Unit -2
Stereochemistry

[Optical isomerism in compounds without chiral carbon, Geometrical isomerism, Chiral Drugs]

Stereoisomerism:
The phenomenon exhibited by two or more compounds with the same molecular and structural formula, but different spatial arrangements of atoms or groups, is known as stereoisomerism. Stereoisomerism can be categorized into two categories:

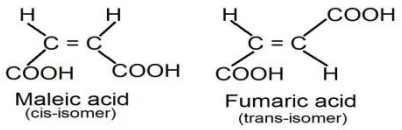
I. Geometrical isomerism
II. Optical isomerism

Geometrical isomerism: *The geometrical isomerism arises when atoms or groups are arranged differently in space due to restricted rotation of bonds in a molecule.*

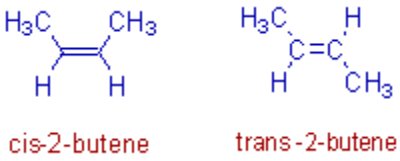
cis or trans isomers

When a similar group is placed at an adjacent position the compound is named with the prefix *cis*
When a similar group is placed at the opposite position the compound is named with the prefix *trans*

1) butenedioic acid:



2) cis-2-butene and trans-2-butene



E-Z notation
According to this method, if the groups with higher priorities are present on the opposite sides of the double bond, that isomer is denoted by E.Where E = Entgegen (the German word for 'opposite')

However, if the groups with higher priorities are on the same side of the double bond, that isomer is denoted by Z.Where Z = Zusammen (the German word for 'together')

The following procedure is to be adopted to denote the geometrical isomers by E & Z descriptors.

- First determine the higher priority group on each end of the double bond.

- If the higher priority groups are on the opposite sides of double bond, the isomer is denoted by the descriptor, E.
- Otherwise if they are on the same side of double bond, the Z descriptor must be used.
- The priorities are assigned by following **Cahn-Ingold-Prelog sequence rules (CAN rules)** described below.

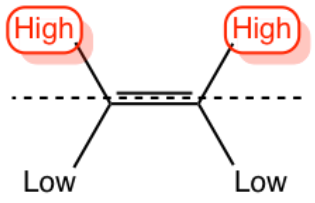
(i) Rank the atoms directly attached to the olefinic carbon according to their atomic number. High priority is given to the atom with higher atomic number.

(ii) If isotopes of same element are present, the higher priority is given to the isotope with higher atomic mass. E.g.

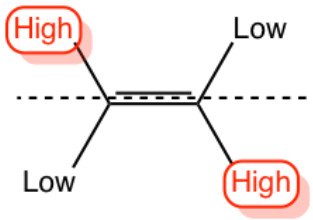
(iii)The Deuterium isotope (H^2 or D) has more priority than protium (H^1 or H).

(iv)The C^{13} isotope has more priority than C^{12}.

(v) If the atoms are still identical, examine the next atoms along the chain until a "first point of difference" is found. This is done by making a list of atoms linked directly to the first atom. Each list is arranged in order of decreasing atomic number. Then the higher priority is given to the list which contain atom with higher atomic number at first point of difference.

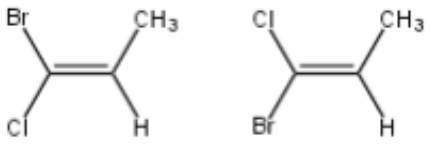


***Z* - isomer**

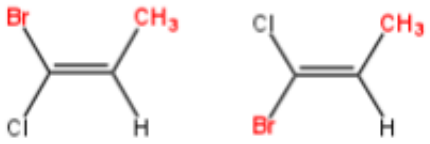


***E* - isomer**

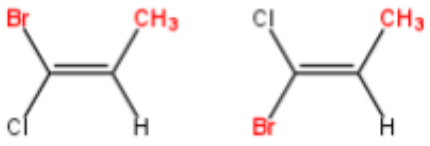
Example 1



Step 1: Identify the higher priority groups.



Step 2: Assign E/Z based on orientation.



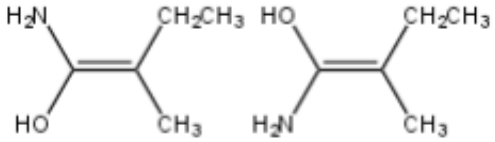
same side -> Z

(Z) Isomer

opposite sides -> E

(E) Isomer

Example 2



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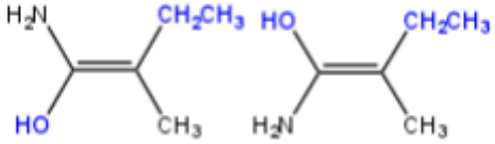

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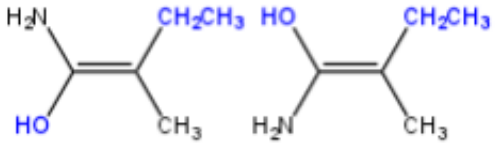


opposite sides -> E

(E) Isomer

same side -> Z

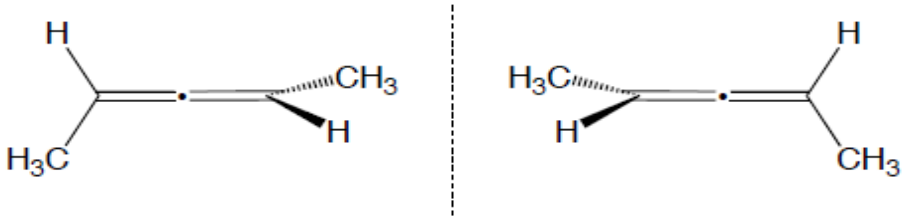
(Z) Isomer

Optical isomerism of Organic compounds without chiral carbon

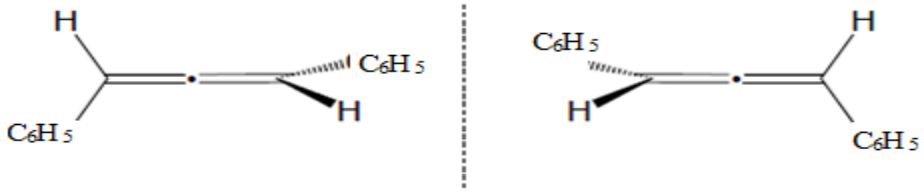
Some compounds which do not have asymmetrically substituted carbon atoms (or any other atom type) may still be chiral if they feature two perpendicular planes which are not symmetry planes. If these *disymmetric* (chiral) planes cannot freely rotate against each other, the corresponding compounds are chiral.

There are some molecules that do not contain chiral carbons but are chiral. E.g.

(i) Allenes: Compounds containing a C=C=C unit are called allenes. In allene, the central C atom is sp hybridized, but the two outer carbons are sp^2 and the planes containing the substitutents on either end of the double bonds are aligned perpendicular to each other. The whole molecule does not lie in the same plane. An allene is chiral if each end has two distinct substituents.

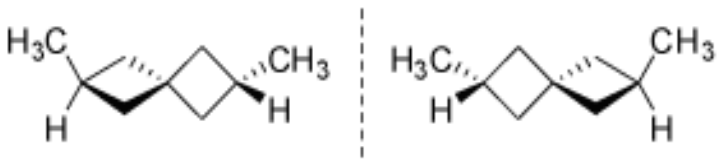


2,3-propadiene



1,3 Diphenyl propadiene

(ii) Spiro compounds :A spiro compounds are bi- or polycyclic organic compounds with rings connected through just one atom. The rings can be different in nature or identical. These two rings are perpendicular to each other .Because of restricted rotation spiranes exhibit optical isomerism. The connecting atom is also called the spiro atom .

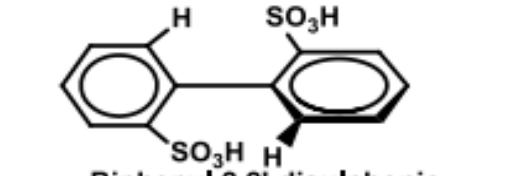


enantiomers

2,6-dimethyl-spiro[3.3]heptane

(iii) Biphenyls: Biphenyls also exhibit optical isomerism due to restricted rotation around the single bond between the two benzene nuclei. In the biphenyls, the *ortho*-substitutents must be large enough to

prevent rotation around the central single bond; if hydrogen atoms are present in these positions the barrier of rotation may be too small to prevent interconversion of the enantiomeric .



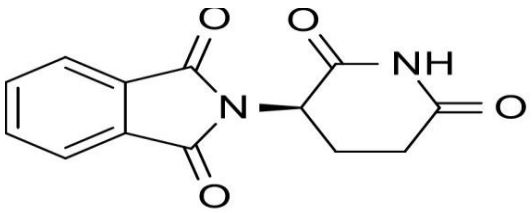
Biphenyl-2,2'-disulphonic
chiral, optically active and resolvable

Chiral Drugs

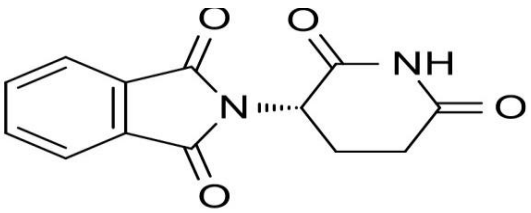
- Chirality is a property of an object which is non-superimposable with its mirror image.
- Drugs that exhibit chirality are referred to as chiral drugs.
- A chiral molecule is a molecule having at least one asymmetric carbon. Carbon is not the only atom that can act as an asymmetric center. Sulfur, phosphorus and nitrogen can sometimes form chiral molecules.
- In pharmaceutical industries, 56% of the drugs currently in use are chiral molecules and 88% of the last ones are marketed as racemates (or racemic mixtures), consisting of an equimolar mixture of two enantiomers.
- Although the enantiomers of chiral drugs have the same chemical connectivity of atoms; they exhibit marked differences in their pharmacology, toxicology, metabolism etc. Therefore, when chiral drugs are synthesized, as much effort goes towards the rigorous separation of the two enantiomers.

Few examples of chiral drugs, whose enantiomers vary drastically in their properties

1. ***thalidomide*.**
The R-enantiomer is an effective sedative, which has a soothing effect that relieves anxiety and makes the patient drowsy; while, the S-enantiomer is known to cause teratogenic birth defects.



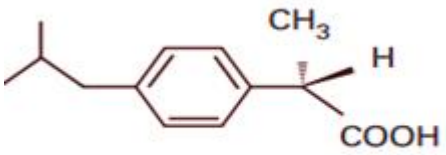
(R)-thalidomide



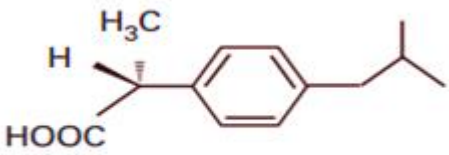
(S)-thalidomide

2. Ibuprofen:

A well-known painkiller, ibuprofen, the (S)-enantiomer has the desired pharmacological activity while the (R)-enantiomer is totally inactive.



(+)-(S)-ibuprofen



(–)-(R)-ibuprofen

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