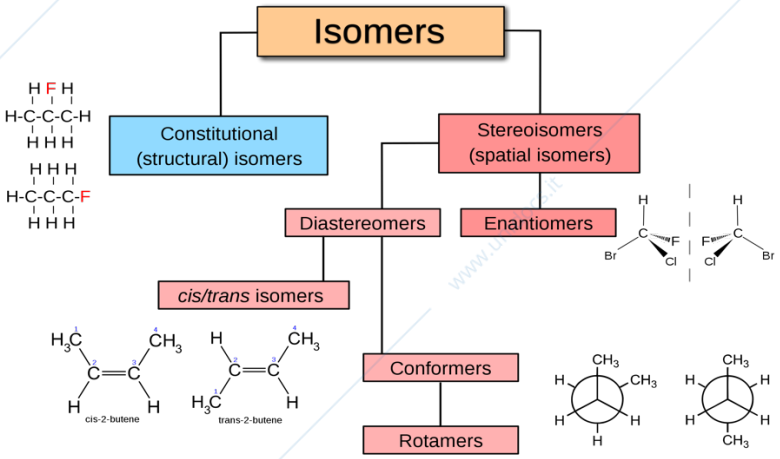
STEREOCHEMISTRY

The study of stereochemistry focuses on **STEREOISOMERS**, which by definition have the **same molecular formula and sequence of bonded atoms** (constitution) but **differ in the three-dimensional orientations of their atoms in space**. For this reason, it is also known as 3D chemistry—the prefix "stereo-" means "three-dimensionality".

This contrasts with **STRUCTURAL ISOMERS**, which share the **same molecular formula, but the bond connections or their order differs.** By definition, molecules that are stereoisomers of each other represent the same structural isomer.



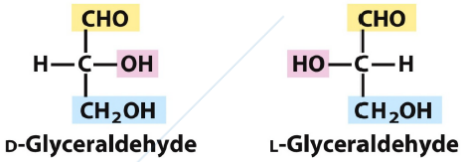
Enantiomers: molecules that aren't superimposable mirror images, but they aren't superimposable.
Diastereomers: stereoisomers not related through a reflection operation. They aren't mirror images of each other.
Epimers: in the special case where two diastereomers differ at only one chirality center but are the same at all others.

ENANTIOMERS and the Tetrahedral Carbon

Molecules that are not superimposable mirror images are kinds of stereoisomers called enantiomers from the greek word "*enantio",* meaning "opposite". Enantiomers are related to each other as a right hand is related to a left hand, they are mirror images of each other that cannot appear identical simply by rotation and result whenever a tetrahedral carbon is bonded to four different substituents.

Ex. Hands are mirror images. If my palms are facing each other and lined them up the thumb and the pinky meet, they are mirror images.
If I place one hand on the top of the other, they won't perfectly line up, so they aren't superimposable.

Enantiomers, also known as **optical isomers**, are two stereoisomers that are related to each other by a reflection: they are mirror images of each other that are non-superposable. Human hands are a macroscopic analogue of this.
For example, both enantiomers of the lactic acid are found in sour milk, but only the (+) enantiomer occurs in muscle tissue.



The meaning of **SYMMETRY PLANE**.
An object like the flask has a symmetry plane cutting through it, making right and left halves mirror images. An object like a hand has no symmetry plane; the right "half" of a hand is not a mirror image of the left half.

A molecule that has a plane of symmetry in any of its possible conformations must be identical to its mirror image and hence must be nonchiral, or achiral.

CHIRALITY

In chemistry we say that anything with a non-superimposable mirror images has chirality.
The simplest example of chirality is a carbon with four different groups attached to it.
The central carbon is the chiral or chirality centre.
If we try to line them up we found that they aren't superimposable but they are mirror images so they are also called enantiomers, they are opposite images.
Esempio a catena aperta: lactic acid (chiral). Esempio ciclico: 2-methilcyclohexanone

ACHIRALITY

In chemistry we say that anything with a superimposable mirror images has achirality.
Esempio a catena aperta: propanoic acid (achiral). Esempio ciclico: methylcyclohexane

The most common, although not the only, cause of chirality in an organic molecule is the presence of a carbon atom bonded to four different groups—for example, the central carbon atom in lactic acid. Such carbons are now referred to as chirality centers, although other terms such as *stereocenter, asymmetric center,* and *stereogenic center* have also been used formerly. Note that *chirality* is a property of the entire molecule, whereas a chirality *center* is the *cause* of chirality.

A molecule with *n* chirality centers can have up to 2^n stereoisomers (although it may have fewer).

Take the amino acid threonine (2-amino-3-hydroxybutanoic acid), for example. Since threonine has two chirality centers (C2 and C3), there are four possible stereoisomers.

The four stereoisomers of 2-amino-3-hydroxybutanoic acid can be grouped into two pairs of enantiomers. The 2*R*,3*R* stereoisomer is the mirror image of 2*S*,3*S*, and the 2*R*,3*S* stereoisomer is the mirror image of 2*S*,3*R*. But the 2*R*,3*R* isomer and the 2*R*,3*S* isomer they are *diastereomer.*

OPTICAL ACTIVITY

The study of stereochemistry originated in the early 19th century during investigations by the French physicist Jean-Baptiste Biot into the nature of *plane polarized light.* A beam of ordinary light consists of electromagnetic waves that oscillate in an infinite number of planes at right angles to the direction of light travel. When a beam of ordinary light is passed through a device called a *polarizer,* however, only the light waves oscillating in a **single plane** pass through and the light is said to be plane-polarized. Light waves in all other planes are blocked out. Biot made the remarkable observation that when a beam of plane-polarized light passes through a solution of certain organic molecules, such as sugar or camphor, the plane of polarization is rotated. Not all organic substances exhibit this property, but those that do are said to be optically active.

In enantiomer molecules can rotated the polarized light on left or right.
Molecules that turn on the left are called laevorotatory and they're given the symbol L/-.
The one which turn to right are called dextrorotatory D/+.

The specific rotation, $[a]_D$, of a compound is defined as the observed rotation when light of 589.6 nanometer wavelength is used with a sample pathlength of 1 decimeter and a sample concentration *C* of 1 g/mL. (Light of 589.6 nm, the so-called sodium D line, is the yellow light emitted from common sodium lamps.) $[a]_D$ is a physical constant characteristic of a given optically active compound.

Polarimetry is an experimentally determined property, which means we have stick enantiomers in a polarimeter to see how they rotate light.
Opposite enantiomers will turn plane-polarized light in the same amount in opposite directions.

SEQUENCE RULES FOR SPECIFYING CONFIGURATION

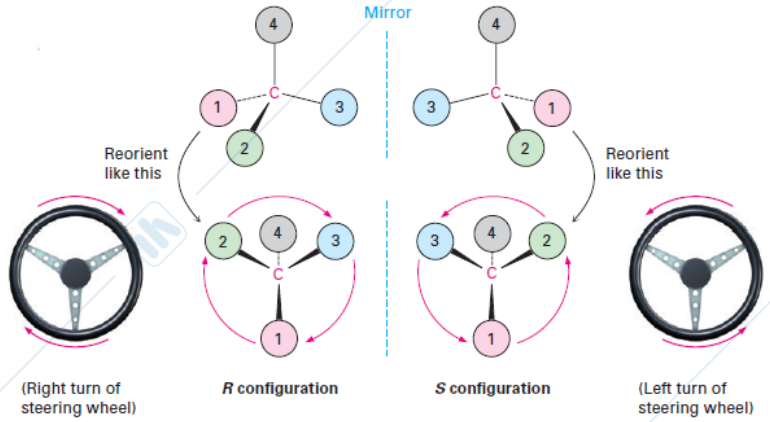
To name enantiomers, we adopt the Cahn-Ingold-Prelong convention, where the chiral centers of a molecule are labeled R for right-handed and S for left-handed.
Like all puzzles in organic chemistry we have rules we can follow and a pattern we can learn.
This convention said that the first step is assigning the priority to the four group around the chiral center. We have to pay attention to the atomic number.

Rule 1 Look at the four atoms directly attached to the chirality center and assign priorities in order of decreasing atomic number. The atom with the highest atomic number is ranked first; the atom with the lowest atomic number (usually hydrogen) is ranked fourth.

Rule 2 If a decision can't be reached by ranking the first atoms in the substituents, look at the second, third, or fourth atoms outward until a difference is found.

Rule 3 Multiple-bonded atoms are equivalent to the same number of single-bonded atoms.

Having assigned priorities to the four groups attached to a chiral carbon, we describe the stereochemical configuration around the carbon by orienting the molecule so that the group of lowest priority (4) points directly back, away from us. We then look at the three remaining substituents, which now appear to radiate toward us like the spokes on a steering wheel. If a curved arrow drawn from the highest to second-highest to third-highest priority substituent (1 n 2 n 3) is clockwise, we say that the chirality center has the *R* configuration (Latin *rectus,* meaning "right"). If an arrow from 1 n 2 n 3 is counterclockwise, the chirality center has the *S* configuration (Latin *sinister,* meaning "left").



One further point needs to be mentioned—the matter of absolute configuration.
How do we know that our assignments of *R*, *S* configuration are correct in an absolute, rather than a relative, sense? Since we can't see the molecules themselves, how do we know that the *R* configuration belongs to the dextrorotatory enantiomer of lactic acid? This difficult question was finally solved in 1951, when J. M. Bijvoet of the University of Utrecht reported an X-ray spectroscopic method for determining the absolute spatial arrangement of atoms in a molecule. Based on his results, we can say with certainty that the *R*, *S* conventions are correct.

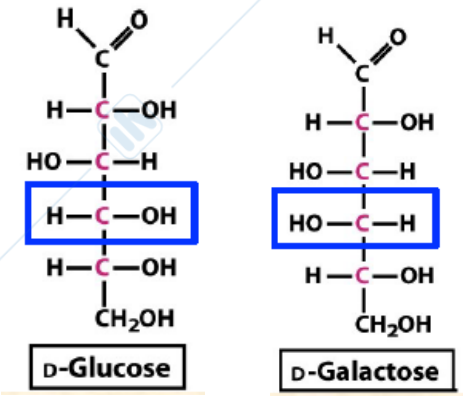
DIASTEREOMERS

Diastereomers are stereoisomers not related through a reflection operation. They are not mirror images of each other.

Enantiomers have opposite configurations at *all* chirality centers, whereas diastereomers have opposite configurations at *some* (one or more) chirality centers but the same configuration at others. Most biological molecules are chiral, and usually only one stereoisomer is found in nature.

EPIMERS

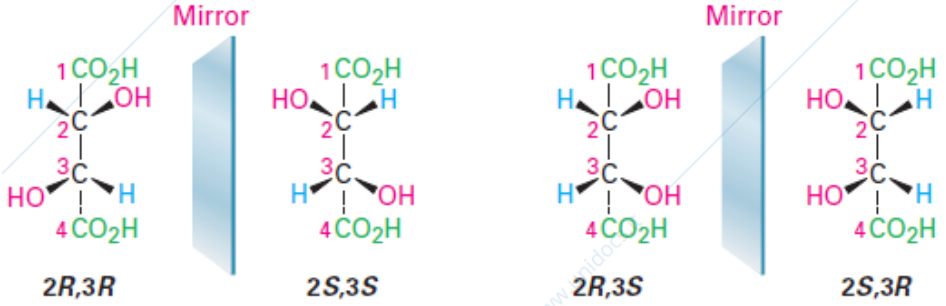
In the special case where two diastereomers differ at only one chirality center but are the same at all others, we say that the compounds are epimers. Cholestanol and coprostanol, for instance, are both found in human feces and both have nine chirality centers. Eight of the nine are identical, but the one at C5 is different. Thus, cholestanol and coprostanol are *epimeric* at C5.



MESO COMPOUNDS

A **meso compound** or **meso isomer** is a non-optically active member of a set of stereoisomers, at least two of which are optically active. This means that despite containing two or more stereogenic centers, the molecule is not chiral.

Let's look at one more example of a compound with more than one chirality center, the tartaric acid used by Pasteur. The four stereoisomers can be drawn as follows:



The mirror-image 2*R*,3*R* and 2*S*,3*S* structures are not identical and therefore represent a pair of enantiomers. A close look, however, shows that the 2*R*,3*S* and 2*S*,3*R* structures *are* identical, as can be seen by rotating one structure 180°.

The 2*R*,3*S* and 2*S*,3*R* structures are identical because the molecule has a plane of symmetry and is therefore achiral. The symmetry plane cuts through the C2–C3 bond, making one half of the molecule a mirror image of the other half. Because of the plane of symmetry, the molecule is achiral, despite the fact that it has two chirality centers.

Compounds that are achiral, yet contain chirality centers, are called meso compounds.
Thus, tartaric acid exists in three stereoisomeric forms: two enantiomers and one meso form.

The (+)- and (-)-tartaric acids have identical melting points, solubilities, and densities but differ in the sign of their rotation of plane-polarized light. The meso isomer, by contrast, is diastereomeric with the (+) and (-) forms. As such, it has no mirror-image relationship to (+)- and (-)-tartaric acids, is a different compound altogether, and has different physical properties.

RACEMIC MIXTURES AND THE RESOLUTION OF ENANTIOMERS

Racemic mixtures show no optical rotation because the (+) rotation from one enantiomer exactly cancels the (-) rotation from the other. Such a mixture is called a racemic mixture, or *racemate,* and is denoted either by the symbol or the prefix *d*, *l* to indicate an equal mixture of dextrorotatory and levorotatory forms.
The most common method of resolution uses an acid–base reaction between a racemic mixture of chiral carboxylic acids (RCO_2H) and an amine base (RNH_2) to yield an ammonium salt.

The two salts are diastereomers; they are different compounds, with different chemical and physical properties. It may therefore be possible to separate them by crystallization or some other means. Once separated, acidification of the two diastereomeric salts with a strong acid then allows us to isolate the two pure enantiomers of lactic acid and to recover the chiral amine for reuse.

ADDITION REACTIONS OF H2O

There are **two possible scenarios** for the starting alkene that we can have;

1) the starting material alkene has no chiral centers

2) there is a chiral center in the alkene.

STEREOCHEMISTRY OF REACTIONS: ADDITION OF H2O TO AN ACHIRAL ALKENE

For example, an Acid-catalyzed addition of H2O to 1-butene in the laboratory yields 2-butanol, a chiral alcohol. The 2-butanol produced is a racemic mixture of *R* and *S* enantiomers.

As a general rule, formation of a new chirality center by reaction between two achiral reactants always leads to a racemic mixture of enantiomeric products.

So to summarize, addition reactions of **alkenes with no stereogenic center** that form a **product with one stereogenic center produce a racemic mixture of enantiomers**.

1-Butene is first protonated to yield an intermediate secondary (2°) carbocation. Since the trivalent carbon is sp^2-hybridized and planar, the cation has no chirality centers, has a plane of symmetry, and is achiral. As a result, it can react with H_2O equally well from either the top or the bottom. Reaction from the top leads to (*S*)-2-butanol through transition state 1 (TS 1), and reaction from the bottom leads to *R* product through TS 2. *The two transition states are mirror images.* They therefore have identical energies, form at identical rates, and are equally likely to occur.

Prochirality

An unsymmetrical ketone like 2-butanone is prochiral because it can be converted to the chiral alcohol 2-butanol by addition of hydrogen.

STEREOCHEMISTRY OF REACTIONS: ADDITION OF H_2O TO A CHIRAL ALKENE

If the starting alkene contains a chirality center, and the addition to the double bond creates a new chirality center, then the products are **diastereomers**

The asymmetric center in the starting material is not changed since it does not participate in the reaction.

As a general rule, the reaction of a chiral reactant with an achiral reactant leads to unequal amounts of diastereomeric products.

If the chiral reactant is optically active because only one enantiomer is used rather than a racemic mixture, then the products are also optically active.

CHIRAL DRUGS

The Penicillin enantiomer, which does not occur naturally but can be made in the laboratory, has no antibiotic activity. Ibuprofen, for example, has one chirality center and is sold commercially under such trade names as Nurofen, Moment, Brufen as a racemic mixture of *R* and *S*. It turns out, however, that only the *S* enantiomer is active as an analgesic and anti-inflammatory agent. The *R* enantiomer of ibuprofen is inactive, although it is slowly converted in the body to the active *S* form.