

FUNDAMENTAL OF STEREOCHEMISTRY

PART- 1

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Scope

- **Stereochemistry** (from the Greek *stereos*, meaning solid) refers to **chemistry in space** i.e., in three dimensions and **describes chemistry as a function of molecular geometry**. Since most molecules are three-dimensional (3D), stereochemistry, in fact, pervades all of chemistry.
- **Stereochemistry can be factorised into its static and dynamic aspects**. **Static stereochemistry** (stereochemistry of molecules) deals with the counting of stereoisomers (isomeric compounds of identical structure but differing in the arrangement of the atoms in three-dimensional space), with their structure (i.e., molecular architecture), with their energy, and with their physical and most of their spectral properties.

Scope

- **Dynamic stereochemistry** (or stereochemistry of reactions) deals with the stereochemical requirements and the stereochemical outcome of chemical reactions, including interconversion of conformational isomers or topomers; this topic is deeply interwoven with the study and understanding of reaction mechanisms.
- Today, the scope of stereochemistry extends considerably beyond the static description of molecular geometry and of the physical properties related to such geometry; stereochemistry is concerned also with the relationships in space between the different atoms and groups in a molecule during chemical reactions and the way in which chemical equilibria and rates of reaction are affected by those spatial relationships.

History

- The origins of stereochemistry stem from the discovery of plane-polarized light by the French physicist Malus (1809). In 1812 another French scientist, Biot discovered that a quartz plate, cut at right angles to its crystal axis, rotates the plane of polarized light through an angle proportional to the thickness of the plate; this constitutes the **phenomenon of optical rotation**.
- Some quartz crystals turn the plane of polarisation to the right, while others turn it to the left. Biot (1815) extended these observations to organic substances-both liquids (such as turpentine) and solutions of solids (such as sucrose, camphor, and tartaric acid). Biot recognized the difference between the rotation produced by quartz and that produced by the organic substances he studied.

History

- According to Biot, the rotation produced by quartz is a property of the crystal. It is observed only in the solid state and depends on the direction in which the crystal is viewed, whereas the latter (rotation produced by the organic substances) is a property of the individual molecules, and may, therefore, be observed not only in the solid, but in the liquid and gaseous states, as well as in solution.
- With respect to the question of the cause of optical rotation, the French mineralogist Hauy had already noticed in 1801 that quartz crystals exhibit the phenomenon of *hemihedrism*. Hemihedrism may be defined as the absence of a plane, centre, or alternating axis of symmetry in the crystal. In crystals presenting hemihedrism, there are faces that make such crystals non-superposable with their mirror images. Such mirror-image crystals are called “enantiomorphous,” from the Greek *enantios* meaning opposite and *morphe* form.

History

- In 1822, Sir John Herschel, a British astronomer, observed that there was a relation between hemihedrism and optical rotation. All the quartz crystals having the odd faces inclined in one direction rotate the plane of polarized light in one and the same sense, whereas the enantiomorphous crystals rotate polarized light in the opposite sense.
- Louis Pasteur extended this correlation from the realm of crystals, such as quartz, which rotate polarized light only in the solid state, to the realm of molecules, such as *dextro*-tartaric acid, which rotate both as the solid and in solution. [*dextro*-Tartaric acid, henceforth denoted as (+)-tartaric acid, rotates the plane of polarized light to the right.

History

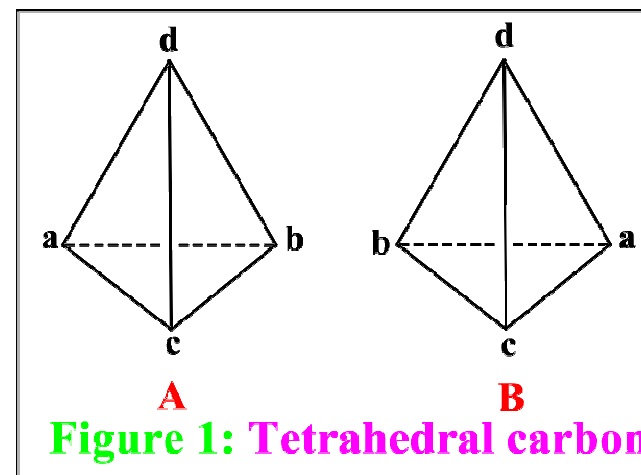
- In 1848 Pasteur had succeeded in separating crystals of the sodium ammonium salts of (+)- and (-)-tartaric acid from the *racemic* (nonrotating) mixture. When the salt of the mixed (*racemic*) acid, which is found in wine caskets, was crystallized by slow evaporation of its aqueous solution, large crystals formed which displayed hemihedric crystals similar to those found in quartz.
- By looking at these crystals with a lens, Pasteur was able to separate the two types (with their dissymmetric facets inclined to the right or left) by means of a pair of tweezers. When he then separately redissolved the two kinds of crystals, he found that one solution rotated polarized light to the right [the crystals being identical with those of the salt of the natural (+)-acid], whereas the other rotated to the left. [(-)-Tartaric acid had never been encountered up to that time.]

History

- Pasteur (1860) soon came to realize the analogy between crystals and molecules. In both cases the power to rotate polarized light was caused by *dissymmetry*, that is the non-identity of the crystal or molecule with its mirror image, expressed in the case of the ammonium sodium tartrate crystal by the presence of the hemihedric faces.
- Similarly, Pasteur postulated, the molecular structures of (+)- and (-)-tartaric acids must be related as an object to its mirror image. The two acids are thus enantiomorphous at the molecular level. They are called as *enantiomers*. [The ending *-mer* (as in isomer, polymer, etc., come from the Greek *meros* meaning part) usually refers to a molecular species.]

History

- In 1874, van't Hoff (1874, 1875) and Le Bel (1874) independently and almost simultaneously proposed the case for enantiomerism in a substance of the type Cabcd: the four substituents are arranged tetrahedrally around the central carbon atom to which they are linked.
- The four linkages to a carbon atom point toward the corners of a regular tetrahedron (**Figure 1**) and two nonsuperposable arrangements of atoms or groups (enantiomers) are thus possible.
- The model corresponding to a given enantiomer (e.g., **Figure 1; A**) and the molecule that it represents are called “*chiral*” (meaning handed, from Greek *cheir*, hand) because, like hands, the molecules are not superposable with their mirror images.



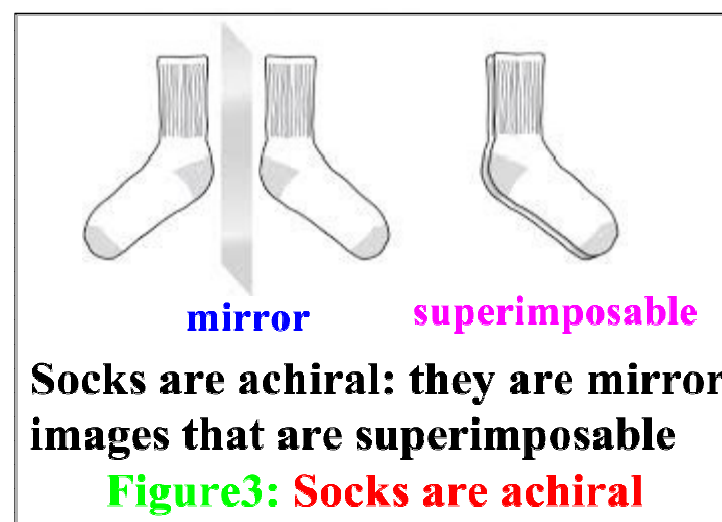
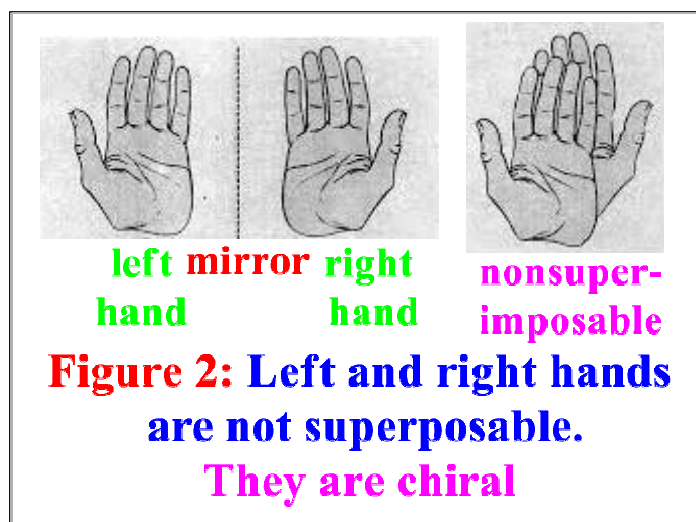
Chiral Molecules and Chiral Samples

- When a *molecule* is *chiral*, it must be either “right-handed” or “left-handed”. But if a *substance or sample* is said to be *chiral*, this merely means that it is made up of *chiral* molecules; it does not necessarily imply that all the constituent molecules have the same “*sense of chirality*”.
- The statement that a macroscopic sample (as distinct from an individual molecule) is *chiral* is ambiguous. It may be *racemic* or *non-racemic*.
- ***Chiral and non-racemic sample:*** The sample is made up of molecules that all have the same sense of chirality (homochiral molecules).
- ***Chiral but racemic sample:*** The sample is made up of equal (or very nearly equal) numbers of molecules of opposite sense of chirality (heterochiral molecules).

Chiral Molecules and Chiral samples

- There is, however, little ambiguity about the meaning of “*chiral, racemic*”: *Chiral, racemic* means that the sample is made up of equal numbers of molecules of opposite sense of chirality. But in a “*chiral, non-racemic*” sample there can be some molecules of a sense of chirality opposite to that of the majority; that is, the sample may not be enantiomerically pure (or enantiopure).
- **Everything has a mirror image.** What’s important in chemistry is whether a molecule is identical to or different from its mirror image. **Some molecules are like hands. Left and right hands are mirror images of each other, but they are not identical (Figure 2).** If one hand is placed on the other, they can never superimpose either all the fingers, or the tops and palms. **Socks, on the contrary, are superposable to each other (Figure 2).**

Chiral and Achiral Molecules



- To superimpose an object on its mirror image means to align all parts of the object with its mirror image. With molecules, this means aligning all atoms and all bonds.
- A molecule (or object) that is not superimposable on its mirror image is said to be *chiral*.

Chiral and Achiral Molecules

- Other molecules are like socks. Two socks from a pair are mirror images that are superimposable. One sock can fit inside another. A sock and its mirror image are identical.
- A molecule (or object) that is superimposable on its mirror image is said to be *achiral*.

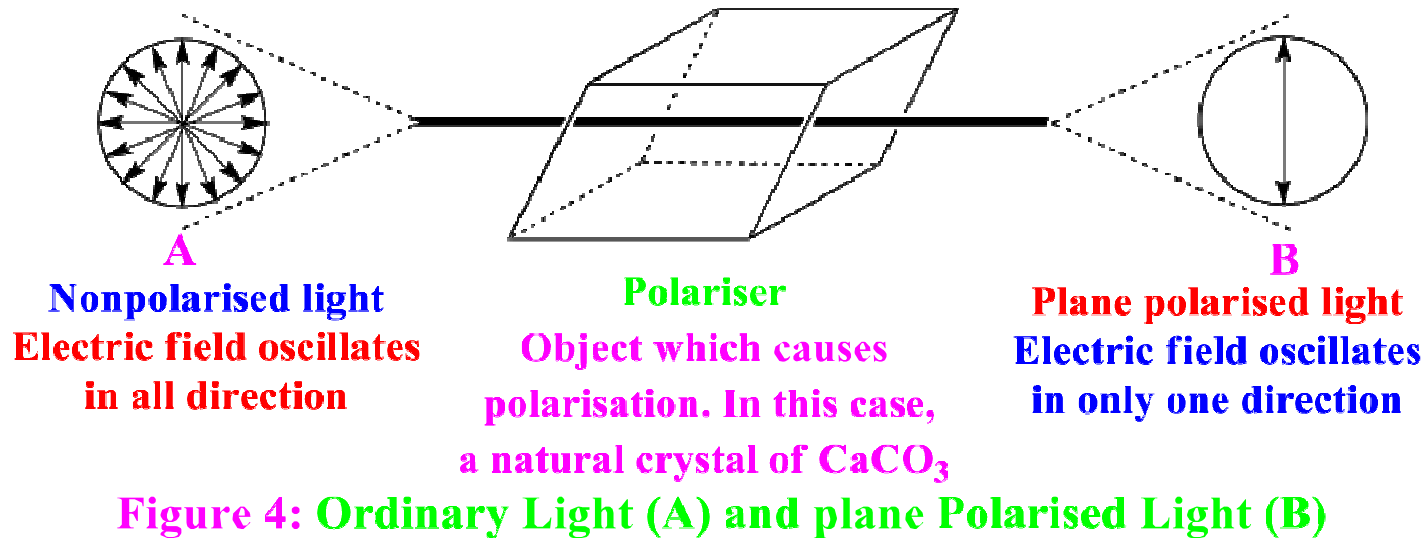
Answer the Following Questions

1. There are twenty-six letters in English language. How many of them are symmetric and how many of them are non-symmetric, considering them as two-dimensional.
2. Classify the following as *chiral* or *achiral*. Give reasons.
(a) H_2O (ii) CH_2BrCl (iii) CHBrClF

Ordinary Light and Plane Polarised Light

- An **ordinary light** beam consists of a group of electromagnetic waves of a range of different wavelengths that vibrate in many different planes at right angles to the direction of propagation of the light ray. It vibrates in all directions as in **Figure 4A**.
- When such a beam strikes a polarising film or a **Nicol prism** (made from a crystal of calcium carbonate) only those waves vibrating in a specific plane with respect to the axis of the film or prism may pass through; all others are blocked out. Upon emergence the light beam is plane polarised as in **Figure 4B**. Here, all of its waves vibrate in a single plane (or, more precisely, in parallel planes). Light of this kind is said to be **polarised**. French physicist Malus discovered this light in 1809.

Ordinary Light and Plane Polarised Light



- **Monochromatic light:** Monochromatic light, such as emitted by a sodium lamp ($\lambda = 589 \text{ nm}$), is of discrete wavelength but still vibrates in an infinite number of planes.
- The term monochromatic derives from the Greek words *monos*, meaning one or sole, and *chromos*, meaning color.

Isomers

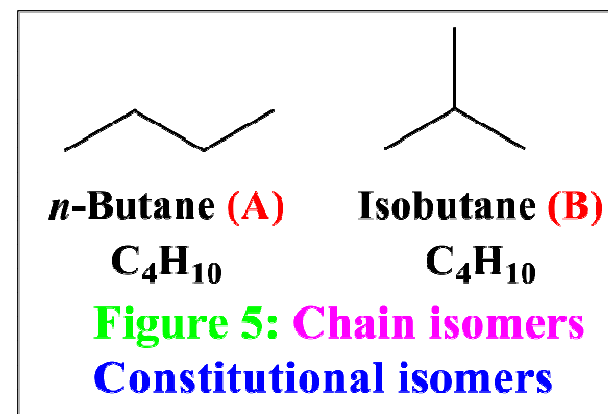
- In organic chemistry, isomers are molecules with the same molecular formula (i.e. the same number of atoms of each element), but different structural or spatial arrangements of the atoms within the molecule. Therefore, isomers are the different compounds with the same molecular formula.
- On the basis of **bonding connectivity** (The term **connectivity**, or **bonding** sequence, describes the way atoms are connected together, or their **bonding** relationships to one another, in covalent compounds. For example, in the methane molecule one carbon is connected to four hydrogen atoms simultaneously, while each hydrogen atom is connected to only one carbon.), isomers are divided into two major classes: **constitutional or structural isomers and stereoisomers**.

Constitutional or Structural Isomers

- Constitutional or structural isomers are compounds with the same molecular formula but different structural formulae. In isomerism, constitutional isomers are molecules of different connectivity. Therefore, constitutional isomers differ in the way the atoms are connected to each other.
- **Constitutional isomers have:**
 1. different IUPAC names
 2. different bonding connectivity
 3. the same or different functional groups
 4. different physical properties, so they are separable by physical techniques such as distillation.
 5. different chemical properties. They behave differently or give different products in chemical reactions.

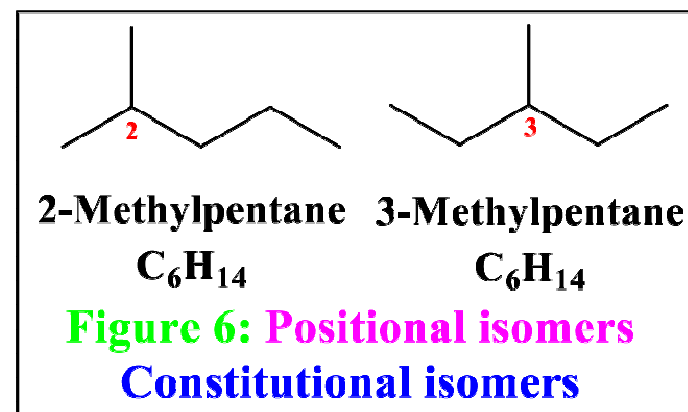
Constitutional or Structural Isomers

- Structural isomers can be split again into three main subgroups: chain isomers, position isomers, and functional group isomers.
- **Chain isomers** are molecules with the same molecular formula, but different arrangements of the carbon ‘skeleton’. Organic molecules are based on chains of carbon atoms, and for many molecules this chain can be arranged differently (**Figure 5**): either as one, continuous chain, or as a chain with multiple side groups of carbons branching off.
- For example, there are two isomers of butane, C_4H_{10} . In one of them (**A**), the carbon atoms lie in a “straight chain” whereas in the other (**B**) the chain is branched.

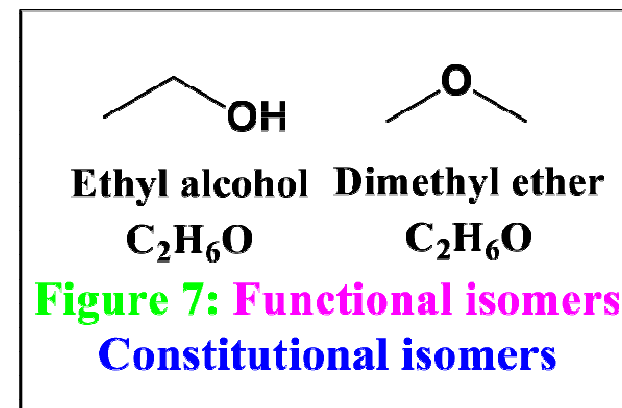


Constitutional or Structural Isomers

- **Positional isomers** are constitutional isomers that have the same carbon skeleton and the same functional groups but differ from each other in the location of the functional groups on or in the carbon chain (**Figure 6**).



- **Functional isomerism** occurs when substances have the same molecular formula but different functional groups. This means that functional isomers belong to different homologous series. They can be alcohols and ethers; aldehydes and ketones; carboxylic acids and esters, etc.

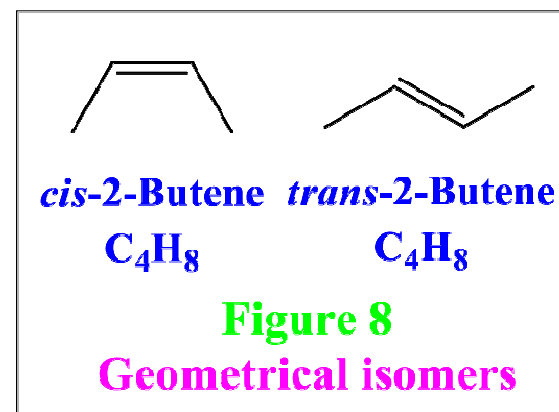


Stereoisomers

- In stereochemistry, stereoisomerism, or spatial isomerism, is a form of isomerism in which molecules have the same molecular formula and sequence of bonded atoms (bonding connectivity), but differ in the three-dimensional orientations of their atoms in space. This contrasts with structural isomers, which share the same molecular formula, but the bond connections or their order differs.
- Stereoisomers have identical IUPAC names (except for a prefix like *cis* or *trans*). Because they differ only in the three-dimensional arrangement of atoms, stereoisomers always have the same functional group(s).
- There are two main types of stereoisomerism-geometric isomerism, and optical isomerism.

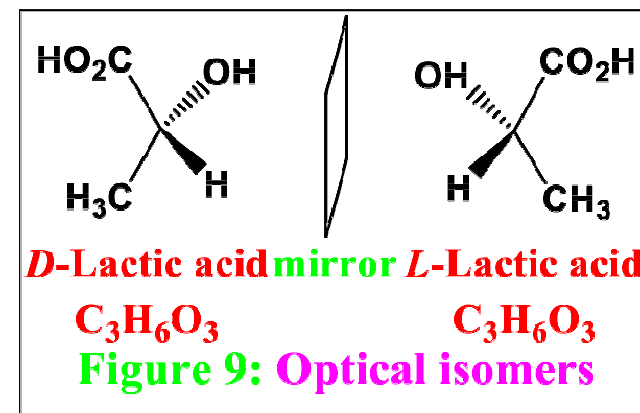
Geometrical Isomers

- Stereoisomerism ascribed to different directional arrangements of specifically located groups in the molecule and usually considered to be caused by prevention of free rotation in parts of the molecule (as by a double bond or a ring).
- This type of isomerism most frequently involves in compounds containing carbon-carbon double bonds with suitable substituents. Rotation of these bonds is restricted, compared to single bonds, which can rotate freely.
- This means that, if there are two different atoms, or groups of atoms, attached to each carbon of the carbon carbon double bond, they can be arranged in different ways to give different molecules (**Figure 8**).



Optical Isomers

- **Optical isomers** are two compounds which contain the same number and kinds of atoms, and bonds (i.e., the connectivity between atoms is the same), and different spatial arrangements of the atoms, but which have non-superimposable mirror images. Each non-superimposable mirror image structure is called an *enantiomer*.
- Optical isomers are so named due to their effect on plane-polarised light, and come in pairs. They usually (although not always) contain a *chiral* centre – this is a carbon atom, with four different atoms (or groups of atoms) attached to it.
- These atoms or groups can be arranged differently around the central carbon, in such a way that the molecule can't be rotated to make the two arrangements align (**Figure 9**).



Classification of Isomers

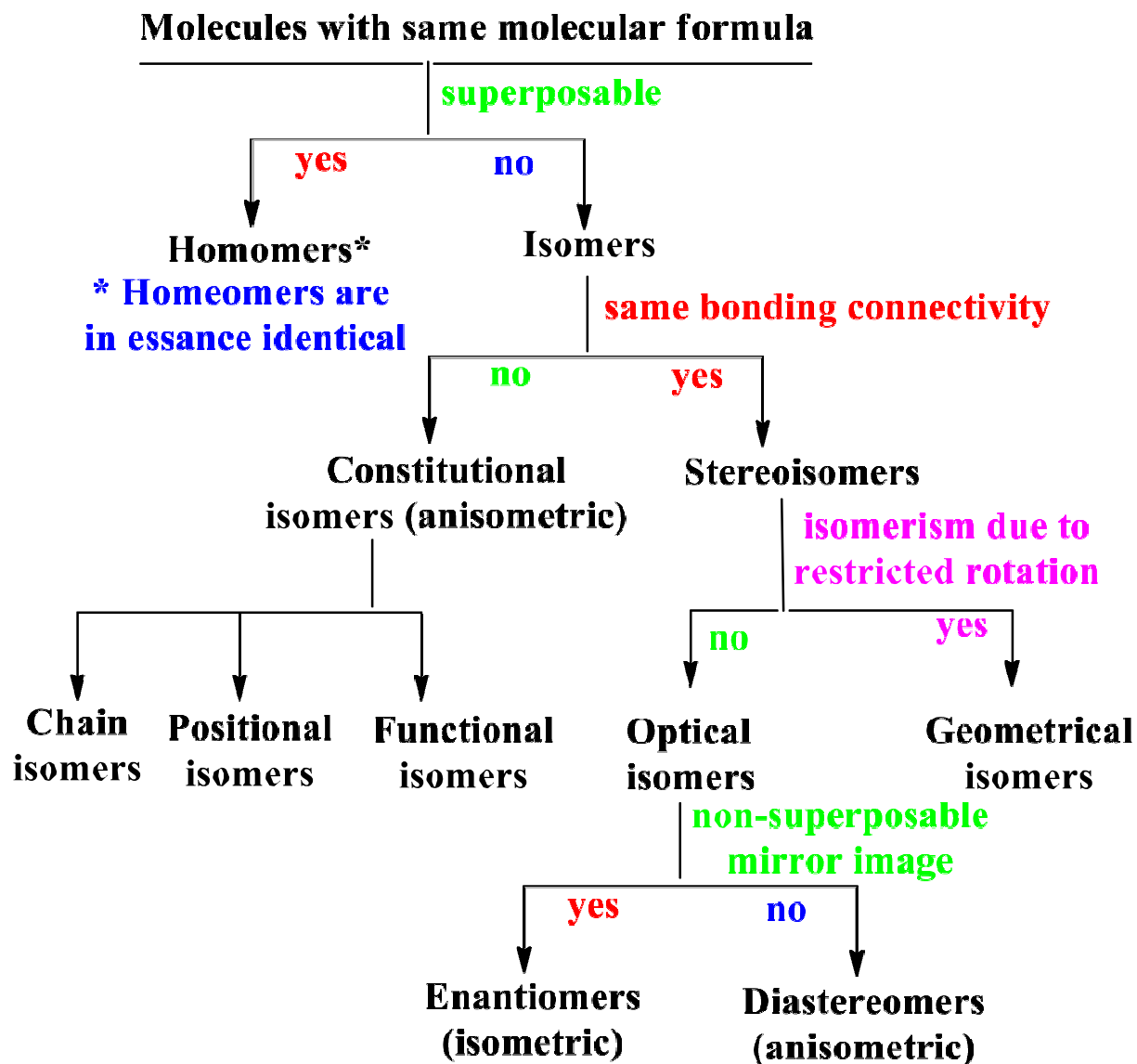
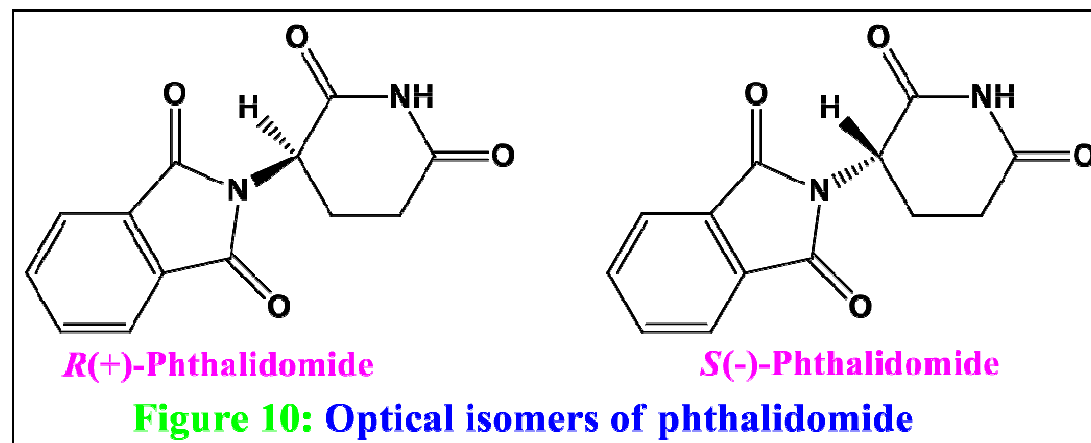


Figure 11: Symmetry-based classification of isomers

The Importance of Isomerism

- Isomers of the same molecule have the potential to have different physical or chemical properties. These differences can have some important implications.
- Thalidomide (**Figure 10**), a drug was prescribed in the 1950s and 60s to treat morning sickness in pregnant women; however, unknown then was that the (*S*)-enantiomer could be transformed in the body into compounds that caused deformities in embryos. The two enantiomers also interconvert in the body, meaning that even if just the (*R*)-enantiomer could be isolated, it would still produce the same effects.
- This emphasised the importance of testing all of the optical isomers of drugs for effects, and is part of the reason why present-day pharmaceuticals have to go through years of rigorous tests, to ensure that they are safe.



THANK YOU