

Chirality of Molecules

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Chirality is the existence of different configurations (three dimensional arrangements) of a substance with an identical chemical formula. The word **Chirality** is derived from the Greek word *chéri* meaning hand. A chiral object has a handedness, hence is not superimposable on its mirror image (Figure 1). These non-superimposable mirror images are called optical isomers or enantiomers. When an organic molecule has a tetrahedral centre, bonded to four different atoms or groups, it is called a chiral centre or a stereogenic centre.

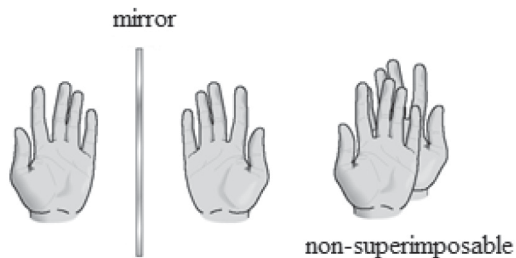


Figure 1: Left and right hands are mirror images, but they are not identical, or superimposable.

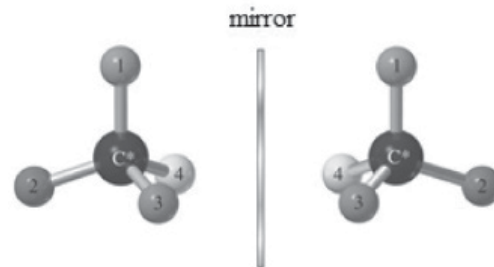


Figure 2: Ball-and-stick representation of an enantiomeric pair.

In contrast, achiral objects such as a plain round ball, a nail, etc. do not have handedness. The chirality of an object is related to its symmetry. If an object possesses a plane, a line or a point in or through it, about which a rotation or reflection leaves the object in a configuration, indistinguishable from the original, it must be achiral.

To distinguish one enantiomer from the other,

organic chemists Robert Sidney Cahn, Christopher Kelk Ingold, and Vladimir Prelog devised a naming system using a set of sequencing rules called Cahn-Ingold-Prelog (CIP) priority rules. According to CIP priority rules, first, each atom bonded to the stereocenter is assigned a priority, based on atomic number. The higher the atomic number, the higher its priority. If identical atoms are attached to the stereogenic centre, then priorities are determined based on the atomic number of the next atom attached. If atoms are bonded to a double or triple bond, they are considered to be bonded to an equivalent number of similar atoms by single bonds. After the priorities are assigned, molecule must be oriented with the lowest priority group pointing away from the observer. After getting the correct view, draw a circular arrow from connecting substituents 1 to 2 to 3 from highest to lowest priority (ignore the substituent 4). If the arrow moves clockwise (right turn) then the configuration is called R. The R notation is originated from the Latin word *rectus*, meaning right. If the arrow moves counter-clockwise (left turn) then the configuration is S (derived from the Latin word *sinister*, meaning left). A stereogenic centre thus has two different designations, R or S, depending on the orientation of the substituents.

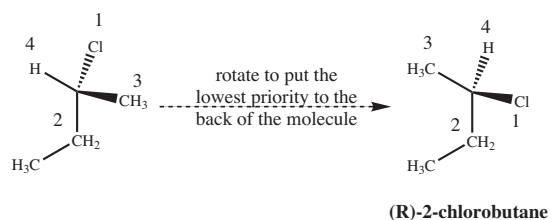


Figure 3: CIP nomenclature of 2-chlorobutane.

Molecules with more than one chiral (stereogenic) center can have enantiomers where all stereocentres are inverted and another type of stereoisomers which differ at least at one, but at less than all stereocentres. Therefore, they are not mirror images, not enantiomers of each other. They are called diastereomers. Molecules with multiple chiral centers may or may not be chiral. A meso compound is an achiral compound that has more than one chiral center and a plane of symmetry.

Chirality is an extremely important phenomenon in the pharmaceutical industry. Many drug molecules possess at least one chiral center, resulting enantiomers. Enantiomers have identical physical properties (such as solubility, melting point, boiling point) and chemical

reactivities towards achiral reagents. However, they are differentiated by chiral environments such as receptors and enzymes. As a consequence, the enantiomers can have different physiological responses in the human body. One classic example of the effect of different enantiomers is thalidomide, where R-thalidomide is responsible for the therapeutic sedative effect and S-thalidomide has teratogenic properties.

Prochirality

An achiral center can be transformed into a chiral center by replacement of a "prochiral" substituent (usually hydrogen) with another substituent or by converting a sp^2 carbon into a chiral sp^3 carbon via an addition reaction.

Replacement of the H atoms in achiral 2-cyclohexylethanol would lead to a chiral R and S mixture as shown below. When the H atom is replaced by Deuterium to result the chiral compound R, then that H atom is called pro-R. When the Hydrogen is replaced by Deuterium to result the chiral compound S, then that H atom is called pro-S (Figure 4). These two hydrogens, HA and HB are called "heterotopic" (from Greek "heteros" = different and "topos" = place) and the carbon which the two hydrogens are attached is called "prochiral center".

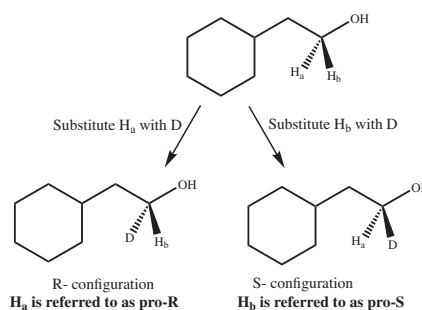


Figure 4: Pro-R and pro-S substituents.

Prochiral carbonyl carbon is a sp^2 hybridized carbon that is reacted with a nucleophile to form a sp^3 hybridized chiral carbon. The two sides of the carbonyl group (front and back) are referred to as "faces". When the priorities (according to the Cahn-Ingold-Prelog priority order) of three substituents of the carbonyl group are oriented clockwise (1 to 2 to 3) on the face we look at, it is called the *re* face (*rectus* face) and the face where the highest to lowest substituents are oriented in counterclockwise is referred to as the *si* face (*sinister* face). Nucleophiles may attack carbonyl groups from the *re* face or the *si*

face. The stereochemistry of the product (enantiomer) depends upon which face of the planar carbonyl group undergoes the nucleophilic attack and the priority of the incoming group (figure 5).

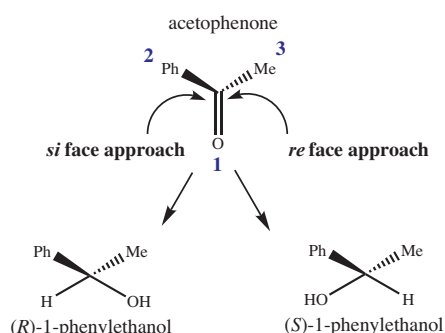


Figure 5: Hydride attack on carbonyl carbon from the re face or the si face.

In biological systems, the two 'identical' groups bound to a prochiral center of an incoming substrate molecule is differentiated since they occupy different regions in three-dimensional space. Similarly, the two planar 'faces' of a prochiral sp^2 - hybridized carbon is also recognized by the enzymes. One example is the NAD^+ catalyzed oxidation of ethanol by yeast alcohol dehydrogenase. Studies with deuterium labelled substrates have shown that the oxidation of ethanol occurs with exclusive removal of the pro-R hydrogen from ethanol and with addition only to the re face of NAD^+ (figure 6).

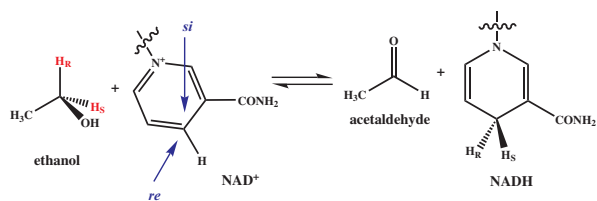


Figure 6: NAD^+ catalyzed oxidation of ethanol by yeast alcohol dehydrogenase.

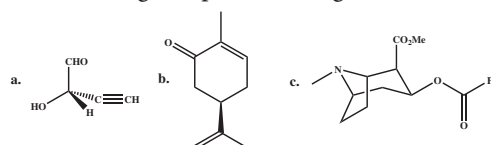
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Problems:

- Determine the configurations of the stereocentres of the following compounds using R/S nomenclature.



- Which enantiomer is formed from attack of a methyl Grignard reagent on the si face of benzaldehyde?

