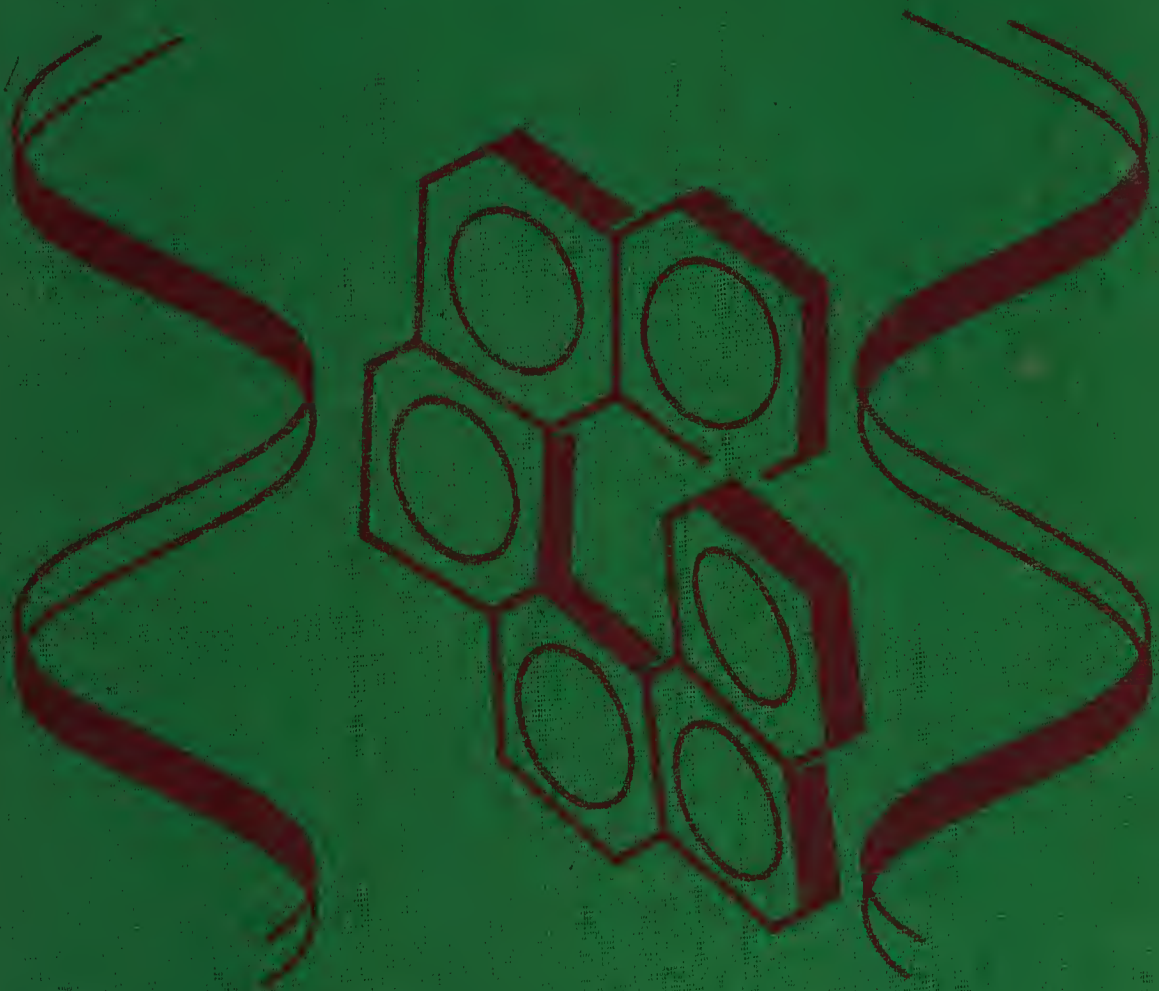
STEREO-CHEMISTRY

CONFORMATION AND MECHANISM

P S KALSI



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FOREWORD

The discovery of optically active naturally occurring organic molecules led to the hypothesis of asymmetry of such molecules (L. Pasteur, 1859), which was rationalised in terms of tetrahedral arrangement of carbon valencies (van't Hoff and Le Bel, 1874). Chemistry has come a long way since then, and several excellent texts on stereochemistry are currently available. Thus, there should be a special reason for writing another monograph on the subject. From the chapter headings and their contents it appears Professor Kalsi wishes to emphasise the stereochemical aspect of organic molecule reactivity. To treat this aspect, he has elaborated in considerable detail the basic concepts of stereochemistry (and conformational analysis). The treatment of various topics is thorough and up-to-date. Thus, this book can serve as a good material for students preparing for bachelor and master's degrees in organic chemistry. A thorough understanding of stereochemical aspects of organic chemistry is crucial to its practice. To emphasise this, Professor Kalsi has drawn up several interesting questions and problems for the student to check his competence. To assist him in this, answers to these problems have been given at the end of the book.

On the whole, I feel the book should prove useful to both students and teachers, alike.

SUKH DEV

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Department of Chemistry,
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New Delhi

PREFACE

The French chemist Louis Pasteur (1850) was the first to reveal that optical activity at the molecular level was due to an asymetric placement of atoms in a molecule. He further recognized that enantiomers had equal and opposite etfects on polarized light. vant Hoff and Le Bel in 1874 (Nobel Prize) proposed the tetrahedral model for the carbon as the cause of molecular dissymetry and the resultant optical rotation. This was the beginning of stereochemistry which forms a massive and an integral part of organic chemistry.

In recent years stereochemistry has not only expanded in depth but, with the development of new kinds of nomenclature and concepts, it has also almost taken on an entirely new perspective. These developments offer knowledge of great interest to students and the present book incorporates this knowledge not only for the uninitiated student but for the expert as well.

The intention of this book, is to give equal weightage to various aspects of stereochemistry *viz.,* chirality, stereochemical course of various reactions, molecular rearrangements and methods of assigning configurations. Though treated lightly, but several examples from the major special areas of organic chemistry:Terpenoids, steroids, alkaloids and carbohydrates have been presented to explain various stereochemical, mechanistic and conformational aspects.

The book runs into various chapters each of which is reasonably complete in itself. The first chapter describes chirality and some related aspects to provide a necessary background for understanding mechanisms and conformations presented in subsequent chapters and is important in its own right. Some emphasis has also been laid on spectral methods in solving stereochemical problems.

I have tried to develop an internal order of almost all the basic concepts, to help the student to be able to apply the knowledge gained to new situations. Special attention is paid in illustrating the introduction to each chapter in some depth. The student may thus, not find himself in a situation where his understanding a concept requires knowledge that he has not gained. Special attention is paid to serve the needs of students in a way that will enhance their comprehension of the subject of stereochemistry.

It is now recognized that Hückel-Möbius approach can be gainfully and effectively used to explain pericyclic reactions, therefore, I have introduced this as the only approach to make several aspects of these reactions more understandable.

Problems and their solutions are provided at the end of each chapter and these are designed to test the students understanding of each topic up to that point. Chapter summaries are presented in the appendix.

Advances in a scientific field are often reported in somewhat condensed communications, and find elaboration in papers and books after a lapse of some years. My acknowledgement, therefore, is to many authors who have preceded me in this task of authorship and from whose efforts I have drawn innumerable facts, ideas and theories. Particularly to some of these sources, mentioned in refrences, I am indebted.

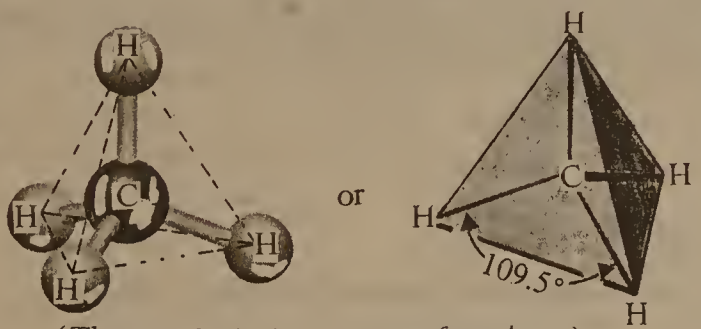
P.S. KALSI

CONTENTS

1
CHIRALITY

1.1 INTRODUCTION

In 1874, the structural formulas originated by Kekule, Couper and Butlerov were advanced into three dimensions by the independent work of J.H. van't Hoff and J.A. Le Bel who provided evidence that the four bonds of the carbon atom in methane, for example, are arranged in a way, so as to point towards the corners of a regular tetrahedron if the carbon atom was placed at its center.



(The tetrahedral structure of methane)

Fig. 1.1

It is interesting, however, to know that Hermann Kolbe, one of the outstanding organic chemists of the time, who was almost nearing the end of his career, had reacted sharply to a publication of van't Hoff in 1877 wherein he had argued that the spatial arrangement of groups around the carbon atom was tetrahedral. Within 10 years of Kolbe's comments, however, overwhelming evidence accumulated to substantiate the so-called "childish fantasy" of van't Hoff, who in 1901 was named the first recipient of the Nobel Prize for chemistry. Together, the work of van't Hoff and Le Bel marked the beginning of a field of study of the third dimension in organic chemistry, that is concerned with the structures of molecules in three dimensions: stereochemistry.

1.2 ISOMERS

Isomers are different compounds that have the same molecular formula. When two molecules, at different times occupy the same position in space, they are identical and are termed homomers. If one examines the two structures* (a) and (b) Scheme 1.1 of CH_2Cl_2, it does not immediately become

* Broken and solid wedges (*i.e.*, dashed and heavy lines) are the out-of-plane representations of bond lines (sec. 1.3B)

clear whether or not these are similar, however, their molecular models show that these are superimposable and homomers. If with the molecules with the same molecular formula the criterion of superimposability is not met then the relationship between these is isomeric, which may be structural or stereoisomeric.

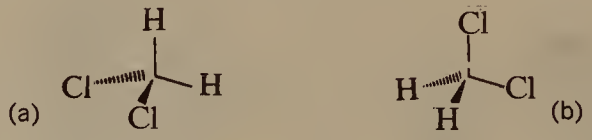
(A) Structural Isomers

Isomers which differ in the attachment of atoms without regard to the three-dimensional arrangement of atoms in space are called structural isomers or constitutional isomers. The three types of structural isomers are:

(1) Chain isomers which differ in the arrangement of the carbon skeleton in the molecule (1) Scheme 1.1.

(2) Position isomers which differ in the position of the functional group along the carbon skeleton (2).

(3) Functional isomers which differ in the nature of the functional group present in the molecule (3).



identical representations of dichloromethane

homomers

Molecular Formula	*Structural isomers*		
C_4H_{10}	$CH_3CH_2CH_2CH_3$ Butane	$CH_3CH(CH_3)CH_3$ Isobutane	1
C_3H_7Cl	$CH_3CH_2CH_2Cl$ 1-Chloropropane	$CH_3CH(Cl)CH_3$ 2-Chloropropane	2
C_2H_6O	CH_3CH_2OH Ethanol	CH_3OCH_3 Dimethyl ether	3

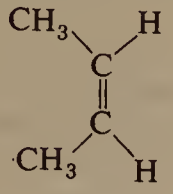
Scheme 1.1

(B) Stereoisomers

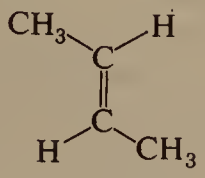
Isomers which show the same order of attachment of atoms but differ only in the three-dimensional arrangement of atoms in space are called stereoisomers. There are two kinds:

(1) Geometric isomers (also known as *cis-trans* isomers) result from restricted freedom of rotation about double bonds (π–diastereo-

isomerism[1]) or in a cyclic structure where no double bond is involved (σ-diastereoisomerism). Such isomers have different physical properties.



cis-2-Butene

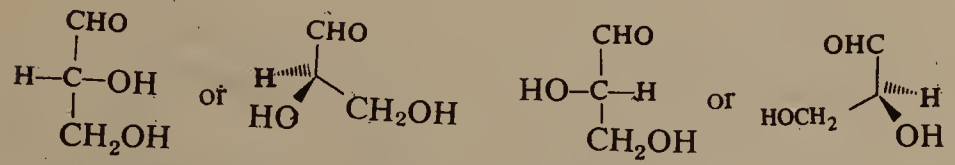


trans-2-Butene

Stereoisomers are not structural isomers

Scheme 1.2

(2) Optical isomers (enantiomers) are encountered in compounds that can rotate plane-polarized light. Isomeric chiral molecules that are nonsuperimposable mirror images (*e.g.*, *D*-and L-glyceraldehyde) are examples of optical isomers as they rotate plane-polarized light in opposite directions with-identical amplitude.



D-glyceraldehyde

L-glyceraldehyde

Enantiomers

(*Optical isomers*)

Scheme 1.3

Stereoisomers are further subdivided into two general categories—enantiomers and diastereomers. Enantiomers are stereoisomers which are mirror images of each other while diastereomers are stereoisomers which are not mirror images of each other.

Cis- and *trans*-2-butene are not mirror images of each other, *i.e.*, if a structural model of *cis*-2-butene is shown to a mirror, the arrangement which one sees in the mirror is not *trans*-2-butene. However, *cis*-and *trans*-2-butene are stereoisomers and, since they are not related to each other as an object and its mirror image, they are thus diastereomers.

1.3 CHIRAL MOLECULES OPTICAL ISOMERISM

Enantiomers *i.e.*, optical isomers occur only with those compounds whose molecules are chiral. A chiral molecule can be defined as one that is not superposable on its mirror image.

(A) The Term Chiral

The term chiral (Greek word *kheir* meaning hand) is used to designate molecules, since enantiomers are related to each other in the way a left hand is related to a right hand.

Several common objects are chiral and the chirality of some of these objects is clear because one normally speaks of them as having "handedness." One speaks for example, of nuts and bolts as having right or left-handed threads or of a propeller as having a right or left-handed pitch. The chirality of objects

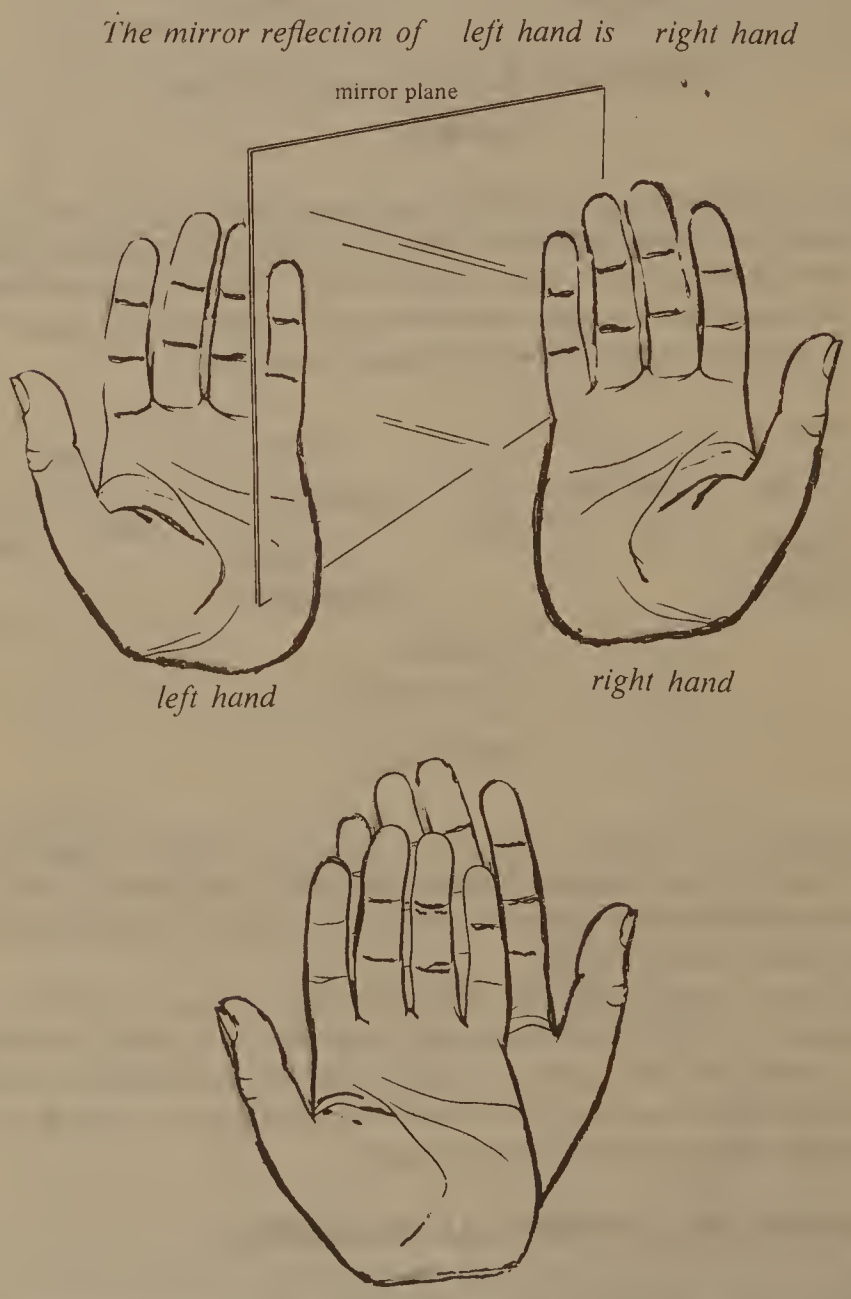


Fig. 1.2

and molecules becomes clear when one applies the test of nonsuperposability of an object or a molecule on its mirror image (sec. 1.3 C).

Objects and molecules which are superposable on their mirror images are called achiral. Socks, for example, are achiral while gloves are chiral. *Cis*-2-butene is achiral but it has a stereoisomeric form *i.e., trans*- 2-butene with which it shares a diastereoisomeric relationship.

A pair of enantiomers can possibly be found to exist for all molecules that contain a single chiral carbon. A chiral carbon (chiral centre) is a carbon atom that has four different groups attached to it (e.g., glyceraldehyde, Scheme 1.3) and is also designated as asymmetric carbon . The discussion in this text is limited, mainly to molecules in which the chiral centre is a carbon atom, although organic molecules with chiral heteroatoms, such as N, P, Si and S, are common.

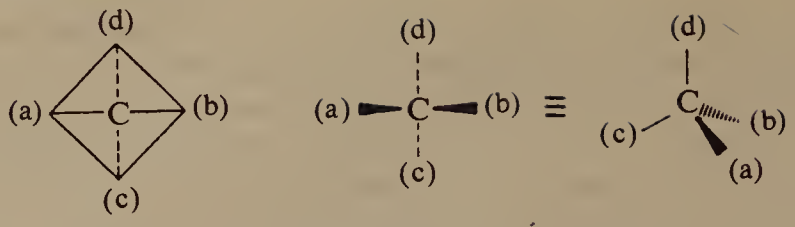
A molecule Cabcd is necessarily chiral when $a \neq b \neq c \neq d$ and none of these ligands are themselves chiral. (In some cases a chiral ligand can generate mirror symmetry on a molecule Cabcd as explained in Section 1.11, meso compounds). The ligands can be alkyl, aryl, heteroatomic or their combination. The chirality of this centre is retained even when two substituents show as small a difference as a hydrogen atom and its isotope deuterium (sec. 1.5). All molecules with a single chiral atom belong to point group C_1.

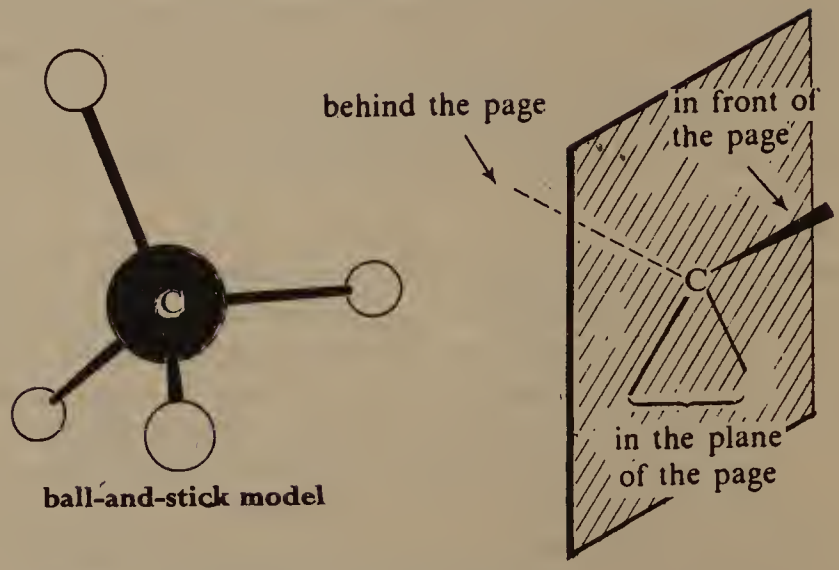
The α-amino acids, $RCH(NH_2)COOH$ (Sec. 1.6A) are an important class of chiral compounds and many contain only one chiral centre. These are the building blocks of proteins. The presence of a chiral centre is however, not the only necessary condition for molecular chirality. The elements which characterize chiral molecules are chiral centres (*i.e.,* α-amino acids), chiral axes (*i.e.,* biphenyls), chiral planes (*i.e.,* paracyclophanes) or their combination. Another element of chirality is helicity (*i.e.,* hexahelicene).

(B) optical Isomers—Wedge Representation

There are two different ways of arranging the four groups around a chiral carbon and these two arrangements are mirror images of each other as shown for glyceraldehyde (Scheme 1.3). Since these two arrangements are not superimposeable, they must represent a pair of isomers, called enantiomers or optical isomers. This type of isomerism is known as enantiomerism, or optical isomerism, because the most readily detectable difference between the isomers is that, one of them will rotate the plane of polarization of plane-polarized light to the left, the other to the right with identical amplitude. In most other respects, the isomers cannot be differentiated; they have identical melting points, boiling points, solubilities, etc. However, some pairs of optical isomers have different smells. Thus, (—)—menthol has a fresh, mint smell, while (+)—menthol smells musty; (+)—limonene smells of oranges (—)—limonene of lemons.

Since our major method of communication is illustrations on paper (two-dimensional), various graphical methods have been developed to depict three-dimensional objects. The tetrahedral model (I), with a carbon atom substituted by four ligands *a, b, c* and *d* at the vertices of a tetrahedron is not





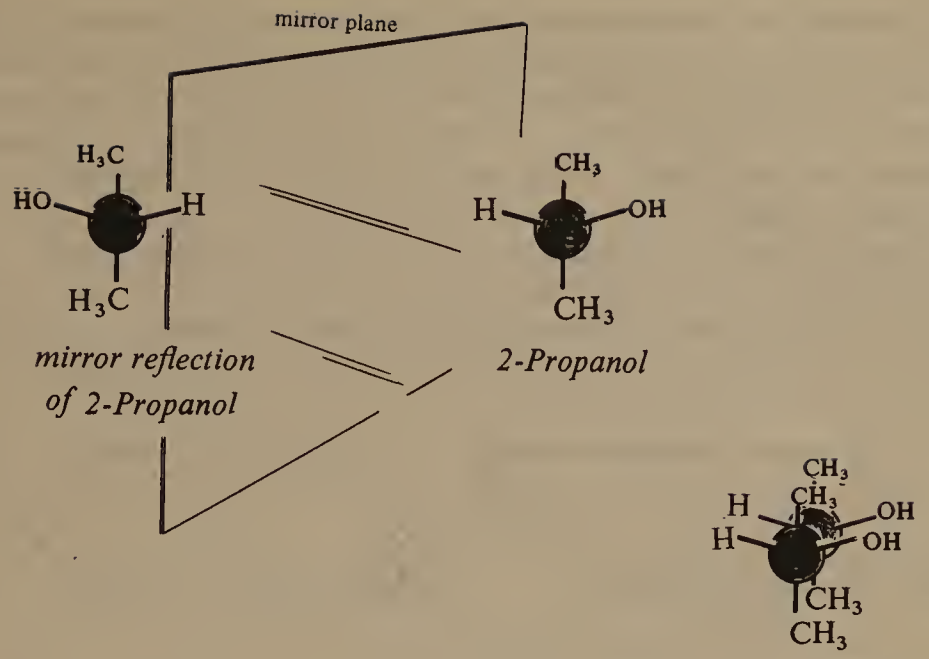
the three-dimensional shapes

Scheme 1.3 a

used, since the chemical bonds are not apparent (Scheme 1.3a). Probably the most common representation (II,III) is the wedge formula. A solid wedge (or a heavy line) represents a bond projecting above the plane of the paper (*i.e.*, bonds pointing toward the observer) and a broken wedge (or a dashed line) a bond below the plane (*i.e.*, bonds pointing away from the observer). Solid lines (or continuous lines) are bonds in the plane of the paper. A simplification of the wedge representation is the Fischer projection, examined in depth in section 1.7.

(C) Superimposability of a Molecule on its Mirror Image

When two or more of the groups which are attached to a sp^3 hybridized carbon atom are identical, the molecule is superposable on its mirror image and is therefore, achiral. In 2-propanol this is so since two identical methyl groups are attached to the central carbon atom. If one writes three-dimensional formulas of 2-propanol one finds that one structure can be superposed on its mirror image. It may be noted, however, that Fischer projections are two-dimensional representations of three-dimensional molecules. In order to visualize if or not two structures are identical these projections can be manipulated only in specified ways (sec. 1.7).



Scheme 1.4

1.4 SYMMETRY ELEMENTS, OPERATIONS, POINT GROUPS AND STEREOCHEMICAL PROPERTIES

The phenomenon of rotation of the plane of the polarized light by some compounds is known as optical activity. A molecule which shows optical activity, or can be resolved into optical antipodes, is known as a chiral molecule while one which does not show optical activity is an achiral molecule. A chiral molecule usually, though not always, contains at least one chiral carbon atom. Optical activity can also result from lack of molecular symmetry and molecules which do not have a chiral carbon, such as some biphenyls, can also be optically active. Two definitions of chirality may be considered; a molecule is described as chiral if it cannot be superposed on its mirror reflection, or, alternatively, if it does not possess an alternating axis of symmetry. These definitions complement each other, the first projects a pictorial aspect while the second a mathematical approach.

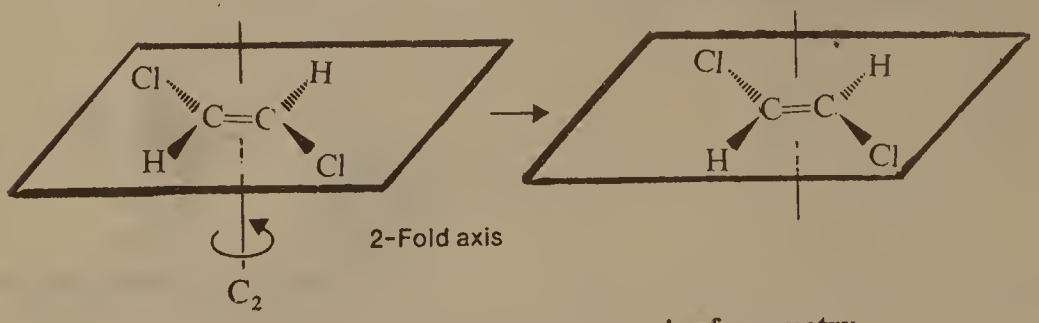
The first definition can be gainfully explored by the use of a set of molecular models and a mirror, but the second must be supplemented by the following explanation.

(A) Axis of Symmetry (C_n)

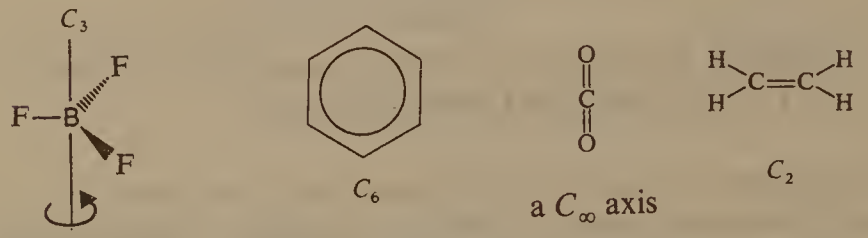
A compound is said to have a simple axis of symmery if a line can be drawn through its molecular model in such a way that its rotation through a certain number of degrees about the line leads to an arrangement which is indistinguishable from the original. For example, (*E*)-1, 2-dichloroethene

has a simple axis of rotation that passes through the midpoint of the molecule and is perpendicular to the plane described by the atoms of the molecule. Rotation through 180° about the axis leads to an arrangement identical to the original. Boron trifluoride has, in a similar way an axis passing through its midpoint, about which a 120° rotation produces an orientation indistinguishable from the original (scheme 1.5).

The difference between the axes of rotation for *(E)*-1, 2-dichloroethene and boron trifluoride is specified by what is called the multiplicity *i.e.*, the "foldedness" of the rotation, the multiplicity (designated by C_n) being defined as equal to $360°/\theta$, where θ is the number of degrees of rotation required for



Molecules containing simple axis of symmetry

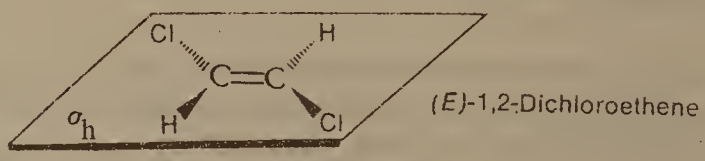


Scheme 1.5

superposition on the original. Therefore, the axis of rotation in *(E)*-1, 2-dichloroethene is two-fold (C_2), while in boron trifluroide it is three-fold (C_3). The planar forms of cyclobutane and cyclopentane can be shown to have four-fold and five-fold simple axes of rotation, respectively, and benzene has a six-fold (C_6) simple axis of rotation. All linear molecules have a C_∞ axis as in O=C=O; an equivalent arrangement is always obtained whatever be the angle of rotation.

(B) Plane of Symmetry (σ)

A molecule possesses a plane of symmetry if,
(*i*) All the atoms of the molecule are in the same plane. For example, *(E)*-1,



Scheme 1.6

2-dichloroethene possesses a plane of symmetry which is the plane of the molecule and includes all the atoms (scheme 1.6).

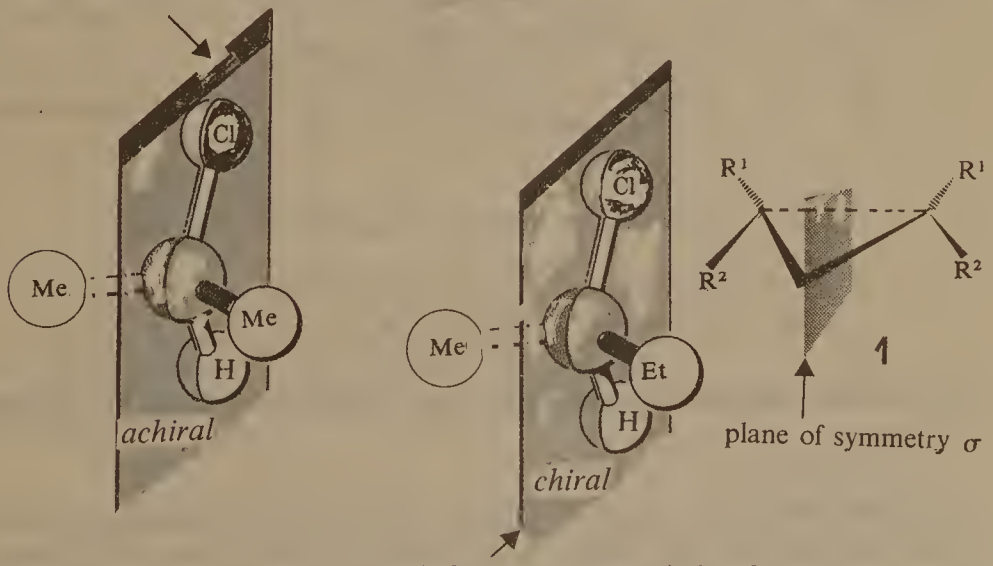
The designation sigma (σ) for planes of symmetry comes from the German word spiegel (meaning mirror).

Thus, all planar molecules possess atleast one plane of symmetry, identical with the molecular plane. Linear molecules have an infinite number of σ planes which intersect along C_∞. The planes of symmetry which are perpendicular to the principal axis are termed σ_h(h for horizontal) whereas those containing the principal axis are marked σ_v (v for vertical).

(*ii*) A molecule has a plane of symmetry if an imaginary double-sided mirror imagined to be inserted through the molecule reflects both the halves so that the new arrangment is indistinguishable from the original molecule. In other words, if a plane (mirror-plane) can be passed through the molecule so that it divides the molecule into two symmetrical halves, one half-reflecting the other as in case of 2-chloropropane and compound 1 in Scheme 1.7 and not in case of 2-chlorobutane.

A plane of symmetry is equivalent to a one-fold alternating axis of symmetry. Some molecules have symmetry planes in addition to simple axes of rotation, while some others have a symmetry plane as their sole symmetry-element (scheme 1.8).

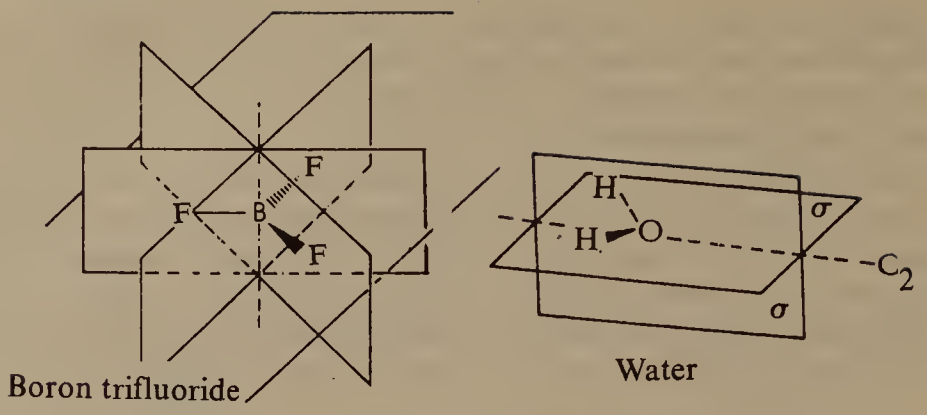
2-Chloropropane has a plane of symmetry



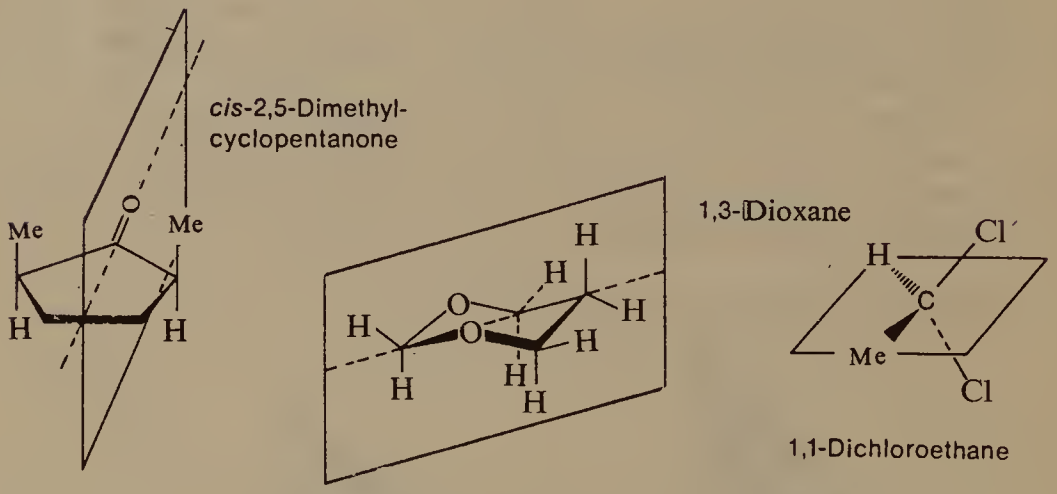
A demonstration of chirality
2-Chlorobutane does not possess a plane of symmetry

Scheme 1.7

The cyclopropane derivative 1 scheme 1.7 is an example of a compound that has a plane of symmetry but no axes of symmetry. Water has two multually perpendicular σ-planes both containing the C_2 axis and intersecting along it. All planar molecules such as water, must contain at least one symmetry plane which is the molecular plane.



Compounds Possessing Planes and Axes of Symmetry

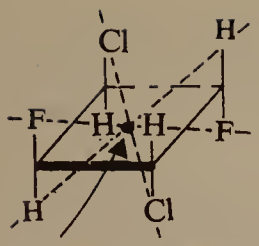


Compounds Possessing a Single Plane of Symmetry
and No Axes of Symmetry

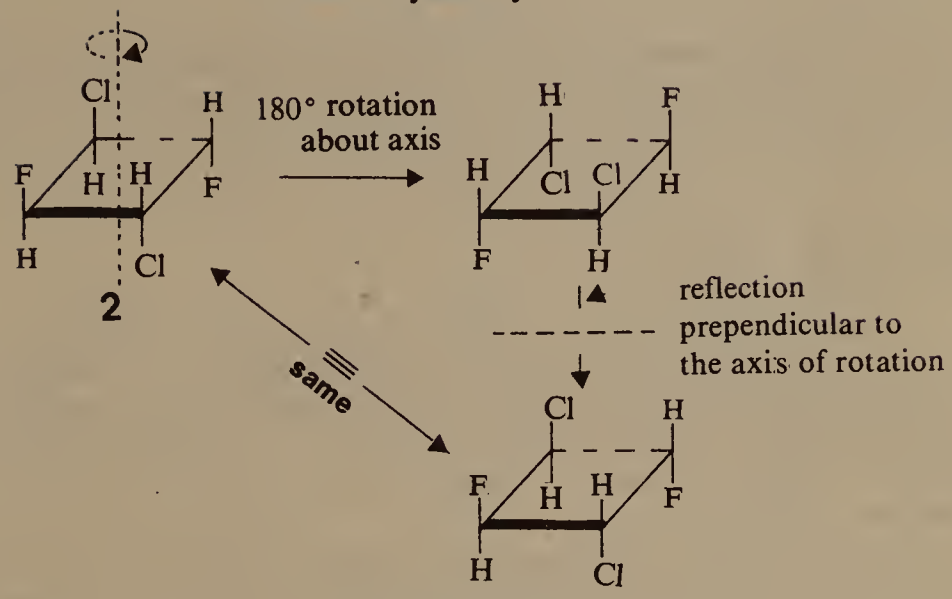
Scheme 1.8

(C) Centre of Symmetry and Rotation — Reflection Axes, S_n (Alternating Axes)

A molecule is said to have a center of symmetry if all straight lines that can be drawn through the center of the molecule meet identical atoms at the same distance from the center. Thus, an isomer of 1,3-dichloro-2,4-difluorocyclobutane 2 Scheme 1.9 has a center of symmetry as its only symmetry element. A center of symmetry is equivalent to a twofold alternating axis of symmetry. A molecule is said to have an alternating axis of symmetry if an arrangement identical to the original is restored when (*i*) the molecule is rotated through θ degrees about an axis passing through the molecule, and (*ii*) the rotated molecule is reflected in a mirror that is perpendicular to the axis of rotation in Ist step, Scheme 1.9. For example, when 2 is rotated 180° about the axis passing through the center of the molecule and then reflected



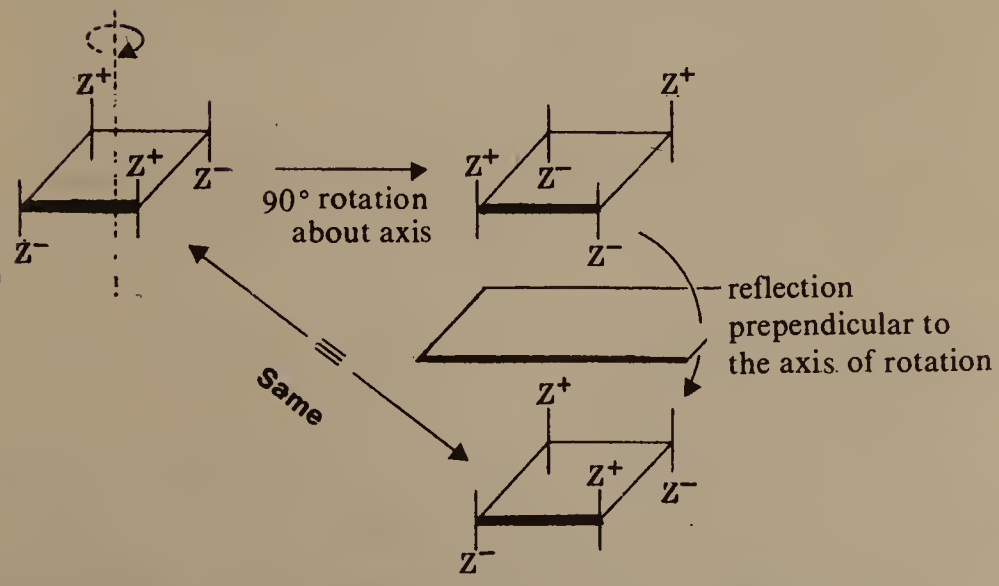
Centre of symmetry



Center of symmetry

(two-fold alternating axis of symmetry) in 2

Scheme 1.9



This contains a four-fold alternating axis of symmetry

(Z^+ is the nonsuperiin posable mirror image of Z^-)

Scheme 1.10

in a mirror perpendicular to this axis, an arrangement superimposable on the original is obtained. The multiplicity *i.e.*, the foldedness of the alternating axis is given by the extent of the rotation in Ist step *i.e.*, 360°/180°= 2; thus. 2 has a twofold axis.

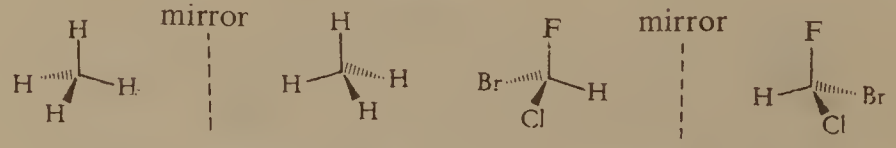
Under the S_n operation the equivalent atoms are carried from one side of the reflection plane to the other in an alternating sequence, hence the name alternating axis.

A molecule contains a fourfold alternating axis of symmetry if after a 90° rotation about an axis followed by a reflection perpendicular to that axis leads to an arrangement identical to the original. Few organic compounds are known in which this symmetry element is the only one present. One type of compound in which this situation occurs is shown in Scheme 1.10.

(D) Reflection Symmetry

A fundamental property of a molecule is its ability or inability to be superimposed on its mirror reflection. When a molecule is reflected in a mirror the condition for superimposability is the exact fit of the image in to the space occupied by the original molecule. Thus, methane has reflection symmetry. In fact, any molecule which has an internal mirror plane has reflection symmetry.

However, bromochlorofluoromethane is chiral, since it has no reflection symmetry. The image and object molecules are distinct molecular species. Bromochlorofluoromethane has no element of symmertry whatever (Scheme 1.11) and such chiral molecules are termed asymmetric (sec. 1.5).



methane has reflection symmetry

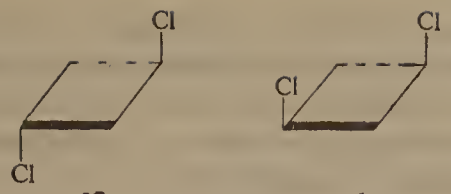
bromochlorofluoromethane chiral

Scheme 1.11

1.5 SYMMETRY ELEMENTS, ASYMMETRY, CHIRALITY A COMBINED LOOK

Consider *trans*-1, 3-dichlorocyclobutane 3. It cannot exist in optically active forms because it has both a plane and centre of symmetry; and the *cis* isomer 4 cannot exhibit the phenomenon because it has two planes of symmetry.

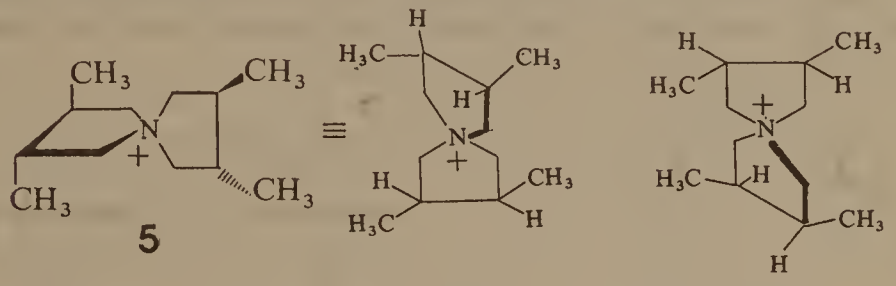
Care must be used if this approach is adopted; for example, the spiro-compound 5 Scheme 1.13 possesses neither a centre nor a plane of symmetry, but it cannot exist in enantiomeric forms because it possesses a four-fold alternating axis of symmetry (S_4). Indeed 5 is superimposable on its mirror



3 4

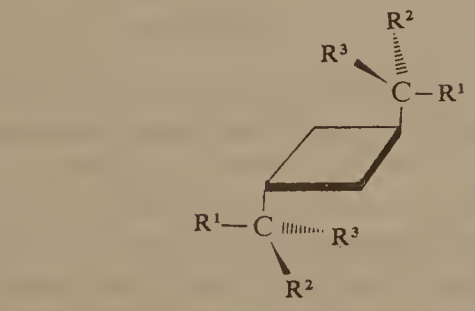
Scheme 1.12

image. To show that 5 does contain a four-fold alternating axis of symmetry, an orientation of 5 *i.e.*, (a) is rotated through 90° about the co-axis of both rings to get (b). Reflection of (b) through the central plane (*i.e.*, through the *N* atom) perpendicular to this axis yields a molecule similar to (a).



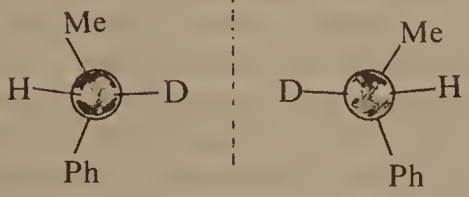
5 (a) (b)

Scheme 1.13



6

mirror



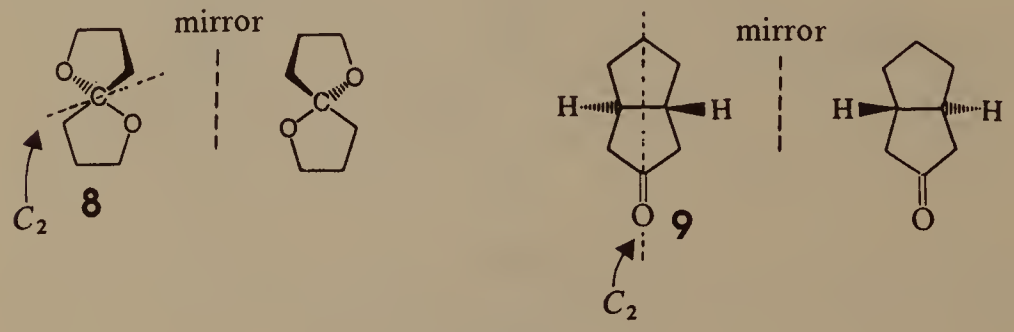
α-Deuterioethylbenzene 7
enantiomers

Molecules are not superimposable on their mirror images
(simple three-dimensional picture)

Scheme 1.14

The compound **6** has a two-fold alternating axis of symmetry and is achiral even though it has two asymmetric carbon atoms. A closer look at **6** shows that it has a centre of symmetry. In a case of substitution of hydrogen by deuterium shows that two atoms are sufficiently different as in **7** to give rise to optical isomerism as shown in scheme 1.14.

It is not a necessary condition for chirality that a molecule should have no symmetry elements. A necessary and sufficient condition for a molecule to have a non-superimposable mirror image is that it must not contain a plane, a centre or a four-fold alternating axis of symmetry. However, these requirements do not preclude the presence of a simple axis of symmetry in a chiral molecule. There are several examples of such compounds *e.g.*, **8** and **9** in Scheme 1.15 with non-superimposable mirror images; (chiral compounds), in which a symmetry element is detectable. Thus a molecule containing a C_2 axis and no mirror plane is also chiral. The allenes provide yet another example of chiral molecules with C_2 axes (Sec. 1.21).



Scheme 1.15

To distinguish compounds from those that are truly asymmetric *i.e.*, which do not contain symmetry element of any kind, term dissymmetric molecules is often used. Although the distinction is important in some stereochemical situations in the majority of the cases, however, the only concern is whether the mirror images are superimposable or not. It is only to simplify matters, that, the term chirality has been used. Any molecule that has a non-superimposable mirror reflection is termed as a chiral molecule; any molecule that has a superimposable mirror reflection is classed as an achiral molecule.

One may group together the molecules on the basis of the symmetry operations that can be performed on them. These operations are termed point symmetry operations, since, under such symmetry operations one point, the centre of mass always remains unchanged. Molecules which possess identical symmetry elements, and only these elements, belong to the same group, To be exact these belong to the same point group. The point group of a molecule "X" is the ensemble of the symmetry operations which transform X to a molecule to which it is superposable. These symmetry operations are dependent on symmetry elements and both terms are essential to define symmetry. Point groups can be further classified into two main groups (*i*) structures lacking reflection symmetry and (*ii*) structures possessing reflection symmetry.

No chiral structure can have a σ plane and if a $C_n(n>1)$ is also absent, the structure lacks all symmetry elements and is termed asymmetric belonging to point group C_1 Thus, when a chiral compound (CHClBrF) is considered as a molecular model, a C_n axis, a plane of symmetry and a centre of symmetry all are found to be absent and this molecule, therefore, belongs to C_1 point group. The molecules which belong to C_1 are, therefore, chiral.

All the molecules which are chiral do not, however, belong to C_1. Consider a disubstituted allene (sec. 1.21) which has a C_2 axis and the C_2 symmetry. It is best seen *via.*, the "head-on" view. There are no planes of symmetry and S_4 axis in this molecule hence it belongs to the C_2 point group. The molecules which belong to C_n point groups are chiral.

Let us now consider achiral molecules. Molecules with only a σ plane and no C_n axes belong to the point group C_s *e.g.*, a monosubstituted cyclopropane derivative.

Some examples of molecules which have an S_n axis but no σ plane are known and these belong to point group S_n (n being even). Clearly, such molecules have reflection symmetry to show that a σ plane is not a necessary condition for reflection symmetry, the spiro compound, 5 is an example.

In several cases, achiral molecules have both σ planes and C_n axes. With one C_n and $n\sigma$ planes intercepting at C_n the point groups are C_{nv} and the planes are σ_v, *e.g.*, water belongs to C_{2v} and chloroform to C_{3v} point group.

Molecules which have one C_n axis and one σ_h plane (σ_v planes being absent) belong to the group C_{nh} *e.g., trans*, 1-2-dichloroethylene (Sec-1.4B) belongs to C_{2h} group. Molecules with one C_n axis and nC_2 axes (*i.e.*, with dihedral symmetry) and having $n\sigma_v$ plane (σ_h plane being absent) belong to D_{nd} groups where D denotes diagonal. In case σ_h plane is also present then the point groups are D_{nh}. Thus benzene belongs to D_{6h} point group since it has one C_6, six C_2, six σ_v and one σ_h, similarly acetylene has $D_{\infty h}$ symmetry *i.e.*, cylindrical symmetry.

TABLE 1.1 : Main Point Groups

Chiral groups		Achiral groups	
Type of group	Elements	Type of group	Elements
C_1	No symmetry element (asymmetric)	C_s	σ
		S_n	S_n (n even)
C_n	$C_n(n>1)$ (dissymmetric)	C_{nv}	C_n, $n\sigma_v$
		C_{nh}	C_n, σ_h
		D_{nd}	C_n, nC_2, $n\sigma_v$
		D_{nh}	C_n, nC_2, $n\sigma_v$, σ_h
		T_d	$4C_3$, $3\,C_2$, 6σ
		O_h	$3C_4$, $4C_3$, $6C_2$, 9σ
		K_h	All symmetry elements

Lastly mention may be made of the point groups T_d which is applicable to regular tetrahedral molecules like, CH_4, CCl_4 etc. and O_h, octahedral point group to which the well known compound cubane belongs. The final high

symmetry point group is K_h which is applicable to objects having all symmetry elements. Molecules, however, cannot have K_h symmetry and this point group is applicable only to single isolated atoms.

1.6 CONVENTIONS DESCRIBING CONFIGURATIONS *D-L* AND *R-S* SYSTEM

The configuration of an asymmetric carbon (chiral centre) is the specification of the relative spatial arrangement of the four groups attached to it. Absolute configuration specifies their order so as to distinguish the two enantiomers and thereby define their chirality. The term relative configuration specifies the relation of the two asymmetric atoms to each other, *i.e.*, whether the placement of two groups on these atoms is *cis* or *trans*.

The former *DL* system[2,3] to denote absolute configuration is not without faults and, therefore, this system is seldom used today except for some classes of compounds like carbohydrates and amino acids.

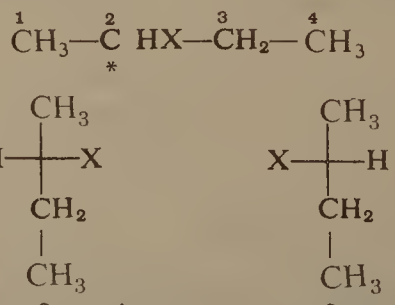
(A) The *D* and *L* Designations

Fischer assigned configurations to optically active compounds by choosing glyceraldehyde as standard. The dextrorotatory form of glyceraldehyde was arbitrarily assigned structure which is said to possess the *D* configuration. The levorotatory form of glyceraldehyde was assigned a structure which is said to possess the *L* configuration. The configurations of other optically active compounds were later established relative to that of the two enantiomeric glyceraldehydes.

D(+)-glyceraldehyde L(−)-glyceraldehyde

Scheme 1.16

For a compound with the general formula where X is a group which is attached to the chiral carbon (C*) by a hetero atom (a non-carbon atom), the correct Fischer projection formulas for its two enantiomers are :



D-configuration L-configuration

With X = Cl, Br, OH, NH_2, etc. projection formulas

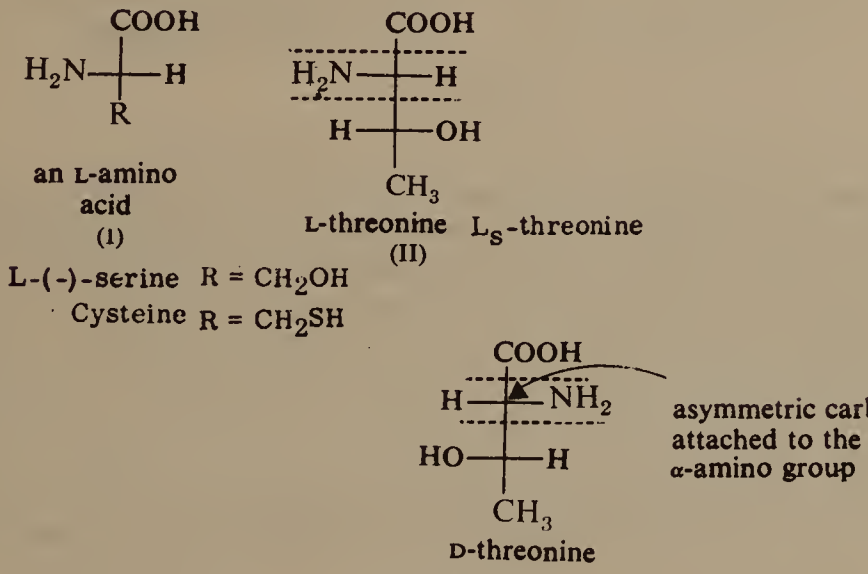
Scheme 1.17

The configurations of these two forms are denoted by the symbols D and L depending on whether the group X is to the right or to the left of the vertical line representing the chain of carbon atoms. It should be remembered that the symbols D and L are in no way intended to denote the direction in which an optically active compound will rotate the plane of polarized light (*i.e.*, D ≠ d and L ≠ l).

α-amino acids are carboxylic acids with an amino group attached to the carbon atom adjacent to the carboxyl group (the α-carbon). With the exception of glycine ($NH_2—CH_2—COOH$), all naturally occurring α-amino acids are chiral molecules and exhibit optical activity. The α-carbon in

$$R—\overset{*}{C}H(NH_2)—COOH$$

is asymmetric if R ≠ H. The position of the α-amino group with respect to the vertical line in a Fischer projection formula determines the configuration of the compound as shown in the case of threonine. (Scheme 1.18).

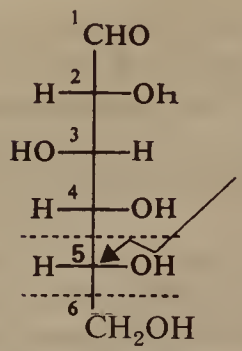


Scheme 1.18

Essentially all naturally occurring α-amino acids obtained from animal proteins belong to the L-series.

The Fischer projection formulas of monosaccharides are drawn by keeping the following conventions in mind:

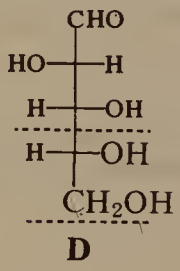
(*i*) The longest carbon chain is vertical; (*ii*) the most highly oxidized end of the chain is at the top; and (*iii*) at each center along the main chain the vertical bonds point backwards. Sugars containing more than one asymmetric carbon (chiral carbon) are designated as D-sugars if the —OH group attached to the highest numbered asymmetric carbon is on the right of the vertical line in a Fischer projection and as L-sugars if —OH group is on the left. Significantly most naturally occurring monosaccharides belong to the D-family.

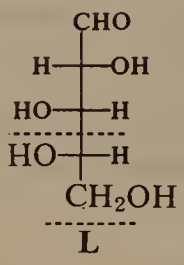


highest numbered chiral carbon

Fischer projection formula of D-glucose;

abbreviated projection formula of D -glucose





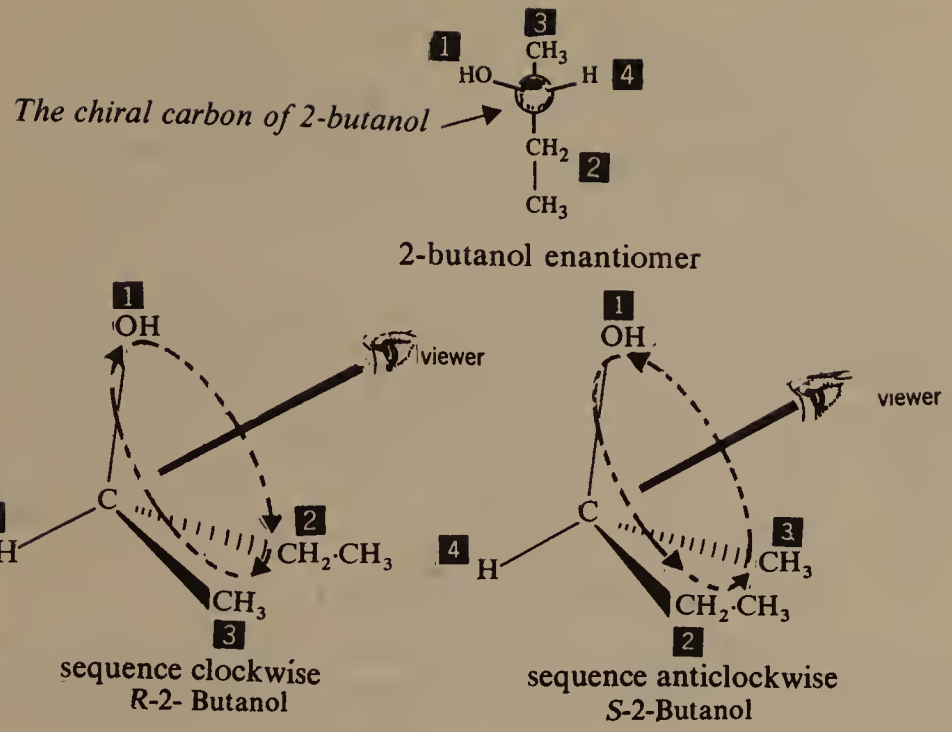
a monosaccharide *whose highest numbered chiral carbon* has the configuration as D - (+) - glyceraldehyde is designated as a D sugar; one whose highest-numbered chiral carbon has the same configuration as L-glyceraldehyde is designated as an L sugar

Scheme 1.19

Some weaknesses of **D-L nomenclature**: The projection nomenclature (*i.e.*, D and L) is restricted to those molecules which can be unambiguously drawn in the Fischer projection and which simultaneously obey all relevant rules. Several difficulties were faced for distinct chemical classes like amino acids which resulted in the development of the amino acid nomenclature. While L(-)- serine (**I**; R=CH_2OH) Scheme 1.18 could be easily designated according to the carbohydrate nomenclature, the original D-threonine (**II**) designation is not consistent with serine. It has to be altered to L_s -threonine (**III**), where the subscript indicate the serine series; the subscript g is then used for the glyceraldehyde series. Moreover, these nomenclatures, as were originally conceived and used, indicated nothing beyond relative configurations.

(B) The *R* and *S* Designations

The system now widely used is the Cahn-Ingold-Prelog (R-S) system [2,4,5] (which relates all compounds with only one set of rules) in which the four groups attached to the asymmetric carbon atom (*i.e.*, a chiral centre) are numbered 1, 2, 3 and 4 and are ranked according to a set of sequence rules so that they can be assigned priorities for arrangement in a sequence 1>2>3>4. In a simple case the priorities follow the order of decreasing atomic number of the atom that is directly attached to the chiral carbon, *i.e.*, Br. (35), Cl(17), S(16), O(18), N(7), C(6) and H(1). The application of the rule can be illustrated with 2-butanol enantiomer (Scheme 1.20) which has a sequence OH, C_2H_5, CH_3 and H.



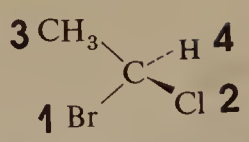
Scheme 1.20

Thus oxygen has the highest priority (1) and the hydrogen the lowest atomic number priority (4).To make the priority assignment for the methyl and ethyl groups where the atom that is directly attached to the chiral carbon is a carbon atom the next sets of atoms in the groups are examined. Thus the ethyl group takes precedence (C,H,H) as compared with methyl (H,H,H). A three dimensional model of the isomer to be designated is viewed from the side opposite the group of lowest priority (Scheme 1.20). The priority sequence 1→2→3 (decreasing priority) of the remaining three groups is determined and if it is found clockwise, the symbol (*R*) is used to designate the configuration and if the sequence is counter clockwise the symbol (*R*) is used. (*R*) and (*S*) are from Latin words *rectus* and *sinister* meaning right and left respectively.

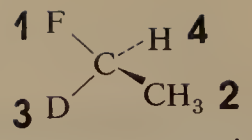
Double or triple bonds are treated as separate single bonds, thus -CHO is regarded as C(O, O, H) and-COOH as C(O, O, OH) and, therefore, the latter group takes precedence over the former.

(C) A Summary of Sequence Rules

1. If the four atoms attached to the chiral center are different, priorities depends on atomic numbers, the atom of higher atomic number is assigned higher priority. It two atoms are isotopes of the same element, the atom of higher mass number has the higher priority.
2. If the relative priorities of two groups cannot be determined as above these are decided by a comparison as done in the case of methyl and ethyl groups of 2-butanol.

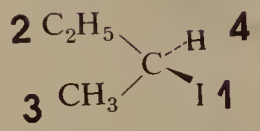


(S)-1-bromo-1-chloroethane

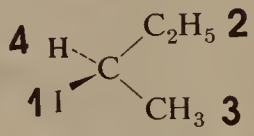


(R)-1-deuterio-1-fluoroethane

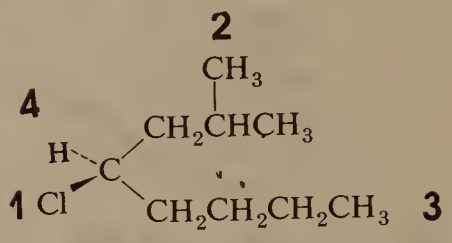
Scheme 1.21



(S)-2-iodobutane



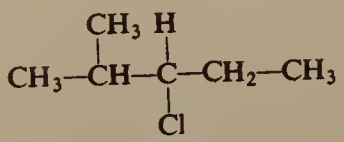
(R)-2-iodobutane



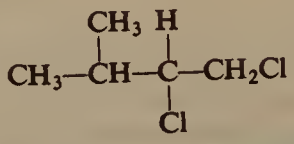
(R)-4-chloro-2-methyloctane

Scheme 1.22

In 3-chloro-2-methylpentane the (C, C, H) of isopropyl takes priority over the (C, H, H of) ethyl, and the complete sequence of priority is Cl, isopropyl, ethyl, H.



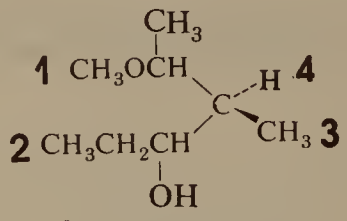
3-Chloro-2-methylpentane



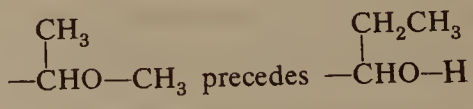
1,2-Dichloro-3-methylbutane

Scheme 1.23

In 1, 2-dichloro-3-methylbutane the Cl, H, H, of CH_2Cl takes priority over the C, C, H of isopropyl as chlorine has higher atomic number than carbon. In some cases, one has to make a choice at a branch point as to which branch to follow. The rule here is, that one decides by proceeding along the branch of higher priority as in the following example.

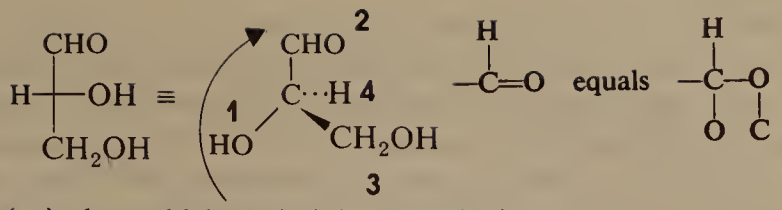


(S) configuration



Scheme 1.24

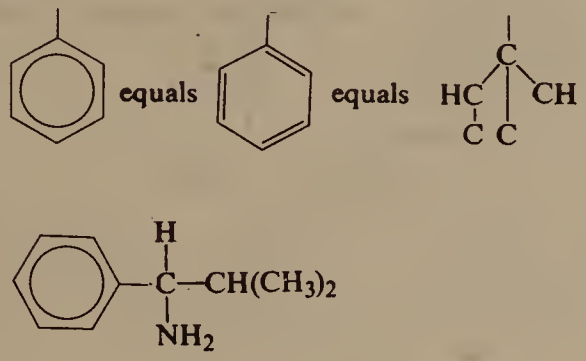
3. In the case of, double or triple bond, both atoms are considered to be duplicated or triplicated. For example, in glyceraldehyde the —OH group has the highest priority of all, and the O, O, H of —CHO takes priority over the O, H, H of $—CH_2OH$. The complete sequence is thus —OH, —CHO, $—CH_2OH$, —H.



D(+)-glyceraldehyde is (*R*)-glyceraldehyde

Scheme 1.25

The phenyl group, C_6H_5—is considered as one of the Kekule structures. The vinyl group, $CH_2=CH$—, takes priority over isopropyl, $—CH(CH_3)_2$. In 1-amino-2-methyl-1-phenylpropane (Scheme 1.26), therefore, the C, C, C, of phenyl take priority over the C, C, H of isopropyl, but not over N, which has a higher atomic number. The sequence is thus $—NH_2$, C_6H_5—, C_3H_7—, H.



1-amino-2-methyl-1-phenylpropane

Scheme 1.26

(D) The Comparison Between D, L and R, S Conventions

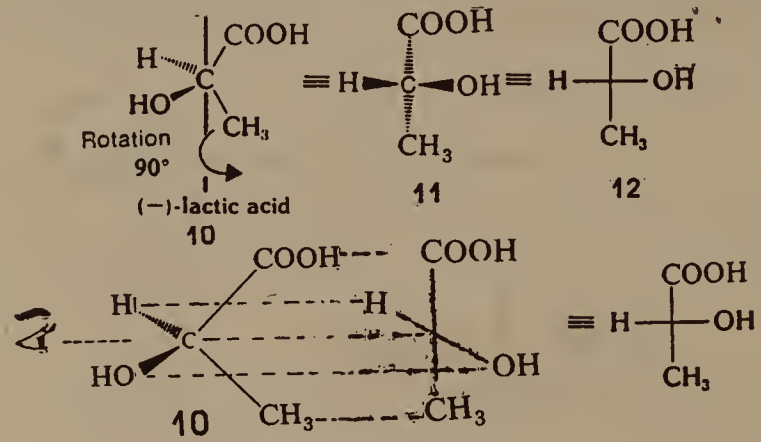
An important caution about the sequence rule is that chemical and biogenetic families are not necessarily correlated *e.g.*, the natural α-amino acids can be respresented as structure (**I**) in fischer projections (the L-configuration). Most of the amino acids, with (—)-serine (**I**; R=CH_2 OH), as the standard in the series, have the (S)-configuration. Cysteine (**I**; R=CH_2 SH), however, has the (R) -configuration due to perturbation of the sequence by the sulfur atom since-CH_2SH precedes —COOH.

Failure of the sequence rule in consistently revealing stereochemical correlations is the reason why the "local" systems such as the D and L nomenclature for carbohydrates and amino acids, and the α, β nomenclature for steroids are not falling into disuse.

1.7 FISCHER PROJECTION FORMULAS

As the number of chiral centers increases in a compound, it becomes more and more cumbersome to draw the three-dimensional formulas of a molecule using dotted lines and wedges. In order to circumvent this difficulty, chemists

have adopted the use of Fischer projections. These are two-dimensional projection models originally developed by Fischer for carbohydrates and amino acids. In this convention, the three-dimensional formula *i.e.*, **10** (Scheme 1.27) of lactic acid is first rotated so that the two groups are above the plane of the paper, and two are below it. The molecule is then represented by two lines intersecting at right angles, the central carbon atom is at the point of intersection of the lines representing the chiral center and is not shown. Substituents above the plane of the paper are then attached to the horizontal line which represent bonds directed towards the viewer. The substituents below the plane of paper are attached to the vertical line and are directed away from the viewer. Conventionally, the projection is drawn so that the longest carbon chain in the molecule is vertical.



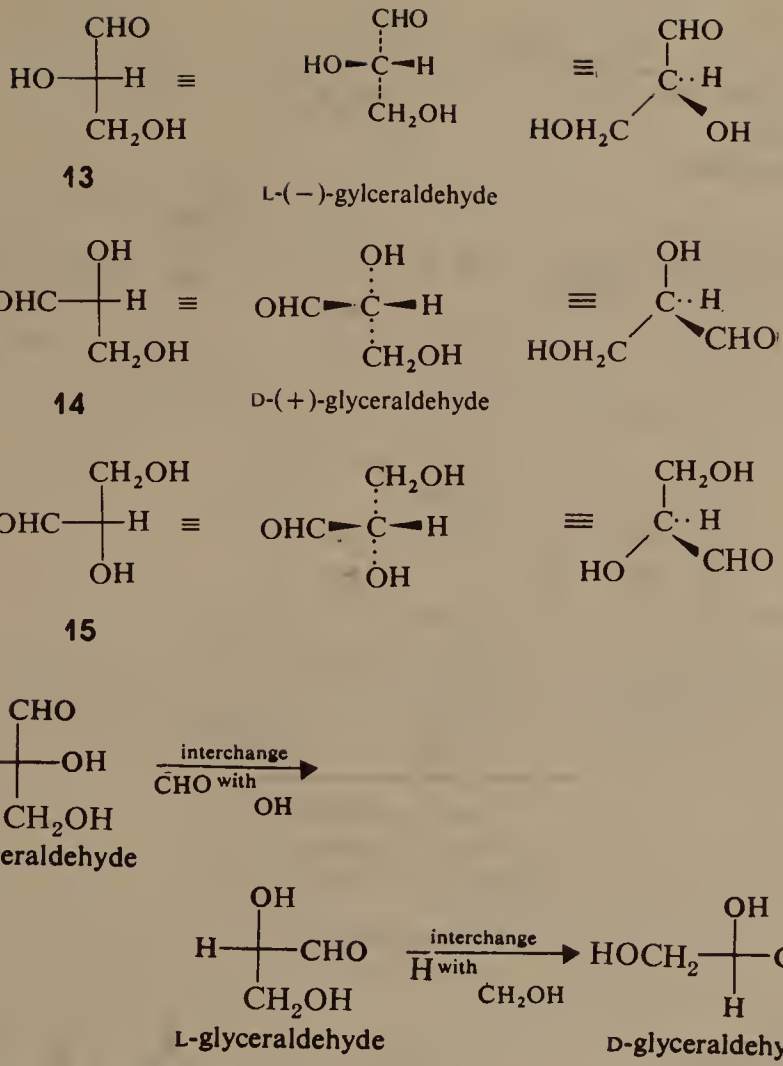
Scheme 1.27

It is important to remember that Fischer projections are two-dimensional representations of three-dimensional molecules. In order to find out whether the two structures are identical or not these projections can be manipulated only in specified ways.

The following points are very important to remember:

1. Interchange of any two groups in a projection like **12** or**13** changes it to the mirror image of the original. On interchanging a second pair one obtains the original molecule, although the groups may now occupy different positions than the original arrangement. This can he explained by carrying out two interchanges of groups in the projection of glyceraldehyde, Molecules **13** and **15** (Scheme 1.28) therefore represent the same optical isomer and **14** the mirror image.

2. A 90° rotation of the projection formula about the chiral center inverts the configuration of the original structure, as does an exchange of the position of any two groups as shown in the case 2-bromobutane (Scheme 1.29). In other words, the perspective formulas can be turned over or rotated in any direction and these manipulations do not change the configuration of the original molecule. Fischer projection formulas retain their configurations only if molecule is rotated by 180°, in the plane of the paper. Thus, it is not permitted to lift the molecule out of the plane of the paper and flip it over. These operations if done, are same as breaking of a bond to alter the configuration of



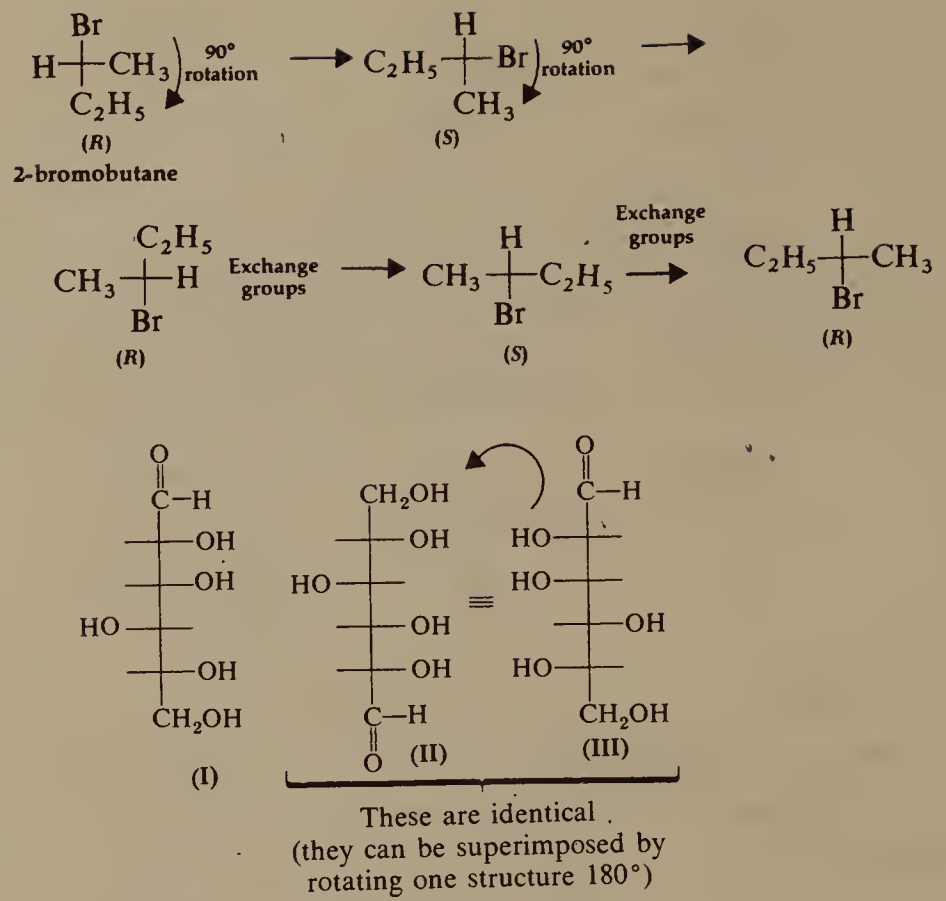
Scheme 1.28

the original molecule. For example, if **II** (Scheme 1.29) is rotated end to end in the plane of the paper *i.e.,* 180° rotation, one finds that the resulting arrangement, **III** is equal to **II.** Comparison of **III** with **I** shows that these are enantiomers. If one simply lifts the arrangement **II** out of plane of the paper and flips it over, resulting arrangement would be exactly like **I.** However, by doing so one has changed the configuration of the original molecule **II.**

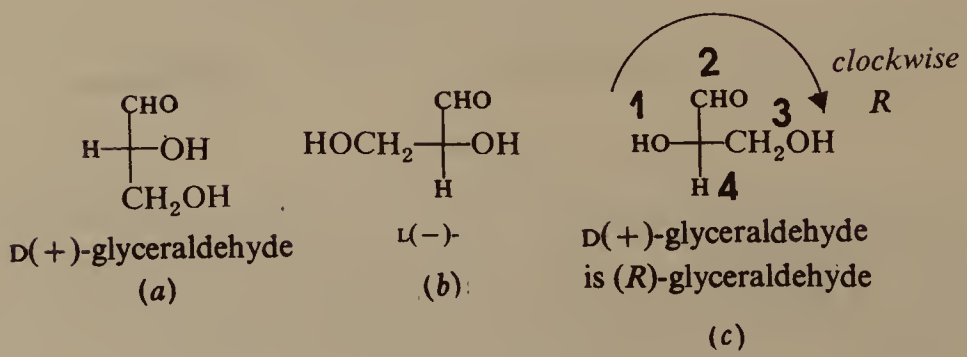
1.8 FISCHER PROJECTION AND *R* AND *S* DESIGNATION

When a compound is written in the Fischer projection the sequence rule designation of an asymmetric centre can be made without constructing the model. The Fischer projection is rewritten to put the group of the lowest priority at the bottom (Scheme 1.30), bearing in mind that in so doing one is inverting the isomer.

Thus in D (+)-glyceraldehyde, Scheme 1.30 (a) when —H and —CH_2OH are



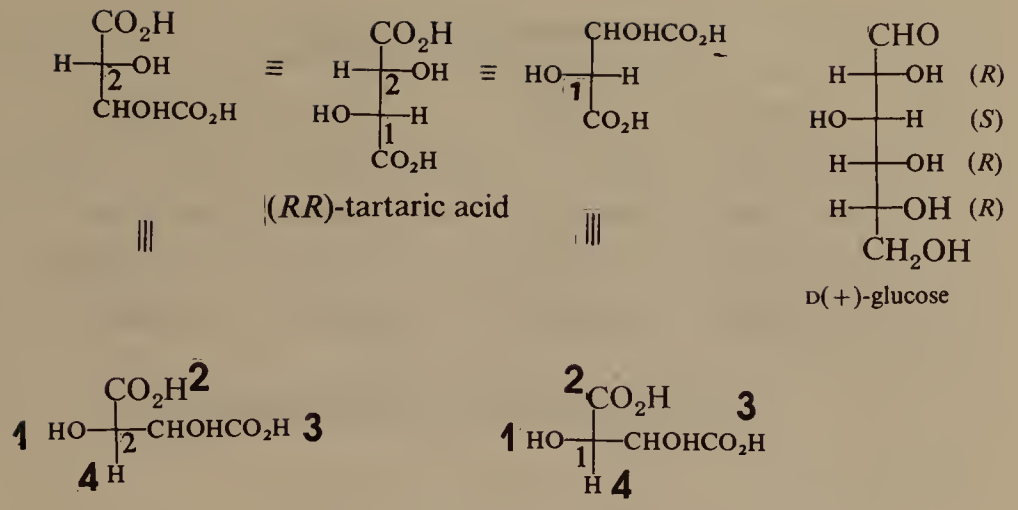
Scheme 1.29



Scheme 1.30

interchanged to put the group of lowest priority (H) at the bottom one gets (b) which is L(-)-glyceraldehyde. To get the original configuration(c) one has to interchange two groups again *i.e.*, —OH with —CH_2OH. This configuration is seen to be (R) from the rewritten Fischer projection of D-glyceraldehyde and the same conclusion could be reached by resorting to its model.

To name a compound with more than one chiral centre each centre is examined separately and assinged a configuration. The terms (R) and (S) are then added with the systematic name as shown in the case of (+)-tartaric acid and (+)-glucose (Scheme 1.31).



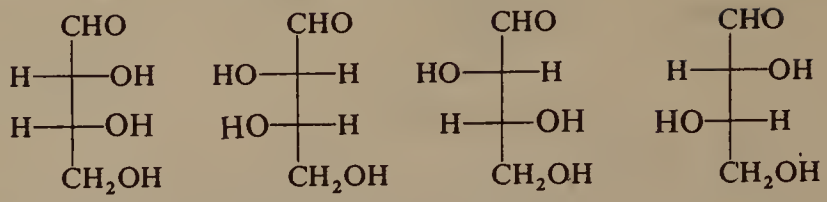
Scheme 1.31

1.9 STEREOISOMERISM RESULTING FROM MORE THAN ONE CENTRE OF CHIRALITY (THREO AND ERYTHRO NOMENCLATURE, DIASTEREOISOMERS AND STEREOREGULAR POLYMERS)

Molecules with two asymmetric atoms have been particularly used in mechanistic studies and as a result special nomenclature for these compounds is employed. This nomenclature is derived from the names of the four-carbon sugars erythrose and threose. When an acyclic molecule has n non-identical centres of chirality, it exists as 2^n stereoisomers which are enantiomeric in pairs; moreover, such a molecule exists as 2^{n-1} diastereoisomeric pairs of enantiomers. However, restrictions of molecular symmetry or geometry may prevent the existence of some of these (Sec. 1.11) meso compounds. In the case of a molecule with two asymmetric centres, there can be four such arrangements, classic example being the four-carbon sugars—the tetroses which have two asymmetric carbon atoms and are shown in Scheme 1.32 as Fischer projections. Another case (n=2) is well illustrated by ephedrines (Sec. 7.3 C). Inspection of these structures reveals that 1 and 2 (Scheme 1.32) are mirror images of each other and are thus the optical isomers of a single substance and similar is the case with 3 and 4. A comparison of either of the threoses with either of the erythroses shows that, although they are stereoisomers, they are not mirror images. Such stereoisomers, which are not mirror images of each other, are termed diastereoisomers. Unlike enatiomers, diastereoisomers differ from each other in physical and chemical properties.

In all systems of the type R-Cab-Cac-R′, when the two like groups in a projection formula are on the same side, the isomer is named erythro form 5 (Scheme 1.32) and if these are on opposite sides 6 (Scheme 1.32) the isomer is called the threo form. The projection formulae, however, represent the mole

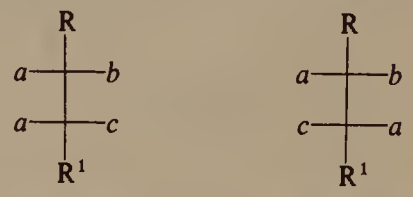
Fischer projection formulae



(−)-erythrose (+)-erythrose (−)-threose (+)-threose

1 **2** **3** **4**

These molecules are in an eclipsed conformation

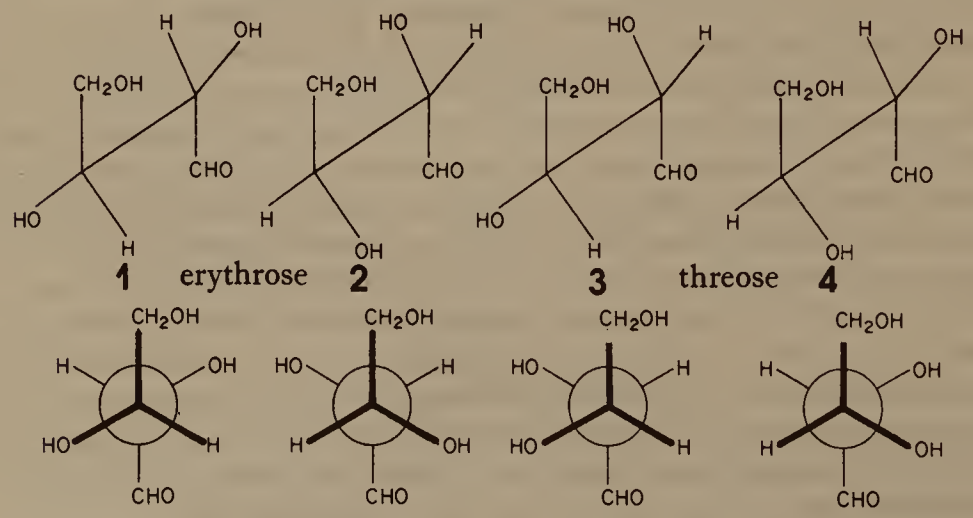


Erythro **5** Threo **6**

Scheme 1.32

cule in the eclipsed form, whereas, while considering the reactions of the molecule, it is necessary to depict it in its actual staggered form (Scheme 1.33) which can be realised when C-2 and C-3 are rotated with respect to each other through 60°

Sawhorse and Newman formulae for one of the staggered conformations of each of the aldotetroses

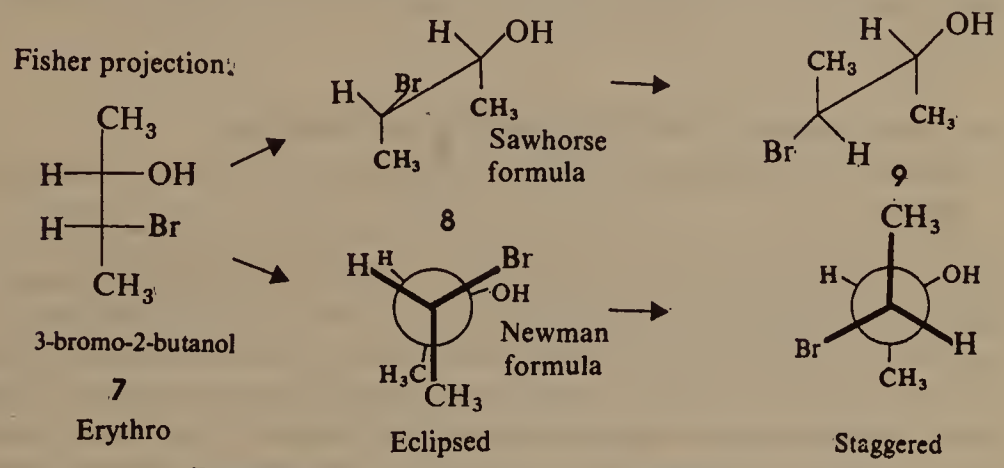


1 erythrose **2** **3** threose **4**

in reality they must largely exist in one of the more stable staggered conformations

Scheme 1.33

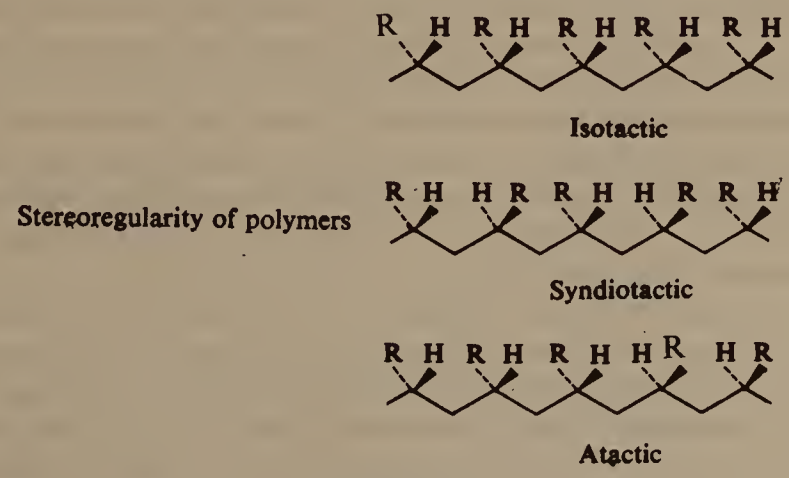
While dealing with stereochemical problems it is necessary that one is able to translate one set of representation of a compound into the other. A shift from the Fischer projection formula to either a sawhorse or Newman projection formula is particularly necessary. In one of the ways, a model corresponding to the Fischer projection is drawn, its rotation gives the staggered form and from it sawhorse or Newman projection is drawn. Another way which does not require the use of models is to translate directly the Fischer projection **7** into an eclipsed sawhorse or Newman projection **8** which is then rotated through 180° around C-2 and C-3 bond to provide the actual sawhorse or Newman representation **9** as shown in the case of one enantiomer of *erythro*-3-bromo-2-butanol (**7**) (Scheme 1.34).



Scheme 1.34

Polymerization of vinyl compounds of the type CH_2=CHR, leads to long chain polymers with large number of chiral centres. Three different types of polymers are recognised due to different spatial relationships of the R groups (Scheme 1.35):

(a) **Isotactic polymers** in which the monomers are joined in a regular



Scheme 1.35

head-to-tail sequence and the R groups are all on one side of the polymeric backbone.

(b) **Syndiotactic polymers** in which the monomers are joined in a regular head-to-tail sequence with alternating R groups appearing on opposite sides of the plane containing the polymeric backbone.

(c) **Atactic polymers** in which the monomers are not joined in a regular sequence and there is no pattern in the steric distribution of the R groups.

Organometallic catalysts give polymers with a high degree of stereospecificity and polymers like polypropylene polystyrene, occur in isotactic form. Polypropylene made under different conditions is syndiotactic. Stereoregular polymers are exceptional in having high crystallinity, densities and melting points.

1.10 SOME ASPECTS OF GEOMETRIC ISOMERISM

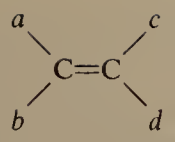
(π Diastereoisomerism and Torsional Chirality in Carbon Carbon Double Bonds)

In case the rotation about a bond joining two mutlivalent atoms is restricted, then suitable substitution leads to isomerism. The most common method of preventing rotation about a bond is either the formation of a multiple bond, as in π-diastereoisomerism or by the incorporation of the bond in a ring system as in σ-diastereoisomerism. Isomerism arises in both cases I and II, when $a \neq b$ and $c \neq d$. Since both of the resulting molecules possess alternating axes of symmetry, they are not optical isomers (sec. 1.2 B), but represent different chemical entities known as geometrical isomers. Isomers with similar groups on the same side of the molecule are known as *cis* and those with similar groups on opposite sides are known as *trans*.

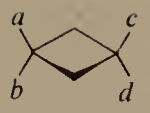
(A) The *E-Z* System of Nomenclature

Now, the *E-Z* system[5] which is based on the priorities of groups on the Cahn-Ingold-Prelog convention, is used to designate diastereomeric alkenes. The terms *cis* and *trans* are unambiguous only when used to designate the stereochemistry of disubstituted alkenes. If, however, the alkene is trisubstituted or tetrasubstituted these terms either become ambiguous or cannot be applied at all. For example, in the case of the alkenes **10** and**11** (Scheme 1.36) it is not possible to designate these as *cis* or *trans* since no pair of groups are the same. The alkene **11** is called *cis* since the configuration of the longest chain of carbon atoms is as shown in **12**.

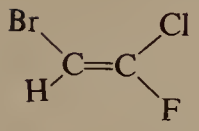
In the *E-Z* system the two groups attached to each carbon of the double bond are arranged in order of priority *i.e.*, Cl>F and Br>H. If the two groups of higher priority are located on the same side of the double bond as in **10** the alkene is designated *Z* isomer (from the German word *Zusammen* meaning together). If on the other hand, the two groups of higher priority are on opposite sides of the double bond then the alkene is designated *E* isomer (from



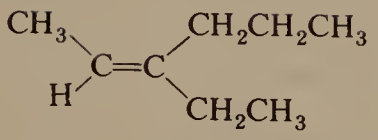
(I)



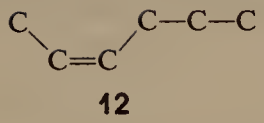
(II)



10 (Z)

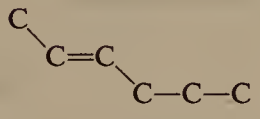


11 (Z)



12

rather than

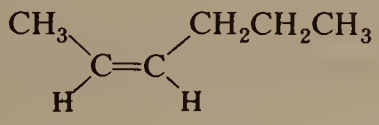


Scheme 1.36

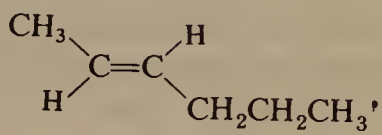
the German word, *Entegegen* meaning opposite).

Becuase of the ranking CH_3>H and C_3H_7>H. *cis* and *trans-2-* hexenes are designated as below :

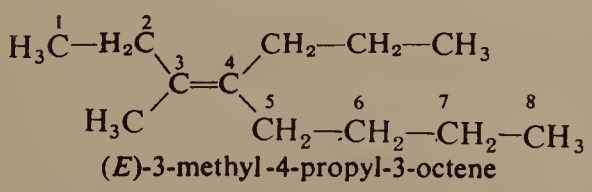
The compound **13** should be designated as an E olefin because the ethyl group (the group of higher priority on C_3) and the butyl group (the group of higher priority on C_4) are on opposite sides.



(*Z*)-2-Hexene
(*cis*-2-hexene)

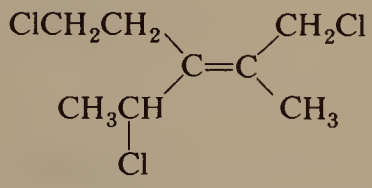


(*E*)-2-Hexene
(*trans*-2-hexene)

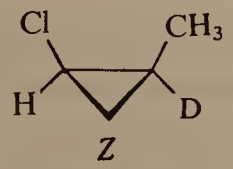


(*E*)-3-methyl-4-propyl-3-octene

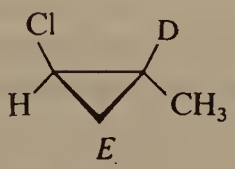
13



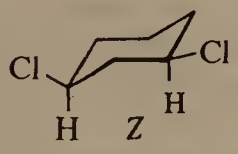
(*E*)-1,4-dichloro-3-(2-chloroethyl)-2-methyl-2-pentene



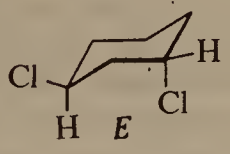
Z



E



Z

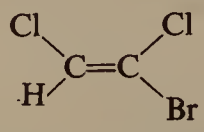


E

Scheme 1.37

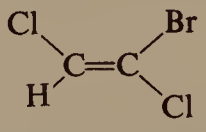
The *E-Z* nomenclature can also be used to designate cyclic compounds, when the two higher priority groups are on the same side of the ring the compound is *Z* and when these are on opposite sides of the ring it is *E*.

Significantly, the *Z* isomer is not necessarily always the one which would be called *cis* under the old system as shown in compounds 14 and 15.



(*E*)-1-Bromo-1,2-dichloroethene
cis-1-bromo-1,2-dichloroethene

14



(*Z*)-1-Bromo-1,2-dichloroethene
trans-1-bromo-1,2-dichloroethene

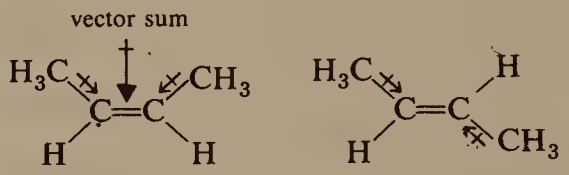
15

Scheme 1.38

(B) Determination of the Configuration of the Geometrical Isomers

(a) Physical Methods: The *trans*-isomer generally has a higher m.p. and a lower b.p. while the *cis*-isomers have higher solubilities. The solubilities of maleic and fumaric acids in water are noteworthy, maleic acid 79.0 g/100 ml at 20°C; fumaric acid 0.7g/100 ml at 20°C.

The *cis*-isomers have generally the greater dipole moment, *cis*-2-butene, for instance, has a significant dipole moment since the two methyl groups are attached to the same side of the double bond and the inductive effects are additive. *Trans*-2-butene, on the other hand, has one methyl group and one hydrogen atom on each side of the double bond and hence the bond moments cancel out each other.



$\mu = 0.33$ D

cis-2-butene

$\mu = 0$ D

trans-2-butene

Scheme 1.39

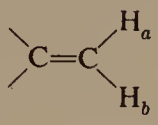
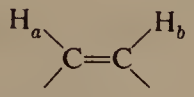
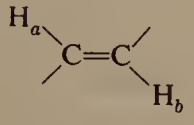
IR: Infrared spectra are used with advantage to distinguish between *cis* and *trans*-isomers of the type RCH=CHR'. Isomer having a *trans* configuration is readily identified by the appearance of a strong band near 970-960 cm^{-1}. This band is not observed in the spectrum of the *cis*-isomer.

NMR: Magnitude of the coupling constant *J* between vinyl hydrogens varies with structure. For two hydrogens which are attached to the same carbon (geminal hydrogens) the coupling constant is relatively small. In simple alkenes, J_{ab} is about 2 Hz.

The magnitude of *J* differs for *cis* and *trans* hydrogens. Although the ranges of both sets overlap, for a pair of isomeric *cis* and *trans* alkenes J_{trans} *is*

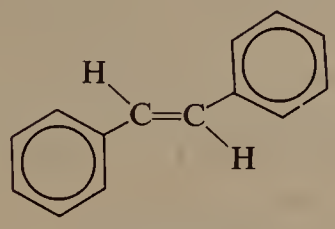
invariably greater than J_{cis}. The difference between J_{cis} and J_{trans} is an important tool for distinguishing *cis* and *trans* alkenes.

In a monosubstituted ethylene, CH_2=CHY, all three hydrogens are non-equivalent. They all split each other to yield a complex multiplet that cannot be analysed by our first-order approximation.

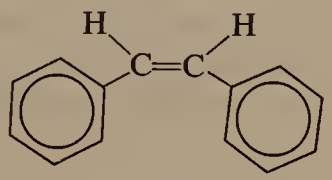
Structure		J_{ab}, Hz
	geminal	0–3 ~2 in simple alkenes
	*cis*	5–14
	*trans*	11–19

Scheme 1.40

UV: 1,2-Diphenylethylene (stilbene) allows comparison of *cis* and *trans* isomers on the basis of *U V* spectra. *trans*-stilbene has no significant steric interactions and has an extended coplanar π-system. In *cis*-stilbene (Scheme 1.41), however, the two phenyl groups are on the same side of the double bond and sterically interfere with each other. Both rings cannot be coplanar with the double bond, and π-conjugation is thus not as effective as it is in the case of *trans* isomer. The result is a small change in λ_{max} but a large decrease in the extinction coefficient.



trans-stilbene
λ_{max} = 295 nm
ϵ = 27,000

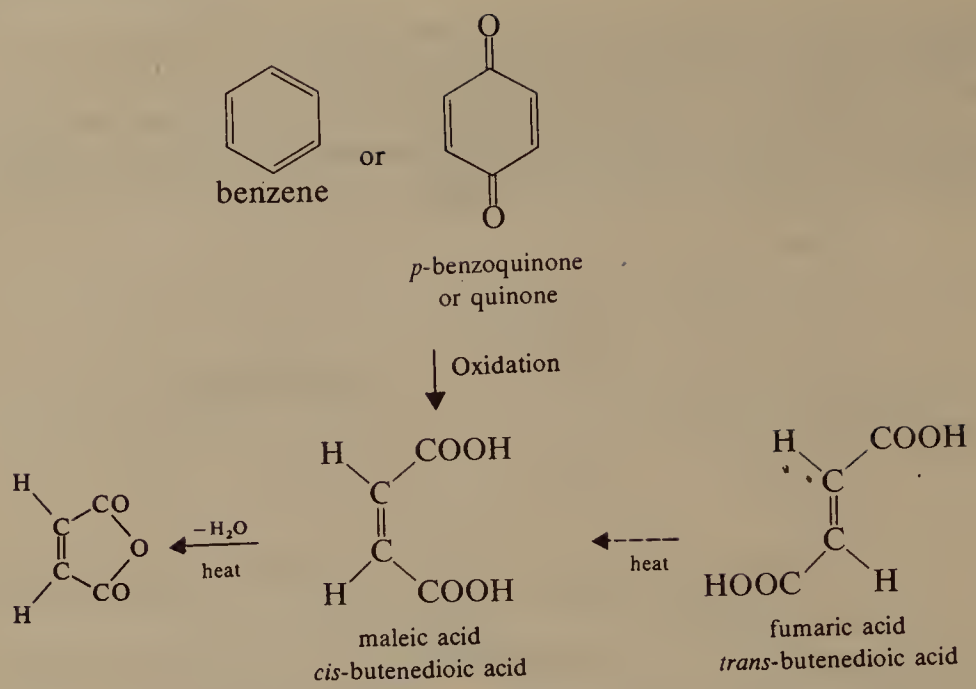


cis-stilbene
λ_{max} = 280 nm
ϵ = 13,500

Scheme 1.41

(*b*) Chemical Methods: (i) Method of preparation from cyclic compounds: Benzene or quinone on oxidation affords an unsaturated dicarboxylic acid m.p. 130°C. In both benzene and quinone the configuration of the double bond is *cis*, therefore, maleic acid, (m.p. 130°C) must be *cis* and the other isomer fumaric acid (m.p. 302°C) must be *trans*.

(ii) Method of formation of cyclic compounds: The geometric isomers can often be distinguished via reactions that lead to the formation of rings. A *cis*-isomer is expected to undergo ring closure much more readily than the *trans*-isomer as it is almost impossible to have a double bond in a ring



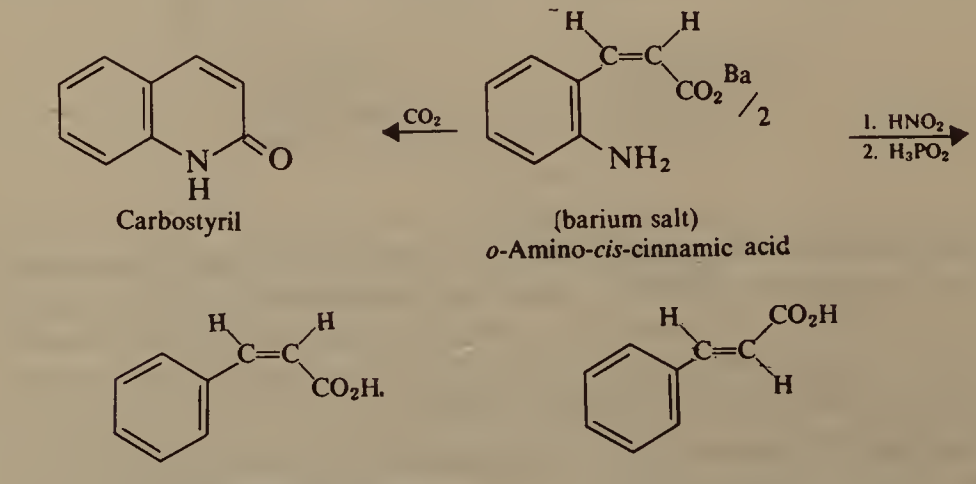
Scheme 1.42

ower than a seven membered.

Maleic acid readily loses water when heated to about 150°C to afford an anhydride, whereas fumaric acid does not give the anhydride at this temperature, however, it must be heated to 300°C to get the same anhydride. Hydrolysis of the anhydride yields only maleic acid.

Thus, maleic acid is the *cis*-isomer and fumaric acid is the *trans*-isomer. The latter forms the anhydride via the formation of maleic acid, since high temperature ruptures π bond and rotation of the carboxyl groups towards each other occurs followed by reformation of the π bond and loss of water.

The Ba-salt of an isomer of *ortho*-aminocinnamic acid on treatment with CO_2 at room temperature gives carbostyril (Scheme 1.43). This shows that the



Scheme 1.43

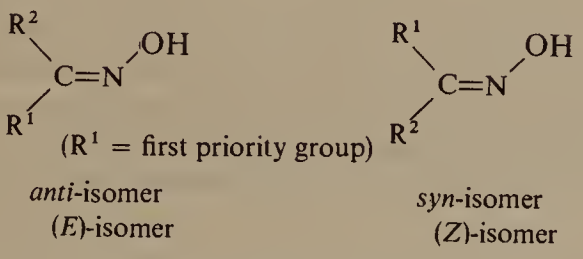
carboxyl group and the substituted phenyl group must be *cis* in this isomer of *ortho*-aminocinnamic acid. The Ba-salt-of the other isomer of *ortho*-aminocinnamic acid does not give carbostyril under the same condition and, therefore, it must have the *trans*-configuration.

Deamination of the isomer which is readily cyclized (*cis* configuration) gives the cinnamic acid, m.p. 68°C, which should, therefore, be the *cis* isomer. It differs from the common cinnamic acid, m.p. 133°C, which is obtained from the other isomer of *o*-aminocinnamic acid to which *trans* configuration is assigned.

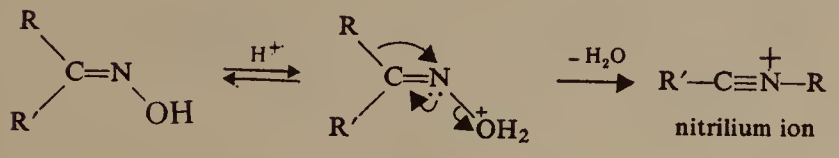
(C) Geometrical Isomerism of Oximes (Beckmann Rearrangement)

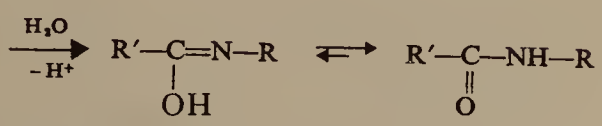
1. Geometrical isomerism arises in oximes as well, in which the double bond between the carbon and nitrogen atoms restricts rotation. The isomers are commonly known as *anti* and *syn* in this case though the *E*- and *Z*-notation is more convenient. In the *syn* oxime, the hydroxyl group on nitrogen and hydrogen or the first named of the two groups on the carbon atom are on the same side, whereas in the *anti* isomer these are on opposite sides.

2. Oximes undergo a rearrangement under acidic conditions to yield substituted amides (eq. 1, Scheme 1.45)



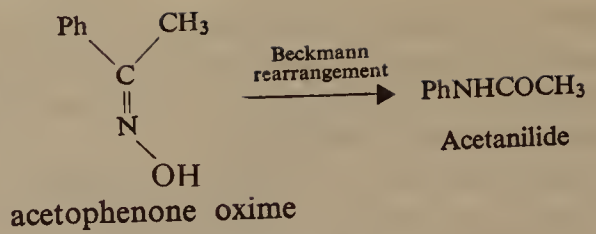
Scheme 1.44





Scheme 1.45

3. The Beckmann rearrangement is stereospecific: the group *anti* to the leaving group migrates, Thus, acetophenone oxime, with the stereochemistry shown in Scheme 1.46 gives only acetanilide.

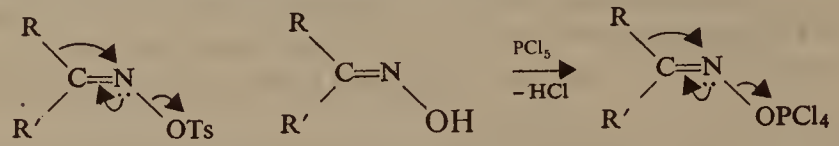


Scheme 1.46.

4. If the carbon atom which migrates is chiral, it retains its configuration during the reaction to show that this rearrangement is intramolecular.

5. The rearrangement is also induced by reagents other than proton acids, toluene-*p*-sulphonyl chloride forms the oxime tosylate which eliminates the stable tosylate anion.

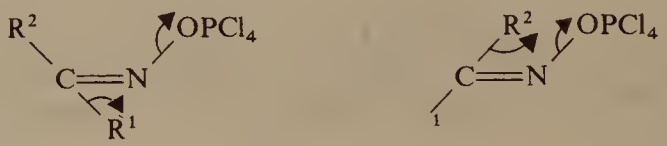
6. Phosphorus pentachloride, normally used in ether, induces rearrangement by providing a phosphate as leaving group (Scheme 1.47).



Scheme 1.47

7. Since there is a geometric relation between the migrating and the leaving groups, it follows that migration must proceed simultaneously with departure of the leaving group, and that migration of the *anti*-group must proceed more readily than migration of the *syn*-group.

8. *Anti*-migration keeps the migrating and departing groups well apart so that repulsions are minimized. On the contrary, the approach to the transition state for *syn*-migration forces the migrating and departing groups into close contact, causing repulsion and raising the energy of the transition state (Scheme 1.48).

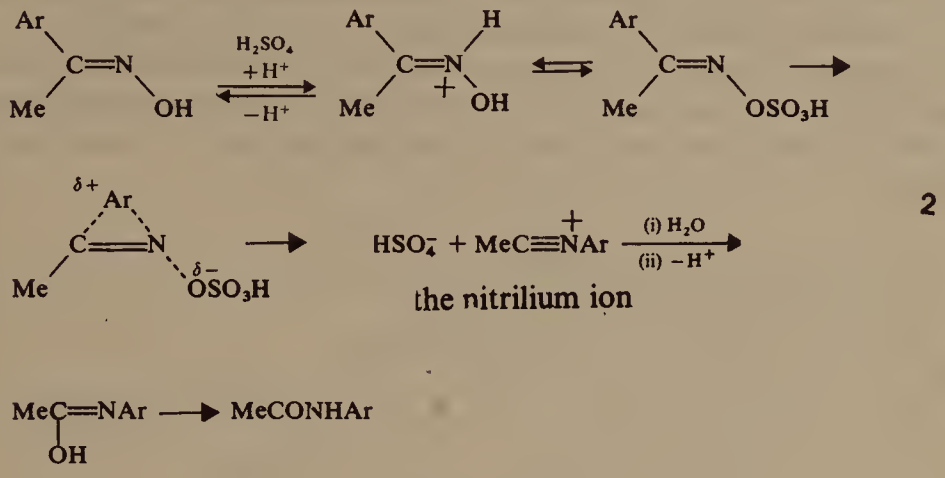


Scheme 1.48

Reaction therefore proceeds through the lower-energy transition state, so that only *anti*-migration is observed. The requirement that the migrating and departing groups in the starting material are *anti* is known as stereoelectronic requirement.

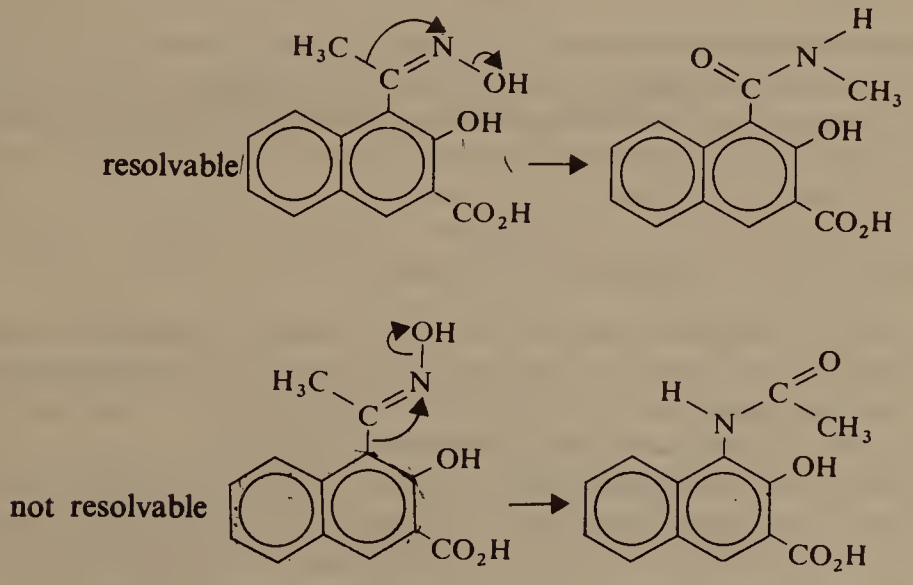
9. Beckmann rearrangement of *ortho*-substituted acetophenone oximes (eq.

2. Scheme 1.49) in the present of sulphuric acid led to the detection of the nitrilium ion *via IR* spectra. The detection of oxime *O*-sulphonic acid has been achieved by *NMR* spectroscopy.



Scheme 1.49

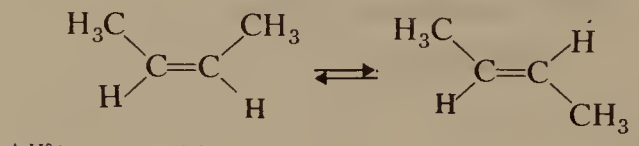
10. An interesting case of configurational assignment relates to the oximes of 1-acetyl-2-hydroxynaphthalene-3-carboxylic acids. The *anti*-methyl oxime is resolvable as the hydroxyl group of the oxime interferes with that of the ring hydroxyl group and produces restricted rotation. The *syn*-methyl oxime is, however, not resolvable since rotation about the bond attached to the C_1 atom of the ring is not sufficiently restricted. The Beckmann rearrangement of these oximes proceeds in *anti* fashion, as expected (Scheme 1.50).



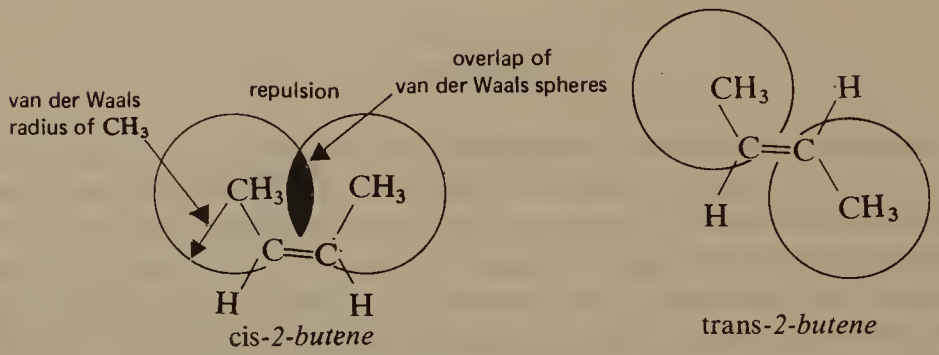
Scheme 1.50

(D) Interconversion (Stereomutation) of Geometrical Isomers

Heats of formation have been evaluated for several alkenes. These values show that *trans* alkenes are generally more stable than the isomeric *cis* alkenes by about 1 kcal mole^{-1} (a more negative heat of formation ΔH_f corresponds to a more stable compound). The distance between the adjacent methyl groups in *cis*-2-butene is around 3 Å. As the sum of the van der Waals radii for two methyl groups is 4 Å, the hydrogens in these two groups are sufficiently close so that there is a net repulsion which is not present in the *trans* compound. This effect of repulsion for sterically congested systems is called steric hindrance.



ΔH_f°: −1.9 −3.0 $\Delta H^\circ = -1.1$ kcal mole^{-1}



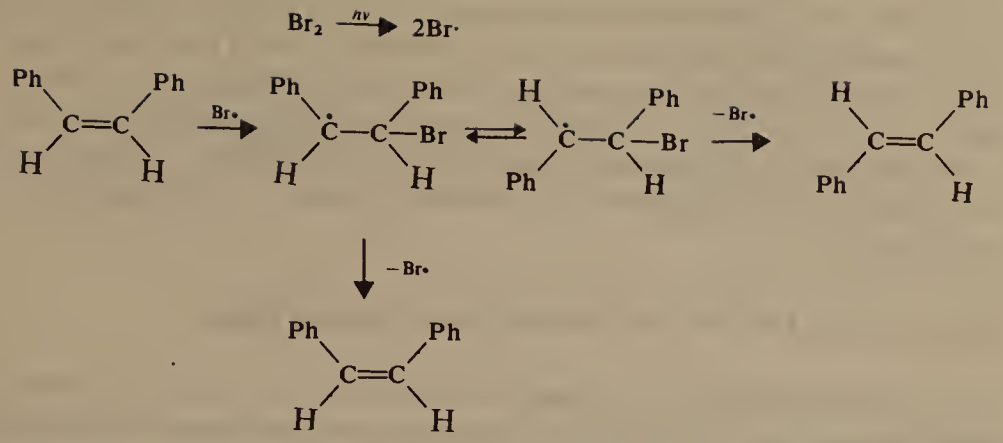
Scheme 1.51

The *cis*-isomer being the more labile form, is readily converted into the *trans* -form under suitable physical or chemical conditions. The usual chemical reagents used for stereomutation are halogens. Heating above the melting point also usually converts the *cis*-isomer into the *trans*, but in general, the result is a mixture of the two isomers.

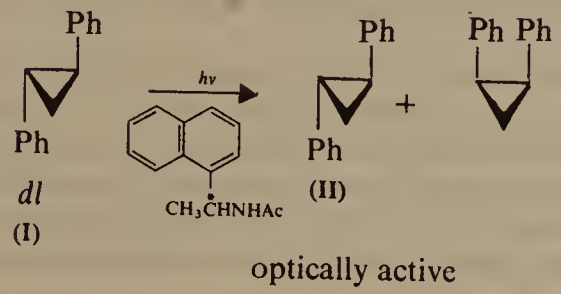
Photochemical *cis-trans* isomerization is effected in the presence of bromine or iodine by a plausible mechanism (Scheme 1.52).

It is possible to irradiate by the use of a filter system, at a wavelength at which only one isomer will absorb. This allows the complete conversion to the other isomer, and this technique is known as optical pumping. The less stable *cis* isomers are often prepared by the use of this method.

Asymmetric induction (chiral synthesis, sec. 1.20B) is also effected by the use of optically active sensitizers[6]. Irradiation of *dl-trans*-1,2-diphenyl cyclopropane (**I**) Scheme 1.53 in the presence of an optically active sensitizer gave a photostationary state in which the *trans*-isomer (**II**) had acquired optical activity

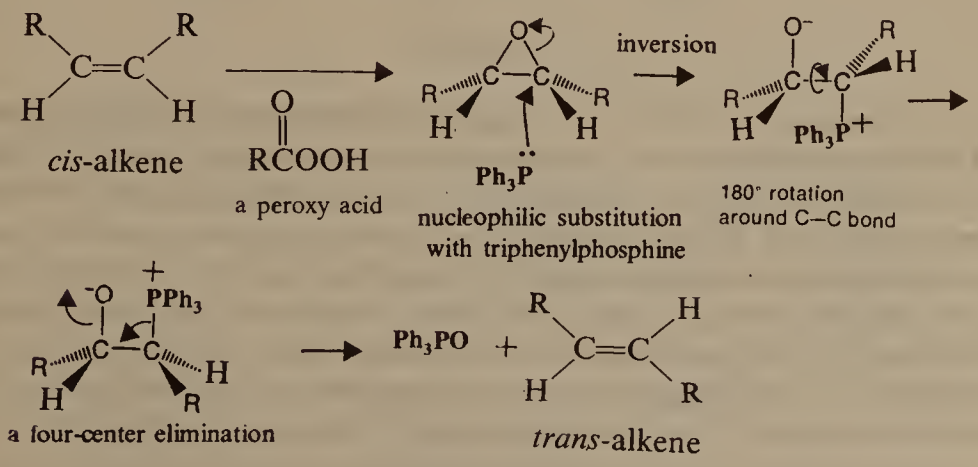


Scheme 1.52



Scheme 1.53

Interconversion of double bond diastereomers can also be brought *via* epoxidation deoxygenation sequence. The nucleophilic attack by the phosphorus reagents *e.g.*, triphenylphosphine at the oxirane carbon leads to inversion of configuration and yields a charge-separated intermediate (a betaine). This undergoes elimination *via* a four center cyclic transition state which requires a 180° rotation around the C-C bond to establish the appropriate geometry. The stereochemical outcome of these reactions is to



Scheme 1.54

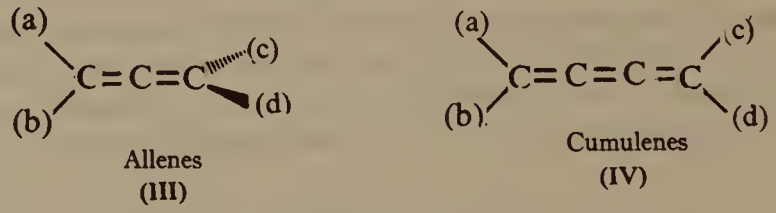
put the *R* groups attached to the oxirane carbons in a different stereochemical relationship in the oxirane and alkene (Scheme 1.54). Therefore, if these are *cis* in the oxirane they become *trans* in the alkene. Since the epoxidation of alkenes proceeds in a *syn* fashion, this provides a method to invert the configuration of the groups attached to a C = C bond. Since inversion accompanies the substitution the overall elimination on the epoxide is *anti* (sec. 5.2, C iv).

(E) Torsional Chirality in Carbon-Carbon Double Bonds

In a compound with one carbon-carbon double bond; the four substituents lie in the same plane, and the C = C axis then constitutes an axis of diastereoisomerism. However, the allenes (Scheme 1.55) are C-C double bond systems in which the four substituents lie on two perpendicular planes so that an axis of chirality can be visualized depending on the nature of four substituents a,b,c and d.

Cumulenes have a chain of two or more cumulated carbon-carbon double bonds, and have four substituents *a,b,c* and *d*. The condition for stereoisomerism is $a \neq b$ and $c \neq d$. Moreover, if the four substituents lie in the same plane, the molecule possesses an axis of diastereoisomerism; which is detected in cumulenes with an odd number of double bonds IV. However, if the number of double bonds is even, the four substituents occupy two different planes and a chiral axis exists.

Therefore, if the condition that $a \neq b$ and $c \neq d$ is fulfilled, the axis of stereoisomerism in cumulenes will be an axis of diastereoisomerism or of enantiomerism, depending on the coplanarity or noncoplanarity of a and b versus c and d.



Scheme 1.55

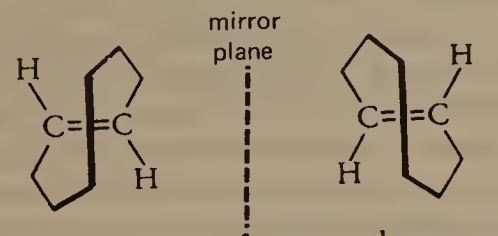
The four substituents *a, b, c* and d assume noncoplanarity in twisted olefins.[7a] Two diastereoisomers *i.e.*, the *cis*- and the *trans*-isomers (V) and (VI) (Scheme 1.56) respectively of 4,4′-bi-1,1′, 2,2′, 3,3′—hexahydrophenanthrylidene have been synthesized. These diastereoisomers are sterically overcrowded[7] leading to distorsion and nonplanarity about the olefinic bond and therefore, the axis visulized along this bond represents an axis of chirality. In keeping with this, resolution of the two diastereoisomers into their enantiomers has been achieved. The configuration of the enantiomers is gainfully specified in terms of helicity, (V) a simple helix, and (VI) being a double helix.

Other olefins are known which would remain chiral even if the distorted π

(V) (VI)

Scheme 1.56

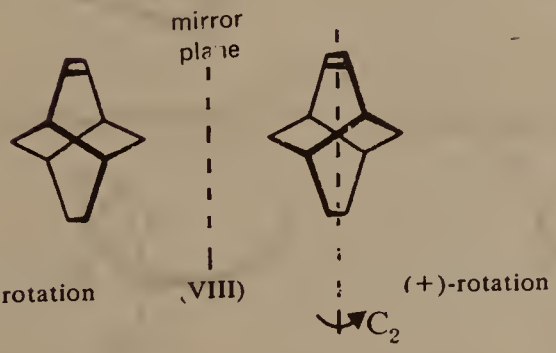
bond is forced into planarity. Thus, chirality resulting from torsion is not the only element of chirality in the molecule. *Trans* cyclooctene (VII) scheme 1.57 has been discussed (sec 1.20) in terms of its plane of chirality, however, in this olefin a substantial π bond torsion exists.[8] This additional element of chirality, however, cannot vary independently from the configuration about

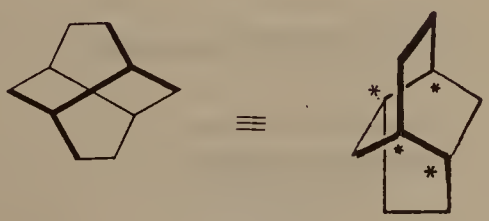


two enantiomers of *trans*-cyclooctene

(VII)

Scheme 1.57





Twistane

Scheme 1.58

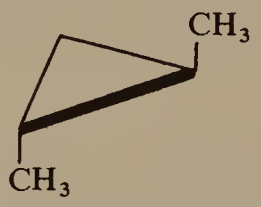
the plane of chirality: (*R*)—(—)-*trans*-cyclooctene has (*P*)-helicity (sec 1.22) along the olefinic bond, but cannot have (*M*)-helicity. Two elements of chirality are associated with *trans*-cyclooctene, however, it exists only as two enantiomers, and not as four stereoisomers.

In the case of twisted olefin twistene (VIII, Scheme 1.58), both the enantiomers have been synthesized[9,10] and their absolute configuration determined, the (+)— enantiomer has (*R*)— configuration on the four chiral carbons and (*P*)-helicity when the molecule is viewed, both along the C_2 axis, and along the olefinic and—CH_2—CH_2—bonds.

Twistane has an interesting bridged ring structure which in fact represents a cyclohexane in a twist-boat form having two additional dimethylene bridges. Twistane has been prepared in optically active form and has four chiral centres, however, chirality of the molecule as a whole is more obvious and spectacular.

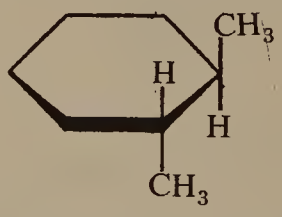
(F) Geometric Isomerism in Alicyclic Compounds

Geometric isomerism is due to hindered rotation about a bond. Such hindrance, however, is not confined to double bonds only, cyclic compounds such as the derivatives of cyclopropane, cyclobutane, cyclopentane and cyclohexane also exhibit *cis-trans* isomerism as the basic condition for such isomerism is the presence of sufficient hindrance to rotation about a linkage between atoms, one may presume that the carbon atoms of a cyclic structure form a plane (this assumption is, however, not correct). The plane of the ring is considered horizontal with the edge of the ring shown as thicklined

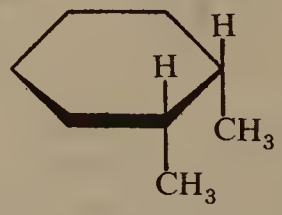


trans-1,2-Dimethylcyclopropane

cis-1,2-Dimethylcyclopropane



trans-1,2-Dimethylcyclohexane



cis-1,2-Dimethylcyclohexane

SUBSTITUENTS ON OPPOSITE SIDES OF RING (*trans*)

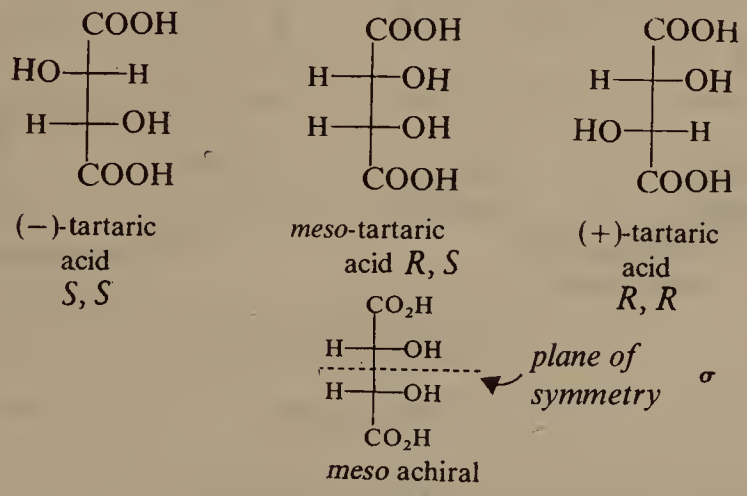
SUBSTITUENTS ON SAME SIDE OF RING (*cis*)

Scheme 1.59

projects toward a viewer. In a cyclic compound, each carbon atom is joined to its neighbouring ring carbon atoms and also to two other atoms or groups which are shown by vertical lines. When an atom or a group is placed at the top of a vertical line, it is above the plane of the ring, and when it is attached to the bottom of the vertical line, it was below the plane of the ring. Often broken line indicates that a group is below the plane of the ring, while a solid line represents it to be above. As one has seen in the case of *cis*- and *trans*-alkenes, when the two groups are on opposite sides of the ring they are *trans* and when they are on the same side they are *cis*. Several methods to establish stereochemistry in such systems, have been presented in the following chapters.

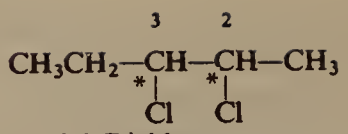
1.11 MESO COMPOUNDS

When the substituents on the two chiral carbon atoms in a molecule are similar, a special situation arises. If the two chiral centres have opposite configurations, *i.e.*, *R* and *S* then the molecule becomes achiral. Among tartaric acids, the optically inactive *meso*-form is achiral, even though it has two chiral carbon atoms. This is due to the fact that it has a plane of symmetry. In the optically active forms both asymmetric atoms have the same configuration, *i.e.*, *S,S* and *R,R* (Scheme 1.60).



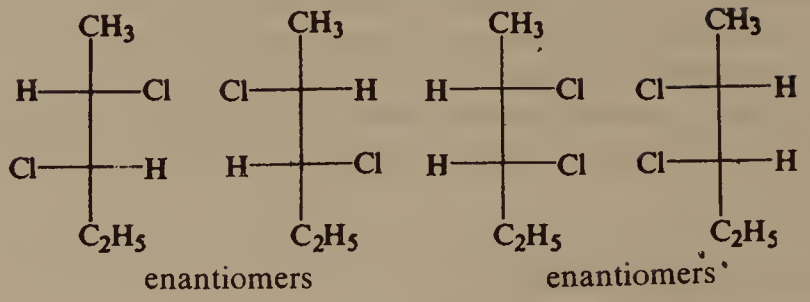
Scheme 1.60

To emphasise this point one may consider two compounds 2,3-dichloropentane **16** (Scheme 1.61) and 2,3-dichlorobutane. **17** (Scheme 1.62) both having two chiral carbons. The four stereoisomers of **16** can be written as in the case of four carbon sugars erythrose and threose (Scheme 1.32). However, in the case of **17**, the groups on the two chiral carbons being same only three stereoisomers exist, one with a plane of symmetry being the *meso*-compound. Its mirror image **18** (Scheme 1.62) when turned end-for-end (*i.e.*, a 180° rotation, Scheme 1.29) becomes superimposable on it.



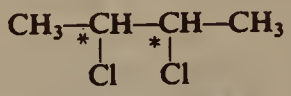
2,3-Dichloropentane

16



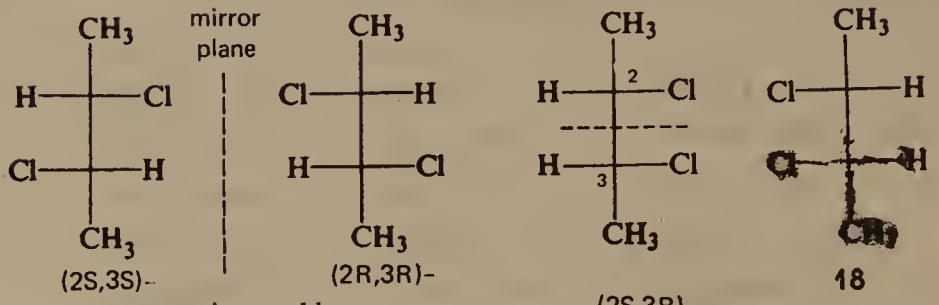
enantiomers enantiomers

Scheme 1.61



2,3-Dichlorobutane

17



(2S,3S)- (2R,3R)- (2S,3R)- 18

Not superimposable *Superimposable*

Enantiomers *Meso-* compound

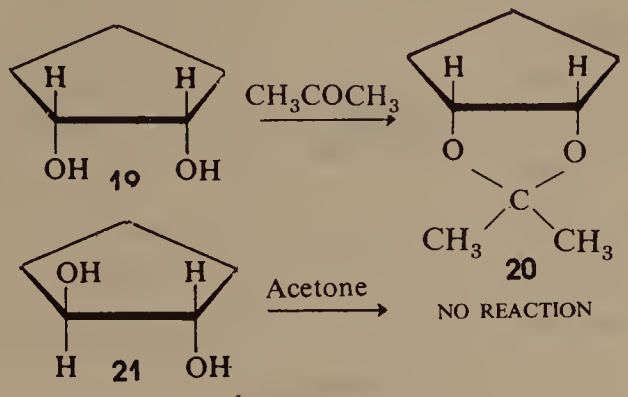
the 2,3-*dichlorobutane isomers*

Scheme 1.62

1.12 PROPERTIES OF DIASTEREOISOMERS

Optical isomers, have similar physical properties, while diastereoisomers display different physical and chemical behaviour. In a pair of optical isomers the individual components are mirror-images, all the interatomic distances in both molecules remain the same. Physical and chemical properties depend on the atoms in a molecule and their interatomic distances. A pair of diastereoisomers no doubt contain identical atoms, and moreover each atom is joined to the same atoms in each molecule, however, there is a difference in arrangement of the atoms in space. Consequently, diastereoisomers differ in energy content, and they, therefore, show different chemical

and physical properties. Among the cyclopentane 1,2-diols; the *cis*-isomer **19** (Scheme 1.63) readily forms a ketal **20** with acetone, while the *trans*-isomer **21** does not react.



Scheme 1.63

The energy difference between a pair of diastereoisomers provides the basis of a method for separating pairs of optical isomers.

1.13 RESOLUTION OF RACEMIC MIXTURES

The term resolution is used to describe the separation of a racemic mixture into its enantiomeric constituents. This can be achieved by the following methods.

(A) Mechanical Separation

Some enantiomeric compounds (*e.g.*, *dl*-sodium ammonium tartrate) form left-handed and right-handed crystals which permit their separation manually under a magnifying glass.

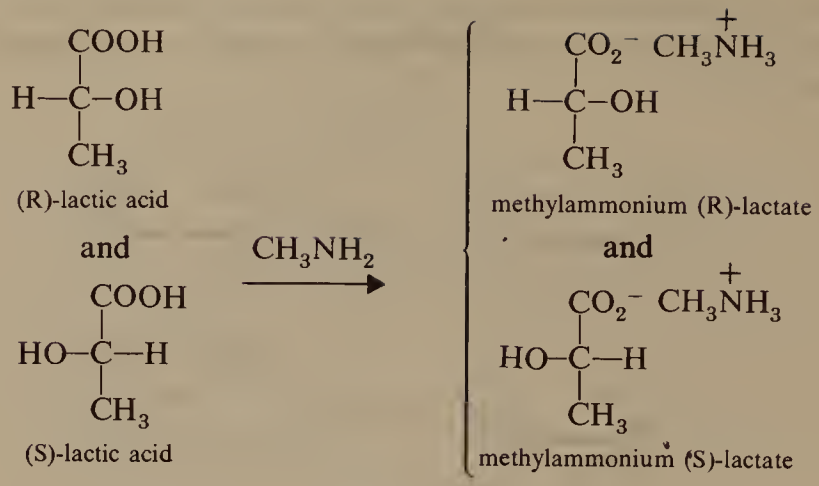
(B) Bacterial Action (Asymmetric Destruction)

Certain bacteria tend to destroy selectively only one of the enantiomeric forms and are useful in the isolation of the other. For example, *Penicillium glaucum* can be used to remove *d*-ammonium tartrate from a racemic mixture to leave back only the *l*-ammonium tartrate after a suitable time interval.

(C) Chemical Methods (*via.*, Diastereoisomers)

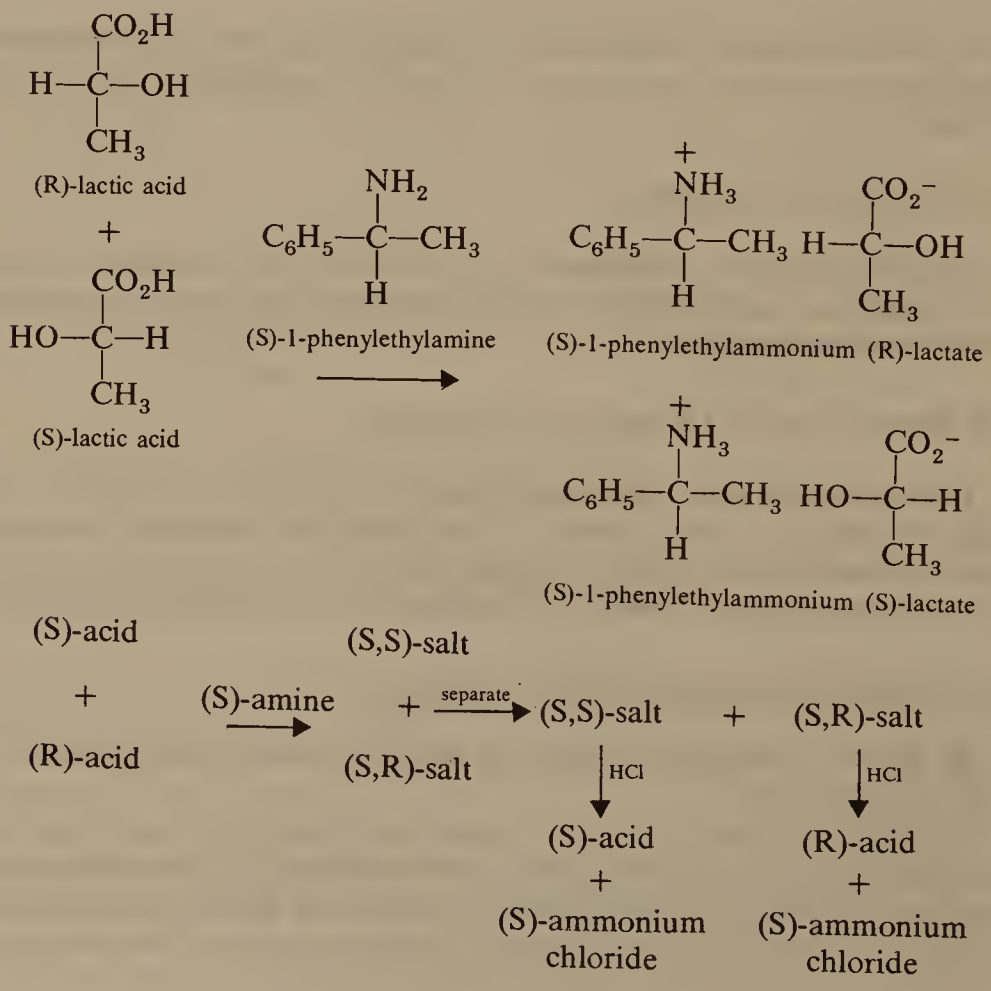
By far the most common method to resolve a racemic mixture involves the following procedure:

Consider a racemic mixture of lactic acid. The two enantiomers have identical physical properties and cannot be separated by crystallization or distillation techniques. The mixture reacts with methylamine to yield a racemic mixture of methylammonium lactates (Scheme 1.64), which also



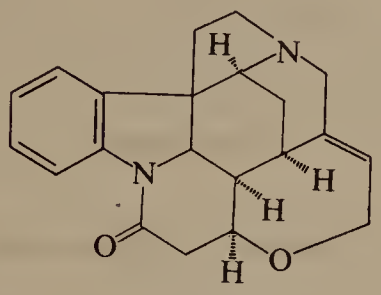
Scheme 1.64

When, however, one enantiomer of a chiral amine is used to form the salt, the two salts are diastereomeric rather than enantiomeric. These will now have different physical properties. For example, the (*S, R*) salt may be more soluble in some solvents than the (*S, S*) salt. Because of this difference, the two salts



can be separated by fractional crystallization (Scheme 1.65). Each of the diasteromeric salts on treatment with acid liberates the free carboxylic acid. Acidification of the (*S, R*) salt yields enantiomerically pure (*R*)-lactic acid, whereas similar treatment of the (*S, S*) salt gives pure (*S*)- lactic acid. Of course, in order to use this technique for resolution, suitable optically active amines must be available.

A number of such compounds are readily available as naturally occuring alkaloids in the form of enantiomers and strychnine (Scheme 1.66) is a typical example.



Strychnine

Scheme 1.66

Thus the following are the outlines of the chemical methods :

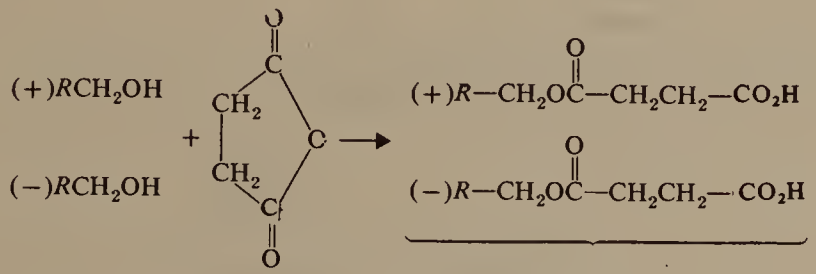
(1) Treat the racemic mixture with an optically active substance to give two diastereomeric products.

(2) Separate the two diastereomers utilising the differences in physical properties (*e.g.*, melting point, solubility, etc.)

(3) Regenerate, through suitable reactions, individual enantiomer from each of the separated diastereomer.

Racemic acids may be resolved by treatment with an optically active base and racemic bases may be resolved by an optically active acid (*d*-tartaric acid)

Racemic compounds that are neither acid nor bases are often resolved by first attaching an acidic "handle". A racemic alcohol, for example, can react with a cyclic anhydride to yeild a product that is both an ester and an acid (Scheme 1.67).

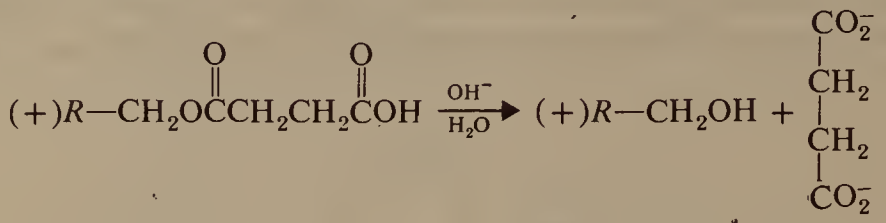


Racemic alcohol | Succinic anhydride | Racemic acid

Scheme 1.67

The racemic acid thus produced is separated *via* diastereomeric salts and converted back to the enantiomeric acids. The acidic "handle" is then removed by hydrolysis of the ester group and the separate alcohol enantiomers are obtained as shown for the (+)-ester (Scheme 1.68).

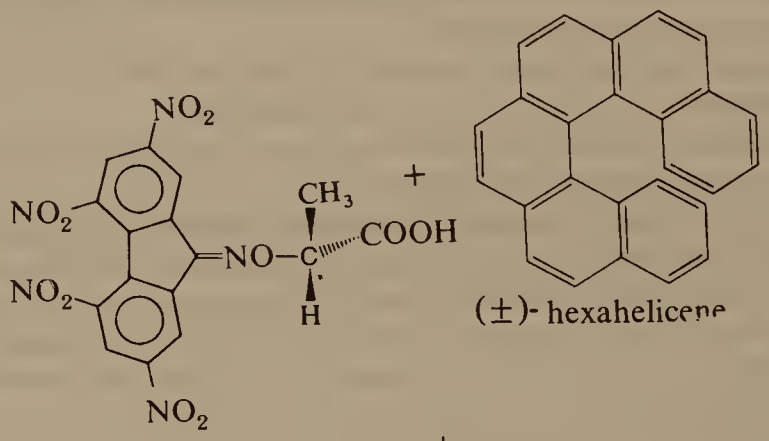
The compounds which cannot be converted readily into acidic or basic derivatives are usually obtained in optically active forms by synthesis from an



Scheme 1.68

optically active precursor. There are, some special methods of resolution *via* diastereoisomers.

The diastereoisomeric molecular complexes formed with an optically active reagent are employed for resolution. The optically active fluorenone derivative **22** (Scheme 1.69) is used, for example, to resolve derivatives of aromatic compounds *e.g.*, hexahelicene[11] which complexes with it. The



Diastereomeric molecular complexes

Separation by fractional crystallization

(+)-Complex and (−)-complex

Decomposition

(+)-Hexihelicene and (−)-Hexihelicene

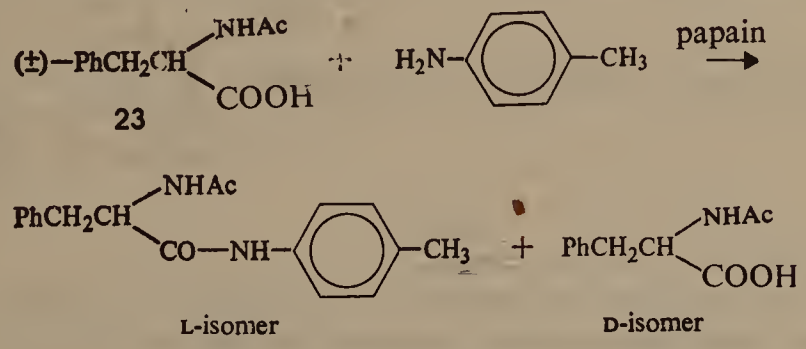
Scheme 1.69

diastereoisomers are then reconverted easily into the reactants by heating or through chromatography. A related method employs the inclusion complexes (clathrates) formed by certain dissymmetric compounds.

In several cases enantiomers are separated by chromatography on an optically active support; equilibration occurs with diastereoisomeric adsorbates which have different stabilities, so that the enantiomer forming the less stable adsorbate is eluted first.

(D). Biochemical Methods

The reaction of racemic acetylphenylalanine with *p*-toluidine catalyzed by the enzyme papain gives the *p*-toluidide of acetyl-*L*-phenylalanine (Scheme 1.70) and leaves behind unchanged *D*-phenylalanine in a technique called asymmetric kinetic resolution.



Scheme 1.70

(E) Other Methods

Another method is to seed a saturated solution of the enantiomers with a crystal of one form which induces the crystallization of the same enantiomer. If a crystal of one form is not available, it is sometimes possible to induce selective crystallization by seeding with a crystal of an optically active form of another molecule. Often one enantiomer may crystallize spontaneously from a supersaturated solution.

Finally, resolution may be achieved by inducing a photochemical reaction with circularly polarized light: irradiation of racemic $CH_3CH(N_3)CONMe_2$ preferentially destroys one enantiomer, depending on the direction of polarization of the light, and leaves the reactant enriched in the other enantiomer.

1.14 MEASUREMENT OF OPTICAL ACTIVITY

Light is a wave phenomenon in which vibrations take place at right angles to the direction in which the light travels. Infinite number of planes pass through the line of propagation and in ordinary light vibration takes place in all these planes. Plane polarized light is light in which vibrations take

place in only one plane, and this is realised by passing ordinary light through a polarizer which forms an important component of a polarimeter (Fig. 1.3).

An optically active compound is one which rotates the plane of polarized light.

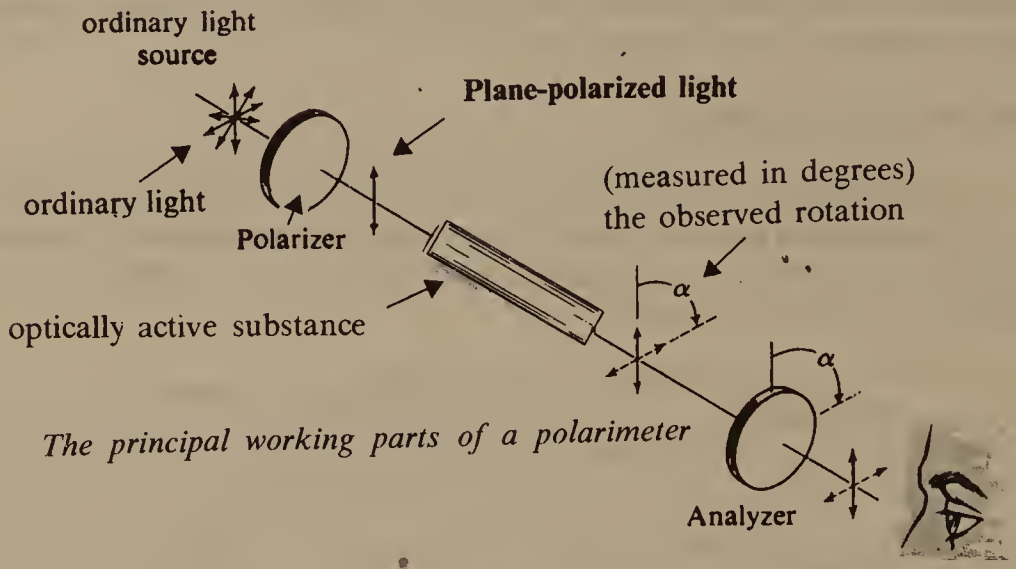


Fig. 1.3

An optically active substance which rotates the plane-polarized light to the right (clock-wise) is said to be dextrorotatory often abbreviated by the letter *d* , and its optical rotation is given a + sign. A substance is said to be levorotatory (often abbreviated by the letter *l*) if it rotates plane-polarized light to the left (counterclockwise), and its optical rotation is given a — sign.

Opitcal rotation is a function of concentration, sample thickness, temperature, wavelength of polarized light, etc. It is usually recorded in the literature in terms of specific rotation $[\alpha]_{\lambda}^{t}$, or molecular rotation $[M]$

$$[\alpha]_{\lambda}^{t} = \frac{\alpha \times 100}{l \times c}$$

$$= \frac{\alpha}{l \times d}$$

$$[M]_{\lambda}^{t} = \frac{[\alpha]_{\lambda}^{t} \text{mol.wt}}{100}$$

where t = temperature measurement in °C

λ = wavelength of polarized light (usually sodium D line, 5893 Å)

α = observed angle of rotation in degrees

l = sample thickness in decimeters

c = concentration of solution in g/100 ml

d = density of pure liquid in g/ml

1.15 THE NUMBER OF OPTICAL ISOMERS

The number of optical isomers possible for a given compound in which the configurations around the chiral carbons are not clearly defined is calculated from the number of chiral carbons, *n*, present in the molecule (see Table 1.2).

TABLE 1.2 Calculation of number of optical isomers

	The compound if contains :	Optically active forms	Optically inactive forms
1.	n Different chiral carbons, and the molecule cannot be divided into two equal and similar halves	2^n	0
2.	An even number n of chiral carbons, but the molecule can be divided into two equal and similar halves	$2^{(n-1)}$	$2^{(n-2)/2}$
3.	An odd number n of chiral carbons, but the molecule can be divided into two equal and similar halves *via;* the central carbon	$2^{(n-1)}$—$2^{(n-1)/2}$	$2^{(n-1)/2}$

If chiral carbons are present in a molecule in addition to a double bond or a ring residue, both optical and geometric isomerism will be possible. In such cases, the total number of stereoisomers will be equal to the number of optical isomers, if the chiral carbons coincide with the terminals responsible for geometric isomerism (example 4). The total number of stereoisomers will be double the number of optical isomers, if the chiral carbon is away from the terminals responsible for geometric isomerism (example 2).

Example 1

The compound **24** has two chiral carbons (n=2) and the molecule cannot be divided into two equal and similar halves.

Therefore, number of optical isomers = 2^2 = 4(2 *dl* pairs)

Number of geometric isomers = 0

(Since compound does not contain a ring or a double bond)

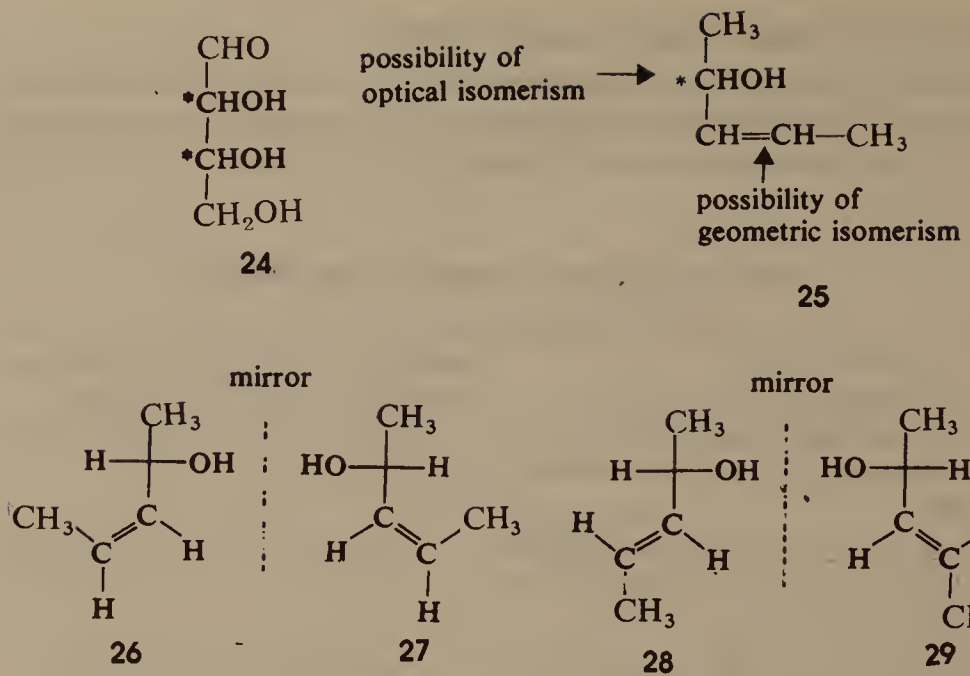
Therefore, total number of stereoisomers = 4 + 0 = 4

The four isomers are of erythrose and threose (sec. 1.9).

Example 2

The compound **25** has one chiral carbon (n = 1) and a double bond, hence both optical isomerism and geometric isomerism are possible. Since the chiral carbon does not coincide with one of the terminals of the double bond, there should be a total of $2(2^1)$ = 4 stereoisomers **26** to **29** (Scheme 1.71).

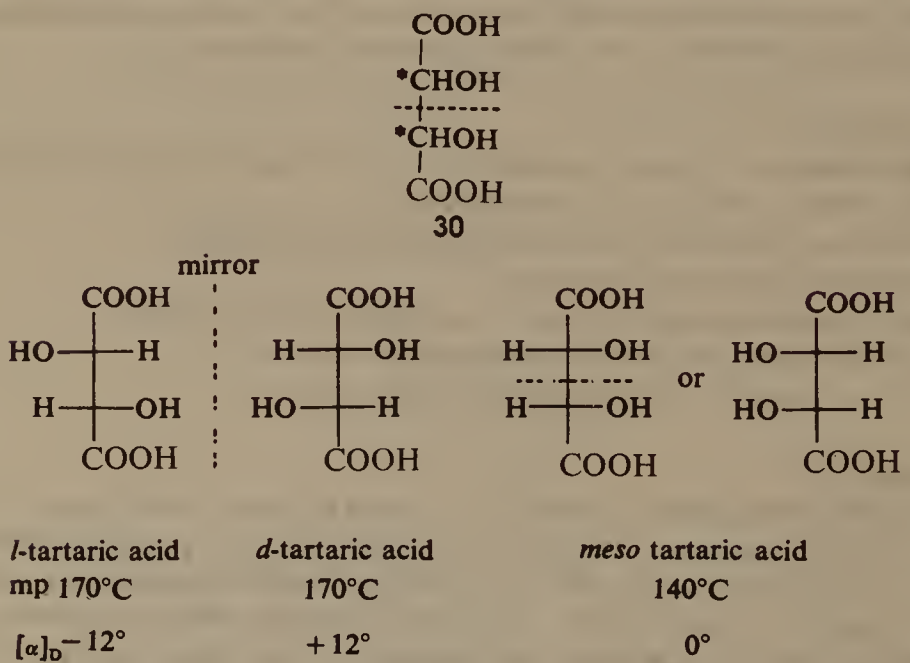
The pairs **26, 27** and **28, 29** are enantiomers; the pairs **26, 28; 26, 29; 27, 28** and **27, 29** represent diastereoisomers.



Scheme 1.71

Example 3

The compound **30** (Scheme 1.72) has two chiral carbons (n = 2), however, the compound can be divided into two equal halves, thus:



l-tartaric acid	*d*-tartaric acid	*meso* tartaric acid
mp 170°C	170°C	140°C
$[\alpha]_D$ −12°	+12°	0°

Scheme 1.72

The number of optically active forms = $2^{(2-1)} = 2$ (a *dl* pair)
The number of optically inactive forms = $2^{(2-2)/2} = 2^{\circ} = 1$ (*meso* form)
The number of geometric isomers = 0
(as there is no double bond or ring residue)
Total number of stereoisomers = 2 + 1 + 0 = 3
These represent three tartaric acids.

Physical properties of the tartaric acid stereoisomers are compiled. The properties of the *d* and *l* isomers are identical (other than the direction of optical rotation) and are different from those of the *meso* form. We also find that the melting point of racemic acid 206 °C is different from that of either of the *d* or *l* isomers of which it is composed. Racemic mixtures usually have melting points higher than the melting point of either of the pure enantiomers.

Intermolecular attractions between *d* and *l* enantiomers within the crystal lattice are generally stronger than those between either of the pure enantiomers.

Example 4

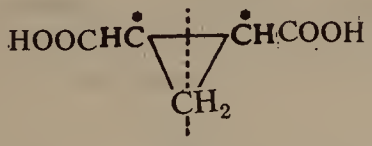
The compound 31 (Scheme 1.73) has two chiral carbons ($n = 2$) and it can be divided into two equal halves. The restricted rotation associated with the ring structure also makes geometrical isomerism a possibility.

∴ Number of optically active forms = $2^{(2-1)} = 2$ (a *dl* pair)

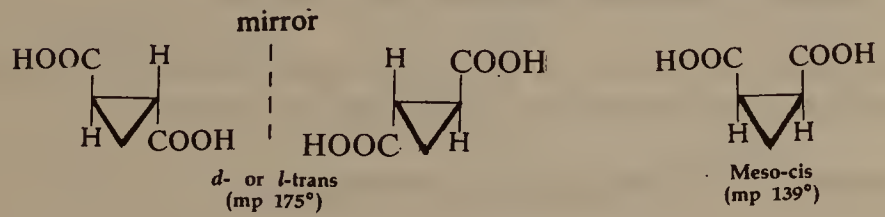
Number of optically inactive forms = $2^{(2-2)/2} = 2^{\circ} = 1$ (*meso* form)

∴ Total number of stereoisomers = 2 + 1 = 3.

Since the two chiral carbons coincide with the two ring carbons responsible for geometric isomerism, the total number of stereoisomers is the same as the number of optical isomers. The *cis-trans* relationship of the two carbonyls at the two terminals responsible for geometric isomerism is defined in each of the optical isomers.



31



cyclopropane-1,2-dicarboxylic acid

Scheme 1.73

Example 5

The compound 32 (Scheme 1.74) contains three chiral carbons (n=3), but the molecule can be divided into two equal halves.

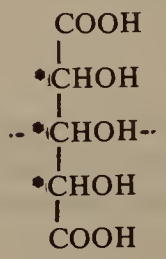
Therefore, number of optically active forms = $2^{(3-1)} - 2^{(3-1)/2} = 2^2 - 2^1$
$= 4 - 2 = 2$ (a *dl* pair)

Therefore, number of optically inactive forms = $2^{(3-1)/2} = 2^1 = 2$ (*meso* forms).

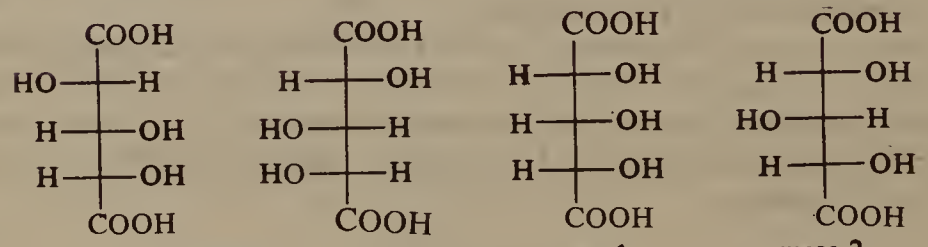
∵ Number of geometric isomers = 0

∴ Total number of stereoisomers = 2 + 2 + 0 = 4

Cyclic systems with two or more rings joined in the fused or the bridged fashion may have some constraints which may limit the stereochemical and structural possibilities in a given system. Thus. camphor has two chiral centres yet only two optical isomers are known. For a detailed discussion see sec. 4.15 A.



32



a *dl* pair *meso* 1 *meso* 2

Scheme 1.74

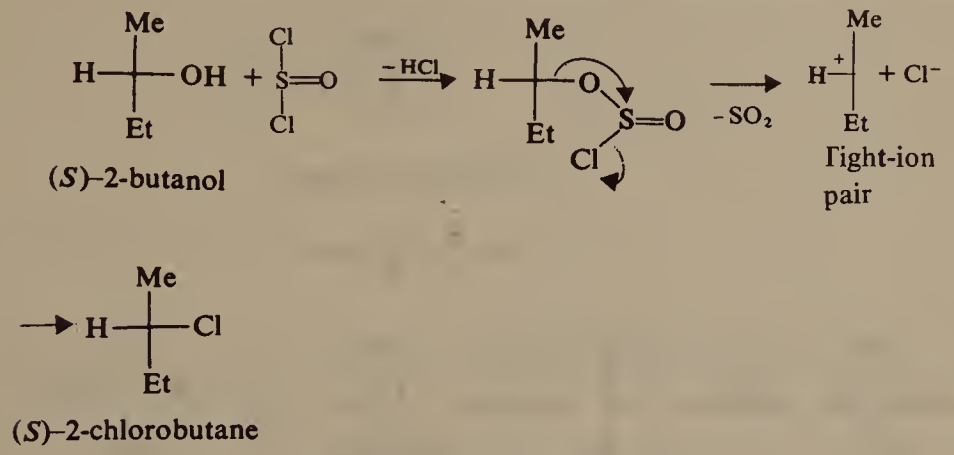
1.16 OUTLINES OF THE FATE OF CHIRAL CARBON IN SOME ORGANIC REACTIONS

When the chiral carbon of an enantiomer is the site of nucleophilic substitution, three stereochemical situations may arise :—

(A) Retention of Configuration S_Ni Reactions

If (*S*)-2-butanol (Scheme 1.75), an optically active alcohol is converted to the corresponding chloride by the action of thionyl chloride, the new C—Cl bond is formed at the same face where the old C—O bond is broken. Internal

displacement reactions (S_Ni) of this type are strongly favourable for retention of configuration (for further details of the mechanism see sec. 3.8). The first step is without any effect on the configuration because it is only a replacement of the hydroxyl hydrogen atom by the —SOCl group. The next step is crucial in which sulphur dioxide is eliminated leading to an ion-pair, which is probably surrounded by a solvent cage. This ion pair collapses to give a covalent chloride, the relative orientation of the ion ensures the retention of configuration of the original alcohol.



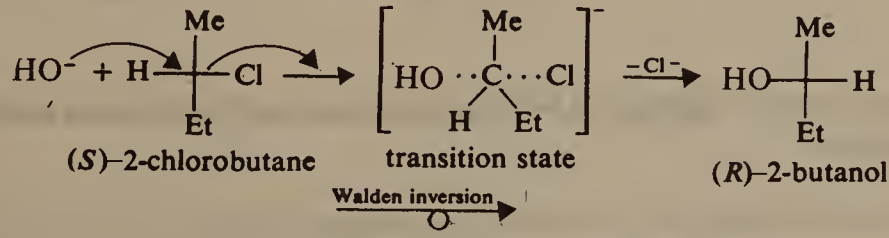
Retention of Configuration

S_Ni for *substitution, nucleophilic and intramolecular*

Scheme 1.75

(B) Normal S_N2 Reactions with Inversion of Configuration

If the attack of the nucleophile is initiated from the side opposite to the departing group (chlorine) the reaction always leads to an inversion of configuration (Scheme 1.76) often referred to as the Walden inversion and symbolized by a loop in the arrow.



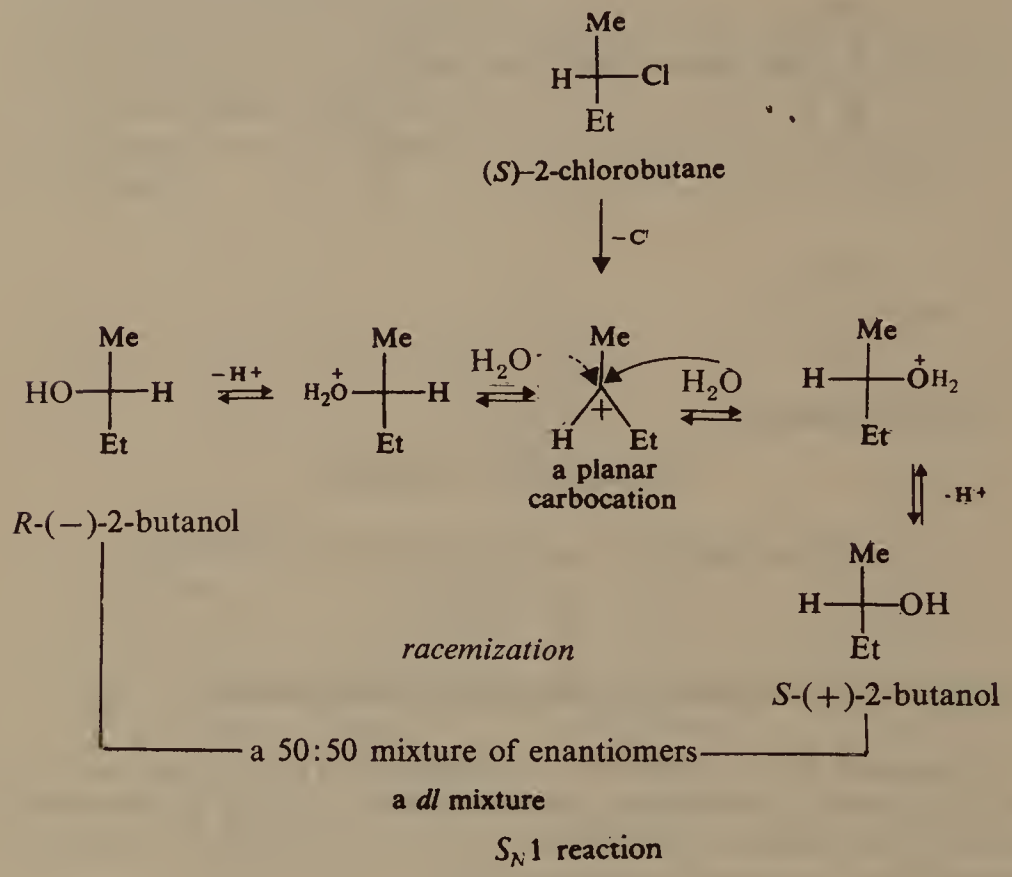
Inversion of Configuration

S_N2 reaction

Scheme 1.76

(C) Racemization under S_N1 Reactions

The racemization of an enantiomer occurs when a bond attached to the chiral carbon is completely broken before a new bond is formed. If the intermediate so formed assumes a planar configuration (as in the case of a symmetrically solvated carbocation in an S_N1 reaction), because of the equal probability of new bond formation from either side of the plane, a 50:50 mixture of the *d* and the *l* forms will be formed, leading to racemization. More examples of racemization are given under Sec. 1.17.



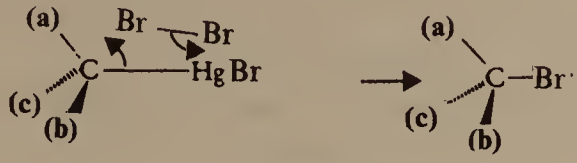
Scheme 1.77

(D) Retention of Configuration by Neighboring group Participation and S_E2 Reactions.

Retention of configuration may also be observed through two successive inversions of the configuration. This usually happens when there is another functional group in the substrate that can play a transient part in the reaction. An assisted reaction by a more or less remote functional group is called the neighboring group effect (discussed in detail in Sections 2.3 and 3.7).

Finally the retentive mechanism is the S_E2 mechanism, (substitution, electrophilic, bimolecular). This mechanism is the electrophilic analogue of

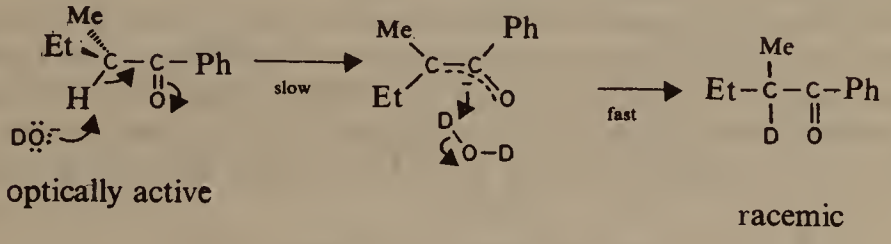
S_N2. However, it proceeds with opposite stereochemistry. Moreover, this mechanism is limited to organometallic derivatives. The stereochemical usefulness of the S_E2 mechanism is limited because many chiral organometallics are not known. Organolithium and Grignard reagents, moreover, racemize too rapidly to be useful. Organomercurials are stereochemically inert and as a result bromination of mercurials has been investigated, and shown to occur with retention of configuration (Scheme 1.78).



Scheme 1.78

(E) Other Electrophilic Substitution Reactions

(*a*) S_E1 (Substitution Electrophilic Unimolecular leading to Racemization) is a multistep electrophile interchange with bond-breaking (the rate-limiting step) preceding bond-making. The reaction is of first order in substrate and zero order in attacking electrophiles. This reaction is the electrophile analog of the S_N1 mechanism. The intermediate (R^-) is a carbanion, which generally inverts more rapidly than it is attacked by X^+, leading to racemization (or epimerization) if the reaction site is a chiral center. A common example of the S_E1 mechanism is the removal of a proton attached to carbon with a strong base (scheme 1.79). and in the reaction the rate of deuterium exchange is the same as the rate of racemization.

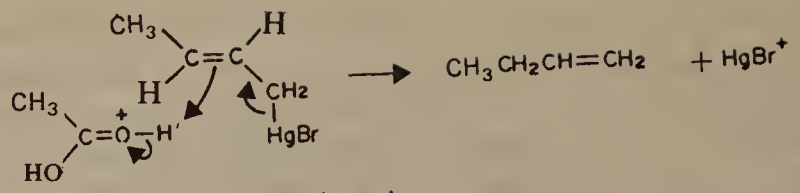


S_E1 reaction

Scheme 1.79

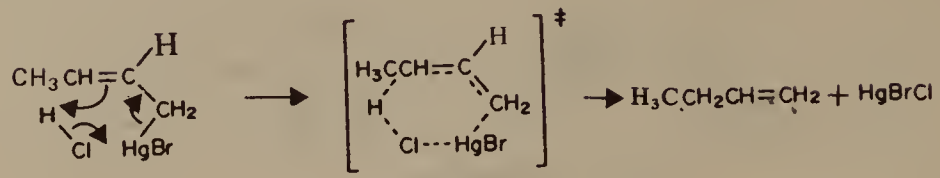
(*b*) S_E2' (Substitution Electrophilic Bimolecular with Rearrangement) is a mechanism kinetically identical to the S_E2 process, but involving formation of a rearranged product, in the presence of acetic acid-perchloric acid (Scheme 1.80).

(*c*) S_Ei' (Substitution Electrophilic Internal with Rearrangement) is a concerted electrophile interchange involving a multicenter transition state and formation of rearranged product.



S_E2' reaction

Scheme 1.80



S_Ei' reaction

Scheme 1.81

1.17 RACEMIC MIXTURES AND RACEMIZATION

Racemic mixture or a racemate is an equimolar mixture of two enantiomers. Since a racemic mixture contains equal numbers of *dextro*rotating and *levo*rotating molecules, the net optical rotation is zero. A racemic mixture is often symbolized by (±) or (*dl*).

The physical properties of a racemic mixture are not necessarily the same as those of the pure enantiomers. A sample composed solely of right-handed molecules will experience different intermolecular interactions than will a sample composed of equal numbers of right- and left-handed molecules.

A racemic mixture may crystallize in several different ways. In some cases, separate crystals of the (+) and (—) forms result and in this case, the crystalline racemate is a mechanical mixture of two different crystalline compounds. The melting-point diagram for such a mixture is like that for any other mixture of two compounds (Fig. 1.4). The eutectic point in this case is

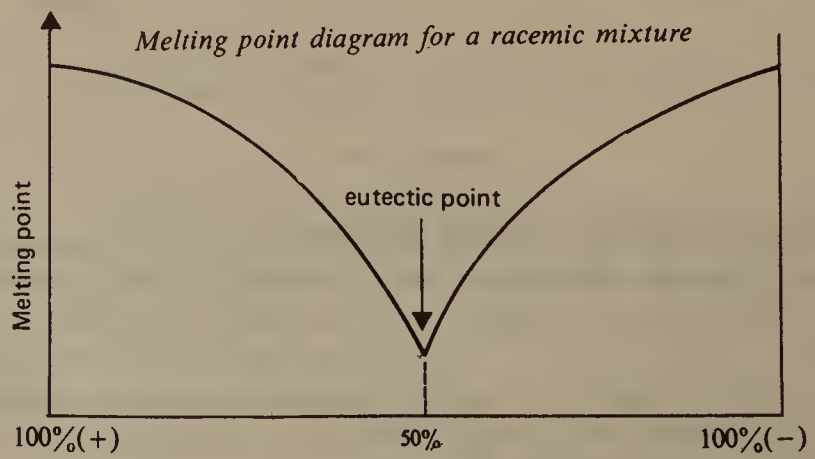
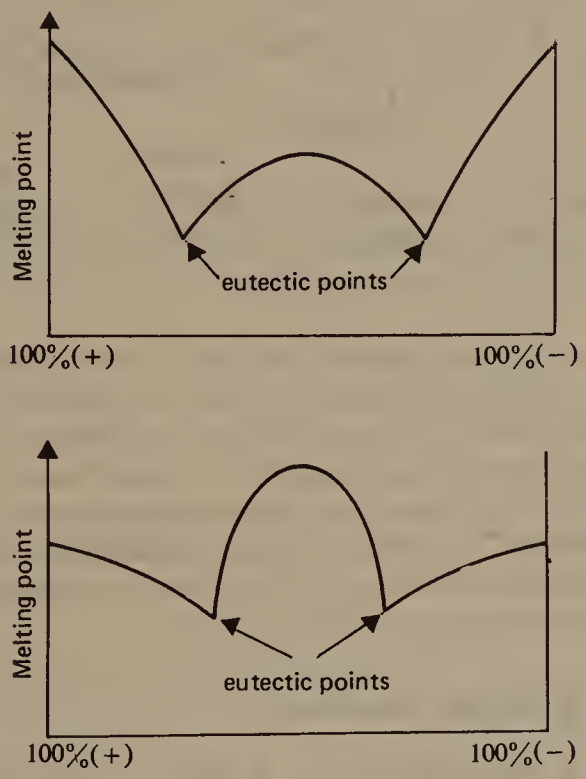


Fig. 1.4

always at the 50:50 point. Addition of a little of either of the pure enantiomers will cause the melting point of the mixture to rise. The racemate may also crystallize as a racemic compound. In this case only one type of crystal is formed which contains equal numbers of (+) and (-) molecules. The racemic compound behaves like a separate compound and its melting point is a peak on the phase diagram. The racemic compound may melt either at higher or lower temperature than either of the pure enantiomers. Addition of a small amount of either pure enantiomer leads to a fall in the melting-point (Fig. 1.5). For example both (+)— and (—)—tartaric acids melt at 170°C,



Melting point diagrams for racemic compounds

Fig. 1.5

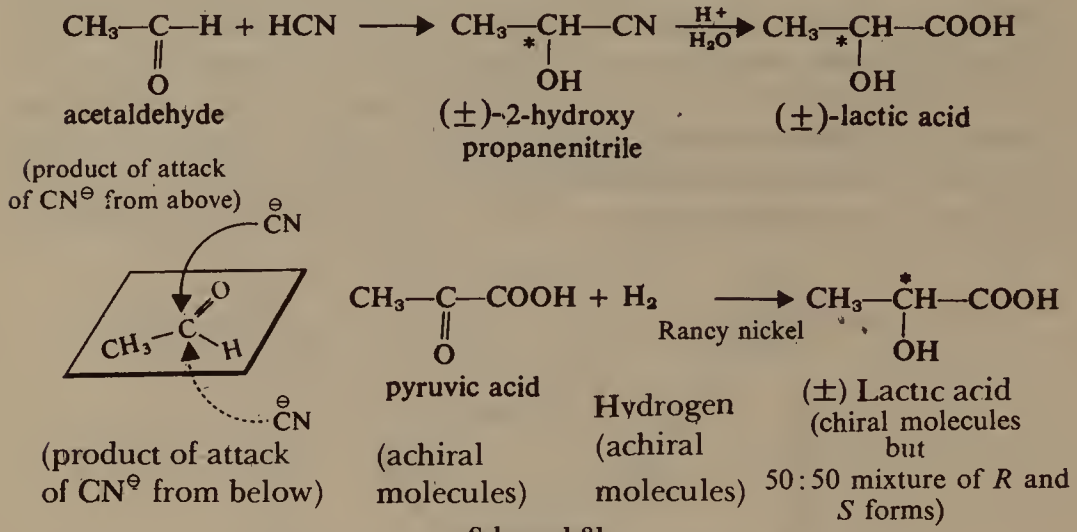
whereas the mixture of equal parts of (+)— and (—)— enantiomers melts at 206°C and the racemic system in this case is indeed a racemic compound.

The process whereby a pure enantiomer is converted into a racemic mixture is called racemization. Racemization may be accomplished in a trivial sense by simply mixing equal amounts of two pure enantiomers. Racemization may also result from the following chemical interconversions.

(A) Racemization During Synthesis

Formation of 2-hydroxypropanenitrile from acetaldehyde and hydrogen cyanide in the absence of any optically active substance, yielding an excess of one enantiomer over the other, would constitute an absolute asymmetric

synthesis that is creation of an optically active compound in a symmetrical environment from symmetrical reagents (Scheme 1.81).



Scheme 1.81

This is obviously unlikely for the given example because there is no reason for cyanide ion to have anything other than an exactly equal chance of attacking above or below the plane of the acetaldehyde molecule, thus producing equal number of molecules of each enantiomer.

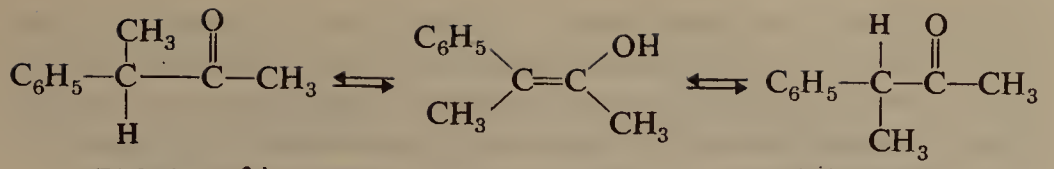
Thus, the chemical syntheses involving the introduction of an asymmetric center into a compound originally without this centre often yield a racemic mixture containing an equal amount of the *d* and the *l* forms of the product, as is also seen in the reduction of pyruvic acid.

(B) Racemization From One Enantiomer

Racemization is the formation of a racemic modification from one enantiomer. It is, however, an undesirable process. When it is necessary to synthesize an optically active compound, it is essential to aviod steps which result in racemization.

(*a*) **By rotation about a single bond:** The biphenyls and related compounds, in which optical activity is due to the restriction of rotation about a single bond, racemize when enough thermal energy is employed for the energy barrier between the enantiomers to be surmounted at a practicable rate.

(*b*) **Via an enol or enolate anion:** Racemization occurs in those compounds in which a carbonyl function is attached to a chiral centre that also carries a hydrogen. When (*R*)—3—phenyl—2—butanone is dissolved in aqueous ethanol that contains NaOH or HCl, the optical rotation of the solution gradually drops to zero, to yield a racemic mixture of the (*R*) and (*S*) enantiomers (Scheme 1.82). This rate of racemization is found to be proportional to the concentration of ketone and the concentration of NaOH or HCl. Racemization thus, occurs by way of the intermediate enol form in which the former chiral carbon becomes planar (achiral).



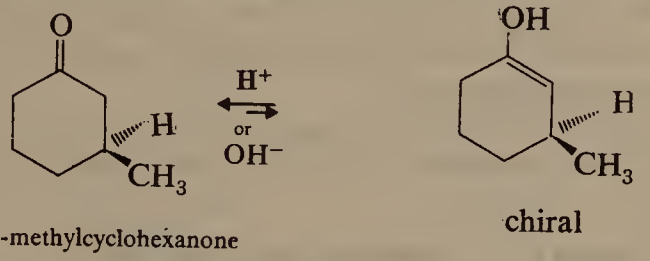
Scheme 1.82

As racemization involves the formation of the enol form, the rates of racemization and enolization are found to be exactly equal.

$$\text{rate} = k[\text{ketone}][H^+] \quad \text{or} \quad k'[\text{ketone}][OH^-]$$

Scheme 1.83

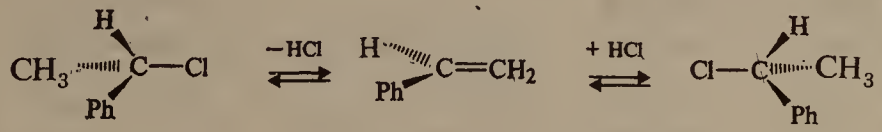
Racemization occurs only if the chiral carbon is α to the carbonyl group. If the aldehyde or ketone is chiral because of asymmetry at some other carbon, the enol form is also chiral and enolization does not lead to racemization.



Scheme 1.84

(c) Via a cation: Carbocations are coplanar at the tervalent carbon atom and if the ion $RR'R''C^+$ is formed from an enantiomer $RR'R''C{-}X$ by the reversible removal of X with its bonding-pair, racemization occurs (sec. 1.16C).

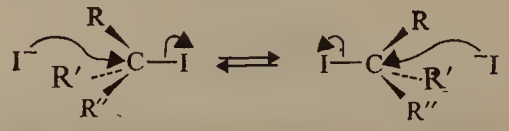
(d) Via reversibly formed, inactive intermediates: The mechanism here is similar to methods (b) and (c) above but for the intermediate is a relatively stable compound as compared with the transient carbanions and carbocations. Thus optically active α -phenethyl chloride racemizes in polar solvents like formic acid *via* optically inactive styrene (Scheme 1.85).



Scheme 1.85

(e) By S_N2 reaction : The racemization of optically active halides, particularly iodides, where the halogen is linked to the chiral carbon, occurs in the presence of the corresponding halide ion. This is due to the fact that the S_N2-reaction leads to inversion of the configuration. A similar reaction, run

under same reaction conditions, uses radioactive iodide (^{128}I) as the nucleophile. This experiment allows the rate of the chemical reaction, exchange of iodide for iodide, to be measured by using radioactive counting methods. The specific rate constant for the chemical reaction is found to be exactly one-half of the rate constant for the loss of optical activity.



Scheme 1.86

(C) Optical Purity (OP) and Optical Yield (OY)

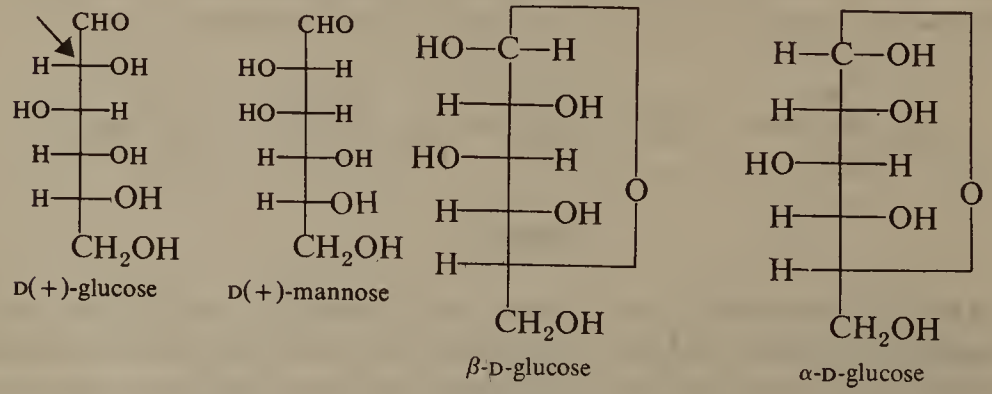
A sample of an optically active compound which contains a single enantiomer is said to be optically pure. An optically pure sample of S-(+)-2-butanol shows a specific rotation of + 13°.52′ *i.e.*, $[\alpha]_{\lambda}^{25} = 13°.52'$ On the other hand, a sample of *S*-(+)-2-butanol that contains less than an equimolar amount of *R*-(−)- 2-butanol will show a specific rotation which is less than +13°52′ but greater than 0°. Such a sample is said to have an optical purity less than 100%. The term optical purity is applied to one enantiomer or to mixture of enantiomers only.

The optical yield (OY), is the optical purity of the products from the reaction of a pure enantiomer regardless of the chemical yield.

1.18 EPIMERIZATION, EPIMERS, AND ANOMERS

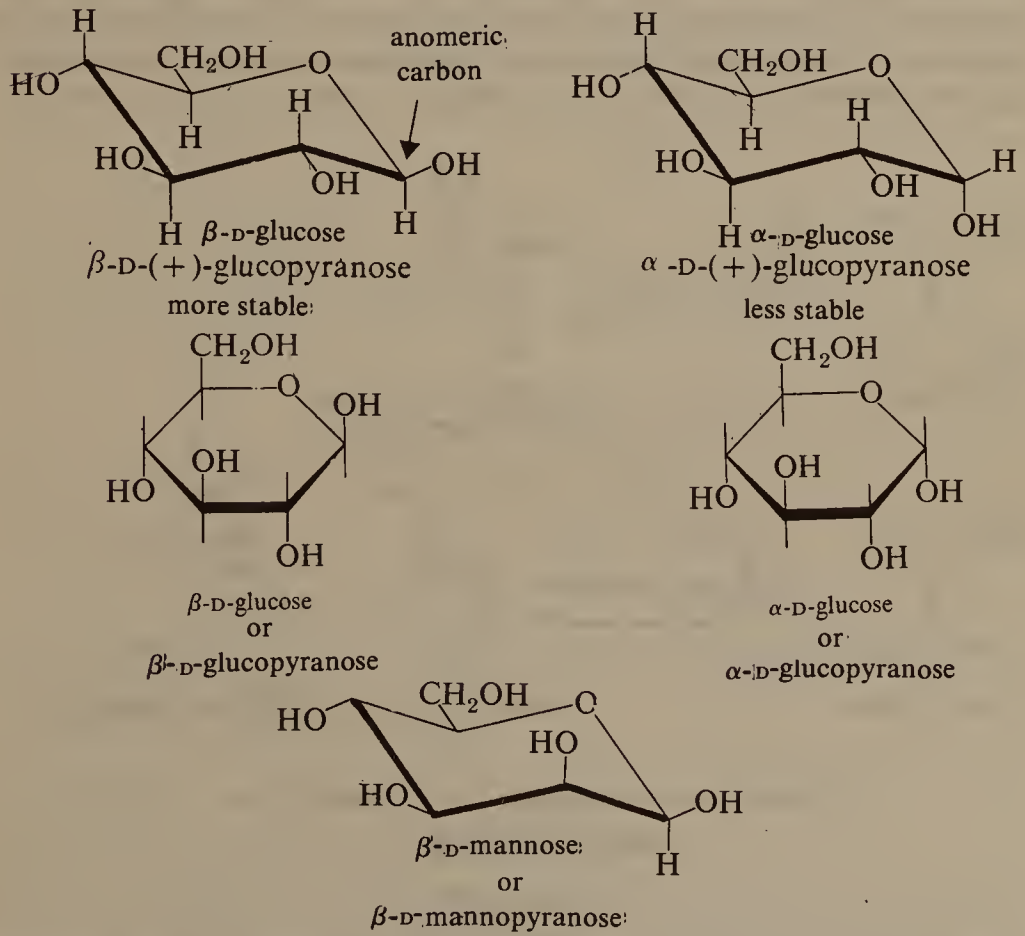
Epimerization is a change in configuration at one chiral centre in a compound which has more than one such centre. It leads to the formation of a diastereoisomer and not the enantiomer, of the starting material. The mechanisms of epimerization parallel those of racemization. Thus, glucose and mannose are epimers differing in configuration at one of the chiral centres shown by an arrow (Scheme 1.87).

Generally all the simple sugars exist in the six-membered ring form and



Scheme 1.87

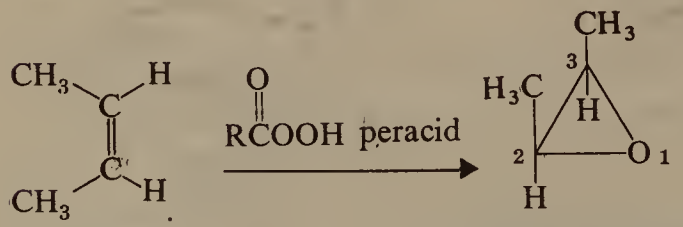
when the hemiacetal is formed, the former aldehyde carbon becomes asymmetric. Therefore two cyclic forms of glucose exist; the two cyclic isomers of glucose differ only in the stereochemistry at C-1 (anomeric carbon) *i.e.*, the acetal carbon and are called anomers. These anomers are differentiated by the Greek letters α and β. The convention used to denote the stereochemistry at anomeric carbon is that, the—OH at C-1 in the β anomer is written to the left and that in the α anomer is to the right. In a Haworth projection, the sugar ring is depicted as a planar hexagon with the oxygen in the upper right vertex and substituents are indicated by straight lines through each vertex, either above or below the plane. The —OH at the anomeric carbon is up in the β anomer and down in the α anomer. The stereochemistry of pyranoses can be best appreciated from their conformations *i.e.*, the chair conformation (Scheme 1.88). Thus β-D-glucose is the most widely distributed sugar since it has the stable all equatorial conformation. The α-form differs in having the anomeric hydroxyl group in the axial position. β-D-Glucose and β-D-mannose are C-2 epimers; in mannose the C-2 hydroxyl group is having opposite stereochemistry (axial) as compared to glucose (equatorial).



Scheme 1.88

1.19 STEREOSPECIFIC AND STEREOSELECTIVE REACTIONS

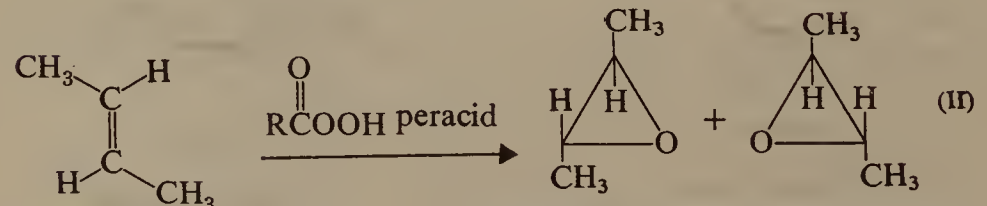
The alkenes react with peracids (Sec. 6.6) to give epoxides (oxiranes) and the reaction is stereospecific. As a result, *cis*-2-butene gives *cis*-2, 3-dimethyloxirane (eq. I, Scheme 1.89) while *trans*-2-butene on the other hand affords *trans*-2, 3-dimethyloxiranes (eq. II) as the only product. Epoxidation of alkenes with peracids involves *syn* addition of oxygen. Such an addition on either face of *cis*-2-butene thus leads to the same *meso* compound (eq. III, Scheme 1.90). A similar *syn* addition of oxygen to *trans*-2-butene at one face gives one enantiomer while at the other face it affords the other enantiomer (eq. IV, Scheme 1.90). The epoxidation of *trans*-2-butene gives a racemic modification since the additions have same energies of activation and therefore, occur at same rates to yield the enantiomers in equal quantity. These epoxidation reactions may be used to explain stereospecific reactions which are those reactions in which stereoisomeric reactants give diastereomerically different products. The epoxidation of *cis*- and *trans*-2-butene is stereospecific, since the alkenes are stereoisomers (alkene diastereomers). The product of reaction I or III, *i.e.*, a meso compound has a diastereomeric relationship with either of the enantiomers formed in the reaction II or IV. A stereoselective reaction is that reaction which affords an excess of one diastereomer regardless of the stereochemistry of the reactant, *e.g.*, the enzymatic reduction of pyruvic acid is stereoselective (Sec.1.20, d).



(I)

cis-2-Butene

cis-2,3-Dimethyloxirane
(*a* meso *compound*)



(II)

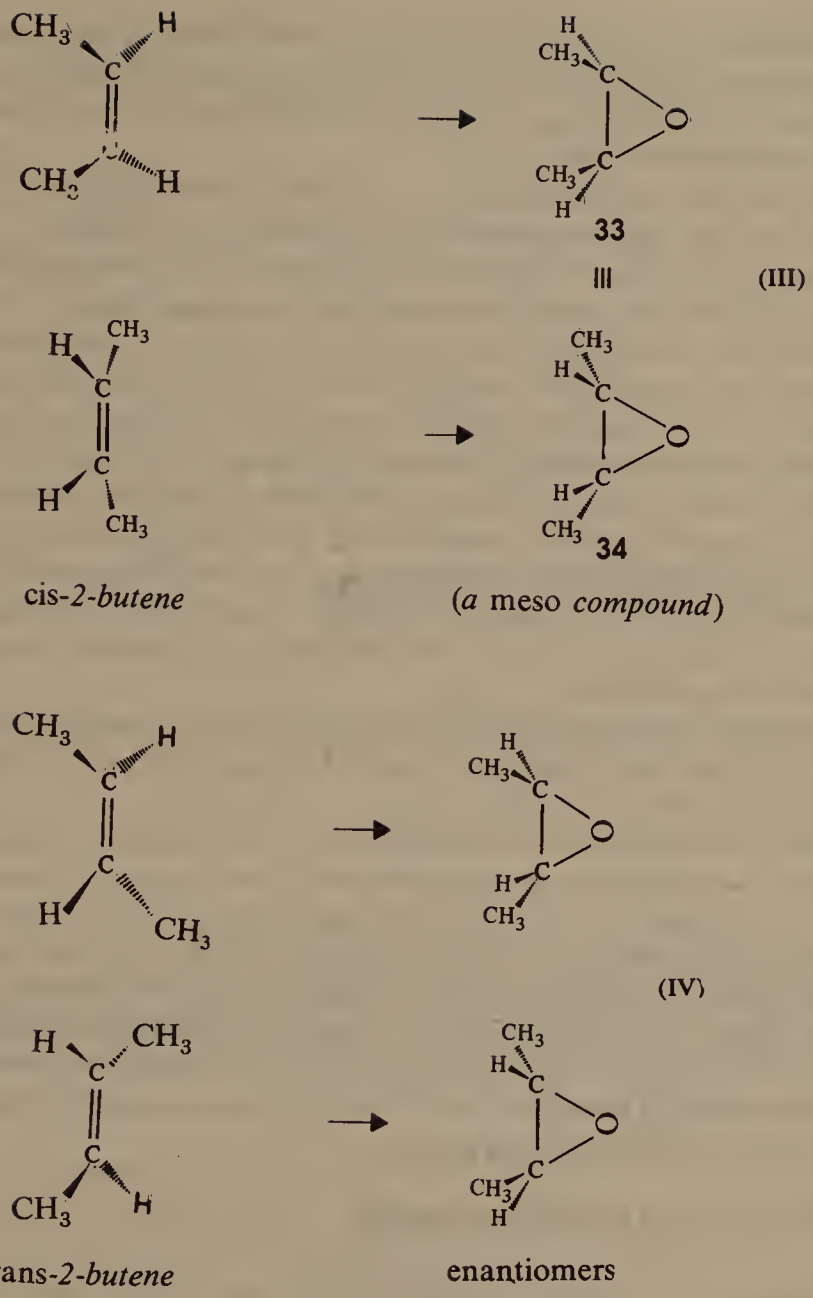
trans-2-Butene

Enantiomeric *trans*-2,3-dimethyloxiranes

Epoxidation of alkenes takes place in a *stereospecific* way

Scheme 1.89

The terms stereoselective and stereospecific are, however, not mutually exclusive. All reactions that are stereospecific are of necessity stereoselective; the reverse, however, is not true. The enzymatic reduction of pyruvic acid is



Scheme 1.90

stereoselective, but it is not stereospecific. It is not stereospecific, because the reactant cannot exist in stereoisomeric forms. Other reactions may be stereoselective but not stereospecific.

1.20 CONCEPT OF PROSTEREOISOMERISM AND CHIRAL SYNTHESIS (ASYMMETRIC INDUCTION)

As already discussed the usual outcome of reactions carried out on optically inactive (achiral) starting materials under achiral conditions is the formation of an optically inactive racemic mixture *i.e.*, the chiral molecules of the product are formed as a 50:50 mixture of enantiomers. Thus catalytic

hydrogenation of pyruvic acid affords a racemic modification of lactic acid (50:50 mixture of *R* and *S* forms). Hydrogen, absorbed on the surface of the catalyst has an exactly equal chance of attaching below or above the plane of pyruvic acid molecule (Sec. 1.17, A).

However, when a new chiral centre is created in a molecule which is already optically active, the formation of an exactly 1:1 mixture of the two diastereomers in reactions is not expected. This is so, because the direction of attack by the reagent is now determined by the groups already present. It is this control of stereoselectivity exerted by an existing chiral centre on the formation of a new chiral centre which is called chiral synthesis. Chiral synthesis (referred to in the older terminology or even now as asymmetric synthesis) may be divided into two types: (1) partial chiral synthesis, which is also termed as the relative chiral synthesis and (2) absolute chiral synthesis. Thus, asymmetric synthesis comprises of those reactions which create an element of chirality in substrate molecules, and which occur with product stereoselectivity. In other words, an asymmetric synthesis converts a prochiral unit into a chiral unit with the formation of unequal amounts of stereoisomeric products.[12]

Thus, firstly chiral synthesis (asymmetric synthesis) requires the presence of a prochiral unit in the substrate molecule. It may be either enantiotopic or diastereotopic group or a face.

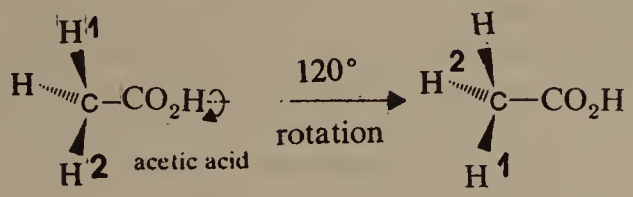
Asymmetric induction is brought about by the presence of an element of chirality which plays an active role in the reaction: chiral reagent, chiral solvent, chiral catalyst, circularly polarized light, or element of chirality in the substrate molecule. The element of chirality, is thus part and parcel of the transition states which as a result, are diastereoisomeric. Before presenting some examples of chiral synthesis we shall learn about prostereoisomerism and the nomenclature of chiral synthesis. Prostereoisomerism can be considered either by symmetry operations or by substitution rule and for each concept both criteria are being presented.

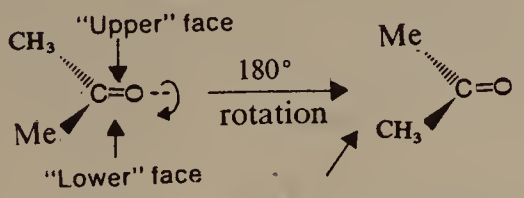
(A) The Concept of Prostereoisomerism

(a) Homotopic atoms, groups and faces: The three hydrogens of acetic acid are stereochemically equivalent (homotopic) as each hydrogen is indistinguishable from the others by any experimental test. The molecular environment is, however, a tedious criterion of equivalence which is explored by simple symmetry considerations. The latter show that groups are homotopic if they can be interconverted by rotation about an axis of symmetry C_n ($\infty > n > 1$). In acetic acid, for example, the three hydrogens of the methyl group are equivalent as a 120° rotation around the C—CO_2H axis leads to an arrangement indistinguishable than in the original. Similarly the methyl groups as well as the two faces of the carbonyl group in acetone (Scheme 1.91) are equivalent as is evident by a 180° rotation around the axis of the C=O bond.

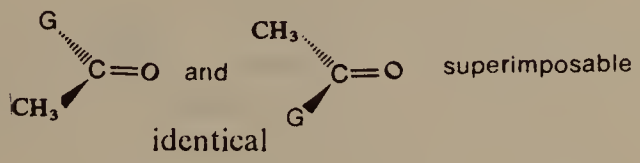
Topicity is the name given to relationships within molecules and it can be

gainfully tested by the substitution rule. The substitution rule operates by studying the result of replacing sequentially two or more constitutionally identical ligands, by a test group (*i.e;* G in acetone, scheme 1.91) that is





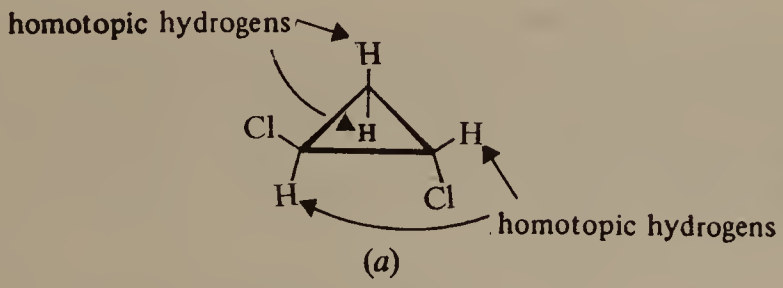
acetone homotopic methyl groups of acetone

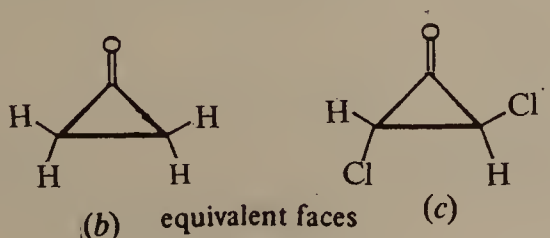


Scheme 1.91

different from all other ligands. Thus the substitution of either of the methyl groups of acetone by the test group G leads to identical compounds.

The hydrogen atoms on C-1 and C-2 of *trans*-1, 2-dichlorocyclopropane (*a*) in Scheme 1.92 are homotopic since the substitution of either hydrogen of the set by another atom *e.g.*, Br gives an identical chiral molecule.



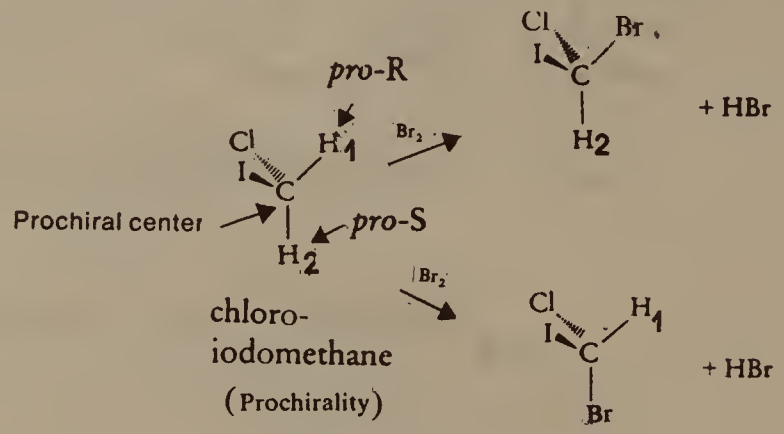


Scheme 1.92

Both cyclopropanone (*b*, achiral) and *trans*-2,3-dichlorocyclopropanone (*c*, chiral) have equivalent faces. The two faces of (*Z*)-2-butene are homotopic while those of (*E*)-2-butene are enantiotopic (Sec. 1.20A, e).

(*b*) Enantiotopic atoms and groups: If one considers iodomethane (CH_3I), the substitution of any single hydrogen atom *e.g.*, with chlorine yields an identical molecule to that produced on any other substitution. The hydrogen atoms are therefore indistinguishable and are called homotopic.

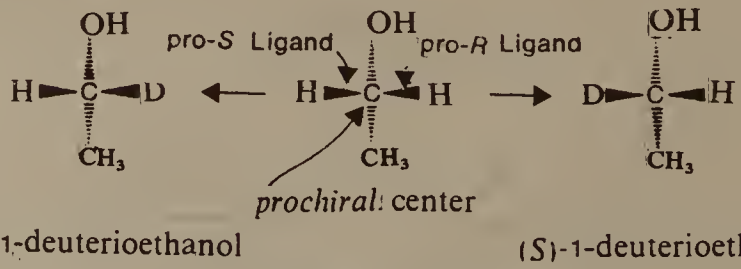
In the case of chloroiodomethane, however, the replacement of H_1 or H_2 (Scheme 1.92*a*) has different stereochemical outcome, as enantiomers are formed on substitution (Bromine is a substituent). Ligands which yield enantiomers on application of the substitution rule are called enantiotopic.



Scheme 1.92 (a)

Atoms or groups are defined as enantiotopic if they can be interchanged only by a rotation-reflection operation (*i.e.*, an alternating axis of symmetry operation) to give a structure identical to the original. Mostly, the compounds in which enantiotopic relationships exist have a plane of symmetry.

(*c*) Prochirality: If the replacement of one of the pair of enantiotopically related groups by a different group creates a chiral center, the original center is said to be prochiral. The hydrogens of the methylene group in ethanol are enantiotopic; replacement of one of them by deuterium creates a chiral center and yields (*R*)-or (*S*)-deuterioethanol (Scheme 1.93), depending on which of the hydrogens is replaced. The methylene group of ethanol, therefore, is said to be prochiral.



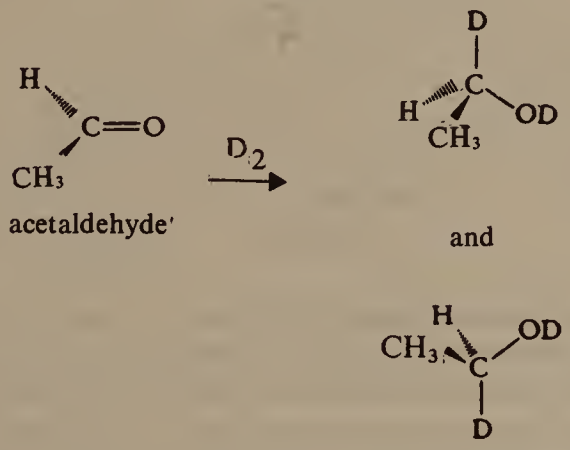
(*R*)-1-deuterioethanol (*S*)-1-deuterioethanol

(*Prochirality* of ethanol)

Scheme 1.93

(*d*) **Nomenclature of enantiotopic ligands:** Enantiotopic ligands can be specified by the modified application of the (*R, S*) system. The ligand to be labelled is arbitrarily assigned a higher priority over the other. The sequence rules are then applied in the usual way; a clockwise path demands that the ligand be labelled *pro-R* (sometimes H_R) and an anticlockwise path specifies it as *pro-S*. The application of these rules to ICH_2Cl gives H_1 as *pro-R* (H_2-lowest priority: I>Cl>H_2) and H_2 as *pro-S*.

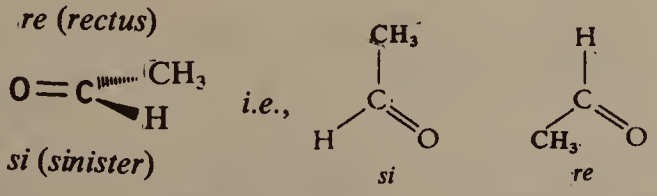
(*e*) **Enantiotopic faces and their nomenclature:** The analysis of prochirality can also be applied to trigonal centers, *i.e.*, to the faces of suitable molecules. In acetaldehyde, the two faces of the molecule are not equivalent, but are enantiotopic, because chirality can be generated by an addition to a face. If acetaldehyde is reduced by deuterium, enantiomeric alcohols are formed (Scheme 1.94).



acetaldehyde' enantiomeric alcohols

Scheme 1.94

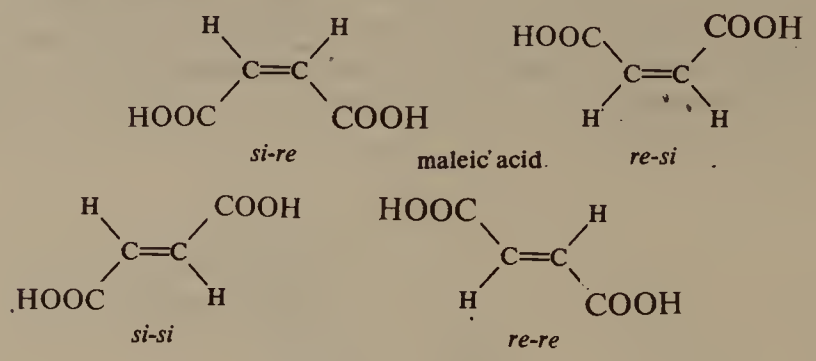
Addition to one face gives *R*-alcohol while addition to the other leads to the *S*-isomer. When addition to opposite faces of a π-system gives enantiomers, they are said to be enantiotopic faces. The two faces of *E*-2-butene (*trans*-2-butene) are enantiotopic while those of *Z*-2-butene (*cis*-2-butene) are homotopic. One may consider the epoxidation reaction on these alkenes (Secs. 1.19 and 6.6). The epoxide from *E*-2-butene is chiral while from *Z*-2-butene is achiral (plane of symmetry), therefore, the faces of the butenes from which these are formed are enantiotopic and homotopic respectively.



Scheme 1.95

On viewing the molecule of acetaldehyde from above (scheme 1.95), the ligands define a clockwise path, while a view from below affords a counterclockwise path. The upper face is defined as *re* (rectus), the opposite face is *si* (sinister), *i.e.*, the sequence rule is used in two dimensions.

In the case of a carbon-carbon double bond, the *re-si* nomenclature is used for both ends independently. Fumaric acid therefore, has a *re-re-* and a *si-si*-face, (Scheme 1.96), while maleic acid has two equivalent faces (*re-si*) due to the presence of a C_2 axis.

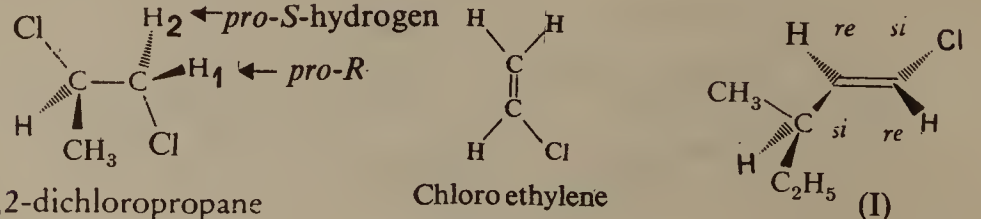


fumaric acid

Scheme 1.96

(f) Diastereotopic atoms groups and faces (proachiral centre): Diastereotopic groups are located in diastereoisomeric environments, cannot be interchanged by any symmetry operation and on substitution by chiral or achiral groups give diastereoisomeric structures. Thus ligands can be labelled as diastereotopic provided the application of sequence rule leads to diastereoisomers. Hydrogen atoms H_1 and H_2 are diastereotopic in *R*-1,2-dichloropropane (Scheme 1.97). In chloroethylene, the two geminal hydrogen atoms are diastereotopic, because replacement of one hydrogen affords (*Z*)- and (*E*)-diastereoisomers. As no element of prochirality exists in chloroethylene molecule the carbon atom carrying the two hydrogens is designated as a proachiral center. The diastereotopic ligands are named by following the procedures used for enantiotopic groups, H_1 is *pro-R* and H_2 is *pro-S* while the carbon atom bearing H_1 and H_2 is prochiral.

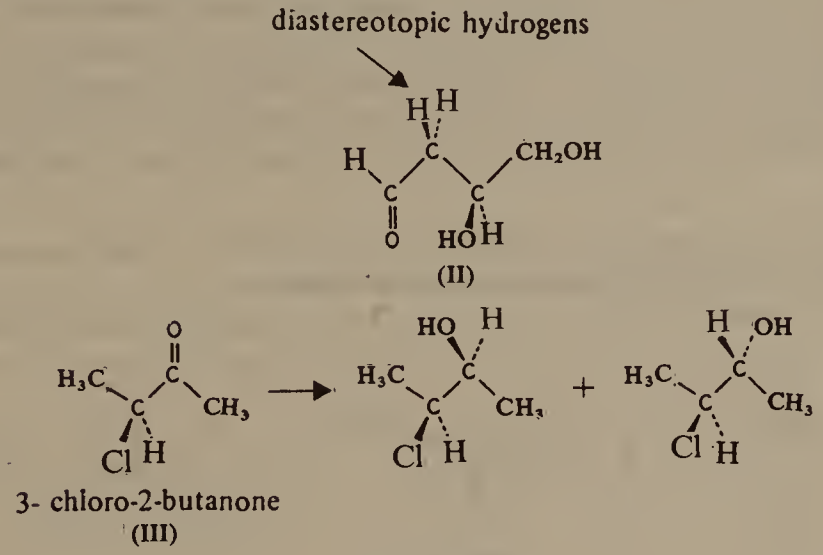
A compound can have diastereotopic faces if addition to each face yields diastereoisomers and the most common condition for a pair of diastereotopic faces is the presence of a prochiral sp^2 centre and a chiral centre in the same molecule, as in the case of (I, Scheme 1.97). The molecule (I) has



Scheme 1.97

diastereotopic faces since the *syn* addition of say deuterium affords a pair of diastereoisomers.

Two additional examples are of compounds (II) and (III) in Scheme 1.98. In (II), the replacement of methylene hydrogens α to the carbonyl group by—OH, yields the diastereoisomers erythrose and threose (Sec. 1.9), therefore, these hydrogens are diastereotopic.



Scheme 1.98

The chiral compound, 3-chloro-2-butanone has diastereotopic faces since LAH reduction yields two diastereoisomers.

TABLE 1.3. : Summary of relationships between constitutionally identical groups in molecules

Nature of Group	Symmetry	Consideration by Substitution	Presence of Elements of prostereo-isomerism
Homotopic	Interchangeable by C_n ($\infty > n > 1$)	Substitution with test groups does not yield isomers	None
Enantiotopic	Interchangeable by S_n only	Substitution with achiral or chiral test groups leads to enantiomers or diastereoisomers, respectively.	Prochiral center
Diastereotopic	Not interchange-able by any symmetry operation	Substitution with chiral or achiral test groups yields diastereoisomers.	Prochiral or proachiral center

(B) Chiral Synthesis

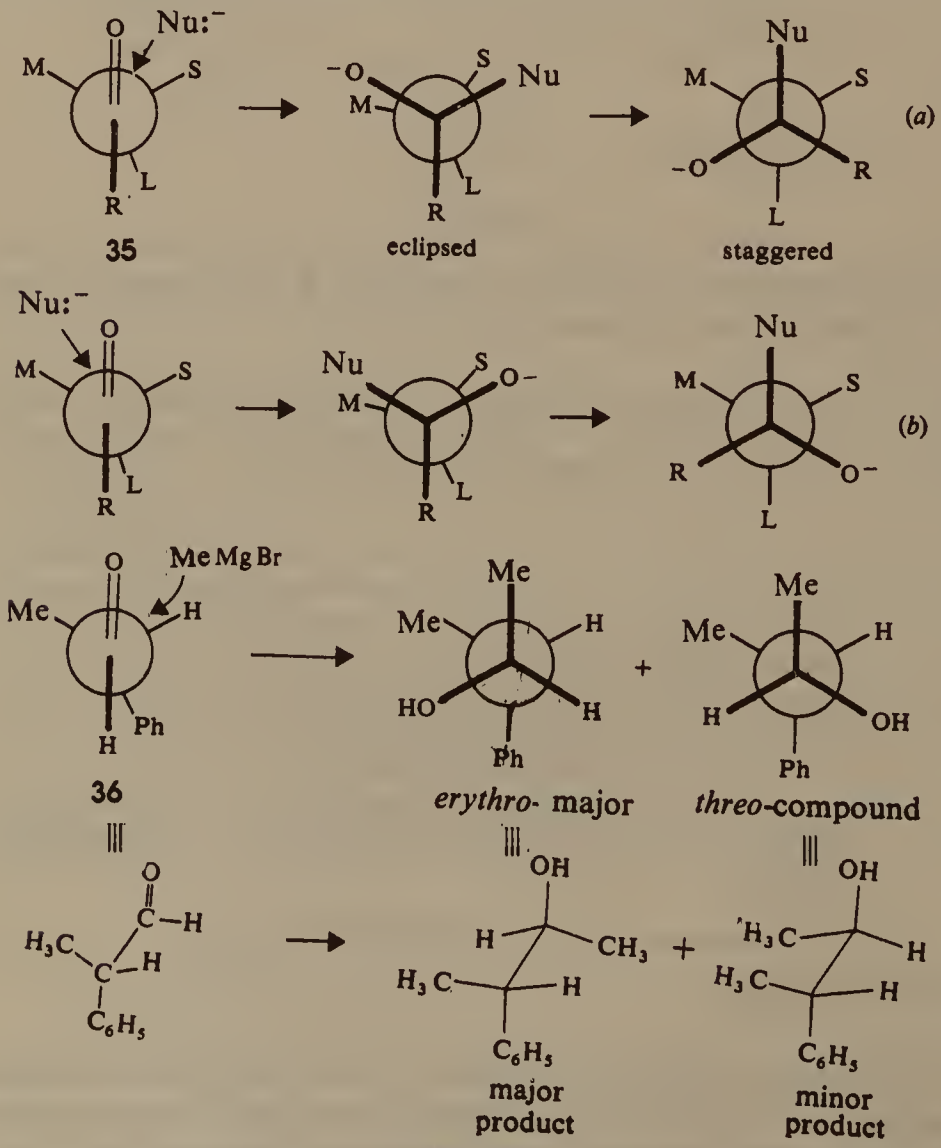
In the absence of a chiral influence, the reactions leading to enantiomers have transition states with identical energies, and therefore, occur at same rates, to give equal quantities of enantiomers. During chiral synthesis, a chiral agent

plays an active part it the reaction, if being integral to the transition state. Consequently two diastereoisomeric transition states are formed leading to the generation of one stereoisomer more rapidly than the other.

Chiral synthesis is thus brought about by using chiral reagent, chiral solvent, chiral catalyst, physical force (circularly polarized light) or by using the element of chirality in the substrate molecule itself. The present discussion is under these headings. Asymmetric synthesis can also be studied under the two broad categories enantiodifferentiation (enantiotopic and enantioface differentiation) and diastereodifferentiation (diastereotopic and diastereoface differentiation). In the present discussion the stereoheterotopic units *i.e.*, enantiotopic and diastereotopic groups and faces have also been used.

(*a*) Chiral syntheses conditioned by the presence of a chiral centre in the reacting substance (Diastereoface differentiation):

(*i*) Cram's rule: For certain additions to the carbon-oxygen double bond of



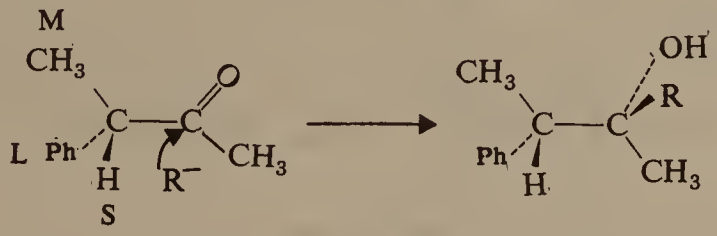
Scheme 1.99

aldehydes and ketones having a chiral α -carbon, Cram's rule is useful to predict which diastereomer will predominate. If the molecule is observed along its axis, it may be represented as in **35** (Scheme 1.99) where S, M and L designate small, medium and large groups respectively. The oxygen of the carbonyl orients itself so as to be between the small and the medium-sized groups. The rule is that the incoming groups preferentially attack on the side of the plane containing the small group. By this rule, it can be predicted that reaction (*a*) should be preferred over (*b*) as depicted in Scheme 1.99. Thus, reaction of optically active α -phenylpropionaldehyde **36** with Grignard's reagent of the two diasteromeric alcohols yields the erythro compound as a major product.

Many reactions of this type are known, in some of which the extent of favouritism approaches cent per cent. The farther away the reaction site is from the chiral center, the less influence the latter has and the more equal the amounts of diastereomers formed.

For further clarity one may consider an equivalent illustration of Cram's rule, "In a kinetically controlled addition to a carbonyl carbon atom which has a chiral centre in the α -position, an anion attacks from the side containing the small group when the chiral group is so oriented that the medium group is in the eclipsing position to the carbonyl group."

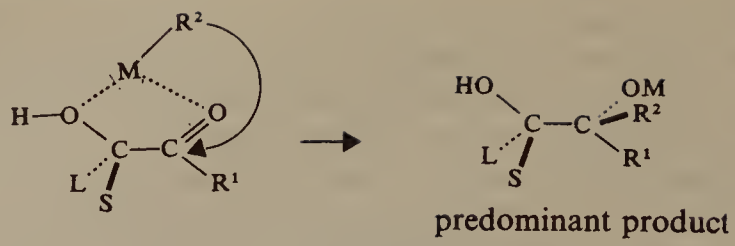
In keeping with this model it is found that the degree of diastereoface differentiation increases with the increasing size of the attacking group (Scheme 1.100).



R	optical yield %
CH_3	66
CH_2CH_3	75
Ph	83

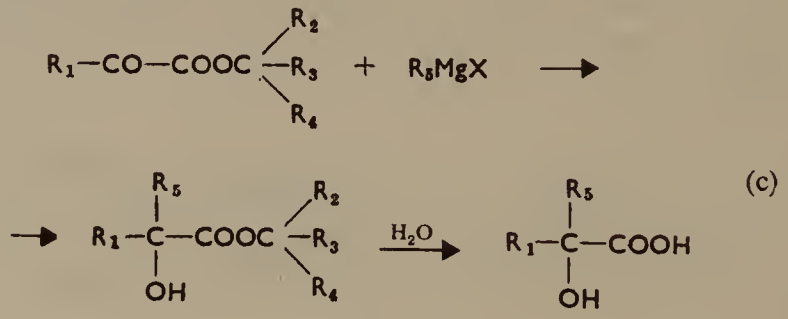
Scheme 1.100

The rule, however, is to be modified when one of the groups on the chiral carbon is polar, like hydroxyl or alkoxyl which has a high coordinating ability. According to the modified rule the polar group is oriented so as to eclipse the carbonyl group, and the reagent (Grignard's reagent or organolithium) then bridges among the polar and the carbonyl group (Scheme 1.101), the attack occuring from the least hindered side.



Scheme 1.101

(*ii*) **Prelog's generalisations:** Another example of asymmetric reactions of this kind is the reaction of an equimolar amount of a Grignard's reagent with the ester derived from an α-keto acid and an optically active alcohol. The keto group, which is considerably more reactive towards organomagnesium compounds as compared with the esterified carboxyl, is converted into a tertiary carbinol, while the ester group remains unchanged. The end product of such a reaction after saponification is an optically active tertiary α -hydroxy acid (eq.c, scheme 1.102). The preferred formation of one of the enantiomers is due to asymmetric induction, conditioned by the different thermodynamic stabilities of the transition states formed by coordination of the organomagnesium halide to opposite sides of the planar arrangement of the bonds at the carbonyl carbon atom.

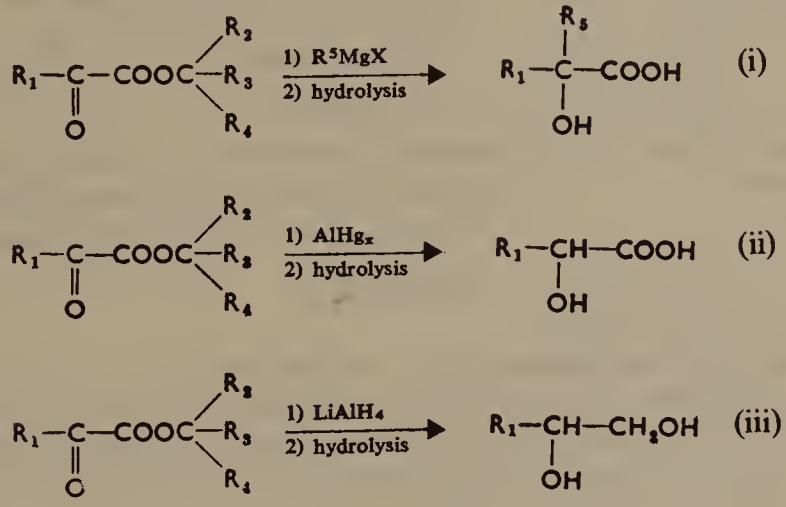


Scheme 1.102

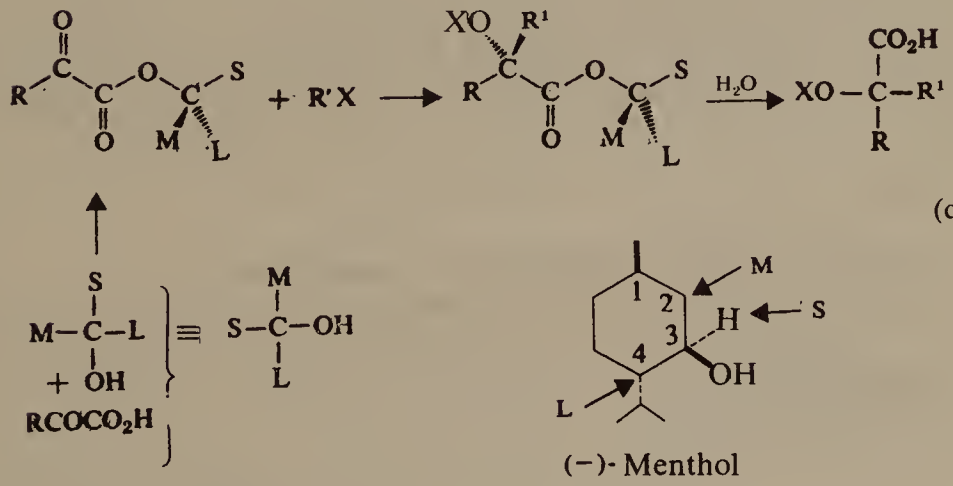
The esters of α-keto acids react with other nucleophilic reagents, like lithium aluminium hydride or aluminium amalgam. Reduction with amalgam also affords α -hydroxy acids, however, in contrast to the reaction with the Grignard's reagents, the hydroxyl group is now secondary. The hydride attacks both functions capable of reduction, the ketone as well as ester grouping, and leads exclusively to glycols with one primary and one secondary hydroxyl. However, the optical yield is in the order (i) > (ii) > (iii) as shown in Scheme 1.103.

Prelog has given an empirical correlation between the arrangement of the groups (configuration) in the isomer formed predominantly in these types of syntheses and the corresponding arrangement in the optically active alcohol *i.e.*, (—)-menthol used as an auxiliary reagent in a synthesis. This correlation is often termed Prelog's rule (eq. d, scheme 1.104). According to the rule, the arrangement of the groups in the starting material has to be specified as there are several bonds around which the molecule may rotate. Conventionally, the

molecule is oriented in such a way so as to place the carbonyl groups in antiparallel relationship and the smallest group(s) in the alcohol portion is eclipsed by the ketone carbonyl. The direction of attack of the incoming reagent R′ on the ketone carbonyl group will be from the side of the smaller of the remaining two groups in the alcohol part of the molecule, *i.e.*, from the side of the medium-sized group(M).



Scheme 1.103

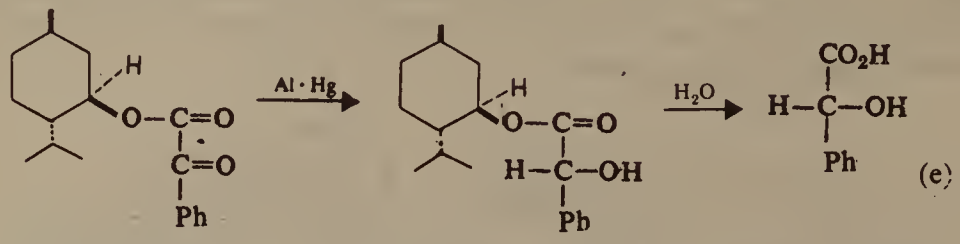


Prelog's generalisation

Scheme 1.104

Consider the chiral synthesis of (—)-mandelic acid. The phenylglyoxylate ester of (—)-menthol on reduction with aluminium amalgam yields the mandelate ester of (—)—menthol (eq. e, scheme 1.105). In this reaction, however, the ester of (—)—mandelic acid is formed to a larger extent as compared with the corresponding (+)-enantiomer. In keeping with the Pelog's rule one has to consider the bulk of the groups in menthol molecule at

C-3; where the small group(s) is H, the medium sized group (M) is the methylene at C-2 while the larger group (L) is the methine substituted with the isopropyl group at C-4.



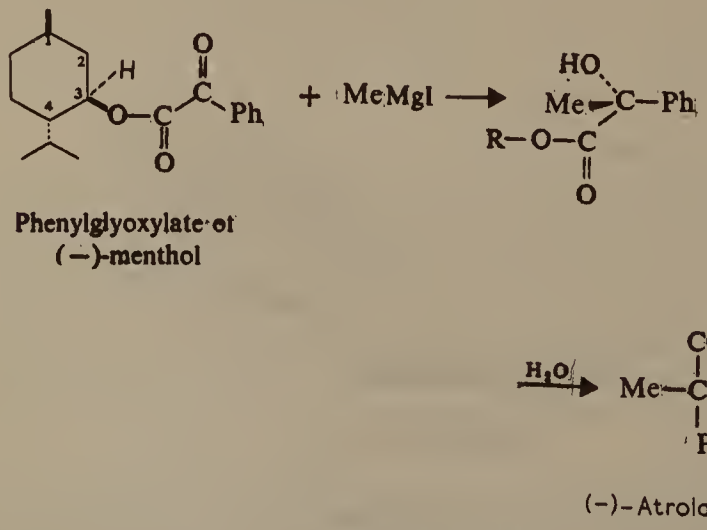
(−)-Menthyl phenyl glyoxylate

(−)-Menthyl (−)-mandelate the most populated conformation

(−)-Mandelic acid predominant enantiomer

Scheme 1.105

***(iii)* Prelog's rule and assignment of configuration:** The application of Prelog's rule has been used to determine the configuration of hydroxy acids and alcohols. An ester derived from a keto acid and an alcohol of established configuration *e.g.*, (—)—menthol is either reduced or reacted with a Gringard's reagent to yield the ester of the appropriate hydroxy acid. On the basis of the Prelog's rule, the configuration of the predominant enantiomer, formed preferentially is now known, which is related to the chiral alcohol *i.e.*, (—)— menthol. The ester is hydrolysed quantitatively to afford an acid of known configuration whose rotation is measured. Thus from these discussions (—)-atrolactic acid has the configuration as shown in scheme 1.106.



Phenylglyoxylate of (−)-menthol

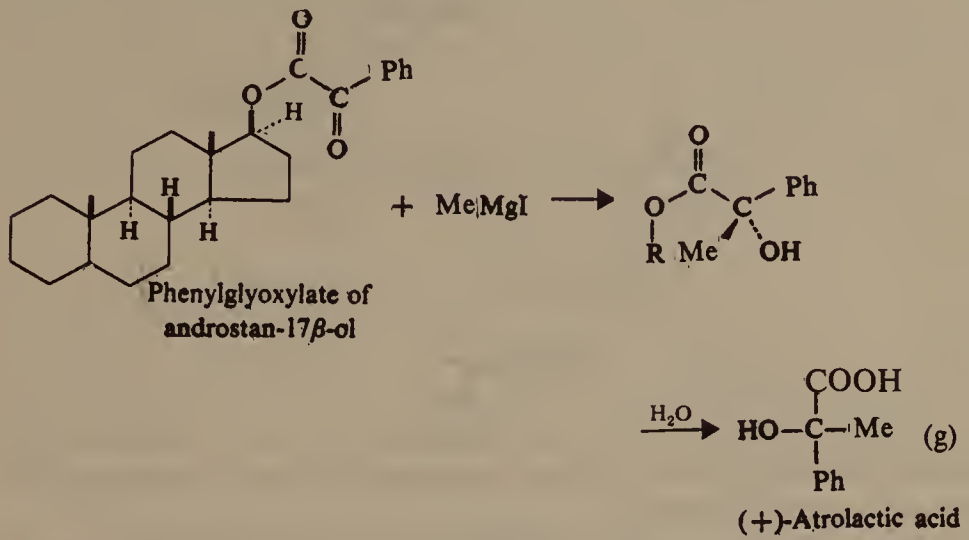
(−)-Atrolactic acid

Scheme 1.106

In a similar way one can find out the configuration of an unknown alcohol. The alcohol is esterified with phenylglyoxylic acid and the ester is reacted with methyl-magnesium iodide. From the sign of rotation of atrolactic acid

thus formed after hydrolysis, the configuration of the unknown alcohol can be determined.

Therefore, the configuration at C-17 in the case of androstan - 17 β-ol could be established as shown in eq. g. Scheme 1.107.



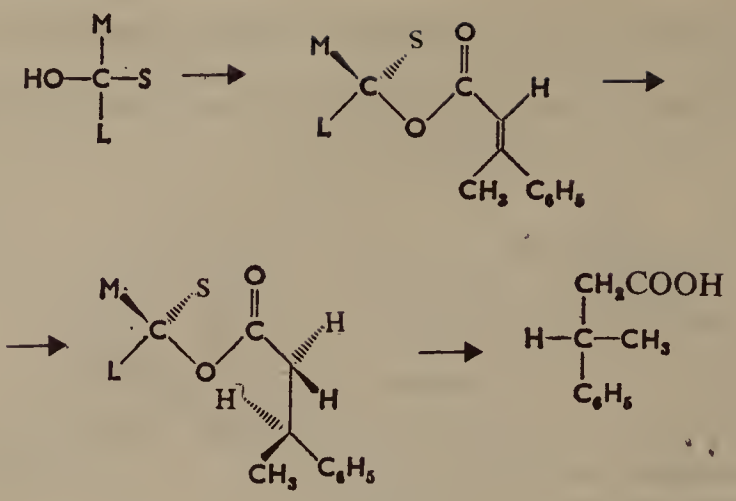
Scheme 1.107

This method helped Prelog *et al* to establish the absolute configuration of steroid hydroxy-derivatives and therefore, of the entire steroid molecule. This found agreement with the independently executed determination by means of three-dimensional X-ray technique. It is also proved that pentacyclic triterpenoids have the same absolute configuration as the respective part of the steroid molecule. This discovery was of great significance for the elucidation of the genetic relationships between plant products of these two types and has been verified by comparing the optical rotatory dispersion curves.

As in the case of Cram's rule, reversing the order in which the groups are introduced in the molecule reverses their arrangement in the predominant product. Therefore, the reaction of (—)—menthylphenylglyoxylate, $C_6H_5COCO_2C_{10}H_{19}$ with CH_3MgI followed by hydrolysis yields predominantly (—)- atrolactic acid, whereas reaction of (—)—menthyl pyruvate, $CH_3COCO_2C_{10}H_{19}$, with phenylmagnesium bromide instead gives predominantly the stereoisomeric (+)-atrolactic acid.

***(iv)* Asymmetric addition to double bond between two carbon atoms:** The catalytic hydrogenation of the esters of *trans*- β-methylcinnamic acid with optically active alcohols followed by hydrolytic decomposition is used to prepare optically active β-phenylbutyric acid (eq.h, scheme 1.108). If it is assumed that the compound approaches the planar surface of the catalyst from the side of the smallest substituent at the chiral carbon, one may derive the relationship between the configuration of the original alcohol and the acid formed.

The interpretation of the reaction is of course impeded by the uncertainty

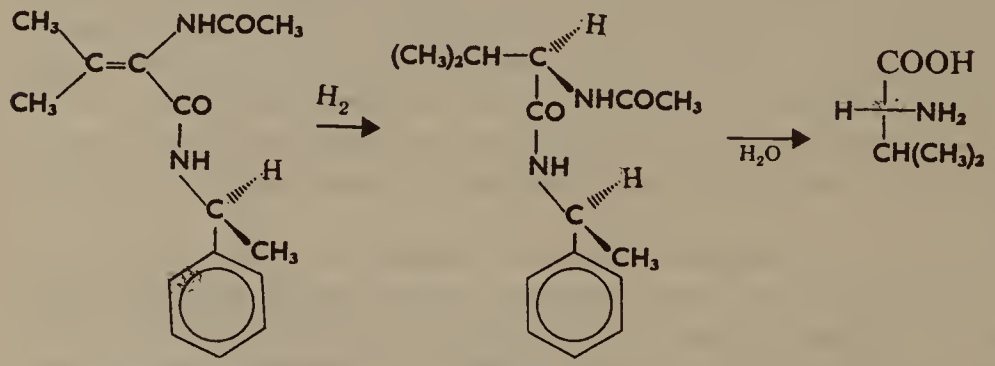


(h)

Scheme 1.108

regarding the actual conformation of the ester at the time of addition. The conformation used in (eq.h) follows from reactions with compounds of known absolute configuration.

The catalytic hydrogenation of the (—)-α -phenylethylamide of α-acetamido-β, β-dimethylacrylic acid on Raney nickel leads to a saturated amide, the hydrolysis of which yields D-valine of 39% optical purity (eq.i, scheme 1.108a).



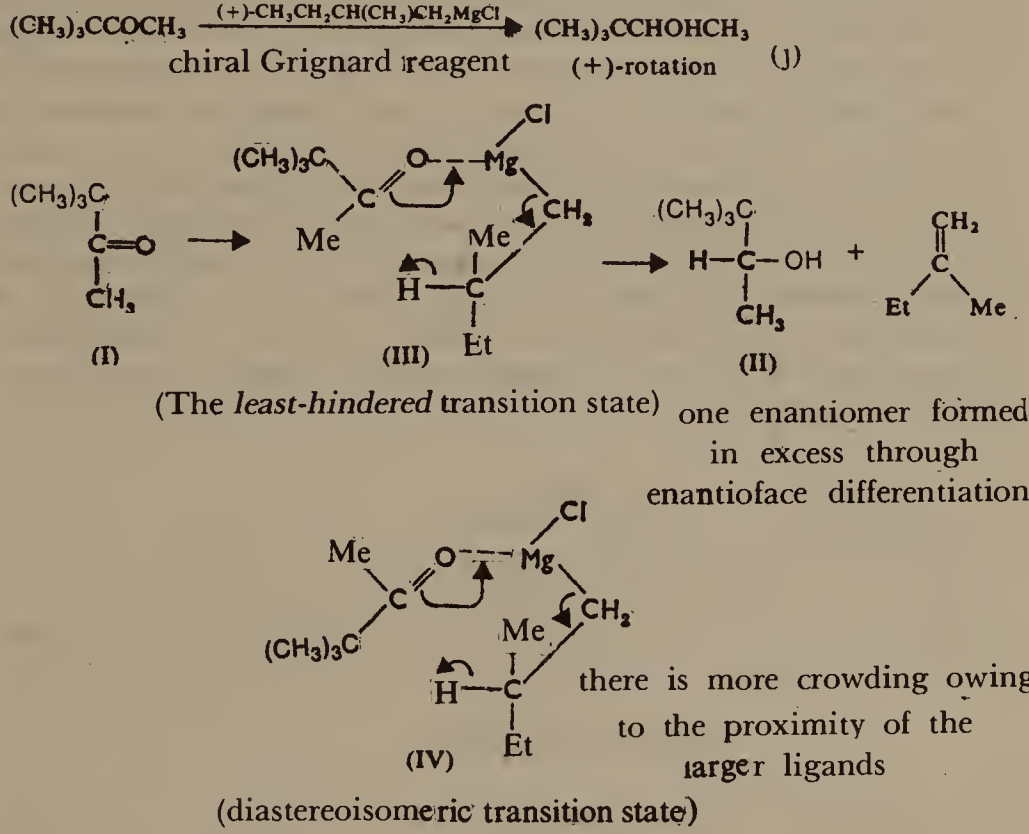
(i)

Scheme 1.108(a)

***(b)* Chiral syntheses conditioned by the presence of a chiral centre in the reagent molecule (Enantioface differentiation):** Numerous reactions are known during the course of which the optically active component may not be chemically bound to the reacting substance or to the reaction product even temporarily and even then the product is optically active. Moreover, the chirality of the auxiliary optically active substance is, as a rule, eliminated.

As a typical example, we will discuss the asymmetric reduction of ketones by means of sterically hindered, chiral Grignard reagents, *e.g.*, the reaction of *t*-butyl methyl ketone (I) in scheme 1.109 with (+)-2-methylbutyl-magnesium chloride (eq. j). Depending on the face attacked by the reagent, two diastereoisomeric transition states are generated and the reaction shows a

significant product stereoselectivity. It is postulated that the predominant product will be the one which is derived from the least hindered transition state. The secondary alcohol, thus, formed, 3,3-dimethyl-2-butanol (II), is optically active. Grignard's reagents act as reducing agents through a cyclic mechanism *via* a complex in which the magnesium atom is co-ordinated with the oxygen atom of the carbonyl, and the hydrogen atom at the β-carbon of the reagent is used for the reduction step. Moreover, the reduction proceeds



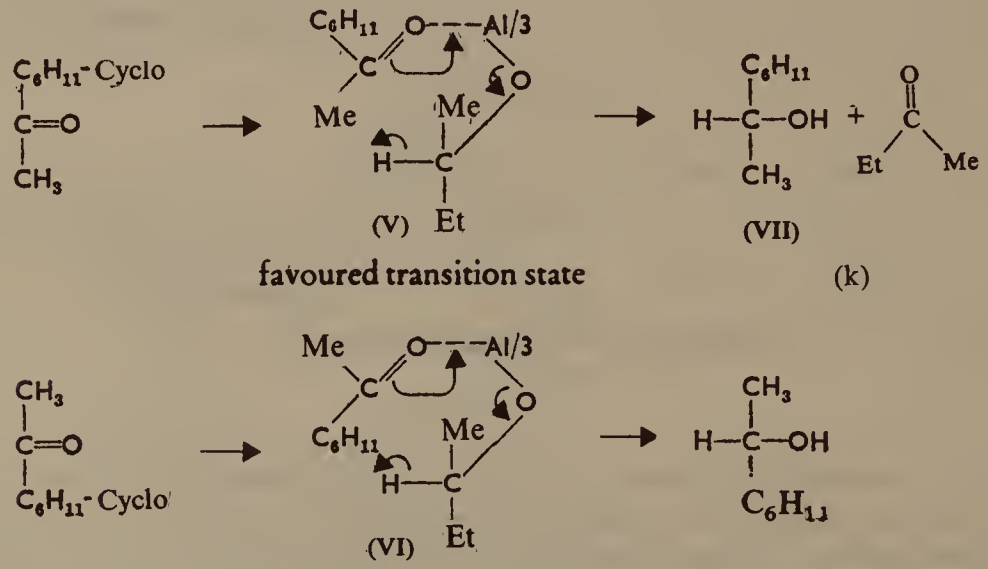
Scheme 1.109

most smoothly if the β-carbon is tertiary. If the β-carbon of the reducing agent is also asymmetrically substituted, two different transition states need consideration. Probabilities of formation of these will differ because of the differing nonbonded interactions between the side chains. The asymmetric course of the reduction therefore, can be explained by the preferential formation of lower energy six-centred transition state (III), since the larger of the groups in ketone *i.e.*, *t*-butyl and the methyl group of the reagent are well separated. Transition state (IV) however, is less probable, because there is more crowding due to the proximity of the larger groups.

The reduction of (I) involves a hydrogen atom transfer from the chiral β-carbon atom of the Grignard reagent. It has been shown that isopropyl phenyl ketone is reduced by $PhMeCHCH_2CH_2MgCl$, in which on the other hand the β-carbon atom is not chiral, to give excess of one enantiomer of $PhCHOHPr^i$. In this case the two hydrogen atoms in the Grignard reagent

are diastereotopic (by internal comparison) and so produce diastereoisomeric transition states with the ketone, thereby resulting in the formation of excess of one enantiomer over the other.

Similar considerations can be taken into account to rationalise the asymmetric reductions of ketones carried out by means of alkoxides derived from optically active alcohols in which the hydroxyl group is attached directly to the asymmetrically substituted carbon atom (eq.k, scheme 1.110). The two cyclic transition states possible during the Meerwein-Ponndorf reduction with aluminium alkoxides differ again from each other by the ease of their formation. Lower activation energy is required to achieve the favoured transition state (V), with the cyclohexyl group predominantly on the same side as the methyl group of the butoxide, than is necessary for state (VI); the former will therefore predominate and determine the configuration of the predominant enantiomer (VII). In the case of homologous alkoxide with the chiral carbon atom in the α-position to the hydroxyl group, a cyclic transition state cannot be achieved with the asymmetrically substituted atom as a component of the ring. The attempts, therefore, to perform chiral reduction with the help of (—)-aluminium 2-methylbutoxide failed but is possible in principle.



Scheme 1.110

With the reagent diborane, $(BH_3)_2$, alkenes undergo hydroboration to yield alkylboranes, R_3B (eq. 1, scheme 1.111), which on oxidation yield alcohols (eq. 2). Diborane is the dimer of the hypothetical BH_3 (borane) and in the reactions that concern us, acts much as though it were BH_3. The hydroborationoxidation process gives products corresponding to anti-Markovnikov addition of water to the carbon-carbon double bond.

$$RCH{=}CH_2 \xrightarrow{BH_3} RCH_2CH_2BH_2 \xrightarrow{RCH=CH_2} (RCH_2CH_2-)_2BH \quad \mathbf{1}$$

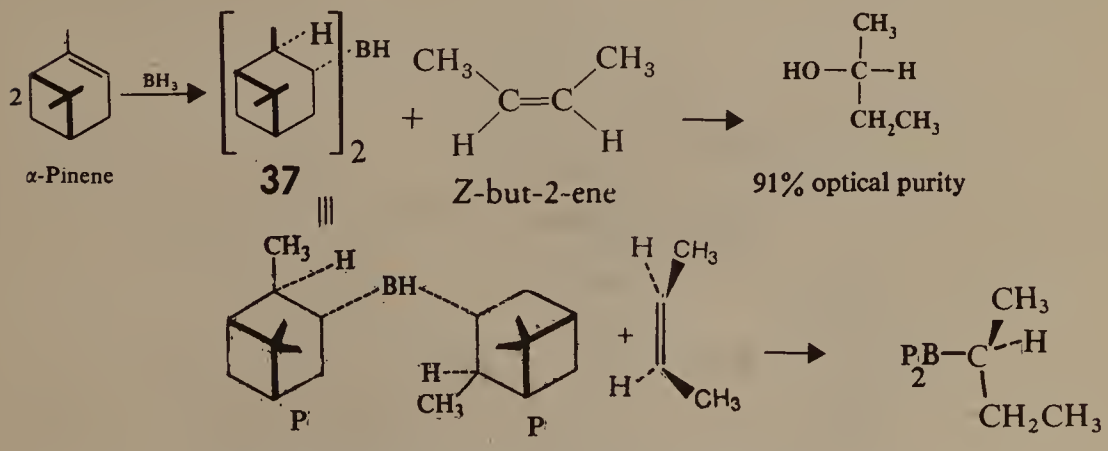
$$\xrightarrow{RCH=CH_2} (RCH_2CH_2-)_3B$$

$$R_3B + \bar{O}OH \longrightarrow R_2B^{-}(R)-O-OH \longrightarrow R_2B{-}OR + OH^- \longrightarrow R_2B{-}OH + RO^-$$

$$\xrightarrow{H_2O} R_2BOH + ROH + OH^- \quad \mathbf{2}$$

Scheme 1.111

Some hindered olefins afford only dialkyl boranes and some of these, because of their size are themselve highly selective hydroborating agents. With the use of such a borane derived from an optically active compound like α-pinene *i.e.*, diisopinocampheylborane **37** (scheme 1.112), optically active compound can be synthesized from inactive reactants. For example, enantioface differentiation of symmetrically substituted *Z*-alkenes is observed *via* the unsymmetrical addition of this chiral reagent *i.e.*, **37**. Reaction of **37** with *Z*-but-2-ene after treatment with alkaline H_2O_2 results in the formation of an alcohol with an optical purity of around 90% and represents one of the most efficient of the chiral syntheses known. The borane addition product shown (scheme 1.112) is the diastereoisomer formed in excess, and is stereoselectively converted to the alcohol. Differentiation of the enantiofaces of propene, however, is not that effective because the borane displays regioselectivity for



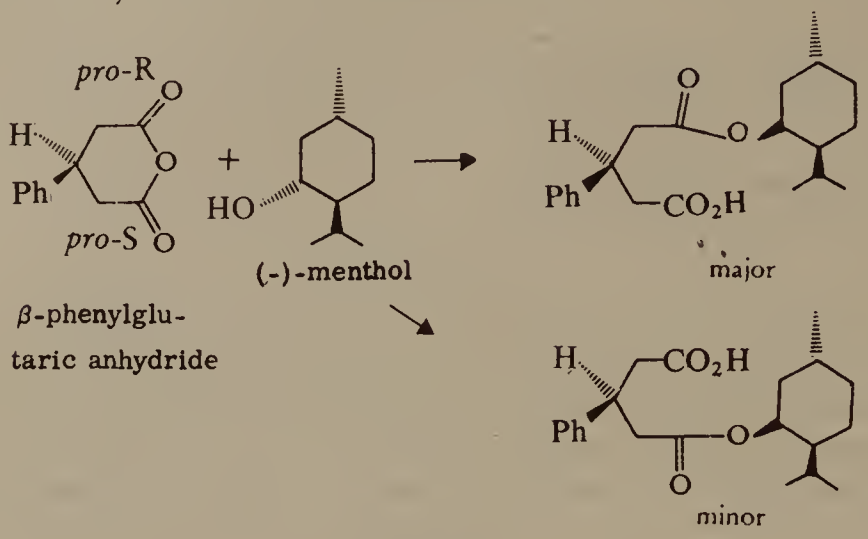
Enantioface differentiation by a Chiral borane

Scheme 1.112

addition to the CH_2 carbon atom, which is more remote from the prochiral centre.

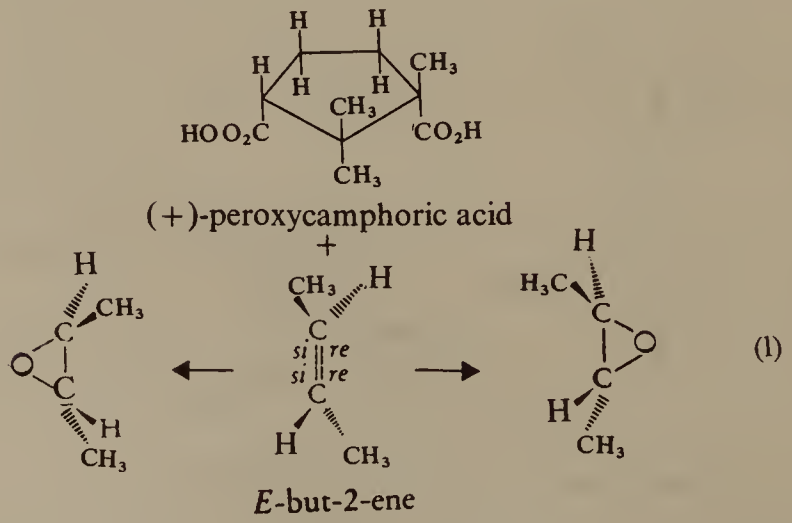
The reaction of β-phenylglutaric anhydride with (—)-menthol involves the differentiation of a enantiotopic face by a chiral reagent. The nucleophilic

attack of the alcohol (scheme 1.113) can take place either on the carbonyl carbon of the *pro-R* branch or on the *pro-S* branch. The two products of the reaction are the diastereoisomeric monomenthyl esters. The stereoselectivity of the reaction, however, is very low (54:46 ratio) probably the reaction is under thermodynamic rather than kinetic control.



Scheme 1.113

When alkenes are epoxidised with optically active peracids optically active epoxides are formed (eq.1 scheme 1.114). This is an example of addition to carbon-carbon double bond and represents an enantioface differentiation reaction. Under some defined conditions, epoxidation of *E*-but-2-ene by peroxycamphoric acid affords unequal yields of enantiomeric epoxides.



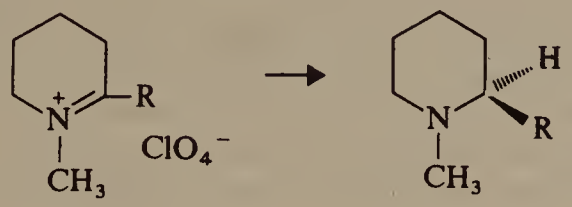
Epoxidation of *E*-but-2-ene
(enantioface differentiation reaction)

Scheme 1.114

A special case of chiral synthesis is *via* reductions with the help of optically active alkoxylithium aluminium hydrides, *i.e.*, reagents prepared by the reaction of lithium aluminium hydride with one equivalent of an optically active alcohol *e.g.*, (—)—menthol (eq. m, Scheme 1.115).

The reduction of 1-methyl-2-alkyl-Δ^2-piperidine salts yields partially optically active 1-methyl-2-alkylpiperidines (VIII). Asymmetric reduction of ketones is also carried out in a similar fashion. It has been proved that the reduction involves the hydride hydrogens and that a modification of the Meerwein-Ponndorf reaction by the generated alkoxide is not the possibility.

$$LiAlH_4 + ROH \rightarrow LiAlH_3(OR) \rightarrow Al(OR)H_3^- \quad (m)$$

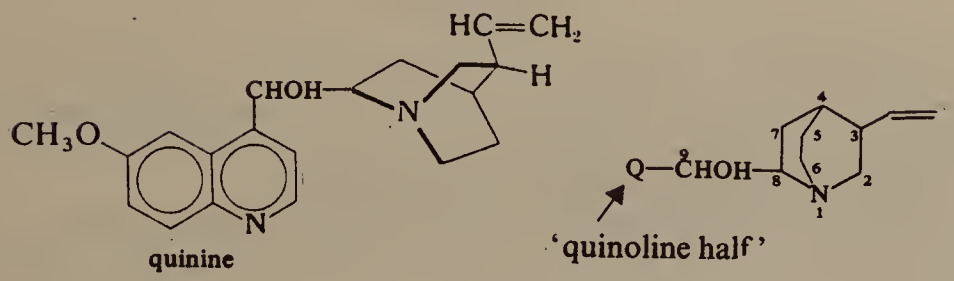


(VIII)

$$CH_3COC_2H_5 \longrightarrow CH_3CHOHC_2H_5$$

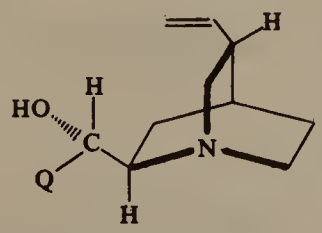
(+)-rotation

Scheme 1.115

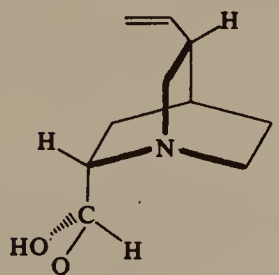


quinine

'quinoline half'



(+)-cinchonine
(+)-quinidine



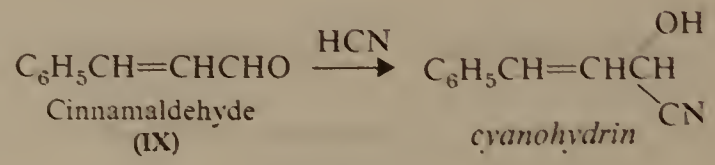
(−)-cinchonidine
(−)-quinine

Scheme 1.116

The relationship between the absolute configurations of the optically active alcohol and the reduction product was in this case determined with the help of cinchona alkaloids as the starting optically active alcohols. The reduction of methyl alkyl ketones and methyl aryl ketones in the presence of (-)-quinine and (-)-chichonidine (Scheme 1.116) gave the dextrorotatory carbinols. Conversely, however, in the presence of dextrorotatory quinidine and cinchonine alkaloids, which are epimers of the first pair at the C-8 and C-9 atoms, the levorotatory carbionals are preferably formed.

(*c*) **Chiral syntheses conditioned by participation of an optically active catalyst:** Relatively a few asymmetric reactions brought about by the presence of a simple chemical catalyst are known. The chiral synthesis of cyanohydrins, catalysed by the presence of optically active bases (alkaloids) is a typical example. The product of the reaction of an aldehyde with hydrogen cyanide is an optically active α-hydroxy nitrile which is more or less racemized depending on the nature of the catalyst and the reaction time.

The addition of hydrogen cyanide to cinnamaldehyde (IX) catalysed by cinchona bark alkaloids (Scheme 1.117) always leads to an optically active product. The optical yield is influenced principally by the configuration at C-9.



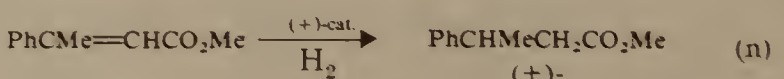
Cinnamaldehyde (IX)

cyanohydrin

Scheme 1.117

Chiral synthesis by asymmetric catalysis is being actively explored. In these reactions, a prochiral element reacts with an achiral reagent under the influence of a chiral catalyst. Examples are found in the catalytic hydrogenation of alkenes having enantiotopic faces.

Reduction of the olefinic double bonds to afford optically active compounds has thus, been achieved by using rhodium complex containing for instance (+)- or (-)-PhCHMeNHCHO as ligands (eq.n. Scheme 1.118).

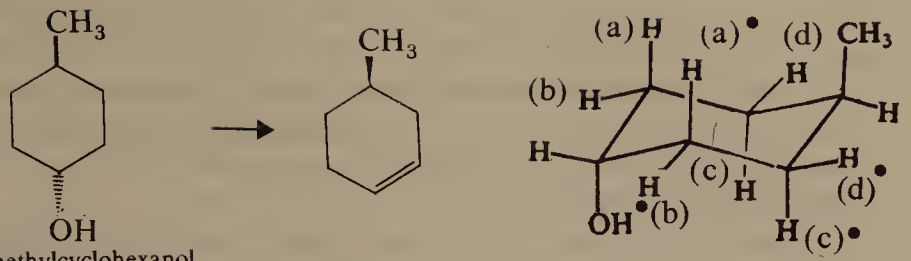


(+)-

(n)

Scheme 1.118

On dehydration, using chiral acid as a catalyst *trans*-4 methylcyclohexanol affords the olefin in small optical yield (Scheme 1.118a). The pairs of enantiotopic hydrogen atoms in the substrate have been labelled using the same small letter. For dehydration only H(a) and H(a)• have an *anti*-relationship with the hydroxyl group and it is the differentiation of these which leads to the formation of the chiral alkene.

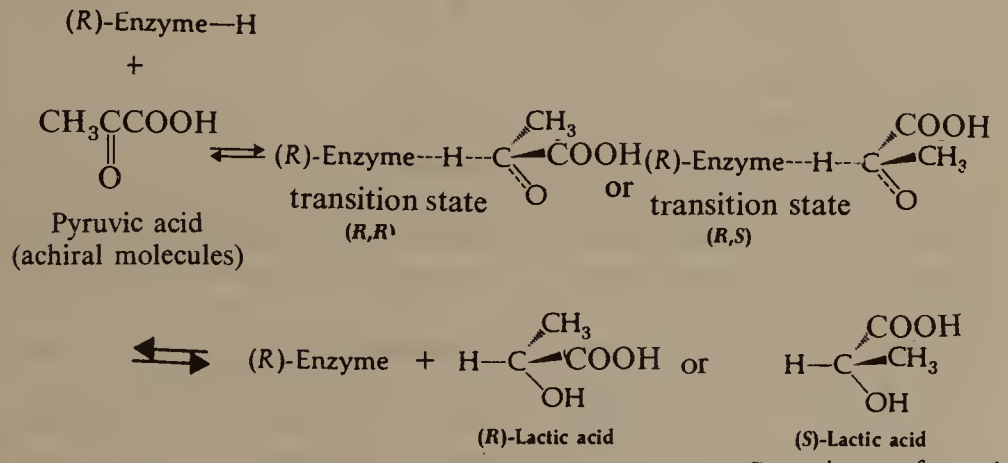


trans-4-methylcyclohexanol

Scheme 1.118a

(*d*) Chiral syntheses in biochemical systems: It may be mentioned here that in biochemical systems, the chiral synthesis is dramatically cent per cent efficient. Thus, in the laboratory, hydrogenation of pyruvic acid affords racemic modification of lactic acid, while in muscle cells this conversion is catalysed by an enzyme, lactic acid dehydrogenase (complexed with NADH) which affords only one enantiomer, *S*- (+)- lactic acid (Scheme 1.119). This stereoselectivity of the enzyme catalysed reduction is due to the fact that the pyruvate ion can bind itself to the enzyme-NADH complex is only one favourable way. NADH, therefore, is capable to transfer its hydride ion (H^-) to only one face of the pyruvate ion.

If one uses a schematic model to see why asymmetric induction is observed, he has to assume *e.g.*, that the enzyme has an (*R*) configuration. (The actual enzyme possesses many chiral centres). Transfer of hydride from the enzyme to the carbonyl group passes through transition states which lead to either (*R*) or (*S*) products. The two transition states, (*R, R*) and (*R, S*), are diastereomers, which differ in energy.



Scheme 1.119

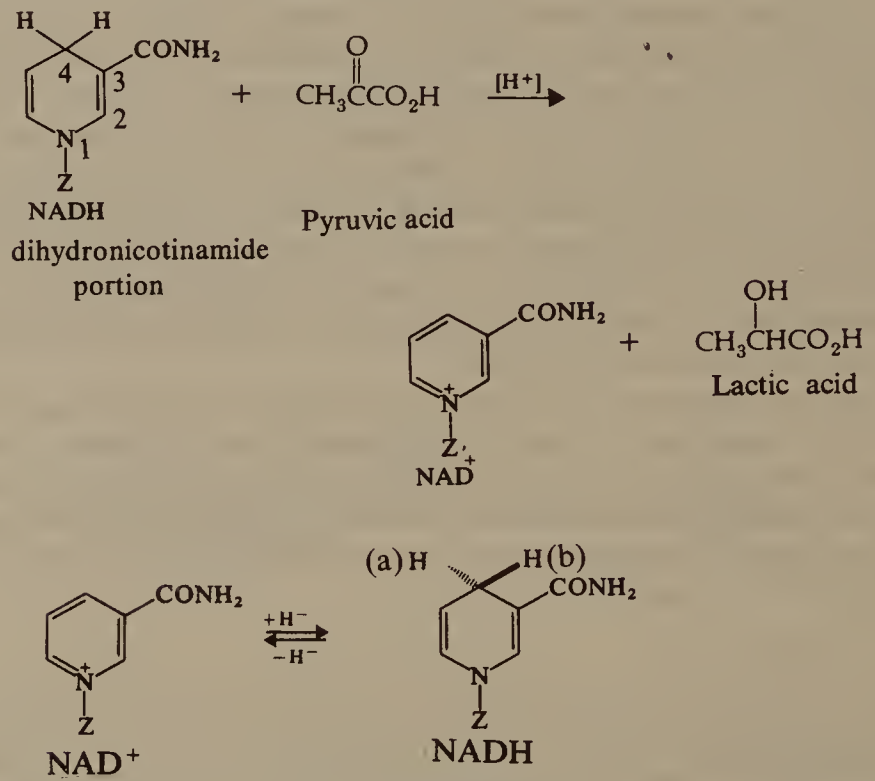
The pathway to one of the enantiomers is indeed more favourable than the one leading to the formation of the other.

Reduction of carbonyl groups in biological systems by the coenzyme nicotinamide adenine dinucleotide (NADH) is an extremely important oxidation-reduction process. The dihydronicotinamide portion of the

nucleotide transfers a hydrogen atom (presumably as a hydride) from C-4 to a carbonyl group (Scheme 1.120). Zinc ions present in the active enzyme apparently function as Lewis acids to polarize the carbonyl group.

The cofactor NAD has a pair of enantiotopic (prochiral) faces. When a hydride ion is accepted, NADH is formed which contains enantiotopic (prochiral) hydrogens at C-4.

The NAD^+-enzyme complex is stereospecific, only one hydrogen (H_a or H_b) reacting exclusively. Which face of NAD^+ is attacked and which hydride ion from NADH is transferred is dependent on the nature of the enzyme.



Scheme 1.120

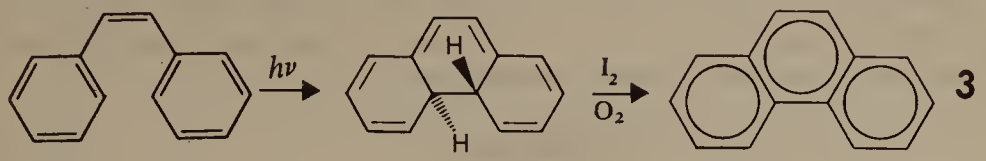
The photosynthesis of glucose in plants from carbon dioxide and water affords only the D-enantiomer to show again that at each of the four chiral carbons the synthesis is specific. Significantly the *L*-enantiomer is "unnatural" and is not metabolized by animals. Likewise, the *L*-amino acids which are the components of proteins have the *L*-configuration.

Every biochemical process is catalysed by enzymes. Enzymes are large protein molecules which have several asymmetric centres, a fact which explains the stereospecificity of biochemical reactions.

(C) Absolute Chiral Syntheses

Absolute chiral syntheses involve the formation of optically active compounds without the incorporation of other optically active compounds, *i.e.*, without the aid of the usual resolving agents. One of the most interesting

of some of the known examples of absolute chiral syntheses involves the light-induced cyclization (photoreactions) of 1,2-diarylethylenes to dihydrophenanthrene derivatives followed by oxidation with iodine and oxygen to the phenanthrene (3). When the 1,2-diarylethylene is subjected to these reactions in the presence of circularly polarized light to induce cyclization, optically active octahelicene (4) is formed (study the chirality of



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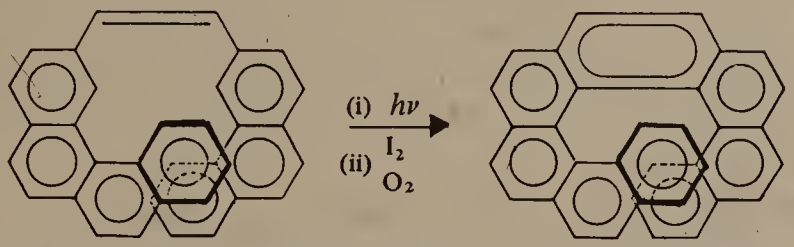


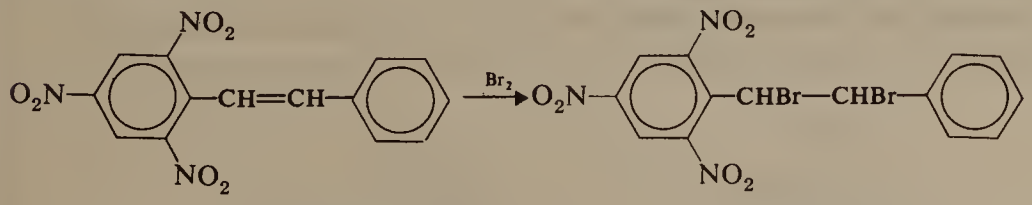
4

right-circularly polarised light ⟶ (−)-Octahelicene
left-circularly polarised light ⟶ (+)-Octahelicene

Scheme 1.121

hexahelicene). With right-hand circularly polarized light the (-)-enantiomer is formed in 2% optical purity, while, with the left-hand circularly polarized light the (+)-enantiomer is formed to the same extent. The chiral reagent here is the circularly polarized light and the two forms of the product have a nonsuperimposable mirror image relationship to each other. The role of circularly polarized light is reminescent of an optically active compound in a conventional resolution. It combines with individual enantiomers of the diarylethylene, forming a pair of excited states which are diastereomerically related and, are thus, formed and then decomposed at different rates.

Similarly, the addition of bromine to 2,4,6-trinitrostilbene (Scheme 1.22) in a beam of right-circularly polarised light gave a dextrorotatory product (5).



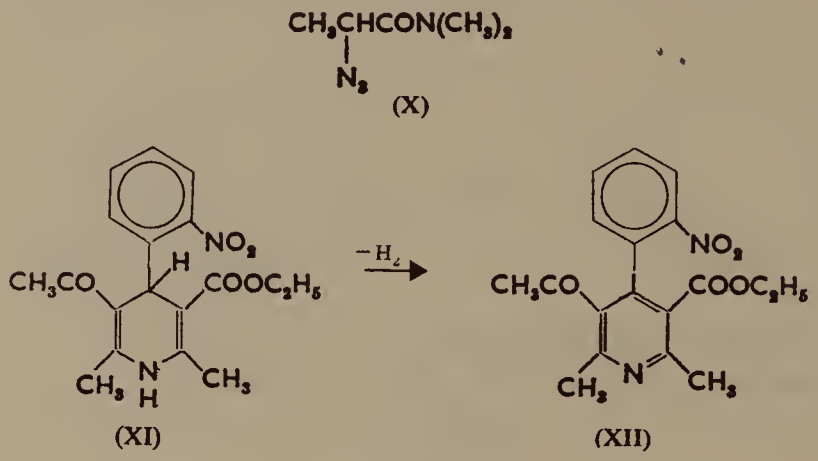
5

(+)-rotation

Scheme 1.122

Right- and left-circularly polarised light is unequally absorbed by enantiomers, provided the light has a wavelength in the neighbourhood of the characteristic absorption bands of the compound. The photochemical decomposition of (±)—*N*, *N*—dimethyl-α-azidopropionamide (*X*) in

(Scheme 1.123) may serve as an example. The decomposition occurs at a greater rate for one enantiomer than for the other, so that the unchanged amide becomes optically active. Another interesting example is the photodehydrogenation of the dihydropyridine derivative (**XI**) leading to the chiral product (**XII**). The activity of the latter is due to atropisomerism of the biphenyl type (Sec 1.21,B). In the course of the reaction, the elimination at the asymmetric carbon occurs to different extents for the two possible configurations. The configuration of the atropisomer formed is related to the configuration of the more reactive enantiomer.

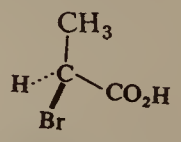


Scheme 1.123

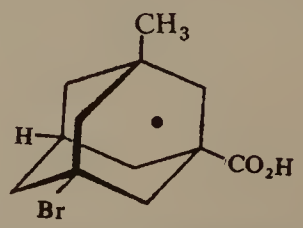
1.21 OPTICAL ACTIVITY DUE TO A CHIRAL AXIS

The chiral compounds discussed so far contain one or more chiral carbons and have their chirality specified at one or more such centres. As an additional and a specific case of chirality one may consider the suitably substituted adamantanes with four different groups at the bridgehead positions which are chiral and therefore display optical activity. The adamantane derivative presented below may be regarded as the formal analogue of 2-bromopropionic acid and is a kind of expanded tetrahedron with the same symmetry properties as any tetrahedron.

However, in some compounds with nonsuperimposable mirror images it is not possible to identify a chiral centre and it then becomes necessary to focus



2-bromopropionic acid



3-methyl-5-bromoadamantanecarboxylic acid

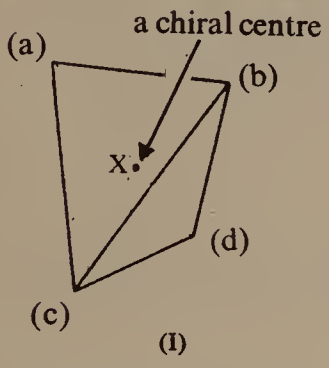
Scheme 1.124

our attention on a larger portion of the molecule. In the same sense as we have spoken of the centre of chirality in the case of compounds with a chiral carbon, we may in the case of some other compounds speak of the axis of chirality.

Whilst for models with a centre of chirality all the four groups have to be different, for ones with an axis of chirality a smaller number of differences are sufficient. As we will see later on; for models with a plane of chirality, even one difference is enough.

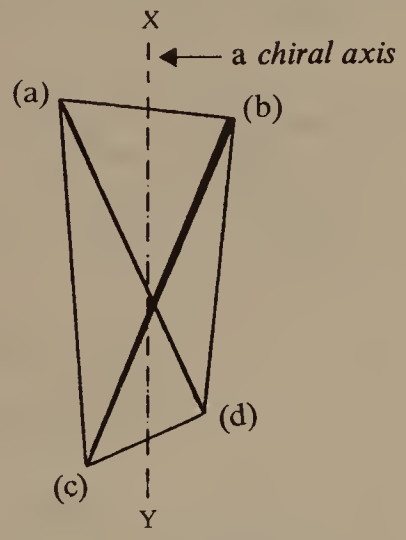
Thus, the presence of a centre of chirality is not a necessary and sufficient condition for molecular dissymmetry. The overall chirality of a molecule can be factorized into three elements[19–23], chiral centres, chiral axes, and chiral planes, while still another element of chirality is helicity.

Several important classes of chiral compounds have one or more chiral centres. Thus, for example, a chiral centre *X* can be detected in a molecule when the four different ligands *a, b, c* and *d* of a central atom *X* are located on



(I)

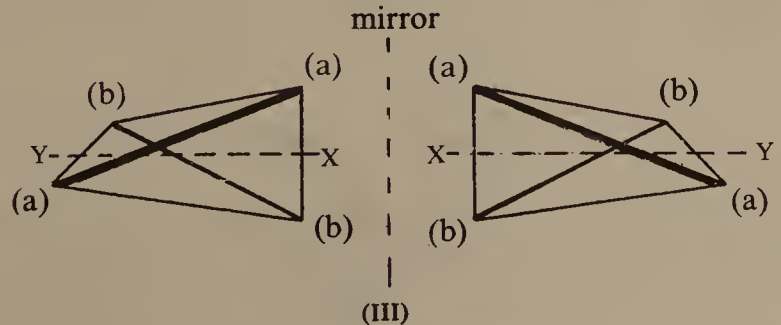
a tetrahedral molecule



an elongated tetrahedron

(II)

Production of a chiral axis by notional elongation of a tetrahedron



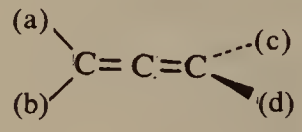
(III)

Scheme 1.125

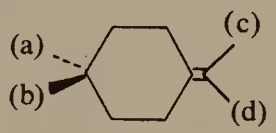
corners of a tetrahedron (I, Scheme 1.125). On speculative elongation of this tetrahedron as in II, the chiral center is extended to produce a chiral axis *XY*. In this type of an extended tetrahedron on which axial chirality is based, the conditions for chirality are much less stringent when compared to a regular tetrahedron. Indeed a reference to III shows that an extended tetrahedron will be chiral if the pair of ligands at the X end of the axis and the pair at the *Y* end constitute two different ligands, *i.e.*, the minimum condition for chirality is that the ligand $a \neq b$.

A few examples of compounds which may have a chiral axis, depending on the nature of the ligands a, b, c, d are shown in Scheme 1.126, namely, allenes **IV**, alkylidenecycloalkanes **V**, spiranes **VI**, adamantanes **VII**, biphenyls **VIII** and analogous biaryl derivatives singly bridged biphenyls, like **IX** and doubly bridged biphenyls and substituted anilines **X** and styrenes **XI.**

Several axially chiral molecules can have two fold axis as the sole element of symmetry as is the case where $a = c$ and $b = d$ for allenes **IV**, alkylidenecycloalkanes **V**, spiranes **VI**, adamantanes **VII**, and biphenyls **VIII.**

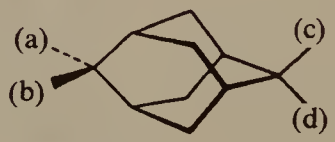


(IV)

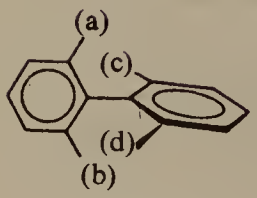


(V)

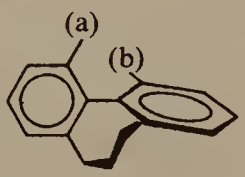
(VI)



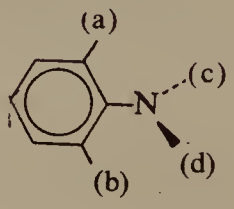
(VII)



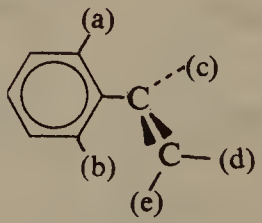
(VIII)



(IX)



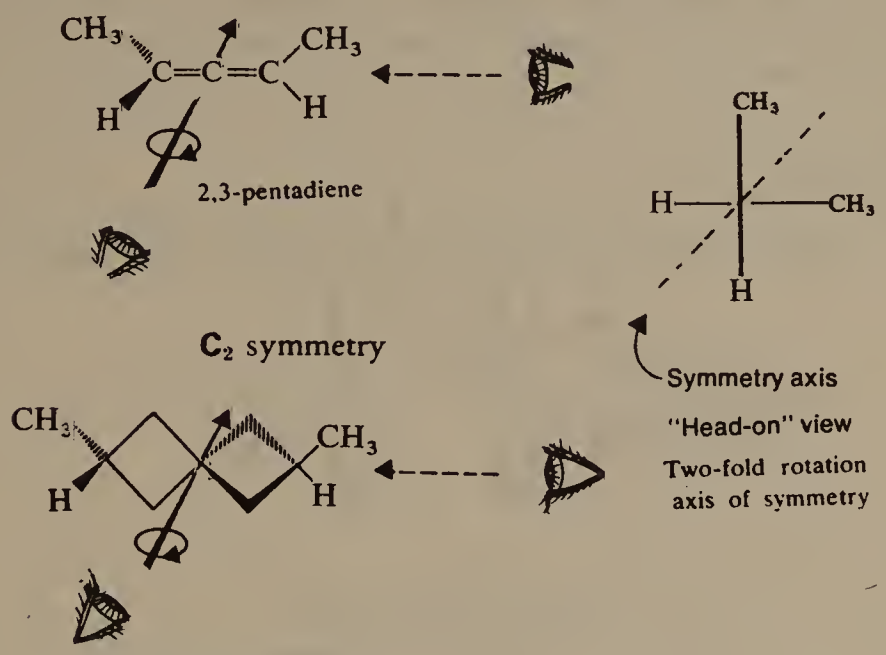
(X)



(XI)

Scheme 1.126

For example, a shrewd eye for symmetry will realize that 2, 3-pentadiene and 2,6-dimethylspiro [3,3] heptane have symmetry axes (C_2) passing through the center of the system. These axes are not easy to perceive, as these are inclined at 45° to the planes described by the terminal groups, as indicated by the "end-on" projection representations in Scheme 1.127. In many axially chiral compounds all the four ligands (a,b,c and d) may be different. These compounds are chiral with C_1 symmetry, having no symmetry elements, *e.g.*, an asymmetric allene (Scheme 1.127).



chiral allene

asymmetric $a \neq b \neq c \neq d$

(no symmetry elements) C_1 symmetry

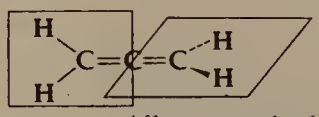
Scheme 1.127

(A) Optical Isomerism of Allene and its Derivatives

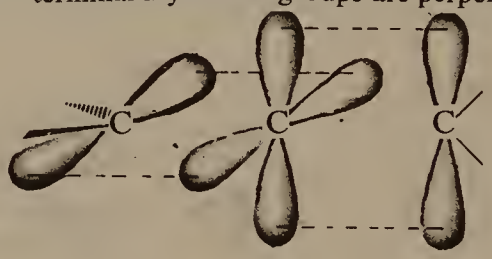
In the spatial arrangement of the cumulative double bonds of allene, the four substituents of the allene grouping are situated at the apexes of an imaginary tetrahedron, which, in contrast to the tetrahedron formed by the substituents around one carbon atom, is not regular. The irregularity of the tetrahedron (elongated tetrahedron) causes the impossibility of cyclic interchange of the

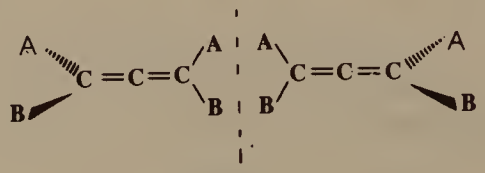
substituents. The distances between pairs of substituents differ and, therefore, in order to produce chirality it is not necessary for all of the substituents to differ. It is sufficient to have each substituent different from its nearest neighbour.

In allenes the central carbon is *sp*-bonded. The remaining two *p* orbitals are perpendicular to each other, and each overlaps the *p* orbital of one adjacent carbon atom (Scheme 1.128), forcing the two remaining bonds of each carbon into perpendicular planes. Therefore, allenes of the type ABC=C=CAB ($A \neq B$) are chiral, (not superimposable on their mirror images) and exist as enantiomers despite the absence of asymmetric atoms. Thus, in allenes one has a situation of restricted rotation giving rise to perpendicular disymmetric planes.



Allene terminal mythelene groups are perpendicular to each other

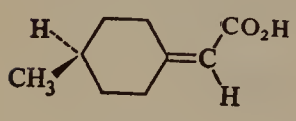




Mirror

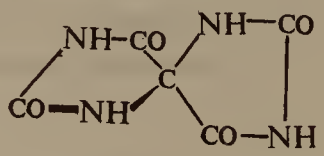
Scheme 1.128

The replacement of one double bond in an allene by a ring does not alter the basic geometry of the system and suitably substituted compounds, therefore,

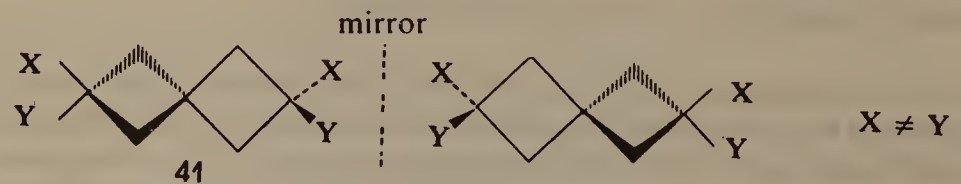


38

39



40



41

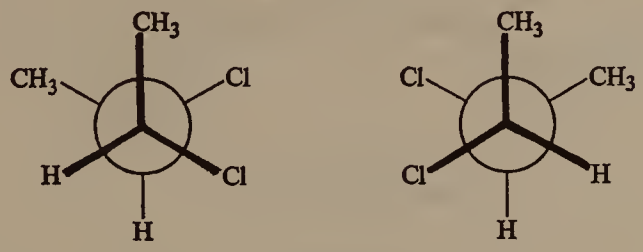
Scheme 1.129

exist in optically active forms, *e.g.*, 4-methylcyclohexylideneacetic acid **38** (Scheme 1.129). Related compounds in which sp^2 - carbon is replaced by nitrogen,*e.g.*, compound **39** has also been obtained as enantiomers.

The replacement of both double bonds in an allene by ring systems gives a spiran; appropriately substituted compounds have been obtained in optically active forms, *e.g.*, **40** and **41**.

(B) Optical Isomerism in Biphenyls (Atropisomerism)

The two conformations of *meso*-2, 3-dichlorobutane are nonsuperimposable mirror reflections of each other (Scheme 1.130). It is, however, not possible to separate the enantiomeric forms since rotation about the central C-C bond occurs very rapidly resulting in the inter-conversion of the two conformations. When the barrier to rotation about a C-C exceeds about 80 kJ per mole in some suitably substituted compounds, the rotation at room temperature is slow enough to allow isolation of the two optically active isomers. This is so in the case of some biphenyls.

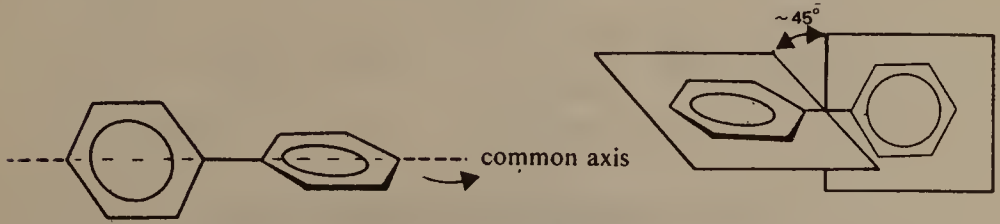


meso-2,3-dichlorobutane

Scheme 1.130

In the crystal, both benzene rings of biphenyl lie in the same plane (Scheme 1.131). However, in solution and vapour phase the two rings are twisted with respect to each other by an angle of 45^0 due to steric interactions between the 2,2′ and 6,6′ pairs of hydrogens. These interaction effects are further enhanced by *ortho* substituents larger than hydrogen so that:

1. The rotation about the bond linking the two phenyl rings does not occur due to steric hindrance between the bulky *ortho* substituents.
2. The two rings lie in different planes to make it impossible for the molecule to achieve a symmetrical structure shown for example by the planar formula of *O,O′* - difluorodiphenic acid (Scheme. 1.133).



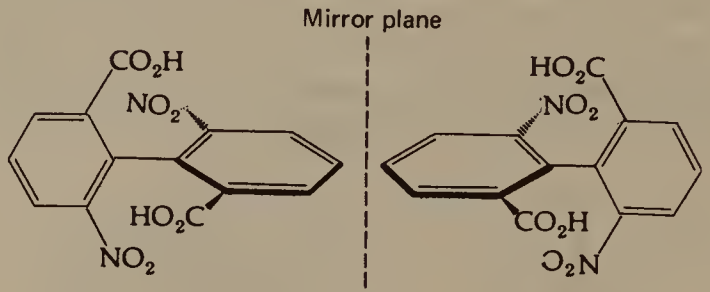
biphenyl

42

Scheme 1.131

Isolable stereoisomers resulting from restricted rotation about single bonds are called atropisomers, while rotamers are stereoisomers obtained by rotation about a single bond (Sec. 4.1).

In their geometry, atropisomers approach allene derivatives and, have the axis of chirality but not the centre of chirality. Optical activity is generated even if the substituents are the same, as in the case of the allenes. This means that each aromatic ring has to be asymmetrically substituted with regard to the axis passing through the single bond between the phenyl groups and the *para* positions as in **42** (Scheme 1.131). Thus 6,6′ - dinitrobiphenyl-2,2′ dicarboxylic acid **43** (Scheme 1.132) can be resolved into its enantiomers and each enantiomer is stable indefinitely. The nitro and carboxylic groups are so bulky that they cannot pass by each other.

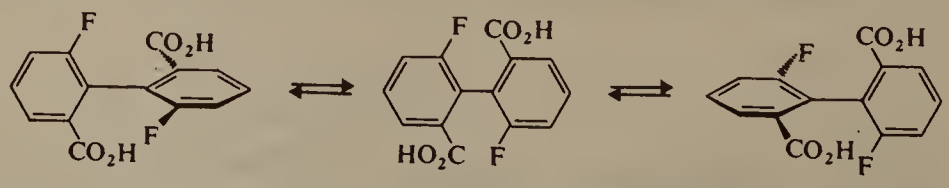


43

Biphenyl atropisomers

Scheme 1.132

In the case of compounds with an asymmetric atom, or in the case of allenes, one enantiomer may interconvert into the other only if a chemical bond is ruptured and formed again, *i.e.*, by means of a chemical reaction. In the case of atropisomers, however, the other enantiomer may be formed if the substituent in one *ortho*-position is successful in "pushing through" past the smaller *ortho*-substituent on the second ring. The stability of the optical activity of atropisomers may thus serve as a measure of the size (effective volume) of the substituents. When the bulky nitro groups are replaced by the smaller fluorine atoms the resulting compound, 6,6′-difluorobiphenyl-2,2′-dicarboxylic acid can still display optical activity (Scheme 1.133). However, the compound racemizes readily, *i.e.*, the enantiomers are readily



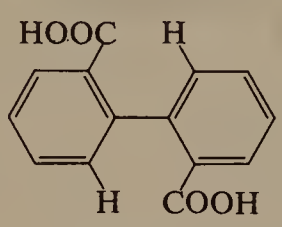
planar

6,6′-difluorobiphenyl-2,2′-dicarboxylic acid

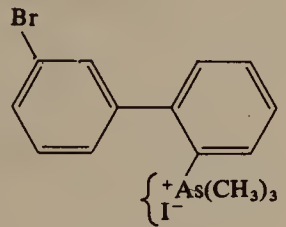
Scheme 1.133

interconverted involving the squeezing of the fluorines past the adjacent carboxyl groups *via* the planar conformation. Once they reach the planar conformation the chirality is lost and racemization results. This transition state is congested, involves energy and is measurably slow. All attempts to resolve diphenic acid have failed, the slipping of a small hydrogen past the carboxylic acid group is easy and leads to rapid racemization of enantiomers.

Although the hydrogen atom is quite small, optically active compounds exist with two or even three *ortho*-positions of the biphenyl occupied by hydrogen. In the second case the benzene ring that is unsubstituted in the *ortho*-positions must have a substituent in a *meta*-position. The *meta*-substituent has no influence on rotation but it creates the necessary chirality of the molecule; 3-bromobiphenyl-2-trimethylarsonium iodide 44 (Scheme 1.134) may serve as an example.



diphenic acid



44

Scheme 1.134

Its (+)-camphorsulphonate undergoes mutarotation. The trimethylarsonium group is large enough to be impeded by the *ortho*-hydrogen atoms. Attempts to isolate the active biphenyl compound have failed because it racemized rapidly.

Usually, however, two and more, often three or four *ortho*-positions are occupied. Measurements have shown that the sum of the effective radii of two groups in *ortho*-positions in different rings has to be larger than 2.9 Å, in order to prevent the molecule from occupying a symmetrical conformation with its two rings in one plane. The effective radii of certain atoms and groups are shown in Table. If for instance, there is a hydrogen in one *ortho*-position, at least a bromine atom has to be attached to the second ring to stand a chance of getting an optically active compound.

TABLE 1.4 : Effective Radii of Atoms and Groups (Å)

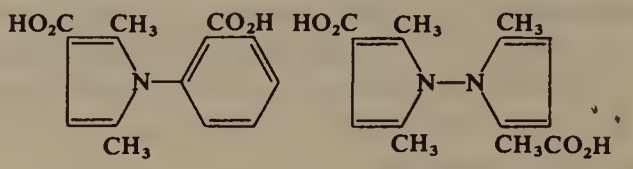
Group	F	H	OH	CO_2H	NH_2	CH_3	Cl	NO_2	Br	I
Radius	1.39	0.94	1.45	1.56	1.56	1.73	1.89	1.92	2.11	2.20

Atropisomerism is not limited to biphenyl derivatives. It is encountered in the series of binaphthyls, bipyridyls, phenylpyrrole, bipyrrole, *etc.*

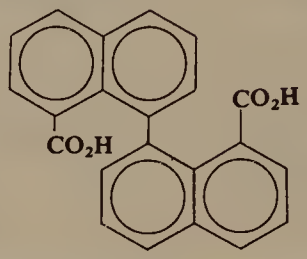
Atropisomers may also be formed by compounds in which one benzene

ring is replaced by a substituted ethylene group or another suitable group, *i.e.*, one has other examples of restricted rotation about single bonds.

In the case of 5-amino-2,4,6-triiodo-N,N,N′, N′-tetramethyl-isophthalamide, the *cis* and *trans* isomers have been synthesized. The $CONH_2$ groups are imprisoned between the two bulky iodine atoms and the situation, therefore, does not leave any room for these groups to rotate. The *cis*-isomer is a meso form, while the *trans*- isomer is chiral and has been resolved.

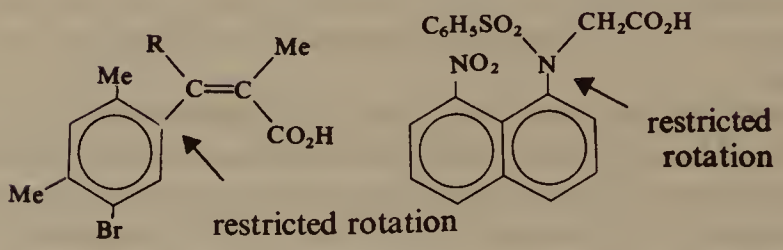


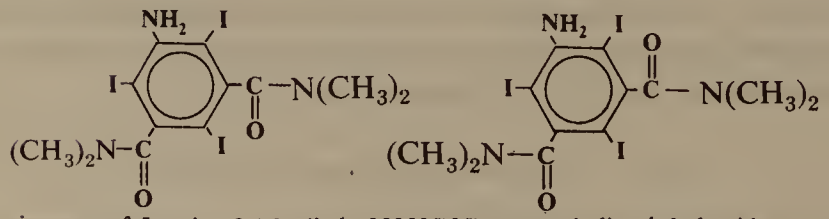
N-phenylpyrrole *N,N′*-bipyrryl



1,1′-Binaphthyl-8,8′-dicarboxylic acid

Scheme 1.135





isomers of 5-amino-2,4,6-triiodo-N,N,N′,N′-tetramethylisophthalamide

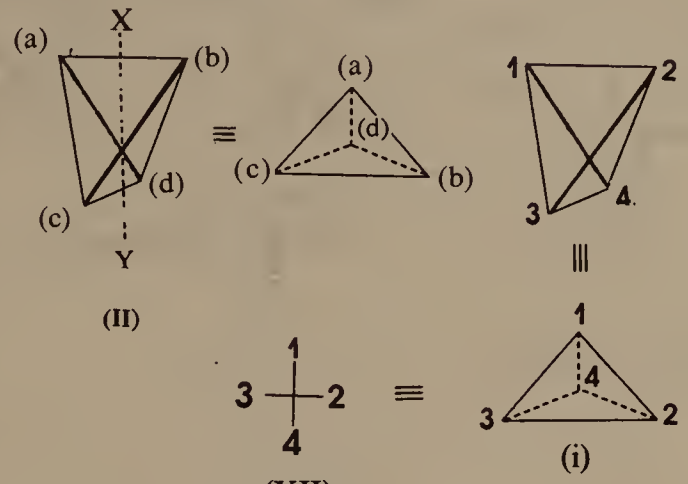
cis trans

Scheme 1.136

(C) Nomenclature of Some Compounds with Chiral Axis

When the sequence rule is to be applied to axial chirality for the specification of absolute configuration, an additional rule in needed which

states that the *two near groups precede the two far groups.* By doing this the *(R)* or *(S)* designation of a chiral axis becomes independent of the way the axis is viewed. When one views structure **II** (Scheme 1.137) from the X end, and if a > b and c > d, the sequence ot priorty shown in (i) is obtained and according to usual procedure (sec. 1.8) if (i) is viewed from the side remote from 4, then **XII** is obtained which displays a clockwise path 1→ 2→ 3 to show that the arrangement II is *R* - configuration.

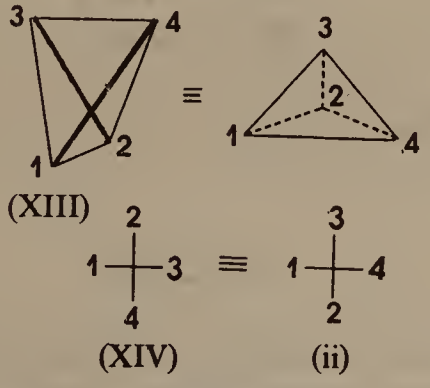


(XII)

(*R*)-configuration

Scheme 1.137

However, if **II** is viewed from Y end , then pair (c) and (d) will represent 1 and 2 and pair (a) and (b) will be 3 and 4 to give **XIII** (Scheme 1.138) and then (ii) which by two interchanges of groups gives **XIV**, which still represents a clockwise path (1→2→3), *i.e.*, *R*-configuration.

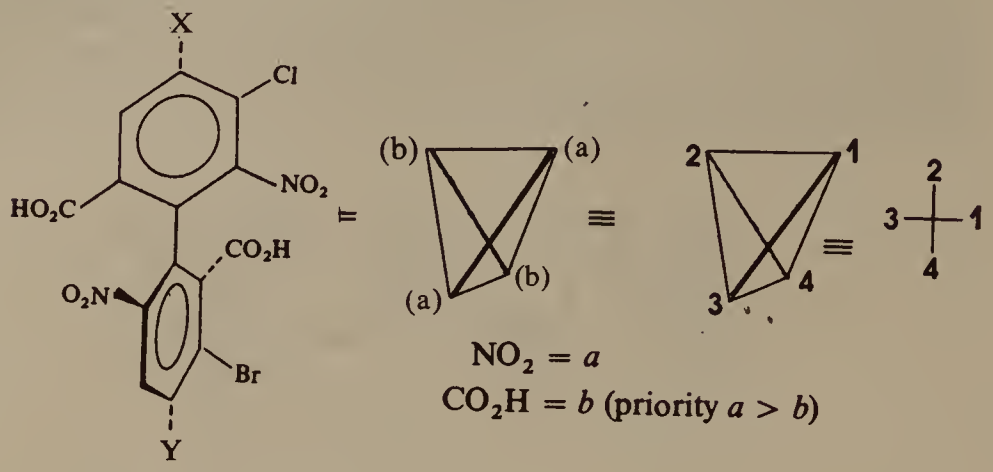


two interchanges

Scheme 1.138

In the case of chiral biphenyls[24], firstly the four *ortho*-substituents are examined and in case these are different as pairs *i.e.*, 2-6 and 2′-6′ these are selected for nomenclature purposes. Thus molecule **XV** (Scheme 1.139) is of

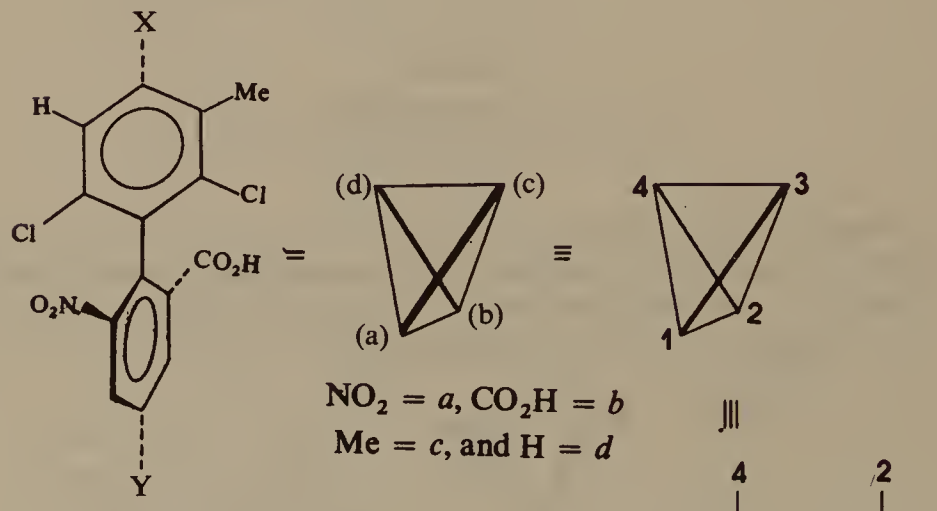
S-form (1→ 2→ 3 anticlockwise). In the case of XVI, however, since *ortho*-substituents in upper ring are identical *i.e.*, (Cl), the groups H and CH_3 — are selected as a pair and the configuration of **XVI** is found to be *(S)*.



$NO_2 = a$

$CO_2H = b$ (priority $a > b$)

(XV) (*S*)-form



$NO_2 = a$, $CO_2H = b$

Me = *c*, and H = *d*

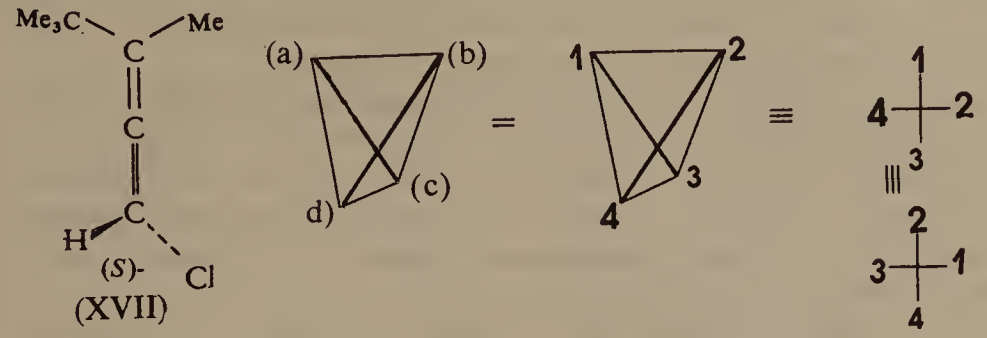
(XVI) (*S*)-form

Scheme 1.139

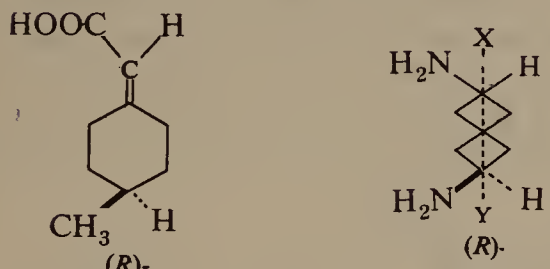
Specification of absolute configuration of other classes of compounds with chiral axis is done in way similar to that of biphenyls. Thus, allene **XVII** (Scheme 1.140) in which the chiral axis passes through the double bonds has the (*S*) configuration. Other examples of a spirane **XVIII** and alkylidenecycloalkane **XIX** are presented.

Some spiranes like **XX** and **XXI** (but not **XIX**) are now recognized to be centrally chiral. Indeed, besides the centrally chiral molecules lacking any element of symmetry, molecules with one twofold-axis of symmetry can

possess chiral centers of stereoisomerism whose configuration is not to be defined on the lines of axially chiral compounds.[22,23]



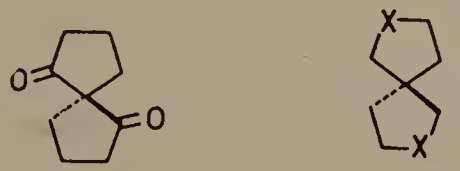
(XVII)



(XVIII) (XIX)

Scheme 1.140

For compounds with several elements of chirality, the designation of the absolute configuration of the chiral axis as (*R*) and (*S*) may lead to insufficient clarity. For these molecules the prefixes (a*R*) and (a*S*) are used to show that the stereochemical descriptor refers to a chiral axis.



(XX) (XXI)

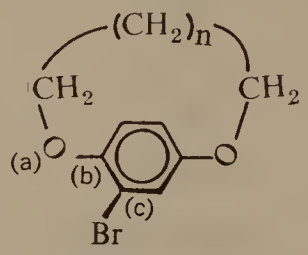
Scheme 1.141

1.22 OPTICAL ACTIVITY DUE TO A CHIRAL PLANE

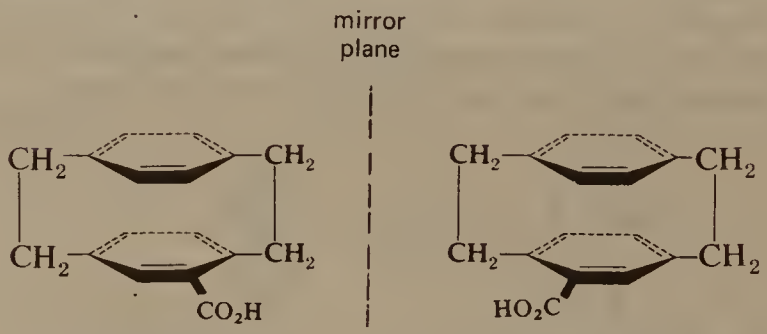
If one examines a compound[7a] like **45** (Scheme 1.142), the plane containing the substituted benzene ring and the two oxygen atoms specifies a plane of chirality. The molecule is chiral, though it does not have any center or axis of chirality. The other enantiomeric form of **45** will have the bridge on the opposite side of the chiral plane. Consider the analogous molecule 2-bromohydroquinone without the polymethylene bridge. The plane containing the

substituted benzene ring and the two oxygen atoms now represents the plane of symmetry and this attains the status of a chiral plane only when the polymethylene bridge is incorporated into 2-bromohydroquinone. Thus, the derivatives of hydroquinone, polymethylene ethers and substituted paracyclophanes are optically active having a plane of chirality.

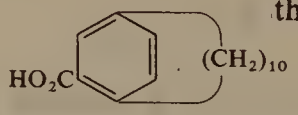
Optically active forms of **45** have been isolated. The methylene ring is perpendicular to the plane of the benzene ring; substituent —Br, prevents the rotation of the benzene nucleus inside the large ring. Paracyclophanes **46** have also been isolated in optically active forms. In this molecule, the planes of the two benzene rings are approximately parallel, the carboxyphenyl ring cannot rotate to give the enantiomer. When each bridge contains four methylene groups, the compound can not be resolved as the carboxyphenyl ring can now rotate to give the enantiomer. The simple paracyclophane **47** has been resolved because its benzene ring cannot rotate in such a way that the carboxyl group goes through the alicyclic ring.



45 (*R*)-



paracyclophane **46** the carboxyphenyl ring cannot rotate to give the enantiomer



47

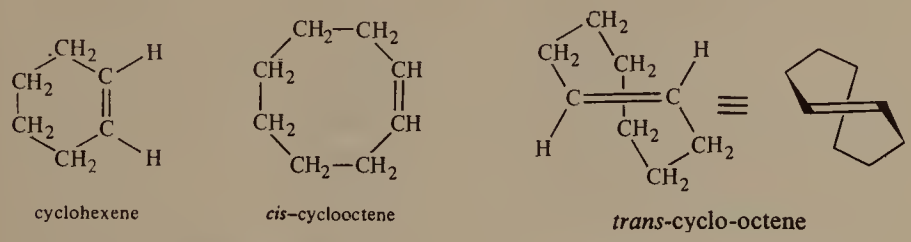
Scheme 1.142

To assign configuration to compounds with chiral planes the sequence rule is extended by choosing a pilot atom. This is a priority atom directly linked to the plane. In arrangement **45**, the pilot atom is the carbon atom of

the methylene group on left-hand side. One starts from this atom and classifies (sequence rule) the atoms of the plane as these are encountered along the bonds. One then searches the sequence-rule- preferred path from the pilot atom, till a clockwise (*R*) or counterclockwise (*S*) rotation could be traced while viewing the arrangement in the molecule from the pilot atom. In the molecule 45 this path is O—C—C (Br), which is clockwise and thus the configuration is (*R*). The prefixes (*pR*) and (*pS*) are used to show that the designation relates to planar chirality.

Another special example of planar chirality is *trans*-cyclooctene (Scheme 1.143). The introduction of a *trans*-double bond into rings containing six carbon atoms or less is not possible since it would introduce large strain in the molecule. *Trans*-cycloheptene has only been detected with spectrometers. It has a short lifetime and has not been isolated.

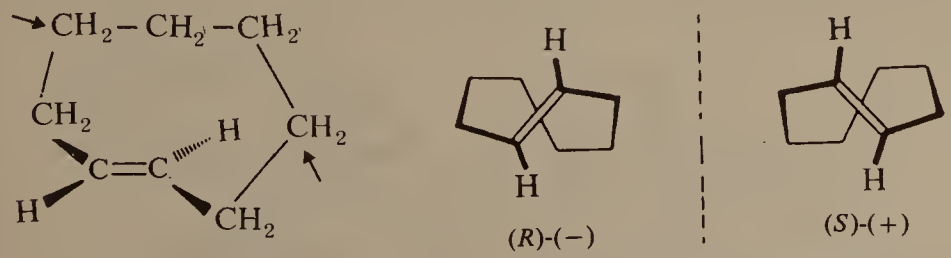
Trans-cyclooctene, on the other hand, has been isolated. The ring is large enough to accommodate the geometry required by a *trans* double bond, and thus *cis*- and *trans*- forms of cyclooctene have independent existence.



Scheme 1.143

In *trans*-cyclooctene, like some biphenyls, the rotation around the bonds in the system is indeed severely restricted to make the molecule capable of existing as enantiomers. In *trans* cyclooctene the interconversion of enantiomers requires a double rotation process *i.e.,* a rotation of the methylene groups at C-5 and C-6 through the ring followed by a similar rotation of the *trans*-disubstituted double-bond portion of the molecule. The energy barrier for this process is significantly high so that the rotation is slow enough to allow the preparation and characterisation of its enantiomers.

In the case of larger cyclo-alkenes, their enantiomers can exist, however, the

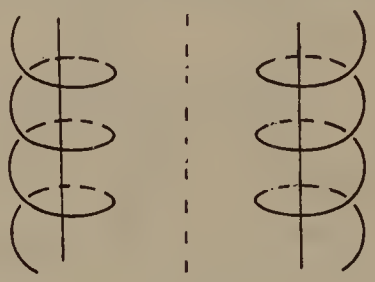


Scheme 1.144

barriers to rotation are low, leading to short lifetime of the pure enantiomers at room temperature. In *trans*-cyclooctene[7a] **XXII** (Scheme 1.144), the chiral plane contains the two double-bonded carbon atoms, as well as the two hydrogens and the two carbons immediately adjacent. Two equivalent pilot atoms therefore, can be detected in the arrangement drawn in **XXII**. Each leads to the (*S*)-configuration, because both paths are C—C=C. The enantiomers of *trans*-cyclooctene have been resolved and their absolute configuration determined as (*R*)—(-) and (*S*)—(+). For the discussion of helical chirality of *trans*-cyclooctene see (Secs. 1.10E and 1.23).

1.23 OPTICAL ACTIVITY OF COMPOUNDS DUE TO HELICITY

Helices **XXIII** (Scheme 1.145) are chiral objects, a right-handed helix (a clockwise rotation when viewed along the axis and moving from the front to the rear) is designated *P* (plus) while a left-handed helix is *M* (minus).



M- (minus, left-handed) *P*- (plus, right-handed)

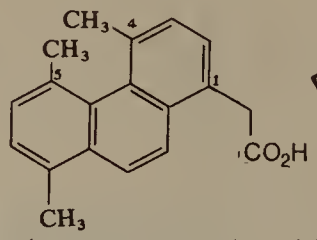
(XXIII)

helical configuration

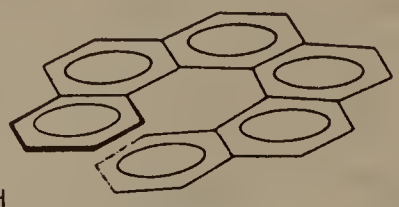
Scheme 1.145

The concept of helicity provides a simple method for designating the chirality of compounds with this feature.

The terminal benzene rings in hexahelicene (Scheme 1.146), for example, cannot occupy the same plane without coming in serious conflict with one another. Therefore, the molecule is forced to adopt a nonplanar shape in which one side of the molecule must lie above the other because of crowding.



4,5,8-trimethyl-1-phenanthrylacetic acid

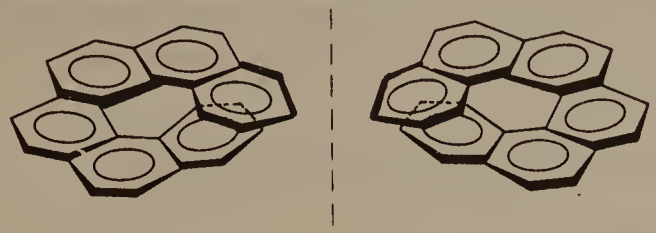


hexahelicene

(P)-(+)

Scheme 1.146

Hexahelicene is chiral by virtue of its helical shape which could be either left- or right-handed in orientation. The entire molecule is infact less than one full turn of the helix, but this is enough to generate chirality in hexahelicene, it has been resolved into remarkably stable enantiomers (Scheme 1.147) which display spectacularly high optical activity and correspond to 'right' and 'left-handed' spirals.

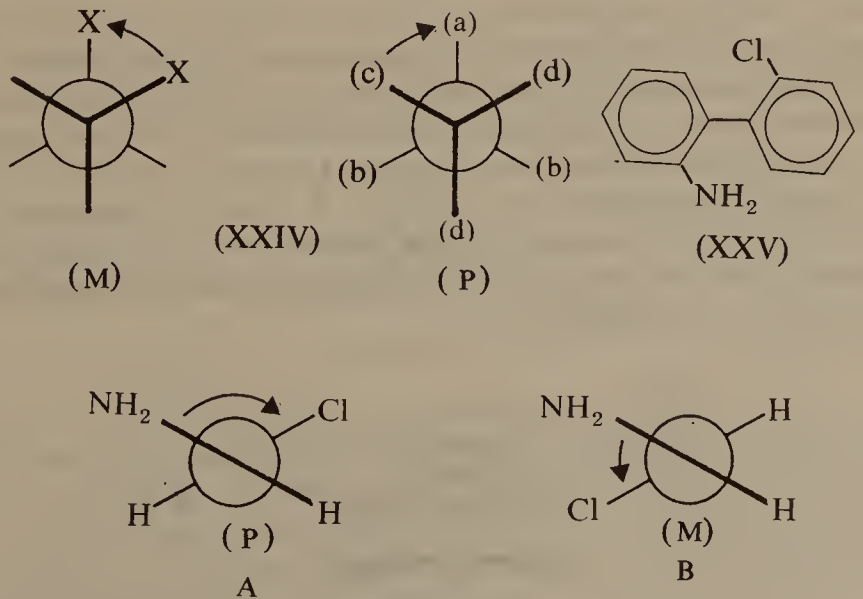


Enantiomeric forms of hexahelicene

Scheme 1.147

In hexahelicene the middle rings (3 and 4) lie in a plane, while the terminal rings (1 and 6) fall above and below the plane respectively.

Aromatic compounds represent another category, in which suitable substitution forces the molecule to buckle from the most favourable, planar arrangement. For example, phenanthrene, a planar molecule, when substituted in positions 4 and 5, for instance, by methyl groups becomes somewhat skewed and exists as two enantiomers. Consequently it has been possible to isolate the optically active 4,5,8-trimethyl-1-phenanthrylacetic acid (Scheme 1.146). Conformational helicity is encountered in some secondary structures of polypeptides, and many proteins have significant portions of their chains stabilized in the *α-helix*, which can be either left-or right-handed.

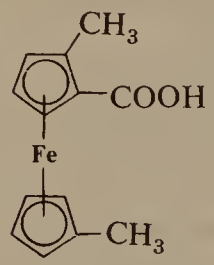


Scheme 1.148

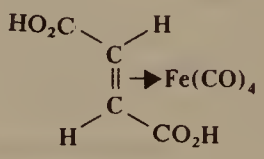
The helical nomenclature of the configuration or conformation may be useful to designate molecules whose helicity is not externally clear. Chiral conformations of ethane derivatives, for example, can be designated by the helicity nomenclature. The sequence-rule-preferred ligands are considered in **XXIV** (Scheme 1.148). The stereochemistry of biphenyls can also be described in terms of helicity and is particularly useful in the case of unresolvable biphenyls such as **XXV**, where a configurationally stable chiral axis is absent. In this case the use of the essentially configurational descriptors *R* and *S* would not be sufficient.

1.24 CHIRALITY IN METALLIC COMPLEXES

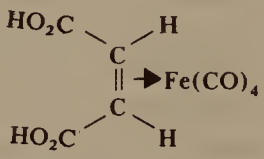
Several metallocenes like **48** (Scheme 1.149) substituted with atleast two different groups on one ring become chiral and have been resolved. Fumaric acid-iron tetracarbonyl **49** has also been resolved while its corresponding maleic acid compound **50** has a plane of symmetry and is therefore achiral[25]



48



49

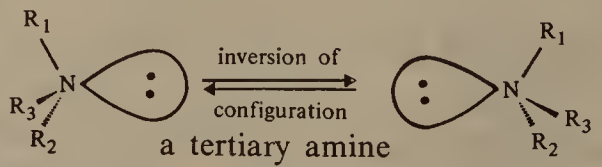


50

Scheme 1.149

1.25 CHIRALITY INVOLVING ATOMS OTHER THAN CARBON

An atom which is an analogue of carbon in terms of a chiral centre is nitrogen. It has the same tetrahedral arrangement of electron pairs as the sp^3-hybrid carbon atom. The only difference from carbon being that one of these electron-pairs is usually a lone pair, which is not involved in bonding. Thus, nitrogen generally has three substituent groups. Tertiary amines of the type presented in Scheme 1.150 are chiral, but do not, however, display optical activity due to chirality at the nitrogen atom. The reason for this is believed to be that the groups on the nitrogen atom undergo rapid inversion as indicated in the equilibrium.



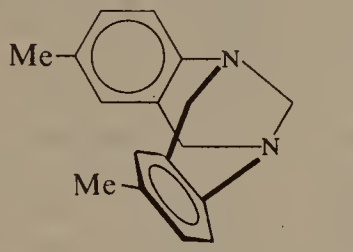
Amine invertomers

Scheme 1.150

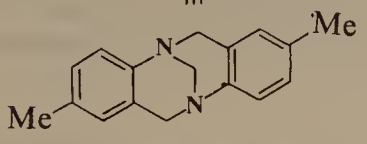
In fact, no bonds are broken in the change and the configuration nomenclature is retained as the change can be described as $S \rightarrow R$ or $R \rightarrow S$. The amine interconversion is described as an inversion (turning inside-out of an umbrella) and to avoid confusion, the enantiomers are termed invertomers. When the lone pair is donated to a substituent, giving the $[NR^1R^2R^3R^4]^+$ species, this rapid inversion is prevented. The tetra-alkyl ammonium salts with four different alkyl groups display optical activity.

When the nitrogen atom is present at a ring junction in bridged ring systems pyramidal inversion is no longer possible without bond cleavage. With proper substitution the tricoordinate nitrogen becomes a stable center of chirality, as in Tröger's base (Scheme 1.151).

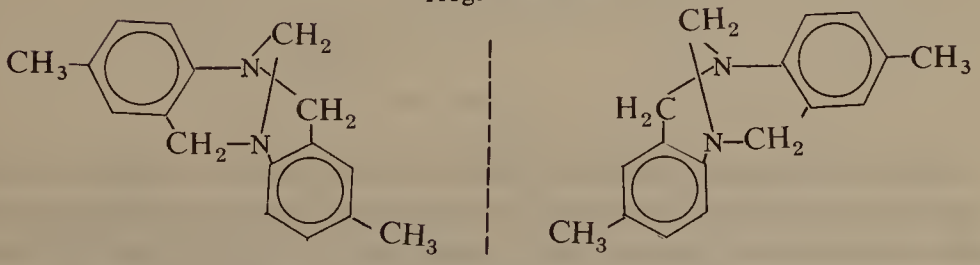
Optical stability is the measure of resistance of a pure enantiomer toward racemization under a given set of conditions.



III



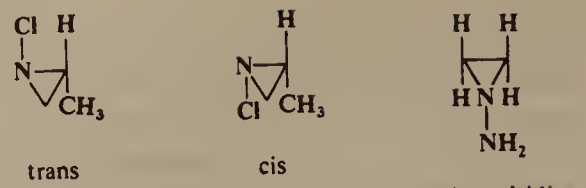
Tröger's base



Tröger's base enantiomeric forms

Scheme 1.151

Two types of nitrogen atom invert particularly slowly, *i.e.*, a nitrogen atom in a three-membered ring and a nitrogen atom connected to another atom with an unshared pair. However, even in these compounds, the umbrella effect is too rapid to permit isolation of isomers and success was achieved only when compounds were synthesized in which both features are combined *i.e.*, a nitrogen atom in a three-membered ring joined to an atom containing an unshared pair (Scheme 1.152).



trans
1-chloro-2-methylaziridine

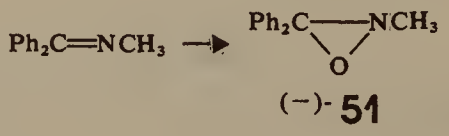
cis

1-aminoaziridine

Scheme 1.152

The two isomers of 1-chloro-2-methylaziridine have been separated, and these do not interconvert at room temperature. Similarly it has been established that aziridines in which the ring nitrogen atom is connected to a nitrogen or oxygen atom are also conformationally stable. NMR spectra indicate that two of the ring protons of 1-aminoaziridine are not equivalent to the other two. This proves that the amino group remains on the same side of the ring as two of the hydrogens and does not interconvert at room temperature. However, in no case a compound could be prepared which was optically active solely because of an asymmetric ternary nitrogen atom. This has now been achieved with the syntheses of several oxaziridines, both enantiomers of a compound 51 (Scheme 1.153) which is chiral solely because of an asymmetric ternary nitrogen atom, have been prepared[26]. Note that in this case as well, the nitrogen is connected to an atom with an unshared pair.

A chiral synthesis of 2-methyl-3,3-diphenyloxaziridine 51 involves the epoxidation of *N*-diphenylmethylene-methylamine with (1 *S*) - (+) -peroxy-camphoric acid.



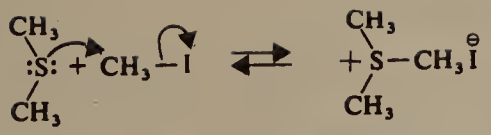
(−)- **51**

Scheme 1.153

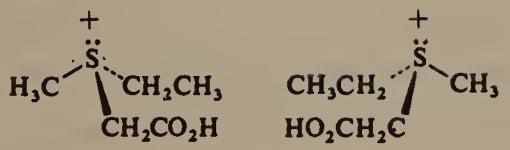
Organic sulfides undergo two important reactions involving the electron pairs on sulfur. They are easily oxidized to sulfoxides as sulfones, and they act as nucleophilic agents toward substances which undergo nucleophilic displacement readily to give sulfonium salts. The formation of sulfonium salts from alkyl halides is reversible, and heating of the salt causes dissociation into its components. Sulfonium salts are identical with quaternary ammonium salts; sulfonium hydroxides, $R_3S^+ OH^-$, like quaternary ammonium hydroxides, $R_4N^+ OH^-$ are strong bases.

A special feature of sulfonium ions is that when these are substituted with three different groups (Scheme 1.154), they can usually be separated into enantiomers. Thus the reaction of methyl ethyl sulfide with bromoacetic acid gives a sulfonium ion which is separable into enantiomers (on crystallization as the salt of an optically active amine).

The chirality of these ions results from the nonplanar configuration of the bonds formed by sulfonium sulfur. The optically active forms of unsymmetrically substituted sulfonium ions are stable as compared with the



trimethylsulfonium iodide



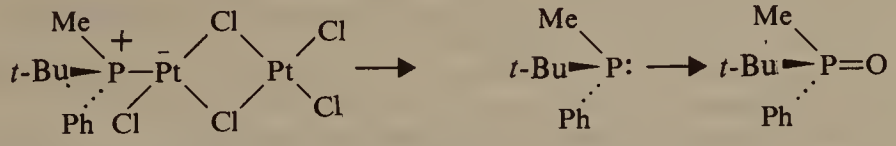
enantiomers of methylethyl(carboxymethyl)-sulfonium ion

Scheme 1.154

low configurational stability of analogously constituted amines.

Nonplanar compounds of the type R_3Y:, where Y is an element in the second row of the periodic table, undergo inversion much less readily than similar compounds for which Y is a first-row element. Thus, phosphorus compounds resemble sulfur compounds in this respect, and several chiral phosphines (R_1 R_2 R_3 P:) have been resolved.

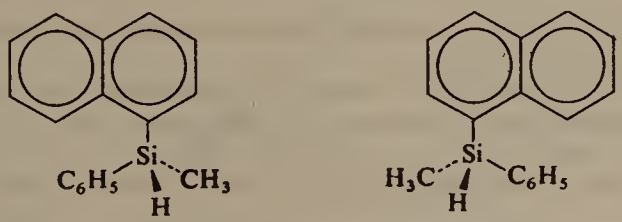
t-Butyl methyl phenyl phosphine gets complexed with a platinum complex donating its lone pair of electrons to the platinum, and the complex, **52** (Scheme 1.155) has been resolved. Separation of phosphine and subsequent oxidation yields phosphine oxide which retained its optical activity. The phosphine oxides donate the lone pair of electrons to oxygen to make the configuration stable.



52

Scheme 1.155

Silicon is usually tetracovalent in organosilicon compounds and, thus, like carbon, the bonds are of the sp^3 type and the substituent groups are regarded to be tetrahedrally disposed in space. Evidence of this comes from the successful resolution of several silicon compounds having a center of chirality at the silicon atom, for example, both enantiomers of 1-naphthylphenylmethylsilane (Scheme 1.156) have been isolated.



1-naphthylphenylmethylsilane

Scheme 1.156

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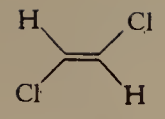
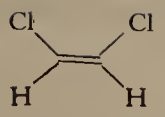
EXERCISES AND PROBLEMS

1. Water has a twofold axis of symmetry (C_2), while benzene has a C_6 axis. Comment on the molecules with C_0 and C_1 axis.
2. Explain briefly a relation between elements of symmetry and optical activity.
3. Depict the symmetry planes on structures of dichloromethane and *cis*-1,2-dichlorocyclopropane molecules.
4. How can you demonstrate a highly symmetrical molecule like methane to have multiple S_4 axes.
5. Label the following pairs of compounds as homomers, constitutional isomers, enantiomers or diastereoisomers.

(a)





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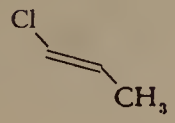

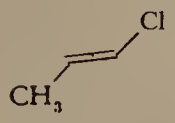

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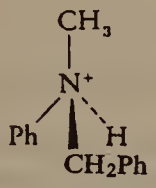
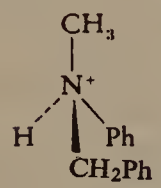
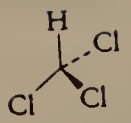
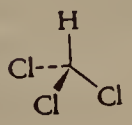


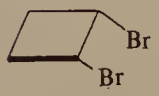


(d)

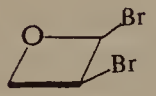


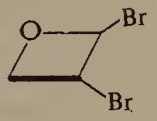


(e)

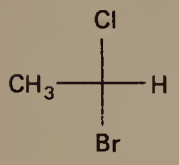


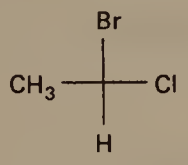
(f)

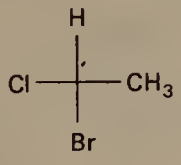


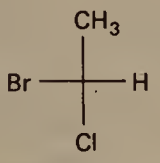


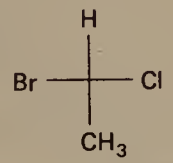
Given the following Fischer projections, indicate: (a) relation of one projection with other: (b) their names and assignment to (*R*) or (*S*).

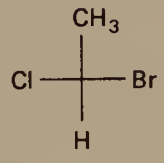




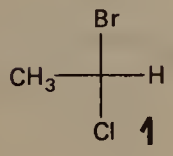


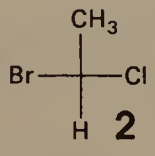


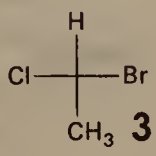


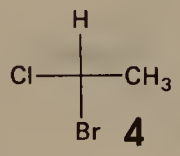


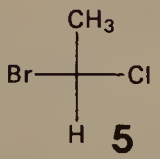
7. Comment on the identity of the compounds 1 to 8.

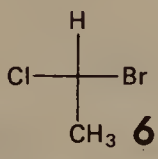


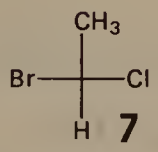


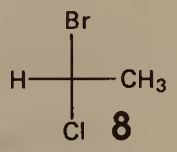




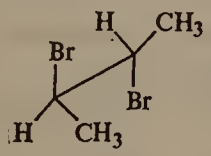




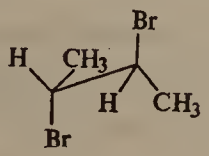




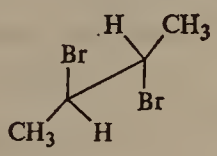
8. Write the Fischer projection for (*R*)-2-iodobutane and convert it into its "Wedge and dotted line" representation.
9. How are the following conformations of 2,3-dibromobutane related with one another ?



(a)

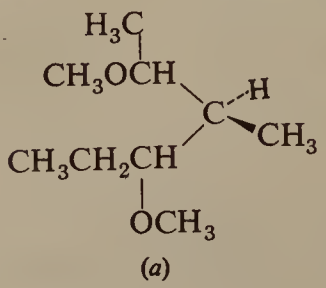


(b)

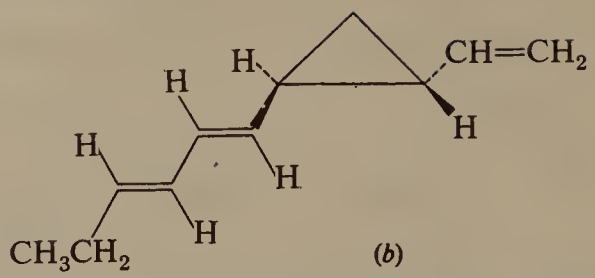


(c)

10. Suggest IUPAC nomenclature to the following compounds.

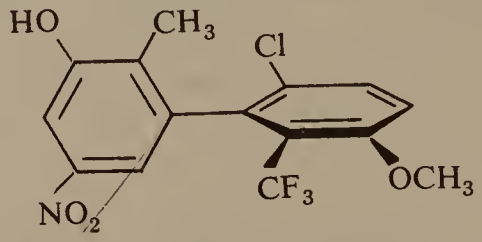


(a)

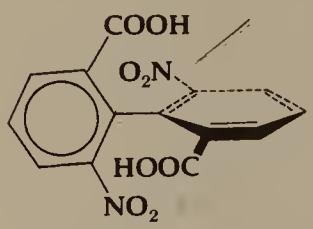


(b)

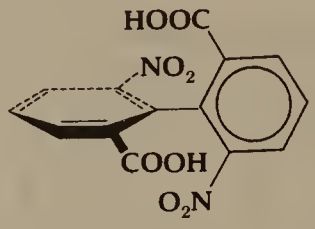
11. Butane on monochlorination gives a mixture of 1-chloro and 2-chlorobutane. Comment on their chirality by writing their stereostructures.
12. (*S*)-1-Chloro-2-methylbutane has (+) rotation. On lightinitiated chlorination (-) 1,4-dichloro-2-methylbutane and (±)-1,2-dichloro-2-methylbutane are formed in addition to other products. Write the absolute configuration of (-)-1,4-dichloro-2-methylbutane formed in the reaction and assign the proper (*R*) or (*S*) label. 1,2-Dichloro-2-methylbutane formed is totally racemic. Comment on the reaction mechanism and the nature of the intermediates.
13. Free radical chlorination of (*S*)-*sec*-butylchloride, gives several isomeric products. Draw the stereostructure of (*R*)-1,2-dichlorobutane formed as one of the products and comment on the stereochemistry of the reaction.
14. The following biphenyl is chiral. Designate its configuration.



15. Comment on the optical isomerism of the following biphenyls.



(a)



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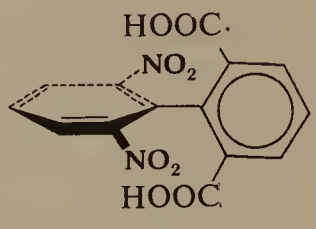
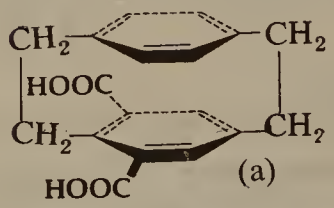
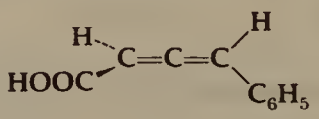


(c)

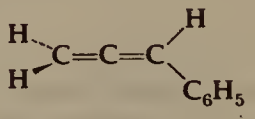
16. Which of the following molecules are chiral.



(a)

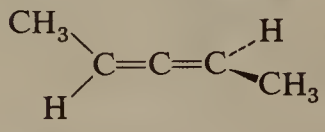


(b)

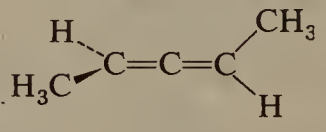


(c)

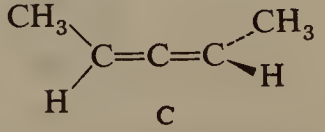
17. Comment on the identity and optical activity of the following structures of penta-2,3-diene.



A

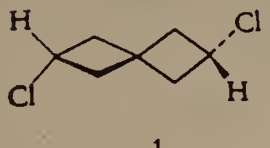


B

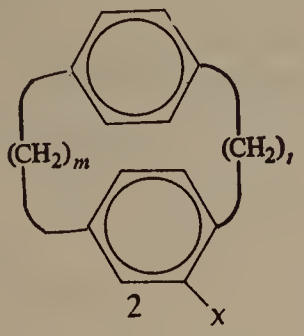


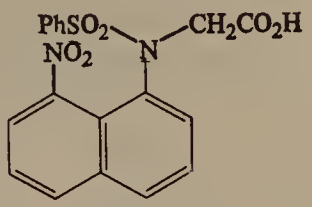
C

18. Label each compound as either having centre, axes or planes of symmetry. How the chirality of compound 2 depends on m, n and x. Assign the order of priorities to individual ligands in compounds 4 and 5.

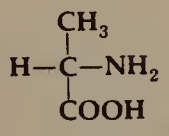


1

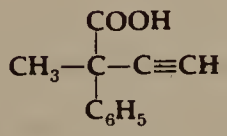




3

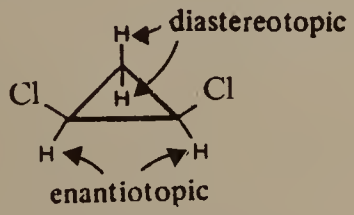


4

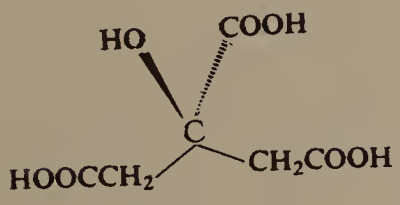


5

19. What is the number of possible stereoisomers for 2-bromo-4-hydroxycyclohexane-carboxylic acid? Indicate their breakdown into enantiomers, racemates and diastereomers. Draw the conformations of the two enantiomers of the most stable diastereomer. Draw the 2-epimer of the most stable diastereomer in perspective and indicate the *cis-trans* relation of the pairs of the substituents. What will be the conformation of 2-epimer on ring flipping?
20. Using symmetry considerations, show if or not the two H's of CH_2Cl F are homotopic.
21. The hydrogen atoms on C-1 and C-2 in *cis*-1,2-dichlorocyclopropane have been labelled as shown below. Give arguments.

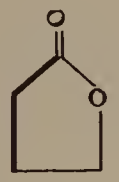


22. Locate giving arguments, enantiotopic or diastereotopic groups or faces in the following compounds.

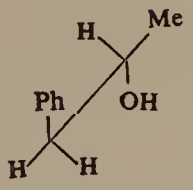


Citric acid

1

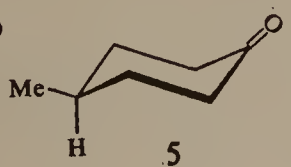


2



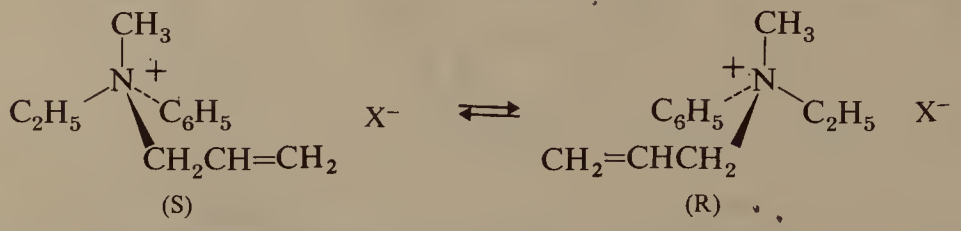
3

4



5

23. The two enantiomers of a chiral amine readily interconvert by a process known as nitrogen inversion. In the case of quaternary ammonium compounds, such inversion is not possible, and chiral ions may be separated into enantiomers which are relatively stable. The optically active allylethylmethylphenylammonium halides undergo racemization slowly in solution. Rate of racemization is temperature dependent and is faster with the iodide than with the bromide. Give a mechanism for this racemization.



(S) (R)

24. Write the structure of the lowest molecular weight alkane, which is chiral. Depict its isomeric structure as well.
25. Write the structures of the geometric isomers of 1,2-cyclopentanediol and comment of their stereochemistry.
26. What are the essential conditions for a compound to be optically active? The presence of a chiral carbon is not always essential for a compound to exhibit activity. Explain.
27. Why is it not possible under ordinary conditions to resolve amines even though three different groups are attached to nitrogen atoms?

2

REACTIONS OF CHIRAL MOLECULES S_N2, S_N1 REACTIONS AND NEIGHBORING GROUP PARTICIPATION

2.1 INTRODUCTION

During substitution at a saturated carbon atom *i.e.,* a process in which one of the groups attached to an sp^3-hybridized carbon atom is substituted by another, the changes in configuration, reflected in the variation of optical activity, provide a powerful tool for understanding the mechanism of these reactions. The configuration at a saturated carbon atom can undergo three possible changes.

(1) Inversion,
(2) Retention,
(3) Conversion to a mixture, which may result from a true process of racemization in which the reaction procceds through an achiral intermediate, or it may result from reactions of type (1) and (2) proceeding together but not necessarily to the same degree.

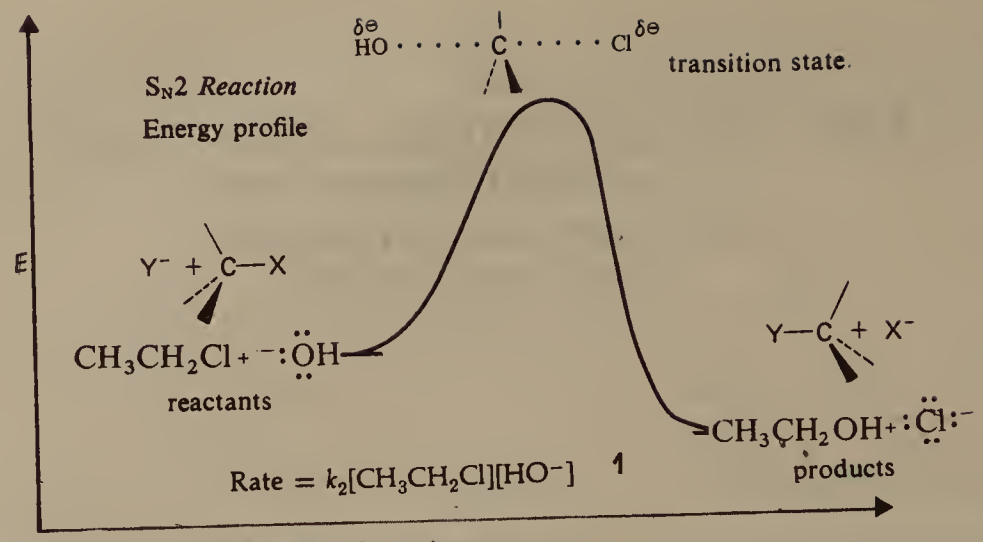
The first process is characteristic of bimolecular substitution reactions, the third is characteristic of unimolecular substitution reactions, while the second of unimolecular substitutions in which the special factor of neighboring-group participation is operative.

2.2 SUBSTITUTION WITH INVERSION S_N2 REACTIONS

The rate expression eq.1 is for the reaction of ethyl chloride with sodium hydroxide (eq.2 in second order). Experiments have shown that the reaction rate depends on the concentration of ethyl chloride as well as on the concentration of hydroxide ion.

Thus, the transition state for the rate limiting step of the ethyl chloride reaction involves both a hydroxide ion and an ethyl chloride molecule and that the reaction is bimolecular *i.e.,* S_N2 reaction, meaning, Substitution, Nucleophilic Bimolecular, is the shorthand script of organic chemists.

A simple example of a bimolecular substitution reaction is attack of a nucleophile such as hydroxide ion, on an alkyl halide. Nucleophiles are always electron rich, sometimes negatively charged, as in the above case, and hence seek out any electron-deficient or positive centre. In the above example, the carbon atom bears a slight positive charge due to the electron-



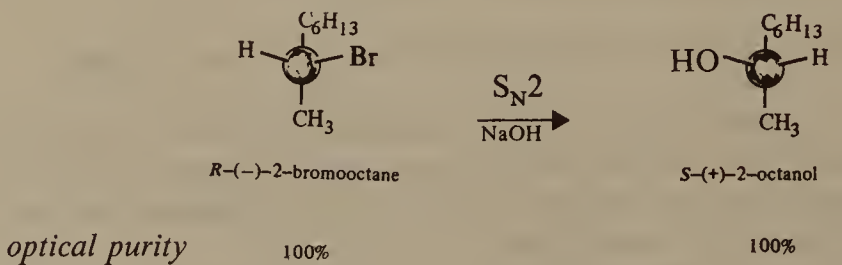
$$CH_3CH_2Cl + HO^- \xrightarrow{H_2O} CH_3CH_2OH + Cl^- \quad 2$$

Ethyl chloride — Ethanol

Scheme 2.1

withdrawing properties of the halogen atom, so it is readily attacked by the nucleophile.

The S_N2 reactions occur with inversion of configuration (Walden inversion symbolized by a loop in the arrow) of the carbon that undergoes substitution. One cannot observe an inversion of configuration when the substrate for the reaction is an achiral molecule such as ethyl chloride. But, one can not detect an inversion of configuration when the S_N2 reaction takes place with a chiral substrate.



Scheme 2.2

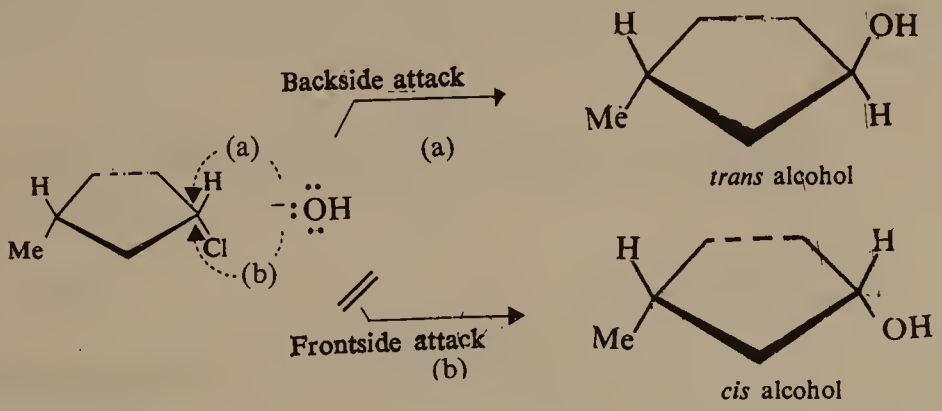
R-(-)-2-Bromooctane reacts with sodium hydroxide to yield *S*-(+)-2-octanol (Scheme 2.2). This reaction is of second order and occurs with complete inversion of the configuration. The inversion of the configuration is consistent with the mechanism (eq.3, Scheme 2.3) in which the nucleophile attacks the carbon atom bearing the leaving group from the opposite side. The bond making and bond breaking are simultaneous processes and in the

transition state the carbon appears to be pentavalent. The three substituents acquire a cc ınar geometry.

3

Scheme 2.3

That, indeed, in an S_N2 reaction the nucleophile attacks from back side and not from front side and leads to inversion of configuration has been demonstrated in an inversion of configuration in the cyclic molecules. When *cis*-3-methylcyclopentyl chloride, for example, reacts with hydroxide ion in an S_N2 reaction, the product is *trans*-3-methylcyclopentyl alcohol (Scheme 2.4).



Scheme 2.4

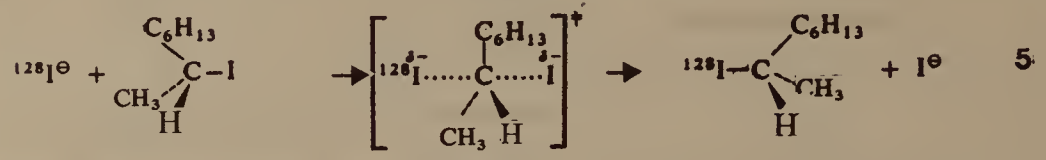
Conclusive proof that inversion of configuration occurs during an S_N2 reaction was provided by studying the reaction between optically active 2-iodooctane and radioactive iodide ions (eq.4, Scheme 2.5). This is one of the simplest possible types of bimolecular substitution reaction, and involves replacement of iodide ions by radioactive iodide ions, so that product and starting material are chemically identical. The process also involves inversion of configuration, and is thus accompanied by a loss of optical

$$^{128}I^- + C_6H_{13}\underset{\text{optically active 2-iodooctane}}{\underset{|}{\overset{I}{C}}HCH_3} \rightleftharpoons I^- + C_6H_{13}\overset{^{128}I}{\underset{|}{C}}HCH_3 \qquad 4$$

Scheme 2.5

activity. It was seen that the rate of loss of optical activity is twice the rate of incorporation of radio active iodide ions.

In case the process involves an achiral intermediate, like a carbocation the rate of racemization will be equal to the rate of incorporation of radioactivity. On the other hand, in an S_N2 reaction every substitution (eq. 5, Scheme 2.6) involves inversion. Racemization is, therefore, complete when half of the material gets inverted (and has incorporated radioactivity) so that the rate of

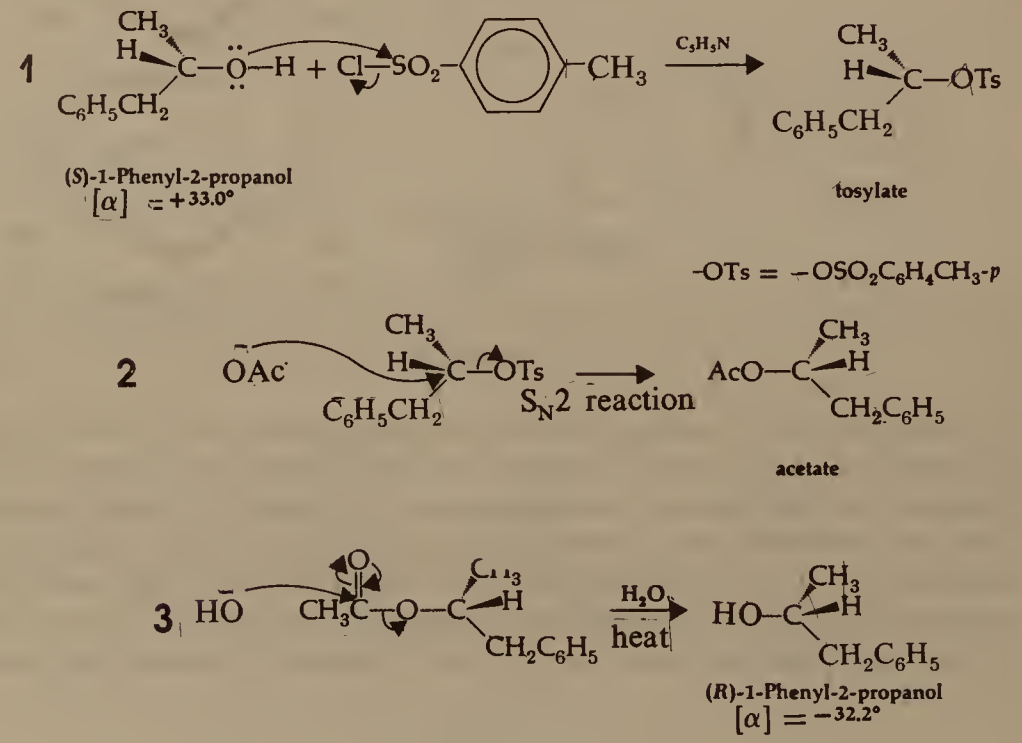


Scheme 2.6

racemization is twice the rate of incorporation of radioactivity.

This experiment provides the most convincing proof to date that an S_N2 reaction is accompanied by inversion of configuration.

An example of inversion of stereochemistry in an S_N2 reaction (Walden inversion) is the conversion of phenyl-2-propanol, an optically active alcohol to its enantiomer through several reactions (Scheme 2.7). The first



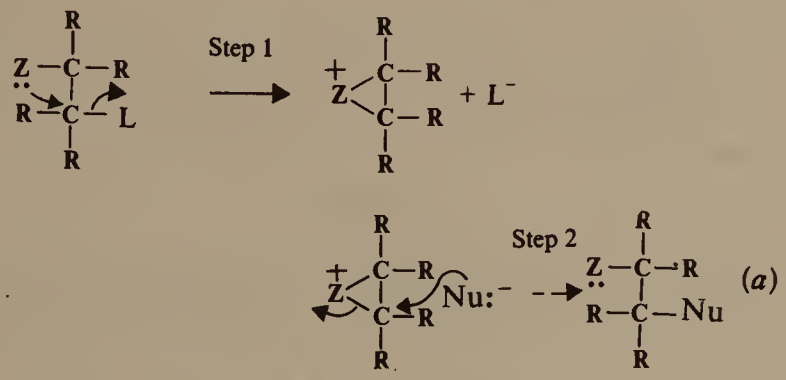
Scheme 2.7

step (formation of the tosylate) and the third step (hydrolysis of the acetate ester) do not involve reactions at the chiral centre. No change in configuration, therefore, occurs during these two steps.

The second reaction, substitution of acetate for tosylate occurs at the chiral carbon. As the total sequence proceeds with inversion of configuration, the stereochemical outcome of step 2 must be inversion.

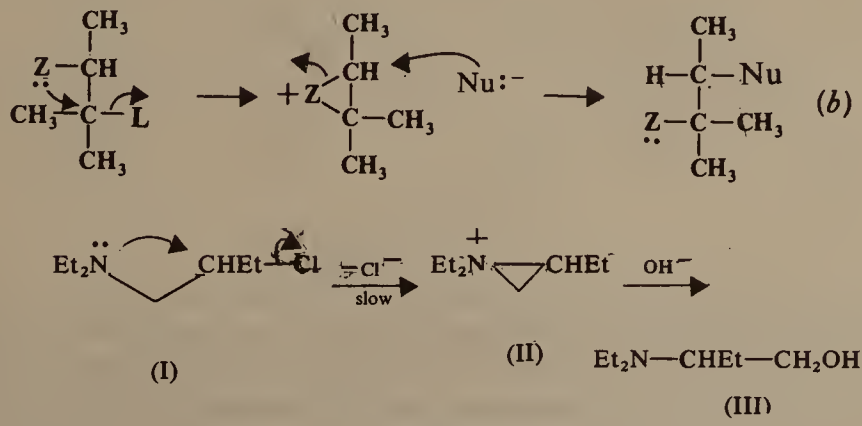
2.3 SUBSTITUTION WITH RETENTION OF CONFIGURATION (OUTLINES OF NEIGHBORING GROUP PARTICIPATION) AND ANCHIMERIC ASSISTANCE

Often the rate of a reaction is greater than expected and retention of configuration at a chiral carbon may be observed and not inverted or racemized. This usually happens when there is a group *(Z)* in the substrate with an unshared pair of electrons in a position β to the leaving group which can play a transient part in the reaction. These assisted reactions by a more-or-less remote functional group is termed the neighboring group mechanism[1], and involves two successive inversions of configuration. In other words the neighboring group effect involves essentially two S_N2 substitutions, each causing inversion, the net result being retention of configuration. In the first step (Scheme 2.8) the neighboring group *Z* acting as a nucleophile pushes out the leaving group but still retains attachment to the molecule. In the subsequent step the external nucleophile pushes out the neighboring group (eq. a).



Scheme 2.8

Often when the neighboring group effect is operative, one may not get the substitution product but a rearrangement. In these situations the nucleophile does not attack the carbon from which the leaving group had left but instead

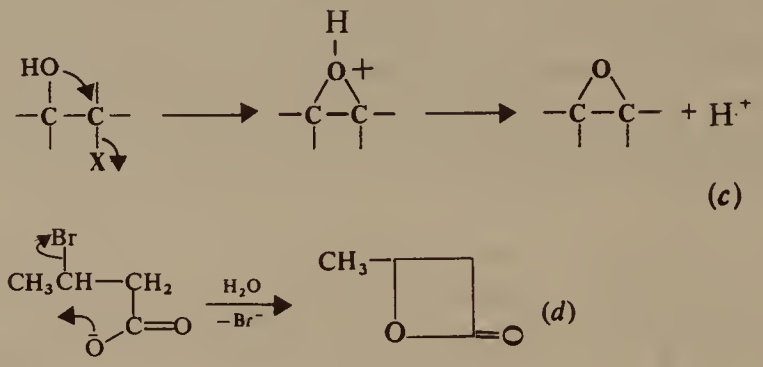


Scheme 2.9

attacks the carbon to which the neighboring group was originally linked (eq.b, Scheme 2.9). Thus the alkaline hydrolysis of (I) affords the rearranged product (III). The cyclic intermediate (II) formed after the neighboring group participation by nitrogen undergoes attack at the methylene (—CH_2—) group rather than (—CHEt) because of less steric crowding on the former carbon atom.

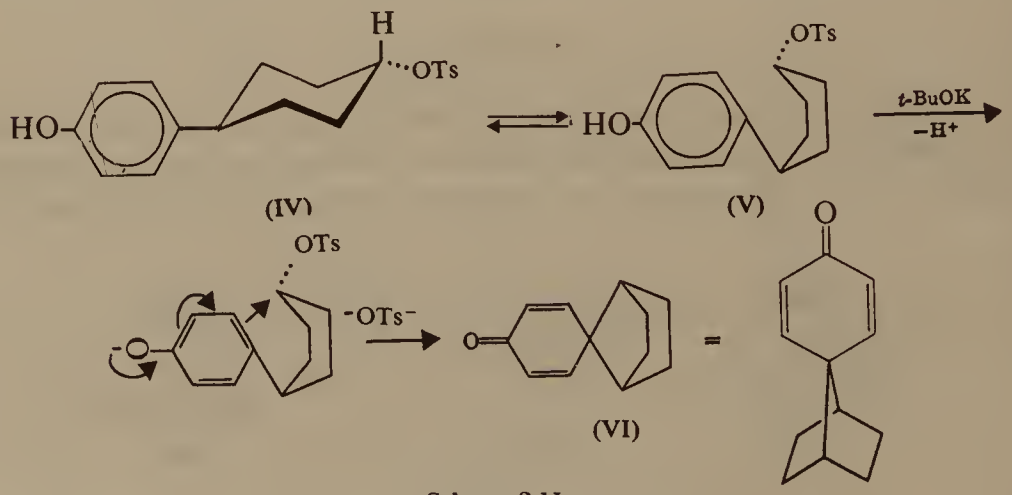
In such cases both substitution and rearrangement occur

It is also possible that the intermediate after neighboring group participation may stabilize in some other way, *i.e.*, the nucleophile does not attack at all (eqs. c and d, Scheme 2.10). Examples are formation of an epoxide and a β-lactone).



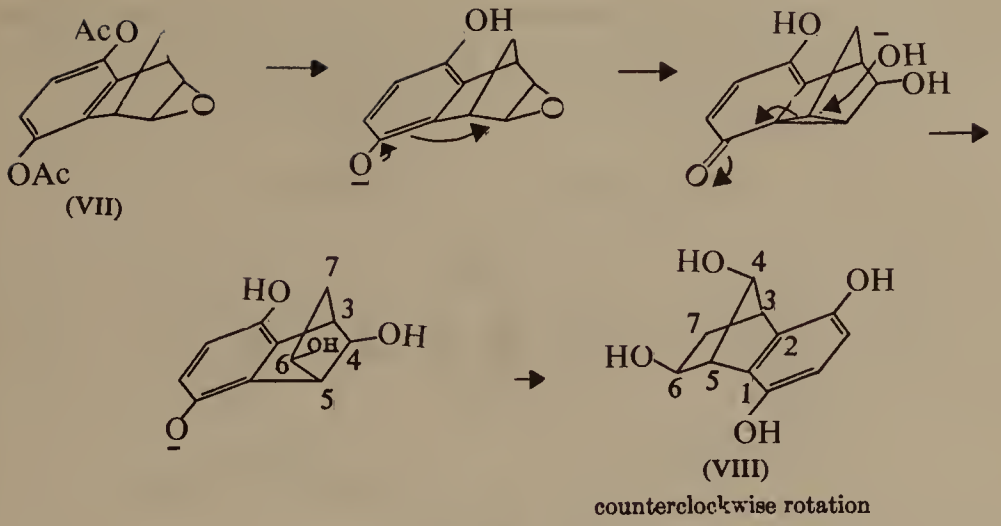
Scheme 2.10

An example of aryl participation is the conversion of *trans*-4-(4′-hydroxycyclohexyl)-phenol tosylate (IV) into the spiroketone (VI, Scheme



Scheme 2.11

2.11). For the aryl participation the chair conformation of cyclohexane changes into boat (V). Another excellent example of aryl group participation leading to both substitution and rearrangement is of the norbornyl derivative (VII). The norbornene epoxide is resistant to nucleophilic attack, the fused hydroquinone ring has a dramatic role, as on saponification, (VII) undergoes a rearrangement to afford (VIII).



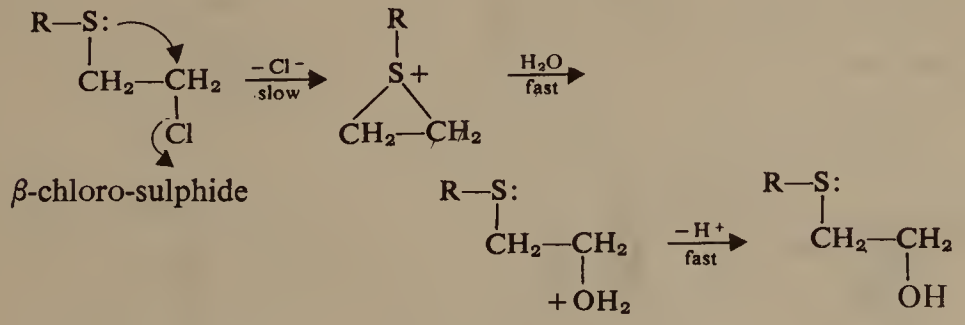
(VII)

(VIII)

counterclockwise rotation

Thus the neighboring group effect involves intramolecular nucleophilic attack from the back side of the leaving group. Therefore, the spatial relationship of the neighboring group and the leaving group must be *anti* in an open-chain compound and *trans* diaxial in a cyclic compound.

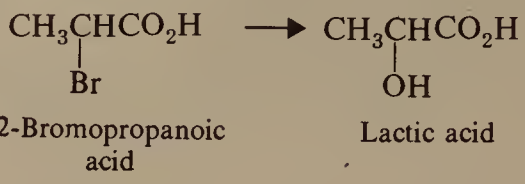
In some cases (usually in solvolysis reactions), a neighboring group may not actually migrate, but plays a part in the expulsion of the leaving group in the rate-determining step. The departing group is then said to have received anchimeric assistance from the neighboring group. For example, the β-chloro-sulphide $RSCH_2CH_2Cl$ is hydrolyzed in aqueous dioxan ten thousand times faster than its ether analogue $ROCH_2CH_2Cl$ (Scheme 2.13). This has been ascribed to the participation of the sulphur atom, as sulphur containing groups are particularly effective neighboring groups. Significantly the S_N1 solvolysis of chloroethane, a related reaction, does not occur at a measurable rate.

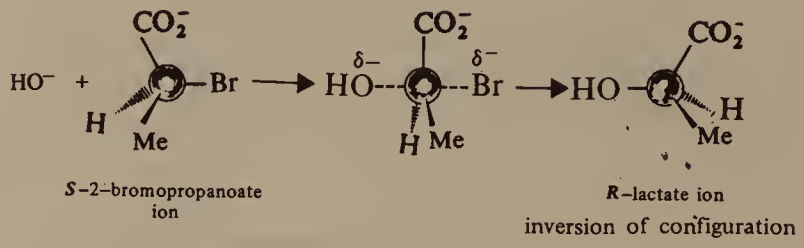


Scheme 2.13

Two relatively fast reactions occur. In the first, stlphur acts as an internal nucleophile. This step is favoured than the intermolecular reaction with water because of the much more favourable entropy of activation for the intramolecular process and it is favoured as compared with the reaction of the

oxygen analogue since sulphur is a more powerful nucleophile than oxygen.





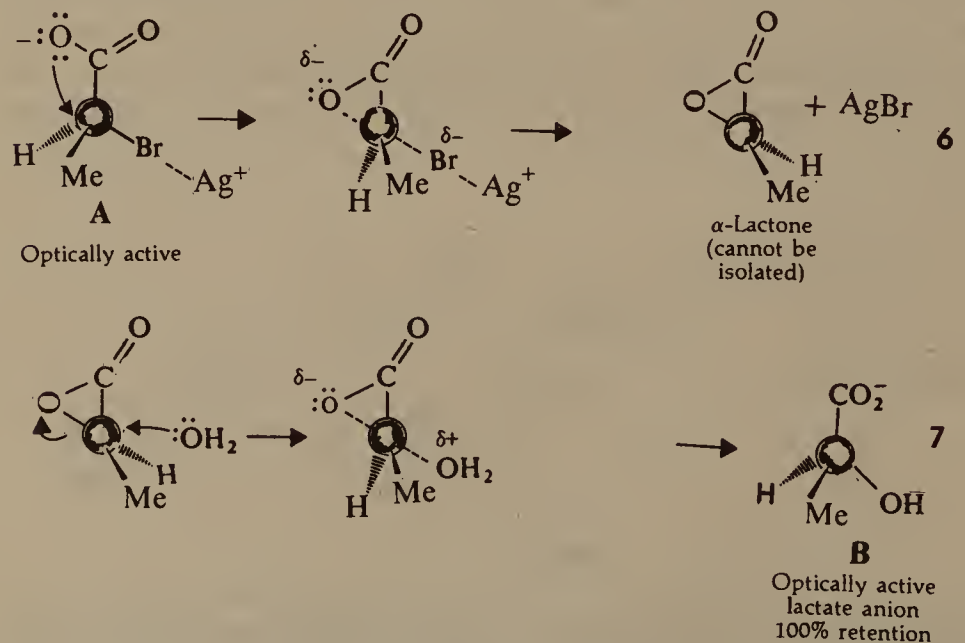
a normal S_N2 process

Scheme 2.14

In the second step, the three-membered ring is opened upon attack by water.

Consider the reaction of 2-bromopropanoic acid, with a concentrated solution of a strong nucleophile like hydroxide ions. The anion of this acid reacts by a normal S_N2 process with inversion of configuration (Scheme 2.14).

Significantly when a weak nucleophile like silver oxide is used (eqs. 6-7, Scheme 2.15) 2-bromopropionic acid, on the other hand, is hydrolysed with retention of configuration.



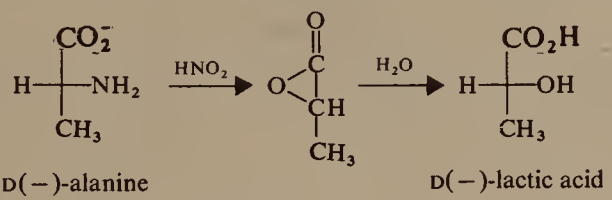
complete reaction thus involves two inversions

Scheme 2.15

In this graphic reaction the carboxylate group acts as a nucleophile, being in a favourable position to attack the adjacent carbon atom to displace the bromide ion. In the absence of a potent nucleophile, such as hydroxide ion, this is the main reaction. The process is believed to give the highly strained intermediate α-lactone.

Reaction in eq. 6, involves inversion of configuration, so that the α-lactone has the opposite configuration compared to the original 2-bromopropanoic acid and its anion **A**. The α-lactone has an unstable and strained structure, so it readily undergoes attack by even a very weak nucleophile like a water molecule (eq. 7) giving the hydroxy acid. Reaction 7 like reaction 6 involves inversion of configuration. The complete reaction sequence thus involves two inversions. The overall result is therefore retention of configuration, *i.e.;* **B** has the similar configuration as the starting material **A**.

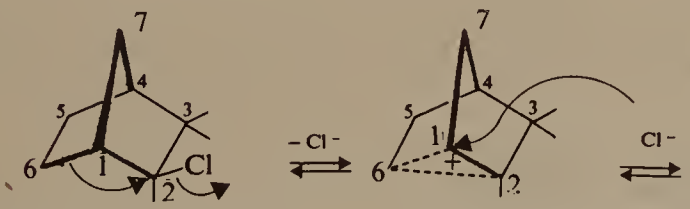
The deamination of optically active alanine with nitrous acid yielded optically active lactic acid with retention of configuration (Scheme 2.16). This is due to neighbouring group participation of the α -carboxylate anion.



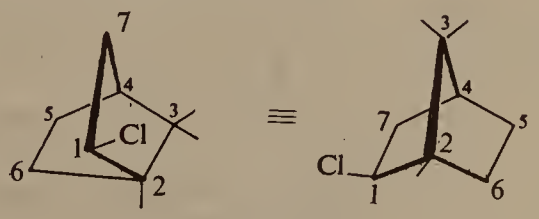
D(−)-alanine D(−)-lactic acid

Scheme 2.16

Even electrons in a σ bond can behave as a neighboring group in providing anchimeric assistance to a leaving group. This can be seen in the rearrangement of camphene hydrochloride to isobornyl chloride (Scheme 2.17) in polar solvents, a Wagner-Meerwein rearrangement (Sec. 8.1A). Cations showing the spreading of a positive charge through the



camphene hydrochloride *nonclassical carbocation*



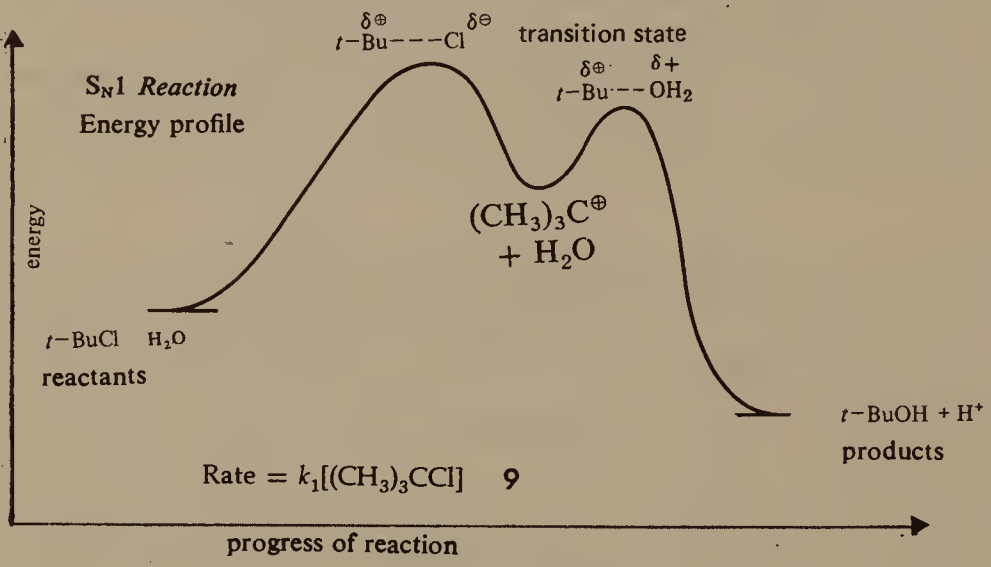
isobornyl chloride

Scheme 2.17

delocalization of bonding σ electrons (see the dotted lines) are known as nonclassical carbocations (see Sec. 3.7. E).

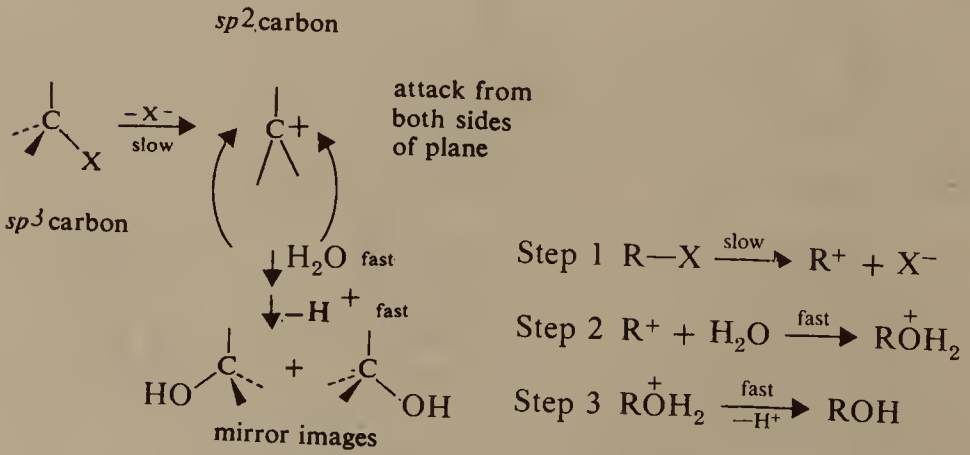
2.4 SUBSTITUTION WITH PARTIAL INVERSION (S_N1 REACTIONS-ION PAIRS)

The third type of reaction the S_N1 reaction (Substitution, Nucleophilic, unimolecular) involves ionization of the substrate to give a carbocation. In contrast to the hydrolysis of ethyl bromide (S_N2), during the hydrolysis of *t-butyl* chloride (eq. 8, Scheme 2.18), the rate (eq. 9) depends only on the concentration of *t*-butylchloride.



$$(CH_3)_3C{-}Cl \quad (\textit{tert}\text{-Butyl chloride}) \quad + H_2O \xrightarrow{\text{Acetone}} (CH_3)_3C{-}OH \quad (\textit{tert}\text{-Butyl alcohol}) \quad + HCl \quad 8$$

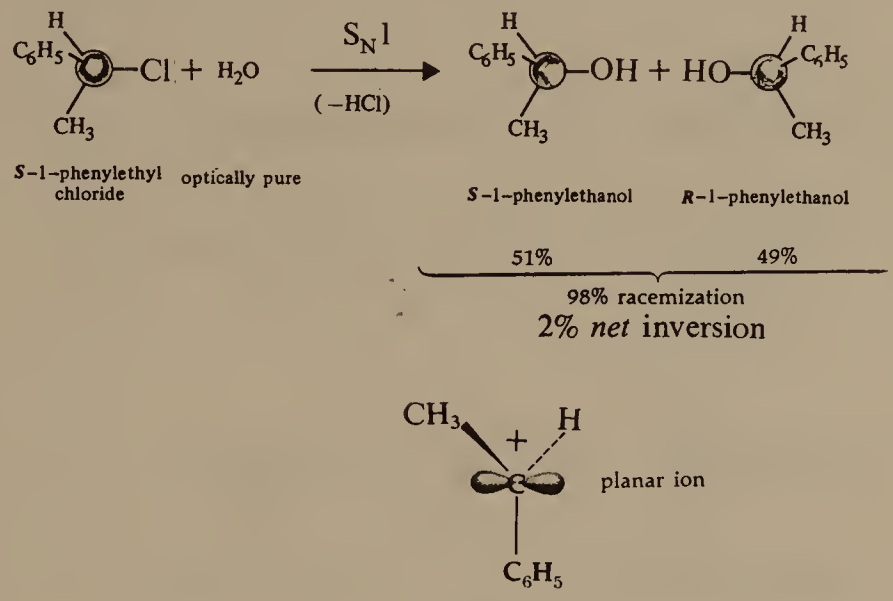
Scheme 2.18



Scheme 2.19

Since the carbocation carbon atom has sp^2 hybridization, it is expected to be planar, and therefore achiral. Equal amounts of enantiomeric products are formed, in an extreme case, during the reaction of a chiral substrate by attack at either side of the plane with equal probability.

Starting with an optically active substrate, it is usually found to give a mixture of inversion and racemization (scheme 2.20). Reaction cannot



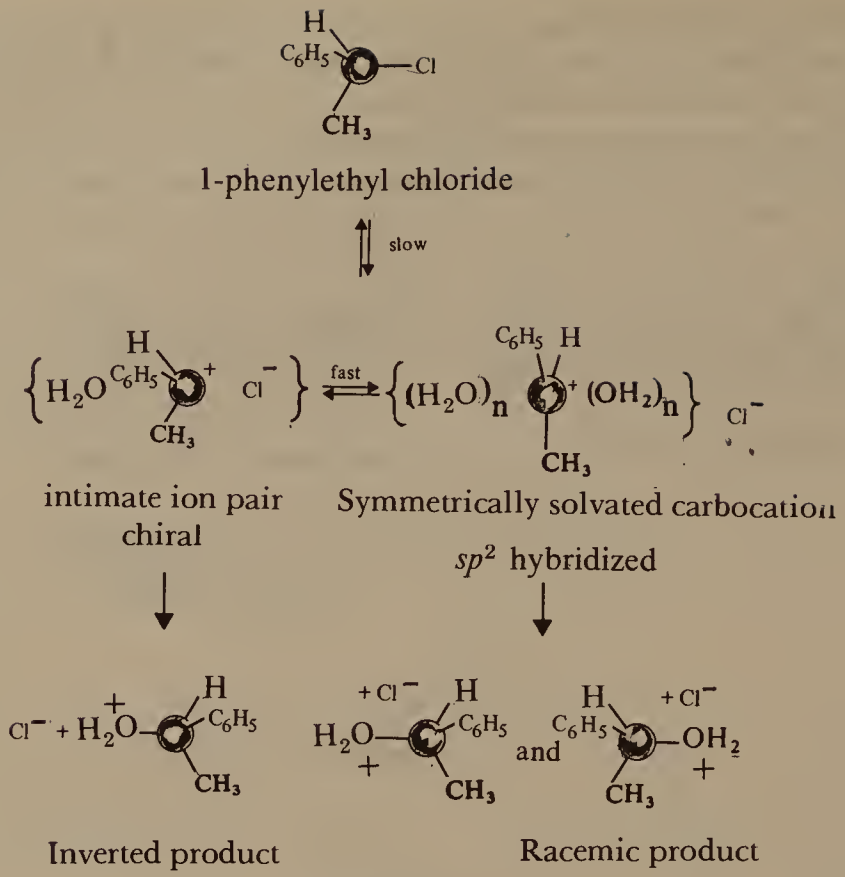
Scheme 2.20

then be presumed to proceed entirely through a planar intermediate. The carbocation frequently exists in solution not as a free ion, but as an ion pair[2]. This can react as it is, or it can separate to give a planar carbocation. The ion pair essentially consists of a carbocation which is stabilized by close contact with an anion, which is often, though not always, the one liberated in the ionization reaction. The anion stabilizes the carbocation by the supply of electrons to it. Since this charge is supplied to the vacant orbital of the carbocation carbon atom, it indeed prevents the ion from becoming planar.

Thus a detailed mechanism to account for the stereochemistry of 1-phenylethylchloride reaction is being presented (Scheme 2.21). The ion from this reaction is not really free; it is surrounded by solvent (solvation) as well as the leaving group and possibly by the nucleophile itself.

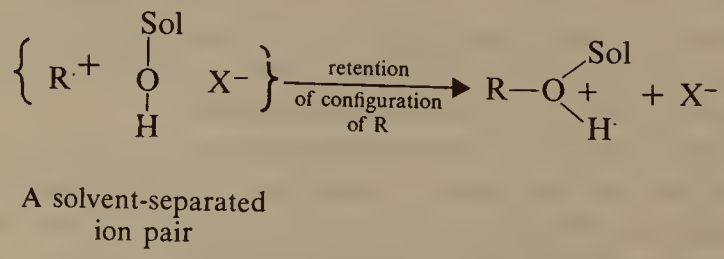
Some carbocations do have lifetimes sufficient for them to become symmetrically solvated by the excess of solvent molecules of the reaction medium with equal probability from either side of the molecule. Product originating from this symmetrically solvated ion will be racemic. Very short-lived carbocations do not have lifetimes long enough for them to become symmetrically solvated and instead exist as intimate ion pairs.

The leaving group crowds and thus shields one side of the molecule, so that the nucleophile preferentially approaches from the opposite side. The result is an inversion of configuration in the unimolecular process. A "solvent-



Scheme 2.21

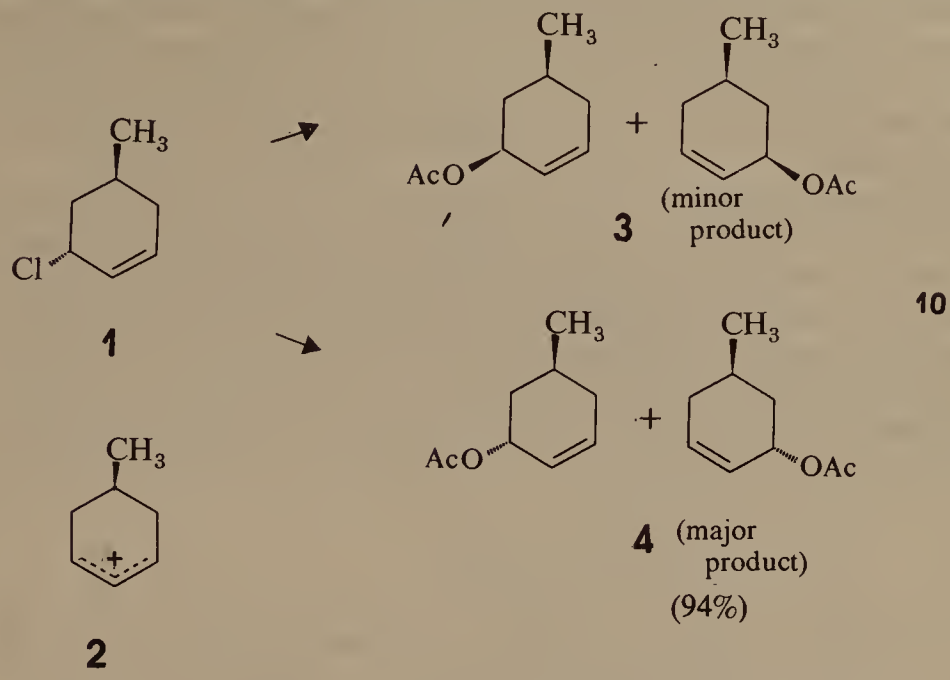
separated" ion pair may also intervene between the intimate ion pair and the symmetrically solvated carbocation. A solvent separated ion pair, is one in which a molecule of solvent is situated between the carbocation and the anion (Scheme 2.22). There is also evidence that solvent separated ion pairs sometimes preferentially react with the intervening solvent molecule by a mechanism that takes place with retention of configuration. Attack by another nucleophile may occur with inversion.



Scheme 2.22

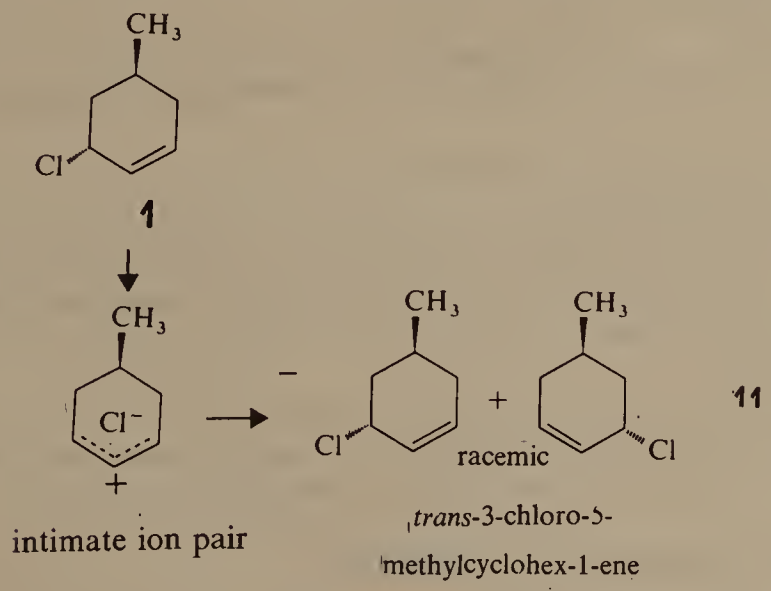
A graphic demonstration of the existence of ion pairs has a base in a study of the acetolysis of *trans*-3-chloro-5-methylcyclothex-1-ene, 1 (eq. 10, Scheme 2.23). On solvolysis optically active chloride afforded racemic mixture of

cis-and *trans*-acetates 3 and 4 respectively. This is due to the fact that the allylic cation 2, possesses a plane of symmetry. The rate at which optical



Scheme 2.23

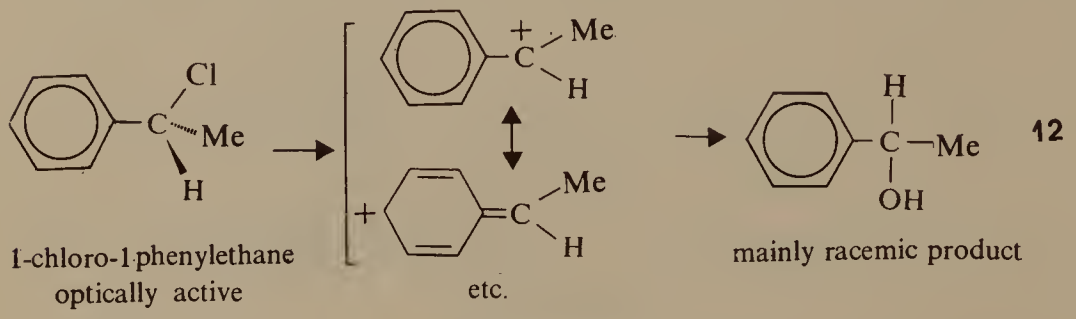
activity was lost in this reaction was found to be faster by a factor of about four. Additionally it was shown that the chloride racemized without even undergoing solvolysis and the loss of its optical activity occurs within an ion pair (eq. 11, Scheme 2.24), the product being the racemic *trans*-3-chloro-5-

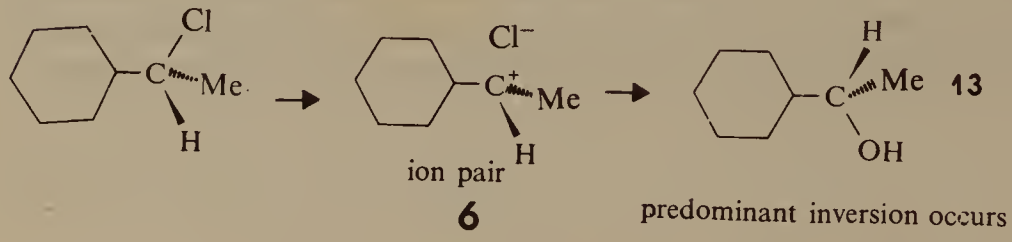


Scheme 2.24

methyl-cyclohex-1-ene. This is so since in the tight ion pair the ions are in close contact and, therefore, prevent the movement of the chloride ion from one face of the cyclohexane ring to the other. The same, but, more convincing evidence was provided by the study of *cis*-isomer. The carbocation reacted with acetic acid to afford an acetate; 95 per cent *trans*, whereas the parallel reaction leading to the collapse of the ion pair gave the racemic *cis*-chloride as the sole product.

On the basis of above data, one should expect the formation of racemic product from a substrate which gives a stable carbocation. When a carbocation is already stabilized by electron-donating groups or by charge delocalization, the anion hardly makes any contribution towards its stability. During the hydrolysis of 1-chloro-1-phenylethane (eq. 12, Scheme 2.25) the benzene ring stabilizes the intermediate carbocation, 5 and as a consequence the optically active starting material undergoes a predominant (80%) racemization.





Scheme 2.25

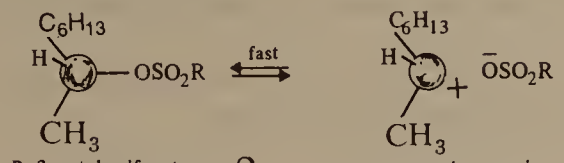
On replacing the benzene ring by a cyclohexane ring the ion **6** formed in the reaction derives most of its stability from the intimate ion pair. Thus, it does not readily ionize to the free ion. Therefore, the product originates mostly by the nucleophilic attack on the ion pair, leading to almost exclusive inversion of configuration.

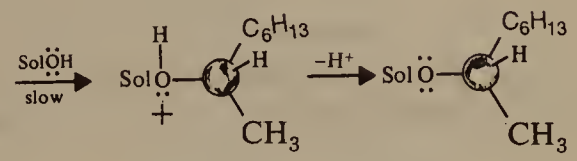
The overall balance between racemization and inversion is very sensitive to several factors such as solvent and negative ion and the above two reactions provide extreme situations, most reactions coming between the two.

2.5 ION PAIR FORMATION—A SUMMARY

Recent work has shown that in several S_N2 reactions, (in particular solvolysis

reactions) an intimate ion pair mechanism may be the route as an alternative to the Ingold mechanism (Scheme 2.27), and occurs with inversion of configuration. The energy profile of these reactions is reminiscent of S_N1 energy profile diagram.





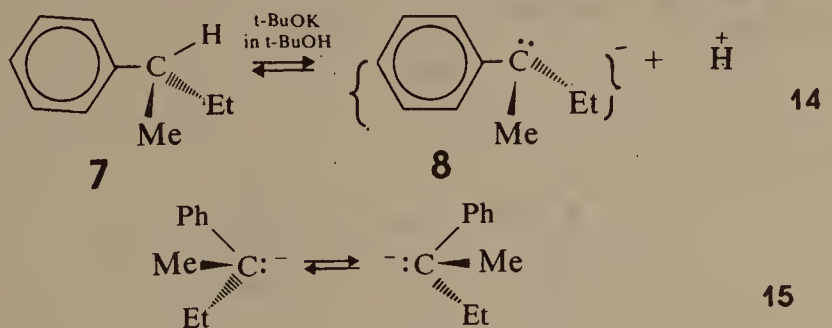
Scheme 2.27

TABLE 2.1 : Ion-Pair Formation

Species	Representation	Reaction with Nucleophiles
Substrate	R—X	inverted product by S_N2 mechanism.
Intimate ion pair	R^+X^-	Nucleophilic attack affords inverted product by mechanism that is borderline between S_N1 and S_N2.
Solvent-separated ion pair	$R^+ \| \| X^-$	Nucleophilic attack affords mainly inverted product by S_N1 mechanism.
Free ion (i.e. solvent-solvated ion)	R^+	Nucleophilic attack affords racemic product by S_N1 mechanism.

2.6 REACTIONS INVOLVING CARBANIONS AND FREE RADICALS

One of the most common types of reactions where racemization occurs via the formation of a carbanion-enolate ion has been explained earlier (sec. 1.17B). A carbanion, 8 (Scheme 2.28) like a tertiary amine is chiral if the three ligands

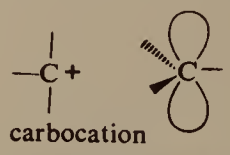


Scheme 2.28

are different. However, after its formation (eq. 14) from **7** it undergoes a rapid inversion (eq. 15) and thus exists as an equilibrating mixture of the two mirror-image forms.

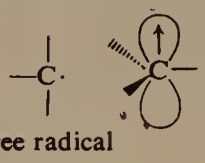
Therefore, if a reaction involves the intermediate formation of a carbanion from a chiral carbon, it will yield a racemic product unless an ion pair mechanism is operative.

At this point a comparison of the stereochemical features of carbocations, free radicals and carbanions is presented (Scheme 2.29).



carbocation

sp^2 carbon, planar with no electron in the empty p orbital



free radical

sp^2 carbon, probably planar with one electron in the p orbital

carbanion

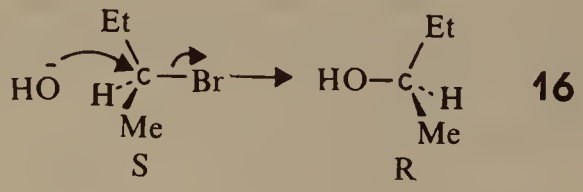
sp^3 carbon, pyramidal with rapid inversion with two electrons in a nonbonding orbital

Scheme 2.29

Free radical reactions lead to loss of optical activity at a chiral carbon atom involved in the reaction.

2.7 INVERSION OF CONFIGURATION

Inversion of configuration is the conversion of a molecule into another which has the oppositive relative configuration. Inversion does not necessarily require a change in designated absolute configuration and nor does a change in designated absolute configuration require an inversion. Thus, although reaction **18** (Scheme 2.30) proceeds with inversion like **16** and **17** but in the former (*S*)-reactant gives (*S*)-product (see problem 12, ch.1).



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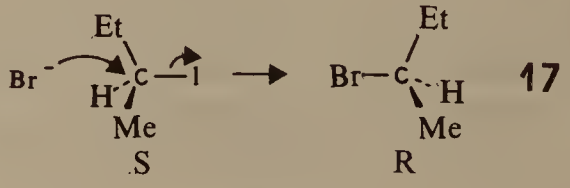

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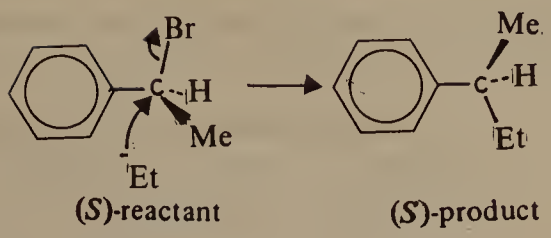

Scheme 2.30

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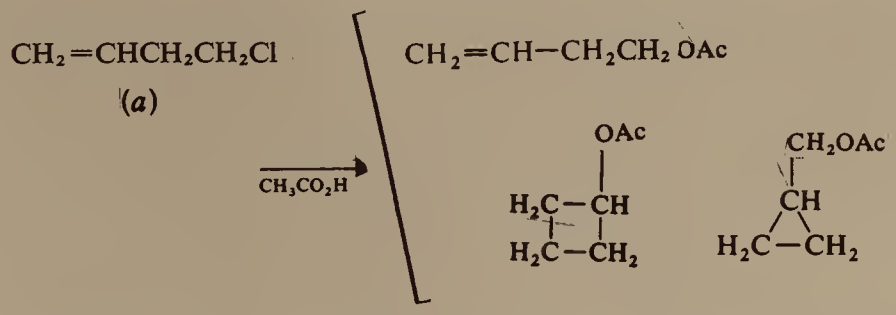
1. Review — Capon *Q. Rev. Chem. Soc.* **18** : 45-111 (1964).
2. Reviews — J.M. Harris, *Prog. Phys. Org. Chem;* 11 : 89-173 (1974); D.J. Raber, J.M. Harris, and P.V.R. Schleyer in *"Ions and Ion Pairs in Organic Reactions"*, Vol. 2, pp. 247-374 John Wiley & Sons, New York, 1974.

EXERCISES AND PROBLEMS

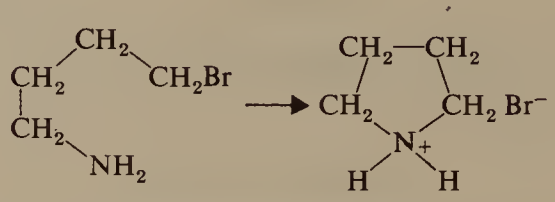
1. Give examples of reactions which are characterized by:
   (a) rentention of configuration
   (b) inversion of configuration
   (c) racemization, and
   (d) that are inhibited by steric hindrance.
2. Treatment of butanol with sulfuric acid gives dibutylether, but if sodium bromide is added very little ether is formed. Explain.
3. In a slow reaction with NaOH *R*-2-chloro-butane yields *S*-2-butanol. This reaction gets catalysed at room temperature with a trace of iodide ion. Explain the role of iodide ion and the configuration of the alcohol formed under iodide catalysis.
4. Reaction (a) below is a typical S_N2 reaction which displays second-order kinetics. The cyclisation (b) of analogous 4-bromobutylamine displays first order kinetics. Explain.



5. (+)-2-Bromopentane loses its optical activity in solution with sodium bromide in acetone Explain.

6. How do you account for the formation of cyclic compounds during the following acetolysis of the homoallylic system (a) ?

$$CH_3Br + CH_3NH_2 \longrightarrow (CH_3)_2NH_2^+Br^- \qquad (a)$$



(b)

7. What explanation can you provide for the fact that S_N1 reactions often display either complete racemization or partial inversion. Optically active α-phenylethyl chloride on phenolysis gives an ether with partial retention, give a mechanism.

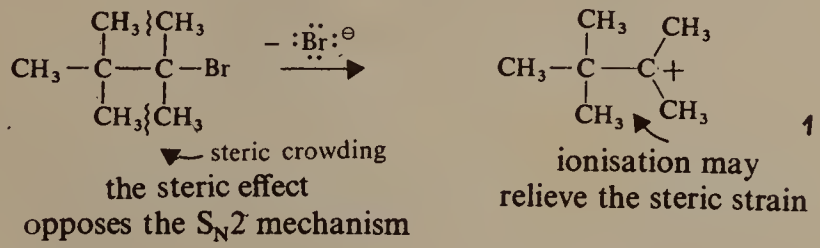
8. The special salt effect on addition of $LiClO_4$ or LiBr during the acetolysis of some tosylates leads to an initial steep rate acceleration which then decreases to the normal linear acceleration (caused by the ordinary salt effect). Explain.

3

STEREOCHEMICAL AND OTHER EFFECTS IN NUCLEOPHILIC SUBSTITUTION

3.1 INTRODUCTION

S_N2 reactions proceed *via* a transition state in which the central carbon atom has five groups attached to it. The transition state represents the energy maximum so that factors which lower its energy will increase the rate of reaction. As the transition state is crowded, having five groups on a carbon atom instead of four, one should expect that S_N2 reactions would be sensitive to steric effects. This is indeed observed; steric crowding reduces the rate of bimolecular reactions (eq. 1, Scheme 3.1).



Scheme 3.1

This is also shown by the sequence of rate constants of various substrates (Table 3.1). The effect of changing from methyl to neopentyl, *i.e.*, replacing a

TABLE 3.1

Substrate	$10^3 \times k_2$ ($s^{-1}mol^{-1}$litre) at 55°C	Activation energy (kJ mol^{-1})
Me—Br	34.4	84
Et—Br	1.95	88
i-Bu—Br	0.058	95
Neopentyl—Br	0.000 008 26	111

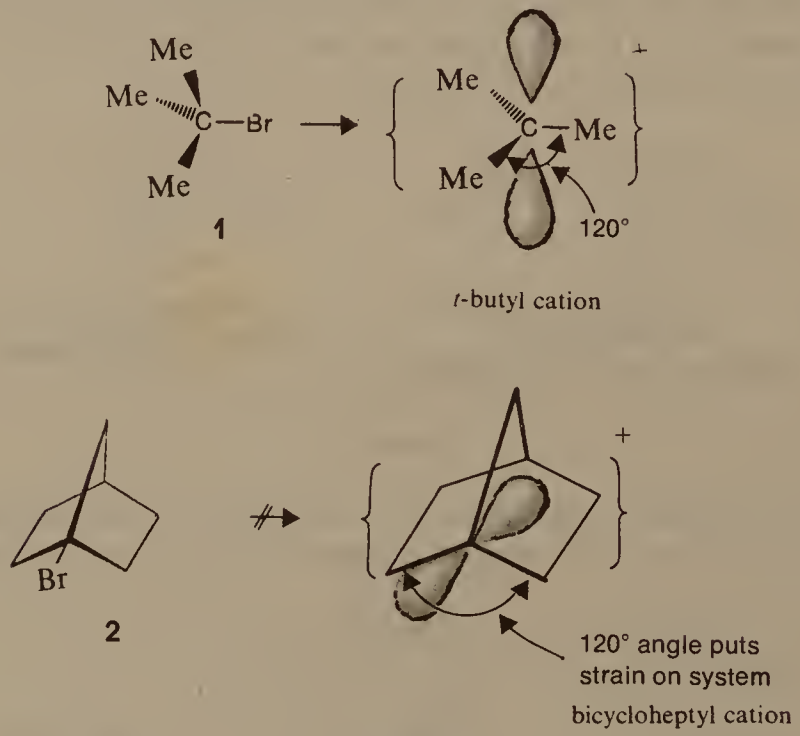
hydrogen of the methyl group with a *t*-butyl group, decreases the rate of the bimolecular reaction by a factor of approximately four million. Therefore, increased crowding of the transition state raises its energy and thus slows

down the reaction.

In S_N1 reactions the effect of bulky groups close to the reaction centre is to increase the rate of departure of the leaving group. The intermediate involved in the reaction is a carbocation where the sp^2-hybridized carbon atom has only three attached groups, compared to four in the substrate. As a result, steric strain in the substrate is decreased by the ionization process. Ionization is therefore accelerated by bulky substituents (eq.1, Scheme 3.1).

3.2 EFFECT OF STRUCTURE OF THE CARBON FRAMEWORK ON S_N1 AND S_N2 REACTIONS

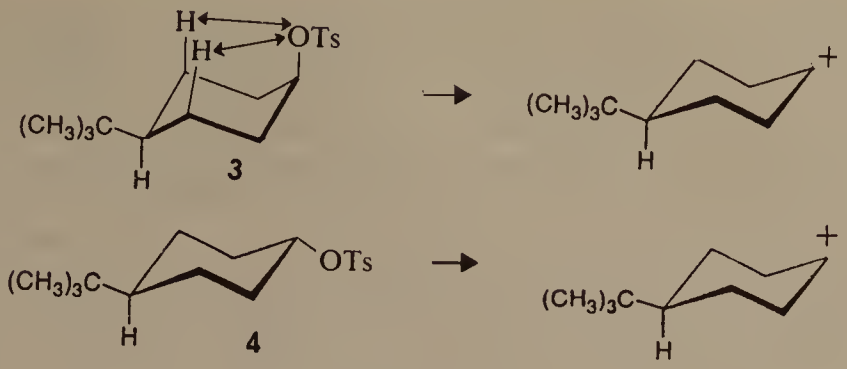
Carbon frameworks capable of stabilizing carbocations facilitate the S_N1 reactions, the stabilization generally increasing in the order $CH^+_3 < RCH^+_2 < R_2CH^+ \simeq C=C-C^+ < R_3C^+ < ArC^+$. Stable carbocations are planar and thus compounds like *t*-butyl bromide 1 undergo a facile replacement of bromine with the formation of the cation $(CH_3)_3C^+$, since it can assume a planar configuration as required by the sp^2- hybridized central carbon. However 1-bromobicyclo [2.2.1] heptane 2 (Scheme 3.2) reacts in an S_N1 reaction



Scheme 3.2

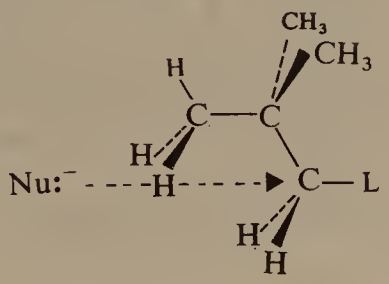
extremely slowly, as the constraints imposed by the bridged ring system prevent the bridgehead carbon from becoming planar, except with an excessive strain.

Consider the acetolyses of *cis*- and *trans*-4-*t*-butyl cyclohexyl tosylates, 3 and 4 (Scheme 3.3). In the case of *cis* compound 3, the tosyl group is in the axial position and thus, suffers from steric 1:3 non-bonded interactions with

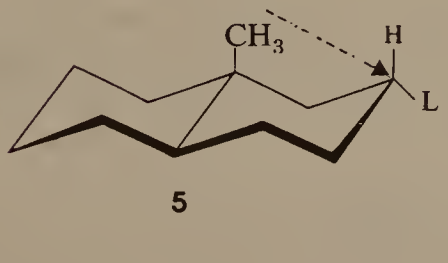


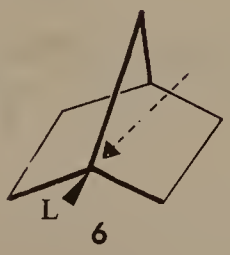
Scheme 3.3

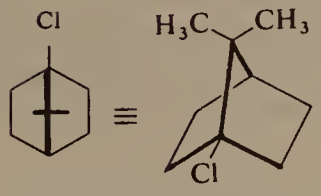
the axial hydrogens. This leads to a faster reaction than with *trans*-equatorial isomer 4 by a factor of about 3.4.



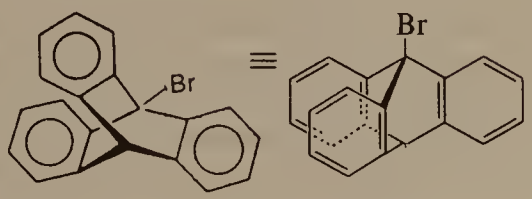
S_N2 *reaction at neopentyl compounds*







1-Chloroapocamphane



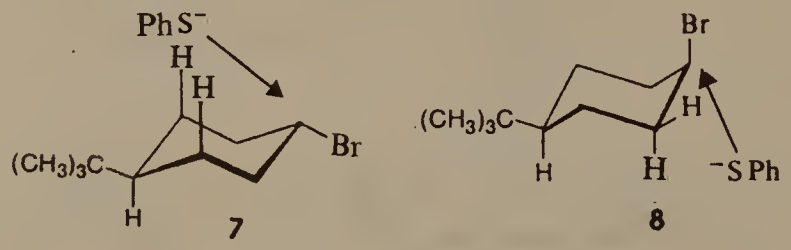
1-bromotriptycene

Scheme 3.4

In the S_N2 reactions, the entering group approaches the backside of the carbon carrying the leaving group (L) and the ease with which the substitution takes place is decreased by anything that hinders this approach. Thus, groups attached to the α- or the β-carbon, or otherwise suitably situated to interfere with the backside approach of the entering group retard S_N2

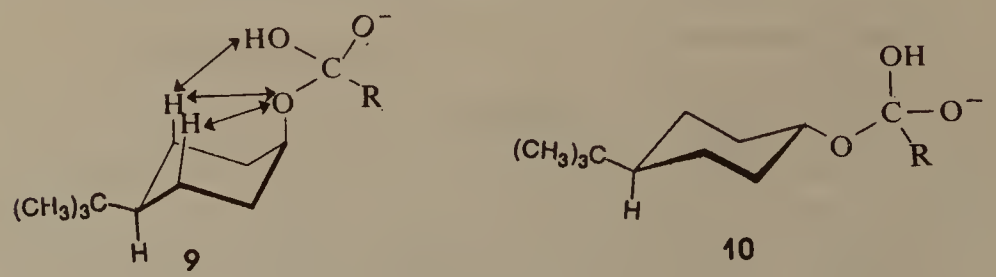
reactions, the reactivity of alkyl frameworks generally increasing because of steric considerations in the order $R_3C < R_2CH < RCH_2 < CH_3$ (*i.e.*, the opposite to the reactivity sequence for S_N1 reactions). In the neopentyl compound (Scheme 3.4), in addition to crowding in the transition state the very bulky *t*-butyl group interferes with the approach of the nucleophile from the backside of the primary carbon atom. In the case of bicyclo [4.4.0] decane **5** the axial angular methyl group similarly hinders the approach of the nucleophilic reagent to the backside of the reaction centre, whereas in the 1-substituted bicyclo [2.2.1] heptane **6**, it is almost impossible for the nucleophile to approach the backside of C-1 from the "inside" of the molecule. Therefore, in extreme cases steric effects tend to prevent biomolecular reactions completely as in the case of 1-chloroapocamphane and 1-bromotriptycene. These compounds are indeed inert to unimolecular substitution. As a result, therefore, the reaction with nucleophiles occur only under extreme conditions of temperature and reaction time. Similarly, the attack of the thiophenoxide ion on equatorial 4-*t*-butylcyclohexyl bromide **7** (Scheme 3.5) is hindered by the β-axial hydrogens and therefore, the S_N2 reaction takes place about 60 times slowly as compared with the reaction of the axial isomer **8**, where the approach of the reagent to the carbon atom having the bromine atom is rather easy.

Reactions in which the rate-determining step is the addition of a



Scheme 3.5

nucleophile to a carbonyl carbon atom, *e.g.*, ester saponification, however, show a reverse order of reactivities. The reagent no doubt can approach from any direction, however, repulsion between an axial carbonyl addition complex and axial hydrogens leads to a decrease in the stability in **9** (Scheme 3.6), as compared to the equatorial isomer **10**.

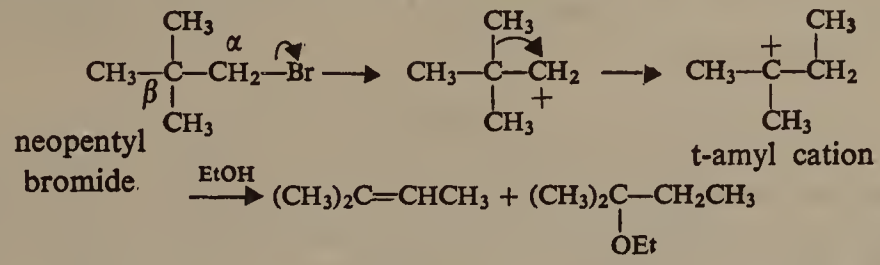


Scheme 3.6

Saponification of the equatorial 4-*t*-butyl cyclohexyl acid phthalate ($R = C_6H_4CO_2H$), thus proceeds faster by a factor of 10 as compared to the saponification of the axial isomer.

3.3 REARRANGEMENT OF CARBON FRAMEWORK IN S_N1 REACTIONS

A molecular (skeletal) rearrangement occurs frequently in S_N1 reactions, while it is rare in the case of S_N2 processes. This is particularly likely to occur if the compound from which the carbocation is derived is highly substituted at the β-carbon. The simplest example is the solvolysis of neopentyl-bromide (Scheme 3.7). In a polar solvent such as ethanol, S_N1-heterolysis leads to neopentyl cation, a methyl group migrates to give the *t*-amyl cation, and this undergoes part-elimination and part-substitution.

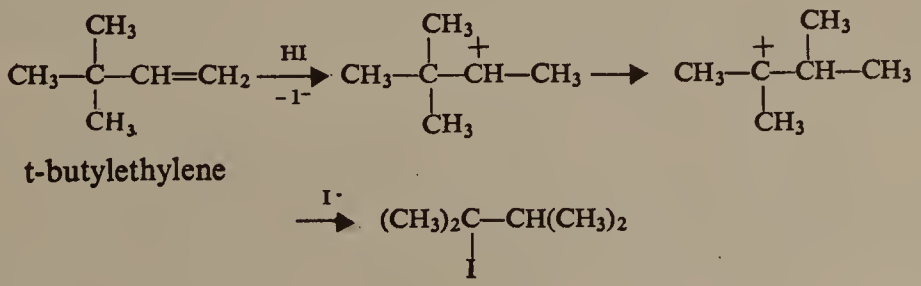


Scheme 3.7

The chief characteristics are:

(*a*) The thermodynamic driving-force for the migration is the increased stability of the tertiary carbocation over the primary carbocation. This step is rapid, for it competes successfully with the expected rapid attack of the solvent on the initially formed carbocation.

(*b*) Other reactions leading to carbocations which can rearrange to give more stable ions also result in rearrangement. For example, the addition of hydrogen iodide to *t*-butylethylene gives mainly a rearranged product (Scheme 3.8).



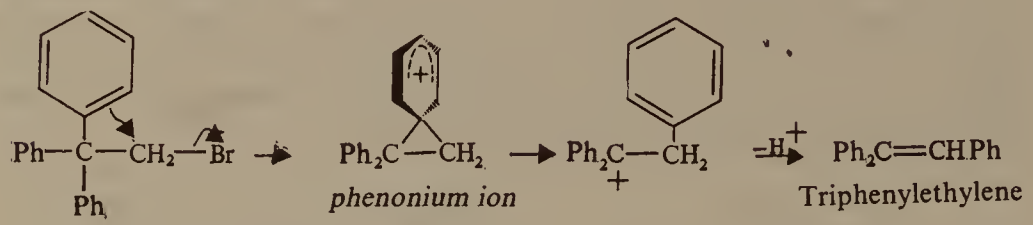
Scheme 3.8

Therefore, the possibility of rearrangement may be considered when S_N1 and El reactions and electrophilic addition to double bonds are concerned.

(*c*) In related compounds where two or three different groups are attached

to the β-carbon, that group migrates which is best able to supply electrons to the carbocation, *e.g.*, phenyl migrates in preference to methyl.

Aryl groups on the β-carbon not only have a much stronger tendency than alkyl groups to migrate, but also speed up the reaction by participating in the rate-determining step. Thus neophyl bromide undergoes solvolytic rearrangement about 10^5 times faster than neopentyl chloride because the rate-determining step in the former case involves the formation not of the high energy primary carbocation, $Ph_3CH^+_2$, but of the delocalized ('bridged') phenonium ion (Scheme 3.9).



Scheme 3.9

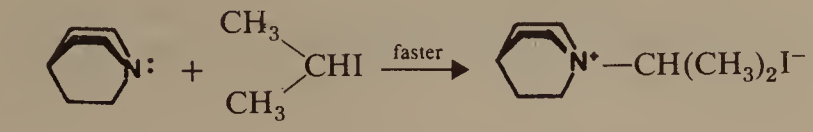
A reaction involving the formation of an ion in which positive charge is delocalized over an aromatic system, the rate of reaction is increased by the presence of electron-releasing groups in the aromatic ring and retarded by electron-withdrawing groups.

3.4 EFFECT OF NUCLEOPHILE ON S_N1 AND S_N2 REACTIONS

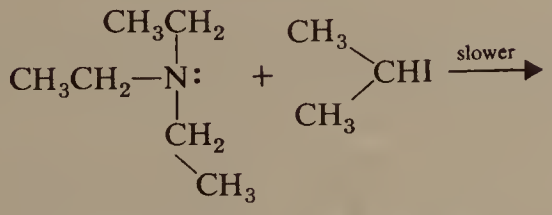
The stronger the incoming nucleophile, the greater is the tendency for the reaction to occur *via* the S_N2 pathway; on the other hand, the weaker the incoming nucleophile the greater is the tendency for the reaction to proceed *via* the S_N1 pathway. The nucleophilic reactivity (*nucleophilicity*) of a reagent is dependent on various factors *i.e.*, charge, basicity, polarizability and size. Therefore, a negatively charged nucleophile is more reactive than a neutral nucleophile; a strong base is more reactive than a weak base, a more polarizable group is a better nucleophile than a less polarizable group, and a small nucleophile usually displays a better reactivity than a larger (more sterically hindered) nucleophile.

The nucleophilicity of the anions derived from first-row elements increases in the order $F^- < RO^- < R_2N^- < R_3C^-$, the basicity also increases in the same order, basicity being inversely related to the acidity of the conjugate acid (*i.e.*, the acidity order of the conjugate acids is $HF > ROH > R_2NH > R_3CH$). Nucleophilicity, however, is the ability of a moiety to donate an electron pair to carbon (*i.e.*, displacement on carbon; $CH_3O^- + CH_3I \rightarrow CH_3OCH_3 + I^-$), while basicity is a measure of its ability to donate an electron pair to a proton (displacement on hydrogen, *e.g.*, $CH_3O^- + H\text{-}OH \rightarrow CH_3OH + OH^-$). Thus, a change in the structure of the reagent does not necessarily change its basicity and nucleophilicity in precisely the same fashion. The changes in size of the

nucleophile, thus may have a more pronounced effect on nucleophilicity than on basicity because of the very different steric demands for displacement



Quinuclidine



Triethylamine

Scheme 3.10

on carbon as contrasted with displacement on hydrogen. Therefore, the nucleophilicity of alkoxides decreases in the order $CH_3O^- > C_2H_5O^- > (CH_3)_2CHO^- > (CH_3)_3CO^-$, even though their basicities follow the opposite order. Partly because of their geometry and minimal steric demands, the linear nucleophiles like CN^- and N^-_3 are typical reactive species. The S_N2 reaction of isopropyl iodide and quinuclidine takes place at a rate 700 times faster than the corresponding reaction of isopropyl iodide and triethylamine (Scheme 3.10), even though both nucleophiles are tertiary amines. The cage structure ties back the substituents in quinuclidine, while the freely rotating ethyl substituents of triethylamine partly cover the lone pair of electrons on nitrogen.

3.5 EFFECT OF THE LEAVING GROUP ON S_N1 AND S_N2 REACTIONS

The halogens are good leaving groups which are easily displaced by other nucleophiles. The more the "leaving ability" of a group the greater is the tendency for the reaction to follow the S_N1 pathway; conversely, the poorer the leaving ability the more is the tendency for the S_N2 pathway. Generally the leaving ability parallels the acidity of the conjugate acid of the leaving group. Thus, Cl^- is a better leaving group than OH^- (*i.e.*, HCl is a stronger acid than HOH), and $C_6H_5O^-$ is a better leaving group than CH_3O^- (*i.e.*, C_6H_5OH is a stronger acid than CH_3OH). The leaving ability is also related with the electronegativity of the group, decreasing from group VII elements (halogens) to group VI elements (oxygen, sulfur) to group V elements (nitrogen) to group IV elements (carbon)

Groups which are positively charged in the starting compound and, therefore, can leave as neutral entities are much better leaving groups than their uncharged counterparts, *i.e.*, the loss of R_3N from $R\text{-}N^+R_3$ occurs easily than the loss of R_2N^- from $R—NR_2$. Similarly, the loss of H_2O from $R—O^+H_2$

occurs readily than the loss of OH^- from R—OH. Thus, the nucleophilic substitution on an alcohol occurs normally only in solutions which are acidic enough to transfer a proton to the alcohol, to convert it to the oxonium salt ROH_2^+. In a similar way, alkyl halides easily convert to esters on treatment with carboxylate anions in presence of silver ions. The silver ion acts as a Lewis acid that attaches itself to the halogen (acting as a Lewis base) and facilitates its exit.

3.6 EFFECT OF SOLVENT ON S_N1 AND S_N2 REACTIONS

A solvent used in a nucleophilic substitution reaction can have a profound effect on the rate of the reaction. In reactions where product formation is favored by charge development in the transition state (*e.g.*, R—L → $[R^{\delta+}\text{---}L^{\delta-}]$), the solvents with high dielectric constant favor the process. Conversely, in reactions in which reduction or dispersal of charge in the transition state favors product formation (*e.g.*, Nu + R—L → $Nu^{\delta-}\text{----}R\text{---}L^{\delta-}$]), solvents of low dielectric constant will favor the process.

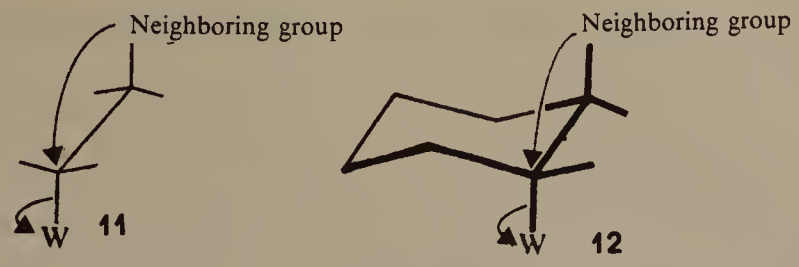
TABLE 3.2 : Dielectric Constants of Some Common Organic Solvents

Solvent	Dielectric Constant (E)	Solvent	Dielectric Constant (E)
Cyclohexane	2.015	Acetone	20.7
Carbon tetrachloride	2.238	Ethanol	24.3
Benzene	2.38	Methanol	32.63
Diethyl ether	4.34	Dimethyl-formamide	37.0
Chloroform	4.806	Dimethyl-sulfoxide	46.3
Acetic acid	6.15	Water	78.5

Therefore, S_N1 reactions and those S_N2 reactions which involve uncharged nucleophiles are accelerated by using high dielectric constant solvents, since charge is developed in the transition state. S_N2 reactions involving negatively charged nucleophiles, conversely, take place more rapidly in low dielectric constant solvents. Several solvents are nucleophilic and, therefore, can react with a compound containing a leaving group to afford stable products. Such reactions are called solvolysis reactions. The hydrolysis, ethanolysis, and acetolysis reactions are typical examples.

3.7 FURTHER EXAMPLES OF NEIGHBORING GROUP PARTICIPATION

Earlier (Sec. 2.3), several examples of this important aspect of intramolecular nucleophilic substitution have been presented. It was pointed out that for such a reaction *anti* relationship between the neighboring group and the leaving group is essential for the back side attack as shown in 11, (Scheme



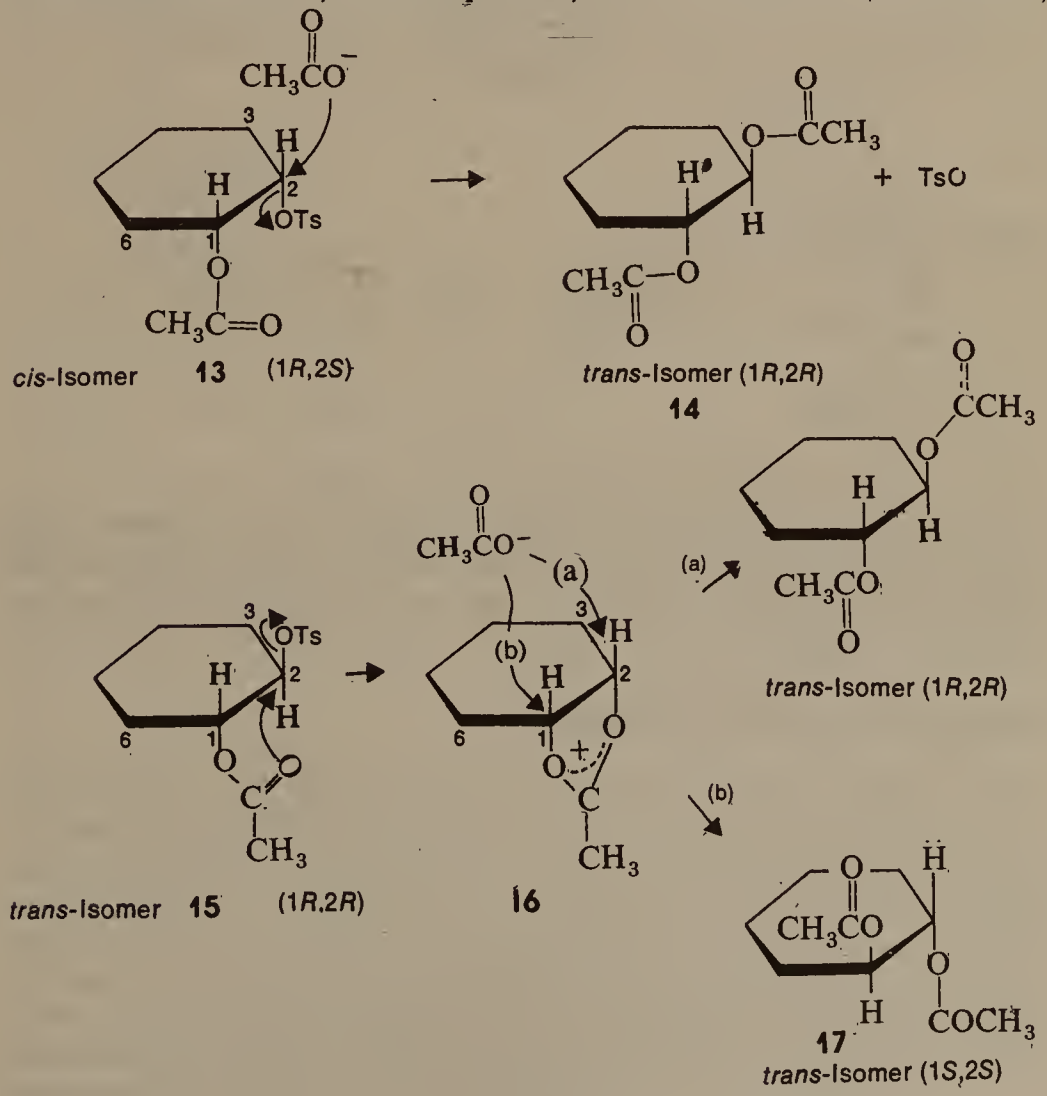
Scheme 3.11

3.11), whereas, in cyclohexane derivatives **12** only *trans* 1,2-groups (diaxial) can assume *anti* relationship.

The role of sulphur, carboxyl group and the σ electrons as neighboring groups has been explained.

(A) Neighboring Acetoxyl Group

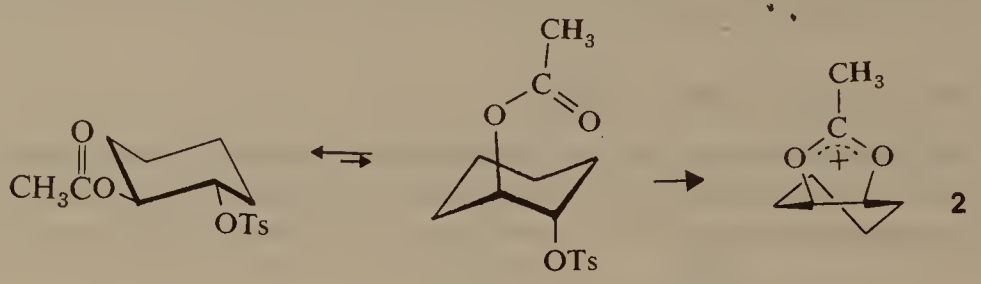
The *cis* and *trans* isomers of 1-acetoxy-2-tosyloxycyclohexane undergo solvolysis in acetic acid to afford 1, 2-diacetoxycyclohexane at different rates and *via* stereochemically different pathways. The *cis*- isomer **13** (Scheme 3.12)



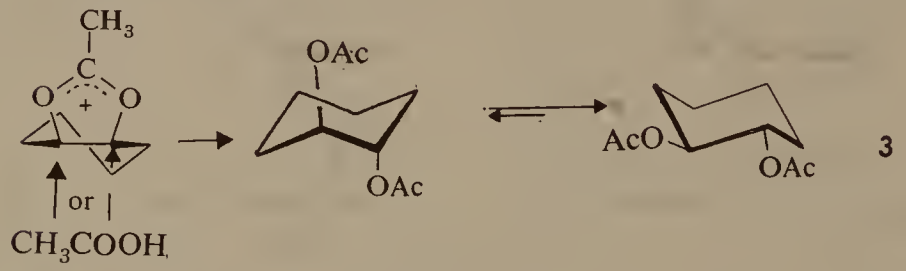
Scheme 3.12

affords the *trans* diacetate 14 in a slow substitution reaction with inversion of configuration (S_N2 process).

However, the *trans*- tosylate 15 forms it 800 times faster. Moreover, optically active *trans*-tosylate 15 yields optically inactive (racemic) *trans*-diacetate, The rate enhancement in the case of 15 is due to the fact that only the *trans*-tosylate can show the neighboring acetoxy group participation because it alone can assume a conformation which allows the acetoxy group to be *anti* (*trans*-diaxial) to the tosyloxy group (eq. 2, Scheme 3.13). In this particular case the cyclic intermediate is a symmetrical entity **16** which can be attacked with equal probability either at C-1 or at C-2 (eq.3, Scheme 3.14).



Scheme 3.13



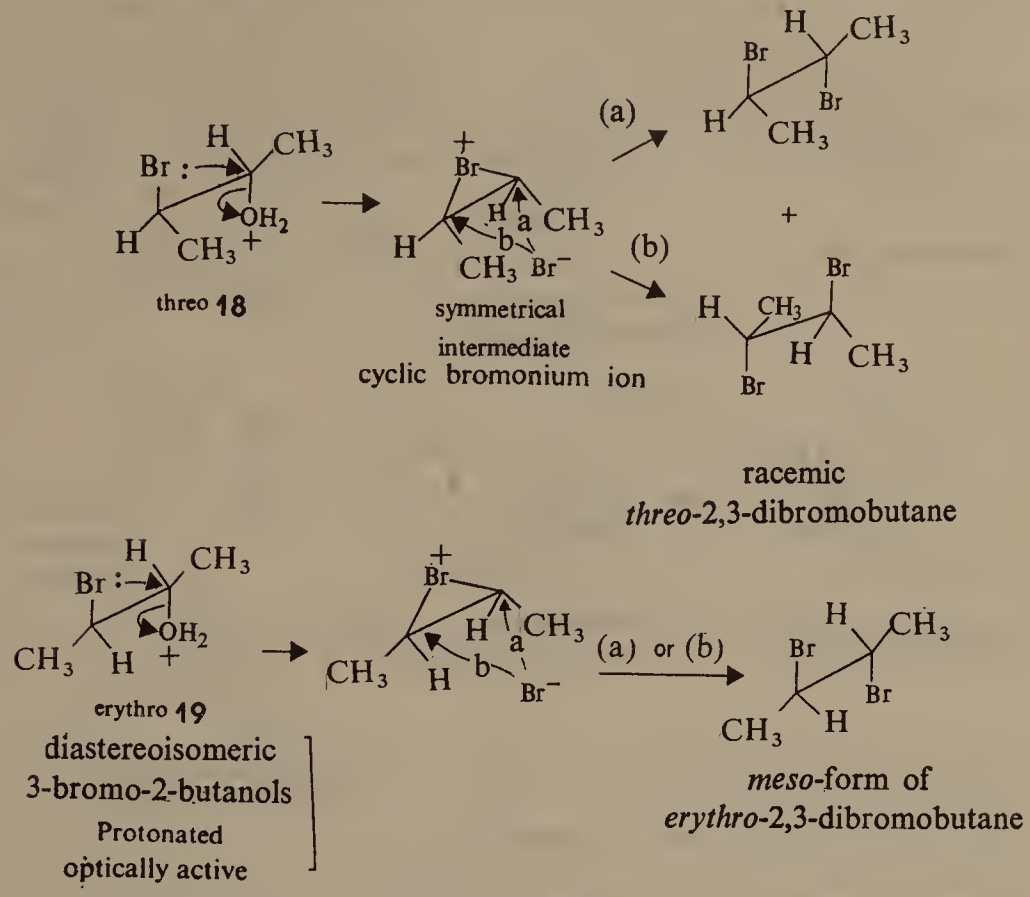
Scheme 3.14

With attack of acetate at C-2, (*a*) there is overall retention of configuration at both C-1 and C-2 and with attack of acetate at C-1, (*b*) there is overall inversion of configuration at both C-1 and C-2. The products resulting from these alternative pathways are enantiomers and are formed in equal amount.

(B) Halogen As Neighboring Group

The reaction of diastereoisomeric 3-bromo-2-butanols **18** and **19** (Scheme 3.15) with hydrobromic acid yields dibromo derivatives with the same configuration. The reaction course can be explained gainfully by the formation of a cyclic bromonium ion identical with the postulated intermediate ion in the addition of bromine to an unsaturated compound. If one starts with the optically active *threo*-isomer racemic *threo*-2,3-dibromobutane is obtained, the reaction proceeding through the symmetrical cyclic bromonium ion intermediate[1]. The *erythro*-isomer yields the *meso*-form of *erythro*-2,3-bromobutane. This is so, because the neighboring

bromine fixes the stereochemistry of the intermediate ion, in a way similar to that in which the *trans* addition of bromine to olefins is controlled.

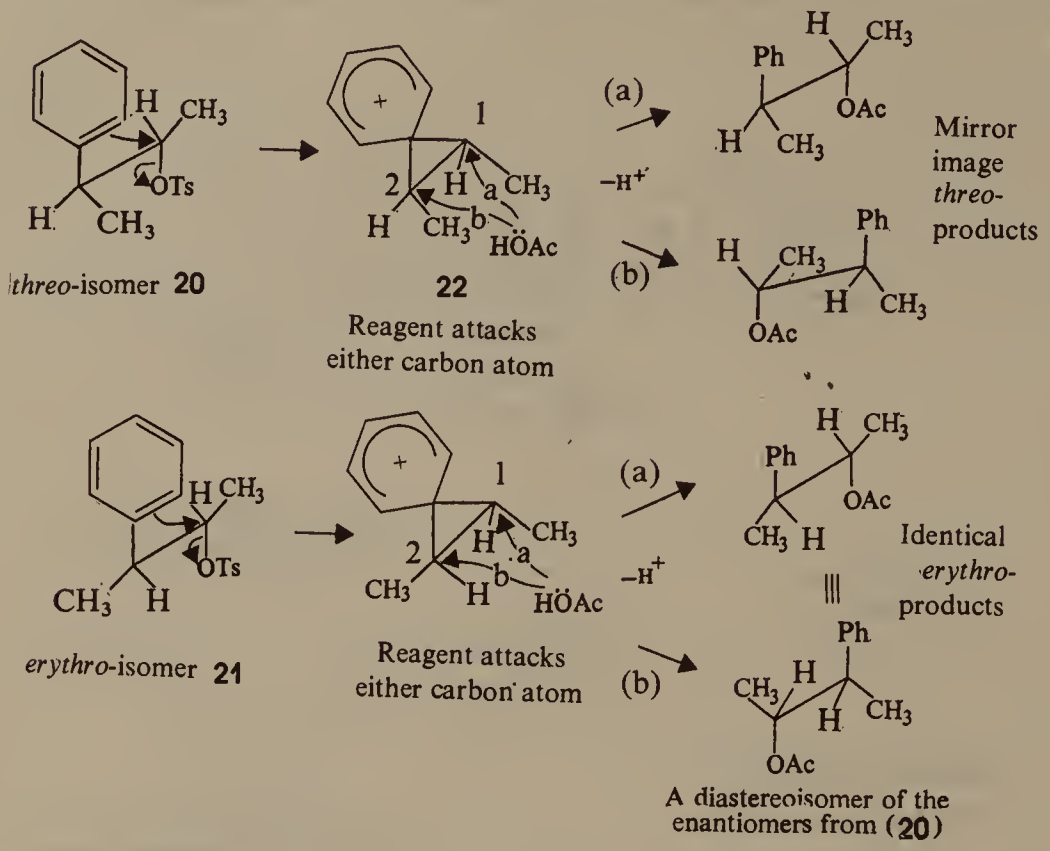


Scheme 3.15

(C) Effect of Neighboring Phenyl Group

In all the cases stated untill now, the groups present in the reacting molecule and influencing the course of the substitution had at least one free electron pair available. As the aromatic ring also has nucleophilic properties to a certain extent, one may expect that their presence in the β-position under certain conditions will influence the substitution by the formation of a cyclic ion (phenonium ion). The first to prove the validity of this assumption was Cram in the course of the reaction of stereoisomeric toluene-*p*-sulphonates of 3-phenyl-2-butanols **20** and **21** (Scheme 3.16) with acetic acid. While reacting the optically active *erythro*-isomer or *threo*-isomer, he obtained in both cases 3-phenyl-2-butyl acetates of the same configuration as the original alcohol. The difference was only in the fact that the optically active *threo*-isomer **20** yielded racemic product only, and the *erythro*-isomer **21** yielded optically active product. The absence of the *erythro*-isomer in the reaction products when one starts from the *threo*-isomer and *vice versa* shows that in the course of the formation of the phenonium ion (sec. 8.1, A, iii) a change of the configuration at C-1 takes place, and when it opens, the configuration changes either at C-1 or at C-2. The loss of optical activity in the case of the

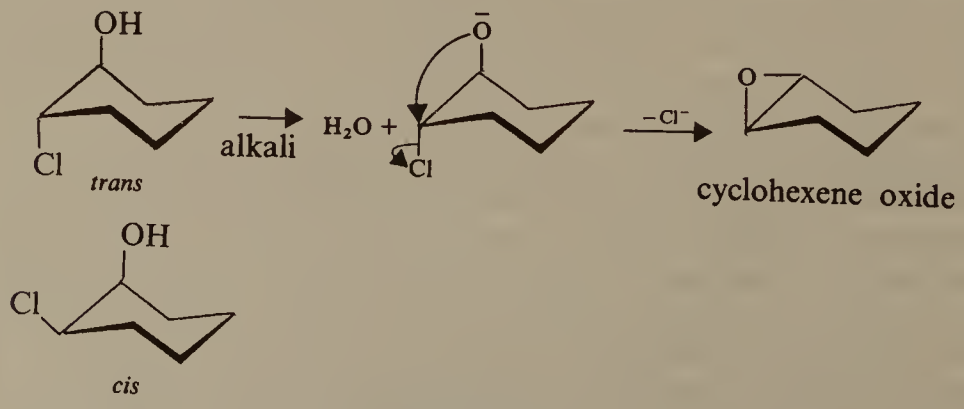
threo-isomer is caused by the formation of the absolutely symmetrical ion **22**.



Scheme 3.16

(D) Effect of Neighboring Groups Containing Oxygen Atom (Hydroxyl or Alkoxyl Groups)

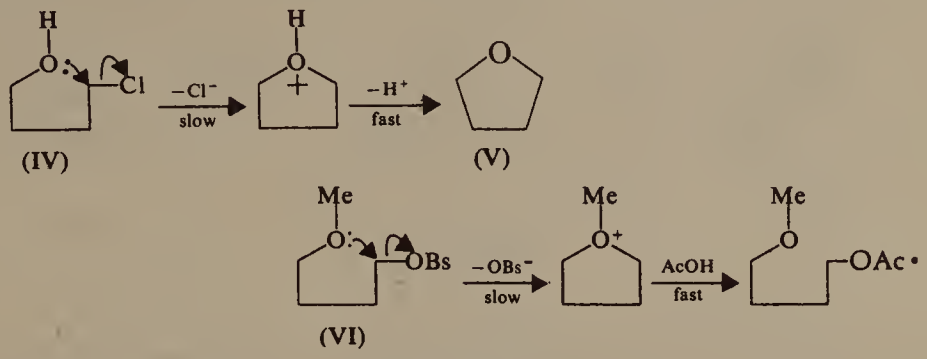
The stereochemistry of epoxide formation from halohydrins with alkali is related to neighboring group participation. In the case of cyclohexane derivatives it proceeds best and at a fast rate because the groups involved are both axial. This is so, as the axial alkoxide is favorably located for a rear attack on the carbon bearing the axial halogen. This situation does not exist in the *cis*-isomer (Scheme 3.17).



Scheme 3.17

In chlorohydrins of the type $Cl(CH_2)_n OH$ anchimeric assistance is greatest when $n = 4$ leading to a five-membered ring and less for $n = 5$ and is absent for other values of n. Tetramethylene chlorohydrin **IV** (Scheme 3.18) in water is converted into tetrahydrofuran (**V**) about 10^3 times faster as compared to ethylene chlorohydrin (conversion to ethylene epoxide).

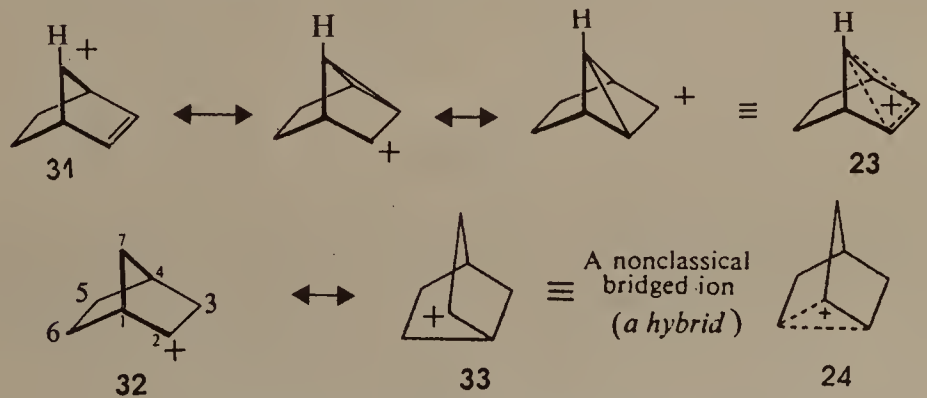
Alkoxyl groups show similar behavior. Thus, the acetolysis of 4-methoxybutyl brosylate (**VI**) is 650 times faster than that of *n*-butyl brosylate.



Scheme 3.18

(E) Neighboring Group Participation by π and σ Bonds (Nonclassical carbocations[2])

Regarding the neighboring-group participation by C=C π bonds and C—C and C-H σ bonds, there has been a great deal of heated debate over whether such bonds can act as neighboring groups and also regarding the existence and structure of the intermediates involved. These intemediates are called nonclassical (or bridged) carbocations. In the case of classical carbocations, the positive charge is either localized on one carbon atom, or delocalized by resonance involving an unshared pair of electrons or a double or a triple bond in the allylic position. In a nonclassical carbocation however, the positive charge is delocalized by a double or triple bond which is not in the allylic position or by a single bond. Examples are the 7-norbornenyl cation **23** and the norbornyl cation **24** (Scheme 3.19). The cation **31** is called a

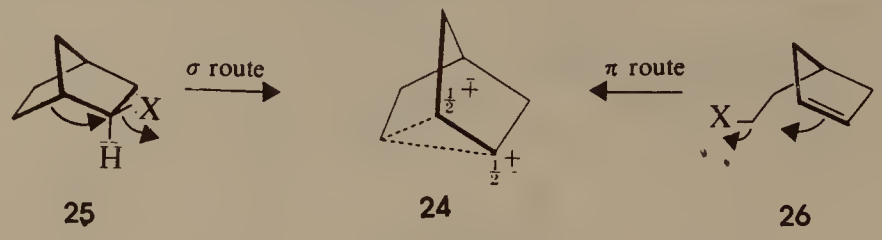


norbornyl cation, for example, is a bridged ion, 32 and 33 are contributing structures to resonance hybrid

Scheme 3.19

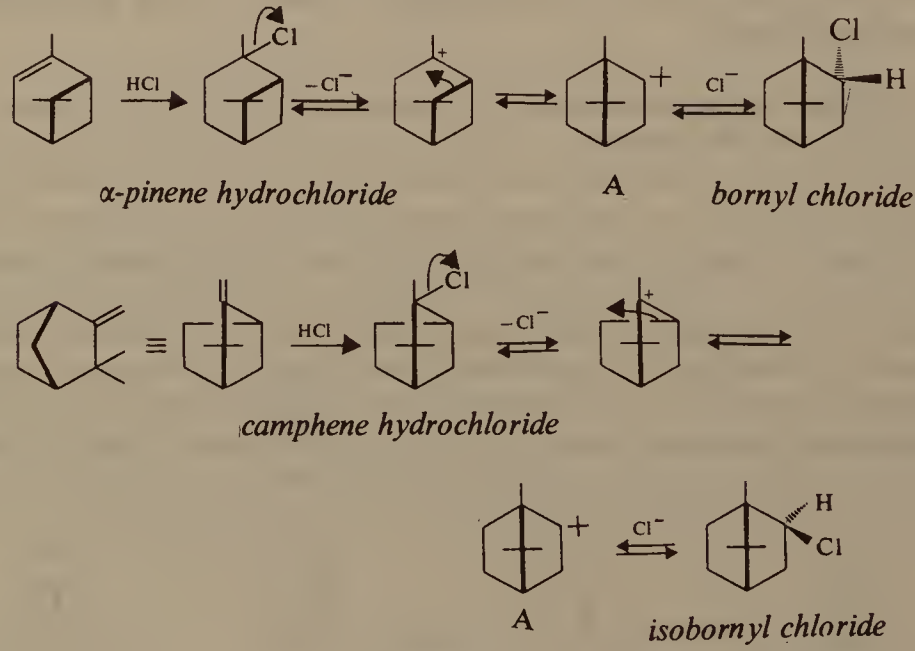
homoallylic carbocation, since in **31**(a) there is one carbon atom between the positively charged carbon and the double bond. A nonclassical carbocation may be produced in more than one way depending on the substrates involved. For example **24** (Scheme 3.20) can be generated by departure of a leaving group from **25** or from **26**.

Indeed non classical carbocations are involved in several Wagner-Meerwein rearrangements. In case a carbocation mechanism is operative, one



Scheme 3.20

cannot explain the formation of epimers, *e.g.*, on reaction of α -pinene and camphene with HCl, since in both, the same carbocation **A** (Scheme 3.21) is involved.

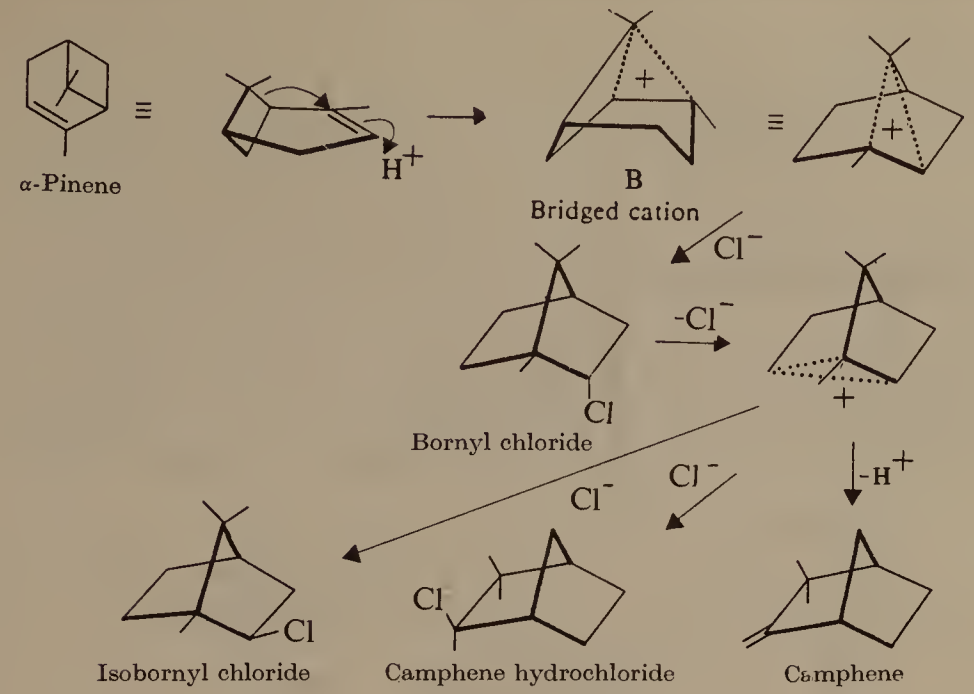


Scheme 3.21

In fact, this discrepancy and the transformation of α-pinene to the derivatives of the *p*-menthane, camphane, isocamphane and fenchane series can be gainfully explained on the basis of the formation of the nonclassical carbocation **B** (Scheme 3.22). This ion is easily formed when α -pinene is protonated in accordance with the Markovnikov rule at C-3.

The subsequent fate of the ion **B** depends on the conditions of the reaction:

1. Reaction with a nucleophile.



Scheme 3.22

2. Loss of a proton to yield α- or β-pinene.
3. Rearrangement to give a new carbon skeleton, due to the relief in angle strain when the four membered ring opens.

Under very mild conditions with anhydrous hydrogen chloride true α-pinene hydrochloride can be isolated. However, under ordinary conditions bornyl chloride is formed and the exclusive formation of *endo* isomer is due to the attack of **B** on C-2 from the side opposite to the bond which is breaking, thus, yielding stereospecifically the *endo* product with inversion.

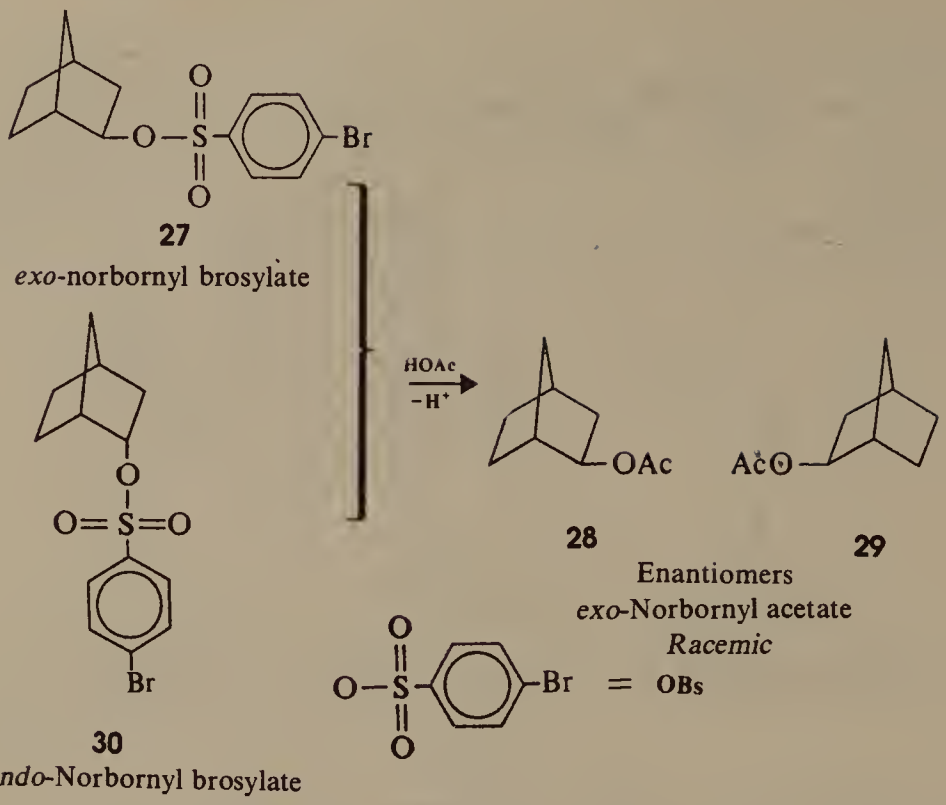
1. Neighboring Group Participation of C—C single Bonds

Neighboring group participation of C—C bonds is best observed in cyclic systems where the rigid structure holds this bond in a suitable place for participation at all times. The classic example of these reactions is the norbornyl system (Sec. 4.12A and 4.15A), and the following points may be noted:

(*a*) When optically active *exo*- or *endo*-2-norbornyl brosylates **27** and **30** (Scheme 3.23) respectively undergo acetolysis the product is *exo*- norbornyl acetate which is entirely racemic in the first case and almost racemic in the second.

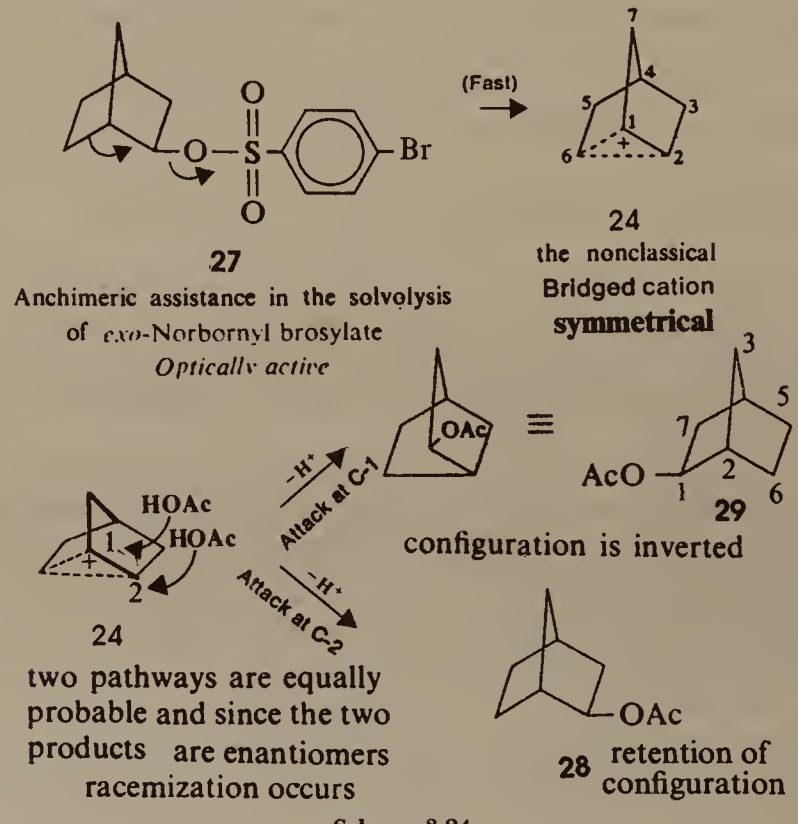
(*b*) Significantly the *exo*-isomer reacts several hundred times faster as compared to the *endo*-isomer.

(*c*) These data were interpreted by Winstein to show that in the *exo*-isomer neighboring group participation was operative. Thus, in the *exo*-isomer **27** the electrons of the C-1, C-6 bond which are located suitably at the backside of the carbon to which the leaving group is attached, assist (*i.e.*,



Scheme 3.23

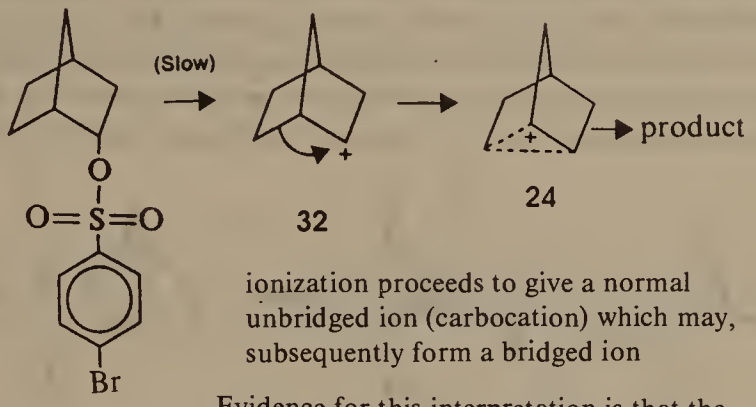
act as a neighboring group) the departure of the leaving group, involving a "bridged" carbocation (*i.e.*, nonclassical carbocation) **24** (Scheme 3.24).



Scheme 3.24

Overall retention of configuration is due to two inversion steps. Racemization of the optically active material during acetolysis confirms the formation of a symmetrical bridged cation which reacts with acetate either at C-1 or C-2 with equal probability.

(*d*) Winstein further argued that solvolysis of the *endo*-isomer, **30** is not assisted by the 1,6-bond because it is not in a favourable position for backside attack and thus solvolysis of **30** occurs at the normal rate. It involves the initial formation of a carbocation **32** in which the electrons are not delocalized. After its formation, the ring system no longer has the rigid stereochemistry of the starting compound and it interacts with the electrons of the C-1, C-6 bond leading to the same nonclassical carbocation **24**.



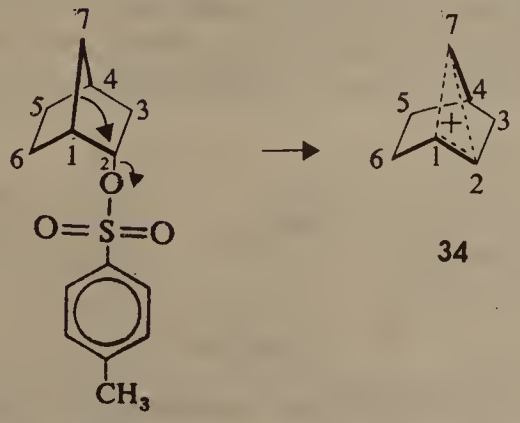
30
endo-

ionization proceeds to give a normal unbridged ion (carbocation) which may, subsequently form a bridged ion

Evidence for this interpretation is that the product from solvolysis of 30 is not racemic but contains somewhat more 28 than 29 (corresponding to 3 to 13% inversion, depending on the solvent), suggesting that when 32 is formed, some of it goes to give 28 before it can collapse to 24.

Scheme 3.25

(*e*) It may be mentioned that in the case of *endo*-isomer **30**, an identical



30

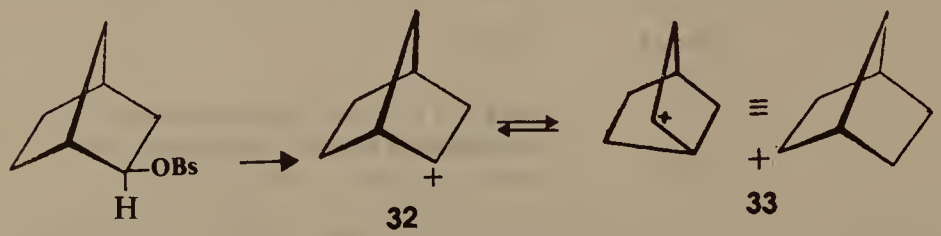
Scheme 3.26

migration of the electrons of the C-1, C-7 bond may occur to afford the non classical ion 34.

The ion 34 if formed, would involve the contraction of one of the five-membered rings of the norbornyl system. This instability factor does not allow the formation of ion 34, therefore, the electrons of the C-1, C-7 bond do not assist the departure of the leaving group in the *endo*-isomer.

(*f*) Once formed from 32, the ion 24 again reacts either at C-1 or C-2 which are equivalent. As with delocalized ions, reaction of the ion 24 with a nucleophile occurs from the opposite side to the partial bond. Thus the attack either at C-1 or at C-2 in 24 affords the product which is atleast 99.5% *exo*-norbornyl acetate. Reaction at C-1 or C-2 in 24 is equally likely, 28 being the mirror image of 29, racemization is the net result.

(*g*) Two very important points may be noted. The nature of the bridged cation has been a subject of heated debates. According to one interpretation it is considered to be an equilibrium mixture of rapidly interconverting localized carbocations, *i.e.*, "classical" carbocations 32 and 33.

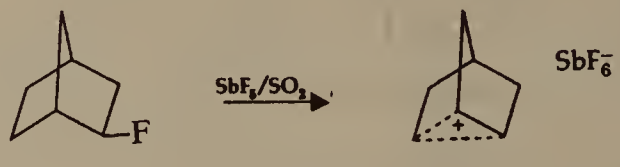


a pair of equilibrating open carbocations. Substitution is exclusively *exo* because the *endo* face of each cation lies in a fold of the molecule, and is screened from attack.

Scheme 3.27

According to the second interpretation, it is considered to be a single entity 24, a non classical carbocation.

(*h*) The presence of single entity, *i.e.*, a non classical carbocation (norbornyl cation) in the reactions of norbornyl and related systems is generally accepted by chemists[3,4] ^{13}C-NMR studies have led to the detection of this non classical carbocation in superacid media (Scheme 3.28). It is of interest to note that 2-phenylnorbornyl cation **B** (Scheme 3.29), has the classical

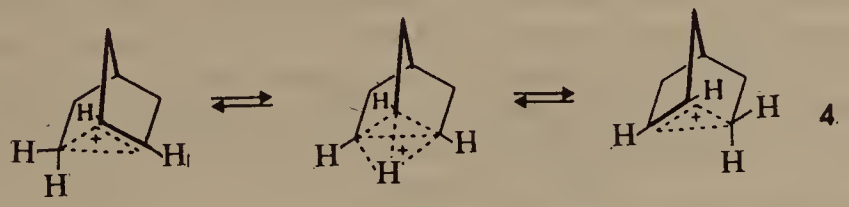


Scheme 3.28

structure. This benzylic cation gets stabilized by π electrons of the benzene ring and bridging (when the +ve charge is distributed over C-1 and C-2) has no advantage. The tertiary 2-methylnorbornyl cation **A**, has some bridging which is weaker as compared to the unsubstituted cation.

Scheme 3.29

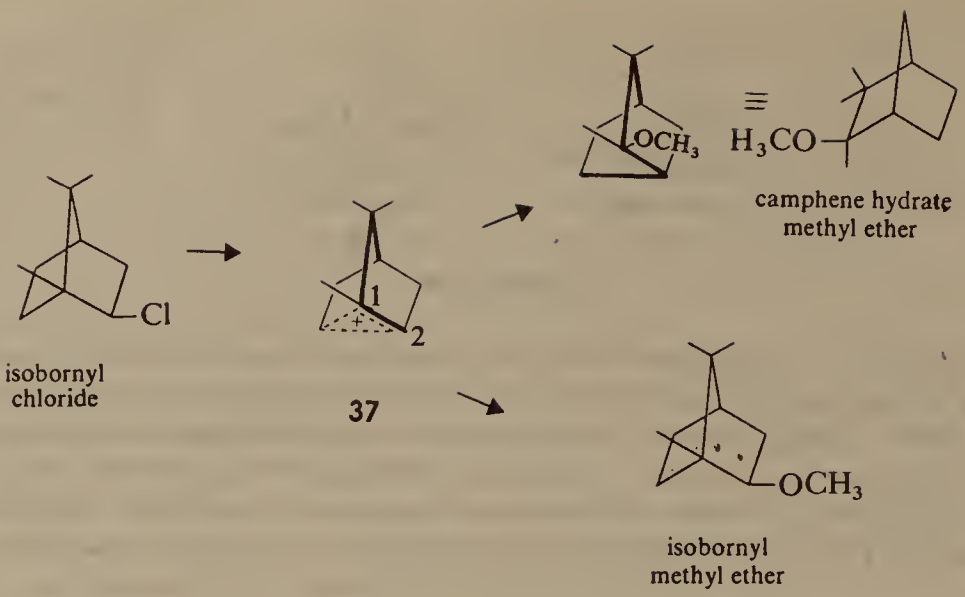
(i) This is an oversimplified picture of the norbornyl cation which seems to be inadequate by the study of the labelled molecule (with radioactive carbon). Labelled compound **35** (Scheme 3.30) should lead us,on the basis of the above mechanism, to the equal distribution of label between C-1, C-2, C-3 and C-7. However, the product was found to have 15 per cent of the label on C-5 and C-6 in **36**. This pattern of labelling points to the fact that if



Scheme 3.30

the ion undergoes a 6 → 2 hydride shift *via* a cyclic transition state mechanism which can be shown as in equation 4 (Scheme 3.30). Due to the symmetry of the system, this only generates a new mirror image ion of the original ion. Since this ion can also react with the nucleophile at either C-2 or C-6, similarly as the original ion, this therefore, provides another machanism for racemization of the product.

The reactions of norbornyl derivatives display simplicity due to the unusual symmetry of the system, but when one deals with some naturally occurring terpenoids (the trimethyl norbornanes) a part of this symmetry is lost.The basic principles of the rearrangements in bridged ions, no doubt remain unchanged; the difference being that the reactions which end up with racemization in the norbornyl system now give rearrangement. The methanolysis of isobornyl chloride is cited as an example. Ionization affords a bridged ion **37** (Scheme 3.31) as in norbornyl derivatives. The ion can now behave in the same way,reacting at either C-1 or C-2. The decreased symmetry

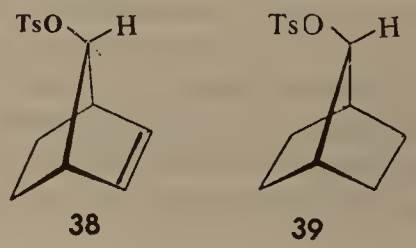


Scheme 3.31

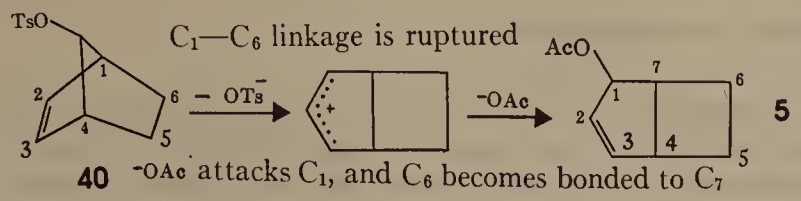
of the system however, means that reactions at C-1 and C-2 yield different compounds. The carbon atoms not being equivalent, the products, as expected, are not formed in equal amounts. The solvolysis of isobornyl chloride with sodium methoxide in methanol yields products based on reaction at the sterically more hindered tertiary atom C-1 (99%) and only 1% reaction at the secondary atom C-2. The electron distribution in the bridged ion can no longer be symmetrical; the greater part of the charge is concentrated at the tertiary rather than the secondary atom, therefore, the nucleophile gets largely directed toward this atom.

2. Effect of Neighboring Double Bond

For some time it has been known that the toluene-*p*-sulphonyl esters of steroid 3, β-hydroxyderivatives containing a double bond between the carbon atoms C-5 and C-6 react with nucleophiles, retaining the configuration (sec. 7.3, B V) at C-3. A difference in reactivity due to a double bond has been observed for many bicyclic compounds; for example, of the toluene-*p*-sulphonyl esters of 7-hydroxybicyclo [2,2,1] hept-2-ene, the *anti*-isomer **38** (Scheme 3.32), undergoes acetolysis at a 10^{11} times greater rate than the saturated compounds **39**. The *syn*-isomer **40** reacts at 10^{7} times lesser rate than the *anti*-isomer, yielding mainly the rearranged product (eq. 5).



38 39

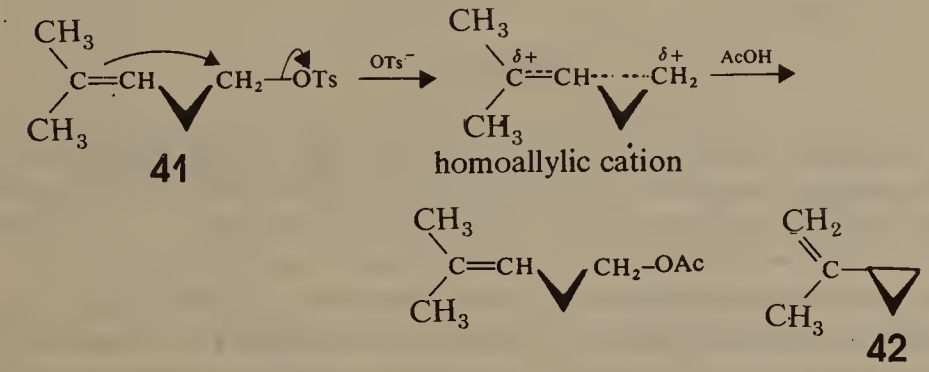


Scheme 3.32

The rate data alone does not necessarily prove that acetolysis of 38 involves a non classical intermediate (eq. 6, Scheme 3.33), but it is certainly strong evidence that the C=C group assists in the departure of the OTs.

Scheme 3.33

Double bonds act as neighboring groups in acyclic systems *e.g.*, the acetolysis of 4-methylpent-3-enyltosylate 41, is about 1000 times faster than that of ethyl tosylate, and one of the product 42, is a cyclopropane derivative (Scheme 3.34).



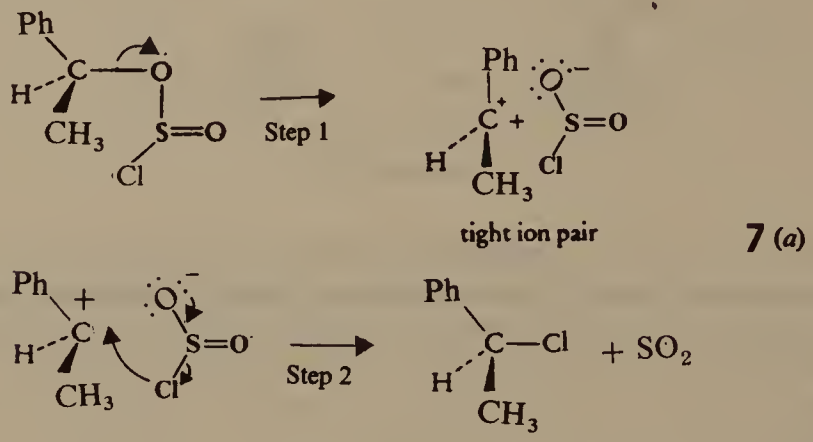
Scheme 3.34

(F) Effect of Neighboring Hydrogen Atom and Hydrocarbon Group

Several organic reactions involve the migration of hydrogen atoms. An example is the reaction of the toluene-*p*-sulphonate of 2-butanol-[1—^{14}C] with acetic acid. The distribution of radioactivity in the reaction products points to a 1,2-shift of the hydrogen atom. The ethanolysis of *cis*-2-methylcyclohexyl toluene-*p*-sulphonate, in which the hydrogen can be in an *anti*-periplanar position to the substituent group and thus facilitate its ionisation, proceeds at 71 times greater rate than with the *trans*-isomer and leads to a substitution product of *cis*-configuration. Methyl shifts are common, for instance, in the course of the reactions of neopentyl systems.

3.8 THE S_Ni MECHANISM

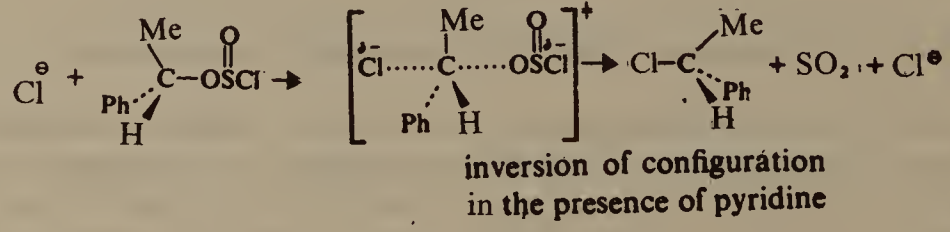
In some reactions, nucleophilic substitution proceeds with retention of configuration even where there is no possibility of a neighboring-group effect. In the S_Ni mechanism (Substitution, nucleophilic, internal) part of the leaving group is able to attack the substrate, detaching itself from the rest of the leaving group in the process. The first step is the same as the first step of the S_N1 mechanism (dissociation into an intimate ion pair). However, in the second step, part of the leaving group attacks, necessarily from the front, since it is unable to get to the rear. This leads to retention of configuration (eq. 7a, Scheme 3.35).



Scheme 3.35

The example shown is the most important case of this mechanism yet discovered, since the reaction of alcohols with thionyl chloride to give alkyl halides usually proceeds in this way, with the first step in this case being ROH + $SOCl_2$ → ROSOCl (these alkyl chlorosulfites can be isolated).

Evidence for this mechanism is that the addition of pyridine to the mixture of alcohol and thionyl chloride leads to the formation of alkyl halide with inverted configuration (Scheme 3.36). Inversion takes place because pyridine

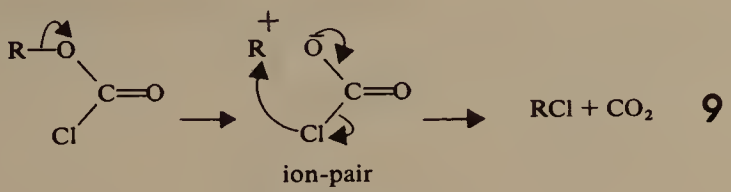


Scheme 3.36

reacts with the initially formed ROSOCl to give $ROSON^+C_5H_5$, before anything further can take place. The Cl^- freed in this process attacks from the rear (S_N2). The reaction between alcohols and thionyl chloride is second order, which is predicted by this mechanism. However, the decomposition of

ROSOCl by simple heating is first order. Although this reaction is a one-step process (sec. 1.16A), the fact that $Me_2CHCHMeOSOCl$ on heating afforded Me_2CClCH_2Me shows that an ion pair must have been present as there is no other way to explain the rearrangement (eq. 8, Scheme 3.37), where an initially formed secondary carbocation rapidly rearranges to the more stable tertiary carbocation.

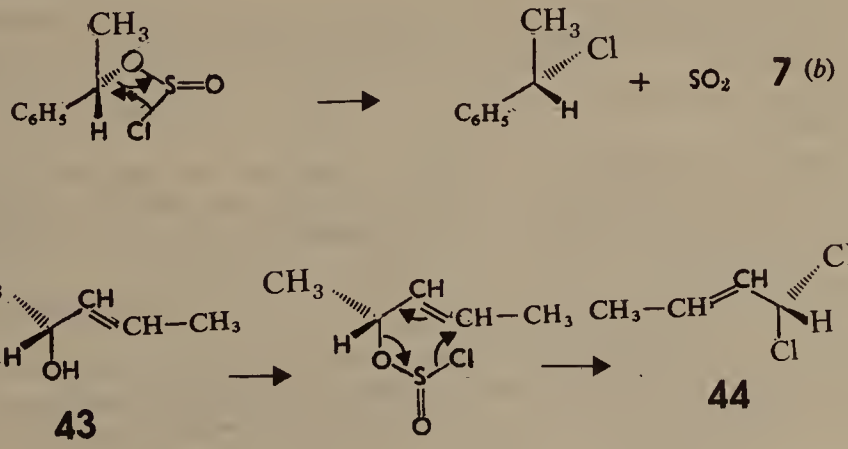
The S_Ni mechanism is relatively rare and another example is the decomposition of alkylchloroformates with retention of configuration (eq. 9).



Scheme 3.37

An S_Ni reaction probably occurs even in the reaction of hydrogen halides with alcohols at low temperatures. (—)—α—Phenylethanol and anhydrous hydrogen bromide at-80°C gives (—)—α—phenylethyl bromide of the same configuration. The higher the temperature, the greater is the amount of the product with inverted configuration. The reactions of amines with nitrous acid or nitrosyl halides also sometimes occur by an S_Ni mechanism.

Intramolecular substitution has also been detected in the case of allyl compounds (S_Ni'). The reaction of thionyl chloride with optically active *trans*-α, γ-dimethylallylcarbinol 43 gave a chloride of opposite configuration 44 (Scheme 3.38).

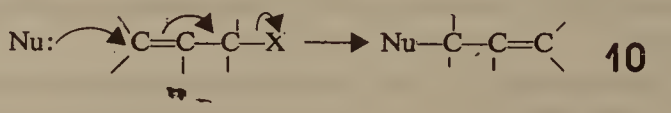


Scheme 3.38

Conjugated (allylic) systems can undergo substitution with rearrangement

(S_N2' reaction) in addition to the S_N2 reaction (eq. 10, Scheme 3.39).

The S_N2' reaction normally occurs only when the S_N2 process is sterically hindered. For example, α-methylallyl chloride reacts with diethylamine to give a crotylamine derivative (eq. 11).



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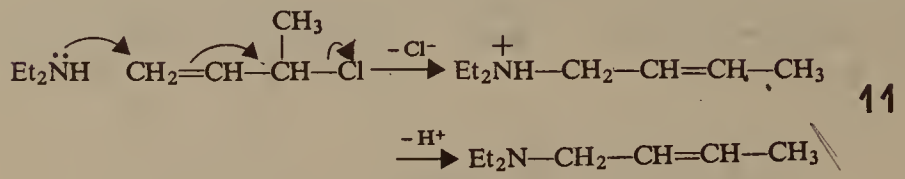

11

Scheme 3.39

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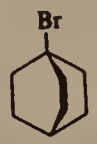
3. G.A. Olah, Liang, D. Mateescu and J.Louise-Reimenschneider, *J.Amer.Chem.Soc., 95*: 8698 (1973).
4. G.A.Olah, *J.Amer.Chem.Soc., 94*: 808, 1972; *Acc.Chem.Res.*, **9** : 41-52 (1976).

EXERCISES AND PROBLEMS

1. Comment on the following observations:—
   (a) Neopentyltosylate reacts at a slow rate with lithium iodide but resists reaction with lithium chloride while *n*-butyll tosylate reacts with either of the nucleophiles at a reasonable rate.
   (b) 1-Phenylethyl chloride solvolyzes much faster than 2,2-dimethyl-1-phenylpropyl chloride.
   (c) Optically active *sec*-butyl chlorosulfite on warming in dioxan affords *sec*-butyl chloride with 97% retention, while the same reaction carried in isooctane leads to 43% inversion.
   (d) Tri-*tert*-butylcarbinol solvolyzes much more rapidly in acid solutions as compared with *tert*-butyl alcohol.
   (e) The yields of substitution product in the reactions of *sec*-butyl chloride with $(CH_3)_2N$,$(CH_3)_3CO^-$, CH_3O^-, and I^- increase in the order given.
2. During displacement on alkyl halides (R—X), the ratio of rates with two amines (Rate ratio = quinuclidine : triethylamine) is given below; with triethylamine it being always slower. How do you account for this rate difference and for its increase in the given series:—

CH_3X	57
C_2H_5X	252
$(CH_3)_2CHX$	706

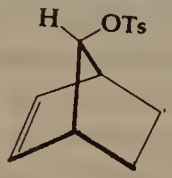
3. Name some ionizing and non-ionizing solvents..
4. A *trans*-1,3 cyclohexyl derivative ($BrC_6H_{10}COO^-$) spontaneously eliminates bromide ion to give a lactone while the *cis* isomer is inert. Explain.
5. Compounds (a) and (b) below are subjected to solvolysis in ethanol. It is observed that the rate of solvolysis does not change on the addition of ethoxide ion and (a) solvolyzes faster as compared to (b). Explain.



a

b

6. What conclusions do you draw from the fact that solvolysis of **A** in the presence of hydride ions ($NaBH_4$) affords **B** and **C**?



A

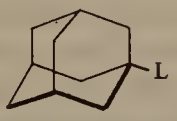
B

C

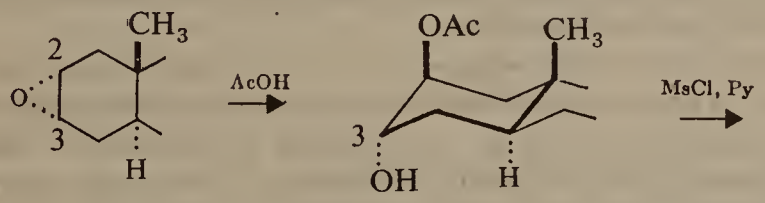
7. Primary halides of the type, $ROCH_2X$ apparently display S_N1 reactivity while most primary halides do not. Propose a resonance based explanation.
8. How can you explain the relative rates of solvolysis in ethanol of the following chlorides?

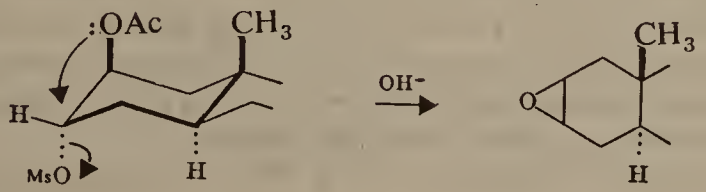
$C_6H_5CH_2Cl$	$C_6H_5CHCH_3$ | Cl	$(C_6H_5)_2CHCl$	$(C_6H_5)_3CCl$
(0.08)	(1)	(300)	(3×10^6)

9. The bridged cyclic compound shown below is extremely unreactive in S_N2 reactions. Explain. How will you explain the fact that compounds of this type are also more uncreative in S_N1 reactions than similar noncyclic compounds?



10. Explain the following series of reactions in the case of steroid.





4

CONFORMATIONS OF ACYCLIC AND CYCLIC SYSTEMS

4.1 RESTRICTED ROTATION ABOUT SINGLE BONDS—CONFORMATIONS OF ETHANE (ROTAMERS, CONFORMERS, CONFORMATIONS)

In the early days of chemistry, it was found that the saturated aliphatic compounds did not show isomerism of the type associated with restricted rotation about a bond. It was concluded, then, that rotation about C—C single bonds was completely free. The experimental observation that rotation about the carbon-carbon sigma bond of ethane is not completely free poses the question as to what is inhibiting the motion. The question has however, never been answered completely. It seems that small repulsive interactions between the carbon-hydrogen bonds on adjacent carbon atoms do exist. Repulsive interaction between bonds on adjacent atoms which lead to restricted rotation is termed as torsional strain.

The magnitude of the energy associated with torsional strain in simple molecules is indeed small, normally less than 5 kcal/mol (20 kJ/mol). At room temperature thermal energy is sufficient to overcome torsional strain so that interconversions between potential isomeric forms is rapid. The readily interconvertible torsional structures are known as conformations[1-3] and the compounds which they represent as conformational isomers.

Consideration of Newman projection formulas is the best method to follow the changes in molecular geometry that occur during rotation about the carbon-carbon bond of ethane. The minimum in torsional energy occurs when the carbon-hydrogen bonds of one methyl group are as far away as possible from those of the other. This spatial relationship with dihedral angle of 60°, is termed staggered conformation.

As the methyl groups rotate 60° relative to each other, the dihedral angle becomes 120° (or 0°). The carbon-hydrogen bonds are at their closest approach in a spatial arrangement known as the eclipsed conformation. These conformational isomers may be called conformers. The energy changes associated with such rotation are represented in Fig. 4.1.

It is seen that of the infinite number of conformations, the one with minimum energy is the one where hydrogen atoms on adjacent carbon atoms are as far apart as possible, *i.e.*, the staggered conformation, while the conformation with maximum energy is that with the hydrogen atoms as close as possible. *i.e.*, the eclipsed conformation.

In a sample of ethane at 300°K 99% of the molecules are in or near the

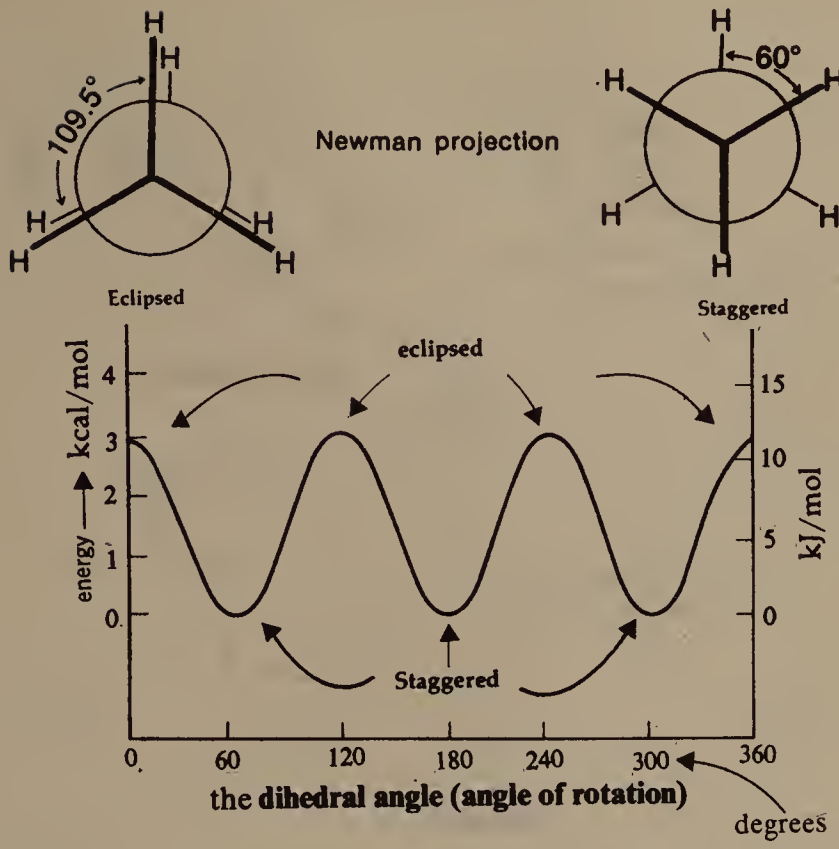


Fig. 4.1

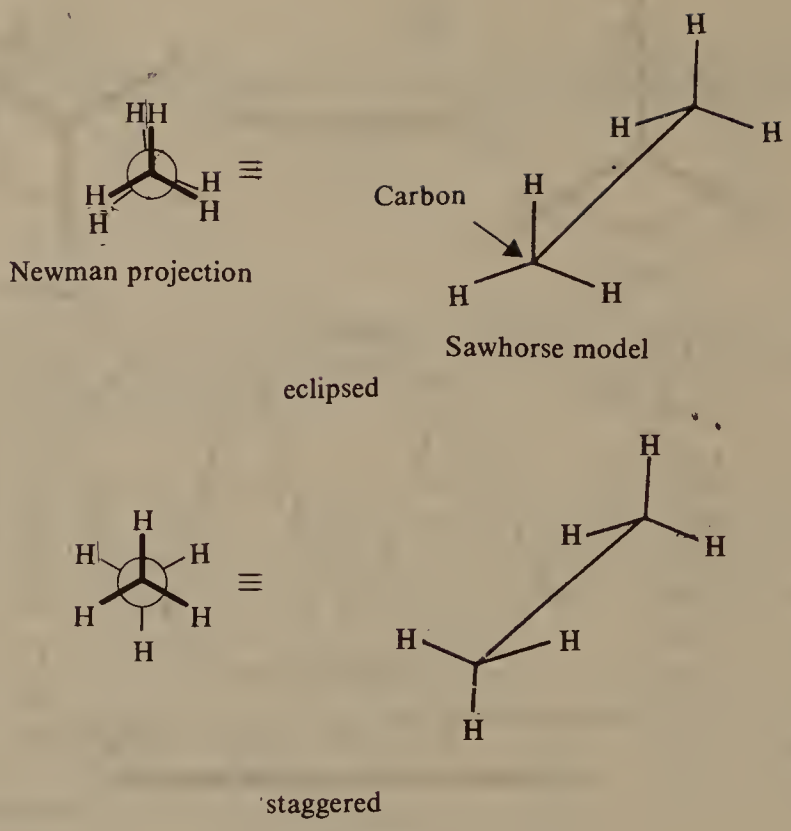
staggered conformation, it being the configuration of minimum energy. The low barriers of 12 kJ mol^{-1} allow easy passage from one staggered form to another; at any given time about one per cent of the molecules are making this passage and are thus in or near the eclipsed form. To draw a Newman projection, one looks along the bond under study, and represents the front carbon atom by a dot, and the back carbon atom by a circle with the dot as centre. Substituents on the front carbon atom are then drawn radiating from the dot, those on the back carbon atom radiating from the circle.

An useful alternative to the Newman projection is the sawhorse projection, which is illustrated below for comparison with the Newman projections.

4.2 CONFORMATIONS OF BUTANE

As one side of the molecule of *n*-butane rotates through 360° relative to the other, three eclipsed and three staggered conformations are encountered. The staggered rotamer in which methyl groups are farthest apart is called *anti* (or *trans*) and is the most stable conformation. The staggered rotamers with adjacent methyl groups (dihedral angle 60°) are the *gauche* conformations.

The energy association with a methyl-methyl interaction is greater than that with a methyl-hydrogen interaction, which in turn, is greater than that with a hydrogen-hydrogen interaction[4,5]. The repulsive forces due to interactions between bonds on adjacent atoms are similar in each case. There

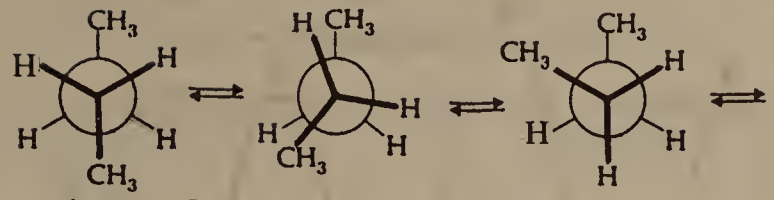


Scheme 4.1

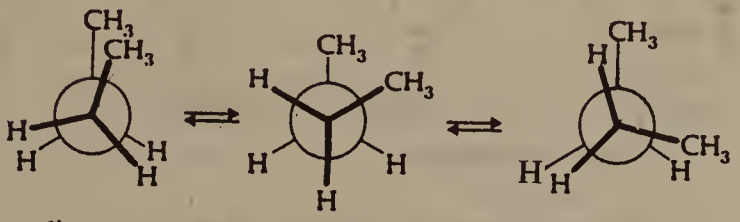
is, however, additional repulsion between the substituent groups. These nonbonded repulsions are a result of spatial interactions between atoms.

The *anti*-staggered conformation 1 (Scheme 4.2) has the lowest conformational energy and is assigned the value of zero on a relative scale. On rotation about the central carbon-carbon bond conformation 2 is realised in which eclipsing occurs between hydrogen atoms and methyl groups. The combination of torsional strain and nonbonded repulsion accounts for an unfavorable energy value of 3.8 kcal/mol (15.9 kJ/mol). As rotation continues, the least favorable conformation 4, in which methyl groups are eclipsed is obtained. Eclipsed conformations **(2,4,6)** are energetically unfavourable and are generally considered only as transitional orientations between staggered forms. Relative energies for rotation are depicted in Fig. 4.2.

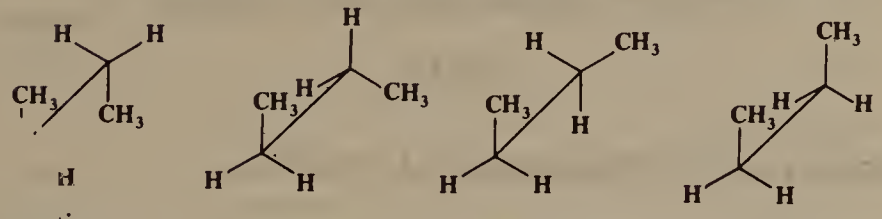
The rotational barriers about most single bonds are small so that essentially free rotation occurs at room temperature, however, differences in average rotamer populations do exist. Butane is calculated to exist about 70 percent in the *anti*-form and 15 per cent in each of the *gauche*-forms at 25°C. The gauche conformation of butane, *i.e.*, 3 is chiral. The lack of optical activity in 3 is due to the fact that it exists with its mirror image 5 in equal quantity and these interconvert too rapidly for separation. The four extreme conformations of *n*-butane are also presented in the sawhorse projections



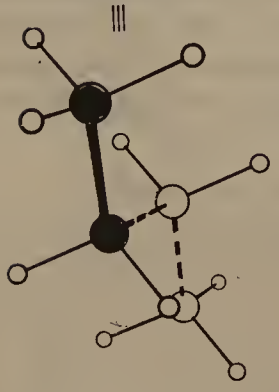
anti-staggered 1 eclipsed 2 guche-staggered 3



eclipsed 4 gauche-staggered 5 eclipsed 6



anti or antiperiplanar anticlinal gauche or synclinal synperiplanar



butane

Stereo representation

Scheme 4.2

with distinctive nomenclature.

At very low temperatures it should be theoretically possible to cool butane to the point where interconversion of the *anti*- and *gauche*-forms is slow enough to permit isolation of one rotamer in pure form. Experimentally the liquid-butane freezes and the conformations are no longer free to interconvert. The *anti*-form, which packs best into a crystal, crystallizes first, the *gauche*-form converts rapidly to the *anti*- and crystallizes out. Significantly, each of the *gauche*-forms (3 and 5) is chiral, but resolution of the enantiomers is impossible because there is rapid interconversion.

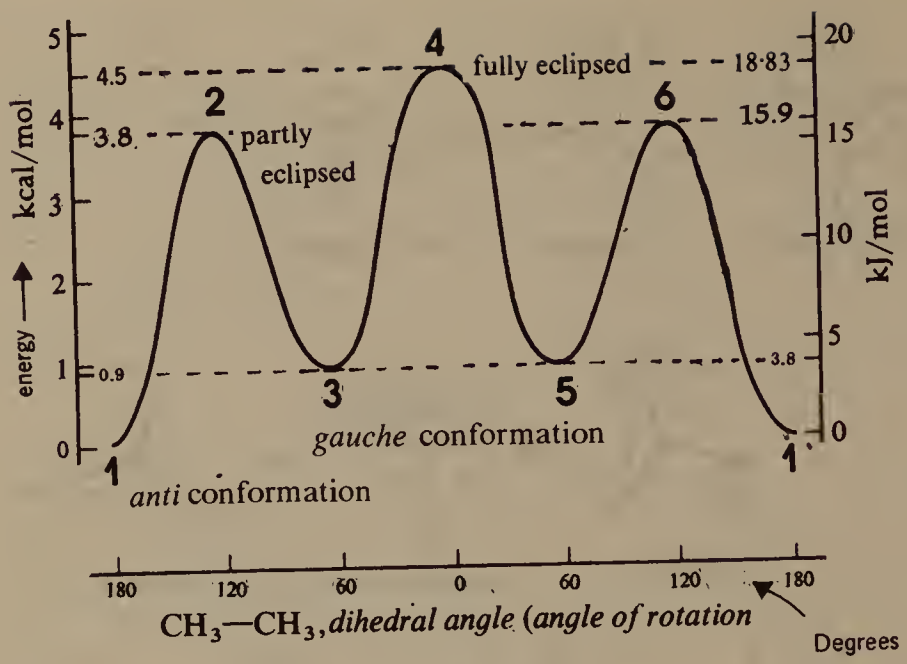


Fig. 4.2

4.3 ORIGIN OF CONFORMATIONAL ENERGY

An inspection of the model of ethane shows that the hydrogen atoms on adjacent carbon atoms are far apart making steric interaction negligible. The basic cause of the energy barrier could be studied only after accurate measurements of the energy difference between the maxima and minima for a number of molecules were made with the help of microwave spectroscopy.

TABLE 4.1 : Conformational Energy Barriers of Various Compounds

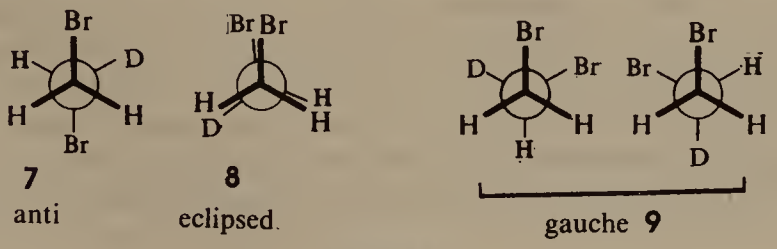
Compound	Energy barrier (kJ mol^{-1})	Compound	Energy barrier (kJ mol^{-1})
	(a)		(b)
$CH_3—CH_3$	11.5	$CH_3—CHO$	4.8
$CH_3—CH_2F$	13.8	$CH_3—COCH_3$	3.6
$CH_3—CH_2Cl$	14.9	$CH_3—COCl$	5.7
$CH_3—CH_2Br$	14.9	$CH_3—CO_2H$	2.0

The results in Table 4.1 reveal the lack of importance of steric effects. The barrier is not significantly changed when hydrogen is replaced by any of the halogens. A difference between the barrier heights however, exists as given in the two columns of the table, and it is significant that the barriers (a) are for the rotation of an sp^3-hybridized carbon relative to an sp^3-hybridized carbon, while (b) are for the rotation of an sp^3-hybridized carbon relative to an sp^2-hybridized carbon. The bond hybridization has therefore, importance. The barrier must, therefore, arise mainly from interaction of the bonding electrons on adjacent carbon atoms. In simple molecules like ethane, this

indeed is the main source of the energy barrier. However, when substituent groups become bulky steric effects make their contribution.

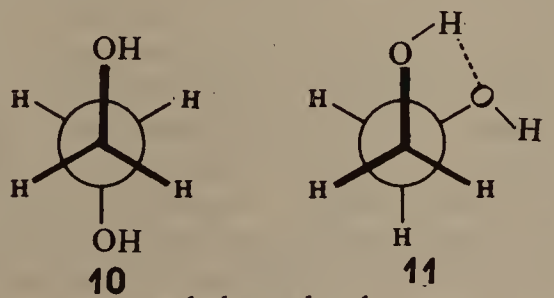
4.4 SPECTRAL EVIDENCE FOR THE PREFERRED CONFORMATIONS

In the i.r. spectrum of 1, 2-dibromoethane the number of bands is more than calculated for a simple rigid molecule with eight atoms. This shows that 1, 2-dibromoethane exists in more than one form, *i.e.*, in more than one conformation due to rotation around a C—C bond. On freezing, the spectrum loses almost half of its bands, and since rotations about single bonds slow down on cooling, it shows that at least one form disappears. The spectrum indicates that the molecule has the symmetry associated with the *anti*-isomer of the dihaloethane. The spectrum with the symmetry of either an eclipsed-form or a *gauche*-form is obtained by substracting the solid from the liquid spectrum. A distinction between these two was made possible by using deuterium-labelled compound. On replacing one hydrogen atom of 1, 2-dibromoethane by deuterium the symmetry of both the *anti*-form as well as the eclipsed-form allows them to exist as one isomer *i.e.*, **7** and **8** respectively (Scheme 4.3). However, inspection of the *gauche*-forms reveals that one has a molecule in which two positions of hydrogen can be differentiated. As either of these may be occupied by deuterium, therefore, the mono-deuteriated form of *gauche*-1,2-dibromoethane has to exist as a mixture of two rotational isomers **9.**

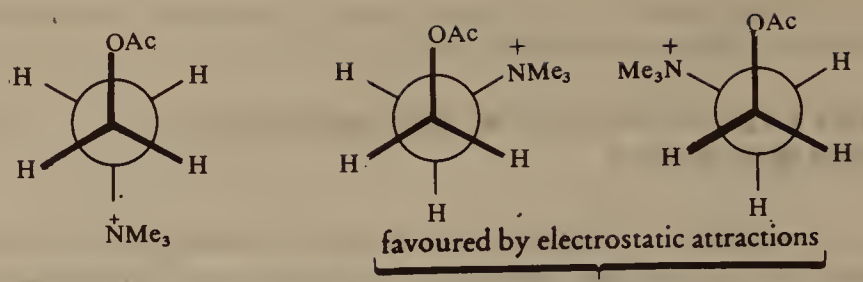


Scheme 4.3

The i.r. spectrum of the mono-deuteriated form of 1,2-dibromoethane reveals that every band assigned to the eclipsed or *gauche*-form is indeed split into a pair on deuteriation. Thus, the i.r. spectrum points to the *gauche*-form, and not the eclipsed-form.



ethylene glycol



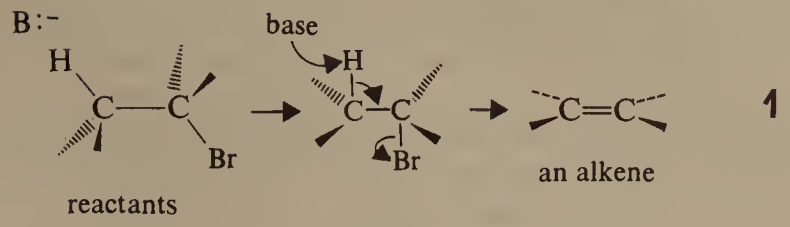
Conformations of acetylcholine

Scheme 4.4

Mostly disubstituted ethanes exist as *anti*- and *gauche*- forms in the liquid phase, and can be frozen to give the pure *anti*- form in the solid phase. Among the exceptions mention may be made of ethylene glycol, which adopts entirely a *gauche*-form in the liquid phase. At high dilutions, in CCl_4, as expected, the i.r. band due to intermolecular hydrogen-bonding disappeared, as the molecules exist far apart from one other. The absorption band due to intramolecular hydrogen-bonding, however, persisted. Intramolecular hydrogen-bonding (between the two OH groups in one molecule) can occur only in the *gauche* form 11 (Scheme 4.4). In the *anti*-form **10** the hydroxyl-groups are too far apart geometrically to involve themselves in hydrogen bond formation. Thus the gauche form predominates in the solution phase over the sterically-favored *anti*-form due to the through-space interactions, *i.e.,* intramolecular hydrogen-bonding. In several situations, electrostatic attraction may be responsible to favor the *gauche* conformations, in apparently sterically hindered molecules. This is so in acetylcholine $CH_3COOCH_2CH_2N^+(CH_3)_3$; in this molecule there is electrostatic attraction between the positively charged quaternary ammonium nitrogen atom and the negative oxygen atom in the acetyl group. This attraction is so strong that it forces the dihedral angle in the gauche conformation closer to 0° rather than 60°

4.5 CONFORMATION AND CHEMICAL REACTIVITY (E2 ELIMINATION AND PINACOL REARRANGEMENT)

Under this section two reactions are discussed, *i.e.,* E2 elimination and the molecular rearrangement (pinacol type) of a β-amino-alcohol, where the conformation adopted by the reacting molecule has significance. Before a discussion of these reactions is taken up, it is necessary to have some basic ideas about these two type of reactions. The requirement that the migrating and the departing groups in the starting compound are *anti* is termed as the stereoelectronic requirement. In the bimolecular (E2) elimination (eq. 1, Scheme 4.5), the elimination of HBr from an alkylbromide by treatment with base gives an alkene. This reaction has a stereoelectronic requirement; H and the Br atoms in the starting compound have to be *trans*- and coplanar (*anti* to each other, *i.e., anti* periplanar).



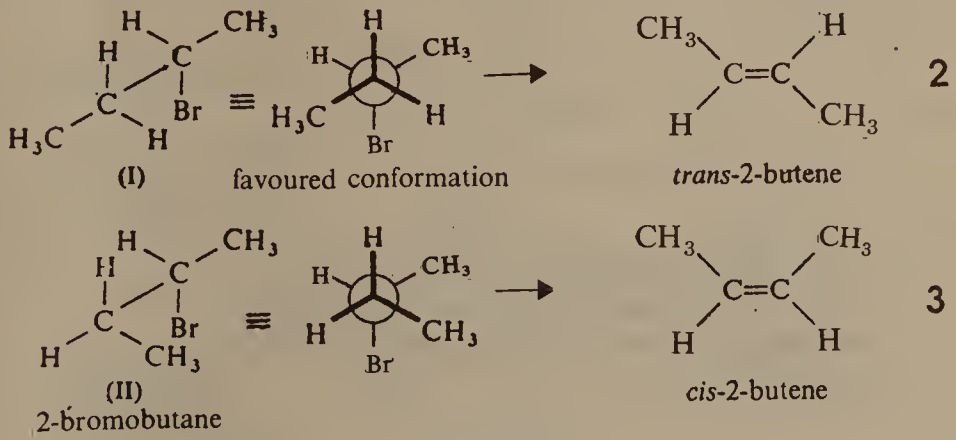
Scheme 4.5

In intramolecular molecular rearrangements of electrophilic type one may notice in appropriate cases three stereochemical situations, (*a*) the migrating group retains its configuration as in Hofmann rearrangement (Sec. 8.1), (*b*) there is inversion of configuration at the migration origin as seen at C-1 in the conversion of camphene hydrochloride into isobornyl chloride (Sec. 2.3), and (*c*) there is inversion of configuration at the migration terminus. The third property is shown in reactions of the pinacol type.

Consider an alkyl bromide, 2-bromobutane. On E2 elimination it can either give the *cis*- or the *trans*- isomer of butene. The stereoelectronic requirement of this elimination reaction must involve only those conformations of bromobutane molecule in which the ligands to be eliminated attain an antiperiplanar arrangement. The conformations I and II satisfy the coplanarity condition. Thus I gives rise to the *trans*- olefin while II to its *cis* isomer. It has been found experimentally that the reaction gives mainly the *trans* alkene to prove that the elimination involving rotamer I proceeds more readily than *via* II.

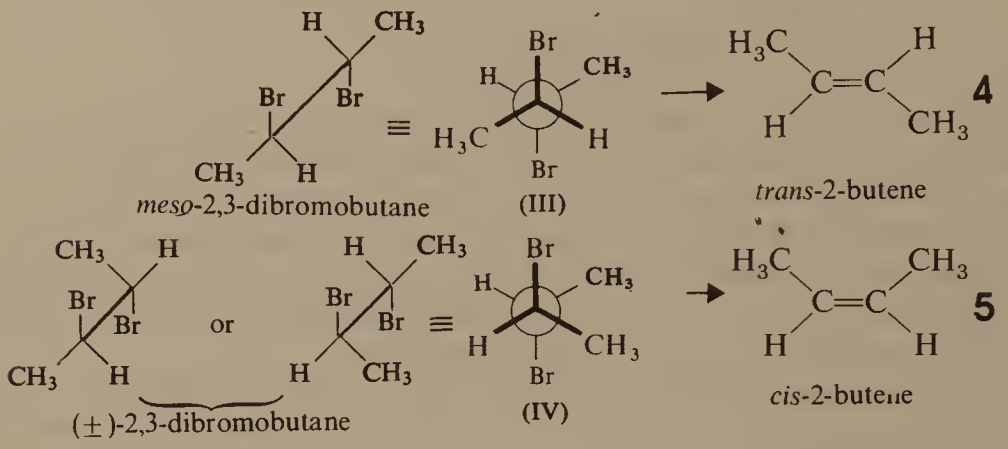
The two arrangements (I and II) of bromobutane are however, just two of infinite number of possible rotamers.

It is now clear that reaction 2 (Scheme 4.6) is favoured since both the conformation of the starting compound I and the structure of the *trans*-alkene product are thermodynamically more stable in comparison to their respective alternatives depicted in eq. 3. Thus, the transition state for reaction 2 which must be intermediate between the starting material and product, must be preferable to the one involved in reaction 3.



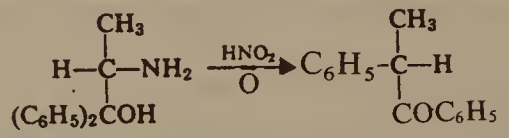
Scheme 4.6

These stereoelectronic requirements also apply to the bimolecular elimination (E2) of a molecule of bromine from a dibromide, either with iodide ions or by the action of a metal, such as zinc. Elimination can occur only *via* a conformation of the starting compound which places the two bromine atoms in an *anti*-periplanar arrangement, regardless of the fact if or not this is the most stable conformation (Scheme 4.7). In reaction 4, the *meso*,

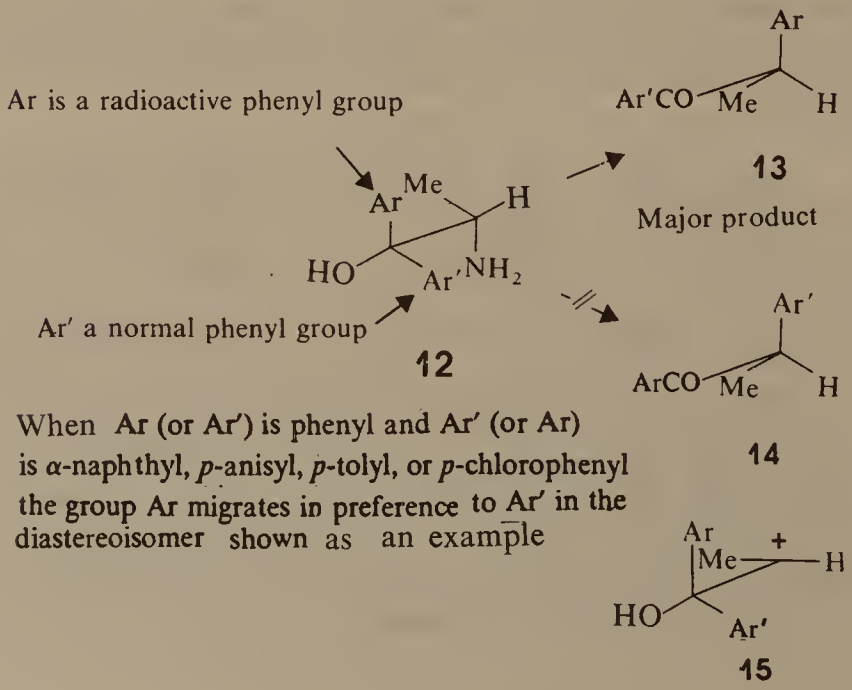


Scheme 4.7

2,3-dibromobutane can eliminate bromine gainfully only from the conformation III, to give *trans*-2-butene, while in reaction 5, (±)-2,3-



1,1-diphenyl-2-aminopropanol-1

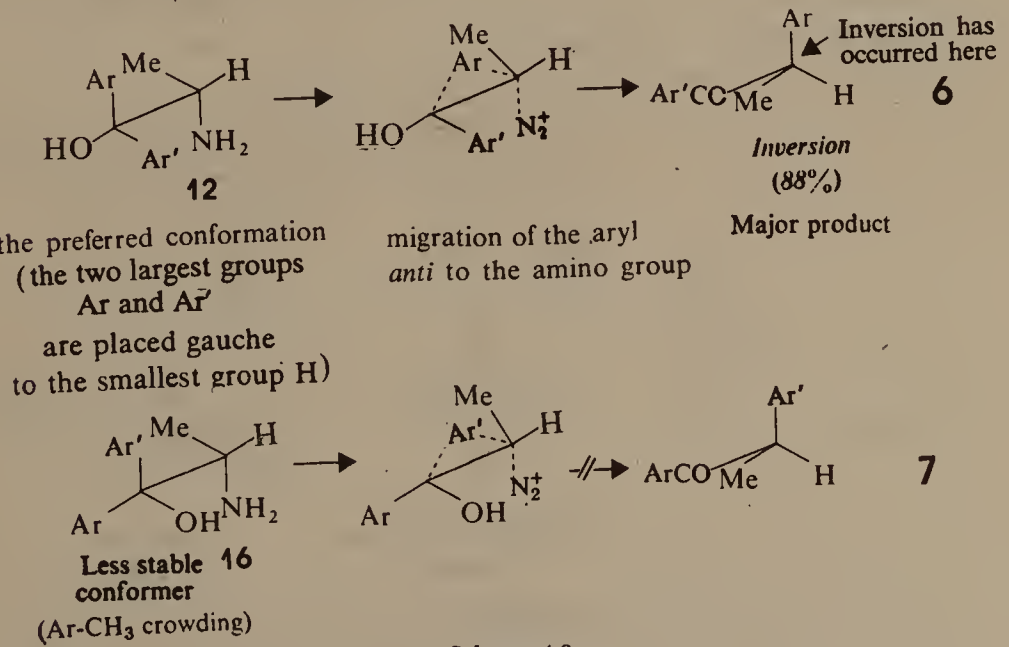


Scheme 4.8

dibromobutane IV, reacts to yield only the *cis*-isomer. Reaction of the (±)-isomer involves a less stable transition state compared to the *meso*-isomer, so that elimination with iodide ions is slower by a factor of about two for the (±)-than for the *meso*-isomer.

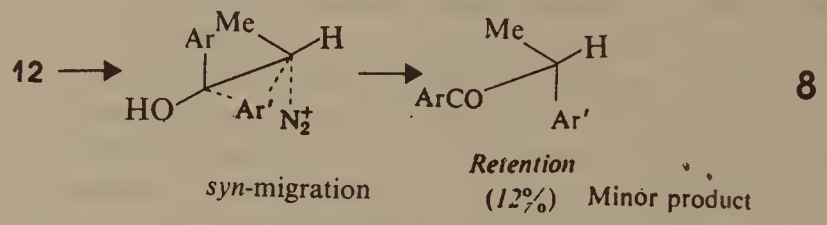
A somewhat more complicated type of a reaction is the pinacolic deamination of **12** (Scheme 4.8) on treatment with nitrous acid (Sec. 8.1a, ii). This rearrangement is used to reveal stereochemical features while learning more about relation between conformation and reactivity. This reaction proceeds with the migration of an aryl group to give a ketone. As, either aryl group can migrate because of rotation around the central carbon-carbon bond to place either of these groups in the favorable *anti* position for migration, two compounds, **13** and **14** may be formed. Moreover, if this reaction involves the intermediate formation of a carbocation **15**, equal amounts of **13** and **14** should be formed. This would be so, since either aryl group would have an almost equal chance of migration particularly when electron-directing substituents on the aryl groups are absent.

In a simple system this molecular rearrangement has been studied on a compound in which Ar is radioactive phenyl group while Ar′ a normal phenyl group. This outcome of such a reaction showed that the major product formed, involves the migration of the labelled phenyl group to the extent of 90% and is attended with inversion of configuration at the migration terminus. The minor product, 10% of this reaction involves the migration of the unlabelled group and that too with retention of configuration at the migration terminus. The formation of the major product (eq.6, Scheme 4.9) obviously involves the migration of the aryl group *anti* to the amino group in the preferred conformation of the compound **12**. The minor product with retention of configuration however, is not formed by a similar *anti* migration



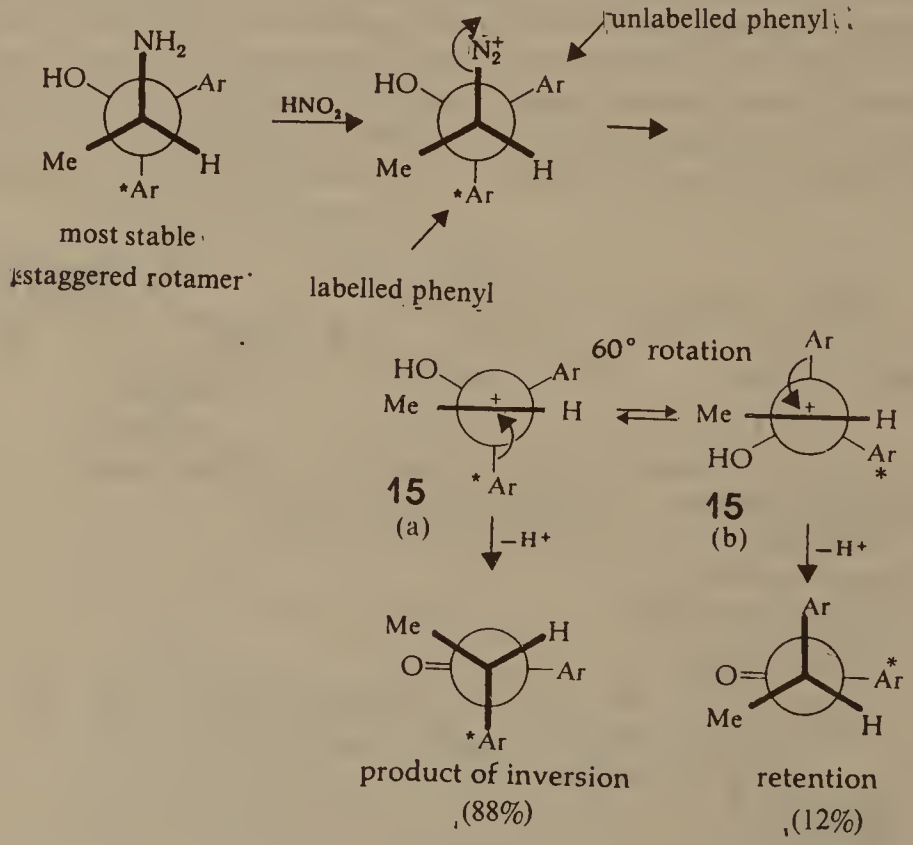
Scheme 4.9

of the unlabelled phenyl group involving a less populated conformation **16** since such a migration would again lead to an inversion of configuration. It has been therefore, suggested that the minor product is formed from the stable conformation **12** of the compound by a *syn*-migration as shown in reaction 8 (Scheme 4.10). The transition state for the reaction 8 is expected to be less stable than the one involved in reaction 6, so the latter should predominate, a fact observed experimentally. One may picture the course of this



Scheme 4.10

rearrangement invoking the intermediate formation of a carbocation **15** (Scheme 4.11). The open carbocation **15** (a) formed from the most stable rotamer (in which the two phenyl groups flank the smallest atom hydrogen) is converted to the major product *via* the migration of the labelled phenyl group, which is suitably located in the plane of the vacant *p* orbital of the



Scheme 4.11

carbocation, leading to inversion of configuration. To explain the formation of the minor product with retention of configuration, only a 60° rotation in 15 (a) needs to be invoked leading to another carbocation 15 (b) in which the migration of the unlabelled phenyl group can occur with retention.

In the reactions which do not necessarily have a dominant stereoelectronic requirement, (esterification, saponification, chromic acid oxidation and reduction) the consideration of steric effects in the transition state becomes very important compared to the reactions discussed above. An example of this type of reaction is the reduction of a ketone with lithium aluminium hydride or Grignard reagents (Sec. 1.20B).

4.6 ANGLE AND PITZER STRAIN

Angle strain is also referred to as Baeyer strain. The normal angle between the carbon bonds in an alkane is about 111°; when the carbon atom forms part of a ring, the angle will be controlled by the geometric requirements of the ring. Three-membered ring system in cyclopropane must be flat (since, mathematically, three points define a plane) so that the bond angles within the ring are forced to be 60° thereby causing strain. The amount by which the bond angle deviates from normal is a measure of the bond-angle strain.

Baeyer (1885) proposed a theory of angle strain for cycloalkanes in which the difference between a tetrahedral angle (109.5°) and the internal angle of the appropriate polygon is used as a measure of molecular stability. Cyclopropane, he suggested, would have angle strain related to the difference between 109.5° and 60° (Scheme 4.12). Cyclopentane would be essentially strain-free (109.5°—108°), whereas larger cycloalkanes would possess an increasing degree of Baeyer angle strain.

The Baeyer theory, however, is not, consistent with experimental data. Cycloalkanes larger than cyclopentane show only a small increase in strain energy, and very large cyclic molecules actually become almost strain-free. The problem lies in Baeyer's simple assumption that the rings are flat polygons (geometrical figures).

	cyclopentane	cyclobutane	cyclopropane	Cyclohexane
bond angle if planar:	108°	90°	60°	
angle strain (109.5° − bond angle):	1.5°	19.5°	49.5°	

Scheme 4.12

One sees that only C_3 and C_4 rings have large angle-strain, while the medium-size rings (C_8—C_{12}) possess moderate strain, and large rings show only small strain energies. Though one often draws cyclic compounds as if they were planar geometric figures, the data in Table 4.2 clearly shows that their

structures are not planar.

Pitzer strain is also referred to as bond-eclipsing strain of *gauche* and eclipsed conformations. Bond eclipsing has already been encountered in acyclic compounds, where it is generally relieved by rotation to give a staggered conformation. In a cyclic compound a rotation may be impossible and therefore the strain resulting from eclipsing of bonds to neighboring carbon atoms will make a contribution, often, substantial, to the strain in the ground state. The amount of strain due to the cyclization of a chain can be determined experimentally by measuring the heat of combustion per CH_2 group and comparing it to the value for the acyclic analog (Table 4.2). The two main contributions to the cyclic strain are the Baeyer strain and the Pitzer strain.

TABLE 4.2 : Strain in Cycloalkanes, Calculated from Heat of Combustion Data, assuming Cyclohexane to be strainless.

Carbocycle	n	Strain per CH_2 group		Strain for the molecule	
$(CH_2)_n$		kJ/mol	kcal/mol	kJ/mol	kcal/mol
Small rings	3	38.6	9.2	116.0	27.6
	4	27.2	6.5	109.0	26.0
	5	5.0	1.2	25.1	6.0
Normal rings	6	0.0	0.0	0.0	0.0
	7	3.8	0.9	26.4	6.3
	8	5.0	1.2	40.2	9.6
Medium rings	9	5.9	1.4	52.8	12.6
	10	5.4	1.3	54.5	13.0
Large rings	12	2.9	0.7	35.2	8.4

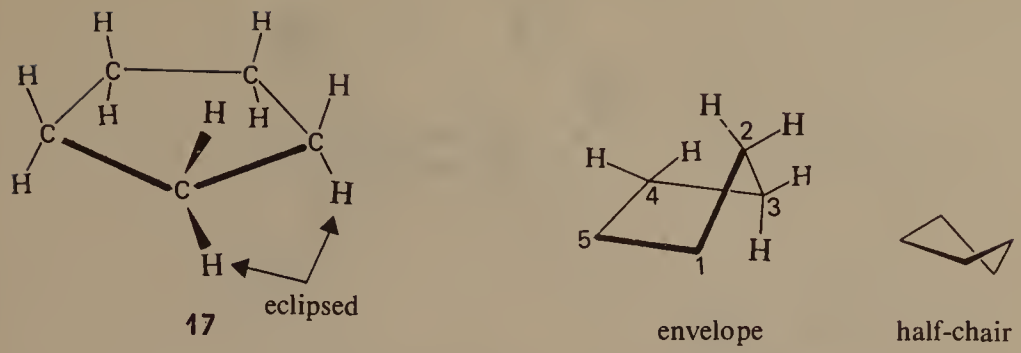
In small rings, the Baeyer strain is particularly significant, while it is less important or negligible in common rings (normal), in medium rings (8- to 11- membered), and in large rings (12- and higher membered). In all cycloalkanes the Pitzer strain is operative and tends to be relieved by deviations from planarity of the carbon skeleton. In large rings, transannular interactions account for the relatively marked strain.

4.7 CYCLOALKANE RINGS OTHER THAN CYCLOHEXANE

An inspection of Table 4.2 shows as to how strain decreases stability and causes the heat of combustion per methylene group to rise.

If one considers a planar pentagonal structure of cyclopentane **17**(Scheme 4.13), one would have C—C—C bond angles of 108°, a value so close to the normal tetrahedral angle of 109°.30′ that no significant strain effect would be expected. However, in such a structure, all of the hydrogens are completely eclipsed and it would have about 10 kcal $mole^{-1}$ of strain energy.

As a result, the angle strain in cyclopentane is believed to be somewhat larger than 1.5°. The molecule finds it energetically worthwhile to distort substantially from a planar conformation even though it increases the angle

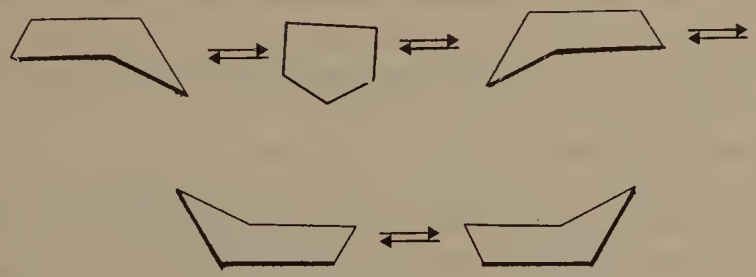


Structure of cyclopentane

Scheme 4.13

strain. The actual structure is of "envelope" shape. The additional bond-angle strain involved in this arrangement is more than compensated by a decrease in eclipsed hydrogens. The out-of-plane methylene group is approximately staggered with respect to its neighbors.

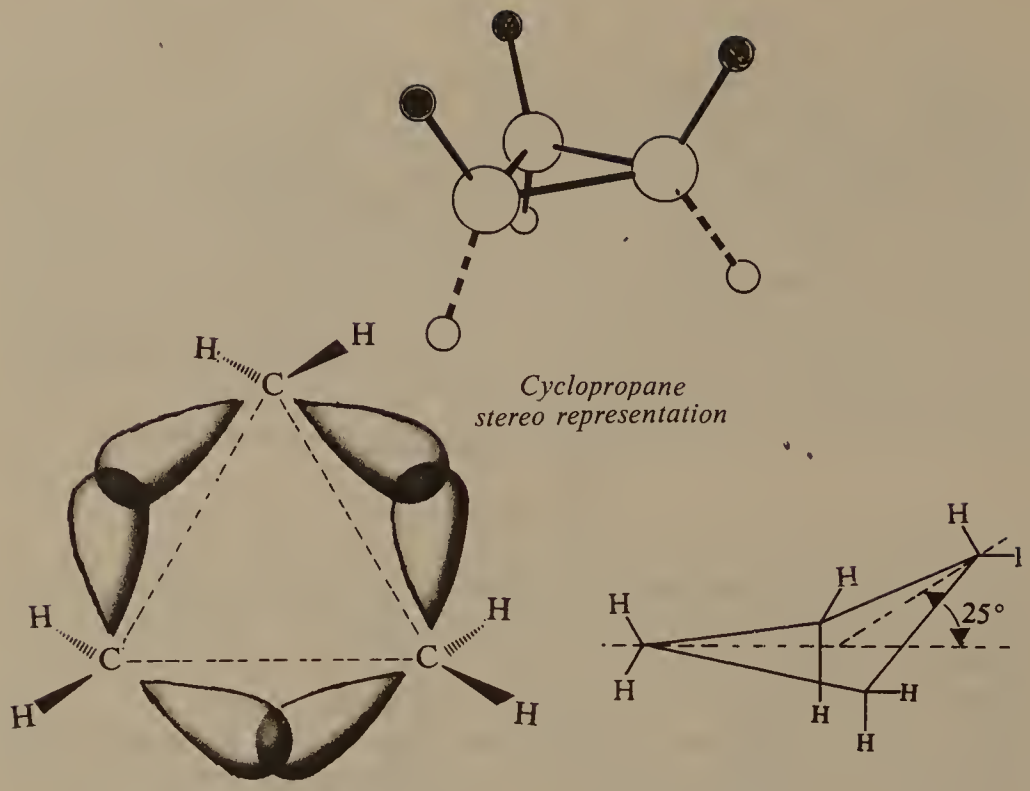
The envelope conformation of cyclopentane is dynamic. By twisting about the various C—C bonds, successive conformations are realised in which four carbons are in a plane and the fifth is out of plane. The concerted ring motions of all the carbon atoms lead to a series of structures, which appear as if the molecule were rotated through 360° in 72° steps and constitute a form



Scheme 4.14

of molecular motion known as pseudorotation. Another puckered conformation of cyclopentane is the half-chair and the energy difference between these two forms is small.

In cyclopropane, one wonders as to how the three carbon atoms are connected in a ring without seriously violating the concept of bond angles. However, it is important to know that the highest electron density of the C—C bonds does not lie along the lines connecting the carbon atoms. Bonding electrons lie principally outside the triangular internuclear lines resulting in bent bonds (Scheme 4.15).



bent bonds of cyclopropane conformation of cyclobutane

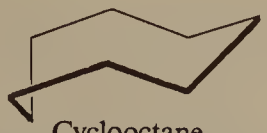
Scheme 4.15

In cyclobutane, the internuclear angles of 90° are not as small as in cyclopropane. The C—C bonds are not so bent, and there is less strain per bond. However, there are four strained bonds rather than three and there are eight pairs of eclipsed hydrogens rather than six.

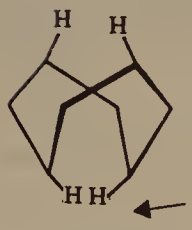
As three points define a plane, the carbon framework of cyclopropane must have a planar structure. However, cyclobutane can exist in a nonplanar conformation. Spectroscopic studies show that cyclobutane and many of its derivatives possess nonplanar structures in which one methylene group is bent at an angle of about 25° from the plane of the other three ring carbons. In this conformation, some increase in bond angle strain is compensated by the reduction in the eclipsed hydrogen interactions. The strain that is present in the C_7 to C_{10} compounds is not the result of angle strain (the molecules being puckered), but due to interfering hydrogen atoms.

Cycloheptane, cyclooctane, and cyclononane also exist in nonplanar conformations. The small instabilities of these higher cycloalkanes appear to be due, primarily to torsional strain and van der Waals repulsions between hydrogens across rings. The nonplanar conformations of these rings, however, are essentially free of angle strain. Although not known with certainty, the most stable conformations of cycloheptane and cyclooctane appear to be those shown in Scheme 4.16.

Cycloheptane
the twist-chair

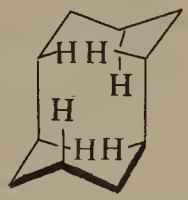


Cyclooctane
the 'boat-chair' form



transannular interaction

the boat–boat cyclooctane



cyclodecane

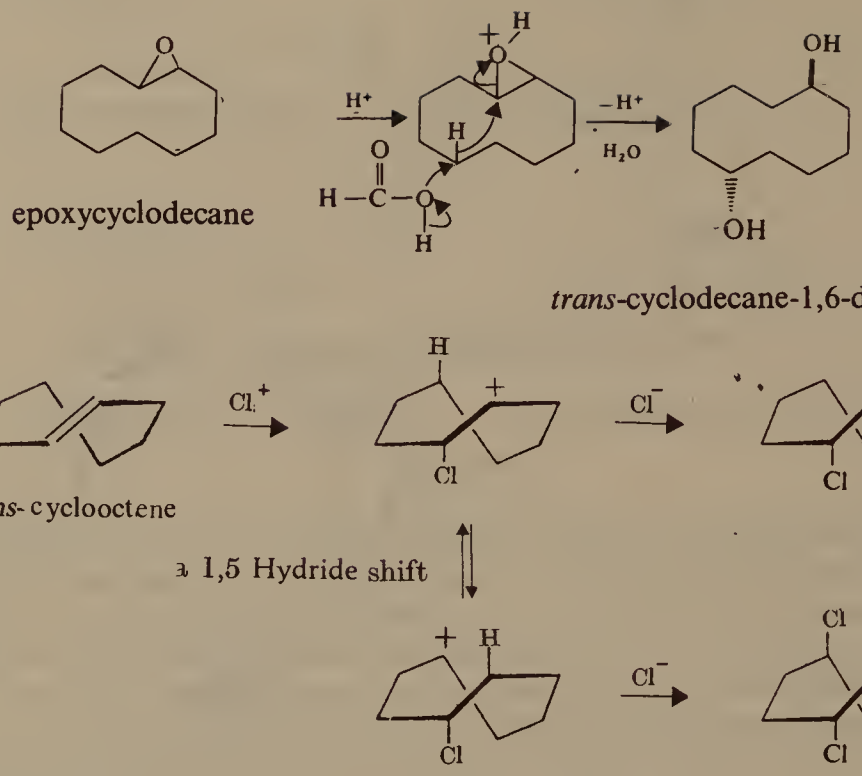
Scheme 4.16

Puckered cyclooctane can assume no less than seven high symmetry forms which interconvert through inversions, pseudorotations or *via* their combinations. Cyclooctane is the smallest ring in which transannular interactions may occur. The boat-boat conformation has the carbon skeleton which corresponds to a fragment of the diamond lattice (compare with adamantane). A model of this conformation reveals that two hydrogen atoms compete for the same region of space. This is therefore high-energy conformation. This type of transannular interactions can be quite severe in cyclooctane and other medium rings compounds.

X-ray analysis studies on some cyclodecane derivatives have indicated that its conformation is derived from two-chair conformations of cyclohexane joined by 1, 3-axial bonds. It is these more complicated conformations which make the medium rings very different from large rings in respect of several chemical and physical properties. This anomalous behaviour has been explained on the basis of bond opposition strain, angle strain and steric strain. The steric strain is very important contributing factor and is due to the interactions among the atoms on opposite sides of the ring. This type of interaction has been termed transannular interaction, and produces transannular strain. X-ray crystallographic studies of cyclodecane reveal that the most stable conformation has carbon-carbon bond angles of 117°. This indicates some angle strain. The wide bond angles apparently allow the molecule to expand and thereby minimize unfavorable transannular repulsions between hydrogens. A distinctive feature of medium sized rings is that they display transannular reactions. These reactions do not involve the neighboring atoms; and occur among atoms on opposite sides of the ring.

An example of this type of anomalous reaction is the formolysis of epoxycyclodecane to give *trans*-cyclodecane-1,6-diol by a transannular hydride shift. Normally such a reaction from a cyclic or an acyclic epoxide affords a 1,2-diol (Sec. 6.6). *Trans*-cyclooctene displays this reaction during the addition of chlorine, when 1,4-dichlorocyclooctane is obtained (10%) involving a 1,5-hydride shift (Scheme 4.17) in the ion in addition to the

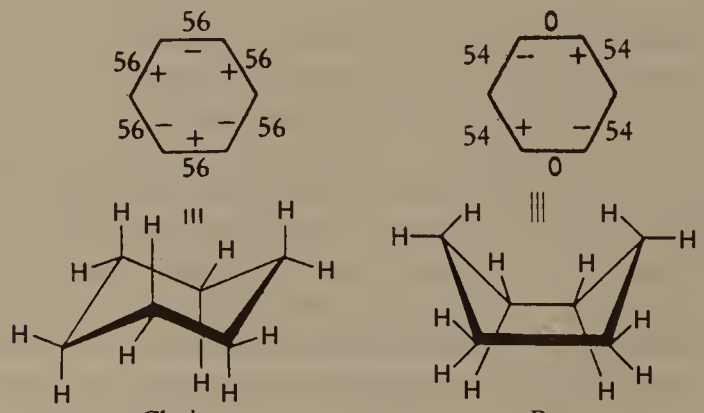
normal product.



Scheme 4.17

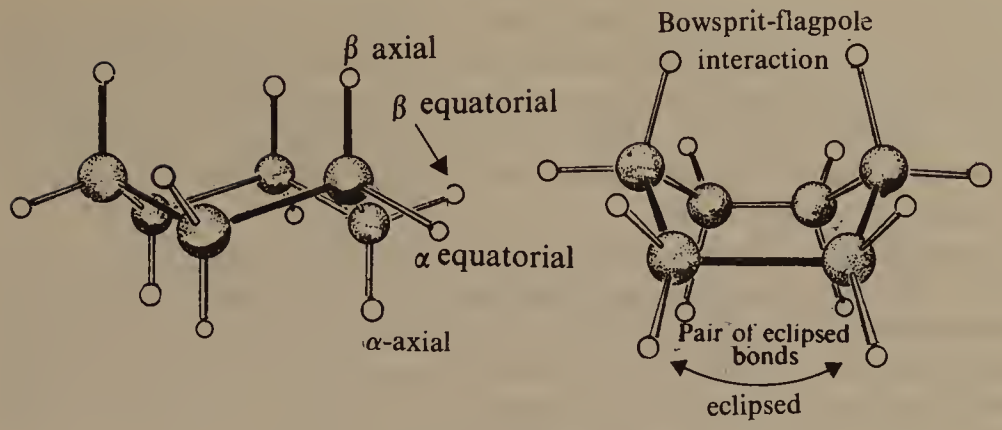
4.8 CYCLOHEXANE

The importance of Baeyer strain was first appreciated in 1890 by Sasche, who pointed out that two non-planar models of cyclohexane could be constructed in which all the bond angles were 109°-28′, so that the systems were free of Baeyer strain. One of these was a fairly rigid form, shaped roughly like a chair and the other was a flexible form whose most symmetrical form was shaped like a boat (Scheme 4.18).



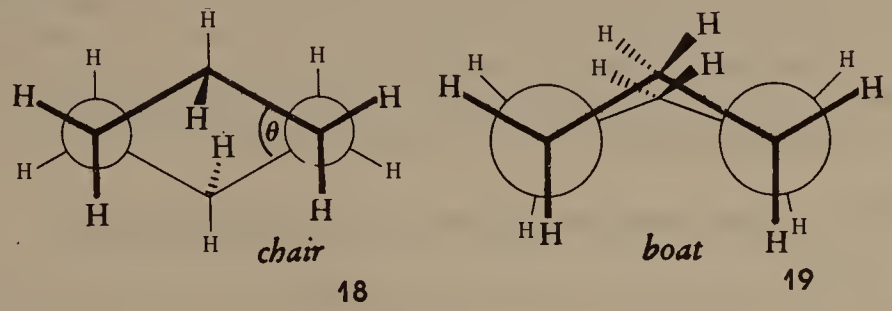
Chair
6-fold alternating axis of symmetry

Boat
(1-fold alternating axis of symmetry)



Scheme 4.18

Models of these two structures clearly show that all the bonds in the chair form of cyclohexane **18** (Scheme 4.19) are staggered, so that the system is also free from bond eclipsing strain, but that the boat form **19** has complete eclipsing of the hydrogens attached to the carbon atoms forming the sides of the boat.

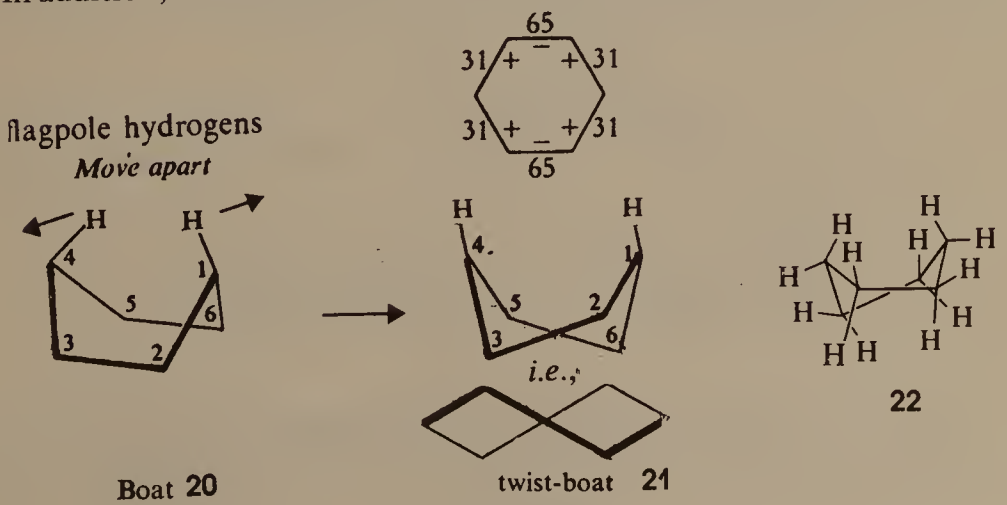


Newman projection

Cyclohexane

Scheme 4.19

In addition, nonbonded interaction shown in **20** (Scheme 4.20) between the



Scheme 4.20

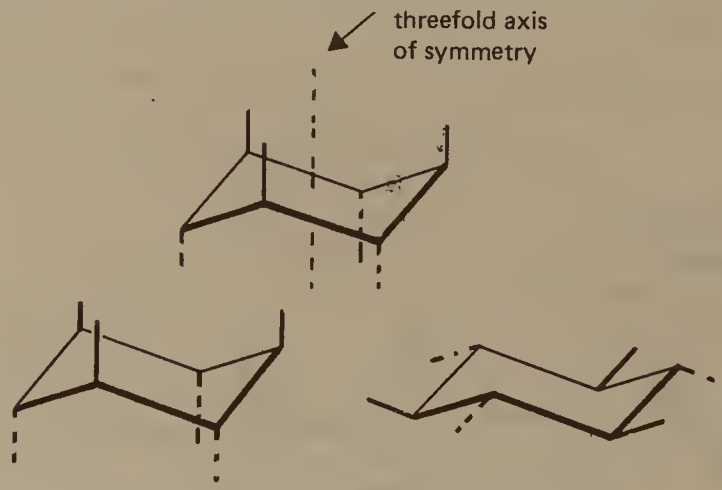
two hydrogen atoms across the ring from each other (often called the flagpole hydrogens) is unfavorable. This is van der Waals strain due to crowding between the "flagpole" hydrogens, which lie only 1.83 Å apart, considerably closer than the sum of their van der Waals radii (2.5 Å). The boat conformation of cyclohexane is about 6.5 kcal/mol (27 kJ/mol) higher in energy than the chair form.

A modified boat conformation known as the twist-boat **21** (or in some cases the skew-boat) has been suggested to minimize all these torsional and nonbonded interactions. The boat form is easily twisted so that the flagpole hydrogens move to either side of the molecule and the torsional interactions are also reduced as in **22**. The twist-boat is estimated to be about 1.5 kcal/mol (6 kJ/mol) lower in energy than the boat form at 25°C.

An ideal chair form of cyclohexane would possess dihedral angles of 60°, and C—C—C bond angles of 109° 30′. As the normal C—CH_2—C bond angle is 112° 24′, the angle strain for this form would be around 1 kcal/mol (4 kJ/mol). Moreover, a bond angle of 112° 24′ corresponds to dihedral angles of 52° (a Pitzer strain of 2.9-3.3 kJ/mol i.e., 0.7-0.8 kcal/mol). The real cyclohexane chair balances these strains with bond angles of 111° and dihedral angles of 56° . In the hexagonal representation of cyclohexane each ring C—C bond is given a number that corresponds to the torsion angle θ, and a sign corresponding to a clockwise (+) or anticlockwise (–) rotation for θ. In **18**, θ is positive. In the boat conformation the two bonds, labelled 0,0, are completely eclipsed, thereby increasing the Pitzer strain.

4.9 EQUATORIAL AND AXIAL BONDS IN CYCLOHEXANE

The twelve C-H bonds in the chair form of cyclohexane are of two types. Six of these are parallel to the three-fold axis of symmetry of the chair. These are represented by vertical lines in the plane of the paper and are designated as axial (Scheme 4.21). The remaining six bonds are inclined at an angle of



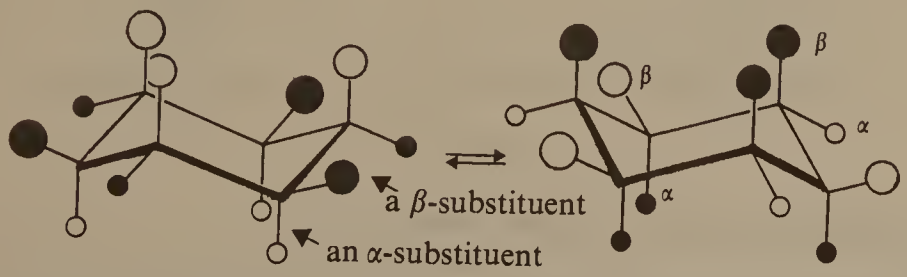
Cyclohexane bonds

Scheme 4.21

$109^0\ 28'$ to the three-fold axis and are described as equatorial.

At each carbon atom one hydrogen is directed upwards and the other downwards. The six hydrogens that are upwards are called β-hydrogens and are often designated by full-line bonds. The hydrogens which are downwards are called α-hydrogens and are often represented by dotted lines.

At room temperature cyclohexane interconverts rapidly to a mirror image chair conformation. As one chair form converts to the other, often referred to as ring inversion or ring flip, all the equatorial hydrogen atoms become axial and all the axial hydrogens become equatorial without losing their identity as α- or β- (Scheme 4.22). The equatorial-axial interconversion is so rapid at room temperature that all hydrogen atoms on cyclohexane can be considered equivalent. The energy barrier between the conformations I and II is only 10 kcal/mole (Fig. 4.3). Thus flipping occurs rapidly at room temperature.



black circles the equatorial (*e*) bonds black circles the axial (*a*) bonds

flipping back and forth of the two chair conformations

Scheme 4.22

The ring inversion process (Scheme 4.23) is believed to take place by movement of one side of the chair structure to produce the boat or better, twist-boat and then movement of the other side of the twist-boat to give the other chair form. The free energy difference between chair and boat conformers is relatively small, but it is still large enough so that the chair forms constitute over 99.9 percent of cyclohexane at equilibrium.

the rapid interconversion of the chair forms

Scheme 4.23

In the ring flipping sequence and related energies (Fig. 4.3) the boat conformation is included, however, it may not be on the interconversion pathway.

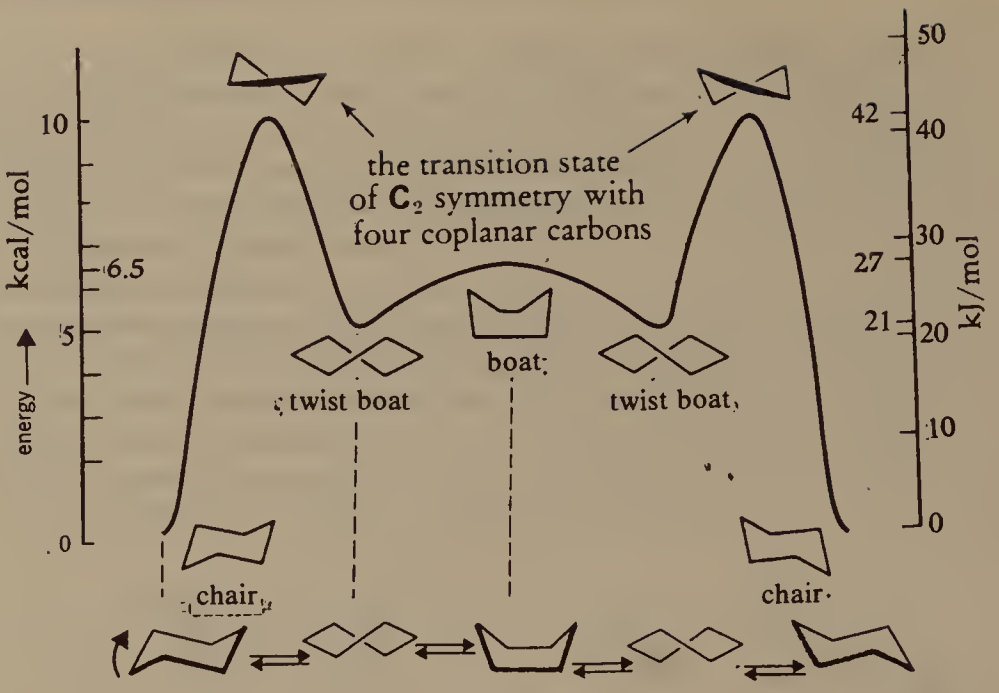
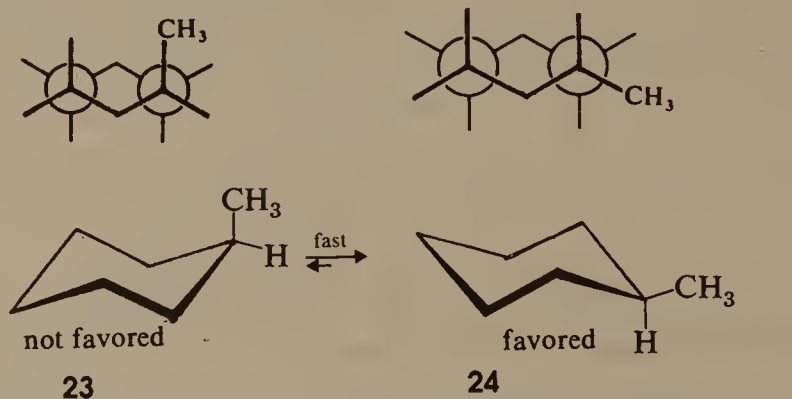


Fig. 4.3

4.10 MONOSUBSTITUTED CYCLOHEXANES

The substituent in a mono-substituted cyclohexane like methylcyclohexane can occupy either an axial or an equatorial position. These structures are isomeric and it is not possible to isolate the two conformational isomers. Since the rate of their interconversion through ring flipping is very rapid, there being little energy barrier to the flip. Thus, axial-1-methyl in methylcyclohexane **23** (Scheme 2.24) becomes equatorial-1-methyl **24** without losing its identity as β-oriented.



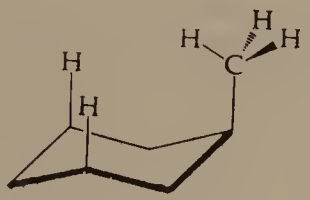
Scheme 4.24

These two isomers normally have different energies because there are repulsive forces between the axial substituent and the hydrogen atoms on C-3 and C-5 (1:3 non-bonded interactions). These repulsive forces are not present

when the substituent is equatorial.

The magnitude of the repulsive effects in the unstable conformer 23 (drawn as in 25 to depict the two β-axial-hydrogens) is provided in 26 (Scheme 4.25) No strain is produced due to the interaction of 1:3 α-axial hydrogens since these are as far apart (the sum of their van der Waals radii is 2.5Å).

On the β-face of the compound, each of the two axial hydrogens (only one is depicted in 26) is only 2.33 Å apart from the two hydrogens of the methyl group. This results in considerable van der Waals strain, which would tend to increase if more axial groups are present



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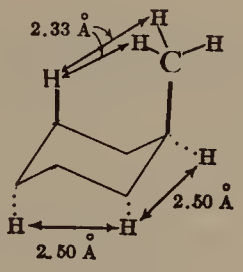
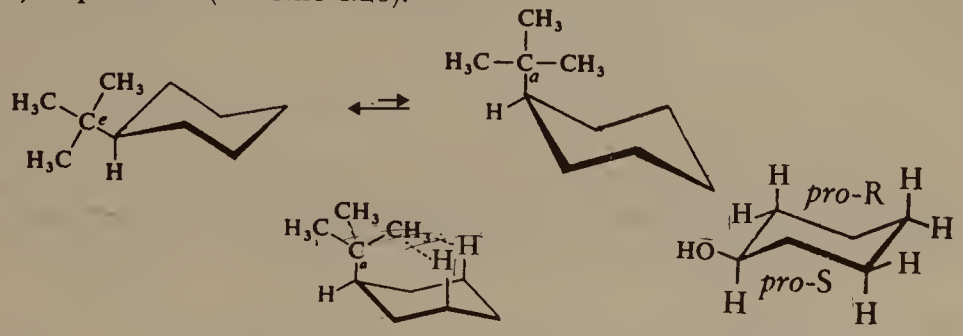


26

Scheme 4.25

Most methylcyclohexane molecules will have the methyl in the more stable equatorial orientation, but a few at any given moment will be axial, since the energy difference is small. Energy differences for selected substituents are given in Table 4.3. The bulky groups like isopropyl, phenyl and *t*-butyl are so large that these will not tolerate the conformational flip into an axial orientation, thus, *t*-butyl group is often used to "lock" a substituted cyclohexane in just one of its two possible chair conformations: that with *t*-butyl equatorial (Scheme 4.26).



1,3 Interactions in a cyclohexane ring with an axial *t*-butyl group

Cyclohexanol

Scheme 4.26

One can gainfully study the stereoisomerism in cyclohexane derivatives by considering the prostereoisomerism of a mono-substituted cyclohexane derivative, *i.e.*, cyclohexanol. Cyclohexanol is achiral, however, it contains five centres of prochirality (carbons 1,2,3,5 and 6). The two enantiotopic ligands of C-1 are the two edges of the ring and are designated *pro-R* and *pro-S*. The other four prochiral carbons carry diastereotopic hydrogens,

while carbon-4 has two diastereotopic hydrogen atoms and itself proachiral (replacement of either of the hydrogens leads to achiral diastereoisomeric 1,4-disubstituted cyclohexane derivatives).

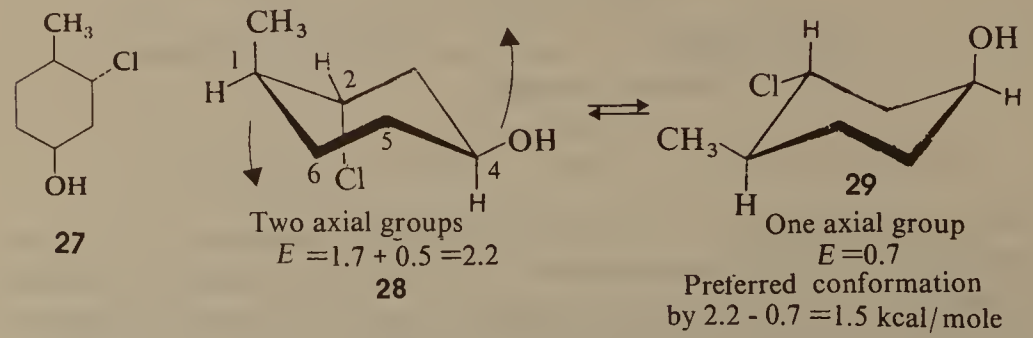
4.11 CONFORMATIONAL ANALYSIS OF POLYSUBSTITUTED CYCLOHEXANES

These properties allow a basis for conformational analysis of polysubstituted cyclohexanes. In brief, any cyclohexane can take up either of the two chair forms, as a result of ring flipping. The conformer with more equatorial substituents is the preferred one. In case of doubt, calculations can be made by adding energies of axial substituents from Table 4.3 for each of the two possible chair forms. The *t*-butyl group must always be placed equatorial. The energies of Table 4.3 for axial substituents are valid, provided the other two axial substituents on the same side of the ring are hydrogens; *cis*-diaxial substituents have much more steric hindrance (several kilocalories per mole) and consequent strain energy. In flipping the ring from one chair form to the other, all substituents which are above the ring (β-oriented) stay above when the ring flips even though they interchange axial and equatorial environments; substituents below the ring stay below; *cis* substituents stay *cis*, etc.

TABLE 4.3 : Axial-Equatorial energy differences for substituents on chair cyclohexane.

Substituent	ΔF, kcal/mol	Substituent	ΔF, kcal/mole
$-CH_3$	1.7	Cl, Br, I	0.5
$-CH_2CH_3$	1.8	OH, OR	0.7
$-C(CH_3)_3$	5-6 (Very large)	COOR(H)	1.1
C_6H_5	3.1	CN	0.2

Thus for compound **27** (Scheme 4.27), the conformation **29** is the preferred one. Note that the groups on C-1, and C-4 are β-*cis* (above the ring) while the substituent at C-2 is α- (below the ring).



4.12 STEREOISOMERISM OF CYCLIC COMPOUNDS (*Cis-* and *Trans-* ISOMERS AND CHIRALITY)

In case the rotation about a bond joining two multivalent atoms is restricted, then suitable substitution leads to isomerism. The most common method of preventing rotation about a bond is either the formation of a multiple bond or by the incorporation of the bond in a ring system.

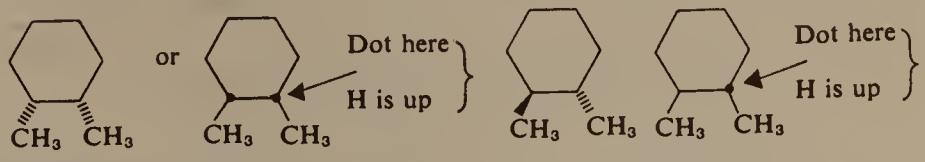
(A) Disubstituted Cyclohexanes

Single substituents in a cyclohexane ring invariably prefer the equatorial position, but when a second substituent is introduced one must consider if it is *cis-* or *trans-* to the first substituent, and whether it is on C_2, C_3, or C_4. In disubstituted derivatives of cyclohexane, the conformational preference will be for a chair containing both substituents equatorial, or, when this is not possible, for the bulkier of the substituents to be equatorial.

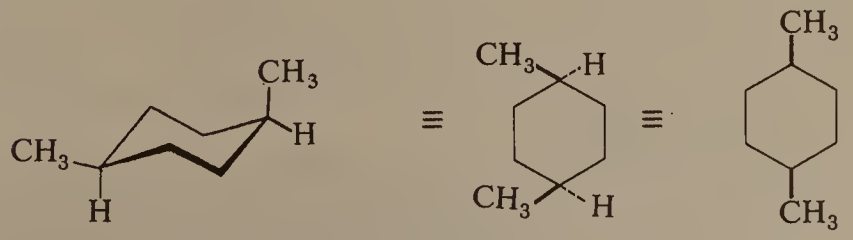
Thus, for disubstituted cyclohexanes, stereoisomerism is possible. The *cis-trans* nomenclature is used to distinguish the isomers. There are two 1,4-dimethylcyclohexanes in one isomer, both methyls project up when the ring is viewed from the side. In this isomer, one substituent is equatorial and the other is axial, but both substituents project above the general plane of the ring. While writing a flat projection of such substituted ring compounds, substituents that project above the ring are indicated by heavy (thick) lines and groups that project below the ring are shown by dotted lines. Hydrogens are often omitted, for convenience as shown for *cis*-1,2-dimethylcyclohexane (Scheme 4.28).

In the other 1,4-dimethylcyclohexane stereoisomer, one methyl group projects above the ring and the other below it. The substituents are on opposite sides of the ring, this isomer is, therefore, called *trans*.

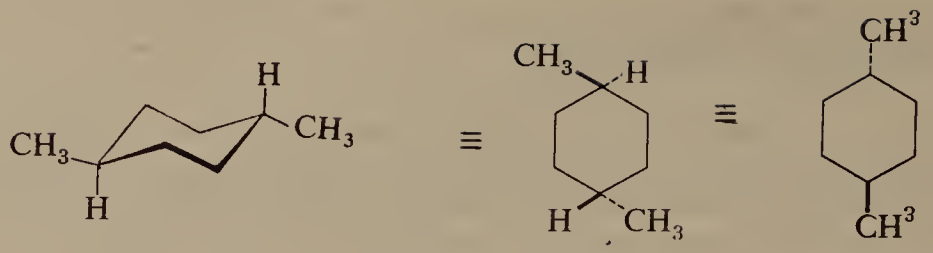
Both the stereoisomeric 1,4-dimethylcyclohexanes are achiral. The lower energy of equatorial substituents compared to axial is also seen in the



cis-1,2- dimethylcyclohexane *trans*-1,2-dimethyl cyclohexane



cis-1,4-dimethylcyclohexane



trans-1,4-dimethylcyclohexane

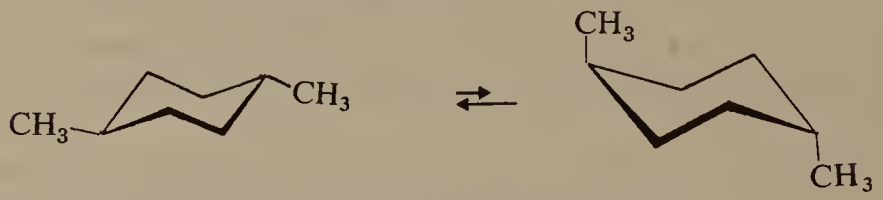
Scheme 4.28

disubstituted compounds. Thus *trans*-1,4-dimethylcyclohexane is more stable than the *cis* isomer by 1.9 kcal mole^{-1}. In the *trans* isomer both methyl groups can be accommodated in equatorial positions whereas in the *cis* isomer one methyl must be axial.

Cis- and *trans*-1,4-dimethylcyclohexane can exist in two chair conformations. In the case of *cis* isomer, the two conformations are of equal energy, since each has one axial substituent and one equatorial substituent.

In the case of *trans* isomer, one conformation has both substituents axial while the other has both substituents equatorial and the diequatorial conformation predominates greatly at equilibrium (Scheme 4.29).

cis-1,4-dimethylcyclohexane, $\Delta G^\circ = 0$



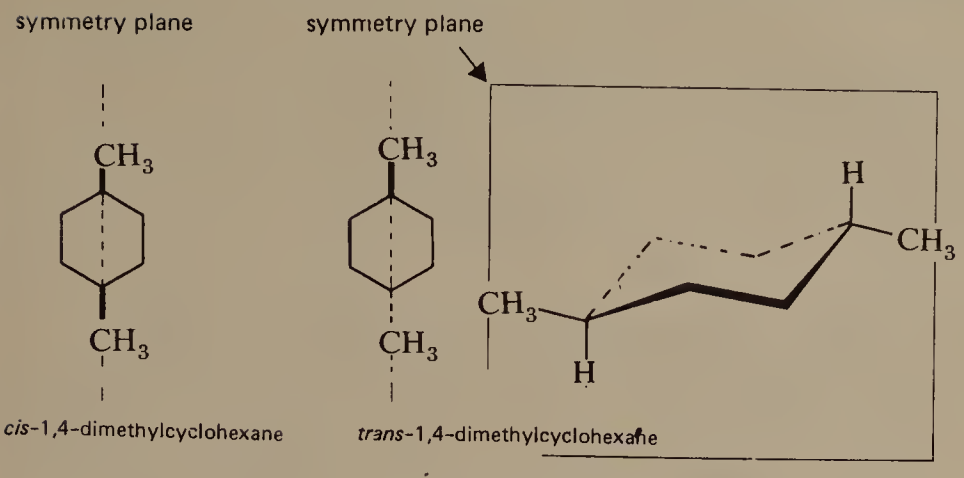
trans-1,4-dimethylcyclohexane, $\Delta G^\circ \approx 3.4$ kcal mole^{-1}

Scheme 4.29

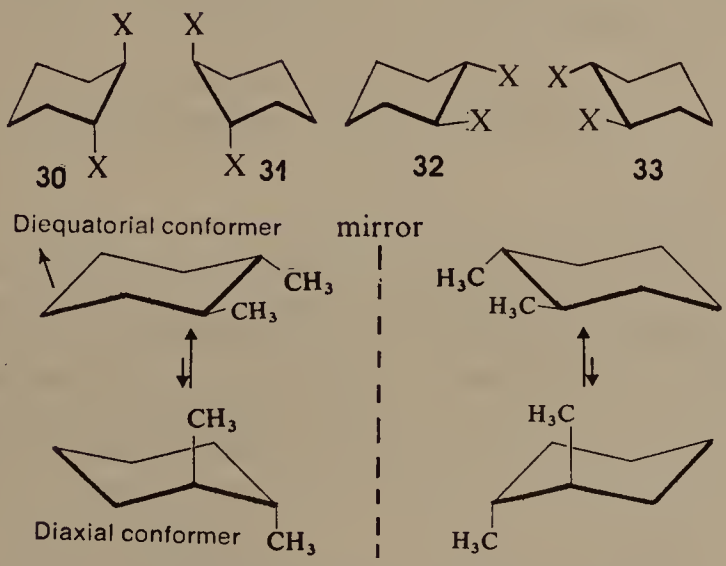
One may easily recognize *cis*- and *trans*- 1,4-dimethylcyclohexane as a pair of diastereomers. Both compounds are achiral (Scheme 4.30), because the symmetry plane passes through C-1 and C-4 and the two methyl groups.

In the chair conformation, however, the symmetric planes may also be seen, but with somewhat difficulty.

Three geometrically different relationships exist between the substituents, X, in a 1,2-disubstituted cyclohexane of the formula $C_6H_{10}X_2$ (Scheme 4.31). Each substituent may be axial as in **30**, each may be equatorial as in **32**, or one may be axial and the other equatorial as in **34**. The three structures are also



Scheme 4.30

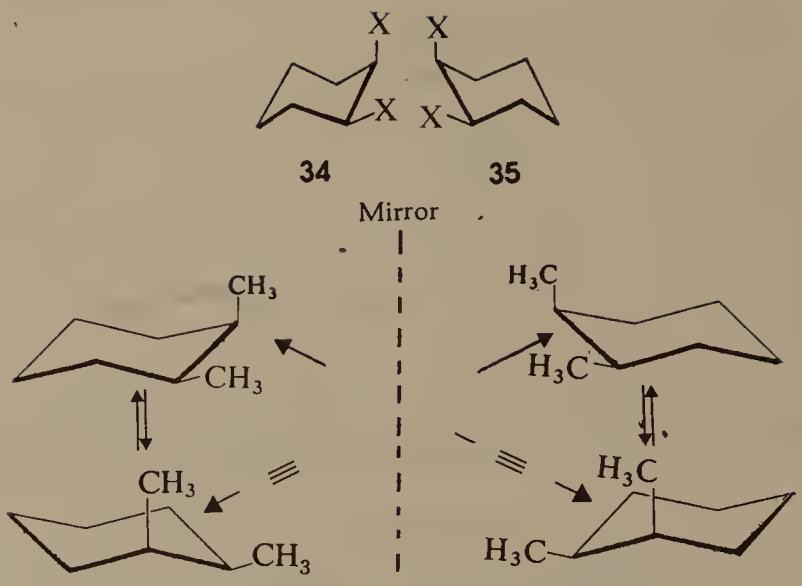


Scheme 4.31

shown together with their mirror images.

None of the conformations is immediately superimposable upon its mirror reflection and three pairs of enantiomers may be expected. However, in practice there are fewer stereoisomers because of the rapid ring-flipping of chair conformations. Thus, **30** is in equilibrium with **33** (as can be seen by flipping **30** into the alternative chair conformation and rotating this through 120° about the axis of symmetry) and similarly **31** is in equilibrium with **32**.

These four (*trans*) structures, therefore, constitute one pair of enantiomers. The remaining pair **34** and **35** (Scheme 4.32) are superimposable by chair-flipping, and therefore, constitute an optically inactive *dl*-pair, unresolvable because they interconvert very rapidly.



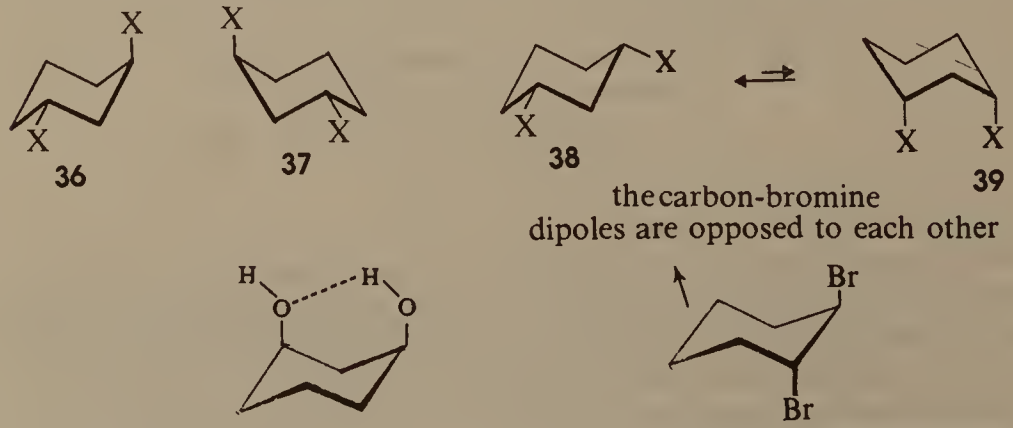
Axial-equatorial conformers of *cis* isomer

cis-1,2 -dimethylcyclohexane

optically inactive and not resolvable

Scheme 4.32

The *trans* isomer is usually more stable when the substituents are both equatorial *e.g.*, for X = CH_3, ΔG is about 2.7 kcal per mole, thus only about one molecule out of hundred is present in the diaxial form. The *trans* isomer is more stable than the *cis* isomer, in which one substituent is necessarily in the unfavourable axial position *e.g.*, for X = CH_3, ΔG is about 1.8 kcal per mole. The 1,3-compounds exist in three discrete stereoisomeric forms, an enantiomeric *trans* pair in which one group is axial and the other equatorial, **36** and **37** (Scheme 4.33) and a *cis* isomer which has a plane of symmetry and



the carbon-bromine dipoles are opposed to each other

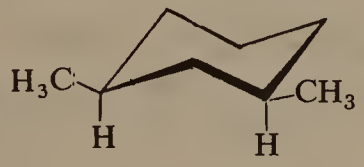
cis-Cyclohexane-1,3-diol
the hydroxyl groups are diaxial
strongly hydrogen bonded

trans-1,2-dibromocyclohexane
diaxial conformation
is stabilised

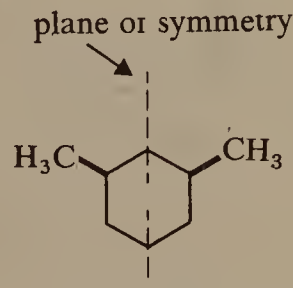
Scheme 4.33

has interconvertible conformational isomers having both groups respectively equatorial **38** and axial **39**, the former predominating. The *cis* isomer in this case is more stable *e.g.*, for X = CH_3, by 1.8 kcal/mol. Cyclohexane-1,3-diol **40** has however; been shown to have the diaxial rather than the diequatorial orientation. This is explained on the basis that intramolecular hydrogen bonding possible only in the diaxial form stabilizes the diaxial form. Similarly, in *trans*- 1,2-dibromocyclohexane the diaxial conformation (unlike diequatorial) makes more contribution, as the C—Br dipoles are opposed to each other.

In the case of 1,3-dimethylcyclohexane a plane of symmetry is easily detectable in the *cis* isomer. Since this compound (in contrast to the 1.4-dimethyl isomer) has chiral carbons, *cis*-1,3-dimethylcyclohexane is, therefore, a *meso* compound.



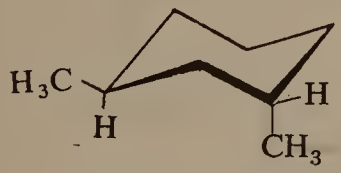
cis-1,3-dimethylcyclohexane
both methyls equatorial



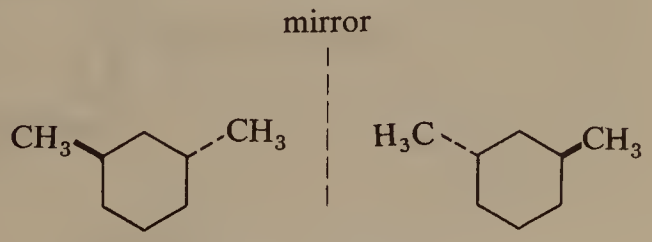
a *meso* compound

Scheme 4.34

However, no symmetry plane or center of symmetry can be detected in the *trans* isomer (Scheme 4.35). Thus, there are two enantiomeric *trans*-1,3-dimethylcyclohexanes.



trans-1,3-dimethylcyclohexane
one methyl equatorial



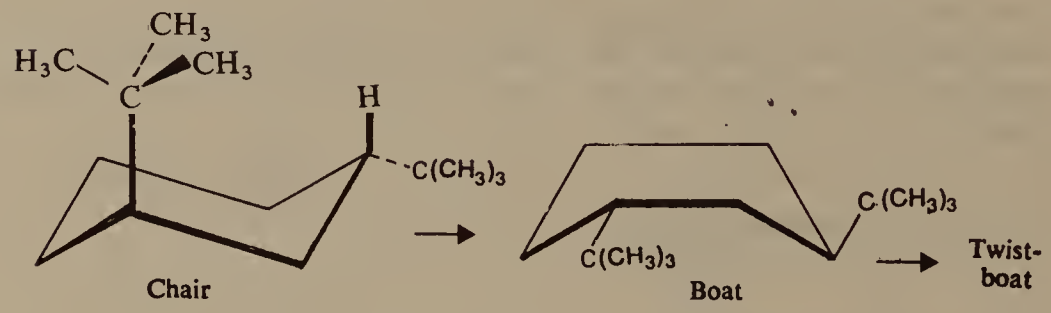
a pair of enantiomers

Scheme 4.35

Because of its bulk, the *t*-butyl group has effective preference for an equatorial position. When excessive strain is involved, a distortion of the cyclohexane ring occurs. For example, phenyl and *t*-butyl are both bulky groups. A crystal structure analysis of a compound that has a *cis*-4-phenyl-1-*t*-butylcyclohexane structure shows that the ring has been stretched out somewhat but still has essentially a chair conformation with axial-phenyl and equatorial-*t*-butyl groups.

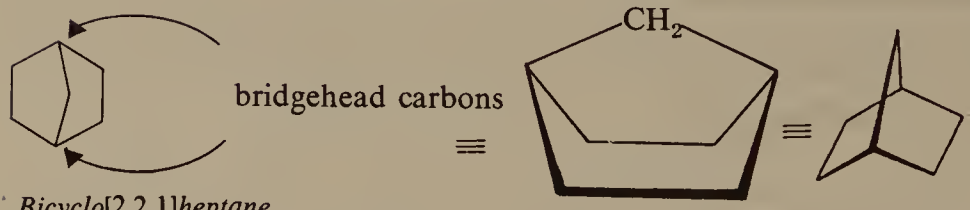
In *trans*-1,3-di-*t*-butylcyclohexane a chair-cyclohexane ring would require

one *t*-butyl group to be axial, in this compound the cyclohexane ring is twisted in order to avoid placing the *t*-butyl group in an axial position to attain a so-called "twist-form" or "skew-boat" structure (Scheme 4.36). This skew-boat form occurs in several compounds containing bulky groups but is not a significant conformation for cyclohexane itself. Adamantane has three fused cyclohexane rings in their chair conformation. Twistane is the twist-boat isomer of adamantane where the six-membered ring is forced to maintain twist-boat conformation. In norbornane the six-membered ring is maintained in the boat form.



Conformations of trans-1,3-*di*-t-*butylcyclohexane*

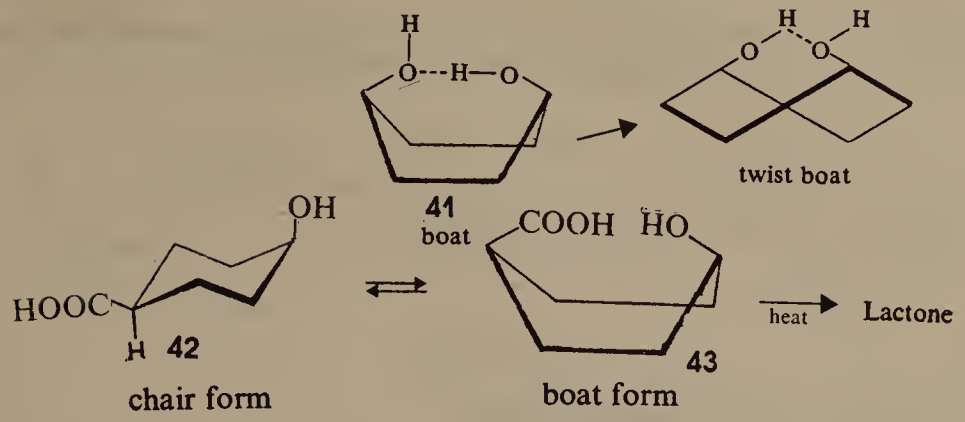
Adamantane *Twistane*



Bicyclo[2.2.1]*heptane*
(*norbornane*)

Scheme 4.36

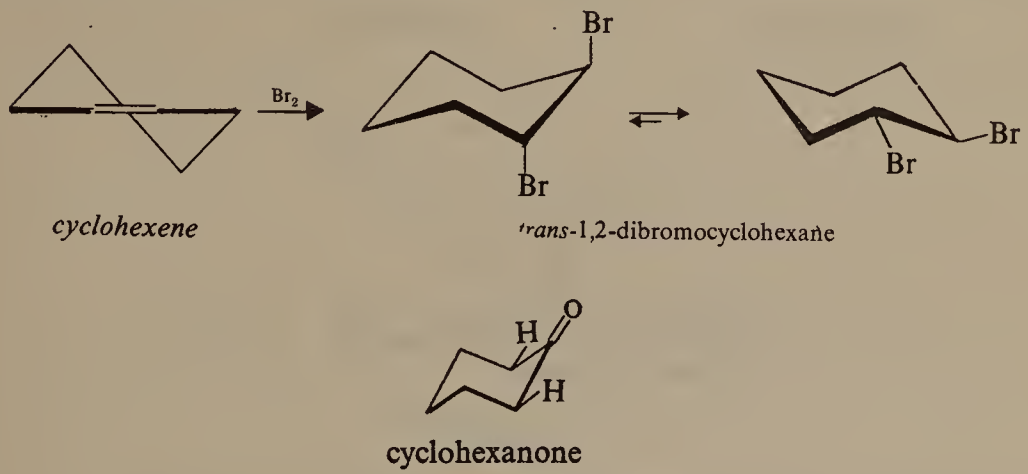
When intramolecular hydrogen bonding is possible between groups in the 1 and 4 positions, a cyclohexane may then assume a boat conformation **41** (Scheme 4.37) in which case only this hydrogen bonding is possible. However, what have been presumed to be boat conformation may be twist-boat form. Even when compounds exist predominantly in the chair form, the boat form, though sparsely populated, may be of importance in some reactions. An example is the lactonization of *cis*-4-hydroxy-cyclohexane-carboxylic acid **42** which must proceed *via* the boat conformation **43**, the *trans* isomer does not lactonize.



Scheme 4.37

(B) Cyclohexene and Cyclohexanone

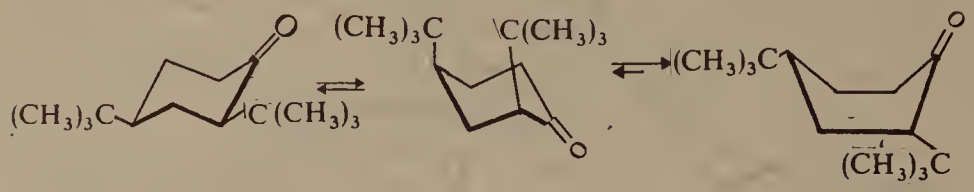
The four groups attached to a double bond in cyclohexene must lie in the same plane in order to provide the most effective overlap for the π bond. In cyclohexene this constraint gives a structure which is a half-chair to provide effective staggering of the four CH_2 groups and thus has little strain. The heat of hydrogenation of cyclohexene 28.4 kcal $mole^{-1}$ is comparable with that of *cis*-2-butene. Cyclohexene behaves as a typical *cis*-alkene. Addition reactions which involve *trans* addition give first the diaxial cyclohexyl product which then goes rapidly over to the corresponding diequatorial conformer (Scheme 4.38).



Scheme 4.38

Compared with cyclohexene, the ring in cyclohexanone is buckled slightly from the chair conformation in order to accommodate the trigonal carbon atom whose optimal C—C angle is 120° The equatorial hydrogen atoms on the α-carbon atom then nearly become eclipsed by the carbonyl oxygen, thus the equatorial substituents are somewhat destabilized by steric repulsions. In some cases this leads to a greater stability of the axially substituted conformational isomer (*e.g.*, 2-bromo-cyclohexanone). In other situations,

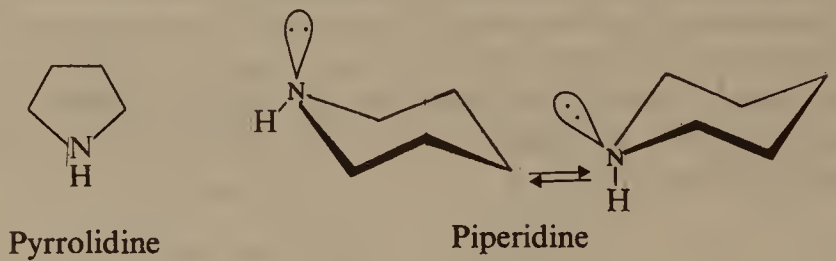
the boat-shaped conformation *e.g.*, as in *cis*-2,4-di-*t*-butylcyclohexanone predominates due to the same reasons (Scheme 4.39).



Scheme 4.39

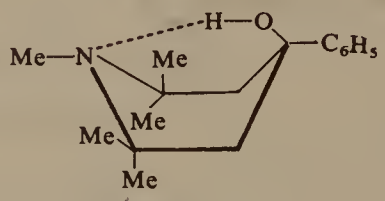
(C) Ring Systems Containing Nitrogen

Pyrrolidine has been shown, from spectroscopic data and X-ray analysis, to be a puckered ring similar to cyclopentane and also, like cyclopentane, undergoes *pseudo*-rotation (Scheme 4.40). Piperidine exists in the chair form[6]. Because of intramolecular hydrogen bonding, cyclohexane-1,4-diol exists in the boat form (or twist-boat form); in some highly substituted 4-hydroxypiperidines boat form is present for the same reason.



Pyrrolidine

Piperidine



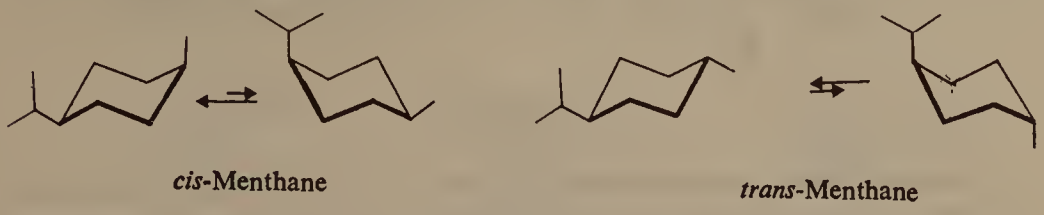
1,2,2,6,6-pentamethyl-4-hydroxy-4- phenylpiperidine

Scheme 4.40

(D) Equilibria of Disubstituted Cyclohexanes and Related Systems

Monosubstituted cyclohexanes occur as equilibrium systems in which axially and equatorially substituted compounds interconvert rapidly through the flipping of the ring, although one or the other conformational isomer usually predominates. Disubstituted and more complex cyclohexanes on the other hand can exist in stereoisomeric forms which are not normally interconvertible, whether or not the ring is able to flip. Thus, *cis*- and *trans*-menthane exist (Scheme 4.41) as separate compounds although ring-

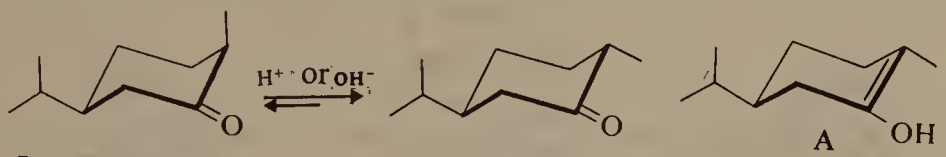
flipping occurs in each. Similarly *cis*- and *trans*-decalins exist as separate compounds, because ring-flipping cannot interconvert the two.



cis-Menthane *trans*-Menthane

Scheme 4.41

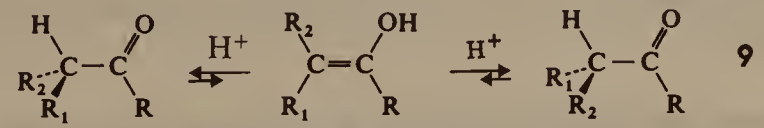
However, the presence of some structural situations allows the interconversion of such stereoisomers under some conditions. For



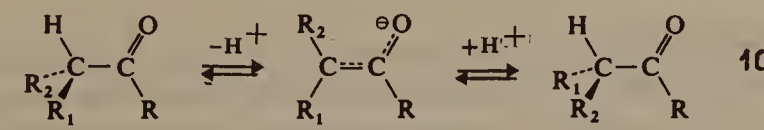
Isocarvomenthone 20% Carvomenthone 80%

Scheme 4.42

example,the incorporation of a carbonyl group in menthane gives *cis*- and *trans*-isomers which are interconvertible in both acidic and basic conditions *via* enol **A**. The *trans* isomer, in which both alkyl substituents are equatorial, predominates.



Acid-catalyzed enolization

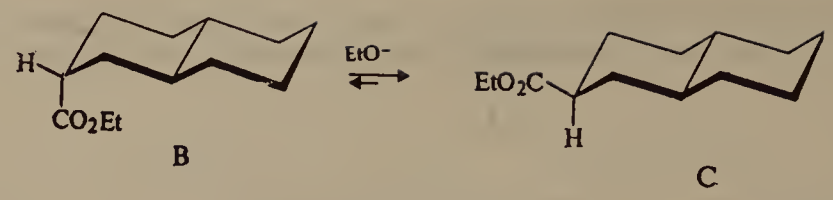


Base-catalyzed enolization

Scheme 4.43

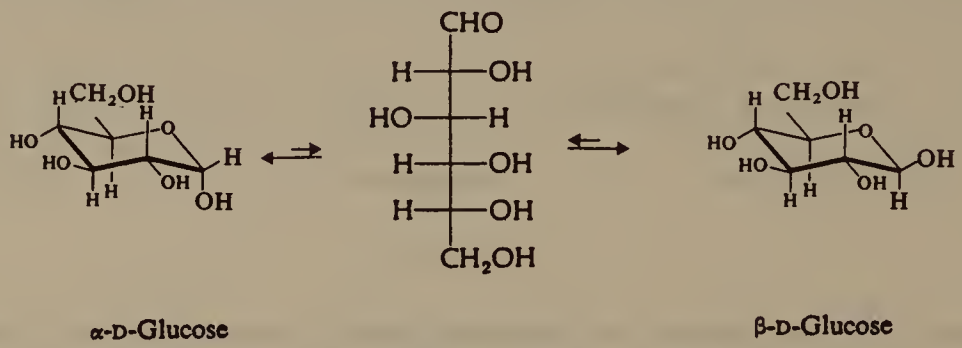
Interconversion occurs, in acid conditions, through the enolic tautomer of the ketone (eq.9, Scheme 4.43) and, in basic conditions, through the enolate anion, *i.e.*, carbanion (eq.10).

The interconversion of the decalin derivatives **B** and **C** by the action of ethoxide ion (Scheme 4.44) involves a carbanion as the critical intermediate. Equilibrium lies to the right because **C** has its carboethoxyl group in the equatorial orientation.



Scheme 4.44

Interconversion can also be brought about provided the ring system readily undergoes ring-opening and ring-closure. The best known example is glucose, α-D-Glucose and β-D-Glucose are interconverted fairly rapidly in soultion through the open-chain tautomer (Scheme 4.45), the β form predominates, as all the substituents are in equatorial positions.



Scheme 4.45

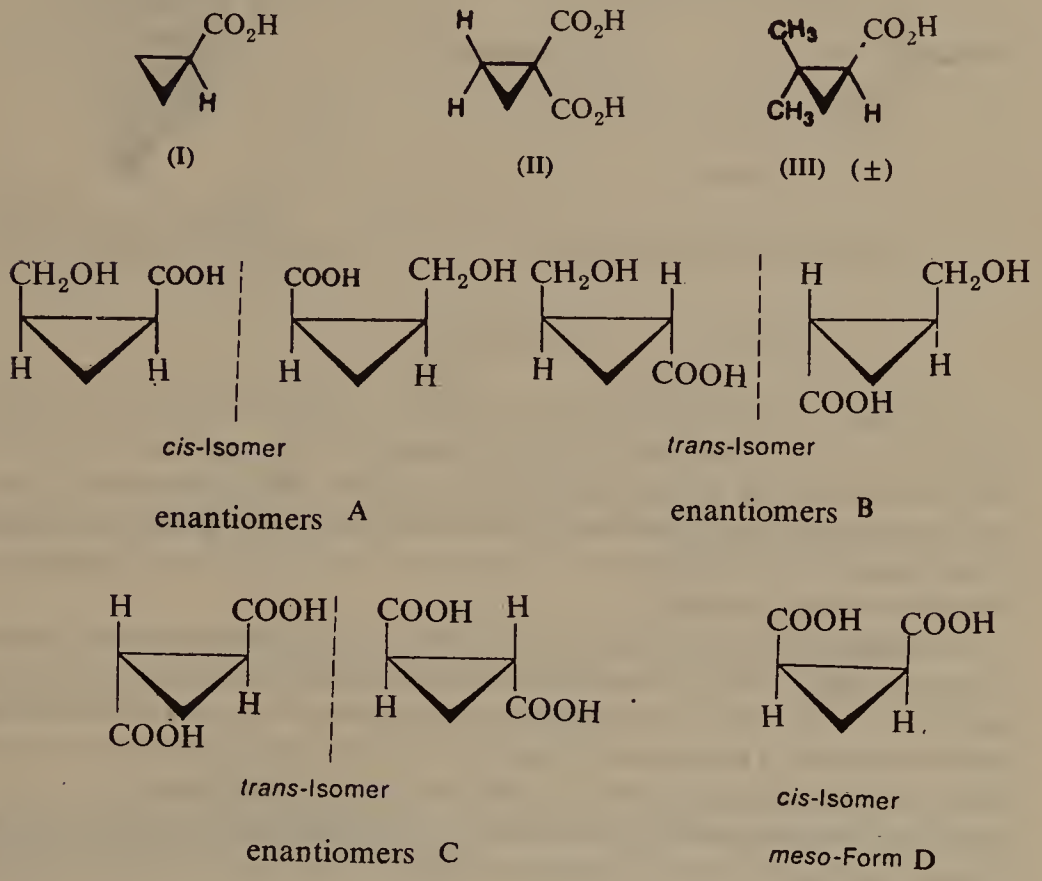
When crystalline α-D-glucose is dissolved in water, the initial specific rotation of the solution (111°) falls gradually to an equilibrium value of 52° 30′; the β form has specific rotation 19°. The phenomenon is known as mutarotation.

4.13 STEREOISOMERISM OF CYCLIC COMPOUNDS CONSIDERING PLANAR RINGS

A three-membered ring must be plannar and in contrast a six-membered ring is not planar. However, it is often convenient to depict the rings like, say, cyclohexane as planar for delineating the stereochemistry of cyclic systems.[7] A monosubstituted compound like cyclopropanecarboxylic acid (I) in Scheme 4.46 always has a plane of symmetry. The substituted carbon is not chiral because one comes across the same atoms going around the ring in either direction. Similarly a 1,1-disubstituted cyclopropane (II) exists only in one form. 2,2-Dimethylcyclopropanecarboxylic acid (III) has (+) and (—) forms.

A non-geminally disubstituted odd-membered ring has two chiral carbon atoms and there are, therefore, two diastereoisomeric pairs of enantiomers. When the two substituents are the same, as in cyclopropane-1,2-dicarboxylic acid, a *dl* pair and a *meso*-form exist as seen in tartaric acid. 2-hydroxymethyl-1-1cyclopropanecarboxylic acid has two chiral centres which are differently substituted. Four stereoisomers are possible, consisting of two pairs of

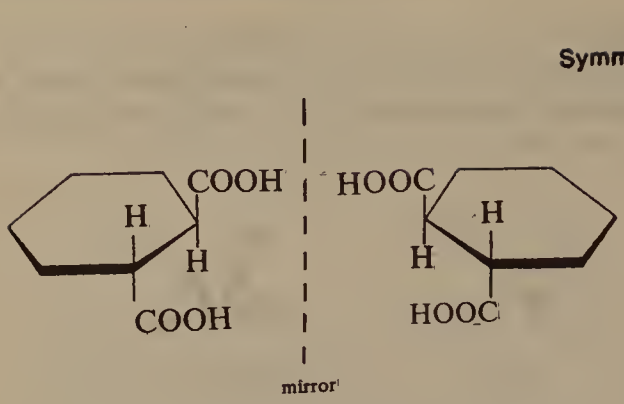
enantiomers **A** and **B**. Oxidation of the hydroxymethyl group of the cyclopropyl compound yields cyclopropane-1, 2-dicarboxylic acid, a compound which has two identically substituted chiral centres and therefore, has one pair of enantiomers **C** and one *meso*-form **D**.



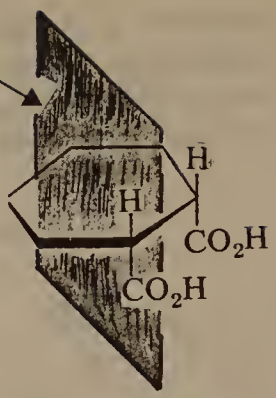
Scheme 4.46

These considerations also apply to all odd-membered rings, no matter whether the substituents are 1,2; 1,3; 1,4 or in any other position relative to each other.

Inspection of even-membered rings shows that there is a slight additional complexity. When the substituents lie across the ring from each other (on C_1 and $1 + n/2$ in an n-membered ring) the molecule will invariably possess a plane of symmetry (provided if the substituents are not in themselves dissymmetric) and, therefore, no active forms exist, although the molecule may still display *cis-trans* isomerism. This has already been shown in the case of 1,4-substituted cyclohexanes (Sec. 4.12A). In the case of cyclohexane derivatives one easily recognises a *dl* pair **E** (Scheme 4.47), in the case of *trans,* isomer and a *meso*-form **F** in the case of the *cis* isomer of cyclohexane-1,2-dicarboxylic acid.



trans Isomer: an enantiomeric pair **E**



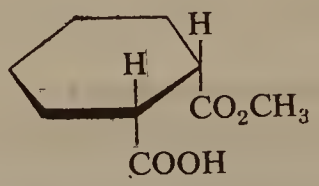
cis Isomer: a *meso* form **F**
(contains a plane of symmetry)

Scheme 4.47

Conversion of cyclohexane-1,2-dicarboxylic acid to its half-ester yields a compound with two differently substituted chiral centres. Thus, four stereoisomers **G** and **H** (Scheme 4.48) are possible (two enantiomeric pairs). On moving these groups to the 1,4-positions on the ring a plane of symmetry is generated, enantiomerism disappears, and only two *meso*-forms (diastereoisomers) remain.

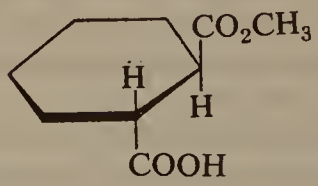
On placement of three or more groups on a cycloalkane ring increases the stereoisomeric possibilities and additionally complicates the nomenclature problem as well. Thus, 3,5-dimethylcyclohexanol exists as a pair of *meso*-forms and a pair of enantiomers. Each form can be designated in terms of the (*R*) or (*S*) configuration at each of the three centres of chirality.

It is however convenient to have a means of specifying the relation between the substituents in terms analogous to the *cis, trans* prefixes which are used



cis Isomer: an enantiomeric pair
G

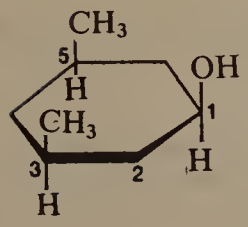
cis Isomer: a *meso* form



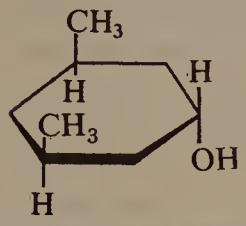
trans Isomer: an enantiomeric pair
H

trans Isomer: a *meso* form

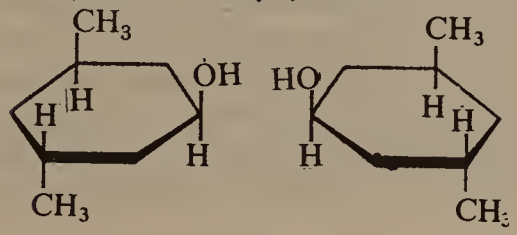
Scheme 4.48



cis-3,*cis*-5-Dimethylcyclohexan-*r*-1-ol *meso* form



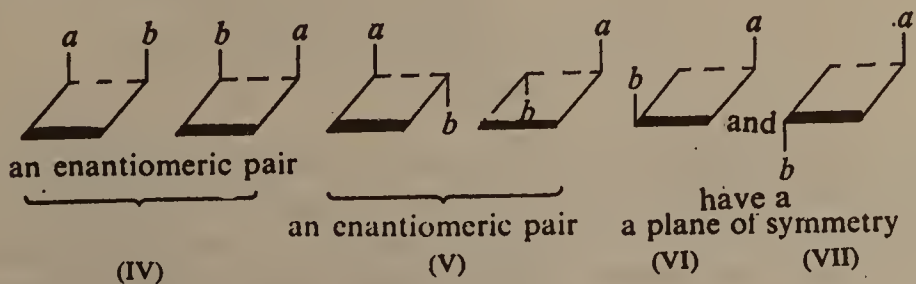
trans-3,*trans*-5-Dimethylcyclohexan-*r*-1-ol *meso* form



cis-3,*trans*-5-Dimethylcyclohexan-*r*-1-ol enantiomeric pair

Scheme 4.49

for the disubstituted cycloalkanes. In one method, a reference group in the molecule (designated by the prefix "r") is chosen based on the priority sequence rules. For 3,5-dimethylcyclohexanol, the hydroxyl group is the reference group, and the *cis* or *trans* relationship of the methyl groups with the hydroxyl group is specified (Scheme 4.49). Mono and 1,1-disubstituted cyclobutanes occur in only one form as is the case with cyclopropanes, whereas 1,2-disubstituted cyclobutanes exist as diastereoisomeric pairs of enantiomers IV and V (or a pair of enantiomers and a *meso*-form if a = b). However, both the *cis* and the *trans* 1,3-disubstituted derivatives VI and VII have a plane of symmetry, so that there are only two isomers and none of them is optically active.

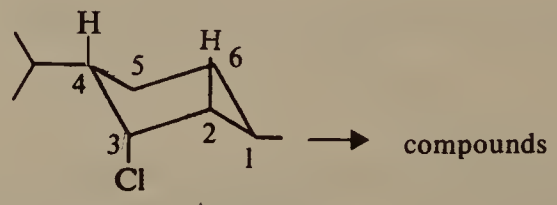


Scheme 4.50

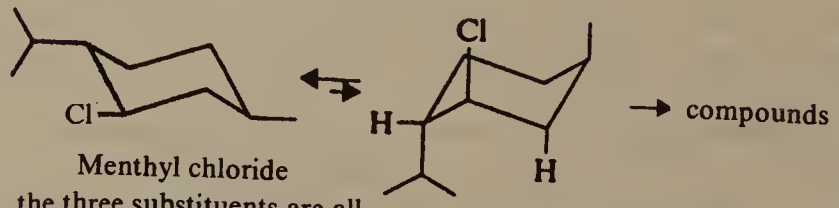
4.14 CONFORMATION AND REACTIVITY IN MONOCYCLIC CYCLOHEXANE RING SYSTEMS

Introduction of a *t*-butyl group into a cyclohexane ring gives a system which is conformationally biased since it exists mainly in one conformation, but is not conformationally rigid; given enough energy, it can still undergo flipping.

An example of a reaction which is forced to occur *via* an unfavourable conformation is provided by elimination of the elements of HCl from the menthyl chlorides by the action of sodium ethoxide in ethanol. The stereoelectronic requirement for bimolecular elimination is that the eliminating groups have to be *anti* periplanar and this can only be met by substituents in a cyclohexane ring, if they are both axial and *trans* to each other. This condition is indeed met by the stable conformation of neomenthyl chloride, in which the chlorine and the hydrogens at both C-4 and C-2 are axial (Scheme 4.51). Thus, it undergoes a facile elimination to give the products. In the preferred conformation of menthyl chloride, however, the chlorine is equatorial; reaction must, therefore, occur through ring flip to the unfavourable chair conformation (VIII). As a result, menthyl chloride reacts slowly as compared with neomenthyl chloride by a factor of .189 at 125°C.



Neomenthyl chloride

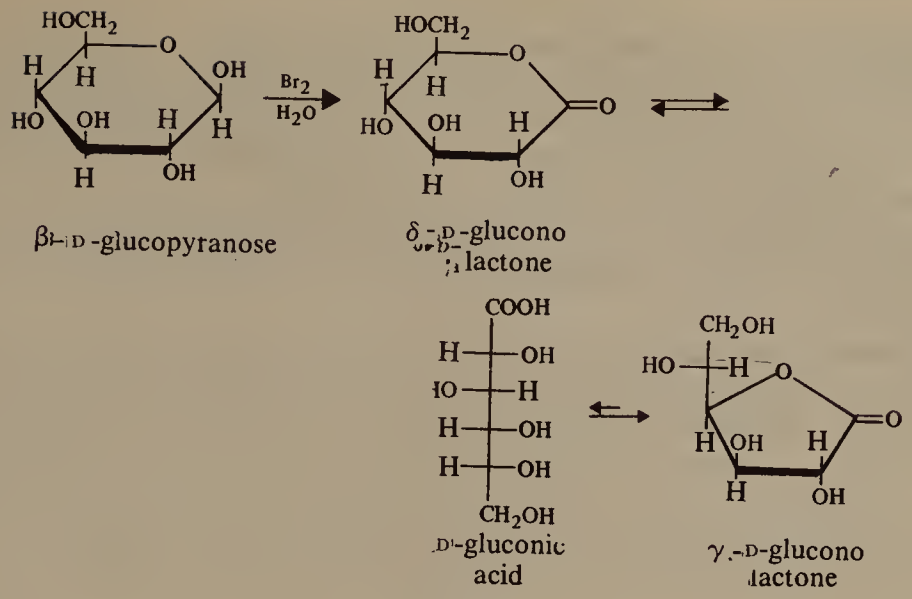


Menthyl chloride
the three substituents are all equatorial, is the more stable chair conformation

(VIII)
Anti-periplanarity of the leaving groups requires that they be diaxial even if this is the conformation of higher energy

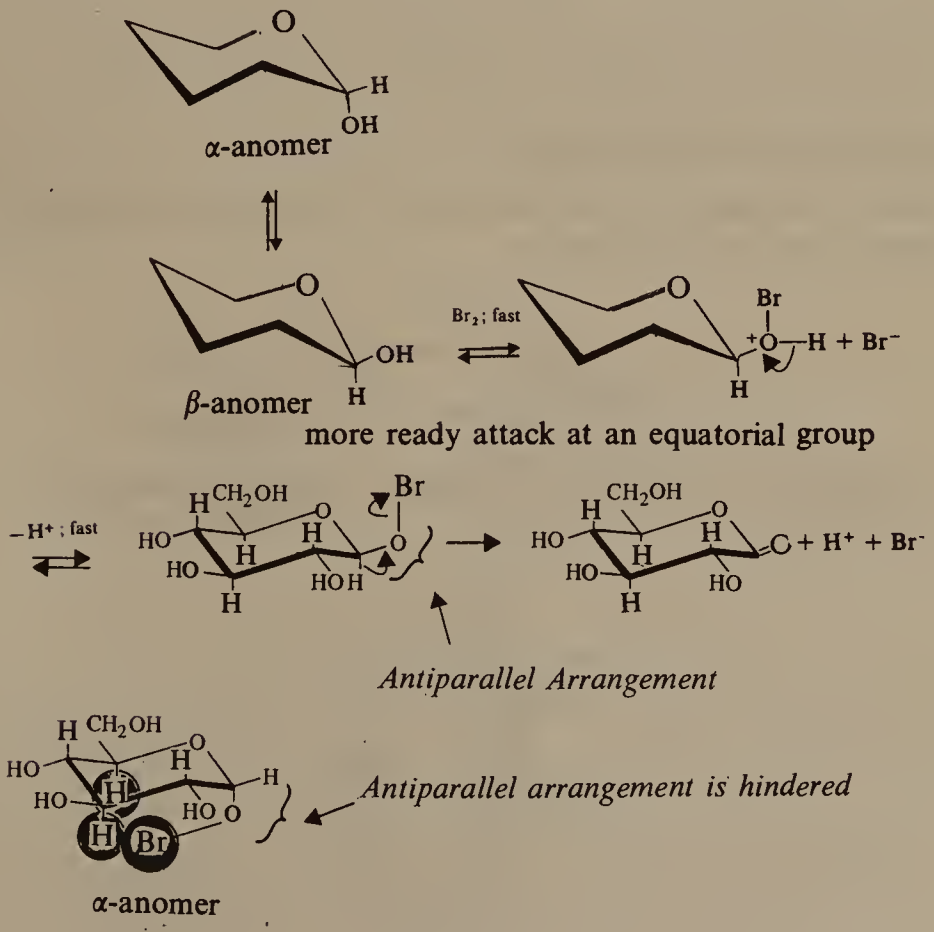
Scheme 4.51

Bromine water is a reagent of choice that brings about the conversion of an aldose to an aldonic acid. That is, it selectively oxidizes the —CHO group to a —COOH group (Scheme 4.52). Bromine water specifically oxidizes the β anomer, and the initial product being a δ-aldonolactone. This compound may then hydrolyze to an aldonic acid, which may undergo a subsequent ring closure to form a γ-aldonolactone.



Scheme 4.52

An α-aldopyranose also undergoes this oxidation, however, it reacts much more slowly. Thus the rate of oxidation of β-D-glucopyranose is 250 times faster than that of α-D-glucopyranose. The slow rate of oxidation of α-D-glucopyranose reflects its conversion to the β-anomer (followed by



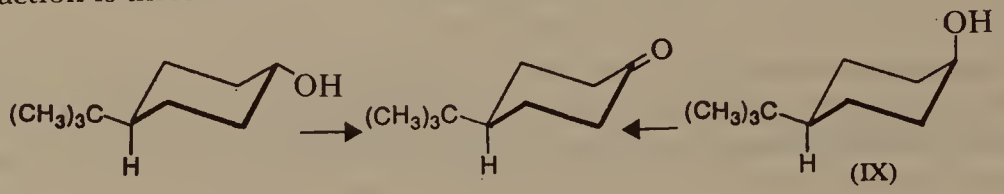
Scheme 4.53

oxidation), rather than direct oxidation of the α-anomer.

A mechanism that accounts for this behaviour requires attack by Br^+ at the anomeric oxygen followed by loss of HBr from an intermediate in which the H and OBr groups are antiparallel (i.e., *anti*-periplanar) to each other. β-Anomers can achieve this stereochemistry easily.

With α-anomers the α-axial hydrogens at the 3 and 5 positions hinder the attainment of an *anti*-parallel arrangement (1:3 nonbonded interactions with bulky Br).

Reactions which do not have a stereoelectronic requirement also display rate differences between reactions of axial and equatorial isomers. Oxidation of both *cis*- and *trans*-4-*t*-butyl-cyclohexanols with chromic acid affords the same ketone. In the preferred conformation the *cis*-isomer IX (Scheme 4.54) has an axial hydroxy group which is removed in the oxidation to allow relief from steric interaction (1:3 interactions with β-axial hydrogens) and the reaction is three times faster for the *cis*-isomer (steric acceleration).

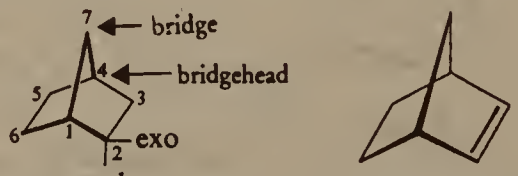


Scheme 4.54

4.15 POLYCYCLIC COMPOUNDS AND THEIR REACTIVITY

(A) Norbornanes - Bridged Rings

Bicyclic hydrocarbons such as norboranane and norbornene are named systematically as shown in Scheme 4.55.

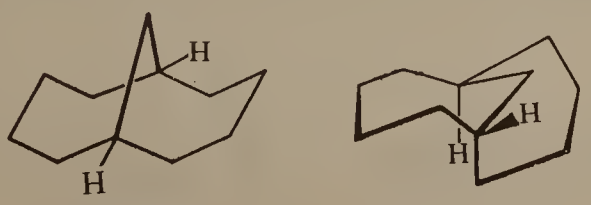


Systematic name	bicyclo [2·2·1] heptane	bicyclo [2·2·1] hept-2-ene
Trivial name	norbornane	norbornene

Scheme 4.55

The prefix bicyclo- shows that two rings are sharing two or more common atoms. The prefix hept- (the 'a' of 'hepta' is dropped) in the names refer to the total number of carbon atoms in the bicyclic system. The -ane and -ene endings indicate a saturated and an olefinic system respectively. The numbers in brackets denote the number of carbon atoms separating the two bridgeheads in all possible directions, and are given in order of decreasing magnitude. The numbering of carbons begins from one bridgehead and goes to the other by following the longest path of separation first, the second longest path next and the shortest path last. The spatial relationships of substituents with respect to the methylene bridge are described by *exo-* and *endo-* prefixes. When a multiple bond is present in the bicyclic system, the path containing the unsaturation is given the lowest possible numbers.

Cyclic systems with two or more rings joined in the "fused" or "bridged" fashion may lead to some constraints on the number of stereoisomers and structural possibilities for a given system. The bridged-ring compound norbornane is a rigid molecule where the cyclohexane ring is forced in the boat conformation. Norbornane has fewer isomers than predicted, for it may be thought that a bicyclo [2.2.1] heptane structure can exist in which the bridging carbon is linked to the topside of the cyclohexane ring at C-1 and the bottomside at C-4. This system however, would be too strained to be isolated and only a single bicyclo [2.2.1] heptane is known. On the other hand, bicyclo [4.4.1] undecane, constitutes a system with a methylene group bridging a considerably larger and more flexible ring than cyclohexane. It exists in two isomeric forms. A consideration of molecular models shows this difference rather clearly, and reveals that the *trans* isomer of bicyclo [2.2.1] heptane cannot be constructed while the *trans* isomer of bicyclo [4.4.1] undecane is easily built.



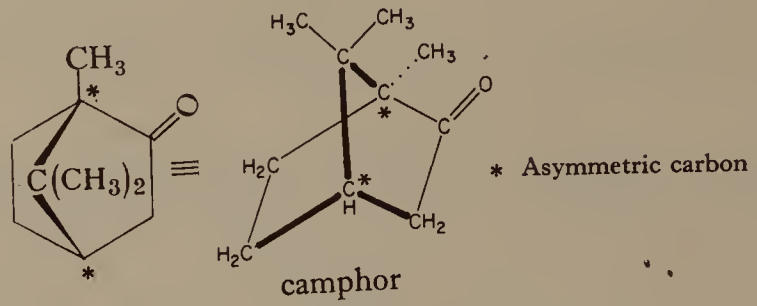
cis- Bridge *trans*- Bridge

Bicyclo [4.4.1] undecane

Scheme 4.55A

In norbornane (Scheme 4.55) there is non-identity of positions 7 (bridge), 1 or 4 (bridgehead) and 2,3,5 or 6 (peripheral). To an extent, a configurational restriction is associated with norbornane and related systems. The molecule of camphor has two asymmetric carbon atoms (starred) and yet only one *dl* pair is known to exist as can be seen by constructing a model. The bridge has to be *cis* and, therefore, the configurations of the bridgehead carbons are not independent. Thus for these steric reasons, C-1 and C-4 behave as a single element of chirality. Therefore, the number of stereoisomers is always one

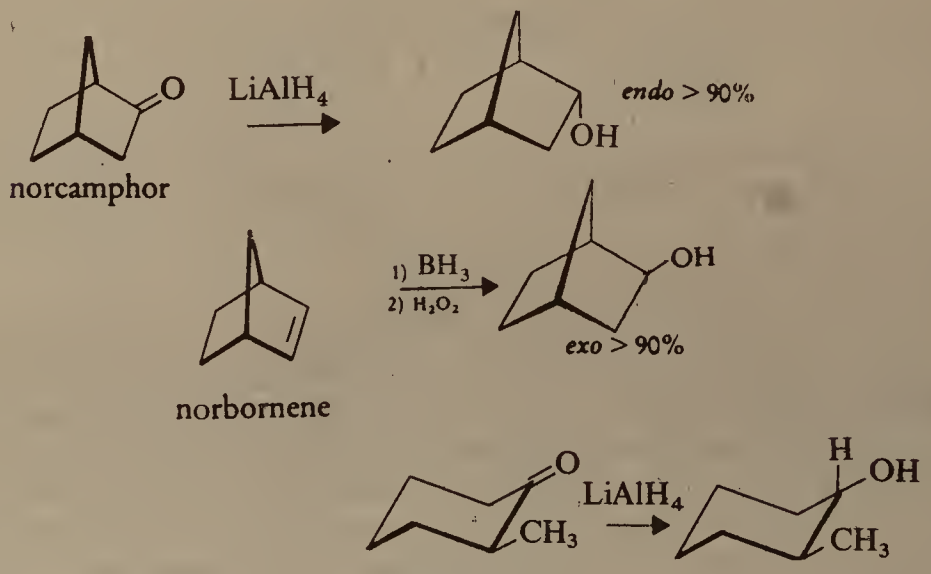
half of what would be expected if this restriction is not there. Similarly norbornane monosubstituted in the 2-position has three asymmetric carbons therefore four stereoisomers exist for such derivatives, i.e., (+) - and (-)-endo and (+)- and (-)-*exo*.



Scheme 4.55B

(B) Reactivity in Bridged Rings

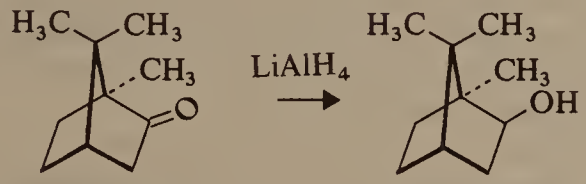
The methylene bridge in norbornane firmly locks the six membered ring into a strained boat conformation (norbornane has strict C_{2v} symmetry). A particularly interesting aspect of norbornane is its rigidity and the effect of its structure on reactivity. Substitution at C-2 can afford four distinct compounds; an *exo*- and an *endo*-substituted form and an enantiomer of each. The exo- and *endo*- substituted forms represent stable spatial isomers which are diastereoisomers as these cannot be interconverted by conformational changes. Generally compounds with *exo*-substituents are lower in energy than their *endo*-diastereoisomers, because of less steric hindrance in the former. This is illustrated in the preferential approach of reactants to the *exo* side of the molecule in the norbornane derivatives (Scheme 4.56).



Scheme 4.56

Lithium aluminium hydride reduction of simple acyclic and monocyclic ketones, usually affords the more thermodynamically stable alcohol (the product development control factor). In rigid bicyclic ketones like norcamphor steric hindrance to the approach of the reagent to the carbonyl function becomes the predominant factor (the steric-approach control factor). So 2-methyl-cyclohexanone affords 70% of the *trans* diequatorial alcohol as compared with norcamphor which affords the less stable *endo*-alcohol by attack of the reagent from the less hindered *exo*- side.

Substitution at the bridge almost entirely hinders *exo* approach, so that *endo* attack becomes preferred. The reduction of camphor is an example of preferential *endo* attack which affords the less stable of the two possible alcohols—isoborneol (Scheme 4.57).



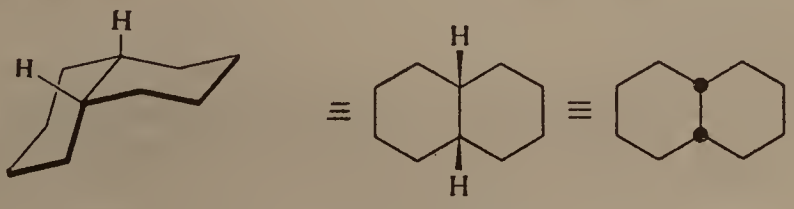
camphor isoborneol

Scheme 4.57

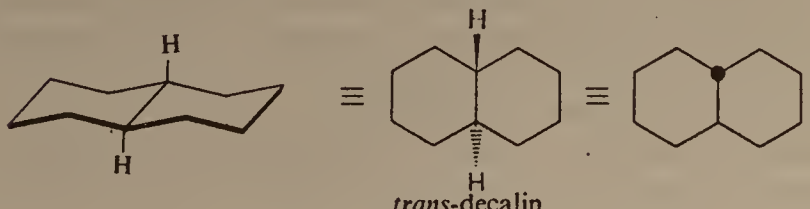
(C) Fused-Rings : The Decalins

The compound bicyclo [4,4,0] decane, better known as decalin, exists in two diastereoisomeric forms depending on the way in which the two cyclohexane rings are fused together. Heavy dots at ring junctions represent hydrogen atoms above the plane of the paper (Scheme 4.58). It is also readily determined from the models that *cis* and *trans*-decalins are diastereoisomers as they cannot be interconverted by bond rotations.

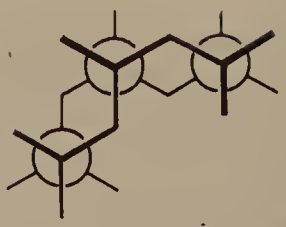
Decalin may be considered as a fusion of a four carbon chain *i.e.*, $-CH_2CH_2CH_2CH_2-$ to the chair form of cyclohexane. *Trans*-decalin is fused with this four-carbon chain (equivalent to largest groups) in equatorial



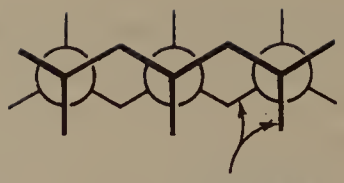
cis-decalin



trans-decalin



cis-Decalin
11kJ mol^{-1} less stable
than the *trans*-isomer
has three more gauche, butane-like
interactions than *trans*-decalin



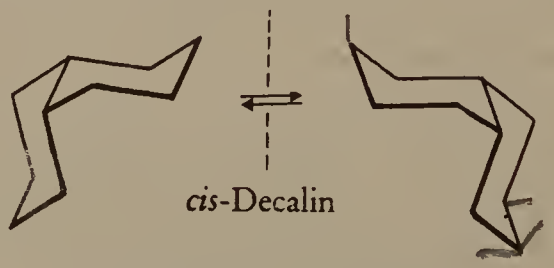
Butane-gauche
interaction

trans-Decalin

Scheme 4.58

positions while in *cis*-decalin this fusion involves equatorial-axial positions (Scheme 4.58). As a result in *cis*-decalin the two hydrogens attached at the point of fusion between two rings lie on the same side of the ring while in *trans*-decalin, they are on opposite sides.

In fact, *cis*-decalin exists as an equilibrium between two enantiomeric all-chair conformations which are interconvertible as a result of conformational flipping which is typical of monocyclic cyclohexanes. As a result, any substituent attached to the *cis*-decalin system is more or less free to



cis-Decalin

two enantiomeric conformations

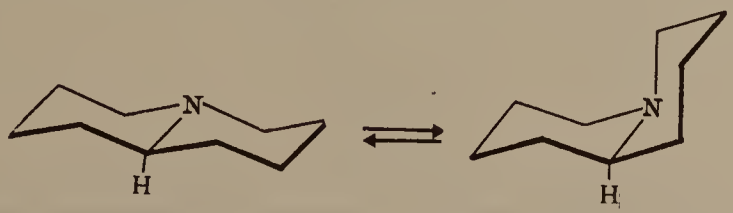
Scheme 4.59

adopt the equatorial orientation. *Cis*-decalin is disymmetric in both conformations which are non-superimposable mirror images of each other. Because of rapid ring flipping between these forms the compound is a non-resolvable *dl*-pair.

On the other hand, *trans*-decalin has a unique and rigid conformation, inversion of which is not possible, as it would otherwise afford a highly strained system with one ring attached to the other by two axial bonds. As a result, a substituent is constrained to remain in a particular conformation which is dependent on its configuration. The rigid conformation of *trans*-decalin has been used in the same manner at *t*-butyl groups to study the relative rates of equatorial and axial substitution. The hindered approach to axial positions has been demonstrated. *Trans*-decalin has a centre of symmetry and is therefore optically inactive. It may be further noted that substituents located at the point of fusion between two rings (angular positions) in *cis*-decalins are axial with respect to one ring while equatorial

with respect to the other, however, in the case of *trans*-decalins these are axial with respect to both the rings. It may be remembered that simple rotation of groups about carbon-carbon bonds cannot bring about inter-conversion of *cis*- and *trans*-decalins. Therefore, in this respect decalins resemble the *cis*- and *trans*-1,2-disubstituted cyclohexanes and as has already been said, in decalins the 1,2-substituents are the two ends of four carbon chain. *Trans*-declain as a result is stabler by about 2.7 kcal/ mole (11.3 k J/mol) as compared with *cis*-form.

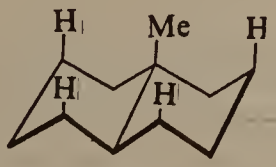
The barrier to interconversion of *cis*- and *trans*-decalin can be decreased by heteroatom substitution in some cases (Scheme 4.60). If a nitrogen atom occupies a bridgehead position *cis* and *trans* forms cannot be isolated. The rapid interconversion of the *cis* and *trans* forms in this case is the result of an easy inversion of configuration at nitrogen which eliminates the need for a *trans*-diaxial transition state.



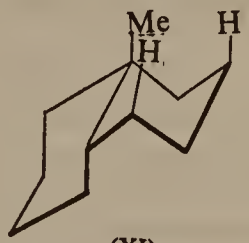
interconversion by ring flipping of azadecalin

Scheme 4.60

When an angular methyl group is introduced, the *cis*-form becomes slightly more stable than the *trans*-form. Steroids and several other natural products contain the 9-methyl decalin system. The introduction of an angular methyl group reduces the differences in energy between the decalins, because in the *trans*-compound (X), the methyl group is sterically compressed by four axial hydrogen atoms (on C_2, C_4, C_5 and C_7) and by only two (C_2 and C_4) in the case of *cis*-isomer (XI).



(X)



(XI)

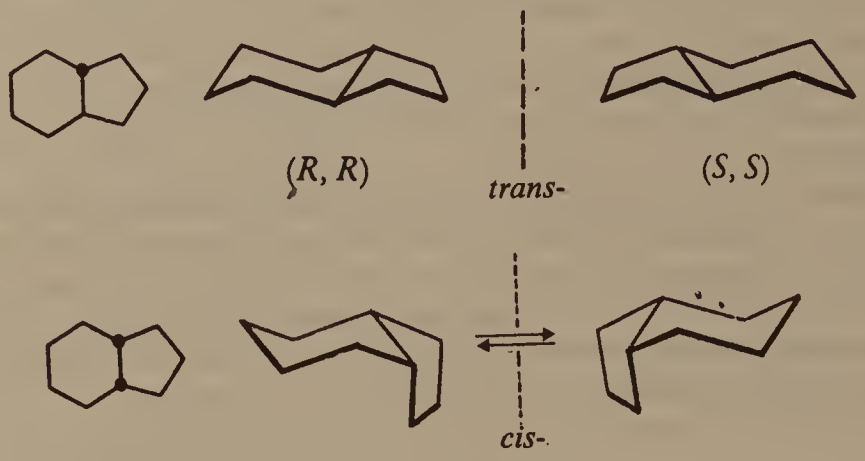
there are four sets of 1,3-diaxial interactions involving the bulky methyl group and the axial hydrogens

Scheme 4.61

(D) Fused Rings : The Hydrindanes

In hydrindane molecule rings of different sizes are fused and these are

represented as the rings C and D of steroids. The dissimilarity of the two rings makes the ring-fused carbon atoms chiral. Hydrindane exists as two stable *trans*- enantiomers and a *meso cis*-isomer (Scheme 6.42).



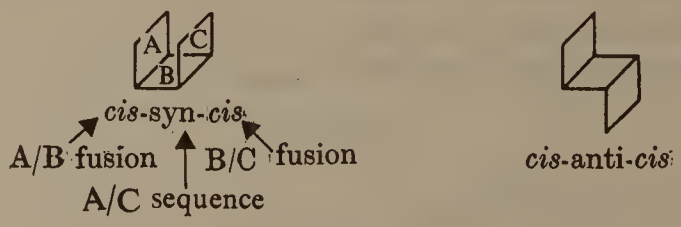
Hydrindanes

Scheme 4.62

As with the decalins, *trans*-hydrindanes are conformationally rigid molecules, while *cis*-hydrindane is flexible and exists as a (*dl*)-pair of conformers. The free energy of activation of this conformational inversion is considerably smaller than the inversion barrier of *cis*-decalin. Moreover, the *cis*- and *trans*-diastereoisomers of hydrindane have an energy difference around 2.9 kJ/mol (0.7 kcal/mol), a significantly smaller value as compared with that of decalin diastereoisomers. This is due to the more planar structure of the five-membered ring and as a result there is less strain in the fused system.

(E) Fused Rings: The Steroid Nucleus, Bridged Alkaloids, Relation between Conformation and Reactivity

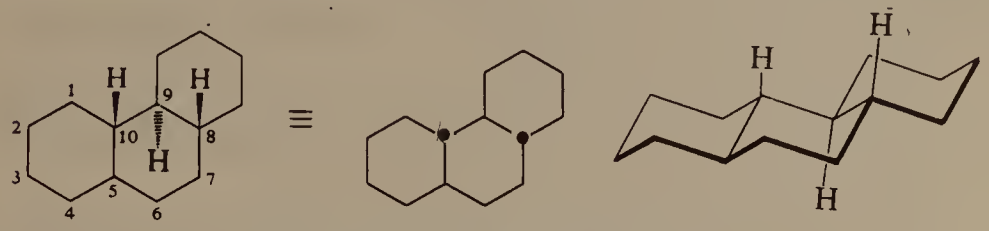
The tetracyclic ring system of perhydrocyclopentanophenanthrene is found in steroids and is composed of three fused 6-membered rings. Perhydrophenanthrene itself exists in ten stereoisomeric forms; four enantiomeric pairs and two *meso* isomers. The prefixes *cis*- and *trans*- refer to the stereochemistry at the bonds of fusion between rings while *syn*- and *anti* (Scheme 4.63) have reference to the orientation of terminal rings with respect



Scheme 4.63

to each other. The most stable of these is the *trans- anti- trans* form, an all-chair conformation (Scheme 4.64). The *trans- syn- trans* form is the least stable as this structure can be realised only when the middle ring has the energetically unfavourable boat conformation.

The steroids are naturally-occurring compounds with three cyclohexane rings and one cyclopentane ring. Steroids can belong to one of two families that resemble the decalins at the **A** and **B** rings. The cholestane family has an



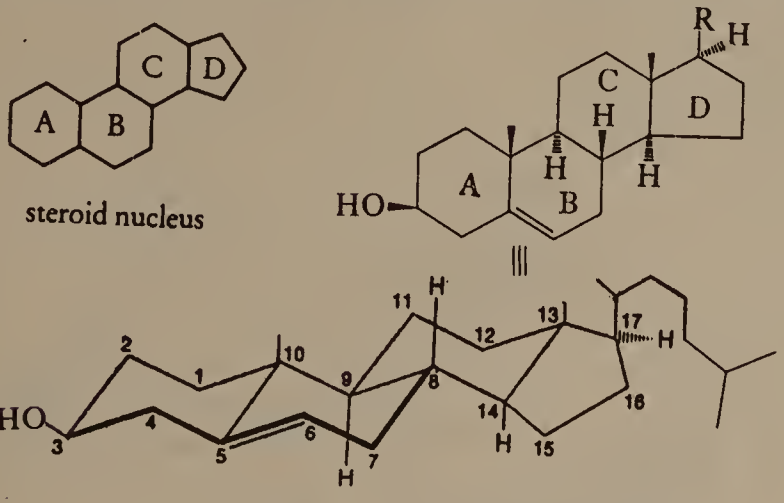
trans-anti-trans-perhydrophenanthrene

Scheme 4.64

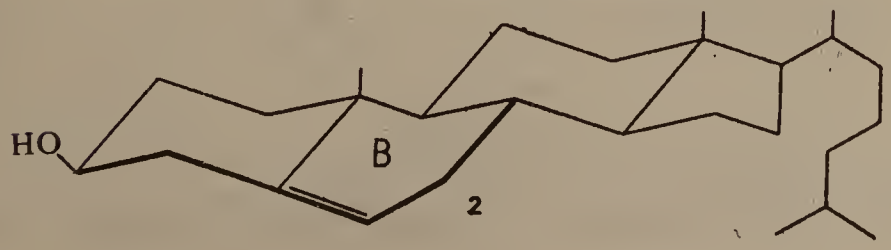
A-B *trans*-decalin ring system and the coprostane series has it as a *cis*-decalin system.

Interestingly the presence of a series of rings confers rigidity on both the series. Although boat conformations can be attained, even the coprostane series cannot exchange axial and equatorial positions by ring flips.

Based on the above knowledge it is easy to understand the conformation of cholesterol (Scheme 4.65). Although for simplicity ring **B** in the



1 Conformation of cholesterol



2

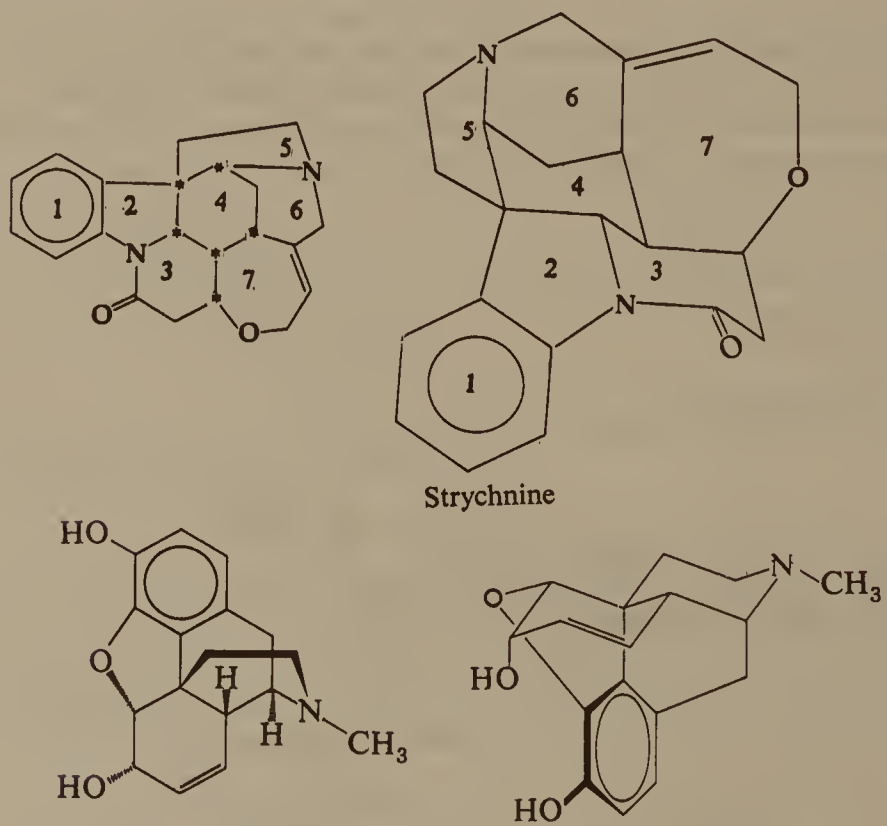
Scheme 4.65

conformation of cholesterol 1 is depicted as a chair cyclohexane, however, since in cyclohexene the fragment C—C=C—C is coplanar, the actual conformation of cholesterol should be as respresented in 2.

Similarly in the two-dimensional structure of strychinine (Scheme 4.66) six asymmetric carbon atoms are shown starred. Thus, strychnine is theoretically capable of existing in 2^6=64 stereoisomers. A more realistic conformational formula helps to deduce and make the stereochemistry look comparatively simpler by considering the following points:

1. Ring 4 is in chair conformation thus forcing the bridging of ring 6 with it *via* the *cis*- diaxial bonds.
2. This makes the fusion of ring 5 with 6 *via* one axial and one equatorial bond, *i.e., cis* fusion as it is geometrically impossible to bridge 1,2-diaxial *trans* positions with a ring of ordinary size.
3. Ring 2 is also *cis* fused with ring 4 *i.e.,* its bond with nitrogen is equatorial. Similarly, ring 7 is also *cis* fused and the juncture of rings 3 and 4 is obviously *trans.*

Based on similar arguments, the conventional formula of morphine when interpreted in the conformational representations, imposes the stereochemistry for the ring system.

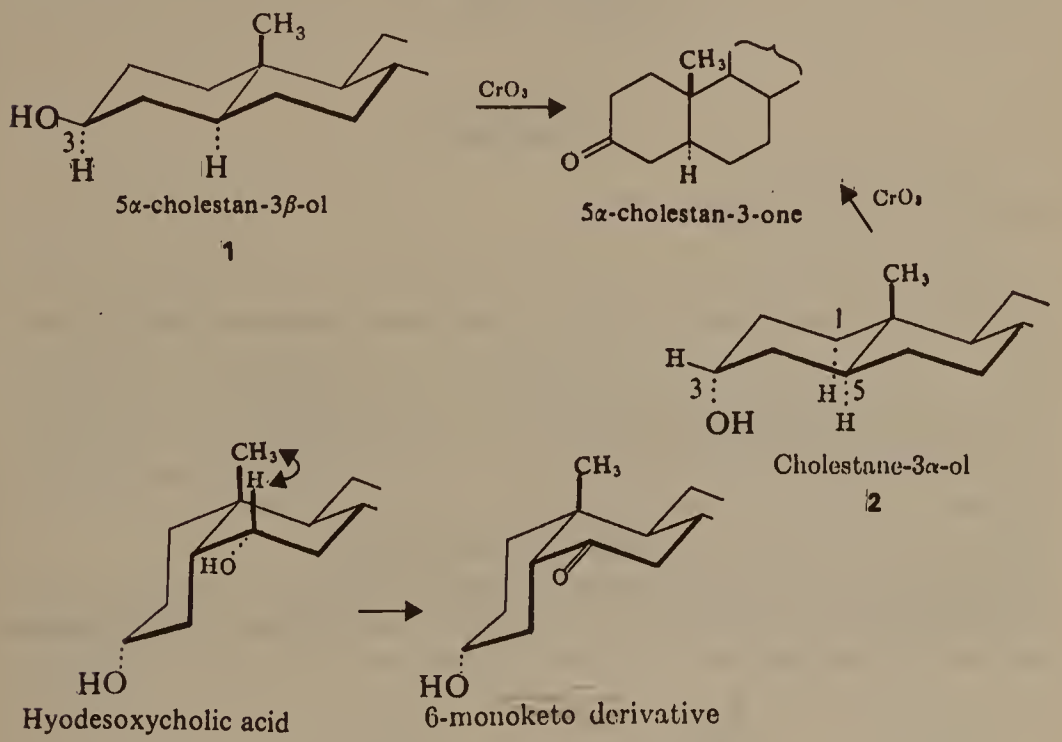


Scheme 4.66

The steroidal skeleton confers a special reactivity on the molecule. The

presence of two angular methyl groups at C-10 and C-13 and the side chain at C-17 hinder the β-face of the molecule. The attacking reagents, therefore, attack it from the α-side (Secs. 6.8 and 6.13). Here two important reactions namely steric acceleration of oxidation and selective acylation and hydrolysis are being presented.

Ordinarily, an equatorial alcohol is less susceptible to oxidation than the axial epimer. Cholestan-3α-ol, 2 (Scheme 4.67) (axial OH) is oxidised faster when compared with 3β-ol, 1 on oxidation with chromic acid. Two points need consideration. Firstly, the rate-determining step during these oxidations is the removal of the hydrogen on the hydroxylated carbon atom. Thus in 2, the 3β-hydrogen which is attacked is equatorial (more accessible), while in the case of 1, it is axial, secondly, the conversion of the tetrahedral carbon carrying a hydroxyl group to a trigonal carbon may remove the repulsive 1:3 non-bonded interactions. In the case of 2 there are two 1:3, H:OH interactions which are eliminated on oxidation to ketone, while 1 is free from such strain. (1:3, H:H interactions in this case being negligible)



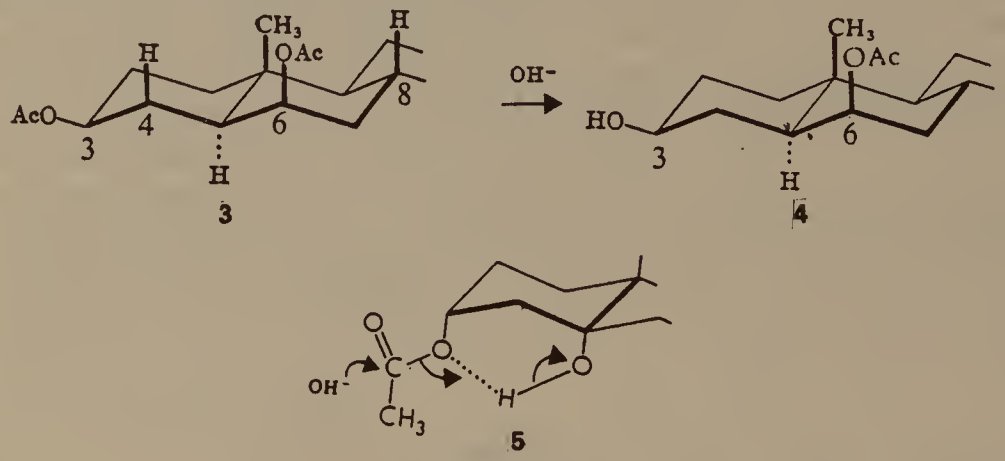
Scheme 4.67

Selective oxidation of hydroxycholic acid, a diequatorial diol to the 6-monoketo compound is due to the relief of 1:3 steric strain between the angular methyl group and 6β-axial hydrogen.

Among saturated steroidal alcohols, an equatorial hydroxyl group being less hindered is acylated more readily as compared to its axial epimer and the same relationship applies to the hydrolysis of ester groups. Thus with the diester 3 (Scheme 4.68) it is possible to obtain the 6-monoacetate 4 by partial

(controlled) saponification.

Although the above principles are generally valid, there are exceptions. It has been found that the monoacetate of the *cis*-1,3-diaxial diol 5 is hydrolysed faster as compared with the corresponding equatorial acetate and this difference may be explained by the fact that hydrogen bonding increases the electrophilic character of the ester carbonyl group. On the other hand, this intramolecular hydrogen bonding can not occur in the 3β-isomer.



Scheme 4.68

4.16 STRAINED CARBOCYCLES

The linear geometry of a triple bond has put a limit to the preparation of stable cycloalkynes to rings of eight or more atoms. Double bonds with the *Z* (cis) configuration are accommodated by a monocycle of any size. Cyclobutene is a stable compound (bp 2°C) while cyclopropene has been isolated only at temperatures below -80°C. Cyclohexene is a strain-free compound with an estimated strain energy of 1 kcal/mol (4 kJ/mol). Only its *Z* geometrical isomer is known. Cyclooctene is the smallest cycloalkene of which both the *Z* and *E* isomers have been isolated.

Several small bicyclic molecules can accommodate double bonds as long as the multiple bond is not located at a bridgehead carbon atom. Norbornene is a well-known example, but its isomer XII (Scheme 4.69) with a bridgehead

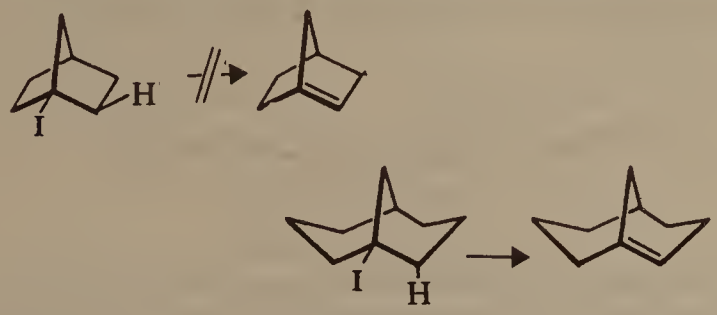
Bicyclo [2.2.1] hept-1-ene can not be isolated (XII)

Bicyclo [5.2.1] dec-1-ene has been isolated (XIII)

Scheme 4.69

double bond is an unknown compound. Bredt's rule states that small bicyclic compounds like XII with the double bond at a bridgehead are highly strained.

It may suffice to explain that in XII the *trans* double bond is contained in a six-membered ring to make it incapable of existence. In the case of XIII, however, the *trans* double bond is instead contained in a nine-membered ring and thus the compound has been prepared and isolated.



Scheme 4.70

Thus, during β-eliminations in bicyclic systems, the bridgehead atoms are not involved, provided the ring bearing the incipient "*trans*" double bond has at least eight atoms.

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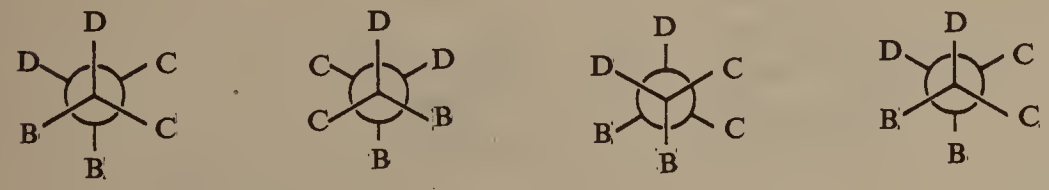
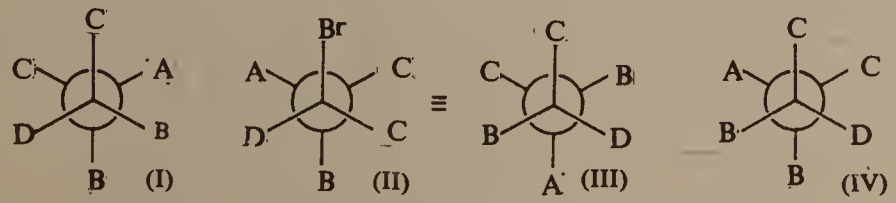
EXERCISES AND PROBLEMS

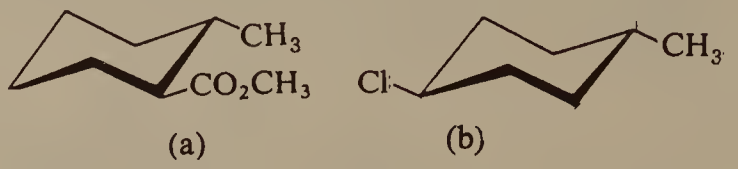
1. Comment on the stereochemical and the identity aspects of the following Newman projections.



2. Comment on the relationship among the Newman projectsions (I-IV).

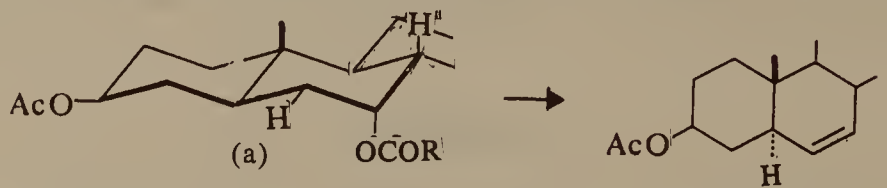


3. Give quantitative data and conformational analysis for cyclopentane.
4. Considering planar ring for cyclohexane, comment on the stereoisomerism of 3,5-dimethylcyclohexanol.
5. Draw the conformation of *trans- syn - trans-* perhydrophenanthrene and comment on its chirality.
6. Label each of the following compounds as *cis* - or *trans*, and comment on their chirality.

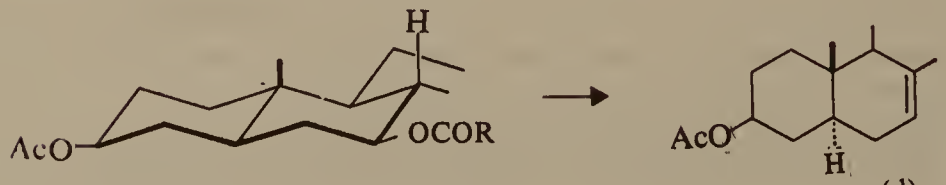


(a) (b)

7. Comment on the configurational and conformational aspects of disubstituted cyclohexane derivatives. How their chirality depends on the nature of substituents R and R′.
8. The stereochemistry of the B/C ring fusion in steroids was confirmed by Barton by the pyrolysis of 7α-benzoyloxycholestanyl acetate (a) and its β-epimer (b). The 7-α ester yielded the Δ^6-cholestene (c) while the 7-β epimer gave the Δ^7 olefin. Explain.

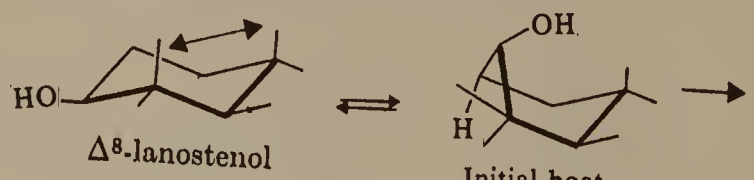


(a) (c)

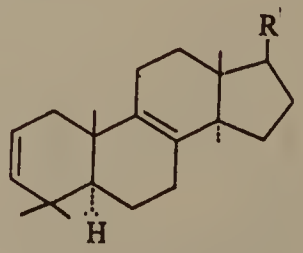


(b) (d)

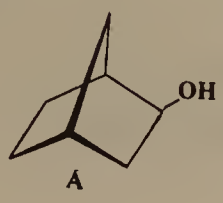
9. In the Δ^8-lanostenol molecule the C-3 hydroxyl group is equatorial and as such this group cannot attain an *anti* relationship with a neighboring hydrogen. However, Δ^8 lanostenol undergoes E2 elimination ($POCl_3$ and pyridine). Explain.



Δ^8-lanostenol Initial boat



10. The bicyclic alcohol **A** on elimination can give **B** or **C**, explain. Can bicyclo [3.3.1]-1-nonene be synthesized ?



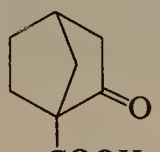
A

B

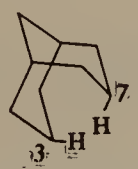
C

Bicyclo [3.3.1]-1-nonene

11. The following β-keto acid is highly resistant to decarboxylation, explain.



12. Comment on the strain in the conformation of bicyclo [3.3.1] nonane. Name a related structure entirely free of strain.



Bicyclo [3.3.1] nonane
chair-chair form

5
STEREOCHEMISTRY OF ELIMINATION REACTIONS

5.1 INTRODUCTION

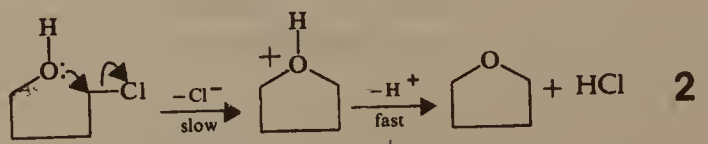
The term elimination normally refers to the loss of two atoms or groups from a molecule and in the commonly known elimination reactions multiple bonds are formed through the loss of groups bonded to adjacent atoms. The process is usually termed 1,2-elimination or β-elimination because of the relation between the two departing ligands eq.1 (Scheme 5.1).

$$\overset{\beta}{R}\overset{2}{C}H_2\overset{\alpha}{\overset{1}{C}}H_2X + OH^- \longrightarrow RCH{=}CH_2 + H_2O + X^- \qquad 1$$

(A 1,2- or β-elimination)

Scheme 5.1

Other elimination reactions may also occur in organic compounds, with the departing groups located at 1,3 or more remote sites in the molecule to yield cyclic products. This type of elimination reaction is actually an intramolecular substitution. eq. 2 (Scheme 5.2).



2

(A 1,5-elimination)

Scheme 5.2

Still another mode of elimination may involve two groups departing from the same atom. Such 1,1-or α-eliminations are used for producing the very reactive species known as carbenes eq. 3 (Scheme 5.3).

$$HCCl_3 \xrightarrow[(-HCl)]{\text{Base}} [\ \ddot{C}Cl_2] \qquad 3$$

(A 1,1- or α-elimination)

Scheme 5.3

Elimination reactions always face a competition from substitution reactions, since all nucleophiles are potential bases as all bases are potential nucleophiles. Thus, an alkyl halide reacts with hydroxide ion to yield an

alcohol as well, in a substitution reaction (compare eqs. 1 and 4 scheme 5.1 and 5.4). In E1 vs S_N1 it is rather difficult to change the ratio since the two sets of products are formed from a common carbocation intermediate in the rate-determining step. However, control of substitution to E2 elimination is easy as discussed in sec.5.2c,ii.

$$RCH_2CH_2X + OH^- \xrightarrow[\text{substitution}]{} \underset{\text{an alcohol}}{RCH_2CH_2OH} + X^- \qquad 4$$

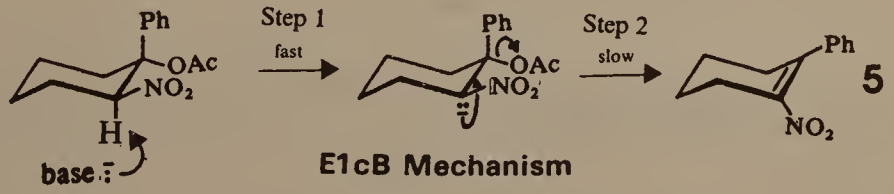
Scheme 5.4

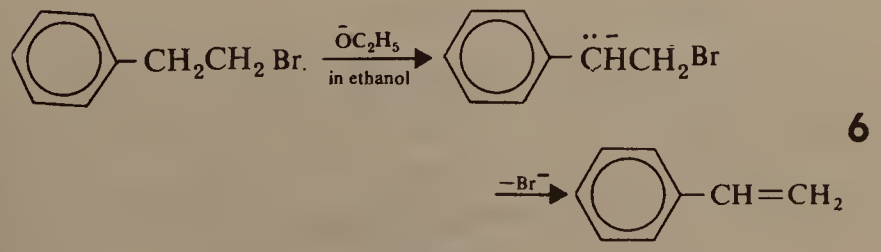
Elimination reactions [1,2] can occur by a variety of mechanisms and three mechanistic pathways are normally distinct routes for β-elimination reactions. Of these E2 and E1 are the most common. These two processes are closely related to the S_N2 and S_N1 mechanisms of substitution. A third mechanism is designated as E1cB, although less common, it provides one extreme in the possible elimination pathways.

5.2 MECHANISMS

(A) Carbanion Mechanism (E1cB Mechanism)

Carbanion mechanisms operate when the β-hydrogens are appreciably acidic, a situation which obtains when the β-carbon of the substrate has a strong electron-withdrawing group. In this reaction, the first step is removal of a proton by a base to give a carbanion. This step is fast and reversible, thus





Scheme 5.5

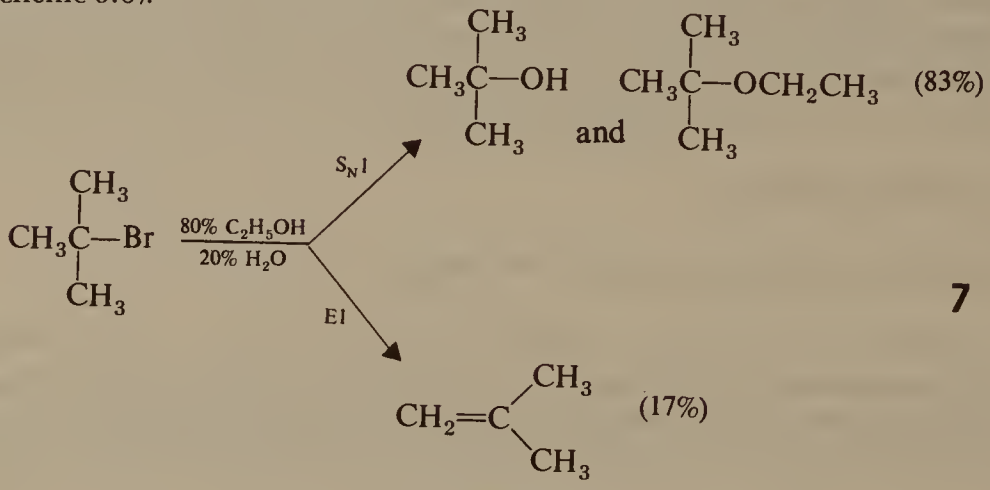
the mechanism can be easily detected by the fact that the substrate exchanges with a deuteriated solvent. In the rate-determining step, the electron pair of the carbanion displaces the group in the β position, giving an olefin eq. 5 (Scheme 5.5). This reaction is relatively uncommon, and occurs only when the leaving group is not a strong electron-withdrawing group, and when the molecule is capable of stabilizing a carbanion (eq. 6). Since the carbanion structure is not configurationally stable, the reaction does not have any

important stereochemical consequences or limitations.

(B) Carbocation Mechanism (E1 Mechanism)

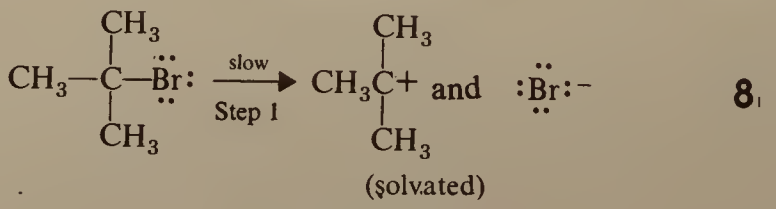
In these elimination reactions the initial step involves cleavage of the bond between the leaving group and its carbon with the generation of fully dissociated carbocation. These elimination reactions are called, E1 reactions (Elimination unimolecular).

E1 reactions almost always compete with S_N1 reactions as the initial step for both the reactions is similar. When *tert*-butyl bromide is treated with 80% aqueous ethanol at 25°C, for example, the reaction produces more of the substitution products than the elimination product (2-methyl-propene) eq.7 (Scheme 5.6).



Scheme 5.6

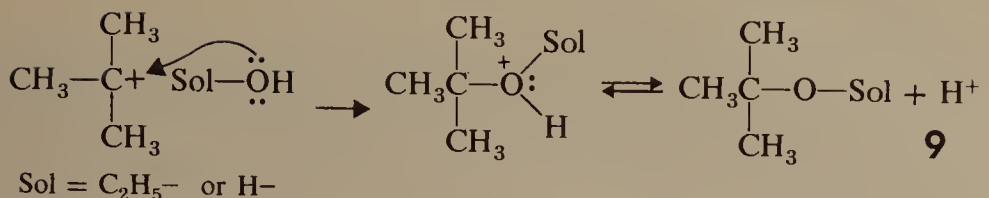
The initial step for these reactions is the formation of a *tert*-butyl cation (or an ion pair) and represents the rate-limiting step for both the reactions eq. 8 (Scheme 5.7).

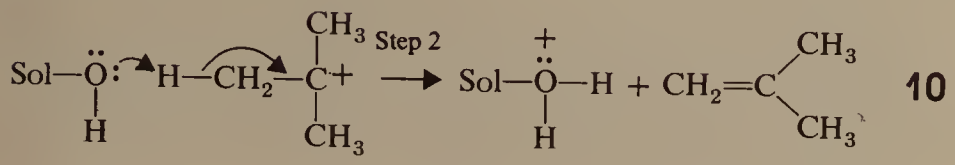


E1 Mechanism

Scheme 5.7

If a solvent molecule reacts as a nucleophile at the positive centre of the *tert*-butyl cation eq.9 (Scheme 5.8) the product is either ethyl *tert*-butyl ether or *tert*-butyl alcohol (S_N1). However, if a solvent molecule acting as a base, accepts one of the β-protons (eq.10), the product is 2-methyl-propene (E1).

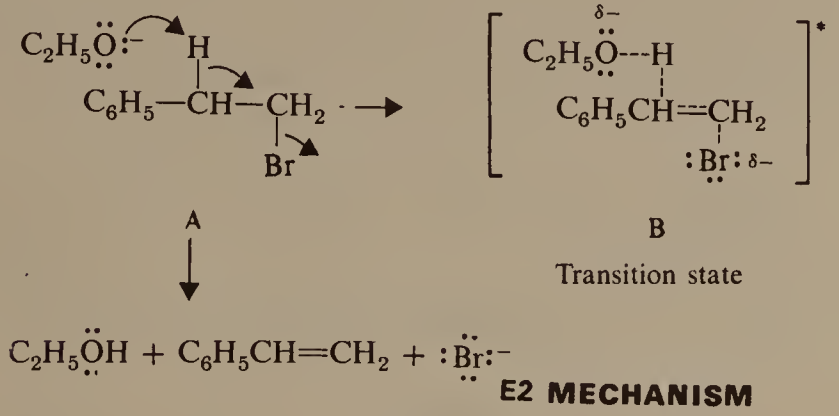




Scheme 5.8

(C) The Concerted Reaction (E2 Mechanism)

(i) Mechanism: Both the substrate and the nucleophile participate in the single step. Reaction kinetics are typically second-order. The nucleophile which is commonly a base abstracts a proton from the β- atom to the leaving group.



Scheme 5.9

The sequence shown in **A** (Scheme 5.9) with 2-phenylethyl bromide is a more general way (related to an S_N2 reaction) of showing only the flow of electrons. A more precise mechanism may involve a transition state **B**, in which the cleavage occurs to some extent in both the C—H and the C—X bonds.

The following evidences support the existence of these general mechanistic representations.

(*a*) The rate expressions for the reactions are proper second order.

(*b*) The reactions display considerable hydrogen-deuterium isotope effect. When eliminations are carried out by replacing leaving hydrogen with deuterium, the reaction rates get slow. Breaking a carbon-deuterium bond is slower than cleaving a similar carbon-hydrogen bond (kinetic isotope effect). Therefore, these results are consistent with a mechanism which involves carbon-hydrogen bond

cleavage in the transition state.

(*c*) The reactions also show a substantial element effect. The relative reactivity of 2-phenylethyl halides towards ethoxide ion is in the order:

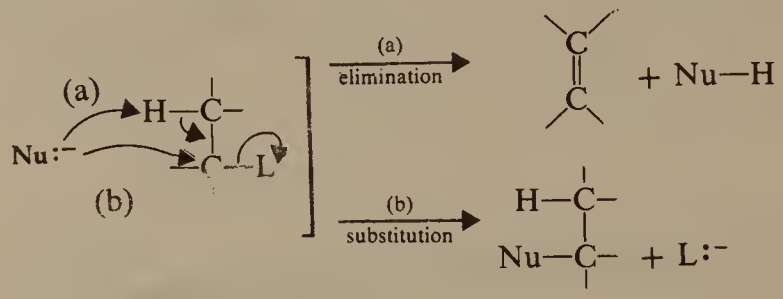
$$C_6H_5CH_2CH_2I > C_6H_5CH_2CH_2Br > C_6H_5CH_2CH_2Cl > C_6H_5CH_2CH_2F$$

An element effect of this kind is again in keeping with a transition state involving carbon-halogen bond cleavage. Thus, 2-phenylethyl iodide reacts fastest because the carbon-iodine bond is weakest; 2-phenylethyl fluoride reacts slowest as the carbon-fluorine bond is strongest.

(*d*) E2 reactions, generally, are not accompanied by rearrangements. This is consistent with a mechanism which does not involve the formation of carbocations.

(*e*) The most compelling evidence for E2 mechanism is however, the stereochemical outcome. This mechanism is stereo-specific as illustrated in sec. 5.2 C, iii.

(ii) Substitution and elimination in E2 reactions: E2 reactions require generally a high concentration of a rather strong base (a high concentration of a strong nucleophile). Therefore, substitution reactions by an S_N2 path have competition with the elimination reaction. When the nucleophile attacks a β-hydrogen, elimination takes place and when it attacks the carbon carrying the leaving group substitution results eq.11 (Scheme 5.10).



11

Scheme 5.10

If the substrate is a primary halide and the base is ethoxide ion, substitution is a highly favorable reaction eq.12 (Scheme 5.11).

$$C_2H_5O^-Na^+ + CH_3CH_2Br \xrightarrow[(-NaBr)]{C_2H_5OH} \underset{90\%}{CH_3CH_2OCH_2CH_3} + \underset{10\%}{CH_2{=}CH_2} \qquad 12$$

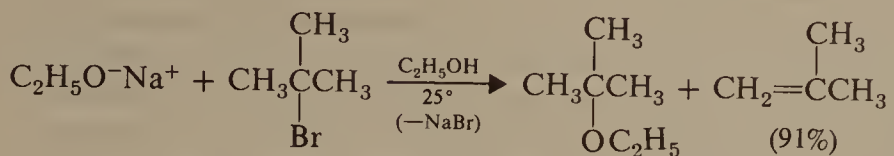
Scheme 5.11

With secondary halides, the elimination reaction 13 is favoured.

$$C_2H_5O^-Na^+ + CH_3\underset{Br}{C}HCH_3 \xrightarrow[(-NaBr)]{C_2H_5OH,\ 55^\circ} \underset{(21\%)}{CH_3\underset{OC_2H_5}{C}HCH_3} + \underset{(79\%)}{CH_2{=}CHCH_3} \qquad 13$$

Scheme 5.12

With tertiary halides the elimination reaction 14 is highly favored particularly if the reaction is carried out at high temperatures (Scheme 5.13). Thus, tertiary substrates as expected, do not undergo S_N2 reactions with strong bases, on the other hand, nonbasic nucleophiles like I^-, Cl^- and CN^- strongly favor S_N2 reactions.



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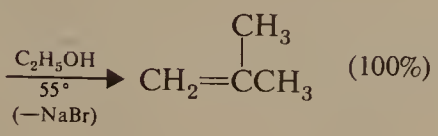
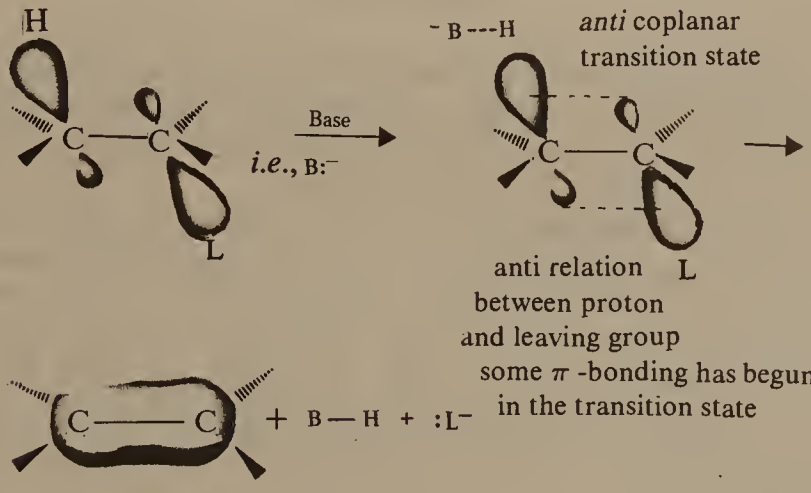


Scheme 5.13

Elimination is favored over substitution at elevated temperatures. Another way is the use of a strong sterically hindered base *e.g.*, the *tert*-butoxide ion (sec. 5.4). The bulky methyl groups of the *tert*-butoxide ion tend to inhibit its reaction by substitution, so elimination reactions are favored.

(iii) Stereochemistry of anti E2 reactions: E2 eliminations are usually stereospecific. With most open-chain compounds E2 reactions take place from a transition state in which the proton being eliminated and the leaving group are *anti* to each other (Scheme 5.14) *i.e.*, the eliminated ligands are in a



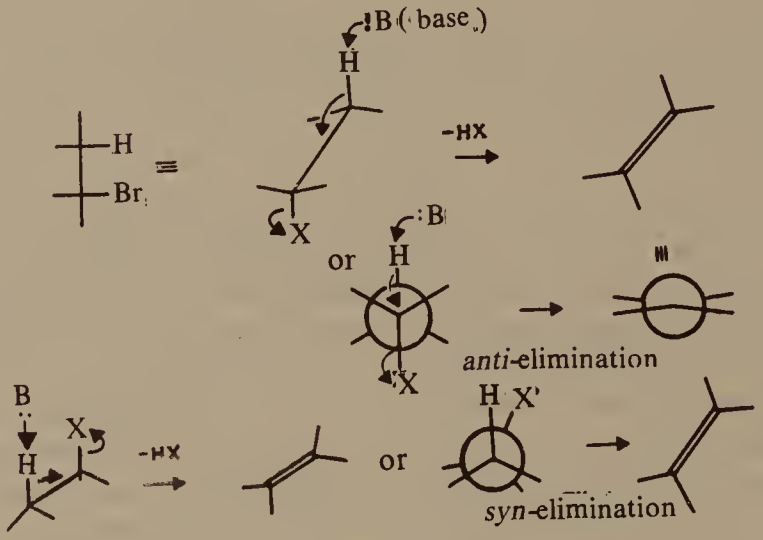
Scheme 5.14

*anti*periplanar conformation. Another distinct stereospecific elimination is the *syn* elimination (sec. 5.3).

An explanation which has been given to account for a preferred *anti*

orientation is that it allows the large lobe from the C—H bond to interact with the small lobe of the C—L bond. E2 reaction resembles the S_N2 reaction in that an electron pair of the C—H bond displaces the leaving group from the back side.

In short, El eliminations are mostly non-stereospecific while in the bimolecular elimination reactions an important role is played by steric factors. These manifest themselves in the form of stereoelectronic requirements i.e., requirement of a definite spatial orientation of the electronic orbitals involved in the elimination. The heterolytic 1, 2 -elimination reactions by the E2 mechanism generally occur in the case of **anti** arrangement of the groups participating in the reaction. E2 elimination however, may also occur with the **syn**-arrangement of the groups (Scheme 5.14 a).



Scheme 5.14 (a)

(iv) Examples of anti elimination: Some examples of *anti* elimination had been given (Sec. 4.5) to explain the relation between conformation and reactivity. The following examples provide additional stereochemical data in support of *anti* stereospecificity for E2 reactions.

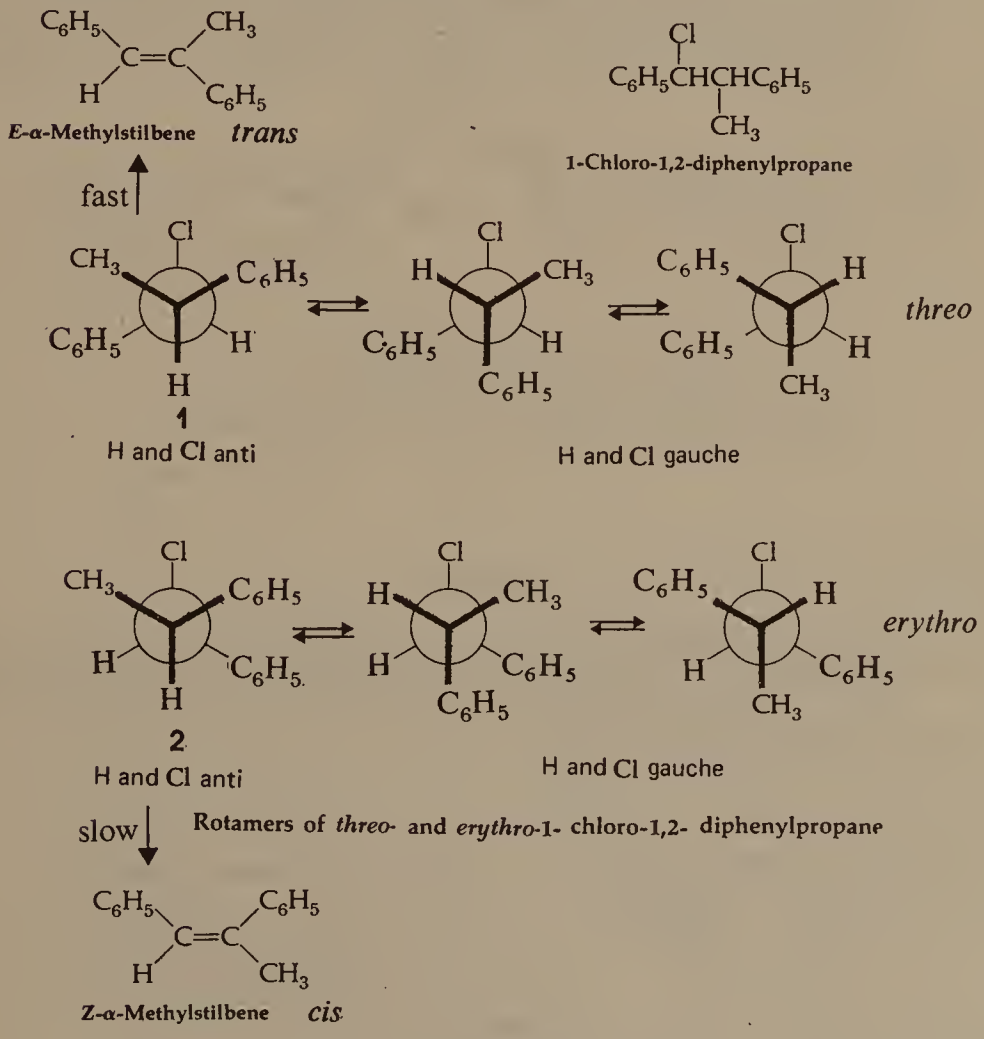
(*a*) 1-Chloro-1,2-diphenylpropane is a chiral molecule with two chiral carbon atoms. It has four isomeric forms, the two pairs of enantiomers. When the diastereomers are separated and reacted under E2 elimination reaction conditions, one of them forms exclusively E alkene, while the other yields the Z-form (Scheme 5.15). The elimination reaction of each diastereomer proceeds in a stereospecific manner and there is a moderate rate difference for elimination from the diastereoisomers.

Consideration of the staggered rotamers of the *threo* and *erythro* substrates gives an explanation of the reaction stereospecificity. E2 reaction involves loss of a proton from one carbon atom simultaneously with departure of a chloride from the other. In case HCl is eliminated from *threo* rotamers other than 1, the alkene formed

would have a *Z* configuration, however, the *E* alkene is actually produced from the *threo* isomer. Only *threo* rotamer **1** can eliminate HCl by a concerted process to give the *E* alkene, with the ligands eliminated in the proper antiperiplanar conformation. The explanation for the relative rates in the case of **1** and **2** has its base in the difference in steric crowding in the transition states which lead to elimination. Phenyl groups being bulky, have a greater steric effect than the methyl group. Therefore, the steric crowding in the elimination transition state of **1** is more as compred to that of **2**.

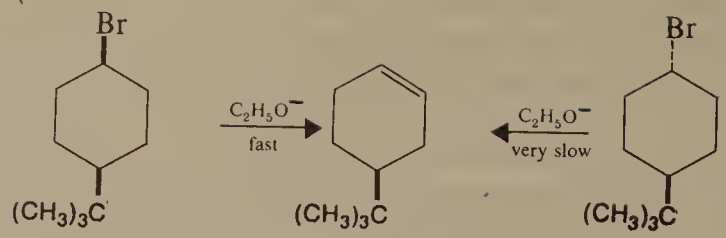
One reaches a similar conclusion from the formation of the *Z* alkene from the *erythro* reactant **2** (Scheme 5.15).

(*b*) The strict *anti* requirement for elimination may also be seen in elimination reactions of cyclohexyl derivatives. Thus, *trans*-1-bromo-



Scheme 5.15

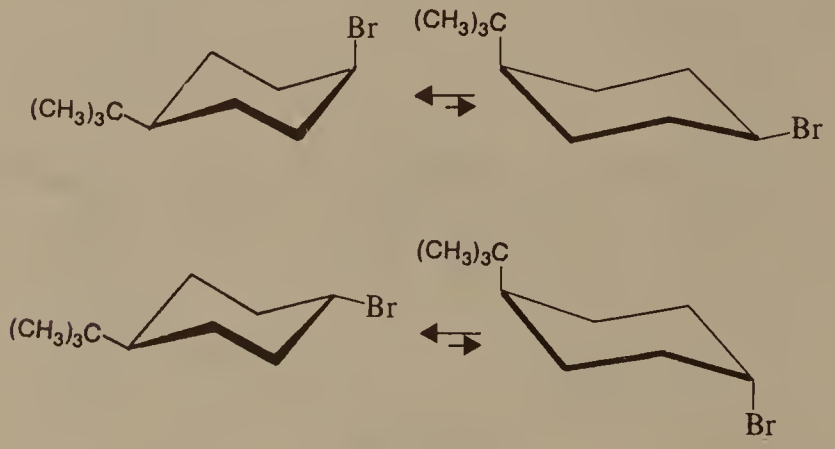
4-*t*-butylcyclohexane reacts only slowly with sodium ethoxide in ethanol to give 4-*t*-butylcyclohexene. However, the *cis* isomer undergoes elimination rapidly eq.15 (Scheme 5.16).



15

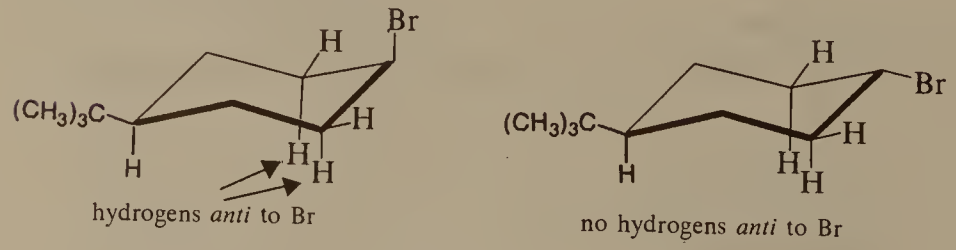
Scheme 5.16

The *t*-butyl group is highly sterically demanding so that it effectively controls the conformation of the moelcule of *cis*-1-bromo-4-*t*-butylcyclohexane from flipping thus, it exists almost entirely in the axial-bromo conformation, and the *trans* isomer in the equatorial-bromo conformation (Scheme 5.17). In other words, the tertiary butyl group lacks the ring of a cyclohexyl derivative into a particular conformation.



Scheme 5.17

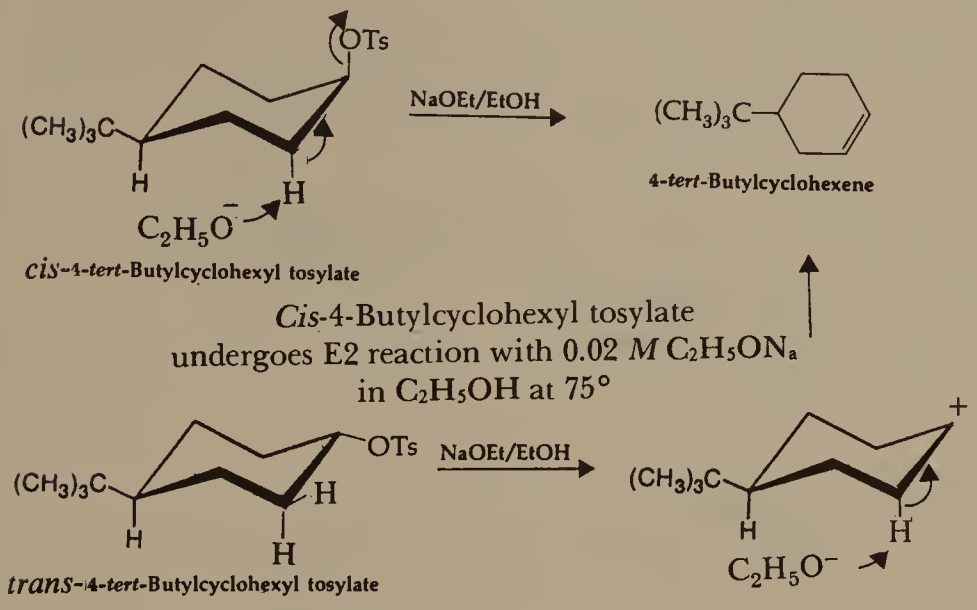
In the *cis* isomer alone, there are a significant number of molecules in which the bromine has an *anti* periplanar relationship to a hydrogen (Scheme 5.18).



Scheme 5.18

Similarly the *cis* and *trans* isomers of 4-*tert*-butyl-cyclohexyl tosylate will have the smaller tosylate group in the axial and equatorial positions, respectively (Scheme 5.19). Only the *cis* isomer has the tosylate and a hydrogen atom in a proper configuration for an E2 *anti*-periplanar elimination. In contrast, the *trans* isomer does not

undergo E2 elimination. The equatorial tosylate cannot attain coplanarity with any β-hydrogen. Slow elimination therefore occurs but, by a unimolecular mechanism.

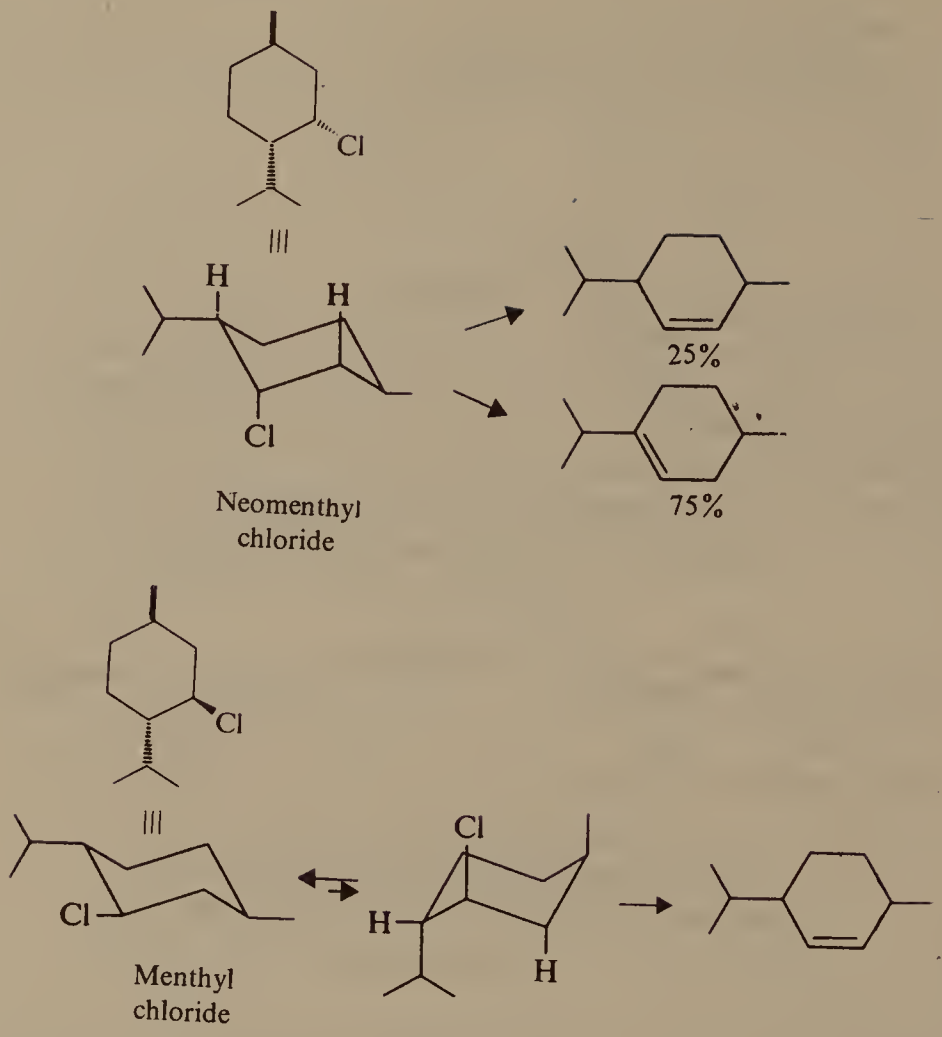


Scheme 5.19

(*c*) A strong tendency for *anti*-periplanar elimination is used as a basis to reveal configurations to some isomers. Menthyl chloride and neomenthyl chloride are derived from the terpenoid alcohols menthol and neomenthol. These isomers differ only in the configuration of the carbon atom having the chloro (or hydroxy) group.

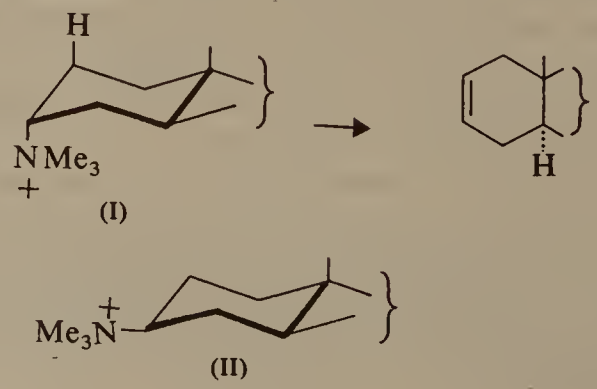
When menthyl chloride is reacted with sodium ethoxide in ethanol, elimination takes place slowly to produce 2-menthene. Under similar conditions neomenthyl chloride rapidly yields a mixture of 2- and 3-menthenes (Scheme 5.20). If one assumes that *anti* elimination occurs, neomenthyl chloride must be the isomer with an axial chlorine atom. Loss of either of two different *anti*-periplanar β-hydrogen atoms readily leads to the observed products.

Menthyl chloride is thus, the isomer with an equatorial chlorine atom. Anti elimination can proceed only from the suitable *anti*-periplanar conformation, *i.e.*, if the ring is forced to flip to the all axial, less energetically favourable conformation. The conformational inversion, required prior to *anti*-elimination accounts for the slower rate of reaction.



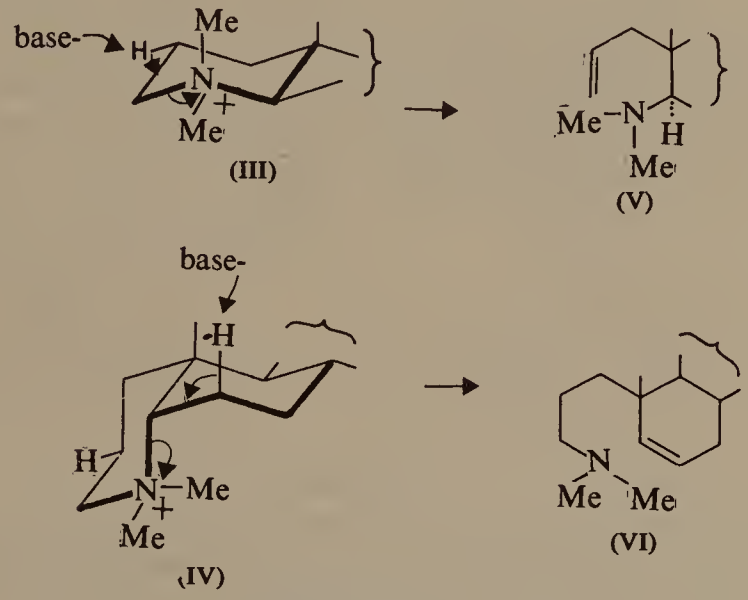
Scheme 5.20

Graphic examples of the stereospecificity[3] of the Hofmann elimination are found in the behaviour of the epimeric 3-trimethylammoniumcholestanes I and II (Scheme 5.21). The axial epimer easily affords the olefin. The 3β-epimer yields no olefinic products, therefore clearly confirming an *anti* elimination mechanism.



Scheme 5.21

Consider Hofmann elimination with the two epimeric 4-azacholestanes III and IV (Scheme 5.22). In III, only the 2 α-hydrogen and the nitrogen are *anti* periplanar, and therefore as expected the major product is V. In IV, a *trans* diaxial arrangement also exists between the nitrogen and the 6β-hydrogen which leads to fission to yield VI. Significantly the direction of the fission, relieves a severe interaction[4] between the methyl groups of the nitrogen and ring B and this factor discriminates the formation of VI over the pathway involving 2 β-hydrogen.

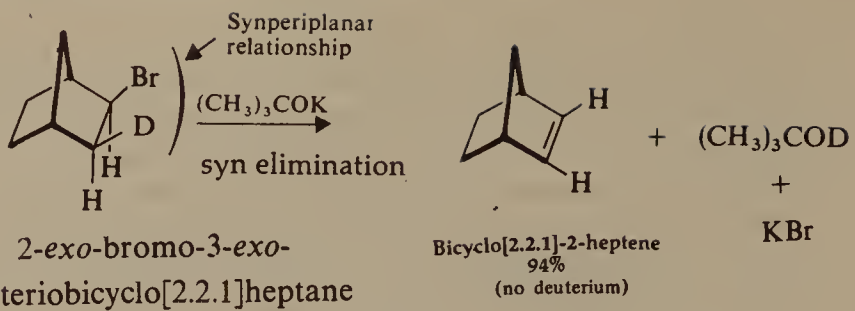


Scheme 5.22

5.3. SYN ELIMINATION VERSUS ANTI ELIMINATION

Some rigid molecules are not able to attain the favorable *anti*-periplanar conformation of the departing groups. Elimination is, thus, inhibited and may proceed by another mechanistic or stereochemical pathway. The conformationally rigid 4-*tert*-butylcyclohexyl tosylates, therefore, undergo E1 or E2 elimination depending upon the stereoisomer involved.

It has been shown that arrangements in which the departing groups are coplanar on the same side of the molecule may undergo concerted elimination. The groups are termed to be *syn*-periplanar, and the process represents a *syn* elimination.[5] The deuterated norbornyl bromide shown in scheme 5.23, gave 94% of the product with no deuterium. In this case the *exo* Br group cannot achieve *anti*-periplanarity *i.e.*, a dihedral angle of 180° with an *endo* β-hydrogen due to the rigid structure of the molecule, the dihedral angle being only 120°. In this situation therefore the leaving groups prefer to undergo a *syn*-elimination with a dihedral angle around 0° (*syn*-periplanarity) compared to *anti*-elimination when the angle available is only around 120°.



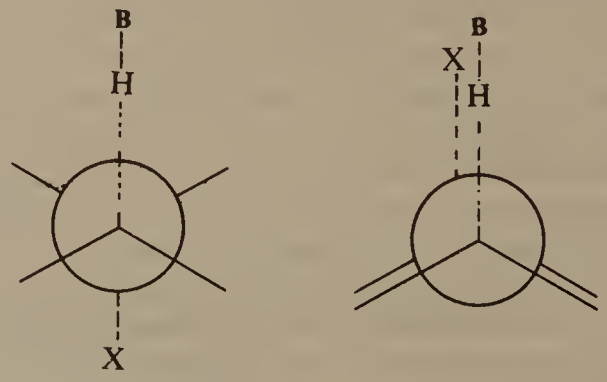
Scheme 5.23

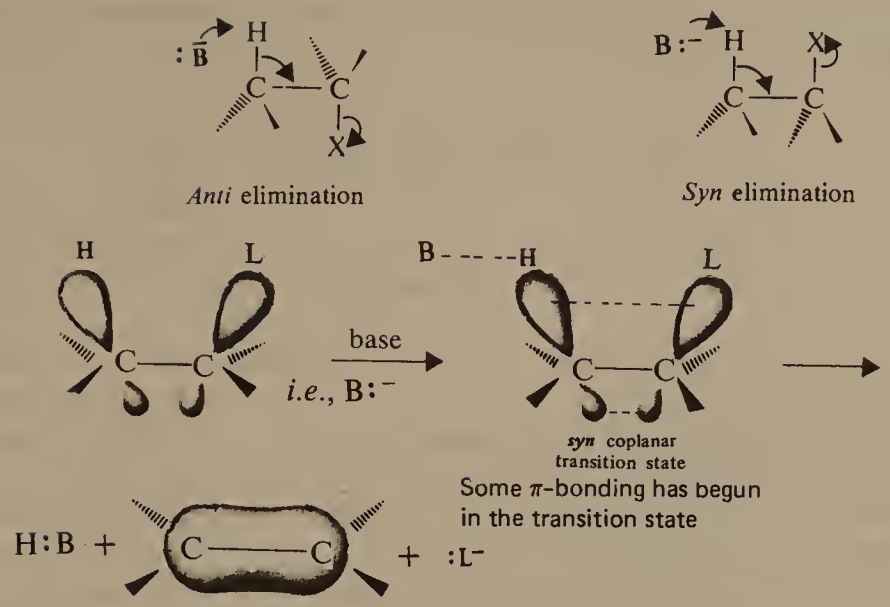
The arrangements in molecules A and B provide remarkable examples[6] to justify the need for a planar transition state (Scheme 5.24), during elimination reactions. In B each Cl has *trans* hydrogen on the adjacent carbon. In case the planarity of the leaving ligands was not the essential condition, compound B would have readily undergone *anti*-elimination.

Scheme 5.24

Due to the crowding in the rest of the molecule, a dihedral angle of around 120° is forced on the leaving groups. As a result, elimination of HCl from *B* is slower than the corresponding non-bridged compounds. Moreover, *syn*-elimination from *B* is even less likely compared to *anti*-elimination. The arrangement in *A*, represents the *trans*-isomer of *B* in which the dihedral angle between the leaving groups is around 0°. Thus an almost *syn*-periplanar arrangement is available and *A* eliminates HCl by *syn*-elimination about ten times faster than *B*.

Stereoelectronic considerations show that *syn*-periplanarity of leaving groups allows a reasonable conversion of the reactant molecular orbitals to the *pi* orbital of alkene product (scheme 5.25). Based on this information, it is





Scheme 5.25

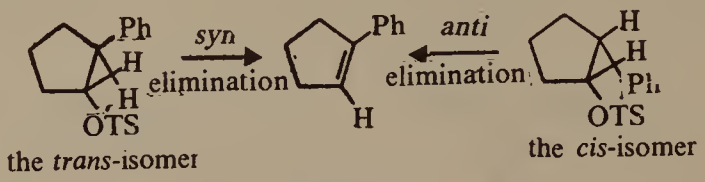
clear that in E2-eliminations the significant condition for the reactions is that the departing groups should be coplanar no matter *anti* or *syn*. In *anti*-eliminations the incoming and outgoing bonding electrons are kept as far apart as possible. In *syn*-eliminations, however, the eclipsing of the groups in the reaction leads to a less favourable situation, thus *syn*-eliminations are considerably less favourable, occuring at a slower rate than *anti*-eliminations.

Two points may be noted. Firstly, *anti* elimination requires a dihedral angle of 180°. If this angle cannot be achieved, *anti* elimination is slowed or entirely prevented. Secondly, for the simple systems *syn* elimination does not occur to any significant extent unless *anti* elimination is greatly prevented by failure to achieve the 180° dihedral angle.

Six-membered rings singularly, from among rings of four to thirteen members present systems where strain-free *anti*-periplanar conformations can be achieved. It is, therefore, not surprising that *syn* elimination is rare in six-membered rings. Cycloalkyltrimethylammonium hydroxides on elimination give the following percentages of *syn* elimination products with ring sizes: four-membered 90%; five-membered 46%; six-membered 4%; seven-membered 31 to 37%. It may be noted that the $^{+}NMe_3$ group has a greater tendency for *syn* elimination than other common leaving-groups such as OTs, Cl and Br.

It appears, therefore, that in the absence of a suitable *anti*-periplanar arrangement, the eliminations can advance through the *syn*-periplanar arrangement, however, this happens only provided there is no other lower energy pathway. A study of *anti*-eliminations is therefore undertaken with suitable cyclohexyl systems which undergo E2-elimination to the exclusion of any *syn*-elimination. This indeed is the only possible mode in these systems since the departing groups can adopt a conformation in which these are

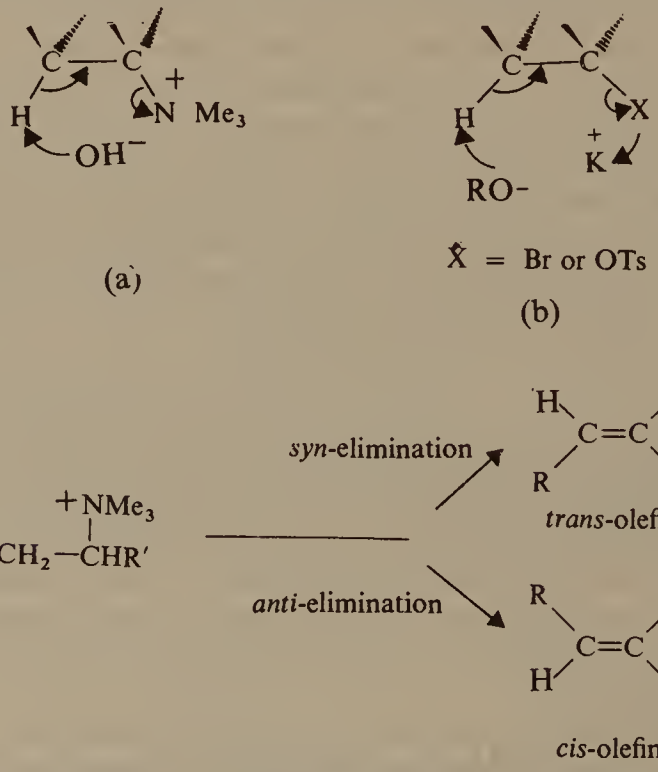
coplanar. A similar study, which makes the same point, is the elimination on the *cis*-and *trans*- isomers of a cyclopentane derivative (Scheme 5.26). Both the isomers yielded the same olefin by E2-elimination, thus the *trans* isomer



Scheme 5.26

undergoes *syn*-elimination while the *cis*-isomer an *anti*-elimination. Moreover *anti*-elimination has been shown to proceed slightly faster than *syn*-elimination. This is understandable, since in cyclopentane, only small twisting of the fairly flexible ring is needed to attain a *syn*-periplanar arrangement of the groups *cis* to each other. An attainment of the *anti*-periplanar relationship of the groups *trans* to each other is somewhat difficult as the ring shall have to be bent well away from planarity.

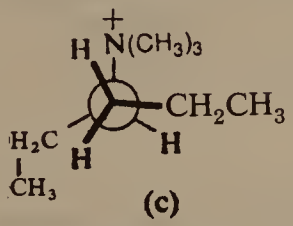
It has been shown that *syn*-elimination is favored under conditions which favor the formation of an ion-pair between the base and the substrate. In the case of quaternary ammonium hydroxides the hydroxide ion is present as a



Scheme 5.27

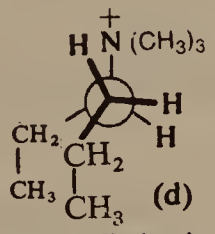
close ion pair with the positively charged nitrogen atom which removes a proton from the β-carbon (Scheme 5.27) and the overall reaction occurs within a cyclic transition state (a). To explain *syn*-elimination from *p*-

toluenesulphonates or bromides, an ion pair of the type (b) is advanced. This type of ion pair will clearly be less stable than (a) and so will not much affect the overall course of the reaction; a fact in keeping with the experimental results. In reactions of quaternary ammonium compounds where either *cis*-or *trans* olefins can form through either *syn*- or *anti*- elimination, the *cis*-olefin mainly arises from *anti*- elimination, and the *trans*-olefin from a *syn*-elimination (the *syn-anti* dichotomy). It is suggested that *syn*-elimination requires the molecule to adopt a completely eclipsed conformation before reaction, and that the ground state (c) scheme 5.28, which affords a *trans*-product, is more stable than the ground state (d) leading to a *cis*-product *e.g.*, in the case of hex-3-yl trimethyl ammonium compounds.



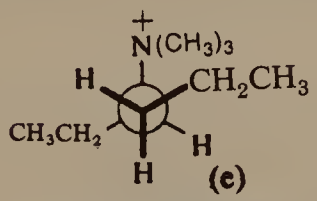
(c)

for *syn*-elimination
to give *trans*-hex-3-ene



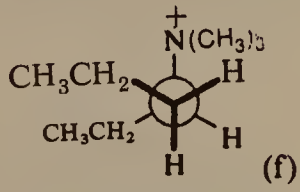
(d)

for *syn*-elimination
to give *cis*-hex-3-ene



(e)

for *anti*-elimination
to give *trans*-hex-3-ene



(f)

for *anti*-elimination
to give *cis*-hex-3-ene

(ground states)

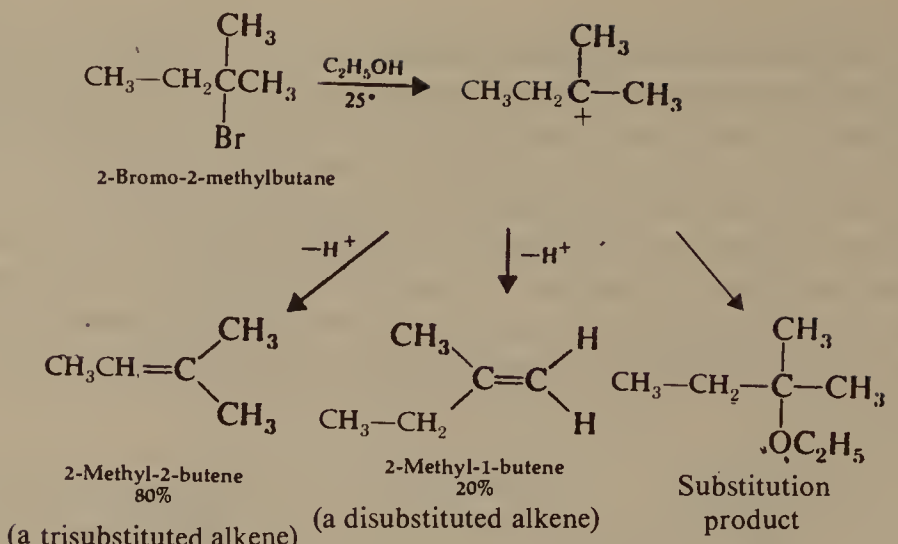
Scheme 5.28

However, a consideration of the models of the ground states (e and f) for *anti*-elimination from the same compound, points that this as well should give a *trans*-product. Thus, steric factors considered above, may not be entirely controlling the direction of elimination.

5.4 ORIENTATION IN ELIMINATION REACTIONS

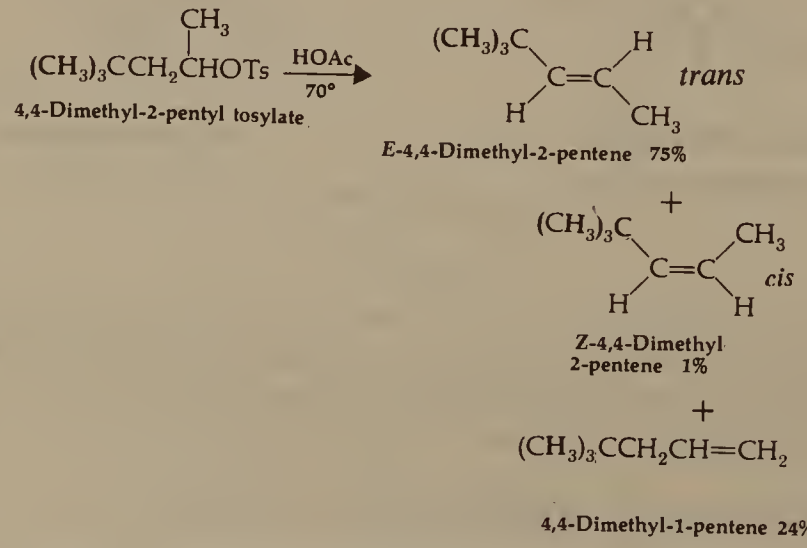
The elimination reactions of unsymmetrical substrates often afford mixtures of all possible products and the alkene formation during these reactions is governed by two empirical rules.

(i) Formation of More Substituted Alkene (Saytzeff Rule): When the carbocation formed in an E1 reaction can lose a proton in more than one way the product formed is usually the highly substituted alkene. This is seen in the solvolysis of the neutral substrate, 2, bromo-2-methyl butane, and the process is said to proceed by Saytzeff orientation (Scheme 5.29).



Scheme 5.29

The most-substituted alkene product will normally exist as a mixture of *E* and *Z* stereoisomers. The *E* to *Z* isomer ratio depends on the steric interactions in the transition state leading to each isomer. Formation of the isomer with large groups on opposite sides of the double bond is generally favored (Scheme 5.30).



Scheme 5.30

One accounts for Saytzeff rule on the basis of the transition state theory and the relative stability of alkenes. Trisubstituted alkenes, are stable than disubstituted alkenes, and disubstituted alkenes are stable than mono-substituted alkenes. As the transition state leading to an alkene has considerable double bond character, the transition state will be stabilized by those factors that stabilize the alkene. The reaction with a transition state

leading to the more stable *i.e.*, highly substituted alkene will have a lower energy of activation and will, therefore, occur faster.

The rule also applies to most of the E2 eliminations, thus, neomenthyl chloride (sec. 5.2C, iv) on E2 elimination gives 75% of more substituted alkene.

(ii) Formation of Less Substituted Alkene (Hofmann Rule): While most eliminations involving small neutral substrates like halogen (eq. 15) tend to follow the Saytzeff rule, eliminations with charged substrates (eq. 16 and 17) tend to follow the Hofmann rule and yield predominantly the least substituted alkene.

$$C_2H_5O^-Na^+ + CH_3CH_2\underset{\underset{Br}{|}}{C}HCH_3 \xrightarrow[25^\circ]{C_2H_5OH} \quad \textbf{15}$$

$$CH_3CH{=}CHCH_3 + CH_3CH_2CH{=}CH_2$$
(75%) (25%)

$$CH_3CH_2\underset{\underset{+N(CH_3)_3}{|}}{C}HCH_3 \quad OH \xrightarrow{150^\circ} \quad \textbf{16}$$

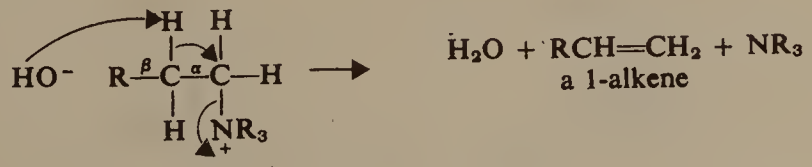
$$CH_3CH{=}CHCH_3 + CH_3CH_2CH{=}CH_2$$
(5%) (95%)

$$CH_3CH_2\underset{\underset{+S(CH_3)_2}{|}}{C}HCH_3 \quad OC_2H_5 \longrightarrow \quad \textbf{17}$$

$$CH_3CH{=}CHCH_3 + CH_3CH_2CH{=}CH_2$$
(26%) (74%)

Scheme 5.31

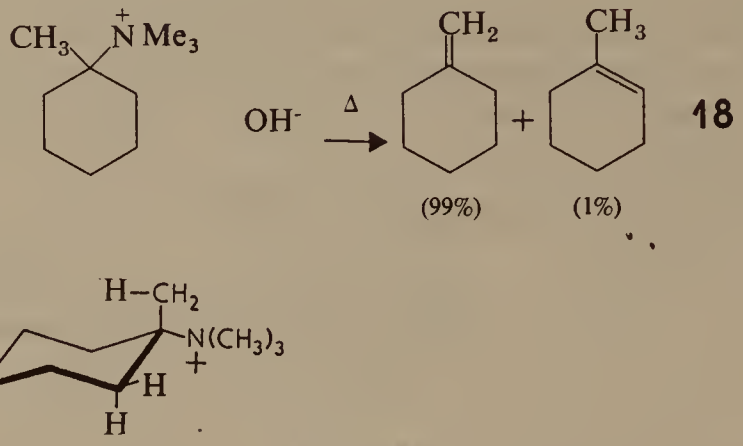
In Hofmann degradation, (which is considered here to explain Hofmann rule) quaternary ammonium hydroxides on heating undergo a β-elimination (Scheme 5.32). The reaction is E2 elimination in which hydroxide ion is the attacking base.



Scheme 5.32

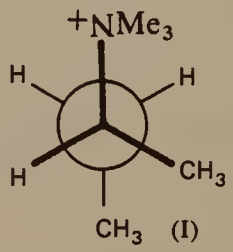
When the quaternary ammonium hydroxide has two or more different β-hydrogens, more than one alkene is formed in the elimination. However, unlike normal E2 eliminations with alkyl halides (eq. 15) the Hofmann

elimination (eq. **16**) yields predominently the less highly substituted alkene as is so in the case of cyclic compound as well (eq. **18**, Scheme 5.33). Clearly, the bulky trimethylammonium ion must occupy the equatorial position, and makes it impossible to have an *anti*-periplanar relation to a β-hydrogen of the ring.



Scheme 5.33

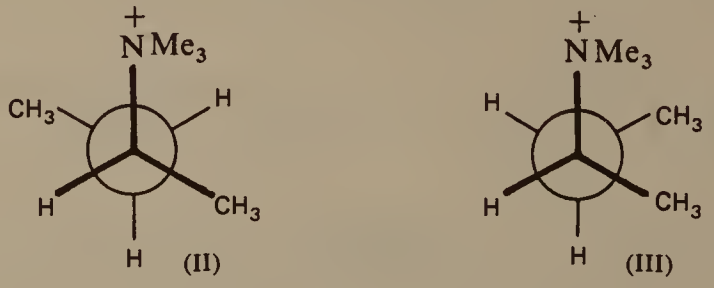
Several factors may contribute to the formation of the less substituted alkene, but it is generally believed that steric interactions are very important. Thus, considering the 2-butyl case (eq. **16**), the most stable conformation may be represented by the Newman projection of the C_2—C_3 bond as in Scheme 5.34,



Most stable conformation, but not suitable for elimination

Scheme 5.34

but this conformation has no *anti*-hydrogen at C-3. Thus, the E2 elimination can occur only in the conformations II and III (Scheme 5.35), so that the



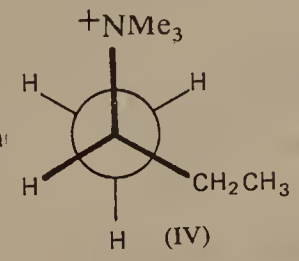
Less stable conformations but suitable for elimination

Scheme 5.35

conformation of the reactant in the transition state is not necessarily the most stable.

Both conformations (II and III) have a methyl group *gauche* to the bulky trimethylammonium group which is comparable in size to *t*-butyl. Hence, the populations of these conformations are small, in consequence the more substituted alkene which is a minor product in the Hofmann elimination is formed. However, all conformations (with respect to the C_1-C_2 bond) which have *anti* hydrogen are less crowded (IV, Scheme 5.36) leading to the less

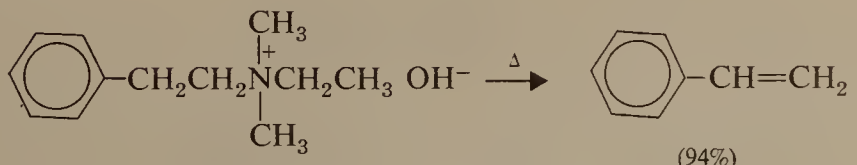
the most stable conformation



(IV)

Scheme 5.36

substituted alkene as the major product. When electron-withdrawing groups are attached to one of the β-carbons (Scheme 5.37), the Hofmann rule is not applicable.



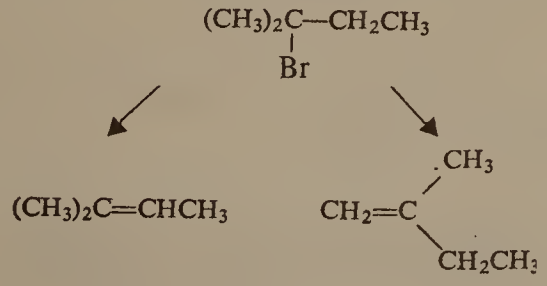
(94%)

$+ CH_2{=}CH_2$

(6%)

Scheme 5.37

Evidence that steric factors are indeed important in controlling orientation during concerted elimination is based on the size of the base (Scheme 5.38).

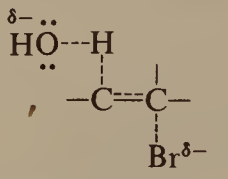


Base	(%)	(%)
EtO^-	70	30
Me_3CO^-	28	72

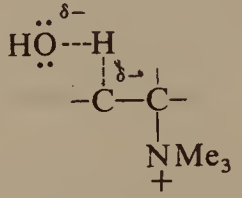
Scheme 5.38

The steric bulk of a large base like *t*-butoxide ion favors the formation of less-substituted alkene even when the leaving group is a halide.

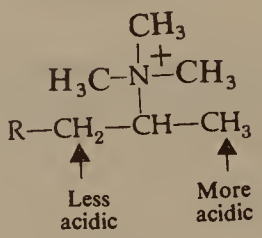
Another possible explanation is that the transition states of elimination reactions with charged substrates have considerable carbanion character. Thus, these transition states show little resemblance to the final alkene product and therefore, are not appreciably stabilized by a developing double bond. With a charged substrate, therefore, the base removes the most acidic hydrogen (Scheme 5.39).



Alkenelike transition state
Saytzeff orientation



Carbanionlike transition state
Hofmann orientation

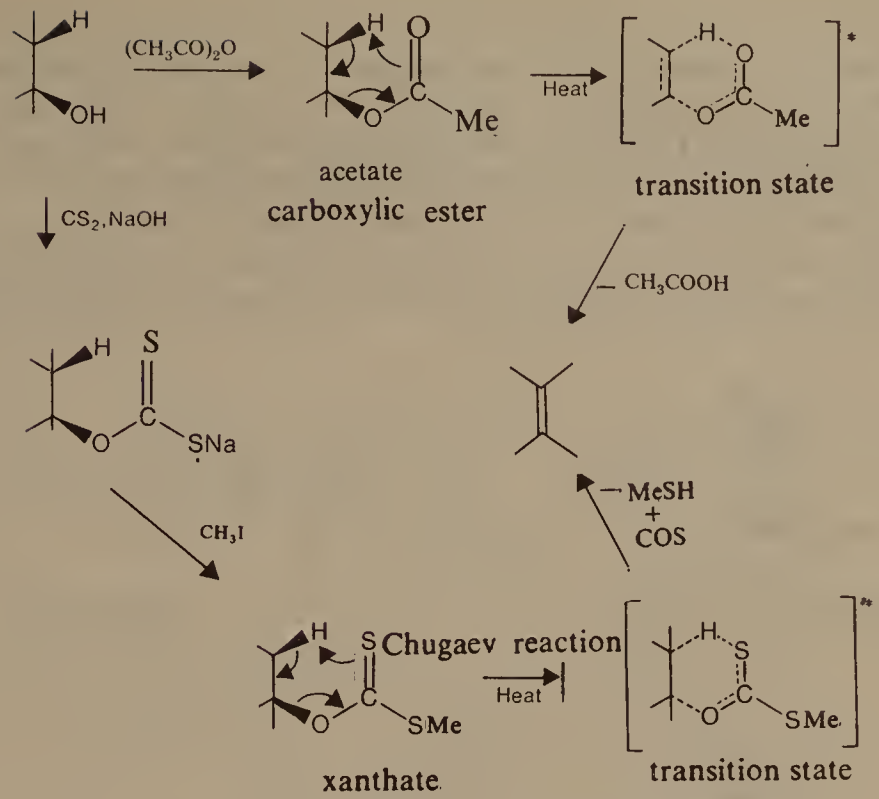


Scheme 5.39

Relative acidity of the terminal and internal β-hydrogen atoms, thus, may be taken into account as a possible factor for the alkene product ratio. A terminal hydrogen atom tends to be more acidic because the conjugate base, a less-substituted carbanion, is more stable ($1° > 2° > 3°$). The charged groups exert a strong electron-withdrawing effect to make differences in acidity more manifest compared with less electron-withdrawing neutral groups. Thus a change to a positive leaving group is to cause the E2 mechanism to shift toward the E1cB end of the spectrum.

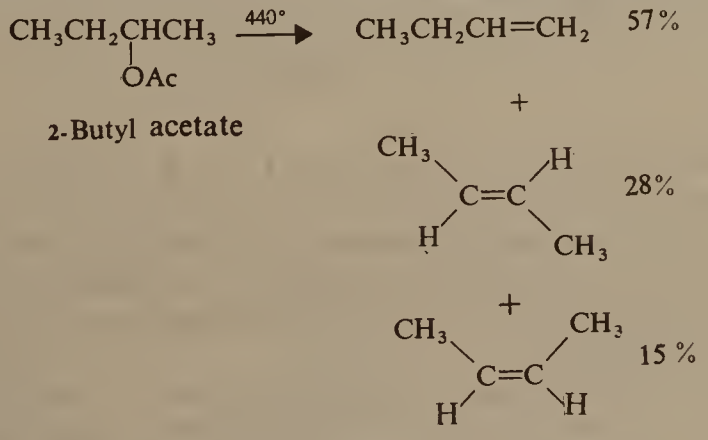
5.5 STEREOCHEMISTRY OF NON-IONIC ELIMINATION THERMAL REACTIONS

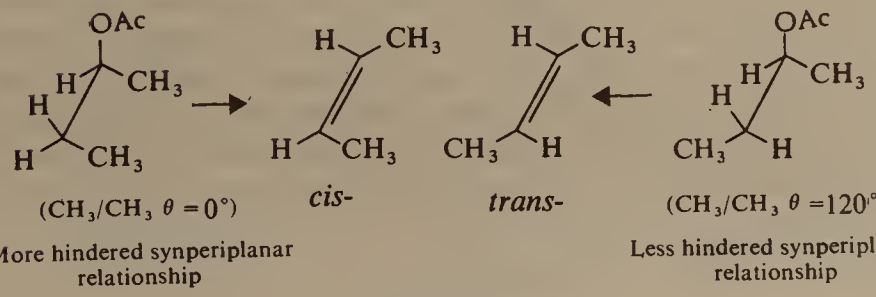
Pyrolytic elimination[7] reactions of acetates, benzoate, xanthates and amine oxides take place through cyclic six-membered transition states which require a *syn* periplanar (*cis*) arrangement of the leaving groups as shown in scheme 5.40. The order of ease of decomposition among commonly used esters is xanthate > benzoate > acetate.



Scheme 5.40

Like *syn*-elimination during reactions in solution, the pyrolytic reactions also require that the groups to be eliminated be readily brought into an

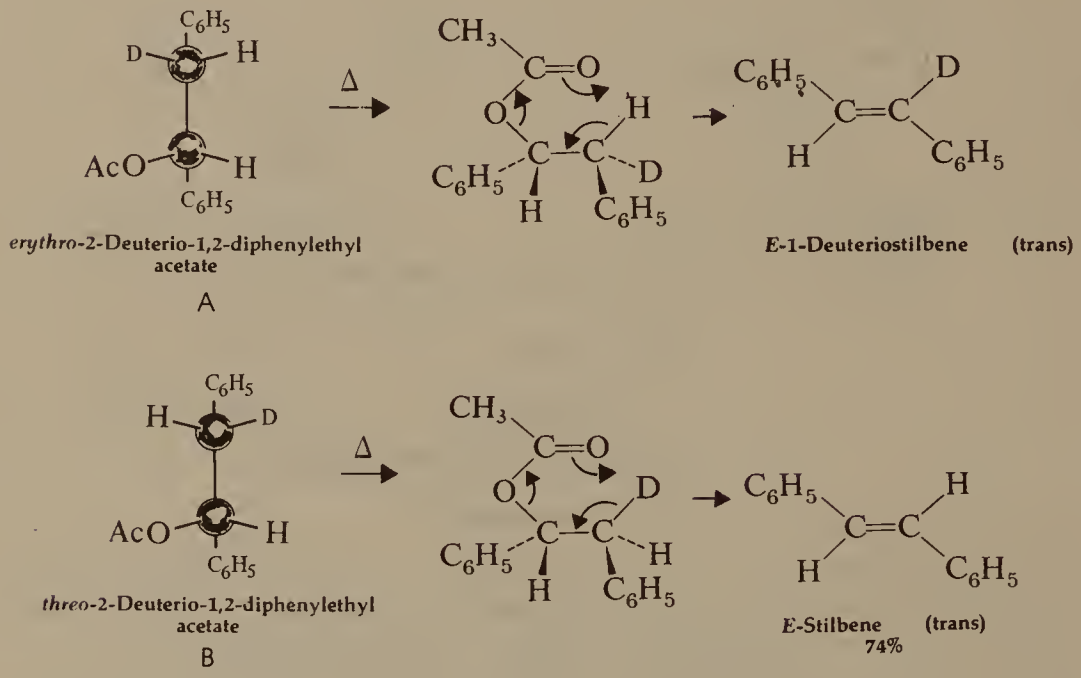




Scheme 5.41

eclipsed arrangement (*syn*-stereochemistry) in the transition state, even if they are not eclipsed in the starting material. In case two or more *syn* periplanar arrangements are available, the one with least crowding is preferred, generally leading to the product in which the bulky groups are *trans*. Thus, pyrolysis of 2-butyl acetate affords a mixture of 1-butene, *cis*-2-butene, and *trans*-2-butene, with the *trans/cis* ratio around 2.

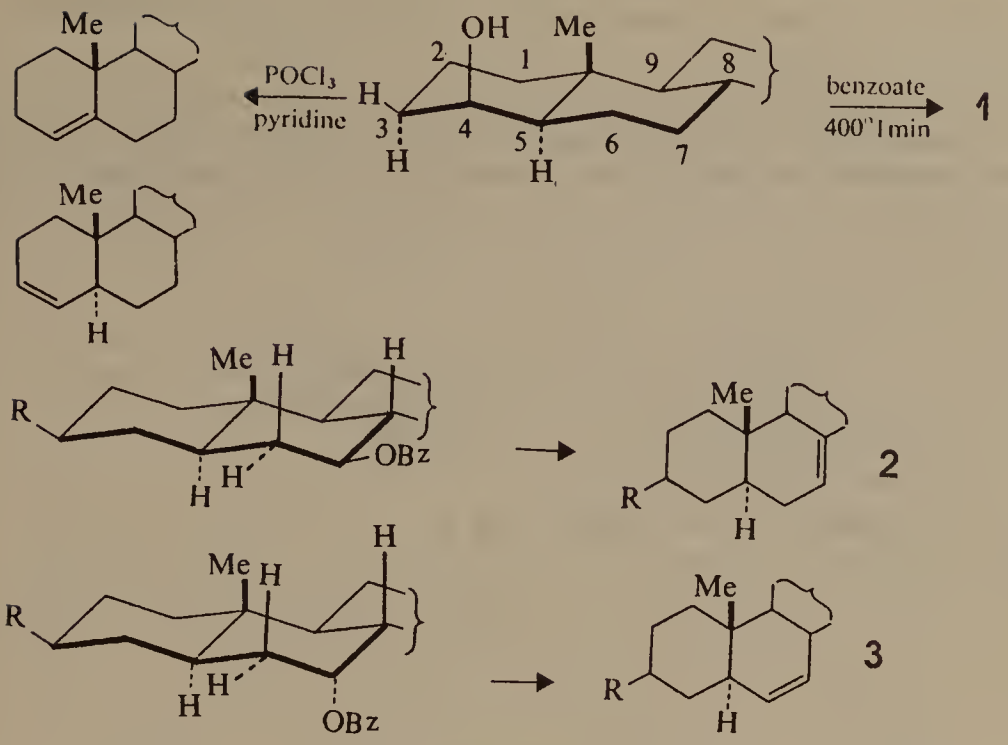
When the diastereomeric acetates **A** and **B** (Scheme 5.42) are heated, both yield *trans*-stilbene. The major product from **A** contains deuterium; however,



Scheme 5.42

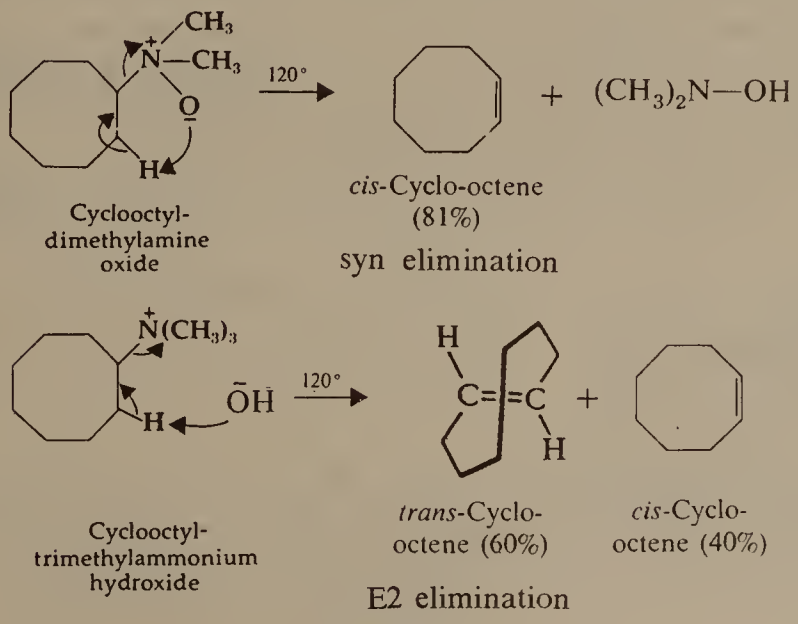
that from **B** does not. As presented, **A** and **B** are the less favored eclipsed conformations being more crowded (Ph/Ph θ=0°). Thus the elimination takes place from the arrangements shown in transition states. The most favored conformations have the phenyls on the opposite sides, and therefore, the favored conformation from **A** has a hydrogen near the acetoxy and the one from **B** a deuterium.

Consequently pyrolytic eliminations from cyclohexyl derivatives are possible only when the groups to be eliminated are *cis* to each other (*i.e.*, one group must be axial and other equatorial). Elimination of *trans*-diequatorial groups is not possible. The differing stereochemical preferences of E2 and pyrolytic eliminations make them complementary methods for creating specific olefinic centres (eq. 1, Scheme 5.43). In case, hydrogen function is stereochemically suitably located on both sides to the departing group (eq. 2, axial hydrogens on C-6 and C-8) the preference is for the formation of a highly substituted olefin as shown by the dehydration of 4- and 7-hydroxy compounds in the 5 α- cholestane series.



Scheme 5.43

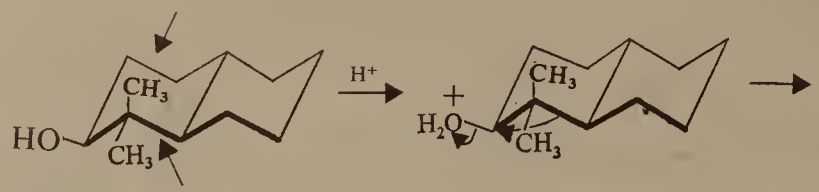
Tertiary amine N-oxides undergo the elimination (Cope elimination) of a dialkylhydroxylamine on being heated. The temperatures required, however, are considerably lower than those required for acetate pyrolysis. The Cope elimination is also a *syn* elimination and proceeds through a cyclic five-membered transition state. It is interesting to compare the results of Cope elimination with Hofmann elimination in the cyclooctyl system (Scheme 5.44).



Scheme 5.44

5.6 MOLECULAR REARRANGEMENT DURING ELIMINATION

When the achievement of the *anti* conformation is not possible, molecular rearrangement may precede elimination. Thus in the *trans* decalin derivative, the hydroxyl group is held in the equatorial position because the ring system cannot flip, but two of the ring residues (shown by arrows Scheme 5.45) are in

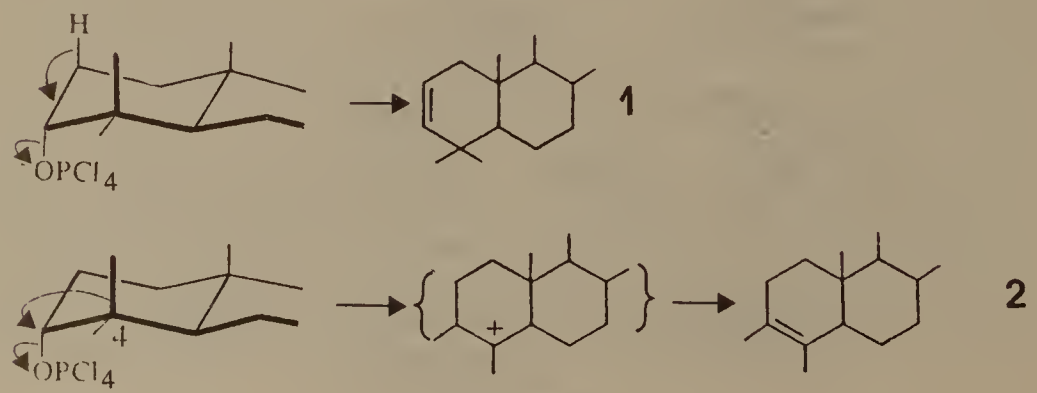


the *trans*-decalin derivative

Scheme 5.45

the appropriate *anti*-periplanar position for rearrangement, and in the presence of acid, ring-contraction occurs. Interestingly, of the two ring residues that one migrates which leaves behind the more stable carbocation.

In the case of related axial 3 α-hydroxy derivative (eq. 1, Scheme 5.46) in the intermediate chloro-ester (reaction with PCl_5), the ester group has an *anti* relationship on one side with the axial 4 β-methyl group and on the other side with an axial 2β-hydrogen atom. As a result, with this compound a molecular rearrangement of 4β-methyl group occurs on one hand (eq. 2) while an elimination of C-2 hydrogen on the other, to afford a mixture of the rearranged Δ^3-compound and Δ^2 compound. 1,3-Molecular rearrangement is the exclusive reaction in the case of 3β-equatorial alcohol.

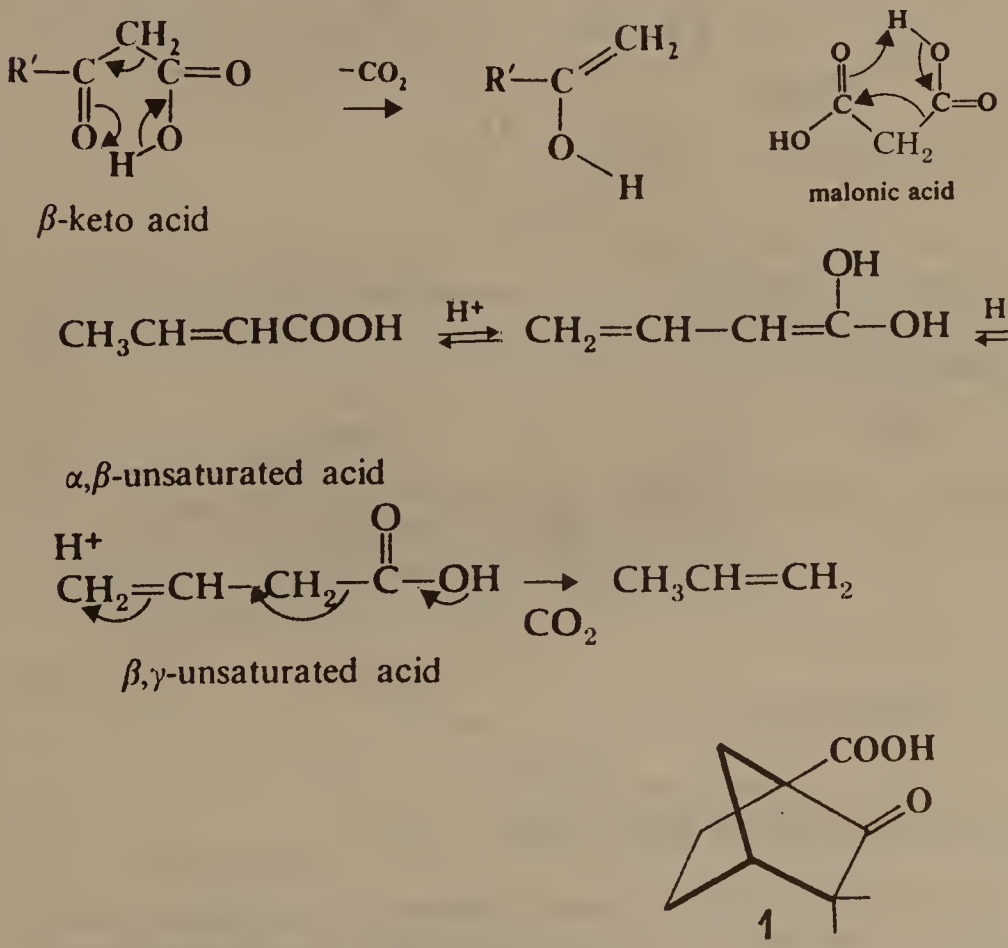


Scheme 5.46

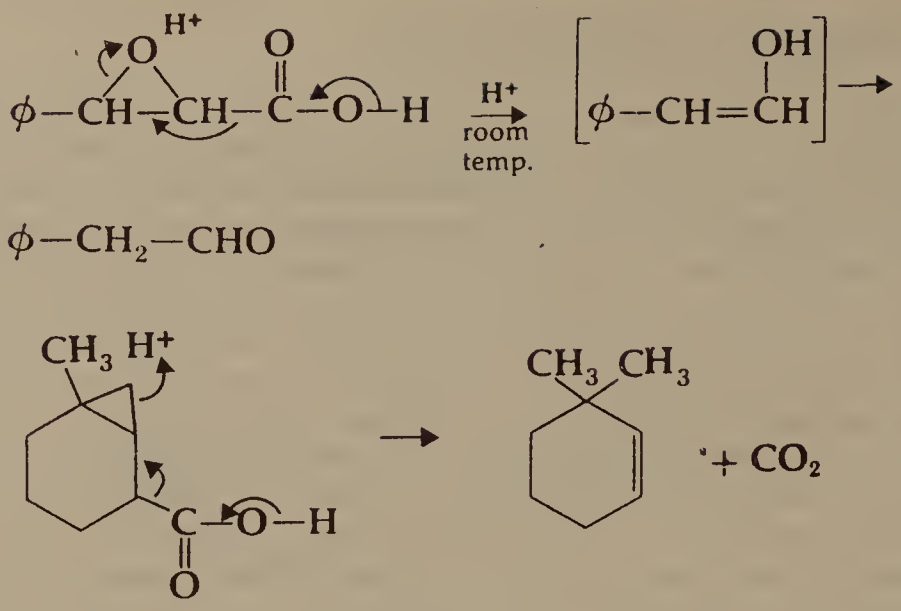
5.7 DECARBOXYLATION REACTIONS

Decarboxylation represents an elimination reaction, thermodynamically favored by the low energy of carbon dioxide. Decarboxylation occurs; if an electron-acceptor is present next to the carboxyl. Malonic or β-keto acids provide examples where initially formed enol tautomerizes to the product, *via* a six-centre mechanism. Some α-, β-unsaturated acids also undergo decarboxylation by this mechanism by isomerization to the β-, γ-isomers prior to actual decarboxylation. In keeping with this mechanism bicyclic β-keto acids like 1(Scheme 5.47), are resistant to decarboxylation. In these compounds the six-membered cyclic transition state cannot exist, for steric reasons, and if it could, formation of the immediate enol product would be a violation of Bredt's rule. Other groups which promote decarboxylation are the three-membered rings where the angle strain is relieved by opening.

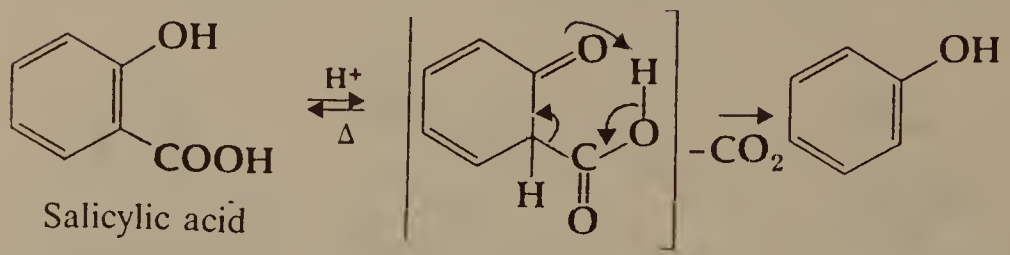
Aromatic phenols are highly enolic, the enol can first ketonize in a highly unfavorable equilibrium to provide a desired ketone for decarboxylation. Using their own acid catalysts, *o*-and *p*-hydroxybenzoic acids (Scheme 5.49) decarboxylate at their melting point.



Scheme 5.47

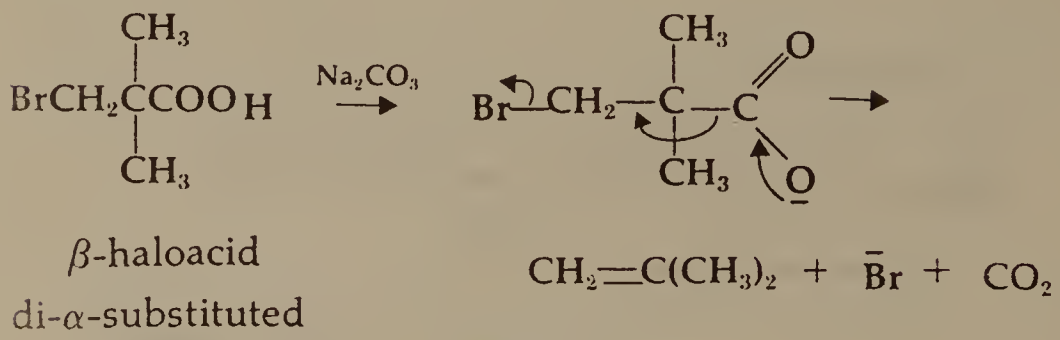


Scheme 5.48



Scheme 5.49

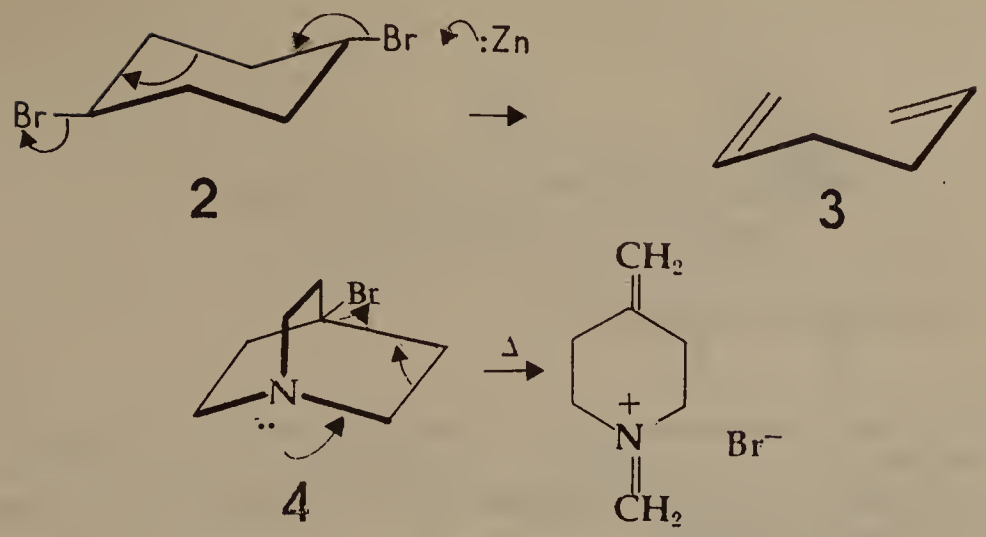
The salts of β-haloacids undergo decarboxylative elimination, particularly with di- α-substituted acids where no proton is available for the normal β-elimination.



Scheme 5.50

5.8 FRAGMENTATION REACTIONS

A process basically similar to the *anti* elimination of vicinal dihalides is also applicable to 1,4-dihalides and other 1,4 difunctional molecules which can



Scheme 5.51

suffer elimination accompanied by fission of a carbon-carbon bond, if the geometry of the compound is favorable *i.e., anti*-periplanar orientation of the groups required in the central elimination reaction exists (*i.e.,* the leaving group and the C-C bond which breaks must be *anti*). This can be illustrated by the fission of *trans*-1,4-dibromocyclohexane 2 (Scheme 5.51), to 1, 5 hexadiene 3 and fission of compound 4.

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3. J.Mc. Kenna, and J.B. Slinger, *J.Chem.Soc.,* (London) **2959** (1958).
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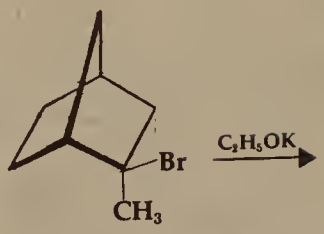
EXERCISES AND PROBLEMS

1. Predict the major elimination product from the following reactions:

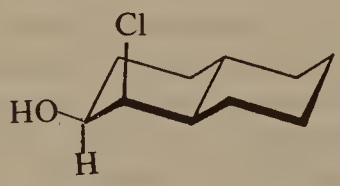
(a) $CH_3CH_2CH_2\underset{\displaystyle Br}{\underset{|}{C}}(CH_3)_2 \xrightarrow{C_2H_5ONa}$

(b) $CH_3CH_2CH_2\underset{\displaystyle (CH_3)_3\overset{+}{N}I^{-}}{\underset{|}{C}}(CH_3)_2 \xrightarrow[\Delta]{Ag_2O}$

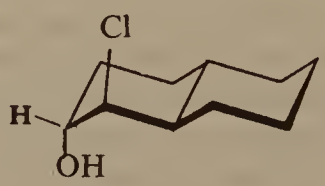
(c) 

(d) $C_6H_5CHCH_2CH_2CHC_6H_5$ (Br, Br) $\xrightarrow{Zn}$

2. On pyrolysis $Me_2CHCHMeOAc$ gave $Me_2CHCH{=}CH_2$ (80%) and $Me_2C{=}CHMe$ (20%). Explain.
3. An α-ketoacid is reacted with hydroxylamine followed by pyrolysis. Indicate the products formed with mechanism.
4. Depict the behaviour of chlorohydrins (a) and (b) on reaction with a base.

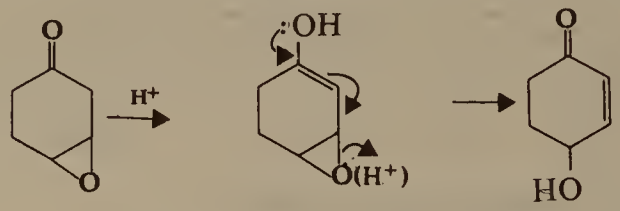


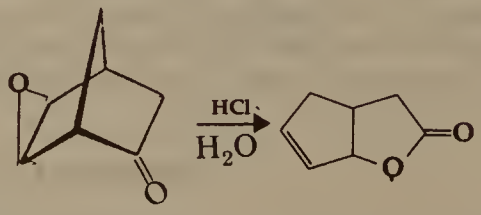
(a)



(b)

5. Eight geometrical isomers are possible for hexachlorocyclohexane which is used as an insecticide. All of these exist in chair form. Write the conformation of the isomer which is expected to undergo loss of hydrogen chloride with a base with greatest difficulty.
6. Epoxide of 3-cyclohexanone on treatment with aqueous hydrochloric acid reacts by the mechanism shown below. Suggest a mechanism for the reaction of the bicyclic epoxide





7. Comment on the mechanism of the oxidation of a tosylate with dimethylsulphoxide (DMSO) and subsequent reaction with a base.

6
STEREOCHEMISTRY OF SOME ADDITION REACTIONS

Four different ways may be recognised for addition to a double bond. These addition reactions are regiospecific, stereospecific and may take place by either *syn* or *anti* pathway. Three kinds of mechanisms are two step processes involving initial attack by an electrophile, a nucleophile or a free radical. The second step involves combination of the resulting intermediate with a negative species, a positive species or a neutral entity. In the last type of mechanism, attack on the two carbon atoms of the double or triple bond occurs simultaneously.

6.1 BROMINATION OF ALKENES (ELECTROPHILIC ADDITION)

In an alkene the electron density of a *pi* bond is maximum below and above the plane of the double bond. The most favourable way for the attack of the electrophile based on stereoelectronic considerations is along these electron-rich regions *i.e.*, perpendicular to the plane of the double bond. The attacking total reagent might be divided into an electrophilic and a nucleophilic portion (E-Nu). Each part of this reagent may add to the double bond of the reactant molecule from the same side (*syn* addition) or from opposite side (*anti* addition). An important reaction of alkenes is addition of an electrophilic species like bromine.

Bromination reactions point to two important generalizations.

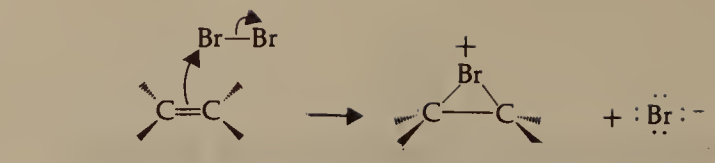
(*a*) If bromine is added to an olefin in the presence of a large concentration of chloride ions a mixture of the dibromide and the chlorobromide results. Similar mixed additions are observed in the presence of other anions, *e.g.*, bromohydrins are formed in the presence of hydroxide ions.

(*b*) If bromine is added to a cyclic olefin, the bromine atoms in the product are *trans* to each other.

The mechanism[1] which matches best with these observations in two step process and is shown in (eq. 1, Scheme 6.1). The reaction is an electrophilic addition, the intermediate bridged bromonium ion reacts with an anion; the reaction taking place by attack from the side of the molecule opposite to that carrying the bromine (S_N2 manner). Hence, *anti*-addition occurs as seen in the case of cyclopentene (Scheme 6.2).

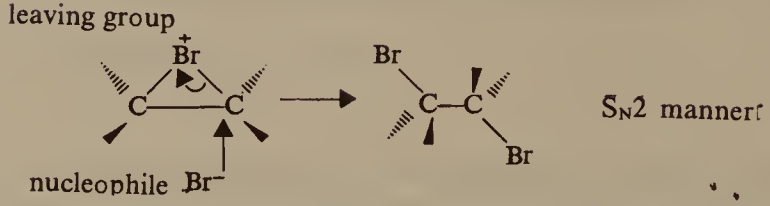
In the case of equally substituted carbon atoms, the nucleophile (Br^- in this case) can attack either of the carbons of the halonium ion (eq. 2, Scheme 6.3).

In conformationally rigid systems, the *trans*-product formed is diaxial

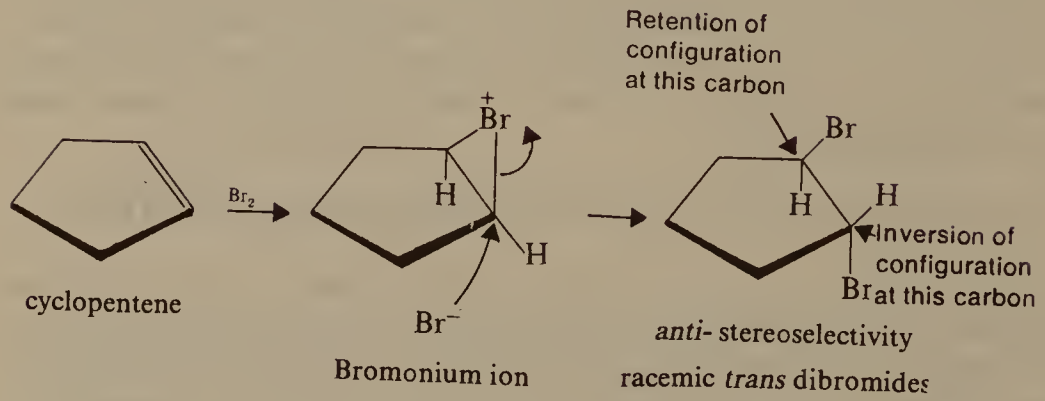


A bromonium ion

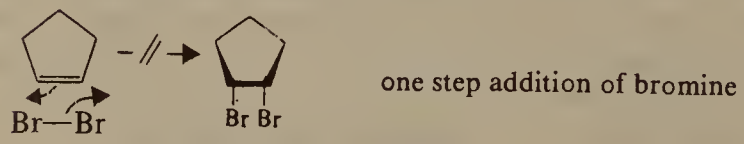
1



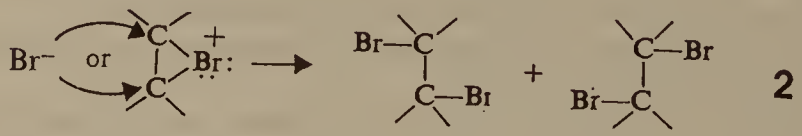
Scheme 6.1



The addition must be at least a two-step process



Scheme 6.2



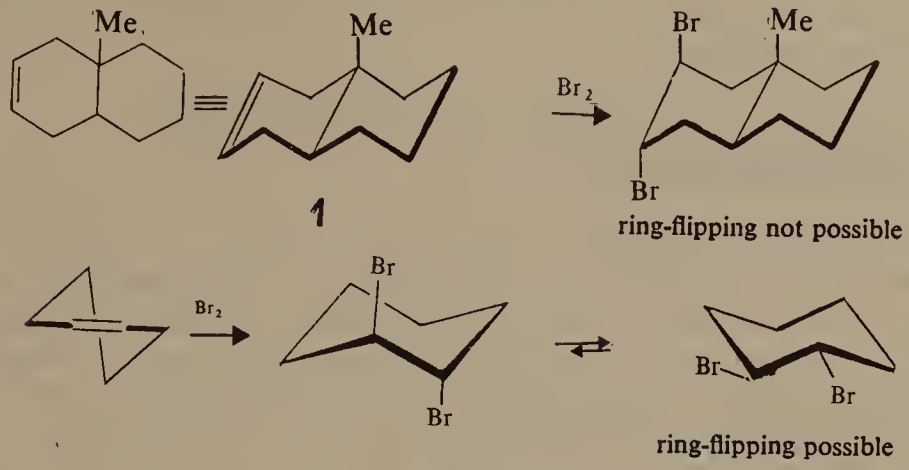
2

Scheme 6.3

rather than diequatorial (Scheme 6.4). This can be illustrated by the rigid *trans*-decalin structure in the conformation **1** (stereoelectronic requirement for *trans* addition).

When bromine is added to cyclohexene, the initial addition reaction affords the *trans*-diaxial dibromide, but this immediately equilibrates with the *trans*-di-equatorial dibromide. Significant amounts of both conformations are

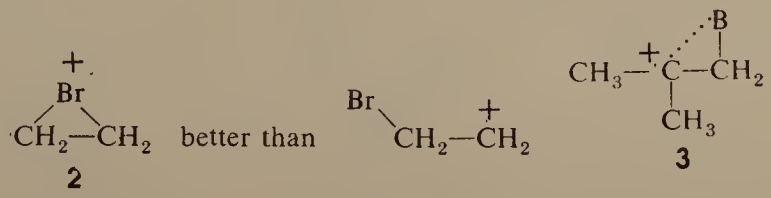
present, as the dipole interactions which destabilize the diequatorial form are comparable to the steric and electronic effects which destabilize the diaxial conformation.



Scheme 6.4

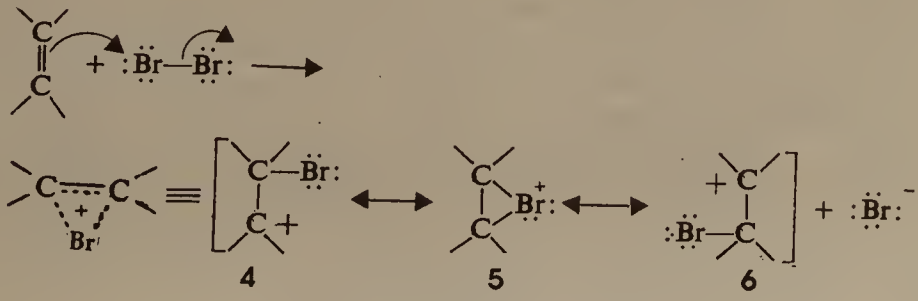
6.2 RESONANCE IN HALONIUM ION (BROMONIUM ION)

The tendency for the initial species *i.e.*, cyclic bromonium ion to retain the cyclic form depends on the stability of the derived 'open' carbocation. The intermediate formed from the addition of bromine to ethylene may be best described as a symmetrical bromonium ion with relatively strong C—Br bonds. The alternative open form is a highly unstable primary carbocation. The ion formed by addition of bromine to isobutylene is better described as a tertiary carbocation with a long and weak bond to bromine as shown in 3 (Scheme 6.5).



Scheme 6.5

Cations such as these may be described in terms of three resonance structures (Scheme 6.6). The actual ion is a hybrid of the three structures 4, 5 and 6.



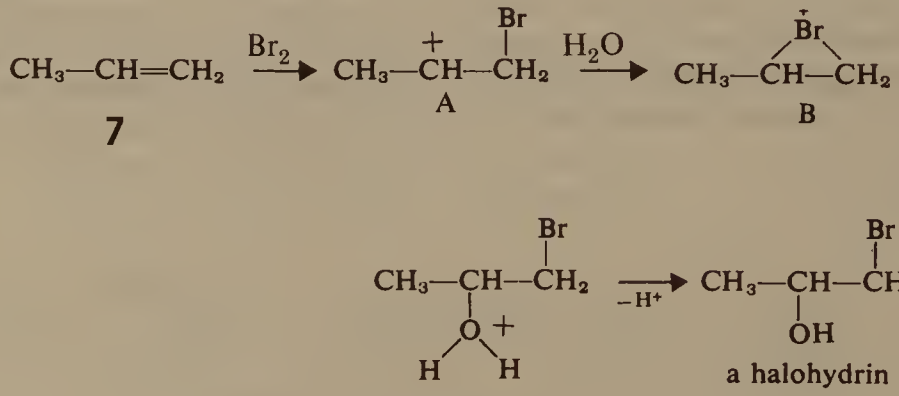
Scheme 6.6

If both 4 and 6 correspond to unstable carbocations, then structure 5 is a more important contributor to the actual structure of the ion. If either 4 or 6 corresponds to a relatively stable carbocation, then that structure contributes more and the ion has substantial carbocation character without as much halonium ion character.

6.3 EVIDENCE FOR RESONANCE AND INVOLVEMENT OF HALONIUM ION

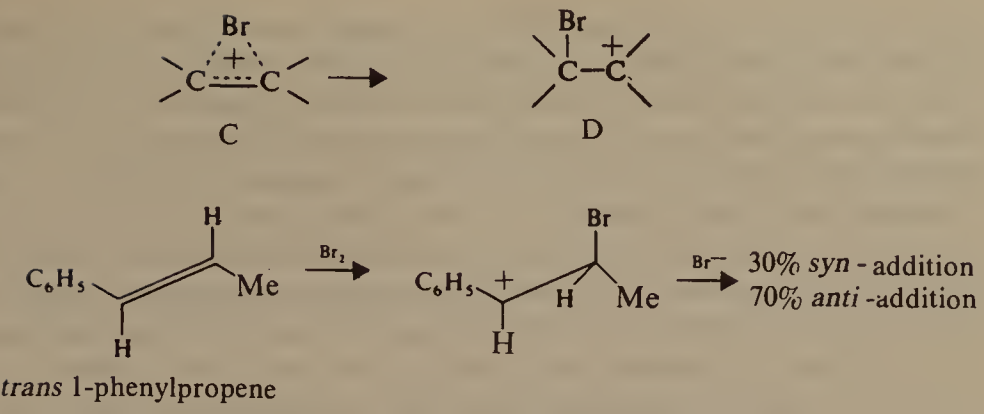
Some examples are presented below to show the involvement of the species 4, 5 and 6 in electrophilic additions to a double bond. Two points need mention on the basis of available evidence. Firstly, if there is no restriction to rotation about the connecting covalent bond, the preferred species is the carbocation of greater stability; secondly, in a compound in which rotation is restricted by a ring system the cyclic bromonium ion is the key intermediate.

In order to study the direction of attack on the bromonium ion, the bromination reaction is carried out in the presence of an excess of another nucleophile, like water. It is observed that the nucleophile attacks a bromonium ion from a simple unsymmetrical aliphatic olefin 7 (Scheme 6.7) at the most substituted carbon atom, which is also the most sterically hindered.



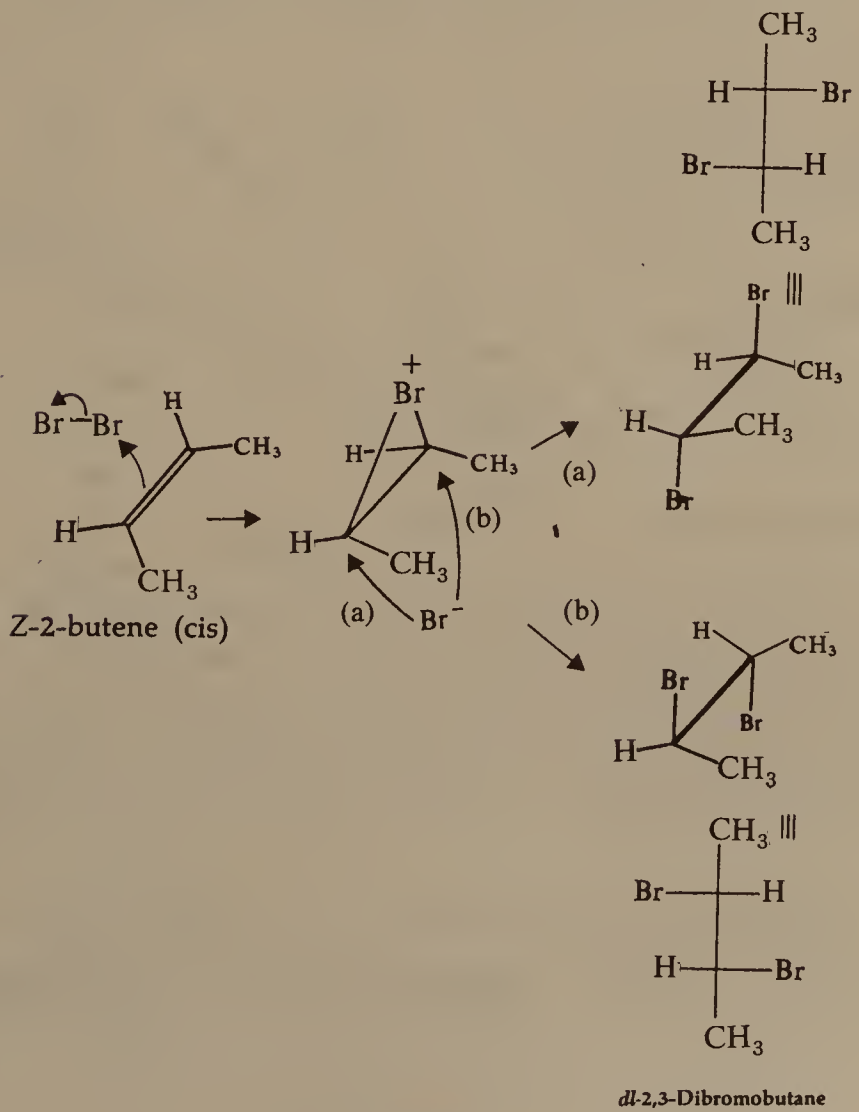
Scheme 6.7

This direction of attack shows that the carbon atom of the bromonium ion has probably partial positive charge and its attraction for a nucleophile is enough to overcome steric factors and in the reaction 7, **A** has more significance than **B**. In case a carbon atom can stabilize the positive charge as a consequence of being attached in strong electron donating group then it can accommodate a larger share of the charge than the other two atoms. In an extreme case, therefore, the charge concentrates on a single carbon atom, effectively converting the bromonium ion **C** into a bromo-carbocation **D** (Scheme 6.7a). The addition of nucleophile to such species could proceed without any stereoelectronic requirement, and the outcome of such a reaction will not be restricted to give only *trans* products.



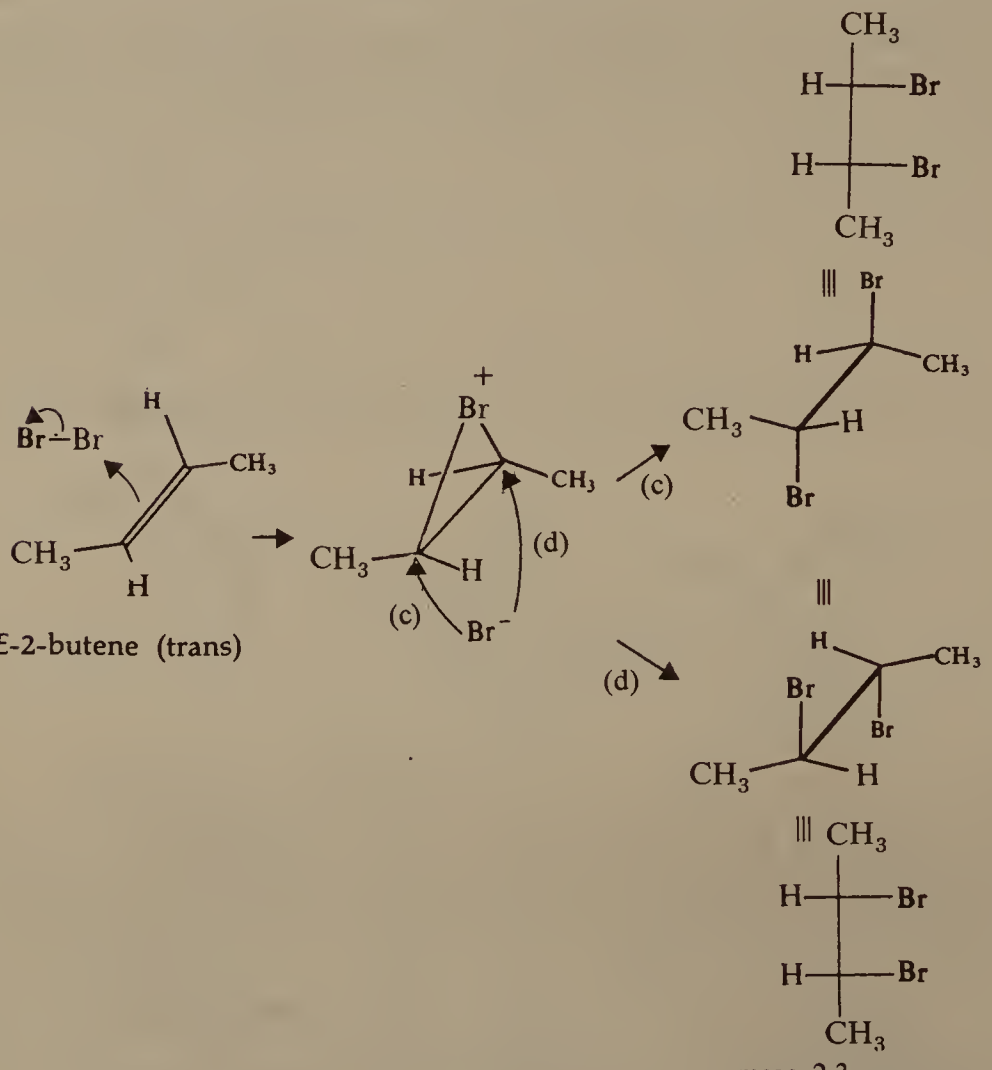
Scheme 6.7a

The degree of *anti* stereoselectivity in the addition of halogens to alkenes therefore depends on the relative stability of a cyclic halonium ion compared



Scheme 6.8

with its carbocation species. The structural features which lead to the stabilization of carbocation may lead to less *anti* stereoselectivity, and it is found to be so with *trans* 1-phenylpropene which generates a delocalized benzyl type carbocation (Scheme 6.7a). In confirmation, one finds hundred percent *anti* stereoselectivity with *trans* 2-butene where a similar delocalization is not possible. The same point is made by studying the addition of chlorine to alkenes which is less stereoselective than the addition of bromine. This is due to the higher electronegativity of chlorine than that of bromine and thus with the corresponding reluctance to share its electron pairs. Additionally increase in the polarity and ion-solvating ability of the solvent also stabilizes a carbocation than the bromonium ion intermediate which as expected leads to a decrease in *anti* stereoselectivity. This is seen in

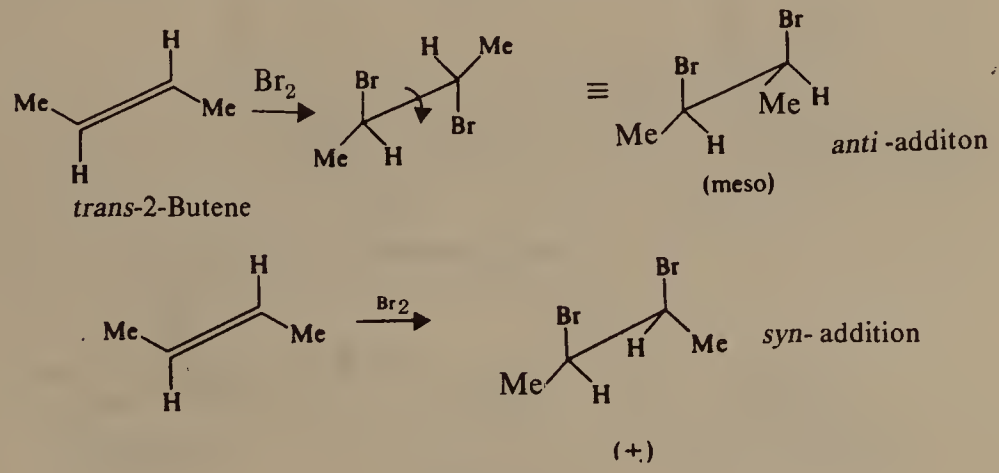


Scheme 6.9

the addition of bromine to stilbene to give 95% *anti* addition in solvents of low di-electric constants but is only 50% *anti* in a solvent with $\epsilon = 35$.

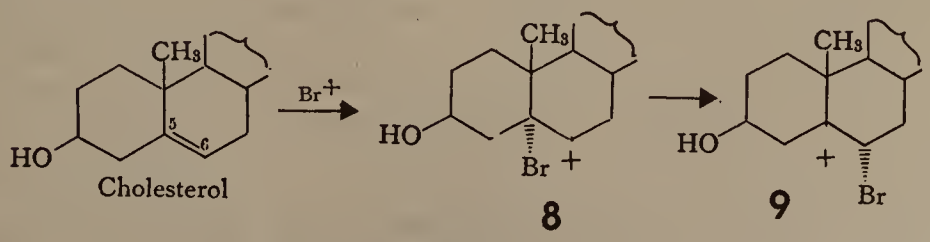
The addition of bromine to *cis*-and *trans*-2-butene is illustrative; the former gives *dl*-2, 3-dibromobutane and the latter gives *meso*-2, 3-dibromobutane (Schemes 6.8 and 6.9). This stereospecificity indicates that the intermediate carbocation (corresponding to 4 or 6) cannot undergo rotation about the bonds to the trivalent carbon before reaction is completed, and to account for this it has been suggested that the carbocation's stereochemistry is held by interaction between the ion and the electrophile which has been added, *e.g.*, for bromination, a cyclic bromonium ion is involved.

For further clarity one may consider the bromination of *trans*-2 butene (Scheme 6.10), where the two bromine atoms add on from opposite sides of the planar alkene leading to *anti* addition. The product is the symmetrical *meso* dibromide. If addition had occured *syn* the unsymmetrical (±) dibromide would have been the product. This stereoselectivity can be further explained only on the basis of the involvement of a cyclic bromonium ion.



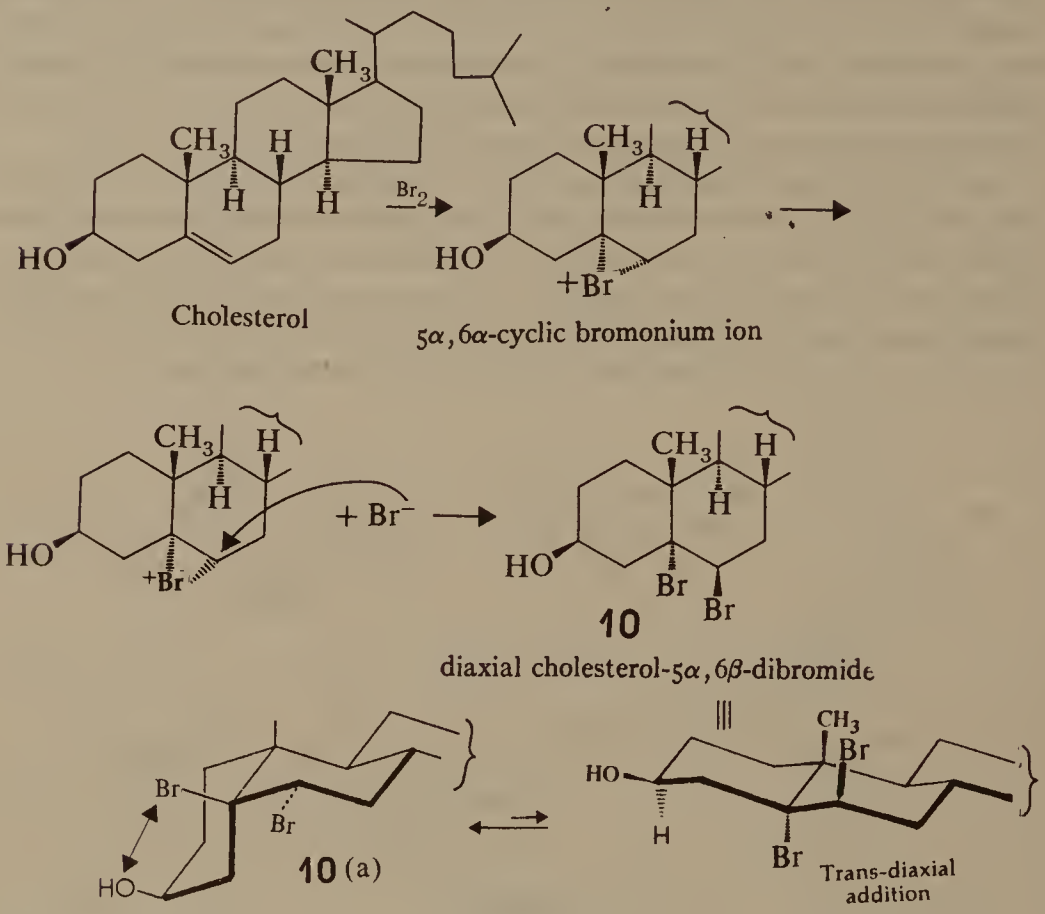
Scheme 6.10

An inspection of the formula of cholesterol (Scheme 6.11) indicates that the β-face, is shielded by the two angular methyl groups and the side chain, whereas the α-face, *i.e.*, rear side, is relatively flat and unshielded. This spatial difference accounts for a general tendency for a reagent to attack from the rear to produce an α-linked compound. This rule of rear attack, although not infallible, holds for the majority of reactions involving functional groups at



Scheme 6.11

various positions in the steroid structure. If cholesterol, shown in the partial formula were to suffer rear attack by Br^+ to form a carbocation the ion **9**; it being tertiary, would have preference over the secondary carbocation **8**. The *trans* reaction product from **9** would then be the 5β,6α-dibromide, whereas the actual product is the 5α,6β-dibromide **10** (Scheme 6.12).



Scheme 6.12

The formation of **10**, is explained by the attack of Br^+ on the rear unhindered side of cholesterol to yield a 5α,6α-cyclic bromonium ion. This ion is then opened up by the attack of Br from the β-face (S_N2 reaction) at the less hindered 6 position.

The diaxial cholesterol-5α,6β-dibromide is stable as a crystalline solid, however, its solution in chloroform on keeping for a few weeks affords an equilibrium mixture from which the major isomeric component 5β,6α-dibromide **10**(a) can be isolated. The diequatorial dibromide **10**(a) is not formed from a ring flip which is restricted but originates by a molecular rearrangement which involves a Walden inversion at the C-5 and C-6 chiral centres. Its formation relieves the original strain, since both bromines are now equatorial.

Thus, initially, *trans* diaxial addition occurs, however, the product equilibrates with the more stable diequatorial isomer. This example

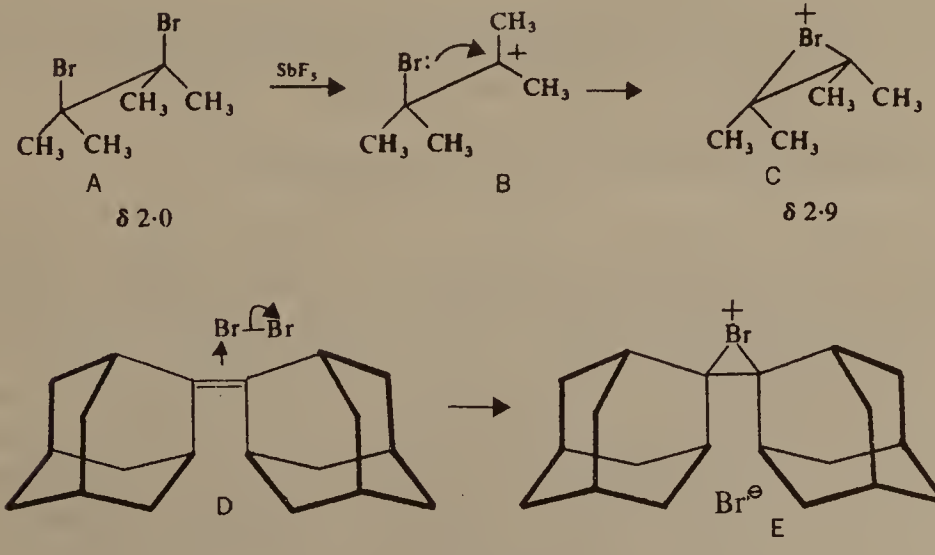
represents a diaxial-diequatorial rearrangement.

Extensive data is available to show that the equilibrium becomes less favorable towards the diequatorial isomer when a bulky group occupies the C-3 equatorial position in the diaxial isomer. An inspection of the models shows that this substituent becomes *syn*-axial with one of the bromines after epimerisation. Data presented in the table shows that the direction of equilibration is dependent on the size of the substituent at C-3 and that the 1,3-diaxial interactions follow the sequence Br—H<Br—OH<Br—OBz<Br—Cl< Br-Br.

TABLE 6.1 Substituent at C-3 and Direction of Equalibration.

3β-substituent	5α, 6β	5β, 6α
H	1	99
OH	14.5	88.5
OBz	20	80
Cl	87	13
Br	90	10

Evidence supporting the existence of cyclic bromonium ions has come from a number of different fields. Thus reaction of the 1,2-dibromide, **A** with SbF_5 in liquid SO_2 at —60°C (Scheme 6.13) afforded an ion pair which did not display the expected *two* signal n.m.r. spectrum for **B**. Presence of only *one* signal (δ 2.9) showed that all twelve protons were equivalent, *i.e.*, what is being detected is indeed the bromonium ion **C**.

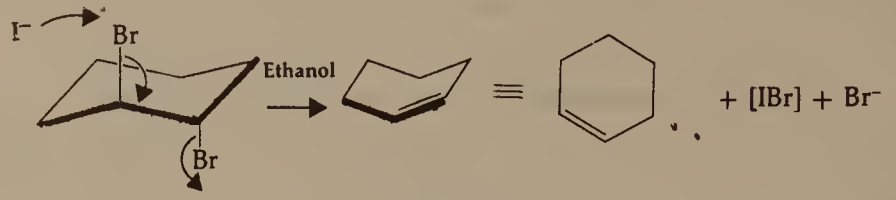


Scheme 6.13

Addition of bromine to a remarkable alkene **D** has led to the trapping of cyclic bromonium ion **E**. This is possible since, further attack by Br on the initially formed intermediate is prevented by the cage-like structures which shield at each end of the original double bond from attack.

6.4 UTILITY OF DEHALOGENATION

Dehalogenation by iodide ion or zinc dust is a stereospecific process which proceeds by an *anti* stereochemical pathway. Iodide functions in the same manner as the base in dehydrohalogenation. Loss of the halogen atoms is synchronous with formation of the double bond in this E2 reaction (Scheme 6.14).



Scheme 6.14

An interesting application of dehalogenation is in the purification of certain alkenes. Most dibromides are solids which can be easily purified by recrystallization. An impure alkene is converted to dibromide. The dibromide is then purified and converted back to the original alkene. When crude cholesterol extracted from gallstones is purified by treating its solution in either with a solution of bromine in acetic acid, cholesterol-5α, 6β-diaxial dibromide crystallizes immediately. Pure cholesterol is then isolated by the treatment of this initially formed *trans*-diaxial dibromide with electron-transfer agents. Zinc is commonly used as the reducing agent and thus the E2 elimination occurs readily.

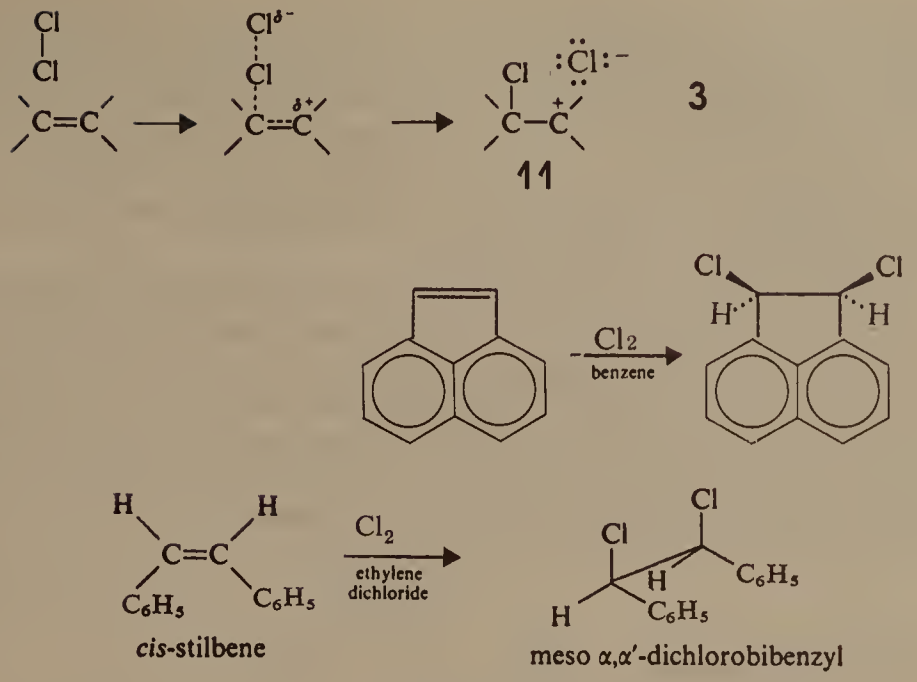
On the other hand, as expected, the slow reaction of the more stable isomeric *trans*-diequatorial dibromide proceeds probably through conversion to the less favoured *trans*-diaxial conformation.

6.5 ELECTROPHILIC ADDITION OF CHLORINE

The ability of a chlorine atom to stabilize a positive charge is less than that of the bromine atom. Although many addition reactions of chlorine to a double bond proceed *via* a chloronium ion to afford a *trans*-dichloride, examples of reaction *via* a chloro-carbocation are also known. In the latter situations, reaction of Cl_2 with a double bond (in a poor ionizing solvent) gives a tight chloro-carbocation ion pair 11 (eq.3, Scheme 6.15). The dichloride is formed possibly by the rapid collapse of the ion pair, to give a *cis*-dichloride. Separation of the ion pair and attack of Cl^- on the chloro-carbocation can afford a mixture of both *cis*-and *trans*-dichlorides. In poorly ionizing solvents the ion-pair formation predominates, and the main product is the *cis*-dichloride.

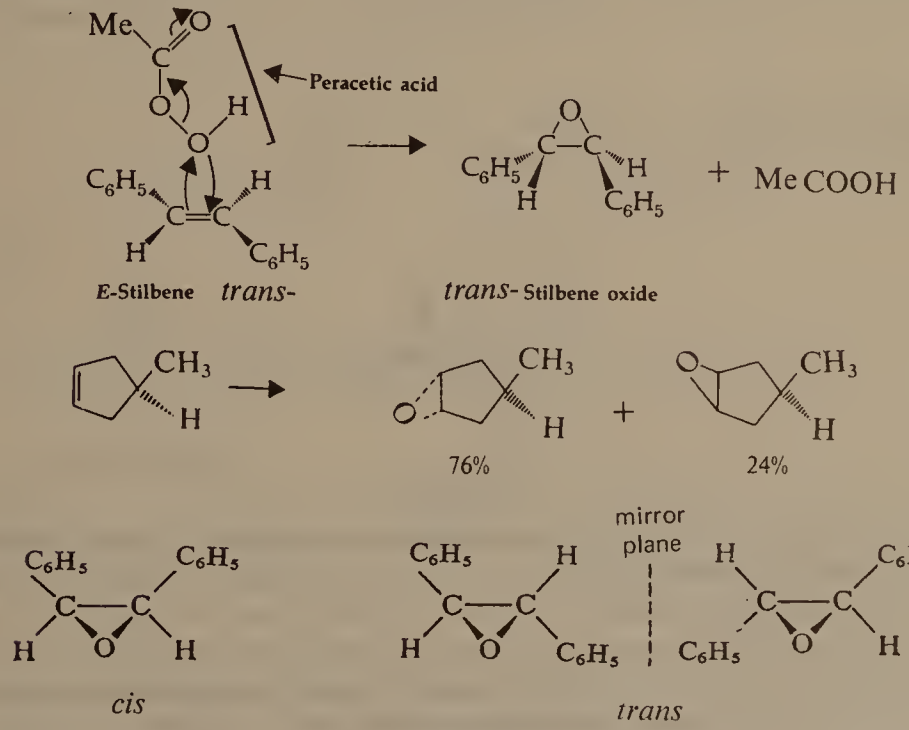
6.6 FORMATION AND REACTIONS OF EPOXIDES

The laboratory preparation of epoxides is usually accomplished by using a



Scheme 6.15

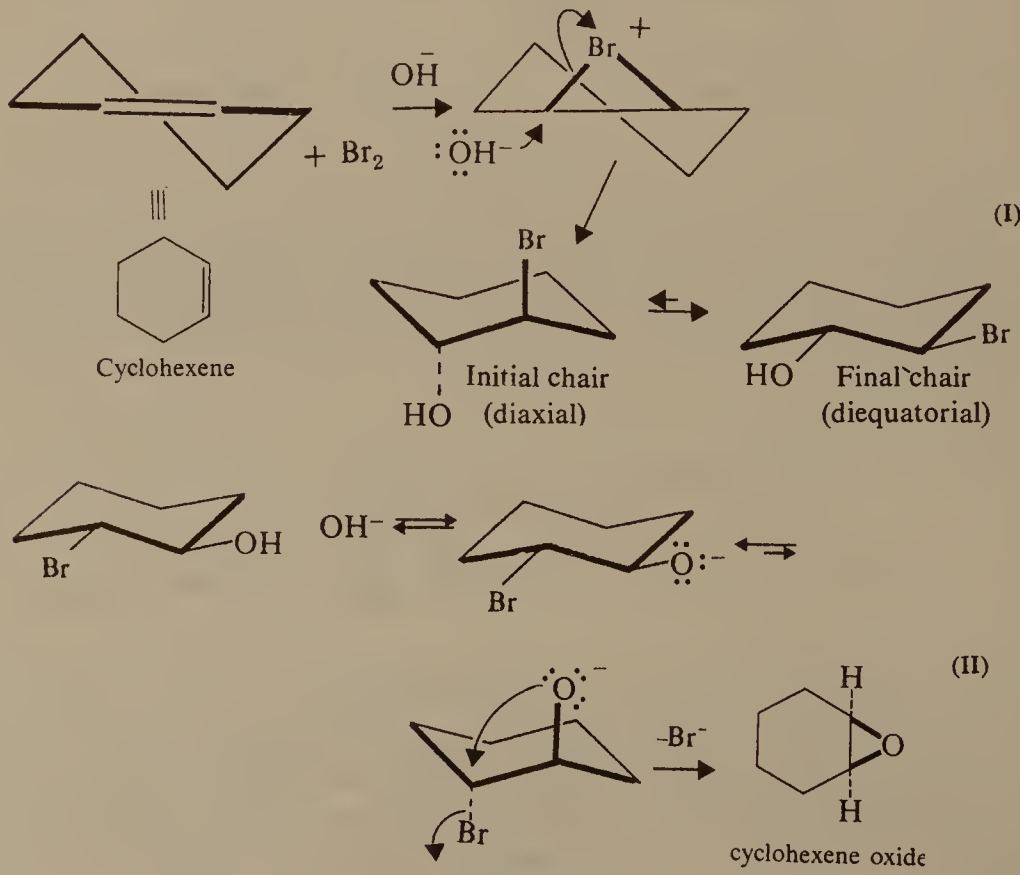
peracid (also called a peroxy acid). Epoxidation accomplishes *syn* addition of an oxygen atom to the double bond. The stereospecificity of the reaction (Sec. 1.19) indicates that ring formation occurs in essentially one step, or at least does not involve a free carbocation, *i.e.*, a *trans*-alkene gives a *trans*-epoxide and a *cis*-alkene gives a *cis*-epoxide.



Scheme 6.16

In the case of cyclic compounds, aspects of steric orientation have also to be considered. During *syn* addition to an unsymmetrical cyclic olefin, the two groups may come in from the more hindered side or from the less hindered side of the double bond. The rule is that *syn* addition occurs usually, though not always, from the less hindered side. Thus epoxidation of 4-methylcyclopentene (Scheme 6.16), gives 76% addition from the less hindered and 24% from the more hindered side.

Epoxides are also formed from halohydrins. Mechanistically one looks to a series of reactions in the case of cyclohexene. Significantly the cyclic bromonium ion initially gives the diaxial product which on ring flipping (not possible in the rigid steroid molecules) affords the more stable diequatorial isomer (eq. I, Scheme 6.17). For the epoxide formation (S_N2 type reactions), again the molecule adopts a conformation in which the groups assume a diaxial (*anti*-periplanar) orientation (eq.II).



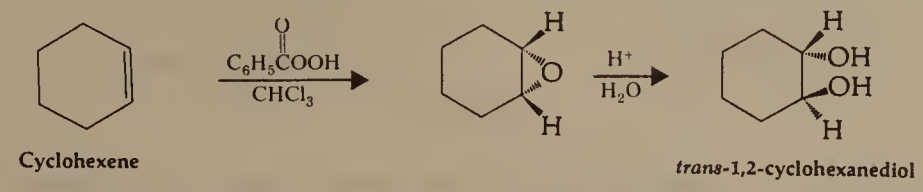
Scheme 6.17

Substituted epoxides display both geometrical and optical isomerism and stilbene oxide is an example. The epoxide from *E*-stilbene is chiral while the one from *Z*-stilbene is achiral.

Although epoxides are stable compounds, their three-membered rings are readily opened up by nucleophilic reagents using acidic and basic reagents (Scheme 6.18). Hydration (addition of water) of an epoxide is a common method used for glycol (1, 2-diol) formation. The ring opening proceeds to

give the glycol corresponding to *anti* hydroxylation of the original alkene.

Opening the epoxide ring by nucleophilic attack has important stereoelectronic requirements. The nucleophile must approach one of the



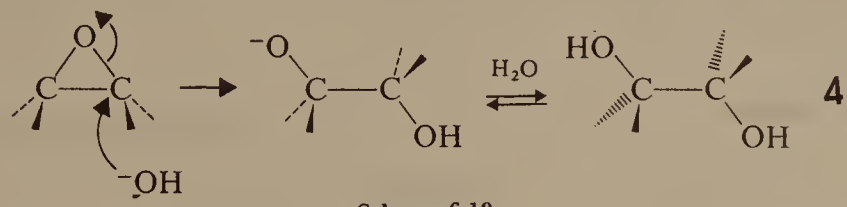
Cyclohexene

trans-1,2-cyclohexanediol

Anti hydroxylation

Scheme 6.18

carbon atoms bearing the oxygen from the side opposite to the epoxide ring, displacing the electrons of the C—O bond as in a bimolecular nucleophilic substitution reaction (eq. 4, Scheme 6.19).



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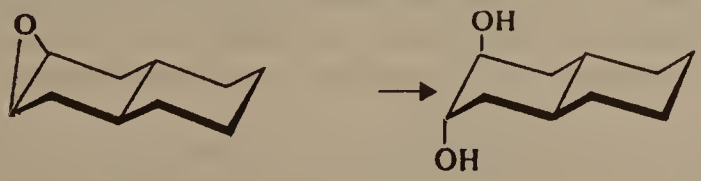
Scheme 6.19

Consequently, the bimolecular opening of an epoxide ring in which the epoxy ring is attached to a rigid cyclic system will usually give the *trans*-diaxial product. This can again be illustrated by taking the *trans*-decalin system as an example (eq. 5, Scheme 6.20).

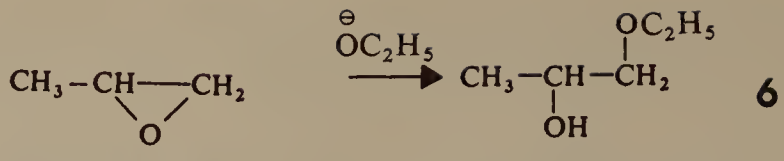


5

Scheme 6.20

6.7 EPOXIDE OPENING, ORIENTATIONAL PREFERENCES (ACID AND BASE CATALYSED REACTIONS)

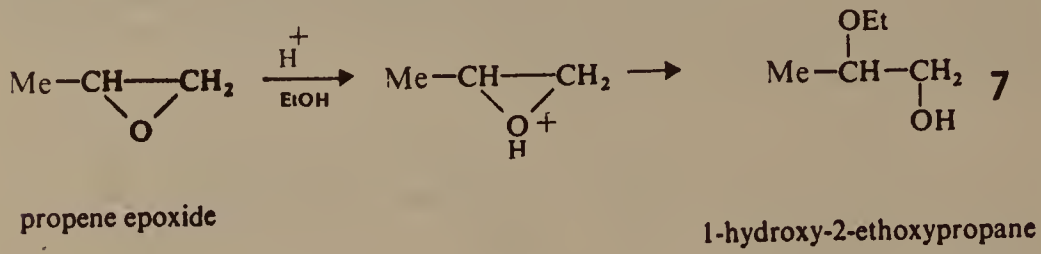
The direction of epoxide opening in acid and base catalysed reactions is revealed by studying the products formed from the reaction of unsymmetrically substituted epoxides with nucleophiles such as alkoxide ions. The reaction of propene epoxide with sodium ethoxide (Scheme 6.21) yields 1-ethoxy-2-hydroxypropane, the nucleophile having attacked the less substituted carbon atom (eq.6). This would be expected for any simple bimolecular reaction, as steric hindrance to the approach of the reagent is less at this atom. Thus, base-catalyzed opening of an epoxide is an S_N2 displacement reaction with an alkoxide ion as the leaving group and has no



Scheme 6.21

counterpart with normal ethers. It occurs with epoxides only because the relief in ring strain provides a potent driving force for the reaction.

Reaction of propene epoxide in ethanolic sulphuric acid *i.e.*, acid catalysed conditions, however, proceeds with reverse orientation to give reaction predominantly on the secondary carbon atom (eq. 7, Scheme 6.22).

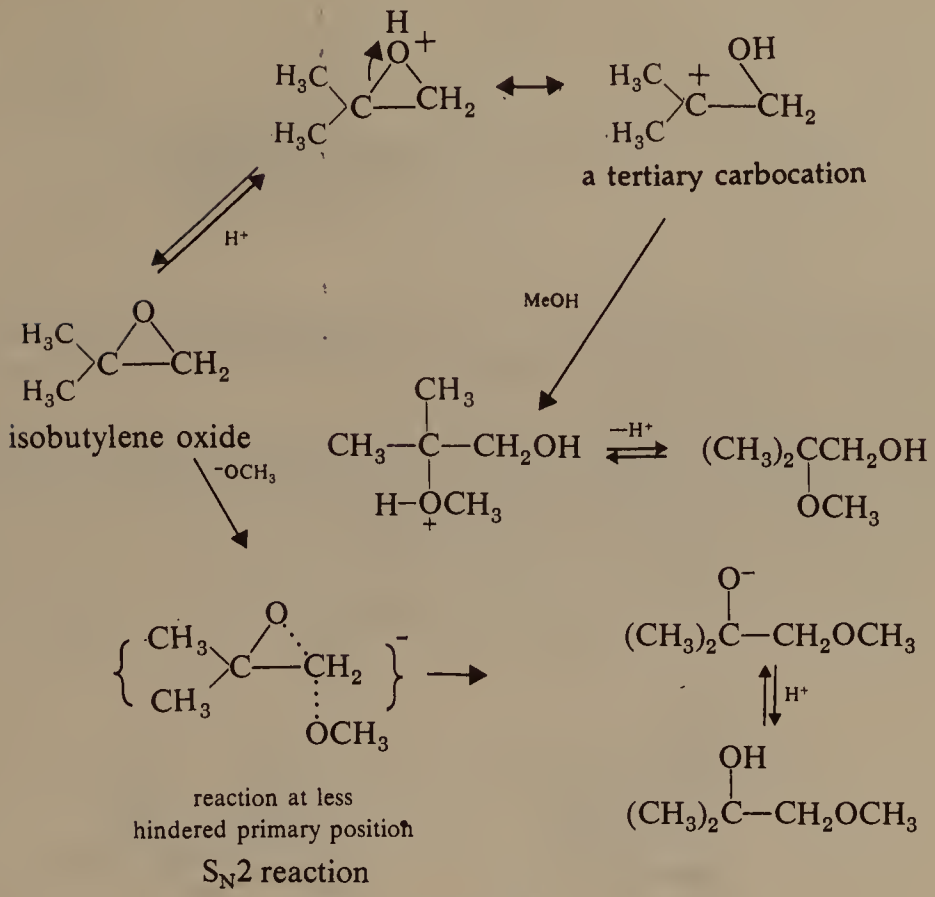


Scheme 6.22

It is believed that the reaction proceeds by spontaneous opening of the protonated epoxide ring. Clearly, the charge has been stabilized by being spread from the oxygen atom onto the carbon atoms, and the most substituted carbon atom has taken the larger share of the charge, and hence becomes the more reactive. Thus, the acid catalysed reaction at first sight may look to be essentially a carbocation reaction (*i.e.*, S_N1) unlike the S_N2 type reaction during base catalysed reaction. It is again seen in the case of isobutylene oxide (Scheme 6.23).

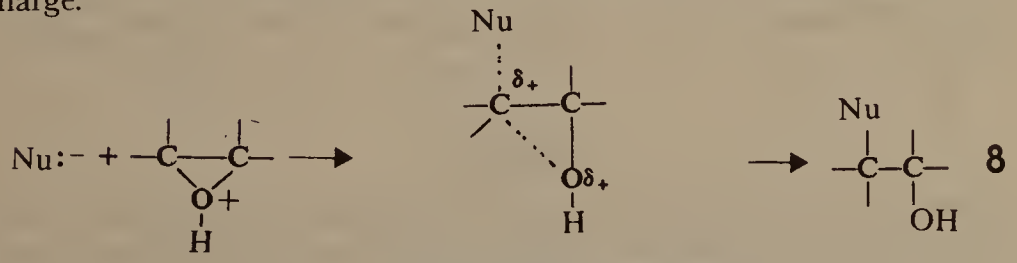
The evidence, however, shows clearly that both the reactions are of the S_N2 type (cleavage of the carbon oxygen bond and attack by the nucleophile occuring in a single step). One may account for the difference in the orientation in particular, for S_N2 attack at the more hindered position in acid-catalyzed cleavage by the following arguments. In the acid-catalyzed cleavage of an epoxide, the carbon-oxygen bond, already weak because of the angle strain of the three-membered ring, is further weakened by protonation. Although both bond-breaking and bond-making occur in the transition state (eq. 8, Scheme 6.24) bond-breaking has proceeded further than bond-making. The leaving group has taken electrons away to a much greater extent than the nucleophile has brought them in, therefore, the carbon acquires a considerable positive charge.

Crowding is thus relatively unimportant, because leaving group and nucleophile are far apart. Stability of the transition state is now determined mainly by electronic factors and not by steric factors. One calls such a reaction as having considerable S_N1 character. The attack occurs not at the less



Scheme 6.23

hindered carbon, but at the carbon that can best accommodate the positive charge.

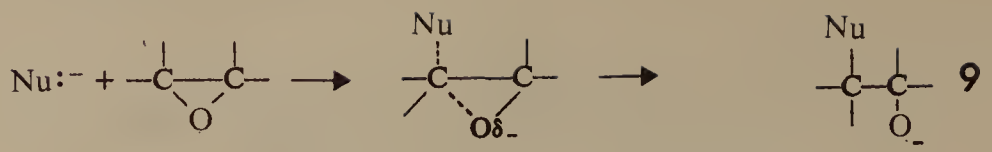


positive charge on carbon
Bond-breaking exceeds bond-making

Scheme 6.24

On the other hand in base-catalyzed opening, bond-breaking and bond-making are almost balanced, and reactivity is controlled in the usual way, by steric factors, attack occuring at the less hindered carbon (eq. 9, Scheme 6.25).

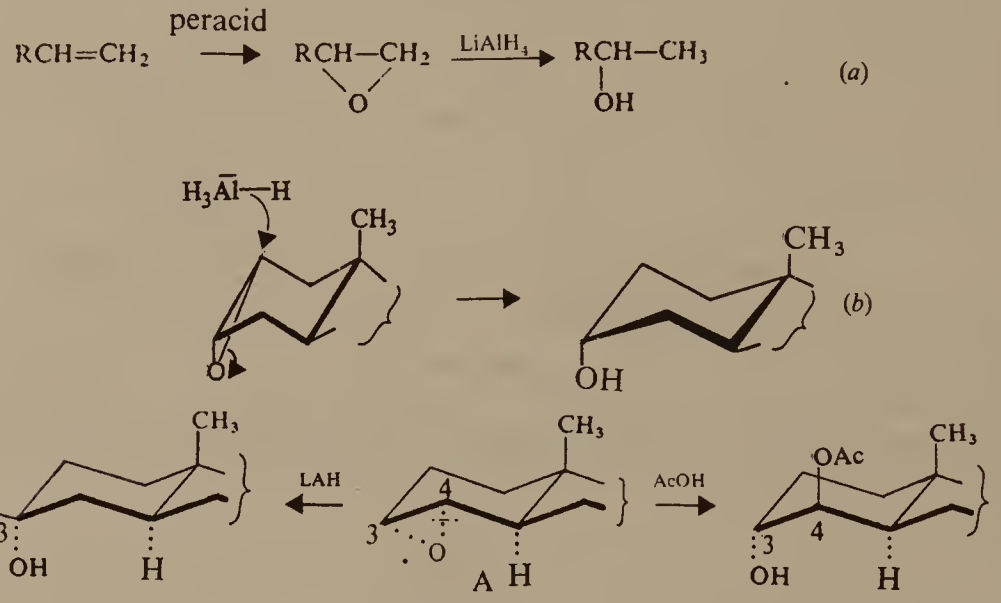
In the end, mention should be made of the reduction of epoxides with lithium aluminium hydride. Epoxides are reduced to alcohols by lithium aluminium hydride, and since epoxides are prepared from olefins, the reaction constitutes hydration of the olefin. The method is complementary to



Scheme 6.25

the hydroboration method (Sec. 6.14), as the hydride ion attacks selectively the less substituted carbon of the epoxide ring to give the more substituted alcohol (eq. *a*, Scheme 6.26).

The reaction displays stereochemistry characteristic of S_N2 reactions and, therefore in a rigid cyclic system an axial alcohol is formed (eq. *b*), while the acid cleavage always gives a diaxial diol derivative.



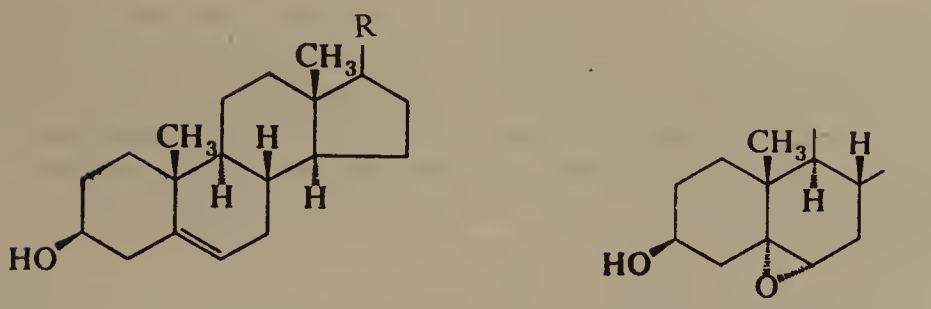
Scheme 6.26

Thus, the two cleavages shown for the epoxide **A**, follow these rules. Reduction with lithium aluminium hydride cleaves the C-4, O bond to yield the axial 3α-ol, the alternate mode of fission would instead give the 4α-ol which would be equatorial.

6.8 *ANTI* HYDROXYLATION OF ALKENES

In unsymmetrical cyclic alkenes, the peracid usually attacks from the less hindered side to yield the epoxide as seen in the case of cholesterol (Scheme 6.27).

When cyclopentene oxide is subjected to acid-catalyzed hydrolysis, water attacks from the side opposite the epoxide ring (S_N2 conditions). The product of the reaction is a *trans*-glycol (*trans*-1, 2-cyclopentanediol). Thus



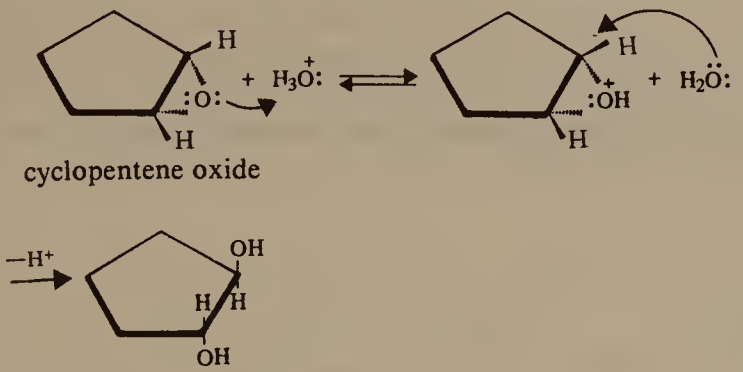
Cholesterol

5α,6α-Oxidocholestan-3β-ol

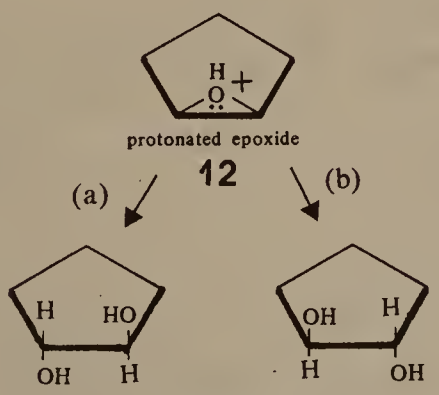
Scheme 6.27

epoxidation followed by acid-catalyzed hydrolysis, affords a method for hydroxylating a double bond (*i.e.*, a method for adding a hydroxyl group to each carbon). This hydroxylation technique, moreover, amounts to a net *anti* hydroxylation, and its mechanism parallels closely the mechanism for bromination of an alkene discussed earlier.

Moreover from this reaction a racemic modification of the *trans,* 1,2-



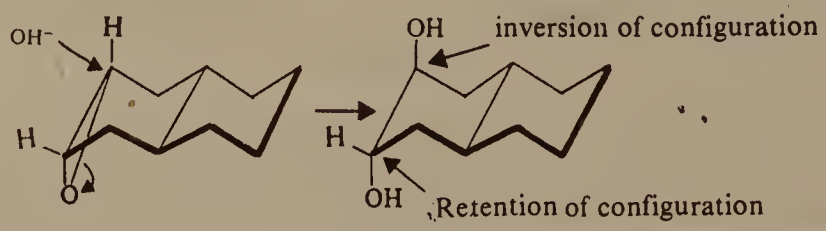
Scheme 6.28



Scheme 6.29

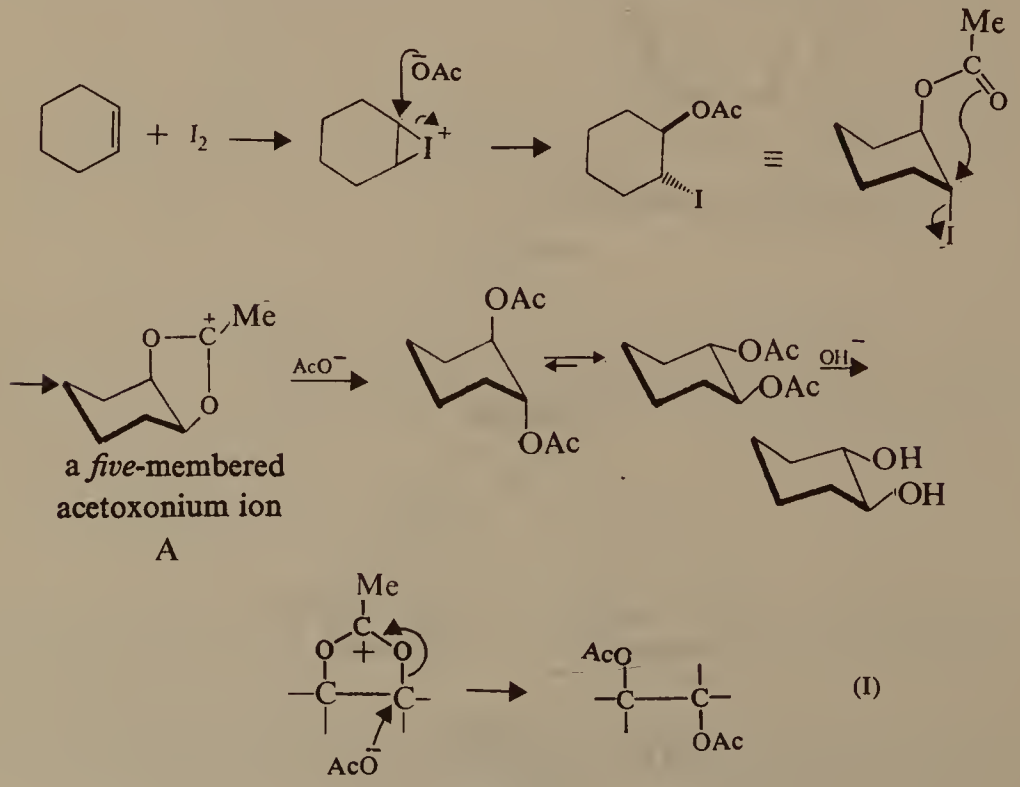
cyclopentane diol results. This is so, because from the symmetrical protonated epoxide **12** (Scheme 6.29), the rate of ring opening from paths (a) or (b) are equal and the enantiomers **13** and **14** are formed in equal amounts.

Like the action of aqueous acid on epoxides, base also gives a 1,2-diol. The product again has the *anti* stereochemistry as a result of the stereospecificity of S_N2-displacements *e.g.*, the ring-opening of epoxides from rigid cyclohexenes yields *trans*-diaxial products.



Scheme 6.30

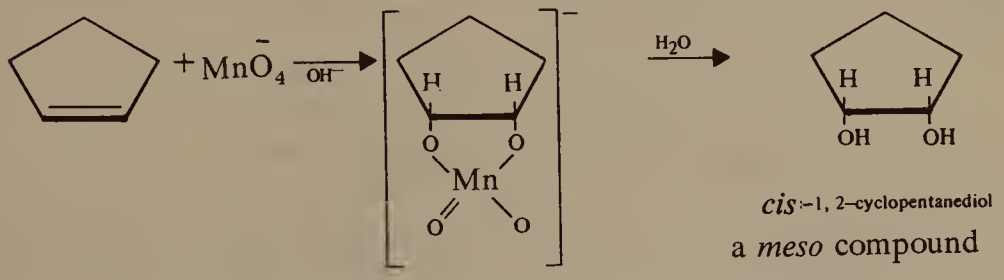
Trans-diols are formed from acetoxonium ion by reaction with a nucleophile *i.e.*, acetic acid under dry conditions. Treatment of an olefin with iodine and silver acetate yields the *trans*-iodo-acetate, by normal *trans*-addition to a double bond. Iodide ion is eliminated under the influence of the neighboring acetoxy group; and the acetoxonium ion **A** (Scheme 6.31) reacts with acetate ion at the alkyl carbon in a S_N2 manner to yield a *trans*-diacetate (eq. I).

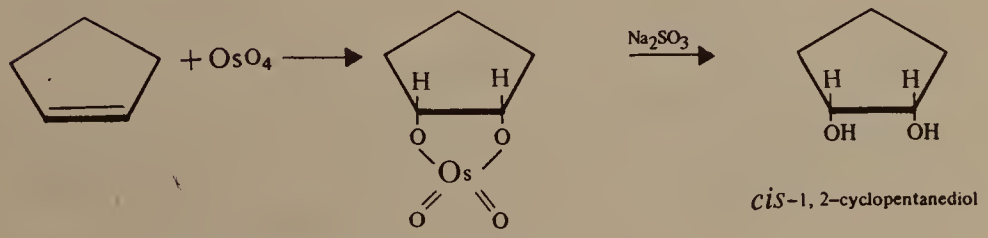


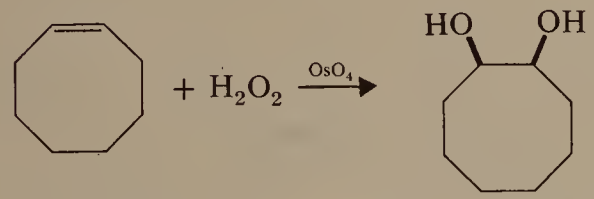
Scheme 6.31

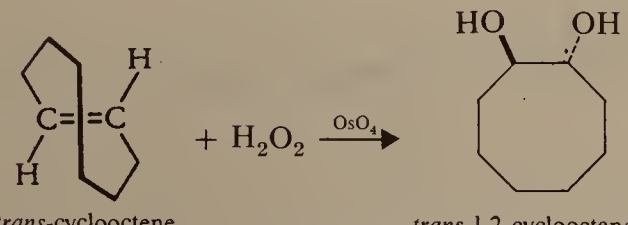
6.9 *SYN* HYDROXYLATION

The best known examples of molecular additions to double bonds are the hydroxylations of olefins with osmium tetroxide or potassium permanganate, which yield *cis*-glycols. The course of these reactions is *syn* hydroxylation. This can be seen, readily, when cyclopentene reacts with cold dilute potassium permanganate (in base) or with osmium tetroxide (followed by treatment with Na_2SO_3). The product in either case is *cis*-1,2-cyclopentanediol (Scheme 6.32). These hydroxylation processes are stereospecific. *Syn* hydroxylation of a cyclic alkene with a *cis* double bond gives a *cis* diol, *e.g.*, like cyclopentene, *cis*-cyclooctene also gives *cis*-1,2-cyclooctanediol. However, if the double bond in the ring has *trans* geometry then *syn* hydroxylation gives a *trans* diol (Scheme 6.32).



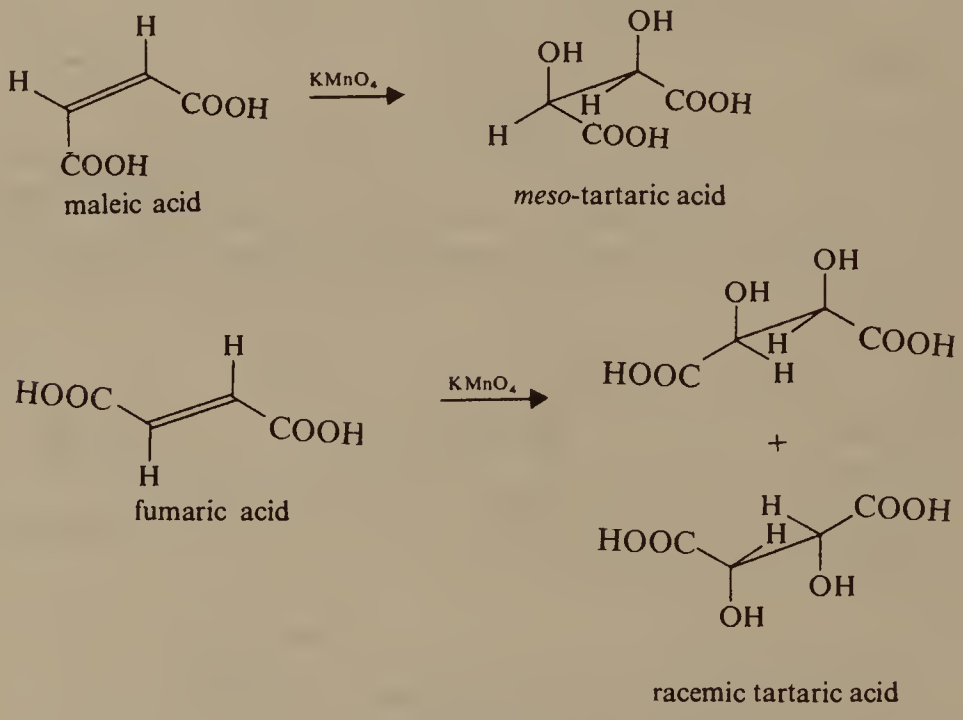




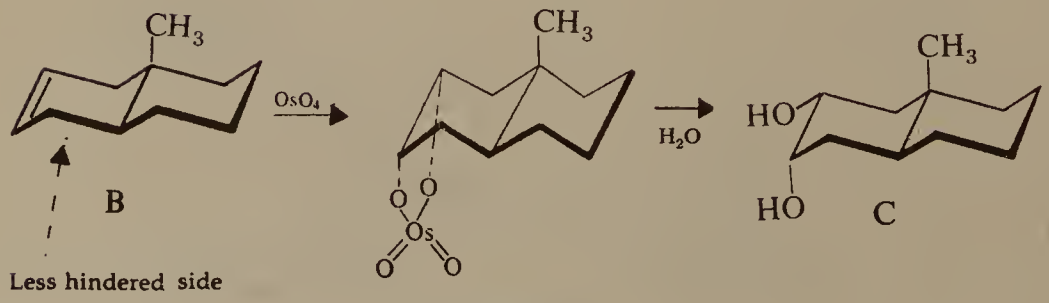


Scheme 6.32

A single product is obtained from this reaction because the product is a *meso* compound. (Addition of OsO_4 from either above or below the plane of the ring produces the same compound). The reason why these reactions give *syn*-addition, in contrast to the *anti*-additions is that both bonds to the olefin carbon atoms are formed in the cyclic intermediate, which is decomposed by fission of the bonds between the oxygen atoms and the metal. In addition of olefins involving a cyclic intermediate, a *trans* product is formed when the intermediate on the other hand is cleaved by bimolecular attack which causes inversion at the point of attack to give *trans* product. Another remarkable example to demonstrate *syn* hydroxylation is the oxidation of maleic acid with permanganate to give *meso* tartaric acid and of fumaric acid to give racemic tartaric acid. The formation of a particular racemic acid is possible only if the added hydroxyl groups are *cis* to each other *i.e.*, the overall process is *syn*.



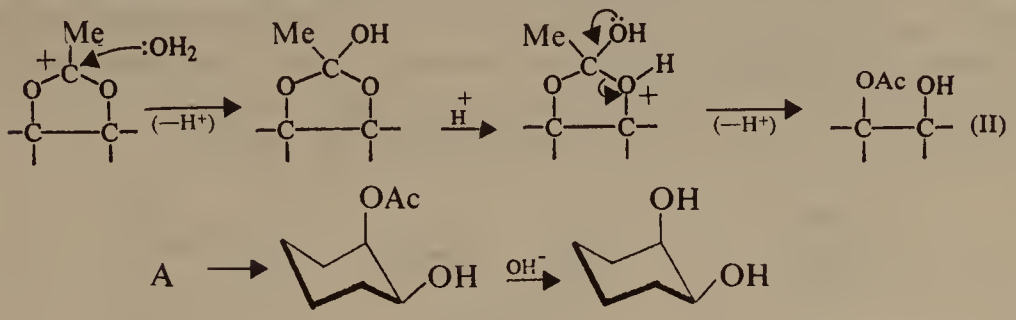
Scheme 6.33



Scheme 6.34

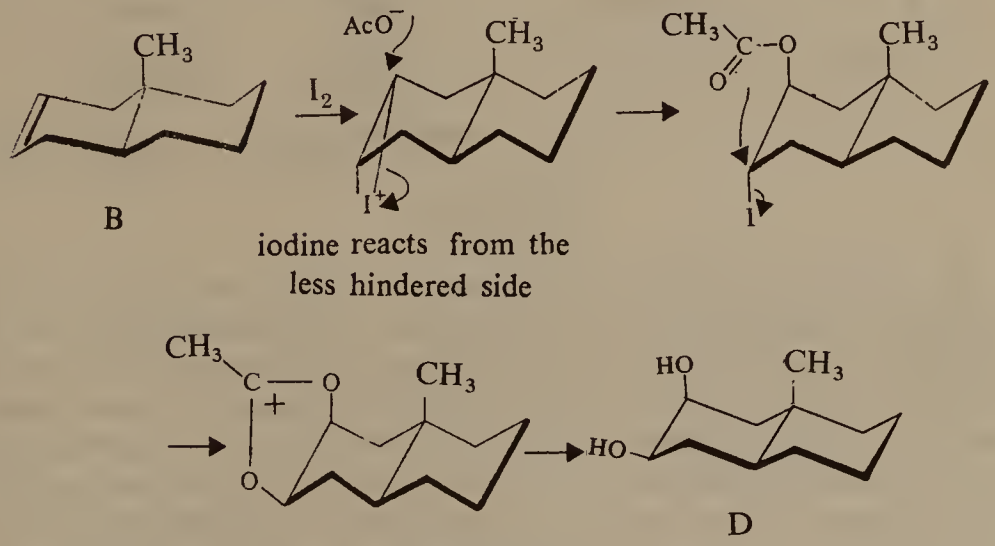
The reagent osmium tetroxide and potassium permanganate attack rigid cyclic systems (Scheme 6.34) from the less hindered side to afford the more stable of the two possible *cis*-diols as compared to the diol formed from such a system with iodine and silver acetate under wet conditions.

The cyclic acetoxonium ion **A** is opened by a nucleophile *i.e.*, water at the acetoxy-carbon atom to yield ultimately a *cis*-hydroxyacetate (eq II, Scheme 6.35). Thus unlike the *trans* diol formed from **A** with acetic acid under dry conditions, in the presence of water this ion yields a *cis* diol.



Scheme 6.35

Stereochemistry of this reaction forces the formation of less stable *cis*-diol isomer **D** from **B** (Scheme 6.36) as compared with **C** obtainable from the reaction of **B** with osmium tetroxide.



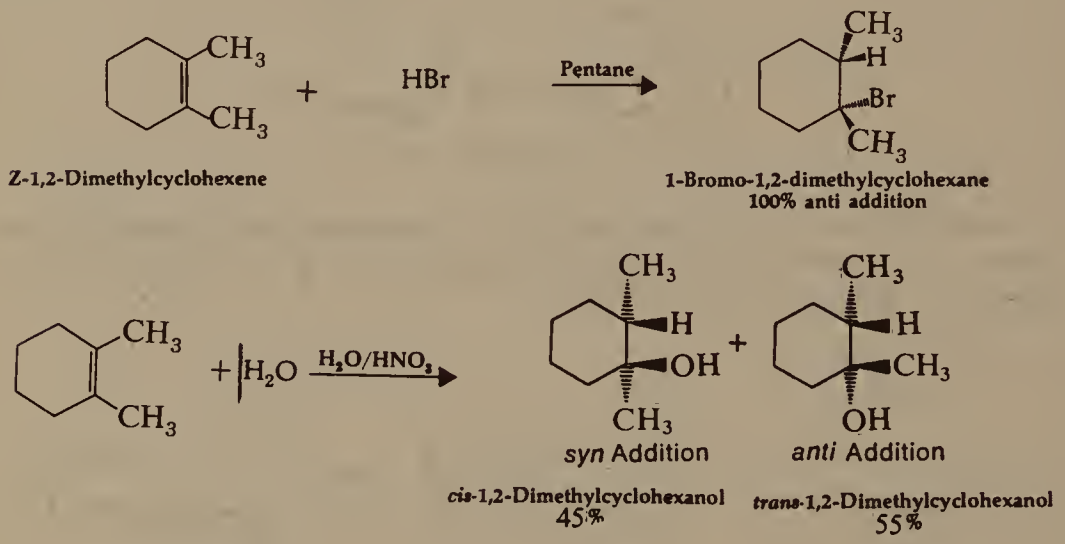
Scheme 6.36

6.10 STEREOCHEMICAL COURSE OF ADDITION OF ELECTROPHILES OTHER THAN Br^+

Reagent-substrate interaction makes an important contribution in some way to the configurational stability during addition reactions. This conclusion has a base in the fact, that several of these reactions are not only

stereoselective, but some are even stereospecific. The addition of HX to alkenes. Where X is normally a halogen or —OH is mostly *anti*, however the reaction is not so stereospecific as found for halogen addition.

During electrophilic additions in which the electrophile is not Br^+ or its carrier, varying results have been observed. Cyclic iodonium ions suffer from less competetion than open cations when compared with bromonium ions. The attack by I^+ therefore, usually leads to *anti* addition. When proton is the electrophile, the possibility of a cyclic intermediate is reduced. This is so, because hydrogen is not that capable to stabilize the positive charge as the halogens. Reactions of predominant *syn, anti* and non-stereoselective addition of HX are known. Thus, predominant *anti* addition is observed on treatment of *Z*-1,2-dimethylcyclohexene with HBr, while addition of water affords equal amounts of *cis* and *trans* alcohols (Scheme 6.37).

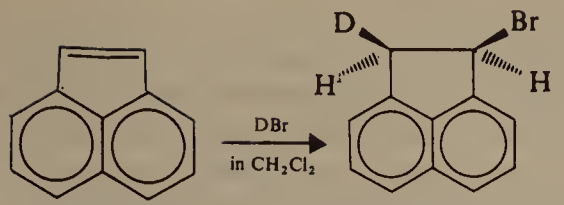


Scheme 6.37

The addition of DBr to acenaphthalene on the other hand, gives a predominant *syn* addition[2]. The stereoselectivity of hydrogen halide addition is therefore, identical to the addition of halogens *i.e., anti* addition generally predominates with simple non-conjugated cyclic alkenes. In contrast to this, both *anti* and *syn* additions are observed with several conjugated double bonds (eq. 11, Scheme 6.38). An interesting case of electrophilic *syn* addition is also observed with *trans*-cyclooctene. This compound gives *trans*-1,2-disubstituted cyclooctanes. The preference for *syn* addition is due to the inaccessibility of the rear face of the double bond which is shielded by the chain of methylene groups of the eight membered ring (Sec 1.22).

The proposed mechanism for the addition of hydrogen halides to alkenes involves a protonium ion as the initial species to explain *anti* addition. This ion (Scheme 6.39) has an unstable 3-membered ring like bromonium ion or may represent a loose complex of the proton with the *pi* electrons.

It has been shown that the rate determining step involves one molecule of

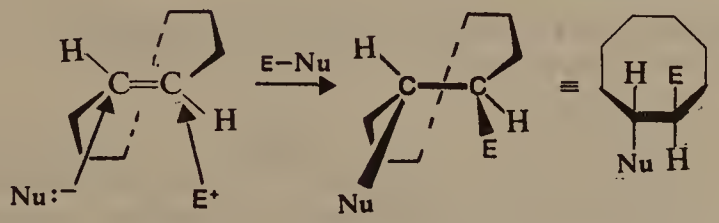


acenaphthylene predominant syn addition

$C_6H_5CH{=}CHCH_3 + DCl \xrightarrow{CH_3NO_2} C_6H_5\underset{Cl}{C}HCHDCH_3$ **11**

E-1-Phenyl-1-propene

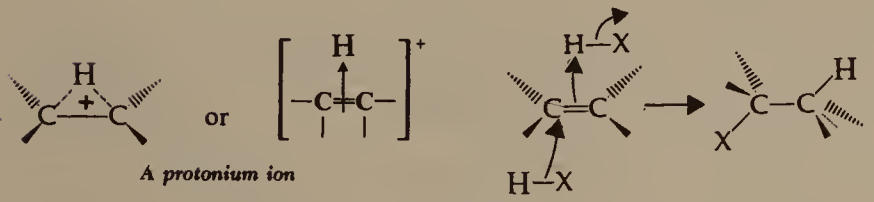
1-Chloro-2-deuterio-1-phenylpropane
65% anti addition
35% syn addition



trans-cyclooctene *trans*-1,2-disubstituted cyclooctanes

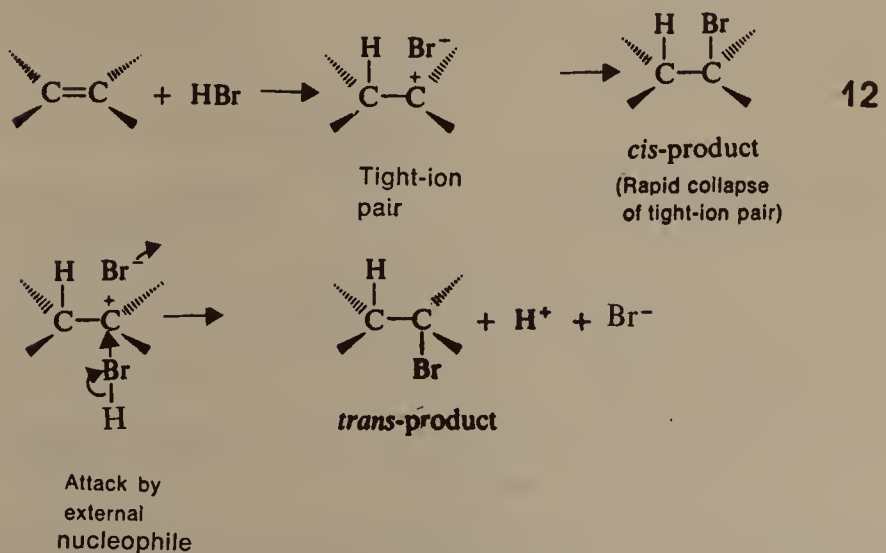
Electrophilic *syn* addition

Scheme 6.38



A protonium ion

Scheme 6.39



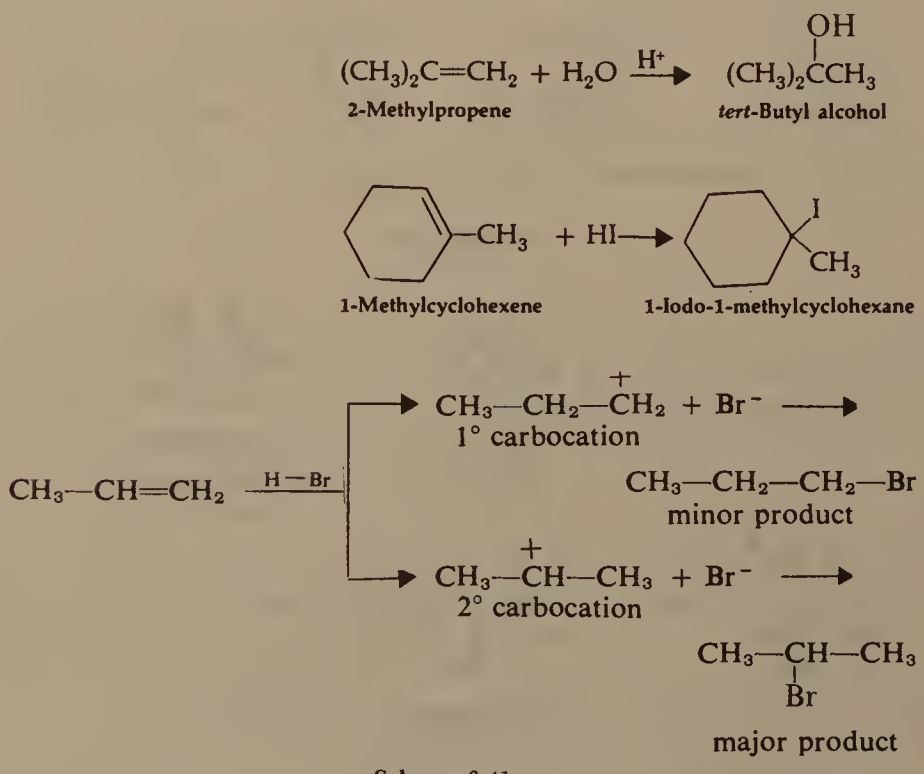
12

Scheme 6.40

alkene and two molecules of the hydrogen halide. The kinetics are termolecular under the reaction conditions when the HX is expected to be unionized. To account for *anti* addition, it is suggested that each molecule of HX attacks from the opposite face of the double bond to provide a nucleophile and an electrophile. One suggestion advanced to explain the *syn*-and *anti*-addition is the formation of a "tight ion-pair" (eq. 12, scheme 6.40), in which the nucleophile is so closely associated with the carbocation that it attaches itself at the cationic centre without letting the bond to undergo rotation. This leads to *syn* addition to give a *cis*-product. The ion-pair may also be attacked by a second molecule of the acid to result in *anti* addition to yield a *trans*-product.

6.11 ADDITIONS TO UNSYMMETRICAL ALKENES (MARKOVNIKOV RULE)

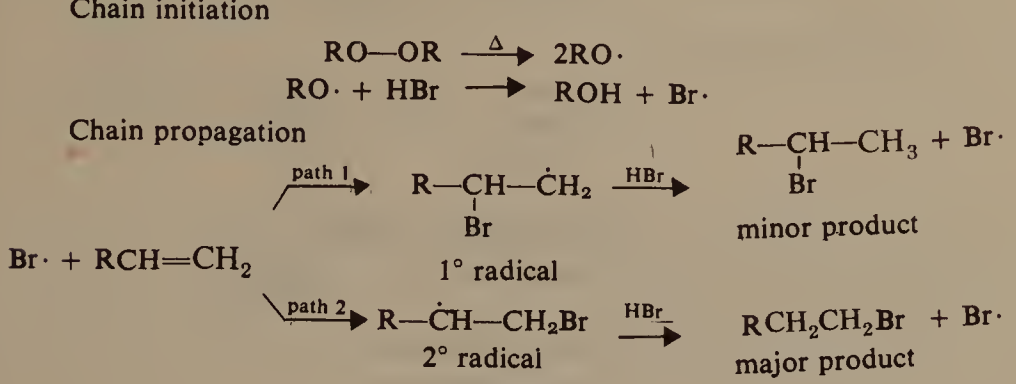
When one considers the acid catalysed addition of water to 2-methylpropene and HI to 1-methylcyclohexene (Scheme 6.41), it is found that the electrophile adds to the double bond so as to form the more stable carbocation. Since addition of the electrophile is the rate-controlling step, one states that the more stable carbocation intermediate forms *via* the energetically more favorable transition state. This forms the modern statement of the Markovnikov rule.



Scheme 6.41

The rule applies only to ionic additions. The free radical addition of HBr (presence of peroxides) involves the addition of the bromine radical to the

olefin in the first step of the reaction which proceeds to afford the more substituted and thus the more stable radical and is termed as anti-Markovnikov addition to an olefin (Scheme 6.42).



Scheme 6.42

6.12 ADDITION OF CARBENES (METHYLENE) TO ALKENES

(A) Spin Multiplicity of Divalent Carbenes

Carbenes are highly reactive, electrophilic divalent carbon species with two unshared electrons. The spin of an electron about its own axis may assume a value of either + 1/2 or – 1/2. The spin multiplicity of a carbene intermediate is given by (2S + 1) where S is the sum of the spin of the two unshared electrons. If both unshared electrons occupy the same orbital, the spins of the two electrons must be paired (*e.g.*, ↑↓ CH_2), and the carbene is said to be in the singlet state as S = (+ 1/2) + (— 1/2) = 0 and 2S + 1 = 2(0) + 1 = 1. On the other hand, if the two unshared electrons occupy two different orbitals; their spins are unpaired (*e.g.*, ↑↑CH_2) and the carbene is said to be in the triplet state as S = (+ 1/2) + (+ 1/2) = 1 and (2S + 1) = 2(1) + 1 = 3. It is generally believed that carbenes in the triplet state are more stable than those in the singlet state.

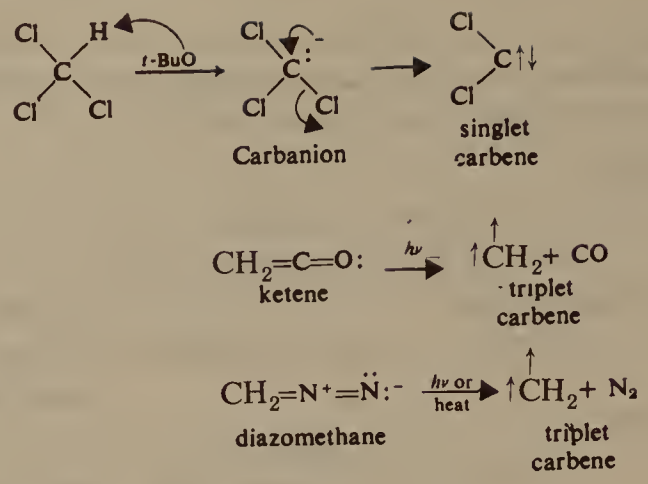
(B) Generation of Divalent Carbon Species

The generation of carbenes may be accomplished in a number of ways, but it is usually carried out in the presence of the intended olefinic reactant during the synthesis of cyclopropane derivatives.

It is generally believed that carbenes generated by photolysis are initially formed as singlet species and will add stereospecifically to liquid olefins. However, in the gaseous phase with low olefin concentration, such species may lose energy to become the more stable triplet species through collision with the container wall or with inert gas molecules (*e.g.*, N_2).

(C) Addition of Singlet and Triplet Methylene to an Olefin[3]

The triplet species add to a gaseous olefin under high dilution in a

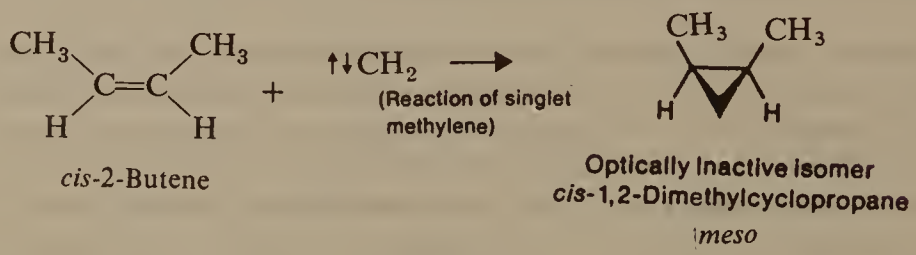


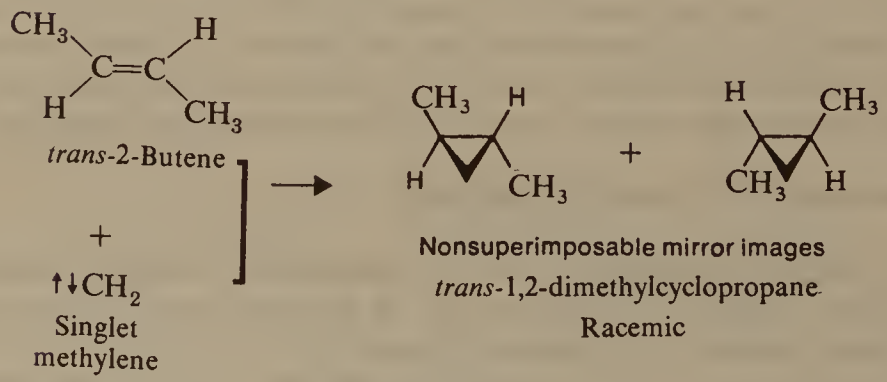
Generation of carbene

Scheme 6.43

nonstereospecific manner.

Singlet methylene reacts with an alkene stereospecifically, *e.g.*, *cis*-2-butene and its *trans* isomer react as shown in scheme 6.44.

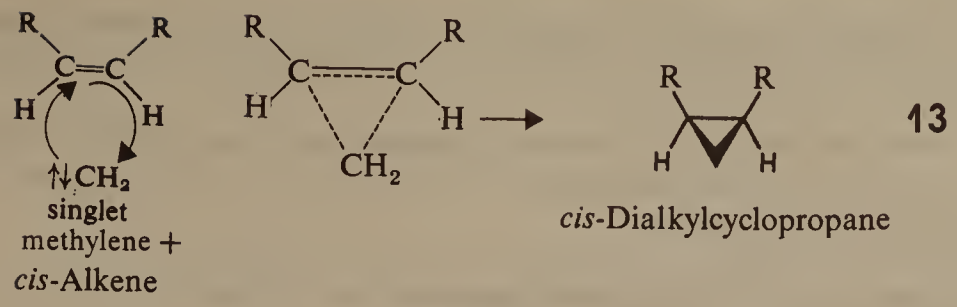




Scheme 6.44

However, when triplet methylene reacts with either *cis*-or *trans*-2-butene the reaction is nonstereospecific, each isomer yielding a mixture of *cis*-and *trans*-1,2-dimethylcyclopropanes.

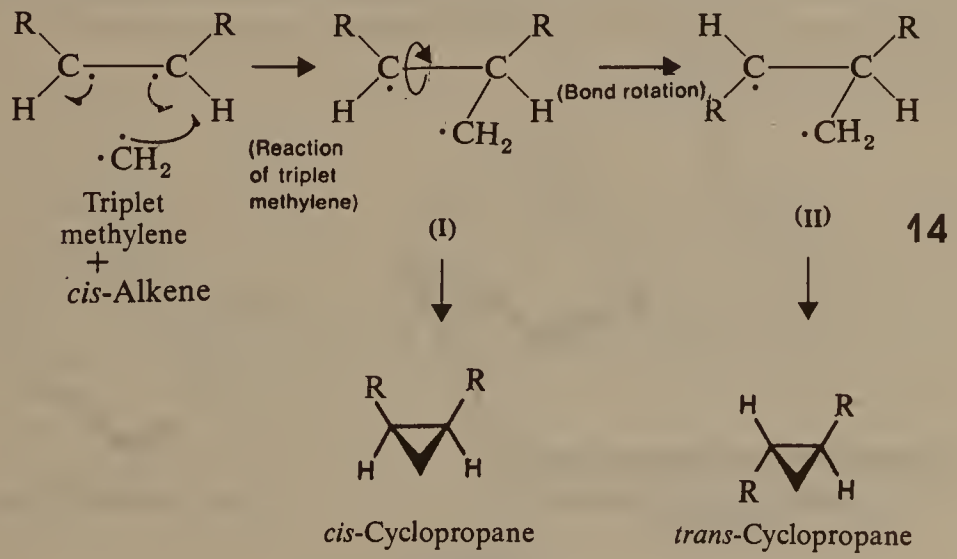
The difference in this stereochemical outcome is due to the fact that the mechanisms of the two reactions are not the same. Singlet methylene adds to the double bond in one step, bond formation between the carbon of singlet methylene and the carbons of the alkene occurs at the same time. Thus, the



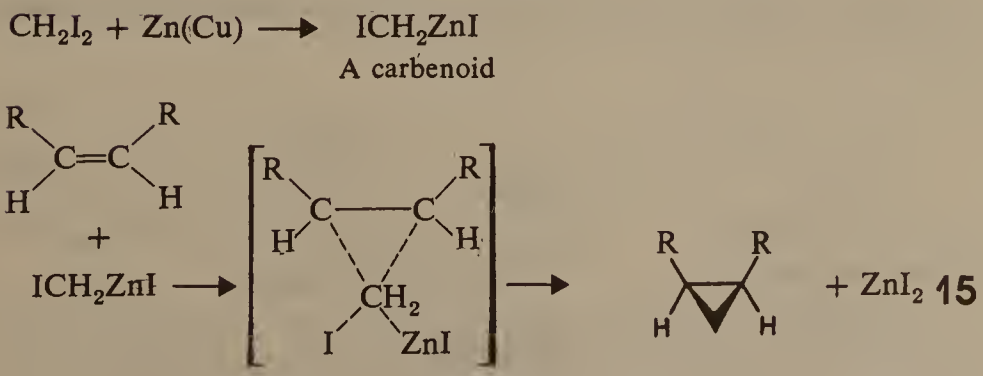
Scheme 6.45

stereochemistry of the alkene is preserved in the product (eq. 13, Scheme 6.45).

The electrons in triplet methylene are not paired, therefore it reacts in a stepwise process (eq. 14, Scheme 6.46). Triplet methylene, a diradical itself reacts with the alkene to afford an intermediate biradical in the form of conformation (I). The biradical (I) has sufficient lifetime to allow rotation of groups joined by single bonds to afford another conformation (II). The ring closure on (I) and (II) yields diastereomerically different cyclopropanes.



Scheme 6.46



Scheme 6.47

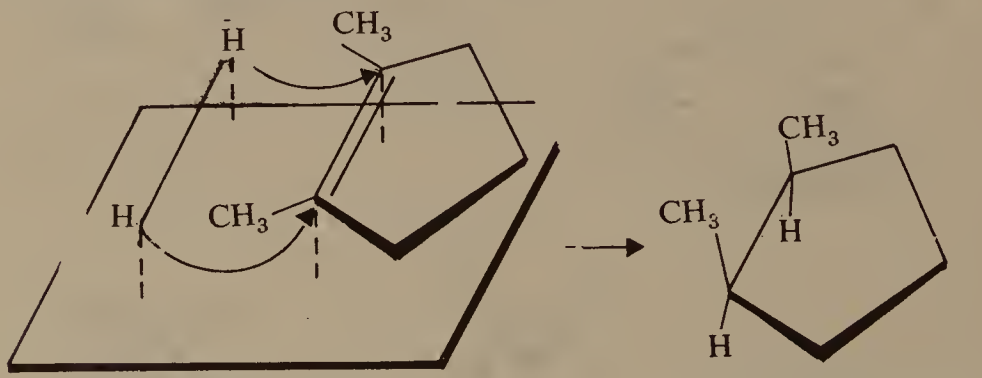
Stereospecific addition has also been observed in reactions involving complex carbenes which are not free species, the carbenoids (eq. 15, Scheme 6.47).

In this addition diiodomethane and zinc-copper couple are stirred together with an alkene. The diiodomethane and zinc react to yield a carbene like species called a carbenoid.

6.13 HYDROGENATION OF ALKENES AND ALKYNES

(A) Catalytic and Metal Ammonia Reductions

Hydrogenation of an olefin in the presence of a catalyst (*e.g.*, Ni, Pt, Pd) takes place under varying conditions of heat and pressure. The catalyst is believed to provide a surface to form a complex with the olefin and at the same time promote the activation of the adsorbed hydrogen molecule. Under the reaction conditions, the molecular hydrogen splits into hydrogen atoms which then add simultaneously to the olefin and form two new C-H bonds on the same side of the ring. This type of addition is called *syn* addition and a *cis*-disubstituted cycloalkane will be obtained if the reactant is a 1,2-disubstituted cycloalkene.

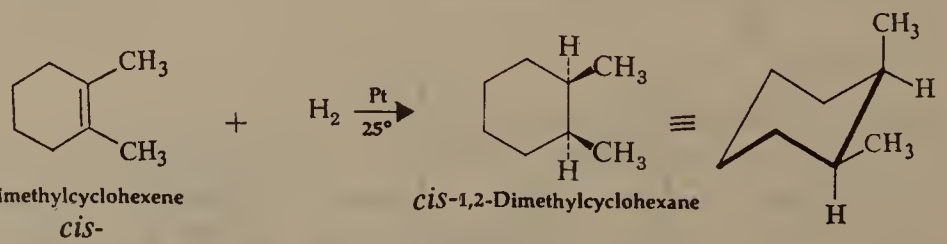


Hydrogen and alkene complexed to catalyst surface

a *syn* stereospecificity

Scheme 6.48

For example, 1,2-dimethylcyclohexene gives *cis*-1,2-dimethylcyclohexane as shown below:



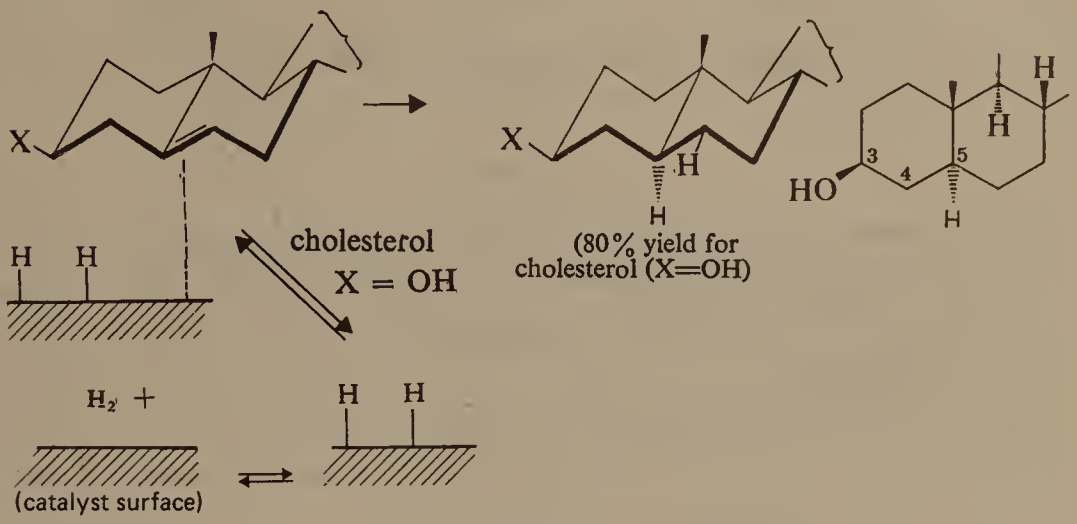
Z-1,2-Dimethylcyclohexene
cis-

cis-1,2-Dimethylcyclohexane

Scheme 6.49

In rigid ring systems, the direction of addition is from the less hindered

side, *e.g.*, cholesterol gives mainly *trans* ring-junction on reduction, since the angular methyl group hinders the fit of the catalyst on the opposite side of the double bond.

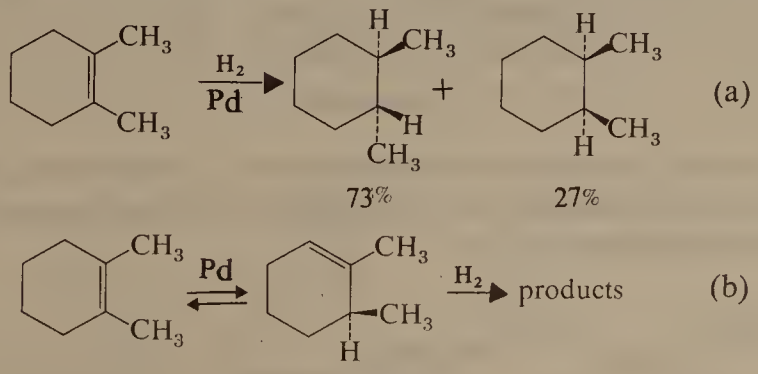


Scheme 6.50

However, when the substituent **X** is axial, the fit to the catalyst is hindered on both sides and reduction gives a mixture of *cis* and *trans* decalins in comparable amounts.

Although *syn* addition is the general rule, *anti* addition is sometimes observed, (eq. a, Scheme 6.51). *Anti* addition probably results when double bond isomerization occurs more rapidly than hydrogenation. In the case shown below, it has been established that isomerization precedes reduction (eq. b). Palladium is particularly prone to catalyze double bond isomerization. Platinum, rhodium, or iridium should be used, if isomerization is a problem.

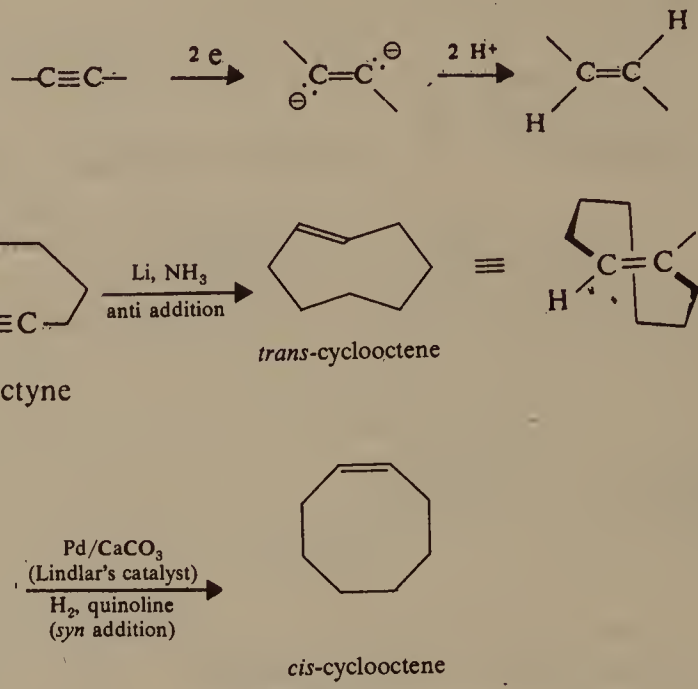
Electrons are transferred more readily to acetylenes as compared to olefins



Scheme 6.51

(greater reactivity of acetylenes towards nucleophiles). The reagents of choice are the metal-amine and metal-ammonia systems. The reduction is selectively *anti*, since the charges in the dianion optimally assume the configuration in which they are further apart (Scheme 6.52). Therefore, this method is

complementary to the stereospecifically *syn* addition of hydrogen during catalytic methods. Thus, both *cis*- and *trans*-cyclooctene can be obtained from cyclooctyne.



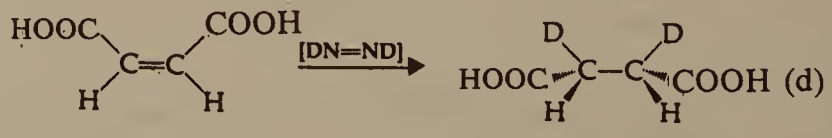
Scheme 6.52

(B) Diimide Reductions

An interesting compound often used for the hydrogenation of carbon-carbon multiple bonds is diimide[4,5], an unstable material which is formed by oxidation of hydrazine (eq. c) or its derivatives. Diimide is generated in the reaction mixture as needed.

Scheme 6.53

Reduction of non-substituted alkenes proceeds most effectively. Deuterated diimide was used to demonstrate that addition of hydrogen proceeds by a *syn* stereochemical pathway (eq. d).

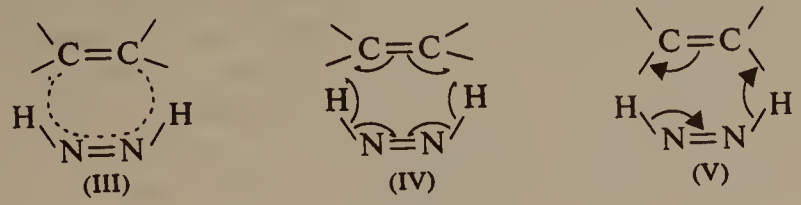


Maleic acid — *meso*-2,3-Dideuteriosuccinic acid

95%

Scheme 6.54

Diimide transfers its two hydrogen atoms *via* a non-polar transition state III (Scheme 6.55) to a symmetrical double (N=N, C=C) or triple bond (C≡C).



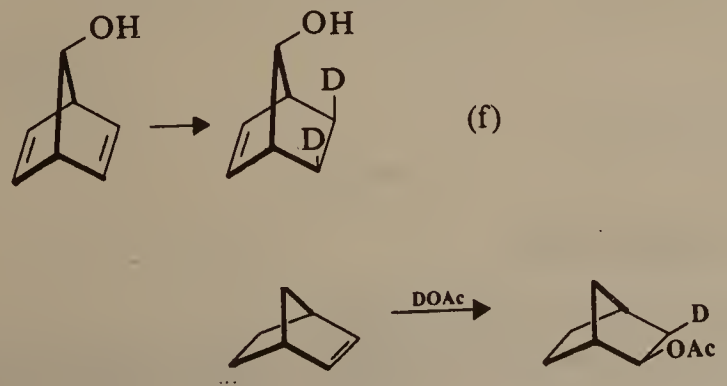
Scheme 6.55

In general diimide does not normally transfer its hydrogen atoms to an unsymmetrical double or triple bond (N=O, C=N, C=O C≡N) or cause hydrogenolysis, even of a labile S—S bond so that the hydrogen atoms are probably transferred as atoms (IV) and not as protons and hydride ions (V). In many cases, diimide attacks the olefin molecule from its least hindered side, which may lead to the thermodynamically less stable hydrogenation product. Thus, α-pinene gives mostly *cis*-pinane (Scheme 6.56) containing an axial methyl group.

α-pinene

Scheme 6.56

The driving force for the diimide reduction is the greater stability of the nitrogen molecule compared with the system —N=N—. However, several 7-substituted norbornadienes react with dideuterodiimide in such a way that the hindered double bond is attacked, and that too from the hindered *exo* side (eq. f, Scheme 6.57). The electron donating effect of the oxygen atom of the 7-substituent can play a part in stabilizing the N=N bond of the transition state involving an *exo* approach, but not an *endo*. Stereochemical orientation and preferential approach of the reactants to the *exo* side of the molecule in the norbornane derivatives has already been presented (Sec. 4.15,B).



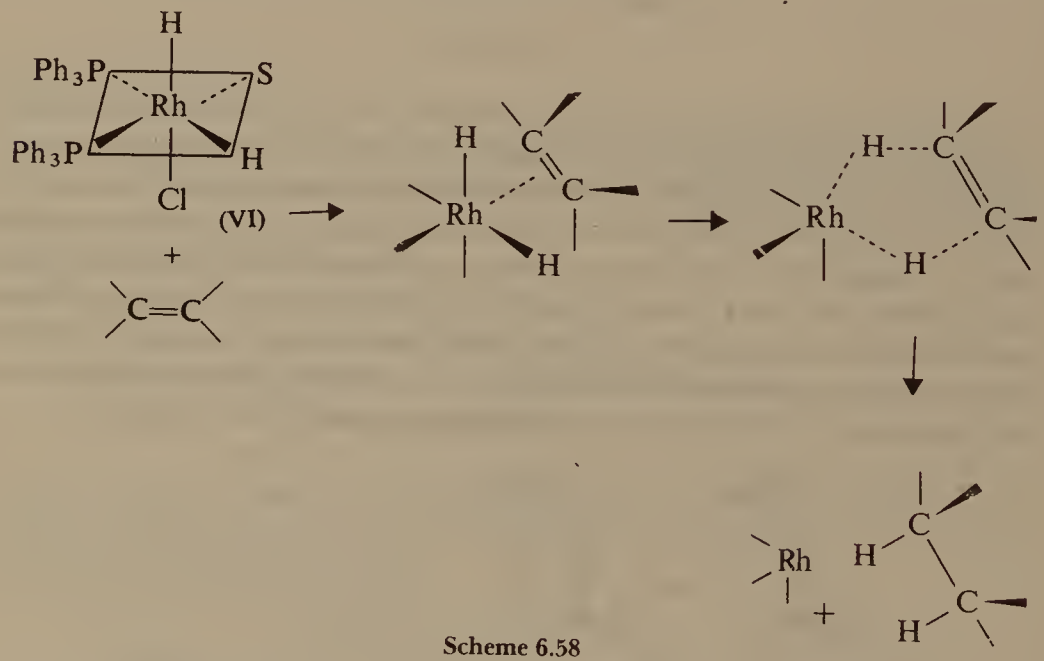
Scheme 6.57

It may suffice to mention here that during *anti* addition to a cyclic substrate, the initial attack by the electrophile is also from the less hindered side. However, several electrophilic additions to norbornene and similar strained bicycloalkenes are *syn* additions. The attack, is always from the *exo* side. When the *exo* side is blocked by substituents in the 7 position, *endo* attack predominates. Thus, 7,7-dimethylnorbornene undergoes *syn-endo* epoxidation and hydroboration. However, addition of DCl and oxymercuration of C-7 methyl substituted norbornene occurs *syn-exo* in disregard to the presence of the methyl groups at C-7.

(C) Homogeneous Hydrogenation

In this technique[6], hydrogen is activated not by chemisorption on the surface of the metal catalyst but by its incorporation into the co-ordination sphere around the metal atom, often of the group VIII.

Cis dihydridorhodium species $RhCl(H_2)(PPh_3)_2$ are formed reversibly when a solution of tris (triphenyl phosphine) chlororhodium is exposed to hydrogen gas. The active species (VI, Scheme 6.58) has two metal-hydrogen bonds, with a solvent(s) molecule occupying the last octahedral position. The olefin to be reduced displaces the solvent molecule. A stereospecific *syn* transfer of hydrogen atoms is then supposed to occur *via* a transition state similar to that involved in diimide reductions.

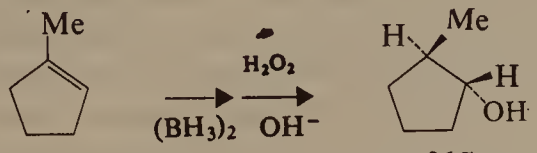


Scheme 6.58

6.14 HYDROBORATION

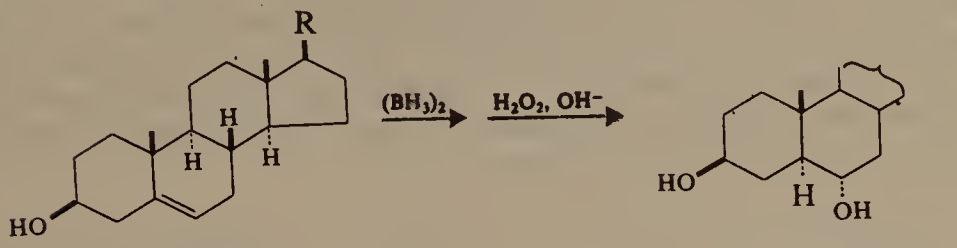
Hydroboration[7] involves addition of BH_3 to the double bond (or, in following stages, BH_2R and BHR_2), with hydrogen becoming attached to one doubly-bonded carbon, and boron to the other. The alkylborane can be oxidised. In

the process the boron is replaced by —OH. The hydroboration-oxidation process, therefore, gives products corresponding to *anti*-Markovnikov addition of water to the carbon-carbon double bond. The stereochemistry of the hydroboration-oxidation involves overall *syn* addition as seen in the following examples.



86%

1-methylcyclopentene *trans*-2-methylcyclopentanol

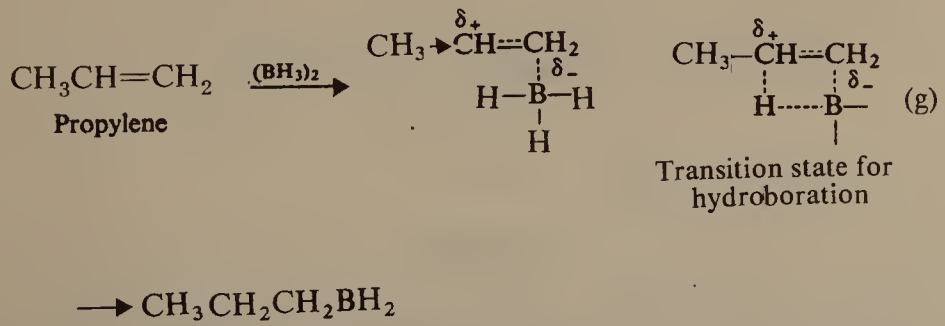


Cholesterol Cholestane-3β, 6α-diol

Scheme 6.59

We have seen (Sec. 1.20, B, b) that the sequence involving hydroboration of alkenes to yield alkyl boranes followed by oxidation and hydrolysis to afford alcohols involves the migration of an alkyl group with its electron pair from boron to oxygen. The reaction is promoted by the addition of a nucleophile (peroxide anion) to boron and proceeds with retention of configuration in the migrating group.

There is a vacant orbital on boron and thus, it acts as an electrophile to attack the π electrons of an alkene. In accordance with the Markovnikov rule the positive charge develops on that unsaturated carbon which is best able to support it and the intramolecular hydride shift completes the hydroboration process (eq. g, Scheme 6.60).



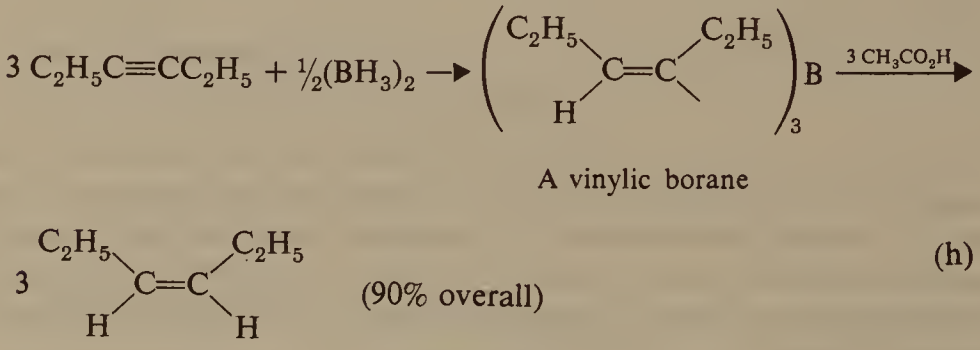
Scheme 6.60

The mechanism is probably one-step, cyclic four-centre one. The addition in hydroboration has been shown to be stereospecific and *syn* with attack

occuring from the less hindered side *i.e.*, oxygen atom is introduced at the less hindered side (as also seen in the case of α-pinene, Sec. 1.20B, b) and bridged systems (Sec. 4.15B). Since, no free carbocation is involved, the rearrangement in the alkene is not expected. The role of an organoborane in the synthesis of optically active compounds from inactive *Z*-olefins with considerable specificity has been described in Sec 1.20 B, b. Migration of alkyl groups from boron to electron deficient nitrogen and carbon leading to the synthesis of a variety of compounds has been presented in Sec. 8.1, d.

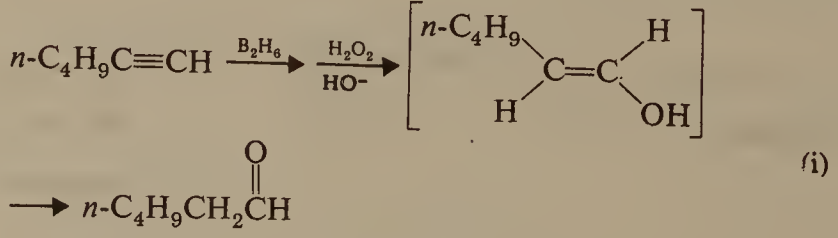
Hydroboration of alkynes is a useful process for the synthesis of several types of compounds. Diborane reacts with alkynes at 0° to produce the intermediate trivinylborane.

The vinylboranes, like alkylboranes display several useful reactions. They undergo protonolysis to give the resulting alkene when treated with acetic acid. Protonolysis involves replacement of boron by the hydrogen of the carboxylic acid with retention of configuration. The overall process of hydroboration-protonolysis is, therefore, a method for *syn* hydrogenation of an alkyne to an alkene (eq. h, Scheme 6.61).



Scheme 6.61

The C—B bond of a vinylborane can also be cleaved with alkaline hydrogen peroxide (oxidation). The initial product is a vinyl alcohol that rearranges quantitatively to the corresponding aldehyde or ketone (eq. i, Scheme 6.62).



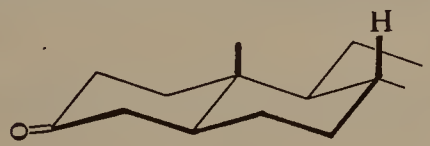
Scheme 6.62

The overall effect of hydroboration-oxidation is that of hydration of the triple bond and with terminal alkynes, aldehyde is formed (anti-Markovnikov hydration) whereas with direct H_2SO_4-$HgSO_4$ hydration ketone is the product.

6.15 THE STERIC COURSE OF ADDITION REACTIONS TO THE CARBONYL GROUP

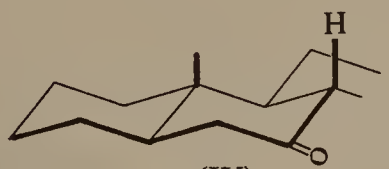
Examples of reductions have been presented (Sec. 4.15, B) where the major product is formed by addition of a hydride ion from the less hindered side of the carbonyl group. When the steric environment is almost comparable on each side of the carbonyl group, as in 2-methylcyclohexanone (4.15, B) the major reduction product is usually the more stable product *i.e.*, an equatorial alcohol as it is usually the major product formed by reduction of a cyclohexanone.

The steric course of the hydride reduction of steroidal ketones has been studied in detail. The factors which control this reduction are the tendency of the reagent to approach from the less hindered side of the molecule, which is normally the α-side to afford β-ols. The greater thermodynamic stability of equatorial alcohols also leads to their preferential formation. The importance of steric factor tends to increase with the bulk of the reagent, $LiAlH_4 < NaBH_4 < LiAlH(OBu^t)_3$ and the extent of hindrance of the carbonyl group at the expense of the thermodynamic factor. On $LiAlH_4$ reduction the relatively unhindered 5α-cholestan-3-one VII, (Scheme 6.63) gives the equatorial 3-ol in almost quantitative yield. However, with the same reagent and under similar reduction conditions, the highly hindered 5α-cholestan-11-one (VIII) gives, in same yield, the axial 11 β-ol. Interestingly, as expected, 5α-cholestan-7-one (IX) with an intermediate degree of hindrance, yields almost equal amounts of axial 7α-ol and the equatorial 7β-ol.



(VII)

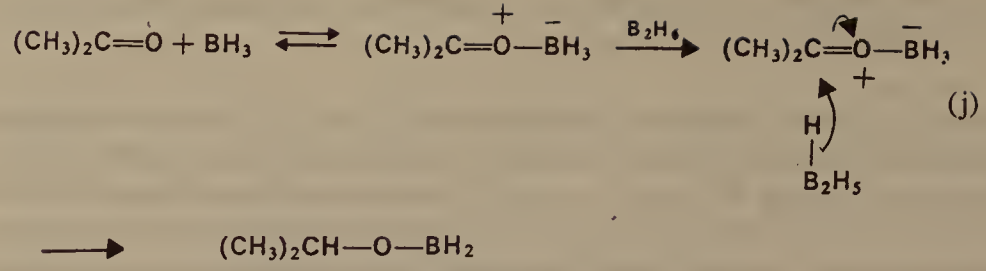
(VIII)



(IX)

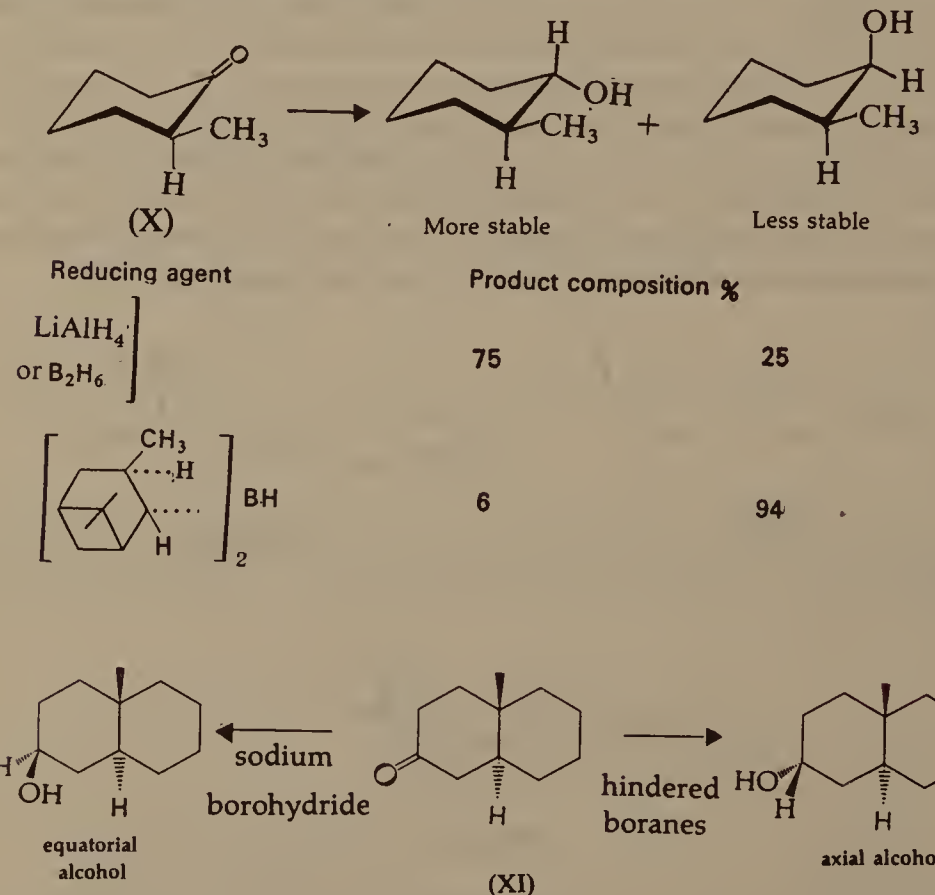
Scheme 6.63

The stereochemical outcome of reduction of ketones with diborane is similar to the results obtained with the metal hydride anions. This reduction, which may be catalyzed with the Lewis acid boron trifluoride, may involve an initial electrophilic attack by borane (BF_3, if this catalyst is used) to form a complex which is then attacked by a molecule of diborane to form an alkoxyborane (eq. J, Scheme 6.64).



Scheme 6.64

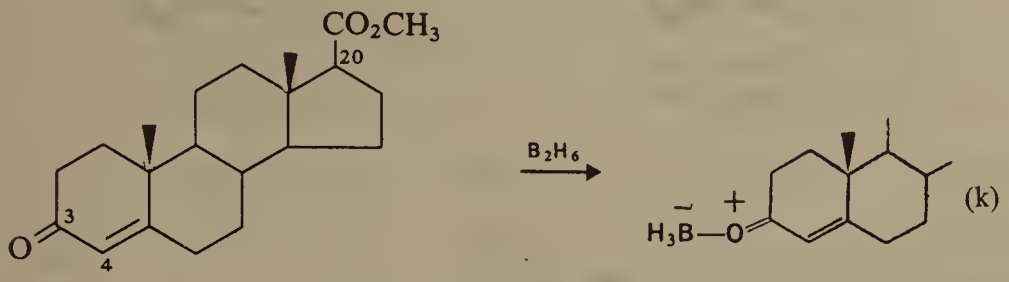
Alkyl substituents increase the steric bulk of the reducing borane (Sec. 1.20 B, b) and attack by such bulky reducing agents tends to occur from the less hindered side of even relatively unhindered ketones such as X (Scheme 6.65) to yield the less stable alcohol epimer. For comparison purposes, outcome of reduction with LAH of (X) is also given, and identical results are obtained during the reduction of compound (XI).



Scheme 6.65

In the reduction of the diketone, progesterone, formation of the presumed intermediate complex (eq. k, Scheme 6.66) would be more favorable at the conjugated carbonyl group where more delocalization of the positive charge is available. It is probably this factor, accompanied by steric hindrance at the

saturated ketone which permits the reduction of the conjugated ketone in preference to the saturated ketone.



Scheme 6.66

Whilst reduction of (X) with the help of complex hydrides like $LiAlH_4$ and $NaBH_4$ gives predominantly hydroxy compounds with the hydroxyl in equatorial position, catalytic addition of hydrogen (PtO_2) particularly in an acidic medium leads to alcohols with the hydroxyl group in the axial position. A new asymmetric carbon is formed in the course of all these additions to the carbonyl group, with the exception of symmetrical ketones as starting materials. If a chiral centre is present in the vicinity of the carbonyl group, so-called assymetric induction effects the course of the addition of nucleophilic reagents (Sec. 1.20 B). The rule has been applied with success to the analysis of the ratio of diastereoisomeric alcohols obtained by the reduction of ketones with the help of complex hydrides, alkali metals and sodium amalgam, and in the course of the addition of organometallic reagents.

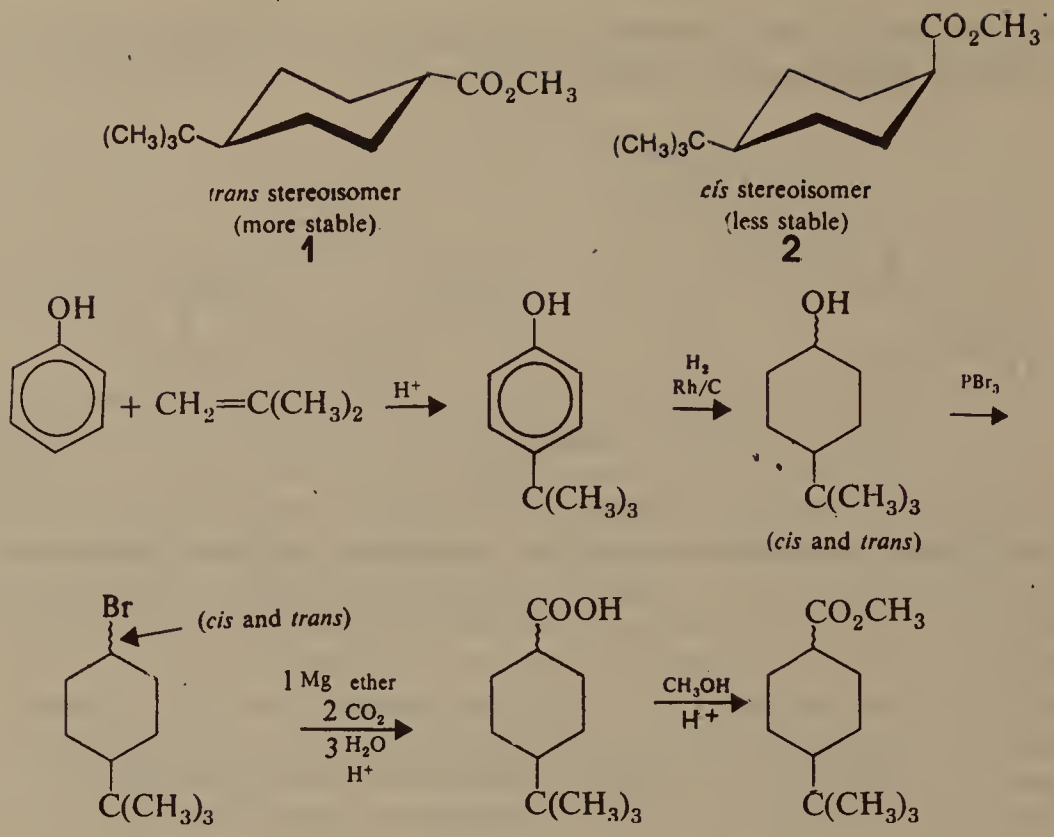
6.16 THERMODYNAMIC AND KINETIC CONTROL

During synthetic sequences one may control the stereochemistry in two ways. *i.e.*, thermodynamically or kinetically

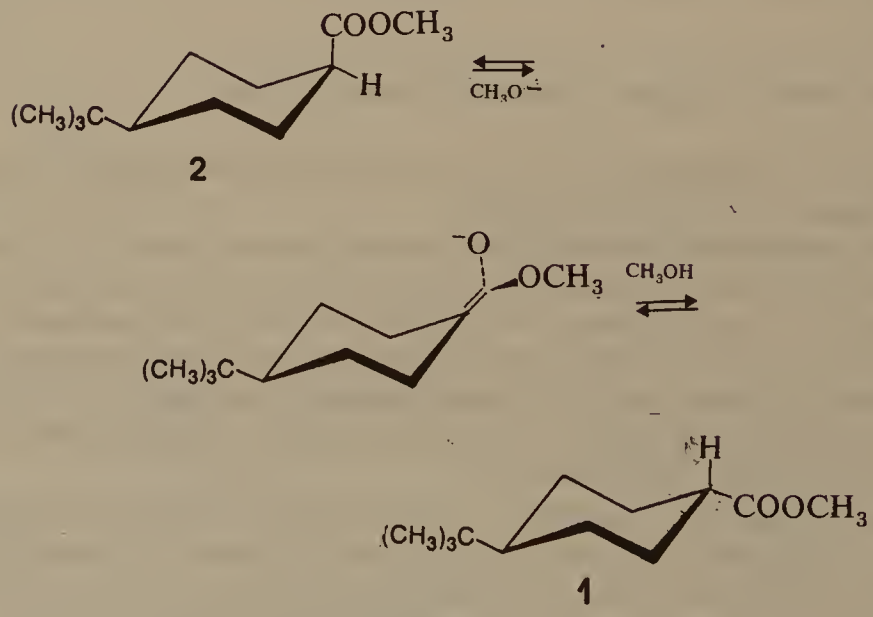
(a) Thermodynamic Control: If the stereoisomer one wishes to synthesize is the comparatively more stable stereoisomer, the synthesis may be carried out in such a way that either the product, or one of its precursors, can equilibrate with its stereoisomers. In methyl *trans*-4-*t*-butylcyclohexane-carboxylate, 1 (Scheme 6.67) both substituents are equatorial, it is, therefore, more stable than its *cis* isomer 2. A synthesis of this compound starting with phenol, is being presented.

The stereochemical outcome of the reactions is often difficult to predict and therefore, a mixture of *cis* and *trans* isomers will be formed. Formation of a mixture of stereoisomers however, does not pose a problem. One may simply equilibrate the product mixture by treating it with sodium methoxide in anhydrous methanol when the more stable *trans* isomer predominates at equilibrium (Sec. 4.12, d).

(b) Kinetic Control: If on the other hand the desired stereoisomer is not the more stable one, one must carry out the synthesis in such a way that the less



Scheme 6.67



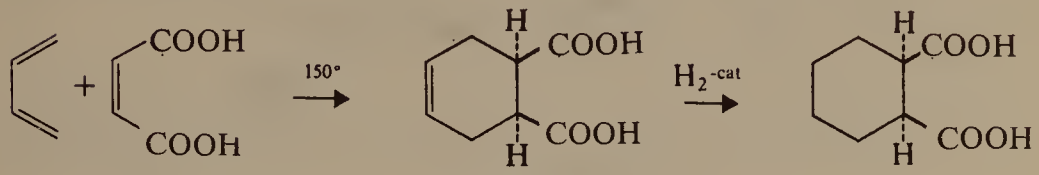
Scheme 6.68

stable stereoisomer is formed at a rapid rate than the more stable stereoisomer. Consider the synthesis of *cis*-cyclohexane-1,2-dicarboxylic acid 4. The desired product is less stable than the *trans* stereoisomer 3, therefore, one must

introduce stereochemistry by a kinetic method. The diacid can be gainfully synthesized by the following route (Scheme 6.69).

trans stereoisomer
(more stable)
3

cis stereoisomer
(less stable)
4



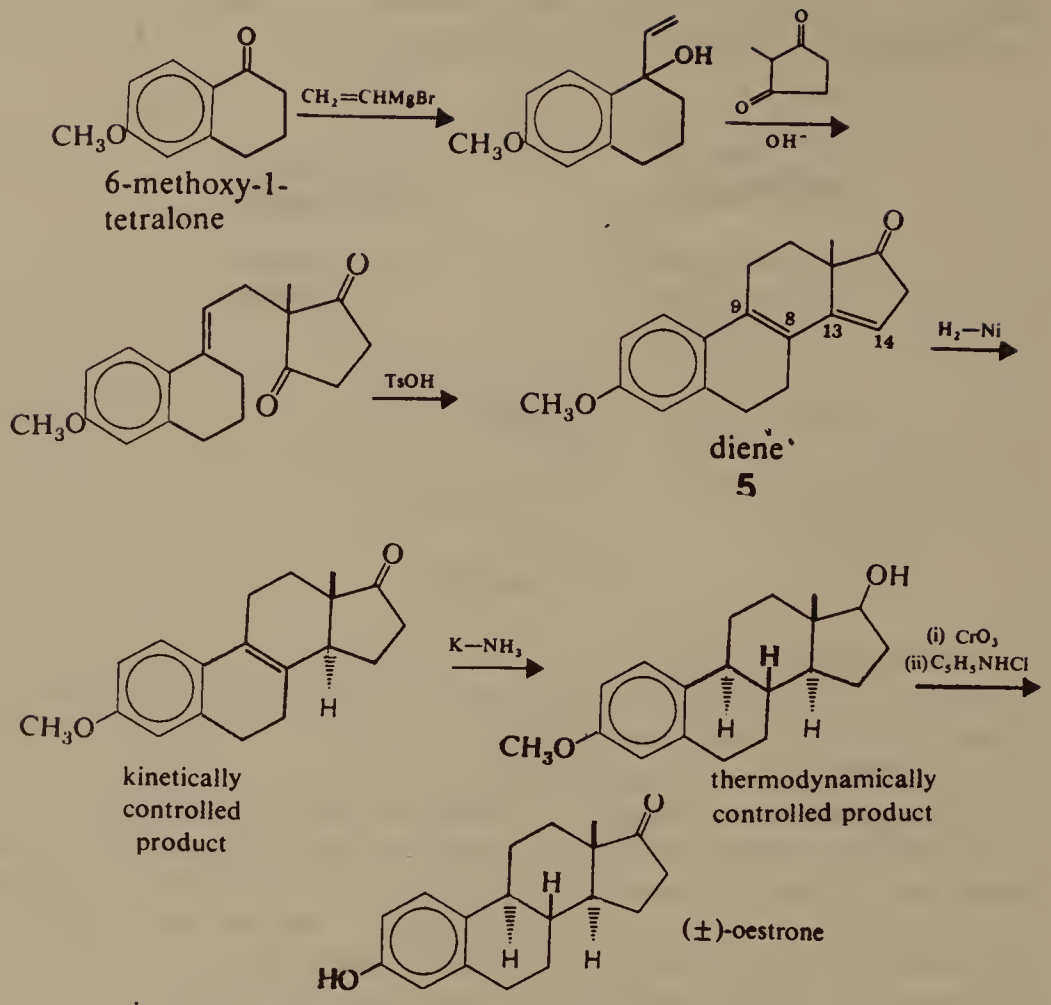
Scheme 6.69

Stereochemistry is established in the Diels-Alder reaction because this pericyclic reaction proceeds *via* an aromatic $4n+2$ transition state, the *cis* isomer is produced much more rapidly compared to the *trans*. Hydrogenation of the double bond yields the desired compound.

(c) Applications in Torgov Synthesis of Estrone: The principles of stereochemical control may be gainfully studied by taking the Torgov synthesis of estrone. Estrone has four chiral centers, therefore in all sixteen stereoisomers are possible. Only the isomer estrone has significant physiological activity. Among the numerous syntheses of estrone, the most efficient is one discovered by the Russian chemist I.V. Torgov.

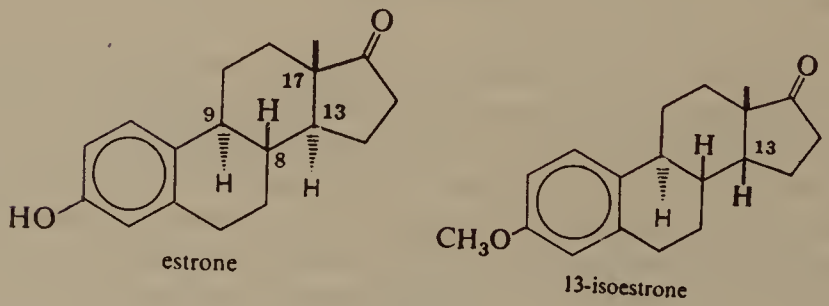
The two double bonds in the diene **5** have to be reduced in such a way that the proper stereoisomer is produced. Estrone, however, is not the most stable of the sixteen stereoisomers; it is 13-isoestrone (Scheme 6.71) which is the most stable. Thus, chirality must be imparted to C-13 by a suitable kinetic method.

Selective catalytic hydrogenation of the diene **5** reduces the double bond between C-13 and C-14 stereospecifically, as it is more easily accessible. The angular methyl group, projects over the β face of the nearly flat molecule and shields this face from the surface of the catalyst. Thus, the less stable stereoisomer is formed and the stereospecificity is achieved by the addition of hydrogen from the α-face. The double bond between C-8 and C-9 may be reduced under conditions of thermodynamic control, as the desired stereochemistry at these centers is the thermodynamically favored. This is gainfully achieved by treating the compound with potassium in liquid ammonia; both the ketone and the double bond are reduced. The important feature is, however, the stereochemistry. The alkali metal-ammonia reducing medium has the important property to yield the most stable reduction product (See 6.13A). The secondary alcohol is oxidized back to a ketone, and the aryl methyl ether is cleaved to give (±) estrone.



(Torgov synthesis of estrone)

Scheme 6.70



Scheme 6.71

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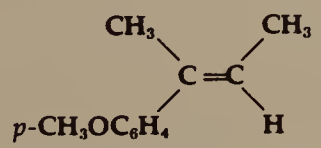
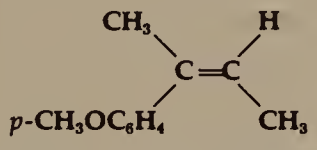
EXERCISES AND PROBLEMS

1. What product will be formed on hydroxylation of oleic acid with osmium tetroxide?
2. What products do you expect by the hydroboration oxidation of *cis*- and *trans*-2-*p*-anisyl-2-butenes *via* the expected *syn* addition? Write the stereostructures of the products.

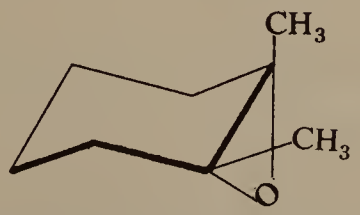


cis-2-*p*-Anisyl-2-butene

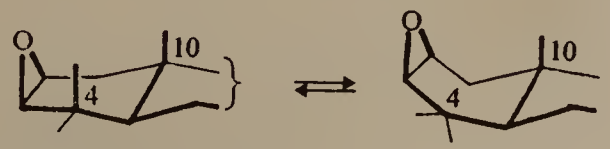


trans-2-*p*-Anisyl-2-butene

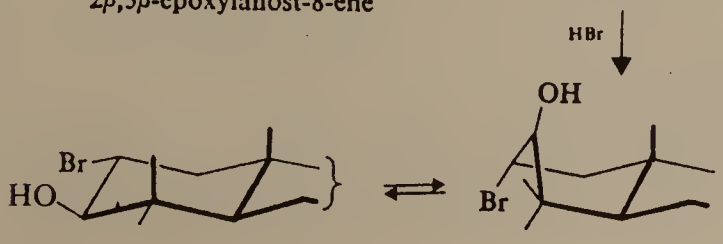
3. Write the conformations of the products of opening of the following epoxide with (a) dilute sulfuric acid and (b) $LiAlH_4$.



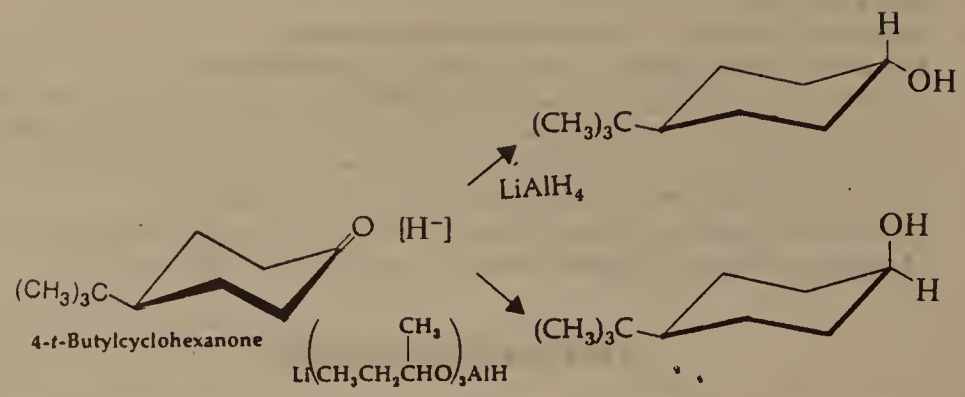
4. Opening of an epoxide in a rigid cyclohexane system leads to *trans*- diaxial products. An exception to this rule is the opening of the following, 2β-, 3β-epoxylanost-8-ene with HBr. Explain.



2β,3β-epoxylanost-8-ene



5. Explain the stereochemistry of the following hydride reduction.



7

DETERMINATION OF RELATIVE AND ABSOLUTE CONFIGURATION

7.1 DETERMINATION OF ABSOLUTE CONFIGURATION

Several chemical reactions are carried out to enable us to ascribe unequivocally a constitutional formula to an unknown compound. Additionally, the correct stereostructures have to be assigned to diastereoisomers and enantiomers. The determination of the relationship between the substance—the chemical individual—and the spatial formula or molecular model, respectively, is usually designated as the determination of the relative or absolute configuration.

In summary, the relative configuration depicts the relationships between the configuration of two chiral molecules. If one interconverts chemically two such molecules, without breaking a bond directly linked to a chiral center, the two molecules then have the same relative configuration. These configurations are independent of the direction of rotation of the plane of polarized light as well as of *R* and *S* designation.

The absolute configuration of a molecule is the specification of *R* or *S* at every chiral center in a molecule (Sec. 2.7).

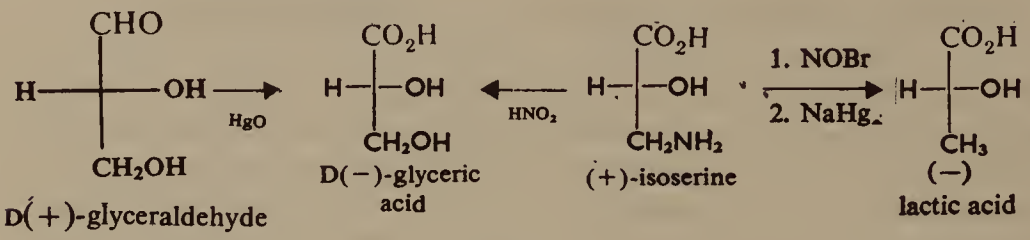
(A) Correlation without Displacement at the Chiral Centre

Until about the second half of this century, it was possible to determine the configuration of a compound only in relation to a similar compound which had been chosen as a standard. The most important standard compound is glyceraldehyde, the (+) -enantiomer of which was assigned the configuration as shown in scheme 7.1. Glyceraldehyde forms the basis of correlation for all carbohydrate compounds first of all, and for a series of further compounds with a chiral carbon of the secondary carbinol type. Similarly, the standard for natural amino acids is the (+) -enantiomer of serine, which was assigned the analogous formula. Standard compounds with an arbitrarily determined configuration were selected in the same way for other types of optically active compounds. The configuration, determined by forming a chemical relationship (correlation) of the compound to the standard, was correct only if the configuration of the standard was correct.

Fortunately, it was proved that the chosen configurations of glyceraldehyde and consequently the configuration of serine, represented the true spatial arrangement, so that all the formulas defined by their relationship to these basic compounds express the absolute configuration of the compounds directly.

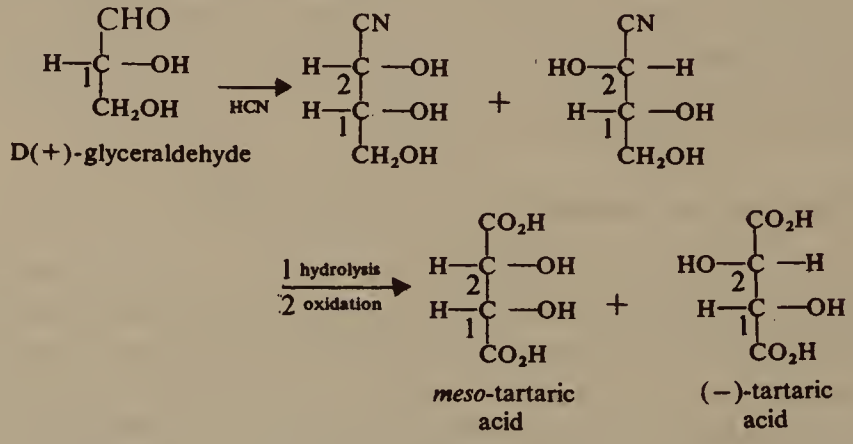
The basic requirement for correlation by means of chemical reactions is that no bond joined to the chiral centre is ever broken. A determination of the configuration complying with this basic requirement is generally accepted as fully valid. The greater the stability of the chiral atom, the larger the number of changes one may carry out in another part of the molecule.

The configuration of glyceric acid obtained by the oxidation may be derived directly from the standard glyceraldehyde. The acid may then be related in two steps with lactic acid, thus, determining the configuration of the latter as well.



Scheme 7.1

The configuration of tartaric acid is determined for example by the cyanohydrin synthesis on *D*-glyceraldehyde.

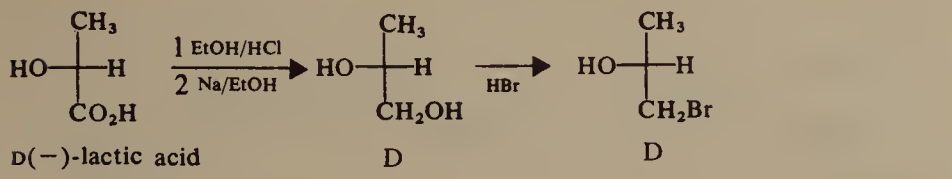


Scheme 7.2

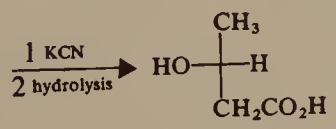
β-Hydroxybutyric acid may be prepared from lactic acid, the configuration of which is already known to us.

β-Hydroxybutyric acid may be reduced, in several steps, to optically active butan-2-ol (Scheme 7.4), the simplest chiral alcohol.

The direction of the synthesis is irrelevant for the correlation. One may start from a compound of known configuration and synthesize a compound whose configuration one wants to determine as well as the other way round. One may proceed in both directions simultaneously by preparing a third compound from the known as well as from the determined compound. The configuration may be determined with the same reliability, even if the two-

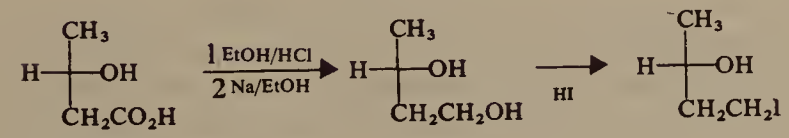


D(−)-lactic acid D D

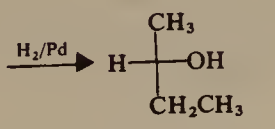


D(−)-β-hydroxybutyric acid

Scheme 7.3



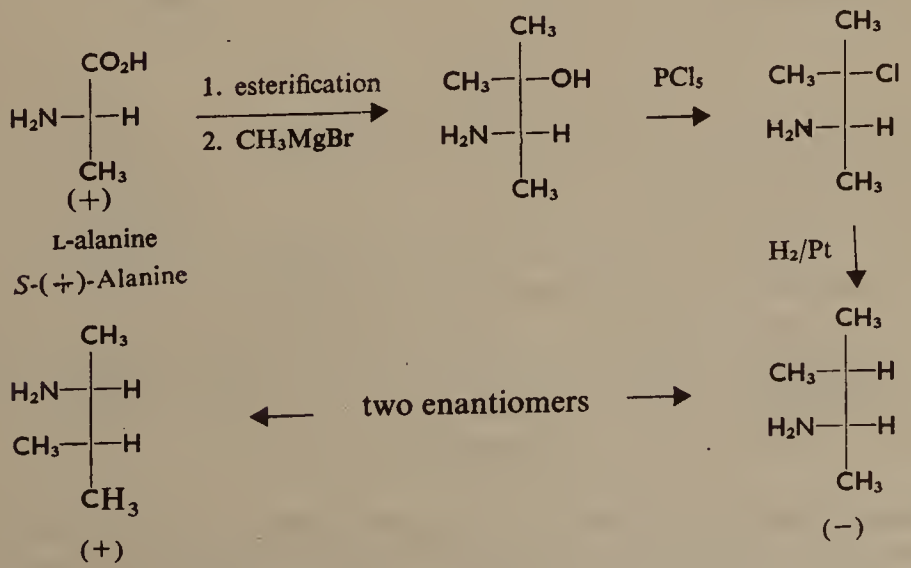
L(+)-β-hydroxy butyric acid L L



L(+)-butan-2-ol

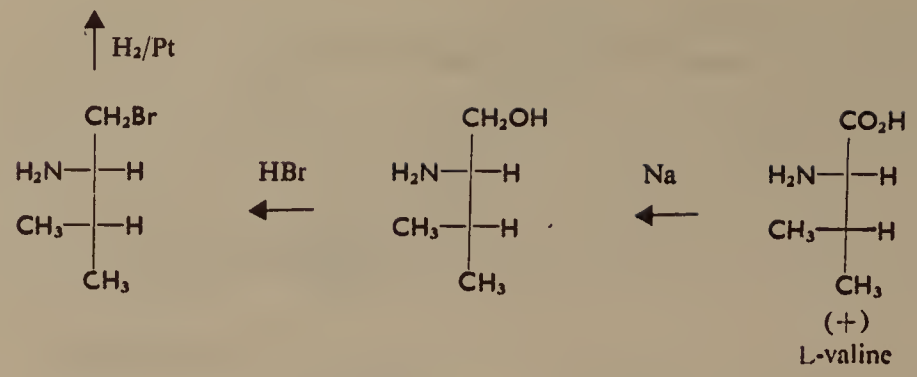
Scheme 7.4

way synthesis does not produce identical compounds but enantiomers. Correlation in the field of organic bases and amino acids is given in Scheme 7.5.



L-alanine

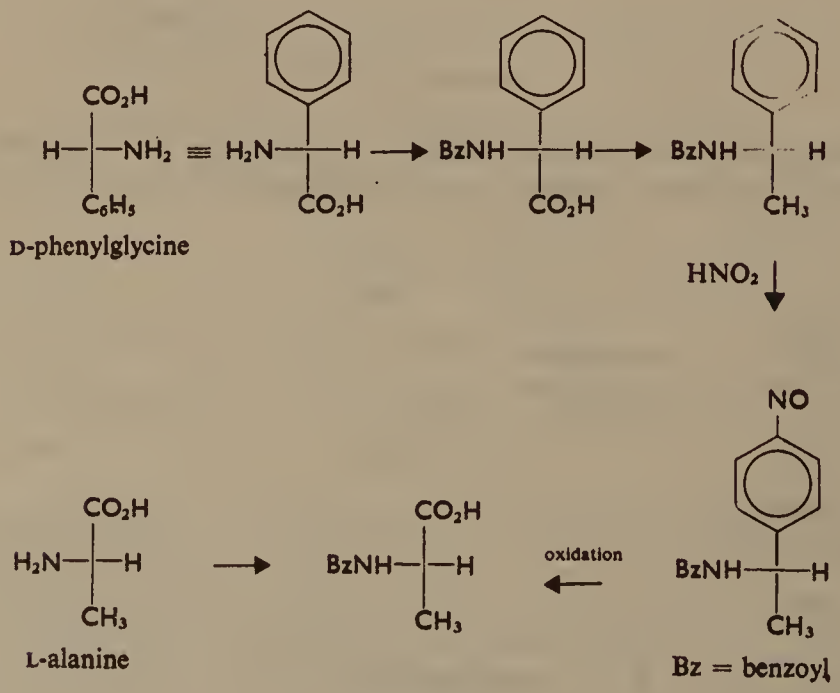
S-(+)-Alanine



Scheme 7.5

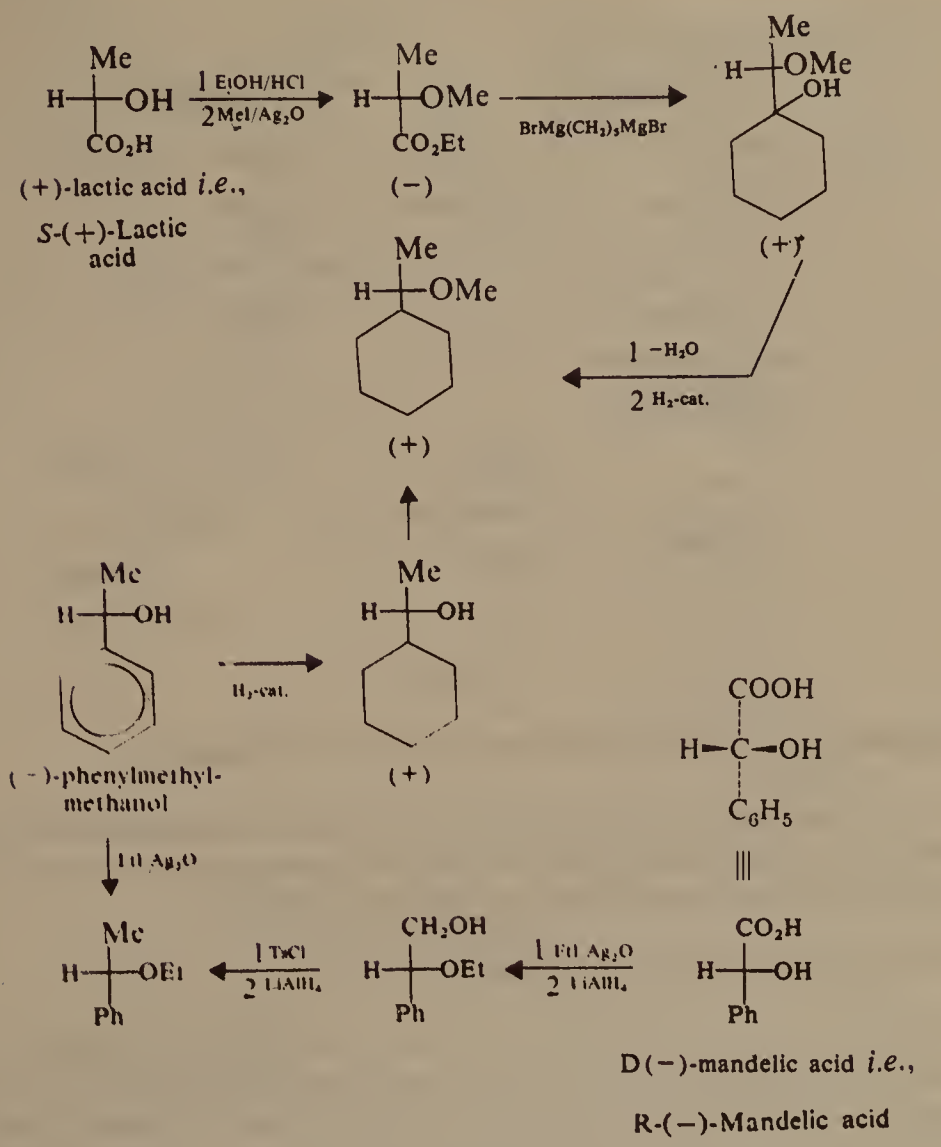
The above examples deal with acyclic or alicyclic compounds. When, however, the compound contains a phenyl group attached to the chiral carbon atom, correlation with glyceraldehyde is done either by degrading the phenyl group, leaving CO_2H attached to the chiral carbon atom, or by building up a cyclohexane ring from a CO_2H group and preparing this compound by reduction of the original phenyl-group containing compound.

One may give outline of the correlation between aliphatic and aromatic amino compounds. Scheme 7.6 shows that *L*-alanine and *D*-phenylglycine may easily be directly related.



Scheme 7.6

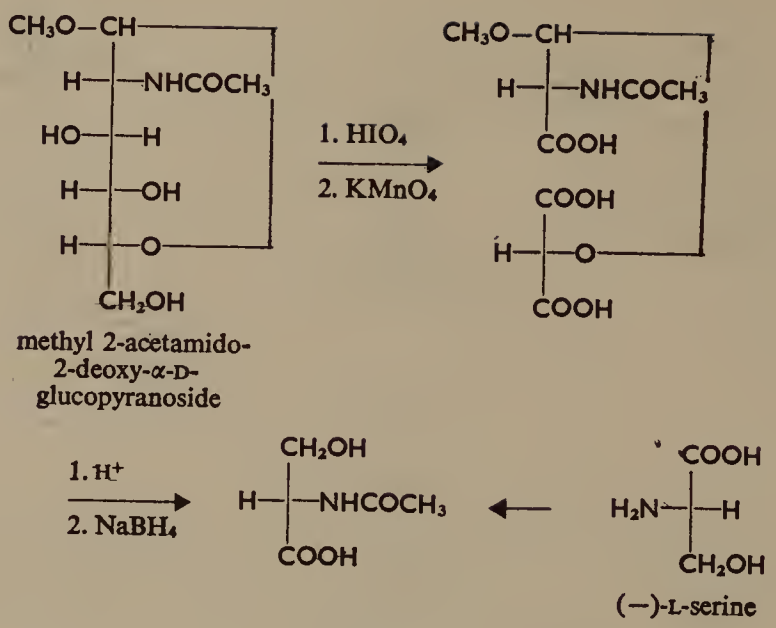
Another example of this method is the correlation of (+) -lactic acid with (—) -mandelic acid (Scheme 7.7).



Scheme 7.7

The relation between glyceraldehyde and serine was established by means of a derivative of *D*-glucosamine as the key compound. The conversion of *D*-glucosamine (2-aminoglucose) into *D*-glucose or *D*-mannose with nitrous acid (Scheme 7.8) established the configuration of the hydroxyl groups in relation to glyceraldehyde. The relationship between the chiral carbon attached to the amino group and serine was established by means of the oxidation of methyl 2-acetamido-2-deoxy-α-*D*-glucopyranoside with periodic acid; oxidation of the aldehydic groups to carboxyl groups and by the reduction of the original aldehydic function after the cleavage of the acetal group.

The relationship, therefore, confirmed again the configuration previously "arbitrarily" assigned to serine in relation to the configuration of glyceraldehyde which was also assigned arbitrarily.



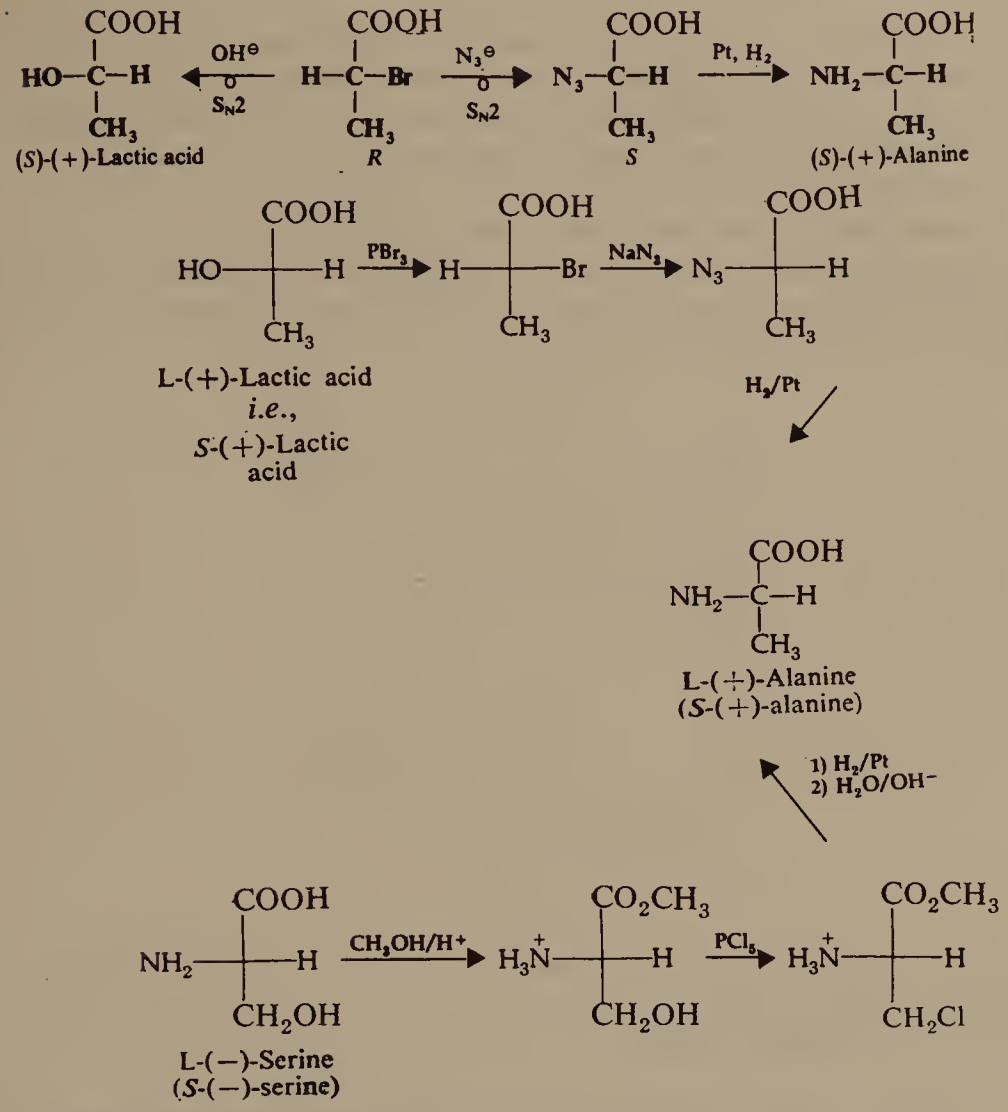
Scheme 7.8

(B) Conversion at the Chiral Centre with known Mechanism

The S_N2 reactions (Sec. 2.2) proceed with inversion of configuration at a chiral carbon. These series of reactions (Sec. 1.16) have been employed (Scheme 7.9) to relate the configurations of lactic acid, alanine, and serine.

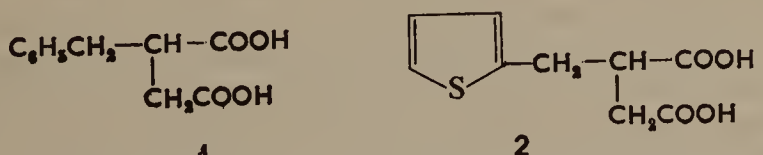
(C) The Method of Quasi-Racemates

While discussing the nature of racemic substances, we illustrated the ndividual possibilities with the help of diagrams of the melting points of mixtures of optical enantiomers (Sec. 1.17). Similar diagrams of melting points, however, may be shown by certain pairs of other substances which, although not enantiomers, but are structurally similar and have a mutually enantiomeric spatial arrangement. In these cases as well, one may assume the formation of an eutectic mixture as well as the formation of a solid solution without an expressive extremum on the curve, and finally an analogy with the formation of a racemic compound with the two enantiomeric components in ratio 1:1. The last situation obtains in cases when the two substances are very similar as regards structure, so that they may isomorphically represent real enantiomers in a crystalline lattice. Fredga, thus, employed the so-called quasi-racemate formation procedure for the determination of the absolute configuration of compounds which may not be mutually correlated by chemical means, especially for compounds with a carbon chain branched just at the chiral carbon atom. A significant example is the determination of the absolute configuration of (+) -methylsuccinic acid by comparison with (—) -mercaptosuccinic acid and (—) -chlorosuccinic acid, because the absolute onfigurations of most natural terpenoids could be related to methylsuccinic



Scheme 7.9

acid structure as the standard. Another example is provided by benzylsuccinic acid 1 and α-thiqphenylmethylsuccinic acid 2 (Scheme 7.10).



1

benzylsuccinic acid

2

α-thiophenylmethylsuccinic acid

Scheme 7.10

The absolute configuration of 1 is known from chemical correlation, while that of 2 is determined from the quasi-racemate technique:

1. Diagram (a) Figure 7.1 is that expected of the mixture of (+) - and (—) -isomers of **2**; the formation of a solid compound (Sec. 1.17).
2. Diagram (b) is the mixed melting points of (+) -isomer of **2** and (—) -isomer of **1**, formation of quasi-racemic compound.
3. Diagram (c) represents the mixed melting points of (+) -isomer of **2** with (—) -isomer of **1**, *i.e.*, the formation of eutectic mixture.

Since the diagrams of melting points of the mixture of the enantiomers of **1** and **2** show the formation of a quasi-racemate, the two compounds thus have opposite configurations at the chiral carbon atom.

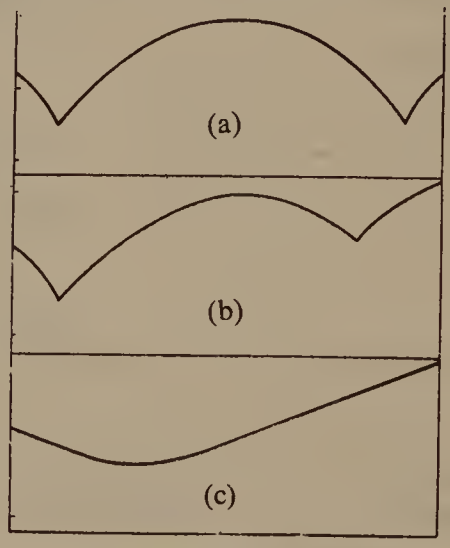


Figure 7.1

(D) Optical Rotatory Dispersion

The amount of rotation when a chiral compound rotates the plane of polarized light depends on the wavelength of the polarized light. In optical rotatory dispersion (ORD), rotations are measured over a range of wavelengths covering the UV as well as the visible regions. A plot of the rotation as a continuous function of the wavelength in some compounds may give a plain curve (no maximum or minimum) while others exhibit the Cotton effect. These curves are called optical rotatory dispersion (ORD) curves of compounds. A curve of a substance which exhibits a sine-wave form is referred to as a Cotton effect. This type of curve has a peak and a trough. The peak is labelled positive, if it is at a longer wavelength and *vice versa* (Figure 7.2). The molecular optical rotation, $[\phi]$ (also denoted by [M]; is defined as

$$[\phi] = [\alpha] \times \text{molecular weight}/100$$

To facilitate comparison of compounds of different molecular weights, it is advantageous to use molecular rotations, $[\phi]$, rather than specific rotations. The shape of the curves is useful for structural investigations comprising the determination of the position of the chromophore group, the spatial arrangement of the substituents in its vicinity as regards relative configuration, the details of conformation and finally absolute configuration.

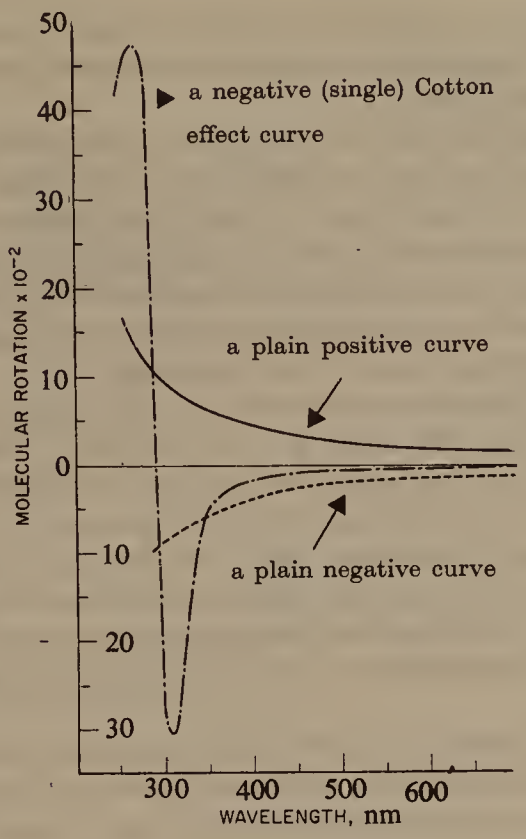
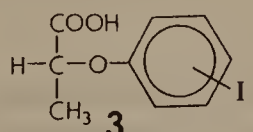


Figure 7.2

(i) Plain curves: Plain curves are highly useful in the detection of optical activity when the measurement at the usual wavelength, 589 nm corresponding to the D line of sodium, does not show activity. In some cases the rotation at the D line of sodium is so small that it cannot be detected; however, it is usually greater in the ultraviolet region. Some compounds on the other hand may remain optically inactive throughout the accessible region and thus may constitute a racemic mixture.

The great power of even plain curves over monochromatic measurements is shown by studies on some 2-phenoxypropionic acid derivatives **3** (Scheme 7.11).



3

a: ortho-I
b: meta-I
c: para-I

Scheme 7.11

The analogous *para* and *meta* isomers display very similar plain positive curves and show positive rotations at the D line. The related *o*-iodo isomer on

the other hand has a negative rotation at the D line, however, in keeping with the identical configuration as compared with *m* and *p* isomers it, too, shows a plain positive ORD curve.

(ii) Curves with Cotton effect: The curves which exhibit Cotton effects are much more useful and give information on structure, configuration and conformation of the molecules. Studies on the ORD curves of steroid and terpenoid skeletons showed that the sign, magnitude and overall shape of the Cotton effect curve can be closely correlated with the immediate structural and stereochemical environment of the carbonyl group and are little affected by the structural changes away from this group.

The keto group absorbs in the ultraviolet radiation around 280-290 nm and this absorption generally leads to a Cotton effect. Thus, the position or configuration of a carbonyl group in a compound can be found by comparing its Cotton effect curve with those of suitable analogs.

(iii) Octant rule: The octant rule is an empirical generalization which makes it possible to predict the sign of the Cotton effect for a substituted cyclohexanone by consideration of the spatial arrangement of the substituents relative to the carbonyl group. This rule has greatly widened the scope of ORD.

The method of application of the octant rule with a cyclohexanone ring in the chair conformation having an equatorial methyl group is as under:

1. The ring containing the carbonyl group is viewed as shown in the Figure 7.3.
2. Three planes at right angles are drawn through the carbonyl group to produce eight octants.
   (*a*) first plane (**A**) (vertical in diagram) passes through the carbonyl group and C-4.
   (*b*) second horizontal plane (**B**) is put through C-1 and the cyclohexanone is so tilted that it also passes through C-2 and C-6.
   (*c*) third plane (**C**) passes about midway through the C = O bond at right angles.
3. The contribution of a substituent to the sign of the Cotton effect is then determined by its position in these octants.
4. Since only rarely substituents bend over the carbonyl group toward the oxygen and beyond, the four octants which are nearest the observer are usually vacant.
5. According to octant rule:
   The substituents lying on the coordinate planes make no contribution to the rotatory dispersion. Thus, as seen in the diagram, equatorial substituents at C-2 and C-6 make little contribution as these lie on the plane (B). Similarly, substituents at C-4, both axial and equatorial make no contribution since they lie on plane (A).
6. Axial substituents at C-2 and all substituents at C-5 make a positive contribution.
7. Axial substituents at C-6 and all substituents at C-3 make a negative contribution.

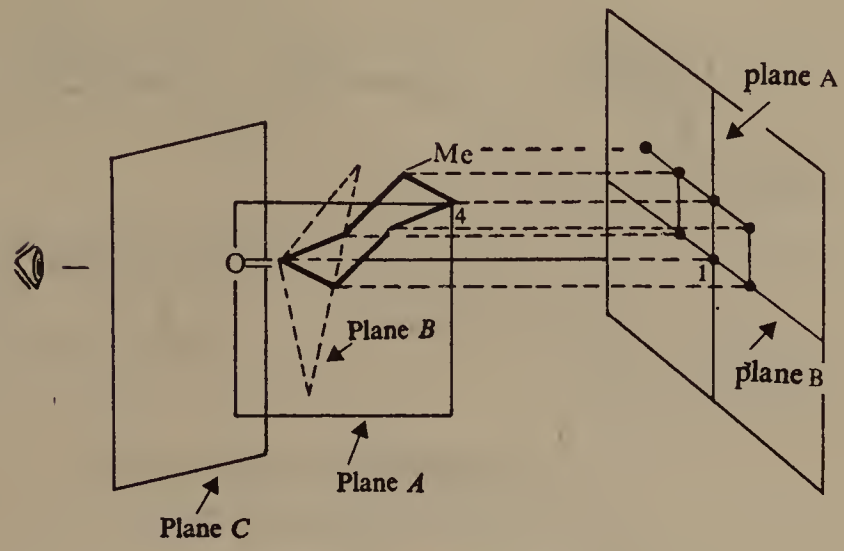


Figure 7.3

It is however, customary to simplify the octant diagram to look as shown in scheme 7.12. It is its planar representation.

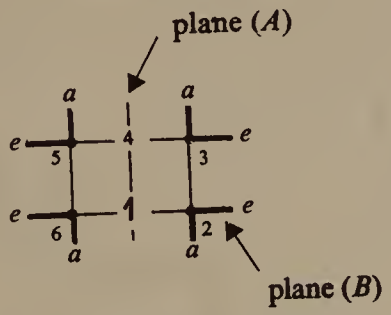
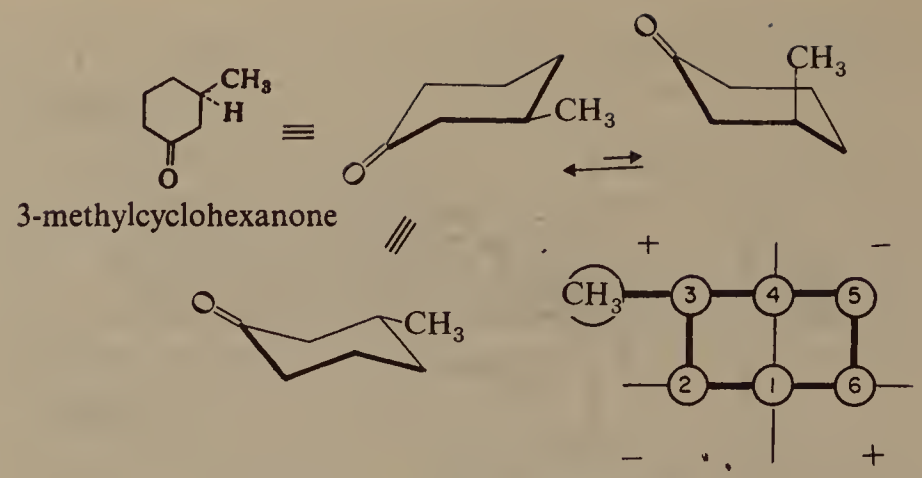


Diagram 2

Scheme 7.12

(iv) **Study of conformations and configuration via octant Rule:** (+)-3-Methylcyclohexanone is known to have the (*R*) configuration (consider a model). Based on conformational analysis the equatorial isomer will predominate (Scheme 7.13). If the preferred conformation of the ketone is oriented appropriately for the application of the octant rule the only effective contributor is thus in a positive octant and therefore, a positive Cotton effect for the equatorial conformer is predicted. In confirmation with these expectations the Cotton effect is indeed positive. On the other hand the axial conformer is predicted to have a negative Cotton effect.

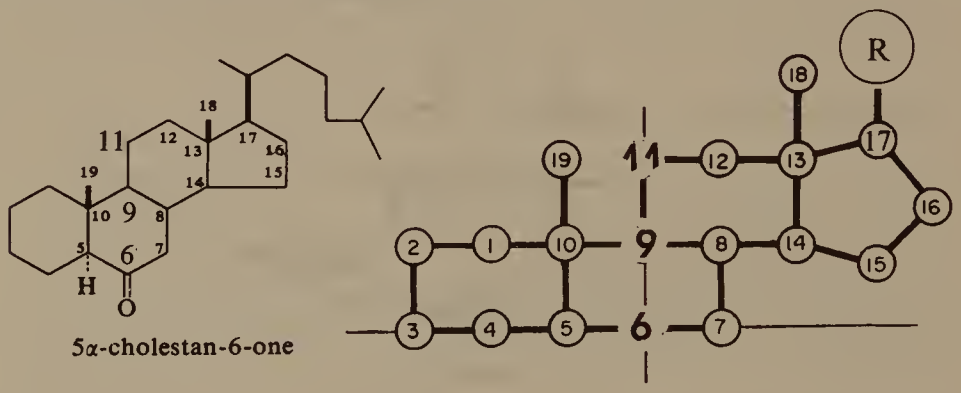
The octant rule is easily applied to six-membered ring ketones without the use of models (whereas, the use of models makes the problem very easy). The conformation is drawn and is then suitably oriented for the application of the octant rule and its planar octant projection is examined. After the substituents are put in a particular configuration, the Cotton effect is predicted by the sign of the most occupied octant. An otherwise complex example which yields an



(+)-3-Methylcyclohexanone is known to have the R configuration

Scheme 7.13

immediate answer by using models is cholestan-6-one. The carbons on plane **A** and **B** do not make any contribution; since the bulk of the substituents make negative contributions the prediction is negative and indeed cholestan-6-one displays a negative Cotton effect curve.

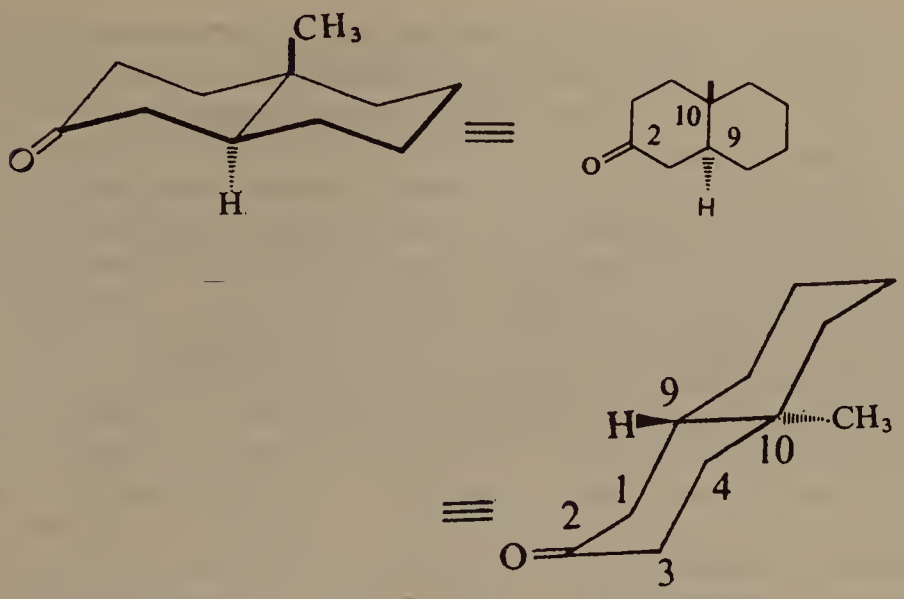


Scheme 7.14

Similarly if (+)-*trans*-10-methyl-2-decalone has the configuration as indicated, then obviously C-5 and the angular methyl group being on plane **A** make no contribution and a positive Cotton effect is predicted and in confirmation with the absolute configuration indicated, the compound displays a positive Cotton effect.

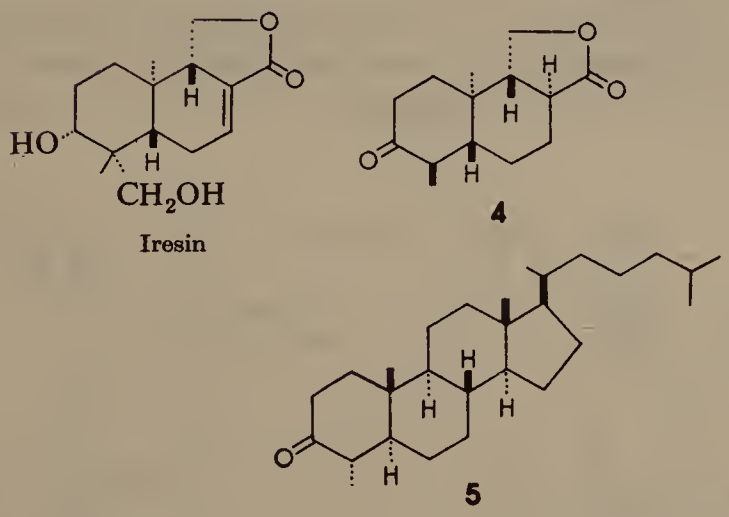
A norketone derived from a sesquiterpenoid lactone, iresin was proved to have configuration 4, as its Cotton effect curve was negative while that of the available model steroidal ketone **5** of established absolute configuration was positive (Scheme 7.16). Both 4 and 5 are structurally similar in the vicinity of the carbonyl group and thus they are of opposite configuration.

Iresin was the first bicyclofarnesol sesquiterpenoid to be discovered and significantly it belongs to a group of compounds which have an abnormal



(+)-*trans*-10-methyldecal-2-one

Scheme 7.15



Scheme 7.16

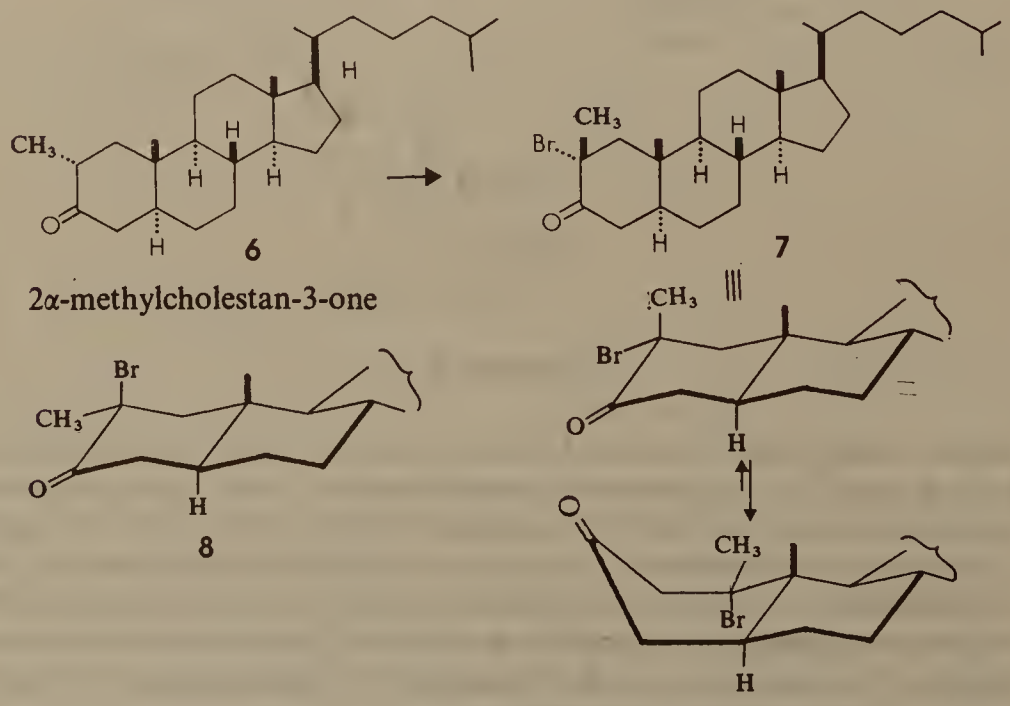
configuration which is antipodal to that of the triterpenoids and steroids. In keeping with the assignment of stereochemistry using optical rotatory dispersion studies, the chemical degradation pointed to the same conclusion.

It may be emphasized that octant rule has to be applied only to the cyclohexanones in the chair conformation when the conformational rigidity and symmetry simplify the application of this rule. An example which shows the utility of octant rule to show the existence of a cyclohexanone derivative in a boat conformation is presented here.

The bromination of 2α-methylcholestan-3-one **6** (Scheme 7.17) affords a

product which was first assigned 2β-bromo-2α-methylcholestan-3-one structure **8** which may be formed by the usual axial attack of bromine in a kinetically-controlled reaction. However, such a structure was ruled out by employing a combination of physical and chemical techniques particularly ORD and it was realised that the product is instead 2α-bromo-2β-methylcholestan-3-one **7** in which the ring **A** assumed a preferred flexible conformation. This example presents the elucidation of conformation of this compound with the help of ORD. Cholestan-3-one shows a strong positive Cotton effect and the application of the octant rule predicts a very strong positive Cotton effect for the product of bromination if it is in the chair conformation. In practice, the product of bromination instead shows a negative Cotton effect which is, therefore, incompatible with the chair conformation. It was, therefore, concluded that the monobromo product exists in the best conformation. The existence of the **A** ring in chair form in **7** would have suffered from two serious interactions, namely, an axial 1,3-dimethyl interaction and an equatorial bromoketone interaction. During the bromination of **6** obviously the halogen does not get delivered axially because of the hindrance by the C-10 methyl group. Significantly, as expected, on bromination a 2-methyl-19-norsteroid-3-ketone affords an axial 2-bromo compound.

Treatment of **B** with hydrogen bromide caused the epimerization at C-2 to afford the thermodynamically more stable 2β-bromo isomer in which the ring **A** adopts the chair conformation and the bromine occupies the axial position.



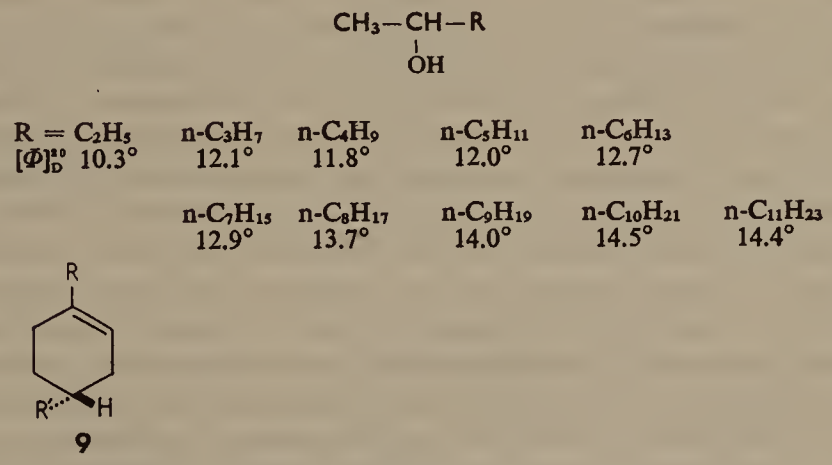
Scheme 7.17

7.2 MONOCHROMATIC ROTATION MEASUREMENTS (EMPIRICAL RELATIONSHIPS BETWEEN ROTATION AND STRUCTURE)

The measurement of the optical rotation of a compound at one wavelength (usually the sodium "D line," 589 nm) has been a part of the routine characterization of the new compounds. Chemists have attempted to discover in these measurements consistencies of sign or magnitude which would be of value in assigning stereostructures to other compounds and the result in this direction has been the formulation of a number of empirical rules which have proved of considerable value.

(A) Single Measurement Conclusions

The absolute configuration of a wide range of trisubstituted methanes (in which there is only one chiral carbon) may be established by comparison of rotations with those of known homologues. Within a particular homologous series values tend to approach a limiting value with increased chain length. The limits thus formed by short and long chain homologues are sometimes sufficiently small to allow deductions of structure as well as configuration.



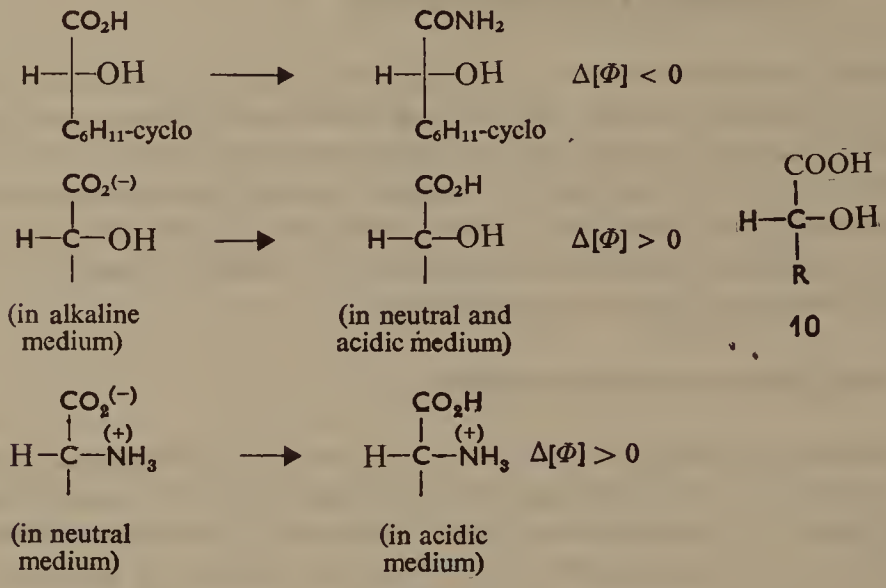
Scheme 7.18

Mills observed that several compounds of the general structure **9** (where R and R′ may be $-CH_3$, $-CH(CH_3)_2$, $-CH_2OH$, $-C(CH_3)_2$ OH, and derivatives) have molecular rotations in the range +130-170°.

(B) Rule of Shift

Small chemical change in the substituent directly adjacent to the chiral carbon atom affects the rotation characteristically according to the rule of shift which states that analogous compounds with the same configuration

change their rotaion in the same direction, if the corresponding substituents are changed in the same way. An important representation of the specific conclusions

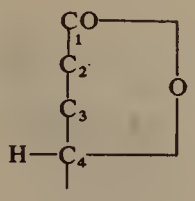


Scheme 7.19

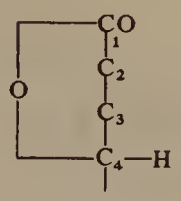
following from the rule of shift is the Hudson amide rule: all α-hydroxy acids, the rotation of which is shifted to the right by their conversion into amides have configuration **10** (Scheme 7.19). The transformation of the carboxylic group into the carboxylate anion is also attended by a positive shift of rotation in the case of compounds with the absolute configuration shown, regardless of whether we compare the pair α- hydroxy acid/carboxylate ion or the α-amino acid salt with mineral acid/free amino acid in aqueous solution (the so-called Lutz-Jirgensons rule). The lactone rule gained importance first in the carbohydrate chemistry and more recently has been used for a number of other compounds. Hudson studied the rotation of the lactones derived from the aldonic acids. If one uses the usual projection formulas, the lactone ring will be either on the right or left depending on the stereochemistry of hydroxyl group on C-4. Hudson proved that if the lactone ring was on the right, the compound was *dextro*-rotatory and if the ring was on the left, then it was *levo*-rotatory. This rule also applies to δ-lactones. An extension of this rule, which has been shown to apply to a number of polycyclic compounds, has been devised by Klyne; the difference in rotatcon between a lactone of absolute configuration **11** (Scheme 7.20) and its corresponding acid is positive and that of its enantiomer **12** is negative.

(C) Configuration from Molecular Rotation Contributions

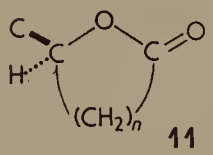
In the use of optical activity, two factors—the determination of conformation and the vicinal effects frequently pose great difficulties. With the long, flat, rigid skeletons of the steroids and triterpenes, however, conformational and vicinal factors are comparatively easy to control. The study of molecular rotations in these compounds, has led (D.H.R. Barton) to structural and stereochemical assignments which are both extensive and



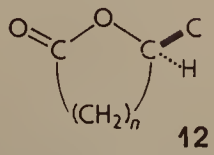
dextrorotatory



laevorotatory



11



12

Scheme 7.20

secure. Molecular rotation values are assigned to each "parent" and different alternations in this structure result in characteristic changes in molecular rotation.

Thus, for example, molecular rotation value assigned to 5α-cholestane (scheme 7.21) is +91; molecular rotation contributions of hydroxyl groups in ring **A** have been assigned as:

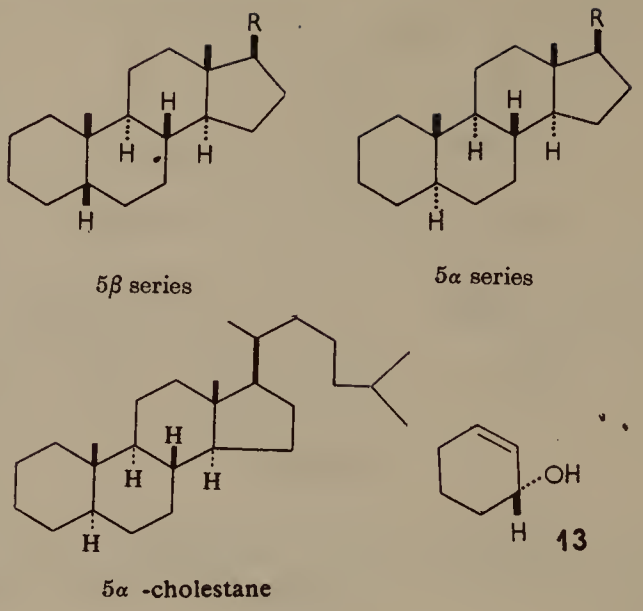
TABLE 7.1

Position	α-OH	β-OH
1	+35	-17
2	+37	+49
3	+ 5	- 2
4	-75	+22

One could, therefore, locate the position and stereochemistry of hydroxyl group in ring A from these data. The molecular rotation of cholestan-2α-ol, for example, would be calculated by adding the $[\phi]_D$ value for cholestane and the contribution of an α-OH at C-2, *i.e.*, +91+37 = +128° and the experimentally determined value is +120°.

There are again large differences in molecular rotation contributions of functional groups in 5α-and 5 β-series. This contribution, for example, in the case of Δ^2-double bond is +170° for 5α-cholestane and—24° for 5β-cholestane. Thus, one could distinguish between a 5α-and a 5β-steroid or between a steroid and a triterpenoid molecule. Values which do not follow the known patterns would show that the functional group is located at an unprecedented position or in an hitherto unknown skeleton.

From a study of monoterpenes, Mills formulated a rule which correctly predicts the absolute configuration of steroids: allylic alcohols of absolute configuration 13 have more positive rotations than their epimers; esterification increases this difference.



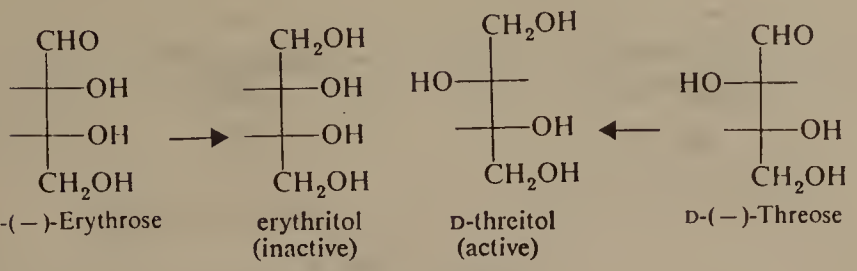
Scheme 7.21

7.3 METHODS OF APPROACH TO RELATIVE STEREOCHEMISTRY (SOME EXAMPLES FROM NATURAL PRODUCTS)

One may determine the mutual relationship of chiral centres in the individual diastereoisomers, the so-called relative configuration, *e.g.*, the *erythro*-and *threo*-configurations, respectively, of compounds with two chiral atoms. Simpler procedures are used for the determination of the mutual relationship of several centres in the same molecule. Such methods determine the distribution of substituents in the molecule with relative reliability, and thus also allow the formulation of relationship between the individual configurational series.

(A) By Introducing Plane of Symmetry

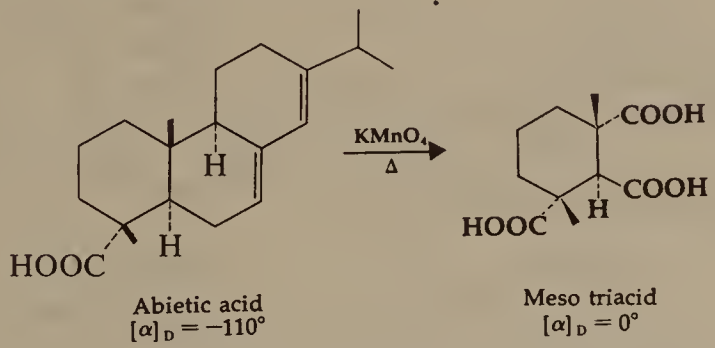
One may determine the relative configuration of compounds with two identical chiral atoms. From the analysis of the conditions of optical activity the inactive *meso*-form of a compound with two chiral atoms must have the *erythro*-configuration, and the second diastereoisomer therefore has to be the *threo*-form. If one succeeds in resolving one of the two synthetic diastereoisomers of this type into optically active compounds, the resolvable isomer has to have the *threo*-configuration, and the other one the *erythro*-configuration. Optically active erythrose may be reduced to a tetritol (erythritol) which is optically inactive, whereas its diastereoisomer, threose, affords on reduction optically active threitol. Optical activity or inactivity of the products of reduction quite unequivocally determines the relative relation of both chiral atoms of the original tetroses, *i.e.*, the *erythro*-configuration of erythrose and the *threo*-configuration of threose. The designation to series *D* or *L*, *i.e.*, the



Scheme 7.22

absolute configuration, has indeed to be determined by other means by the chemical correlation with glyceraldehyde or by physical methods.

Vigorous oxidation of optically active diterpenoid abietic acid, gave the optically inactive triacid. This acid is *meso,* therefore, there are only two possible configurations for it. The correct one, with *trans* carboxyl groups, was established by a comparison of its pK_a with synthetic model acids. This simple study established the relative stereochemistry of three out of the four chiral centres in abietic acid (Scheme 7.23)

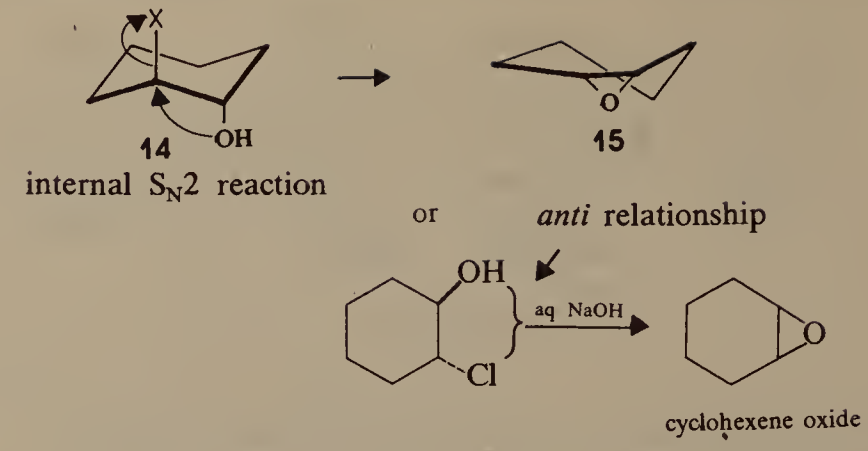


Scheme 7.23

(B) Ring Forming Reactions

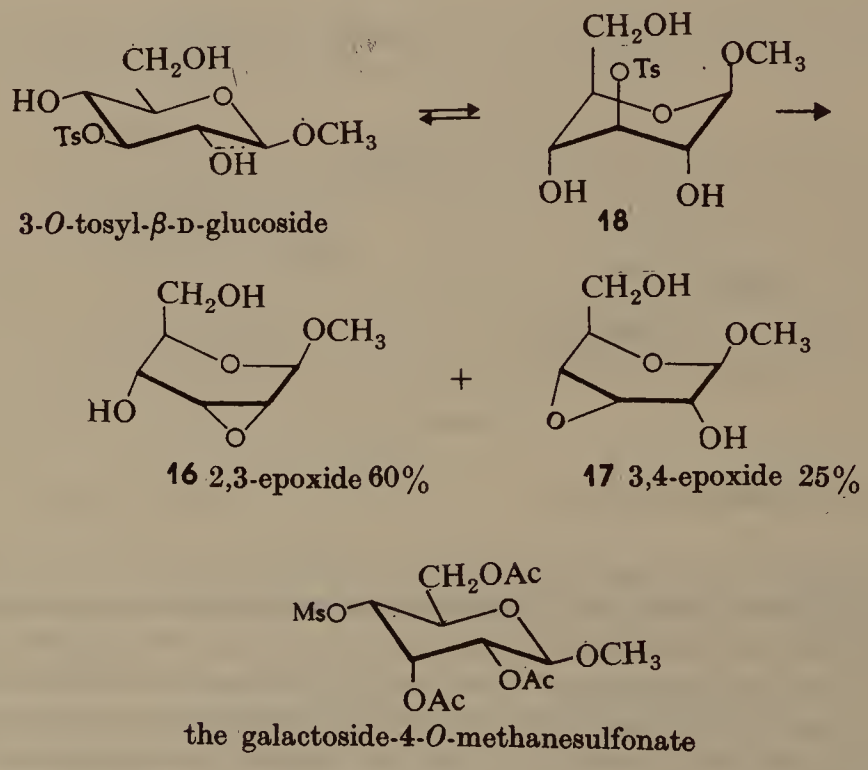
(*i*) *Epoxide Formation*: For the formation of epoxides the progenitor substituents have to be vicinal and *trans* oriented. In the cyclohexane series, these substituents must be capable of assuming a *trans* diaxial arrangement **14** (Scheme 7.24) allowing intramolecular S_N2 displacement of the leaving group X, and it should be noted that the product **15** assumes roughly the same conformation as in cyclohexene. A *trans* diequatorial arrangement of the substituents is not favorable, however, in several cases conformational inversion to a *trans* diaxial orientation allows the epoxide formation to proceed readily.

When 3-*O*-tosyl-*β*-*D*-glucoside is treated with mild alkali, the 2,3-epoxide **16** (Scheme 7.25) is formed giving 60% yield, alongwith 25% of the 3,4-epoxide **17**. The reaction must proceed by way of the all-axial conformation **18** and this confirms the *trans* orientation[6] of the 2,3, and 4 substituents in



Scheme 7.24

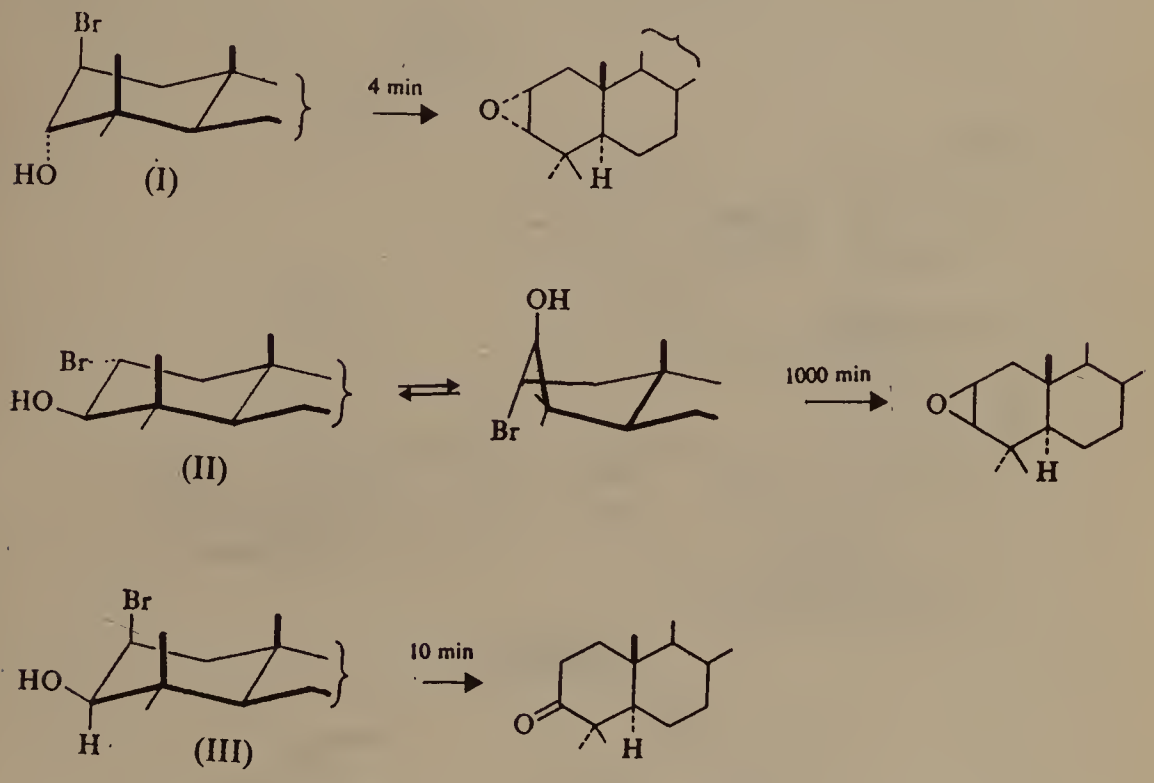
glucopyranosides. In contrast, the galactoside-4-*O*-methanesulfonate does not form an epoxide when treated with sodium methoxide. It suffers simple deacetylation to show the *cis* orientation of the 3 and 4 substituents.



Scheme 7.25

The *trans* diaxial requirement for the participating groups is further illustrated by the reactions of the isomeric 2-bromo-3-hydroxylanostane derivatives (I-III) scheme 7.26. Using standard conditions, I in which the bromine and hydroxyl are both axial undergoes an elimination quickly to give the α-epoxide. The diequatorial isomer II eliminates slowly to give the

β-epoxide. It has been suggested that for the elimination to occur the ring **A** of this compound must adopt a boat conformation when the two groups attain *anti*-periplanarity. The derivative III eliminates rapidly to give the 3-ketone (Sec. 7.3B).

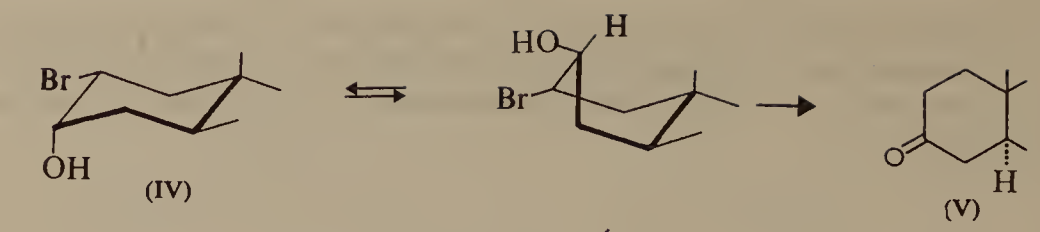


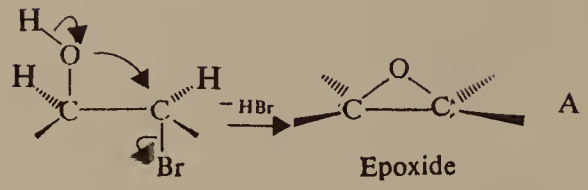
Scheme 7.26

On treatment with alcoholic alkali the bromohydrin IV gave a ketone V Formation of a ketone from IV must be a result of *anti* elimination of HBr (eqs. **A** and **B**) to give the enolic form of the ketone as the eliminated 3-H is β, the 2-Br must be α- as shown in IV. In fact this is the proof of the *cis* contiguration of the bromohydrin which indeed reacts in the boat form to afford the ketone V.

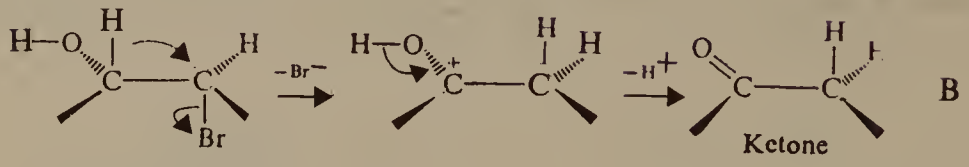
(*ii*) *Higher Membered Cyclic Ethers*: A well known example is the ready cyclization of scopine to the cyclic ether scopoline[7] on treatment with an acid or a base. In scopoline the oxide and nitrogen bridge can only be *trans* to each other (Scheme 7.28). This conversion involves an S_N2 displacement, therefore, the hydroxyl group in scopine must have the α-orientation, *i.e.*, it is axial to the chair piperidine ring. In keeping with the stereochemical inferences thus drawn for both scopine and scopoline, the epimeric β-alcohol from scopine (pseudoscopine) is not easily isomerized.

When dealing with natural products containing two or more hydroxyl groups on adjacent carbon atoms, it is sometimes possible to know their configuration by forming such a derivative so as to cause the hydroxyl groups



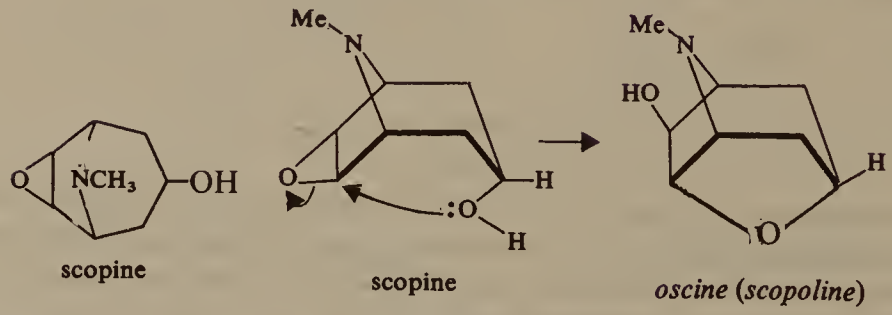


Trans-Bromohydrin



Cis-Bromohydrin

Scheme 7.27

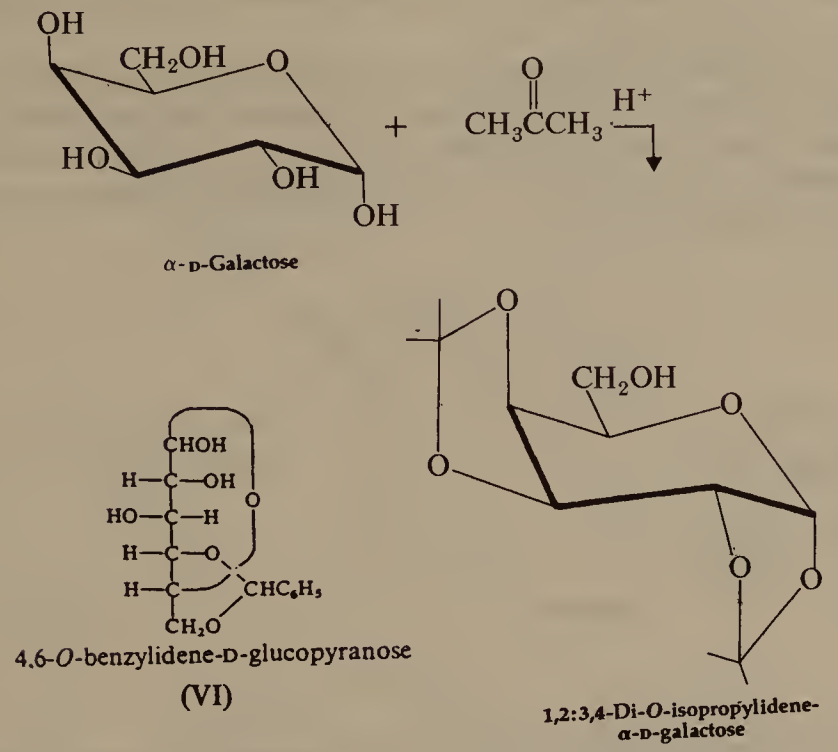


Scheme 7.28

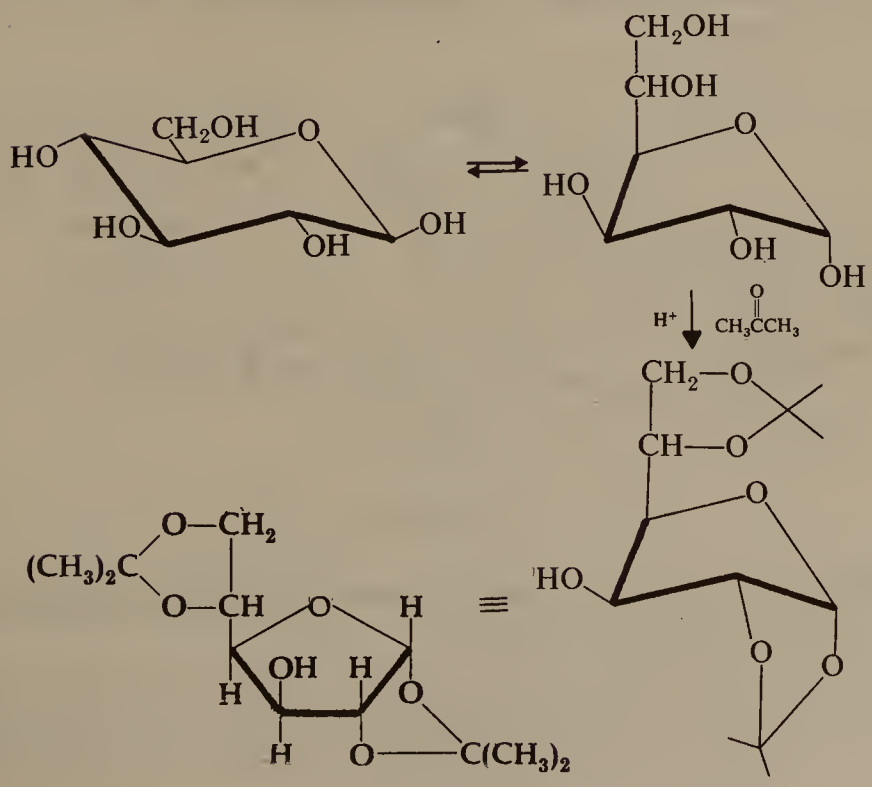
to become part of a new ring. The most common type of cyclic ether derivative (acetonide) used for this purpose is obtained by the reaction of the polyhydroxy compound with acetone. If the diol is itself cyclic, the acetal or ketal is formed only when the two OH groups are *cis*, for geometric reasons and in a cyclohexane derivative these have to be axial and equatorial.

Sugars being polyhydroxy[8,9] compounds; undergo this reaction. However, the reaction is often complicated by the fact that the ring size in the product is not the same as it is in the free sugar. This usually occurs when the more stable pyranose form does not have a pair of *cis* vicinal hydroxy groups, but the furanose form does. Thus, galactose reacts with acetone to give the diketal. Since it is in the α-form, which is present under the acidic conditions of the

reaction, there are two pairs of *cis* vicinal OH groups. Glucose, on the other



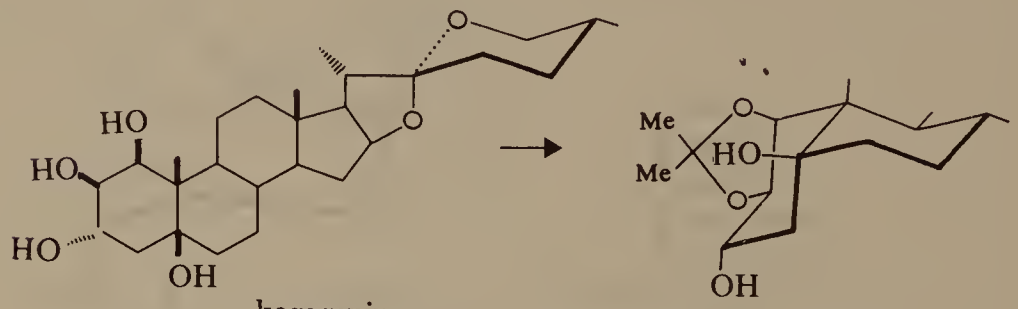
Scheme 7.29



Scheme 7.30

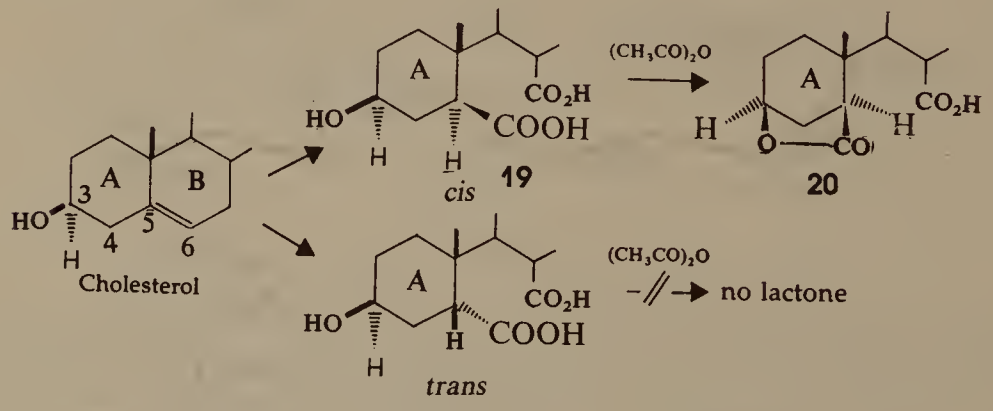
hand, reacts in manner of the furanose form. In kogagenin[10], the C-1, C-2 hydroxyl groups must have relative *cis*-stereochemistry since it readily affords a monoacetonide (Scheme 7.31).

During acetal and ketal formation it is often difficult to attain selectivity, but it is generally found that, at equilibrium, the aldehyde reagents usually give six-membered cyclic acetals and ketone reagents five membered cyclic ketals. Thus, glucose reacts with benzaldehyde to give (VI, Scheme 7.29) by reacting with 1, 3 cis-hydroxy groups.



Scheme 7.31

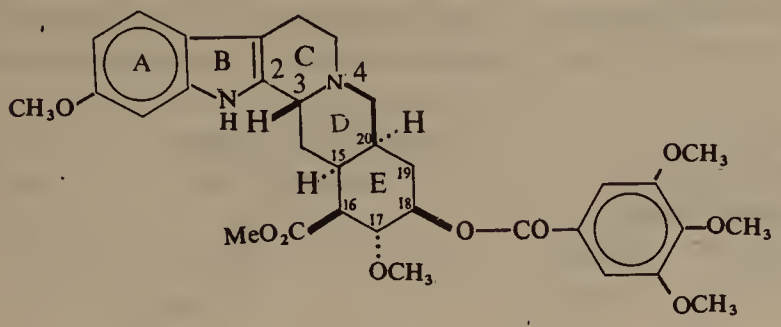
(*iii*) *Lactone Formation* : Cholesterol was converted to a diacid derivative **19** (Scheme 7.32). The configuration of C-5 carboxyl group relative to that of the hydroxyl at C-3 is proved to be *cis* by lactone formation **20**, and confirmed by showing that the alternative configurations at either C-3 or C-5 (*trans*) do not yield a lactone.



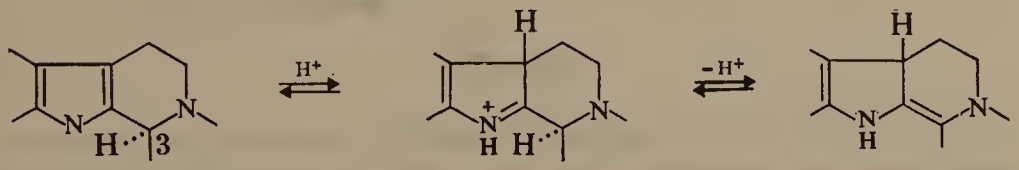
Scheme 7.32

Thus lactone formation provided a conclusive proof of the β-orientation of the C-3 hydroxyl group in cholesterol.

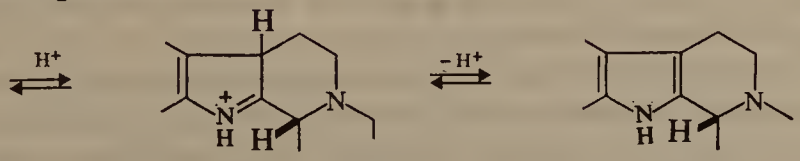
Reserpine undergoes epimerization at C-3 very easily on acid treatment to afford 3-isoreserpine (Scheme 7.33) as all the substituents in the latter are equatorial.



Reserpine



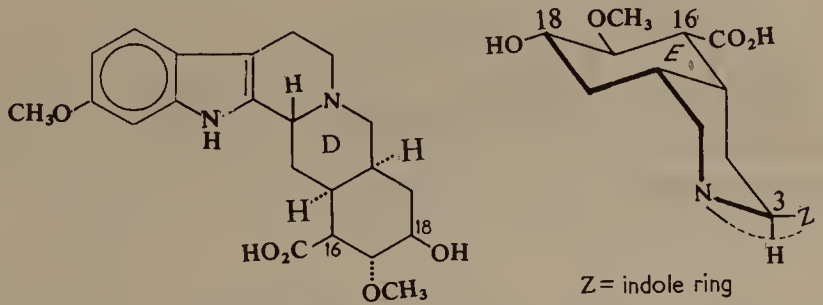
3-isoreserpine



reserpine

Scheme 7.33

Reserpic acid (Scheme 7.34) is obtained by the hydrolysis of reserpine which has the bulky aromatic substituent axially oriented.



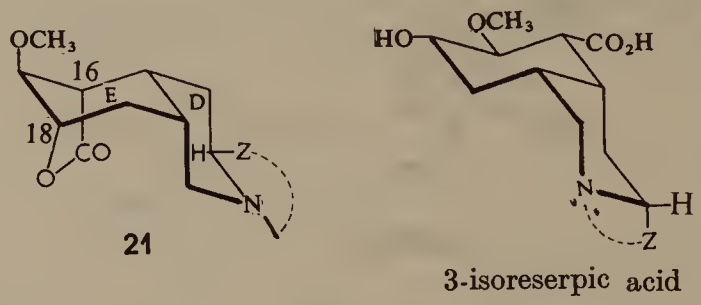
reserpic acid

Scheme 7.34

Reserpic acid on reaction with acetic anhydride affords a lactone 21 (Scheme 7.35) and, therefore, a conformational inversion must occur to bring C-16 and C-18 substituents in axial positions for this lactone formation,

thereby making the indole ring in the lactone equatorial.

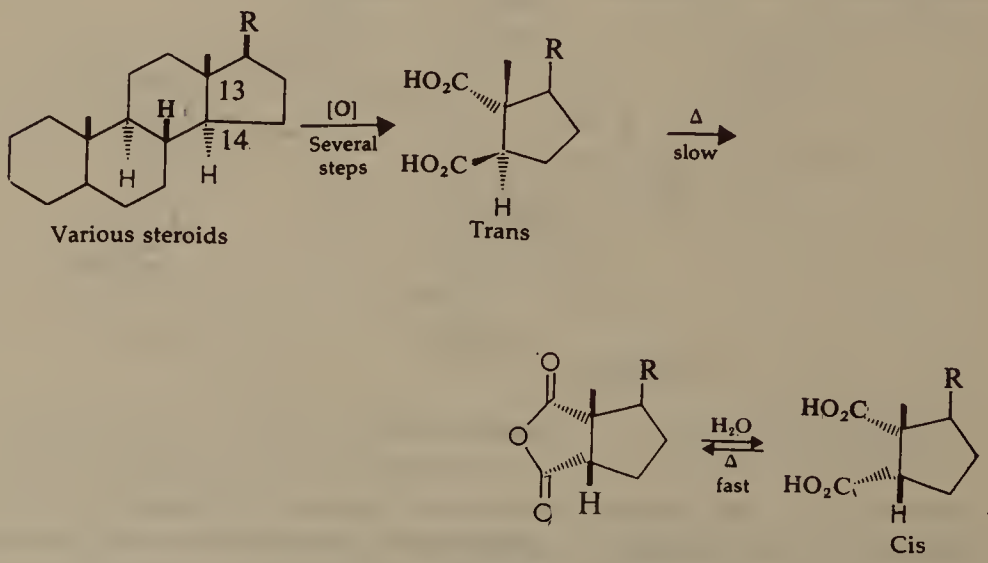
In 3-isoreserpic acid all the substituents (including the bulky indole group) are equatorial. Interestingly and as expected 3-isoreserpic acid does not undergo lactonization using the reaction conditions employed for reserpic acid as a large energy barrier opposes the lactonization[11,12] as all substituents on rings **D** and **E** shall have to adopt an unfavourabl all-axial conformation.



Scheme 7.35

(*iv*) *Anhydride Formation*: Another approach alternative to the method ot lactone and cyclic ether formation in the field of stereochemistry consists of degrading a natural product to a suitable dicarboxylic acid capable of forming an anhydride depending on the stereochemistry of the carboxyl groups. This method has been widely applied to steroids, and several of the early conclusions concerning their stereochemistry were based on it.

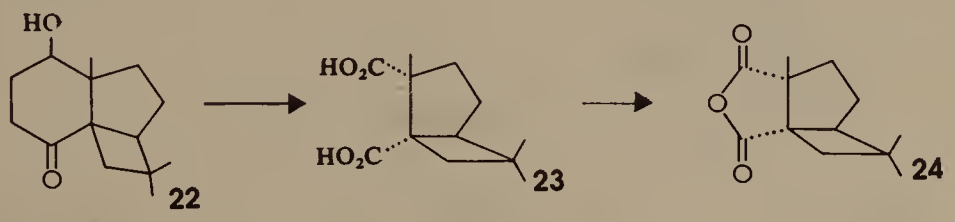
The nature of the ring junction between rings **C** and **D** was, for example, found by this method. In a multistep degradation by oxidation the **D**-ring portion of the steroid molecule is isolated as a diacid (Scheme 7.36) without loss of the configuration at C-13 and C-14. This diacid on vigorous pyrolysis, slowly yields an anhydride, which on hydrolysis affords an epimeric diacid. This second diacid affords the same anhydride very easily on heating.



Scheme 7.36

Thus, the second diacid must have *cis* carboxyl groups so that the original diacid, and also the steroid **C/D** ring junction, must be *trans*. The proof is completely similar to that of the maleic and fumaric acids (Sec. 1.10 B, b). In the slow pyrolysis of the *trans* diacid, the lower carboxyl is first enolized and so epimerized by its own acid catalysis on heating.

A key deduction of the stereochemistry of caryophyllene was achieved through this brilliant investigations by Barton. The compound **22** obtainable from caryophyllene[13] was converted by successive oxidations to a dicarboxylic acid **23** (Scheme 7.37) which was found to yield an anhydride **24** with remarkable ease. It is known that substituted succinic acids form anhydrides with particular ease, thus confirming a five-membered *cis* anhydride as shown in **24**.

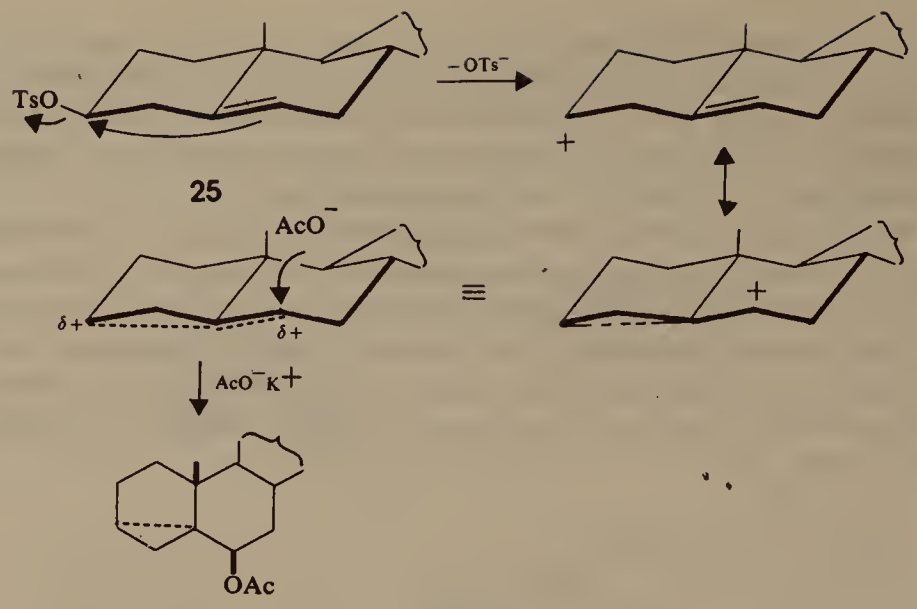


Scheme 7.37

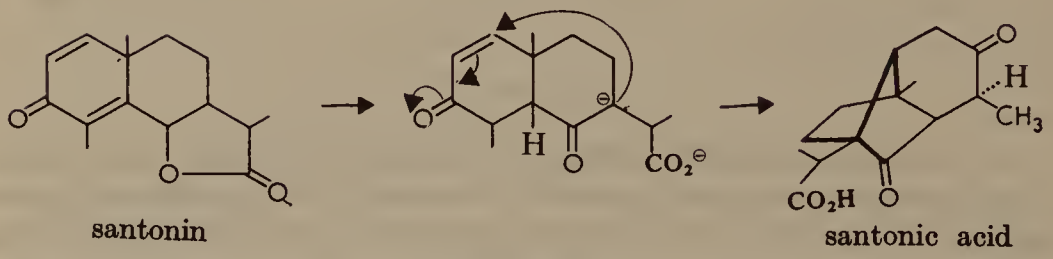
(*v*) *Carbon-carbon Bridge Formation*: Cholesteryl chloride on solvolysis with methanol affords the expected 3β-methoxy derivative. However, in the presence of potassium acetate a rearrangement occurs with the formation of a cyclopropane derivative which is hydrolysed to 3α, 5α-cyclocholestan-6β-ol, often called 'i-cholesterol'. On reaction with dilute sulphuric acid it undergoes the reverse rearrangement to afford cholesterol. Cholesteryl tosylate **25** (Scheme 7.38) behaves similarly and this i-steroid rearrangement takes place only when the leaving group at C-3 is β-oriented. The mechanism of this reaction involves homoallylic participation and thus displays stereospecificity. Substitution reactions at C-3 in cholesterol are known to procced with retention of configuration and these results can be accounted on the basis of homoallylic participation.

A graphic example of bridging[14] through a carbanion intermediate is the conversion of santonin to santoic acid (Scheme 7.39), the structure of which is due to Woodward, *et al.* The reaction is pictured as an intramolecular Michael addition and imposes the stereochemistry shown in santoic acid for the ring system.

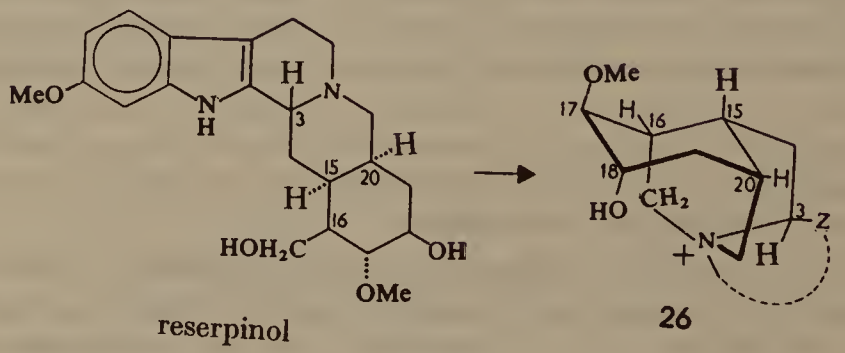
(*vi*) *Cyclic Quaternary Salts*: Lithium aluminium hydride reduction of methyl reserpate gives reserpinol which on reaction with *p*-toluenesulphonyl chloride affords a quaternary salt **26** (Scheme 7.40), by intramolecular nucleophilic attack by the nitrogen[15]. This reaction shows that all hydrogens at C-16, C-15, C-20 are *cis* and thus the **D/E** rings are *cis*-fused and the hydroxymethyl group at C-16 is *trans* with respect to the bridgehead hydrogens.



Scheme 7.38



Scheme 7.39

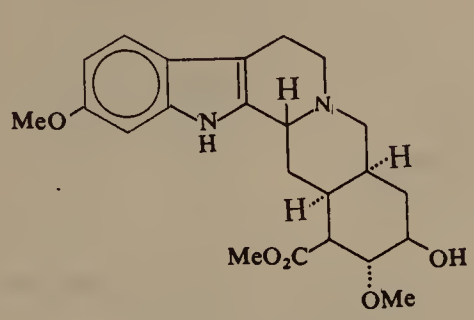


Scheme 7.40

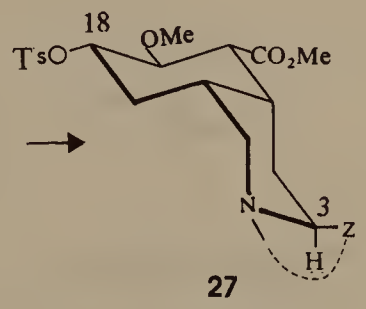
The tosyl group in reserpinol lies on a primary carbon, therefore, an inversion of configuration is not possible. When however, methyl reserpate is tosylated at C-18 followed by reaction with dimethyl-formamide an intramolecular quaternization occurs. The results are hard to interpret on the basis of a direct S_N2 displacement **28**, the orientation of the tosyl group being unfavorable.

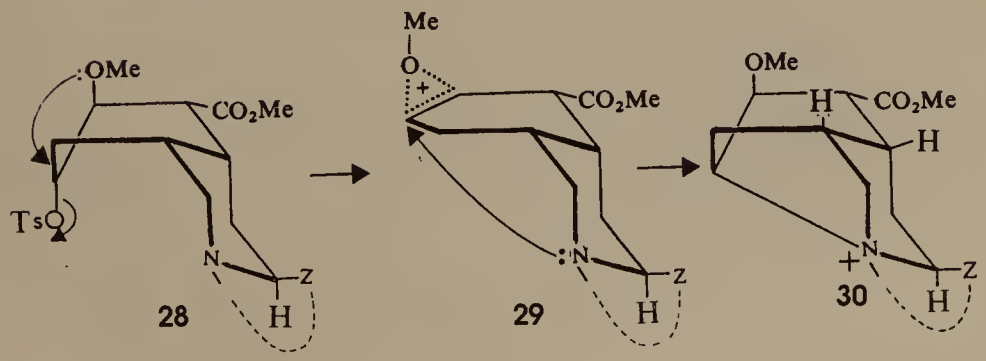
In the reserpine series, however, substitution reactions of a C-18 tosylate **27**

are observed to occur with retention of configuration and this must involve a neighboring group participation effect involving the C-17 methoxyl group. In the boat form **28**, the *anti* arrangement of the tosyl and methoxyl groups satisfies the coplanarity condition for the exit of the tosylate. The intermediate ion **22** thus formed would then undergo normal opening to give the cyclic salt **30**. The rationalization of these mechanistic results confirms the configurational assignment at C-18 and also confirms the stereochemistry of the ring fusions at C-17 in the tosylate 27.



methyl reserpate



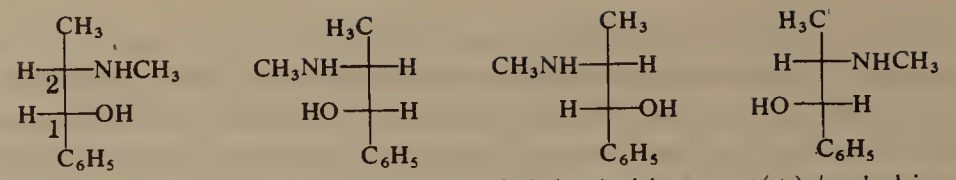


Scheme 7.41

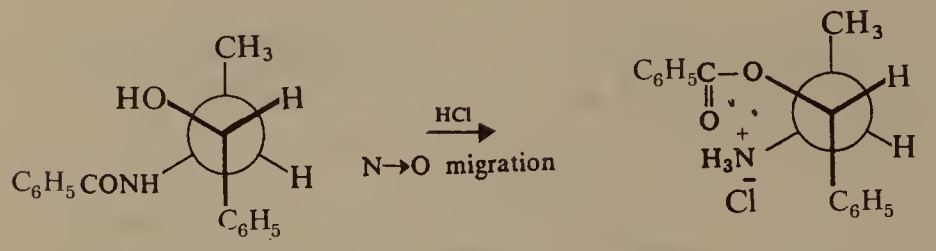
(C) Proximity Effects and Cyclic Transition States

Ephedrine (Scheme 7.42) a constitutionally unsymmetrical molecule has two dissimilar chiral centres (n=2), therefore, four optically active forms exist, in which carbons 1 and 2 are asymmetric. The (1*S*;2*R*)-(+) and (1*R*;2*S*)-(-) stereoisomers possess an enantiomeric relationship because they have opposed configurations on every chiral centre; these represent the *erythro* series (the proper ephedrines). The (1*R*;2*R*)-(-)- and (1*S*;2*S*)-(+)- stereoisomers are also enantiomers and represent the *threo* series; they are also named pseudoephedrines. Between any *erythro*-isomer and any *threo*-isomer, the relationship is that of diastereoisomerism. Two such stereoisomers have one chiral centre with opposed configurations, and one with similar configuration; therefore, they cannot be mirror reflections of each other.

Significantly *N*-benzoylnorpseudo-ephedrine upon treatment with alcoholic hydrogen chloride is immediately converted into the hydrochloride of the

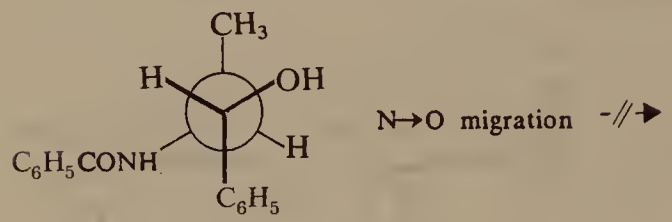


the *erythro*-configuration the *threo*-configuration

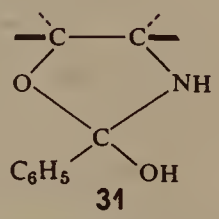


N-benzoylnor-ψ-ephedrine

the *O*-derivative



N- benzoylnorephedrine

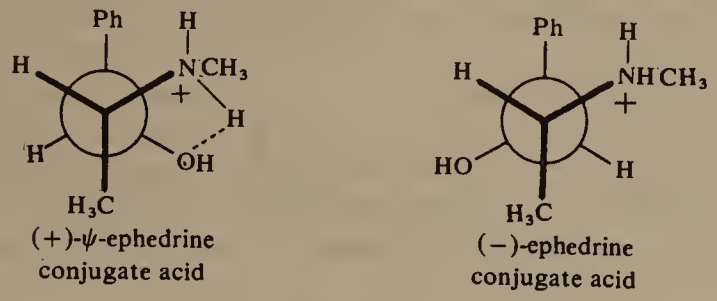


31

Scheme 7.42

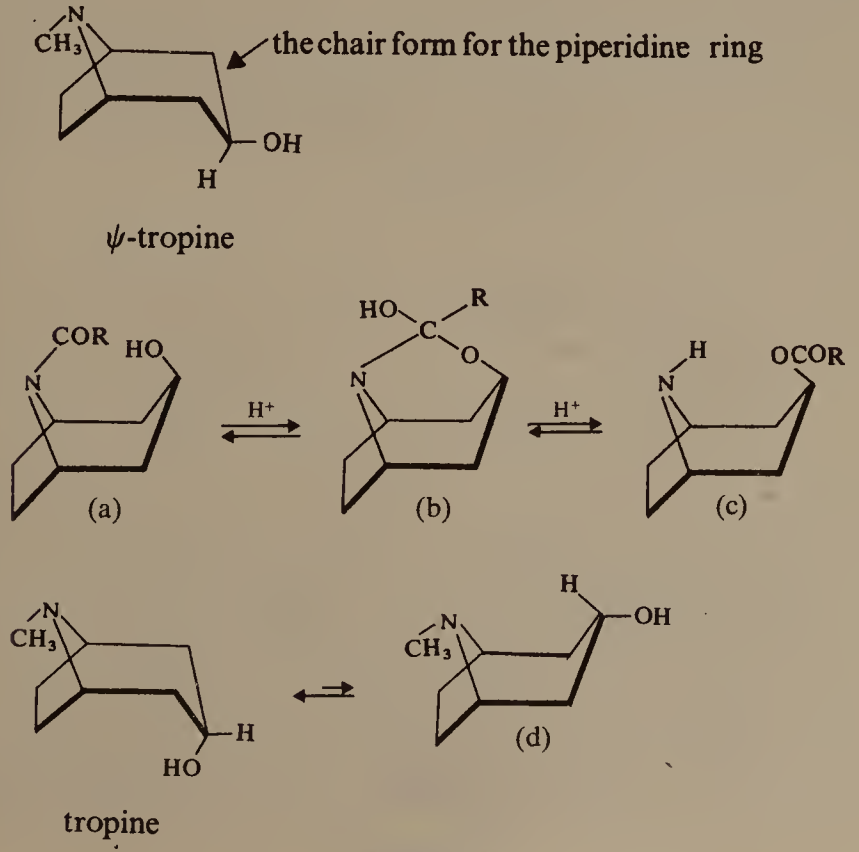
O-benzoyl derivative, while *N*-benzoylnorephedrine remains unchanged[16] under these conditions. This change is a result of suitable relative stereochemistry of the groups concerned for the migration *via* the formation of cyclic intermediate 31. Because of the *threo*-configuration in the pseudo-ephedrine derivative the benzamido and hydroxyl groups are close, *i.e.*, *gauche* and the methyl and phenyl groups are *anti*, while in the ephedrine derivative (*erythro*-configuration) the attainment of the transition state for N→O migration is repressed since the phenyl and methyl groups would be crowded together in *gauche* positions. Ephedrine (pK_a 9.14) is a weaker base than (+)- ψ-ephedrine (pK_a 9.22). In the conjugate acid of pseudo-ephedrine, hydrogen bonding is possible and thus conjugate acid is more stable than that of ephedrine. In ephedrine, rotation about the single bond could bring the OH and NH_2Me groups nearer (Scheme 7.43) for hydrogen bonding but this

conformation would suffer from strong steric interactions among the *gauche* methyl and phenyl groups (Scheme 7.43).



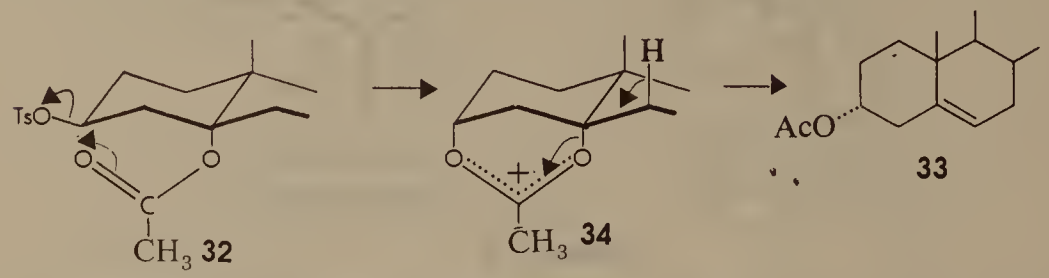
Scheme 7.43

This interesting approach has also been successfully applied to the determination of stereochemistry of the tropane alkaloids (Scheme 7.44), which have been shown to contain a chair form for the piperidine ring (sec. 4.12, c). In ψ-tropine the hydroxyl group is equatorial while in tropine it is axial. It has been shown that *N*-acetyl or benzoyl-nor-ψ tropine undergoes *N*→*O* acyl migration *via* a cyclic intermediate (b). Thus in ψ-tropine the hydroxyl group is equatorial and therefore, comes in close proximity to the acyl group while the piperidine ring assumes a boat conformation (a). Since the axial epimer nor-tropine derivative fails to react even in the boat form (d) for geometric reasons, a cyclic intermediate formation is not possible.



Scheme 7.44

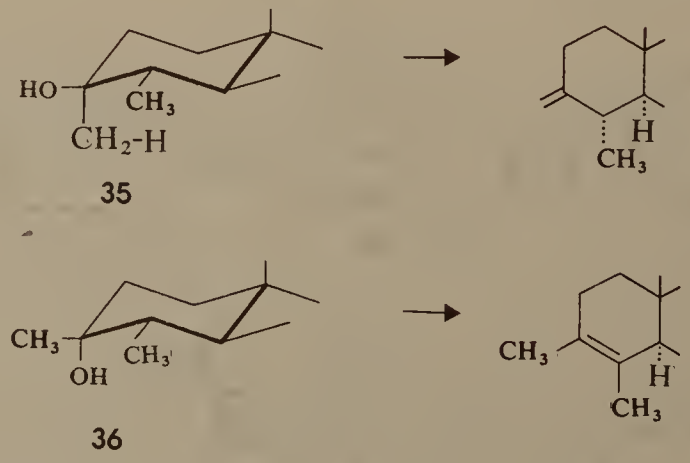
The formation of a different type of a cyclic intermediate involves the conversion of the tosylate of 5α-acetoxycholestan-3β-ol **32** (Scheme 7.45) to epicholesteryl acetate **33** under conditions of solvolysis. The reaction reflects the involvement of the cyclic intermediate **34** which explains the stereochemistry of **33** and establishes the α-orientation of the 5-acetoxyl group in **32**.



Scheme 7.45

(D) Conclusion

In conclusion mention may be made of several reaction mechanisms which a compound may undergo to provide an insight into the relative stereochemistry of the groups. For example *anti* periplanar relationship of the departing groups is the necessary condition, if a compound undergoes an E2 elimination. Thus, one may decide the relative stereochemistry[17] of the methyl and hydroxyl groups in **35** and **36**. In the steroid derivative **35** the equatorial hydroxyl group cannot achieve an *anti* periplanar relationship with the ring hydrogens. This relationship can only be attained with the hydrogen of the C-3 methyl group, so that the result of an E2-elimination is the formation of an *exo*-olefin. In the case of **36** axial hydrogens are available both on C-2 and C-4 for the C-3 axial hydroxyl group and the net result is the formation of a more substituted *endo*-olefin.



Scheme 7.46

Several other examples of reactions which have particular stereochemical requirements have been presented in various chapters *e.g.*, under pyrolytic eliminations, equilibration of active centres.

7.4 STEREOCHEMICAL APPLICATIONS OF SPECTROSCOPY

Several stereochemical reactions have been discussed in the text which throw light on the stereochemistry of the molecules undergoing these reactions. Stereochemical correlations involve the assessment of the unknown absolute configuration of a given molecule by deriving it from the molecule with known absolute configuration. Here some outlines of the spectral methods are given which provide information about conformations and some aspects of stereochemistry.

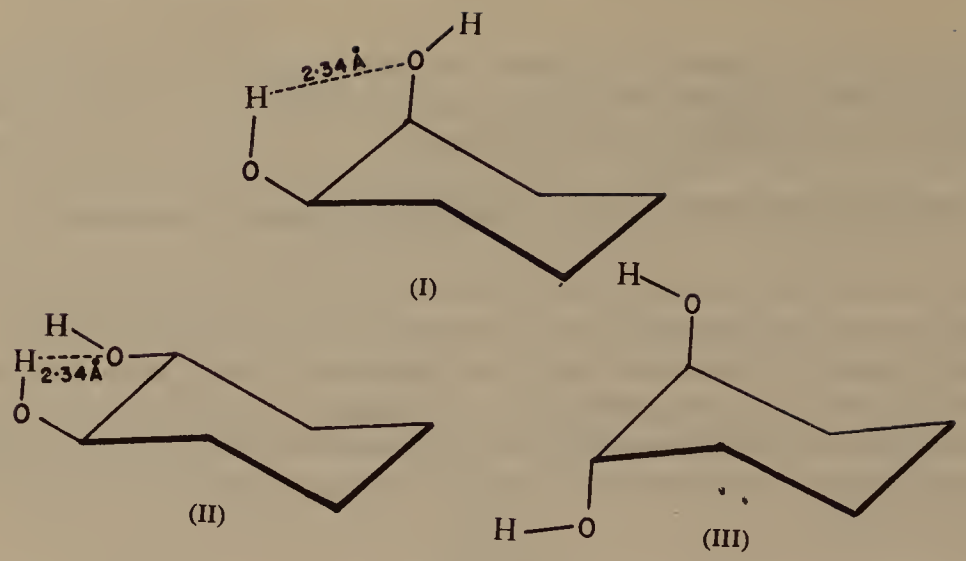
(A) Infrared (IR) Spectroscopy

This is an achiral technique of considerable utility for the study of diastereoisomers. The functional groups in diastereoisomeric molecules experience different molecular environments, these, therefore, absorb at different frequencies. IR spectroscopy has made significant contributions on conformational analysis [18] and in the study of intramolecular H bonds. The lower absorption frequency of hydrogen-bonded groups as compared to unbonded ones is the criterion. Some examples of the use of IR spectroscopy in study of conformations, hydrogen bonding and transannular effects are presented.

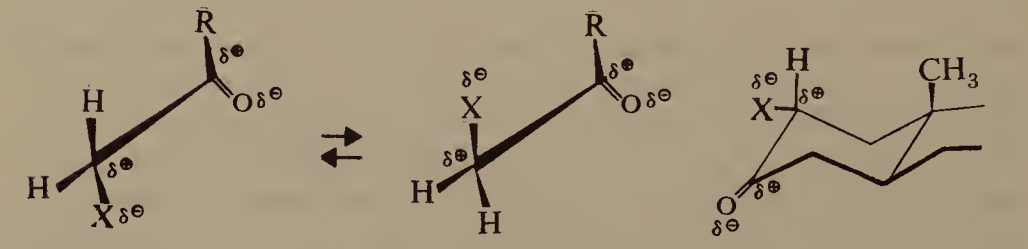
Cis-cyclohexane-1,2-diol exists in one form, one of the hydroxyl bonds is equatorial and the other is axial I (Scheme 7.47). Assuming normal values for the bond lengths and valence angles, the —OH..O bond is computed to be 2.34 Å .This compound shows an associated hydroxy band (3587 cm^{-1}), displaced 39 cm^{-1} from the free hydroxyl band.

The *trans*-cyclohexane-1,2-diol can have two conformations. One with both C—OH bonds equatorial (II) and the other with both axial (III). For the diequatorial structure an —OH...O-bond length of 2.34 Å is computed, and for the axial structure the bond, if formed, would be longer than 3.3Å. In the spectrum an associated hydroxyl band occurs from which it may be concluded that the diol has the diequatorial conformation.

Two or more polar groupings situated in the same molecule but insulated electronically from each other by single bonds, influence one another if brought close together. These dipolar, non-bonded interactions (field effects) are of electrostatic origin. These display themselves particularly well in α-haloketones, where a strongly electronegative atom can be brought near in space to a carbonyl moiety. A simple acyclic α-haloketone, $RCOCH_2X$ is normally free to adopt several conformations, two of which (**A** and **B**) are shown in Scheme 7.48, but the coplanar, 'opposed' conformer (**A**) is found to have a higher carbonyl frequency. However, two carbonyl frequencies are displayed proving that both rotational isomers are present. In rigid systems, such as that of the 2-halo-3-keto-steroid (**C**) only one frequency is recorded.



Scheme 7.47



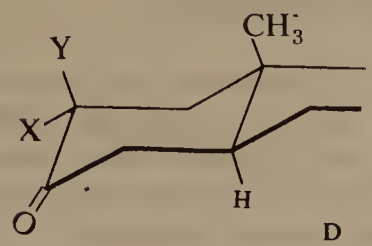
Scheme 7.48

Introduction of a second halogen on the α-carbon in steroids **D** (Scheme 7.49) did not alter the frequency (though it altered the intensity), however when the second chlorine was introduced at α′ (other adjacent carbon atom) a further frequency rise was observed (**E**).

In the equatorial halo ketone (**C**) the halogen eclipses carbonyl oxygen and causes an increase in carbonyl frequency as compared to (**D**, X=H, Y=H). In the axial isomers the halogen is quite far from carbonyl oxygen and hence in such compounds the carbonyl frequency is same as that of the parent.

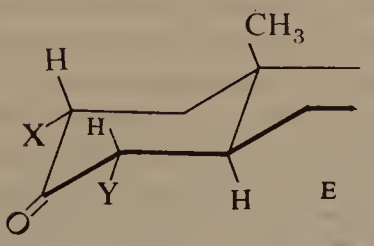
Yet another proximity effect may be operative *i.e.*, electron donation from a hetero atom to a carbonyl grouping has been found to occur transannularly in some medium ring systems (**F**), where it is revealed by the unusually low carbonyl frequency. Models show that the nitrogen lone pair can approach very close to the carbonyl carbon. Thus, the naturally occuring alkaloid protopine, **G** shows its C=O stretching at 1658 cm^{-1} (Scheme 7.50).

IR spectra of compounds in the solid state are sensitive to the crystalline form and therefore allow differentiation between optical antipodes and racemates[19]



D

	ν(CO) (cm⁻¹)
X = H Y = H	1718
X = Br Y = H	1733
X = Br Y = Br	1735
X = Cl Y = H	1738
X = Cl Y = Br	1742

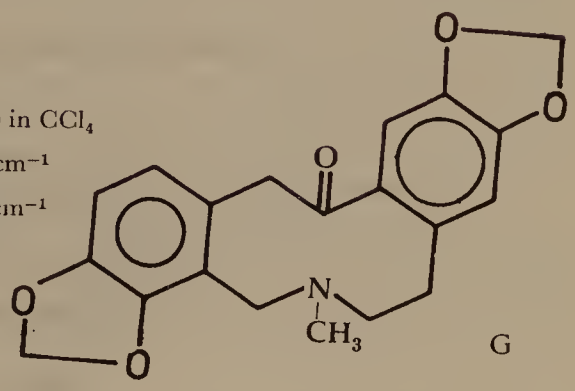


E

X = Br Y = Br	1756
X = Cl Y = Br	1758

Scheme 7.49

	ν(CO) in CCl_4
X = NMe	1681 cm^{-1}
X = CH_2	1705 cm^{-1}



G

Scheme 7.50

(B) Ultraviolet (UV) Spectroscopy

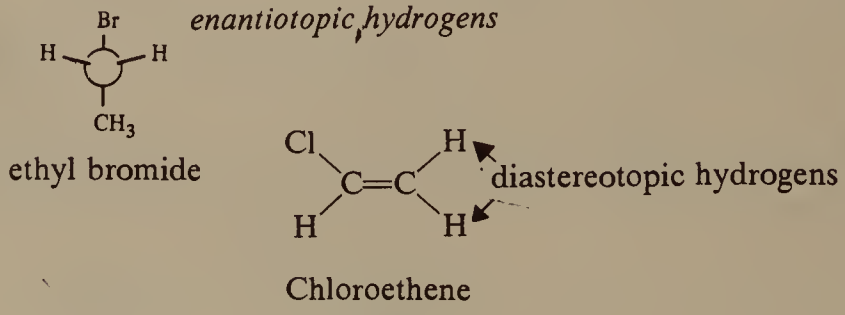
It is also an achiral method and cannot discriminate between enantiomeric molecules. Deviation from planarity as a result of steric effects of substituents decreases the delocalization of π electrons in suitable molecules. This feature is particularly detected in UV spectrum by a distinct, but smaller λ_{max} and a large decrease in ϵ.

A significant stereochemical application of UV spectroscopy is the study of configurational diastereoisomers particularly the π diastereoisomerism in conjugated systems. The effective length of the conjugated system is greater for the *trans*- compared to the *cis*-configuration. Thus often larger wavelengths and higher intensities of absorption are observed for the *trans*- compared to the *cis*-isomer (Sec. 1.10, B).

(C) Nuclear Magnetic Resonance (NMR) Spectroscopy

The interpretation of a ^{1}H-NMR spectrum rests on two main approaches, *i.e.*, the use of chemical shifts and the coupling contants. The diastereoisomers can be discriminated by NMR spectroscopy. In the diastereoisomers of stilbene (Sec. 1.10, B) the two olefinic protons are more deshielded in the *trans*-isomer compared to the *cis*-isomer, δ = 6.99 and 6.49 ppm, respectively[20].

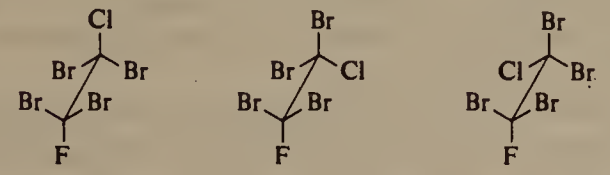
In addition to distinguishing protons in diastereoisomeric molecules, ^{1}H-NMR spectroscopy also discriminates between diastereotopic protons. Enantiotopic hydrogens have the same chemical shift as seen in the case of ethyl bromide (The enantiotopic hydrogens, however, may not have the same chemical shift if the compound is dissolved in an optically active solvent). The diastereotopic protons, however, display different chemical shifts as is the case with two diastereotopic geminal hydrogens of chloroethene (Sec. 1.20, f). This molecule, therefore, gives signals from three non-equivalent protons[21].



Scheme 7.51

Rotations about single bonds slow down as the temperature of the compound is lowered and this allows to detect the different conformations of a molecule. An example of the use of NMR in the study of rotations within molecules is given by the fluorine 19_F resonance spectrum of 1-chloro-2-fluoro-1,1,2,2- tetrabromoethane (Scheme 7.52). This molecule has three staggered rotamers (IV-VI). Out of these, (v) and (vi) will display identical NMR spectra. However, the fluorine of rotamer (iv) has a different environment, it being located between Br and Br, and as expected it displays a different chemical shift as compared with the fluorines of conformations (v) or (vi). In principle, thus, separate NMR resonances for the isomers are expected. At 122°C, rotation around the C—C bond is faster to change the conformations, and only a single fluorine resonance line is observed. At 40°C one, however, observes separate resonances for (iv) and its rotamers. Studies of the changes in line shape of the NMR spectrum of 1-chloro-2-fluoro-1,2,2, tetrabromoethane with temperature provide a method to estimate the amount of energy to be supplied to the molecules for rotation to occur. The halogens are bulky and do not move past

each other easily, it takes 15 kcal/mole of thermal energy to interconvert (iv), (v) and (vi). At 25°C, the rate of this interconversion is around 100 times per second.

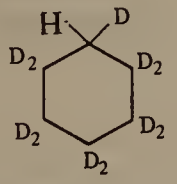


(IV) (V) (VI)

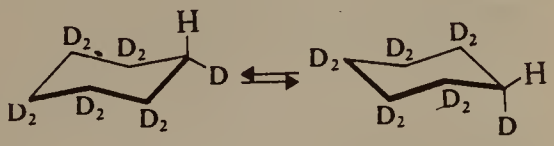
Scheme 7.52

The ^1H NMR spectra of cyclohexane and its derivatives have been examined to study the interconversions of the boat and chair forms. Cyclohexane displays itself in its spectrum as a single line at room temperature because of rapid inversion (~ 10^6 times per second) which averages to zero, the chemical-shift differences of the equatorial and axial protons. At — 100°C, the spectrum of cyclohexane is very complicated because the axial protons have different chemical shifts compared with the equatorial protons and subsequent complex spin-spin interactions. At - 100°C, however, undecadeuteriocyclohexane displays only two unsplit signals of equal intensity. These signals correspond to the axial and equatorial hydrogens of the two chair conformations shown below in Scheme 7.53.

Interconversions between these conformations do occur even at this low temperature, but they happen slowly enough for the NMR spectrometer to detect the individual conformations. However, at room temperature a single line is observed as expected.



undecadeuteriocyclohexane



Scheme 7.53

In addition to chemical shift data, other stereochemical information available from NMR spectra are the coupling constants (J). These are a measure of the spin-spin interactions between atoms A and B, and result in splitting patterns of the resonance signals. The magnitude of $J_{HH'}$ between vicinal protons (H—C—C—H′) is influenced by three molecular parameters[22].

(i) The dihedral angle θ between the vicinal protons :

$J_{HH'} = a \cdot \cos^2\theta - c$ (Karplus equation)

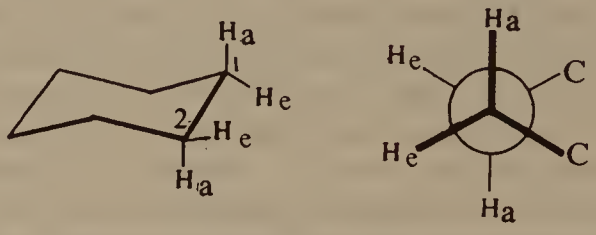
The value of *a* is dependent on the system, being greater for $0^0 \leq \theta \leq 90^0$ than it is for $90^0 \leq \theta \leq 180^0$; c is a constant which is normally small or nil.

(*ii*) The electronegativity of substituents :

Generally an increased electronegativity of the substituents decreases $J_{HH'}$, (*i.e., a* in Karplus equation) will have smaller values.

(*iii*) The C—C—H bond angles :

It is apparent from the equation that J will be maximum when the vicinal protons are *anti*-periplanar ($\theta = 180^0$) and minimum when the protons are at right angles. One of the most important consequences of the Karplus equation is on the order of magnitude of diaxial, axial-equatorial and diequatorial coupling constants (J_{aa}, J_{ae} and J_{ee} respectively) in a cyclohexane ring chair system (Scheme 7.54).



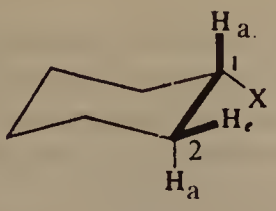
	Karplus equation	Observed Usual
J_{aa}	9	10–13
J_{ae}	1·8	2–5
J_{ee}	1·8	2–5

Scheme 7.54

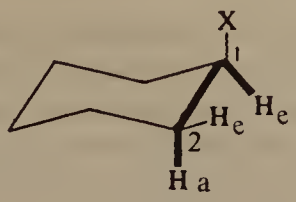
Karplus equation in its modified form is applied to vicinal couplings in olefins (H—C=C—H′) and predicts that *trans*-olefinic coupling constants ($\theta = 180^0$) will be larger than *cis*-olefinic coupling constants ($\theta = 0^0$). This indeed is found to be so (Sec. 1.10, B).

For cyclic systems, it has been shown[23,24] that the effect of an electronegative substituent (X) on the vicinal coupling constant is dependent on the orientation of X with respect to the coupling protons (Scheme 7.55). Thus, J_{ae} in a cyclohexane chair conformation is about 5.5 Hz for an equatorial substituent (vii, X = OH, OAc, Br), but only about 2.5 Hz for an axial substituent (viii, X = OH, OAc, Br).

These differences are displayed despite the similar dihedral angles (60^0) involved in both cases. In (vii and viii) the bonds through which the relevant vicinal couplings occur are marked with thick lines. The effect of X in reducing J_{vic} is greater when X is *anti*-periplanar with respect to the C-2 proton (H_a in viii) than when the angle between X and the C-2 proton (H_e in vii) is around 60^0. Therefore, the stereochemistry of the electronegative substituents can be deduced from the magnitude of the axial-equatorial coupling constants.



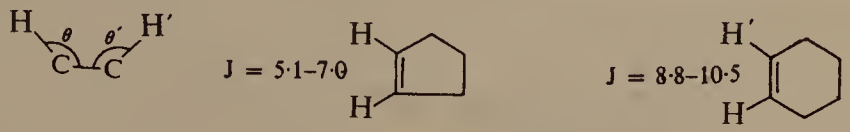
(VII)



(VIII)

Scheme 7.55

Vicinal coupling constants depend markedly on the angles θ and θ' subtended by the carbon-carbon and carbon-hydrogen bonds (Scheme 7.56). On decreasing the ring size from a six-membered to a five membered the angles (θ and θ') between the olefinic protons increase and this leads to a decrease in J_{vic}.



Scheme 7.56

Some optically active solvents [25] like 2,2,2-trifluoro-1-phenylethanol lead to small differences in the chemical shifts (lesser than 0.1 ppm) of some resonance signals of enantiomeric solutes. The chiral lanthanide shift reagents (LSR) consists of a six-coordinate metal complex which on expanding its coordination sphere, can accept more ligands. Hetereoatoms with Lewis basicity provide the required ligands, leading to the formation of paramagnetic lanthanide complexes and as a result, large pseudocontact shifts (lanthanide-induced shifts, LIS) are induced in nuclei [26, 27] close to the heteroatoms.

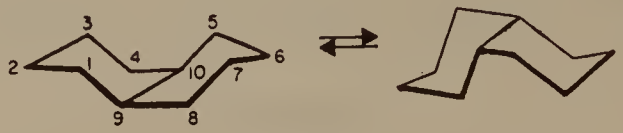
Achiral LSR provide several applications in stereochemical studies, like increased resolution and assignment of signals from diastereoisomeric and diastereotopic protons and in conformational studies.[28–30] Chiral LSR, on the other hand helps in the study of enantiomers.

^{13}C Shieldings and $^{13}C—^{1}H$ coupling constants[31] provide dramatic stereochemical information. Carbon-13 spectra when recorded with proton decoupling often display separate resolved signals for every individual carbon. The different environments of corresponding carbons in diastereoisomeric molecules are reflected in chemical shift differences which are much more than the analogous differences found in ^{1}H-NMR spectra. A methyl group displays different $^{\delta}C$ in *endo*- or *exo*-, axial- or equatorial-, *cis*- or *trans*- positions.

Cyclohexane itself cannot be studied by ^{13}C NMR, it being a unique case. Ring inversion processes in substituted cyclohexanes and practically all other ring systems can be better studied by ^{13}C than by ^{1}H NMR, since the $^{13}C—^{1}H$ spectrum will be free of any coupling and, therefore, will display a simple

picture. The ^{1}H spectrum of *cis*-decalin is a broad, unresolved spectrum showing no variation with temperature thus rate process could not be studied. The ^{13}C spectrum indeed displays the effects of a ring inversion process. At high temperatures (rapid inversion) it gives three distinct carbon resonances from $C_{9,10}$, $C_{1,4,5,8}$ and $C_{2,3,6,7}$ (intensity 1:2:2).

The ring inversion is arrested on cooling, one observes the spectrum of the single conformer, now, with five distinct signals. The bridging carbons $C_{9,10}$ have same chemical shifts in the two conformers and are thus not affected by the inversion process. The other carbons however, as expected are affected. The single conformer has a twofold axis of symmetry (C_2) so that $C_{1,5}$; $C_{2,6}$; $C_{3,7}$ and $C_{4,8}$ are identical by symmetry; ring inversion equates $C_{1,5}$ after cooling with $C_{4,8}$ and $C_{2,6}$ with $C_{3,7}$. The signals of *trans*-decalin remain sharp and independent of temperature as there is no comparable ring inversion process for the *trans*- decalin which exists entirely in the single conformation.



Scheme 7.57

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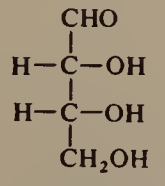
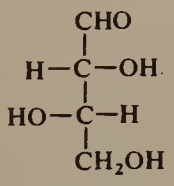
EXERCISES AND PROBLEMS

1. How can you confirm the following structures assigned to erythrose and threose on the basis of oxidation studies ?

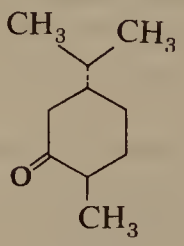


(−)-erythrose

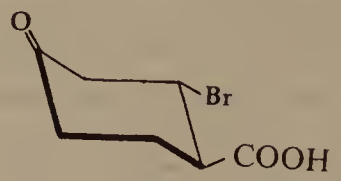


(+)-threose

2. Predict the Cotton effect by the sign of the most occupied octant in the following compounds

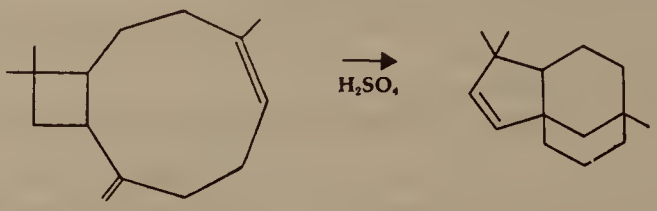


Dihydrocarvone



2-bromo- cyclohexan-4-one carboxylic acid

3. The sesquiterpene caryophyllene on treatment with acid undergoes a molecular rearrangement to an isomeric compound clovene. Depict the mechanism.



Caryophyllene

Clovene

8

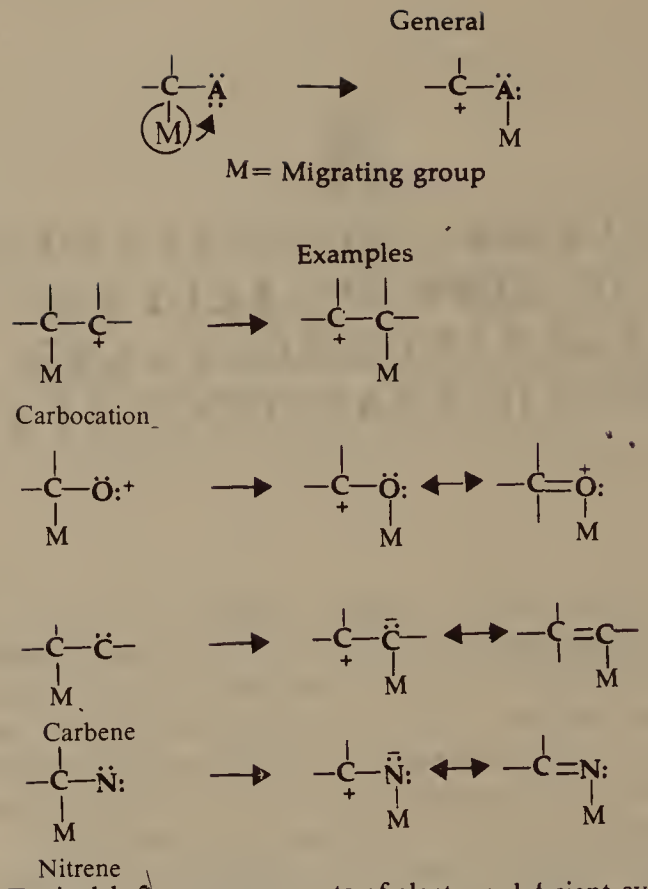
THE STEREOCHEMICAL COURSE OF SOME MOLECULAR REARRANGEMENTS AND PERICYCLIC TRANSITION STATES

Most of the reactions involve changes at functional groups, the carbon frameworks of the reactants remain structurally invariant throughout the course of reaction. One, however, comes across some examples where functional groups migrate within molecules and carbon skeletons are modified and these transformations are termed molecular rearrangements. The most important of the molecular rearrangements involve migration of a group from one atom to another within the molecule itself.

Many molecular rarrangements may be explained by the 1,2-shift mechanism. The migrating group M (Scheme 8.1) may move with its bonding pair of electrons to an electron deficient atom (these may be named nucleophilic or anionotropic rearrangements where the migrating group may be regarded a nucleophile), without its bonding pair of electrons to an electron rich atom (electrophilic or cationotropic rearrangements and when hydrogen is migrating prototropic rearrangements, sec. 8.2) and lastly with only one electron (free-radical rearrangements, sec 8.3).

8.1 ELECTRON DEFICIENT SKELETAL REARRAGEMENTS

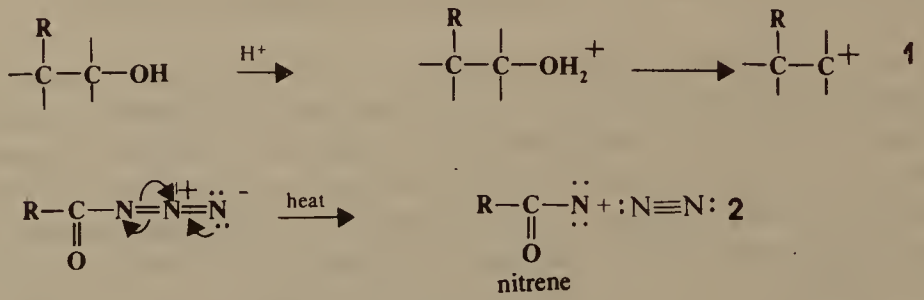
The most important group of molecular rearrangements involves the migration of a group from one atom to an adjacent atom which is electron deficient (1, 2-shifts). The atom from which migration begins (the migration origin) and the atom to which the migrating group moves (the migration terminus) are usually adjacent to each other; *e.g.*, 1.2-migrations are more common (Scheme 8.1). The electron deficient atom to which migration occurs mav be charged (*i.e.*, a cation) or electrically neutral (*i.e.*, carbenes and nitrenes). Without going deep at the level of sophistication, these rearrangements may be thought to occur in three steps. The first step involves the generation of an electron deficient centre *i.e.*, an open sextet (eqs. 1 and 2, Scheme 8.2). The second step consists of actual migration (Scheme 8.1). The third step involves the acquiring of an octet by the atom at the migration origin, which had an open sextet after the migration.



Typical 1, 2-rearrangements of electron-deficient systems

Scheme 8.1

Systems with an open sextet may be generated in several ways and two of these are presented here. A carbocation is formed by the acid treatment of an alcohol (eq. 1, Scheme 8.2) while a nitrene is formed by the decomposition of an acyl azide (eq.2).



Scheme 8.2

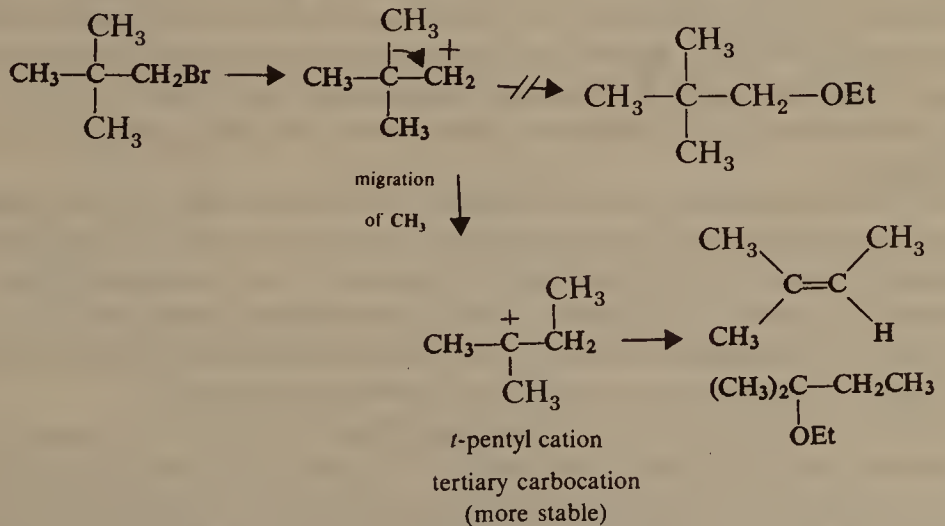
These rearrangements have been presented to proceed in three steps, indeed, some reactions do occur in a step-wise fashion (sec. 8.1, A i). However, in several others, two or all the three steps may be concerted, *i.e.*, simultaneous, (sec. 8.1, A, ii). Majority of the 1,2 shifts are intramolecular. The

migrating group M, therefore, does not become free and keeps attached to the substrate in some way. The strongest evidence for this nature of migration is, that if the migrating group is attached *via* a chiral carbon atom, the latter preserves its configuration even in the final product. Conversely, a change of configuration occurs at the carbon atom to which the group M migrates (sec. 8.1, B). The stereochemical course may be explained satisfactorily by the assumption that the forming and breaking of bonds is a simultaneous process and that its energy is lowest if the migrating group replaces the leaving group from the opposite side. There is more on mechanistic and stereochemical possibilities under Sec. 8.1, A,iii:

(A) Migration to a Carbocation Center

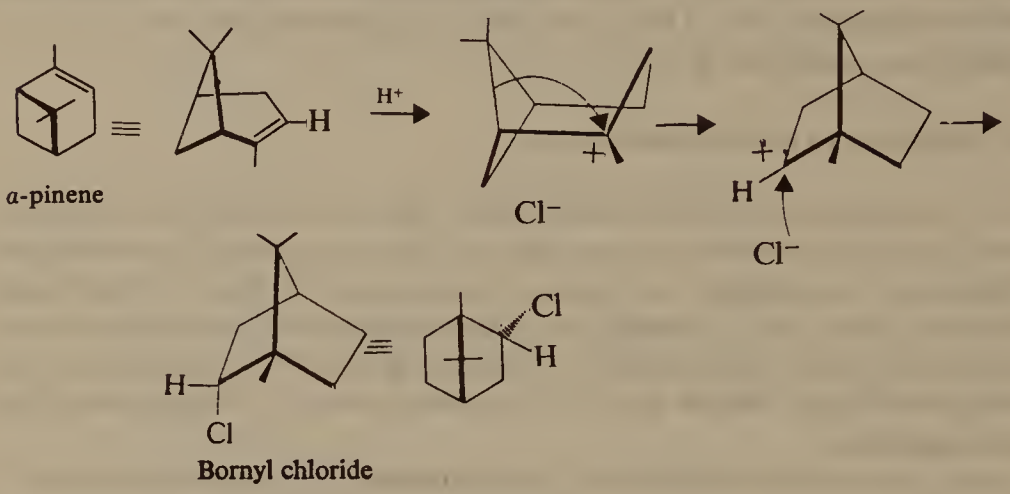
(*i*) *Wagner-Meerwein Rearrangement*: The reactions which involve an intermediate formation of a carbocation can lead to products of substitution, elimination, or addition with a rearranged carbon skeleton. A rearranged product is formed in preference when the carbocation can be converted to a more stable ion by the 1,2-shift of an adjacent group. These migrations to an electron-deficient carbon atom are broadly termed as Wagner-Meerwein rearrangements.

A simple system within which carbon migrates, with its bonding-pair, to an electron-deficient carbon atom is the neopentyl cation (Scheme 8.3). The primary neopentyl cation often proposed to explain this rearrangement has a short lifetime and may not even be an intermediate. Intramolecular migration of a methyl group leads to a tertiary cation at a rate much faster than intermolecular reaction with solvent; products almost always have the rearranged structure. Thus, the solvolysis of neopentyl bromide in ethanol gives a mixture of trimethylethylene and ethyl *t*-amyl ether.



Scheme 8.3

The relief of strain in cyclic systems can provide a driving force for rearrangement. The addition of hydrogen chloride to α-pinene gives the rearranged product, bornyl chloride (Scheme 8.4). The four-membered ring in the carbocation expands to the less strained five-membered analogue, even though the former contains a tertiary and the latter a secondary carbocation. In fact it has been shown that the species involved in this rearrangement are non-classical carbocations (Sec. 3.7, E).



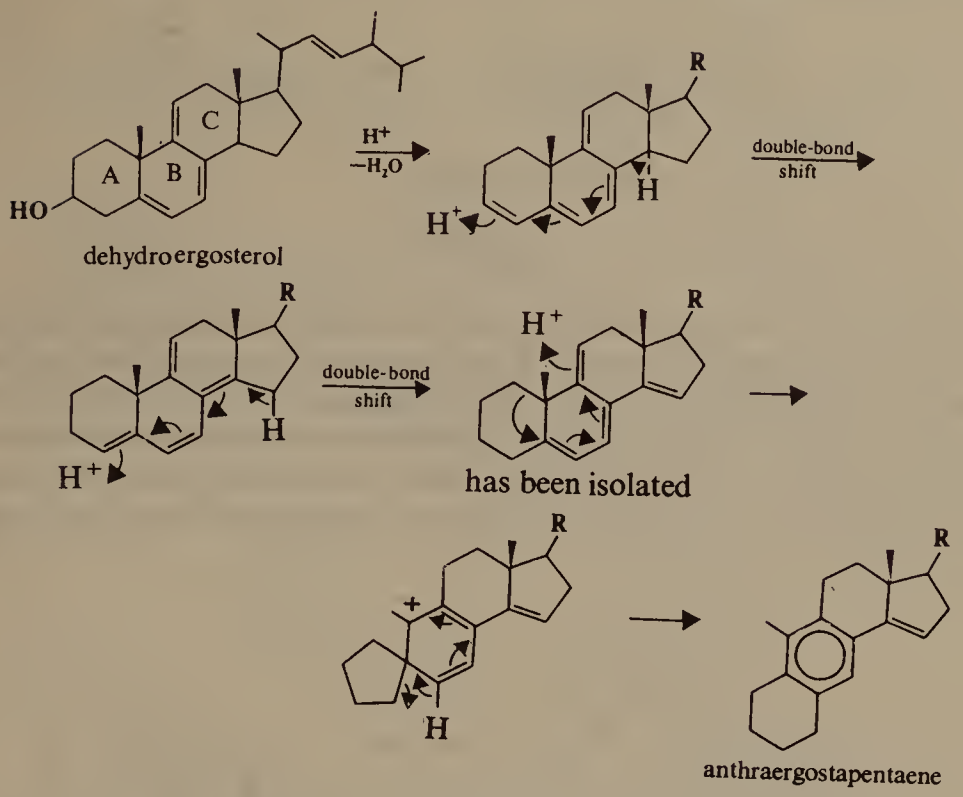
Scheme 8.4

In the steroid series the A-B-C rings of a steroid dehydroergosterol are changed from an angular (phenanthrene-like) arrangement to a linear (anthracene-like) type in the so-called the anthrasteroid rearrangement.

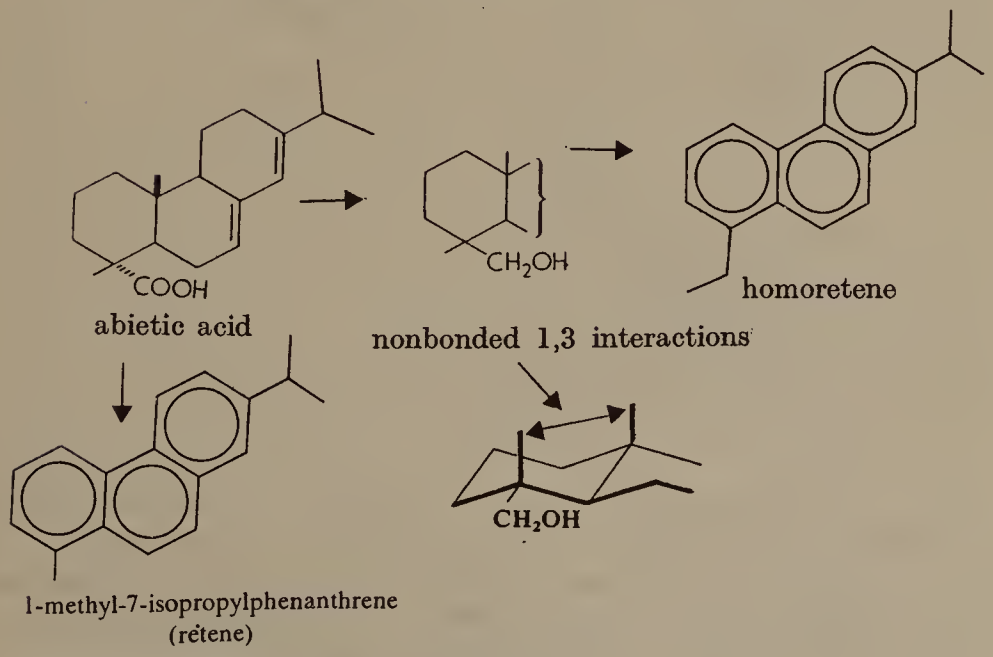
Abietic acid on dehydrogenation gives retene in confirmation with the assigned carbon skeleton. Reduction of its ester to the corresponding alcohol and dehydration with phosphorus pentachloride gave a triply unsaturated hydrocarbon. This hydrocarbon on dehydrogenation afforded methylretene involving the Wagner shift of the axial methyl group which relieves the unfavourable non-bonded 1,3-interactions during dehydration. This experiment indeed locates the position of carboxyl group in abietic acid to ring A as indicated.

The Wagner-Meerwein rearrangement is stereospecific; the migrating group approaches the electron-deficient carbon atom from the direction opposite to that in which the departing group is moving just as in the S_N2 reaction. Examples to support this requirement have been presented *i.e.*, conversion of camphene hydrochloride to isobornyl chloride (Sec. 2.3) and the ring A contraction in the case of triterpenoids (Sec. 5.6).

Under the conditions of dehydration (Scheme 8.7) the Wagner type migration of the 4, 5 bond is concerted with the loss of hydroxyl and for this C-3, C-4, C-5 and oxygen are required to be *trans* and coplanar which is only possible if the C-3 hydroxyl is equatorial. Use of standard methods subsequently gives useful information about the structure of ring A. This classic diagnostic test of ring A contraction for these stereochemical require-



Scheme 8.5



Scheme 8.6

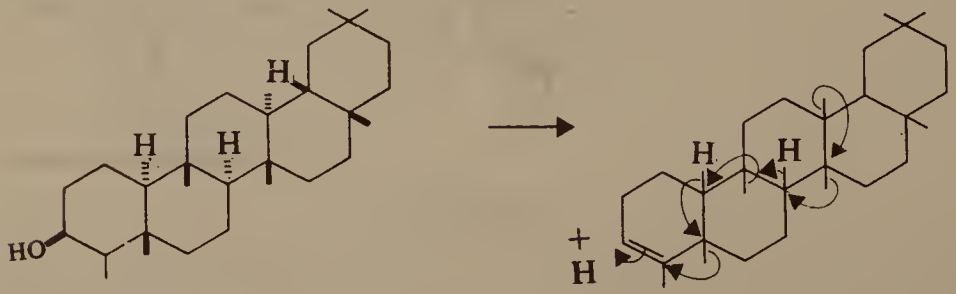
ments is very useful and as expected, the epimeric, axial 3α-alcohols dehydrate without ring contraction.

In some cases several of these arrangements occur in a molecule in a rapid succession *e.g.*, in friedelin. Its corresponding alcohol 3β-friedelanol on acid

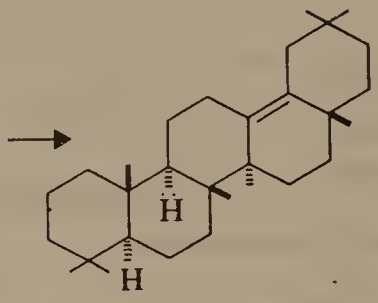
ring A of the triterpenoids

Scheme 8.7

catalysed dehydration undergoes many 1,2 shifts. Of these four are methyl, and three hydrogen shifts (Scheme 8.8). In each case migration takes place over the same side of the molecule on which the migrating group exists (stereospecific shifts). The loss of a proton leads to the formation of the double bond in D ring. The reaction may not be entirely concerted, since an intermediate has been isolated, and this evidence excludes the presence of discrete uncharged intermediates.



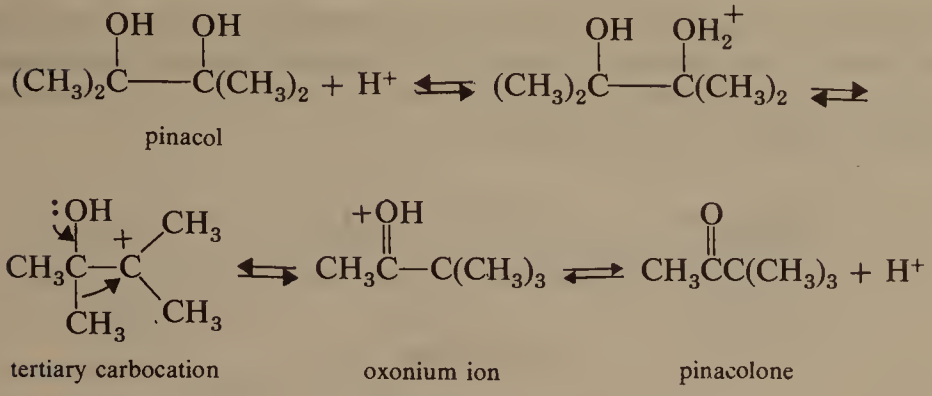
friedelanol



Scheme 8.8

(*ii*) *Pinacol Rearrangement (Migratory Aptitudes) with Acid:* Dehydration of 1,2-diols (pinacols) leads to the reaction—the pinacol rearrangement—is believed to involve initial formation of a carbocation followed by migration of an alkyl, an aryl group or a hydride. The remaining hydroxy oxygen atom imparts stability to the new cationic center (Scheme 8.9).

In addition to 1,2-diols, α halohydrins undergo this rearrangement in the presence of Lewis acids. Deamination of α-amino alcohols *via* the diazonium ion on treatment with nitrous acid resembles the pinacol rearrangement and is often termed semipinacol rearrangement.

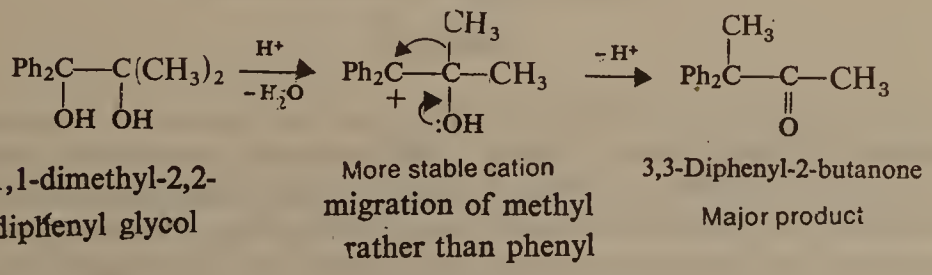


Scheme 8.9

Scheme 8.10

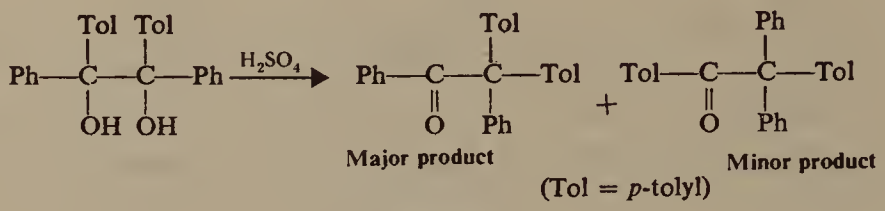
The pinacol rearrangement has been used as a model to study the characteristics of migration to a carbocation center. When a pinacol with two different groups on the carbinol carbon atom is allowed to react with acid, there are different rates of migration (migratory aptitudes). Since rearrangement involves movement of the migrating group with its bonding electrons to an electron-deficient center, therefore, migratory aptitudes are greatest for groups in which the migrating atom is most electron rich.

Although like other rearrangements of this category it is convenient to depict it as involving carbocations, the rearrangement is actually a concerted process. The outcome of this rearrangement depends on three factors: (*a*) site of carbocation formation, (*b*) the migratory aptitude of the neighboring groups (hydrogen, alkyl, aryl), and (*c*) the stereochemical requirements of the reaction and conformational effects. The carbocation forms at that site where the cation is better stabilized. This factor takes precedence over the migratory-aptitude factor (Scheme 8.10a).



Scheme 8.10a

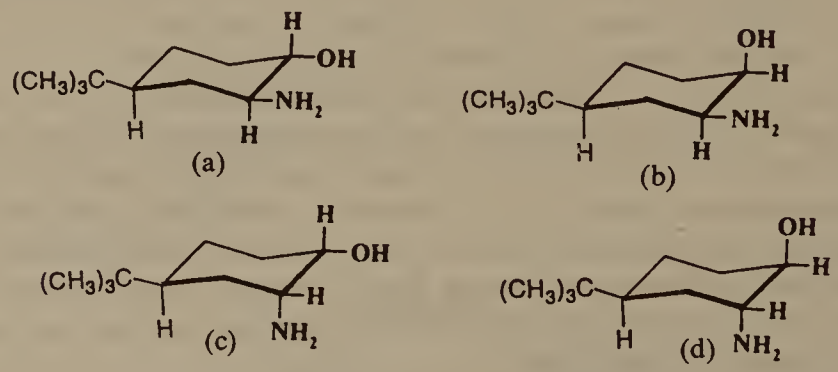
The migratory aptitudes of aryl groups generally are greater than those of alkyl groups, and amongst aryl groups the migratory aptitude increases as the aromatic nucleus is made increasingly electron-rich (*i.e.*, *p*-chlorophenyl < phenyl < *p*-tolyl < *p*-anisyl (Scheme 8.11).



Scheme 8.11

The migratory aptitude of hydrogen in the pinacol rearrangement is more difficult to assess. In some cases hydrogen migrates less rapidly and in other cases more rapidly as compared to alkyl groups.

Migratory aptitudes, arising from the electronic differences of groups, are superceded, however, by the requirement that the migrating and leaving groups be *anti* to each other (*i.e.*, *anti*-periplanar conformation). This requirement has important consequences in alicyclic systems. Thus with the use of conformationally rigid molecules, it is shown that deamination is highly stereoselective. The four isomeric 4-*t*-butyl-2-aminocyclo hexanols were treated with nitrous acid (Scheme 8.12), and in each case only one product was isolated.

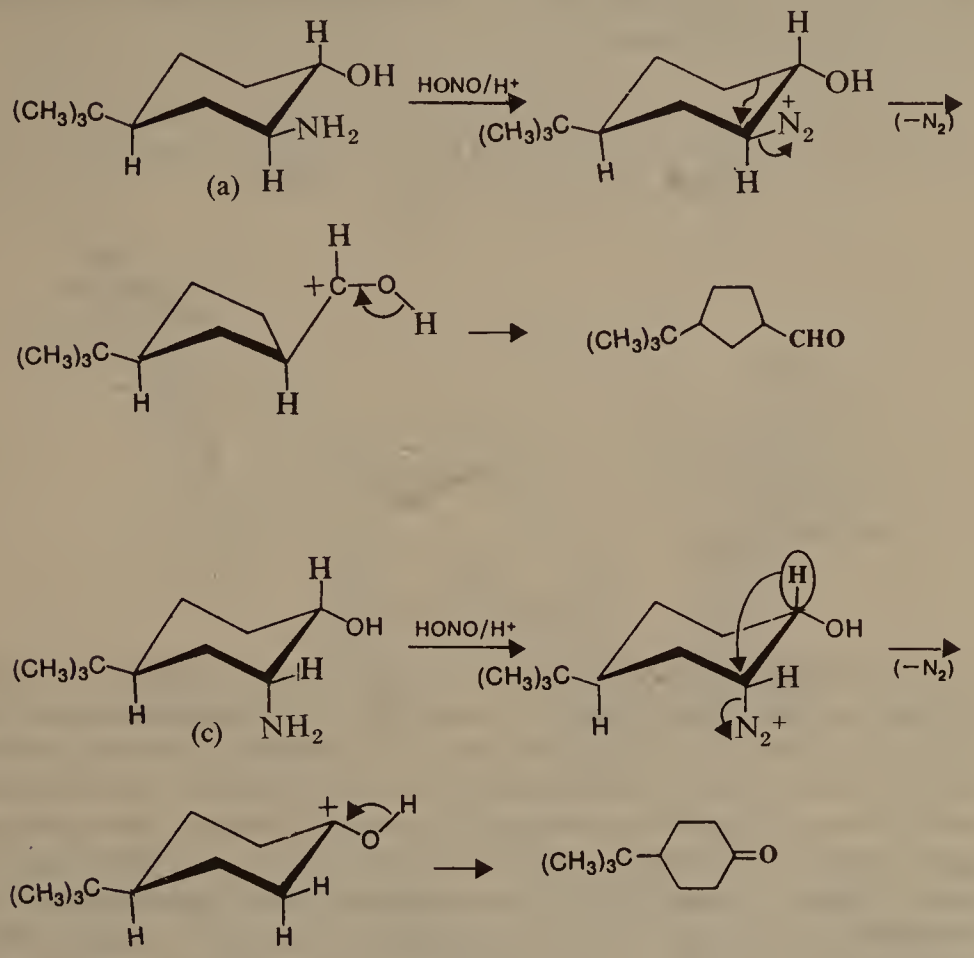


four isomeric 4-*t*-butyl-2-aminocyclohexanols

Scheme 8.12

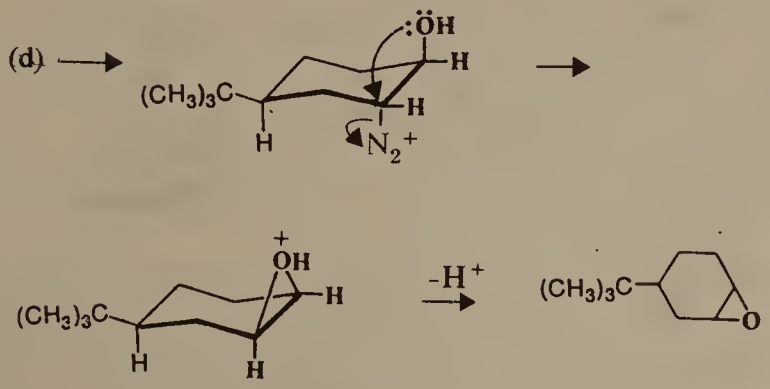
In the reaction of nitrous acid with a pair of epimers of 2-amino-4-*t*-butylcyclohexanol (a and c, Scheme 8.13), the amino group acts as a leaving group. In the epimer (a) in which the hydroxyl and amino functions are both equatorial, the group that is *anti* to the amino function is a ring residue *i.e.*, C—C bond of the ring; migration of a ring carbon takes place resulting in ring contraction. In the epimer (c) in which the hydroxyl function is equatorial and the amino function is axial, the group that is *anti* to the amino group is a

C-H bond. Hence migration of a hydrogen takes place and a cyclohexanone is formed.



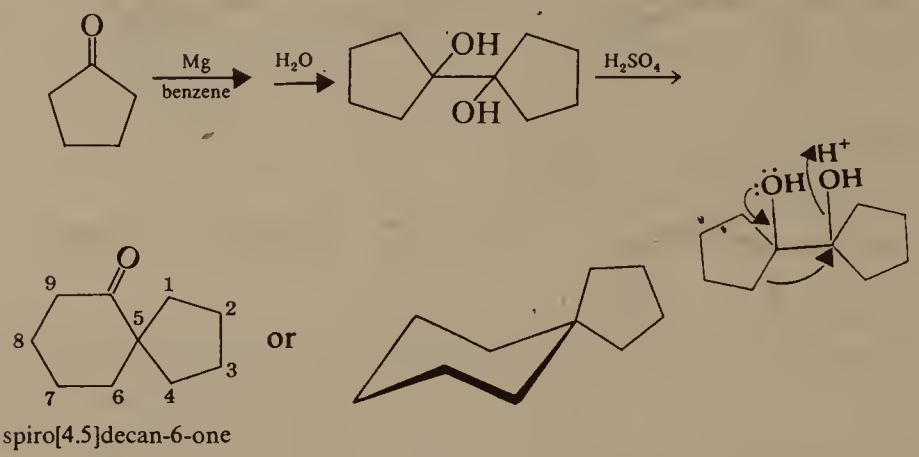
Scheme 8.13

Similarly (b) also affords the same ring contracted aldehyde as formed from (a). In the case of (d) Scheme 8.4 an epoxide is formed, because the axial hydroxyl group forms a bond with the carbocation carbon.



Scheme 8.14

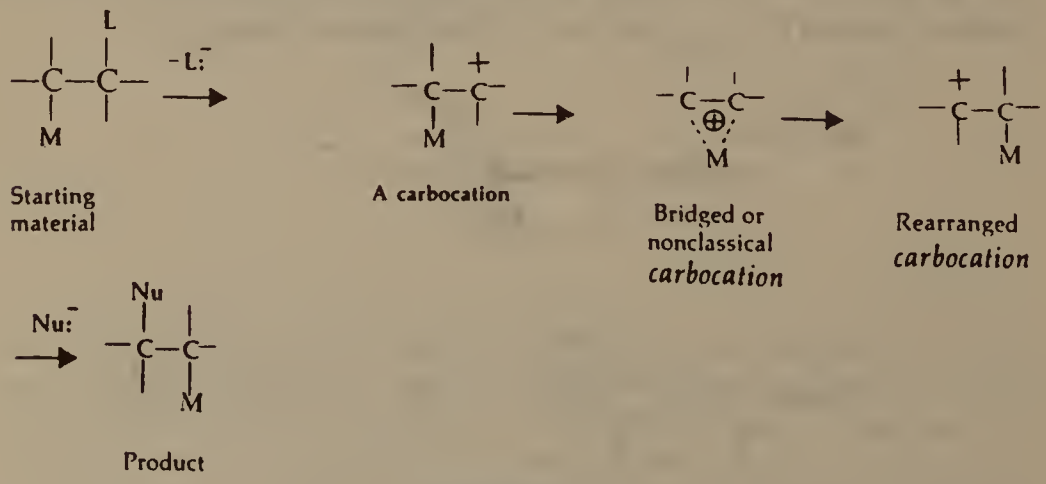
By combining the pinacol reaction with this acid-catalyzed molecular rearrangement process (Scheme 8.15), interesting and unusual compounds may be prepared, *i.e.*, spirocyclic compounds and compounds with contracted and expanded rings.



spiro[4.5]decan-6-one

Scheme 8.15

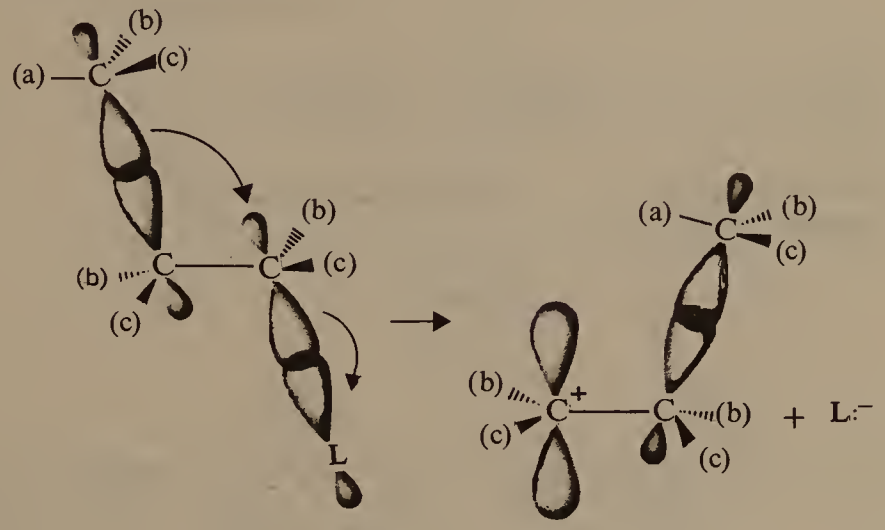
(*iii*) *General Mechanistic and Stereochemical Possibilities:* A general mechanism of these rearrangements usually involves initial formation of the electron-deficient center, *e.g.*, the carbocation migration terminus (Scheme 8.2). In fact the various cations probably do not fully develop. The remarkable and strict stereochemical outcome of these rearrangements (discussed later) support this fact. Another possibility is that the migration of the group M is concerted with departure of the leaving group. The migrating group then functions as an internal nucleophile to displace the leaving group and the process is S_N2 like. The migrating group thus bridges the migration origin and terminus. Extensive efforts have been made to find out if this bridged ion is a transition state or an intermediate—a question encountered in the discussion of neighboring group participation.



Scheme 8.16

In several cases the results show that a bridged species is indeed a discrete intermediate and its tenuous existence has been proved by spectral methods. A few examples in support of these views will be presented.

When one views the orbital picture of these rearrangements (Scheme 8.17) the retention of configuration in the migrating group and inversion at the migration terminus during a concerted process is made clear, and the importance of stereoelectronic factors during these molecular rearrangements come to light.



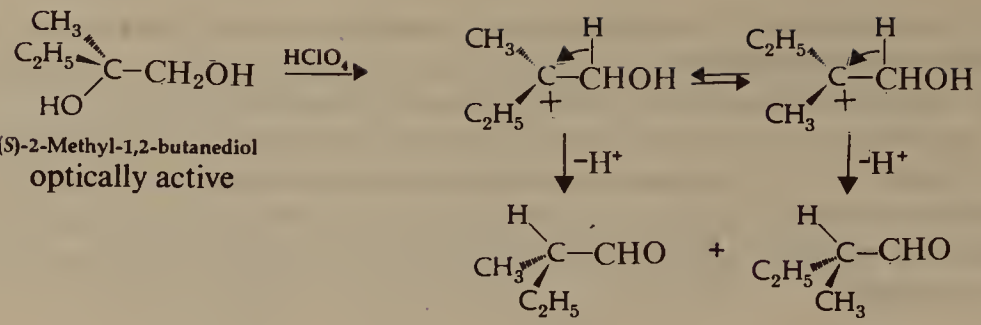
Scheme 8.17

The lifetime of the intermediate cation is also important and deserves consideration. During rearrangement of optically active 2-methyl-1,2-butanediol, the relatively slow hydride migration provides enough time for the carbocation to rotate to yield racemic product. In the case of the analogous rearrangement initiated by deamination, a more rapid reaction leads to significant inversion of configuration at the migration terminus.

The importance of the involvement of a stable conformation, concertion and carbocations has been discussed in an experiment in which an isotopically labelled or unlabelled phenyl group could undergo migration (Sec. 4.5).

Wagner-Meerwein rearrangement is often presented as a stepwise process in which the leaving group comes off before the migrating group moves. Evidence that an aromatic group can begin to move prior to departure of the leaving group is however, available. In certain solvolysis-rearrangement reactions β-aryl group provides neighboring group assistance and makes reaction rates faster.

Participation by aryl groups was inferred by observing the stereochemical course of acetolysis of 3-phenyl-2-butyl tosylate in acetic acid. The *threo* tosylate yields 96 percent *threo* acetate while a similar reaction of the *erythro* diastereomer yields namely *erythro* acetate (Sec. 3.7 C). Solvolysis proceeds with retention, as is expected, when back-sided neighboring group participation is operative.

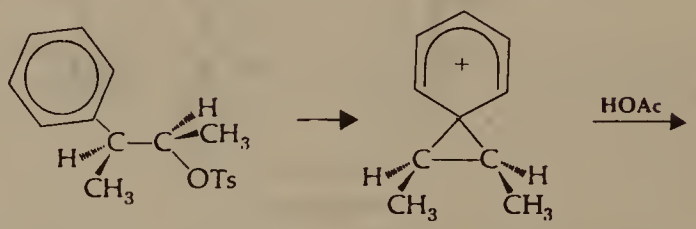


(*S*)-2-Methyl-1,2-butanediol
optically active

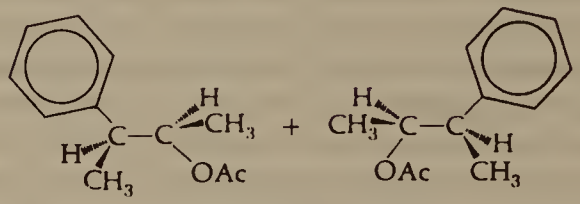
(*S*)-2-Amino-2-methyl-1-butanol
optically active

2-Methylbutanal (30% inversion)

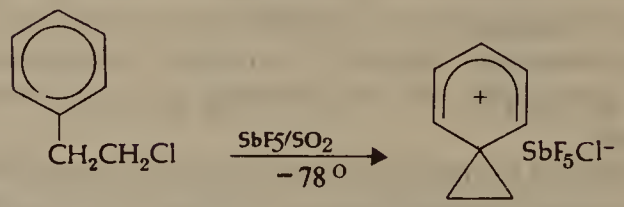
Scheme 8.18



3-phenyl-2-butyl tosylate
threo



96 percent threo acetate
retention



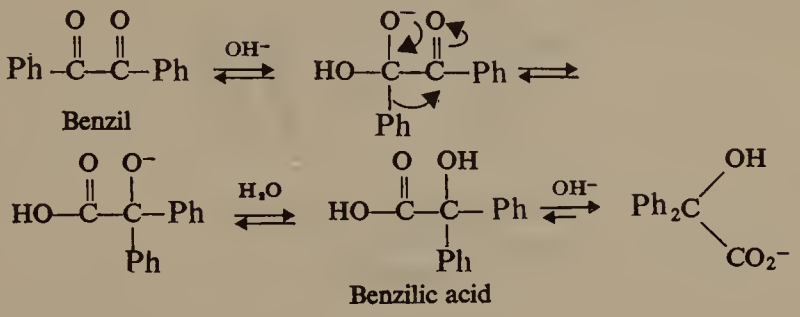
2-phenylethyl chloride

a phenonium ion

Scheme 8.19

The phenonium ion (Scheme 8.19) is depicted as a spiro cyclopropane in which the positively charged aromatic ring is perpendicular to the cyclopropane plane. Reaction of 2-phenylethyl chloride with antimony pentafluoride in chlorosulfuryl chloride at −78°C affords an intermediate cation which has ^{13}C-NMR spectral properties in keeping with the charge delocalized structure of a phenonium ion.

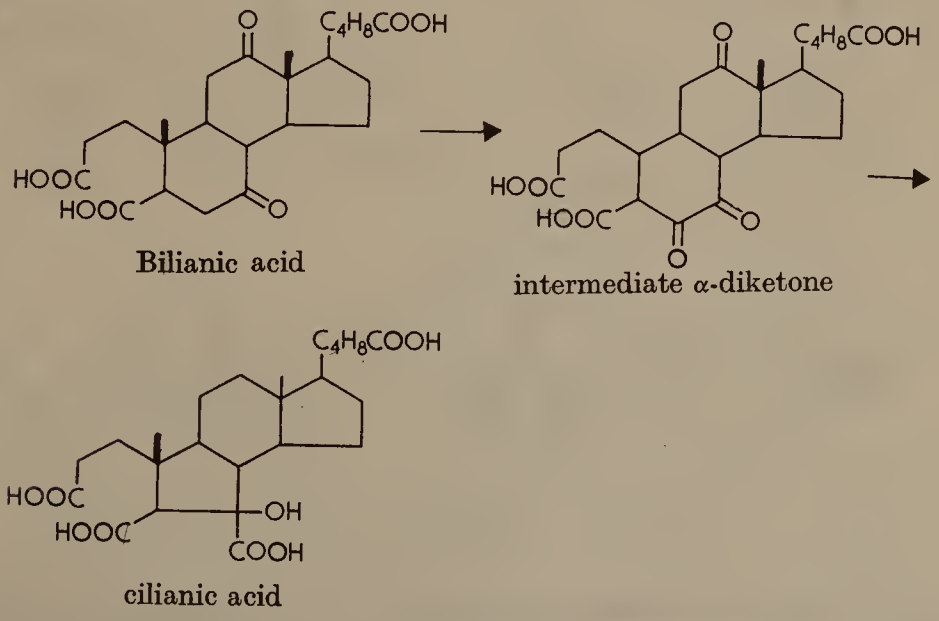
(*iv*) *The Benzilic Acid and Acyloin Rearrangements:* 1,2-diketones (α-diketones) are induced to undergo a molecular rearrangement on treatment with strong aqueous base to yield α-hydroxy-acids (Scheme 8.20).



Scheme 8.20

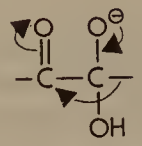
The mechanism is thought to involve nucleophilic addition of hydroxide followed by a 1,2 shift of an *R* group concomitant with the formation of a carboxylic acid group.

Benzilic acid rearrangement is indeed involved in the degradation of the bile acids (Scheme 8.21). Bilianic acid formed during the alkaline permanganate oxidation of dehydrocholic acid affords cilianic acid, formed through the intermediate α-diketone.

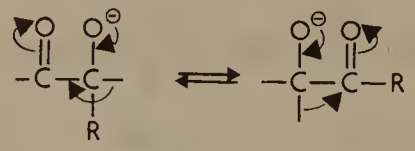


Scheme 8.21

The acyloin rearrangement is very similar to the benzilic acid change, however, the negative charge on the carboxylate ion prohibits the reversibility of the benzilic acid change while the acyloin change is indeed reversible.



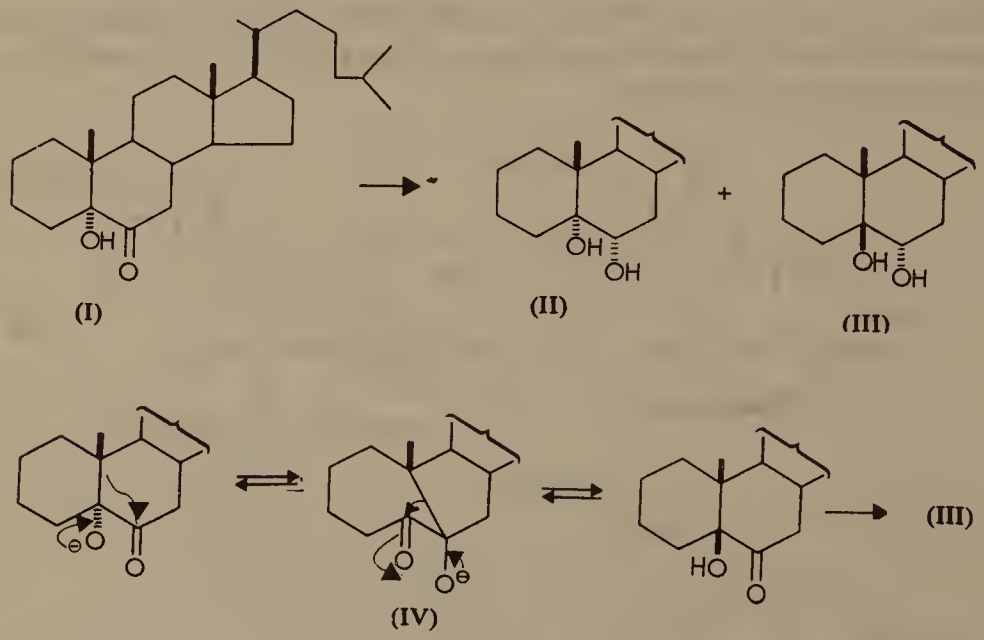
benzilic acid rearrangement



the acyloin rearrangement

Scheme 8.22

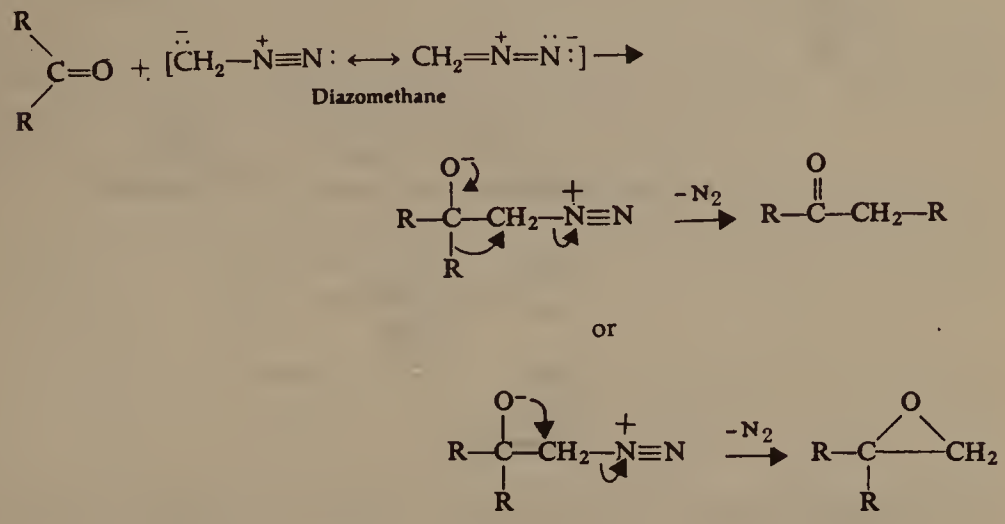
The reversibility of the acyloin rearrangement is well illustrated in the reduction of 5-hyuroxycholestan-6-one (I) with sodium and n-propanol (Scheme 8.23) which produced both cholestan-5 α, 6α-diol (II) and coprostan-5β, 6α-diol (III). The formation of III does not, of course, involve (II) as an intermediate, and the epimerization is best represented by (IV).



Scheme 8.23

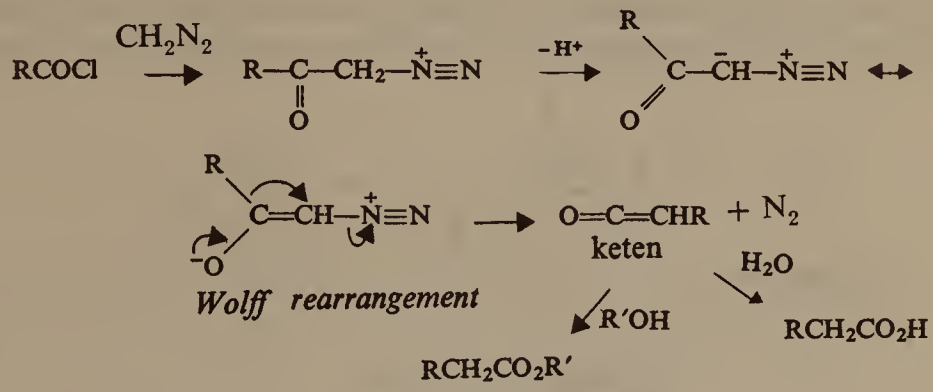
(*v*) *Rearrangements Involving Diazomethane :* Diazomethane is a useful reagent for the carbon insertion; thus it converts aldehydes and ketones to

next higher homologues. In these reactions diazomethane acts first as a carbon nucleophile giving a derivative from which nitrogen is lost readily (Scheme 8.24). A ring closure to form an epoxide competes with rearrangement and is often the principal reaction.



Scheme 8.24

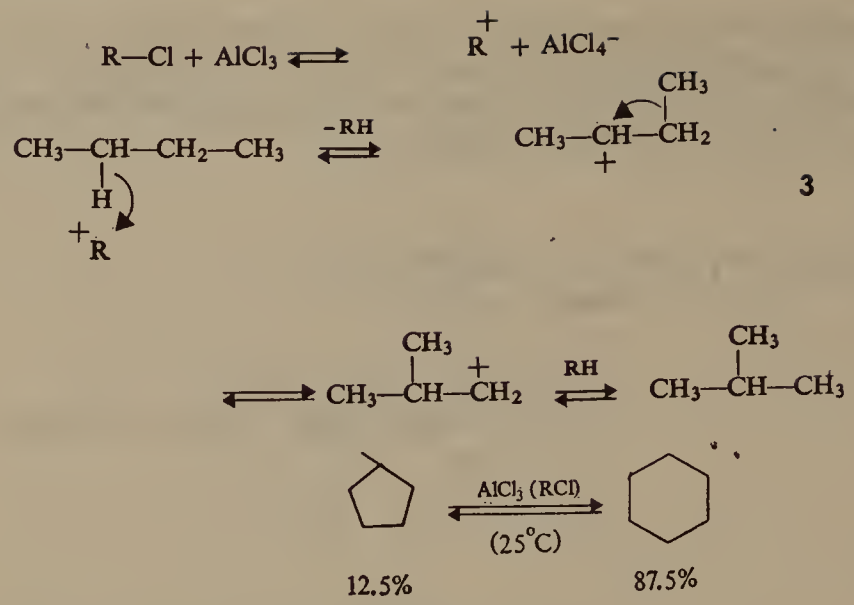
The Arndt-Eistert reaction involves the treatment of an acid chloride with diazomethane to yield a diazoketone, which on heating with silver oxide undergoes the Wolff rearrangement to give a ketene.



Scheme 8.25

(vi) Rearrangement of Paraffins: Saturated nydrocarbons display molecular rearrangements when heated with a Lewis acid in the presence of a catalytic agent often an organic halide and involve carbocations.

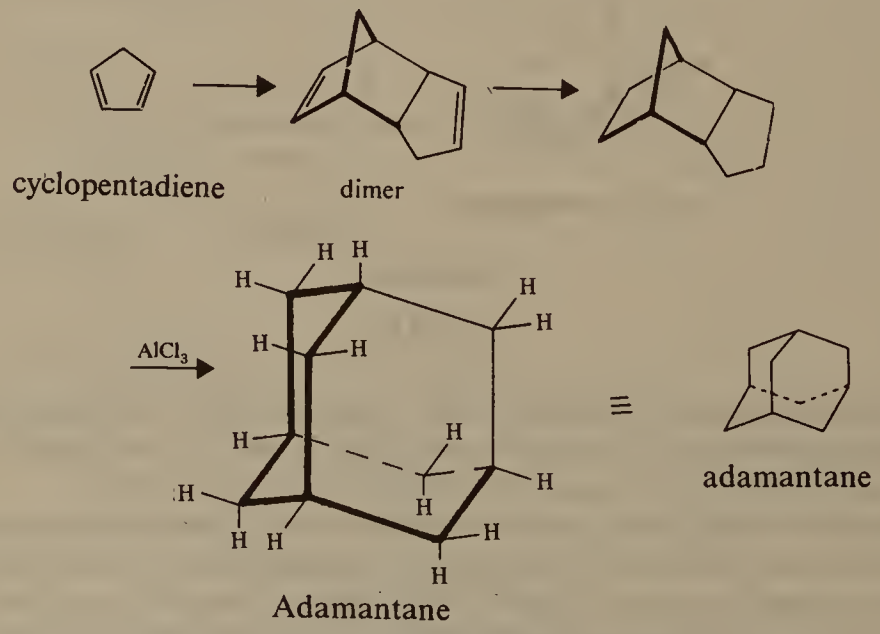
The predominant product may be derived from the least stable carbocation. Thus, isobutane is formed following the rearrangement of a secondary to a primary carbocation (eq. 3, Scheme 8.26). This is, however, in conflict with the direction of rearrangements already discussed and is due to the fact that whereas these reactions are kinetically controlled, the former rearrangements are thermodynamically controlled.



Scheme 8.26

The relative energies of isomeric acyclic hydrocarbons differ to a small extent. This difference leads to the formation of a mixture of products. With alicyclic compounds, however, there are greater differences in relative free energies due to strain in the ring systems. Thus, the isomerization of methylcyclopentane gives cyclohexane with the exclusion of ethyl- or dimethylcyclobutane.

A remarkable application of this rearrangement is the synthesis of adamantane (Scheme 8.27). Catalytic reduction of the readily available dicyclopentadiene (Sec. 8.5, D) gives *endo*-tetrahydro-dicyclopentadiene which, on reac-



Scheme 8.27

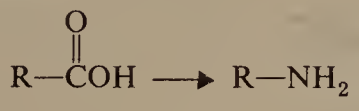
tion with aluminium trichloride affords adamantane (15%), the most stable of the saturated hydrocarbons of molecular formula $C_{10}H_{16}$.

(B) Migration to Electron Deficient Nitrogen

(i) The Hofmann, Curtius, Schmidt and Lossen Rearrangements: All these four reactions accomplish the same overall process-conversion of a carboxylic acid to an amine of the same configuration with loss of the carboxy carbon of the acid (eq. 4, Scheme 8.28). Racemization does not occur in the degradation of acid amides displaying atropisomerism (v).

The Hofmann rearrangement begins with an amide, the Curtius reaction with an acyl azide, the Schmidt reaction with an acid and the Lossen rearrangement with a hydroxamic acid, the four reactions are related machanistically. In each case, the crucial intermediate is probably the same, an acyl nitrene.

The mechanism for the Hofmann rearrangement in the first two steps involves the base-catalyzed halogenation of the amide (Scheme 8.29), which is similar to the base-catalysed halogenation of ketones. The *N*-haloamide anion formed in the reaction rearranges, with loss of bromide to an



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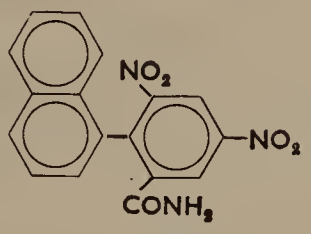


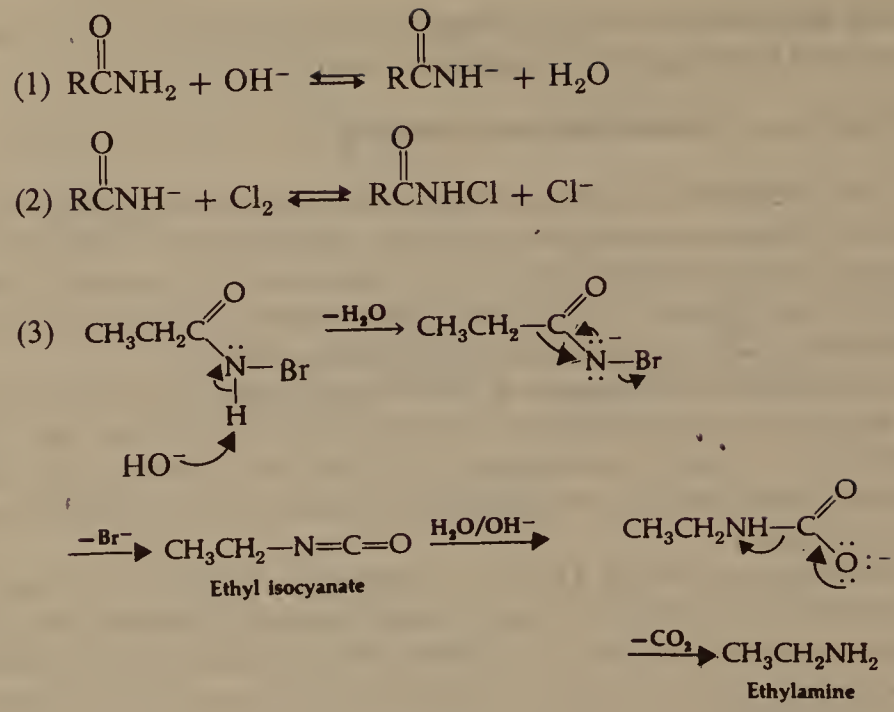
(V)

Scheme 8.28

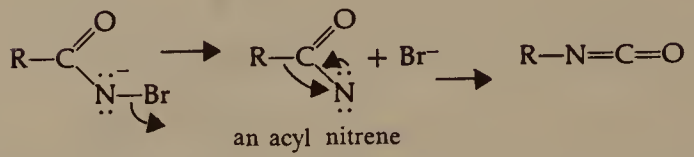
isocyanate. Water gets added to the isocyanate to produce a carbamic acid which readily loses carbon dioxide to yield an amine. Strong evidence in support of the proposed mechanism has been obtained. Both the *N*-haloanion and isocyanate intermediates have been isolated in certain cases.

Another possibility is that loss of halide occurs before the rearrangement. The electron-deficient intermediate, known as a nitrene, resembles the carbene of the Wolff rearrangement.

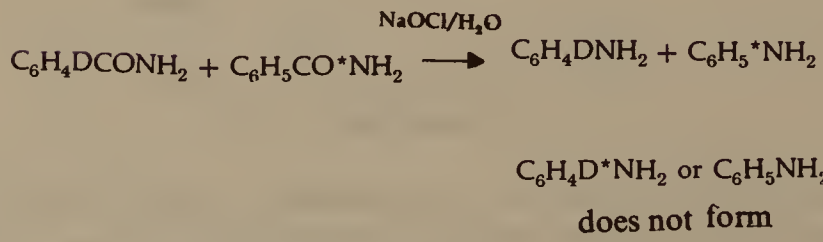
The intramolecular nature of the rearrangement was demonstrated by carrying out the reaction with a mixture of 3-deuteriobenzamide and ^{15}N-benzamide. Mixed anilines could not be isolated to indicate that the migrating group does not separate during the rearrangement.



Scheme 8.29



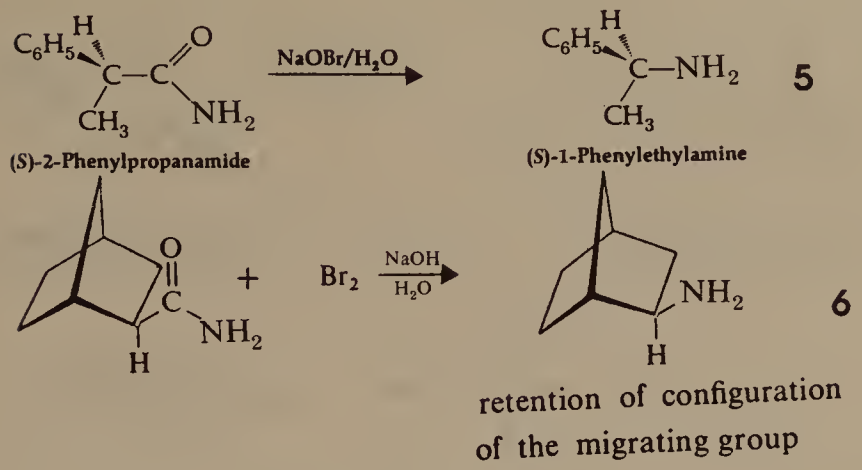
Scheme 8.30



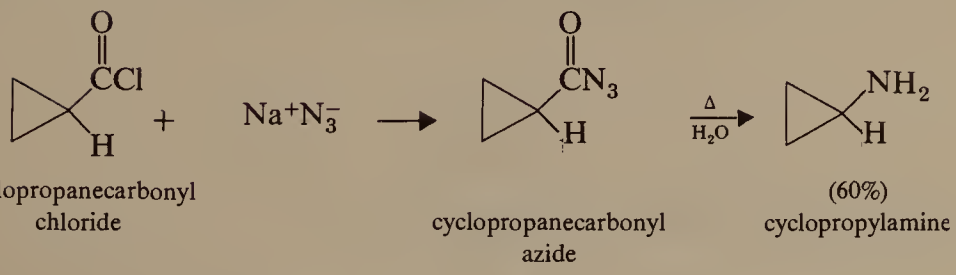
Scheme 8.31

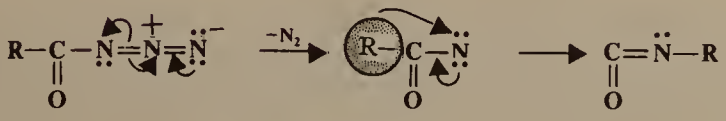
In keeping with these results, the migration proceeds with retention of configuration of the migrating chiral group (eq. 5 and 6).

In the Curtius rearrangement, acyl azides undergo pyrolysis to yield isocyanates and subsequent hydrolysis yields amines (Scheme 8.33). The *O*-acyl derivatives of hydroxamic acids also give isocyanates on treatment with bases or on heating and this rearrangement is called Lossen rearrangement (Scheme 8.33).

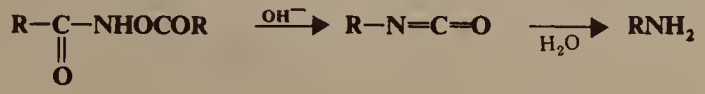


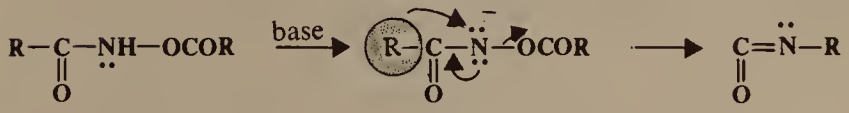
Scheme 8.32





Curtius



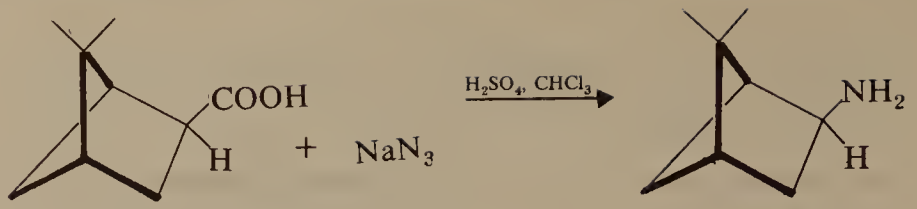


Lossen

Scheme 8.33

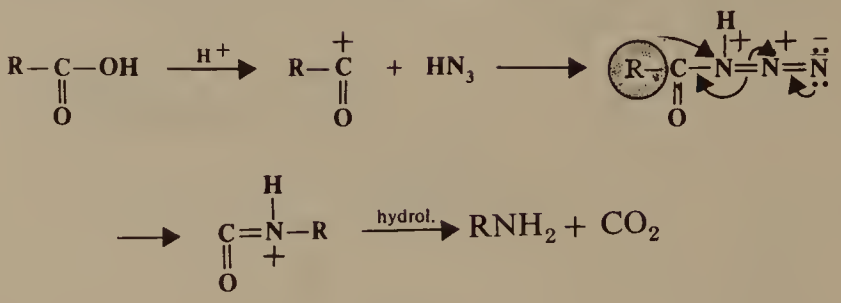
The Schmidt reaction also proceeds *via* the formation of an acyl azide (Scheme 8.34), which is formed by reaction of the carboxylic acid with hydrazoic acid, HN_3, under the acidic conditions. The mechanism in this case involves the rearrangement on the protonated azide.

(*ii*) *The Beckmann Rearrangement:* A detailed discussion of this molecular rearrangement has been done in Section 1.10C.



exo-5,5-dimethylbicyclo[2.1.1]-hexane-2-carboxylic acid

exo-2-amino-5,5-dimethyl bicyclo[2.1.1]hexane

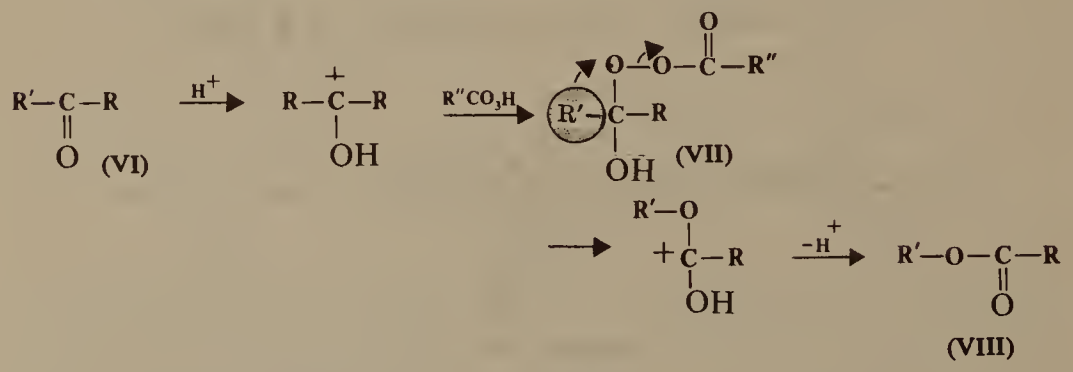


Schmidt

Scheme 8.34

(C) Rearrangement to Electron Deficient Oxygen

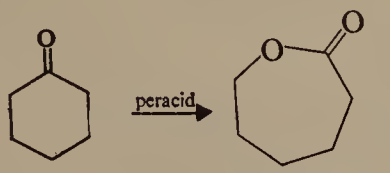
(*i*) *The Baeyer-Villiger Rearrangement*: Reaction of ketones (VI) with peracids such as perbenzoic or peracetic acid, or with other peroxy compounds in the presence of acid catalysts, gives esters (VIII) by "insertion" of oxygen (Scheme 8.35). The reaction when applied to cyclic ketones, gives lactones (ring expansion).



Scheme 8.35

For unsymmetrical ketones the approximate order of migration is tertiary alkyl > secondary alkyl, aryl > primary alkyl > methyl. Since the methyl group has a low migrating ability, the reaction provides a means of cleaving a methyl ketone R'COMe to produce an alcohol or phenol R OH (by

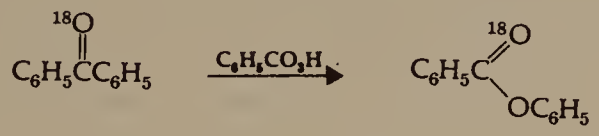
hydrolysis of the easter R'OCOMe). The migrating ability of aryl groups is increased by electron-donating and decreased by electron-withdrawing substituents.



ϵ-Caprolactone

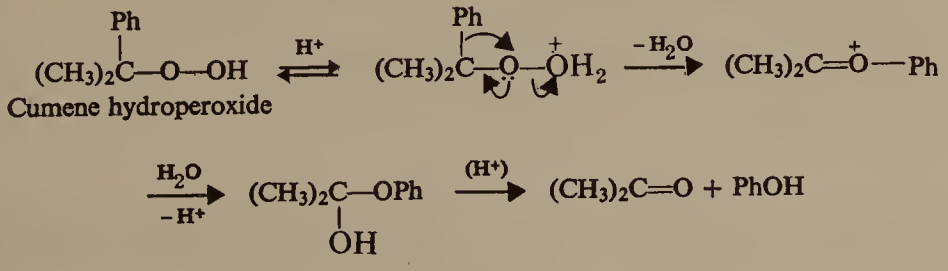
Scheme 8.36

Baeyer-Villiger rearrangement occurs with retention of configuration. Though, the initial adduct (VII) has not been isolated, other evidence supports this mechanism. Reaction of an ^{18}O-labelled ketone showed that the ketone oxygen atom becomes the carbonyl oxygen of the ester.



Scheme 8.37

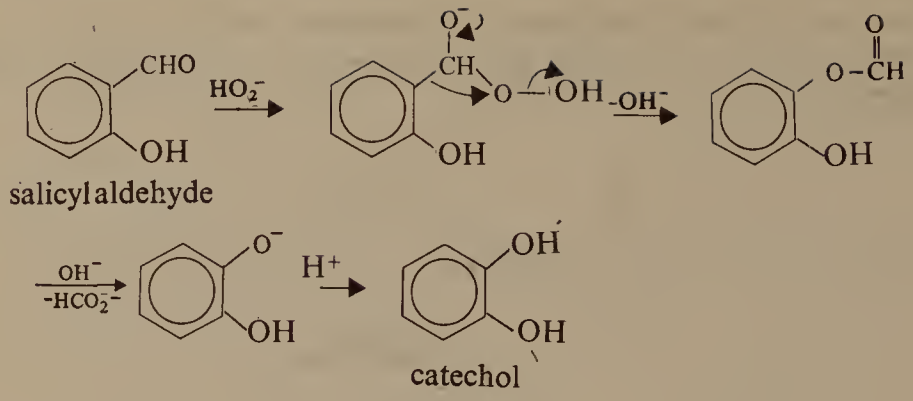
(*ii*) *Dakin Rearrangement:* The acid-catalyzed rearrangement of tertiary hydroperoxides is similar to the Baeyer-Villiger reaction. The product from the migration is a hemi-acetal which is hydrolyzed in the reaction conditions. Cumene is cheaply available from the Friedel-Crafts alkylation of benzene with propylene. It readily forms the hydroperoxide by autoxidation like other tertiary hydrocarbons. Thus this reaction is of industrial importance.



Cumene hydroperoxide

Scheme 8.38

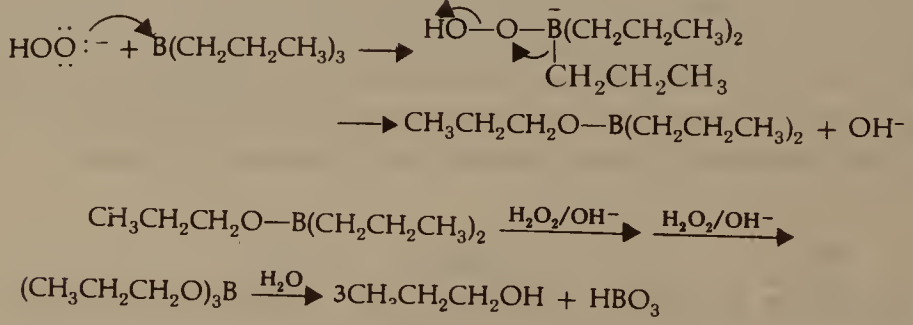
Benzaldehydes containing *ortho*-and *para*-hydroxyl groups are converted into catechols and quinols, respectively on treatment with alkaline hydrogen peroxide through a reaction known as Dakin rearrangement (Scheme 8.39).



Scheme 8.39

(D) Migration from Boron to Electron Deficient Oxygen, Nitrogen and Carbon

For the preparation of alcohols alkylboranes prepared by hydroboration of alkenes are useful intermediates. The sequence involves migration of an alkyl group from boron to oxygen, and is similar to the reactions studied earlier in this chapter in that the migrating alkyl group moves with its pair of bonding electrons. These reactions proceed with retention of configuration in the migrating group. The reaction is promoted by addition of peroxide anion to boron. A sequence of three such rearrangements leads to a borate ester which on hydrolysis gives an alcohol (Scheme 8.40).

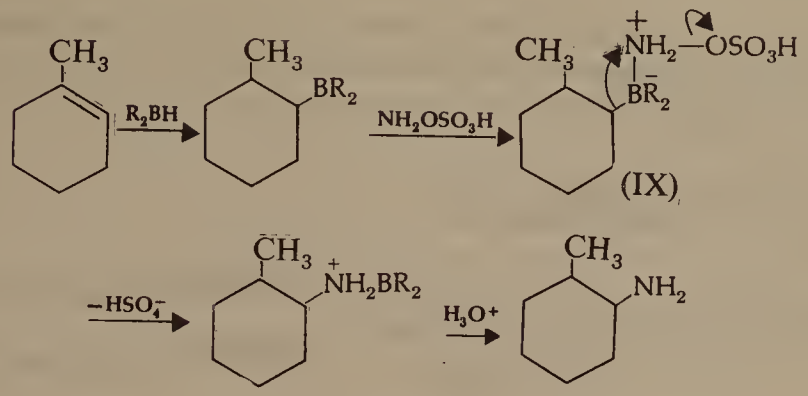


Scheme 8.40

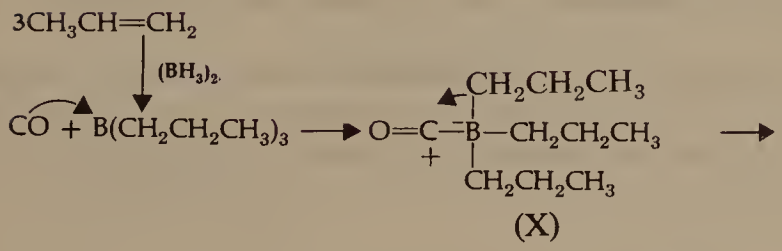
When alkyl group migrates from boron to nitrogen, amines can be prepared from alkylboranes. The alkylborane is treated with hydroxylamine-*O*-sulfonic acid leading to an intermediate ammonium boride, which undergoes rearrangement (IX, Scheme 8.41).

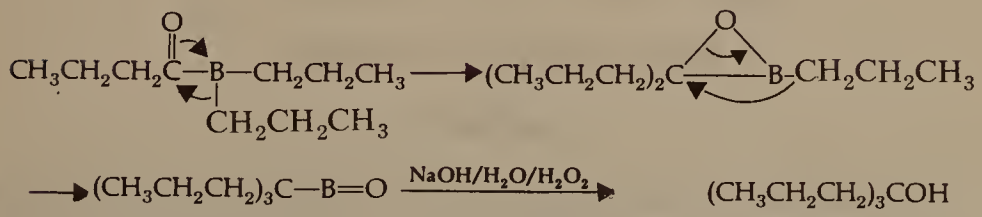
Rearrangement of an alkyl group from boron to carbon leads to alcohols with one more carbon atom than the original alkene, the nucleophile being carbon monoxide.

A trialkylborane-carbon monoxide adduct (X) may be formed initially from which alkyl migration occurs. Rearrangement of all the three alkyl groups gives a tertiary alcohol after oxidation and hydrolysis (Scheme 8.42).



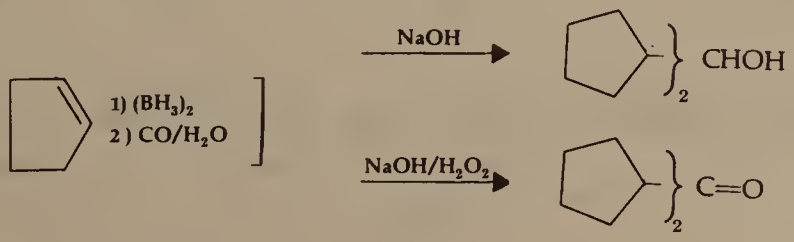
Scheme 8.41





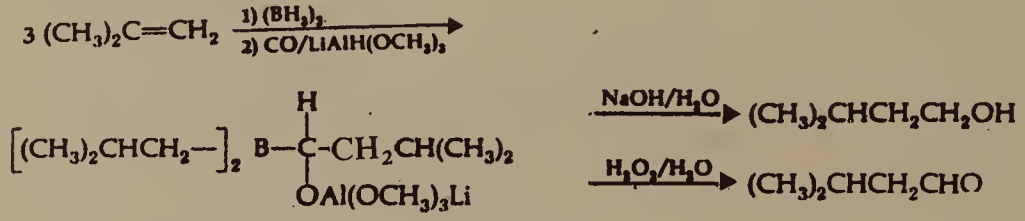
Scheme 8.42

In line with the proposed mechanism, primary or secondary alcohols may be prepared by stopping the reaction when one or two alkyl groups have migrated, and such modifications of the reaction have been achieved. Addition of an equimolar quantity of water to the reaction mixture inhibits migration of the third alkyl group. Water is thought to hydrolyze the intermediate borepoxide and further hydrolysis leads to a secondary alcohol. In the presence of peroxide during this hydrolysis, the corresponding ketone is formed.



Scheme 8.43

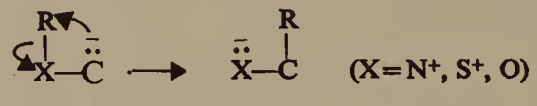
When the reaction is carried out in the presence of a reducing agent, only one alkyl group unergoes migration and, this sequence of reactions leads to a primary alcohol or an aldehyde (Scheme 8.44).



Scheme 8.44

8.2 REARRANGEMENTS TO ELECTRON RICH CARBON

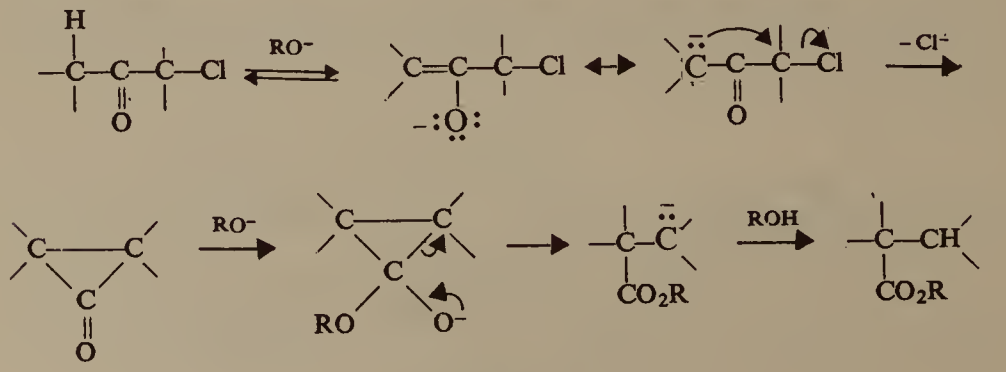
These include reactions which are initiated by the formation of an anion and are usually referred to as anionic rearrangements (eq. 7). Most anionic reactions begin with the removal of a proton by a strong base and these rearrangements may proceed by ionic or free-radical pathways.



R migrates without its bonding-pair. 7

Scheme 8.45

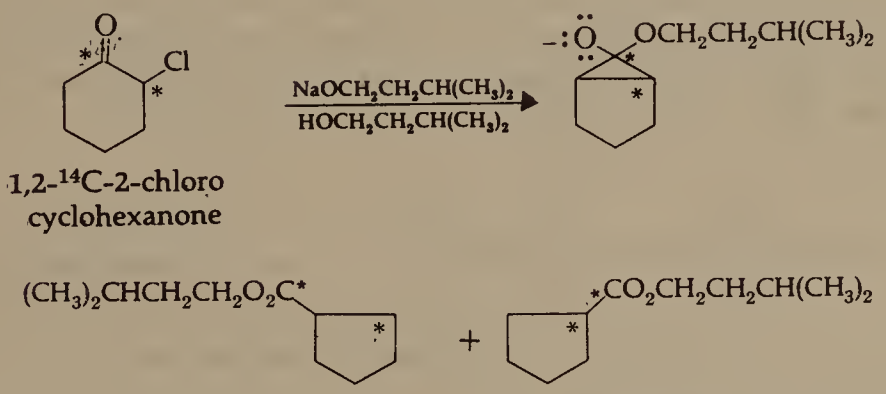
(*i*) *Favorskii Rearrangement:* Reactions of α-halo ketones with hydroxide or alkoxide yields carboxylic acids or esters and the process, known as the Favorskii rearrangement, has been carried out with both acyclic and cyclic reactants. The rearrangement can be employed to bring about ring-contraction in cyclic systems. The mechanism of the Favorskii rearrangement proceeds *via* a generally accepted cyclopropanone intermediate that results from intramolecular displacement of halide by an initially formed α-carbanion (eq. 8).



8

Scheme 8.46

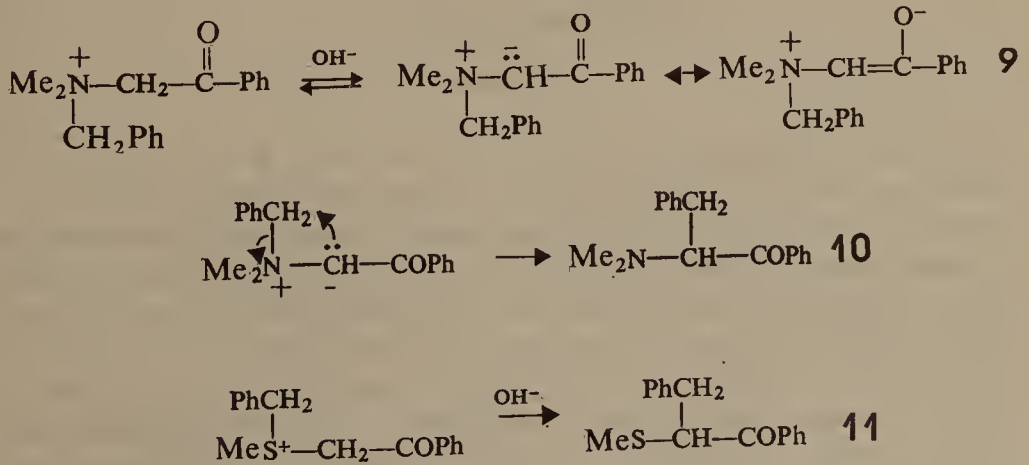
Cyclopropanones being unstable compounds, are not isolated during this rearrangement. Evidence for their participation is, however, quite strong. Reaction of 1,2-^{14}C-2-chloro-cyclohexanone with sodium isoamyloxide afforded isoamyl cyclopentanecarboxylate. The C-1 and C-2 carbons of the cyclopentane were found equally labelled with 25 percent of the original ^{14}C, while the ester carbonyl group contained 50 percent of the ^{14}C. The carbonyl group carbon atom label remained unchanged compared with the starting material, while the original C-2 label is equally distributed between two atoms of the product. This proves that a symmetrical cyclic intermediate must be involved from which the ring openning can occur in either direction with equal probability, and accounts for the observed labelling pattern in the product.



1,2-^{14}C-2-chloro cyclohexanone

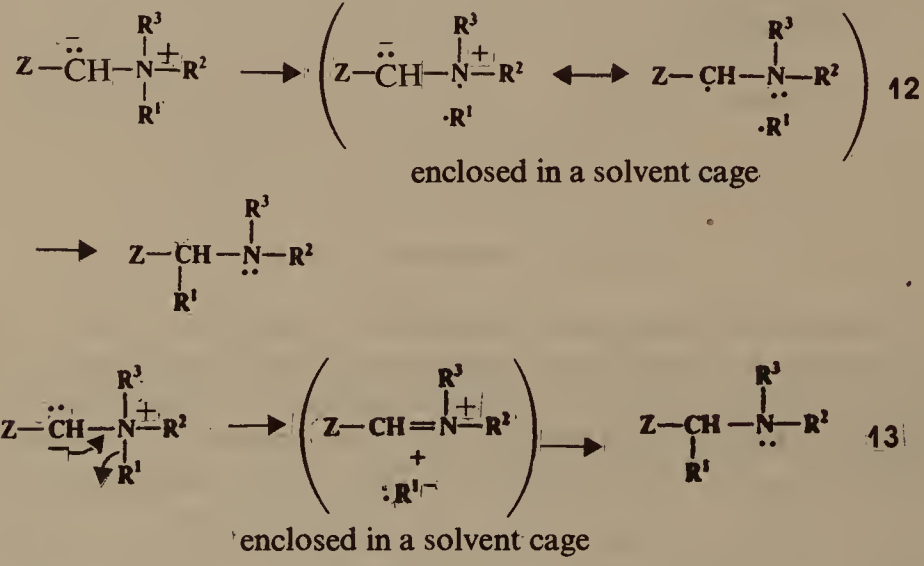
Scheme 8.47

(*ii*) *Stevens Rearrangement:* Quaternary ammonium ions with β-hydrogen atoms undergo E2 (Hofmann) elimination with base (Sec. 5.4). In case none of the alkyl groups has a β-hydrogen atom but one has a β-carbonyl group, an α-hydrogen is removed by the base to give an ylide in which the negative charge is delocalized (eq. **9**). Stevens rearrangement may then be



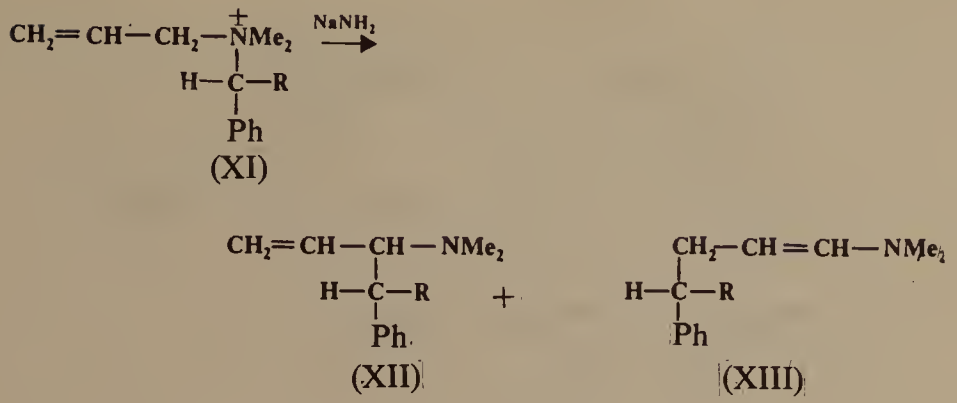
Scheme 8.48

represented as in (eq. 10). The sulphonium ions behave similarly (eq. 11). Thus, generally speaking, in the Stevens rearrangement a quaternary ammonium salt with an electron-withdrawing group (Z) on one of the carbons attached to the nitrogen on treatment with strong base like NaOR or $NaNH_2$ gives rearranged tertiary amine, Z is a group like RCO, ROOC, or phenyl. The common migrating groups are allyl, benzyl etc., though even methyl migrates to a sufficiently negative center. When an allyl group migrates, it may or may not involve an allylic rearrangement within the migrating group, depending on the substrate and reaction conditions. The rearrangement is intramolecular and shows retention of configuration in R. After the loss of the acidic proton the product may be formed directly from a free-radical precursor (radical-pair mechanism eq. 12). The radicals are held together by the solvent cage and must recombine rapidly to account for the fact that R^1 does not racemize. Other evidence in favor of this mechanism is that in some cases small quantities of coupling products (R^1R^1) have been isolated, which would be expected if some of R^1 free radical escaped from the solvent cage.



Scheme 8.49

However, mechanism shown in eq.13 involving ion pair may also be operative. Although the electrophilic mechanism (eq.10) has been accepted for Steven, rearrangement for several years, however, recent evidence shows that mechanisms 12 and 13 may indeed be operative. Thus, optically active XI (Scheme 8.50) rearranged to XII with the benzyl migration and XIII by a 1,4 shift. The benzyl group retained its configuration in XII as expected and interestingly in XIII as well. If the benzyl group migrated without its electrons (mechanism 10) then it would have to move over this long distance either as a relatively free carbocation to be racemized or in an S_Ni' process (Sec. 1.16A) to be inverted (eq.14).



Scheme 8.50

Scheme 8.51

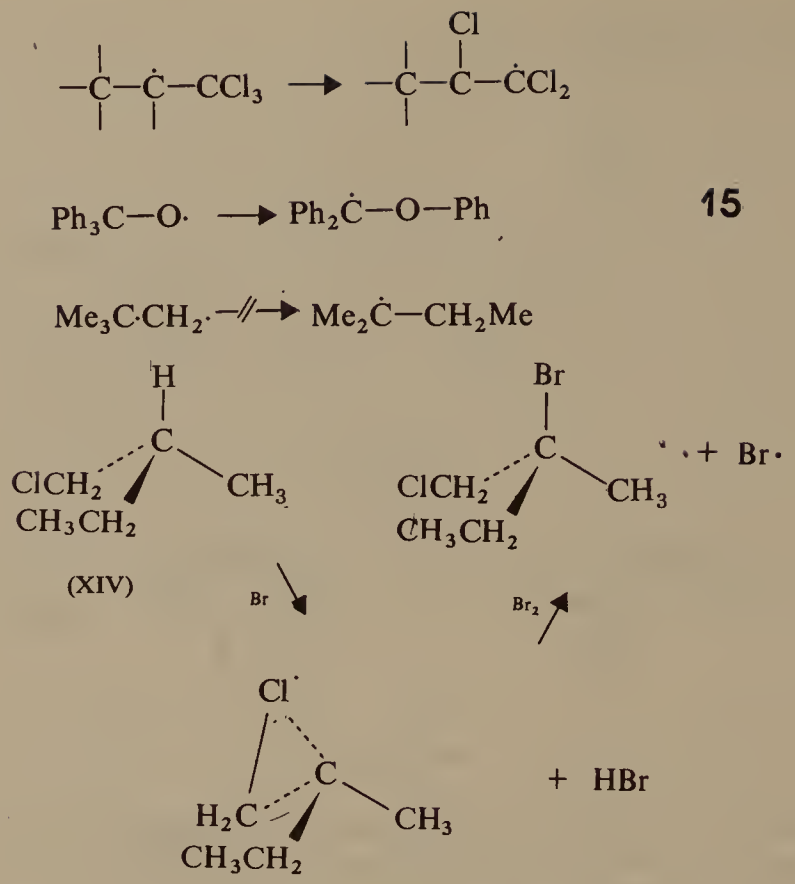
Therefore, the 1,4 shift appears to operate by mechanism **12** or **13** to make the mechanism **10** unlikely for the 1,2 shift as well. Additionally an argument against mechanism **10** is that the principle of orbital symmetry conservation requires that a concerted migration of this type should take place with inversion at R′, a migration with retention being forbidden. Since the actual migration takes place with retention, it cannot, according to this argument, proceed by a concerted mechanism **10**.

8.3 RADICAL REARRANGEMENTS

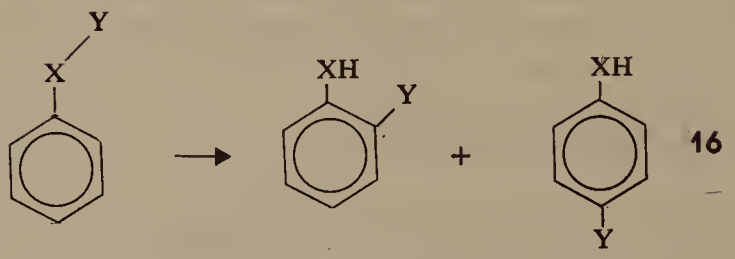
Radical rearrangements are much less common as compared to more electron-deficient species, however, the 1,2-shift of a chlorine or bromine atom, the 1,2-shift of an aromatic or vinyl group, or the 1,5-hydrogen transfer reactions are known. The driving force for these rearrangements is the formation of a more stable radical (eq. **15**). If the new radical has same or lower stability as compared with the original, rearrangement if at all occurs to a small extent. Somewhat controversial halogen-bridged radicals have been invoked to explain the high stereospecificity of some bromination reactions, *e.g.*, bromination of optically active chloride (XIV) gives optically active 1-chloro-2-bromo-2-methylbutane.

8.4 AROMATIC REARRANGEMENTS

Several rearrangements occur in aromatic compounds (eq.**16**). The element X is mostly nitrogen or may be oxygen and inter and intramolecular migrations are known.



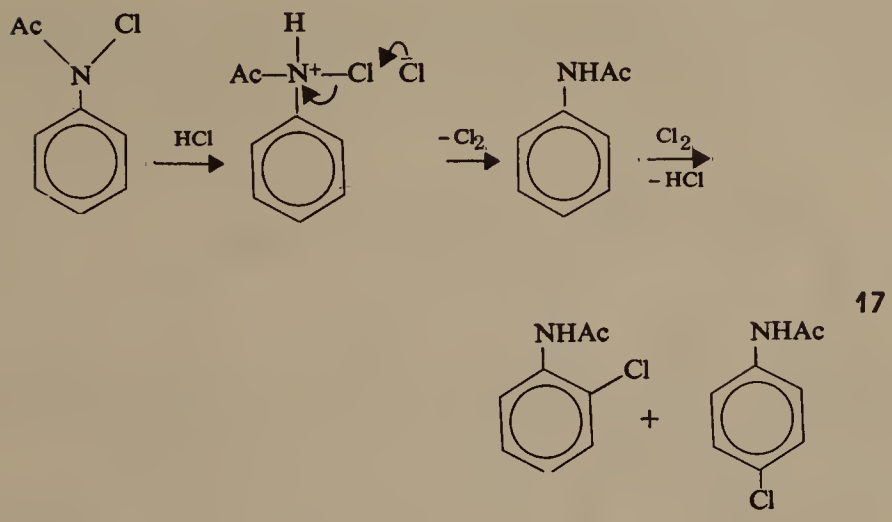
Scheme 8.52



Scheme 8.53

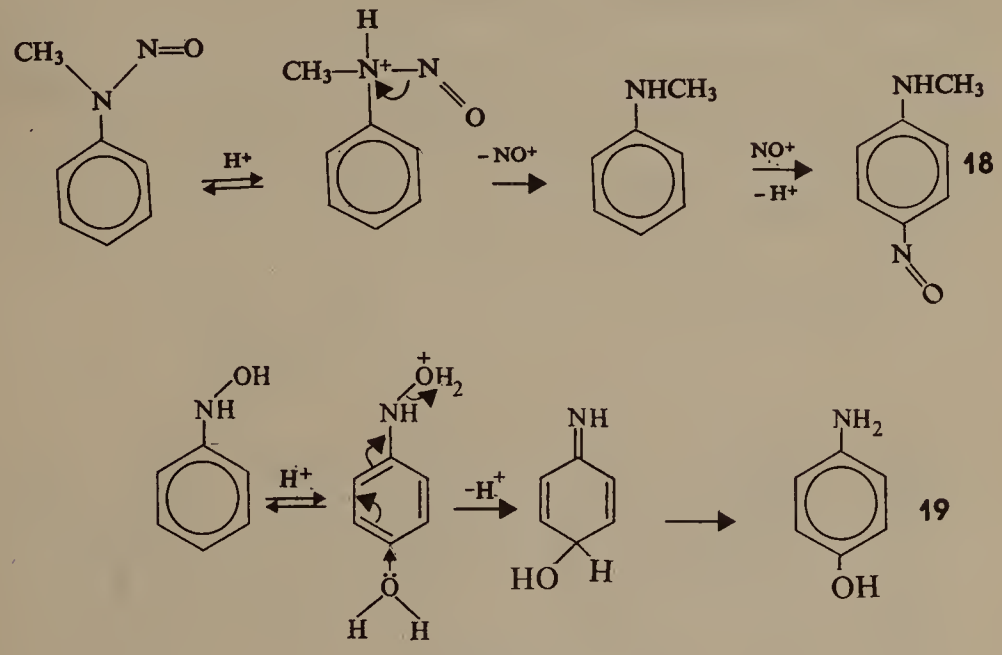
(A) Intermolecular Migration from Nitrogen to Carbon

Derivatives of aniline display rearrangement in the presence of acid. The conjugate acid of the amine eliminates an electrophilic species by the subsequent attack at the activated *ortho* and *para* positions of the amine. *N*-chloro-acetanilide and hydrochloric acid give a mixture of *o*- and *p*-chloroacetanilide in the same ratios as in the direct chlorination of acetanilide (eq. 17).



Scheme 8.54

The nitrosonium ion is released from the conjugate acid of the amine which nitrosates the nuclear carbon atoms, to afford the *p*-nitroso product (eq.18). The rearrangement of arylhydroxylamines to aminophenols involves a nucleophilic attack by the solvent on the conjugate acid of the hydroxylamine (eq.19).

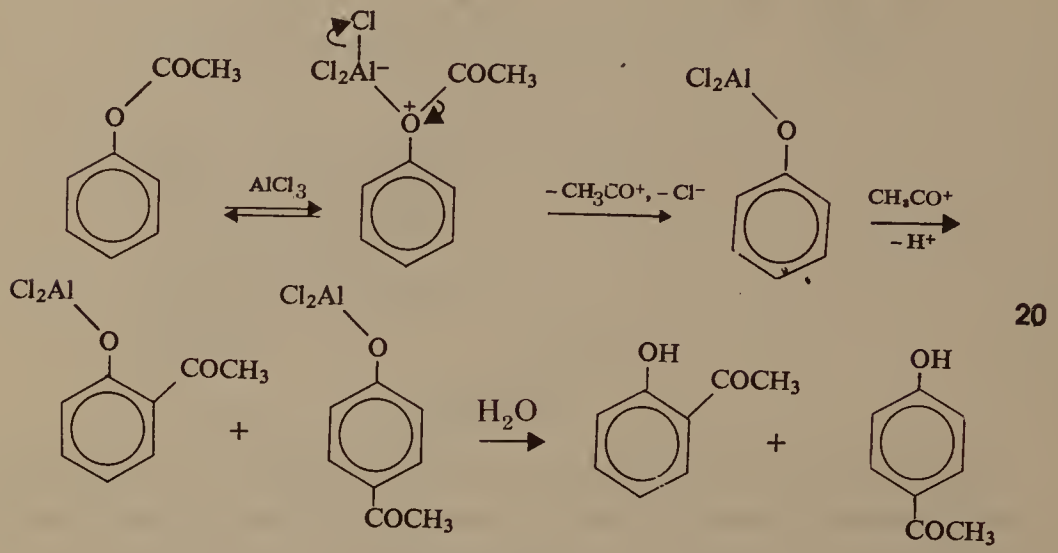


Scheme 8.55

(B) Intermolecular Migration from Oxygen to Carbon

The Fries rearrangement is an example, wherein aryl esters on treatment with Lewis acids yield *ortho* and *para* hydroxy-ketones. The complex

between the ester and the Lewis acid eliminates an acylium ion which gets substituted at the *ortho* and *para* positions, as in Friedel-Crafts acylation (eq.**20**).

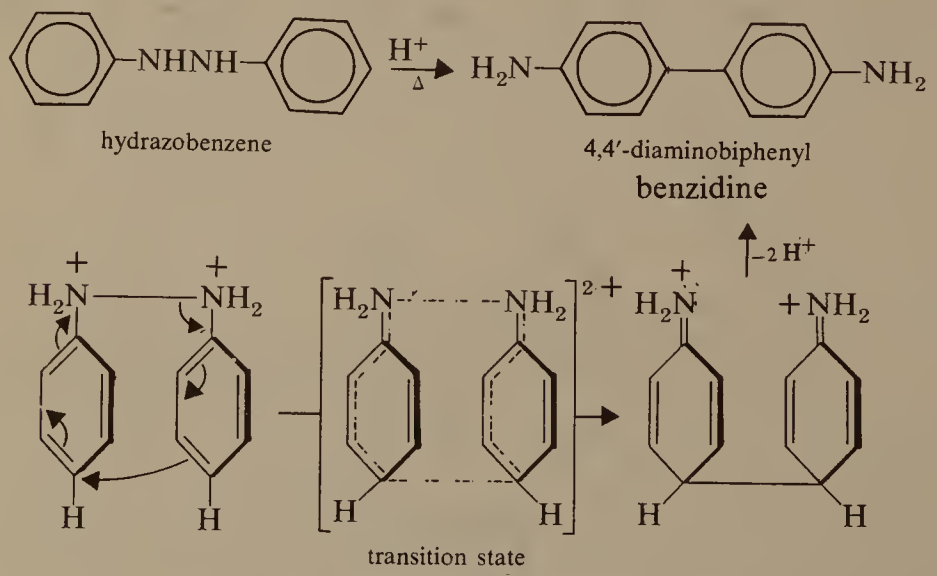


20

Scheme 8.56

(C) Intramolecular Migration from Nitrogen to Carbon

Benzidine rearrangement may be cited as an example of this class. Hydrazobenzenes yield benzidines on treatment with acids (eq. **21**).



21

Scheme 8.57

In this remarkable reaction the N—N bond of a mono- or diprotonated salt in which bonding occurs between the *para* positions, is broken.

(D) Intramolecular Migration from Oxygen to Carbon

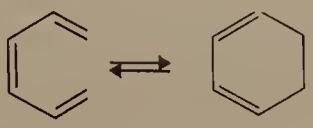
The Claisen rearrangement, a [3,3]-sigmatropic reaction (Sec. 8.5, e, vii) is an example of this class.

8.5 PERICYCLIC TRANSITION STATES (REACTIONS)

(A) Introduction

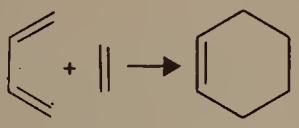
A variety of reactions *e.g.*, additions, eliminations and rearrangements proceed through cyclic transition states and examples are the Diels-Alder reaction — the Claisen and Cope rearrangements. Their transition states are related to benzene and the facility of these reactions is gainfully compared with the aromatic character of benzene. The comparison is indeed accurate and these and many other reactions can be treated as cyclic electronic systems to which the Huckel $(4n+2)$ rule is applicable. The basis of the classification is mechanistic and each pericyclic reaction has four criteria : (*i*) these are concerted reactions; no radical or ionic intermediates can be detected, (*ii*) the rates of pericyclic reactions are not affected by either catalysts or changes in the solvent, (*iii*) the reagents used are neither nucleophilic nor electrophilic and (*iv*) finally is the condition defining pericyclic reactions that at least two bonds be made and cleaved in a single concerted step with a cyclic transition state. Three classes of pericyclic reactions are :

1. Electrocyclic ring openings and closures. An electrocyclic ring closure is that in which a σ-bond is formed between two termini of a conjugated π-system. The product, therefore, has one less π-bond than the reactant. The opposite of this process is an electrocyclic ring opening (Scheme 8.58).



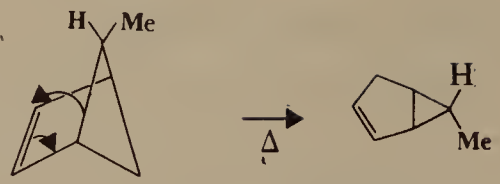
Scheme 8.58

2. Cycloaddition reactions are those reactions in which two σ-bonds are formed between the termini of two isolated π-systems (Scheme 8.59).



Scheme 8.59

3. Sigmatropic rearrangements involve the migration of an atom or group across a π-electron framework (Scheme 8.60).



Scheme 8.60

(B) The Huckel-Mobius Approach [1-3] (4*n* ± 2 Versus 4*n*) for the Study of Pericyclic Reactions

The Huckel-Mobius analysis (PMO method) can be applied to any type of pericyclic reaction and this approach is much easier when compared to Woodward-Hoffmann rules.

The Mobius-Huckel concept, no doubt has its base in molecular-orbital theory, but can be used to analyze pericyclic reactions without using the proper molecular orbitals. Each atom of the interacting system is assigned a *p* orbital with one lobe black and one lobe white. A hydrogen atom taking part in the reaction is shown by a circle and represents an *s* orbital. For simplicity, one draws each reactant with the black lobes on one side and the white lobes on the other.

Lobes representing the points of bond making are then connected together in a way that represents the suprafacial or antarafacial (conrotatory or disrotatory) character of the reaction. Thus, Huckel and Mobius systems constitute cyclic arrays of orbitals. They differ, only in respect of the number of inversions of sign in the wave function describing the array; a change in sign corresponding to an orbital node. Huckel systems, are characterized as having either no inversions of sign, *i.e.,* no nodes, or an even number of inversions of sign, *i.e.,* an even number of nodes. The molecular orbitals (MO's) of benzene have zero, two, four or six inversions of sign. Mobius systems, on the other hand, are characterized as having an odd number of inversions of sign. Huckel systems are aromatic, when they contain 4*n*+2 electrons, and are non-aromatic, when they contain 4*n* electrons. Mobius (or anti-Huckel) systems, on the contrary, are stabilized (aromatic) when they contain 4*n* electrons and are nonaromatic when they contain 4*n*+2 electrons.

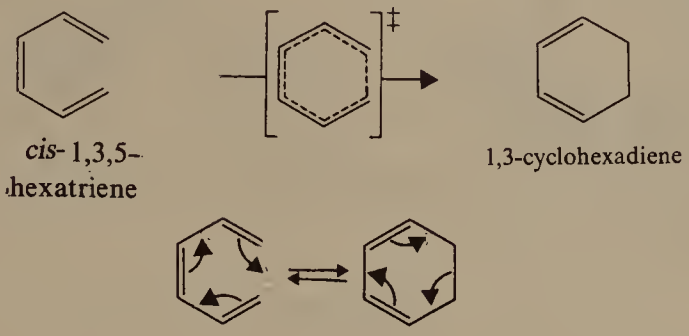
TABLE 8.1 : Characteristics of Huckel and Mobius Systems

System	Sign Inversions (Nodes)	Aromatic	Nonaromatic
Huckel	0, or an even number	4*n*+2 electrons	4*n* electrons
Mobius	Odd number	4*n* electrons	4*n*+2 electrons

In the Huckel Mobius approach if or not a pericyclic reaction is allowed is determined from the examination of the transition states for the number of electrons and numbers of inversions of sign (nodes). Systems with 4*n*+2 electrons and a node are non-aromatic while systems with 4*n* electrons and a node are aromatic and therefore stable in the ground state. Thermal reactions occur *via* aromatic transition states while photochemical reactions proceed through anti-aromatic transition states.

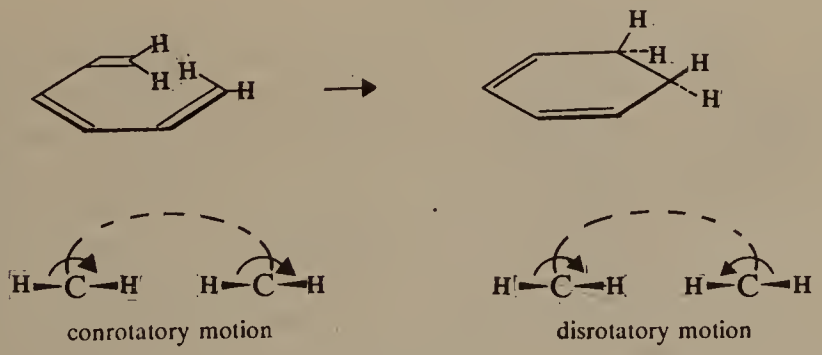
(C) Electrocyclic Thermal Reactions

(*i*) *Conrotatory and Disrotatory Motion: Cis*-1,3,5-Hexatriene on heating undergoes a facile transformation to yield 1,3-cyclohexadiene and the reaction can be depicted to proceed *via* a cyclic six-membered transition state (Scheme 6.61).



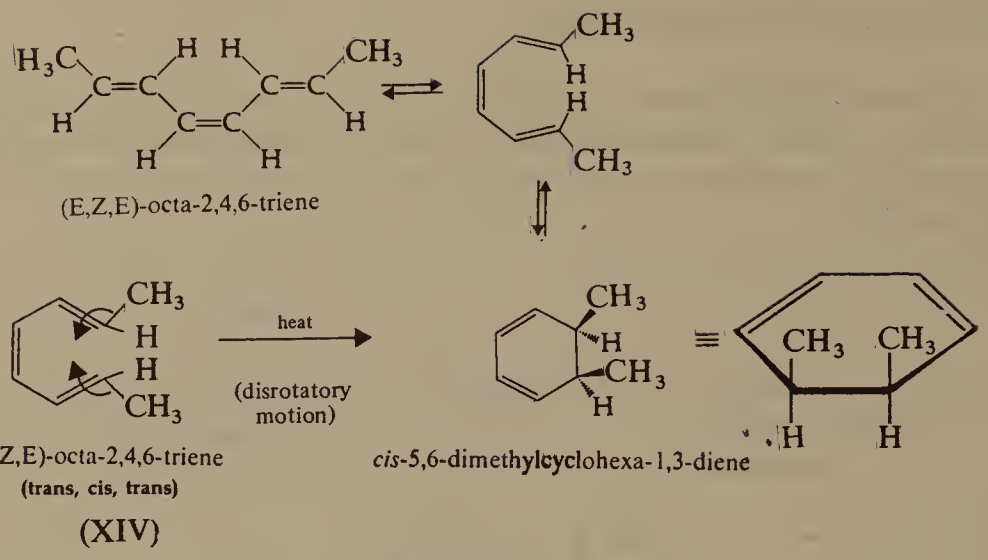
Scheme 8.61

In the open-chain hexatriene best π-overlap of the double bonds can be achieved provided all carbons and hydrogens are in the same plane (including both terminal methylene groups). In the cyclohexadiene the two methylene groups form a part of a ring and therefore, do not remain coplanar *i.e.*, in this transformation the terminal methylene groups are forced to rotate out of coplanarity. The two possible modes for these rotations which are general for electrocyclic reactions are called conrotatory and disrotatory (scheme 8.62). These terminal methylene groups can both rotate in the same sense when viewed from the same direction (conrotatory motion) or in the opposite sense (disrotatory motion).



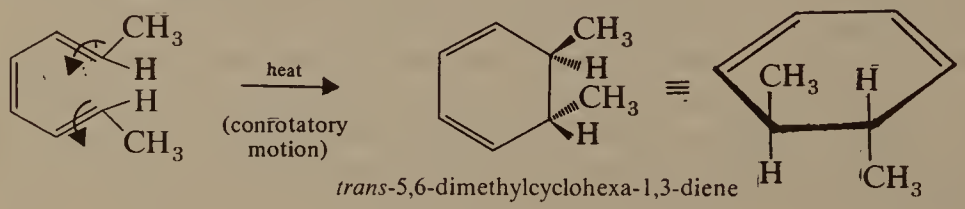
Scheme 8.62

(*ii*) *Stereochemistry of Ring Closure* (*Hexatrienes*): When substituents are located at the ends of the polyene, this cyclisation follows a unique stereochemical path. The reactions are highly stereospecific. Consider *E,Z,E*-2,4,6-octatriene (XIV, Scheme 8.63).



Scheme 8.63

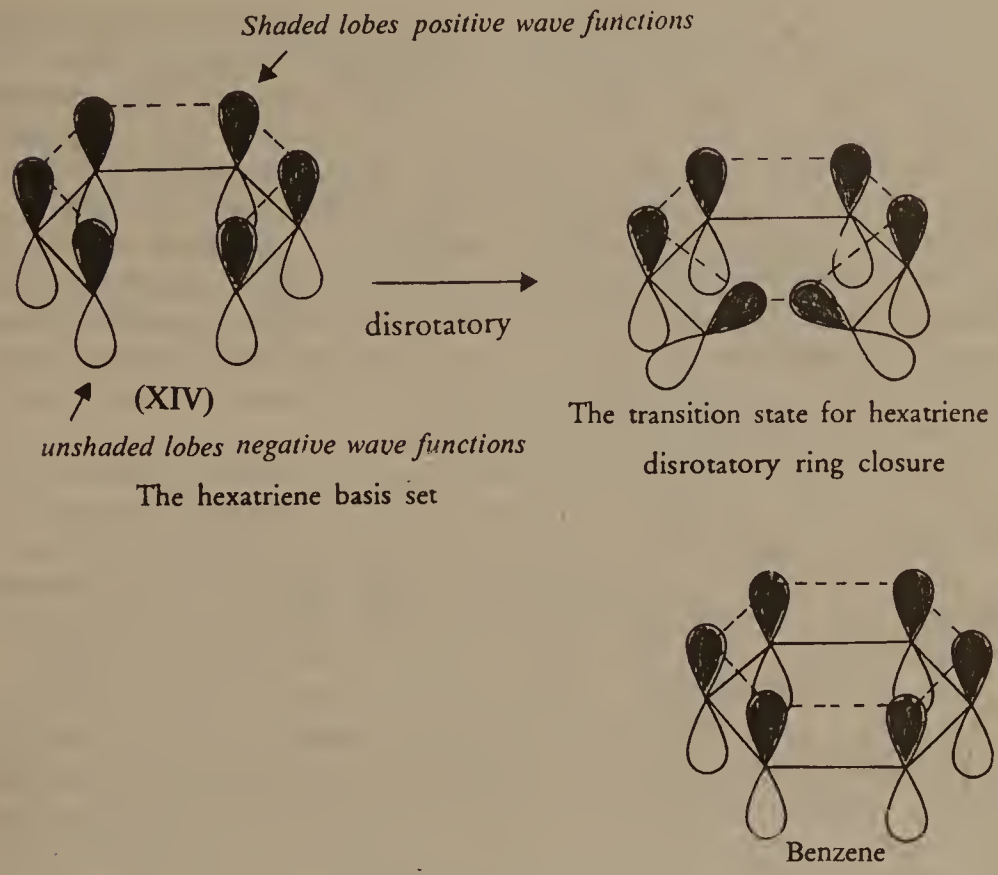
If both end groups rotate in opposite directions in disrotatory fashion, the product is the *cis*-dimethyl-cyclohexadiene, which is formed exclusively, even though this isomer is thermodynamically less stable than the alternative *trans*-isomer. The *trans* isomer could have arisen by the conrotatory ring closure (Scheme 8.64).



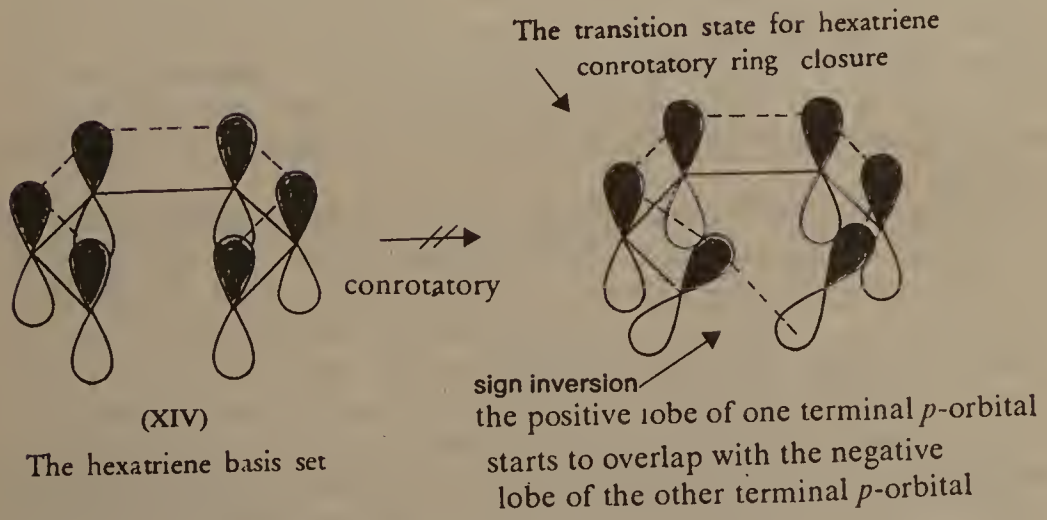
Scheme 8.64

(*iii*) *Study of Stereochemistry, Orbital Interactions (Hexatrienes)*: This electrocyclic reaction involves the conversion of the two terminal *p*-orbitals from π-bonding to σ-bonding. One may examine the signs of the orbital wave functions to know whether the involved orbital overlaps are bonding *i.e.*, positive or antibonding (negative). In hexatriene the *p*-orbitals have signs assigned to the wave functions to give the most positive overlaps and lead to a set of π-molecular orbitals which describe the electronic structure (for clarity only the overlap dotted line at the top is shown in Scheme 8.65). In the transition state for disrotatory closure both terminal methylene groups rotate so that the positive lobes interact to give positive overlap throughout, and this is reminiscent of related benzene basis set of *p*-orbitals, arranged so, that the lobes of the same phase are adjacent. Although, the alignment of orbitals in the transition state for disrotatory ring closure is not exactly as in benzene, however, the overlap characteristics are the same in both *i.e.*, the orbital overlaps are all positive about the ring. In conrotatory motion on the other

hand, the positive lobe of one terminal *p*-orbital has to overlap the negative lobe of the other terminal *p*-orbital (Scheme 8.66).



Scheme 8.65



Scheme 8.66

The disrotatory transition state, thus, closely resembles orbital interactions in benzene, and as a result the electrocyclic reaction of hexatrienes is entirely disrotatory.

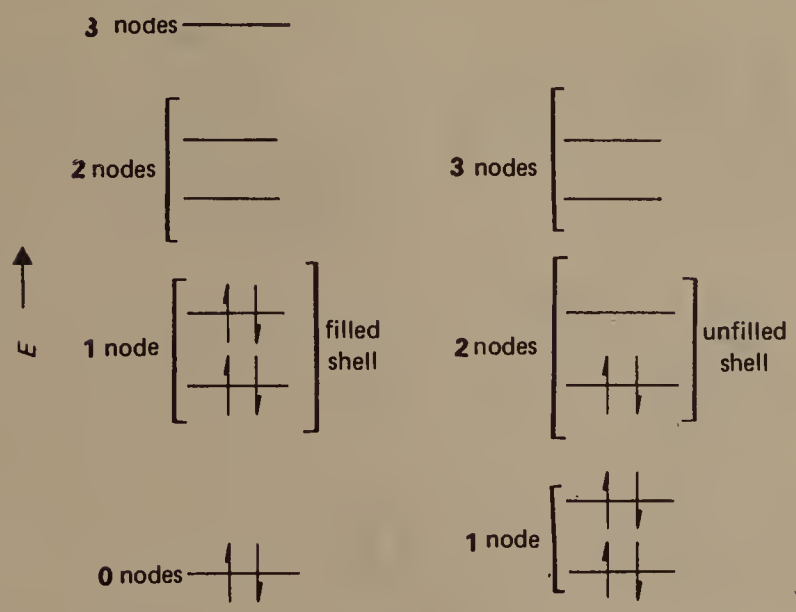
(*iv*) *Molecular Orbital Energies of Disrotatory and Conrotatory Ring Closure* (Hexatrienes) : The considerable difference in activation energies for these ring closures is directly related to the stabilization energies of aromatic systems having cyclic π-systems with $4n+2$ electrons. A cyclic system of *p*-orbitals leads to a pattern of molecular orbitals in a distinct fashion. A lowest lying molecular orbital with zero nodes is followed by the molecular orbitals which occur as degenerate pairs with one, two, and so on, nodes. In the benzene-like transition state for disrotatory ring closure scheme (8.67) this symmetry pattern is so disturbed that the higher molecular orbitals do not now occur as degenerate pairs, but the molecular orbitals within each pair still possess energies and are close together and still represent orbital "shells" that provide aromatic-like stability on filling.

For the conrotatory ring closure negative overlap is required which leads to an entirely different pattern of molecular orbital energies. The negative overlap is a node, therefore, there can be no molecular orbital with zero nodes. On the other hand, one finds a pair of molecular orbitals of similar energy with one node each, a higher pair with two nodes, and so on. As a result six electrons leave the second shell unfilled, a situation of relative instability.

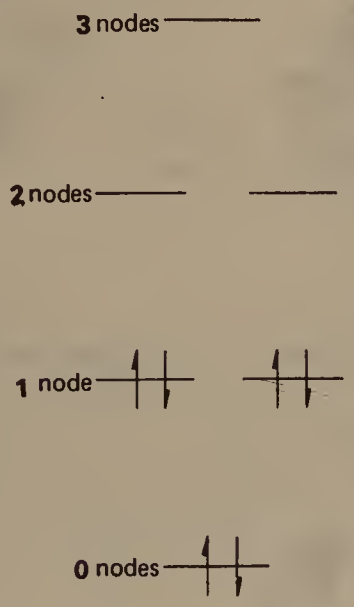
(*v*) *Huckel and Mobius Molecular Orbital Systems:* Names for these two patterns of molecular orbital levels have been suggested. The pattern for disrotatory closure is a Huckel molecular orbital system which provides filled molecular orbital shells with $4n+2$ electrons. The conrotatory pattern on the other hand is termed Mobius molecular system and has the significant characteristic to yield filled molecular orbital shells with $4n$ electrons.

(*vi*) *Electrocyclic Ring Closure of Octatetraene:* In contrast to the ring closure of (*E,Z,E*)-dimethyl-hexatriene the (*E,Z,Z,E*)-dimethyloctatetraene gives on the other hand the *trans*-dimethyl-cyclooctatriene as the exclusive product. This thermal reaction proceeds through a conrotatory ring closure. The alkene (Scheme 8.68) is drawn in the all—*s-cis* conformation, which is not extensively populated, however, it is the only conformation which leads to products.

In disrotatory ring closure for this reaction, no doubt, overlaps involved are all positive and give rise to a Huckel pattern of molecular orbital energy levels, however, the eight electrons now involved do not fit the $4n+2$ rule. Disrotatory ring closure for this reaction would therefore, proceed through an anti-aromatic eight electron Huckel system. This would lead to instability due to an unfilled orbital shell. Whereas, the conrotatory transition state gives rise to a Mobius pattern of molecular orbital levels. The eight electrons (Scheme 8.70) fill the first two shells to gain the stability due to filled orbital shells. For the conrotatory ring closure, the transition state basis set reveals one phase dislocation at the site of σ bond formation. The transition state is phase dislocation at the site of σ bond formation. The transition state is therefore, more favorable an eight electron aromatic Mobius system than the



transition states for ring closure of (XIV)

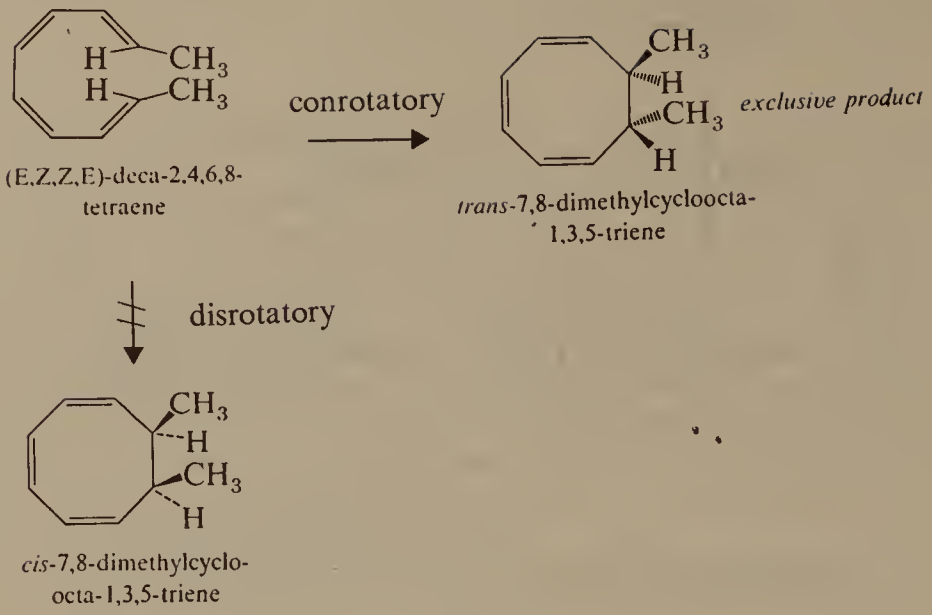


benzene

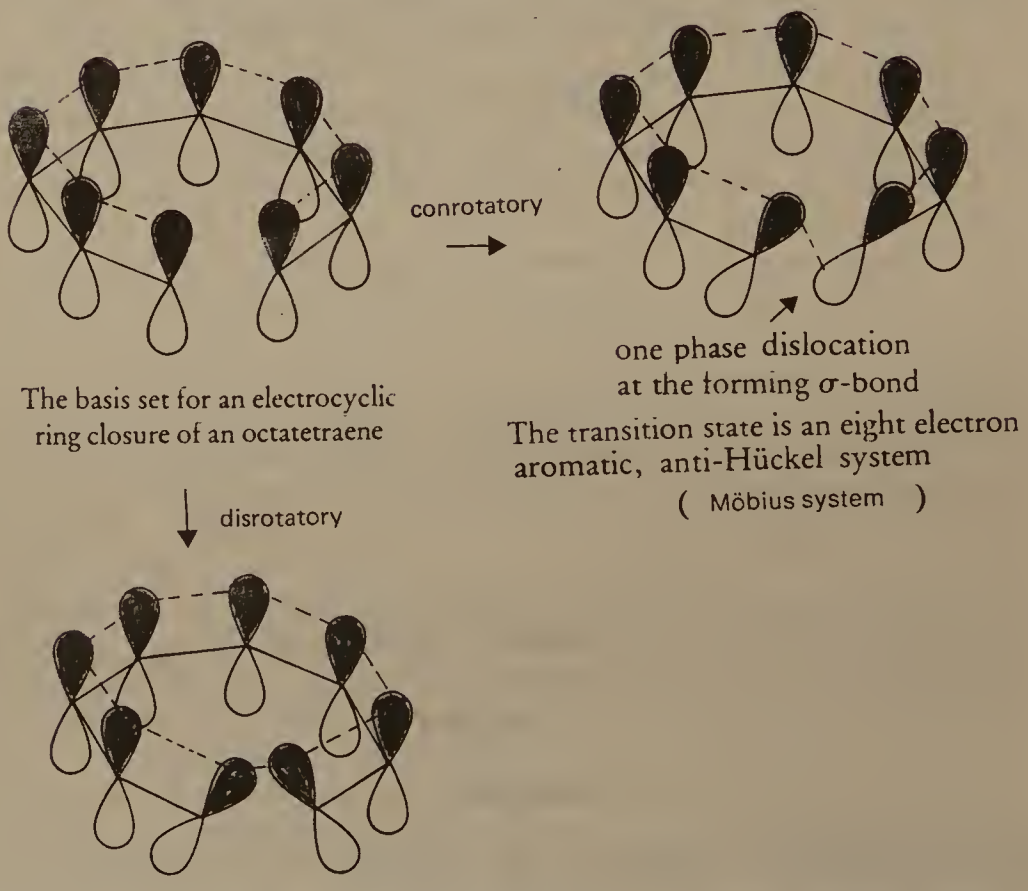
Scheme 8.67

Huckel antiaromatic character of the transition state involved in the disrotatory ring closure.

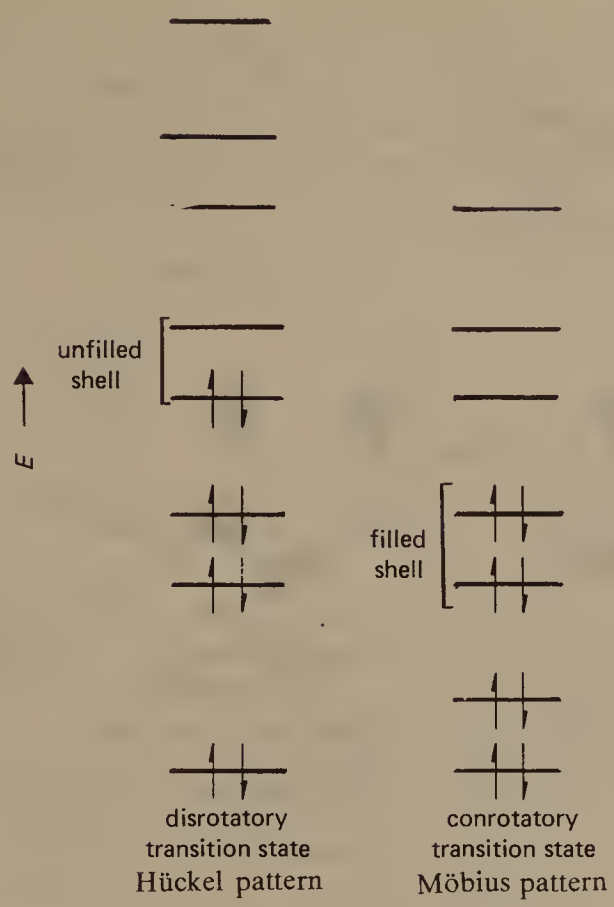
(*vii*) *Thermal Ring Opening of Cyclobutenes to Butadienes:* The thermal electrocyclic ring opening of *cis*-3,4-dimethyl cyclobutene is a smooth and completely stereospecific process which yields (*E,Z*)-hexa-2,4-diene. The reaction involves a four-electron cycle. The basis set for the transition states



Scheme 8.68



Scheme 8.69

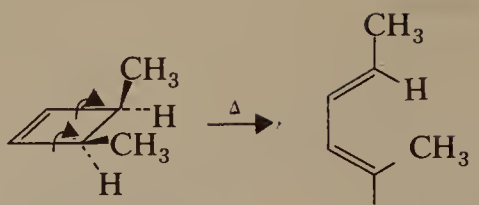


Energy level of molecular orbitals
cyclization of octatetraene

Scheme 8.70

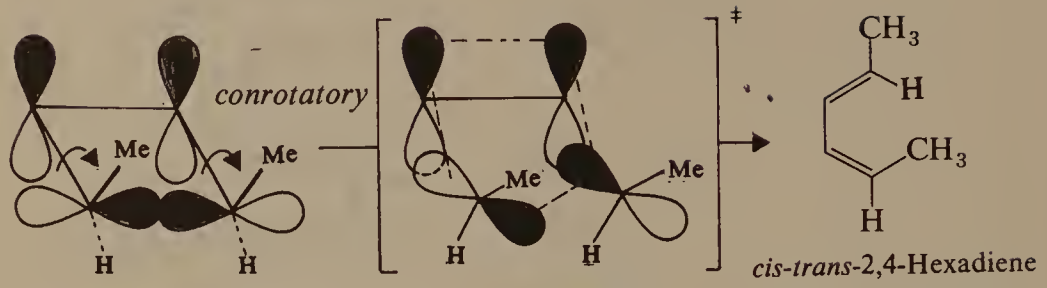
for conrotatory and disrotatory ring opening are drawn in schemes 8.71 and 8.72 which are to be analyzed for aromaticity. In the transition state for conrotatory ring opening, there is one sign inversion, this therefore, represents an *anti*-Huckel system with four electrons. The conrotatory transition state for cyclobutene ring opening thus represents a Mobius system and is therefore, aromatic. Disrotatory ring opening, on the other hand, would require a Huckel cyclic system, which with four electrons would be *anti*-aromatic.

Conrotatory openings have both rotations in the same direction, shown as clockwise, however, the equally likely rotation in the anticlockwise direction also leads to the same product. Disrotatory openings have rotations in opposite directions. The disrotatory mode giving the *E,E* isomer for *cis*-3,4-dimethylcyclobutene thermolysis has been presented. There is another disrotatory mode which will lead to the *Z,Z* alkene has not been illustrated. The two disrotatory modes lead to diastereoisomers and are not thus of equal energy or probability. The electrocyclic ring opening of cyclobutenes is a four-electron reaction and is allowed thermally in the conrotatory mode. Two



cis-3,4-dimethylcyclobutene

(E,Z)-hexa-2,4-diene



cis-3,4-dimethylcyclobutene

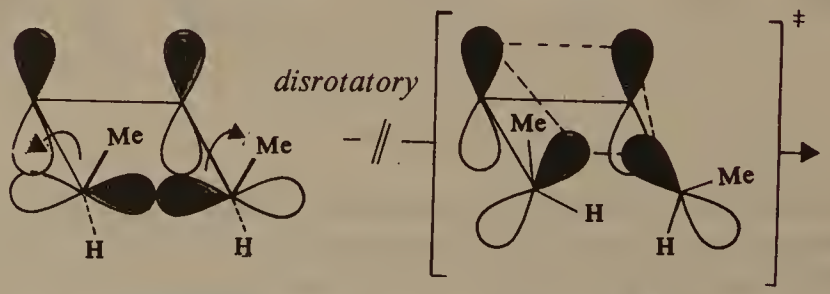
Basis set for conrotatory cyclobutene ring opening

One sign inversion
Möbius system

4 Electrons in cyclic array of orbitals; aromatic, allowed process

cis-trans-2,4-Hexadiene
(E,Z)-hexa-2,4-diene

Scheme 8.71

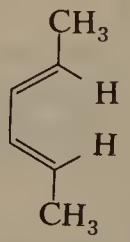


cis-3,4-dimethylcyclobutene

Basis set for disrotatory cyclobutene ring opening

No sign inversions
Hückel system

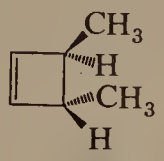
4 Electrons in cyclic array of orbitals; nonaromatic, forbidden process



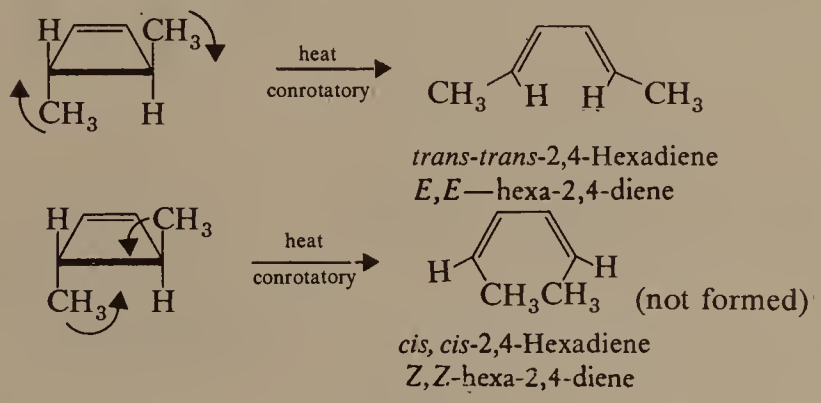
trans-trans-2,4-Hexadiene
E,E

Scheme 8.72

products could be produced by conrotatory opening of *trans*-3,4-dimethylcyclobutane. The *Z,Z*-diastereoisomer cannot adopt an *s-Z* conformation for steric reasons and consequently the transition state leading to its formation would be highly hindered. The only product formed on thermolysis of *trans*-3,4-dimethylcyclobutane is, therefore, *E,E*-hexa-2,4-diene (Scheme 8.73).



trans-3,4-Dimethylcyclobutene



trans-trans-2,4-Hexadiene
E,E—hexa-2,4-diene

cis, cis-2,4-Hexadiene
Z,Z-hexa-2,4-diene

Scheme 8.73

(*viii*) *Generalisation of Thermal Electrocyclic Reactions—a Comparison with Photochemical Reactions:* Thermal electrocyclic reactions which involve $4n+2$ electrons react with disrotatory motion so that the orbitals involved can overlap in the Huckel sense. Thermal electrocyclic reactions which involve $4n$ electrons react with conrotatory motion so that the orbitals involved can overlap in the Mobius sense. These generalizations hold both for ring closure or ring opening (principle of microscopic reversibility).

$4n$ electrons (4,8,12, etc.) conrotatory motion

$4n+2$ electrons (2,6,10,14, etc) disrotatory motion.

The above rules apply to thermal reactions only. For photochemical reactions, the rules are usually exactly opposite, since electronic excited states have some important symmetry differences from ground states. Additionally photochemical electrocyclic reactions are often not concerted reactions.

(D) Cycloaddition Reactions

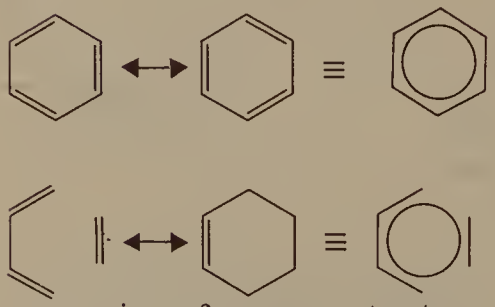
(*i*) *Introduction*: Cycloaddition reactions may be analysed by examining the transition states as is done for electrocyclic reactions. A typical example of

a cycloaddition reaction is the Diels-Alder reaction, the addition of ethene to butadiene (Scheme 8.74).

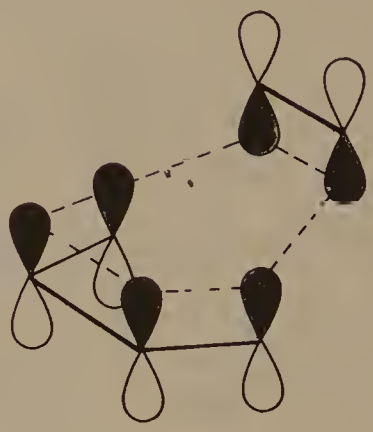
(I)

Diene Alkene (dienophile) Cyclohexene (adduct)

[4 + 2] cycloaddition



comparison of resonance structures



(XV)

No sign inversions
Hückel system

6 Electrons in cyclic array of orbitals; aromatic, allowed process

Scheme 8.74

Diels-Alder reactions involve the formation of two σ-bonds and one π bond from the two π bonds of a diene and the π bond of a monoene. Thus, generally, Diels-Alder reaction is classed ($4^{\pi} + 2^{\pi}$) cycloaddition. If one labels the orbitals involved, one sees that the normal Diels-Alder reaction involves a Huckel transition state with six electrons (*i.e.*, aromatic transition state). By contrast ($2^{\pi} + 2^{\pi}$) cycloaddition reactions are forbidden. Ethene, *e.g.*, does not dimerize thermally, even under high pressure, despite the large favorable enthalpy for forming cyclobutane (eq. II, Scheme 8.75).

$\Delta H^{\circ} = -18.2$ kcal mole^{-1} (II)

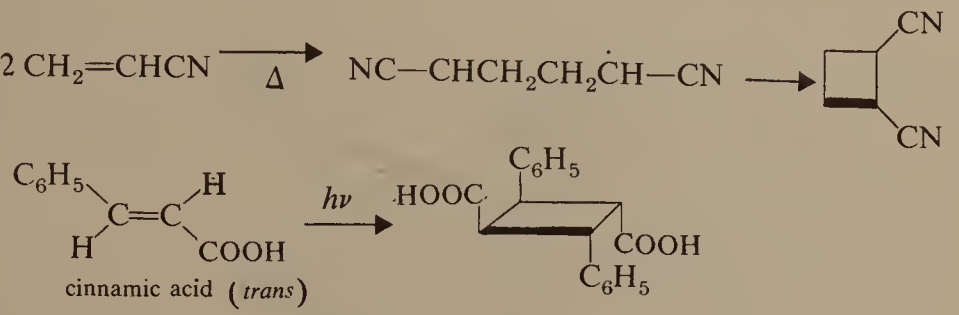
Alkene Alkene Cyclobutane

[2 + 2] cycloaddition

(XVI)

Scheme 8.75

A thermal cycloaddition reaction in the ($2^{\pi} + 2^{\pi}$) manner is ruled out since it would involve a transition state **XVI** of the antiaromatic Huckel system (since four electrons $\neq 4n+2$). In the transition state for ethene dimerization two ethene molecules are assumed to approach in the simplest manner appropriate to σ-bond formation; along the principal axes of the *p* orbitals. Thus, ethene, instead undergoes linear polymerization to give polyethylene. Several compounds on the other hand, undergo cycloadditions to give cyclobutanes, however, in every case the mechanism appears to involve a diradical intermediate rather than a cyclic transition state.



Scheme 8.76

In contrast, several photochemical ($2^{\pi} + 2^{\pi}$) cycloadditions are known, when a $4n$ cyclic transition state is acceptable, though several of these reactions may also involve diradical intermediates. An example of a photochemical cycloaddition is the exposure of cinnamic acid to sunlight.

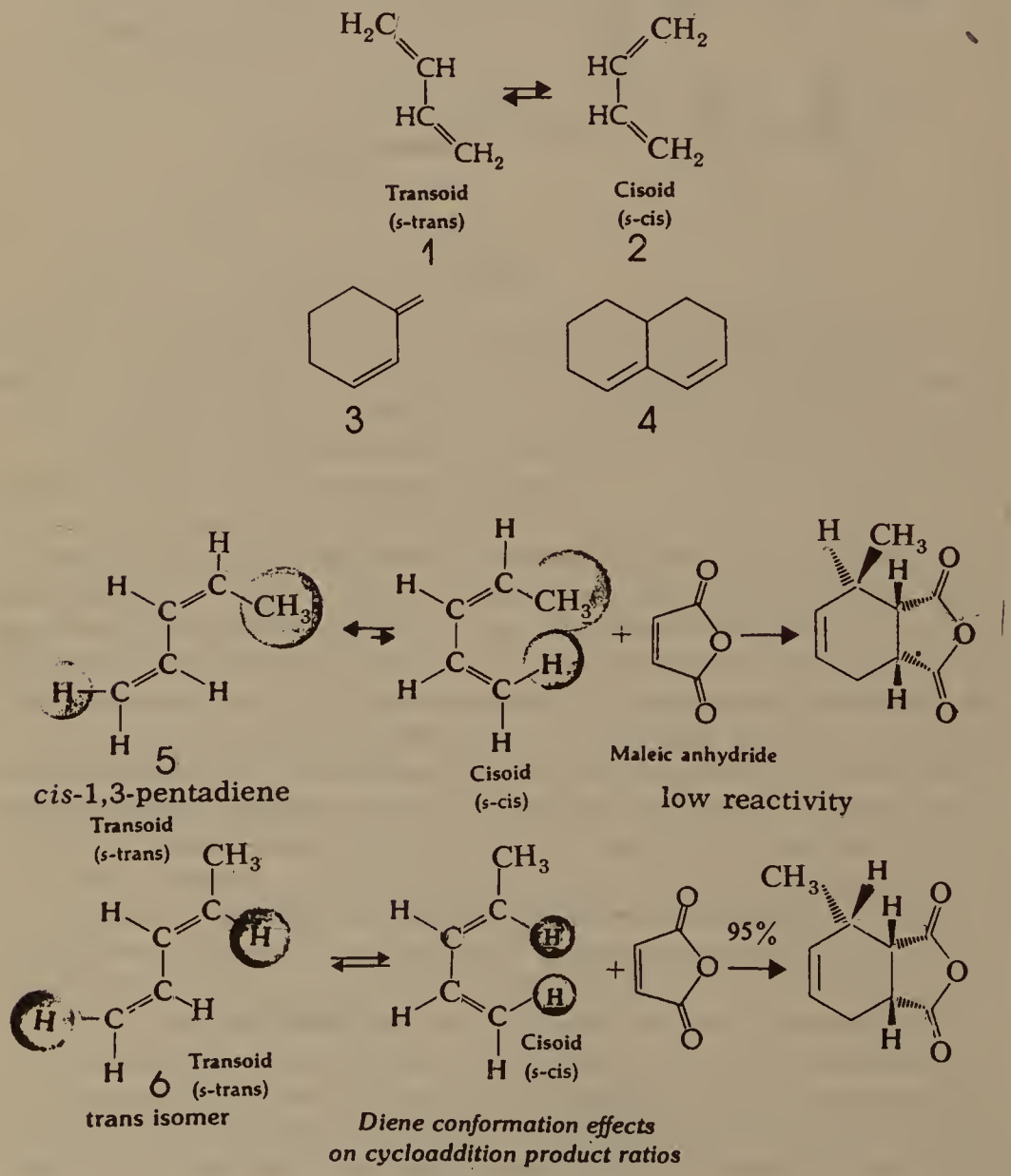
(*ii*) *Details of Diels-Alder Reaction* (*Suprafacial-Suprafacial Cycloaddition*): As seen in other pericyclic reactions Diels-Alder reactions are often stereospecific, due to the concerted nature of the reaction (Scheme 8.78).

The preceding results confirm the geometry of approach of reactants as shown in (XV). Additions of this type where the termini of each π system bond to the same face on the other are called suprafacial-suprafacial additions symbolized by a subscript *s*. In antarafacial additions new sigma bonds are formed on opposite faces of a π-system symbolized by a subscript *a*.

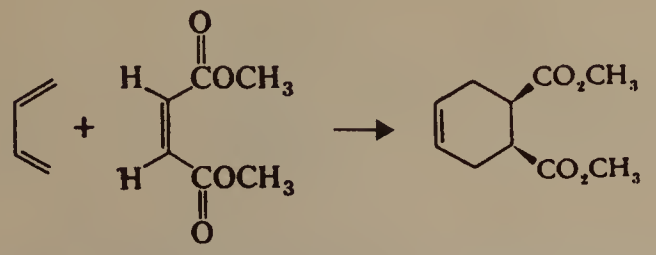
Diels-Alder reactions are therefore, classed as $4^{\pi}{}_{s} + 2^{\pi}{}_{s}$, cycloadditions. When analysing pericyclic reactions one has to concentrate on the electrons directly involved in the transition state. The reactions (Scheme 8.79) are $4^{\pi}{}_{s} + 2^{\pi}{}_{s}$ cycloadditions despite the conjugation with other π-bonds in the alkene fragments. Suprafacial-suprafacial thermal cycloadditions are allowed for $4n+2$ electron transition states and forbidden for $4n$ electron systems. As said before, the photochemical selection rules are opposite, *i.e.*, $4n$ electron photochemical suprafacial-suprafacial cycloaddition reaction are allowed.

Formation of a cyclic product from a Diels-Alder reaction imposes severe stereochemical restrictions on this reaction. The diene must react in its *s-cis* form (cisoid) 2, an orientation in which the double bonds are on the same side of the single bond which connects them. An acyclic diene can rotate about its

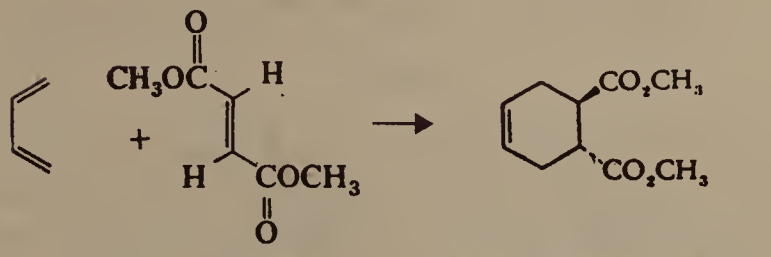
central single bond, thereby converting the *s-trans* orientation 1 (transoid) to the requisite *s-cis* geometry (Scheme 8.76a). The essential involvement of a *s-cis* diene conformer in Diels-Alder reactions is seen in the unreactive nature of fixed transoid dienes 3 and 4, and rather low reactivity of *cis*-1, 3-pentadiene 5 than its *trans* isomer 6. This is due to severe nonbonded compressions in the *s-cis* conformer of the *cis* isomer. Diels-Alder reactions are highly stereospecific *i.e.,* the configurational relationships of the substituents on the diene and the dienophile are preserved in the adduct (Schemes 8.77 and 8.78).



Scheme 8.76a

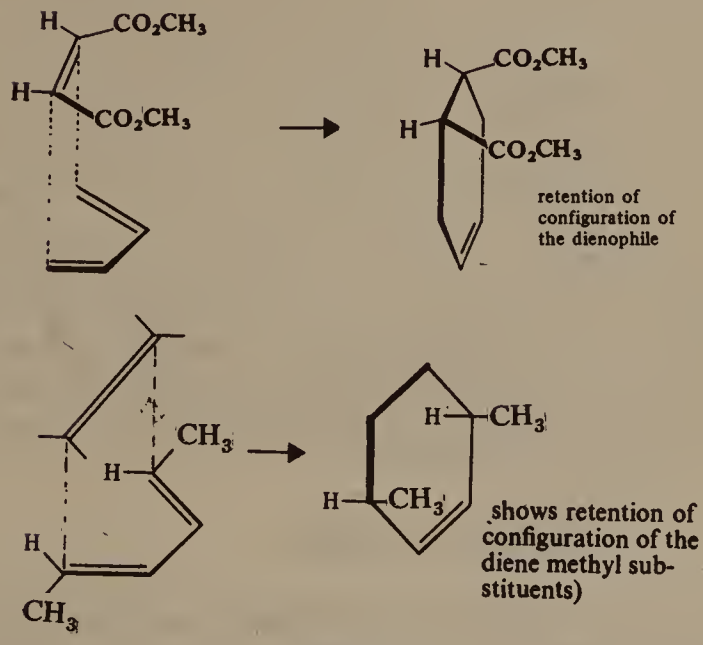


Dimethyl maleate (a *cis*-dienophile) — *cis*-4,5-Dicarbomethoxy-cyclohexene



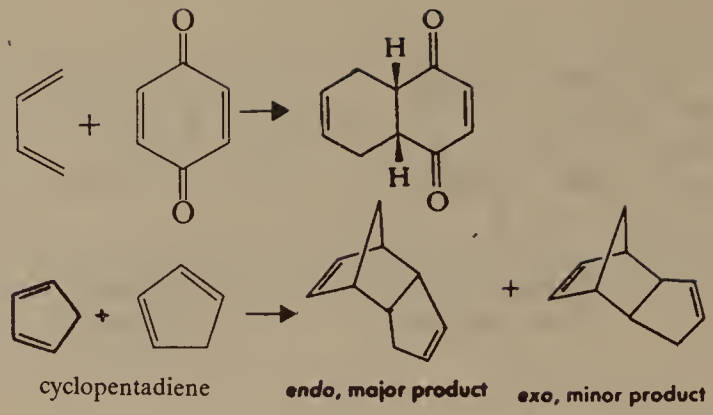
Dimethyl fumarate a *trans*-dienophile — *trans*-4,5-Dicarbomethoxy-cyclohexene

Scheme 8.77



Scheme 8.78

Additional stereochemical situation applies when the diene is cyclic, *e.g.*, in the dimerization of cyclopentadiene. Here one molecule acts as diene and the other as dienophile; two orientations in the product are possible and each is formed from suprafacial-suprafacial interaction of the reactants. Most of the time, the thermodynamically less stable *endo* product predominates. This



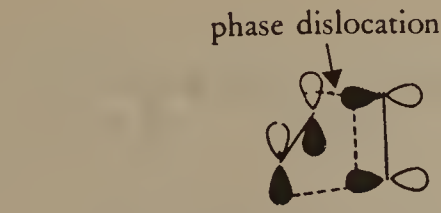
Scheme 8.79

has been explained by considering a secondary interaction of orbitals in the transition state for *endo*-addition which is sterically prohibited for *exo*-addition. This secondary interaction does not lead to bonding in the product. Since the overlapping orbitals are of like phase, it only stabilizes the transition state.

(*iii*) *Antarafacial-Superafacial Cycloadditions*: Antarafacial-Suprafacial cycloaddition is highly sterically hindered and is, therefore, less common. In case two ethylene molecules are brought together in such a way that a Mobius activated complex (XVII) can be realized, the process becomes a suprafacial-antarafacial addition. This process should be allowed since it is a Mobius system with four electron and a node. For this process to be realized the ethylene molecules have to approach each other in a perpendicular geometry. The completion of this addition involves distortion of the carbon frame work. The process, therefore, is difficult although allowed. For this reason simple alkenes do not display this addition. The highly strained triene (XVIII) however spontaneously dimerizes thermally and represents ${}_{12}\pi_a + {}_2\pi_s$ transition state. Reaction of heptafulvalene with tetracynoethylene is a remarkable example of a ${}_{14}\pi_a + {}_2\pi_s$ thermal cycloaddition leading to a product of *trans* addition. The transition state involves a negative overlap which corresponds to a Mobius cyclic electronic system, a favourable transition state for a 16-electron ($4n$) cyclic system (Scheme 8.80).

(E) Sigmatropic Thermal Rearrangements

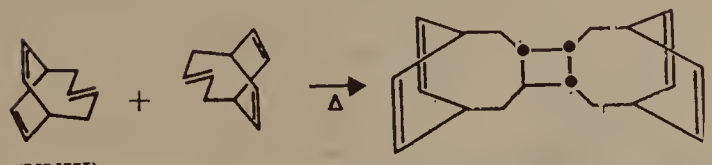
(*i*) *Classification*: In a sigmatropic change a σ-bond adjacent to one or more π-electron systems, moves to a new position in the molecule the π system becoming reorganized. The order of the reaction [*i, j*] is then expressed by the position of the new bond, relative to the original, and the number of electrons in the cyclic transition state. The termini of the original σ-bond are labelled, 1,1 followed by numbering the chains sequentially. After the reaction, the termini of the new bond define the order. Some reactions like Cope reaction can involve two π-systems.



The phase relationships

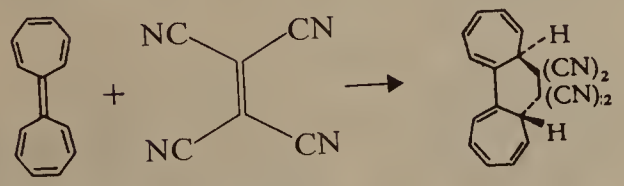
the $_2\pi_a + _2\pi_s$ transition state

(XVII)



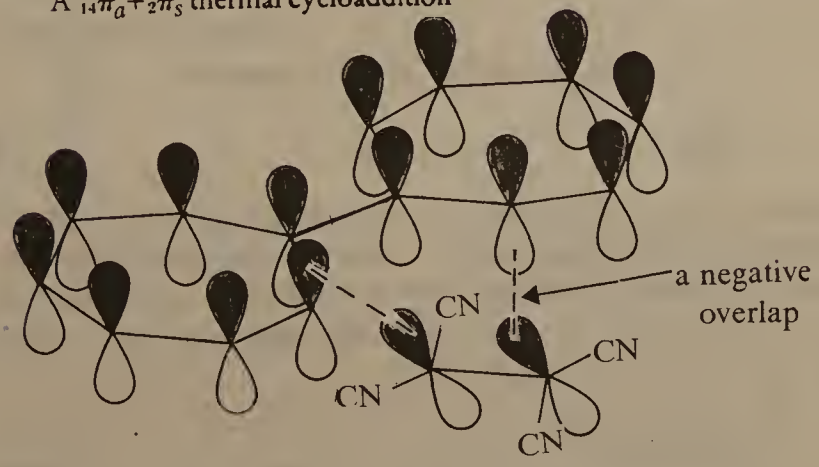
(XVIII)

A $_2\pi_a + _2\pi_s$ thermal cycloaddition



heptafulvalene tetracyanoethylene

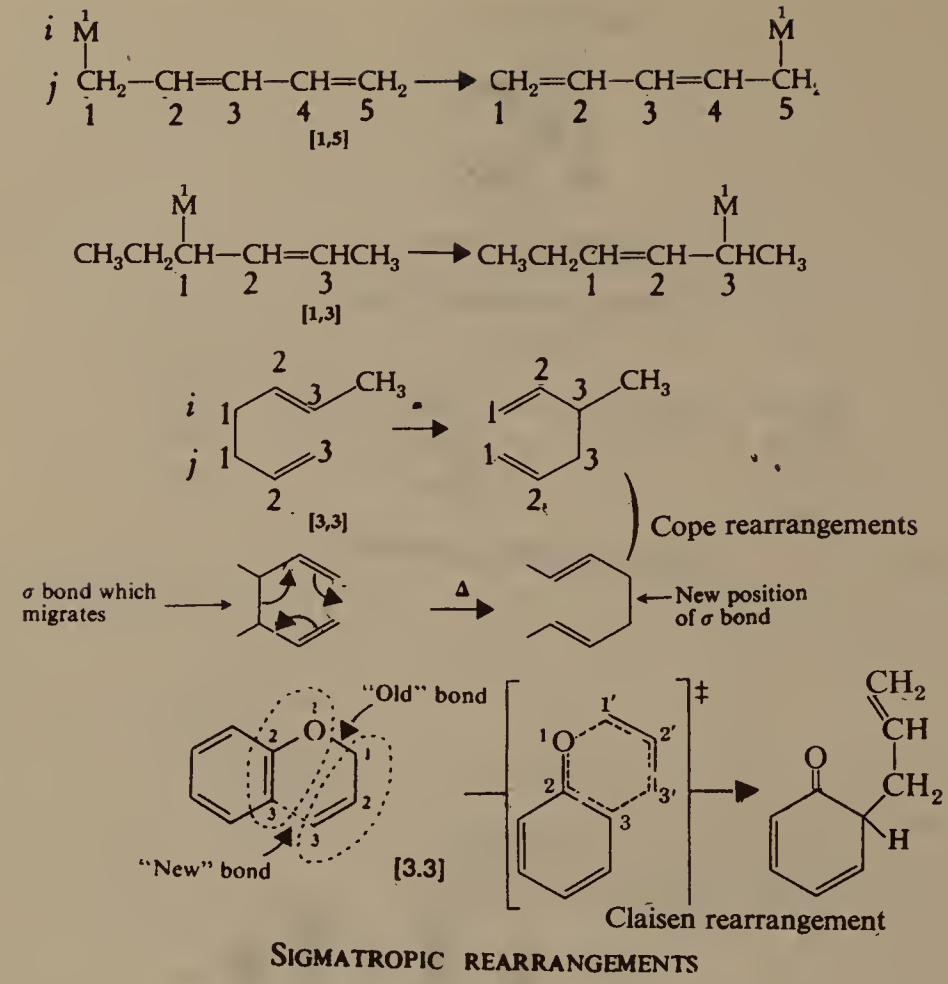
A $_{14}\pi_a + _2\pi_s$ thermal cycloaddition



Scheme 8.80

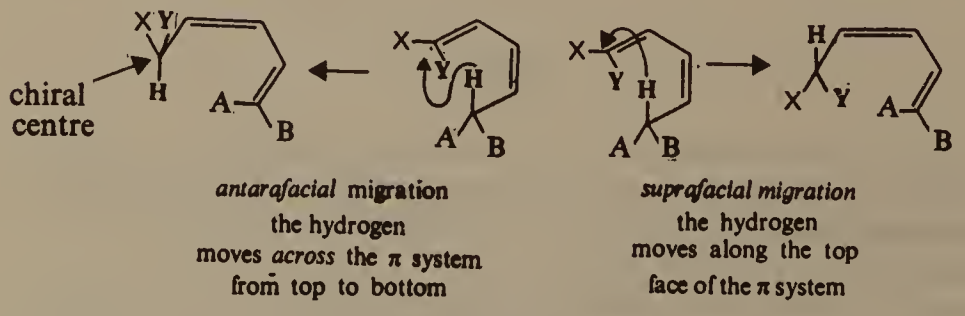
The Claisen rearrangement of allyl phenyl ether is a [3,3] sigmatropic rearrangement as it has one oxygen atom and two aromatic ring carbons between the old and new bond on one side, and the three carbons between the old and new bond on the other.

(*ii*) [*1,5*] *Sigmatropic Shift of Hydrogen*: Consider the [1,5] sigmatropic shift in 1,3-pentadiene (Scheme 8.82). There are two geometrical pathways by means of which a hydrogen can migrate from one terminus to the other. In one of the two ways, the hydrogen moves across the top or the bottom face of



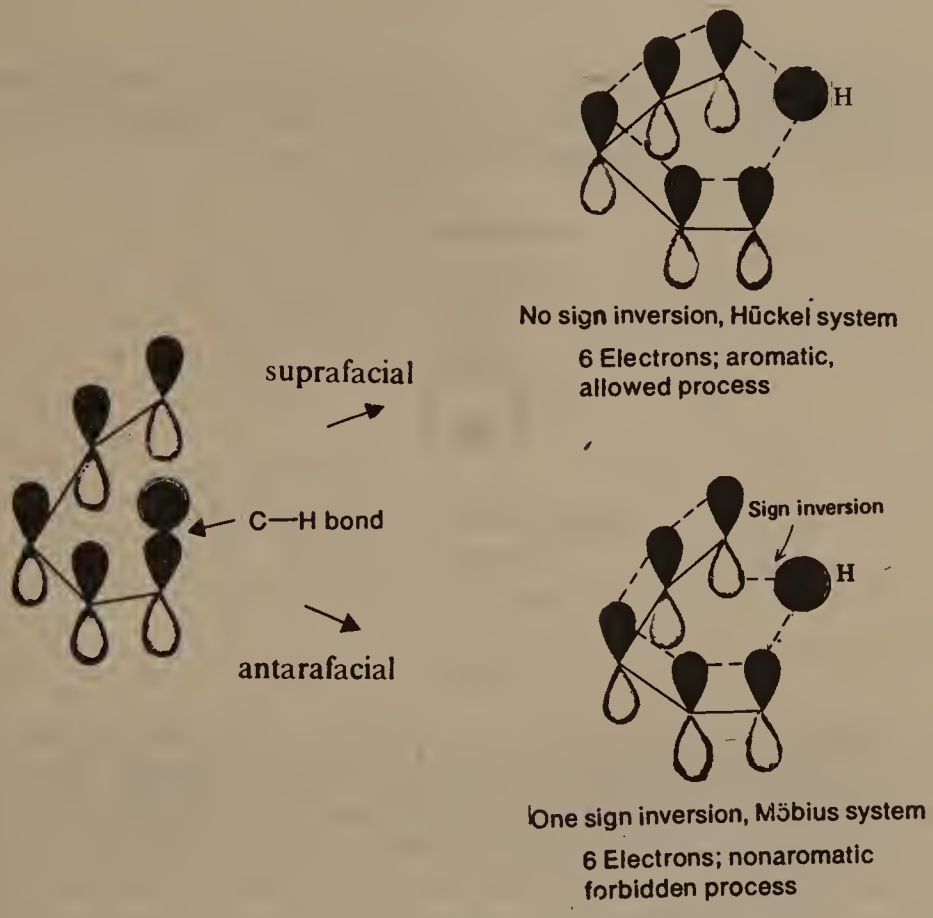
Scheme 8.81

the pentadiene system (the suprafacial route). In other pathway, the hydrogen moves from the top side at one end to the bottom side at the other or vice versa (the antarafacial route). Starting with the substrate where the migration origin is a chiral carbon, two migration pathways for hydrogen are considered.



Scheme 8.82

The pentadienyl system is represented by five *p* orbitals, and the hydrogen atom by a circle. When hydrogen migration takes place by a suprafacial process, no sign inversion is observed (Huckel pattern) and the process is allowed since six *pi* electrons are involved. If one depicts the process as antarafacial, one sign inversion is involved, *i.e.*, a Mobius system and since the system has six *pi* electrons, it would not be allowed on symmetry consideration. Indeed in keeping with these predictions, in thermal rearrangements of optically active pentadienyl systems, the absolute configuration at the new chiral centre is in keeping with a suprafacial 1, 5 transfer of hydrogen (Scheme 8.83).



[1,5] sigmatropic shift of a hydrogen atom
pentadienyl system

Scheme 8.83

(*iii*) [*1,3*] *Sigmatropic Hydrogen Migration*: The [1,3] shift takes place by a migration across an allyl framework and only two π-electrons are involved in the transition state. Consider the phase interactions in the basis set. Just like [1,5] sigmatropic migrations, the transition state has an even number *i.e.*, no phase dislocations and is, therefore, a Huckel system for the suprafacial processes. The [1,3] migration, being four-electron, is thermally forbidden.

Suprafacial process

[1,3]
Hückel system; 4 electrons,
nonaromatic
forbidden process

Scheme 8.84

On the other hand, one can easily conclude that the allowed pathway would be antarafacial (*i.e.,* in the transition state there is one sign inversion, Mobius system, 4 electrons thermally allowed process).

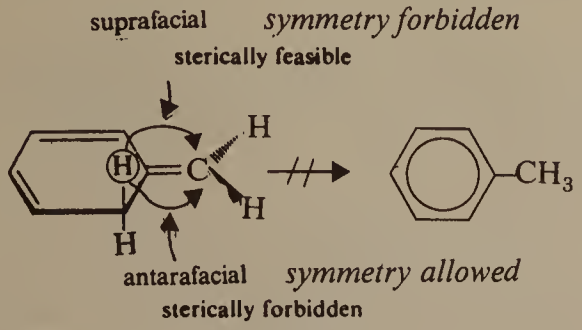
Antarafacial process

[1,3]
Möbius system; 4 electrons,
aromatic
allowed process

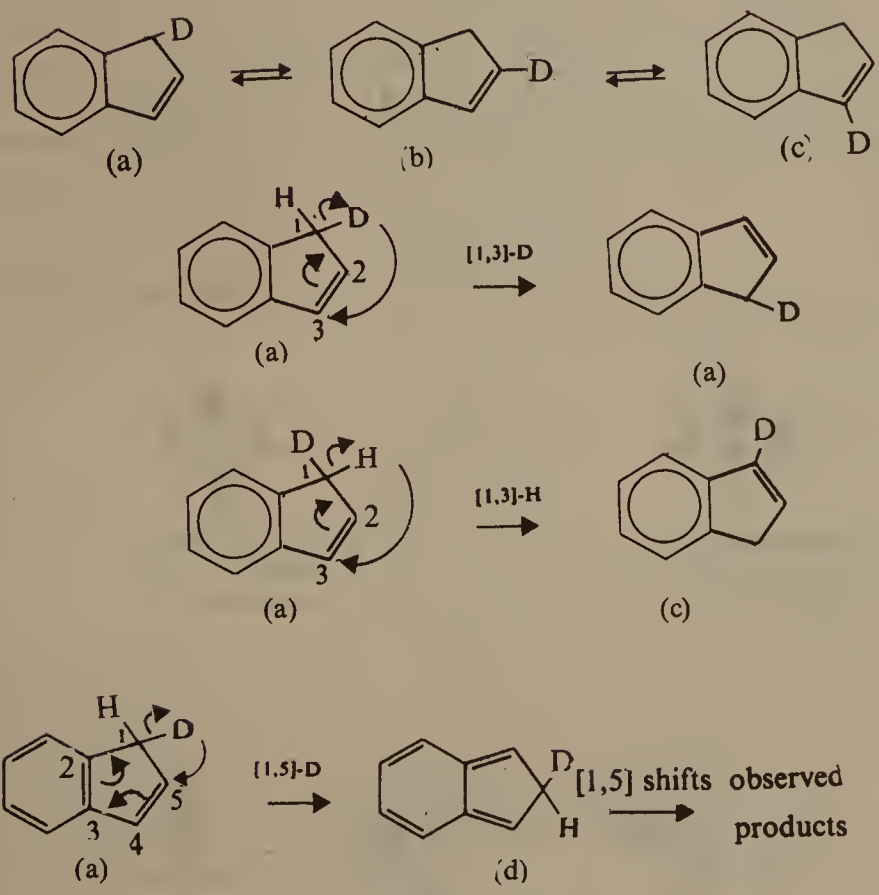
Scheme 8.85

(*iv*) *Sigmatropic Hydrogen Shifts and Geometry of System*: We have seen above that an antarafacial [1,5] sigmatropic shift of a hydrogen atom is a forbidden process. A sigmatropic rearrangement depends both on the symmetry requirements as well as the geometry of the system. Particularly [1,3] and [1,5] antarafacial shifts should be extremely difficult, since they would require the π framework to be twisted far from the planarity that it requires for delocalization of electrons. Thus a [1,3] sigmatropic hydrogen migration does not occur in methylenecyclohexadiene to convert it into much more stable toluene. Indeed [1,3] sigmatropic shifts of hydrogen are not known. [1,5]-H Shifts indeed show preference over [1,3]-H shifts. (Scheme 8.86).

On heating of 3-deuterioindene (a) scrambling of the label to all three non-aromatic positions takes place. One, however, cannot account for the formation of (b) Scheme 8.87 on the basis of [1,3] shifts *i.e.,* migration of D would regenerate (a); migration of H would afford only (c).



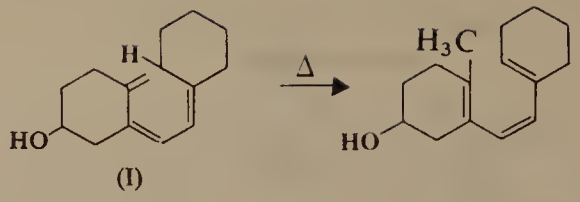
Scheme 8.86



Scheme 8.87

If one includes the *p*-orbitals of the benzene ring, a [1,5] shift of D would give the unstable non-aromatic intermediate (d). This can then transfer H or D by [1,5] shifts to yield all the compounds, formed.

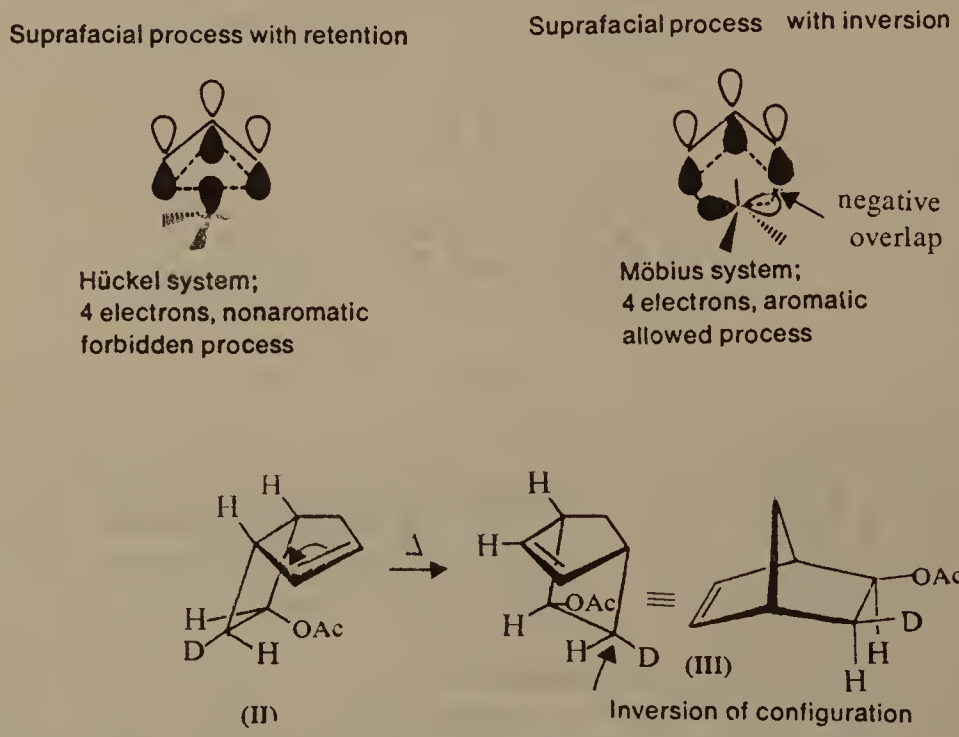
An example of the antarafacial [1,7] thermal migration (8, electrons, one sign inversion, Mobius system, aromatic) is I (Scheme 8.88) which shows that special steric factors are necessary for such migrations. The π-system is twisted out-of-plane because of the steric hindrance and the migrating hydrogen has to always migrate from one face of the π-system to the other.



(I)

Scheme 8.88

(*v*) [*1,3*] *Sigmatropic Carbon Shifts in an Allyl System*: If one considers a [1,3] sigmatropic rearrangement in which a carbon is the migrating entity, in addition to the consideration of the geometry of the migration pathway, one has also to consider the stereochemistry of the migrating group; *i.e.*, if it becomes attached to its new position with retention or inversion of configuration. Compare the transition states for retention and inversion in a 1,3-suprafacial shift (Scheme 8.89). The inversion transition state is a four electron Mobius system and, therefore, aromatic. In actual experimentation inversion of the configuration has indeed been detected in the conversion of (II) to (III).

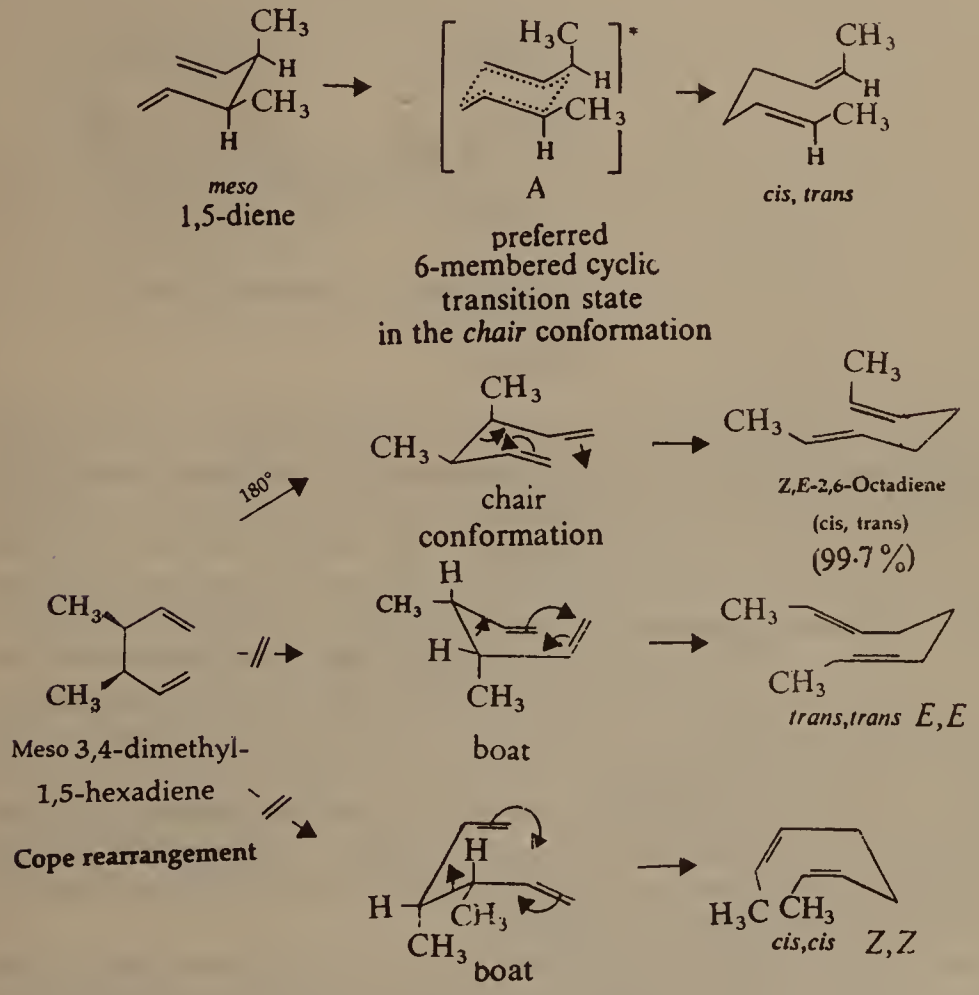


[1,3]sigmatropic carbon shift in an allyl system

Scheme 8.89

(*vi*) *The Cope Rearrangement*: One common example of the Cope rearrangement involves sigma bond migration *i.e.*, [3,3] sigmatropic rearrangement of 1,5-dienes. In acyclic systems, there is overwhelming evidence that the

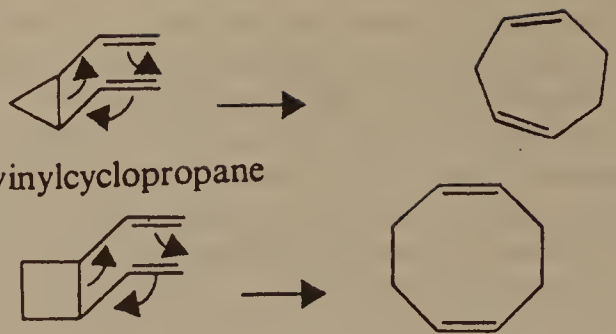
reaction proceeds through a six electron transition state which takes up the low energy chair form **A** rather than the boat like form. When the groups located on the 1,5-diene skeleton allow the stereochemical course to be followed the reaction is found to be stereospecific. For example, *meso*-3,4-dimethyl-1,5-hexadiene (Scheme 8.90) rearranges almost exclusively to *ZE* 2, 6-octadiene (*cis-trans* isomer) consistent only with a chair-shaped transition state; a boat-shaped transition state would however, yield either the *trans, trans*- or the *cis, cis*-product, depending on conformation, leading to the transition state.



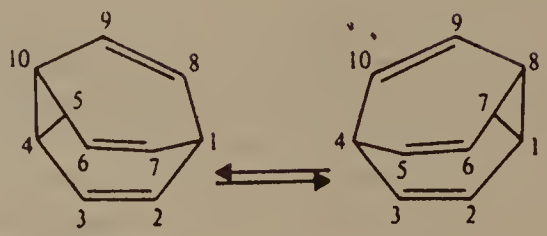
Scheme 8.90

In case the structure of the molecule does not allow the attainment of a chair-shaped transition state, the reaction occurs through the boat shaped transition state. This indeed is so in the case of divinylcyclopropanes and cyclobutanes (Scheme 8.91) during Cope rearrangement.

The rearrangement of *cis*-1,2-divinylcyclopropane is very rapid and thus this compound cannot be isolated at room temperature. The Cope rearrangement in bullvalene changes the position of the cyclopropane ring from 4,5,10



cis-1,2-divinylcyclopropane



bullvalene **Cope rearrangement**

Scheme 8.91

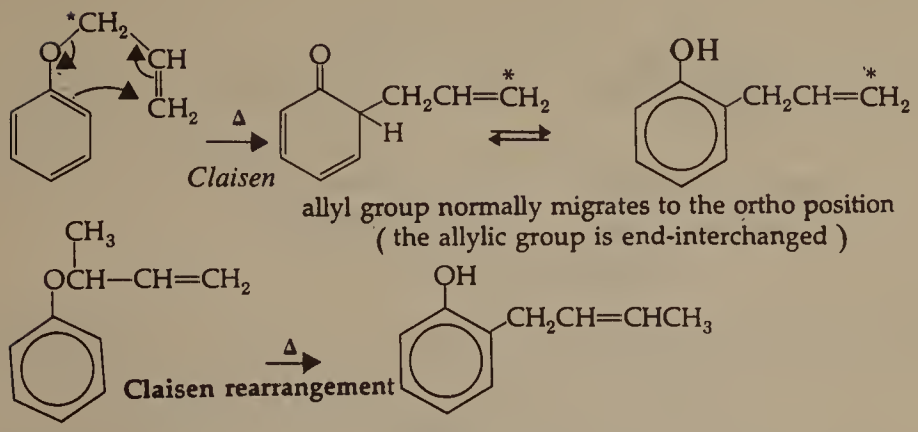
to 1,7,8. However, the molecule could also have undergone the rearrangements to put this ring at 1,2,8 or 1,2,7-position. Any of these structures could then undergo several Cope rearrangements and as a result over a million identical forms exist. The cyclopropane ring can be at any three carbons which are adjacent. Since each of these tautomers is equivalent to all the others, this has been named as an infinitely degenerate Cope rearrangement.

(*vii*) *The Claisen Rearrangement*: The sigmatropic rearrangement known as the Claisen rearrangement involves [3,3] shifts. The Claisen rearrangement is the thermal conversion of aryl or vinyl allyl ethers to allyl phenols. The allyl group normally migrates to the *ortho* position of the aromatic ring. However, if both *ortho* positions are blocked, rearrangement to the *para* position occurs. The transition state has the six-electron aromatic conjugation characteristic of benzene. A related type of transition has been noted in the Diels-Alder reaction. (Scheme 8.93).

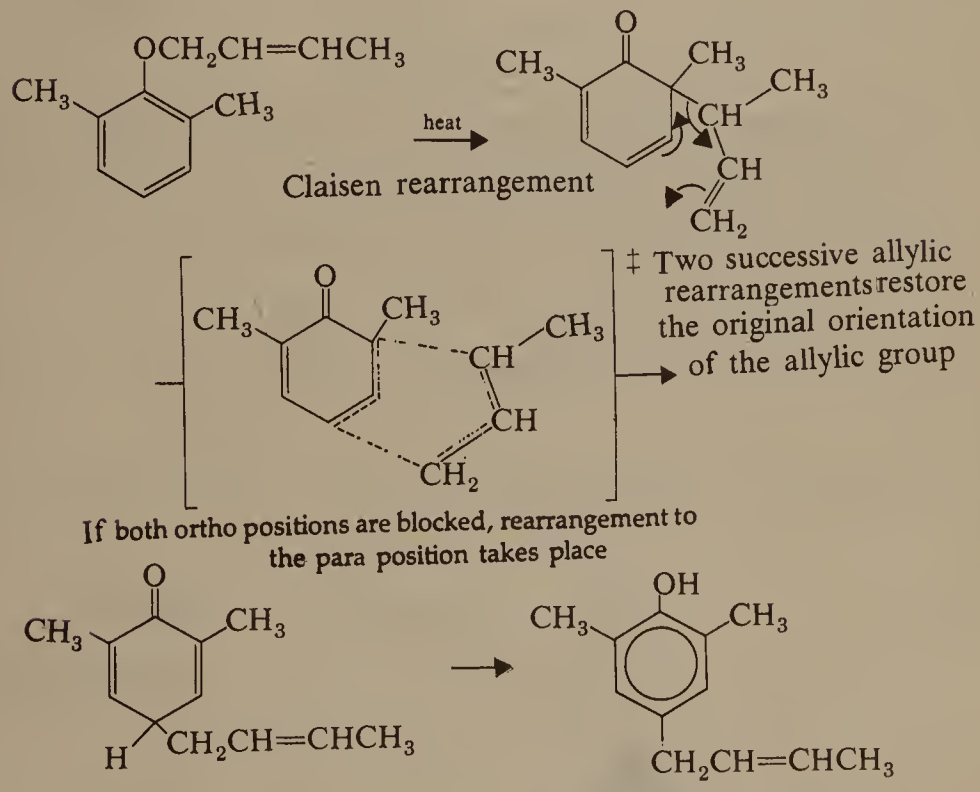
Studies using migrating groups labeled with ^{14}C or with substituents show that the allylic group is end-interchanged during the *ortho* rearrangement. These and other results which show that the Claisen rearrangement is intramolecular provide strong support for a concerted mechanism.

If no *ortho* hydrogen is available, enolization to the phenol cannot occur, and a second rearrangement occurs to the para position. (Scheme 8.92).

As seen in the case of Cope rearrangement (the all carbon rearrangement of a 1,5 diene) the Claisen reaction also occurs with aliphatic allyl ethers and a transition state of chair conformation is preferred; for example, *trans, trans*-crotyl propenyl ether IV (Scheme 8.94) rearranges to the *threo*- and not the *erythro* 2,3-dimethylpentenal.



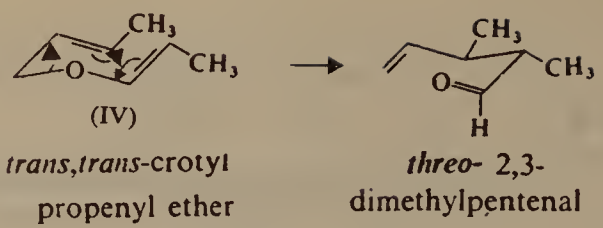
Scheme 8.92



Scheme 8.93

The mechanism in the case of these allyl vinyl ethers is similar to that of allyl aryl ethers. In keeping with the concerted pericyclic [3,3] sigmatropic rearrangement optically active (v) rearranges to (vi) which retaines its optical activity

(*viii*) *1,2-Rearrangements*: Alkyl migrations are most familiar in carbocation and other electron-deficient species and the stereochemistry observed is one that is predicted by a pericyclic transition state *e.g.*, Wagner-Meerwein rearrangement. This reaction can be termed as two electron [1,2] pericyclic reaction. In the transition state only positive orbital overlaps are involved, hence the system is therefore of Huckel type and has aromatic stabilization for



(IV)

trans,trans-crotyl propenyl ether

threo- 2,3-dimethylpentenal

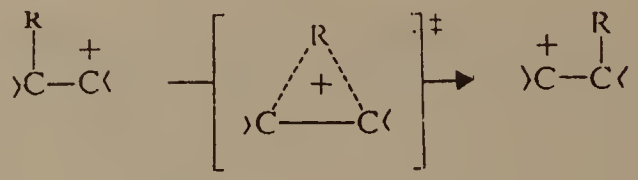
(+) (V)

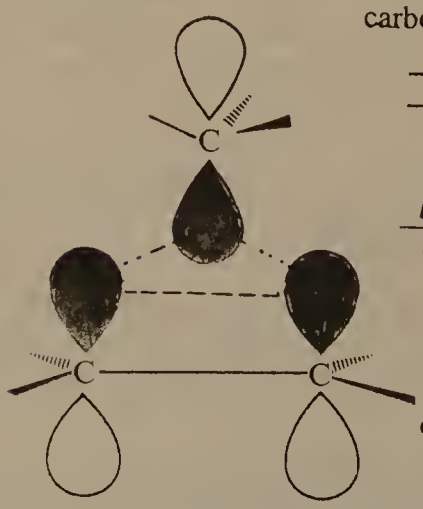
(−) (VI)

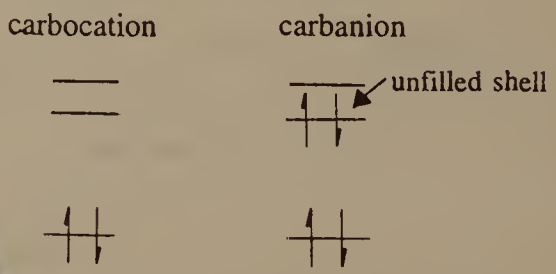
Scheme 8.94

two electrons. These rearrangements, however do not occur for carbanions.

The 1,2-rearrangement of carbanions would be described as a four-electron, 1,2- rearrangement and would be antiaromatic. Such rearrangements do, however, occur but not by a concerted mechanism.







carbocation case has two electrons and a stable filled shell MO pattern

carbanion case with four electrons and an unfilled shell is unstable

1,2-rearrangement involves a three-center pericyclic transition state

Scheme 8.95

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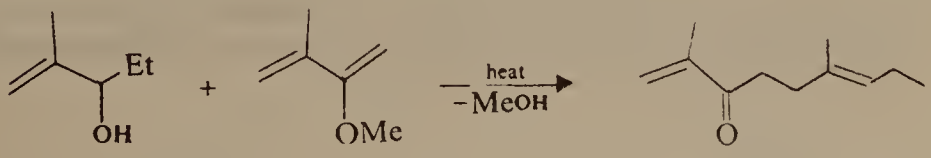
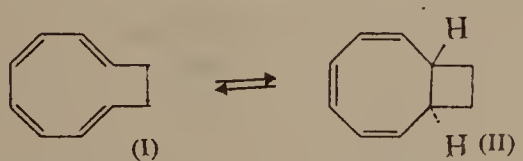
EXERCISES AND PROBLEMS

1. Explain the mechanism of the following synthesis.

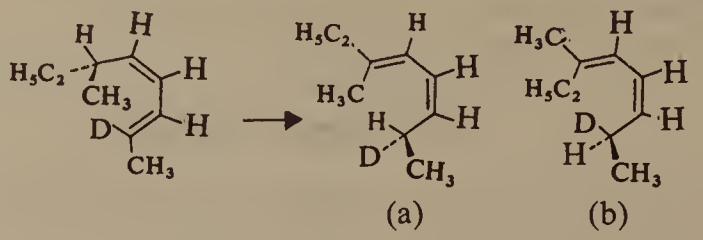


2. The compounds I and II rapidly interconvert on heating. Comment on the stereochemistry of the reaction.

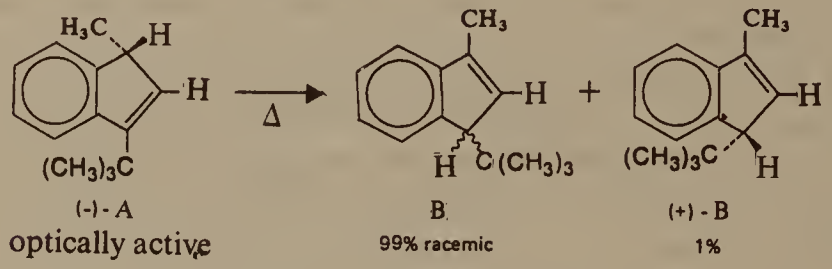


(*E,Z,Z,E*)-1,3,5,7-cyclodecatetraene ⇌ *trans*-bicyclo[6.2.0]deca-2,4,6-triene

3. Classify the order of sigmatropic shift which yielded each of the following products (a) and (b). Indicate for each product, if it is derived from antarafacial or suprafacial migration.

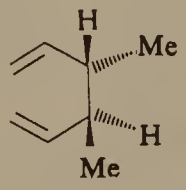


4. Consider the intramolecular, thermal rearrangement of (—) 1-methyl-3-*t*-butylindene (A). Optically active (A) on heating to 140°C and partial isomerisation gave (B) as 99% racemic mixture. Rest 1% has the configuration (+)-B, an overall suprafacial hydrogen shift for the minor product formation. Suggest a mechanism for the formation of racemic B. Formation of (+)-B can be explained by invoking a concerted thermal [1,3] sigmatropic hydrogen shift or a series of thermal [1,5] sigmatropic shifts along the bridgehead carbon atoms. Explain.



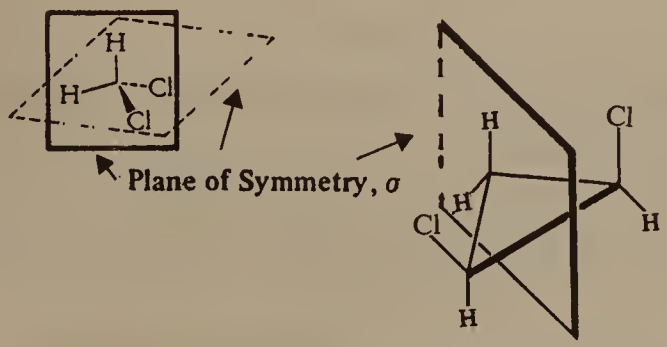
5. Give a mechanism for the following reaction.

6. The stereopecificity of the Cope rearrangement in the following compound may proceed through the chair or boat like transition state to give different stereoisomeric dienes. Write the structures of the dienes from both the pathways.

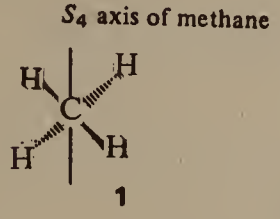


ANSWERS TO PROBLEMS

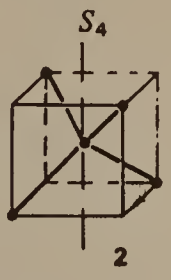
CHAPTER 1

1. Linear molecules like acetylene have a C_∞ axis. In this case even an infinitesimal rotation (360°/∞) about this axis leads to an orientation indistinguishable from the original. The trivial onefold axis C_1 is never considered, as all molecules have an infinite number of C_1 axis.
2. If a molecule is not superimposable on its mirror image, then it can display optical activity. Such molecules are (*i*) asymmetric *i.e.*, these do not have any symmetry elements (except a trivial axis, C_1) or (*ii*) dissymmetric; these possess proper axes but no alternating axis of symmetry *i.e.*, improper axis. Thus, if a molecule has an S_n axis, then it is not optically active. If it has no S_n axis, then it is optically active. If a C_n axis is the only symmetry element present in a molecule then it is optically active.
3. 

cis-1,2-dichlorocyclopropane
4. The axis depicted in 1 passes through the middle of the molecule and bisects opposite HCH angles. If one considers the clockwise rotation of the molecule by 90° around this axis and subsequent reflection in a plane perpendicular to it, one gets an orientation of the molecule superimposable on the original. One can easily depict not only the same axis by inscribing the tetrahedral model of methane in a cube 2, but the other S_4 axes as well. The S_4 axis shown bisects the opposite sides of the cube. A cube has six equivalent faces, therefore, there are three S_4 axes. Notably each S_4 in methane molecule is also a C_2.



1



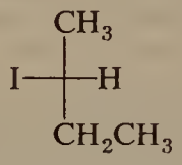
2

5. (a) Diastereoisomers
   (b) Homomers
   (c) Enantiomers

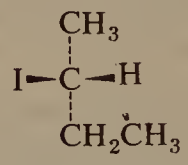
(d) Homomers
(e) Homomers
(f) Diastereoisomers

6. These structures are all equivalent, a structure being written by interchanging any two pairs of groups. The compound is (*R*)— 1-bromo 1-chloroethane.
7. Interchanging any two groups, a projection for the enantiomer is generated. A Fischer projection can only be rotated in the plane of paper by 180° and not by 90°. Therefore 1,2 and 3 represent the same (*S*) compound while 4 is (*R*). Compounds 5 and 6 are identical while 7 is different from 8.

8.



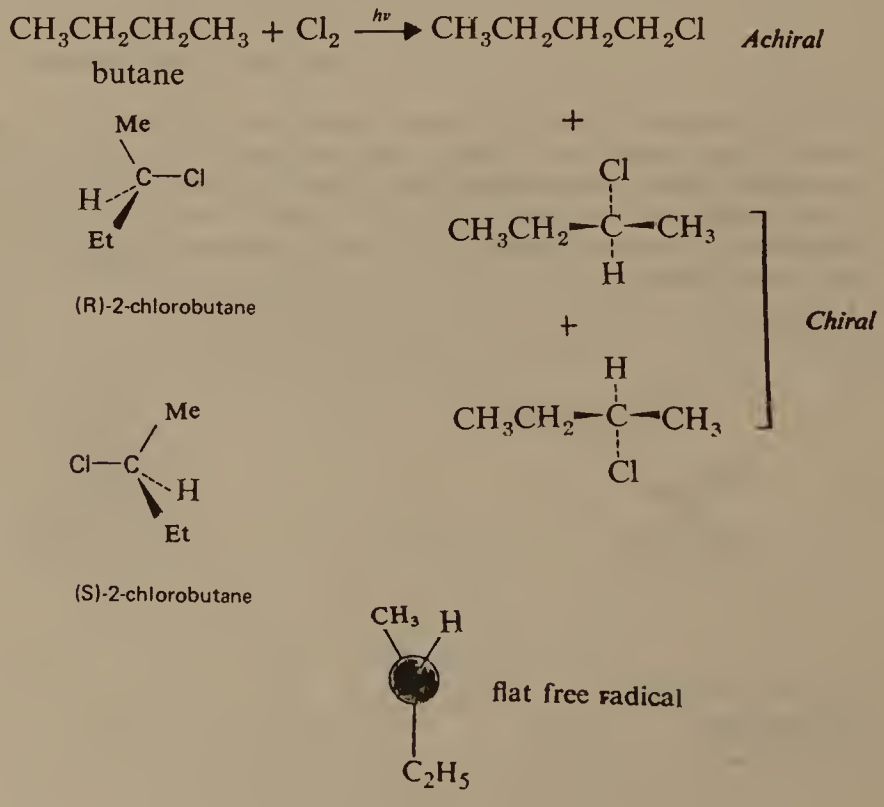
Fischer projection



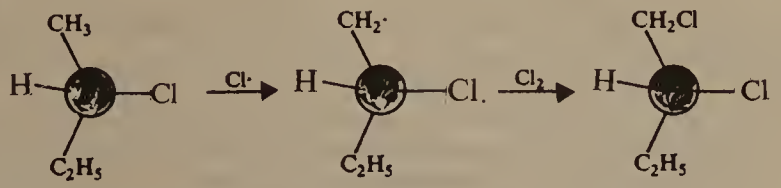
"wedge- and-dotted line" structure

(R)-2-iodobutane

9. Conformations (a) and (b) are an enantiomeric pair while (c) is the *meso*- form.
10. (a) (*R*)
(b) *Trans*-1-(1-*E*, 3*E*-hexadienyl)-2-ethenylcyclopropane.
11. 1-Chlorobutane is achiral. The 2-chlorobutane formed in this reaction is a racemic mixture *i.e.*, an equimolar mixture of (*R*)-2-chlorobutane and (*S*)-2-chlorobutane. The reactive intermediate in the reaction leading to 2-chlorobutane is the *sec*-butyl free radical, which is almost planar and therefore is achiral and reacts with Cl_2 on either side of the molecule.



13. The reaction involves the retention of configuration about the chiral centre in the product of chlorination, since the reaction does not involve the breaking of a bond to the chiral centre.



(S)-*sec*-Butyl chloride **(R)-1,2-Dichlorobutane**

configuration is retained

14. (*R*)-Configuration.
15. The biphenyls (a) and (b) have the two differently substituted *ortho* positions on each ring, the groups being indeed large to pass each other on rotation about the central bond. Thus, these represent chiral molecules; a pair of enantiomers. Compound (c) is a structural isomer with a plane of symmetry. therefore, it is not chiral even though in this case the rotation is equallv restricted.
16. Only (b).
17. It is a chiral allene, A and B are enantiomers and B and C are equivalent.
18. Compounds of the type 2 (paracyclophanes) have been resolved when m and n are fairly small (m = 3, n = 4 and X = CO_2H). It is then that the benzenoid rings cannot rotate at a significant rate. When the connecting methylene chains are long, rotation is so fast that the enantiomers rapidly equilibrate.

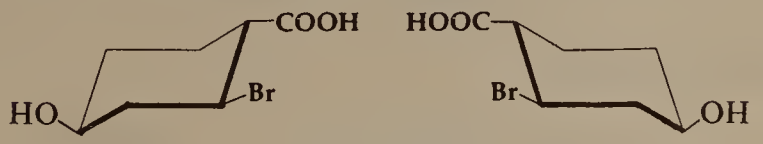
sequence

4 NH_2, COOH, CH_3, H
1 2 3 4

5 COOH, C_6H_5, C≡CH, CH_3
1 2 3 4

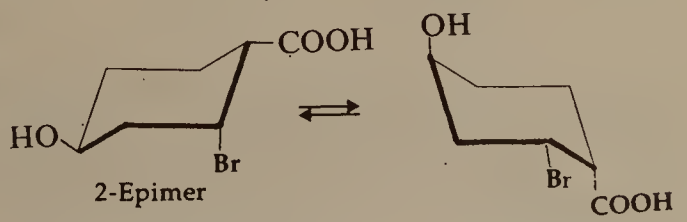
19. (a) 2^3 = 8 Stereoisomers or 4 diastereomeric pairs of enantiomers *i.e.*, 4 diastereomeric racemates. All substituents equatorial:

(b)



enantiomers

(c)



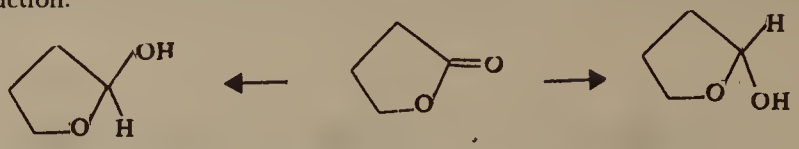
2-Epimer

HO, Br trans; Br, COOH cis;
HO, COOH trans

ring-flipping

20. Not homotopic because of the absence of a C_n, $n > 1$.

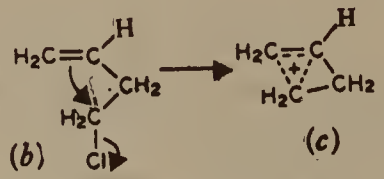
22. 1. The two — CH_2COOH groups are enantiotopic.
    2. The two faces of the carbonyl group in the lactone are enantiotopic, as shown by reduction.



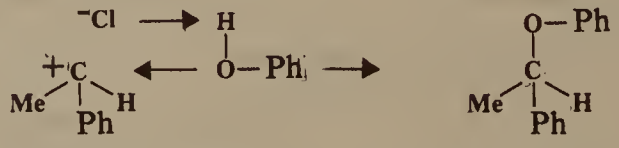
    3. In 1-phenylisopropanol, C-2 is asymmetric and the molecule is chiral. C-1 is prochiral since replacement of the stereoheterotopic hydrogens by a group different from other ligands generates diastereoisomeric molecules because of two centres of chirality. The two C-1 hydrogen atoms, therefore, are diastereotopic groups adjacent to a prochiral centre.
    4. Cyclohexanone has homotopic faces.
    5. Monosubstituted derivatives of cyclohexanone have two diastereotopic faces.

CHAPTER 2

3. The slow reaction is the bimolecular substitution which is attended with inversion of configuration. The iodide ion initially displaces chloride with inversion of configuration to yield *S*-2-iodobutane which is then attacked by hydroxide ion to yield alcohol, again with configurational inversion and liberation of iodide ion. The net result in the presence of iodide ion is the formation of (*R*)-2-butanol with overall retention
5. S_N2 reaction affords the enantiomer which undergoes another S_N2 reaction at identical rate to give the initial enantiomer and the process results ultimately in net racemization.
6. It probably is related to an allylic shift by an S_N2 type of mechanism. One may gainfully explain the formation of products by the neighboring group participation by π electrons as shown in (b) to afford an ion (c).



7. Due to ion-pair formation.

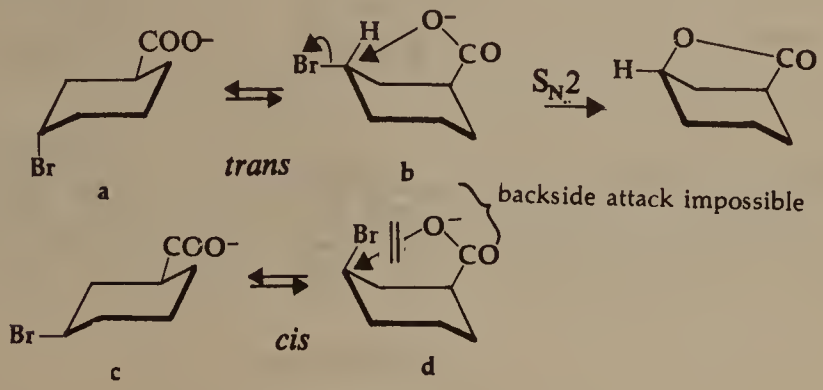


8. This is due to special salt effect. The ClO_4^- (or Br^-) traps the solvent-separated ion pair to give $R^+||ClO_4^-$. This being unstable under the conditions, goes to product. Thus the amount of solvent-separated ion pair which would have returned to the starting material is reduced, and the rate of the overall reaction is increased. This provides an example of shifting the position of the equilibrium by removing a product.

CHAPTER 3

3. Ionizing, DMF, CH_3CN, DMSO, $(CH_3)_2CO/H_2O$. Non-ionizing, ether, Alkanes, $CHCl_3$, CCl_4.

4. In the case of *trans*- conformer b, the carboxylate anion is suitably located for the S_N2 displacement of the bromide ion, in an internal displacement reaction leading to cyclization. In the case of *cis*-isomer, in none of the conformers c or d, backside attack is possible.



5. It is an S_N1 reaction. The involved carbocations from both (a) and (b) would be strained, however, the compression of a larger bicyclic system to a flat carbocation is easier, the larger the ring.

6. Neighboring group participation by the suitably located π electrons in the *anti* tosylate involving the intermediate D.

D

10. Conversion of an epoxide into its stereoisomer is brought about by the diaxial opening in acetic acid of the epoxide ring to a diol monoester. This on mesylation affords a mesylate which on treatment with base gives the inverted epoxide. This sequence of reactions is useful, because initially a steroidal epoxide formed from the sterically least hindered side of the molecule can be converted into its stereoisomer.

CHAPTER 4

1. At the first glance the staggered conformations as these are drawn seem to have enantiomeric relationship. However, keeping in mind:
   (a) That a compound cannot be chiral if any rotamer is non-disymmetric or if each chiral conformation is in equilibrium with its enantiomer.
   (b) Rotation about single bonds has to be considered to prove or disprove identity.
   One finds the arrangements to be homomers and since manipulation of any of the conformations leads to the same eclipsed form having a reflection symmetry, the compound is achiral.

2. While comparing stereochemical relationships of two compounds it is not sufficient to compare only one conformation of each compound. Rotation about single bonds is necessary to find the closest correspondence. Newman projections (I) and (II) have the same constitution and the two conformers shown as such, seem to be conformationally

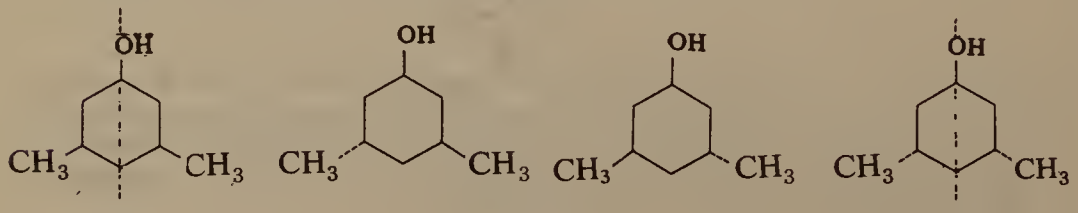
diastereoisomeric, but instead these are enantiomeric. With the conformation (I) fixed, one can change the conformation of (II) to know the closest stereochemical relationship. In (III), one has the rotated (as a whole), Newman projection (II) through 120° in an anticlockwise way. The arrangement of the front carbon atoms in (I), and (III) are now enantiomeric. Rotation of the rear carbon atom by 120° in a clockwise direction reveals that (I) and (II) are indeed enantiomers; further rotation, however, is unable to give rise to homomeric conformations.

3.

Cyclopentane

In the envelope form, one atom projects out of the plane of the four other atoms. It has C_s symmetry (presence of a plane of symmetry σ). The other flexible form is the half-chair form wherein three neighboring carbon atoms are coplanar, while the other two are above and below the plane, respectively, and equidistant from it. This conformer has C_2 symmetry. The envelope and half-chair forms interconvert through intermediate conformations with no symmetry.

4. Four, but not eight-stereoisomers exist for this compound. Two of these have plane of symmetry, and are, therefore, *meso*. The other two are enantiomers.



(*meso*) (±) (*meso*)

5.

trans-syn-trans
(*meso*)

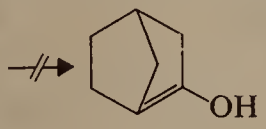
It is a *meso*- form, since a plane of symmetry is evident, however, the *trans- anti- trans* form (4.15,E) is chiral.

6. (a) *Trans,* chiral.
   (b) *Trans,* achiral.
7. (i) 1,1-disubstituted cyclohexanes are achiral.
   (ii) 1,2-disubstituted derivatives, *cis* chiral if $R \neq R'$; achiral if $R = R'$.
   trans chiral.

(iii) 1,3-disubstituted derivatives, *cis* chiral if R ≠ R′; achiral if R = R′
trans chiral

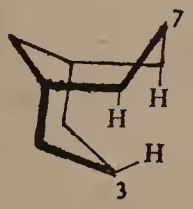
(iv) 1,4-disubstituted derivatives
cis achiral
trans achiral

8. It is a pyrolytic *syn* elimination. In the case of (a) 7α-ester group (axial) has therefore the only choice to eliminate C-6α-hydrogen. In the case of (b), there are two possibilities 7β-ester group (equatorial) being *cis* to C-8 (axial) hydrogen as well as C-6β-hydrogen. However, the major product is formed by eliminating C-8 hydrogen, the olefin in this case being more substituted.
9. An equatorial group on a cyclohexane ring can attain an *anti*-arrangement with a neighboring hydrogen by adopting a boat form. In this case, the severe 1,3-diaxial interaction between the methyl groups at the angular position and at C-4 are relieved in the ring A boat form.
10. In small bridgehead bicyclic systems elimination always occurs away from the bridgehead, therefore, C will not be formed. Yes, it can be synthesised.
11. The mechanism of decarboxylation of β-keto acids involves a cyclic six-centre transition state to give an enol which quickly tautomerizes to the ketone. In this case of the bridgehead bicyclic keto acid the product would be highly strained bridgehead-enol.



12. Bicyclo [3.3.1] nonane constitutes a1, 3 fusion of two cyclohexane chairs which are free of angle strain. However the molecule in the conformation suffers from serious transannular interaction between the axial hydrogens at C-3 and C-7. The more attractive conformation is thus the chair boat form.

Adamantane is the compound obtained by bridging the conflicting methylene groups, C-3 and C-7 in the chair-chair form.

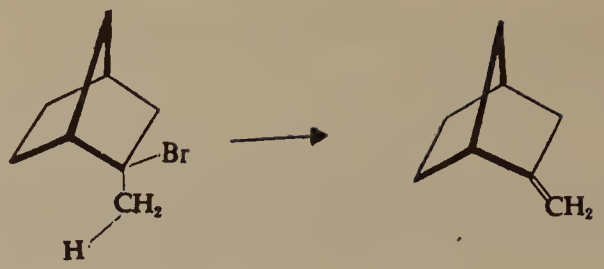


chair-boat form of bicyclo[3.3.1]nonane

adamantane

CHAPTER 5

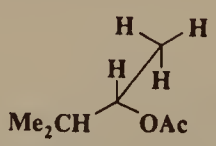
1. (a) 2-Methyl-2-pentene
(b) 2-Methyl-1-pentene
(c) Methylenic double bond will be generated, as Br cannot attain *anti*-periplanarity with the ring hydrogen, although the product would be more substituted.



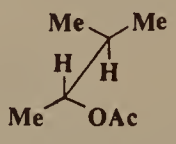
(d) $C_6H_5-CH(Br)-CH_2-CH_2-CH(Br)-C_6H_5 \rightarrow 2C_6H_5CH=CH_2 + ZnBr_2$

(Br ← :Zn)

2. If β-hydrogen is present in an open chain system, a conformation is always therein which it is *cis* to the departing group. Nevertheless, one must consider an eclipsing effect out of the two trasition states, the one which yields a larger quantity of olefin. *i.e* (a) is less eclipsed when compared to (b).

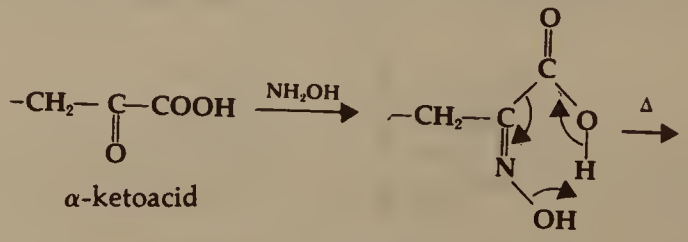


(a)



(b)

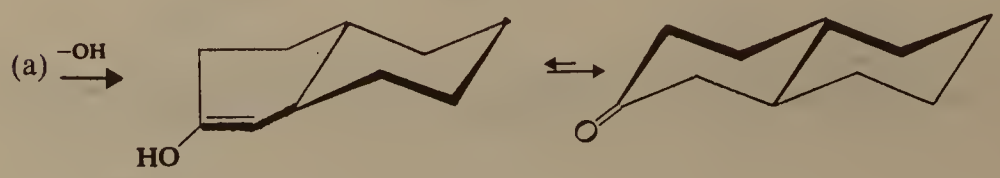
3. The oximes undergo decarboxylative fragmentation when bonded to a carboxyl group. The oximes of α-ketoacids, therefore, show fragmentation to afford nitriles on heating.

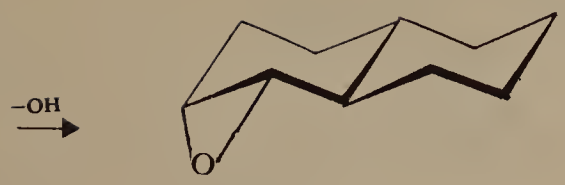


α-ketoacid

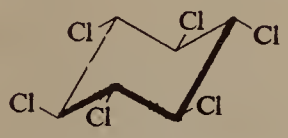
$$-CH_2-CN + CO_2 + H_2O$$

4. The conformationally rigid epimeric chlorohydrins (a) and (b) either eliminate to an enol or undergo internal S_N2 displacement to give an epoxide depending on *trans*-diaxial orientation of the reacting groups.



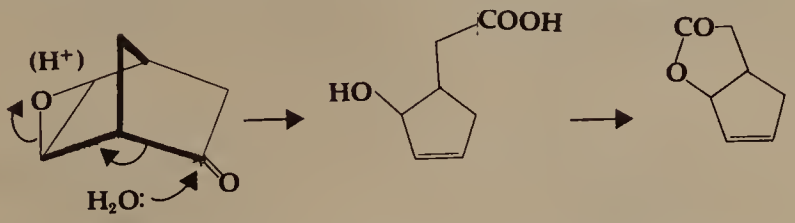
(b) 

5. This is the β-isomer, since it does not have any axial hydrogen next to an axial chlorine in the chair conformation.

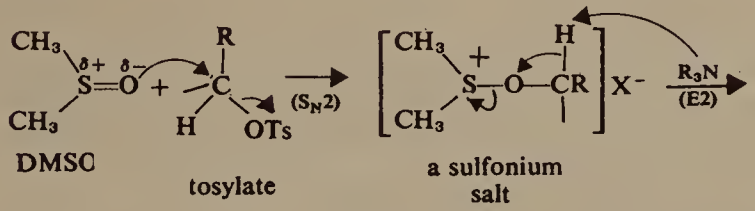


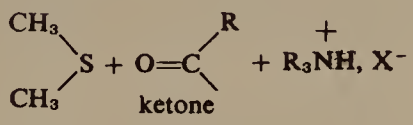
β-Benzene hexachloride

6. In the case of bicyclic compound the ketone cannot enolize toward the epoxide (violation of Bredt's rule).



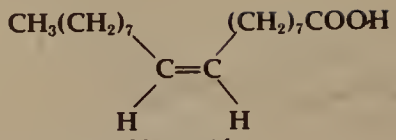
7. It is an oxidation reaction which follows a substitution-elimination sequence.



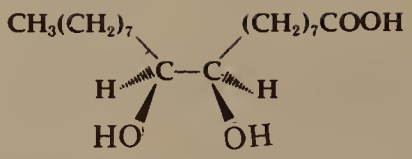


CHAPTER 6

1. The reaction is *syn*-hydroxylation and occurs from the less hindered side of the double bond to give *erythro*-9,10-dihydroxystearic acid.

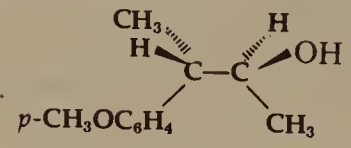


Oleic acid

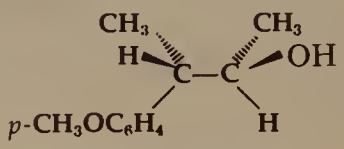


erythro-9,10-Dihydroxystearic acid

2. The *cis*-olefin gives *threo*-product while the *trans* olefin affords the *erythro* isomer.

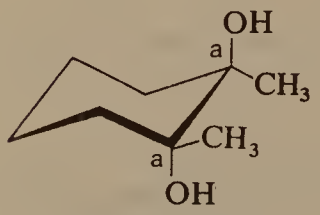


erythro-3-*p*-Anisyl-2-butanol

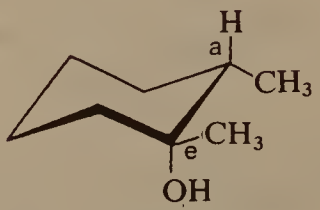


threo-3-*p*-Anisyl-2-butanol

3.



(*a*) *trans*-1,2-Dimethyl cyclohexane-1,2-diol

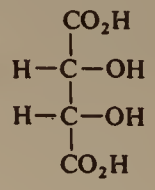


(*b*) *trans*-1,2 -Dimethylcyclohexanol

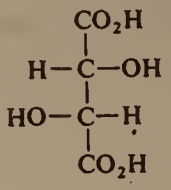
4. The chair conformation of ring A is destabilized by 1:3 type of non-bonded interactions among the epoxy oxygen and the two β-oriented methyl groups at C-4 and C-10. Therefore, ring A attains a boat conformation in which the diaxial addition takes place and a ring flip gives the diequatorial product.
5. During the reduction of 4-*t*-butylcyclohexanone the bulky *t*-butyl group locks the conformation and acts as conformational label for the stereochemistry of the reaction. With the larger reagent the less hindered equatorial approach of the hydride is preferred to yield axial alcohol.

CHAPTER 7

1. On oxidation with nitric acid (-)-erythrose gives *meso*-tartaric acid, while (+)-threose gives optically active form of the same acid *i.e.*, (+)-tartaric acid.

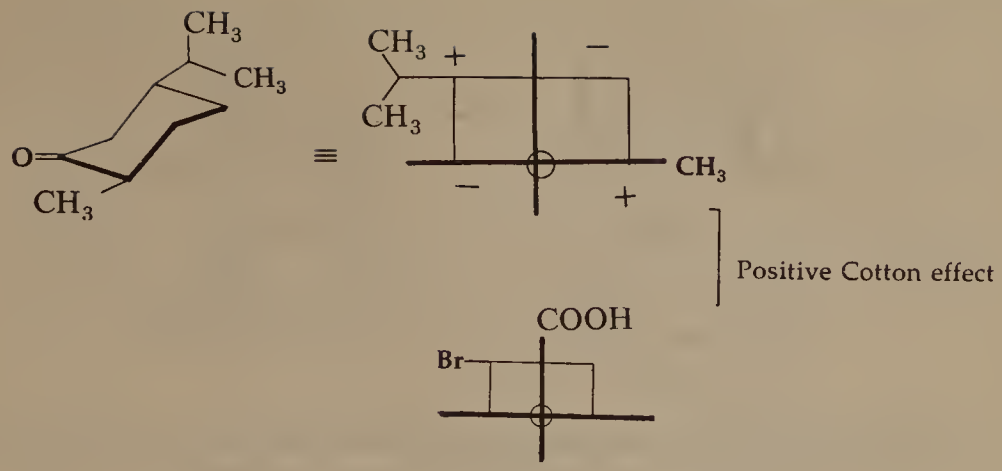


meso-tartaric acid

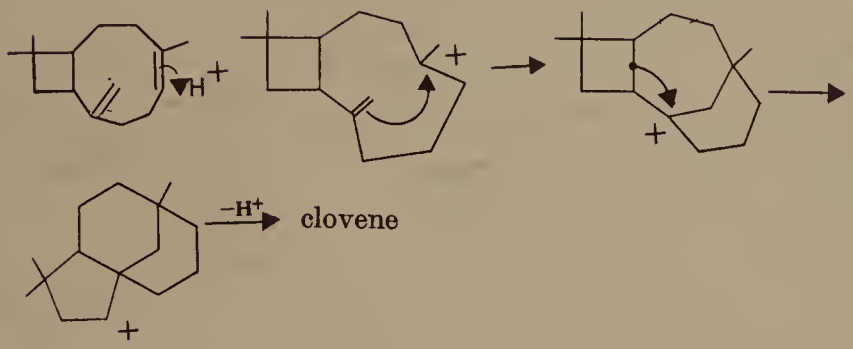


(+)-tartaric acid

2.

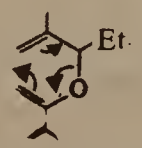


3.

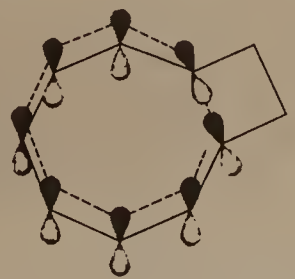


CHAPTER 8

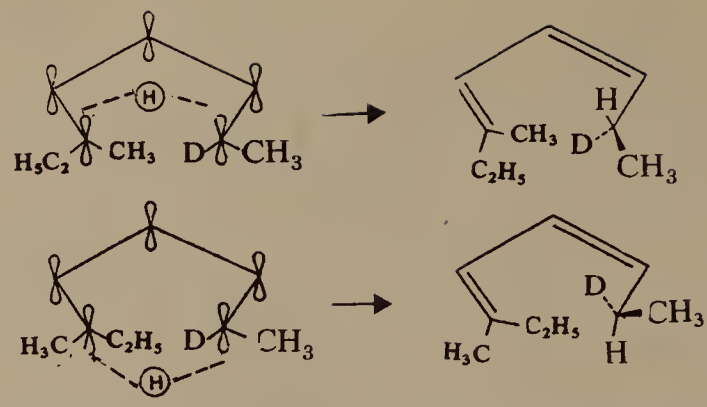
1. This is a wellknown technique for the synthesis of polyolefinic ketónes *via* an isoprene unit buildup. The mechanism involved is the aliphatic Claisen rearrangement in the product of condensation after the loss of methanol.



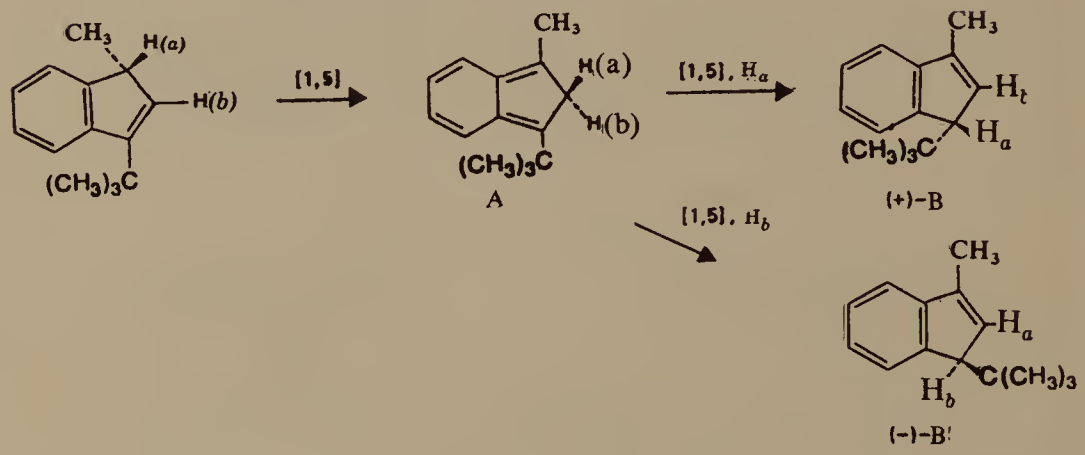
2. It is an electrocyclic reaction. The transition state has eight electrons connected in a Mobius array (one sign inversion) since the number of electrons is of the form 4n, Mobius is the only allowed (conrotatory) pathway.

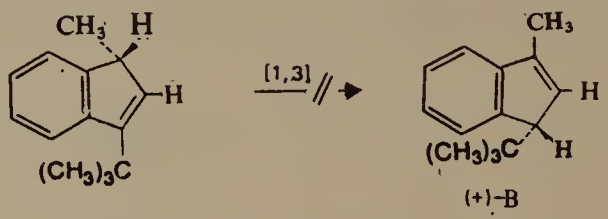


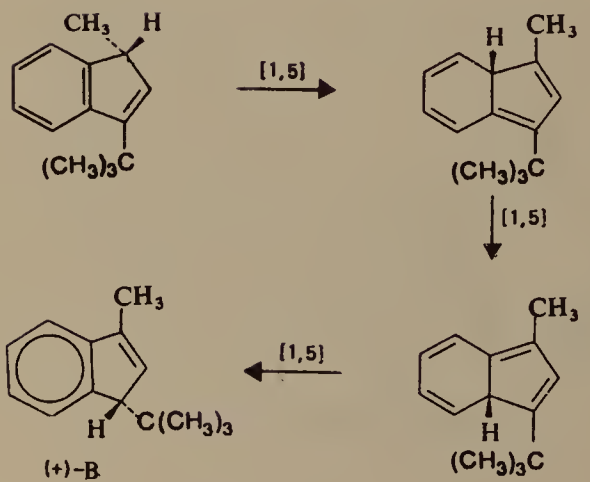
3. Both (a) and (b) are formed by the suprafacial [1,5] hydrogen shift.



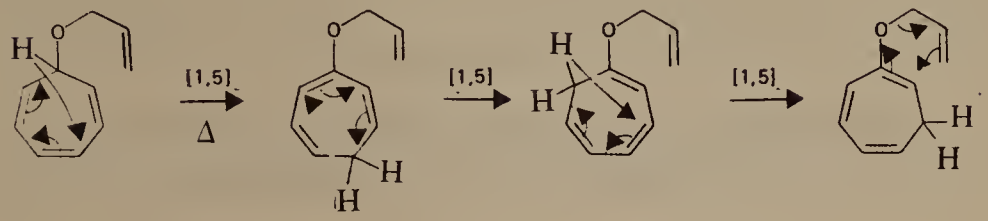
4. H_a and H_b in the achiral intermediate (A) are equivalent. Migration of either is equally likely, so this mechanistic route leads to racemic (B) as shown below.

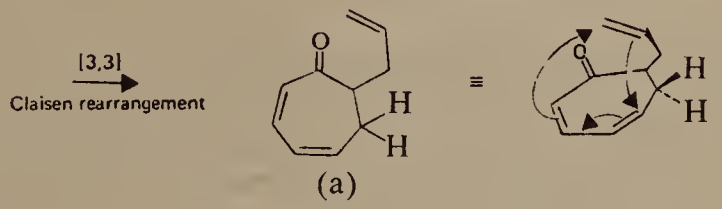






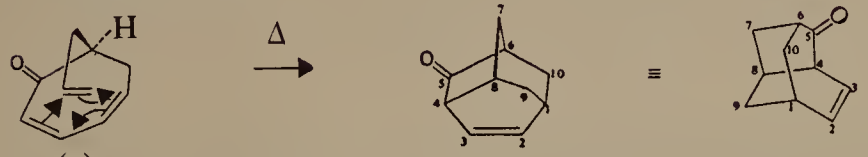
5. The reactions occur through a series of [1,5] sigmatropic hydrogen shifts followed by Claisen rearrangement and intramolecular Diels-Alder reactions.





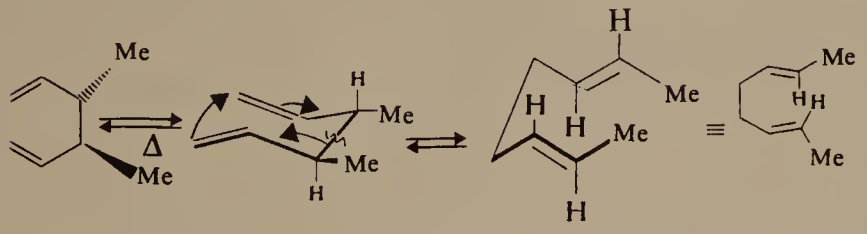
(a)

$(_4\pi_s + _2\pi_s)$
cycloadditions



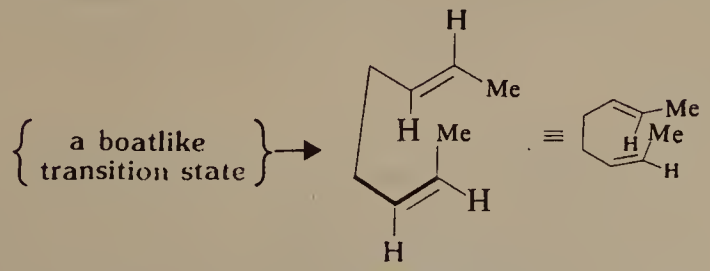
(a)

6.



chairlike

trans,trans diene



trans,cis diene

APPENDIX

SUMMARY OF THE SALIENT POINTS AND ADDITIONAL PROBLEMS

A. SYMMETRY IN ORGANIC COMPOUNDS

Grouping the molecules according to their symmetry properties, helps in predicting and understanding their behaviour and stereochemical properties. Axis of symmetry (C_n) describes the behaviour of a molecule on rotation about an imaginary axis, and its order, n, is given by the relationship that a rotation of $360°/n$ leads to an arrangement indistinguishable from the parent. The principal axis in a compound is the axis with highest n, Plane of symmetry (σ) is a plane passed through a molecule or an object in a way that all the features on one side of the plane are a reflection of equivalent parts on the other side. Considering such a plane as mirror, one refers to such a plane as mirror plane of symmetry. Planes perpendicular to the principal axis are called σ_h and those having the principal axis σ_v. Rotation-reflection (S_n) a separate element, is a combination of C_n and σ_h so that $S_n = C_n \times \sigma_h = \sigma_h \times C_n$.

A molecule has a centre of symmetry i if any straight line passing through its center encounters identical environments on both sides of the center point. Molecules which are superimposable on their mirror images posses reflection symmetry and are called achiral. Molecules which are not superimposable on their mirror reflections are called chiral.

Problem A.1

Identify the two perpendicular mirror planes of symmetry which intersect on the C_2 symmetry axis in boat cyclohexane. Locate the center of symmetry in the chair conformation of *trans*-1, 4-dichlorocyclohexane.

B. CHIRALITY

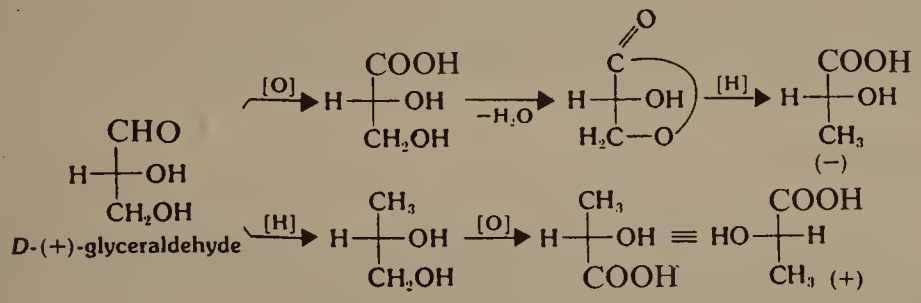
A molecule without reflection symmetry is called chiral and three elements *i.e.*, chiral centres, chiral axes and chiral planes characterise chiral molecules. A helix is a special case of axial symmetry. Fischer projection is a good method to depict the absolute configuration of enantiomers, which is designated by the *R,S* or *D,L* systems. The *R, S* system of nomenclature is

unambiguous and should always be used. The *DL* system to denote absolute configuration is now only used for some classes of compounds like carbohydrates and amino acids. Sugars are designated as D-sugars if the -OH group attached to the highest numbered chiral carbon is on the right of the vertical line in the Fischer projection and L-sugars if this -OH group is on the left.

Unlike a three-dimensional representation, a Fischer projection of a molecule on rotation changes the configuration *i.e.*, a 90° rotation inverts the configuration.

Problem B.1

Glyceraldehyde could be converted into lactic acid by the following two reaction sequences. Would (+) lactic acid have D or L configuration ?



Problem B.2

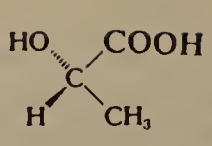
Interconvert the Fischer projection (*i.e.*, The all-eclipsed conformation) of (+)- tartaric acid to sawhorse representation.

When a chiral influence is absent, a chemical reaction leads to equal amounts of enantiomers; *i.e.*, a racemic modification. A molecule with n different chiral centres has 2^n stereoisomers and 2^{n-1} paris of enantiomers. When two or more identical chiral centres are present in a compound fewer stereoisomers exist. Meso compounds have two or more chiral centres, but they are not chiral molecules because of the presence of a mirror plane. Epimers represent diastereoisomers which have different configuration at only one of the carbon centres.

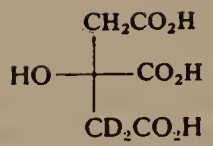
Problem B.3

Comment on the application of Cahn-Ingold-Prelog sequence rules on the compounds 1 and 2.

One can observe conformational isomers, though these are difficult to separate. Stereoisomers separated by an energy barrier lower than 60 kJ mol^{-1} are conformational isomers. On the other hand, an energy barrier of 100 kJ



1

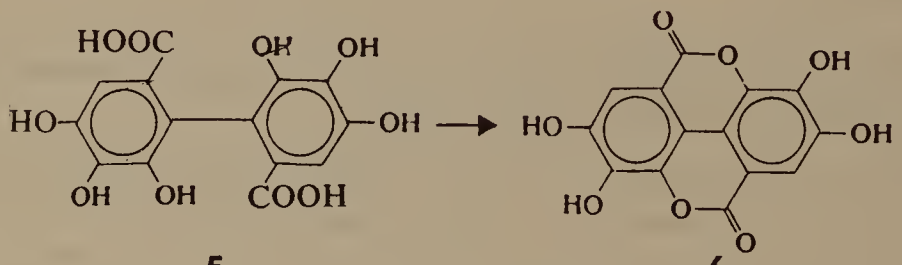


2

mol^{-1} can define configurational isomers which can be separated and isolated. The stereo isomers obtained *via* rotation around a single bond are termed rotamers; atropisomers are the stereoisomers which can be isolated and can exist due to restricted rotation around single bonds; the enantiomers which interchange readily by non-bond cleavage inversion at an atom *i.e.,* nitrogen are called invertomers. Biphenyls are conjugated systems, however, their planar conformations are highly crowded due to interactions between *ortho* hydrogen atoms. When these hydrogens are substituted by bulky groups. The twisted conformations become more stable than the planar conformation. That these molecules have stable twist conformations is shown by the fact that unsymmetrically substituted biphenyls can be resolved into enantiomers.

Problem B.4

An optically active biphenyl derivative 5, on standing slowly transforms into optically inactive 6. Why 6 is optically inactive ? If 5 is regenerated by the hydrolysis of 6, will it be optically active ? Explain.



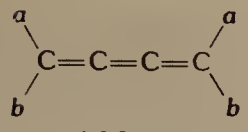
5 6

Problem B. 5

Chiral secondary and tertiary amines cannot be resolved. Indicate the planar transition state in the rapid interconversion of the enantiomers (*i.e.,* invertomers.)

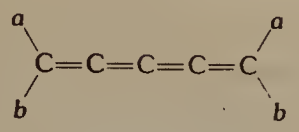
Problem B. 6

Cis-trans isomerism is displayed by 1,2,3-trienes 7, while these compounds do not display enantiomerism, on the other hand, cumulated tetraenes 8 display enantiomerism and not geometric isomerism. Explain.



1,2,3-triene

7

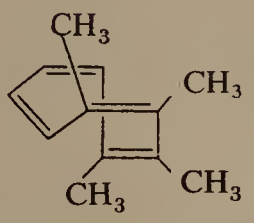


cumulated tetraene

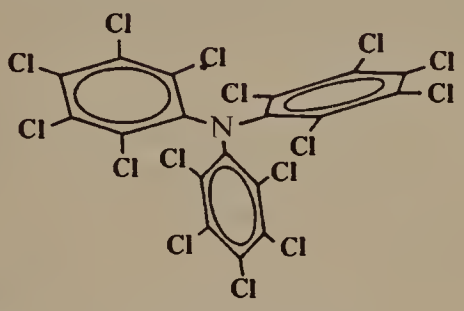
8

Problem B. 7

Explain the reasons for the chirality of 1,2,3,4-tetramethyl-cyclooctatetraene and perchlorotriphenylamine.



1,2,3,4-Tetramethylcyclooctatetraene



perchlorotriphenylamine

One can separate enantiomers manually in rare cases, but generally *via* chemical methods. The racemic mixture is transformed to a pair of diastereoisomers which are then separated by physical methods. Enantiomers in their pure form are isolated by their separate regeneration.

C. CHIRAL SYNTHESES

An asymmetric synthesis involves the selective formation of a new chiral unit and needs the presence of some kind of a chiral influence. Chirality can be generated at prochiral centers, *i.e.*, a centre which has enantiotopic or diastereotopic ligands or is a part of a *pi*-system with enantiotopic or diastereotopic faces. If on sequential substitution of a pair of constitutionally identical ligands, one ends up with enantiomers, then these ligands are termed enantiotopic, if diastereoisomers are formed the ligands are called diastereotopic, and finally if identical compounds are formed the ligands are called homotopic. Similarly the presence of stereoheterotopic faces can be detected *via* a symmetrical addition across a face.

D. NUCLEOPHILIC SUBSTITUTION REACTIONS

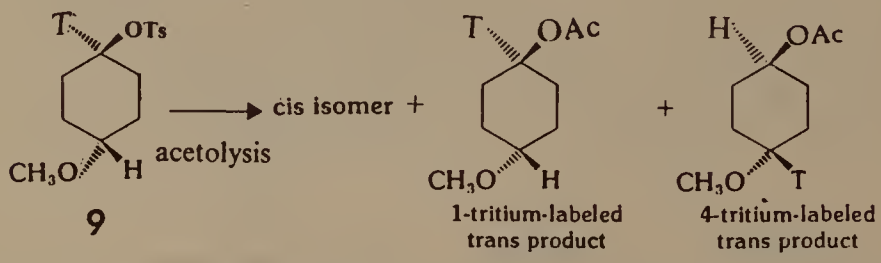
S_N2 reactions are usually attended with inversion of configuration with rate = k [substrate] [nucleophile], while racemization occurs during S_N1 reactions where rate = k [substrate]

Retention of configuration may be due to two successive inversions as with

neighbouring group participation or due to the operation of S_Ni mechanism when a cyclic intermediate decomposes to yield an ion pair. S_E2 reactions, typical of organomercurials are concerted bimolecular reactions which lead to retention of configuration *via* front side attack.

Problem D. 1

The tritium-labeled *trans*-4-methoxycyclohexyl tosylate 9 gives a 3:1 mixture of *cis* and *trans* acetate esters on acetolysis. The *trans* product contains 35% more tritium in the 1 position than in the 4 position. Give an explanation for the retention of configuration in the *trans* acetate and the apparent migration of the isotopic hydrogen label.



9

1-tritium-labeled trans product

4-tritium-labeled trans product

S_N2 reactions do not involve any intermediates and are favoured by unhindered substrates *i.e.*, CH_3-X > 1^0 > 2^0 > 3^0 the nucleophile attacking from the rear. Favorable nucleophiles for S_N2 reaction are $C_6H_5S^-$, CN^-, I^-. The S_Ni reactions, on the other hand, involve planar carbocation intermediates which lead to racemization. Often inversion accompanies racemization since the approach of the nucleophile at one side of the planar intermediate may be hindered by the leaving group. Hindered substrates 3^0 > 2^0 > 1^0 > CH_3 X prefer to undergo S_Ni reactions due to the relief of the steric strain during the formation of the carbocation. One can change the balance between S_Ni and S_N2 reactions by choosing proper solvent, structure of the substrate, nucleophile, leaving group and temperature.

E. CONFORMATION

A molecule may adopt more than one conformation (*via* rotation about single bonds) *i.e.*, arrangement of characteristic geometry which defines the bond angles, bond lengths, dihedral angles and configurations. The compounds with the same molecular formula, an identical sequence of covalently bonded atoms, but with different spatial orientations of these atoms are called stereoisomers. The conformational stereoisomers interconvert easily at room temperature *via* rotation around single bonds. The stereoisomers which interconvert under normal conditions only with difficulty and which can be separated are called configurational stereoisomers. The interconversion in the case of configurational stereoisomers normally involves a bond-fission.

The angle subtended by two given groups on viewing along a bond about which rotation is possible is known as the dihedral angle. Normally simple

C-C single bond rotations have barriers of 12-20 kJ mol^{-1}. The lowest energy conformation in the case of simple hydrocarbons is the one in which the bulky groups are at a maximum distance apart. This conformation is called *anti*periplanar. The preference for the *anti*periplanar conformation is due to the fact that steric hindrance and through-space interactions are eliminated. However, electrostatic attraction or intramolecular hydrogen bonding between two groups may stabilize *syn*clinal or *syn*periplanar conformations at the cost of *anti*periplanar conformation.

Alicyclic rings may be small (3-4 membered), normal (5-7 membered), medium (8-11 membered) or large (12-17 membered). The strain in the rings is due to angle deviation from 109^0 (Baeyer strain) and due to non-bonded interactions (Pitzer strain). One can measure ring strain from heat of combustion which is found to be large for small rings, low for normal rings, higher for medium rings, while it is absent in large rings. The rings, therefore assume non-planar conformations so as to distribute the strain optimally between Pitzer and Baeyer strain, since a planar conformation of any cycloalkane will necessarily be fully eclipsed. From among the conformations available to cyclohexane *i.e.*, planar, boat, twist and chair, the strain-free low energy chair conformation is so much more stable than the other conformations that 99.9% of the molecules in a sample at 25 °C have this conformation.

Cyclohexane has two distinct, but equivalent chair conformations and these interconvert rapidly by ring flip, involving rotations about bonds. In case a substituent occupies an equatorial postition it experiences less severe non-bonded interactions than when it has an axial orientation, A bulky *t*-butyl substituent will effectively freeze the ring system in that chair conformation in which it has an equatorial orientation. Such freezing is necessary during the study of reaction mechanisms. Another way to lock the ring system in a particular conformation is by means of bridging the carbon atoms, as in norbornane. Two diastereoisomeric decalins are known, and of these *trans*-decalin is rigid and cannot undergo ring-flipping, since for such a process a *trans*-diaxial transition state would be required. *Cis*-decalin has two enantiomeric forms in which both the six-membered rings (chair conformations) rapidly interconvert by simultaneous flipping of both the rings.

F. ADDITION REACTIONS OF ALKENES

These addition reactions are regiospecific, stereospecific and may be either *syn* or *anti*. Thus, for example, the electrophilic addition of halogen acids is regiospecific and follow the Markovnikov rule *i.e.*, the product formed involves the most stable carbocation.

Hdyroboration is stereospecifically a *syn* addition. The boron generally becomes attached to the less substituted and sterically less hindered carbon. The net result of the reaction is the conversion of an alkene to an alcohol by the addition of water with predominant *anti*-Markovnikov regiochemistry.

Syn addition of hydrogen to alkenes occurs when transition metal catalysts like platinum are employed.

Addition of halogens is a two step process involving the intermediate

formation of a cyclic halonium ion, one side of the original alkene molecule keeps occupied as a result of this initial addition, leading to retention of configuration at the alkene carbon atoms. *Anti* stereospecificity is explained by approach of the bromide anion by opposite side of the bromonium ion.

Addition of chlorine has several similarities to bromine addition, however stereoselectivity is often less than addition of bromine. The initial cyclic chloronium ion formation helps to expain the stereochemistry of addition in many cases.

Hydrogen halide additions show a similar stereoselectivity as displayed during the addition of halogens. Simple unconjugated cyclic alkenes undergo *anti* addition. while, both *anti* and *syn* additions are observed with several conjugated double bonds. The intermediate formation of a cyclic protonium ion is often proposed.

Addition of water under acidic conditions is regiospecific and follows the Markovnikov orientation, however, stereochemically it proceeds by relatively random *syn* and *anti* pathways.

During epoxidation of alkenes the two new carbon-oxygen bonds are formed at one time. Therefore, the epoxidation reaction is stereospecific addition reaction in which the new bonds are formed in a *syn* manner. During the hydrolysis of the epoxide, water attacks from the backside of the expoxide leading to *anti* hydroxylation of the original double bond. On the other hand, osmium tetroxide and cold basic potassium permanganate oxidize alkenes to 1,2 -diols by *syn* addition.

Carbene addition in the singlet state (*i.e.*, in the most common state) is a stereospecific *syn* addition of new carbon-carbon bonds probably by a one step mechanism. However, in the triplet state the carbenes add non-stereospecifically probably by a diradical mechanism.

The reduction of an alkyne with metal-ammonia systems is selectively **anti** leading to *trans*alkenes. This method is complementary to the stereospecifically *syn* addition of hydrogen. Di-imide is another reagent for the hydrogenation of carbon-carbon multiple bonds which proceeds by a *syn* stereochemical pathway. Homogeneous hydrogenation (*syn* addition) involves the activation of hydrogen by its incorporation into the co-ordination sphere around the metal atom of the group VIII.

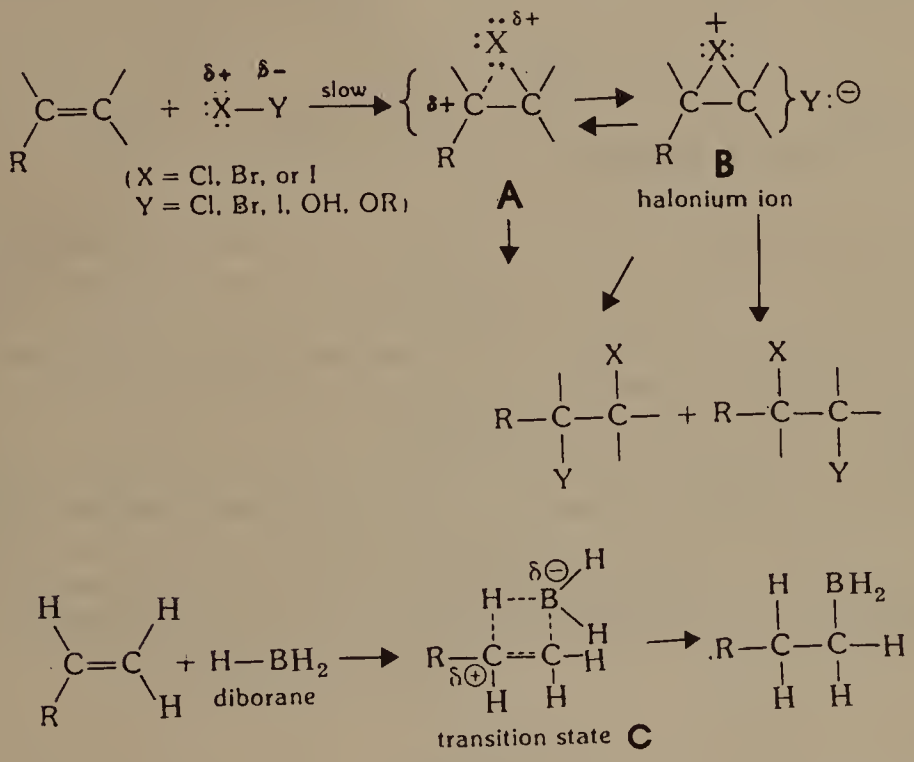
During the hydride addition to a carbonyl group *e.g.*, from lithium aluminium hydride, the hydride ion is generally added from the less hindered side of the carbonyl group.

Problem F.1

Write the stereostructure of the addition product from the following reaction

At this point, it is tempting to explain all the addition mechanisms. The two-step carbocation mechanism during the addition of Bronsted acids to alkenes seems reasonable, since these reactions show variable stereochemical outcome and are also prone to molecular rearrangement. The corresponding addition reactions of other electrophilic reagents, however, show that a different reaction path is followed in these situations. Moreover, the stereochemical facts force us to propose different mechanisms for reactions initiated by electrophilic halogen species *e.g., trans* addition of X_2 and those involving diborane *syn* addition.

An important feature of the mechanism for electrophilic halogen addition is the stabilizing interaction which may exist between the developing carbocation and the electron-rich halogen atom. The interaction becomes stronger when the neighbouring halogen atom becomes larger *i.e.*, Cl < Br < I. The ion-pair



intermediate formed in these reactions may be an unsymmetrically bonded ion A or the symmetrical halonium ion B; a factor which will depend on alkene structure and the strength of the halogen interaction.

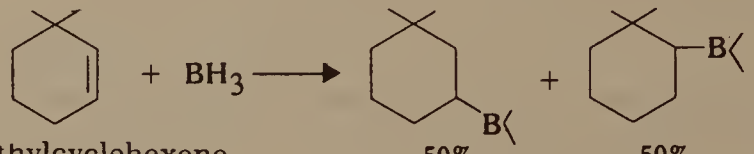
Rearrangement is therefore, less likely because the positive charge in the intermediate which may be symmetrical or unsymmetrical species is not concentrated on a single carbon atom.

The strong bias for *anti* additionin thesereactions is expected if one assumes that the three-membered cyclic intermediate is opened by attack of the nucleophile, from the back side.

In a case the intermediate ion pair is unsymmetrically bonded, (*i.e.*, A) the product isomer with Markovnikov orientation predominates, as a significant

positive charge must reside on one of the carbon atoms of the double bond. If the intermediate ion pair resembles the symmetrical halonium ion, products having *anti*-Markovnikov orientation may be formed; since nucleophilic displacement will occur at the least substituted carbon atom.

The accepted four-membered cyclic transition state of a single-step mechanism for diborane addition to alkenes resticts the geometry of these reactions to *syn* addition. To account for the highly selective bonding of boron to the least substituted carbon atom of the double bond, one, however, must assume that such a transition state is either sensitive to steric-hindrance or has some dipolar character to favor the formation of that carbon cation which has the greater number of alkyl substituents. Strong steric hindrance is no doubt responsible for the exclusive attack of diborane at the least hindered side of, for example, α-pinene, the hydroboration of 3,3-dimethylcyclohexene is non selective. This



3,3-dimethylcyclohexene 50% 50%

shows that moderate to small steric factors in some of these reactions do not significantly control the product forming step. One may, therefore, conclude that the major directing factor in the diborane addition mechanism is polar in nature, as indicated in C. The extent of positive charge development in the transition state is, however, small, as molecular rearrangements are not observed during diborane addition reactions.

Both O_sO_4 and MnO_4^- have similar configuratons, the metal atom occupies the centre of a tetrahedral grouping of negatively charged oxygen atoms. Even then, such species readily attack the nucleophilic double bond like electrophilic reagents. This is because an empty *d* orbital of the transition metal overlaps with and accepts electrons from the *pi* bond, and the two of the nucleophilic oxygen atoms start bonding with the carbon atoms of the double bond.

structure of O_sO_4 and $MnO_4^{\ominus}$

G. ELIMINATION REACTIONS

During a 1,2 -elimination reaction groups are lost from two adjacent atoms of a molecule with the formation of a multiple bond. Stereospecific eliminations can be *syn* or *anti*. In a *syn*-elimination the groups are eliminated from the

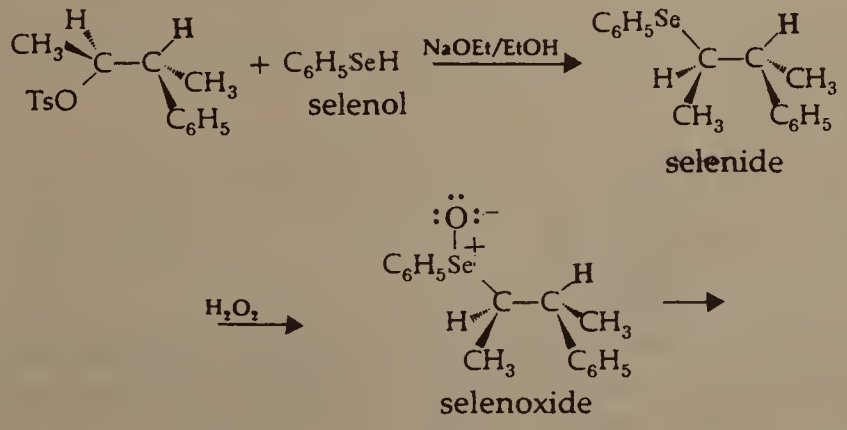
same side of the molecule, while in *anti*-elimination, the groups depart from the opposite side of the molecule. Most *anti*-eliminations are bimolecular E2 eliminations which are normally preferred. However, stereoelectronic considerations of the interacting molecular orbitals suggest that coplanarity of the departing groups is the highly important factor. Thus in compounds in which the departing groups are coplanar on the same side of the molecule may also undergo E2 elimination. *Anti*-elimination requires a dihedral angle of 180° and if this angle is not attained, *anti*-elimination is slowed or prevented completely. *Syn*-elimination, on the other hand, requires the molecule to adopt a completely eclipsed conformaton.

Unlike E2 eliminations where both groups depart simultaneously in an E1 elimination, the departing group leaves first to yield an intermediate, carbocation in the rate controlling step. The E1$_c$B process involves the initial loss of a β-proton to yield an intermediate carbanion. The loss of the leaving group from the anion may be either slow or a fast step in the elimination process.

Pyrolytic elimination reactions are often designated as Ei *i.e.,* elimination internal. These are concerted reactions which proceed through cyclic six-membered transition states in a stereospecific manner. The intramolecular cyclic mechanism forces *syn* coplanarity of the departing groups.

Problem G. 1

Selenoxides represent the organoselenium analogs of amine-oxides and sulfoxides. These can be prepared by the nucleophilic substitution on a tosylate by a selenol to yield a selenide which on subsequent oxidation with hydrogen peroxide gives a selenoxide. Discuss the formation of products on warming the selenoxide around room temperature.



When two different β-hydrogens can be lost, *i.e.,* when an elimination is not regioselective a mixture of alkenes will form. The formation of a more-substituted alkene is said to follow the Saytzeff orientation whereas the formation of the less substituted alkene is said to obey the Hofmann orientation. E2 eliminations of neutral substrates, *syn*-eliminations and generally E1

eliminations follow the Saytzeff rule. In E2 elimination reactions the transition state is alkene-like, the end product reflects the greater stability of more highly substituted alkene. E2 eliminations on charged substrates follow the Hofmann orientation.

There is always a competition between elimination and closely related substitution reactions. With strong bases elimination is predominant, while good nucleophiles favour substitution. The relative rates of elimination and substitution are also influenced by structure of the substrate and reaction conditions. Generally substitution is favored over elimination.

H. DETERMINATION OF CONFIGURATION

Configuration to an unknown compound can be assigned *via* its chemical correlation with a compound of known configuration using a series of stereochemically established transformations.

The Cotton effect for ORD is used gainfully to correlate compounds of established configuration with the compounds where configuration is not known *via* octant rule. The position of a substituent in a compound is used to predict its effect on the sign of the Cotton effect, the technique being useful for the determination of absolute configuration.

Several empirical rules based on optical rotation *e.g.,* Hudson amide rule Mills rule etc, have been used gainfully to assign stereostructures to new compounds.

Relative configuration to groups in a molecule may be assigned on the basis of outcome of a suitable reaction carried out on such a compound. Thus the two hydroxyl groups in a 1, 2-diol will be *cis* if the diol reacts with acetone to give an acetonide. E2 eliminations are usually facile and stereospecific reactions. This elimination takes place from a transition state in which the eliminated groups are *anti* to each other. Thus, the success or failure of such a reaction reflects on their stereochemistry.

I. MOLECULAR REARRANGEMENTS AND PERICYCLIC REACTIONS

In a molecular rearrangement atoms or groups migrate within molecules and a change in the molecular skeleton often occurs. The most common rearrangements involve migration of the group alongwith its bonding pair of electrons to an electron deficient center *e.g.,* a carbocation. Such reactions become the favored ones, provided the migration ends up in the generation of a more stable carbocation. The migration of an electron rich group is generally favored.

Normally during migrations to an electron deficient center, the migrating group retains its configuration while the stereoselectivity at the migration terminus tends toward inversion. The aryl group migration is normally stereospecific because of the formation of a cyclic phenomium ion intermediate.

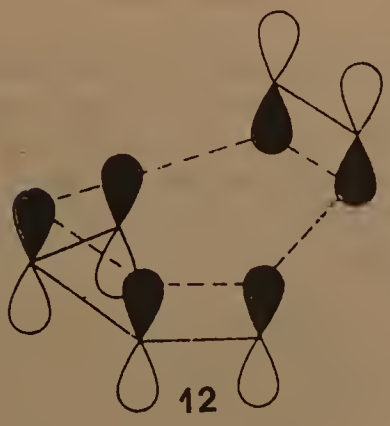
In addition to migrations to an electron deficient carbon, migration to the carbon atom of a carbene, and to electron deficient nitrogn or oxygen atoms occurs. The rearrangements through intermediate free radicals or carbanions are less common. Some molecular rearrangements occur through pericylic pathways.

The concerted reactions which have cyclic transition states and are not affected by solvents, catalysts, electrophilic or nucleophilic reagents are known as pericylic reactions. In electrocyclic reactions a σ-bond is formed between two termini of a conjugated π system, or its reverse; cycloaddition reactions involve the interaction of two isolated π-systems to form two new σ-bonds and finally in a sigmatropic reaction a sigma-bond migrates across a π-system. The classification of pericyclic reactions, as 'allowed' or 'forbidden' has its base in the Woodward-Hofmann rules.

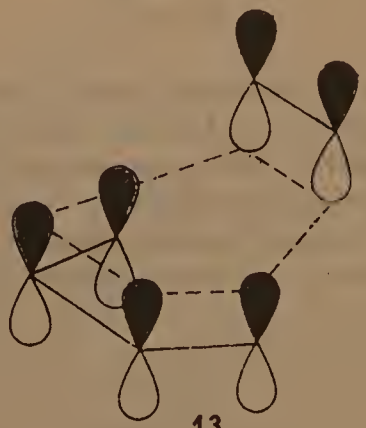
Aromatic transition state with $4n + 2$ electrons in a Huckelarray or $4n$ electrons in *anti-Huckel* system (Mobius system) are allowed processes (usually with low energy), while *anti-aromatic* transition states are forbidden for thermal reactions. One examines the basis set of atomic orbitals in a transition state, the rules are : Zero or an even number of phase dislocations in a Huckel system ($4n + 2$ electrons) as allowed, and same is the case with an odd number of phase dislocations in a Mobius system ($4n$ electrons), in pericyclic thermal reactions. Photochemical reactions, however, follow the opposite path to that of thermal reactions.

Problem I. 1

Consider the two phase relationships (12 and 13) in the transition state of the Diels-Alder thermal reaction. Considering the Mobius-Huckel analysis, predict if the reaction would be "allowed" or "forbidden".



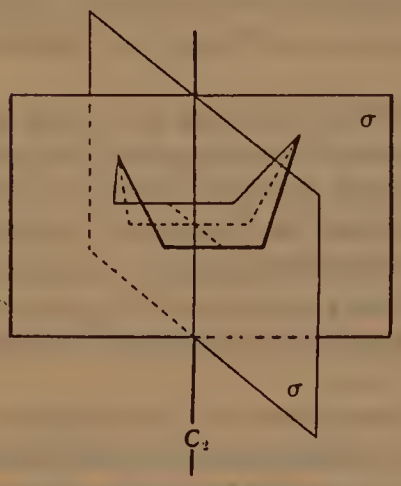
12



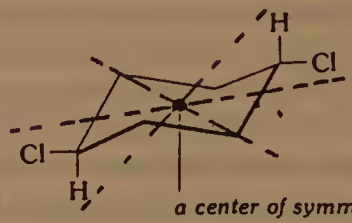
13

ANSWERS TO PROBLEMS OF APPENDIX

A.1



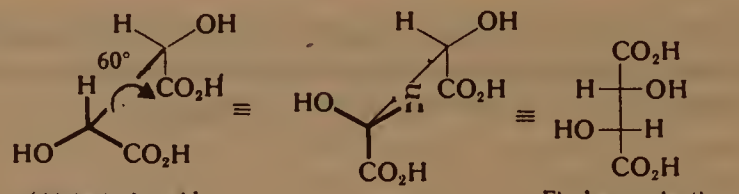
Symmetry elements in boat cyclohexane



trans-1,4-dichlorocyclohexane

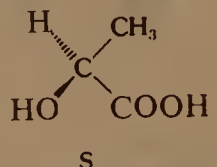
B.1 This is a good example to show the ambiguity of the D, L system of nomenclature. In the first series of reactions one relates the levorotatory lactic acid to D-(+)-glyceraldehyde,thus (—)- lactic acid has also a D-configuration. In the second reaction sequence, one finds that the enantiomeric (+)-lactic acid is also related to D-(+)- glyceraldehyde. Both enantiomers, however, cannot have the same configuration.

B.2



(+)-tartaric acid — Fischer projection

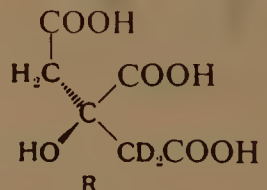
B.3 In the stereorepresentation of compound 1, the sequence rule can not be applied as the ligand of lowest priority *i.e.*, H is not directed away from the observer. The configuration is, therefore, as shown in 3 and is *S*. Compound 2 is the Fischer projection, the sequence rule can be applied either by putting the group of lowest priority at the bottom of the projection or by converting it into its stereorepresentation as in 4.



S

HO > CO_2H > CH_3 > H

3



R

HO > CO_2H > CD_2 > CH_2

4

B.4 Compound 6 is achiral as it has a flat and coplanar configuration. Regeneration of 5 which is chiral from 6 will lead to an optically inactive sample, since the enantiomers will be formed in equal amounts.

B.5

planar transition state

B.6 In the triene 7 the outside π orbitals are oriented at right angles to the central π orbital (the two central carbon atoms are *sp*-hybridized). The terminal carbon units are thus coplanar. Therefore, the geometry of this molecule represents an elongated alkene. On the addition of another cumulated double bond, as in tetraene 8, the terminal carbon units once again become perpendicular to one another. Thus, when any odd number of cumulative double bonds are present, the orbital overlap forces the four groups to become coplanar and as a result *cis-trans* isomerism may be displayed, In case, any even number of cumulative double bonds are present, the situation becomes similar to that of allenes and optical activity is possible if a and b are different.

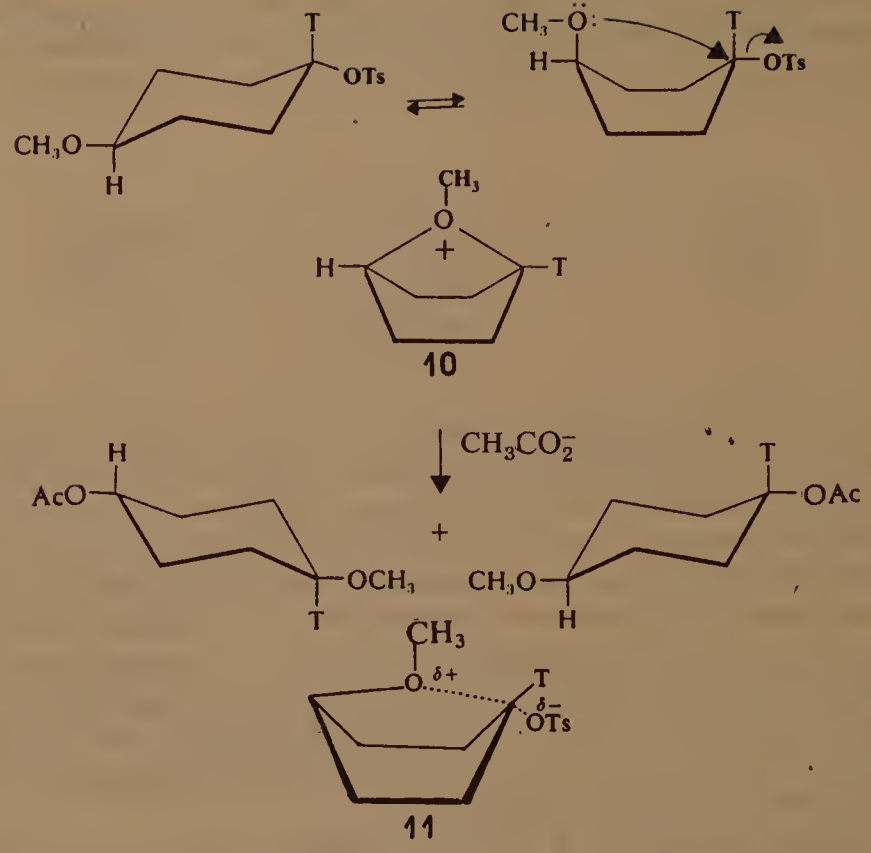
B. 7 Cyclooctatetraene is a conjugated eight carbon ring system, which however, does not display any of the aromatic characteristics of the benzene hydrocarbons. This is due to its nonplanarity. A planar octagon has angles of 135° while sp^2 angles are most stable with a value of 120°. To aviod this angle strain, the molecule adopts a tublike shape. 1, 2, 3, 4-Tetramethyl-cyclooctatetraene is chiral due to its tub shape and no plane of symmetry.

cyclooctatetraene

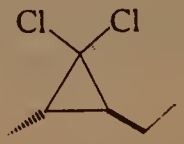
The propellar-shaped, tertiary amine is chiral (it has been resolved) due to hindered rotation.

D.1 Displacement of tosylate anion by an S_N2 reaction would have yielded the *cis*-acetate exclusively. The *trans* product and the apparent shift of the label must involve a neighbouring group interaction by the methoxyl group.

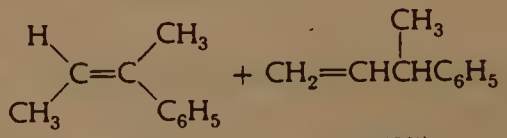
Had all the *trans* product come from 10, the fully covalently bonded intermediate, then the label would have been equally distributed between the 1 and 4 positions. Indeed an intermediate ion pair 11 is most probably involved which may go to 10 or afford the substitution product directly.



F. 1 It is the stereospecific *syn*-addition of dichlorocarbene



G. 1 It is a pyrolytic *syn*-elimination reaction and is expected to yield the following products:



(15%) (30–40%)

One may expect the orientation to be statistical **i.e.**, depending on the number of β-hydrogens available, therefore, Hofmann rule may be operative.

I. 1 In either of the transition states a Huckel system is predicted, since either zero or two phase changes are indicated. The $4n + 2$ *pi* electrons of the Diels-Alder reaction is thus an "allowed" thermal suprafacial-suprafacial process.

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