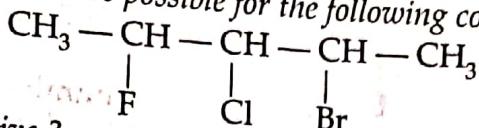


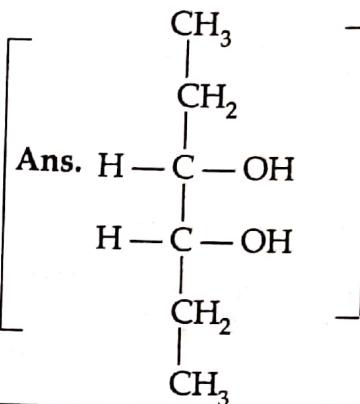
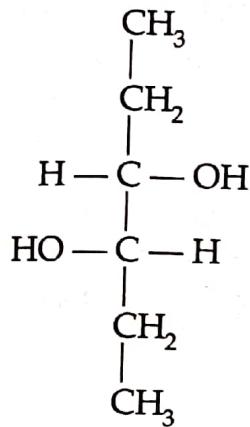
Problem 7.6. Which of the following compounds can have a meso form ?
 (i) 2, 3-Dichloropentane (ii) 2, 4-Dichloropentane (iii) 2, 4-Dichlorohexane

Problem 7.7. How many stereoisomers are possible for the following compound ? [Ans. (ii) can have a meso form]



How many of them are optically active ?

Problem 7.8. Draw a structure which is a diastereomer of the structure given below but is not optically active ? [Ans. Eight. All are optically active]



7.11. RACEMISATION

It has been stated earlier that an optically inactive mixture containing equal quantities of enantiomers of a substance is known as **racemic mixture or racemate**. It is denoted by using the prefix (\pm) or (*dl*) or (*RS*) before the name of the compound. For example, a racemic mixture of lactic acid is denoted as (\pm) lactic acid.

Racemic mixtures can be formed in one of the following three ways :

- (i) Synthesis of chiral compounds from achiral reactants (please see sec. 1.14)
- (ii) Mixing of equal amounts of two enantiomers (already described)
- (iii) Racemisation.

We will now consider the process of racemisation and its mechanism.

7.11.1. Racemisation

The conversion of an optically active compound into a racemic mixture containing equal amounts of the original compound and its enantiomer is known as **racemisation**.

Racemisation can be brought about by one of the following methods depending upon the nature of the compound.

(1) **By the action of heat.** Quite often an optically active enantiomer changes into a racemic mixture by the action of heat. For example, when (+) tartaric acid is strongly heated with water it gets converted into a mixture of racemic and meso tartaric acids.

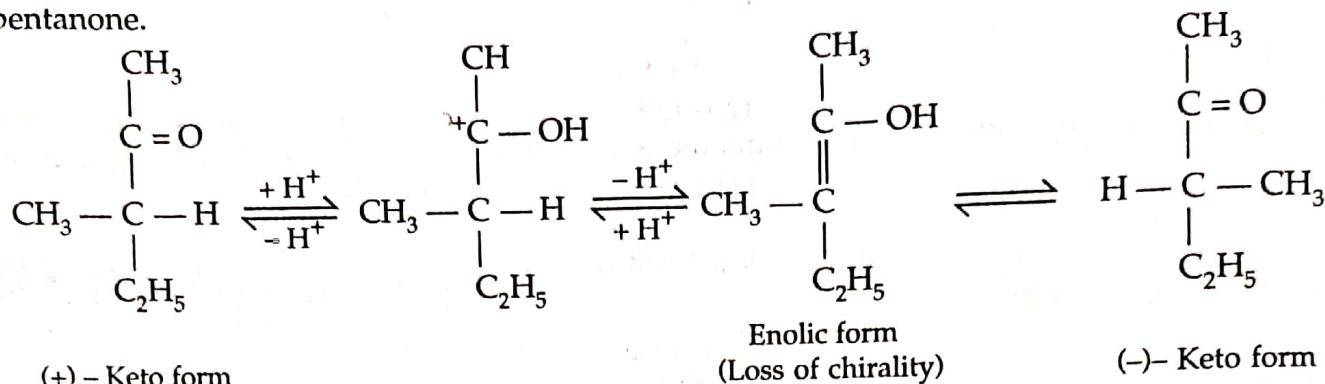
(2) **By the action of chemical reagents.** Racemisation is also brought about by the presence of foreign substances (particularly acids and bases) in the solution of an optically active substance. For example, addition of sodium hydroxide to (+) or (-) lactic acid leads to the formation of a racemic mixture.

(3) **Autoracemisation.** In some cases, racemisation takes place by merely keeping the substance at room temperature for some time. This is known as **autoracemisation**. For example, any one of the enantiomers of dimethylbromosuccinate changes into a racemic mixture on standing at room temperature.

Mechanism of racemisation. Different mechanisms have been developed for the racemisation of different types of compounds. But in majority of cases, racemisation is believed to take place through the formation of some intermediate which is no longer chiral in nature as explained ahead.

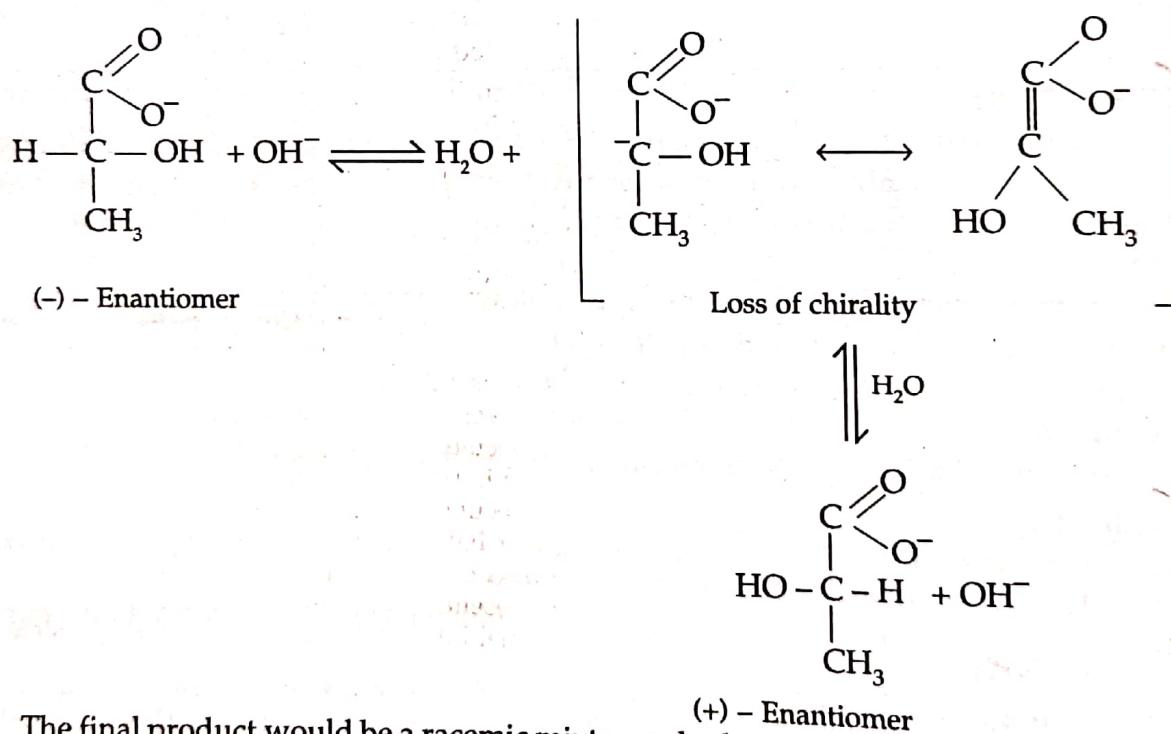
KB

Acid catalysed racemisation of an optically active aldehyde or ketone in which the chiral carbon carries a hydrogen and is in α -position with respect to the carbonyl group takes place through **enolisation** i.e. the intermediate formation of an achiral enol by tautomeric change. The enolic form, being unstable, reverts to the chiral keto form but in doing so it produces (+) and (-) enantiomers in equal quantities and thus racemisation takes place. This is shown ahead with the help of 3-methyl-2-pentanone.



Irrespective of whether the starting compound is (+) or (-) 3-methyl- 2-pentanone, the final product is a racemic mixture since both the enantiomers are formed in equal quantities.

Base catalysed racemisation of (-) lactic acid takes place through the formation of an **achiral carbanion** as shown below :



The final product would be a racemic mixture whether we start with (-) or (+) - enantiomer of lactic acid.

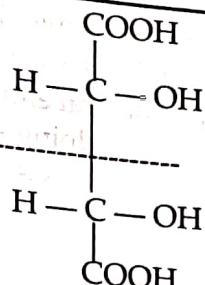
We will come across many examples of chemical reactions in the text (such as S_N^1 reactions of alkyl halides discussed in chapter 9) which are accompanied by complete or partial racemisation. Partial racemisation means that one enantiomer may be formed in larger amount than the other so that the mixture of the two will not be completely inactive.

7.12. INTERNAL AND EXTERNAL COMPENSATION

7.12.1. Internal Compensation

It has been stated above that meso compounds are optically inactive because their molecules are not chiral even though they contain two (or more) chiral centres. For example, it is clear from the structural formulae of mesotartaric acid that the top half of the structure is the mirror image of

Plane of symmetry



the bottom half. As such the optical activity due to one chiral centre is counterbalanced by the optical activity due to the other and the compound is optically inactive. *The counterbalancing of optical activity of one half of a molecule by the other half is known as internal compensation* and the molecule is said to be **internally compensated**.

An internally compensated molecule is *permanently inactive*.

7.12.2. External Compensation

In an equimolar mixture of two enantiomers [say (+) and (-) lactic acids], the molecules of one enantiomer are present in a quantity equal to those of the other enantiomer. This means that for every possible orientation of one enantiomer (which can cause rotation in a particular direction, say towards right), a molecule of the other enantiomer would be in a mirror-image orientation (which would cause rotation in the opposite direction). Therefore, *exact cancellation of all rotations would take place and the equimolar mixture would be optically inactive. The cancellation of rotation of one enantiomer by the other in an equimolar mixture of two enantiomers is known as external compensation* and the racemic mixture is said to be **externally compensated**.

It may be pointed out that if the two enantiomers are *not mixed in equimolar quantities*, the rotation caused by one enantiomer is *not exactly cancelled* by the other. As such this mixture still exhibits some optically activity. The direction of rotation corresponds to that of the enantiomer present in larger quantity but the specific rotation is lesser. In this way partial compensation takes place and the mixture formed is said to be partially **racemised**.

✓ Comparison of External and Internal Compensations

External Compensation	Internal Compensation
<ol style="list-style-type: none"> This is due to the mirror-image relationship between the structures of the molecules of <i>two enantiomers mixed together</i>. In this type of compensation the molecules of one enantiomer cancel the rotation of the other enantiomer. The racemate formed is a <i>mixture</i> of two isomeric compounds. It is possible to have complete or partial external compensation of rotation so as to cause complete or partial racemisation. It is a <i>reversible process</i> and the racemic mixture can be resolved into (+) and (-) enantiomers. 	<p>This is due to the mirror-image relationship between the structures of two halves of the <i>same molecule</i>. In this type of compensation one half of the molecule counter-balances the rotation of the other half. Meso or internally compensated compound represents a <i>single pure compound</i>. Partial internal compensation is not possible.</p> <p>It is <u>permanent effect</u> and it is not possible to resolve an internally compensated molecule into optically active forms.</p>

7.13. RESOLUTION OF RACEMIC MIXTURE

The process of separating a racemic mixture into its enantiomers is called **resolution**. It is not easy to carry out resolution in actual practice. This is because enantiomers have identical physical and chemical properties which makes their separation from each other very difficult. Therefore, special methods have been introduced for this purpose.

7.13.1. Mechanical Separation

If the enantiomers of a substance exist in well defined crystalline forms, the separation can be done by "hand picking" with the help of a magnifying lens and a pair of tweezers. For example, the enantiomers of sodium ammonium tartarate can be separated by this method.

KB

Limitations. (i) This method has a very limited application as very few enantiomeric substances exist in the form of mechanically separable crystals.

(ii) The method is very laborious and time consuming.

7.13.2. Biochemical Separation

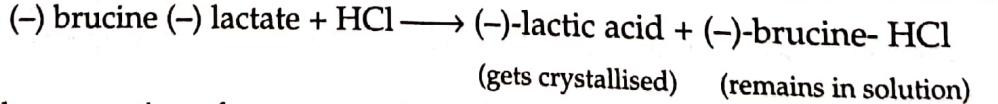
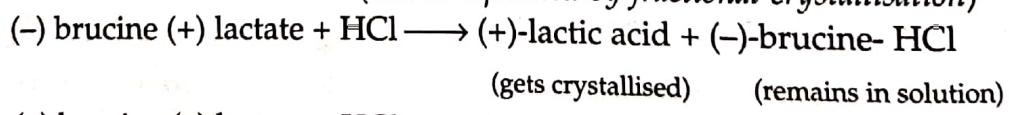
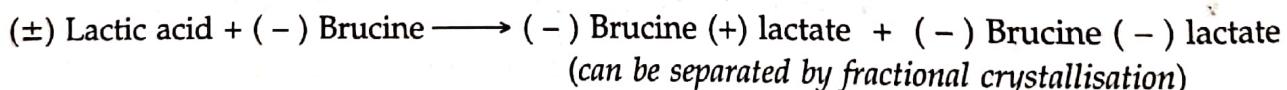
This method involves the use of micro-organisms for bringing about resolution. If certain bacteria, yeasts or moulds are allowed to grow in a dilute solution of a racemic modification, one of the enantiomers is *selectively consumed* by the micro-organism while the other is left behind. For example, when the mould *Penicillium glaucum* is allowed to grow in a solution of racemic ammonium tartarate, the mould completely destroys (+) ammonium tartarate while (-) ammonium tartarate is left practically unaffected.

Limitation. (i) The main disadvantage of the method is that one half of the material is destroyed during separation.

(ii) As the separation is carried out only in dilute solutions, the process is very slow and only small amount of materials can be separated.

7.13.3. Chemical Separation

This is probably the best method of resolution. It involves the conversion of racemic mixture into a mixture of diastereomers of some other substance by reaction with an optically active reagent. Since diastereomers have different physical properties, the mixture of diastereomers can be easily separated through fractional crystallisation, fractional distillation, chromatography, etc. Each of the diastereomers is then suitably treated to generate a pure enantiomer of the original substance. For example, if a racemic mixture of (+) and (-) lactic acids is treated with a single enantiomer of an optically active base, say (-) brucine, it would result in the formation of a mixture of two crystalline salts. The two salts formed would be (-) brucine (+) lactate and (-) brucine (-) lactate. While brucine part of these salts has the same configuration in both cases, the acid parts have non-superimposable mirror image configurations in two cases, so that the two salts represent two diastereomers. As such the crystals of two salts differ in their solubilities and can be separated by fractional crystallisation. Once the separation has been achieved, reaction of each salt with hydrochloric acid would generate a free lactic acid in pure enantiomeric form.



Apart from the separation of racemic acids or bases by this method, it can also be employed for the separation of racemic alcohols, aldehydes, etc. by treatment with suitable optically active reagents.

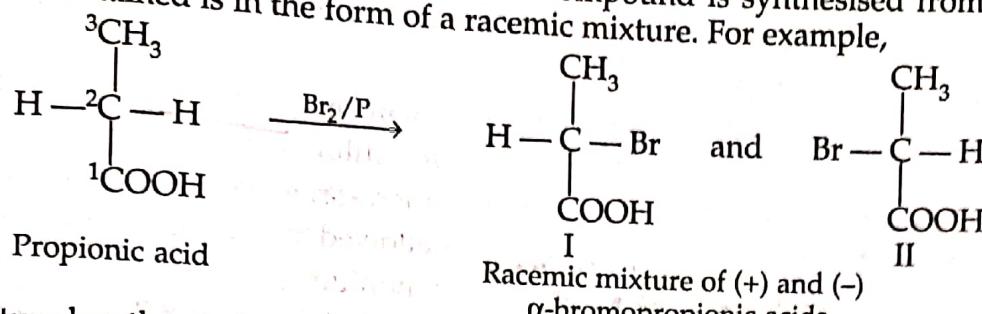
7.13.4. Chromatography

These days chromatographic techniques such as adsorption chromatography using optically active adsorbents, paper chromatography and gas chromatography are also being used for resolution.

In adsorption chromatography, the solution of racemic mixture in a suitable solvent is passed through a column packed with optically active adsorbent when differential adsorption of the enantiomers takes place. This is followed by elution with suitable solvents to get each enantiomer separately.

7.14. ASYMMETRIC OR ENANTIOSELECTIVE SYNTHESIS

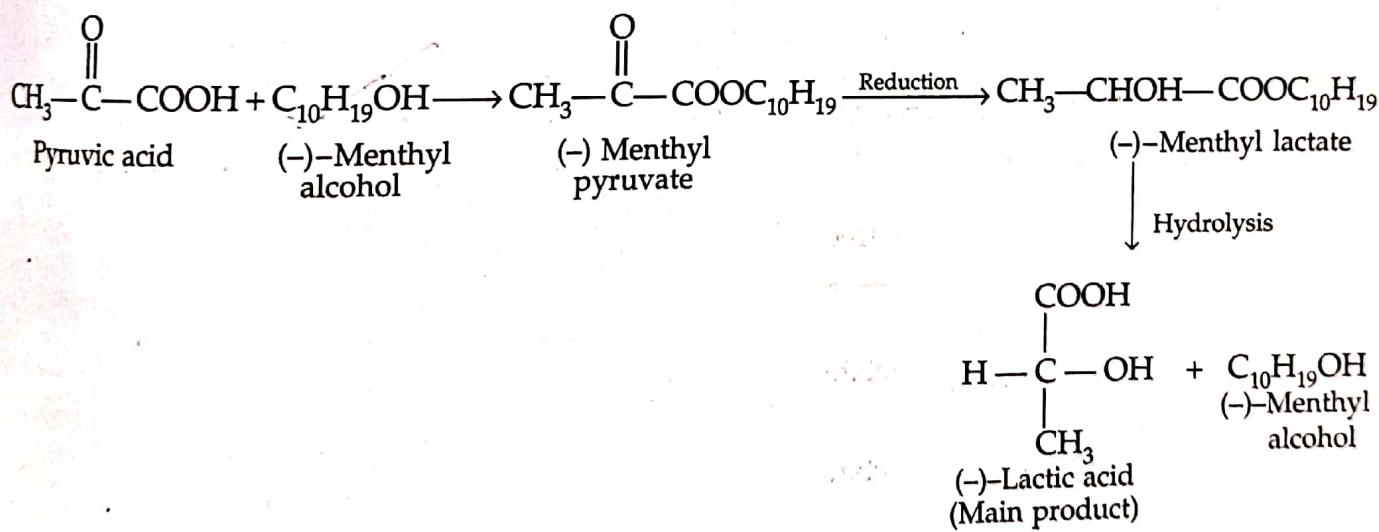
It has been already pointed out that when a chiral compound is synthesised from achiral compounds, the product obtained is in the form of a racemic mixture. For example,



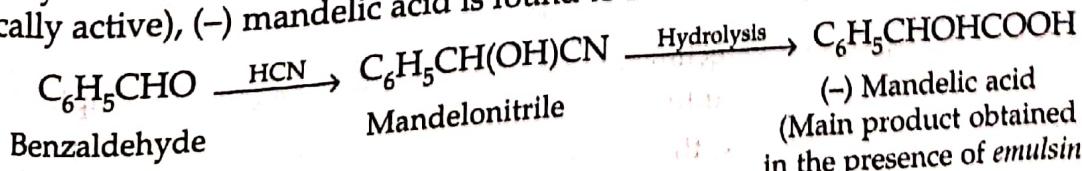
The racemic mixture has then to be resolved into the enantiomers through methods described on previous page.

It is, however, found that if the chiral compound is prepared from achiral compounds under the influence of some optically active substance (which is subsequently removed), the product formed is optically active. This method of directly preparing an optically active isomer from achiral molecules under the influence of some other optically active substance is called asymmetric or enantioselective synthesis. It may be pointed out that even in asymmetric synthesis, both the (+) and (-) enantiomers are formed but one of these is obtained in predominating amounts so that the product exhibits a net optical rotation. The following examples illustrate the applicability of this process.

1. Synthesis of (-) lactic acid. Lactic acid obtained by the direct reduction of pyruvic acid as such is found to be in the form of a racemic modification. However, if pyruvic acid is first esterified with an optically active alcohol such as (-) menthyl alcohol and the ester formed is subjected to reduction and then hydrolysis, we get a product having excess of (-) lactic acid.



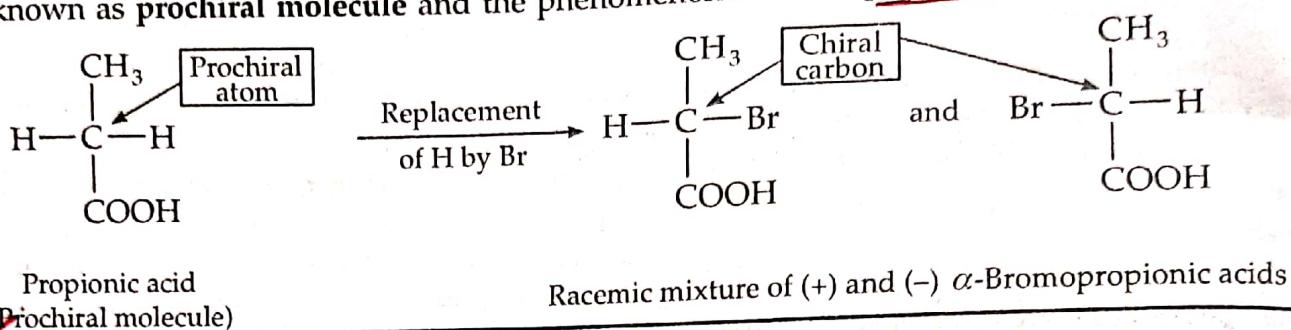
2. Synthesis of (-) mandelic acid. Mandelic acid, $\text{C}_6\text{H}_5-\text{CH}(\text{OH})\text{COOH}$, may be obtained in racemic form by the reaction of benzaldehyde with hydrogen cyanide followed by hydrolysis. But when the same synthesis is carried out in the presence of an enzyme *emulsin* (like most other enzymes, it is also optically active), (-) mandelic acid is found to be the main product.



Most of the chiral compounds formed in nature, such as alkaloids and proteins, are obtained in optically active form. This is because they are synthesised in nature under the influence of other optically active species.

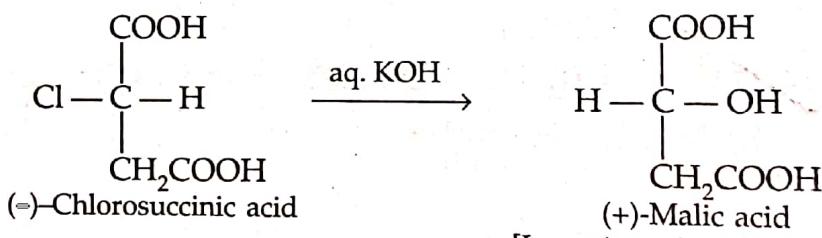
Prochirality : Prochiral atom

It has been shown above that the replacement of one of the hydrogens attached to C-2 of propionic acid (which is optically inactive) by bromine gives rise to a racemic mixture of optically active products. This is because C-2 is originally achiral in nature but in the product formed it becomes chiral. Such an atom is known as **prochiral**. A prochiral atom may be defined as *the central atom in a molecule the replacement of one of the H-atoms attached to which by a substituent atom or group generates a chiral centre*. The molecule containing the prochiral atom is known as **prochiral molecule** and the phenomenon is called **prochirality**.

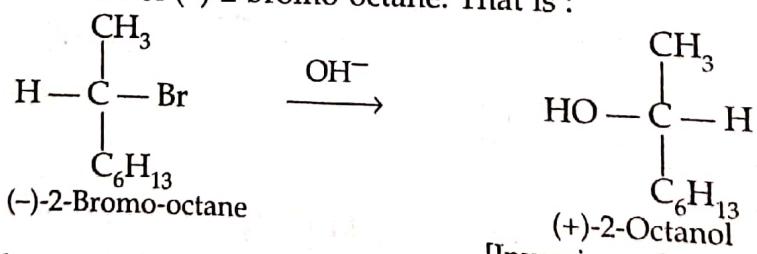
**7.15. INVERSION OF CONFIGURATION : WALDEN INVERSION**

If an atom or group of atoms directly attached to a stereogenic centre is substituted by some other atom or group, the configuration of new compound is sometimes found to be different from that of the original compound. This is known as **inversion of configuration** or **optical inversion**. This phenomenon was first discovered by Walden and is, therefore, also known as **Walden inversion**. For example :

(i) When (-)-chlorosuccinic acid is treated with aqueous potassium hydroxide, the product obtained is (+)-malic acid having a different configuration than the starting compound.

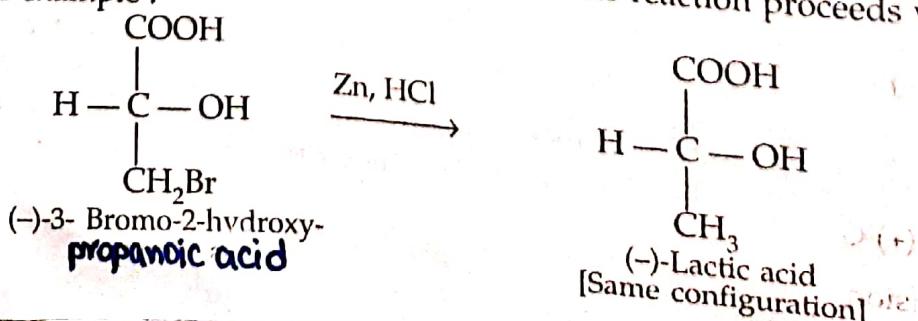


(ii) When treated with aqueous KOH, (-)-2-bromo-octane gives (+)-2-octanol which has configuration opposite to that of (-)-2-bromo-octane. That is :



It may be noted, however, that change in configuration may or may not be accompanied by change in direction of rotation.

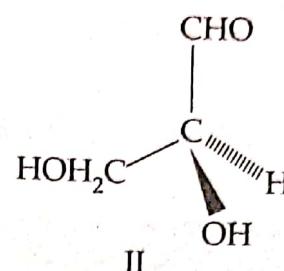
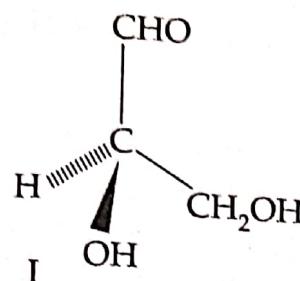
Retention of configuration. If a compound containing a stereogenic centre is converted into another without breaking any of the bonds with the stereogenic centre, the product has the same configuration as the original compound. This means that the reaction proceeds with **retention of configuration**. For example :



~~7.16. CONFIGURATION AND ITS SPECIFICATION~~

~~7.16.1. Configuration~~

The arrangement in space of the atoms or groups constituting a stereoisomer is called its configuration. For example, the configurations of the two enantiomers of lactic acid are I and II shown below. One of these configurations represents dextro or (+) lactic acid while the other represents laevo or (-) lactic acid.



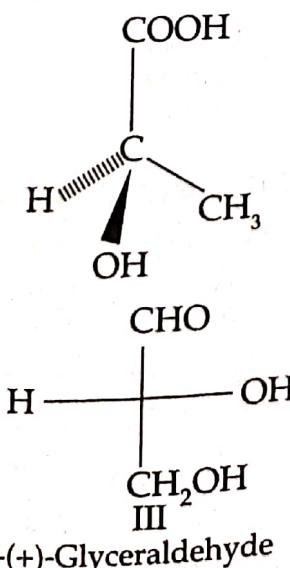
~~7.16.2. Specification of configuration : D and L Notations~~

When we state that one of the enantiomers of lactic acid has the configuration I while the other has the configuration II (given above), we merely represent the two possible configurations of the enantiomers of lactic acid. What is not indicated is which configuration represents which isomer, i.e. which one of the two enantiomers, (+) or (-), has the configuration I and which has the configuration II. In other words, we do not know the actual or absolute configuration of each of the two enantiomers.

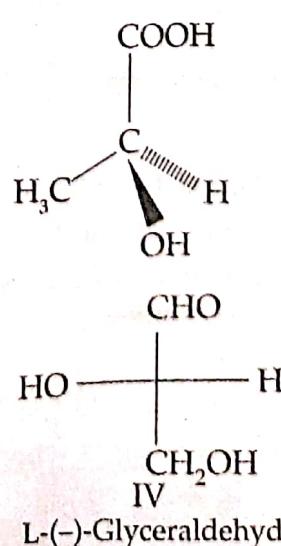
In the earlier days of the study of stereochemistry, it was not found possible to determine the absolute configurations of the compounds. Fortunately, it is not always necessary to know the absolute configuration of an optically active compound. On the other hand, we are more interested in knowing the relative configurations of different compounds. For example, when an optically active compound undergoes a chemical reaction, we are mainly interested in whether the configurations of the reactant and its product are same or different and not in their actual configurations.

Relative configurations : Standard reference compound. To assign relative configurations to various optically active compounds and to indicate their relationship, what was done was to choose a standard reference compound and fix its configuration arbitrarily as proposed by Emil Fischer (1885). The compound chosen as the standard was glyceraldehyde ($\text{CH}_2\text{OHCHOHCHO}$) and its two enantiomers were designated by the symbols D (read as "dee") and L (read as "ell"). [It must be made clear that the symbols D and L refer to configurations and are quite different from the prefixes d and l (read as "dextro" and "laevo") which refer to the direction of rotation].

(+)-Glyceraldehyde was arbitrarily assigned the configuration III (in which the -OH group attached to chiral carbon is towards right) and was given the symbol D. The (-)-enantiomer was assigned the configuration IV (in which the -OH group attached to chiral carbon is towards left) and was given the symbol L.



D-(+)-Glyceraldehyde



L-(-)-Glyceraldehyde

(Three dimensional and planar representations of two enantiomers of glyceraldehyde).

KB

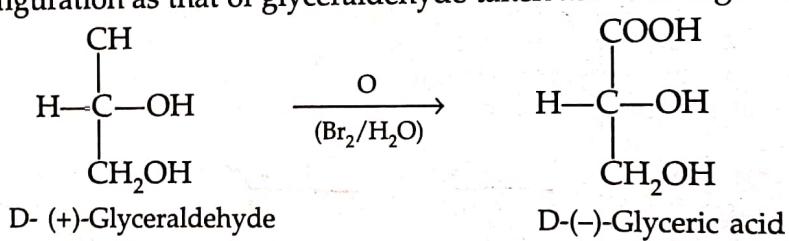
Reasons for selecting glyceraldehyde as the standard. Glyceraldehyde was chosen as the standard mainly because of the following reasons :

(i) It is the simplest carbohydrate – an aldotriose – and its configuration could be easily related to those of the other carbohydrates (which are stereochemically very important compounds).

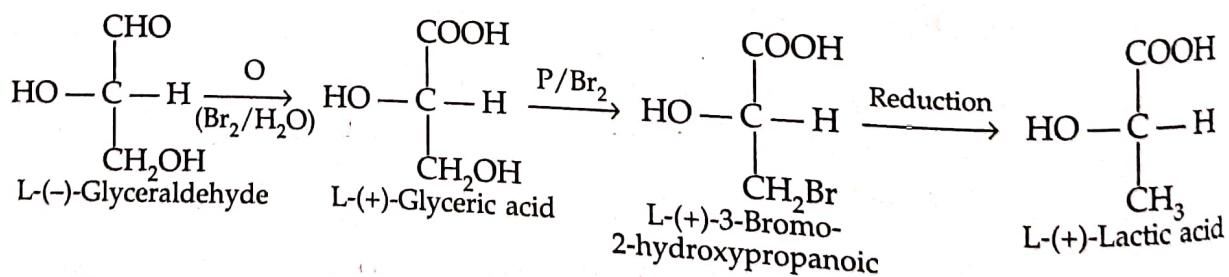
(ii) Since glyceraldehyde contains very reactive functional groups it could be converted into many other types of compounds. In this way it could be configurationally related to a large number of compounds.

Correlation of configuration. Many other compounds were then assigned *relative configurations* by relating their configuration to that of D- or L-glyceraldehyde. For this purpose either the compound under examination is converted into D- or L-glyceraldehyde or D- or L-glyceraldehyde is converted into the given compound by means of reactions which *do not involve breaking of bonds to a chiral centre*. The general principle involved in correlating the configurations of two compounds is that *if a reaction does not involve the breaking of a bond about a chiral centre, the configuration about that stereogenic centre remains unchanged*. Some important examples of the correlations of the configurations are given below :

(i) (-)-Glyceric acid can be obtained by the oxidation of D- (+)-glyceraldehyde as shown below. Since this reaction does not involve breaking of bonds about the stereogenic centre, (-)- glyceric acid must have the same configuration as that of glyceraldehyde taken i.e. D configuration.



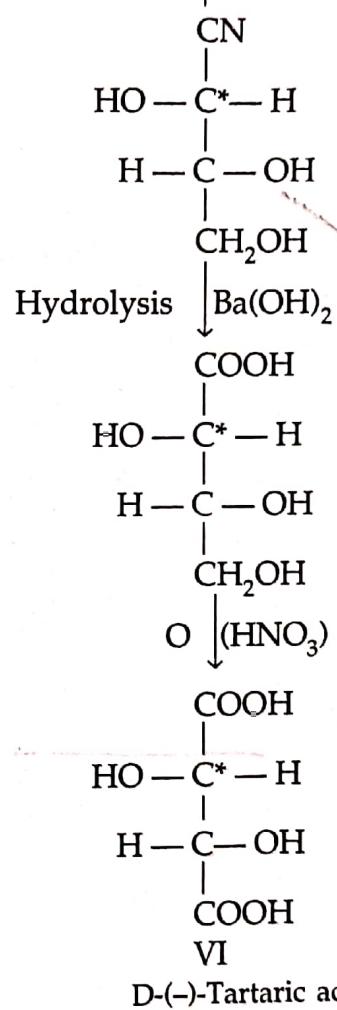
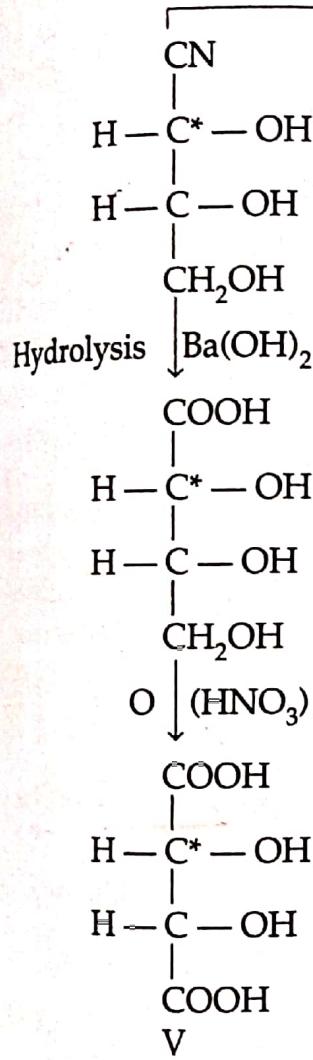
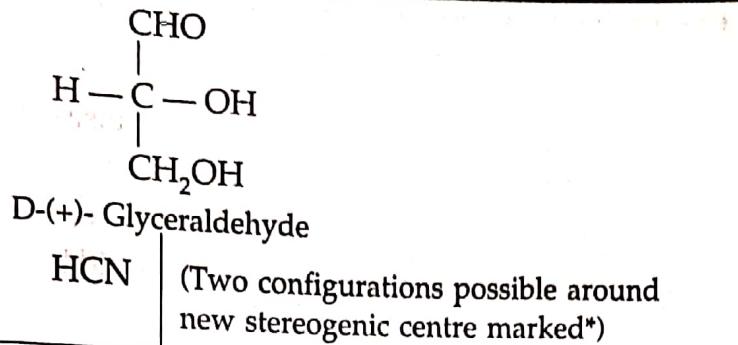
(ii) The configuration of (+)- lactic acid was established to be similar to that of L-(-)-glyceraldehyde by the following reactions :



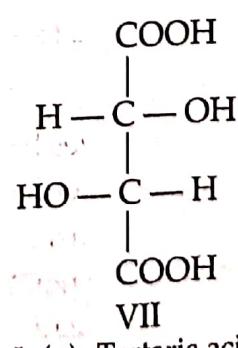
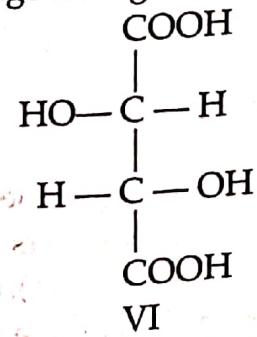
(None of the reactions involves breaking of bonds about the stereogenic centre)

(iii) When D- (+)-glyceraldehyde was converted into tartaric acid by the series of reactions shown below, a mixture of two products was obtained. These two products differed from each other in their configuration around newly created stereogenic centre (marked *). One of the products was the inactive or mesotartaric acid (V). The other was the optically active tartaric acid which rotated the plane of light to the left i.e. it was (-)- tartaric acid. Since it was obtained from D-glyceraldehyde by reactions which did not involve breaking of bonds around the original chiral centre, it was assigned D-configuration i.e. the same as that of starting glyceraldehyde.

KB

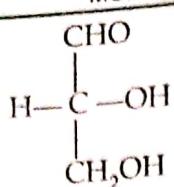


Since D-(-) tartaric acid was assigned configuration VI, L-(+) tartaric acid would naturally have the mirror image configuration i.e. VII.

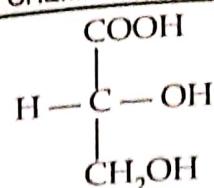


If rotation of polarised light. Two substances may have similar relative configurations and yet may rotate the plane of light in different directions. For example, D-(+)- glyceraldehyde and D-(-)-glyceric acid have similar configuration even though the former is dextrorotatory while the latter is levorotatory.

KB

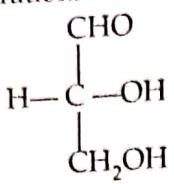


D-(+)-Glyceraldehyde

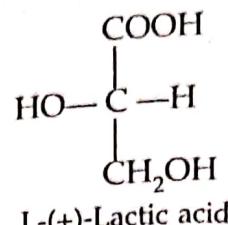


D-(-)-Glyceric acid

Similarly two compounds may have different configurations and even then they may rotate the plane of light in the same direction. For example, D-(+)- Glyceraldehyde and L-(+)-lactic acid have opposite configurations but the same sign of rotation.



D-(+)-Glyceraldehyde

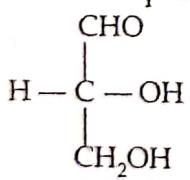


L-(+)-Lactic acid

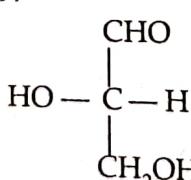
7.16.3. Absolute configuration

It was only in 1951 that by using X-ray diffraction studies, Bijvoet was able to determine the absolute configuration of a compound i.e. the *actual arrangement in space of the atoms or groups constituting a particular stereoisomer*. The first compound whose absolute configuration was determined was sodium rubidium salt of (+)-tartaric acid. Bijvoet found that (+)-tartaric acid *actually* has the same configuration which it was previously *assumed to have* on the basis of configurational relationship between glyceraldehyde and tartaric acid (as described above). If the assumed configuration of (+)-tartaric acid was correct, the *assumed configuration of the two enantiomers of glyceraldehyde must also be correct*. As such the configuration of all other compounds derived by correlation with glyceraldehydes must be correct ones. Thus the relative configuration assigned to D-(-)- glyceric acid, L-(-)- lactic acid (discussed above), carbohydrates and a large number of other compounds actually represent their absolute configuration.

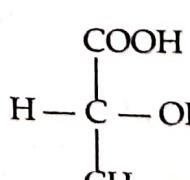
The absolute configurations of some simple but stereochemically important compounds are given below in the planar form :



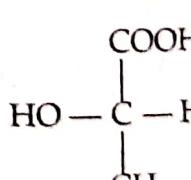
D-(+)-Glyceraldehyde



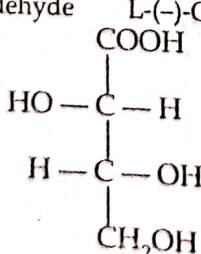
L-(-)-Glyceraldehyde



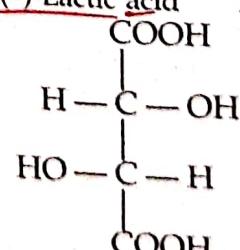
D-(-)-Lactic acid



L-(+)-Lactic acid



D-(-)-Tartaric acid



L-(+)-Tartaric acid

7.16.4. Limitations of D and L system of configurations

The system of designating the configurations as D and L is essentially based upon the configurational relationship to one or the other enantiomer of glyceraldehyde. But the procedure followed has certain limitations. It has been found that in some cases, a given compound can be related by a sequence of reactions to a known compound having D-configuration. But at the same time by another sequence of reactions, the given compound can also be related to the L-enantiomer of the known compound. This leads to an ambiguous situation where the same compound may be assigned either D or L configuration.

KB

It may, however, be pointed out that in the case of **carbohydrates** and **amino acids**, certain conventions have been adopted due to which the system of assigning D and L configurations is found very useful in these classes of compounds.

7.17. RECTUS AND SINISTER OR R AND S SEQUENCE FOR SPECIFICATION OF CONFIGURATION

In view of the limitations of D- and L-system of configurations, Cahn, Ingold and Prelog suggested a very simple procedure to specify a particular configuration of a substance in terms of prefixes **R** or **S**. The procedure involves the following two steps :

Step 1. The four atoms or groups of atoms bonded to the chiral centre are assigned a sequence of priorities in accordance with a set of rules known as sequence rules.

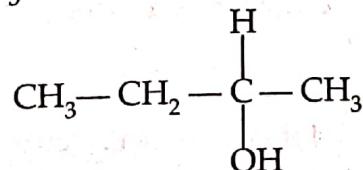
Sequence rules. The sequence rules are as follows :

Rule 1. If all the four atoms directly attached to the chiral centre are different from one another, sequence of priorities is determined by their atomic numbers. The atom of highest atomic number gets the highest priority while the one with the lowest atomic number comes last in order of priority. For example, in the compound 1-bromo-1-chloro-ethane, $\text{CH}_3\text{CH}(\text{Cl})\text{Br}$, the four groups attached to chiral carbon are CH_3 , H, Cl and Br. Their sequence of priorities will be $\text{Br} > \text{Cl} > \text{CH}_3 > \text{H}$.

Similarly the order of priorities of the groups $-\text{CH}_3$, $-\text{OH}$, $-\text{NH}_2$ and $-\text{H}$ is $\text{OH} > \text{NH}_2 > \text{CH}_3 > \text{H}$.

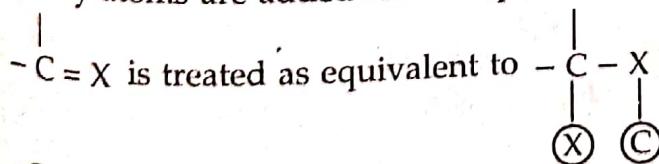
If two isotopes of the same element are involved, the isotope with the **higher mass number** gets higher priority. For example, out of hydrogen (${}^1\text{H}$) and deuterium (${}^2\text{H}$), deuterium gets higher priority.

Rule 2. If the first atoms of two or more groups attached to the chiral centre have the same atomic number, the relative priorities may be fixed by comparing the next atoms in the groups. If even this does not solve the problem, the comparison may be extended further to the next atom and so on. For example, in sec. butyl alcohol the relative priorities of CH_3 and C_2H_5 are decided as follows. Each of these groups is linked to the chiral centre through the same atom, i.e. carbon. The next atoms in CH_3 are H, H and H while in C_2H_5 they are C, H and H. Since carbon has a higher atomic number than hydrogen, C_2H_5 gets higher priority than CH_3 .



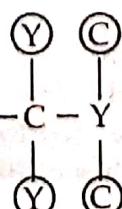
Therefore, the complete sequence of priorities is — $\text{OH} > \text{CH}_3 - \text{CH}_2 - > \text{CH}_3 - > \text{H}$

Rule 3. If a group contains a **double** or **triple bond** between two atoms, it is *treated* as equivalent to two single bonds or three single bonds between the two atoms. In other words each pi bond is supposed to be broken and atoms at each end of the pi bond are duplicated. While doing so, two imaginary atoms are added for each pi bond broken. From instance,



[X and C are imaginary atoms added due to breaking of π bond]

Thus it is considered that the group $-\text{C}=\text{X}$ contains 2 atoms of X attached to carbon.

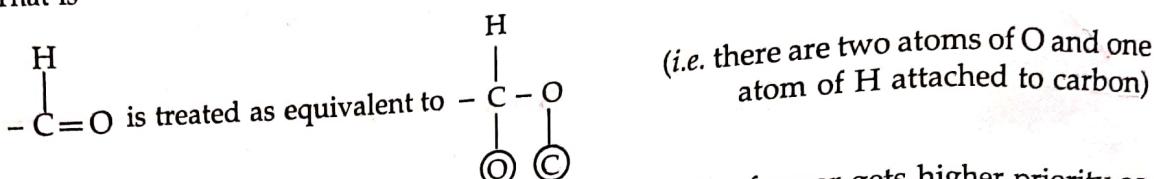


Similarly $-\text{C}\equiv\text{Y}$ is treated as equivalent to

KB

Therefore, the group $-C \equiv Y$ is considered to contain 3 atoms of Y attached to carbon.

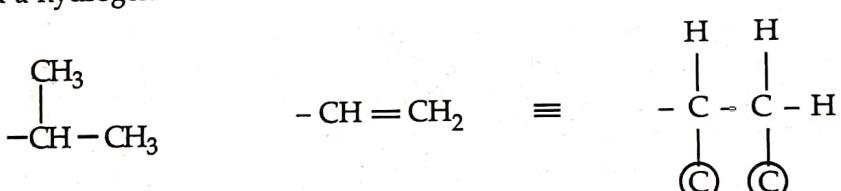
To take a specific example, in the group $-C=O$, next atoms to carbon are equivalent to O, O and H. That is



Therefore, if we compare the groups $-CHO$ and $-CH_2OH$, the former gets higher priority as in it the atoms next to carbon are O, O and H while in $-CH_2OH$, they are O, H and H.

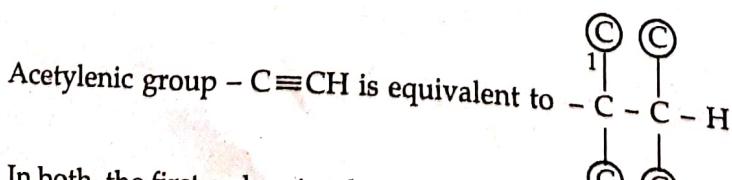
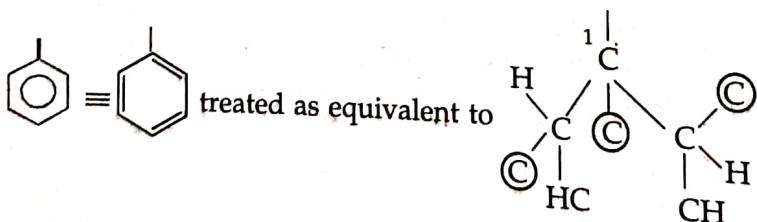
Comparison of the priorities of some typical groups. Let us compare the relative priorities of

vinyl ($-CH=CH_2$) and isopropyl $\left(\begin{array}{c} CH_3 \\ | \\ -CH-CH_3 \end{array}\right)$ groups. In isopropyl group, the first carbon is attached to 2 carbons and a hydrogen. In vinyl group also the first carbon is treated as linked to two carbons and a hydrogen.



But in vinyl group, the second carbon is further attached to one carbon C and two hydrogens. On the other hand, in isopropyl the second carbon is attached to only hydrogens. Therefore, vinyl group gets priority over isopropyl group.

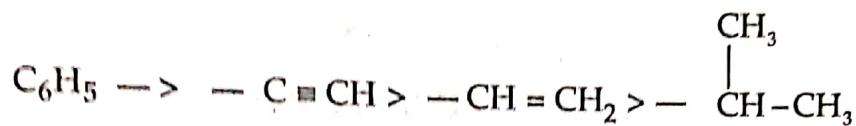
Similarly phenyl group () gets priority over acetylenic group ($-C \equiv CH$). Phenyl group is considered as if it has one of Kekulé structures. That is :



In both, the first carbon is taken as attached to three carbons. In phenyl two of the three carbons attached to first carbon are further attached to two carbons and a hydrogen while the third is a duplicated carbon. In acetylene only one of the three carbons attached to first carbon is further

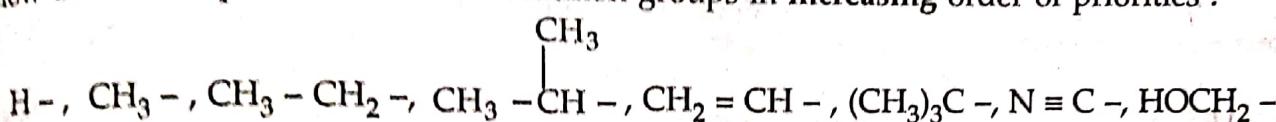
attached to two carbons and a hydrogen while the other two are duplicated carbons. Therefore, phenyl group gets priority over acetylenic group.

It is very evident that phenyl or acetylenic group would get priority over vinyl or isopropyl group. This is because in phenyl or acetylenic group the first carbon is attached to **three** carbons while in vinyl and isopropyl the first carbon is attached to only **two** carbons. Thus the order of priorities of these groups would be



Relative priorities of some common groups :

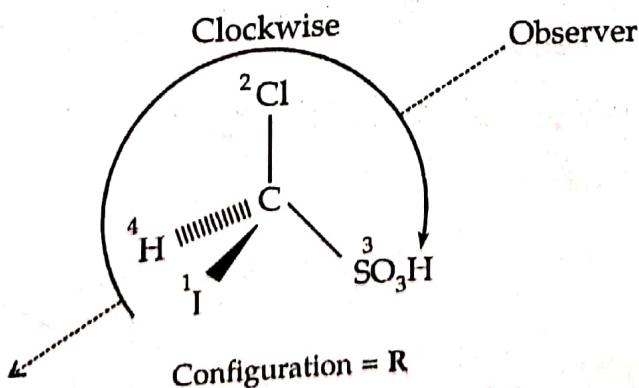
To sum up the above discussion on the determination of priorities of different groups, we give below the relative priorities of some common groups in increasing order of priorities :



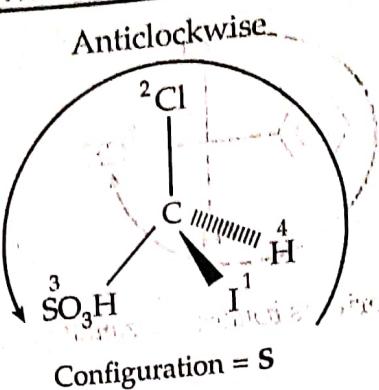
Step 2. Having decided the sequence of priorities, the molecule is imagined to be in a position where the group of lowest priority is directed away from us. Now, we look at the arrangement of remaining groups in **decreasing order of their priorities** (i.e. highest or number 1 downwards). If in doing so, the eye travels in **clockwise** direction, the configuration is specified as R (Latin : *rectus* = right). If, on the other hand, if the eye travels in **anticlockwise** direction, the configuration is specified as S (Latin : *sinister* = left).

Let us illustrate the above rules by considering some specific examples :

(1) **Chloroiodomethane sulphonic acid, $\text{CH}(\text{Cl})(\text{I})\text{SO}_3\text{H}$** . The sequence of decreasing priorities of groups attached to stereogenic carbon is (1) I, (2) Cl, (3) SO_3H and (4) H. To assign configuration to it, the isomer shown below is held in a position so that H (which has the lowest priority) is pointed away from the observer. Now if the remaining groups are arrived in order of decreasing priorities (i.e. I → Cl → SO_3H), the eye has to travel in **clockwise** manner as shown ahead. Therefore the configuration of this isomer is R.

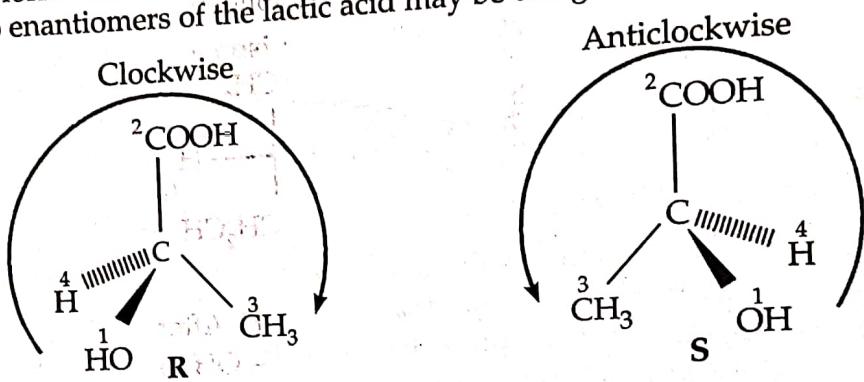


Proceeding in the same manner, the configuration of the enantiomeric form of the above structure would be S.



(2) Lactic acid, $\text{CH}_3\text{CH}(\text{OH})\text{COOH}$.

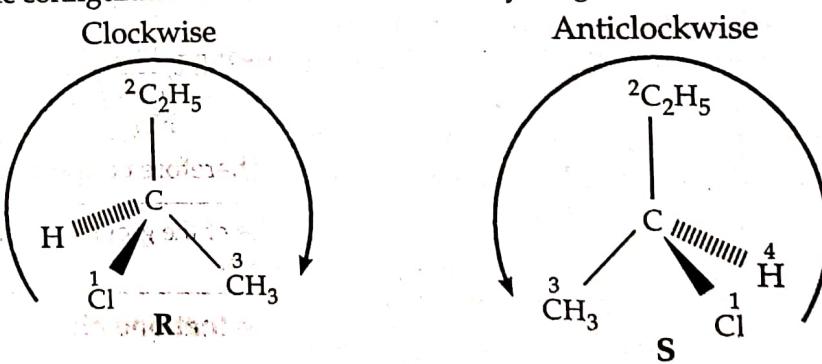
The sequence of priorities in decreasing order is OH, COOH, CH_3 , H. Therefore, the specific configuration of the two enantiomers of the lactic acid may be designated as :



(3) 2-Chlorobutane $\text{CH}_3 - \text{CHCl} - \text{C}_2\text{H}_5$

The sequence of priorities is Cl, C_2H_5 , CH_3 , H.

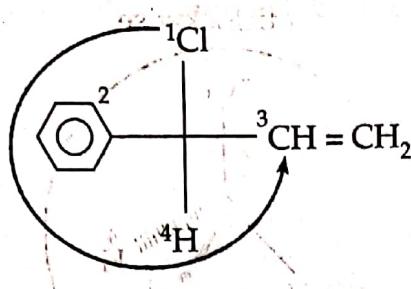
Therefore specific configurations of its enantiomers may be given as :



7.17.1. Configuration on the basis of projection formulae

While assigning configuration to a stereoisomer on the basis of projection formula, two kinds of situations may arise :

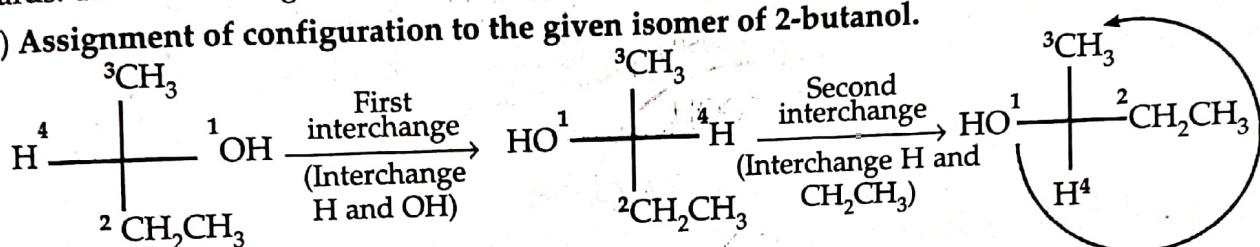
1. If the group of lowest priority is *bonded vertically* (i.e. pointing away from the observer), the configuration is assigned by following exactly the same procedure as in case of three dimensional formulae. For example, in the structure given below, the sequence of priorities is Cl, $\text{CH}=\text{CH}_2$, H. The group of lowest priority (i.e., H) is bonded vertically (i.e. pointing away from us). The movement of the eye is moving from —Cl to  to $-\text{CH}=\text{CH}_2$ is anticlockwise. Therefore, configuration is S.



2. If the group of lowest priority is *bonded horizontally*, (i.e. pointing towards the observer), an additional step is required.

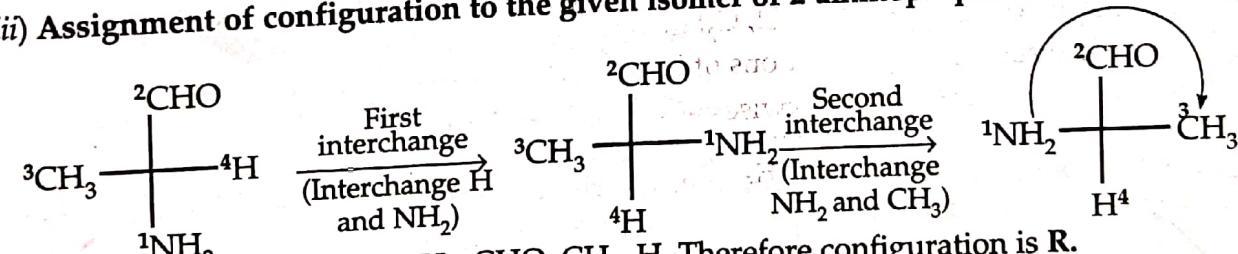
In such cases the given formula is converted into another *equivalent* projection formula by making two interchanges so that the atom or group of lowest priority is placed vertically downwards or upwards. Then the configuration is assigned by following the usual procedure. For example :

(ii) Assignment of configuration to the given isomer of 2-butanol.



The sequence of priorities is OH, CH₂CH₃, CH₃, H. After the second interchange, H is bonded vertically in the projection formula. In moving from —OH to —CH₂CH₃ to —CH₃, the eye travels in anticlockwise direction. Therefore, configuration is S.

(iii) Assignment of configuration to the given isomer of 2-aminopropanal.



The sequence of priorities is NH₂, CHO, CH₃, H. Therefore configuration is R.

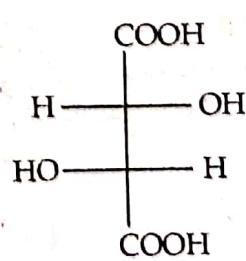
It may be recalled that if we carry out two interchanges of the groups attached to chiral carbon, the configuration remains equivalent to the original configuration.

~~7.17.2. Configuration of compounds containing more than one chiral centre~~

In such cases the configuration about each chiral centre is ascertained separately. The specification of each atom alongwith its number is then prefixed before the name of the compounds as illustrated below :

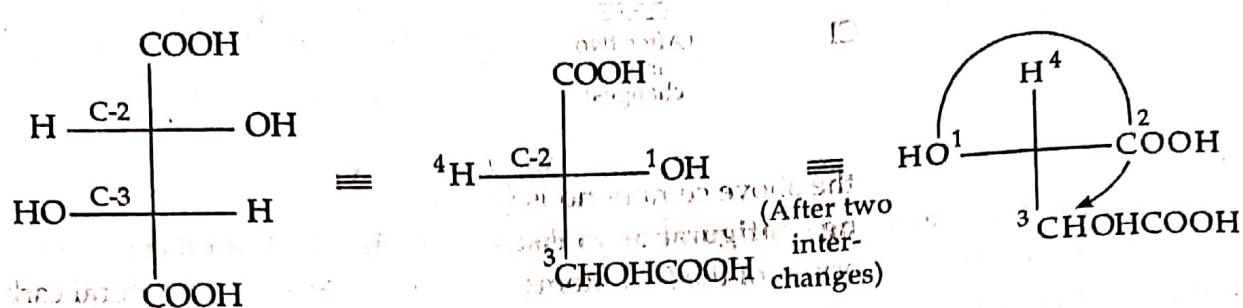
(i) Let us consider one of the forms of tartaric acid, given on the right hand side.

Each chiral centre (carbon 2 and carbon 3) in this molecule has the same set of four groups attached to it (i.e. —COOH, —H, —OH and —CHOH — COOH). The sequence of priorities of these groups is OH, COOH, CHOH — COOH, H.



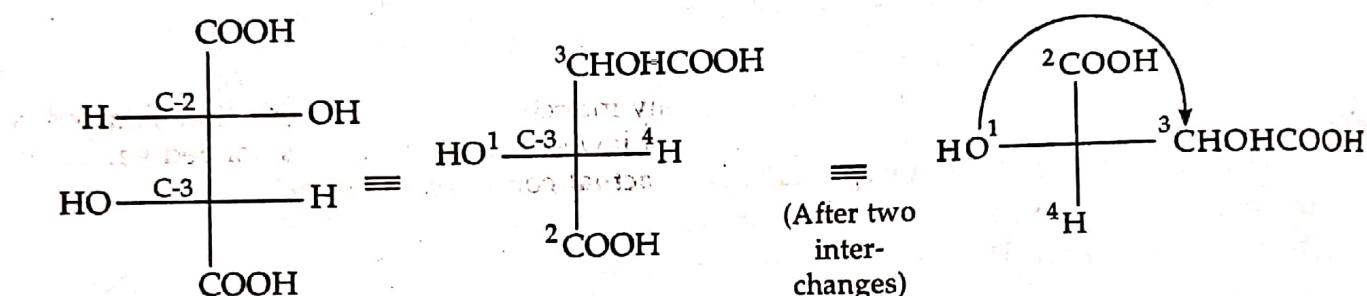
KB

The configuration around C - 2 may be assigned as follows:



Since the eye has to travel clockwise in moving from OH to COOH , the configuration around C-2 is R.

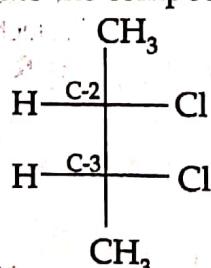
Similarly the configuration around C-3 may be assigned as follows :



It may be seen that configuration around C-3 is also R.

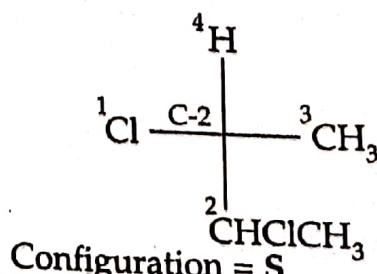
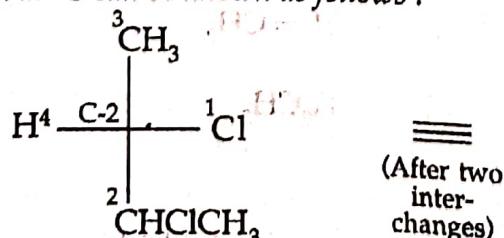
Thus the configurations around each of the chiral centres is S so that the compound may be designated are (2R, 3R)-tartaric acid.

(ii) Let us now assign configuration to the compound.

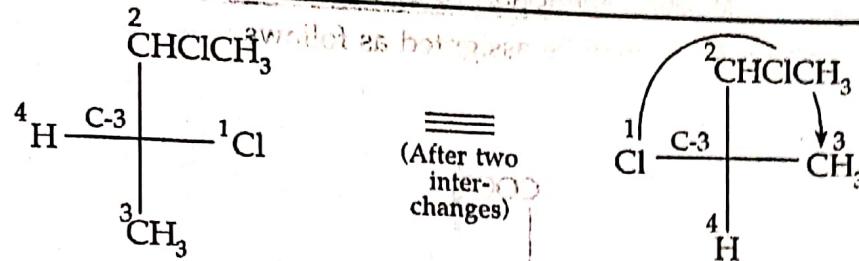


Each of carbon atoms 2 and 3 has the groups CH_3 , H, Cl and CHClCH_3 attached to it. The order of priorities of groups is : Cl, CHClCH_3 , CH_3 , H.

Configuration at ^2C can be known as follows :



Configuration at ^3C can be obtained as follows :



Hence the configuration of the above compound is (2S, 3R).

Useful shortcut for assigning configuration to Fischer's projection formulae :

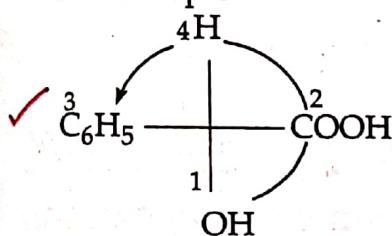
Decide the sequence of priorities of the four atoms or groups attached to the chiral carbon.

Determine the configuration without making any interchange in the given projection formula.

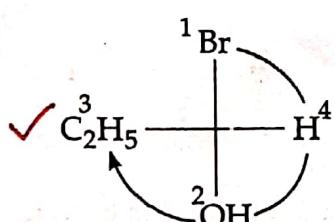
If the atom or group of lowest priority is bonded vertically (either upward or downward) in the projection formula, the configuration determined as above gives the actual configuration.

If the atom or group of lowest priority is bonded horizontally (either left or right) in the projection formula, change the configuration obtained above from R to S or vice versa to get the actual configuration.

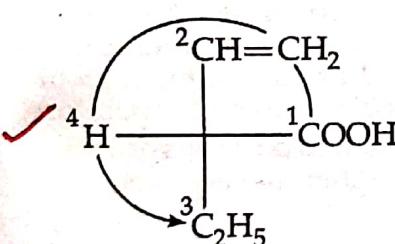
For example



Without making any interchanges, the configuration obtained is S. Since the atom of lowest priority (i.e. H) is bonded vertically, this represents the actual configurational.

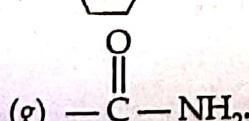
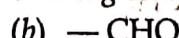


Without making any interchanges, the configuration obtained is R. Since the atom of lowest priority (i.e. H) is bonded horizontally in the projection formula, change R to S.



Therefore without making any interchanges, the configuration obtained is S. Since the atom of lowest priority (i.e. H) is bonded horizontally in the projection formula, change S to R. Therefore actual configuration is R.

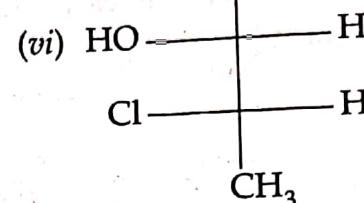
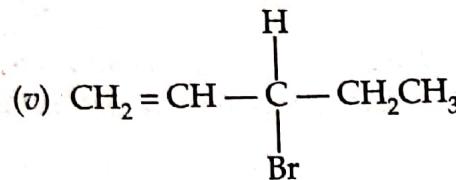
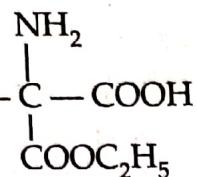
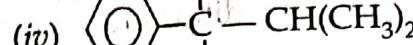
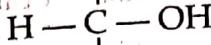
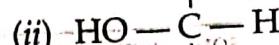
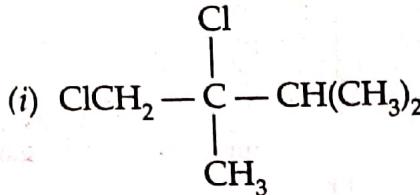
Problem 7.9. Arrange the following groups in decreasing order of priorities :



[Ans. (g) > (b) > (a) > (c) > (e) > (d) > (f).]

KB

Problem 7.10. Assign R and S configurations to the following



Hint : No interchanges are required for (i), (iv) and (v)

[Ans. (i) S, (ii) 2S, 3S (iii) R, (iv) R (v) R (vi) 2R, 3S.]

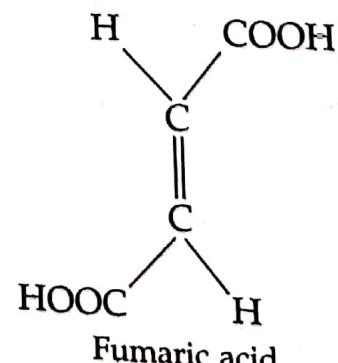
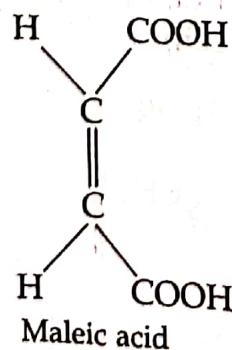
7.18. GEOMETRICAL ISOMERISM : HINDERED ROTATION AROUND CARBON-CARBON DOUBLE BOND

7.18.1. Geometrical isomerism and its cause

Geometrical isomerism is a type of stereoisomerism which is exhibited by certain compounds containing double bonds and arises due to hindered rotation about the double bond. We will first discuss geometrical isomerism in compounds containing carbon-carbon double bond and then consider other types of compounds which also exhibit geometrical isomerism.

A carbon-carbon double bond consists of a sigma and a pi bond. While the σ bond is formed by the overlapping of sp^2 hybrid orbitals of two carbon atoms along the inter-nuclear axis, π bond is formed by the sideways overlapping of the unhybridised p -orbitals of the two carbon atoms above and below the plane of atoms. Because of this type of overlapping, rotation around carbon-carbon double bond is strongly hindered and can take place only if the π bond breaks. But this would require about 284 kJ of energy per mole which is not available to the molecules at room temperature.

Due to hindered rotation around carbon-carbon double bond, the relative positions of groups attached to doubly bond carbon atoms get fixed. As a result several higher alkenes (and other substituted products) can exist in two distinct isomeric forms which differ from each other in the relative distribution of groups in space around the double bond. For example, maleic acid and fumaric acid afford a very well-known example of compounds which exist in geometrically isomeric forms as shown below :



These two isomers are like one another with respect to which atoms are attached to which other atoms but differ from each other in the relative arrangement of atoms in space. In maleic acid,

the two carboxylic groups lie on the same side of the molecule while in fumaric acid the two carboxylic groups lie on opposite sides. Such isomers which have the same structural formulae but differ in the relative spatial arrangement of atoms about the double bond are called **geometrical isomers** and the phenomenon is known as **geometrical isomerism**.

It is obvious that geometrical isomerism represents a type of stereoisomerism. Since the stereoisomers which are not mirror images of each other are called **diastereomers**, geometrical isomers can also be regarded as diastereomers.

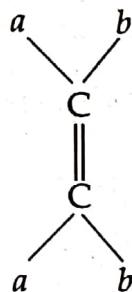
It may also be pointed out that in case of optical and geometrical isomers, the different structures of optical or geometrical isomers cannot be interconverted except by breaking or making of bonds. As such these two types of stereoisomers are also collectively known as **configurational isomers**.

7.18.2. Conditions for geometrical isomerism

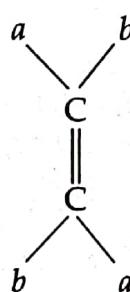
There are two necessary conditions for a compound to exhibit geometrical isomerism. These are :

(i) *The molecule must contain a carbon-carbon double bond, the rotation around which is strongly hindered.*

(ii) *Each of the two doubly bound atoms should have two unlike groups attached to it as, for instance, $abC = Cab$. The formula $abC = Cab$ can have two arrangements in space which represent the geometrical isomers as shown below.*

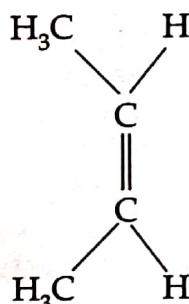


Similar groups on
same side of double bond

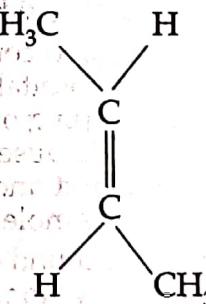


Similar groups on
opposite sides of double bond

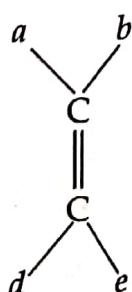
For example, 2-butene ($\text{CH}_3 - \text{CH} = \text{CH} - \text{CH}_3$) exists in the form of geometrical isomers as depicted below :



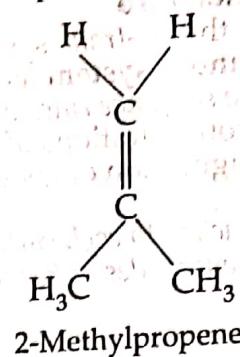
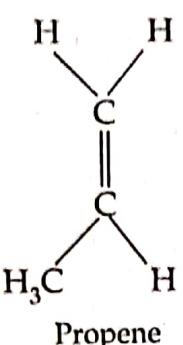
Geometrical isomers of 2-butene.



Sometimes the two groups attached to one doubly bound carbon may be altogether different than those attached to the other carbon atom such as $abC = Ccd$. Even then geometrical isomerism would be exhibited (However, this is not an essential condition).



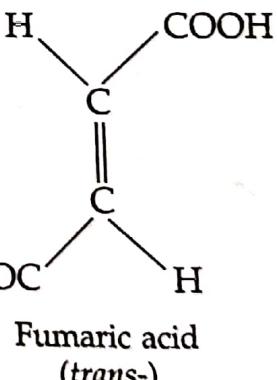
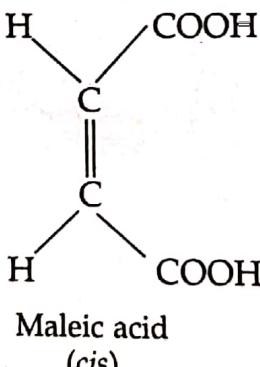
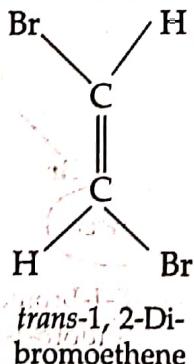
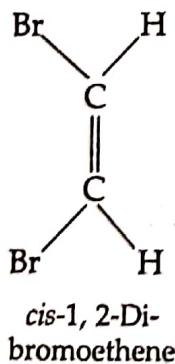
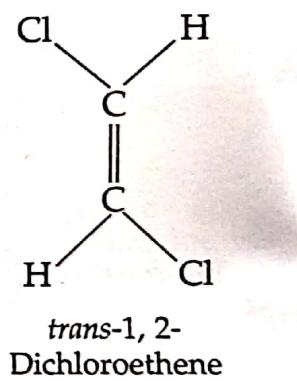
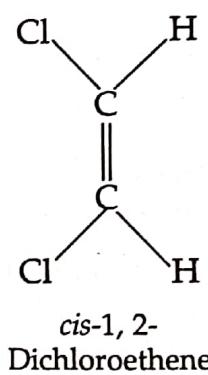
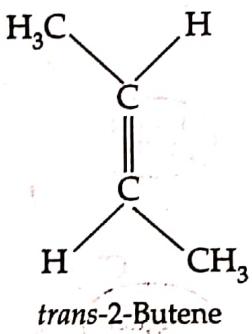
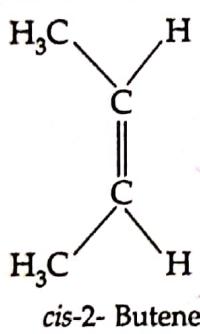
Compounds like propene and 2-methylpropene contain carbon-carbon double bond but still do not display geometrical isomerism. This is because one or both carbons involved in the formation of double bond carry two similar groups as shown below :



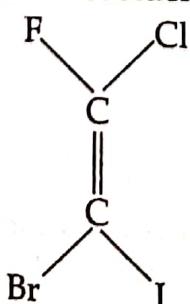
No geometrical isomers possible

7.18.3. Nomenclature of geometrical isomers : cis- and trans-system

The method originally used for denoting the configurations of geometrical isomers is known as **cis-trans system**. In this system the names of the geometrical isomers having different configurations are distinguished by using the prefix **cis** (which means on the same side) or **trans** (which means across) before the name of the compound. The prefix **cis** is used when similar groups are on the same side of the molecule while the prefix **trans** is used when similar groups are on opposite sides as illustrated below :



Limitations of cis and trans system of nomenclature. The *cis* and *trans* system of nomenclature of geometrical isomers is not universally applicable. It cannot be employed in case of compounds where all the four substituents attached to the two doubly bound carbon atoms are different from each other (i.e., abC = Cde). For example, let us consider the following compound :



Here we can see that I and Cl are *cis* to each other. But we can also equally well say that Br and Cl are *trans* to each other. Therefore, it becomes difficult to name such a substance either as *cis* or *trans* isomer.

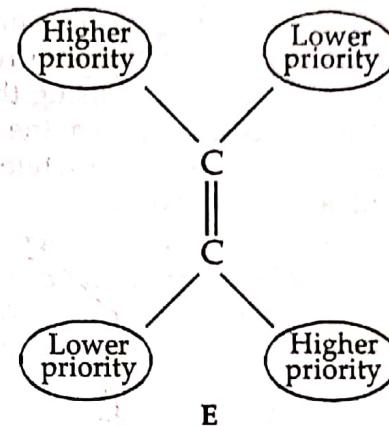
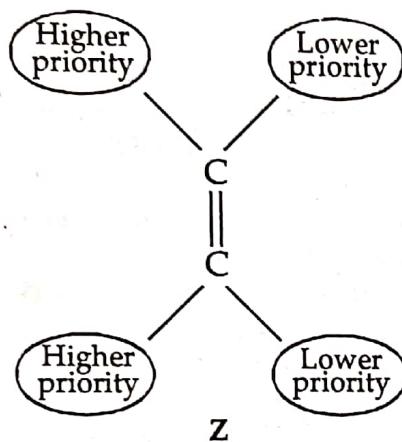
7.18.4. E and Z system of nomenclature

In view of the limitations of the *cis-trans* system, a more general system of nomenclature of geometrical isomers, known as **E and Z system**, is now being adopted.

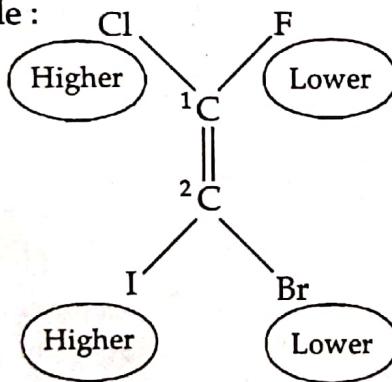
E, Z system is based upon the *sequence rules* originally developed by Cahn, Prelog and Ingold for R and S systems of specifying configurations of optical isomers (please refer to section on R and S systems). For specifying the configuration of geometrical isomer as E or Z, the following rules are followed :

(i) The two atoms or groups attached to each carbon of the double bond are assigned a higher or lower priority according to the priority sequence rules of R and S system of optical isomers.

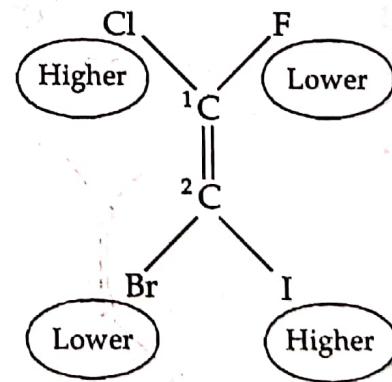
(ii) If the higher priority atoms or groups on each carbon of the double bond are on the same side, the configuration is designated as **Z** (from the German *Zusammen* = together). On the other hand, if the atoms or groups of higher priority are on opposite sides, the configuration is termed as **E** (from the German *entgegen* = across). Thus we have :



For example :



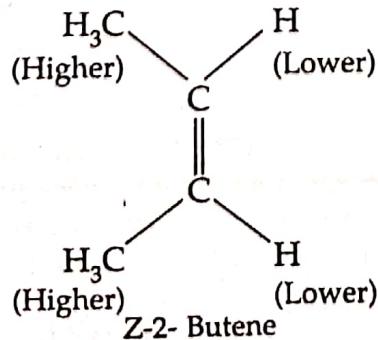
Z-1-Bromo-2-chloro-
2-fluoro-1-iodoethene



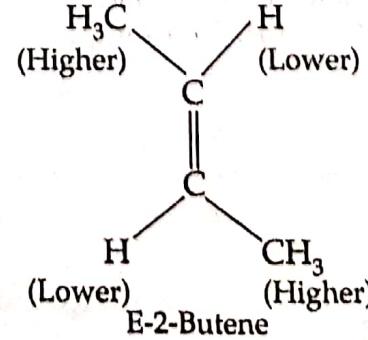
E-1-Bromo-2-chloro-
2-fluoro-1-iodoethene

We know that atoms having higher atomic number have higher priority. Therefore, out of F and Cl attached to ¹C, Cl has higher priority. In the same way, out of Br and I attached to ²C, I has higher priority.

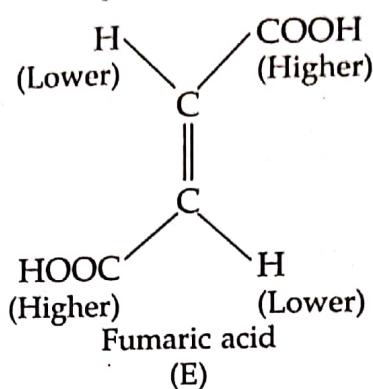
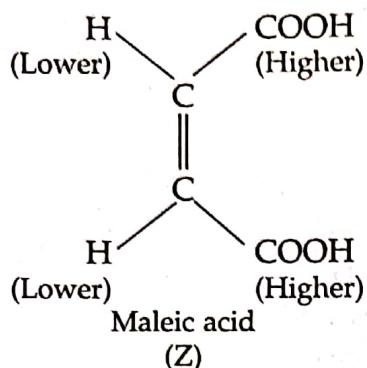
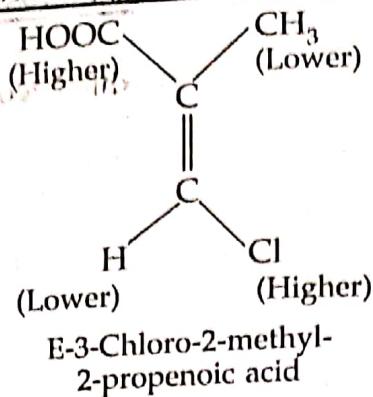
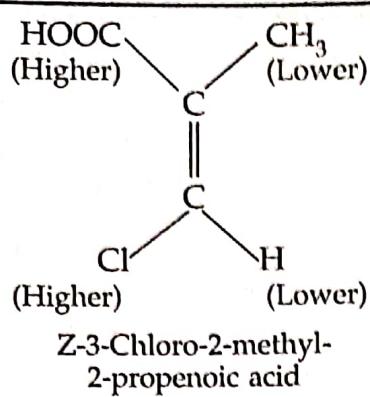
Some more examples of assigning E and Z designation are given below :



Z-2- Butene



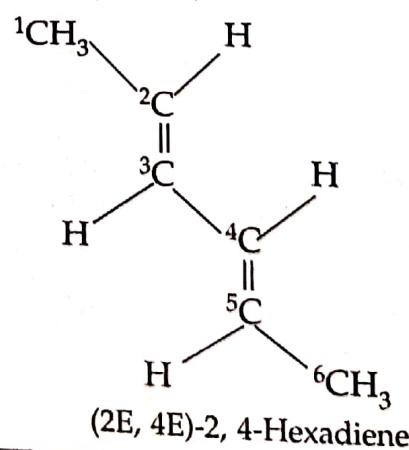
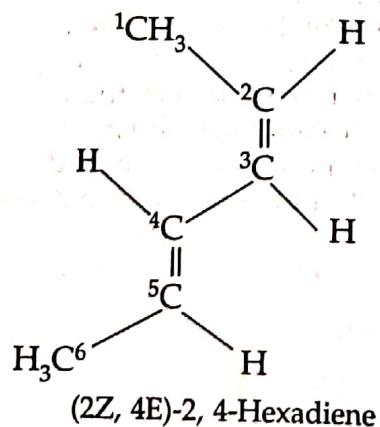
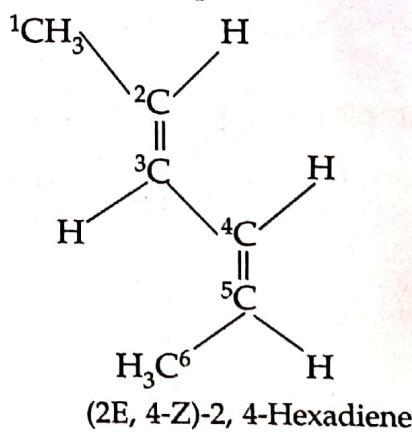
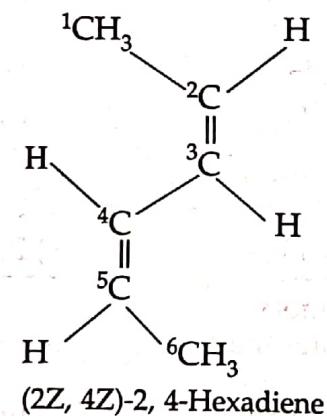
E-2-Butene



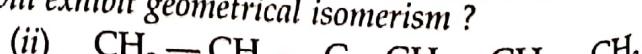
It may be noted that most of the compounds that we would normally designate *cis* are designated "Z". Similarly most of the compounds that we would designate *trans* are designated "E".

7.18.5. Nomenclature of compounds containing more than one double bond

If a compound contains two or more double bonds around which geometrical isomerism is possible, E and Z designations are given to each double bond. For example :

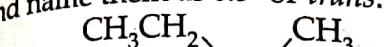


Problem 7.11. Of the following structures, which will exhibit geometrical isomerism ?

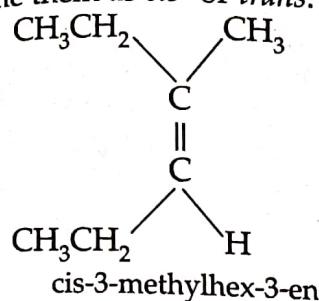


(iii) $\text{CH}_2 = \text{CH} - \text{CH} = \text{CHCl}$

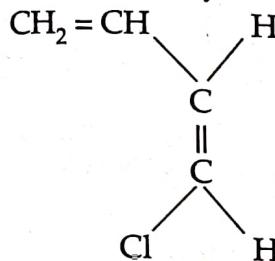
(iii) For the compounds which
and name them as *cis*- or *trans*.
 $\text{CH}_2\text{CH}=\text{CH}_2$ $\text{CH}_2=\text{CHCH}_3$



(ii)



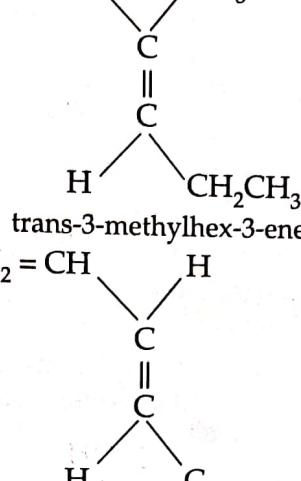
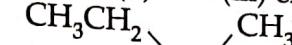
(iii)



cis-4-chlorobuta-1, 3-diene

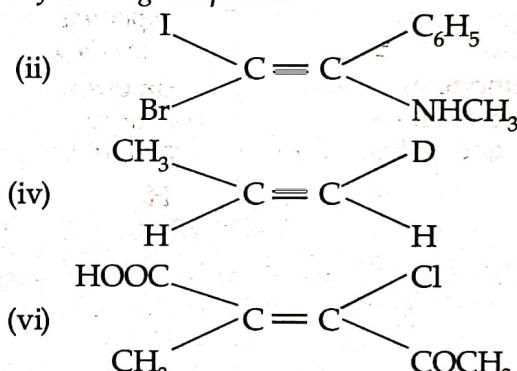
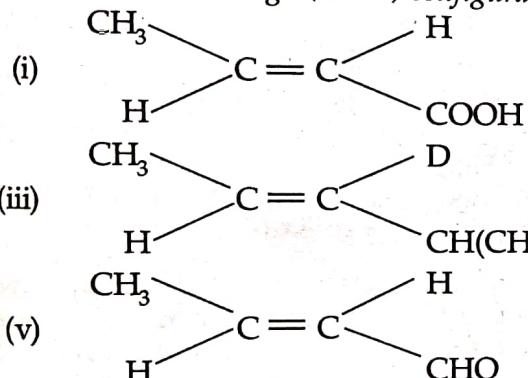
(iv) $\text{CH}_3\text{CH}_2\text{CH}=\text{CH}-\text{CH}_2-\text{CH}_3$

[Ans. (ii) and (iii) exhibit geometrical isomers]



II C

Problem 1.12. Assign (*E* – *Z*) configurations to the following compounds :

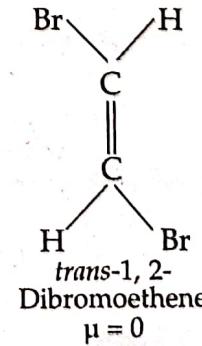
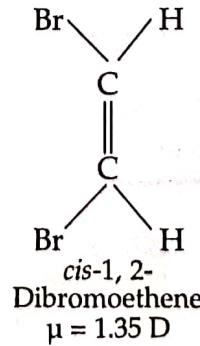
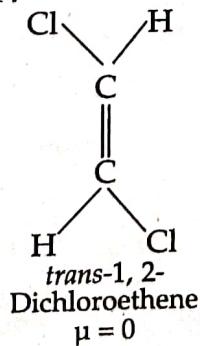
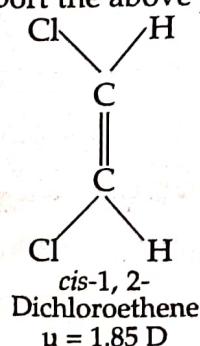


[Ans. (i) E, (ii) E, (iii) E, (iv) Z, (v) E, (vi) Z]

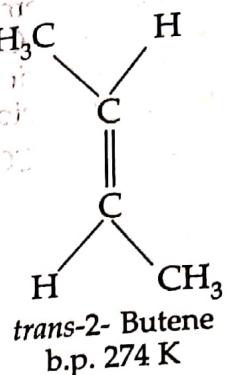
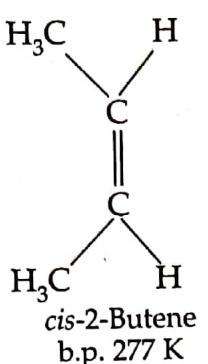
7.18.6. Determination of configuration of geometrical isomers

The following methods can be employed for determining the configurations of geometrical isomers:

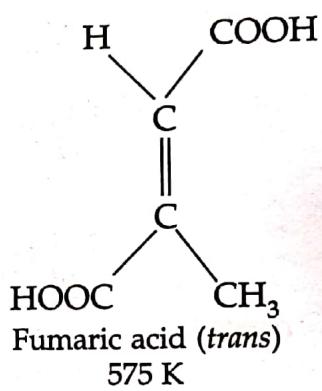
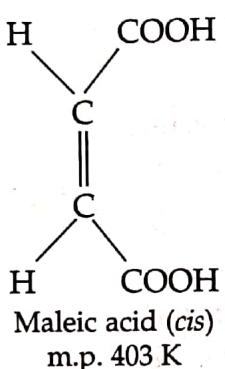
(1) From dipole moment. Determination of the dipole moment of a pair of geometrical isomers can be quite helpful in designating a particular isomer as *cis* or *trans*. For instance, in case of compounds of the type $abC = Cab$, the net dipole moment of a *trans* isomer is expected to be zero. This is because the similar groups are on opposite sides of the molecule and, therefore, the bond polarities cancel out each other. In contrast, the bond polarities are not cancelled in case of *cis* isomer and, therefore, it has a definite dipole moment. Thus *cis*-2-butene should have a small dipole moment while the dipole moment of *trans*-2-butene should be zero. The following experimental data goes to support the above prediction :



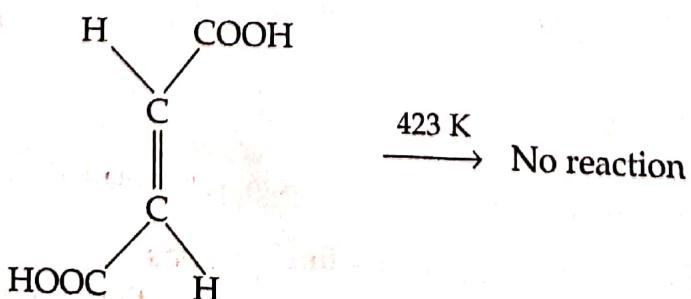
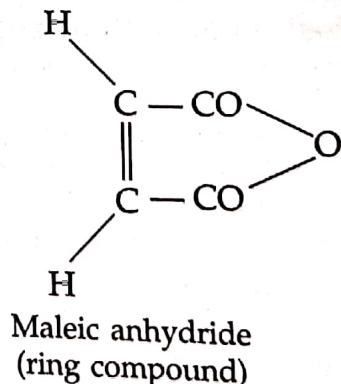
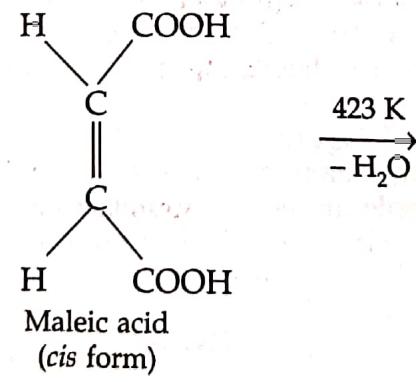
(2) From boiling points. In general, *cis* isomers have higher boiling points than *trans* isomers. This is evidently because of the higher polarities and higher dipole moments of *cis* isomers which leads to greater inter-molecular attraction. For example, the boiling point of *cis*-2-butene is 277 K while that of *trans* isomer is 274 K.



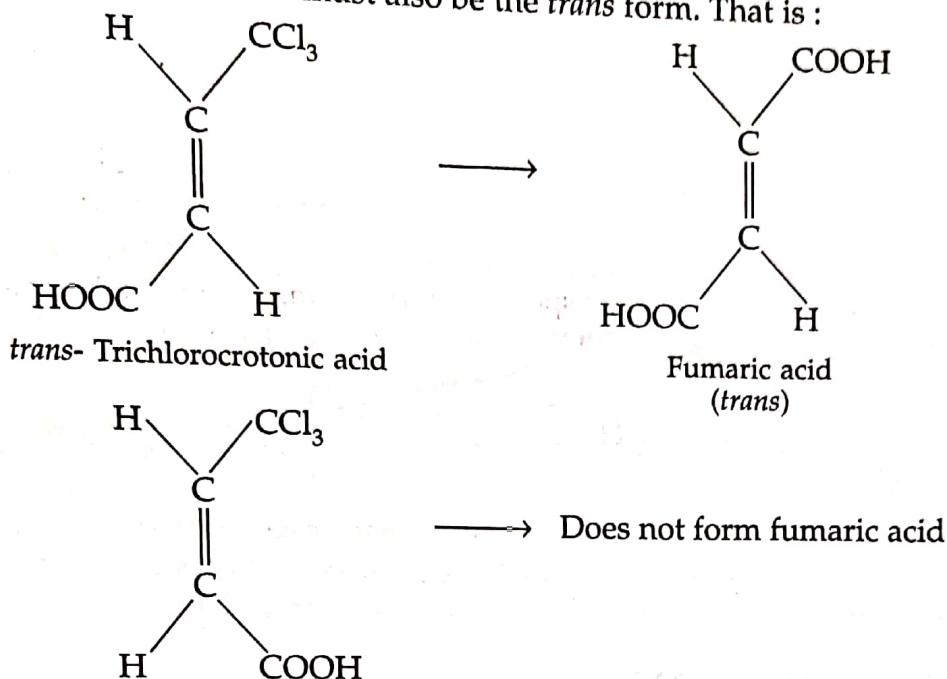
(3) From melting points. Generally speaking *trans* isomers have higher melting points than *cis* compounds. This is because *trans* isomers are more symmetrical and can be more closely packed in the crystal lattice. For example,



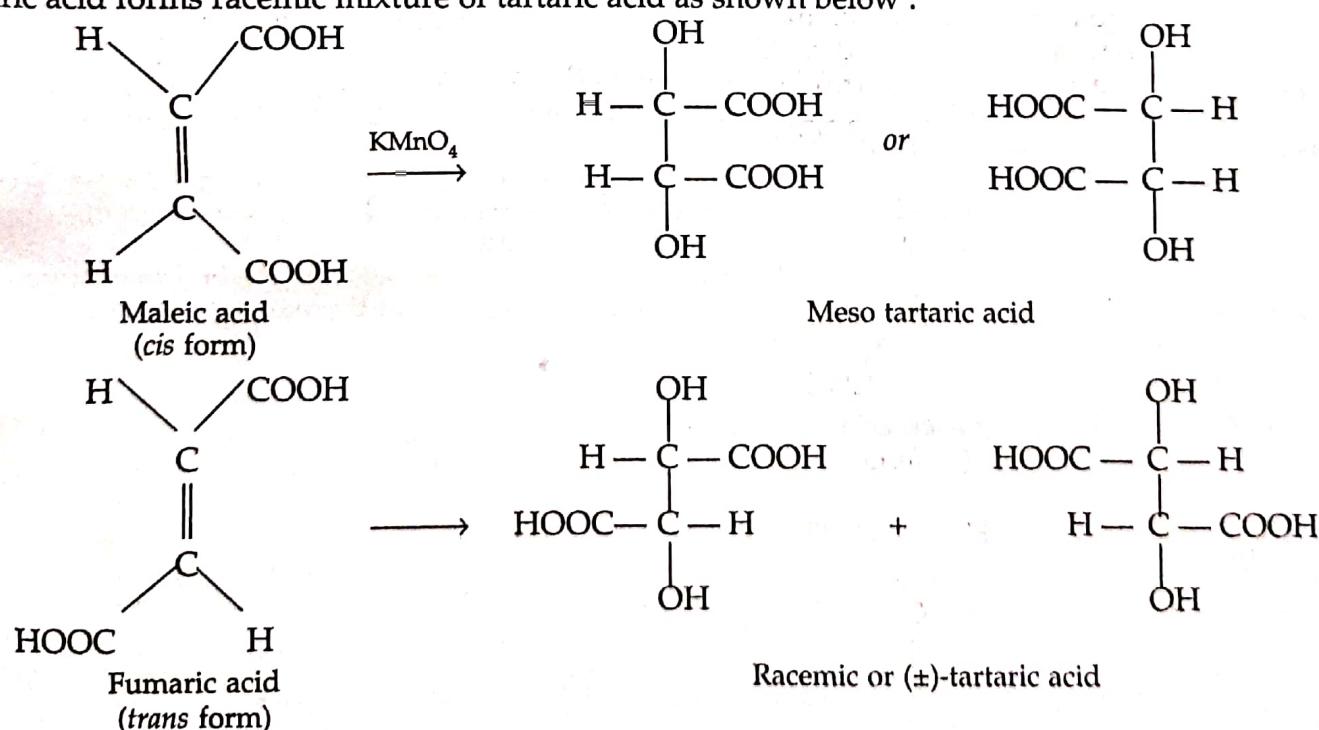
(4) From the formation of ring compounds. Sometimes it is possible to distinguish between two geometric isomers by chemical reactions which lead to the formation of rings. *cis*-isomer is likely to undergo ring closure much more readily than the *trans*-isomer. For example, maleic acid (*cis* form) loses water when heated to 423 K to form maleic anhydride (ring compound). On the other hand, fumaric acid (*trans* form) does not give the anhydride at this temperature.



(5) By conversion into compounds of known configuration. Sometimes a particular geometrical isomer can be converted into a compound of known configuration without any change in configuration around double bond. From the configuration of the product formed, the configuration of the starting compound can be deducted. For example, one of the geometrical isomers of trichlorocrotonic acid ($\text{CCl}_3\text{CH}=\text{CHCOOH}$) on hydrolysis yields fumaric acid while the other isomer does not. Since fumaric acid has a *trans* configuration, the isomer of trichlorocrotonic acid which changes into fumaric acid must also be the *trans* form. That is :



(6) From the formation of type of optical isomer. In certain reactions, geometrical isomers having carbon-carbon double bond change into products having newly created stereogenic centres. From the type of optical isomer formed, the *cis*- or *trans* nature of the starting compound can be determined. For example, maleic acid on hydroxylation with KMnO_4 gives meso-tartaric acid while fumaric acid forms racemic mixture of tartaric acid as shown below :

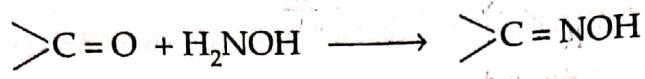


7.18.7. Geometrical Isomerism in compounds other than alkenes

Geometrical isomerism can also be exhibited by compounds in the molecules of which there may be hindered rotation due to some other reason than the presence of carbon-carbon double

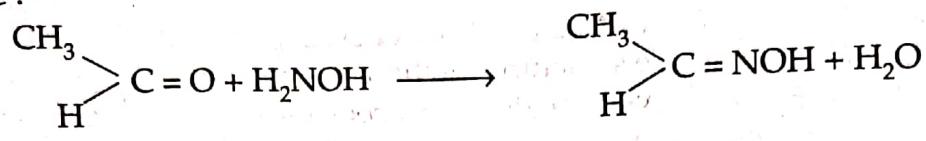
bond. Thus geometrical isomerism is also shown by compounds having carbon-nitrogen double bond (oximes), nitrogen-nitrogen double bond (azo compounds) and even some cyclic compounds which do not contain any double bond as discussed below :

(1) **Geometrical isomerism in oximes.** Oximes are the compounds formed by reaction between aldehydes or ketones and hydroxylamine. That is :

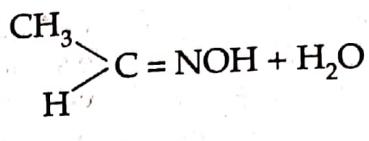


Aldehyde or
ketone

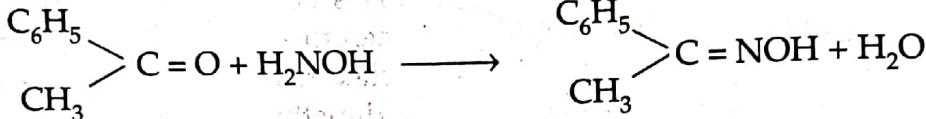
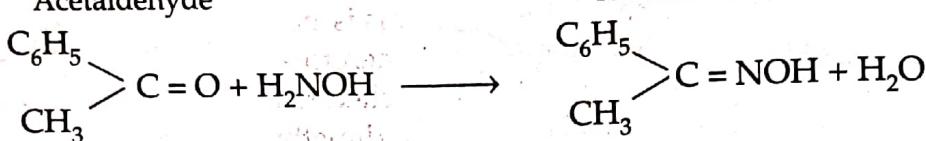
For example :



Acetaldehyde

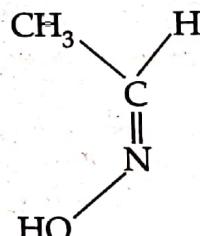
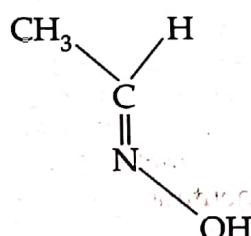


Acetaldoxime



Oximes exhibit geometrical isomerism due to hindered rotation around carbon-nitrogen double bond. While the doubly bound nitrogen carries only —OH group attached to it, the doubly bound carbon must have two **unlike groups** attached to it for geometrical isomerism to be possible.

For example :



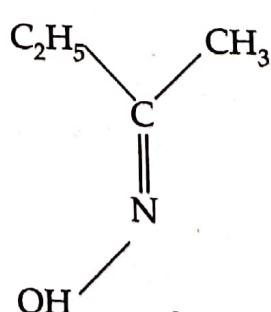
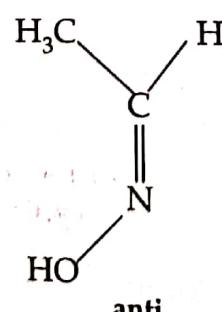
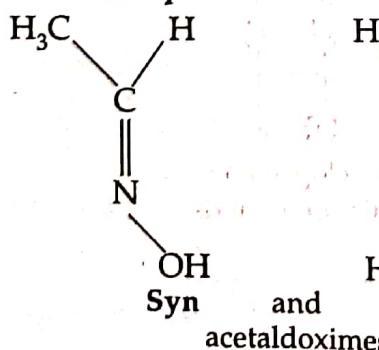
Geometrical isomers of acetaldoxime

The configurations of geometrical isomers of oximes are usually denoted by prefixes **syn** and **anti** instead of *cis*- and *trans* respectively.

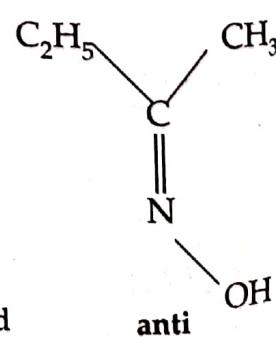
In case of **aldoximes**, the isomer is named as **syn** if —OH group attached to nitrogen is on the same side as hydrogen bonded to carbon. If the —OH group attached to nitrogen is on the opposite side to hydrogen attached to carbon, the isomer is called **anti**.

In case of **ketoximes**, the isomer is named as **syn**, if the —OH group attached to nitrogen is on the same side as the group attached to carbon which comes first in the name of the compound. If they are on opposite sides, the name is **anti**.

For example :

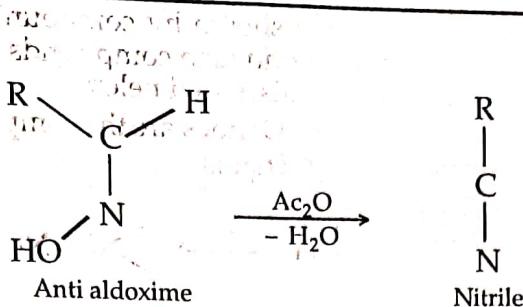


Syn and
ethylmethyl ketoxime



Determination of configuration of oximes. The actual configuration of geometrical isomers of aldoximes is determined by their *relative ease of dehydration*. When treated with a dehydrating agent such as acetic anhydride, an **anti** aldoxime undergoes dehydration easily to form nitriles.

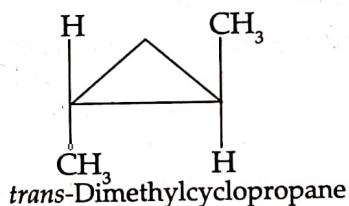
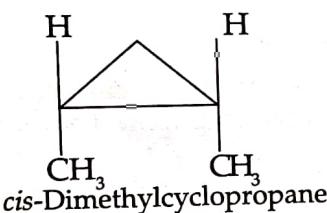
For example :



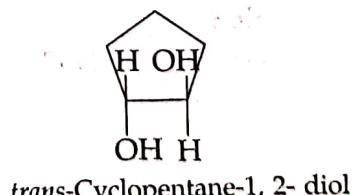
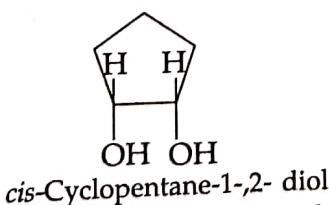
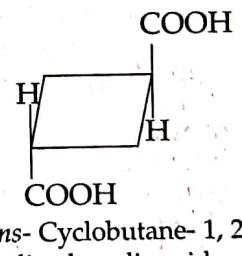
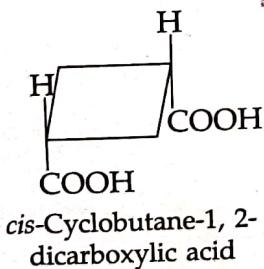
On the other hand, when a syn-nitrile is treated with acetic anhydride followed by aqueous solution of sodium carbonate, original oxime is regenerated.

The configurations of *ketoximes* are determined on the basis of *Beckmann rearrangement*. When treated with an acidic reagent such as PCl_5 , P_2O_5 and SOCl_2 , the oxime undergoes rearrangement to form a substituted amide. The structure of the amide thus formed helps to establish the configuration of the oxime. However, the detailed procedure would be discussed later.

2. Geometrical isomerism in alicyclic compounds. There are many substituted alicyclic compounds which show geometrical isomerism. This is because the presence of a ring can also prevent rotation around carbon-carbon single bond. Therefore **geometrical isomers** become possible if there are two carbons on a ring each of which is attached to two unlike groups. These two carbons may or may not be adjacent to each other. For example, dimethylcyclopropane exists in two geometric forms; one in which the two methyl groups are on the same side of the ring and the other in which they are on opposite sides of the ring as shown below :



Similarly cyclobutane-1-, 3-dicarboxylic acid and cyclopentane 1, 2-diol also exhibit geometrical isomerism.



(It may be pointed out that E and Z nomenclature is not used for cyclic compounds).

7.19. CONFORMATIONS

It is well-known that a single or sigma bond between two atoms is formed by overlapping of their orbitals along the *inter-nuclear axis*. The electron distribution of the σ bond thus formed is, therefore, *symmetrical* around the axis as shown in Fig. 7.11 for a single bond between sp^3 hybrid orbitals of two carbon atoms.

KB

Due to its axial symmetry, the single bond allows *freedom of rotation* about it. As a result of this, the molecules of a compound can have different relative arrangements of their atoms in space which can be converted one into the other by rotation around the single bond. Such arrangements in space of the atoms in a molecule that can be readily interconverted by rotation around single bonds are called **conformations or conformers (conformational isomers)**. The existence of different conformations of a compound constitutes a special type of stereoisomerism. We will discuss some aspects of this phenomenon with reference to alkanes and cycloalkanes.

7.19.1. Conformations of Ethane

Ethane is the simplest molecule for which an infinite number of conformations are possible. The central bond in the molecule of ethane is a single bond between two carbon atoms, each of which is further linked to three hydrogen atoms. If one of the carbon atoms of ethane is allowed to rotate around the central bond while the other is held still, a very large number of arrangements of the hydrogens of one carbon with respect to the hydrogens of the other carbon can be obtained. The basic structure of the molecule and various bond lengths and bond angles, however, remain the same in all these arrangements or conformations.

Of the infinite number of possible conformations of ethane, two conformations represent the extremes. These are called the **eclipsed conformation** and the **staggered conformation**. In the eclipsed conformation, the hydrogens of one carbon are *directly behind* those of the other. In the staggered conformation, the hydrogens of the two carbon atoms are *staggered* with respect to one another (Figs. 7.13 and 7.14).

7.19.2. Representation of Conformations

Since it is not very convenient to represent three dimensional formulae on paper, certain conventions have been adopted for projecting the conformations on paper. The two commonly used methods are as follows :

(1) **Sawhorse formulae (or Andiran formulae)**. In this representation the molecule is viewed slightly from above and from the right and then projected on the paper. The bond between the two carbon atoms is drawn *diagonally* and of a *relatively greater length* for the sake of clarity. The lower left hand carbon is taken as front carbon and the upper right hand carbon as the back carbon. The three atoms or groups attached to each carbon are shown tetrahedrally in space. The sawhorse representations of eclipsed and staggered conformations of ethane are shown in Fig. 7.13.

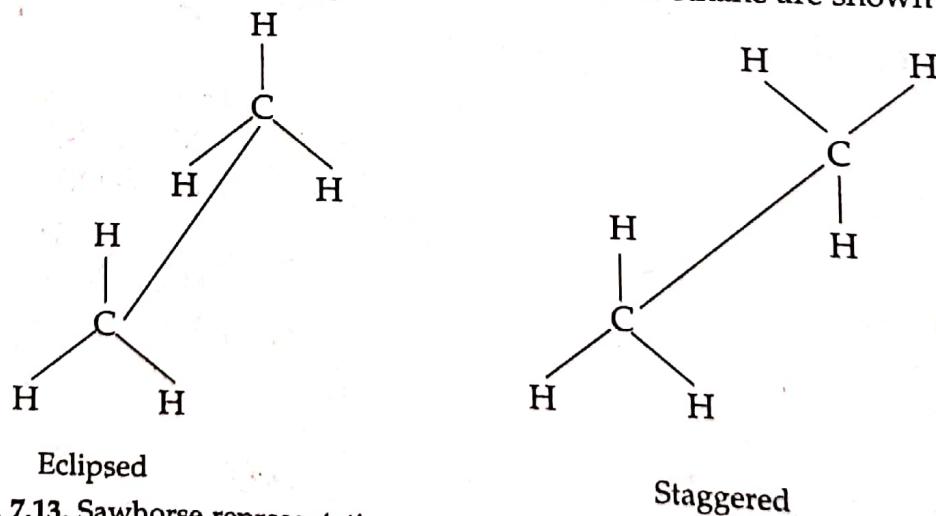


Fig. 7.13. Sawhorse representations of eclipsed and staggered conformations of ethane.

(2) **Newman projection formulae**. Newman devised a very simple method of projecting three dimensional formulae on paper which are known as **Newman Projections**.

In these formulae the molecule is viewed from the front. The carbon atom *nearer to the eye* is represented by a point and the three atoms or groups are shown attached to it by three lines at an

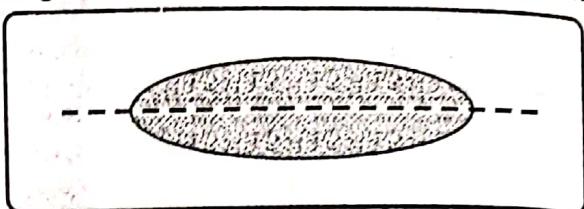
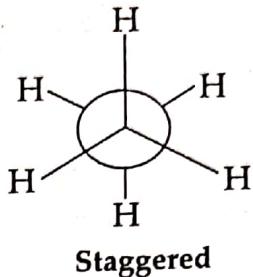
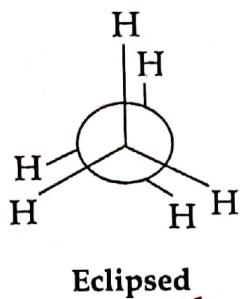


Fig. 7.12. Symmetrical electron distribution representing a single bond between sp^3 hybrid orbitals of two carbon atoms.

angle of 120° to each other. The carbon atom *further from the eye* is represented by a circle and the three atoms or groups are shown attached to it by shorter lines (ending at the circumference of the circle) at the angle of 120° to each other. Newman projections for eclipsed and staggered conformations of ethane are shown below in Fig. 7.14.

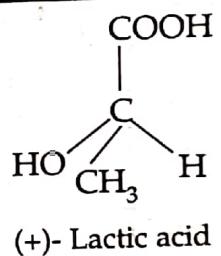
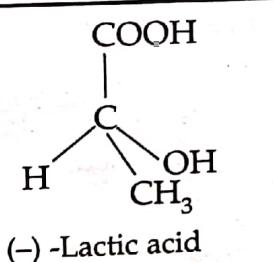


~~Fig. 7.14.~~ Newman projections for the conformations of ethane.

7.20. DIFFERENCE BETWEEN CONFORMATION AND CONFIGURATION

Conformations. As stated above, conformations are *three dimensional arrangements in space of the atoms in a molecule that can be interconverted merely by rotation around single bonds*. For example, Fig. 7.13 depicts two such arrangements (known as eclipsed and staggered conformations) of ethane which are readily interconvertible by rotation around carbon-carbon single bond.

Configurations. As already studied configurations are *three dimensional arrangements in space of the atoms in a molecule that cannot be interconverted merely by rotation about a bond*. For example, the configurations of (-)-lactic acid and (+)-lactic acid (which are not interconvertible by rotation about a bond) are shown below in Fig. 7.15.



~~Fig. 7.15.~~ Configurations of (-) and (+)- lactic acid.

In the light of above definitions, the main points of difference between conformations and configurations may be summed up as follows :

Conformations	Configurations
<ol style="list-style-type: none"> These are three dimensional arrangements in space of the atoms in a molecule which are interconvertible by rotation around a single bond. Their interconversion does not require any breaking and making of bonds. Their existence leads to the phenomenon of conformational isomerism. Since conformations are readily interconvertible, they cannot be isolated from each other. As such conformational isomers exist only as mixture of different conformations. 	<ol style="list-style-type: none"> These are three dimensional arrangements in space of the atoms in a molecule which are not interconvertible by rotation around a bond. Their interconversion is possible only through breaking and making of bonds. Their existence is involved in the phenomena of geometrical and optical isomerisms which are also collectively known as configurational isomerism. Since configurations are not easily interconvertible, they can be isolated from each other and stored as pure substances. As such configurational isomers can exist as pure individual substances.

7.21. CONFORMATIONAL ANALYSIS OF ETHANE

It has been stated earlier that a single bond allows freedom of rotation around it. However, it must be pointed out that rotation around the single bond is *not completely free*. If it were so, the potential energy for different conformations of a compound should have been the same. But in actual practice, the potential energy of the molecule changes somewhat with the rotation around the C—C single bond. The study of energy changes which occur in a molecule due to rotation around C—C single bonds is known as conformational analysis. Let us first study the energy changes taking place in ethane.

The potential energy of an ethane molecule is minimum for the staggered conformation, increases with rotation and becomes maximum for the eclipsed conformation; the difference between the two extreme conformations being $12.55 \text{ kJ mol}^{-1}$ (Fig. 7.16). This difference in energy constitutes an **energy barrier** to rotation around the single bond. The energy barrier to rotation in ethane is said to be due to **torsional strain** and the energy required to rotate the ethane molecule about the carbon-carbon bond is called **torsional energy**. (These terms are explained a little later in sec. 7.24)

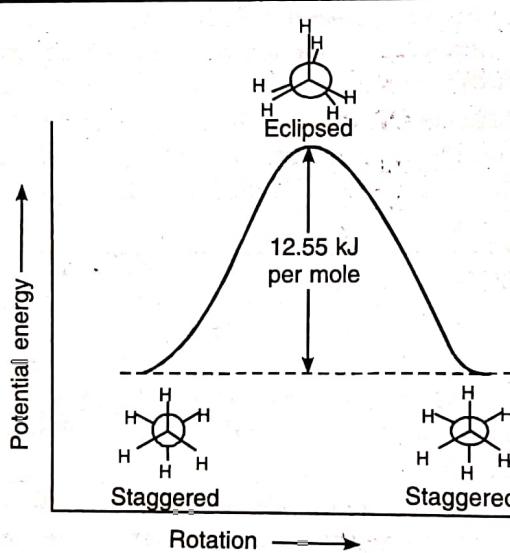


Fig. 7.16. Changes in potential energy during rotation about C—C single bond of ethane.

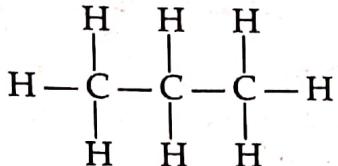
The energy barrier to rotation described above is, however, not large enough to prevent rotation altogether. Even at ordinary temperature, the molecules possess sufficient thermal or kinetic energy to overcome the energy barrier through effective collisions and thus the conformations keep on changing from one to the other.

In other words, rotation around the single bond can still take place *nearly freely*, being only slightly restricted by the energy barrier. As such it is not possible to separate different conformations of ethane. It is quite obvious, however, that at any moment most of the ethane molecules would exist in the staggered conformation due to its minimum energy and, therefore, maximum stability. In other words, any molecule spends most of its time in the staggered conformation which is the most stable.

7.22. CONFORMATIONAL ANALYSIS OF PROPANE

If one of the hydrogens of ethane is replaced by another atom or group, the situation remains practically unchanged. For example, let us consider the case of propane in which one of the hydrogen atoms of ethane has been replaced by a methyl group. That is :

KB



In propane, rotation can take place about either of the two carbon-carbon bonds. Even though the methyl group is considerably larger than hydrogen, the energy difference between the two extreme conformations, eclipsed and staggered, is 13.8 kJ mol^{-1} which is nearly the same as in case of ethane.

The most stable and preferred conformation is, of course, the staggered conformation although it can almost freely change into the eclipsed conformation and *vice versa*.

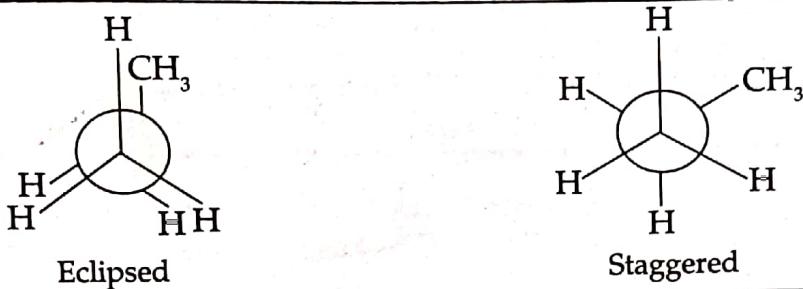
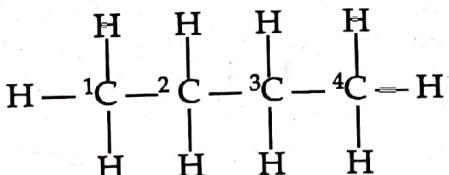


Fig. 7.17. Newman's projections for the conformations of propane.

7.23. CONFORMATIONAL ANALYSIS OF *n*-BUTANE

The molecule of *n*-butane (which may be considered as disubstituted ethane) is somewhat more complex for conformational studies. If we consider the rotation only around the single bond between the two inner carbon atoms (C_2 and C_3) of *n*-butane, we have a molecule similar to ethane but with a bulky group (*i.e.* methyl group) in place of a hydrogen atom of each carbon.



In contrast with ethane, *n*-butane can have several different staggered and eclipsed conformations due to the presence of the methyl groups. Four of the important conformations are : anti, eclipsed, gauche and fully eclipsed. These are shown in Fig. 7.18.

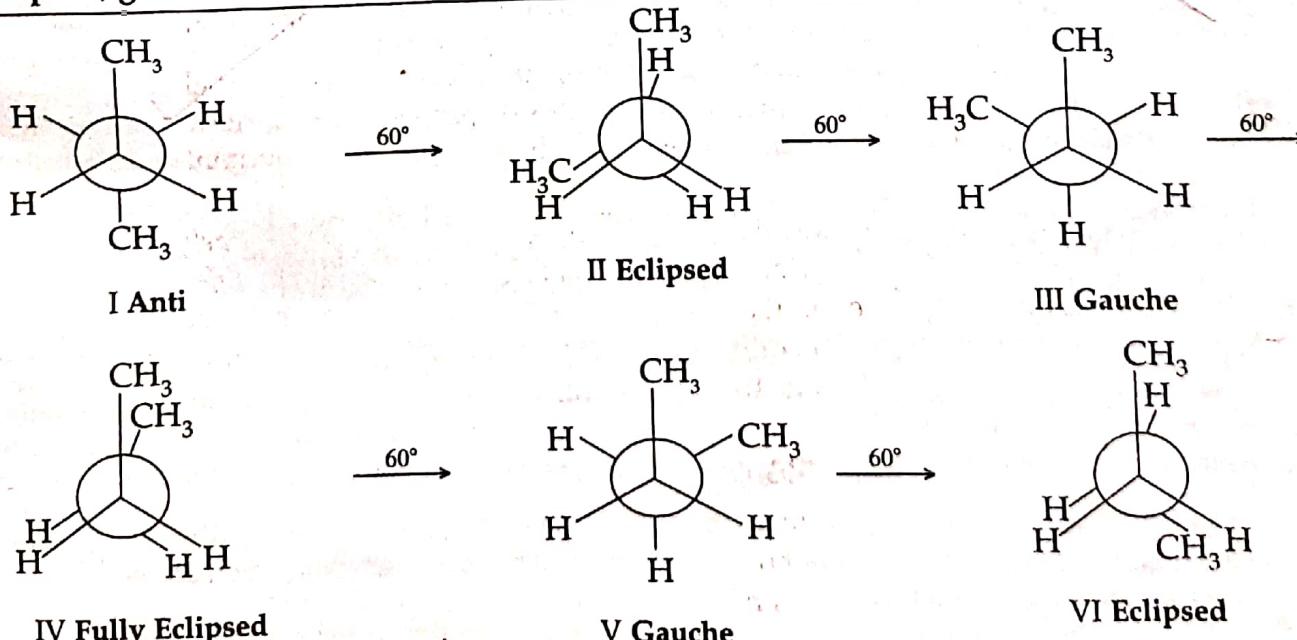
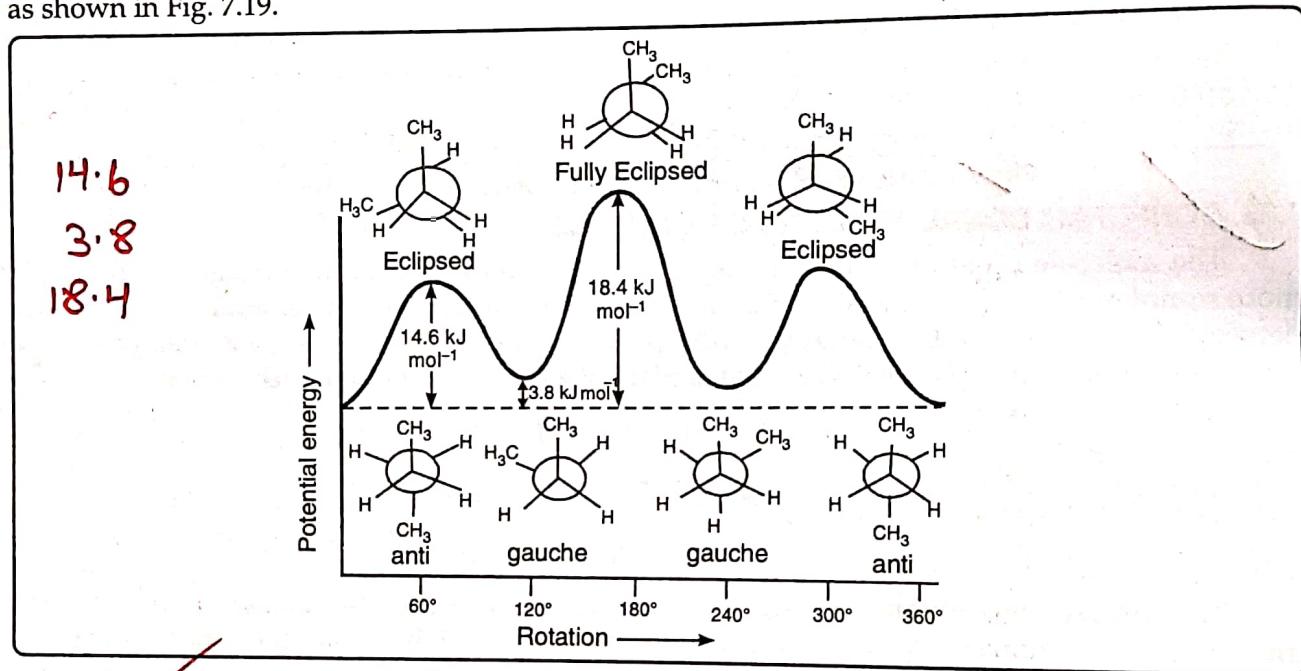


Fig. 7.18. Important conformations of *n*-butane.

The anti-conformation (1) is an extreme staggered conformation in which the methyl groups are as far apart as possible. If the angle of rotation around the C_2-C_3 single bond is assumed to be zero for this conformation and one of the C_2 or C_3 carbon atoms is rotated through an angle of 60° , an eclipsed conformation (II) results. In this conformation, the methyl group attached to one carbon is not at the back of the methyl group attached to the other carbon but is at the back of hydrogen attached to this carbon. Rotation by another 60° leads to another staggered conformation called gauche conformation (III) in which the two methyl groups are only 60° apart. Further rotation by 60° gives rise to the fully eclipsed conformation (IV) in which the two methyl groups are at the back of each other. On further successive rotations by 60° , we pass through another gauche conformation (V) and another eclipsed conformation (VI) and finally arrive at the anti-conformation again on completion of 360° .

The difference in energy contents between conformations (1) and (IV) is about 18.4 kJ mol^{-1} between (I) and (II or VI) about 14.6 kJ mol^{-1} , and between (I) and (III or V) only about 3.8 kJ mol^{-1} as shown in Fig. 7.19.



~~Fig. 7.19.~~ Changes in potential energy during rotation about C_2-C_3 single bond of *n*-butane.
Therefore the order of stabilities of different conformations of *n*-butane is :

Anti > Gauche > Eclipsed > Fully eclipsed.

It is apparent that due to very small difference in their energies, anti-conformation is only slightly more stable than Gauche conformation. (The difference in the energies of anti and gauche forms is due to steric strain which is discussed in sec. 7.24).

It can be easily seen that the rotation about the carbon-carbon single bond in *n*-butane is again nearly free and the different conformations cannot be isolated. At any time, *n*-butane consists mainly of an equilibrium mixture of anti and gauche conformations with the anti conformation having the highest percentage (about 67% at 295 K).

It will be interesting to compare the spatial arrangements of the two gauche conformations (III and V) of *n*-butane. It may be easily seen that these two conformers are also mirror images and hence enantiomers of each other. Such conformational isomers which are also mirror images of each other are known as **conformational enantiomers**. However, unlike configurational enantiomers, conformational isomers are readily interconvertible by rotation around a bond.

If we compare the anti conformation (I) of *n*-butane with its gauche conformers (III and V), it is found that I and III (or I and IV) are not mirror images of each other. Such pairs of conformers are termed as **conformational diastereomers**.

Thus we find that conformational isomers can also exist as pairs of enantiomers or diastereomers which, however, are readily interconvertible.

7.24. FACTORS WHICH INFLUENCE CONFORMATIONAL STABILITY

Having discussed that rotation around single bond is not entirely free and the different conformations of a molecule have slightly different energies or stabilities, we would now consider the factors which influence conformational stability.

(1) **Torsional strain.** This is the basic factor which influences the stability of a conformation. It is believed to be due to the interaction between the electron clouds of the bonds attached to the central bond around which rotation is being studied. For instance, in the molecule of ethane there are six carbon-hydrogen bonds attached to the central carbon-carbon bond. In the staggered conformation of ethane molecule, the electron clouds of these carbon hydrogen bonds are as far apart as possible. But when the staggered conformation changes into the eclipsed conformation, these electron clouds rotate closest to each other. Naturally there must be some repulsive interaction between the electron clouds in this position which goes to increase the energy of the molecule and thus decreases its stability. *This repulsive interaction between the electron clouds affecting the stability of conformation is known as torsional strain.* As a result of torsional strain, the energy of eclipsed conformation is more than that of staggered conformation and consequently its stability is less.

The energy required for rotation around a single bond on account of torsional strain is called **torsional energy**. It constitutes the basic energy barrier to rotation about a single bond. In case of ethane, the entire difference in energy between the staggered and eclipsed conformations, (i.e., $12.55 \text{ kJ mol}^{-1}$) is due to torsional energy or torsional strain. This is because no other factor affecting the energy or stability of conformation has any appreciable influence in this case. The situation is practically the same in propane.

(2) **Steric strain due to van der Waal's forces.** When the hydrogen atoms attached to the two singly bonded central carbon atoms are replaced by bulky atoms or groups, another factor called steric strain begins to influence the energy or stability of different conformations. Steric strain arises out of van der Waal's forces of repulsion between the different parts of the same molecule. To understand their influence, let us go back to the molecule of *n*-butane. Here two hydrogens, one each of the two central carbon atoms, have been replaced by two bigger methyl groups. These methyl groups are farthest apart in case of anti-conformation of *n*-butane but are brought closer in the gauche and eclipsed conformations (Fig. 1.19). Due to the crowding together of bulky groups in these conformations, van der Waal's forces of repulsion come into play between these groups and cause a **steric strain** in the molecule. Due to this strain the energy of the molecule increases and its stability decreases. For instance, if we compare the anti and gauche conformations of *n*-butane, both are free of torsional strain due to their staggered nature. But gauche conformation is subjected to steric strain due to the nearness of methyl groups which are only 60° apart while the anti-conformation is free from this strain also. That is why the energy of gauche conformation is slightly (3.8 kJ mol^{-1}) more than that of anti-conformation and its stability is correspondingly less.

If we consider the fully eclipsed conformation of *n*-butane, it is immediately obvious that both torsional and steric strains are operating to the maximum in this case. Accordingly its energy is higher than that of anti-conformation (which is free of torsional strain as well as steric strain) by as much as 18.4 kJ mol^{-1} and its stability is the least of all the conformations.

It may be pointed out that the steric strain does not have any appreciable influence in case of propane as only one carbon atom carries a methyl group.

Ordinarily van der Waal's forces are considered to operate between the non-bonded atoms of different molecules and are attractive in nature. But these forces can also operate between the different parts of the same molecule and here the forces can be either attractive or repulsive depending upon the nature and size of groups and their relative locations.

(3) **Dipole-dipole interaction.** In case of molecules having partially polar bond attached to the central single bond, dipole-dipole interactions can occur between the different parts of the same molecule. In the conformations in which **oppositely charged poles** are close together, the dipole-dipole interactions are attractive in nature and, therefore, have a stabilising effect. On the other hand, in the conformations in which **similarly charged poles** are brought together these interactions

KB

are repulsive and, therefore, have a destabilising effect. For example, if we consider the different conformations (Fig. 7.20) of 1, 2-dibromoethane ($\text{CH}_2\text{Br}-\text{CH}_2\text{Br}$), it is evident that the most stable and preferred conformation would be the anti-conformation. This is because this conformation has practically no van der Waals repulsion between the bulky bromine atoms as well as practically no dipole-dipole repulsion between the negative ends (i.e. bromine ends) of the polar bonds.

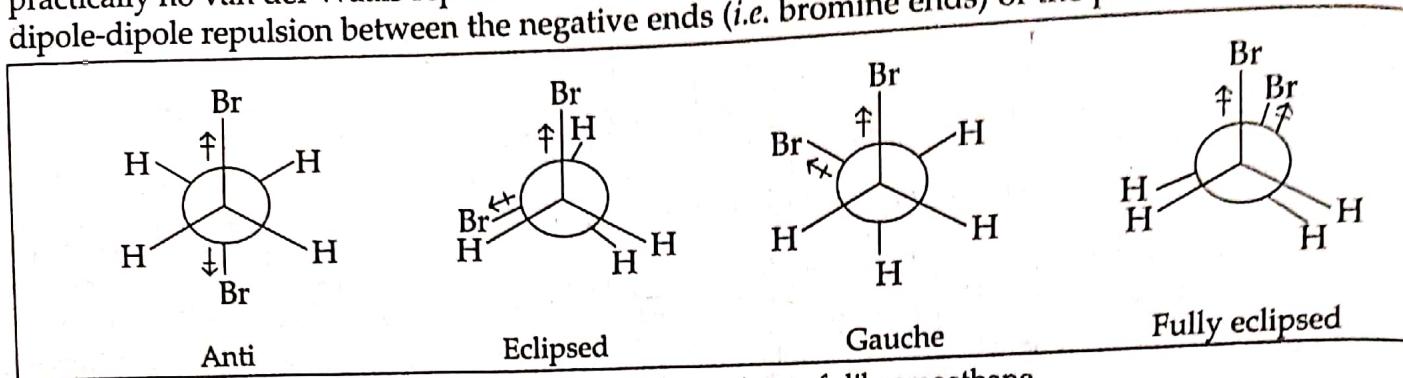


Fig. 7.20. Important conformations of dibromoethane.

(4) Angle strain. For sp^3 hybridised carbon atoms, the normal bond angle is $109^\circ 28'$. Any deviation from this angle leads to an angle strain which makes the conformation less stable. This factor operates in case of cycloalkanes and other cyclic compounds (This is discussed in the chapter on cycloalkanes).

7.25. CONFORMATIONS OF CYCLOHEXANE

We have so far studied the conformations of open chain compounds. Let us now have a look at the conformations of cycloalkanes by considering the case of cyclohexane. Cyclohexane is a *multiplanar or puckered ring* compound in which carbon atoms are in sp^3 hybridised state and all the bond angles are equal to normal tetrahedral angle.

Of the various possible conformations of cyclohexane, the two most important conformations are :

- (i) Chair conformation : and
- (ii) Boat conformation.

(1) **Chair conformation.** This is the most stable and, therefore, the most preferred conformation of cyclohexane. In this conformation all the bond angles are tetrahedral and all the C — H bonds on adjacent carbon atoms are in staggered position (Fig. 7.21). At the same time there is no steric interference or dipole-dipole interaction between the non-bonded atoms. Thus, this conformation is essentially *free of strain* and has minimum energy. In other words, *this is most stable conformation of cyclohexane.*

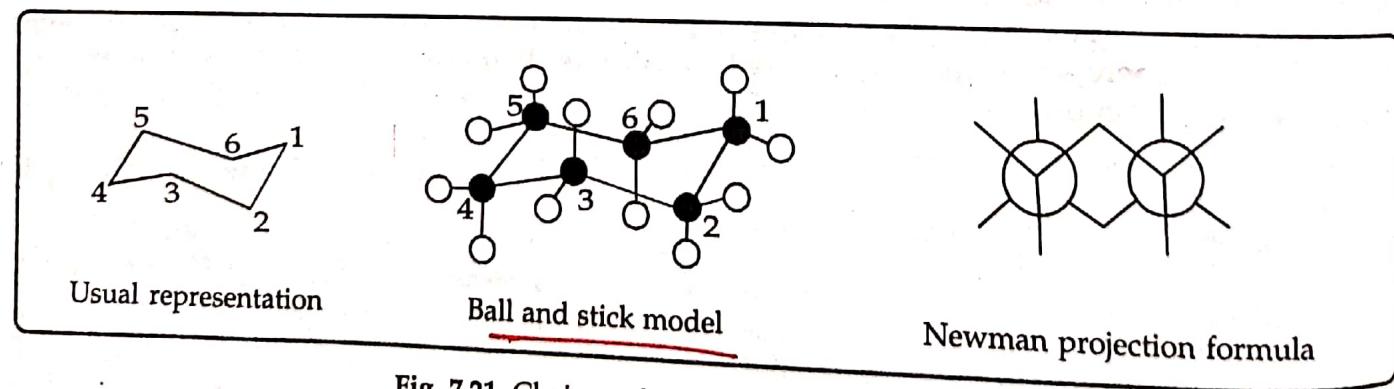


Fig. 7.21. Chair conformation of cyclohexane.

(2) **Boat conformation.** This is the second most important conformation of cyclohexane and is depicted in Fig. 7.22.

As in the chair conformation there is no angle strain in the boat conformation since all the bond angles in it are tetrahedral. But in boat conformation, the hydrogens on four of the carbons (C_2 and C_3 , C_5 and C_6) are eclipsed. As a result, there is considerable torsional strain.

KB

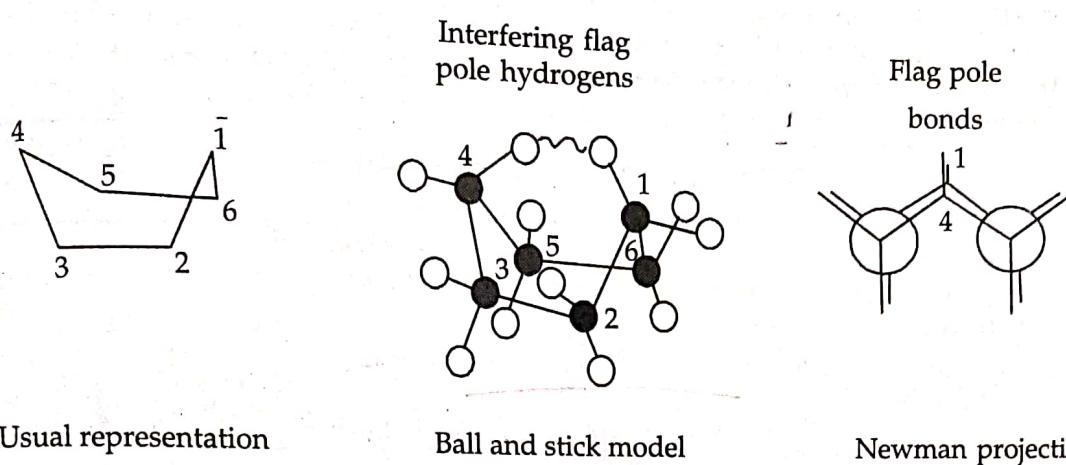


Fig. 7.22. Boat conformation of cyclohexane.

At the same time, the two hydrogens pointing towards each other at C₁ and C₄ (known as "flagpole" hydrogens) are very close together; the distance between them being only (183 pm or 1.83 Å) while the sum of their van der Waals radii is (250 pm or 2.5 Å). This gives rise to van der Waals strain also in the molecule.

Due to torsional and van der Waals strain in it, the boat conformation is naturally much less stable (by 28.8 kJ mol⁻¹) than the chair conformation. As such only very few molecules of cyclohexane (only one in about one thousand, at room temperature) exist in boat conformation.

Other conformations. In addition to the chair and boat forms of cyclohexane, several other conformations are also possible as discussed below :

(3) **Twist boat or skew boat conformation.** Let us consider a model of the boat conformation of cyclohexane as shown in Fig. 7.23 (a). Suppose we hold C₂ and C₃ in one hand and C₄ and C₅ in the other and twist the molecule so that C₃ and C₆ go down while C₂ and C₅ come up. It will be noticed that during this twisting the flagpole hydrogens on C₁ and C₄ (marked H_a and H_b in the figure) move apart and at the same time two hydrogens on C₃ and C₆ (marked H_c and H_d in the figure) begin to move closer together.

In this way, we get another conformation called **twist boat or skew boat conformation**, in which the distance between H_a and H_b is equal to that between H_c and H_d. It is quite evident that in this conformation the van der Waals strain between flagpole hydrogens is minimum. At the same time the torsional strain on C₂ and C₃; C₅ and C₆ is also appreciably reduced. As such the twist boat conformation is more stable than the boat conformation by about 6.7 kJ mol⁻¹ although it is still less stable than chair conformation by 23 kJ mol⁻¹.

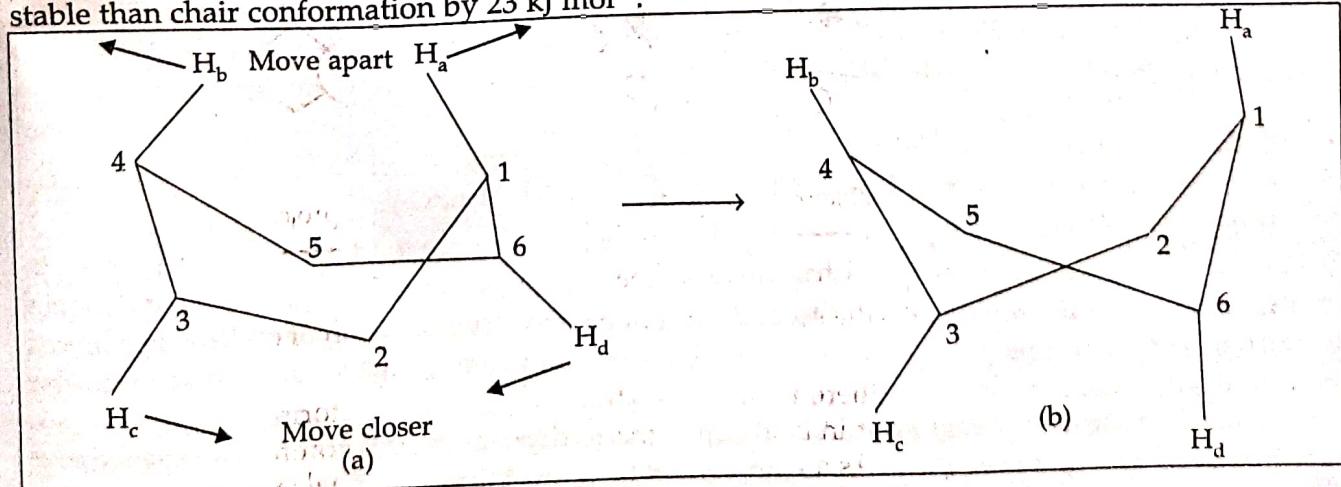


Fig. 7.23. Twisting of boat conformation.

KB

(4) **Half-chair conformation.** In between the chair conformation and twist boat conformation lies yet another conformation known as **half-chair conformation** (Fig. 7.24). It has both angle and torsional strains and has about 46 kJ mol^{-1} higher energy than chair form. In fact it represents merely a *transition state* conformation.

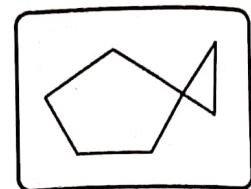


Fig. 7.24. Half-chair conformation.

7.25.1. Energy Relationships between Different Conformations

The energy relationships between the different conformations of cyclohexane have been shown in Fig. 7.25. It must be pointed out, that the energy difference between any two conformations is too small to permit their isolation.

It is evident that the order of relative stabilities of different conformations of cyclohexane is :

Chair conformation > Twist boat conformation > Boat conformation > Half-chair conformation.

7.25.2. Equatorial and Axial Bonds in Cyclohexane

Since the chair conformation is the most preferred and the most important conformation of cyclohexane, let us examine it a little more closely.

Although the cyclohexane ring is not flat, we can imagine an "average" or "general" plane of the ring. Now, if we consider the positions of various hydrogen atoms in the chair conformation we find that there are two different kinds of hydrogens. Six of the hydrogens (marked H_e in Fig. 7.26) point side-way along the general plane of the ring and are called **equatorial hydrogens** (because they are situated along the general plane of "equatorial belt" of the molecule). The other six hydrogens (marked H_a) in two groups of three each, lie above or below the general plane and point along an axis perpendicular to the ring. These are known as **axial hydrogens**. *The bond by which an equatorial hydrogen is held is called an equatorial bond and the bond by which an axial hydrogen is held is called an axial bond.* There is one equatorial and one axial bond on each carbon in the chair conformation of cyclohexane.

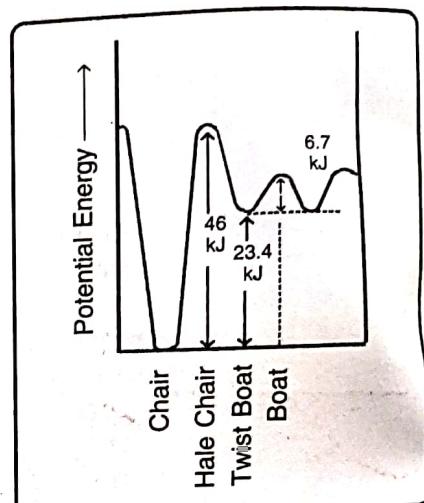


Fig. 7.25. Energy relationships between the various conformations of cyclohexane.

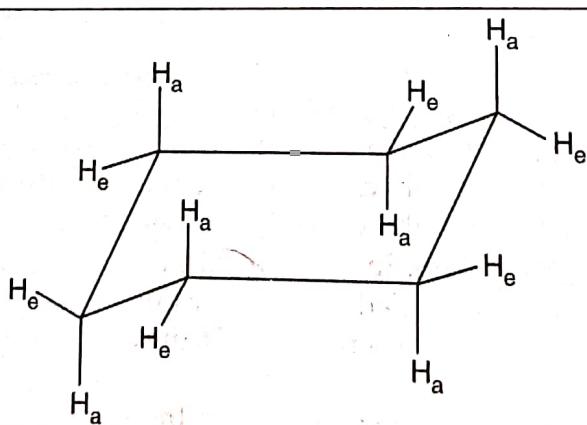


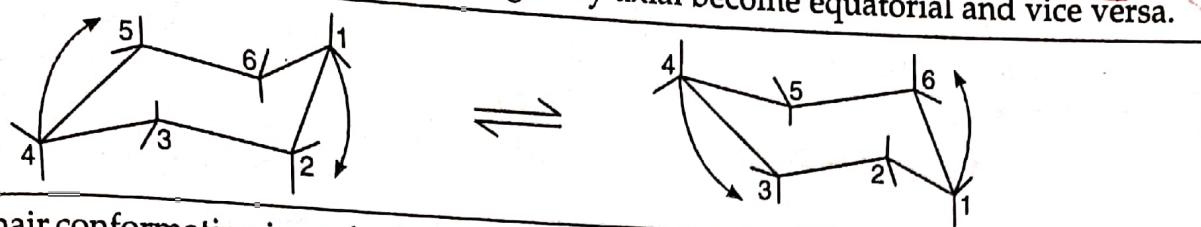
Fig. 1.26. Equatorial and axial bonds in cyclohexane.

It may be pointed out that the distance between hydrogens on adjacent carbon atoms in cyclohexane is 230 pm (2.3 Å) which is the same as in staggered ethane. However, axial hydrogens on the same side of the molecule are situated rather close together even though they are linked to alternate carbon atoms. But it may be noted that the distance between such hydrogens is also 230 pm (2.3 Å).

It is interesting to note that the axial and equatorial hydrogens in cyclohexane can interchange their position. This is because the chair conformation of cyclohexane is flexible and one chair

KB

conformation can change into another chair conformation by process known as ring inversion or ring flipping. As this happens, all hydrogens originally axial become equatorial and vice versa.



But one chair conformation is perfectly equivalent to the other and they cannot be distinguished from each other.

7.25.3 Conformations of Mono substituted Cyclohexane Derivatives

As the two bonds on each carbon of cyclohexane ring are not equivalent in position, a **mono substituted cyclohexane derivative** should exist in two isomeric forms according as the substituent group is in an equatorial or axial position. Such equatorial and axial conformations of substituted cyclohexane can interconvert into each at room temperature by *ring flipping*. But they are not equivalent to each other in energy. The conformation having the substituent in equatorial position has slightly lesser energy than the other and is somewhat more stable. The reason for this can be understood by constructing their models. It can be seen from the models that substitution of an axial hydrogen by bigger atom or group leads to considerable crowding between this substituent and the two axial hydrogens on the same side of the molecule. The interaction resulting from such crowding of axial atoms or groups is called **1, 3-diaxial interaction**. To illustrate the operation of such interactions, let us consider methyl cyclohexane. Fig. 7.27 shows the two possible chair conformations of methyl cyclohexane ; one having the methyl group in an axial position [Fig. 7.27 (a)] and the other having this group in an equatorial position [Fig. 7.27 (b)].

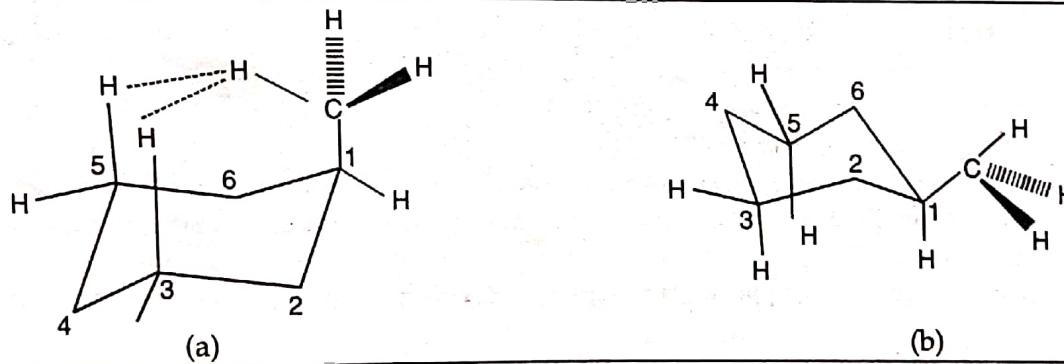


Fig. 7.27. The two possible chair conformations of methyl cyclohexane.

It can be seen (Fig. 7.27a) that one of the hydrogens of axial methyl group on C-1 is very close to the axial hydrogens on C-3 and C-5. But there is no such significant crowding when the methyl group is in equatorial position (Fig. 7.27b). In other words, axial methyl group is more crowded than the equatorial methyl. The resulting 1,3-diaxial interaction is responsible for the lesser stability of axial conformation than the equatorial conformation; the difference in the relative stability of the two being 7.5 kJ mol^{-1} .

Since the difference of 7.5 kJ mol^{-1} of energy between the axial and equatorial conformations of methyl cyclohexane is due to 1, 3-diaxial interaction between one methyl group and two hydrogens, it is reasonable to expect that 1, 3-diaxial interaction between each axial hydrogen and methyl group leads to difference of 3.75 kJ mol^{-1} . This can enable us to predict the relative stabilities of the various conformations of substituted cycloalkanes having more than one methyl group.

As stated above, the equatorial methylcyclohexane and axial methylcyclohexane can interconvert into each other readily and exist in equilibrium with each other. But at room temperature, 95 per cent of the molecules of methylcyclohexane are in the chair conformation having equatorial methyl group and only 5 per cent molecules are those having axial methyl group. This is apparently due to lesser energy or greater stability in case of equatorial methyl group.

KB

~~7.26. CONVERSION OF FISCHER PROJECTION FORMULAE INTO SAWHORSE FORMULAE AND NEWMAN'S PROJECTION FORMULAE~~

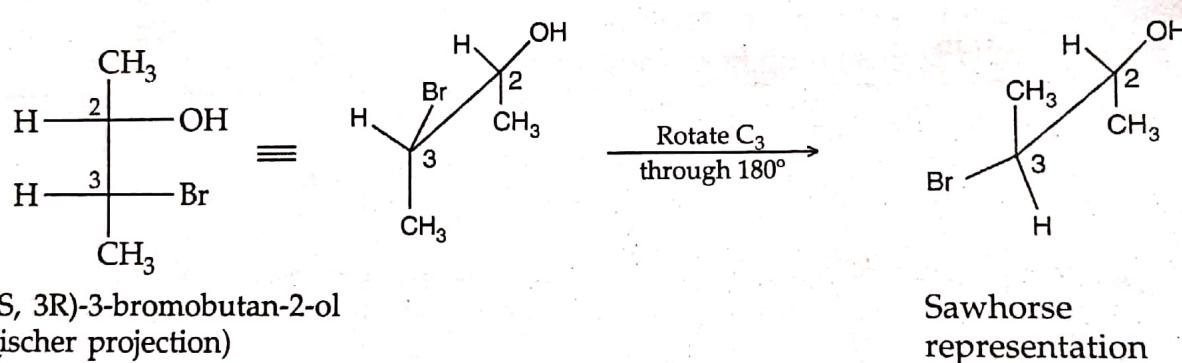
In conclusion of the discussion on the stereochemistry of organic compounds, we may point out an interesting drawback of Fischer projection formulae of diastereomers having two chiral carbon atoms. The Fischer projection formulae of such compounds correspond to the less stable **eclipsed conformation** involving maximum crowding between the substituent groups attached to the two chiral carbon atoms. But actually the molecules acquire the shape which corresponds to the **staggered form** in which the substituents are as far apart from each other as possible. Therefore, the best way of representing such molecules is to depict them in their staggered forms by means of Sawhorse formulae or Newman's projection formulae as explained below.

7.26.1. Conversion of Fischer projection formula into Sawhorse formula.

This involves two steps as given below :

- Write the Fischer projection formula and change it into its equivalent eclipsed representation in terms of Sawhorse formula.
- Rotate one of the chiral carbon atoms by angle of 180° around the bond between the two chiral carbons to get the Sawhorse representation of the staggered form.

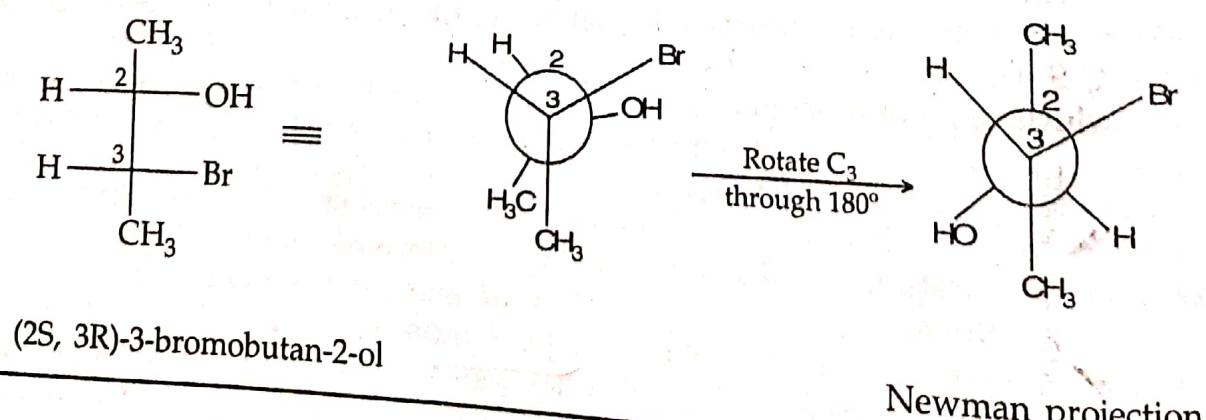
For example, let us convert (2S, 3R)-3-bromobutan-2-ol from Fischer projection formula to Sawhorse formula.



7.26.2. Conversion of Fischer projection formula into Newman's projection formula.

This also involves a similar procedure in which the Fischer projection formula is first translated into the equivalent eclipsed form in terms of Newman's projection formula. The latter is then changed into the staggered form by rotating through an angle of 180° around the bond between the two chiral carbons.

For example,

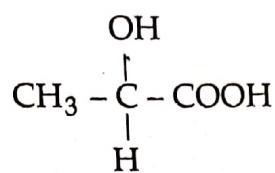


Newman projection

KB

Illustrative Conceptual Questions *with Answers*

Q. 1. Draw the structure of a carboxylic acid having the formula $C_3H_6O_3$ which is optically active.
Ans. The structure of the given acid is :

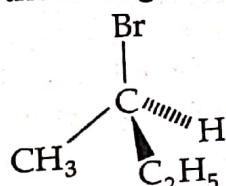


Q. 2. The concentration of an optically active compound dissolved in chloroform is 6.15 g per 100 ml of the solution. A portion of this solution in a 5 cm polarimeter tube causes a rotation of -0.6° . Compute its specific rotation.

Ans. Specific rotation =
$$\frac{\text{Observed rotation}}{\text{Length of polarimeter} \times \text{Concentration of}} \\ \text{tube (in decimetre)} \quad \text{solution (in } g \text{ ml}^{-1}\text{)}$$

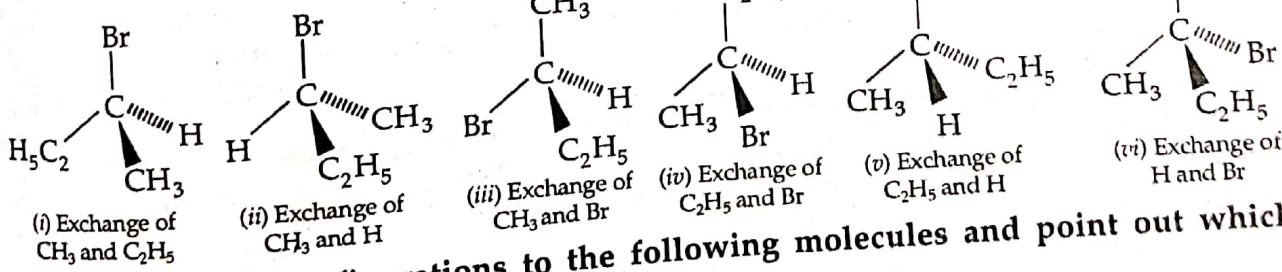
$$= \frac{-0.6}{0.5 \times \frac{6.5}{100}} = -19.5^\circ.$$

Q. 3. (R) - 2 - Bromobutane has the configuration given below :

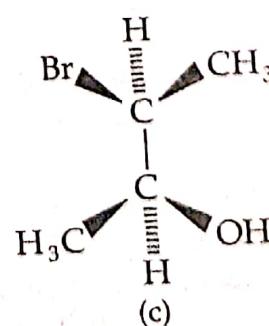
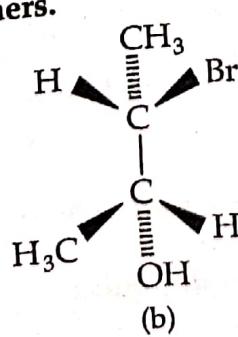
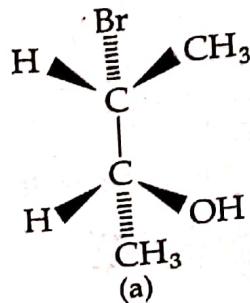


Draw the configuration of (S)-2-bromobutane in six different ways.

Ans. Knowing the configuration of (R) - 2-bromobutane we can draw the configuration of (S) - enantiomers by exchanging any two substituents of the (R) - configuration. The six views of (S) configuration possible are as shown below :



Q. 4. Assign R, S configurations to the following molecules and point out which are enantiomers and which are diastereomers.



KB