PHARMACEUTICAL CHEMISTRY

Stereochemistry

Shamim Ahmad
Department of Chemistry
Faculty of Science
Jamia Hamdard
New Delhi-110062

(25-01-2008)

CONTENTS

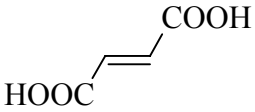
Keywords
Stereoisomers, chiral, configuration, conformation, geometrical isomers, optical isomers, stereoselective, stereospecific, enantiotopic, diastereotopic,

Introduction

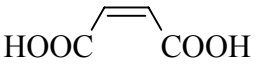
Isomers are different compounds with the same molecular formula. These compounds are grouped into two broad classes: structural isomers and stereoisomers. Structural isomers differ in their bonding sequence; their atoms are connected differently. Stereoisomers have the same bonding sequence but they differ in the orientation of their atoms in space. Thus we can say that stereochemistry is the study of the three dimensional structure of molecules.

Stereoisomers often have remarkably different physical, chemical and biological properties. For example, the *cis* and *trans* isomers of butanedioic acid are a special type stereoisomer called geometric isomers (or *cis-trans* isomer). Both compound have the formula HOOC-CH=CHCOOH but they differ in how these atoms are arranged in space. The *cis* isomer is called maleic acid, and the *trans* isomer is called fumaric acid.

Fumaric acid is an essential metabolic intermediate in both plants and animals but maleic acid is toxic and irritating to tissues.



Fumaric acid
m.p.= 287^0c



Maleic acid
m.p.= 138^0c

Types of Stereoisomers

There are two categories of stereoisomers:

A. Configurational Isomers: Configurational isomers differ in their arrangement in space in such a way that they can not be interconverted without breaking a bond. They are of two types:

i. Geometric isomers

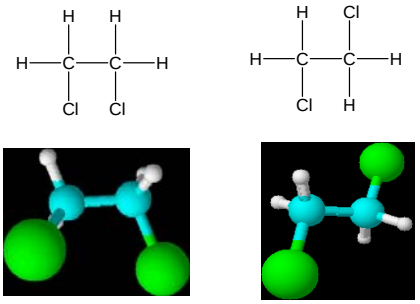
ii. Optical isomers

B. Conformational Isomers: They also differ in spatial arrangement of atoms/groups but they can be interconverted easily by rotation around a single bond.

Geometric isomers

Geometric isomerism (also known as cis-trans isomerism or E-Z isomerism) is a form of stereoisomerism describing the orientation of functional groups within a molecule. In general, such isomers contain double bonds, which cannot rotate, but they can also arise from ring structures, wherein the rotation of bonds is greatly restricted.

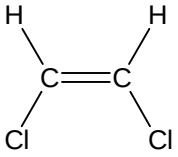
Think about what happens in molecules where there is unrestricted rotation about carbon bonds - in other words where the carbon-carbon bonds are all single. The diagram given below shows two possible configurations of 1,2-dichloroethane.



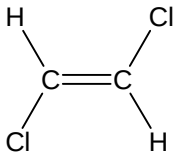
Two types of geometric isomers exist:

1. *Cis* isomers – have identical groups on the same side of the molecule. The two chlorine atoms are locked on the same side of the double bond. This is known as the ***cis*** isomer. (*cis* : from latin meaning "on this side")

2. *Trans* isomers – have identical groups on the opposite site of the molecule. The two chlorine atoms are locked on opposite sides of the double bond. This is known as the ***trans*** isomer. (*trans* : from latin meaning "across").

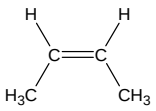


Cis-1,2-dichloroethane

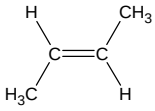


Trans-1,2-dichloroethane

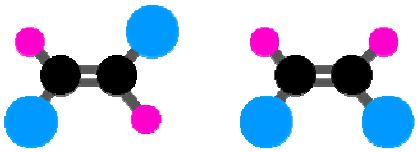
These two molecules aren't the same. The carbon-carbon double bond won't rotate and so you would have to take the models to pieces in order to convert one structure into the other one. The most likely example of geometric isomerism is but-2-ene. In one case, the CH_3 groups are on opposite sides of the double bond, and in the other case they are on the same side.



Cis-but-2-ene



Trans-but-2-ene



These two molecules have similar chemical properties but different physical properties for example *cis* isomer has a higher boiling point than the *trans* isomer.

The table shows the melting point and boiling point of the *cis* and *trans* isomers of 1,2-dichloroethene.

Table 1

Isomer	melting point (°C)	boiling point (°C)
Cis	-80	60
Trans	-50	48

This is common. The same effect can be seen with the *cis* and *trans* isomers of but-2-ene:

Table 2

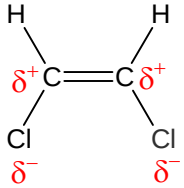
Isomer	melting point (°C)	boiling point (°C)
Cis	-80	60
Trans	-50	48

Why is the boiling point of the cis isomers higher? There must be stronger intermolecular forces between the molecules of the *cis* isomers than between *trans* isomers.

Taking ***1,2-dichloroethene*** as an example:

Both of the isomers have exactly the same atoms joined up in exactly the same order. That means that the Van der Waals dispersion forces between the molecules will be identical in both cases.

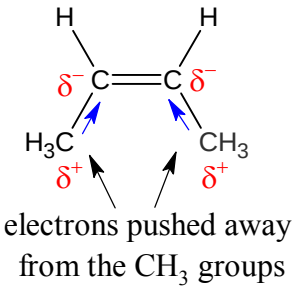
Both molecules contain polar chlorine-carbon bonds, but in the *cis* isomer they are both on the same side of the molecule. That means that one side of the molecule will have a slight negative charge while the other is slightly positive. The molecule is therefore polar.



Because of this, there will be dipole-dipole interactions as well as dispersion forces - needing extra energy to break. That will raise the boiling point.

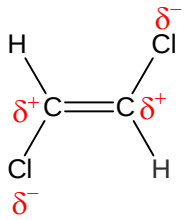
A similar thing happens where there are CH_3 groups attached to the carbon-carbon double bond, as in ***cis-but-2-ene***.

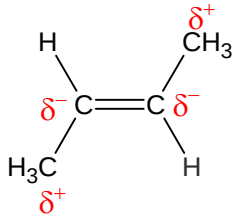
Alkyl groups like methyl groups tend to "push" electrons away from themselves. You again get a polar molecule, although with a reversed polarity from the first example.



electrons pushed away from the CH_3 groups

By contrast, although there will still be polar bonds in the *trans* isomers, overall the molecules are non-polar.





The slight charge on the top of the molecule (as drawn) is exactly balanced by an equivalent charge on the bottom. The slight charge on the left of the molecule is exactly balanced by the same charge on the right.

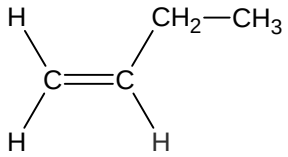
This lack of overall polarity means that the only intermolecular attractions these molecules experience are van der Waals dispersion forces. Less energy is needed to separate them, and so their boiling points are lower.

Why is the melting point of the cis isomers lower? In order for the intermolecular forces to work well, the molecules must be able to pack together efficiently in the solid.

Trans isomers pack better than *cis* isomers. The "U" shape of the *cis* isomer doesn't pack as well as the straighter shape of the *trans* isomer.

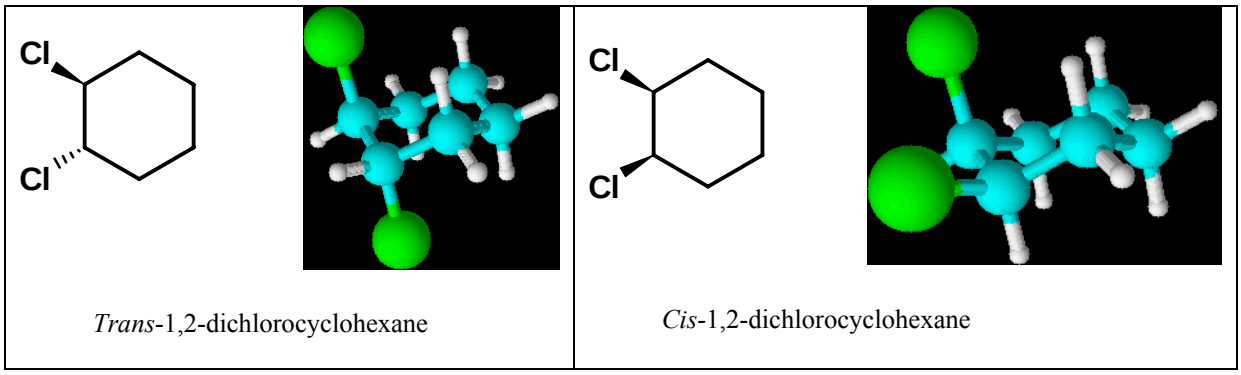
The poorer packing in the *cis* isomers means that the intermolecular forces aren't as effective as they should be and so less energy is needed to melt the molecule - a lower melting point.

Molecules, which have two identical groups on one end of the double bond, cannot exist as geometrical isomers. For example, but-1-ene:



But-1-ene

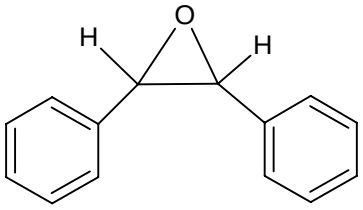
Alicyclic compounds can also display cis-trans isomerism. As an example of a geometric isomer due to a ring structure, consider 1,2-dichlorocyclohexane:



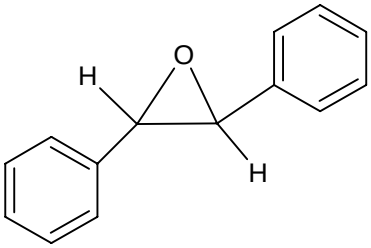
Trans-1,2-dichlorocyclohexane

Cis-1,2-dichlorocyclohexane

Example: Stilbene Oxide



cis-isomer

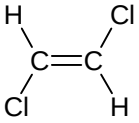


trans-isomer

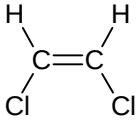
The E-Z System

The problem with the cis-trans system for naming geometric isomers

Consider a simple case of geometric isomerism.



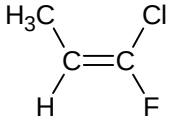
trans-1,2-dichloroethene

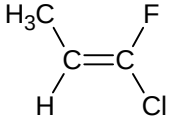


cis-1,2-dichloroethene

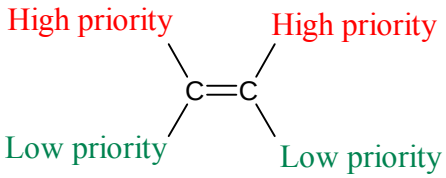
One can tell which is the cis and which the trans form just by looking at them. All you really have to remember is that trans means "across" (as in transatlantic or transcontinental) and that cis is the opposite. It is a simple and visual way of telling the two isomers apart. So why do we need another system?

There are problems, as compounds get more complicated. For example, is the following isomer of 1-chloro-1-fluoro-1-propene the *cis*- or the *trans*- stereoisomer?

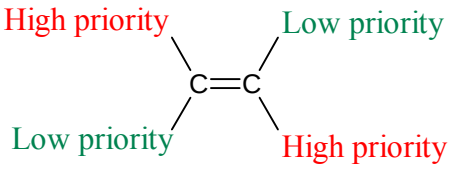




The problem is that *cis* means that the two groups used as references are on the same side of the double bond and *trans* means that they are on opposite sides. But which are the reference groups? Often, two like groups are used as references, as was the case with 1,2-dichloroethene. However, the preceding example does not have two like groups. To designate the configuration of such compounds, a set of rules is needed to determine which of the two groups on each end of the double bond has higher priority and will therefore be used as references. To avoid confusion with the older cis-trans method, the newer method uses different terms to indicate whether the high priority groups are located on the same or opposite sides of the double bond. If the high priority groups are on the *same side* of the double bond, the configuration is designated *Z* (from the first letter of the German word *zusammen,* which means "together"), and if the high priority groups are on opposite side, the configuration is designated as *E* (from the German word *entgegen,* which means "opposite").



Z

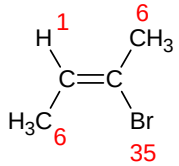


E

The rules for assigning E-Z designations are as follows:

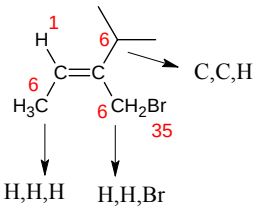
1. Rank atoms directly attached to the double bond according to their **atomic number**
2. If there is a "tie" at any substituent, look at the second, third, etc., until a difference is found
3. Multiple bonds count as **multiples** of that same atom
4. If the highest priority groups are on the **same side** of the double bond, the molecule is **Z**; if the highest priority groups are on **opposite sides**, the molecule is **E**

(atomic number shown in red)



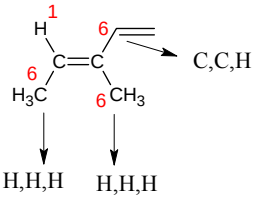
Z-2-bromo-2-butene

Z-3-bromomethyl-4-methyl-2-pentene

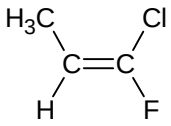


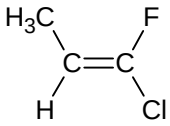
(these indicate the atom attached to each of the atoms directly attached to alkene)

E-3-methyl-1,3-pentadiene



Let's look at the example we've been talking about.



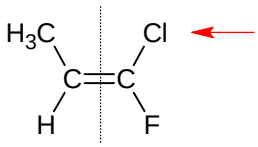


Just consider the first isomer - and look separately at the left-hand and then the right-hand carbon atom. Compare the atomic numbers of the attached atoms to work out the various priorities.

Carbon has higher atomic than hydrogen

Chlorine has higher atomic than flourine

Methyl has the higher priority →

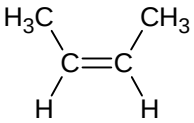


← Chlorine has the higher priority

Notice that the atoms with the higher priorities are both on the same side of the double bond. That counts as the (Z)- isomer.

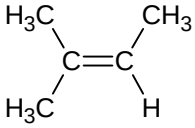
The second isomer obviously still has the same atoms at each end, but this time the higher priority atoms are on opposite sides of the double bond. That's the (E)- isomer.

Comparison of E-Z with cis-trans



Z-2-butene

Cis-2-butene

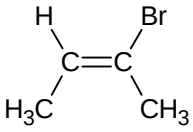


E-2-butene

Trans-2-butene

To a certain extent, the Z configuration can be regarded as the *cis*- isomer and the E as the *trans*- isomers. This correspondence is exact only if the two carbon atoms are identically substituted.

Think about this relatively uncomplicated molecule.



This is clearly a cis- isomer. It has two CH_3 groups on the same side of the double bond. But work out the priorities on the right-hand end of the double bond.

The two directly attached atoms are carbon and bromine. Bromine has the higher atomic number and so has the higher priority on that end. At the other end, the CH_3 group has the higher priority.

That means that the two higher priority groups are on opposite sides of the double bond, and so this is an (E)- isomer - NOT a (Z)-.

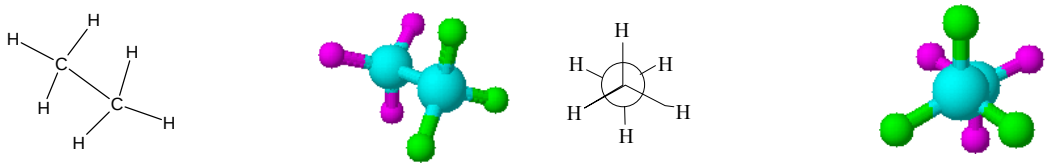
Never assume that you can convert directly from one of these systems into the other. The only safe thing to do is to start from scratch in each case.

B. Conformational isomers

Conformational isomers (or **conformers** or **rotational isomers** or **rotamers**) are stereoisomers produced by rotation about single bonds, and are often rapidly interconverting at room temperature.

Conformational isomers are represented in two ways; in **Sawhorse representations** the carbon-carbon bond are viewed from an oblique angle and indicated spatial orientation by showing all the C-H bonds. **Newman projections** view the carbon-carbon bond directly end-on and represented the two carbon atoms by a circle. Bonds attached to the front carbon are represented by lines going to the centre of the circle, and bonds attached to the rear carbon are represented by lined going to the edge of the circle. The advantage of Newman projections is that they are easy to draw and the relationships among substituents on the different carbon atoms are easy to see.

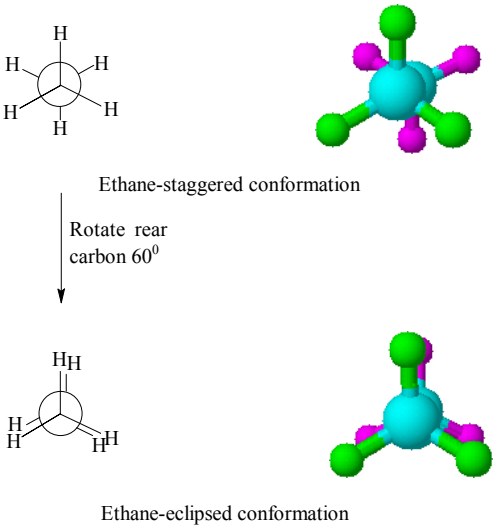
Conformations of Ethane



Sawhorse representation

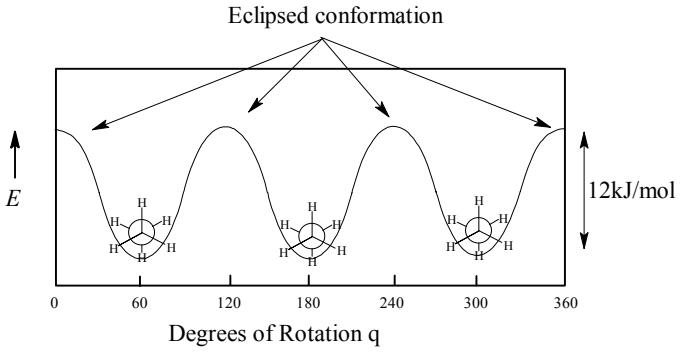
Newman projection

Experiment shows that there is small 12kJ/mol barrier to rotation and that some conformations are more stable than others. Rotation about the **C-C** bond in ethane produces different ***conformations***. Although an infinite number of conformations are possible, the ***staggered*** *and* ***eclipsed*** conformations which represent the most and least stable respectively are the two most important. The differences between these two conformations are most apparent when viewed directly down the **C-C** bond, as in a Newman projection, see below:



The 12 kJ/mol of extra energy present in the eclipsed conformation of ethane is called **torsional strain.** Its cause was the subject of controversy for some years, but most chemists now believe that torsional strain is due to the slight repulsion between electron clouds in the C-H bonds as they pass close by each other in the eclipsed conformer.

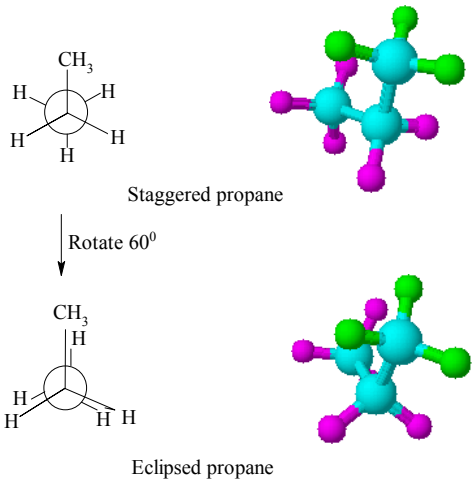
Since the total strain is 12kJ/mol, and since the strain is caused by three equal hydrogen-hydrogen eclipsing interactions, we can assign a value of approximately 4.0 kJ/mol to each single interaction. The barrier to rotation that results can be represented on a graph of potential energy versus degree of rotation in which the angle between C-H bonds on front and back carbons as viewed end-on (the *dihedral angle*) goes full circle from 0^0 to 360^0. Energy minima occur at staggered conformations, and energy maxima occur at eclipsed conformations, as shown below.



Conformations of Propane

Although there are two carbon-carbon single bonds in propane, they are equivalent and rotation produces conformations that are similar to those of ethane except that the "extra" methyl group is interacting with the H atoms. The barrier is slightly higher in propane than in ethane-14kJ/mol versus 12kJ/mol.

In the eclipsed conformer of propane, there are two ethane type hydrogen-hydrogen interactions and one additional interaction between a C-H bond and a C-C bond. Since each hydrogen-hydrogen interaction has an energy cost of 4.0kJ/mol, we can assign a value of 14-(2 x 4.0) = 6.0 kJ/mol to the eclipsing interaction between the C-C bond and the C-H bond.



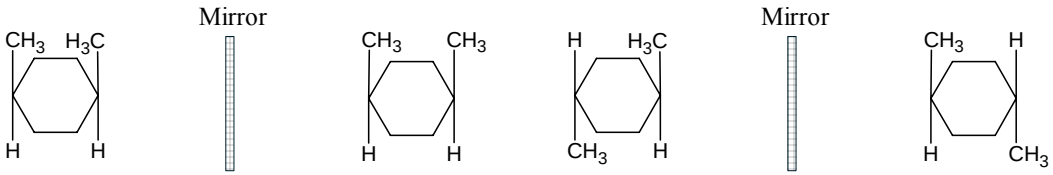
Chirality

Molecules that are not superposable on their mirror images are said to be chiral (Greek: *chair, hand).* Chirality is encountered in three dimensional objects of all sorts. We can tell whether an object is chiral by looking at its mirror image. Every physical object has a mirror image, but a chiral object has a mirror image that is different from the original object. An object and its mirror image are superposable if one of them can be oriented in space so that all its features (corners, edges, points, design etc) correspond exactly to those in the other member of the pair. If this can be done, the object and its mirror image are identical: the original object is achiral. An **achiral** object is one that lacks chirality. Examples of objects lacking chirality are a chair, a spoon, a regular tetrahedron, a cube and perfect sphere.

Chiral objects (non-superimposable mirror image)

Chirality and Enantiomerism

Two molecules are said to be superimposable if they can be placed on top of each other and the three dimensional position of each atom of one molecule coincides with the equivalent atom of the other molecule. For example consider the two geometric isomers of 1,4-dimethyl cyclochxane. The *cis* isomer is achiral ("not chiral") since its mirror image is superimposable on the original molecule.



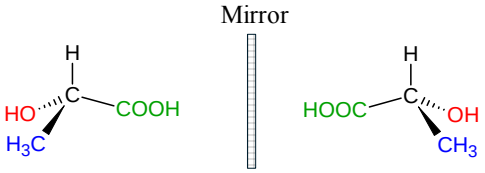
Cis-1,4-dimethylcyclohexane (achiral) Trans-1,4-dimethylcyclohexane (chiral)

The mirror image of trnas 1,4-dimethyl cylcloxehxane is different from the original molecule. Such nonsuperimposable mirror image molecules are called enantiomers. A chiral compound always has an enantiomer (a nonsuperimposable mirror image). An achiral compound always has a mirror image that is the same as the original molecule.

Chiral Carbon Atoms

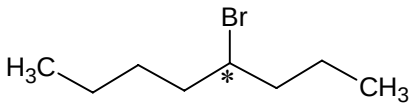
The most common feature (but not the only one) that lends chirality is a carbon atom that is bonded to four different groups. Such a carbon atom is called as chiral carbon atom, an asymmetric carbon atom, or a stereocentre. For example, lactic acid (2-hydroxypropanoic acid) exists as a pair of enantiomers because there are four different groups (-H, -OH, OCH_3, -COOH) bonded to the central carbon atom. The enantiomers are called (+) lactic acid and (-) lactic acid.

Lactic acid: four different groups bonded to central carbon atom



(+)-Lactic acid (-)-Lactic acid

Detecting chiral centre in a complex molecule takes practice because it is not always immediately apparent that four different groups are bonded to a given carbon. For example, 4-bromo-octane is a chiral molecule because four different groups are bonded to C-4, the chiral center (marked by an asterisk):



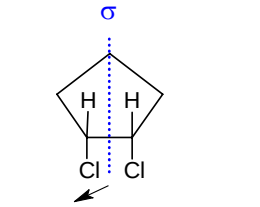
Substituent on C-4

- H
- Br
- CH_2-CH_2-CH_3
- CH_2-CH_2-CH_2-CH_3

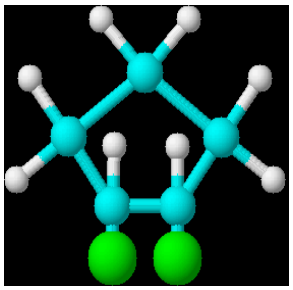
A propyl substituents is similar to butyl substituents but is not identical.

Mirror Plane of Symmetry

It is an imaginary plane passing through the molecule dividing it such that one half is the reflection of the other half. Let us consider the case of *cis*-1,2-dichlorocyclopentane



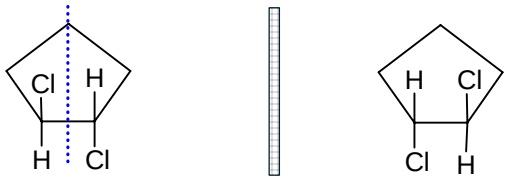
internal mirror plane of symmetry (σ)



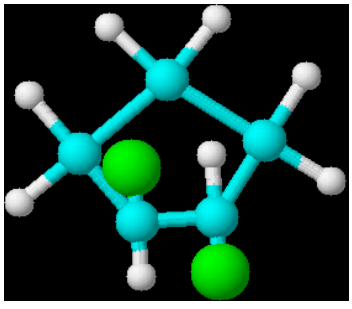
If we draw a line down the middle of *cis*-1,2-dichlorocyclopentane, bisecting a carbon atom and two hydrogen atoms, the part of the molecule that appears to the right of the line is the mirror image of the part on the left. This kind of symmetry is called an **internal mirror plane**, sometimes symbolized by the Greek lowercase letter sigma (σ). Since the right hand side of the molecule is the reflection of the left hand side, the molecules mirror image is the same as the original molecule.

Notice below that the chair *trans* isomer of 1,2-dichlorocyclopentane does not have a mirror plane of symmetry.

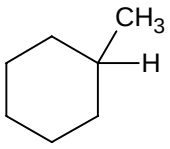
not a plane of symmetry



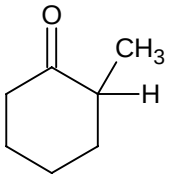
Enantiomers



As other examples, look at methyl cyclohexane and 2-methyl cyclohexanone.

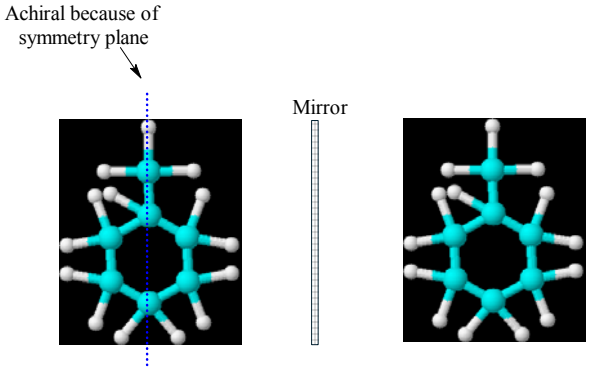


methylcyclohexane
(achiral)



2-methylcyclohexanone
(chiral)

Methyl cyclohexane is achiral because no carbon atom in the molecule is bonded to four different groups. In another way methyl cyclohexane has a symmetry plane passing through the methyl group and through C-1 and C-4 of the ring.

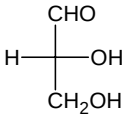


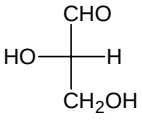
The situation is different for 2-methylcyclohexanone. It has no symmetry plane and is chiral because no C-2 is bonded to four different group; a $–CH_3$ group, an H-atom, a $–COCH_2$- ring bond (C-1), and a $–CH_2$-CH_2- ring bond (C-3).

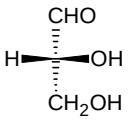
Nomenclature of Chiral Compound

D and L Nomenclature (Relative configuration)

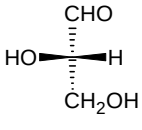
An optical isomer can be named by the spatial configuration of its atoms. *Relative configuration* compares the arrangement of atoms in space of one compound with those of another. The D/L system does this by relating the molecule to glyceraldehyde. Glyceraldehyde is chiral itself, and its two isomers are labeled D and L.





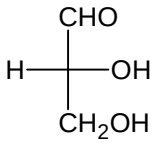


D-configuration

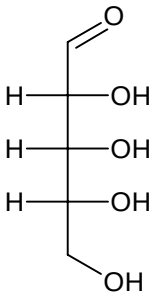


L-configuration

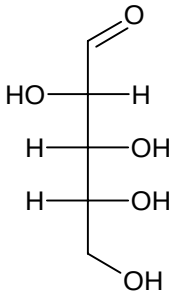
Fischer projection places the most highly oxidised carbon at top and the bottom chiral centre determine D or L.



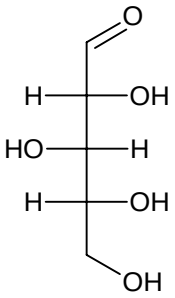
D-Glyceraldehyde



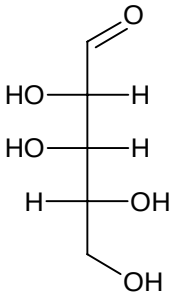
D-Ribose



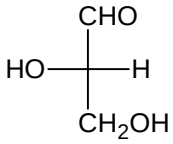
D-Arabinose



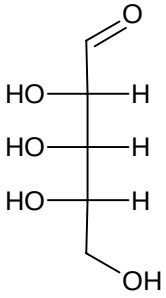
D-Xylose



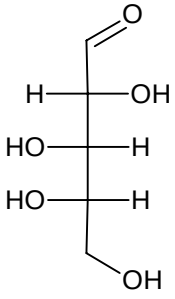
D-Lyxose



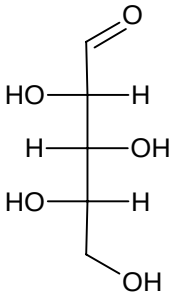
L-Glyceraldehyde



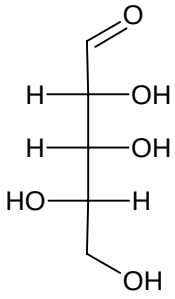
L-Ribose



L-Arabinose



L-Xylose



L-Lyxose

In this system, compounds are named by analogy to glyceraldehyde, which, in general, produces unambiguous designations, but is easiest to see in the small biomolecules similar to glyceraldehyde. One example is the amino acid alanine, which has two optical isomers, and they are labeled according to which isomer of glyceraldehyde they come from. On the other hand, glycine, the amino acid derived from glyceraldehyde, has no optical activity, as it is not chiral (achiral). Alanine, however, is chiral.

The D/L labeling is unrelated to (+)/(−); it does not indicate which enantiomer is dextrorotatory and which is levorotatory. Rather, it says that the compound's stereochemistry is related to that of the dextrorotatory or levorotatory enantiomer of

glyceraldehyde—the dextrorotatory isomer of glyceraldehyde is, in fact, the D isomer. Nine of the nineteen L-amino acids commonly found in proteins are dextrorotatory (at a wavelength of 589 nm), and D-fructose is also referred to as *levulose* because it is levorotatory.

Although this notation is still applied to carbohydrates and amino acids, it required chemical transformations to establish group relationships, and proved to be ambiguous in its general application. A final solution to the vexing problem of configuration assignment was devised by three European chemists: R. S. Cahn, C. K. Ingold and V. Prelog. The resulting nomenclature system is sometimes called the **CIP** system or the **R-S** system.

***R* and *S* Nomenclature**

The most widely accepted system for naming the configuration of chiral carbon atoms is the **Cahn – Ingold – Prelog convention**, which assigns to each carbon atom a letter *R* or *S*. This procedure involves the following steps.

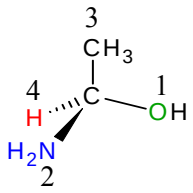
STEP – 1: The four atoms or groups of atoms attached to the chiral carbon atom are assigned priorities in accordance with the following sequence rules:

Sequence Rule 1: Atom with higher atomic numbers gets higher priorities. For example, if the four groups bonded to a chiral carbon atom were H, CH_3, NH_2, and OH, the oxygen atom of OH group (atomic number 8) would have the highest priority, followed by nitrogen atom of NH_2 group (atomic number 7), then by the carbon atom of the methyl group (atomic number 6). Note that we look only at the atomic number of the atom directly attached to the chiral carbon, not the entire group. Hydrogen comes last.

With different isotopes of the same element, the heavier isotopes have higher priorities. For example, tritium (3H) receives a higher priority than deuterium (2H), followed by hydrogen (1H).

Examples of priority for atoms bonded to a chiral carbon:

$$\mathbf{I > S > O > N > {}^{13}C > {}^{12}C > Li > {}^{3}H > {}^{2}H > {}^{1}H}$$

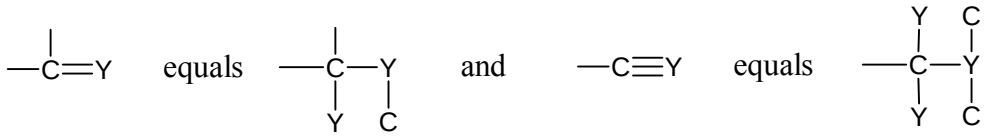


Sequence Rule 2: If rule 1 fails to decide the relative priority of two groups of atoms attached to a chiral carbon atom (e.g. the two groups may be $–CH_3$ and CH_2CH_3, carbon is attached directly, in either case, to the chiral carbon), the priority may be determined by comparing the next atom in the group. If it is still not possible to decide the priority of the two groups, the comparison may be continued to the next atom, and so on. Thus, a isopropyl $–CH(CH_3)_2$ has higher priority over ethyl $–CH_2CH_3$ (because the second atom in $–CH(CH_3)_2$ is C, C, H where as those in CH_3 are H, H, H).

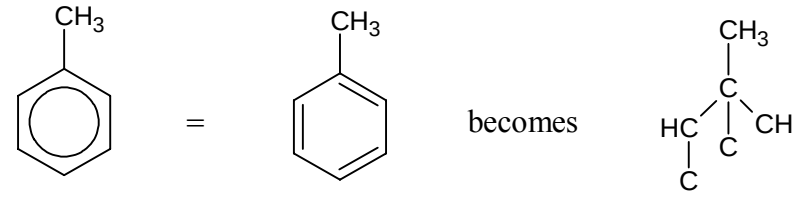
Examples,

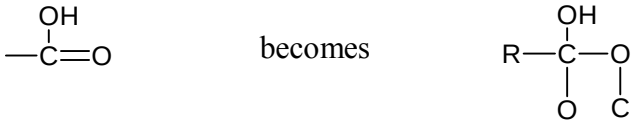
$-CH_2Br > -CHCl_2 > -C(CH_3)CH_2F > -CH(CH_3)_2 > -CH_2CH_3$

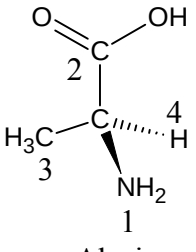
Sequence Rule 3: A doubly or triply bonded atom is equivalent to two or three such atoms. For this method imagine that each pi bond is broken and the atoms at both ends duplicated or triplicated.



For examples;



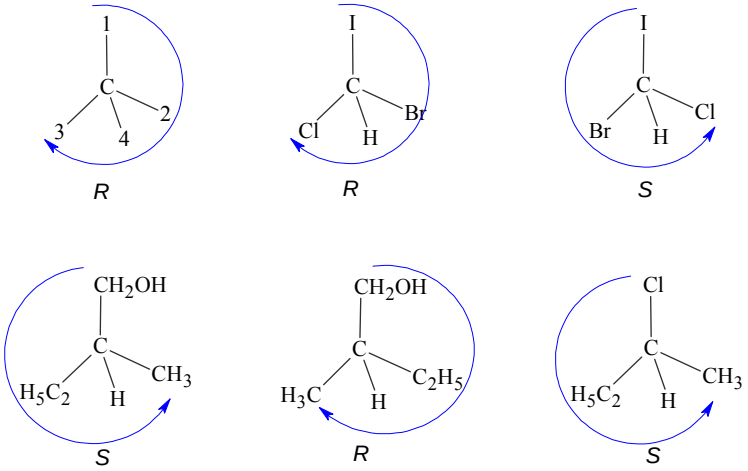




Alanine

STEP – 2: When the priorities of the four atoms or groups attached to an asymmetric or chiral carbon have been decided, the molecule is visualised so that the atom or group of the lowest priority is directed away from us. Draw an arrow from the first priority group, through the second, to the third: if the arrow points clockwise, the chiral carbon atom is

called *R* (Lattin, *rectus*, "upright"). If the arrow points counter clockwise, the chiral carbon atom is called *S* (Lattin, *sinster,* "left").

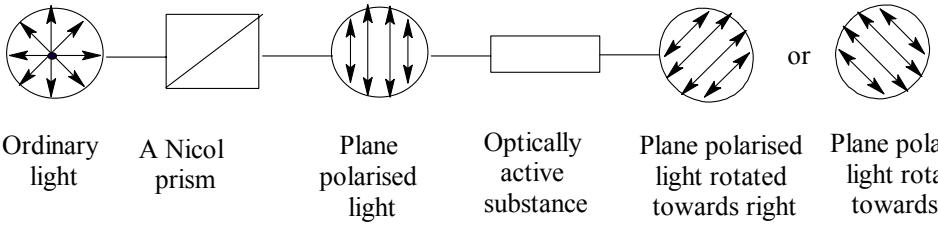


Optical Activity: Plane Polarised Light

Ordinary light consists of rays of different wavelengths vibrating in all directions perpendicular to the direction of propagation. Even monochromatic light, i.e. light of single wavelength consists of waves vibrating in many planes at right angles to the direction of propagation. By passing it through Nicol prism (made of calcite, a special crystalline form of calcium carbonate) however, these vibrations can be so adjusted that they occur in a single plane only. Light whose vibrations occur in only one plane is called the plane polarized light. The device that brings about polarization of light is called a polariser.

Rotation of Polarised Light

Substances which rotate the plane of polarized light are said to be optically active and this property is called optical activity. The phenomenon of optical activity was discovered in 1815 by the French physicist Biot. The extent to which the plane of polarized light rotates varies, among other things, with the substance, and it can be measured with the help of an instrument known as polarimeter. The general arrangements of different parts of polarimeter can be shown as:



The substance which rotate the plane of polarized light to the right (or clockwise direction) are called **dextrorotatory,** from the Greek word *dexios*, meaning "toward the right" while those which rotate to the left (or in the anticlockwise direction) are called **laevorotatory**, from the Latin word *laevus,* meaning "toward the left". These terms are sometimes abbreviated by lowercase *d* or *l*. the direction of rotation is often specified by the (+) or (-) sign of the rotation.

Two enantiomers have identical physical properties, except for the direction they rotate the plane of polarised light.

Enantiomeric compound rotate the plane of polarized light by exactly the same amount but in opposite direction. If *R* isomer rotates the plane 30^0 clockwise the *S* isomer will rotate it 30^0 counterclockwise. If *R* enantiomer rotates the plane 5^0 counterclockwise, the *S* enantiomer will rotate it 5^0 clockwise. *R* and *S* are simply names, while the direction and magnitude of rotation are physical properties that must be measured.

Specific Rotation

The rotation of polarized light by an optically active compound is a characteristic physical property of that compound, just like the boiling point or the density. The rotation (α) observed in polarimeter depends on the concentration of the sample solution, the path length of the cell, and how strongly optically active the compound is. For example, twice as concentrated a solution would give twice the original rotation. Similarly, a 20 cm cell gives twice the rotation observed using a similar, a 10 cm cell.

To use the rotation of polarized light as a characteristic property of a compound, we must standardise the conditions for measurement. We define a compound's **specific rotation** [α] as the rotation found using a 10 cm (1dm) sample cell and concentration of 1g/ml. Other cell lengths and concentrations may be used, as long as the observed rotation is divided by the path length of the cell (l) and the concentration (c).

$$[\alpha] = \frac{\alpha \text{ (observed)}}{c.l}$$

where

α (observed) = rotation observed in the polarimeter

c = concentration, g/ml

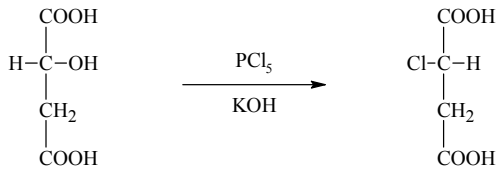
l = length of sample cell (path length), decimeters (dm)

A rotation depends on the wavelength of light used and also on the temperature, so these data are given together with the rotation. Thus the specific rotation $+66.5^0$ of sucrose solution at 20^0c, using sodium light (D line of the sodium spectrum) is denoted as follows;

$$[\alpha]_D^{20} = +66.5^0$$

Reaction at The Chiral Centre

When a reaction takes place at a chiral carbon atom, it may change the configuration of the chiral carbon. An inversion of configuration gives product whose stereochemistry is opposite that of the reactant. Walden in 1893 observed the following conversions associated with enantiomers of maleic acid.



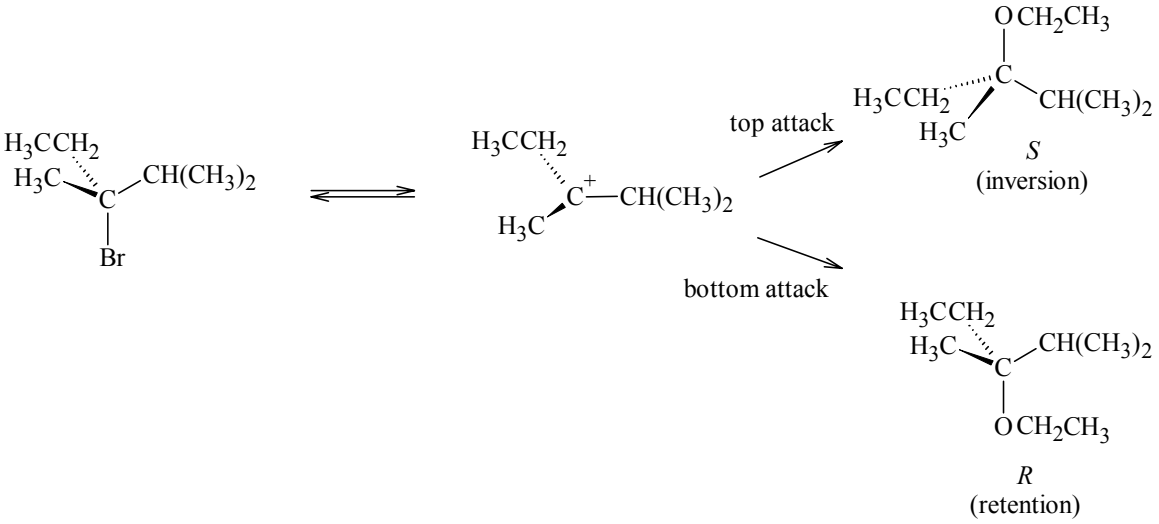
D(+) malic acid L(-) 2-chlorosuccinic acid

Walden first proved that a substitution reaction had inverted the configuration of a chiral carbon. In his honor, a substitution that inverts the configuration at a chiral carbon atom is called a **Walden Inversion**.

Racemisation

When reactions of optically active compounds show neither clean inversion of configuration nor clean retention of configuration, the result is called racemisation. If the product is 50:50 mixture of two chiral enantiomers, the mixture is known as racemic mixture or racemate, and is denoted by the symbol (±) or by the prefix *d,l* to indicate a mixture of dextrorotatory and levorotatory forms. Racemic mixtures show zero optical rotation because they contain equal amounts of (+) and (-) enantiomers.

Racemisation takes place in most reaction where the chiral carbon atom is converted to a carbocation. Carbocations are flat and achiral, and the original stereochemistry is lost. The product from such a reaction is usually racemic mixture. For example;

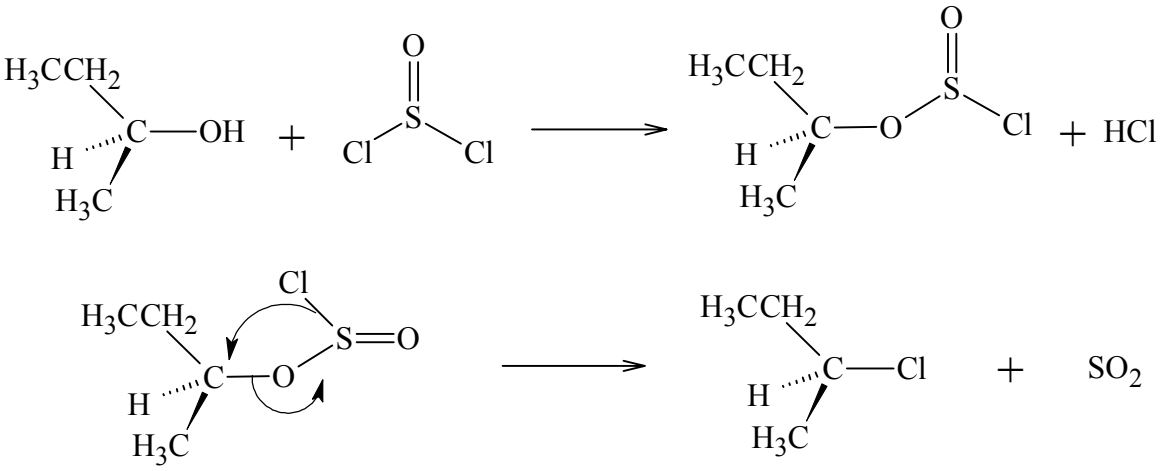


The intermediate carbocation is planar and achiral. Ethanol can attack the carbocation on either face, leading to racemisation. Attack on the top face leads to a product with the (*S*) configuration (inversion of configuration); attack on the bottom face gives the (*R*) configuration (retention of configuration).

Retention of Configuration

If the reaction at chiral carbon atom gives product having the same configuration as the starting material; the result is called retention of configuration. For example, the reaction

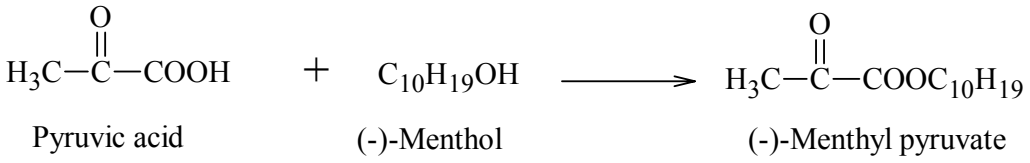
of an alcohol with thionyl chloride provides a method for converting alcohols to alkyl chlorides with retention of configuration.



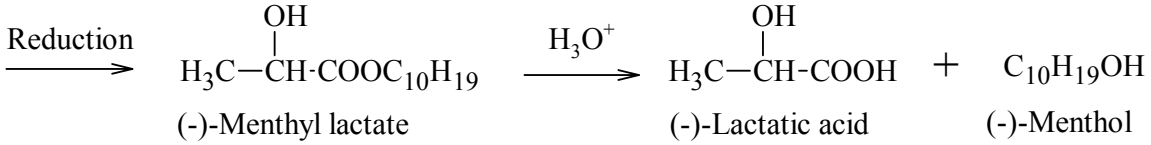
Reaction that generate a New Chiral Carbon Atom (Asymmetric Synthesis)

When propanoic acid (an achiral compound) is brominated, the racemic mixture of α-bromopropionic acid, a chiral compound is formed. In fact, this is a general phenomenon and synthesis of chiral compounds from achiral reagent always yields the racemic mixture. Let us now consider the synthesis of chiral compounds from achiral reagents under the influence of some optically active substance.

Direct reduction of pyruvic acid yields the racemic mixture of lactic acid, as expected. However, when pyruvic acid, pre-esterified with an optically active alcohol for example (-) menthol, is reduced and resulting alcohol hydrolysed, we get predominantly (-) lactic acid.

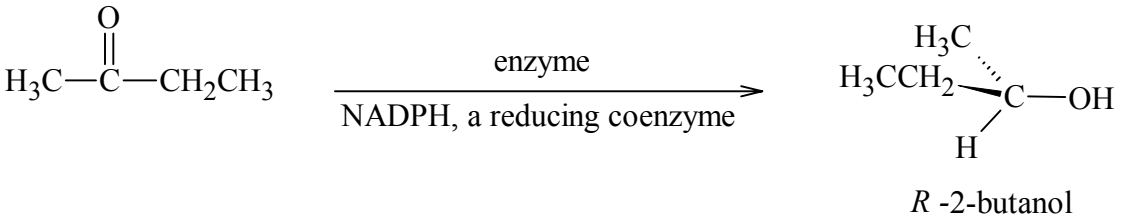


Pyruvic acid (-)-Menthol (-)-Menthyl pyruvate



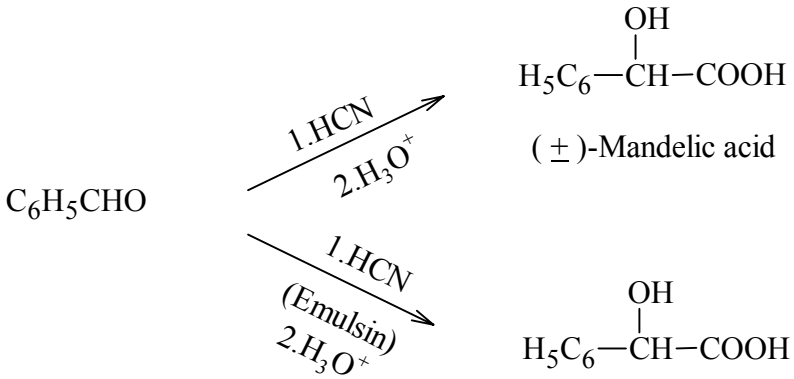
(-)-Menthyl lactate (-)-Lactatic acid (-)-Menthol

The reduction of 2-butanone can be accomplished in a stereospecific manner by an enzyme. In this case an achiral starting material is converted to an optically active product by a chiral catalyst. The enzyme selectively catalyses the addition of hydrogen to just one of the faces of the C=O double bond.



R -2-butanol

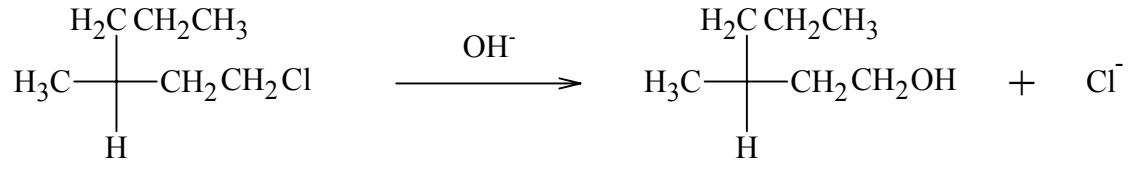
Again when benzaldehyde is treated with hydrogen cyanide and the resulting cyanohydrin is hydrolysed the product is the racemic mixture of mandelic acid. However when the same synthesis is carried out in the presence of an optically active enzyme emulsin, the main product is (-) mandelic acid.



The optically active substance like (-) menthol and emulsin used in the foregoing reaction sequences control the geometry of the main reactants in such a way that specific enantiomers are formed as the main products in subsequent steps. The synthesis of the type described above is referred as **asymmetric synthesis** as they lead to the formation of asymmetric compounds showing optical activity.

Reaction Involving Chiral Centre

If the reaction involving chiral centre does not break any of four bonds to the chiral centre, then the relative positions of the groups bonded to the chiral centre will not change. For example, when (*S*)-1-chloro-3-methylhexane reacts with hydroxide ion, the relative positions of the groups bonded to the chiral centre remain the same because reaction does not break any of the bonds to the chiral centre.

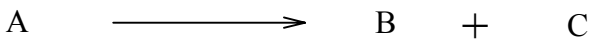


S-1-chloro-3-methylhexane

S-3-methyl-1-hexanol

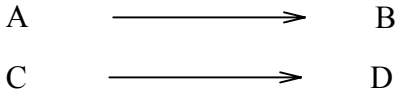
Stereoselective and Stereospecific Reaction

Stereoselective refers to the preferential formation of a stereoisomer. If a reaction that generates a carbon-carbon double bond or a chiral centre in a product leads to the preferential formation of one stereoisomer over another, it is stereoselective reaction. In other words it selects for a particular stereoisomer. Depending on the degree of preference for a particular stereoisomer, a reaction can be described as being moderately stereoselective, highly stereoselective, or completely stereoselective.



More B is formed then C where B and C are stereoisomers.

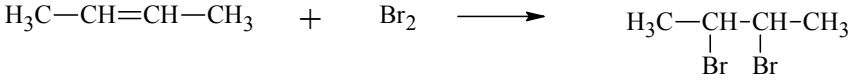
A reaction is stereospecific if reactant can exist as stereoisomers and each stereoisomeric reactant leads to a different stereoisomeric product or a defferent set of stereoisomeric products.



A and C are stereoisomers
B and D are stereoisomers

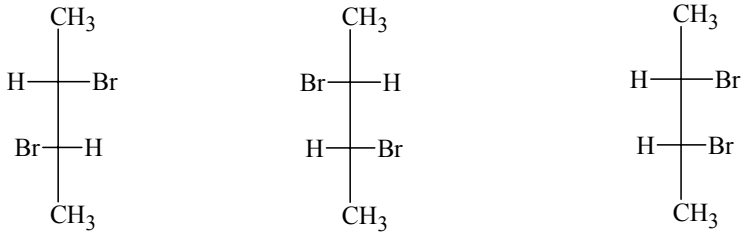
In the preceding reaction, stereoisomer A forms steroisomer B but does not form D, so the reaction is stereoselective in addition to being stereospecific. All stereospecific reactants therefore are also stereoselective. All stereoselective reactions are not stereospecific, however, because there are stereoselective reactions in which the reactant does not have a carbon-carbon double bond or chirality centre, so it can not exist as stereoisomers.

Example of stereospecific and stereoselective reaction: Let us consider the addition reaction of bromine to 2-butene.



2,3-dibromobutane

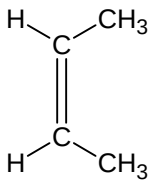
In this reaction two chiral centres are generated, which can exist as a pair of enantiomers and a *meso* compound.



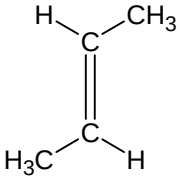
S,S *R,R* *Meso*

Enantiomer

The reactant also exists as stereoisomers i.e. as *cis* and *trans*.

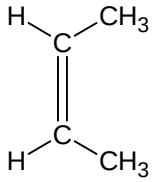


Cis

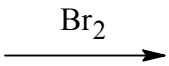


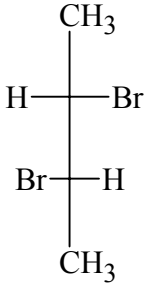
Trans

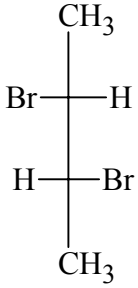
The *cis* isomer yields only racemic 2,3-dibromobutane while the *trans* isomer yields only *meso*-2,3-dibromobutane.



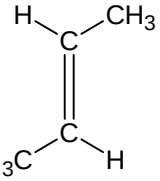
Cis



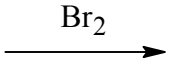


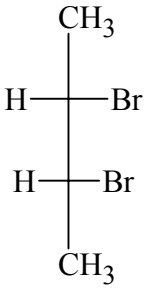


Racemic-2,3-dibromobutane



Trans

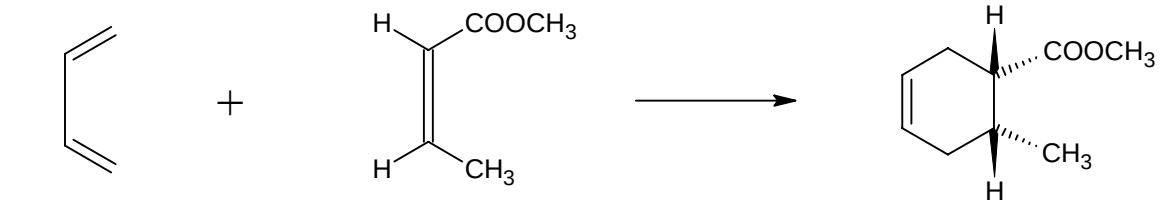




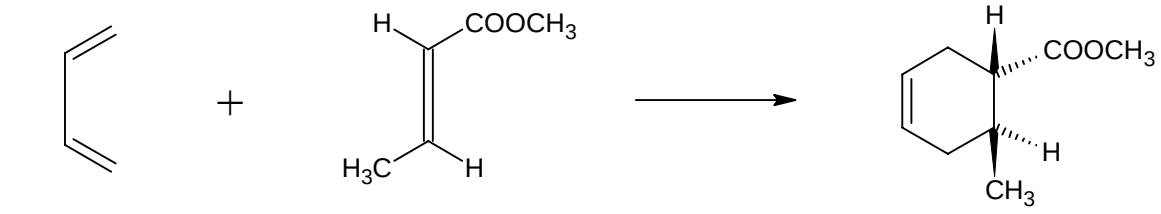
Meso-2,3-dibromobutane

Here two different products are obtained by the reaction of bromine with *cis* and *trans* alkene, so the reaction is stereospecific. Further, *cis* and *trans* alkene yields predominantly one stereoisomer (or one pair of enantiomer) of several possible diastereomers, so the reaction is called stereoselective reaction.

Another example of stereospecific and stereoselective reaction is Diels Alder reaction. The cyclo addition reaction of *cis*-dienophile, such as methyl *cis*-2-butenoate with 1,3-butadiene yields only the *cis*-substituted cyclohexene product. Conversely Diels Alder reaction with methyl *trans*-2-butenoate yields only the *trans*-substituted cycolhexene product.



1,3-Butadiene Methyl (Z)-2-butenoate *Cis*-product

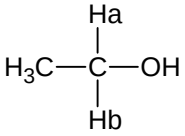


1,3-Butadiene Methyl (E)-2-butenoate *Trans*-product

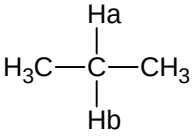
Since two different products are obtained from two stereoisomeric reactants (*cis* and *trans*), the reaction is said to be stereospecific reaction.

Enantiotopic and Diastereotopic Ligands

If a carbon is bonded to two hydrogens and to two different groups, the two hydrogens are called **enantiotopic hydrogens.** For example the two hydrogens (H_a and H_b) in the CH_2 group of ethanol are enantiotopic hydrogens because the other two groups bonded to the carbon (CH_3 and OH) are not identical. They are called enantiotopic hydrogens because replacing one of them by a deuterium (or any other atom or group other than CH_3 or OH) would make the compound an enantiomer. The two hydrogens (Ha and Hb) in the CH_2 group of propane are not enantiotopic hydrogens because the other two groups bonded to the carbon (CH_3 and CH_3) are identical. The Ha and Hb hydrogens of propane are called **homotopic hydrogens**.

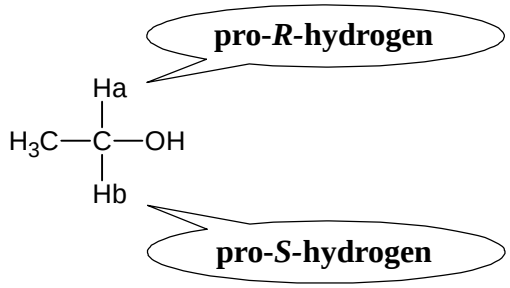


H_a and H_b are enantiotopic hydrogens



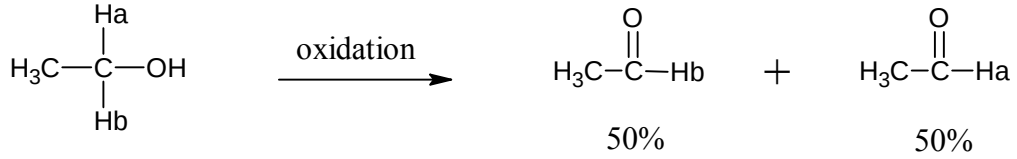
H_a and H_b are homotopic hydrogens

If one of the enantiotopic hydrogen in ethanol were replaced by a deuterium, the carbon to which the enantiotopic hydrogens are attached would become a chirality centre. If the H_a hydrogen were replaced by a deuterium, the chirality centre would have the *R* configuration. Thus, the H_a hydrogen is called **pro-*R* hydrogen.** The H_b hydrogen is called the **pro-*S* hydrogen** because if it were replaced by a deuterium, the chirality centre would have the *S* configuration.

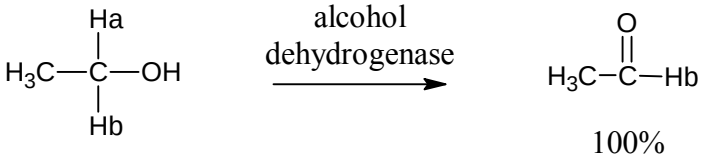


The carbon to which the enantiotopic hydrogens are attached is called **prochirality centre** because it would become a chirality centre if one of the hydrogens were replaced by a deuterium (or any group other than CH_3 or OH) because four different groups would then be bonded to the carbon. The molecule containing the prochirality centre is called a prochiral molecule because it would become a chiral molecule if one of the hydrogens were replaced.

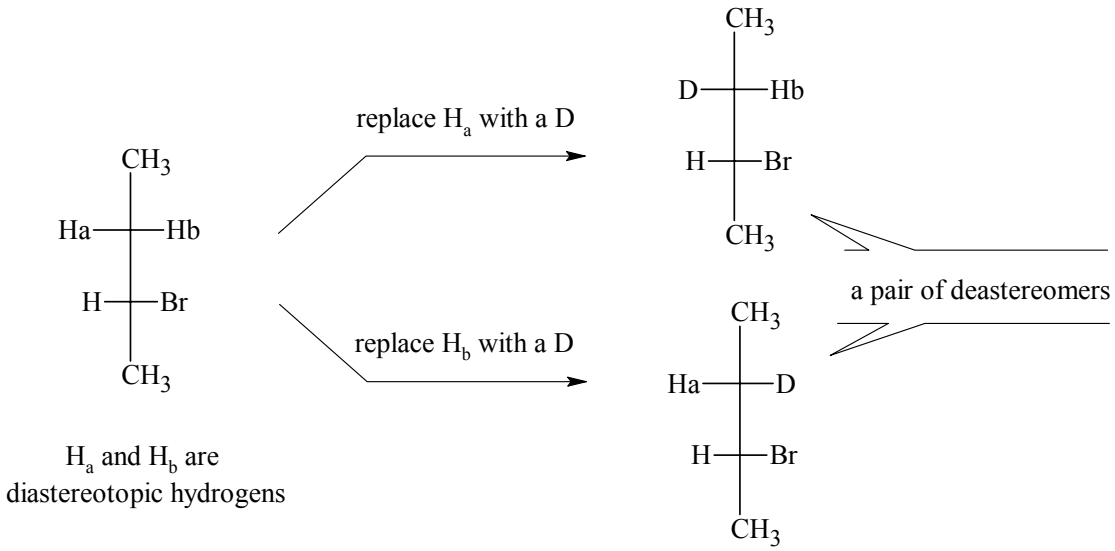
The pro-*R* and pro-*S* hydrogens are chemically equivalent, so they have the same chemical reactivity and cannot be distinguished by achiral chemical reagents. For example, when ethanol is oxidized to acetaldehyde, one of the enantiotopic hydrogen is removed. Because the two hydrogens are chemically equivalent, half the product results from removing the H_a hydrogen and the other half results from removing the H_b hydrogen.



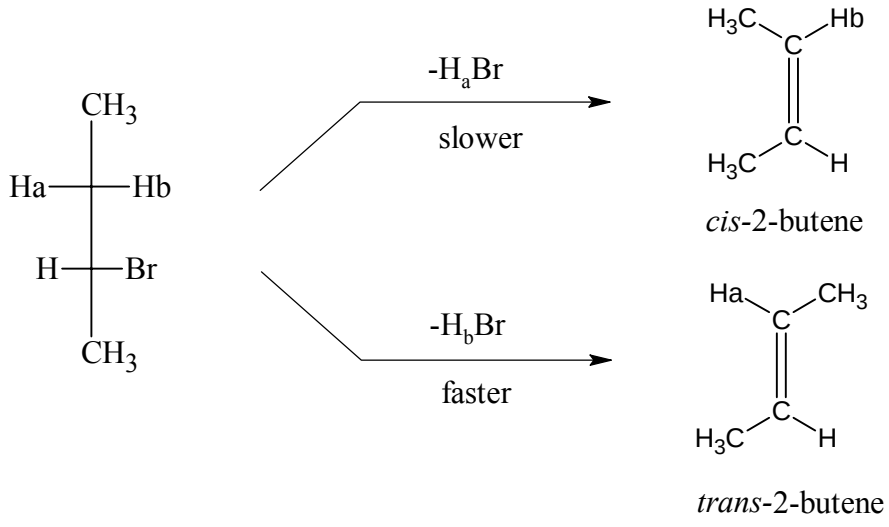
Enantiotopic hydrogens, however, are not chemically equivalent in enzyme-catalysed reactions. An enzyme can distinguish between them because an enzyme is chiral. For example, when the oxidation of ethanol to acetaldehyde is catalaysed by the enzyme alcohol dehydrogenase, only the H_a hydrogen is removed.



If a carbon is bonded to two hydrogens and replacing each of them in turn with deuterium (or another group) creates a pair of diastereomers, the hydrogens are called **diastereitopic hydrogens.**

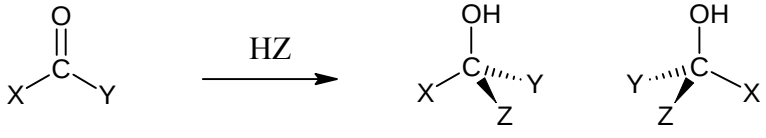


Unlike enantiotopic hydrogens, diastereotopic hydrogens do not have the same reactivity with achiral reagents. For example, because *trans*-2-butene is more stable than *cis*-2-butene, removal of H_b and Br to form *trans*-2-butene occurs faster than removal of H_a and Br to form *cis*-2-butene.



Enantiotopic and Diastereotopic Faces

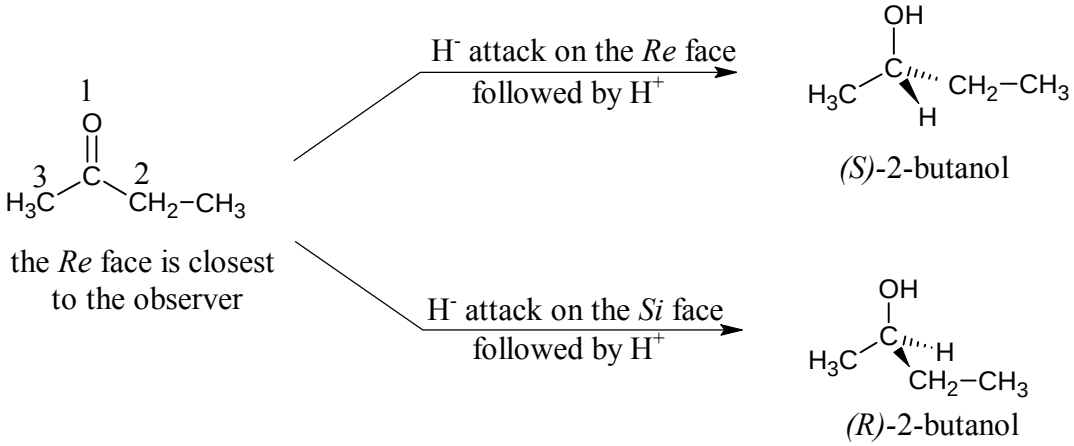
A carbonyl carbon bonded to two different substituents is a **prochiral carbonyl carbon** because it will become a chirlaity centre if it adds a group unlike either of the groups already bonded to it. The addition product will be a pair of enantiomers.



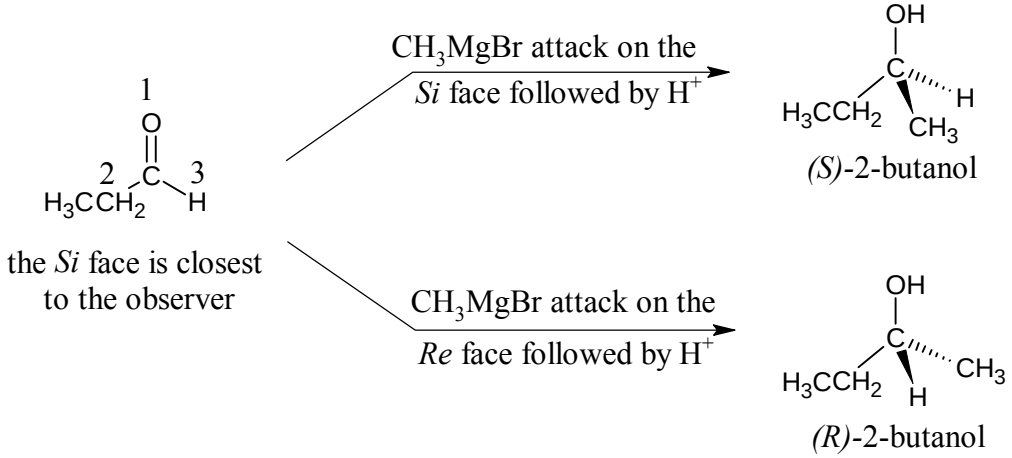
a pair of enantiomers

The carbonyl carbon and the three atoms attached to it define a plane. The nucleophile can approach either side of the plane. One side of the carbonyl compound is called the *Re* face, and the other side is called the *Si* face; *Re* is for *rectus* and *Si* is for *sinister* (similar to *R* and *S*). To distinguish between the *Re* and *Si* faces, the three groups attached to the carbonyl carbon are assigned priorities using the Cahn-Ingold-Prelog system of priorities that is used in *E, Z* and *R, S* nomenclature. The *Re* is the one closest to the observer when decreasing priorities (1>2>3) are in a clockwise direction, and the *Si* face is the opposite face- the one closest to the observer when decreasing priorities are in a counterclockwise direction.

Attack by a nucleophile in the *Re* face forms one enantiomer, whereas attack on the *Si* face forms the other enantiomer. For example, attack by hydride ion on the *Re* face of butanone forms (*S*)-2-butanol, and attack on the *Si* face forms *(R)*-2-butanol.



Whether attack by a nucleophile on the *Re* face forms the *R* or *S* enantiomer depends on the priority of the attacking nucleophile compared with the priorities of the groups attached to the carbonyl carbon, for example, attack by hydride ion on the *Re* face of butanone forms *(S)*-2-butanol, but attack by a methyl Grignard reagent on the *Re* face of propanal forms *(R)*-2-butanol.



Because the carbonyl carbon and the three atoms attached to it define a plane, the *Re* and *Si* faces have an equal probability of being attacked. Consequently, an addition reaction forms equal amounts of the two enantiomers.

Depending upon the structure of the rest of the molecule, there can also be diastereotopic faces: attachment of a ligand to one or the other of them gives rise to one or the other of a pair of diastereomers.

Suggested Readings

- Stereochemistry Conformation and Mechanism by P.S. Kalsi, 6th edition.
- Organic Chemistry by Paula Yurkanis Bruice, 3rd edition.
- Organic Chemistry by Robert T. Morrison and Robert Neilson Boyd, 6th edition.
- Organic Chemistry by K. Peter C. Vollhardt and Neil E. Schore, 4th editeion.