# CHAPTER 1

# Chirality

## 1.1 INTRODUCTION—WHAT TYPE OF COMPOUNDS DISPLAY CHIRALITY

Kekulé described correctly the tetravalent nature of carbon. Chemistry was however, still viewed in a two-dimensional way until 1874. In that year, J. Van't Hoff and Le Bel added a third dimension to carbon. They proposed that the four bonds of carbon are not randomly oriented but have a specific spatial orientation. Van't Hoff (Nobel Prize 1901) further advanced the idea and proposed that the four atoms to which a carbon atom is bonded sit at the corners of a regular tetrahedron, with carbon its center.

A representation of a tetrahedral carbon atom is shown in Fig. 1.1. The conventions used to show three-dimensionality are: solid lines represent bonds in the plane of the paper; solid wedged lines represent bonds coming out of the plane of the paper toward ones eyes; while dashed lines represent bonds receding into the plane away from the viewer.

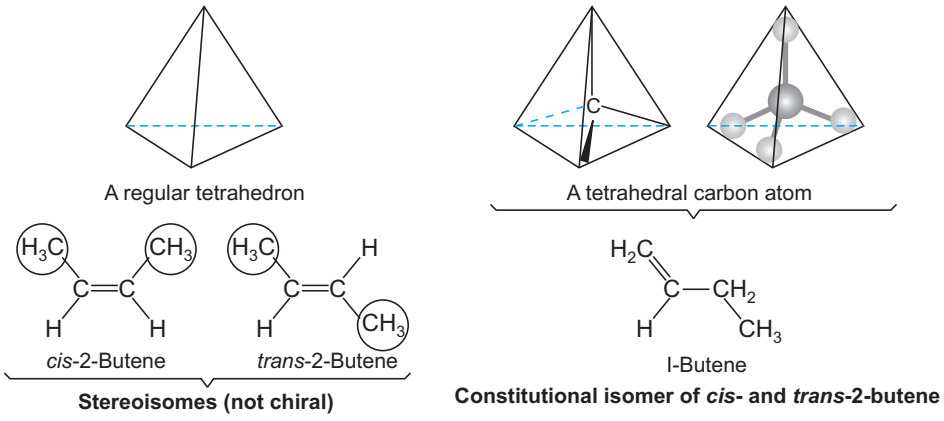
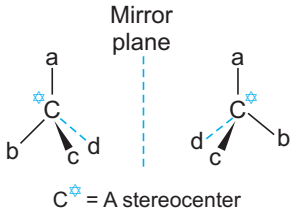



Fig. 1.1

In this chapter, one will learn about stereoisomerism and chirality. The word chiral (Greek "handed") describes the phenomenon of handedness of molecules. Chirality is a phenomenon which pervades the universe. The human body is structurally chiral, with the heart lying to the left of center, and the liver to the right. For evolutionary point of view, most people are right handed. All but one of the 20 amino acids of proteins are chiral, and all of them are classified as left handed.

The naturally occurring sugars are almost all right handed, including the sugar that occurs in DNA. DNA, itself, has a helical structure, and all naturally occurring DNA turns to the right.

Stereoisomers most of which are chiral are isomers that differ only in how their atoms are oriented in space, however, their atoms are bonded in the same order. Thus, *cis*- and *trans*-2-butene have the same connectivity of bonds, and are not constitutional isomers. They are stereoisomers because they differ only in the spatial orientation of the groups attached to the double bond. The *cis* isomer has the two methyl groups on the same side of the double bond, while the *trans* isomer has them on opposite sides. On the other hand, 1-butene is a constitutional isomer of *cis*- and *trans*-2-butene.




*In a tetrahedral carbon of the four bonds to central carbon two are in the plane of paper (continuous lines), third is below this plane (dashed wedge) and fourth is above this plane (solid wedge))*

The enantiomeric pair of a chiral molecule $C_{abcd}$.

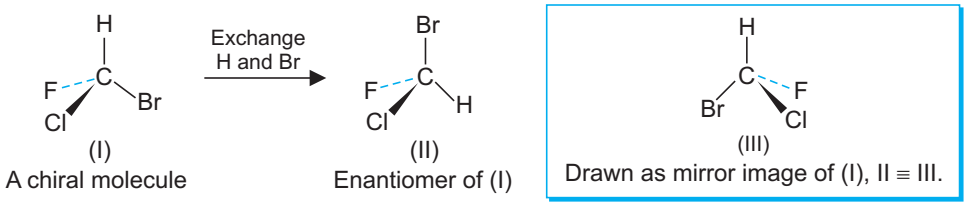



**Fig. 1.1a**

The tetrahedral geometry of carbon and a few other atoms (pyramidal) *e.g.*, N, P, Si and S and trigonal geometry of $sp^2$ hybrid carbon are key to the study of organic stereochemistry. The regular tetrahedron (Fig. 1.1) is highly symmetrical with four equivalent vertices. When these are occupied by four different achiral atoms or groups, symmetry disappears and a chiral complex is obtained ($C_{abcd}$) which is non superimposable on its mirror image (Fig. 1.1*a*).

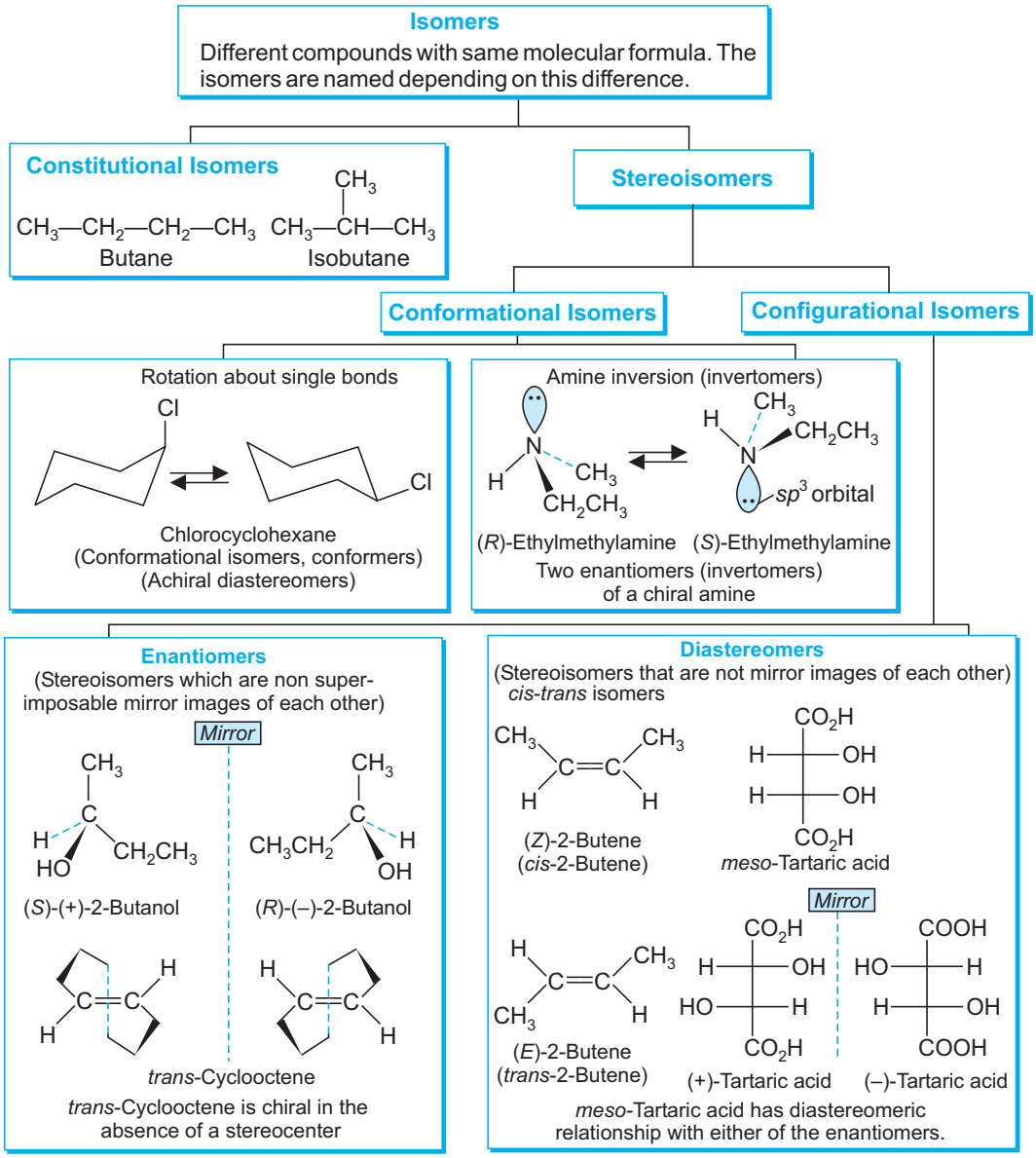
The tetracovalent carbon (the fifth point) placed at the center of the tetrahedron is termed a stereocenter whose presence usually generates molecular chirality. A unique feature of a stereocenter is that an exchange of any two ligands reverses its chirality to give a new stereoisomer. This *e.g.*, may be seen in a situation if all the ligands in $C_{abcd}$ are achiral and such an exchange then gives the mirror image—the enantiomer (Fig. 1.1*a*).

**Stereochemistry and Chirality**

- *Stereochemistry deals with the chemical and biochemical consequences of the arrangement of atoms in space. It deals with the study of molecules as three-dimensional objects.*
- *Chirality is the property of handedness of molecules and arises when the object and its mirror image are not superposable, e.g., a spiral binding on a note book is chiral.*

## 1.2 ISOMERS

Isomers are defined as different compounds that have the same molecular formula. These are named depending on the difference which may be constitutional or stereoisomeric (scheme 1.1).




**SCHEME 1.1**

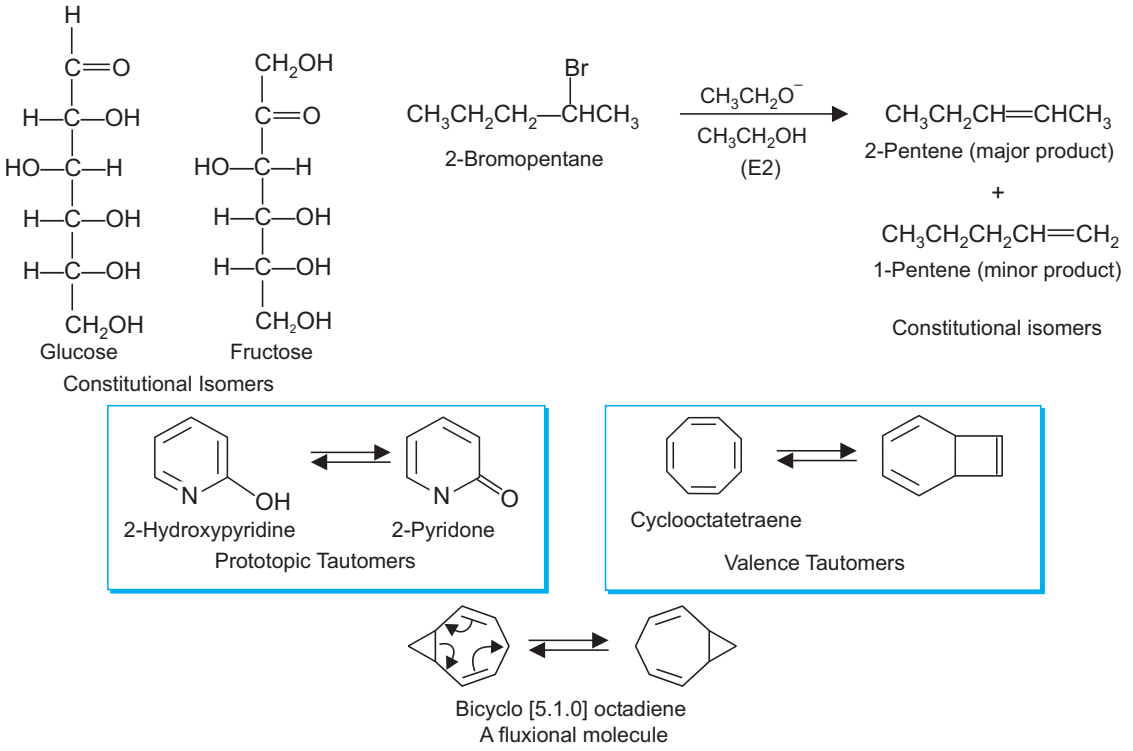
## (A) Constitutional Isomers

Constitutional isomers differ in the connectivity of atoms including bond multiplicity; disregarding configuration and conformation. The equivalent older term structural isomers is obsolete and redundant. All isomers are structural isomers and structure includes constitution, configuration and conformation.

Glucose and fructose (scheme 1.1*a*) are constitutional isomers, glucose is an aldehyde while fructose is a ketone. E2-elimination is regioselective since more of one constitutional isomer is formed.

Some other examples of constitutional isomers include:

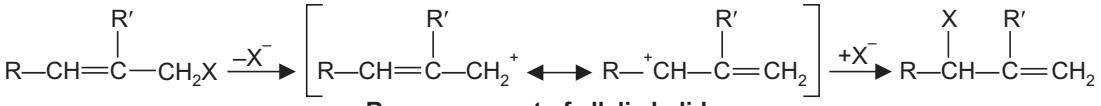
- *Tautomers.* Isomers of different energies which are interconvertible *via* a low energy barrier, the isomerization involves atom or group migration.
- *Proton tautomers* (*Prototropy*). Enol-keto isomerization is an example of prototropy (*i.e.*, a change in the position of a proton) and the interconversion of the tautomers, 2-hydroxypyridine and pyridone is an example (scheme 1.1*a*) of prototropy *i.e.,* change in the position of a proton and involves proton tautomers.
- *Valence isomers*. These isomers or degenerate species that are interconvertible by reorganization of some of the bonding electrons. The interconversion is accompanied by atom movement and not atom migration. Thus valence isomers are not tautomers. Valence isomers can be separately identified and in case these have the same structure (degenerate species) the individual atoms can be separately identified. The interconversion of cyclooctatetraene and its bicyclic isomer is an example of valence isomers (scheme 1.1*a*)




**Constitutional isomers**

**SCHEME 1.1a**

- *Fluxional molecules.* Molecules which undergo rapid degenerate rearrangement *i.e.*, a rearrangement into indistinguishable molecules *e.g.*, *via* bond reorganization (scheme 1.1*a*).
- *Allylic isomers.* These isomers result due to a rearrangement involving the allyl (propenyl group) and is recognized separately. These rearrangements may occur *via* the intermediate formation of a delocalized ion or a radical. The loss of X at one end and its return to the opposite end of the allyl system (scheme 1.1*b*) leads to the overall rearrangement. The allylic isomers arise due to a 1, 3-rearrangement.

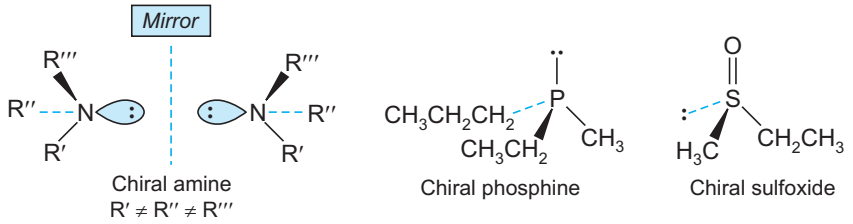



Rearrangement of allylic halides

SCHEME 1.1b

## Invertomers—Stereogenic Nitrogen and Phosphorus—Conformational and Configurational Isomers

Acyclic amines of the type (scheme 1.1*c*) in which the three groups are different and the lone pair on nitrogen is classed as a formal substituent meet all the requirements of a stereocenter. However, no optical activity is observed in amines of this type, even though these are chiral. This is due to very rapid pyramidal inversion (energy barrier to inversion is small ~25 kJ $mol^{-1}$) which interconverts enantiomers (called invertomers), further details are in schemes 1.5 and 1.142. Inversion is however, slower for third-row elements. Thus, phosphines, ($R_3P$) high energy barrier ~150 kJ $mol^{-1}$ and sulfoxides ($R_2S{=}O$) can be obtained in optically active form to result in configurational isomers. Amine inversion is an example of conformational isomers (invertomers), while biphenyl enantiomers may be isolated due to restricted rotation. Such isomers are called atropisomers.

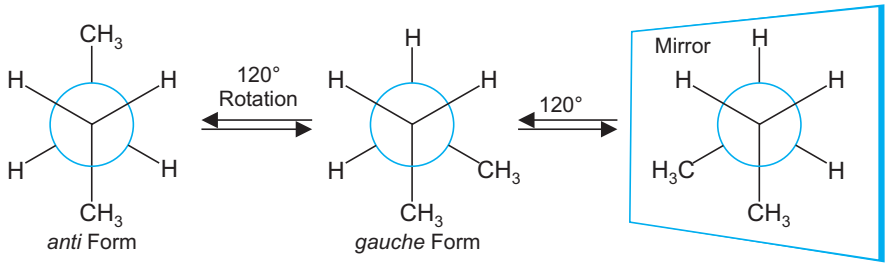



SCHEME 1.1c

**The Distinction between Conformation and Configuration**

- *Based on symmetry criteria, stereoisomers may be enantiomers (related as object and nonsuperimposable mirror image) and when these are not so related, these are termed diastereomers. The diastereomers occur in compounds with more than one stereocenter, cyclic compounds and compounds with double bonds (scheme 1.1).*
- *Based on energy barrier criterion, configurational isomers are separated by a high energy barrier > 100 kJ $mol^{-1}$. The two enantiomers of 2-butanol (scheme 1.1) are separated by high energy barrier since their interconversion involves a σ bond breaking. They represent configurational enantiomers. In the isomerisation of cis- and trans-2-butene a π bond is disrupted which requires an appreciable amount of energy ; they are also configurational diastereomers. The stereoisomers which on the other hand are separated by comparatively low energy barrier < 60 kJ $mol^{-1}$ so that interconversion is easy under ordinary conditions, are called conformational isomers. In some crowded molecules e.g., biphenyls however, rotation about a single bond may be sufficiently restricted to give stable and isolable conformers known as atropisomers which are configurational isomers (scheme 1.1e).*

*The distinction between conformation and configuration is in fact subtle and not agreed upon universally. The acyclic amine inversion (scheme 1.1) has a typically low energy barrier (33.5 kJ/mol) and may be considered either a configurational or a conformational change. These invertomers are however, better considered as conformers or as conformational enantiomers. However, these arguments do not apply to chiral phosphines (scheme 1.1c) where inversion is associated with high energy (~ 150 kJ/mol) to result in configurational isomers. Rotation around a single bond may be easy to give conformational isomers e.g., in n-butane (scheme 1.1d). Gauche butane is chiral. Two enantiomers interconvert by a conformational change (conformational enantiomers). Anti butane is achiral and either of the gauche butanes is its diastereomer (conformational diastereomers). Gauche butane is an example of racemization.*




**SCHEME 1.1d**

*Similarly chlorocyclohexane (scheme 1.1) represents a pair of conformational diastereomers. In fact chlorocyclohexane shows conformational isomerism at room temperature while configurational isomerism at –150°C (see Fig. 4.2). Another interesting example of conformational enantiomers is in (scheme 4.33).*

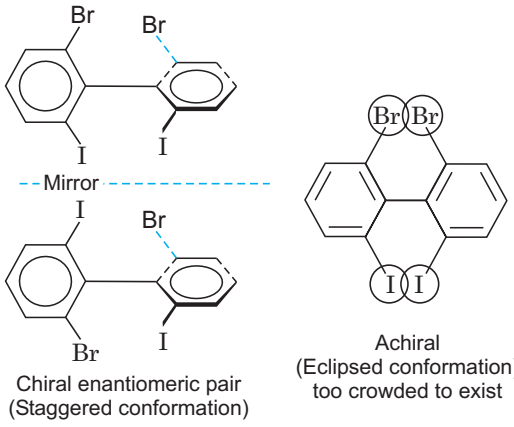
## (B) Stereoisomers—An Introduction

When the isomers have the same sequence of covalent bonds, but differ in the relative disposition of their atoms in space, then the difference is stereoisomeric (scheme 1.1) (also see Fig. 1.1). Some examples are, enantiomers, diastereomers (epimers, anomers), conformational isomers (atropisomers and invertomers).

### 1. Enantiomers—Optical Isomerism

#### (*a*) Simple organic molecules

Consider a simple molecule *e.g.*, a compound with an $sp^3$ hybridized carbon with four different substituents as in 2-butanol (scheme 1.1). The molecule cannot be superimposed on its mirror image and such molecules are said to be chiral (or handed). The pair of butanol molecules are termed enantiomers (from the Greek 'enantio' meaning opposite) which are defined as pair of molecules related as non-superimposable mirror images. The enantiomers of 2-butanol are drawn (scheme 1.1) in the three dimensional projection formulas (a procedure to draw these projections is depicted in scheme 1.15). Another example of enantiomers is in D and L-glyceraldehydes and D- and L-glucose drawn now in another projection (scheme 1.2) called a Fischer projection, (a procedure to draw these projections is detailed in scheme 1.17). The D-sugars have the OH group on the bottom stereocenter on the right in the Fischer projection. The unnatural L-series of sugars are the enantiomers of the natural D-series.

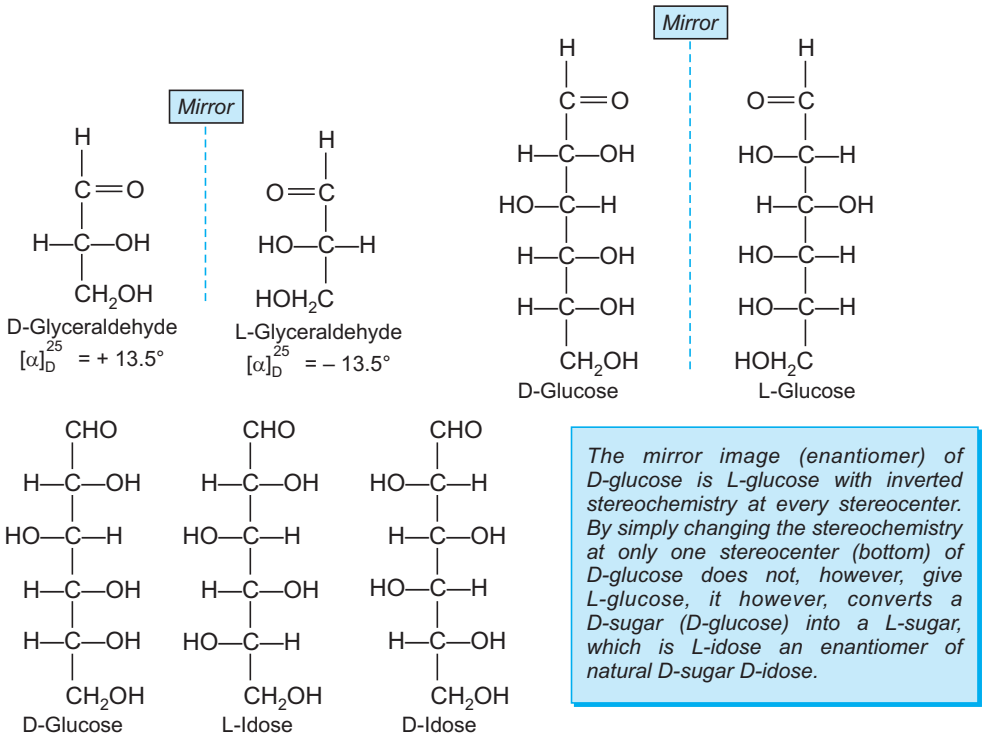



*Stable conformational isomers (atropisomers) exist in compounds, e.g., biphenyls due to steric strain between the ortho substituents. These isomers become chiral when both rings are unsymmetrically substituted. The biphenyl then gets locked in one of the two chiral enantiomeric staggered conformations. This biphenyl would have been achiral if a symmetric (planar) high energy eclipsed conformation could be achieved (an impossible situation.)*

**SCHEME 1.1e**

Compounds can be chiral and thus exist as a pair of enantiomers in the absence of stereocenters as in *trans*-cyclooctene (scheme 1.1, further details are in schemes 1.136–1.138). Another example of compounds which are chiral in the absence of stereocenters are biphenyl derivatives (scheme 1.1*e*, further details are in Sec. 1.16, B).

Thus compounds of the type $C_{abcd}$ exist in enantiomeric forms and are described as chiral and the carbon atom with four different achiral atoms or groups as substituents is called a stereogenic centre of simply a stereocenter. The phenomenon of enantiomers is also known as optical isomerism. An important property of compounds of type $C_{abcd}$ *i.e.*, a molecule




*The mirror image (enantiomer) of D-glucose is L-glucose with inverted stereochemistry at every stereocenter. By simply changing the stereochemistry at only one stereocenter (bottom) of D-glucose does not, however, give L-glucose, it however, converts a D-sugar (D-glucose) into a L-sugar, which is L-idose an enantiomer of natural D-sugar D-idose.*

**SCHEME 1.2**

with one tetrahedral atom with four different groups attached to it is enantiomerism as in glyceraldehyde (scheme 1.2). An important property of such enantiomers (*i.e.*, a chiral tetrahedral model) is that on interchanging any two groups at the stereocenter converts one enantiomer into another. In addition to the compounds of the type $C_{abcd}$ with one stereocenter *e.g.*, glyceraldehyde (scheme 1.2) and 2-butanol (scheme 1.1) which fulfill the conditions for the occurrence of enantiomeric pairs, several other structural situations may give rise to optical isomerism. These include compounds with more than one stereocenter (as in glucose, scheme 1.2), stereocenters other than carbon (sec. B, IV) and compounds which are optically active in the absence of stereocenters (scheme 1.1*e*).

**Chiral Organic Compounds**

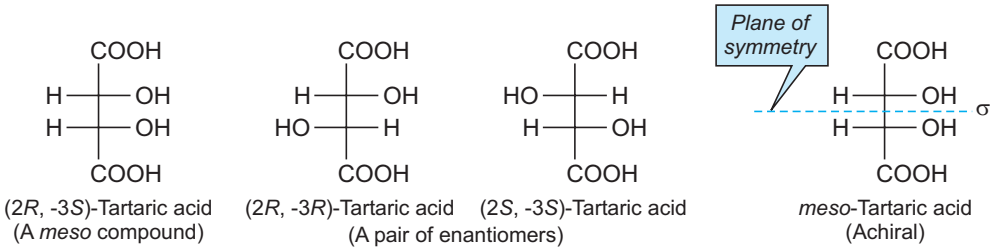
- *The presence of a stereocenter usually leads to molecular chirality.*
- *A tetrahedral atom or a pyramidal atom with three ligands (the lone pair of electrons serves as the fourth ligand) gives a stereocenter provided an interchange of any two ligands (this process reverses the chirality of the center) leads to a new stereoisomer.*
- *The presence of a stereocenter in an organic molecule is a sufficient condition for chirality, however it is not a necessary condition.*
- *Several molecules display chirality (optical isomerism) in the absence of stereocenters e.g., chiral biphenyls. Thus a compound is chiral if it is not superimposable on its mirror image.*
- *Organic stereochemistry is based on tetrahedral geometry of carbon which is absolutely central to its study. Study of stereochemistry is also based on atoms like N, P, Si and S and to a lesser extent on the trigonal geometry of $sp^2$ hybrid carbon and nitrogen.*

In tartaric acid (scheme 1.2*a*) one has two stereocenters. A molecule with two stereocenters can give rise to a maximum of four stereoisomers ($2^n$ as also in 2-bromo-2-butanol, see scheme 1.33). However, if the two stereocenters carry an identical set of substituents, the number of stereoisomers is less than $2^n$, since there will be a *meso* compound (scheme 1.2*a*). The *meso* tartaric acid has a plane of symmetry and is achiral (it has a mirror image which is, however, superimposable on it). The name *meso* is given to an achiral member of a set of a diastereomers which also includes at least one chiral member. Tartaric acid stereoisomers are drawn in Fischer projections (The Fischer projections are the eclipsed conformations).

**Chirality and Stereocenters**

- *Chirality is a necessary and sufficient condition to generate enantiomerism and requires the absence of Sn (alternating axis of symmetry of any order).*
- *The presence of a stereocenter usually imparts molecular chirality. A unique feature of such a stereocenter is that exchange of any two ligands inverts the chirality of the stereocenter to yield a new stereoisomer. When all the ligands are achiral, the exchange gives an enantiomer, however, if one or more of the ligands are chiral, a diastereomer will be formed. This is seen in the case of tartaric acid. When one interchanges the groups on one stereocenter in meso-tartaric acid (see, scheme 1.2a) an enantiomer of tartaric acid is formed and vice versa.*
- *Thus an organic molecule with one stereocenter must be chiral, however, molecules with two or more stereocenters are not all chiral.*

Stereocenters *e.g.,* in tartaric acid stereoisomers are assigned *R* and *S* configurational descriptors, so as to specify stereochemical features of each stereoisomer. The enantiomer of (+) tartaric acid is its nonsuperimposable mirror image (–) tartaric acid and these constitute an enantiomeric pair. Notice that pairs of enantiomers (as expected) have opposite configuration at every stereocenter.




**Stereoisomers of tartaric acid in Fischer projections**

### Physical properties of stereoisomers of tartaric acid

| | Melting point, °C | $[\alpha]_D^{25°C}$ | Solubility, g/100 g $H_2O$ at 15°C |
|---|---|---|---|
| *(2R, 3R)-(+)-Tartaric acid* | 171 | + 12.7° | 139 |
| *(2S, 3S)-(–) Tartaric acid* | 171 | – 12.7° | 139 |
| *(2R, 3S)-Tartaric acid* | 140 | 0° | 125 |
| *(±)-Tartaric acid* | 206 | 0° | 20.6 |

**SCHEME 1.2a**

### (*b*) Complex organic molecules and biomolecules

Except for few low molecular weight organic compounds, the organic substances found in living systems both animals and plants are chiral. No doubt these molecules (with several stereocenters) can theoretically exist as a number of stereoisomers, almost invariably only one stereoisomer is found in nature. Naturally occurring alkaloid brucine has several stereocenters which are located in fused ring systems, however, nature makes only one enantiomer (–)-brucine. Naturally occurring amino acids (with the exception of achiral glycine) are chiral. There are two possible enantiomers (optical isomers) for each amino acid, but only one of them (L-form) exists in the body. Enzymes are proteins which are derived from chiral amino acids, thus an enzyme is also chiral and can exist as enantiomers, however only one enantiomer exists naturally (since an amino acid exists only as one enantiomer these will construct only one mirror image form of the enzyme). Thus enzymes provide a chiral environment.

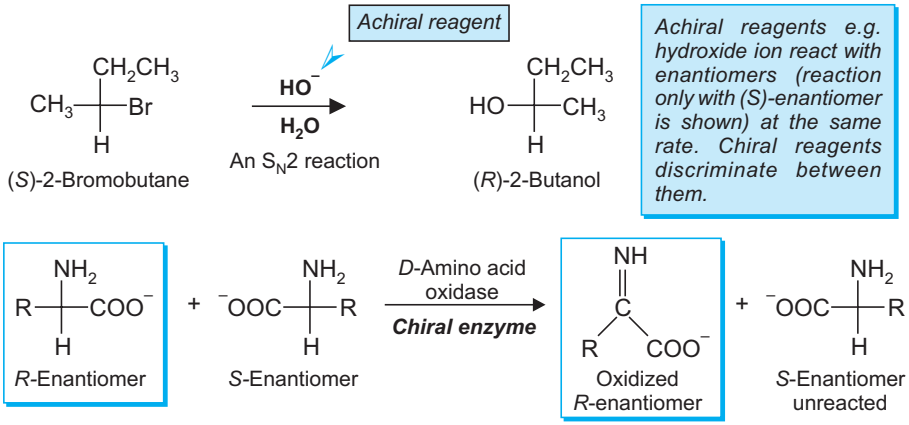
**Enzymes catalyzed reactions are stereospecific and stereoselective**

- *For definition of terms, stereospecific and stereoselective (see Sec. 1.13).*
- *Enzymes are chiral and enantiomerically pure.*
- *Enzymes display stereospecificity and stereoselectivity (see Sec. 2.3 D).*
- *All stereospecific reactions are necessarily stereoselective, however, the converse is not true.*

## 2. Properties of Enantiomers

Each enantiomer of a pair has the same physical and chemical properties in achiral environments with the important exceptions of their interactions with (*i*) plane polarized light (optical activity) and (*ii*) chiral reagents. When plane polarized light is passed through the solution of each enantiomer (in the same solvent, using the same cell and same concentration), then the plane of polarized light is rotated in opposite directions by the same amount as in glyceraldehyde enantiomers (scheme 1.2). Similarly the enantiomers of tartaric acid have *e.g.*, the same melting point (171°C), the same value of $pK_a$ (25°C $pK_1$ = 2.98 ; $pK_2$ = 4.34), but different signs of specific rotation (+)-tartaric acid + 12.7 while (–)-tartaric acid – 12.7 (scheme 1.2*a*). Each enantiomer shows the same chemical reactivity with achiral reagents *i.e.*, enantiomers react with achiral reagents

*Plane polarized light is in fact an equal mixture of left and right circularly polarized light which propagates through space as left handed and right handed helices respectively. Due to the chirality of the circular components of the plane polarized light the two enantiomers of a compound react with it differently.*




**SCHEME 1.2b**

at the same rate. Thus *e.g.* (*S*)-2-bromobutane reacts with achiral hydroxide ion to give (*R*)-2-butanol (scheme 1.2*b*) by an $S_N2$ mechanism. The rate of this reaction is found to be the same with the enantiomeric (*R*)-2-bromobutane with hydroxide ion to give (*S*)-2-butanol. When, however, the reagent is chiral *e.g.,* an enzyme, the two enantiomers will react at different rates. Thus the enzyme D-amino acid oxidase reacts only with one of the enantiomers–the (*R*)-enantiomer, the (*S*)-enantiomer remaining unchanged (scheme 1.2*b*). Another example is found during the kinetic resolution of amino acids (See, scheme 1.86).

This is an example of stereospecificity in general and the reaction with only one enantiomer shows that the enzyme displays total enantioselectivity.

Receptors are proteins which are chiral and thus these will bind one of the enantiomers better than the other *i.e.*, one enantiomer binds with a particular receptor whereas the other does not. Receptors located on the exterior of nerve cells in the nose are thus able to differentiate odours. The enantiomers of carvone (scheme 1.2*c*) smell different since each fits into a different receptor.

In summary chiral substances react only with substances that match their own chirality. This forms the basis for an enzyme to distinguish between two enantiomers of a compound, during enzyme catalyzed reactions. The enzyme first positions a molecule at the binding site on its surface (via, hydrogen bonds, electrostatic attractions, dispersion forces or even covalent