# 7. STEREOISOMERISM

Two or more compounds that have the same molecular formula but different physical or chemical properties are called **isomers** and the phenomenon is called **isomerism.** The difference in their properties is due to different modes of arrangement of atoms within the molecule. There are two main types of isomerism.
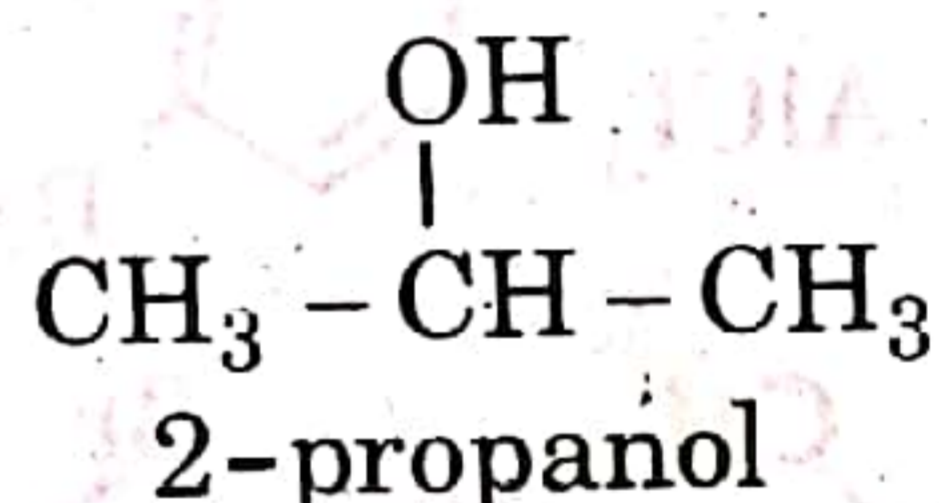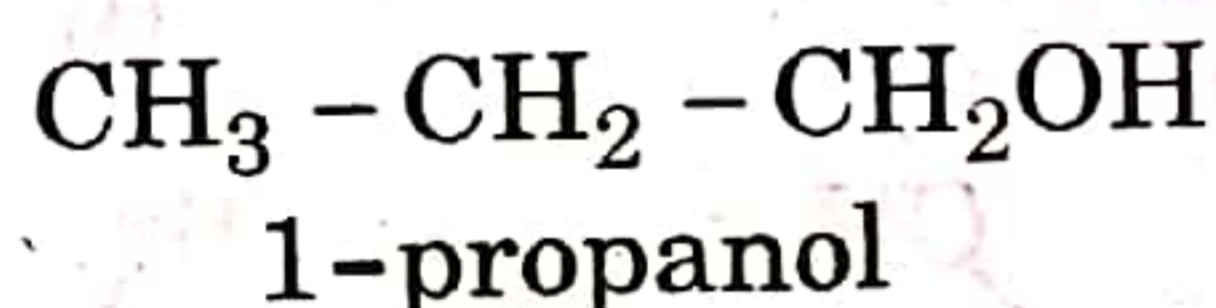 1. Structural (constitutional) isomerism. 2. Steroisomerism

1. **Structural Isomerism.** Structural isomers have the same molecular formulae but different structural formula. The structural isomers are distinguished by two-dimensional structures. Structural isomerism are of five types:

  (a) Chain isomerism
  (b) Position isomerism
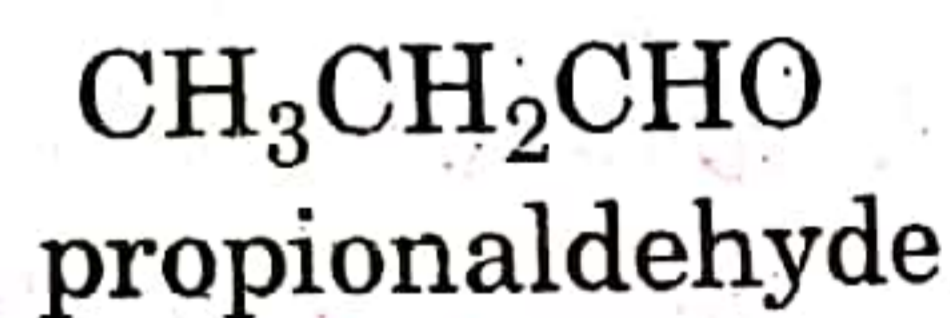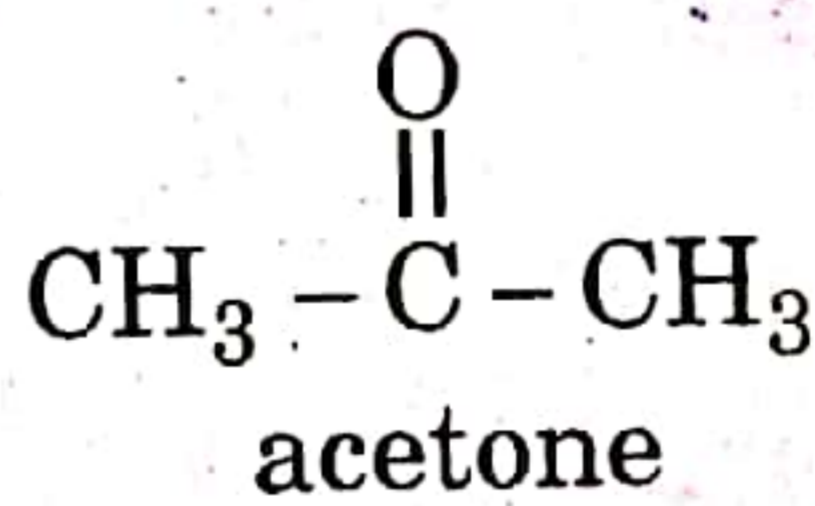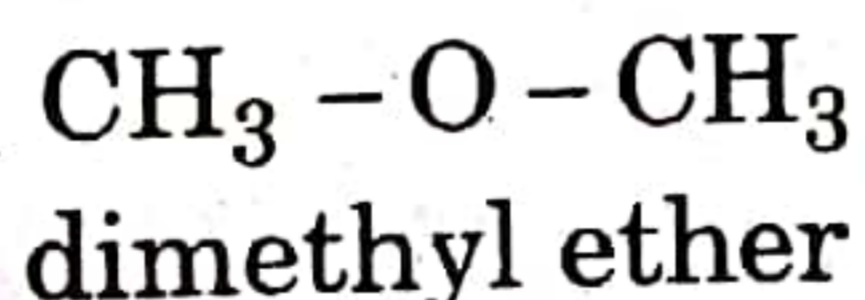 (c) Functional isomerism
  (d) Metamerism
  (e) Tautomerism

(a) Chain isomerism. Chain isomers have the same molecular formula but different carbon chains or skeletons, e.g.,

$$CH_3 - CH_2 - CH_2 - CH_3$$
n-butane

$$\begin{array}{c} CH_3 \\ | \\ CH_3 - CH - CH_3 \end{array}$$
2-methylpropane
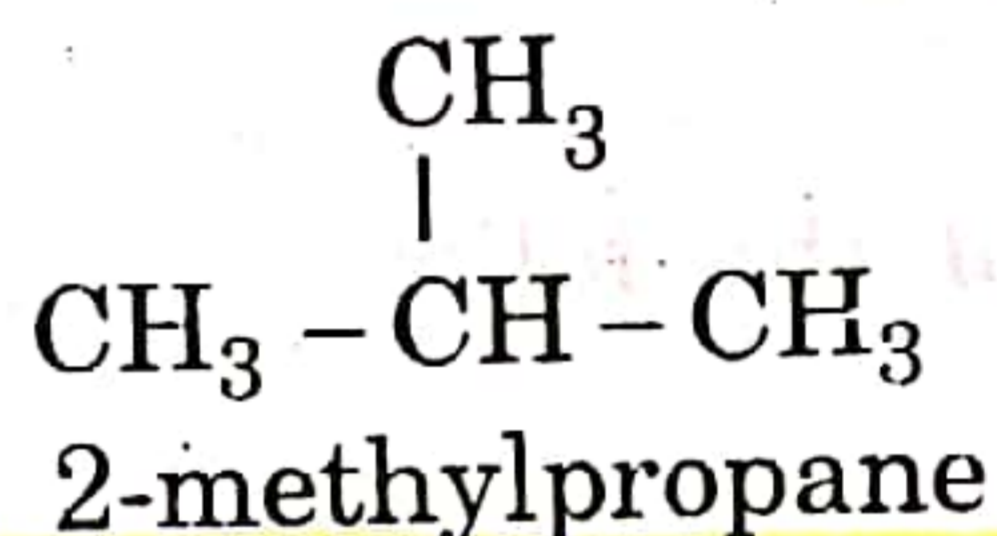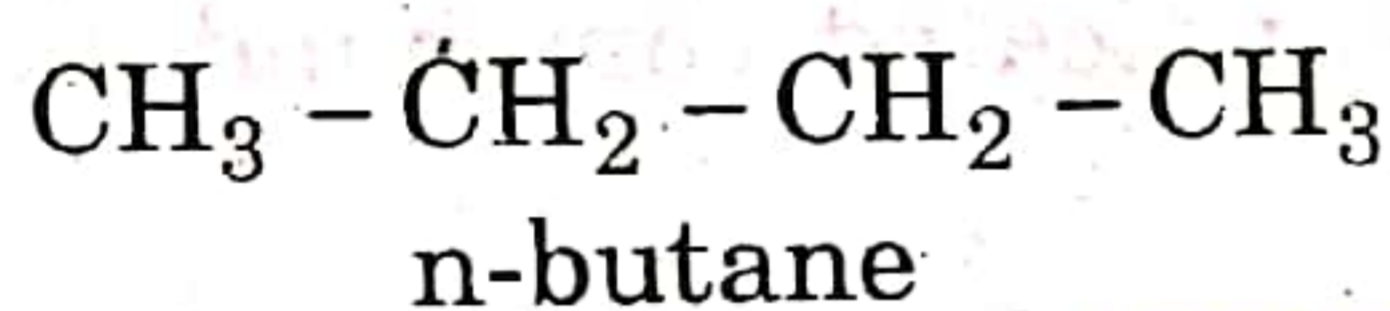
(b) Position isomerism. Position isomers have the same molecular formula but differ in the position of functional group on the carbon chain, e.g.,

$$CH_3 - CH_2 - CH_2OH$$
1-propanol

$$\begin{array}{c} OH \\ | \\ CH_3 - CH - CH_3 \end{array}$$
2-propanol

(c) Functional isomerism. Functional isomers have the same molecular formula but different functional groups and have different chemical properties. For example:

$$CH_3 - CH_2OH$$
Ethanol

$$CH_3 - O - CH_3$$
dimethyl ether

$$\begin{array}{c} O \\ || \\ CH_3 - C - CH_3 \end{array}$$
acetone

$$CH_3CH_2CHO$$
propionaldehyde

(d) Metamerism. Structural isomers within the same class in which the isomers differ by the nature of alkyl group attached to the same polyvalent atom is known as metamerism. For example, diethyl ether and methyl propyl ether show metamerism.

$$CH_3CH_2 - O - CH_2CH_3$$
Diethyl ether

$$CH_3 - O - CH_2CH_2CH_3$$
Methyl propyl ether
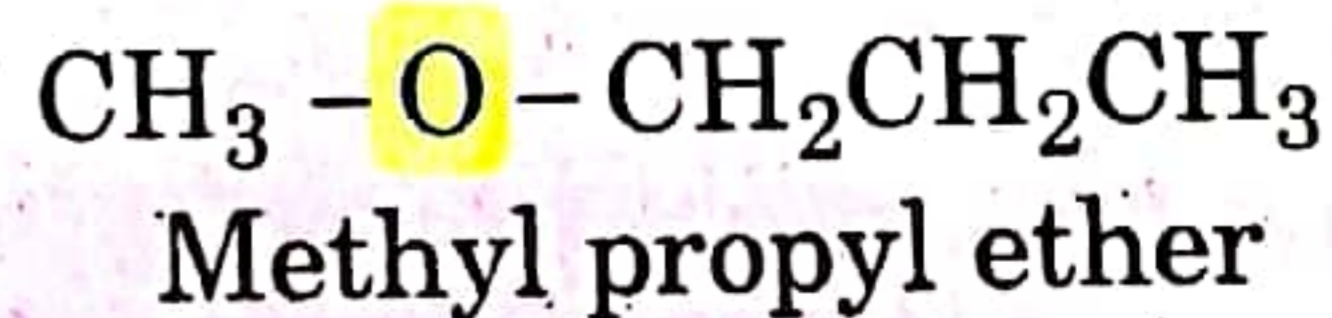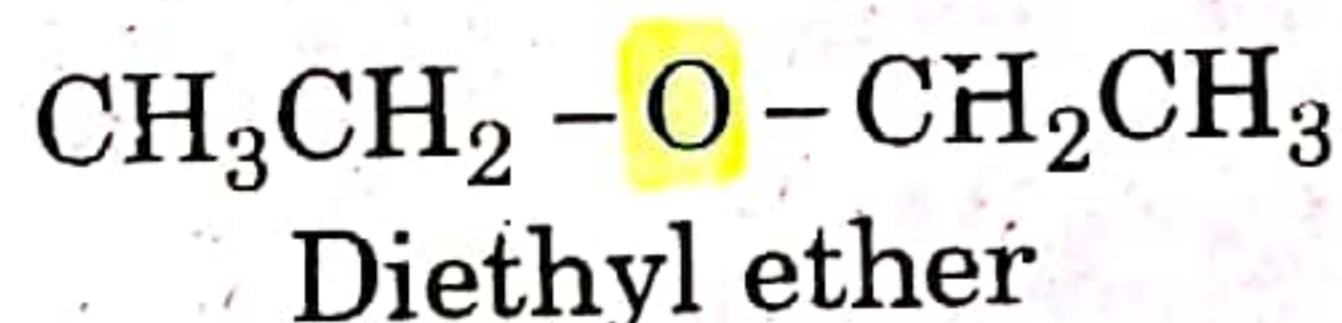
(e) Tautomerism. Two structural isomers which differ in the relative positions of their atoms, exist in dynamic equilibrium and are readily interconvertible, are called **tautomers,** the phenomenon is called **tautomerism** and their interconversion is called **tautomerization.** For example, acetoacetic ester is an equilibrium mixture of the following two forms.

$$CH_3 - \overset{\overset{\text{O}}{\|}}{C} - CH_2COOC_2H_5$$

Keto - form (93%)

$$CH_3 - \overset{\overset{\text{OH}}{|}}{C} = CH - COOC_2H_5$$

enol form (7%)
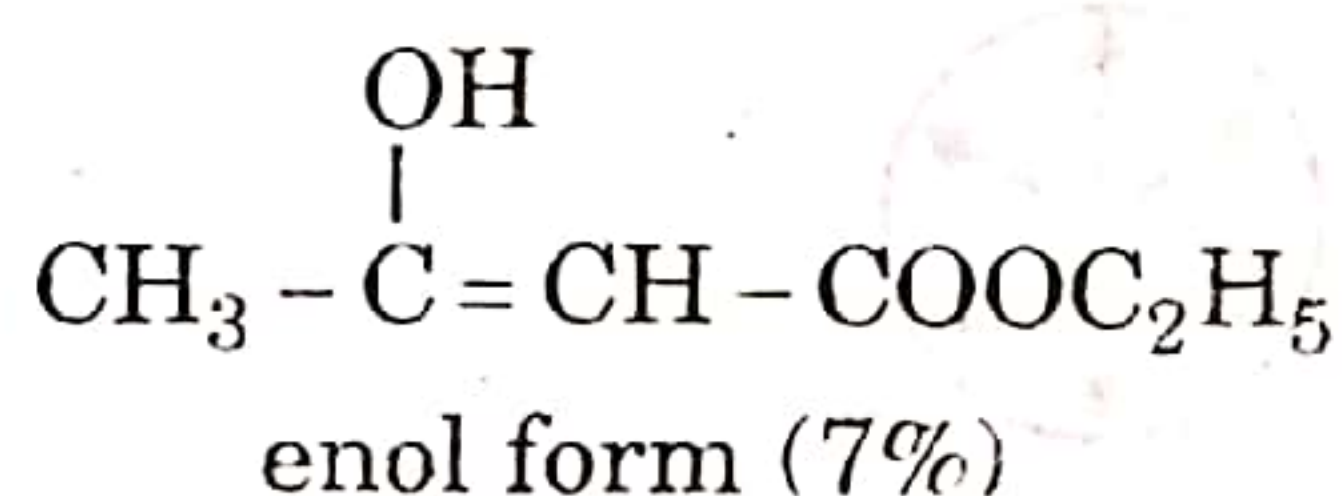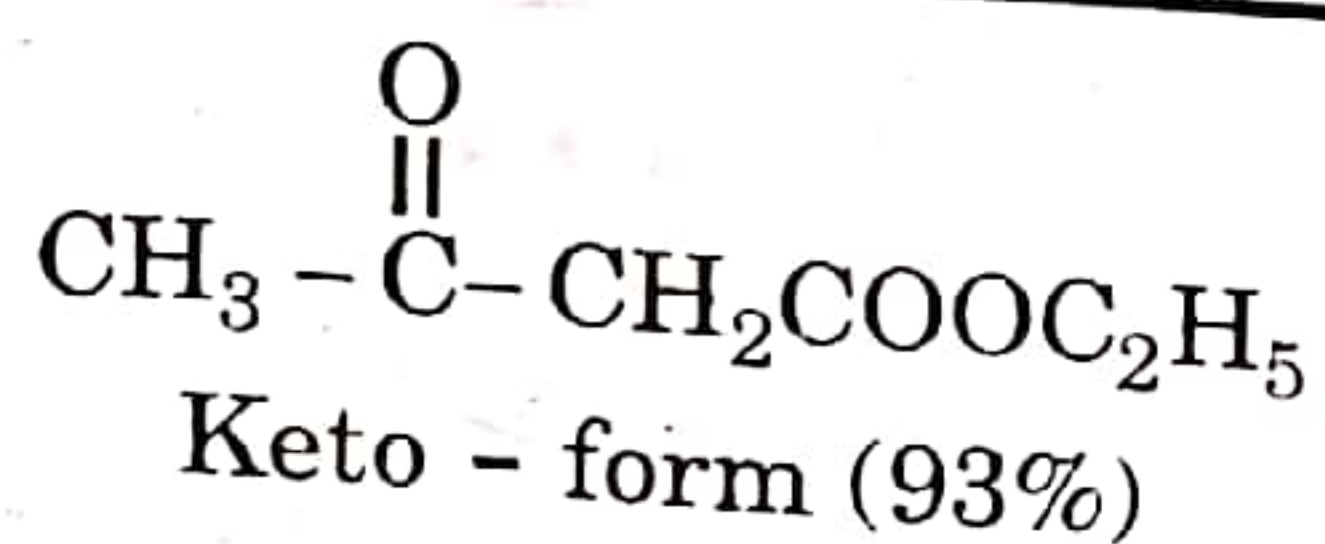
2. STEREOISOMERISM

Isomers that have the same structural formulas but differ in the arrangement of atoms in the three dimensional space are called **stereoisomers** *and the phenomenon is called* **stereoisomerism.** The stereoisomers cannot be distinguished by two-dimensional structures but only by three-dimensional structures. Stereoisomers are roughly divided into two classes.

1. Configurational stereoisomers   2. Conformational stereoisomers

Stereoisomers that can be interconverted only by breaking and making the bonds and can be isolated are called **configurational stereoisomers,** the structures of these stereoisomers are called **configurations,** and the isomerism is known as **configurational isomerism.** The configurational isomerism is further divided into two types:

1. Optical isomorism   2. Geometrical isomerism

Stereoisomers that can be interconverted by rotation about a single bond are called **conformational stereoisomers** or **conformers** or **rotamers,** the structures of the conformers are called **conformations** and the isomerism is called **conformational isomerism.**

OPTICAL ISOMERISM

Optical Activity

Ordinary light is composed of electromagnetic radiations of different wavelengths vibrating in all possible planes perpendicular to the direction of propagation. The same is true of monochromatic light, i.e., light of a single wavelength. For measuring optical activity, monochromatic light is always used, which is obtained by passing the ordinary light through a device known as **monochromator.** When monochromatic light is passed through the polarizing Nicol prism (made of calcite, $CaCO_3$) or **polaroid** lens, the emergent light is plane polarized. The light radiation vibrating only in one plane is called **plane-polarized** light. The polarization of the monochromatic ray transmitted through a Nicol prism, called **analyzer.** The polarized light from the polarizer passes through the analyzer only if they are placed in parallel position. On the other hand, when they are at right angles to each other, the transmission is zero (i.e., no light would pass).

If a solution of an optically active substance (e.g., solution of sucrose) is placed between polarizer and analyzer with their axes perpendicular to each other, light would not pass through the analyzer(second Nicol prism) because the solution of the optically active substance has the property of rotating plane of polarized light.

Electromagnetic radiation   Nicol prism   plane polarized light
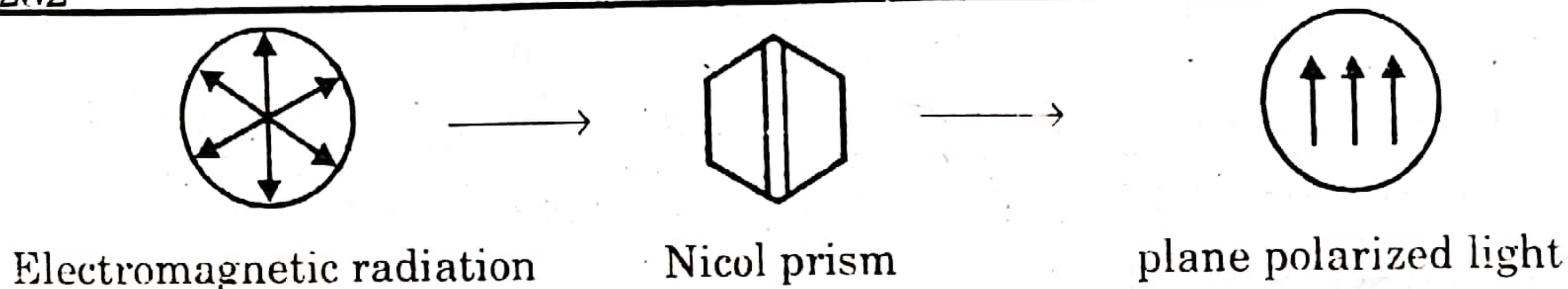
A compound which, when placed in the path of the plane-polarized light, rotates the plane of polarization to the left or right, is said to be **optically active** and this property of a compound of rotating the plane of polarization is called **optical activity.** The direction and extent of the plane of polarized light can be measured by the **instrument known as polarimeter**

Measurement of Optical Activity: The polarimeter

The principal working parts of a polarimeter are (1) a light source usually a sodium lamp, (2) a fixed Nicol prism, known as polarizer, to produce polarized radiation, (3) a tube for holding the test liquid or solution in the light beam (4) a second Nicol prism known as analyzer, attached to disc graduated in degrees and fractions of a degree, that can be rotated, to measure the amount of rotation of the plane of polarization by the liquid or the solution.

As the arrows indicate, the optically active substance in solution in the tube is causing the plane of the polarized light to rotate.

The plane of polarization of the emerging light is not the same as that of the entering polarized light.
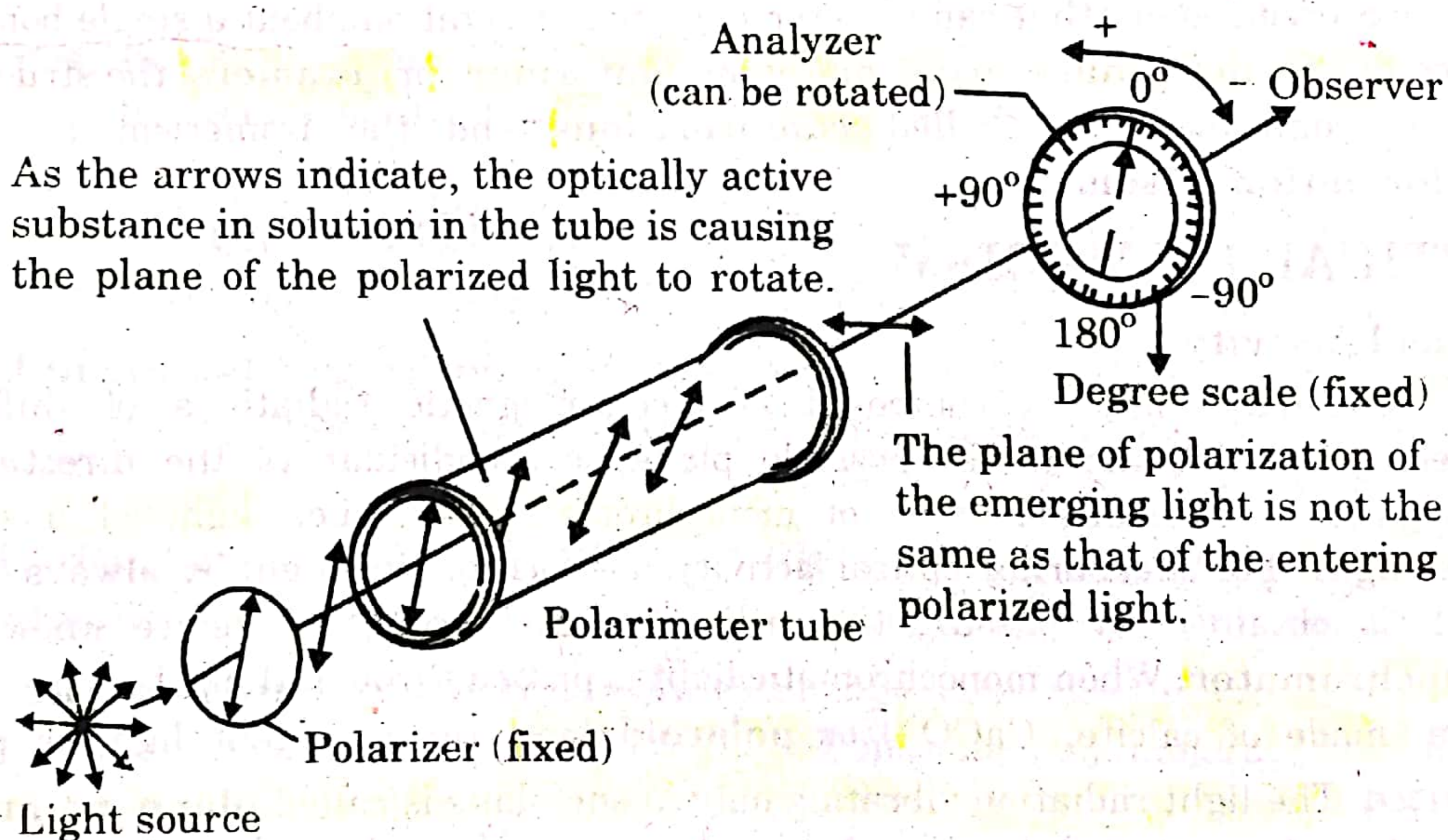
Fig. 7.1 The principal parts of a polarimeter and the measurement of optical rotation.

If the tube of the polarimeter is empty, or if an optically inactive substance is present, the axes of the plane-polarized light and the analyzer will be exactly parallel when the instrument reads 0°, and the observer will detect the maximum amount of light passing through it. On the other hand, if the tube contains optically active substance (e.g., solution of sucrose), the plane of polarization of the light will

be rotated as it passes through the tube. In order to detect the maximum brightness of light, the observer will have to rotate the axis of the analyzer in either a clockwise direction or anticlockwise direction. If the analyzer is rotated to the right, i.e., clockwise direction, the rotation a, is said to be positive (+) and the optically active substance is said to be **dextrorotatory.** If the rotaton is to the left, i. e., anticlockwise, the rotation is said to be negative (-) and the optically active substance is said to be **levorotatory.**

The angle through which the plane of polarization is rotated is known as **optical rotation** (α) and is given the sign (+) or (-) depending on whether the rotation is dextro or levo.

Specific Rotation. The angle of rotation depends on (1) the concentration of the solution (2) the nature of the substance (3) the length of the tube (4) the wavelength of the light employed, (5) the temperature.

For comparison of the rotating powers of the optically active substance, the above factors are kept constant and the results are expressed in terms of specific rotation [a] defined as

$$[\alpha]_\lambda^t = \frac{\alpha}{l \times c} \text{ for solution} \quad ; \quad [\alpha]_\lambda^t = \frac{\alpha}{l \times c} \text{ for liquids}$$

Where α = observed rotation, t = temperature, λ = wavelength of light, c = concentration of the active substance in kgm^{-3}, l = length of the sample in metre, and d = density of liquids.

The rotation produced by one metre length of the solution containing 1kg substance per metre of the solution for particular wavelength at given temperature is known as **specific rotation.** A specific rotation might be given as follows.

$$[\alpha]_D^{25} = + 3.12°$$

This means that D line (wavelength = 589.6nm) lamp was used for the light at a temperature of 25°C and that a sample containing 1 kg/m of the optical substance, in a 1 metre tube produced a rotation of 3.12° in a clockwise direction.

The **molar optical rotatory power** of a compound, at a given temperature and for a given wavelength, is the rotation produced by a column of solution 1m long and of concentration 1 mol m^{-3}. The molar rotation $[M]_\lambda^t$ is the specific rotation multiplied by the molecular mass divided by 100 to reduce the size of the figure.

Asymmetric carbon atom and Optical Isomerism (Chirality and optical activity)

A carbon atom which is bonded to four different groups is called an **asymmetric** or **chiral carbon atom, (or chiral centre)** and it is found that in all cases where such an atom is present, the compound is capable of showing optical activity. For example, in 2- butanol, the chiral carbon is carbon-2. The four different groups that are attached to 2- butanol are hydroxy group, a hydrogen, a methyl
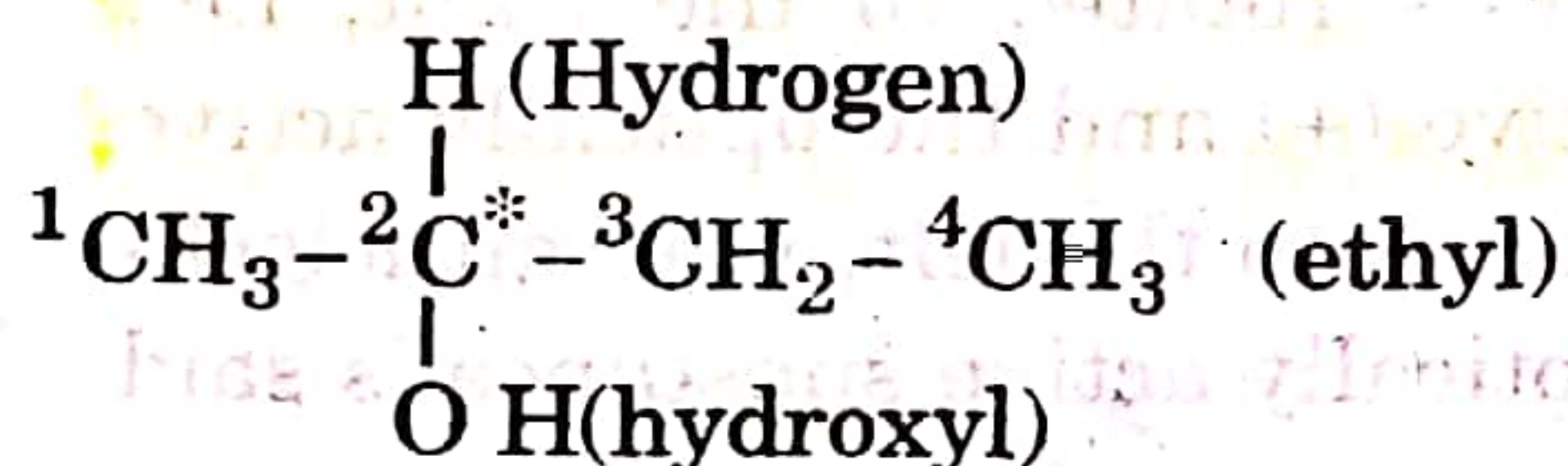
group and an ethyl group.

$$^1CH_3-^2C^*-^3CH_2-^4CH_3 \quad (\text{ethyl})$$

H (Hydrogen)

O H(hydroxyl)

Fig. 7.2 The chrial carbon of 2-butanol. (By convention chiral carbons are often designated with an asterisk).

A chiral molecule is defined as one that is nonsuperimposable on its mirror image. Chiral molecules can be represented by two spatial arrangements such that one is the mirror image of the other, but cannot be superimposed on one another, e. g., 2-butanol and lactic acid. The property of nonsuperimposability of an object on its mirror image is called **chirality.**

If two or more of the groups that are attached to a tetrahedral atom are the same, the molecule is superposable on its mirror image and is **achiral.** The compound does not rotate the plane of polarized light; it is optically inactive, e. g., 2-propanol is achiral molecule, since two identical methyl groups attached to the central atom.
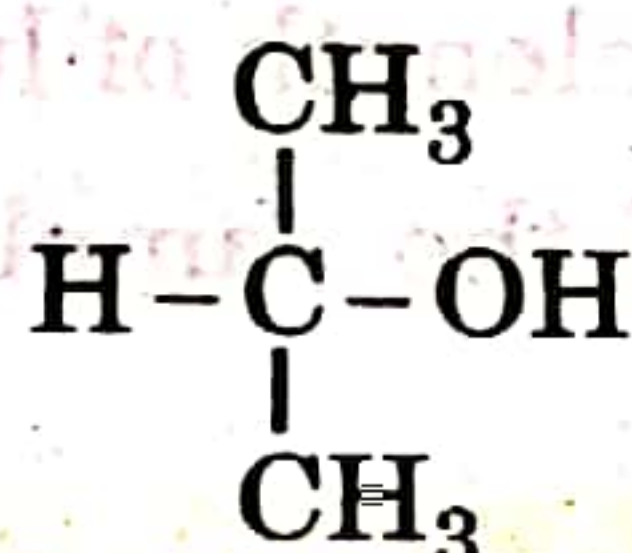
$$CH_3$$
$$H-C-OH$$
$$CH_3$$

Fig. 7.2 2-propanol, achiral molecule, optically inactive, has only one form.

The ultimate criterion, for optical activity is chirality.

Enantiomers. *Stereoisomers that are related like an object and its mirror image but are nonsuperimposable on their mirror reflections* are called **enantiomers.** Enantiomers occur only with compounds whose molecules are chiral. The enantiomers have identical physical and chemical properties but they differ only in their behaviour toward the plane–polarized light. They rotate the plane of polarized light in opposite directions but in equal amounts. The stereoisomer that rotates the plane of polarized light to the right (clockwise direction) is known as **dextrorotatory** (or dextro) isomer and is designated (d – or (+) isomer, while the other that rotates the plane of polarized light to the left (anticlockwise direction) is known as **levorotatory** (or levo) isomer and is designated (l – or (–)–isomer since **enantiomers** differ only in their behaviour toward the plane – polarized light, therefore enantiomers are called optical isomers and the phenomenon is called **optical isomerism.**

A molecule containing only one chiral carbon atom is always chiral and has two stereoisomers which are nonsuperimposable mirror reflections of each other. For example, 2– butanol and lactic acid, each has two stereoisomers (i.e. optical isomers)
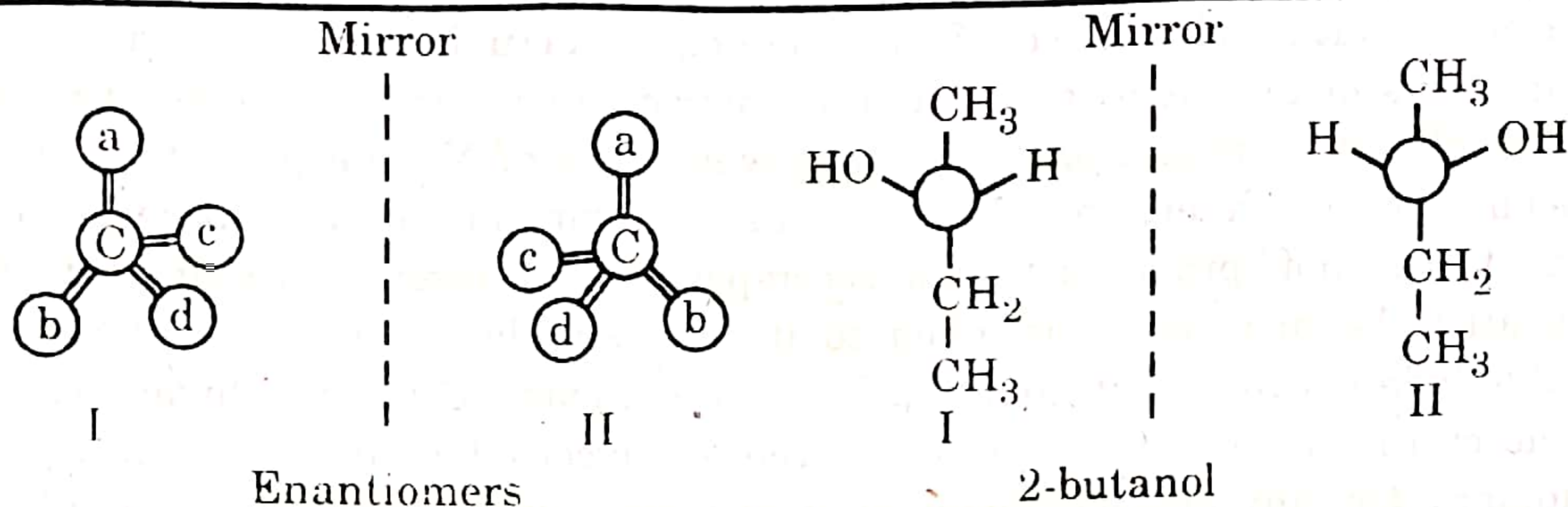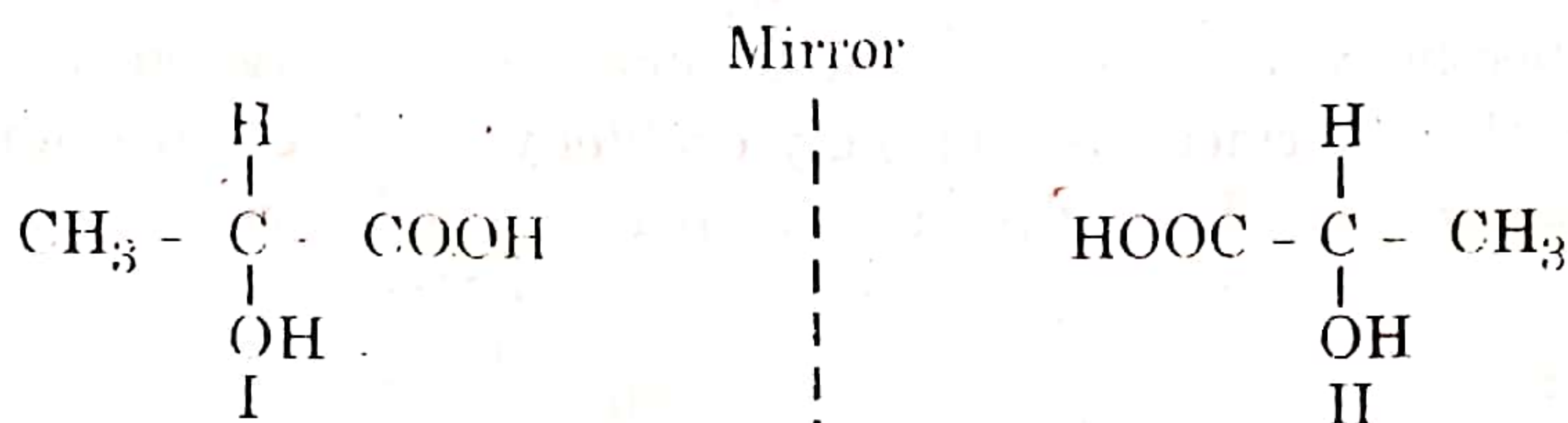
Fig. 7.2 2-butanol

Enantiomers

2-butanol

Fig. 7.3 2-hydroxypropanoic acid (lactic acid)

Fischer projection Formulas.

For a thorough understanding of stereochemistry, it is useful to examine molecular models. However, this is not feasible when we write the stereostructures on paper or the blackboard. Chemists sometimes represent structures for chiral molecules with two-dimensional formulas called **Fischer projection formulas.** These two-dimensional formulas are especially useful for compounds with several chiral carbons because they save space and easy to write.

By convention, Fischer Projections are written with the main carbon chain extending from top to bottom and with all groups eclipsed. Vertical lines represent bonds that project behind the plane of the paper (or that lie in it). Horizontal lines represent bonds that project out of the plane of the paper. The intersection of vertical and horizontal lines represents a chiral carbon. The Fischer formula for lactic acid is written as follows:
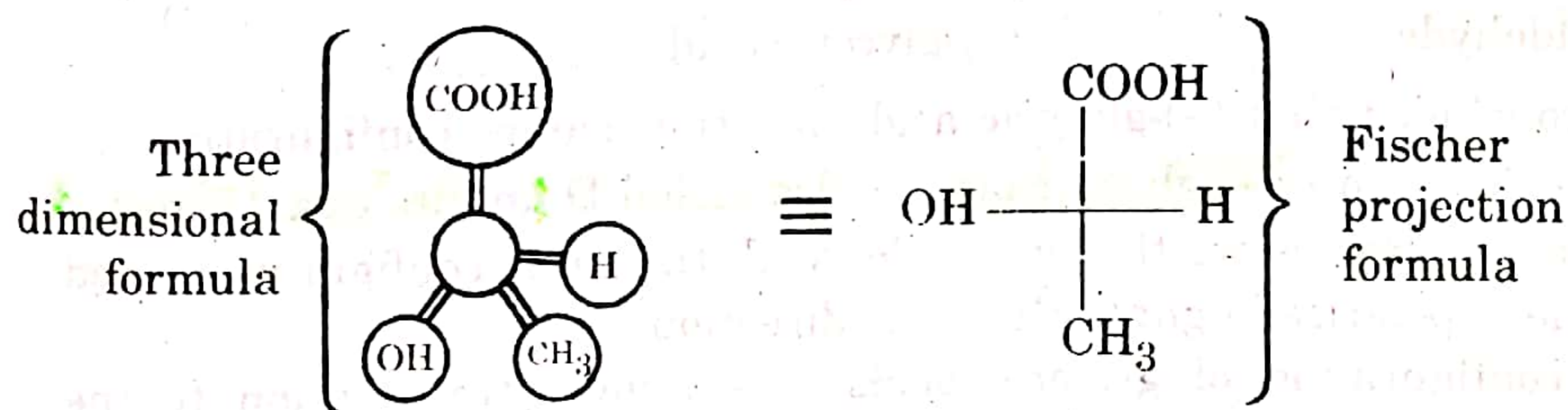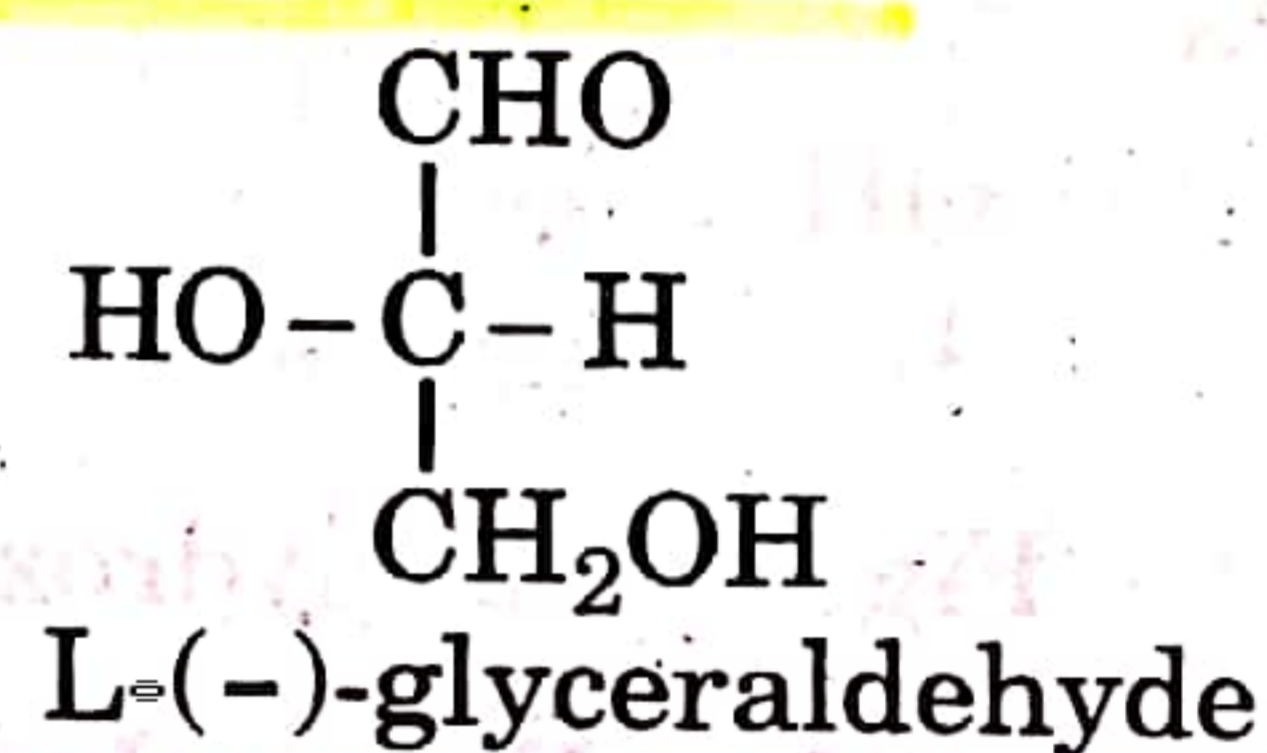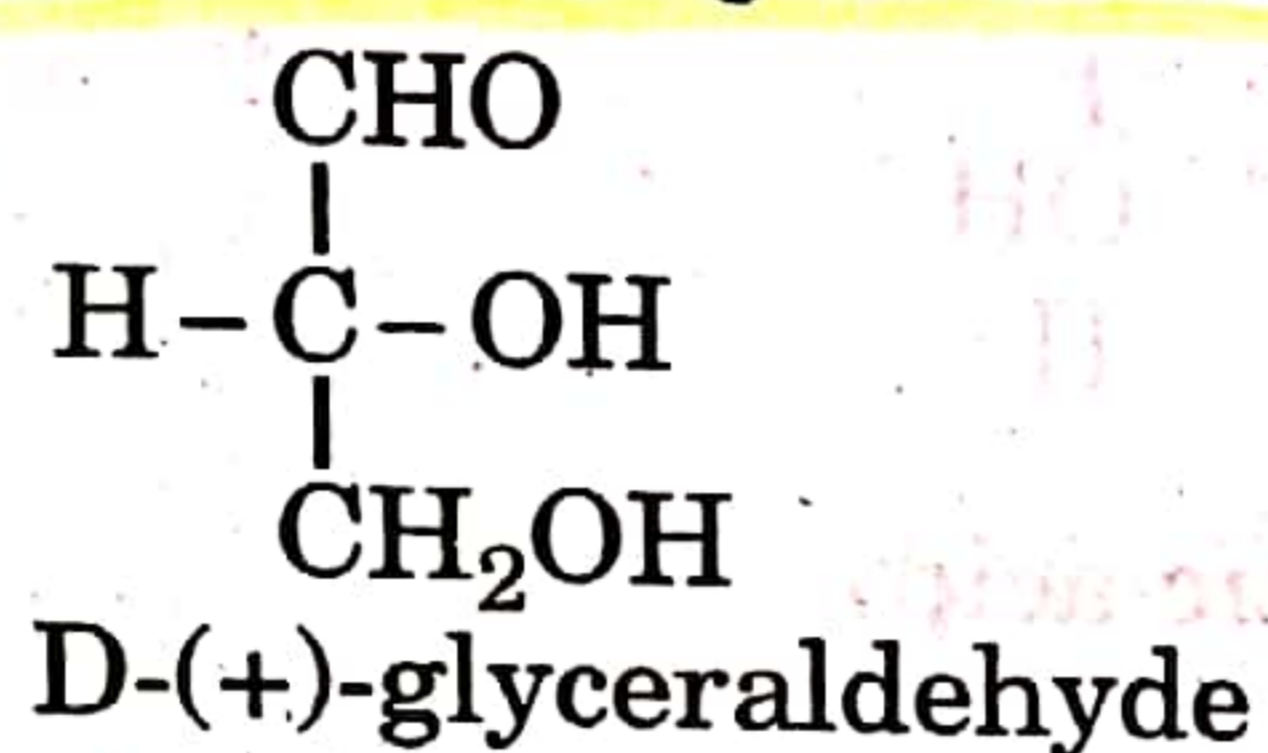

The configurations of optical isomers are now mostly represented by Fischer projections.
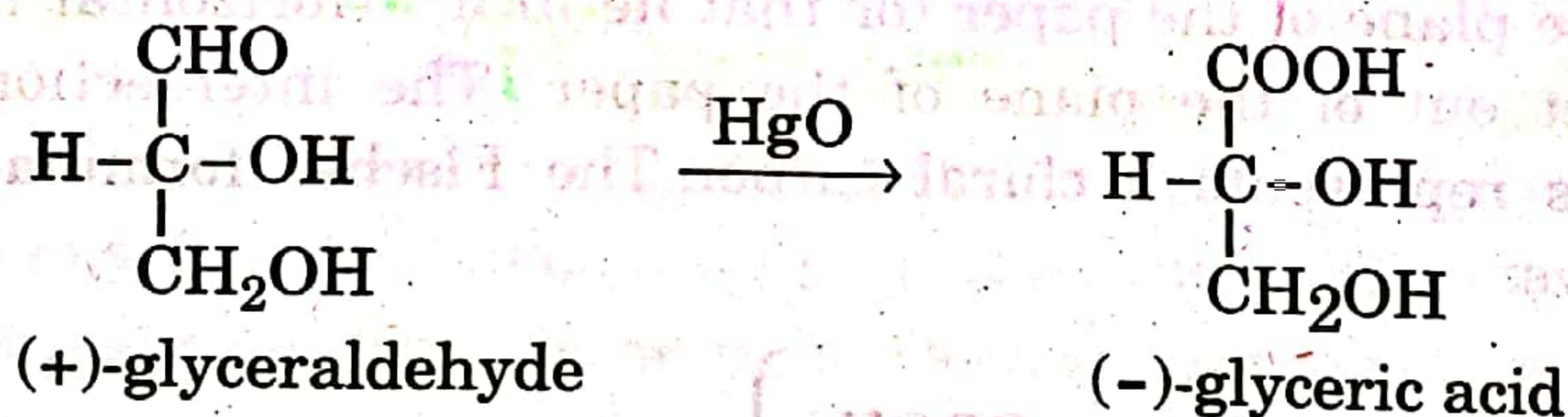
Relative and Absolute Configuration

The sign of rotation associated with an optically active compound gives no

information about its absolute configuration i.e., the actual arrangement in space of the four atoms or groups attached to asymmetric (chiral) carbon. Before 1951 only relative configurations of chiral molecules were known. No one prior to that time had been able to determine the absolute configuration of an optically active compound. Rosanoff proposed that one compound be chosen as a standard and a configuration be arbitrarily assigned to it. The standard compound chosen was glyceraldehyde because of its relationship to the sugars. Glyceraldehyde molecules have one chiral (asymmetric) carbon; therefore, glyceraldehyde exists: as a pair of enantiomers. One glyceraldehyde enantiomer is dextrorotatory (+) and the other, of course, is levorotatory (-). The two configurations of glyceraldehyde were denoted by symbols D and L respectively and the (+) enantiomer was assigned the D-configuration and was then termed as D-(+)-glyceraldehyde. The levorotatory enantiomer was then designated as L-(-)-glyceraldehyde as shown below.

$$
\begin{array}{ccc}
\text{CHO} & & \text{CHO} \\
| & & | \\
\text{H}-\text{C}-\text{OH} & & \text{HO}-\text{C}-\text{H} \\
| & & | \\
\text{CH}_2\text{OH} & & \text{CH}_2\text{OH} \\
\text{D-(+)-glyceraldehyde} & & \text{L-(-)-glyceraldehyde}
\end{array}
$$

Once a standard was chosen, the configurations of other compounds could then be related to it. "The configuration of a compound with reference to the arbitrarily assigned configuration of the reference compound is known as its **relative configuration.**"

The classical chemical methods for the assignment of relative configuration depend on the assumption that no change in configuration occurs so long as bonds to the asymmetric atom are not involved. For example, when (+) glyceraldehyde is oxidized with mercuric oxide, it gives (-)-glyceric acid without changing the configuration at the asymmetric carbon atom.

$$
\begin{array}{ccc}
\text{CHO} & & \text{COOH} \\
| & & | \\
\text{H}-\text{C}-\text{OH} & \xrightarrow{\text{HgO}} & \text{H}-\text{C}-\text{OH} \\
| & & | \\
\text{CH}_2\text{OH} & & \text{CH}_2\text{OH} \\
\text{(+)-glyceraldehyde} & & \text{(-)-glyceric acid}
\end{array}
$$

It can be concluded that (-)-glyceric acid has the same configuration as (+)-glyceraldehyde. Therefore (-)-glyceric acid is also called D and its enantiomer is called L. This example emphasizes that molecules with the same configuration need not rotate the plane of polarized light in the same direction.

Once the configuration of glyceric acids was known (in relation to the glyceraldehydes), it was then possible to relate other compounds to either of these and each time a new compound was related, indirectly, to D- or L-glyceraldehyde. Any compound configurationally related to D-(+)-glyceraldehyde is said to belong the D-series, even though it may be levorotatory, and its enantiomer will belong to L-series. Even compounds without asymmetric atoms, such as biphenyls and allenes,

have been paced in the D - or L-series. When a compound has been placed in the D- or L-series, its absolute configuration is said to be known.

Absolute configuration is the actual configuration of the moleucle in space. In spite of the widespread use of D and L convention to designate absolute configuration, the system is not without shortcomings. A serious drawback of this system, is that the designation of a particular enantiomer as D or L can depend on the compound to which it is related. Examples are known where an enantiomer can be related by a certain route to a known D compound, and by some other route it can be related L enantiomer of the same compound. Another draw back of this system is that the letter D and L have sometimes been confused with *d* and *l*, which denote the dextro and the levo nature of a substance. Because of such flaws, the D, L system is seldom used today, except for certain classes of compounds such as carbohydrates and aminoacids.

(R)-(S) system of Nomenclature of enantiomers

Another system of nomenclature called the (R)-(S) system, or **Cahn-Ingold-Prelog system,** was developed and is widely used. In this system, there are again two symbols (R) (from the Latin rectus meaning "right") and (S) (from the Latin sinister meaning. "left").The main feature of this system is that it allows one to decide unambiguously how to name all molecules containing chiral carbons. A racemic mixture is still designated as a *dl* mixture, since there is no ambiguity here.

(R) and (S) designation are assigned as follows:

1. Substituents are listed in order of priority of decreasing atomic number of the atom directly attached to the chiral carbon atom. Thus the priority order of the groups of 1,1-bromochloroethane, $CH_3CHClBr$, will be $Br > Cl > CH_3 > H$.

2. When two or more of the atoms connected to the chiral carbon are the same, the atomic number of the second atom determines the order of priority. For example, in the molecule $(CH_3)_2CH-CHBr-CH_2OH$, the CH_2OH group takes precedence over the $(CH_3)_2CH$ group because oxygen has higher atomic number than carbon. If two or more atom connected to the second atom are the same, the third atom determines the precedence, etc.

3. When an atom is linked by a double or triple bond, it is counted twice or thrice as if it was split into two or three single bonds, respectively:

$$(-C \equiv N > -C_6H_5 > -C \equiv CH > -CH = CH_2)$$
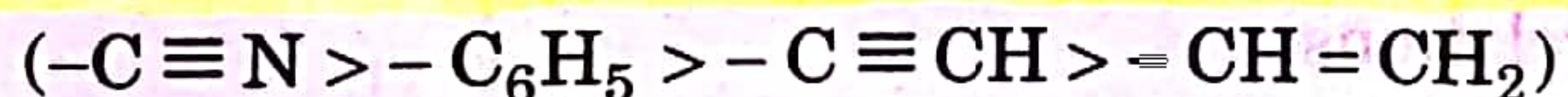
4. In case of isotope, an isotope with higher atomic mass takes precedence over the one with lower atomic mass: $(-T > -D > -H)$.

By application of the above rules, the decreasing order of priority for some of the common substitutents is: $-I, -Br, -Cl, -SO_3H, -SH, -F, -OCOR, -OR, -OH, -NO_2, -NR_2, -NHR, -NH_2, -COOR, -COOH, -COC_6H_5, -COCH_3, -CHO, -CH_2OH,$ phenyl, $-C \equiv CH, -C_2H_5, -CH_3, -D, -H$.

Once the priority is determined, the molecule is held so that the lowest group

in the sequence is pointed away from the viewer. Then if the other groups, in the order listed, are oriented clockwise, the molecule is designated (R), and if anticlockwise, (S). For glyceraldehyde, the (+) enantiomer is R, in which the sequence of the substituents, -OH, -CHO, - CH_2OH is clockwise as viewed from the side opposite to the substituent H.
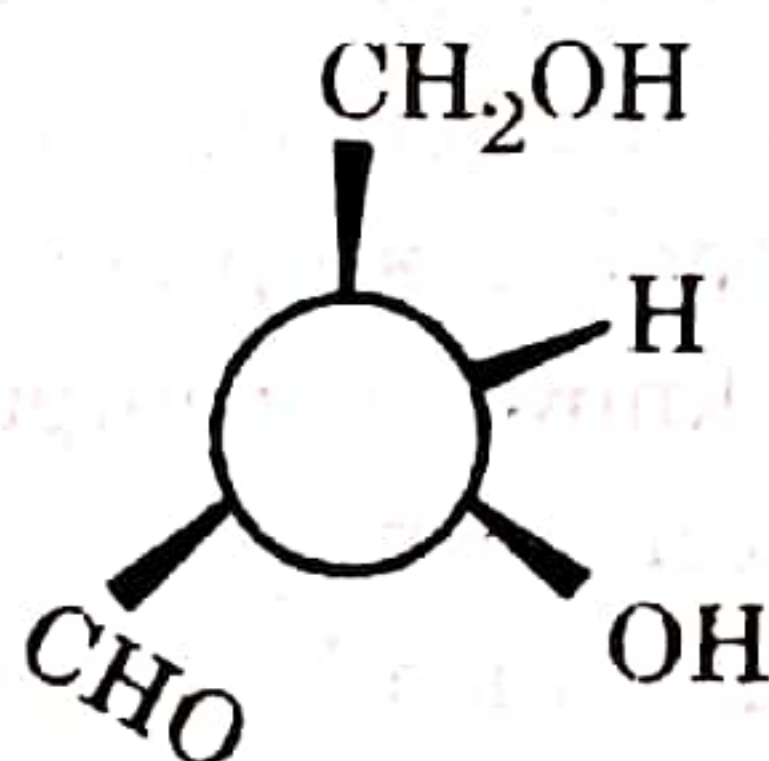
Note that when a compound is written in the Fischer projection, the configuration can easily be determined without constructing the model. If the lowest - ranking group is at the bottom, the (R) configuration is present if the other three groups in descending order are clockwise, e. g.,

(R)-Glyceraldehyde   S-Glyceraldehyde
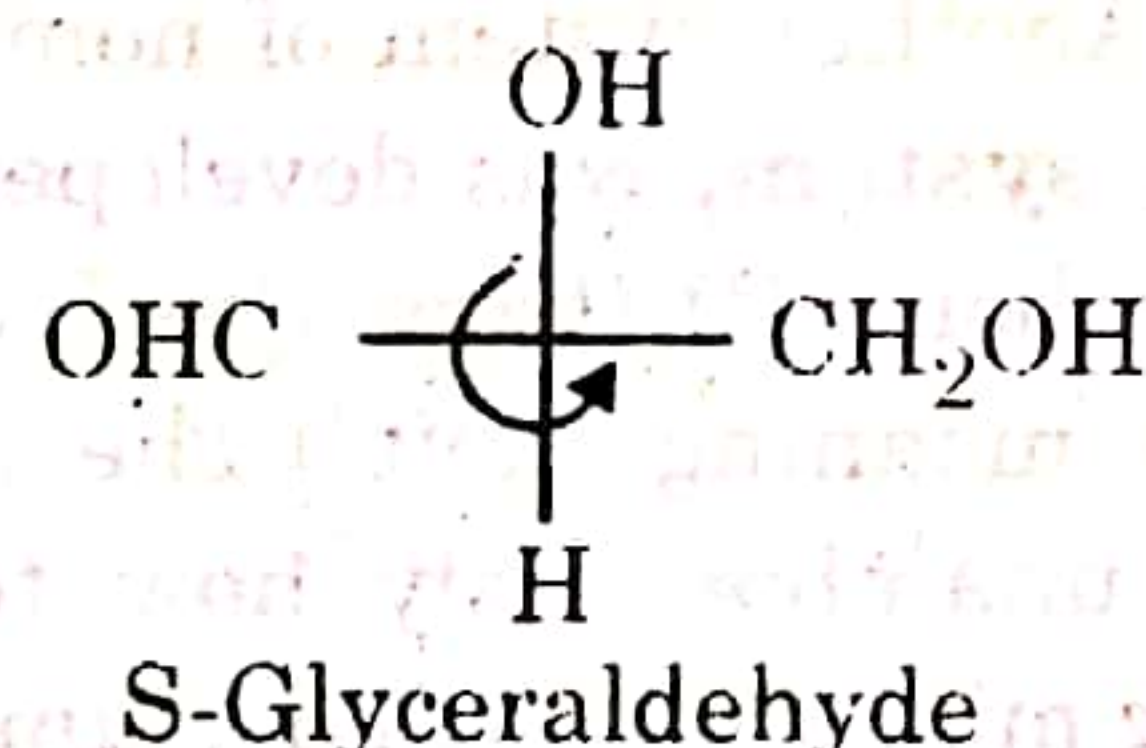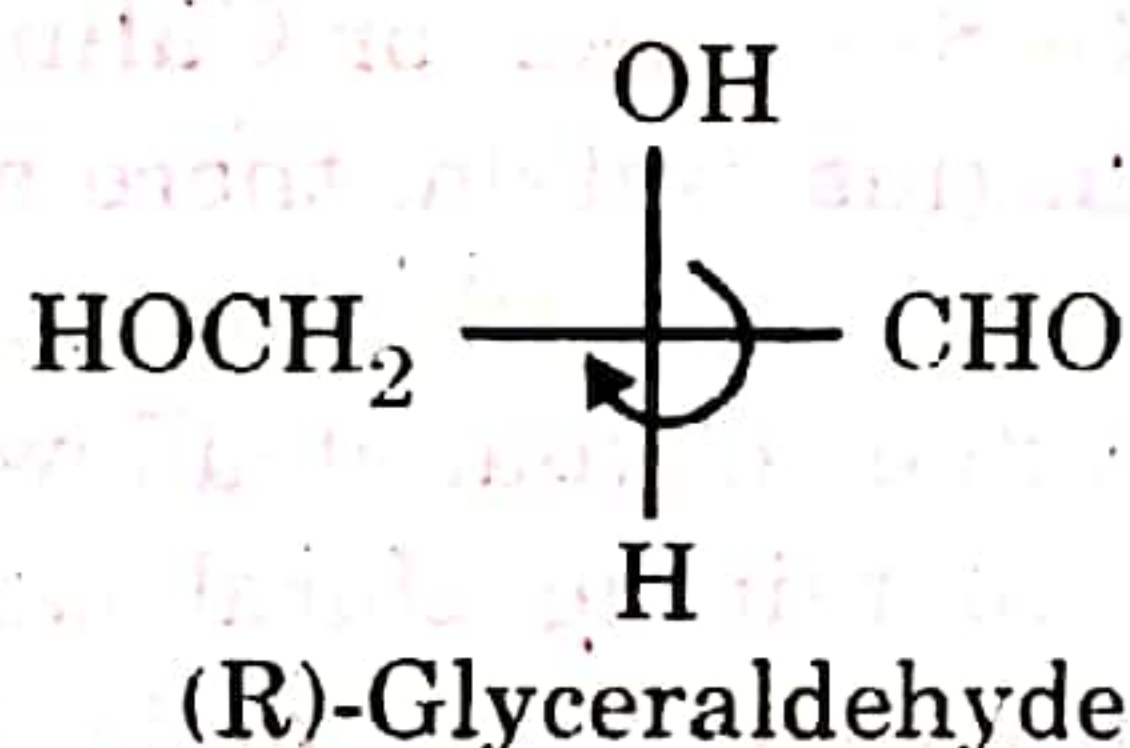
If the lowest - ranking group is not at the bottom, one can simply interchange it with the bottom group, keeping in mind that in so doing one is inverting the isomer.
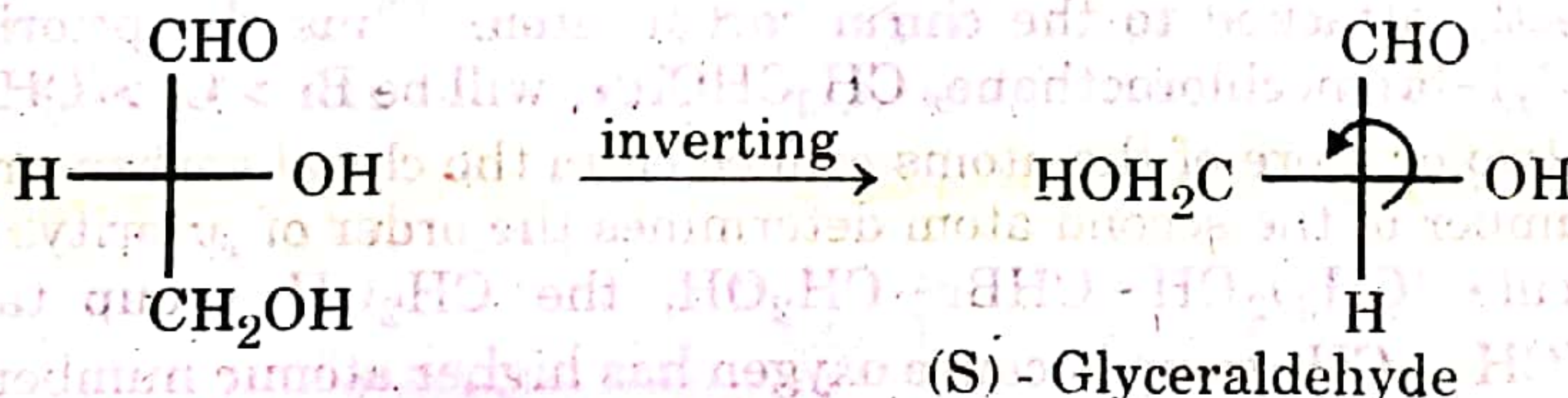
(S) - Glyceraldehyde

Therefore the original compound was (R) - glyceraldehyde.

The (R)-(S) system of nomenclature is unambiguous and does not depend on correlation. However, the configuration must be known before the system can be applied and this depend on correlations:

The Racemate

An equimolar mixture of a pair of enantiomers is called a **racemate** or a **racemate mixture** and is denoted by the prefix (±) or dl. A racemate does not show optical activity. A racemate of (R)-(−)-2-butanol and (S)-(+)-2-butanol can be indicated as (±)-2-butanol or as (±) $CH_3CH_2CHOHCH_3$. An optically active compound with one chiral carbon exists in three different forms. Thus lactic acid exists in the three different forms, (+) lactic acid, (−) lactic acid and (±) lactic acid.

When a chiral compound is prepared from an achiral compound, the product is always a racemic mixture provided the reagents and reaction conditions are all symmetrical. For example, bromination of propanoic acid at the 2- position gives (±) 2-bromopropanoic acid (i.e., racemate) inspite of the fact that a chiral carbon is created as a result of the reaction.

$$CH_3 CH_2 COOH \quad + \quad Br_2 \quad \xrightarrow{P} \quad CH_3 CHBr COOH$$

propanoic acid   2-bromopropanoic acid
(achiral molecule)   (achiral molecule)   (chiral molecule)
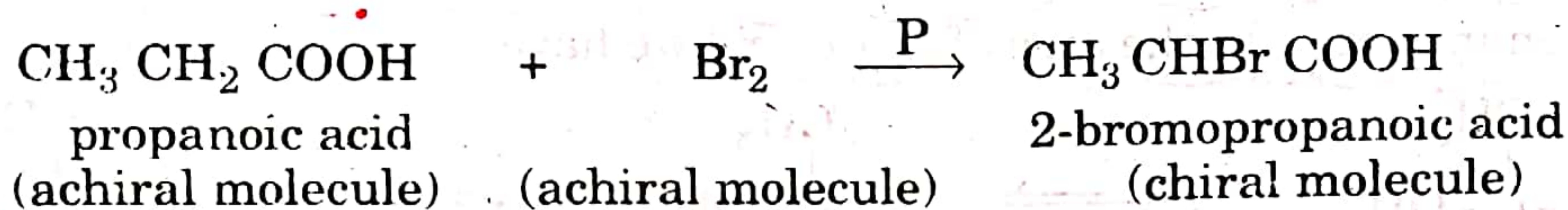
A racemate behaves like a single compound. It has a sharp melting point and a constant boiling point. When a racemate reacts with an optically active compound, the product is also a racemate. For example, racemic 2- butanol on treatment with HBr gives racemic 2- bromobutane.

Creation of asymmetric carbon and Racemization

"The conversion of an enantiomer into a racemate is called Racemization". In other words, conversion of an optically active compound (either enantiomer) into a racemic form is called **racemization.**
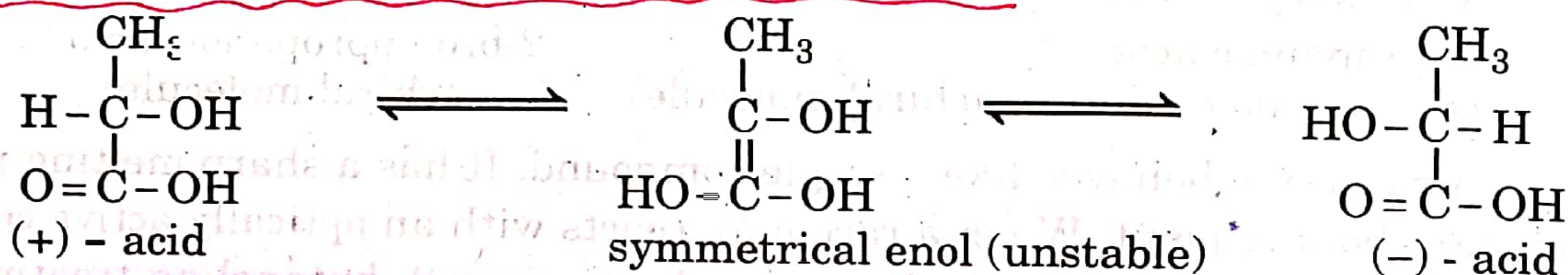
An asymmetric carbon is sp^3 hybridized and has tetrahedral structure. For racemization the procedure is to break one of the tetrahedral bonds and remake it in order to get back the tetrahedral or asymmetric carbon structure. The breaking of one of the tetrahedral bonds would convert the remaining three to become coplanar (as an sp^2 carbon) with a plane of symmetry. (The reaction causes the chiral molecule to be converted to an achiral molecule intermediate or transition state that can react further to form either enantiomer with an equal probability). The group removed is then replaced from the opposite side to produce the enantiomer **(inversion);** returning the group to the same side results in **retention** of configuration. For example, when a solution of one of the enantiomers of 2-iodobutane, say the (S)-2-iodobutane, is treated with a solution of Na I, an iodide ion in the solution displaces an iodide ion from the compound by attacking from the opposite side.

(S)-2-iodobutane   (R)-2-iodobutane
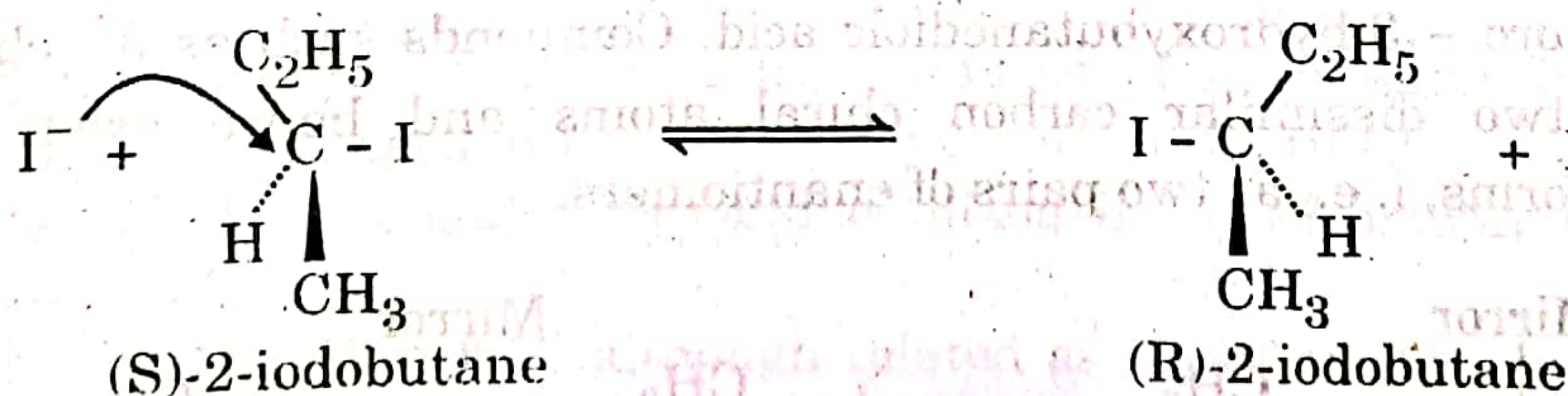
Consequently, the (R)-2- iodobutance is formed. However, this too can react, in the reverse manner, to generate the (S)-2-iodobutane and eventually a point is reached when equal amounts of two enantiomers are in dynamic equilibrium in equal amounts, as a racemate.

Racemization occurs readily with compounds having some unsaturated

function adjacent of a chiral carbon atom carrying a hydrogen atom that can undergo a tautomeric change. For example, lactic, maleic and tartaric acids in the presence of a base. All these compounds have a carboxyl group adjacent to a asymmetric carbon atom carrying a hydrogen. The racemization has been interpreted to take place through the formation of an enol which at once changes to the other enantiomer. In the case of lactic acid we have:

$$
\begin{array}{ccc}
CH_3 & CH_3 & CH_3 \\
| & | & | \\
H-C-OH & C-OH & HO-C-H \\
| & || & | \\
O=C-OH & HO-C-OH & O=C-OH \\
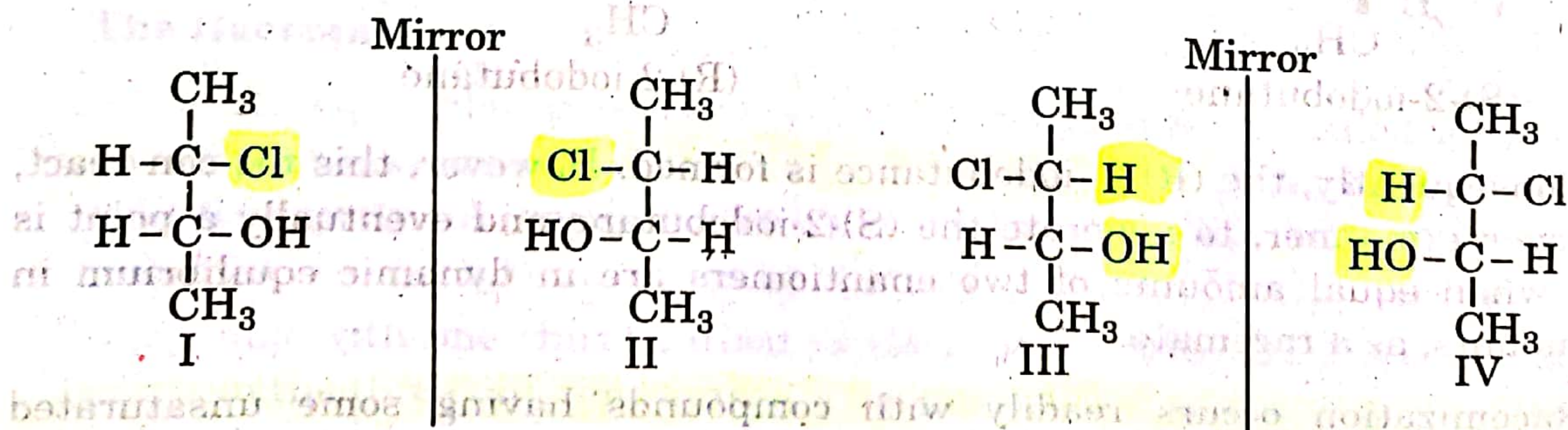(+) - acid & symmetrical\ enol\ (unstable) & (-) - acid
\end{array}
$$

The changes shown above are reversible and the equilibrium thus obtained contains (+)-acid and (-)-acid, i.e., the racemic mixture of the acid. Similarly either enantiomer of 2 methyl butanal yields a racemic mixture. *Inversion of configuration at one chiral carbon of a molecule having more than one chiral carbon, atom is known as epimerization and product is an epimer of the original compound.*

Compounds with Several Chiral Carbon Atoms

As the optical rotation of a compound depends upon the presence of a chiral carbon, the number of optically active forms increases with the increasing number of chiral carbon atoms. A compound containing n chiral carbons will exist in 2^n optically active forms, provided chiral atoms are not identically substituted. Thus 3-chloro-2-butanol. $CH_3\ CH\ (OH)\ CH\ (Cl)\ CH_3$ in which the two chiral carbon atoms are dissimilar, exists in $2^2 = 4$ optically active forms. The two chiral carbon atoms of tartaric acid ($HOOC - CHOH - CHOH - COOH$), on the other hand, are identically substituted and hence the total number of optical isomers cannot be predicated by the application of 2^n formula., the number of isomers is reduced.

Compounds with two Dissimilar Chiral Carbon atoms: Diastereomers

Compounds of this type may be represented by Ca b d. Ca b e, e.g., 3- chloro-2-butanol, 2-chloro - 3-hydroxybutanedioic acid. Componds such as 3 - chloro - 2-butanol have two dissimilar carbon chiral atoms and hence exists in four stereoisomeric forms, i. e., as two pairs of enantiomers.

$$
\begin{array}{cccc}
\textbf{Mirror} & & \textbf{Mirror} & \\
CH_3 & CH_3 & CH_3 & CH_3 \\
| & | & | & | \\
H-C-Cl & Cl-C-H & Cl-C-H & H-C-Cl \\
| & | & | & | \\
H-C-OH & HO-C-H & H-C-OH & HO-C-H \\
| & | & | & | \\
CH_3 & CH_3 & CH_3 & CH_3 \\
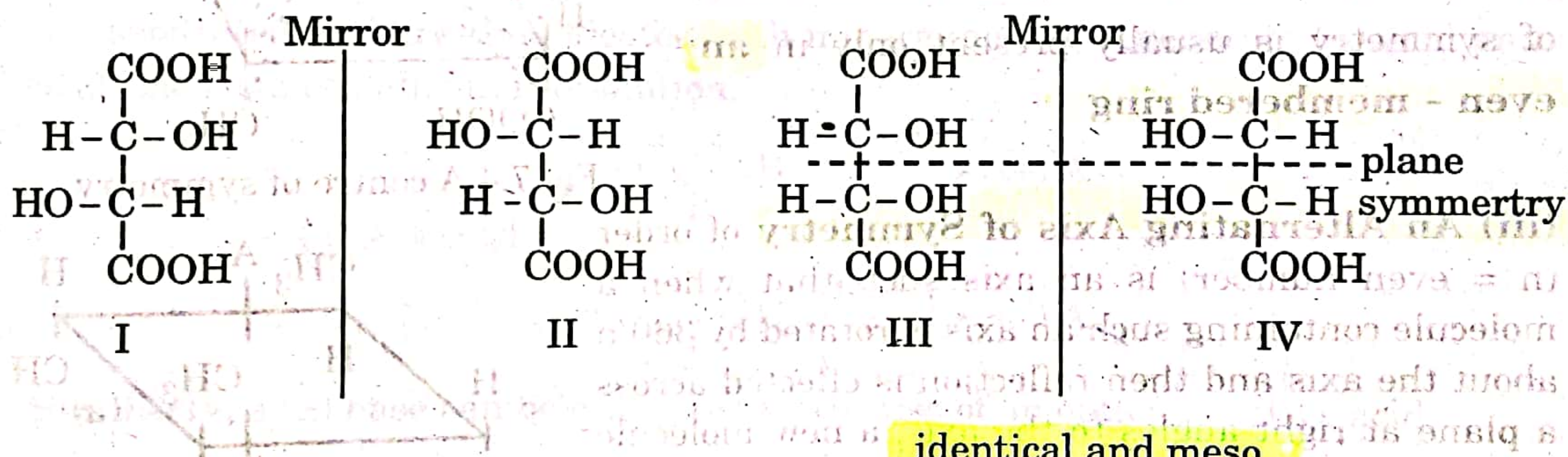I & II & III & IV
\end{array}
$$

Structures I and II are enantiomers, since they are related to each other as an object to its mirror image, have equal and opposite rotations and if mixed in equal amounts will give rise a racemic mixture. Similarly structures III and IV are enantiomers, but their magnitude of rotation would be different form that of the first pair, and equimolar mixture of these enantiomers gives a racimic mixture.

The structures **I and III** are not **mirror images** (enantiomers); yet they are optically active. Same is the case with II and IV. Such stereoisomers which are not enantiomers are called **diastereomers.**

"**Diastereomers** are stereoisomers that are not enantiomers and they have the same configuration at one chiral centre but different configuration at the other". Diastereomers behave like different compounds. They have different physical properties such as melting point, boiling point, solubility, etc. They also differ in chemical reactivity. Diastereomers differ in specific rotation; they may have the same or opposite signs of rotation, or some may be inactive.

Compounds with two Similar Chiral (asymmetric) Carbon Atoms

Compounds of the type Cabd - Cabd, e. g., tartaric acid. COOH-*CHOH-*CHOH-COOH. 2, 3 – butanediol, CH_3-*CHOH-*CHOH-CH_3. The best known example of this class is tartaric acid with two chiral carbon atoms. The following four projection formulae are possible for tartaric acid.

```
        Mirror                              Mirror
   COOH    |    COOH            COOH    |      COOH
    |      |     |               |      |       |
  H-C-OH   |  HO-C-H           H-C-OH   |    HO-C-H
    |      |     |          ----+----------------+---- plane
  HO-C-H   |   H-C-OH         H-C-OH    |    HO-C-H  symmertry
    |      |     |               |      |       |
   COOH    |    COOH            COOH    |      COOH

     I             II             III           IV
```

identical and meso

Structures I and II are mirror images of each other but they are not superimposable on each other. Therefore, each is optically active and the two constitute a pair of enantiomer, and if mixed in equal amounts form a racemic mixture.

Structures III and IV although related as object and mirror image. The two structures are superposable. It means that III and IV do not represent a pair of enantimers. In fact III & IV represent the same isomer. Therefore, there are only three isomers of tartaric acid and not four. The molecule represented by str·cture III or IV is not chiral even though it contains chiral carbons, because the plane divides the molecule into two halves that are mirror images of each other. Such an isomer which has chiral carbon atoms but is still achiral is called **mesoisomer.**

*A compound which contains two or more chiral carbon atoms but is optically inactive due to internal copmensation is called a **Meso compound**.*

Elements of Symmetry

Although the ultimate test for chirality of a molecule is its nonsuperimposability on its mirror image, there are other tests that can be used to see whether a molecule is chiral or achiral. A molecule will be achiral if it has some sort of symmetry. There are three main types of symmetry which are known as the elements of symmetry: (i) a plane of symmetry (ii) a centre of symmetry and (iii) an alternating axis of symmetry. If there is not any elements of symmetry present, the molecule will be chiral and will show optical activity.

(i) A Plane of symmetry (also called a mirror plane) is defined as an imaginary plane that divides a molecule in such a way that one half is the mirror image of the other half. One of the stereoisomers of tartaric acid has a plane of symmetry. 2-Chloropropane has a plane of symmetry, while 2- chlorobutane does not.

(ii) A centre of symmetry is a point at which all the straight lines joining identical points in the molecule cross each other. For example, the molecule of 2, 4-dimethyl-cyclobutane-1, -3-dicarboxylic acid. A centre of symmetry is usually present only in **an even – membered ring**
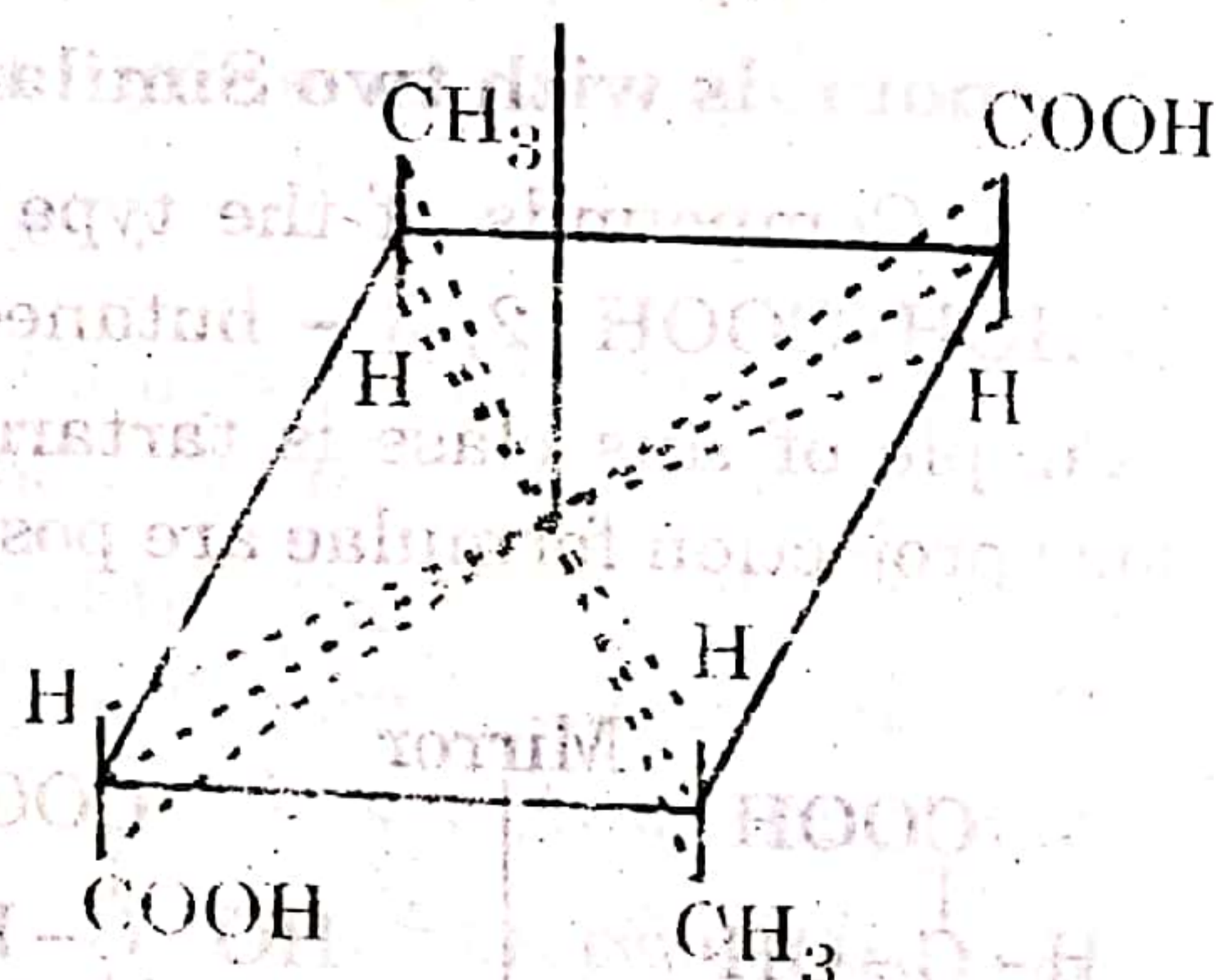
Fig.7.4 A centre of symmetry

(iii) An Alternating Axis of Symmetry of order (n = even number) is an axis such that when a molecule containing such an axis is rotated by 360/n about the axis and then reflection is effected across a plane at right angles to the axis, a new molecule is obtained that is indistinguishable from the original one. For example, 1, 2, 3, 4 -tetramethylcyclobutane (a) has a four fold alternating axis of symmetry because its rotation by 90° (360/4) about the axis AB (passing through the centre of the ring perpendicular to its plane) gives, (b) whose reflection from a plane xy perpendicular to the axis AB appears like (a)
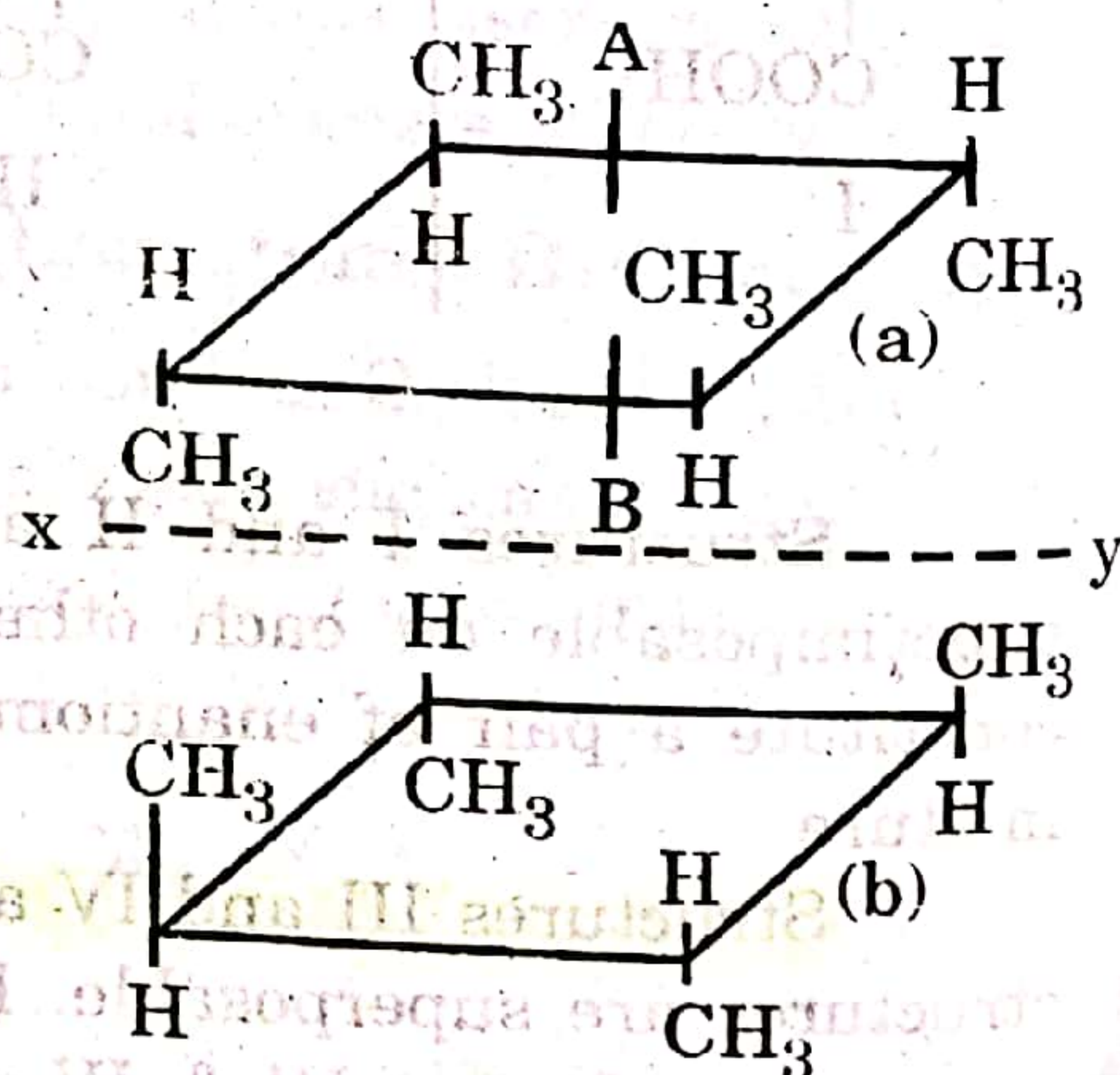
Fig. 7.5

Resolution of Racemate or Racemate Mixture

The separation of a racemic mixture into the individual enantiomers is termed as resolution. Since the two enantiomers in a racemic mixture have identical
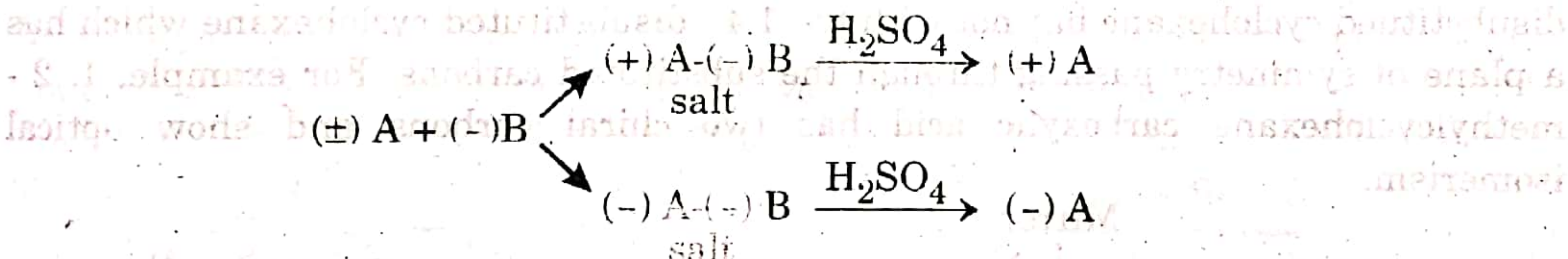
physical and chemical properties except towards optically active reagents, hence the separation of racemic mixtures into their active components is of considerable importance. There are various methods for the resolution of racemates, some of these are described below.

1. Mechanical Separation. The method is applicable only to solid substances which form well defined crystals that can be distinguished as enantiomers.
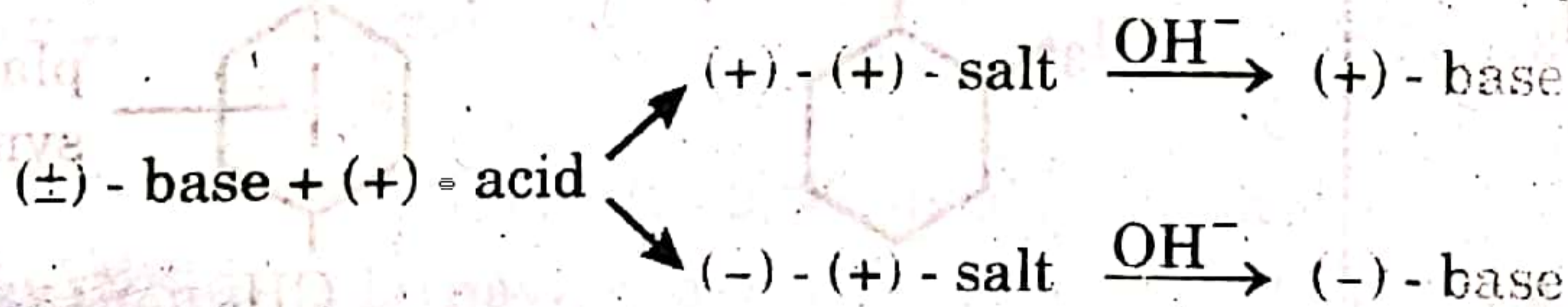
Pasteur adapted this method in separating the enantiomers of sodium ammonium tartarate. A racemic mixture on crystallization may give a mixture of two types of crystals, one set being mirror image of the other. The two sets are separated by hand - picking with the help of a pair of tweezer and a lens. In some cases only one form is obtained.

2. Chemical Method: conversion into Diastereomers. In this method, a racemic mixture is treated with an optically active reagent, to give a pair of non-identical diastereomers. Since the diastereomers are not mirror images each, they will differ in their physical properties and hence it is possible to separate them by physical means such as fractional distillation, crystallization, etc. The pure diastereomers are then converted back into the individual enantiomers.
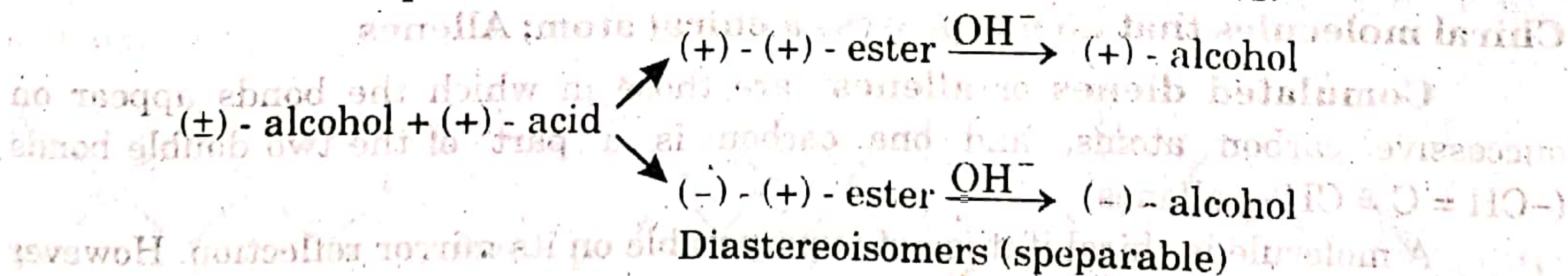
In order to separate a acid, say (±) A, it is treated with an optically base, say (-)B, such as (-) brucine, or (-) cinchonine, or (-) morphine of an optically active amine, two (+) A-(-) B and (-) A- (-) B diastereoisomers (salts) are obtained, which are separated and are then treated with mineral acid to regenerate (+) acid and (-) acid, the base remains in the solution.

$$(\pm) \text{ A} + (-)\text{B} \nearrow \begin{array}{l} (+) \text{ A-}(-) \text{ B} \quad \xrightarrow{\text{H}_2\text{SO}_4} \quad (+) \text{ A} \\ \text{salt} \\ \\ (-) \text{ A-}(-) \text{ B} \quad \xrightarrow{\text{H}_2\text{SO}_4} \quad (-) \text{ A} \\ \text{salt} \end{array}$$

Similarly, a (±) base can be separated by the use of an optically active acid.

$$(\pm) \text{- base} + (+) \text{- acid} \nearrow \begin{array}{l} (+) \text{-} (+) \text{- salt} \quad \xrightarrow{\text{OH}^-} \quad (+) \text{- base} \\ \\ (-) \text{-} (+) \text{- salt} \quad \xrightarrow{\text{OH}^-} \quad (-) \text{- base} \end{array}$$

Racemic mixtures which are not acids or bases can often be separated by making them into derivatives with acid groups and separating the resulting mixture as above. For example, a racemic alcohol can be resolved as follows:

$$(\pm) \text{- alcohol} + (+) \text{- acid} \nearrow \begin{array}{l} (+) \text{-} (+) \text{- ester} \quad \xrightarrow{\text{OH}^-} \quad (+) \text{- alcohol} \\ \\ (-) \text{-} (+) \text{- ester} \quad \xrightarrow{\text{OH}^-} \quad (-) \text{- alcohol} \end{array}$$

Diastereoisomers (speparable)

The chemical method of resolution is widely used and has the advantage that both the enantiomers are obtained.

(iii) Biochemical Method. Certain micro-organisms such as yeast, moulds and bacteria, when are allowed to grow in the solution of a racemic mixture, they assimilate one form selectively leaving the other in solution. The form left in solution can be separated by fractional distillation. For example, when pencillium glaucum (a mould) is added to a solution of (±) tartaric acid, the solution becomes levorotatory due to destruction of dextro form. This method is of limited use because a proper microorganism has to be found, one of the enantiomer is des royed and cannot be applied to (±) mixtures of poisonous substances.

(iv) Differential absorption. When a racemic mixture is poured on a chromatographic column, if the column consists of chiral substances, then in principle the enantiomer should move along the column at different rates and should be separable without having to be converted into diastereomers. For example, racemic mandelic acid has been almost completely resolved by column chromatography on starch.

Optical isomerism in Cyclic Compounds: (Disubstituted cyclohexane derivatives

Any molecule having a chiral carbon atom is chiral provided it has no element of symmetry. This principle is also applicable to cyclic compounds. If two or more substituents are properly situated with respect to one another in a cyclic compound, the substituted carbon will be chiral and the compound may exhibit optical isomerism. Optical isomerism is possible with both the 1, 2 - and 1, - 3 - disubstitued cyclohexane but not with the 1,4 - disubstituted cyclohexane which has a plane of symmetry passing through the substituted carbons. For example, 1, 2 - methylcyclohexane carboxylic acid has two chiral carbons and show optical isomerism.


Mirror

COOH
CH₃

cis - 1,2 -
Racemate

COOH
CH₃

COOH

plane of
symmetry

CH₃

1, - 4 - methylcyclo -
hexanecarboxylic acid.
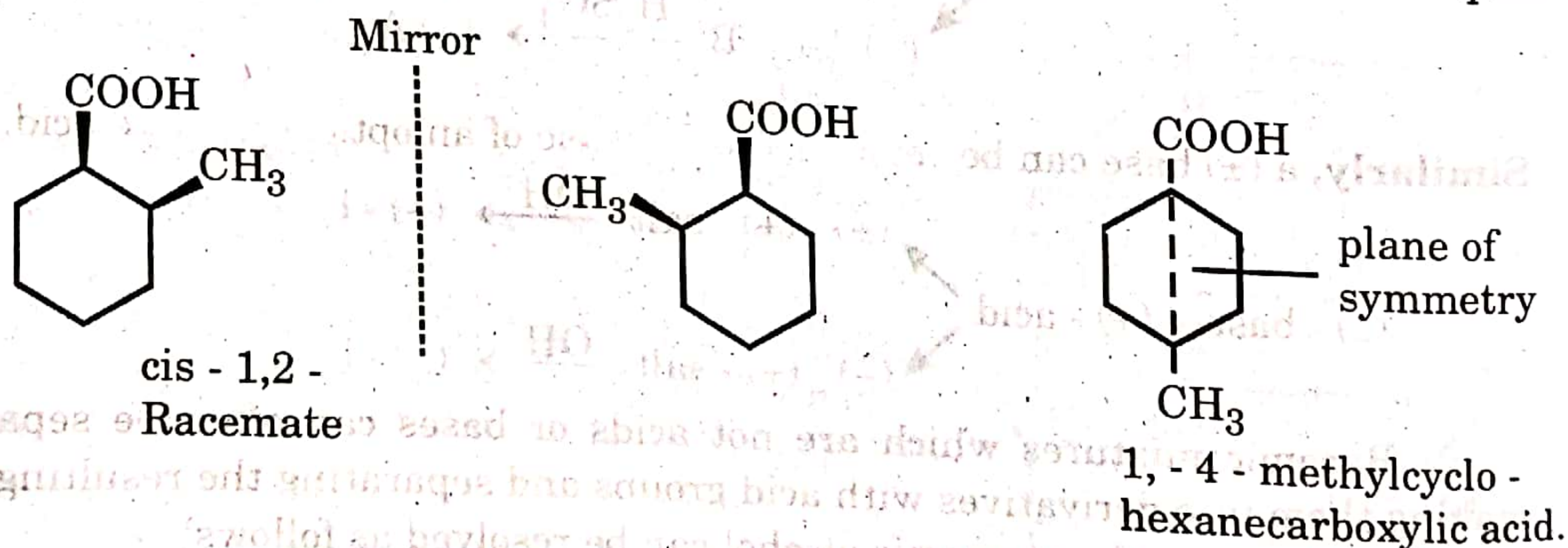
Chiral molecules that do not possess a chiral atom; Allenes

Comulated dienes or allenes are those in which the bonds appear on successive carbon atoms, and one carbon is a part of the two double bonds (−CH = C = CH −; allenes)

A molecule is chiral if it is not superposable on its mirror reflection. However

many chiral molecules are known that do not have chiral atom. For example, some derivatives of allene ($H_2C = C = CH_2$) exhibit optical isomerism, for example 1,3 - diphenylpropanediene. The planes of the π bonds of allenes are perpendicular to each other. The geometry of the bonds causes the groups attached to the end carbon to lie in perpendicular planes and because of this, allenes with different substituents on the end carbons are chiral. (Allenes do not show cis - trans isomerism.

Mirror

1, 3 - diphenylpropanediene
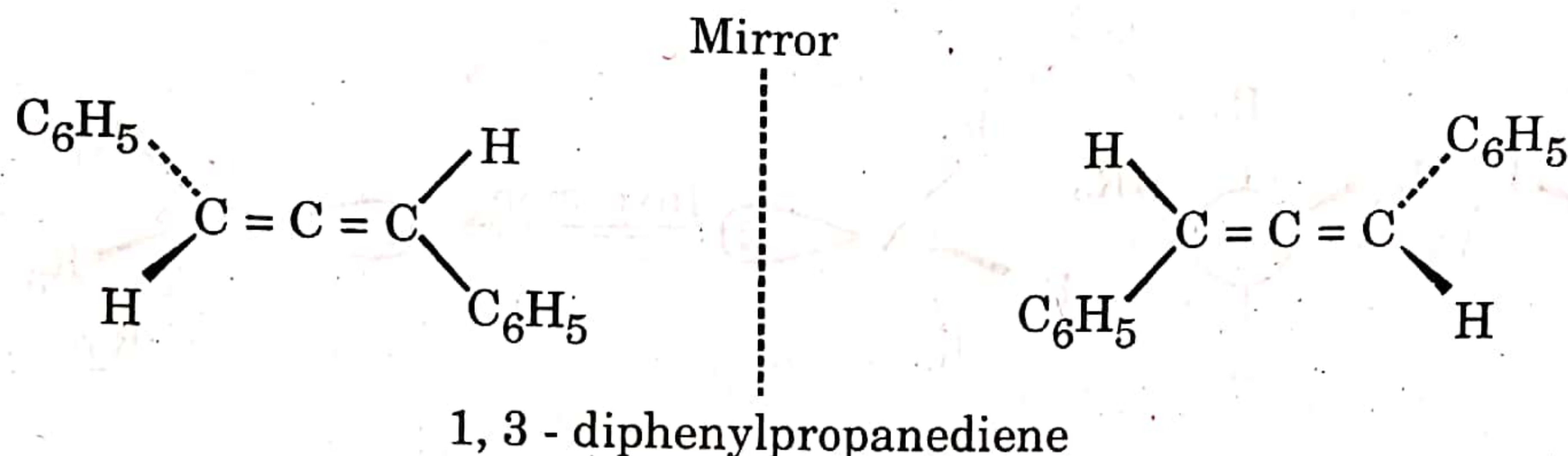
It should be noted that if either of the terminal atoms of an allene has two identical substituents (e.g., $aa \, C = C = C \, aa$), there will be no optical isomerism because the molecule now possesses a plane of symmetry. Moreover, stereoisomerism of the cis-trans type does not exist with allenes.

Biphenyl Derivatives

The substituted biphenyl would be chiral if the two phenyl rings are permanently noncopplanar. Thus substituted biphenyls show optical isomerism when substituents in the ortho positions are large enough to prevent rotation about the bond joining the two benzene rings due to steric hindrance. For example, biphenyl-2, 2'-disulphonic acid exists in two enantiomeric forms.

Mirror
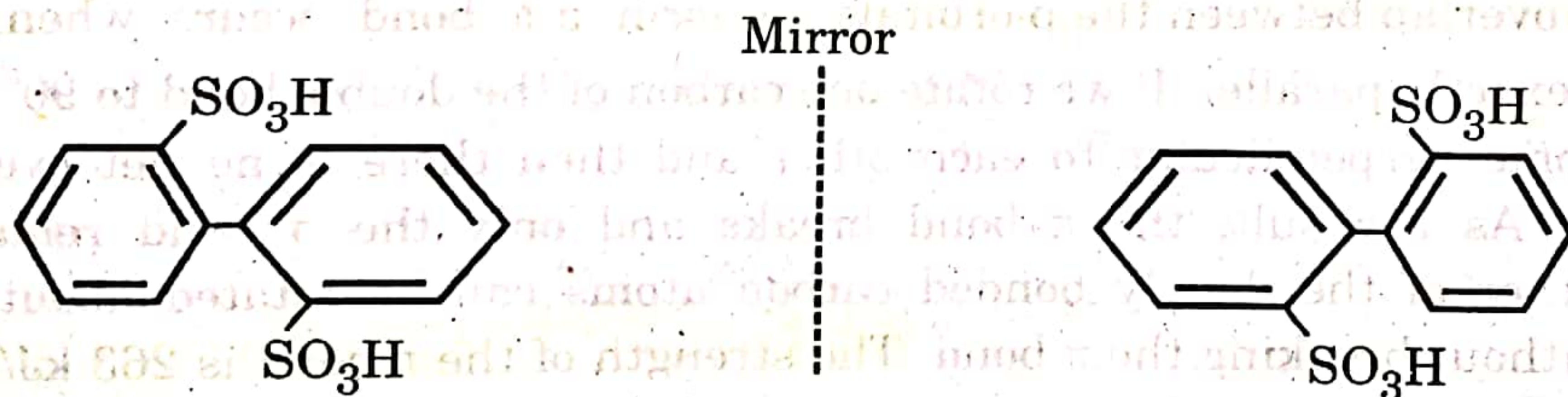
Biphenyl - 2, 2' - disulphonic acid

Spiranes: Compounds having a carbon atom common to two rings are called spiranes. Thus, spiranes may be regarded similar to allenes in which both the double bonds are replaced by rings. These two rings are perpendicular to each other. Properly substituted spiranes as shown below are capable of exhibiting optical activity.

Spirane
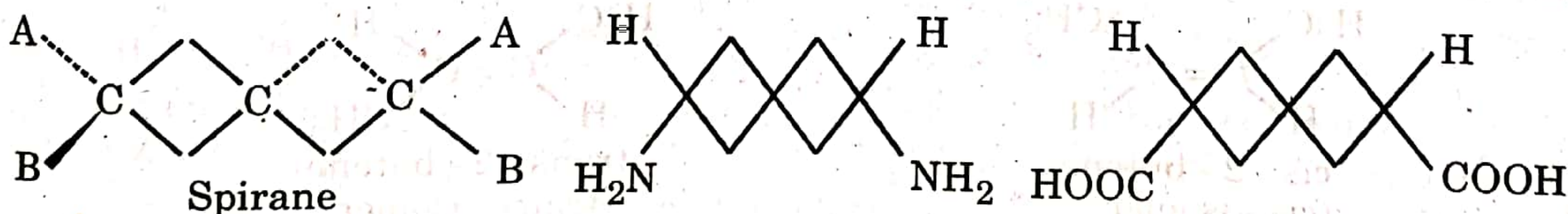
Optical isomerism with a chiral atom other than carbon

Any tetrahedral atom with four different groups attached to it is a chiral atom. Si and Ge are in the same group of the Periodic Table as carbon. They form tetrahedral compounds as carbon does. When four different groups are attached around the central atom in silicon and germanium compounds, the molecules are chiral and the enantiomers can be separated.
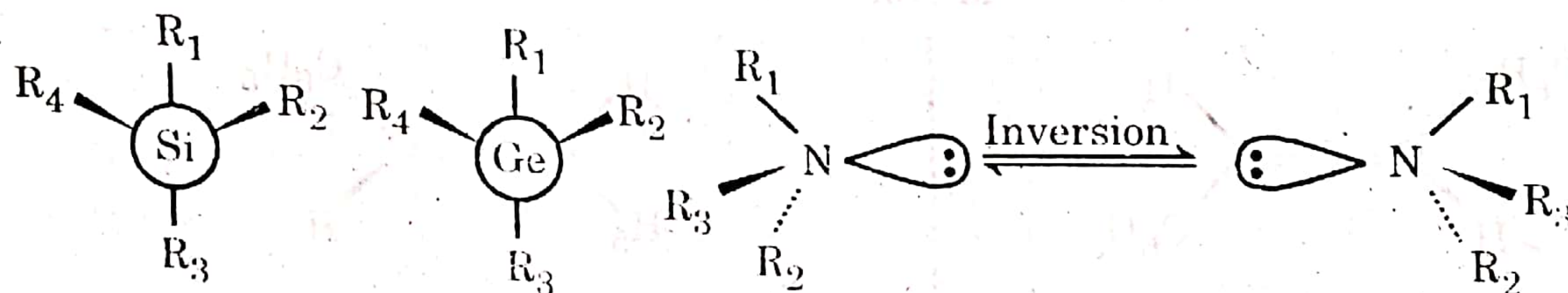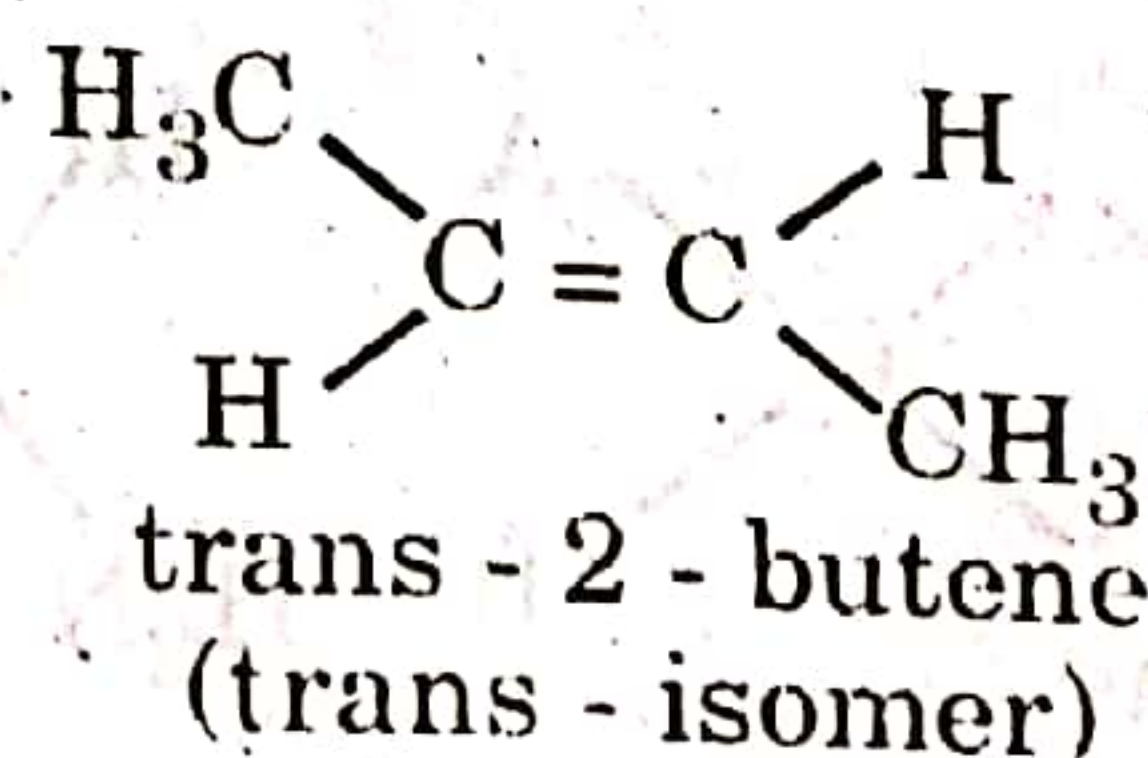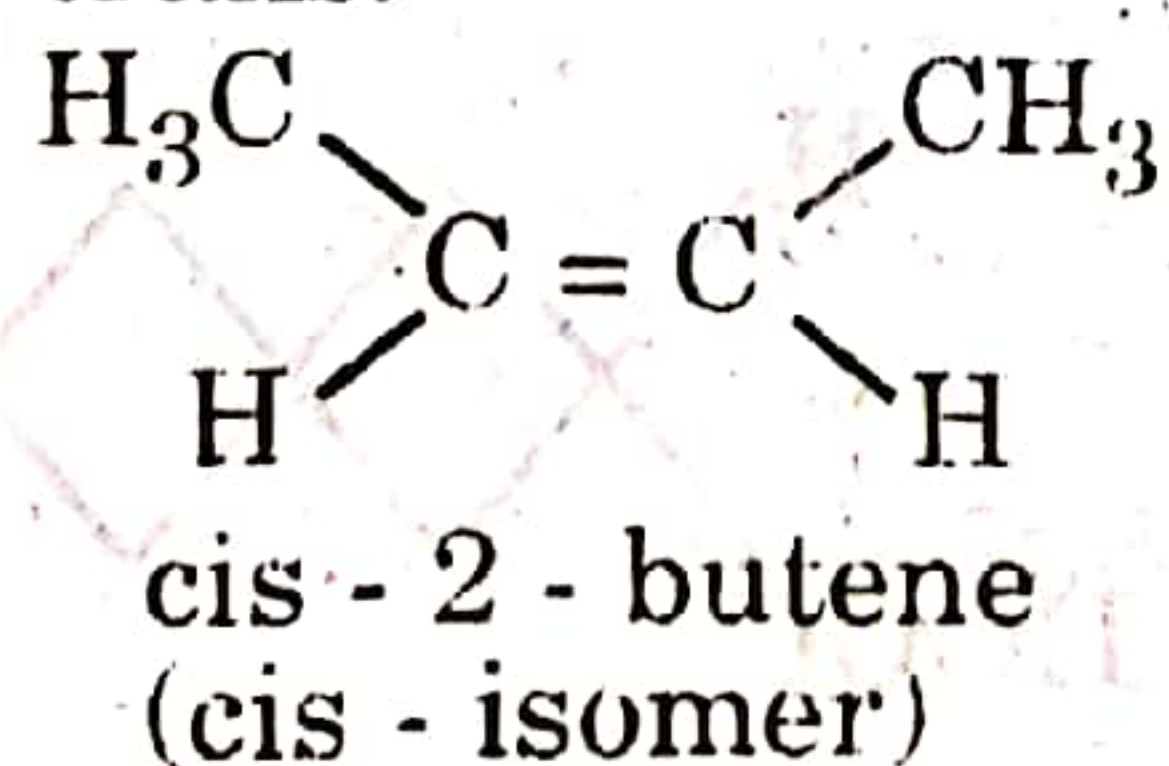

The nitrogen atom of a tertiary amine is also tetrahedral if one considers the unshared pair as occupying one corner of the tetrahedron. The enantiomers of these amines cannot be separated due to their rapid interconversion.

GEOMETRICAL ISOMERISM

Geometrical isomerism (also called cis-trans isomerism) results from a restriction in rotation about double bonds or about single bonds in cyclic compounds.

The carbon atoms of the carbon – carbon double bond are sp^2 hybridized. The C – C double bond consists of a σ (sigma) and a π (pi) bond. The σ bond is formed by the overlap of sp^2 hybrid orbitals. The π bond is formed by the overlap of p orbitals. The maximum overlap between the p orbitals to form a π bond occurs when the p orbitals are exactly parallel. If we rotate one carbon of the double bond to 90°, the p orbitals become perpendicular to each other and then there is no net overlap between them. As a result, the π bond breaks and only the σ bond remains. Therefore, neither of the doubly bonded carbon atoms can be rotated about the double bond without breaking the π bond. The strength of the π bond is 263 kJ/mol which is the barrier to rotation about the double bond. This energy barrier is markedly higher than the thermal energy available to molecules at room temperature. The rotation about carbon-carbon double bond is therefore restricted.

The restriction of rotation about the carbon-carbon double bond is responsible for geometrical isomerism in alkenes. Consider, the molecule of 2-butene which exists in two geometrical isomer and are distinguished from each other by the terms cis and trans.

cis - 2 - butene
(cis - isomer)

trans - 2 - butene
(trans - isomer)

The isomerism due to the difference in spatial arrangement of groups about the doubly bonded carbons atoms is called geometrical isomerism.

The cis isomer is one in which two similar groups are on the same side of the double bond. The trans isomer is that in which two similar groups are on the opposite side of the double bond. This type of isomerism is often called cis-trans isomerism. Geometrical isomers are stereoisomers, because they have the same structural formula but different spatial arrangement of atoms. Geometrical isomerism is possible only when each carbon atom of the double bond possesses two different groups.

When a molecule contains a chiral carbon along with a double bond, it exhibits geometrical as well as optical isomerism and has four isomers, i.e., a cis pair of enantiomers and a trans pair of enantiomers:

Z or cis dl pair   E or trans dl

4 - methyl - 2 - hexene

If the two atoms or groups on any of the double-bonded carbons are identical, the compound does not exshibit geometrical isomerism, e.g., $(CH_3)_2C = CH_2$, $Cl_2C = CHCl$

If a molecule contains more than one double bond which can individually lead to geometrical isomerism, the number of isomers in such case is 2^n, where n is the number of double bonds with different substituents at each end, as in 2, 4 – heptadiene. The number of geometrical isomers may be decreased if some of the double bonded carbons have both the substituents identical, as in 2,5 – heptadiene.

cis, cis -   trans, trans -   cis, trans -   trans, cis

2, 4 - heptadiene

cis, cis - or   cis - trans or   trans-trans or
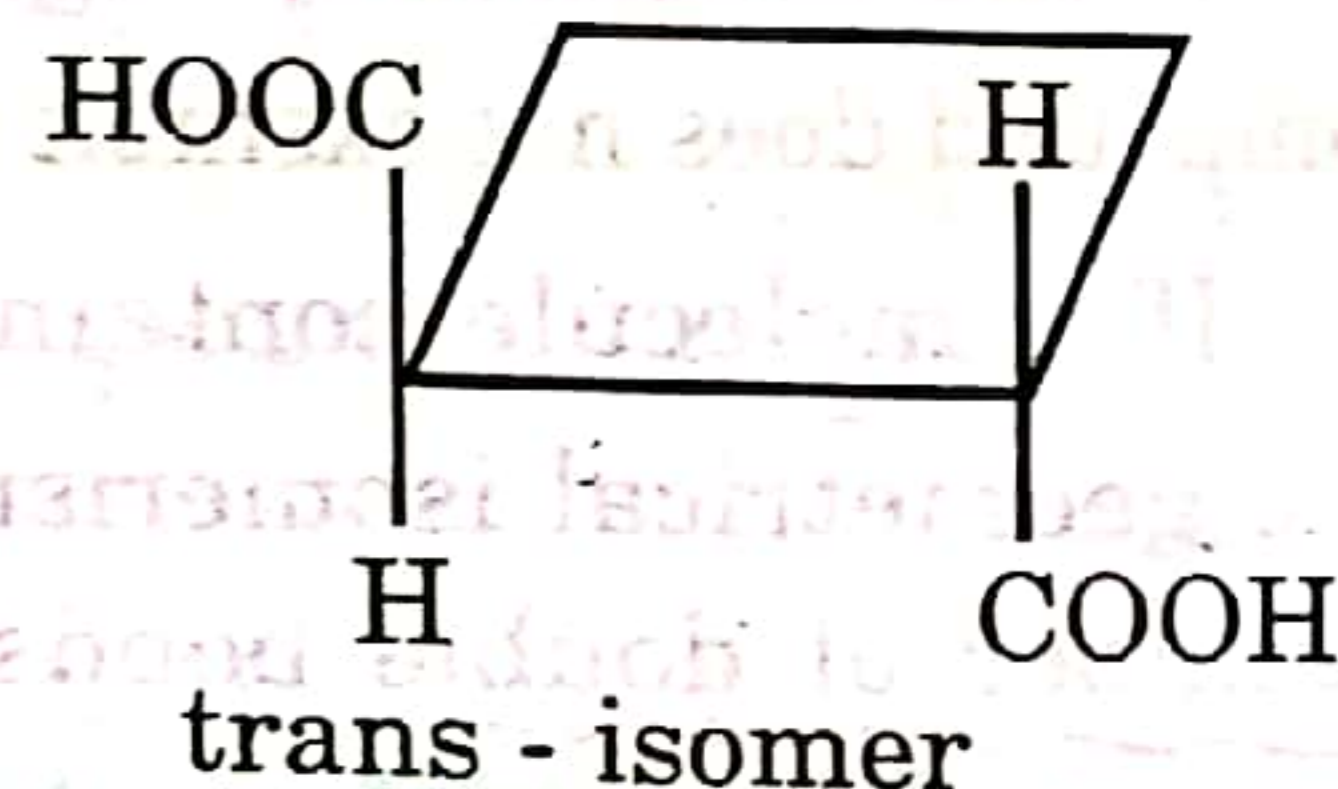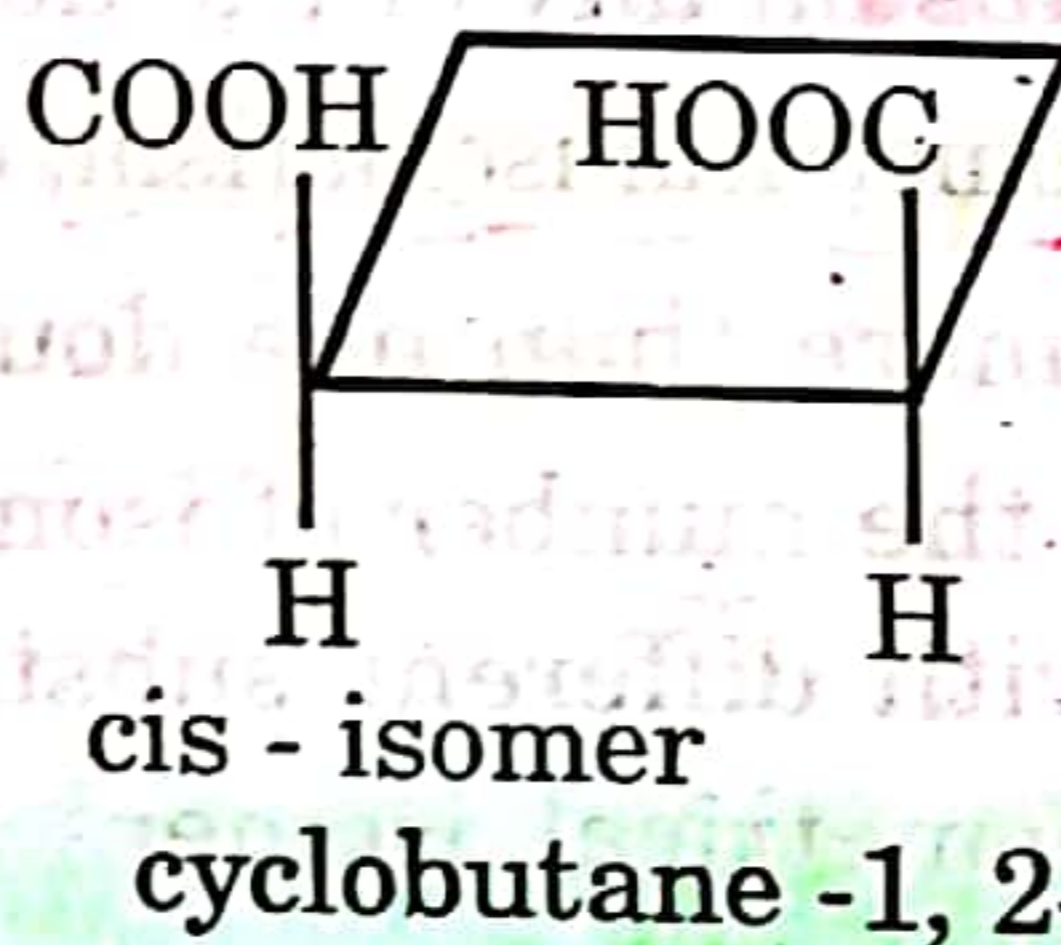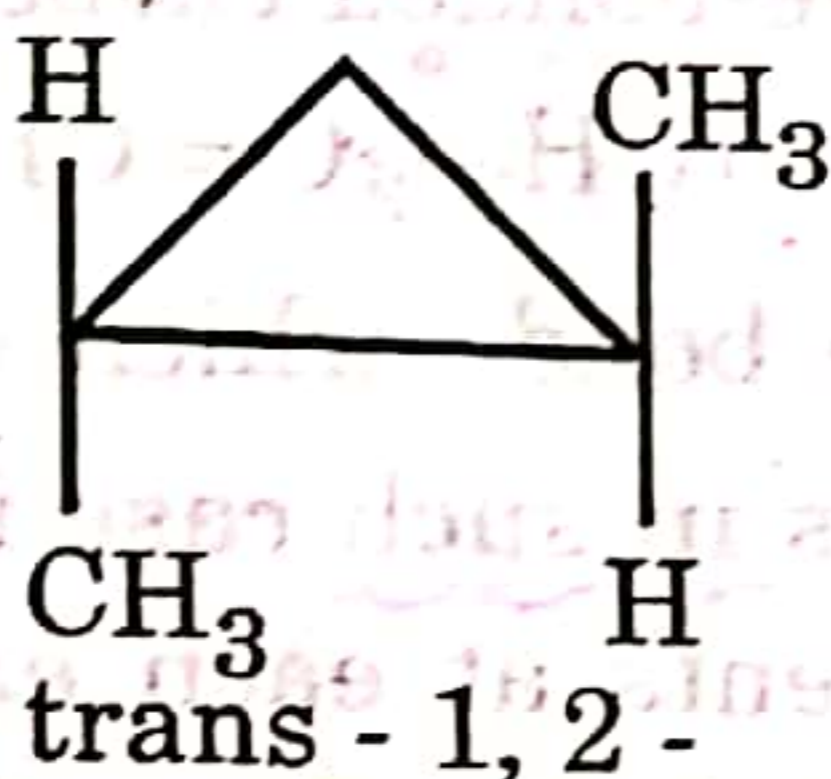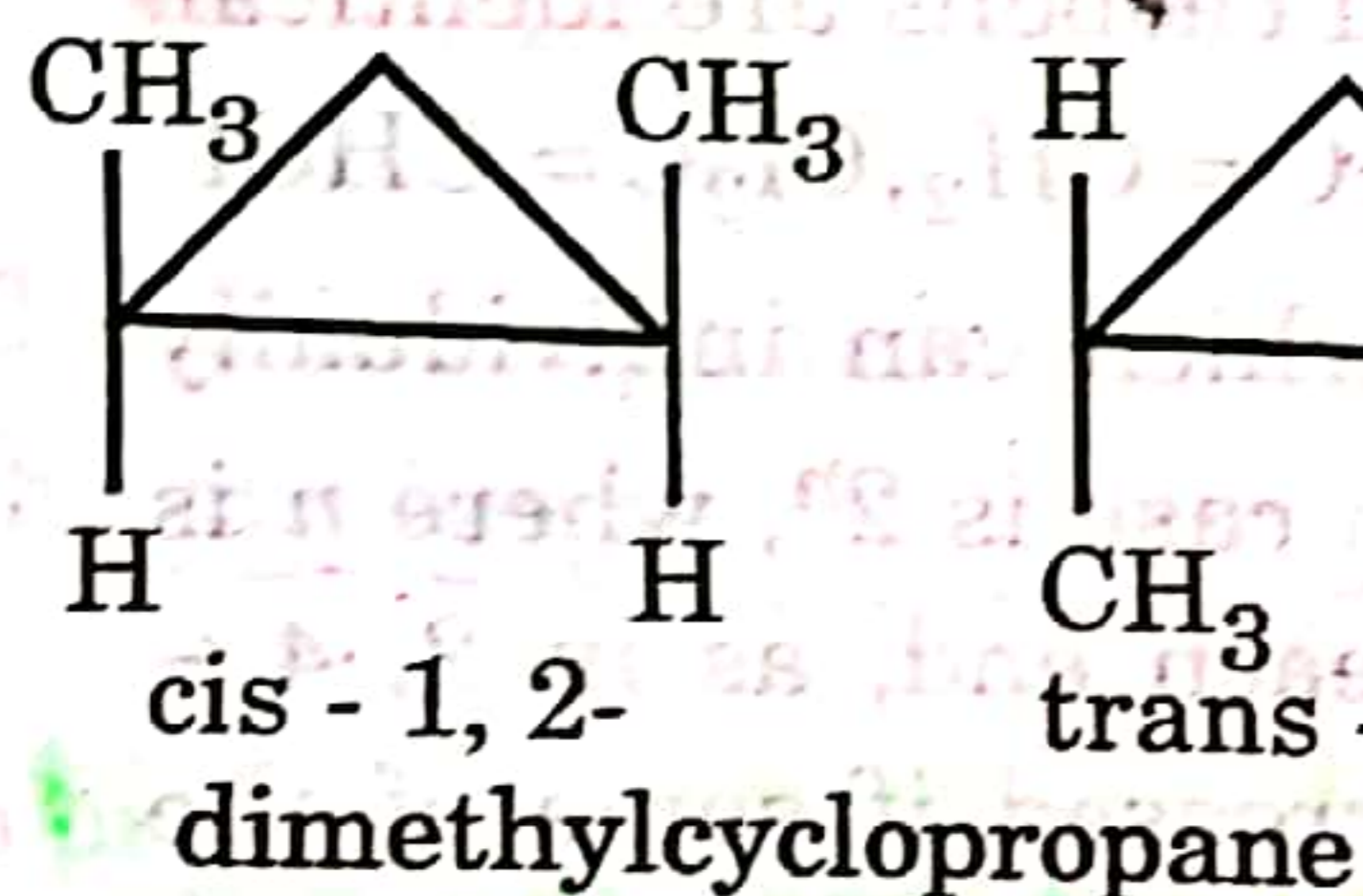Z – Z   Z – E   E – E

2,5-heptadiene

Geometrical isomerism with other double bonds

Geometrical isomerism also exists in molecules that possess carbon-nitrogen, nitrogen-nitrogen double bonds. Oximes (of aldehydes and unsymmetrical ketones) and azobenzenes are typical examples. In nomenclature, the prefixes syn and anti are adapted instead of cis and trans. In the syn-oxime the hydroxy group on nitrogen and hydrogen on the carbon are on the same side and in anti-isomer are on the opposite side.

syn - form
(α - benzaldoxime)

anti - form
(β - Benzaldoxime)

syn - Azobenzene

anti - azobenzene
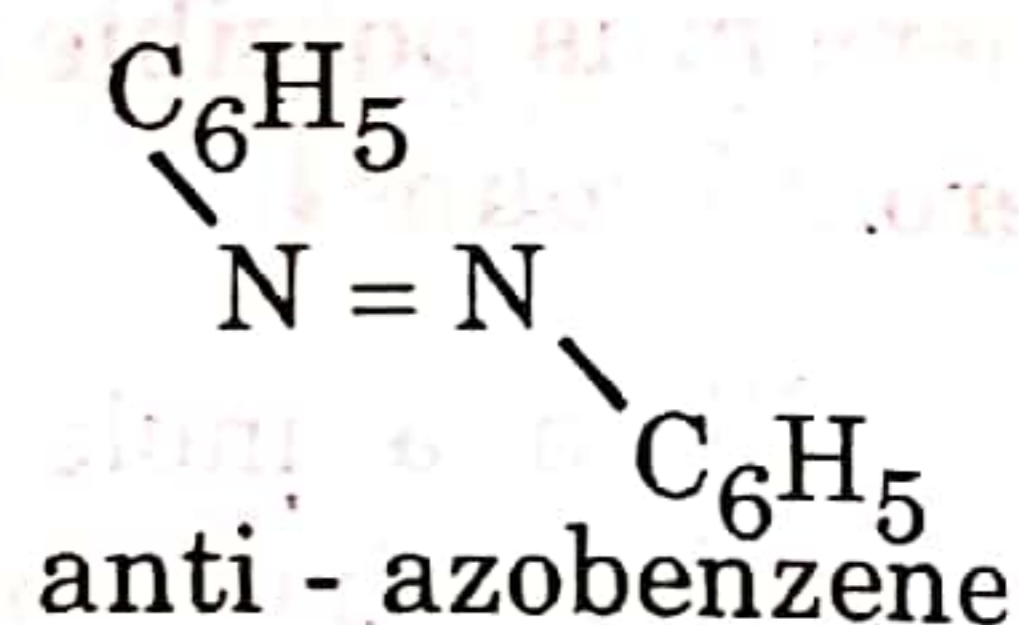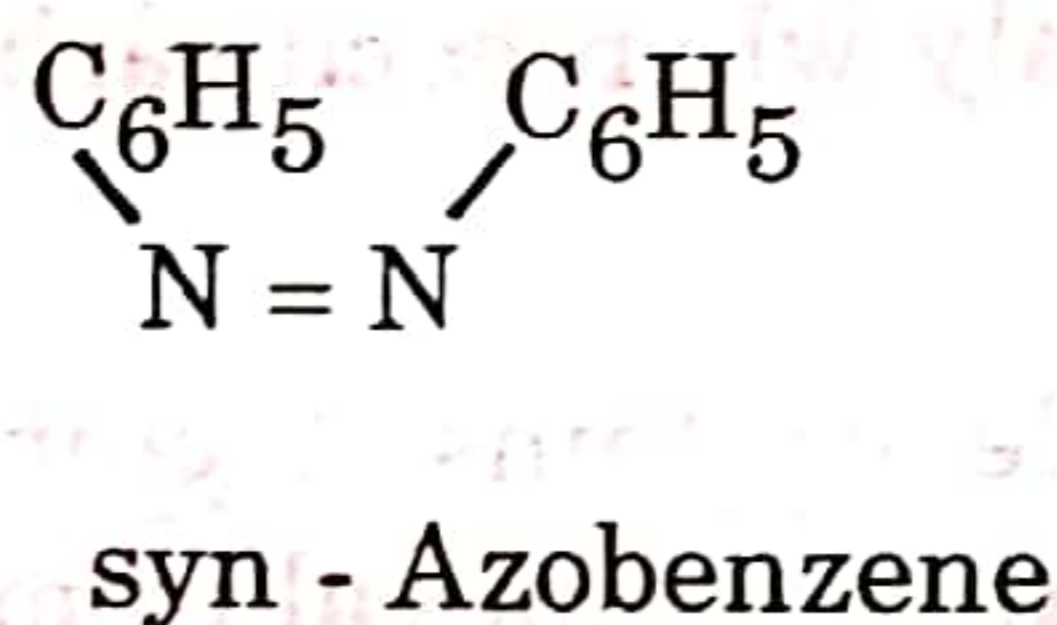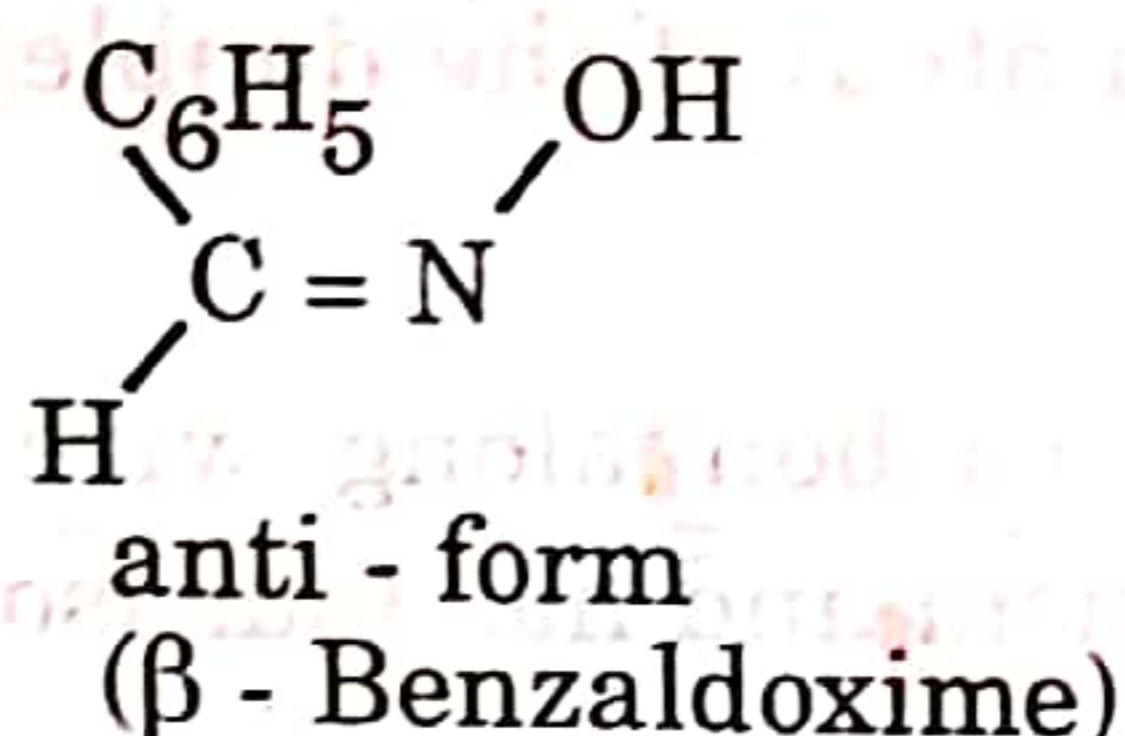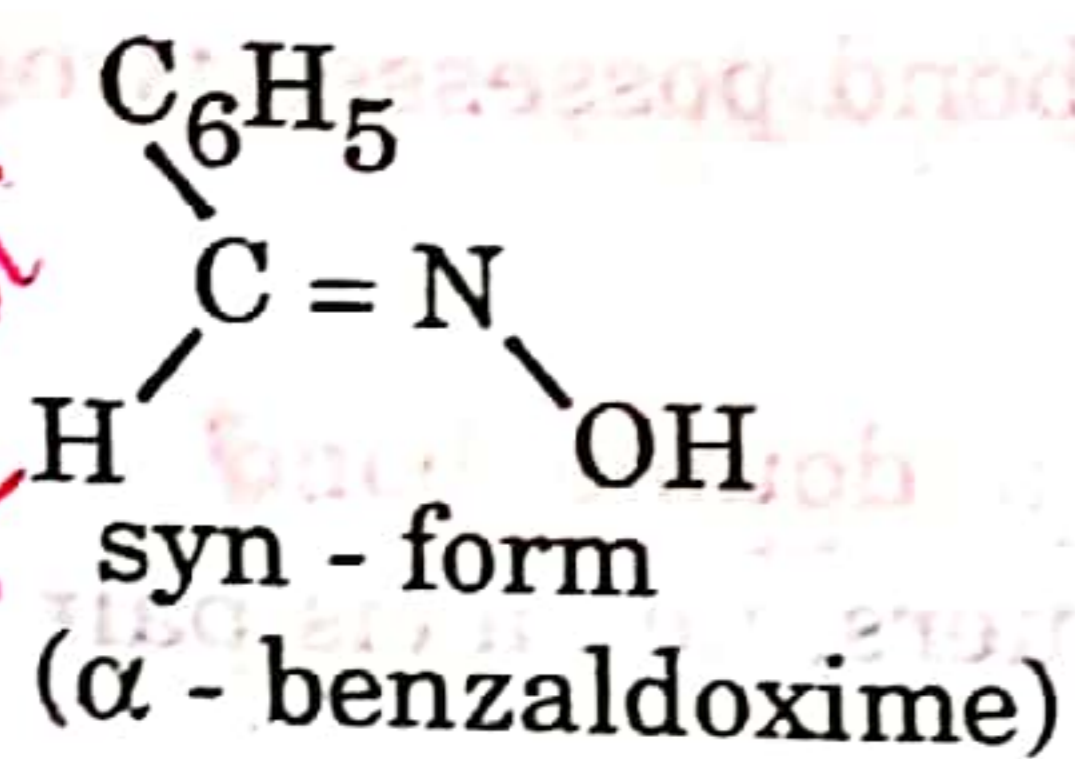
Geometric isomerisum in cyclic compounds

Geometrical isomerism is also possible when any two carbons of a cyclic compounds have substituents on them, each have two different groups. There can be no rotation about C-C single bonds forming a ring because rotation would break the bonds and break the ring. If the substituents are on the same side, then it is cis -, if on the opposite side, then it is trans -. Example of cis - trans isomerism in cyclic compounds are given below.

cis - 1, 2-
dimethylcyclopropane

trans - 1, 2 -

cis - isomer

trans - isomer
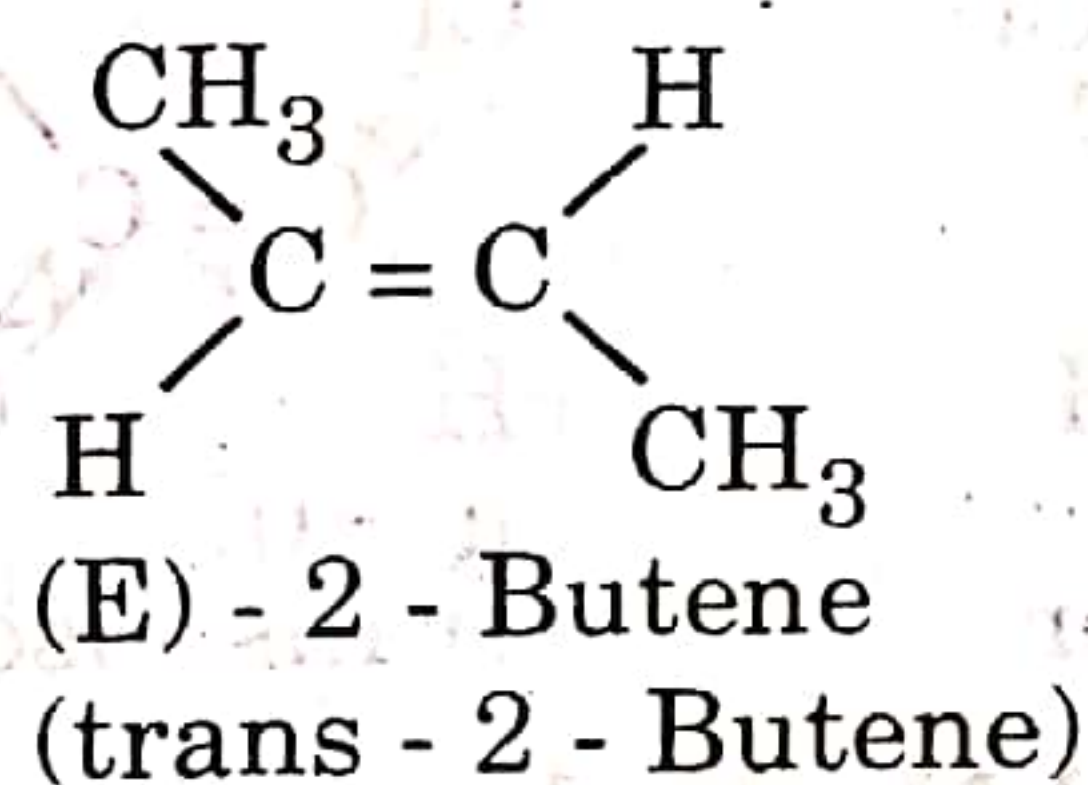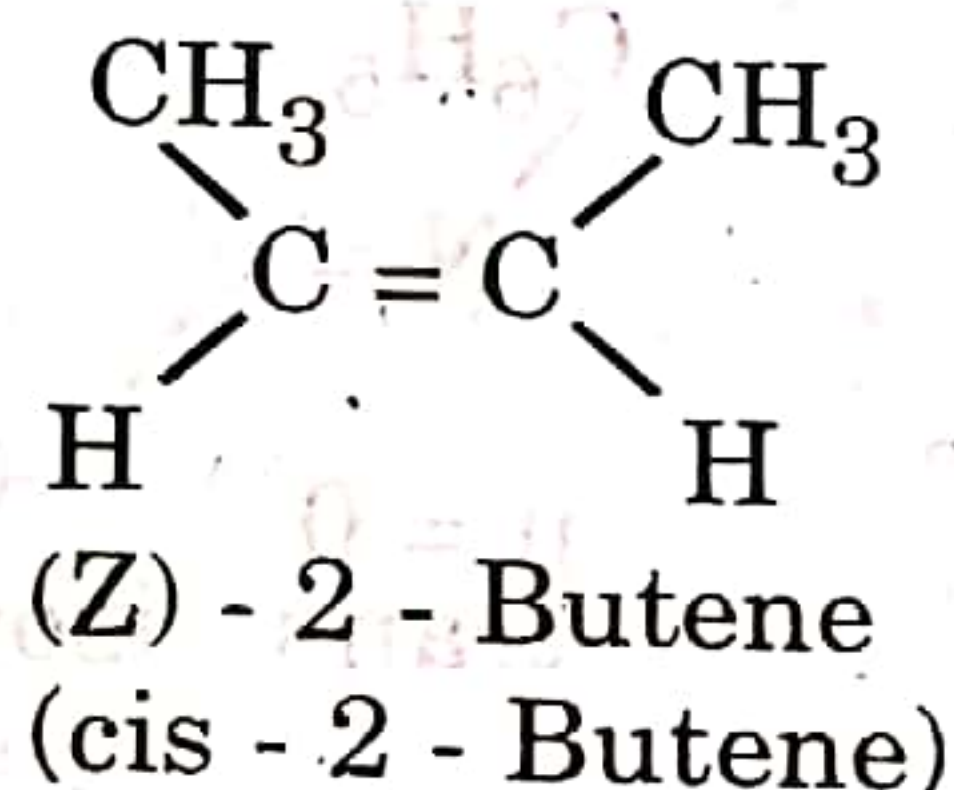cyclobutane -1, 2-dicarboxylic acid

Sometimes, a double bond may be present in a ring. In small rings (cyclopropene to cycloheptene) the double bonds are so constrained that they must be cis. The cyclooctene ring is large enough to permit the trans isomers to exist and for rings larger than 10 - membered, the trans isomers are more stable.
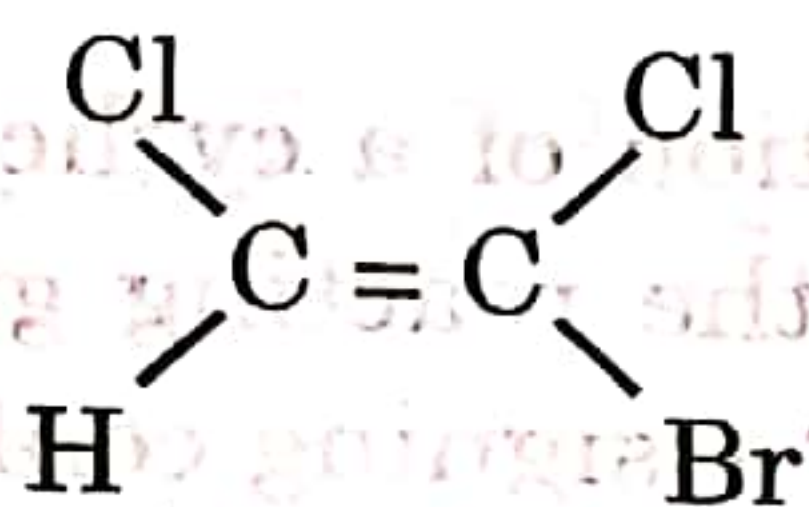
Nomenclature of Geometrical Isomers: (E-Z Convention)

The system of nomenclature cis and trans of geometrical works very well for alkenes in which both carbons of the double bond have two identical groups. However, when there are three or four different groups attached to carbon atoms of the double bond, it is difficult to assigne cis or trans designations to the geometrical isomers. To remove this difficulty, a new system of nomenclature called the (E) -(Z) system based on the Cahn–Ingold–prelog sequence rules originally applied to chiral molecules and is applicable to all cases of geometrical isomerism. According to this system, the two groups on each carbon of the double bond are ranked in order of priority, as was done in the case of chiral molecules. If both the groups of higher

priority are on the same side of the double bond, the geometrical isomer is designated as Z (from the German word Zusammen meaning together), if on the opposite sides, then it is designated as E (from the German word entgegen meaning opposite). A few examples are given below:

$$CH_3\quad CH_3$$
$$\diagdown\;/$$
$$C = C$$
$$/\;\diagdown$$
$$H\qquad H$$

(Z) - 2 - Butene
(cis - 2 - Butene)

$$CH_3\qquad H$$
$$\diagdown\;/$$
$$C = C$$
$$/\;\diagdown$$
$$H\qquad CH_3$$

(E) - 2 - Butene
(trans - 2 - Butene)

(handwritten in margin: 2 = Zusammen, E = opposite)

$$Cl\qquad Cl$$
$$\diagdown\;/$$
$$C = C$$
$$/\;\diagdown$$
$$H\qquad Br$$

(E) - 1 - Bromo - 1, 2 - dichloroethene
(cis - 1 - Bromo- 1, 2 - dichlorethene

$$Cl\qquad Br$$
$$\diagdown\;/$$
$$C = C$$
$$/\;\diagdown$$
$$H\qquad Cl$$
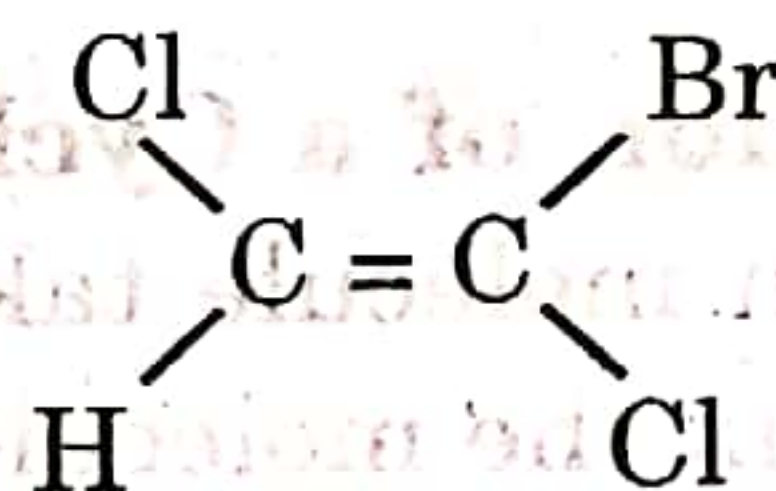
(Z) 1 - Bromo - 1, 2- dichloroethene
(trans-1-Bromo - 1, 2 - dichloroethene)

Note that the prefixes Z and E are not necessarily correspond to the cis and trans respectively.

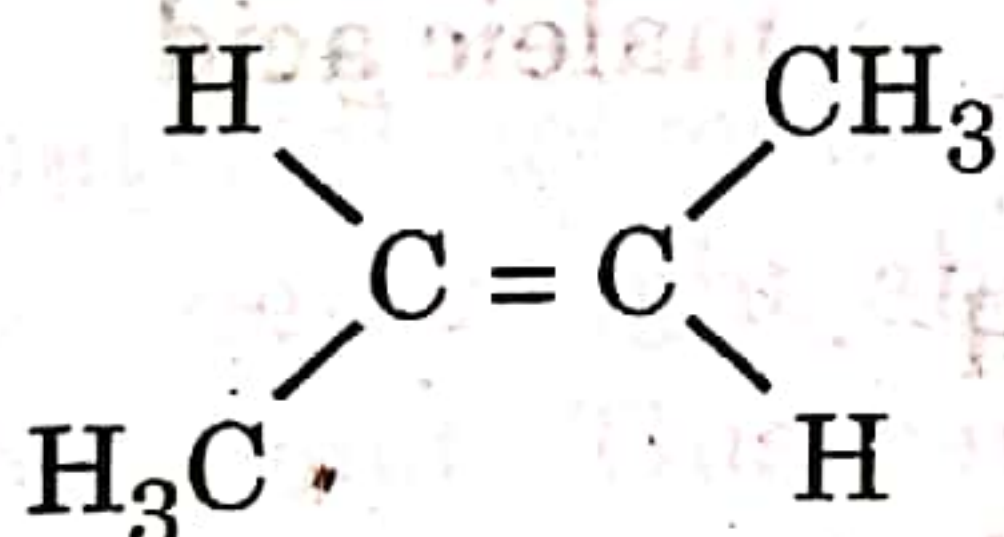## Determination of the Configuration of the Geometrical Isomers

There is no absolute method for the determination of the configuration of geometrical isomers. A number of methods have been used for the determination of configuration of geometrical isomers depending on the nature of the compound. Some of them are described below:
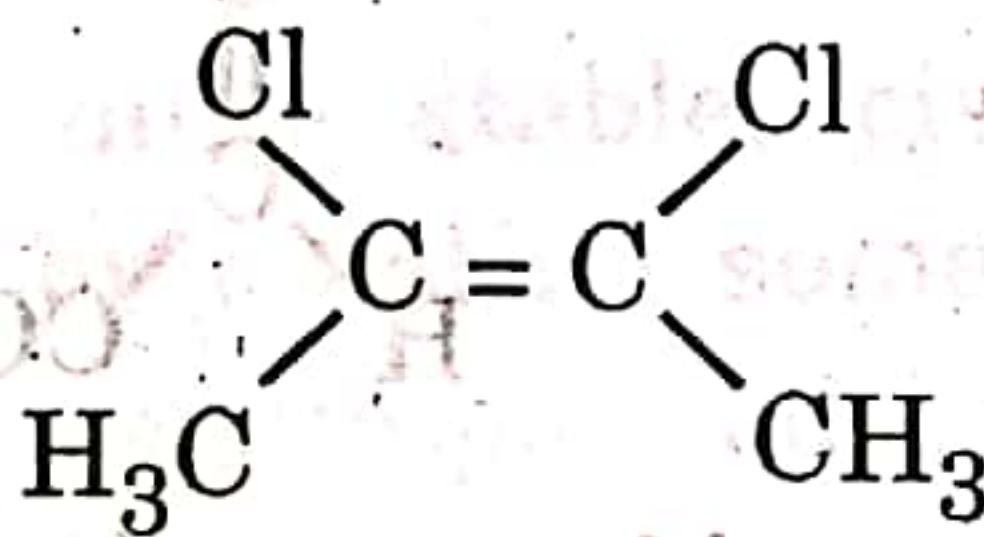
1. Physical Methods

(i)   **Melting points, boiling points and solubility.** The trans-isomer has, in general, a higher m.p. and a lower boiling point. The cis - isomers have higher solubilities.
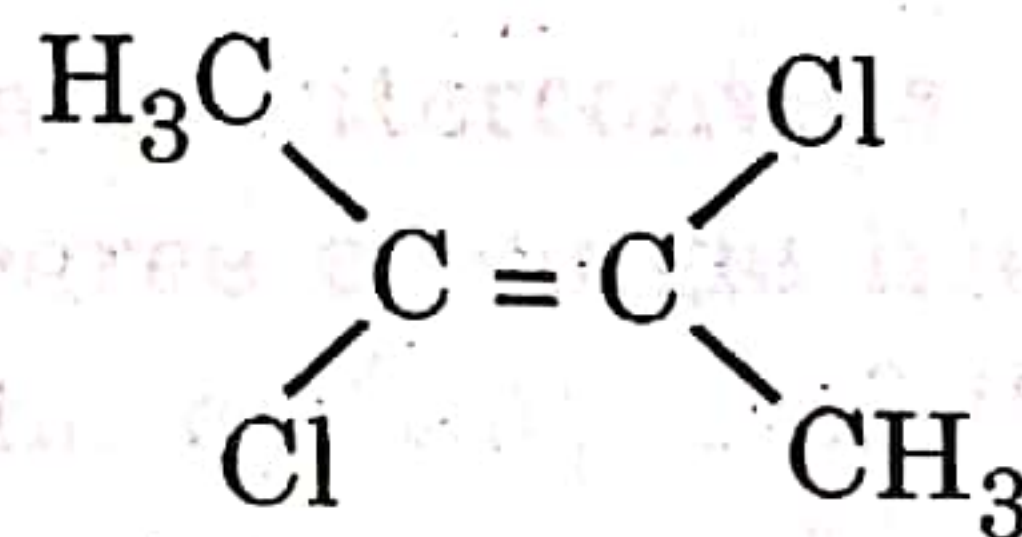
$$H_3C\qquad CH_3$$
$$\diagdown\;/$$
$$C = C$$
$$/\;\diagdown$$
$$H\qquad H$$
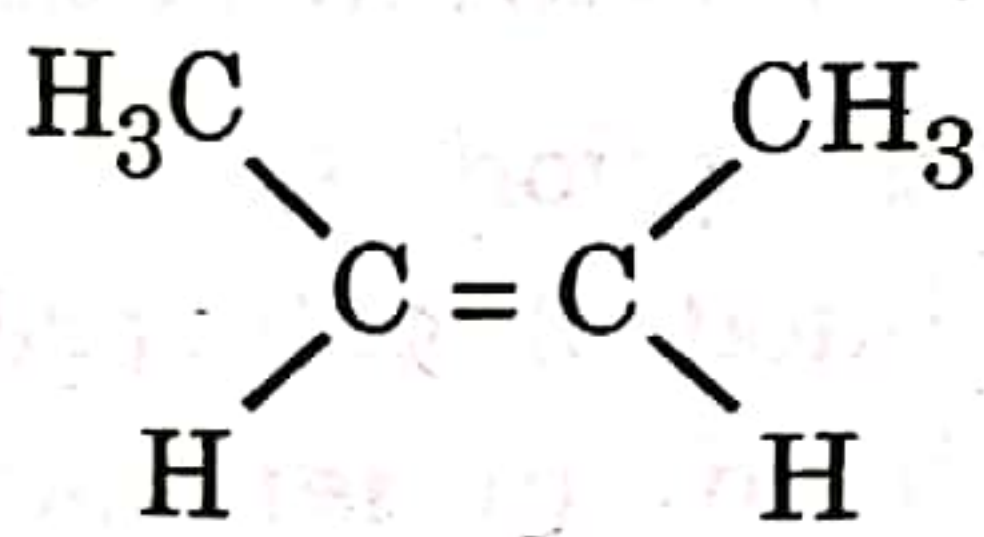
cis–2–butene
m.p. - 139°C
b.p. 3.73°C

$$H\qquad CH_3$$
$$\diagdown\;/$$
$$C = C$$
$$/\;\diagdown$$
$$H_3C\qquad H$$

trans–2–butene
m.p. – 105.5°C
b.p. 0.9°C

$$Cl\qquad Cl$$
$$\diagdown\;/$$
$$C = C$$
$$/\;\diagdown$$
$$H_3C\qquad CH_3$$

2,3 – dichloro –
cis – 2 – butene
b.p. = 126°C

$$H_3C\qquad Cl$$
$$\diagdown\;/$$
$$C = C$$
$$/\;\diagdown$$
$$Cl\qquad CH_3$$

2,3 – dichloro –
trans–2–butene
b.p. 103°C

The solubilities of maleic and fumaric acids are 79.0g/100 cm^3 and 0.7g/100 cm^3 at 20°C.

(ii)   **Dipole moment.** The cis-isomer, in general, has a higher dipole moment than the trans-isomer. The cis-isomer of 1,2-dichloroethene has higher dipole

moment because the two chloro groups are attached to the same side of the double bond and the combined inductive effects are additive, trans-1,2-dichloroethene has one chloro and one hydrogen on each side of the double bond and hence the bond moments cancel each other.
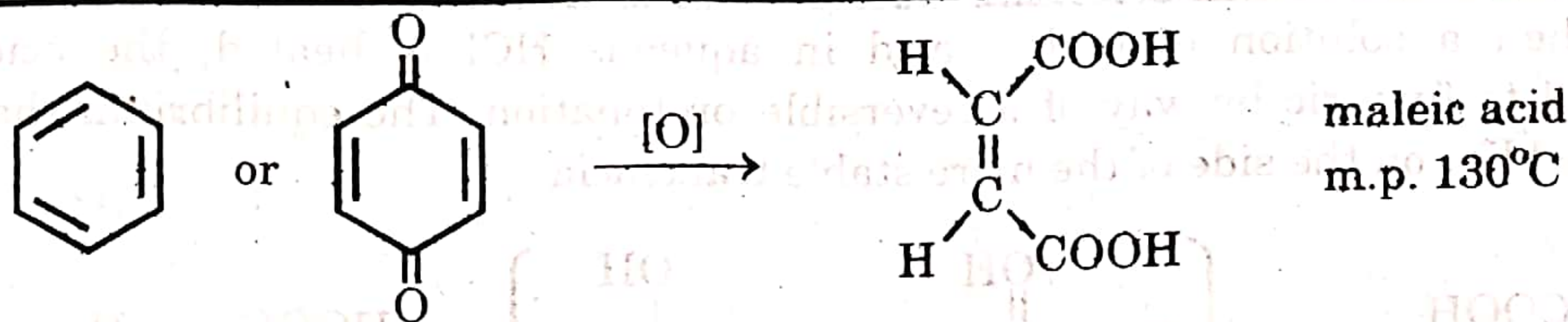

$\mu = 1.85$
cis - isomer

$\mu = 0$
trans - isomer

$\mu = 3.0$
cis - isomer

$\mu = 0$
trans - isomer
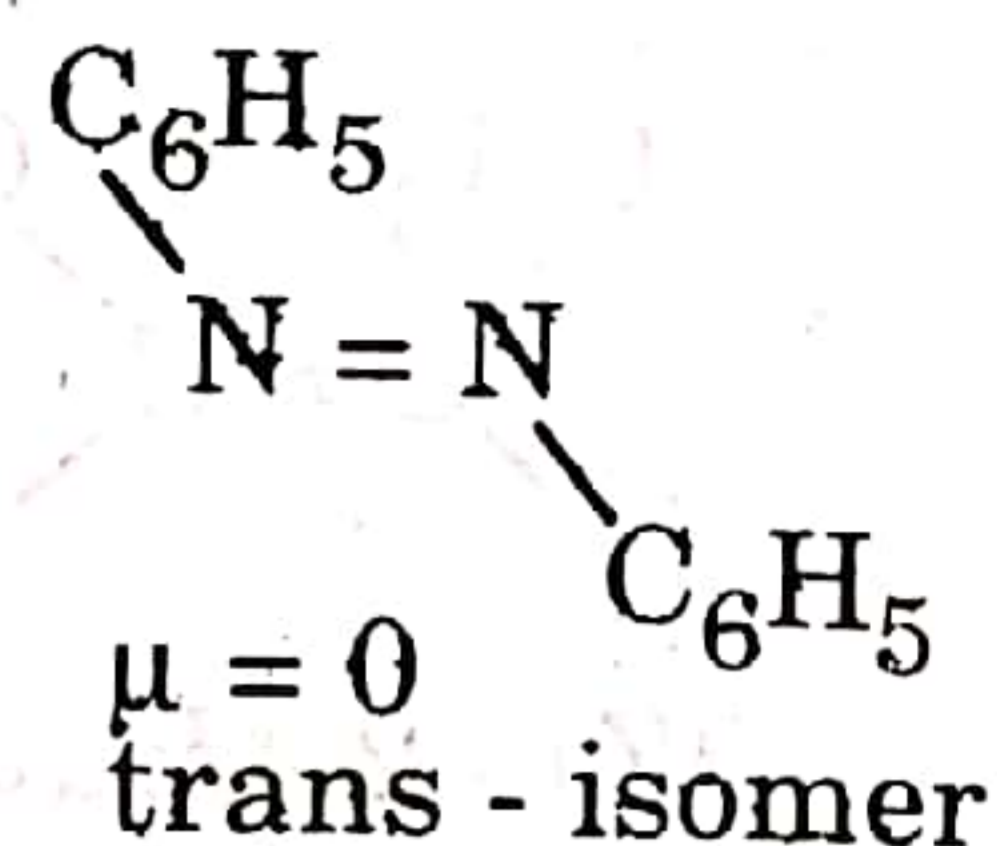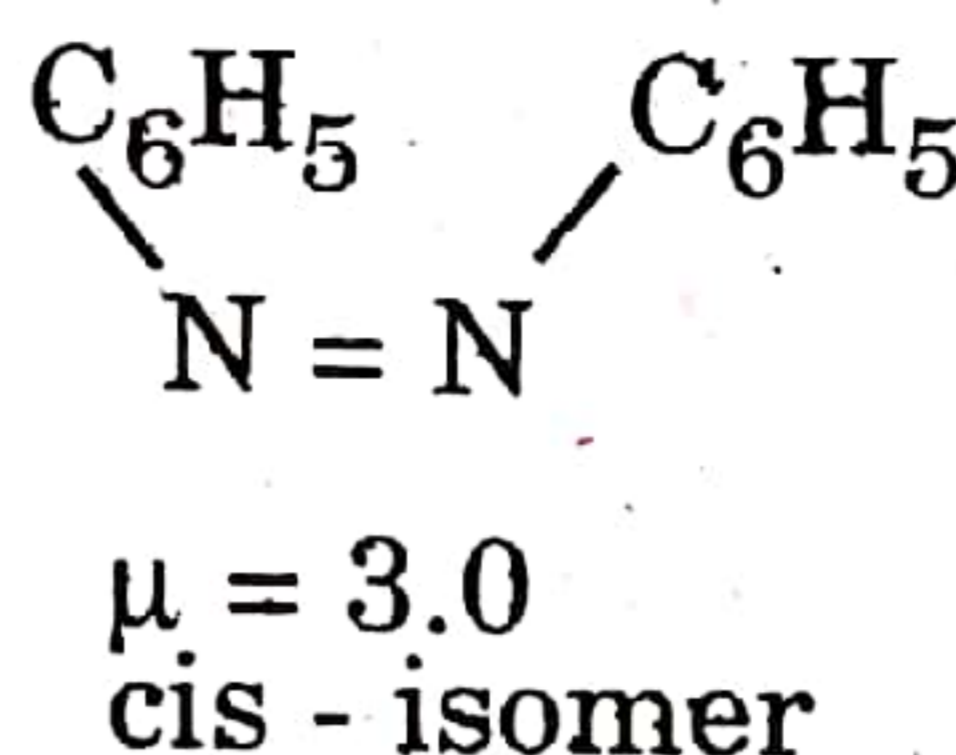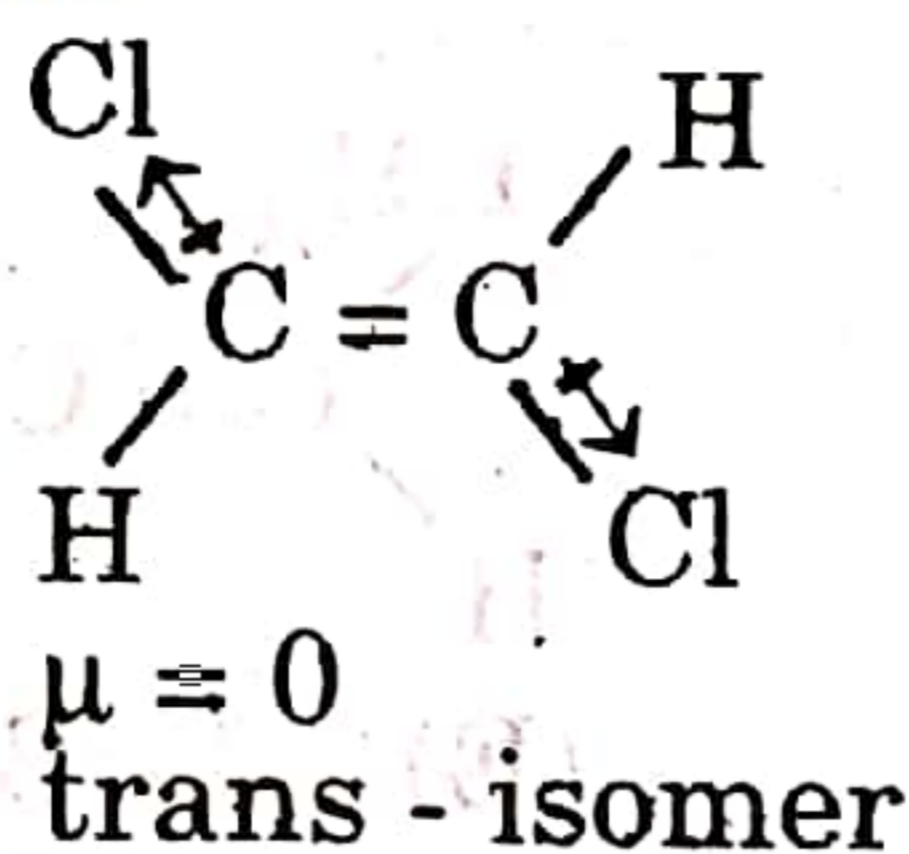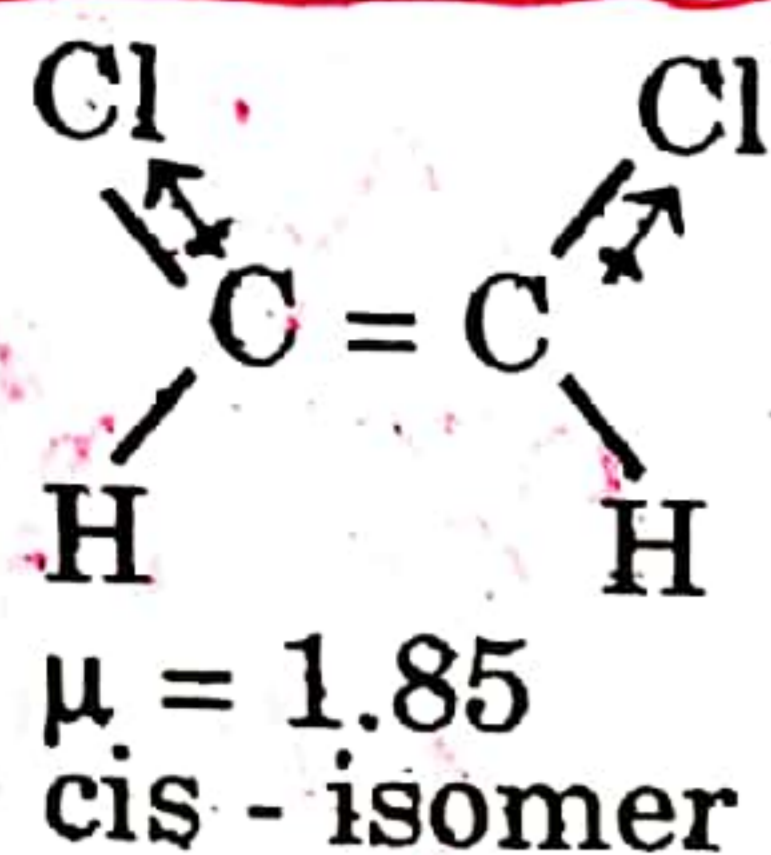
2. Chemical Methods

(i) By Formation of a Cyclic Compound. The formation of a cyclic molecule from an open chain molecule takes place easily only when the reacting groups are close to each other in the molecule. This fact is very useful in assigning configuration to cis-trans isomers in which doubly bonded carbon atoms carry groups that are capable of reacting with each other. It is expected that cis-isomer will undergo ring closure much more readily than the trans-isomer. The configuration of maleic and fumaric acids is established on this basis. The maleic acid (the cis-isomer) is converted to maleic anhydride by the dehydration of maleic acid at 140°C, whereas fumaric acid does not undergo cyclization at this temperature, but when it is heated to a high temperature (250 – 300°C), isomerization takes place and maleic anhydride is formed. Hydrolysis of the anhydride yields only maleic acid.

maleic acid

$\xrightarrow[-H_2O]{140°C}$

maleic anhydride

$\xleftarrow[-H_2O]{300°C}$

Fumaric acid

hydrolysis
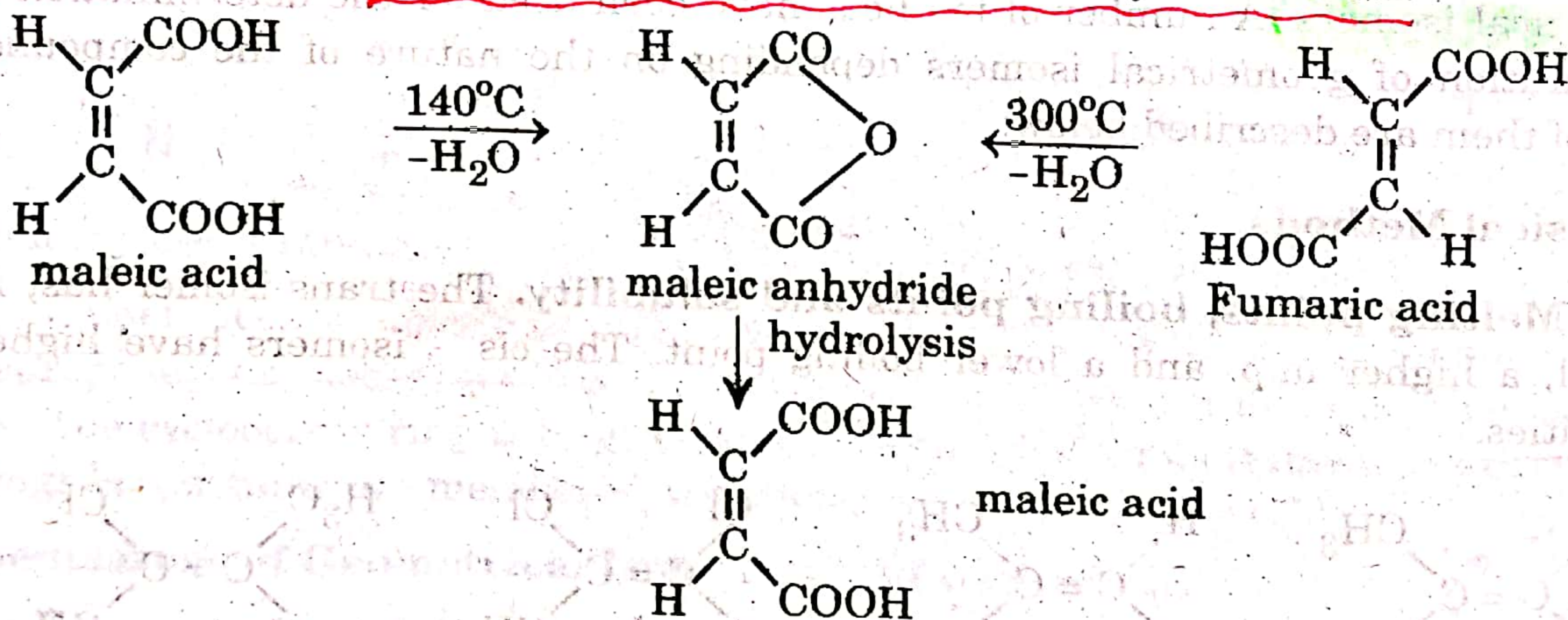
maleic acid

It is, therefore, reasonable to conclude that maleic acid is the cis-isomer and fumaric acid is the trans-isomer.

(ii) Formation of open chain compounds from cyclic Compounds. Benzene or quinone on oxidation gives dicarboxylic acid (m.p. 130°C). From the structure of benzene or quinone, it becomes clear that the two carboxyl groups must be on the same side (cis). Therefore, maleic acid (m.p. 130°C) must be cis and the other isomer fumaric acid (m.p. 302°C) must be trans.

$$\text{[benzene or quinone]} \xrightarrow{\text{[O]}} \begin{array}{c} H \quad COOH \\ C \\ \parallel \\ C \\ H \quad COOH \end{array} \quad \begin{array}{l} \text{maleic acid} \\ \text{m.p. } 130°C \end{array}$$

(iii) Correlation with Compounds of known Configuration.

Configurations of the geometrical isomers may be determined by correlation with the compounds of known configuration. For example, if the cis-crotonic acid is converted into 2-butene by the following series of the reactions, the butene produced is the cis-isomer, if the butene produced were the reference compound of known configuration, its preparation from crotonic acid would prove the configuration of the crotonic acid.

$$\begin{array}{c} CH_3 \quad COOH \\ C = C \\ H \quad H \end{array} \xrightarrow{LiAlH_4} \begin{array}{c} CH_3 \quad CH_2OH \\ C = C \\ H \quad H \end{array} \xrightarrow{C_6H_5SO_2Cl} \begin{array}{c} H_3C \quad CH_2OSO_2C_6H_5 \\ C = C \\ H \quad H \end{array}$$

cis – crotonic acid

$$\downarrow LiAlH_4$$

$$\begin{array}{c} CH_3 \quad CH_3 \\ C = C \\ H \quad H \end{array}$$
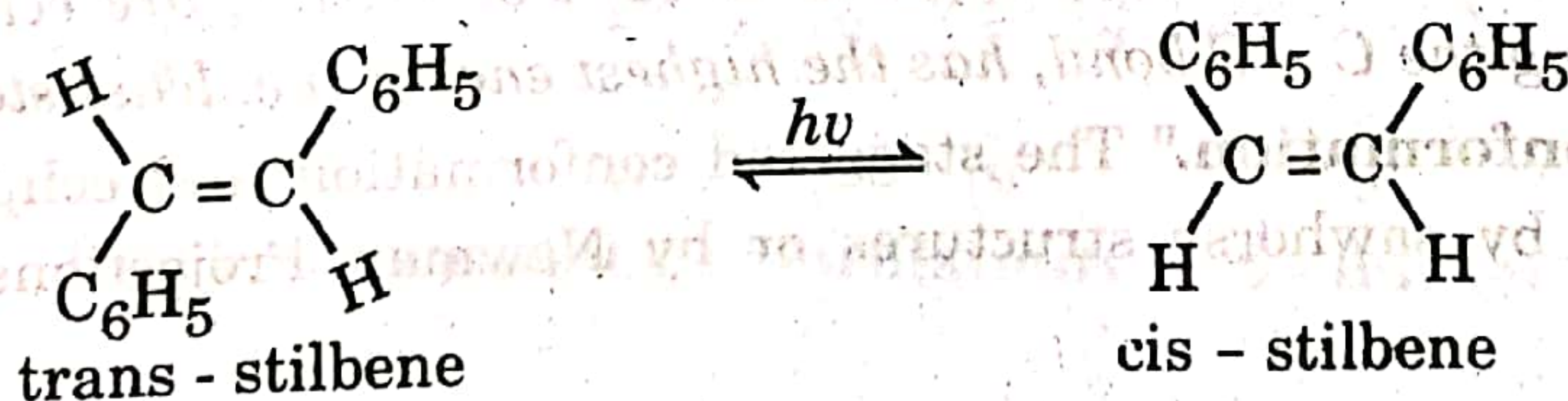
cis–2–butene
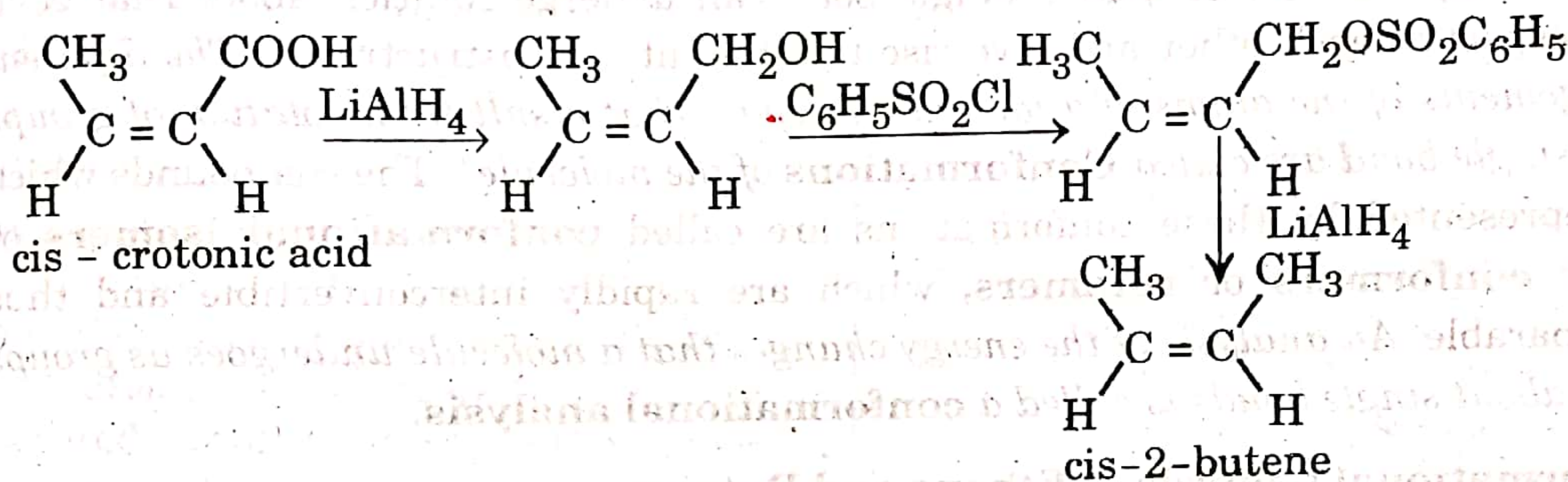
Comparison of Stability of cis and trans isomers

The stability of cis-isomers are lower than those of the corresponding trans-isomers. The density, refractive index, solubility, heat of combustion, dipole moment and the dissociation constant of the cis-are greater than those of the trans-isomers. It can be seen from these properties that the cis-isomer is usually the labile form.

It is possible by suitable means, to convert the labile cis-isomer into the stable trans-isomer.

Interconversion of Geometrical Isomers

Although geometrical isomers are quite stable, cis-trans interconversion about double bonds can be brought about by creating some degree of single bond character in the double bond. This can be accomplished by the excitation of the molecule by heat, or by exposure to light, or by transitory addition, for example of a proton to the double bond. Irradiation of trans-stilbene with ultraviolet light causes isomerization to the less stable cis-isomer.

$$\begin{array}{c} H \quad C_6H_5 \\ C = C \\ C_6H_5 \quad H \end{array} \quad \underset{hv}{\rightleftharpoons} \quad \begin{array}{c} C_6H_5 \quad C_6H_5 \\ C = C \\ H \quad H \end{array}$$

trans - stilbene   cis – stilbene

When a solution of maleic acid in aqueous HCl is heated, the acid is isomerized to fumaric by way of a reversible protonation. The equilibrium that is established lies on the side of the more stable trans-acid.

maleic acid   capable of free rotation   fumaric acid
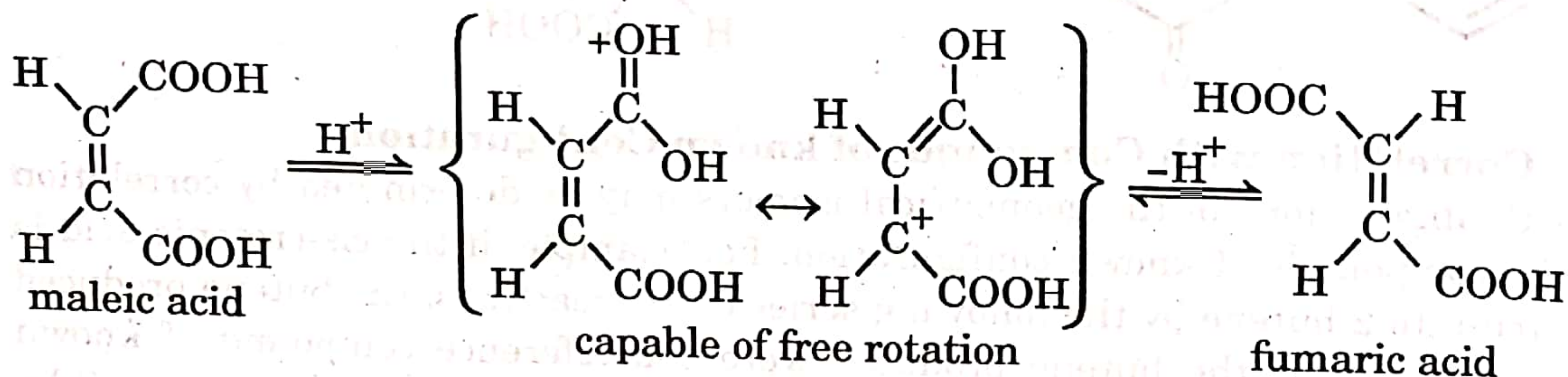
CONFORMATIONAL ISOMERISM

Groups bonded only by a single bond can undergo rotation about that bond with respect to each other and give rise to different stereostructures. "*The different arrangements of the atoms of a molecule in space that result from rotation of groups about single bond are called* **Conformations** *of the molecule*". The compounds which are represented by these conformations are called **conformational isomers** or simply **conformers** or **rotamers,** which are rapidly interconvertible and thus nonseparable. *An analysis of the energy changes that a molecule undergoes as groups rotate about single bonds is called a* **conformational analysis.**

Conformational analysis of Ethane and Butane

Ethane. In ethane, rotation of one CH_3 group with respect to the other about the carbon-carbon single bond gives an infinite number of different conformations, each of which has a certain energy associated with it. For ethane there are two extremes, a conformation of highest and one of lowest potential energy.

The conformation in which the hydrogen atoms attached to each carbon are at a maximum distance apart, i.e., are perfectly staggered, has the lowest potential energy and is called **staggered conformation.** As the bond rotates, the energy gradually increases until the eclipsed conformation is reached, where the energy is at a maximum. Further rotation decreases the energy again. The angle of rotation is known as the **angle of torsion.** It is also called **dihedral angel.** In the eclipsed conformation the distance between H atoms on adjacent C atoms is at a minimum, leading to a condition of maximum repulsion between H atoms, it is, therefore, of highest energy and has the least stability. "*The conformation in which the H atoms attached to each carbon are directly opposite to each other, i.e., are eclipsed when viewed head on along the C – C bond, has the highest energy (i.e, least stable) and is called* **eclipsed conformation.**" The staggered conformation and eclipsed can be represented either by sawhorse structures or by Newman Projections as shown below:

Staggered   eclipsed   Staggered   eclipsed

Sawhorse Structures   Newman Projections

Fig. 7.6 conformation of ethane
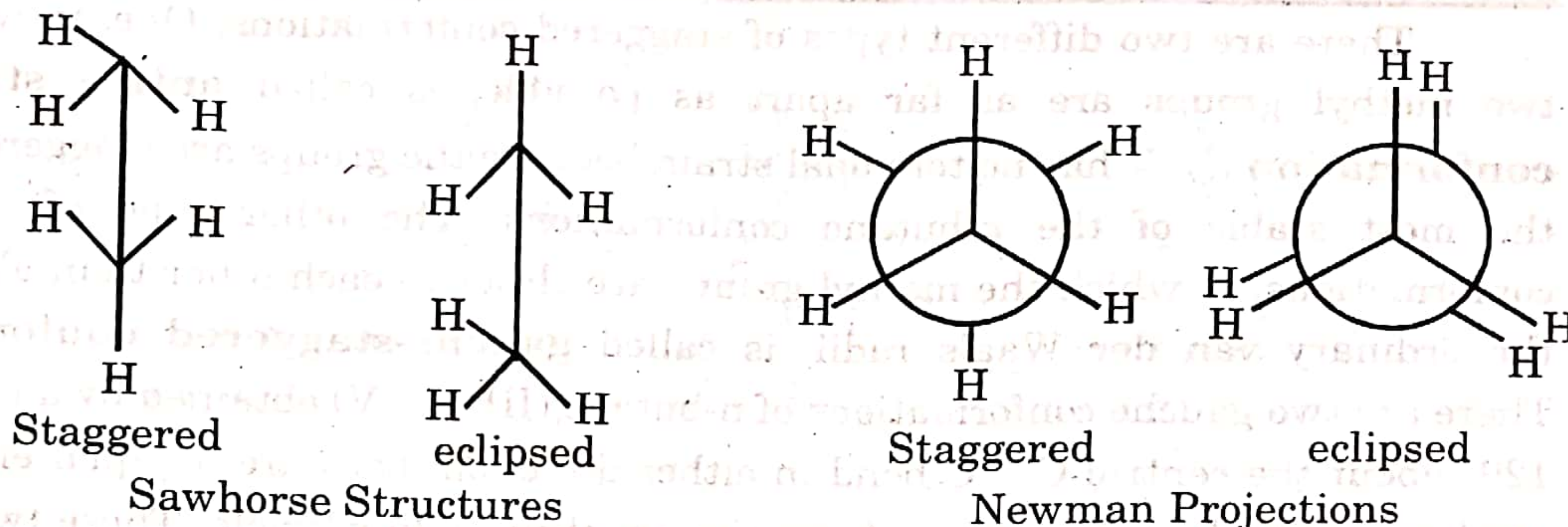
For ethane the difference in energy between the staggered and eclipsed conformations is 12.1 kJ/mole. This difference in energy is called the energy barrier. This small barrier to rotation is also called the torsional barrier of the single bond or torsional strain of the molecule. A molecule of ethane, therefore, has to surmount this energy barrier in passing from one staggered conformation to another, unless the temperature is extremely low (−250°C) some ethane molecules (at any given moment) will have enough energy to surmount this barrier. Most molecules will wag back and forth with their atoms in staggered or nearly staggered conformations. The more energetic ones will rotate through eclipsed conformations to other staggered conformations.

The energy changes accompanying the conformation rotation can be represented graphically by plotting the energy of an ethane molecule as a function of rotation about the C–C bond. The energy changes that occur are shown in Fig.7.7.
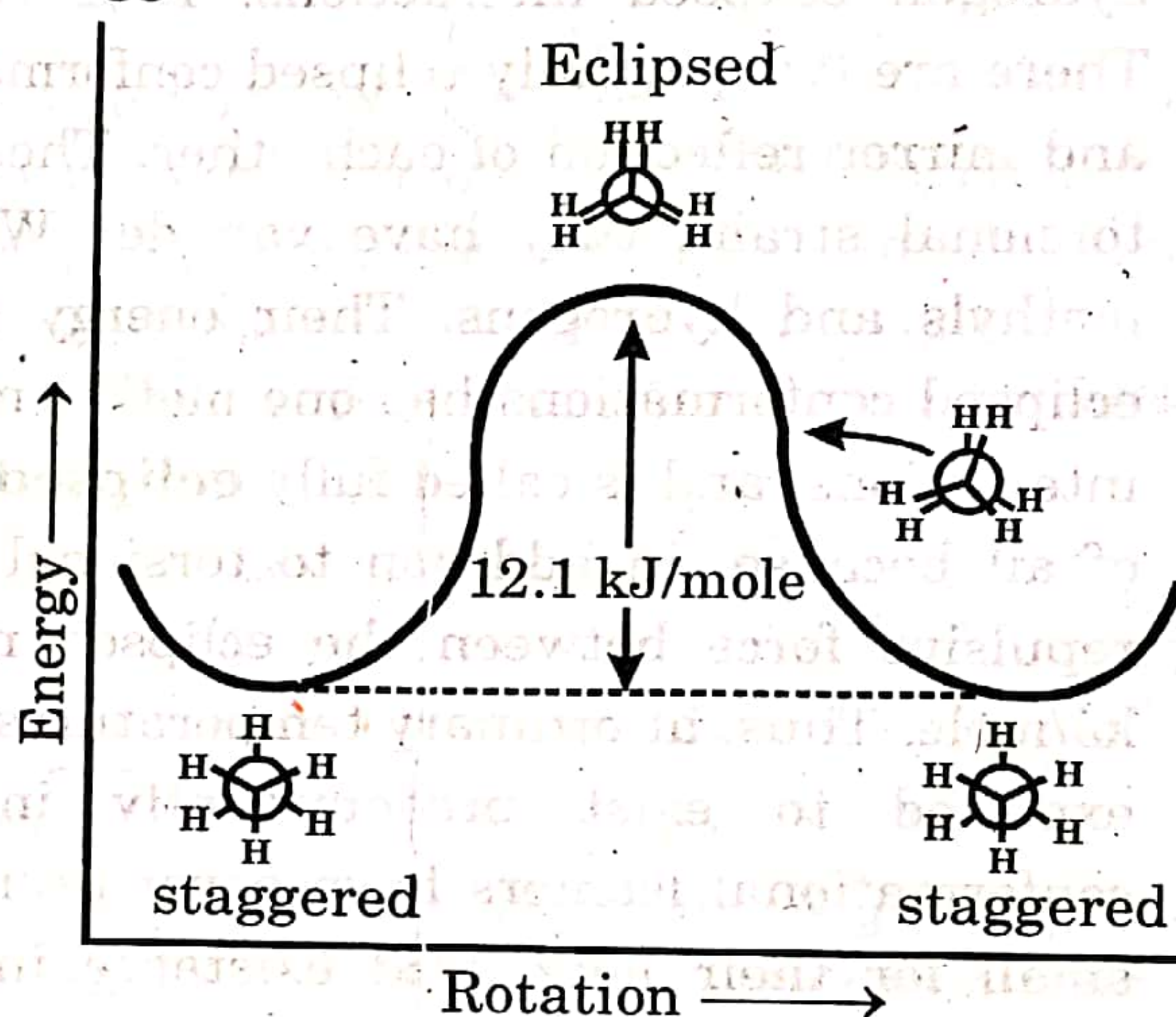

Fig. 7.7 Potential energy changes that accompany rotation of groups about the C–C bond of ethane.

n-Butane. We may construct n-butane as 1,2-dimethyl ethane. In butane, a gradual rotation of one part of the molecule relative to the other about the central C–C bond gives different types of staggered and eclipsed conformations.
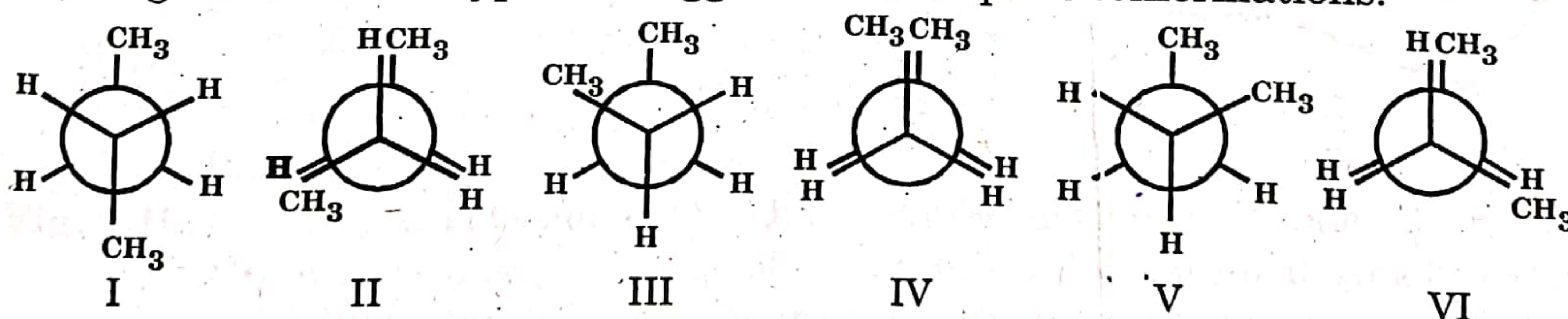

I   II   III   IV   V   VI

Fig. 7.8 Potential Conformations of n - butane

There are two different types of staggered conformations. One, in which the two methyl groups are as far apart as possible, is called **anti - staggered conformation** (I). It has no torsional strain because the groups are staggered and is the most stable of the n-butane conformations. The other type of staggered conformations, in which the methyl groups are closer to each other than allowed by the ordinary van der Waals radii, is called **gauche-staggered conformation**. There are two gauche conformations of n-butane (III and V) obtained by a rotation of 120° about the central C – C bond in either direction; both are of equal energy but are less stable than the anti conformation by about 3.35 kJ/mole. These two gauche conformations are in fact mirror image of each other.

In performing a 360° rotation, we come across two different types of eclipsed conformations. In one type there are two methyl-hydrogen and one hydrogen - hydrogen eclipsed interactions. It is called **partially eclipsed conformation**. There are two partially eclipsed conformations (II and VI), both are of equal energy and mirror reflection of each other. These conformations (II and VI) not only have torsional strain, they have van der Waals repulsions arising from the eclipsed methyls and hydrogens. Their energy barrier is 15.9kJ/mole. The other type of eclipsed conformations has one methyl-methyl and two hydrogen-hydrogen eclipsed interactions, and is called fully **eclipsed conformation.** It has the greatest energy of all because, in addition to torsional strain, there is the large van der Waals repulsive force between the eclipsed methyl groups. Its energy barrier is 18.8 kJ/mole. Thus, at ordinary temperatures and in most reactions the n-butane can be, expected to exist predominantly in the anti-staggered conformation. The conformational isomers have never been isolated since the energy barriers are too small for their long lived existence in such a non-rigid system. However, it is possible to separate them by working at a very low temperature, below – 230°C. The relative energies of the varous conformations of n-butane are shown in Fig. 7.9.
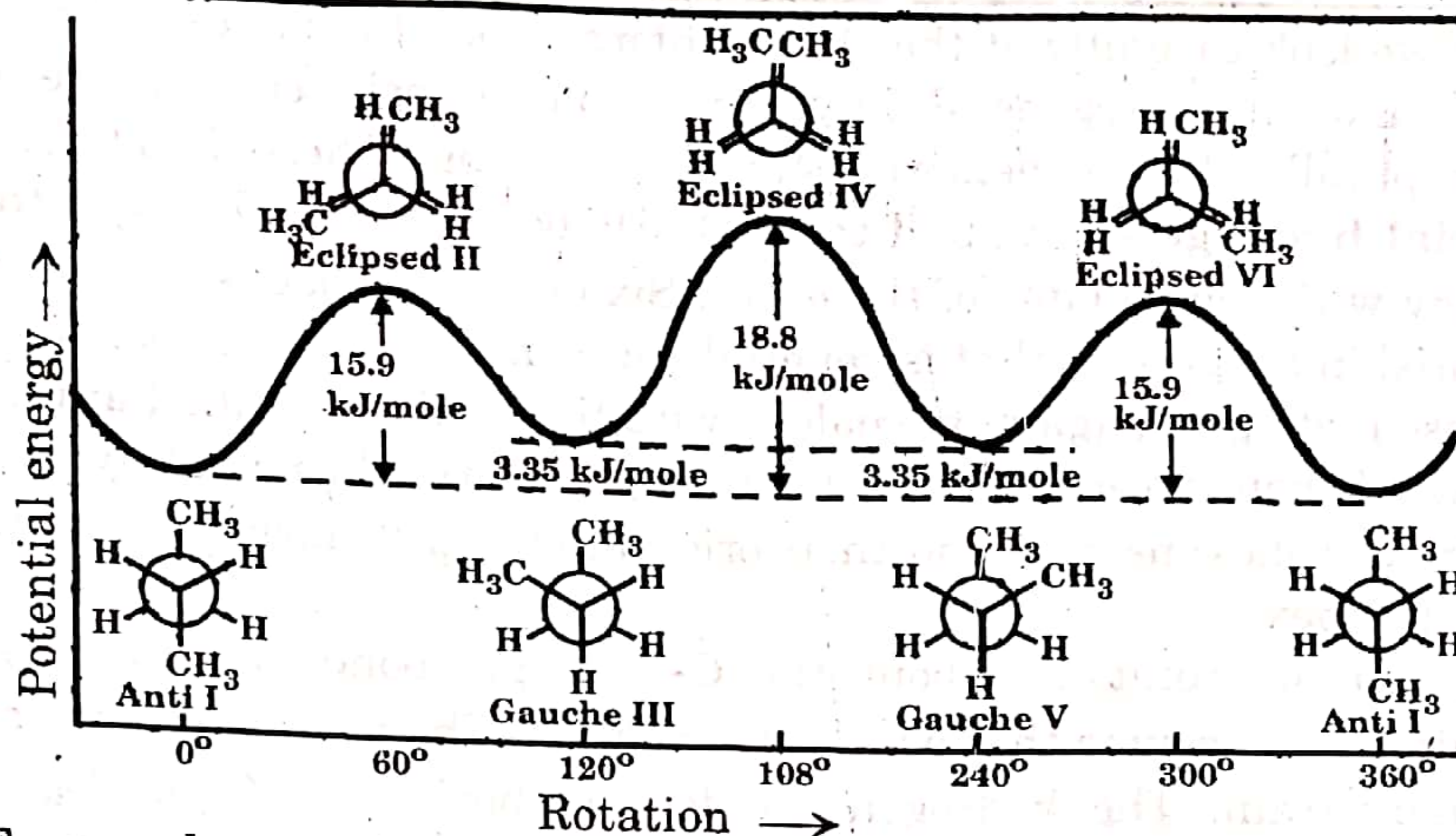
Fig. 7.9. Energy changes that arise from rotation of the central bond of n - butane

Conformations of Cyclohexane

Cyclohexane is a non - planar molecule and the C – C bond angles are all tetrahedral, 109.5 and are thus free of angle strain. The Cyclohexane ring is therefore said to **Puckered.** There are two extreme conformations in which all the angles are tetrahedral, and both are free of angle strain. These are called the **boat** and the **chair conformations** because of their shape. The chair form of cyclohexane is more stable than the boat form.

Chair   Boat   Twist
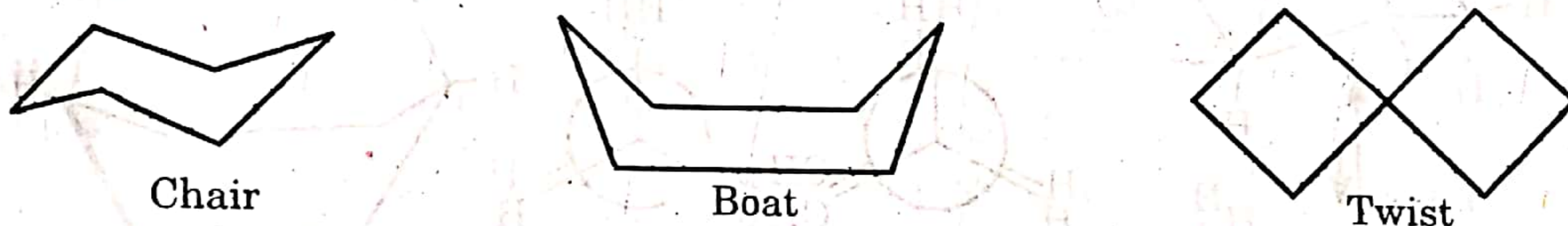
The chair conformation is also free of torsional strain. When a model of chair conformation is viewed along the C–C bonds of any side, the hydrogen atoms are seen to be perfectly staggered. Moreover, the hydrogen atoms on carbons at opposite corners of the cyclohexane ring are far apart as possible (Fig. 7.10c).

(a)   (b)   (c)
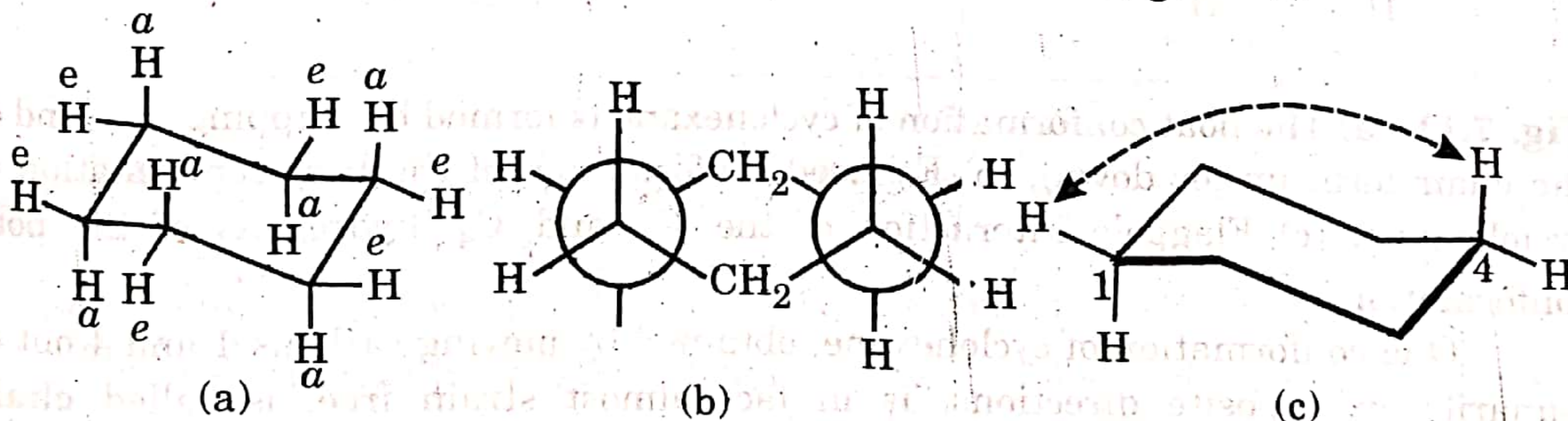
Fig. 7.10. (a) Representation of the chair, conformation of cyclohexane.
         (b) A Newman projection of the chair conformation of cyclohexane.
         (c) Illustration of large separation between hydrogens at opposite corners
              of the ring (indicated C_1 and C_4)

If we look carefully at the chair conformation of cyclohexane, we can see two different kinds of hydrogens. Six hydrogens, one on each carbon, are oriented in a direction parallel to the general plane of the ring. These hydrogens are called **equatorial hydrogens,** (e), and these C – H bonds are called **equatorial bonds,** by analogy with the equator of the earth. Six other hydrogens, one on each carbon, are oriented in a direction that is generally perpendicular to the average plane of the ring. These hydrogens, again by analogy with the earth, are called **axial hydrogens** and the C – H bonds are called axial bonds. There are three axial hydrogens on each face of the cyclohexane ring and their orientation (up or down) alternates from one carbon to the next.

By simple rotations about the C-C single bonds of the ring, the chair conformation can assume the "boat" conformation. The boat conformation is not free of trosional strain. The hydrogens on four carbons, i.e., C_2, C_3, C_5 and C_6, are eclipsed. Additionally, two of the hydrogen atoms on C_1 and C_4 are close enough to each other to cause van der Waals repulsion (Fig. 7.11c). These hydrogens are called **"flagpole"** hydrogens and this effect is the "flagpole" interaction of the boat conformation. Torsional strain and flagpole interaction make the boat conformation considerably less stable than the chair conformation.
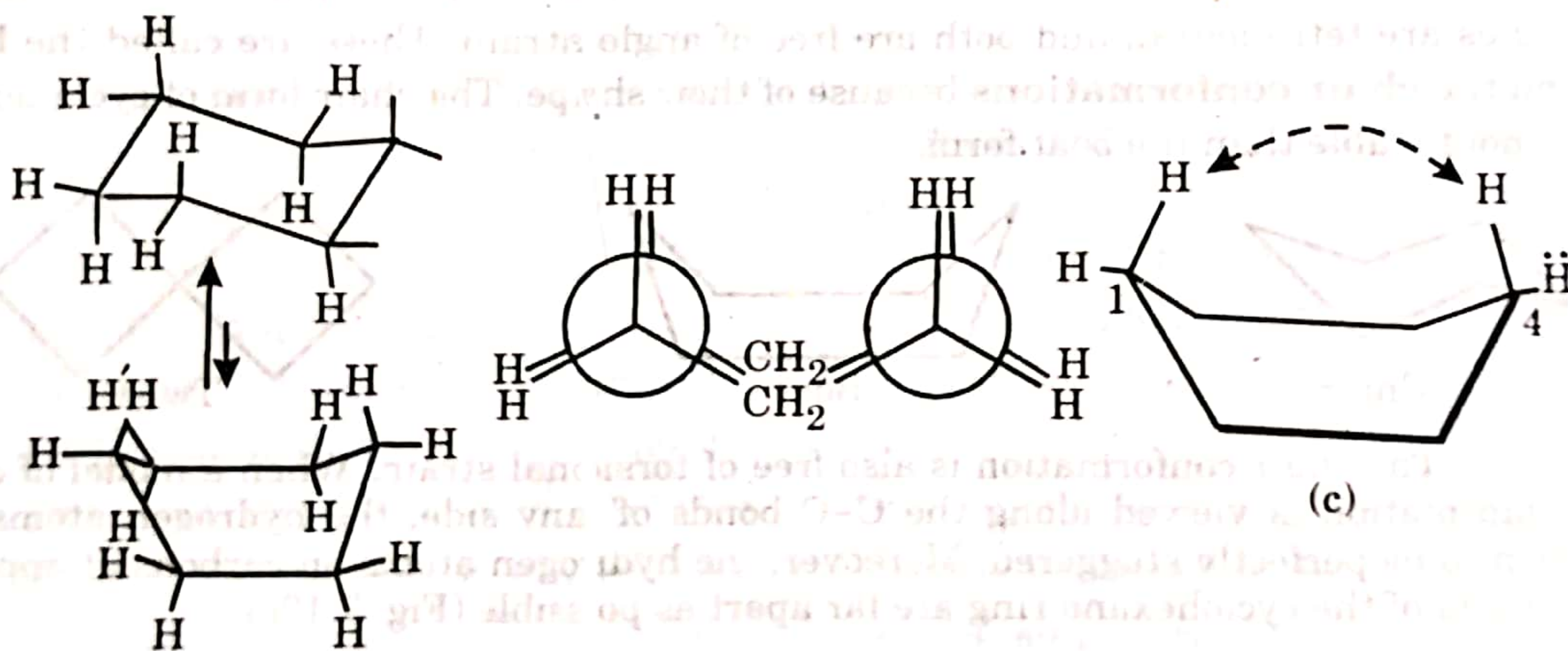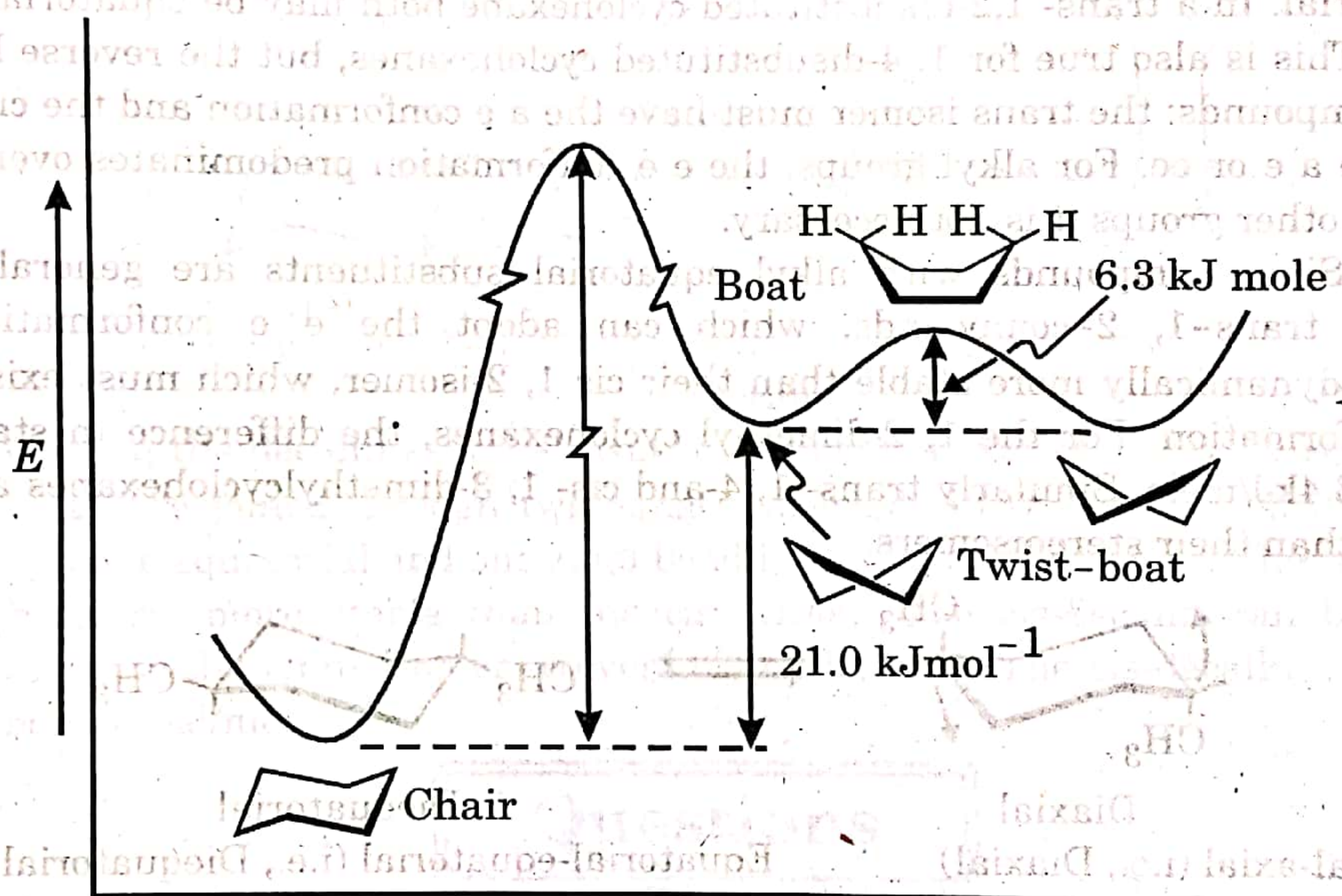

Fig. 7.11. (a) The boat conformation of cyclohexane is formed by "flipping" one end of the chair form up (or down), (b) Eclipsed conformation of the boat conformation of cyclohexane. (c) Flagpole interaction of the C_1 and C_4 hydrogens of the boat conformation.

One conformation of cyclohexane, obtained by moving carbons 1 and 4 out of planarity in opposite directions, is in fact almost strain free, is called **chair conformation** of cyclohexane and is rigid. There are other, less-stable but nevertheless readily accessible, conformations of cyclohexane. One is the boat **conformation,** in which carbons 1 and 4 are out of the plane in the same direction.

The chair conformation is more stable than the boat conformation by about 27.2 kJ/mol. The reasons for this difference are the eclipsing of eight hydrogen atoms at the base of the boat and the unfavourable steric hindrance due to the close proximity of the two inside hydrogens in the boat frame-work.

Boat cyclohexane is fairly flexible. If one of the bond is twisted relative to second, the boat form can be somewhat stabilized by the partial removal of the inside hydrogen interactions. The new conformation obtained is called the **twist- (or skew) boat** conformation of cyclohexane. The twist conformation is about 6.3 kJ/mole more stable than the boat conformation because it has less eclipsing interactions. The chair conformation is more stable than the twist conformation by about 21 kJ/mol. As shown, there are two possible twist-boat forms. They interconvert rapidly through the boat conformer as a transition state. Thus, the boat cyclohexane is not a normal isolable species, the twist boat is present in very small amounts, and the chair form is the major conformer. There are also two rapidly interconverting chair conformers of cyclohexane.


Reaction coordinate to conformational interconversion

Fig. 7.12 Potential energy diagram for the interconversion of the various conformer of cyclohexane.

Substituted Cyclohexanes (Mono and Disubstituted Cycloalkanes)

In monosubstituted cycloalkanes, the substituent normally prefers the equatorial position because in the axial position there is interaction between the substituent and the axial hydrogens in the 3 and 5 positions, but the extent of this preference depends greatly on the nature of the group. Alkyl groups have a greater preference than polar groups and for alkyl groups the preference increases with size.

Methylcyclohexane has two possible chair conformations and these are interconvertible through partial rotation. In one conformation the methyl group occupies an equatorial position while in the other the methyl group occupies an axial position. Studies indicate that the conformation with the methyl group equatorial is more stable than the conformation with the methyl group axial by about 7.5kJ/mole. Thus in the equilibrium mixture, the conformation with the methyl group in the equatorial position is the predominant one.

(a) Axial   ⇌   (b) Equtorial
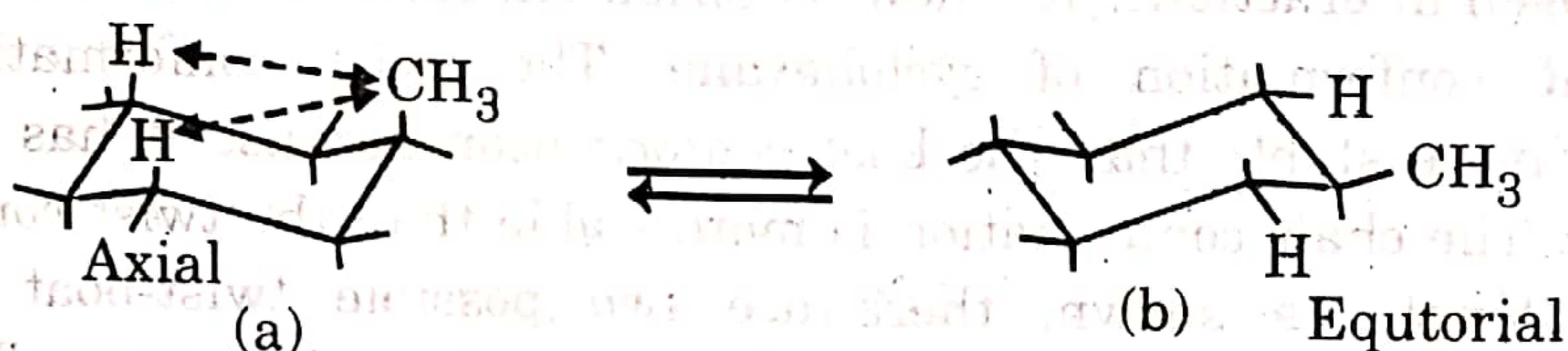
In disubstituted cycloalkanes, the rule for alkyl groups is that the conformation is such that as many groups as possible adopt the equatorial position. In a cis- 1,2-disubstituted cyclohexane, one substituent must be axial and the other equatorial. In a trans- 1,2-disubstituted cyclohexane both may be equatorial or both axial. This is also true for 1, 4-disubstituted cyclohexanes, but the reverse holds for 1, 3-compounds: the trans isomer must have the a e conformation and the cis isomer may be a e or ee. For alkyl groups, the e e conformation predominates over the a a but for other groups it is not necessary.

Since compounds with alkyl equatorial substituents are generally more stable, trans–1, 2–compounds, which can adopt the e e conformation, are, thermodynamically more stable than their cis 1, 2-isomer, which must exist in the ae conformation. For the 1, 2-dimethyl cyclohexanes, the difference in stability is about 8.4kJ/mole. Similarly trans- 1, 4-and cis- 1, 3-dimethylcyclohexanes are more stable than their stereoisomers.
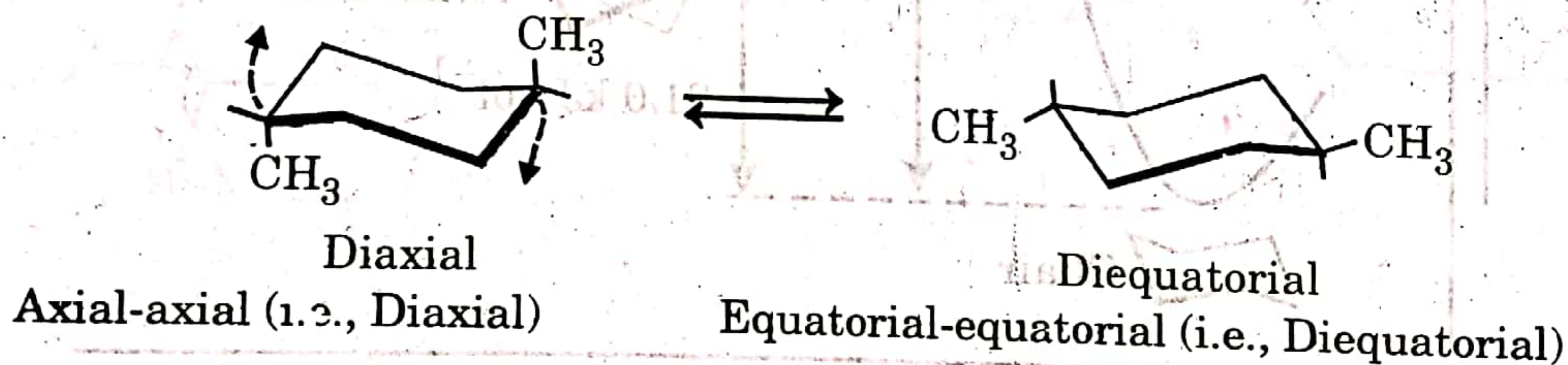

Diaxial   Diequatorial
Axial-axial (i.e., Diaxial)   Equatorial-equatorial (i.e., Diequatorial)

Fig. 7.13. The two chair conformations of trans- 1, 4-dimethylcyclohexane. (all other C–H bonds have been omitted for clarity).

Equatorial-axial   Equatorial-axial
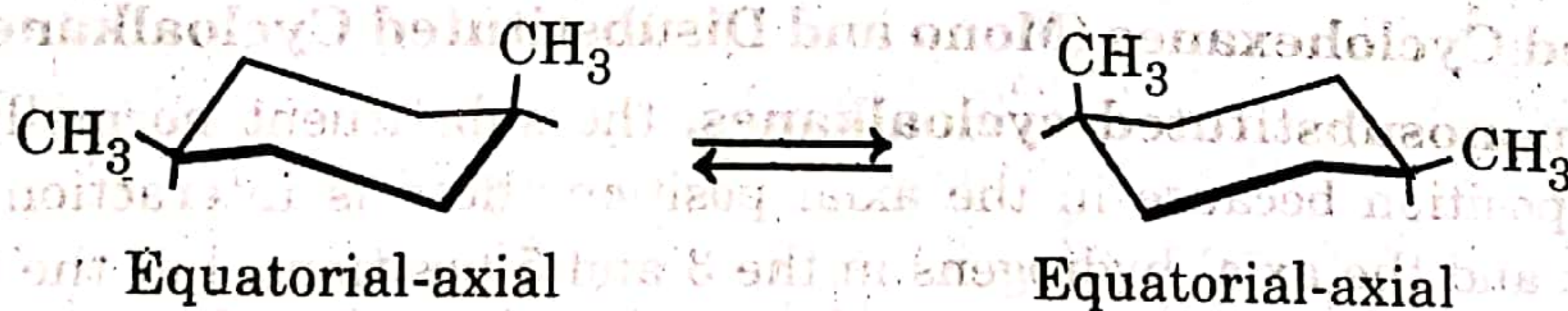
Fig. 7.14. Equivalent conformations of cis 1,4 -dimethylcyclohexane.

Conformations of Higher Cycloalkanes

Cycloheptane, cyclooctane and cyclononane and other higher cycloalkanes also exist in nonplanar conformations. The small instabilities of these higher cycloalkanes appear to be caused by torsional strain and van der Waals repulsions between hydrogens across rings. The nonplanar conformations of these rings, however, are essentially free of angle strain.

X-ray crystallographic studies of cyclodecane show that the most stable conformation has C – C bond angles of 117 . This indicates some angle strain. The wide bond angles apparently allow the molecule to expand and therefore minimum unfavourable repulsions between hydrogens across the ring.

Conformational Analysis of Bicyclic Compounds.

One of the most important bicyclic system is bicyclo (4, 4, 0) decane, commonly called decalin. In decalin the two chair forms of the two cyclohexane rings are fused together in 1, 2- positions giving *rise to cis or trans–decalin* depending on whether the two rings are connected through equatrial or axial bonds.

trans
(Equatorial-equatorial)

cis
(Equatorial-axial)
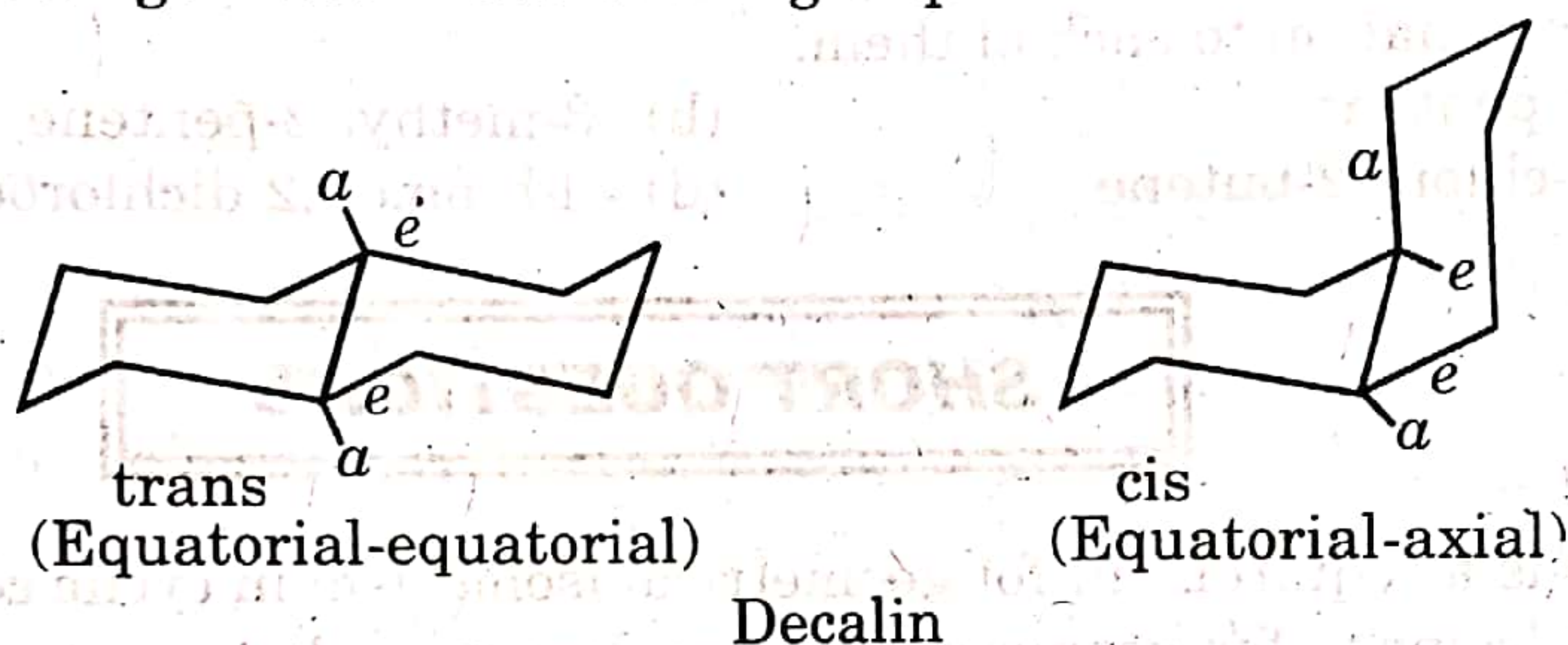
Decalin

Considering the decalin as 1,2 – disubstituted cyclohexanes, it can be seen that the two rings are joined through two equatorial bonds in the trans configuration and through one equatorial and one axial bond in the cis configuration. The trans isomer is, therefore, more stable than the cis isomer. The cis-decalin can be smoothly converted to the trans-isomer irreversibly on heating. The cis-decalin is less stable by about 10 kJ/mol.
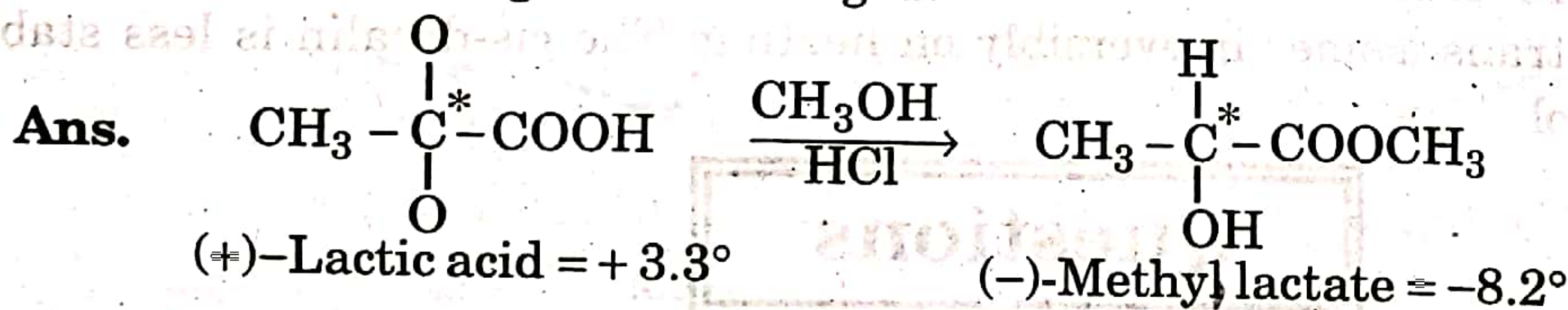
Questions

1. Explain what do you understand by optical isomerism and discuss optical isomerism with reference to tartaric acid.   P.U. 1983

2. Explain the following terms giving two examples of each
   (a) Metamerism (b) Tautomerism (c) Chiral molecules (d) Racemates
   (e) Optically active compounds   P.U. 1984,93,2001

3. Explain the following terms with examples,   (a) Confers   (b) Enantiomers
   (c) Diastereoisomers (d) Geometric isomers   (e) Tautomers (f) Asymmetric
   carbon atom (g) Conformation   (h) Meso compounds   P.U. 1995,2003

4. Explain the following terms with examples, (a)Enantiomers (b)Diastereomers
   (c) Racemization (d) Optical rotation (e) Specific rotation   P.U. 1992.

5. Define conformation and describe the conformations of (n-butane and cyclohexane.

P.U. 1991.

6. What is Geometrical isomerism? How do you explain it on the electronic basis? Describe various methods for assigning cis-trans configuration to different isomers. Give two methods for the interconversion of various isomers.

P.U. 1988.

7. Discuss Geometrical isomerism in detail.

P.U. 1986.

8. Define racemization and explain two methods for racemization.

9. What is meant by racemization? Discuss two methods for resolution of racemic mixture.

B.Z.U. 1989, (P.U. 2003)

10. What is optical activity? How is it measured?

11. Explain with examples the difference between:

(a) Constitutional isomerism and stereoisomerism

(b) Enantiomers and diastereomers   (c) Configuration and conformation

(d) Absolute and relative configuration   (e) Meso form ad racemic form

(f) Anti-staggered and gauche-staggered   (g) Torsional strain and angle strain

12. Draw both the geometrical isomers of the following compounds and assign Z or E designation to each of them.

(a)   2-pentene

(b)   3-methyl-2-pentene

(c)   2-chloro-2-butene

(d)   1-bromo-1,2-dichloroethene.

SHORT QUESTIONS

1. Which is a requirement for geometrical isomerism in cyclic compounds?

Ans. A requirement for geometrical isomerism in cyclic compounds is that there must be at least two other groups besides hydrogens on the ring and these must be on different ring carbon atoms.

2. Esterification of (+)-lacttic acid with methyl alcohol gives(-)-methyl lactate. Has the configuration changed?

Ans. $CH_3 - \overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{C^*}} - COOH \quad \xrightarrow[HCl]{CH_3OH} \quad CH_3 - \overset{\overset{H}{|}}{\underset{\underset{OH}{|}}{C^*}} - COOCH_3$

(+)-Lactic acid = +3.3°   (-)-Methyl lactate = -8.2°

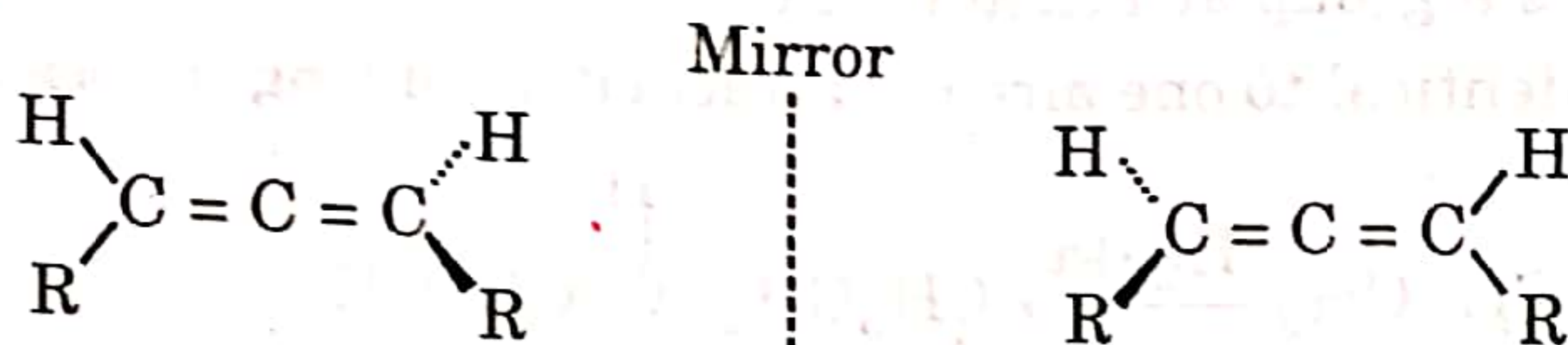NO; even though sign of rotation changes, there is no breaking of bonds to the chiral C^*.

3. Point out which of the following are chiral.

(a) Screw   (b) your ear   (c) your nose (d) tree   (e) Nail   (f) T-shirt   (Coat with buttons   (h) shoes   (i) Foot

Ans: (a), (b), (d), (g), (h), (i).

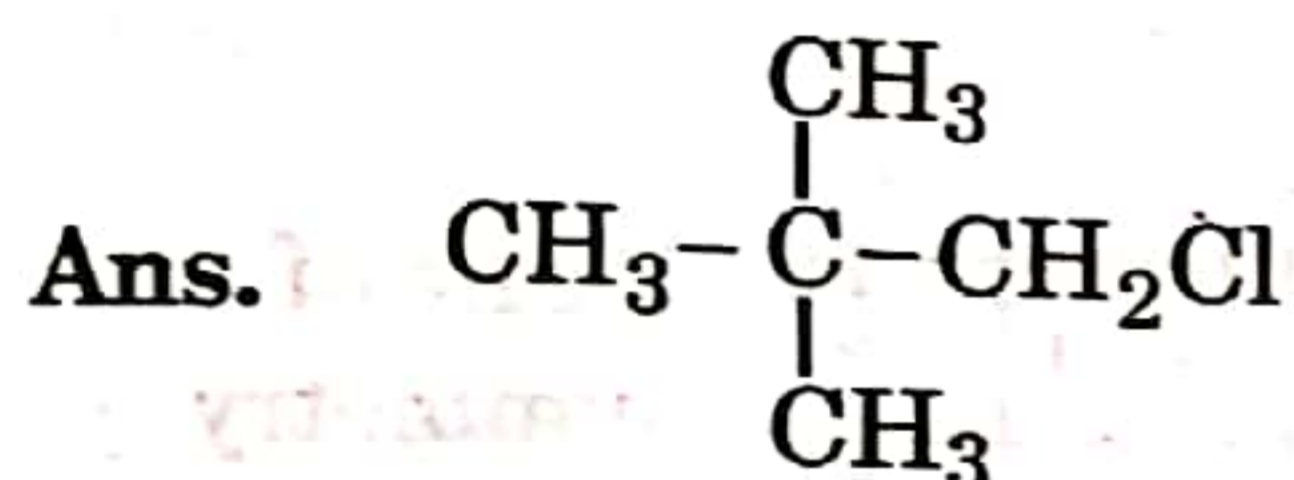4.(a) What is the necessary and sufficient condition for the existence of

enantiomers? (b) Are all substances with chiral atoms optically active and resolvable? (c) Are enantiomers possible in molecules that do not have chiral carbon toms.

Ans. (a) Chirality in molecules having nonsuperimposable mirror image.

(b) No. Racemic forms are not optically active but are resolvable.

(c) Yes. The presence of a chiral atom is sufficient but not necessary condition for enantiomerism. For example, properly disubstituted allenes have no plane of symmetry but are chiral.
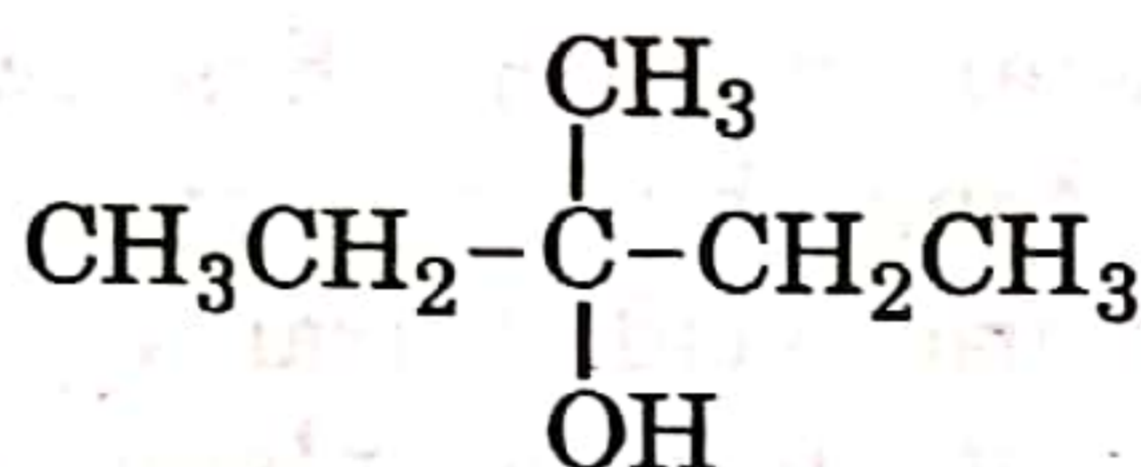
Mirror

$$H \quad \quad \quad H \quad \quad | \quad \quad H \quad \quad \quad H$$
$$\diagdown C = C = C \diagup \quad \quad | \quad \quad \diagup C = C = C \diagdown$$
$$R \quad \quad \quad R \quad \quad | \quad \quad R \quad \quad \quad R$$

A chiral Allene. (nonsuperimposable enantiomer)

5. Are neopentyl chloride and 3-methyl-3-pentanol have enantiomers.

Ans.
$$CH_3$$
$$CH_3-\overset{|}{\underset{|}{C}}-CH_2Cl$$
$$CH_3$$

Neopentyl chloride

$$CH_3$$
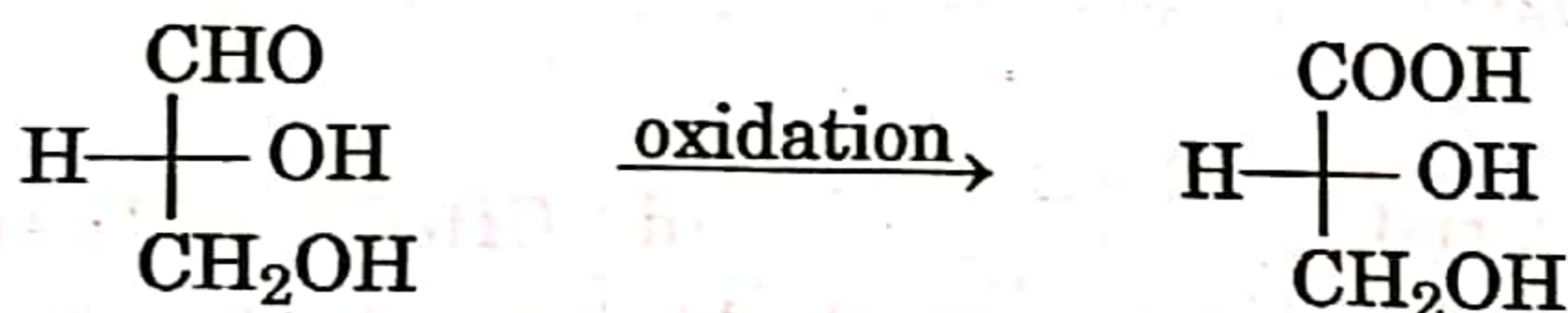$$CH_3CH_2-\overset{|}{\underset{|}{C}}-CH_2CH_3$$
$$OH$$

3–methyl–3–pentanol.

Both neopentyl chloride and 3-methyl-3-pentanol have no chiral carbon and therefore no enantiomers.

6. D-(+)-Glyceraldehyde is oxidized to (–)-glyceric acid, $HOCH_2CH(OH)COOH$. Give the D,L designation of the acid.

Ans. Oxidation of the D-(+)-aldehyde does not affect any of the bonds to the chiral C. The acid has the same D configuration even though the sign of rotation is changed.

$$\begin{array}{c} CHO \\ H \!-\!\!\!\!-\!\!\!\!- OH \\ CH_2OH \end{array} \xrightarrow{\text{oxidation}} \begin{array}{c} COOH \\ H \!-\!\!\!\!-\!\!\!\!- OH \\ CH_2OH \end{array}$$

D-(+)-Glyceraldehyde   D-(–)-Glyceric acid

7. Account for the disappearance of optical activity observed when (R)–2–butanol is allowed to stand in aq. H_2SO_4 and when (S)–2–iodooctane is treated with aq.KI solution.

Ans. Optically active compounds become inactive if they lose their chirality because the chiral centre has no longer 4 different groups, or if they undergo racemization. In the two reactions cited, C remains chiral and it must be concluded that in both reactions racemization occurs.

8. (a) Are the staggered and eclipsed conformations the only ones possible for ethane? (b) Indicate the preferential conformation of ethane molecules at room temperature. (c) What conformational changes occur as the temperature rises?

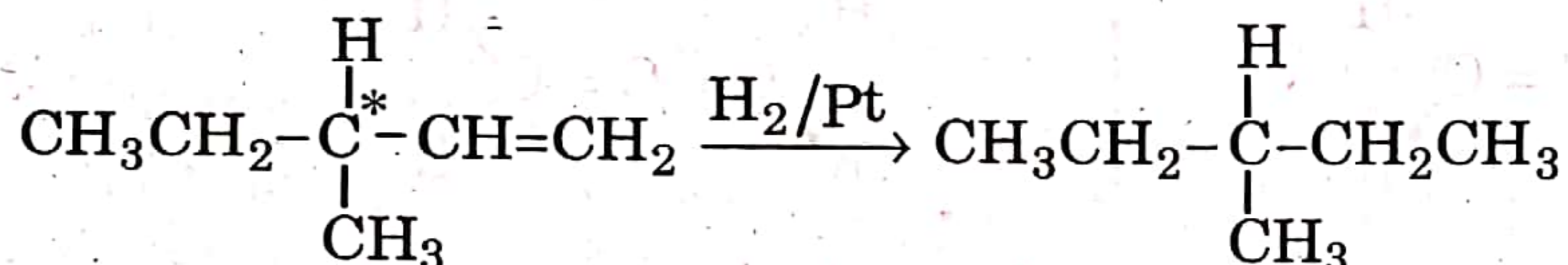**Ans(a)** No. there are an infinite number with energies between those of the

staggered and eclipsd conformations. For simplicity we are concerned only with conformations at minimum and maximum energies.

(b) The staggered from has the minimum energy and hence is the preferred conformatios.

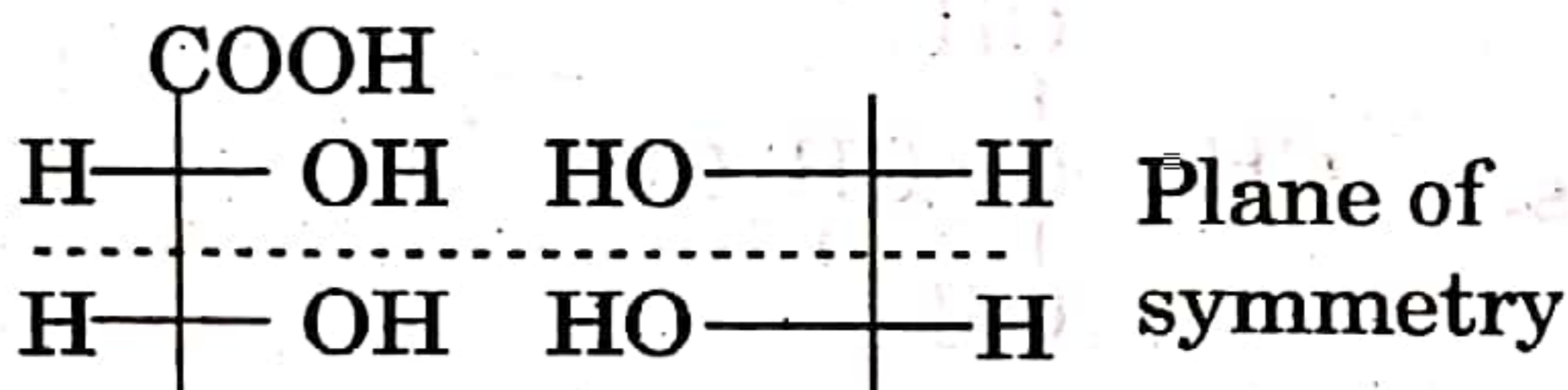(c) The eclipsed–like conformations become more prevalent.

9. Deduce the structural formula for an active alkene, C_6H_{12}, which reacts with H_2 to form an optical inactive alkane, C_6H_{14}.

Ans. The alkene has a group attached to the chiral C which must react with H_2 to give a group identical to one already attached, resulting in loss of chirality.
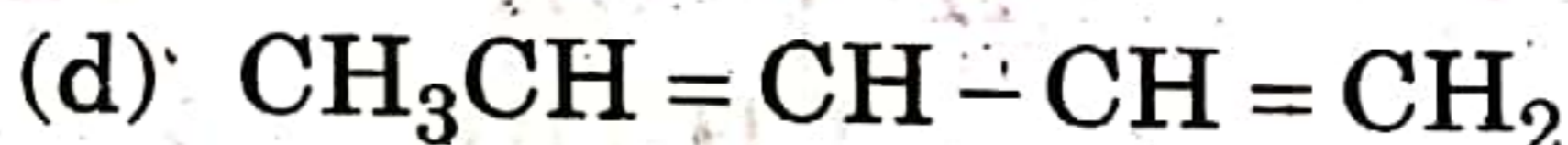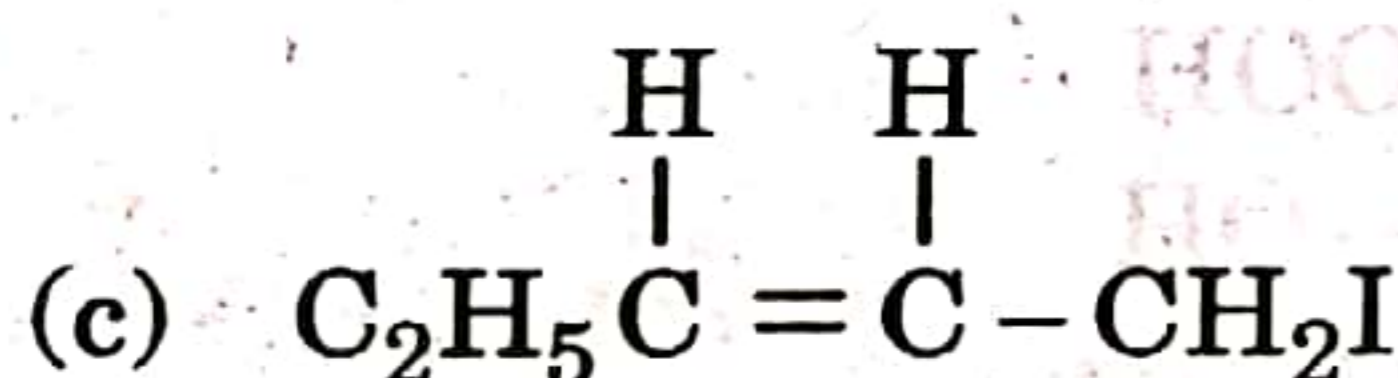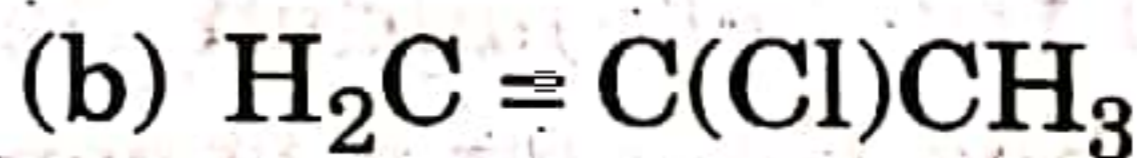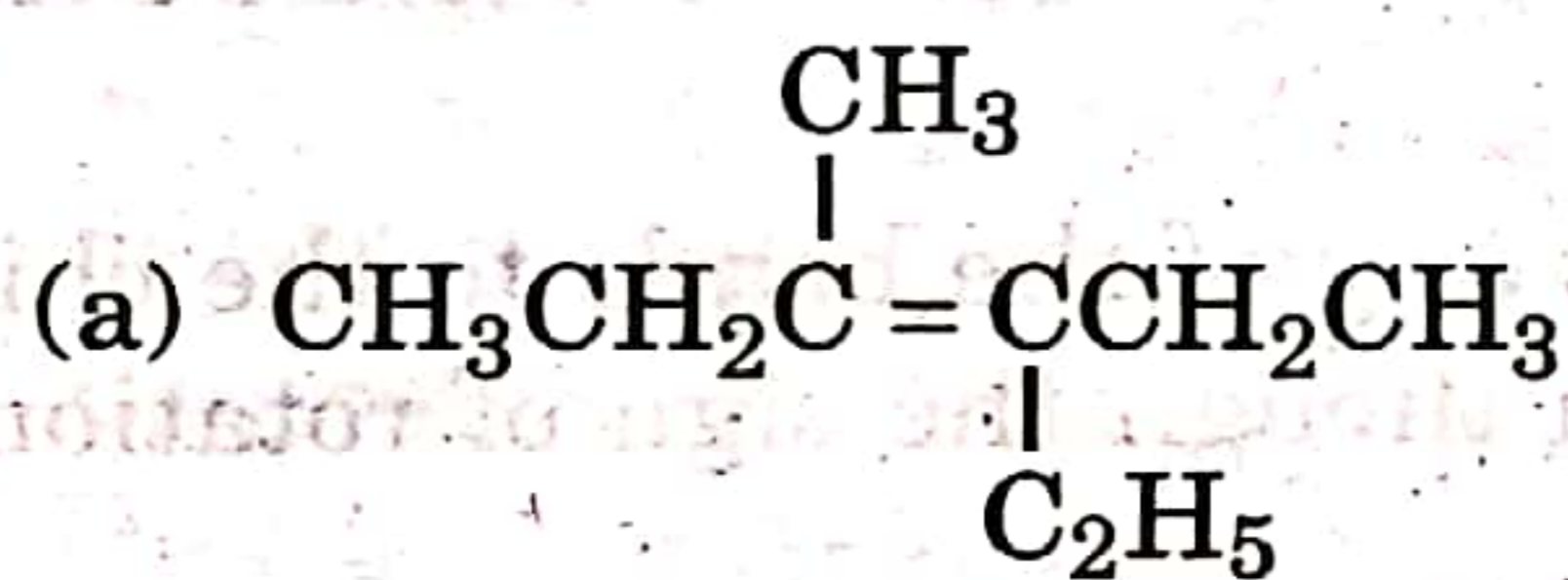
$$CH_3CH_2-\overset{\overset{H}{|}}{\underset{\underset{CH_3}{|}}{C^*}}-CH=CH_2 \xrightarrow{H_2/Pt} CH_3CH_2-\overset{\overset{H}{|}}{\underset{\underset{CH_3}{|}}{C}}-CH_2CH_3$$

10: Why meso-tartaric acid is optically inactive although it has two chiral carbon atoms?
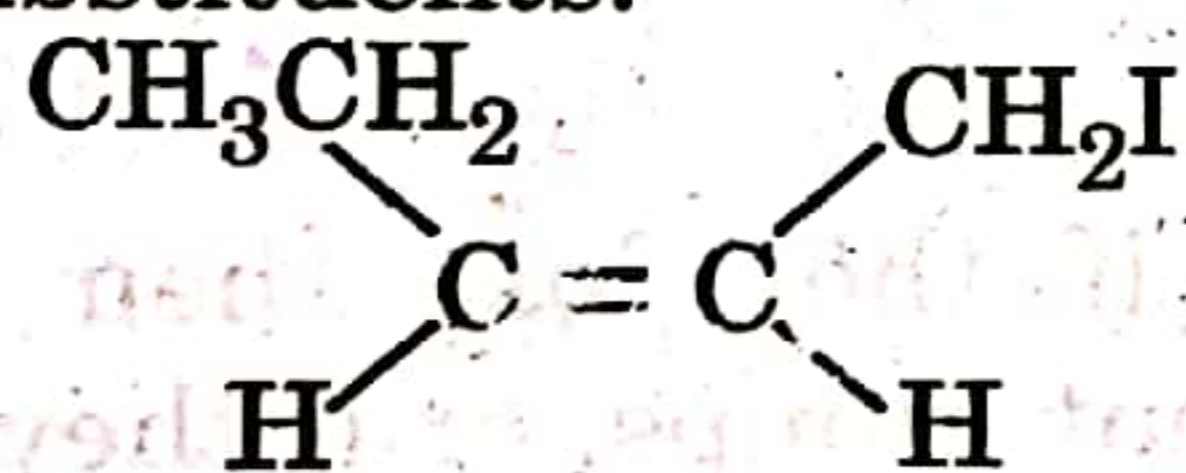
Ans. Although meso-tartaric acid has two chiral carbon atoms but it may not make meso-tartaric acid chiral as a whole because it has a plane of symmetry. Hence meso-tartaric acid can have a superimposable mirror image, hence it is optically inactive.
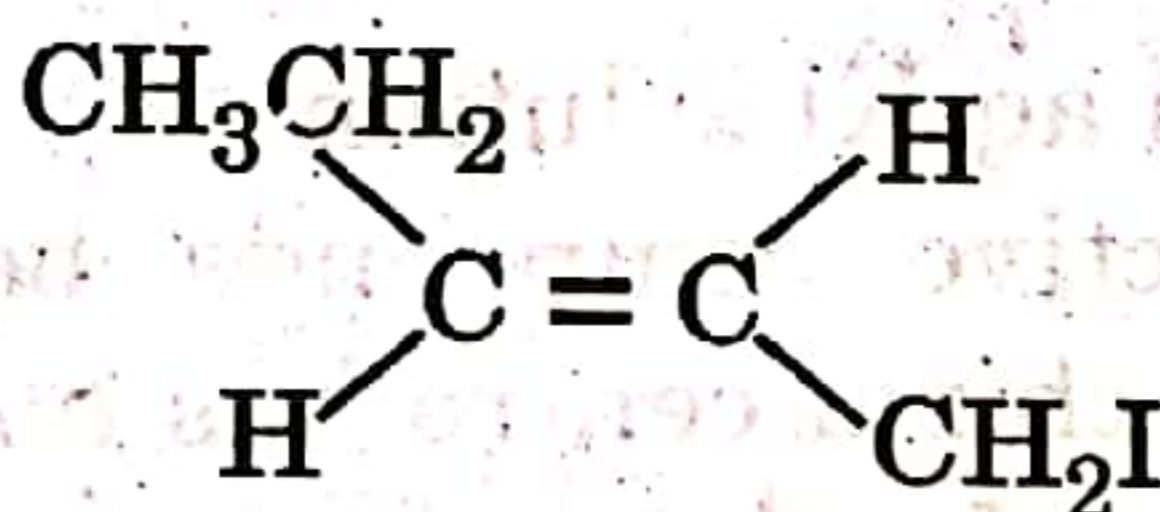
$$\begin{array}{c} COOH \\ H-\!\!\!\begin{array}{|c|}\hline\quad\\\hline\end{array}\!\!\!-OH \quad HO-\!\!\!\begin{array}{|c|}\hline\quad\\\hline\end{array}\!\!\!-H \\ \text{-----}\!\!:\!\!\text{----------}\!\!:\!\!\text{-----} \\ H-\!\!\!\begin{array}{|c|}\hline\quad\\\hline\end{array}\!\!\!-OH \quad HO-\!\!\!\begin{array}{|c|}\hline\quad\\\hline\end{array}\!\!\!-H \\ \text{Identical and meso-tartaric acid} \end{array}$$

Plane of symmetry

11. Which of the following alkenes exhibit geometric isomerism? Write structural formulas and names for the isomers.

(a) $CH_3CH_2\overset{\overset{\displaystyle CH_3}{|}}{C}=\overset{}{\underset{\underset{C_2H_5}{|}}{C}}CH_2CH_3$

(b) $H_2C=C(Cl)CH_3$

(c) $C_2H_5\overset{\overset{H}{|}}{C}=\overset{\overset{H}{|}}{C}-CH_2I$

(d) $CH_3CH=CH-CH=CH_2$

Ans. (a) No geometric isomers because one double bonded C has 2 C_2H_5 groups.

(b) No geometric isomers because one double bonded C has two hydrogens.

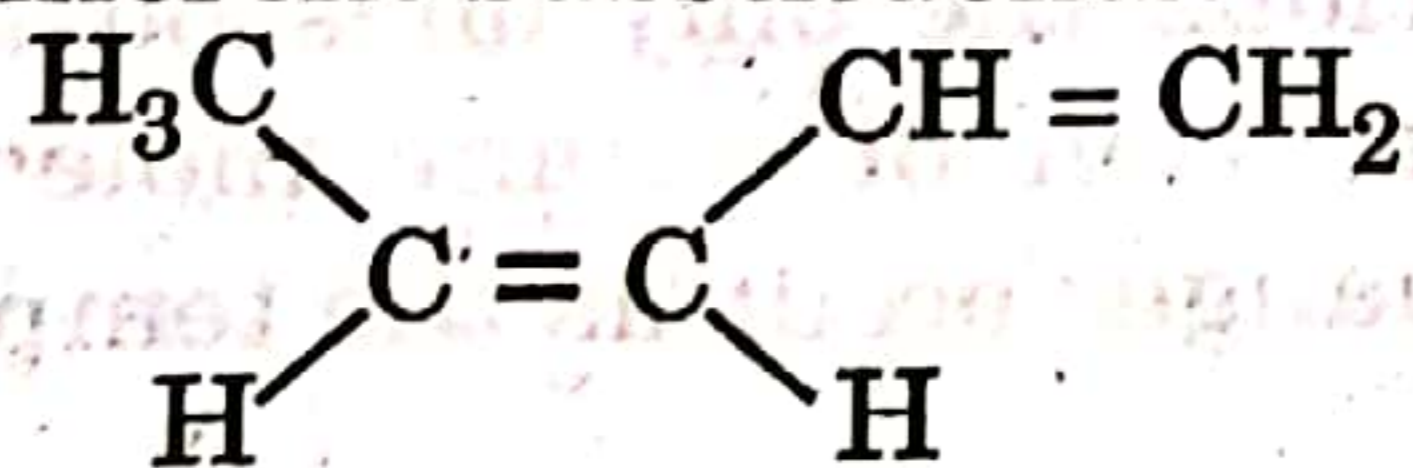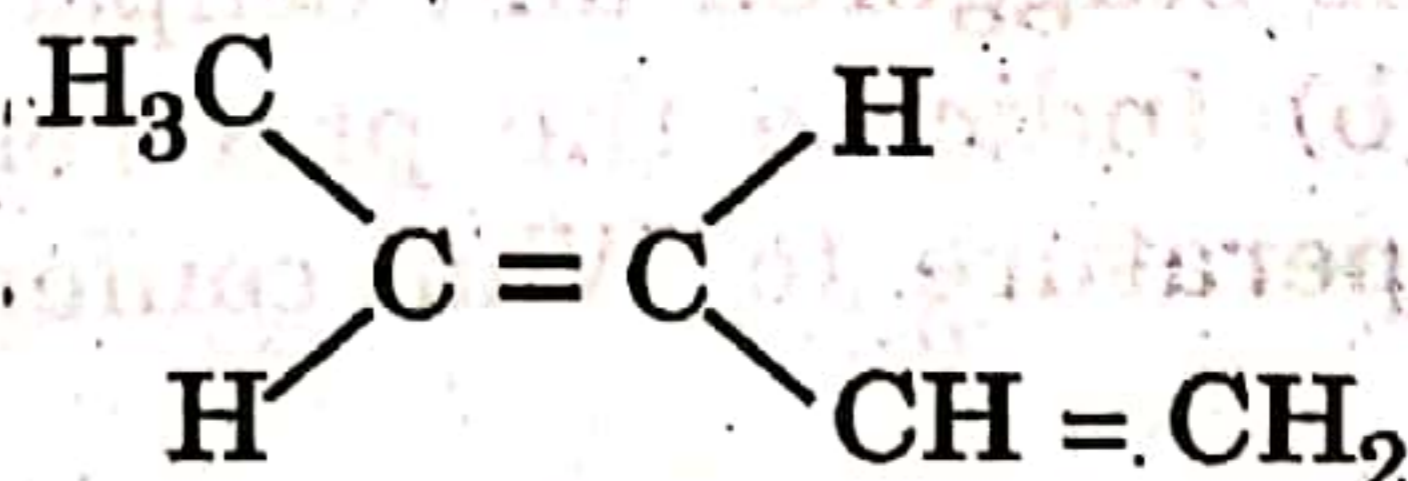(c) has geometric isomers because each double-bonded C has two different substituents.

$$\underset{\text{cis-or (Z)-1-Iodo-2-pentene}}{\overset{\displaystyle CH_3CH_2}{\underset{\displaystyle H}{\diagup}}C=C\overset{\displaystyle CH_2I}{\underset{\displaystyle H}{\diagdown}}} \qquad \underset{\text{trans-or (E)-1-Iodo-2-pentene}}{\overset{\displaystyle CH_3CH_2}{\underset{\displaystyle H}{\diagup}}C=C\overset{\displaystyle H}{\underset{\displaystyle CH_2I}{\diagdown}}}$$

(d) There are 2 geometric isomers because one of the double bonds has two different substituents.

$$\underset{\text{(Z)-1,3-Pentadiene(cis)}}{\overset{\displaystyle H_3C}{\underset{\displaystyle H}{\diagup}}C=C\overset{\displaystyle CH=CH_2}{\underset{\displaystyle H}{\diagdown}}} \qquad \underset{\text{(E)-1,3-Pentadiene (trans)}}{\overset{\displaystyle H_3C}{\underset{\displaystyle H}{\diagup}}C=C\overset{\displaystyle H}{\underset{\displaystyle CH=CH_2}{\diagdown}}}$$

12. What are the necessary conditions for the existence of geometric isomerism?

Ans. The following two conditions are necessary for the existence of geometric isomerism.

(i) The molecule must have a double bond or a cyclic ring.

(ii) Two different groups must be bonded to each carbon bonded to the double bond.

13. Why cis–2–butene has higher boiling point than trans–1–butene?

Ans. cis–2–Butene is a polar molecule while trans–2–butene is non-polar molecule. Therefore, cis–2–butene has higher b.p. than trans–2–butene.

14. What is meant by torsional energy?

Ans. The energy required to rotate the molecule about the C–C bond is called *torsional energy* and is regarded a combination of van der Waals repulsive forces and the interactions among the electron clouds of the C–H bonds. This is also torsional strain or Pitzer strain.

15. Why the chair conformation of cyclohexane is more stable than the boat conformation?

Ans. The chair conformation is free of torsional strain because all the H atoms are completely staggered with respect to each other. On the other hands, the boat conformation has four pairs of eclipsed hydrogen and is, therefore, not free of torsional strain. Also, two of the H atoms on C_1 and C_4 are close enough to each other to cause nonbonded van der Waals repulsion and this effect is called " flagpole" interaction of the boat conformation. Torsional strain and flagpole interaction make the boat conformation considerably less stable than the chair conformation. (See fig boat conformation and chair conformation in the book).

Multiple Choice Questions

1. Which of the following will not show cis–trans isomerism?

(a) CH_3 , H C=C CH_3 , CH_3

(b) CH_3 , H C=C Br , CH_2CH_3

(c) CH_3 , CH_3 C=C H , H

(d) CH_3 , H C=C H , CH_2CH_3
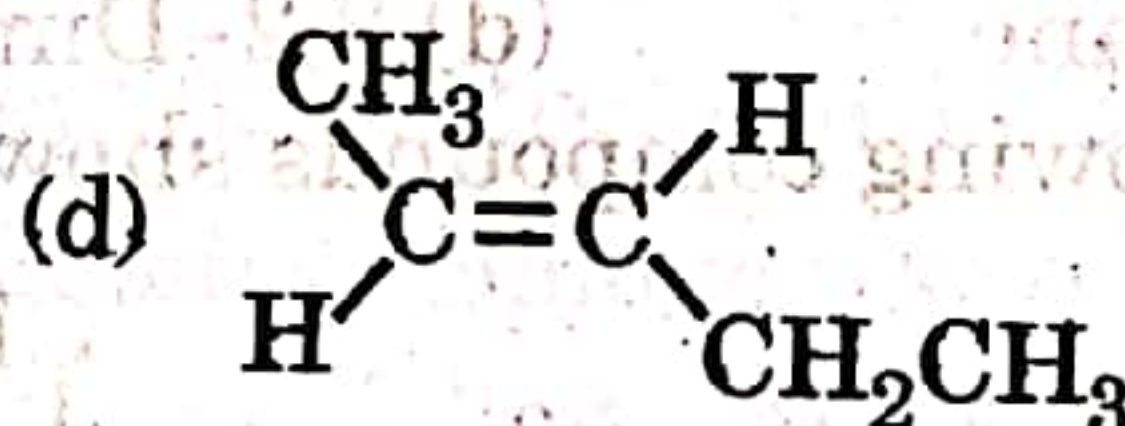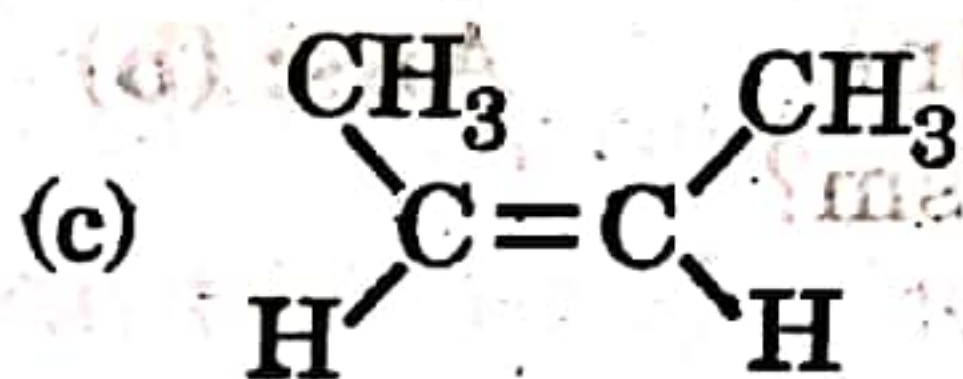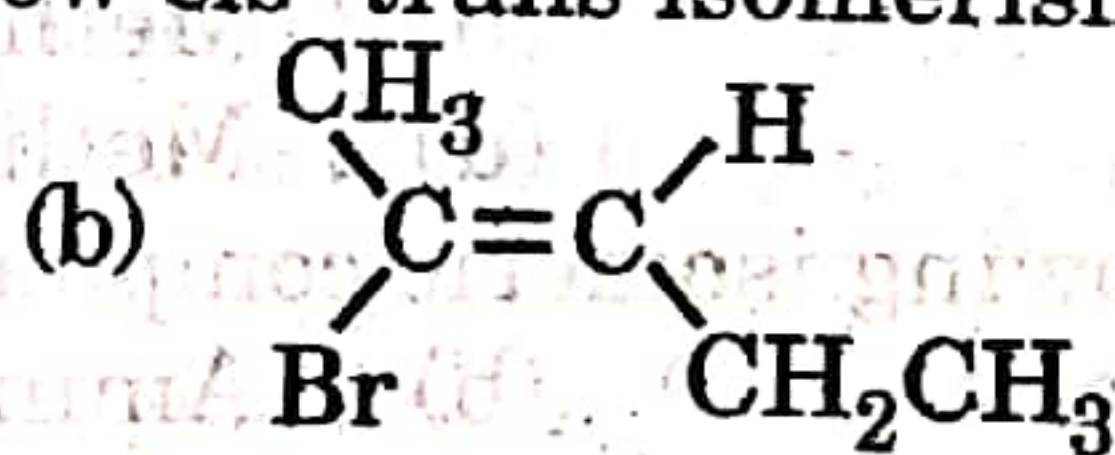
Ans: (a)

2. Which one of the following is not isomers of butanone.

(a) 2,3–epoxybutane   (b) ethyl vinyl ether

(c) 1,2–butenol   (d) tert–butyl ether   **Ans:(d)**

3. Which one of the following reactions is not usually stereospecific?

(a) Free redical substitution   (b) E2

(c) addition of halogens to olefins   (d) S_NI **Ans:(a)**

4. The best way to distinguish the presence of two enantiomers would be.

(a) compare their melting points   (b) Examine them for colour differences

(c) place one of them into solution and pass polarized light through it

(d) compare their respective abilities.   **Ans:(c)**

5. Which of the following instruments may be used to measure the optical activity of compounds?
    (a) Infrared spectrometer   (b) Atomic absorption spectrometer
    (c) Flouroscope   (d) Polarimeter   **Ans:(d)**

6. Consider the following Fisher projections:

$$
\begin{array}{cc}
CH_3 & CH_2CH_3 \\
H-\!\!\!-\!\!\!-OH & HO-\!\!\!-\!\!\!-H \\
H-\!\!\!-\!\!\!-OH & HO-\!\!\!-\!\!\!-H \\
CH_2CH_3 & CH_3
\end{array}
$$

These compounds are
    (a) identical   (b) enantiomers
    (c) diastereomers   (d) meso   **Ans:(a)**

7. The statements below concern trans-1,2-dimethylcylohexane; indicate which of these statements is (are) correct.
    I. It is a non-superimposable molecule.
    II. trans-1,2-dimethylcyclohexane can exist in two conformations, with the $-CH_3$ groups being on the opposite sides of the ring in each case
    III. The preferred conformation of the molecule is a boat form, with methyl groups pointing away from the ring.
    (a) I only   (b) I and II only   (c) I and III only   (d) I,II and III **Ans:(c)**

8. Which of the following is an R enantiomer of a chiral compound?

(a)
$$
\begin{array}{c}
H \quad Cl \\
\diagdown \diagup \\
C \\
\diagup \diagdown \\
H \quad Br
\end{array}
$$

(b)
$$
\begin{array}{c}
CH_3 \quad H \\
\diagdown \diagup \\
C \\
\diagup \diagdown \\
CH_3CH_2 \quad Cl
\end{array}
$$

(c)
$$
\begin{array}{c}
CH_3 \quad H \\
\diagdown \diagup \\
C \\
\diagup \diagdown \\
Br \quad Cl
\end{array}
$$

(c)
$$
\begin{array}{c}
H \quad CH_2CH_3 \\
\diagdown \diagup \\
C \\
\diagup \diagdown \\
Br \quad CH(CH_3)_2
\end{array}
$$
    Ans: (d)

9. Which of the following compounds exhibit geometrical isomerism?
    (a) 1-Pentene   (b) 2-Methyl-2-pentene
    (c) 2-Pentene   (d) 2-Methyl-2-butene   **Ans:(c)**

10. Which of the following isomeric compounds show optical isomerism?
    (a) 1-Aminopentane   (b) 2-Aminopentane
    (c) 3-Aminopentane   (d) 2,2-Dimethylpropylamine   **Ans: (b)**

11. Which of the following compounds show optical isomerism?

    (a) $CH_3-\underset{\underset{Br}{|}}{C}H-CH_3$ (b) $CH_3-\underset{\underset{CH_3}{|}}{C}H-CH_2CH_3$

    (c) $CH_3-\underset{\underset{OH}{|}}{C}H-COOH$ (d) $CH_3CH_2-\underset{\underset{NH_2}{|}}{C}H-CH_2-CH_3$ **Ans: (c)**

12. The structures shown are: $H_3C-\underset{\underset{OH}{|}}{\overset{\overset{H}{|}}{C}}-OH \qquad OH-\underset{\underset{OH}{|}}{\overset{\overset{H}{|}}{C}}-CH_3$

    (a) identical   (b) enantiomers
    (c) diastereomers   (d) constitutional isomers   **Ans: (b)**