). The cis and the trans isomers are equilibrated by heating with Pd (Allinger and Freiberg 1960) and the thermodynamic parameters are as follows: $\Delta H = 25.0$ kJ mol^{-1}, $\Delta S = 20.5$ JK^{-1} (from trans to cis). The high value of ΔS is consistent with the flexible form for the trans isomer and that of ΔH also agrees with the calculated value (difference in chair and twist forms) which is approximately 22.0 kJ mol^{-1}. More recently, the cis isomer of 1,2-di-*t*-butylcyclohexane has been shown by low temperature NMR (Kessler et al 1968) to exist as an equilibrium mixture of a chair and a number of flexible conformers (as XXXV).

5. Reflex effect. If two or more substituents are placed in 1,3-diaxial positions in cyclohexane, a considerable amount of steric interaction results. To avoid the steric strain, the ring flattens on the side of the substituents and in so doing, the axial positions on the other side of the ring become congested. Thus the strain on one side of the ring is reflected on the other side and this effect is known as the *reflex effect* (Ourisson et al). The reflex effect also interferes with the normal conformational analysis and will be discussed in connection with polysubstituted cyclohexanones (Section 10.5.1).

10.4.4 Conformation of polysubstituted cyclohexanes

The conformational analysis of polysubstituted cyclohexanes is rendered more difficult because of the increased number of interactions among the substituents. A few typical examples are discussed here which have been studied through chemical equilibrium between two or more diastereomers at different temperatures. The preferred conformation of each diastereomer is evaluated on the basis of various interactions and the experimental thermodynamic parameters compared with the calculated values. In general, the conformers with the higher number of equatorial substituents are more stable.

1. 1,3,5- Trimethylcyclohexanes. 1.3.5- Trimethylcyclohexane is capable of existing in two meso diastereomers, the cis represented by the formula (XXXVI) and the trans by XXXVII (Figure 10.14). The alternative conformers obtained by ring inversion are too unstable due to 1,3-diaxial Me-Me interaction and may be ignored. Their equilibria at different temperatures have been studied by heating with palladium. The values of $\Delta H_{25}°$ and $\Delta S_{25}°$ are 8.8 kJ mol^{-1} and 9.6 JK^{-1} mol^{-1} respectively which agree fairly well with the calculated values (ΔH corresponds to two gauche butane interactions in the trans, i.e. 7.5 kJ mol^{-1} and ΔS corresponds to Rln3 or 9.2 JK^{-1} mol^{-1} in favour of the cis isomer which has a symmetry number 3 in contrast to 1 for the trans isomer). The conformations of 1,2,3-trimethylcyclohexanes have been studied by ^{13}C-NMR (Dalling and Grant 1972).

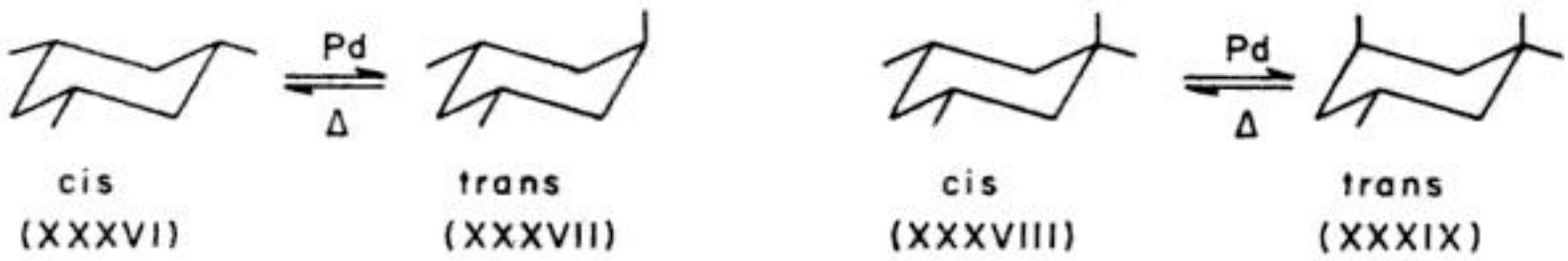


Figure 10.14 Equilibration of tri- and tetramethylcyclohexanes

2. 1,1,3,5-Tetramethylcyclohexanes. 1,1,3,5-Tetramethylcyclohexane exists in a meso cis form (XXXVIII) and a resolvable (±)-trans form (XXXIX) (Figure 10.14) and their chemical equilibrium at different temperatures has been studied (Allinger and Miller 1961). The cis isomer has the preferred triequatorial conformation (XXXVIII), the inverted conformation with three methyls in synaxial position being too unstable. The trans isomer (XXXIX) on ring inversion leads to an equivalent conformation. From the temperature-dependent equilibria, the values of $\Delta H°$ and $\Delta S°$ (at 300°C) are found to be 15.5 kJ mol^{-1} and 6.9 JK^{-1} mol^{-1} respectively, the cis isomer being more stable than the trans. Both the cis and trans isomers have two gauche butane interactions. But the latter (XXXIX) has, in addition, a 1,3-diaxial Me-Me interaction. The difference in their enthalpies, 15.5 kJ mol^{-1} thus corresponds to the last-named interaction—a value which is generally accepted. Although this severe interaction may lead to some distortion in the geometry, the molecule essentially retains the chair form as evidenced by the entropy change (6.9 as against a calculated value of 5.8 JK^{-1} mol^{-1}).

The equilibration of the cis and trans isomers of 3,3,5-trimethylcyclohexanols (using aluminium isopropoxide) gives a value of 10.0 kJ mol^{-1} for the 1,3-diaxial interaction between Me and OH (Eliel and Haubenstock 1961).

3. Menthols. 2-Isopropyl-5-methylcyclohexanol (menthols) contains three asymmetric centres and exists in 4 (±)-pairs, known as menthol (XL), neomenthol (XLI), isomenthol (XLII), and neoisomenthol (XLIII) (Figure 10.15, only one enantiomer of each is shown). The first two and the last two form epimeric pairs and can be equilibrated with aluminium isopropoxide. They are written in order of their thermodynamic stability, menthol with all the groups equatorial being the most stable and neoisomenthol with Me and OH axially disposed being the least stable. The bulkiest isopropyl group remains equatorial in all these conformations although in the case of neoisomenthol, there may be substantial population of the inverted conformer. The four diastereomeric menthyl amines are similarly analysed.

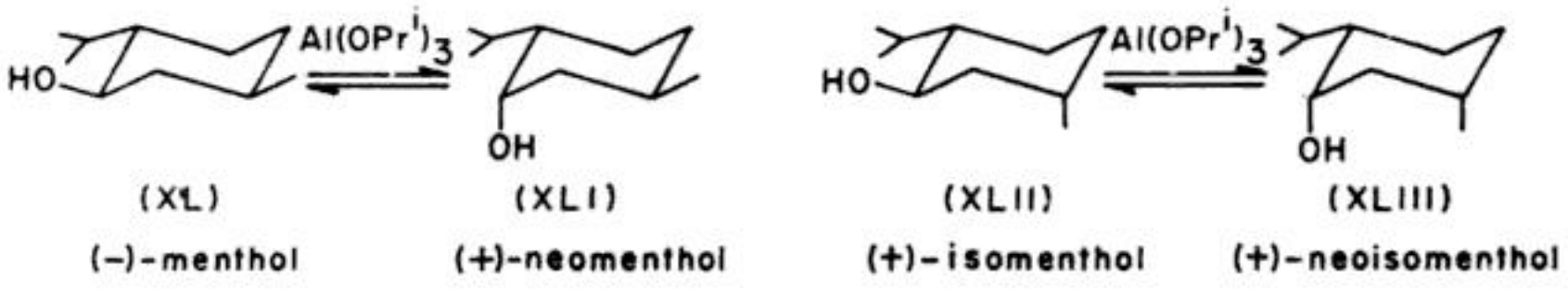
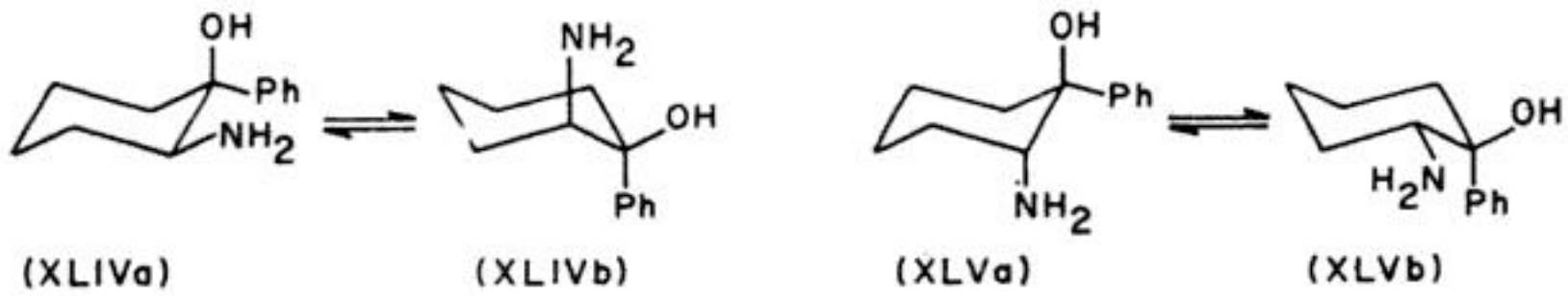


Figure 10.15 Configurations and conformations of menthols

4. 1-Phenyl-2-aminocyclohexanol. The cis isomer of 1-phenyl-2-aminocyclohexanol exists in two conformers (XLIVa) and (XLIVb) (Figure 10.16) both



(XLIVa) (XLIVb) (XLVa) (XLVb)

Figure 10.16 Conformers of *cis*- and *trans*-1-phenyl-2-aminocyclohexanols

capable of forming intramolecular H-bond between OH and NH_2 with OH stretching frequency lower than 3600 cm^{-1}. Although the former (XLIVa) has the bulky Ph group equatorial, the conformer is very congested,. The other conformer (XLIVb) with axial Ph interacting minimally with 3-H and 5-H (see Section 10.4.1) may, therefore, predominate. For the trans isomer, however, the conformer (XLVa) with Ph equatorial is clearly preferred over the other (XLVb). Indeed the isomer does not show any trace of intramolecular H-bonding.

5. 1,2,4,5-Tetramethylcyclohexanes. 1,2,4,5-Tetramethylcyclohexane exists in five diastereomeric forms (Table 10.5). Their chemical equilibrium at different temperatures has been determined (Werner et al 1970). Their enthalpies and relative populations are given in the Table which approximately correspond to the calculated values (interactions are shown).

1 2 3 4 5

Table 10.5 Conformations of 1,2,4,5-tetramethylcyclohexanes

Conformers: (preferred)	1	2	3	4	5
% at 300°C	53.2	35.1	9.3	1.9	0.5
Δ H° (kJ mol^{-1})	0 *	+ 7.9	+ 12.1	+ 16.3	+ 23.4
Interactions	2g	4g	5g	6g	4g + syn-1,3-Me_2

*The arbitrary base value includes two gauche interactions which are offset in the computation of all ΔH°values)..

It is interesting to know how the increasing substitution affects the barrier energy of cyclohexane ring inversion. 1,1-Dimethylcyclohexane has almost the same $\Delta G^{\ddagger}$ value (42.6 kJ mol^{-1} at 298 K) as cyclohexane itself while 1,1,4,4-tetramethylcyclohexane has a slightly higher $\Delta G^{\ddagger}$ value (47.7 kJ mol^{-1} at 211 K). All-*cis*-1,2,4,5-tetramethylcyclohexane has a barrier to ring inversion of 51.8 kJ mol^{-1} at 261 K and all-*cis*-1,2,3,4,5,6-hexamethylcyclohexane has a barrier of 71.8 kJ mol^{-1} at 338 K which shows that in general two or three alkyl substituents do not increase the barrier energy very much but when the number of substituents is higher, the barrier increases appreciably. Sometimes, even two groups increase the barrier if they are sufficiently bulky. Thus *cis*-1,2-di-*t*-butylcyclohexane has a barrier of 68.1 kJ mol^{-1} at 310 K. The ring inversion parameters are available in a recent text (Oki 1984).

6. Hexachlorocyclohexanes. 1,2,3,4,5,6- Hexachlorocyclohexane in principle should exist in eight configurational isomers one of them being resolvable and the

rest meso. Five of them, designated α (a,a,e,e,e,e), β (e,e,e,e,e,e), γ (a,a,a,e,e,e), δ (a,e,e,e,e,e), and ϵ (a,e,a,e,a,e) (only preferred conformations are indicated), have been investigated by electron diffraction experiments in the gas phase (Hassel et al).There has been close agreement between the experimentally determined enthalpies and those obtained by calculation. The γ isomer is the insecticide gammexane.

7. Inositols. Of the polyhydroxycyclohexanes known as cyclitols, the inositols are most well known because they occur in nature. Like hexachlorocyclohexanes, inositols exist in eight isomeric forms all of which are known and their configurations determined by spectroscopic data and chemical reactions (see Eliel et al 1965). The following points are to be noted:

(*i*) Seven of the isomers are meso and the eighth one (a,a,e,e,e,e,) is resolvable giving a total of nine stereoisomers.

(*ii*) In the case of two isomers (a,e,a,e,a,e) and (a,a,a,e,e,e), the ring inversion gives the same conformation. In the case of one (a,e,a,a,e,e), the two conformers are non-superposable mirror images of each other which makes this isomer non-resolvable (±) -pair.

(*iii*) The higher the number of e-OH, the higher is the stability and the preferred conformer of any isomer is selected on that basis. For isomers with three a-OH groups, the two conformers are equally populated. The number of isomers are predictable from the planar structure (Leonard et al).

10.5 Cyclohexane ring with one and two sp^2 carbons

Introduction of an sp^2-hybridised carbon into a cyclohexane ring brings about several changes: one or more valence angles are increased, the ring slightly flattens in the vicinity of the sp^2 carbon decreasing torsion angles and increasing torsional strain, and finally, the steric interactions among the substituents and between the substituents and the ring change perceptibly. As a result, there is an overall increase in enthalpy of cyclohexanes with an sp^2 hybridised ring atom relative to simple cyclohexanes. Cyclohexanone with one sp^2 carbon has been most thoroughly investigated and illustrates the above points.

10.5.1 Cyclohexanone ring system

In the absence of any complicating factor, cyclohexanone exists almost exclusively (99% at 25°C) in the chair form (XLVIa) which on inversion gives a topomer (XLVIb). A small amount (ca 1% at 25°C) remains in the flexible forms (XLVIc) and (XLVId) (Figure 10.17). The conformational aspects of cyclohexanones are discussed under the following headings.

1. Geometry. The geometry of the cyclohexanone chair differs slightly from that of cyclohexane:

CH_2- CH_2 bond length = 0.1545 nm (154.5 pm)
CH_2- CO bond length = 0.151 nm (151.0 pm)
C-CO-C bond angle* = 116°

*It is less than 120° which means that flattening is resisted by torsional strain and angle strain does develop.

The torsion angles between pairs of adjacent carbon atoms are given for each conformation according to Klyne-Prelog convention (Bucourt 1974) which shows flattening of the ring at the site of the carbonyl group. The chair form (XLVIa) has only a vertical σ plane passing through C-1, and C-4 and belongs to point group C_s while the flexible forms belong to chiral point groups C_1 and C_2. Due to flattening, the e-H's at C-2 and C-6 in XLVIa are partially eclipsed with the carbonyl oxygen ($\theta = 4.3°$) while the a-H's lean slighlty outwards. The combined effect of angle strain and torsional strain slightly destabilises cyclohexanone relative to cyclohexane. The lower thermodynamic stability of cyclohexanone is manifest in the equilibrium of cyclohexanone cyanohydrin ($sp^2 \rightleftharpoons sp^3$) which lies more towards the cyanohydrin side than that of di-*n*-octyl ketone (K is 70 times as great) *. Similarly, the lower kinetic stability of cyclohexanone is manifest in the fact that it is reduced with sodium borohydride at a rate 355 times as fast as di-*n*-hexyl ketone. These manifestations of strain have long been known; the term I-strain (internal strain) has been coined by Brown for this (see later).

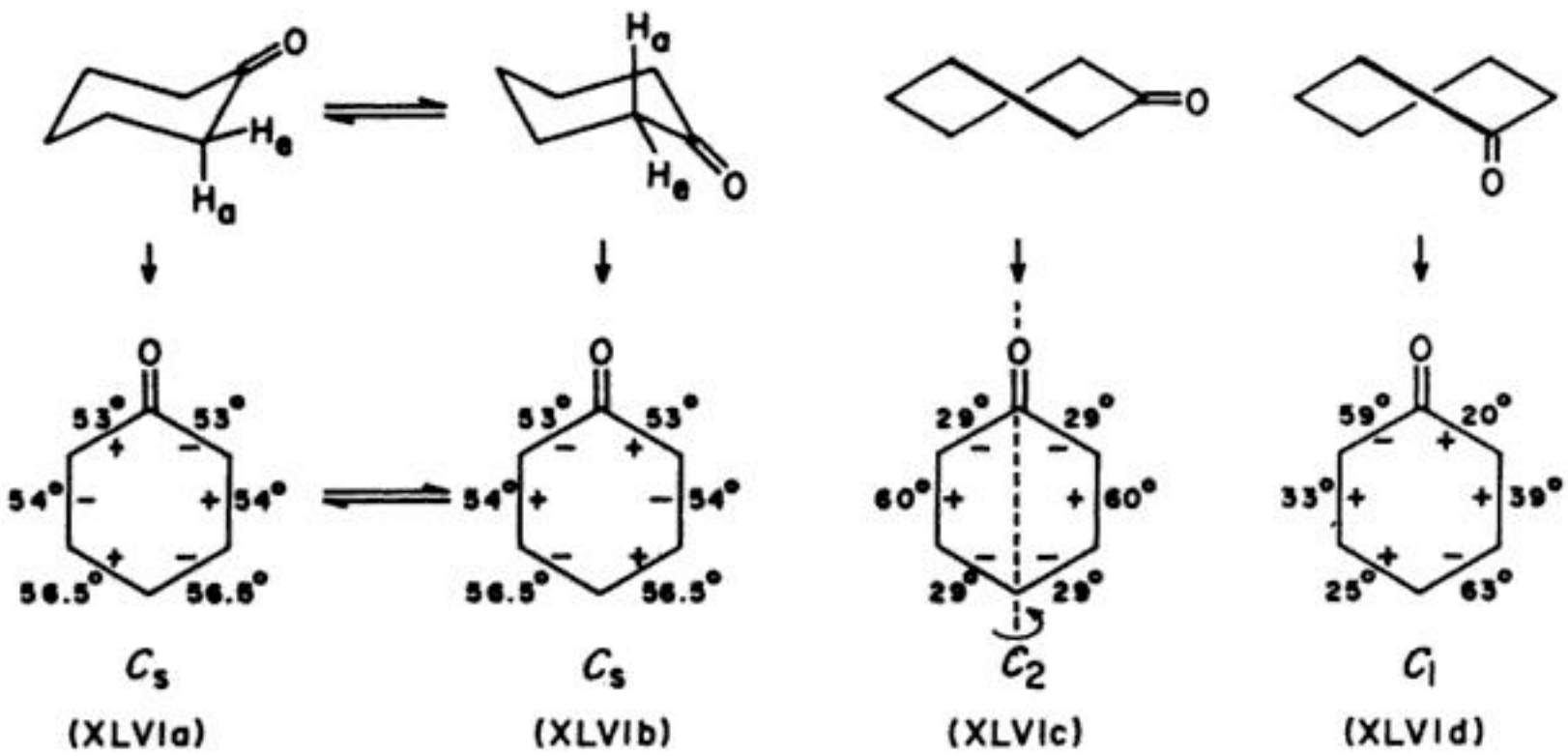


Figure 10.17 Conformation and geometry of cyclohexanone

In comparison to cyclohexane, the flexible forms here are slightly more stabilised due to the absence of eclipsing of adjacent e-H's with the carbonyl oxygen in the twist-boat forms (XLVIc) and (XLVId) and due to the partial absence of eclipsing between cis H's in the boat forms. Of the two twist-boats, the one (XLVIc) is stabler than the other (XLVId), their respective enthalpies (calculated) being 13.4 and 16.7 kJ mol^{-1} above that of the chair form which are considerably lower than that in the cyclohexane system (22.2 kJ mol^{-1}). The two boat conformers (not shown), one a C_s boat and the other a C_1 boat have slightly higher energy. The flexible forms may be substantially populated in cyclohexanones with bulky substituents, more so than in analogous cyclohexanes (Allinger et al 1966).

2. **Ring inversion.** Because of lower torsional barrier around an sp^3-sp^2 carbon

*The presence of one or more axial substituents, however, reverses the direction of the equilibrium due to 1,3-diaxial interaction (see Eliel 1962, p. 243).

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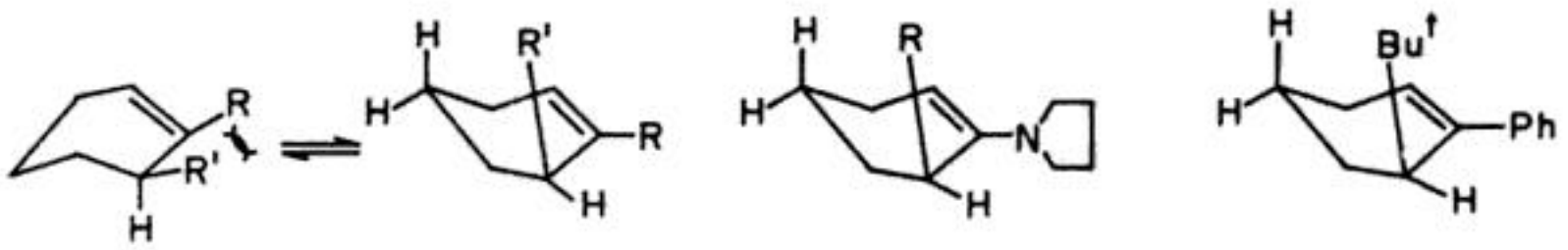
(Figure 10.22), if R and R′ are moderately large, they will interfere sterically with each other in the equatorial conformer (LIXa) to such an extent that the axial conformer (LIXb) will be preferred. As already stated, the dihedral angle between 6-e-substituent and 1-substituent is considerably less than the normal value of 60°. When both the substitutents are Me, an enthalpy difference of 1.5 kJ mol^{-1} (approximately) has been calculated in favour of the axial conformer (which contains a 1,3-diaxial Me/H interaction) corresponding to a mixture of 64:36 at ambient temperature (see also Allinger et al 1968). $A^{1,2}$-strain is not a powerful effect and becomes manifest only when the groups are bulky e.g., Ph. Thus the enamine (LX) and 1-phenyl-6-*t*-butylcyclohexene (LXI) exist predominantly in the axial conformers (NMR evidence).

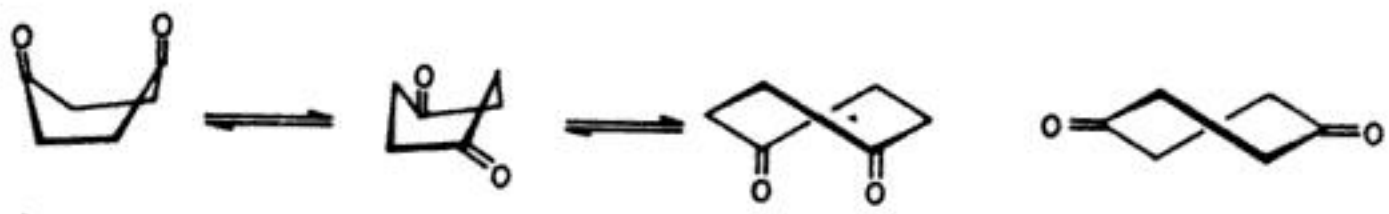


(LIXa) (LIXb) (LX) (LXI)

Figure 10.22 Allylic 1,2-strain

10.5.4 Cyclohexane-1,4-dione

The spectroscopic data (IR and Raman) of cyclohexane-1,4-dione show conclusively that it exists in a single, non-chair conformation both in the liquid and in the solid state. Four flexible conformers (LXIIa)—(LXIId) (Figure 10.23) are possible of which the last one (LXIId) is the most stable. The dipole moment of cyclohexane-1,4-dione is very small but non-zero.



(LXIIa) (LXIIb) (LXIIc) (LXIId)

C_{2v} C_2 C_2 D_2

Figure 10.23 Conformations of cyclohexane-1,4-dione

10.6 Carbocycles other than cyclohexane

As stated elsewhere, carbocyclic rings may be divided into four categories: small rings (3- and 4-membered), common rings (5- to 7-membered), medium rings (8- to 11-membered), and large rings (12-membered and above). The cyclopropane ring is necessarily planar and there is no question of conformation, stereoisomers being confined to rigid diastereomers and enantiomers. Conformational heterogeneity starts with the cyclobutane ring, becomes well defined in cyclohexane, and grows more complex in medium and large rings.

10.6.1 **Cyclobutane**

Cyclobutane may be represented by two extreme conformations: a planar one (LXIIIa) (point group D_{4h}) and a puckered one (LXIIIb) (point group D_{2d}) (Figure 10.24). The former has the pairs of adjacent H's eclipsed and suffers from torsional as well as angle strain. The puckering of the ring with one carbon atom either above or below the plane of the other three relieves some of the torsional strain and non-bonded interaction at the expense of angle deformation (increased angle strain). Raman spectra and electron diffraction experiments (also X-ray data of substituted cyclobutanes) confirm the puckered conformation (LXIIIb) with an angle of puckering α (the angle between C_1-C_2-C_3 and C_2-C_4-C_1 planes) of approximately 35° (the torsion angles are alternately $+25°$ and $-25°$). A geometrical consequence of puckering is the existence of two types of bonds very similar to equatorial and axial bonds in cyclohexane.

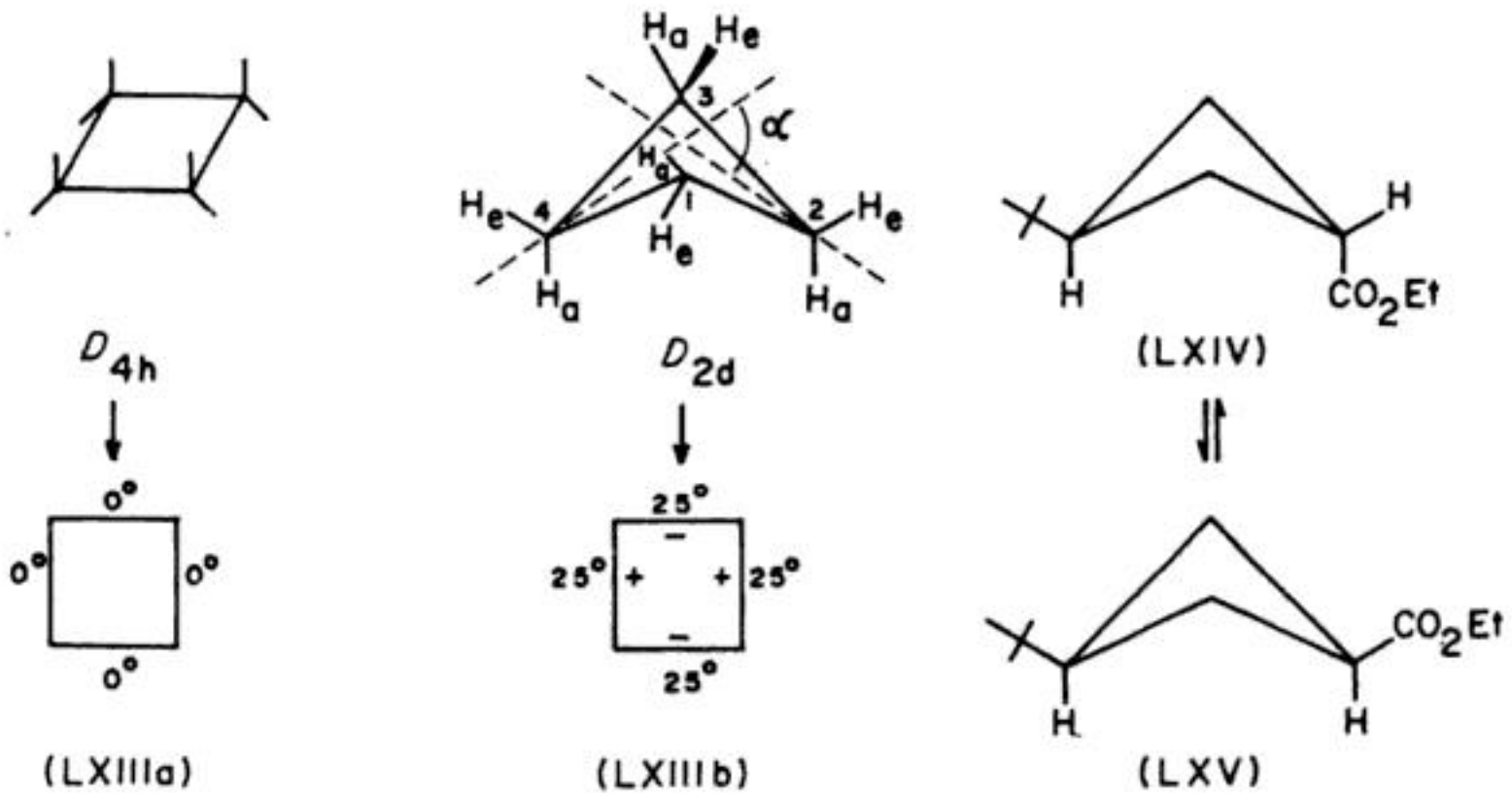


Figure 10.24 Conformations of cyclobutane

The inversion of the ring resembles the wing motion of a butterfly and evidently goes through the planar transition state (LXIIIa) interchanging the equatorial and axial bonds in the process. The energy barrier, however, is very low, around 6.0 kJ mol^{-1} as determined by Raman spectra and may be as low as 4.5 kJ mol^{-1} in some instances. Substituents are preferably placed in equatorial positions, as in cyclohexanes. Thus bromocyclobutane exists predominantly in the equatorial form with very little of the axial conformer. Disubstituted cyclobutane such as the 1.2-dicarboxylic acids show diastereomerism (cis and trans isomerism), the trans having diequatorial and the cis having equatorial-axial substituents. Base-catalysed equilibration of the cis and trans isomers of the dimethyl esters of 1.2-cyclobutanedicarboxylic acid yields a 90: 10 mixture (in favour of the trans) at 65°C comparable to the 93:7 mixture for the corresponding cyclohexane derivatives. Like cyclohexanes, *cis*-1,3-disubstituted cyclobutanes are more stable than the trans isomers, their conformations as e,e and e,a respectively being confirmed by electron diffraction

the nature of substitution, the chair or the envelope form may be more stable. In monosubstituted cyclopentanes, e.g., methylcyclopentane, Me is in the equatorial position at the tip of the envelope (LXVII). The cis and trans isomers of 1,2-dimethylcyclopentane exist, respectively, in e,a and e,e (envelope) conformations, the difference in enthalpy between the two being 7.15 kJ mol^{-1} which is slightly less than that for the dimethylcyclohexanes (7.8 kJ mol^{-1})*. The case of the cis and trans isomers of 1,3-dimethylcyclopentane is interesting since as in the 1,3-dimethylcyclohexanes, the cis isomer (e,e) (LXVIII) is more stable than the trans (e,a) by 2.25 kJ mol^{-1}. This is a direct demonstration of the non-planar structures of cyclopentane derivatives since a planar structure should have a higher energy for the cis.

When one of the ring carbon atom is sp^2 hybridised as in cyclopentanone or is replaced by atoms such as O, S, and N, eclipsing interactions with substituents on two adjacent carbon atoms disappear. The more favourable conformation in this situation is the half-chair form (LXVIb) with the carbonyl carbon or heteroatom in the middle of the three atom-plane (i.e., on the C_2 axis). The substituents at the two non-planar atoms are staggered and the eclipsing interactions among the three atoms in the plane are also minimised. Dipole moment measurements in the 2-halogenocyclopentanone indicate an angle of 77° between halogen and C=O which is close to that calculated for the half-chair but quite different from that calculated for the envelope form.

Cyclopentanone is reduced by sodium borohydride at a much slower rate than acyclic ketones or cyclohexanone. Apparently, the relief of angle strain in the sp^2 to sp^3 change is less than sufficient to compensate for the increased torsional strain in cyclopentanol which implies a negative I-strain in cyclopentanone (relative to cyclohexanone). The cyanohydrin equilibrium also lies on the side of cyclopentanone.

10.6.3 **Cycloheptane**

With the increase of ring size in carbocycles (cycloheptane and above), the number of possible conformers increases due to the greater degree of freedom. Usually, more than one 'family' of conformers are possible. In general, the members of a family pseudorotate into one another whereas a member of one family is converted into a member of the other family by ring inversion (usually a higher energy process).

Cycloheptane exists in two sets (families) of conformers, one set consisting of chair (LXIXa) and twist-chair (LXIXb) forms (Figure 10.26) and the other consisting of boat (LXIXc) and twist-boat (LXIXd) forms, separated by an energy barrier of approximately 35.0 kJ mol^{-1} (less than that in cyclohexane ring inversion). The two enantiomeric twist-chair conformers (LXIXb) and (LXIXb′) (there are seven such enantiomeric pairs) appear to be the preferred conformers and pseudorotate into each other with the true chair (LXIXa) as the transition

*This may not be very meaningful since the cis and trans isomers may have different ring conformation.

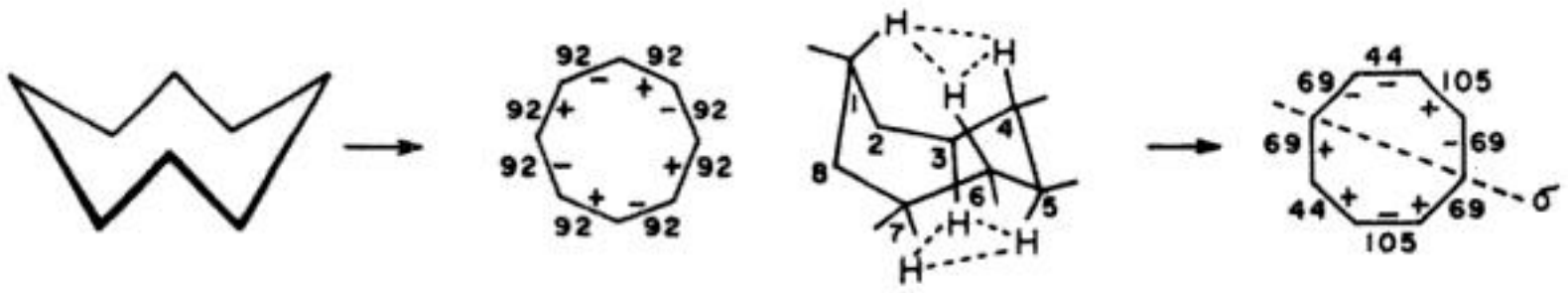


Figure 10.27 Conformations of cyclooctane

2. Cyclononane. Two main families of conformations have been calculated for cyclononane: a twist-chair-boat (LXXIIIa) and a twist-boat-chair (LXXIIIb) (Figure 10.28) belonging to point groups C_2 and D_3 respectively. A chair form (LXXIIIc) with C_s symmetry has also been considered. The ^{13}C-NMR spectrum at −162°C shows two distinct types of carbons in the ratio of 2:1 (Anet and Wagner 1971) which is consistent with the twist-boat-chair form (D_3) and inconsistent with any conformation of lower symmetry. The activation energy ($\Delta G^{\ddagger}$) of 25 kJ mol^{-1} at −162°C is also found to be reasonable for a process in which exchange between two sites occurs.

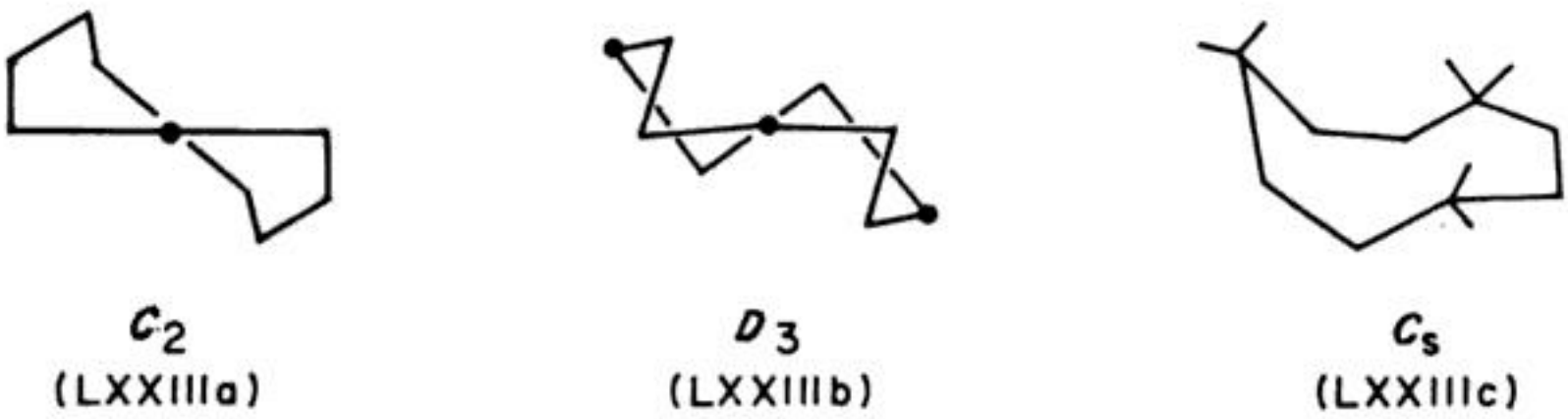


Figure 10.28 Conformations of cyclononane

3. Cyclodecane. Cyclodecane is a typical example in which all the conformational features of the medium rings are exhibited. X-ray crystallographic studies (see Dunitz 1968) have established the boat-chair-boat conformation (LXXIV) shown in two different perspectives (Figure 10.29) for cyclodecane in the solid state. Electron diffraction experiments (Hilderbrandt et al 1973) also show it as the major conformer in the gas phase along with some twist-boat-chair conformation. The following are the characteristic features of this boat-chair-boat conformation:

(*i*) The conformation has a plane of symmetry perpendicular to the C_2 axis (passing through the centres of 3-4 and 8-9 bonds) and belongs to point group C_{2h}. The σ plane passes through C-1 and C-6 and contains the axial and equatorial H's on these carbons.

(*ii*) The torsion angles around the ring are approximately staggered, i.e., torsional strain is minimum. The C-C-C angles are slightly opened up to minimise the transannular interactions (see below) with an average value of 117°.

(*iii*) Unlike cyclohexane which contains only one type of carbon and two types of hydrogens, cyclodecane in this conformation has three different types of carbons

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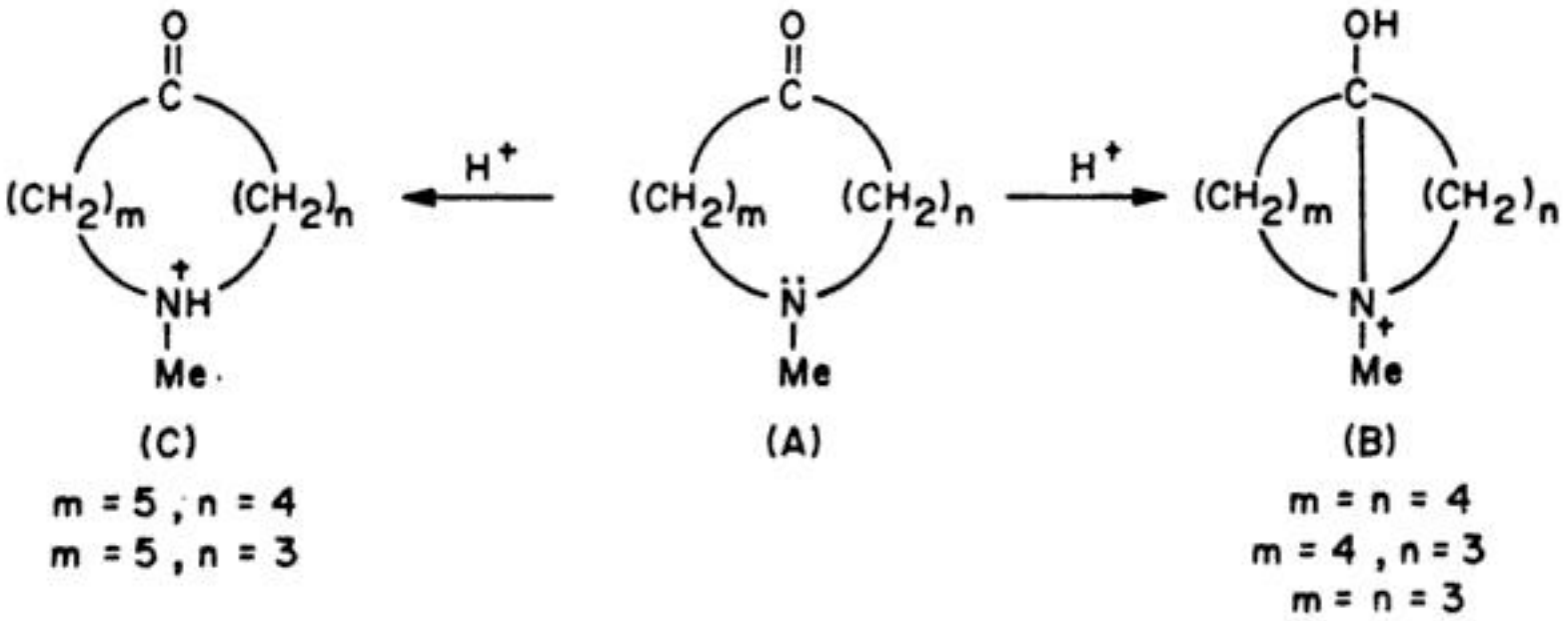

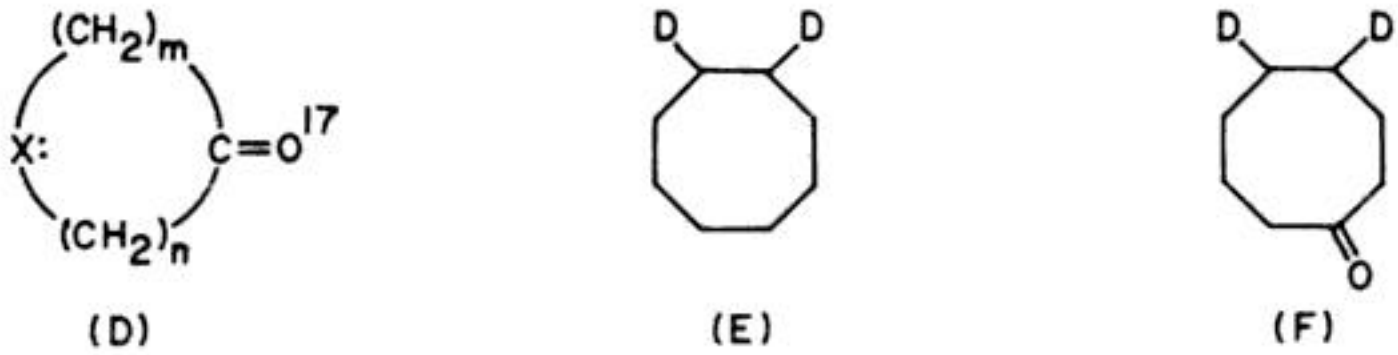

Figure 10.30 Transannular interactions in medium rings

(as B). Thus 8-, 9-, and 10-membered ring amino ketones (A) form respectively bicyclo-[3.3.0], [4.3.0], and [4.4.0] compounds (as B in Figure 10.30). The 11-membered ring amino ketone (A, m = 5, n = 4) does not cyclise to the bicyclo [5.4.0] compound under this condition but instead gives salt (C) which shows C=O absorption.

The medium ring ketones themselves have the C=O frequency around 1690 cm^{-1} which is considerably lower than the normal value (1710—1715 cm^{-1}). Prelog attributed this shift to a transannular H-bond involving 5-H or 6-H in the case of cyclooctanone. However, later work with deuterated compounds (E) and (F) (Allinger and Maul 1968) showed that the C-D stretching frequencies in the two compounds are identical thus eliminating the possibility of H-bonding. The lower stretching frequency for the medium ring ketones is presumably a result of C-CO-C bond angle expansion.

In the amino ketones (as A) or other heterocyclic medium ring ketones (as D), there is a characteristic change in the chemical shift of ^{17}O of the carbonyl group in ^{17}O-NMR due to transannular interaction. Hydration of the carbonyl group as measured by deuterium exchange between the ketone and H_2O is also appreciably slower than in the corresponding six-membered ring ketones with a heteroatom on the other side of the ring, again due to a transannular interaction.

The electronic spectra of paracyclophanes are also affected by transannular interactions (Eliel 1962, p. 261).

6. Transannular reactions. Two groups of workers (Prelog et al and Cope et al) working respectively on cyclodecane and cyclooctane systems have shown that groups across the medium rings which are within reacting distances are often

involved in rearrangement and neighbouring group participation. A few examples are recorded in Figure 10.31.

The trans isomer of cyclodecene (LXXVI) on oxidation with performic acid followed by acid-catalysed ring opening of the protonated epoxide (LXXVII) affords a number of products including cyclodecane-1,6-diol (LXXVIII) which can only result from a transannular hydride transfer as shown (Figure 10.31a). The normal product, cyclodecane-1,2-diol is also formed along with a small amount of *trans*-1-decalol (a result of transannular ring closure). Evidently, the normal backside attack (S_N2 type) by the nucleophile directly at the reaction site is partially prevented by the transannular methylene H's. As an alternative, the nucleophile (HCO_2^-) directs its attack on the transannular carbon which becomes activated by a concomitant hydride transfer across the ring to give LXXVIII. Similarly, *cis*- and *trans*-cyclooctenes on oxidation with performic acid followed by hydrolysis give *cis*- and *trans*-cyclooctane-1, 4-diols respectively. This transannular hydride transfer is observed in cycloundecene but not in cyclohexene, cycloheptene, and cyclododecene (at least not in any significant amount). The transannular rearrangements like all other rearrangements are highly stereospecific.

Acetolysis of cyclodecyl tosylate with labelled carbon (*) (LXXIX) (Figure 10.31b) gives cyclodecyl acetates (LXXX) and (LXXXI) with the acetoxy group positioned at C-5 and C-6 showing that transannular hydride transfer has occurred.

Similarly, bromination (an electrophilic addition reaction) of *cis*-cyclodecene (LXXXII) gives *cis*-1,6-dibromocyclodecane (LXXXIII) (Figure 10.31c). The reaction is assumed to go through a cyclic bromonium ion and Br attacks on the transannular methylene group with a simultaneous transfer of a hydride to the bromonium ion.

An interesting transannular pinacol rearrangement is observed when cyclodecane-1,6-diol (LXXXIV) is treated with acids. A hydride (or deuteride) is transferred from the transannular carbinol carbon giving cyclodecanone or cyclodecanone-6-*d* (LXXXV).

10.6.6 **Large ring compounds**

The member of the first large ring compounds, cyclododecane is solid at room temperature and its conformation has been studied by X-ray crystallography (Dunitz and Shearer 1960) which is depicted by schematic diagram in Figure 10.32. For rings larger than cyclododecane, conformational information is rather scanty; however, the following points are important.

1. The large rings are much more flexible and because of free rotation about C-C bonds, the formal distinction between cis and trans isomers in di- and polysubstituted molecules disappears.

2. It is difficult to freeze the molecules in any definite conformation. IR spectral data suggest that the large rings exist in conformations similar to the arrangement of carbon atoms in small pieces of diamond lattice. This means that most of the butane units have zig-zag (anti) conformations but since a completely zig-zag conformation does not permit ring formation, there must exist a few gauche butanes which will turn the chain into a *square* or a *rectangle*.

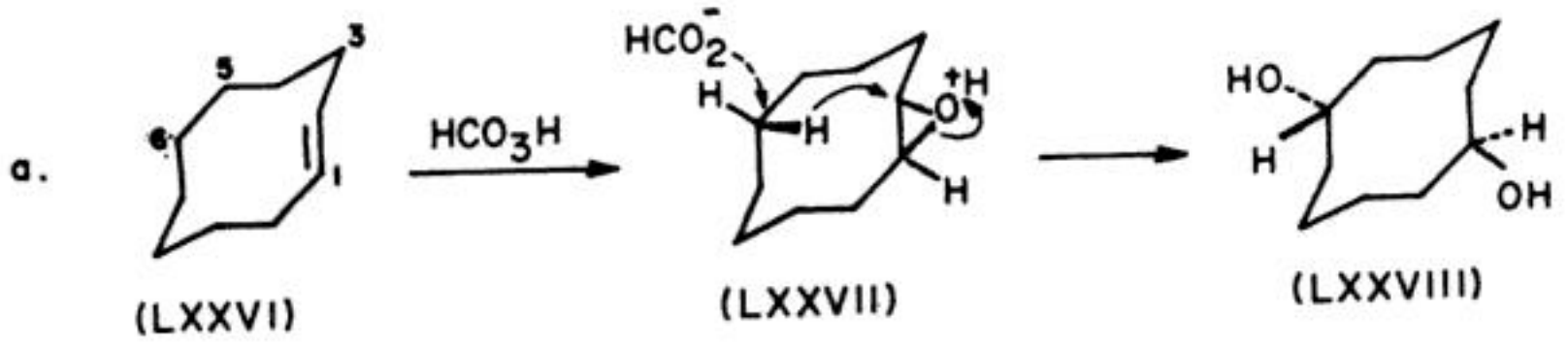

Figure 10.31 Some transannular chemical reactions

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3-alkylketone effects in decalones). The position of equilibrium of the 1-decalones corresponds to 5-10% of the cis isomer.

6. Ring inversion in cis-decalin. *cis*-Decalin and related system undergo ring inversion similar to cyclohexane which can be studied by ^{1}H-NMR. In rigid *trans*-decalin, the equatorial and axial protons are distinguishable and appear as two broad bands due to spin-spin coupling. On the other hand, in *cis*-decalin, the equatorial and axial protons are averaged out due to flipping of the rings and appear as a narrow band at ambient temperature. This can, however, be split up into two broad bands at low temperature and the coalescence temperature gives a value of 53.6 kJ mol^{-1} at $-18°C$ in CS_2 for the free energy barrier of ring inversion. 2,2-Difluoro-*cis*-decalin exhibits a barrier of 51.5 kJ mol^{-1} at $-30°C$ in ^{19}F-NMR. *cis*-Decalin has thus considerably higher barrier energy than cyclohexane and *cis*-1,2-dimethylcyclohexane ($\Delta G^{\ddagger}$=42.0 kJ mol^{-1} at $-60°C$).*

7. Effect of an angular methyl group. Introduction of a methyl group at one of the bridged carbon atoms gives rise to additional gauche interactions : *four* in the trans isomer (II) (two with respect to each ring, Me being axial to both) and *two* in the cis isomer (III) (Me being axial to one ring only) (Figure 11.4). The original difference of three gauche interactions in *cis*- and *trans*-decalins is thus reduced to one in 9-methyldecalins in favour of the trans isomer which is thus more stable than the cis isomer by 3.35 kJ mol^{-1}. This is more or less supported by the experimental values of enthalpy difference as determined by temperature dependence of cis-trans equilibrium and by heat of combustion data, ΔH ranging from 2.5 to 8.4 kJ mol^{-1}.

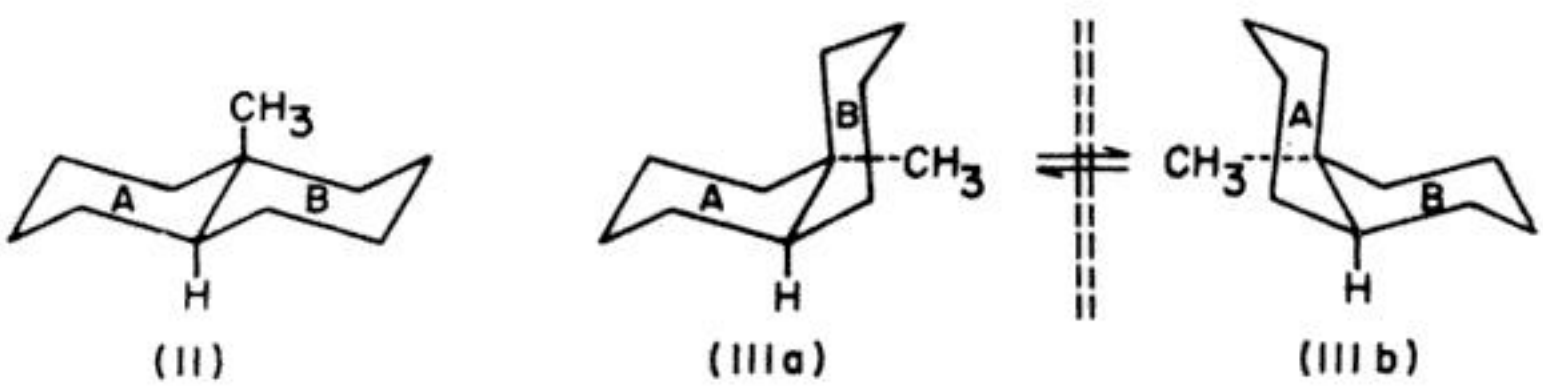

Figure 11.4 *cis*-9-Methyldecalin and *trans*-9-methyldecalin

trans-9-Methyldecalin (II) does not have any C_2 axis but possesses a σ plane passing vertically along the 9-10 bond. It is thus achiral and belongs to point group C_s. The cis isomer, on the other hand, is devoid of any symmetry element and belongs to point group C_1. However, the two enantiomers (IIIa) and (IIIb) are interconvertible by ring inversion and *cis*-9-methyldecalin is a (±)-mixture having an entropy term higher than the trans isomer by Rln2 (5.8 JK^{-1} mol^{-1}). Experimentally, the entropy term favours the cis isomer but not to the extent expected theoretically - a behaviour which appears to be intrinsic in the decalin system.

cis-9-Methyldecalin exhibits a ring inversion barrier of 52.8 kJ mol^{-1}, similar in

*Many of the ring inversion data are available in a monograph by Oki (1985).

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equatorial bond of cyclohexane are engaged in cyclopentane ring formation (XIIIa) is chiral (C_1 point group) but like *cis*-decalin exists as a (±)-mixture, the two enantiomers being interconvertible by ring inversion. *trans*-Hydrindane in which two equatorial bonds are engaged in cyclopentane ring formation is rigid (XIVa). has a C_2 axis but no reflection symmetry (C_2 point group).

The trans isomer has a slightly smaller heat of combustion (by about 5 kJ mol^{-1}) in vapour phase and so is only marginally stabler than the cis isomer. On the other hand. the latter has a higher entropy (by about 9.5 $JK^{-1}mol^{-1}$)—apparently. in the trans isomer. pseudorotation in cyclopentane is considerably restricted—and as a result, at a temperature below 466 K, the trans isomer is slightly more abundant but above that the cis isomer predominates at equilibrium. The small enthalpy difference between *cis*- and *trans*-hydrindanes compared to decalins is due to relatively flat cyclopentane ring in which ring torsion angles may reach a maximum of 42° only without creating much strain. The idealised values of the torsion angles of junction in *cis*- and *trans*-hydrindanes are shown in structures (XIIIb) and (XIVb). In the latter. the torsion angle of junction in the cyclohexane ring shows a considerable opening (from 55° to 68°) which is quite unfavourable (it makes the chair form much more puckered). The situation in *cis*-hydrindane is not so bad, the reduction of torsion angle of junction slightly flattens the cyclohexane chair. That the cyclohexane ring in hydrindanes exists in chair form (slightly deformed) is evidenced from the oxidation rates of cis and trans isomers of 2-oxahydrindane-*cis*-5,6-diols (Eliel 1962, p. 277) with lead tetraacetate which correspond roughly to those of the *cis*- and *trans*-cyclohexane-1-2-diols (OH's staggered) but not to those of the cyclopentane-1.2-diols (OH's nearly eclipsed).

The small enthalpy difference between *cis*- and *trans*-hydrindanes is further reduced by introduction of substituents. Thus in the case of 8-methylhydrindane and 1-hydrindanone. the cis isomers are more stable than the trans isomers (much more so in 1-hydrindanone).

The free energies of activation for ring inversion in *cis*-hydrindane and its derivatives are also much lower than in *cis*-decalins. as determined by dynamic NMR studies. The average barriers to ring inversion (determined by ^{19}F-NMR) are 30.5 and 31.8 kJ mol^{-1} for *cis*-6,6-difluorohydrindane and *cis*-6,6-difluoro-8-methylhydrindane respectively (Lack and Roberts 1968).

11.2.6 **Fused bicyclic systems with small rings**

Either one or both of the rings in bicyclic compounds may be small (3- or 4-membered) in which case two phenomena are usually observed: (*i*) The systems become strained and (*ii*) the cis isomers become more stable than the trans; in extreme cases. the latter may even be non-existent. A few such systems are discussed below.

1 Bicyclo[3.3.0]octane. Bicyclo[3.3.0]octane (XV) (Figure 11.11) in which two cyclopentane rings are fused through adjacent atoms is known under the trivial name, pentalane and can still exist in cis and trans forms. The cis fusion takes place through two nearly eclipsed bonds and is relatively easy. The trans fusion which

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kJ mol^{-1}. This along with two other gauche interactions (6.7 kJ mol^{-1}) should give an energy of 29.3 kJ mol^{-1} to this isomer. Johnson suggested a value of 30.1 kJ mol^{-1} while Allinger et al calculated a value of 37.7 kJ mol^{-1} being the highest in this series. The trans-*c*-trans isomer (the last one) cannot have both ring junctions trans and at the same time 12-H and 13-H cisoid in an all-trans conformation. For this, the central ring must assume a boat or a twist-boat conformation (as M) with the other two rings fused through four boat-equatorial bonds. Johnson has estimated an energy of 23.4 kJ mol^{-1} while Allinger et al have computed for it a slightly higher energy, 29.4 kJ mol^{-1}.

The torsion angles of junctions in the central ring have signs shown in the planar structures (Figure 11.15). The signs are determined from the rule that a β axial substituent is preceded by (+) and followed by (−)* and the reverse for an α axial substituent (the reference bridgehead axial C-H bonds are shown in the puckered structures). In the first five isomers, the signs are the same for each ring junction across bonds which are alternate (1,3) in a cyclohexane ring and are thus consistent with it being in a chair conformation. In the trans-*c*-trans isomer, however, the signs are opposite which suggests a non-chair conformation for the central ring. The use of torsion angles of ring junctions in studying the nature of a cyclohexane ring is specially helpful in steroidal system (Bucourt 1974).

The data so far available on the relative stabilities of the isomers, mainly from the equilibrium study of perhydrophenanthrones, agree with the calculated energies. Preliminary measurements of the composition of a perhydrophenanthrene sample equilibrated over palladium catalyst are also consistent with the calculated values (Allinger et al 1971).

Summarising the results, one can see that the above conformational analysis is based mainly on the following three premises:

(*i*) The system with the larger number of equatorial bonds of the central ring involved in ring fusions is more stable.

(*ii*) In the cases when two axial bonds of the central ring are used in ring fusion, 1,2- and 1,4-diaxial arrangements are preferred over 1,3-diaxial which suffers from a severe 1,3-diaxial interaction.

(*iii*) If the central ring cannot satisfy the configurational requirement by adopting a cyclohexane chair, a boat or twist-boat form for it is assumed with correspondingly increased energy.

11.3.2 **Perhydroanthracenes**

Perhydroanthracenes can be very similarly analysed stereochemically with only two points of distinction. The rings are fused in a linear arrangement so that the terms cisoid and transoid are no longer determined by the steric relations of 1,2 but by 1,3 bridgehead atoms. Secondly, all the four chiral centres are equivalent, the system corresponds to an AAAA type so that the number of stereoisomers is less. Perhydroanthracene exists in five diastereomeric forms: meso-trans-*c*-trans, (±)-cis-*c*-trans, meso-cis-*t*-cis, (±)-trans-*t*-trans, and meso-cis-*c*-cis (Figure 11.16), mentioned in order of their relative stabilities. The stereochemical symbols have the same significance as in perhydrophenanthrenes. The cis-*c*-trans isomer may as

* When seen in a clockwise direction.

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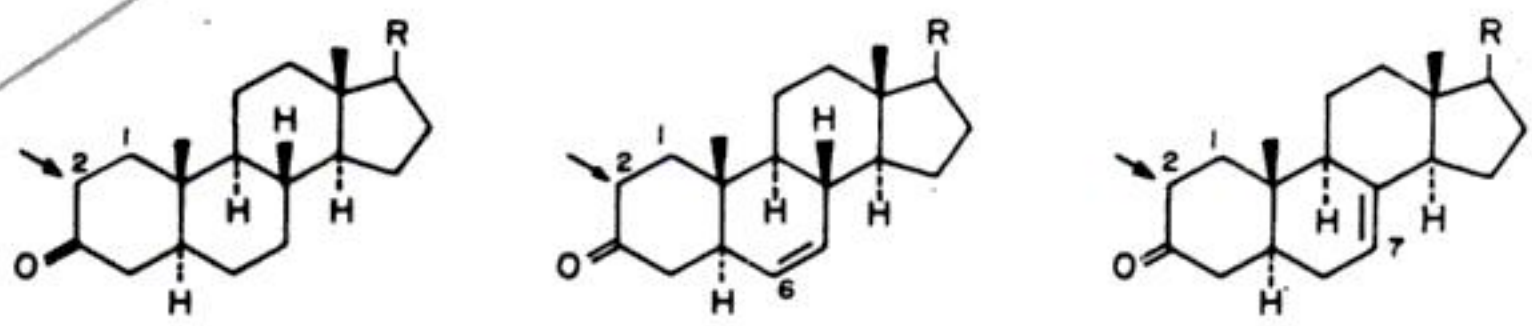

Figure 11.19 Conformational transmission

chemistry. Benzaldehyde condenses with a methylene group (shown by arrows) adjacent to a carbonyl under base catalysis and the rate of formation of the benzylidene derivative may be determined by observation of an absorption band at 292 nm. 3-Ketosteroids (as XXXVII) such as cholestan-3-one, stigmastan-3-one, and 17β-hydroxyandrostan-3-one show a comparable rate of formation, 182, 180, and 188 respectively (relative to an arbitrary value of 100 for lanost-8-en-3-one) Cholcst-6-en-3-one (XXXVIII), on the other hand, has a much higher rate of 645 which is due to a conformational transmission effect. If the double bond is shifted to position 7 as in XXXIX, the rate suddenly drops down to 43.

Conformational analysis of other polycyclic systems such as triterpenes, and alkaloids (Eliel et al 1965, p. 256) follow a similar pattern.

11.4 Bridged ring systems

When two rings are fused through non-adjacent atoms, more than two atoms become common to the rings and bridged ring systems result. They differ from fused ring systems previously discussed in that unless one or both of the rings are large ($\geq$7-membered), only cis fusion is possible and the number of stereoisomers is diminished (actually halved) from what is expected. Such systems are characterised by their relative rigidity, particularly when the rings are small and a substituent or a functional group is held with a fixed topology. They provide excellent models for investigating the stereochemistry and mechanism of many reactions. A good many natural products, both alicyclic and heterocyclic, possess bridged ring systems. A few are discussed, emphasis being laid on bicyclo[2.2.1] heptane and bicyclo[2.2.2]octane because of their importance in stereochemical studies.

11.4.1 Bicyclo[1.1.1]pentane and bicyclo[2.1.1]hexane

Bicyclo[1.1.1]pentane (Figure 11.20) is the smallest bridged ring system possible

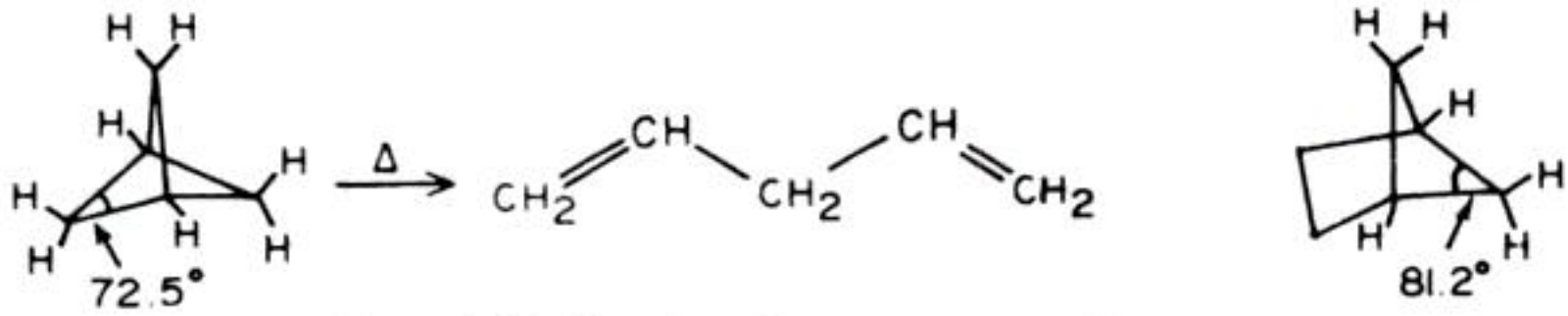

Figure 11.20 Bicyclo[1.1.1]pentane and bicyclo[2.1.1]hexane

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each) located at the methylene carbons; all H_A's are homotopic as are all H_A's (exchangeable by the C_3 axis or the three C_2 axes). Each type, however, is enantiotopic with the other (related by σ planes). There is no distinction between endo and exo and substitution at any methylene carbon can give only two enantiomers. The two bridgehead hydrogens H_B belong to the third type; they are homotopic with each other (related by a C_2 axis) but constitutionally heterotopic with the remaining twelve hydrogens.

In contrast, bicyclo[2.2.1]heptane (LI) (with lesser symmetry) has six types of distinguishable hydrogens: (*i*) Type H_A consists of two hydrogens located at the bridging carbon which are homotopic with each other but constitutionally heterotopic with the remaining ten hydrogens. (*ii*) Types H_B and H_B' (the four exo hydrogens) are enantiotopic with each other (two H_B's and two H_B''s are, however, homotopic). (*iii*) Types H_C and H_C' (the four endo hydrogens) are related in the same way to each other as H_B's and H_B''s. The exo and endo hydrogens are diastereotopic. (*iv*) The two hydrogens H_D on the bridgeheads constitute the sixth type; they are homotopic with each other but constitutionally heterotopic with the remaining hydrogens. Hydrogens with identical subscripts (in both the ring systems) are homotopic, hydrogens with the same subscripts but primed and unprimed are enantiotopic, and hydrogens bearing different subscripts are constitutionally heterotopic or diastereotopic (so anisochronous in ^{1}H-NMR).

3. Bicyclo[2.2.2]octyl cation. Bicyclo[2.2.2]octyl brosylate (LII) (Figure 11.25) exists as a (±)-mixture (one enantiomer is shown). The classical carbocation (LIII) derived from the brosylate is achiral (unlike the norbornyl cation which is chiral) and on participation of 1-6 σ bond may give rise to the non-classical carbonium ion (LIV)* which, in contrast to that in the norbornyl system, is chiral. Here also, solvent molecules can attack either at C-2 or C-1 giving, respectively

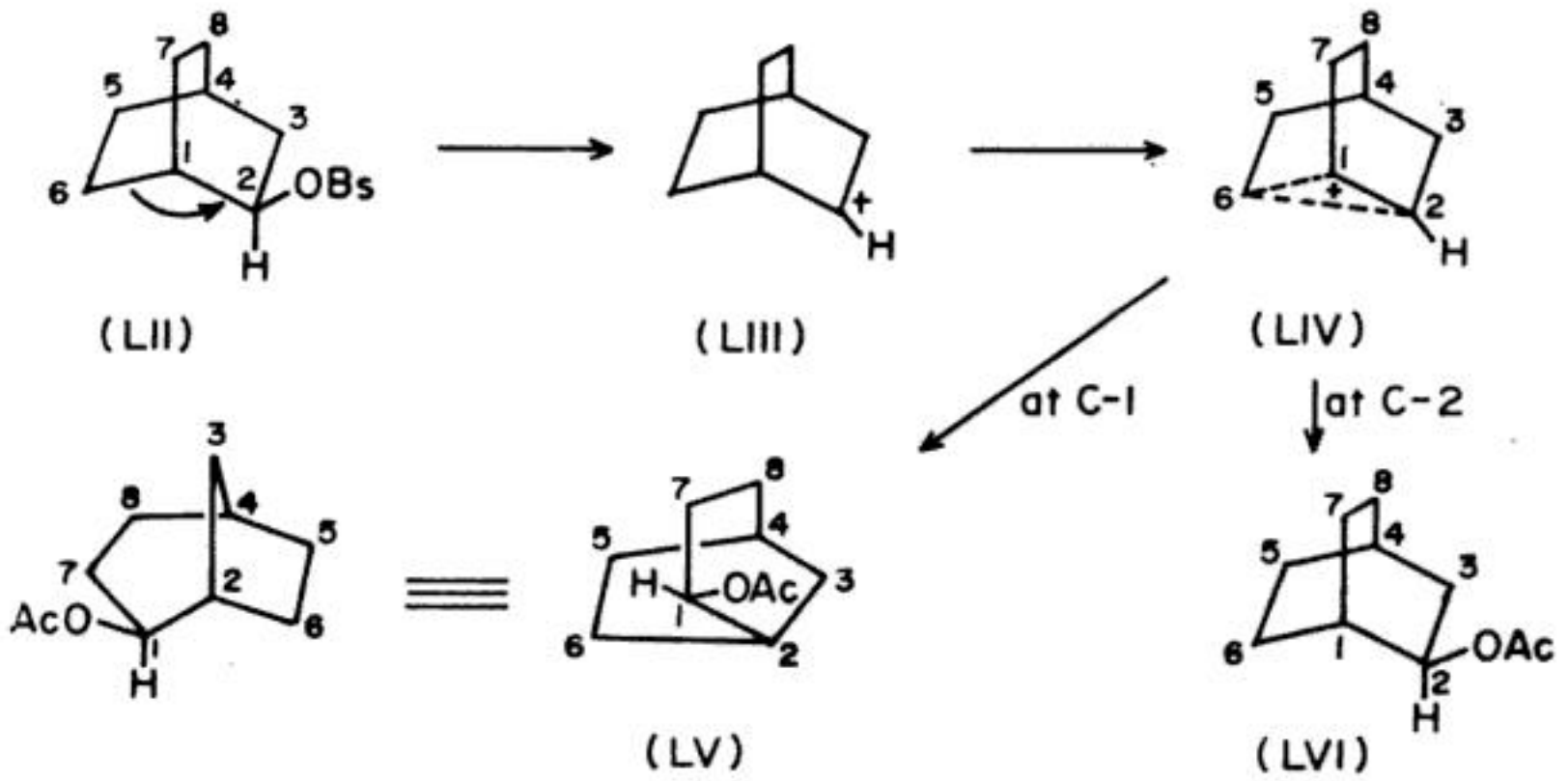

Figure 11.25 Solvolysis of bicyclo[2.2.2]octyl brosylate

*The non-classical carbonium ion can also be formed directly from the brosylate precursor by neighbouring σ bond participation.

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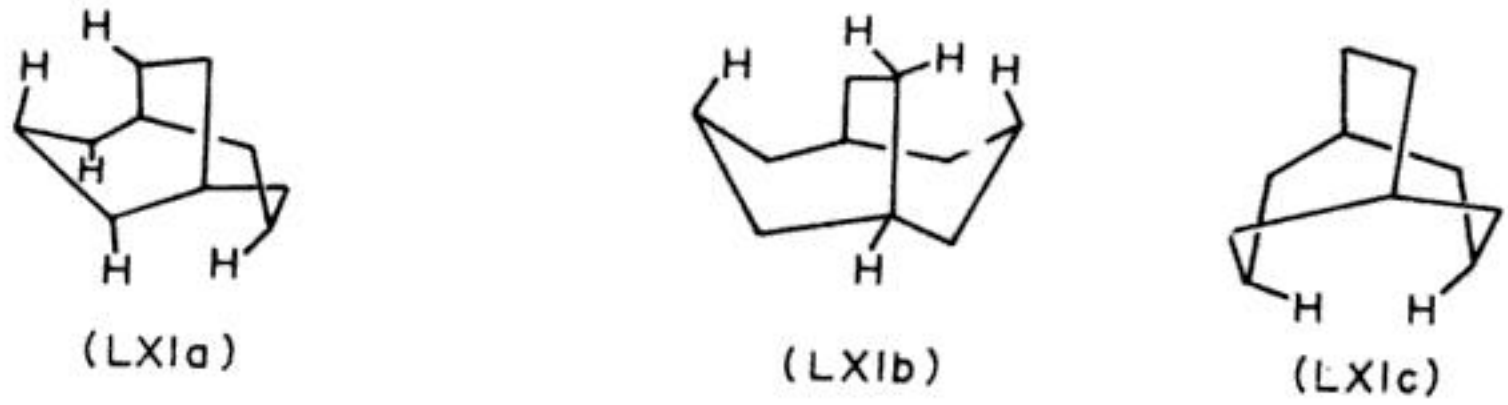

Figure 11.27 Bicyclo[3.3.2]decane

experimental results indicate that there is no single energy minimum geomertry for them but all these conformers coexist differing at most by 0.5 kJ mol^{-1} (Engler et al 1972). These molecules thus constitute another class of flexible ring systems in which the actual conformations depend on the nature of the substituents rather than on the carbon skeleton.(cf. cyclopentane)

Bicyclo[3.3.3]undecane (LXII), a still higher homologue (Figure 11.28), known by the trivial name manxane* is another interesting system. All the middle methylene protons are equivalent in ^{1}H-NMR which is consistent with the symmetrical structure (LXII) belonging to point group C_{3h}. The endo-exo protons (H_A and H_B) are exchanged by inversion of all the three rings which has a barrier energy of aproximately 40 kJ mol^{-1} at -60°C.

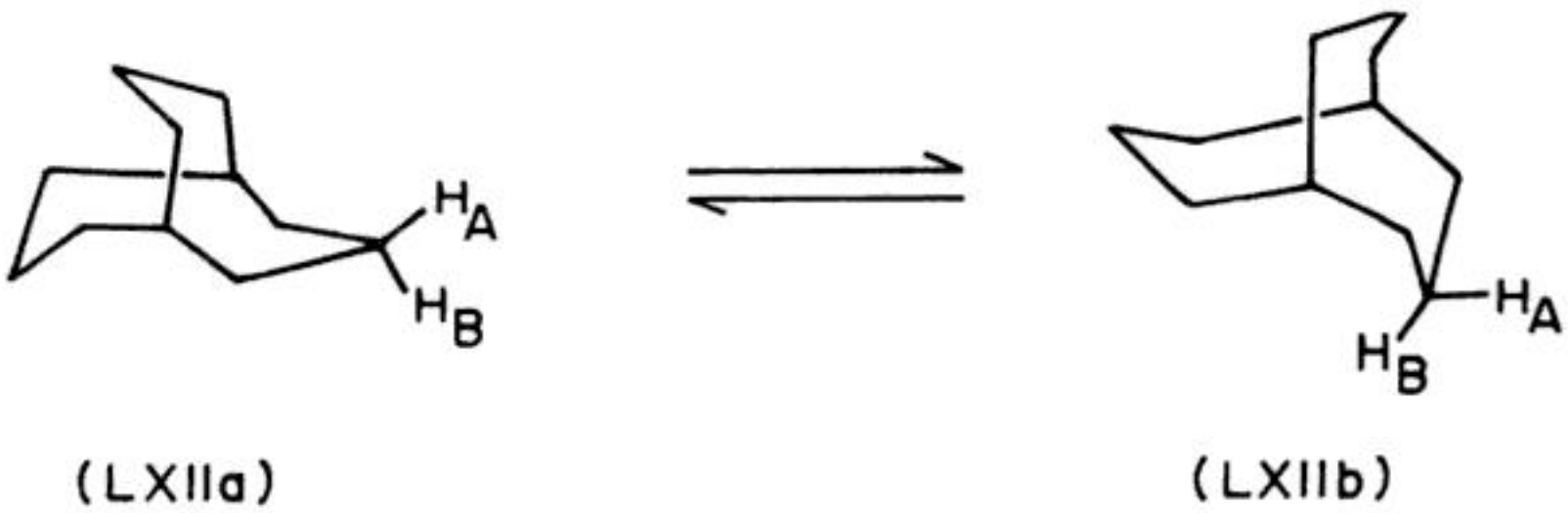

Figure 11.28 Bicyclo[3.3.3]undecane (manxane)

11.4.5. **Bicyclo systems with hetero atoms**

Many heterocyclic analogues of bicyclo compounds are known and some also exist in naturally occurring compounds. Thus tropane (LXIII) which constitutes the parent ring system of a series of alkaloids. e.g., tropine (LXIV) and pseudotropine (LXV) (Figure 11.29) is a derivative of 8-azabicyclo[3.2.1]octane. The chair forms (as shown) are preferred. But the energy required to flip to the boat forms (as LXVI) is not large as evidenced by a facile migration of the benzoyl group from O to N in the benzoyl derivative of norpseudotropine (LXVI). In the boat conformation of norpseudotropine, N-H and 3-OH come close to each other. This rearrangement also proves the syn configuration of 3-OH (with respect to bridging N). In the N-benzoate of the epimeric nortropine (LXVII) (with anti 3-OH) no

*The triskelion is in the coat of arms of the Isle of Man, hence the name.

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inversion) fall under this category. Thus in *trans*-2α-decalol (I) and *trans*-2β-decalol (II) (Figure 12.1a), the OH group is equatorial and axial respectively and remains so during any chemical reaction. Employing these two diastereomers, reaction rates can thus be measured for an equatorial (k_e) and an axial (k_a) OH group. They may be used as standard for conformationally well defined substituents.

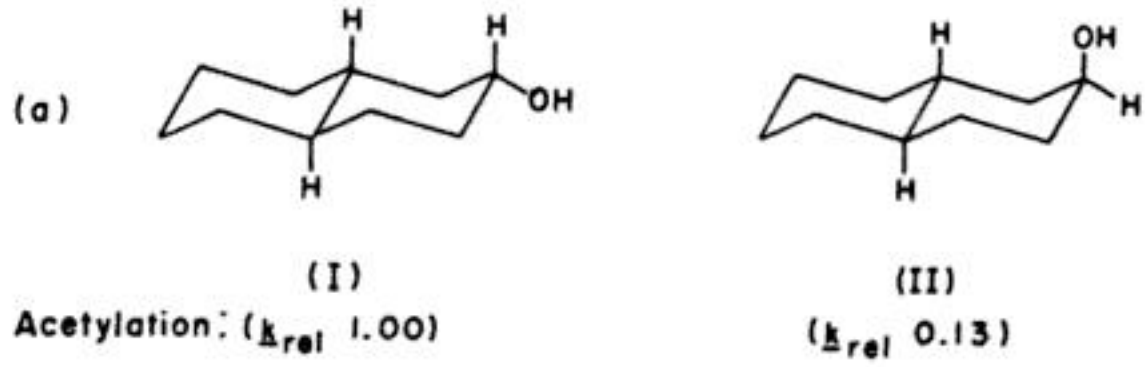

Figure 12.1 (a) Conformationally rigid and (b) anancomeric systems with reaction rates (relative or specific) of axial and equatorial isomers

A second type of substrate which serves the same purpose is represented by cyclohexane derivatives with a bulky group such as *t*-butyl (Winstein and Holness 1955). Because of high preference for equatorial disposition of this group, the equilibrium is displaced almost completely to the side in which *t*-butyl is equatorial (the population of the axial conformer is approximately 1 in 10,000 at ambient temperature) and the system is essentially conformationally homogeneous. The trans and cis isomers of 4-*t*-butylcyclohexanols (III) and (IV) (Figure 12.1b) are examples of this type*. The two epimers show reactions typical of an equatorial and of an axial OH (or any other group to be studied). Such a system is called a conformationally *biased* or more technically an *anancomeric* system. The same reactivity for an equatorial or for an axial substituent is expected, in theory, in the two systems, i.e., rigid and anancomeric,but is seldom observed in fact. The reason for the deviation (which is usually only minor) may lie in an additional 3-substituent in the *trans*-decalins and in the possible deformation of the cyclohexane ring geometry by the presence of the bulky *t*-butyl group. The anancomeric system is more commonly used for conformational analysis because of its ready acces-

*Unlike the conformationally rigid systems, these molecules, however, can undergo facile ring inversion, i.e., their near conformational homogeneity is thermodynamically, not kinetically based. With increase of temperature, the unfavoured conformer becomes more and more populated. In some reactions this less stable conformer may be the only reactive species due to stereoelectronic reasons and as the reaction proceeds, equilibrium is continuously reestablished to maintain a steady supply of this conformer. The rate of the reaction is, however, low because of its low concentration

sibility. *cis*-3,5-Dimethyl- and 3,3,5-trimethylcyclohexane derivatives provide other anancomeric systems.

Studies of these systems reveal that reactions at exocyclic positions, i.e., not involving any ring carbon generally proceed at a faster rate for the equatorial than for the axial isomer. Thus the saponification rate of the trans isomer of ethyl 4-*t*-butylcyclohexanecarboxylate (VI) in 70% ethanolic sodium hydroxide is 20 times as fast as that of the cis isomer (VII). Rates of acetylation of cyclohexanols (III), (IV) and (V) in pyridine at 25°C are shown in Figure 12.1b. The equatorial isomer reacts 3.7 times as fast as the axial isomer while the unsubstituted cyclohexanol reacts at an intermediate rate.

Acyclic molecules rarely exist in rigid conformations except in exceptional cases when a particular conformer is fixed in a crystal matrix or exists as an atropisomer due to steric hindrance around a single bond. The conformation-reactivity relationship in such systems is usually studied with the help of diastereomers (see below).

12.2.2 **Conformationally mobile diastereomers**

For conformationally mobile substrates, both cyclic and acyclic, the relative specific reaction rates of any two diastereomers depend on the corresponding rates for all the constituent conformers and their populations in the equilibrium mixture of each diastereomer. For cyclohexane derivatives, the specific reaction rates of the equatorial and axial conformers are often available from conformationally rigid or anancomeric system (as discussed above). But for acyclic molecules, these rates are generally not available and the analysis is less quantitative. Two situations often arise which simplify the treatment: (*i*) One of the conformers in each diastereomer is highly populated so that comparison of reactivities may be confined to those conformers provided the lesser populated conformers are not exceptionally reactive. (*ii*) Some reactions have specific stereoelectronic requirements and only a certain conformer of each diastereomer satisfies them. In such situations, only the pertinent conformer needs to be considered.

An example of the first kind is provided by 2,3,4-triphenylbutyric acid (Lednicer and Hauser 1958). The compound exists as two diastereomers, threo (VIII) and erythro (IX) (Figure 12.2). The preferred conformations of the threo and the erythro isomers are represented by VIIIa and IXa respectively each of which has two gauche interactions between the bulky groups while the others (not shown) have three (due to placement of four adjoining bulky groups) and so contribute very little to the equilibrium population. The preferred threo structure (VIIIa) has the CO_2H group very close to the $PhCH_2$ group at C-4 and so cyclises (with anhydrous HF) mainly to the tetralone (X). On the other hand, the erythro structure (IXa) has the carboxyl group adjacent to the Ph group at C-3 and so gives a preponderance of the indanone (XI)*.

Iodide-induced debromination of *meso*- and (±)-2,3-dibromobutane (an E2 reaction) provides an example of the second kind. The stereoelectronic factor

*The argument is valid only if the rates of cyclisation of VIIIa and IXa are equal which in this case is probably true.

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