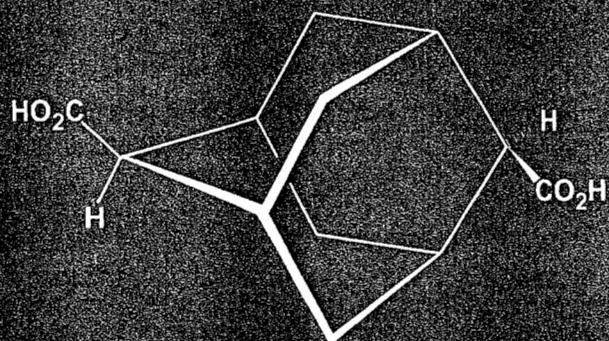
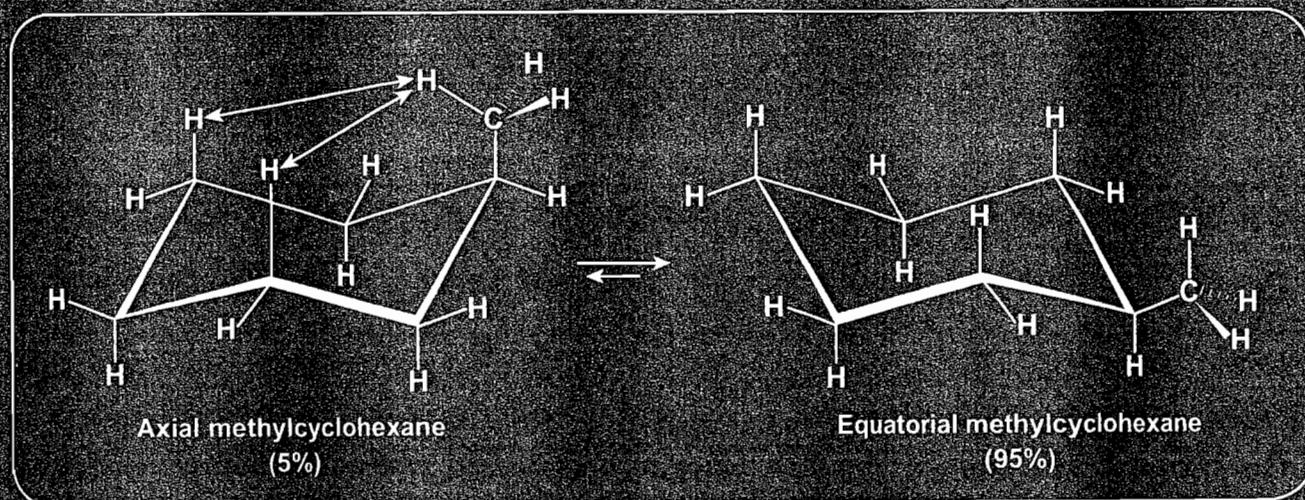
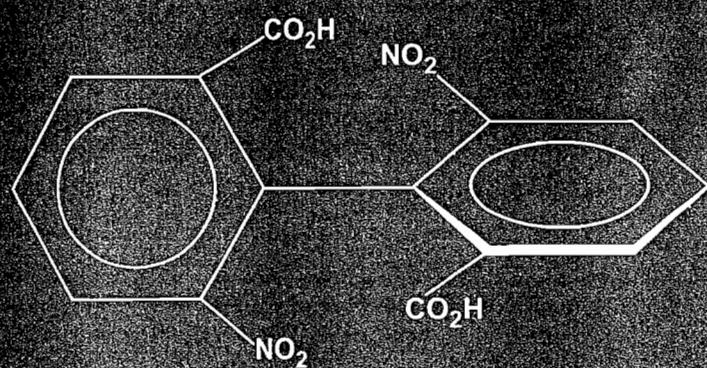


ADVANCED ORGANIC STEREOCHEMISTRY



N. Tewari

[Meant for Chemistry (Hons./Major) students.
Also useful to NET, SLET, GATE candidates]

Advanced Organic Stereochemistry (Problems & Solutions)

Dr. Nimai Tewari, M.Sc., Ph.D.

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Katwa College, Katwa*

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Advanced
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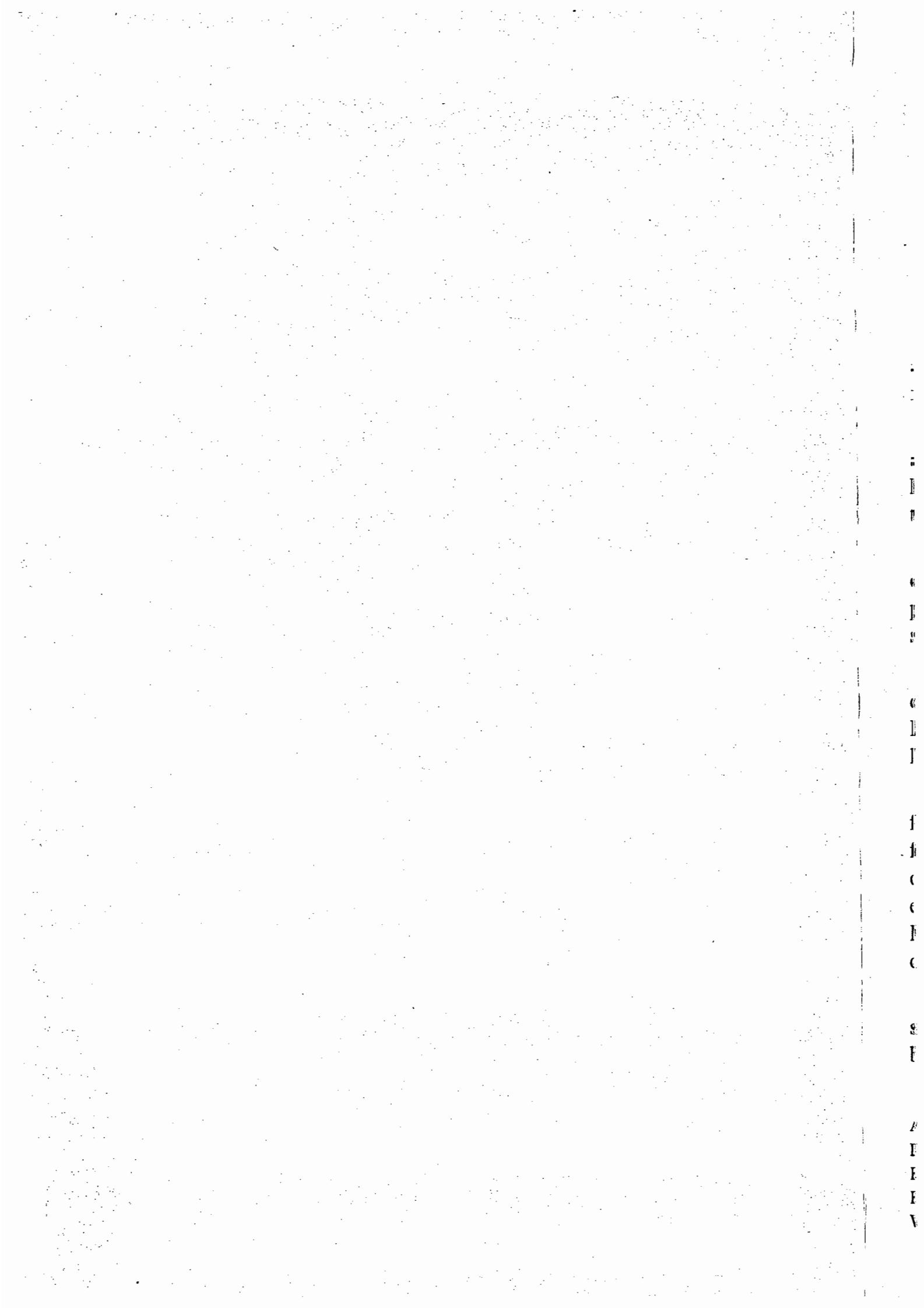
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*Dedicated to
my wife
and
my daughter*

whose forbearance, constant encouragement,
and inspiration, made this work possible



Preface

The subject of stereochemistry has been developed tremendously in recent years and a study of stereochemistry now forms an essential part of the organic chemistry courses in all the universities.

The present volume is intended to provide an up-to-date knowledge of the subject according to the needs of the students. The purpose of the book is also to show as to how an understanding of the concepts of stereochemistry can be usefully applied in thinking about and planning to answer related problems.

The book covers the conventional and the most important topics on stereochemistry of organic molecule in three chapters. All the chapters end with supplementary problems and university questions to afford an opportunity to the students for self-evaluation.

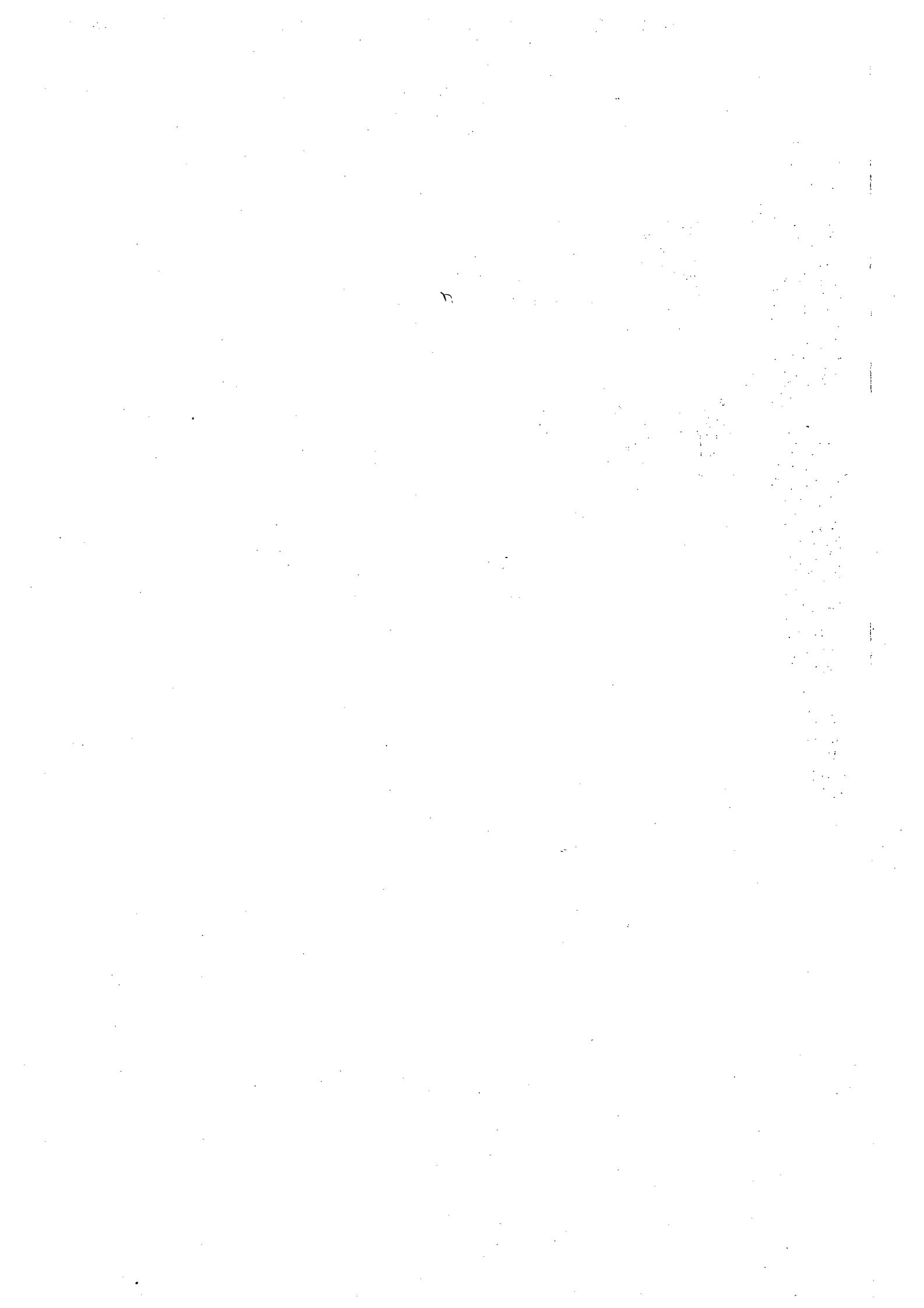
I sincerely hope that the book will be highly useful for the advanced students of chemistry who have had a basic course in stereochemistry in the undergraduate level. It also aims to help the students preparing for competitive examinations like IIT-JEE, NET, GATE, SLET, etc.

I offer my sincere gratitude to Mr. Arunabha Sen, Director, Books & Allied (P) Ltd. for successful publication of the book. I am greatly indebted to Mr. Shyamal Bhattacharya for completing the tedious job of composing the book with great patience. I also owe a debt of gratitude to my colleagues, the library staffs, and my students who encouraged me constantly. I appreciate the interest and enthusiasm shown by my wife Mrs. Dali Tewari and my daughter Miss Aindrila Tewari (Rimi) during the long period of preparation of manuscript.

I will consider my efforts rewarding and encouraging if it is found helpful to the students. Valuable suggestions from the readers for the improvement of the book will be most welcome.

August, 2009
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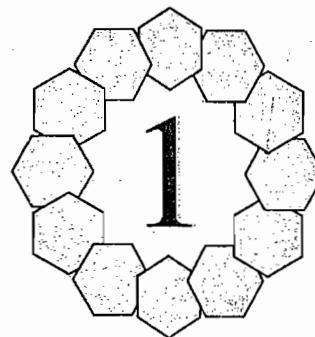
Nimai Tewari



Contents

	Page
1. Stereoisomerism of chiral molecules	1—208
2. Prostereoisomerism, topicity and asymmetric synthesis	209—246
3. Conformations of acyclic and cyclic organic molecules	247—332
4. University Questions (with Hints & Solutions)	333—367





STEREOISOMERISM OF CHIRAL MOLECULES

- **Isomerism and its classification** (Problem 1.1—Problem 1.5)
 - **Symmetry elements** (Problem 1.6—Problem 1.14)
 - **Chirality** (Problem 1.15—Problem 1.28)
 - **Projection formulas of stereoisomers** (Problem 1.29—Problem 1.31)
 - **Configurational nomenclature** (D,L-system, R,S-system, E,Z-system, *threo*, *erythro*-system, etc.) (Problem 1.32—Problem 1.52)
 - **Relative and absolute configuration** (Problem 1.53)
 - **Optical isomerism and optical activity** (Problem 1.54—Problem 1.65)
 - **meso compounds** (Problem 1.66—Problem 1.69)
 - **Chemical and physical properties of enantiomers and diastereoisomers** (Problem 1.70)
 - **Racemic modification and its resolution** (Problem 1.71—Problem 1.76)
 - **Geometric isomerism** (Problem 1.77—Problem 1.79)
 - **Stereochemistry of molecules with more than one chiral centre** (Problem 1.80—Problem 1.84)
 - **Stereochemistry of cyclic compounds** (Problem 1.85—Problem 1.92)
 - **Bicyclic compounds** (Problem 1.93—Problem 1.96)
 - **Labelling of homomers, constitutional isomers, diastereoisomers, and enantiomers** (Problem 1.97—Problem 1.101)
 - **Chirality without chiral centre** (allens, biphenyls, etc.)
(Problem 1.102—Problem 1.112)
-

ISOMERISM AND ITS CLASSIFICATION

► 1.1 What is meant by the term ‘isomerism’?

How many types of isomerism are possible?

Ans. Compounds which have the same molecular formula but possess different physical and chemical properties are called isomers and this phenomenon is known as isomerism. Isomerism exhibited by various compounds are mainly of two broad types : (a) Structural isomerism and (b) Stereoisomerism.

► 1.2 What is structural isomerism?

How many types of structural isomerisms are known? Give examples.

Ans. The isomers that have different molecular constitution i.e., different atom-to-atom bonding sequences or atomic connectivity are structural (constitutional) isomers and this phenomenon is known as structural isomerism. Five types of structural isomerisms are known. These are : (a) Chain or nuclear isomerism, (b) Position isomerism, (c) Functional group isomerism, (d) Metamerism and (e) Tautomerism.

Chain or nuclear isomerism : The arrangement of the carbon atoms linked together in different order in chains gives rise to this type of isomerism.

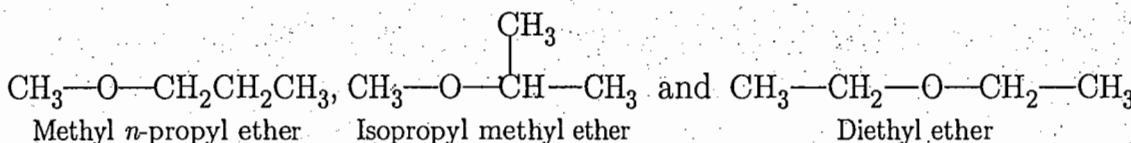
Position isomerism : This type of structural isomerism arises when the carbon-skeleton remains the same, but the substituent group or atom occupies different positions in the skeleton.

Functional group isomerism : This kind of structural isomerism is exhibited by compounds having the same molecular formula, but different functional groups.

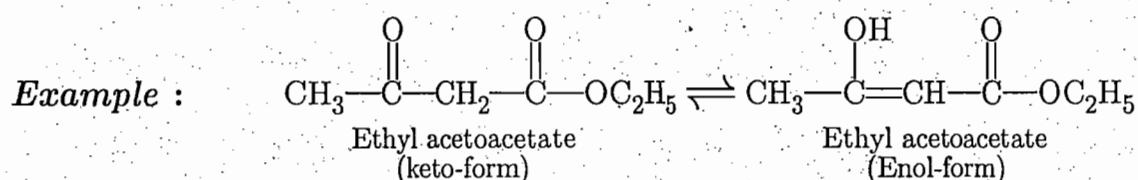
Example : $\text{CH}_3\text{CH}_2\text{OH}$ and $\text{CH}_3-\text{O}-\text{CH}_3$
 Ethyl alcohol Dimethyl ether

Metamerism : This type of isomerism is exhibited by substances of the same class and it is due to the linking of dissimilar alkyl groups to the same polyvalent atom or group.

Example :



Tautomerism : Isomerism in which isomers are reversibly changing into compounds differing in the type of functional group and remain in a dynamic equilibrium is called 'tautomerism'.

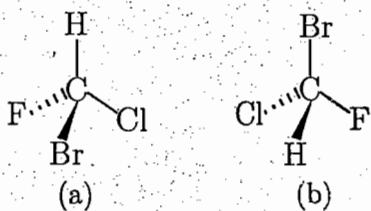


► 1.3 What is stereoisomerism? What are different types of stereoisomerism?

Ans. The isomers with similar molecular constitution but with different spatial arrangement of the various atoms or groups about a rigid part of the molecule (e.g., an asymmetric carbon atom, a double bond, etc.), i.e., with different configuration are called stereoisomers and this phenomenon is known as *stereoisomerism*. This is further classified into two types, namely *optical isomerism* and *geometrical isomerism*.

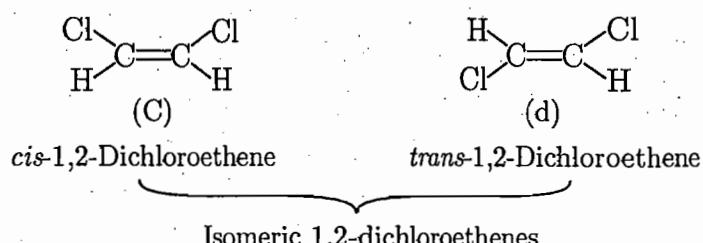
► 1.4 How would you label two molecules as homomers or isomers?

Ans. If two molecules having identical molecular formula are superimposable, they are identical and are called homomers. Therefore, homomers are simply different representations of the same compound. For example, the following two structures (a) and (b) of bromochlorofluoromethane (CHBrClF) are homomers because examination of molecular models shows that they are superimposable. [By the term *superimposable* or *superposable*, we mean that two structures can be placed on each other in such a way that the atoms of one structure coincide with the other.]

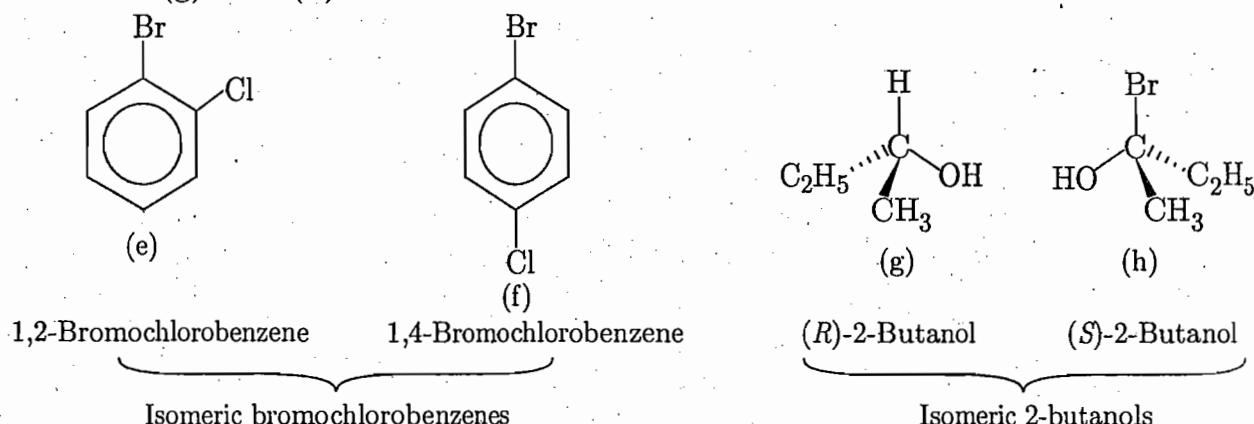


(Two representations of bromochlorofluoromethane)

If two molecules having identical molecular formula are not superimposable, they are called isomers. For example, the following two structures (c) and (d) of 1,2-dichloroethene are isomers because examination of molecular models shows that they are not superimposable.



Similarly, there is an isomeric relationship between structures (e) and (f) and structures (g) and (h).



► 1.5 What is the difference between the terms “configuration” and “conformation”?

Ans. The term configuration is meant to denote the arrangement of the atoms or groups in space around the rigid or dissymmetric part of a molecule (the part of a species which contains a double bond or a ring structure is said to be rigid one as rotation about them is not at all free, while the dissymmetric part usually possess a chiral atom, i.e., an atom carrying different singlebonded atoms or groups with a tetrahedral disposition). The term conformation, on the other hand, is used to denote any one of the infinite number of momentary arrangements of the atoms or groups in space owing to rotations about a single bond. Therefore, a molecule could have an infinite number of conformations, however, only one configuration.

Change from one configuration to another involves breaking and making of bonds. Since this is a high-energy process, stereoisomers maintain their identity and are isolable. Change from one conformation to another involves rotation about a single bond. Since the energy barrier to this rotation is very small, the different conformations are rapidly interconvertible and cannot be isolated, except in a few cases at very low temperatures, or when they possess unusual structure like *ortho*-substituted biphenyls.

SYMMETRY ELEMENTS

► 1.6 What do you understand by the terms 'symmetry operations' and 'symmetry elements'?

Ans. The symmetry of a molecule can be studied by performing certain operations such as rotation and reflection. If after such operation, an arrangement

indistinguishable from the original one, i.e., superimposable on the original one is obtained, the operation is called a *symmetry operation*. In fact, symmetry operations are different ways of interchanging certain parts of the molecule with other parts so that the final appearance of the molecule is indistinguishable from the original.

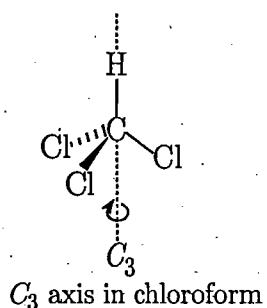
A symmetry element is a geometrical entity such as a line, a point, or a plane with respect to which symmetry operations are carried out.

► 1.7 The following four symmetry elements are required to describe molecular symmetry :

- (a) Simple or proper axis of symmetry (C_n)
- (b) Plane of symmetry (σ)
- (c) Centre of symmetry (i)
- (d) Alternating axis of symmetry (S_n)

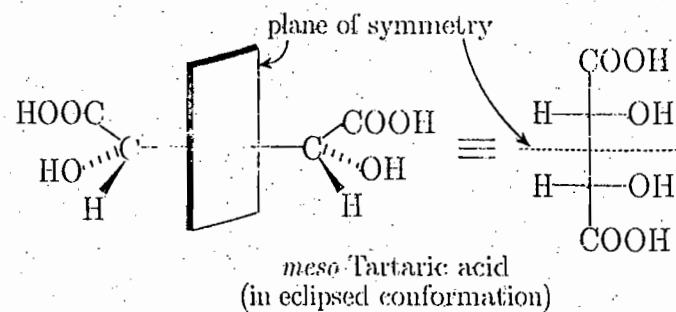
Define these elements of symmetry with suitable examples.

Ans. (a) An n -fold simple or rotational axis of symmetry (C_n) of a molecule is an imaginary line (axis) passing through the molecule such that, if the molecule is rotated by an angle of $360^\circ/n$ around this axis, a structure indistinguishable from the original, i.e., an equivalent structure results. For example, chloroform has a three-fold ($n = 3$) simple axis of symmetry. Rotation of 120° ($2\pi/3$) around the axis along the C—H bond produces a structure indistinguishable from the original (the positions of Cl atoms are changed mutually).



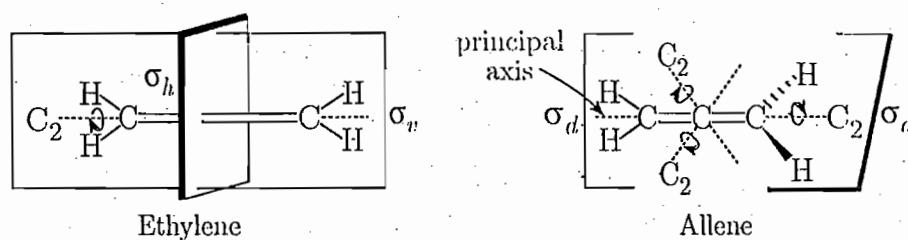
[If a molecule has C_n axis with different values of n , then the C_n axis having maximum value of n (fold or order) is called the *principal axis*. When there are several C_n axes with the same value of n , then the principal axis is one which involves maximum number of atoms of the molecule. Rotation by an angle of 360° about any axis through any molecule gives back the same molecule in the same three dimensional orientation it had originally. Therefore, C_1 axis is known as *trivial axis* and is not included in the category of C_n axis.]

(b) A plane of symmetry (σ) is defined as an imaginary plane that bisects a molecule in such a way that one half of the molecule is the mirror image of the other half (the plane acting as a mirror). The plane of symmetry is also called a mirror plane. For example, the eclipsed conformation of meso-tartaric acid has a plane of symmetry.

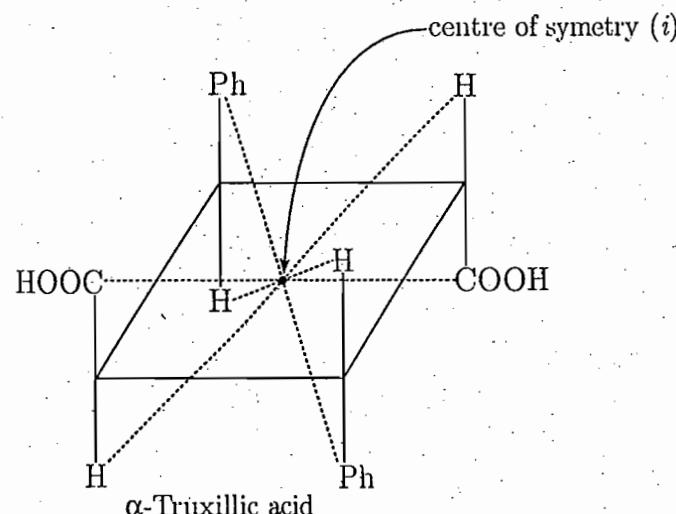


[It is to be remembered that all planar molecule necessarily has a plane of symmetry which is actually the plane of the atomis, i.e., the molecular plane.]

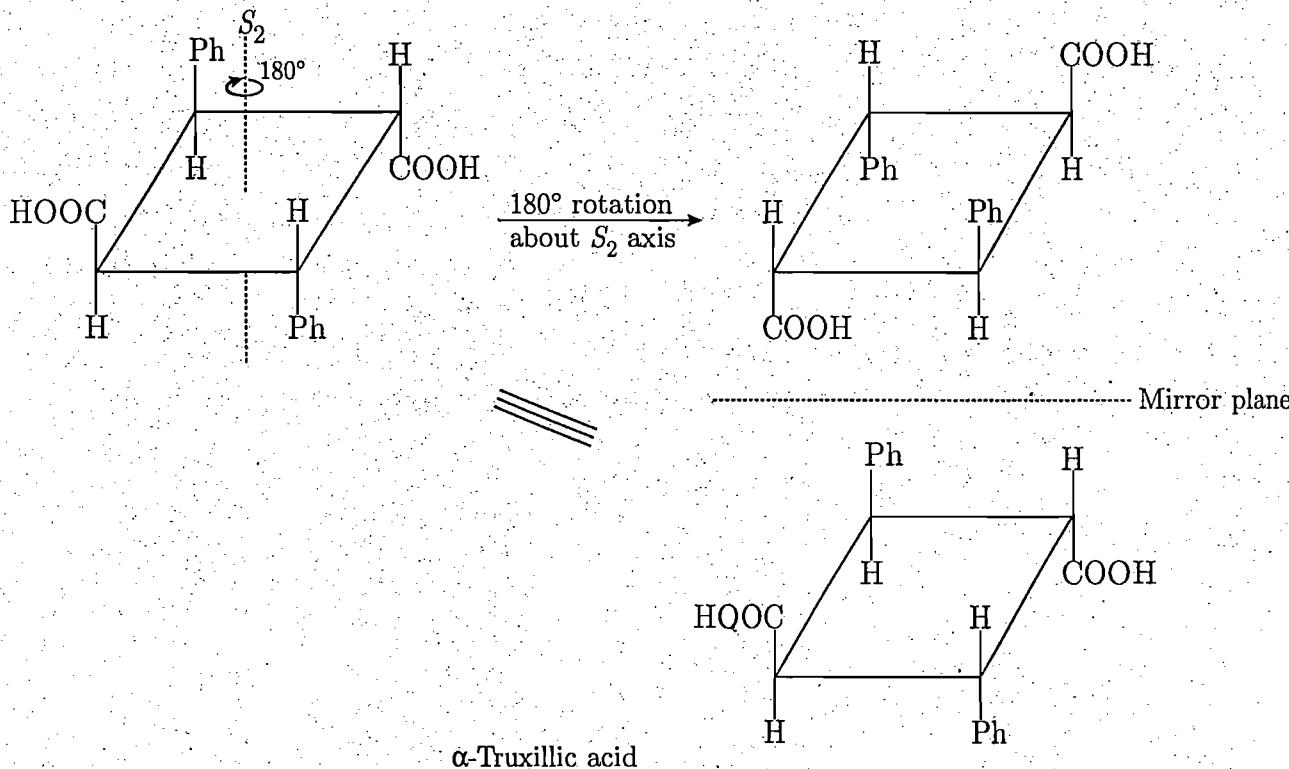
σ_h , σ_v and σ_d : The symbol σ is generally used with three subscripts indicating the position of the plane of symmetry in relation to the principal axis (C_n). σ_h represents a plane perpendicular to the principal axis (h stands for horizontal), σ_v represents a plain containing the principal axis (v stands for vertical) and σ_d represents a plane which contains the principal axis and bisects the angle between the two C_2 axes (d stands for diagonal). For example, ethylene has both σ_h and σ_v and allene has two σ_d .



(c) A centre of symmetry or a point of symmetry or an inversion centre (i) is a point within a molecule such that if a straight line is drawn from any atom of the molecule to this point and then extended equal distance beyond the point, another identical atom will be found at the end of the line. For example, α -truxillic acid has a centre of symmetry.



(d) An alternating or a rotation-reflection axis of symmetry of n fold (or order) is an axis such that a rotation of the molecule about the axis by $360^\circ/n$ followed by reflection in a plane perpendicular to this axis generates a structure indistinguishable from the original. The order of the two operations may be reversed without change in the result. For example, α -truxillic acid has a two-fold alternating axis of symmetry.



[It is to be remembered that a plane of symmetry (σ) is equivalent to one-fold alternating axis of symmetry (S_1) and a centre of symmetry (i) is equivalent to two-fold alternating axis of symmetry (S_2).

► 1.8 What are called C_n , σ , i and S_n operations? What is meant by operation of identity (E)? Give examples.

Ans. The operations involving rotation of the molecule around an imaginary axis by an angle of $360^\circ/n$, reflection of the two halves of the molecule across a plane, inversion of all atoms in the molecule through a point and rotation of the molecule around an axis by $360^\circ/n$ followed by reflection in a plane perpendicular to the axis are called C_n , σ , i and S_n operations respectively.

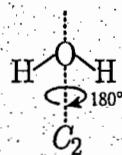
Different manipulations of symmetry elements that transform molecules into identical structures i.e., the operations which leave the molecules unchanged are called operations of identity (E). For example, when a molecule is rotated n times about a C_n axis we get identical structure, i.e., $C_n^n = E$. Reflection of the two halves of the molecule across a plane followed by reflection back again generates an identical structure, i.e., $\sigma^2 = E$. Inversion of a molecule followed by second inversion results in retention of the original orientation, i.e., $i^2 = E$. When n times of S_n operations ($n = \text{even}$) are carried out, we get identical structure, i.e., $S_n^n = E$ and when $2n$ times of S_n operations ($n = \text{odd}$) are carried out, we get identical structure, i.e., $S_n^{2n} = E$.

[It should be noted that the terms '*indistinguishable*' and *identical* have different meaning in the present context. The former refers to any equivalent structure arrived at by exchanging similar atoms or groups while the latter refers strictly to the original.]

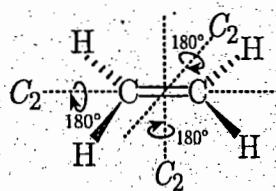
- 1.9 Indicate the simple axes of symmetry present in the following molecules/ions : (a) Water (b) ethylene (c) dichloromethane (d) benzene (e) methyl cation (f) methane (g) ammonia (h) *cis*-1,3-dimethylcyclobutane (i) *trans*-1,3-dimethylcyclobutane (j) acetylene (k) allene (l) 1,3-dimethylallene (m) 2,2-dibromo-6,6-dimethylspiro[3,3]heptane (n) *trans*-2,3,7,8-tetrachlorospiro[4,4]decane (o) eclipsed and staggered conformation of ethane (p) cyclohexane (q) *cis*- and *trans*-1,3-sec-butylcyclobutane (configuration of each asymmetric carbon is *R*) (r) naphthalene (s) *trans*-1,2-dichloroethene.

Ans.

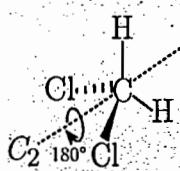
- (a) Water (H_2O) : It has a two-fold simple or rotational axis of symmetry (C_2) bisecting the H—O—H angle.



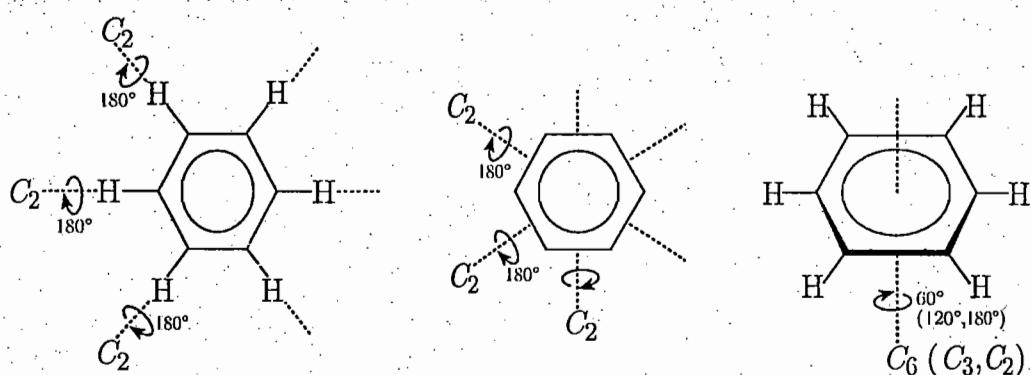
- (b) Ethylene ($\text{CH}_2=\text{CH}_2$) : It has three C_2 axes. One is collinear with the C—C bond axis; the second one is perpendicular to the molecular plane and bisects the C=C bond and the third one is perpendicular to the former two and intersects both at the mid-point of the C=C bond.



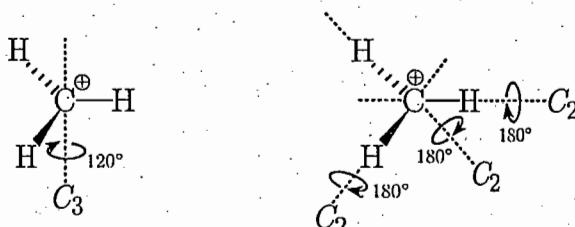
- (c) Dichloromethane (CH_2Cl_2) : It has a C_2 axis which bisects Cl—C—Cl and H—C—H angles.



- (d) Benzene (C_6H_6) : Benzene has a C_6 axis passing through the centre of the regular hexagon. It has six C_2 axes of which three passing through the mid-point of opposite sides (bonds) and three passing through the corners of the molecule. Benzene has also a C_2 and a C_3 axis collinear with C_6 axis, i.e., C_6, C_2 and C_3 are one and the same axis. The C_6 axis is the *principal axis*.

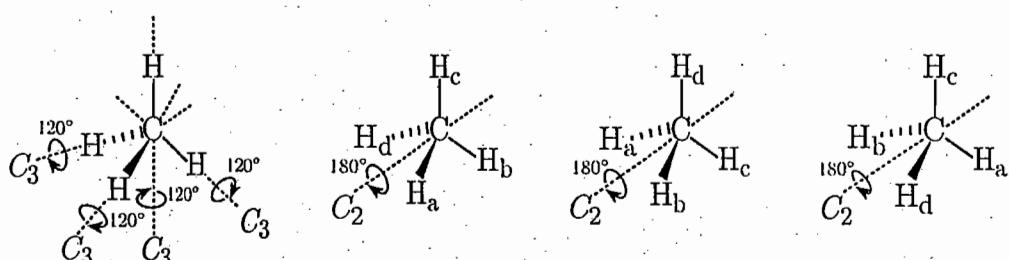


(e) Methyl cation (CH_3^+) : Planar methyl cation has one C_3 axis which passes through the C atom and perpendicular to the plane of the species. It has also three C_2 axes each of which passes through the C atom and one H atom and bisects the angle between two other C—H bonds.

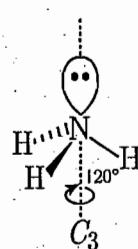


[Boron trifluoride (BF_3) also has one C_3 and three C_2 axes.]

(f) Methane (CH_4) : It has four C_3 axes each of which is perpendicular to the plane of three H atoms and passes through the fourth H atom and the C atom. Also the molecule has three C_2 axes each of which bisects two pairs of H—C—H angles.

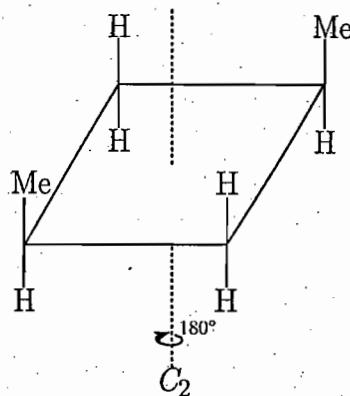


(g) Ammonia (NH_3) : Pyramidal ammonia molecule has a C_3 axis which passes through N atom and perpendicular to the plane of the three H atoms.

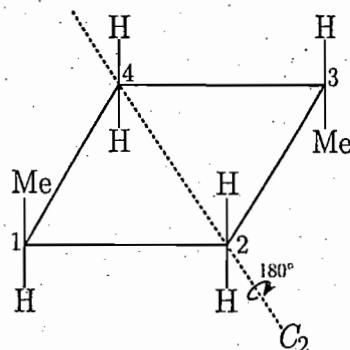


[Isostructural methyl anion (CH_3^-) has a C_3 axis.]

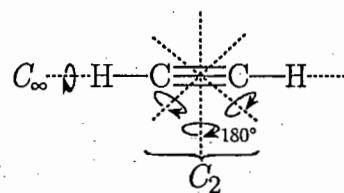
(h) *cis*-1,3-Dimethylcyclobutane : The molecule has a C_2 axis which passes vertically through the centre of the molecule.



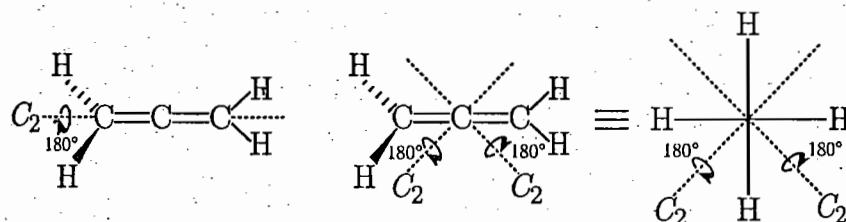
(i) *trans*-1,3-Dimethylcyclobutane : The molecule has a C_2 axis which passes through C-2 and C-4.



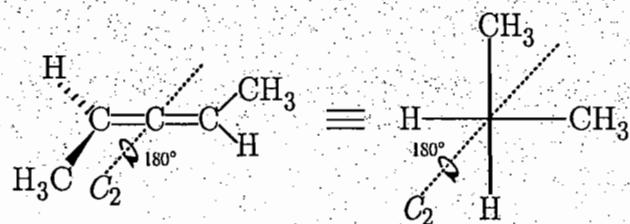
(j) Acetylene (C_2H_2) : It is a linear molecule. It possesses a C_∞ axis coincident with the internuclear axis since rotation around it by any angle gives an equivalent structure. Also, acetylene possesses an infinite number of C_2 axes perpendicular to the centre of the C_∞ axis.



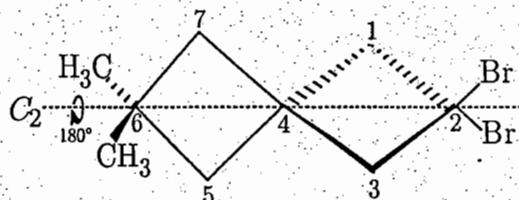
(k) Allene ($CH_2=C=CH_2$) : The molecule has three C_2 axes. One of them passes through the C atoms and each of the rest two passes diagonally through the central sp -carbon atom.



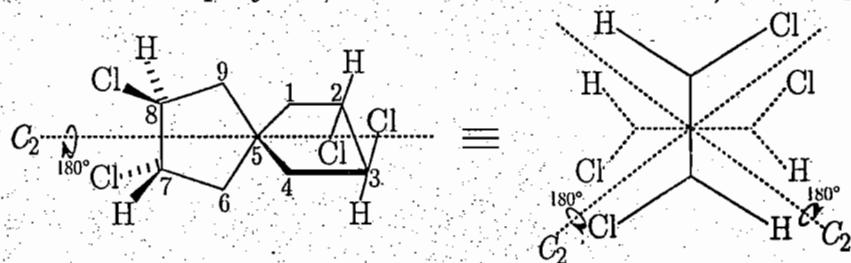
(l) 1,3-Dimethylallene ($CH_3CH=C=CHCH_3$) : The molecule has only one C_2 axis which passes through the central sp -carbon atom. It may be shown clearly by its projection formula.



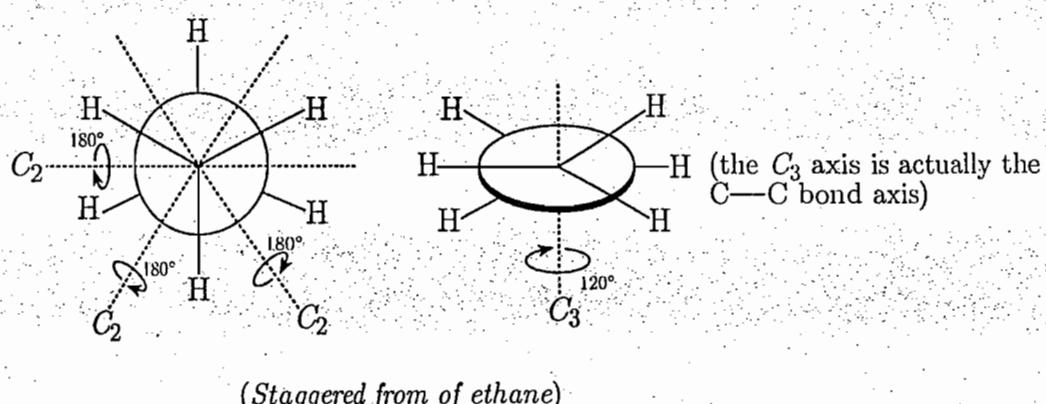
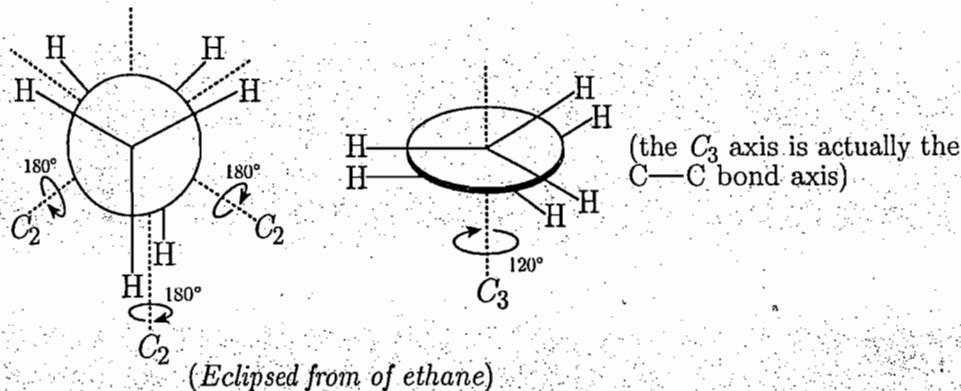
(m) **2,2-Dibromo-6,6-dimethylspiro[3,3]heptane** : The molecule has only one C_2 axis which passes through three ring carbons (C-2, C-4 and C-6).



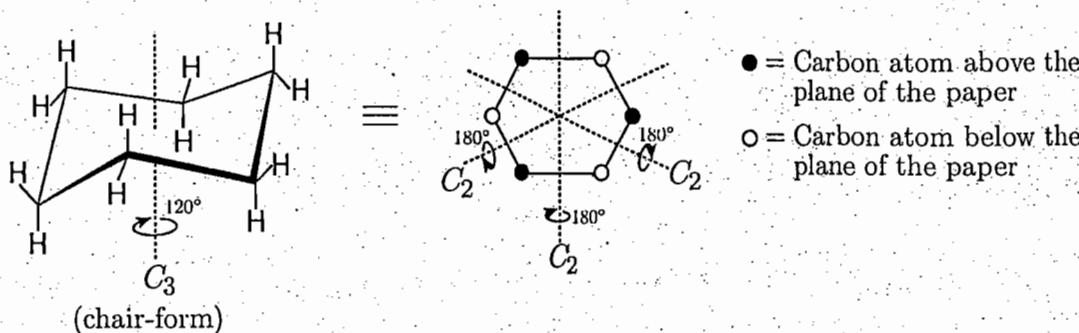
(n) ***trans, trans*-2,3,7,8-Tetrachlorospiro[4,4]decane** : The molecule has three C_2 axes. One axis passes through the spiro C-atom and the mid-points of C-2—C-3 bonds and C-7—C-8 bonds. Each of the other two axes passes diagonally through the spiro C-atom (this may be clear from the projection formula of the molecule).



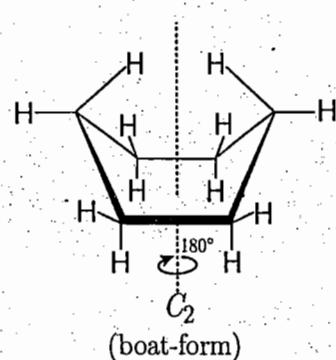
(o) **Eclipsed and staggered conformation of ethane (CH_3-CH_3)** : Both the eclipsed and staggered conformation of ethane have one C_3 and the three C_2 axes. This may be clear from their Newman projections.



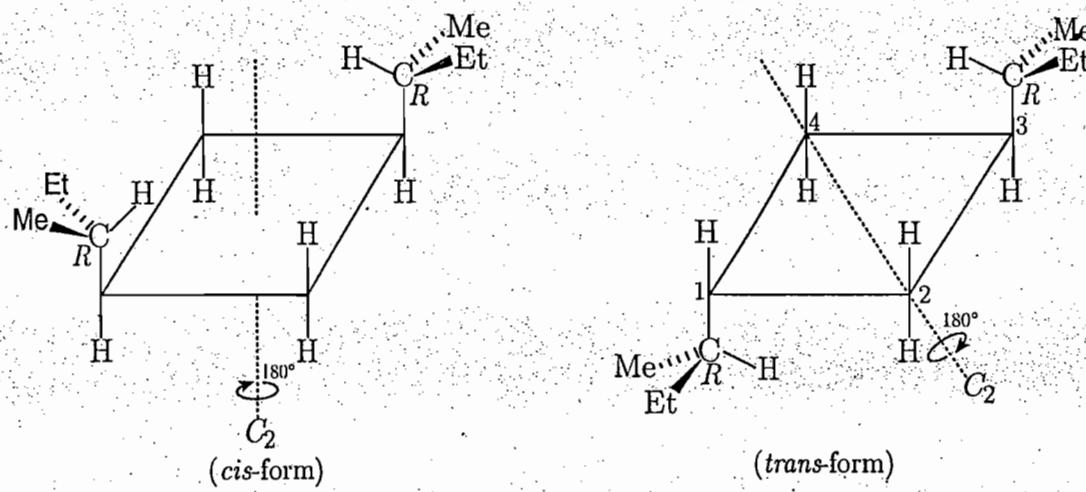
(p) Cyclohexane (C_6H_{12}) : The chair conformation of cyclohexane has a C_3 axis passing vertically through the centre and three C_2 axes passing through the centre and the mid-points of two opposite bonds.



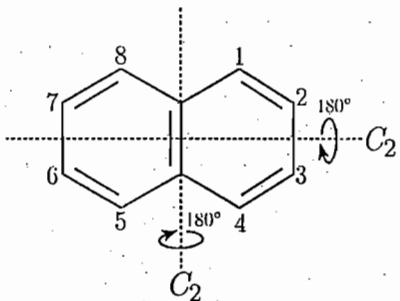
The boat conformation of cyclohexane has a C_2 axis passing vertically through the centre of the boat.



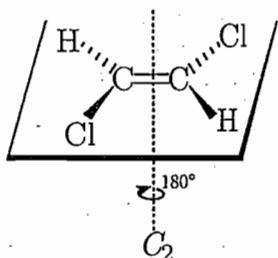
(q) *cis*- and *trans*-Di-sec-butylcyclobutane : The *cis*-isomer of di-sec-butylcyclobutane (with *R* configuration of each asymmetric carbon) has a C_2 axis which passes vertically through the centre of the molecule and the *trans*-isomer has also a C_2 axis which passes through C-2 and C-4.



(r) Naphthalene : Naphthalene has two C_2 axes one of which passes through the carbons common to both the rings and the other passes through the mid-points of C-2—C-3 and C-6—C-7 bonds.

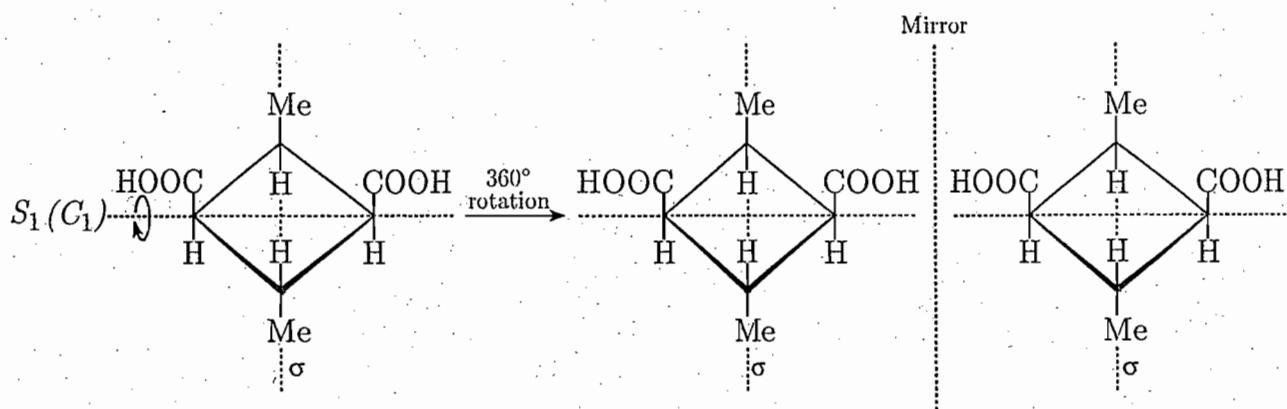


(s) *trans*-1,2-Dichloroethene (*trans*-ClCH=CHCl) : It has a C_2 axis which is perpendicular to the molecular plane and passes through the mid-point of carbon-carbon double bond.



►1.10 A plane of symmetry (σ), is equivalent to one-fold alternating axis of symmetry (S_1). Explain giving example.

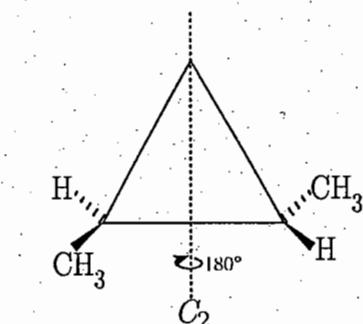
Ans. An S_1 operation involves a C_1 operation and a σ operation. Since the C_1 operation (rotation of the molecule about an axis passing through it in any direction by $360^\circ/1 = 360^\circ$) turns the molecule into the original, the S_1 operation is actually a σ operation, i.e., a plane of symmetry (σ) is equivalent to one-fold alternating axis of symmetry (S_1). For example, this may be shown as follows :



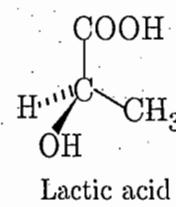
►1.11 What do you mean by asymmetric and diesymmetric molecules? Give examples.

Ans. Molecules in which there is no elements of symmetry, i.e., C_n (except C_1 which is present in all molecules) and S_n axes (i.e., σ , i and other S_n axes) are absent are

known as asymmetric molecules. On the other hand, molecules in which S_n axis is absent, but C_n axis may be present or absent are known as dissymmetric molecules. Therefore, all asymmetric molecules are dissymmetric, but not all dissymmetric molecules are asymmetric. For example, *trans*-1,2-dimethylcyclopropane is a dissymmetric molecule. Since the molecule has a C_2 axis, it is not an asymmetric one. However, the lactic acid molecule may be considered both as an asymmetric and a dissymmetric one because both S_n and C_n are absent in it.



trans-1,2-Dimethylcyclopropane
(a dissymmetric molecule)

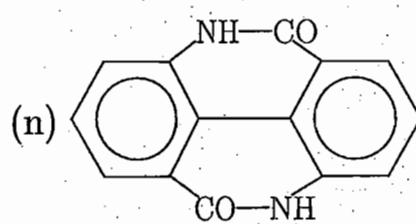
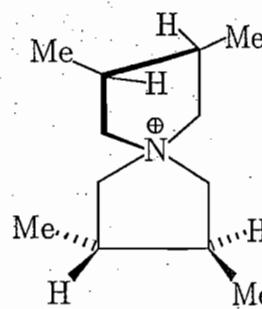
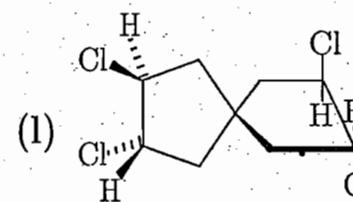
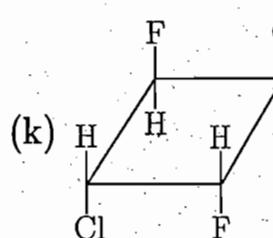


(an asymmetric or a dissymmetric molecule)

[1,3-Dimethylallene ($\text{CH}_3\text{CH}=\text{C}=\text{CHCH}_3$) is another example of dissymmetric molecule which is not asymmetric. It has no element of symmetry except C_2 .]

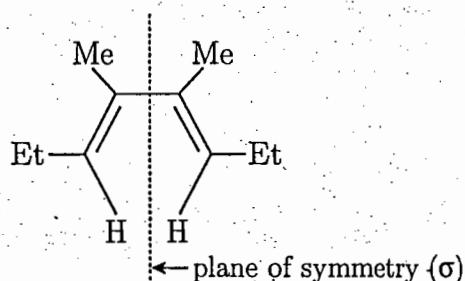
►1.12 Indicate the element(s) of symmetry (other than C_n) present in each of the following molecules :

- (a) *s-cis* (*cisoid*) conformation of (3*E*, 5*E*)-4,5-dimethyl-3,5-octadiene
 - (b) *anti* conformation of *meso*-tartaric acid
 - (c) 2-chloropropane
 - (d) 3-bromo-1,1-dichloropropadiene
 - (e) *trans*-dimethylketopiperazine
 - (f) *trans*-1,4-dichlorocyclohexane
 - (g) *cis*-1,3-dichlorocyclohexane
 - (h) 4-chloropiperidine
 - (i) 8-chlorospiro[4,5]decane
 - (j) *trans*-1,2-dibromoethene

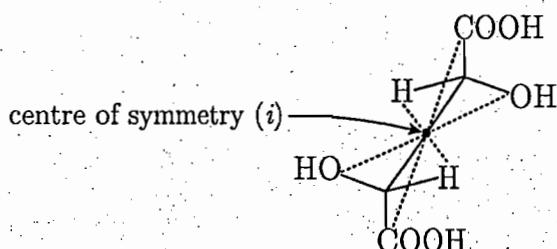


Ans.

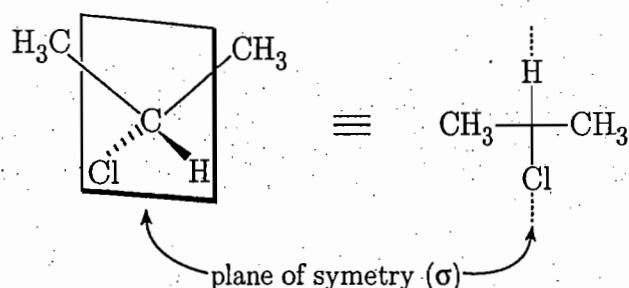
(a) *s-cis* conformation of (*3E, 5E*)-4,5-dimethyl-3,5-octadiene has a plane of symmetry.



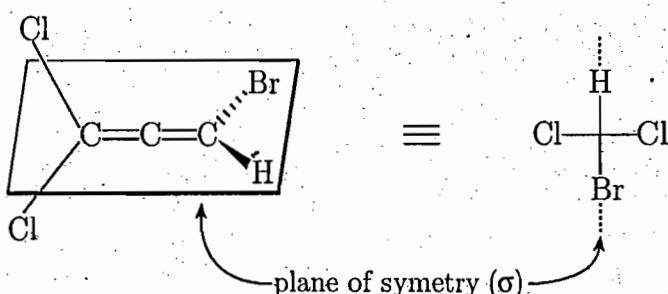
(b) Anti conformation of *meso*-tartaric acid has a centre of symmetry.



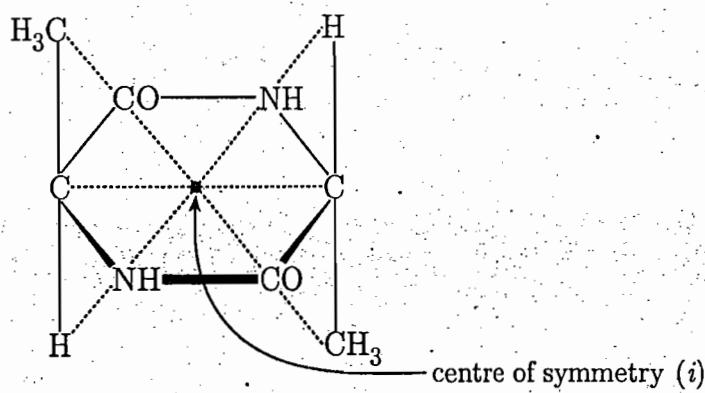
(c) 2-Chloropropane has a plane of symmetry.



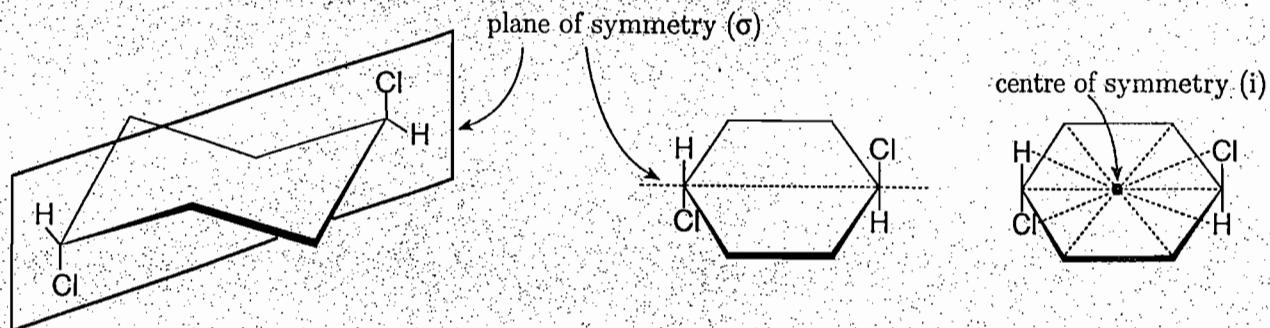
(d) 3-Bromo-1,1-dichloropropadiene has a plane of symmetry.



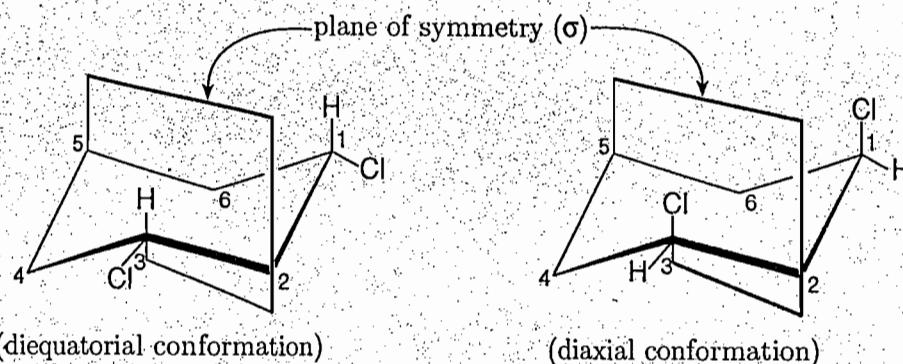
(e) *trans*-Dimethyldiketopiperazine has a centre of symmetry.



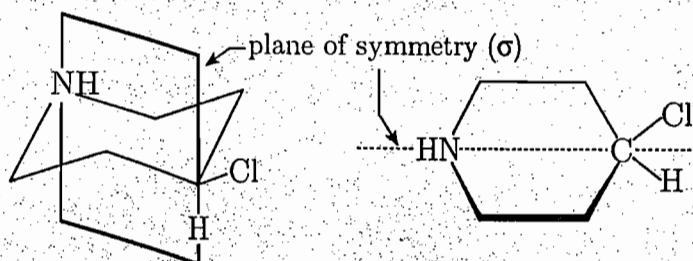
(f) *trans*-1,4-Dichlorocyclohexane has a plane of symmetry (passing through C-1 and C-4). Also the molecule has a centre of symmetry.



(g) Both conformations of the *cis*-1,3-dichlorocyclohexane have a plane of symmetry (passing through C-2 and C-5).



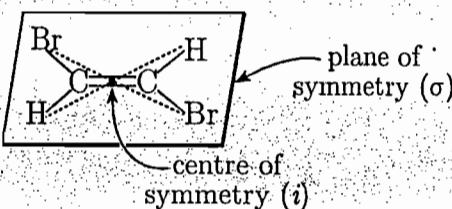
(h) 4-Chloropiperidine has a plane of symmetry.



(i) 8-Chlorospiro[4,5]decane has a plane of symmetry.

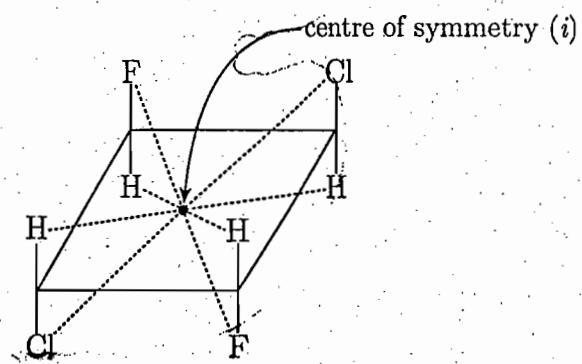


(j) *trans*-1,2-Dibromoethene has a centre of symmetry.

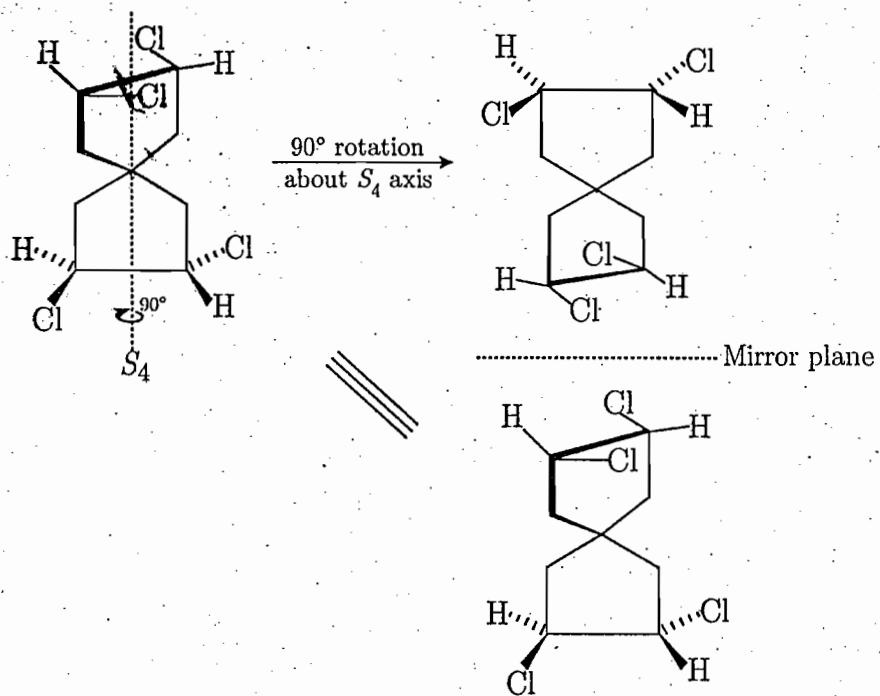


Also, it has a plane of symmetry which is the plane of the molecule.

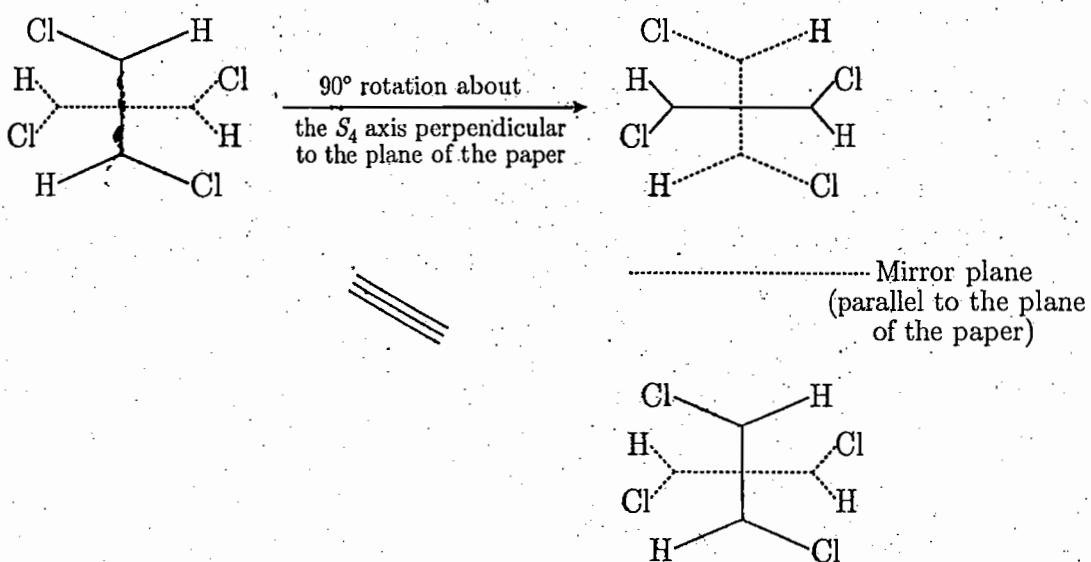
(k) The molecule has a centre of symmetry.



(l) The molecule has a four-fold alternating axis of symmetry (S_4).

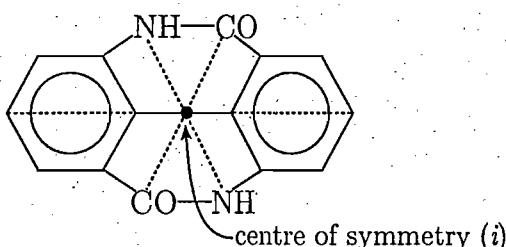


That the molecule has an S_n axis may also be shown by its projection formula.



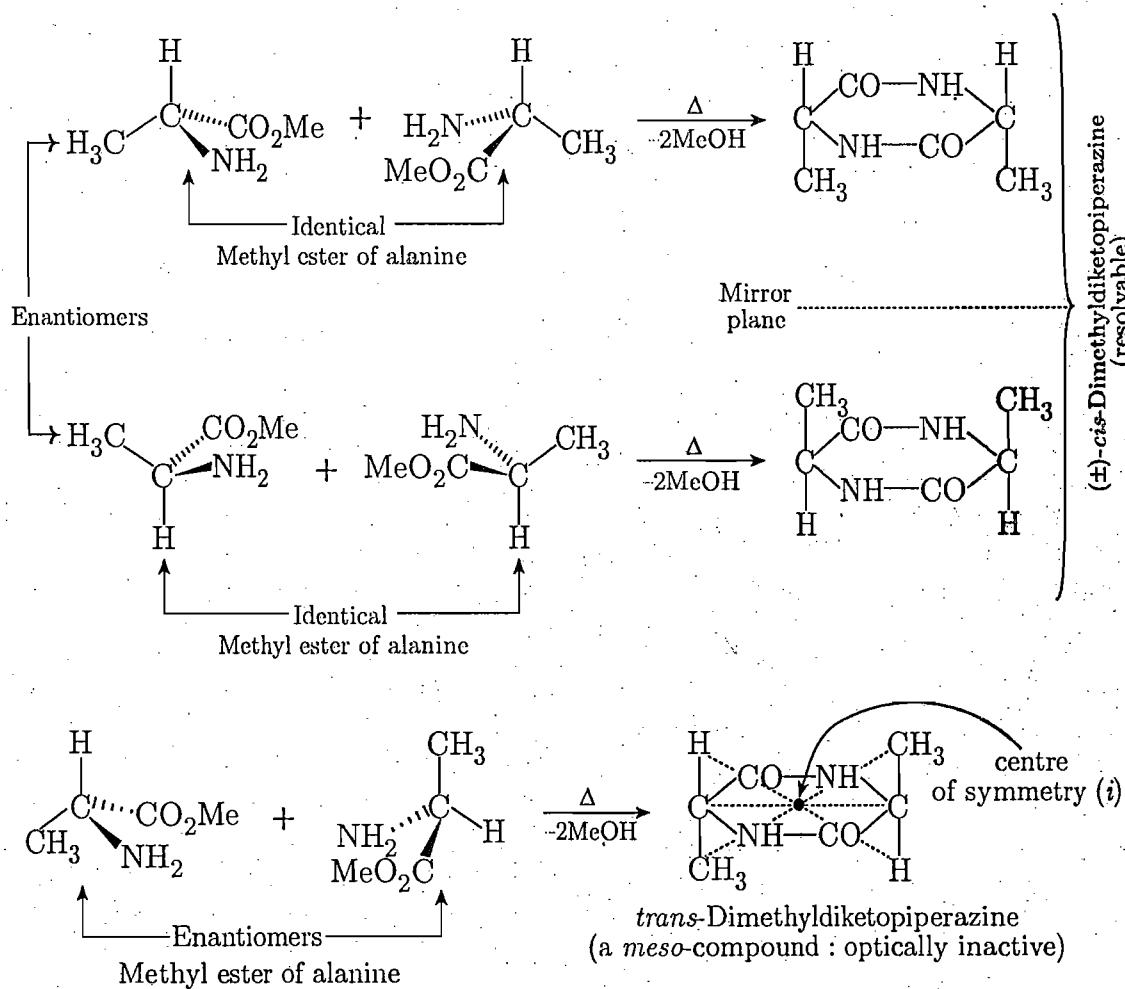
(m) The compound has a four-fold alternating axis of symmetry (S_4) as shown in the previous molecule.

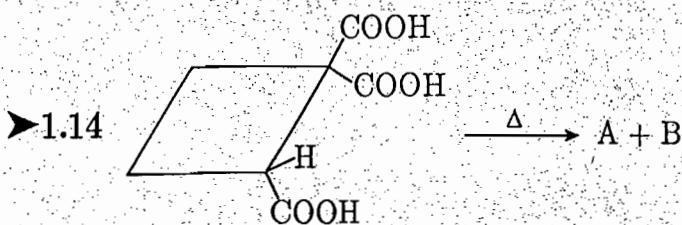
(n) The molecule has a centre of symmetry.



►1.13 When the methyl ester of (\pm)-alanine is heated, two diastereoisomeric dimethyldiketopiperazines are obtained. One of them cannot be resolved. Give the stereochemical course of the reaction and account for the stereochemistry of the products.

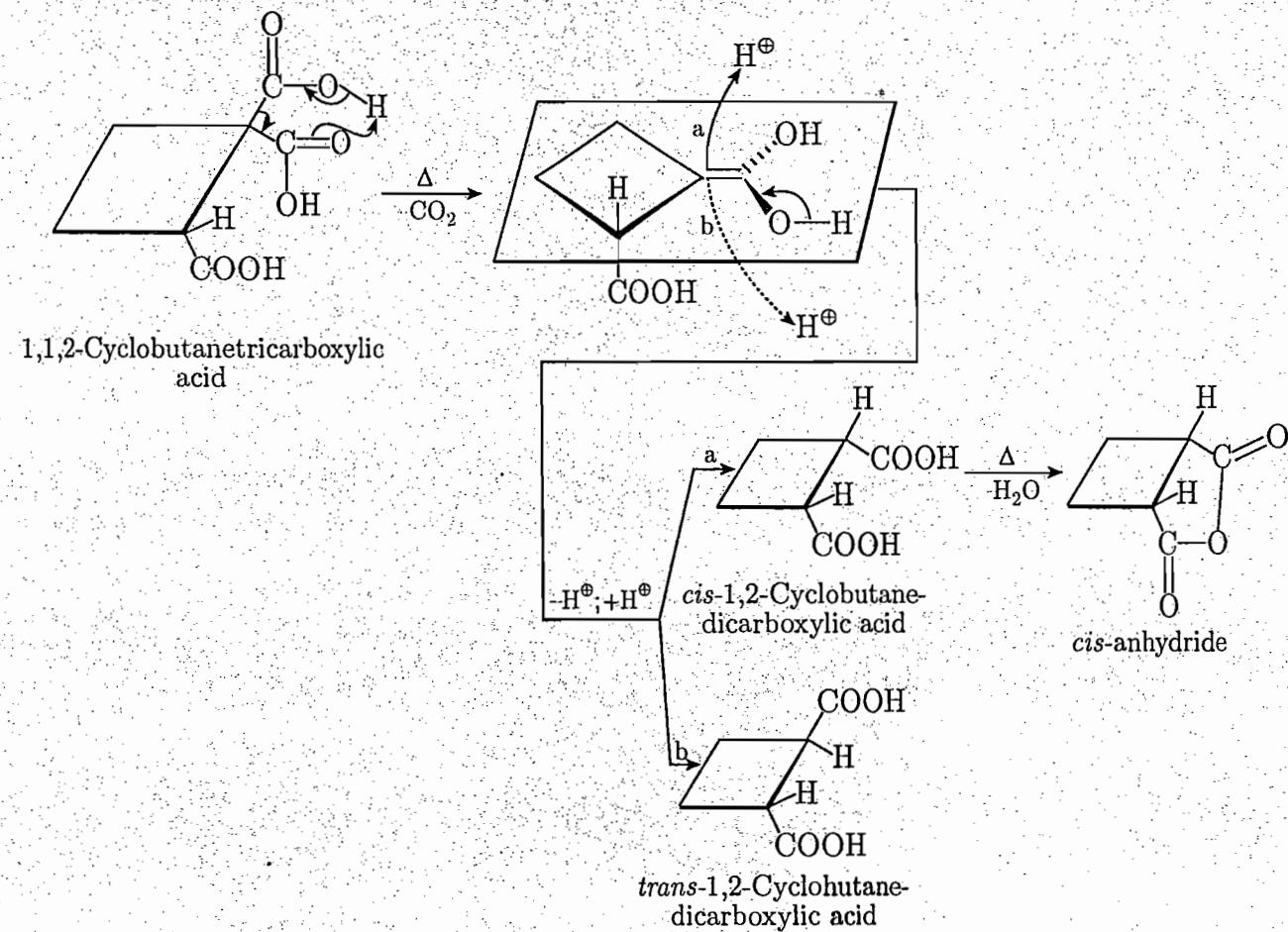
Ans. When heated methyl ester of (\pm)-alanine (two molecules) reacts intermolecularly to give *cis*- and *trans*-dimethyldiketopiperazine (two geometric isomers, i.e., diastereoisomers). The *cis*-isomer is optically active (it has no S_n axis) and resolvable, whereas the *trans*-isomer is optically inactive (it has a centre of symmetry).





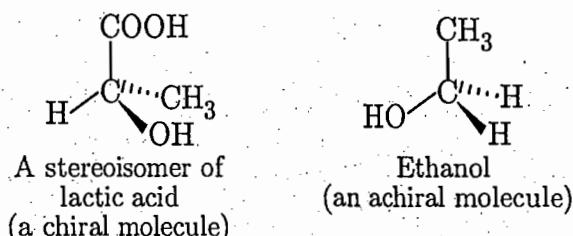
Predict the products of the reaction and explain their formations.

Ans. When heated 1,1,2-cyclobutanetricarboxylic acid undergoes decarboxylation to give an enol which readily tautomerizes to the more stable keto-form, i.e., to the dicarboxylic acids. During tautomerization the double bond takes up H^+ from the top face or from the bottom face to give *cis*- or *trans*-1,2-cyclobutanedicarboxylic acid. Under the reaction conditions the *cis*-isomer undergoes dehydration to give the *cis*-anhydride. The *trans*-isomer, on the other hand, cannot form an anhydride because a five-membered ring cannot be fused *trans* due to steric reason.



- 1.15 (a) What do you mean by a chiral and an achiral molecule? Give examples.
 (b) What is chirality? (c) What is a chiral centre? (d) What is the most common feature which makes a compound chiral?

Ans. (a) If the mirror image of a molecule is not superimposable on the original, the molecule is called a chiral molecule. On the other hand, if the mirror image of a molecule is superimposable on the original, the molecule is called an achiral molecule. A lactic acid molecule is a chiral molecule, whereas an ethanol molecule is an achiral molecule.



(b) The property of any molecule of being nonsuperimposable on its mirror image is called chirality.

(c) A chiral centre is an atom bonded tetrahedrally to four different atoms or groups (also called *ligands*). A chiral centre is usually a C atom (a chiral carbon atom or an asymmetric carbon atom), but may be N, P, S, Si etc. A chiral centre is usually indicated with an asterisk (*).

(d) The most common feature (but not the only one) which makes a compound chiral is the presence of a chiral carbon atom.

[A molecule may be chiral not only due to presence of a chiral centre, but also due to presence of a chiral axis, a chiral plane and helicity. The word chiral comes from the Greek word *cheir*, meaning "hand". Chiral objects are said to possess "handedness". The term chiral is used to describe molecules of enantiomers because they are related to each other in the same way that a left hand is related to a right hand.]

►1.16 What is a stereocentre or stereogenic centre? How is it related to a chiral centre?

Ans. If two ligands attached to an atom are interchanged spatially resulting a new stereoisomer, the atom is called a stereocentre. For example, the C-2 of lactic acid ($\text{CH}_3\overset{*}{\text{C}}(\text{OH})\text{COOH}$) is a stereocentre as well as a chiral centre. But the C-2 and the C-3 carbon atoms of *cis*- and *trans*-but-2-ene are stereocentres but not chiral centre because interchange of H and CH_3 -groups on any of these C-atoms gives a new stereoisomer (a diastereoisomer) which is not an enantiomer. Therefore, all stereocentres are not chiral centres but all chiral centres are stereocentres.

►1.17 What are the practical ways for testing molecular chirality?

Ans. There are two practical ways for testing the chirality of a molecule. These are as follows :

(a) One is to construct a model of the molecule and its mirror image and then determine whether they are superimposable. If the two models are superimposable, the molecule that they represent is achiral and if the models are not superimposable, the molecules that they represent are chiral.

(b) One may look first for a σ -plane (S_1) and an inversion centre (S_2) and then an S_n axis of higher order in the molecule. If these symmetry elements are present in the molecule, it is achiral and if not, the molecule is chiral.

►1.18 The presence or absence of a chiral centre is no criterion of chirality. Explain.

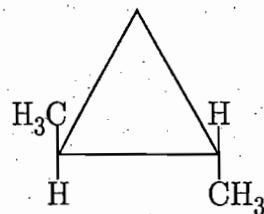
Ans. If a molecule contains only one chiral centre, the molecule must be chiral. However, if a molecule contains more than one chiral centre, it may or may not be chiral. For example, 2,3-dibromopentane ($\text{CH}_3\overset{*}{\text{C}}\text{HBr}\overset{*}{\text{C}}\text{HBrC}_2\text{H}_5$) is chiral, but *meso*-tartaric acid ($\text{HO}_2\overset{*}{\text{C}}\text{CHOH}\overset{*}{\text{C}}\text{HOHCOOH}$) is achiral. Again, there are chiral molecules that contain no chiral centres. For example, suitably substituted allenes (such as $\text{CH}_3\text{CH}=\text{C}=\text{CHCH}_3$), alkylidenecycloalkanes, spirans, biphenyls, etc. are chiral even though they do not have any chiral centre. Therefore, the presence or absence of a chiral centre is no criterion of chirality.

►1.19 (a) What is the lowest molecular-weight alkane (with no isotopic atom) that is chiral? (b) Is there another alkane of the same molecular weight that is also chiral? If there is, give its structure and name also. (c) What is the lowest molecular-weight cyclic alkane (with no isotopic atom) that is chiral?

Ans. (a) 3-Methylhexane [$\text{CH}_3\text{CH}_2\overset{*}{\text{C}}\text{H}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{CH}_3$] is the lowest molecular-weight alkane that is chiral and this is because it contains only one chiral centre.

(b) Yes. 2,3-Dimethylpentane [$\text{CH}_3\text{CH}_2\overset{*}{\text{C}}\text{H}(\text{CH}_3)\text{CH}(\text{CH}_3)_2$] is the alkane of the same molecular weight that is also chiral because it also contains only one chiral centre.

(c) *Trans*-1,2-dimethylcyclopropane is the lowest molecular-weight cyclic alkane that is chiral.

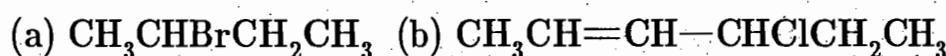


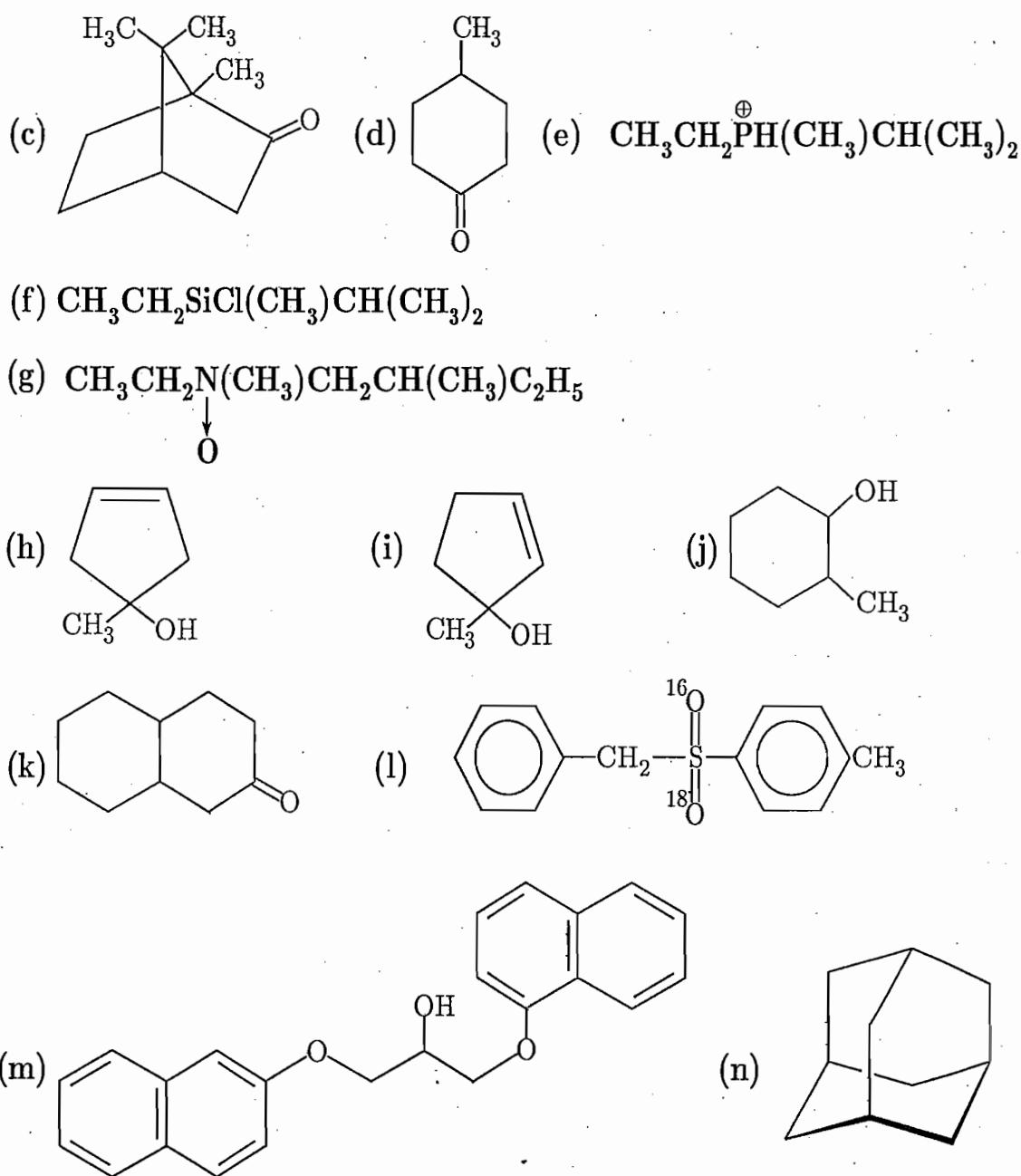
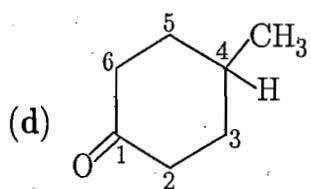
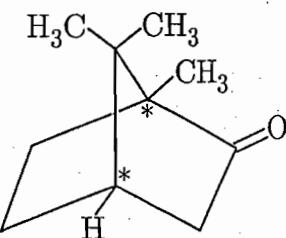
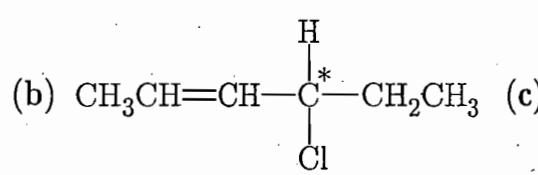
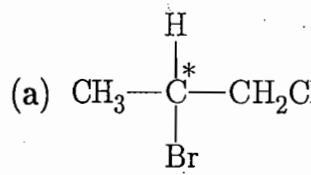
(*trans*-1,2-Dimethylcyclopropane)

►1.20 Explain why the positive carbon of a carbocation cannot be a chiral centre.

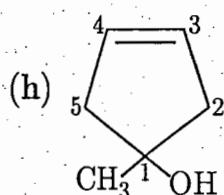
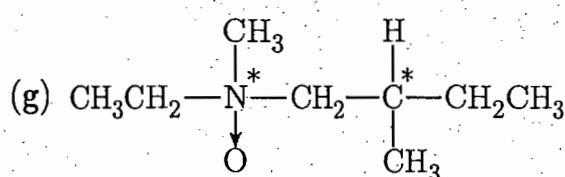
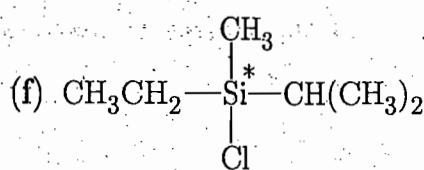
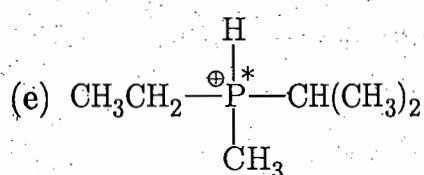
Ans. All planar molecules/ions must be achiral because the plane of the atoms is a plane of symmetry. The positive carbon of a carbocation uses sp^2 hybrid orbitals and has planar geometry. Hence, the C of a carbocation cannot be a chiral centre.

►1.21 Identify the chiral centre(s), if any, in each of the following compounds and indicate each of them with an asterisk :

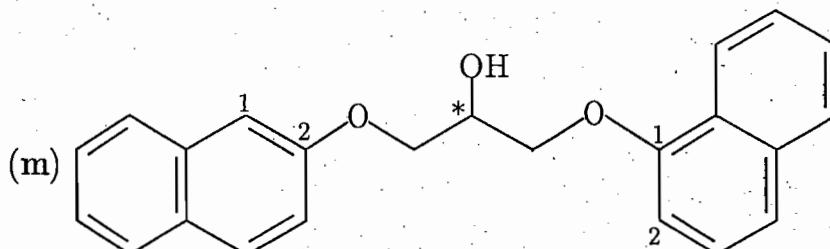
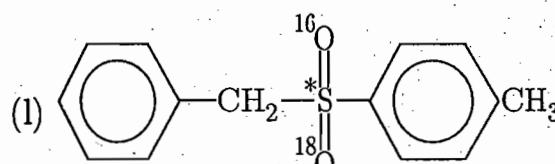
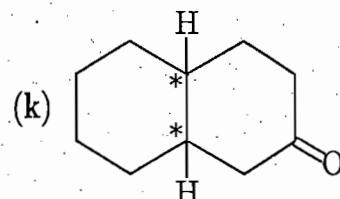
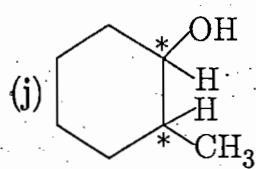
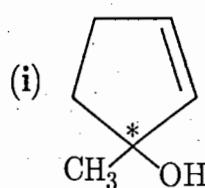


**Ans.**

There is no chiral centre in the molecule (two of the substituents at C-4 are the same).



There is no chiral centre in the molecule (two of the substituents at C-1 are the same).



(n) There is no chiral centre in the molecule (three of the substituents at each of the four bridge head carbons are identical).

►1.22 Classify the following objects as to whether they are chiral or achiral :

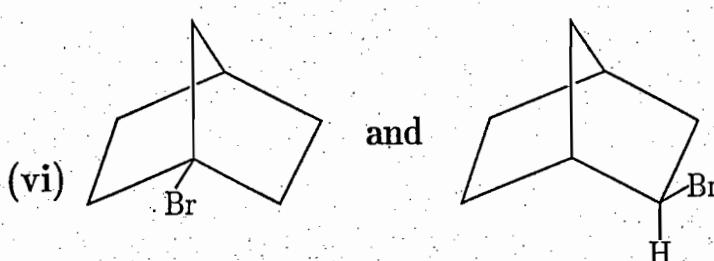
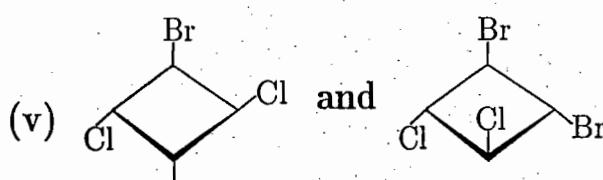
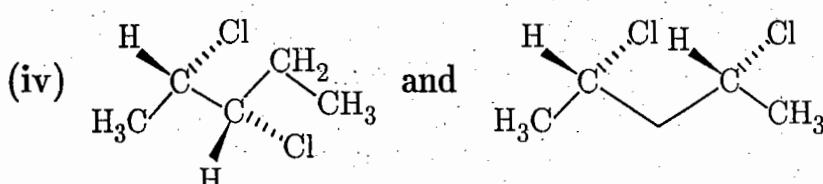
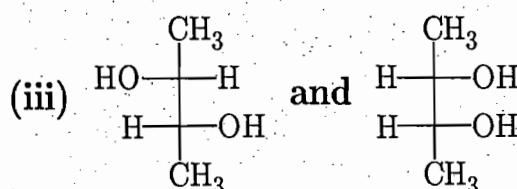
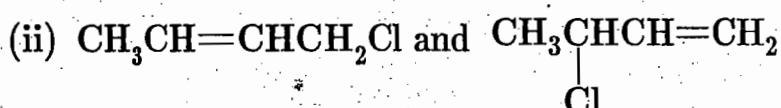
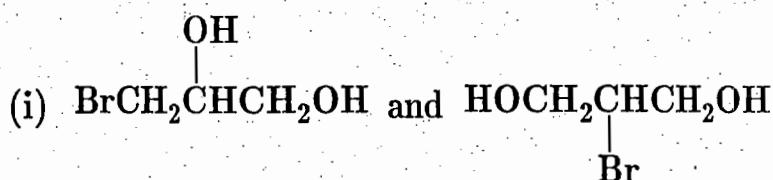
- (a) a cup (b) a screw (c) glove (d) ear (e) nose (f) a spiral staircase
- (g) shoe (h) a pullover sweater (i) a *p* orbital (j) alphabet S (k) a spool of thread
- (l) a five-pointed star (☆) (m) a bicycle (n) a nut
- (o) a bolt (p) a spoon (q) a scarf tied around your neck.

Ans. (a) achiral, (b) chiral, (c) chiral, (d) chiral, (e) achiral, (f) chiral, (g) chiral, (h) achiral, (i) achiral, (j) achiral, (k) chiral, (l) achiral, (m) chiral, (n) chiral, (o) chiral, (p) achiral, (q) chiral.

Each of the objects (a), (e), (h), (l) and (p) has a plane of symmetry, the object (j) has a centre of symmetry and the object (i) has both a plane and a centre of symmetry. So, all these objects are achiral. The objects (b), (c), (d), (f), (g), (k), (m), (n), (o) and (q) have no element of symmetry and so, they are chiral.

►1.23 (a) Which of the isomeric alcohols having the molecular formula $C_5H_{12}O$ are chiral? Which of them are achiral? Give reasons.

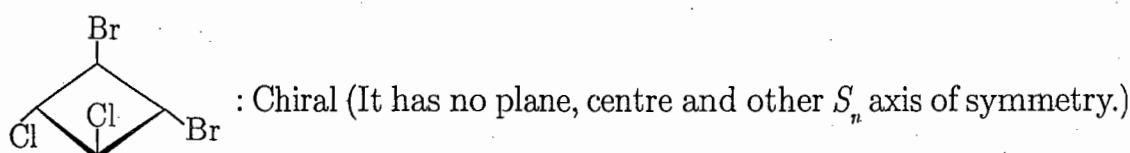
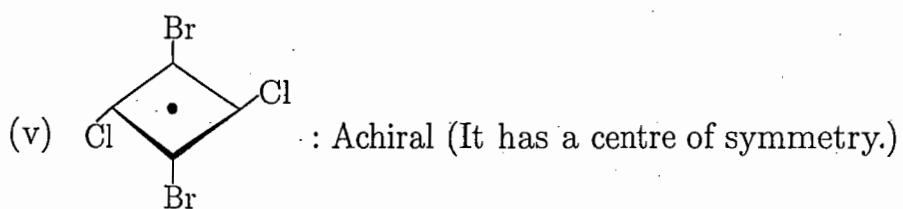
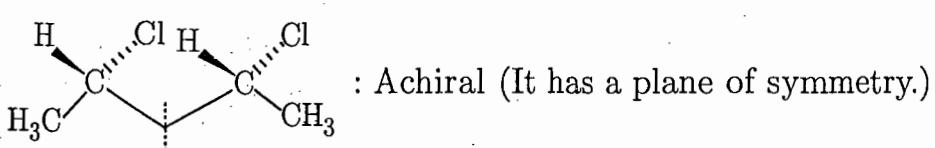
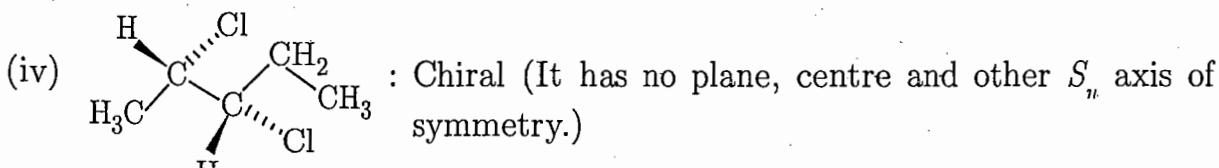
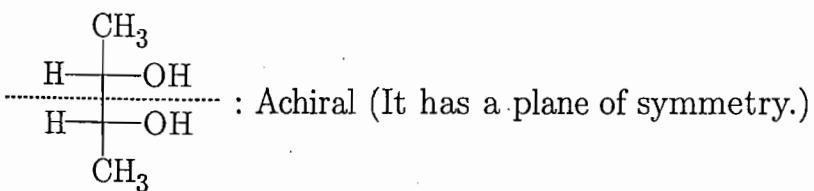
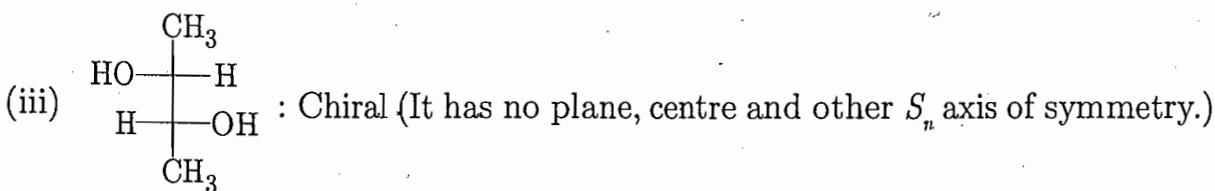
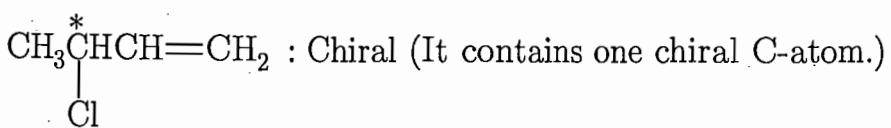
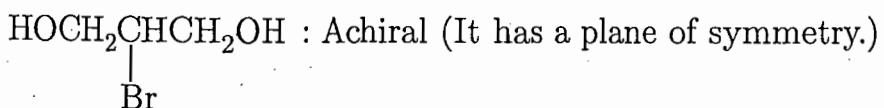
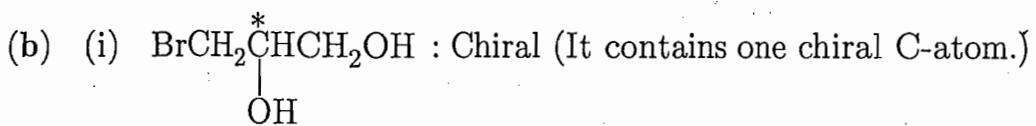
(b) In each of the following pairs of compounds one is chiral and the other is achiral. Identify each compound as chiral or achiral.

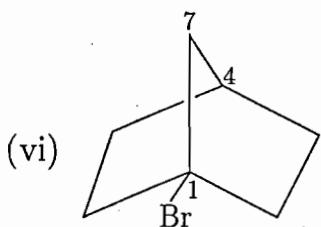


Ans. (a) The isomeric alcohols having the molecular formula $C_5H_{12}O$ are as

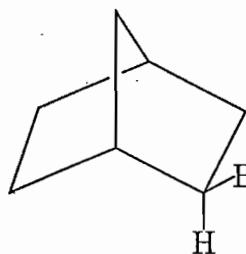
follows : $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$, $\text{CH}_3\text{CH}_2\text{CH}_2\overset{*}{\underset{\text{OH}}{\text{CH}}} \text{CH}_3$, $\text{CH}_3\text{CH}_2\overset{\text{OH}}{\underset{\text{CH}}{\text{CH}}} \text{CH}_2\text{CH}_3$,

Among these seven alcohols only three (II, IV and VII) are chiral because each of them contains one chiral carbon atom. Other alcohols (I, III, V and VI) are achiral because each of them has a plane of symmetry.





: Achiral (It has a plane of symmetry passing through C-1, C-4 and C-7)



: Chiral (It has no plane, centre and other S_n axis of symmetry)

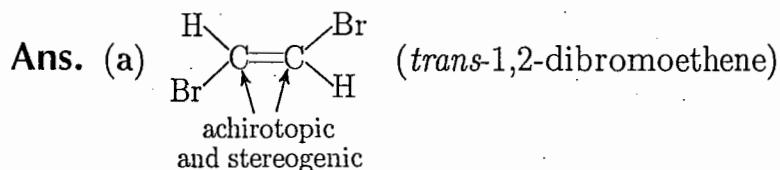
►1.24 What do you mean by a chirotopic and an achirotopic atom in a molecule?

Ans. The site symmetry of atoms in molecules may be classified as chiral and achiral. A chirotopic atom is one whose site symmetry is chiral, i.e., which resides in a chiral environment. All the atoms in a chiral molecule are chirotopic because chirality is an all-inclusive property, as it affects all parts of a chiral molecule. For example, all the five atoms in bromochlorofluoromethane (CHFClBr) are chirotopic. [The molecules bearing chirotopic atom or centre need not be as a whole chiral.]

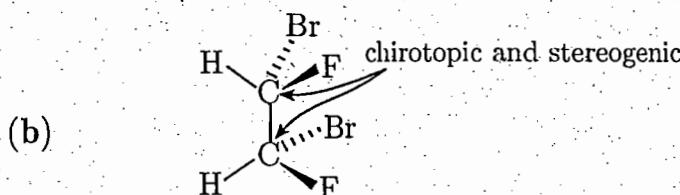
An achirotopic atom is one whose site symmetry is achiral, i.e., the atom lies on a σ -plane or on a centre of symmetry or an alternating axis of symmetry passes through it that intersects its reflection plane. For example, in bromochloromethane (CH_2ClBr) the carbon atom is achirotopic since a σ -plane passes through it.

►1.25 Designate the indicated centres of the following compounds as stereogenic/non-stereogenic or chirotopic/achirotopic. Give reasons.

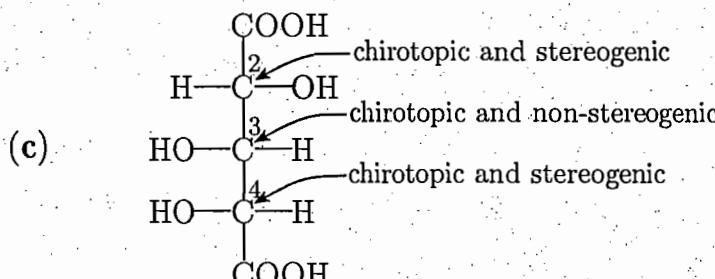
- (a) C atoms of *trans*-1,2-dibromoethene (b) C atoms of *meso*-1,2-dibromo-1,2-difluoroethane (c) C-2, C-3 and C-4 of active 2,3,4-trihydroxyglutaric acid (d) C-2, C-3 and C-4 of one *meso*-2,3,4-trihydroxyglutaric acid (e) the C-atom of bromochloroethane (f) the C-atom of bromochlorofluoromethane.



The carbon centres are achirotopic because they lie on the σ -plane (the molecular plane). They are stereogenic because interchange of ligands generates a new stereoisomer (diastereoisomer).

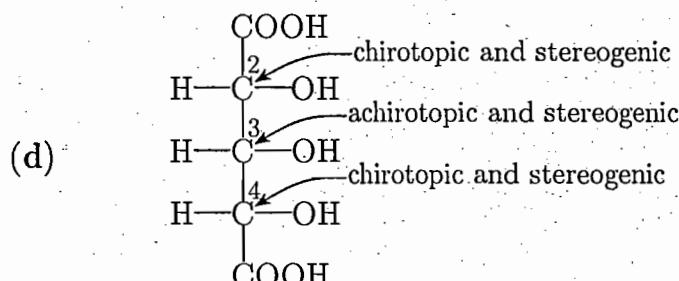


meso-1,2-Dibromo-1,2-difluoroethane



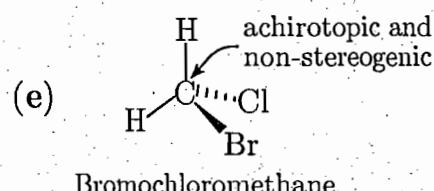
Active 2,3,4-trihydroxyglutaric acid

Since the molecule is chiral, the C-2, C-3 and C-4 atoms are chirotopic. Even though, C-2 and C-4 are stereogenic, C-3 is non-stereogenic because interchange of H and OH at this centre followed by 180° rotation keep the structure unchanged.



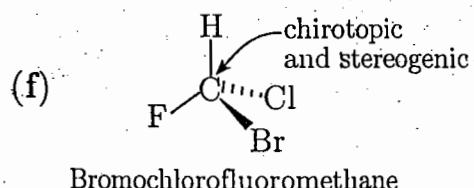
meso-2,3,4-Trihydroxyglutaric acid

C-2 and C-4 are chirotopic because they do not lie on a σ -plane or on a centre of symmetry or on alternating axis of symmetry passes through them that intersects its reflection plane and stereogenic because interchange of H and OH at these centres generates a new stereoisomer (diastereoisomer). Since C-3 resides in a σ -plane, it is achirotopic. However, it is stereogenic because interchange of H and OH at this centre generates a new stereoisomer (another *meso* diastereoisomer). [Such an achirotopic but stereogenic centre is called *pseudoasymmetric*.]



Bromochloromethane

The C-atom is achirotopic because it lies on the plane of symmetry. Again, it is non-stereogenic because interchange of two ligands does not produce a stereoisomer.

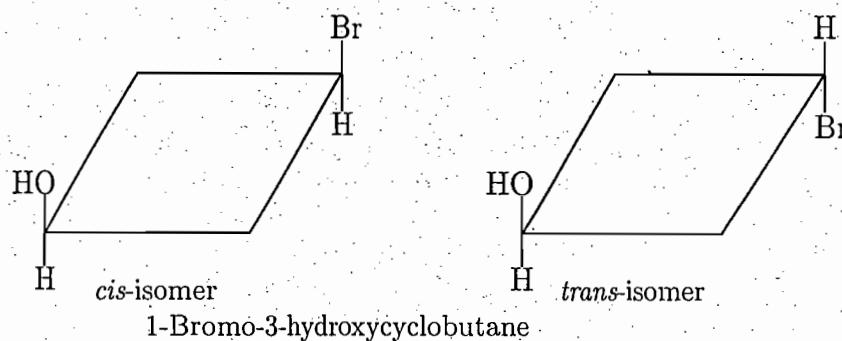


Bromochlorofluoromethane

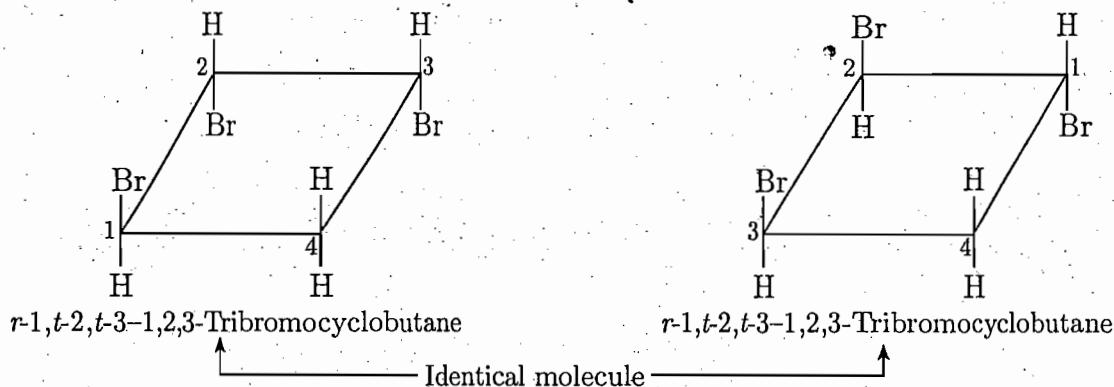
►1.26 Give an example of each of the following :

- A cyclic molecule having an achirotopic but stereogenic centre.
- A cyclic molecule having a chirotopic but non-stereogenic centre.

Ans. (a) 1,3-Disubstituted cyclobutanes having two equivalent or non-equivalent chiral centres exists only in two (diastereomeric) *meso* forms. The C-1 and C-3 centres in such compounds are achirotopic but stereogenic. For example, C-1 and C-3 of 1-bromo-3-hydroxybutane are achirotopic but stereogenic. They are achirotopic because a plane of symmetry passes through them. They are stereogenic because interchange of positions of H and OH on C-1 or H and Br on C-3 of one isomer produces the other.

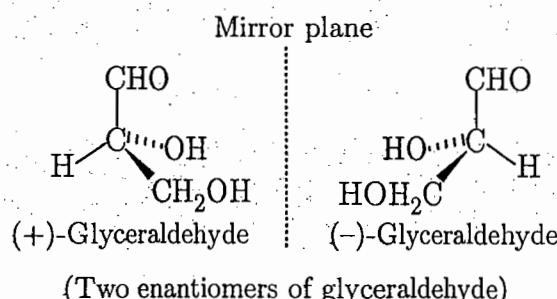


(b) In the following 1,2,3-tribromocyclobutane, C-2 is chirotopic but non-stereogenic. The molecule is chiral and therefore, C-2 is chirotopic. Interchange of positions of Br and H on C-2 does not produce a new stereoisomer. Therefore, C-2 is non-stereogenic.



►1.27 Define (a) enantiomers and (b) diastereoisomers. Give examples.

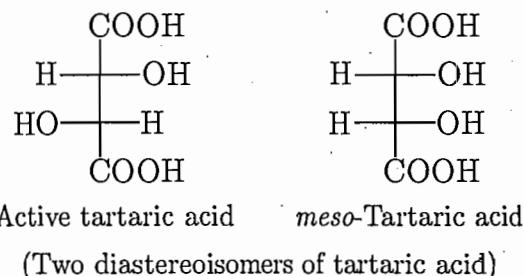
Ans. (a) Stereoisomers which are related to each other as non-superimposable mirror images are called enantiomers. For example, glyceraldehyde ($\text{HOCH}_2\text{CHOHCHO}$) has two stereoisomers having mirror image relationship, but one is not superimposable on the other. Therefore, they represent a pair of enantiomers.



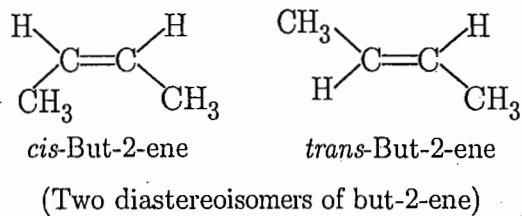
(Two enantiomers of glyceraldehyde)

[Enantiomers are also called enantiomorphs.]

(b) Stereoisomers which are not mirror images of each other are called diastereoisomers or diastereomers. For example, active tartaric acid and *meso*-tartaric acid represent a pair of diastereoisomers.

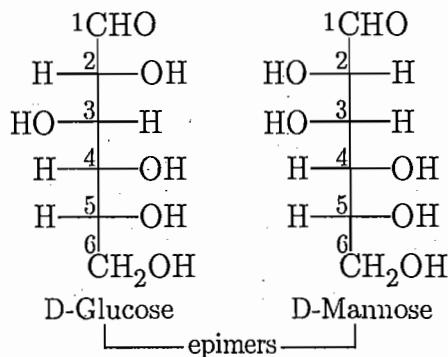


Similarly, *cis*-but-2-ene and *trans*-but-2-ene represent a pair of diastereoisomers.

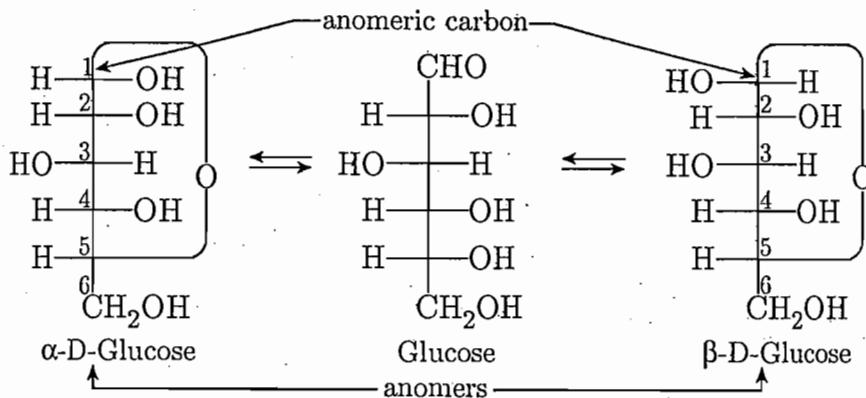


►1.28 What are epimers and anomers? Give examples.

Ans. Two diastereoisomers which differ in the configuration of a single chiral centre are called epimers. For example, D-glucose and D-mannose (two aldohexoses) are epimers because they differ only in the configuration about C-2.



Glucose (and other aldohexoses/ketohexoses) exists as an equilibrium mixture with their cyclic hemiacetal isomers. On cyclisation, the carbonyl carbon atom becomes a new stereocentre. Thus, there are two cyclic forms of glucose which differ only in the stereochemistry at C-1, the hemiacetal or anomeric carbon atom. Such isomers are called anomers. Therefore, anomers are epimers that differ from each other in the configuration about the hemiacetal (hemiketal in the cases of ketoses) or anomeric carbon atom only.



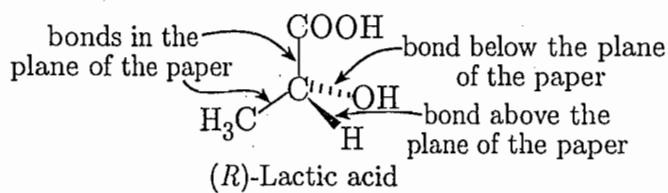
PROJECTION FORMULAS OF STEREOISOMERS

- 1.29 (a) What is meant by the term “Projection formula”? Name some important projection formulas that are used to represent stereoisomers. Illustrate these projection formulas with suitable examples.
 (b) What are the general rules for exchanging ligands or rotating Fischer projections. Illustrate with examples.

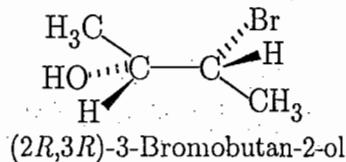
Ans. (a) Formulas used to represent molecules having three-dimensional structures on a two-dimensional surface (paper or blackboard) are called projection formulas.

The important projection formulas that are used to represent chiral or achiral molecule are (i) flying-wedge projection formula, (ii) Fischer projection formula, (iii) sawhorse projection formula, (iv) Newman projection formula, and (v) zigzag projection formula.

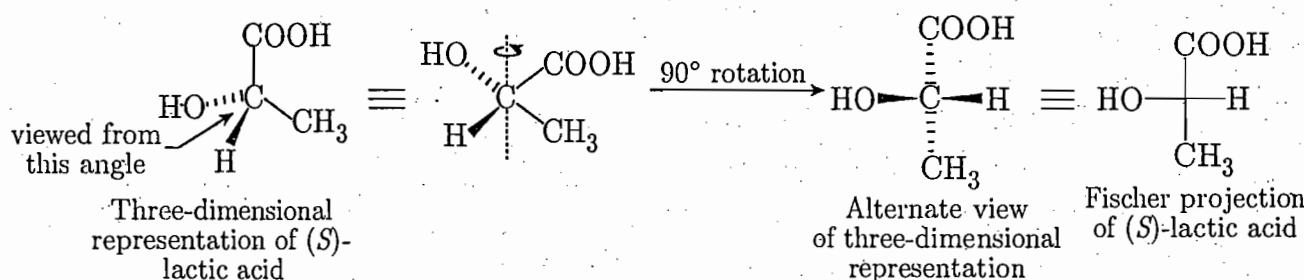
- (i) **Flying-wedge projection formula or three-dimensional representation :** The flying-wedge projection is the most common three-dimensional representation of a three-dimensional molecule on a two-dimensional surface. This kind of representation is usually done for molecules containing chiral centres. In this representation, the ordinary lines represent bonds in the plane of the paper, a solid wedge (---) represents a bond above the plane of the paper and a hashed wedge ($\cdots\cdots$) or a broken line ($\dots\dots$) represents a bond below the plane of the paper. The flying-wedge projection formula of (*R*)-lactic acid, for example, can be shown as follows.



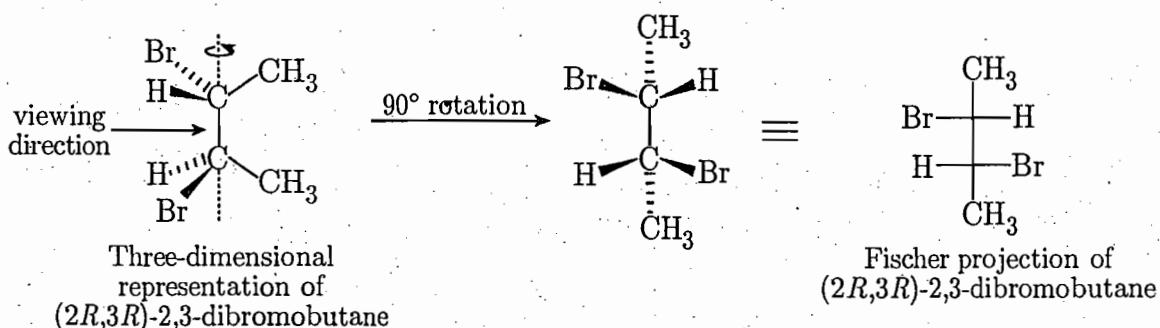
The flying-wedge projection of (*2R,3R*)-3-bromobutan-2-ol (with two chiral carbons) can be shown as follows.



(ii) **Fischer projection formula** : Structures for three-dimensional chiral molecules are sometimes represented with two-dimensional formulas. These two dimensional-formulas are called Fischer projection formulas. In this representation, the chiral carbon lies in the plane of the paper and the four bonds are shown by two vertical lines (which represent bonds projecting behind the plane of the paper, i.e., pointing away from the viewer) and two horizontal lines (which represent bonds projecting behind the plane of the paper, i.e., pointing towards the viewer). The asymmetric carbon (usually not drawn in) lies at the point of intersection of these lines. The Fischer projection, therefore, looks like a cross. To represent the three-dimensional structure of a molecule, for example, (*S*)-lactic acid, in a Fischer projection, the asymmetric carbon is viewed in such a way that the two of the bonds to this carbon are vertical and pointing away from the viewer, and two are horizontal and pointing towards the viewer. When this view is projected on the plane, the Fischer projection of the molecule is obtained.



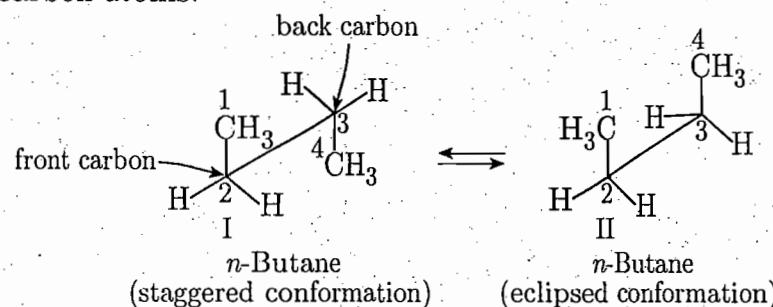
The most useful applications of Fischer projections involve molecules that contain two or more chiral carbons that are part of a carbon chain. In such cases, Fischer projections are drawn with the main carbon chain extending from top to bottom (usually with IUPAC numbering), i.e., along the vertical line with all groups eclipsed. For example, the Fischer projection formula for (*2R,3R*)-2,3-dibromobutane may be drawn as follows.



Fischer projections are not normally used to represent compounds without chiral centres.

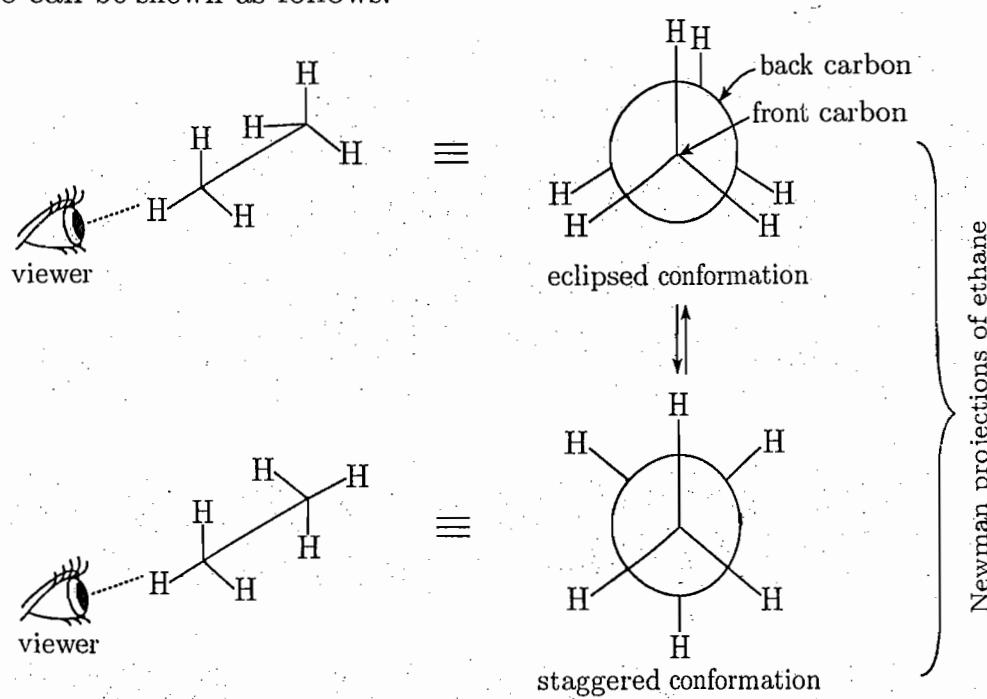
(iii) **Sawhorse projection formula** : The sawhorse projection formula provides a graphic three-dimensional perspective picture used to specify a conformation. This projection shows the spatial relationship between the substituents attached to two adjacent carbon atoms (chiral or achiral). In this representation, the bond between the two carbon atoms is drawn diagonally and is slightly elongated. The remaining bonds are shown by small lines. The molecule is viewed from slightly

above and to the right of the C—C bond. There is free rotation about the C—C bond and the three groups attached to one carbon may be rotated clockwise or counterclockwise in relation to the three groups attached to the other carbon atom. For example, *n*-butane ($\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3$) can be represented by the following sawhorse projections when C-2 and C-3 carbon atoms are taken as the two key carbon atoms.

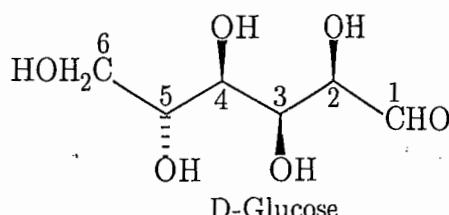


Both I and II represent two conformations of *n*-butane among the infinite number of possible conformations. The conformation I in which the groups on C-2 and C-3 are oriented as far away from each other as possible is known as the *staggered conformation* and the conformation II in which the groups on C-2 and C-3 are nearest is known as the *eclipsed conformation*. One sawhorse projection can be transformed into another simply by rotating one of the two key carbon atoms. However, the configuration of that carbon (if chiral) does not change by this operation.

- (iv) **Newman projection formula :** Another common way to represent a conformation is by a Newman projection. This is also a perspective formula. In the Newman projection, the molecule is viewed along the bond joining the key carbon atoms. The front carbon atom is represented by a central point from which the remaining three bonds emerge (↙). The rear carbon atom is depicted by a circle with the remaining three bonds pointing out from it (○). The angle between any two of these bonds on each carbon is 120° . For example, the Newman projections of ethane can be shown as follows:

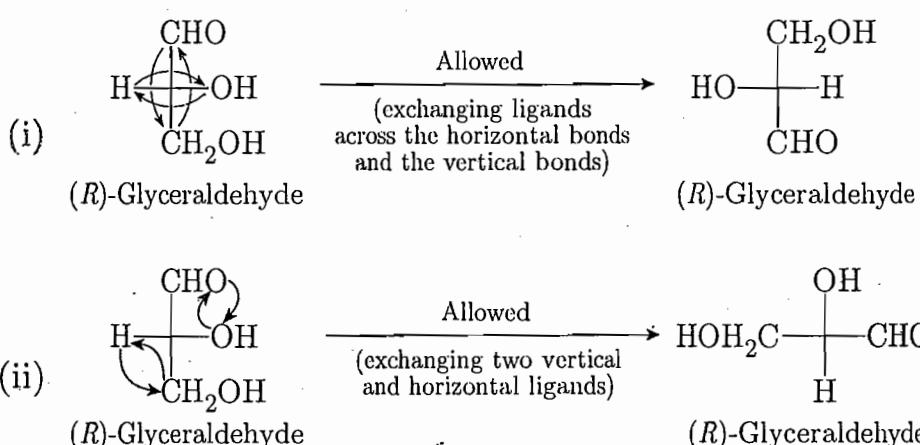


(v) **Zigzag projection formula :** Zigzag projections are generally used to represent compounds containing two or more chiral centres. The projection is shown in staggered conformation and the carbon-backbone of the molecule is placed in the plain of the paper. Bonds above or below the plain are shown by solid wedge and hashed wedge (or broken line) respectively. Zigzag formulas are used only for chiral centres bearing H atom as one of the substituents. This H atom is not drawn in the projection formula. The zigzag projection of D-glucose, for example, may be shown as follows.

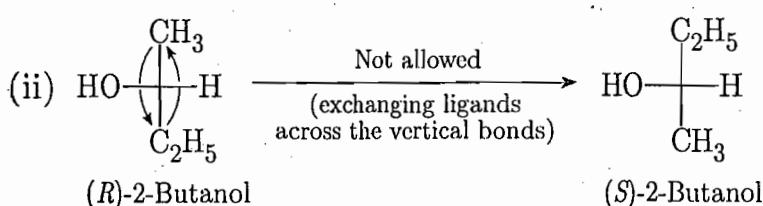
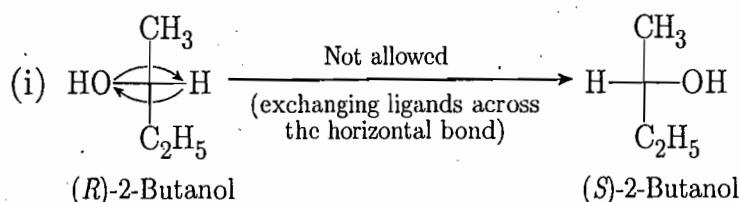


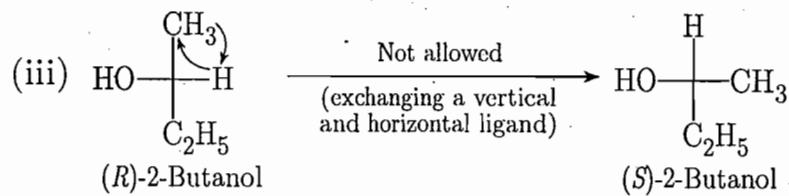
(b) The general rules for exchanging ligands or rotating Fischer structures are as follows :

(I) An even number of switches results in no change in the configuration of a molecule. Therefore, this operation is allowed. For example, no change in configuration of (*R*)-glyceraldehyde results when two switches are made.

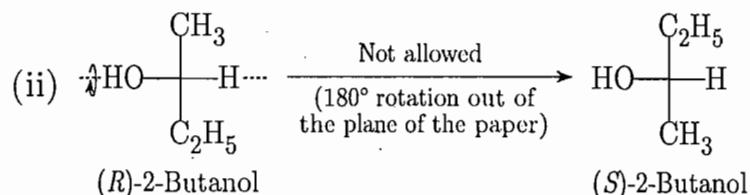
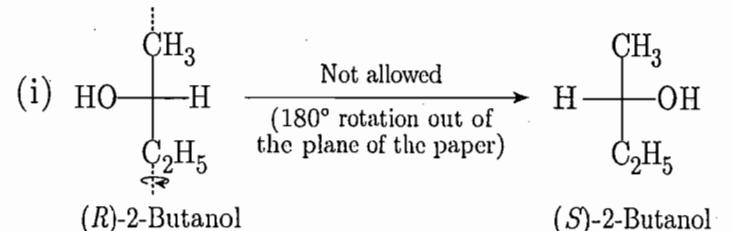


(II) An odd number of switches changes the configuration to that of the enantiomer of the molecule. Therefore, this operation is not allowed. For example, (*R*)-2-butanol becomes (*S*)-2-butanol when only one switch is made.

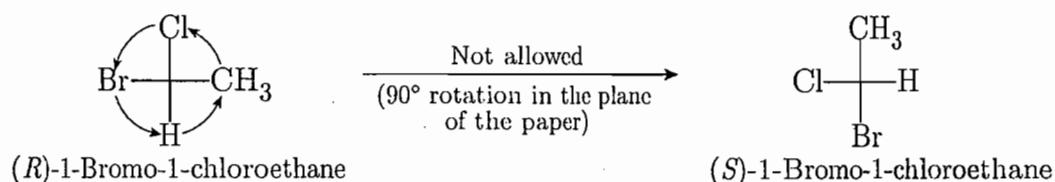




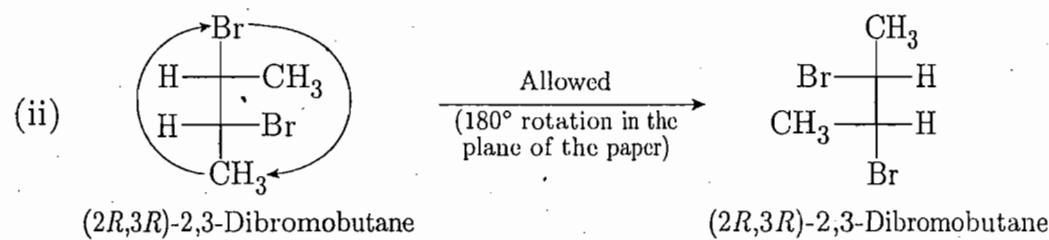
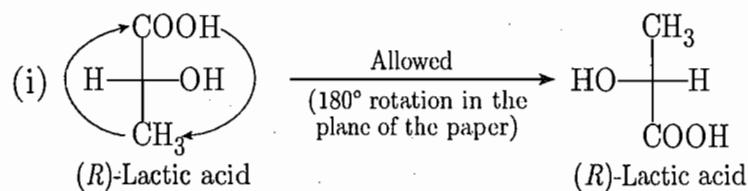
- (III) A 180° horizontal or vertical rotation outside of the plane of the paper changes the configuration to that of the enantiomer. Therefore, this operation is not allowed. For example :



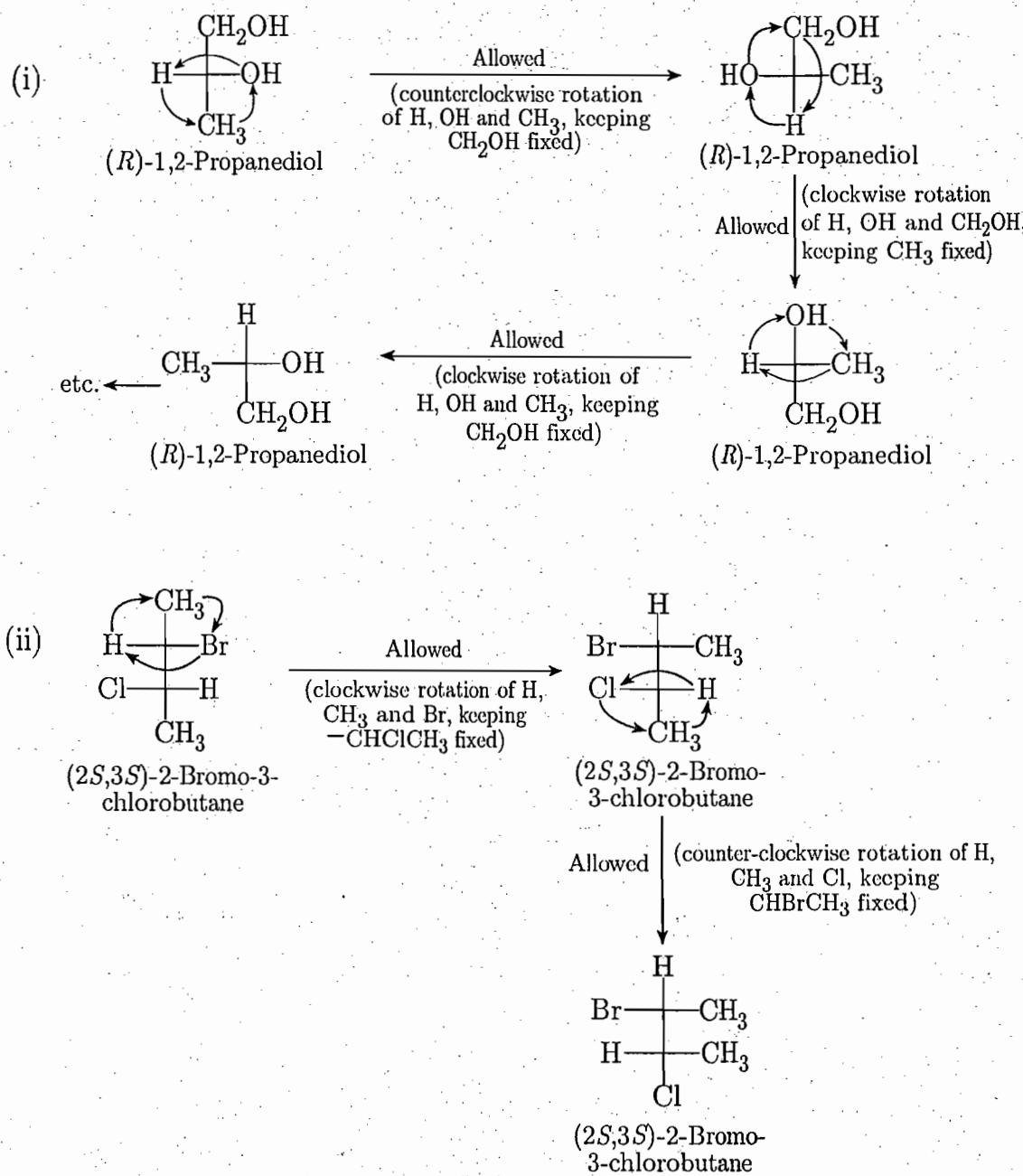
- (IV) A Fischer projection cannot be rotated 90° or 270° in the plane of the paper. This operation is not allowed because the "*horizontal lines forward, vertical lines back*" convention is not maintained and as a result, the original structure is converted into its enantiomer. For example :



- (V) A Fischer projection can be rotated 180° in the plane of the paper. This operation is allowed because the "*horizontal lines forward, vertical lines back*" convention is maintained and as a result, there occurs no change in configuration.



(VI) The operation involving clockwise or counterclockwise rotation of any three groups is allowed because it does not change the configuration. For example :



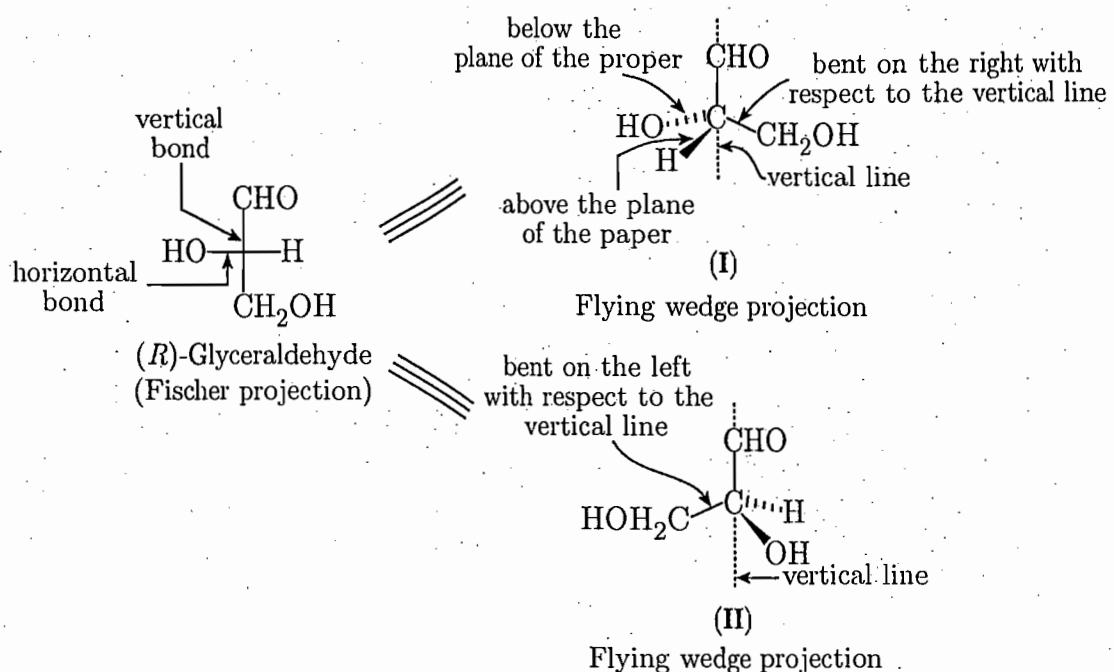
►1.30 (a) Show how the following interconversions may be carried out :

- Fischer projection to flying wedge projection and vice-versa
 - Fischer projection to sawhorse projection and vice versa
 - Sawhorse projection to Newman projection and vice-versa
- (b) Draw the *threo*-enantiomer of a 3-bromobutan-2-ol as indicated below :

flying wedge (staggered form) → Fischer → sawhorse → Newman

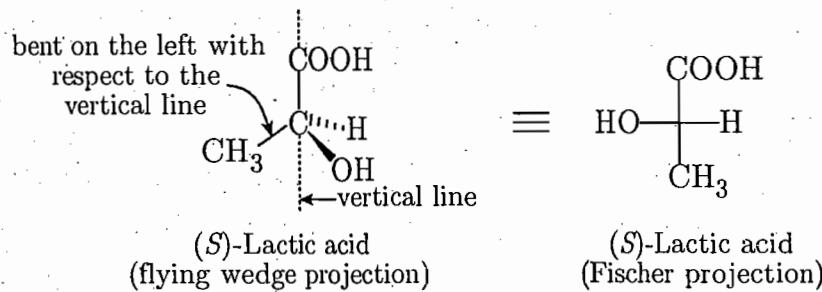
Ans.

- (a) (i) *Fischer projection to flying wedge projection and vice-versa* : This interconversion may be carried out as follows.



In the above example Fischer projection of (*R*)-glyceraldehyde is converted into flying wedge projections (I and II). In this conversion, vertical bonds in Fischer projection are to be placed in the plane of the paper and horizontal bonds are to be placed above and below the plane. If the lower vertical bond in Fischer projection is bent on the right side with respect to the vertical line (as in I), the group on the right side in the horizontal bond in Fischer projection is to be placed above the plane of the paper (represented by solid wedge, —), and the group on the left side is to be placed below the plane (represented by hashed wedge,). Again, if the lower vertical bond in Fischer projection is bent on the left side with respect to the vertical line (as in II), the group on the left side in the horizontal bond in Fischer projection is to be placed above the plane of the paper and the group on the right side is to be placed below the plane.

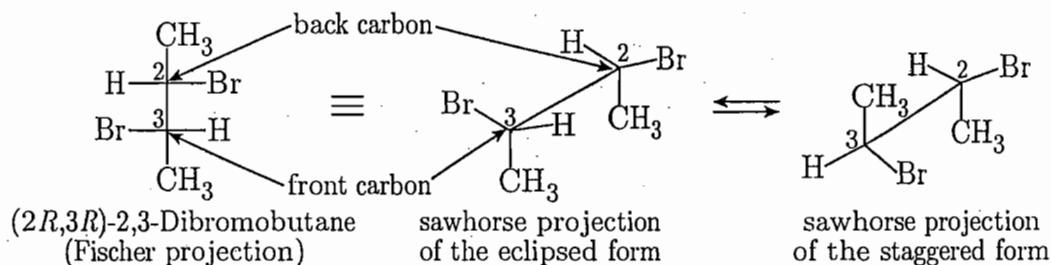
The reverse method is to be followed for converting a flying wedge projection to Fischer projection. For example :



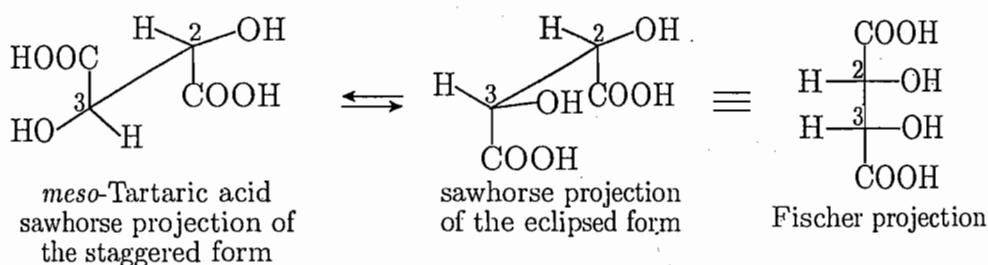
In this flying wedge projection of (*S*)-lactic acid, —COOH and —CH₃ groups are in the plane of the paper. Since the —CH₃ group is bent on the left side with respect to the vertical line, the —OH group, which is above the plane

of the paper is written on the left in horizontal bond in Fischer projection and the H atom which is below the plane is written on the right.

- (ii) *Fischer projection to sawhorse projection and vice-versa* : This interconversion may be carried out as follows.

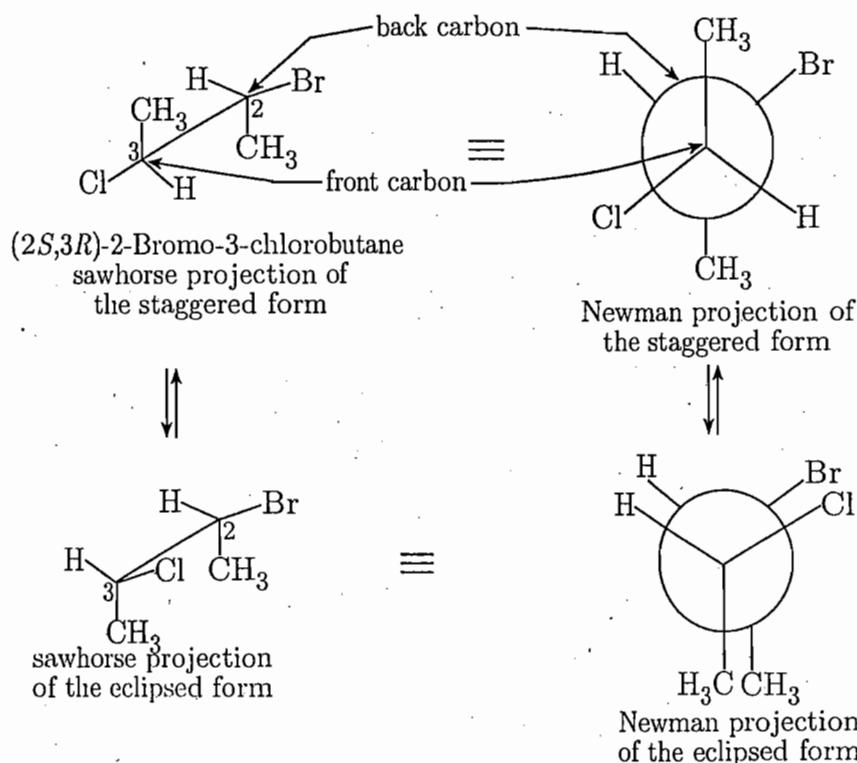


In the above example, Fischer projection of (2*R*,3*R*)-2,3-dibromobutane is converted into the eclipsed form of sawhorse projection. In this conversion the last chiral centre in Fischer projection (counting from the top) is considered as the front carbon in sawhorse projection.



In the above example, sawhorse projection of meso-tartaric acid is converted into Fischer projection through the eclipsed form. The front carbon becomes the last chiral centre in Fischer projection (counting from the top).

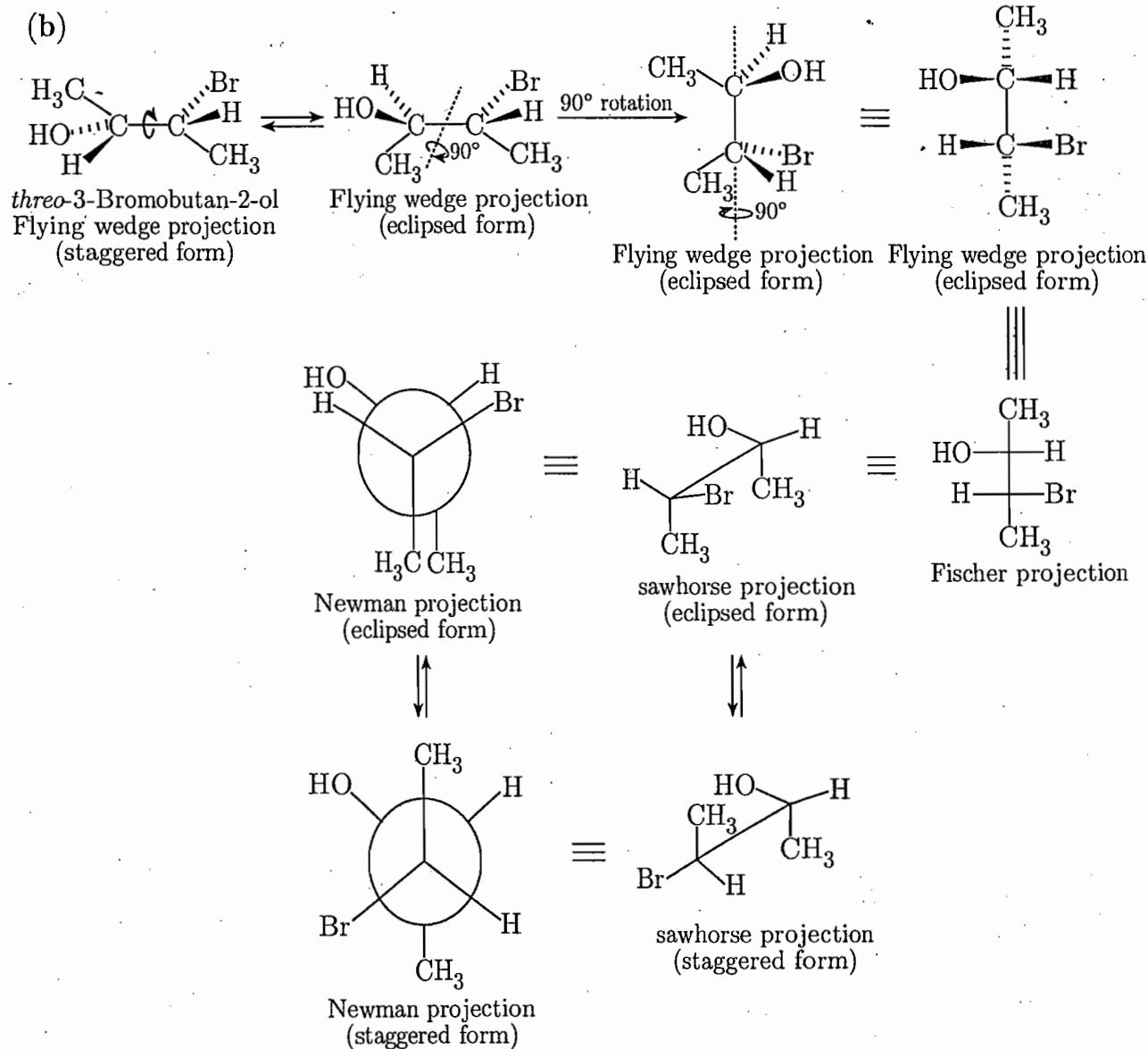
- (iii) *Sawhorse projection to Newman projection and vice-versa* : This interconversion may be carried out as follows.



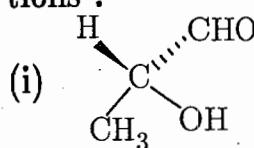
In the above example, sawhorse projection (staggered and eclipsed form) of (*2S,3R*)-2-bromo-3-chlorobutane is converted into Newman projection (staggered and eclipsed form). The front and back carbon in sawhorse projection become the front and back carbon respectively in Newman projection. Bonds attached to each key carbon are placed accordingly.

The reverse method may be followed to convert a Newman projection to sawhorse projection.

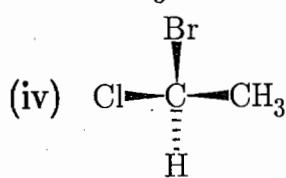
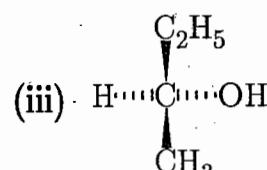
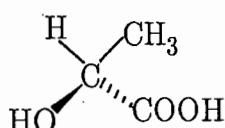
(b)



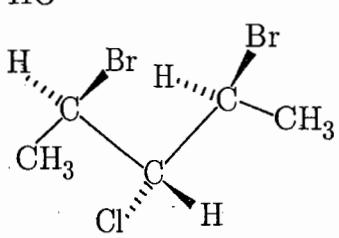
►1.31 (a) Convert the following flying wedge projections into Fischer projections :



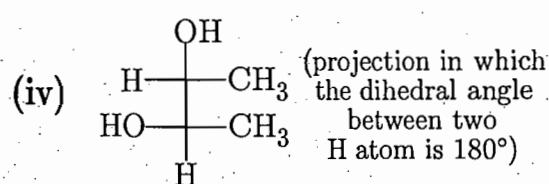
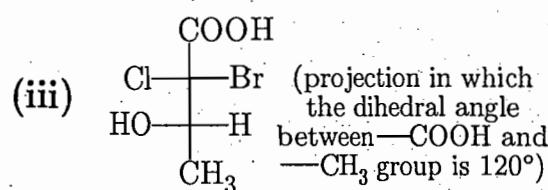
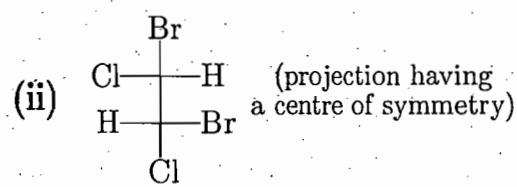
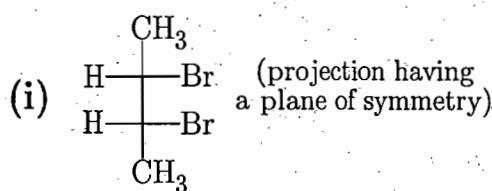
(ii)



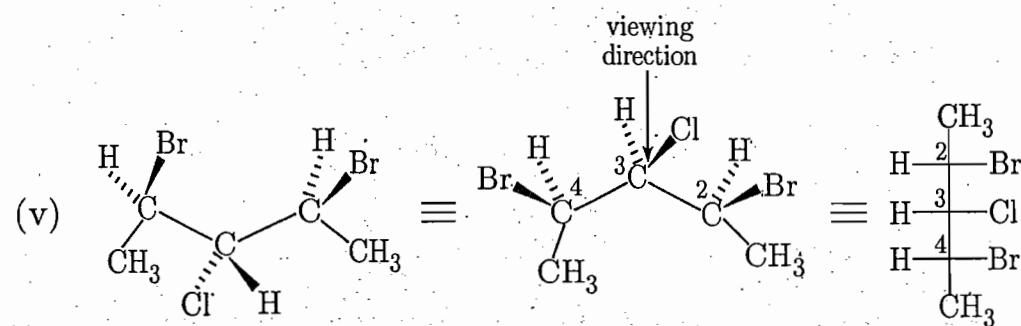
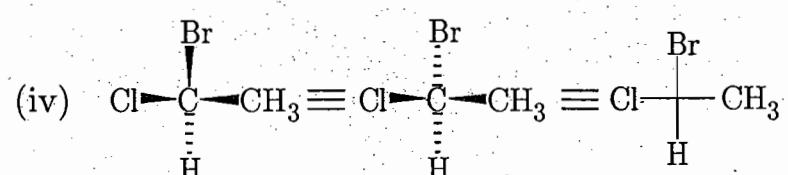
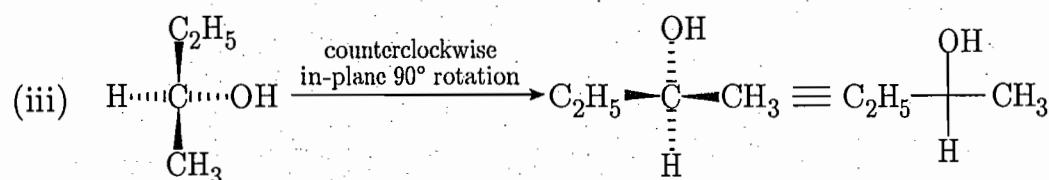
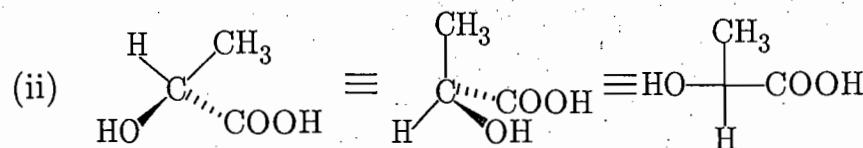
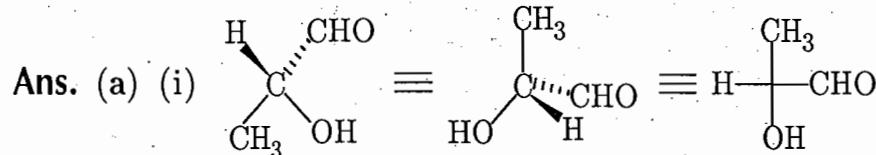
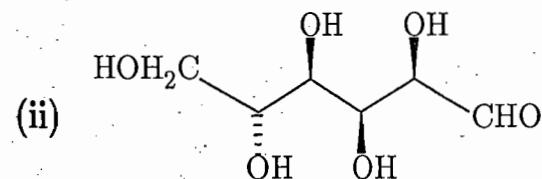
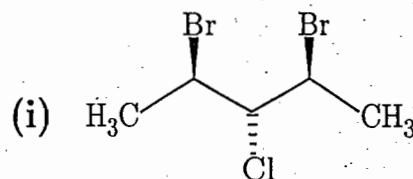
(v)

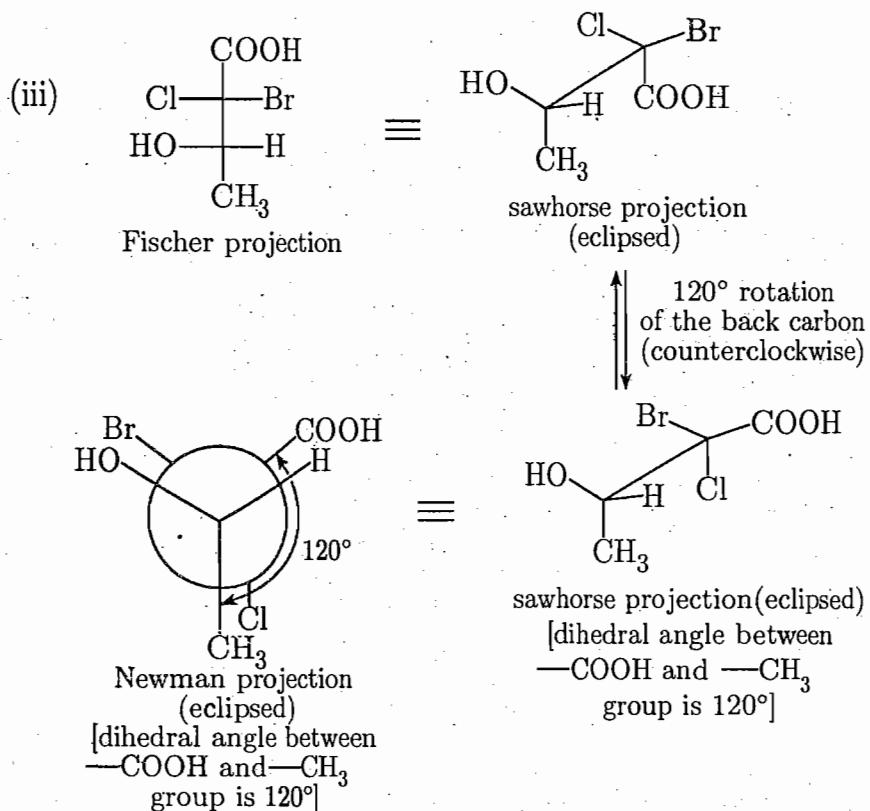
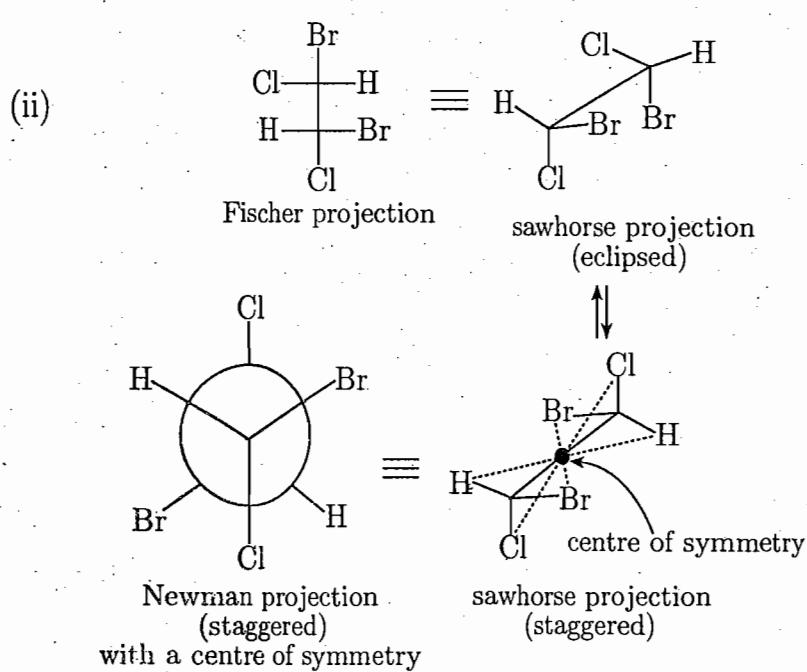
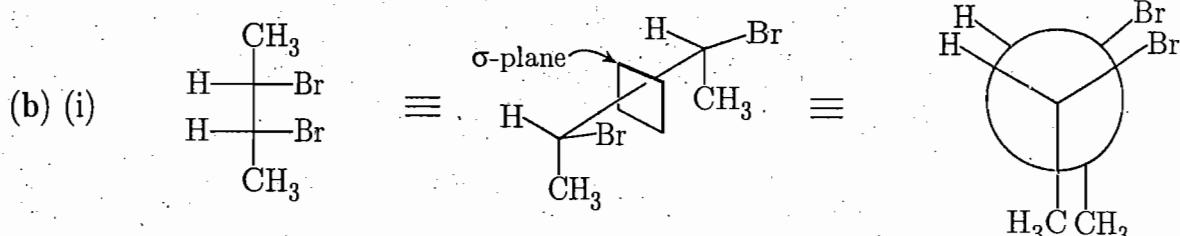


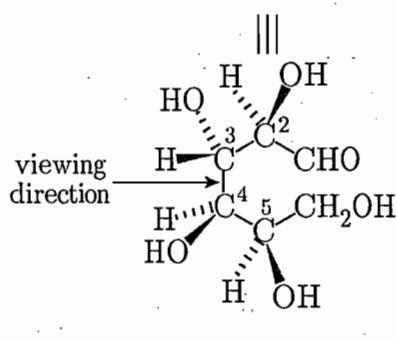
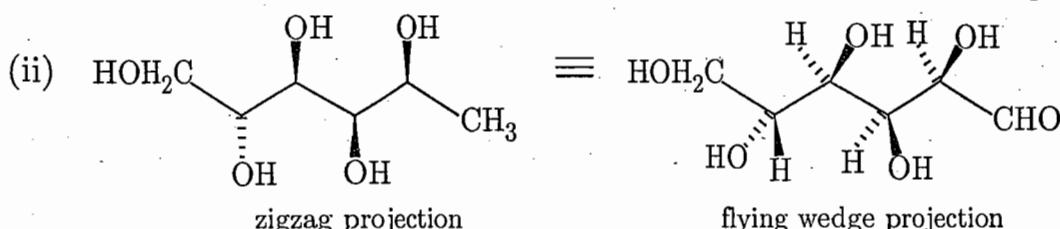
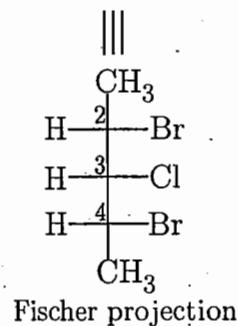
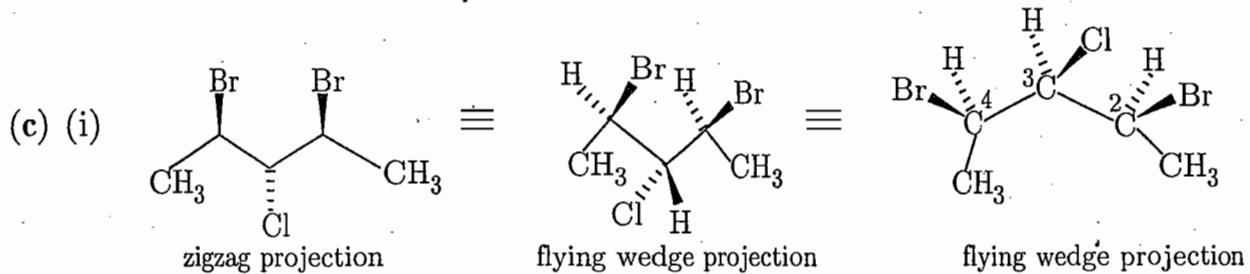
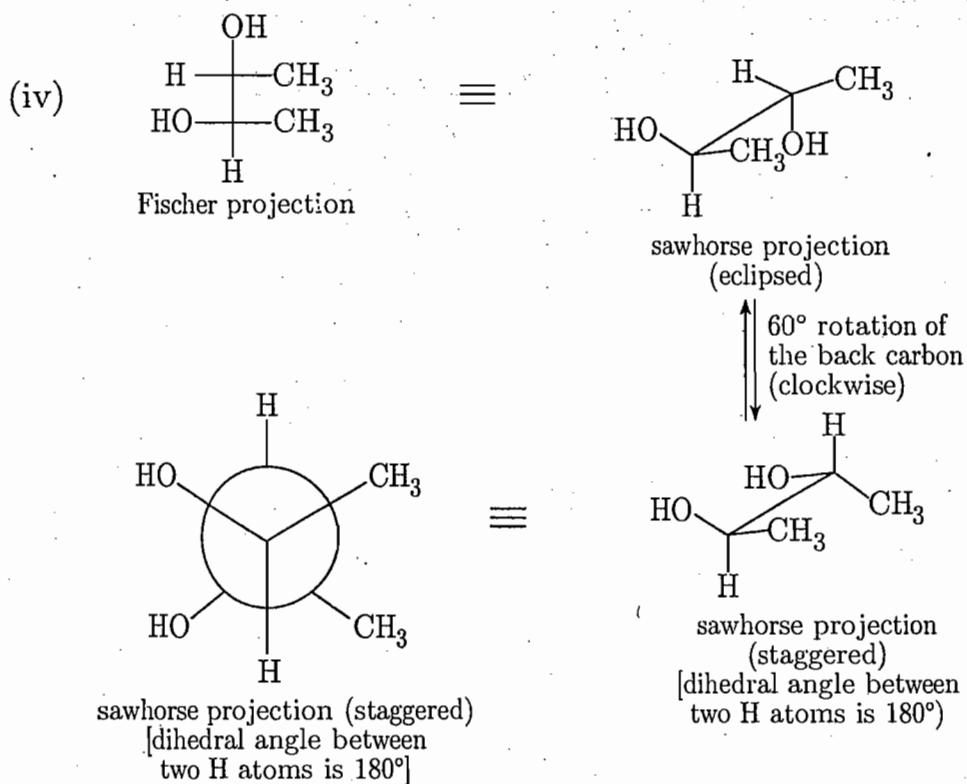
(b) Convert the following Fischer projections into sawhorse and Newman projections as directed :



(c) Convert the following zigzag projections to Fischer projections :



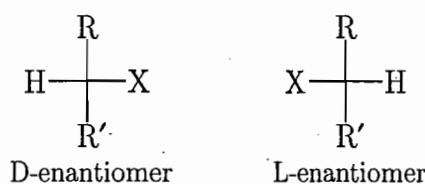




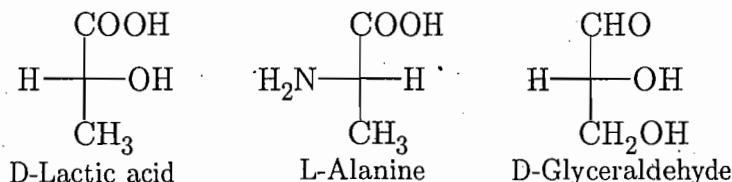
**CONFIGURATIONAL NOMENCLATURE
(R/S, E/Z, threo/erythro, etc.)**

- 1.32 (a) Discuss D,L-system of stereochemical nomenclature.
 (b) Are D,L-symbols related to the sign of rotation of the optically active compounds?

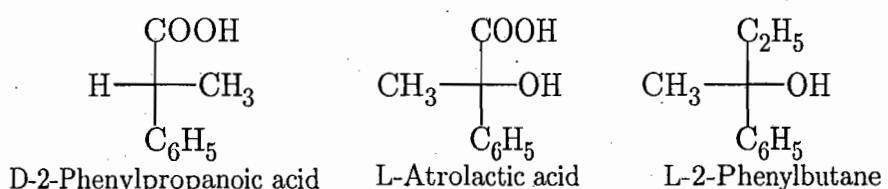
Ans. (a) In D,L-system of stereochemical nomenclature, the molecule of the type RCHXR' is written in Fischer projection such that the carbon atom of the longest chain, R—C—R' are placed on the vertical line with C-1 (according to IUPAC system of nomenclature) at the top. Then, if X is on the right horizontal bond, the compound is designated as D and if X is on the left horizontal bond, it is called L (X is taken to be a negative group).



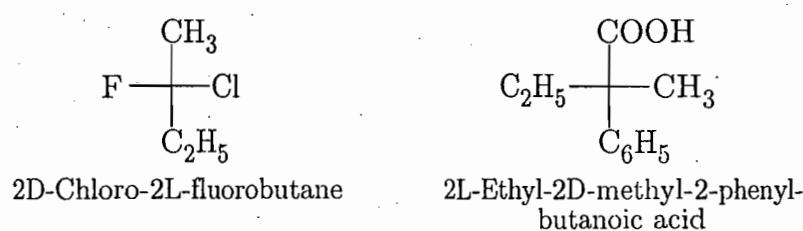
Examples :



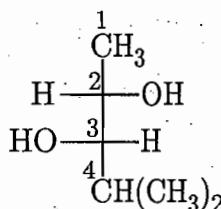
When the chiral centre contains a ring system, then the total number of C-atoms including the ring carbons are to be considered for writing the main chain in Fischer projection and for this, a Ph-group attached to a chiral centre is generally placed at the lower vertical bond in Fischer projection. For example :



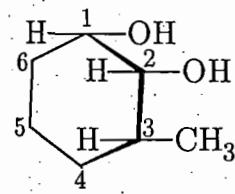
When the chiral centre contains two different ligands of comparable electronegativity, then D,L-symbols are separately used for each ligand to specify the configuration. For example :



D,L-designations to compounds containing more than one chiral centre involve specifying each of the chiral centres by D,L-notations. For example :

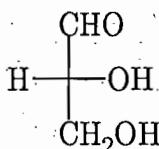


4-Methylpentane-2D,3L-diol

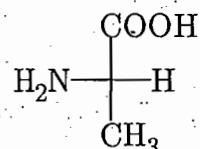


3D-Methylcyclohexane-1D,2D-diol

(b) The sign of rotation is a molecular property and it has no relation with D,L-symbols which indicate configuration of the compound. A dextrorotatory compound may be D or L. For example :



D-(+)-Glyceraldehyde



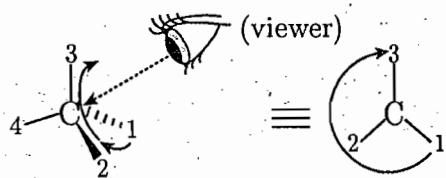
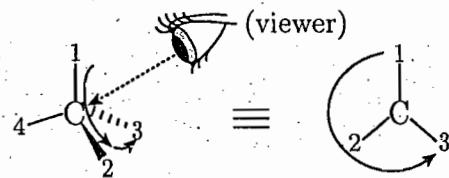
L-(+)-Alanine

►1.33 Discuss R,S-system or CIP system of assigning configurational nomenclature.

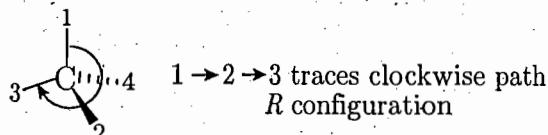
Ans. To overcome some drawbacks associated with the D,L-system of nomenclature, three chemists, R.S. Cahn, C. Ingold and V. Prelog (CIP) developed a new system to designate the configurations of stereoisomers having chiral centres. This system is commonly called CIP or R,S-system of configurational nomenclature and since this type of specifying configurations is independent of any reference compound, the system is often termed *Absolute configuration* assignment. In this system, configurations of stereoisomers are named on the basis of individual chiral centres. For assigning R or S descriptors to any chiral centre of a molecule, certain conventions are to be followed. These are as follows :

(a) The four different ligands attached to each of the chiral centres are identified and to each of the ligands a priority symbol 1,2,3,4 or a,b,c,d based on *sequence rules* is assigned, such that the decreasing order of priority is 1>2>3>4 or a>b>c>d (1 or 'a' having the highest priority and 4 or 'd' the lowest).

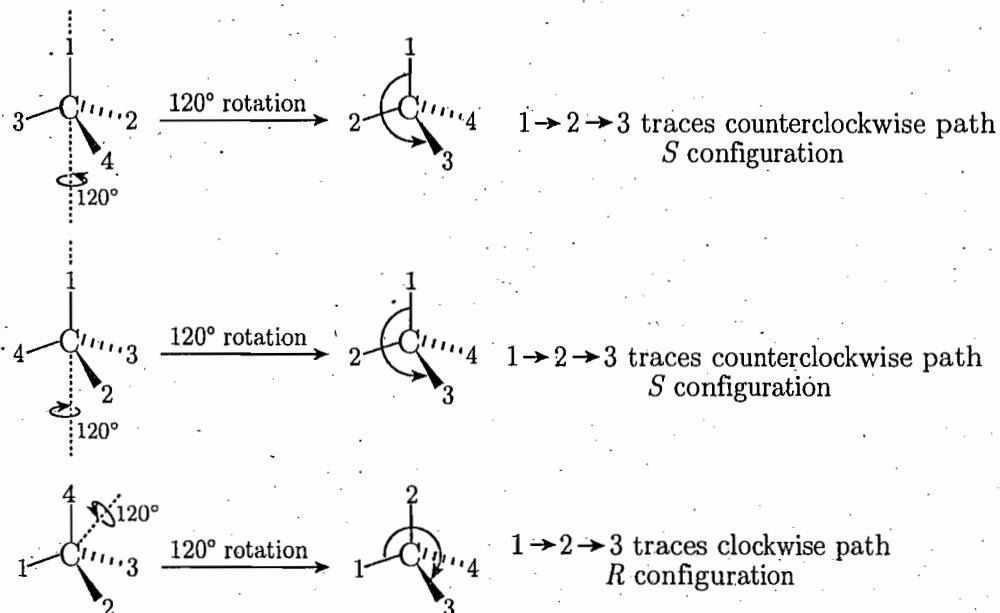
(b) The chiral centre is then viewed from the opposite side of the lowest priority ligand (4 or 'd') and a hypothetical path is traced from the first-priority ligand, through the second, to the third (1→2→3 or a→b→c). If the path describes a clockwise motion, then the stereocentre is said to have R configuration and if the path describes a counterclockwise motion, then the stereocentre is said to have S configuration. [R and S are from the latin words *rectus* and *sinister*, meaning right and left, respectively.] The designation (R)- or (S)- is written in *italics* within parentheses followed by a hyphen before the name of the compound (when necessary with appropriate locants).

1→2→3 traces clockwise path
R configuration1→2→3 traces anticlockwise path
S configuration

If the fourth-priority ligand in the figure is shown below the plane of the paper, the chiral carbon can be viewed directly from the side opposite to it and then, according to the sequence rules, if the tracing sequence of the ligands 1, 2 and 3 is clockwise, the configuration of the stereocentre is *R* and if the tracing sequence of the ligands 1, 2 and 3 is anticlockwise, the configuration is *S*.



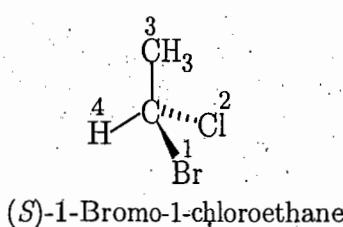
If in the figure, the ligand of lowest priority is shown above the plane of the paper or in the plane of the paper, the molecule is to be rotated by 120° about the axis passing through the central carbon and a ligand in the plane of the paper (or a group of three ligands are to be rotated either clockwise or anticlockwise or two pairs of ligands are to be interchanged) so as to get an orientation with the lowest priority ligand below the plane of the paper and then direct assignment gives the proper configurational descriptor.



CIP system has also been extended to chiral compounds that do not contain chiral atoms.]

Sequence rules or CIP chirality rules for the determination of the priority of ligands attached to a chiral centre :

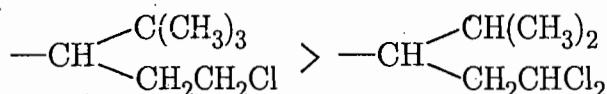
1. If the four atoms directly attached to the stereocentre are different, higher atomic number takes precedence over lower. For example, in 1-bromo-1-chloroethane (CH_3CHClBr) the chiral centre is attached to CH_3 , Br, Cl and H. the atomic numbers of atoms directly attached to the chiral centre suggest that the priority order should be $\text{Br} > \text{Cl} > \text{CH}_3 > \text{H}$ and accordingly the structure given has the *S* configuration.



2. In cases where two of the attached atoms are isotopes of each other, higher atomic mass has priority over lower. For example, a tritium atom (T) takes precedence over deuterium (D), which in turn takes precedence over ordinary hydrogen (H). However, $^{12}\text{CH}_2\text{NH}_2$ will get preference over $^{14}\text{CH}_2\text{CH}_3$ and this is because the atomic number of the second atom (N) in the former group is higher than that of the second atom in the latter group, even though the mass number of methylene carbon in the latter is greater than that in the former. Again, $-\text{CH}_2^{18}\text{OH}$ gets preference over $-\text{CD}_2^{16}\text{OH}$, although D is present in the latter group and this is because ^{18}O has higher atomic number as well as higher mass number. Similarly, $-\text{CH}_2\text{OH}$ gets preference over $-\text{CD}_2\text{NH}_2$.
3. When two or more atoms directly attached to the chiral centre are the same, i.e., if the priority remains undecided, then the atomic numbers of next sets of atoms are to be considered and the exploration is continued until a point of difference is reached. The priorities are then assigned at the first point of difference. For example, in 2-chlorobutane ($\text{CH}_3\text{CHClCH}_2\text{CH}_3$), the chlorine is assigned priority 1 and the hydrogen is assigned priority 4. The two remaining groups are $-\text{CH}_2\text{CH}_3$ and $-\text{CH}_3$. The first point of difference is at the two carbons attached to the stereocentre. The carbon of the methyl group, i.e., C-1 is attached to three hydrogen atoms i.e., to (H, H, H) while the first carbon atom of the ethyl group, i.e., C-3 is attached to one carbon and two hydrogen atoms, i.e., to (C, H, H). Since carbon has higher atomic number than hydrogen, ethyl ($-\text{C}_2\text{H}_5$) gets higher priority over methyl ($-\text{CH}_3$). Similarly, the group $-\text{CH}_2\text{CH}(\text{CH}_3)_3$ takes priority over $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ because at the first point of difference the carbon in isobutyl is attached to (C, C, H), whereas the analogous carbon in *n*-butyl is attached to (C, H, H).

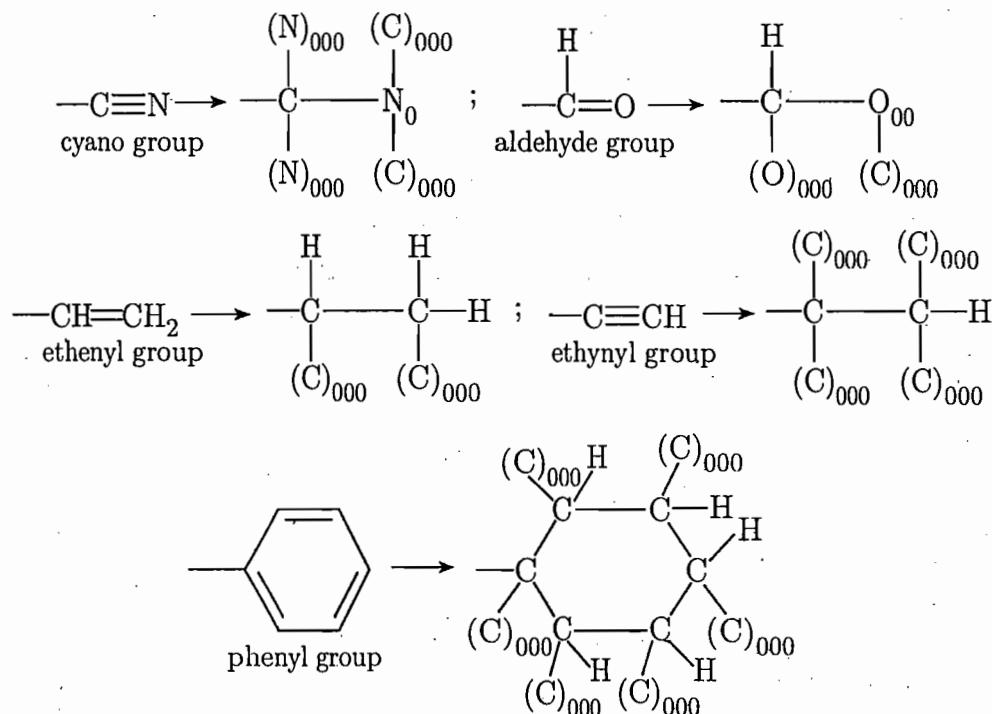
The priorities are also assigned at the first point of difference even if other differences exist further out the chain. For example, in 1,3-dibromo-4-methylpentane ($\text{BrCH}_2\text{CH}_2\text{CHBrCHMe}_2$), the priority order of the four ligands attached to the stereocentre is $\text{Br} > -\text{CH}(\text{CH}_3)_2 > -\text{CH}_2\text{CH}_2\text{Br} > \text{H}$. In this case, the isopropyl and 2-bromoethyl groups are ranked on the basis of the fact that at the first point of difference the carbon in isopropyl has two carbons and one hydrogen bonded to it, whereas the analogous carbon in 2-bromoethyl group has one carbon and two hydrogens bonded to it.

While searching for the first point of difference between two bifurcated groups, one should proceed along that branch which has higher priority atoms. For example, the priority sequence of the following two groups are determined by considering the branches $-\text{C}(\text{CH}_3)_3$ and $-\text{CH}(\text{CH}_3)_2$ respectively.



4. When multiply bonded substituents such as $\text{H}\text{C}=\text{O}$, $\text{CH}=\text{CH}_2$, $-\text{C}\equiv\text{N}$ etc. are present, both atoms attached to the multiple bond are treated as if they are duplicated or triplicated single bond. This pretreatment in order to assign priorities to groups containing multiple bonds is termed as 'replication'. The replicated

atoms are enclosed in parentheses in the expanded form of the substituent. All atoms except hydrogen are formally given a valency of 4. Where the actual valency is less (as in nitrogen, oxygen etc.), phantom atoms (designated by a subscript '0') are used to bring the valence up to four. These phantom atoms are assigned an atomic number of zero and necessarily rank lowest. For example :



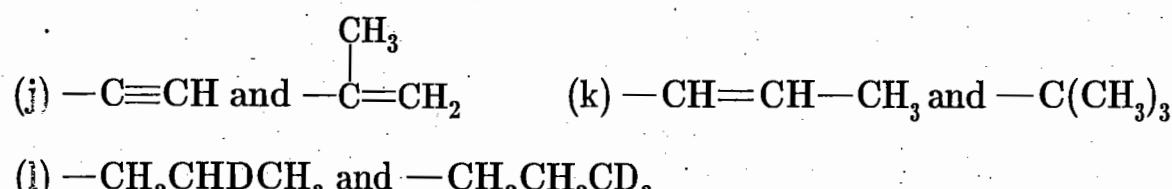
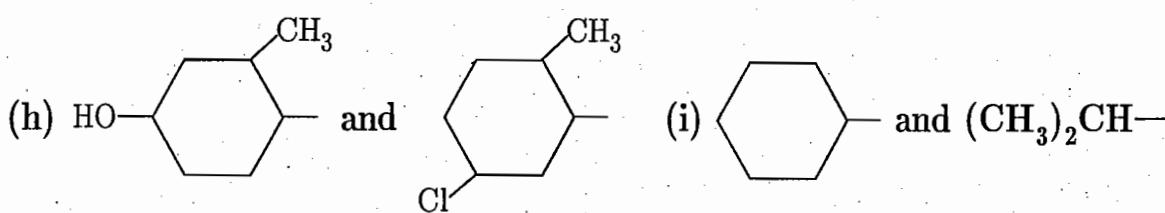
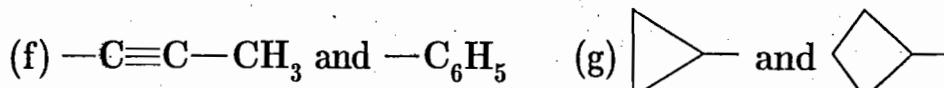
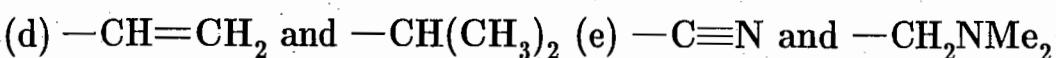
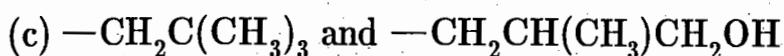
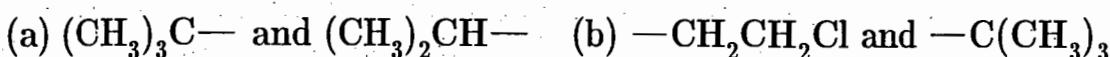
As an exercise, the four groups —CHO , —CH=CH_2 , $\text{—C}\equiv\text{CH}$ and —Ph may be compared. The first atoms are connected, respectively, to $(\text{H}, \text{O}, \text{O})$, $(\text{H}, \text{C}, \text{C})$, $(\text{C}, \text{C}, \text{C})$ and $(\text{C}, \text{C}, \text{C})$. Thus —CHO ranks first and —CH=CH_2 ranks last, since even one oxygen outranks three carbons and three carbons outrank two carbons and a hydrogen. To classify the remaining two groups one must proceed further along the chains. The phenyl group ($\text{—C}_6\text{H}_5$) has two of its $(\text{C}, \text{C}, \text{C})$ carbons attached to $(\text{C}, \text{C}, \text{H})$, while the third is attached to (H) and is thus preferred to $\text{—C}\equiv\text{CH}$, which has one of its $(\text{C}, \text{C}, \text{C})$ carbons connected to $(\text{C}, \text{C}, \text{H})$, while the other two are connected to (H) s.

5. When two enantiomeric substituents are present, the substituent with *R* configuration gets priority over the substituent with *S* configuration. Again (R, R) or (S, S) gets priority over (R, S) or (S, R) configuration.
6. When two substituents having *E* and *Z* configuration is present, then the *Z* substituent gets priority over the *E* substituent.

[A list of common substituents of increasing priority according to the above sequence rules, is given below :

I > Br > Cl > SO_3H > SO_3R > SOR > SR > SH > F > OCOR > OPh > OR > OH > NO_2 > NO > NHCOR > NR_2 > NHR > NH_2 > CX_3 (X = halogen) > COX > CO_2R > COOH > CONH₂ > COR > CHO > CR_2OH > $\text{CH}(\text{OH})\text{R}$ > CH_2OH > C≡CR > C_6H_5 > C≡CH > C(R)=CR₂ > CR₃ > CH=CH—R > CH=CH₂ > CHR₂ > $\text{CH}_2\text{C}_6\text{H}_5$ > $\text{CH}_2\text{C}\equiv\text{CH}$ > $\text{CH}_2\text{CH}=\text{CH}_2$ > CH_2CH_3 > CH_3 > D > H > (...) lone pair of electrons.]

► 1.34 Assign priorities to the following pairs of groups according to CIP rules :



Ans. (a) The priority sequence is : $-C(CH_3)_3 > -CH(CH_3)_2$.

The first point of difference is at the two carbons attached to the stereocentre. The first carbon atoms of the groups $-C(CH_3)_3$ and $-CH(CH_3)_2$ are attached to (C,C,C) and (C,C,H) respectively. Since C > H, $(CH_3)_3C-$ gets priority over $(CH_3)_2CH-$.

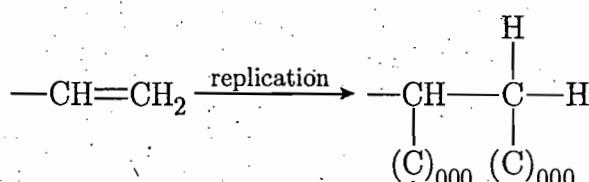
(b) The priority sequence is : $-C(CH_3)_3 > -CH_2CH_2Cl$.

The first point of difference is at the two carbons attached to the stereocentre. The first carbon (C_α) in $-C(CH_3)_3$ is attached to (C,C,C), whereas the first carbon in $-CH_2CH_2Cl$ is attached to (C,H,H). Since C > H, $(CH_3)_3C-$ gets priority over $-CH_2CH_2Cl$, even though C_β bears an atom (Cl) having higher atomic number.

(c) The priority sequence is : $-CH_2CMe_3 > -CH_2CHMeCH_2OH$.

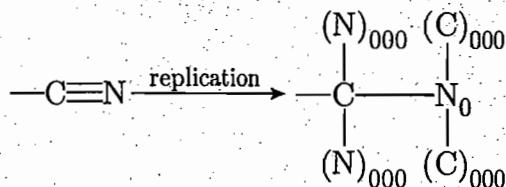
The first point of difference is at the carbons β to the chiral centre. The β -carbons of $-CH_2CMe_3$ and $-CH_2CHMeCH_2OH$ are attached to (C,C,C) and (C,C,H) respectively. Therefore, $-CH_2CMe_3$ gets priority over $-CH_2CHMeCH_2OH$, even though one C_γ bears an atom (O) having higher atomic number.

(d) The priority sequence is : $-CH=CH_2 > -CH(CH_3)_2$.



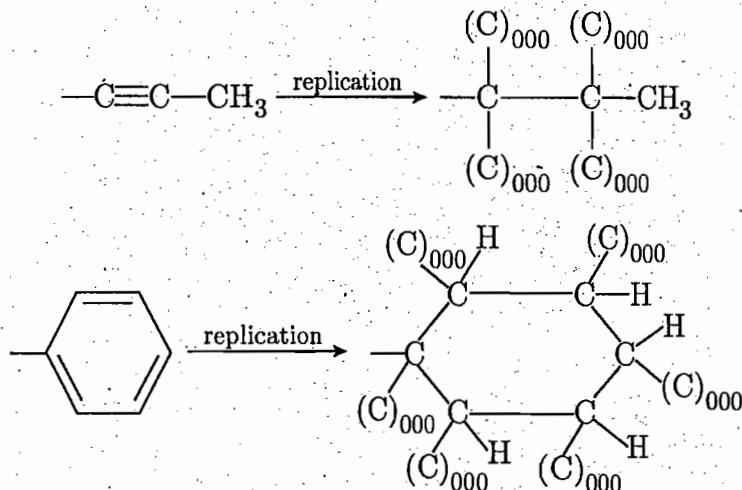
After replication of $-\text{CH}=\text{CH}_2$ group, it becomes clear that the first carbon atom in each of the group is attached to (C,C,H). One of this carbons in $-\text{CH}=\text{CH}_2$ is attached to (0,0,0) and the other to (C,H,H), but each of the β carbons in $-\text{CH}(\text{CH}_3)_2$ is attached to (H,H,H). Since C > H, $-\text{CH}=\text{CH}_2$ gets priority over $-\text{CH}(\text{CH}_3)_2$.

- (e) The priority sequence is : $-\text{C}\equiv\text{N} > -\text{CH}_2\text{NMe}_2$.



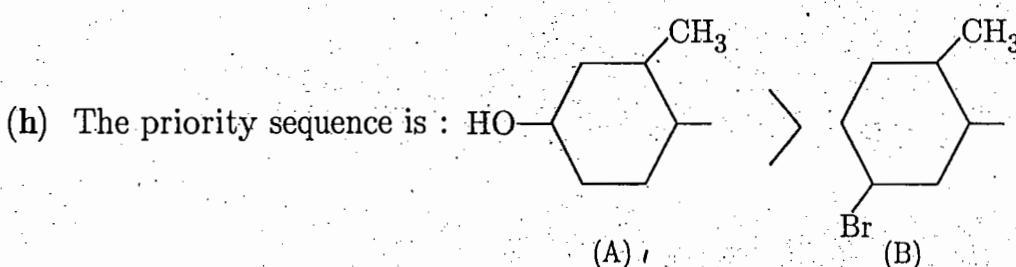
The first carbon atoms (i.e., the carbon atoms directly attached to the chiral centre) in $-\text{C}\equiv\text{N}$ and $-\text{CH}_2\text{NMe}_2$ are attached to (N,N,N) and (H,H,N) respectively. Since N > H, $-\text{C}\equiv\text{N}$ gets priority over $-\text{CH}_2\text{N}(\text{CH}_3)_2$.

- (f) The priority sequence is : $-\text{C}\equiv\text{C}-\text{CH}_3 > -\text{C}_6\text{H}_5$



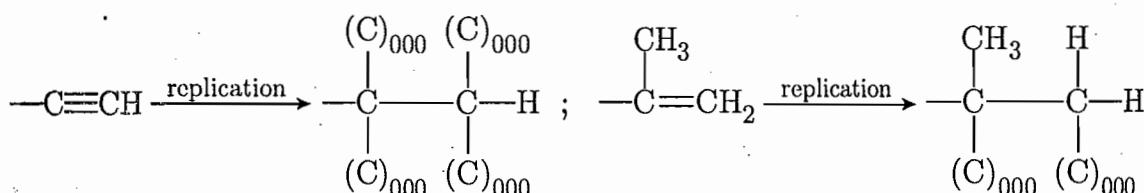
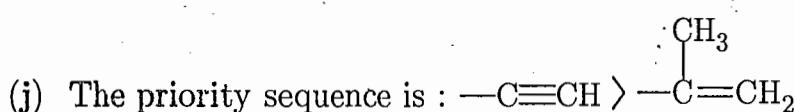
In each of the groups, the carbon directly attached to the chiral centre is attached to (C,C,C). 1-Propenyl ($-\text{C}\equiv\text{C}-\text{CH}_3$) has two of its (C,C,C) carbons connected to (0,0,0), while the third is (C,C,C) and is thus preferred to phenyl ($-\text{C}_6\text{H}_5$), which has only one (0,0,0) and two (C,C,H)s.

- (g) The priority sequence is : cyclopropyl (\blacktriangleright) > cyclobutyl (\blacktriangleleft). The first and second C atoms of the rings in both cyclopropyl and cyclobutyl are identical [both attached to (C,H,H)]. However, the third C atom of the cyclopropyl group is attached to (H,C and the atom of the chiral centre). On the other hand, the third carbon atom of the cyclobutyl group is attached to (C,H,H). Since the atom of the chiral centre > H, cyclopropyl (\blacktriangleright) gets priority over cyclobutyl (\blacktriangleleft).

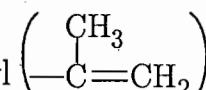


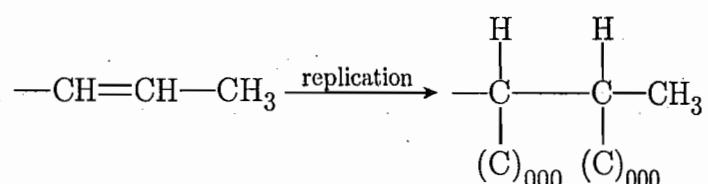
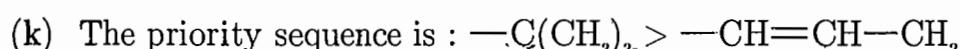
For determining the priority sequence, the senior chains (the chains containing the methyl group) of these two groups are to be considered. The third carbon of the senior chain of 4-hydroxy-2-methylcyclohexyl group (A) is attached to (C,H,O), whereas the third carbon of the senior chain of 5-bromo-2-methylcyclohexyl group (B) is attached to (C,H,H). Since O > H, the group A gets priority over the group B.

(i) The priority sequence is : cyclohexyl () > isopropyl (Me₂CH—). In each of these groups, the first carbon atom is connected to (C,C,H). Both of these carbons in cyclohexyl are connected to (C,H,H), whereas in isopropyl, they are connected to (H,H,H). Since C > H, cyclohexyl gets priority over isopropyl.

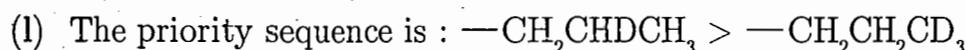


In each of these groups, the first carbon atom is connected to (C,C,C). In ethynyl (—C≡(H), two of these carbons are connected to (000) and one is connected to (C,C,H),

whereas in 1-methylethylene (, one of these carbons is connected to (000), one is connected to (H,H,H) and one is connected to (C,H,H). Since C > H, ethynyl gets priority over 1-methylethylene.

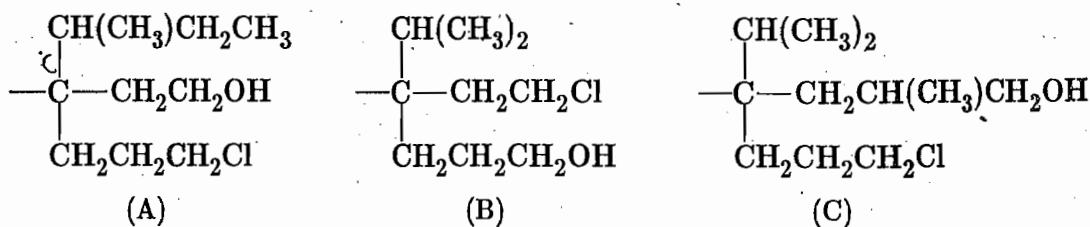


The first carbon atoms (the carbon attached to the stereocentre) of *t*-butyl (—CMe₃) and 1-propenyl (—CH=CHCH₃) are attached to (C,C,C) and (C,C,H) respectively. Since C > H, —C(CH₃)₃ gets priority over —CH=CH—CH₃.



The first point of difference is at the carbons β to the chiral centre. In CH₂CHDCH₃, C_β is attached to (C,D,H), whereas in —CH₂CH₂CD₃, C_β is attached to (C,H,H). Since D > H, —CH₂CHDCH₃ gets priority over —CH₂CH₂CD₃.

►1.35 Arrange the following groups in order of decreasing priority :



Ans. The priority sequence is : A > B > C.

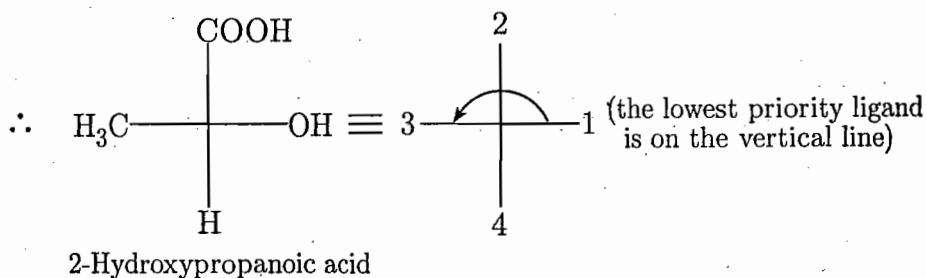
When the atoms attached to the first carbon of each branch are considered, —CHMeEt becomes the seniormost chain in (A) and —CHMe₂ becomes the seniormost chain in (B) and (C). Now, —CHMeEt gets priority over —CHMe₂. So, the highest priority group is (A). The second senior chains of (B) and (C) are —CH₂CH₂Cl and —CH₂CHMeCH₂OH respectively. Since —CH₂CH₂Cl gets priority over —CH₂CHMeCH₂OH, (B) gets priority over (C).

►1.36 Discuss procedures for assigning R,S-designation to stereocentres when a compound is represented by Fischer projection.

Ans. The procedure used to assign R,S-designation to stereocentres when a compound is written in Fischer projection involves two operations : (i) fixing up the priority order of the ligands and (ii) tracing a semicircle joining 1 → 2 → 3 or a → b → c ignoring '4' or 'd', the lowest priority group. When '4' or 'd' is on the vertical line in Fischer projection (no matter if it is at the top or at the bottom), the sequence gives the correct configurational descriptor. That is, if 1 → 2 → 3 or a → b → c traces a clockwise path, the configuration is R, but if the sequence traces an anticlockwise path, the configuration is S.

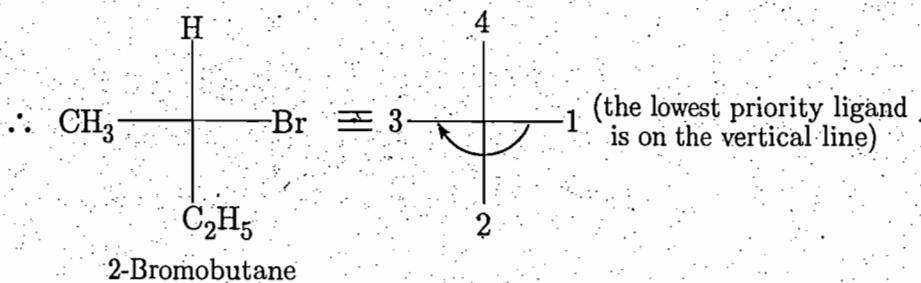
Example :

(a) According to sequence rules, the priority order of ligands in 2-hydroxypropanoic acid ($\text{CH}_3\text{CHOHCOOH}$) is OH > COOH > CH₃ > H.



Since 1 → 2 → 3 traces an anticlockwise path, the absolute configuration of this enantiomer of 2-hydroxypropanoic acid is S, i.e., the compound is (S)-2-hydroxypropanoic acid.

(b) According to sequence rules, the priority order of ligands in 2-bromobutane ($\text{CH}_3\text{CH}_2\text{CHBrCH}_3$) is Br > C₂H₅ > CH₃ > H.

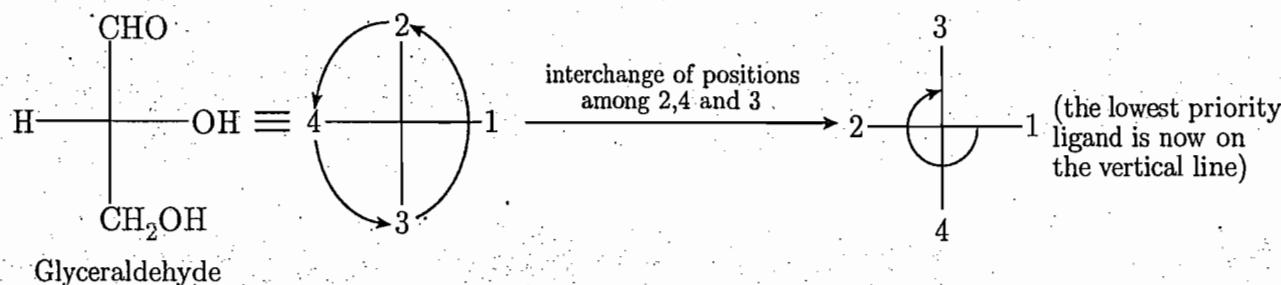


Since $1 \rightarrow 2 \rightarrow 3$ traces a clockwise path, the absolute configuration of this enantiomer of 2-bromobutane is *R*, i.e., the compound is (*R*)-2-bromobutane.

If in Fischer projection, the lowest priority ligand '4' or 'd' is on the horizontal line, it should be brought into the vertical position, either above or below, by changing the positions among three ligands sequentially on the chiral centre without disturbing the position of the fourth or by exchanging two pairs of ligands simultaneously. These operations do not change the absolute configuration of the chiral centre. Now, if $1 \rightarrow 2 \rightarrow 3$ or $a \rightarrow b \rightarrow c$ traces a clockwise path, the configuration is *R* and if the sequence traces an anticlockwise path, the configuration is *S*.

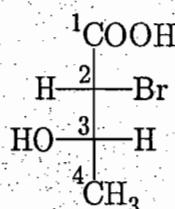
Example :

According to sequence rules, the priority order of ligands in glyceraldehyde is : $\text{OH} > \text{CHO} > \text{CH}_2\text{OH} > \text{H}$.



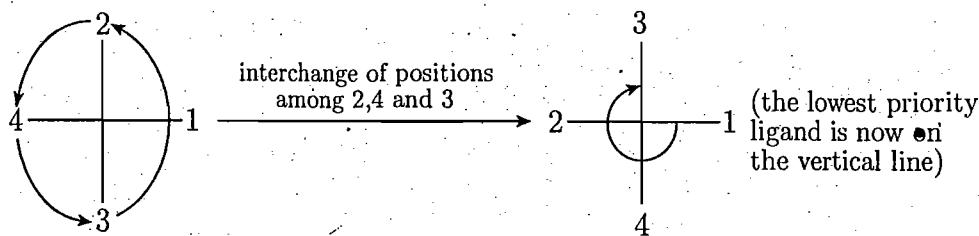
Since $1 \rightarrow 2 \rightarrow 3$ traces a clockwise path, the absolute configuration of this enantiomer of glyceraldehyde is *R*, i.e., the compound is (*R*)-glyceraldehyde.

This procedure is also applicable to Fischer projections with more than one chiral centre. For example :

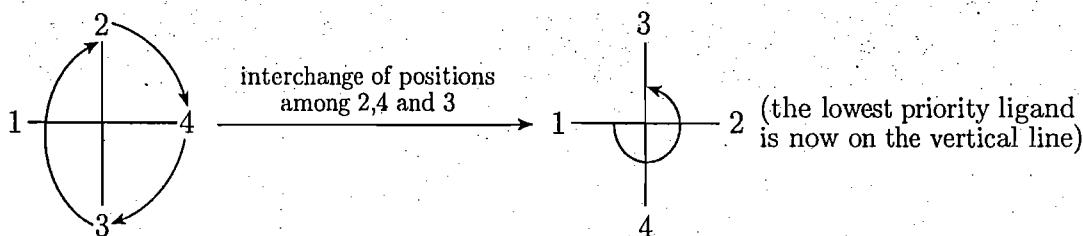


2-Bromo-3-hydroxybutanoic acid

In 2-bromo-3-hydroxybutanoic acid the priority order of ligands attached to C-2 chiral centre is $\text{Br} > \text{COOH} > \text{CHOHCH}_3 > \text{H}$ and the priority order of ligands attached to C-3 chiral centre is $\text{OH} > \text{CHBrCOOH} > \text{CH}_3 > \text{H}$.

Configuration of C-2 :

Now, since $1 \rightarrow 2 \rightarrow 3$ traces a clockwise path, the configuration is *R*.

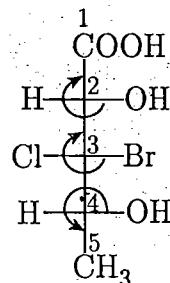
Configuration of C-3 :

Now, since $1 \rightarrow 2 \rightarrow 3$ traces an anticlockwise path, the configuration is *S*. Therefore, the complete stereochemical name of the compound is $(2R,3S)$ -2-bromo-3-hydroxybutanoic acid.

►1.37 What is the “very good” (mnemonic) procedure for assigning absolute configuration to chiral centres? Give an example.

Ans. An alternative procedure for assigning *R,S* descriptors to chiral centres is due to Epling (1982). The procedure, applicable to Fischer projections only, involves two operations : (a) assigning priority symbol 1,2,3,4 or a,b,c,d to each of the ligands and (b) tracing a semicircle joining $1 \rightarrow 2 \rightarrow 3$ or $a \rightarrow b \rightarrow c$ ignoring ‘4’ or ‘d’, the lowest priority group. If ‘4’ or ‘d’ is on either of the vertical bonds, the path traced gives the correct descriptor, i.e., *R* for clockwise and *S* for anticlockwise. But if ‘4’ or ‘d’ remains on a horizontal bond, the counterclockwise path indicates *R* configuration and the clockwise path indicates *S* configuration, i.e., the descriptors arrived at from the sequence $1 \rightarrow 2 \rightarrow 3$ or $a \rightarrow b \rightarrow c$ have to be reversed. This is what is called the very good (mnemonic) method for assigning *R,S*-descriptors to a chiral centre. The procedure is very helpful for assigning absolute configurations to chiral centres in a molecule containing any number of chiral centres.

Example :



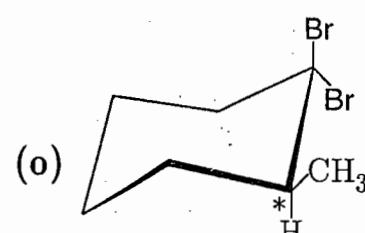
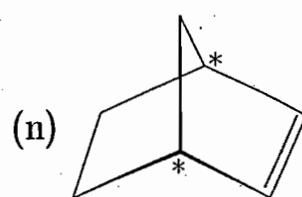
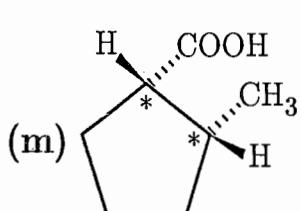
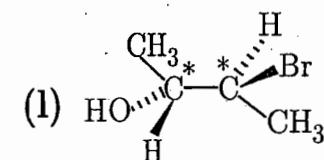
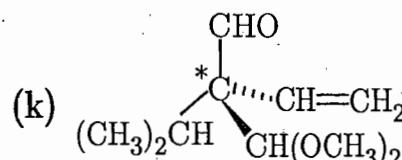
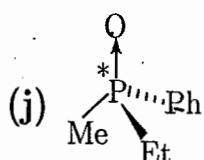
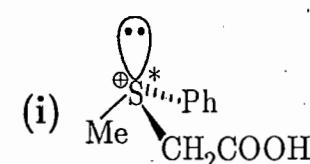
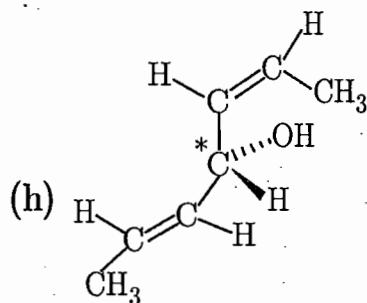
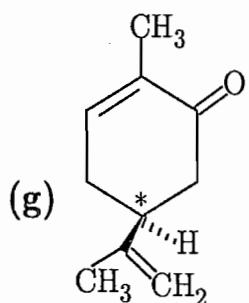
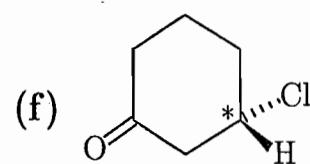
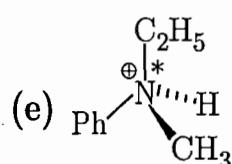
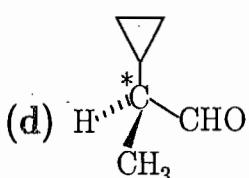
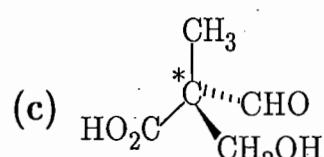
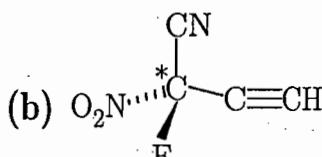
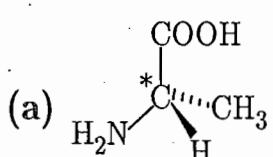
3-Bromo-3-chloro-2,4-dihydroxy-pentanoic acid

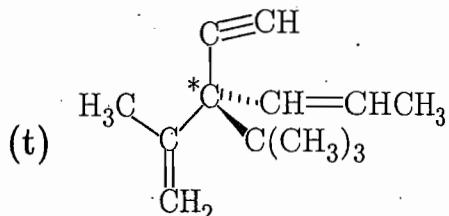
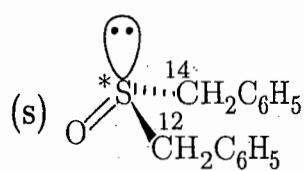
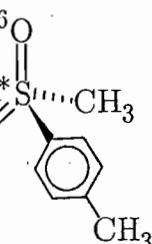
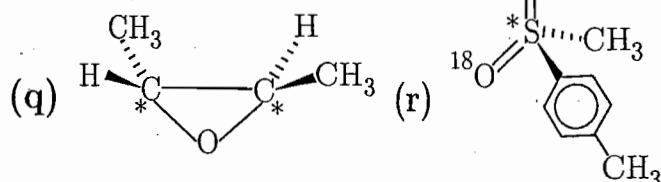
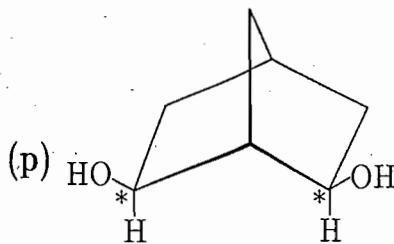
Priorities of ligands in different chiral centres are as follows :



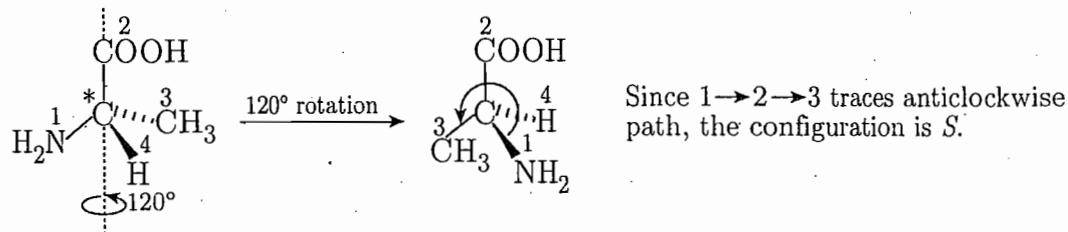
At C-2 and C-4, the lowest priority ligand (H) is on the horizontal bond and, therefore the absolute configuration of C-2 is *S*, because 1→2→3 or a→b→c traces a clockwise path and the absolute configuration of C-4 is *R*, because 1→2→3 or a→b→c traces a counterclockwise path. Since the lowest priority group, i.e., —CH(OH)CH₃ on C-3 is on a vertical bond and the sequence 1→2→3 or a→b→c traces a clockwise path, the absolute configuration of C-3 is *R*. Therefore, the compound is (2*S*,3*R*,4*R*)-3-bromo-3-chloro-2,4-dihydroxypentanoic acid.

►1.38 Assign R/S designation to the following compounds :

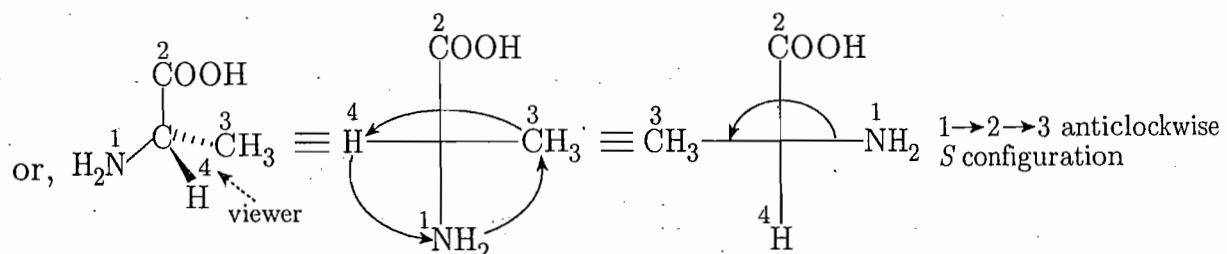




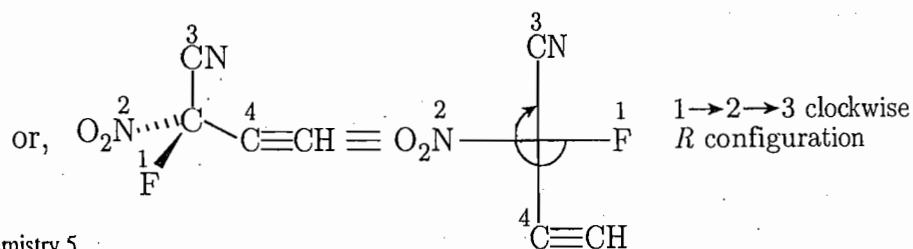
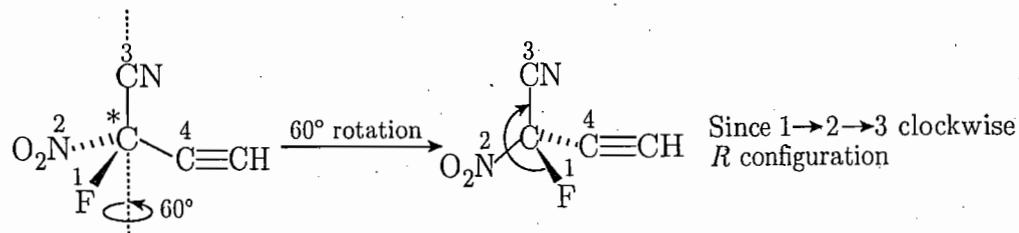
Ans. (a) The priority order of ligands attached to the chiral carbon is



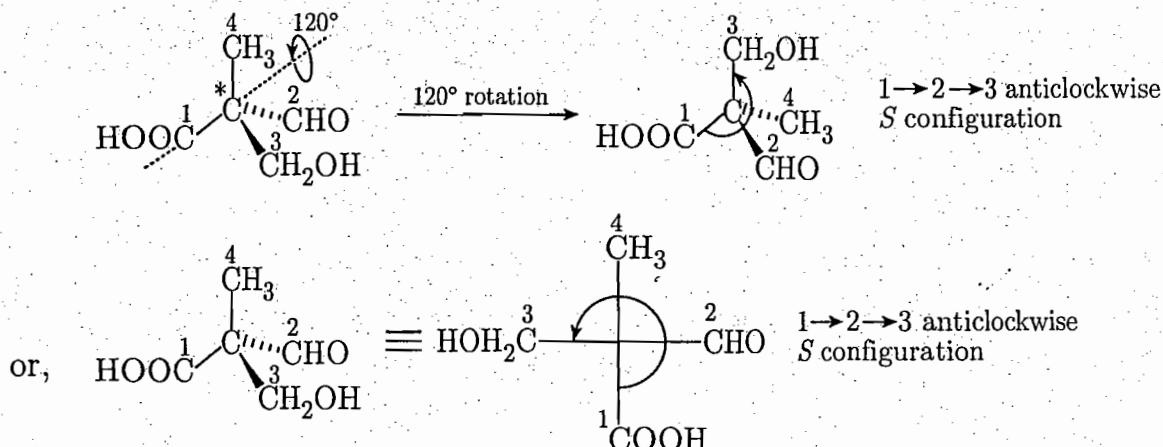
It becomes easier to find out the absolute configuration if one converts three dimensional (flying wedge) structures into Fischer projections.



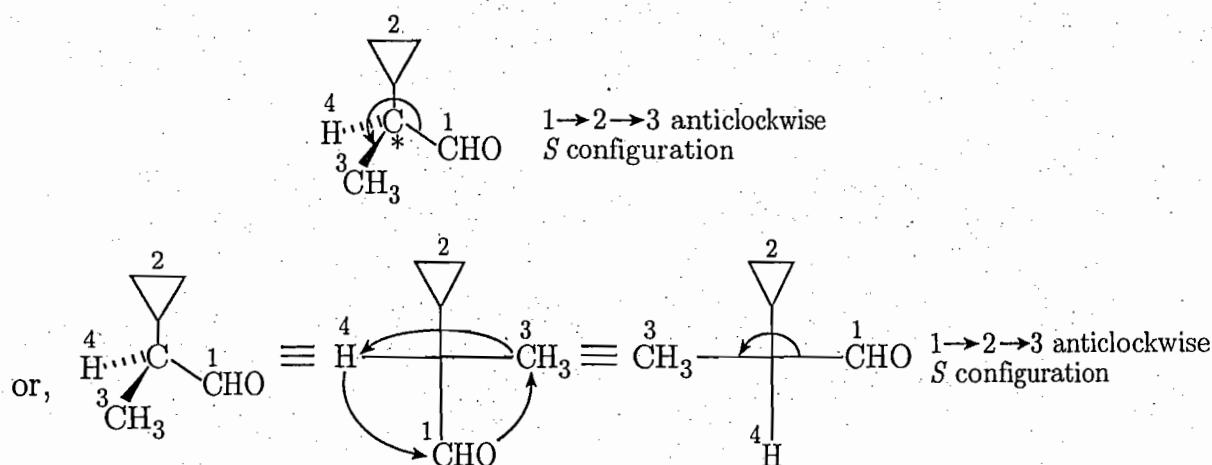
(b) Priority order of ligands : F > NO₂ > CN > C≡CH



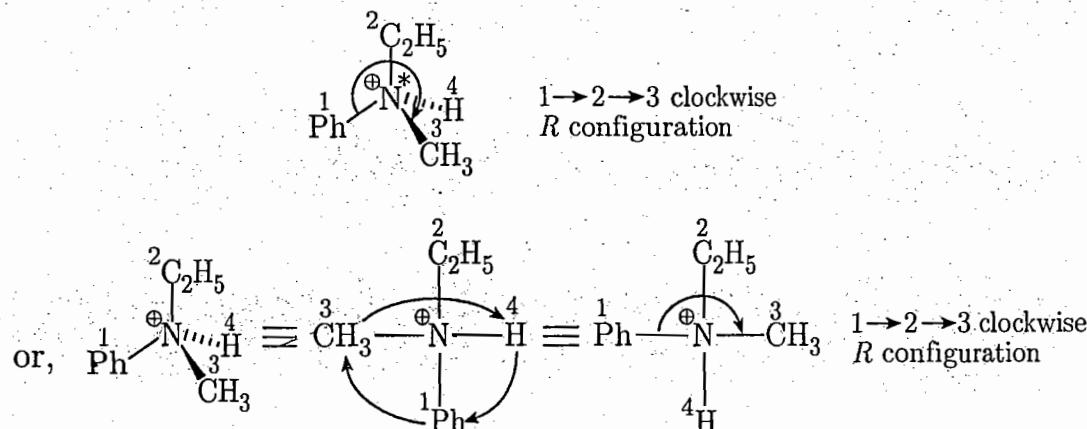
(c) Priority order of ligands : $\text{COOH} > \text{CHO} > \text{CH}_2\text{OH} > \text{CH}_3$



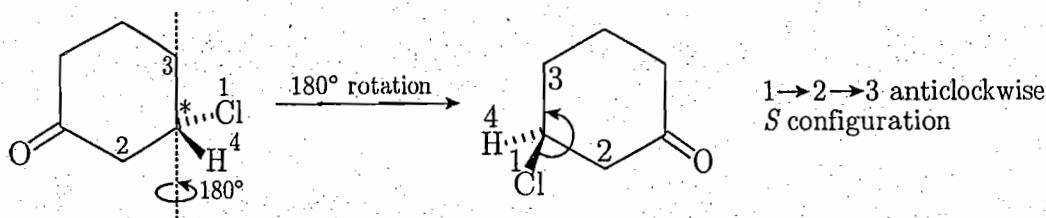
(d) Priority order of ligands : $\text{CHO} > \triangle > \text{CH}_3 > \text{H}$



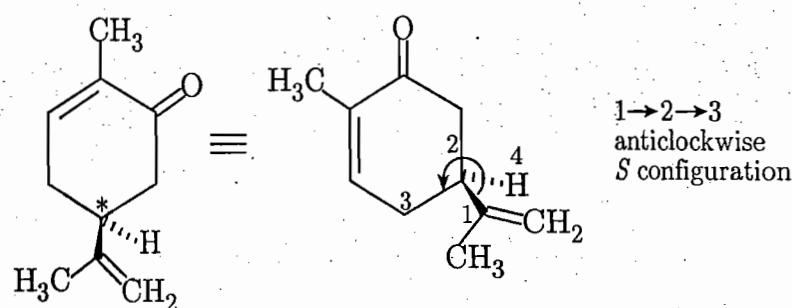
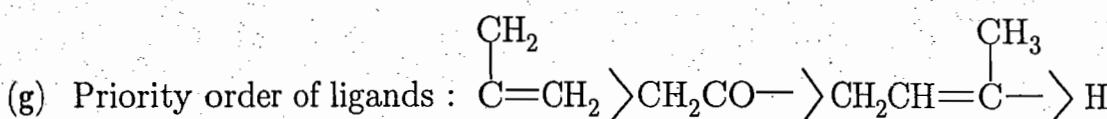
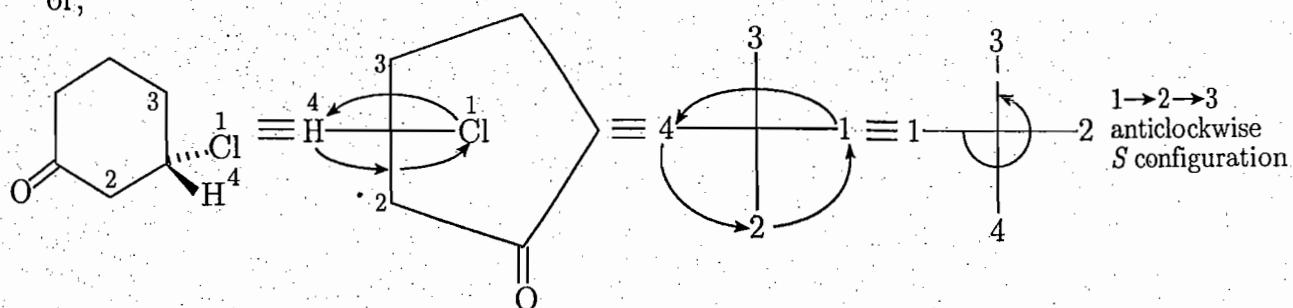
(e) Priority order of ligands : $\text{Ph} > \text{C}_2\text{H}_5 > \text{CH}_3 > \text{H}$



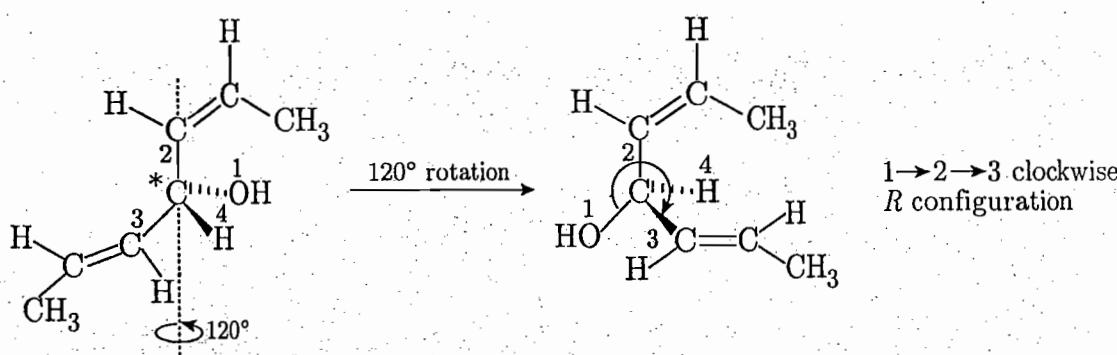
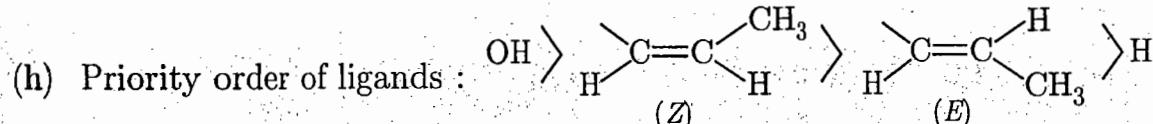
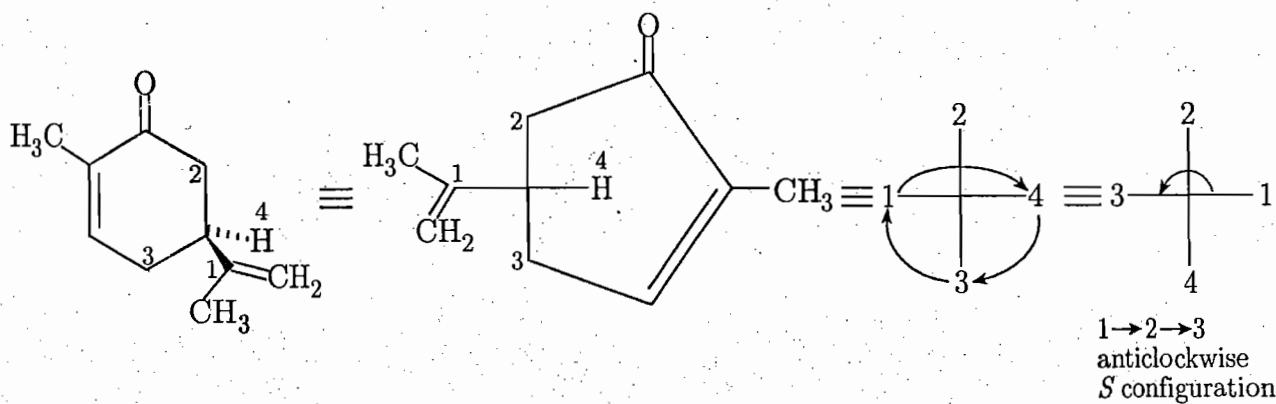
(f) Priority order of ligands : $\text{Cl} > \text{CH}_2\text{CO}- > \text{CH}_2\text{CH}_2- > \text{H}$



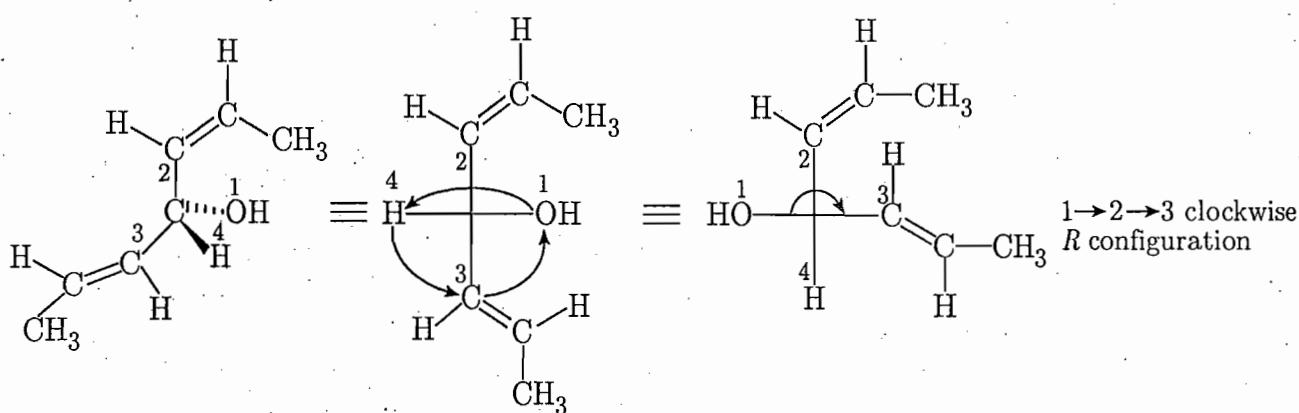
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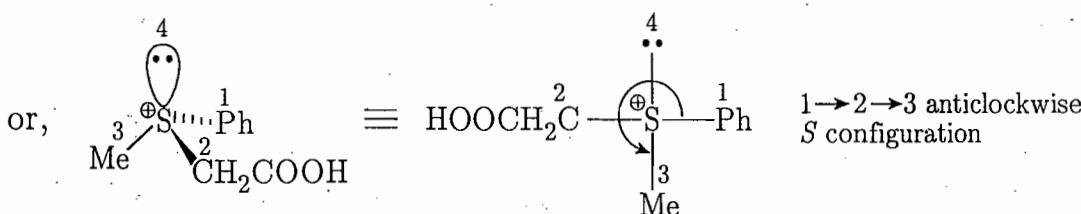
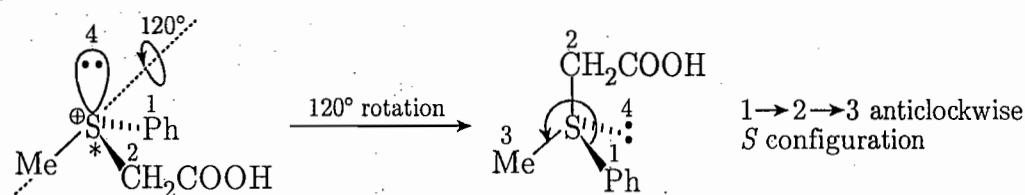
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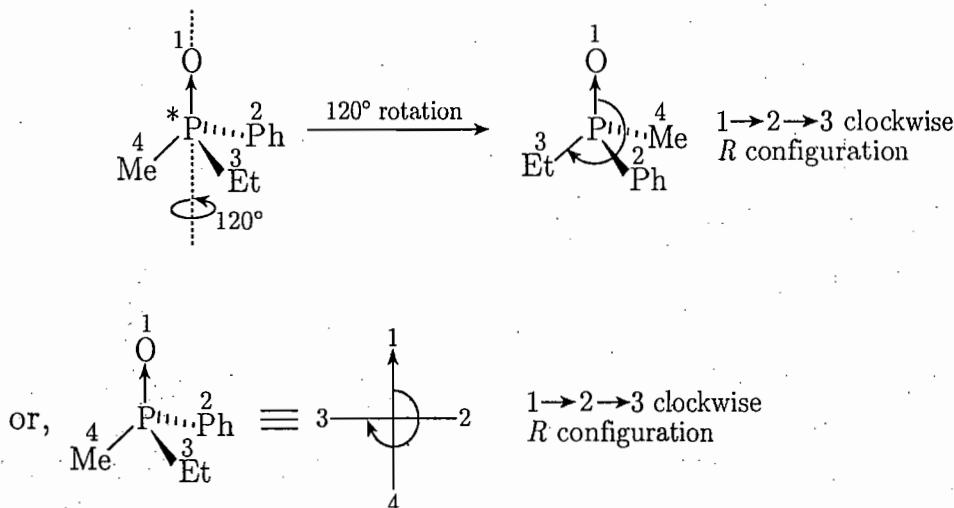
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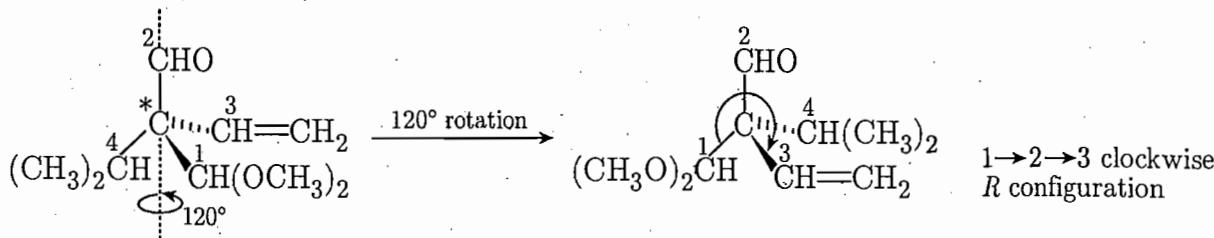
- (i) Priority order of ligands : Ph > CH₂COOH > Me > (·) lone pair of electrons



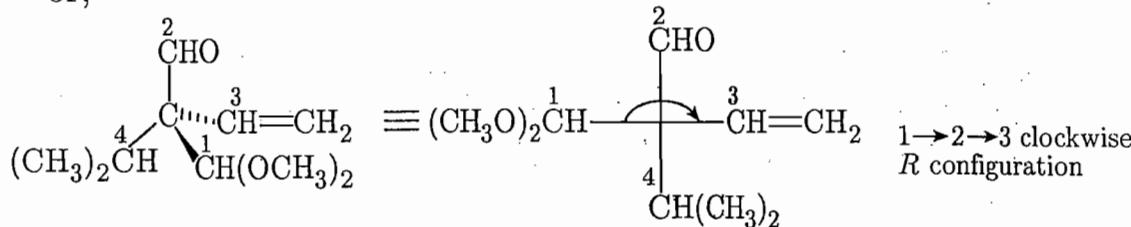
- (j) Priority order of ligands : O > Ph > Et > Me



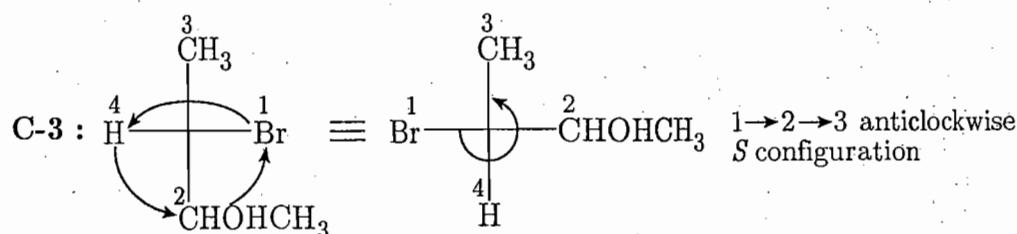
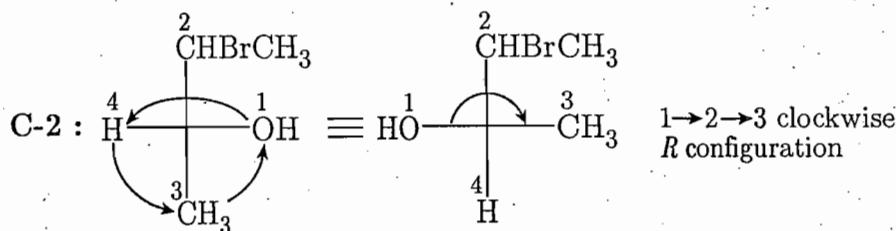
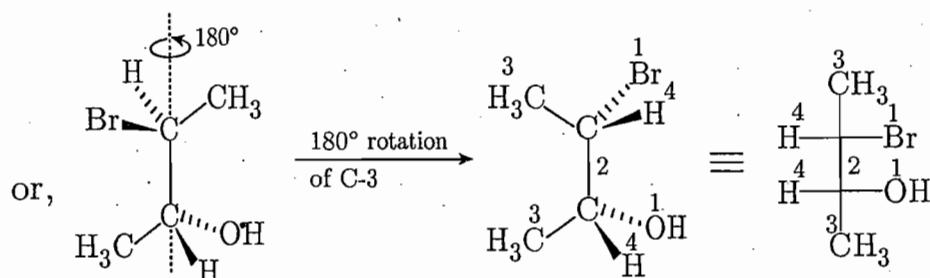
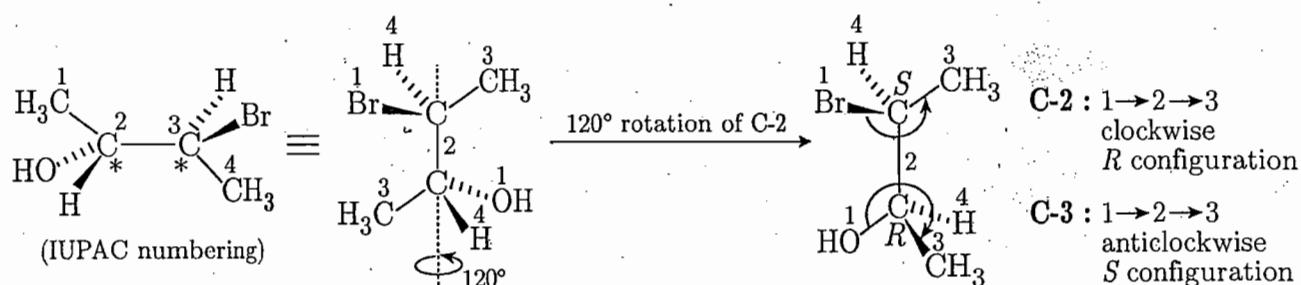
- (k) Priority order of ligands : CH(OCH₃)₂ > CHO > CH=CH₂ > CH(CH₃)₂.



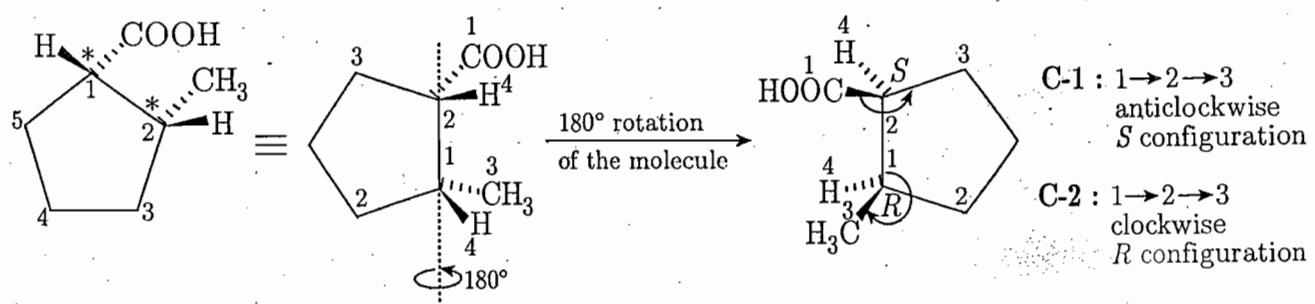
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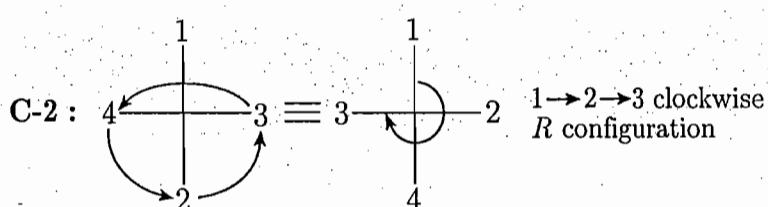
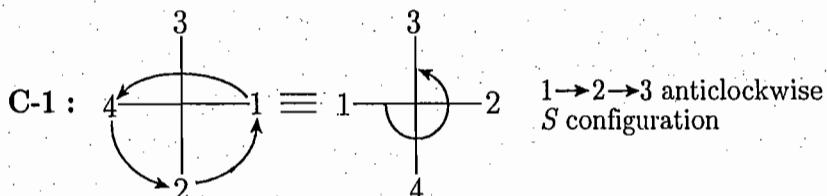
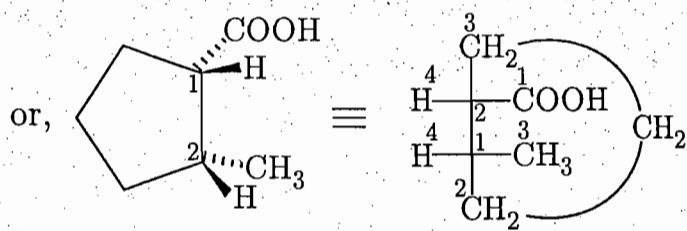


(l) Priority order of ligands at C-2 : OH > CHBrCH₃ > CH₃ > H and at C-3 : Br > CH(OH)CH₃ > CH₃ > H

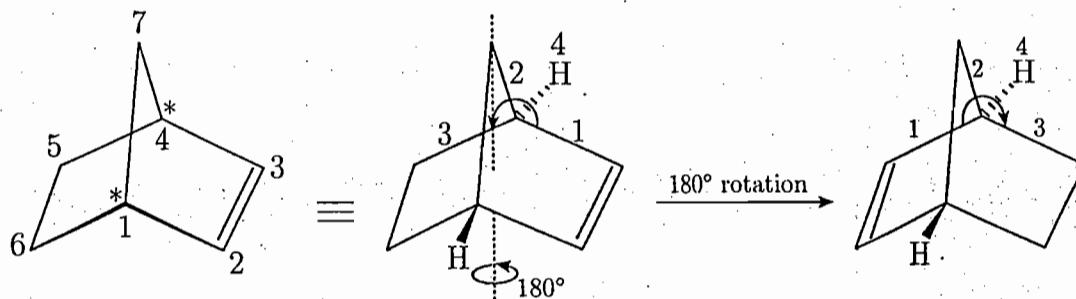


(m) Priority of ligands at C-1 : COOH > CH(CH₃)CH₂— > CH₂CH₂— > H and at C-2 : CH(COOH)CH₂— > CH₂CH₂— > CH₃ > H.



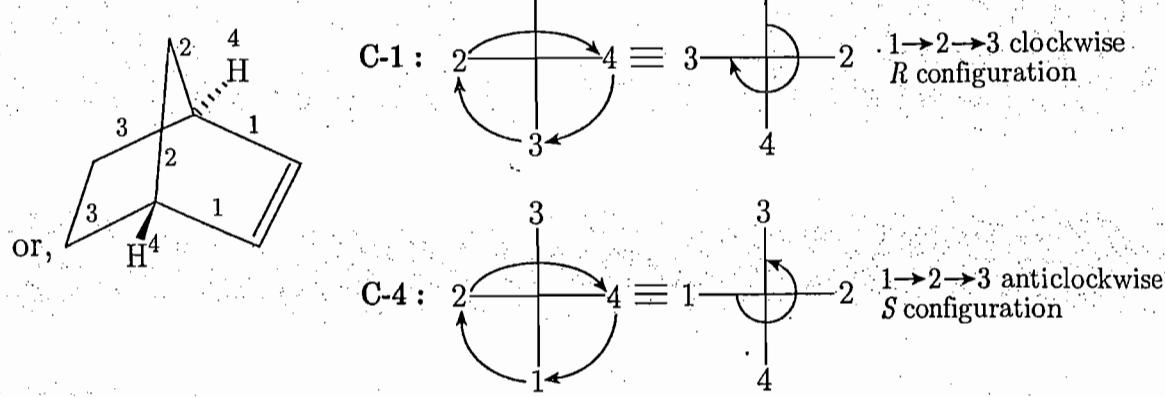


(n) Priority of ligands at C-1 and C-4 : $\text{CH}=\text{CH} - > \text{CH}_2\text{CH}_2\text{C} > \text{CH}_2\text{CH}_2 - > \text{H}$

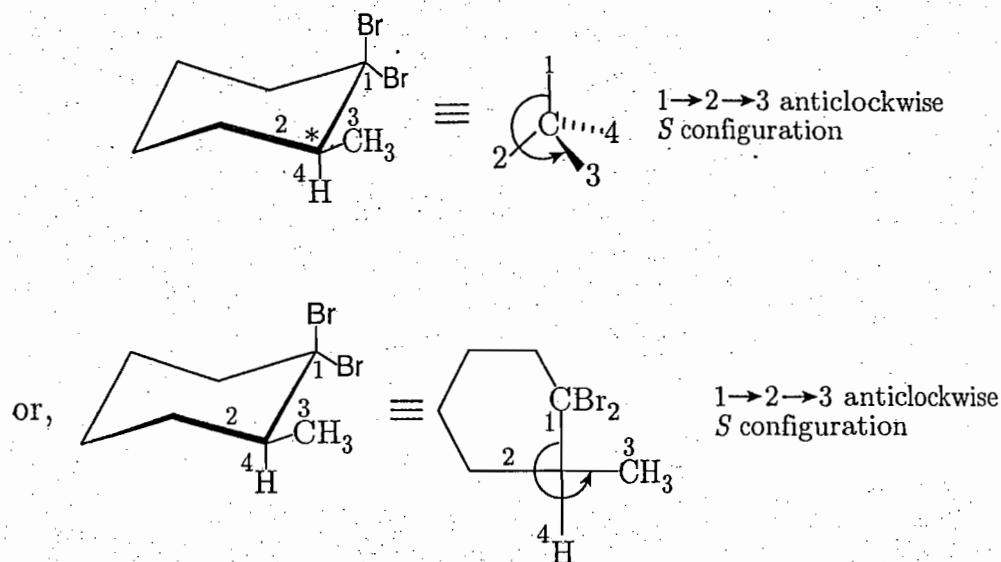


C-4 : $1 \rightarrow 2 \rightarrow 3$ anticlockwise
S configuration

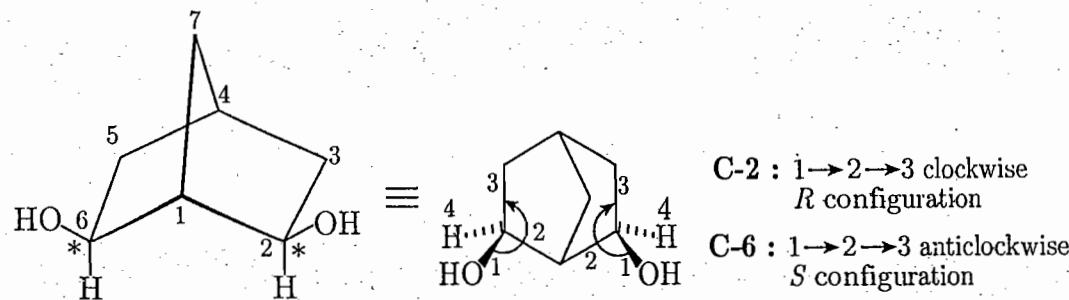
C-1 : $1 \rightarrow 2 \rightarrow 3$ clockwise
R configuration



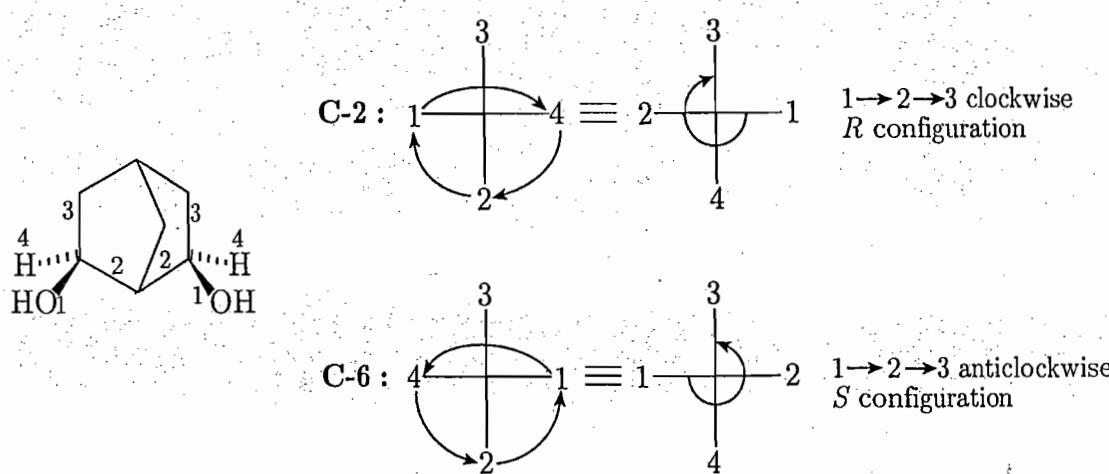
(o) Priority of ligands : $\text{CBr}_2\text{CH}_2 \rightarrow \text{CH}_2\text{CH}_2 \rightarrow \text{CH}_3 > \text{H}$



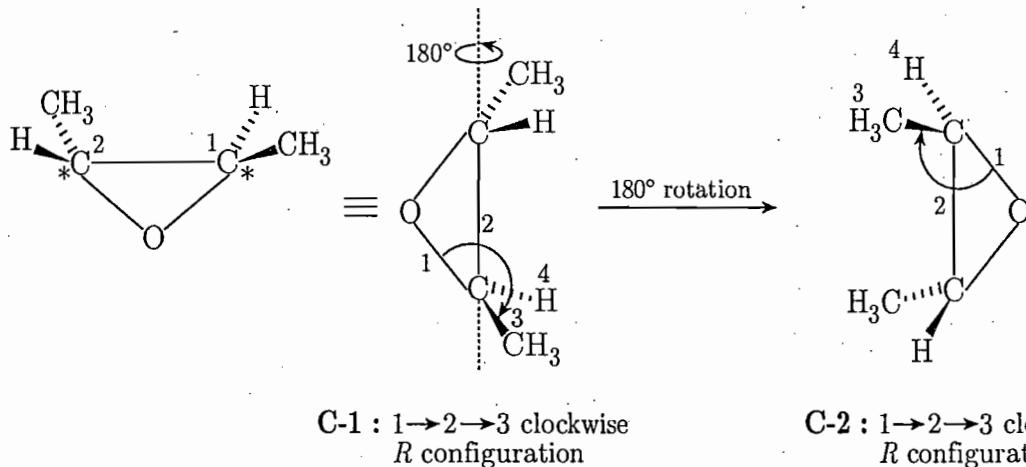
(p) Priority of ligands at C-2 and C-6 : $\text{OH} > \begin{matrix} \text{C} \\ \diagup \\ \text{CH} \\ \diagdown \\ \text{C} \end{matrix} > \text{CH}_2 - \text{C} > \text{H}$



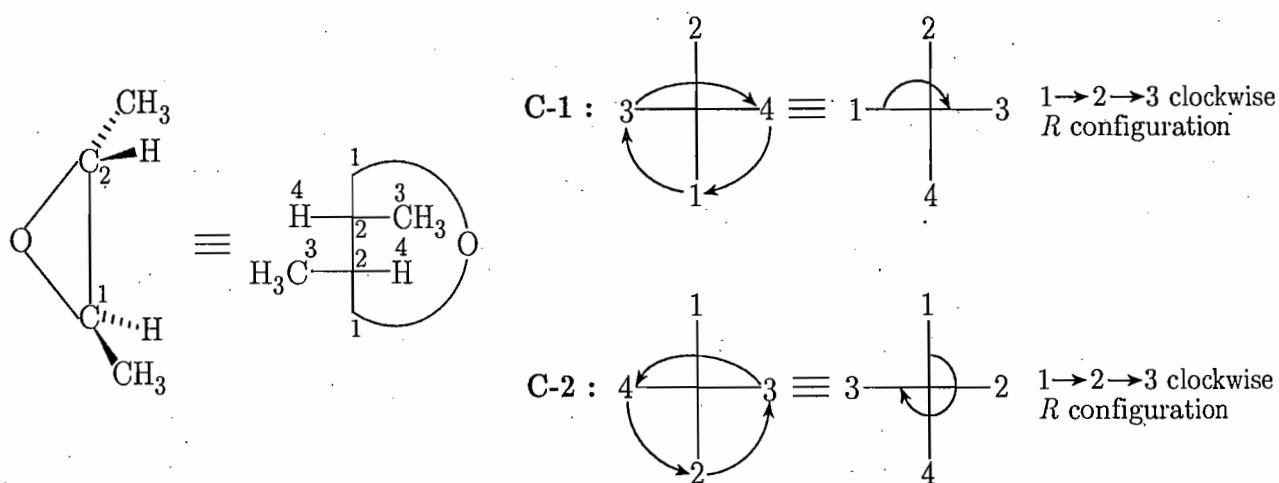
or,



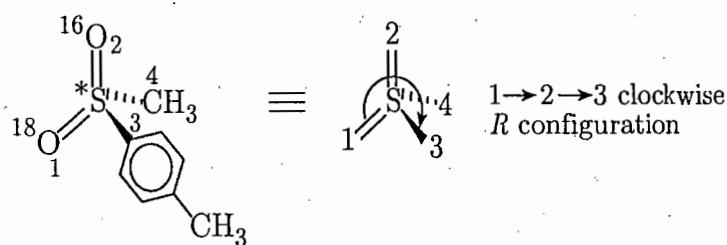
(q) Priority order of ligands at C-1 and C-2 : O > CH(CH₃)— > CH₃ > H



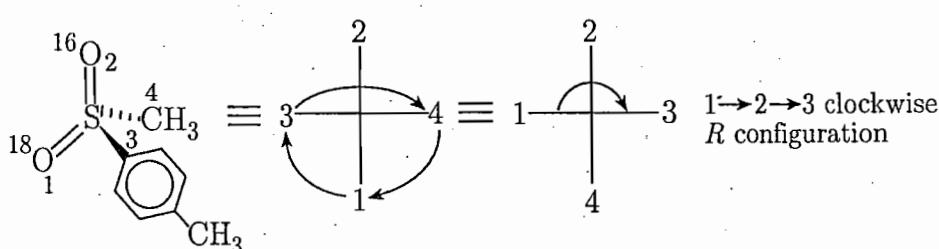
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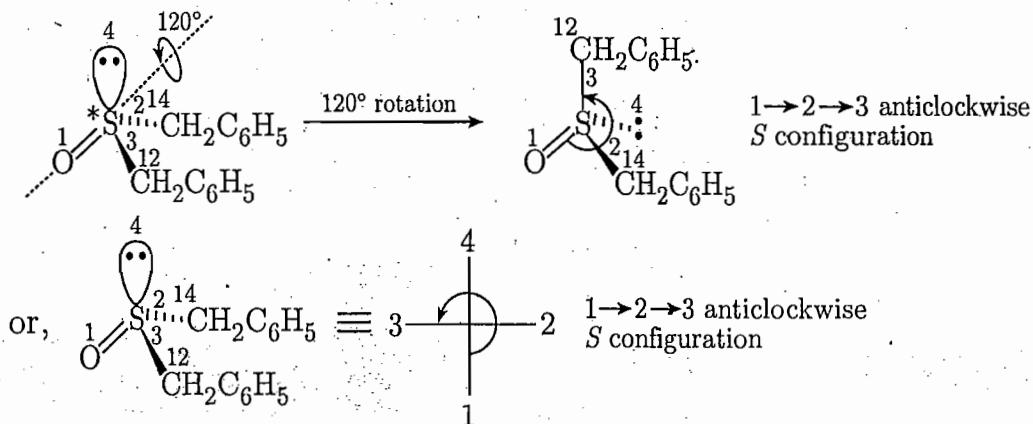
(r) Priority order of ligands : ¹⁸O > ¹⁶O > -CH₃ > CH₃



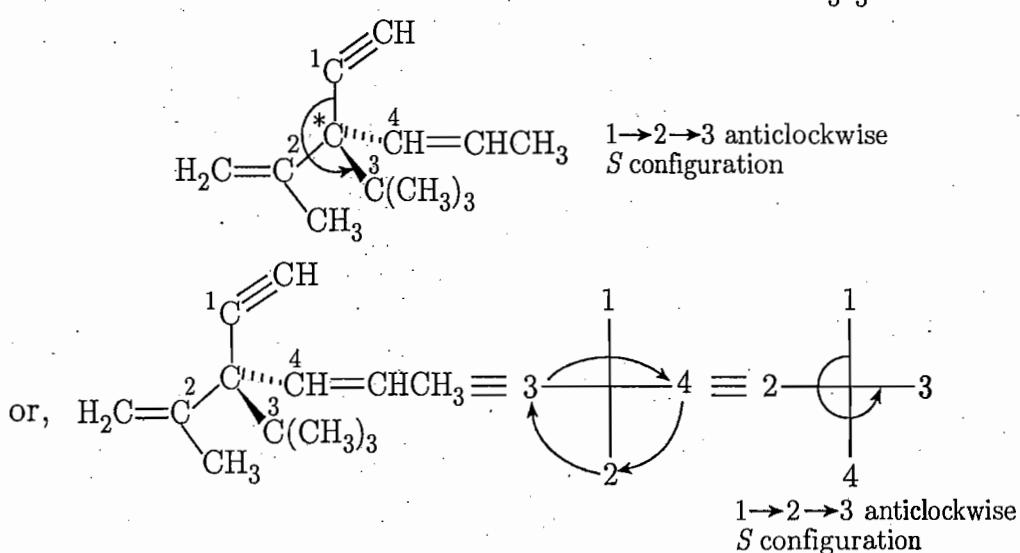
or,



(s) Priority order of ligands : O > $^{14}\text{CH}_2\text{C}_6\text{H}_5$ > $^{12}\text{CH}_2\text{C}_6\text{H}_5$ > (..) lone pair of electrons



(t) Priority order of ligands : C≡CH > C=CH₂ > C(CH₃)₃ > CH=CHCH₃



►1.39 How can you draw flying wedge structures (perspective formulas) for the following compounds :

(a) (R)-2-butanol

(b) (S)-3-bromopentan-1-ol

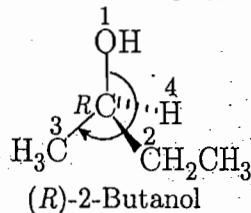
(c) (R)-3-chlorocyclohexanone

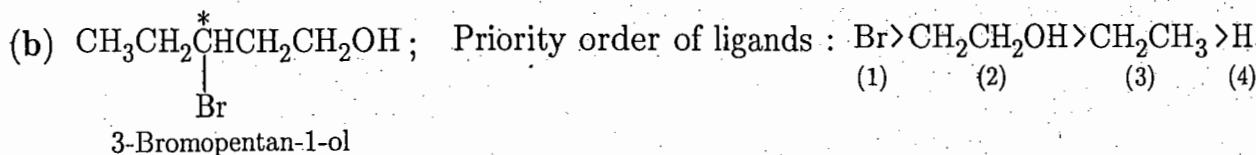
(d) (2S,3R)-3-bromo-2-butanol

(e) (1R,2S)-1-bromo-2-chlorocyclohexane

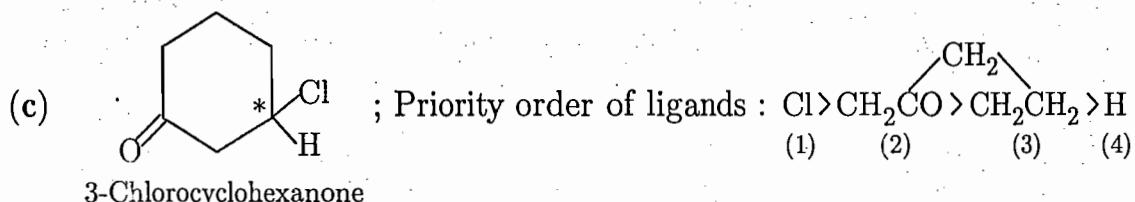
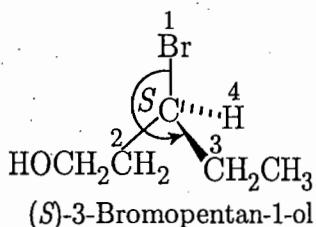
Ans. (a) $\begin{array}{c} \text{CH}_3 \\ | \\ \text{*CHCH}_2\text{CH}_3 \\ | \\ \text{Br} \end{array}$; Priority order of ligands : OH > CH₂CH₃ > CH₃ > H
(1) (2) (3) (4)

The flying wedge structure (perspective formula) of (R)-2-butanol can be drawn by putting the lowest priority ligand (4) on the hatched wedge and other ligands on the remaining bonds such that 1 → 2 → 3 traces a clockwise path.

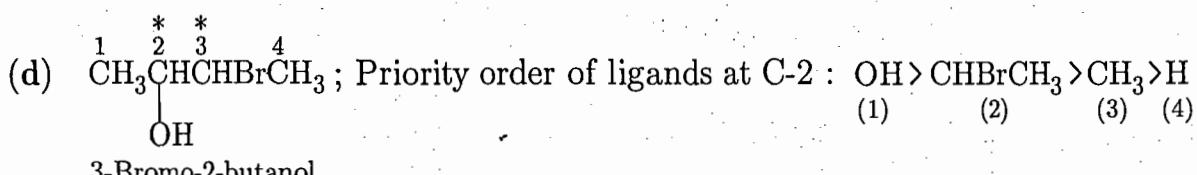
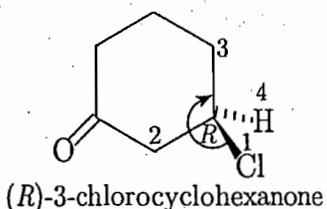




The flying wedge structure (perspective formula) of (*S*)-3-bromopentan-1-ol can be drawn by putting the lowest priority ligand (4) on the hatched wedge and other ligands on the remaining bonds such that $1 \rightarrow 2 \rightarrow 3$ traces an anticlockwise path.



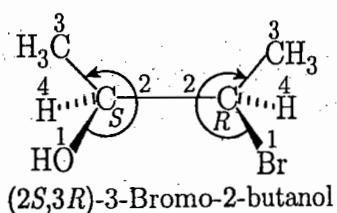
Therefore, the flying wedge structure of the *R* enantiomer is as follows :

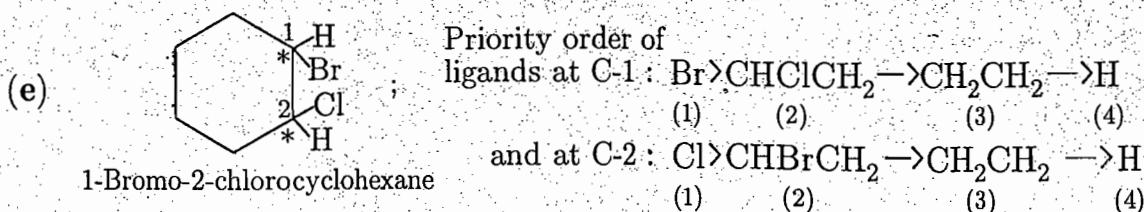


and at C-3 : $\text{Br} > \text{CHOHCH}_3 > \text{CH}_3 > \text{H}$

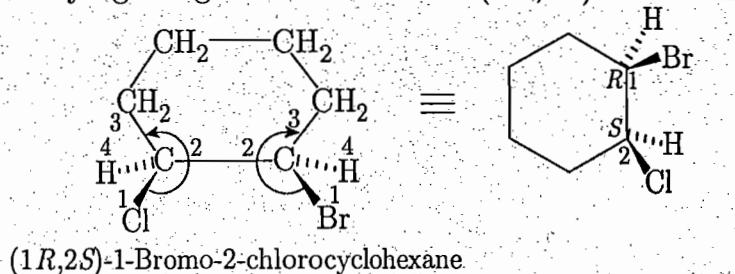
(1) (2) (3) (4)

The flying wedge structure (perspective formula) of (*2S,3R*)-3-bromo-2-butanol can be drawn by putting the lowest priority ligand (4) on the hatched wedges and other ligands (1 and 3) on the remaining bonds (2 becomes automatically fixed after putting 1) such that $1 \rightarrow 2 \rightarrow 3$ traces an anticlockwise path around C-2 and a clockwise path around C-3.





Therefore, the flying wedge structure of the (1*R*,2*S*) enantiomer is as follows :

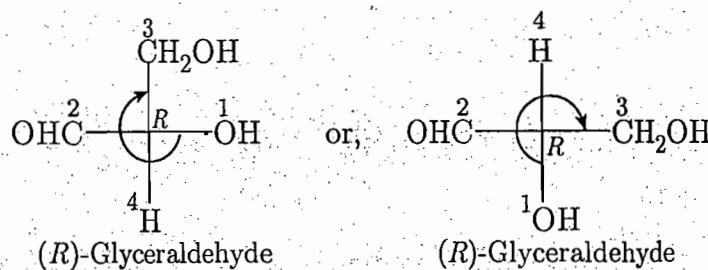


► 1.40 How can you draw Fischer projections for the following compounds :

- (a) (*R*)-glyceraldehyde (b) (*S*)-2-bromobutane (c) (2*R*,3*S*)-3-chloro-2-pentanol.

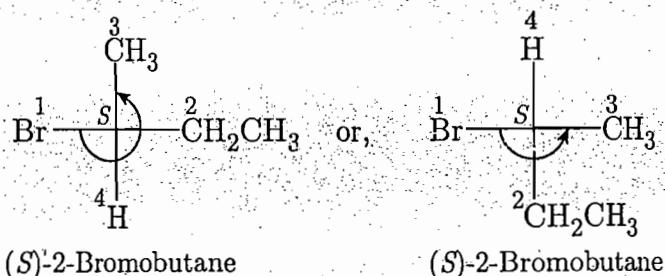
Ans. (a) HOCH₂^{*}CHOHCHO ; Priority order of ligands : OH > CHO > CH₂OH > H
 Glyceraldehyde (1) (2) (3) (4)

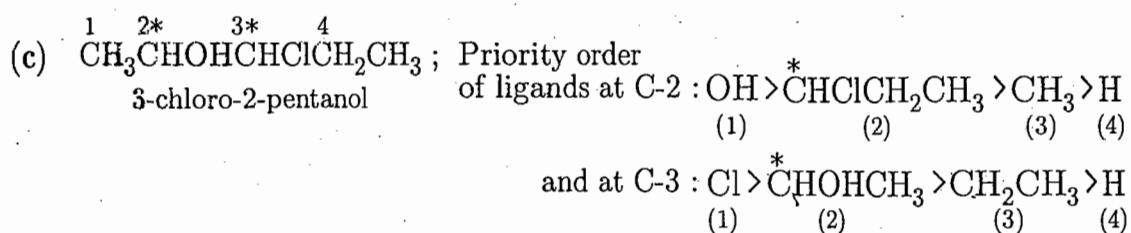
The Fischer projection of (*R*)-glyceraldehyde can be drawn by putting the lowest priority ligand (4) on any of the bonds on the vertical line and other ligands on the remaining bonds such that 1 → 2 → 3 traces a clockwise path.



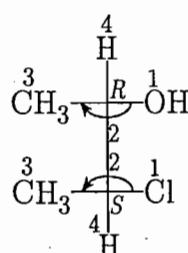
(b) CH₃^{*}CHBrCH₂CH₃ ; Priority order of ligands : Br > CH₂CH₃ > CH₃ > H
 2-Bromobutane (1) (2) (3) (4)

The Fischer projection of (*S*)-2-bromobutane can be drawn by putting the lowest priority ligand (4) on any of the bonds on the vertical line and other ligands on the remaining bonds such that 1 → 2 → 3 traces an anticlockwise path.



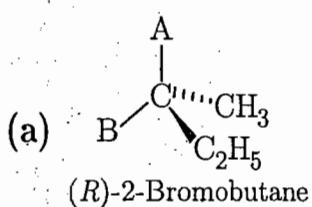


For each chiral centre, the chiral ligand (2) is automatically placed on the vertical bond (lower for C-2 and upper for C-3). The Fischer projection of $(2R,3S)$ -3-chloro-2-pentanol can be drawn by putting the lowest priority ligands (4) on the vertical bonds and two other ligands (1 and 3) on the horizontal bonds such that $1 \rightarrow 2 \rightarrow 3$ traces a clockwise path around C-2 (i.e., 1 is on the right bond and 3 is on the left bond) and an anticlockwise path around C-3 (i.e., 1 is on the right bond and 3 is on the left bond).

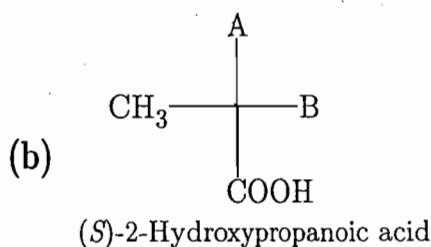


(2*R*,3*S*)-3-chloro-2-pentanol

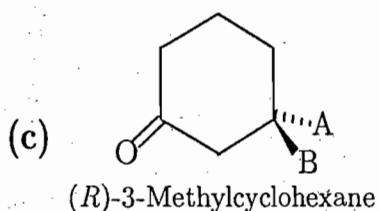
►1.41 Identify the missing ligands (A & B) in each of the following compounds :



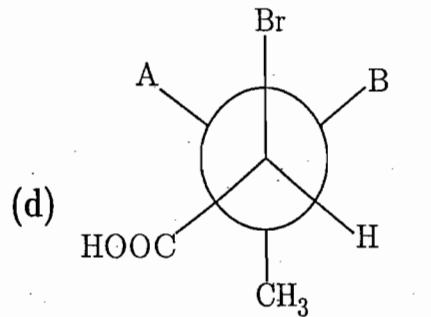
(R)-2-Bromobutane



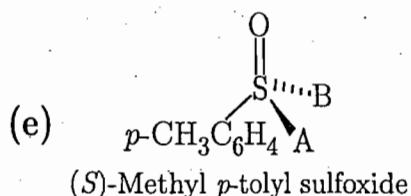
(S)-2-Hydroxypropanoic acid



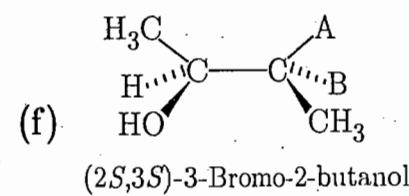
(R)-3-Methylcyclohexane



**(2*S*,3*R*)-3-Bromo-3-chloro-
butanoic acid**



(S)-Methyl *p*-tolyl sulfoxide



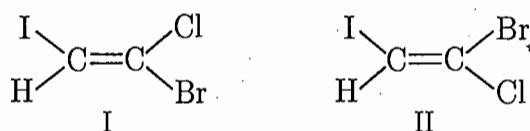
(2*S*,3*S*)-3-Bromo-2-butanol

Ans. (a) A = H, B = Br (b) A = OH, B = H (c) A = H, B = CH₃ (d) A = Cl, B = H (e) A = CH₃, B = (..) lone pair of electrons (f) A = Br, B = H.

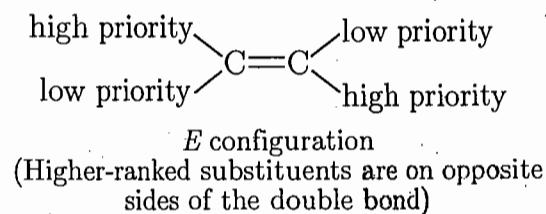
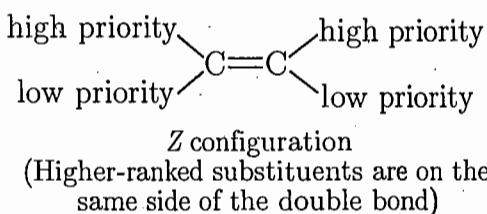
►1.42 (a) Explain why *cis*- and *trans*-prefixes cannot be used unambiguously for designating all geometrical isomers.

(b) Discuss the *E-Z* system of naming geometrical isomers.

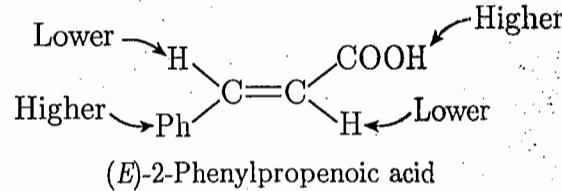
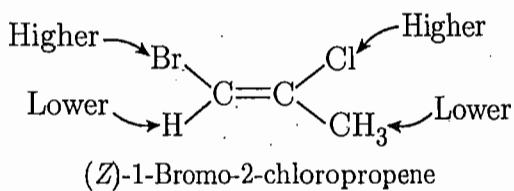
Ans. (a) The terms *cis* and *trans* are unambiguous only when used to designate the stereochemistry of alkenes of the type C_{ab}=C_{ab} or C_{ab}=C_{ac}. But if three or four substituents are different, the terms *cis* and *trans* are ambiguous and cannot be applied at all. For example, it is not possible to designate two isomeric 1-bromo-1-chloro-2-iodoethenes (I and II) as *cis* and *trans* since no pair of substituents are the same.



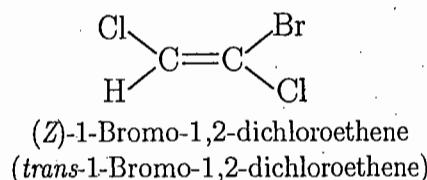
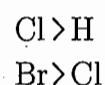
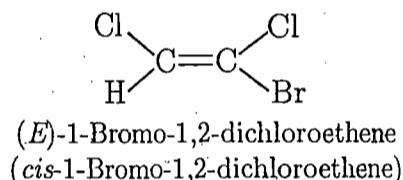
(b) In the *E-Z* system of nomenclature relative priorities of the two groups on each doubly-bonded carbon are determined according to CIP sequence rules and then the relative locations of these groups on each alkene carbon are compared. If the groups of higher priority are on the same side of the double bond, the compound is said to have the *Z* configuration (*Z* from the German word *zusammen*, meaning "together"). If the groups of higher priority are on opposite sides of the double bond, the compound is said to have the *E* configuration (*E* from the German word *entgegen*, meaning "opposite"). The label (*E*) or (*Z*) is added to the name as an italic prefix in parentheses.



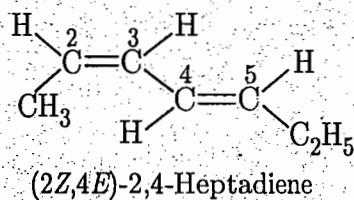
Example :



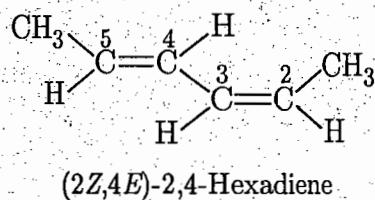
Although in most cases *Z* corresponds to conventional *cis* and *E* corresponds to *trans*, this may not always be the case. For example :



When *cis-trans* isomers contain two or more double bonds, the configuration of each double bond is to be specified with appropriate locants before the stereodescriptors *E* and *Z*. For example :



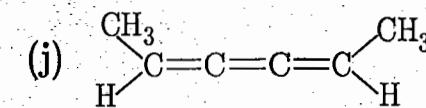
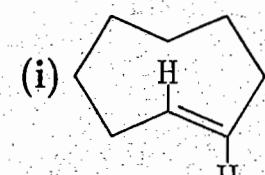
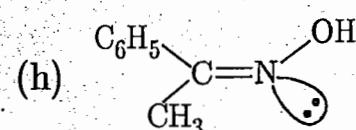
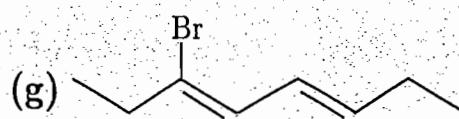
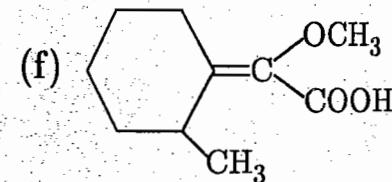
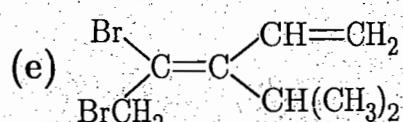
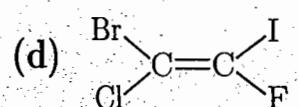
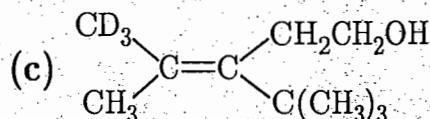
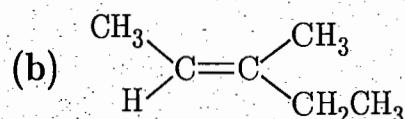
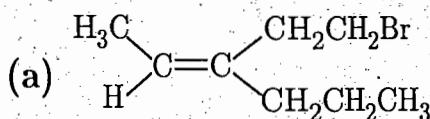
When there is a choice in counting the carbon atoms in a molecule having both (*Z*) and (*E*) descriptors, *Z* gets preference over *E*. For example :

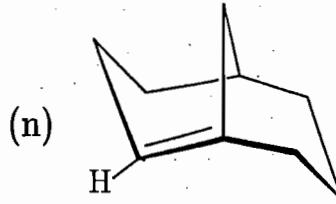
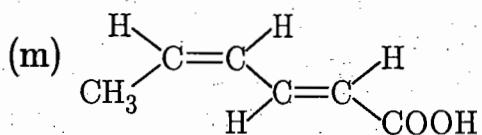
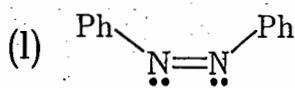
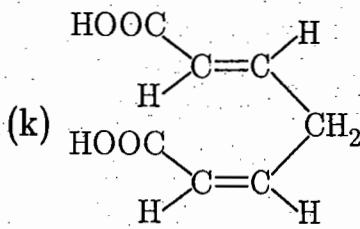


[Lower numbers are assigned to the (*Z*) double bond]

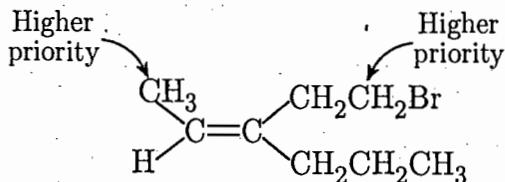
[N.B. *E*, *Z* descriptors are not used for disubstituted cycloalkanes.]

►1.43 Specify the configuration (*E* or *Z*) of each of the following compounds :

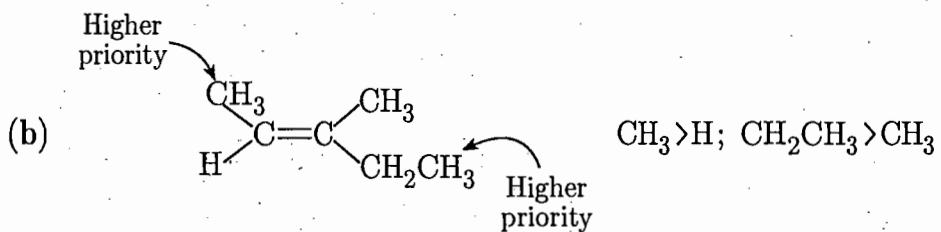




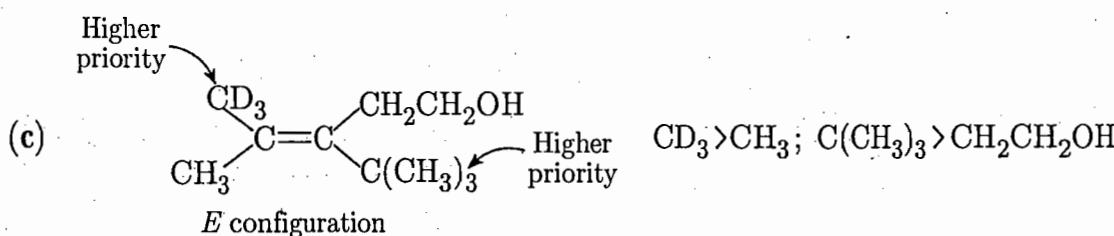
Ans. (a)



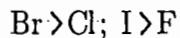
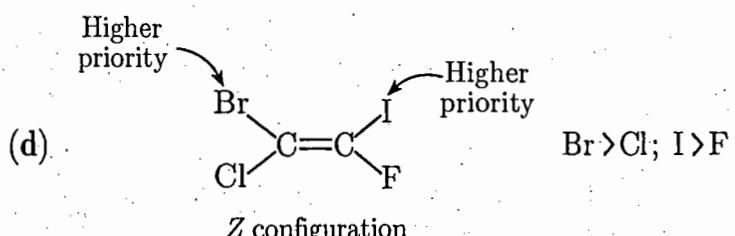
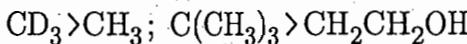
Since the two groups of higher priority are on the same side of the double bond, the alkene has *Z* configuration.



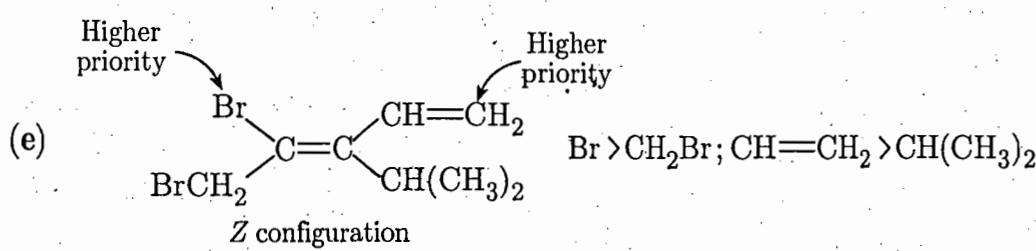
Since the two groups of higher priority are on opposite sides of the double bond, the alkene has *E* configuration.



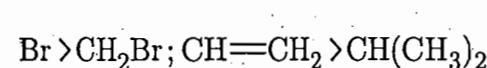
E configuration

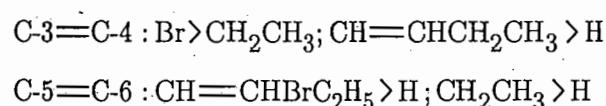
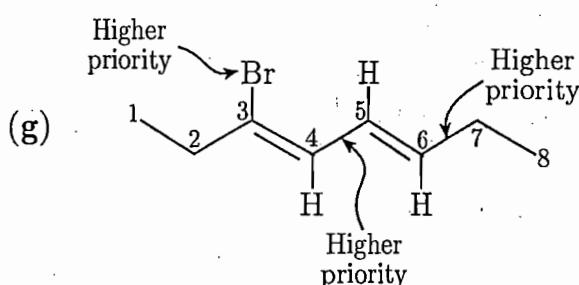
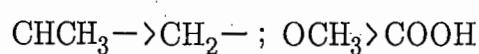
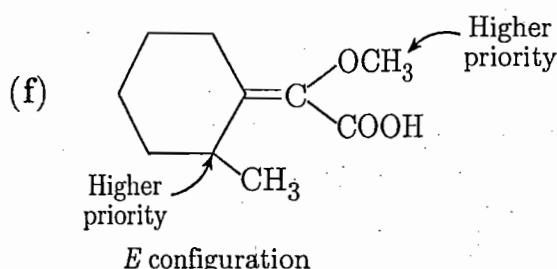


Z configuration



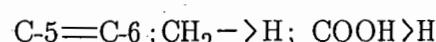
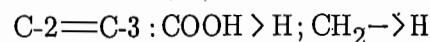
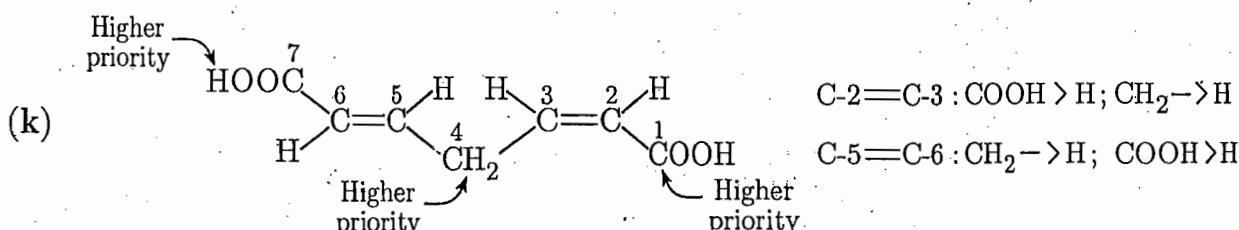
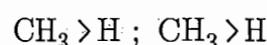
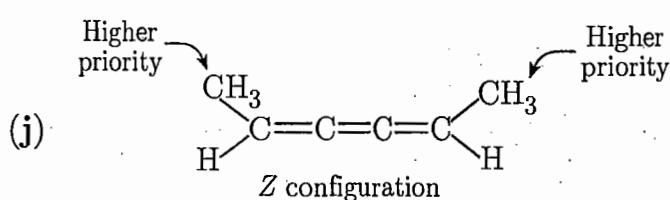
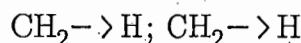
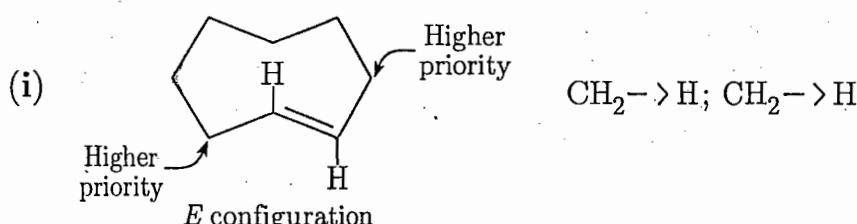
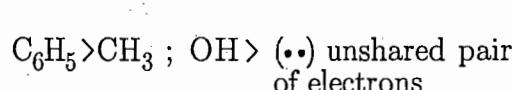
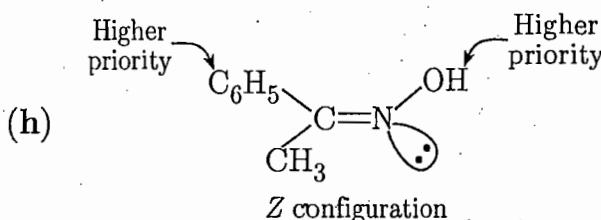
Z configuration





C-3=C-4 : double bond has *Z* configuration

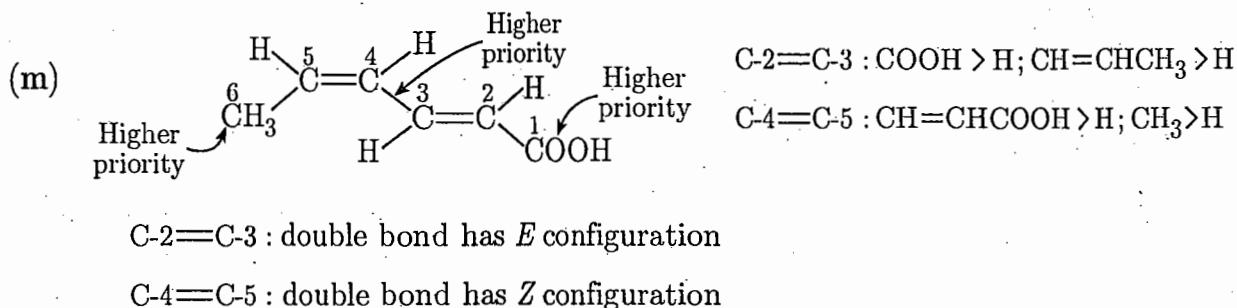
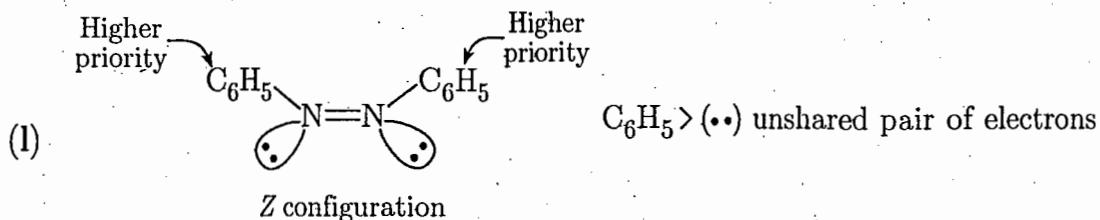
C-5=C-6 : double bond has *E* configuration



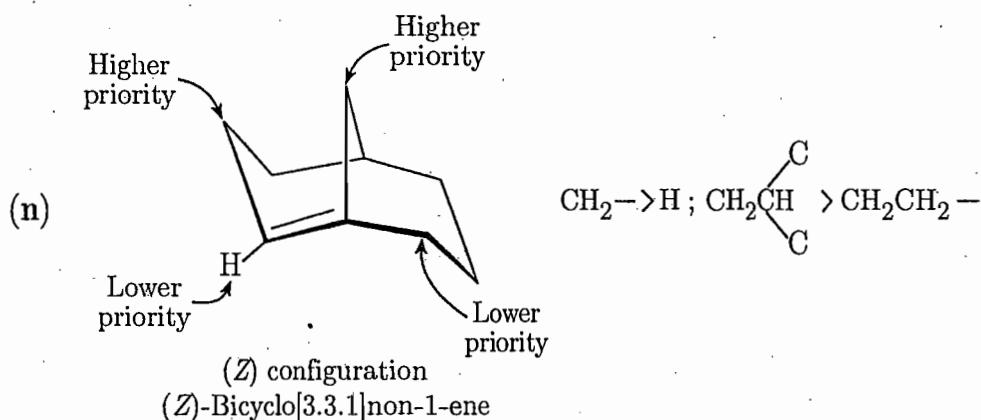
C-2=C-3 : double bond has *Z* configuration

C-5=C-6 : double bond has *E* configuration

(When there is a choice in counting the carbon atoms in a molecule, *Z* gets preference over *E*.)

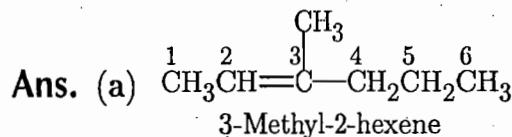


(When an unsymmetrical polyene is considered, then IUPAC rules gets preference in numbering the carbon chain and not the *E* or *Z* descriptors.)

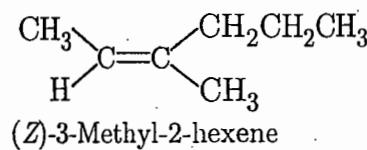


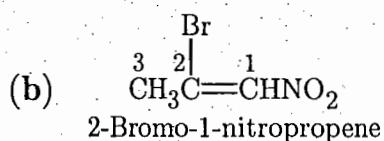
►1.44 Write structural formula for each of the following compounds :

- | | |
|-------------------------------------|---------------------------------------------|
| (a) (<i>Z</i>)-3-Methyl-2-hexene | (b) (<i>E</i>)-2-Bromo-1-nitropropene |
| (c) (<i>E</i>)-Acetophenone oxime | (d) (<i>Z</i>)-1-Chloro-2-methyl-1-butene |
| (e) (<i>Z,E</i>)-Hepta-2,4-diene | (f) (<i>E</i>)-Cyclododecene |
| (g) (<i>E</i>)-Azobenzene | (h) (<i>Z,E</i>)-Benzildioxime |

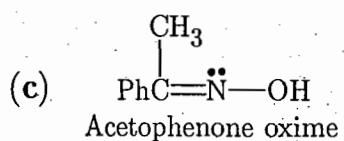
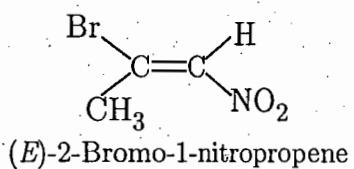


Since, $\text{CH}_3 > \text{H}$ and $\text{CH}_2\text{CH}_2\text{CH}_3 > \text{CH}_3$, the structure of (*Z*)-3-methyl-2-hexene is that in which the higher-ranked groups (CH_3 and $\text{CH}_2\text{CH}_2\text{CH}_3$) are on the same side of the double bond.

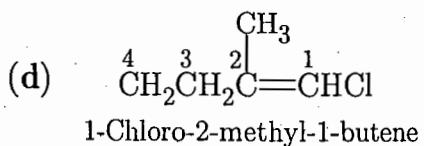
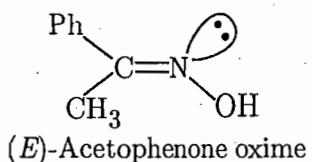




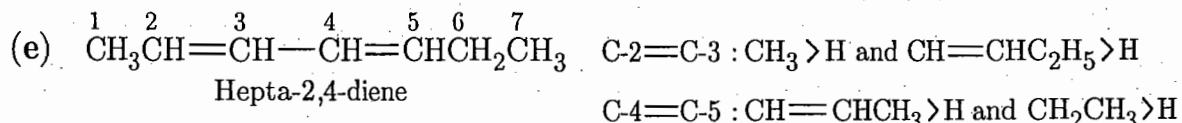
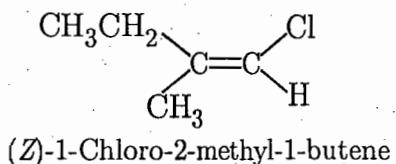
Since, Br > CH₃ and NO₂ > H, the structure of (*E*)-2-bromo-1-nitropropene is that in which the higher-ranked groups (Br and NO₂) are on opposite sides of the double bond.



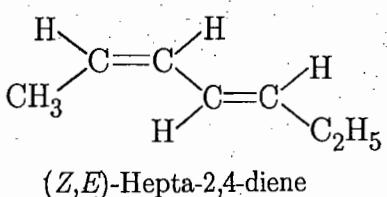
Since, Ph > CH₃ and OH > (..) unshared pair of electrons, the structure of the (*E*)-isomer is as follows :

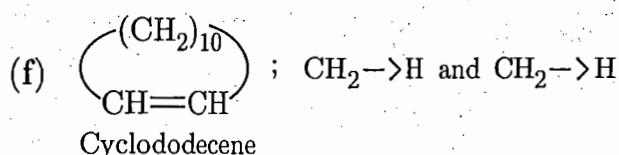


Since, CH₂CH₃ > CH₃ and Cl > H, the structure of the (*Z*)-isomer is as follows :

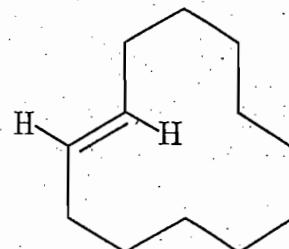


Therefore, the structure of the (*Z,E*)-isomer is as follows :

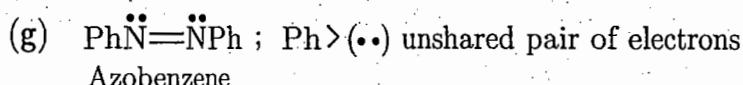




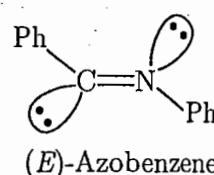
Therefore, the structure of the (*E*)-isomer is as follows :



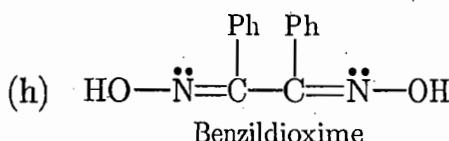
(*E*)-Cyclododecene



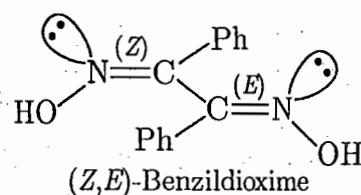
Therefore, the structure of the (*E*)-isomer is as follows :



(*E*)-Azobenzene

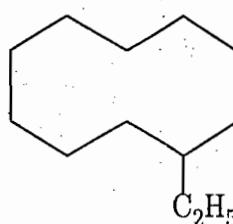


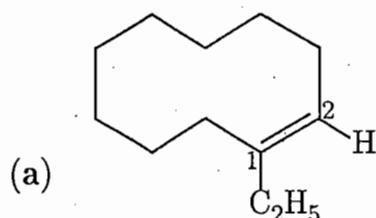
Since, $\text{OH} > (\cdot\cdot)$ unshared pair of electrons and $\text{C}(\text{Ph})=\text{NOH} > \text{Ph}$, the structure of the (*Z,E*)-isomer is as follows :



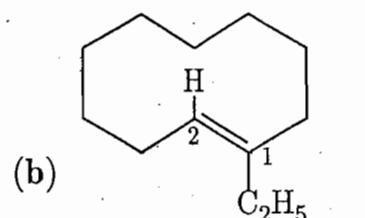
►1.45 Introduce a double bond in the carbon skeleton shown below so as to get the structure of the following compounds :

- | | |
|-------------------------------------|-------------------------------------|
| (a) (<i>Z</i>)-1-Ethylcyclodecene | (b) (<i>E</i>)-1-Ethylcyclodecene |
| (c) (<i>Z</i>)-3-Ethylcyclodecene | (d) (<i>E</i>)-3-Ethylcyclodecene |
| (e) (<i>Z</i>)-5-Ethylcyclodecene | (f) (<i>E</i>)-5-Ethylcyclodecene |

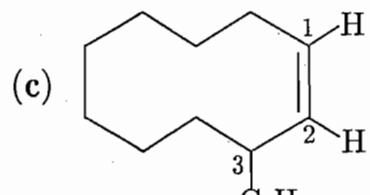


Ans.

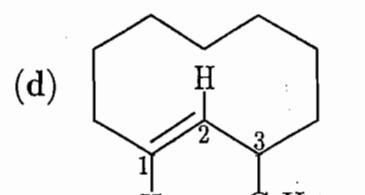
(Z)-1-Ethylcyclodecene



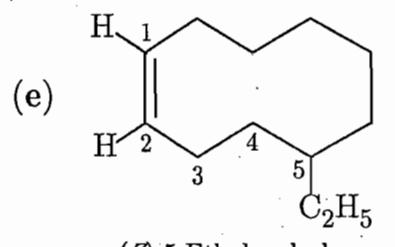
(E)-1-Ethylcyclodecene



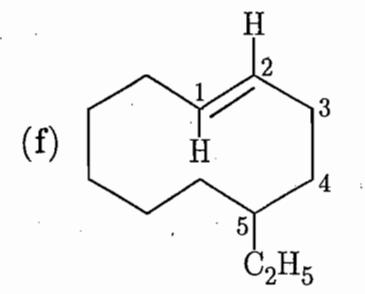
(Z)-3-Ethylcyclodecene



(E)-3-Ethylcyclodecene



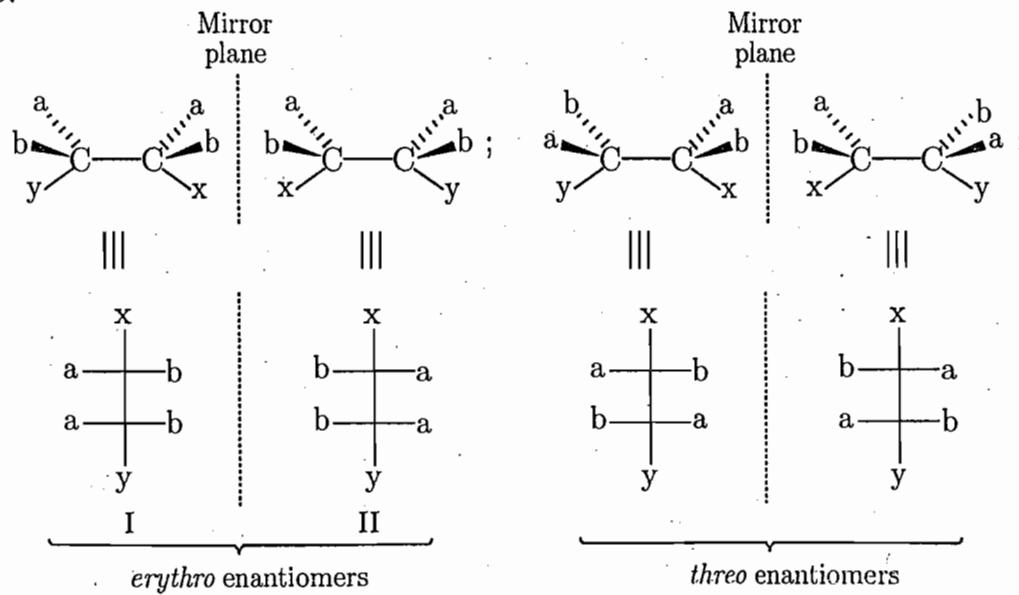
(Z)-5-Ethylcyclodecene



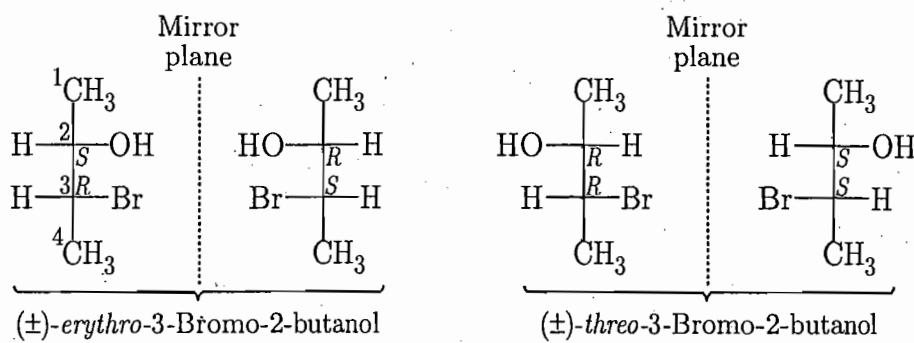
(E)-5-Ethylcyclodecene

►1.46 Write a short note on *threo* and *erythro* nomenclature of compounds with two adjacent chiral centres.

Ans. The terms *threo* and *erythro* are commonly used to describe pairs of enantiomers of molecules of the type $C_{\text{abx}}C_{\text{aby}}$. That enantiomeric pair is designated by the prefix *erythro* in which at least two pairs of similar or like groups eclipse each other and that enantiomeric pair is designated by the prefix *threo* in which only one pair of similar or like groups eclipse each other. Thus, I and II are the *erythro*-forms because in these structures a eclipses a and b eclipses b and III and IV are the *threo*-forms because in these structures a eclipses a and b eclipses b but not both a, a and b, b.

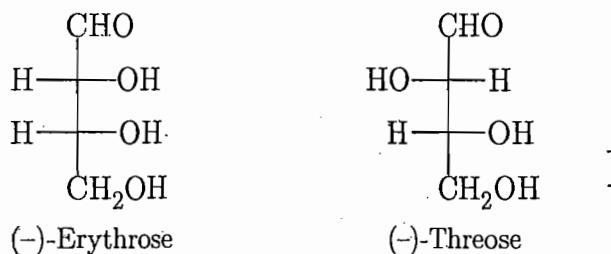


This nomenclature may be illustrated by taking the example of 3-bromo-2-butanol, $\text{CH}_3\text{CHOHCHBrCH}_3$:

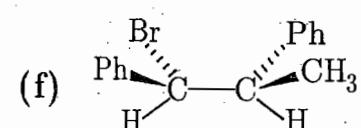
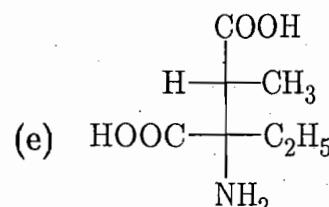
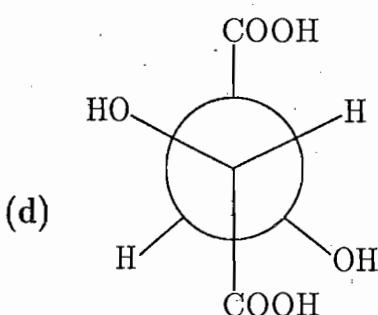
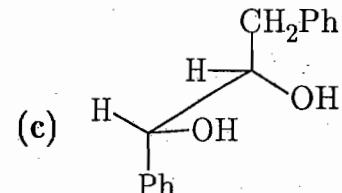
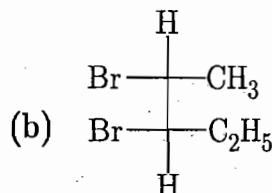
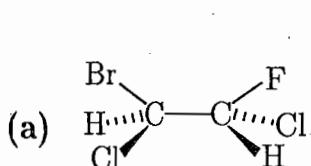


[An *erythro*-isomer is diastereomeric with a *threo*-isomer. Although in the above example the *erythro* isomers have (*S,R*) and (*R,S*) configurations and the *threo* isomers have (*R,R*) and (*S,S*) configurations, there is no automatic relationship between *R/S* designations and the *threo/erythro* terminology.]

The designations *erythro* and *threo* are derived from the names of diastereomeric four-carbon sugars erythrose (in which two pairs of similar groups are eclipsed) and threose (in which one pair of similar groups are eclipsed).



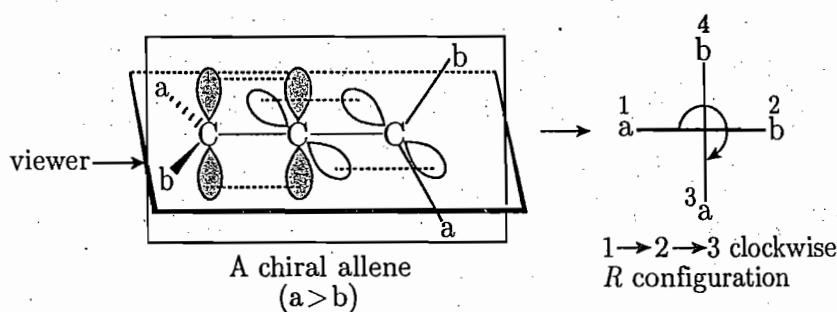
►1.47 Designate each of the following structures with *erythro* and *threo* prefix :



Ans. (a) *threo* form (b) *erythro* form (c) *threo* form (d) *erythro* form (e) *threo* form (f) *threo* form.

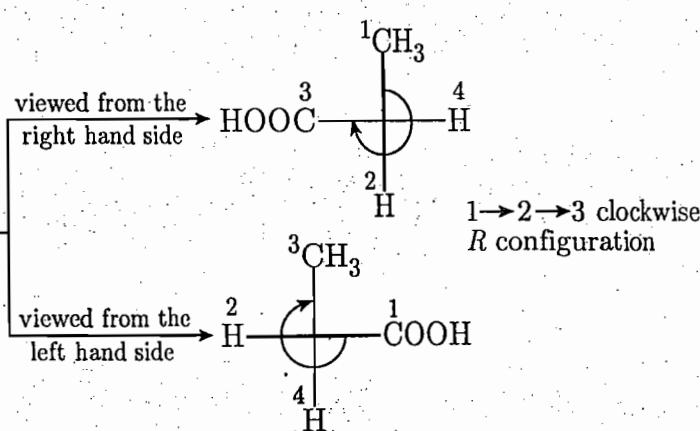
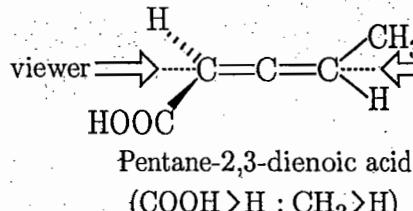
► 1.48 Write a short note on configurational nomenclature of compounds with axial chirality such as (a) allenes, (b) spiranes, alkylidinycloalkanes, oximes and adamantanes and (c) biphenyls.

Ans. (a) *Allenes* : For the assignment of configurational nomenclature (*R/S*) to allenes having chiral axis, the structure of allene is to be regarded as an elongated tetrahedron and to be viewed along the axis. It is immaterial from which end the allene molecule is viewed. The four ligands (two on each terminal sp^2 carbon) are projected onto a plane at right angles to the chiral axis. In the resulting Newman projection formula the near groups are to be given priority over the far groups. For better visualization, the front groups are to be put on a thick line (horizontal or vertical). In the chiral allene $abC=C=Ca$, if the ligand *a* precedes *b*, then the horizontally placed (nearest to the viewer) *a* and *b* are to be numbered 1 and 2 and the vertically placed (rear) *a* and *b* to be numbered 3 and 4 respectively. Then, if $1 \rightarrow 2 \rightarrow 3$ traces a clockwise path, the configuration is *R* (as shown in following figure) and if $1 \rightarrow 2 \rightarrow 3$ traces an anticlockwise path, the configuration is *S*. [The same procedure can be adopted for the assignment of configurational descriptors to cumulenes having even number of double bonds like 4,6,8 etc.]



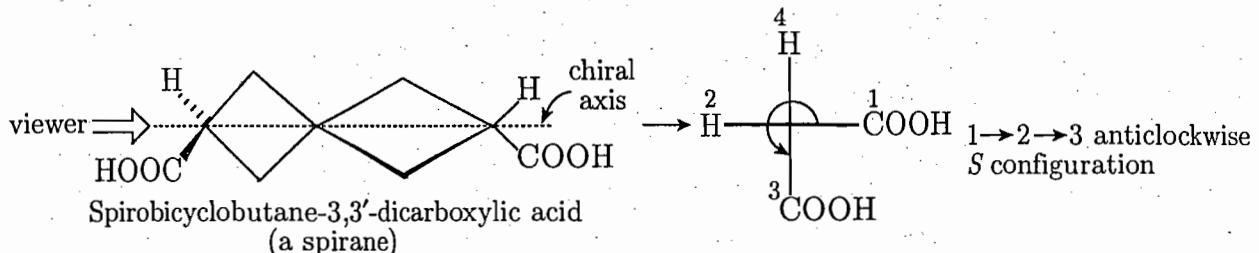
It is to be noted that if in the projection formula the lowest priority group (4) remains in a horizontal bond, it need not be put on any vertical bond before tracing a path from $1 \rightarrow 2 \rightarrow 3$. [Stereodescriptors R_a and S_a , where the subscript 'a' stands for *axial chirality*, are now used to express configurations.]

Example :

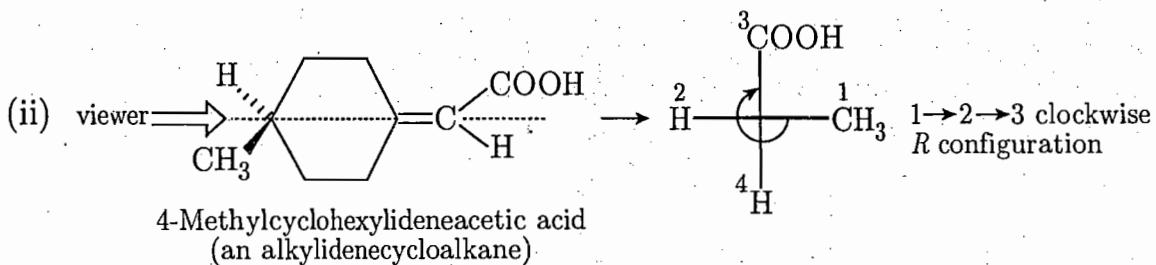


(b) **Spiranes, alkylidenecycloalkenes, oximes and adamantananes** : These compounds possessing axial chirality are assigned configurational descriptors in the same way as discussed for allenes. For example :

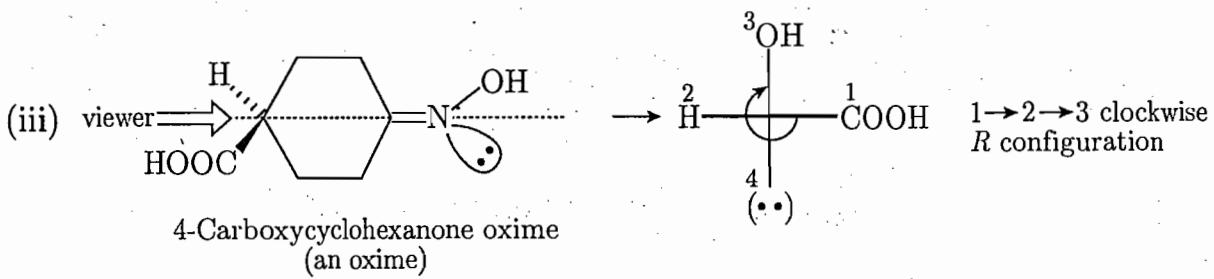
(i)



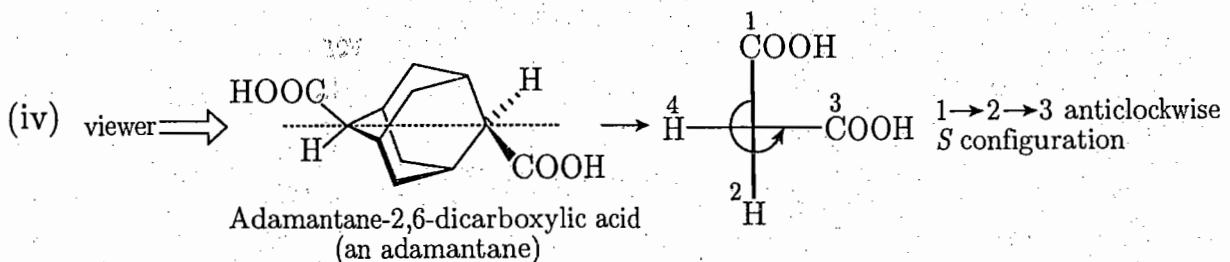
(ii)



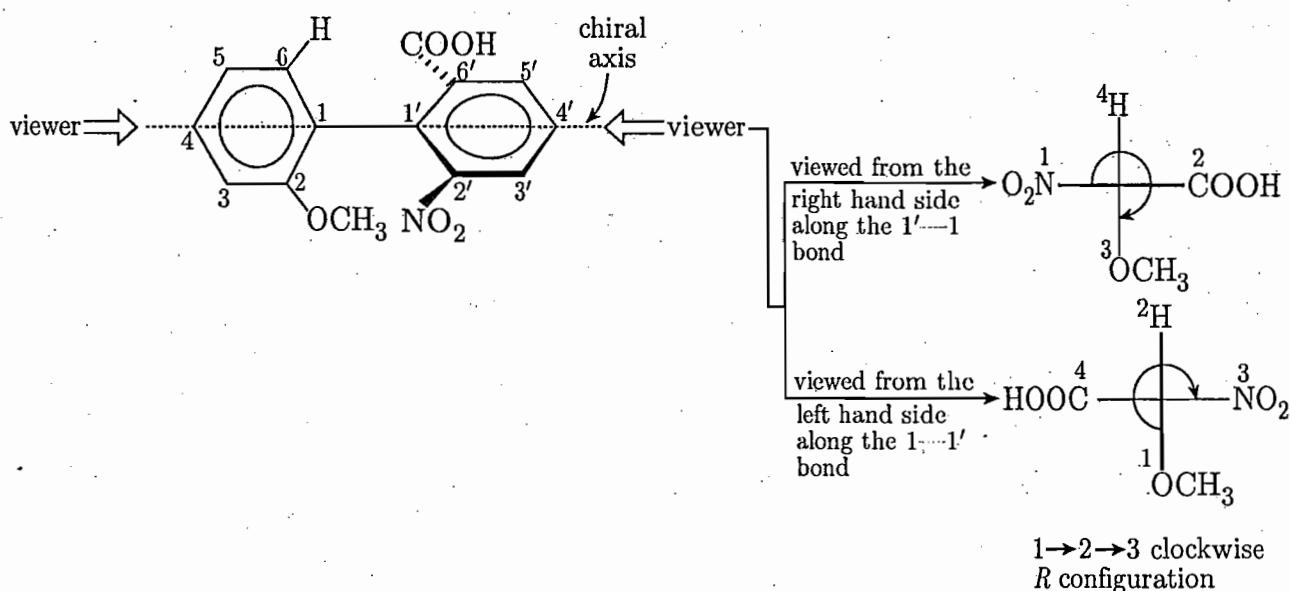
(iii)



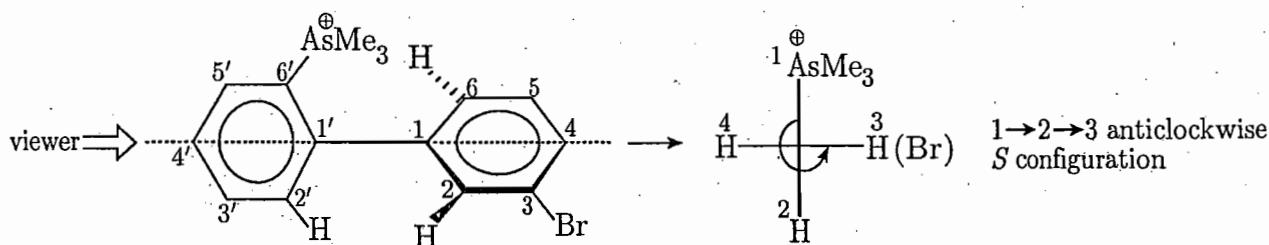
(iv)



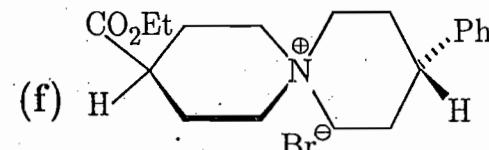
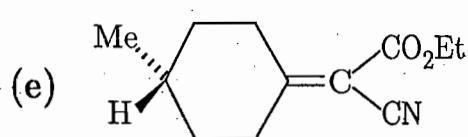
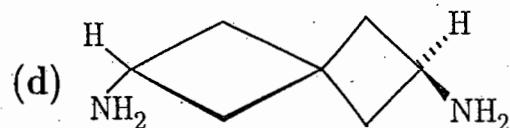
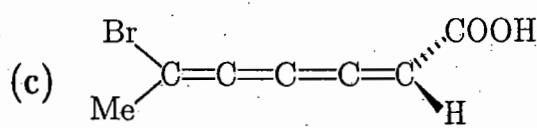
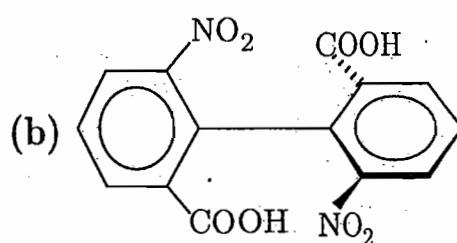
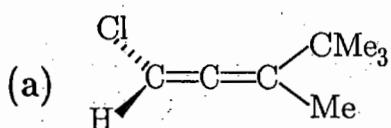
(c) **Biphenyls** : Configurational (*R,S*) descriptors to active biphenyl derivatives can be assigned in the same way as discussed for allenes. In this case, however, the four *ortho* carbon atoms (C-2, C-6, C-2' and C-6') which correspond to four vertices of an elongated tetrahedron are to be sequenced properly according to CIP rules. For example, in the biphenyl derivative given below the priority sequence in the left ring is C-2 > C-6 ($\text{OCH}_3 > \text{H}$) while in the other ring is C-2' > C-6' ($\text{NO}_2 > \text{COOH}$) and therefore, the configuration is *R* when the molecule is viewed from either direction.

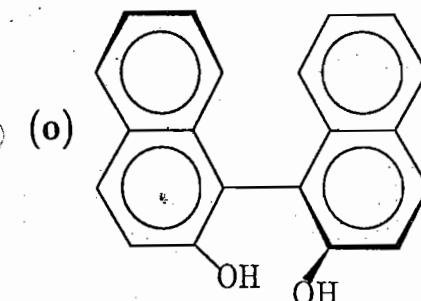
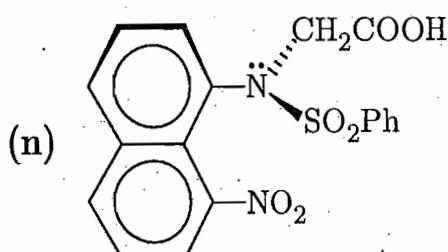
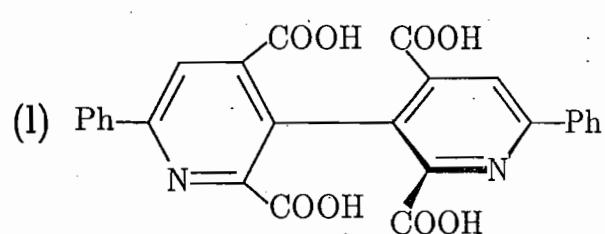
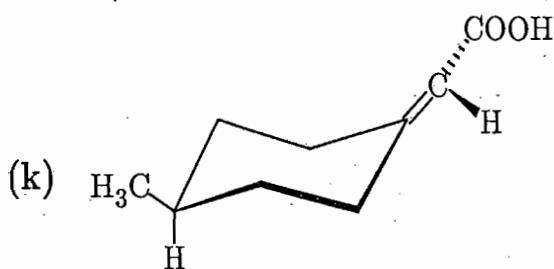
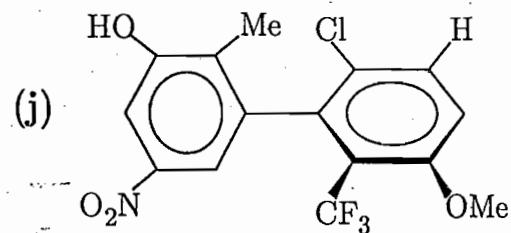
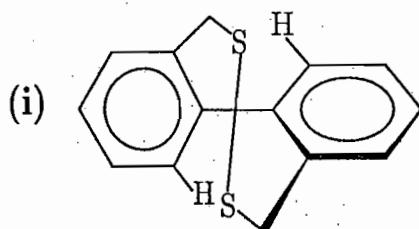
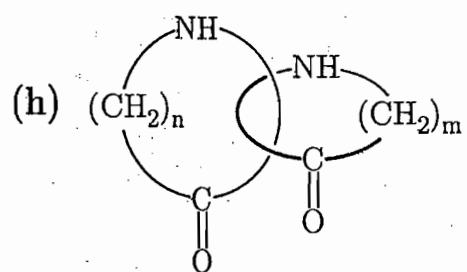
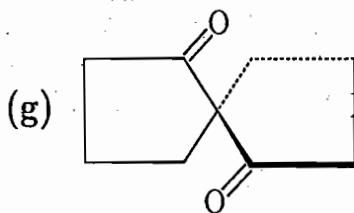
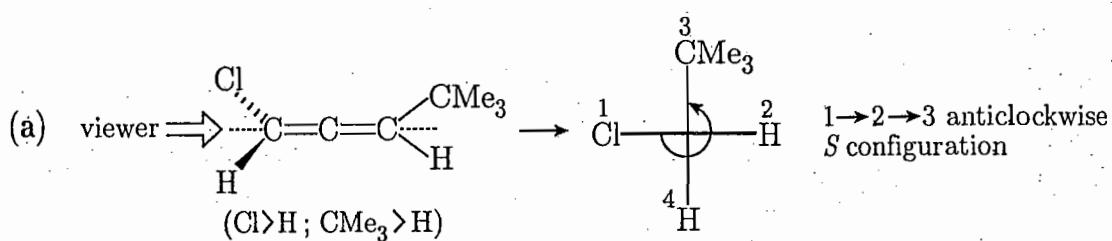


When C-2 and C-6 in a ring are attached to identical atoms and C-3 and/or C-5 are also substituted, the priority order of the *ortho* carbon atoms is then determined through exploration around the ring or side chain. Thus in the following biphenyl derivative the priority order of the *ortho* carbons in the right ring is C-2 > C-6 (Br > H).

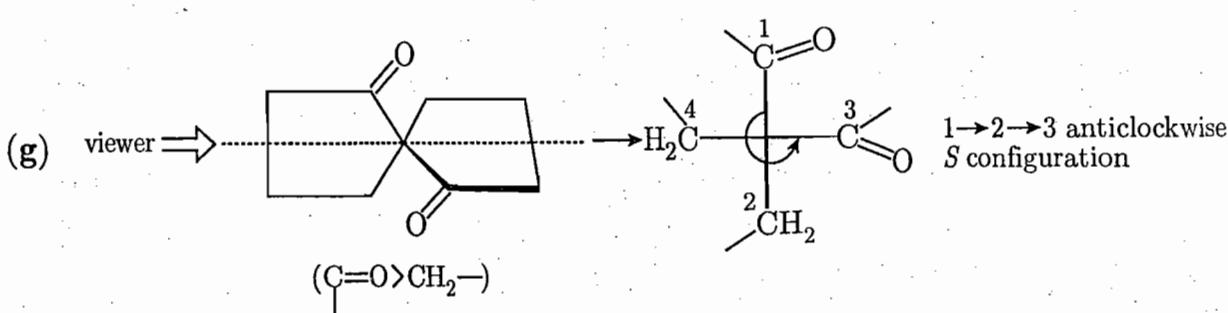
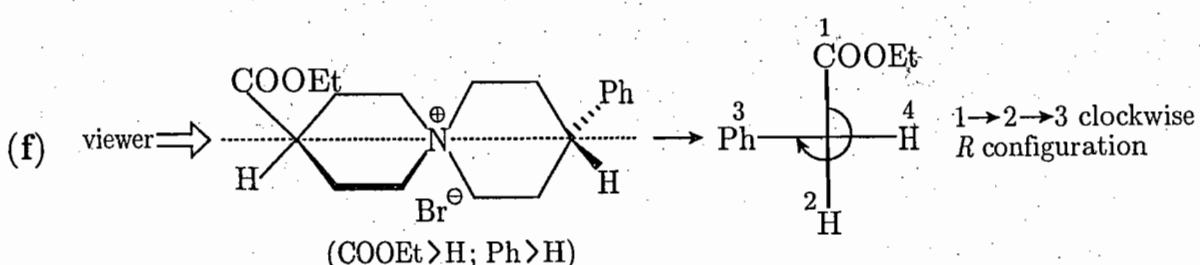
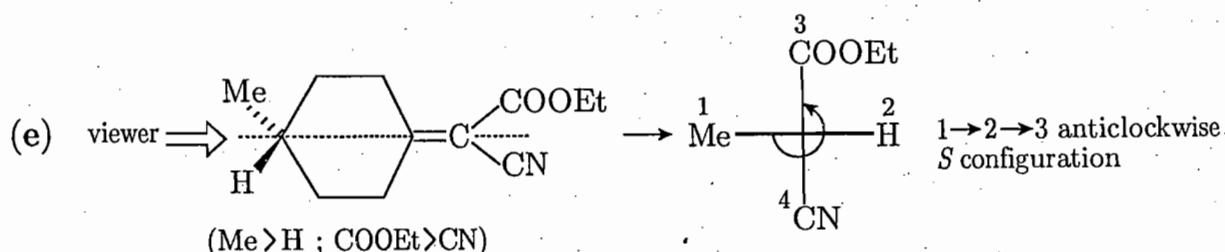
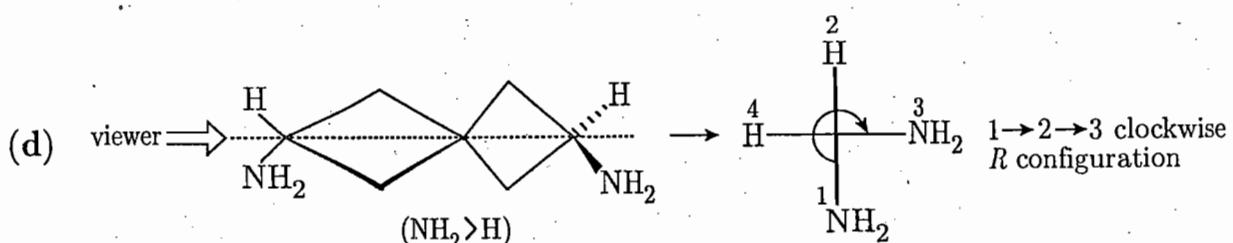
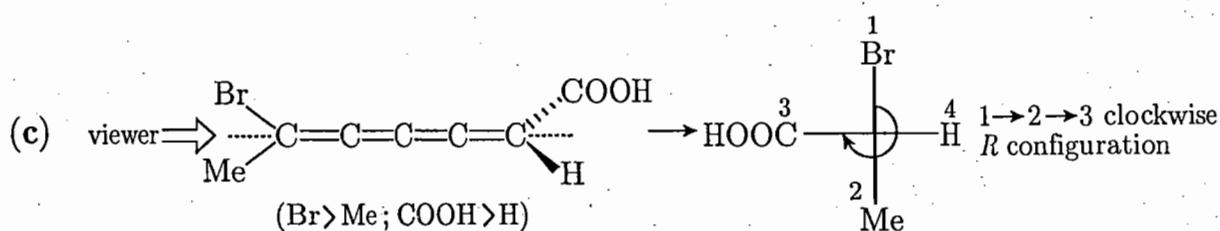
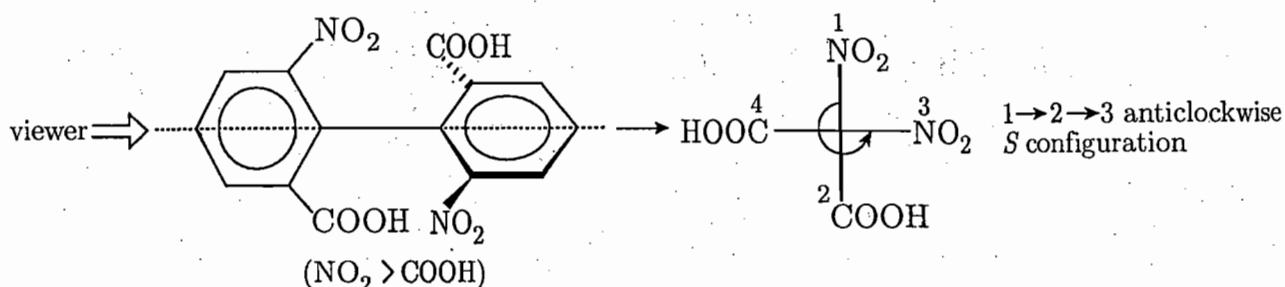


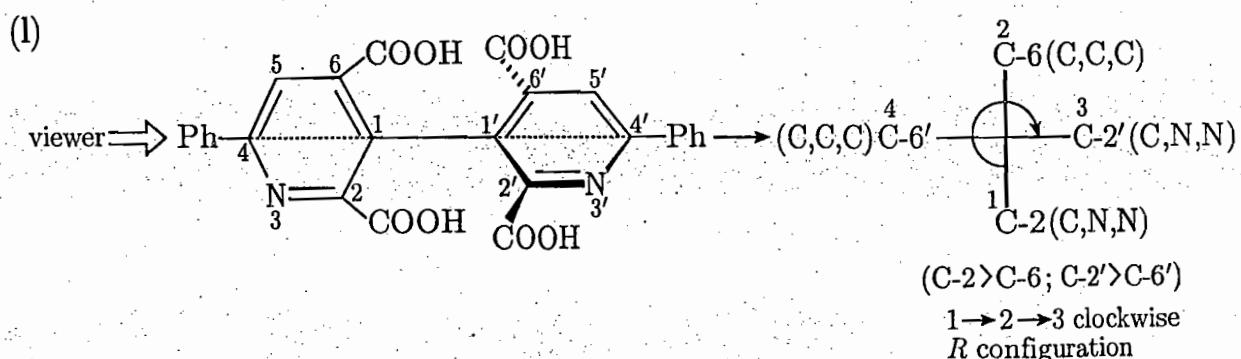
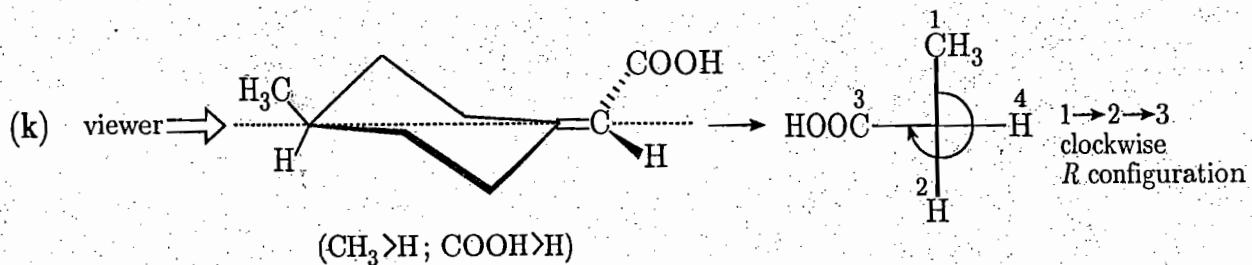
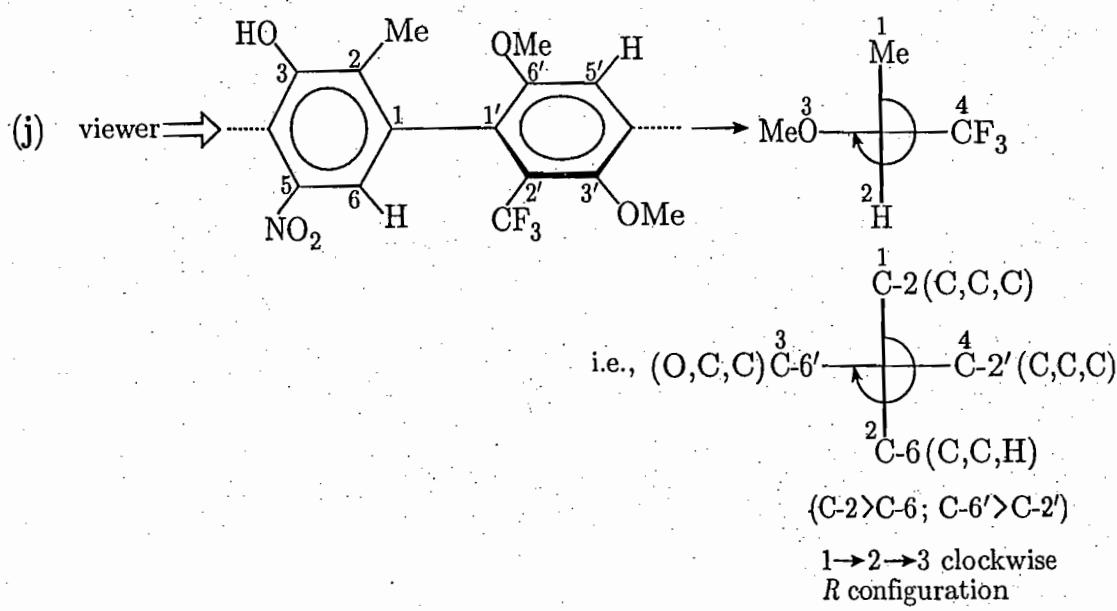
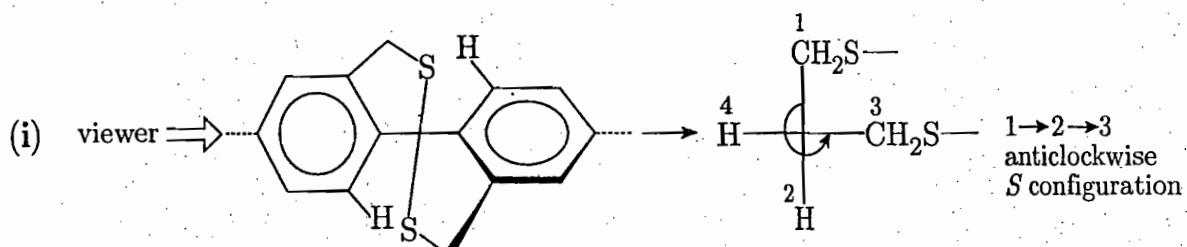
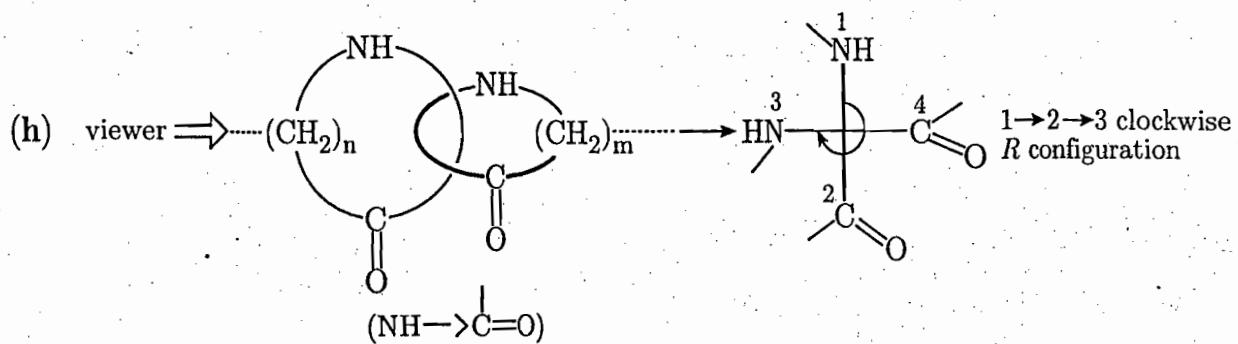
►1.49 Find out the absolute (R,S) configuration of the following axially chiral compounds :

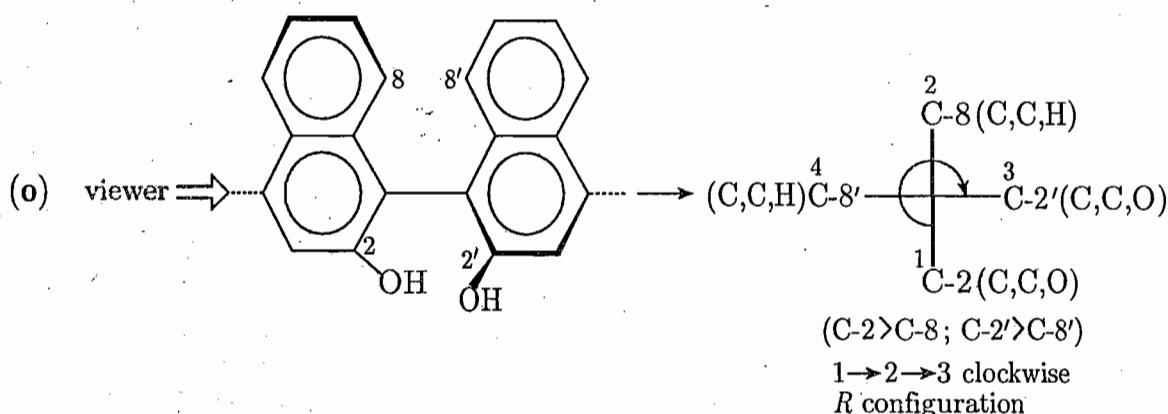
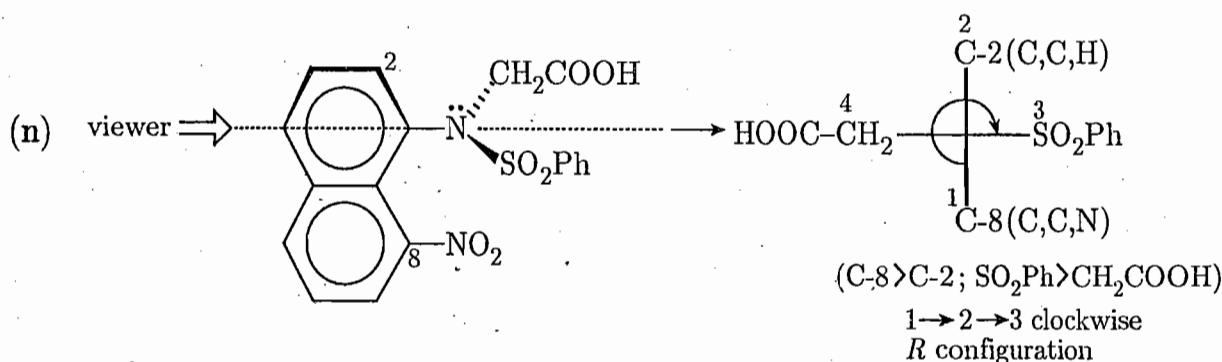
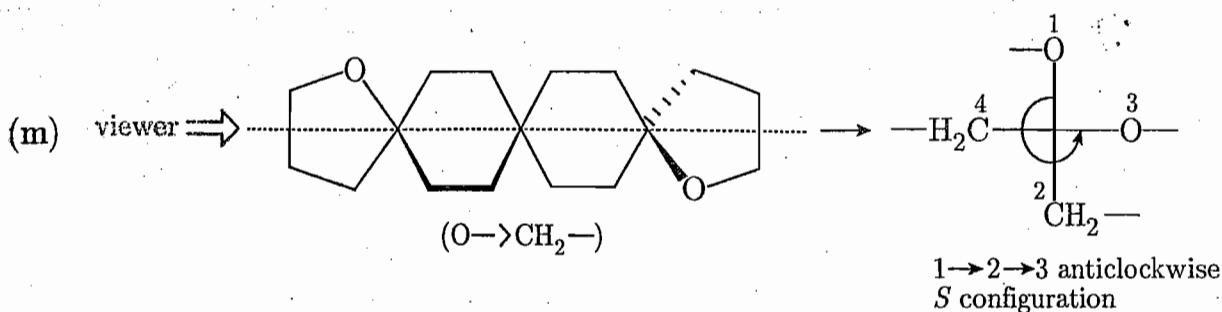


**Ans.**

(b)

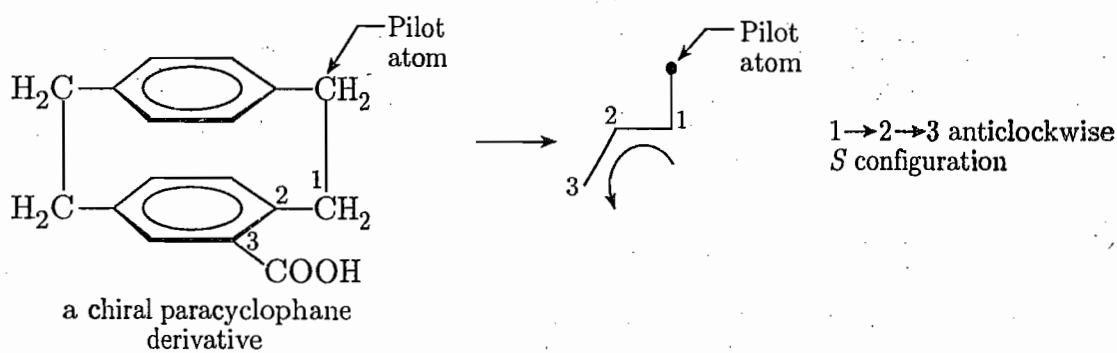
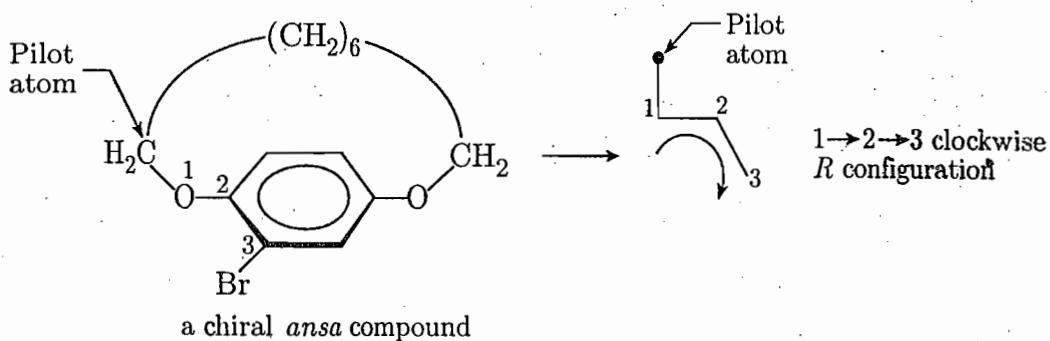






►1.50 Write a short note on the assignment of configurational nomenclature to compounds containing chiral planes.

Ans. For the assignment of configurational (*R,S*) descriptors to compounds containing chiral planes, a pilot atom which is directly bonded to an atom in the chiral plane but itself is not in the plane is to be chosen from that side of the plane which is most preferred (CIP rules). When both sides are equivalent, the pilot atom can be chosen from any side of the plane. Then, counting is started from the first in-plane atom and is continued along the atoms in the plane following the path leading to the more preferred atom. These atoms are labelled by numerals 1,2 and 3 or by a,b and c. Now viewed from the pilot atom, if the order 1 → 2 → 3 or a → b → c traces a clockwise path, the configuration is *R* and if an anticlockwise path, the configuration is *S*. For example, the configuration of the following *ansa* compound is *R* and that of the paracyclophane derivative is *S*. In the former compound the preferred side of the ring is the one with *ortho* bromine atom and the left hand methylene carbon is the pilot atom. In the latter compound the preferred side of the ring is the one with *ortho* carboxyl group and the right hand methylene carbon is the pilot atom.

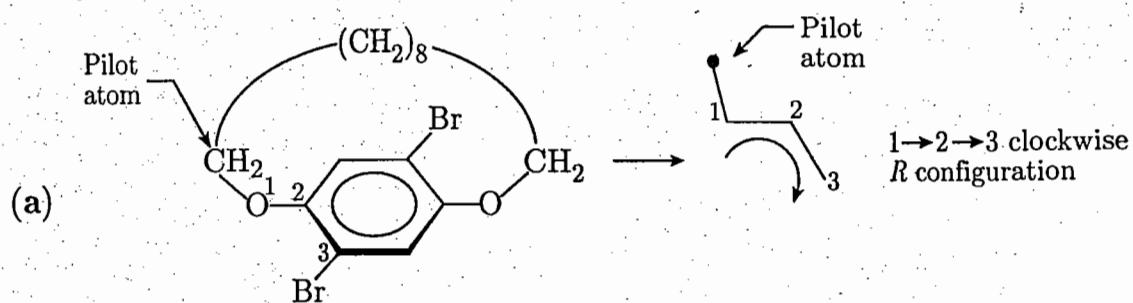


[Stereodescriptors R_P and S_P , where the subscript 'P' stands for chirality plane, are also used to designate configurations.]

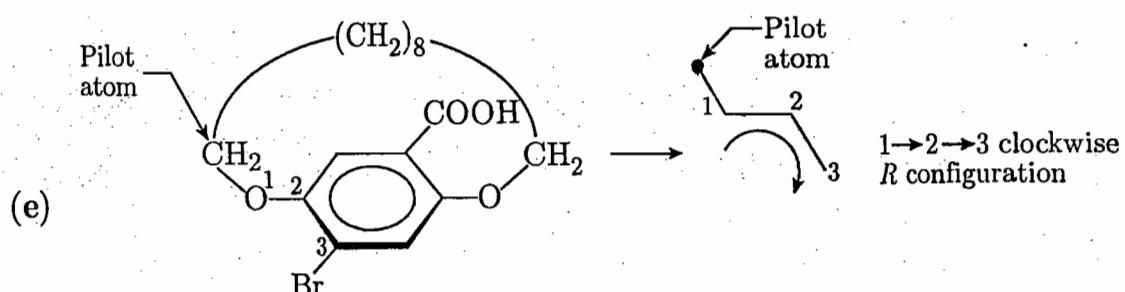
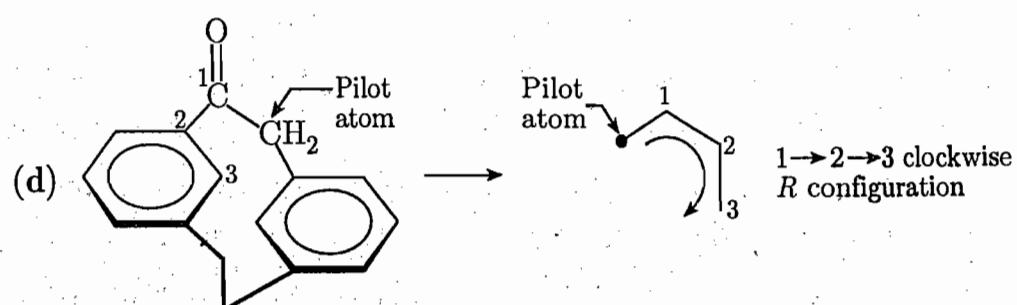
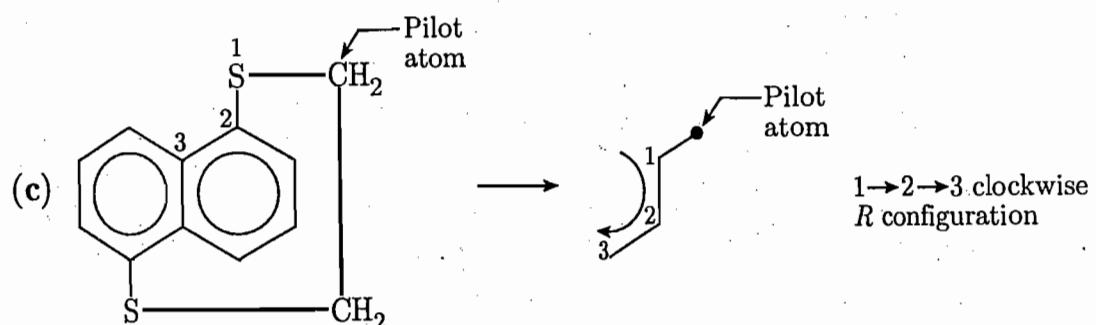
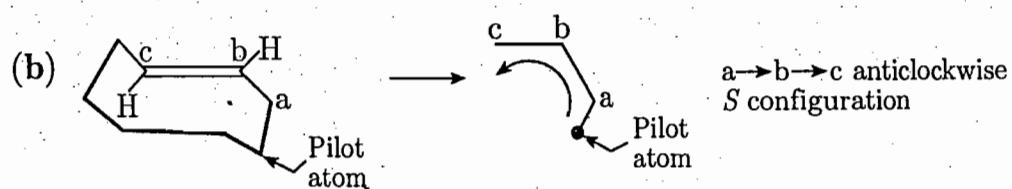
►1.51 Give configurational descriptors to the following compounds with chiral planes :

- Ans.
- (a)
-
- (b)
-
- (c)
-
- (d)
-
- (e)
-

Ans.

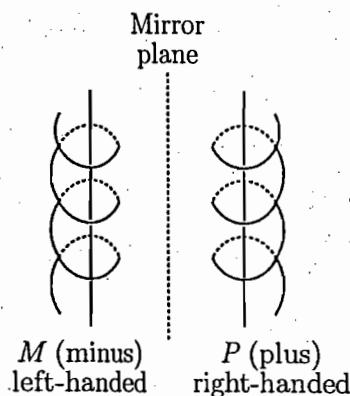


(Since in this case both sides are equivalent, any of the methylene carbons attached to oxygen may be the pilot atom.)

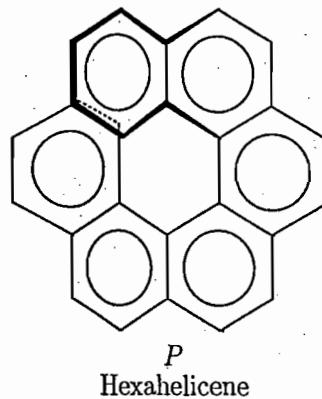


►1.52 Write a short note on the assignment of chiral designation to a helix.

Ans. The assignment of chiral designation to the helix is as follows. 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 (an anticlockwise rotation when viewed along the axis and moving from the front to the rear) is designated *M* (minus).

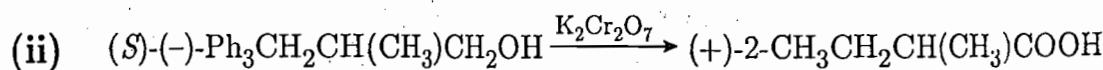
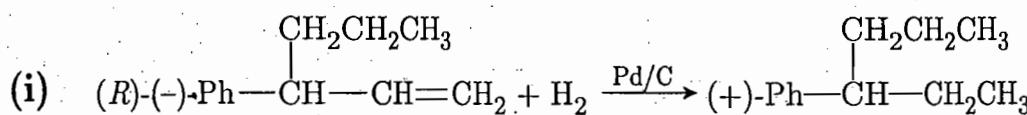


For example, the following enantiomer of hexahelicene is designated *P*.

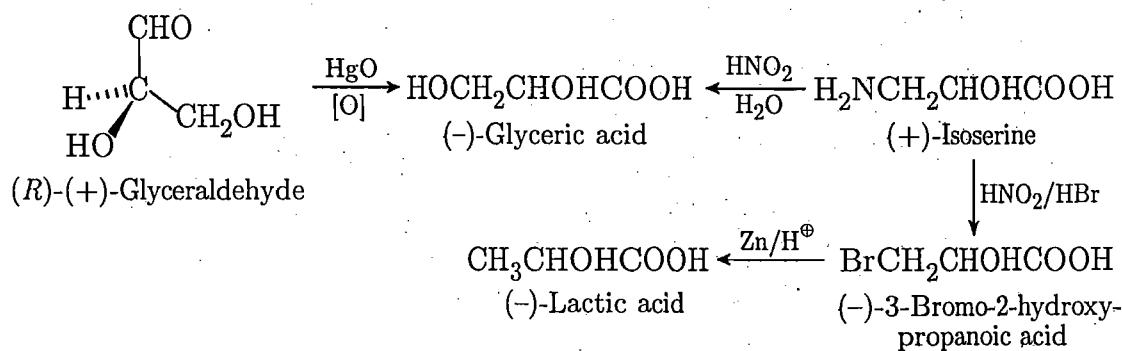


RELATIVE AND ABSOLUTE CONFIGURATION

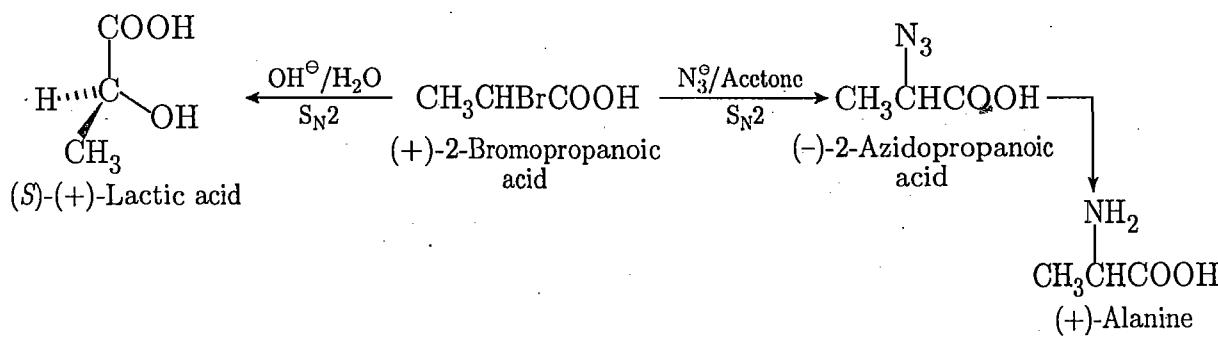
- 1.53 (a) What is meant by "relative configuration". Illustrate with suitable examples.
- (b) What is called absolute configuration? How can one determine the absolute configuration of an optically active compound.
- (c) From the outcome of each of the following transformations, indicate whether the dextrorotatory enantiomer of the product has the (*R*) or (*S*) configuration.



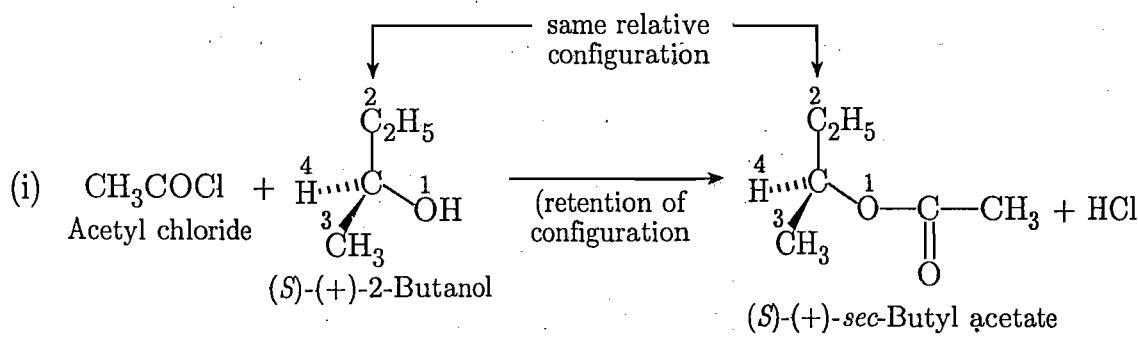
- (d) (-)-Lactic acid could be related to (*R*)-(+)-glyceraldehyde through the following sequence of reactions. What is the configuration of (+)-lactic acid?

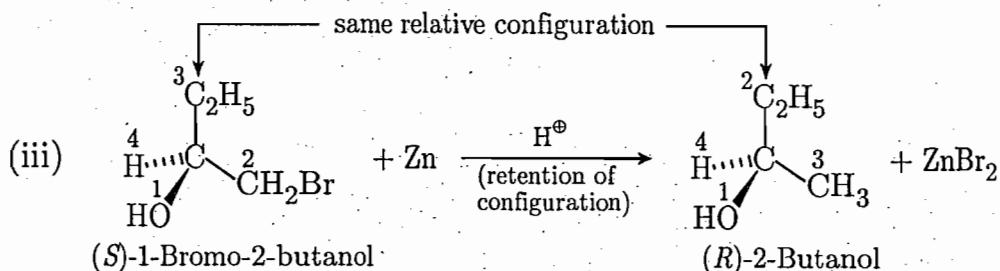
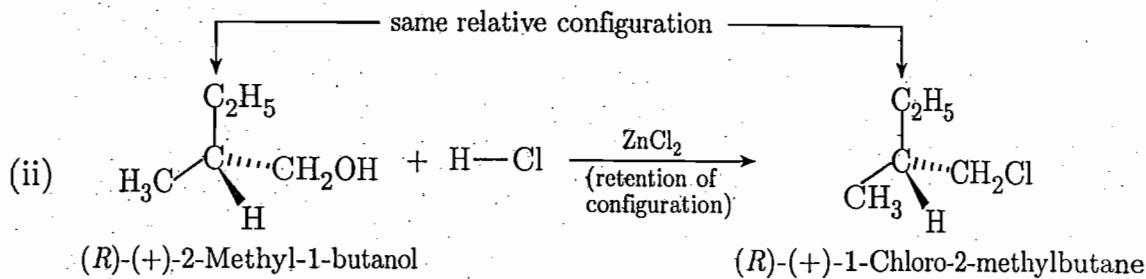


- (e) (+)-Alanine could be related to (*S*)-(+)-lactic acid through the following sequence of reactions. What is the configuration of (-)-alanine?



Ans. (a) Reactions in which no bonds to the stereocentre are broken proceed with retention of configuration, that is, the general spatial arrangement of the groups in the product remains same as that of the reactant. The products of such reactions are said to have the same *relative configurations* as the reactants. For example, in the following three reactions, the reactants and the products have the same relative configurations because none of the reactions does involve cleavage of any of the bonds to the stereocentre.

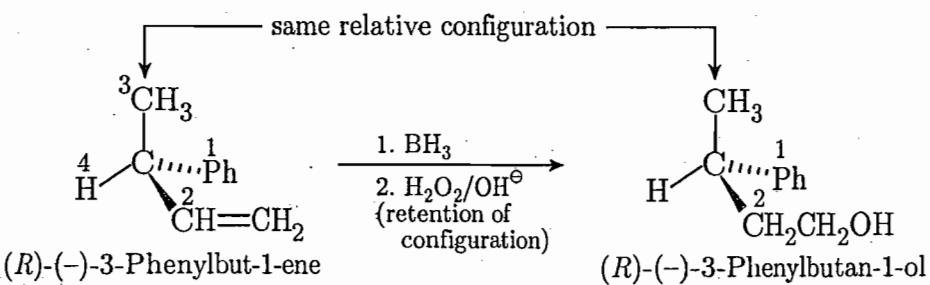




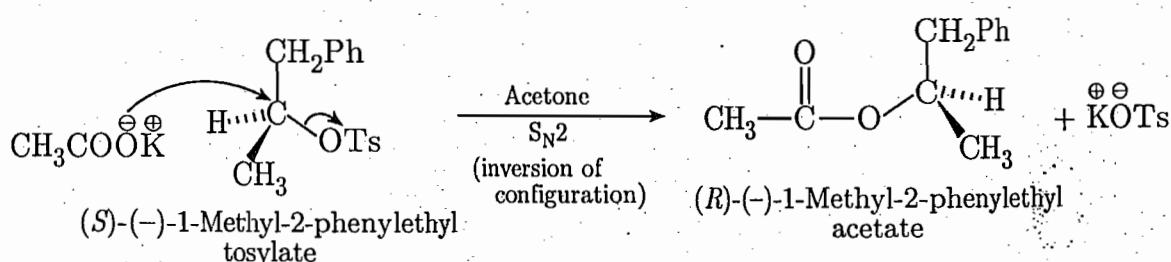
Although the four groups bonded to the chirality centre maintain their relative positions, it does not necessarily mean that an *S* reactant will always yield an *S* product and *R* reactant will always yield an *R* product. In some instances the *R*, *S* designations may change because the relative priorities of groups as defined by the Cahn-Ingold-Prelog (CIP) rules may change [example (iii)].

(b) The actual spatial arrangement of the atoms or groups in any chiral molecule, i.e., the actual configuration of a chiral molecule is called its absolute configuration. [Knowing the absolute configuration of an enantiomer means that you know whether it has the *R* or *S* configuration.]

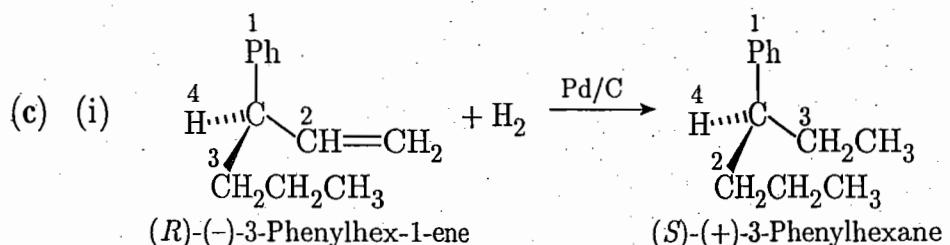
The absolute configuration of most organic compounds are determined by using chemical reactions to correlate them with other compounds of known absolute configuration, that is, by *stereochemical correlation*. The process of stereochemical correlation involves preparation of a compound from another compound (whose absolute configuration is known) by a reaction in which bonds to the asymmetric carbon are unaffected or by a reaction in which bond cleavage occurs, but its stereochemical outcome had already been established. For example, the configuration of $(-)$ -3-phenylbutan-1-ol can be determined by stereochemical correlation as follows. When $(R)\text{-}(-)$ -3-phenylbut-1-ene is subjected to hydroboration-oxidation, it yields $(-)$ -3-phenylbutan-1-ol. The reaction does not break any of the bonds to the asymmetric carbon atom. Thus, the way that the corresponding groups are arranged about the chiral carbon must be the same in both reactant and product. Hence, the resulting $(-)$ -alcohol has the *R* configuration.



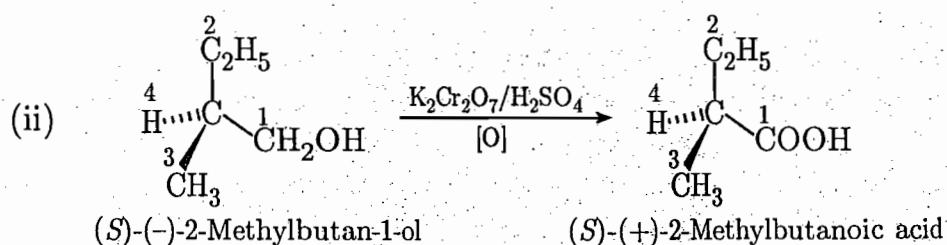
Similarly, the configuration of $(-)$ -1-methyl-2-phenyl acetate can be determined by stereochemical correlation as follows. When (S) - $(+)$ -1-methyl-2-phenylethyl tosylate is subjected to react with CH_3COOK in acetone (an S_N2 reaction), $(-)$ -1-methyl-2-phenylethyl acetate is obtained. Since an S_N2 reaction always occurs with inversion of configuration at the carbon that bears the leaving group, the resulting $(-)$ -ester has the *R* configuration.



[In some reactions involving inversion of configuration (S_N2) the *R,S* designation of the reagent remains same in the product. For example, (S) -1-bromo-1-fluoroethane reacts with NaOMe (an S_N2 reaction) to give (S) -1-fluoro-1-methoxyethane.]

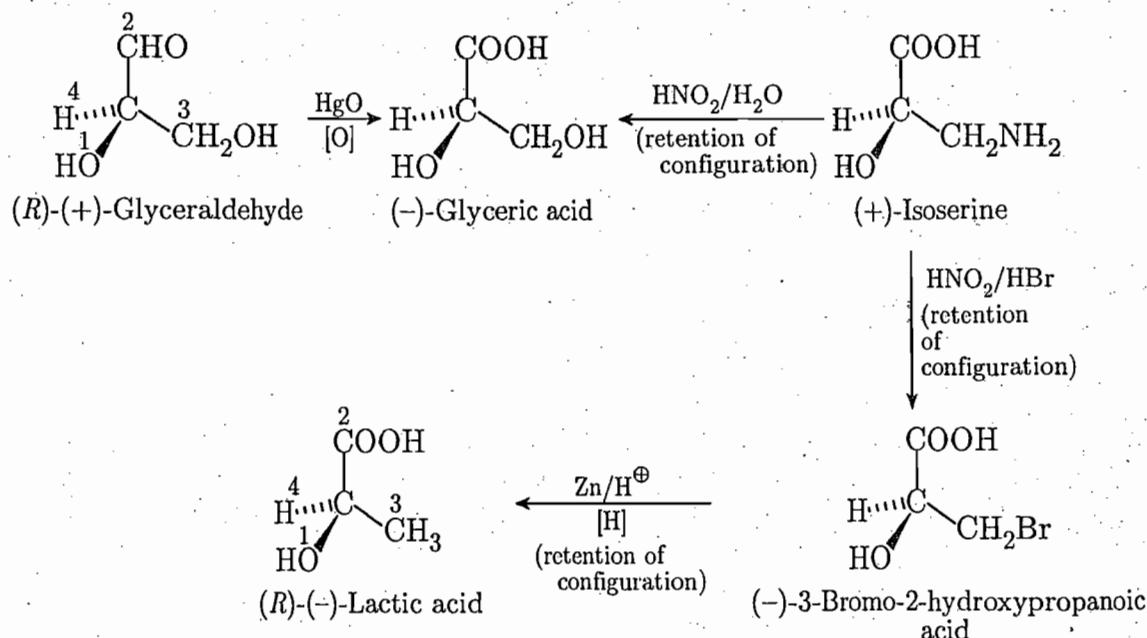


Since $(+)$ -3-phenylhexane is formed from (R) - $(-)$ -3-phenylhex-1-ene without breaking any bonds to the chiral centre, i.e., with retention of configuration, the spatial arrangement of the groups in it is as shown in the figure, i.e., it has the *S* configuration.

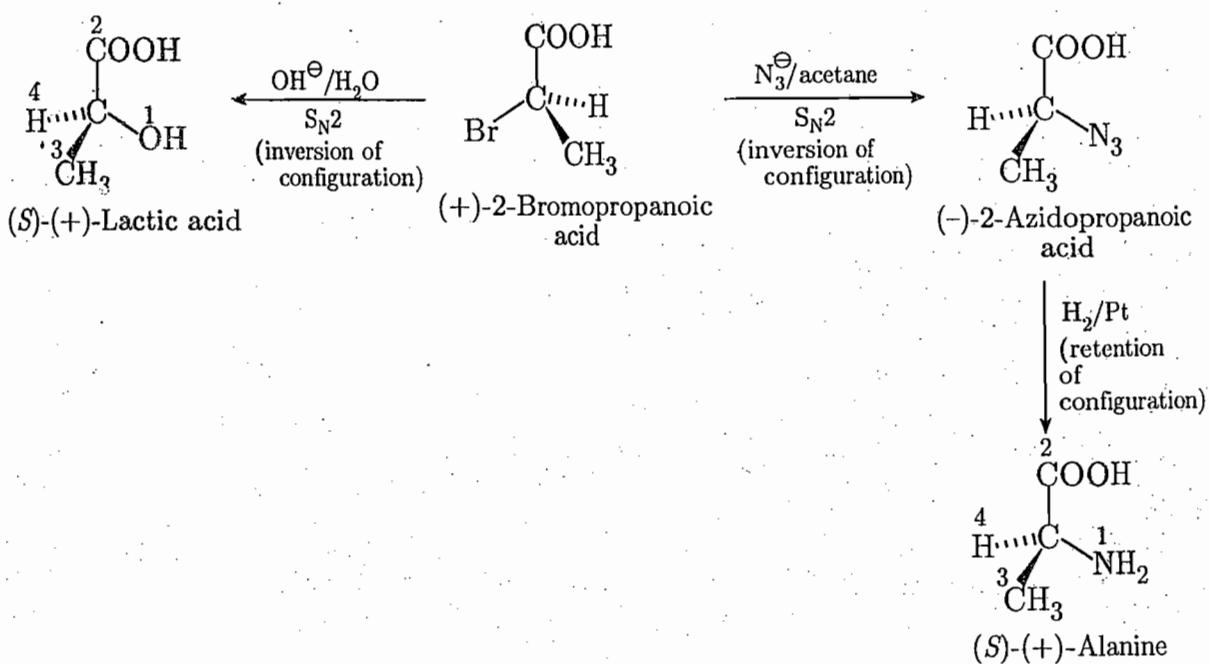


Since $(+)$ -2-methylbutanoic acid is formed from (S) - $(-)$ -2-methylbutan-1-ol without breaking any bonds to the chiral centre, i.e., with retention of configurations the spatial arrangement of the groups in it is as shown in the figure, i.e., it has the *S* configuration.

(d) Since $(+)$ -glyceraldehyde has the *R* configuration and none of these reactions does break a bond to the asymmetric carbon atom, that is, each of these reactions proceeds with retention of configuration, $(-)$ -lactic acid must have the *R* configuration. Hence, $(+)$ -lactic acid has the *S* configuration.



(e) Since the reactions of $(+)$ -2-bromopropanoic acid with $\text{OH}^\ominus/\text{H}_2\text{O}$ to give (S) - $(+)$ -lactic acid and with $\text{N}_3^\ominus/\text{acetone}$ to give $(-)$ -2-azidopropanoic acid proceed with inversion of configuration (both are S_N2 reactions) and the reaction of $(-)$ -2-azidopropanoic acid with H_2/Pt to give $(+)$ -alanine proceeds with retention of configuration, $(+)$ -alanine must have the *S* configuration. Hence, $(-)$ -alanine has the *R* configuration.



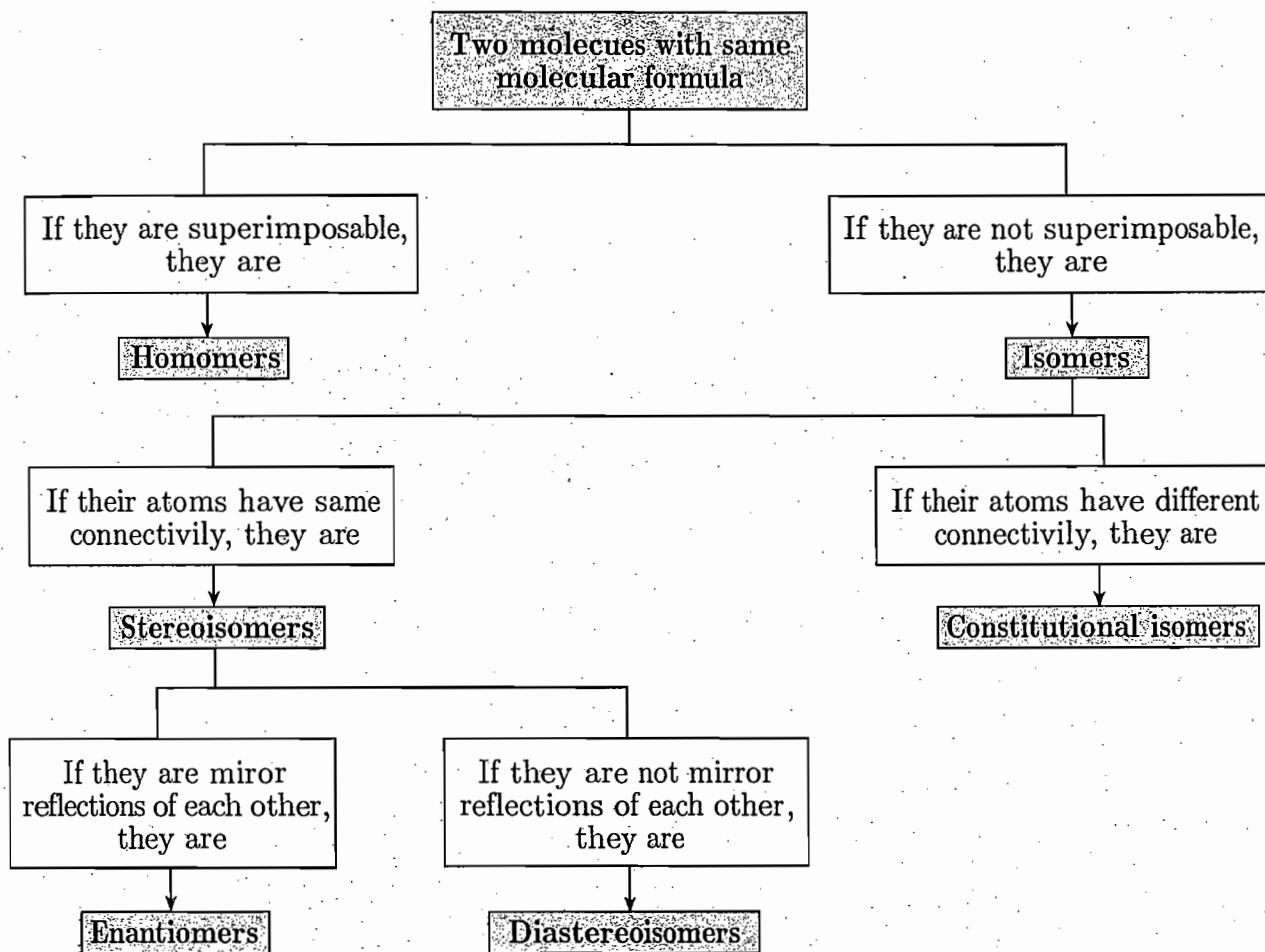
OPTICAL ISOMERISM AND OPTICAL ACTIVITY

►1.54 What is enantiomerism? What is the necessary and sufficient condition for enantiomerism?

Ans. The property of existing as mirror-image isomers gives rise to a type of stereoisomerism known as enantiomerism. Chirality (non-superimposability on mirror image) is the necessary and sufficient condition for enantiomerism.

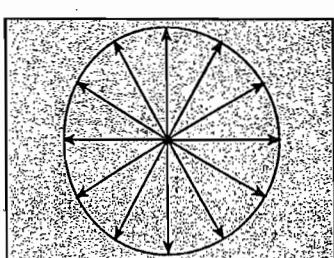
► 1.55 Give a flowchart for determining the stereochemical relationship between two molecules having same molecular formula.

Ans.

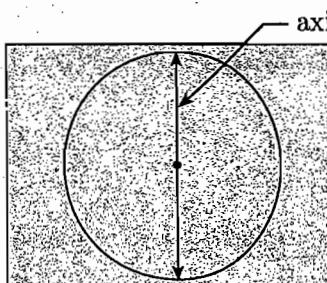


► 1.56 What is plane-polarized light?

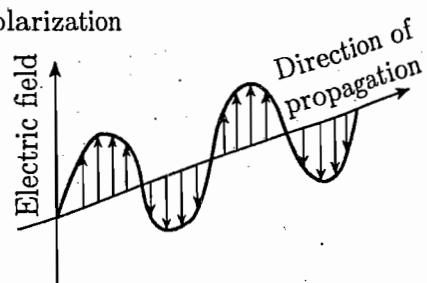
Ans. A beam of ordinary light (composed of rays of different wavelengths) consists of an electric field and a magnetic field which are vibrating at right angles to each other in every plane perpendicular to its direction of propagation. The same is true of monochromatic light, i.e., light of single wavelength. These vibrations can be made to occur in a single plane by passing a beam of monochromatic light through the polarizing *Nicol* prism (made of calcite which is a particular crystalline form of CaCO_3), called polarizer. Such light is called plane-polarized light.



(End-on view of planes of oscillating electric fields of ordinary light)



(End-on view of the plane of oscillating electric field of plane-polarized light)



(Side-on view of the plane of oscillating electric field of plane-polarized light)

►1.57 Why are enantiomers called optical isomers? What are optically inactive compounds?

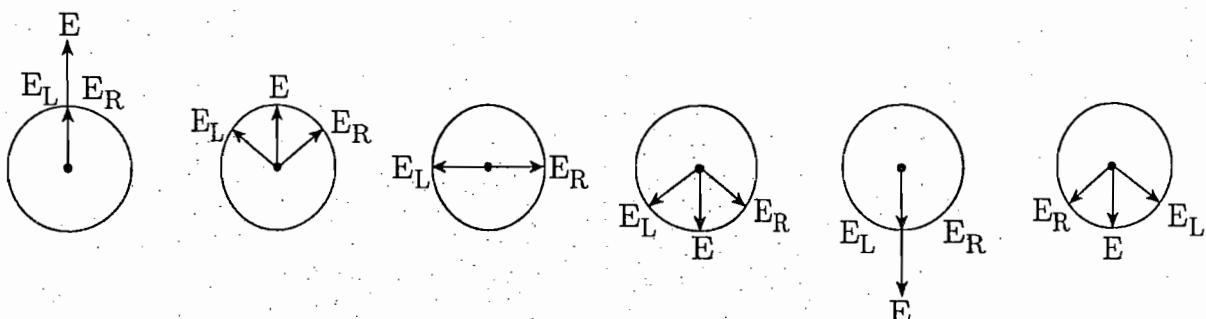
Ans. Enantiomers rotate the plane of polarized light to an equal degree but in opposite directions. Because of their effect on plane-polarized light, separate enantiomers are said to be optically active and because of this property, they are called optical isomers or optical antipodes.

Compounds that do not rotate the plane of polarized light are said to be optically inactive.

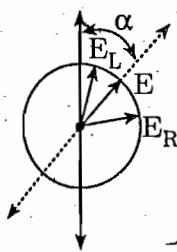
►1.58 (a) What is optical activity? (b) Explain the cause of optical activity?
 (c) Explain why an achiral compound, such as ethanol, is found to be optically inactive.

Ans. (a) Optical activity is an important physical property of chiral substances and is the ability to rotate the plane of polarized light.

(b) The plane-polarized light is composed of two enantiomeric (non-superimposable mirror images of each other) helical waves circulating around the axis of propagation in opposite directions. One of these helical waves having clockwise motion is known as "Right Circularly Polarized light" (RCP) and the other having anticlockwise motion is known as "Left Circularly Polarized light" (LCP). Each helix has an associated electric field vector (E_L and E_R). The vector sum (E) of two counterrotating in-phase circularly polarized beams is a beam of plane-polarized light. When plane-polarized light is passed through a solution containing a chiral compound, a diastereomeric interaction occurs between the chiral compound and the plane polarized light. The two counterrotating circularly polarized beams travel with different velocities (out of phase) through the chiral medium because of their different refractive indices and absorption coefficients in this medium (the origin of the differing velocities has ultimately to do with interactions between the electrical vector of plane-polarized light and the oscillating electrons in the chiral molecule). The result is that the plane of polarization gets rotated with respect to the original plane. This phenomenon is called *circular birefringence*.

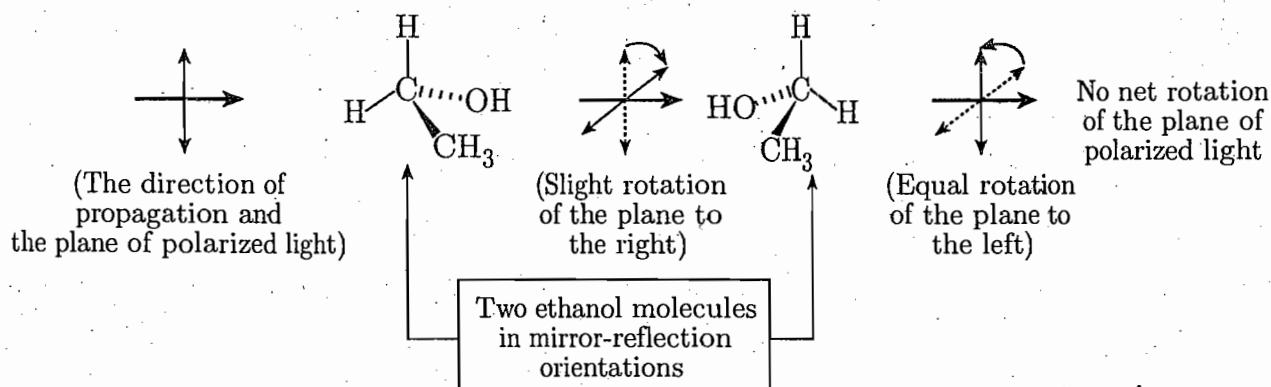


[Two circularly-polarized beams counterrotating at the same velocity (in phase), and their vector sum. The net result is to give plane-polarized light.]



[Two circularly-polarized beams counterrotating at the different velocities after interaction with a chiral molecule and their vector sum. The net result is to give the polarized light whose plane is rotated.]

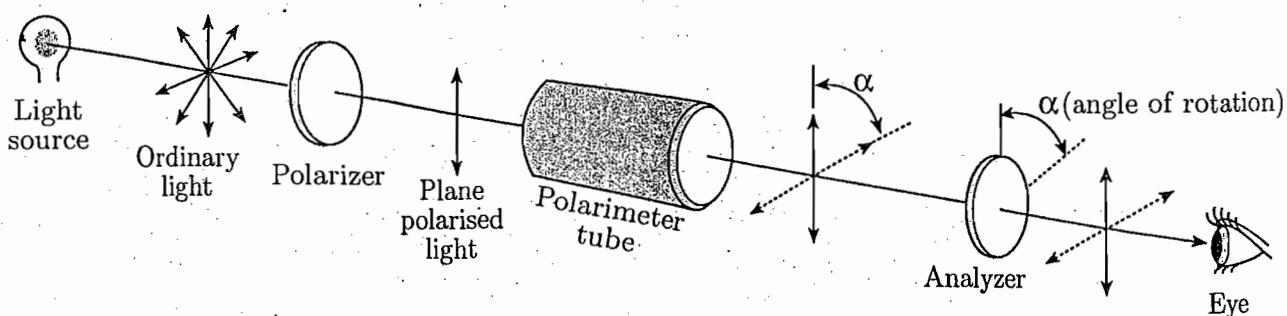
(c) Almost all individual molecules, whether chiral or achiral, are theoretically capable of rotating the plane of polarized light. If the beam of plane-polarized light passes through a solution of the chiral compound ethanol, for example, it should encounter at least two molecules in exactly the mirror-reflection orientations. The effect of these two encounters on the plane-polarized light will be equal in magnitude but opposite in directions. The beam of light, therefore, emerges with no net rotation. Since a large number of molecules are present in a solution, it is statistically certain that for each encounter with a molecule in a particular orientation there will be an encounter with a molecule that is in a mirror-reflection orientation. The result of all these encounters will be such that all the rotations produced by individual molecules will be cancelled and ethanol will be found to be optically inactive.



- 1.59 (a) What is a polarimeter? Discuss in details the working of a polarimeter used in the analysis of enantiomers.
- (b) What are called dextrorotatory and levorotatory compounds? Mention the symbols/signs which are used to distinguish between two enantiomeric forms of a substance.
- (c) What factors affect the value of observed rotation (α)?
- (d) What is specific rotation? Is it a constant value for a particular compound?

Ans. (a) The rotation of a plane-polarized light by an optically active compound is detected and measured by an instrument called a polarimeter?

The schematic representation of a polarimeter is as follows :



(Solid lines represent the plane of polarised light before rotation and broken lines represent the same after rotation)

A polarimeter has a monochromatic light source (usually a sodium lamp) at one end which produces unpolarized light. This light passes through a stationary Nicol prism, called 'polarizer'. The plane-polarized monochromatic light from the polarizer then passes through the polarimeter tube and then through another movable Nicol prism, called 'analyzer' and finally reaches the eye of an observer. Before taken the compound in the tube, the polarizer and the analyzer prisms are so adjusted that the light passes through them without loss of intensity, i.e., maximum amount of light reaches our eye. Then the compound in pure liquid form or as a solution in a suitable solvent (usually water, ethanol, or chloroform) is introduced into the polarimeter tube. If the intensity of light reduces (due to rotation of the plane of the polarized light), the compound is said to be optically active. In that case, the analyzer is to be rotated in either clockwise or anticlockwise direction to bring back the original intensity of light. The angle in degrees that the analyzer needs to be rotated is taken as the observed rotation (α) of the optically active compound. Rotation of the plane of polarized light in the clockwise sense is taken as positive (+), while rotation in the anticlockwise sense is taken as a negative (-) rotation. Enantiomeric compounds rotate the plane of polarized light by exactly the same amount i.e., to an equal degree but in opposite directions.

(b) Compounds that rotate the plane of polarized light to the right (clockwise) are called **dextrorotatory** (Latin *dexter*, meaning "right") and compounds that rotate the plane to the left (counterclockwise) are called **levorotatory** (latin *laevus*, meaning "left").

At one time, the symbols *d* and *l* were used to distinguish between two enantiomeric forms of a substance. Thus the dextrorotatory enantiomer of 2-butanol was called *d*-2-butanol and the levorotatory form *l*-2-butanol. Now-a-days enantiomers are named by prefixing the sign of rotation to the name of the substance. For example, the dextrorotatory enantiomer of 2-butanol is called (+)-2-butanol and the levorotatory form (-)-2-butanol.

(c) The rotation (α) observed in a polarimeter depends on how many molecules the light beam encounters (i.e., on the concentration of the sample solution and the length of the tube containing the solution), as well as the structure of the chiral molecule. Other factors are : the solvent (if present), the temperature and the wavelength of the light used for the measurement.

(d) According to Biot's law the observed rotation (α) is proportional to the concentration of the optically active compound and the path length of the solution through which polarized light passes.

$$\therefore [\alpha] = \frac{\alpha}{cl}$$

where, $[\alpha]$ = the proportionality constant and is called the *specific roation*

α = the observed rotation

c = the concentration of the solution in grams per millilitre of solution (or density in g/mL for a pure liquid)

l = the length of the tube in decimetres (1 dm = 10 cm)

Thus, the specific roation, $[\alpha]$, may be defined as the rotation in degrees brought about by a pure liquid or a solution containing 1 g of an optically active substance per ml of solution, placed in a 1 decimetre polarimetre tube. Because the specific roation $[\alpha]$ is independent of c and l , it is used as the standard measure of optical activity. Because the specific roation of any compound varies with wavelength and temperature, $[\alpha]$ is conventionally reported with a subscript that indicates the wavelength of light used and a superscript that indicates the temperature. Thus, a specific roation reported as $[\alpha]_D^{25}$ tells us that it has been determined at 25°C and the wavelength of light used is a yellow emission line in the spectrum of sodium, called the *sodium D line* ($\lambda = 589.6$ nm). The specific rotation of (+)-2-butanol might be given as follows :

$$[\alpha]_D^{25} = -13.52^\circ$$

[Although the unit of specific rotation is $\text{degree } \text{cm}^2 \text{g}^{-1}$, it is usually expressed in *degree* only. When specific rotation is measured in solvents other than water, the name of the solvent must be mentioned.]

Specific rotation is a constant for an optically active compound if the measurement is carried out under the same condition. [Specific rotation is a physical property of a compound, just as melting point, boiling point, density, and solubility are.]

- 1.60 (a) Calculate the specific rotation of (+)-glyceraldehyde ($\text{HOCH}_2\text{CHOHCHO}$), if a solution containing 2.0 g/10 mL is placed in a 1-dm polarimeter tube and its observed rotation at 25°C using sodium D line is +1.74°. What is the specific rotation of its enantiomer?
- (b) What is the observed rotation of glyceraldehyde if (i) the concentration is doubled and (ii) the length of the polarimeter tube is doubled?
- (c) What is the specific rotation if the concentration and the length of the polarimeter tube is doubled?
- (d) How one can conclude that the rotation of a compound is either dextro (+)- or leavo (-)-?

$$\text{Ans. (a)} \quad [\alpha]_D^{25} = \frac{\alpha}{cl} = \frac{+1.74}{(1)(0.2)} = +8.7^\circ$$

The specific rotation of its enantiomer is -8.7° .

(b) (i) Doubling the concentration doubles the observed rotation because the number of molecules the light beam encounters doubles. Therefore, the observed rotation, $\alpha = +1.74^\circ \times 2 = +3.48^\circ$.

(ii) Doubling the length of the polarimeter tube also doubles the observed rotation due to the same basic reason.

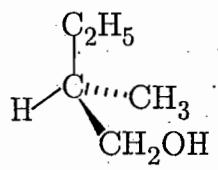
(c) The specific rotation, $[\alpha]_D^{25}$, is a constant and is independent of concentration and the length of the cell.

(d) A single experiment of measurement of rotation of any compound cannot be used to conclude that the rotation is either *dextro* (+)- or *leavo* (-)-. For example, if the observed rotation is reported to be $+20^\circ$, one can conclude that it could be -340° . One can find out the correct direction of rotation by changing the concentration of the solution. If the concentration is reduced by four times, than the decrease in dextrorotation should be four times of $+20^\circ$ and consequently the new value would be $+5^\circ$. Similarly, the change in laevorotation should be four times less that of -340° and the changed value would be -85° . Therefore, if the second reading is $+5^\circ$, the rotation must be *dextro* (+)- and if the second reading is -85° , the rotation must be *leavo* (-)-.

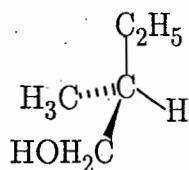
One can also find out the correct direction of rotation by changing the length of the polarimeter tube keeping the concentration unchanged.

►1.61 No correlation exists between the (R) and (S) designation and the direction of rotation of plane-polarized light". Justify the statement.

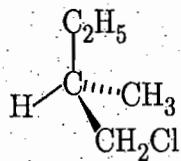
Ans. The rotation of a compound, (+) or (-), is something that we measure in the laboratory with a polarimeter and it depends on how the molecule interacts with light. On the other hand, the (R) and (S) designation is our own artificial way of describing how the atoms or groups are arranged in space around a chiral centre, i.e., the configuration of a particular chiral centre. Therefore, no necessary correlation exists between the (R) and (S) designation and the direction of rotation of plane-polarized light. Dextrorotatory compounds may have (R) and (S) configuration. Similarly, levorotatory compounds may have (R) or (S) configuration. For example :



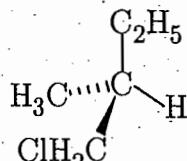
(R)-(+)-2-Methyl-1-butanol
 $[\alpha]_D^{25} = +5.75^\circ$



(S)-(-)-2-Methyl-1-butanol
 $[\alpha]_D^{25} = -5.75^\circ$



(R)-(-)-1-Chloro-2-methylbutane
 $[\alpha]_D^{25} = -1.64^\circ$



(S)-(+)-1-Chloro-2-methylbutane
 $[\alpha]_D^{25} = +1.64^\circ$

- 1.62 (a) What is a racemic modification or racemic mixture or a racemate? Is it optically active? Give reasons.
- (b) What is meant by the terms 'optical purity (OP)' and 'enantiomeric excess (ee)'?
- (c) What is the optical purity of a racemic modification?
- (d) Calculate the ee and the specific rotation of a mixture containing 10 g of (+)-2-butanol and 6 g of (-)-2-butanol. The specific rotation of enantiomerically pure (+)-2-butanol is + 13.5°.
- (e) What is the percentage composition of a mixture of two enantiomers of 2-butanol whose rotation is +2.7?

Ans. (a) An equimolar mixture of two enantiomers is called a racemic modification or racemic mixture or a racemate. A racemic mixture is symbolized by prefixing (\pm) or (*dl*) to the name of the compound. For example, racemic glyceraldehyde would be symbolized by " (\pm) -glyceraldehyde" or "*(dl)*-glyceraldehyde".

A racemic mixture is optically inactive, i.e., we would observe a rotation of zero because the (+)-enantiomer would rotate the polarized light clockwise with a specific rotation of $(+)$ x°, and the (-)-enantiomer would rotate the polarized light counterclockwise by exactly the same amount.

(b) In some cases we deal with mixtures that are neither optically pure nor racemic. In such cases we determine what is known as the *optical purity (OP)* of the mixture which is defined as the specific rotation of a mixture of two enantiomers, expressed as a percentage of the specific rotation of a pure enantiomer.

$$\text{Optical Purity (OP)} = \frac{\text{Observed specific rotation}}{\text{Specific rotation of the pure enantiomer}} \times 100$$

For example, let the specific rotation of an enantiomeric mixture is $+9.72^\circ$ and that of the pure enantiomer is $+13.5^\circ$, then the optical purity of the enantiomeric mixture is equal to

$$\frac{+9.72^\circ}{+13.5^\circ} \times 100\% = 72.0\% \text{ with respect to (+)-enantiomer}$$

This indicates that in the enantiomeric mixture, the excess of (+)-enantiomer is 72% and remaining 28% exists as racemic modification. Thus, the composition of enantiomeric mixture is (+)-enantiomer $(72 + 14) = 86\%$ and (-)-enantiomer 14%.

The *enantiomeric excess* (ee) is just another method (similar to optical purity) of expressing the relative amounts of enantiomers in a mixture; it is the excess of one enantiomer in a mixture of enantiomers expressed as a percentage of the entire mixture. It can be calculated from the expression :

$$\text{ee} = \text{OP} = \frac{|d - l|}{d + l} \times 100\% = \frac{\text{excess of one enantiomer over the other}}{\text{entire mixture}} \times 100\%$$

where d and l represent the amounts of the enantiomers expressed in concentrations, grams or percentages.

The calculation of enantiomeric excess generally gives the same result as the calculation of optical purity.

- (c) Optical purity of racemic modification in zero.
- (d) In $(10 + 6)\text{g}$ or 16 g mixture, there is 4 g excess of the (+)-enantiomer.

$$\therefore \text{OP} = \text{ee} = \frac{|10 - 6|}{10 + 6} \times 100\% = \frac{4}{16} \times 100\% = 25\%$$

The specific rotation of enantiomerically pure (+)-2-butanol is $+13.5^\circ$.

$$\begin{aligned} \therefore \text{observed specific rotation} &= \text{specific rotation of the pure enantiomer} \times \frac{\text{OP}}{100} \\ &= \frac{(13.5^\circ) \times (25)}{100} = +3.37^\circ \end{aligned}$$

(e) $\text{OP} = \frac{+2.7}{+13.5} \times 100\% = 20\%$ [with respect to the (+) enantiomer]

So, 20% of the mixture consists of (+)-enantiomer and 80% is the racemic modification. The total of (+)-enantiomer is thus $(20 + 80/2)\%$ or 60% and remaining 40% is (-)-enantiomer.

[This may be calculated alternatively as follows. Let the mixture contains $a\%$ (+) enantiomer and $(100 - a)\%$ (-)enantiomer. Since the observed rotation is $+2.7$, we can write,

$$\frac{+13.5^\circ a + [-13.5(100 - a)]}{100} = +2.7$$

Simplifying : $27a - 1350 = 270$

or, $27a = 1620$

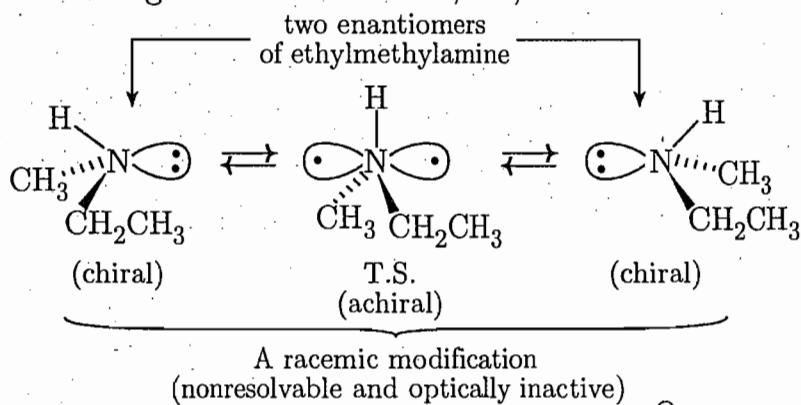
or, $a = 60$

Therefore, the mixture contains 60% (+) enantiomer and $(100 - a)$ or $(100 - 60)$ or 40% (-) enantiomer.]

- 1.63** (a) What is the necessary and sufficient condition for a molecule to show optical activity?
- (b) A compound is found to be optically inactive. Predict the nature of the compound.
- (c) The presence or absence of a chiral centre is no criterion for optical activity. Explain.
- (d) What are the ways of deciding whether a given molecule is optically active or not?

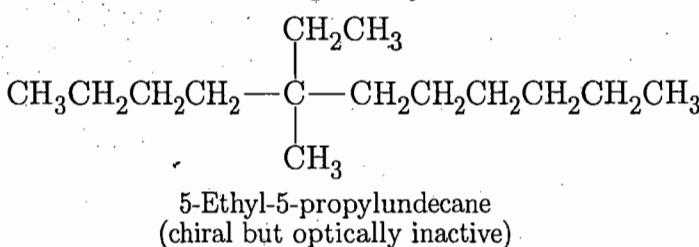
Ans. (a) Chirality (non-superimposability on mirror image) is the necessary condition for a molecule to show optical activity. However, it is not sufficient condition for optical activity because of the following reasons :

- (i) Some chiral molecules/ions are configurationally unstable. Due to rapid *pyramidal inversion (umbrella effect)* such molecules/ions undergo racemization and become optically inactive. For example, ethylmethylamine ($\text{CH}_3\text{CH}_2\text{NHCH}_3$) is found to be optically inactive although the nitrogen has four different "things" around it ($-\text{CH}_2\text{CH}_3$; $-\text{CH}_3$; $-\text{H}$; and a lone electron pair) which are arranged in a tetrahedron, i.e., the molecule is chiral.



Due to the same reason, the chiral carbanion $\text{CH}_3\text{CH}_2^-\text{CHCH}_3$ is optically inactive.

- (ii) Because of very low differences in polarizabilities among the groups, some chiral molecules have a vanishingly small rotation and are found to be optically inactive. For example, the specific rotation of the chiral alkane 5-ethyl-5-propylundecane is too low and actually far below the limits of detection by any existing polarimeter (calculated specific rotation 0.00001°) and so, each of its enantiomers is found to be optically inactive.



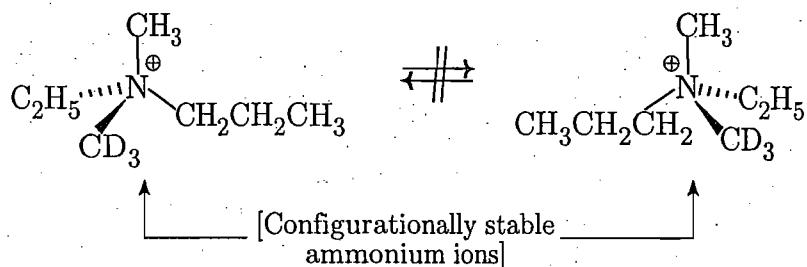
Therefore, the necessary and sufficient for a molecule to be optically active is that the molecule must be chiral, configurationally stable and should have measurable amount of optical activity.

- (b) It may be (i) a compound whose molecules are achiral, (ii) a compound whose molecules are chiral but not configurationally stable, (iii) a compound whose molecules are chiral but each of its enantiomers has immeasurably small optical activity, or (iv) a 50 : 50 mixture of two enantiomers of a compound, i.e., a racemic modification.

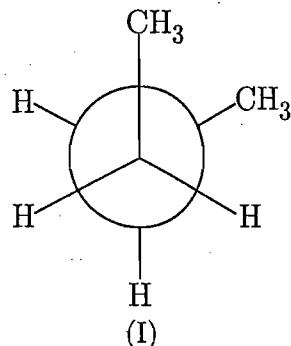
- (c) Chirality is the necessary condition for optical activity. The presence or absence of a chiral centre is no criterion of chirality (see **Problem 1.18**). Therefore, the presence or absence of a chiral centre is no criterion also for optical activity.

- (d) The ways of deciding whether a given molecule is optically active or not are the ways of deciding whether a given molecule is chiral or achiral (see **Problem 1.17**).

Since the energy barrier to inversion is small (6–10 kcal/mol, at room temperature most amines undergo inversion of configuration 10³ to 10⁸ times per second, making it impossible to obtain a pure sample of either enantiomer. If the lone pair on nitrogen of an amine is used in bond formation, this should prevent that electron pair from tunneling through the nucleus of the nitrogen atom. The resulting ammonium ion (NR_4^+) is configurationally stable and, if chiral, separable into enantiomers. For example, the following two enantiomeric ammonium ions can be resolved into enantiomers.

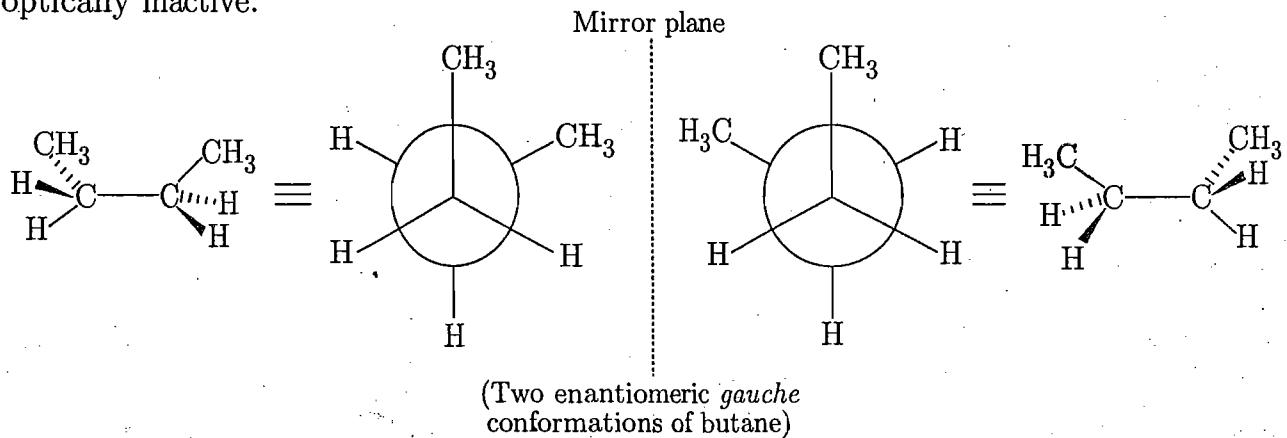


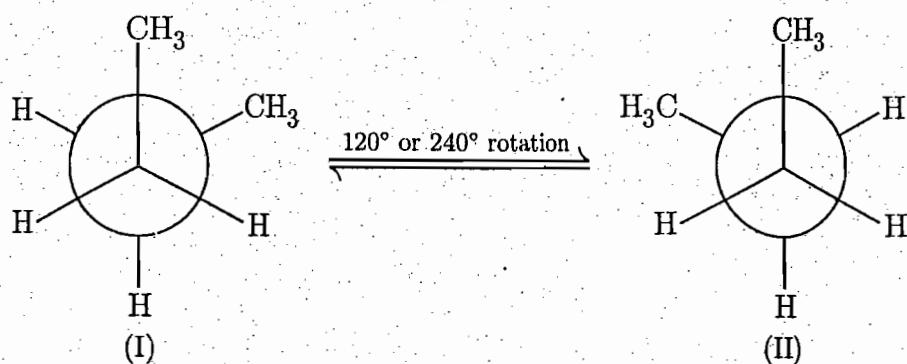
- 1.64 (a) An organic molecule has only one chiral carbon. Is the molecule optically active or inactive?
 (b) The following conformer (I) of butane is chiral, then why is butane optically inactive?



Ans. (a) If there is only one chiral centre in a molecule, we can be certain that the molecule is chiral. Since it is a chiral carbon, it must be configurationally stable. So, the molecule must be optically active.

(b) Butane has another conformation (II) which is a non-superimposable mirror reflection of the given conformer (I). The two enantiomers may interconvert simply by rotation about the central C—C bond. Since rotational barriers are generally rather small, enantiomers such as these interconvert rapidly at room temperature. Since there exists an equimolecular (1 : 1) mixture of two conformational enantiomers I and II, all the rotations produced by individual molecules are cancelled and butane is found to be optically inactive.



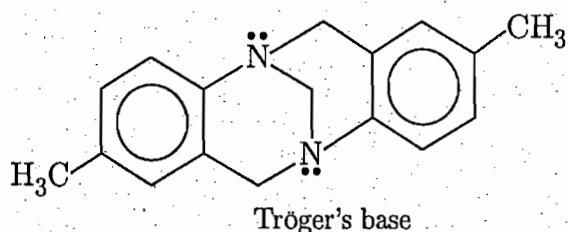


[The enantiomeric gauche conformations of butane do not have stereocentres. Instead, these forms are chiral because of the asymmetric disposition of the groups around the central C—C bond.]

►1.65 (a) What are invertomers?

- (b) Explain why both 1-chloro-2,2-dimethylazidiridine can be resolved into two enantiomers?

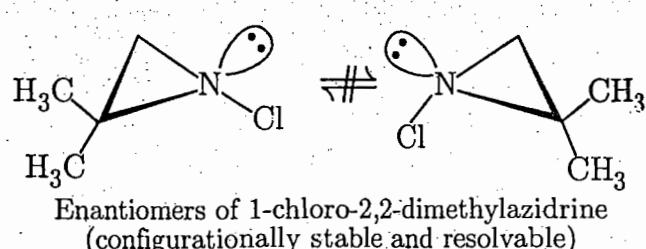
(c) Explain why Tröger's base is optically active?



- (d) Give examples of some compounds which, unlike amines, do not undergo pyramidal inversion at room temperature and can be resolved into enantiomers.

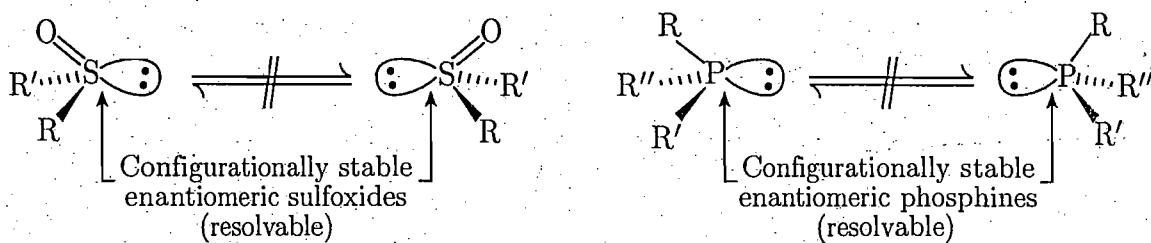
Ans. (a) Two conformers which interconvert by inversion at an atom having a non-bonding electron pair are known as invertomers. Thus, the amine enantiomers (see Problem 1.36) are invertomers.

- (b) A nitrogen atom in a three-membered ring cannot attain the 120° bond angles (sp^2 hybridization) which lead to inversion. Because of this, the azidrine derivative is configurationally stable and can be resolved into two enantiomers.



(c) Since each of the nitrogen atoms in Tröger's base is at a bridgehead, pyramidal inversion is prevented. So, the compound is configurationally stable and is optically active.

(d) Since the activation energy for pyramidal inversion at sulphur or phosphorus is much higher, sulfoxides with two nonidentical substituents on sulphur and phosphines with three nonidentical substituents on phosphorus do not undergo pyramidal inversion at room temperature and can be resolved into enantiomers.



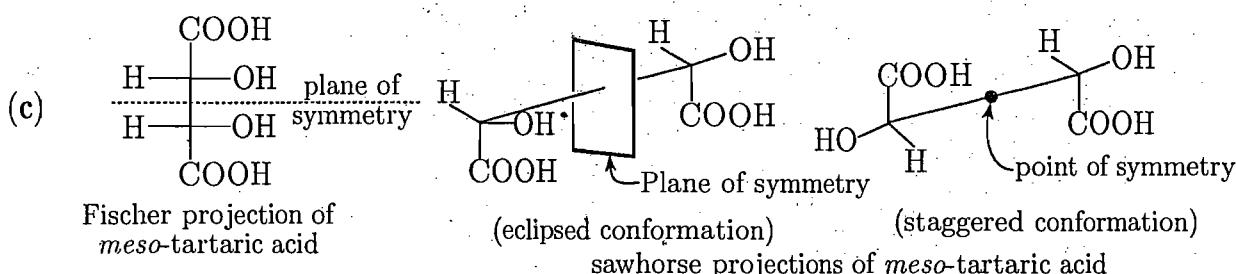
MESO COMPOUNDS

- 1.66 (a) What are *meso* compounds? Are they acyclic or cyclic stereoisomers?
- (b) Why is a *meso* compound achiral?
- (c) Draw *meso*-tartaric acid in the Fischer projection showing a plane of symmetry and in the sawhorse projection showing (i) a plane of symmetry in the eclipsed conformer, and (ii) a point of symmetry in a staggered conformer.
- (d) Neither *cis*-2-butene nor *trans*-2-butene (both achiral) is a *meso* compound—why?
- (e) How do you know whether a compound possesses a *meso* stereoisomer?
- (f) How do you know which of the possible stereoisomers of a compound is *meso*?
- (g) What is the difference between a *meso* compound (optically inactive) and a racemate (optically inactive)?
- (h) Is *cis*-1,2-dibromocyclohexane a *meso* compound? Give your reasoning.

Ans. (a) *Meso* compounds are achiral compounds even though they have chiral centres. Because they are achiral, they are optically inactive.

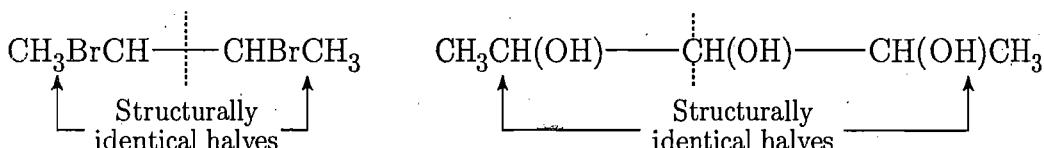
Meso compounds may be acyclic as well as cyclic stereoisomers.

(b) A *meso* compound is achiral because at least one of its conformer has either a plane or a point of symmetry.



(d) Neither *cis*-2-butene nor *trans*-2-butene is a *meso* compound because, although they are achiral stereoisomers, they have no chiral centres, i.e., asymmetric atoms.

(e) A *meso* compound is possible only when a molecule with two or more asymmetric atoms or chiral centres can be divided into structurally identical halves. For example :

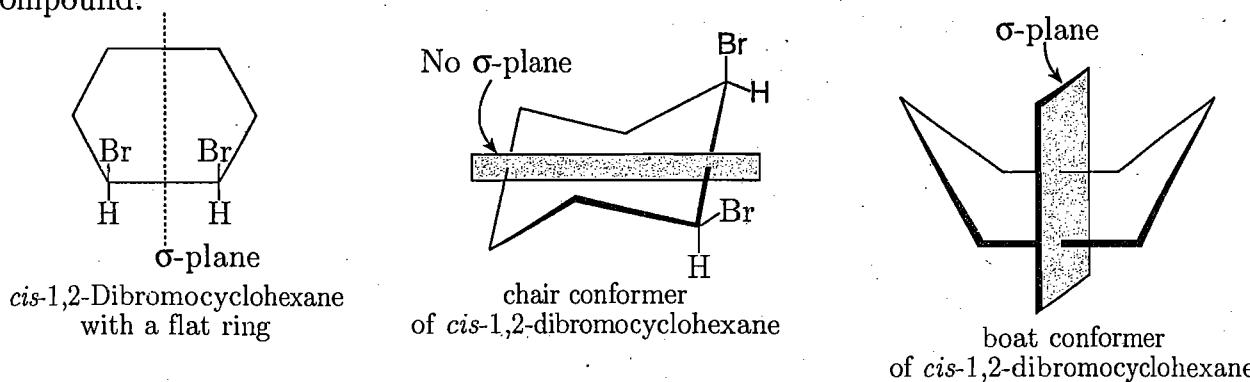


(f) In a *meso* compound, the corresponding asymmetric carbons in each half of the molecule must have opposite configurations. Thus, one asymmetric carbon in *meso*-tartaric acid is *R* and the other is *S*.

Moreover, *meso* compounds may be identified by looking for a plane or a point of symmetry within a molecule which has chiral centres.

(g) Although both are optically inactive, a *meso* compound is a single achiral compound, but a racemate is an equimolar mixture of enantiomers. A *meso* compound is optically inactive due to *internal compensation*, i.e., the rotation due to one half (*R* stereocentre) is cancelled by that caused by the other half (*S* stereocentre). On the other hand, a racemic compound is optically inactive due to *external compensation*, i.e., (+)-rotation of one enantiomer is compensated by the (-)-rotation of the other. Since racemic modification is a mixture, it can be separated into pure enantiomers. *Meso* compounds cannot be resolved.

(h) Yes. *cis*-1,2-dibromocyclohexane contains two similar chiral carbons (bonded to the same four substituents). The structure for the compound drawn with a flat ring suggests that the compound has a plane of symmetry. However, cyclohexane is not a flat hexagon; it exists mainly in the chair conformation and the chair conformer of *cis*-1,2-dibromocyclohexane does not have a plane of symmetry. Only the much less stable boat conformer has a plane of symmetry. As long as any one conformer of a compound has a plane of symmetry, the compound will be achiral, and an achiral compound with two chiral centres is a *meso* compound. Therefore, *cis*-1,2-dibromocyclohexane is a *meso* compound.



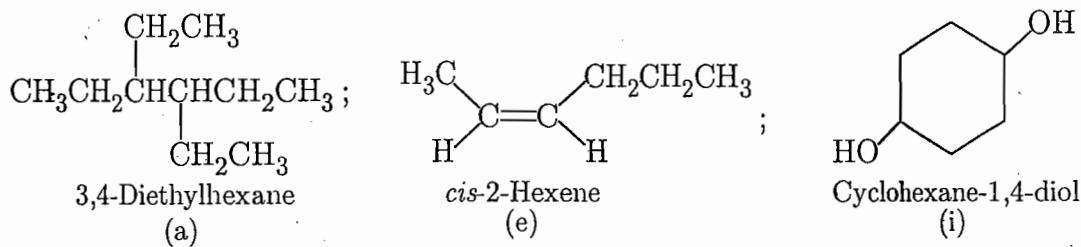
►1.67 Which of the following compounds has a stereoisomer that is a *meso* compound?

- | | |
|---------------------------------|------------------------------|
| (a) 3,4-diethylhexane | (b) 2-chloro-3-methylpentane |
| (c) 1,3-dimethylcyclopentane | (d) pentane-2,3,4-triol |
| (e) <i>cis</i> -2-hexene | (f) 2,4-dibromopentane |
| (g) 1,4-dichloropentane | (h) 1,2-dibromocyclobutane |
| (i) Cyclohexane-1,4-diol | (j) 1,3-dimethylcyclohexane |
| (k) 1-bromo-2-chlorocyclohexane | |

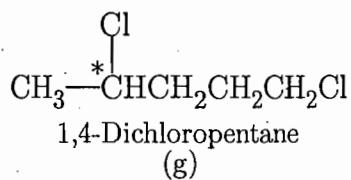
Explain why pentane-2,3,4-triol has two stereoisomers that are *meso* compounds

Ans. The necessary requirement to have a stereoisomer that is a *meso* compound is that the compound must have at least two chiral centre which are bonded to the same four substituents.

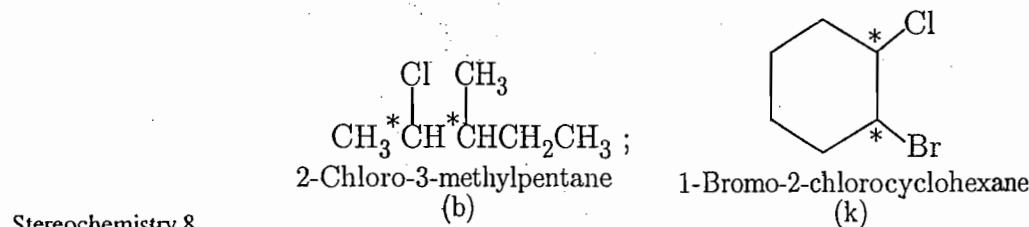
Compounds (a), (e) and (i) do not have a stereoisomer that is a *meso* compound because they don't have any chiral centre.



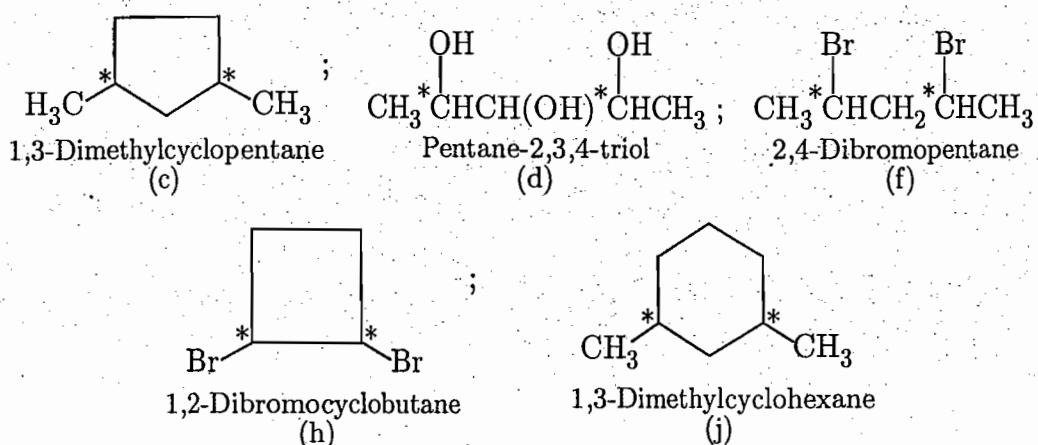
The compound (g) does not have a stereoisomer that is a *meso* compound because it has only one chiral centre.



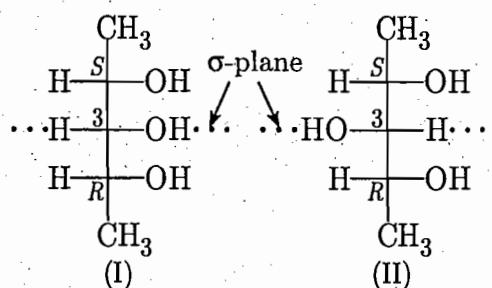
Each of the compounds (b) and (k) have two chiral centres. But each of the chiral centres is not bonded to the same four substituents. Thus, they do not have a stereoisomer that is a *meso* compound.



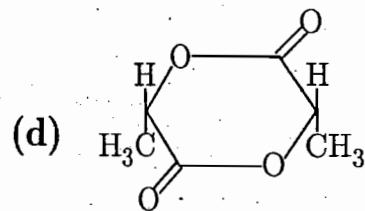
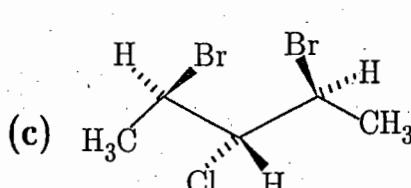
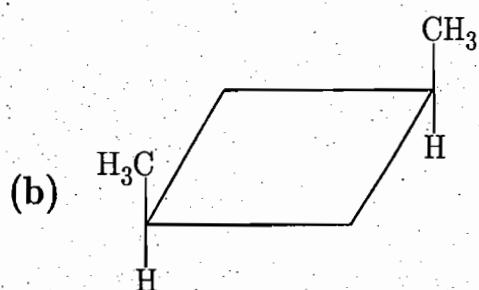
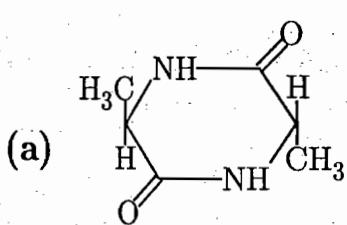
Compounds (c), (d), (f), (h) and (j) have a stereoisomer that is a *meso* compound because each of them has two chiral centres which are bonded to the same four substituents.

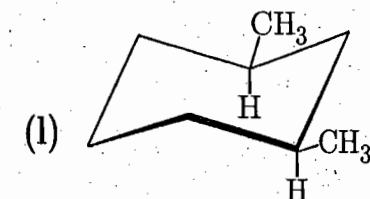
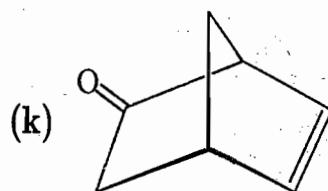
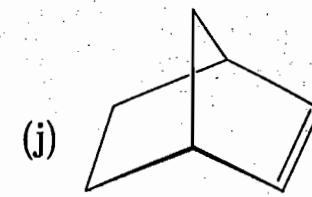
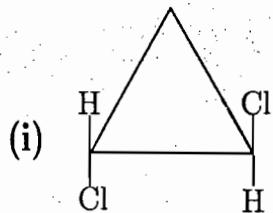
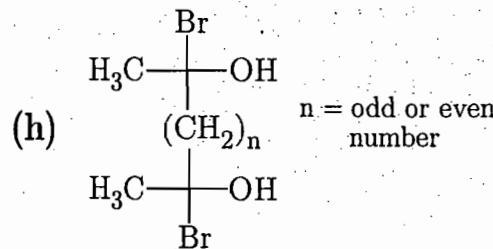
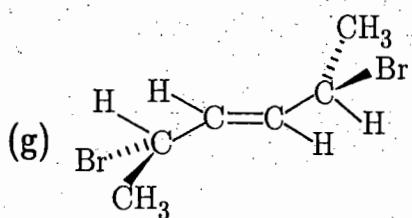
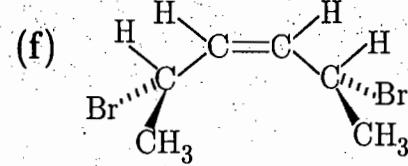
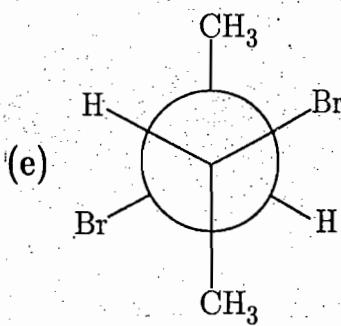


Pentane-2,3,4-triol has two stereoisomers (I and II) that are *meso* compounds because C-3 (through which the σ -plane passes) may have different configurations (in I the —OH group is on the right in the Fischer projection and in II the —OH group is on the left).

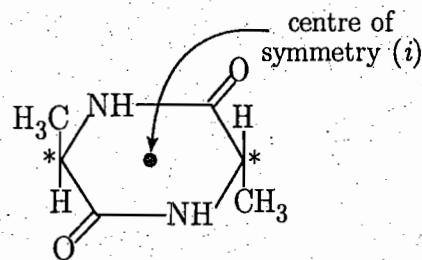


►1.68 Identify the *meso* compounds among the following :

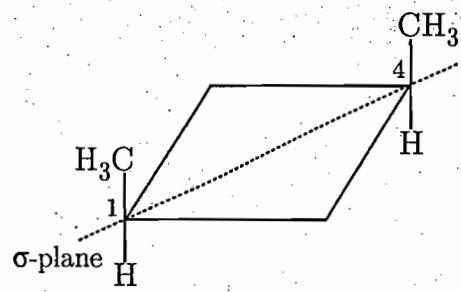




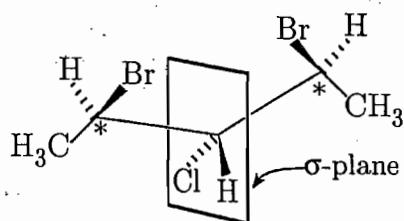
Ans. (a) The compound is achiral because it has a centre of symmetry. However, it contains two chiral centres. So, it is a *meso*-compound.



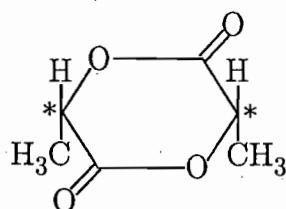
(b) It is not a *meso*-compound because it contains no chiral centre, even though it is achiral due to the presence of a plane of symmetry passing through C-1 and C-4.



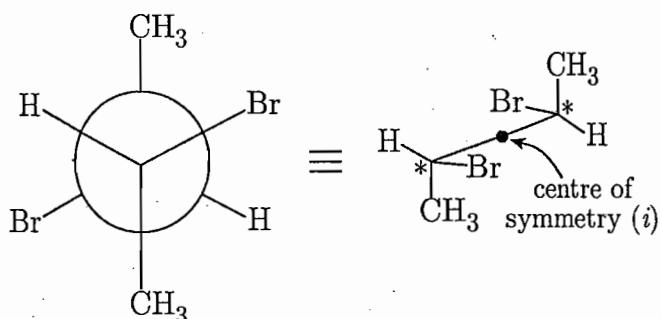
(c) It is a *meso*-compound because it contains two chiral centres and is achiral due to the presence of a plane of symmetry.



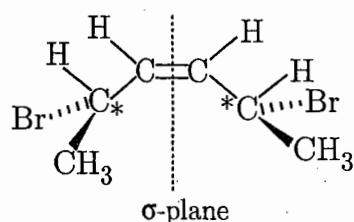
(d) The compound is chiral because it has no plane or centre of symmetry. So, it is not a *meso*-compound.



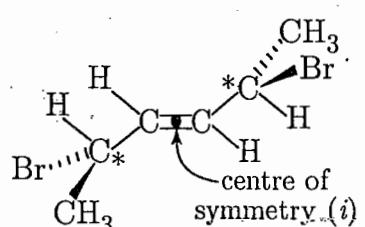
(e) This staggered form of 2,3-dibromobutane is achiral since it has a centre of symmetry. It contains two chiral centres. So, it is a *meso*-compound.



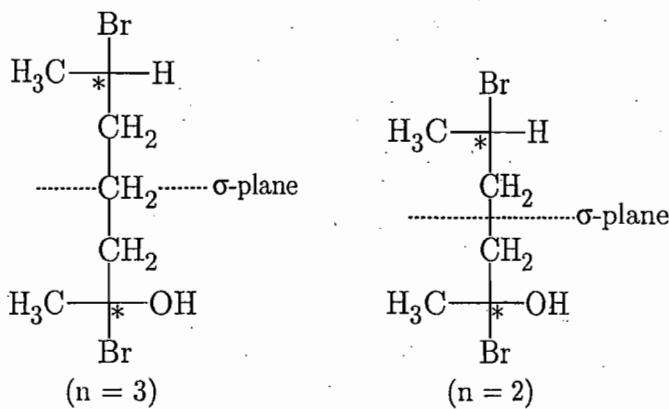
(f) It is a *meso*-compound because it is achiral due the presence of a plane of symmetry and contains two chiral centres.



(g) The compound is achiral by virtue of a centre of symmetry. Since it contains two chiral centres, it is a *meso*-compound.

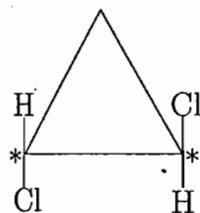


(h) These compounds containing two chiral centres is achiral due to the presence of a plane of symmetry. This is true if n is an odd or an even number. So, the compounds are *meso*-compounds.

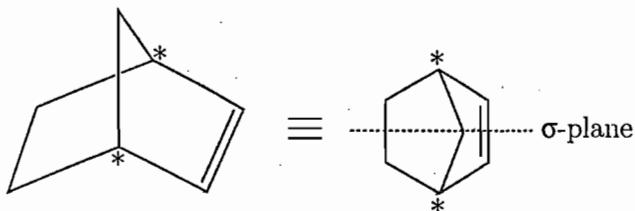


[When n is an odd number, the plane of symmetry cuts through the centre carbon but when n is an even number, the symmetry plane cuts through the central C—C bond.]

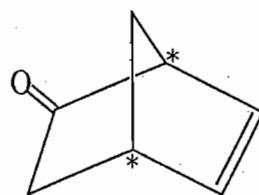
(i) The compound has no plane or centre of symmetry. So, it is chiral and is not a *meso*-compound.



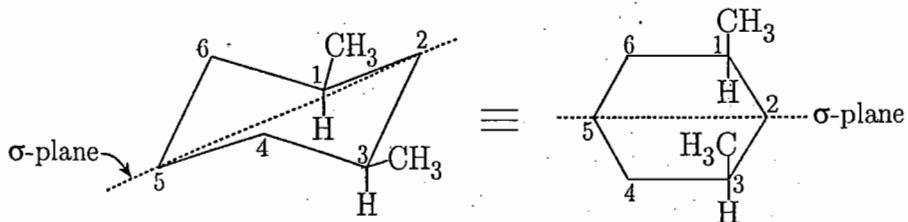
(j) The compound has a plane of symmetry. So, it is achiral. However, it contains two chiral centres. So, it is a *meso*-compound.



(k) Since the compound has no plane or centre of symmetry, it is chiral and is not a *meso*-compound.



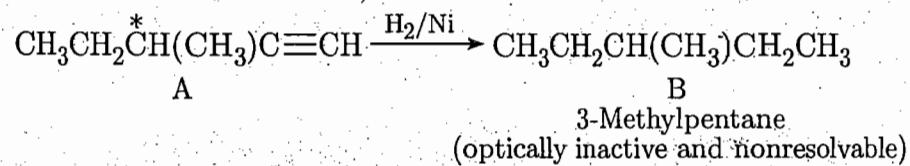
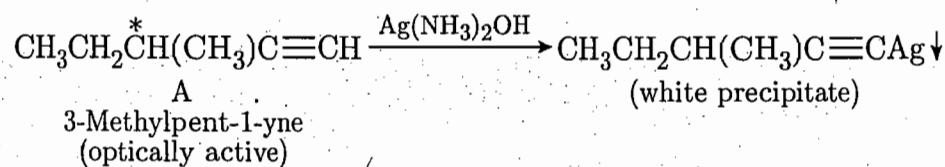
(l) It is a *meso*-compound because it is achiral due to the presence of a σ-plane passing through C-2 and C-5 and contains two chiral centres.



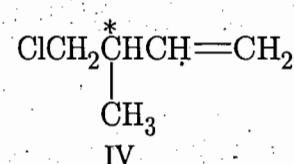
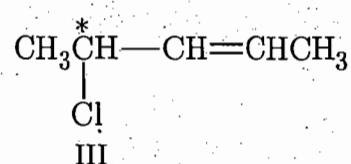
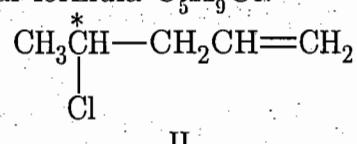
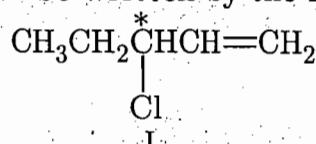
- 1.69 (a) An optically active compound A has the molecular formula C_6H_{10} . This compound gives a precipitate when treated with a solution containing $Ag(NH_3)_2OH$. On catalytic hydrogenation A yields B with molecular formula C_6H_{14} . But compound B is optically inactive and cannot be resolved. Propose structures for A and B and explain the observations.
- (b) A and B are two optically active isomeric alkene (molecular formula C_5H_9Cl). After addition of one mole of H_2 to each, A is converted to C (optically inactive) and B is converted to D (optically active). Give the structures of A, B, C, and D.

Ans. (a) The compound A (C_6H_{10}) is optically active. So, it is chiral and it may contain an asymmetric carbon atom. The compound gives a precipitate when treated with a solution containing $Ag(NH_3)_2OH$. Since terminal alkynes react with $Ag(NH_3)_2OH$ to form a precipitate of silver alkynide, the compound must contain a $-C\equiv CH$ group. The compound A on catalytic hydrogenation produces compound B (C_6H_{14}) which is optically inactive and cannot be resolved. On catalytic hydrogenation the $-C\equiv CH$ group becomes converted to a $-CH_2CH_3$ group by taking up two H_2 molecules ($C_6H_{14} - C_6H_{10} = 4H$). Since on hydrogenation the compound becomes optically inactive, i.e., achiral, the asymmetric carbon must contain the $-C\equiv CH$ group and a group that may be obtained by hydrogenation of $-C\equiv CH$ group, i.e., $-CH_2CH_3$ group. Therefore, the structure of the compound A is $CH_3CH_2C^*H(CH_3)C\equiv CH$ (3-methylpent-1-yne) and that of the compound B is $CH_3CH_2CH(CH_3)CH_2CH_3$ (3-methylpentane).

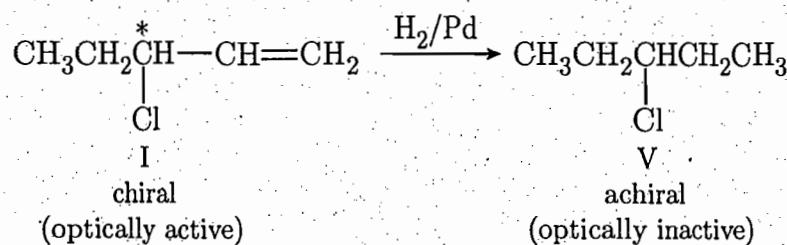
Reactions :



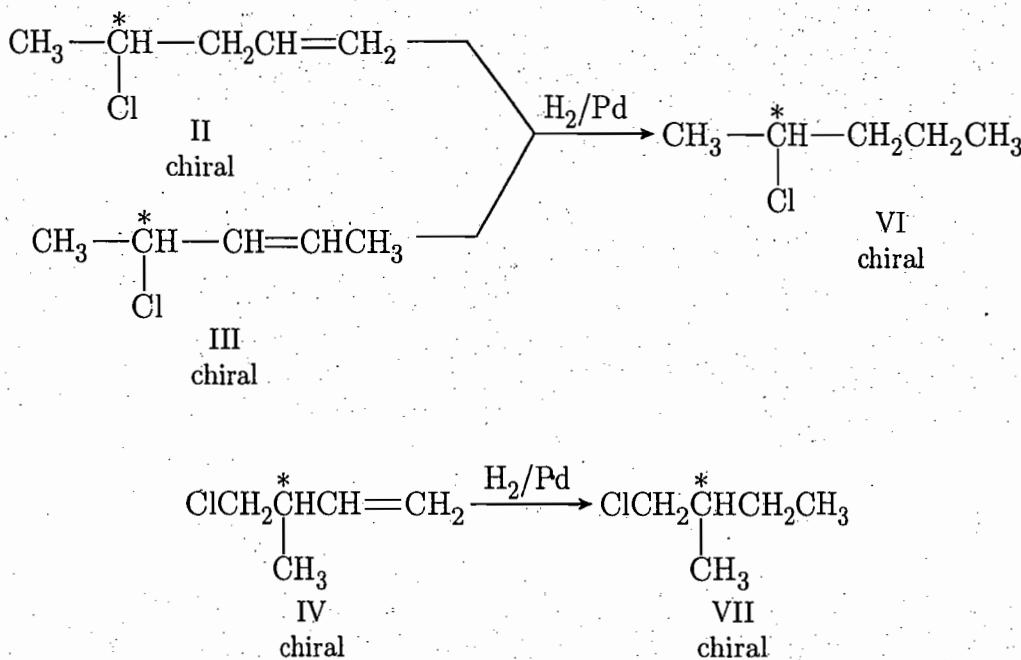
(b) Since both A and B gain two hydrogen atoms on catalytic hydrogenation, they must have a $C=C$ bond and since they are optically active, they must contain one asymmetric carbon atom. Four structures (I-IV) containing one asymmetric carbon and a double bond can be written by the molecular formula C_5H_9Cl .



I on hydrogenation produces an achiral (optically inactive) compound because the $-\text{CH}=\text{CH}_2$ group becomes converted to a $-\text{CH}_2\text{CH}_3$ group.



II and III on hydrogenation produce the chiral compound VI and IV on hydrogenation produces the chiral compound VIII.



Therefore, compound A is I, compound B is II or III or IV, compound C is V and compound D is VI (if B is II or III) or VII (if B is IV).

CHEMICAL AND PHYSICAL PROPERTIES OF ENANTIOMERS AND DIASTEROISOMERS

►1.70 Compare chemical and physical properties of (a) enantiomers and (b) diastereoisomers.

Ans. (a) In two enantiomers, the atoms have exactly the same spatial arrangements with respect to distance and dihedral angles (interactions). The two enantiomers are thus *isometric* to each other. Because of this, enantiomers show the same reactivity (E_{act} values are the same) towards achiral reagents, solvents, catalysts and conditions. However, towards chiral reagents, solvents, catalysts, and conditions, enantiomers react at different rates. The transition states produced from the

individual enantiomers and the chiral reactant are not enantiomeric. In fact, they are diastereomeric, and hence have different free energy of activation (ΔG^\ddagger) due to different enthalpies of activation (ΔH^\ddagger). For this reason, two enantiomers react at different rates with a chiral reagent.

Since the two enantiomers are isometric to each other, they have identical physical properties, e.g., melting points, boiling points, solubilities, densities, refractive indices, dipole moments, etc. However, the two enantiomers differ in their behaviour towards plane-polarized light (rotation in two opposite directions but in same magnitude) because a plane-polarized light is composed of two dissymmetric components, a right-handed and a left-handed circularly polarized light beam and thus constitute a chiral environment.

(b) Diastereoisomers have different spatial arrangements of atoms with respect to distances and dihedral angles (interactions) and are, therefore, *anisometric* relative to one another. Because of this, neither any two diastereoisomers nor their transition states have same energies (E_{act} values are different) and consequently, they react at different rates with both chiral and achiral reagents.

Since any two diastereoisomers are anisometric to each other, they also differ in physical properties like melting points, boiling points, refractive indices, dipole moments, crystalline structures, specific rotations, etc. They may have the same or opposite sign of rotation or some may be optically inactive. Because of their differences in boiling point and solubility, they can be separated from each other by fractional distillation or fractional crystallization. Again because of their differences in molecular shape and polarity, they differ in adsorption and can be separated by chromatography.

RACEMIC MODIFICATION AND ITS RESOLUTION

- 1.71 (a) What is meant by the term “racemization”?
- (b) Explain why racemization is a thermodynamically favourable process?
- (c) Discuss different methods of preparing a racemic modification giving suitable examples.

Ans. (a) The process of producing a racemic modification starting from either of the pure enantiomer is called racemization.

(b) A racemic modification is a mixture (equimolar) of two enantiomers, i.e., a mixture of two different molecular species and, consequently, possesses an entropy of mixing, ΔS . Since mixing causes increase in disorder, ΔS is a positive quantity and, therefore, ΔG in the expression $\Delta G = \Delta H - T\Delta S$ is negative (assuming ΔH constant). For this reason, racemization is a thermodynamically favourable process.

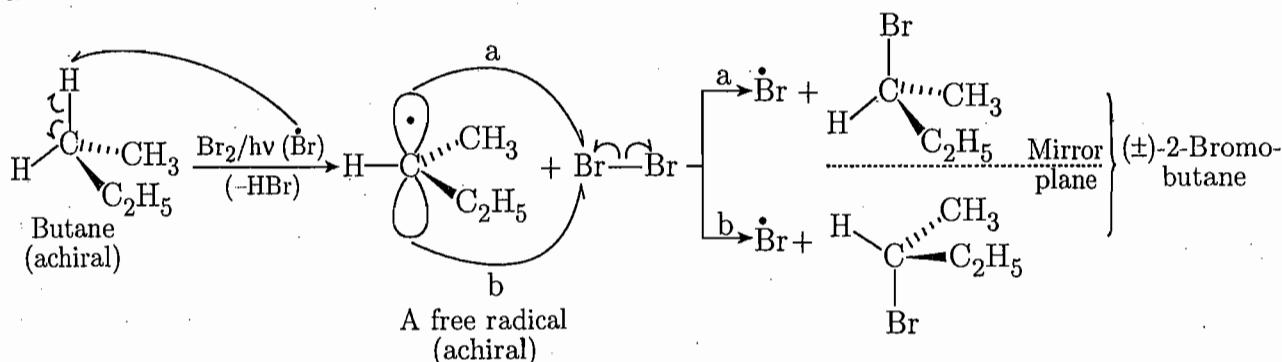
(c) A racemic modification may be prepared by the following methods :

- (I) By generating a chiral centre in a symmetric molecule : Several organic reactions can yield a chiral product from achiral starting materials (reactants

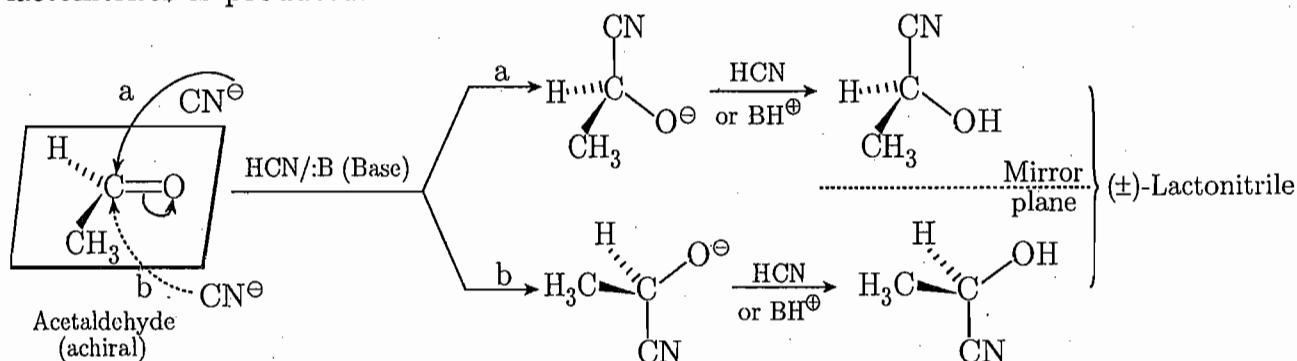
such as $\text{C}=\text{O}$, $\text{C}=\text{C}$, etc. and reagents such as H_2 , Br_2 , HCN , etc.) and in that case both enantiomers of a pair are always formed at identical rates and in equal amounts. That is, the product is always the racemate.

Example :

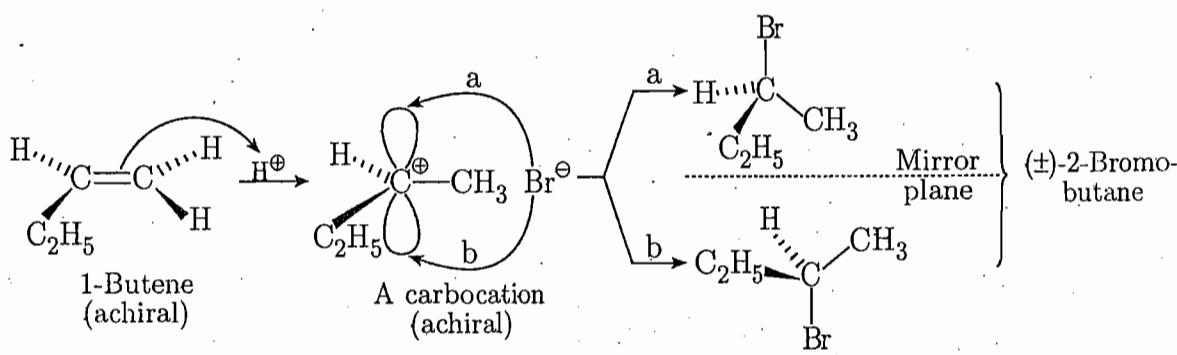
(i) The radical bromination at C-2 of the achiral butane molecule yields a chiral molecule which is obtained in a racemic form. Abstraction of either methylene hydrogen at C-2 by bromine gives an achiral radical. Reaction of Br_2 with this radical then takes place at either the top or the bottom face (two enantiomeric faces) equally well to give a racemic modification.



(ii) Addition of HCN to acetaldehyde produces a racemic lactonitrile. Attack of CN^- ion on the carbonyl carbon from either the top or the bottom face of achiral acetaldehyde (CH_3CHO) molecule is equally likely and as a result, a racemic mixture of lactonitriles is produced.

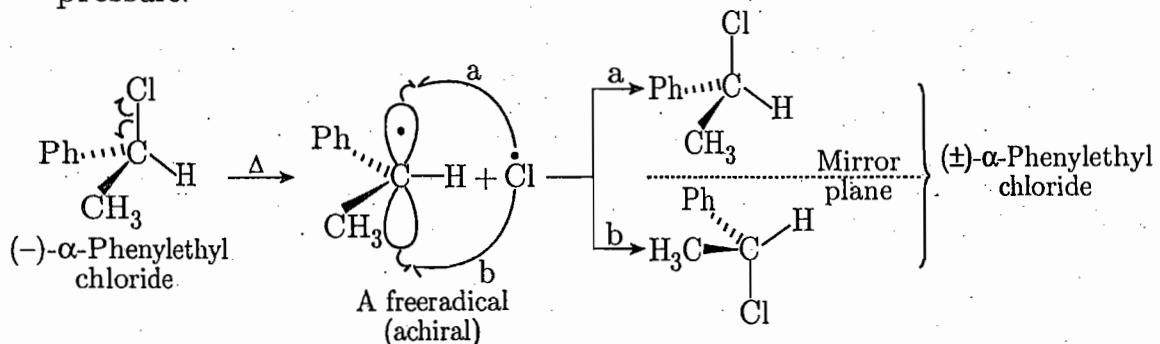


(iii) Addition of HBr to achiral 1-butene molecule produces racemic 2-bromobutane. In the first step, the alkane undergoes electrophilic attack by H^+ on C-1 to form a relatively stable planar (achiral) carbocation. In the second step, Br^- attacks the positive carbon from above and below the plane of the planar carbocation with equal facility to produce a racemic mixture.

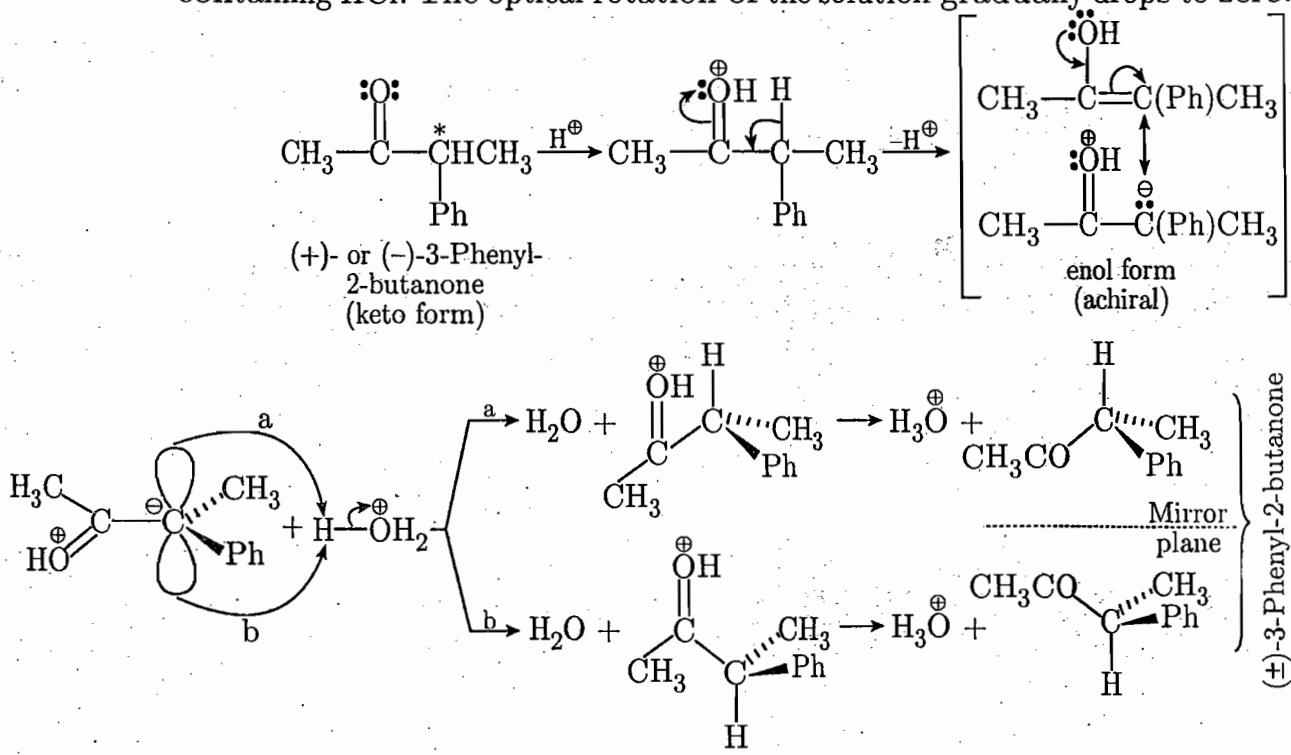


(II) By racemization : Racemization, i.e., formation of a racemic modification starting with one of the pure enantiomer, may be accomplished by the following methods.

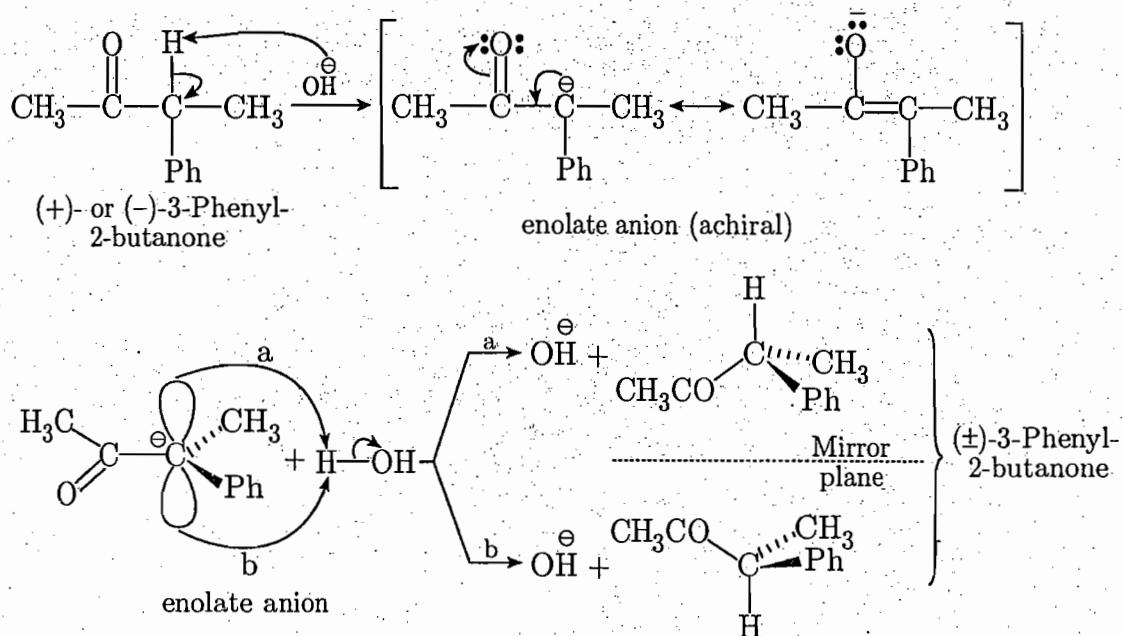
(i) Thermal racemization : This involves temporary breaking of one of the four bonds to an asymmetric carbon atom, by applying heat. Homolytic cleavage of a bond occurs to form an achiral free radical. The radical on the carbon atom (which was originally chiral) then recombines with the breakaway radical from either faces of the sp^2 carbon to form an equimolecular mixture of two enantiomers, i.e., a racemic modification. For example, (+)- or (-)- α -phenylethyl chloride undergoes racemization when distilled at atmospheric pressure.



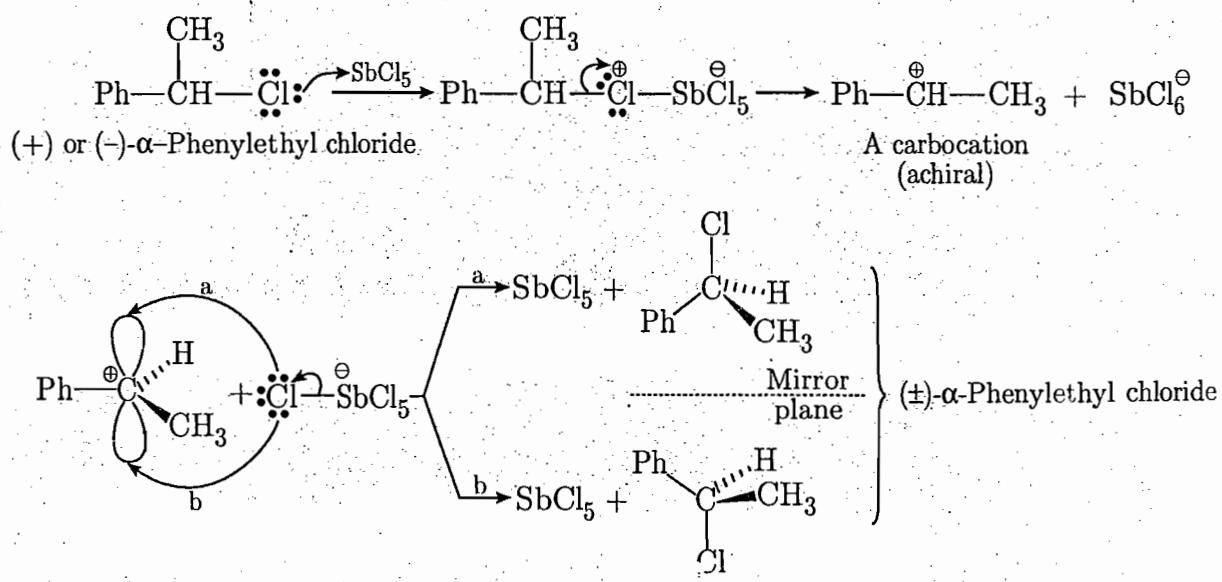
(ii) Acid-catalysed racemization via an enol and base-catalysed racemization via an enolate anion : These involve temporary separation of an acidic hydrogen atom bonded to a chiral centre. Optically active carbonyl compounds of the type $RR'CHCOR$ in which the α -carbon is chiral undergoes racemization in the presence of both acids and bases. The acid-catalysed racemization occurs through the formation of an intermediate enol which is planar (achiral). Proton then recombines with the achiral enol molecule from either side of the double bond equally well to produce a racemic modification. For example, 3-phenyl-2-butanone undergoes racemization when dissolved in ethanol containing HCl. The optical rotation of the solution gradually drops to zero.



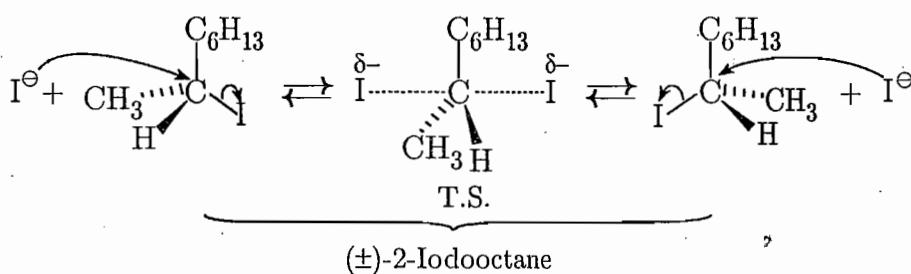
Base catalysed racemization occurs through the formation of a planar (achiral) enolate anion. Recombination of the intermediate enolate anion with the proton occurs from either side with equal facility to give a racemic modification. For example 3-phenyl-2-butanone undergoes racemization when dissolved in ethanol containing NaOH.



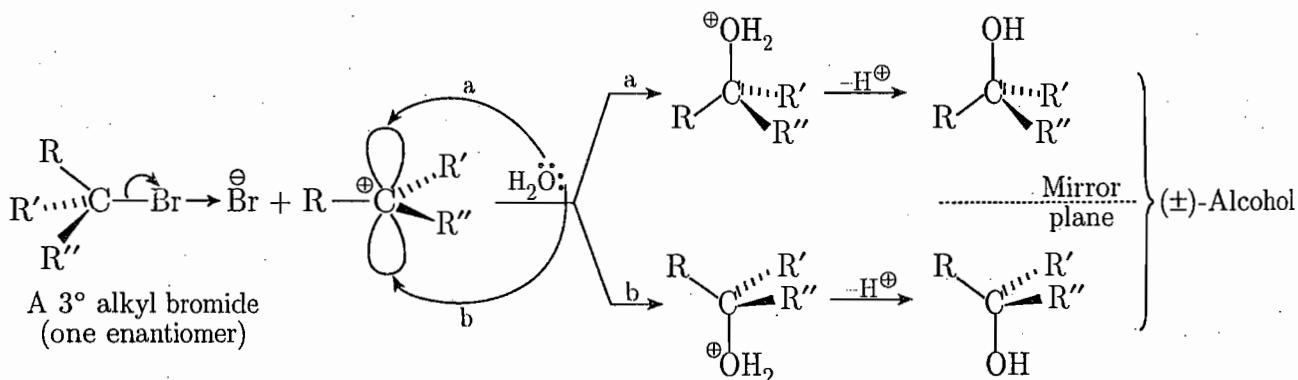
- (iii) **By cation formation :** In this process a carbocation is generated by detaching a group from the chiral centre with an electron pair leaving behind a planar (achiral) carbocation. The anion attacks the intermediate carbocation from either of its two faces with equal probability to form both the enantiomers in equal amounts. This mechanism operates when the substrate is capable of giving rise to a stable carbocation (benzylic, allylic or tertiary). The reagents used are lewis acids such as antimony pentachloride (SbCl_5), aluminium chloride (AlCl_3), boron trifluoride (BF_3) and zinc chloride (ZnCl_2). A mineral acid can also be used. For example, when (+)- or (-)- α -phenylethyl chloride is heated with SbCl_5 , (\pm)- α -phenylethyl chloride is obtained.



- (iv) **By substitution reactions :** In a biomolecular nucleophilic substitution reaction (S_N2) the nucleophile attacks the saturated carbon atom from the side opposite to that from which the leaving group is detached leading to an inversion of configuration about the chiral carbon. In such a process, if the entering and leaving groups are identical, the reaction becomes reversible and an equilibrium is set up between the two enantiomers leading to racemization. For example, when (+)-2-iodooctane is refluxed with KI in acetone, it undergoes racemization. [See **Problem 2.14** of the book '*Advanced Organic Reaction Mechanism*' written by the same author]

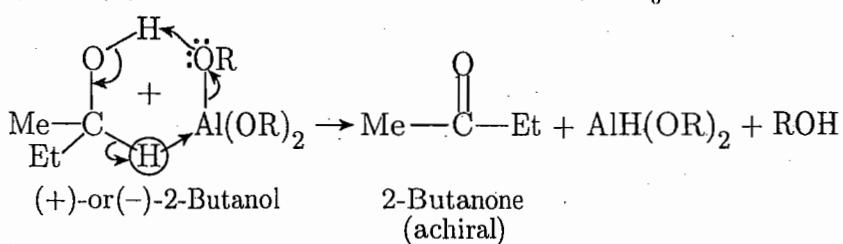


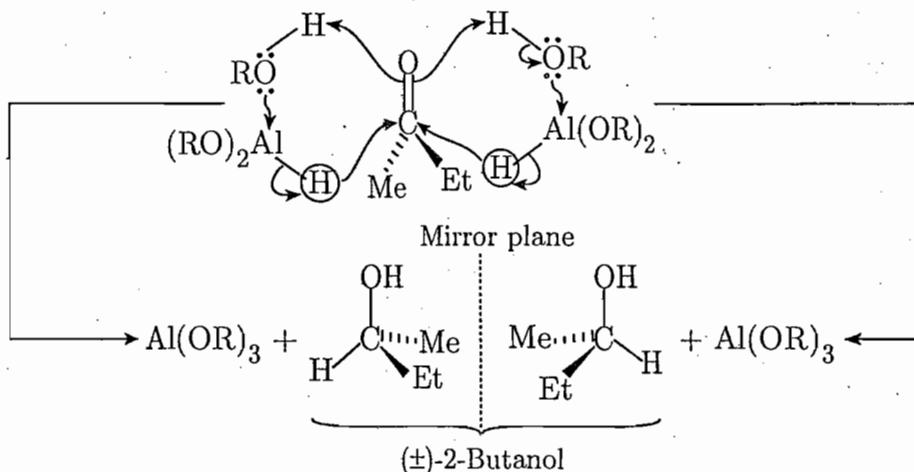
In a unimolecular substitution reaction (S_N1) a planar (achiral) carbocation is formed which undergoes attack by the nucleophile from both sides with equal facility to produce a racemic mixture.



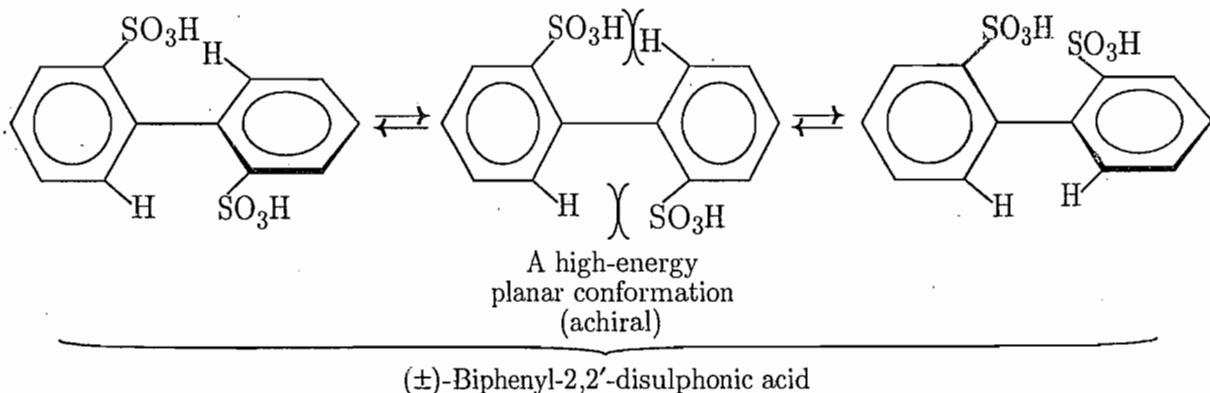
However, the above reaction cannot be treated as a case of racemization because the reactant and product have different structures. Although many S_N1 reactions proceed with racemization, many others proceed with more inversion of configuration than retention. This is due to formation of an ion pair where the leaving group blocks the front side of the carbocation to favour inversion.

- (v) **Through reversible formation of a stable inactive intermediate :** In some cases, racemization occurs by interconversion of the enantiomers through stable achiral intermediate. When treated with sodium or aluminium alkoxide, chiral secondary alcohols undergo racemization through the formation of a ketone. For example, when (+)- or (-)-2-butanol is treated with $Al(OR)_3$, racemization takes place.





- (vi) Through rotation about a single bond : Conformational enantiomers undergo racemization through rotation around a single bond and the interconversion usually takes place readily via an achiral planar conformation. Optically active biphenyls in which optical activity is due to restriction of rotation about a single bond (caused by steric interactions between bulky *ortho* substituents) racemize when enough thermal energy is employed to cross the high-energy (less stable) planar conformation, i.e., to cross the energy barrier between the enantiomers. For example, biphenyl-2,2'-disulphonic acid racemises on heating.



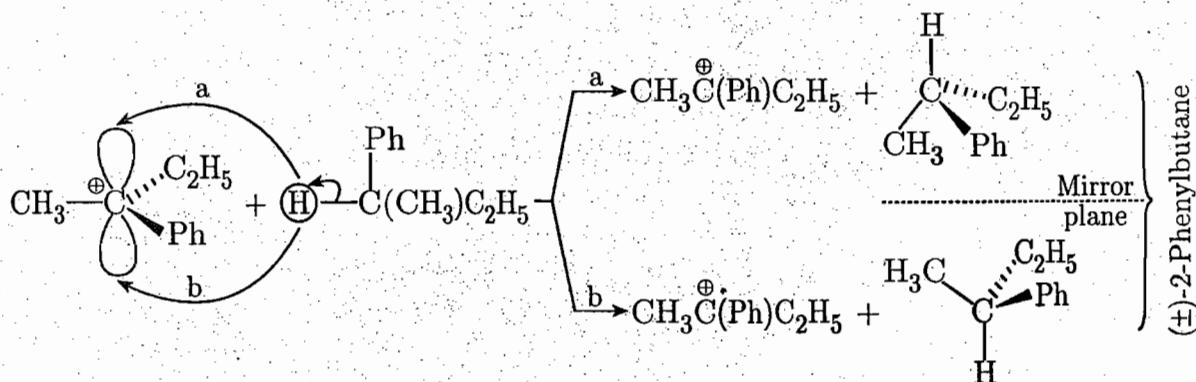
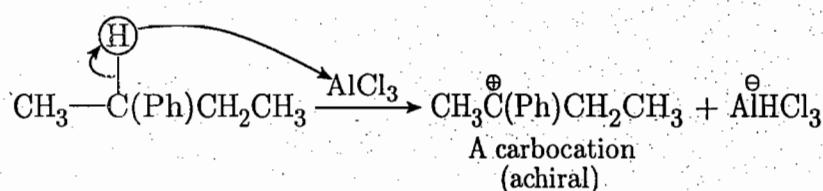
► 1.72 Explain the following observations :

- When a solution of optically active *sec*-butyl phenyl ketone in aqueous ethanol is treated with acids or bases, the solution gradually loses its optical activity.
- The ketone $(+)-\text{CH}_3\text{CH}_2\overset{*}{\text{CO}}\text{CH}(\text{OH})\text{CH}_3$ racemizes on treatment with alkali, whereas the isomeric ketone $(+)-\text{CH}_3\text{COCH}_2\overset{*}{\text{CH}}(\text{OH})\text{CH}_3$ does not.
- $(+)-\text{PhCH}(\text{CH}_3)\text{C}_2\text{H}_5$ racemizes in the presence of AlCl_3 .
- Optically active camphene undergoes racemization on treatment with acid.
- Catalytic hydrogenation of pyruvic acid produces racemic lactic acid.
- Catalytic hydrogenation of 2-ethylpent-1-ene gives a racemic product.

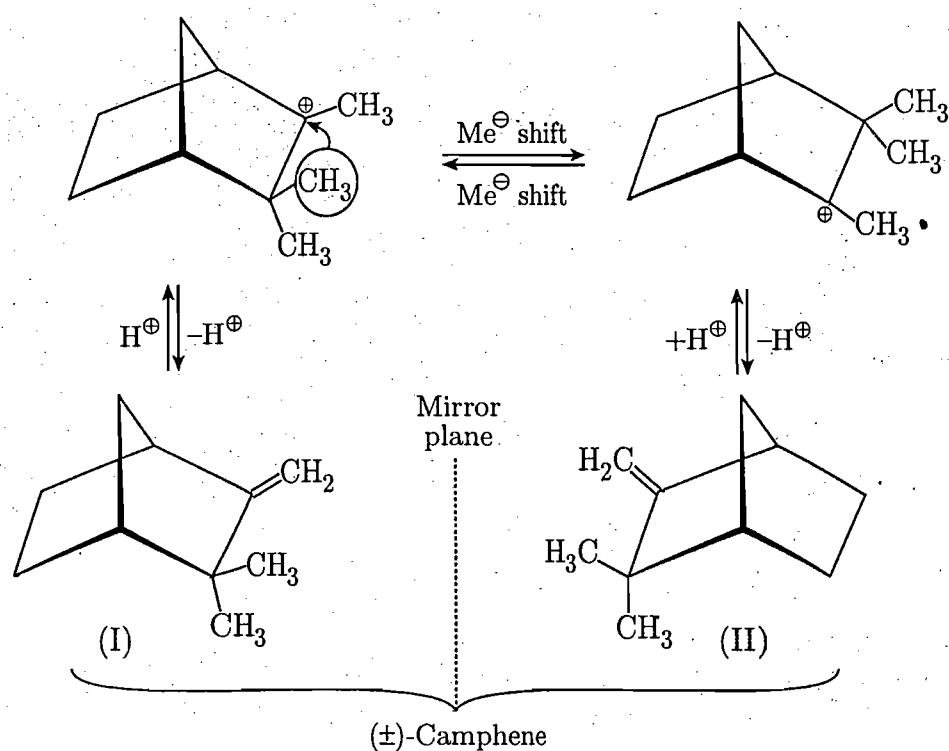
Ans. (a) Since *sec*-butyl phenyl ketone ($\text{PhCOCHMeCH}_2\text{CH}_3$) contains a chiral carbon adjacent to a carbonyl group and that carbon contains one H atom (acidic hydrogen), it undergoes racemization in the presence of acids or bases (through the formation of enol or enolate anion) to give a racemic mixture. Because of this, an ethanolic solution of optically active *sec*-butyl phenyl ketone loses its optical activity when treated with acids or bases. [See **Problem 1.71(c)**]

(b) For racemization to occur the hydrogen attached to the asymmetric carbon atom must be acidic and for this to happen the $\text{C}=\text{O}$ group must be adjacent to the asymmetric carbon atom. The carbonyl function is attached to the asymmetric carbon atom in the ketone $\text{CH}_3\text{CH}_2\text{COCH(OH)CH}_3$ but not in the isomeric ketone $\text{CH}_3\text{COCH}_2\text{CH(OH)CH}_3$. For this reason, the former ketone racemizes on treatment with alkali, whereas the latter ketone does not.

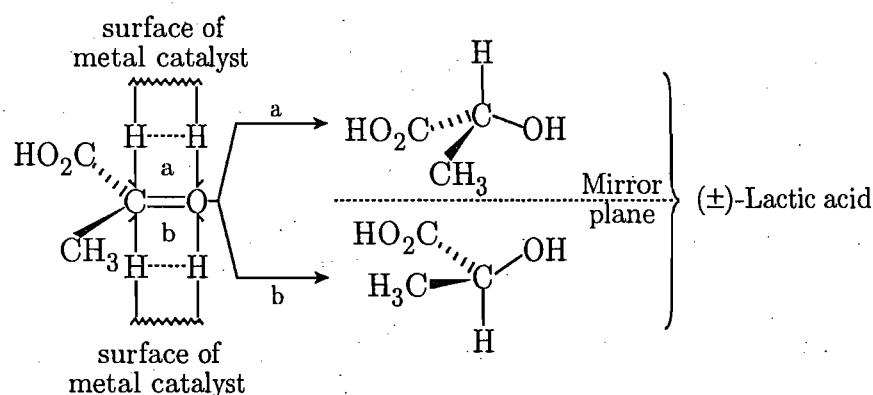
(c) Being a Lewis acid AlCl_3 abstracts the H atom of the chiral carbon of (+)- $\text{PhCH(CH}_3\text{)C}_2\text{H}_5$ as hydride ion and leads to the formation of a planar (achiral) carbocation. A hydride ion from a second molecule of (+)- $\text{PhCH(CH}_3\text{)C}_2\text{H}_5$ then attacks the carbocation from either side with equal facility to form racemic or (\pm) - $\text{PhCH(CH}_3\text{)C}_2\text{H}_5$. [This type of racemization occurs because the intermediate benzylic carbocation (very much resonance stabilized) is formed easily.]



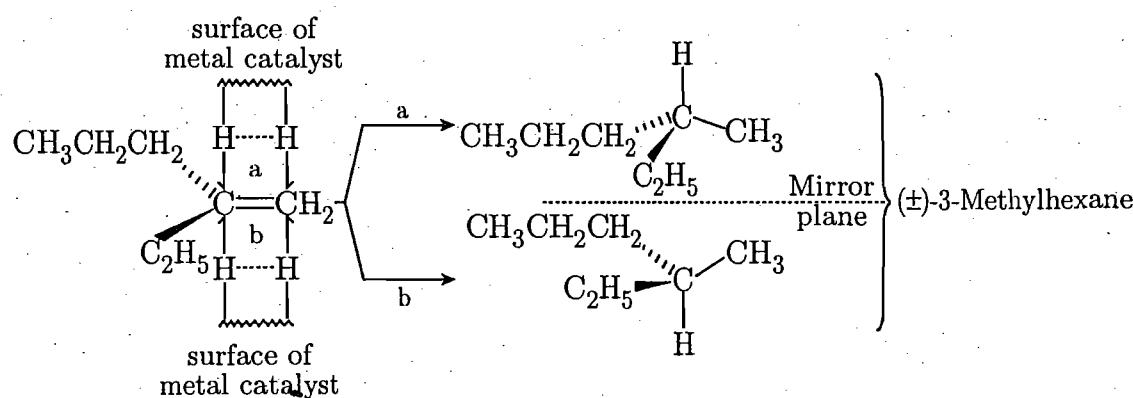
(d) The optically active camphene(I) accepts a proton and forms a carbocation which undergoes a methyl shift with its bonding electrons to give an equivalent carbocation. The resulting carbocation then loses a proton to give the enantiomeric camphene(II). The isomer(II) may be converted to (I) by a similar process. Since the forward and the backward reaction involve an equivalent carbocation, the reaction is reversible and an equilibrium is set up between the two enantiomers leading to racemization.



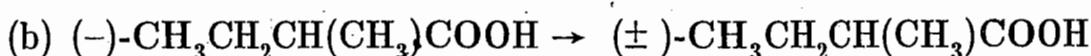
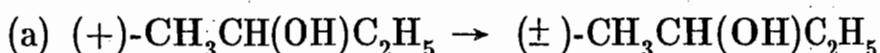
(e) Hydrogen, adsorbed on the surface of the nickel catalyst, adds with equal facility at either face of pyruvic acid (CH_3COCOOH) to form (+)- and (-)-lactic acid in equal amounts.



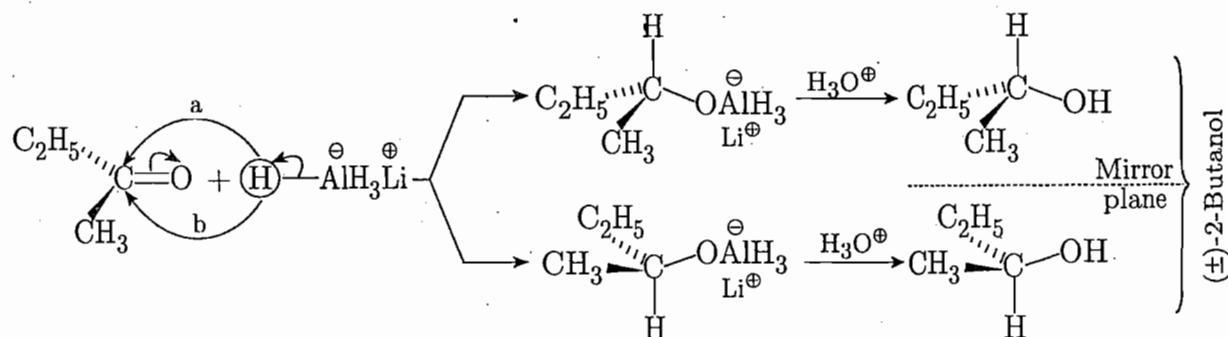
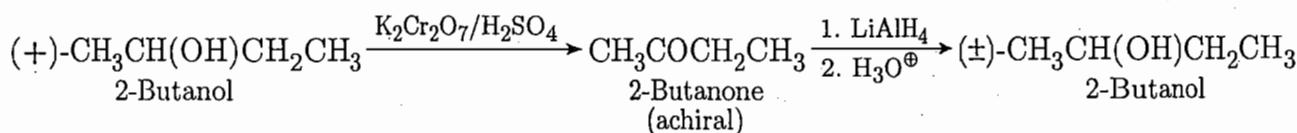
(f) Hydrogen, adsorbed on the metal surface, adds with equal facility at either face of 2-ethylpent-1-ene [$\text{CH}_3\text{CH}_2\text{CH}_2(\text{C}_2\text{H}_5)\text{C}=\text{CH}_2$] to form racemic 3-methylhexane [$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$].



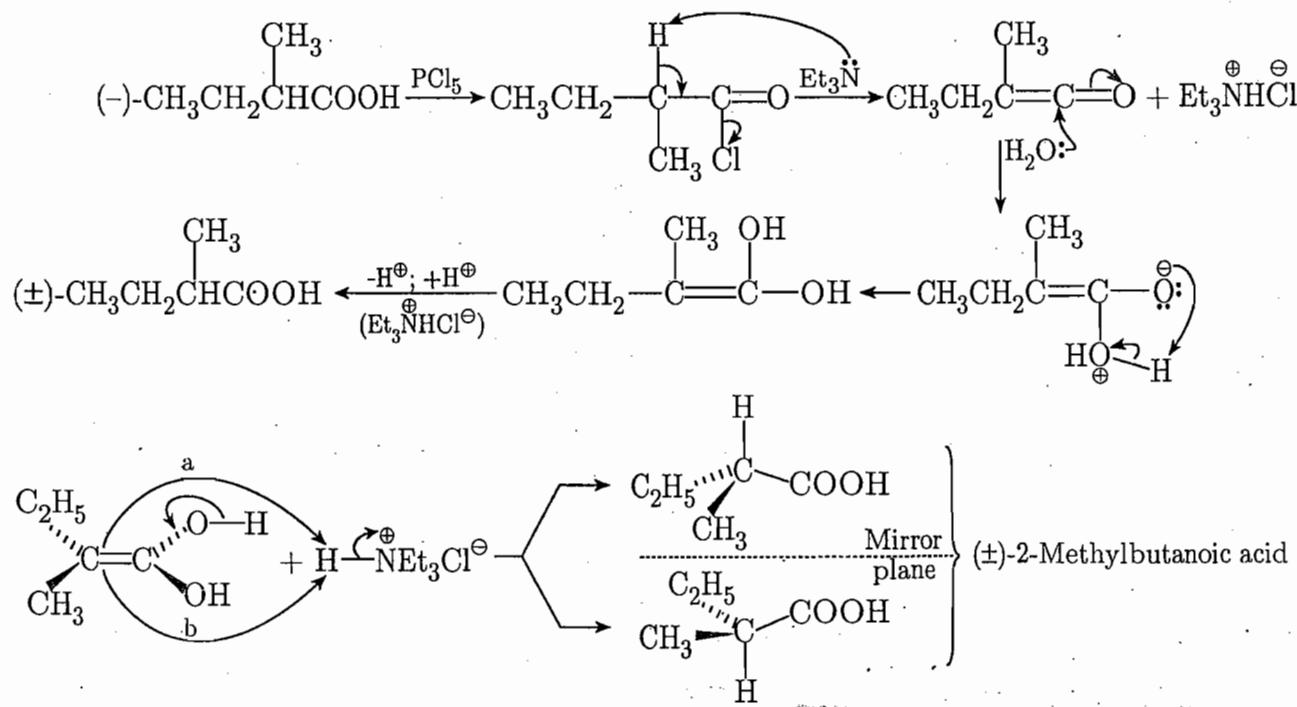
► 1.73 How would you carryout the following transformations?



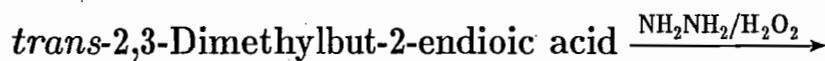
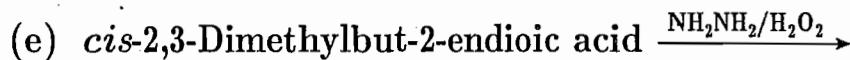
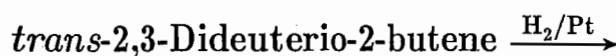
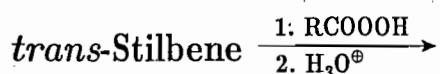
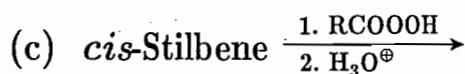
Ans. (a) (+)-2-Butanol ($\text{CH}_3\text{CHOHC}_2\text{H}_5$) is first oxidized by chromic acid ($\text{K}_2\text{Cr}_2\text{O}_7/\text{H}_2\text{SO}_4$) to yield 2-butanone which is achiral and optically inactive. 2-Butanone is then reduced by LiAlH_4 to give (\pm) -2-butanol. The hydride ion from LiAlH_4 attacks the carbonyl carbon from either side equally well to give a racemic product.



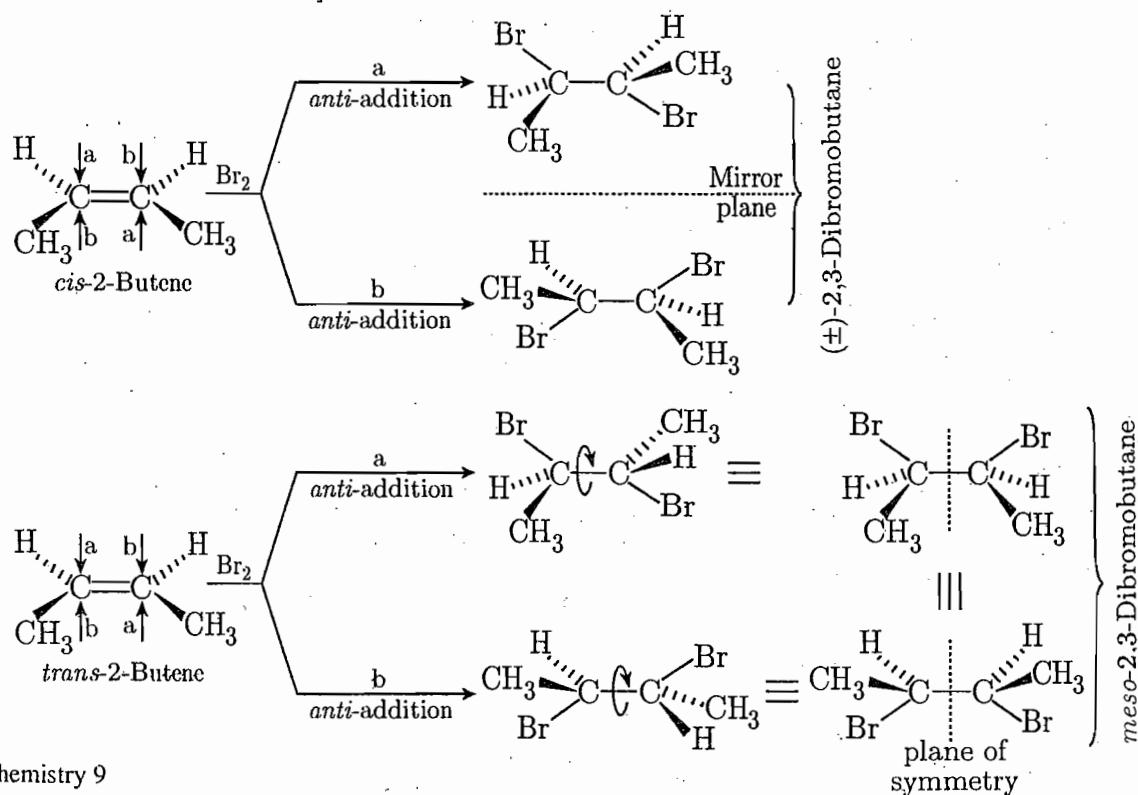
(b) (-)-2-Methylbutanoic acid [$\text{CH}_3\text{CH}_2\text{CH}(\text{CH}_3)\text{COOH}$] is first treated with PCl_5 to form the corresponding acid chloride. The acid chloride is then treated with triethylamine (Et_3N) to form a ketene (achiral and optically inactive). The ketene is finally hydrolyzed to yield (\pm) -2-methylbutanoic acid.



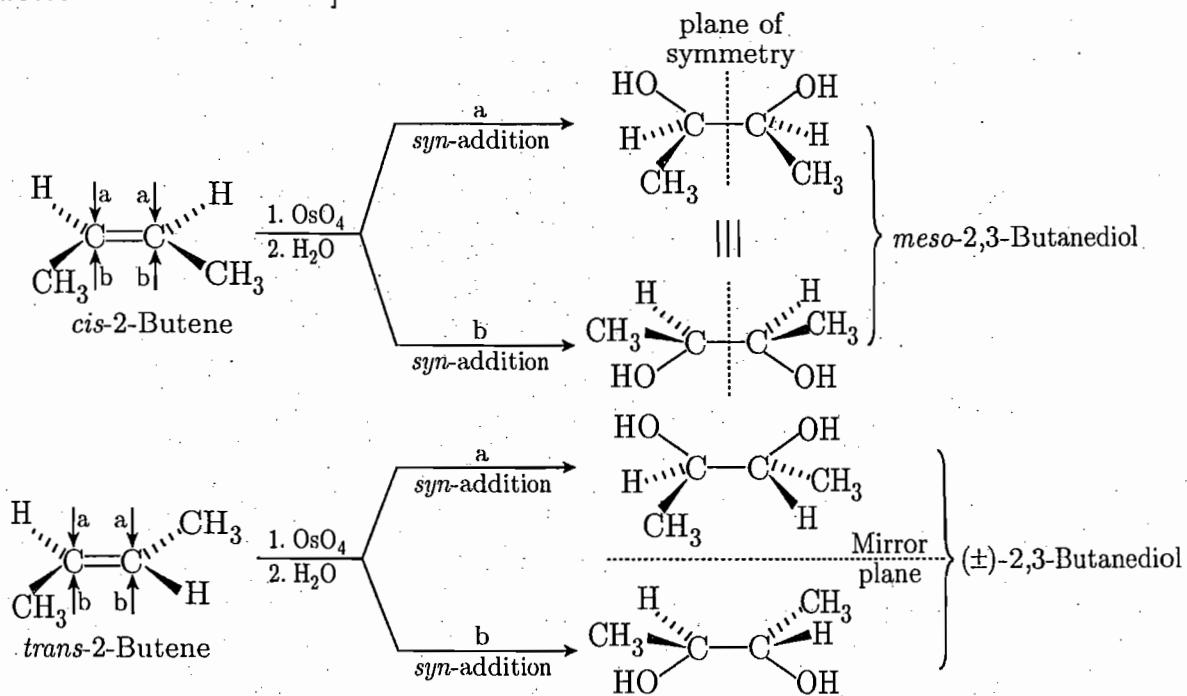
► 1.74 Each of the following reactions gives optically inactive product. Identify each product as a *meso*-compound or a racemic mixture, as appropriate.



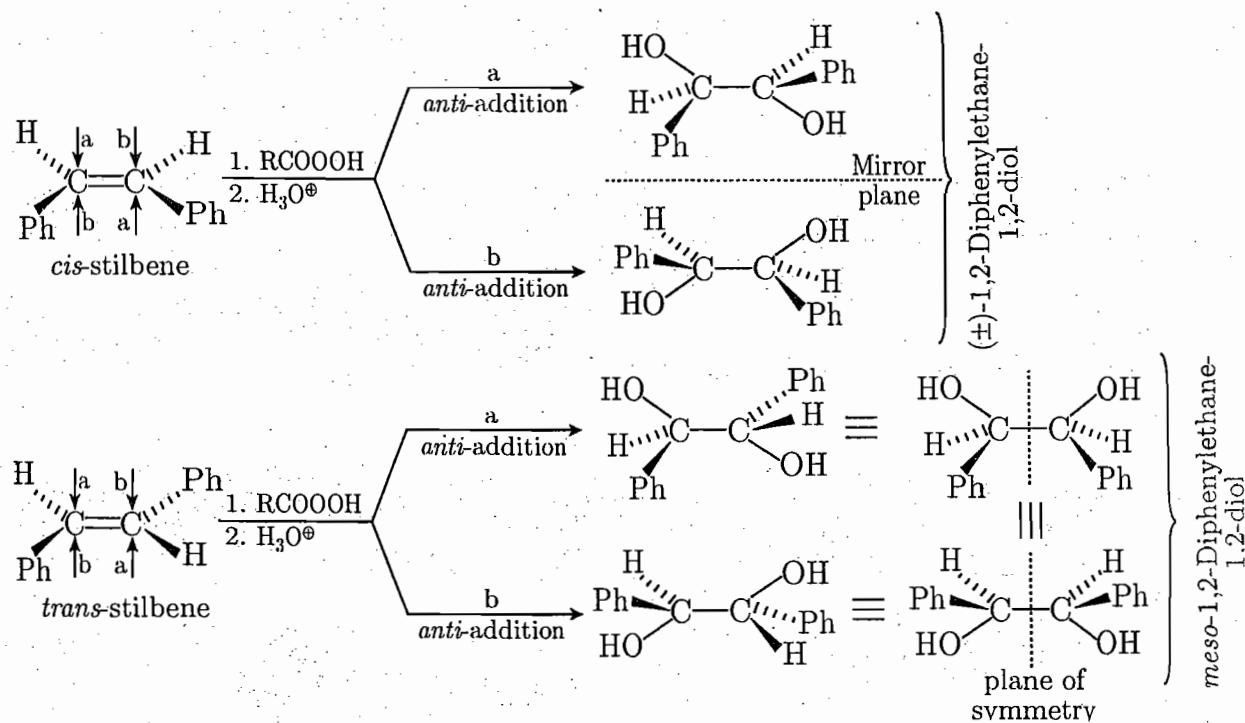
Ans. (a) The addition of bromine to an alkene is a stereospecific *anti*-addition (two bromine atoms adds to two double-bonded carbons from different sides). Therefore, *cis*-2-butene reacts with bromine to give racemic 2,3-dibromobutane and *trans*-2-butene reacts with bromine to give *meso*-2,3-dibromobutane. [For the stereochemical course of the reaction See *problem 4.3* of the book '*Advanced Organic Reaction Mechanism*'.]



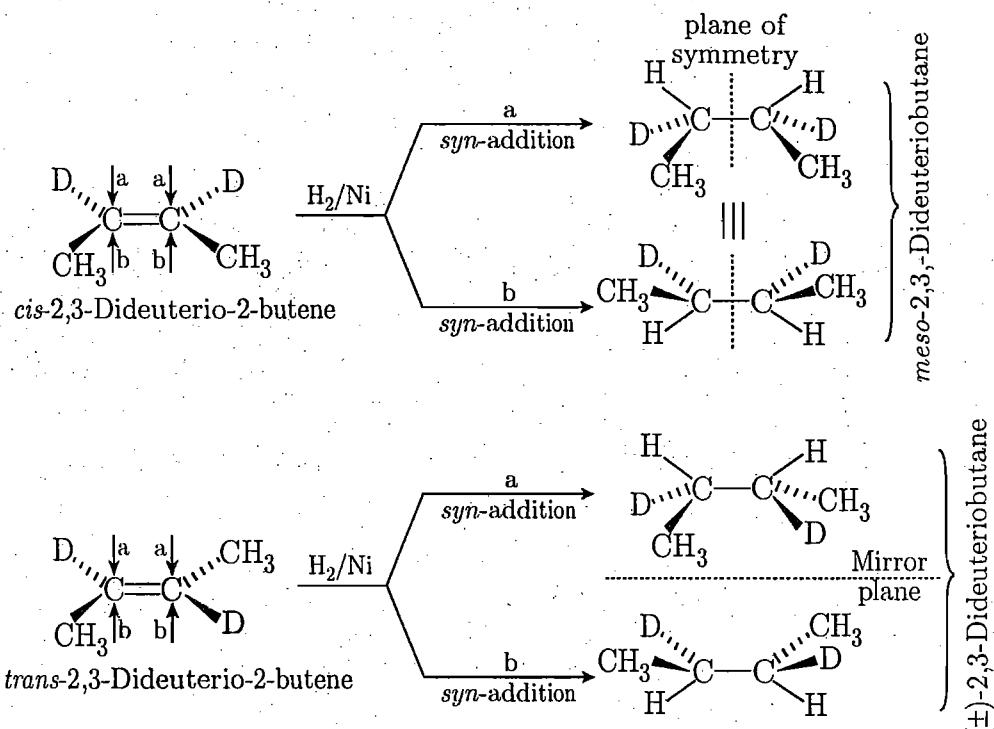
(b) When an alkene is treated with osmium tetroxide (OsO_4) followed by hydrolysis, stereospecific *cis*-hydroxylation occurs (two —OH groups add to two double-bonded carbons from the same side). Therefore, when treated with OsO_4 followed by H_2O , *cis*-2-butene produces *meso*-2,3-butanediol, whereas *trans*-2-butene produces (\pm) -2,3-butanediol. [For the stereochemical course of the reaction see Problem 4.62 of 'Advanced Organic Reaction Mechanism'.]



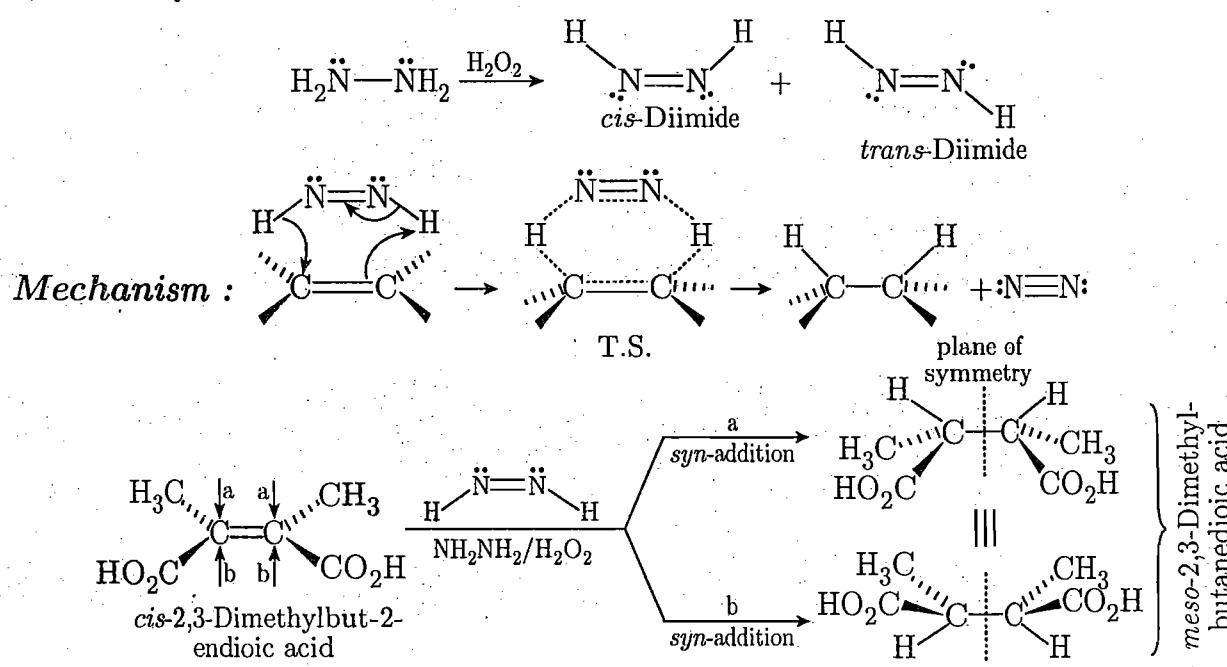
(c) When an alkene is treated with RCOOOH (epoxidation) followed by acid-catalyzed hydrolysis, stereospecific *trans*-hydroxylation occurs (two —OH groups add to two double-bonded carbons from the different sides). Therefore, when treated with RCOOOH followed by H_3O^+ , *cis*-stilbene produces racemic 1,2-diphenylethane-1,2-diol, whereas *trans*-stilbene produces *meso*-1,2-diphenylethane-1,2-diol. [For the stereochemical course of the reaction See Problem 4.64 of 'Advanced Organic Reaction Mechanism'.]

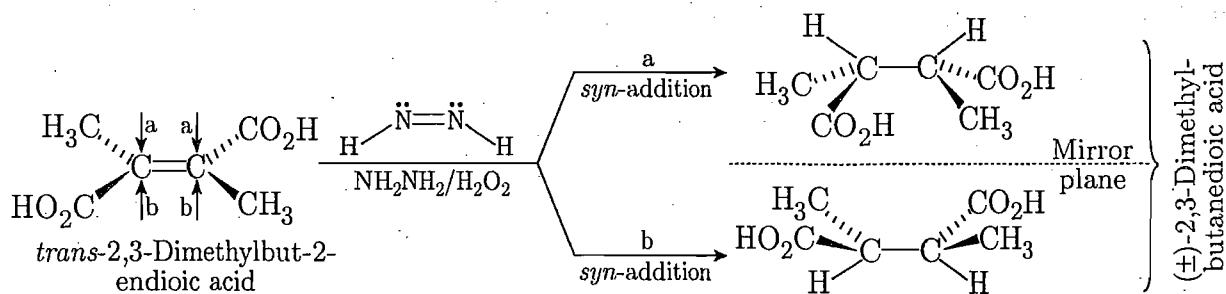


(d) The addition of hydrogen from the surface of the catalyst to an alkene is a stereospecific *syn*-addition (two hydrogen atoms add to two double-bonded carbons from the same side). Therefore, on catalytic hydrogenation *cis*-2,3-dideuterio-2-butene yields *meso*-2,3-dideuteriobutane, whereas *trans*-2,3-dideuterio-2-butene yield racemic 2,3-dideuteriobutane.



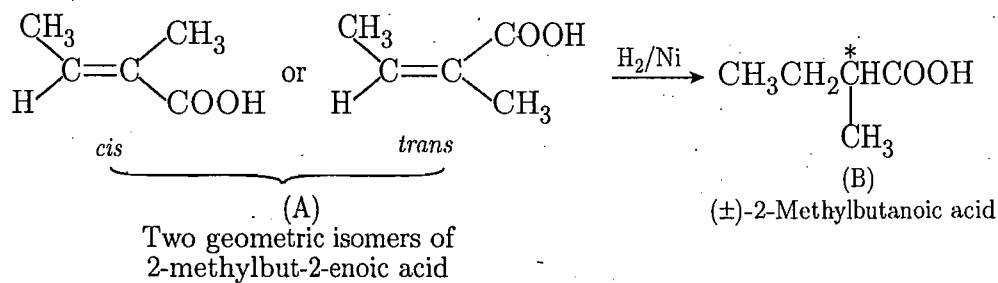
(e) Hydrogenation of carbon-carbon multiple bond may also be effected by diimide ($\text{HN}=\text{NH}$) which is formed by oxidation of hydrazine (NH_2NH_2) by hydrogen peroxide. Although both *anti* and *syn* form of diimide are produced, only the *syn* form reduces the double bond. The reaction proceeds through a six-membered cyclic transition state and therefore, the addition of two hydrogen atoms is stereochemically *syn*. Thus, *cis*-2,3-dimethylbut-2-endioic acid reacts with diimide to produce *meso*-2,3-dimethylbutanedioic acid, whereas *trans*-2,3-dimethylbut-2-endioic acid reacts with diimide to yield racemic 2,3-dimethylbutanedioic acid.





- 1.75 Compound A ($\text{C}_5\text{H}_8\text{O}_2$) liberates CO_2 from NaHCO_3 . It exists in two forms, neither of which is optically active. On hydrogenation it yields B ($\text{C}_5\text{H}_{10}\text{O}_2$) which can be resolved into enantiomers. Suggest structures for A and B.

Ans. The compound A ($\text{C}_5\text{H}_8\text{O}_2$) liberates CO_2 from NaHCO_3 . Therefore, the compound contains a $-\text{COOH}$ group. Since on hydrogenation A takes up one molecule of hydrogen ($\text{C}_5\text{H}_{10}\text{O}_2 - \text{C}_5\text{H}_8\text{O}_2 = 2\text{H}$), it contains a double bond. So, the compound A may be $\text{CH}_2=\text{CH}-\text{CH}_2\text{CH}_2\text{COOH}$, $\text{CH}_3\text{CH}=\text{CHCH}_2\text{COOH}$, $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)\text{COOH}$, $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)\text{COOH}$ or $(\text{CH}_3)_2\text{C}=\text{CHCOOH}$. Since it exists in two forms, i.e., as two geometrical isomers which are optically inactive, it may be $\text{CH}_3\text{CH}=\text{CHCH}_2\text{COOH}$, $\text{CH}_3\text{CH}_2\text{CH}=\text{CHCOOH}$ or $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)\text{COOH}$ (the substituents attached to each of the doubly bonded carbons are different). On hydrogenation the compound A yield B ($\text{C}_5\text{H}_{10}\text{O}_2$) which can be resolved into enantiomers. Only the compound $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)\text{COOH}$ on hydrogenation produces a saturated carboxylic acid (containing one chiral carbon atom) which exists as a racemate. Therefore, the compound A is $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)\text{COOH}$ and the compound B is $\text{CH}_3\text{CH}_2\text{CH}(\text{CH}_3)\text{COOH}$.

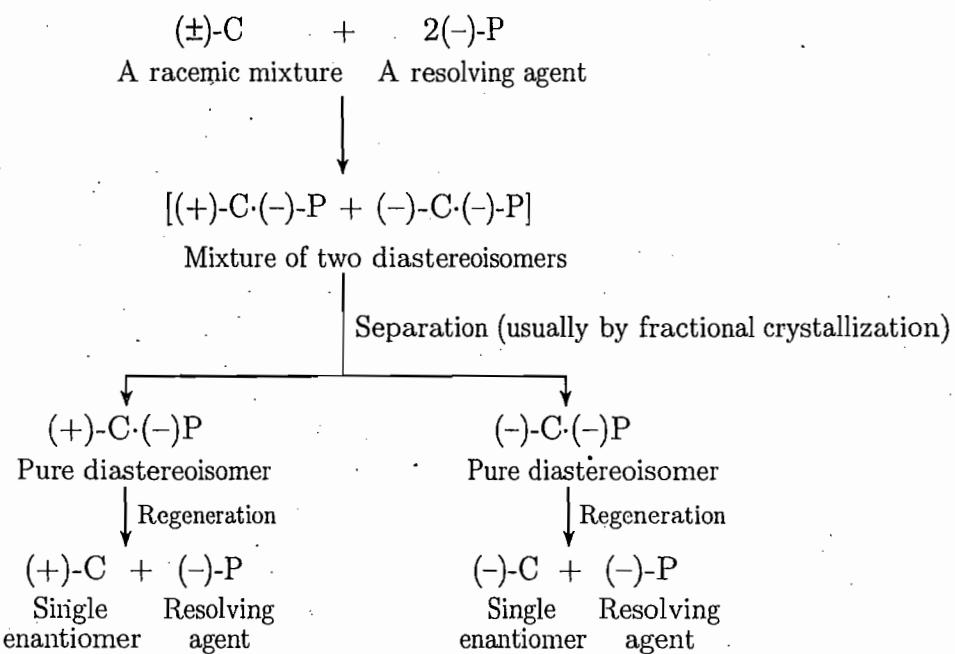


- 1.76 (a) What is resolution? Explain why two enantiomers cannot be separated by usual techniques (physical means).
- (b) Discuss the principle of resolution of a racemic modification by chemical method.
- (c) Discuss the procedure adopted to resolve (i) a racemic carboxylic acid, (ii) a racemic amine and, (iii) a racemic alcohol with suitable examples. Give structures of some of the resolving agents used in each case.
- (d) Explain why an amino acid cannot be resolved as a base or an acid directly. How can a racemic amino acid be resolved. Give example.

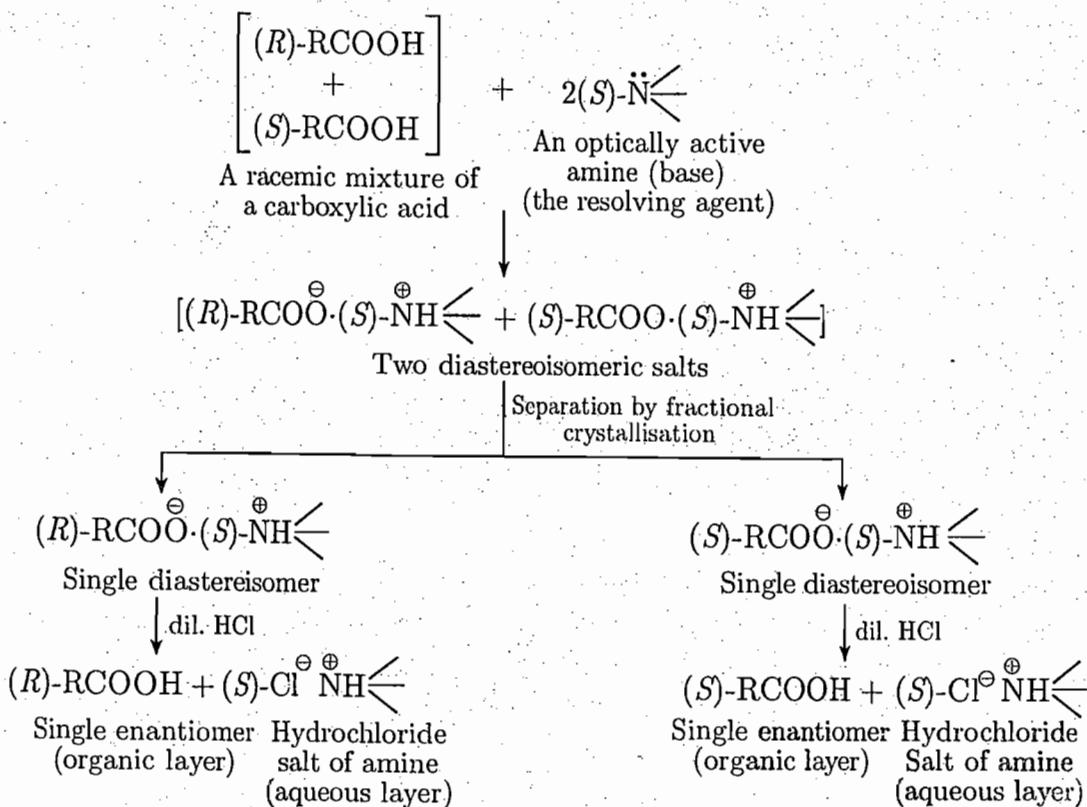
Ans. (a) The process of separation of pure enantiomers from a racemic modification is called resolution.

Since the two enantiomers in a racemic mixture have identical chemical and physical properties except towards optically active reagents, they cannot be separated by the usual techniques such as fractional distillation, fractional crystallization (unless the solvents are optically active), chromatography (unless the absorbents are optically active).

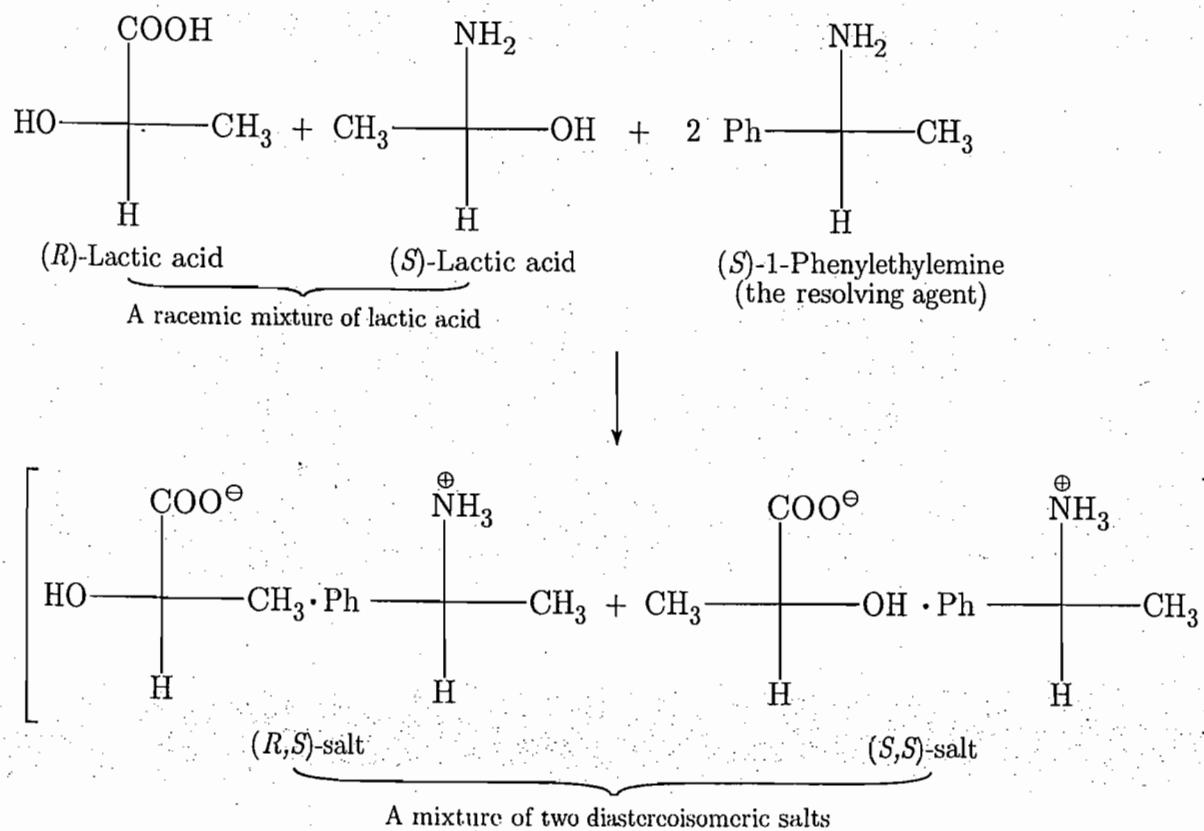
(b) The principle of chemical method of resolution involves the conversion of the enantiomers of a racemic modification into a pair of diastereoisomers by treatment with an enantiomerically pure chiral compound called a resolving agent. Since diastereoisomers, unlike enantiomers, have different physical properties such as solubility, boiling point, absorption coefficient etc., they can be separated by fractional crystallization (if they are solids) or by fractional distillation or chromatography (if they are liquids). An appropriate chemical reaction is then employed to remove the resolving agent from the diastereoisomers, thereby liberating the enantiomers and regenerating the resolving agent. The overall procedure may be shown schematically as follows :

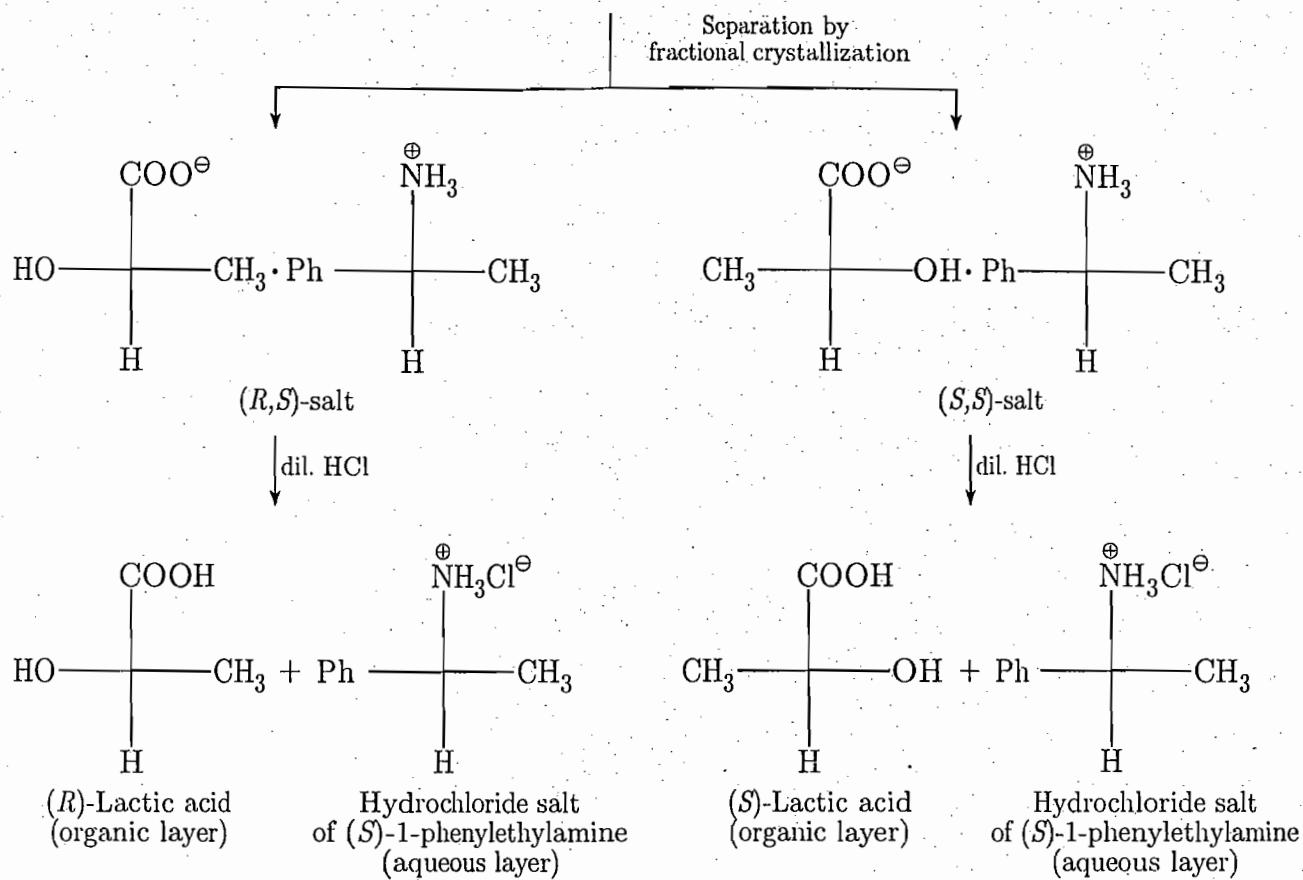


(c) (i) **Resolution of a racemic carboxylic acid :** The racemic modification of a carboxylic acid is first converted into two diastereoisomeric salts by the reaction of optically active base (resolving agent). The bases used are some naturally occurring alkaloids such as brucine, strychnine, ephedrine, quinidine, cinchonine and morphine (menthylamine and 1-phenylethylamine are also used). The diastereoisomeric salts are then separated by fractional crystallisation. Each of the diastereoisomer is then treated with dilute mineral acid (e.g., dil. HCl) to regenerate the enantiomer. Finally, the resolving agent and the enantiomer are isolated. The procedure may be schematically represented as follows :

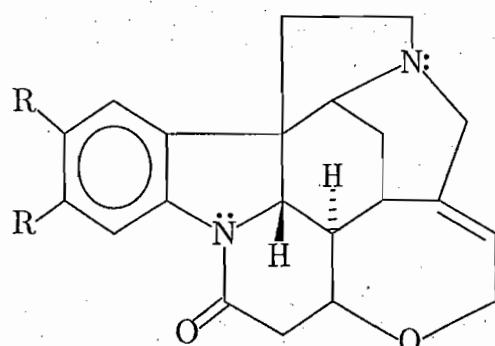


Example :

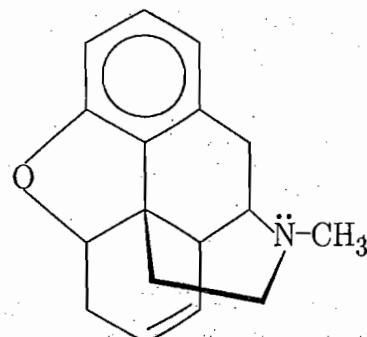




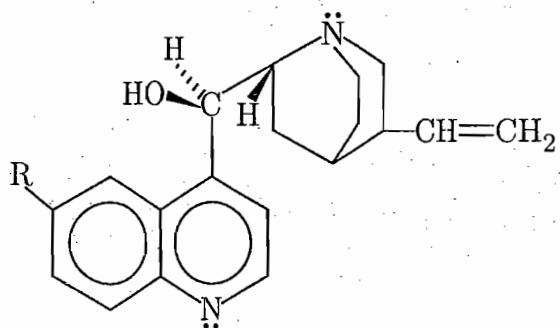
Structures of some other active bases used as resolving agents :



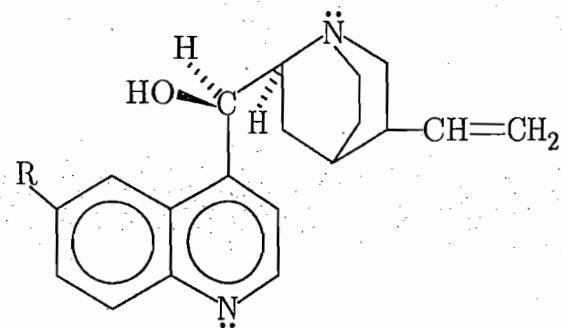
$\text{R} = \text{H}$, Strychnine
 $\text{R} = \text{OCH}_3$, Brucine



Morphine

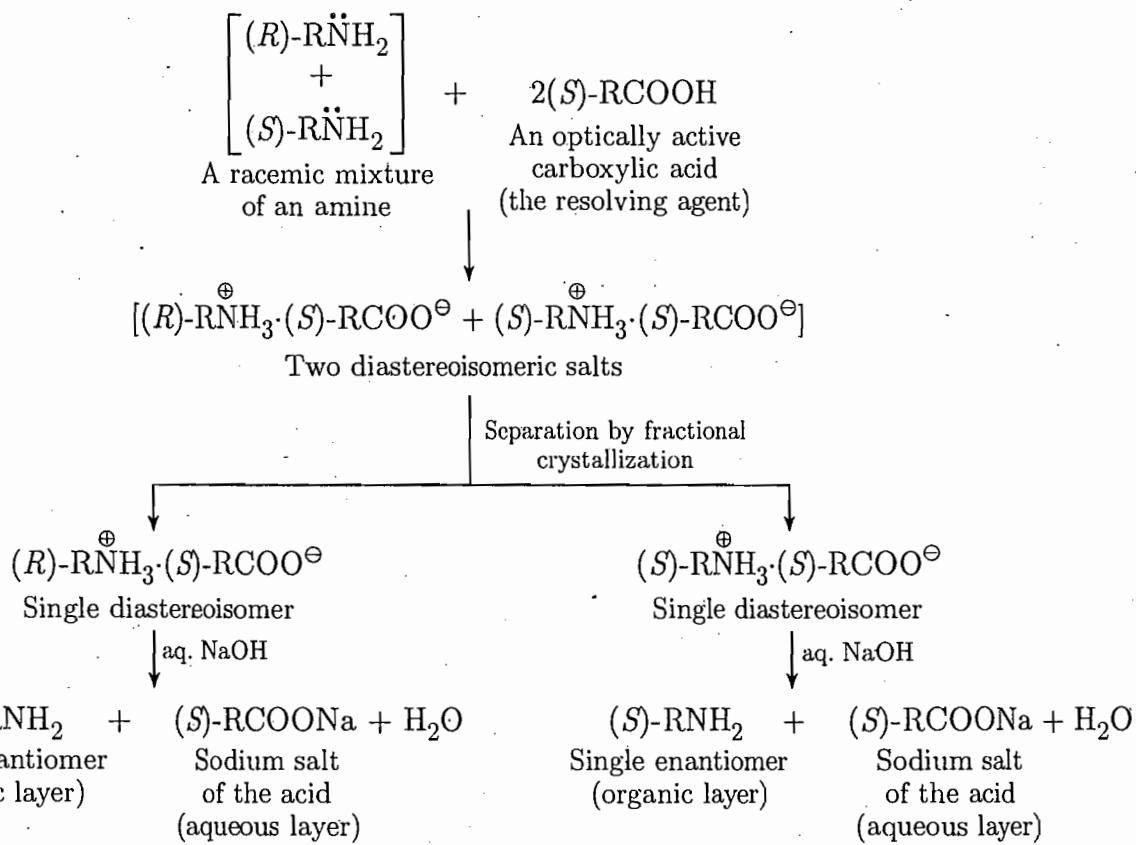


$\text{R} = \text{H}$, Cinchonidine
 $\text{R} = \text{OCH}_3$, Quinine

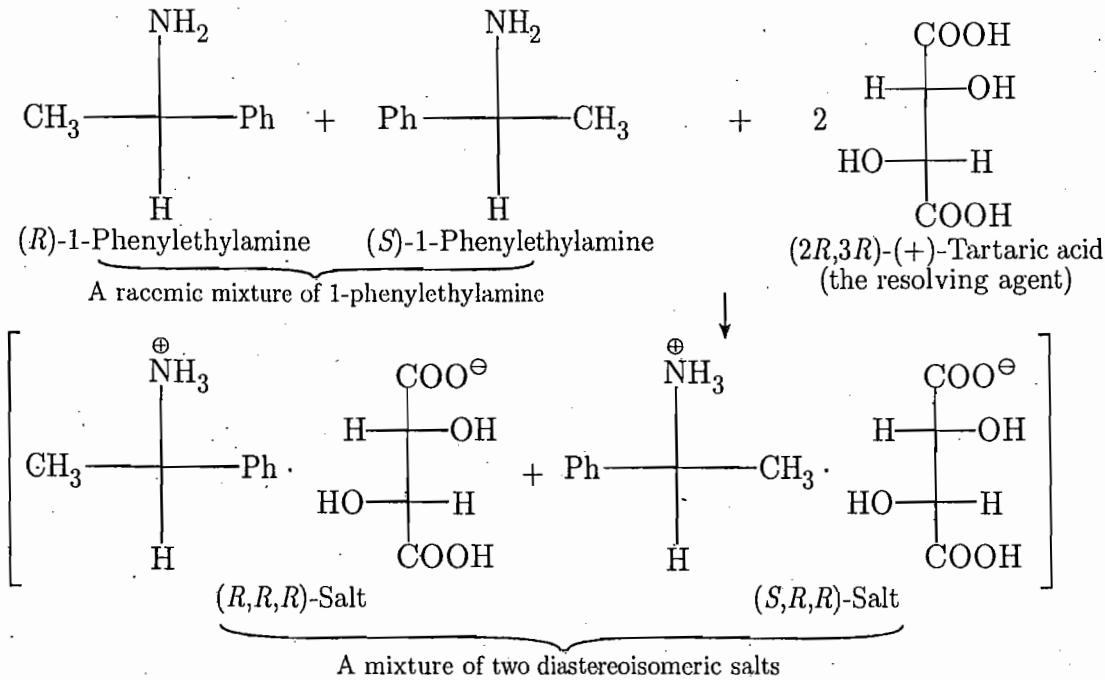


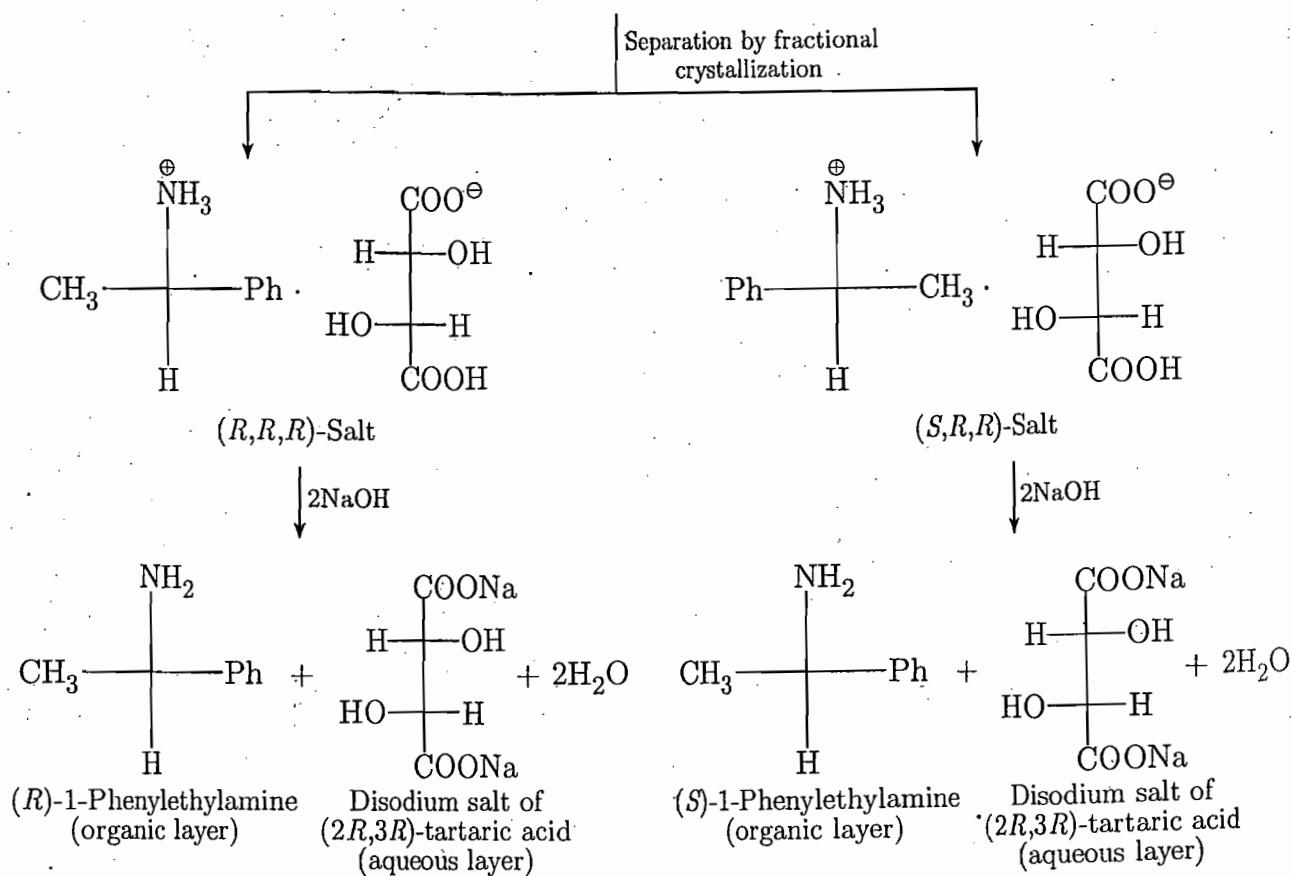
$\text{R} = \text{H}$, Cinchonine
 $\text{R} = \text{OCH}_3$, Quinidine

(ii) **Resolution of a racemic base :** The racemic modification of an organic base is converted into two diastereoisomeric salts by the reaction of an optically active acid (resolving agent). The acids used for this purpose are camphoric acid, camphor-10-sulphonic acid, bromochamphor-sulphonic acid, glutamic acid, tartaric acid, malic acid, etc. The salts are then separated by fractional crystallization. Each of the diastereoisomeric salts is then decomposed with base to liberate optically active amine, leaving the acid in solution as its conjugate base. The procedure may be schematically represented as follows :

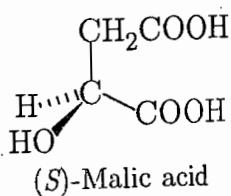
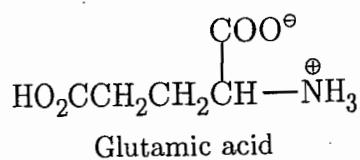
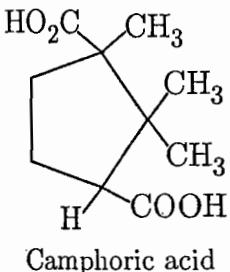
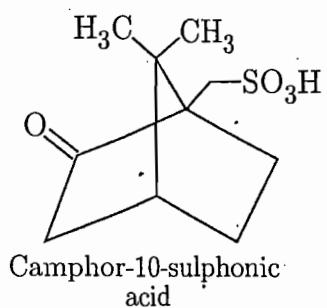


Example : Resolution of racemic 1-phenylethylamine may be shown as follows :



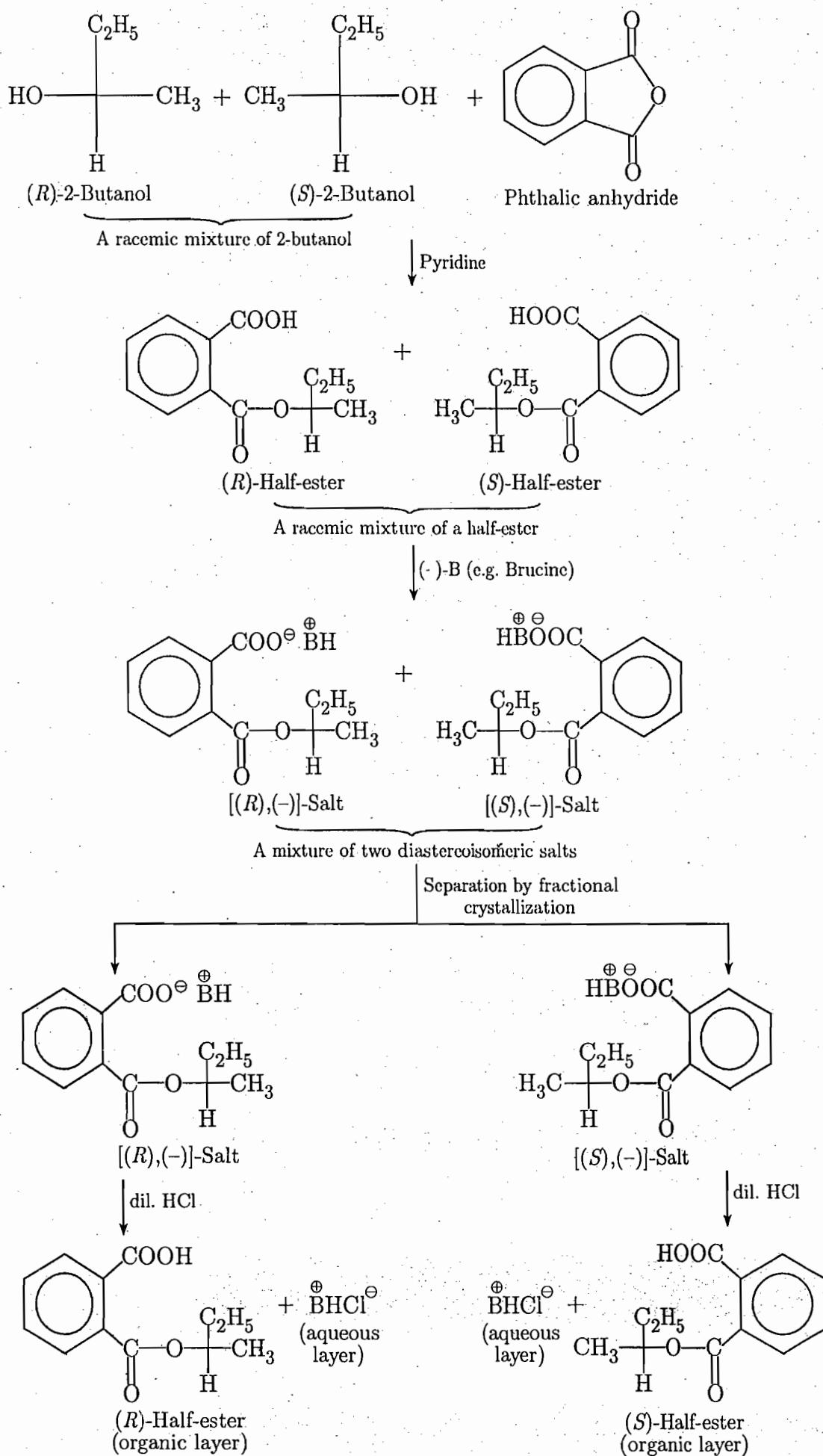


Structures of some other active acids used as resolving agents :

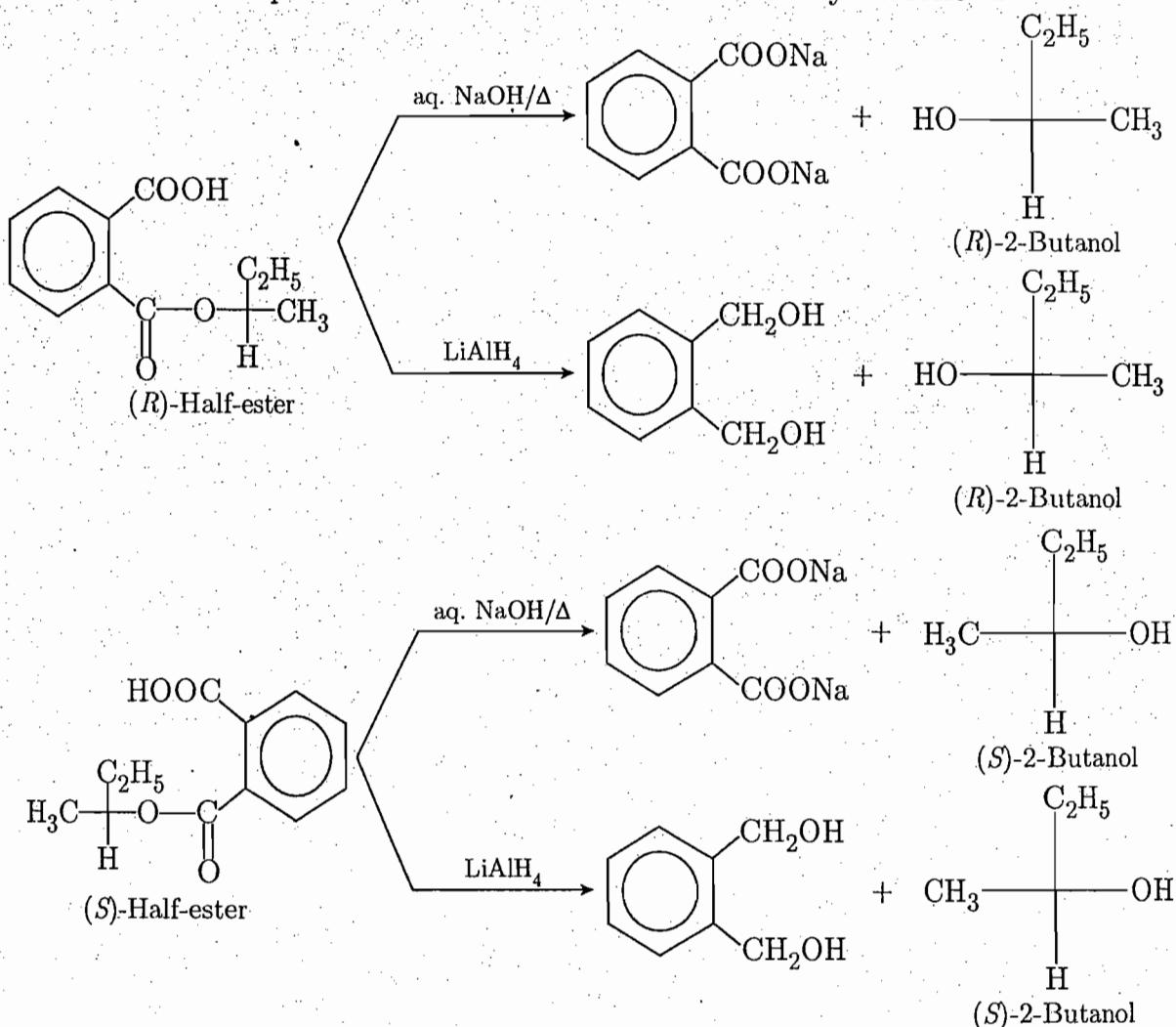


(iii) Resolution of a racemic alcohol : Alcohols are usually resolved by first attaching an "acidic handle" to it by an appropriate reaction and after the racemate is resolved, the handle is removed. Racemic alcohols are first converted into half-esters (both an ester and an acid) by reacting with phthalic or succinic anhydride in the presence of pyridine. The racemic half-esters are then converted into diastereoisomeric salts using brucine, cinchonidine etc. Diastereoisomeric salts are then separated by fractional crystallization and decomposed into half-esters by treating with dil HCl. The half-esters are isolated by extraction with ether and from these alcohols are regenerated either by hydrolysis with hot aqueous sodium hydroxide or by reduction with LiAlH_4 . The reduction is safer because saponification often leads to racemization.

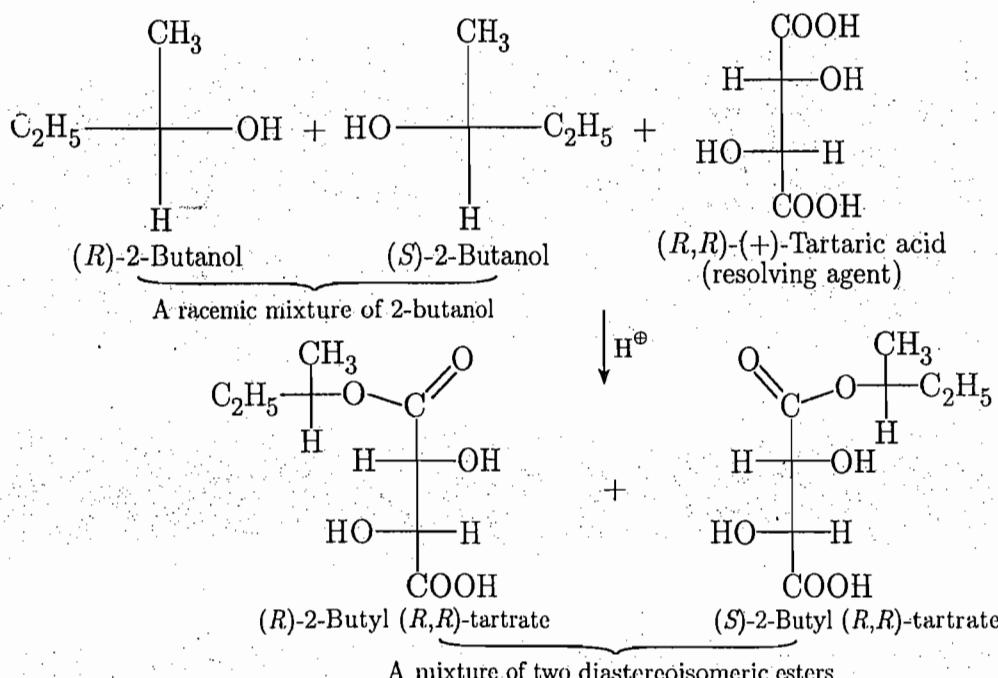
Example : Resolution of racemic 2-butanol by this procedure may be shown as follows :



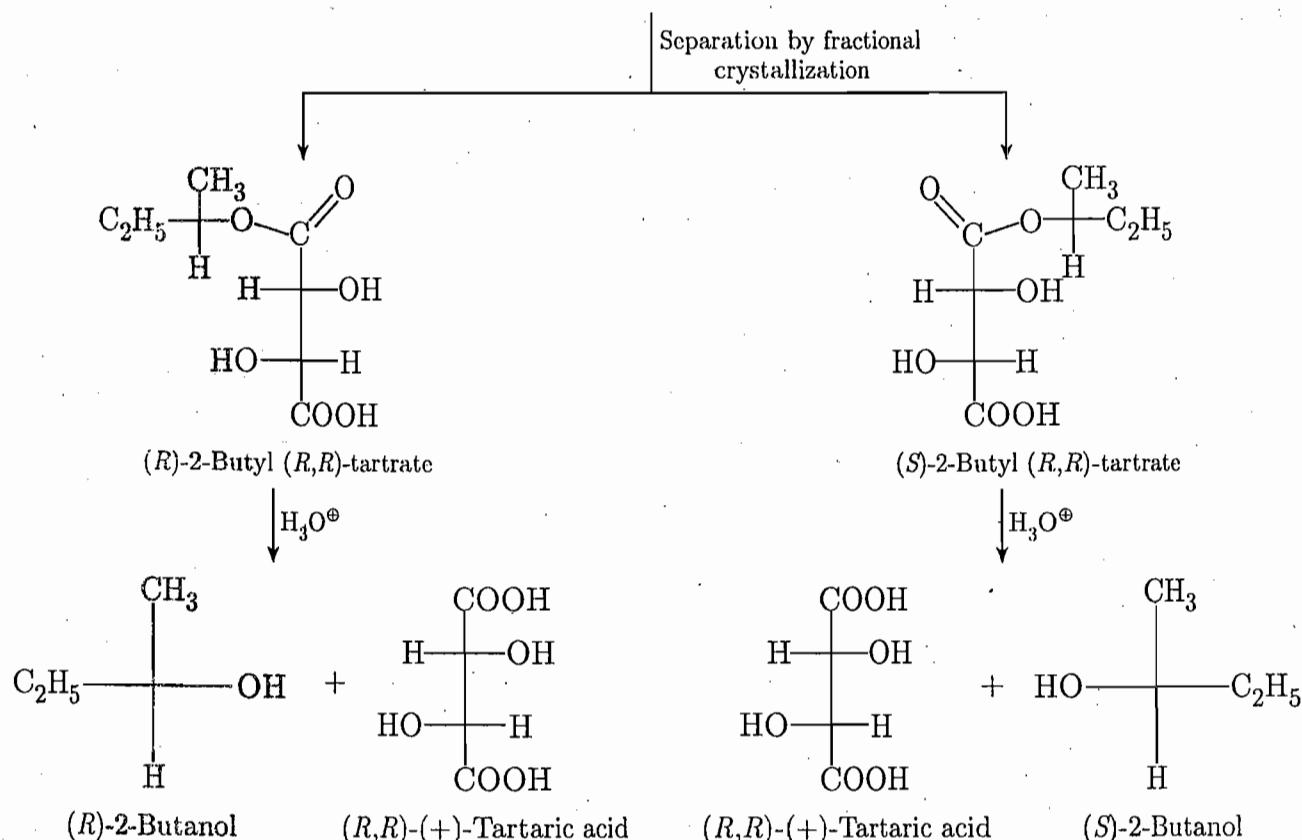
Half-esters are separated and then treated individually as follows :



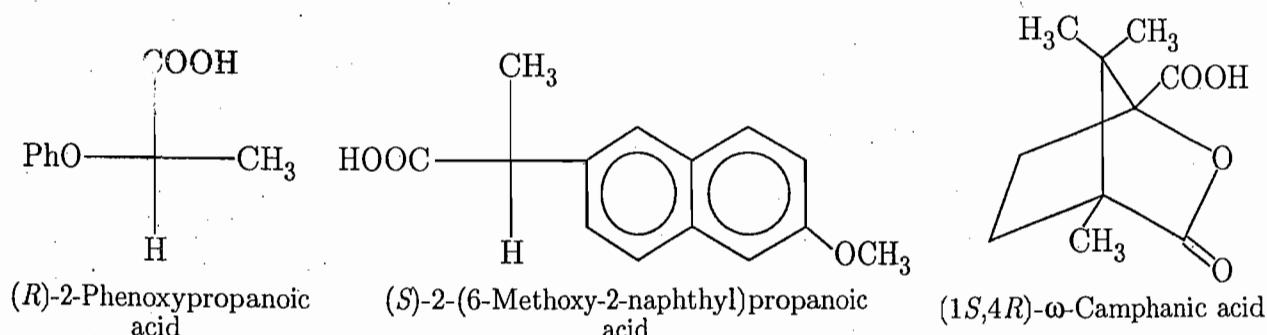
Racemic alcohols can also be resolved by converting them to diastereoisomeric esters of optically active acids (resolving agents) followed by their separation and hydrolysis. Racemic 2-butanol may be resolved by using (+)-tartaric acid as follows :



A mixture of two diastereoisomeric esters



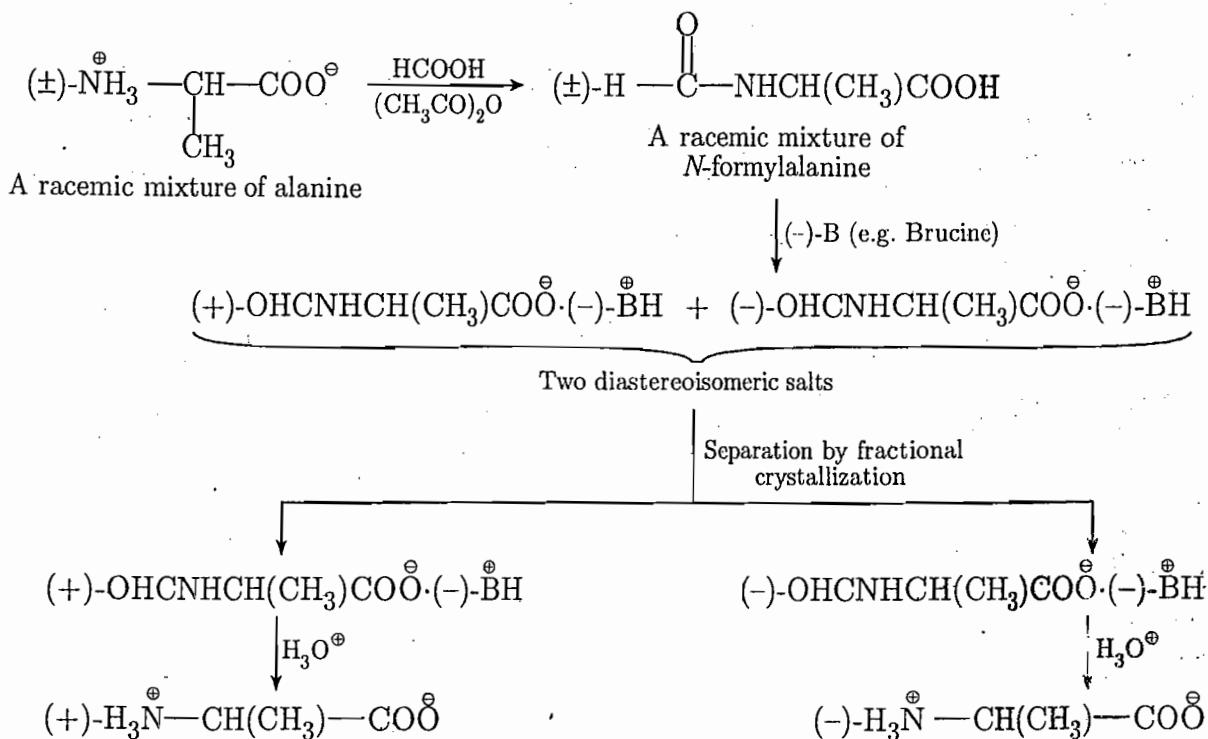
Structures of some other chiral acids used for the preparation of esters :



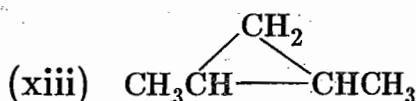
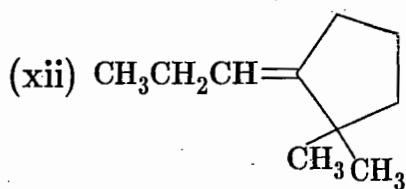
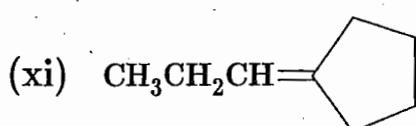
(d) Amino acids containing one $-\text{NH}_2$ group and one $-\text{COOH}$ group remain as inner salts or zwitter ions (dipolar ions) because the acidic carboxyl group and the basic amino group of the same molecule neutralise each other. For example, alanine remains as $\text{NH}_3^+ \text{CH}(\text{CH}_3)\text{COO}^-$ in aqueous solution. For this reason, amino acids cannot be resolved as a base or as an acid.

A racemic amino acid can be resolved by prior conversion to its formyl derivative. When the amino group is formylated ($-\text{NH}_2 \rightarrow -\text{NHCHO}$), its basic character is practically eliminated owing to the $-I$ and $-R$ effects of the carbonyl group and as a result, the amino acid derivative no longer behaves as an inner salt and behaves as an acid. The formyl derivative of the amino acid is then converted into diastereoisomeric salts by treating with an optically active base (the resolving agent). The salts are then separated by fractional crystallization. Separated salts are subjected to acid hydrolysis when both the formyl group ($-\text{CHO}$) and the basic resolving agent get removed from the salt leaving the individual enantiomer of the amino acid behind.

Example : Resolution of racemic alanine may be shown as follows :



GEOMETRIC ISOMERISM



- (e) All geometric isomers are diasteroisomers. Justify the statement.
- (f) What will be number of *cis-trans* isomers in case of polyenes? Comment on the *cis-trans* isomerism of cumulenes.
- (g) Identify the geometric isomers (diastereoisomers) expected to be formed in the following reaction.



- (h) What is the smallest *trans* cycloalkene that has been isolated at room temperature and why?
- (i) What is the smallest bridgehead alkene stable under normal conditions? Explain why the (*E*) form of this compound is less stable than the (*Z*) form.

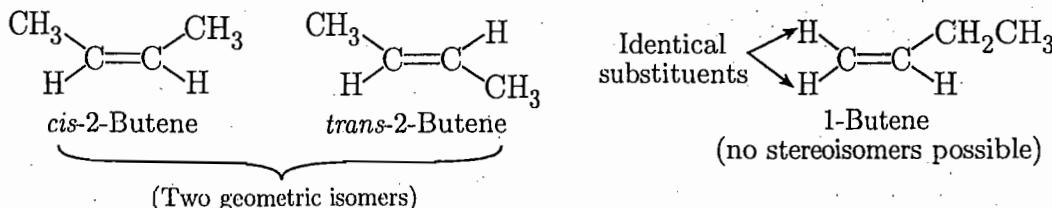
Ans. (a) The phenomenon of existence of isomers having same molecular constitution, i.e., same atom-to-atom bonding sequences or atomic connectivity, but differing in spatial arrangements of groups or atoms owing to the restricted rotation about a double bond ($\text{C}=\text{C}$, $\text{C}=\text{N}$, etc.) or about a ring is known as geometric or *cis-trans* isomerism and the isomers are called geometric or *cis-trans* isomers (now called diastereoisomers in stereochemical system of nomenclature). For example, 1,2-dichloroethene exists in two stereoisomeric forms (I and II) as given below, one being different from the other in the spatial arrangement of two chlorine and two H atoms. The isomer I with similar groups on the same side of the double bond is called the *cis*-isomer and the isomer II with similar groups on opposite sides of the double bond is called the *trans*-isomer.



(b) Carbon atoms involved in double bond formation are sp^2 hybridized so that each carbon atom has three planar sp^2 orbitals and the fourth p orbital having its lobes at right angles to the plane of sp^2 orbitals. The formation of a π bond involves overlapping of p orbitals and to achieve maximum overlap the two p orbitals must be parallel to each other. If either of the two doubly bond carbon is rotated about the double bond, the two p orbitals would cease to overlap and the π bond would be destroyed. Since it takes more energy to break the π bond than is available under normal conditions, the internal rotation about the carbon-carbon double bond is greatly restricted. Therefore, under normal conditions a double bond is stable and rigid. It is the rigidity of the double bond which accounts for the existence of geometric or *cis-trans* isomers.

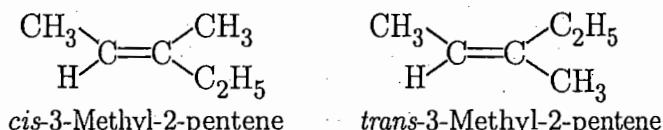
(c) The condition for an alkene to show geometric or *cis-trans* isomerism, i.e., to exist as *cis* and *trans* stereoisomers, is that each of the doubly bonded carbon atoms must be attached to two different atoms or groups. Therefore, an alkene $\text{C}_{ab}=\text{C}_{cd}$ will exist in two isomeric forms if $a \neq b$ and $c \neq d$. It does not matter whether a and/or b are the same as c and/or d . Geometrical isomerism is not possible if one of the doubly bonded carbon atoms is bonded to two identical atoms or groups. For example, 2-butene

$(\text{CH}_3\text{CH}=\text{CHCH}_3)$ in which each of the doubly bonded carbons is attached to two different substituents exists as two geometric isomers, whereas 1-butene ($\text{CH}_2=\text{CHCH}_2\text{CH}_3$) in which one of the doubly bonded carbons is attached to two identical substituents does not exist as two geometric isomers.

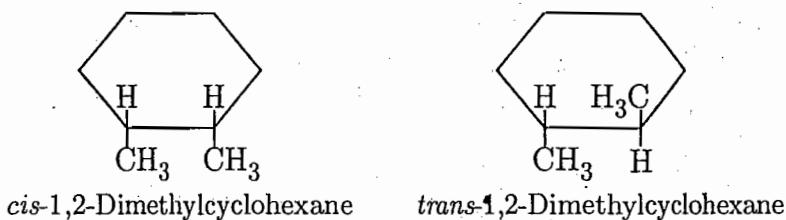


[Reversing the position of the groups attached to any of the doubly bonded carbons of one isomer of 2-butene gives its another isomer. However, reversing the position of the groups attached to any of the doubly bonded carbon atoms of 1-butene gives back the same molecule.]

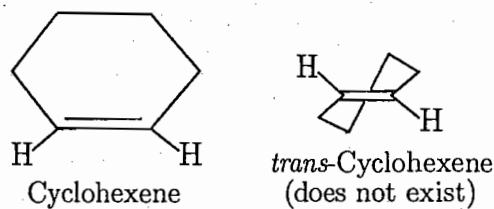
- (d) (i) 2-Methyl-2-hexene [$(\text{CH}_3)_2\text{C} = \text{CHCH}_2\text{CH}_2\text{CH}_3$] cannot exist as *cis-trans* isomers because the substituents attached to one doubly bonded carbon are identical.
- (ii) 3-Methyl-2-pentene can exist as *cis-trans* isomers because the substituents attached to each doubly bonded carbons are different.



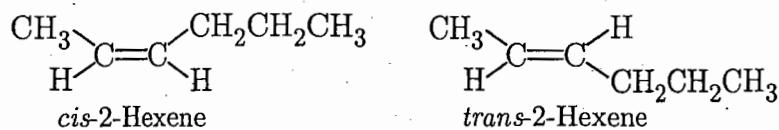
- (iii) 1,2-Dimethylcyclohexane can exist as *cis-trans* isomers.



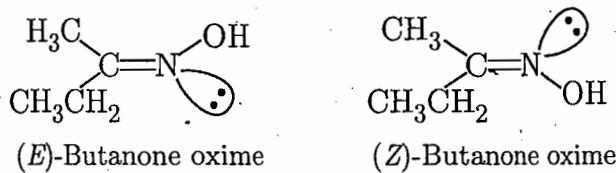
- (iv) Although each doubly bonded carbon atoms in cyclohexene is attached to two different substituents, it can exist only in the *cis* configuration because a *trans*-double bond, due to much angle strain, cannot be geometrically accommodated in a six-membered ring. Since the only isomer possible is *cis*, the *cis* name is not normally used to designate it.



- (v) 2-Hexene can exist as *cis-trans* isomers.

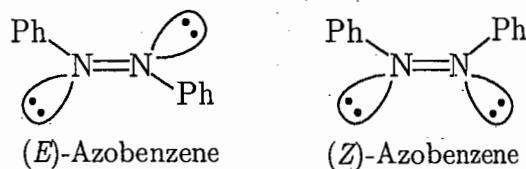


(vi) Butanone oxime shows *cis-trans* isomerism.

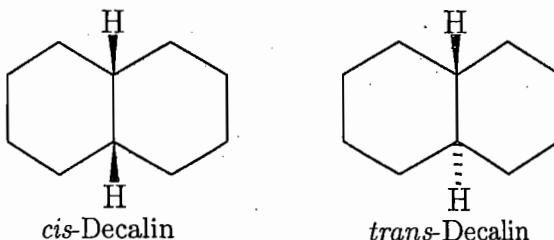


(vii) Acetone oxime [$(\text{CH}_3)_2\text{C}=\text{N}-\text{OH}$] cannot exist as *E,Z* isomers because the groups attached to the doubly bonded carbon are the same.

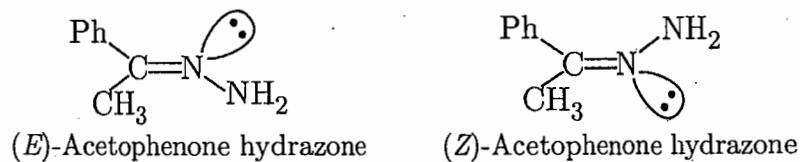
(viii) Azobenzene exhibits *cis-trans* isomerism.



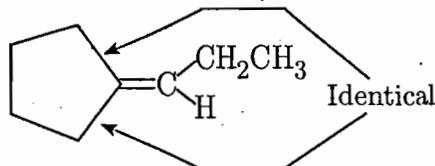
(ix) Decalin can exist as *cis-trans* isomers.



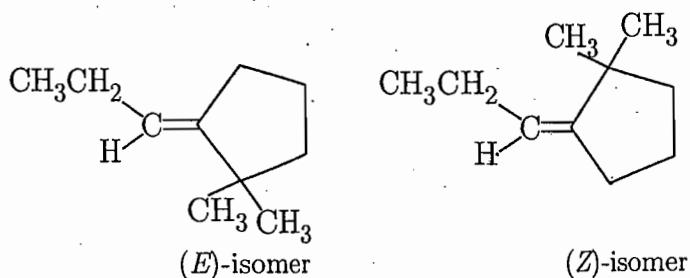
(x) Acetophenone hydrazone exhibits *cis-trans* isomerism.



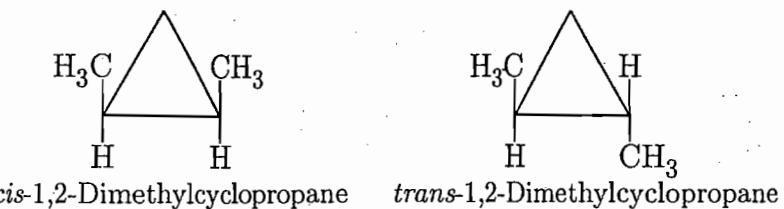
(xi) This compound can not exist as *cis-trans* isomers because the groups attached to one doubly bonded carbon are the same.



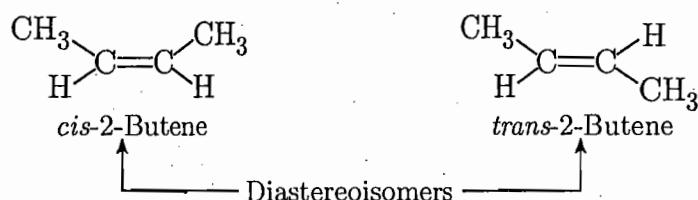
(xii) This compound exhibits *cis-trans* isomerism.



(xiii) The compound exhibits *cis-trans* isomerism.

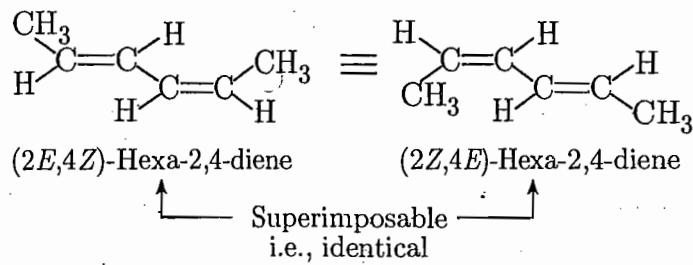
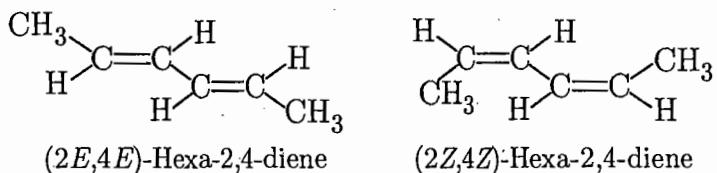
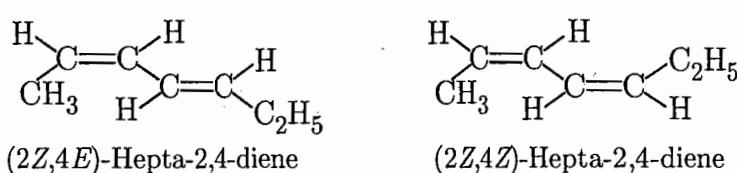
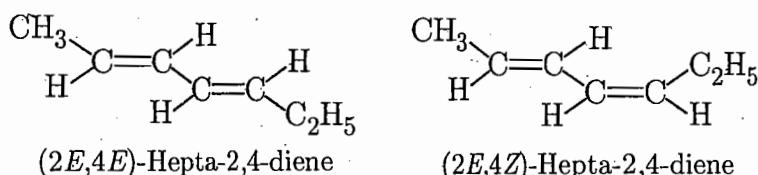


(e) Geometric or *cis-trans* isomers are not related to each other as an object and its mirror image. Therefore, they are all diastereoisomers. For example :

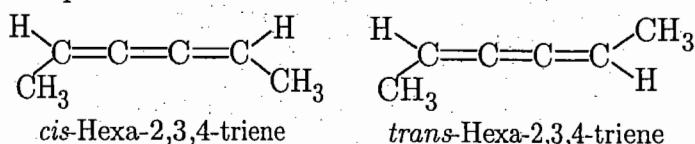


[The term *cis-trans* isomerism is now replaced by the terms π - and σ -diastereoisomerism.]

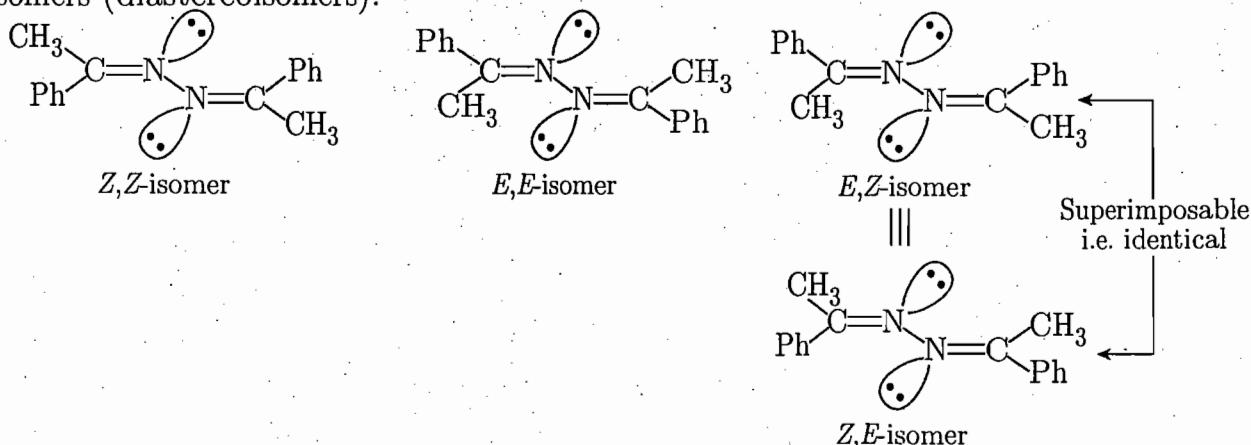
(f) In case of polyenes, the number of *cis-trans* isomers depends on the number of double bond in the molecule as well as the terminal substituents. If the general formula of a polyene is $R-(CH=CH)_n-R'$ (terminal substituents are different), the number of stereoisomers is 2^n and if the general formula is $R-(CH=CH)_n-R$ (terminal substituents are the same), the number of stereoisomers is $(2^{n-1} + 2^{p-1})$, where $p = n/2$ when n is even, and $p = (n+1)/2$ when n is odd. For example, four geometric isomers are possible for hepta-2,5-diene (with different terminal groups) and three geometric isomers are possible for hexa-2,4-diene (with identical terminal groups).



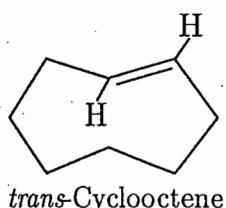
Cumulenes having odd number of double bonds and with different substituents on terminal carbons [$C_{ab}=(C)_n=C_{cd}$, where $a \neq b$, $c \neq d$ and $n = 2, 4, 6, \dots$ etc.] exhibit *cis-trans* isomerism and the number of isomers are always two irrespective of the number of double bonds. For example :



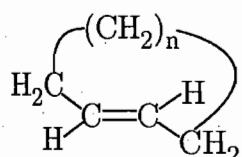
(g) Hydrazine (1 mole) reacts with acetophenone (2 moles) to give three geometric isomers (diastereoisomers).



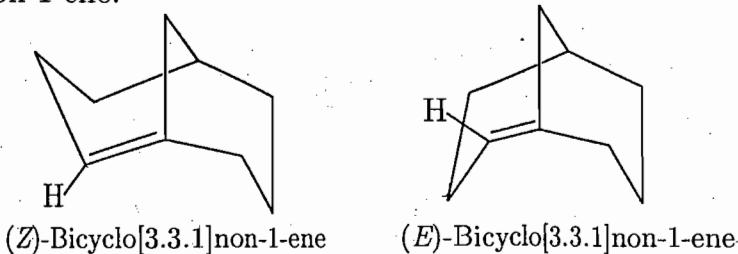
(h) *Trans*-cyclooctene is the smallest *trans* cycloalkene stable at room temperature.



Cyclic alkenes with fewer than eight carbon atoms can exist only in the *cis* configuration because the *trans* isomers are too strained and unstable to be isolated at room temperatures. The reason for this difference in stability is apparent if we consider the size of the carbon chain necessary to bridge the terminal carbon atoms of a *trans*-2-butene moiety. With the aid of molecular models, it has been found that the distance to be bridged (about 4 Å) requires a chain of at least four carbon atoms ($n = 4$, in the fig. below) or there would be excessive twisting of the double bond.



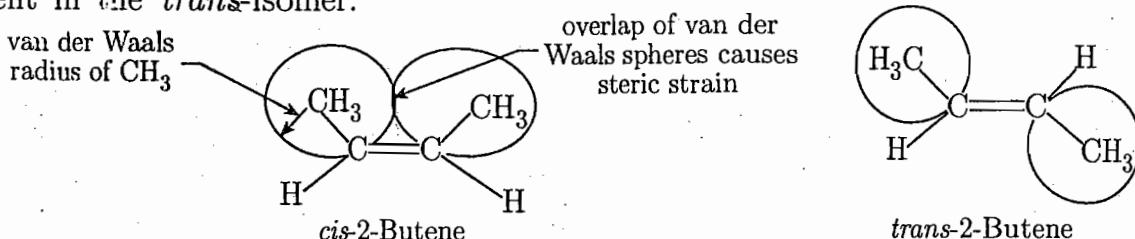
(i) The smallest bridgehead alkene stable under normal conditions is (*Z*)-bicyclo[3.3.1]non-1-ene.



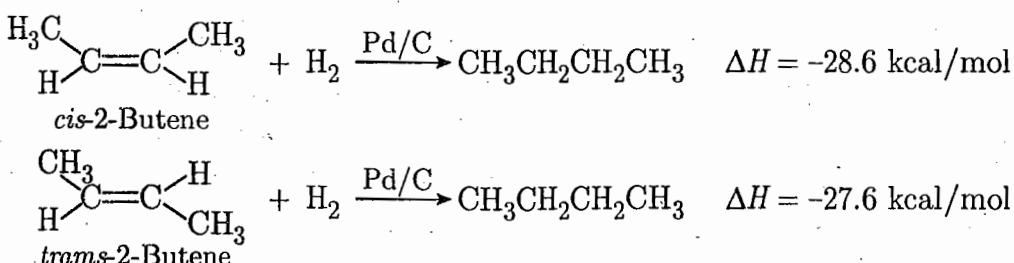
The molecule contains a double bond in two different-sized rings. The double bond of the (*Z*) form is *cis* in the six-membered ring and *trans* in the eight membered ring. On the other hand, in the (*E*) form, the double bond is *cis* in the eight-membered ring and *trans* in the six-membered ring. The smaller the ring, the less stable is a *trans* double bond, so the (*E*) form is less stable than the (*Z*) form.

- 1.78 (a) Compare the relative stabilities of *cis* and *trans* isomers. Give your reasoning.
 (b) How can heats of hydrogenation values be used to measure the relative stabilities of geometric isomers of 2-butene?
 (c) How can the geometric isomers be interconverted?
 (d) How can *cis-trans* isomers be distinguished on the basis of their physical properties?
 (e) How can geometric isomers be distinguished by chemical methods?
 (f) How would you determine the configurations of aldoximes and ketoximes? Illustrate with suitable examples.

Ans. (a) In general *trans* isomers are more stable than *cis*-isomers. The greater stability (lower free energy) of the *trans*-isomer is attributed to steric strain in the *cis*-isomer due to the van der Waals repulsion between the large groups on the same side of the double bond. For example, *trans*-2-butene is more stable than *cis*-2-butene. The distance between the adjacent methyl groups in the *cis*-isomer is about 3 Å. Since the sum of the van der Waals radii for two methyl groups is 4 Å, the hydrogens in these two groups are sufficiently close that there is a net repulsion not present in the *trans*-isomer.



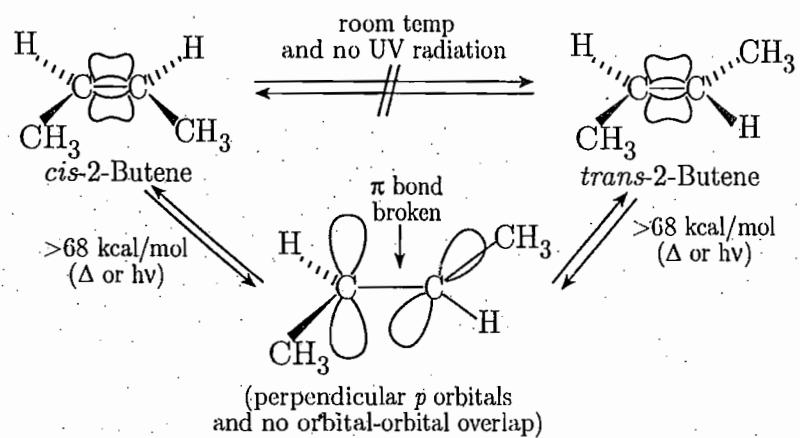
(b) Heat of hydrogenation of *cis*-2-butene is 28.6 kcal/mol and that of *trans*-2-butene is 27.6 kcal/mol.



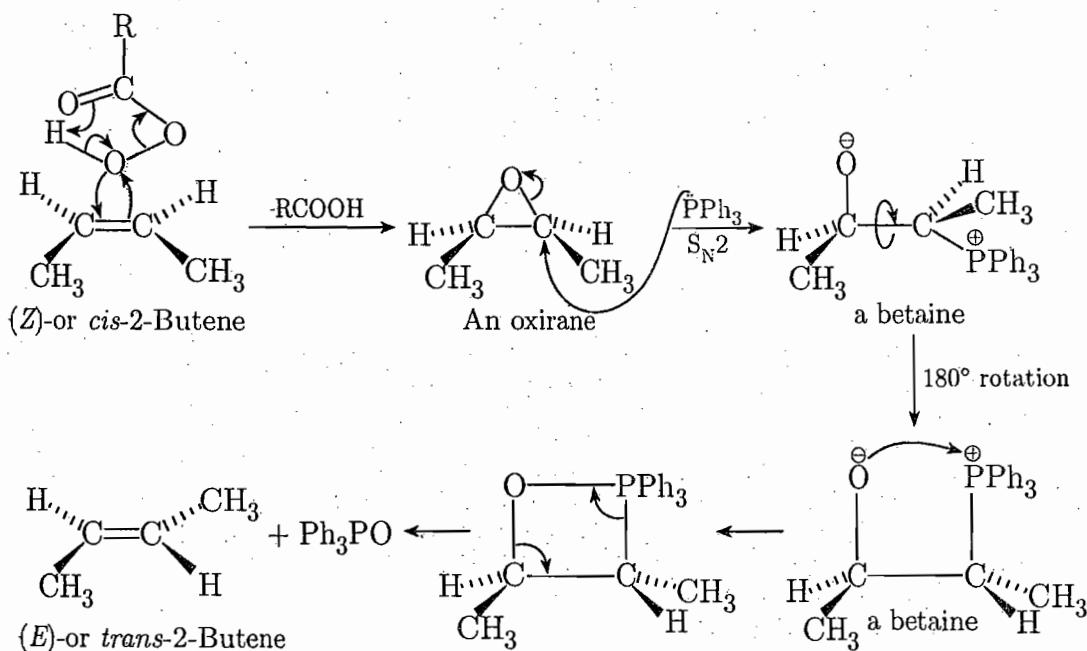
Since the heat of hydrogenation of the *cis*-isomer is greater than that of the *trans*-isomer, the potential energy of the *cis*-isomer is greater than the *trans*-isomer, i.e., the *cis*-isomer is thermodynamically less stable than the *trans*-isomer.

[Also, from heat of combustion values it is possible to measure the relative stabilities of *cis*- and *trans*-2-butene.]

(c) The *cis* and *trans* isomers of alkenes do not interconvert under ordinary conditions because conventional laboratory sources of heat do not provide enough thermal energy (>68 kcal/mol, the π -bond energy) for rotation about the double bond which requires the p orbitals to be twisted from their stable parallel alignment. However, the geometric isomers can be interconverted if energy in excess of 68 kcal/mol is applied by heat or ultraviolet radiation.

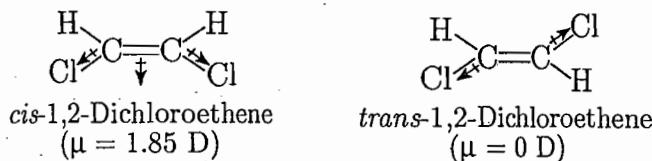


Interconversion of *cis-trans* isomers can also be brought by epoxidation by a peracid followed by deoxygenation of the oxirane by triphenylphosphine. The epoxidation of alkenes proceeds in a *syn* fashion and the stereochemical outcome of deoxygenation is that the R groups attached to oxirane carbons are placed with a different stereochemical relationship in the alkene. Therefore, epoxidation-deoxygenation sequence provides a method to invert the configuration of the groups attached to a carbon-carbon double bond. For example, *cis*-2-butene may be converted to *trans*-2-butene as follows.

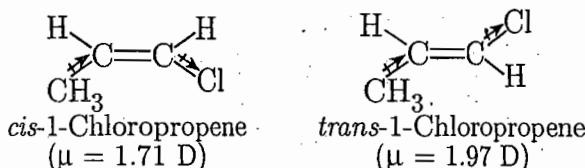


(d) Since *cis-trans* isomers are diastereoisomers, they differ in many physical properties like dipole moment, boiling point, melting point, solubility, etc., and they can be distinguished on the basis of their physical properties.

- (i) **Dipole moment** : In general, *cis*-isomers have higher dipole moment than the *trans*-isomers. For example, *cis*-1,2-dichloroethene, has significant dipole moment since the two Cl atoms are attached to the same side of the double bond and the inductive effects are additive. On the other hand, *trans*-1,2-dichloroethene has one Cl and H atom on each side of the double bond and hence, the bond moments cancel out each other, i.e. the resultant moment is zero. Thus, dipole moment values can be used as a method for identification of geometric isomer.



If, however, one substituent is electron-donating and the other is electron-withdrawing, the bond moments are fully additive in *trans*-isomer. Thus the *trans*-isomer in this case has a higher dipole moment than the corresponding *cis*-isomer. For example :

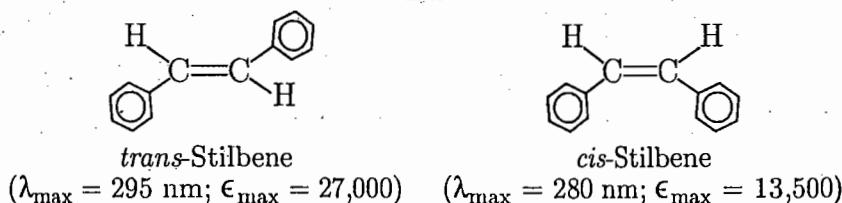


- (ii) **Boiling point** : *Cis*-isomers have usually higher boiling point than *trans*-isomers and this is because dipole-dipole attractions operate among the polar molecules of the *cis*-isomer. For example, the b.p. of *cis*-2-butene is 3.7°C whereas that of *trans*-2-butene is 0.9°C. Thus, boiling point can be used as a method for identification of geometric isomers.
- (iii) **Melting point** : *Trans*-isomers are usually high melting than the *cis*-isomers. This is because the molecules of more symmetrical *trans*-isomer are closely packed in a crystal lattice and consequently more energy is needed for overcoming the intermolecular forces of the crystal. For example, the melting point of maleic acid (*cis*-HO₂CCH=CHCOOH) is 130°C whereas that of fumaric acid (*trans*-HO₂CCH=CHCO₂H) is 302°C. Thus, melting points can also be used as a method for identification of geometric isomers.
- (iv) **Spectroscopic data** : *Cis-trans* isomers can be differentiated by spectral analysis such as follows :

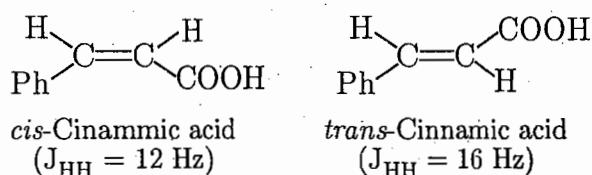
IR : Infrared spectra are sometimes used to distinguish between *cis*- and *trans*-isomers of the type RCH=CHR'. The isomer having a *trans* configuration is readily identified by the appearance of a strong band near 970–960 cm⁻¹. This band (olefinic =C—H bending) is not found in the spectrum of the *cis*-isomer.

UV : UV spectra can be used to distinguish between *cis*- and *trans*-isomers. *Trans*-stilbene, for example, has a higher λ_{\max} value compared to *cis*-stilbene. The *trans*-isomer has no significant steric interactions and has an extended coplanar

π -system. In the *cis*-isomer, however, the two phenyl groups are on the same side of the double bond and sterically interfere with each other. As a consequence, both rings cannot be coplanar with the double bond, and conjugation is thus not as effective as it is in the case of *trans*-isomer. The result is a small decrease in λ_{\max} value but a large decrease in ϵ_{\max} value.

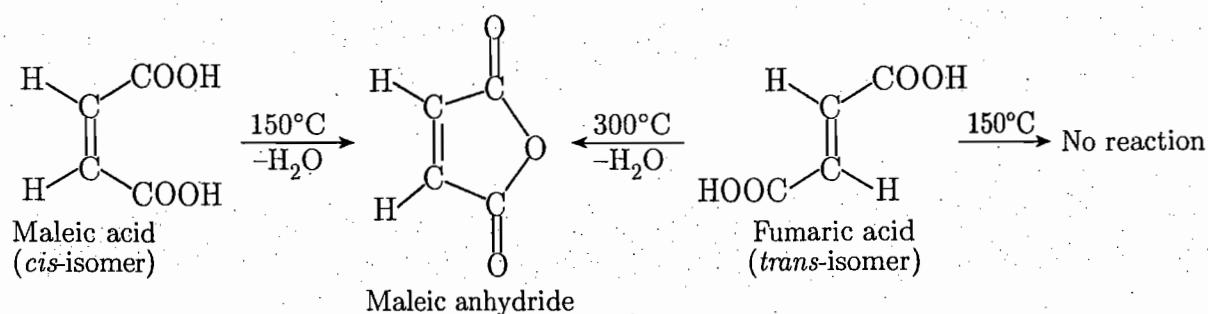


NMR : Nuclear magnetic resonance spectroscopy provides another important tool for distinguishing *cis-trans* isomers. The coupling constant for *trans* protons ($J_{\text{trans}} = 12\text{--}18 \text{ Hz}$) is greater than the coupling constant for *cis* protons ($J_{\text{cis}} = 6\text{--}14 \text{ Hz}$). For example :



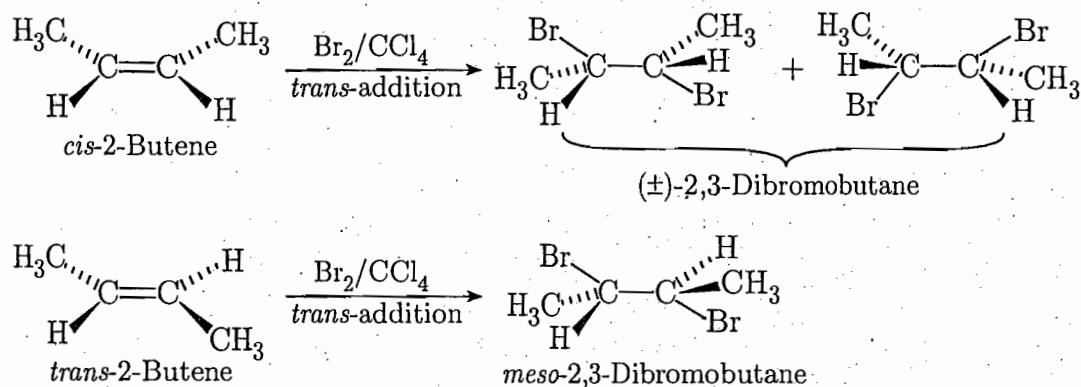
(e) Chemical methods of ascertaining configurations of a pair of *cis-trans* isomers are as follows :

(i) **By formation of cyclic compounds :** Two geometric isomers may be distinguished through 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 practically impossible to have a *trans* double bond in a ring lower than a eight-membered. For example, maleic acid readily loses water when heated to about 150°C to form an anhydride, whereas fumaric acid does not give anhydride at this temperature. However, it gives the same anhydride when heated to 300°C . Thus, maleic acid is the *cis*-isomer and fumaric acid is the *trans*-isomer. At high temperatures, the formation of anhydride from fumaric acid involves rapture of the π bond and rotation of the $-\text{COOH}$ groups towards each other, followed by reformation of the π bond and loss of water.



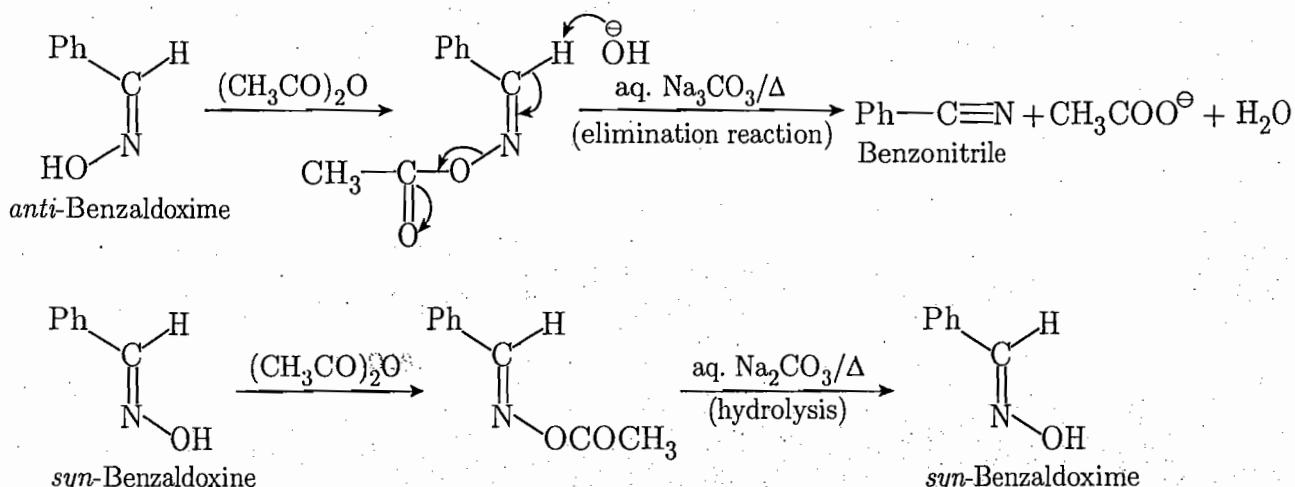
(ii) **By some stereospecific addition reactions :** *Cis*-addition to a *cis*-isomer and *trans*-addition to a *trans*-isomer give rise to a *meso* compound, while *cis*-addition to a *trans*-isomer and *trans*-addition to a *cis*-isomer give rise to a racemic modification. Therefore, configurations of geometric isomers of the structure

$C_{ab} = C_{ab}$ may be determined by performing *cis*- and *trans*-addition reactions and then examining the product. For example, the isomer of 2-butene which on bromination (stereospecific *trans*-addition) gives racemic 2,3-dibromobutane is *cis* whereas the isomer which on bromination gives *meso* 2,3-dibromobutane is *trans*.

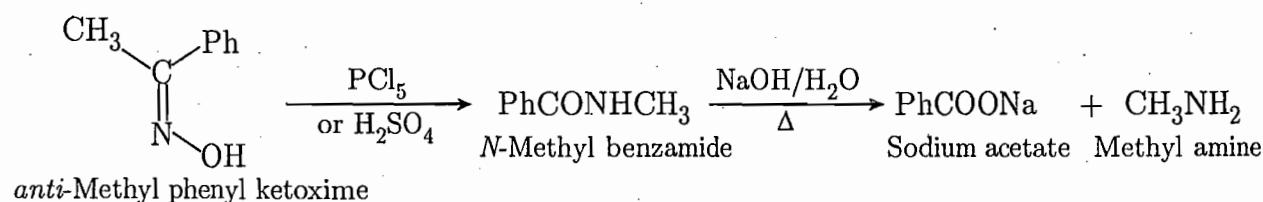
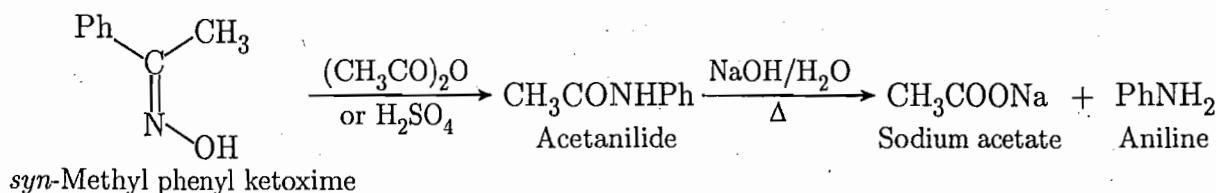


Catalytic hydrogenation (stereospecific *syn*-addition) can also be used for the determination of configurations of geometric isomers.

- (f) Configurations of a pair of aldoximes can be determined by converting them into their corresponding acetates followed by treatment with aqueous sodium carbonate solution. If the original aldoxime is regenerated, the configuration of the isomer is *syn* and if a nitrile is obtained by elimination of a molecule of acetic acid, the configuration of the isomer is *anti*. For example, the isomer of benzaldoxime which is converted into benzonitrile is *anti* and the isomer which regenerates the original aldoxime is *syn*.

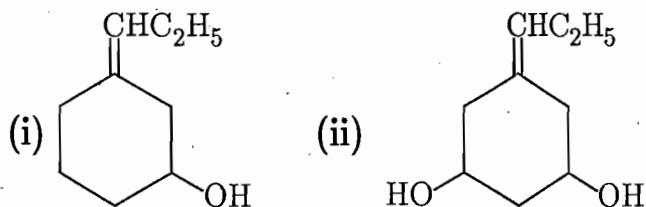


The configuration of a ketoxime can be determined with the help of Beckmann rearrangement. In this reaction, the ketoxime under consideration is treated with acidic reagents such as PCl_5 , SOCl_2 , phosphoric acid, sulphuric acid, etc., when the oxime undergoes a molecular rearrangement to give an isomeric N-substituted amide by migration of the group which is *anti* to the hydroxyl group. Thus, by identifying the acid amide (by identifying the amine and the acid obtained on its hydrolysis) produced after the Beckmann rearrangement, the configuration of the given ketoxime can be determined. For example, the isomer of methyl phenyl ketoxime (acetophenone oxime) which produces aniline and sodium acetate on treatment with PCl_5 or H_2SO_4 followed by hydrolysis is *syn* and the isomer which produces methyl amine and sodium benzoate is *anti*.



[N.B. Aliphatic aldoximes and ketoximes exist only in the *anti*-form. So, the question of determining configuration arises only in the case of aromatic aldoximes and ketoximes.]

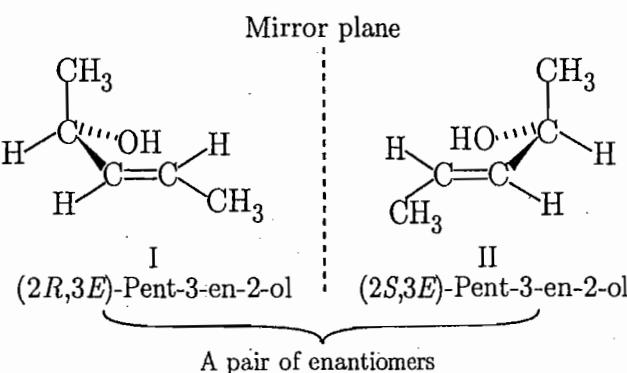
- 1.79 (a) What is “geometric enantiomerism”? Illustrate with suitable examples.
 (b) Predict the total number of stereoisomers for each of the following compounds and identify the enantiomeric pairs.

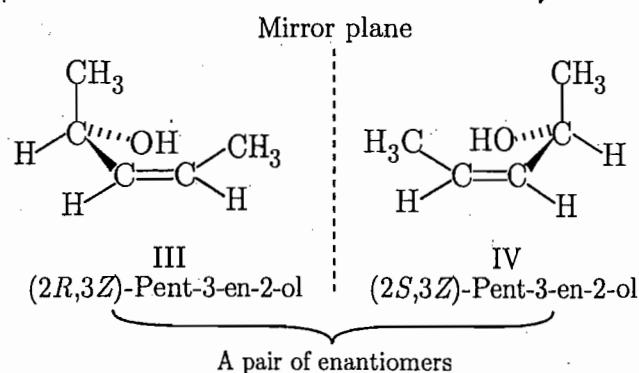


Ans. (a) Geometric isomers are not optically active but if they develop molecular chirality (with or without chiral centre), then they also exhibit optical isomerism. In such cases, the isomerism is known as geometric enantiomerism.

If a molecule contains both chiral centre/chiral axis and an appropriately substituted double bond ($C=C$, $C=N$) or ring to give *E,Z*-isomers, then four stereoisomers are possible. According to CIP system they may be designated as (*R,E*), (*S,E*), (*R,Z*) and (*S,Z*). For example :

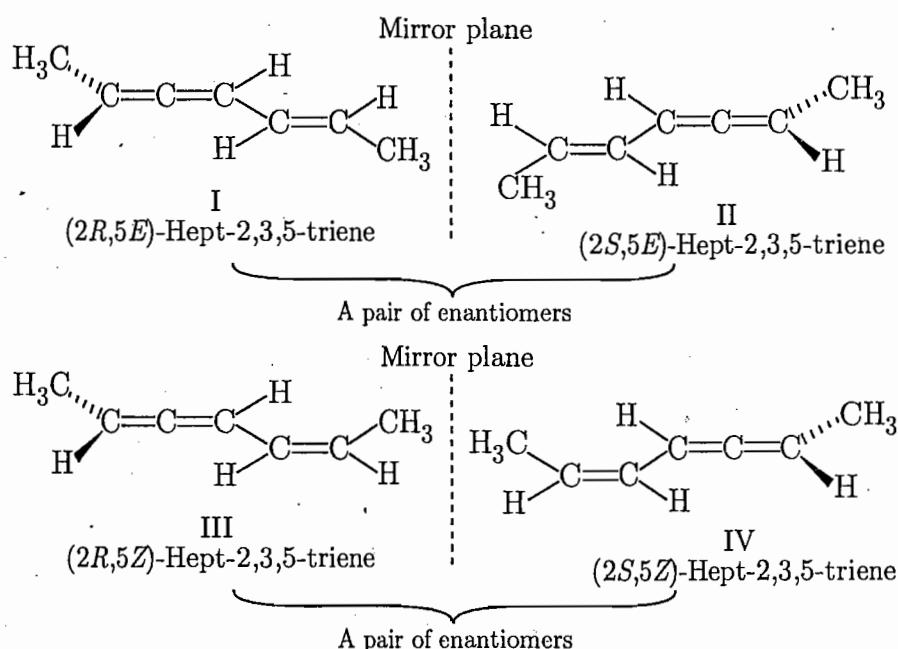
- (i) Pent-3-en-2-ol ($\text{CH}_3\text{CHOHCH}=\text{CHCH}_3$), which contains a chiral centre (*) and a suitably substituted double bond capable of giving geometric isomers, exists as four stereoisomeric forms as shown below :





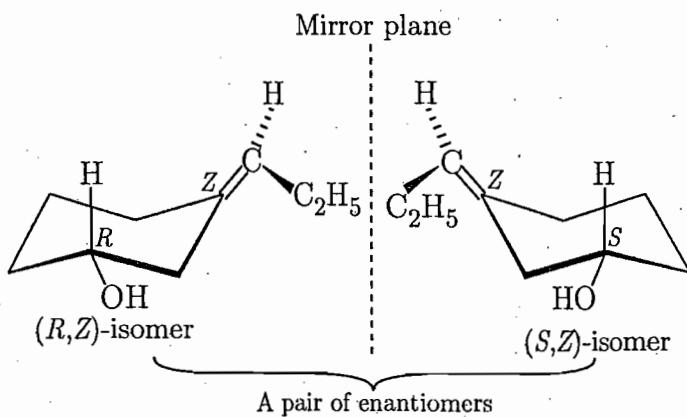
(I, II) and (III, IV) are two pairs of enantiomers. But each of (I, III), (I, IV), (II, III) and (II, IV) represent a pair of diastereoisomers.

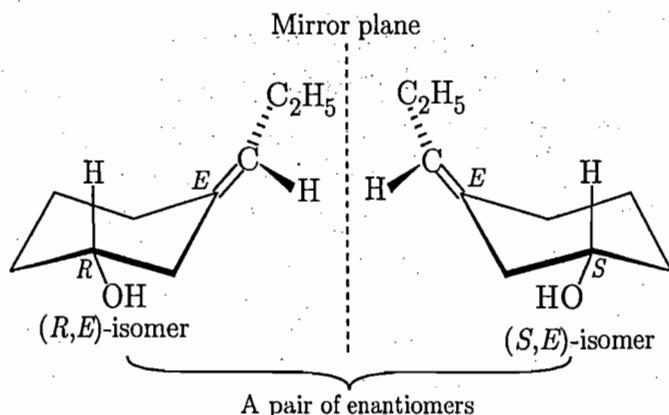
- (ii) Hept-2,3,5-triene ($\text{CH}_3\text{CH}=\text{C}=\text{CH}-\text{CH}=\text{CHCH}_3$) shows geometric enantiomerism because the allene moiety is chiral and the double bond is appropriately substituted to give *E,Z*-isomers. Its four possible stereoisomers are shown below.



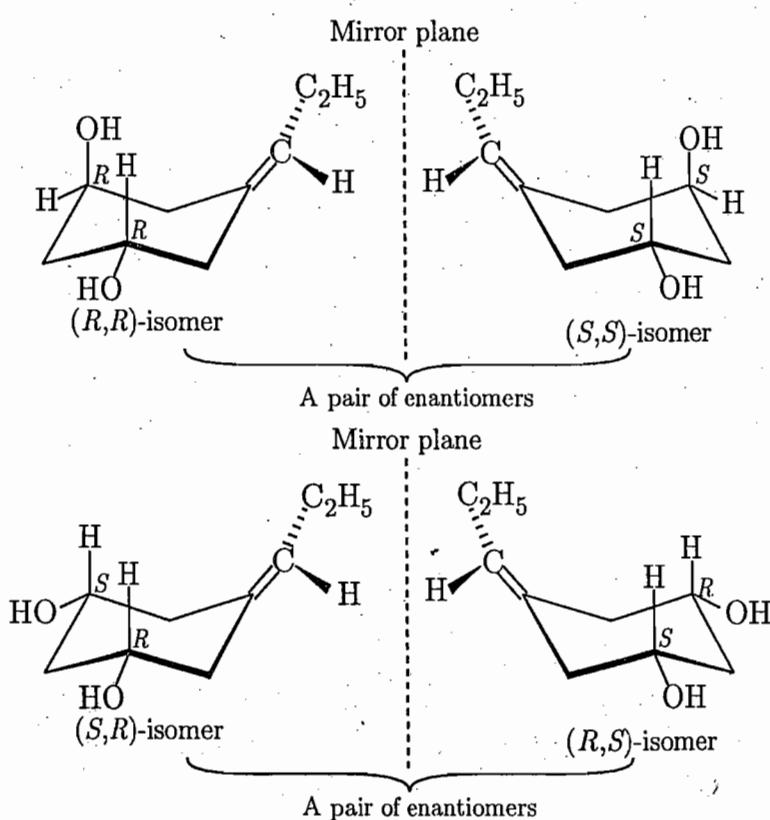
(I, II) and (III, IV) are two pairs of enantiomers. But each of (I, III), (I, IV), (II, III) and (II, IV) represent a pair of diastereoisomers.

- (b) (i) Due to presence of a chiral carbon unit and a suitably substituted double bond capable of giving rise to geometric isomers, the compound exists as four stereoisomeric forms.





- (ii) Since the double bond in this compound is not suitably substituted, geometric isomers are not possible. However, two pairs of enantiomers are possible because it contains two chiral centres.

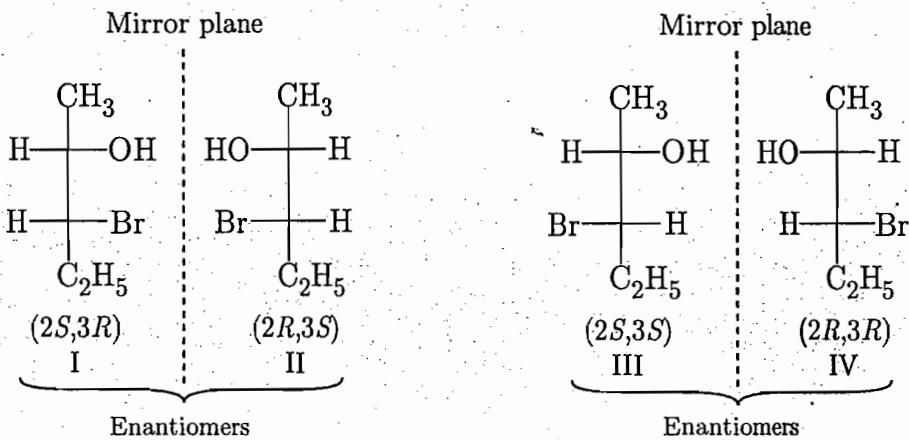


**STEREOCHEMISTRY OF MOLECULES
WITH MORE THAN ONE CHIRAL CENTRE**

- 1.80 (a) What is the maximum number of possible stereoisomers of a compound with more than one chiral centre. Illustrate with suitable examples.
 (b) Give the stereochemical relationships of the stereoisomers of 3-bromo-2-pentanol ($\text{CH}_3\text{CHOHCHBrCH}_2\text{CH}_3$).

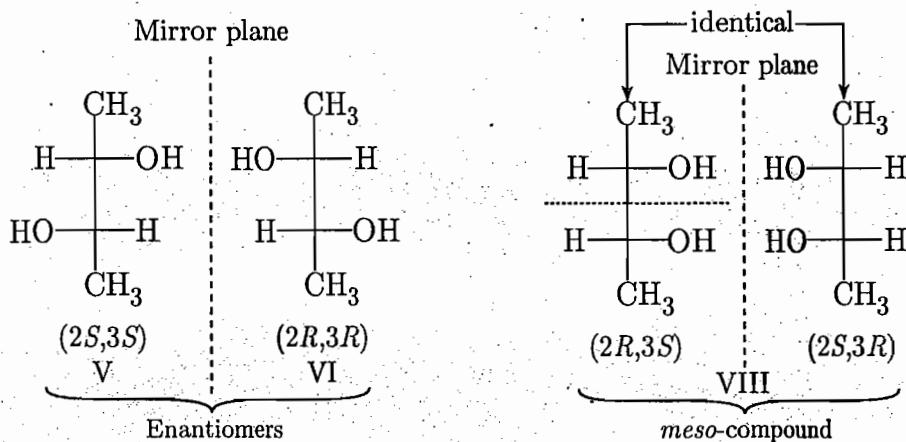
Ans. (a) The number of stereoisomers, both optically active and inactive (*meso* form), in acyclic systems can be calculated from the number of chiral centres present in a molecule. There are three possibilities.

- (i) If the molecule contains 'n' different chiral centres and the molecule cannot be divided into two mirror-image halves in any possible conformations, it can have 2^n optically active isomers and no optically inactive *meso*-compound. For example, 3-bromo-2-pentanol ($\text{CH}_3\text{CHOHCHBrCH}_2\text{CH}_3$) has two dissimilar chiral centres. Therefore, it has $2^2 = 4$ optically active stereoisomers and no optically inactive *meso*-compound. Fischer projections of these four stereoisomers are shown below.



I, II and III, IV represent two pairs of enantiomers and are optically active.

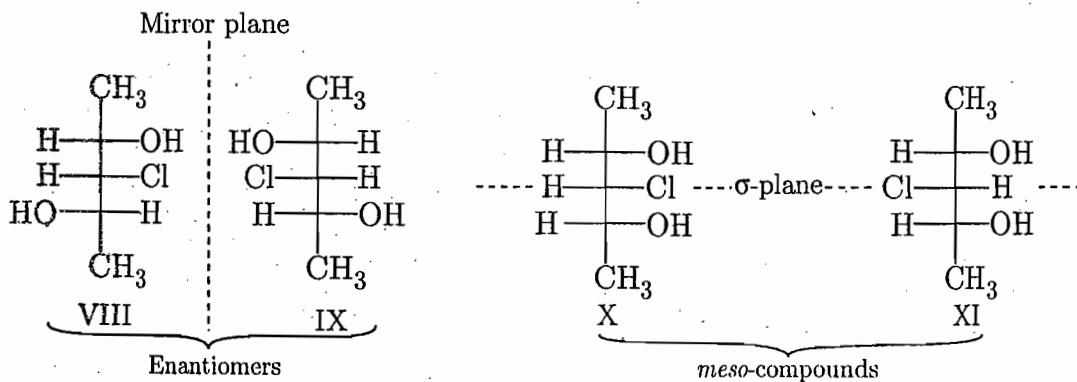
- (ii) If the molecule contains an even number (n) of chiral centres, but the molecule can be divided into two mirror-image halves in one of the possible conformations, it can have $2^{(n-1)}$ optically active isomers and $2^{(n-2)/2}$ optically inactive *meso*-compounds. For example, 2,3-butanediol ($\text{CH}_3\text{CHOHCHOHCH}_3$) has two similar chiral centres and can be divided into two mirror-image halves. Therefore, it can have $2^{(2-1)} = 2^1 = 2$ optically active isomers and $2^{(2-2)/2} = 2^0 = 1$ optically inactive *meso*-compound. Fischer projections of these three stereoisomers are shown below.



V and VI represent a pair of enantiomers and are optically active. VII represent an optically inactive *meso*-compound having a plane of symmetry.

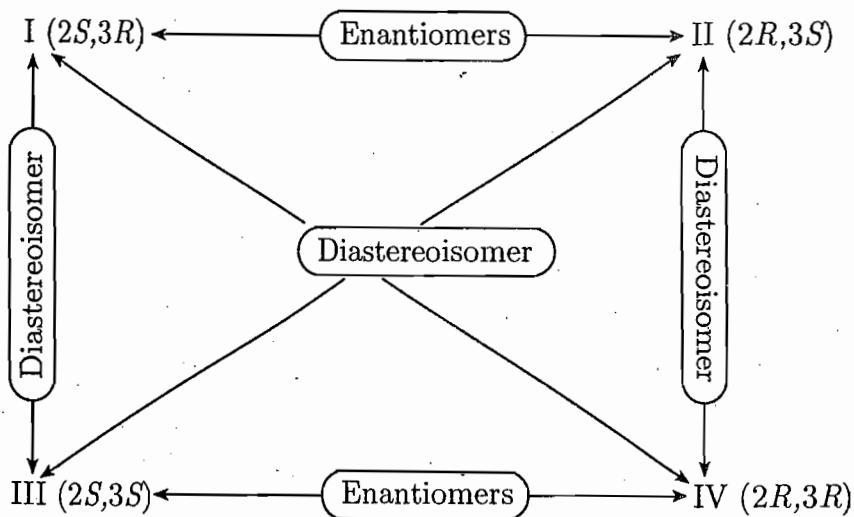
- (iii) If the molecule contains an odd number (n) of chiral centres and the molecule can be divided into two mirror-image halves by a plane passing through the central chiral centre in one of the possible conformations, it can have $2^{(n-1)} - 2^{(n-1)/2}$ optically active isomers and $2^{(n-1)/2}$ optically inactive *meso*-compounds. For example, 3-chloropentane-2,4-diol ($\text{CH}_3\text{CHOHCHClCHOHCH}_3$) has three chiral centres and can be divided into two mirror-image halves by passing a plane through the central chiral centre. Therefore, it can have

$2^{(3-1)} - 2^{(3-1)/2} = 4 - 2 = 2$ optically active isomers and $2^{(3-1)/2} = 2^1 = 2$ optically inactive *meso*-compounds. Fischer projections of these four stereoisomers are shown below.

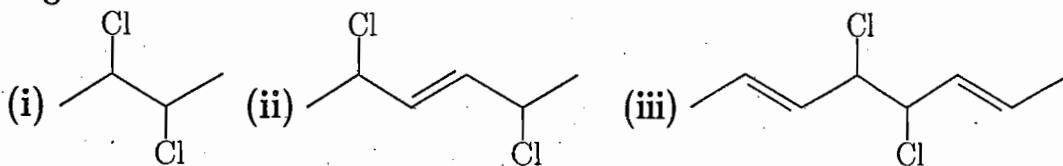


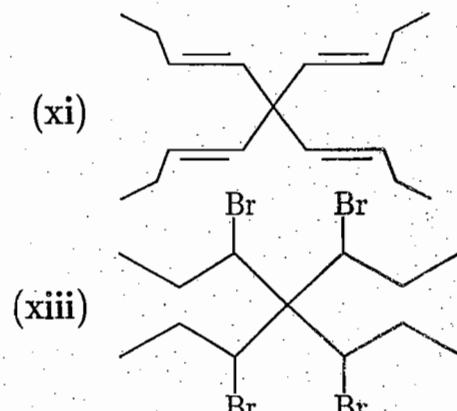
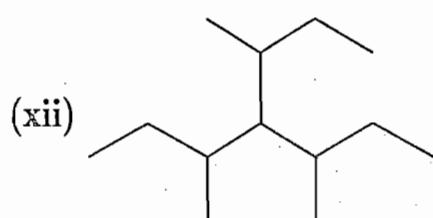
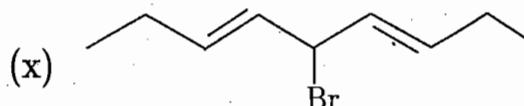
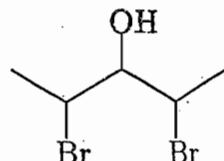
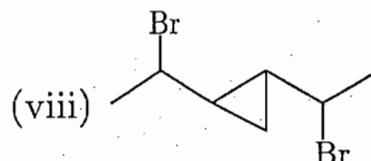
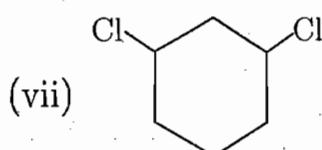
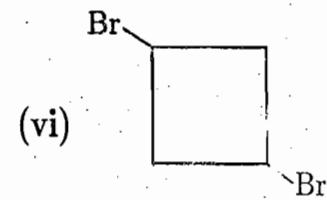
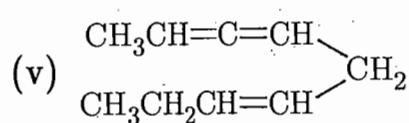
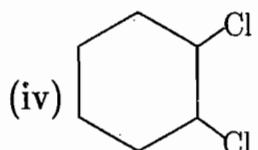
VIII and IX represent a pair of enantiomers and are optically active. X and XI represent two optically inactive *meso*-compounds and both of them have plane of symmetry along the horizontal bonds containing Cl and H atoms.

(b) Fischer projections of four stereoisomers of 3-bromo-2-pentanol ($\text{CH}_3\text{CHOHCHBrC}_2\text{H}_5$) are shown in *Problem 1.80(a)*. I and II represent a pair of enantiomers because they are noncongruent mirror images. Similarly, III and IV represent a pair of enantiomers. There are also diastereomeric relationships among these four compounds. Stereoisomers that are not enantiomers are called diastereoisomers. Therefore, each of I and III, I and IV, II and III, and II and IV represent a pair of diastereoisomers. These relationships are summarized below. In this scheme the horizontal lines connect pairs of enantiomers. All other lines connect pairs of diastereoisomers.



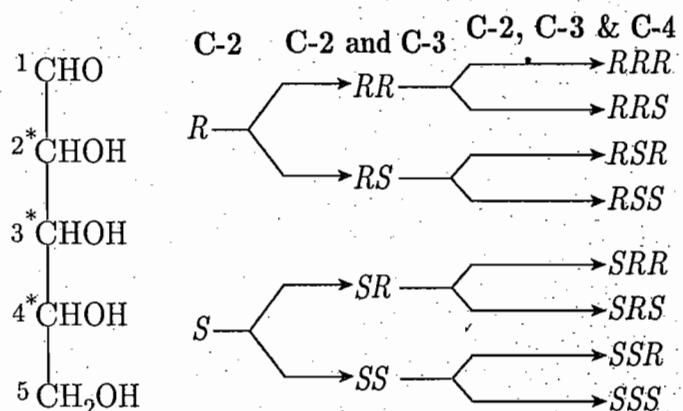
- 1.81 (a) An aldopentose [$\text{HOCH}_2(\text{CHOH})_3\text{CHO}$] has three dissimilar asymmetric carbon atom. List the isomers in terms of *R/S* designation.
 (b) Predict the number of isomers of the following compounds having identical stereogenic centres and list them in terms of *R/S* and *E/Z* designations :



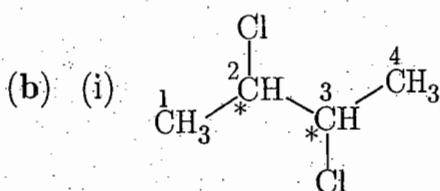


(c) What is a pseudoasymmetric carbon atom? Give an example.

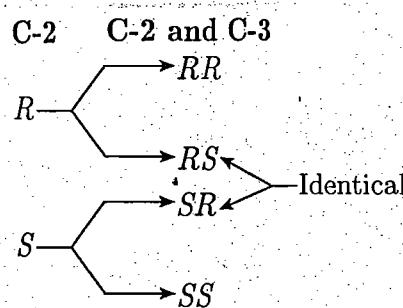
Ans. (a). The aldopentone, HOCH₂(CHOH)₃CHO, containing three dissimilar asymmetric carbon atoms, can have $2^3 = 8$ optically active stereoisomers. These isomers in terms of R/S designation may be obtained as follows :



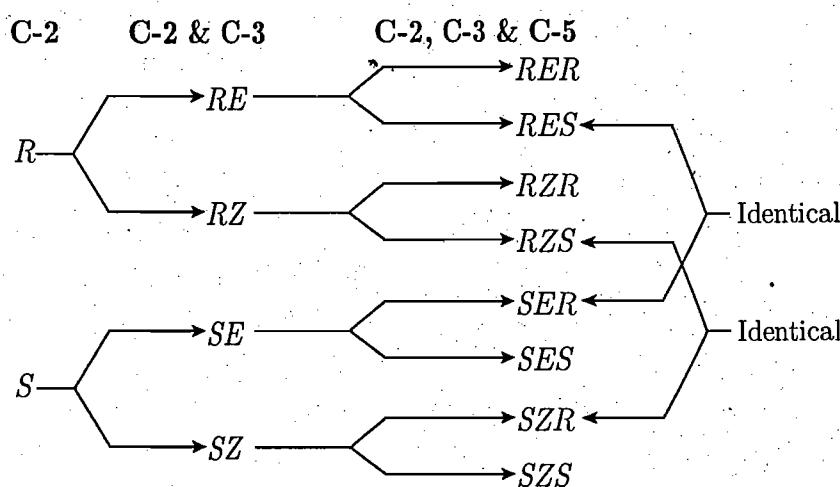
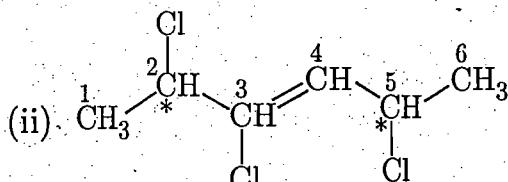
There are four sets of enantiomeric pairs : RRR and SSS; RRS and SSR; RSR and SRS; RSS and SRR.



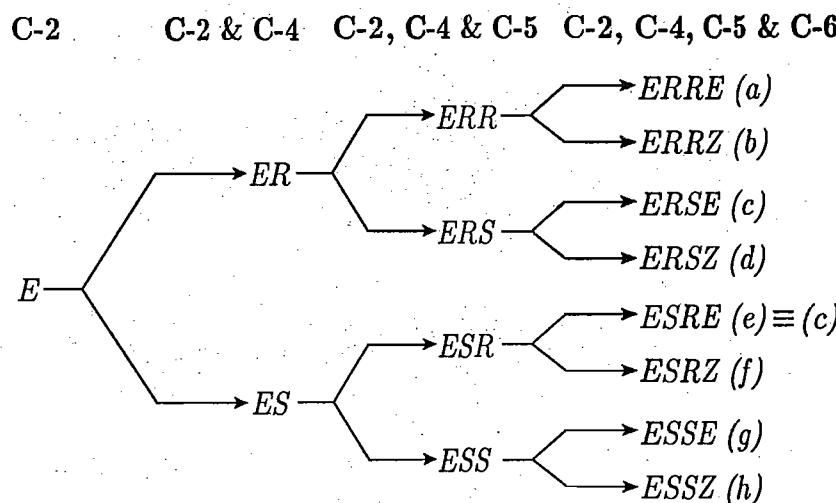
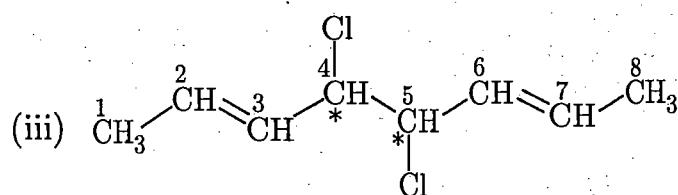
The compound can have $2^{(2-1)} = 2^1 = 2$ optically active isomers and $2^{(2-2)/2} = 2^0 = 1$ optically inactive meso-compound.

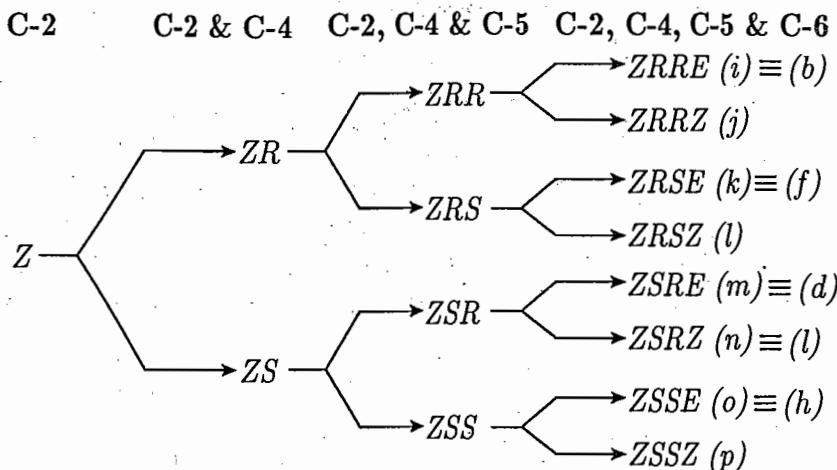


RR and *SS* are two enantiomers and *RS* or *SR* is the *meso*-compound.

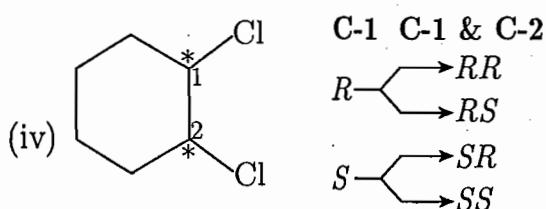


The compound has six stereoisomers. There are two sets of enantiomeric pairs : *RER*, *SES* and *RZR*, *SZS*. *RES* (the same as *SER*) and *RZS* (the same as *SZR*) are two optically inactive *meso*-compounds.

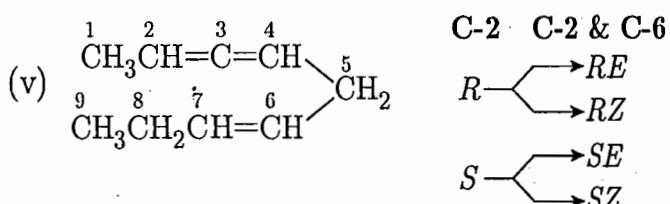




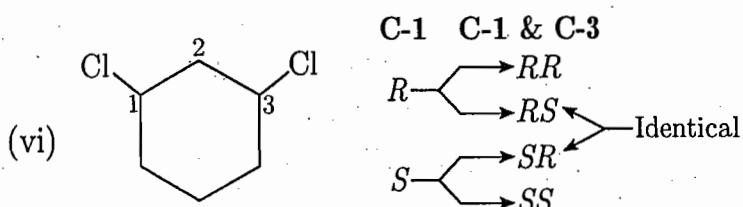
The compound has ten stereoisomers. There are four sets of enantiomeric pairs : (a), (g); (b), (h); (d), (f); and (j), (p). (c) and (l) are two optically inactive *meso*-compounds.



Four stereoisomers are expected for this compound. RR and SS are two resolvable enantiomers, whereas RS and SR are two nonresolvable enantiomers.

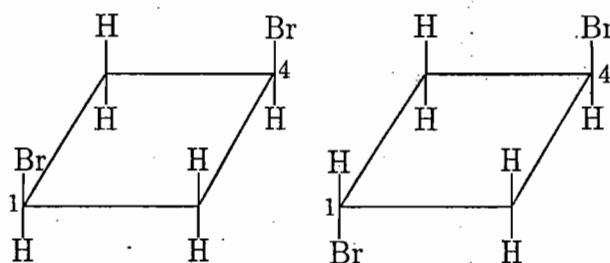


The compound has four stereoisomers. There are two sets of enantiomeric pairs : *RE* & *SE*; *RZ* & *SZ*.



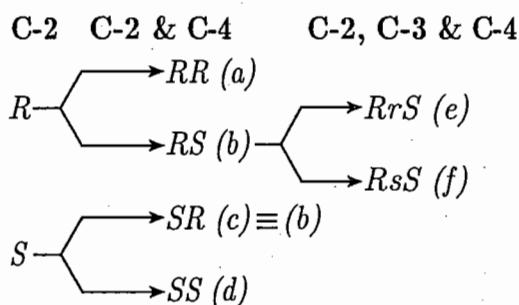
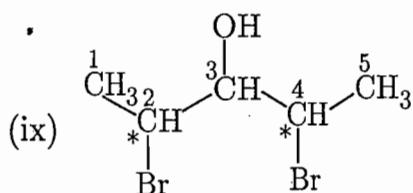
The compound has three stereoisomers. *RR* and *SS* are two enantiomers and *RS* or *SR* is the *meso* compound.

(vii) The compound contains no chiral centre. Two stereoisomers (geometric isomers) are possible. These are as follows :



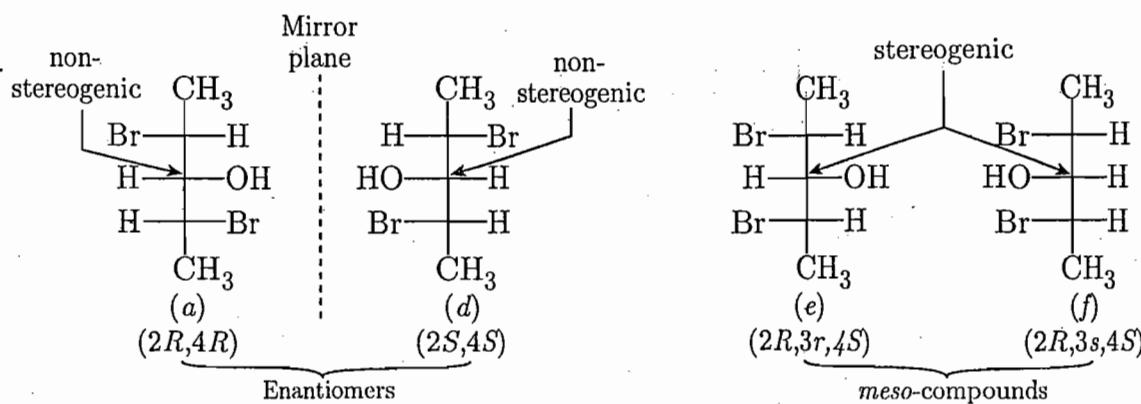
Both of these isomers are optically inactive due to the presence of plane of symmetry (σ) passing through C-1 and C-4.

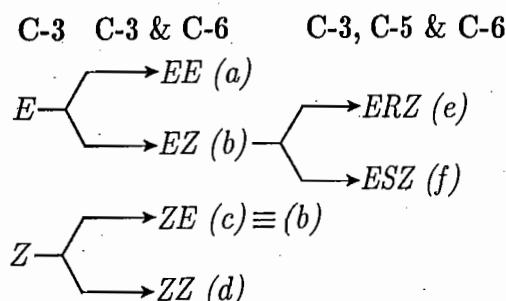
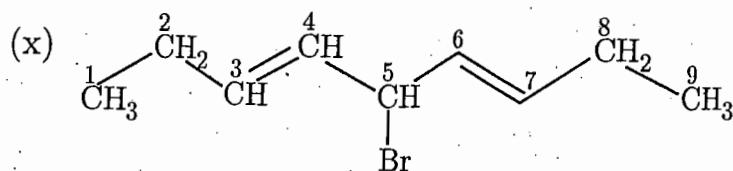
(viii) Same as (ii)



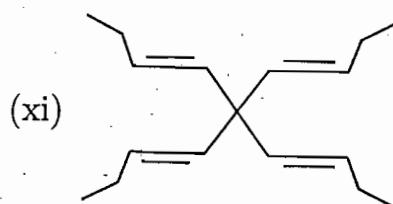
In (a) and (d), C-3 is non-stereogenic. In (b), C-3 is stereogenic (pseudoasymmetric) centre. If C-3 is designated with the configurational descriptors *r* or *s*, then two more combinations (e) and (f) will be obtained.

Therefore, the total number of stereoisomers is four. Among them (a) and (d) are two enantiomers and (e) and (f) are two *meso*-compounds.

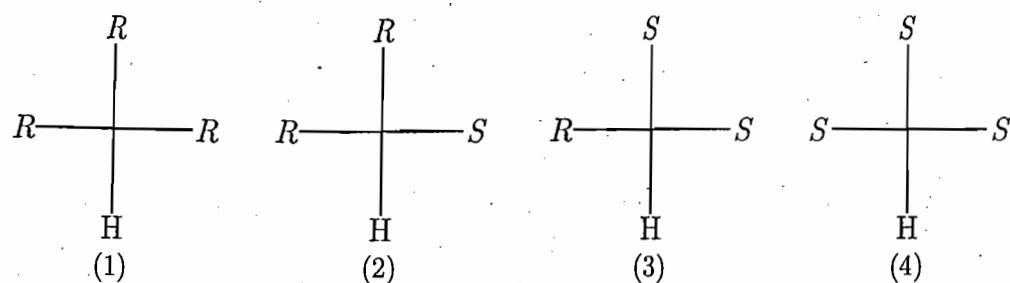
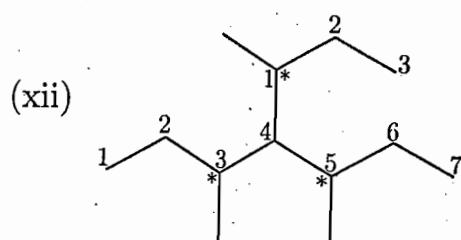
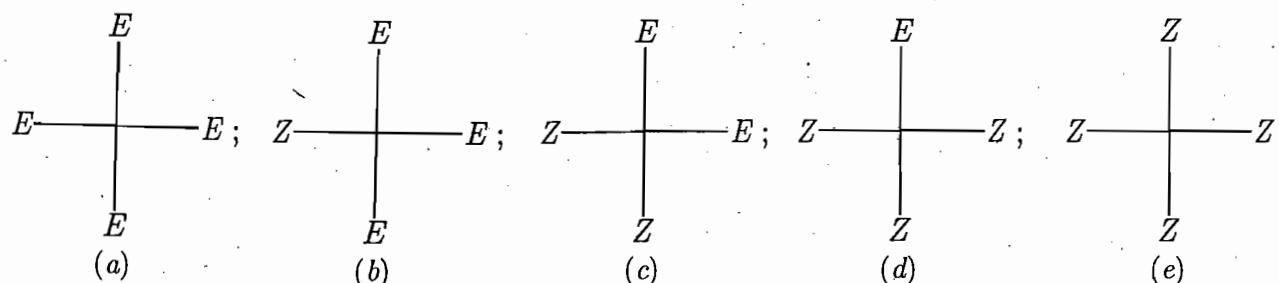




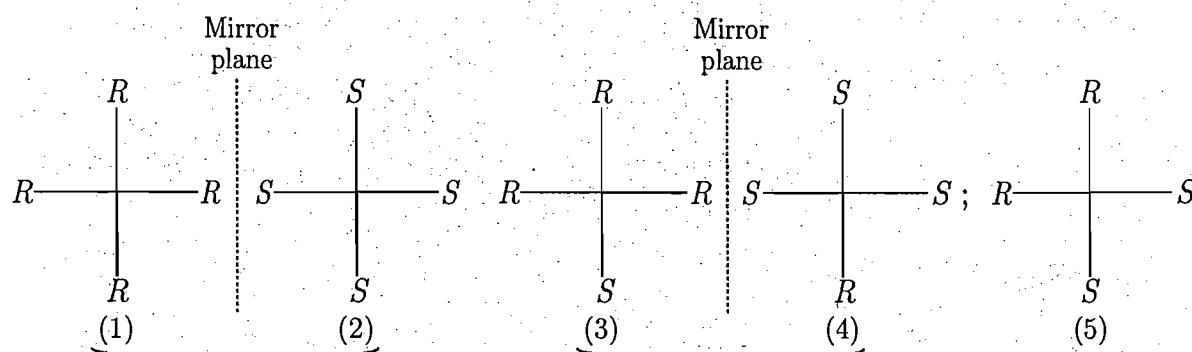
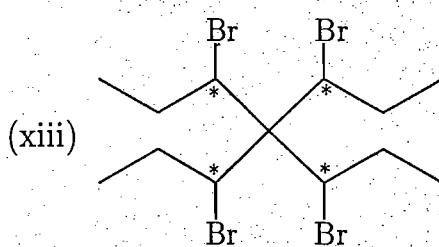
There are four stereoisomers. Among them (e) and (f) are two enantiomers and (a) and (d) are two optically inactive isomers.



There are five stereoisomers and all of them are achiral and optically inactive.

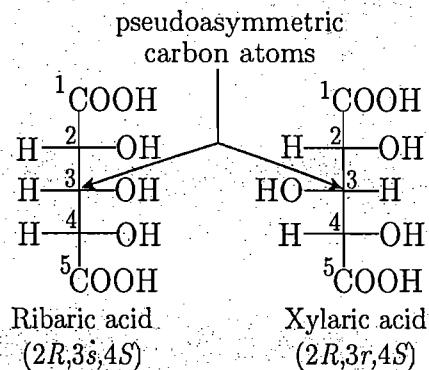


There are two sets of enantiomeric pairs : (1), (4) and (2), (3).



The compound has four optically active and one optically inactive stereoisomers. There are two sets of enantiomeric pairs : (1), (2) and (3), (4). (5) is a *meso*-compound. It has an S_4 -axis.

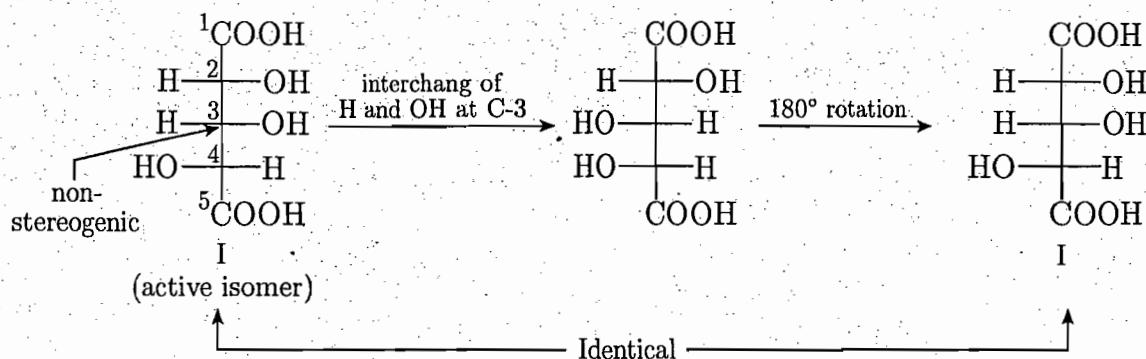
- (c) A pseudoasymmetric carbon atom is one which is attached to two enantiomeric ligands having opposite chirality sense and two other ligands different from the previous two. A pseudoasymmetric carbon is stereogenic but achiral and the stereochemical descriptors for pseudoasymmetric centre are 'r' or 's'. For example, C-3 of both of the aldaric acids is pseudoasymmetric.



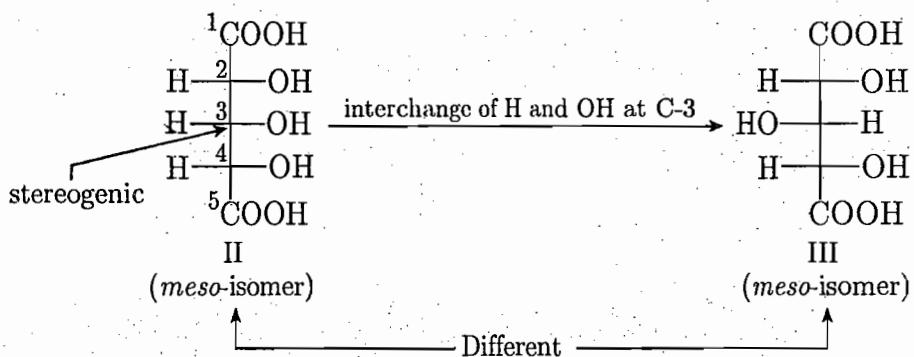
- 1.82 Draw one active and one *meso* isomer of $\text{HOOC}(\text{CHOH})_3\text{COOH}$ in Fischer projection formula. Will the interchange of H and OH at C-3 of the active stereoisomer you have drawn lead to another stereoisomer? What will happen if H and OH is interchanged at C-3 of the *meso* isomer you

have drawn? Explain stating whether C-3 is a stereogenic centre in each case.

Ans.



Interchange of H and OH at C-3 of the active stereoisomer (I) of $\text{HOOC}(\text{CHOH})_3\text{COOH}$ does not lead to another stereoisomer. In fact, when the Fischer projection obtained by this operation is rotated in the plane of the paper through 180° , the original active stereoisomer (I) is obtained. Therefore, C-3 of the active isomer (I) is non-stereogenic.



Interchange of H and OH at C-3 of the meso-isomer (II) leads to another meso-isomer (III). Therefore, C-3 of the meso-isomer (II) is stereogenic.

[For R/S designations see *Problem 1.81 (viii)*.]

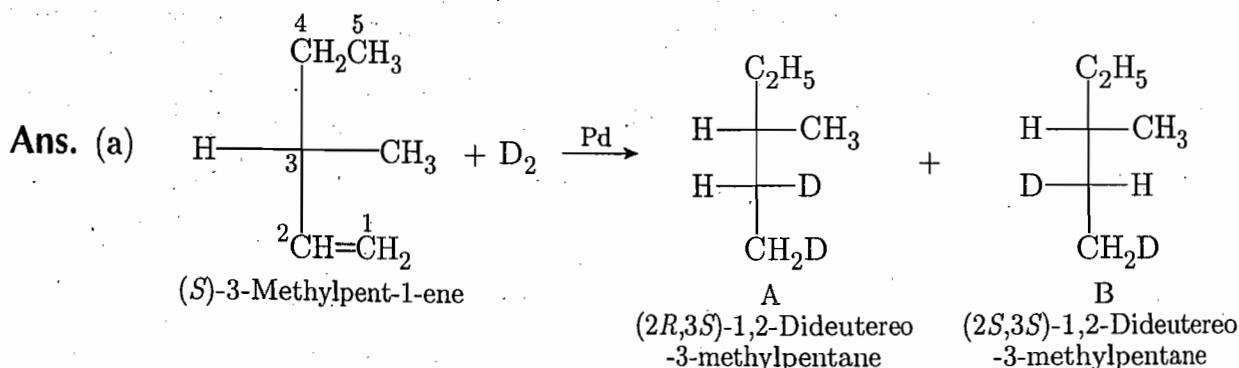
► 1.83 (a) (*S*)-3-Methylpent-1-ene $\xrightarrow{\text{D}_2/\text{Pd}}$ A + B

Draw the structures of the products and give their R/S designations.
How are they related to each other?

(b) Write down the structures of all dichlorinated compounds obtained in the following reaction and give their R/S designations.

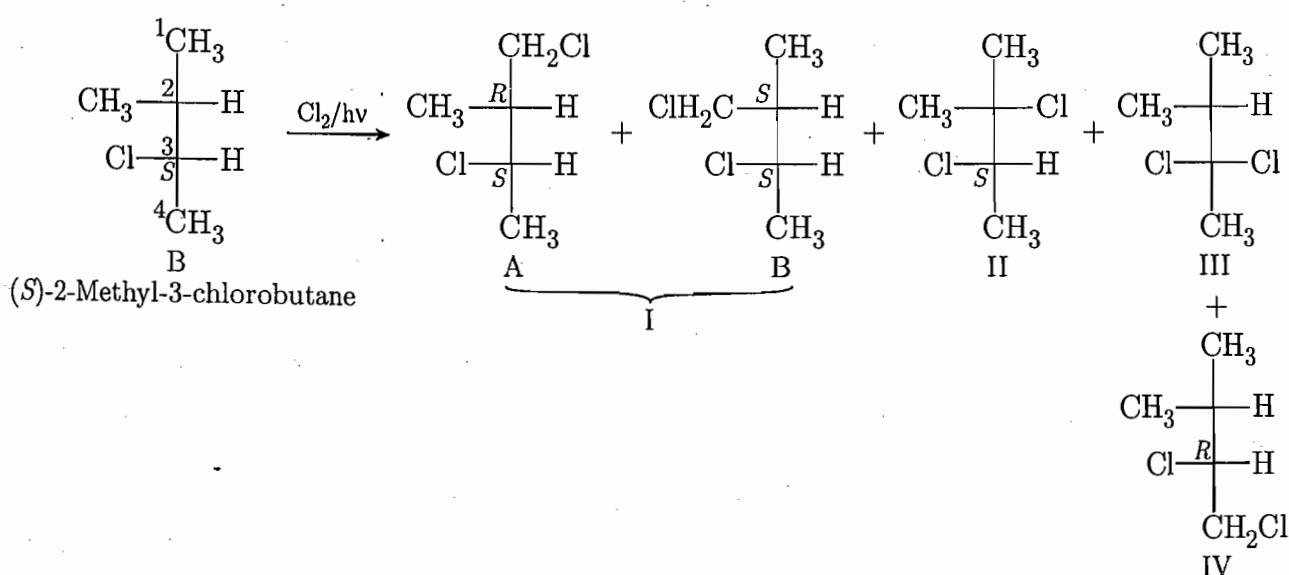
(*S*)-2-Methyl-3-chlorobutane $\xrightarrow{\text{Cl}_2/\text{hv}}$

(c) How can a reaction of one enantiomer at a site other than the chiral centre leads to the formation of an achiral product? Give examples.



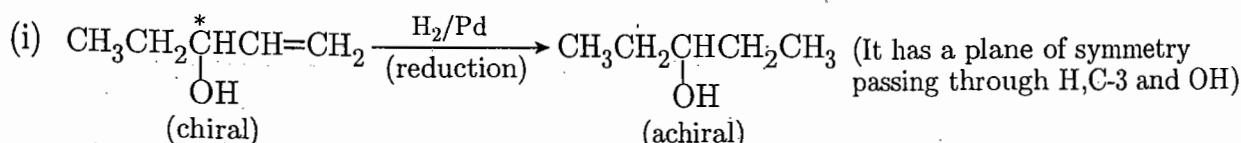
A new chiral centre is created at C-2 which may have *R* or *S* configuration. Therefore, A and B are two diastereoisomers.

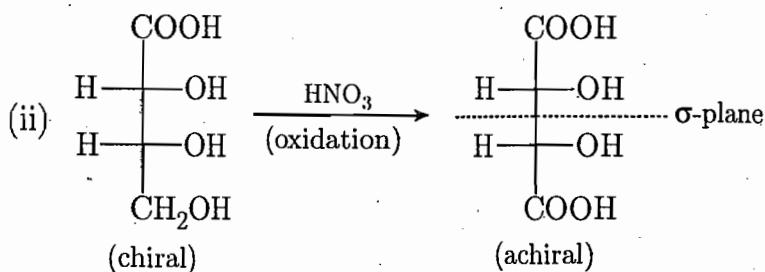
(b)



The reaction leads to the formation of four constitutional isomers (I, II, III and IV). Chlorination at C-1 or at methyl side chain creates a new chiral centre at C-2. Since this asymmetric carbon can have *R* or *S* configuration, two diastereoisomers IA (*2R,3S*) and IB (*2S,3S*) are formed. Chlorination at C-2 gives II, which remains *S*. Chlorination at C-3 gives III. It is achiral because C-3 is no more asymmetric. Chlorination at C-4 gives IV. Although the configuration at C-3 remains unchanged, the priority sequence changes and because of this, the isomer IV is *R*.

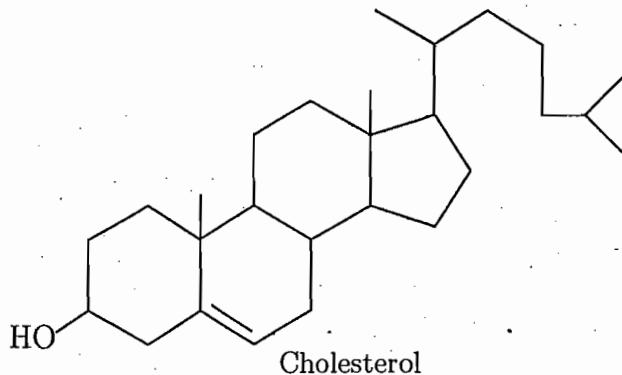
(c) The reaction of an enantiomer, which causes the product molecule to have a plane or centre of symmetry, leads to the formation of an achiral product. For example :



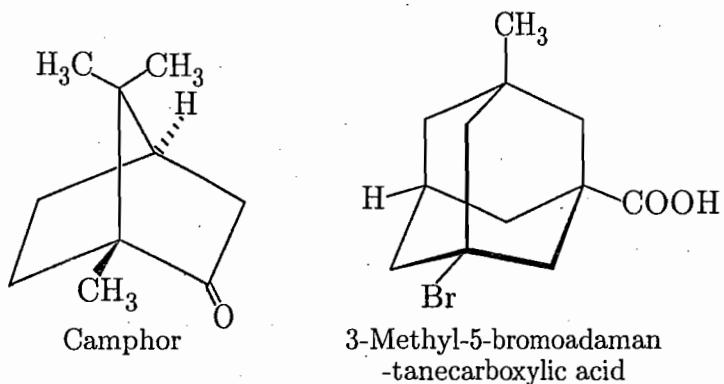


n.

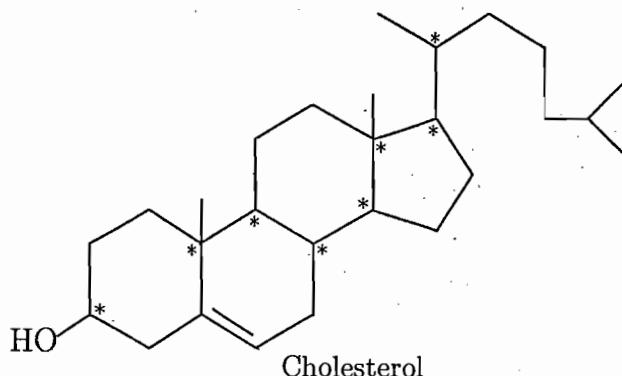
► 1.84 (a) Designate all the chiral carbon atoms in cholesterol by asterisks and state the number of stereoisomers.



(b) Designate the chiral carbon atoms in camphor and 3-methyl-5-bromoadamantanecarboxylic acid by asterisks. Explain why each of them exists only as a pair of enantiomers.

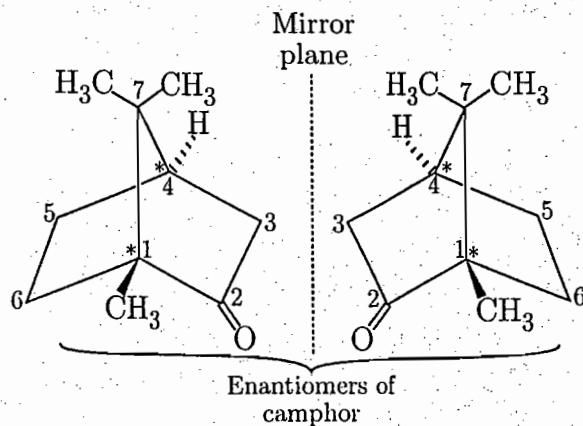


Ans. (a)



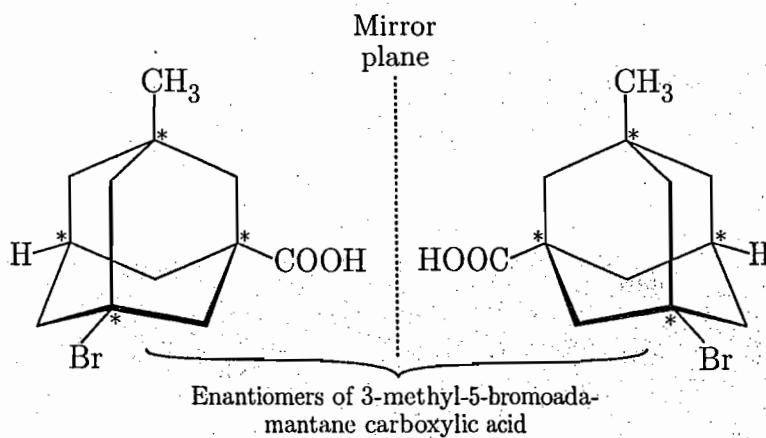
Cholesterol has eight dissimilar chiral centres. Therefore, it can have $2^8 = 256$ stereoisomers.

(b) The molecule of camphor has two chiral centres (C-1 and C-4, the bridgehead carbon atoms).



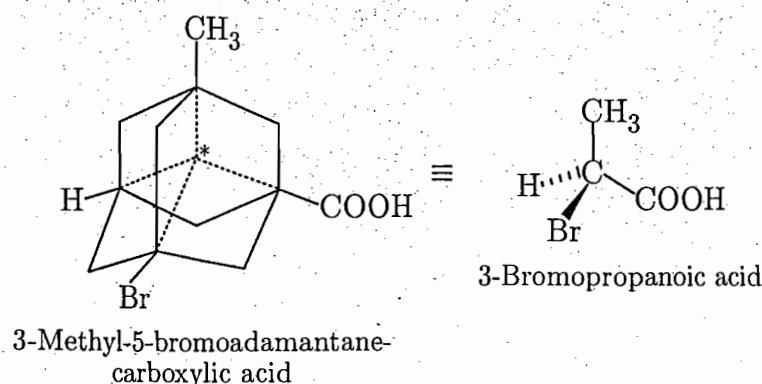
Since camphor contains two dissimilar asymmetric carbon atoms, it might be expected to have 2^2 or four stereoisomers. However, it exists only as a pair of enantiomers because the diastereoisomers having a *trans*-oriented $(CH_3)_2C\swarrow$ bridge is structurally impossible.

The molecule of 3-methyl-5-bromoadamantane carboxylic acid has four chiral centres (the bridgehead carbon atoms shown by asterisks).



Since this substituted adamantane contains four dissimilar chiral carbon atoms, it might be expected to have 2^4 or sixteen stereoisomers. Because of the same structural impossibility of having *trans*-oriented bridge, it also exists only as a pair of enantiomers.

[The substituted adamantane may be regarded as a formal derivative of 2-bromopropanoic acid. The four substituents form a tetrahedral arrangement and the chirality of the adamantane is due to a centre (shown by an asterisk in the unoccupied space).]



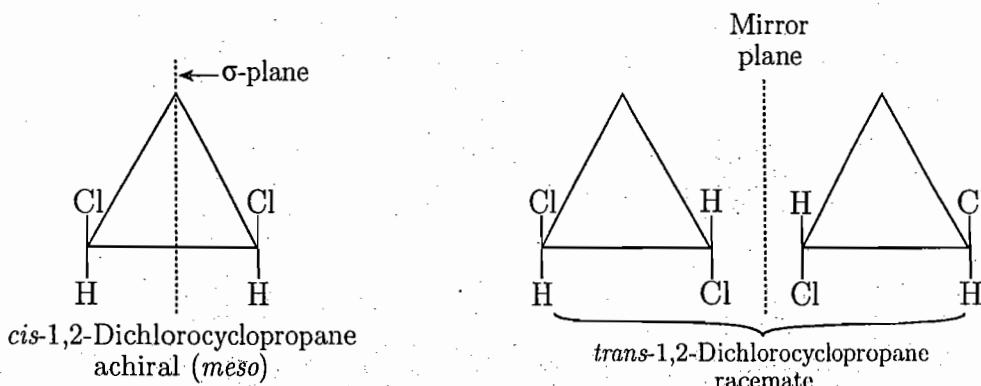
This example shows that the centre of chirality in a molecule will not always lie on an atom itself.]

STEREOCHEMISTRY OF CYCLIC COMPOUNDS

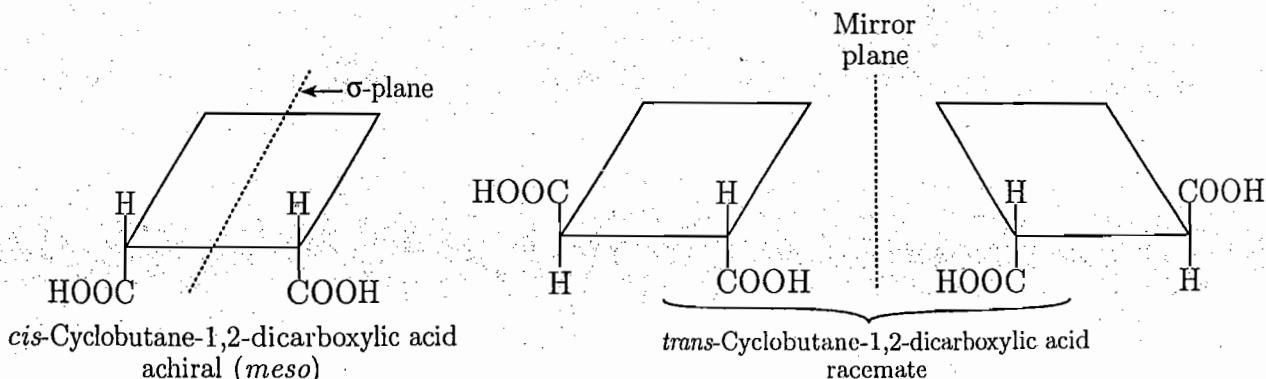
► 1.85 Discuss stereoisomerism of the following cyclic compounds : (a) 1,2-dichlorocyclopropane, (b) cyclobutane-1,2-dicarboxylic acid, (c) 1,3-dimethylcyclobutane, (d) 1,2-dimethylcyclopentane, and (e) 1,3-dimethylcyclopentane.

Ans. Each of these cyclic compounds exist as *cis-trans*-isomers.

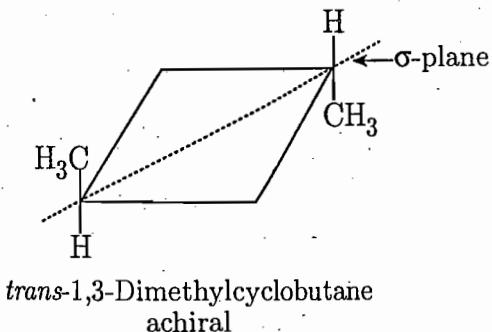
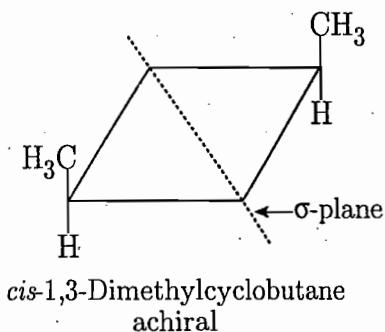
(a) 1,2-Dichlorocyclopropane exists as three stereoisomers. The *cis*-isomer is *meso* and the *trans*-isomer exists as a pair of enantiomers.



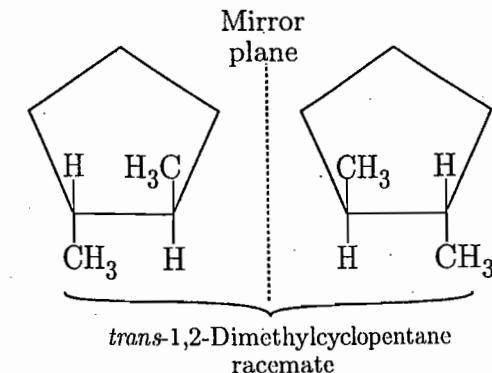
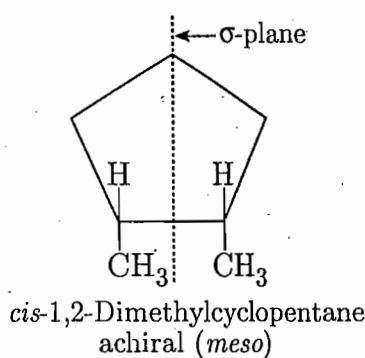
(b) Cyclobutane-1,2-dicarboxylic acid also exists as three stereoisomers. The *cis*-isomer is *meso* and the *trans*-isomer exists as a pair of enantiomers.



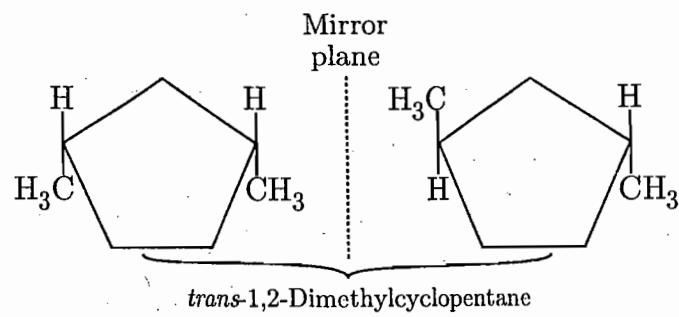
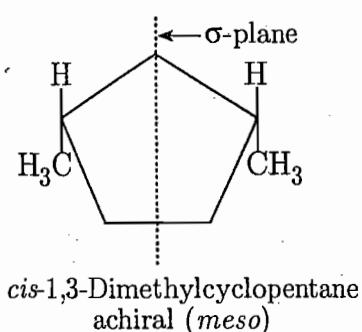
(c) 1,3-Dimethylcyclobutane exists as two stereoisomers. Both the *cis*-as well as the *trans*-isomers are achiral. The *cis*-isomer has a plane of symmetry and the *trans*-isomer has a plane or a centre of symmetry. However, neither of them is a *meso*-compound because of the absence of tetrahedral atoms with four different groups.



(d) 1,2-Dimethylcyclopentane exists in three stereoisomeric forms. The *cis*-isomer is *meso* and the *trans*-isomer exists as a pair of enantiomers.



(e) 1,3-Dimethylcyclopentane also exists in three stereoisomeric forms. The *cis*-isomer is *meso* and the *trans*-isomer exists as a pair of enantiomers.

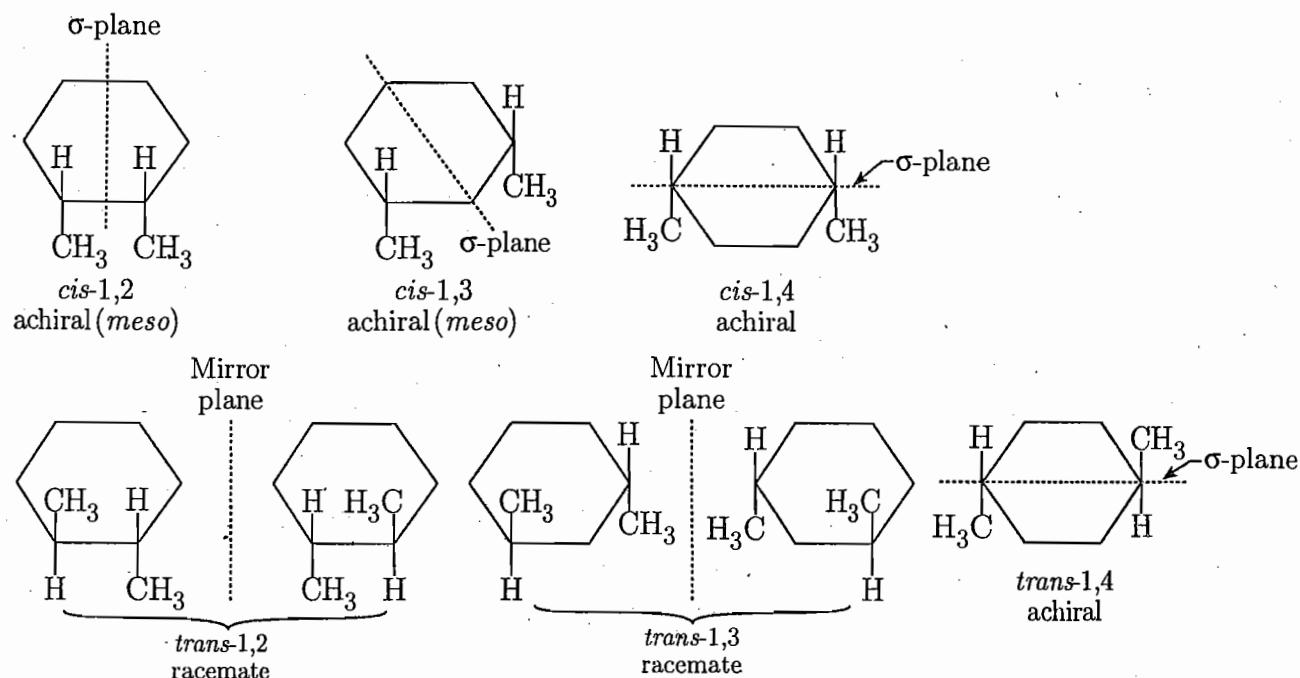


► 1.86 Make a general statement regarding the number of stereoisomers in disubstituted cycloalkanes with identical substituents. Illustrate your statement with dimethylcyclohexanes assuming planar structure.

Ans. All *cis*-disubstituted cycloalkanes with the same substituents are achiral because of having a plane of symmetry. If the substituents are not at the opposite ends of the ring with an even number of carbon atoms, the stereoisomer is *meso*. All *trans*-disubstituted cycloalkanes exist as a pair of enantiomers, unless the substituents are at the opposite ends of the ring with an even number of carbon

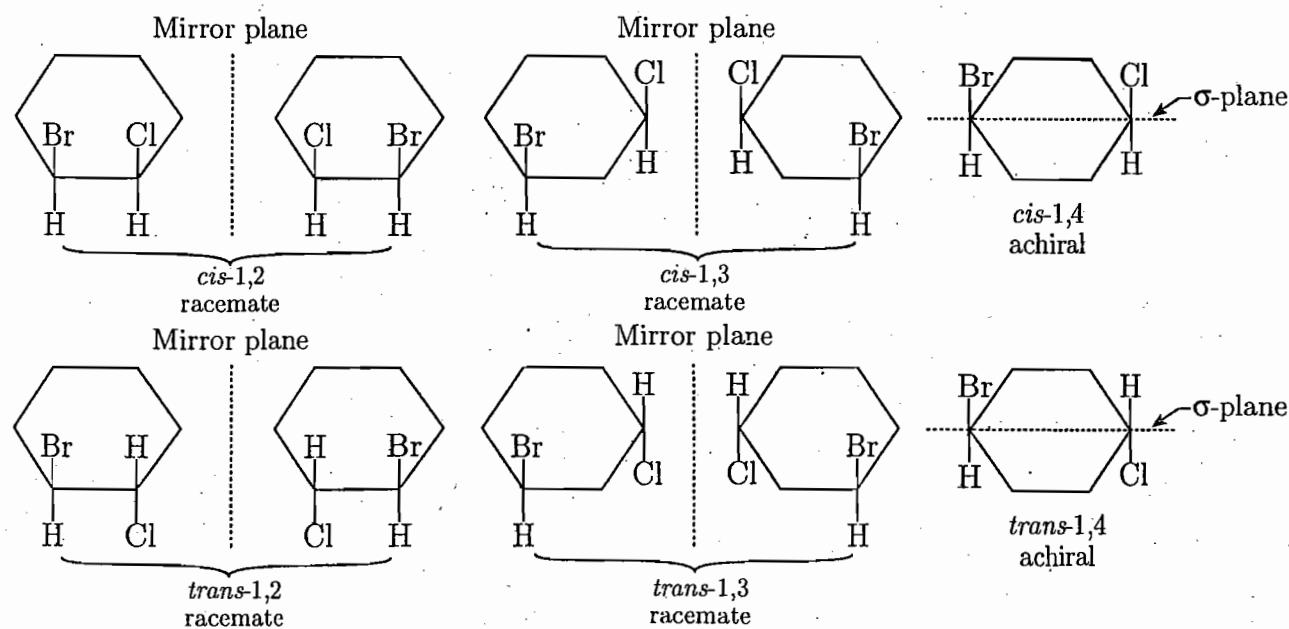
atom. None of the *cis* and *trans* disubstituted cycloalkanes with substituents at the opposite ends of the ring with even number of carbon atoms contains chiral centres. Therefore, the molecules are achiral but not *meso*. The correct number of stereoisomers may be obtained by assuming the rings are flat, even though they may not be.

Dimethylcyclohexanes exist as three different sets of constitutional isomers, e.g. 1,2-; 1,3- and 1,4-isomers.



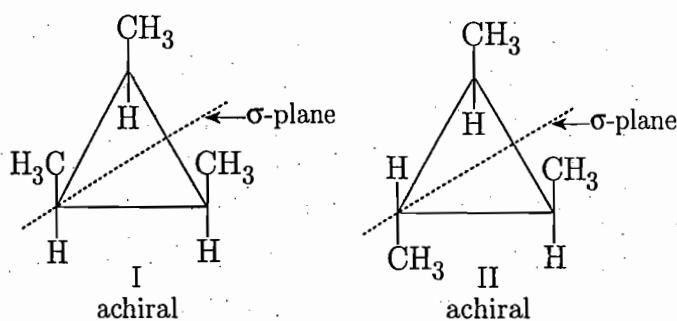
► 1.87 How many stereoisomers of a disubstituted cyclohexane exist if the two substituents are different? Illustrate with an example.

Ans. Each of *cis*-1,2, *trans*-1,2, *cis*-1,3 and *trans*-1,3-isomers is chiral and exists as a pair of enantiomers. Both of *cis*-1,4 and *trans*-1,4-isomers are achiral (optically inactive). The 1,2-, 1,3- and 1,4-isomers of bromochlorocyclohexanes, for example, may be shown as follows :

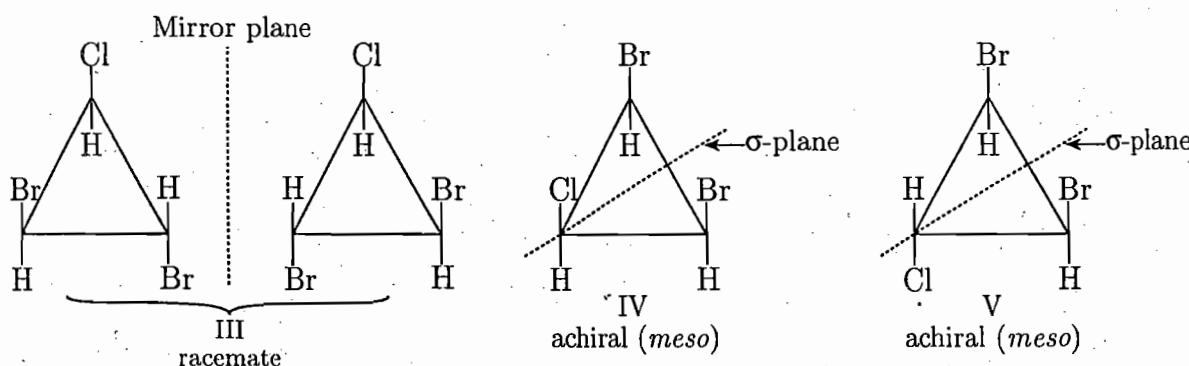


► 1.88 Discuss stereoisomerism of (a) 1,2,3-trisubstituted cyclopropanes and (b) 1,2,3-trisubstituted cyclobutanes.

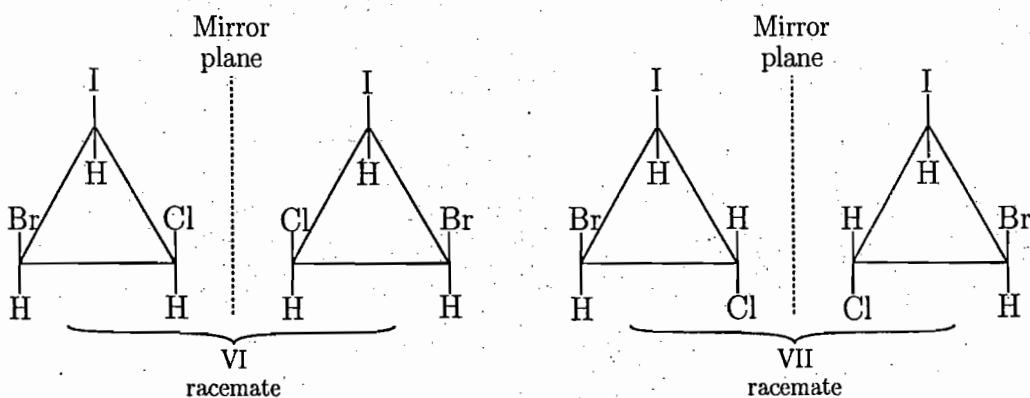
Ans. (a) A 1,2,3-tribubstituted cyclopropane containing three identical substituents exists as two diastereoisomers. Both of them are achiral (optically inactive) due to the presence of vertical plane of symmetry. The two diastereoisomers of 1,2,3-trimethylcyclopropane (I & II), for example, may be shown as follows :

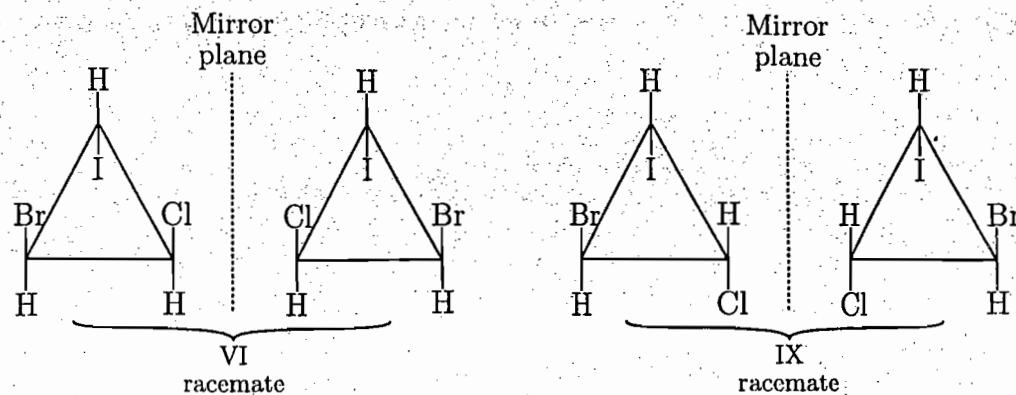


When two of the substituents in a trisubstituted cyclopropane are identical and one is different, then three diastereoisomers are possible. Two of them possess plane of symmetry and, therefore, achiral (*meso*-compounds) and the other is chiral and can exist as a pair of enantiomers. The diastereoisomers of 1,2-dibromo-3-chloropropane (III–V), for example, are shown below :

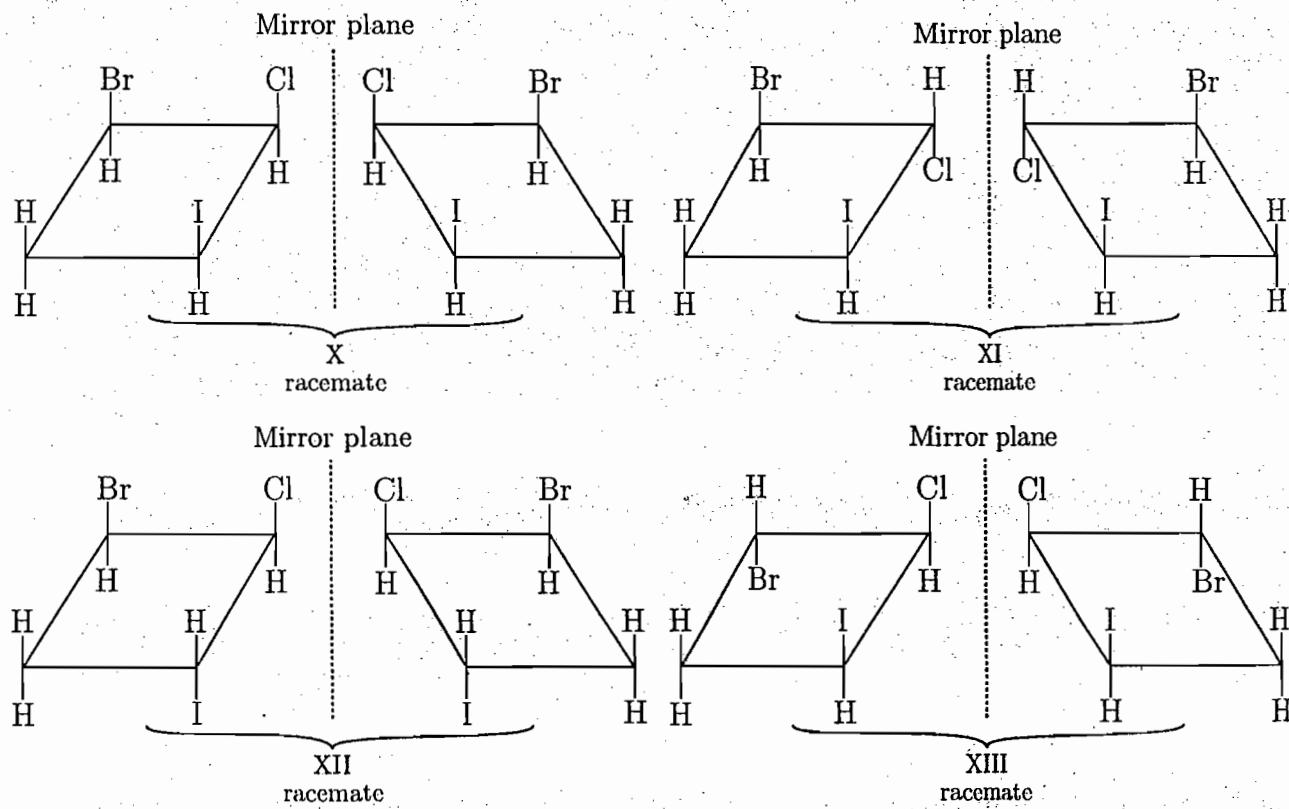


When all the substituents are different then 1,2,3-trisubstituted cyclopropane exists in four diastereomeric forms. All of them are chiral and give four pairs of enantiomers. The diastereoisomers of 1-bromo-2-chloro-3-iodocyclopropane (VI–IX), for example, are shown below :

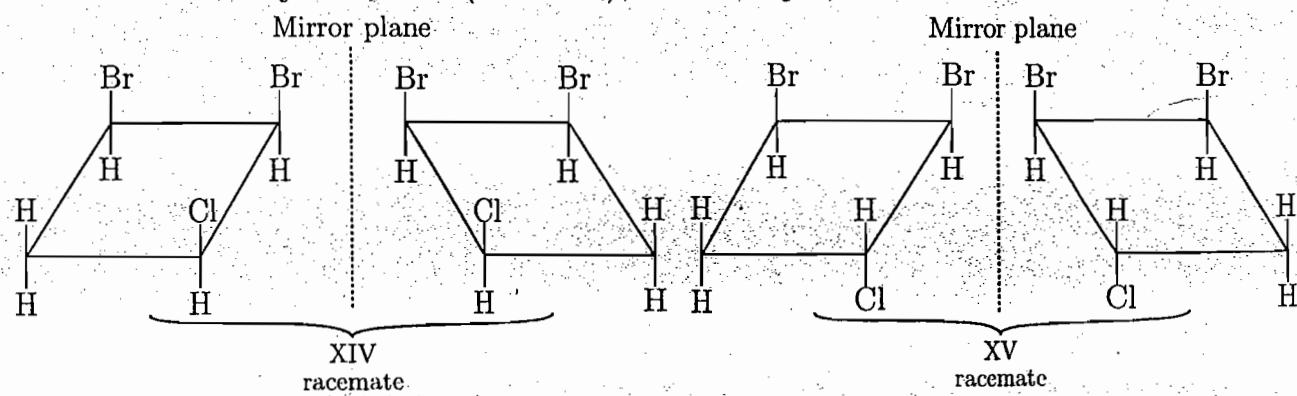


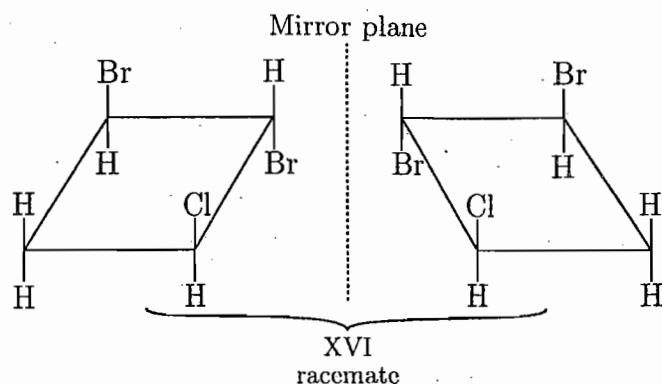


(b) 1,2,3-Trisubstituted cyclobutane having all the substituents different exists in four diastereoisomeric forms. All of them are chiral. Thus, each of the diastereoisomers can exist as a pair of enantiomers. The diastereoisomers of 1-bromo-2-chloro-3-iodocyclobutane (X–XIII), for example, are as follows :

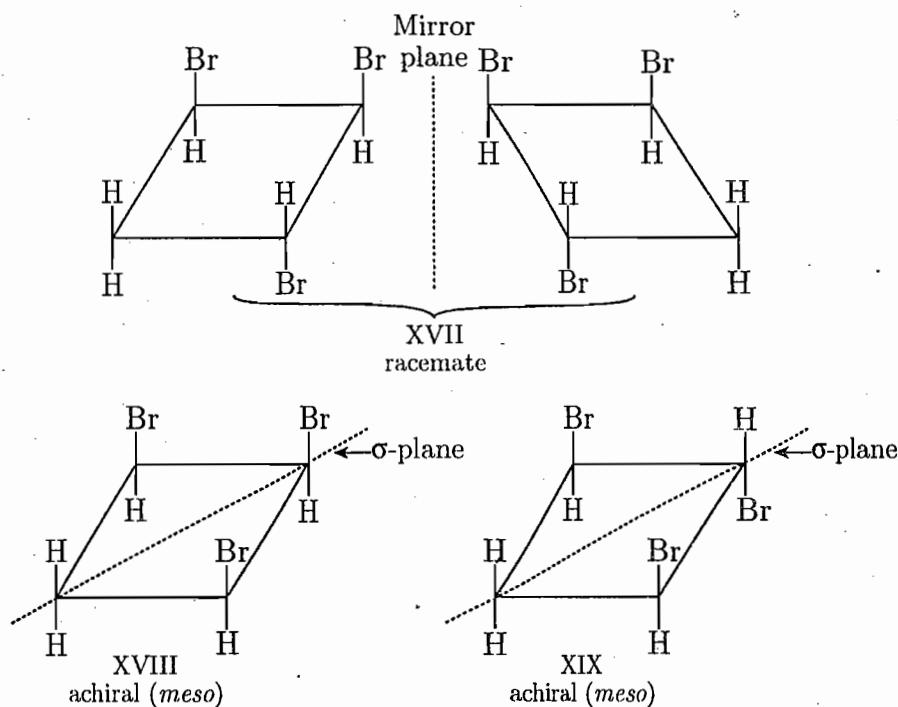


When two of the substituents in 1,2,3-trisubstituted cyclobutane are identical, then three diastereoisomers are possible. All of them are chiral. Thus, each of the diastereoisomer can exist as a pair of enantiomers. The diastereoisomers of 1,2-dibromo-3-chlorocyclobutane (XV–XVI), for example, are shown below :



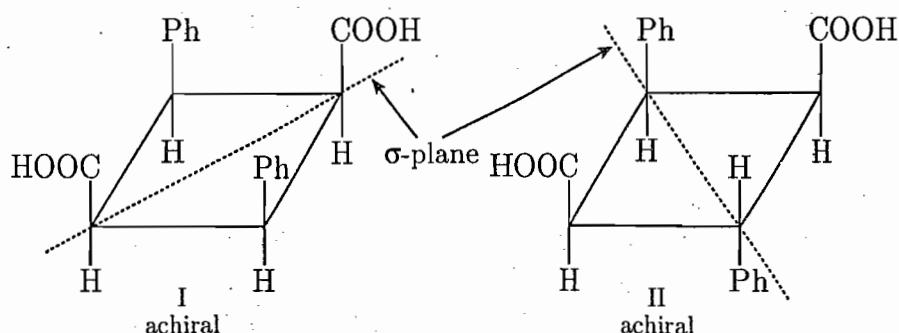


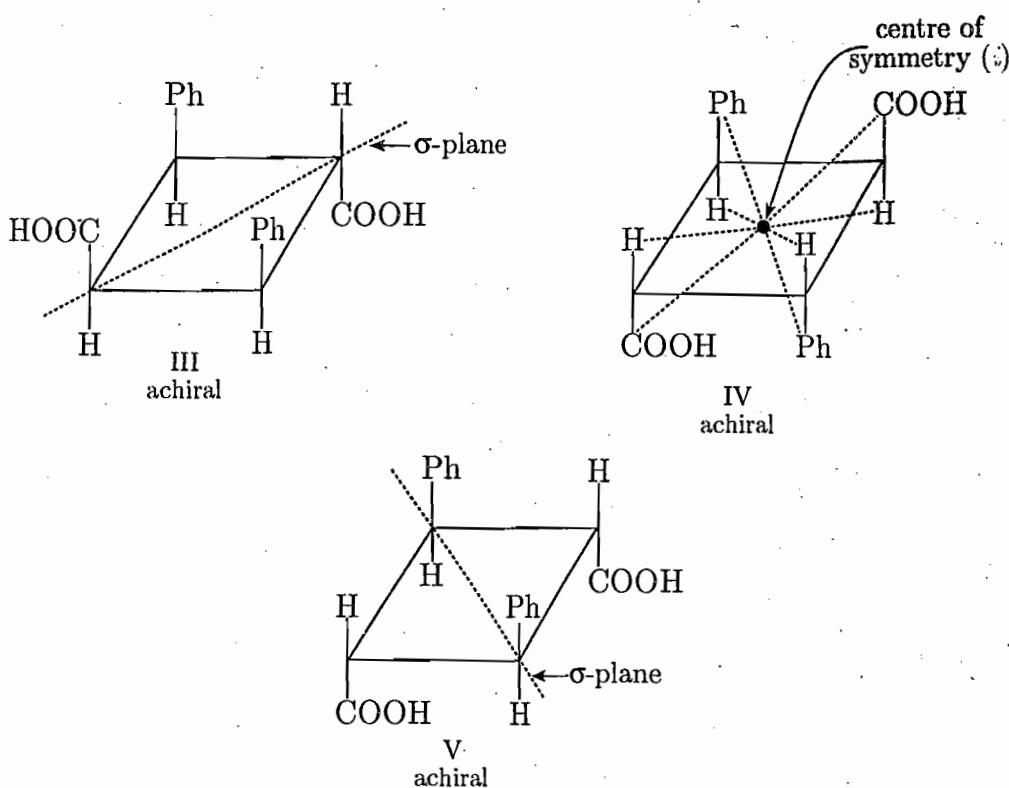
When all the substituents are identical then 1,2,3-trisubstituted cyclobutane exists in there diastereoisomeric forms. Two of them are *meso* and other is active and can exist as a pair of enantiomers. The diastereoisomers of 1,2,3-tribromocyclobutane, (XVII–XIX), for example, are shown below :



► 1.89 How many diastereoisomers are possible for the compound 2,4-diphenylcyclobutane-1,3-dicarboxylic acid. Comment on their optical activity.

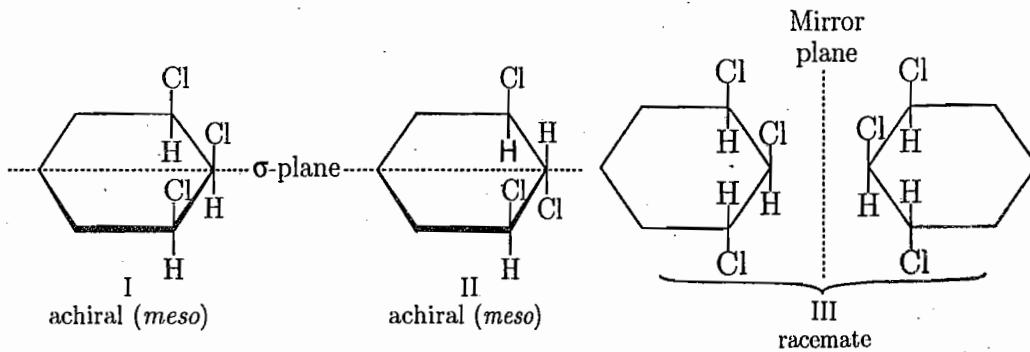
Ans. Five diastereoisomers (I–V) are possible for the compound 2,4-diphenylcyclobutane-1,3-dicarboxylic acid. All of them are achiral and therefore, optically inactive. Their structures are shown below :



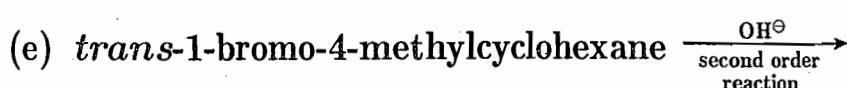
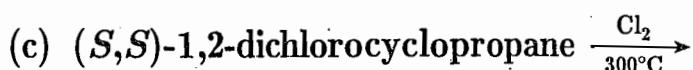
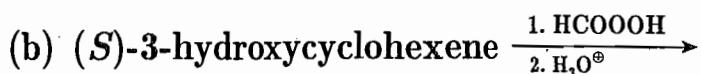


► 1.90 Draw all the stereoisomers of 1,2,3-trichlorocyclohexane and give their stereoidentity.

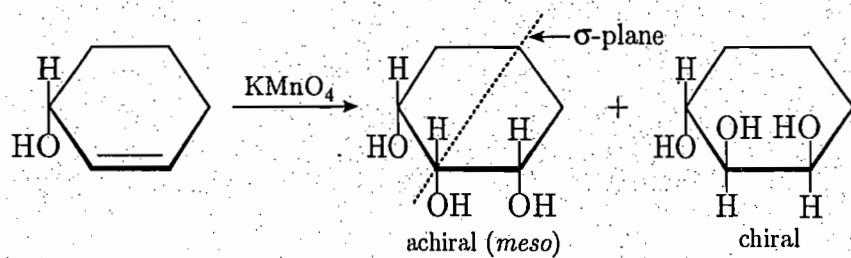
Ans. 1,2,3-Trichlorocyclohexane exists in three diastereomeric forms. Two of them (I & II) are achiral (*meso*-compounds) and the other (III) is chiral. It can exist as a pair of enantiomers.



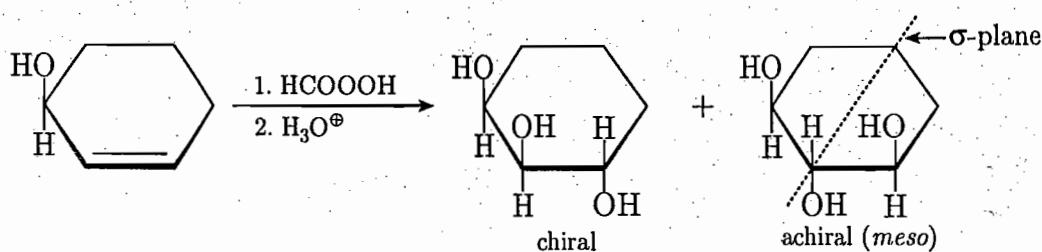
► 1.91 Write down the structures of all the stereoisomeric products in each of the following reactions and label them as chiral or achiral :



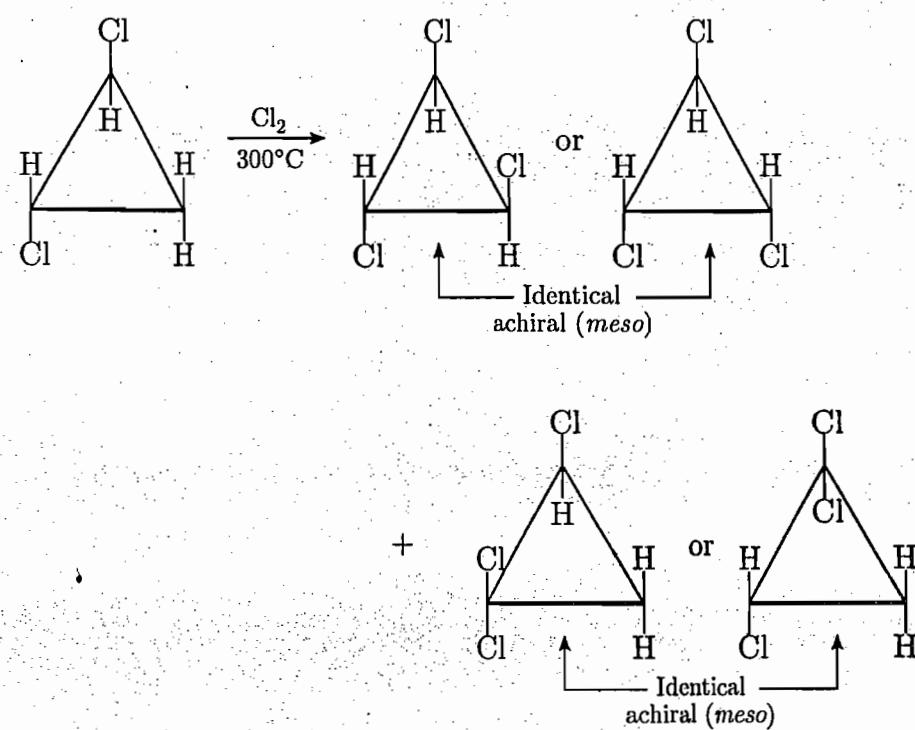
Ans. (a) (*R*)-3-Hydroxycyclohexene undergoes *syn*-hydroxylation by KMnO_4 .



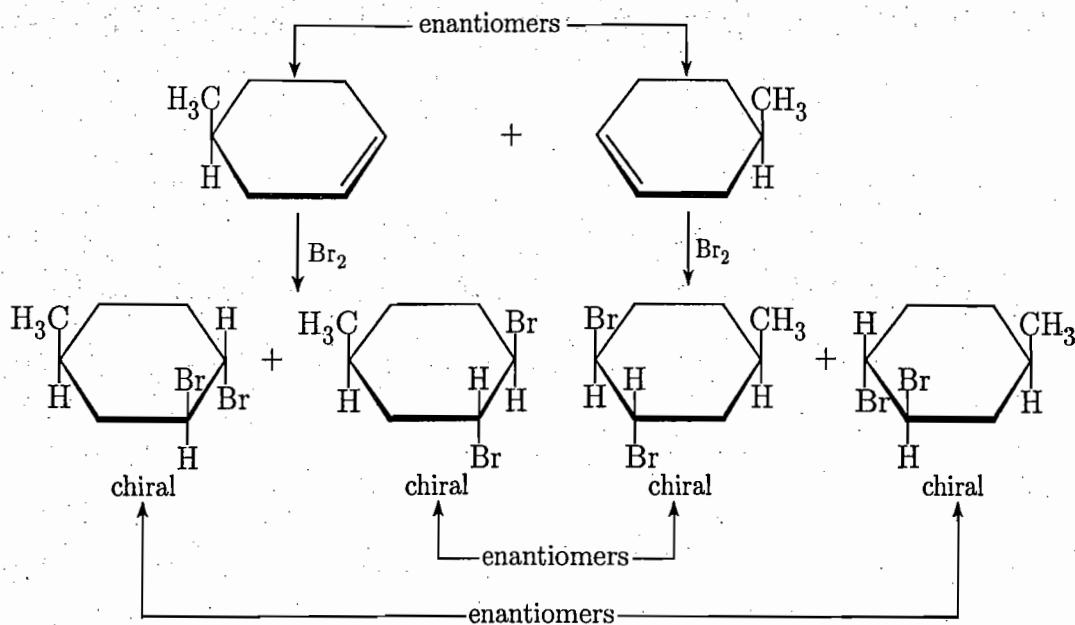
(b) (*S*)-3-Hydroxycyclohexene undergoes *anti*-hydroxylation by HCOOOH followed by hydrolysis.



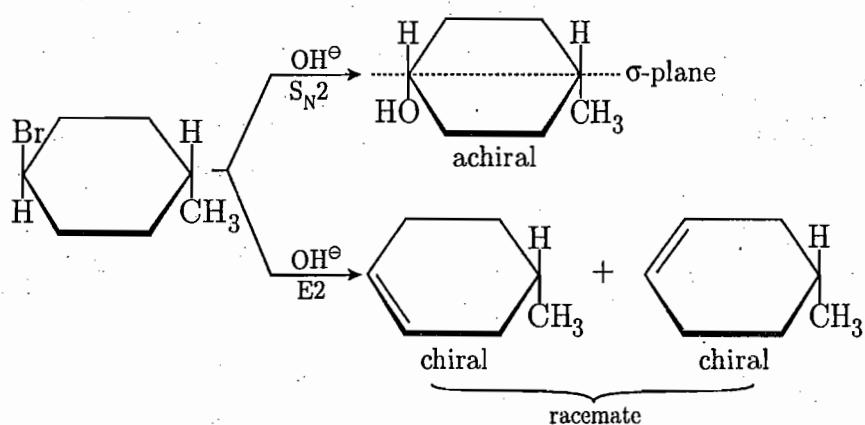
(c) (*S,S*)-1,2-Dichloropropane undergoes free-radical chlorination when treated with Cl_2 at 300°C .



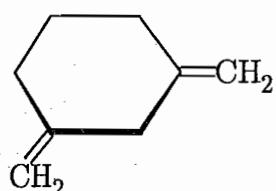
(d) *racemic* 4-Methylcyclohexene undergoes *anti*-addition of bromine when treated with a solution of Br_2 in CCl_4 .



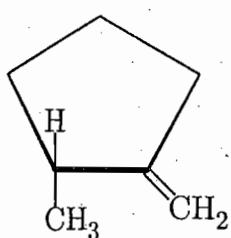
(e) *trans*-1-Bromo-4-methylcyclohexane undergoes S_N2 reaction with complete inversion and E2 reaction with loss of either of two equivalent protons.



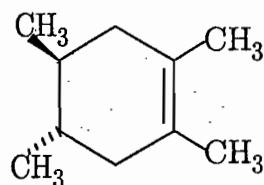
► 1.92 (a) Predict the number of stereoisomers that can be obtained by catalytic hydrogenation of both double bonds in the following compound.



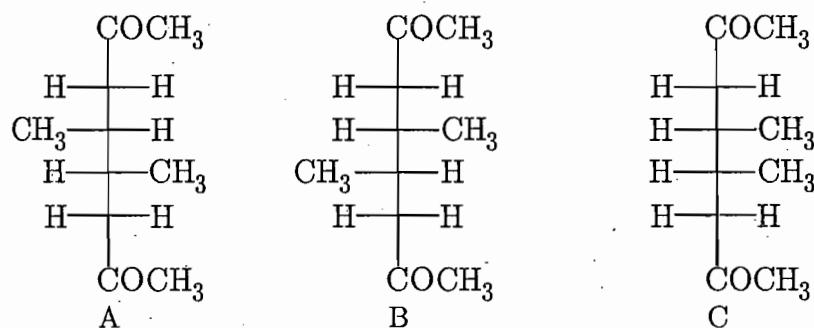
(b) Predict the major and the minor product obtained by catalytic hydrogenation of 2-methyl(methylene)cyclopentane. Which one is chiral?



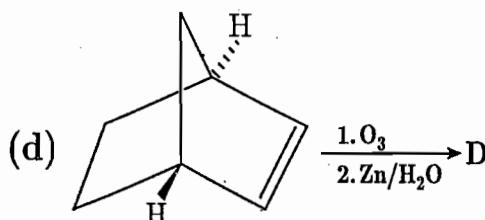
- (c) Consider the ozonolysis of *trans*-4,5-dimethylcyclohexene having the configuration shown below.



Structures A, B and C are three stereoisomeric forms of the ozonolysis product.

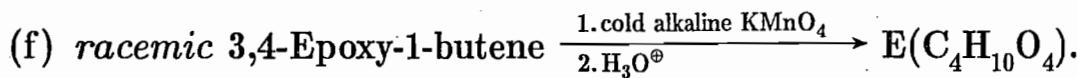


- Designate A, B and C as chiral or achiral.
- Which is the actual product formed in the reaction?
- What product would be formed if the CH₃-groups were *cis* to each other in the starting alkene.



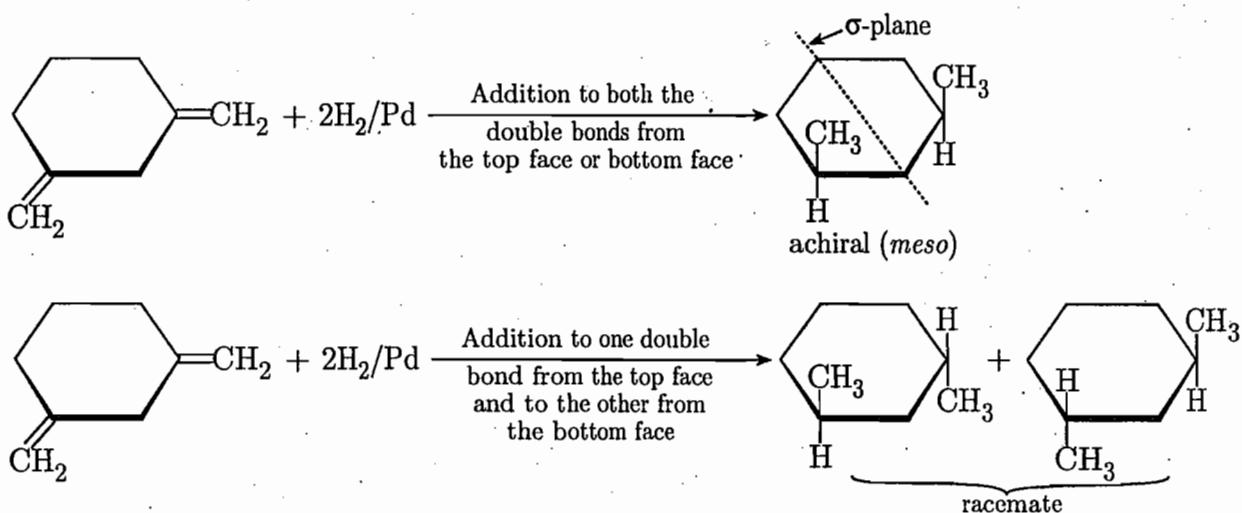
Predict the product D and give its R/S designation. Is it optically active?

- (e) Which stereoisomer of 2-butene ($\text{CH}_3\text{CH}=\text{CHCH}_3$) reacts with peroxyacetic acid to give *meso*-2,3-epoxybutane? Which one gives a racemic mixture. Give R/S designations of all the products.

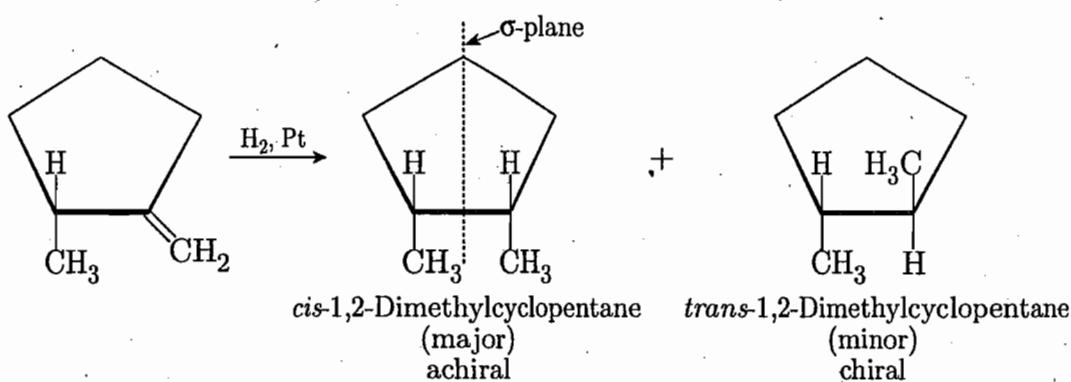


Draw all the stereoisomers of E and designate them as chiral or achiral.

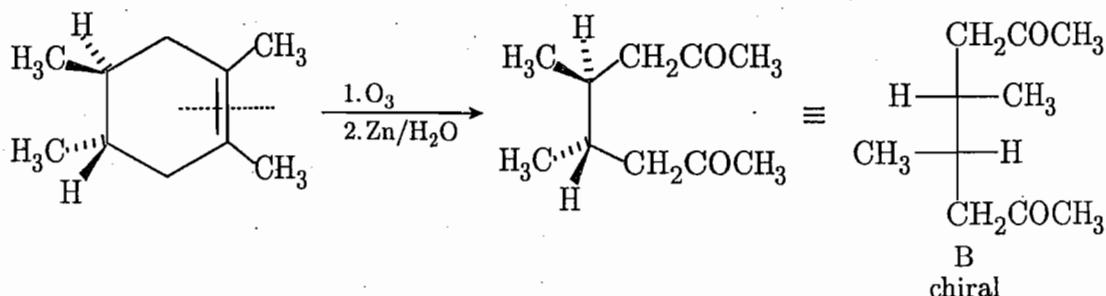
Ans. (a) Three stereoisomers can be obtained on catalytic hydrogenation of the compound. If H_2 adds to both the double bond from the same face, an achiral product (*meso*-compound) will be obtained. But, if H_2 adds to the double bonds from opposite faces two enantiomers will be obtained in equal amounts.



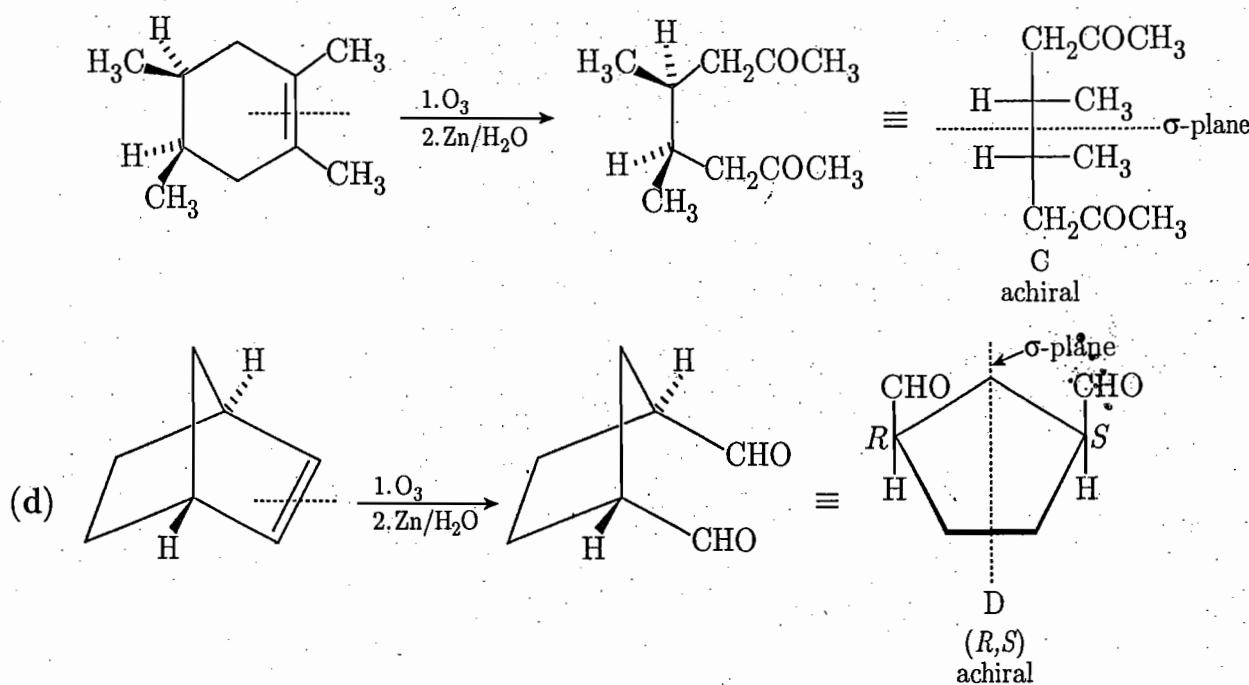
(b) A reaction that introduces a second stereogenic centre into a substrate does not produce equal amounts of two possible diastereoisomers. The major product in this reaction is *cis*-1,2-dimethylcyclopentane. The reason for this is that hydrogenation occurs preferentially at the less hindered side of the double bond (opposite that of the methyl group). The major product is achiral and the minor product is chiral.



- (c) (i) A and B are chiral, whereas C is achiral because it has a plane of symmetry.
(ii) B is the actual product formed in the reaction.

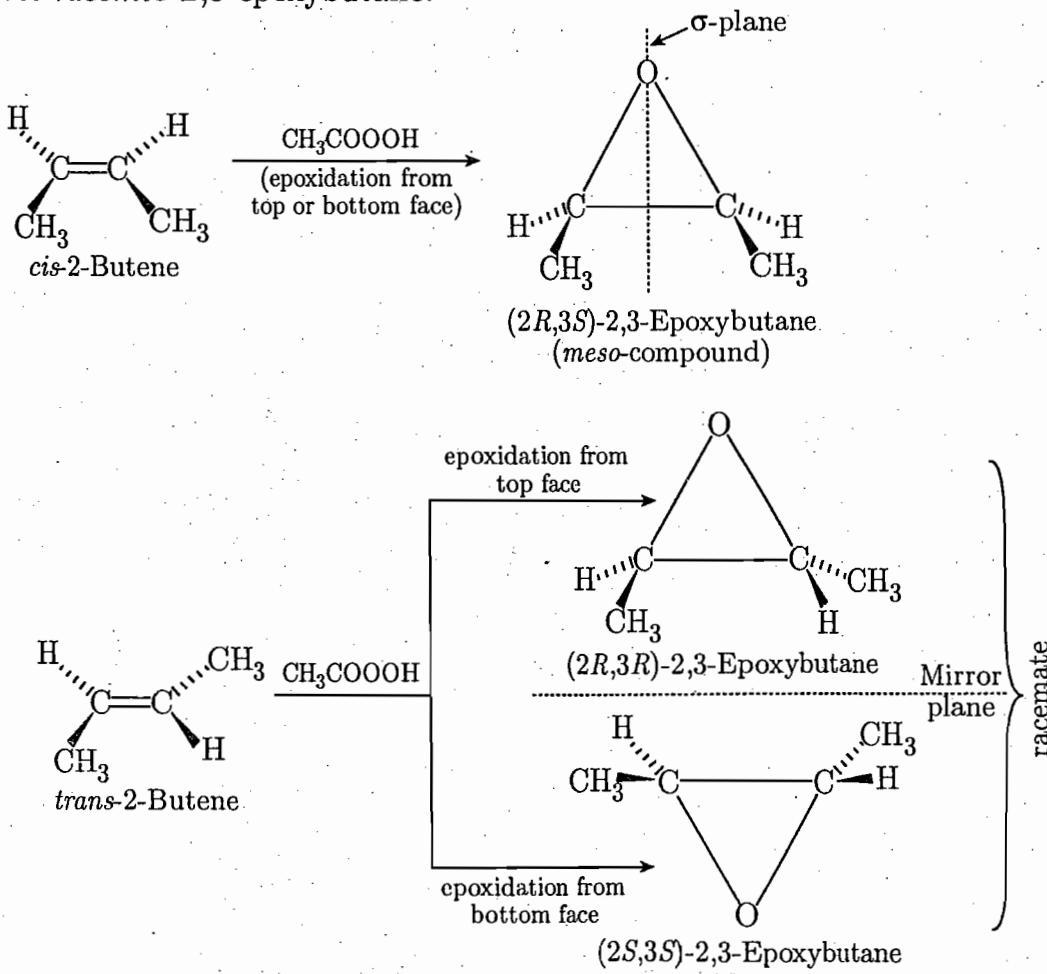


- (iii) The product C would be formed if the CH_3 -groups were *cis* to each other in the starting alkene.

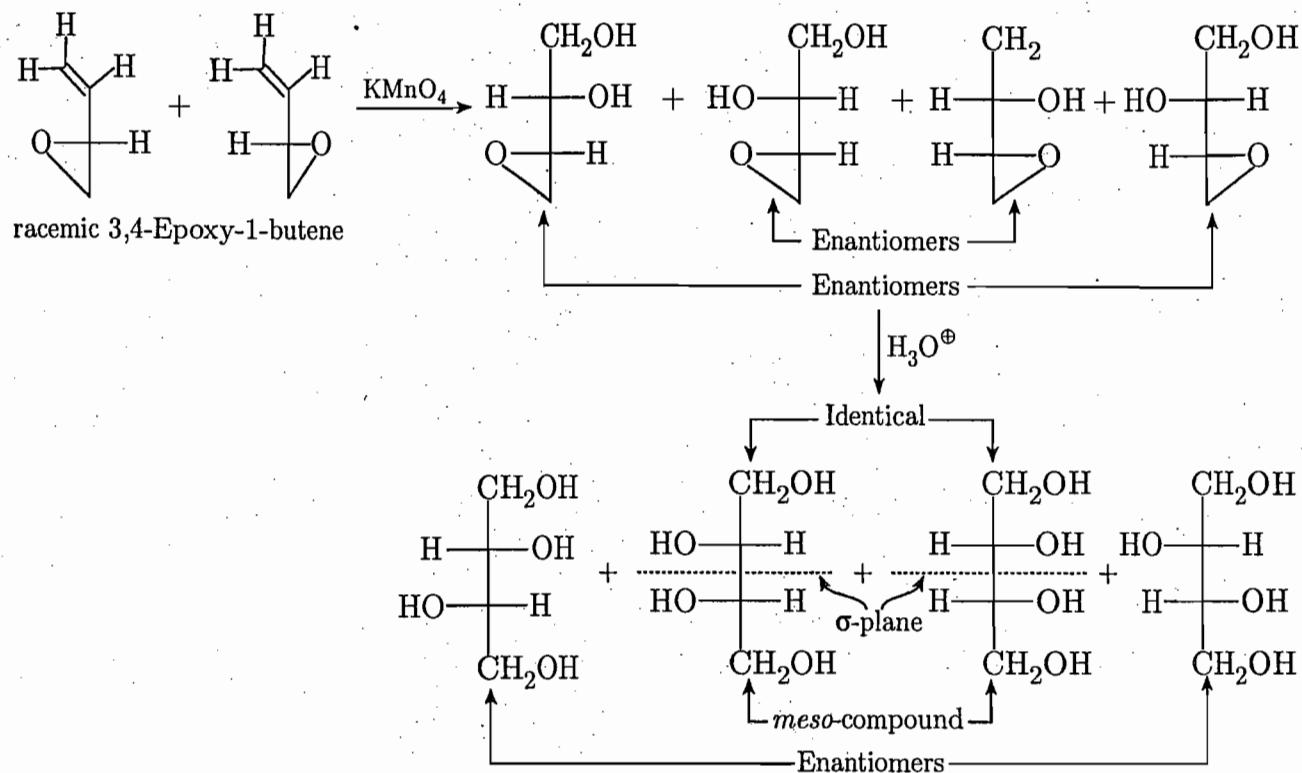


The ozonolysis product D is achiral (a *meso*-compound) and therefore, optically inactive.

- (e) Epoxidation of alkenes by peracids is a stereospecific *syn* addition. Because of this, *cis*-2-butene reacts with peracetic acid to give *meso*-2,3-epoxybutane, whereas *trans*-2-butene gives *racemic* 2,3-epoxybutane.

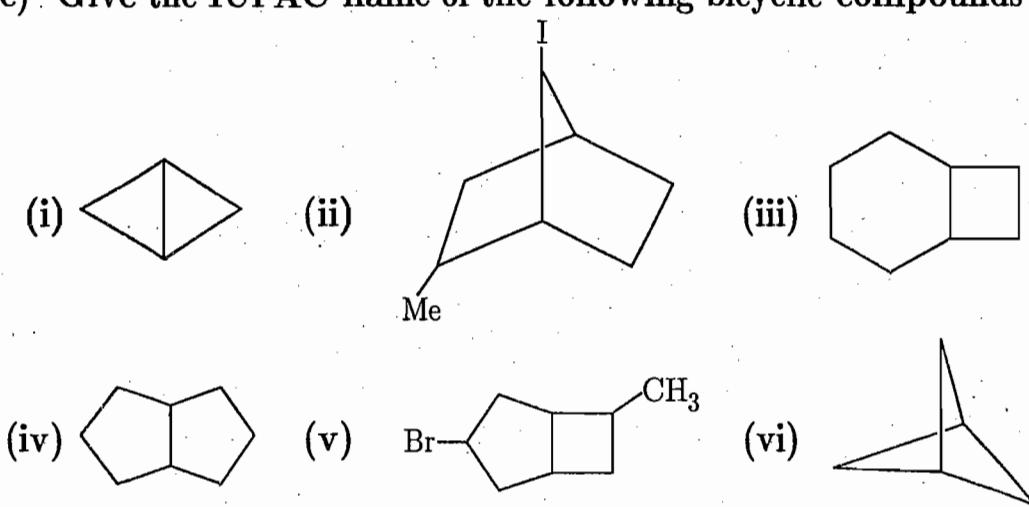


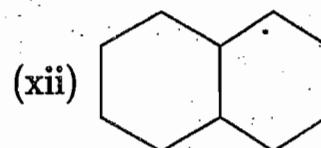
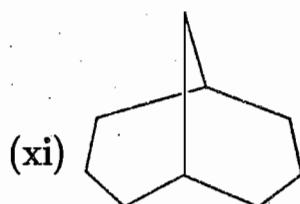
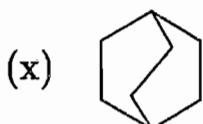
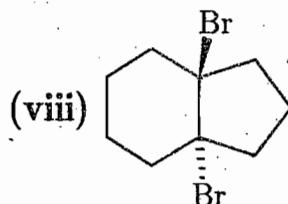
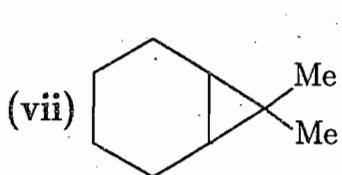
(f) *syn*-Hydroxylation of the double bond (which produces one new chiral carbon) followed by cleavage of the epoxide by dilute acid produces one achiral (*meso*) stereoisomer and two chiral stereoisomers (a pair of enantiomers).



BYCYCLIC COMPOUNDS

- 1.93 (a) Define the following terms and give examples : (i) bicyclic compounds, (ii) bridgehead carbons and bridge carbons, (iii) fused bicyclic compounds, (iv) bridged bicyclic compounds and (v) spirocyclic compounds.
- (b) How are bicyclic compounds named in the IUPAC system?
- (c) Give the IUPAC name of the following bicyclic compounds :

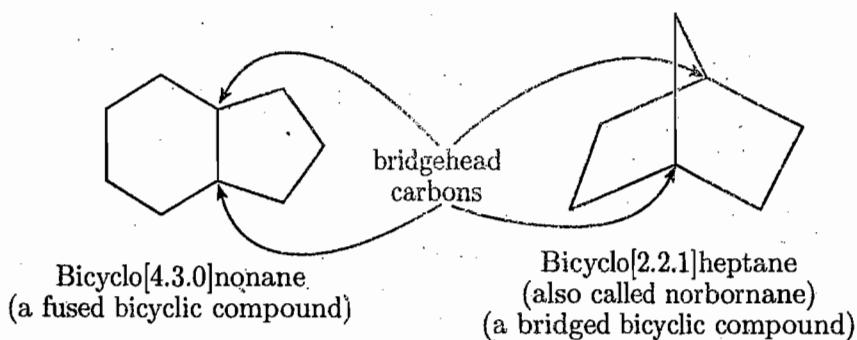




(d) Write structural formula for each of the following bicyclic compounds :

- (i) Bicyclo[3.1.1]heptane, (ii) Bicyclo[3.3.0]octane, (iii) *cis*-Bicyclo[4.4.0]-decane (iv) *trans*-Bicyclo[4.4.0]decane, (v) Bicyclo[2.2.1]hept-2-ene (vi) 2-Bromobicyclo[4.2.0]octane, (vii) 8-Methylbicyclo[3.2.1]octane, (viii) 8-Ethylbicyclo[4.3.0]nonane, (ix) Bicyclo[4.4.1]undecane, (x) 8-Chlorobicyclo[3.2.1]octane.

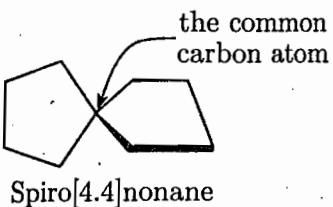
Ans. (a) (i) Bicyclic compounds are compounds that contain two rings. For example :



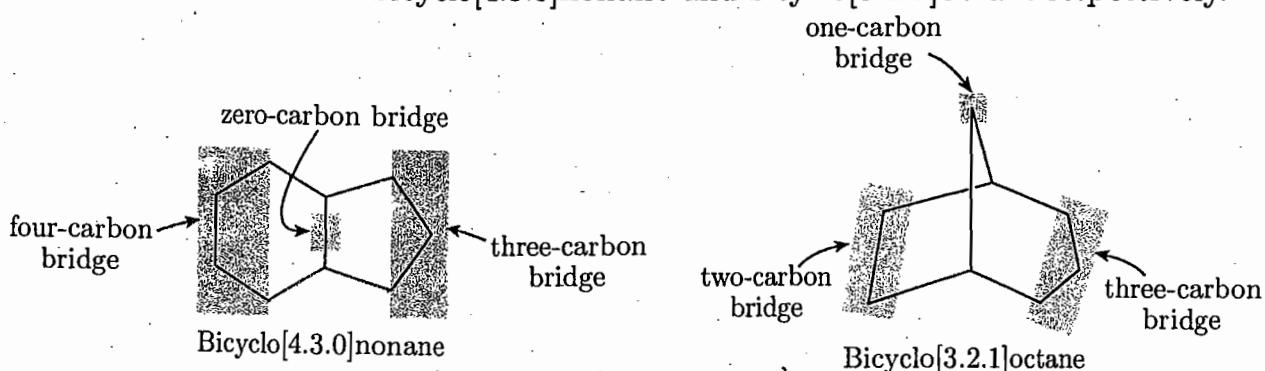
- (ii) The carbon atoms common to both rings in a bicyclic compound are called bridgehead carbons. Bridge carbons are the carbons in the chain connecting but not including the bridgehead carbons.
- (iii) When the bridgehead carbons of a bicyclic compound are adjacent, the compound is called a fused bicyclic compound. For example, bicyclo[4.3.0]nonane is a fused bicyclic compound.
- (iv) When the bridgehead carbons of a bicyclic compound are not adjacent, the compound is called a bridged bicyclic compound. For example, bicyclo[2.2.1]heptane is a bridged bicyclic compound.

[All fused and bridged bicyclic systems have three bridges connecting the two bridgehead carbons where the rings connect.]

- (v) If the two rings in a compound share only one carbon atoms the compound is called a spirocyclic compound. For example :

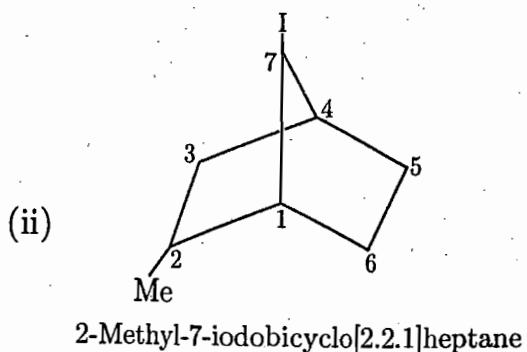


(b) The name of a bicyclic compound in the IUPAC system is based on the name of the alkane having the same number of carbons as there in the ring system. The name follows the prefix *bicyclo* and a set of brackets enclosing numbers indicating the number of carbons in each of the three bridges connecting the bridgehead carbons, in order of decreasing size. For example, the followig bicyclic compounds containing nine and eight carbon atoms are named *bicyclo[4.3.0]nonane* and *bicyclo[3.2.1]octane* respectively.



[It is to be noted that a fused-ring system always has a 0 as one of the bracketed numbers. Therefore, one can distinguish between a fused and a bridged bicyclic compound from their IUPAC names (without drawing their structures).]

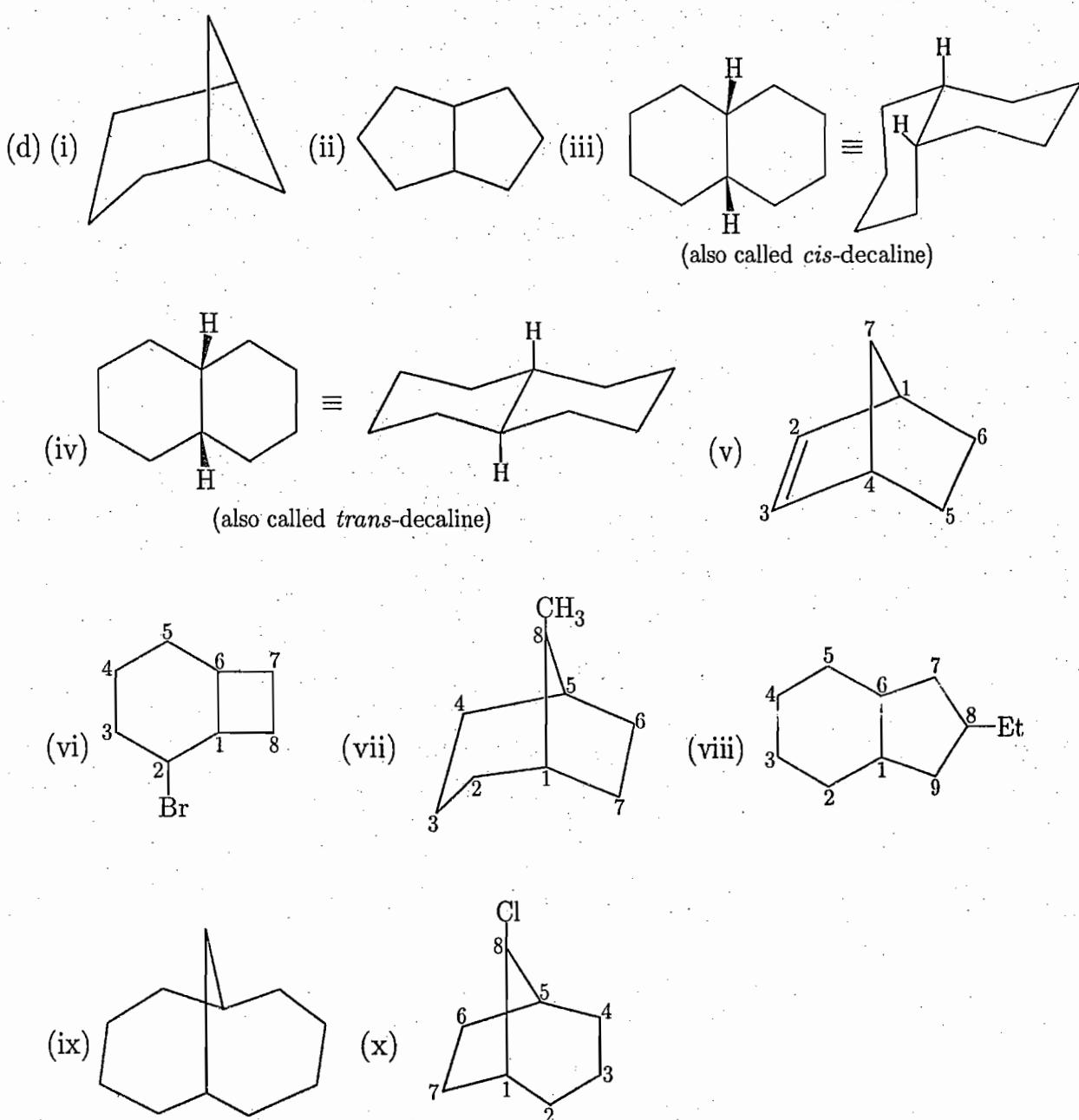
- (c) (i) *Bicyclo[1.1.0]butane*



2-Methyl-7-iodobicyclo[2.2.1]heptane

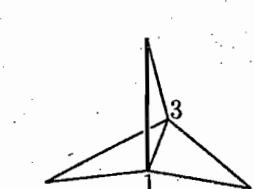
Carbons in bicycles are to be numbered from one bridgehead carbon to another bridgehead carbon along the chains in order of decreasing length.

- | | |
|-----------------------------------------------------|-----------------------------------|
| (iii) <i>Bicyclo[4.2.0]octane</i> | (iv) <i>Bicyclo[3.3.0]octane</i> |
| (v) <i>3-Bromo-6-methylbicyclo[3.2.0]heptane</i> | (vi) <i>Bicyclo[1.1.1]pentane</i> |
| (vii) <i>7,7-Dimethylbicyclo[4.1.0]heptane</i> | |
| (viii) <i>trans-1,6-Dibromobicyclo[4.3.0]nonane</i> | (ix) <i>Bicyclo[3.2.1]octane</i> |
| (x) <i>Bicyclo[2.2.2]octane</i> | (xi) <i>Bicyclo[3.3.1]nonane</i> |
| (xii) <i>Bicyclo[4.4.0]decane</i> | |

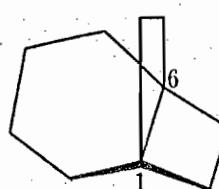


► 1.94 Give two examples of tricyclic compounds. How do you know that these compounds are tricyclic.

Ans. Examples of tricyclic compounds are as follows :



Tricyclo[1.1.1.0^{1.3}]pentane



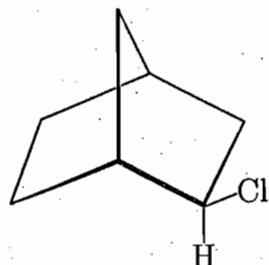
Tricyclo[4.2.2.0^{1.6}]decane

[The superscripts 1 and 3 or 1 and 6 indicate the fused carbon atoms.]

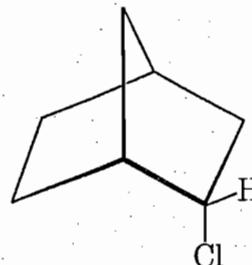
The compounds are tricyclic because three bonds must be broken in each case to get a noncyclic compound.

► 1.95 Discuss *exo-endo* and *syn-anti* terminology in stereoisomerism of bridged bicyclic compounds. Give examples.

Ans. A substituent on a particular bridge of a bridged bicyclic compound is called *exo* if it is on the same side as the smallest bridge and *endo* if it is on the side opposite to the smallest group. For example :

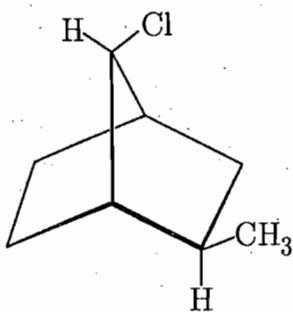


exo-2-Chlorobicyclo[2.2.1.]pentane

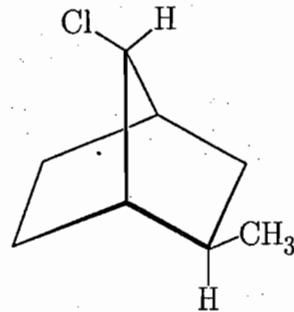


endo-2-Chlorobicyclo[2.2.1.]pentane

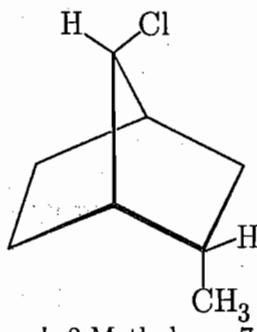
When a substituent on the smallest bridge is directed towards the next smallest bridge or towards the bridge which has substituents, it is called *syn*. When the substituent on the smallest bridge is directed towards the largest bridge or towards the unsubstituted bridge, it is called *anti*. For example :



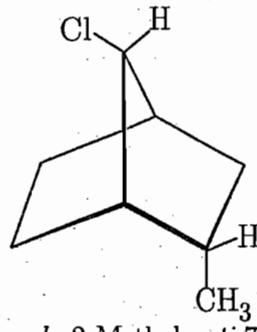
exo-2-Methyl-syn-7-chlorobicyclo[2.2.1]heptane



exo-2-Methyl-anti-7-chlorobicyclo[2.2.1]heptane

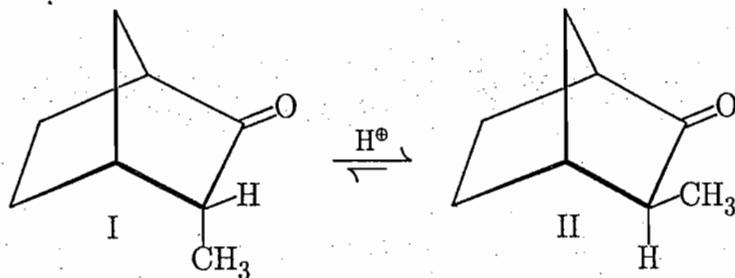


endo-2-Methyl-syn-7-chlorobicyclo[2.2.1]heptane

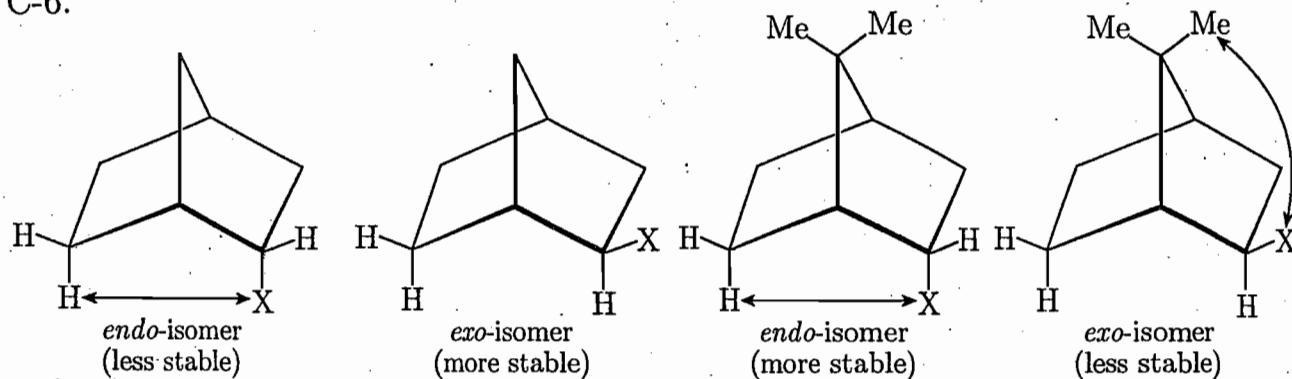


endo-2-Methyl-anti-7-chlorobicyclo[2.2.1]heptane

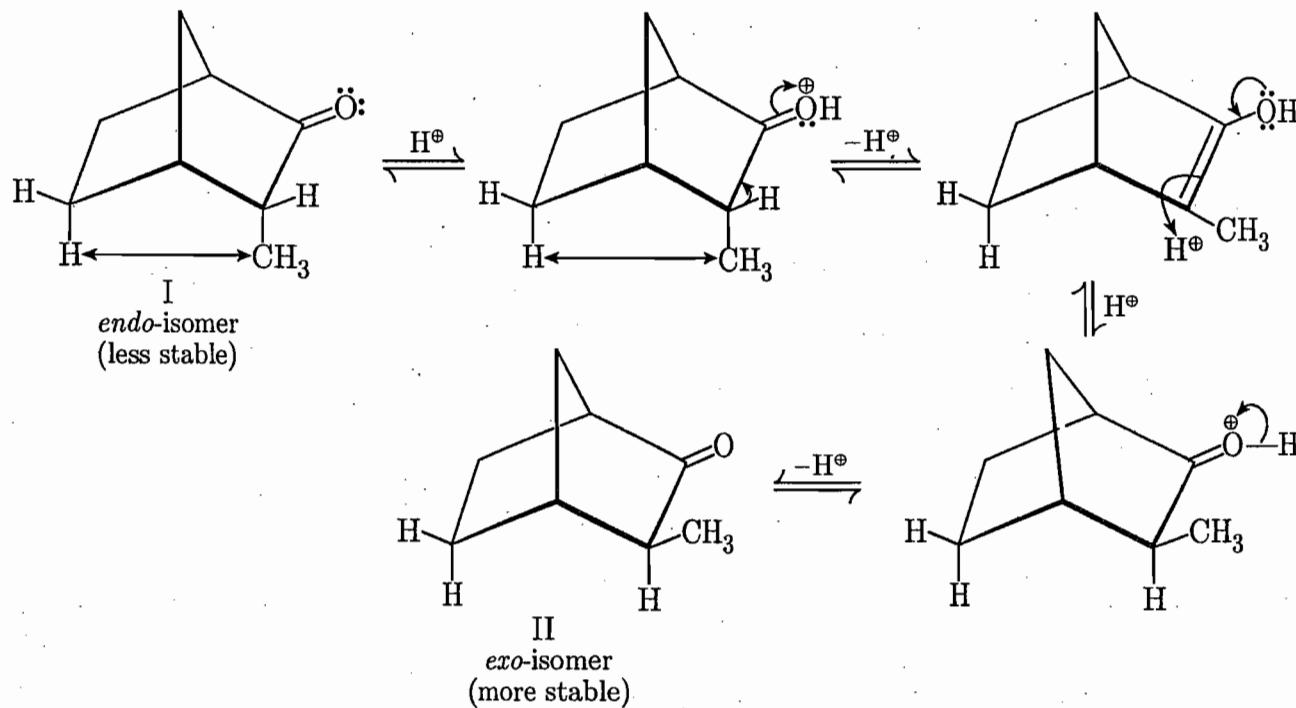
► 1.96 Comment on the stability of *exo*- and *endo*-stereoisomers and explain the following observation :



Ans. In general an *exo*-isomer of a bicyclic compound is thermodynamically more stable than an *endo*-isomer because the *endo*-isomer suffers from steric interaction involving the *endo*-ligand and the *endo*-H atom at C-6. However, when C-7 bears a *gem*-dimethyl group, the *exo*-isomer is less stable than the *endo*-isomer and this is because the steric interaction between the overhanging methyl group at C-7 and the *exo*-ligand is greater than that between the *endo*-ligand and the *endo*-H at C-6.

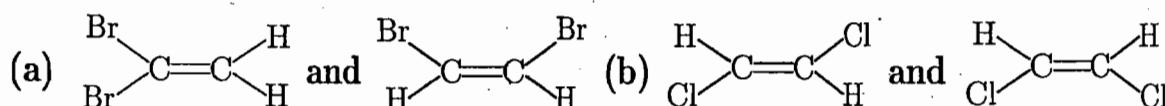


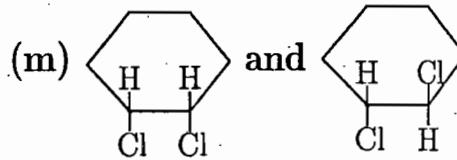
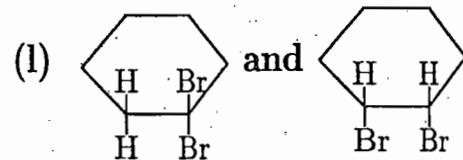
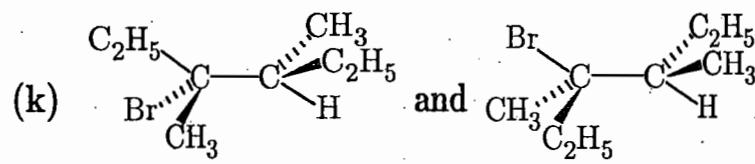
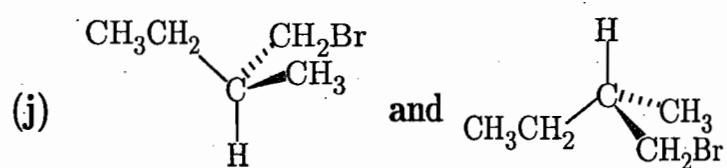
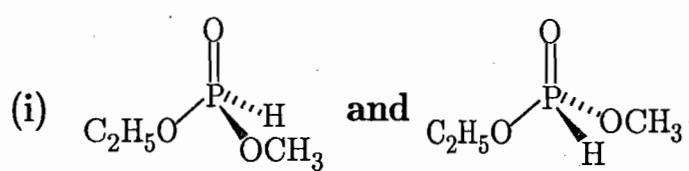
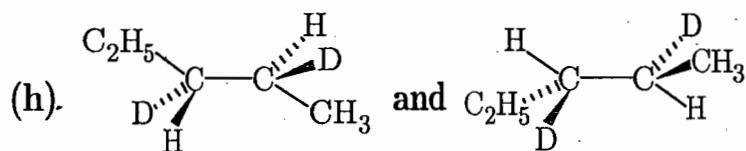
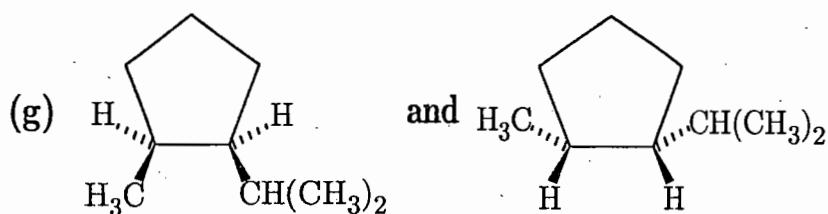
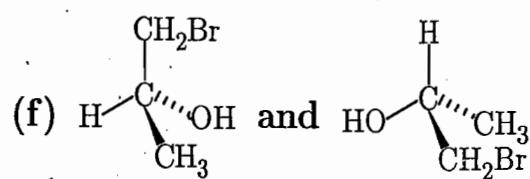
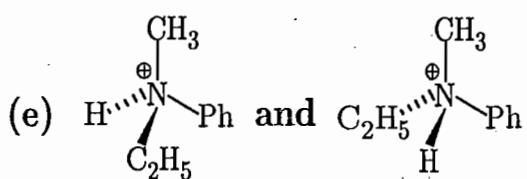
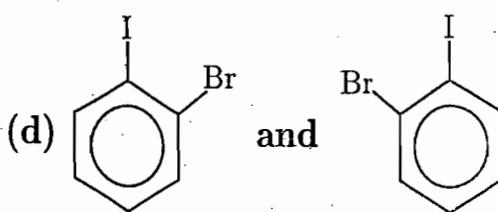
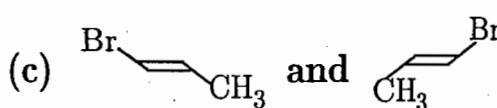
The *endo*-isomer(I) of the ketone is thermodynamically less stable than its *exo*-isomer(II) and because of this, in the presence of acid the *endo*-isomer becomes converted to the more stable *exo*-isomer through the formation of an enol.

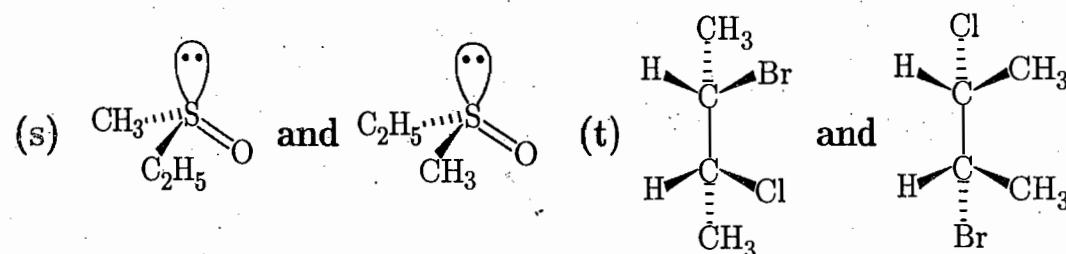
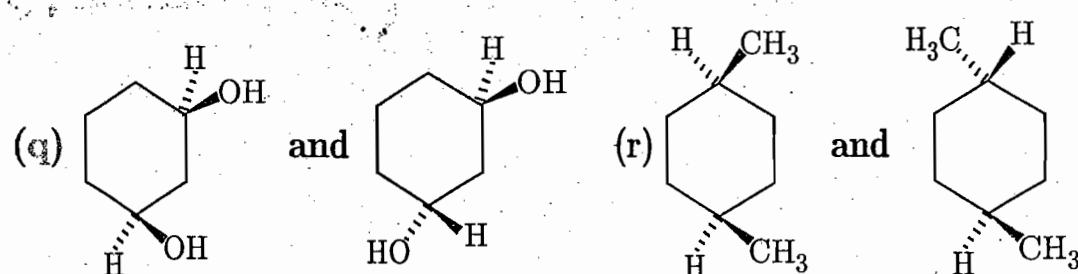
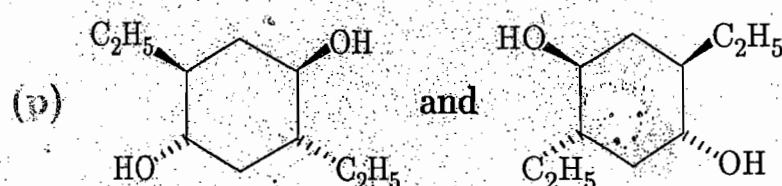
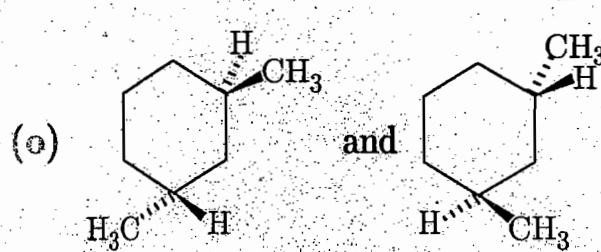
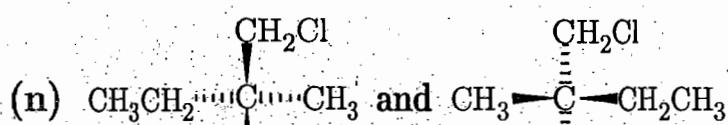


**LABELLING OF HOMOMERS, CONSTITUTIONAL ISOMERS,
DIASTEREOSTERISOMERS, AND ENANTIOMERS**

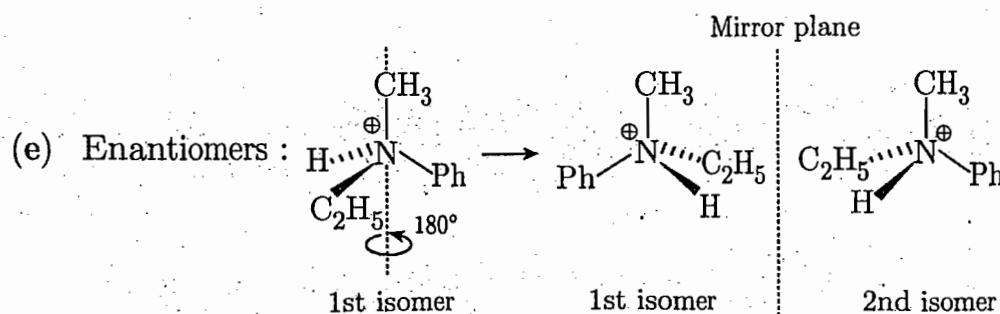
► 1.97 Label the following pairs of structures as homomers, constitutional isomers, diastereoisomers or enantiomers.

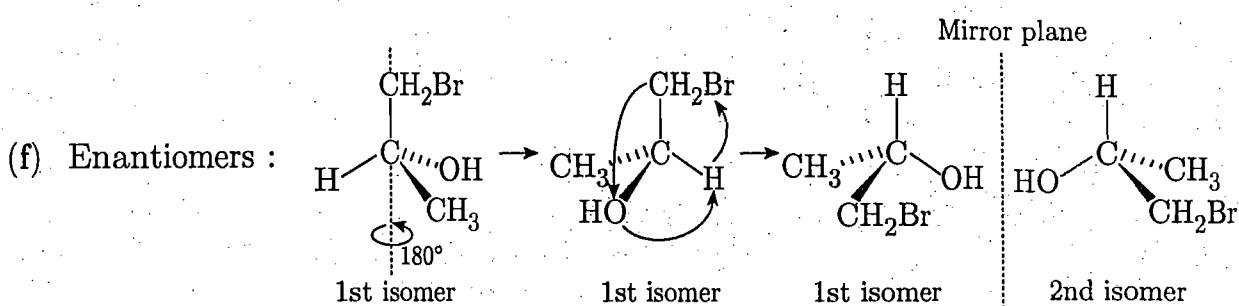




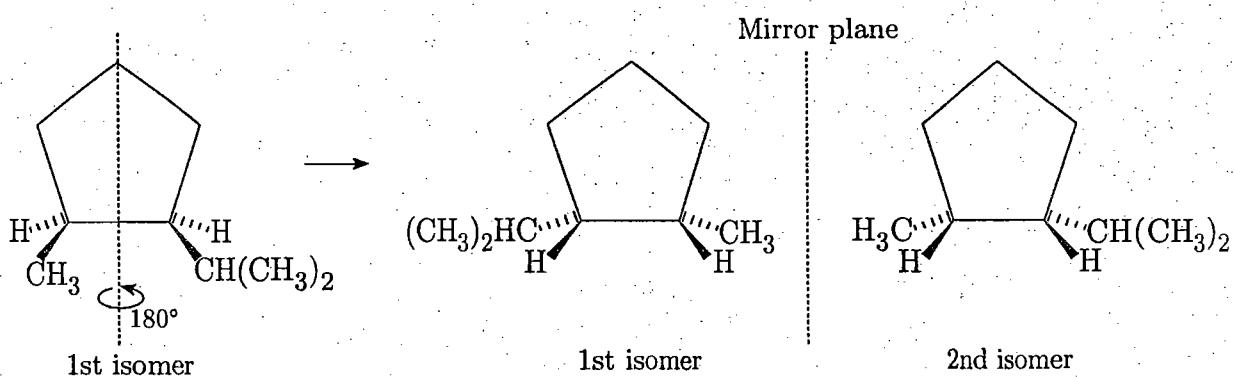


- Ans.** (a) Constitutional isomers (1,1-dibromoethene and 1,2-dibromoethene).
 (b) Diastereoisomers [Geometric or *cis-trans* isomers are diastereoisomers.]
 (c) Homomers [They are superimposable]
 (d) Homomers [They are superimposable]

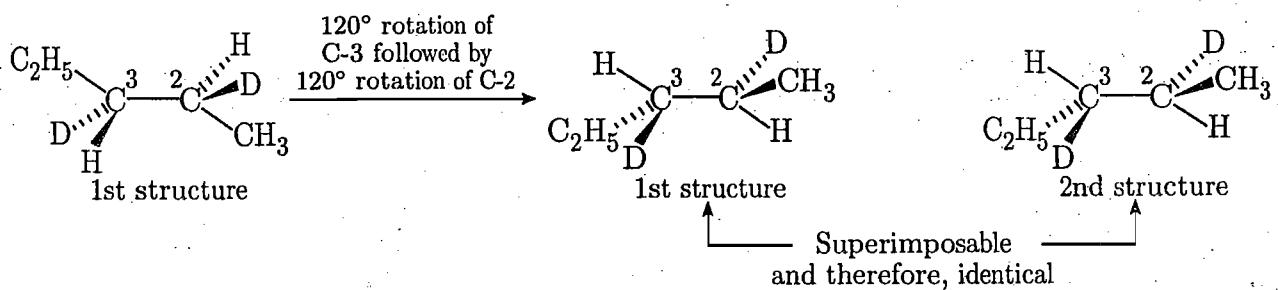




(g) Enantiomers :

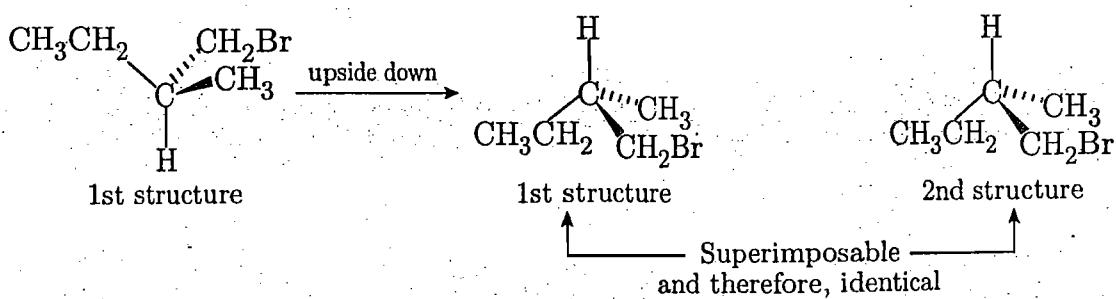


(h) Homomers :

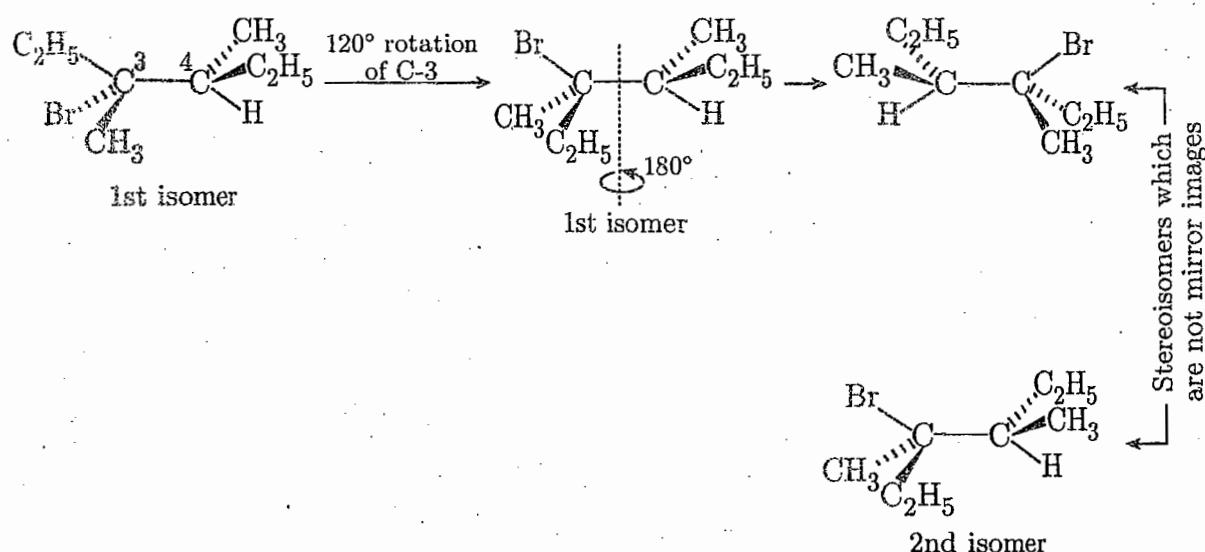


(i) Enantiomers

(j) Homomers :



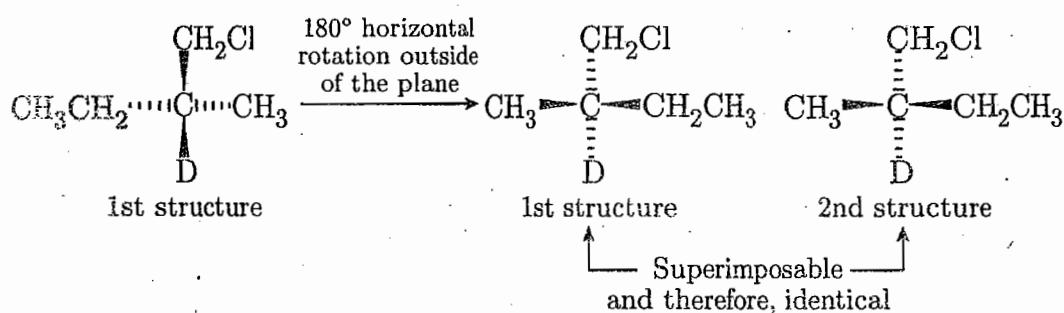
(k) Diastereoisomers :



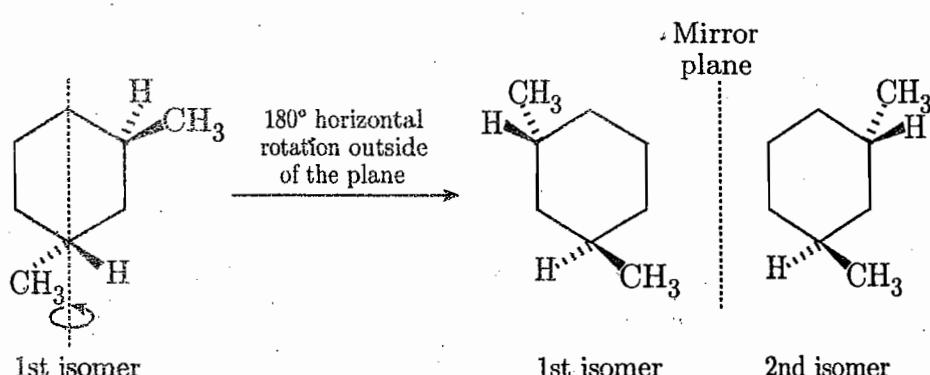
(l) Constitutional isomers (1,1-dibromocyclohexane and 1,2-dibromocyclohexane).

(m) Diastereoisomers [They are geometric or *cis-trans* isomers.]

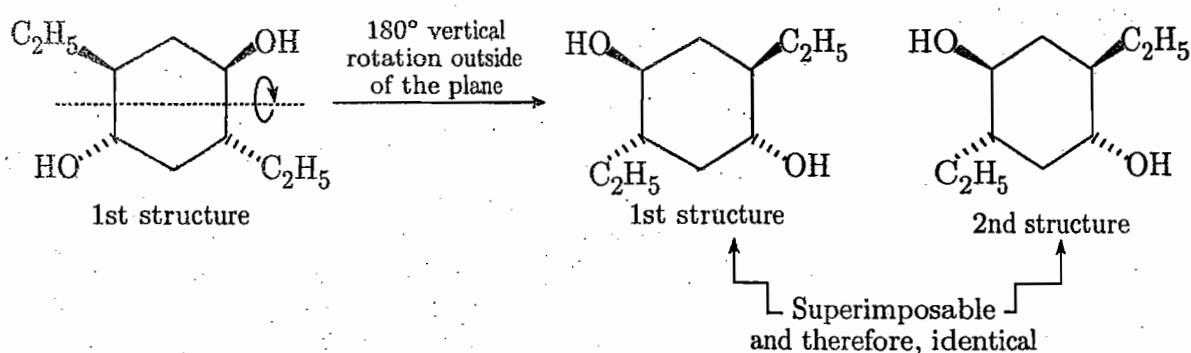
(n) Homomers :



(o) Enantiomers :



(p) Homomers :

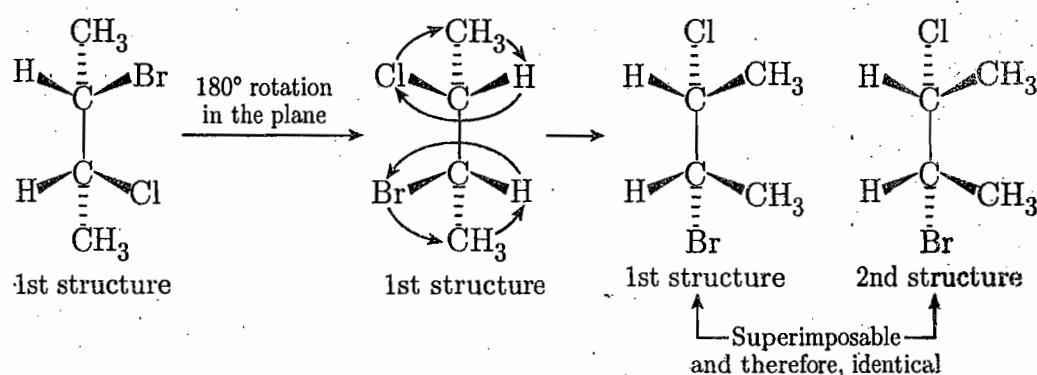


(q) Diastereoisomers [They are geometric or *cis-trans* isomers.]

(r) Diastereoisomers [They are geometric or *cis-trans* isomers.]

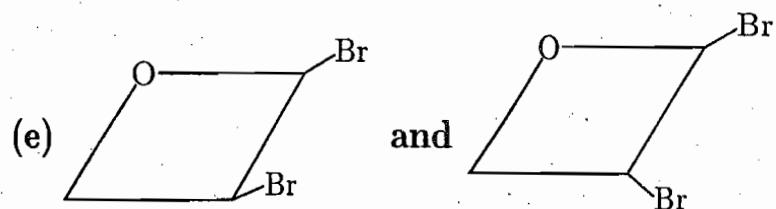
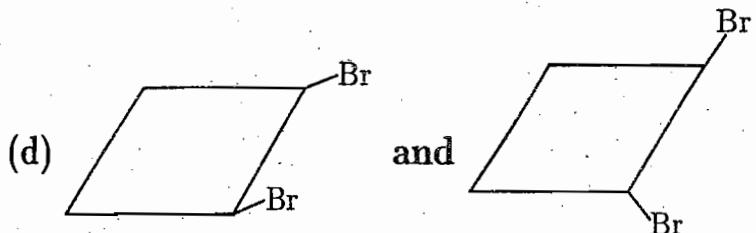
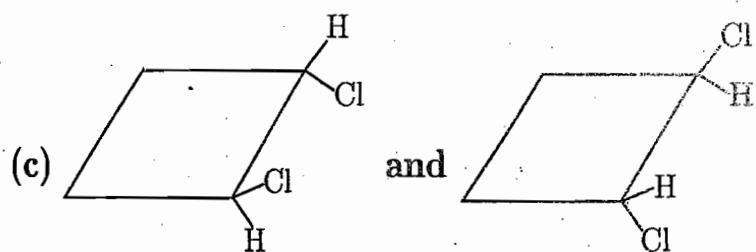
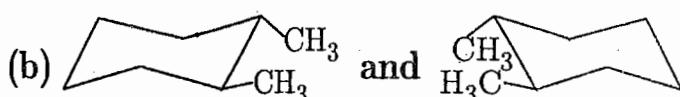
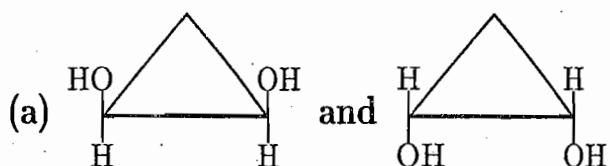
(s) Enantiomers

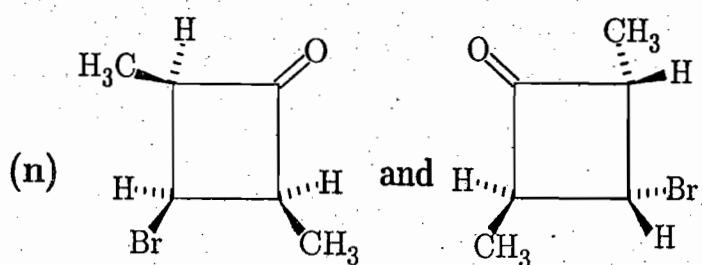
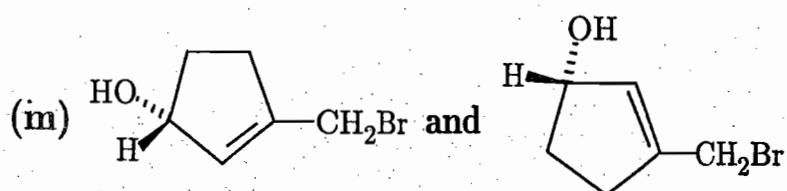
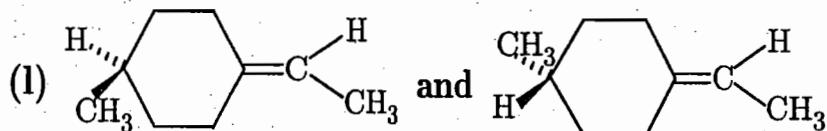
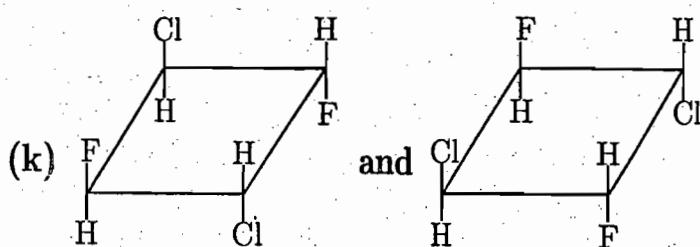
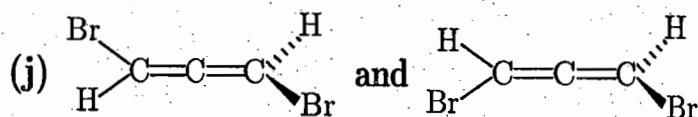
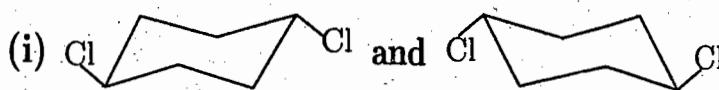
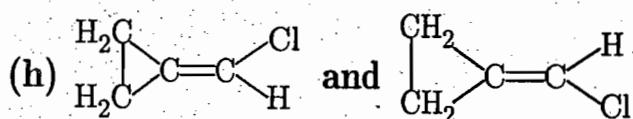
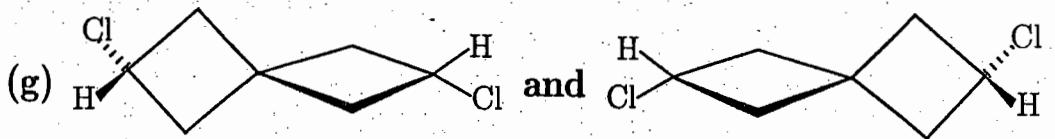
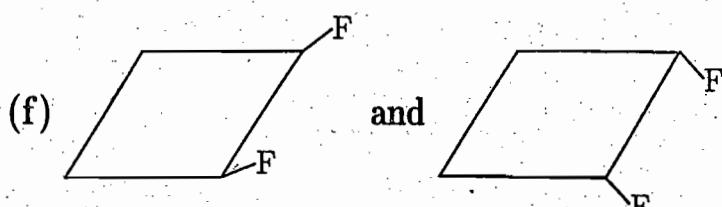
(t) Homomers :

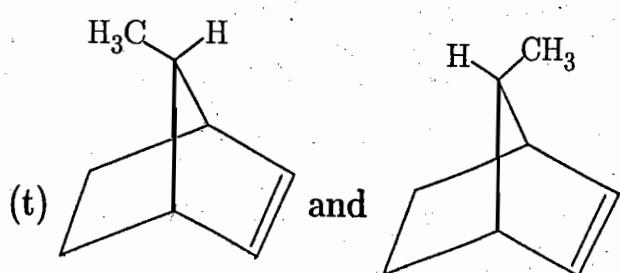
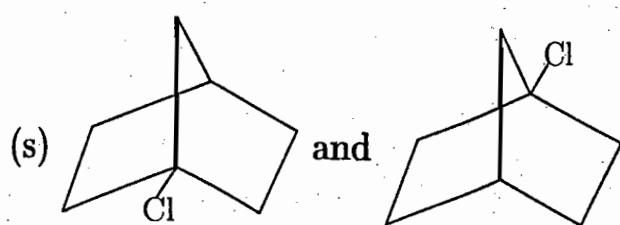
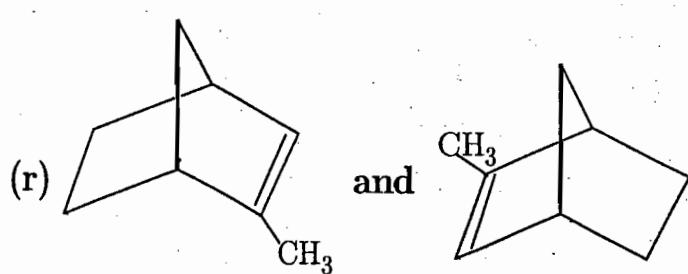
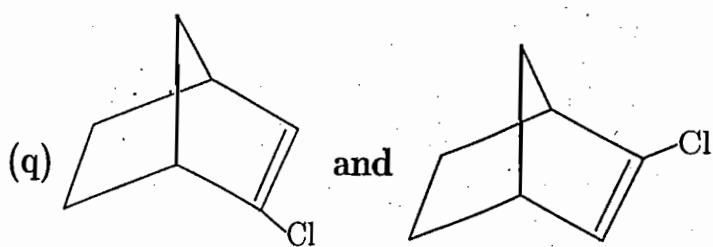
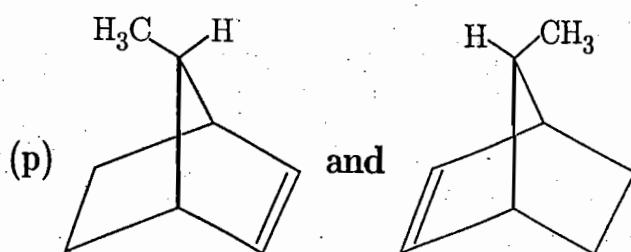
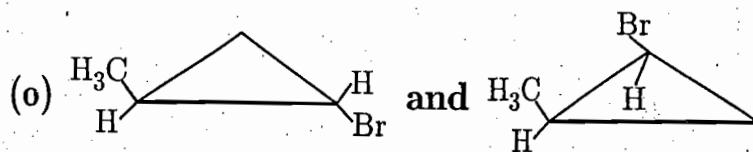


e).

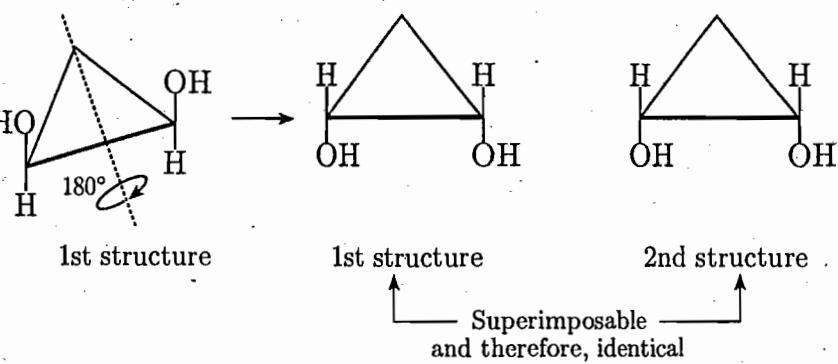
► 1.98 Label the following pairs of structures as homomers, enantiomers or diastereoisomers.





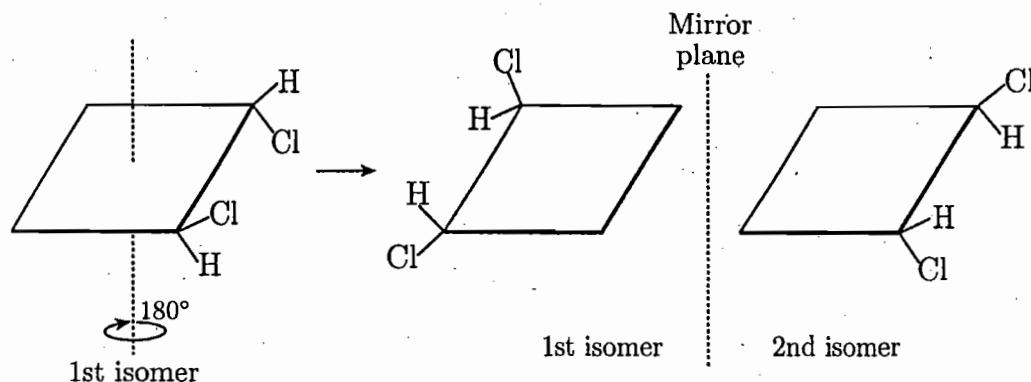


Ans. (a) Homomers :



(b) Enantiomers

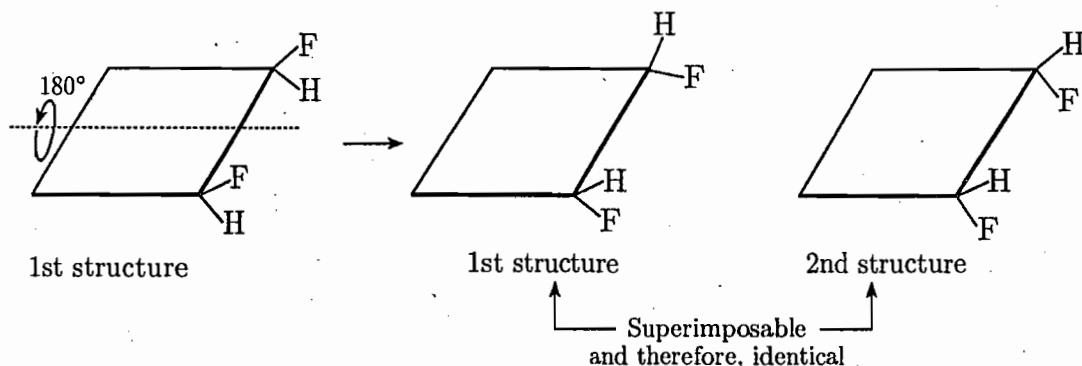
(c) Enantiomers :



(d) Diastereoisomers [They are geometric and *cis-trans* isomers : *cis*-1,2-dibromocyclobutane and *trans*-1,2-dibromocyclobutane.]

(e) Diastereoisomers [They are geometric or *cis-trans* isomers.]

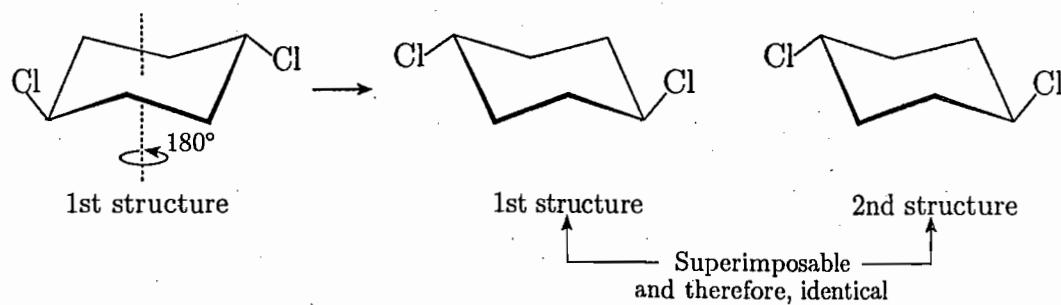
(f) Homomers :



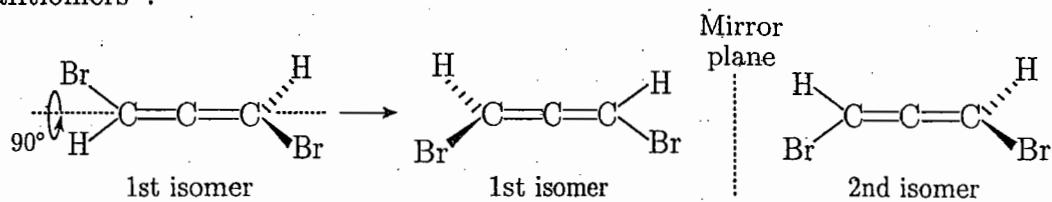
(g) Enantiomers

(h) Homomers

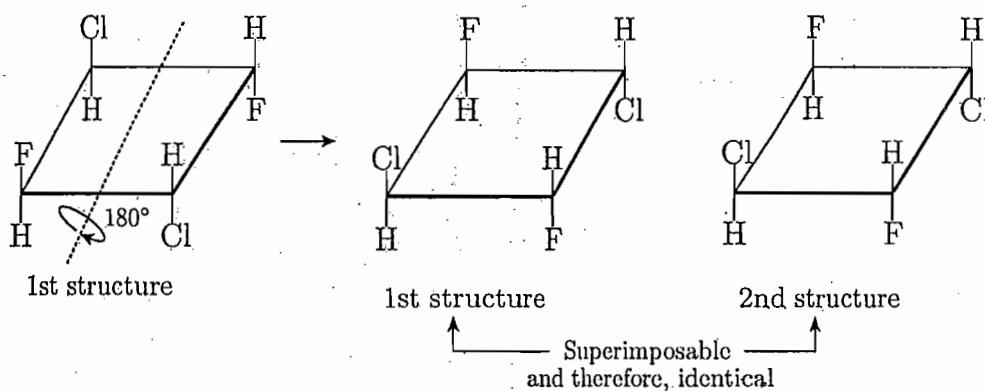
(i) Homomers :



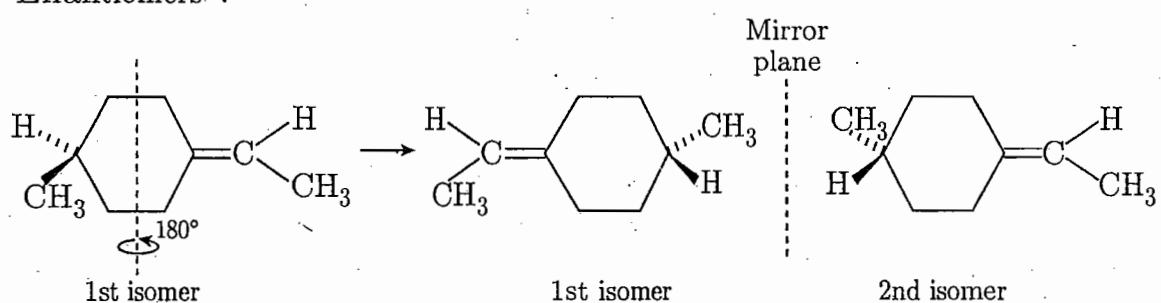
(j) Enantiomers :



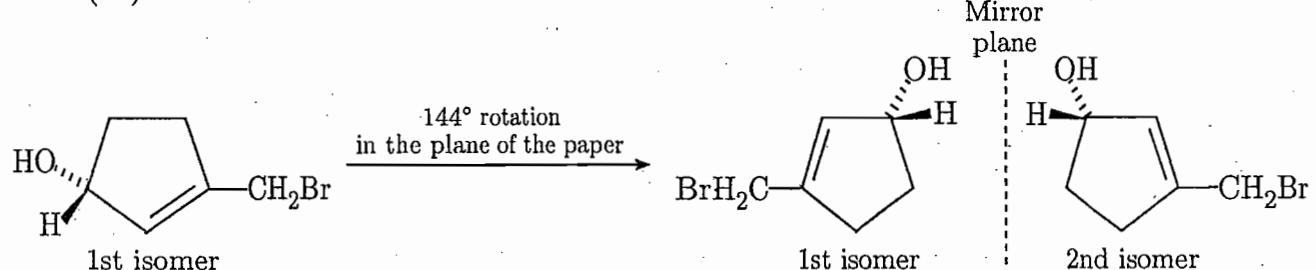
(k) Homomers :



(l) Enantiomers :



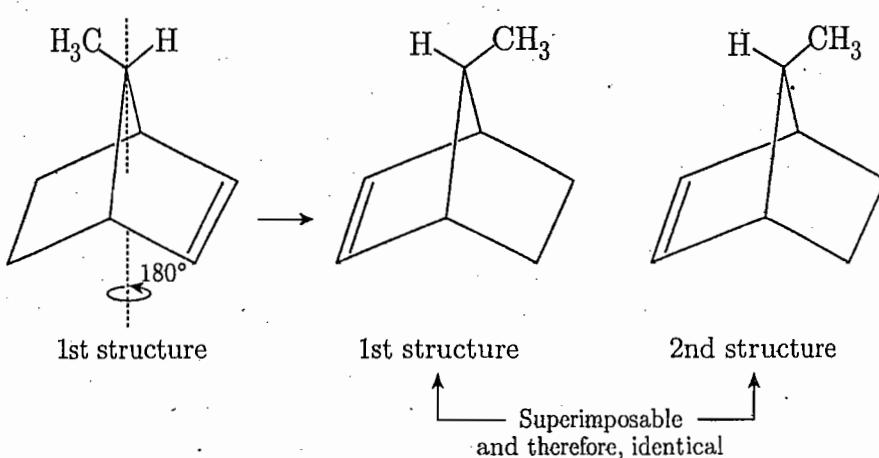
(m) Enantiomers :



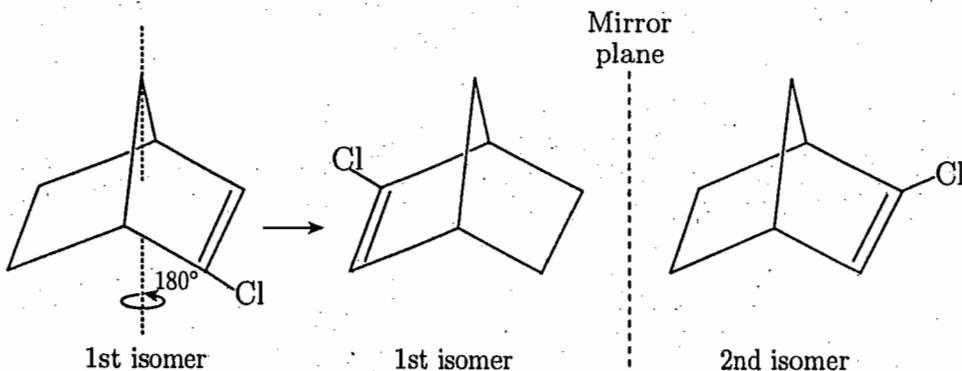
(n) Diastereoisomers

(o) Diastereoisomers [They are geometric or *cis-trans* isomers]

(p) Homomers :



(q) Enantiomers :

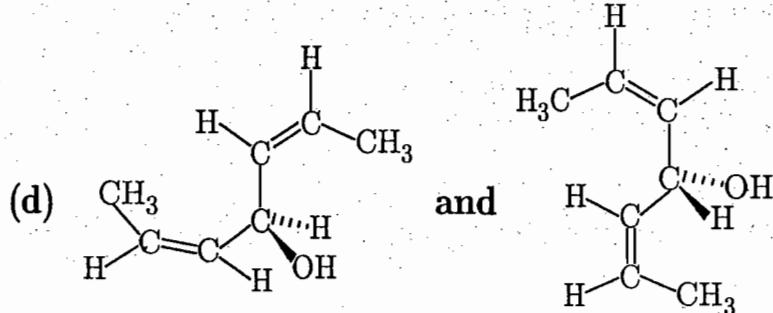
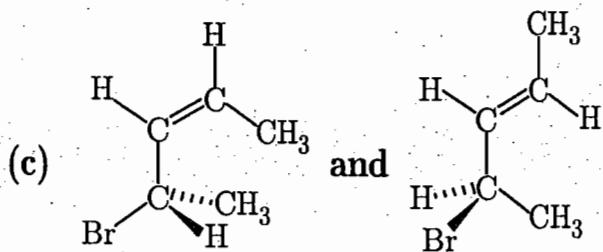
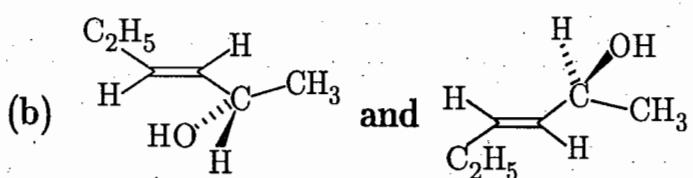
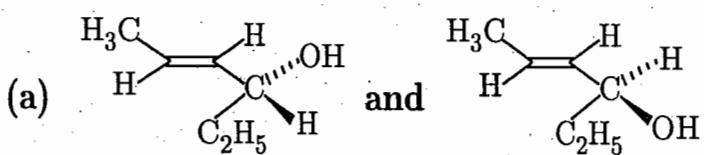


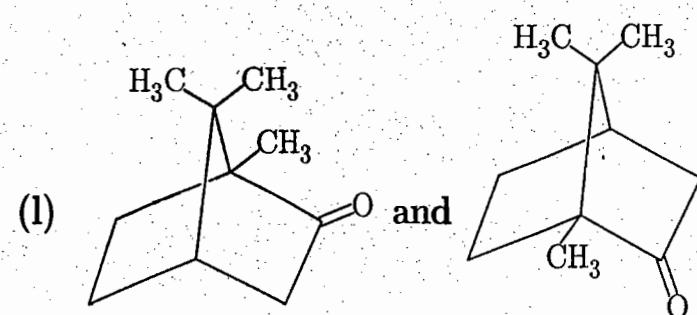
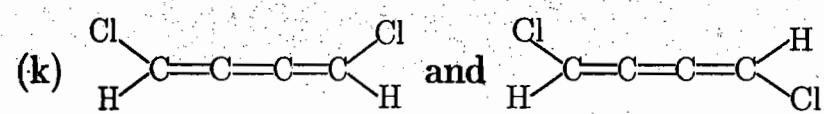
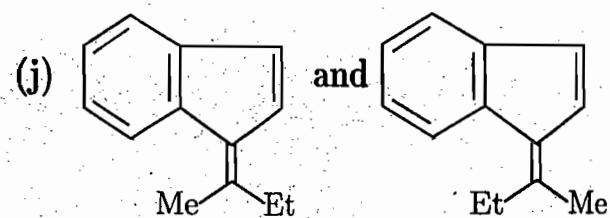
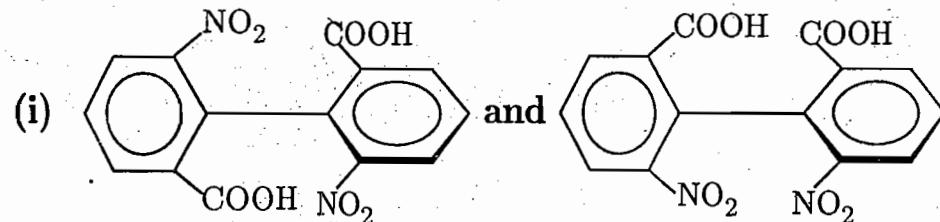
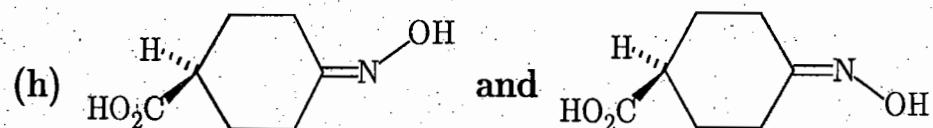
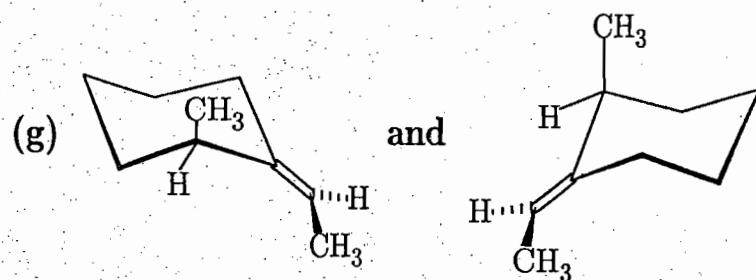
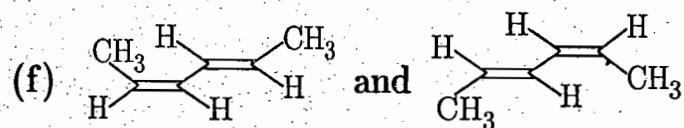
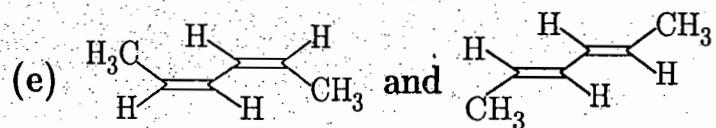
(r) Homomers

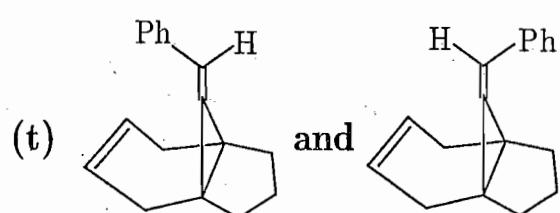
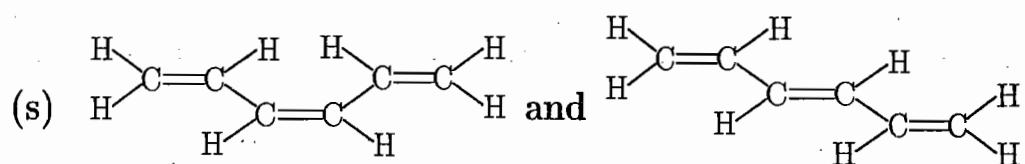
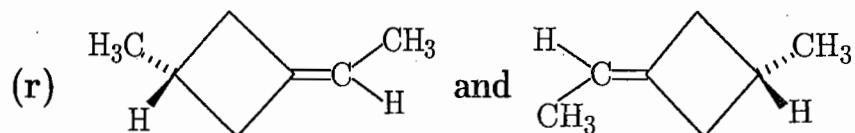
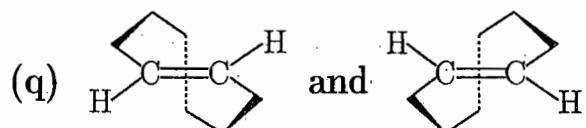
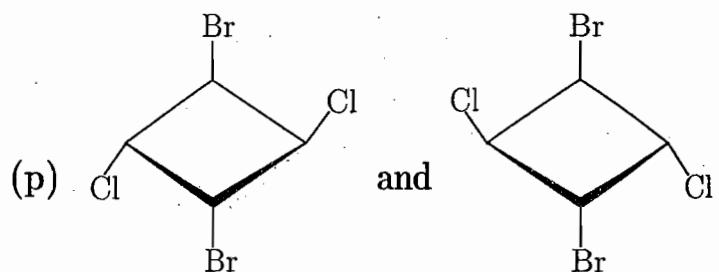
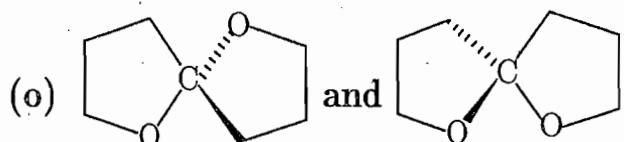
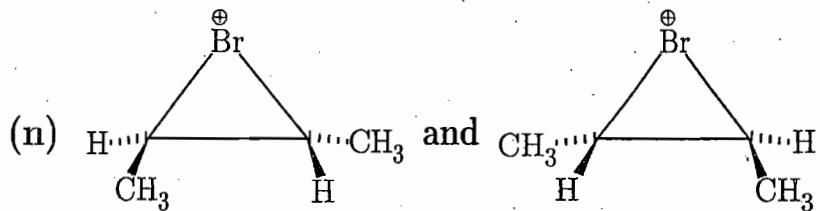
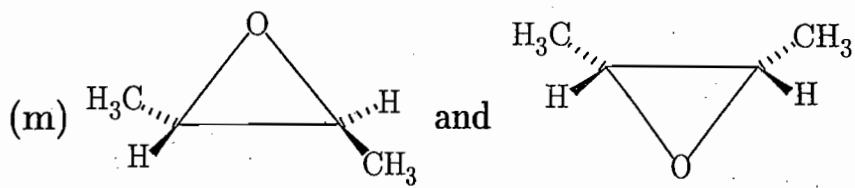
(s) Homomers

(t) Diastereoisomers

► 1.99 Label the following pairs of structures as homomers, enantiomers or diastereoisomers.

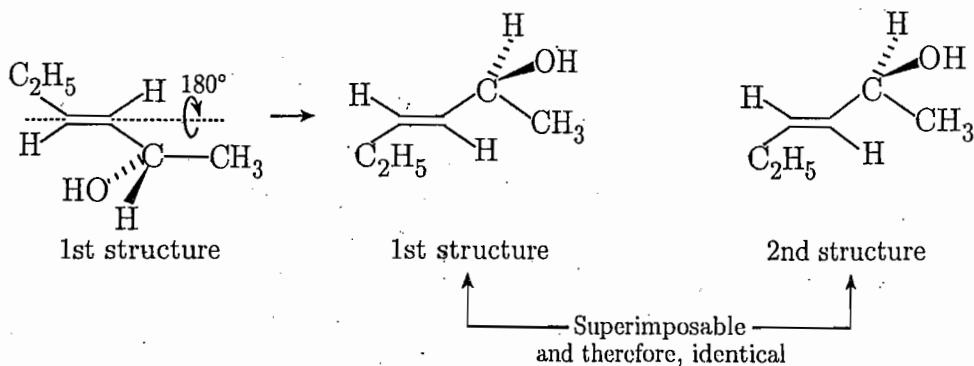






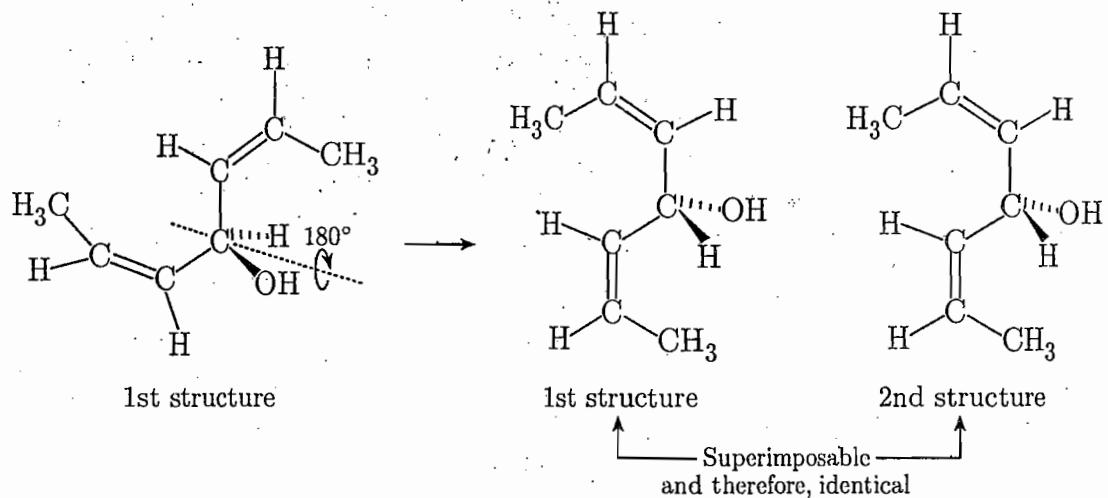
Ans. (a) Enantiomers

(b) Homomers :



(c) Diastereoisomers [(2Z, 4S) and (2E, 4R) isomers of 4-bromopent-2-ene]

(d) Homomers :

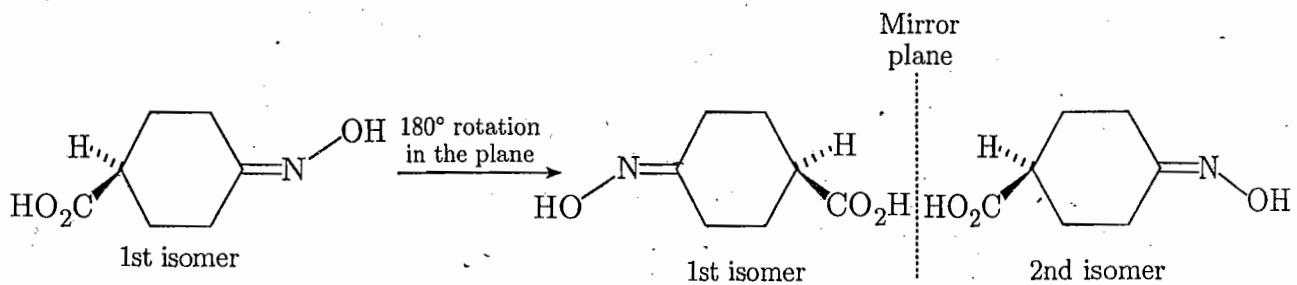


(e) Diastereoisomers [(2Z, 4Z) and (2E, 4E) isomers of 2,4-pentadiene]

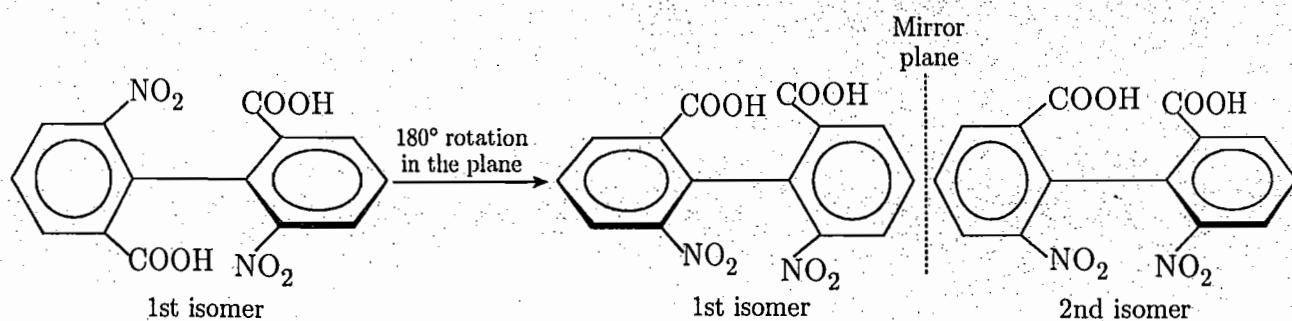
(f) Homomers [1st structure on 180° rotation in the plane of the paper gives the 2nd structure.]

(g) Diastereoisomer [they are (*S*, *Z*) and (*S*, *E*) stereoisomers]

(h) Enantiomers :



(i) Enantiomers :



(j) Diastereoisomers (geometric or *cis-trans* isomers)

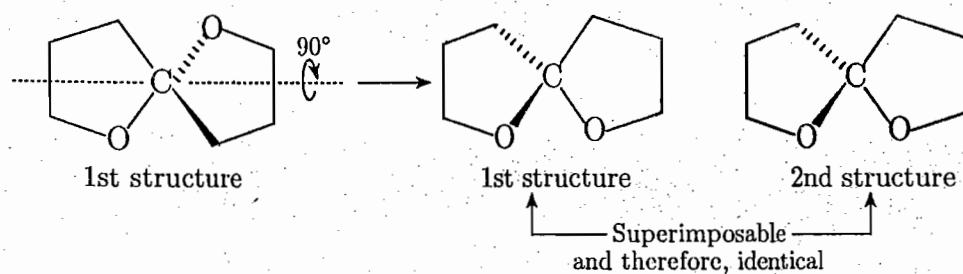
(k) Diastereoisomers (geometric or *cis-trans* isomers)

(l) Enantiomers

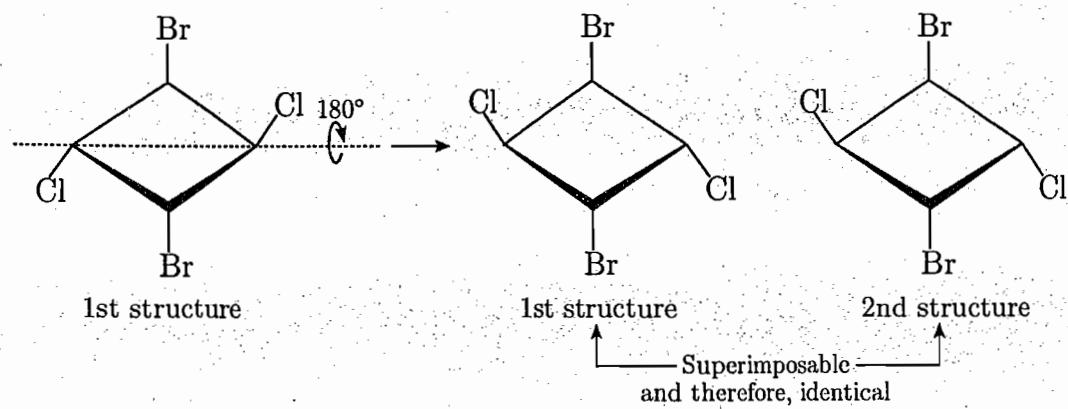
(m) Diastereoisomers (geometric or *cis-trans* isomers)

(n) Enantiomers

(o) Homomers :



(p) Homomers :



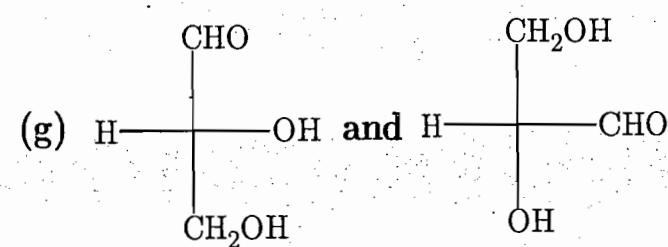
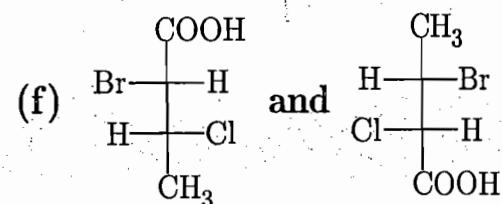
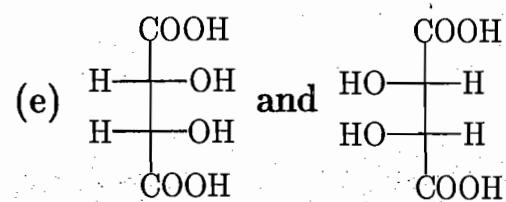
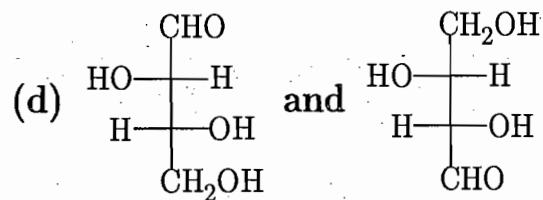
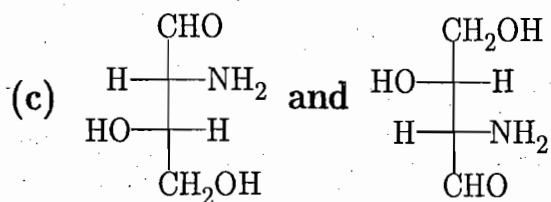
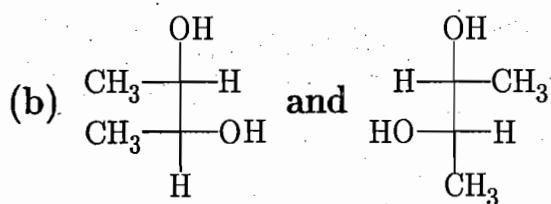
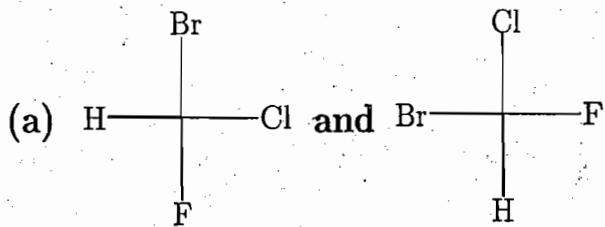
(q) Enantiomers

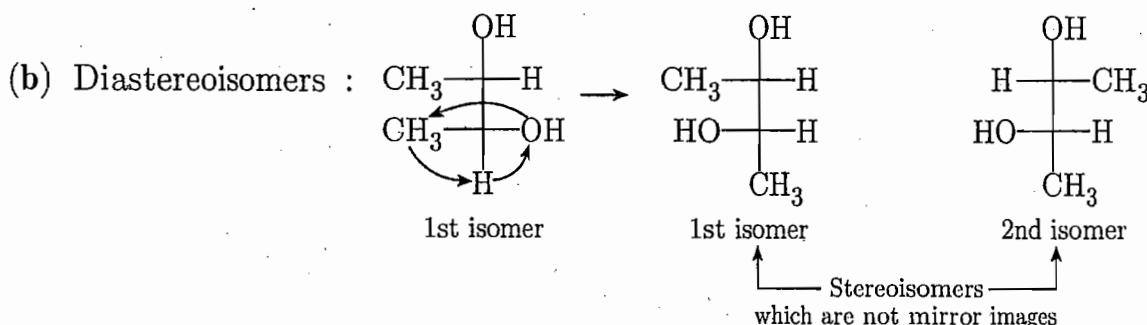
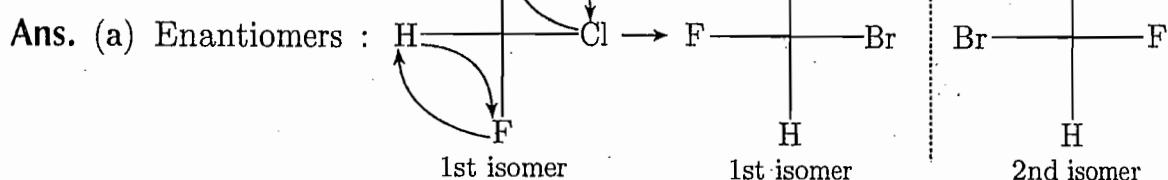
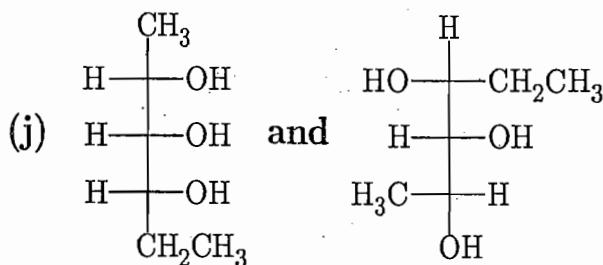
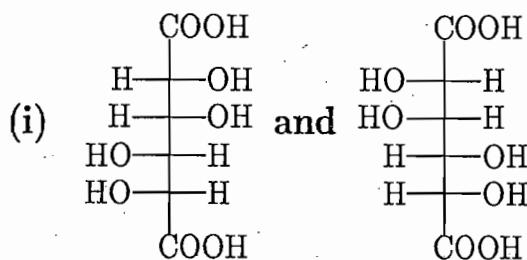
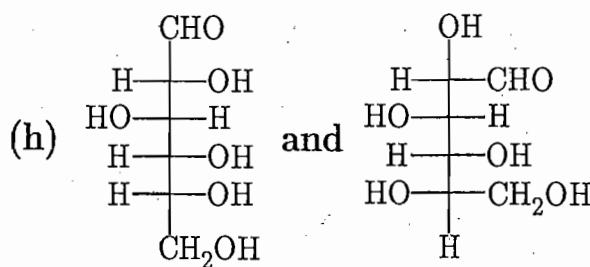
(r) Homomers

(s) Diastereoisomers (geometric or *cis-trans* isomers)

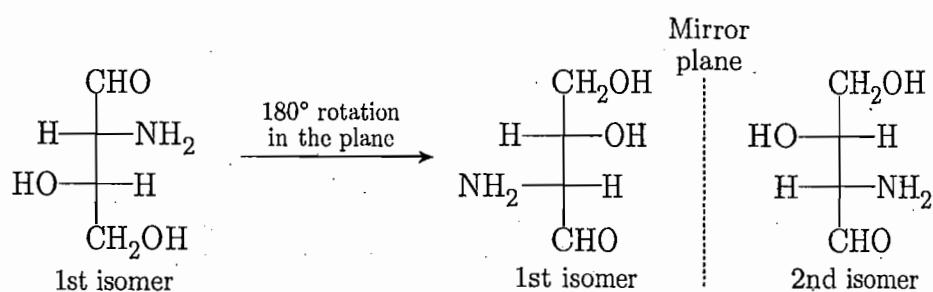
(t) Diastereoisomers (geometric or *cis-trans* isomers)

► 1.100 Label the following pairs of structures as homomers, enantiomers or diastereoisomers.





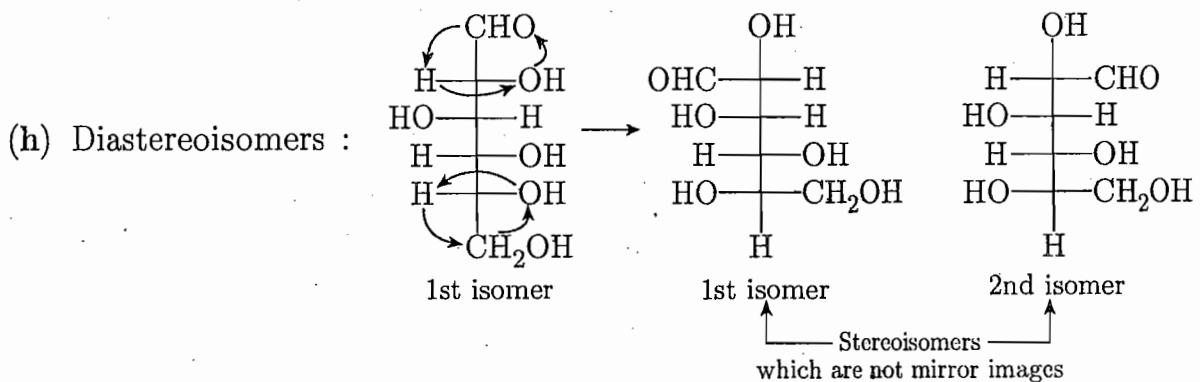
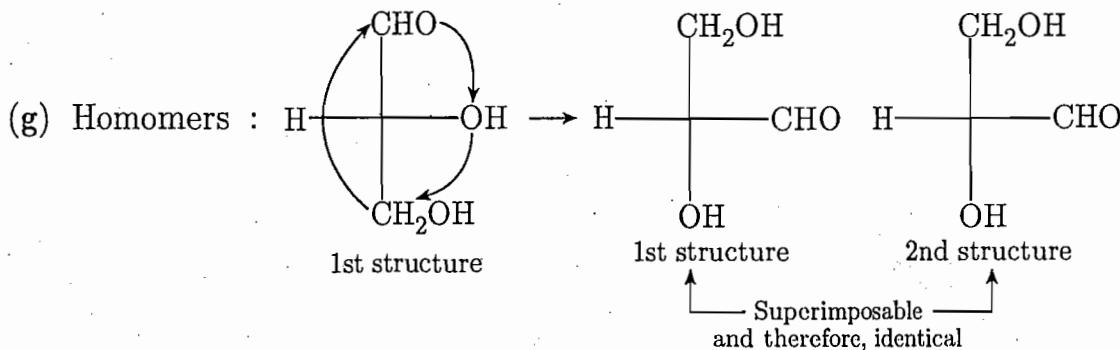
(c) Enantiomers :



(d) Homomers [the 1st structure produces 2nd structure on 180° rotation in the plane of the paper.]

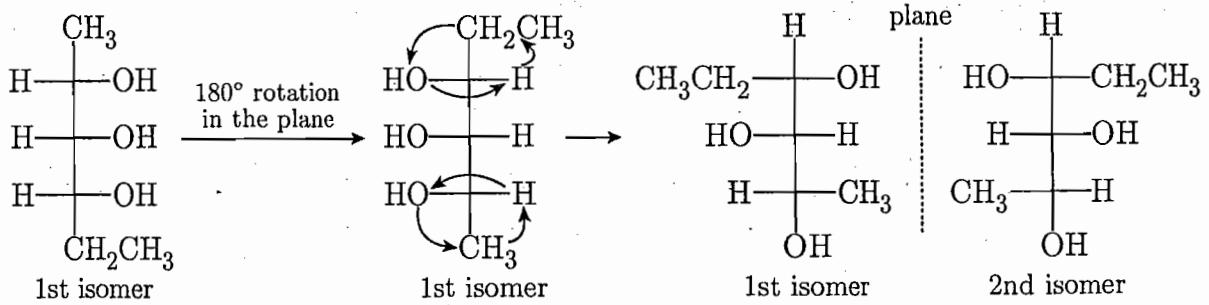
(e) Homomers [the 1st structure on 180° rotation in the plane produces the 2nd structure.]

(f) Constitutional isomers [2-bromo-3-chlorobutanoic acid and 3-bromo-2-chlorobutanoic acid]

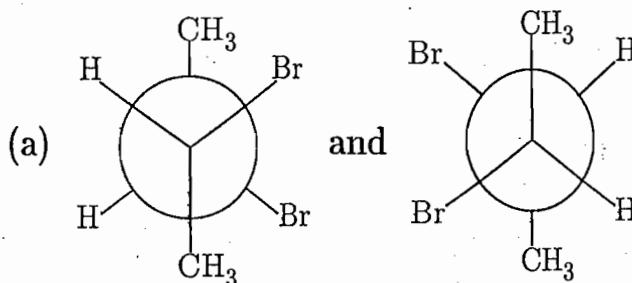


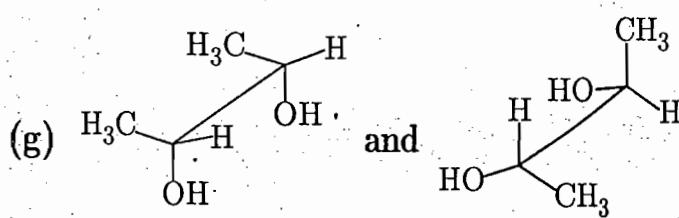
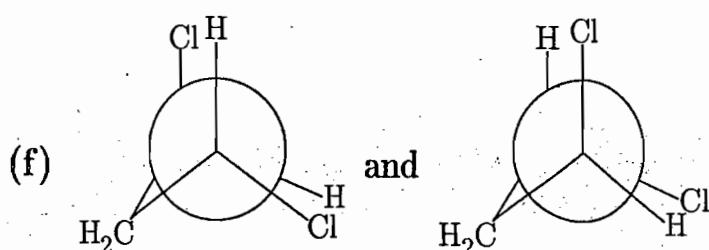
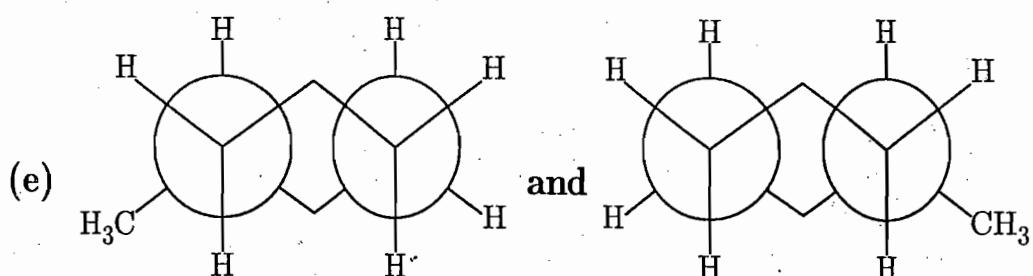
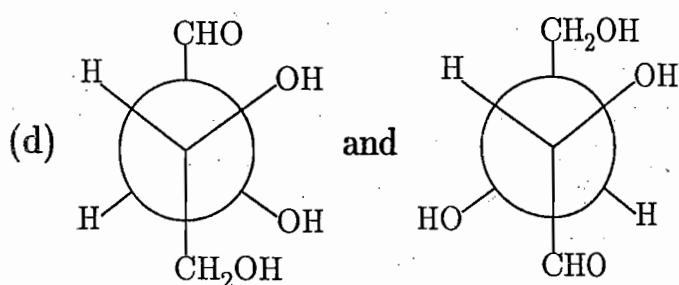
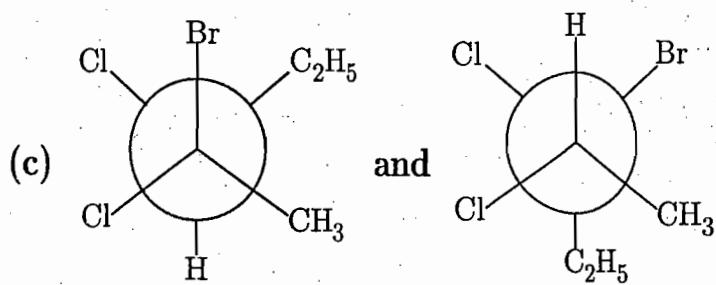
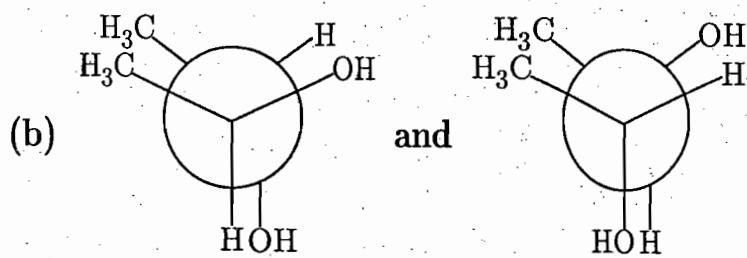
(i) Enantiomers

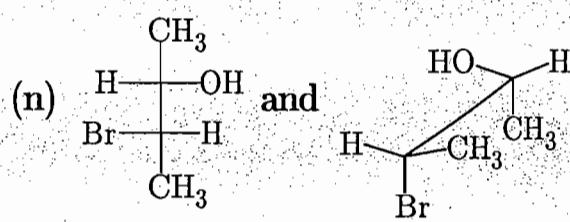
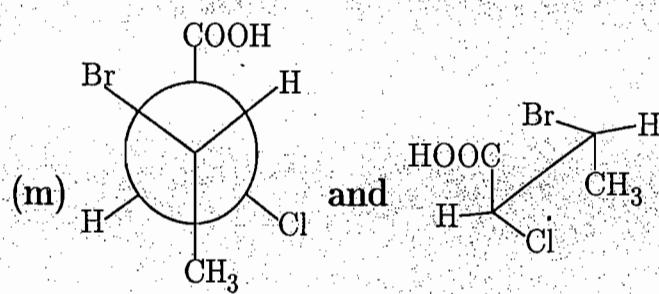
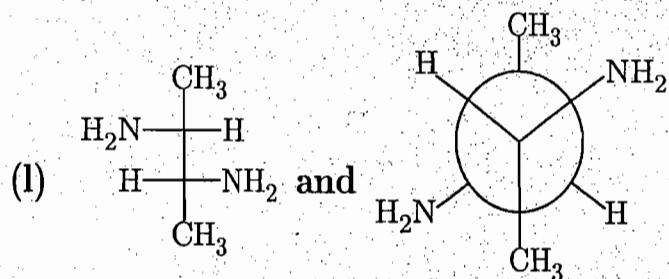
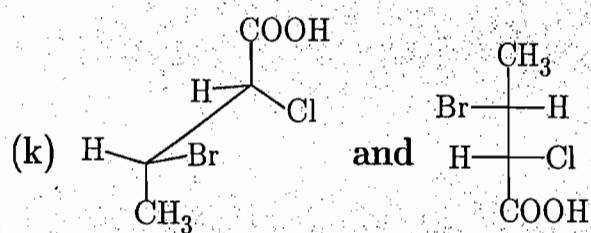
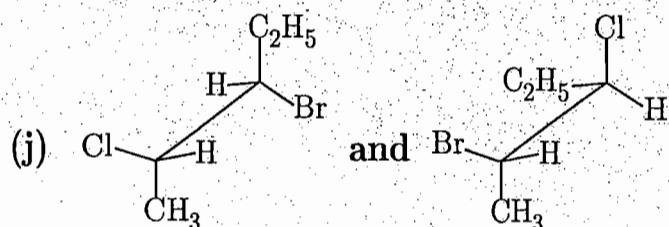
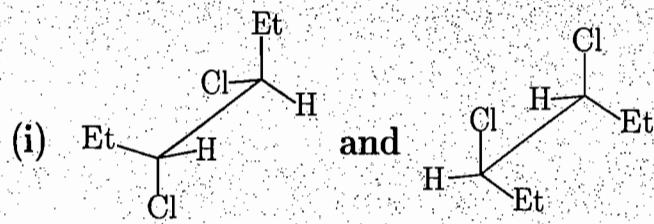
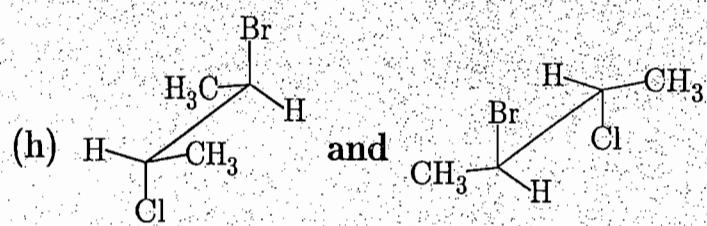
(j) Enantiomers :



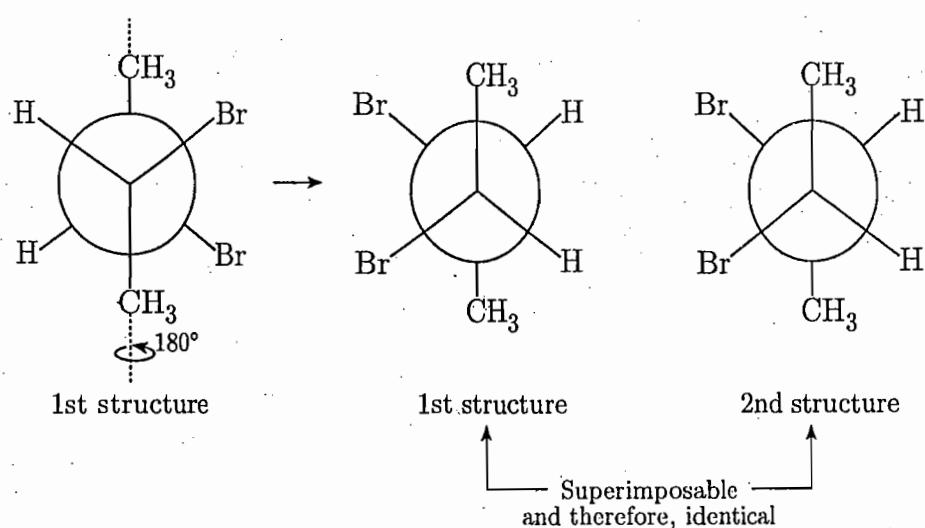
► 1.101 Label the following pairs of structures as homomers, constitutional isomers, enantiomers or diastereoisomers.



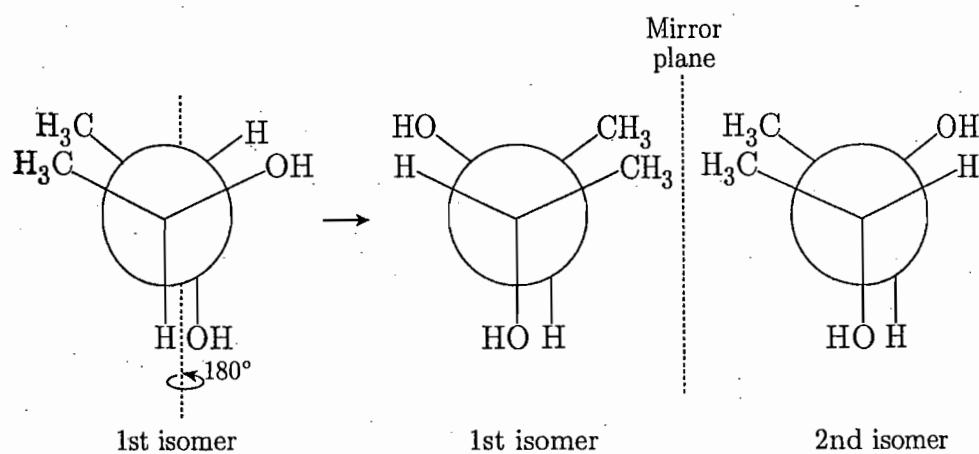




Ans. (a) Homomers :

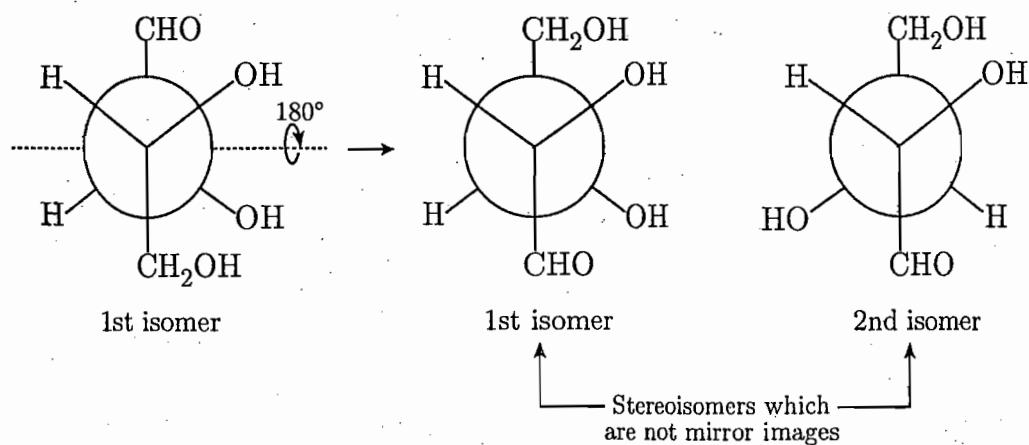


(b) Enantiomers :

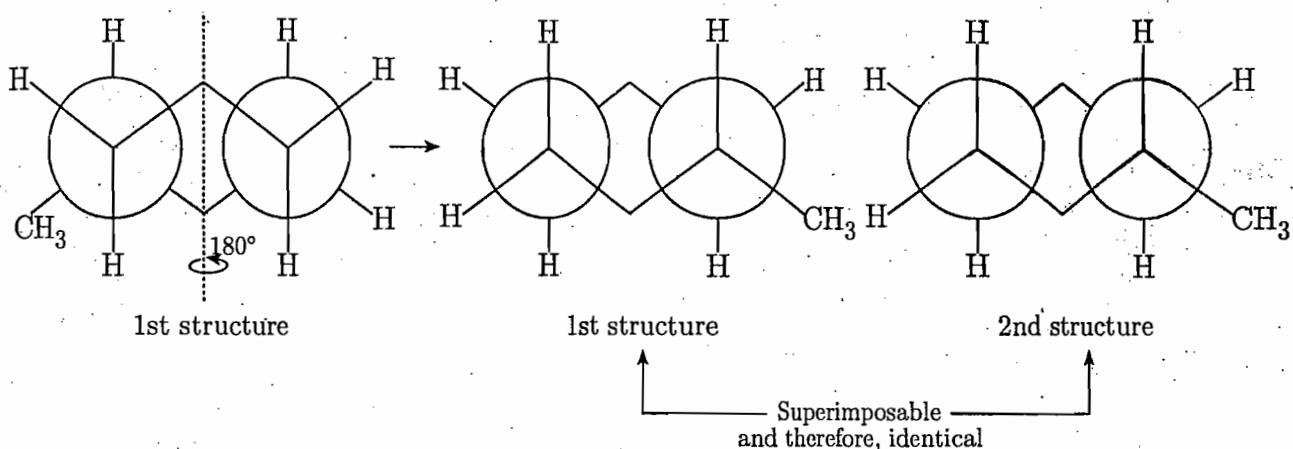


(c) Constitutional isomers [2-bromo-2,3-dichloropentane and 3-bromo-2,3-dichloropentane]

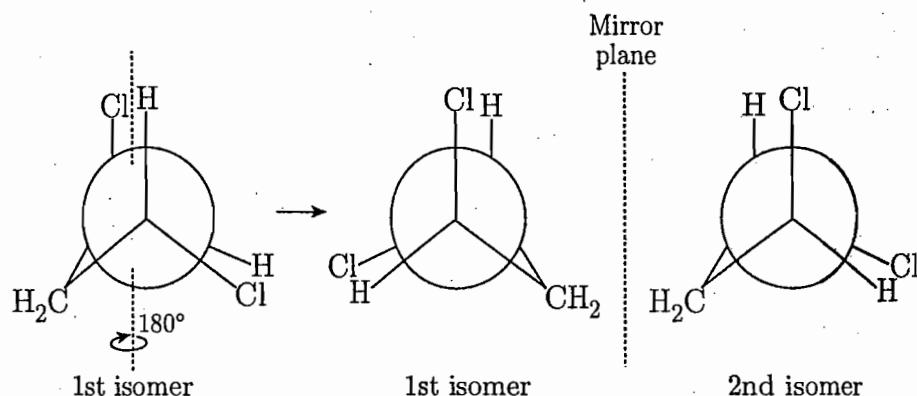
(d) Diastereoisomers :



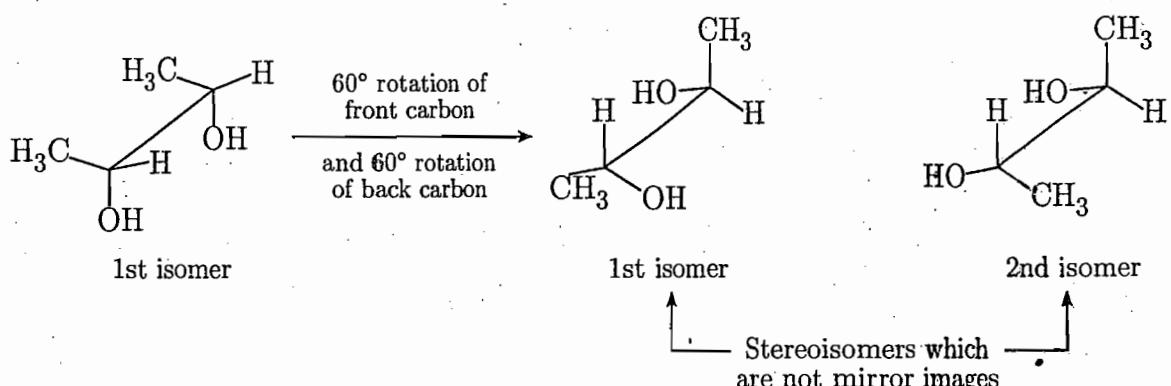
(e) Homomers :



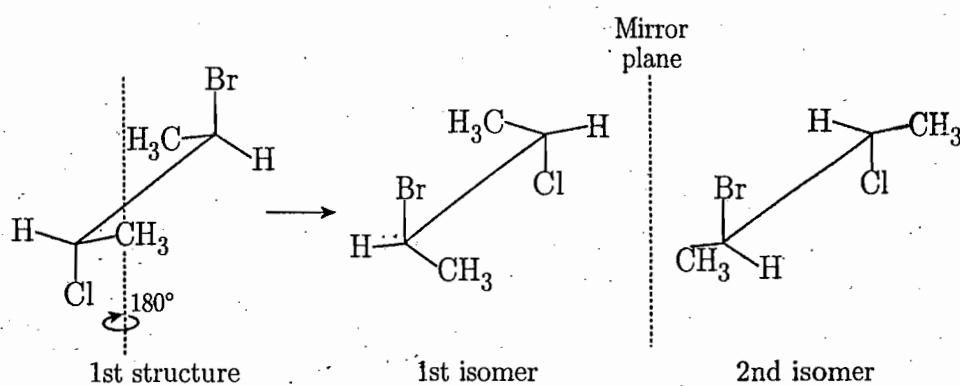
(f) Enantiomers :



(g) Diastereoisomers :



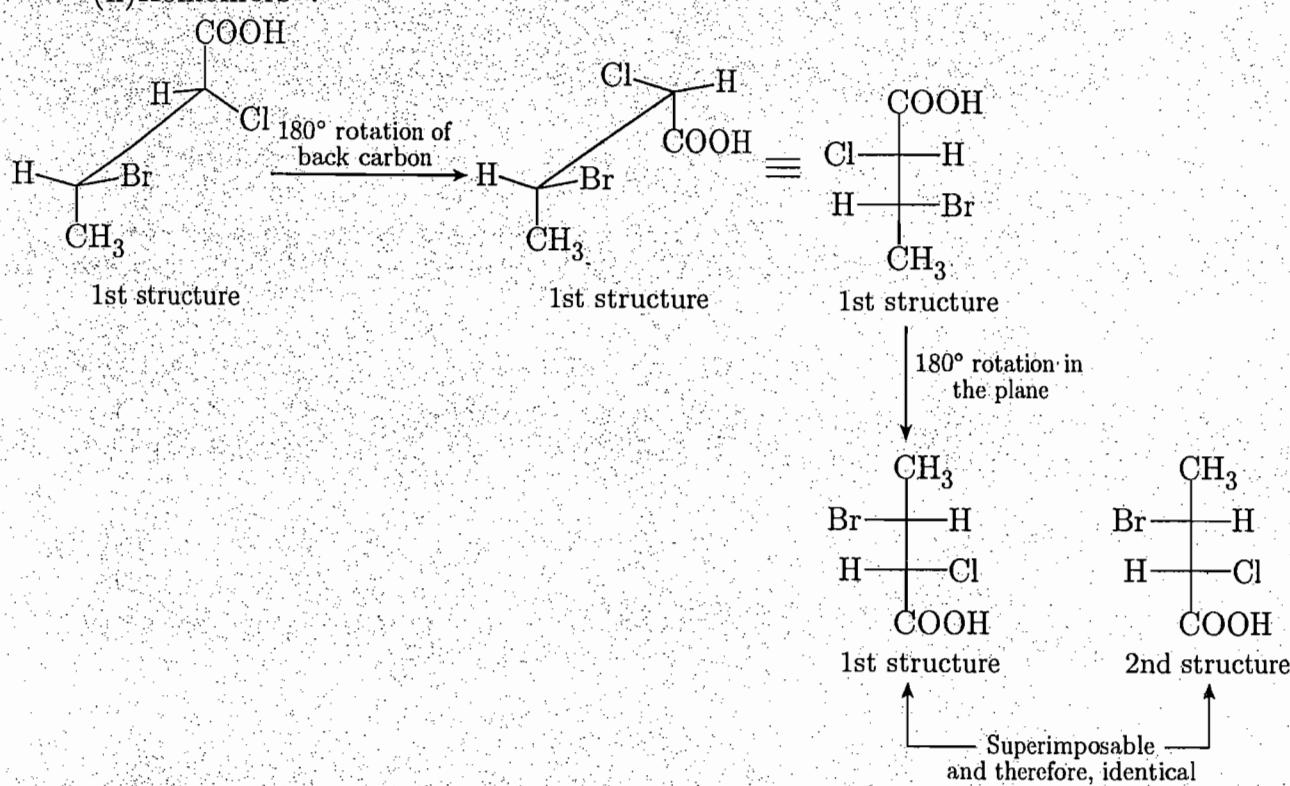
(h) Enantiomers :



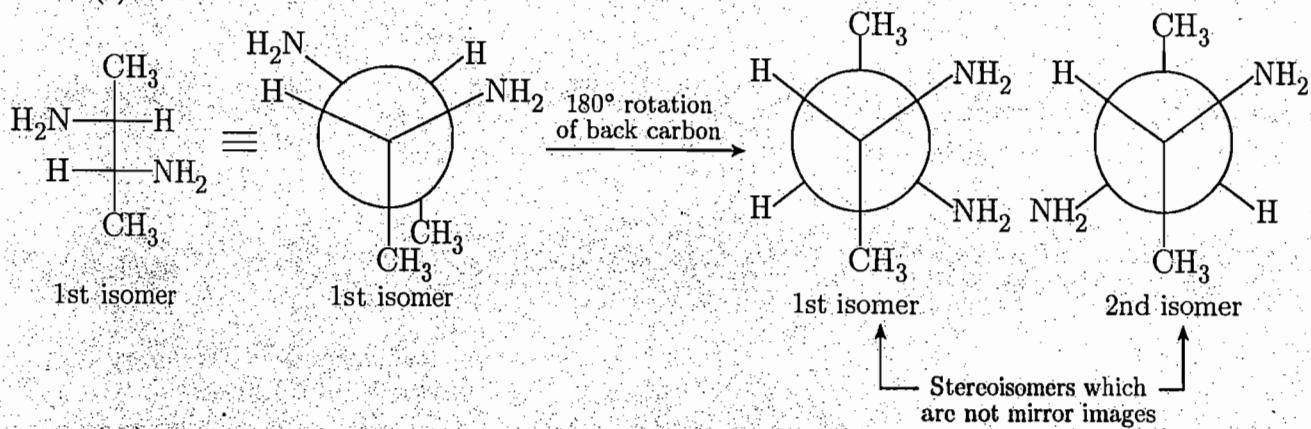
(i) Homomers [180° rotation of front carbon and 120° rotation of back carbon of 1st structure produces the 2nd structure]

(j) Constitutional isomers [3-bromo-2-chloropentane and 2-bromo-3-chloropentane]

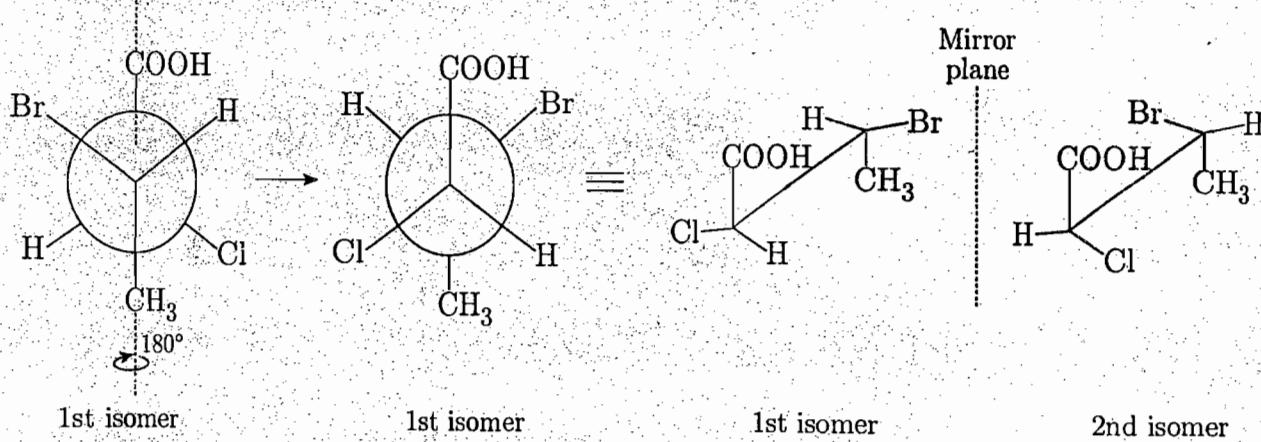
(k) Homomers :



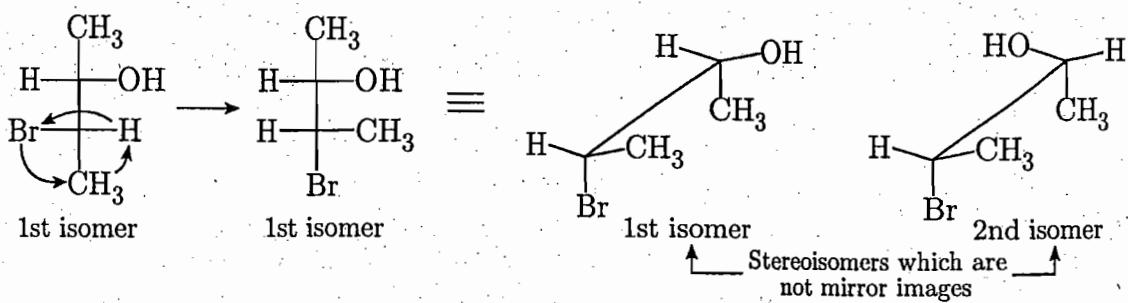
(l) Diastereoisomers :



(m) Enantiomers :



(n) Diastereoisomers :

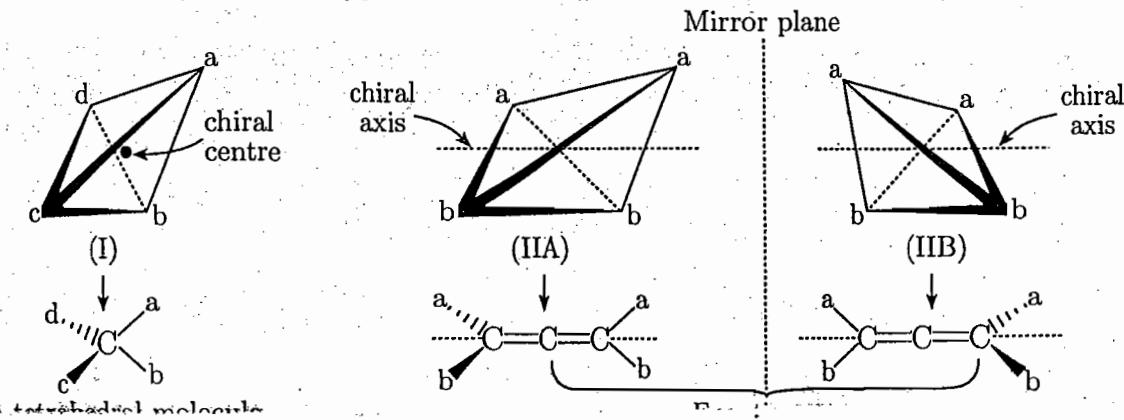
**CHIRALITY WITHOUT CHIRAL CENTRE (allens, biphenyls, etc.)**

► 1.102 The presence of a chiral centre is not always essential for a compound to exhibit chirality. Explain.

Ans. There are several molecules which are chiral not due to having one or more chiral centres (stereocentres) but due to other elements of chirality, namely, axial chirality, planar chirality and helicity. Suitably substituted allenes, alkylidenecycloalkanes, spiranes, adamantoids, biphenyls, *trans*-cycloalkanes, *ansa* compounds, cyclophanes, helicenes and benzophenanthrenes do not contain any formal chiral centre but exhibit enantiomerism due to the presence of a chiral axis or stereoaxis (first five cases), a chiral plane or stereoplane (next three cases) or having a helical structure (last two cases).

► 1.103 Explain the principle of axial chirality.

Ans. Elongated tetrahedron approach can be applied to explain the principle of axial chirality. A chiral centre (stereocentre) can be detected in a molecule when the four different ligands of a central atom are located on corners of a tetrahedron, e.g., C in C_{abcd} molecule (I) is a chiral centre. When this centre is replaced by a linear grouping, e.g., $C-C$ or $C=C=C$, the tetrahedron becomes elongated, i.e., extended along the axis of the grouping. Such an elongated tetrahedron has lesser symmetry than a regular tetrahedron and that elongated tetrahedron will be chiral if only the two ligands at each end of the axis are different, i.e., the minimum condition for chirality is that ligand $a \neq b$. Thus, structure (IIA), which represents an elongated tetrahedron (a desymmetrised tetrahedron of type C_{aabb}) becomes chiral and have enantiomeric relationship with its mirror image (IIB). This is illustrated by an allene $abC=C=Ca'b$. The axis along which the tetrahedron is elongated (shown by dotted line) is called the *chiral axis* or the *stereoaxis* and the molecular chirality of this type is termed as *axial chirality*.

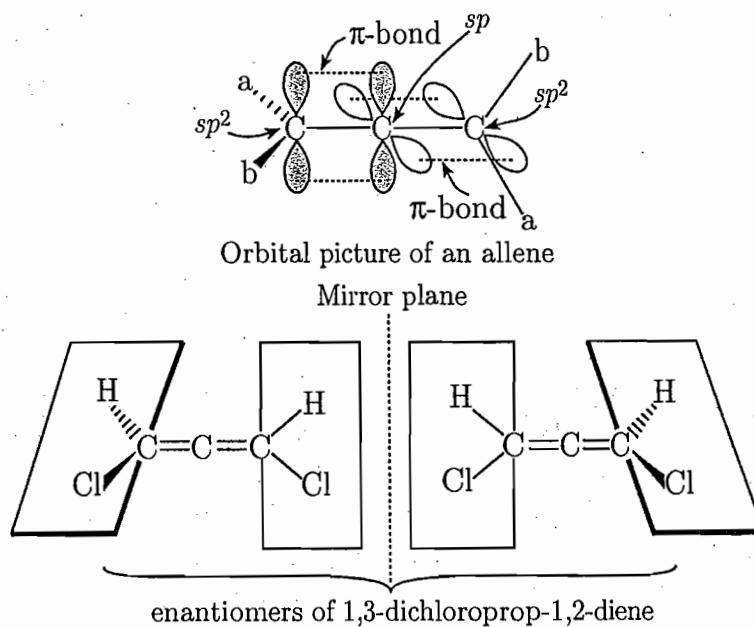


[An exchange of a pair of ligands around the chiral axis of one enantiomer leads to another enantiomer.]

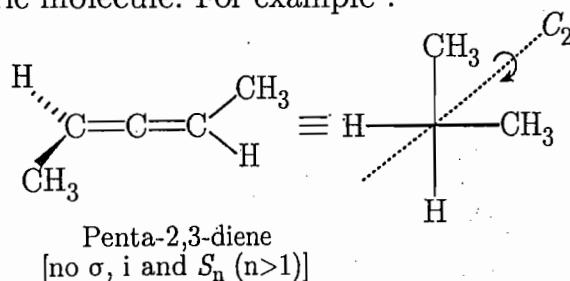
- 1.104 (a) What is the condition for a substituted allene ($abC=C=Ca$) to be chiral?
 (b) Explain with the aid of orbital structures why allenes of the type $abC=C=Ca$, e.g., 1,3-dichloroprop-1,2-diene, is a chiral molecule, even though it has no chiral carbon atom.
 (c) What are dissymmetric and asymmetric allenes? Illustrate with suitable examples.

Ans. (a) The condition for chirality of an allene of the type $abC=C=Ca$ is that the ligand $a \neq b$.

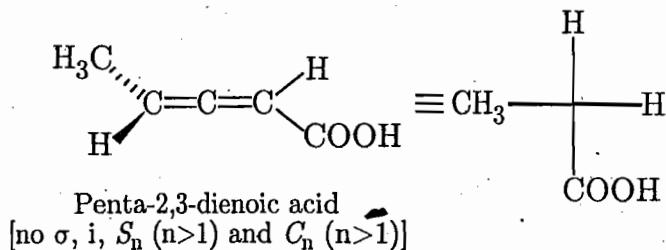
(b) The central carbon atom of an allene is sp hybridized (linear) and the two end carbon atoms are sp^2 hybridized (trigonal). The sp hybridized central carbon atom uses its two mutually perpendicular p orbitals to form two π bonds with the two outer carbon atoms. Therefore, the two π bonds must also be perpendicular. Consequently, the terminal ligands lie in mutually perpendicular planes. This arrangement places the four ligands in the positions of an elongated tetrahedron. It is for this reason, an allene of the type $abC=C=Ca$, e.g., 1,3-dichloroprop-1,2-diene, is a chiral molecule (exists in two enantiomeric forms) even though it has no chiral carbon atom.



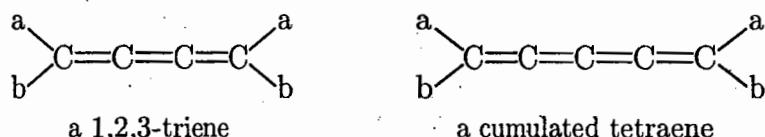
- (c) A chiral allene of the type $abC=C=Ca$ has a C_2 simple axis. Therefore, it represents a dissymmetric molecule. For example :



In a chiral allene of the type $abC=C=Ceb$ or $abC=C=Ced$, even the C_n ($n > 1$) axis is absent. Therefore, it represents an asymmetric allene. For example :

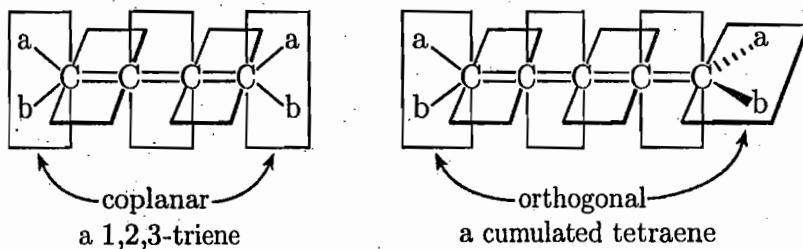


► 1.105 1,2,3-Trienes exhibit *cis-trans* isomerism, but not enantiomerism whereas cumulated tetraenes exist as a pair of enantiomers and do not exhibit *cis-trans* isomerism.



Give reasons for this differences in isomer type, and suggest a rule for predicting the kind of isomerism one would expect from structures of the kind $abC=(C)_n=Cab$.

Ans. The outside π orbitals in the triene are oriented at right angles to the central π orbital (the two central carbon atoms are sp -hybridized). The terminal carbon units (the terminal carbon atoms along with their substituents) are therefore coplanar, and the geometry of this molecule is that of an elongated alkene. Because of this, a 1,2,3-triene in which $a \neq b$ exhibit *cis-trans* isomerism. If still another cumulated double bond is added as in the tetraene, the terminal carbon units become perpendicular to each other and the geometry of the molecule is that of an elongated tetrahedron. Because of this, a cumulated tetraene in which $a \neq b$ exhibit enantiomerism.

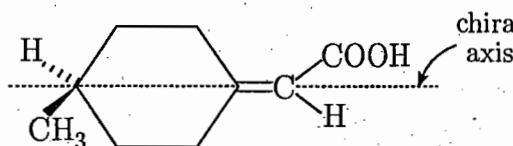


Compounds belonging to the class $abC=C_n=Cab$ will be coplanar and may exhibit *cis-trans* isomerism if n is $0, 2, 4, 6, \dots$ etc. and $a \neq b$. Compounds in which n is odd ($1, 3, 5, \dots$) will not be coplanar and will exhibit enantiomerism if $a \neq b$.

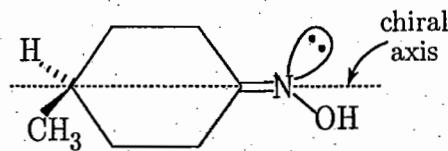
► 1.106 Comment on the chirality of alkylidenecycloalkanes, spiranes and adamantanes.

Ans. The replacement of one double bond in an allene by a ring produces alkylidenecycloalkenes while replacement of both the double bonds in an allene by rings gives spiranes. Since the basic geometry of an allene system remains unchanged (two terminal methylene planes are perpendicular to each other as in allenes), these

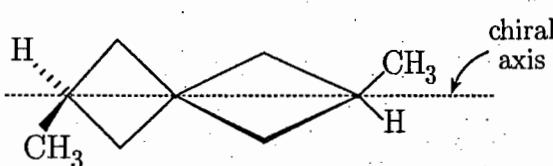
compounds, when suitably substituted (pairs of geminal ligands are non-equivalent, i.e., $a \neq b$), are found to possess axial chirality. Oximes in which the sp^2 -carbon in an alkylidene cycloalkane is replaced by nitrogen has also been obtained as enantiomers. Adamantanes are highly rigid molecules in which the diametrically opposite methylene planes are perpendicular to each other. When appropriately substituted (i.e., $a \neq b$), they are found to possess axial chirality. For example :



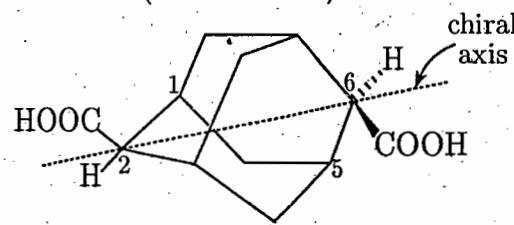
4-Methylcyclohexylidene acetic acid
(a chiral alkylidene cycloalkane)



4-Methylcyclohexanone oxime
(a chiral oxime)



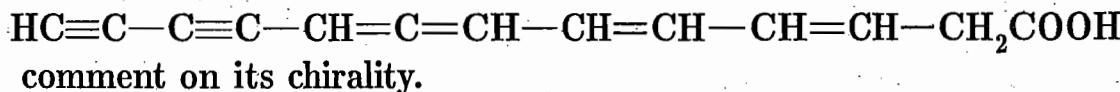
2,6-Dimethylspiro[3,3]heptane
(a chiral spirane)



Adamantane-2,6-dicarboxylic acid
(a chiral adamantan)

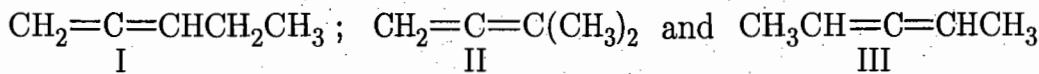
► 1.107 (a) C_5H_8 represents three isomeric allenes. Comment on their chirality.

(b) The structure of the naturally occurring antibiotic mycomycin is as follows :



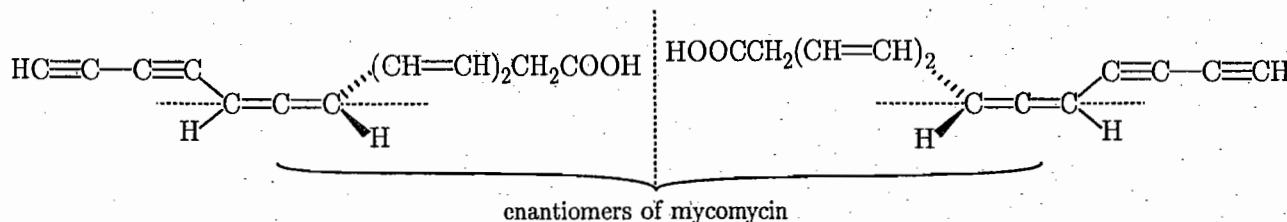
(c) An optically active allene A (C_8H_{14}) when hydrogenated gives a saturated compound B (C_8H_{18}) which is also optically active. Identify the compounds A and B.

Ans. (a) Structures of three isomeric allenes having molecular formula C_5H_8 are as follows :

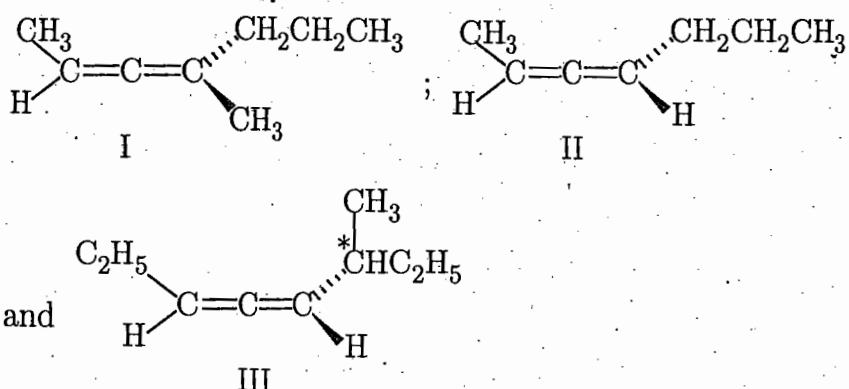


Among these isomeric allenes I and II are achiral, but III is chiral (exists as two enantiomers) because each of the terminal sp^2 carbon atoms contains non-identical substituents.

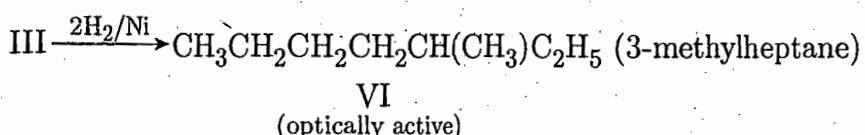
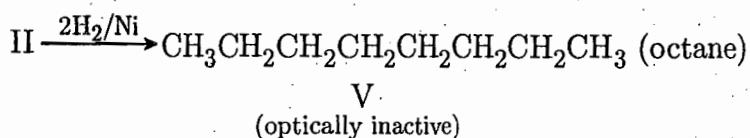
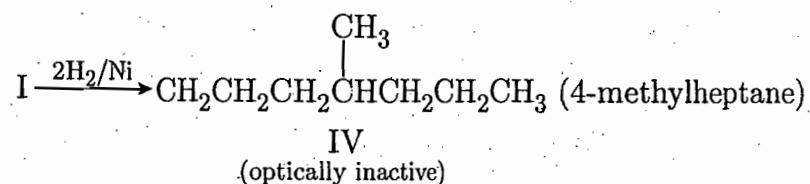
(b) The antibiotic mycomycin is a chiral allene (exists as two enantiomers) in which each of the terminal sp^2 carbon atom contains non-identical ligands. The chirality arises due to nonplanar arrangement of four ligands about an axis called a chiral axis or stereoaxis.



(c) C_8H_{14} represents three optically active allenes (I, II and III) :



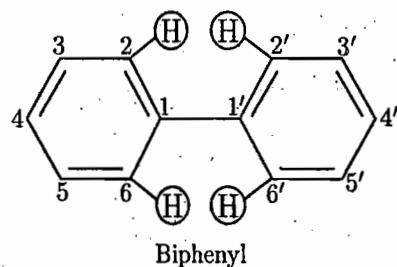
On hydrogenation I and II produce two optically inactive alkanes but III produces an optically active alkane.



Therefore, the compound A is III and the compound B is VI.

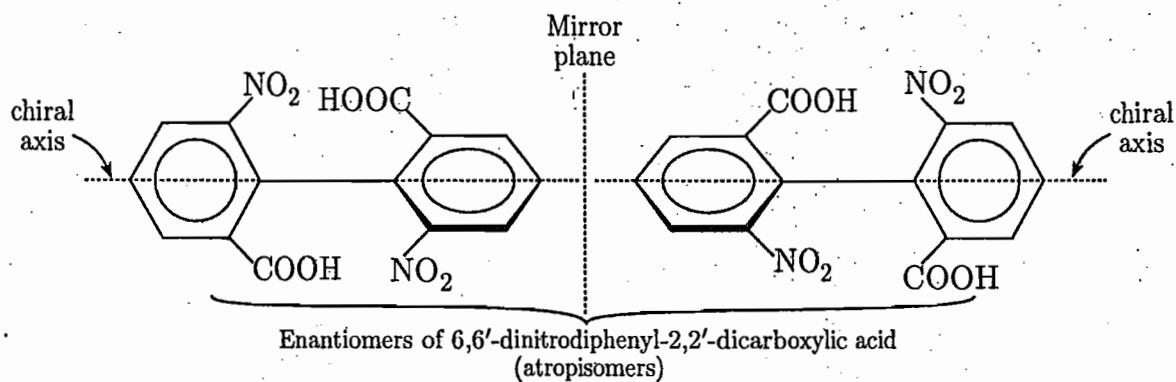
- 1.108 (a) Write the structure of biphenyl. Explain why the rotation about the pivotal bond is not restricted in biphenyl molecule.
- (b) What is meant by the term *atropisomerism*? What are atropisomers? Give examples of two optically inactive atropisomers.
- (c) What are the conditions for chirality in biphenyls?
- (d) Give an energy profile diagram for a 360° rotation around the pivotal bond of an *ortho*-substituted biphenyl.
- (e) Explain why many optically active biphenyls undergo racemization by boiling in solution. What is called *buttressing effect*?
- (f) Unlike allenes enantiomerism of substituted biphenyls is temperature dependent. Explain.
- (g) Give a direct chemical evidence for the non-planar configuration of the optically active biphenyls.
- (h) Give example of a biphenyl which may be optically active despite having the same substituents at 2,6 or 2',6'-positions.

Ans. (a) Biphenyl is represented by the following structure in which the two phenyl groups are linked by a single bond ($C_{sp^2}-C_{sp^2}$), called the *pivotal* bond.



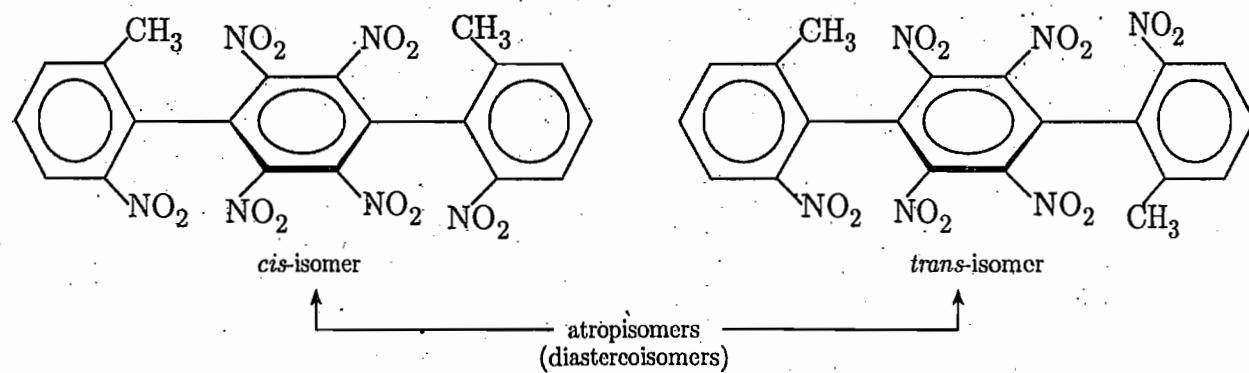
Since the distance between *ortho* hydrogen atoms in adjacent ring in the planar conformation is considerably greater than twice the van der Waals radius of hydrogen, the rotation about the pivotal bond is not restricted.

(b) If *ortho* positions of biphenyl are occupied by sufficiently large groups, free rotation about the single bond joining the two phenyl groups (the *pivotal* bond) is no longer possible because the planar conformations are destabilized due to steric repulsion. As a consequence, the two phenyl planes remain approximately perpendicular to each other. Provided each ring has no vertical plane of symmetry (i.e., dissymmetrically substituted), a non-planar combination of two such phenyl groups would give rise to optical activity because of axial chirality. For example, 6,6'-dinitrodiphenyl-2,2'-dicarboxylic acid have been resolved into its enantiomers.



This type of stereoisomerism due to restricted rotation around a single bond is known as *atropisomerism* and the isomers are called *atropisomers*.

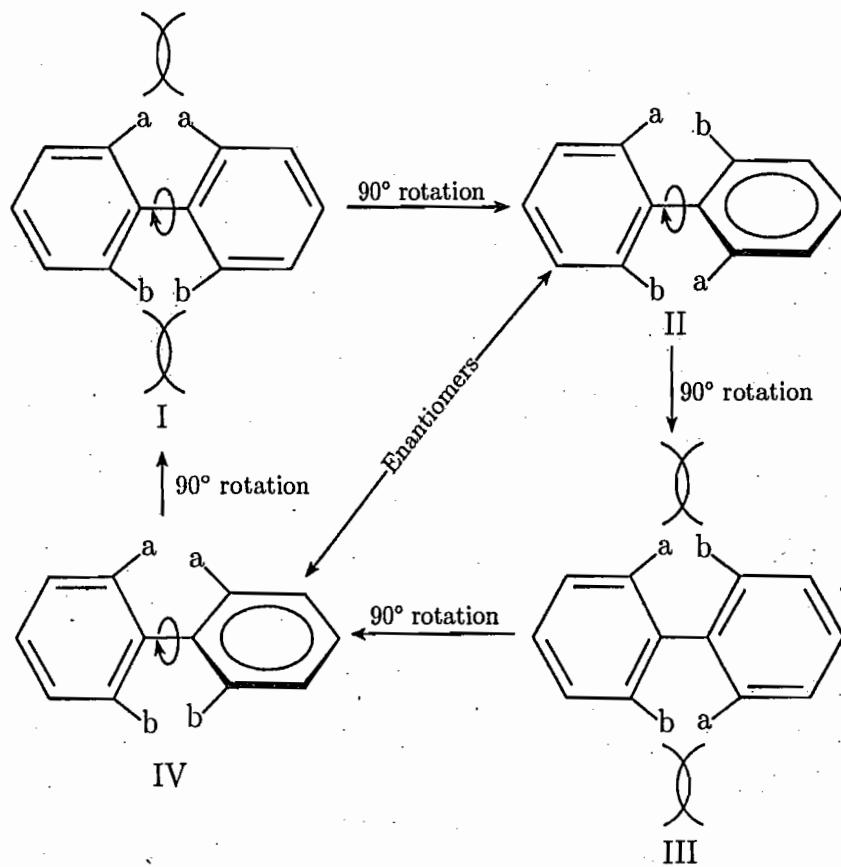
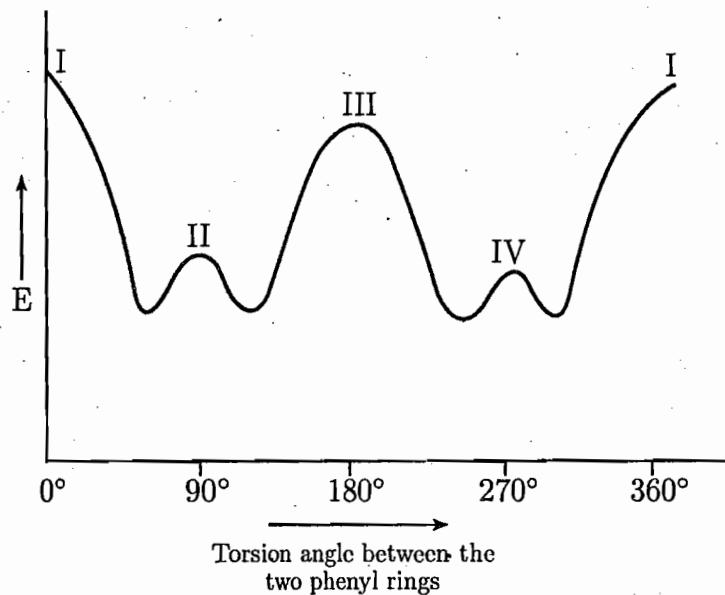
The following terphenyl derivatives are two atropisomers which are optically inactive (achiral) due to the presence of a σ -plane.



(c) The conditions for chirality in biphenyls are as follows :

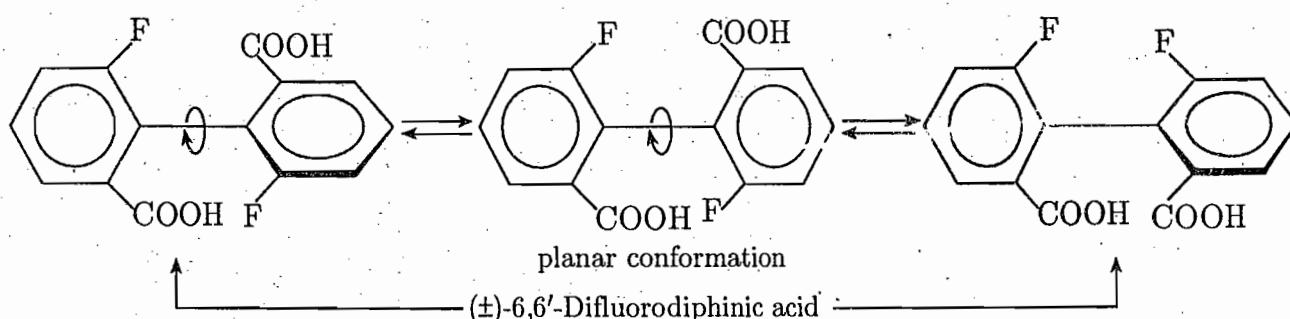
- (i) There must be a chiral axis in the molecule (i.e., orthogonal orientation of the two benzene rings and absence of a vertical plane of symmetry) and
- (ii) the energy barrier separating the enantiomers must have a minimum value ($80-100 \text{ kJ mol}^{-1}$ at room temperature) so that two enantiomers might be stable configurationally.

(d) The energy profile diagram for a 360° rotation around the pivotal bond of an *ortho*-substituted biphenyl is as follows :



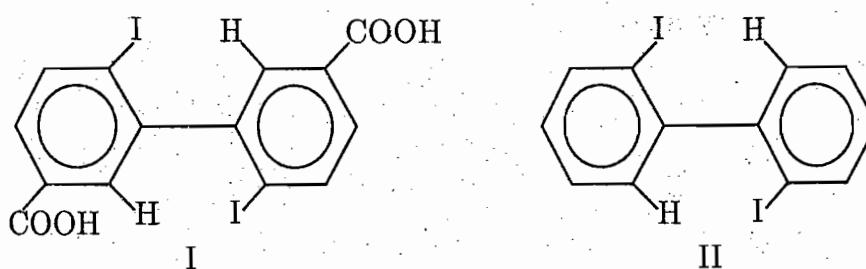
The two chiral conformations (II and IV) are flanked by two minima (in each case). This is because of the fact that the resonance stability arising from *p-p* overlap is minimum when the rings are perfectly orthogonal. When the two rings are coplanar then the steric interaction is maximum. The two minima before and after each chiral conformation are due to a compromise between the steric interaction (a destabilising i.e., energy-increasing factor) and resonance interaction (a stabilising i.e., energy-decreasing factor) and they actually represent the preferred conformations of the enantiomers in which the two phenyl planes are approximately but not exactly perpendicular to each other.

(e) Heating increases the amplitude of vibrations of the substituents and also the amplitude of vibration of pivotal bond (between two aryl groups). In addition to these bond stretchings, the angle between ring and substituents are also deformed. These causes the rings to pass through a common plane easily and as a result, racemization occurs. For example, the following *ortho*-substituted biphenyl undergoes racemization by heating in acetic anhydride for ten minutes.



[In the above energy profile diagram II \rightleftharpoons IV represents a racemization process.]

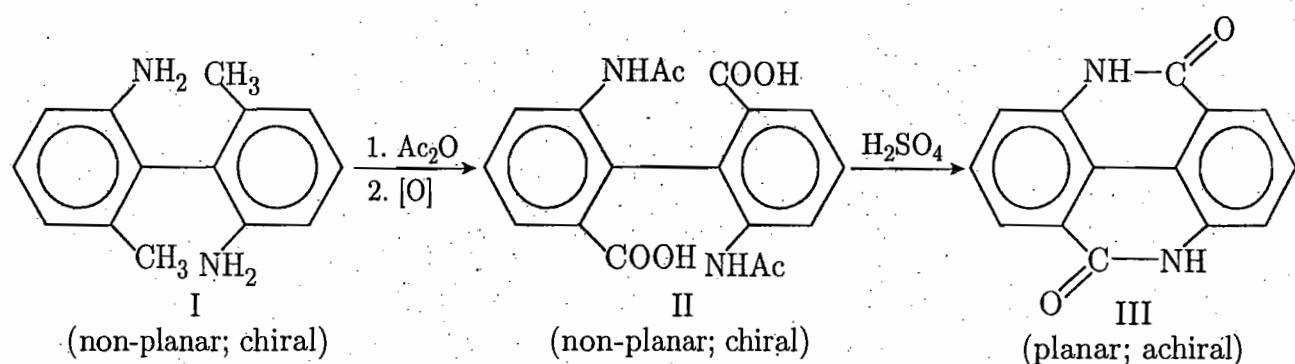
When there present a substituent at the *meta*-position with respect to the pivotal bond, then activation energy for racemization of chiral biphenyls is increased due to prevention of the outward bending of an *ortho*-substituent in the coplanar conformation. This is called *buttressing* effect. For example, the compound I has higher activation energy of racemization than the compound II.



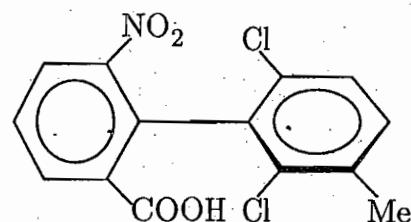
(f) The interconversion between the two atropisomers through rotation about the single bond increases with increase in temperature and above a minimum temperature the rate of interconversion is so high that they cannot be separated. That is, at higher temperature their configurational stability is lost. It thus follows that enantiomerism (i.e., to exist as two enantiomeric forms) of substituted biphenyls is temperature dependent.

On the other hand, interconversion between two enantiomeric allenes is not possible because the two terminal sp^2 carbons are joined not by a single bond but by two cumulated π bonds and their free rotation is not possible.

(g) The compound I and its acetyl derivative II are chiral (resolvable). However, when the *ortho* positions are joined by planar rings, the resulting compound III becomes achiral (non-resolvable). Since atropisomerism disappears by planar ring formation, optically active biphenyls must have non-planar configurations.



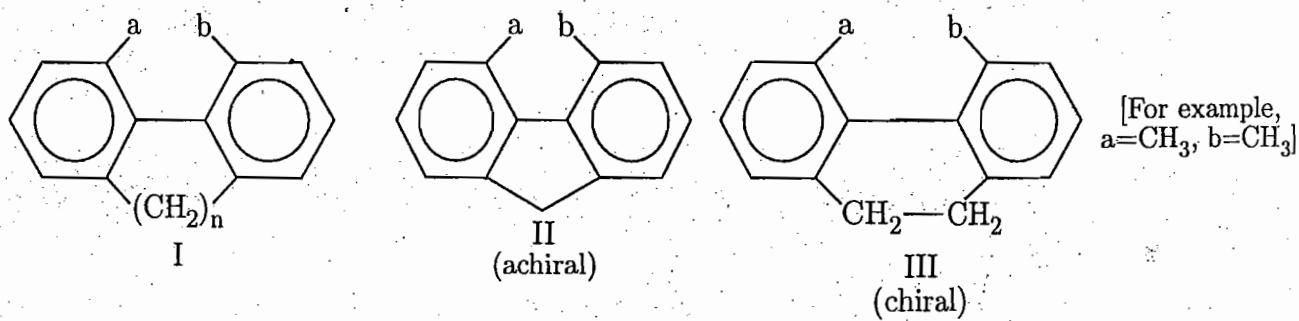
(h) The following biphenyl is optically active despite having the same substituents at the 2,6-positions.



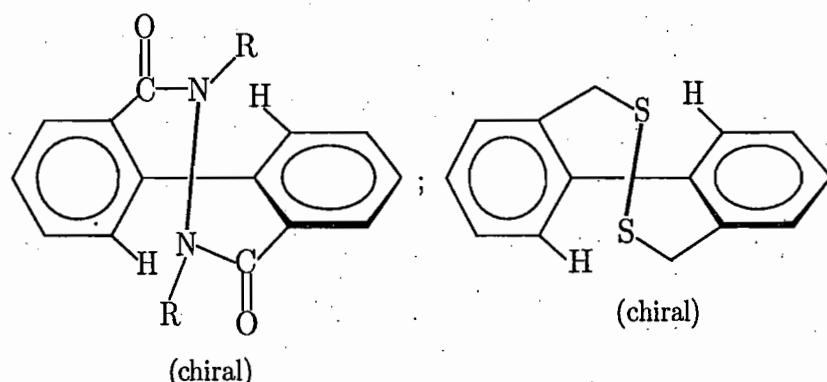
[Regardless of the bulk of the *ortho*-substituents a biphenyl cannot be optically active if the substituents at the 2,6 or 2',6'-positions are the same, i.e., if one ring has a vertical plane of symmetry. However, the addition of a substituent at the *meta* position destroying the symmetry will lead to resolvability.]

► 1.109 Discuss atropisomerism in 2-2' bridged biphenyls.

Ans. When in a biphenyl, 2 and 2'-positions are bridged with rings of different sizes (I), three situations may arise. When $n = 1$, the compound is a planar disubstituted fluorene (II) which does not permit atropisomerism. When $n = 2$, the compound is a dihydropheanthrene (III) and the non-planar six-membered ring can lead to atropisomerism provided the other two *ortho*-positions are substituted with bulky groups (otherwise they slip through the plane readily).

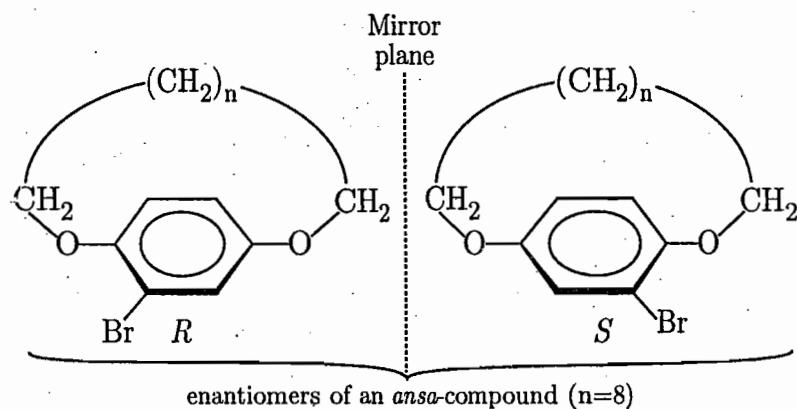


When $n > 2$, the bridged biphenyls will exhibit atropisomerism irrespective of the size of the other two *ortho*-substituents. In such cases the non-planarity is caused by puckering of the rings which in the planar form suffer from angle strain and non-bonded interactions. For example :



► 1.110 Discuss stereoisomerism of compounds with chiral planes such as
 (a) *ansa*-compounds, (b) cyclophanes and (c) *trans*-cycloalkenes.

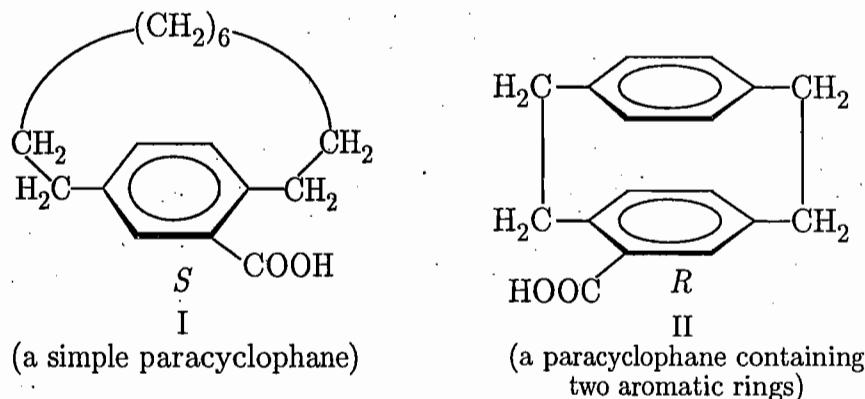
Ans. (a) Some *ansa*-compounds [*ansa* (Latin) means handel] are found to be optically active because of having a chiral plane. In case of the *ansa*-compound shown below, the aromatic ring is dissymmetrically substituted (two-dimensionally chiral) and the polymethylene chain can be either above or below the plane of the aromatic ring giving rise to two enantiomeric forms. Since the polymethylene chain is small enough, the benzene ring is prevented from swivelling through the larger ring, i.e., the rotation of the aromatic ring is hindered and the two enantiomers will be configurationally stable. The compound has a plane of chirality, which is the plane of the aromatic ring.



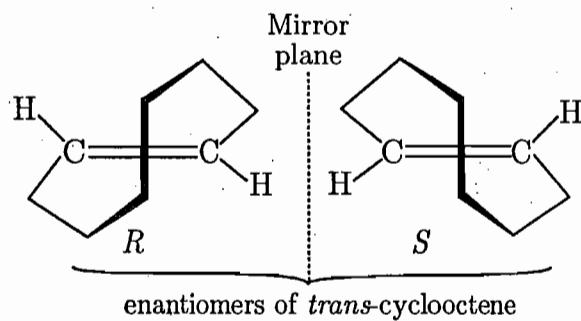
The *ansa*-compound is non-resolvable when $n = 10$. Since the rotational energy barrier is lowered, rotation of the aromatic ring through the large dioxamethylene chain is now rapid enough for racemisation to occur. Therefore, an *ansa*-compound will exhibit enantiomerism if the aromatic ring is dissymmetrically substituted and the molecule is configurationally stable (i.e., the rotation of the ring is hindered).

(b) Cyclophanes are basically similar to *ansa*-compounds. The compound I is a simple paracyclophane with one aromatic ring which has been resolved. The compound

II is also a resolvable paracyclophe in which two aromatic rings are joined together by bridging *para* positions. In this molecule, the planes of the two benzene rings are approximately parallel and the one with the substituent ($-COOH$) cannot rotate to give the enantiomer. Both of the compounds I and II have a plane of chirality, which is the plane of the carboxyl ($-COOH$) substituted ring. Therefore, to be chiral, the aromatic ring in a simple paracyclophe and one of the rings in a paracyclophe must be dissymmetrically substituted and the rotation of the ring must be hindered i.e., the compound must be configurationally stable.

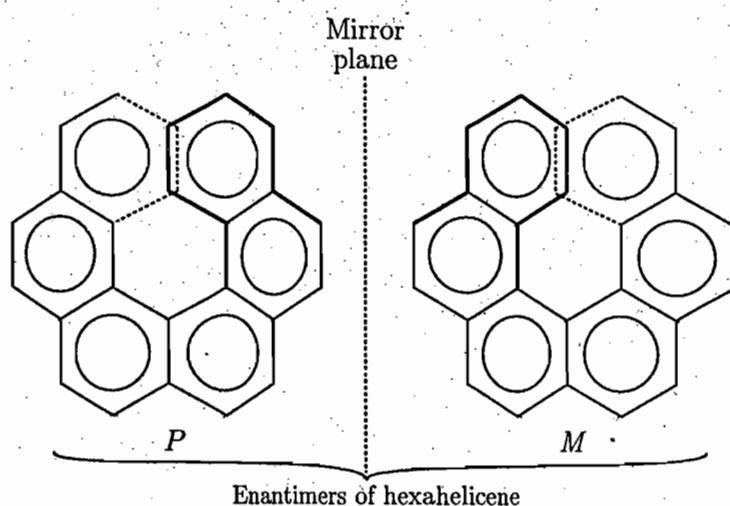


(c) *trans*-Cyclooctene is a chiral molecule due to having a chiral plane. The two sp^2 carbons and the atoms directly bonded to them are in a plane and the polymethylene bridge is skewed to give a three dimensional structure. Therefore, it has a highly twisted structure and two conformations are possible which are mirror images of each other. The interconversion of the enantiomers would require swinging of the tetramethylene chain over and below the chiral plane (the plane of the trigonal atoms) which is seriously opposed by ring strain (angle strain). Because of this, the enantiomers are configurationally stable and have been separated.

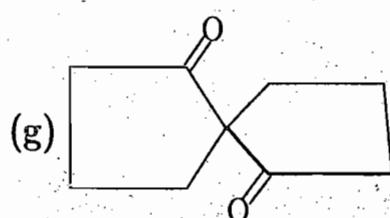
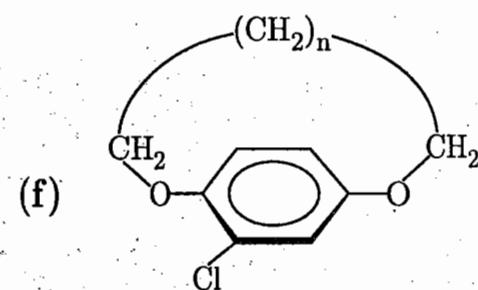
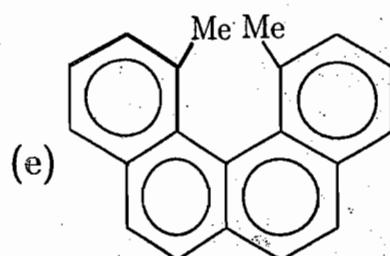
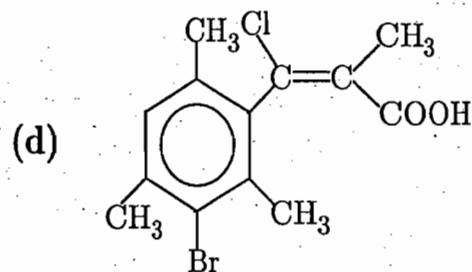
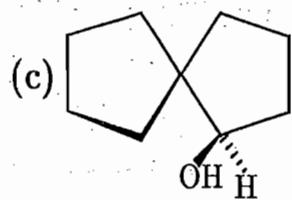
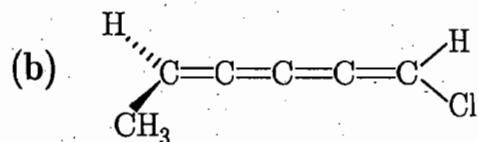


► 1.111 Chirality may arise due to helical shape of molecules (helicity). Explain with a suitable example.

Ans. Molecular overcrowding may lead to helicity and consequently, chirality in molecules. Hexahelicene provides a good example. The molecule is normally expected to be planar. However, due to molecular overcrowding, the terminal benzene rings are forced to remain in different planes. As a result, the molecule assumes a helical shape and exists as two helical enantiomers.



► 1.112 What is the element of chirality present in each of the following molecules?

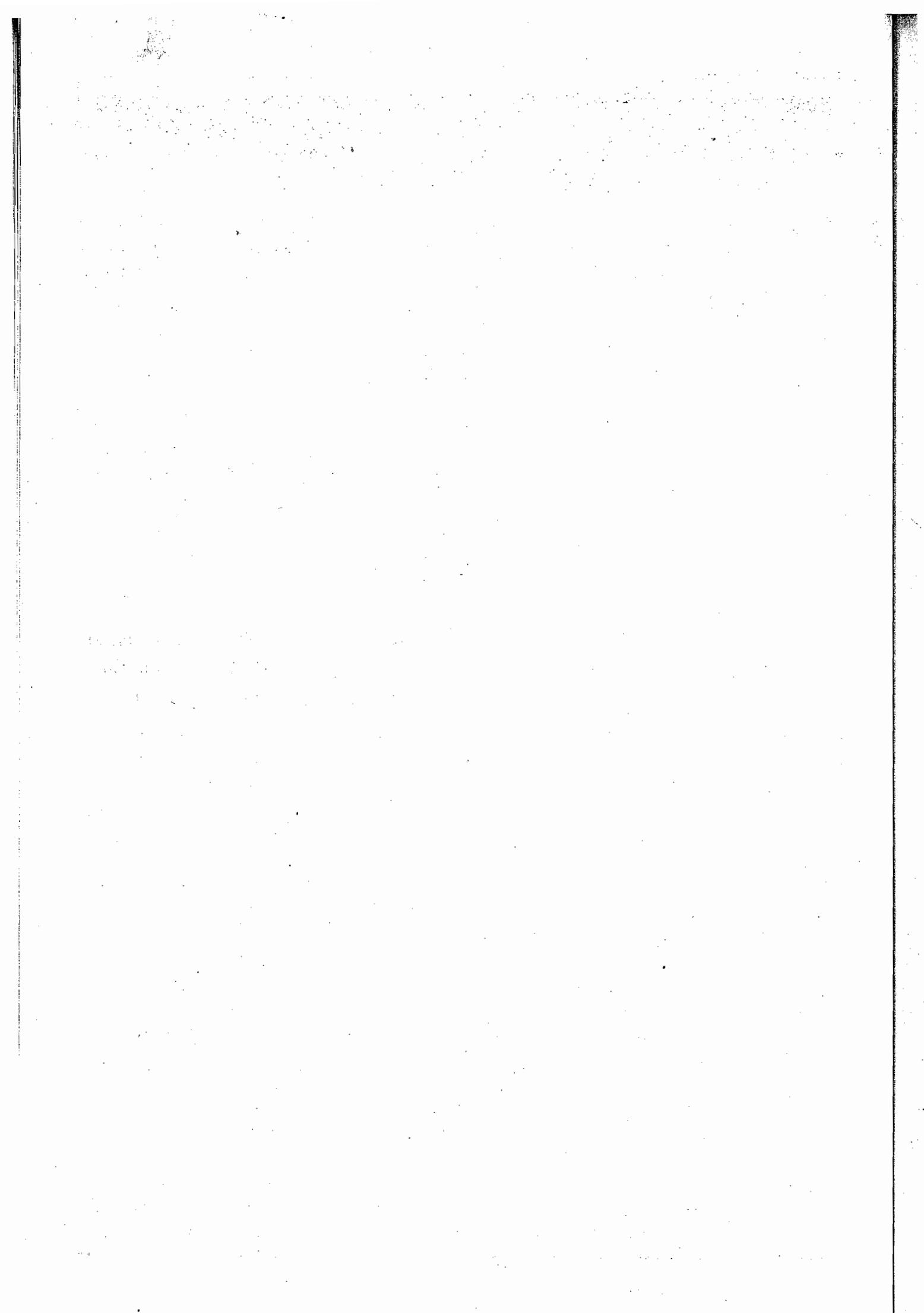


Ans. (a) axial chirality (b) axial chirality (c) central chirality (d) axial chirality
 (e) helicity (f) planar chirality (g) both central and axial chirality.



PROSTEREOISOMERISM, TOPICITY AND ASYMMETRIC SYNTHESIS

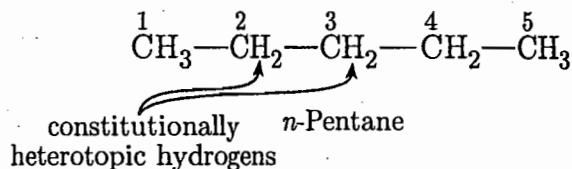
- Homotopic, enantiotopic and diastereotopic ligands and faces**
(Problem 2.1—Problem 2.9)
 - Asymmetric synthesis** (Problem 2.10—Problem 2.17)
-



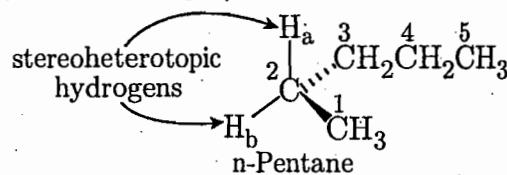
HOMOTOPIC, ENANTIOTOPIC AND DIASTEREOTOPIC LIGANDS AND FACES

- 2.1 What do you mean by constitutionally heterotopic and stereoheterotopic ligands. Give examples.

Ans. In an intact molecule, if the homomeric ligands are bonded to constitutionally different ligating centres, the ligands are called constitutionally heterotopic. For example, H's at C-2 in *n*-pentane are constitutionally heterotopic compared to H's at C-3.

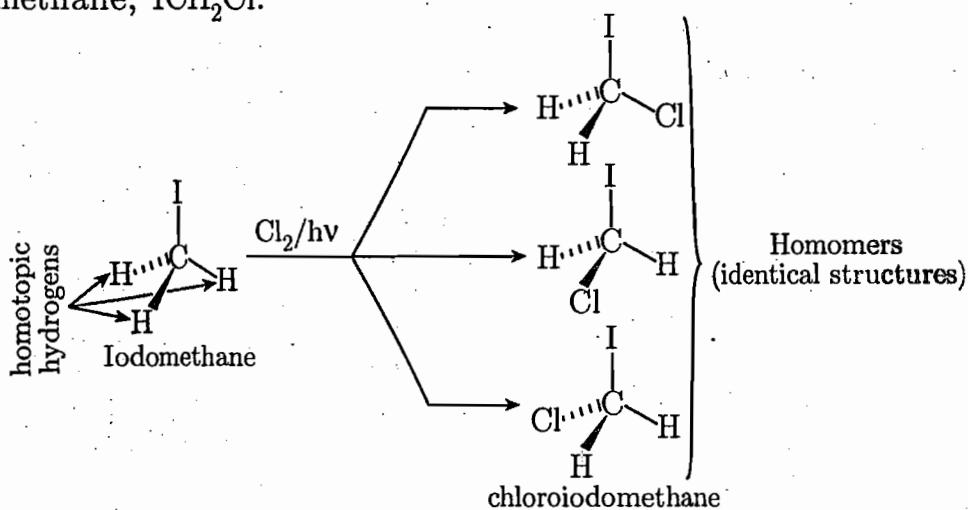


When the spatial relation of two ligands with the rest of the molecule is different, the ligands are called stereoheterotopic. For example, the geminal H's at C-2 (designated as H_a and H_b) of *n*-pentane are stereochemically non-equivalent, i.e., stereoheterotopic (actually enantiotopic).



- 2.2 Define the following terms with suitable examples. (a) Homotopic ligands
 (b) Enantiotopic ligands (c) Diastereotopic ligands (d) Homotopic faces
 (e) Enantiotopic faces (f) Diastereotopic faces (g) Prochiral centre.

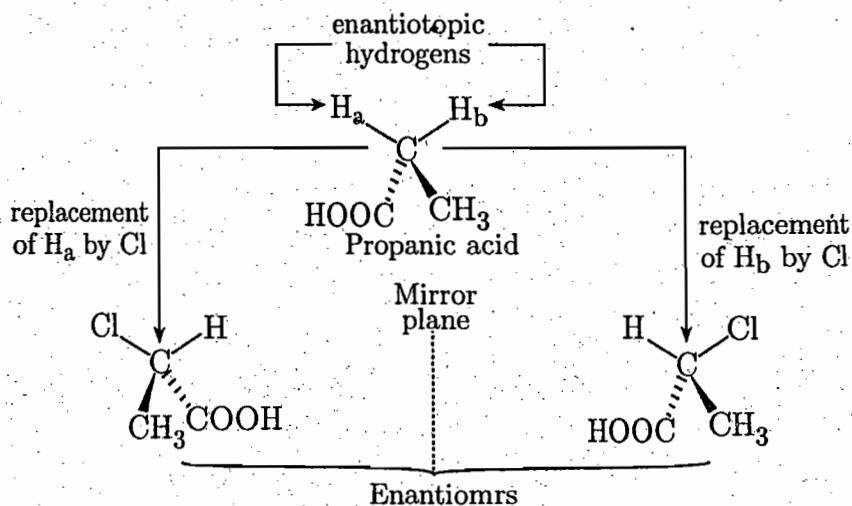
Ans. (a) A pair of ligands (atoms or groups) in a molecule is said to be homotopic if replacement of each of them in turn by a different ligand (different from all other ligands attached to the same carbon) gives rise to identical product. For example, the three hydrogen atoms of iodomethane are homotopic because replacement of any one of these H atoms by Cl atom, one at a time, produces the same molecule of chloroiodomethane, ICH₂Cl.



[Ligands are homotopic if they can interchange positions by rotation around a simple axis of symmetry C_n ($\infty > n > 1$). Thus, the three hydrogens in iodomethane are homotopic because they can interchange positions through rotation around C_3 axis. Similarly, the two

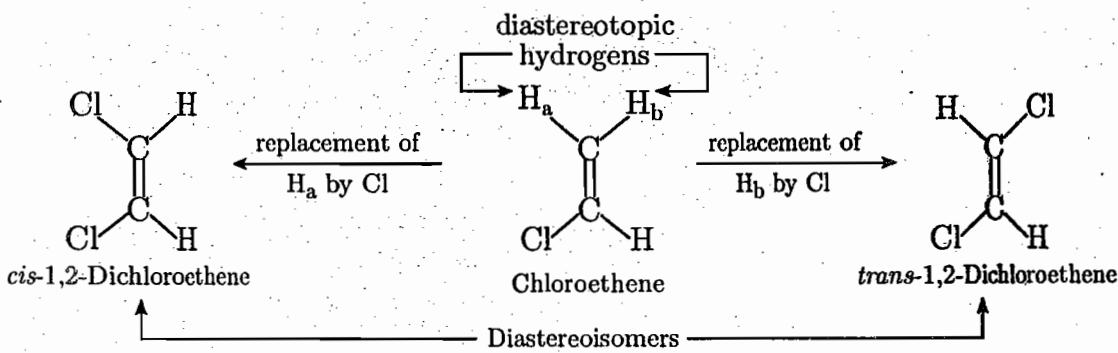
hydrogens in methylene dichloride (CH_2Cl_2) and the four hydrogens in ethylene ($\text{CH}_2=\text{CH}_2$) are homotopic because they can interchange positions through rotations around C_2 axis.]

(b) A pair of ligands (atoms or groups) in a molecule is said to be enantiotopic if replacement of one or the other of them by a different achiral ligand (different from all other ligands attached to the same carbon) gives rise to one or the other of a pair of two enantiomers. For example, the two methylene hydrogens (H_a and H_b) of propanoic acid are enantiotopic because replacements of these hydrogens in turn, say by Cl, give rise to two enantiomers of 2-chloropropanoic acid ($\text{CH}_3\text{CHClCOOH}$).

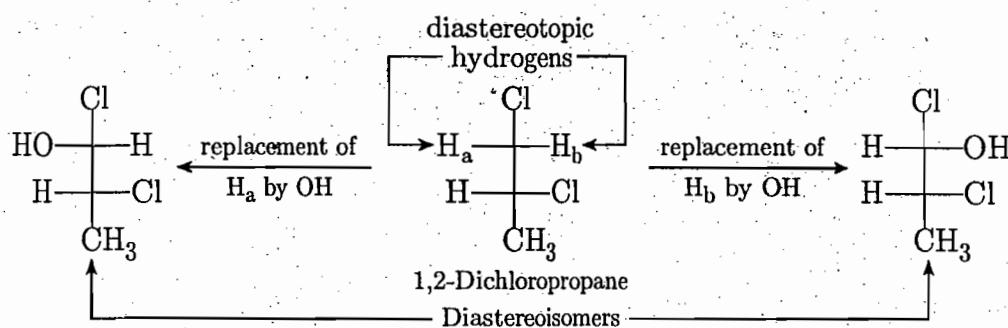


[A pair of ligands are enantiotopic if their positions are interchangable through an operation of a symmetry element of second kind, i.e., by an S_n operation (rotation reflection operation). Since S_1 axis is equivalent to a plane of symmetry (σ) and S_2 is equivalent to a centre of symmetry (i), the positions of enantiotopic ligands are also interchangable by operation of symmetry elements like plane of symmetry and centre of symmetry.]

(c) Two ligands (atoms or groups) in a molecule are said to be diastereotopic if replacement of one or the other of them by a different achiral test ligand gives rise to one or the other isomer of a set of diastereoisomers. For example, the two H atoms on the same carbon (C-2) of chloroethene ($\text{ClCH}=\text{CH}_2$) are diastereotopic because sequential replacements of these hydrogens, say by Cl, result in the formation of a pair of diastereoisomers (two geometric isomers).

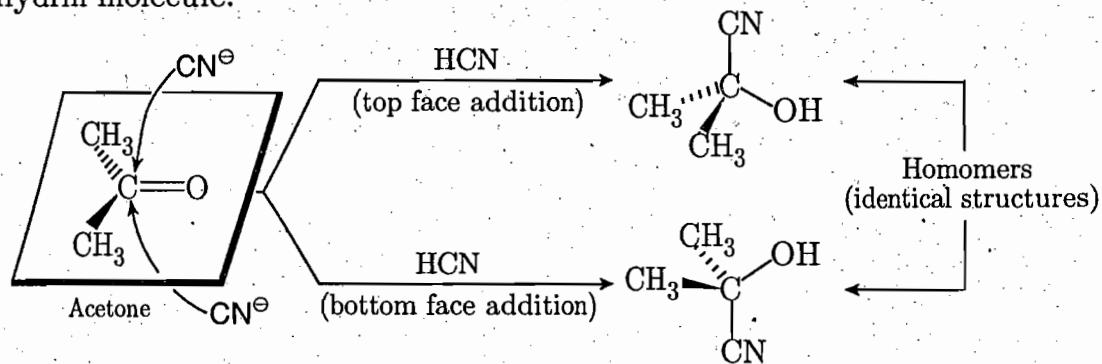


The two hydrogen atoms on C-1 in 1,2-dichloropropane are also diastereotopic because sequential replacements of these hydrogens, say by OH, give rise to a pair of diastereoisomers.

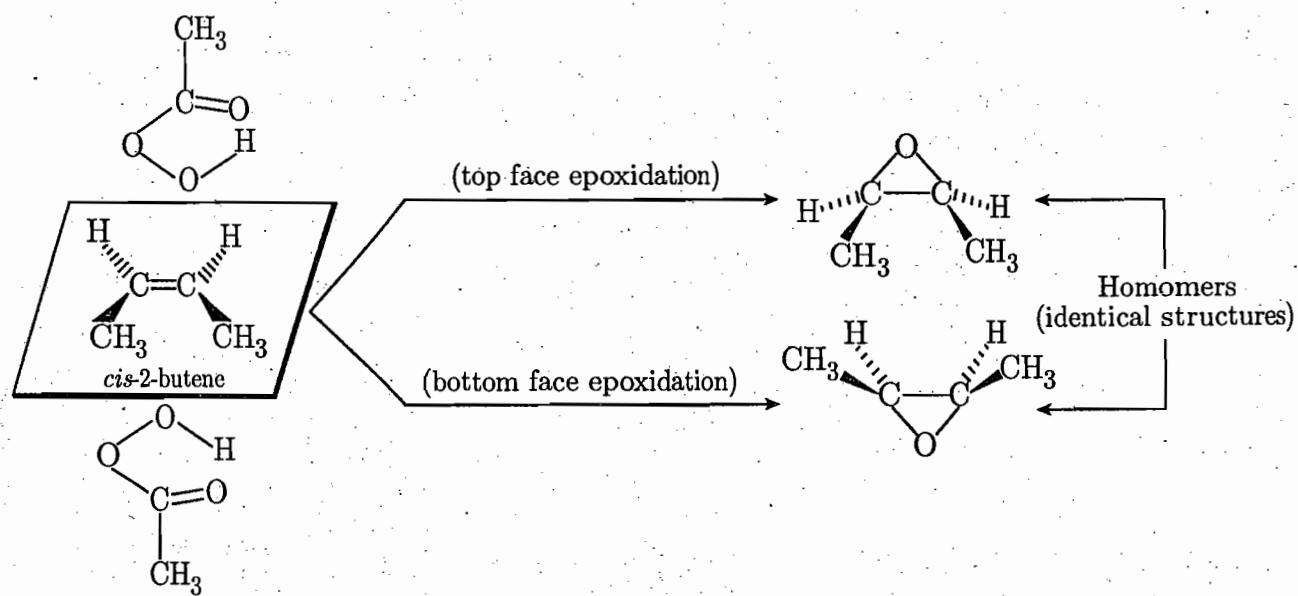


[Diastereotopic ligands cannot be interchanged by any symmetry operations, i.e., C_n (proper axis of symmetry) or S_n (alternating axis of symmetry) and are, therefore, relatively easy to spot.]

(d) The two faces of a double bond (π -system, i.e., $C=O$, $C=C$, etc.) are homotopic if addition of same reagent to either face gives the same product. Thus the two faces of acetone are homotopic since addition of HCN on either face gives the same cyanohydrin molecule.



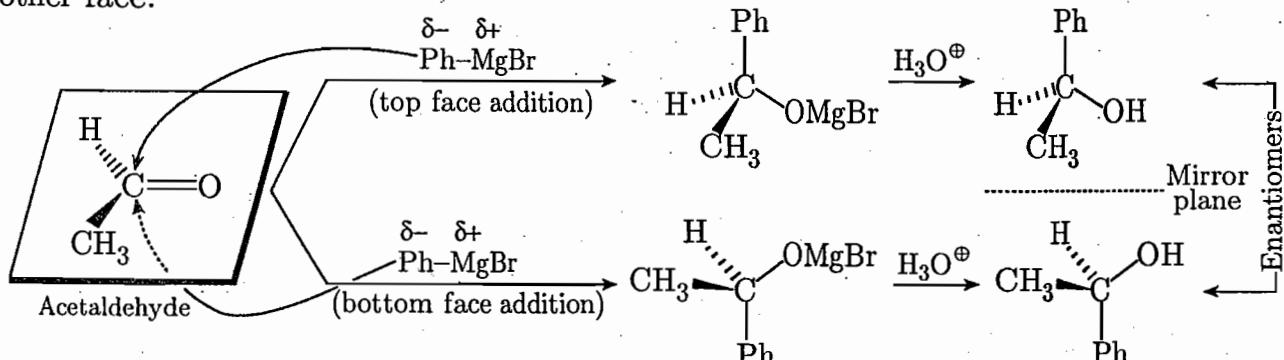
The two faces of *cis*-2-butene are also homotopic since epoxidation by a peracid on either face gives the same *meso* product.



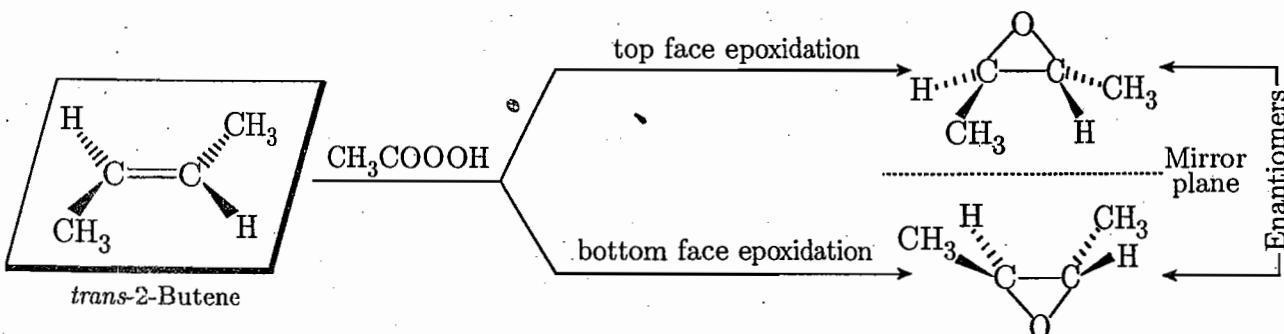
[Homotopic faces of double bonds can be exchanged by rotation around a simple axis of symmetry. C_n ($n = \text{even}$).]

(e) The two faces of a double bond (π -system, i.e., $C=O$, $C=C$, etc.) are enantiotopic, if attack of reagent on one side of the π -bond yields one enantiomer, whereas attack on the opposite side yields the other enantiomer. For example, the two faces of acetalde-

hyde are enantiotopic because reaction with the achiral reagent PhMgBr at one face affords a molecule which is the enantiomer of the molecule formed by reaction at the other face.

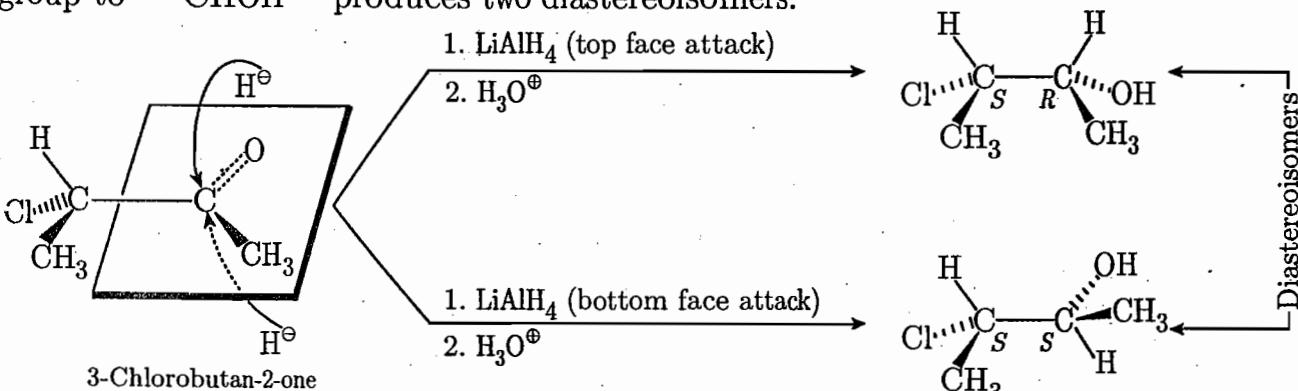


The two faces of *trans*-2-butene is enantiotopic because the molecule formed on epoxidation at one face is the enantiomer of the molecule formed on epoxidation at the other face.



[Enantiotopic faces are interchangeable through operation of plane of symmetry (σ), centre of symmetry (i) and alternating axis of symmetry (S_n , $n = \text{even}$).]

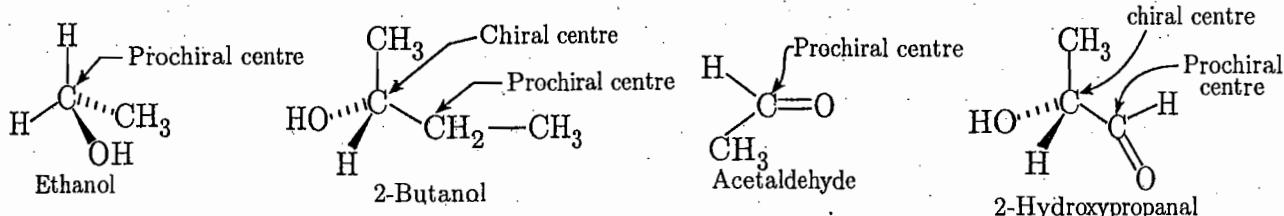
(f) The two faces of a double bond (π -system, i.e., $\text{C}=\text{O}$, $\text{C}=\text{C}$, etc.) are diastereotopic, if attack of a reagent on one side of the π -bond leads to one diastereoisomer, whereas attack on the opposite side leads to the other diastereoisomer. The two faces of a carbonyl group close to a stereocentre is diastereotopic. For example, the two faces of the carbonyl group of 3-chlorobutan-2-one are diastereotopic because reduction of $\text{C}=\text{O}$ group to $-\text{CHOH}-$ produces two diastereoisomers.



[Diastereotopic faces cannot be interchanged by symmetry operations (C_n or S_n).]

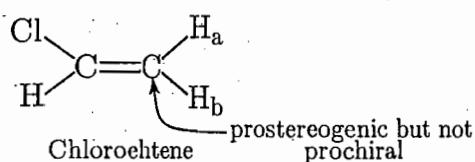
(g) Replacement of one of a pair of enantiotopic or diastereotopic ligands by a different ligand (different from the ligands already present on the achiral centre) creates a chiral centre. Thus, an achiral centre bearing enantiotopic or diastereotopic ligands is called a prochiral centre. For example, C-1 of ethanol, C-3 of 2-butanol, etc. are prochiral centres. Again, if the two faces of an sp^2 hybridized carbon are enantiotopic or

diastereotopic, that carbon is also called a prochiral centre. For example, the carbonyl carbon of acetaldehyde and the carbonyl carbon of 2-hydroxypropanal are prochiral centres.



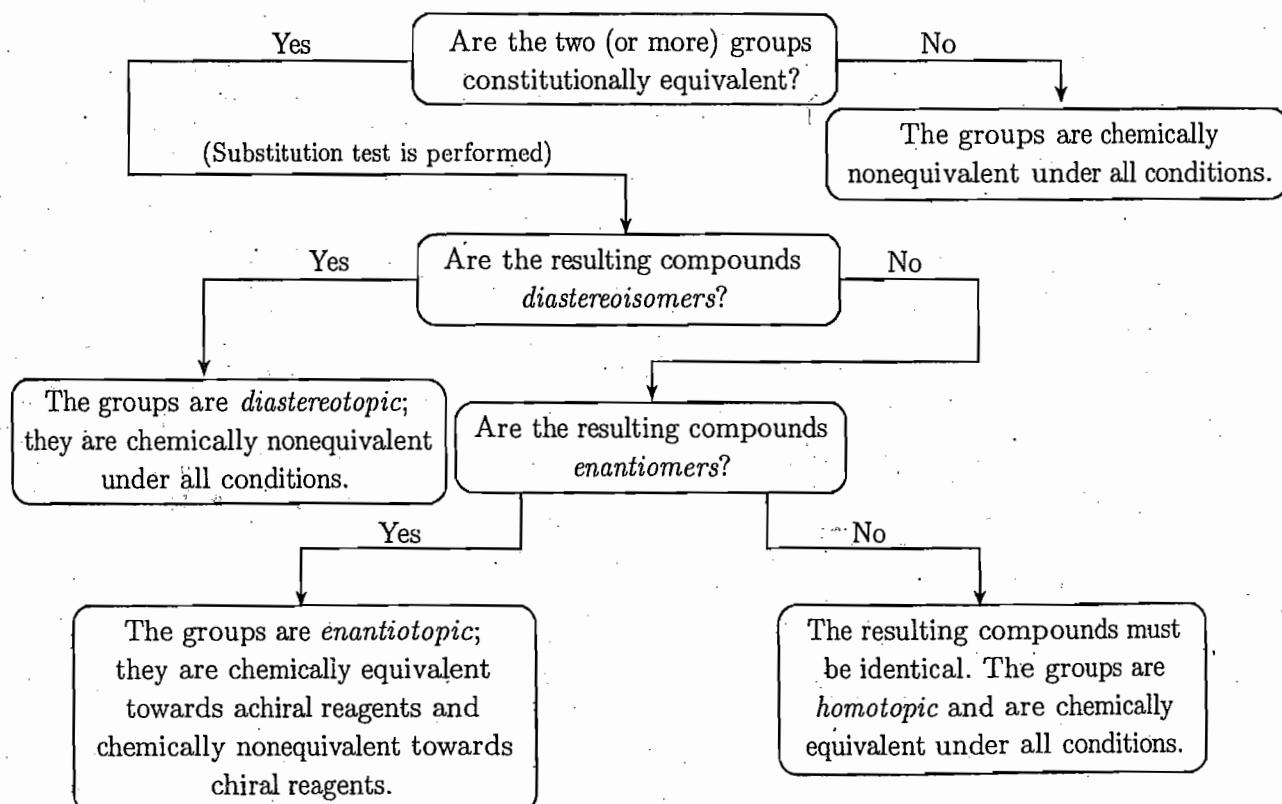
[Molecules that are achiral but which can be converted to molecules with chiral centres by a single chemical reaction (addition or substitution) are said to be prochiral. Ethanol ($\text{CH}_3\text{CH}_2\text{OH}$), acetaldehyde (CH_3CHO), propene ($\text{CH}_3\text{CH}=\text{CH}_2$), etc. are examples of prochiral molecules.]

Prostereogenic centre is defined as the centre which can be converted into a stereogenic centre by replacing one of the homomeric ligands (atoms or groups) by a different ligand. A prostereogenic centre may or may not be prochiral. For example, the C-2 of chloroethene is prostereogenic because on replacement of H_a or H_b by Cl it becomes a stereogenic centre. However, C-2 is not prochiral because it is not converted into a chiral centre.



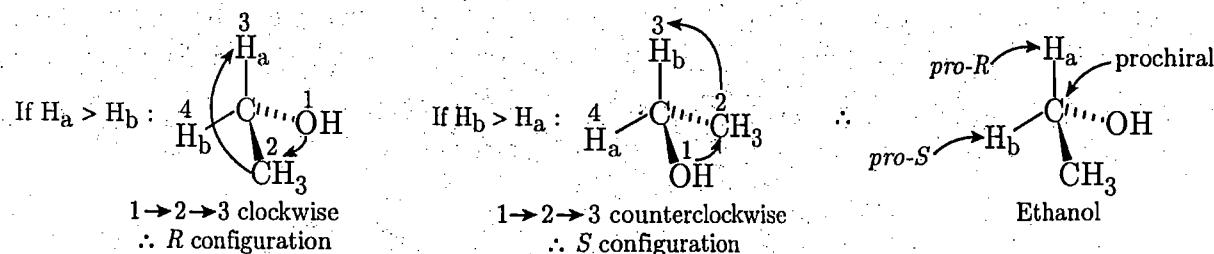
[When one of the homomeric H atoms on C-2 of propanoic acid ($\text{CH}_3\text{CH}_2\text{COOH}$) is replaced by Cl atom, the centre C-2 becomes both stereogenic and chiral. Therefore, in this case, C-2 is both prostereogenic and prochiral.]

The following flowchart can be used to summarize the relationships of groups within a molecule :

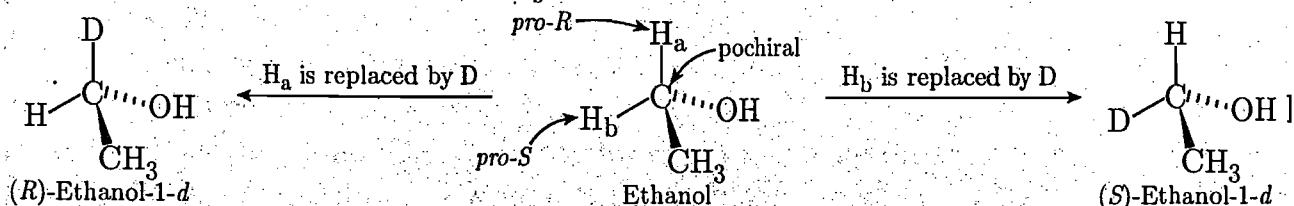


- 2.3 (a) How are the ligands (enantiotopic or diastereotopic) attached to a prochiral centre designated? Illustrate with an example.
- (b) When are two groups in a molecule chemically equivalent (i.e. they behave in exactly the same way toward a chemical reagent) or chemically nonequivalent?

Ans. (a) Enantiotopic or diastereotopic ligands attached to a prochiral centre are designated as *pro-R* or *pro-S* by a modified application of the sequence rules. The ligand to be labelled is arbitrarily assigned a higher priority than the other. The priority rule is then applied in the usual way and the configuration of the prochiral centre is determined. If the configuration is *R*, the ligand is designated as *pro-R* and if the configuration is *S*, the ligand is designated as *pro-S*. For example, if H_a in the following structure of ethanol is arbitrarily preferred over H_b in the sequence rule, the sequence is OH > CH₃ > H_a > H_b and the configuration (hypothetical) of the prochiral centre is then *R*. Therefore, H_a is designated as *pro-R*. Similarly, if H_b is arbitrarily given precedence over H_a, the sequence is OH > CH₃ > H_b > H_a and the configuration (hypothetical) of the prochiral centre is then *S*. Hence, H_b is designated as *pro-S*.



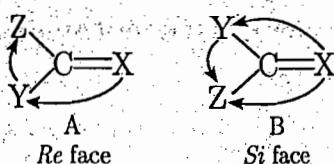
[The same result would have been obtained by replacing in turn the ligands (enantiotopic or diastereotopic) attached to the prochiral centre by a non-equivalent ligand with higher priority than the other (without disturbing the priority order with respect to the remaining ligands). If replacement of the ligand concerned gives the *R* configuration, the ligand is specified as *pro-R*; if the *S* configuration, then as *pro-S*. For example, replacement of H_a in ethanol by D gives (*R*)-ethanol-1-d and hence H_a is *pro-R*. Similarly, replacement of H_b by D gives (*S*)-ethanol-1-d and hence H_b is *pro-S*.



- (b) Homotopic groups are chemically equivalent in all situations. Enantiotopic groups are chemically equivalent toward achiral reagents, but are chemically nonequivalent toward chiral reagents. Constitutionally nonequivalent groups are chemically nonequivalent in all situations and diastereotopic groups are chemically nonequivalent in all situations.

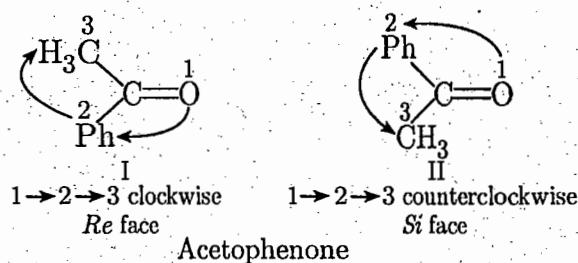
► 2.4 How can enantiotopic and diastereotopic faces be specified? Give examples.

Ans. The enantiotopic and diastereotopic faces can be specified by an extended use of CIP sequence rules in two dimensions. If the three groups of the trigonal centre as arranged by the sequence rules have the order X > Y > Z, that face (when looking from the top of the structure) in which the groups in this sequence are clockwise (as in A) is *Re* face (from Latin *rectus*) and that face in which the groups in this sequence are counterclockwise (as in B) is the *Si* face (from Latin *sinister*).



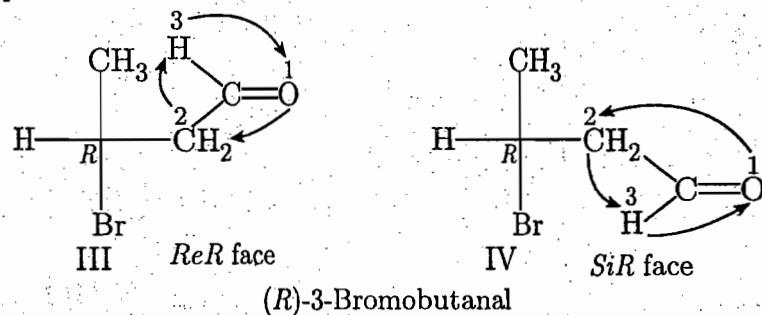
[Structure B (the bottom face of structure A) can be obtained by 180° out-of-plane rotation of structure A.]

For example, the face of the carbonyl group of acetophenone as shown in structure I is the *Re* face because the ligands ($=\text{O} > \text{Ph} > \text{CH}_3$) define a clockwise path, whereas the face as shown in structure II is the *Si* face because the ligands define a counterclockwise path.



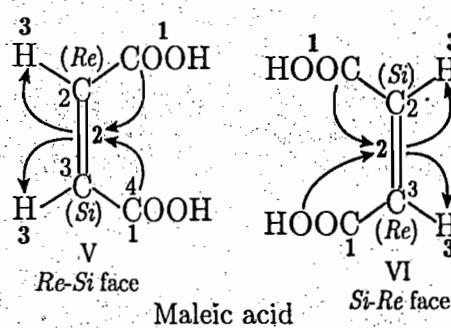
Acetophenone

The two carbonyl faces of (*R*)-3-bromobutanal are diastereotopic (presence of a chiral centre). The face shown in structure III is *Re* and the other face shown in structure IV is *Si*. However, a further subscript *R* (the chirality descriptor of C-3) may be added so that the double-lettered subscripts *ReR* and *SiR* are in true sence diastereotopic.



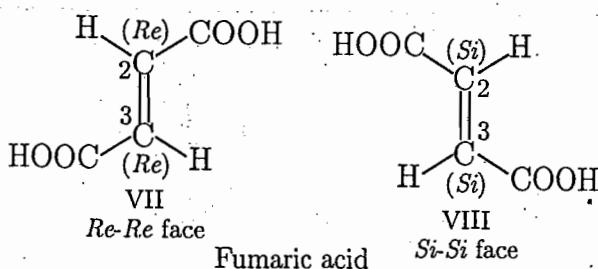
(*R*)-3-Bromobutanal

The two faces of an alkene of the type $\text{RCH}=\text{CHR}'$ (*R* and *R'* may also be same) can be specified as *Re-Re* and *Si-Si* or *Re-Si* and *Si-Re*. For example, the face of C-2 of maleic acid as shown in structure V is the *Re* face because the ligands ($\text{COOH} > =\text{CHCOOH} > \text{H}$) define a clockwise path, whereas the face of C-3 is the *Si* face because the ligands define a counterclockwise turn. Therefore, structure V of maleic acid is a combination of C-2 (*Re*) and C-3 (*Si*) and this face is specified as *Re-Si*. Similarly, the face of maleic acid as shown in structure VI is the *Si-Re* face. Here the two faces are homotopic.



Maleic acid

Structure VII and VIII represent the *Re-Re* and *Si-Si* faces of fumaric acid respectively. The two faces are enantiotopic.

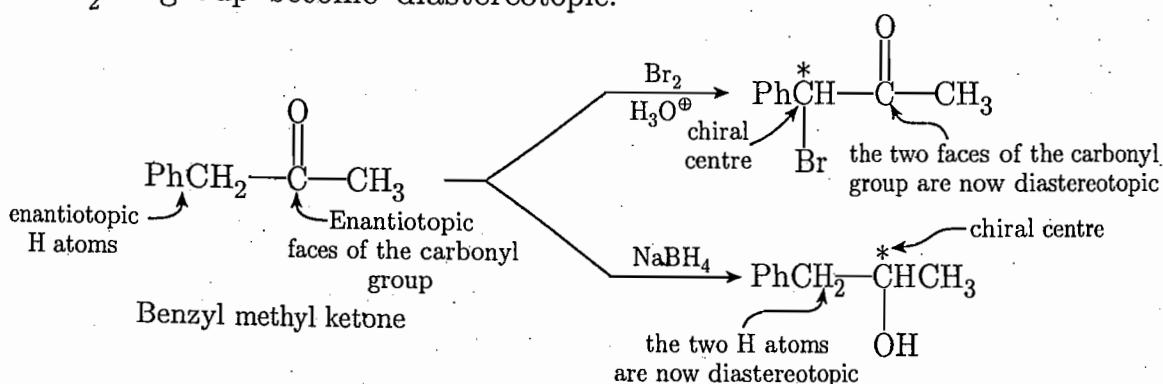


- 2.5 What are the topicities of H atoms of the $-\text{CH}_2-$ group and faces of the $>\text{C}=\text{O}$ group in benzyl methyl ketone ($\text{PhCH}_2\text{COCH}_3$)? How are the topicities of methylene and carbonyl carbon changed when they are separately converted into a chiral centre.

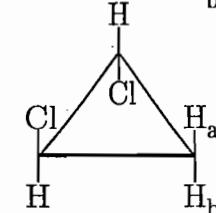
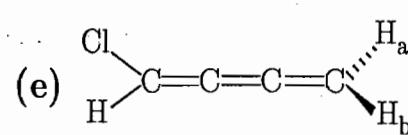
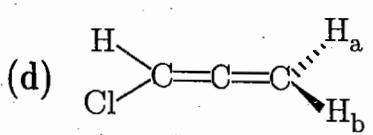
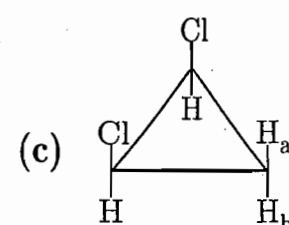
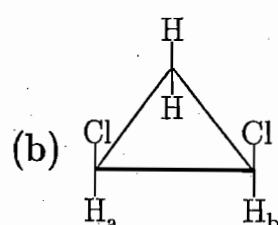
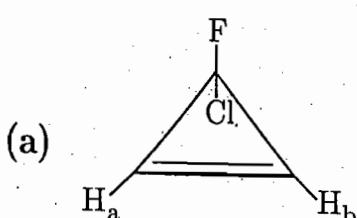
Ans. In benzyl methyl ketone ($\text{PhCH}_2\text{COCH}_3$), the two H atoms of the methylene ($-\text{CH}_2-$) group are enantiotopic because replacement of one or the other of them by a different achiral ligand gives rise to one or the other of a pair of enantiomers.

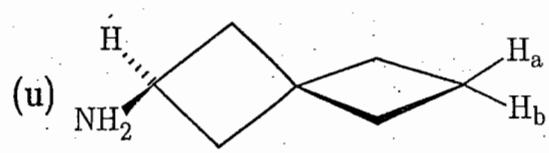
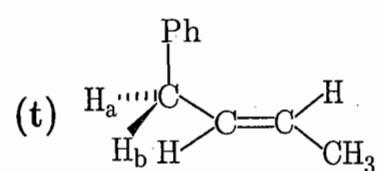
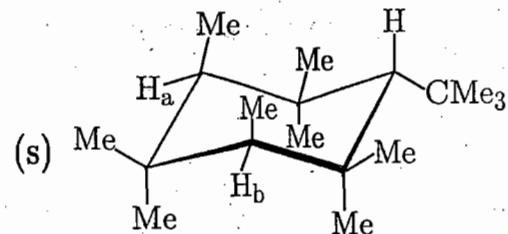
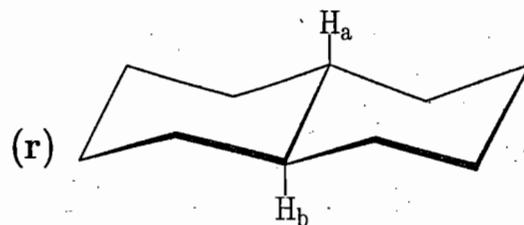
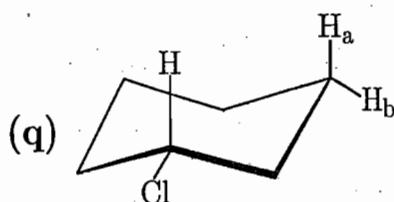
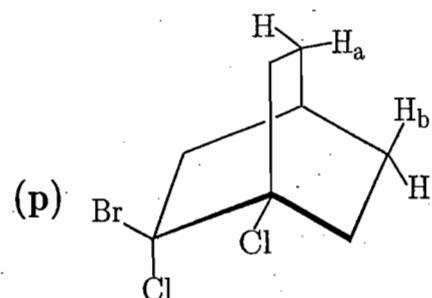
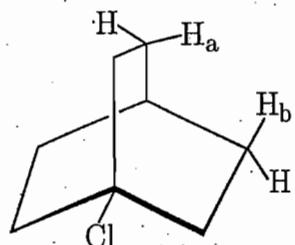
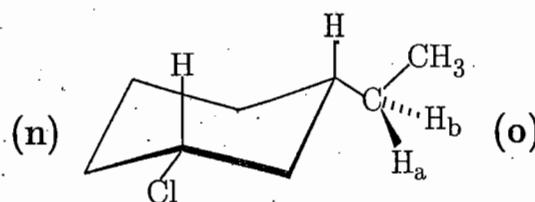
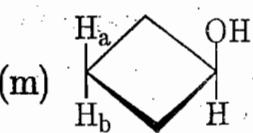
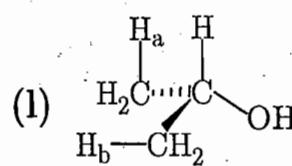
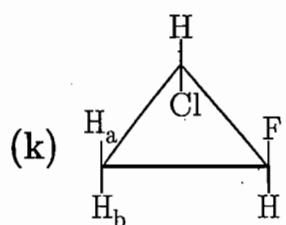
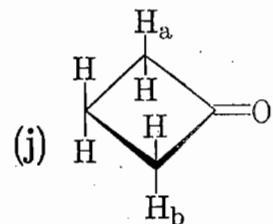
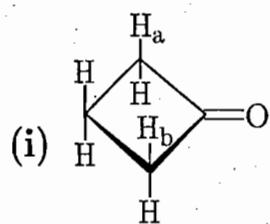
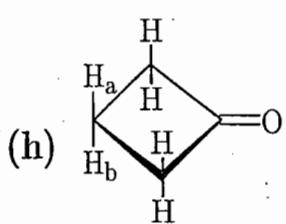
Similarly, the two faces of the planar carbonyl ($>\text{C}=\text{O}$) group are also enantiotopic because attack by a reagent on one side of the π -bond yields one enantiomer, whereas attack on the opposite side yield the other enantiomer.

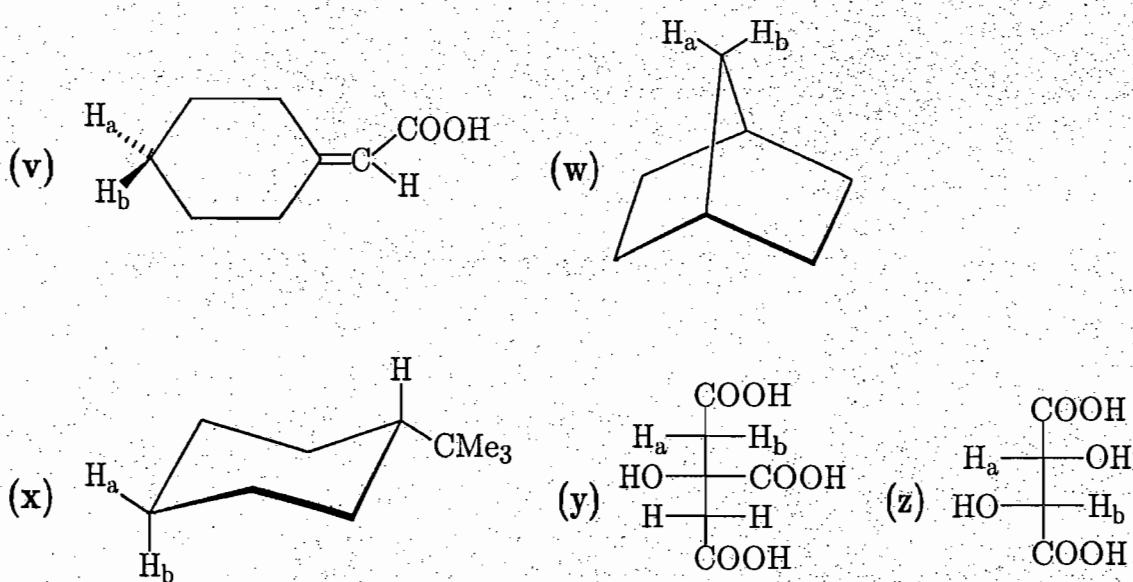
When the carbon of the $-\text{CH}_2-$ group is converted into a chiral centre by replacing one H atom, say by Br ($-\text{CHBr}-$), then the two opposite faces of the $>\text{C}=\text{O}$ group become diastereotopic. Similarly, when the $>\text{C}=\text{O}$ group is converted into a chiral centre, say by reduction ($-\text{CHOH}-$), the two H atoms of the $-\text{CH}_2-$ group become diastereotopic.



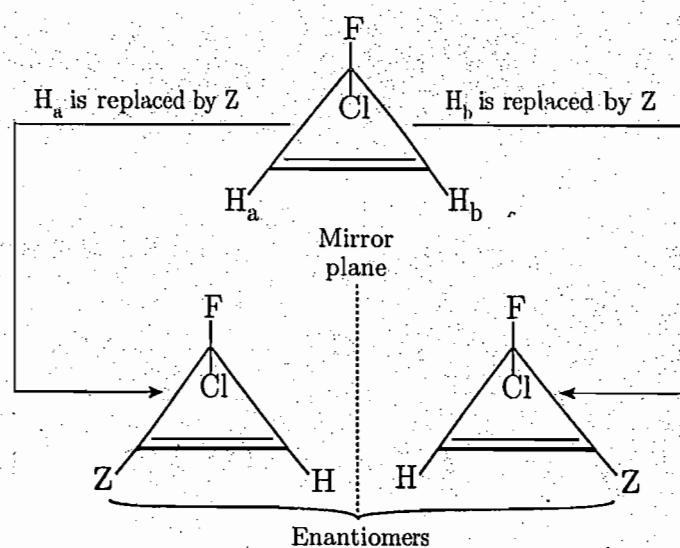
- 2.6 Indicate whether the hydrogens marked H_a and H_b in each of the following compounds are homotopic, enantiotopic or diastereotopic. Give replacement test in each case.



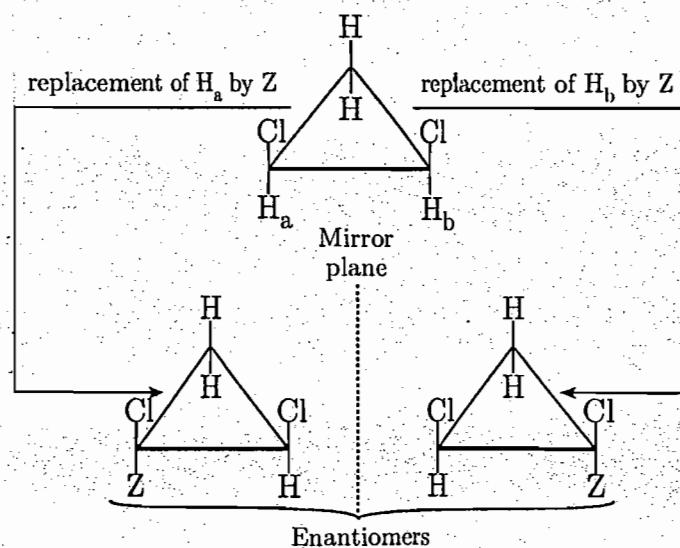




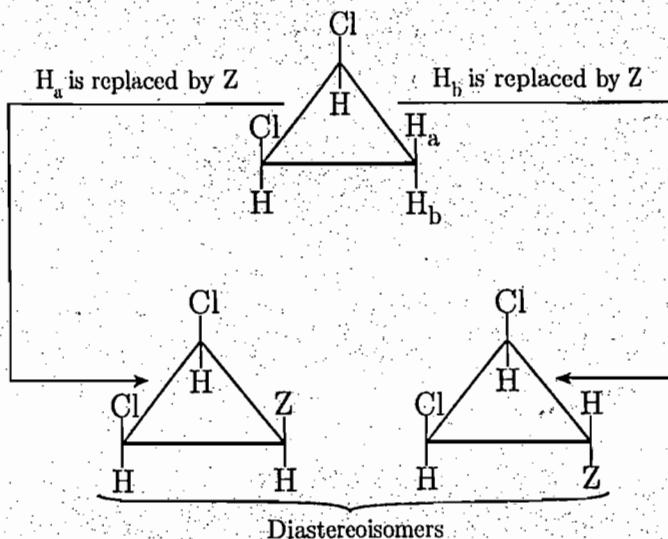
Ans. (a) H_a and H_b are enantiotopic because replacement of one or the other of them by some other ligand Z gives one or the other of a pair of enantiomers.



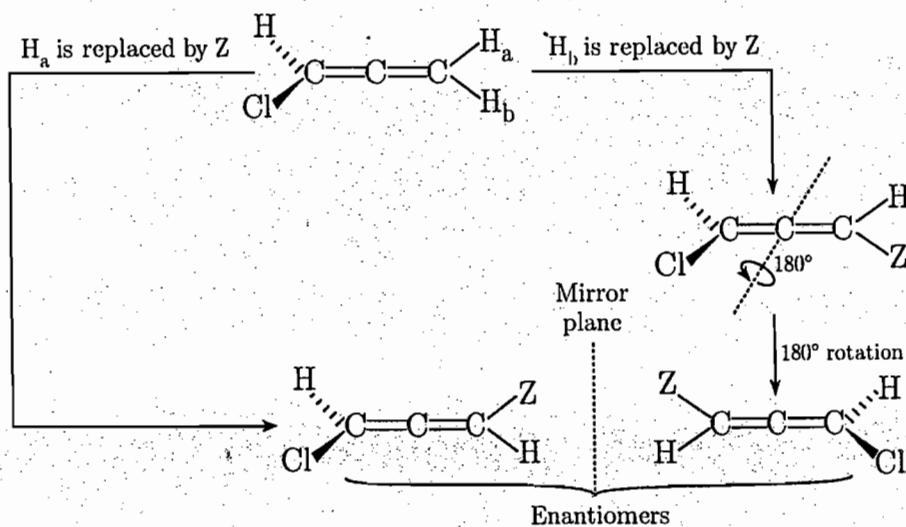
(b) The two hydrogens marked H_a and H_b are enantiotopic.



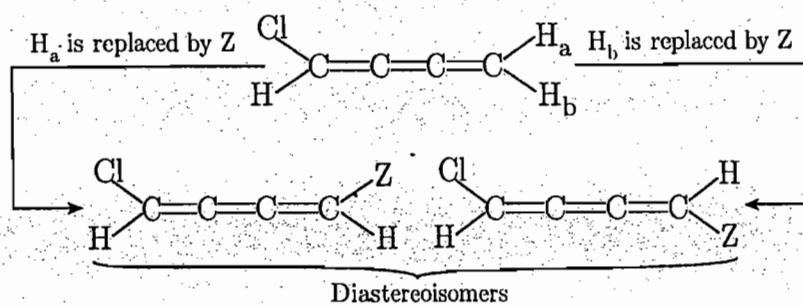
(c) The methylene hydrogens marked H_a and H_b are diastereotopic.



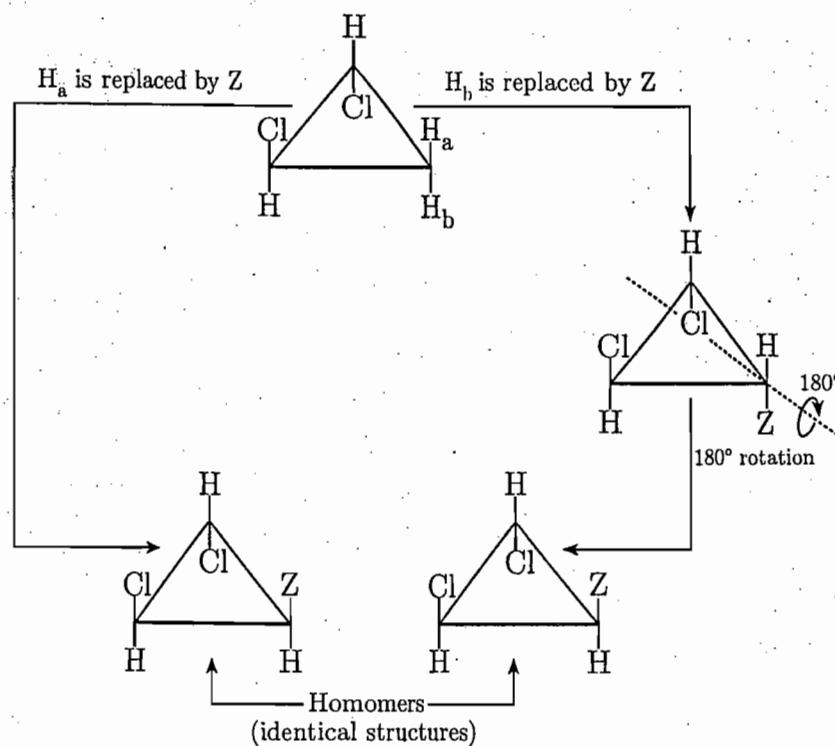
(d) H_a and H_b are enantiotopic.



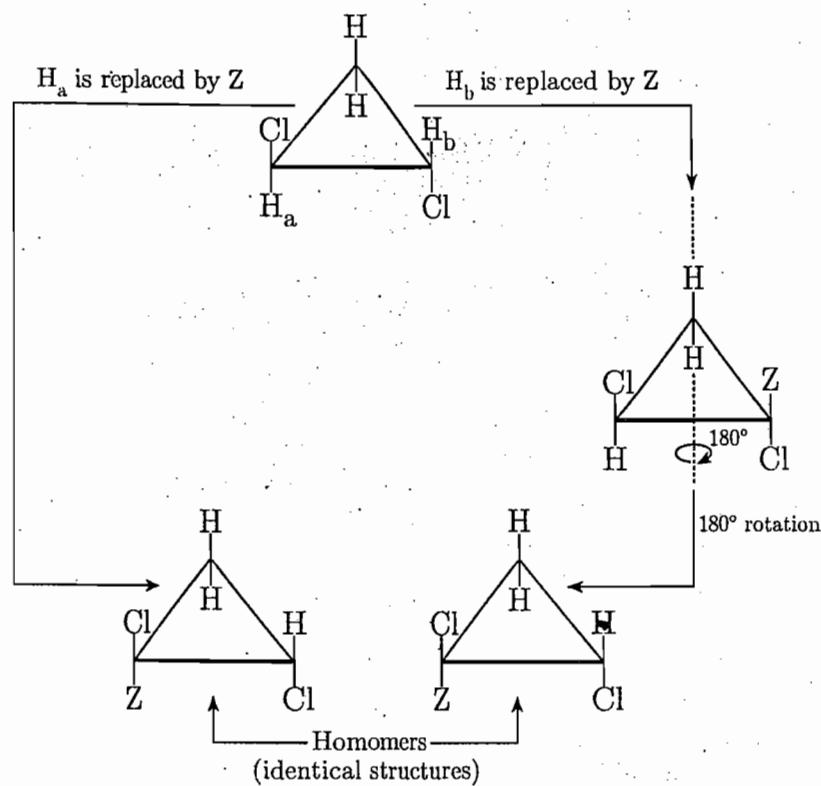
(e) H_a and H_b are diastereotopic.



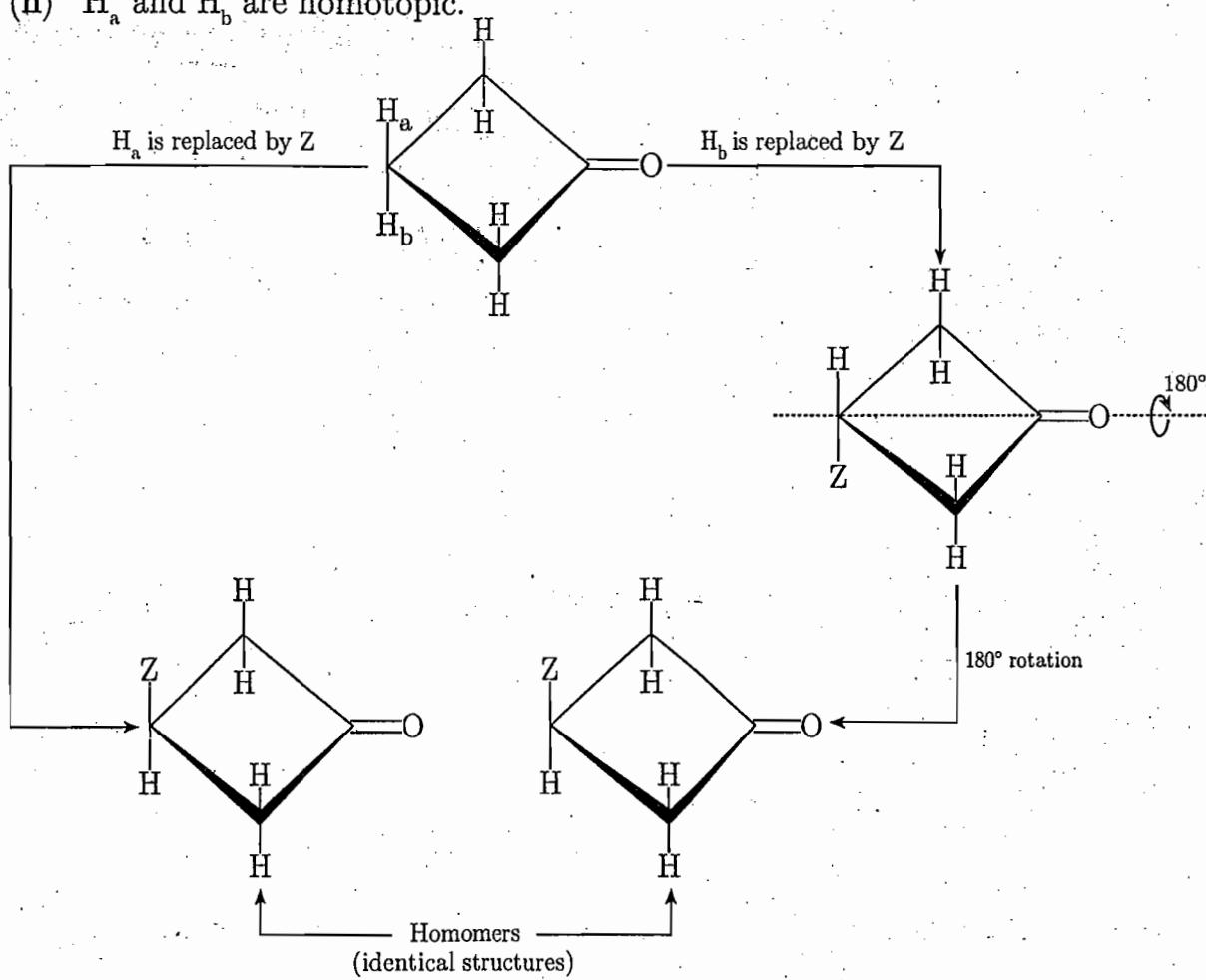
(f) H_a and H_b are homotopic.



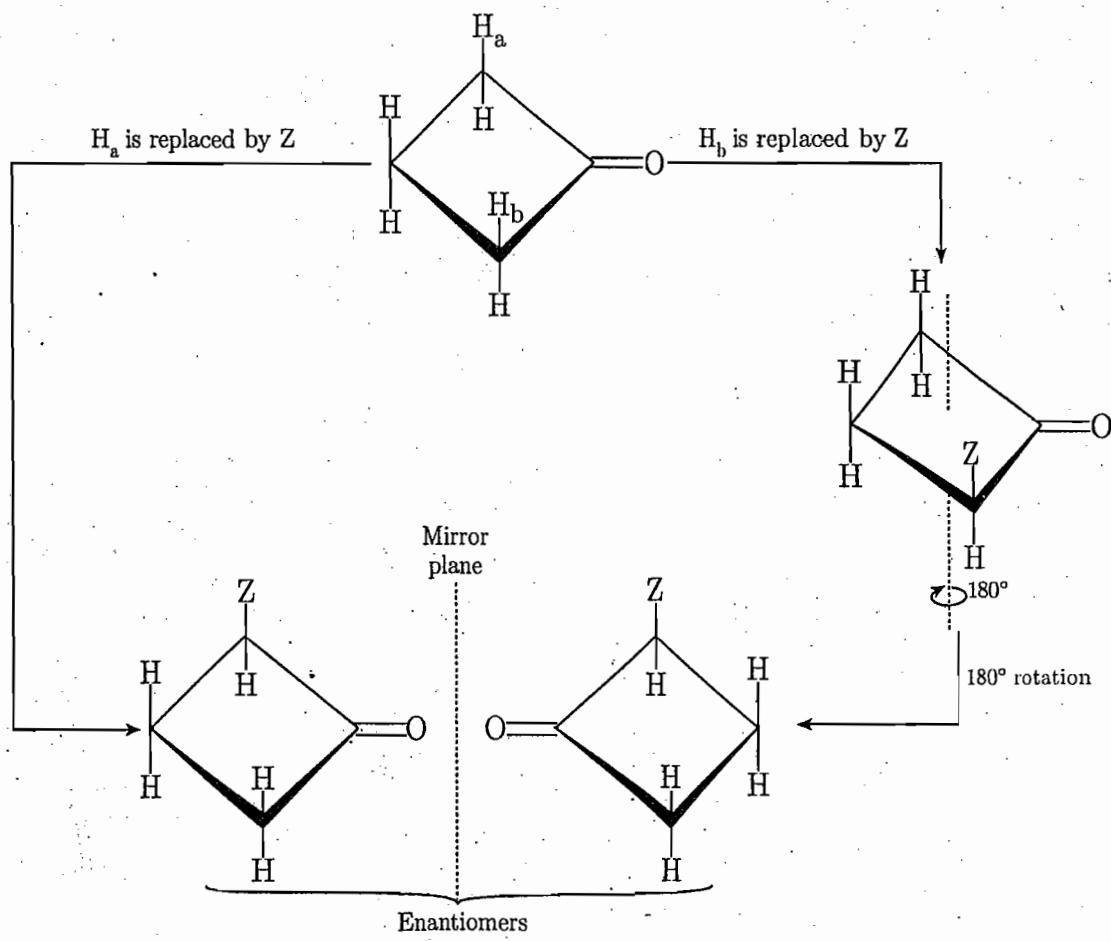
(g) H_a and H_b are homotopic.



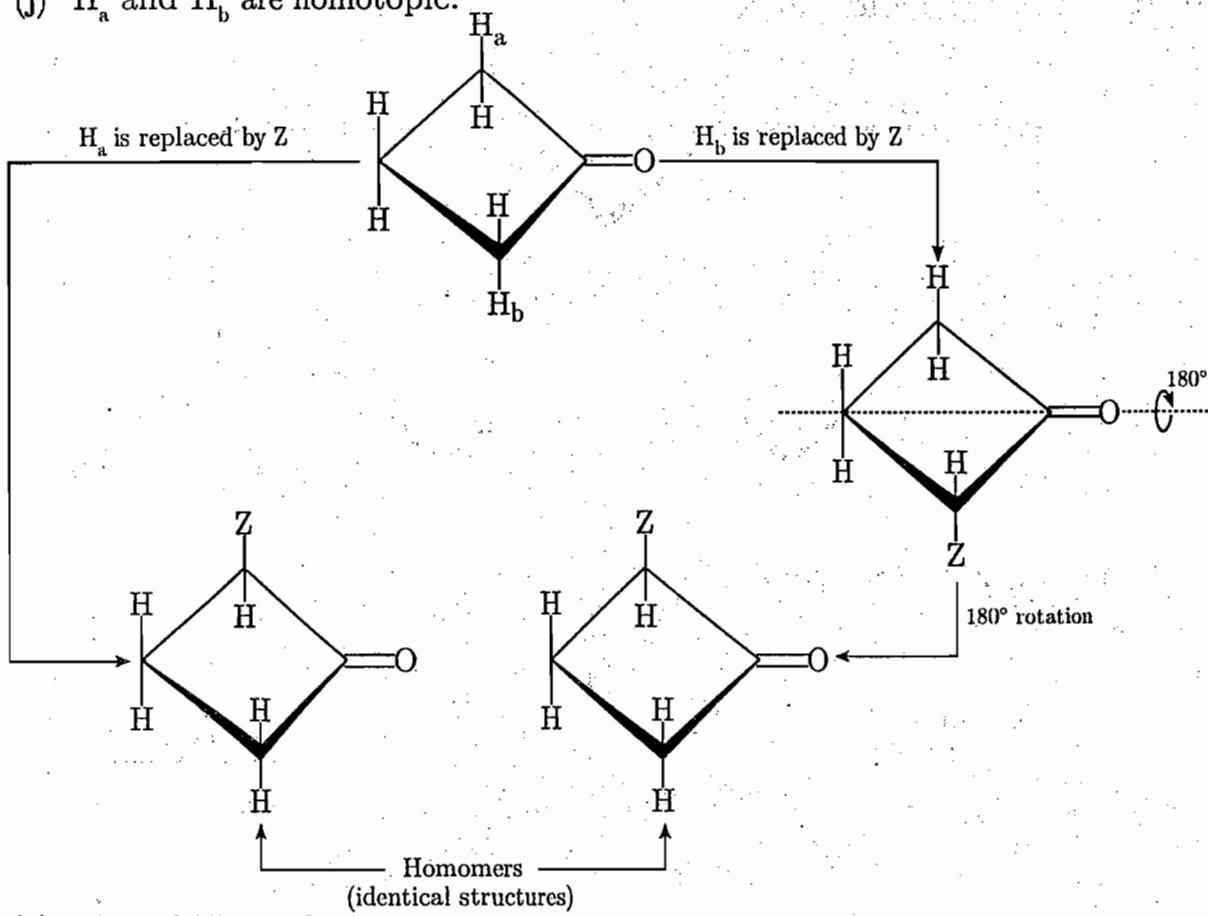
(h) H_a and H_b are homotopic.



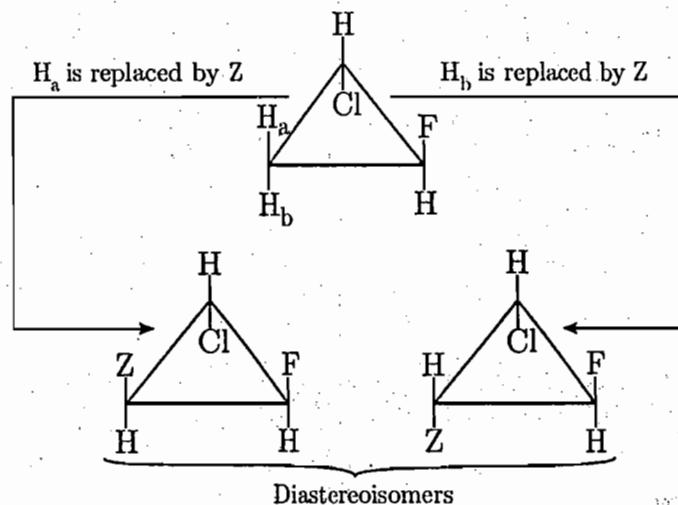
(i) H_a and H_b are enantiotopic.



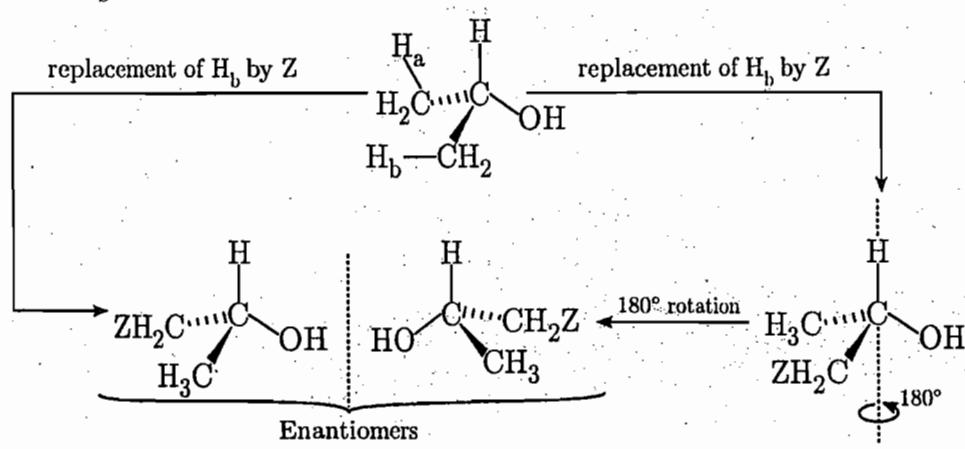
(j) H_a and H_b are homotopic.



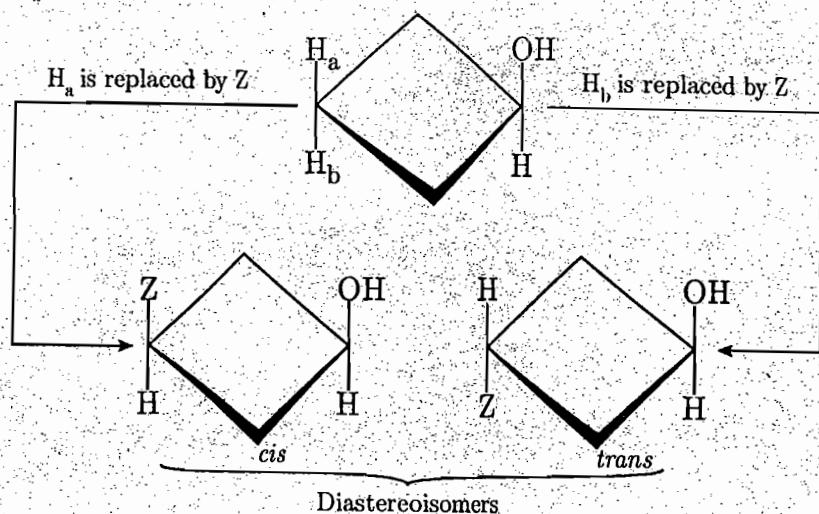
(k) H_a and H_b are diastereotopic.



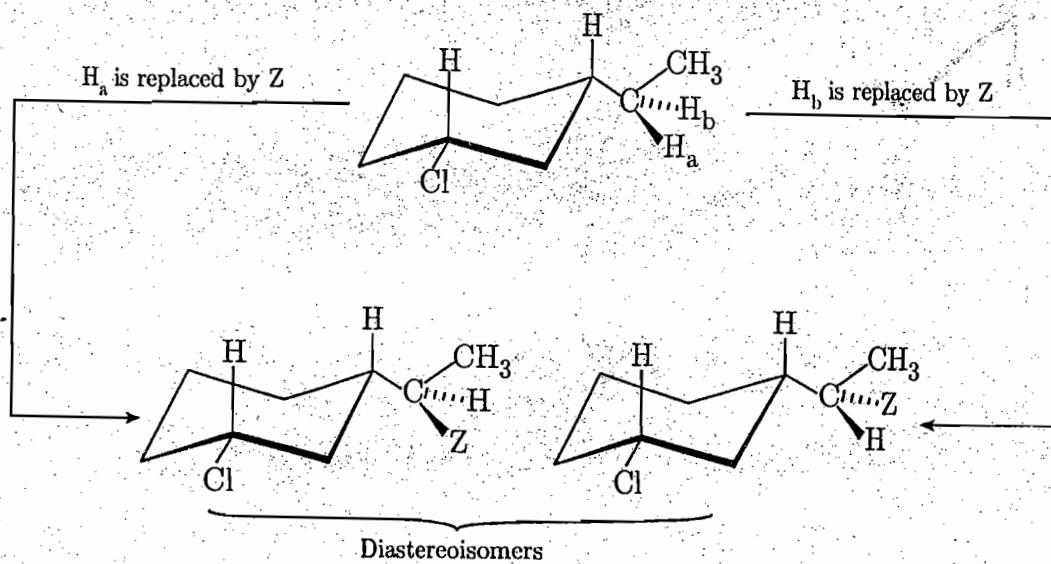
(l) H_a and H_b are enantiotopic.



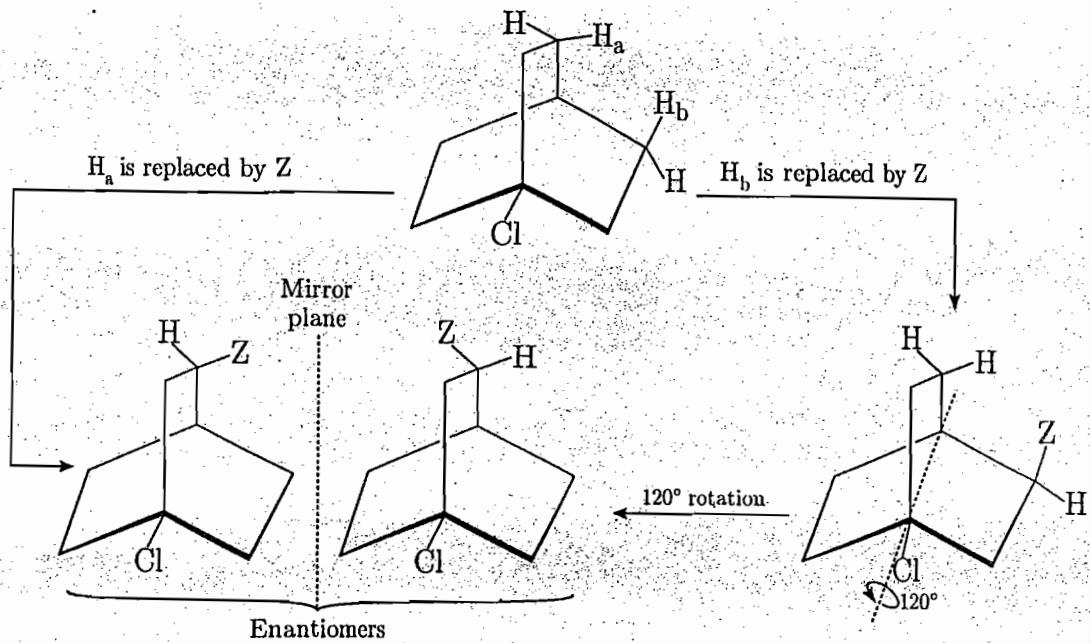
(m) H_a and H_b are diastereotopic.



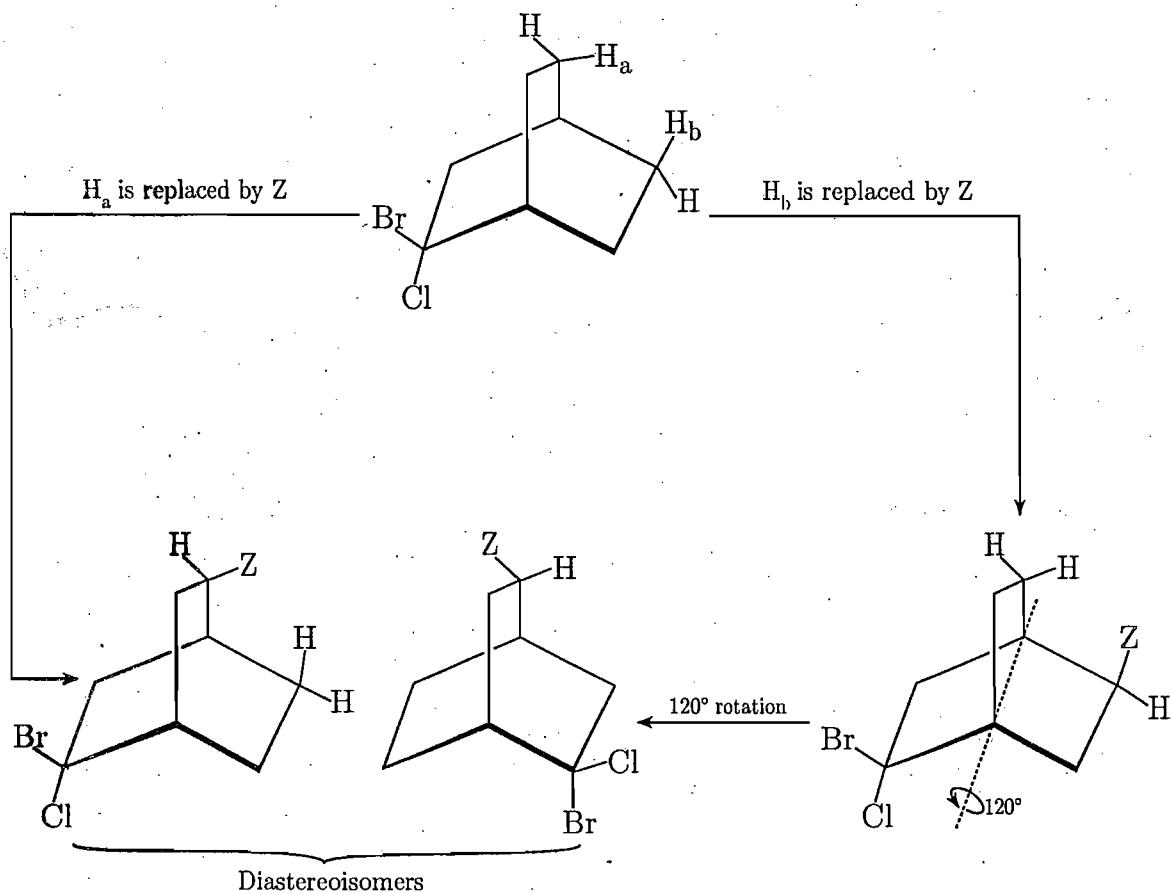
(n) H_a and H_b are diastereotopic.



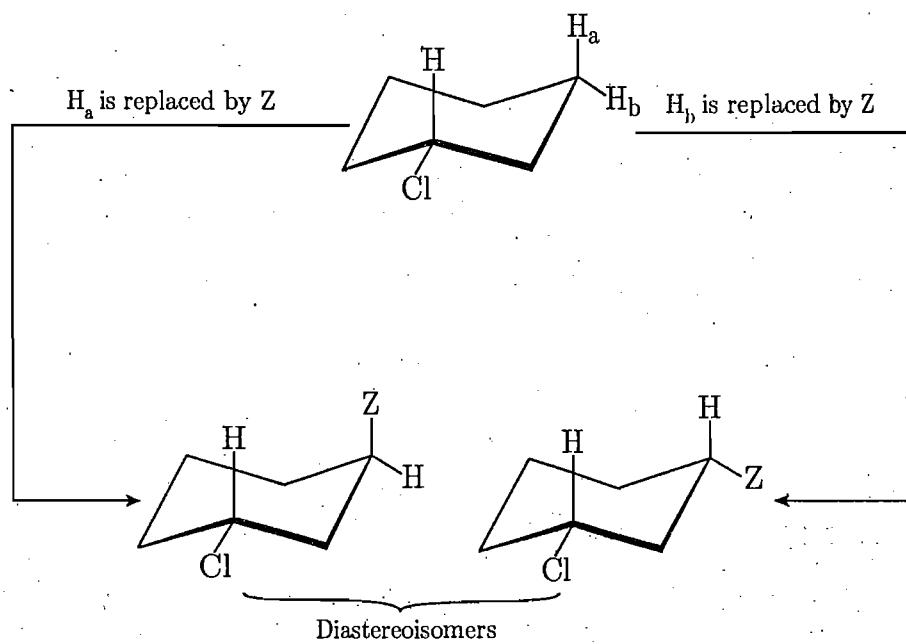
(o) H_a and H_b are enantiotopic.



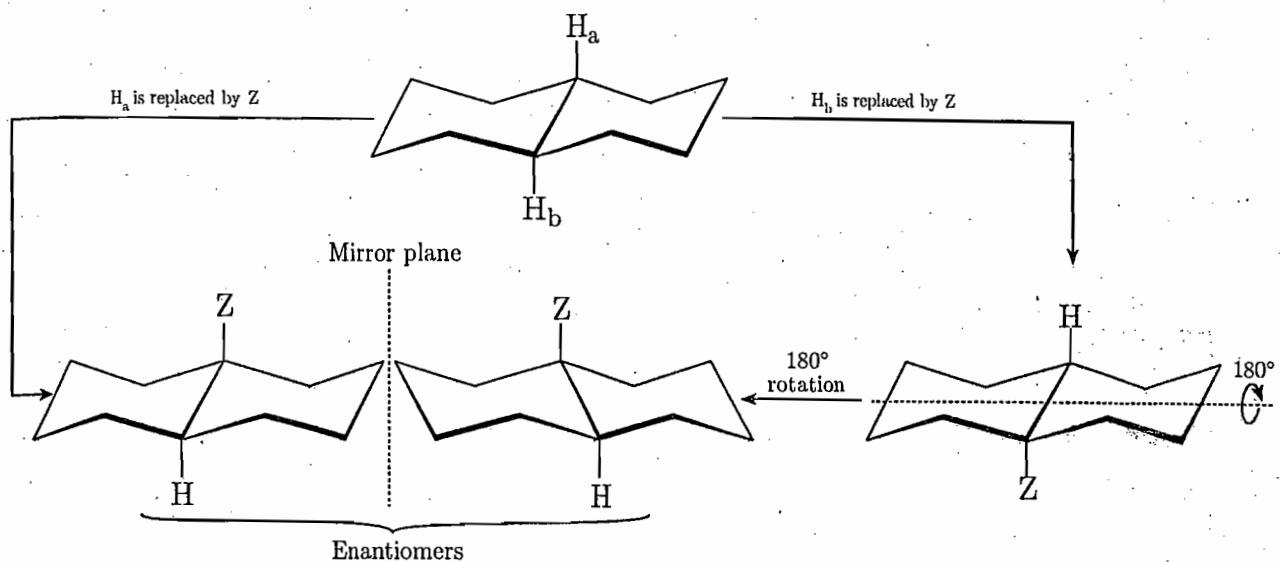
(p) H_a and H_b are diastereotopic.



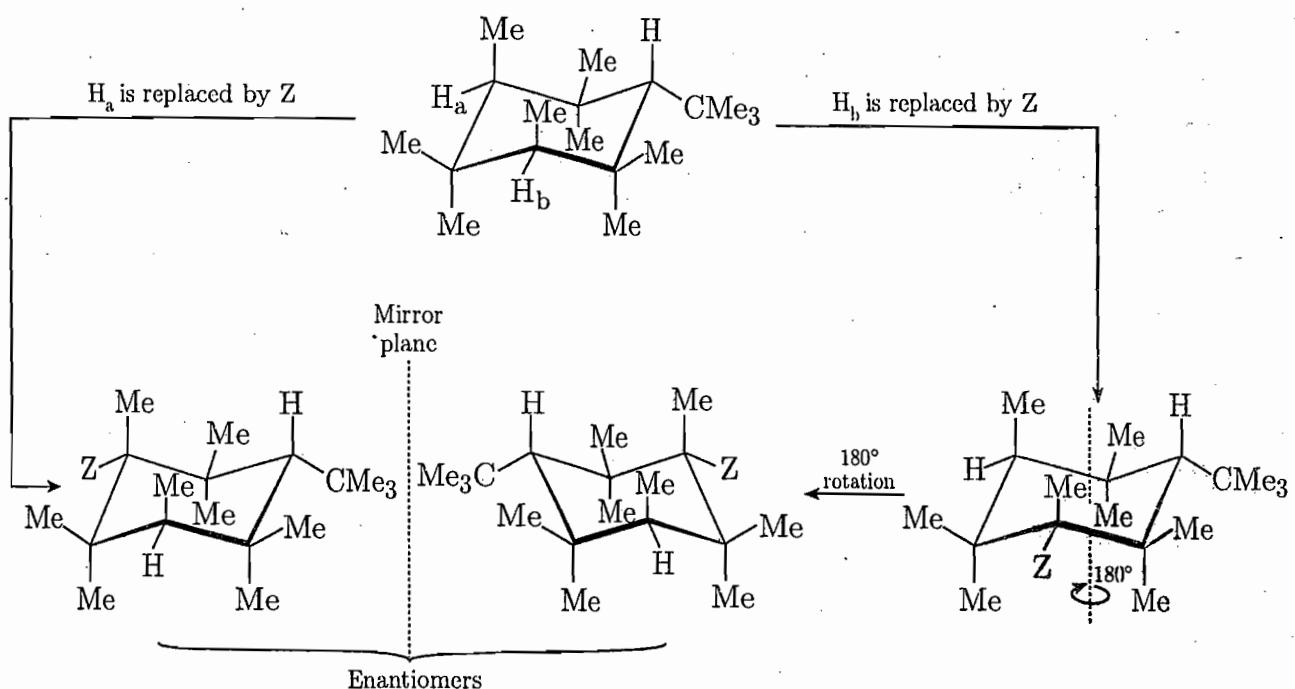
(q) H_a and H_b are diastereotopic.



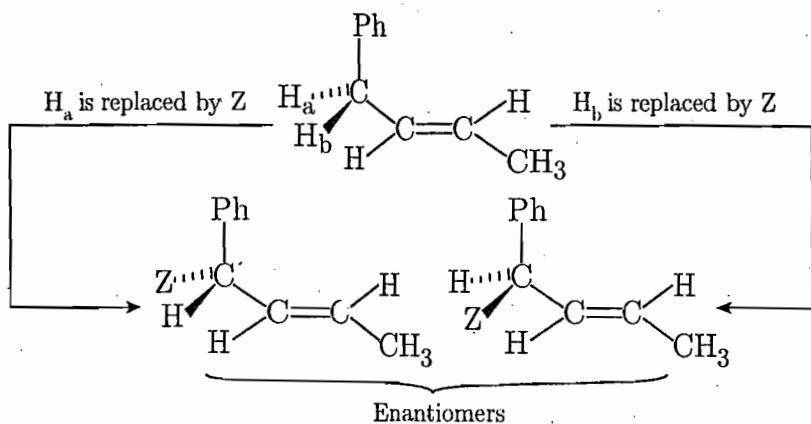
(r) H_a and H_b are enantiotopic.



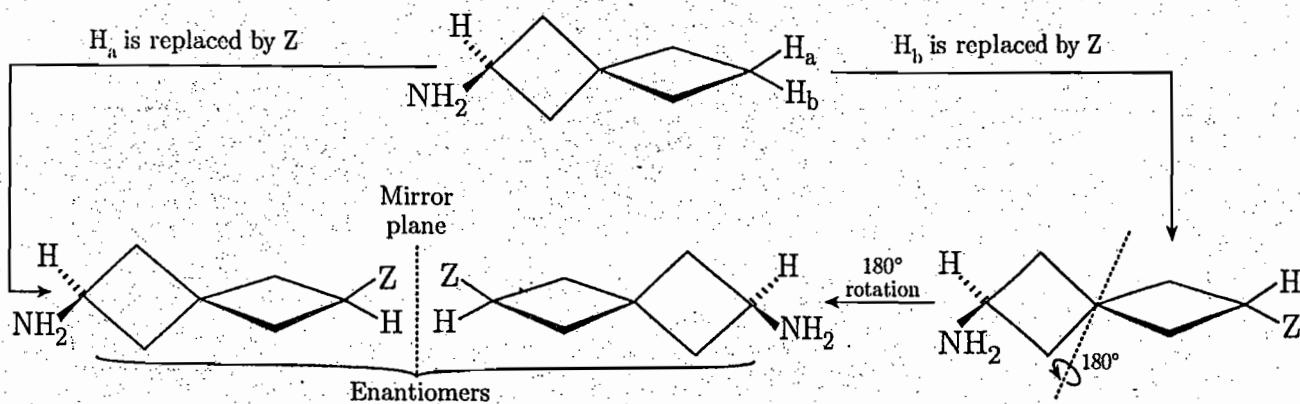
(s) H_a and H_b are enantiotopic.



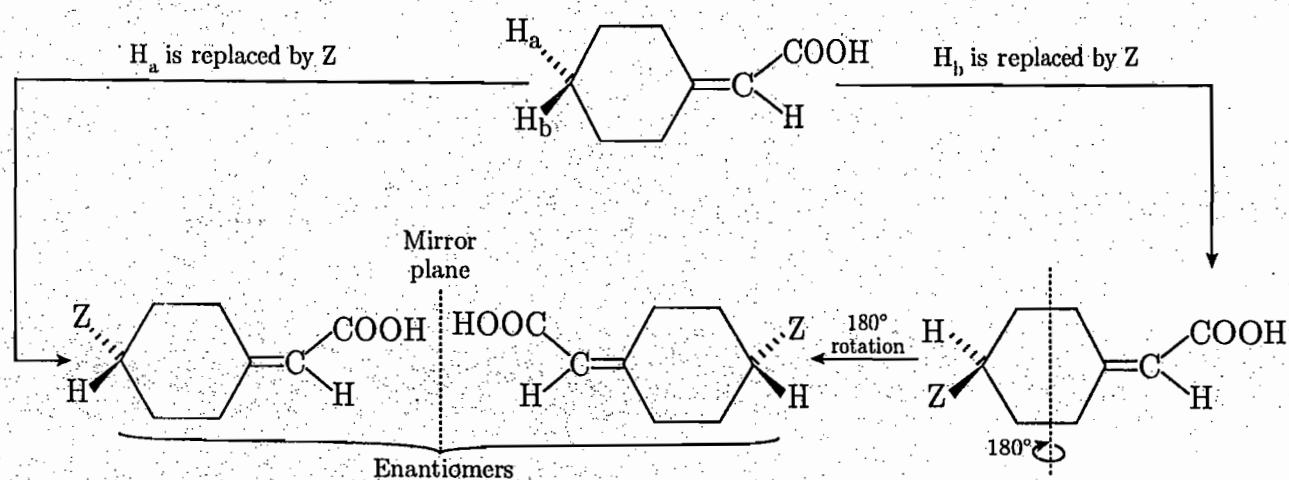
(t) H_a and H_b are enantiotopic.



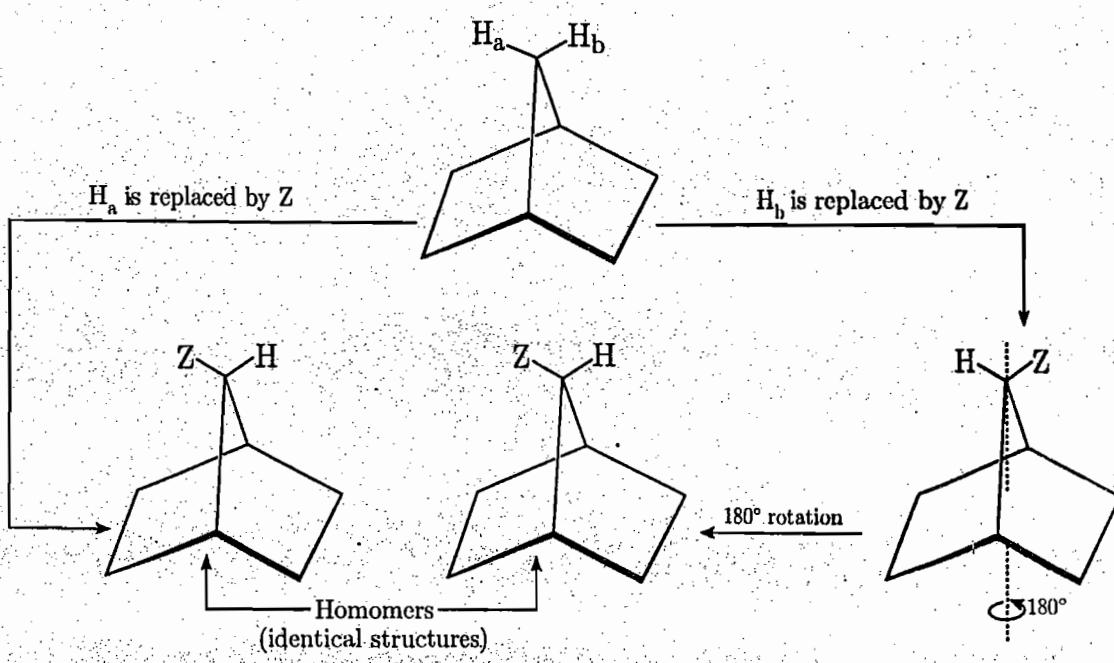
(u) H_a and H_b are enantiotopic.



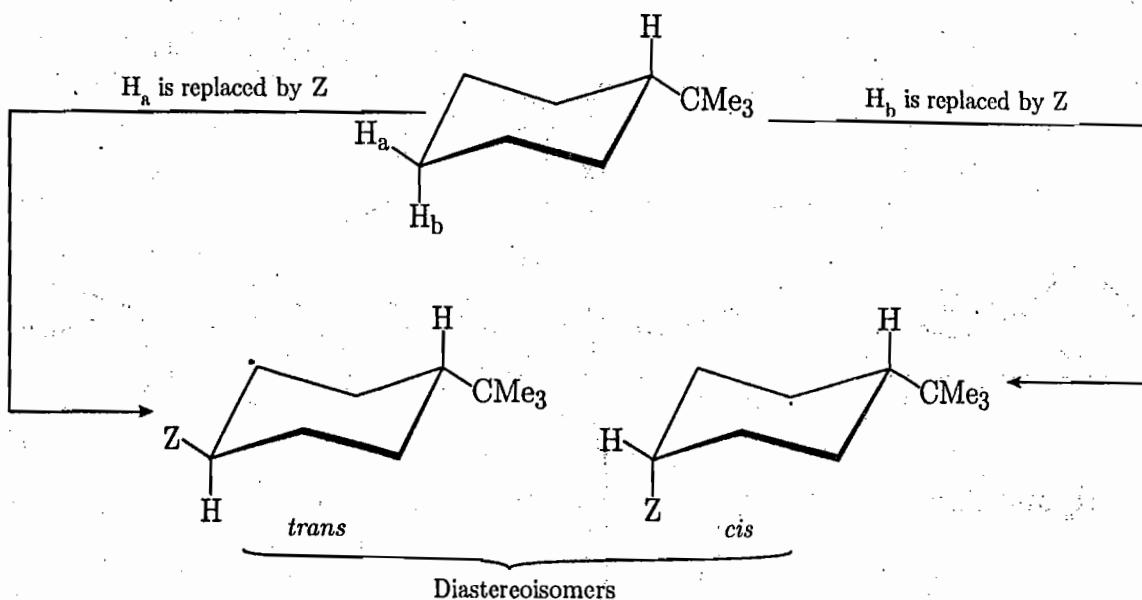
(v) H_a and H_b are enantiotopic.



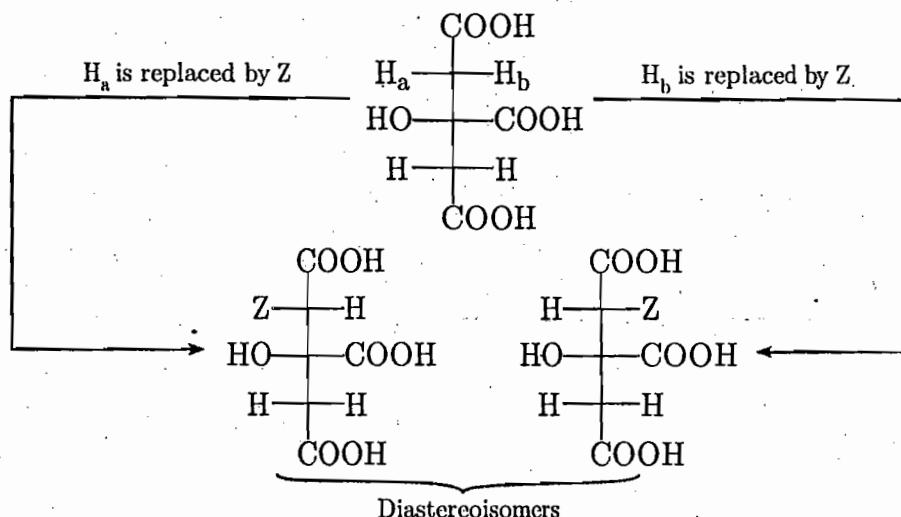
(w) H_a and H_b are homotopic.



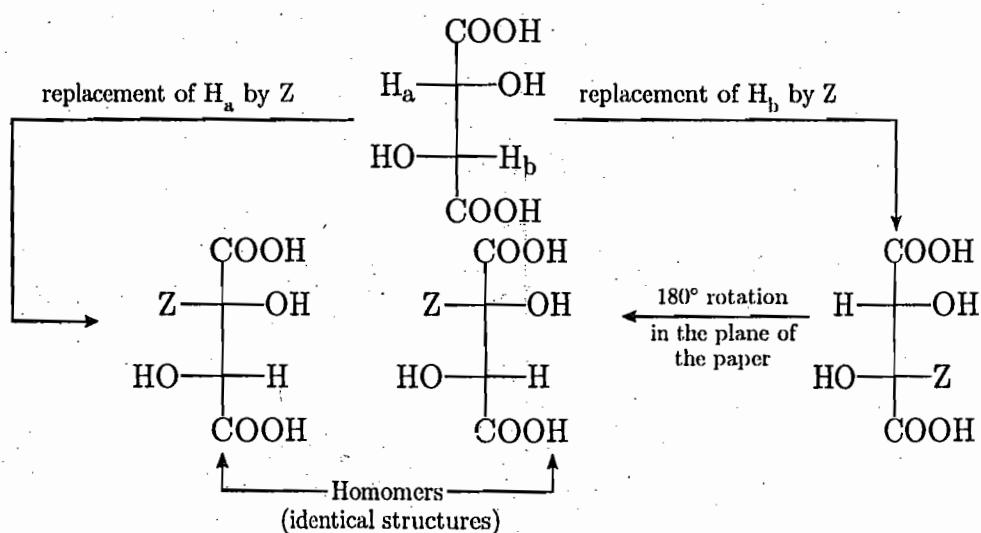
(x) H_a and H_b are diastereotopic.



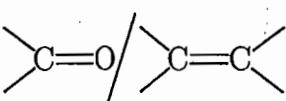
(y) H_a and H_b are diastereotopic.

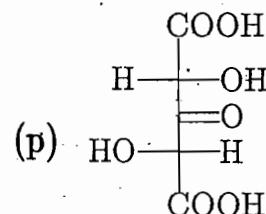
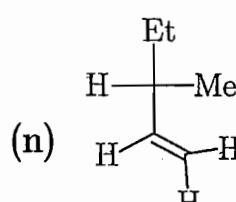
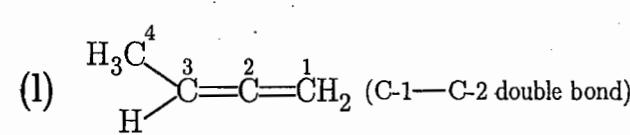
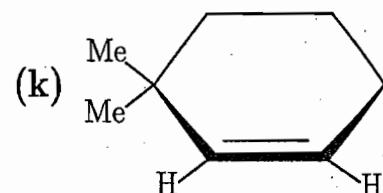
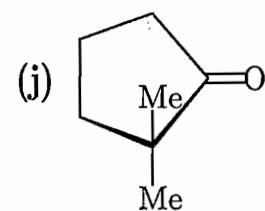
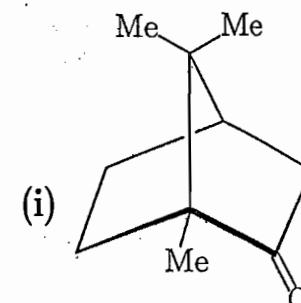
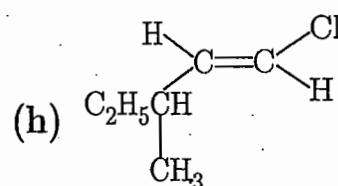
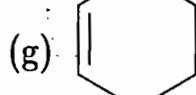
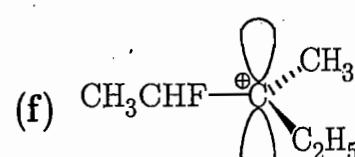
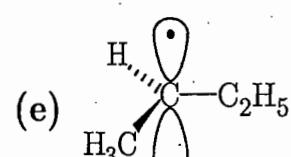
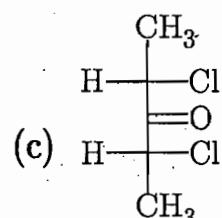
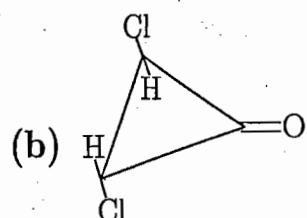


(z) H_a and H_b are homotopic.

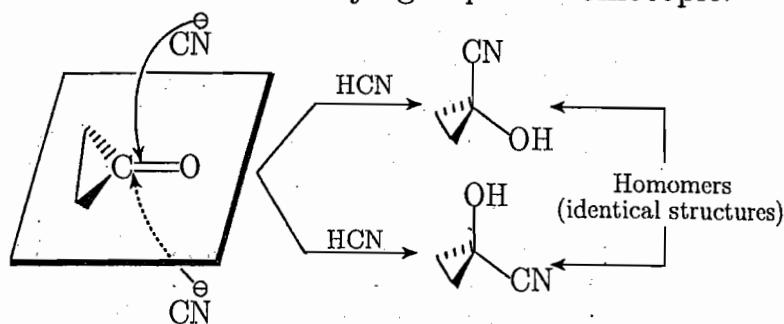


(N.B. The two hydrogens of *meso*-tartaric acid are enantiotopic.)

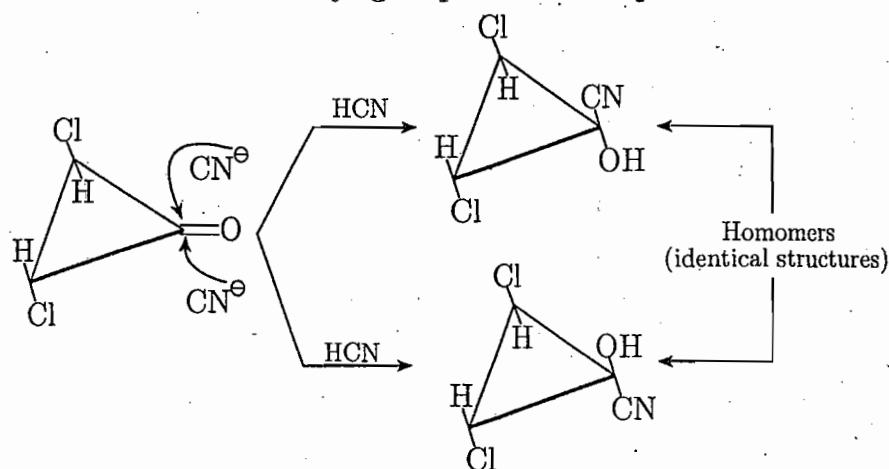
► 2.7 Label the  faces in each of the following compounds as homotopic, enantiotopic or diastereotopic. Demonstrate by suitable reactions.



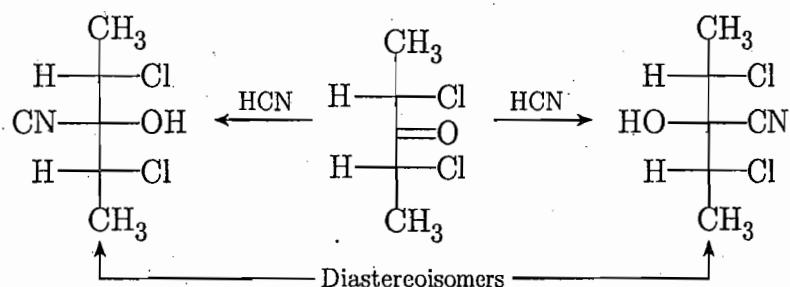
Ans. (a) The two faces of the carbonyl group are homotopic.



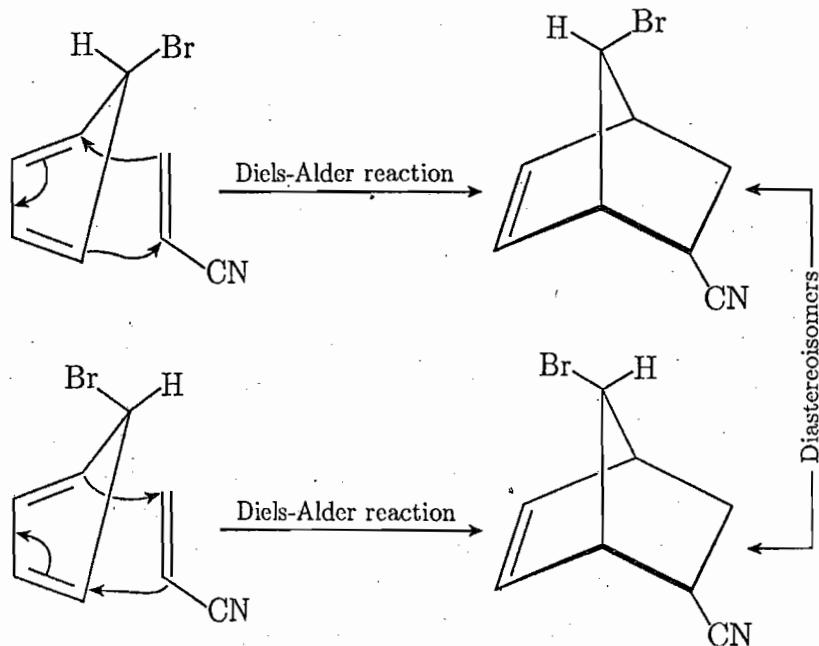
(b) The two faces of the carbonyl group are homotopic.



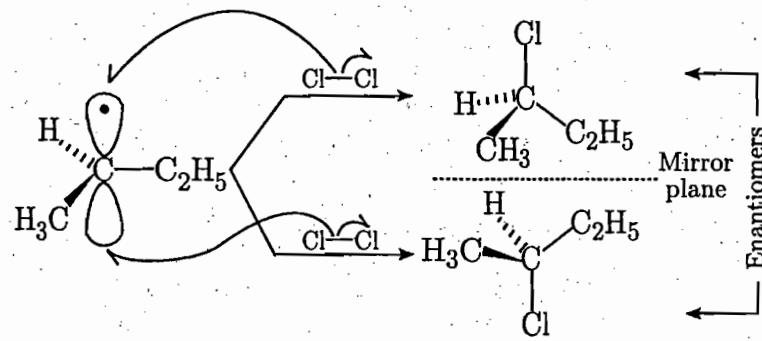
(c) The two faces of the carbonyl group are diastereotopic.



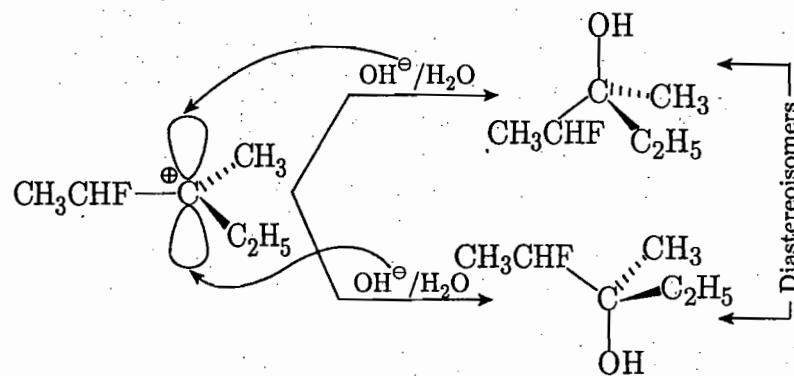
(d) The two faces of the ring are diastereotopic. This may be shown by Diels-Alder reaction.



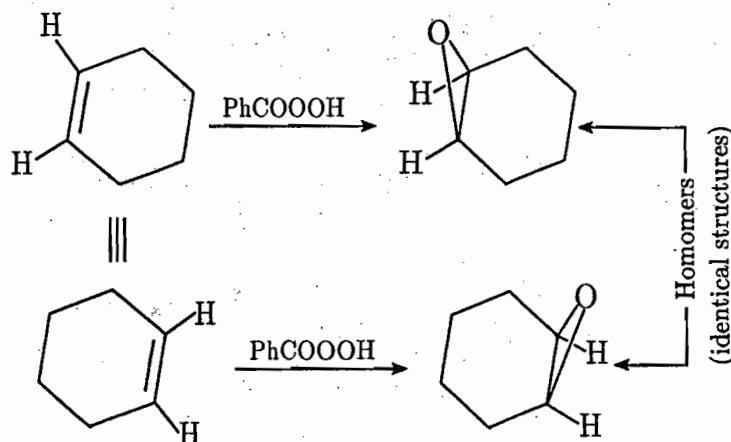
- (e) The two faces of the free radical are enantiotopic because attachment of a fourth ligand, e.g., Cl, to one or the other face gives one or the other enantiomer.



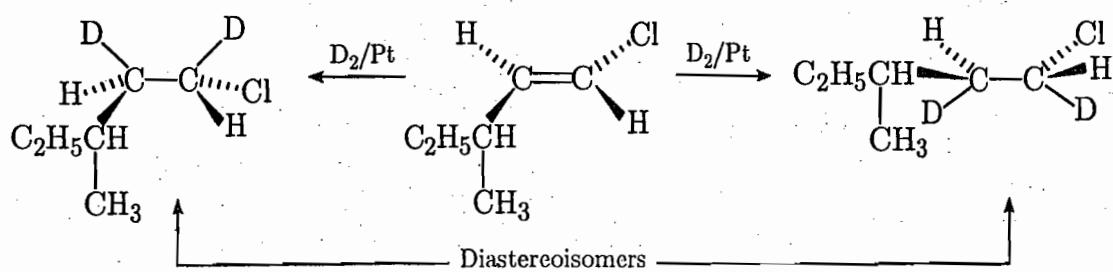
- (f) The two faces of the flat carbocation are diastereotopic.



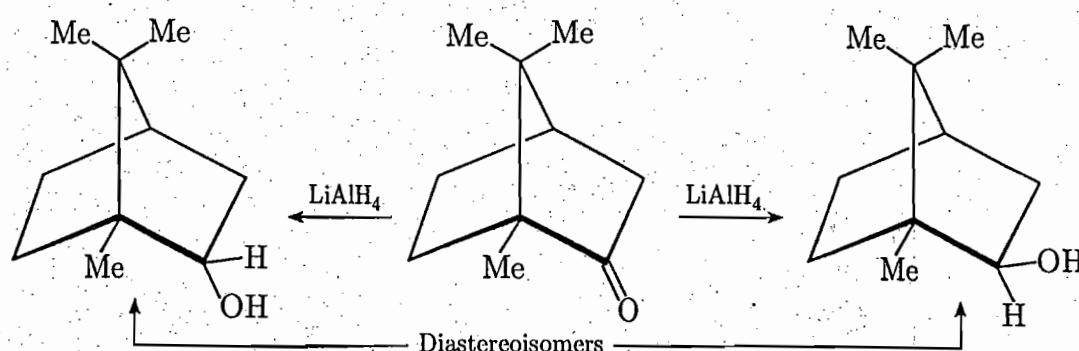
- (g) The two faces of the double bond are homotopic.



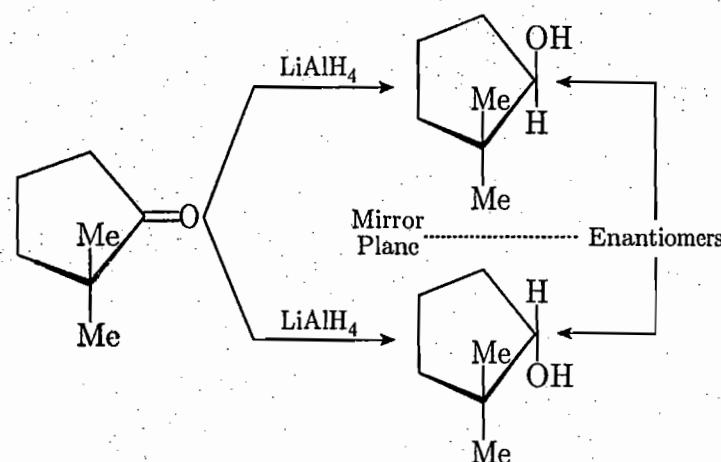
- (h) The two faces of the carbon-carbon double bond are diastereotopic.



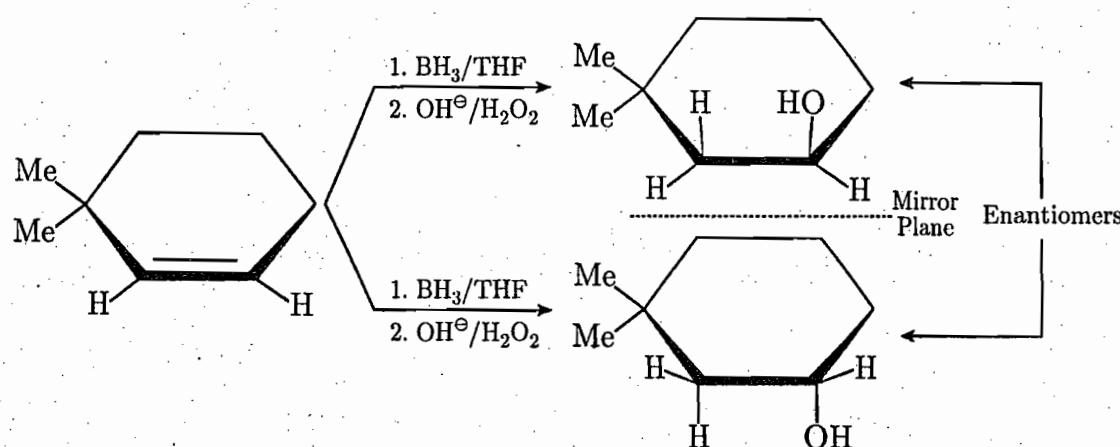
(i) The two faces of the carbonyl group are diastereotopic.



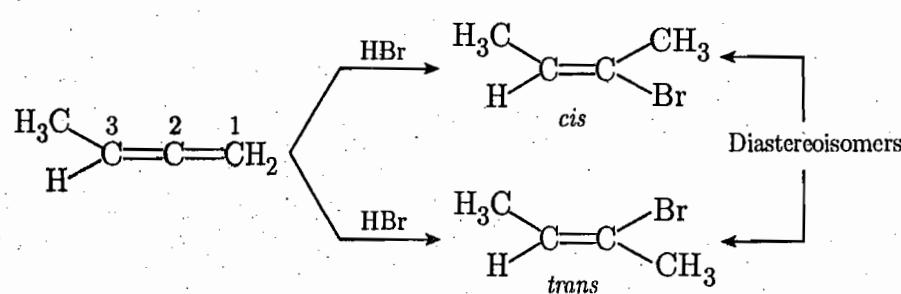
(j) The two faces of the carbonyl group are enantiotopic.



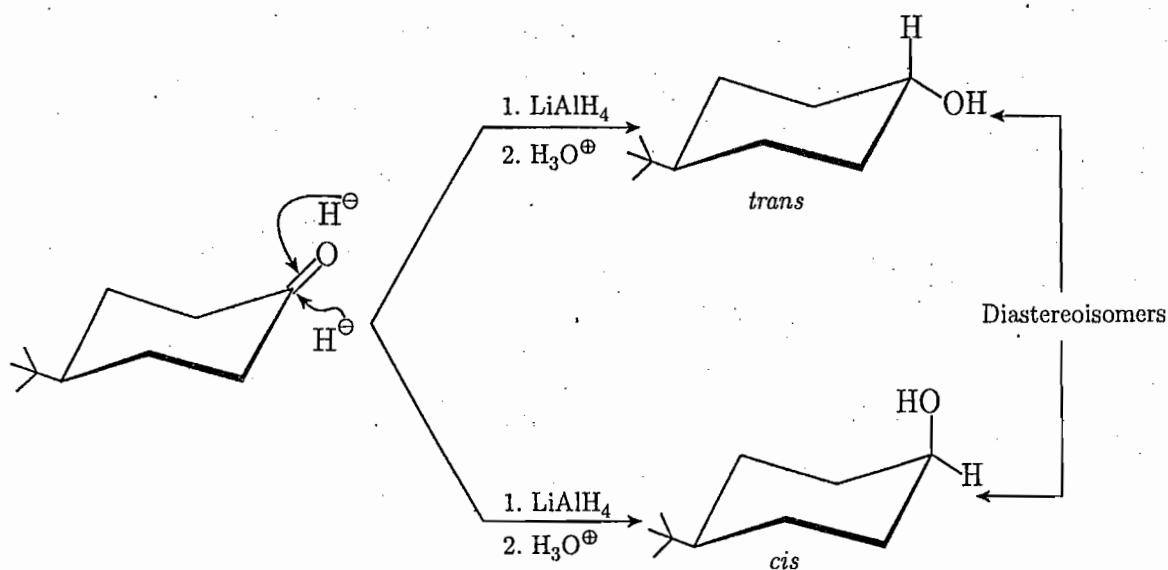
(k) The two faces of the π bond are enantiotopic.



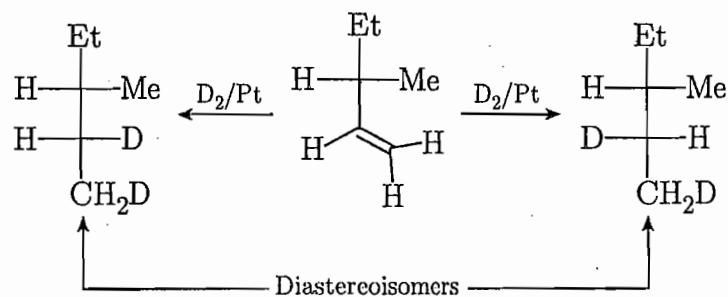
(l) The two faces of the double bond between C-1 and C-2 in this allene are diastereotopic.



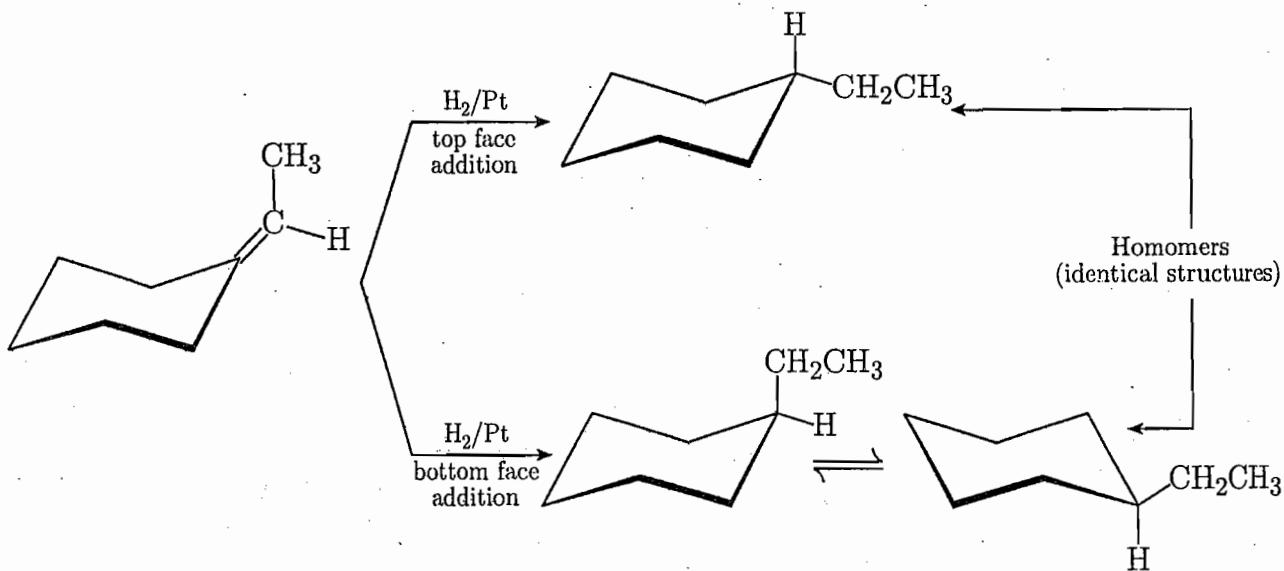
(m) The two faces of the carbonyl groups are diastereotopic.



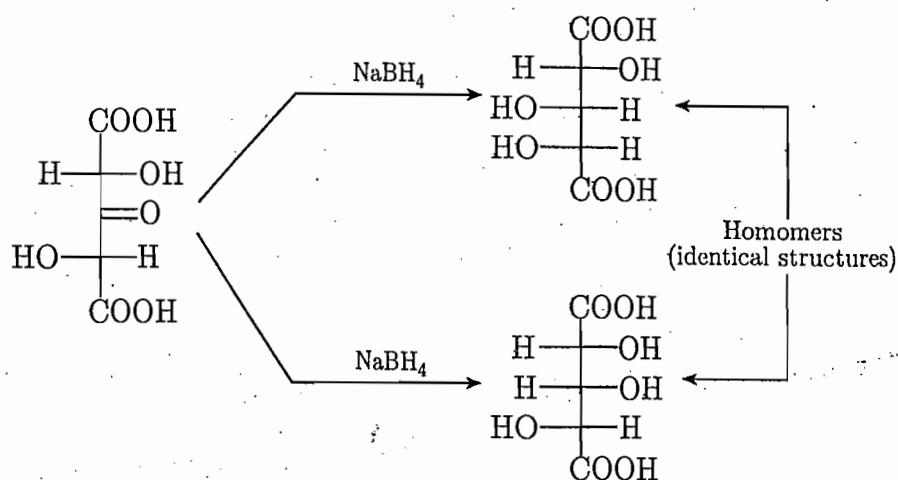
(n) The two faces of the carbon-carbon double bond are diastereotopic.



(o) The two faces of the carbon-carbon double bond are homotopic.

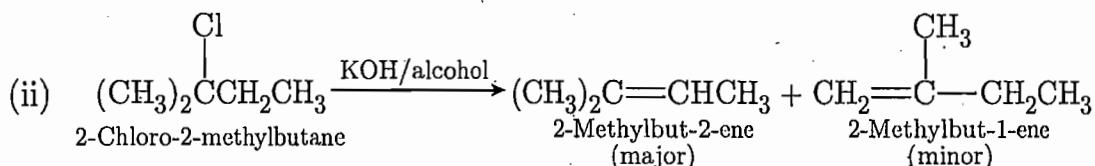
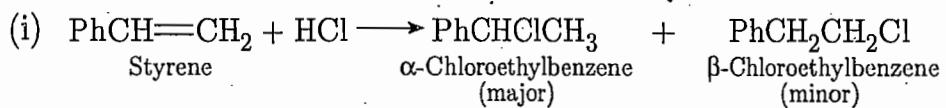


(p) The two faces of the carbonyl group are homotopic.

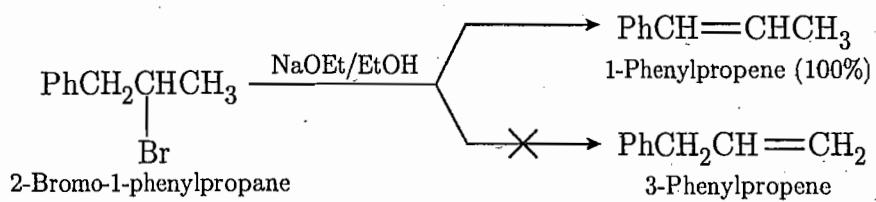


► 2.8 Explain the following terms with suitable examples. (a) Regioselective reaction (b) Regiospecific reaction (c) Chemoselective reaction (d) Stereoselective reaction (e) Stereospecific reaction.

Ans. (a) A reaction is said to be regioselective if one of a possible set of constitutional isomers is produced predominantly. For example :

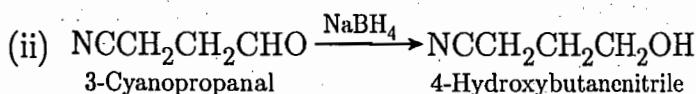
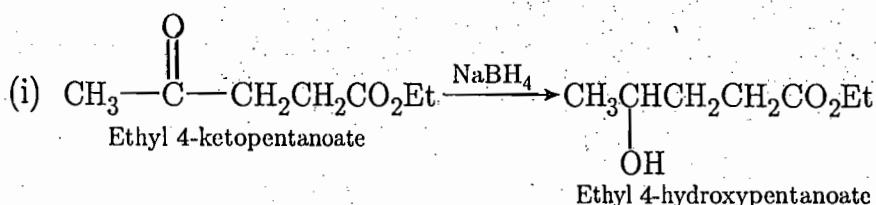


(b) A reaction is said to be regiospecific if one of a possible set of constitutional isomers is produced exclusively. For example :



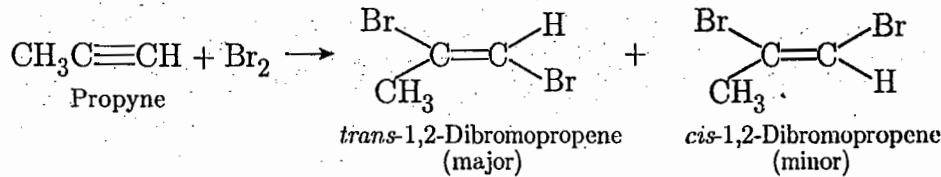
(c) A chemoselective reaction is one in which a reagent can cause change in a particular functional group when other functional groups are also present in the substrate molecule.

Sodium borohydride (NaBH_4) can reduce C=O and $-\text{CHO}$ groups, but not $-\text{COOR}$ and $-\text{CN}$ groups. The following reactions are, therefore, examples of chemoselective reaction.

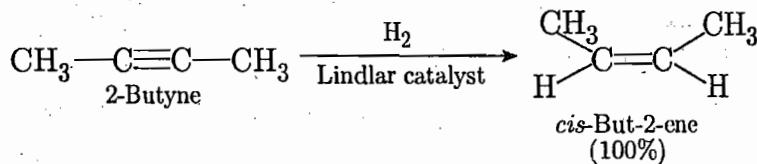


(d) If a reaction that generates a carbon-carbon double bond or a chiral centre in the product leads to the preferential formation of one stereoisomer over another, it is called a stereoselective reaction. For example :

- (i) Addition of Br_2 to propyne is a stereoselective reaction because one diastereoisomeric product, the *trans*-isomer of 1,2-dibromopropene, is formed predominantly.



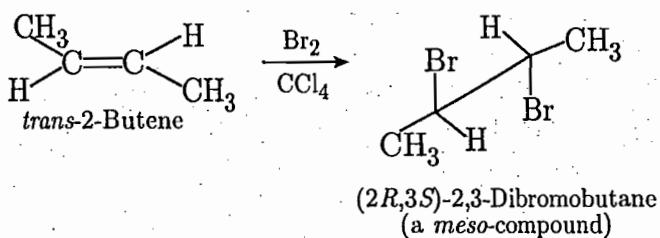
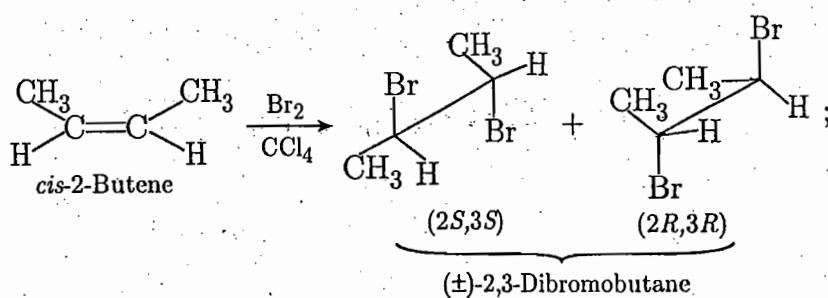
- (ii) Reduction of but-2-yne with H_2 in the presence of Lindlar's catalyst is a stereoselective reaction. Only *cis*-but-2-ene is formed in this reaction with no observable amount of the *trans*-isomer.



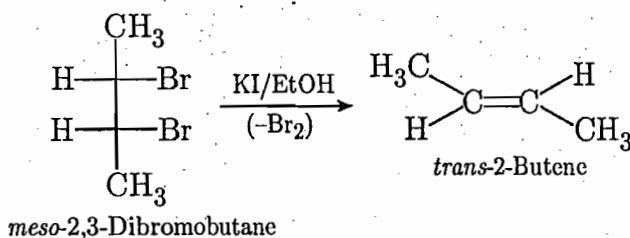
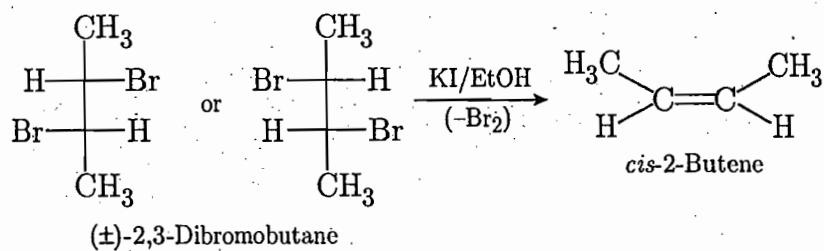
[Depending on the degree of preference for a particular stereoisomer, a reaction is often described as being moderately stereoselective, highly stereoselective, or completely stereoselective.]

- (e) A reaction is stereospecific if the reactant can exist as stereoisomers and each stereoisomeric reactant leads to the formation of a different stereoisomeric product or a different set of stereoisomeric products. For example :

- (i) When *trans*-2-butene adds bromine, the product is the *meso*-compound, (*2R,3S*)-2,3-dibromobutane and when *cis*-2-butene adds bromine, the product is a racemic form of (*2R,3R*)-2,3-dibromobutane and (*2S,3S*)-2,3-dibromobutane. Thus, by definition, both reactions are stereospecific. One stereoisomeric form of the reactant (*trans*-2-butene) gives one product (the *meso*-compound) while the other stereoisomeric form of the reactant (*cis*-2-butene) gives a stereochemically different product (the enantiomers).

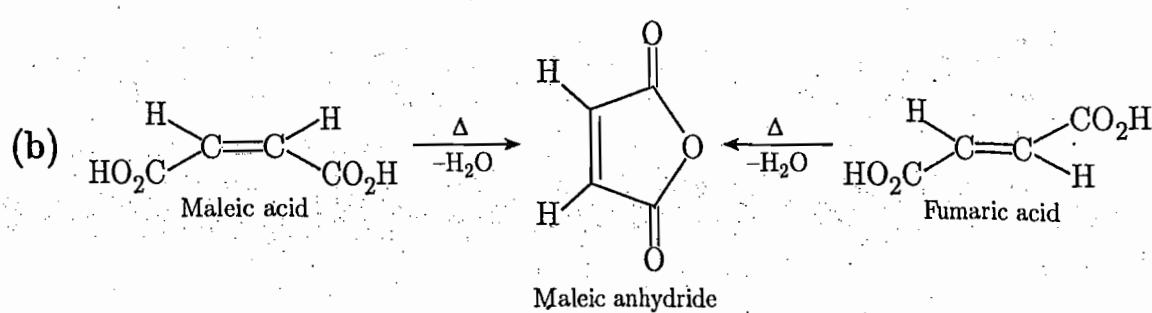
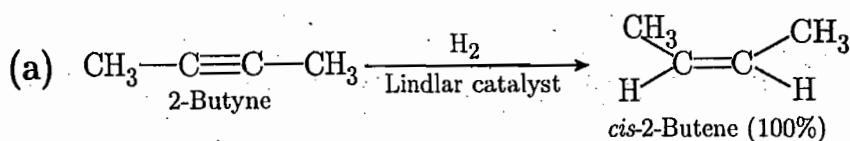


- (ii) Formations of *cis*- and *trans*-2-butene from (\pm) - and *meso*-2,3-dibromobutane respectively represent stereospecific reactions.



[All stereospecific reactions are necessarily stereoselective but all stereoselective reactions are not necessarily stereospecific and this is because there are stereoselective reactions in which the reactant cannot exist as stereoisomers due to absence of a carbon-carbon double bond or a chiral centre.]

► 2.9 Explain why the following reactions are not stereospecific.



Ans. (a) The reaction is not stereospecific because the substrate cannot exist as stereoisomers.

(b) The reaction is not stereospecific because two different stereoisomeric substrates do not lead to two different stereoisomeric products but a common product (the *cis*-anhydride).

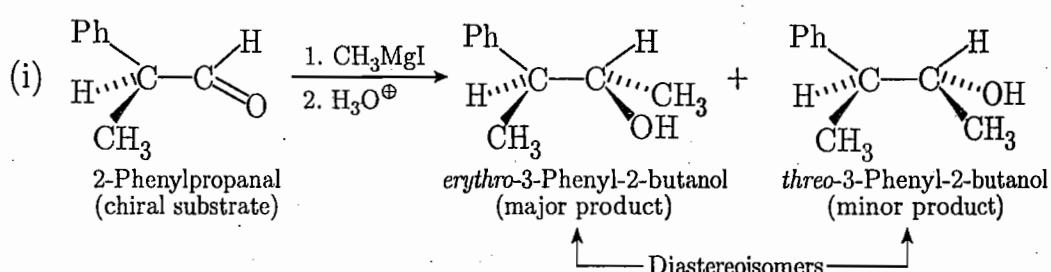
[The reactions are, in fact, completely stereoselective.]

ASYMMETRIC SYNTHESIS

► 2.10 (a) What is asymmetric synthesis? Explain giving examples.

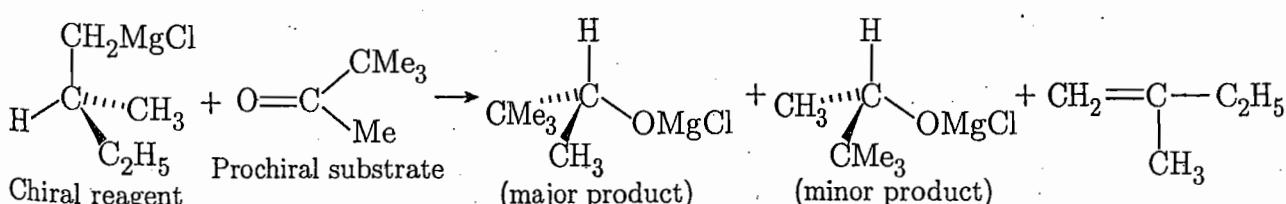
(b) Explain the principle of asymmetric synthesis.

Ans. (a) Reactions in which an achiral substrate produces enantiomeric products in unequal amounts or a chiral substrate produces diastereomeric products in unequal amounts are called asymmetric synthesis. In fact, asymmetric synthesis is a generalised name of stereoselective reactions and therefore, it comprises both enantioselective and diastereoselective reactions. An asymmetric synthesis needs the presence of some kind of chiral influence. Thus, for the preferential formation of one stereoisomer (either enantiomer or diastereoisomer) over the other, the presence of a chiral substrate, reagent, catalyst, solvent or physical force (such as circularly polarized light) is required. The term asymmetric induction is used to mean the control of stereoselectivity exerted by the chiral influence. The following reactions are two examples of asymmetric synthesis.



In this example, preferential attack on one of the diastereotopic faces of the prochiral ketone occurs due to asymmetric induction caused by the existing chiral centre. The reaction is called diastereoselective because it occurs through diastereoface differentiation.

(ii)



In this example, a new chiral centre is created on a prochiral centre by the preferred attack on one of the enantiotopic faces by a chiral reagent. The reaction occurs through enantioface differentiation and is called enantioselective.

[The first example is a case of intramolecular asymmetric induction and the second example is a case of intermolecular asymmetric induction.]

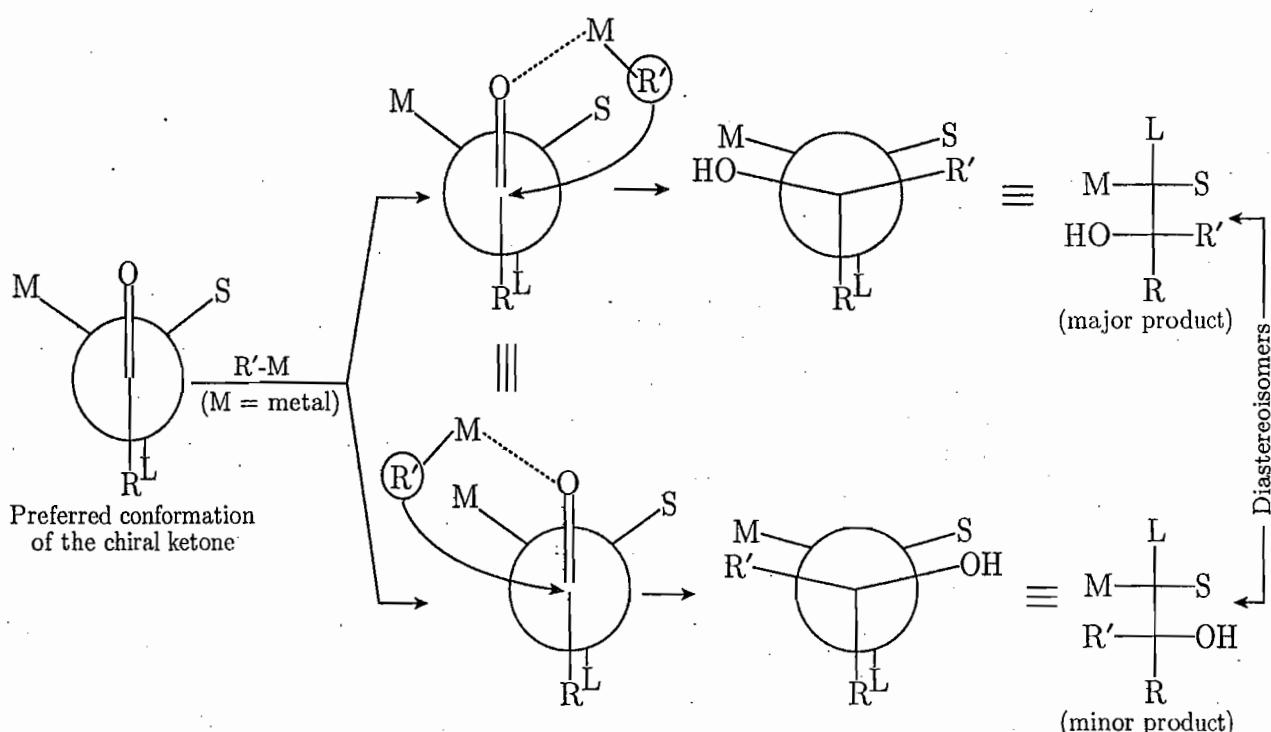
(b) In asymmetric synthesis, the chiral agent plays an active part and be integral to the transition state, so that two diastereoisomeric transition states are produced. Competing reactions with diastereoisomeric transition states have different activation energies (ΔG^\ddagger). For this reason, one stereoisomer is produced more rapidly than and in excess over the other.

► 2.11 (a) State and explain Cram's rule with suitable example.

(b) There are situations when Cram's rule may not be followed.
Illustrate these with suitable examples.

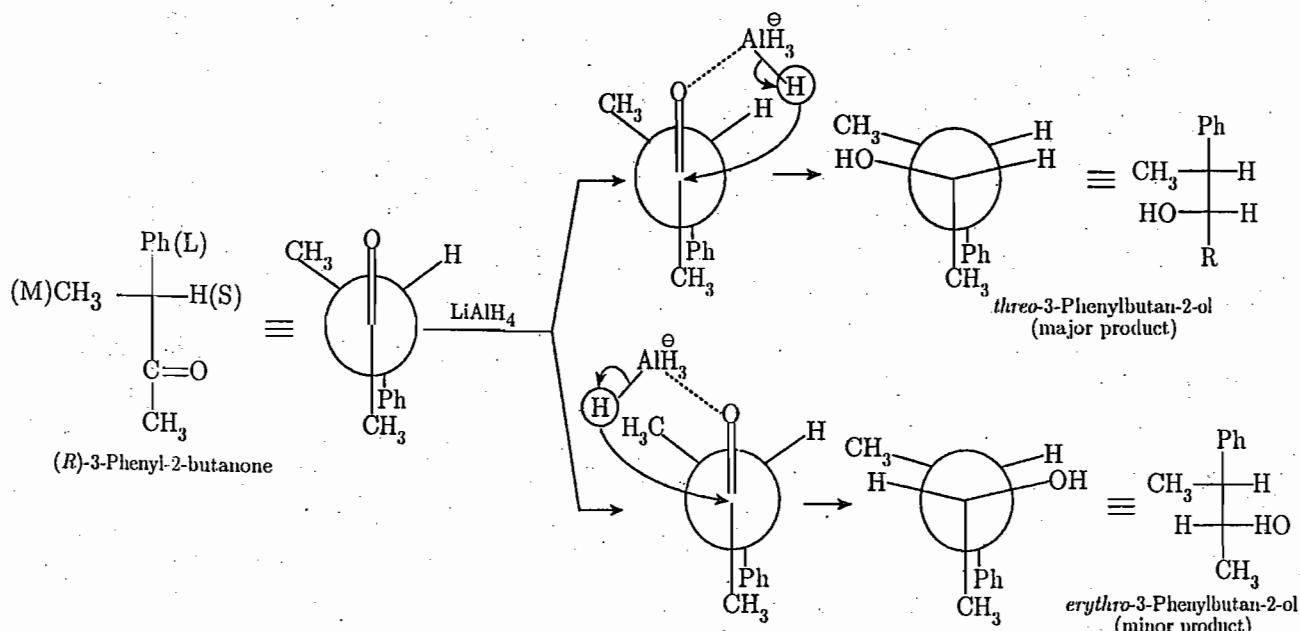
Ans. (a) Cram's rule accounts for the preferential formation of one diastereoisomer in terms of steric interactions involved in the kinetically controlled addition reactions of chiral ketones with organometallic and metal hydride reagents.

According to Cram's rule, nucleophilic addition to a carbonyl carbon atom of a chiral carbonyl compound like RCOCLMS , where L, M and S stand for large, medium and small groups respectively, will take place from the less hindered side, i.e., from the side of the small group (S) in a conformation where the C=O group is flanked by two smaller groups (M and S) with the large group (L) remaining nearly eclipsed with R (the *open chain model*). The C=O group gets complexed with the metallic part of the reagent and becomes effectively the bulkiest group and is thus placed better in between the two smaller groups. A typical Cram's model is shown below as its Newman projection.

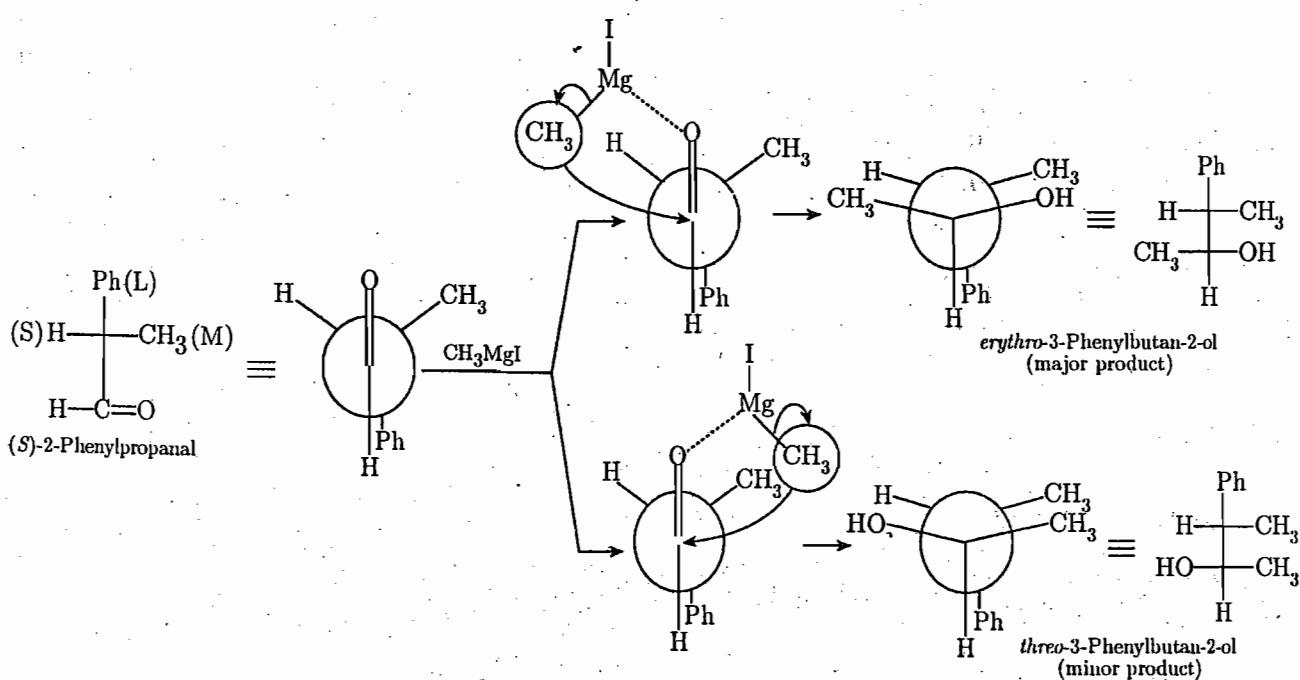


Example :

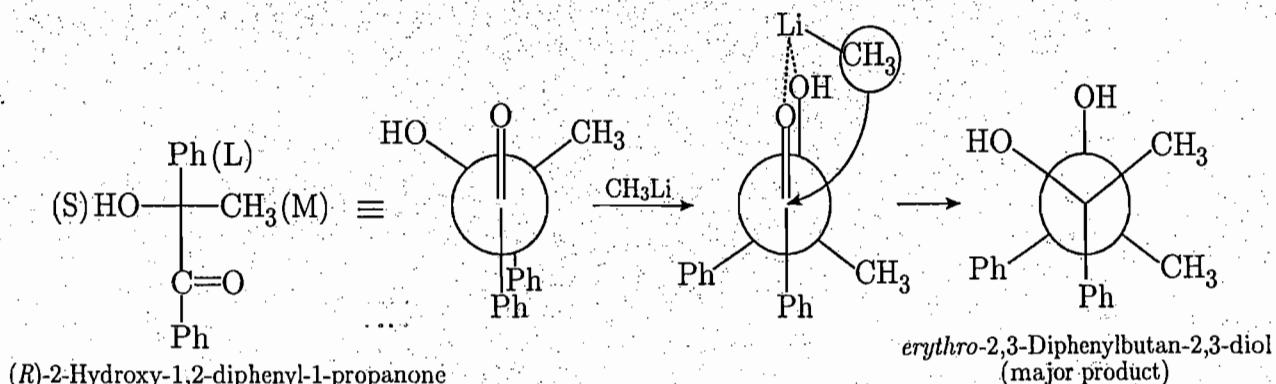
- (i) Lithium aluminium hydride reduction of 3-phenyl-2-butanone having (R) or (S) configuration gives *threo*-3-phenylbutan-2-ol as the major product (70%). This observation could be rationalised by applying Cram's rule. The hydride ion (H^-) from $LiAlH_4$ attacks the carbonyl carbon atom from the less hindered side, i.e., from the side of hydrogen to give the major product.



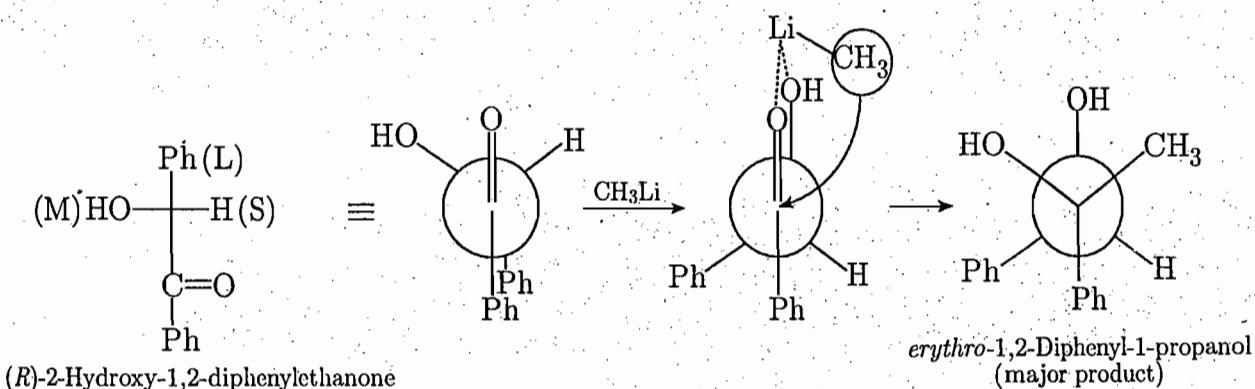
- (ii) (*S*)-2-Phenylpropanal reacts with methylmagnesium iodide to give *erythro*-3-phenylbutan-2-ol as the major product (67%). In the Cram's model, CH_3 from CH_3MgI attack from the less hindered side, i.e., from the side of hydrogen to give the major product.



(b) If one of the substituents on the stereocentre of the ketone is $-\text{OH}$, $-\text{NH}_2$ or $-\text{OR}$ (a group capable of co-ordinating with the reagents), the stereochemistry of the product is predicted not on the basis of *open chain* model but on the basis of a rigid *cyclic model* in which the metallic part of the reagent is doubly co-ordinated to form a five-membered ring. If the complexing group is small(S) or large(L), the stereochemistry of the product can only be predicted on the basis of rigid cyclic model. For example :

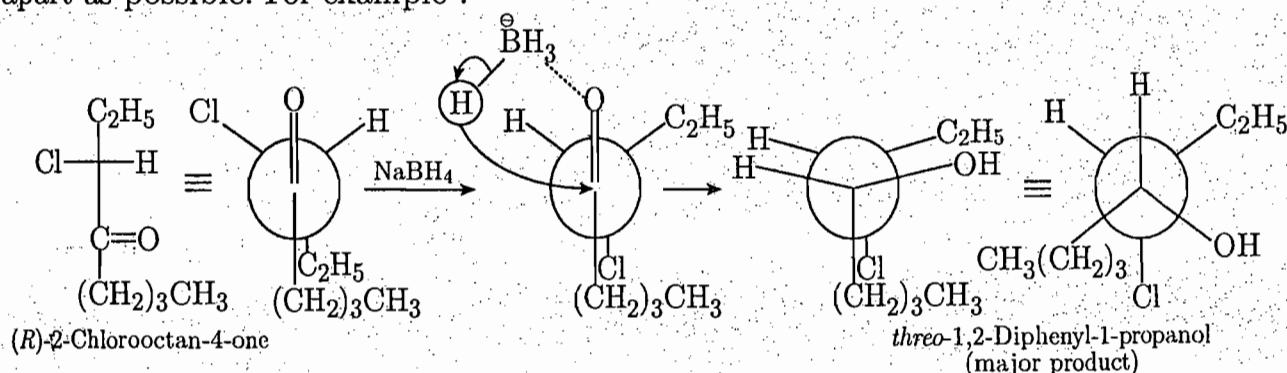


If the complexing group is medium (M), the nucleophile attacks the carbonyl carbon from the side of the small group(S) and the cyclic model predicts the same stereochemistry as the open chain model.



[This model is also referred to as Cram's cyclic (chelate) model.]

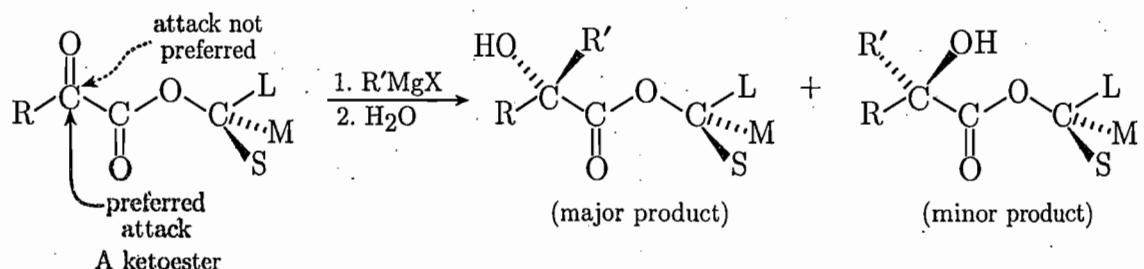
If a strongly electronegative substituent like a halogen atom (e.g., Cl, F) is present on the chiral centre another model, a *dipolar* one is suggested for the prediction of the stereochemistry of the product. In this model, the more stable and preferred conformation is that in which the electronegative atom is in *antiperiplanar* orientation with the $\text{C}=\text{O}$ group. This is because in this conformation repulsion between the negatively polarized oxygen and halogen atoms is minimized since they remain as far apart as possible. For example :



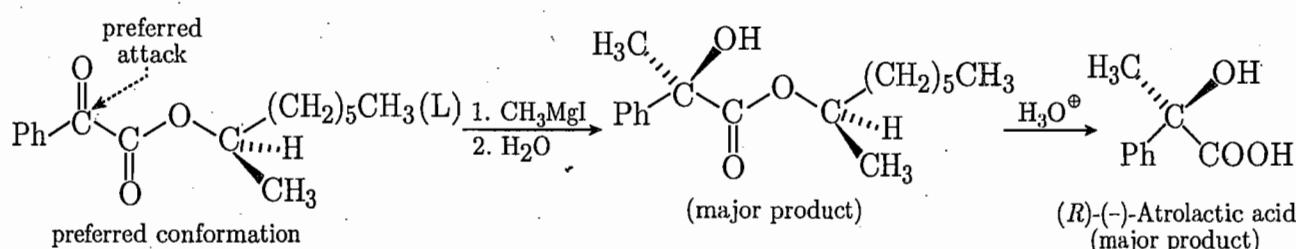
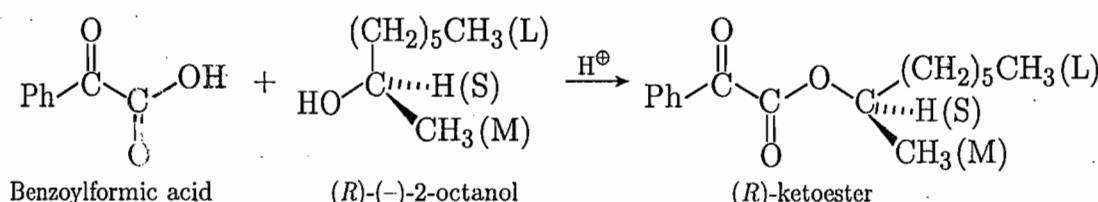
[This model is also referred to as Cram's dipolar model.]

► 2.12 Explain Prelog's rule with a suitable example.

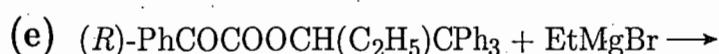
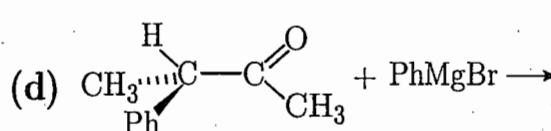
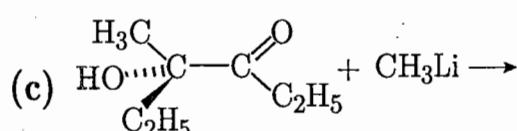
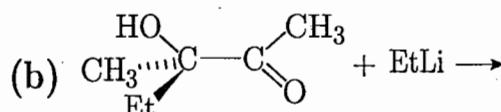
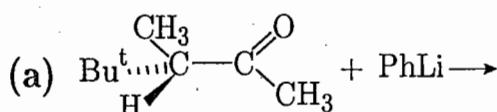
Ans. The stereochemical outcome of nucleophilic addition reactions with ketoesters of the type RCOCOOCSML , Where S, M and L are small, midium and large groups respectively on the chiral centre, be predicted by Prelog's rule. By convention, the molecule is so oriented that the two carbonyl groups are *antiperiplanar* and the large group (L) which lies in the same plane with the rest of the molecule (i.e., RCOCOOCL —L lies in a plane) must be on the same side of the ketonic carbonyl. The reagent (say R'MgX) then approaches from the sterically less hindreed side, i.e., from the side of the small group S to give the predominant diastereoisomer.



For example, if an ester of benzoylformic acid is prepared by reacting with (R)-(-)-2-octanol, then according to Prelog's rule, the ester should give predominantly (R)-(-)-atrolactic acid, when it is subjected to react with methylmagnesium iodide followed by hydrolysis.

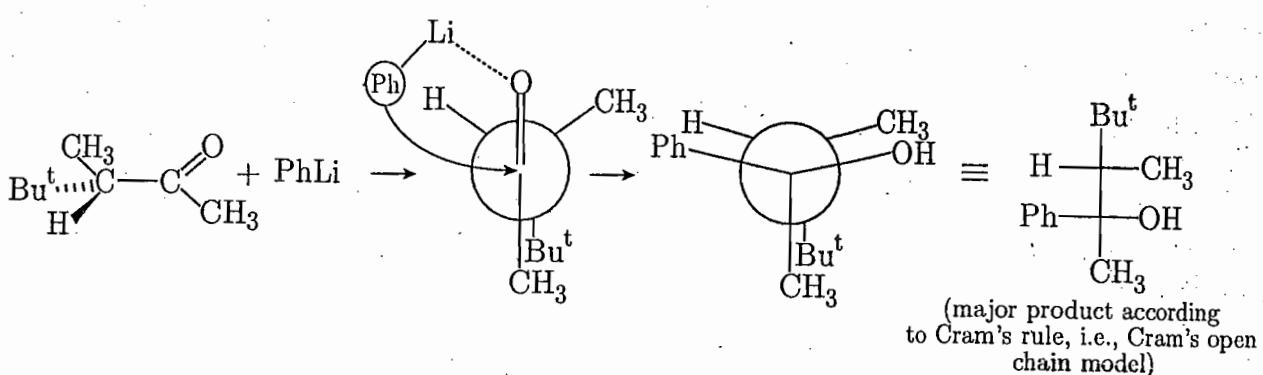


► 2.13 Use Cram's or Prelog's rule to predict the major product in each of the following reactions.

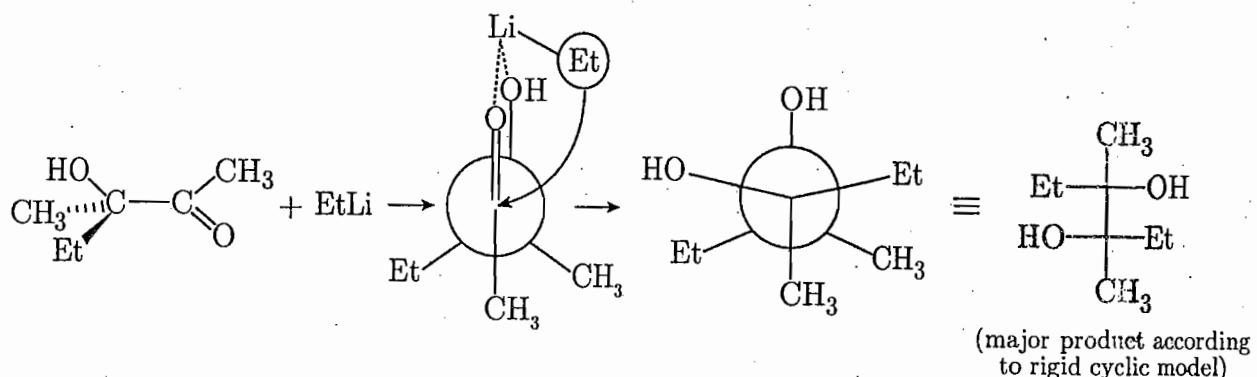


Ans.

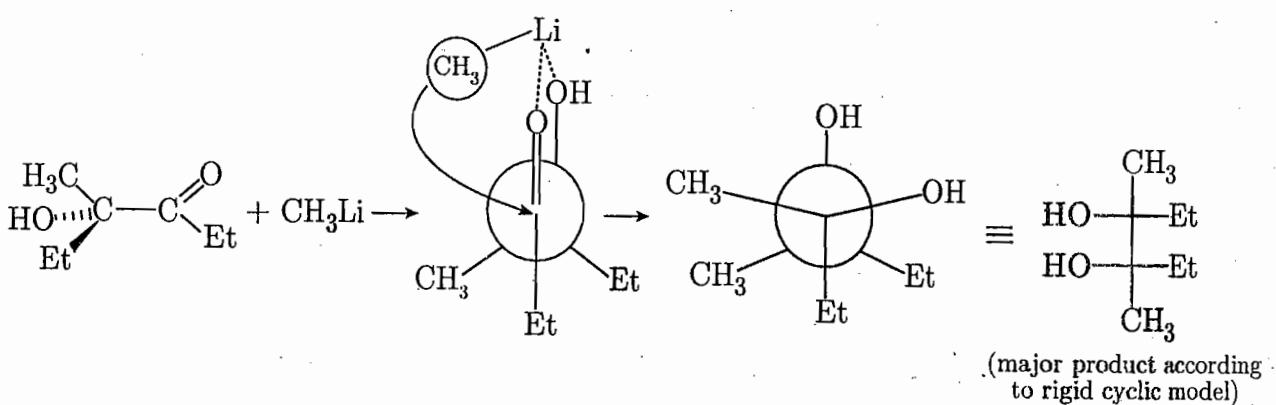
(a)



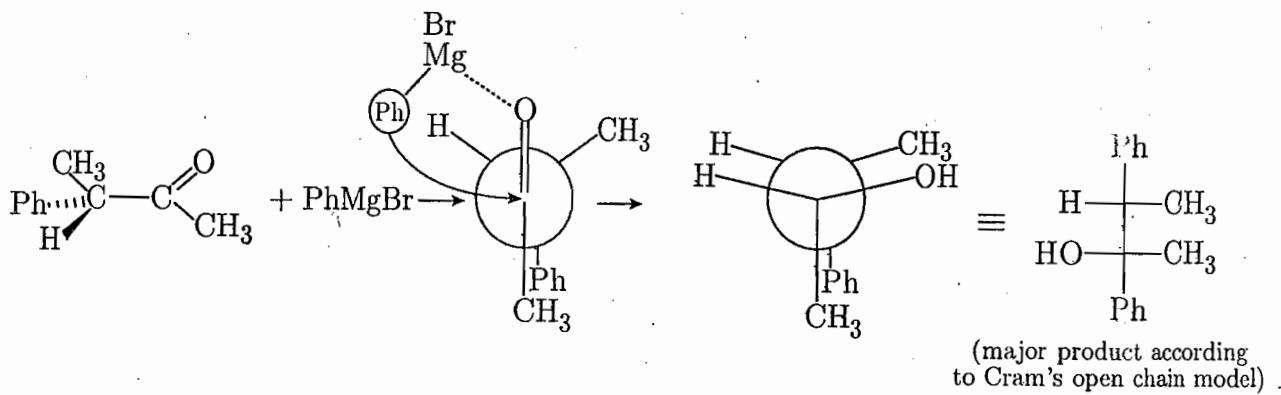
(b)

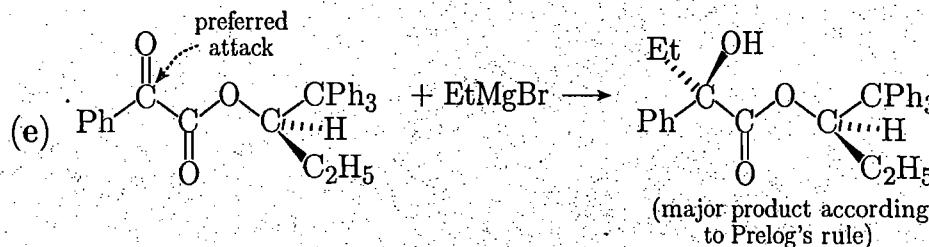


(c)

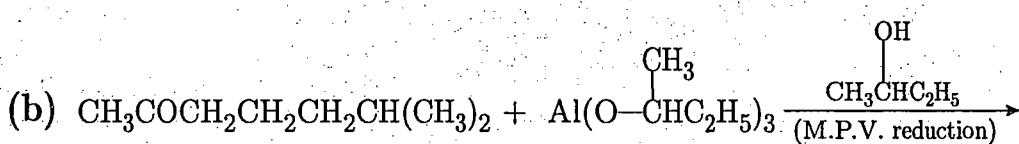
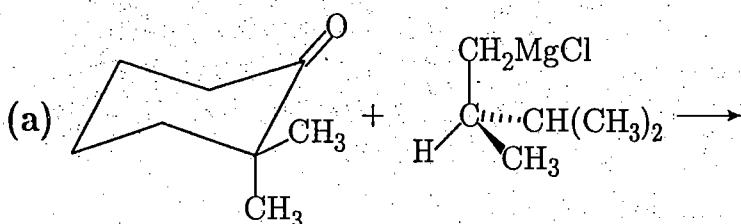


(d)

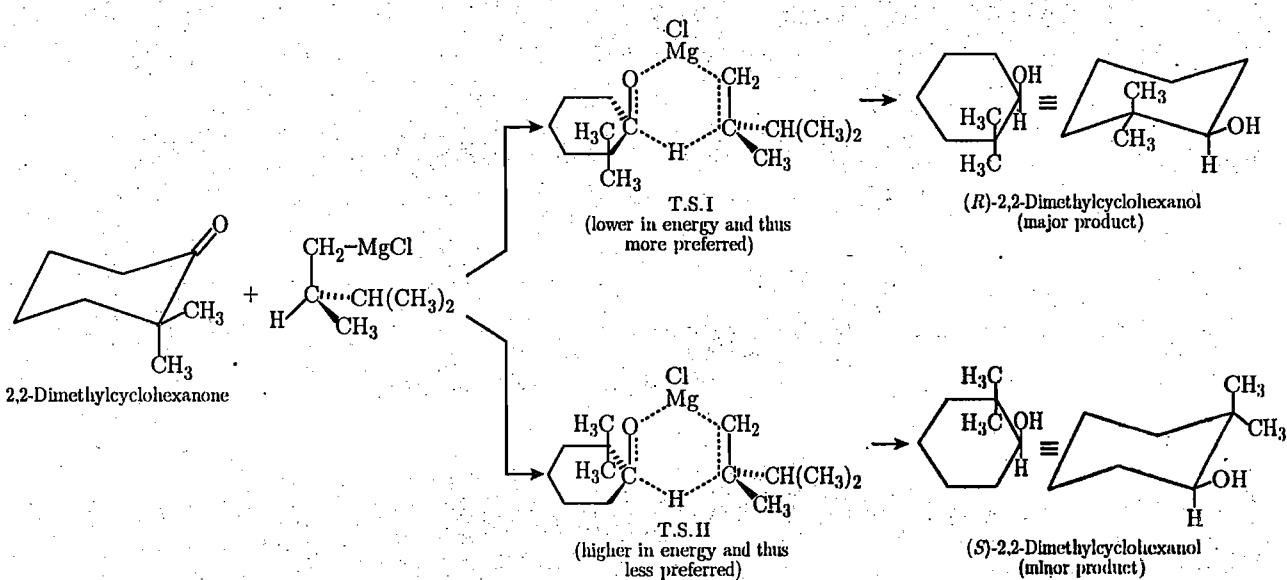




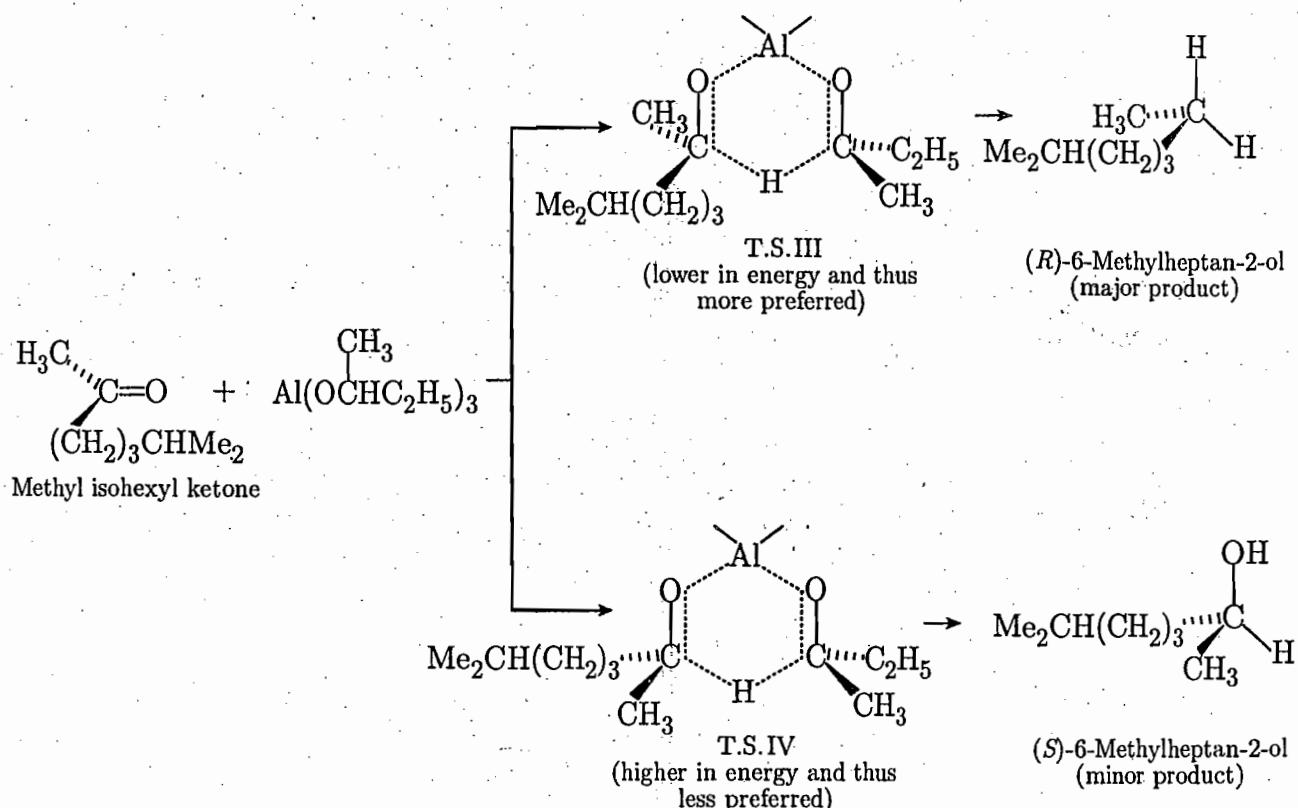
► 2.14 Predict the configuration of the major product in each of the following reactions.



Ans. (a) The reaction proceeds through the low-energy transition state I in which the two bulky groups (isopropyl and C-2 of the ketone) are on opposite sides of the plane of the six-membered ring and as a result, (*R*)-2,2-dimethylcyclohexanol is obtained predominantly.

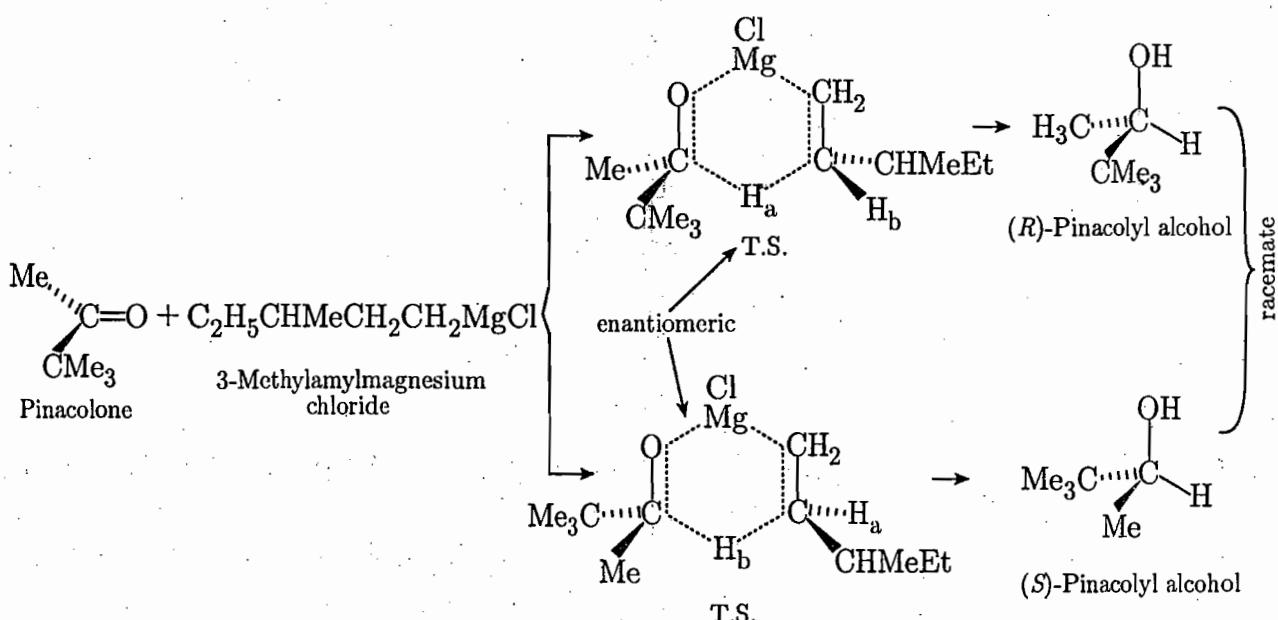


(b) The reaction also proceeds through the low-energy transition state III in which the larger groups ($-\text{Et}$ and $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CHMe}_2$) are on opposite sides of the plane of the six-membered ring and as a result, (*R*)-6-methylheptan-2-ol is obtained as the major product.



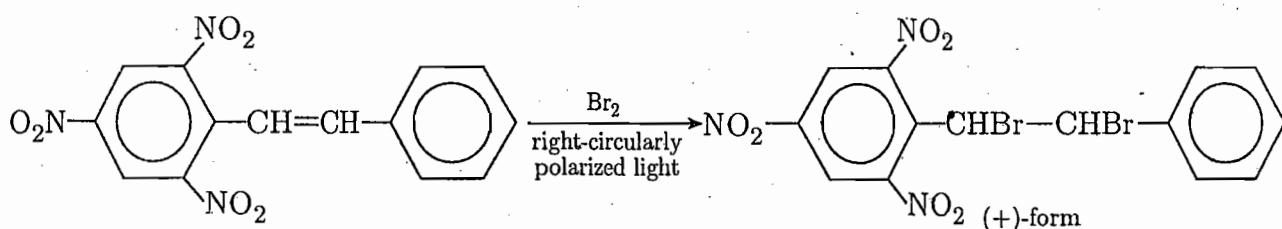
► 2.15 Explain why no asymmetric reduction of pinacolone (MeCOCCMe_3) occurs with 3-methylamylmagnesium chloride ($\text{EtCHMeCH}_2\text{CH}_2\text{MgCl}$), even though the Grignard reagent is optically active.

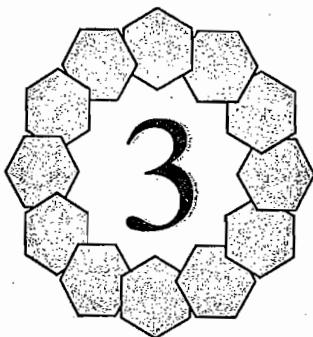
Ans. In this case, the asymmetric centre in the Grignard reagent does not form part of the ring in the cyclic transition state and therefore, the steric fit of the two enantiomeric transition states and their free energies being the same. Because of this, there is no preference for one enantiomer of the pinacolyl alcohol formed over the other, i.e., no asymmetric reduction of pinacolone occurs.



► 2.16 What is absolute asymmetric synthesis? Give an example.

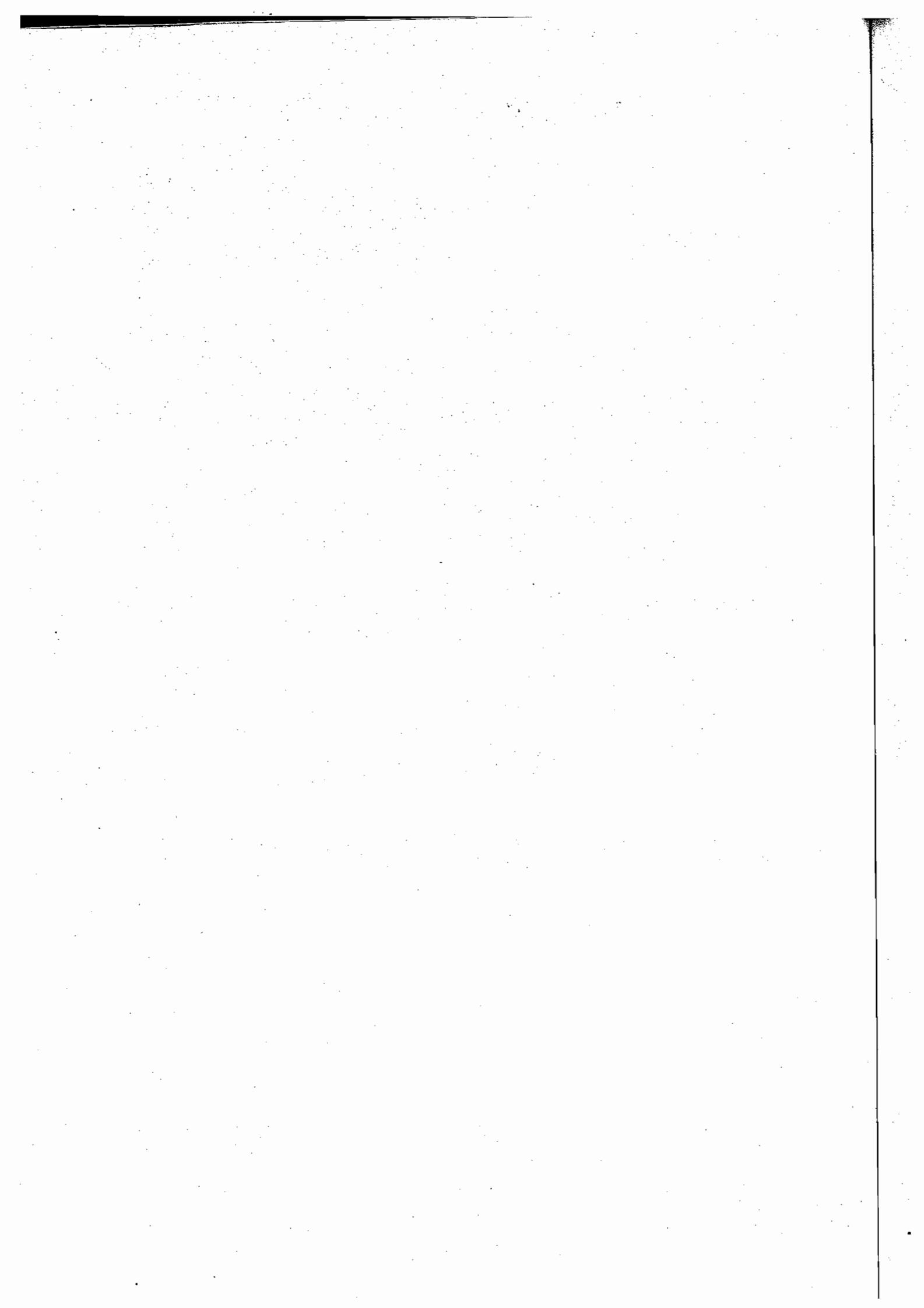
Ans. There are some methods of preparation of optically active compounds from optically inactive substances without intervention of any dissymmetric reagent is known as absolute asymmetric synthesis. Some sort of physically dissymmetric influence, e.g., left- or right-circularly polarised light is required in such syntheses. For example, when bromine is added to 2,4,6-trinitrostilbene in a beam of right-circularly polarised light, a dextro-rotatory dibromo compound is obtained.





CONFORMATIONS OF ACYCLIC AND CYCLIC ORGANIC MOLECULES

- Conformations of acyclic molecules** (Problem 3.1—Problem 3.4)
 - Conformations of cyclic systems other than cyclohexane**
(Problem 3.5 and Problem 3.6)
 - Conformations of cyclohexane and substituted cyclohexanes**
(Problem 3.7—Problem 3.14)
-

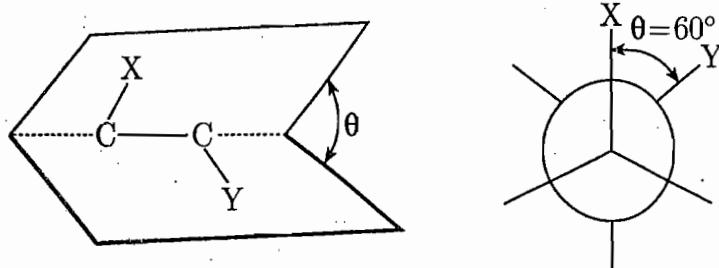


CONFORMATIONS OF ACYCLIC MOLECULES

- 3.1 (a) Define the terms conformation and dihedral angle.
- (b) Name and draw the Newman projection formulas of the two extreme conformations of ethane. What is a skew conformation?
- (c) Explain why the rotation about the C—C σ -bond in ethane is not completely free?
- (d) How does the distribution of conformations change with rise in temperature?
- (e) What is the term used for the energy minimum conformations?
- (f) Draw a potential energy diagram of conformations of ethane as a function of dihedral angle.
- (g) The energy barrier (ΔH) to rotation about the C—C σ -bond in ethane is about 3 kcal/mol at room temperature. Calculate the distribution of staggered and eclipsed conformations at 25°C (the contribution of entropy to ΔG is negligible).
- (h) What is called conformational isomerism? What structural features are necessary for a compound to exhibit conformational isomerism?
- (i) Why are conformers not normally isolable even at temperatures considerably below room temperature? In some cases conformational isomers have been isolated. Give examples.

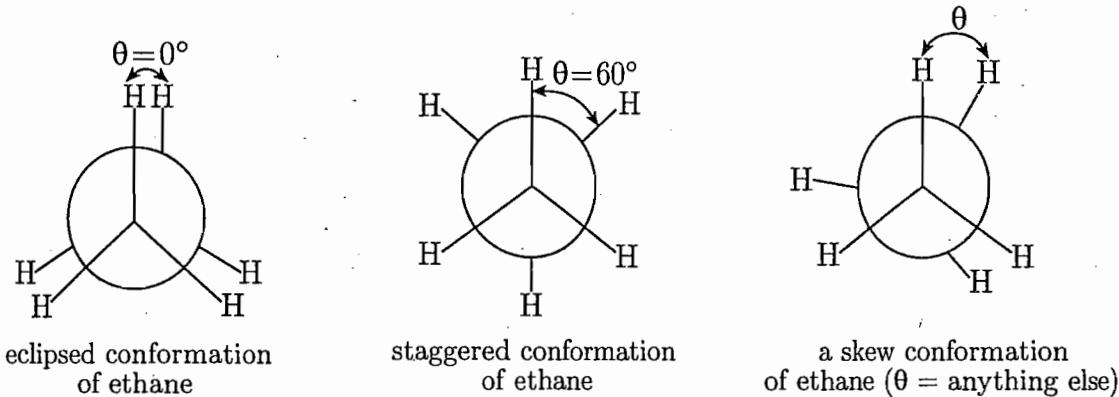
Ans. (a) Structures arising from rotation about single bonds (or flipping of rings) are called conformations. For example, one of the C atoms in a C—C bond may rotate with its substituents around the single bond when the other C atom remains static. This develops an infinite number of spatial arrangements of the substituents attached to the rotating C atom in relation to the positions of the substituents on the static C atom. Each of these spatial arrangements is known as a conformation of the molecule.

The dihedral angle (θ) is the angle between the X—C—C plane and the C—C—Y plane of an X—C—C—Y unit in a molecule. In Newman projection formula, it is the angle between the C—X bond on the front carbon atom and the C—Y bond on the back carbon atom.



[Torsion angle is synonymous with the term dihedral angle.]

(b) The two extreme conformations of ethane having the highest and the lowest energies at room temperature are the *eclipsed* and *staggered* conformations respectively. The conformation with $\theta = 0^\circ$ is called the eclipsed conformation because the Newman projection shows the hydrogen atoms on the back carbon atom to be hidden (eclipsed) by those on the front carbon atom. The conformation with $\theta = 60^\circ$ is called the staggered conformation because the Newman projection shows the hydrogen atoms on the back carbon staggered halfway between the hydrogens on the front carbon. Any other intermediate conformation is called a *skew* conformation.



(c) In the eclipsed conformation, the electron clouds in the eclipsed C—H bonds on adjacent C atoms repel each other. The repulsive destabilization associated with the eclipsing of bonds on adjacent atoms is called *torsional strain*. On the other hand, in the staggered conformation, the electron clouds in the C—H bonds are separated as much as possible and so, the staggered conformation is free from torsional strain. Because of this, the eclipsed conformation is less stable (about 3 kcal/mol or 12.6 kJ/mol higher in energy) than the staggered conformation. Since a molecule must rotate from one staggered conformation to another through the more energetic eclipsed conformation, the rotation about the C—C σ bond in ethane is somewhat restricted, i.e., not completely free. There is an energy barrier of about 3 kcal/mol (12.6 kJ/mol).

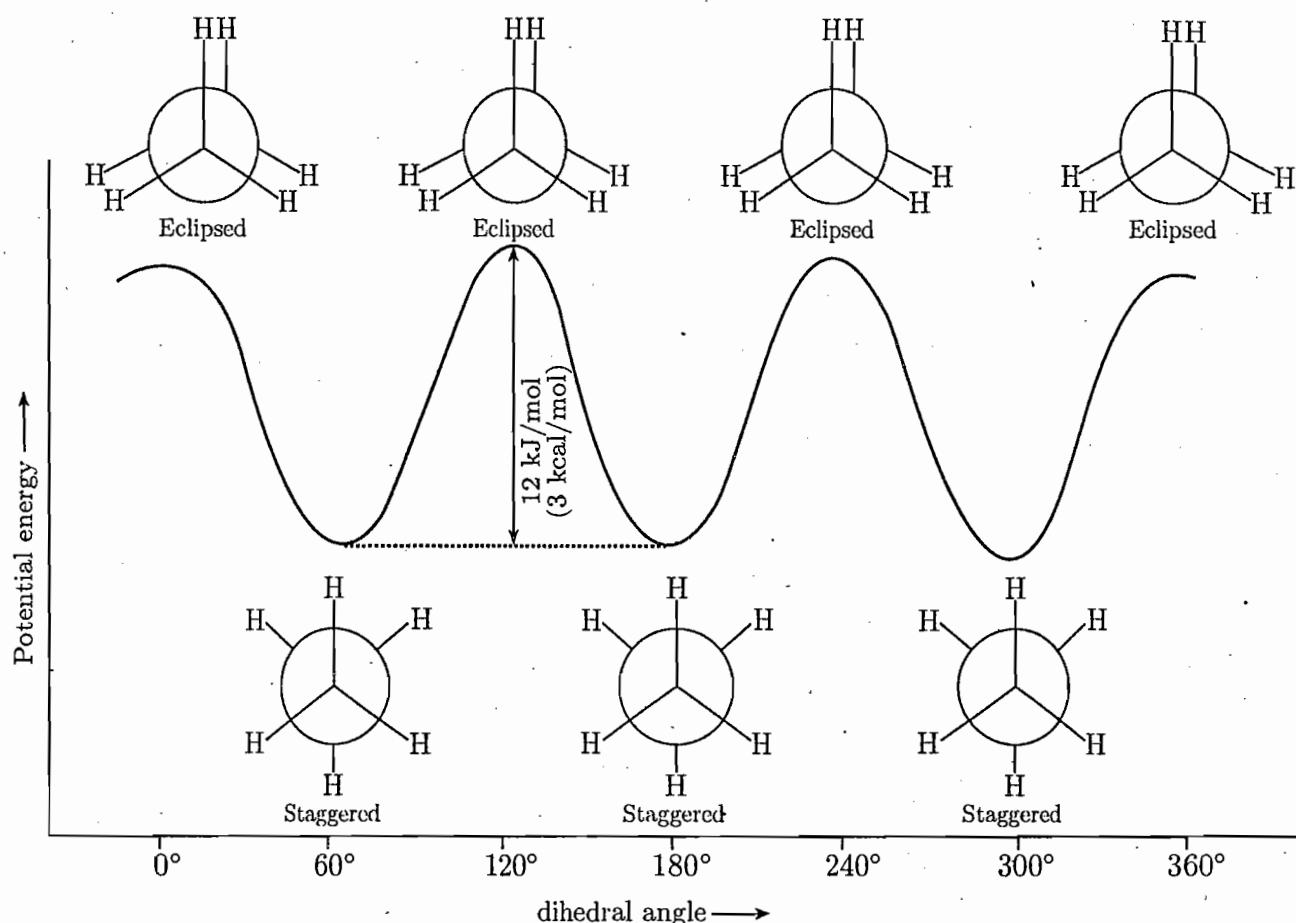
[The steric contribution to torsional strain due to non-bonded interaction between the vicinal hydrogens is negligible since the internuclear distance (0.23 nm) is almost equal to twice the value of van der Waals atomic radius of hydrogen (0.12 nm).]

(d) Since the amount of torsional energy is very small, the internal rotation of ethane is very rapid even at very low temperature. At 25°C a typical ethane molecule undergoes a rotation from one staggered conformation to another at a rate of about 10^{11} times per second. Although the lifetime for any one staggered conformation is very short, an ethane molecule spends most of its time in its staggered conformations, passing only transiently through its eclipsed conformations. However, an internal rotation (a constant succession of jumps from one staggered conformation to another) is more probable at higher temperature because molecules have greater kinetic energy at higher temperature. Therefore, the population of eclipsed conformations increases with rise in temperature.

(e) The energy minimum conformations are called *conformational isomers* or *conformers*.

[They are also called *rotamers*. However, this term is less widely used.]

(f) The diagram showing the variation in energy with the rotation through 360° about the C—C bond of ethane is as follows :



The staggered conformers are at energy minima, whereas the eclipsed conformers are at energy maxima.

(g) For the equilibrium : eclipsed \rightleftharpoons staggered

$$K_{\text{eq}} = \frac{[\text{staggered}]}{[\text{eclipsed}]}$$

Since the contribution of entropy to ΔG is negligible $\Delta G \approx \Delta H$.

Now,

$$\Delta G = -RT \ln K_{\text{eq}}$$

$$\text{or, } \ln K_{\text{eq}} = \frac{-\Delta G}{RT} = \frac{-(-3000 \text{ cal/mol})}{(1.99 \text{ cal/mol.K})(298 \text{ K})} = 5.058$$

$$\text{or, } K_{\text{eq}} = 157$$

$$\text{Thus, } \frac{[\text{staggered}]}{[\text{eclipsed}]} = 157$$

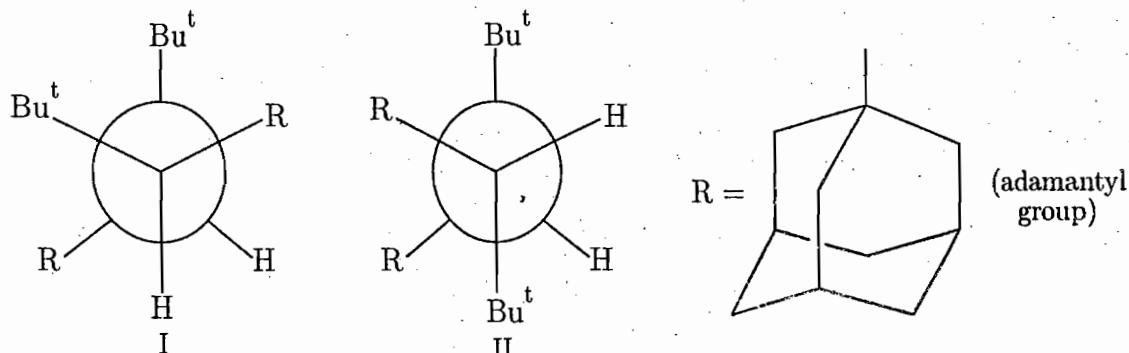
\therefore The percentage of staggered conformation $= \frac{157 \times 100}{158} = 99.36$ and the percentage of eclipsed conformation $= (100 - 99.36) = 0.64$. Therefore, at 25°C over 99% of the molecules remain in the more stable staggered conformation.

(h) Stereoisomers which are separated by low energy barrier are known as conformational isomers (or conformers). The phenomenon of existence of conformational isomers is called conformational isomerism. The structural feature necessary for a compound to exhibit conformational isomerism is that there must be four atoms bonded sequentially only by σ bonds, e.g., H—O—O—H, Cl—C—C—Cl etc.

(i) Conformational isomers or conformers separated by relatively low energy barrier ($< 60 \text{ kJ/mol}$) are rapidly interconvertible even at temperatures considerably below room temperature. Because of this, they are not normally isolable at such temperatures.

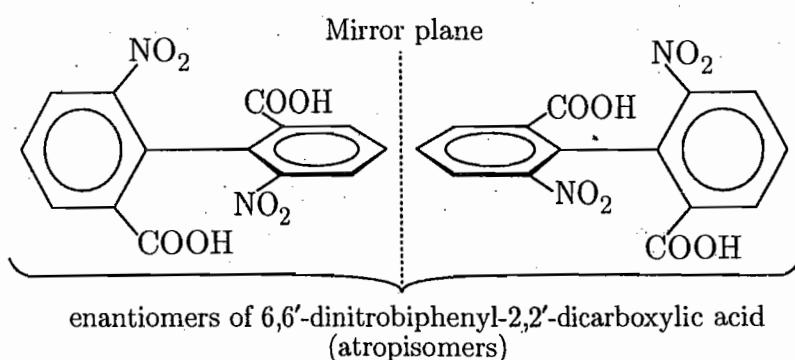
[Stereoisomers separated by high energy barrier ($> 100 \text{ kJ/mol}$) are quite stable and at room temperature are isolable.]

The two conformational isomers (I and II) of the following aliphatic hydrocarbon have been isolated.



3,4-Di(1-adamantyl)-2,2,5,5-tetramethylhexane

Atropisomers represent two conformations of a molecule whose interconversion is very much slow (because of hindered rotation) under a given set of conditions to allow separation and isolation. For example, 6,6'-dinitrobiphenyl-2,2'-dicarboxylic acid can be resolved into its enantiomers.



- 3.2 (a) What is called conformational analysis? Mention the factors on which the stability of a conformation depends and comment on them.
- (b) Give the potential energy diagram for rotation around the central carbon-carbon bond (i.e., C-2—C-3 bond) in butane. Draw and label the Newman projection formula for the conformation at each energy maxima and energy minima. Arrange the conformations in order of increasing stability and explain.
- (c) What is called butane-gauche interaction?
- (d) What is the relation between the two *gauche* conformations?

- (e) The *anti* conformation of butane is more stable than the *gauche* conformation by about 0.9 kcal/mol. Calculate the relative amounts of the two conformers at room temperature (25°C). What happens to the equilibrium : *gauche* \rightleftharpoons *anti* when the temperature is increased?
- (f) Draw the staggered conformations of the following in order of increasing energy :
- 3-methylpentane (considering rotation about the C-2—C-3 bond)
 - 2,3-dimethylbutane (considering rotation about the C-2—C-3 bond)
 - 3,3-dimethylhexane (considering rotation about the C-3—C-4 bond).
- (g) Draw the energy profile diagram of 1,2-dichloroethane for rotation about the C—C bond and label the maxima and minima with appropriate conformations. Compare the relative stabilities of conformations will explanation.

Ans. (a) Determination of the relative stabilities of the conformations of a compound and interpretation of its properties (physical and chemical) in terms of conformation is referred to as conformational analysis.

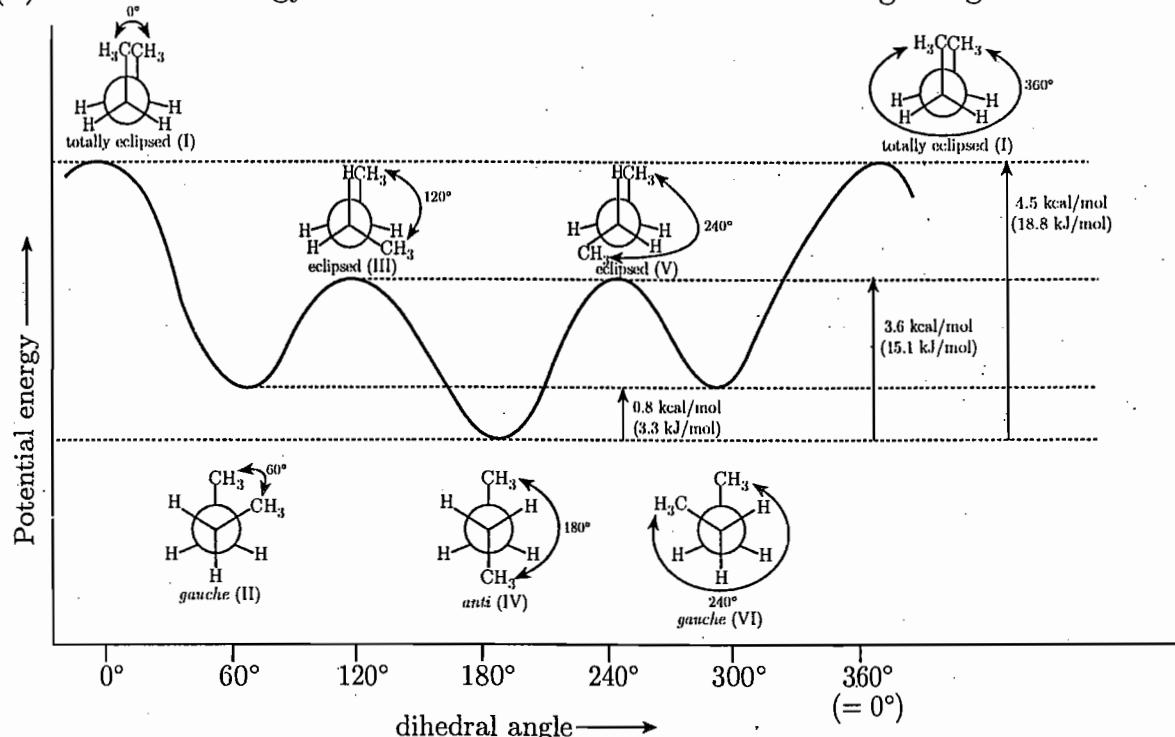
The stability of a conformation depends on four main factors. These are :

(i) Torsional strain, (ii) Angle strain, (iii) van der Waals strain, and (iv) Dipole-Dipole interactions.

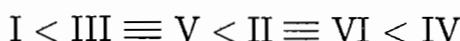
- Torsional strain** : The strain developed in a molecule (when it rotates towards an eclipsed conformation) by the bond-pair bond-pair repulsion, one on each C atom of a C—C single bond, is called torsional strain. The greater the torsional strain, the lower is the stability of a conformation.
- Angle strain** : Any deviation from the usual bond angle (as determined by the nature of bonding orbitals of the concerned atom) will create a strain in the molecule which is called angle strain. The greater the angle strain, the lower is the stability of a conformation.
- Steric strain or van der Waals strain** : If the distance between two substituents is less than the sum of their van der Waals radii (one-half of the equilibrium distance between two equivalent groups or atoms, not bonded to each other, at the point of the energy-minimum), then a repulsive force generates due to repulsion between the electron clouds of the interacting substituents. This destabilizing interaction creates a strain in the molecule which is known as van der Waals strain or steric strain. The greater the size of the non-bonded substituents, the greater is the van der Waals strain and less is the stability of the conformation.
- Dipole-dipole interaction** : Non-bonded substituents on each C atom of a C—C single bond may undergo dipole-dipole interactions of which the H-bonding force is the strongest. If the non-bonded atoms have opposite partial

charge densities, then an attractive force develops between them and as a result, the stability of the conformation increases. If the non-bonded substituents are involved in H-bonding, stabilization of the conformation will be much higher. However, if the non-bonded atoms have like charges, then repulsive force operates which results in destabilization of the conformation.

- (b) Potential energy of butane as a function of dihedral angle is given below.



The order of increasing stability of the conformations of butane is as follows :



The staggered conformations (II, IV and VI) of butane are at energy minima and are thus the stable conformations of butane. However, not all of the staggered conformations (nor the eclipsed conformations) of butane are similar. The conformations with a dihedral angle of $\pm 60^\circ$ (or in Fig. 60° and 300°) between the two C—CH₃ bonds are called *gauche* conformations (II and VI) and the conformation in which the dihedral angle is 180° is called the *anti* conformation (IV) [*gauche* is French meaning "to turn aside" and *anti* is Greek for "opposite of"]. The *anti* conformation (IV) does not have torsional strain because the groups are staggered and the methyl groups are far apart. The methyl groups in the *gauche* conformations are close enough to each other and for this, the *gauche* conformations are destabilized by van der Waals repulsions between nonbonded hydrogens on the two CH₃ groups. This repulsion causes the *gauche* conformation to have approximately 0.9 kcal/mol (3.8 kJ/mol) more energy than *anti* conformation in which no such van der Waals repulsions are present. Therefore, the *anti* conformation is more stable than a *gauche* conformation. The eclipsed conformations (I, III and V) represent energy maxima in the potential energy diagram. Eclipsed conformations III and V not only have torsional strain, they have van der Waals repulsions arising from the eclipsed methyl groups and hydrogen atoms. The eclipsed conformation I has the greatest energy (least stable) of all because, in addition to torsional strain, there is a large van der Waals repulsive force between the eclipsed methyl groups.

(c) The steric interaction between the two methyl groups in the *gauche* conformations of butane ($\theta = 60^\circ, 300^\circ$) makes them less stable (0.9 kcal/mol higher in energy) than the *anti* conformation ($\theta = 180^\circ$). This fundamental interaction is encountered in many organic molecules and is specifically called butane-*gauche* interaction.

(d) The two *gauche* conformations are non-superimposable mirror images of each other, i.e., they are conformational enantiomers. However, because of rapid interconversion, they are not resolvable.

(e) Although the *anti* conformation of butane is more stable than the *gauche* conformation to the extent of about 0.9 kcal (3.8 kj) mol⁻¹, yet the statistical probability of existence of *gauche* conformations is twice that of the *anti* conformation and so there is an entropy advantage of $Rln2$ for the *gauche* conformations.

Thus, $\Delta S^\circ = -R \ln 2$

The equilibrium : *gauche* \rightleftharpoons *anti* has $\Delta H^\circ = -0.9 \text{ kcal/mol}$ (3.8 kJ/mol)

Now from the relation, $\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$ at 25°C i.e., at 298 K,

$$\begin{aligned}\Delta G^\circ &= -0.9 \text{ kcal/mol} - (-RT \ln 2) \\ &= -0.9 \text{ kcal/mol} - (-0.00199 \times 298 \times 2.303 \log 2) \text{ kcal/mol} \\ &\equiv -0.49 \text{ kcal/mol}\end{aligned}$$

$$\text{Now, } \Delta G^\circ = -RT \ln K_{\text{eq}}.$$

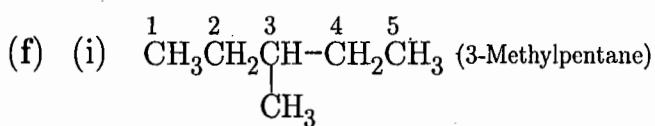
$$\text{or, } \log K_{\text{eq}} = - \frac{\Delta G^\circ}{2.303 RT} = - \frac{(-0.49 \times 1000) \text{ cal/mol}}{(2.303 \times 1.99 \text{ cal/mol. K}) (298\text{K})}$$

$$\text{or, } \log K_{\text{eq}} = 0.3587$$

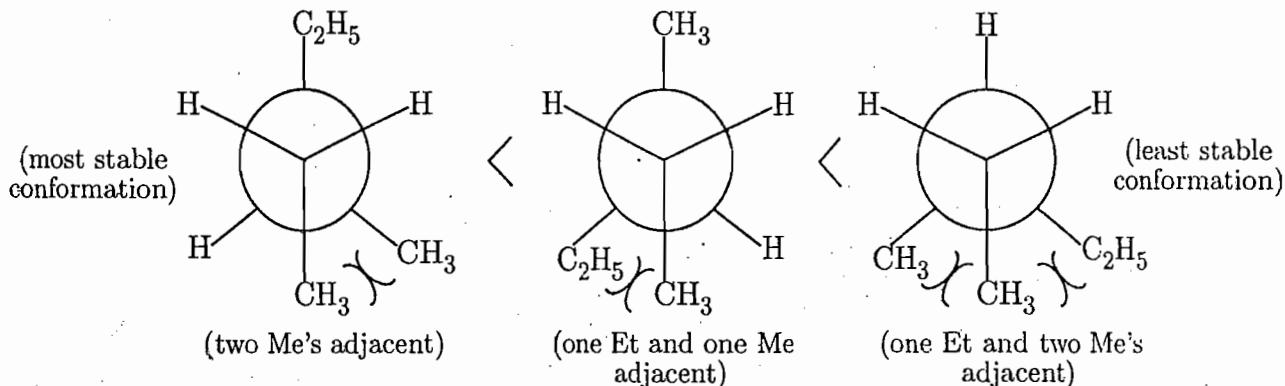
$$\text{or, } K_{\text{eq}} = 2.28$$

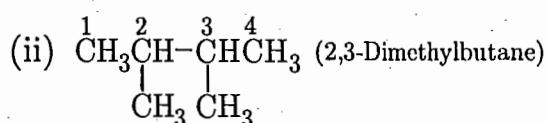
The ratio of $\text{anti}_{\text{eq}}/\text{gauche}$ is 2.28/1 which means that about 69.5% of the molecules are in the *anti* conformation and 30.5% in the *gauche* conformation at any one time, although they are rapidly interconverting.

Since ΔH° and ΔS° for this equilibrium is negative, the value of ΔG° becomes less negative and K_{eq} becomes smaller with increase in temperature. This means that the equilibrium shifts to the left resulting in a larger concentration of the *gauche* conformer.

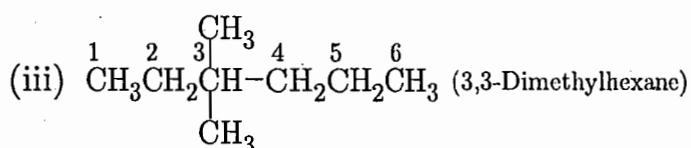
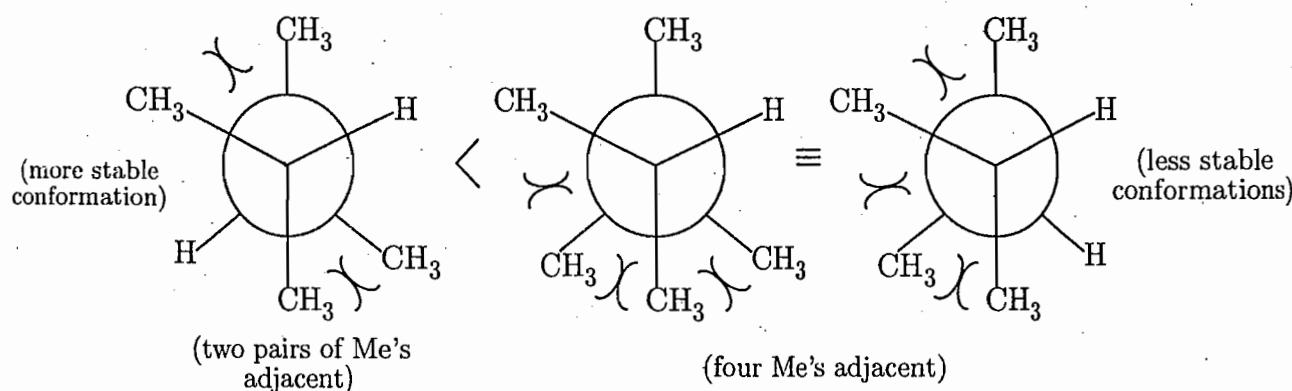


The staggered conformations resulting from rotation about the C-2—C-3 bond of 3-methylpentane may be drawn in increasing energy as follows :

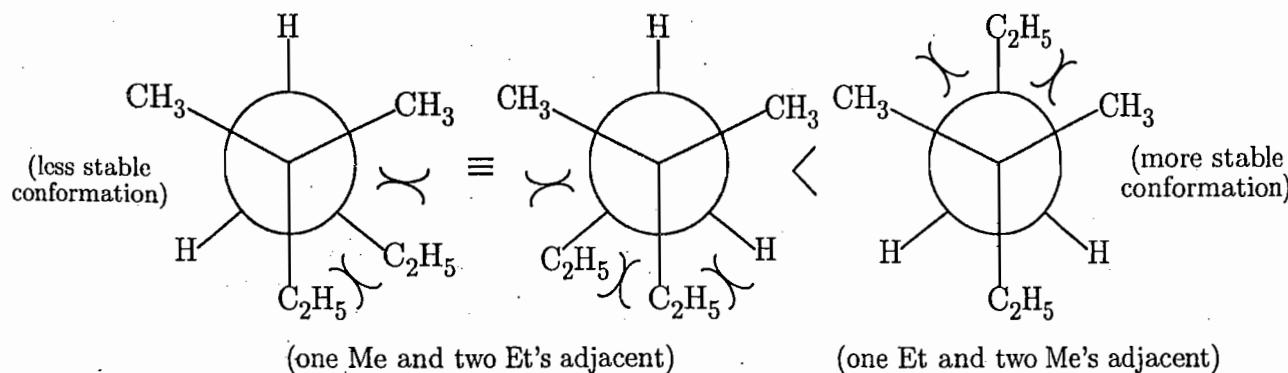




The staggered conformations resulting from rotation about the C-2—C-3 bond of 2,3-dimethylbutane may be drawn in order of increasing energy as follows :

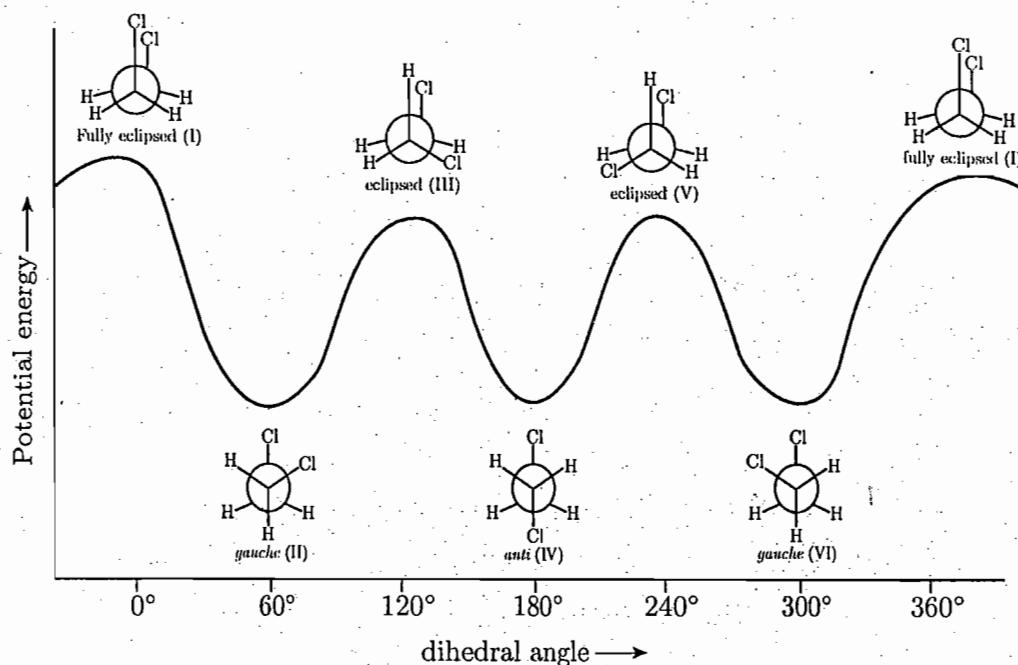


The staggered conformations resulting from rotation about the C-3—C-4 bond of 3,3-dimethylhexane may be drawn in order of increasing energy as follows :



[N.B. Et/Et interaction > Et/Me interaction > Me/Me interaction]

(g) The potential energy of 1,2-dichloroethane (in liquid state) as a function of dihedral angle is given below.



The order of increasing stability of the conformations of 1,2-dichloroethane is as follows : I < III = V < II = IV = VI.

The energy difference between the *anti* and *gauche* conformations of 1,2-dichloroethane in the liquid state is about zero (in the vapour phase, the *anti* conformation is more stable by 1.2 kcal/mole). To account for this observation two opposing forces are to be considered : the dipole-dipole repulsion and the van der Waals attraction between the two Cl atoms. In the liquid phase the dipole-dipole repulsion becomes equal to the van der Waals attraction (in the vapour phase the dipole-dipole repulsion is stronger than van der Waals attraction). Due to the presence of many other 1,2-dichloroethane molecules in the neighbourhood of a particular molecule, the intermolecular dipole-dipole interaction reduce the intramolecular dipole-dipole interaction to such an extent that the van der Waals attraction just cancels the intramolecular dipolar interaction (repulsion) in the *gauche* forms and as a consequence, the energy difference between the *anti* and *gauche* conformations is zero.

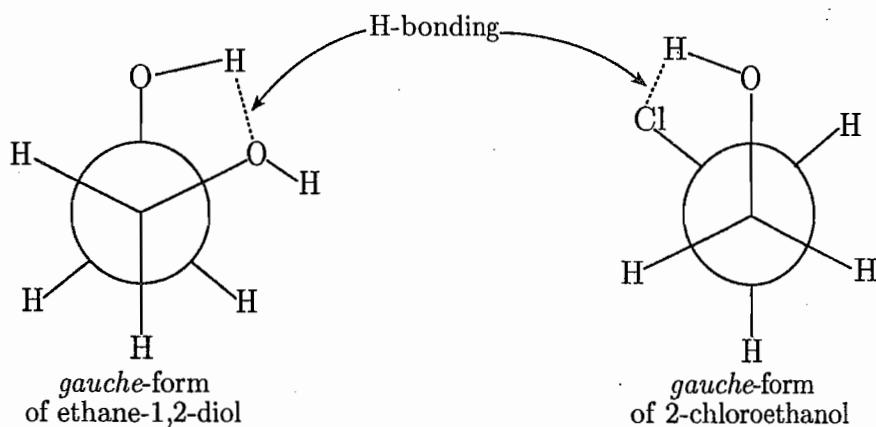
The *anti*- form as well as the *gauche* forms are the most stable insofar as the torsional strain and dipolar repulsions are concerned. The eclipsed forms are less stable than the *anti*- and *gauche* forms mainly because of torsional strain (there is little H/Cl steric effect). The fully eclipsed form is the least stable one because of torsional strain and large electrostatic repulsion between the two negatively polarized Cl atoms which are very close to each other (there is little Cl/Cl steric effect).

► 3.3 (a) Explain the following observations :

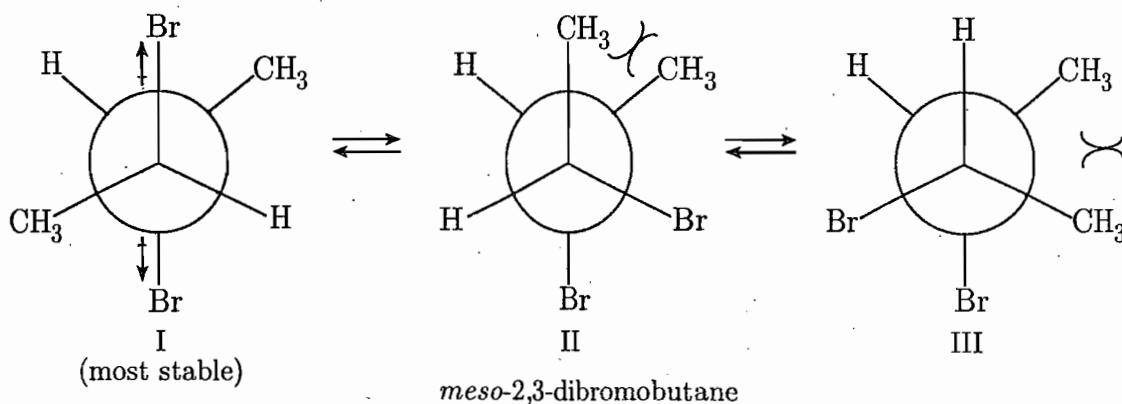
- Compounds having the general formula $\text{HOCH}_2\text{CH}_2\text{X}$ are found to be stable in their *gauche* conformations when $\text{X} = \text{OH}, \text{NH}_2, \text{F}, \text{Cl}, \text{Br}, \text{OR}$ etc.

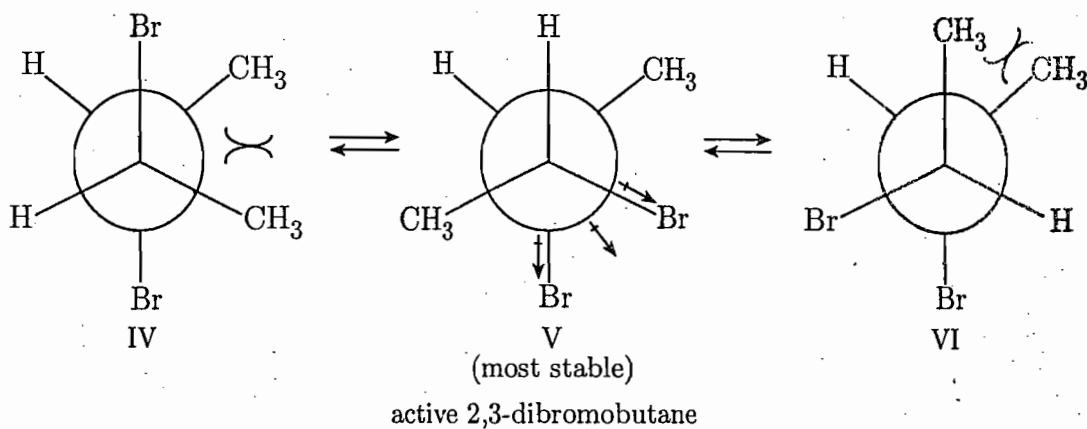
- (ii) The dipole moment of active 2,3-dibromobutane is larger than *meso*-2,3-dibromobutane.
- (iii) In the vapour phase active butan-2,3-diol is more stable than its *meso*-isomer.
- (b) Give the two conformations of buta-1,3-diene resulting from rotation about the C—C single bond. Which one of them is more stable and why?
- (c) Draw the two conformations of furfural. Which one of them is preferred in polar solvent and in gaseous state?
- (d) Write down the *Z* and *E*-conformations of *N*-methylacetamide. Which one of them is more stable and why?
- (e) Ephedrine (PhCHOHCHMeNHMe) is a weaker base ($pK_a = 9.14$) than its diastereoisomer ψ -ephedrine ($pK_a = 9.22$). How would you establish by conformational analysis that ephedrine is the *erythro*-isomer whereas ψ -ephedrine is *threo*?

Ans. (a) (i) Because of stable intramolecular hydrogen bonding compounds having the general formula $\text{HOCH}_2\text{CH}_2\text{X}$ ($\text{X} = \text{OH}, \text{NH}_2, \text{F}, \text{Cl}, \text{Br}, \text{OR}$ etc.) are found to be stable in their *gauche* conformations. For example :



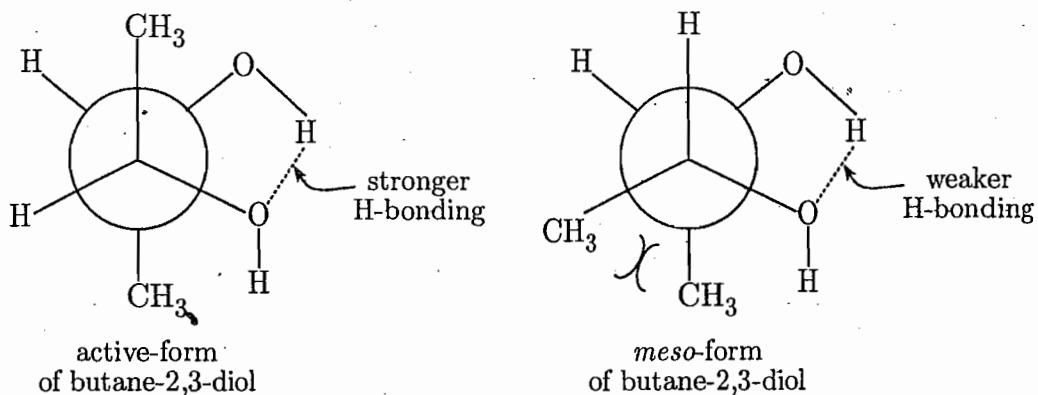
(ii)



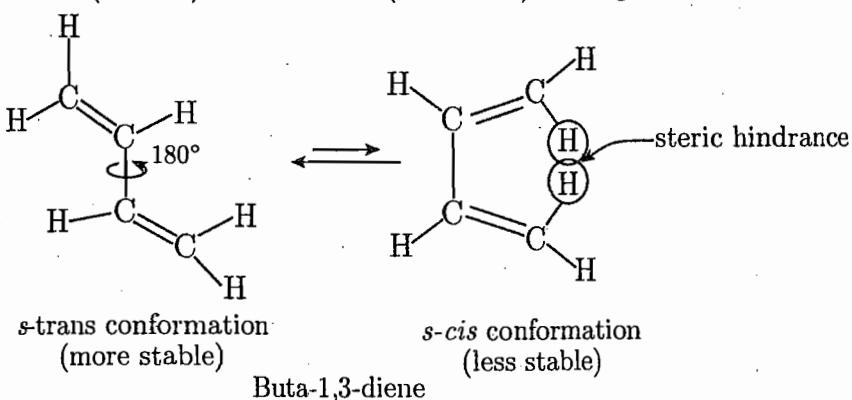


The most populated (most stable) conformation (I) of *meso*-2,3-dibromobutane is nonpolar whereas the most populated (most stable) conformation (V) of active 2,3-dibromobutane is polar. Because of this, the dipole moment of the active isomer is larger than the *meso*-isomer.

- (iii) Both the *meso* and the active form of butane-2,3-diol display intramolecular H-bonding. But in the case of the *meso* form, when the —OH groups are placed in *gauche* conformation, the bulky —CH₃ groups also take up sterically unfavourable *gauche* position. As a result, the intramolecular H-bonding in the *meso* form becomes weaker. On the other hand, in the active form, when the two —OH groups are *gauche*, —CH₃ groups are *anti* and thus in the active form, intramolecular H-bonding is much stronger. Because of this, the active form of butane-2,3-diol is more stable than its *meso* form.

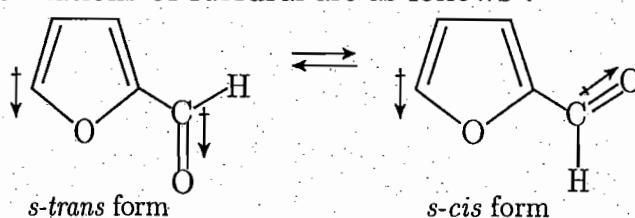


- (b) The two conformations of buta-1,3-diene resulting from rotation about the C—C single bond are *s-cis* (*cisoid*) and *s-trans* (*transoid*). The prefix *s* stands for single bond.



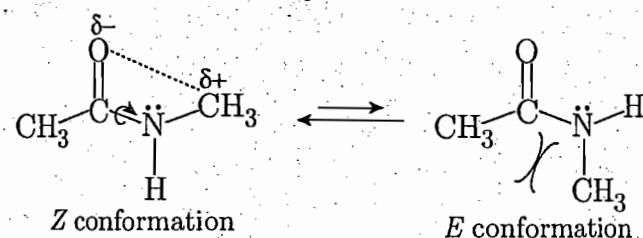
Because of steric interactions between two terminal H atoms, the *s-cis* conformation is less stable than the *s-trans* conformation.

(c) The two conformations of furfural are as follows :

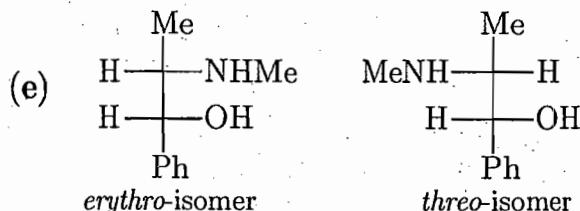


The *s-trans* conformation is found to be more stable in polar solvent which reduces the dipole-dipole repulsion due to ring oxygen and the aldehydic oxygen. Therefore, in the polar solvent *s-trans* conformation is found to be more contributing, i.e., preferred. In the gaseous state, *s-cis* conformation is found to be more preferred due to the dominating polar repulsive interaction between the two oxygen atoms in *s-trans* conformation.

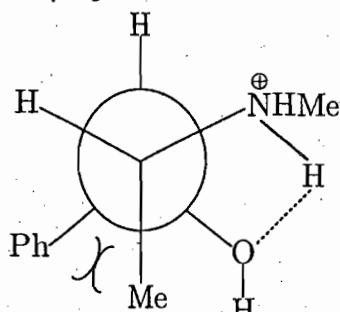
(d) The two conformations of *N*-methylacetamide are as follows :



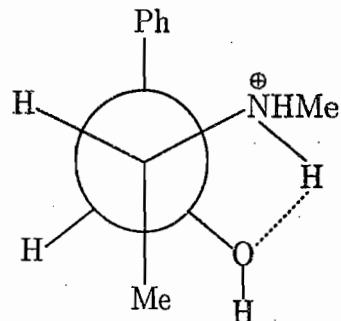
The *Z* conformation is stabilized by charge interaction (attractive) whereas the *E* conformation is destabilized by steric interaction (repulsive). Therefore, the *Z* conformation is more stable than the *E* conformation.



The conjugate acids of both *erythro* and *threo* forms display intramolecular H-bonding. But in the case of *erythro*-isomer, when the —OH and —NH₂Me groups are placed in *gauche* conformation, the bulky —Ph and —Me groups also take up sterically unfavourable *gauche* position. As a result, the intramolecular hydrogen bond becomes weaker. Consequently, the conjugate acid becomes stronger, i.e., the *erythro*-isomer behaves as a weaker base. On the other hand, in *threo*-isomer, when the —OH and —NH₂Me groups are *gauche*, —Ph and —Me groups are *anti*. Thus, in this case, intramolecular H-bonding is much stronger. Consequently, the conjugate acid becomes weaker, i.e., the *threo*-isomer behaves as a stronger base. Therefore, ephedrine is the *erythro*-isomer and ψ -ephedrine is the *threo*-isomer of PhCHOHCHMeNHMe.



conjugate acid of the *erythro*-isomer
(i.e., of ephedrine)



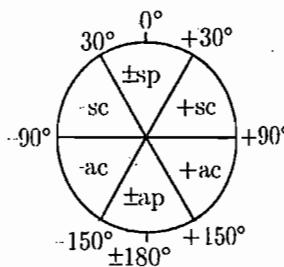
conjugate acid of the *threo*-isomer
(i.e., of ψ -ephedrine)

► 3.4 Discuss Klyne-Prelog system of conformational terminology based on torsion angle.

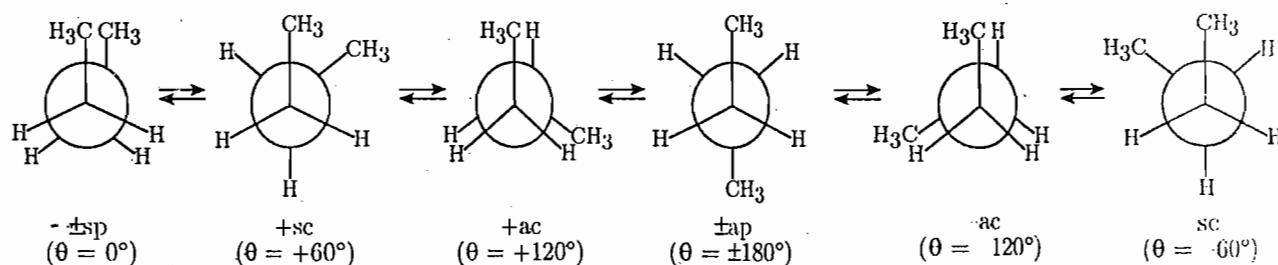
Ans. Approximate values of torsion angle have been used by Klyne and Prelog to assign conformational descriptors to conformational isomers. In Klyne-Prelog system the torsion angle is described in terms of three pairs of designations :

(a) (+) and (-) for a rotation of 0° to 180° in clockwise and counterclockwise directions respectively; (b) syn for a value of 0° - 90° and anti for a value of 90° - 180° in both directors : and (c) periplanar means approximately planar and clinal means inclined. The conformations bear the designation of the torsion angle expressed within $\pm 30^\circ$. Six such combinations for n-butane type of molecules are possible and they are as follows :

- (i) \pm syn-periplanar (\pm sp) : When the torsion angle between the two reference groups is $0^\circ \pm 30^\circ$, the conformation is designated as \pm syn-periplanar (\pm sp).
- (ii) +syn-clinal (+sc) : When the torsion angle between the two reference groups is $+60^\circ \pm 30^\circ$, the conformation is designated as +syn-clinal (+sc).
- (iii) +anti-clinal (+ac) : When the torsion angle between the two reference groups is $+120^\circ \pm 30^\circ$, the conformation is designated as +anti-clinal (+ac).
- (iv) \pm anti-periplanar (\pm ap) : When the torsion angle between the two reference groups is $180^\circ \pm 30^\circ$, the conformation is designated as \pm anti-periplanar (\pm ap).
- (v) -anti-clinal (-ac) : When the torsion angle between the two reference groups is $-120^\circ \pm 30^\circ$, the conformation is designated as -anti-clinal (-ac).
- (vi) -syn-clinal (-sc) : When the torsion angle between the two reference groups is $-60^\circ \pm 30^\circ$, the conformation is designated as -syn-clinal (-sc).



The different conformations of butane, for example, may be designated as follows :



CONFORMATIONS OF CYCLIC SYSTEMS OTHER THAN CYCLOHEXANE

- 3.5 (a) Define cycloalkanes. Give their general molecular formula.
- (b) Explain Bayer strain theory. Why is it not applicable to higher ring compounds?
- (c) Which factors influence the ring strain of cycloalkanes?
- (d) What is called heat of combustion? Give the general equation for combustion of a cycloalkane. Calculate ring strain for cycloalkanes on the basis of their heats of combustion and compare their stabilities.
- (e) Classify cycloalkanes in terms of size and ring strain.
- (f) Predict the relative chemical reactivities of cyclopropane, cyclobutane, and cyclopentane.

Ans. (a) Cycloalkanes are alkanes that contain rings of carbon atoms. Their general molecular formula is C_nH_{2n} .

(b) Cyclobutane is found to be less reactive than cyclopropane, while cyclopentane and higher homologues are found to be much less reactive than these two. In order to account for the above behaviour of three and four-membered ring compounds *vis-a-vis* higher cycloalkanes Adolf von Bayer proposed a theory which is known as *Bayer strain theory*.

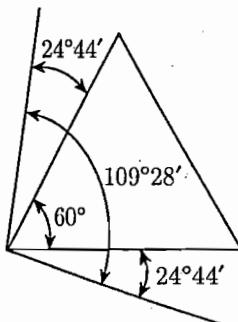
The main assumptions of Bayer strain theory, which is based on a purely mechanical concept of bonding, are as follows :

- (i) When bond angles deviate from the normal tetrahedral value ($109^{\circ}28'$), a strain is set up in the molecule.
- (ii) All the carbon atoms constituting a cycloalkane ring lie in the same plane. Thus, cyclopropane ring is an *equilateral triangle*; cyclobutane ring is a *square* and other cycloalkane rings are regular polygons.
- (iii) When these molecules assume the above-mentioned shapes, there is deviation from the normal tetrahedral angle which causes a lot of strain in the molecule. This strain, commonly referred to as *angle strain* (sometimes called Bayer strain), would depend upon the extent of such deviation. This means greater the deviation of bond angle from $109^{\circ}28'$, the greater is the strain and consequently, less stable (or more reactive) is the ring. However, the sign of deviation does not make any difference.
- (iv) Bond angle strain is expressed in terms of deviation of angle d , according to the following relationship.

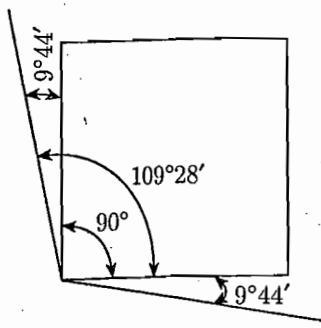
$$d = \frac{1}{2} (109^{\circ}28' - \text{value of the } C-C-C \text{ angle of the planar ring})$$

[In the above expression the factor $\frac{1}{2}$ is put because the distortion of bond angle has been assumed to be equally shared between the two bonds.]

Bayer worked out the deviation from normal angle or what is called angle strain in various cycloalkanes. For instance, cyclopropane has C—C—C bond angles of 60° (the internal angle of an equilateral triangle). This implies that the normal tetrahedral angle of $109^\circ 28'$ between any two bonds is compressed to 60° , and that each of the two bonds involved is pulled by $\frac{1}{2} (109^\circ 28' - 60^\circ) = 24^\circ 44'$. The value represents the angle strain in cyclopropane. In the same way C—C—C angle in cyclobutane would be 90° because each carbon is situated at the corner of a square. The angle strain in cyclobutane is $\frac{1}{2} (109^\circ 28' - 90^\circ) = 9^\circ 44'$.



Angle of deviation in cyclopropane



Angle of deviation in cyclobutane

The angle strain for cycloalkanes calculated for various ring sizes are given in the following table.

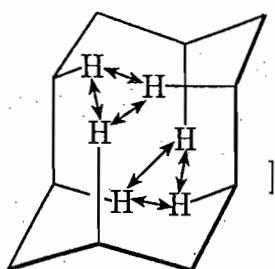
Compound and its geometry	C—C—C angle in planar ring	Angle strain
1. Cyclopropane (equilateral triangle)	60°	$\frac{1}{2} (109^\circ 28' - 60^\circ) = + 24^\circ 44'$
2. Cyclobutane (square planar)	90°	$\frac{1}{2} (109^\circ 28' - 90^\circ) = + 9^\circ 44'$
3. Cyclopentane (regular pentagon)	180°	$\frac{1}{2} (109^\circ 28' - 108^\circ) = + 0^\circ 44'$
4. Cyclohexane (regular hexagon)	120°	$\frac{1}{2} (109^\circ 28' - 120^\circ) = - 5^\circ 16'$
5. Cycloheptane (regular heptagon)	$128^\circ 34'$	$\frac{1}{2} (109^\circ 28' - 128^\circ 34') = - 9^\circ 33'$
6. Cyclooctane (regular octagon)	135°	$\frac{1}{2} (109^\circ 28' - 135^\circ) = - 12^\circ 46'$

It becomes clear from the above data that angle strain decreases from cyclopropane to cyclopentane. Thus, according to Bayer strain theory, cyclopropane should be the least stable cycloalkane and stability should increase gradually from cyclopropane to cyclopentane. This is actually found to be so. Cyclopropane undergoes ring-opening reactions easily; cyclobutane undergoes ring-opening reactions under drastic conditions and cyclopentane does not undergo ring-opening reactions.

According to the Bayer strain theory, cyclohexane and the higher cycloalkanes should become increasingly unstable and hence more reactive. Contrary to this prediction, cyclohexane and the higher homologues are found to be quite stable. They do not undergo ring-opening reactions. Instead they resemble open-chain alkanes in reactivity, that is, they undergo substitution reaction. The higher cycloalkanes, as predicted by Bayer strain theory, are not actually planar; they assume puckered conformation to minimize their strain. Thus, Bayer strain theory satisfactorily accounts for the reactivity of cyclopropane, cyclobutane and cyclopentane, but it is not applicable to cyclohexane and the higher cycloalkanes.

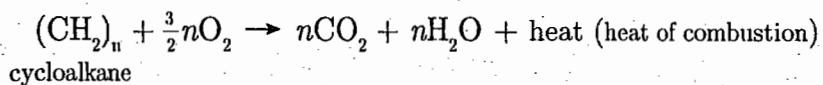
- (c) The factors which influence the ring strain of cycloalkanes are angle strain (or Bayer strain), eclipsing (torsional) strain resulting from eclipsing of adjacent pairs of C—H bonds, butane-*gauche* interactions, and transannular (across the ring) strain arising from the steric repulsion between H atoms on opposite sides of the ring. However, the last one is a source of strain in medium rings (C_7 — C_{12}).

[The transannular interactions in cyclodecane for example, may be shown as follows :



- (d) The heat of combustion of a compound is the amount of heat released when a compound is burned with an excess of oxygen (i.e., the heat of combustion of a compound is the enthalpy change for the complete oxidation of the compound).

The general equation for combustion of a cycloalkane can be written as follows :



Because cycloalkanes are not isomeric, their heats of combustion cannot be compared directly. However, the amount of heat evolved per CH_2 group can be calculated and on this basis, the amounts of ring strain can be calculated and the stabilities of cycloalkanes can be compared.

The heats of combustion of some cycloalkanes are given in the following table.

Cycloalkane, $(CH_2)_n$	n	Heat of combustion (kcal/mol)	Heat of combustion per CH_2 group (kcal/mol)
Cyclopropane	3	499.8	166.6
Cyclobutane	4	655.9	164.0
Cyclopentane	5	793.5	158.7
Cyclohexane	6	944.5	157.4
Cycloheptane	7	1108.2	158.3
Cyclooctane	8	1269.2	158.6
Cyclononane	9	1429.4	158.8
Cyclodecane	10	1586.0	158.6
Cyclopentadecane	15	2362.5	157.5
Unbranched alkane			157.4

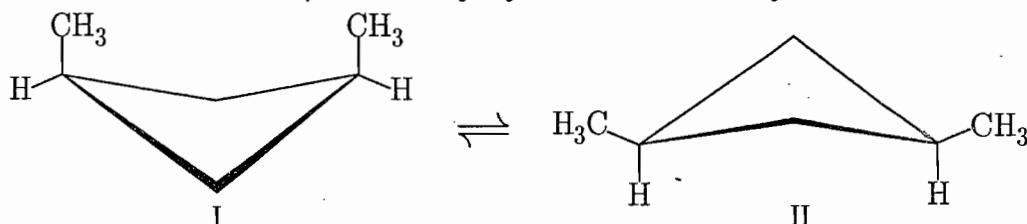
Cyclohexane has the lowest heat of combustion per CH_2 group (157.4 kcal/mol). This amount does not differ from that of an unstrained long-chain alkane. Therefore, we can assume that cyclohexane has no ring strain and that it can serve as the standard for comparison with other cycloalkanes. Ring strain for other cycloalkanes can be calculated by multiplying 157.4 kcal/mol by n and then sub-tracting the result from the heat of combustion of the cycloalkane. Thus, the amounts of ring strain of cycloalkanes, $(CH_2)_n$, where $n = 3$ to 10 are 27.6, 26.4, 6.5, 0, 6.4, 10.0, 12.9 and 12.0 kcal/mol respectively. The more ring strain a molecule possess, the more potential energy it has and less stable it is compared to its ring homologs. It thus follows that cyclopropane having the greatest amount of ring strain is the least stable cycloalkane. Cyclobutane having the second largest amount of ring strain is somewhat more stable than cyclopropane. Cyclopentane and cycloheptane having about the same modest amount of ring strain are less stable than cyclobutane. Eight, nine and ten-membered rings having slightly larger amounts of ring strain are somewhat less stable than cycloheptane. The amount of ring strain then falls off with consequent increase in stability.

(e) Cycloalkanes can be classified by size and ring strain as follows :

- (i) Small rings (C_3 and C_4) have large ring strain.
- (ii) Common rings (C_5 and C_6) have little or no ring strain.
- (iii) Medium rings (C_7 — C_{12}) have little ring strain.
- (iv) Large rings ($>C_{12}$) are strainless.

(f) Cyclopropane is more reactive than any of the other cycloalkanes. Its large ring strain (27.6 kcal/mol) provides an additional driving force that increases its reactivity in ring-opening reactions. The less strained cyclobutane is somewhat less reactive than cyclopropane and in fact, it undergoes ring-opening reactions under more severe reaction conditions than for the more strained cyclopropane. Cyclopentane having low ring strain is less reactive than cyclobutane and in fact, it resists ring-opening reactions. Thus, the chemical reactivity increases in the order cyclopentane < cyclobutane < cyclopropane.

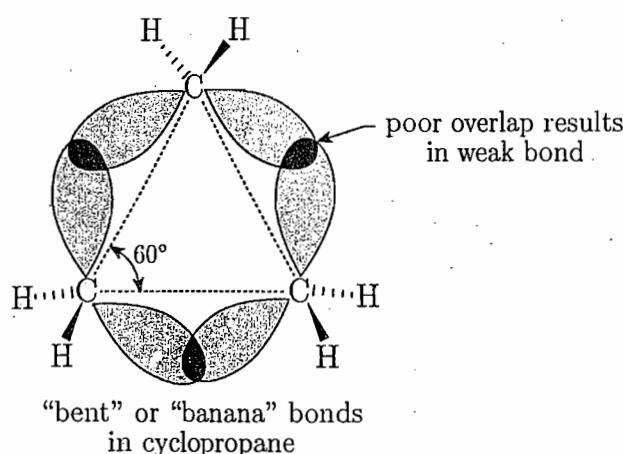
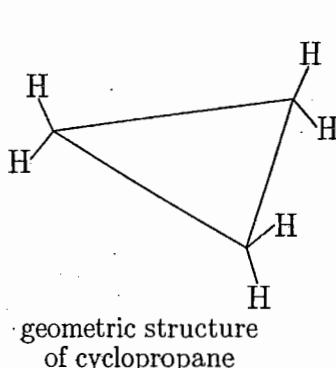
- 3.6 (a) What are the bond angles of a regular polygon with n sides?
- (b) Discuss the geometry of cyclopropane. How does the geometry account for its large ring strain?
- (c) The heat of combustion of *cis*-1,2-dimethylcyclopropane is larger than that of the *trans*-isomer. Explain.
- (d) Discuss the geometry of cyclobutane and account for its ring strain. Draw the two equilibrating puckered conformations of cyclobutane that overcome the eclipsing strain.
- (e) Unlike cyclobutane, oxetane and thietane are planar. Explain these observations.
- (f) Which one of the following do you expect to be the more stable conformation of *cis*-1,3-dimethylcyclobutane? Why?



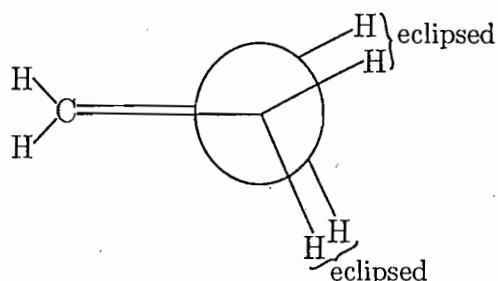
- (g) *trans*-1,2-Dimethylcyclobutane is more stable than its *cis*-isomer whereas *trans*-1,3-dimethylcyclobutane is less stable than its *cis*-isomer. Explain these observations.
- (h) Discuss the geometry of cyclopentane and account for its small ring strain.

Ans. (a) The bond angles of a regular polygon with n sides are equal to $(180^\circ - \frac{360^\circ}{n})$.

(b) Normal σ bonds are formed by perfect head-on overlap of two sp^3 orbitals that point directly towards each other. In cyclopropane, overlapping orbitals cannot point directly towards each other. Instead, overlap is off the axis, resulting less effective "bent" bonds. Because of having shapes that resembles bananas they are often called "banana" bonds.

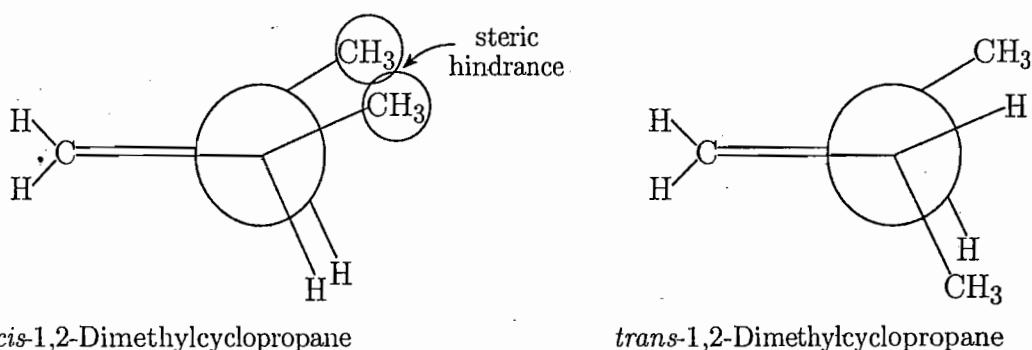


The three carbons in cyclopropane form an equilateral triangle so that their internal angles are 60° , which is 49.5° less than the normal tetrahedral angle of 109.5° . This deviation constitute angle strain which is the most important factor in cyclopropane's large ring strain. In addition to angle strain, the planar three-membered ring also have torsional strain because all the adjacent C—H bonds are eclipsed. The torsional strain is not as great as angle strain, but it helps to account for the large total ring strain in cyclopropane.

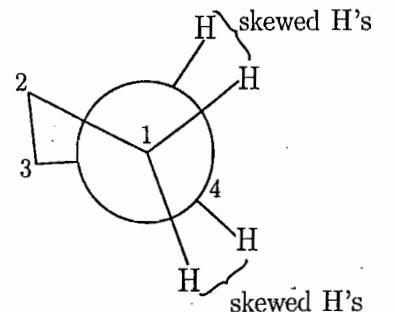
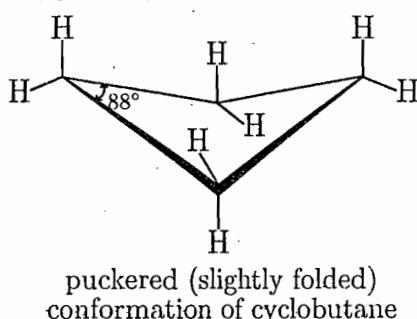


Newman projection of cyclopropane
as viewed along one C—C bond

(c) In *cis*-1,2-dimethylcyclopropane the eclipsed methyl groups are so close together that their electron clouds experience a strong repulsion which is called steric strain or steric hindrance. There is no such steric strain in the *trans*-isomer. So the total ring strain in *cis*-1,2-dimethylcyclopropane is larger than in the *trans*-isomer and because of this, the heat of combustion of the *cis*-isomer is larger than that of the *trans*-isomer.

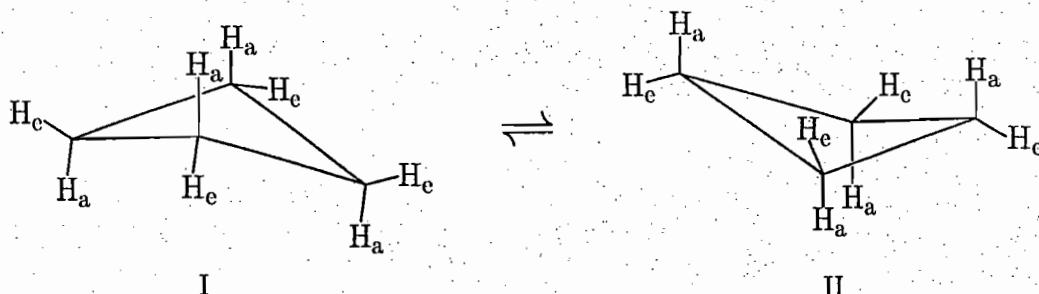


(d) If cyclobutane were perfectly planar and square, it would have 90° bond angles. The deviation from the tetrahedral angle of 109.5° is considerably less than that for cyclopropane and there should be much less angle strain. However, since cyclobutane has four pairs of eclipsing hydrogens (one pair more than in cyclopropane), it should have considerable torsional strain. To reduce this torsional strain, cyclobutane actually assumes a slightly folded form with bond angles of 88° . The relief of some of the torsional strain appears to compensate for a small increase in angle strain due to decrease in bond angles from 90° to 88° .



the puckered conformation
of cyclobutane in Newman projection

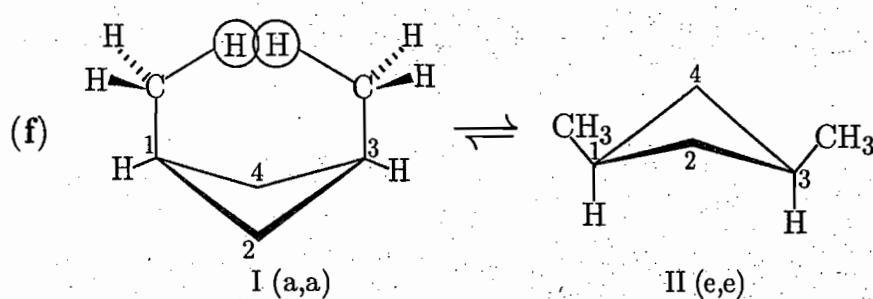
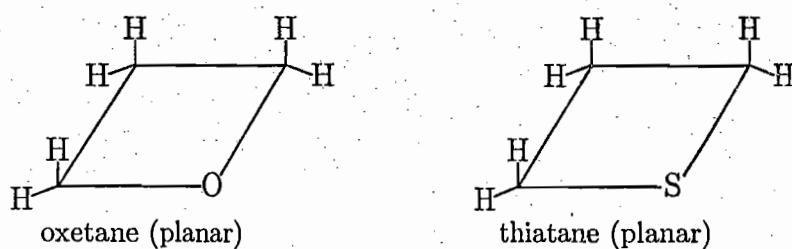
The two equilibrating puckered conformations of cyclobutane are as shown below :



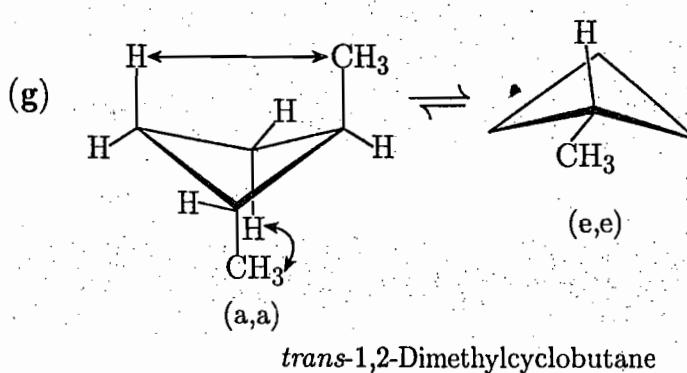
(H_a = axial hydrogen ; H_e = equatorial hydrogen)

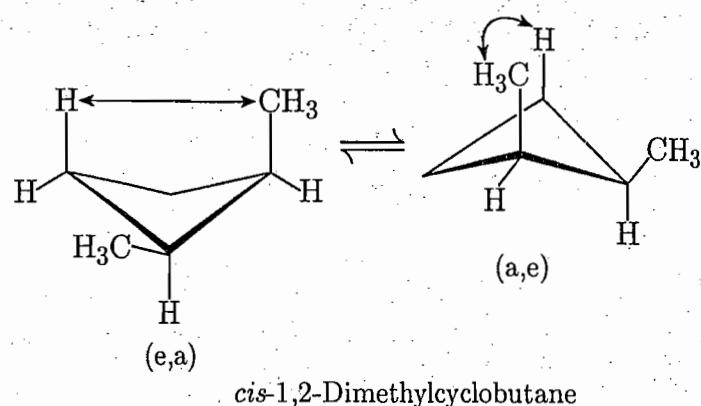
H_a 's and H_e 's in conformation I become H_e 's and H_a 's respectively in conformation II.

(e) One of the CH_2 groups in cyclobutane is replaced by an oxygen atom in oxetane and by a sulphur atom in thiatane. Thus, compared to the planar conformation of cyclobutane, oxetane and thiatane have much less torsional strain. For this reason, unlike cyclobutane, oxetane and thiatane are planar molecules.

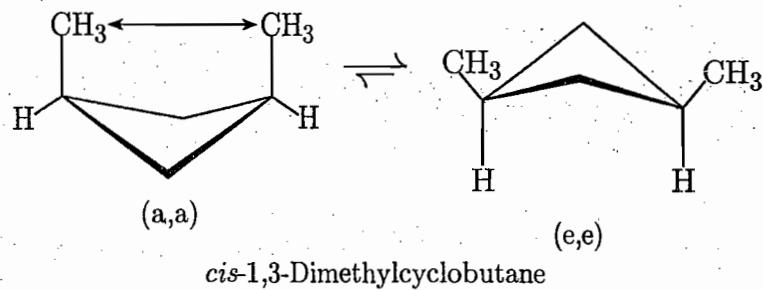
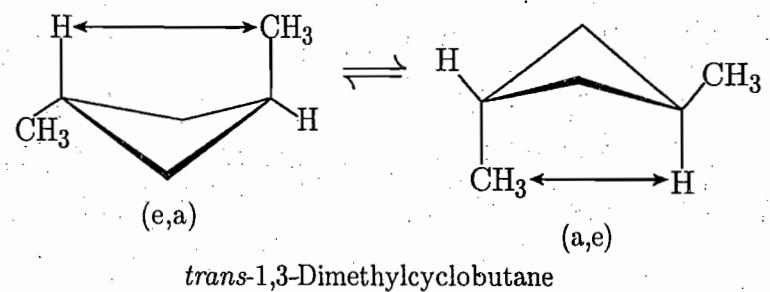


Because of CH_3/CH_3 -1,3-diaxial interaction, the diaxial conformation I of *cis*-1,3-dimethylcyclobutane is less stable than the diequatorial conformation II in which the two methyl groups are held farther apart.



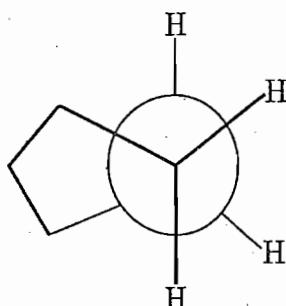
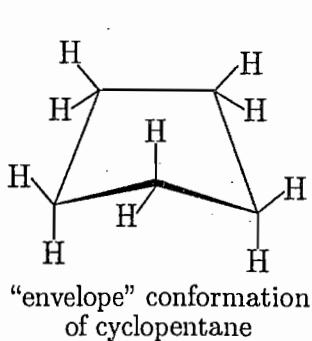


trans-1,2-Dimethylcyclobutane exists nearly exclusively in the more stable (e,e) conformation which has only one *butane-gauch* interaction. Each of the equally stable conformations [(e,a) or (a,e)] of *cis*-1,2-dimethylcyclobutane has two *butane-gauche* interactions. Therefore, *trans*-1,2-dimethylcyclobutane is more stable than its *cis*-isomer.



cis-1,3-Dimethylcyclobutane exists nearly exclusively in the more stable (e,e) conformation which has no additional *butane-gauche* interactions. Each of the equally stable conformations of *trans*-1,3-dimethylcyclobutane has one *butane-gauch* interaction. Therefore, *cis*-1,3-dimethylcyclobutane is more stable than its *trans*-isomer.

(h) If cyclopentane had the shape of a planar, regular pentagon, its bond angles would be 108° , very close to the normal tetrahedral bond angles of 109.5° . Therefore, cyclopentane molecules would have very little angle strain. Planarity, however, would introduce considerable torsional strain because all 10 hydrogen atoms would be eclipsed. Cyclopentane actually assumes a slightly puckered "envelope" conformation that reduces the torsional strain. Slight twisting of C—C bonds can occur with very small change in energy, and causes the out-of-plane atom to move into the plane and causes other to move out. Therefore, the puckered conformation is not fixed and the molecule shifts rapidly from one conformation to another.



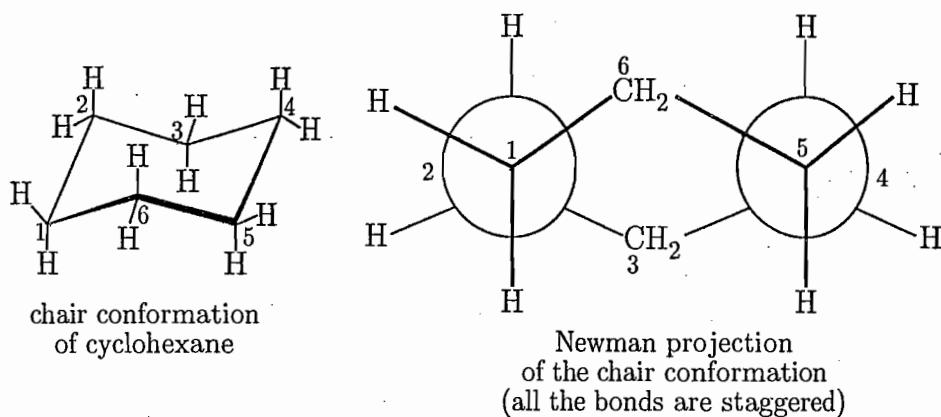
Newman projection of
cyclopentane (as viewed along
one C—C bond) showing relief
of eclipsing strain.

CONFORMATIONS OF CYCLOHEXANES AND SUBSTITUTED CYCLOHEXANES

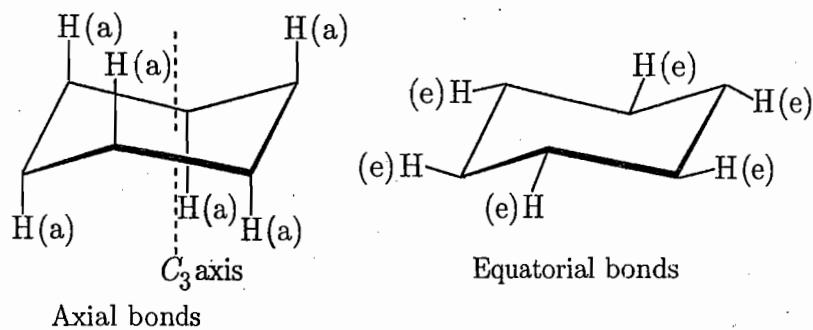
- 3.7 (a) How does the geometry of cyclohexane account for its high stability?
- (b) Based on their spacial orientation, label the two types of C—H bonds in chair form of cyclohexane.
- (c) What is called ring-flip or ring inversion? What happens to the C—H bonds when ring inversion occurs? What is the rate of chair-chair interconversion in cyclohexane at room temperature? How can it be arrested?
- (d) Draw the boat conformation of cyclohexane and its Newman projection. How is the boat conformation formed from the chair conformation? Why is the boat conformation less stable than the chair conformation?
- (e) Discuss the process of ring inversion (flipping of the ring) of cyclohexane chair with energy profile diagram.
- (f) What are the symmetry elements present in chair and boat conformations of cyclohexane?

Ans. (a) A planar regular hexagon would have bond angles of 120° rather than 109.5° , implying some angle strain. A planar ring would also have torsional or eclipsing strain because the bonds on adjacent CH_2 groups would be eclipsed. Since cyclohexane is a very stable cycloalkane, it must have no angle strain and no torsional strain. This can only happen if cyclohexane can assume a nonplanar conformation. In fact, cyclohexane overcomes these strains by being puckered to give a conformation that is almost completely free of strain. This conformation is called the chair conformation. With C—C—C bond angles of $111^\circ 05'$ (close to normal tetrahedral value of $109^\circ 28'$) the chair conformation is nearly free of angle strain. Again all its C—H bonds are staggered (the dihedral angle is 56° instead of 60°), making it free of torsional strain as well. The staggered arrangement of bonds in

the chair conformation is apparent in the Newman projection. Furthermore, the distance between an H atom on one C and that on another C of the chair form (249–251 pm) being greater than twice the van der Waals radii of hydrogen. Thus, there is no non-bonded interaction, i.e., van der Waals (steric) strain in the cyclohexane chair. The only strain present is due to six butane-*gauche* interactions (between neighbouring methylene groups) arising out of six sets of four consecutive carbon atoms i.e., 1–2–3–4, 2–3–4–5, 3–4–5–6, etc. Since all sorts of strain, except butane-*gauche* interactions, being absent in the chair form, it is practically strainless and so it is very stable.



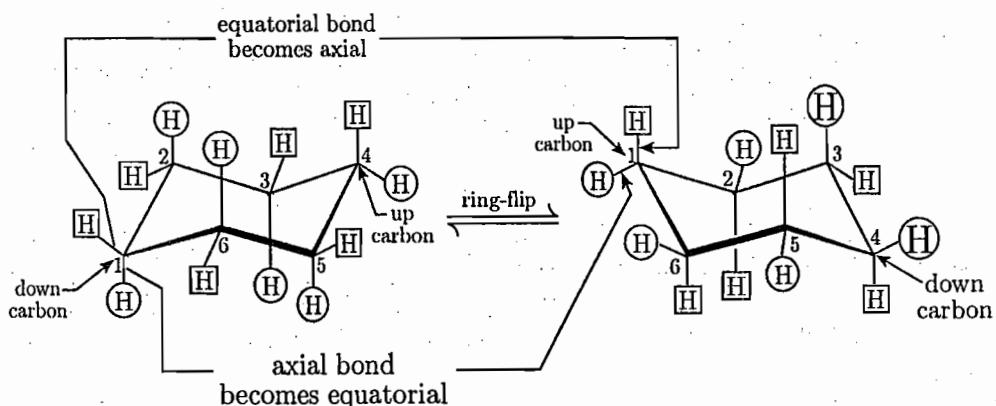
(b) Inspection of the chair conformation of cyclohexane shows that all the twelve C—H bonds are not equivalent; there are two sets of six. In one set, the six C—H bonds are nearly parallel to the C_3 axis (three fold simple axis of symmetry) or S_6 axis (six fold alternating axis of symmetry) of the cyclohexane molecule or perpendicular to the horizontal plane containing any three alternate carbon atoms of the ring. These are called *axial* bonds and are symbolised ‘a’. Three of these axial bonds are directed upward and the other three downward. In the other set, the six C—H bonds are distributed around the periphery of the ring making an angle of $109^\circ 28'$ with the C_3 axis or $\pm 19^\circ 28'$ with the horizontal plane containing any three carbon atoms of the ring. These are called *equatorial* bonds and are symbolised as ‘e’. Each carbon has an axial and an equatorial bond.



[The axial bonds are so designated because they are directed vertically, parallel to the axis of the ring and the equatorial bonds are so designated because they are directed outward, toward the equator of the ring.

Consequently, upward bonds are called ‘ β ’ bonds and downward bonds are called ‘ α ’ bonds. Axial bonds are, therefore, may be β -*axial* or α -*axial*. Similarly, equatorial bonds are classified as α or β , when projected downward and upward respectively.]

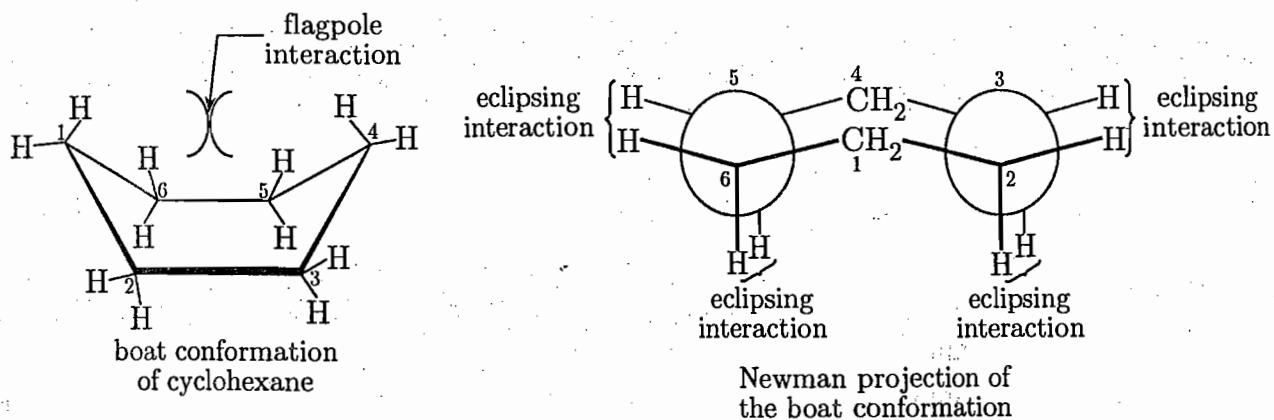
(c) As a result of the ease of rotation about its C—C single bonds, cyclohexane rapidly interconverts between two stable chair conformations. This interconversion is known as ring-flip or ring inversion. When the two chair conformations interconvert, the equatorial bonds become axial while the axial bonds become equatorial. In addition up and down carbons become down and up carbons respectively.



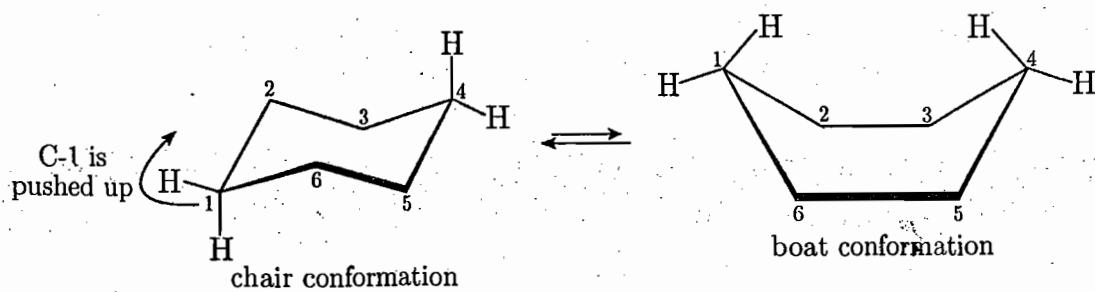
Since the activation energy for the process of ring inversion at room temperature is very low (10.8 kcal/mol), the rate of ring inversion or chair-chair interconversion is very high (approximately 10^5 times per second) at room temperature.

The interconversion can be arrested by cooling cyclohexane to very low temperatures ($\approx 100^\circ\text{C}$).

(d)

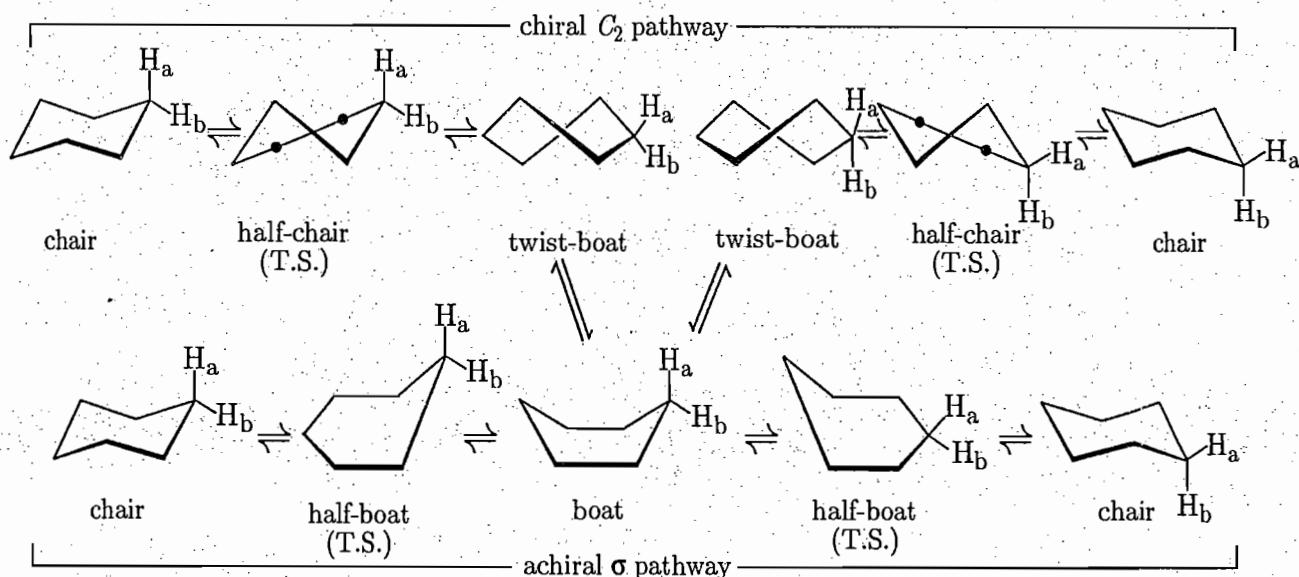


The boat conformation of cyclohexane is formed by “flipping” one end of the chair conformation up (or down). This flip requires only rotation about C—C single bonds.



Like the chair conformation, the boat conformation is free of angle strain. The boat conformation, however, is not free of torsional strain because there is eclipsing of two pairs of hydrogens on each set of gunwale carbons (C-2,C-3 and C-5,C-6). Again, the two flagpole hydrogens (the hydrogens which point upward from the ends of the boat like two flagpoles) on C-1 and C-4 are close enough to each other (which are within 180 pm, less than twice the van der Waals radius of hydrogen, i.e., $120 \times 2 = 240$ pm) to cause van der Waals repulsion (steric strain). This interaction is often called "flagpole" interaction. Torsional strain and "flagpole" interaction cause the boat conformation to have considerable higher energy (6.5 kcal/mole) than the chair conformation, even though the former contains two less buten-gauche interactions. Therefore, the boat conformation is less stable than the chair conformation.

(e) Two different pathways (chiral C_2 pathway and achiral σ pathway) have been considered for ring inversion of cyclohexane chair form and these can be shown as follows :

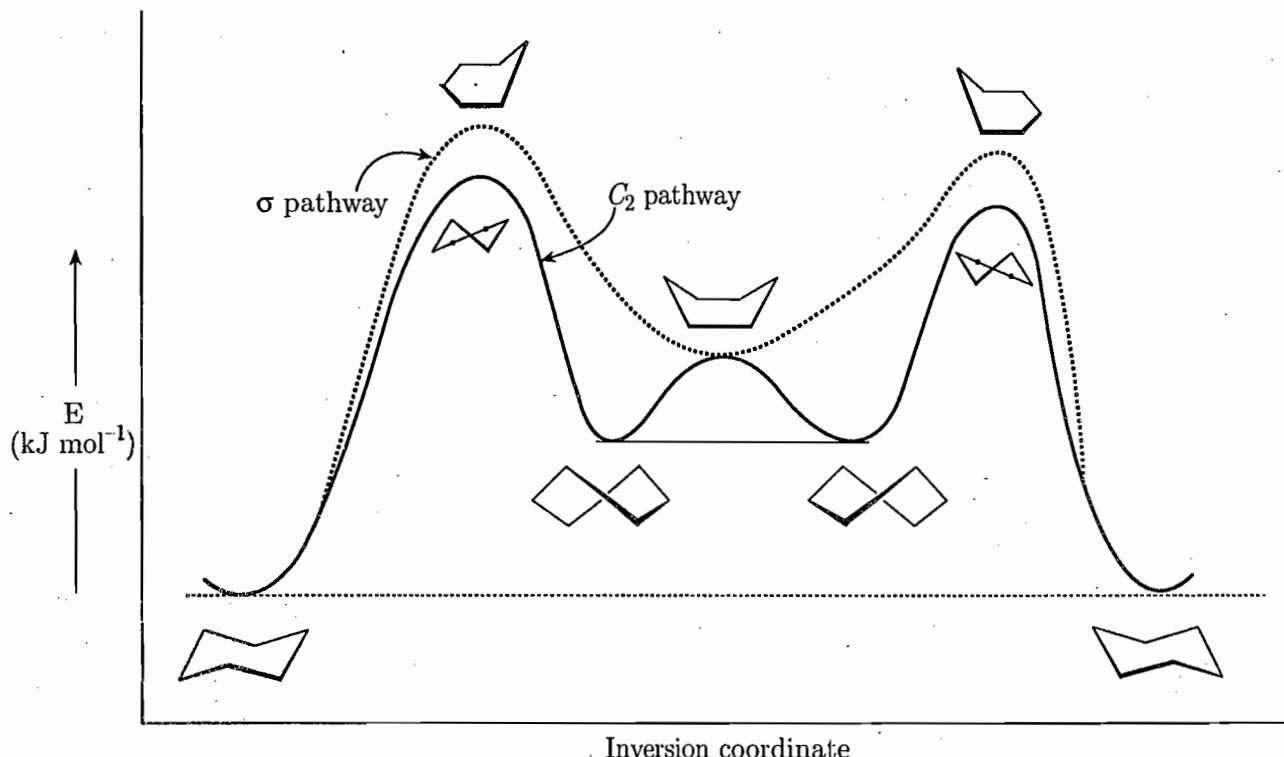


C_2 pathway : The chair conformer may be twisted to get the half-chair conformation (transition state) in which four carbon atoms lie in a plane and the other two alternately above and below the plane. There occurs extensive bond angle deformation accompanied with an increase in torsional strain. The transition state conformation has a C_2 axis but no σ plane. Further change leads to the 'twist-boat' conformation which has no angle strain but suffers from some torsional strain. It corresponds to an energy minimum and is actually a conformer. It leads to a conformation which is the classical boat. The boat conformation in its turn can go back to the original chair or to the inverted chair with equal facility through the enantiomeric twist-boat and half-chair conformation (T.S.) respectively. This pathway is called the C_2 pathway, since C_2 axis of the ground state chair form is retained along the pathway.

σ pathway : The chair form is twisted to an envelope-like half-boat conformation (transition state) with five of the carbon atoms in a plane and the sixth one either above or below it. This conformation has a σ plane and so is achiral. It leads directly to an energy minimum conformation which is the classical boat. The boat conformation in its

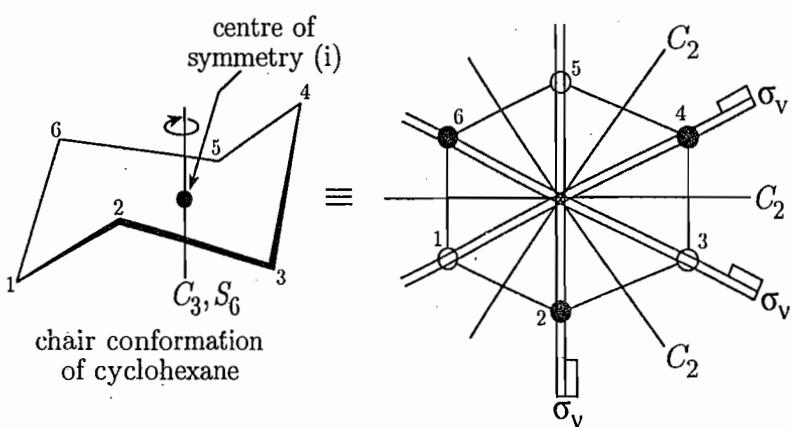
turn can go back to the original chair or to the inverted chair equally well through the equivalent half-boat conformation. This pathway is called a σ pathway, since both the half-boat and the classical boat conformations retain the symmetry plane of the chair ground state.

The energy diagrams of these pathways are shown in the following figure.



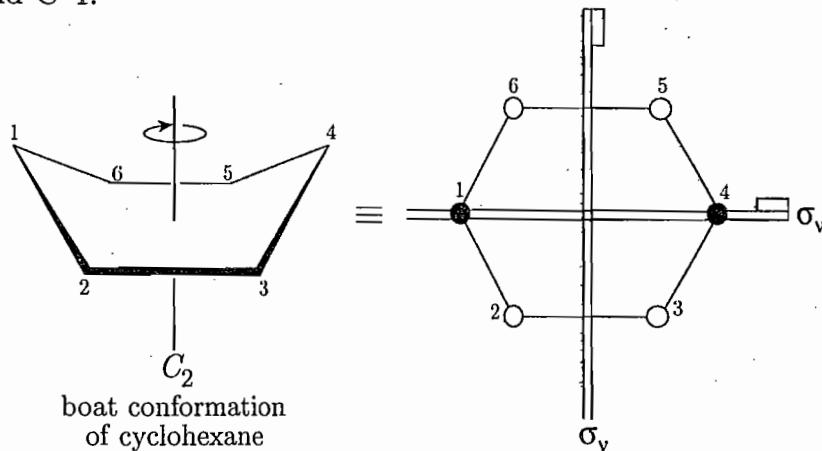
[This type of *homomeric* transformation of one chair form of cyclohexane into another equivalent chair form has been given the general name *topomerisation*. Since the hydrogen atoms which interchange sites are diastereotopic, the ring inversion process is a case of *diastereotopomerisation*.]

(f) The chair conformation of cyclohexane has a three-fold simple axis of symmetry (C_3 axis) and a six-fold alternating axis of symmetry (S_6 axis). The vertical axis passing through the centre of the chair is a C_3 as well as an S_6 axis. In addition, there are three two-fold simple axis of symmetry (C_2 axis) bisecting pairs of opposite sides, a centre of symmetry (i), and three vertical planes of symmetry (σ_v) passing through diagonal carbon atoms and four H atoms.



● = carbon atom above the plane of the paper
 ○ = carbon atom below the plane of the paper

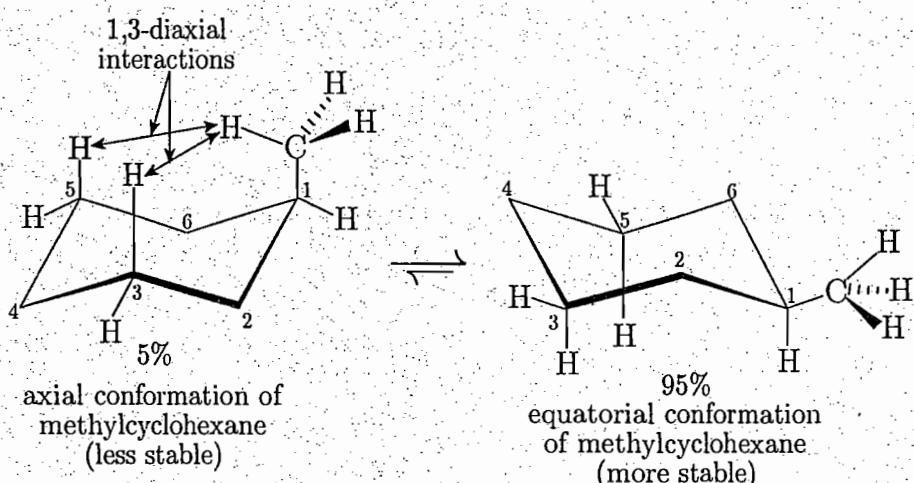
The boat conformation of cyclohexane has a two-fold simple axis of symmetry (C_2 axis) passing through the centre of the boat and two vertical planes of symmetry (σ_v) one of which is bisecting C-2—C-3 and C-5—C-6 bonds and the other is passing through C-1 and C-4.



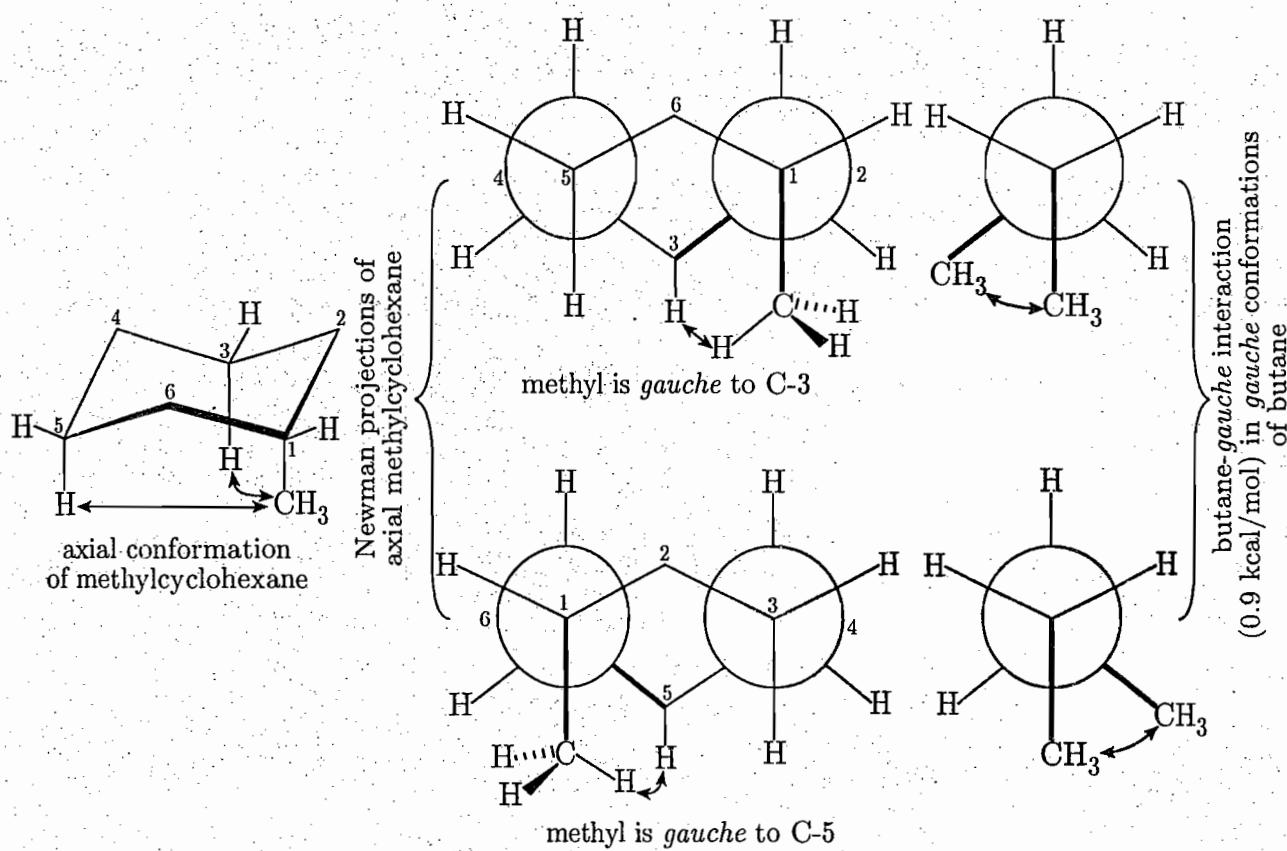
- 3.8 (a) Explain why equatorial methylcyclohexane is more stable than axial methylcyclohexane and thus predominates in the equilibrium mixture.
- (b) Studies indicate that the conformation with the methyl group equatorial is more stable than the conformation with the methyl group axial by about 1.7 kcal/mol. How would you explain this energy difference between the two conformations of methylcyclohexane?
- (c) Calculate the equilibrium constant (K_{eq}) at 25°C for the equilibrium : axial methylcyclohexane \rightleftharpoons equatorial methylcyclohexane (the energy difference between the axial and the equatorial conformation is 1.8 kcal/mol, i.e., $\Delta H = -1.8$ kcal/mol) and from that calculate the percentage composition of the mixture.
- (d) Explain why *tert*-butylcyclohexane exists almost entirely in equatorial chair conformation.
- (e) Why is the *tert*-butyl group characterized as a “holding group”? Explain giving examples.
- (f) Which is the most stable conformation of *cis*-1,4-di-*t*-butylcyclohexane?
- (g) Explain why *cis*-1,4-cyclohexanediol exists preferably in twist-boat conformation?
- (h) 5-Hydroxy-1,3-dioxane prefers to exist in the conformation with OH axial. Why?

Ans. (a) An axial methyl group in methylcyclohexane has one of its hydrogens within 190 to 200 pm of the axial hydrogens at C-3 and C-5 (*syn-axial* hydrogens). This distance is less than the sum of the van der Waals radii of two hydrogens (240 pm) and causes van der Waals strain in the axial conformation. Because the interacting substituents are on 1,3-positions relative to each other, these unfavourable steric interactions are called 1,3-diaxial interactions or *syn-axial interactions*. When the methyl group is equatorial, it experiences no significant crowding because it is

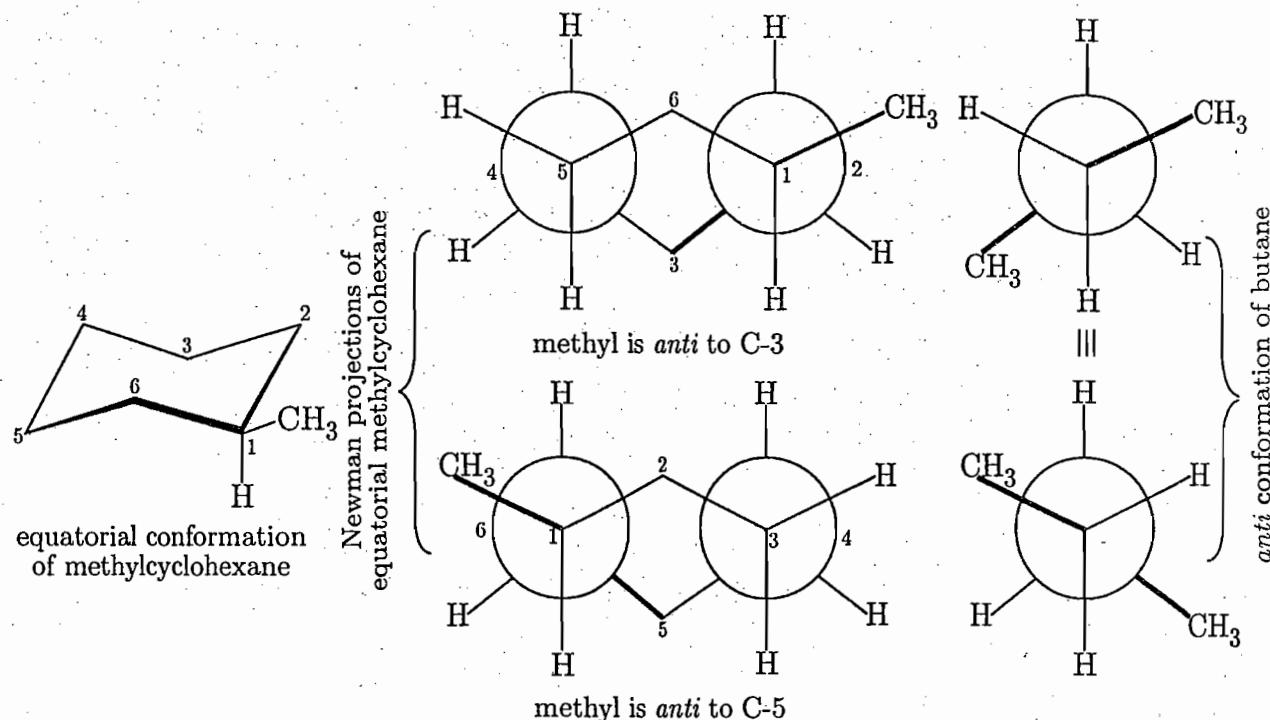
anti to the C-3 and C-5 carbons. Therefore, the substituent extends into space away from the rest of the molecule. Because of this, equatorial methylcyclohexane is more stable than axial methylcyclohexane and as a consequence, it predominates in the equilibrium mixture.



(b) The energy difference between the two conformations of methylcyclohexane can be explained by examining the molecular models and Newman projections of the two conformations. If we make a model of the conformation of methylcyclohexane with axial methyl and hold it so that we can sight along the C-1—C-2 bond, we see that the methyl group and C-3 of the ring have the same relative locations as the two methyl groups in the gauche conformation of butane. This can be shown by a Newman projection. If we now sight along the C-1—C-6 bond, we see similar arrangement but with C-5 taking the place of C-3.



If we make a model of the conformation of methylcyclohexane with equatorial methyl, and sight along the C-1—C-2 bond, we see that the methyl group and C-3 of the ring have the same relative locations as the two methyl groups in the *anti* conformation of butane. This can be shown by a Newman projection. Again, if we sight along the C-1—C-6 bond, we see methyl and C-5 in the *anti* relationship.



Thus, for each 1,3-diaxial methyl-hydrogen interaction there is a butane-*gauche* interaction between the methyl group and a carbon atom of the ring. For each butane-*gauche* interaction, the increase of energy of the system is 0.9 kcal/mol. The axial conformation of methylcyclohexane has two butane-*gauche* interactions whereas the equatorial conformation has no such interaction. Therefore, the axial conformation is higher in energy by 0.9×2 or 1.8 kcal/mol than the equatorial conformation. This value is in good agreement with the experimental value of 1.7 kcal/mol.

(c) Since ΔS for the chair-chair interconversion is very small ($1 \text{ mol} \rightleftharpoons 1 \text{ mol}$), $\Delta G = \Delta H$. Hence, $\Delta G = -1.8 \text{ kcal/mol} = -1800 \text{ kcal/mol}$.

$$\text{Since } \Delta G = -2.303 RT \log K_{\text{eq}}$$

$$\therefore -1800 = -2.303 (2.00 \text{ cal/mol. K}) (298 \text{ K}) \log K_{\text{eq}}$$

$$\text{Hence, } \log K_{\text{eq}} = 1.313 \text{ and } K_{\text{eq}} = 20.6$$

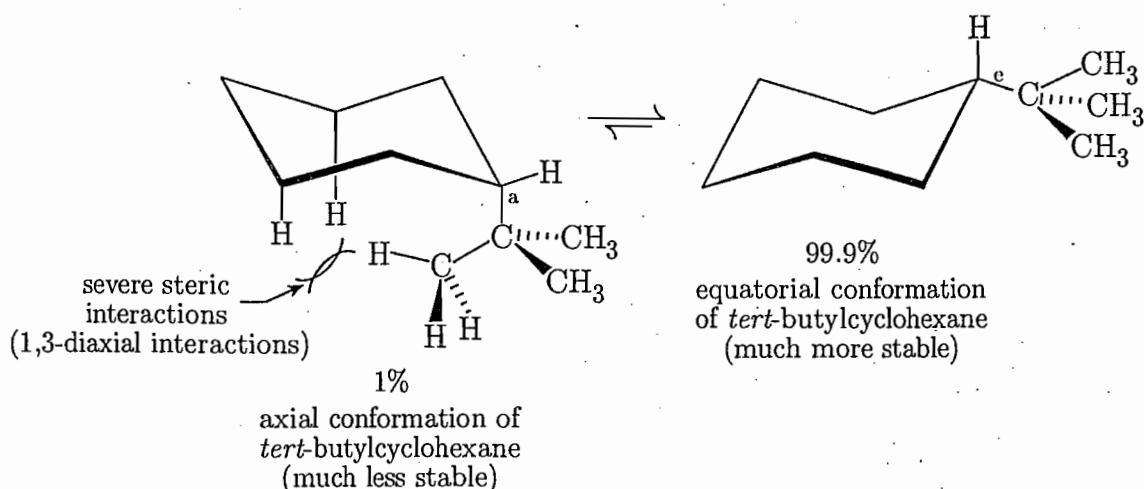
$$\text{Now, } K_{\text{eq}} = \frac{[\text{equatorial conformation}]}{[\text{axial conformation}]} = \frac{20.6}{1}$$

\therefore % of the equatorial conformation

$$= \frac{[\text{equatorial conformation}]}{[\text{equatorial conformation}] + [\text{axial conformation}]} \times 100 = \frac{20.6}{(20.6 + 1)} \times 100 = 95$$

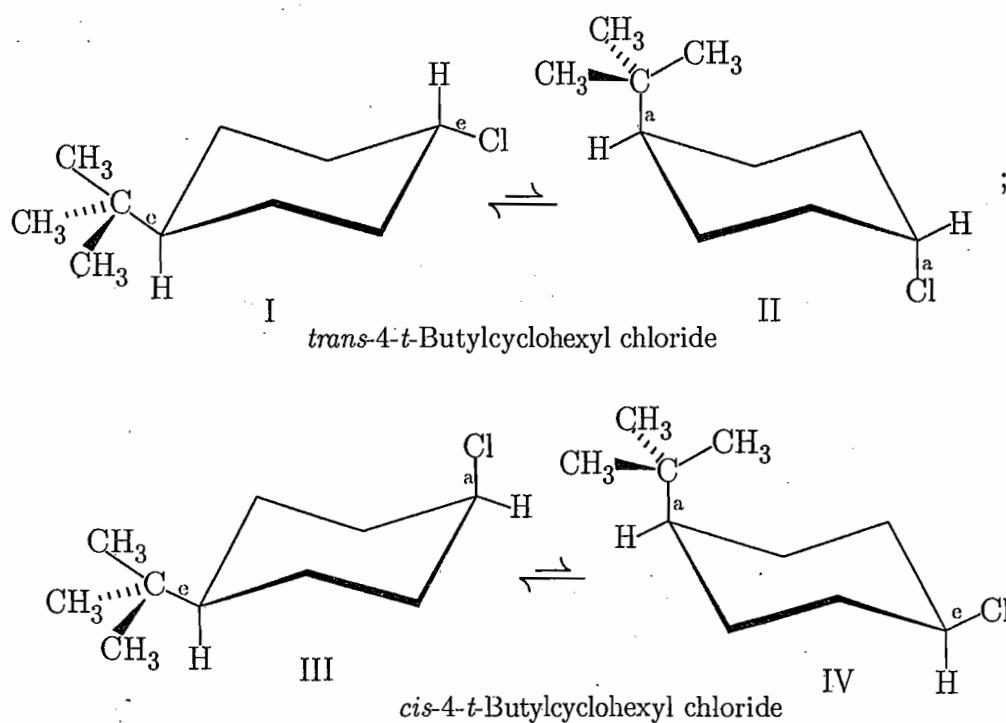
\therefore % of the axial conformation = $(100 - 95) = 5$

(d) In the case of *tert*-butylcyclohexane, the 1,3-diaxial interactions are even more destabilizing because a *tert*-butyl group is much larger than a methyl group. For this reason, *tert*-butylcyclohexane exist practically only (99.9%) in equatorial chair conformation, i.e., it is conformationally locked.



[A substituent has more room if it is in an equatorial position than if it is in an axial position. Therefore, at any instant more monosubstituted cyclohexane molecules exists in the chair conformation with the substituent in the equatorial position than in the chair conformation with the substituent in the axial position. The relative amounts of the two chair conformers depend on the bulk of the substituent. The substituent with greater bulk will have greater preference for equatorial position because it will have stronger 1,3-dixial interactions.]

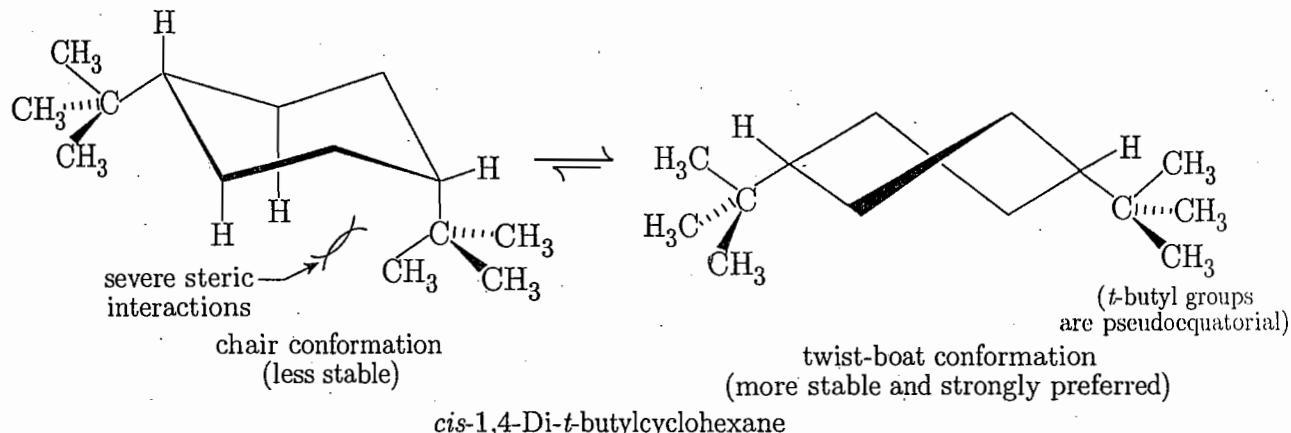
(e) The *tert*-butyl is characterized as a "holding group" because its own tendency to be in the equatorial position helods a smaller substituent axial or equatorial, depending or whether it is *cis* or *trans*. 4-*tert*-Butylcyclohexyl chloride, for example, could exist the cortically in four stereoisomeric chair forms, I, II, III and IV.



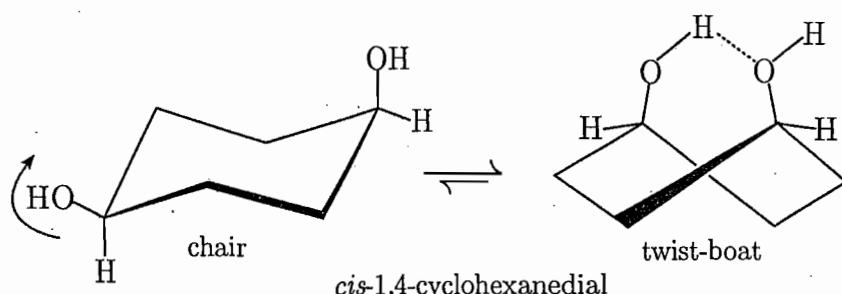
Conformations I and II have the substituents *trans* to one another, but in I they both are equatorial, whereas in II they both are axial. Conformations III and IV have the substituents in the *cis* relationship, with the *tert*-butyl and chlorine equatorial and axial, respectively, in III, and the reverse in IV. A *tert*-butyl group is very large and bulky compared to chlorine and considerable steric hindrance results when *tert*-butyl is axial. For this reason, I and III with *tert*-butyl equatorial are much more favourable than II and IV. That is, in the *trans*-isomer *tert*-butyl holds smaller chlorine atom equatorial and in the *cis*-isomer it holds smaller chlorine atom axial.

[A bulky group which makes the molecule conformationally fixed or atleast biased is also called an "anchoring group". A conformationally biased molecule is called "anancemicic".]

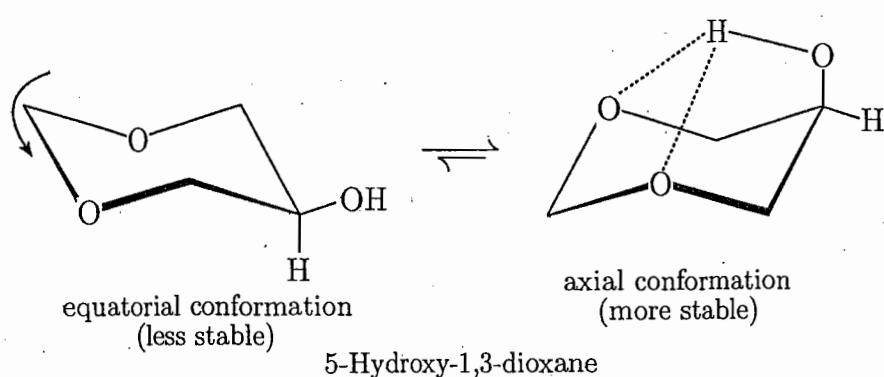
(f) Either of the two chair conformations of *cis*-1,4-di-*t*-butylcyclohexane in which a bulky *tert*-butyl group occupies an axial position is very unstable because of excessive steric interactions (1,3-diaxial interactions). To overcome this steric strain, the molecule assumes a more stable twist-boat conformation in which the two *tert*-butyl groups are so positioned that the strain is minimized.



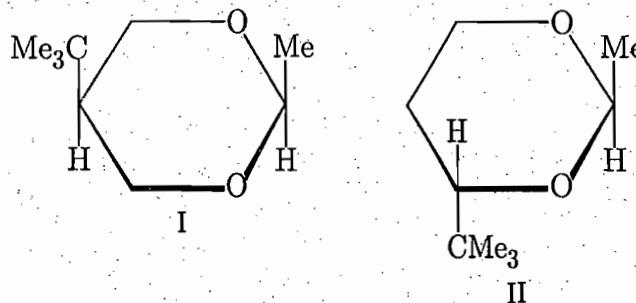
(g) Since in twist-boat conformation the two hydroxyl groups are within hydrogen bonding distance, intramolecular hydrogen bonding occurs which makes this conformation more stable than equatorial-axial conformation which suffers from 1,3-diaxial interactions. For this reason, *cis*-1,4-cyclohexanediol exists preferably in twist-boat conformation.



(h) Because of forming H-bond (a stabilising factor) with the ring O atoms, 5-hydroxy-1,3-dioxane prefers to exist in the conformation with OH axial.

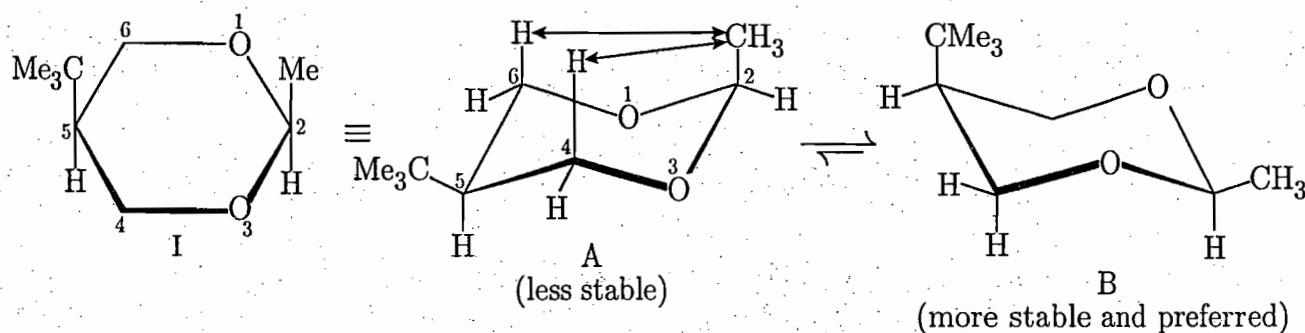


- 3.9 (a) With *cis*-2-methyl-5-*tert*-butyl-1,3-dioxane (I) the conformation with *tert*-butyl axial is more favoured than the conformation with *tert*-butyl equatorial. Explain why this should be so and predict what should be the favoured conformation for *trans*-2-methyl-4-*tert*-butyl-1,3-dioxane(II).



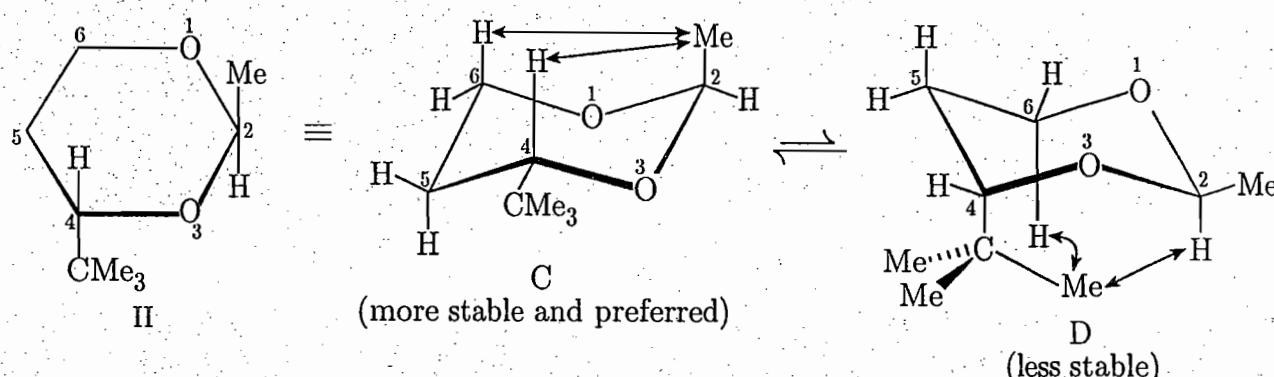
- (b) Predict the most stable conformation of 1-methyl-1-phenylcyclohexane.
- (c) Conformational free energy values of Cl and I atoms are almost identical, even though the size of iodine is larger than chlorine. Offer an explanation.
- (d) What is called anomeric effect? Give example and explain the cause of such effect. Discuss the effect of solvent on anomeric effect.
- (e) Both the conformers of *trans*-2-chlorocyclohexanol are equally populated—comment.
- (f) In gaseous state, the a,a-conformer of *trans*-1,2-dibromocyclohexane is much more stable than the e,e-conformer (a,a : e,e = 95 : 5), but in benzene both the conformers are nearly equally stable (a,a : e,e = 52 : 48). Explain.
- (g) Which one of the two diastereoisomeric 2-bromo-4-*t*-butylcyclohexanones is more polar and why?
- (h) Draw the possible conformations of *N*-methyl-4-chloropiperidine and explain why these conformations are possible.

Ans. (a) The two conformations of *cis*-2-methyl-5-*tert*-butyl-1,3-dioxane (I) are shown below.



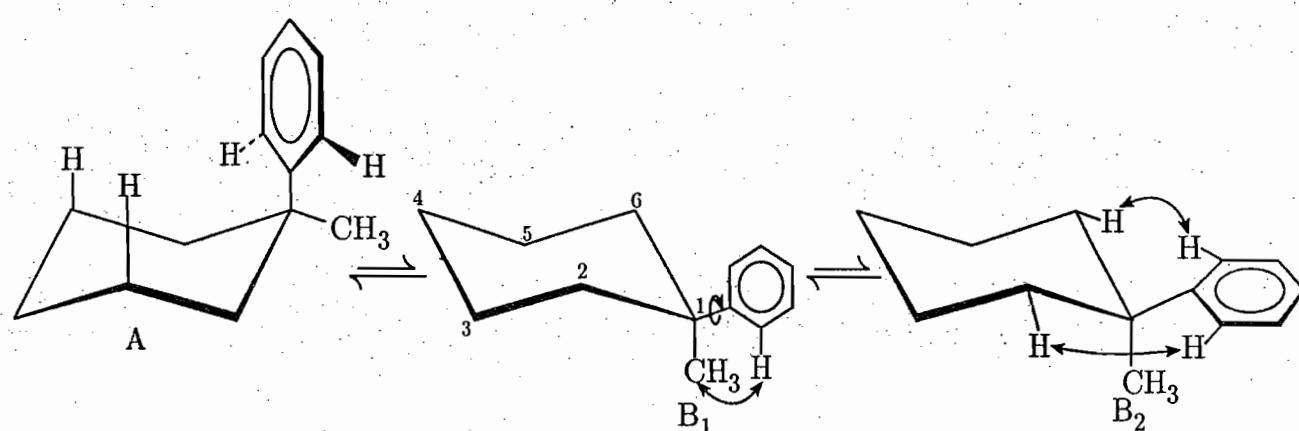
The conformation A is destabilised by *syn-axial* interactions between CH_3 and H's at C-4 and C-6. Although in conformation B, the bulky *tert*-butyl group assumes axial position, it is free of *syn-axial* interaction because 1,3-*syn-axial* positions are now occupied by oxygen atoms having lone pair of electrons which have a smaller steric requirement than the C—H bonds. Since lone pair causes no steric interaction, this conformation is relatively more stable and therefore, the favoured one.

The two conformations of *trans*-2-methyl-4-*tert*-butyl-1,3-dioxane (II) are shown below.



The conformation C is destabilised by *syn-axial* interactions between CH_3 and H's at C-4 and C-6 whereas the conformation D is destabilised by *syn-axial* interaction between CMe_3 and H's at C-2 and C-6. Since *syn-axial* interaction involving a larger *tert*-butyl group is much stronger than the *syn-axial* interaction involving a methyl group, the conformation C is much more stable than the conformation D. Therefore, the conformation C in which the *tert*-butyl group assumes equatorial position is the favoured conformation of *trans*-2-methyl-4-*tert*-butyl-1,3-dioxane.

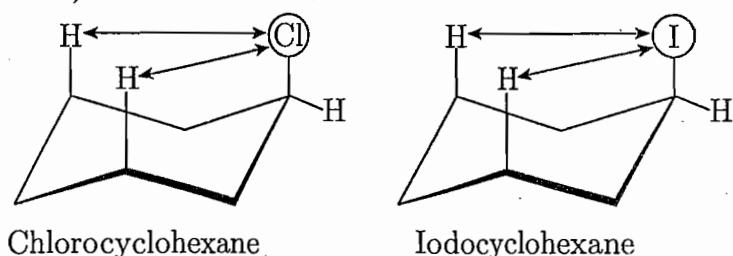
(b) The conformations of 1-methyl-1-phenylcyclohexane are as shown below.



The conformational free energy of the phenyl group is 2.87 kcal/mol and that of methyl group is 1.70 kcal/mol. Therefore, equatorial phenyl-axial methyl conformation (B_1 or B_2) is expected to be the preferred one. In fact, the conformation A with axial phenyl and equatorial methyl is the preferred one (by 0.32 kcal/mol). In conformation B_1 , where the phenyl group is in the same vertical plane passing through C-1 and C-4 of cyclohexane chair, a steric interaction develops between the methyl group and one of the *ortho*-hydrogen atoms of the phenyl group. Again, in conformation B_2 , where the

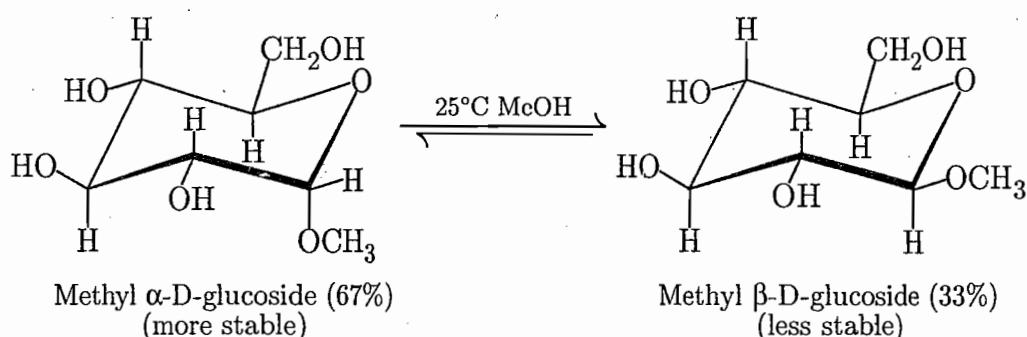
phenyl group is nearly in the same average plane (which bisects each C—C bond) of the cyclohexane chair, there develops serious steric interactions between the equatorial hydrogens at C-2, C-6 and *ortho* hydrogens of the phenyl group. This type of steric interactions are not present in conformation A; the phenyl ring in it is so oriented that it interacts minimally with the axial hydrogens at C-3 and C-5. Therefore, A is relatively more stable and the preferred conformation of 1-methyl-1-phenylcyclohexane.

(c) Since iodine atom is larger in size than chlorine atom, the C—I bond is longer than C—Cl bond and because of this, I remains much away from the *syn-axial* hydrogens at C-3 and C-5 compared to Cl. Thus, the steric interaction which is supposed to be increased on going from chlorine to iodine is compensated by the simultaneous increase in distance between the *syn-axial* hydrogen atoms and the halogen atom. For this reason, conformational free energy values of Cl (2.68 kJ/mol) and I (2.55 kJ/mol) are almost identical, even though the size of iodine (atomic radius = 1.33 Å) is larger than chlorine (atomic radius = 0.99 Å).



[The difference in free energy between an equatorial and an axial conformer is known as the conformational free energy ($-\Delta G_R^\circ$ or A-value) of the substituent (R) and determines the equatorial preference of R.]

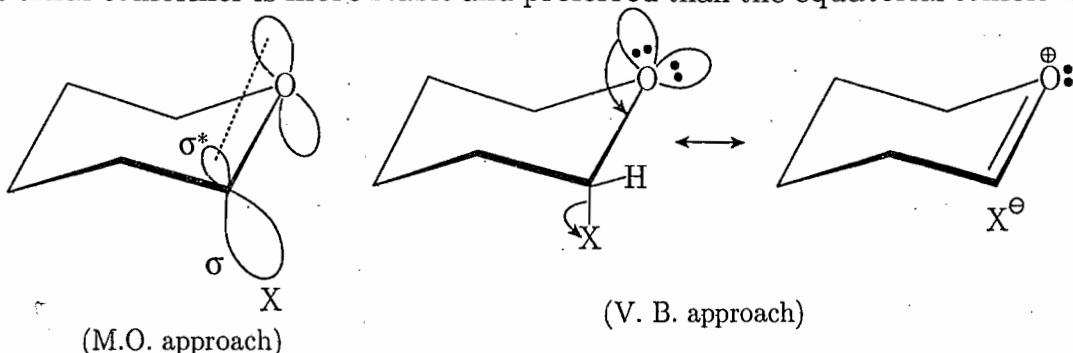
(d) The extra preference for an axial orientation of an electronegative substituent, such as halogens, OAc, OR, etc., at the anomeric carbon over and above that normally expected from its conformational free energy is called the *anomeric effect*. For example, the greater stability of the α -anomer of methyl D-glucoside having axial $-\text{OCH}_3$ than the corresponding β -anomer with equatorial $-\text{OCH}_3$ (although conformationally the β -anomer is expected to be more stable) is due to what is called anomeric effect.



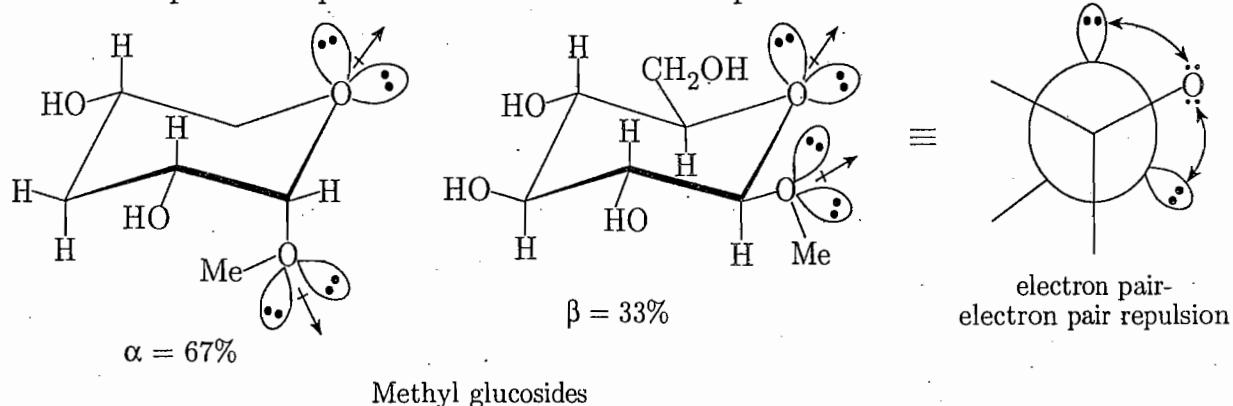
The phenomenon of anomeric effect can be explained as follows :

- When the electronegative substituent at the anomeric carbon is axial, one electron pair on ring oxygen atom is antiperiplanar to the polar C—X (X = OR, NR₂, or halogen) bond. Under this condition *p* orbital on the ring oxygen atom can overlap (interact) with the antibonding sigma orbital of C—X bond ($n-\sigma^*$ interaction) according to M.O. theory. According to V.B. theory, it is a case of resonance involving a double bond between O and C-2

and no bond between C-2 and X. Because of this stabilising electronic effect, the axial conformer is more stable and preferred than the equatorial conformer.

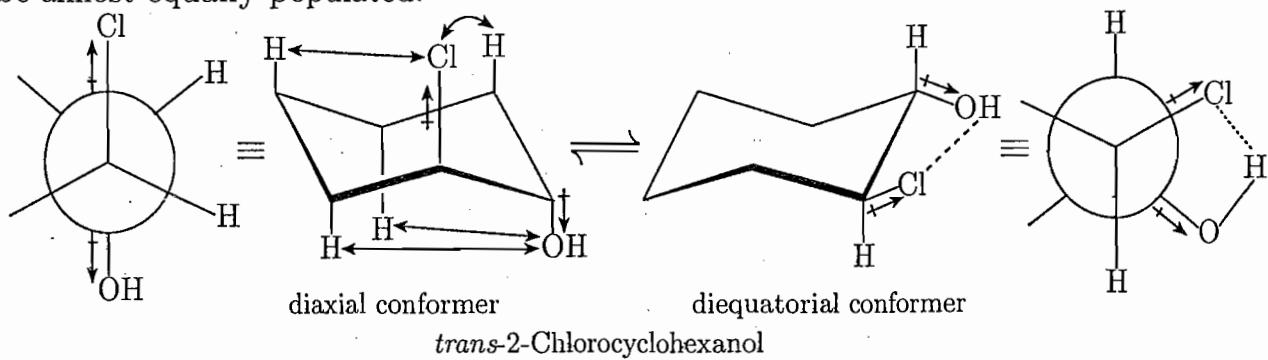


- (ii) The lone-pair electrons of the anomeric substituent have repulsive interactions with the lone-pair electrons of the ring oxygen if the anomeric substituent is in the β -position, but not if it is in the α -position. That is, the equatorial conformer with parallel dipoles is destabilised with respect to the axial conformer.

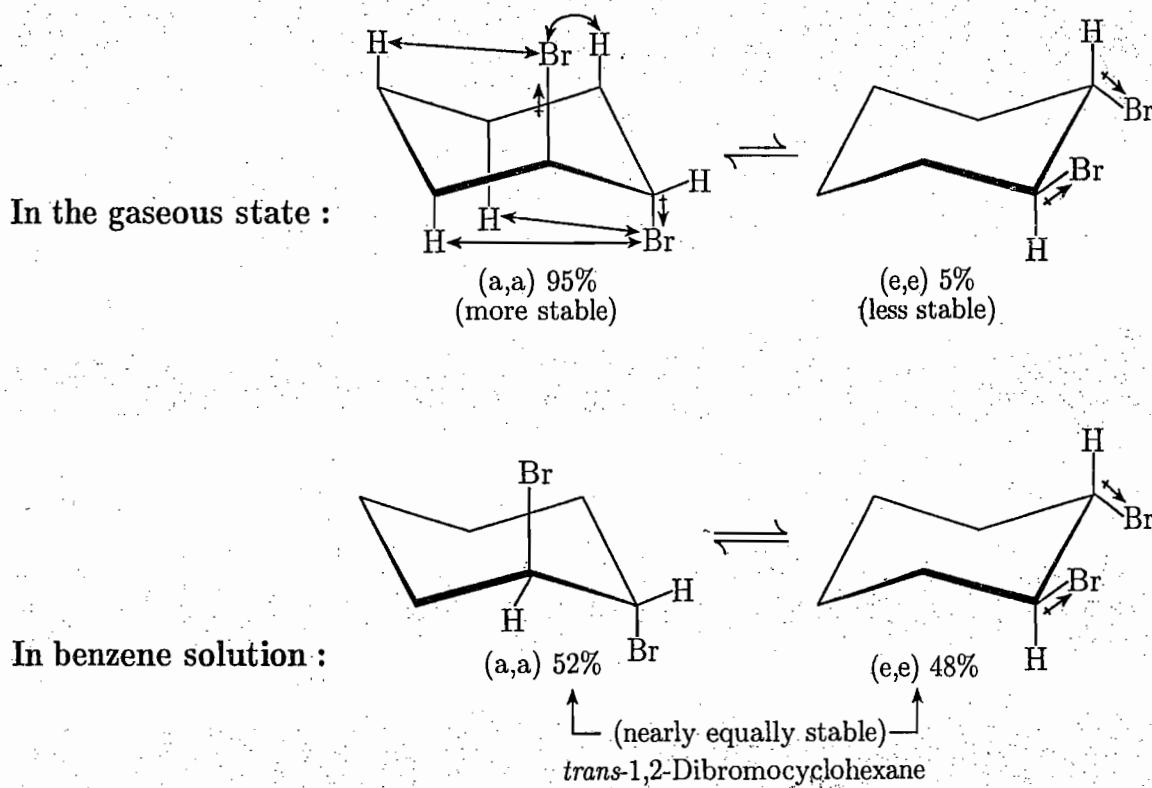


From a study of the effect of solvent polarity on the equilibrium of the α - and β -anomers of D-glucose and related compounds, it becomes apparent that as the polarity of the solvent is increased, the proportion of the β -anomer increases at the cost of the α -anomer. It thus follows that the anomeric effect decreases as the polarity of the solvent increases. A polar solvent with high dielectric constant decreases the dipole-dipole repulsive interaction. As a result, the anomeric effect weakens and this causes the equilibrium to be shifted in the direction of conformationally more stable β -anomer.

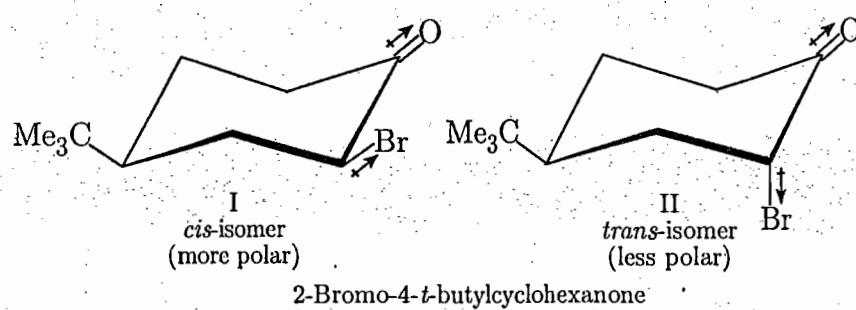
- (e) The diequatorial conformer of *trans*-2-chlorocyclohexanol is stabilised through intramolecular H-bonding, but destabilised by electrostatic repulsion between the two dipoles. On the other hand, although the diaxial conformer has the advantage of the absence of electrostatic repulsion between the two dipoles, it is somewhat destabilised by 1,3-diaxial interactions. A compromise is reached and the two conformers are found to be almost equally populated.



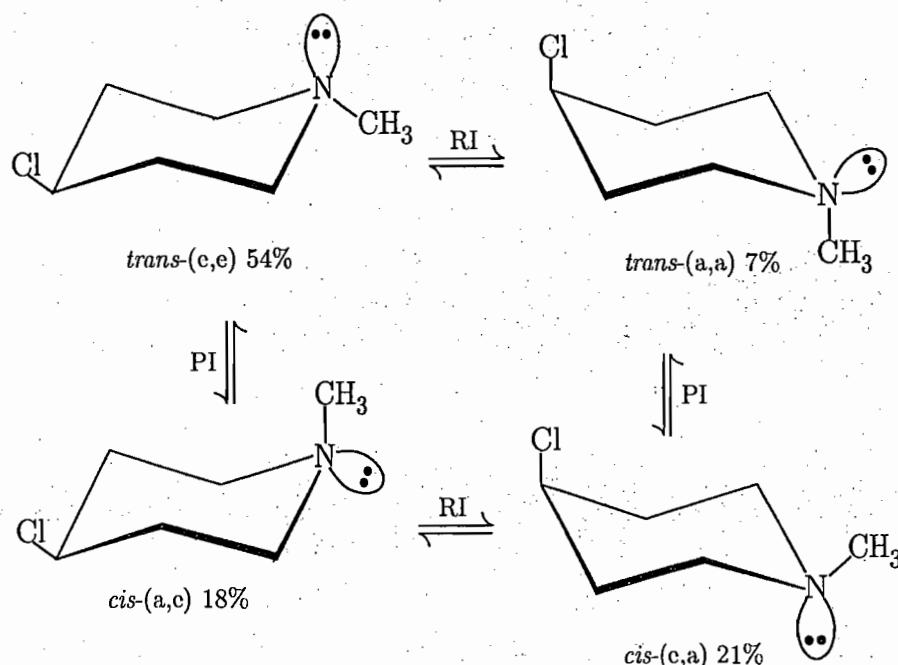
(f) In the diaxial form of *trans*-1,2-dibromocyclohexane, the two dipoles are oppositely placed ($\theta = 180^\circ$). So, its dipole moment is nearly zero and there is no electrostatic repulsion between them. However, it is slightly destabilised by 1,3-diaxial interactions. On the other hand, in the diequatorial conformer, the two dipoles are oriented at a dihedral angle of 60° . So, there is considerable electrostatic repulsion and because of this, it is much destabilised compared to the diaxial conformer. In the gaseous state, the molecules remain much separated from each other and so there operates no intermolecular forces (dipole-dipole interaction) which may stabilise the diequatorial form. As a consequence, the more stable diaxial conformer exists predominately (95 : 5). On the other hand, in benzene solution, the molecules come much closer to each other and as a result, the electrostatic repulsion between the two dipoles in the diequatorial conformer is minimised due to intermolecular dipole-dipole attraction. Consequently, the two conformers become nearly equally stable and remain almost equally populated (52 : 48).



(g) The two diastereoisomeric 2-bromo-4-*t*-butylcyclohexanones (I and II) are enantiomeric (do not easily undergo ring inversion) because of bulky $-\text{CMe}_3$ group at C-4. In II (the *trans*-isomer), $\text{C}=\text{O}$ and $\text{C}-\text{Br}$ bond vectors are not in the same direction as in I (the *cis*-isomer). Consequently, I is more polar than II ($\mu_{\text{I}} = 4.20\text{D}$ and $\mu_{\text{II}} = 3.19\text{ D}$).



(h) In case of *N*-methyl-4-chloropiperidine, four conformations are possible because of ring inversion (RI) and pyramidal inversion (PI).

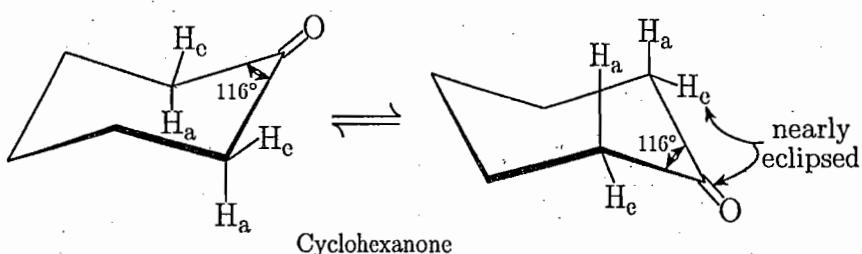


[When N—H in piperidine is replaced by N—R, the conformer with equatorial R and axial lone pair is always preferred.]

- 3.10 (a) Why is cyclohexanone relatively less stable than cyclohexane?
- (b) What is called 2-alkylketone effect?
- (c) Explain why *cis*-5-*t*-butyl-2-methylcyclohexanone is isomerised to the *trans*-isomer in the presence of a base.
- (d) What is called 3-alkylketone effect?
- (e) In *trans*-2-isopropyl-5-methylcyclohexanone (menthone), both the alkyl groups are preferably axially oriented. Explain.
- (f) What is called α -haloketone effect?
- (g) (i) What is called allylic 1,3-strain or A^{1,3}-strain?
(ii) The favoured conformation of (*Z*)-2-methylcyclohexylidineacetic acid is that in which the methyl group is axial, whereas the favoured conformation of the (*E*)-isomer is that in which the methyl group is equatorial. Explain.

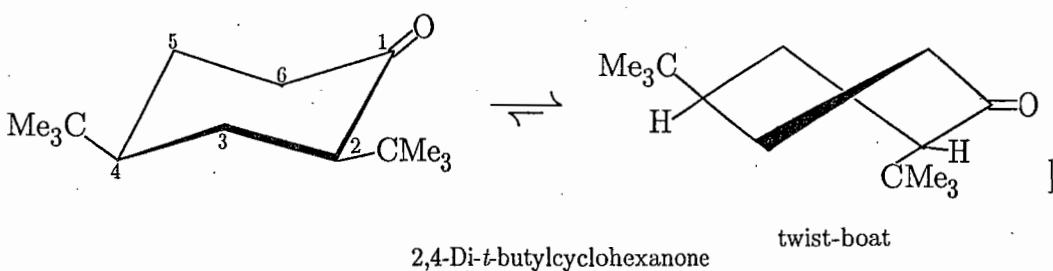
Ans. (a) Unlike cyclohexane, the ring in cyclohexanone is buckled slightly from the chair structure in order to accommodate the trigonal carbon. In fact, due to flattening, the equatorial hydrogens at C-2 and C-6 become almost eclipsed with the carbonyl oxygen ($\theta = 4.3^\circ$). Again, the C—CO—C bond angle in cyclohexanone is 116° which is less than the ideal bond angle of 120° for an sp^2 carbon. So, it has a small amount of angle strain besides the partial bond eclipsing strain. The

combined effect of these two strains makes cyclohexanone less stable than cyclohexane.

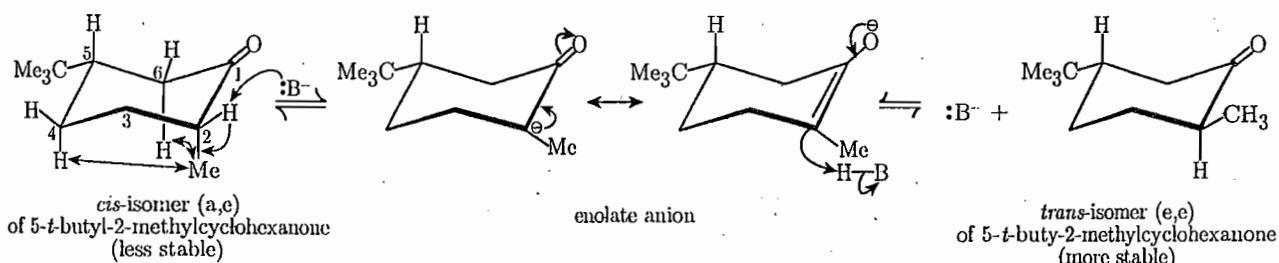


(b) In cyclohexane, if either of the equatorial hydrogen atoms at C-2 and C-6 are replaced by an alkyl group, steric interaction between it and the nearly eclipsed carbonyl oxygen destabilises the equatorial conformer. As a consequence, the energy difference between the axial and equatorial conformations decreases in comparison to that in cyclohexane. This decrease in energy difference (measured by the difference of $-\Delta G_R^\circ$ in cyclohexane and $-\Delta G_R^\circ$ in cyclohexanone) is called 2-alkylketone effect.

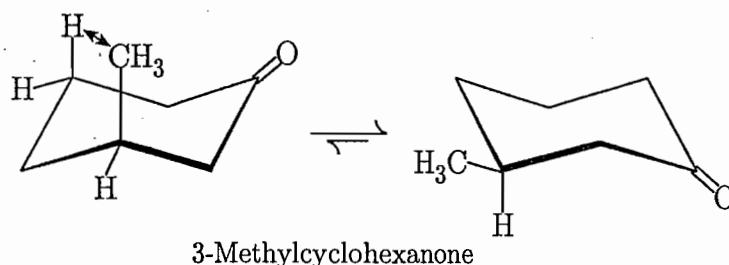
[When R = CH₃, the magnitude of 2-alkylketone effect is very small because the CH₃ group in equatorial position is too far to experience any appreciable steric repulsion with C=O; however, eclipsing of CH₃ with C=O is electronically favourable as evidenced from the preferred conformation of propanal in which C=O and CH₃ groups are eclipsed. The magnitude of 2-alkylketone effect increases as the size of the alkyl group increases. When R = *t*-butyl, the molecule exists largely in twist-boat conformation in which *t*-butyl/C=O eclipsing is avoided.]



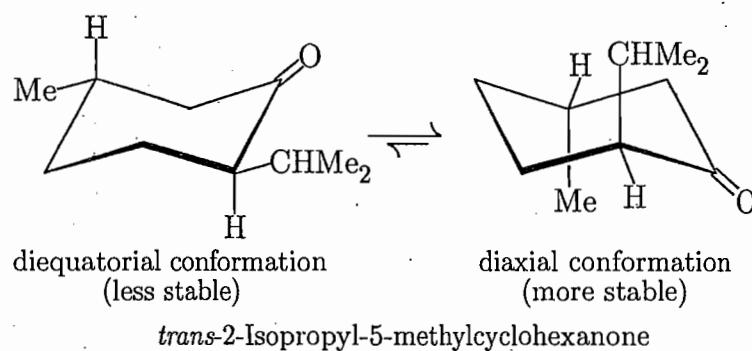
(c) In the *cis*-isomer of 5-*t*-butyl-2-methylcyclohexanone, the bulky —CMe₃ group holds the —CH₃ group axial; therefore, it suffers from 1,3-diaxial interactions. On the other hand, in the *trans*-isomer, although the —CH₃ group is equatorial, it is too far to experience any appreciable steric interaction with C=O and also eclipsing of CH₃ and C=O is electronically favourable. Therefore, the *trans*-isomer is relatively more stable than the *cis*-isomer and because of this, when treated with a base, the *cis*-isomer is isomerised to the *trans*-isomer through the formation of an intermediate enolate anion.



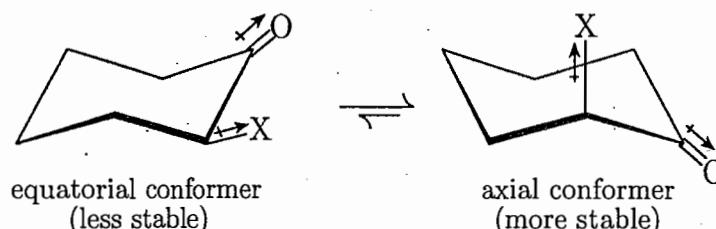
(d) In the case of a 3-alkylcyclohexanone one *syn axial* interaction between the axial R group and axial H is missing. Because of this, the energy difference between the axial and the equatorial conformers is decreased in comparison to that in cyclohexane. This decrease in energy difference (measured by the difference of $-\Delta G_R^\circ$ in cyclohexane and $-\Delta G_R^\circ$ in cyclohexanone) is known as 3-alkylketone effect. For example, this is equivalent to one butane-*gauche* interaction (3.75 kJ/mol) when R is methyl.



(e) In *trans*-2-isopropyl-5-methylcyclohexanone (menthone), the 2-alkylketone effect and the 3-alkylketone effect cooperate with each other to stabilise the diaxial conformation with respect to the diequatorial conformation. Therefore, in menthone both the alkyl groups are preferably axially oriented.

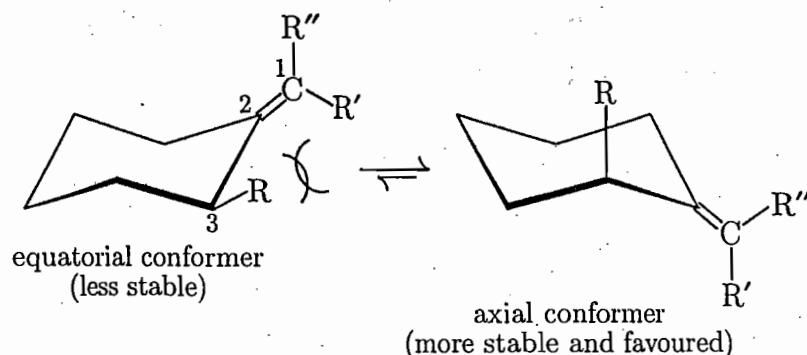


(f) In the case of α -halocyclohexanones, the conformation with axial halogen atom is more stable than that with equatorial halogen. This phenomenon is called α -haloketone effect. The axial conformer is preferred because in addition to the steric interaction in the equatorial conformer due to partial eclipsing of C—X and C=O bonds, there also operates a dipole-dipole repulsive interaction between the almost parallel $\overset{\delta+}{\text{C}}-\overset{\delta}{\text{X}}$ and $\overset{\delta}{\text{C}}=\overset{\delta}{\text{O}}$ dipoles further destabilising the equatorial conformer.

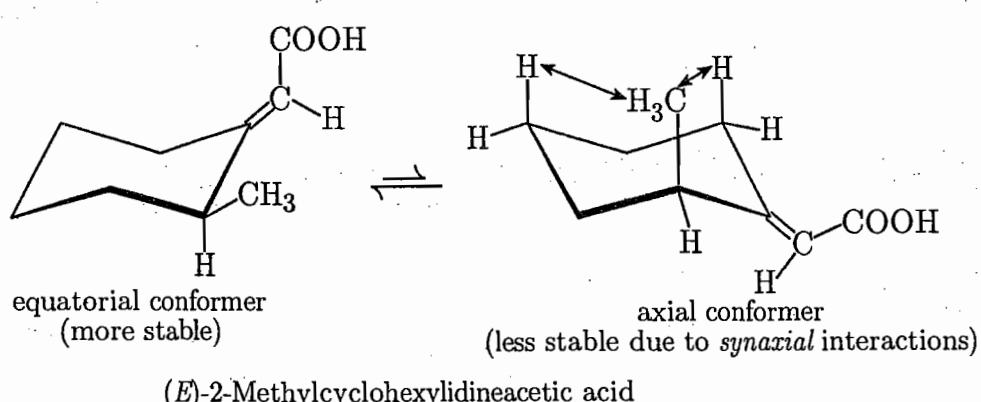
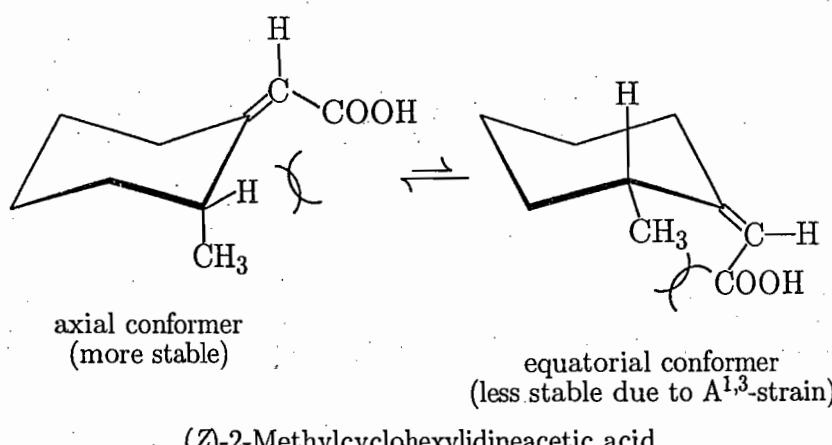


(g) (i) In alkylidencyclohexanes, the C=O group is replaced by C=CR'R''. In the equatorial conformer of a 2-substituted alkylidencyclohexane, the allylic segment R'-C_α=C_β—C_γ—R is almost coplanar and thus R and R' are almost eclipsed giving rise to 1,3-diaxial type of strong steric interaction.

This interaction becomes further unfavourable due to shorter C=C bond in between. This interaction is called allylic 1,3-strain or A^{1,3}-strain since the groups involved are at 1 and 3 positions of an allylic system. This interaction causes the axial conformer to become predominant, particularly if the groups R and R' are bulky.



- (ii) (*Z*)-2-Methylcyclohexylidineacetic acid exists largely with Me axial because the equatorial conformer suffers from A^{1,3}-strain. On the other hand, (*E*)-2-methylcyclohexylidineacetic acid exists largely with Me equatorial because the axial conformer suffers from 1,3-diaxial interactions.

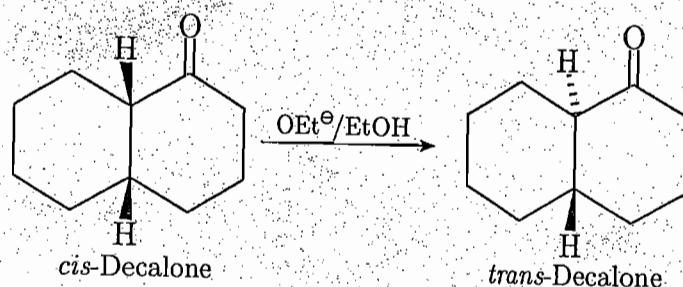


- 3.11 (a) Draw the chair conformation for (i) *cis*- and (ii) *trans*-decalin and comment on their flexibilities. Predict which isomer is chiral and which one is more stable. Why?

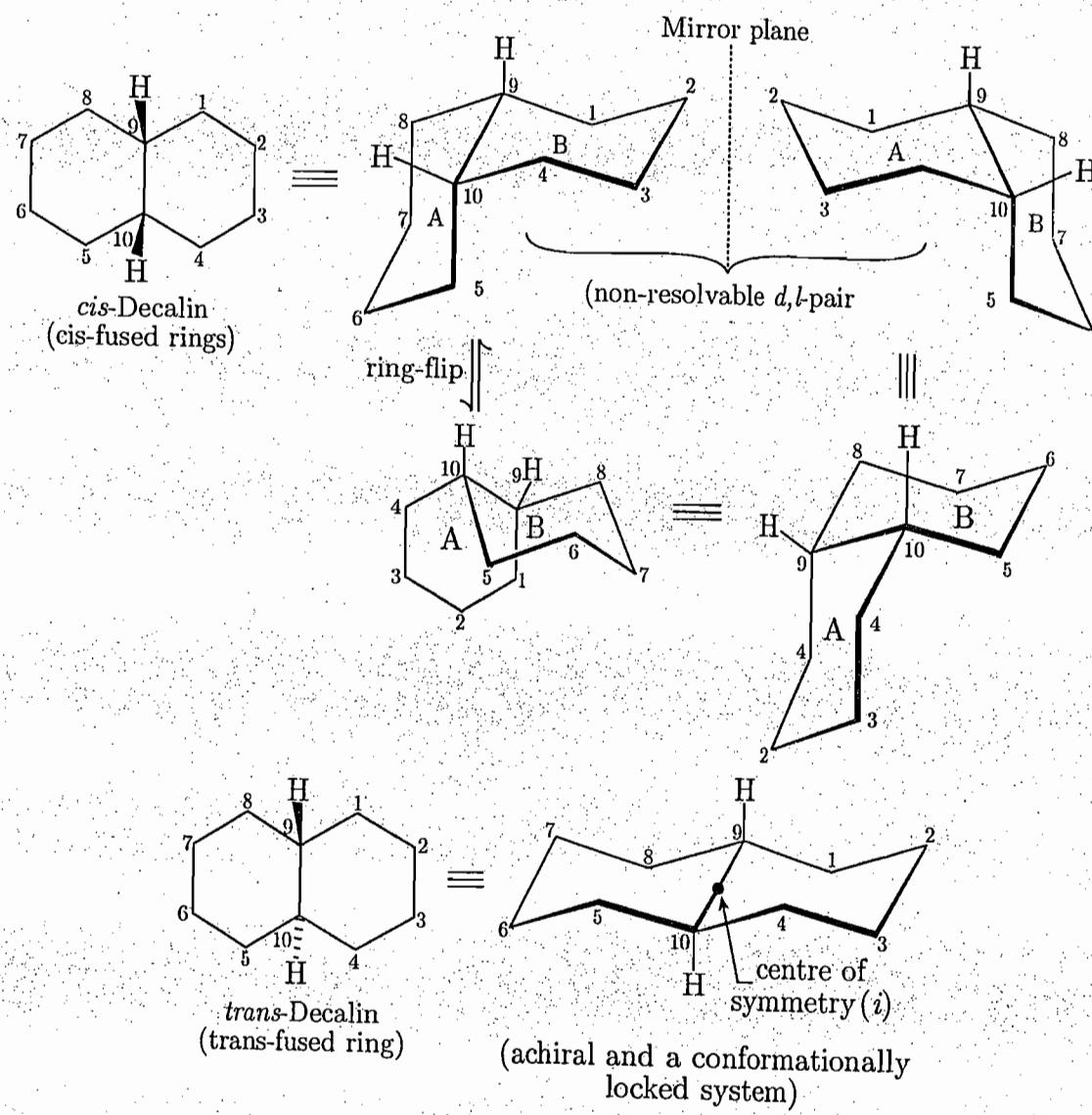
- (b) Introduction of a methyl group at one of the bridgehead carbon atoms decreases the energy difference between *cis*- and *trans*-decalin. Explain.

(c) Unlike decalin, *cis*- and *trans*-diastereoisomers of azadecalin (quinolizidine) cannot be isolated. How do you account for this? Comment on the chirality of the molecule.

(d) Explain the following observation :

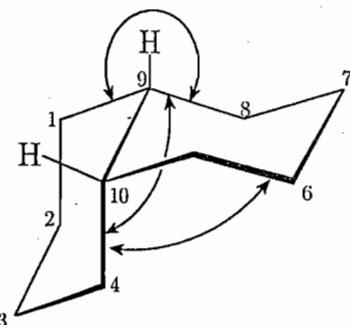


Ans. (a) Chair conformations of the two geometric isomers of decalin (bicyclo[4.4.0]decane) are as follows :



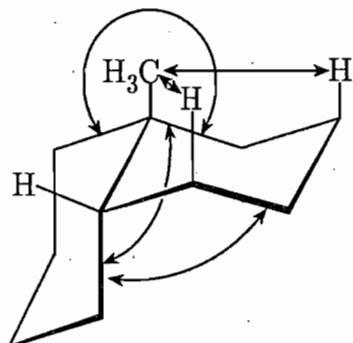
trans-Decalin in which the two rings are fused through e,e bonds has a rigid structure and cannot undergo ring-flip. Flipping leading to a,a ring fusion is impossible because the diaxial bonds point 180° away from each other and thus cannot be bridged by four C atoms to complete the second ring. On the other hand, *cis*-decalin is flexible. The (a,e) conformer can undergo ring inversion to give the (e,a) conformer.

In *trans*-decalin, since each ring is joined through equatorial bonds, no additional *gauche* unit exists (the single *gauch* unit happens to be intra annular and so is not considered). On the other hand, in *cis*-decalin, there exists three additional *gauche* units, namely, C-8—C-9—C-1—C-2, C-8—C-9—C-10—C-4 and C-6—C-5—C-10—C-4, i.e., the *cis*-isomer is destabilised by three butane-*gauche* interactions. The difference of energy (enthalpy) is equal to $3 \times 0.9 = 2.7$ kcal/mol (11.3 kJ/mol). *trans*-Decalin is, therefore, stabler by about 2.7 kcal/mol as compared to *cis*-decalin.

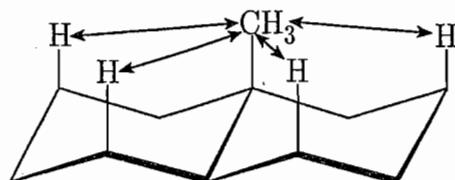


three butane-*gauche* interactions
in *cis*-decalin

(b) Introduction of a methyl group at one of the bridgehead carbon atoms of *cis*- and *trans*-decaline gives rise to two and four additional butane-*gauche* interactions respectively. Before the introduction of the methyl group, the *cis*-isomer had three butane-*gauche* interactions whereas the *trans*-isomer had no such interaction. Therefore, after the introduction of a methyl group, the *cis*-isomer has five butane-*gauche* interactions whereas the *trans*-isomer has four butane-*gauche* interactions. Hence, introduction of a methyl group at one of the bridgehead carbon atoms decreases the energy difference between *trans*- and *cis*-decalins.



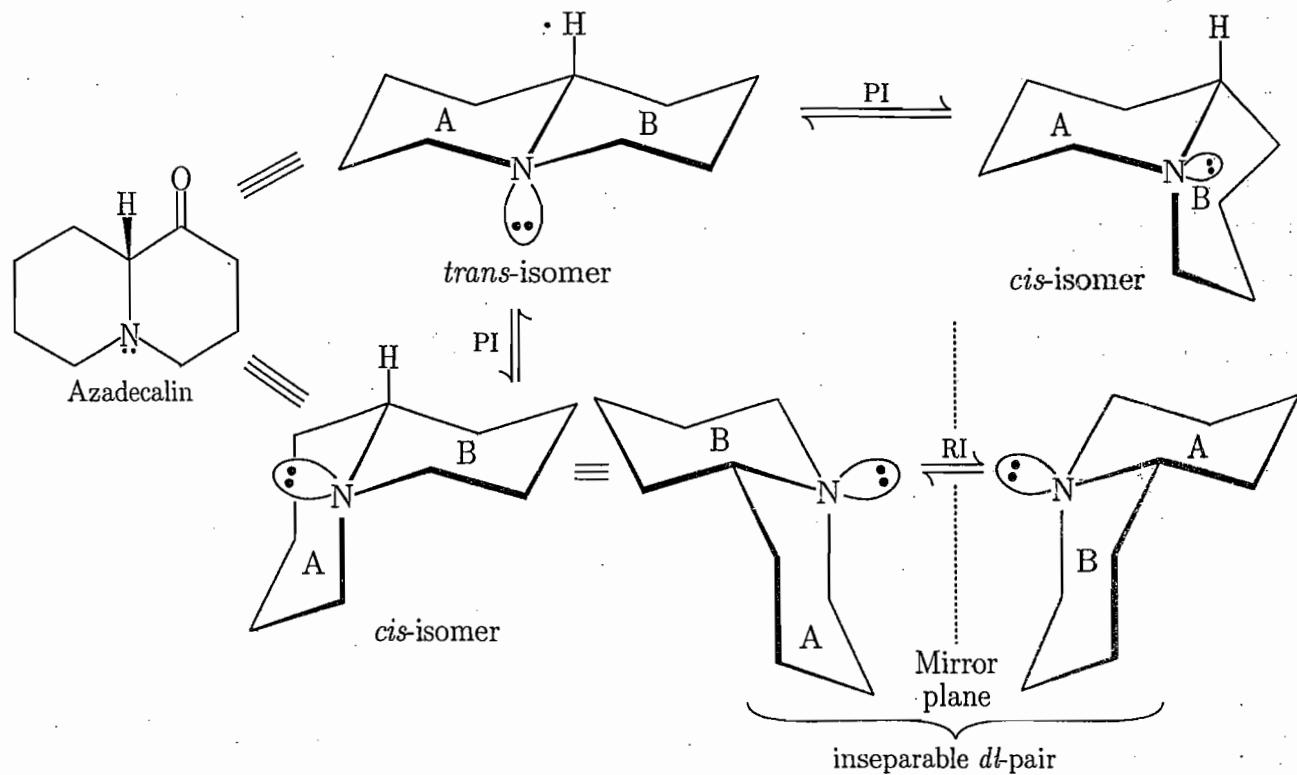
cis-9-Methyldecalin
(five butane-*gauche* interactions)



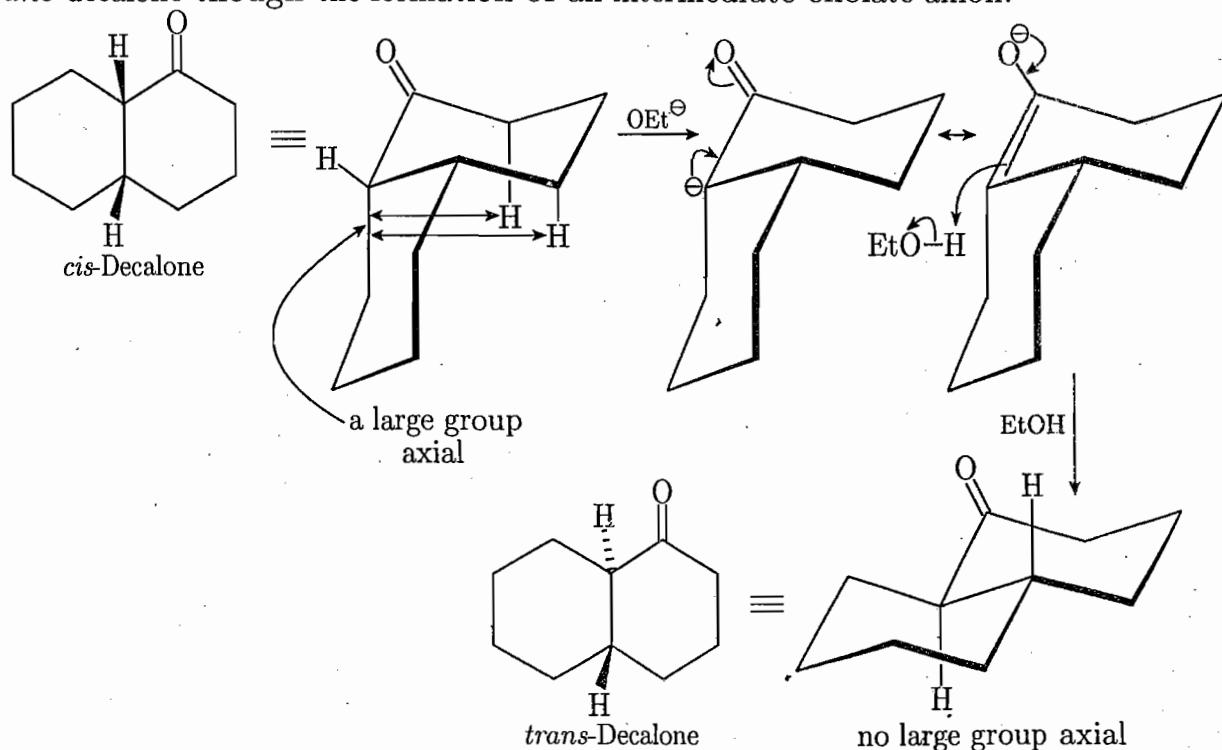
trans-9-Methyldecalin
(four butane-*gauche* interactions)

(c) Azadecalin in which a nitrogen atom occupies a bridge-head position, can undergo easy *cis-trans*-interconversion through pyramidal inversion at nitrogen. Because of this, its *cis*- and *trans*-diastereoisomers can not be isolated.

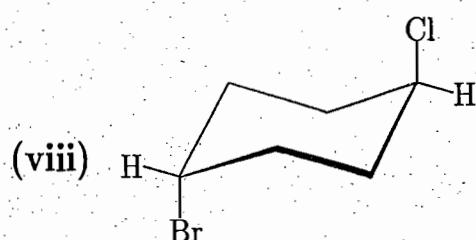
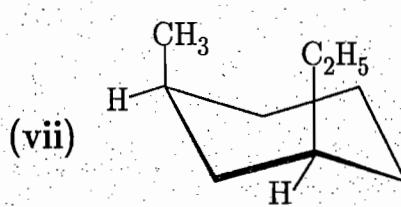
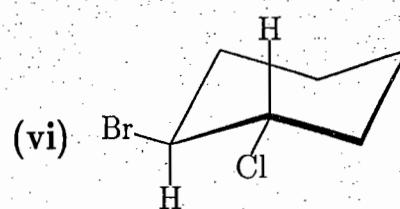
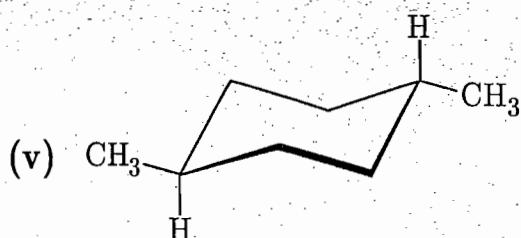
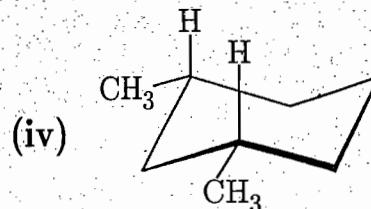
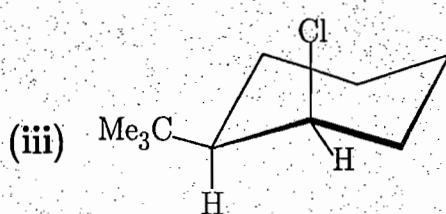
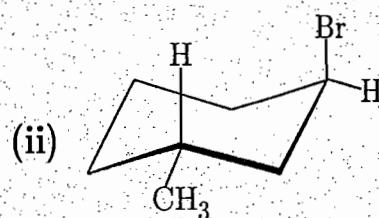
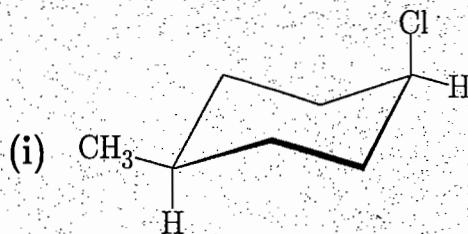
The *trans*-isomer is achiral due to the presence of a vertical plane of symmetry passing through C—N bond of the bridgehead. The *trans*-isomer on inversion at N can give either the *cis*-conformer or its mirror image. The two enantiomers are interconvertible by ring inversion. Therefore, the *cis*-isomer exists as inseparable *dl*-pair. All the three conformers (the *trans*-form and the two enantiomers of the *cis*-form) remain in dynamic equilibrium.



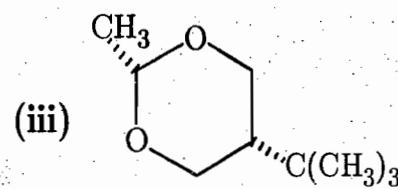
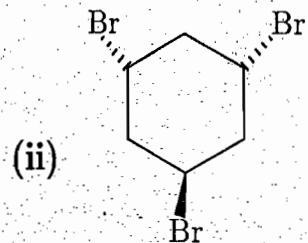
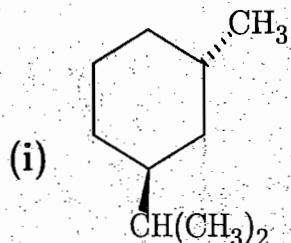
(d) A large group is axial in *cis*-decalone. So it is thermodynamically less stable (because of 1,3-diaxial interaction) than *trans*-decalone in which no large group is axial. For this reason, when treated with base, *cis*-decalone is converted to the more stable *trans*-decalone through the formation of an intermediate enolate anion.



- 3.12 (a) How would you tell whether a disubstituted cyclohexane is the *cis*-isomer or the *trans*-isomer? Illustrate giving suitable examples.
- (b) Determine whether each of the following compounds is a *cis*-isomer or a *trans*-isomer.

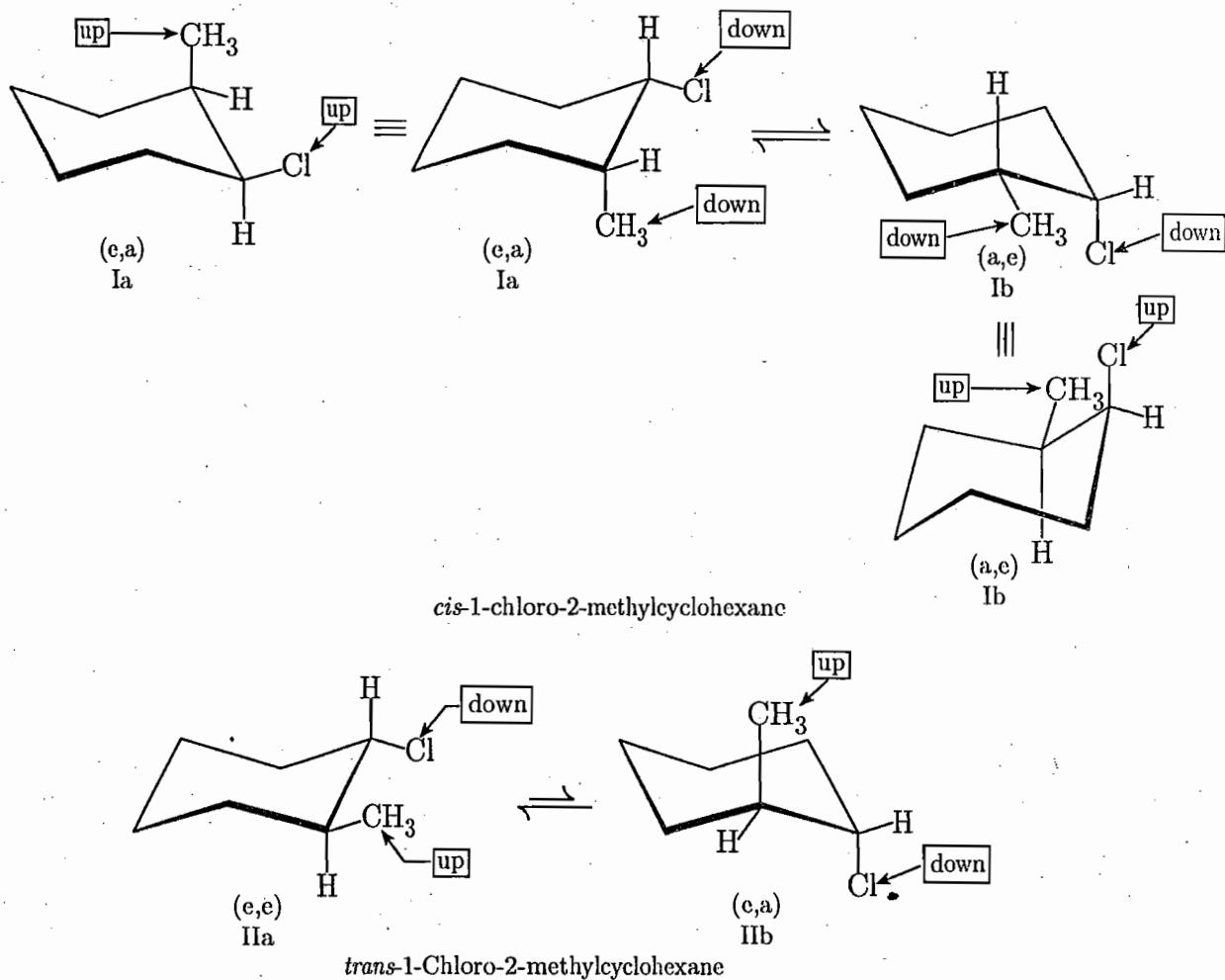


- (c) Which of the two conformations of *trans*-1-ethyl-3-methylcyclohexane is more stable and why?
- (d) How would you draw planar structures for cyclic compounds? Does it convey any conformational information?
- (e) Draw the more stable conformation for each of the following compounds :



- (f) Draw the chair conformations of (*1S,3R*)-3-methyl-1-bromocyclohexane. Predict whether it is a *cis* or a *trans*-isomer.

Ans. (a) The disubstituted cyclohexane in which the bonds bearing the substituents are both pointing upward or both pointing downward is the *cis*-isomer. On the other hand, the disubstituted cyclohexane in which one bond is pointing upward and the other downward is the *trans*-isomer. For example, the conformers Ia and Ib in which the two substituents have a down-down (or an up-up) relationship represent the *cis*-isomer of 1-chloro-2-methylcyclohexane and the conformers IIa and IIb in which the two substituents have an up-down relationship represent the *trans*-isomer of 1-chloro-2-methylcyclohexane.

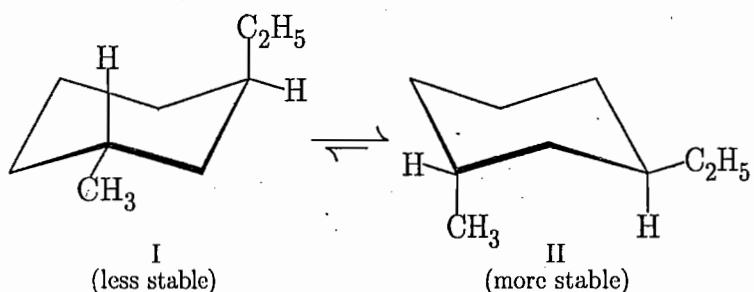


[It is to be noted that the up-up/down-down or up-down relationship is not affected by the conformational equilibrium. Again, the *cis*- or *trans* relationship of the substituents is not altered by the conformational equilibrium. Also, when the substituents in a disubstituted cyclohexane are on asymmetric carbons, the absolute configurations of these carbons do not alter by the conformational equilibrium. The designations *cis* and *trans* specify the relative stereochemical configuration of the two asymmetric carbons, but they say nothing about the absolute configurations of these carbons.]

(b) Two up bonds are *cis*, two down bonds are *cis* and one up and one down bond are *trans*. Therefore, the compound (i) with two up bonds is a *cis*-isomer, the compound (ii) with one up and one down bond is a *trans*-isomer, the compound (iii) with two up bonds is a *cis*-isomer, the compound (iv) with two down bonds is a *cis*-isomer, the compound (v) with one up and one down bond is a *trans*-isomer, the compound

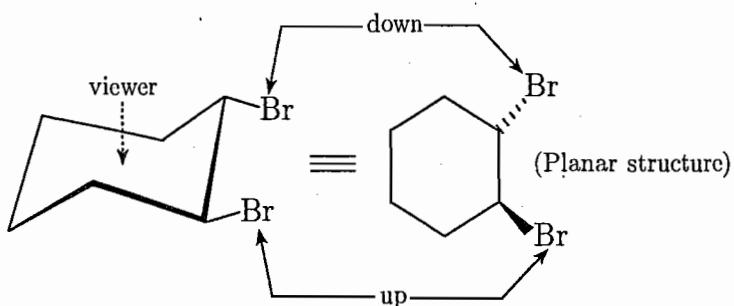
(vi) with one up and one down bond is a *trans*-isomer, the compound (vii) with two up bonds is a *cis*-isomer and the compound (viii) with one up and one down bond is a *trans*-isomer.

(c) Since it is a *trans*-isomer, one of the substituents is on the upward bond and the other on the downward bond. Therefore, the two conformations of *trans*-1-ethyl-3-methylcyclohexane are as follows :

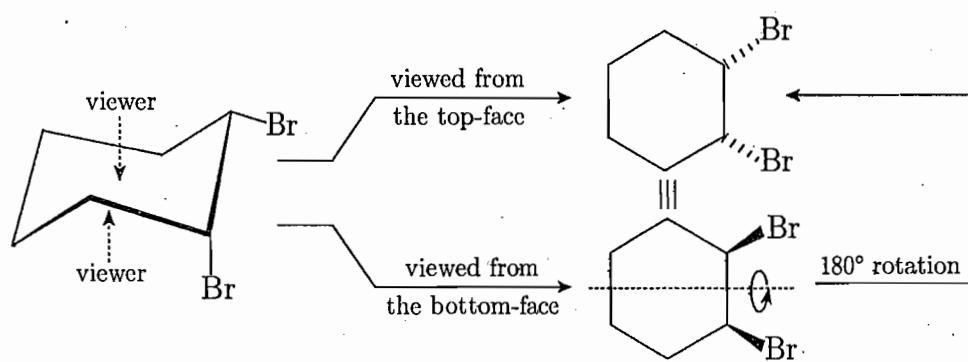


Both of these conformations require one group to be axial and the other is equatorial. The more stable chair conformation is the one in which the larger of the two substituents is in the equatorial position. The ethyl group is bulkier than the methyl group, so the conformation II with the ethyl group equatorial is more stable.

(d) For drawing planar structure, of a cyclic compound, it is to be represented by planar polygons with the stereochemistry of substituents indicated by dashed or solid wedges and the ring is to be viewed from above one face. If a substituent is up, the bond to it is represented by a solid wedge and if it is down, the bond to it is represented as a dashed wedge. In this convention, the planar structure of one enantiomer of *trans*-1,2-dibromocyclohexane can be drawn as follows :

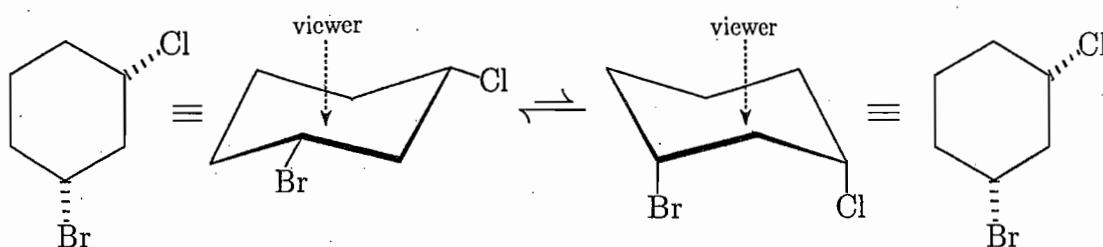


A planar structure for *cis*-1,2-dibromocyclohexane can be drawn in either of two ways (by viewing the ring from each of its two faces) :

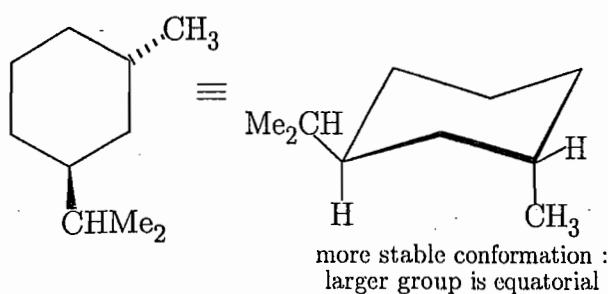


The two planar structures are equivalent.

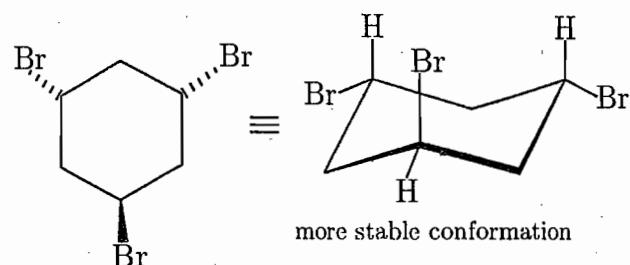
A planar structure does not convey any conformational information. So long as all conformations are viewed from the same face of the ring, flipping does not interchange wedges and dashed lines because it does not change the up or down relationship of the ring substituents. For example, both of the conformers of 1-bromo-3-chlorocyclohexane can be represented by single planar structure.



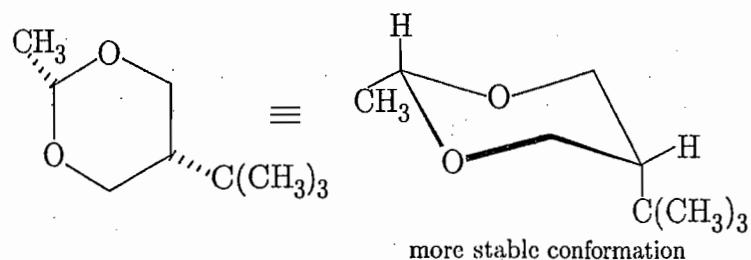
- (e) (i) The stable conformation is that which places the bulkier isopropyl group equatorial.



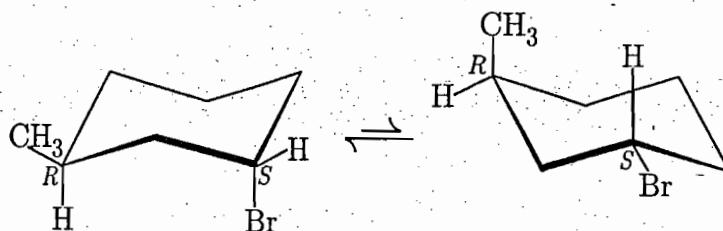
- (ii) The more stable conformation is that which places maximum number of substituents equatorial.



- (iii) The more stable conformation is that which places the bulkier *t*-butyl group axial and that is because it has no 1,3-diaxial interaction.



(f) The two chair conformations of $(1S,3R)$ -3-methyl-1-bromocyclohexane are as follows :



[The absolute configurations of the asymmetric carbons remains unchanged after ring-flip.]

In this disubstituted cyclohexane one bond is pointing upward and the other downward. Therefore, it is the *trans*-isomer.

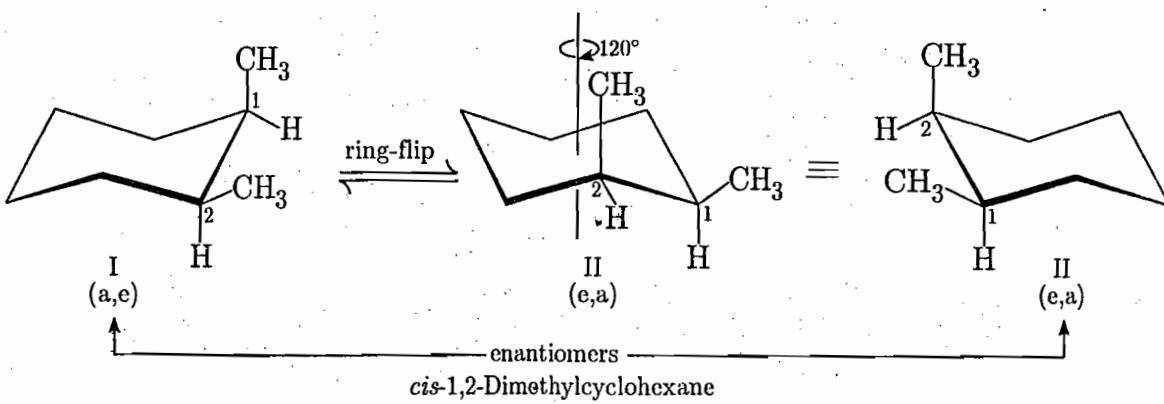
►3.13 (a) Discuss the stereochemistry of each of the following dimethylcyclohexanes :

- (i) *cis*- and *trans*-1,2-dimethylcyclohexane
- (ii) *cis*- and *trans*-1,3-dimethylcyclohexane
- (iii) *cis*- and *trans*-1,4-dimethylcyclohexane

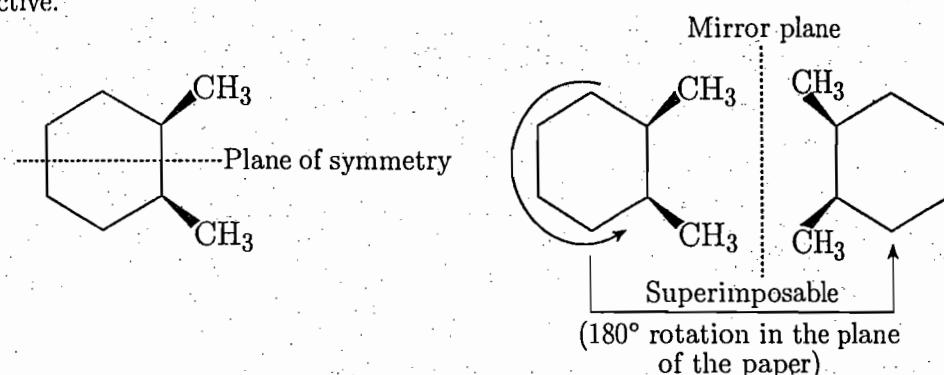
Evaluate the relative stabilities of the equilibrating chair conformations of each diastereoisomer and predict which one of each diastereoisomeric pair is more stable than the other.

(b) Comment on the stereochemistry of disubstituted cyclohexane when the two substituents are different.

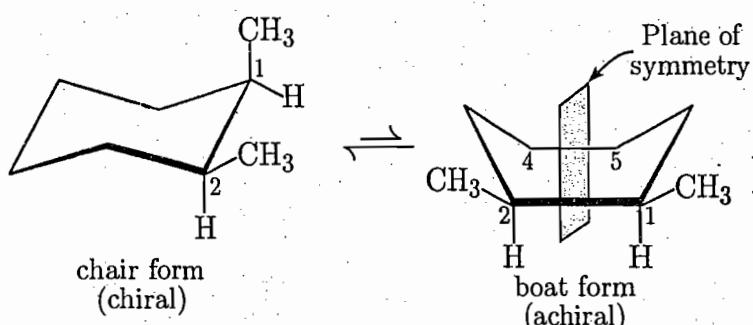
Ans. (a) (i) *cis*-1,2-Dimethylcyclohexane : It exists in two energetically equivalent chair conformations (I and II) each of which places one methyl group axial and one equatorial, i.e., if one is *axial-equatorial* (a,e), the other is *equatorial-axial* (e,a). These conformations are chiral (non-superimposable on their mirror images). However, they are not resolvable (cannot be separated) because one is the nonsuperimposable mirror image (conformational enantiomer) of the other (this can be seen by rotating the conformation II by an angle of 120° around a vertical axis) and are interconverted very rapidly (low potential energy barrier) by ring-flip at ordinary temperatures. Thus, *cis*-1,2-dimethylcyclohexane exists as a nonresolvable *dl*-pair (a racemic mixture). Consequently, it cannot be optically active.



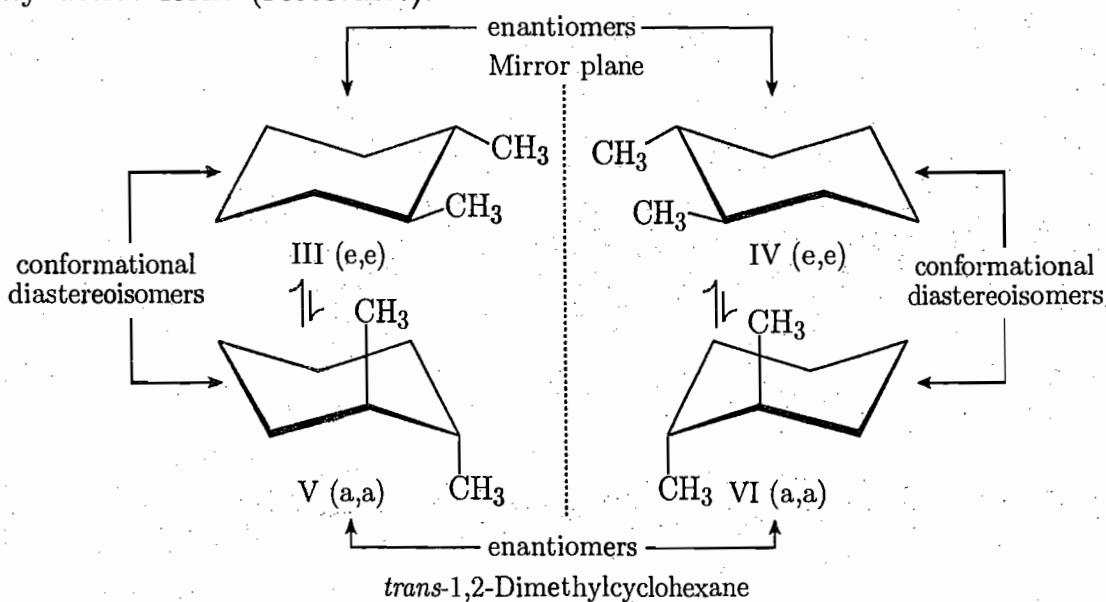
[We can tell whether a compound can be optically active by examining its planar structure. A cyclic compound cannot be optically active if its planar structure has a plane of symmetry or if it is superimposable on its mirror image and on that basis *cis*-1,2-dimethylcyclohexane is expected to be optically inactive.



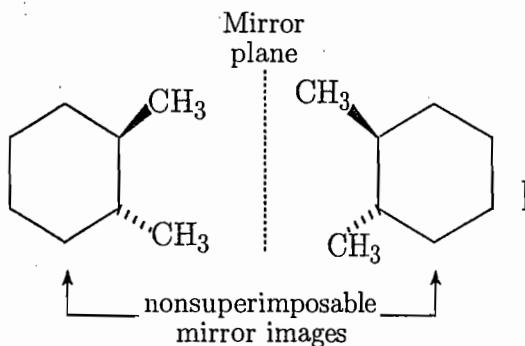
The planar structure shows the *cis*-isomer as a *meso*-compound. Again, by considering the conformations we can say it a *meso*-compound. As long as any conformer of a compound has a plane of symmetry, the compound will be achiral. The much less stable boat conformer of *cis*-1,2-dimethylcyclohexane has a plane of symmetry (bisecting C-1—C-2 and C-4—C-5 bonds). Therefore, *cis*-1,2-dimethylcyclohexane is achiral. This achiral compound with two chirality centres, is a *meso*-compound.



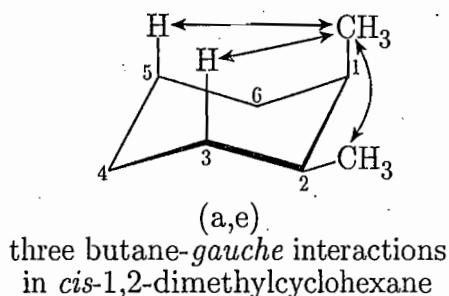
***trans*-1,2-Dimethylcyclohexane :** The compound is chiral, i.e., it has an enantiomer. However, these two enantiomers cannot be interconverted by ring-flip because flipping causes equatorial methyls to become axial methyls. Indeed, the ring-flip converts each enantiomer into a conformational diastereoisomer; the (e,e) conformer becomes the (a,a) conformer and vice versa. Because each enantiomer is capable of independent existence, *trans*-1,2-dimethylcyclohexane can be isolated in optically active form (resolvable).



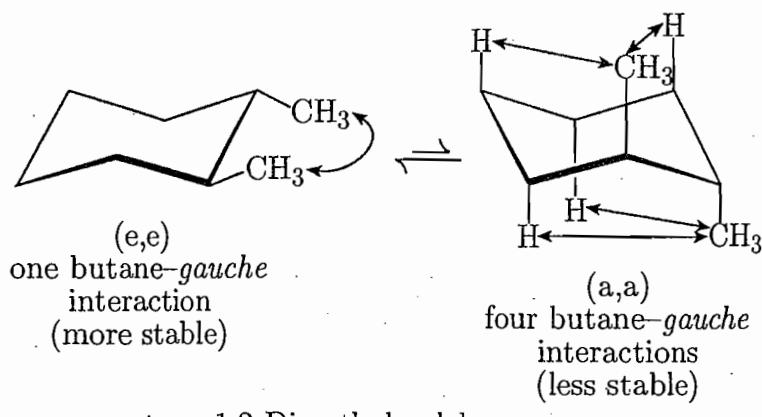
[The planar structure of *trans*-1,2-dimethylcyclohexane also indicate that each enantiomer is capable of independent existance. A cyclic compound can be optically active when a planar structure and its mirror image are nonsuperimposable.



Stability of *cis*-1,2-dimethylcyclohexane : Its two chair conformations (I and II) are equivalent to each other (each containing one axial and one equatorial methyl group) and have the same energy. Each of them has three butane-*gauche* interactions (two originate from two Me/H 1,3-diaxial interactions and one originates from two *gauche* methyl groups) and so, its instability (strain energy) amounts to $3 \times 0.9 = 2.7$ kcal/mol (11.2 kJ/mol).

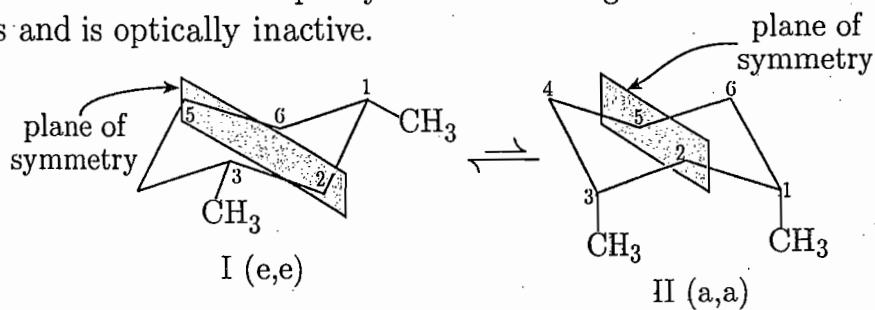


Stability of *trans*-1,2-dimethylcyclohexane : Its diaxial conformer has four butane-*gauche* interactions (originate from four Me/H 1,3-diaxial interactions) and its diequatorial conformer has one butane-*gauche* interaction (originate from two *gauche* methyl groups). The instability of the diaxial conformer amounts to $4 \times 0.9 = 3.6$ kcal/mol (15.12 kJ/mol) and the diequatorial conformer is unstable by an amount of 0.9kcal/mol (4.2 kJ/mol). Therefore, the diequatorial conformer is more stable than the diaxial conformer by an amount of $3.6 - 0.9 = 2.7$ kcal/mol and because of this, the *trans*-isomer exists almost entirely (99%) in the diequatorial (e,e) form at room temperature.



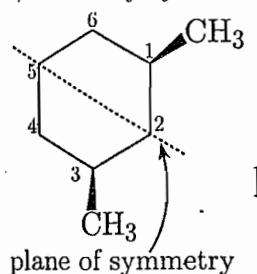
trans-1,2-Dimethylcyclohexane is more stable than *cis*-1,2-dimethylcyclohexane because both methyl groups are equatorial in the more stable conformation of the *trans*-isomer while one methyl group must be axial in the *cis*-isomer (it is a general rule that any substituent is more stable in an equatorial orientation than in an axial one).

(ii) *cis*-1,3-Dimethylcyclohexane : The compound exists in two distinct chair conformations : diaxial (a,a) and diequatorial (e,e). These conformational diastereoisomers are interconvertible by ring flipping. Although each conformation has two asymmetric carbon atoms, neither conformation is chiral because each has a plane of symmetry passing through C-2 and C-5. i.e., both conformations are *meso*. *cis*-1,3-Dimethylcyclohexane is thus a rapidly interconverting mixture of two different *meso* conformations and is optically inactive.

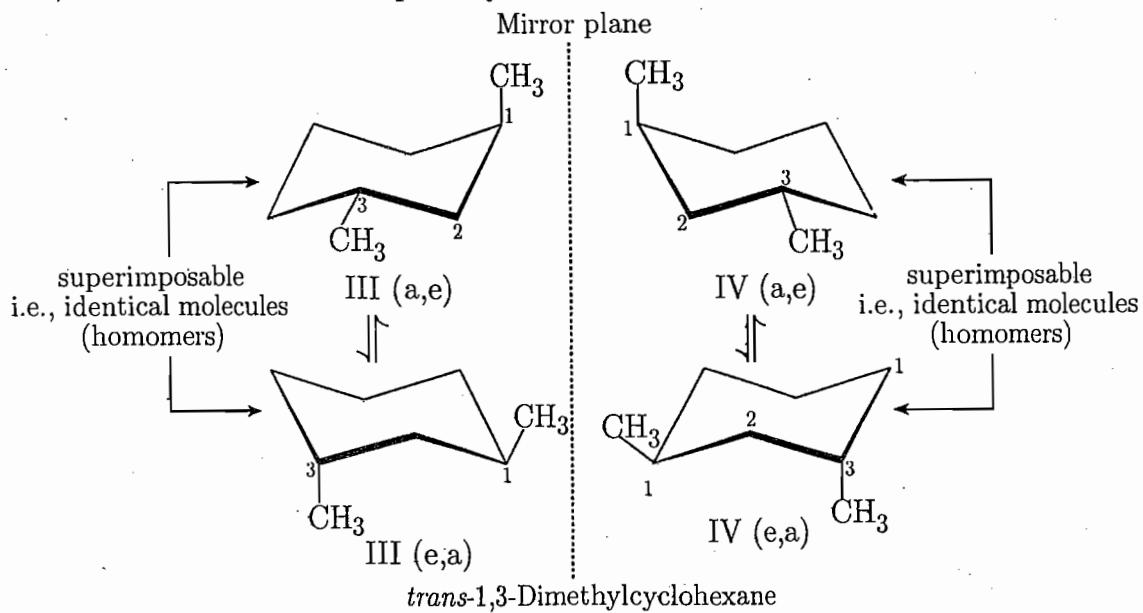


cis-1,3-Dimethylcyclohexane (a *meso*-compound)

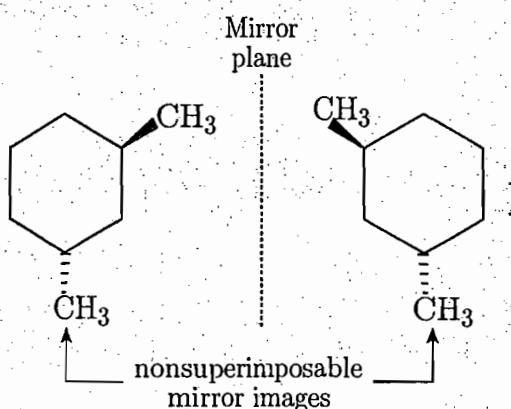
[The planar representation of *cis*-1,3-dimethylcyclohexane also has an internal plane of symmetry.



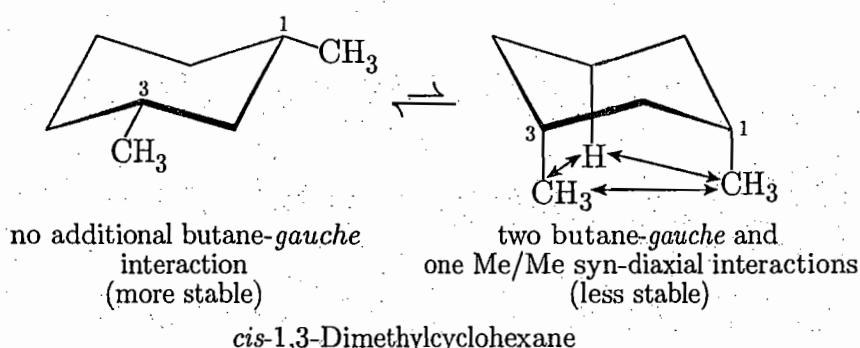
trans-1,3-Dimethylcyclohexane : In this compound one methyl group is always equatorial and the other is axial. This is a chiral molecule (no plane of symmetry) and unilike the case of the *cis*-1,2 compound, flipping the ring converts the molecule, not to its enantiomer, but to a species which is superimposable with the original molecule i.e., they are homomers (topomers). Thus, in this case, the (+) and (-) forms are capable of discrete existence. Therefore, *trans*-1,3-dimethylcyclohexane can exist as a resolvable *dl*-pair, i.e., it can be isolated in optically active form.



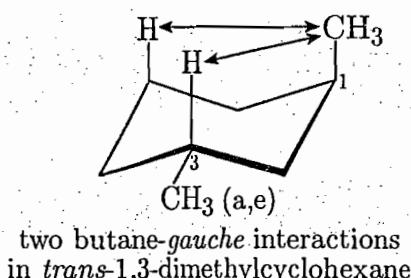
[The planar structures of *trans*-1,3-dimethylcyclohexane also indicate that each enantiomer is capable of independent existence (due to nonsuperimposability on the mirror image).]



Stability of *cis*-1,3-dimethylcyclohexane : Its diaxial conformer has two butane-*gauche* interactions and one *syn*-diazial interaction between the two axial methyl groups. One Me/Me 1,3-diaxial interaction imparts 3.6 kcal/mol. Thus, the instability of this conformer amounts to $(2 \times 0.9 + 3.6) = 5.4$ kcal/mol (22.7 kJ/mol). The diequatorial conformer, on the other hand, has no additional interaction arising out of equatorial methyls. Therefore, it is much more stable than the diaxial form and consequently, the compound exists nearly exclusively in the diequatorial form.

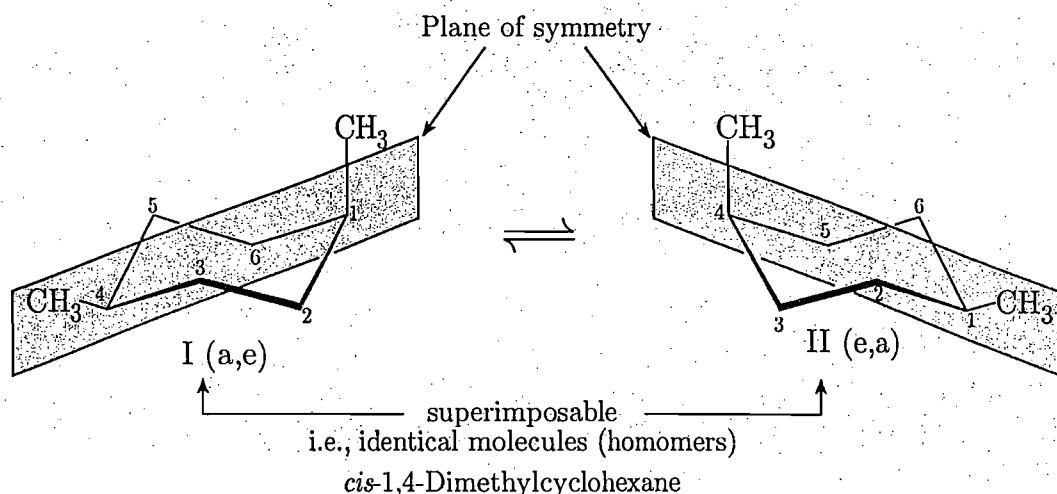


Stability of *trans*-1,3-dimethylcyclohexane : It has two butane-*gauche* interactions due to one axial methyl groups. Its instability amounts to $2 \times 0.9 = 1.8$ kcal/mol (7.56 kJ/mol).

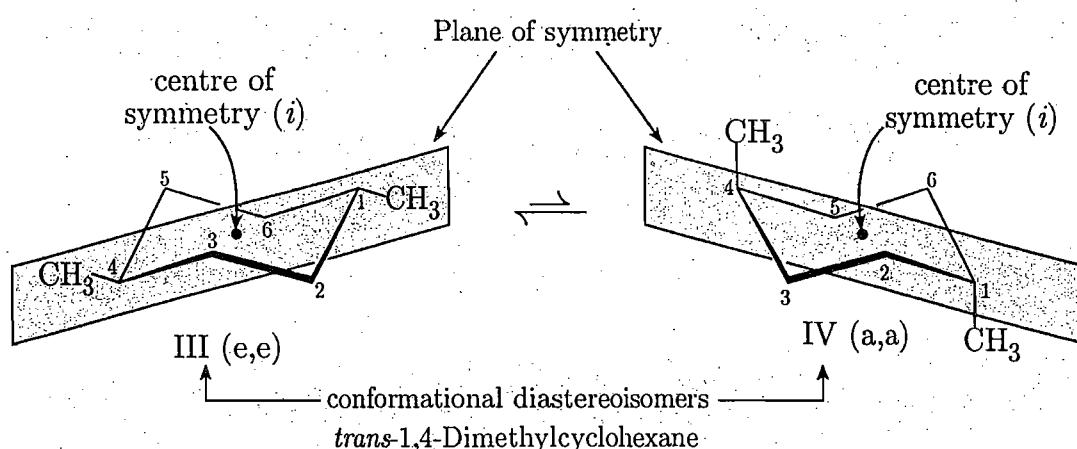


cis-1,3-Dimethylcyclohexane is more stable than *trans*-1,3-dimethylcyclohexane because both methyl groups are equatorial in the more stable conformation of the *cis*-isomer while one methyl group must be axial in the *trans*-isomer.

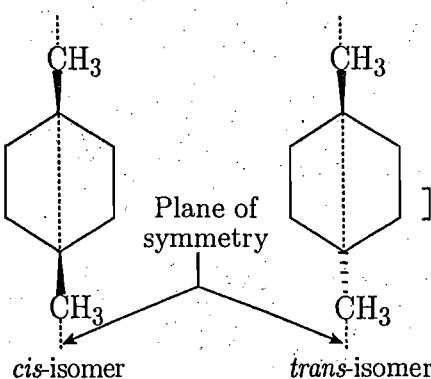
(iii) *cis*-1,4-Dimethylcyclohexane : It exists as two equivalent (one is superimposable on the other) chair conformations, namely, *axial-equatorial* (a,e) and *equatorial-axial* (e,a). Each of them has a vertical plane of symmetry passing through C-1 and C-4. Therefore, the compound is achiral and optically inactive.



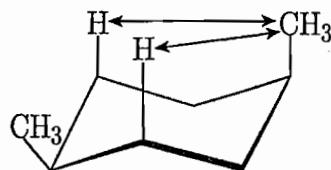
trans-1,4-Dimethylcyclohexane : It exists as two non-equivalent chair conformations : (e,e) and (a,a). Both of them have a vertical plane of symmetry passing through C-1 and C-4 and a centre of symmetry. Therefore, the compound is achiral and optically inactive.



[That both *cis*- and *trans*-1,4-dimethylcyclohexane have a plane of symmetry is also true in planar structures.

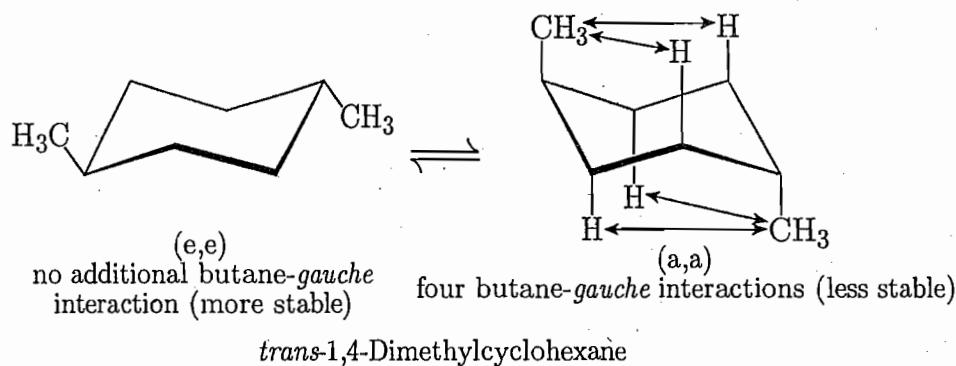


Stability of *cis*-1,4-dimethylcyclohexane : It has two butane-*gauche* interactions due to one axial methyl group. Its interaction energy amount to $2 \times 0.9 = 1.8$ kcal/mol (7.56 kJ/mol).



two butane-*gauche* interactions
in *cis*-1,4-dimethylcyclohexane

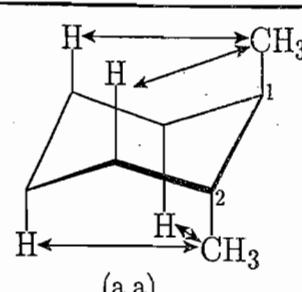
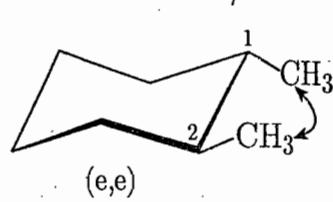
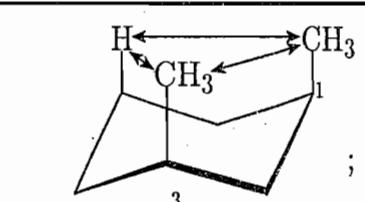
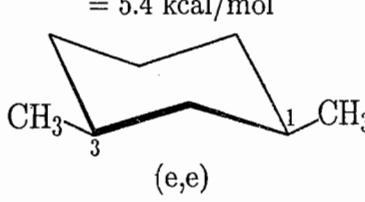
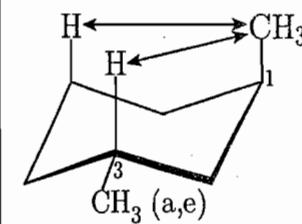
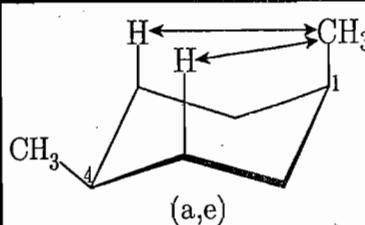
Stability of *trans*-1,4-dimethylcyclohexane : Its diaxial conformer has four butane-*gauche* interactions. Thus, its instability amounts to $4 \times 0.9 = 3.6$ kcal/mol (15.1 kJ/mol). The diequatorial form, on the other hand, has no additional butane-*gauche* interaction. Therefore, it is much more stable than the diaxial form and as a consequence, the compound exists almost exclusively in the diequatorial form.



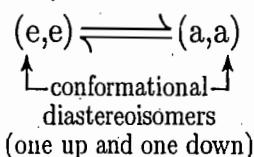
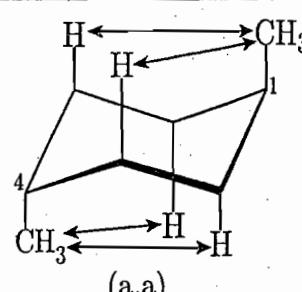
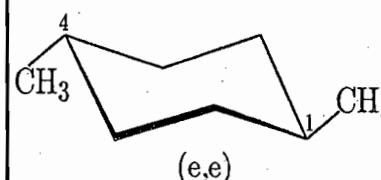
trans-1,4-Dimethylcyclohexane is more stable than *cis*-1,4-dimethylcyclohexane because both methyl groups are equatorial in the more stable conformation of the *trans*-isomer while one methyl group must be axial in the *cis*-isomer.

- The chirality and strain energy of different dimethylcyclohexanes can be quickly reviewed from the table below :

Dimethylcyclohexane	Conformations (orientation of bond)	Optical activity	Strain energy
<i>cis</i> -1,2-	(e,a) (a,e) ↑ conformational enantiomers (one up and one down)	Optically inactive (non-resolvable <i>dl</i> -pair)	 $3 \times 0.9 = 2.7$ kcal/mol

Dimethyl-cyclohexane	Conformations (orientation of bond)	Optical activity	Strain energy
<i>trans</i> -1,2-	$(e,e) \rightleftharpoons (a,a)$ one enantiomer (both up or both down)	resolvable (can be isolated in optically active form)	 (a,a) $4 \times 0.9 = 3.6 \text{ kcal/mol}$  (e,e) 0.9 kcal/mol
<i>cis</i> -1,3-	$(e,a) \rightleftharpoons (a,e)$ conformational diastereoisomers (both up or both down)	optically inactive (a <i>meso</i> -compound having a σ -plane)	 (a,a) $2 \times 0.9 + 3.6 \text{ (for Me/Me)} = 5.4 \text{ kcal/mol}$  (e,e) no additional butan-gauche interaction
<i>trans</i> -1,3-	$(e,a) \rightleftharpoons (a,e)$ one enantiomer (one up and one down)	resolvable (can be isolated in optically active form)	 $2 \times 0.9 = 1.8 \text{ kcal/mol}$
<i>cis</i> -1,4-	$(e,a) \rightleftharpoons (a,e)$ one enantiomer (one up and one down)	optically inactive (σ -plane)	 (a,e) $2 \times 0.9 = 1.8 \text{ kcal/mol}$

contd. next page

Dimethylcyclohexane	Conformations (orientation of bond)	Optical activity	Strain energy
<i>trans</i> -1,4-	(e,e) 	optically inactive (σ-plane and centre of symmetry)	 $4 \times 0.9 = 3.6 \text{ kcal/mol}$  no additional butane-gauche interaction

(b) When the two substituents in a 1,2-disubstituted cyclohexane are different (e.g., 1-ethyl-2-methylcyclohexane), both *cis* as well as *trans* isomers are resolvable. The *trans*-isomer exists in the preferred diequatorial (e,e) conformation while the *cis*-isomer in equatorial-axial (e,a) conformation with the bulkier group predominantly equatorial.

When the two substituents in a 1,3-disubstituted cyclohexane are different (e.g., 1-ethyl-3-isopropylcyclohexane), both the *cis* and *trans* isomers are resolvable. The *cis*-isomer exists in the preferred diequatorial (e,e) conformation while the *trans*-isomer in equatorial-axial (e,a) conformation with the bulkier group predominantly equatorial.

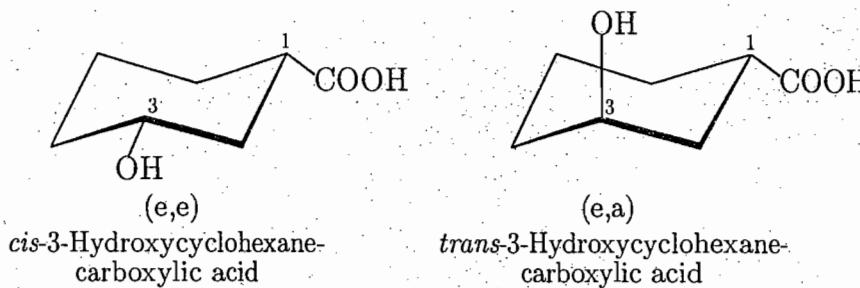
When both the substituents in a 1,4-disubstituted cyclohexane are different (e.g., 1-isopropyl-4-methylcyclohexane), both the *cis* and *trans* isomers are achiral due to presence of a σ plane passing through C-1 and C-4. The *trans*-isomer exists in a preferred diequatorial (e,e) conformation while the *cis*-isomer exists in equatorial-axial (e,a) conformation with the bulkier substituent predominantly equatorial.

- 3.14 (a) *cis*-3-Hydroxycyclohexanecarboxylic acid readily forms lactone on heating whereas the *trans*-isomer does not. Explain.
- (b) *cis*-4-Hydroxycyclohexanecarboxylic acid lactonises on heating but the *trans*-isomer does not. Explain.
- (c) Which one of *cis*- and *trans*-4-*t*-butylcyclohexanecarboxylic acid will act as a stronger acid in water and why?
- (d) Which of the following pair will undergo oxidation with chromic acid at a faster rate and why?

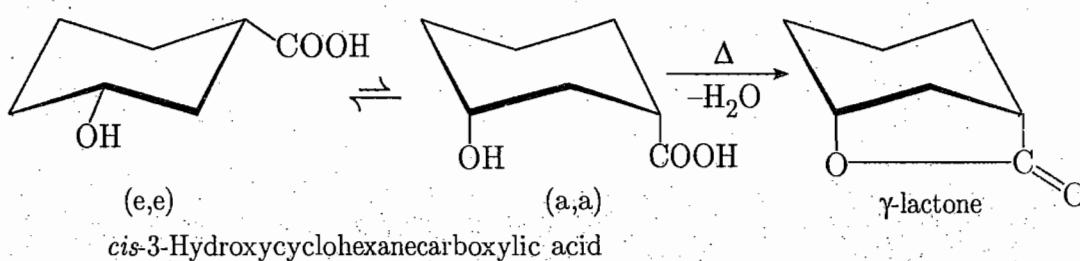
trans-4-*t*-Butylcyclohexanol and *cis*-4-*t*-butylcyclohexanol

- (e) Esters of *trans*-4-*t*-butylcyclohexanecarboxylic acid undergoes saponification at a much faster rate ($K_{trans}/K_{cis} = 20$) than the *cis*-isomer. Explain. Would you expect a similar difference in reaction rate when the cyclohexyl substituent is in the alcohol part?
 - (f) Of the various isomeric 1,2,3,4,5,6-hexachlorocyclohexanes, one isomer undergoes dehydrochlorination by base much more slowly than the others. Which isomer is probably the least reactive one, and why?
 - (g) In which conformation all-*trans*-1,2,3,4,5,6-hexaisopropylcyclohexane prefers to exist and why?

Ans. (a) The more stable conformation of *cis*-3-hydroxycyclohexanecarboxylic acid is that in which the two substituents are equatorial and the more stable conformation of *trans*-3-hydroxycyclohexane carboxylic acid is that in which the bulkier —COOH group is equatorial and the —OH group is axial.

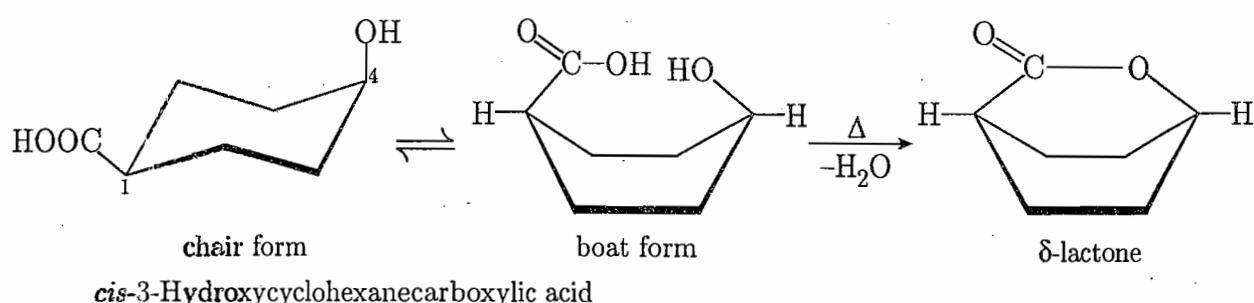


The *cis*-isomer undergoes ready lactonisation on heating through ring inversion process. In the flipped conformation, both the —COOH and —OH groups assume *syn-diaxial* positions and come closer to each other (within reacting distance) to give a lactone. Although the inverted conformation is sterically unfavourable (due to 1,3-diaxial interactions), the reaction is favourable from the standpoint of entropy.

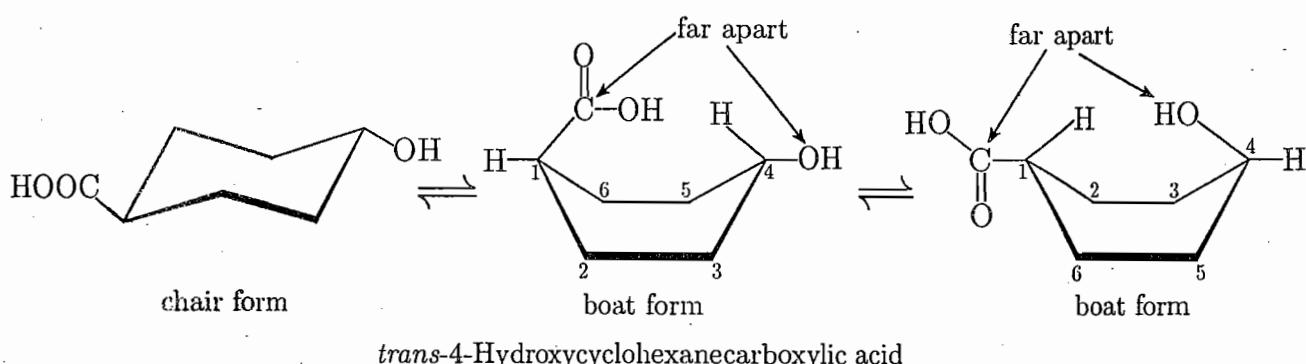


The *trans*-isomer, on the other hand, cannot form lactone on heating because —COOH and —OH groups are far apart (beyond reacting distance), even after ring-flip.

- (b) *cis*-4-Hydroxycyclohexanecarboxylic acid lactonises readily on heating because in its boat conformation the —COOH and —OH groups assume flagpole positions and come within reacting distance.

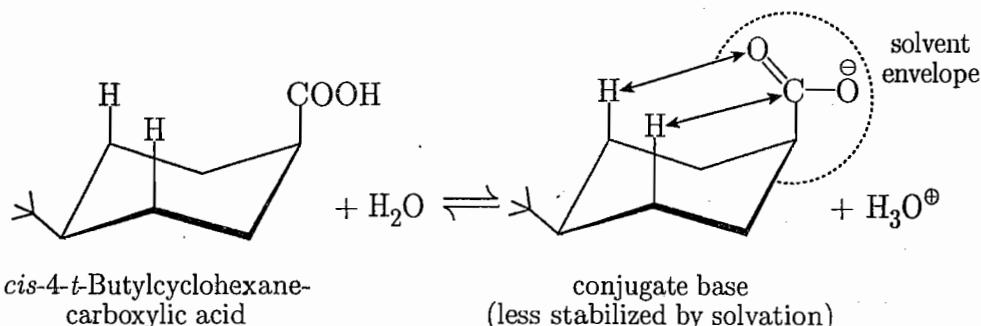


On the other hand, in the boat conformation of the *trans*-isomer only one of the —COOH and —OH groups can assume flagpole position and as a consequence, they do not come within reacting distance. Because of this, the compound does not undergo lactonisation on heating.

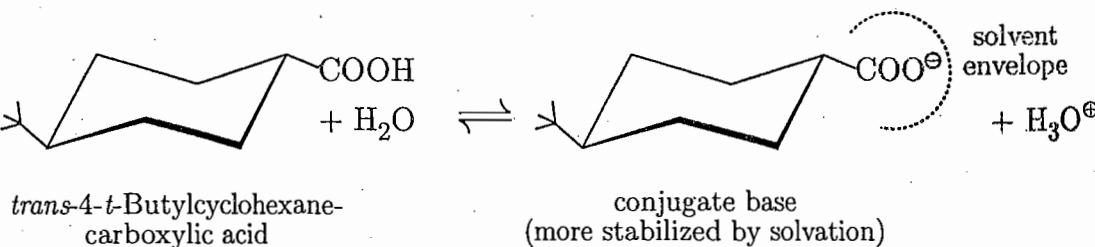


(c) *trans*-4-*t*-Butylcyclohexanecarboxylic acid is more acidic than its *cis*-isomer.

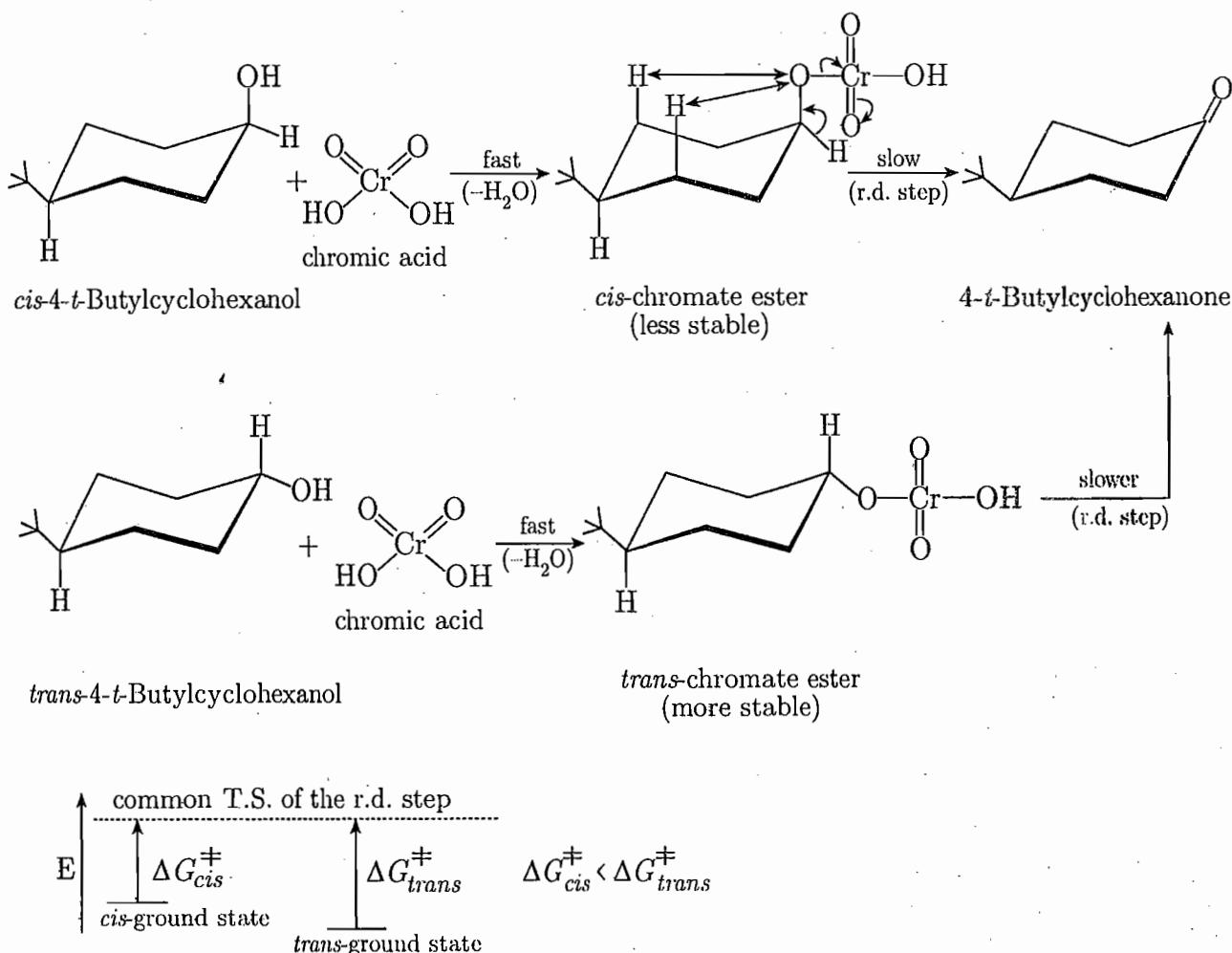
In the more stable conformation of the *cis*-acid, the —COOH group is axial whereas in the more stable conformation of the *trans*-acid the —COOH group is equatorial. In the conjugate base of the *cis*-acid, the axial —COO[⊖] group remains in a sterically crowded environment (1,3-diaxial interaction). So, this carboxylate ion is not well stabilised by solvation involving polar protic water molecules.



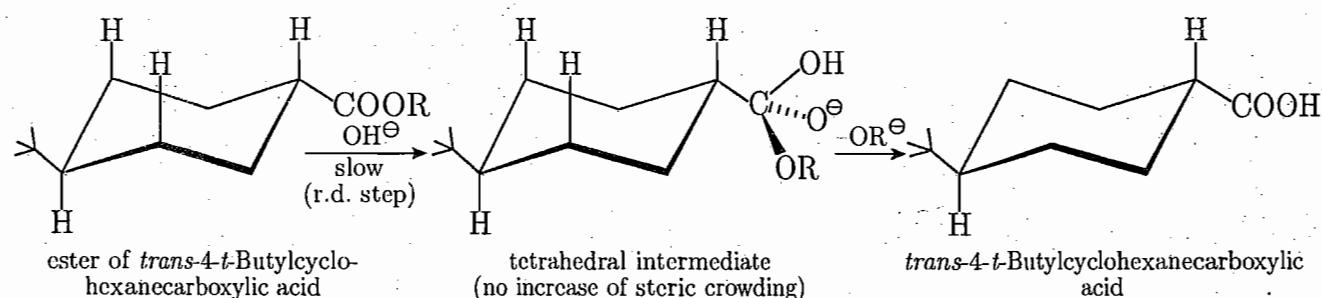
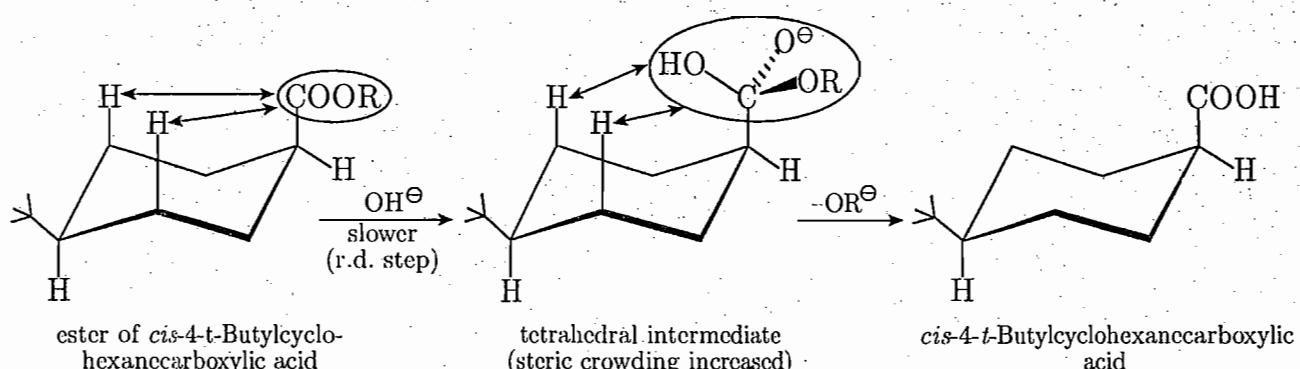
On the other hand, the *trans*-acid with equatorial —COO[⊖] group is well stabilized by solvation because the group is not in sterically crowded environment. Therefore, because of greater stability of the conjugate base, the *trans*-acid is stronger than the *cis*-acid.



(d) The *cis*-isomer of 4-*t*-butylcyclohexanol undergoes oxidation by chromic acid at a faster rate (approximately four times) than the *trans*-isomer and this is said to be a result of *steric acceleration*. In this case, the anancomeric (conformationally biased) cyclohexanols give the common oxidation product 4-*t*-butylcyclohexanone. In the rate-determining step, the initially formed chromate ester undergoes loss of H_2CrO_3 (a β -elimination reaction). The *cis*-ester suffers from 1,3-diaxial interaction and so, there is considerable relief of steric strain in the transition state in going from the chromate ester to ketone. Again, since the transition states involved in the conversion of chromate esters to the common oxidation product have more product (ketone)-like structure, they may be assumed to have similar energies. Now, because of steric reason, the ground state energy of the *cis*-ester is higher than that of the *trans*-ester. Therefore, the difference in energy between the ground state and the common transition state, i.e., the activation energy for the *cis*-ester ($\Delta G_{cis}^{\ddagger}$) is less than that for the *trans*-ester ($\Delta G_{trans}^{\ddagger}$) and for these reasons, the *cis*-alcohol undergoes oxidation at a faster rate than the *trans*-alcohol.

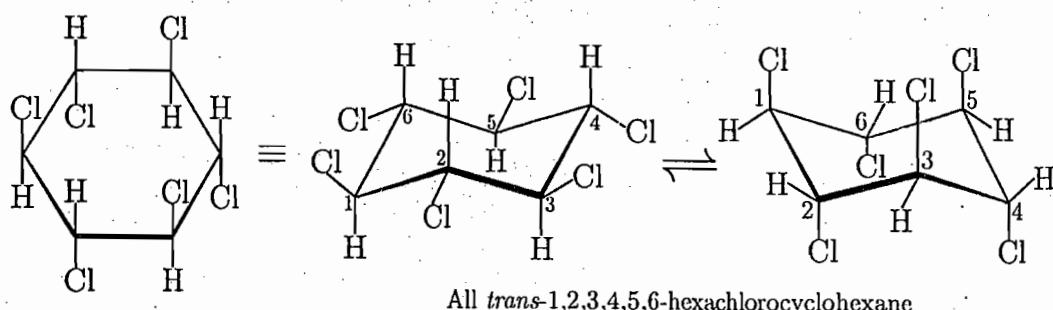


(e) Saponification (alkaline hydrolysis) of esters of cyclohexanecarboxylic acid proceeds through the formation of an intermediate (in the rate-determining step) in which carboxyl carbon atom becomes tetrahedral and therefore, the —COOR group is converted to the more bulkier —C(OH)(OR)O^- group. As a consequence, the steric crowding (1,3-diaxial interaction) is further increased in the case of *cis*-ester with the —COOR group axial but not in the case of *trans*-ester with the —COOR group equatorial. Therefore, the transition state leading to the formation of *cis*-intermediate is relatively more destabilised. Also, the *cis*-intermediate is less stabilised by solvation because the axial —C(OH)(OR)O^- group is in relatively more crowded environment. For these reasons, esters of *trans*-4-*t*-butylcyclohexane carboxylic acid undergoes saponification at a much faster rate than the *cis*-isomer.

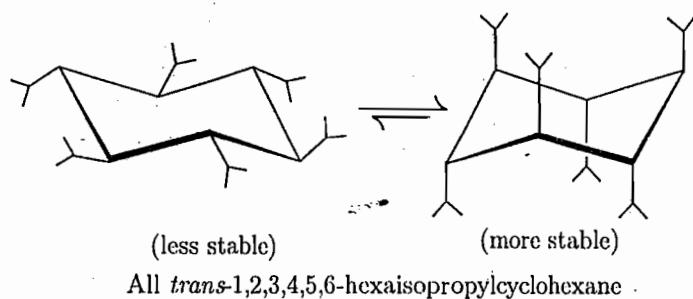


The effect on rate is less pronounced when the cyclohexyl substituent is in the alcohol part of the ester and the reason is that the site of crowding (carbonyl carbon of —COOR group) is not much closer to the ring. In fact, the ester carbonyl is one bond further removed from the cyclohexane ring and steric hindrance has less effect on the reactivity, i.e., on reaction rate.

(f) The low rate of elimination indicates that in both of the conformations of that particular isomer *anti*-periplanar (diaxial) relationship between each Cl atom and a β -H atom does not exist i.e., the least reactive isomer is that in which there exists *syn*-relationship between each Cl and a β -H atom in both conformations (in one conformation all Cl atoms are equatorial and all hydrogens are axial and in other conformation all Cl atom are axial and all hydrogens are equatorial).



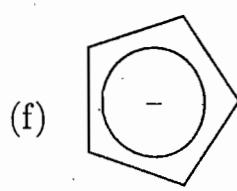
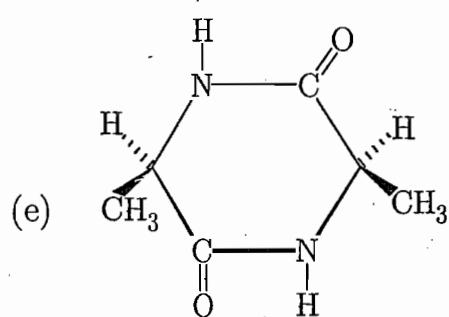
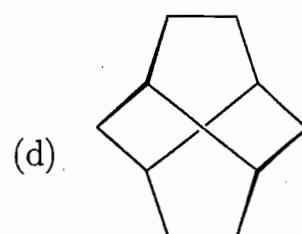
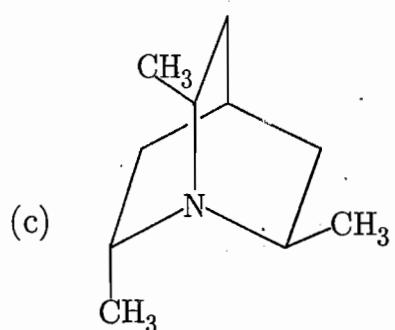
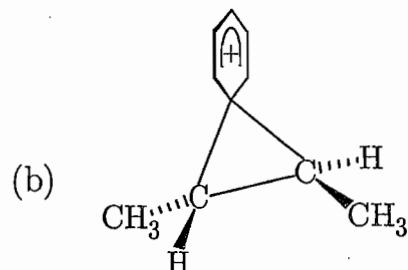
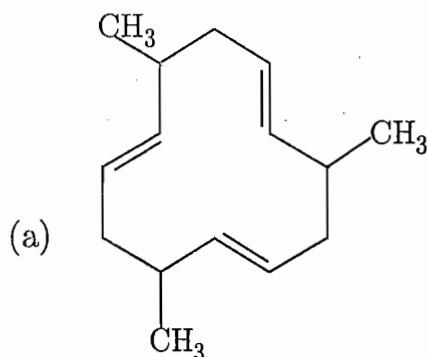
(g) All-*trans*-1,2,3,4,5,6-hexaisopropylcyclohexane prefers to exist in the conformation in which all isopropyl groups are axial and that is because 1,2-steric interactions when two isopropyl groups are equatorial outweigh the usual well known 1,3-diaxial (*syn*-axial) interactions.

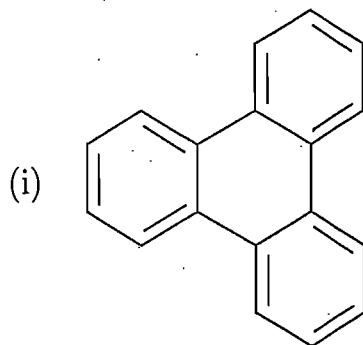
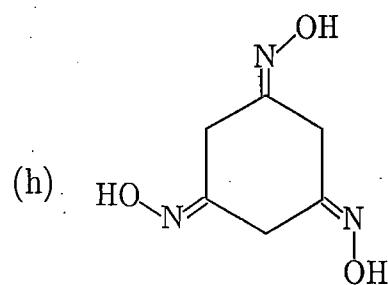
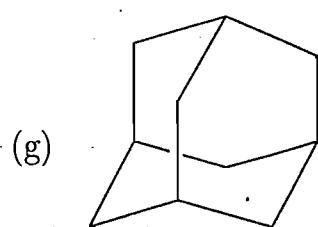


SUPPLEMENTARY PROBLEMS

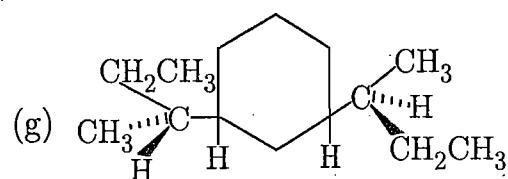
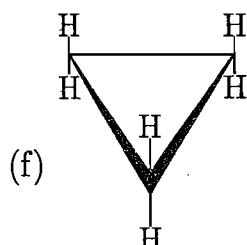
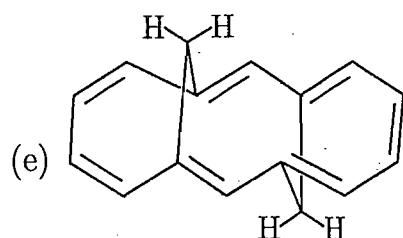
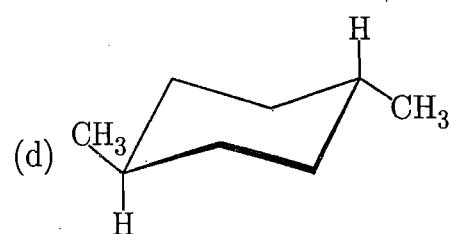
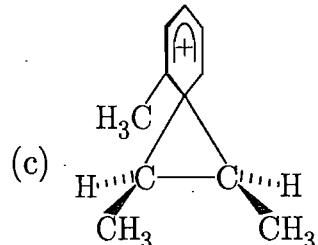
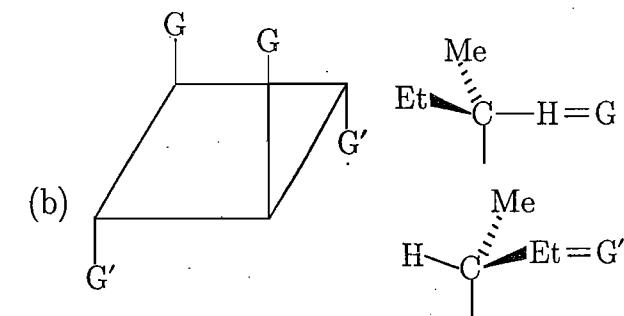
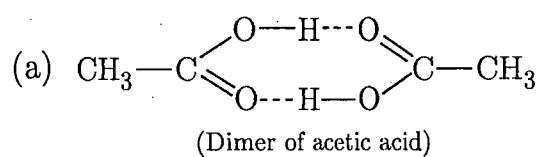
- How do structural (constitutional) isomers differ from stereoisomers? What is meant by configuration?
- What is the essential condition for a compound to be chiral? The presence of a stereocentre is not always essential for a compound to exhibit chirality. Explain.
- Give an example of each of the following compounds :
 - an optically inactive compound containing chiral carbons,
 - an optically active compound containing no chiral carbon.
- What is a chiral molecule? Write the structural formulas for the simplest chiral
 - alkene, (b) alkyne, (c) alcohol, (d) aldehyde, (e) ketone, (g) carboxylic acid and (h) amine with no isotopic atom.
- Distinguish between the following terms :
 - Configuration and conformation (b) Absolute configuration and relative configuration (c) Observed rotation and specific rotation (d) Enantiomers and diastereoisomers (e) *meso*-compounds and racemic mixture.

6. (a) The specific rotation of a pure enantiomer is $+16^\circ$. What will be its observed rotation if it is isolated from a reaction with (i) 80% racemization and 20% inversion (ii) 20% racemization and 80% retention.
- (b) The observed rotation of 2.0 g of a compound in 10 ml of solution in a 25 cm long polarimeter tube is $+134^\circ$. What is the specific rotation of the compound?
- (c) (+)-Phenylglycolic acid has a specific rotation of $+158^\circ$. What would be the observed specific rotation of each of the following mixtures?
- (i) 75% (+)-phenylglycolic acid and 25% (-)-phenylglycolic acid
 - (ii) 50% (+)-phenylglycolic acid and 50% (-)-phenylglycolic acid
 - (iii) 25% (+)-phenylglycolic acid and 75% (-)-phenylglycolic acid
- (d) A solution prepared by mixing 10 ml of a 0.10M solution of (*R*)-tartaric acid and 30 ml of a 0.10M solution of (*S*)-tartaric acid was found to have an observed specific rotation of $+6^\circ$. What is the specific rotation of each of the enantiomers?
7. Indicate the simple axis of symmetry (C_n) present in each of the following molecules/ions :





8. What are the symmetry elements (S_n) present in each of the following molecules/ions?

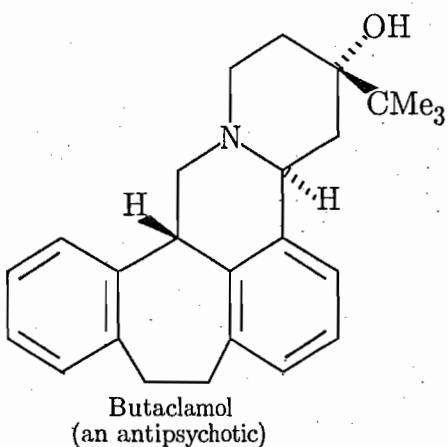
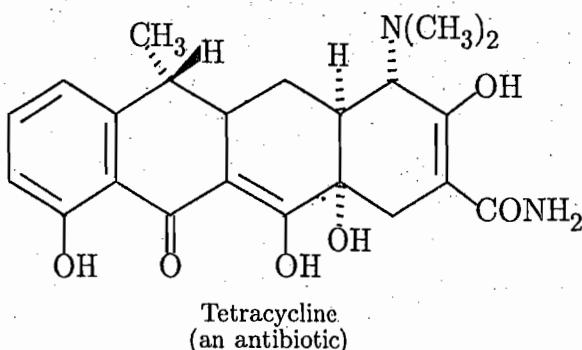


9. (a) Which of the twenty-six letters of English alphabet are symmetric and which of them are non-symmetric? Mention the symmetry elements present in each of the symmetric letters.

(b) Which of the following objects are chiral?

- (i) a nut (ii) a plate (iii) a seven-pointed star (iv) a mug with DAD written opposite the handel (v) a mug with MOM written opposite the handel (vi) a car.

10. How many chirality centres does each of the following compounds have?



11. Which of the following compounds have a stereoisomer that is achiral?

- (a) 2,3-dibromobutane (b) 2,3-dibromopentane (c) 1,3-dichlorocyclobutane
- (d) 1,4-dimethylcyclohexane (e) 3-bromo-2-butanol (f) 1,3-dibromocyclopentane
- (g) 1,2-dibromocyclopropane (h) 1-bromo-4-chlorocyclohexane.

12. Find out the simple axis of symmetry present in each of the following molecules/ions :

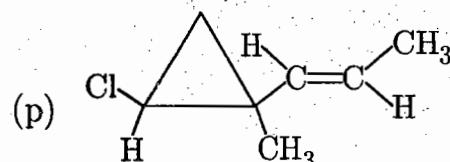
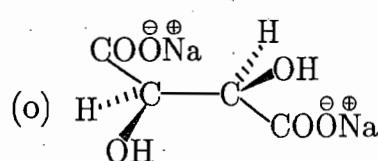
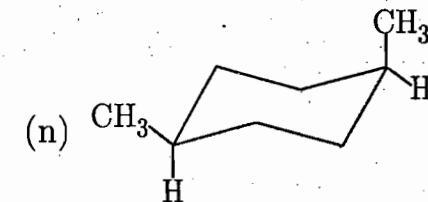
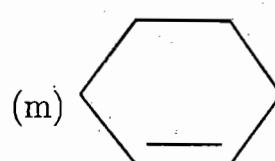
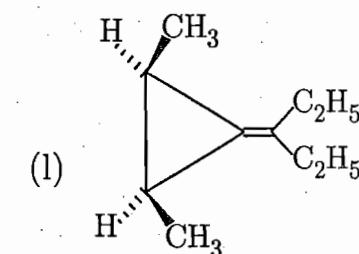
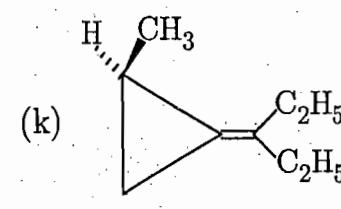
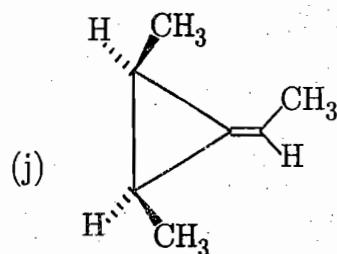
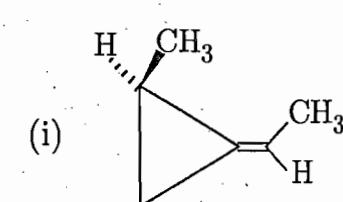
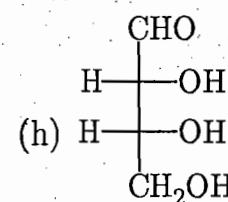
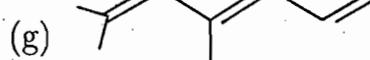
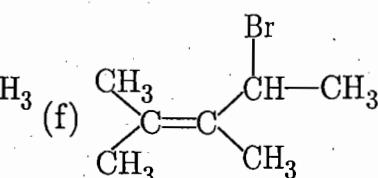
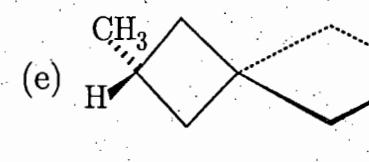
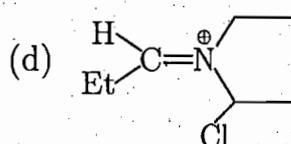
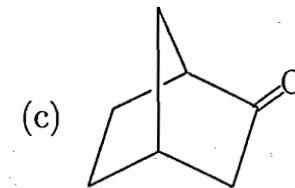
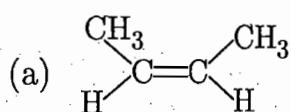
- (a) 1,3,5-tribromobenzene (b) NO_3^- (c) cycloheptatrienyl cation (d) CCl_4
- (e) CO_3^{2-} (f) *meso*-1,2-dibromo-1,2-diphenylethane (the most stable conformer).

13. (a) "All asymmetric molecules are dissymmetric but not all dissymmetric molecules are asymmetric." Establish this statement giving suitable example.

(b) Show that :

- (i) There are three C_2 , two S_1 and one S_3 axis in allene molecule.
- (ii) There are one C_3 , three C_2 , three S_1 and one S_3 axis in the eclipsed conformation of ethane.
- (iii) The most populated conformer of active 2,3-dichlorobutane is dissymmetric but not asymmetric.
- (iv) *trans*-1,2-Dimethylcyclopropane is dissymmetric but not asymmetric.

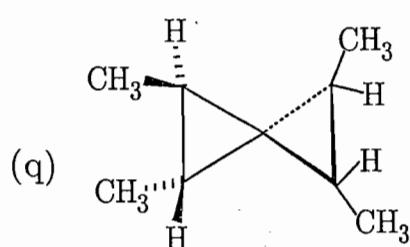
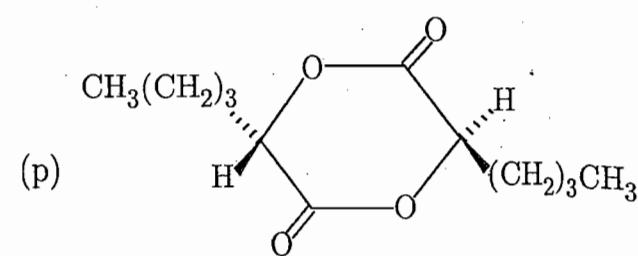
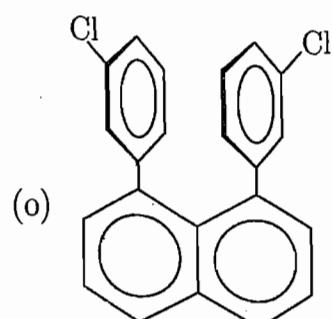
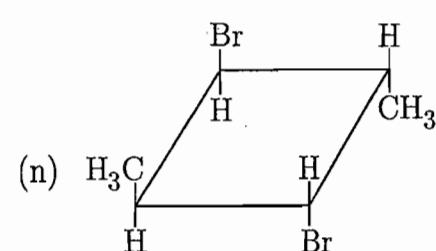
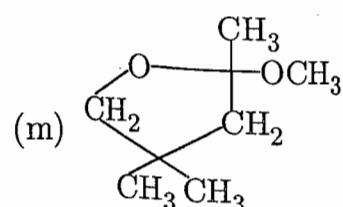
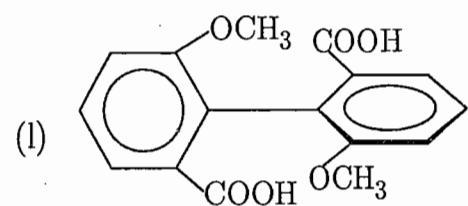
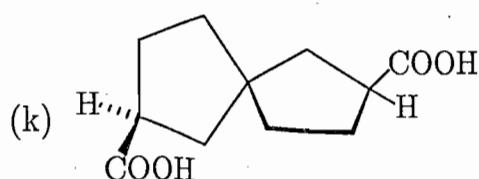
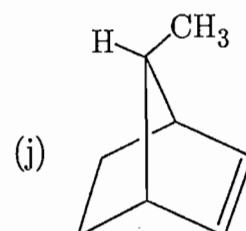
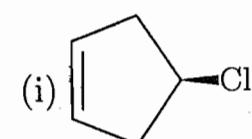
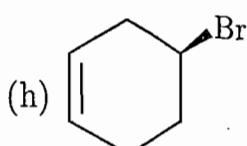
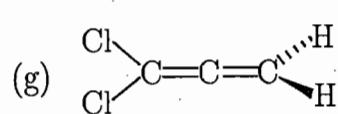
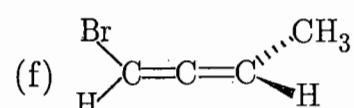
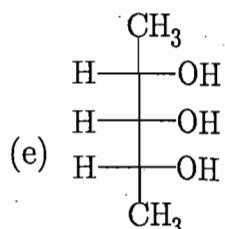
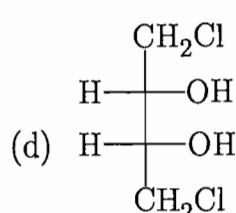
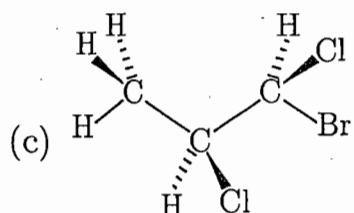
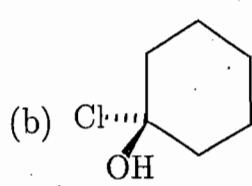
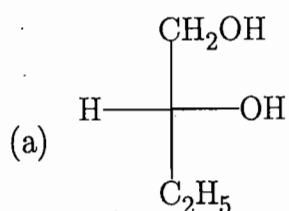
14. Star (*) the stereo centre(s) in each of the following compounds. Which of them are chirality centres?

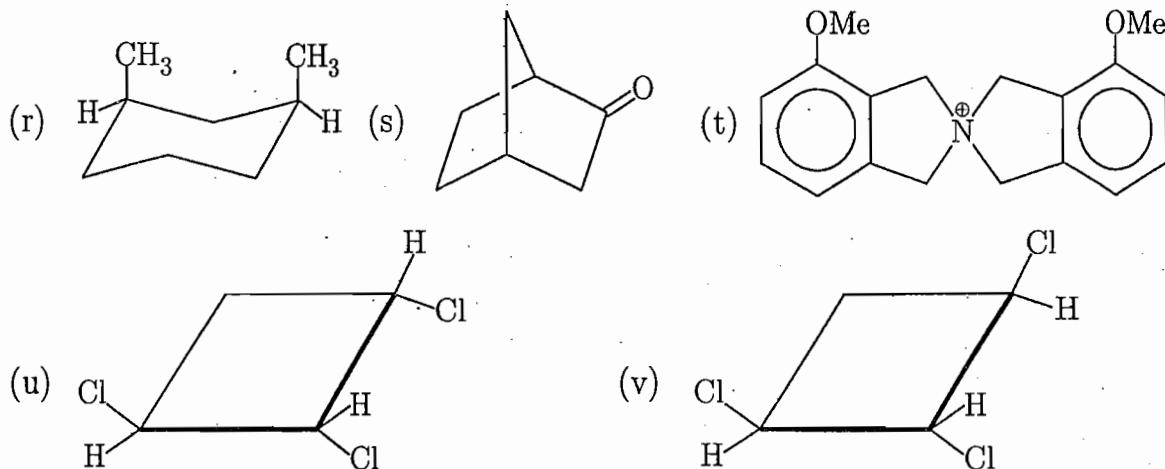


15. (a) Give the stereochemistry of the product isolated from heating 2-hydroxyhexanoic acid and comment on their optical activity.

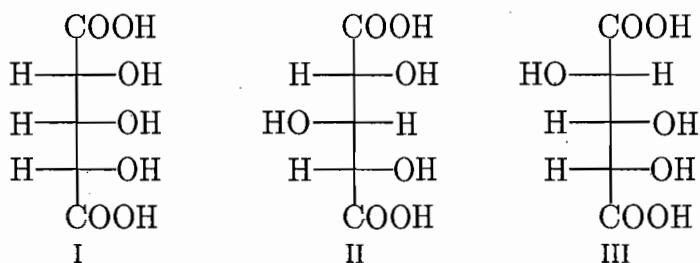
(b) Give the stereochemistry of the ozonolysis product of bicyclo[2.2.1]hept-2-ene and comment on its optical activity.

16. For each of the following structures (i) star (*) any asymmetric C-atom. (ii) Indicate the presence of plane of symmetry, centre of symmetry or alternating axis of symmetry. (iii) Label the structure as chiral or achiral. (iv) Label any meso-compound.

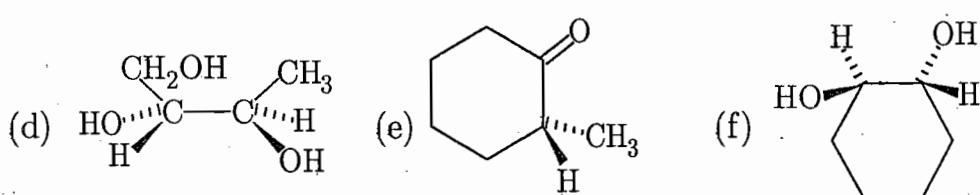
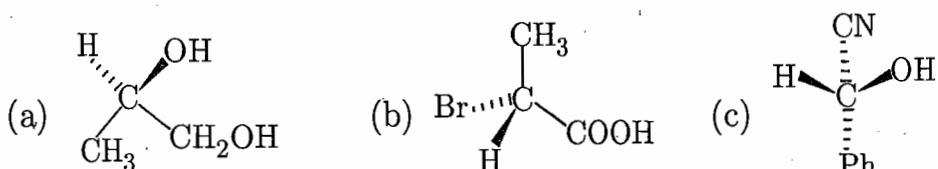


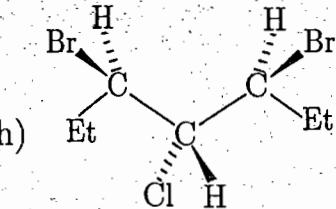
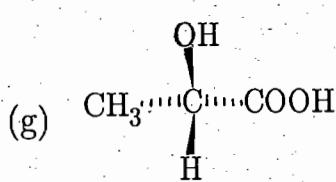


17. (a) Draw all the stereoisomers of 2,3,4-trichloropentane.
 (b) Star (*) the asymmetric carbon atoms, and label each as (*R*) or (*S*).
 (c) In the *meso* compounds, show how C-3 is not asymmetric, nor is it a chirality centre, yet it is stereogenic.
 (d) In the enantiomers, show how C-3 is not stereogenic.
18. Give examples of the following :
 (a) A chirotopic but non-stereogenic centre.
 (b) A chirotopic as well as stereogenic centre.
 (c) A stereogenic but achirotopic centre.
19. Comment on the chirotopicity and stereogenicity of the C-3 centre of the following compounds :

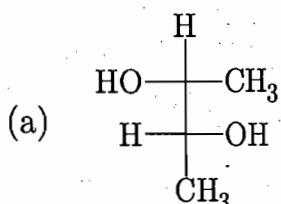


20. Convert the following flying wedge projections into Fischer projections.

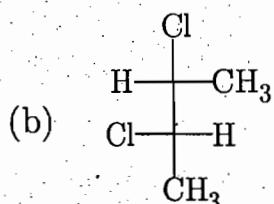




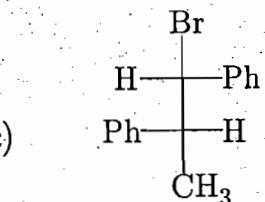
21. Convert the following Fischer projections into sawhorse and Newman projection as indicated below :



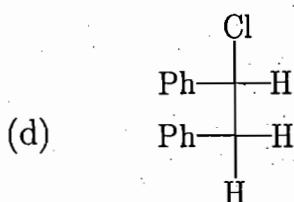
(projection having
a plane of symmetry)



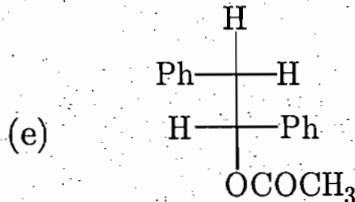
(projection having
a centre of symmetry)



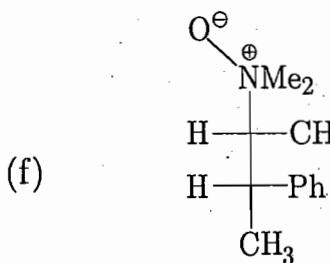
(from which base-
induced dehydrobromination
will take place readily)



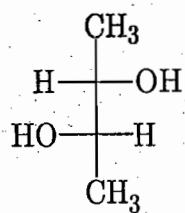
(from which base-induced
dehydrochlorination will
take place at a faster rate)



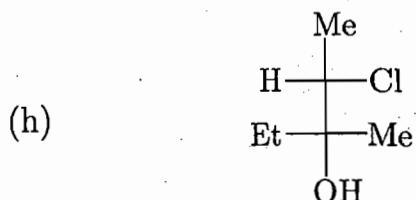
(from which pyrolytic elimination
of CH3COOH will take place
at a faster rate)



(from which pyrolytic elimination
of Me2NOH will take place
readily)

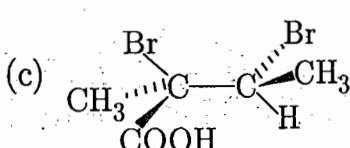
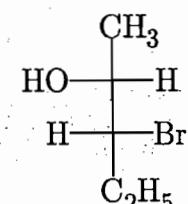
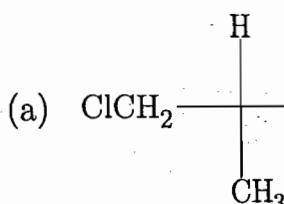


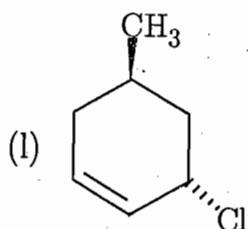
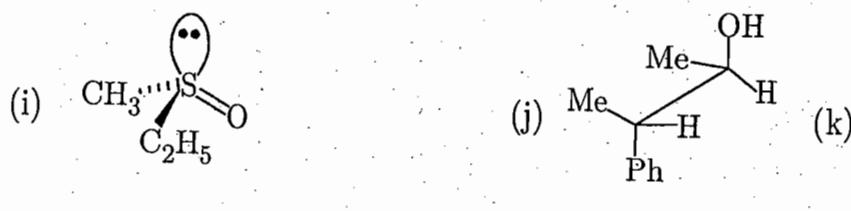
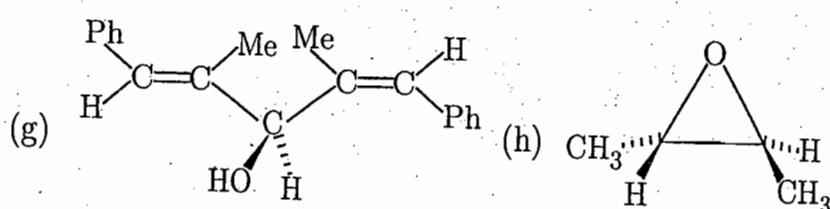
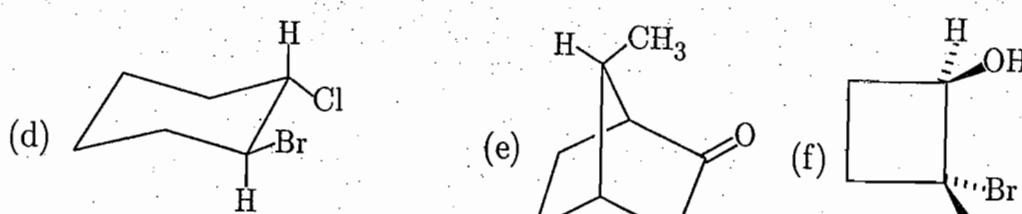
(from which cleavage by periodic acid
will take place readily)



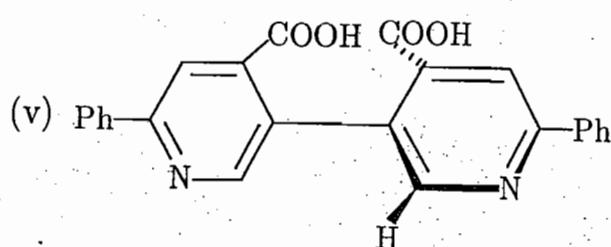
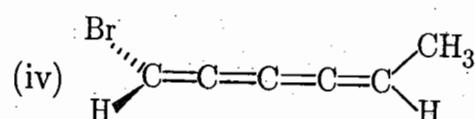
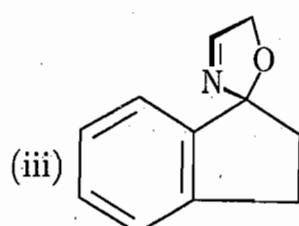
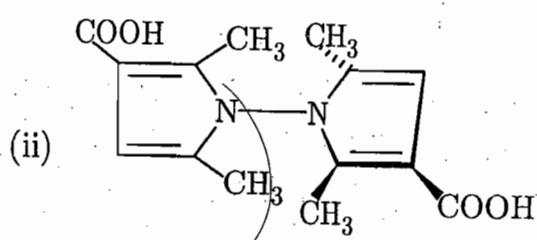
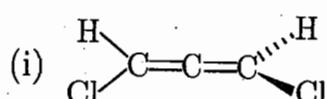
(from which base-induced dehydrochlorination to
form an epoxide occurs readily)

22. Label the chiral centre(s) of each of the following compounds as (R) or (S) :

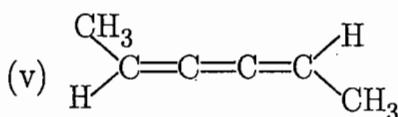
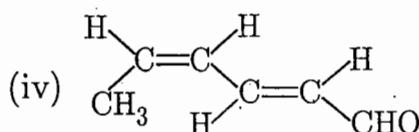
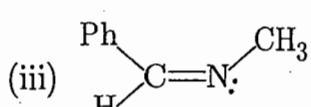
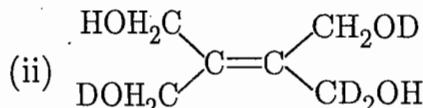
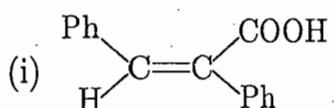




23. (a) Label each of the following molecules as (*R*) or (*S*):



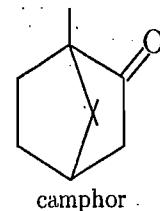
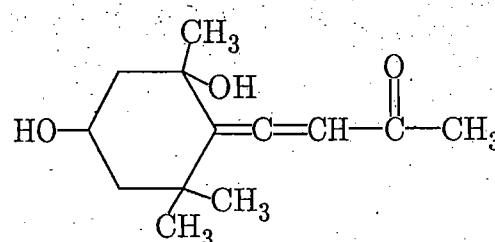
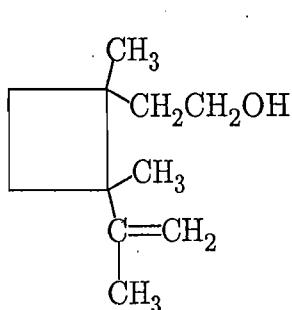
- (b) Give an example of a compound which possesses axial as well as central chirality.
24. (a) Label each of the molecules as (*E*) or (*Z*) :



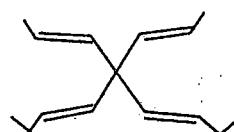
- (b) Predict the number of geometric isomers for the compound with molecular formula $C_2BrClFI$. Write down their structures and label each of them as (*E*) or (*Z*).
25. Draw perspective formulas of the following compounds :
- (a) (i) (*R*)-2-Hydroxypropanoic acid (ii) (*2R,3S*)-2,3-Dibromobutane (iii) (*R*)-*N*-Ethyl-*N*-methylanilinium oxide (iv) (*R*)-4-Methylcyclohexylideneacetic acid
 (v) (*S*)-Penta-2,3-diene (vi) (*S*)-Biphenyl-2,2'-disulphonic acid.
- (b) (i) (*2Z,4E*)-5-chlorohexa-2,4-dienoic acid
 (ii) (*2E,4Z*)-Heptadienedioic acid (iii) (*E*)-Azobenzene
 (iv) (*R*)-Butanone oxime (v) (*2E,4E*)-Hepta-2,4-diene
- (c) Draw all the possible stereoisomers of $\text{PhCHOHCH}=\text{CHCH}_3$. Label them as (*E*) or (*Z*) and (*R*) or (*S*). How are they related to each other?

26. Write down the flying wedge projections of each of the following compounds having the noted configuration and ligands attached to the chiral centre.
- (a) $\text{HC}\equiv\text{C}-$, —Ph, $\text{HC}\equiv^{14}\text{C}-$, —H (with *S* configuration)
 (b) —Br, — CH_2NH_2 , — CH_2CH_3 , — CH_2Cl (with *R* configuration)
 (c) —OD, — ^{18}OD , —OH, —OMe (with *S* configuration)
 (d) —CN, —Ph, —H, —OH (with *R* configuration)
27. Draw all the stereoisomers of cyclopentane-1,2,3-triol and list them in terms of *R/S* designations. Identify the enantiomers, diastereoisomers and *meso* compounds.
28. (a) 2,5-Dimethylcyclopentane-1,1-dicarboxylic acid decarboxylates on heating to give 2,5-dimethylcyclopentanecarboxylic acid. Draw all the stereoisomers of these two compounds and comment on their optical activity.

- (b) Two optically active alkenes, A and B, have the same molecular formula (C_5H_9Cl). On hydrogenation A is converted to C (achiral) and B is converted to D (chiral). Give the structures of A, B, C and D.
29. In which of the following ways should enantiomers differ?
- melting point
 - boiling point
 - sign of specific rotation
 - magnitude of specific rotation
 - absolute configuration
 - solubility in water
 - solubility in chloroform
 - solubility in (+)-2-chloropentane
 - solubility in (-)-2-chloropentane
 - solubility in (\pm) -2-chloropentane
 - refractive index
 - infrared spectrum
 - Pmr spectrum
 - rate of reaction with an optically inactive reagent
 - rate of reaction with an optically active reagent
 - Mass spectrum
 - colour
 - interaction with left circularly polarized light
 - toxicity to human beings.
30. (a) Determine the total number of stereoisomers possible for each compound :

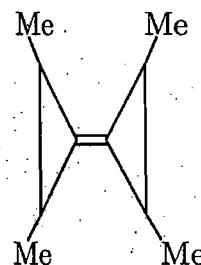


- (b) Predict the number of stereoisomers of the following compound and identify the enantiomers and diastereoisomers.



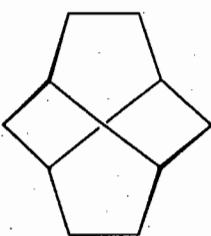
5,5-Bis-(1-propenyl)-nona-3,6-diene

- (c) Draw all the stereoisomers of the following alkene and their ozonolysis products and comment on their optical activity.

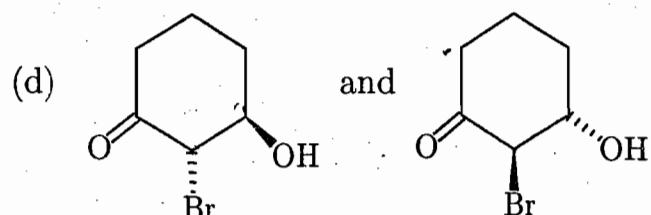
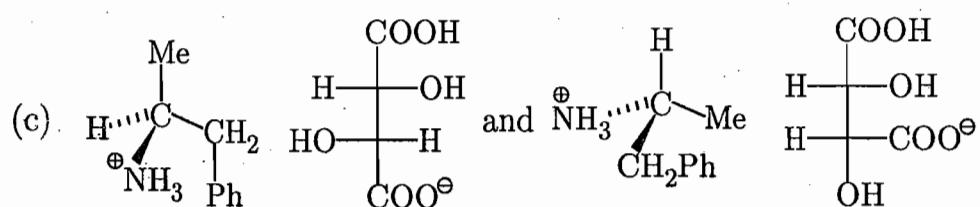
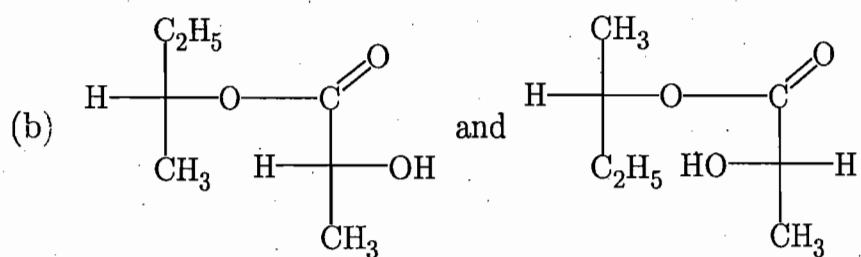
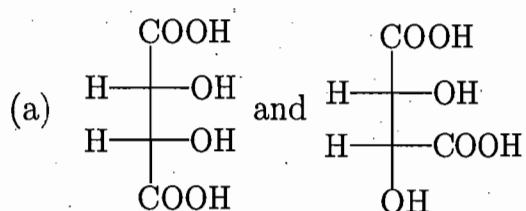


- (d) Draw all the stereoisomers of *trans*-3,6-dimethyl-4-octene and comment on their optical activity.
- (e) Cyclohexene exists only in the *cis*-form, while cyclodecene exists in both the *cis* and *trans* forms. Explain.

- (f) Star(*) the asymmetric carbon atoms in twistane and explain why it exists only as a pair of enantiomers.

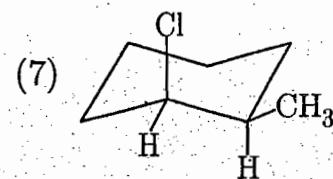
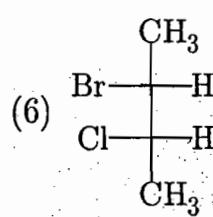
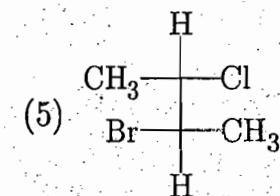
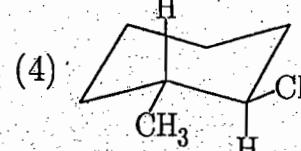
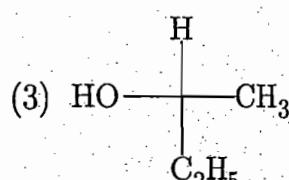
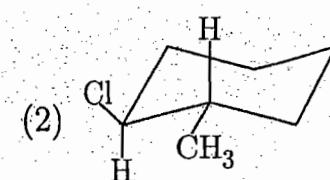
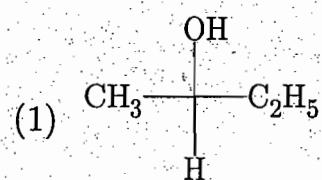
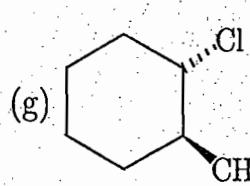
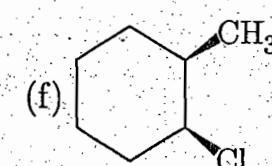
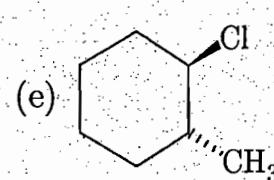
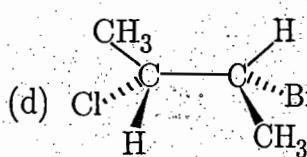
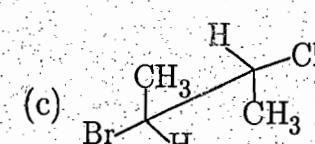
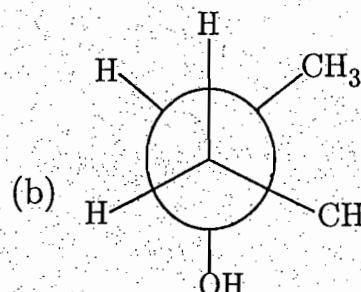
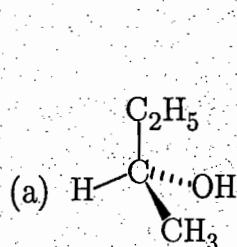


31. Which of the following pairs of compounds could be separated by recrystallization or distillation?

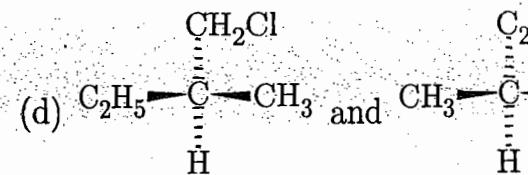
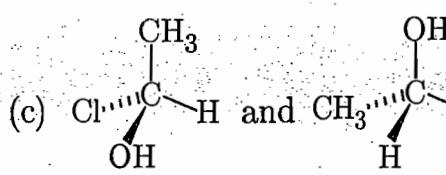
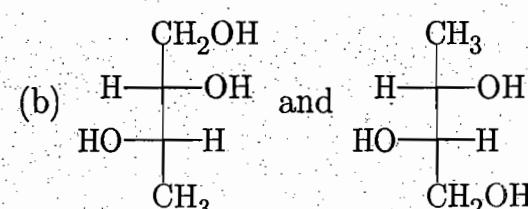
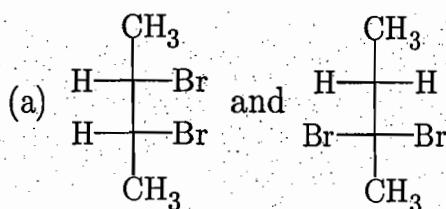


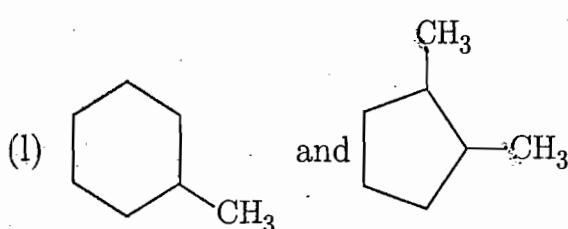
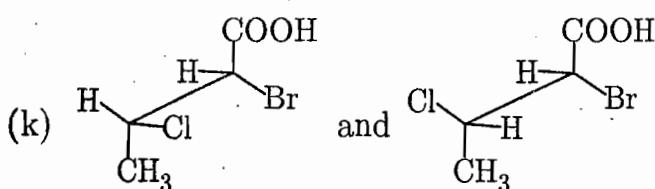
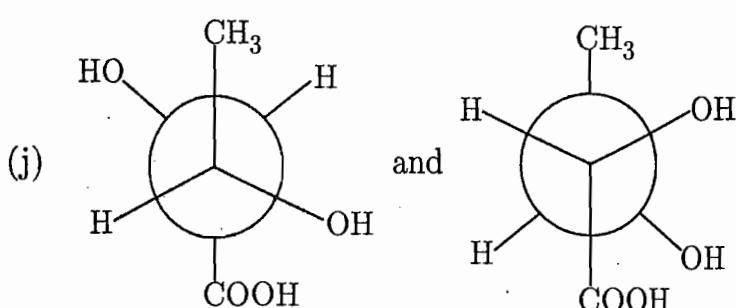
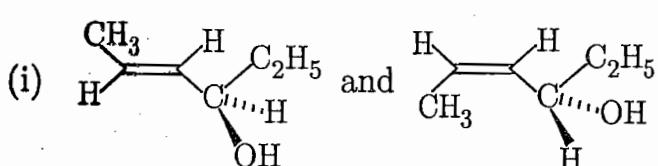
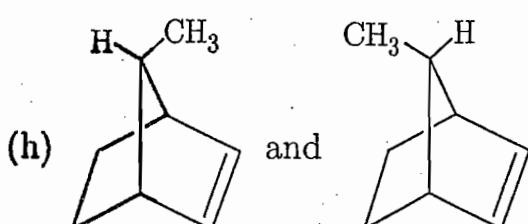
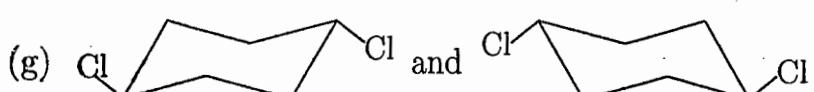
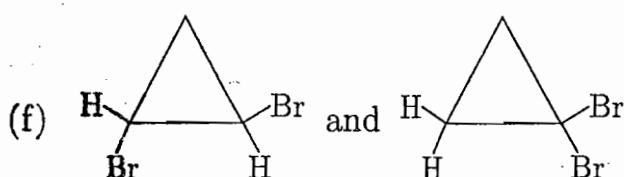
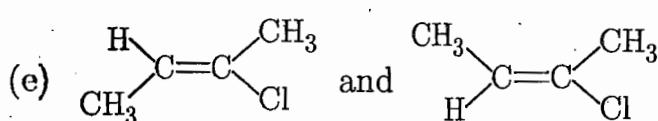
32. (a) Esterification of (+)-lactic acid, $[\alpha]_D^{25^\circ} = +4^\circ$, with methanol give (-)-methyl lactate, $[\alpha]_D^{25^\circ} = -8^\circ$. Has the configuration changed?
- (b) How would you convert (*R*)-2-butanol to (*S*)-2-butanol?
33. When 1-aminobutane ($\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$) reacts with (*R*)-4-chloropentanoic acid ($\text{CH}_3\text{CHClCH}_2\text{CH}_2\text{COOH}$) only one type of salt is produced. However, when 2-aminobutane [$\text{CH}_3\text{CH}_2\text{CH}(\text{NH}_2)\text{CH}_3$] is used, two different salts are formed. Account for this difference. How are the salts produced from 2-aminobutane related to one another?

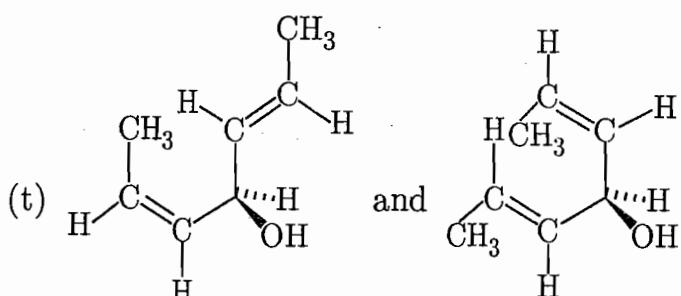
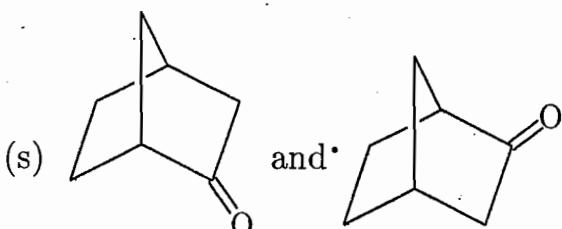
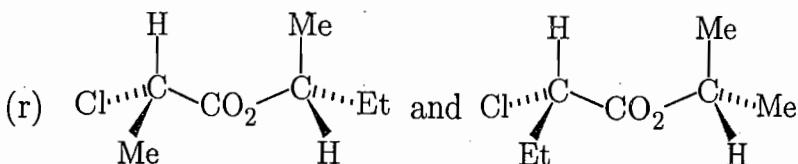
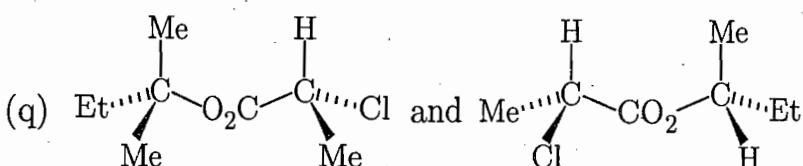
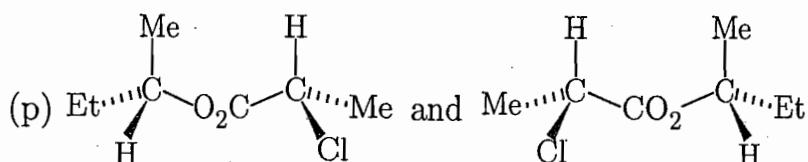
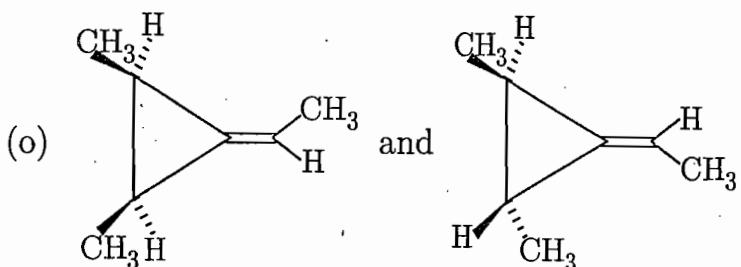
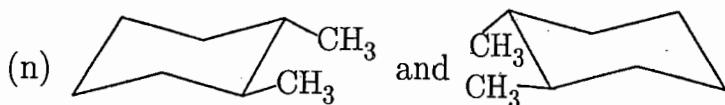
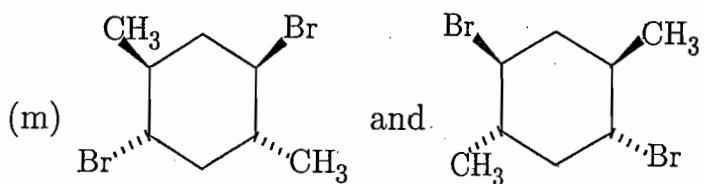
34. Match the structures indicated by letters with identical structures indicated by numbers :



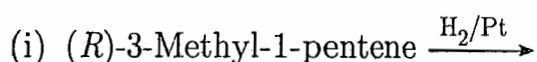
35. Indicate whether each of the following pairs of structures are identical or are enantiomers, diastereoisomers, or constitutional isomers :

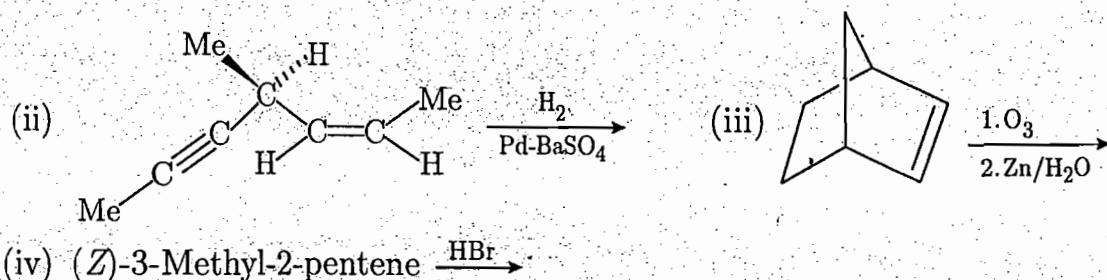




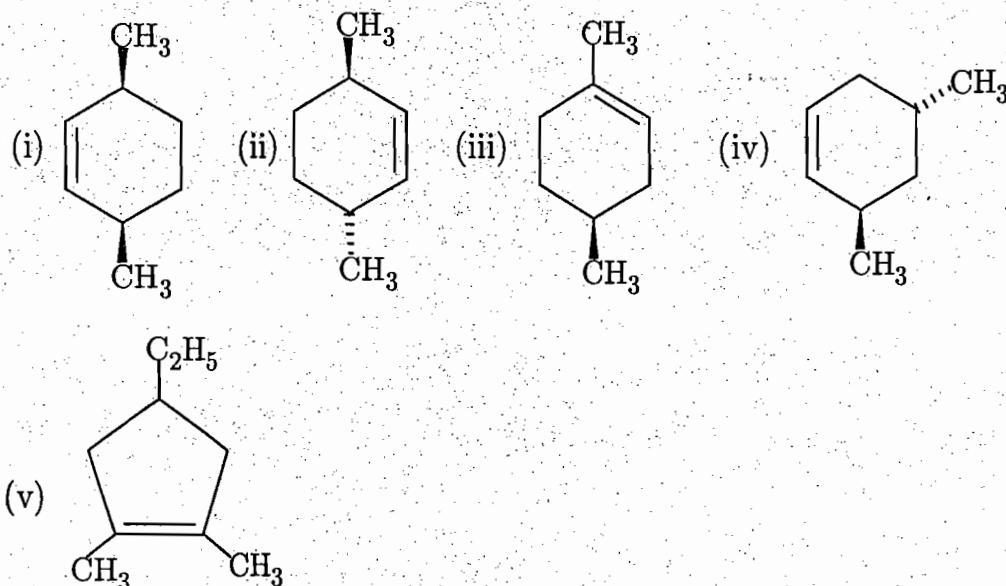


36. (a) Explain why an optically inactive product is obtained in each of the following reactions :

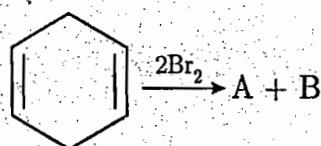




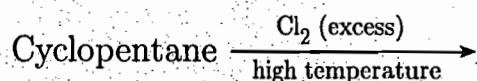
(b) Which of the following compounds undergoes catalytic hydrogenation to give an optically inactive product?



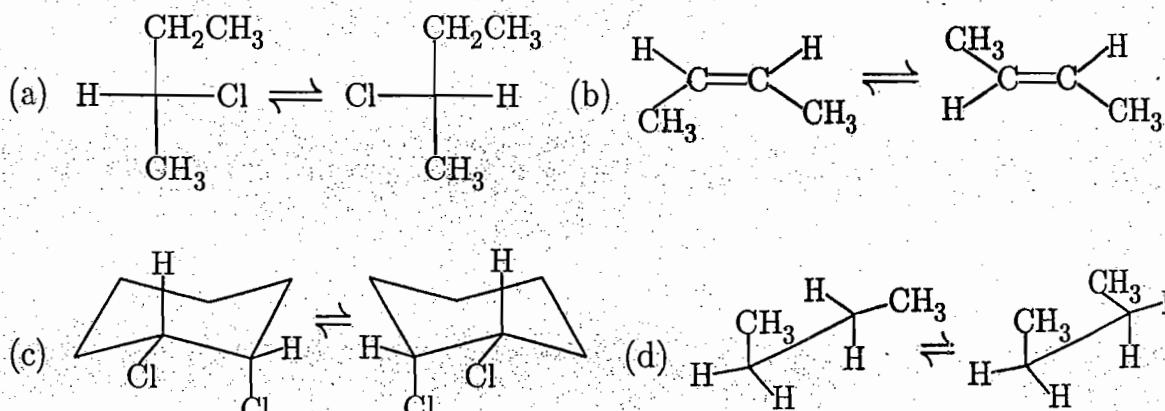
(c) Predict the products and explain why they are optically inactive.



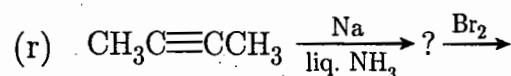
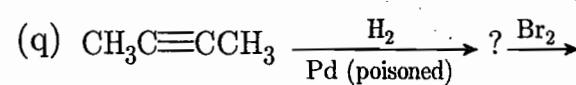
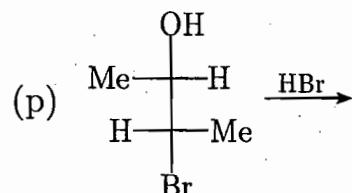
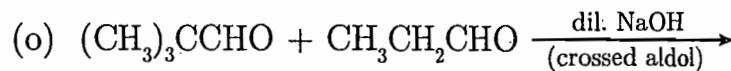
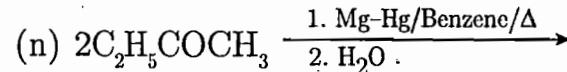
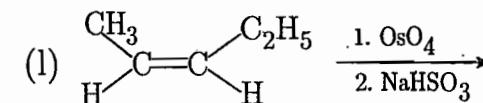
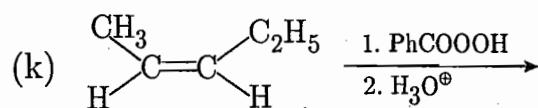
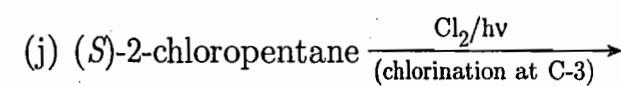
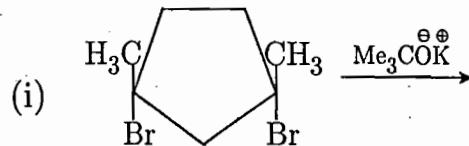
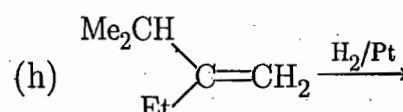
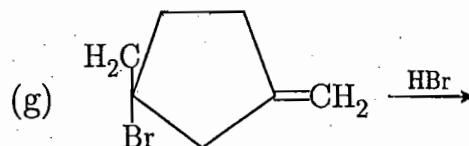
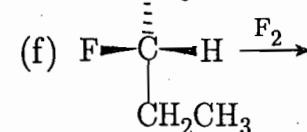
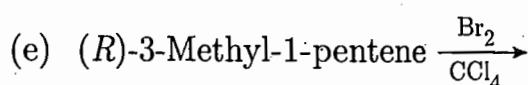
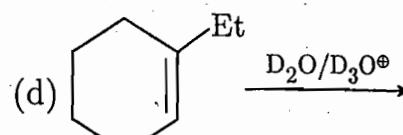
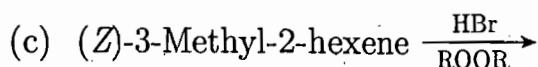
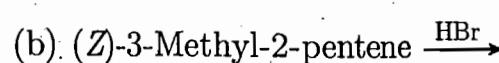
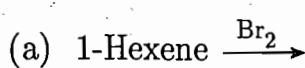
(d) Predict the products and comment on their geometrical isomerism and chirality.



37. Predict the relative magnitude of the activation energy for each conversion :



38. Indicate the stereochemistry of the products in each of the following reactions :



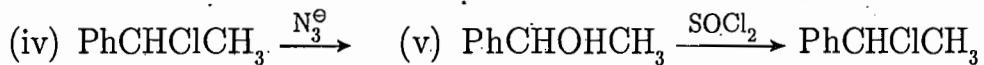
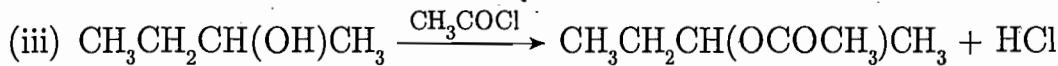
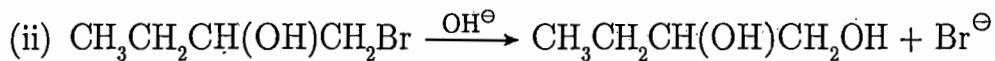
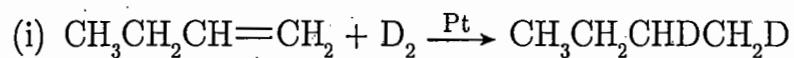
39. Write structures for all the stereoisomers of 1,2,3,4,5,6-hexachlorocyclohexane, labelling *meso* compounds and enantiomers. Which one of these stereoisomers would undergo E2 reactions much more slowly than any of the others and why? Which of these stereoisomers has two identical chair conformations?

40. (a) What are the different ways in which the configuration of one enantiomer can be affected by a chemical reaction at the chiral carbon atom?

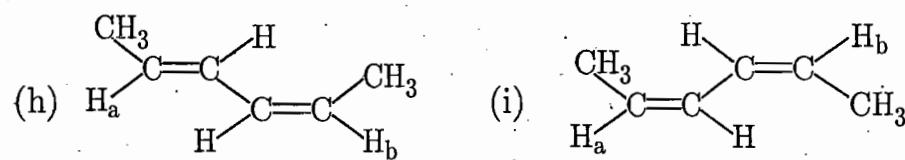
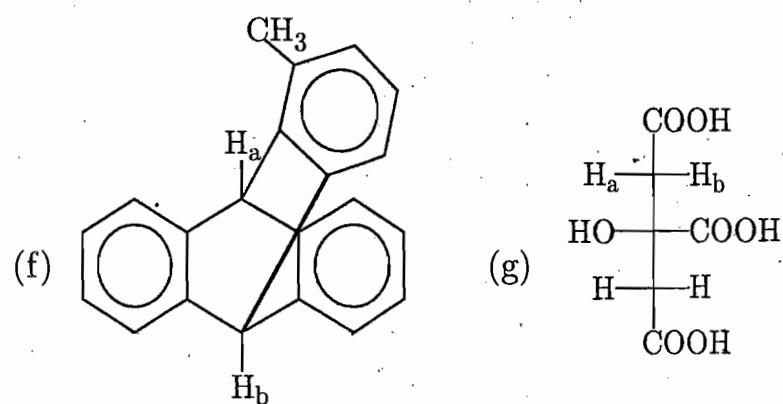
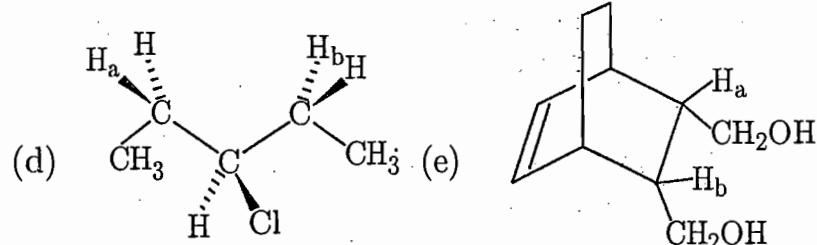
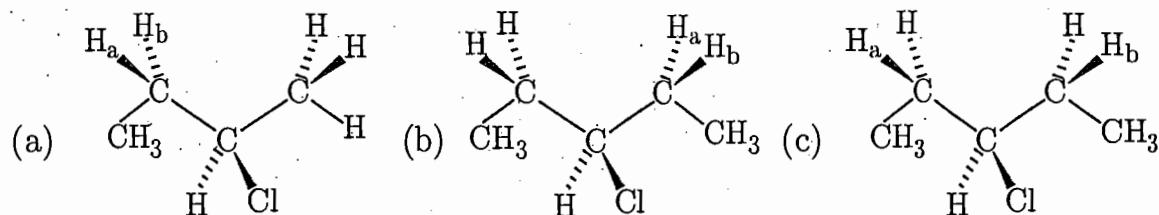
(b) Show with suitable examples :

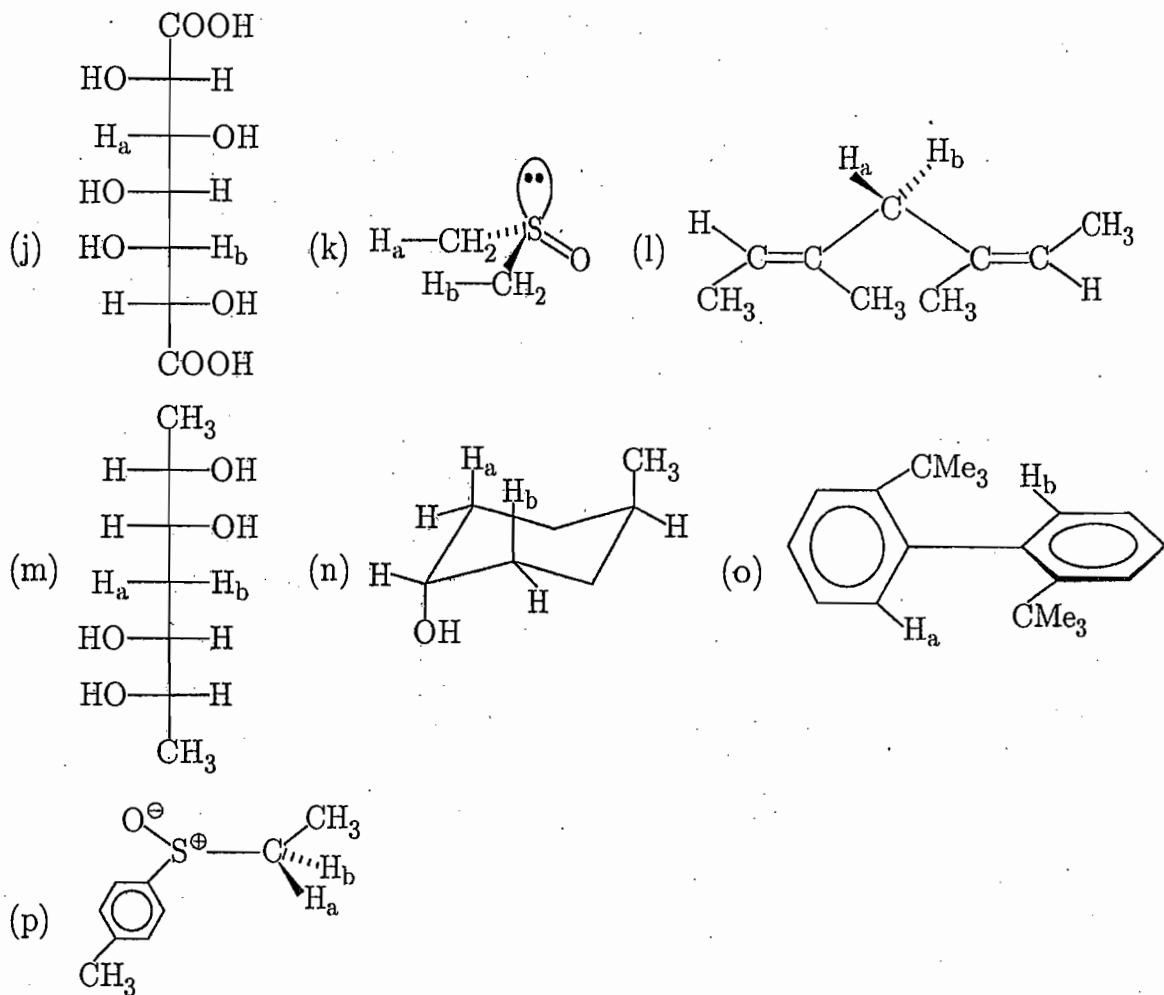
- (i) The change of descriptors from *R* to *S* in a chemical reaction does not necessarily mean that inversion of configuration has taken place.
- (ii) The descriptor (*R* or *S*) may remain unchanged even when absolute configuration of a chirality centre has undergone inversion.

(c) Predict whether the following reactions occur with racemization, retention or inversion of configuration, and give your reasoning.

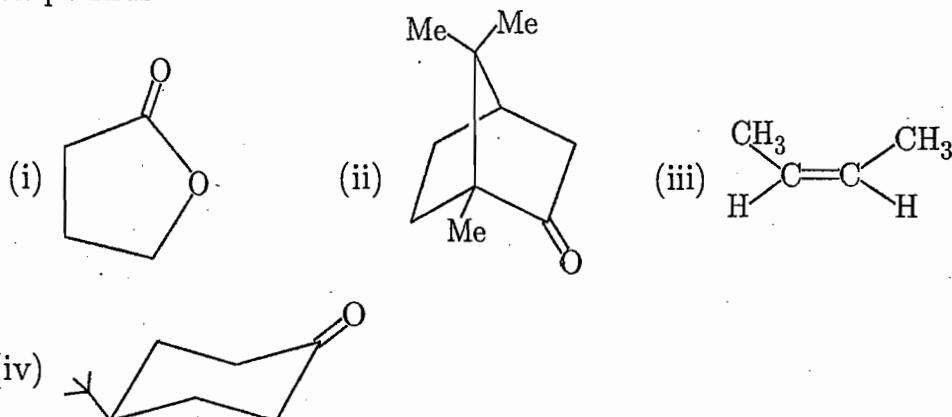


41. Discuss the stereoelectronic factors of S_N2 and E2 reaction giving suitable examples.
42. Explain how heating could lead to racemization of an optically active biphenyl.
43. Indicate whether the hydrogens marked H_a and H_b in each of the following compounds are homotopic, enantiotopic, or diastereotopic.





44. (a) Label the faces as homotopic, enantiotopic and diastereotopic in the following compounds :

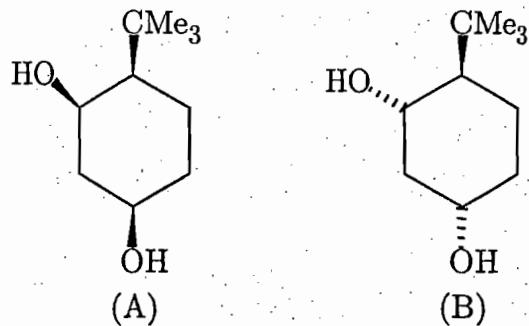


- (b) How would you prove that the two faces (the two lone electron pairs on sulphur) of ethyl methyl sulphide ($\text{Et}-\ddot{\text{S}}-\text{Me}$) are enantiotopic?
 (c) What do you mean by a prochiral centre? Give an example.

45. (a) Draw a potential energy diagram for rotation of the C-2—C-3 bond of pentane through 360° , starting with the most stable conformer.
 (b) Draw the most stable conformer of the following (using Newman projections) :
 (i) 2,2-dimethyl butane, considering rotation about the C-2—C-3 bond.
 (ii) 3-methylhexane, considering rotation about the C-3—C-4 bond.

- (iii) 3-methylpentane, considering rotation about the C-2—C-3 bond.
 (iv) 3,3-dimethylhexane, considering rotation about the C-3—C-4 bond.

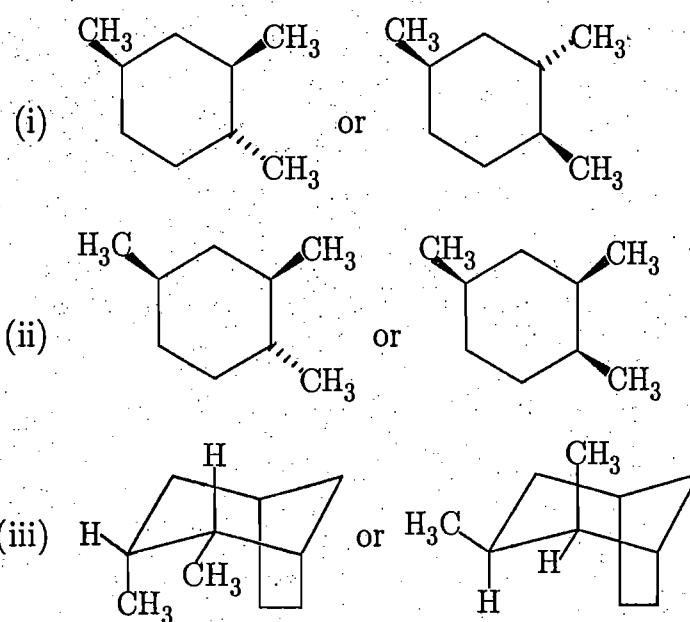
46. (a) Draw the possible staggered conformations of *meso* and active form of 2,3-dichlorobutane. Give the composition of the conformational equilibrium with possible reasons.
- (b) Which rotamer of methylvinyl ketone ($\text{CH}_3\text{COCH}=\text{CH}_2$), 2,3-diazadiene ($\text{CH}_2=\text{N}-\text{N}=\text{CH}_2$) and 2,3-di-*t*-butylbutadiene [$\text{CH}_2=\text{C}(\text{CMe}_3)-\text{C}(\text{CMe}_3)=\text{CH}_2$] will predominate and why?
- (c) Draw the staggered conformations of *erythro* and *threo* isomers of 3-aminopentan-2-ol and identify the preferred conformer. Give your reasoning.
- (d) Draw the preferred conformations of (i) H_2O_2 and (ii) 1,1,2-Trichloroethane.
- (e) When methylester of *trans*-cyclobutane-1,3-dicarboxylic acid was equilibrated in base, a mixture of *cis*- and *trans*-isomers was isolated with *cis*-predominating. Account for this observation.
- (f) Explain the observation that A forms intramolecular hydrogen bonds, while B forms only intermolecular hydrogen bonds.



- (g) Explain why 1,2,2,6,6-pentamethyl-4-hydroxy-4-phenylpiperidine is boat shaped.
- (h) The dipole moment of *trans*-1,3-dibromocyclobutane is 1.1D. Explain why a nonzero dipole moment suggests a puckered structure rather than a planar structure for this compound.
- (i) Equal amounts of (a,a) and (e,e) conformers of *trans*-1,2-dibromocyclohexane exists in nonpolar solvents, but the (e,e) conformer predominates in polar solvent. Explain.
- (j) *cis*-Cyclohexane-1,3-dicarboxylic acid readily forms an anhydride on heating but the *trans*-acid does not. Explain.
- (k) (–)-2,3-Butanediol enhances the conductivity of boric acid more than does the *meso*-isomer. Explain.

47. Comment on the strain in the chair-chair form of bicyclo[3.3.1]nonane. How is it related with adamantane?

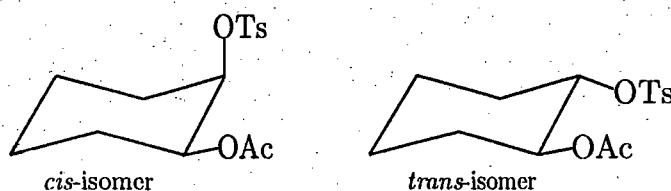
48. (a) Draw the two chair conformations of each of the following disubstituted cyclohexanes and label the more stable conformer in each case :
- cis*-1-ethyl-4-isopropylcyclohexane
 - trans*-1-ethyl-4-methylcyclohexane
 - trans*-1-ethyl-2-methylcyclohexane
 - cis*-1-ethyl-2-methylcyclohexane
 - 1-*t*-butyl-1-methylcyclohexane.
- (b) Identify the more stable stereoisomer in each of the following pairs and give your reasoning :



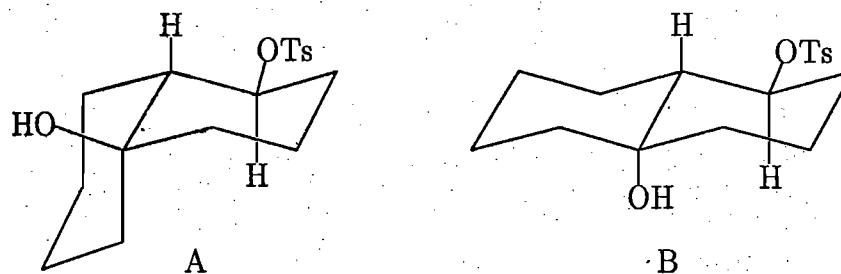
49. Give an example where in a bicycloalkane both *cis*- and *trans* isomers are possible.

50. Explain the following observations :

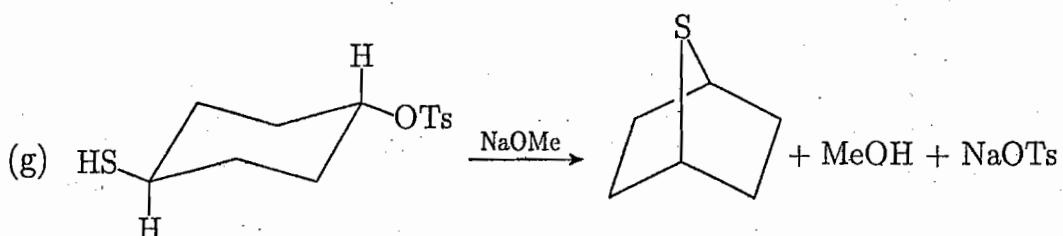
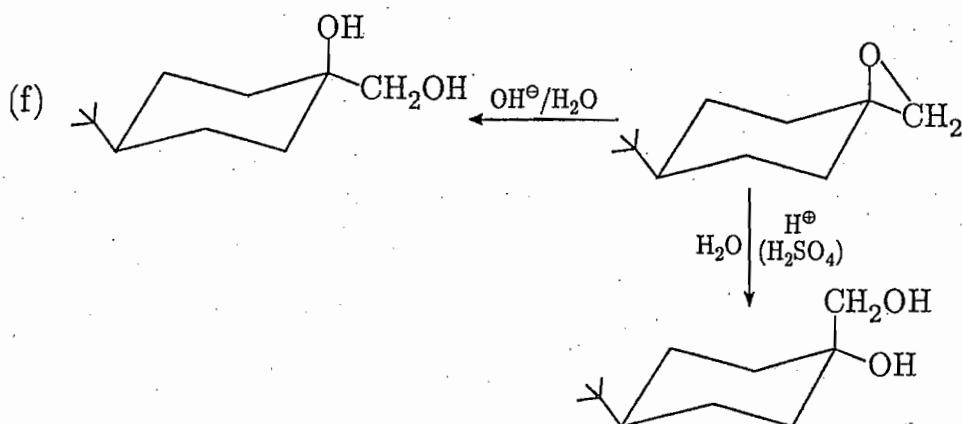
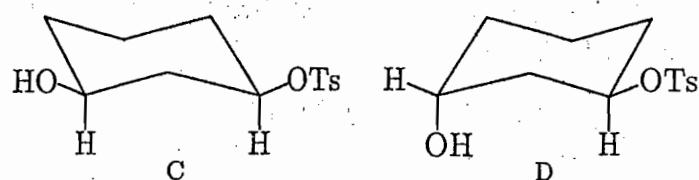
- trans*-4-*t*-Butylcyclohexanecarboxylic acid undergoes esterification reaction at a much faster rate than its *cis*-isomer.
- When 3,3,5-trimethylcyclohexanone is treated with LiAlH₄, the axial alcohol is found to be the major product, but when 4-methylcyclohexanone is treated with LiAlH₄, equatorial alcohol is found to be the major product.
- Acetolysis of both *cis* and *trans*-tosylate shown below give the same *trans*-diacetate.



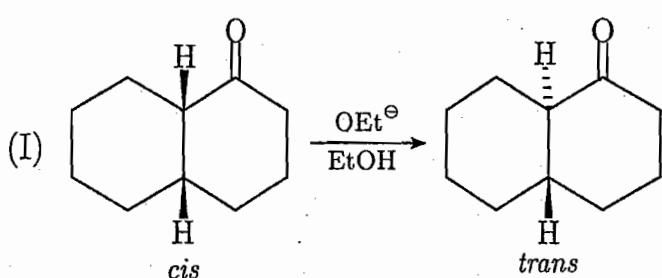
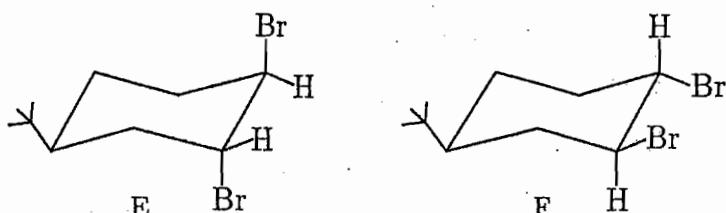
- (d) When treated with a base, compound A and B give the same product.



- (e) The compound C undergoes fragmentation reaction in the presence of *t*-BuOK, whereas the compound D does not.

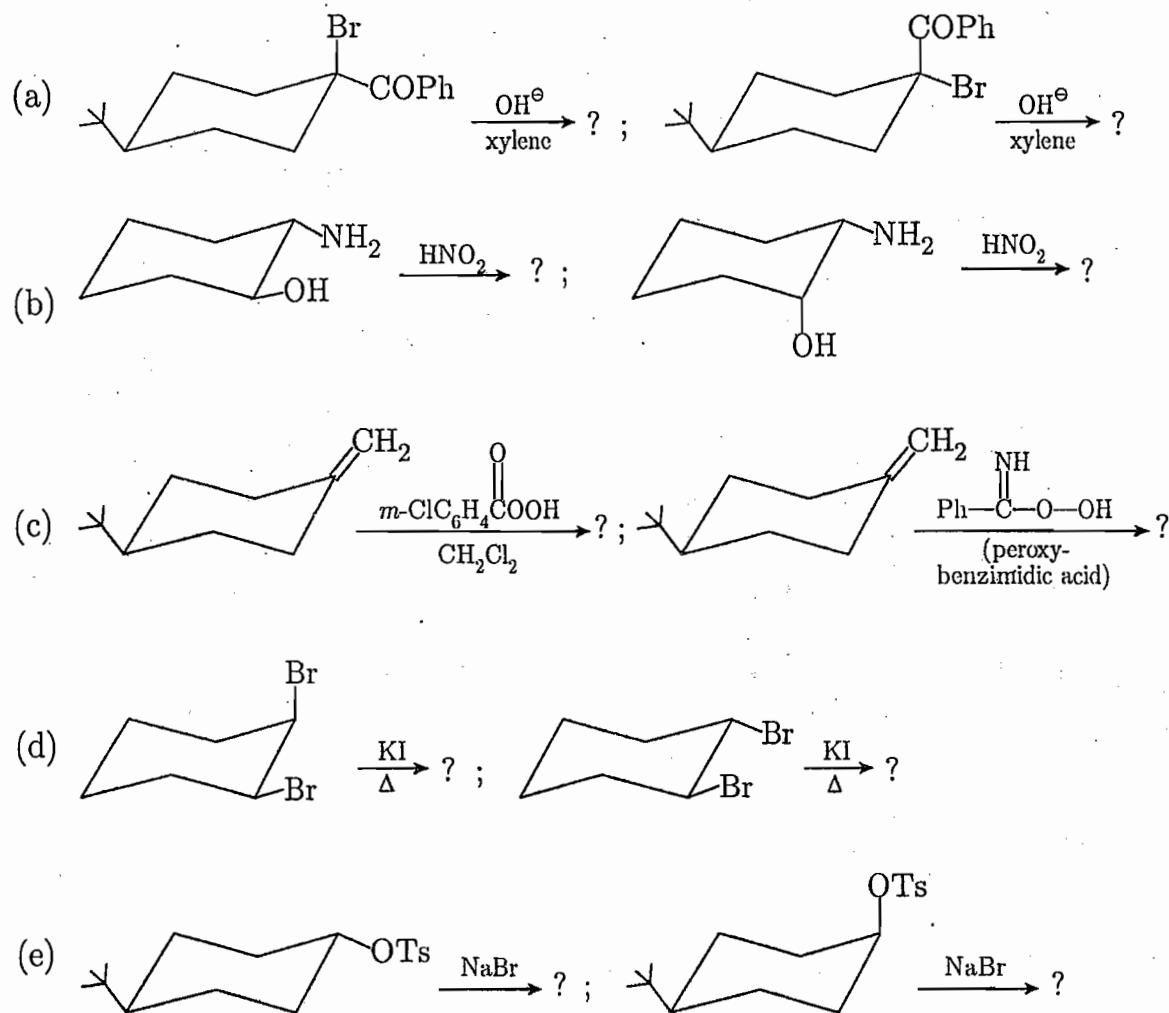


- (h) E readily forms an alkene with I^\ominus but F does not.

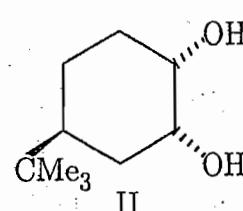
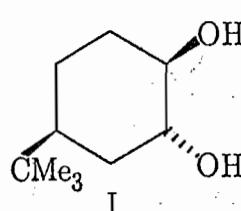


51. (a) How the chirality of disubstituted cyclohexanes depends on the nature of substitutents R and R'?
- (b) Draw the most stable conformation of *trans*-1,2-dimethylcyclohexane. Is it chiral?
- (c) Discuss the stereoisomerism of *cis*- and *trans*-1-*t*-butyl-2-methylcyclohexane.

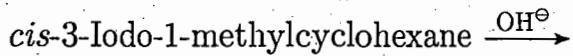
- (d) What is called 1,3-diaxial interaction. Illustrate with an example.
- (e) Draw the Newman projection of the more stable chair conformation of *cis*-1-*t*-butyl-2-methylcyclohexane.
- (f) Write down the preferred conformation of all-*cis* isomer of 1,4-di-*t*-butylcyclohexane-2,5-diol.
52. Predict the product and suggest a mechanism for each of the following reactions :



53. (a) *cis*- and *trans*-Cyclohexane-1,2-diol are each treated with : (i) 1 molecule of $(\text{CH}_3\text{CO})_2\text{O}$; (ii) a second molecule of $(\text{CH}_3\text{CO})_2\text{O}$; Are the rates of first and second acetylation reactions the same or different? Explain.
- (b) Which of the following diols cannot be cleaved by periodic acid (HIO_4) and why?



- (c) *cis*-2-Chlorocyclohexanol with aqueous alkali gives cyclohexanone, whereas the *trans*-isomer give cyclohexene oxide. Explain.
- (d) Predict the configuration of the product :



- (e) Active butane-2,3-diol undergoes oxidative cleavage by lead tetraacetate at a rate faster than *meso*-butane-2,3-diol. Explain.

54. State whether the following statements are true or false. Give your reasoning.

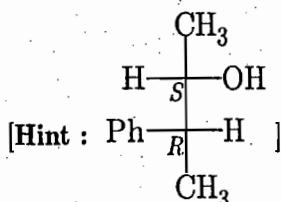
- (a) A compound with *R* configuration is the (+) enantiomer.
- (b) All geometric or *cis-trans* isomers are diastereoisomers.
- (c) An achiral compound can have chiral centres.
- (d) Both asymmetric and dissymmetric molecules can exhibit enantiomerism.
- (e) An optically inactive substance must be achiral.
- (f) When a molecule has only one chiral centre then that chiral centre is both stereogenic and chirotopic.
- (g) All aldehydes except formaldehyde have prochiral face.
- (h) A chiral compound may not have chiral centres.
- (i) If a compound has a diastereoisomer, it must be chiral.
- (j) If a structure has no plane of symmetry, it is chiral.
- (k) Mirror-image molecules are in all cases enantiomers.
- (l) If a compound has an enantiomer it must be chiral.
- (m) An *R* substrate undergoes S_N2 reaction to give always an *S* product.

UNIVERSITY QUESTIONS

University of Calcutta

2001

1. Draw the Fischer projection of the following molecule : $(2S,3R)$ -3-phenyl-2-butanol.



2. Explain the difference between configuration and conformation. Draw the energy diagram of *n*-butane as a function of rotation about C_2-C_3 bond and label the maxima and minima with proper configurations. Is it possible to isolate the different forms? Give reasons.

[Hint : See the answer to *Problems 1.5, 3.2(b) and 3.1(i)*.]

3. Define with example (i) axial chirality and (ii) atropisomerism.

[Hint : See the answer to *Problems 1.103 and 1.108(b)*.]

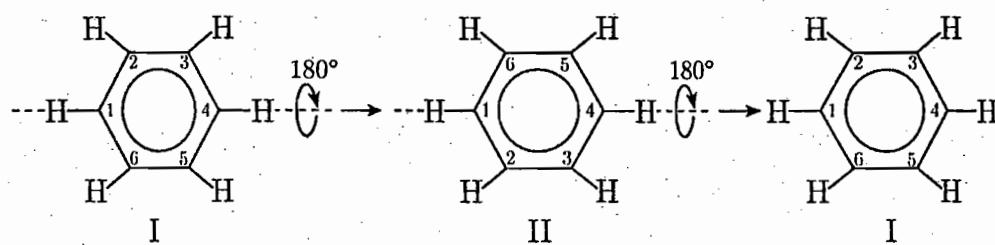
4. An optically pure sample of (*R*)-2-butanol shows a specific rotation of -13.6° . What relative molar proportion of (*S*)-(+)-2-butanol and (*R*)-(−)-2-butanol would give a specific rotation of $+6.8^\circ$?

[Hint : See the answer to *Problem 9, B.U. 2006 (New regulation)*]

5. What is meant by symmetry number? Find out the symmetry number of benzene.

[Hint : The symmetry number (σ) is defined as the number of equivalent positions a molecule can be turned into through simple rotation around an axis or axes.

The benzene molecule has a symmetry number twelve. The six carbons are numbered as in the structure (I). When the molecule is rotated around the C_6 axis passing through C-1 and C-4, a new arrangement (II) is obtained as evident from the positions of the numerals. A second rotation of 180° around the same axis leads to the original (I) which has already been counted. Thus each of the six horizontal C_2 axes contributes one to the symmetry number, i.e., they contributes six in total.

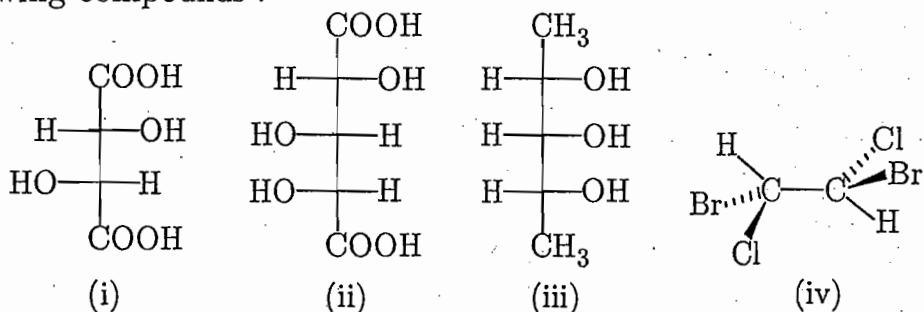


Again, during the rotation of the molecule around the C_6 axis through 360° , six equivalent arrangements result counting the original to which it returns. Therefore, this operation contributes six to the symmetry number making the total twelve.]

6. Draw the most stable conformer of $\text{HOCH}_2\text{CH}_2\text{F}$? Give reasons.

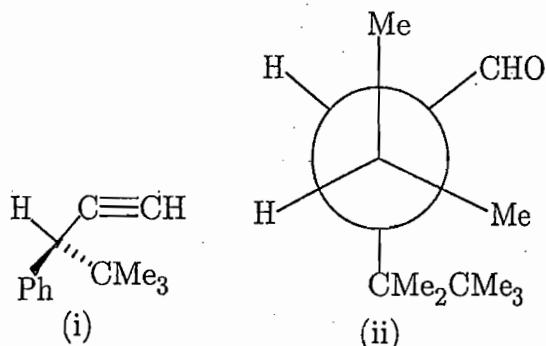
[Hint : See the answer to *Problem 3.3(a)(i)*.]

7. Label the stereogenic, non-stereogenic, chirotopic and achirotropic centres in the following compounds :



[Hint : See the answer to Problem 1.25]

8. Assign R/S-descriptors for the chiral centres present in the following compounds :

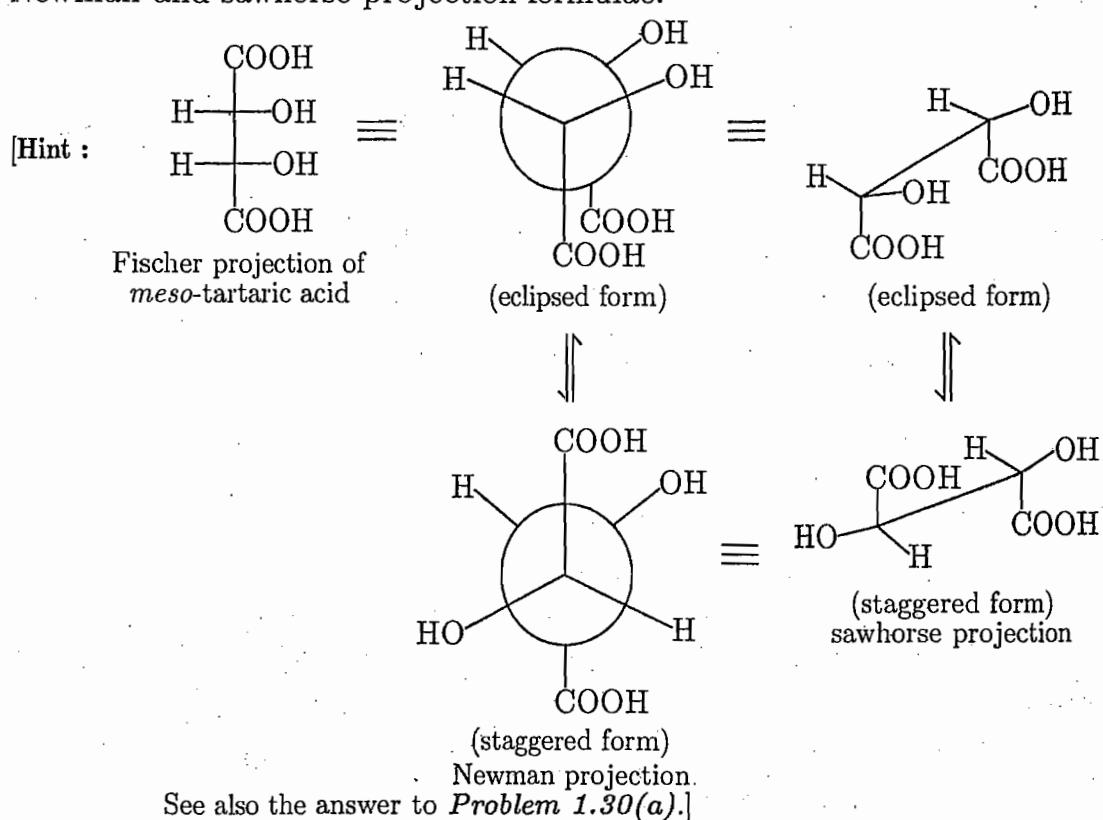


[Hint : (i) Priority order of ligands : Ph > C≡CH > CMe₃ > H : R configuration

(ii) Priority order of ligands : CHO > CMe₂CMe₃ > CHMe₂ > H : R configuration]

2002

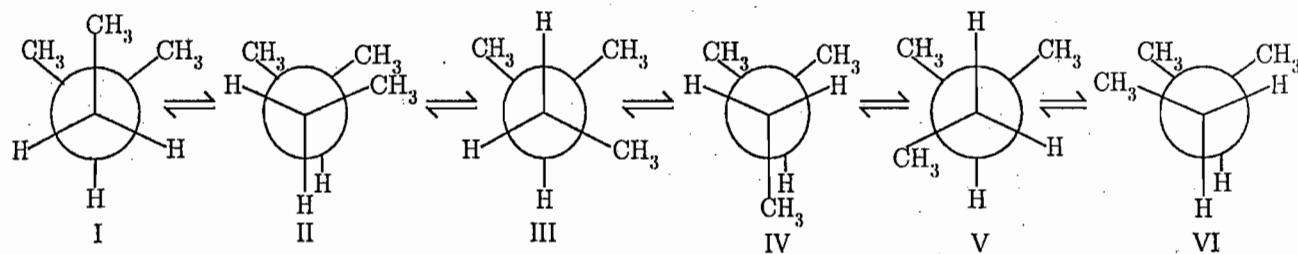
1. Write the Fischer projection formula of *meso*-tartaric acid and represent it in Newman and sawhorse projection formulae.



2. What is gauche-butane interaction? Draw the conformers of 2-methylbutane for rotation about C_2-C_3 bond in Newman projection formula and compare their relative stabilities.

[Hint : See the answer to *Problem 3.2(d)*.]

Conformations of 2-methylbutane for rotation about C_2-C_3 bond :



Stability order of the conformations :

(least stable) II = VI < IV < I < III = V (most stable)

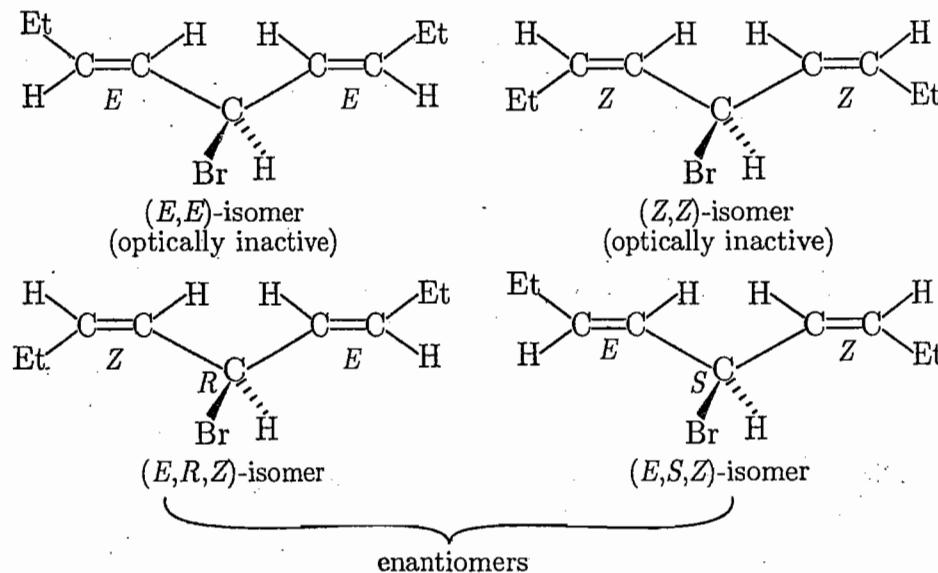
see also the answer to *Problem 3.2(f)*.]

3. Give an example of an optically active compound possessing a C_2 -axis. Indicate the axis.

[Hint : See the answer to *Problem 1.104(c)*.]

4. Draw all the possible stereoisomers of $\text{EtCH}=\text{CH}-\text{CHBrCH}=\text{CHEt}$ and mention whether they are *R* or *S* and optically active or not.

[Hint : Four stereoisomers are possible. These are as follows :

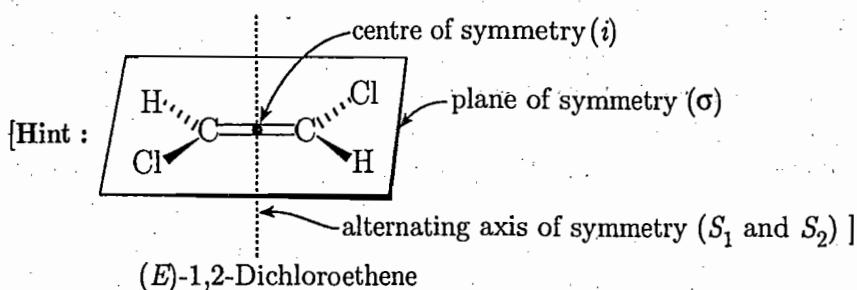


See also the answer to *Problem 1.81(b) (ix)*.]

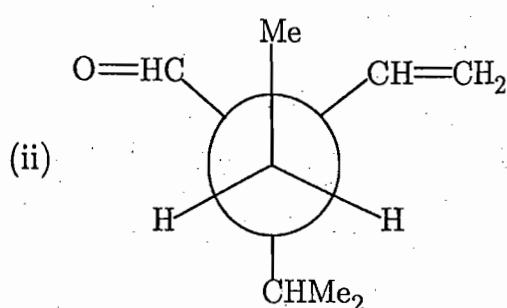
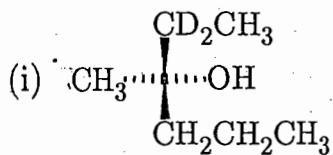
5. How will you carry out the resolution of a racemic alcohol? Outline the reaction steps.

[Hint : See the answer to *Problem 1.78(c) (iii)*.]

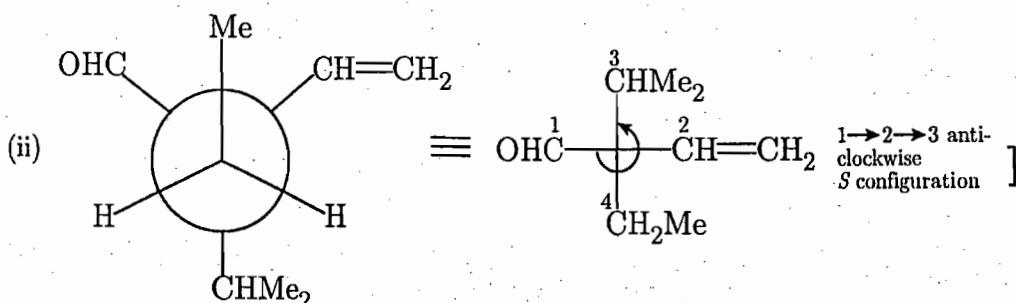
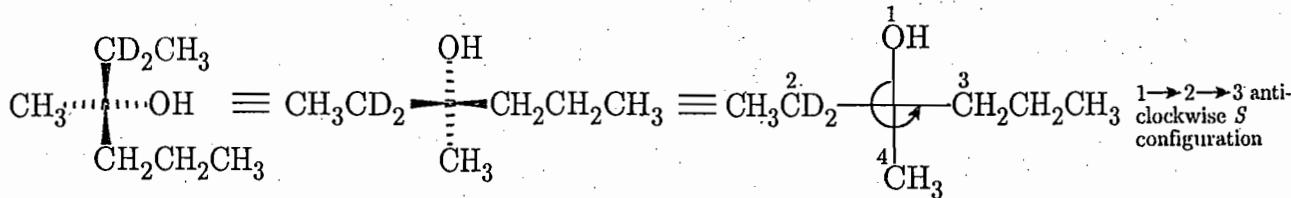
6. Locate σ , i, S_n , if any, in (*E*)-1,2-dichloroethene.



7. Assign *R*-/*S*- descriptors for the chiral centres in the following compounds :



[Hint : (i)]



8. What is meant by stereogenic centre? Are centres of stereogenicity always centres of chirality? Explain with suitable examples.

[Hint : See the answer to Problem 1.16.]

2003

1. What are the symmetry elements present in (i) *trans*-1,2-dichloroethene
(ii) *meso*-tartaric acid (in staggered conformation).

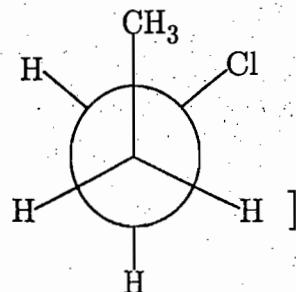
[Hint : (i) Plane of symmetry (σ) and centre of symmetry (i); (ii) centre of symmetry (i).]

2. Explain the terms dihedral angle and torsion angle. Draw (+) sc conformation of 1-chloropropane.

[Hint : See the answer to *Problem 3.1(a)* and *3.4*.]

(+) sc conformation is that in which the torsion angle between the two reference groups is $+60^\circ \pm 30^\circ$.

\therefore The (+) sc conformation of 1-chloropropane is :

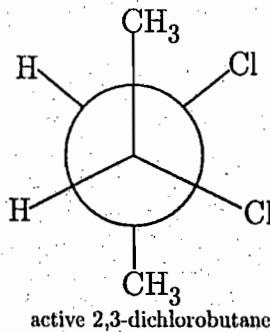


3. Define, with an example, the term 'alternating axis of symmetry'.

[Hint : See the answer to *Problem 1.7(d)*.]

4. What is the most populated conformer of optically active 2,3-dichlorobutane? Is it an asymmetric or a dissymmetric molecule? Explain.

[Hint : The most populated conformer :



Active 2,3-dichlorobutane is a dissymmetric molecule because it has no S_n axis but has one C_2 axis.]

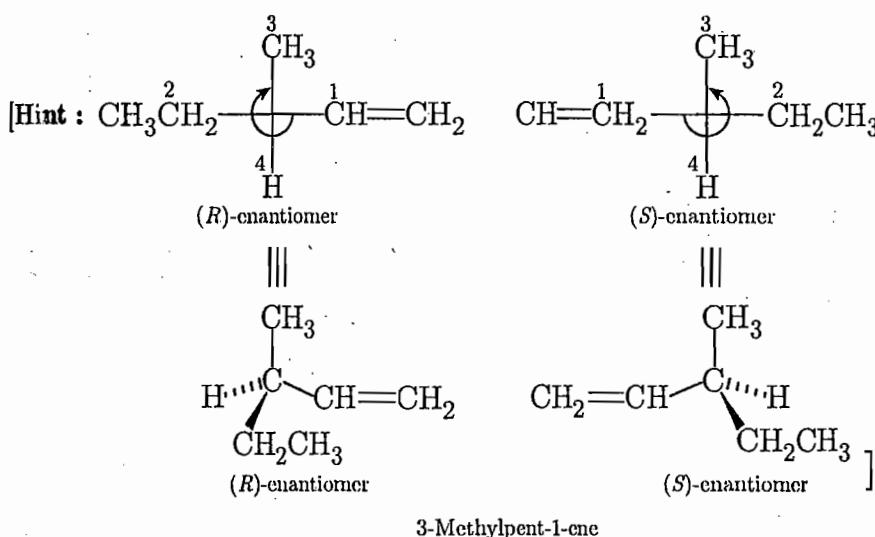
5. Draw the Fischer projection of a meso-isomer of $\text{CH}_3(\text{CHOH})_3\text{CH}_3$ and point out the stereogenic and achirotopic centre(s), if any, in it. Explain.

[Hint : See the answer to *Problem 1.25(d)*.]

6. Explain the stereoisomerism of 6,6'-dinitrodiphenic acid and draw the energy profile for racemisation of its enantiomers.

[Hint : See the answer to *Problem 1.108*.]

7. Write down a Fischer projection formula of each enantiomer of 3-methylpent-1-ene and specify the chiral centre of each as R or S. Draw a corresponding flying-wedge formula of each.



2004

- What are the necessary structural features for a biphenyl compound to be dissymmetric? Explain with a suitable example.

[Hint : See the answer to *Problem 1.108(b) and (c)*.]

- Draw the structure of the product of catalytic hydrogenation of $(Z)\text{-CH}_3\text{CD}=\text{CDCH}_3$ in Fischer projection formula.

[Hint : See the answer to *Problem 1.74(d)*.]

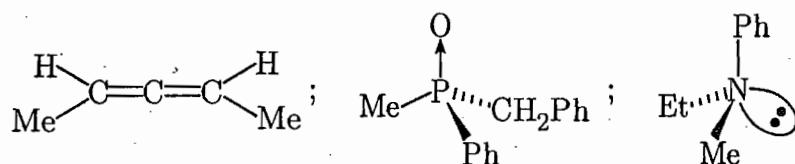
- Justify the statement— S_2 and i are equivalent operations.

[Hint : See the answer to *Problem 1.7(d) and 1.8*.]

- Write the Fischer projection formulae of all possible stereoisomers of 2,3,4-trichloropentane and assign R/S descriptors to the chiral centres in each of them. Label C-3 atom in each structure as stereogenic/non-stereogenic and chirotopic/achirotopic. Comment on the optical activity of the isomers.

[Hint : See the answer to *Problem 1.25(d)*.]

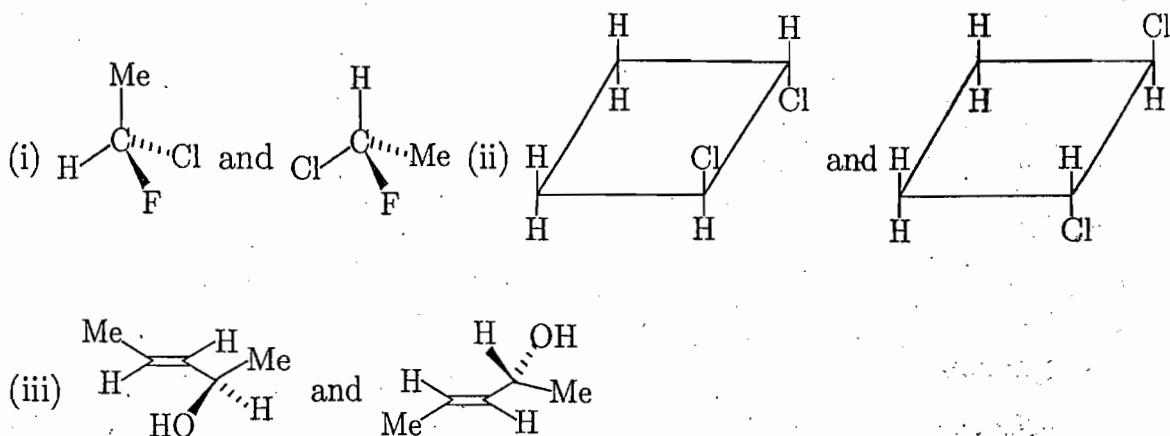
- Explain whether the following compounds are resolvable or not :



[Hint : The allene and the phosphine oxide are resolvable because they are chiral and configurationally stable. The amine is not resolvable because this chiral amine is not stable configurationally due to rapid pyramidal inversion.]

See also the answer to *Problem 1.63*.

6. Label the following pairs of molecules as homomers, enantiomers or diastereomers :



[Hint : (i) Homomers, (ii) Enantiomers, (iii) Homomers.]

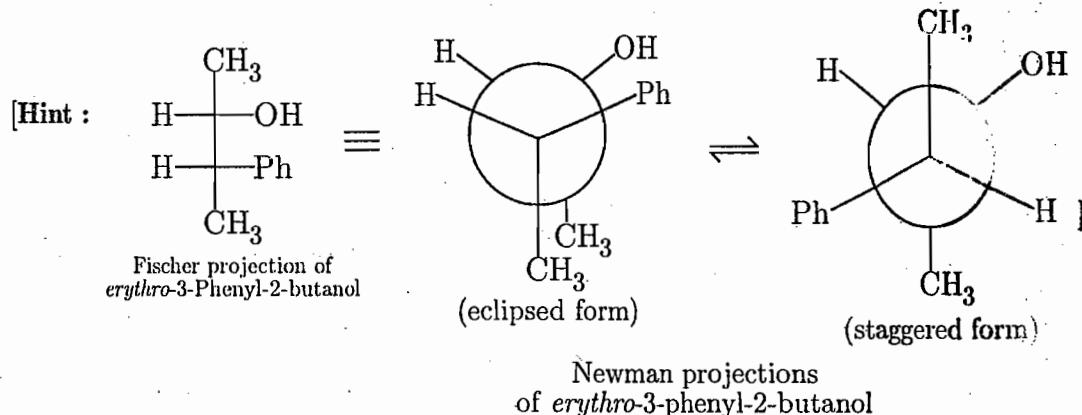
See also the answers to *Problem 1.97 to Problem 1.101.*

7. Draw the energy profile diagram of 1,2-dichloroethane for rotation about C—C bond and label the maxima and minima with appropriate conformations. Compare the relative stability of the conformations with explanation.

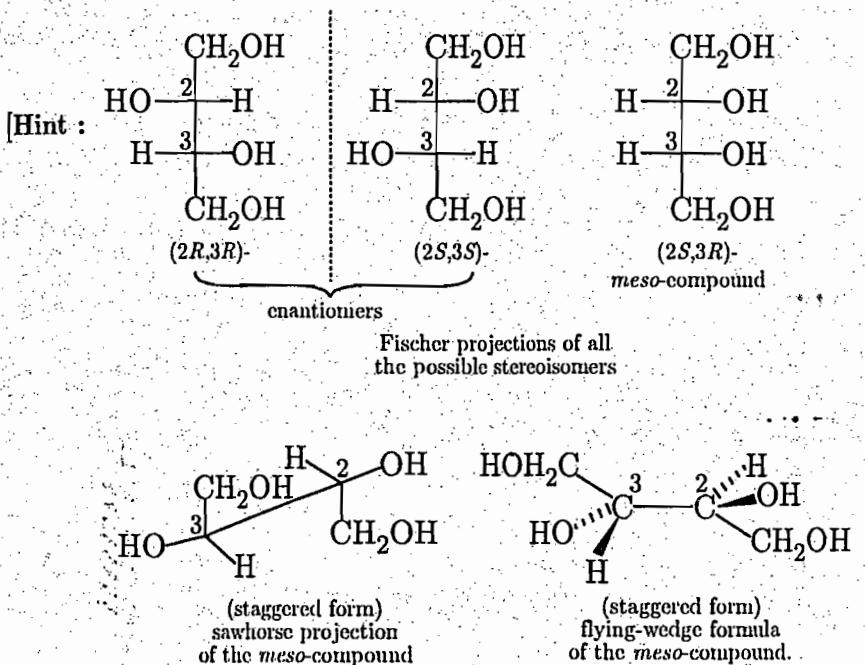
[Hint : See the answer to *Problem 3.2(g).*]

2005

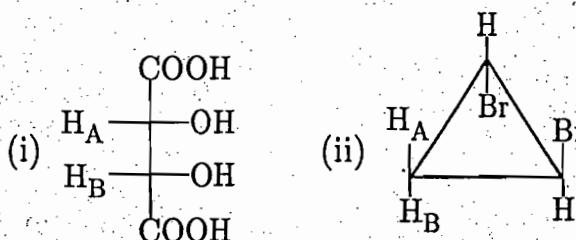
1. Write the Fischer projection formula of *erythro*-3-phenyl-2-butanol and represent it also in Newman projection formula.



2. Draw the Fischer projection formulas of all the possible stereoisomers of $\text{HOCH}_2\text{CHOHCHOHCH}_2\text{OH}$ and name them with *R/S* descriptor. Draw sawhorse and flying-wedge formulas of the staggered form along C-2—C-3 of any one of them.

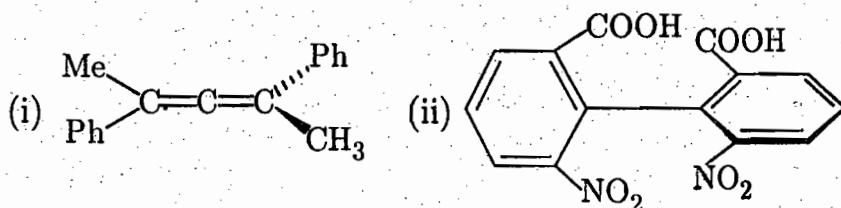


3. Identify H_A and H_B in each of the following structures as homotopic, enantiotopic or diastereotopic and explain.



[Hint : (i) Enantiotopic, (ii) Homotopic. See also the answer to Problem 2.6(f) and (z).]

4. Assign R/S configuration to the following compounds :



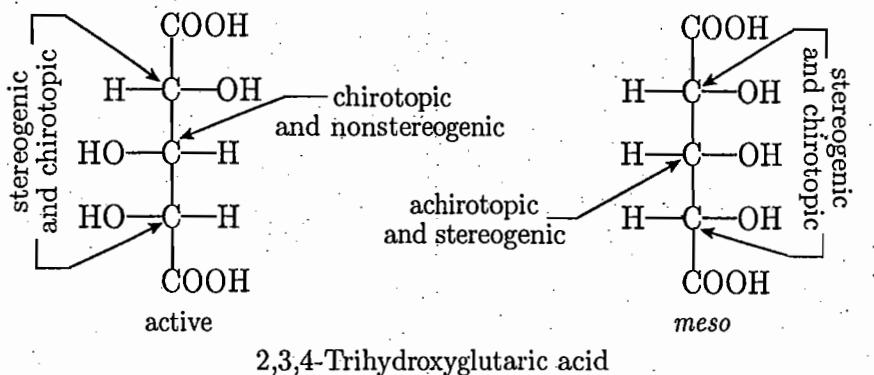
[Hint : (i) S (ii) R; See the answer to Problem 1.48.]

5. Give the principle of a method of resolution of racemic 2-butanol.

[Hint : See the answer to Problem 1.76(C).]

6. Explain the following terms with an example in each case : (i) Stereogenecity
(ii) Chirotopicity.

[Hint : Stereogenecity and chirotopicity are two distinct characters of an asymmetric atom. An atom within a molecular framework is said to be stereogenic if mutual change of any two groups on that atom generates a new stereoisomer. Stereogenic centres of a molecule may or may not be chiral, but all chiral centres are stereogenic. An atom within a molecular framework is said to be chirotopic if its site symmetry is chiral, i.e., the atom resides in a chiral environment (the atom must not lie on a σ -plane or on a centre of symmetry and no alternating axis of symmetry passes through it). The molecules bearing chirotopic centre need not be as a whole chiral. In fact, stereogenecity is dependent on disposition of bonds but chirotopicity is quite independent of it and is determined by local symmetry. For example, C-2 and C-4 of the following active and the *meso*-isomer of 2,3,4-trihydroxyglutaric acid are chirotopic and stereogenic. However, C-3 of the active isomer is chirotopic but nonstereogenic whereas C-3 of the *meso*-isomer is achirotopic but stereogenic. Therefore, stereogenecity and chirotopicity are two distinct properties of a centre and can be delinked.

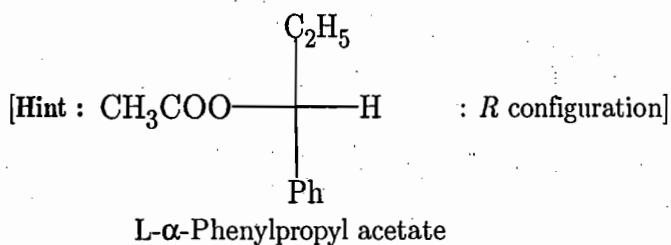


2006

- Convert (*S*)-2-pentanol to (*R*)-2-pentanol.

[Hint : (*S*)-2-Pentanol is to be treated with : (i) $p\text{-C}_6\text{H}_4\text{SO}_2\text{Cl}$ /pyridine (tosylation), (ii) CH_3COOK /acetone ($\text{S}_{\text{N}}2$) and $\text{KOH}/\text{H}_2\text{O}$ (hydrolysis).]

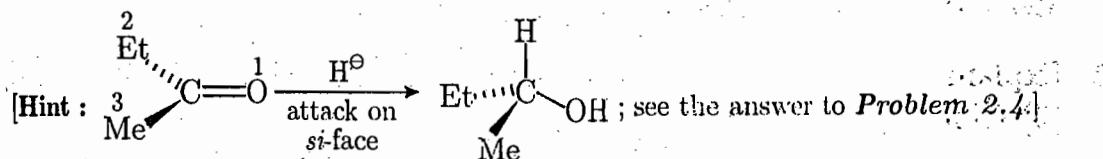
- Draw the Fischer projection formula of L- α -phenylpropyl acetate and assign (R/S) configuration to the chiral carbon atom.



- Explain the nature of stereoisomerism exhibited by the compounds of the formula $\text{XYC}=(\text{C}=\text{)}_n\text{CX}_2$, where $n = 1$ and 2.

[Hint : Optical isomerism, when $n = 1$ and geometric isomerism, when $n = 2$; see the answer to Problem 1.105.]

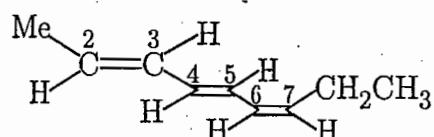
- Write the stereostructure of the alcohol obtainable by attack of hydride on 2-butanone from its *si*-face.



5. What do you mean by conformation and configuration? Explain with suitable examples.

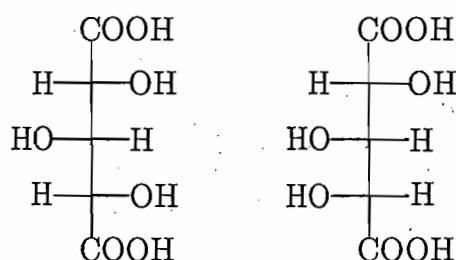
[Hint : See the answer to *Problem 1.5.*]

6. Establish the *E/Z* name of the following molecule.



[Hint : (2*E*,4*E*,6*Z*)- ; see the answer to *Problem 1.42(b).*]

7. Label the C-3 centres of the following molecules as stereogenic/nonstereogenic and chirotopic/achirotopic. Justify your answer.

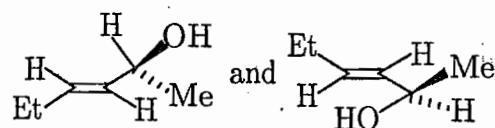
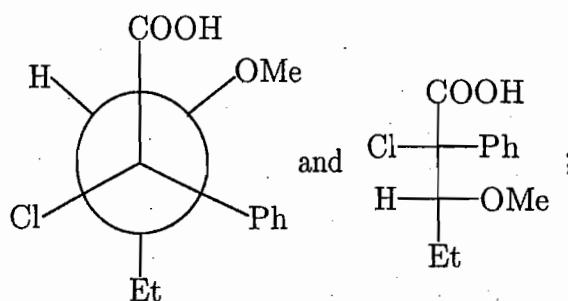


[Hint : See the answer to *Problem 1.25.*]

8. Draw all possible stereoisomers of $\text{CH}_3\text{CH}_2\text{CH}(\text{OH})\text{CH}=\text{CHCH}_2\text{CH}_3$ and designate them by (*R/S*) and (*E/Z*) rotations.

[Hint : See the answer to *Problem 1.79.*]

9. Label the following pairs of molecules as homomers, enantiomers, or diastereoisomers. Explain your answer.



[Hint : 1st pair : diastereoisomers; 2nd pair : enantiomers.]

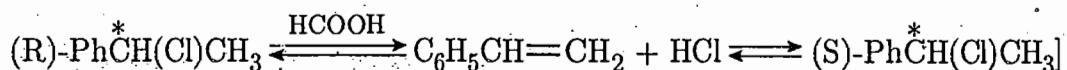
10. Discuss the principle of resolution of a racemic mixture of 2-ethylhexanoic acid.

[Hint : See the answer to *Problem 1.76(c).*]

2007

1. (*R*)-1-Phenylethylchloride racemises when it is dissolved in formic acid—Explain with mechanism.

[Hint : Racemisation occurs through the reversible formation of stable optically inactive intermediates.

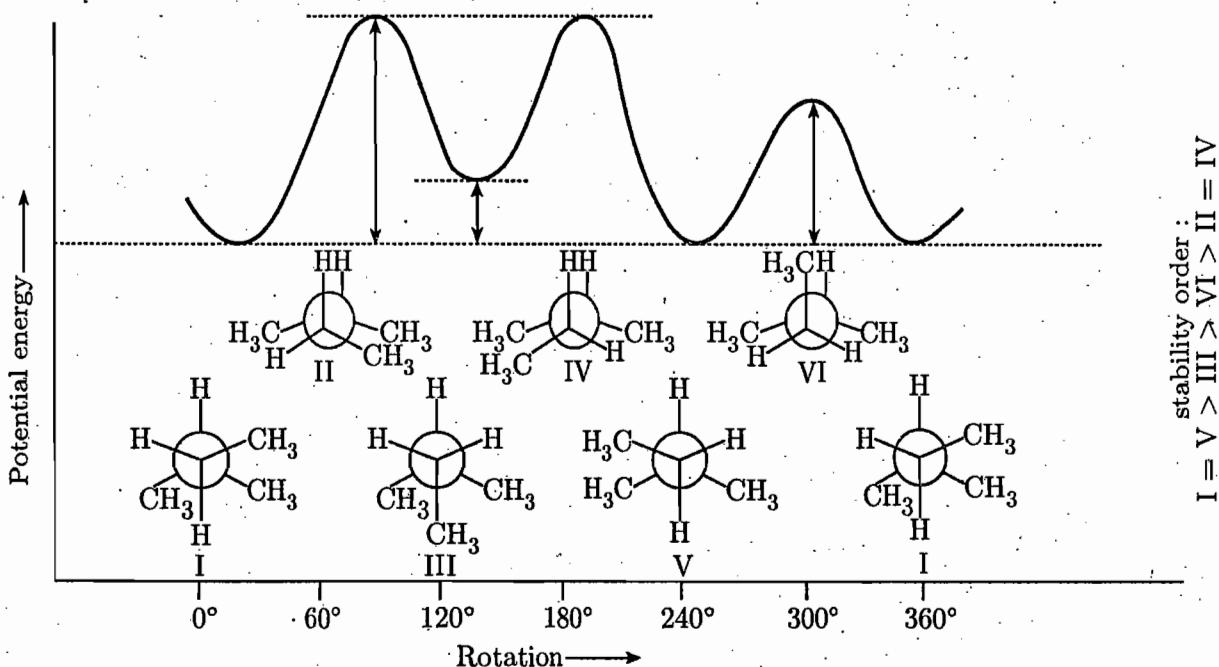


2. Draw the Newman projection formula of the most stable conformation of butane-1,4-diol and justify.

[Hint : The *anti* staggered conformation is the most stable one; See the answer to Problem 3.2(b).]

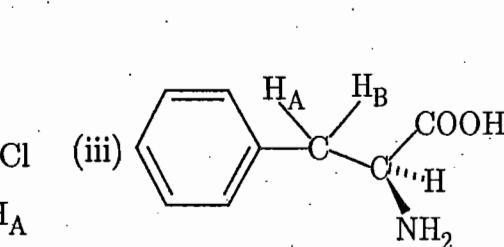
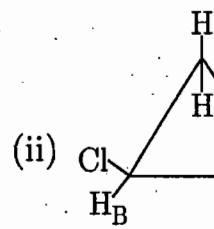
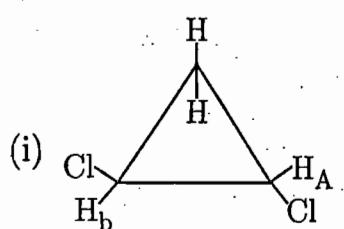
3. Draw the potential energy diagram of 2-methylbutane for rotation around C-2—C-3 bond showing the conformers. Explain the relative stabilities of the conformers.

[Hint :



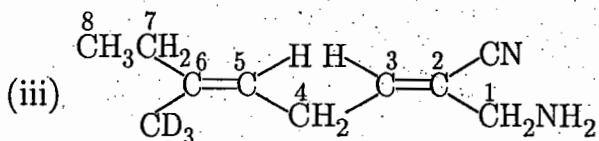
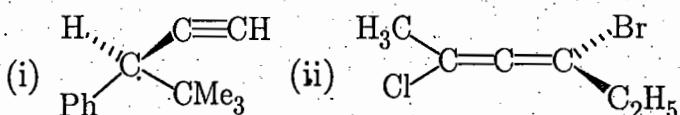
See also the answer to Problem 3.2(b).]

4. Identify H_A and H_B in each of the following structures as homotopic, enantiotopic and diastereotopic and explain.



[Hint : (i) homotopic (ii) enantiotopic (iii) diastereotopic.]

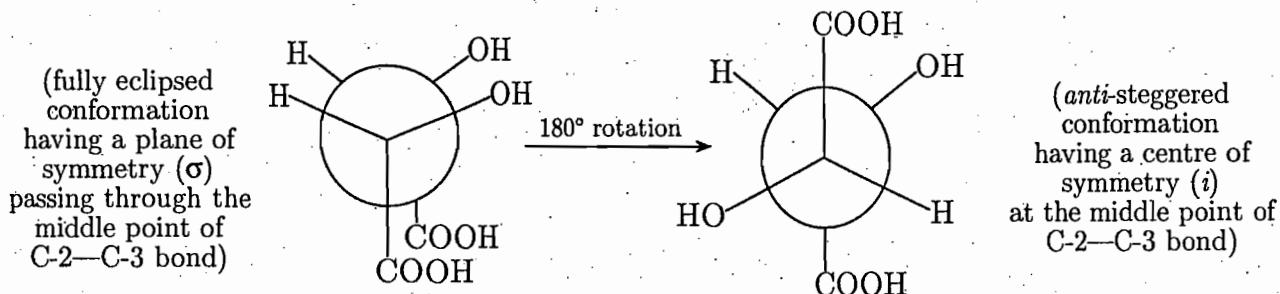
5. Assign *R/S* and *E/Z* configurations of the following compounds.



[Hint : (i) (*R*)- (ii) (*S*)- (iii). (*2E,5E*)-; see the answers to Problem 1.33, 1.48(a) and 1.42(b).]

6. Explain why *meso*-tartaric acid is optically inactive on the basis of Newman projections of its all possible conformers for rotation around C-2—C-3 bond.

[Hint : Due to having a plane and a centre of symmetry in different conformations, *meso*-tartaric acid is optically inactive.



See the answer to Problem 1.66(c).]

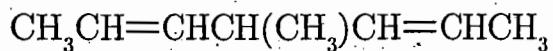
7. How would you resolve (\pm) -CH₃CH(OH)CH₂CH₃?

[Hint : See the answer to Problem 1.76(c).]

8. Give an example of a molecule possessing four-fold alternating axis of symmetry and explain.

[Hint : See the answer to Problem 1.12(l).]

9. Write all possible stereoisomers of the following compound and comment on their optical activity.



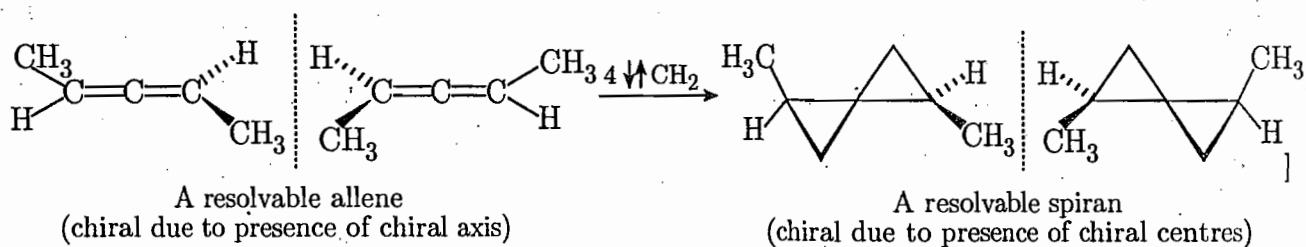
[Hint : See the answer to Problem 1.81(b)(ix).]

10. What is meant by 'enantiomeric excess' (ee)? The pure (+) enantiomer of a compound shows a specific rotation of +80°. Calculate the percentage of the (-)enantiomer of the same compound in a partially resolved sample showing a specific rotation of -20°.

[Hint : See the answer to *Problem 1.62(b) and (e)*.]

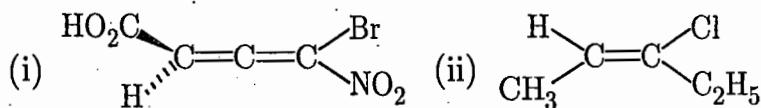
11. Draw the structures(s) of carbene addition product(s) of a resolvable allene. Would the product(s) be resolvable?—Justify.

[Hint :



2008

1. Write the *R/S* or *E/Z* configuration of the following compounds :



[Hint : (i) *R* and (ii) *E*; see the answers to *Problem 1.48(a)* and *1.42(b)*.]

2. Explain the stereoisomerism of 6,6'-dinitrodiphenic acid and draw the energy profile diagram for racemization of its enantiomers on heating. Label each maximum and minimum with appropriate rotamers.

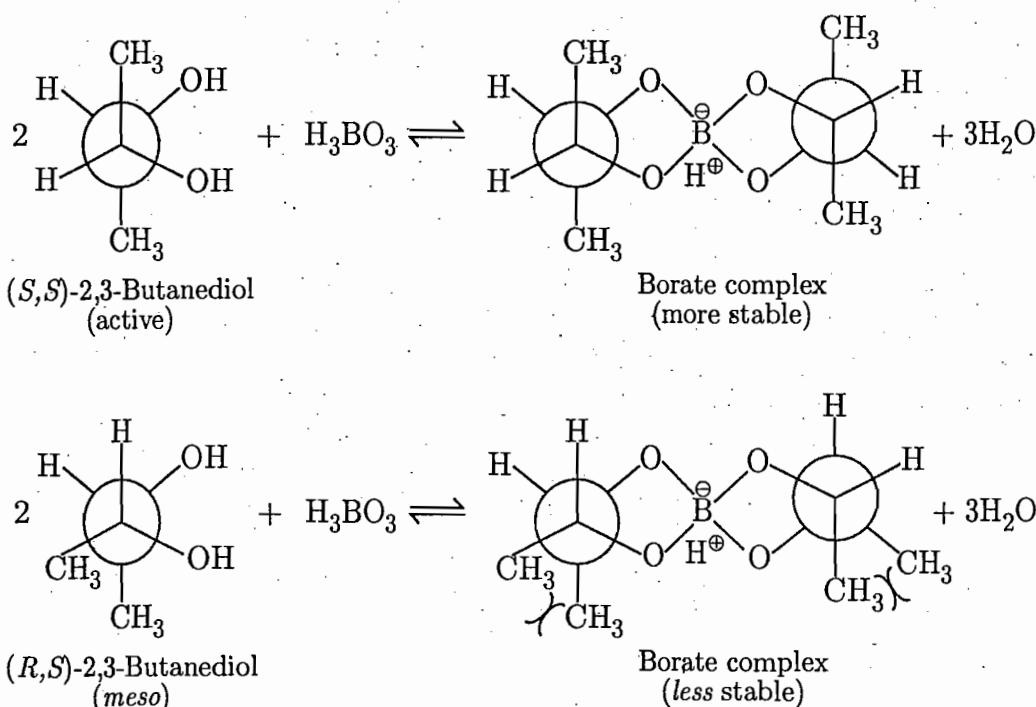
[Hint : See the answer to *Problem 1.108*.]

3. Explain : (i) Enantiotopic and (ii) Diastereotopic faces and ligands with appropriate examples.

[Hint : See the answer to *Problem 2.2*.]

4. What will be the change in conductivity of boric acid if (*R,R*)-2,3-butanediol, (*R,S*)-2,3-butanediol and (*S,S*)-2,3-butanediol are separately treated with boric acid? Explain your answer.

[Hint : The borate complex of an active isomer [(*R,R*)- or (*S,S*)-] is more stable than that of the *meso* isomer because in the former complex the methyl groups are *anti* (sterically more favoured), whereas in the latter complex the methyl groups are *gauche* (sterically less favoured). Therefore, the conversion of the active diol to the borate complex is more favourable than for the *meso* isomer. The conductivity of boric acid increases with increase in concentration of the complex. Thus, active 2,3-butanediol enhances the conductivity of the boric acid more than does the *meso* isomer.]



5. Both *meso*-tartaric acid and *dl*-tartaric acid are optically inactive. State the reasons of their optical inactivity. How can you distinguish between them?

[Hint : See the answer to **Problem 1.66(g)**.]

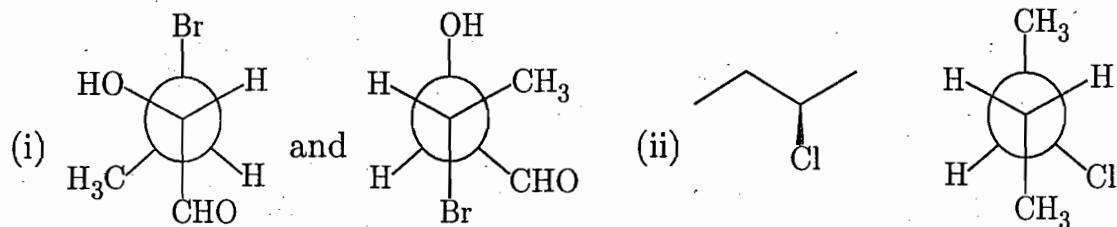
6. Draw the Fischer projection formulae for all the possible stereoisomers of 2,3,4-trihydroxyglutaric acid. Comment on the stereogenicity of C-3 centre in the active and the *meso* forms.

[Hint : See the answer to **Problem 1.82**.]

7. Indicate the symmetry elements present in CHCl_3 and $\text{HC}\equiv\text{CH}$.

[Hint : See the answers to **Problem 1.7** and **1.9**.]

8. Find the stereochemical relationship between the following pairs of compounds :

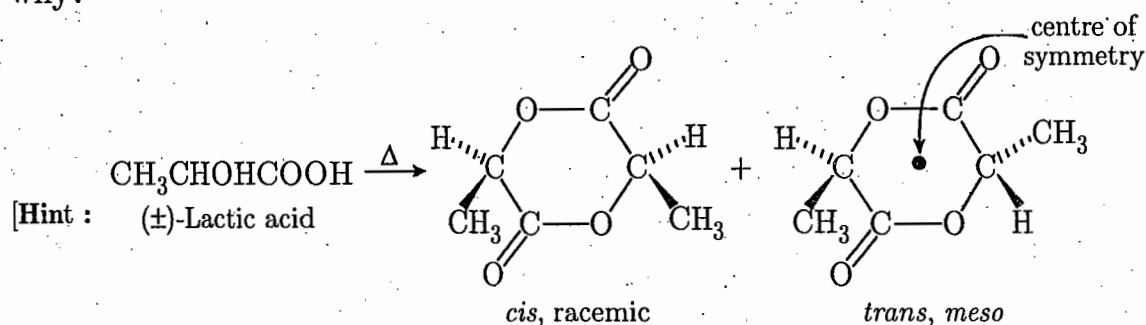


[Hint : (i) Diastereoisomers (ii) Homomers]

9. What is *gauche*-butane interaction. Mention the stable conformations of 1,2-dihydroxyethane, 1,2-dibromoethane and n-propyl chloride with proper justification.

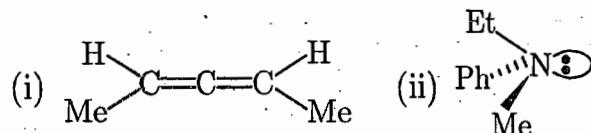
[Hint : See the answers to *Problem 3.2(c)* and *3.3(a)*.]

10. On heating two moles of (\pm)-lactic acid loses two moles of water to give two diastereomeric products of which one is resolvable and the other is not. Draw the structures of the diastereomeric products and indicate which is resolvable and why?



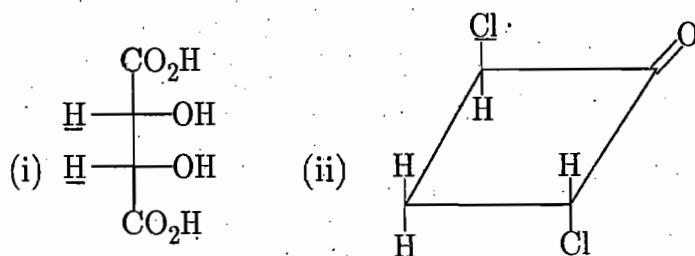
See the answers to *Problem 1.13*.]

11. Explain whether the following are resolvable or not.



[Hint : (i) resolvable (ii) not resolvable. See also the answers to *Problem 1.104(b)* and *1.63(a)*.]

12. Assign the indicated pair of atoms as homotopic, enantiotopic or diastereotopic and justify.

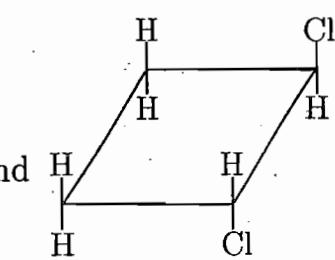
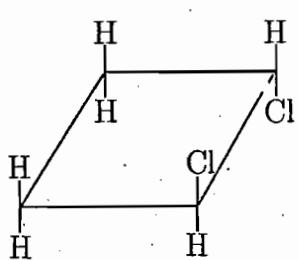
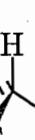
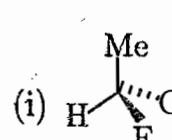


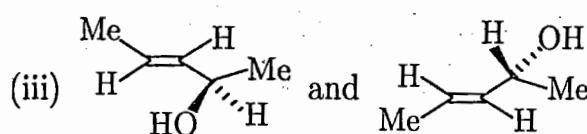
[Hint : (i) Enantiotopic, (ii) Homotopic. See the answer to *Problem 2.2*.]

13. Write Fischer projection formula of each diastereoisomer of 4-methylhex-2-ene. Assign R/S rotation to them.

[Hint : See the answer to *Problem 1.79(a)*.]

14. Label the following pairs of molecules as homomers, enantiomers, or diastereoisomers.

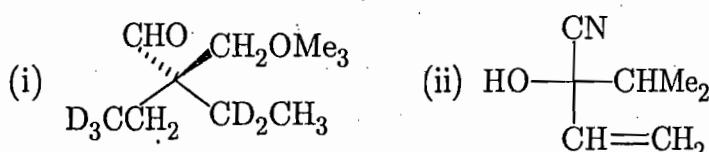




[Hint : (i) Homomers, (ii) Enantiomers, (iii) Homomers.]

2009

1. Designate R/s descriptor of the following compounds indicating priority sequence :

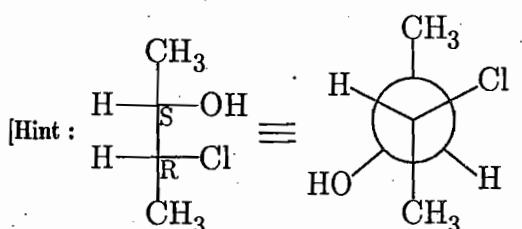


[Hint : (i) (S)- (ii) (S)-]

2. Indicate the symmetry elements present in (i) benzene (ii) dibromomethane.

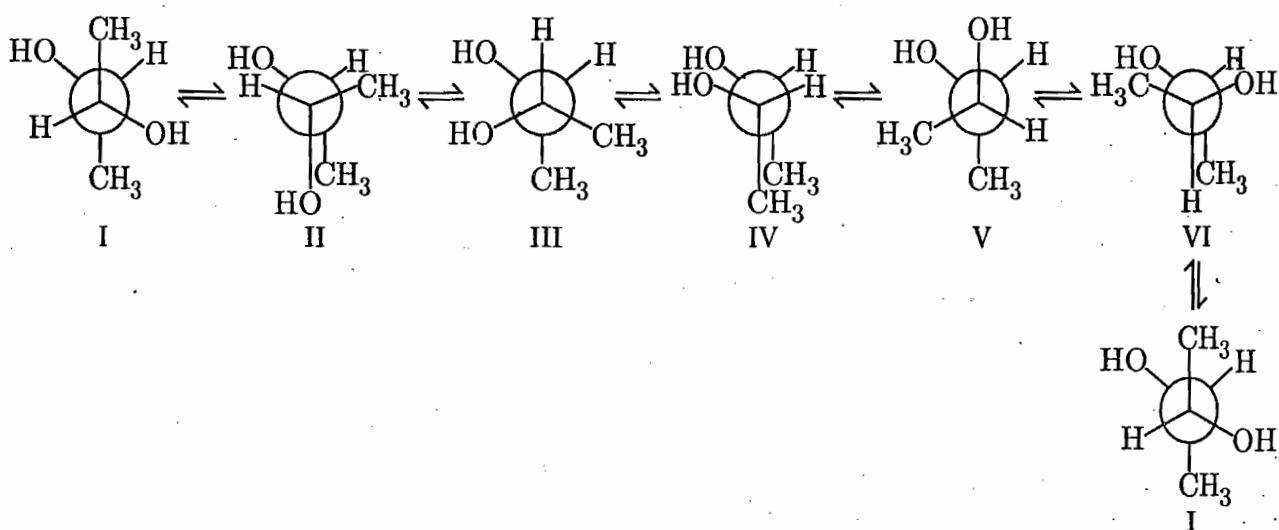
[Hint : See the answer to Problem 1.9]

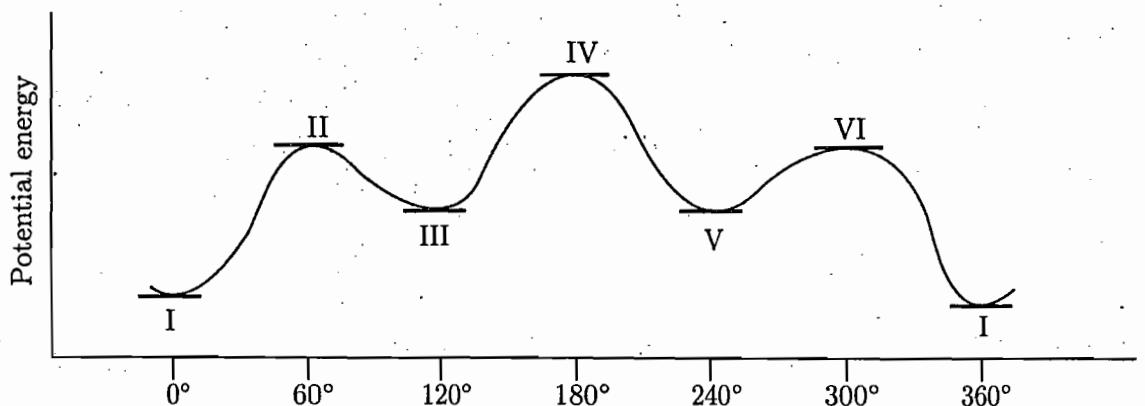
3. Draw the Fischer projection formula of (2S,3R)-3-chlorobutan-2-ol and convert it to Newman projection formula (any conformer).



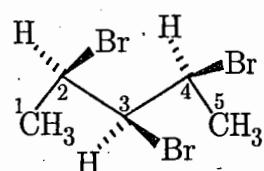
4. Draw the energy profile diagram for rotation around C₂—C₃ bond of *meso*-2,3-butane-diol with proper labelling.

[Hint :





5. Comment on the stereogenecity and chirotopicity of C-3 of the following structure : Rotation \rightarrow



[Hint : See the answer to Problem 1.25.]

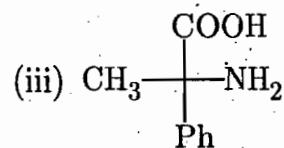
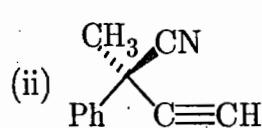
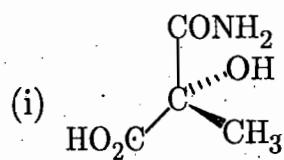
6. Comment on the chirality and optical activity of $\text{CH}_3\text{CH}_2\text{CH}_2\text{N}(\text{Me})\text{CH}_2\text{CH}_3$ and its corresponding N-oxide.

[Hint : The compound is chiral but it is found to be optically inactive due to 'pyramidal inversion'. Its N-oxide is chiral and optically active. In fact, the compound is not resolvable whereas its N-oxide is resolvable.

See also the answer to Problem 1.63.]

2010

1. Give R/S configurational descriptor of the following compounds. Mention the priority sequence of the ligands around the chiral centre (any two).



[Hint : (i) (S)-; -OH>-COOH>-CONH₂>-CH₃ (ii) (S)-; -CN>-Ph>-C≡CH>-CH₃ (iii) (R)-; -NH₂>-COOH>-Ph>-CH₃]

2. Draw the conformational energy diagram of n-butane for rotation around the C₂-C₃ bond. Show all the conformers and comment on their relative stabilities.

[Hint : See the answer to Problem 3.2(b).]

3. Indicate the symmetry elements present, if any, in each of the following molecules.

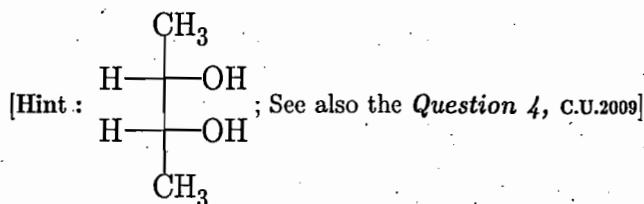
- (i) Staggered ethane (ii) (E)-1,2-dichloroethene

[Hint : (i) centre of symmetry (i); (ii) see the answer to Problem 1.12(j).]

4. Draw the Fischer projection formula of all the possible stereoisomers of $\text{CH}_3\text{CH}(\text{OH})\text{CH}=\text{CH}-\text{COOH}$ and designate any one isomer as R/s, E/z descriptors.

[Hint : See the answer to *Problem 1.79(a)*.]

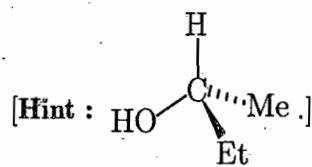
5. Write down the Fischer projection formula of Erythro-2,3-butandiol and present its most stable conformer in Newman projection with explanation.

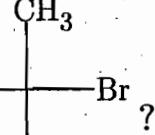


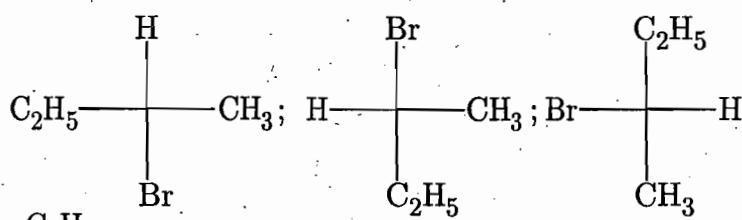
University of Burdwan

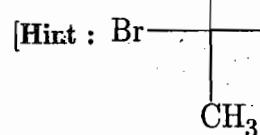
2001

1. Draw the three-dimensional representation of the *R* isomer of 2-butanol.



2. Which of the following is another Fischer projection formula of : ?

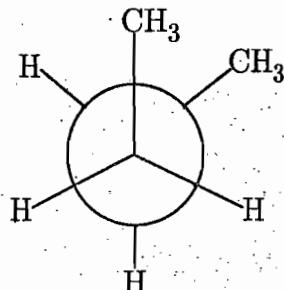


[Hint :  ; See the answer to *Problem 1.29*.]

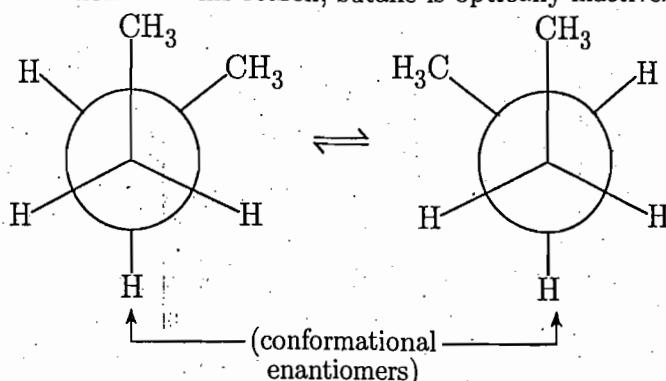
3. Draw the most stable conformation of *trans*-4-*tert*-butyl-1-methylcyclohexane.

[Hint : See the answer to *Problem 3.8(d) and (e)*.]

4. The following conformer of butane is chiral, then why is butane optically inactive?



[Hint : This conformer remains in rapid equilibrium with its enantiomeric conformer i.e., it remains as a racemic modification. For this reason, butane is optically inactive.]



5. What is the difference between conformer and stereoisomer?

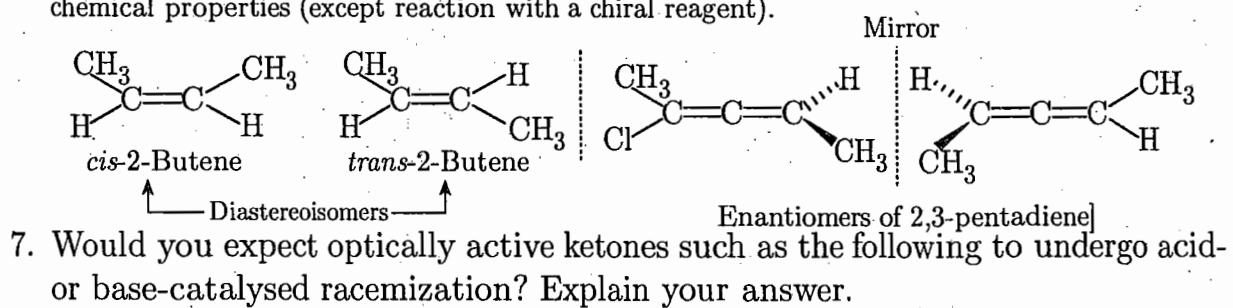
[Hint : Conformers are the different spatial arrangements of atoms or groups that arise owing to the rotation about a single bond of one part of the molecule with respect to the other part. On the other hand, stereoisomers are isomers that arise owing to different spatial arrangement of atoms or groups about a rigid part of the molecule (e.g., about an asymmetric carbon atom, a double bond etc.).]

Since the energy barrier to rotation about a single bond is very small, the different conformers are rapidly interconvertible and are nonisolable. Change from one stereoisomer to another involves breaking and making of bonds. Since this is a high-energy process stereoisomers maintain their identity and are isolable.

See also the answer to **Problem 1.5.**

6. Isomers of $\text{CH}_3\text{CH}=\text{CHCH}_3$ differ widely in chemical properties but those of $\text{CH}_3\text{CH}=\text{C}=\text{CHCH}_3$ do not—why?

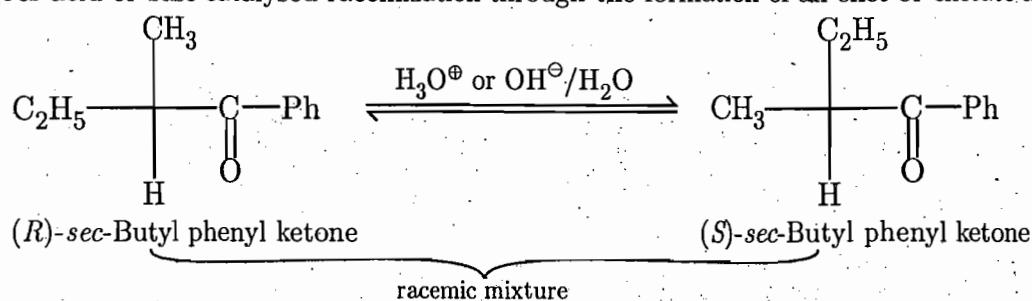
[Hint : Isomers of 2-butene ($\text{CH}_3\text{CH}=\text{CHCH}_3$) are geometric isomers, i.e., they are diastereoisomer and because of this, they differ widely in chemical properties. On the other hand, isomers of 2,3-pentadiene ($\text{CH}_3\text{CH}=\text{C}=\text{CHCH}_3$) are enantiomers and because of this, they do not differ in chemical properties (except reaction with a chiral reagent).]



7. Would you expect optically active ketones such as the following to undergo acid- or base-catalysed racemization? Explain your answer.

- (R)-sec-butyl phenyl ketone
- (R)-neopentyl phenyl ketone

[Hint : (i) Since the asymmetric carbon in (R)-sec-butyl phenyl ketone ($\text{C}_2\text{H}_5\text{CH}(\text{CH}_3)\text{COPh}$) is adjacent to the carbonyl group, the hydrogen attached to it is acidic. Because of this, the compound undergoes acid or base catalysed racemization through the formation of an enol or enolate anion.]



See also the answer to **Problem 1.71(c)**.

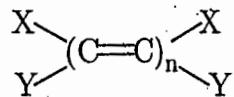
(ii) Neopentyl phenyl ketone is optically inactive. Therefore, the question is incorrect.]

8. Draw one active and one *meso* isomer of $\text{HOOC}(\text{CHOH})_3\text{COOH}$ in Fischer's projection formula. Will the interchange of H and OH at C-3 of the active stereoisomer you have drawn lead to another stereoisomer? What will happen if H and OH is interchanged at C-3 of the *meso* isomer you have drawn? Explain stating whether C-3 is a stereogenic centre in each case.

[Hint : See the answer to **Problem 1.82**.]

2002

1. What are the conditions for the following molecules to be optically active?

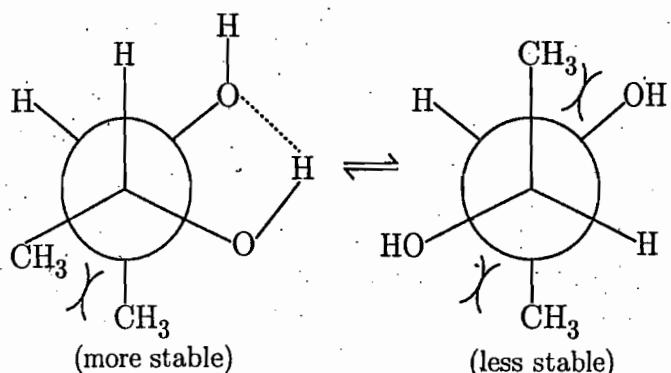
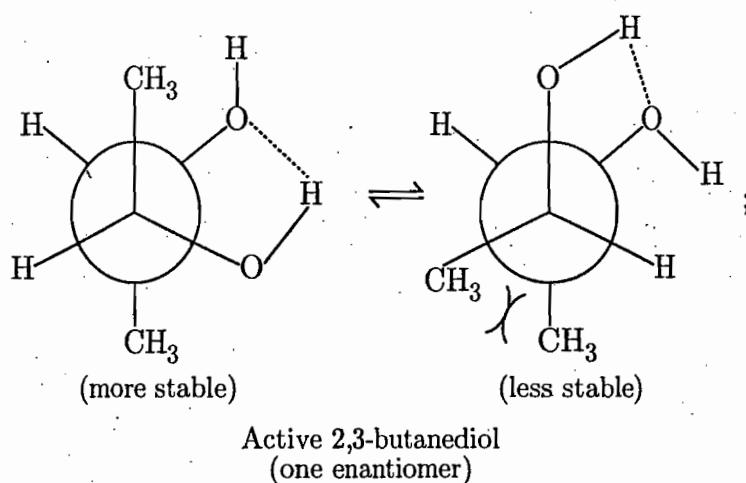


[Hint : The molecules will be optically active if $X \neq Y$ and n is even (2,4,6,.....etc.).]

See also the answer to **Problem 1.105**.]

2. Draw the Newman projection formulae of 2,3-butanediols in their most stable conformations.

[Hint :



meso-2,3-Butanediol

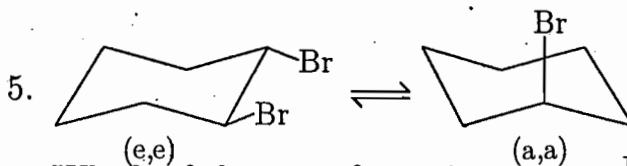
See also the answer to **Problem 3.3(a)**.]

3. Draw the two possible conformations of $\text{CH}_2=\text{CH}-\text{CH}=\text{CH}_2$. Name them and point out the more stable conformation.

[Hint : See the answer to *Problem 3.3(b)*.]

4. Draw structures for the equilibrating chair conformations of *cis*- and *trans*-1,2-dimethylcyclohexanes. Point out the most stable conformer.

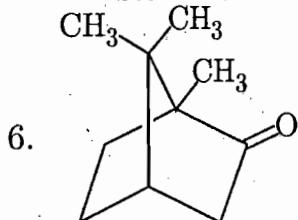
[Hint : See the answer to *Problem 3.13(a)*.]



Which of these conformations is more stable in methanol (CH_3OH) and in *n*-octane?

[Hint : In nonpolar solvent *n*-octane, the diequatorial form, although favoured sterically is destabilized by dipole repulsion ($\text{C}\leftrightarrow\text{Br}$ dipoles are *gauche* to each other). Consequently, the diaxial form is more stable. On the other hand, in polar solvent methanol, the dipole repulsion in the diequatorial form is minimized by the intermolecular dipole-dipole attraction. Therefore, the sterically favoured diequatorial conformer is more stable in methanol.]

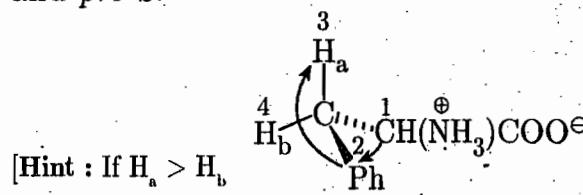
See also the answer to *Problem 3.9(f)*.



How many stereoisomers of this compound would you expect (mathematically speaking) to have? Only two of them are actually isolated. Why?

[Hint : See the answer to *Problem 1.84(b)*.]

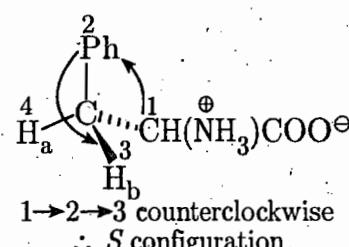
7. $\text{PhCH}_2-\overset{\oplus}{\text{CH}}(\text{NH}_3)\text{COO}^\ominus$ has two diastereotopic ligands. Label them as *pro-R* and *pro-S*.



; If $\text{H}_b > \text{H}_a$

1→2→3 clockwise

∴ R configuration



1→2→3 counter-clockwise

∴ S configuration

Therefore, H_a is designated as *pro-R* and H_b as *pro-S*. See also the answer to *Problem 2.3(a)*.

8. Give example of a biphenyl which may be optically active despite having the same substituents at the 2,6 or 2',6'-positions.

[Hint : See the answer to *Problem 1.108(h)*.]

9. $\text{PhCHO} + \text{HCN} \rightarrow (\pm)\text{-A}$

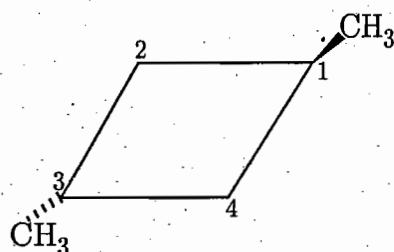
Give a method to prove that (+)-A and (-)-A are produced.



The racemic hydroxyacid (obtained on hydrolysis of racemic cyanohydrin) can be resolved (separated into two pure enantiomers) by forming diastereoisomeric salt. The observation suggests that $(+)$ -A and $(-)$ -A are produced.]

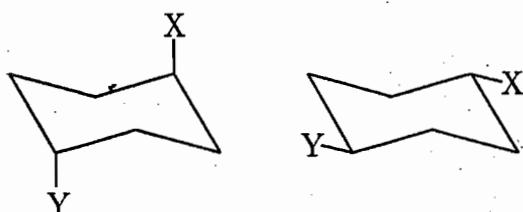
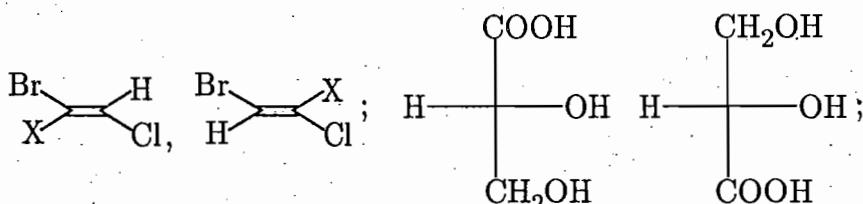
2003

- How many simple C_2 -axis of symmetry are present in :



[Hint : Only one C_2 -axis passing through C-2 and C-4.]

- Designate the following pairs of compounds as diastereoisomers/enantiomers/geometrical isomers etc :



[Hint : 1st pair : constitutional isomers; 2nd pair : enantiomers and 3rd pair : conformational diastereoisomers (the two structures can be interconverted by ring-flip).]

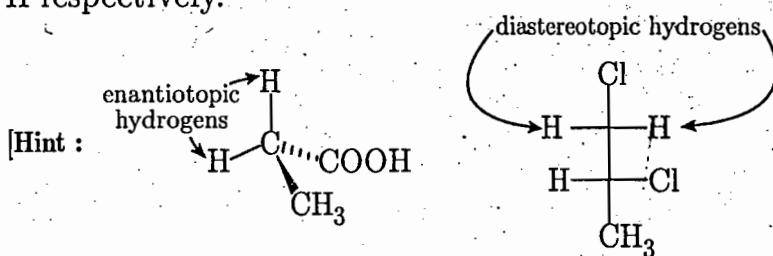
- Draw the three-dimensional representation of the R-isomer of 2-butanol.

[Hint : See Question 1, B.U. 2001.]

- Show why cyclohexyne cannot exist.

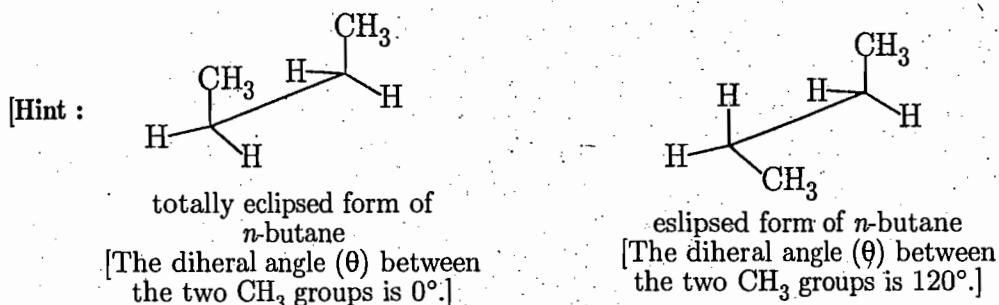
[Hint : The linear structural unit $-\text{C}=\text{C}\equiv\text{C}-\text{C}-$ cannot be bridged with only two carbon atoms. For this reason, cyclohexyne cannot exist.]

5. Write the configurations of two molecules having enantiotopic H and diastereotopic H respectively.



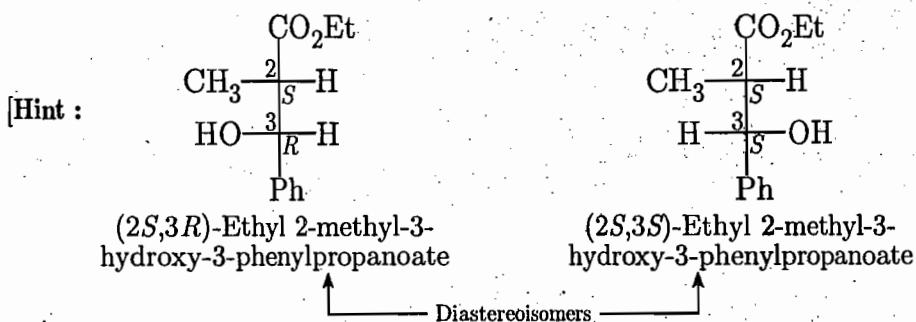
See also the answer to *Problem 2.2(b) and (c)*.

6. Draw the sawhorse-wedge projections for the two eclipsed forms of *n*-butane. What is the dihedral angle between the Me's in the two forms?



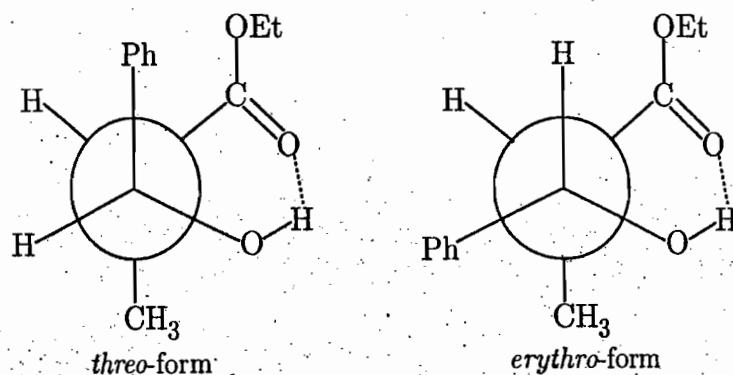
See also the answer to *Problem 3.2*.

7. Draw the structures of two diastereoisomers having the configurations (2*S*,3*R*) and (2*S*,2*S*) of ethyl 2-methyl-3-hydroxy-3-phenylpropanoate. How can you assign these isomers as *erythro*- and *threo*-forms? How can you predict the preferred conformations for these isomers.



The (2*S*,3*R*) diastereoisomer is the *threo*-form and the (2*S*,3*S*) diastereoisomer is the *erythro*-form.

The intramolecularly hydrogen-bonded conformations are the preferred conformations for these isomers.



See also the answer to *Problems 1.40(c) and 1.46*.

8. Draw the most stable conformation of *cis*-1,4-di-*t*-butylcyclohexane and account for its stability. How many planes of symmetry are there in the molecule?

[Hint : See the answer to *Problem 3.8(f)*. The (e,a)-conformation has one plane of symmetry (passing through C-1 and C-4), whereas the twist-boat conformation has no plane of symmetry.]

2004

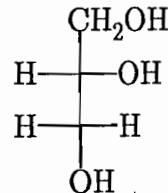
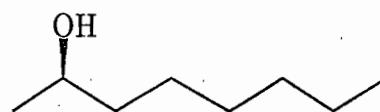
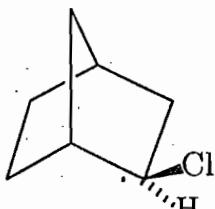
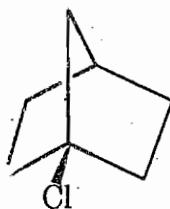
1. Draw the structure of a molecule with a centre of symmetry.

[Hint : See the answer to *Problem 1.7*]

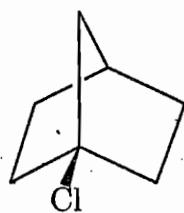
2. Draw the structures for the equilibrating chair conformations of *cis*- and *trans*-1,2-dimethylcyclohexane. Which of them is most stable?

[Hint : See the answer to *Problem 3.13(a)*.]

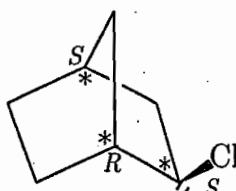
3. Identify the chiral and achiral molecules in the following and designate the carbon of stereogenic centre (if any) as *R*- and *S*- :



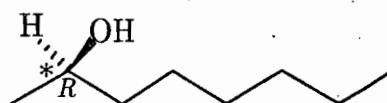
[Hint :



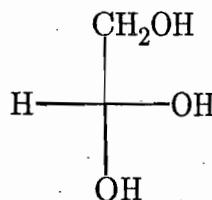
An achiral molecule
(it has a plane of symmetry)



A chiral molecule



A chiral molecule

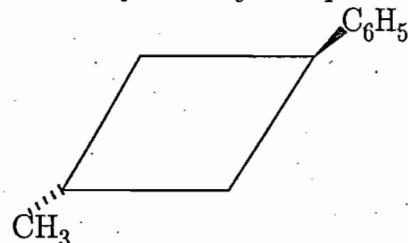


An achiral molecule
(it has a plane of symmetry)

See the answer to *Problem 1.38(n) and (p)*.

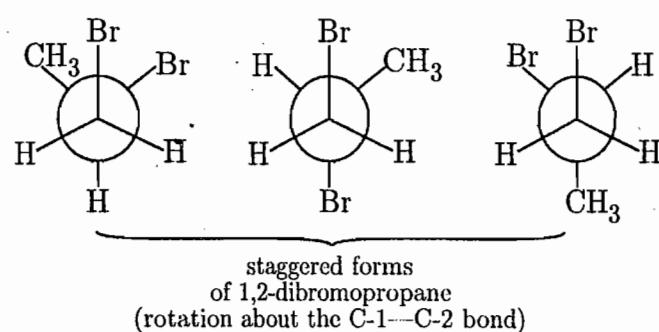
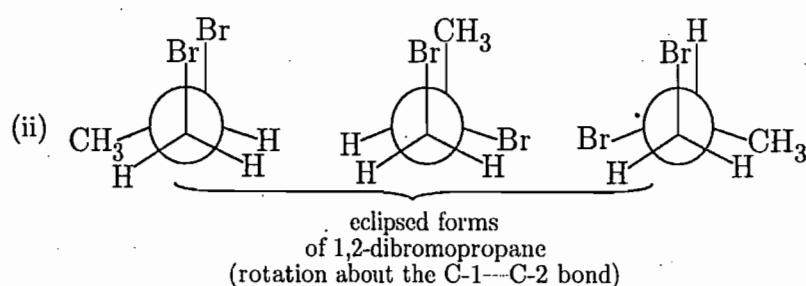
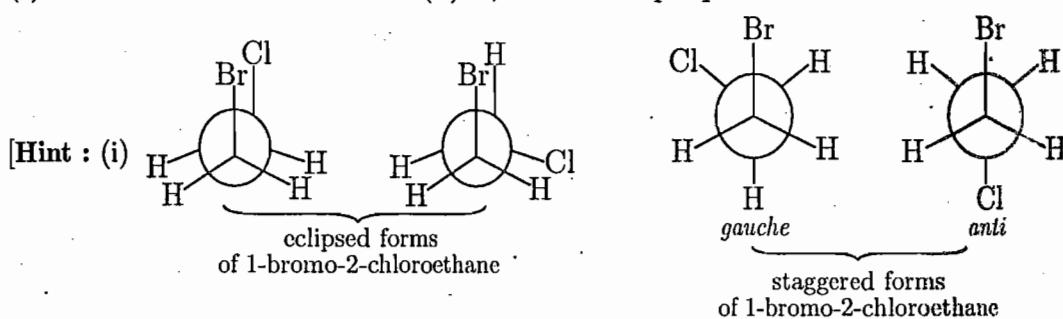
2005

1. How many simple C_2 -axis of symmetry are present in the following molecule?



[Hint : No C_3 -axis of symmetry is present.]

2. Draw the Newman projection formula for the eclipsed and staggered forms of :
 (i) 1-bromo-2-chloroethane (ii) 1,2-dibromopropane



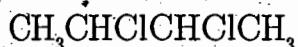
3. What do you mean by 'dihedral angle'?

[Hint : See the answer to *Problem 3.1(a)*.]

4. A sample of 2-methyl-1-butanol {R + form; $[\alpha]_D^{25} = +5.756^\circ$ } has a specific rotation, $[\alpha]_D^{25}$ equal to $+1.151^\circ$.
 (i) What is the % enantiomeric excess of the sample? (ii) which enantiomer is in excess, the (R) or the (S)?

[Hint : (i) ee = OP = $\frac{1.151}{5.756} \times 100\% = 20\%$ with respect to (+)-enantiomer. (ii) (R)-enantiomer]

5. Write three dimensional formulas for all the stereoisomers of the following compound and label the pair of enantiomers and the meso compound :



[Hint : See the answer to *Problem 1.80(a)*.]

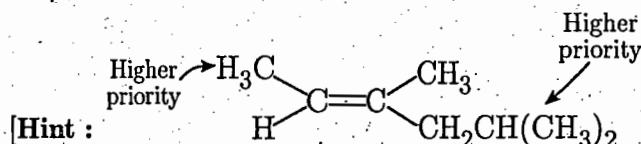
6. What is meant by chirotopicity?

[Hint : See the answer to *Question 6, C.U. 2005*.]

2006

(New regulation)

1. Write structure of the following : (*E*)-3,5-dimethyl-2-hexene.



(*E*)-3,5-Dimethyl-2-hexene

See also the answer to *Problem 1.42(b)*.

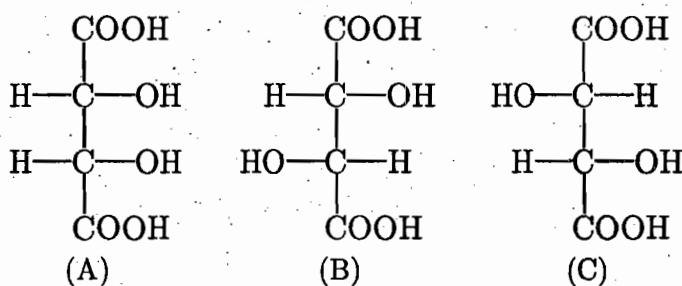
2. Which of the following compounds will exhibit geometrical isomerism?

- (i) Butene-1 (ii) Butene-2

[Hint : Butene-2 ($\text{CH}_3\text{CH}=\text{CHCH}_3$) will exhibit geometrical isomerism.

See also the answer to *Problem 1.77(c)*.

3. Designate what pairs of the following compounds are enantiomers, diastereoisomers.



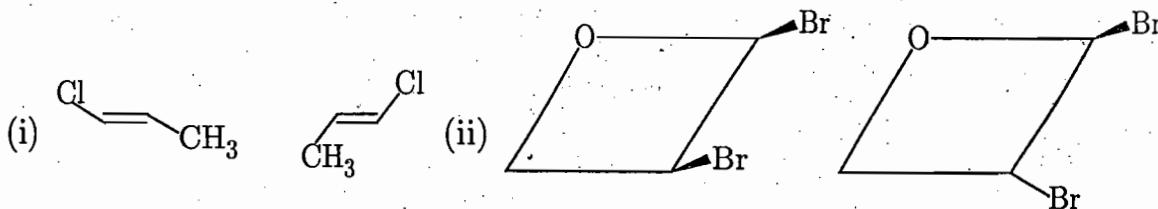
[Hint : (B) and (C) \rightarrow Enantiomers; (A) and (B) \rightarrow Diastereoisomers; (A) and (C) \rightarrow Diastereoisomers.

See also the answer to *Problem 1.80(b)*.

4. Draw the two possible conformations of $\text{CH}_2=\text{CH}-\text{CH}=\text{CH}_2$. Name them and point out the more stable conformation.

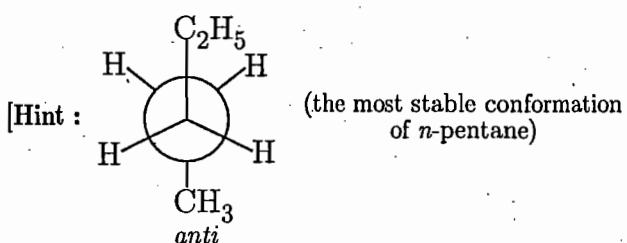
[Hint : See the answer to *Problem 3.3(b)*.]

5. Label the following pairs correctly (Enantiomers/Homomers/Diastereoisomers)



[Hint : (i) Homomers; (ii) Diastereoisomers. See also the answer to Problem 1.97.]

6. Write the most stable conformation of *n*-pentane (in Newman projection formula).



See also the answer to Problem 3.2(b).]

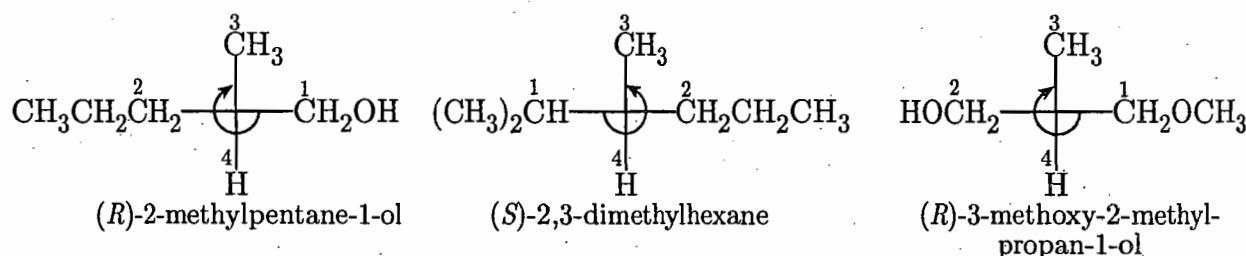
7. Draw the Fischer projection formulae for

(*R*)-2-methylpentane-1-ol

(*S*)-2,3-dimethylhexane

(*R*)-3-methoxy-2-methylpropane-1-ol

[Hint :



See also the answer to Problem 1.40.]

8. Check which of the following compounds are chiral? (i) 1-chloropentane (ii) 1-chloro-2-methylpentane (iii) 2-chloro-2-methylpentane (iv) 4-chloro-2-methylpentane.

[Hint : (i) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl}$ (achiral) (ii) $\text{CH}_3\text{CH}_2\text{CH}_2\overset{*}{\text{CH}}(\text{CH}_3)\text{CH}_2\text{Cl}$ (chiral) (iii) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CCl}(\text{CH}_3)_2$ (achiral) (iv) $\text{CH}_3\text{CHClCH}_2\text{CH}(\text{CH}_3)_2$ (chiral).]

See also the answer to Problem 1.23(b).]

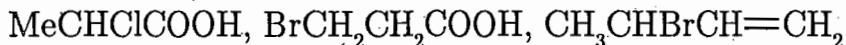
9. An optically pure sample of (*R*)-(−)-2-butanol shows a specific rotation of -13.6° . What relative molar proportion of (*S*)-(+) -2-butanol and (*R*)-(−)-2-butanol would give a specific rotation of $+6.8^\circ$.

[Hint : $\text{OP} = \frac{+6.8}{+13.6} \times 100\% = 50\%$ [with respect to the (+)-enantiomer]]

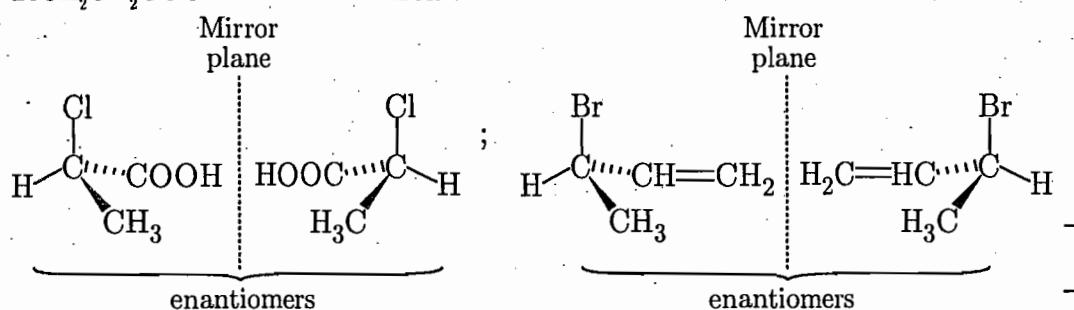
So, 50% of the mixture consists of (+)-enantiomer and 50% is the racemic modification. The total of (+)-enantiomer is thus $(50\% + \frac{50}{2}\%)$ or 75% and remaining 25% in the (-)-enantiomer. Therefore, the relative molar proportion (ratio) of (+)-2-butanol and (-)-2-butanol that would give a specific rotation of $+6.8^\circ$ is 75 : 25 or 3 : 1.

See also the answer to *Problem 1.62.*

10. Draw all possible stereoisomers for :

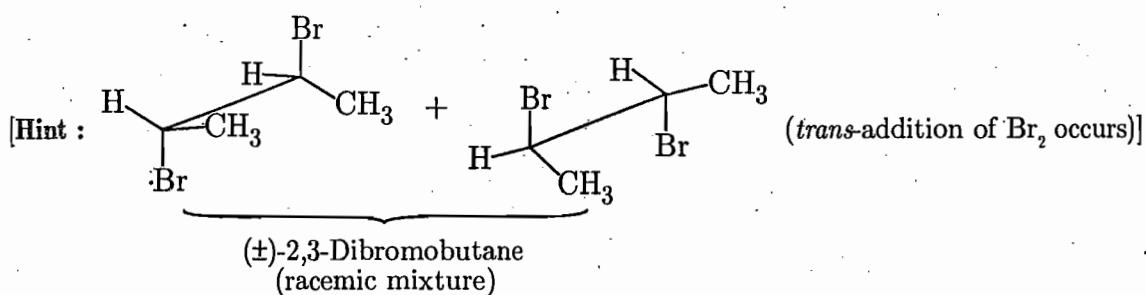
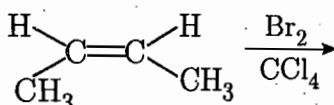


[Hint : Each of MeCHClCOOH and $\text{CH}_3\text{CHBrCH}=\text{CH}_2$ exists as two enantiomers, but $\text{BrCH}_2\text{CH}_2\text{COOH}$ has no stereoisomer.]

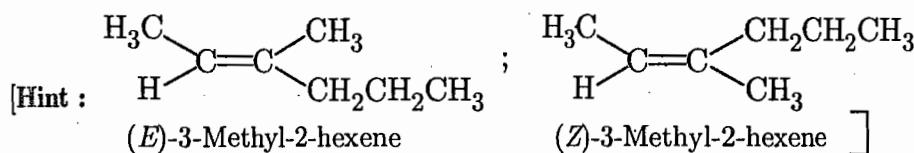


2006
(Old regulation)

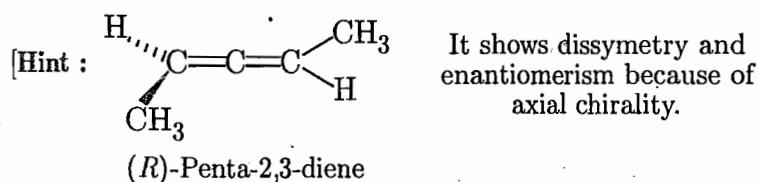
1. In the following reaction which will be the product—



2. Draw the *E*- and *Z*-form of 3-methyl-2-hexene.



3. Give an example of an optically active compound having no chiral atom. Why does it show dissymmetry or chirality and enantiomerism?

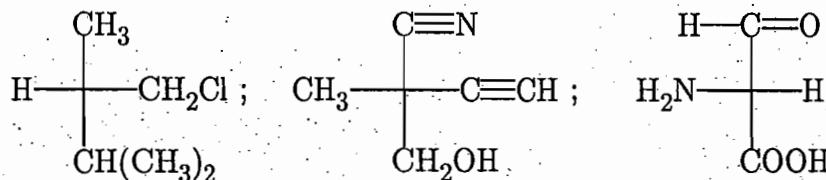


See the answer to *Problem 1.102.*

4. Draw the structures for equilibrating chair conformations of *cis*- and *trans*- 1,2-dimethylcyclohexane. Which of them is most stable?

[Hint : See the answer to Problem 3.13(a).]

5. Identify each of the following as *R* or *S*:

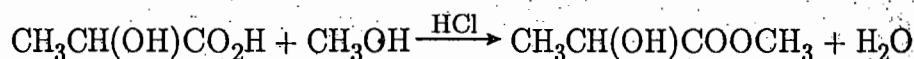


[Hint : (*S*), (*S*) and (*R*) respectively.]

6. What is the simplest alkane that is optically active?

[Hint : 3-Methylhexane ($\text{CH}_3\text{CH}_2\text{CH}_2^*\text{CHCH}_3\text{C}_2\text{H}_5$)]

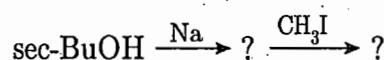
7. Esterification of (-)-lactic acid with methanol gives (+)-methyl lactate :



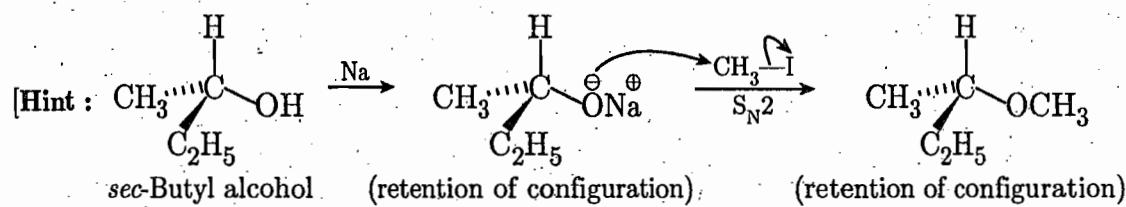
Has the configuration changed?

[Hint : The configuration is not changed (even though the sign of rotation changes) because there is no changing of bonds to the chiral carbon.]

8. The starting material is an optically active form of sec-BuOH and it is subjected to the following reactions :



Complete the equation and state the configuration of the each product.



There is no changing of bonds to chiral C in both the steps.]

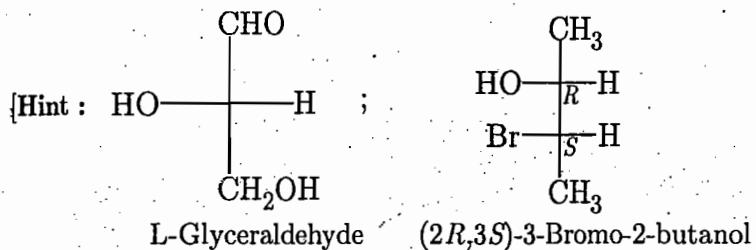
9. $\text{PhCH}_2\text{CH}(\text{NH}_3^+)\text{CO}_2^-$ has two diastereotopic ligands. Label them as *pro-R* and *pro-S*.

[Hint : See the answer to Question 7, B.U. 2002.]

2007
(New regulation)

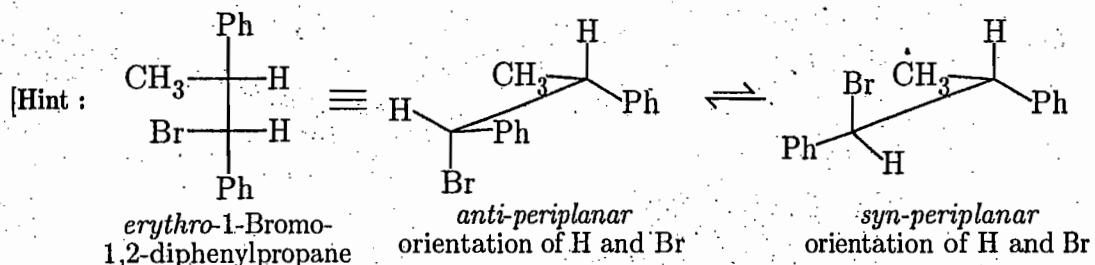
1. Draw the structures for the following compounds :

(L)-Glyceraldehyde, (2*R*,3*S*)-3-Bromo-2-butanol.



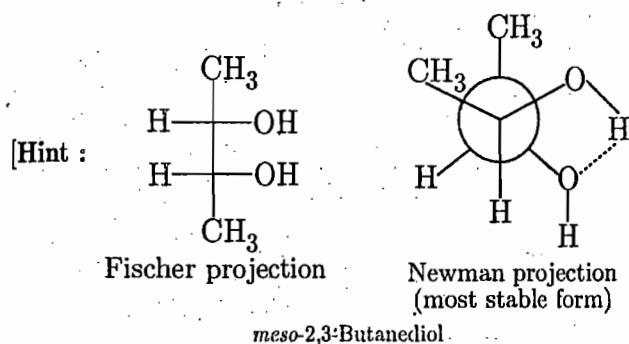
See also the answer to *Problem 1.32 and 1.33.*

2. Draw the *synperiplanar* and *antiperiplanar* conformations of a suitable organic molecule.

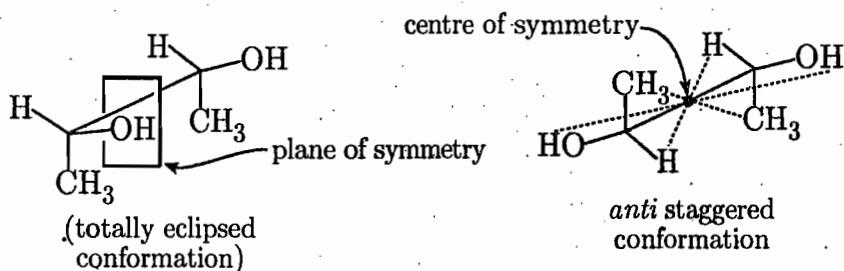


See also the answer to *Problem 3.4*.

3. Draw *meso*-2,3-butanediol in Fischer projection and Newman representation (most stable form)? State the elements of symmetry in this molecule.



There is a plane of symmetry in the totally *eclipsed* conformation and a centre of symmetry in the *anti* staggered conformation.



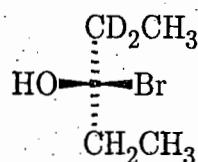
4. Draw all the stereoisomers of 3-bromo-2-pentanol and designate them as enantiomer, diastereoisomer.

[Hint : See the answer to *Problem 1.80(b).*]

5. Discuss a method for resolution of a racemic alcohol.

[Hint : See the answer to *Problem 1.76(c).*]

6. Designate the following compound in the *R/S* system :

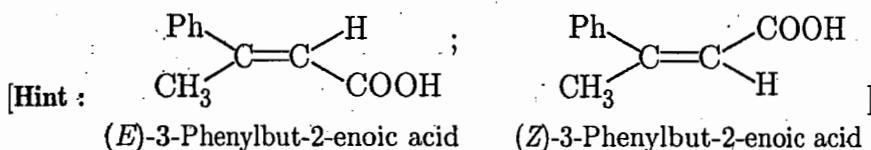


What would be the IUPAC name of the above compound.

[Hint : (*R*)-3-Bromo-2,2-dideuteropentan-3-ol.]

2007
(Old regulation)

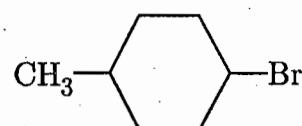
1. Draw the *E*- and *Z*-form of 3-phenylbut-2-enoic acid.



2. Of the possible structures for the molecular formula $\text{C}_5\text{H}_{11}\text{Br}$, how many are optically active?

[Hint : Only two of them are optically active : $\text{CH}_3\text{CH}_2\text{CH}_2^*\text{CHBrCH}_3$ and $(\text{CH}_3)_2\text{CHCH}^*\text{BrCH}_3$.]

3. How many active forms are possible for the following compound :



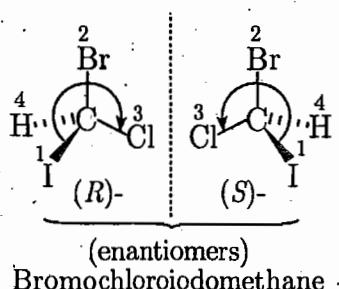
- (i) 2, (ii) 4, (iii) 8, (iv) None of these.

[Hint : (iv); It is an achiral molecule with a plane of symmetry passing through C-1 and C-4.]

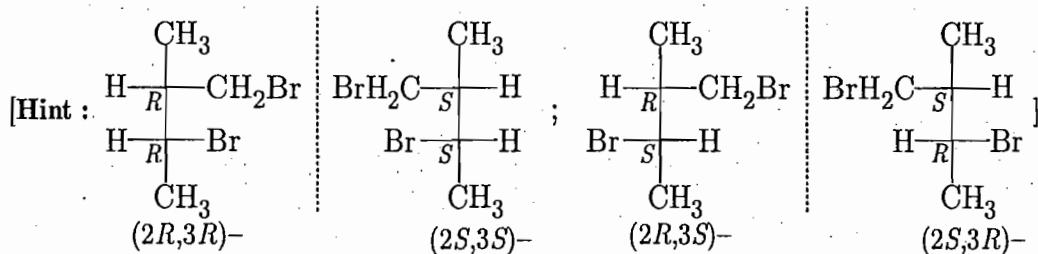
4. How many stereoisomers are possible for bromochloroiodomethane? Draw their three-dimensional structures and label as *R* and *S*.

[Hint : Bromochloroiodomethane contains only one asymmetric C atom.

Therefore, only two stereoisomers are possible for this compound.



5. Give the *R/S* designation of each of the stereoisomers of 1,3-dibromo-2-methylbutane.

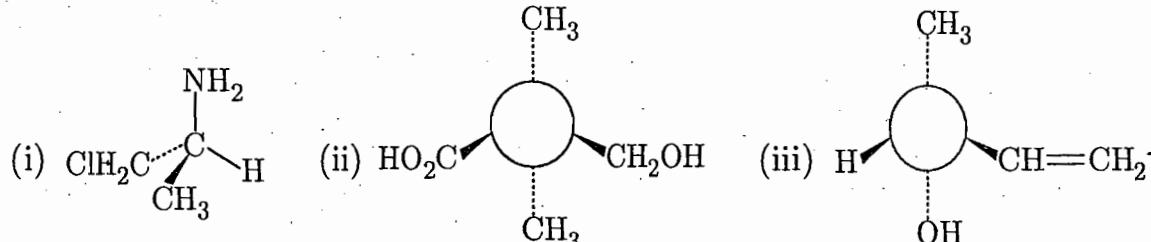


2008
(New regulation)

1. What do you mean by 'stereogenic centre'? Give three essential conditions for optical isomerism.

[Hint : See the answers to Problem 1.16 and 1.63(a).]

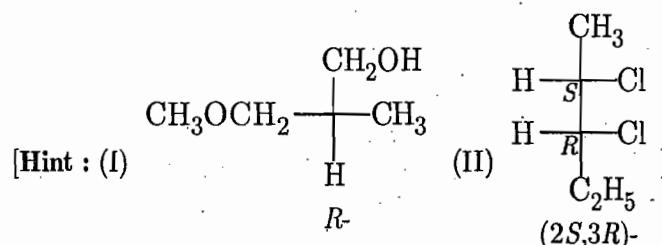
2. Assign *R* and *S* designations to the following compounds :



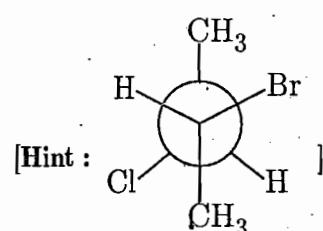
[Hint : (i) *S*- (ii) the molecule is not chiral, (iii) *R*-]

3. Draw the Fischer projection formulae for :

(I) (*R*)-3-methoxy-2-methylpropan-1-ol, (II) (*2S,3R*)-2,3-dichloropentane.

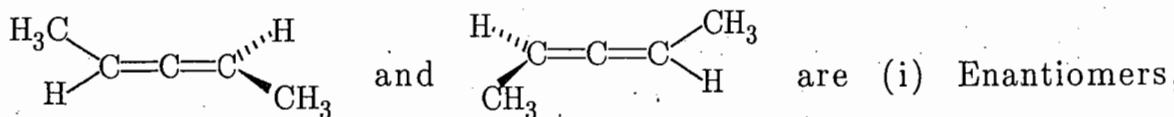


4. Draw the Newmann conformation of *erythro*-2-bromo-3-chlorobutane.



2008
(Old regulation)

1. The following molecules



- (ii) Diastereoisomers, (iii) Structural isomers, (iv) None of these. Which is appropriate?

[Hint : The molecules are enantiomers.]

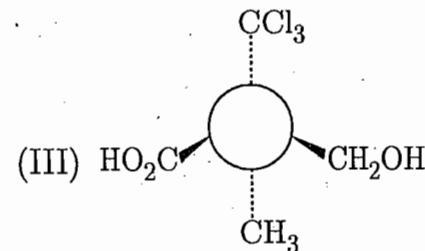
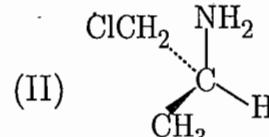
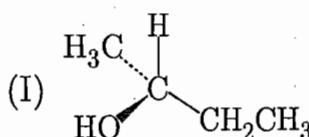
2. The method of designating absolute configuration of asymmetric carbon atom is
(i) R,S, (ii) D,L, (iii) (+), (-).

[Hint : R,S]

3. Which of the following compounds will exhibit geometrical isomerism :
(i) Butene-1, (ii) Butene-2.

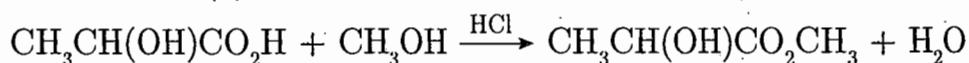
[Hint : Butene-2 ($\text{CH}_3\text{CH}=\text{CHCH}_3$)]

4. Assign R and S designations to the following compounds :



[Hint : (I) $\Rightarrow R$; II $\Rightarrow S$; (III) $\Rightarrow S$]

5. Esterification of (-) lactic acid with methanol gives (+)-methyl lactate :



Has the configuration changed? Explain.

[Hint : Since the bond to the asymmetric carbon is not broken in this esterification reaction, the configuration remains unchanged.]

6. $\text{PhCH}_2\overset{\oplus}{\text{CHNH}_3}\text{CO}_2^\ominus$ has two diastereotopic H-atoms. Label them as pro-R and pro-S.

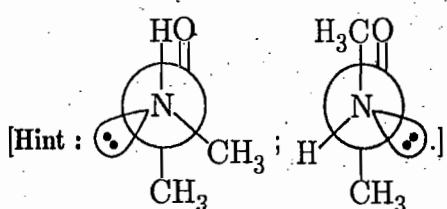
[Hint : See the answer to Problem 2.3(a).]

2009

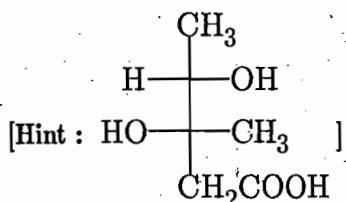
1. Define 'conformation' and 'configuration'.

[Hint : See the answer to Problem 1.5.]

2. Give the two eclipsed conformations for N-methyl acetamide about the C—N bond.



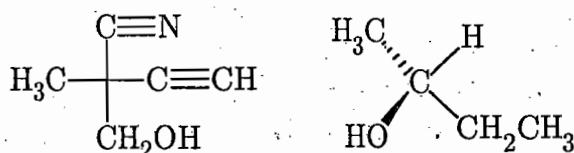
3. Formulate 2D-hydroxy-3D-methyl-3L-hydroxy pentanoic acid.



4. How would you resolve a racemic acid (\pm) RCOOH?

[Hint : See the answer to Problem 1.76(c).]

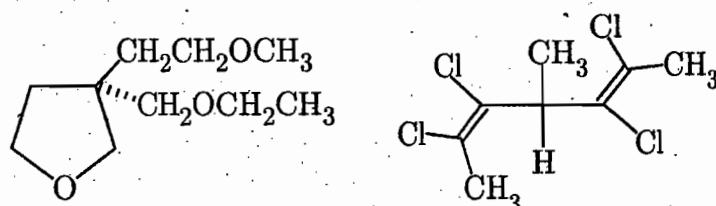
5. Identify each of the following as R or S :



[Hint : S; R]

2010

1. Assign configurational notation (R/S) to the stereogenic centre in the following molecules :



[Hint : S; S]

2. Arrange in order of precedence (CIP rules) :

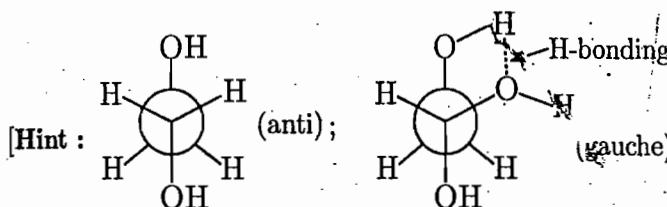


[Hint : $-CMe_2CMe_3 > -C_6H_5 > -CMe_2CHMe_2 > -CMe_3$]

3. Write down the most necessary and sufficient condition of an allene molecule to be optically active.

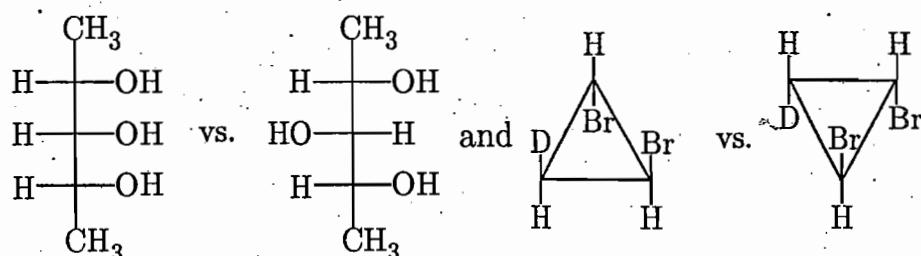
[Hint : See the answer to Problem 1.104(a).]

4. Draw the Newman Projections for the anti and one gauche conformation of 1,2-dihydroxy ethane. Which one is more stable in CCl_4 solution and why?



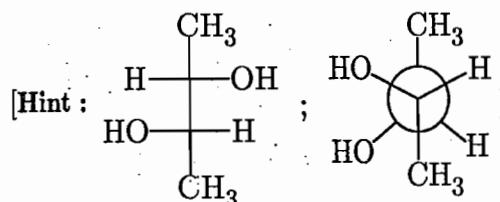
The gauche conformation is more stable in CCl_4 solution.]

5. Label the following pairs as homomers, enantiomers, diastereomers.



[Hint : Diastereomers and homomers.]

6. Write down the structure of 2D,3L-butane diol in Fischer and Newman Projection formulae.



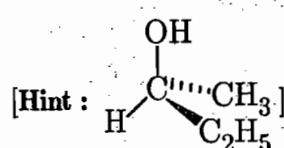
7. Meso-tartaric acid is optically inactive. Explain it using Newman's representation.

[Hint : See the answer to *Question 6, C.U.2007*]

8. Differentiate between enantiomer and diastereomer. What is meant by the term "optical purity"?

[Hint : See the answers to *Problems 1.27 and 1.62(b)*.]

9. Draw the three dimensional representation of the s-isomer of 2-butanol.



8. What is meant by specific rotation of an optically active compound? Define molecular rotation.

[Hint : See the answers to *Problem 1.59(d)*]

$$\text{Molecular rotation } [\Phi]^{t^\circ\text{C}} = \frac{[\alpha] \times M}{100}$$

where, $[\alpha]$ = specific rotation and M = molar mass of the substance]

