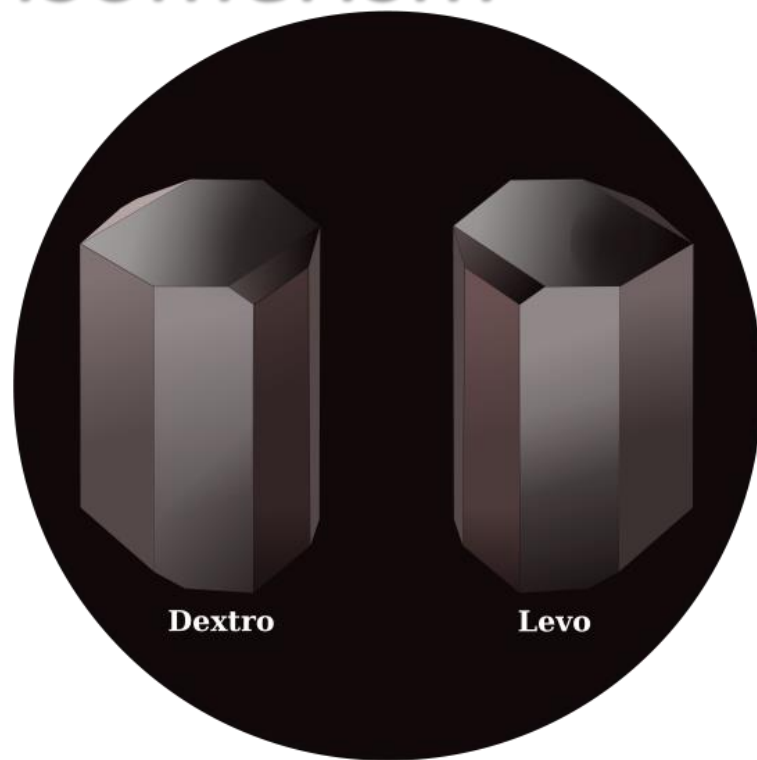


Chapter 5: Stereoisomerism



Stereochemistry

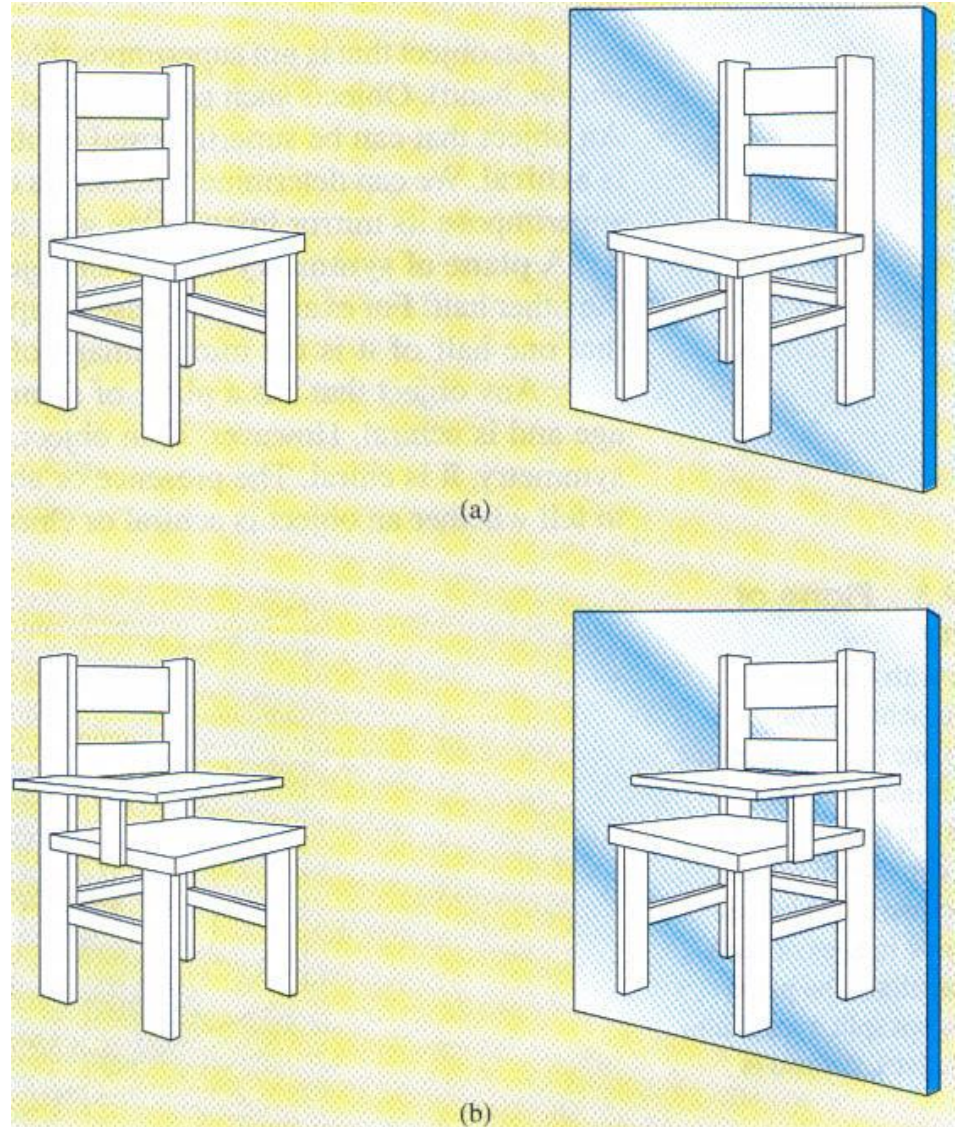
Stereochemistry is the study of the 3D aspects of molecules. *Stereoisomers* are molecules that differ only in the 3D arrangement of their atoms. Stereoisomers possess one or more *chiral* centers. Chiral objects are ones where the mirror image has a different 3D structure, i.e. the mirror image is not *superimposable* on the original object.

Chirality

Objects can be chiral or achiral, i.e.

The top chair is achiral (mirror image is superimposable)

The bottom chair is chiral (mirror image is not superimposable)

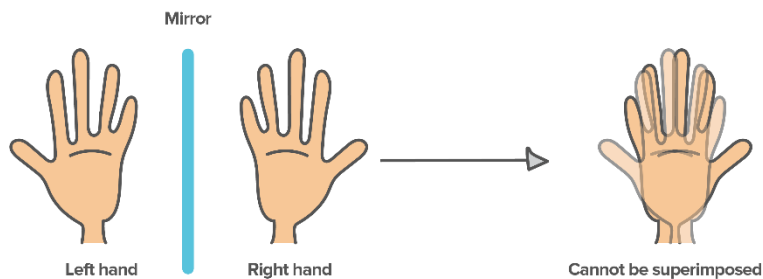


An achiral object will have a *plane of symmetry* in it, i.e. a mirror plane through the object so that one half is a mirror image of the other.

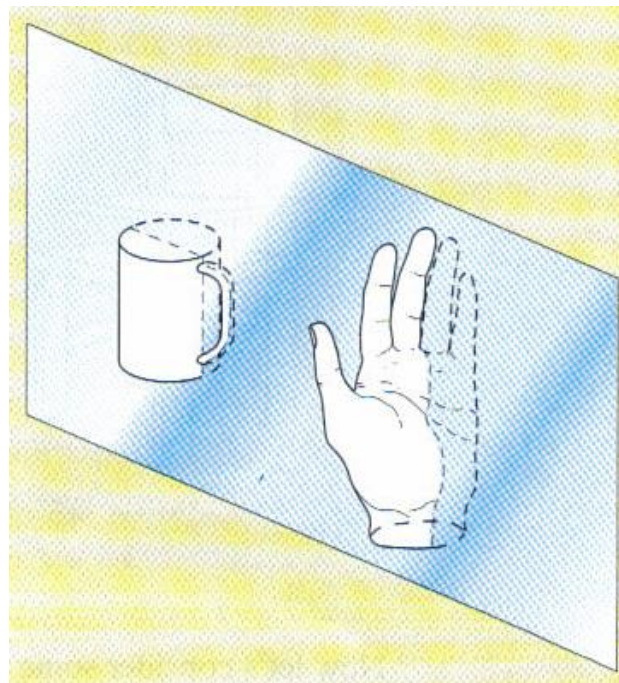
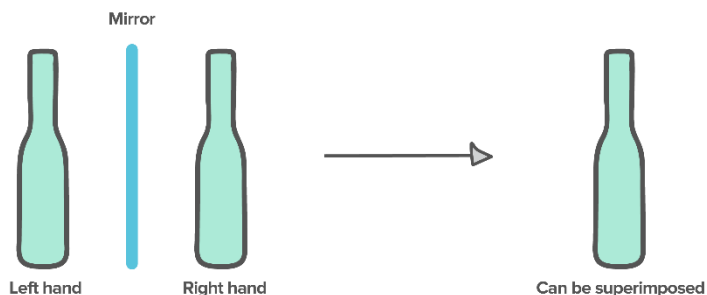
The coffee cup is achiral

While the hand is chiral

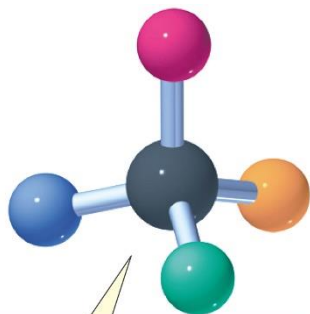
CHIRAL OBJECTS



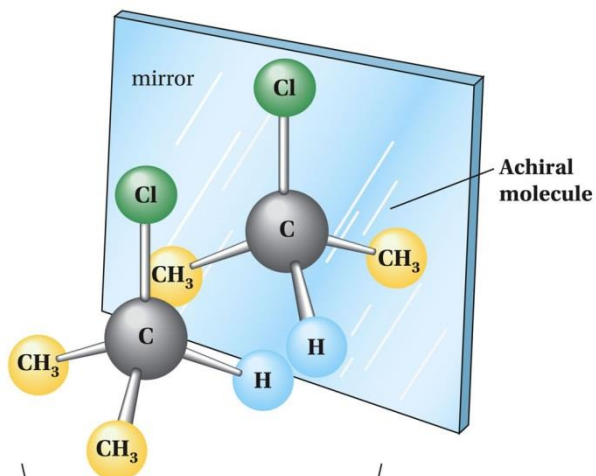
ACHIRAL OBJECTS



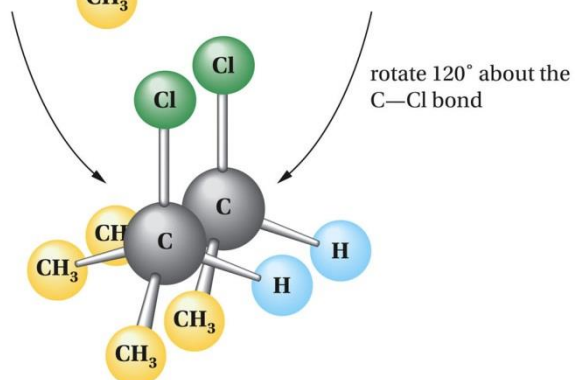
For molecules a chiral center is an sp^3 hybridized C atom with four different groups (atoms) attached. If two or more groups are identical then the molecule will possess a plane of symmetry.



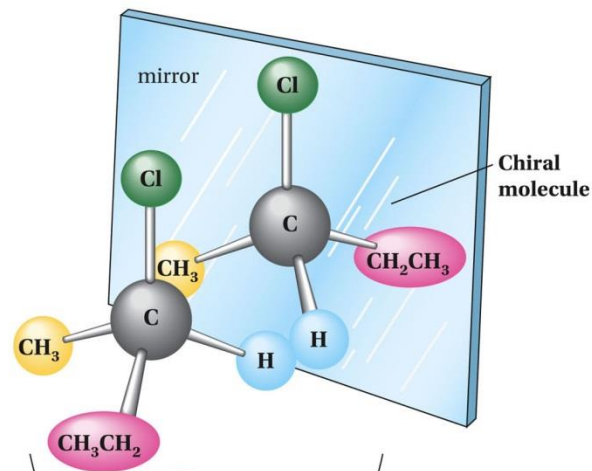
an asymmetric center



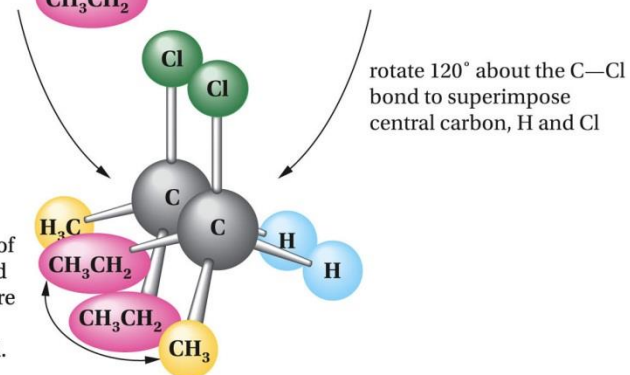
Achiral molecule



rotate 120° about the C—Cl bond



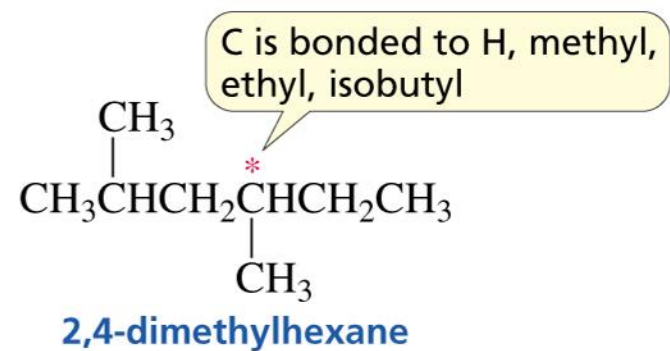
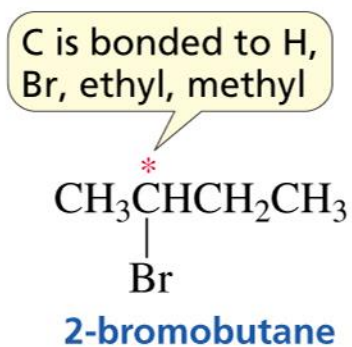
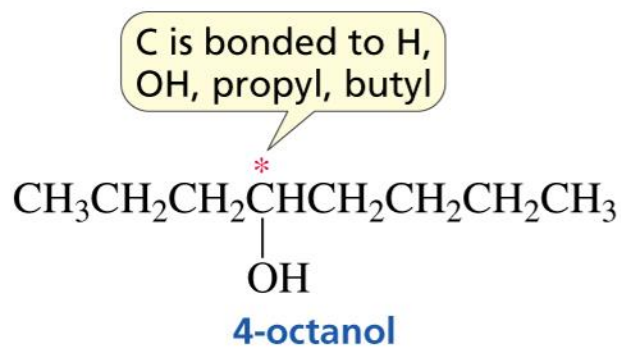
Chiral molecule



rotate 120° about the C—Cl bond to superimpose central carbon, H and Cl

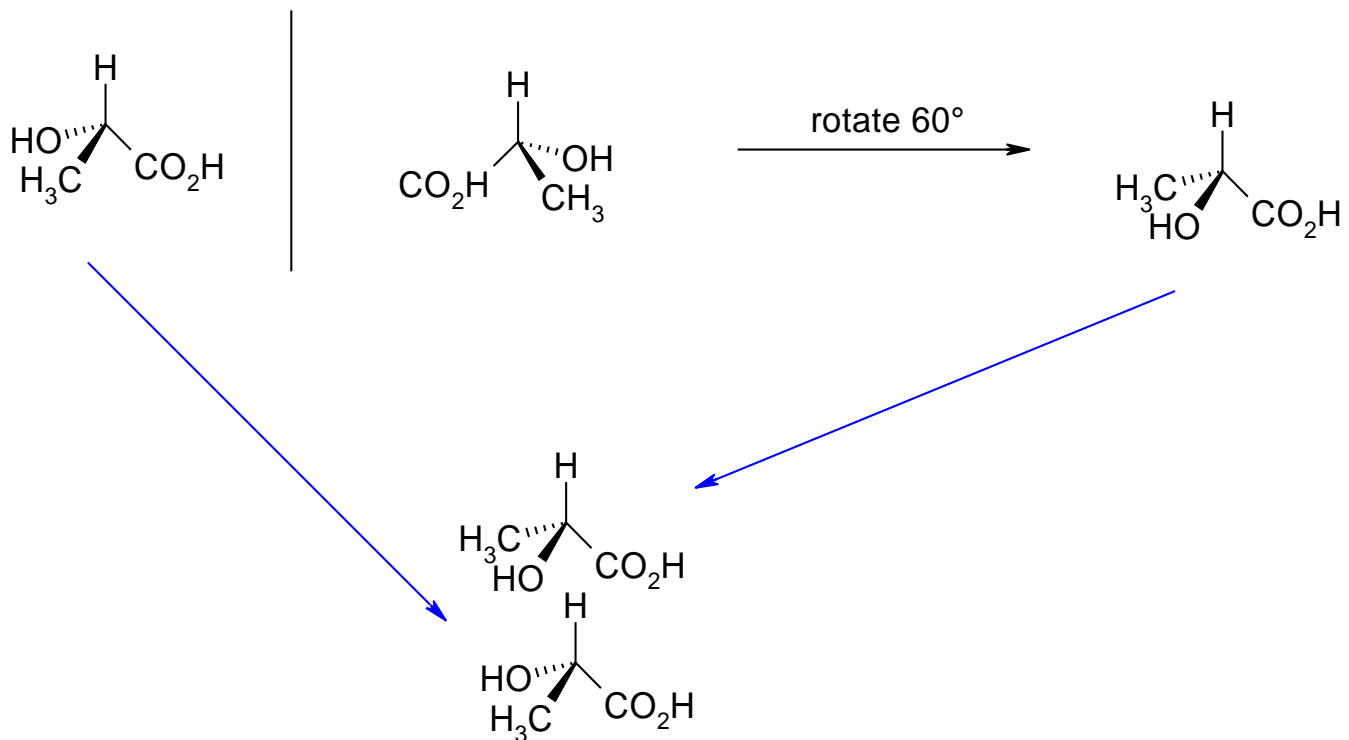
The positions of the methyl and ethyl groups are *not* superimposed.

Compounds with an Asymmetric Center



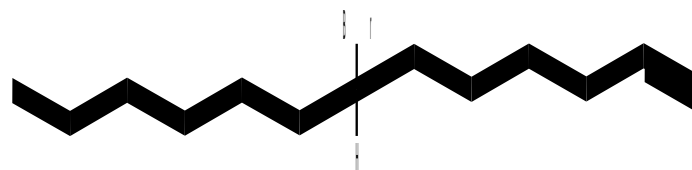
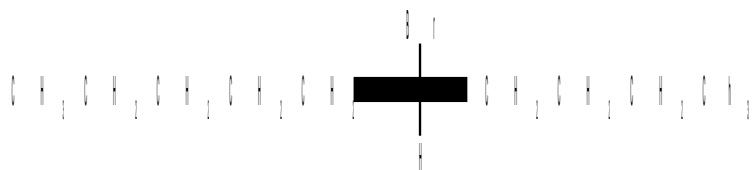
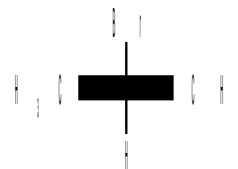
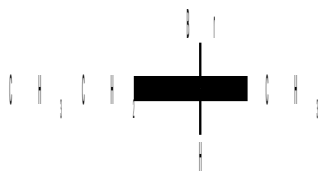
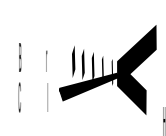
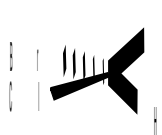
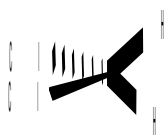
Chirality (cont'd)

Molecules which are non-superimposable mirror images (because they have a chiral or stereogenic center) are *enantiomers*, i.e.



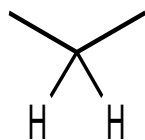
Enantiomers (cont'd)

Chiral or not?

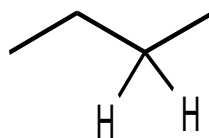


Chemically Equivalent Atoms

Atoms that are related to one another by a mirror plane are chemically equivalent and have the same chemical properties, i.e. propane and butane



h o m o t o p i c H

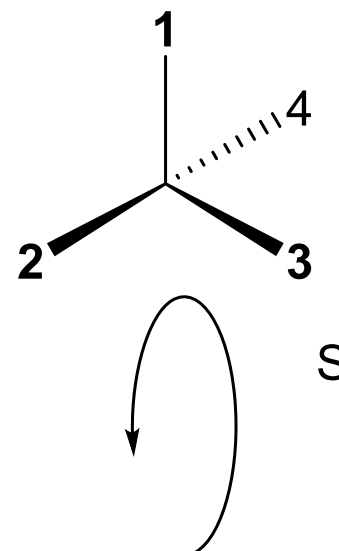
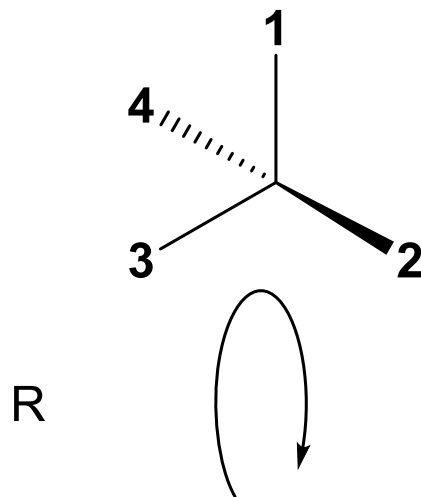


e n a n t i o t o p i c H

Configuration: R/S Nomenclature

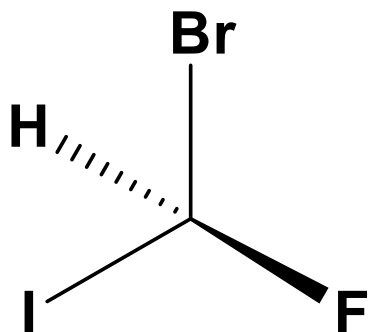
The R/S nomenclature system is used to distinguish between two enantiomers. The method relies on three simple rules for assigning priority to the four groups attached to assign a configuration of R (clockwise) or S (counterclockwise).

**The lowest (#4)
priority group
Pointing away
from us (.....)**



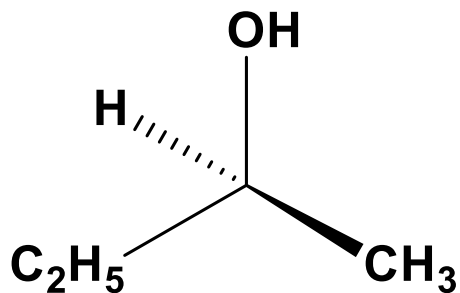
The rules are:

- 1) Atoms attached to the stereogenic center are ranked to atomic numbers (the higher the atomic number the higher the priority)



I, Br, F, then H

- 2) Compare the next atom out in the chain



-CH₃

H,H,H

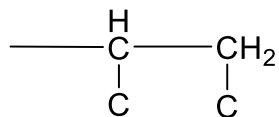
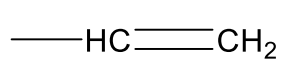
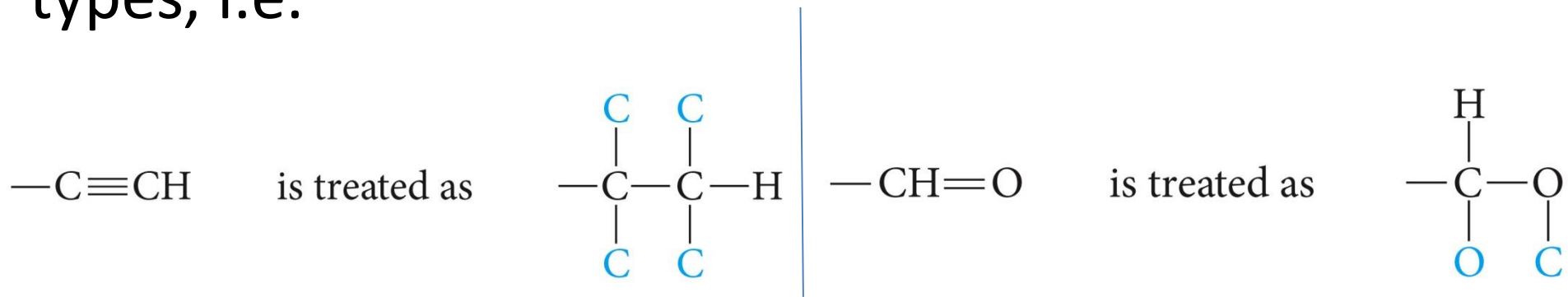
vs.

-CH₂CH₃

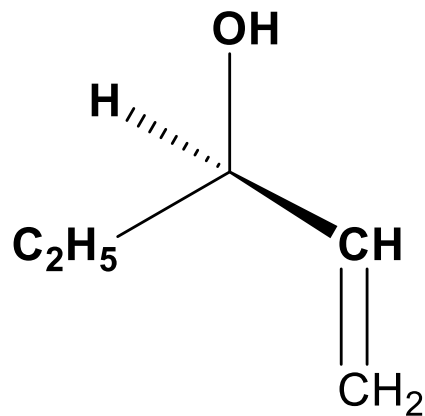
H,H,C

Higher priority

3) Multiple bonds: open the bond as equivalent atom types, i.e.



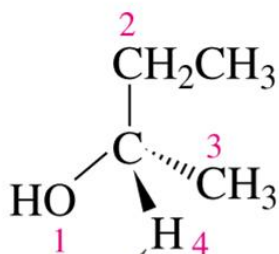
eg *R Or S*



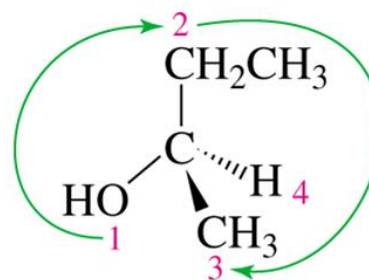
Naming Enantiomers

If the lowest priority group is **not** on a hatched wedge (#4),
switch a pair so it is on a hatched wedge.

Then, name the new compound.



the group with the lowest priority is not bonded by a hatched wedge

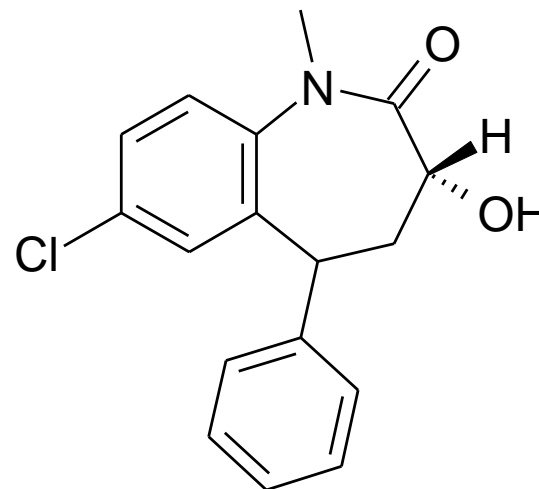
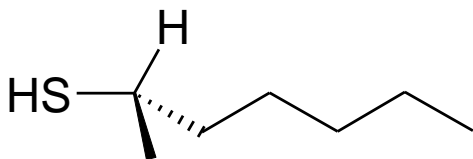
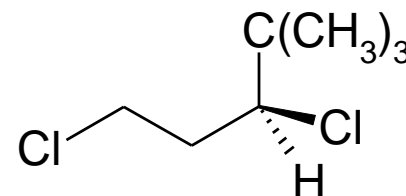
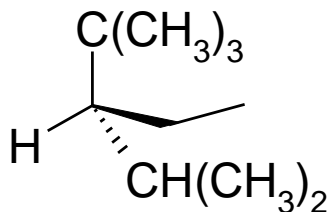
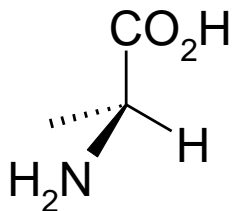


clockwise
arrow

this molecule has the *R* configuration; therefore, the molecule had the *S* configuration before the groups were interchanged

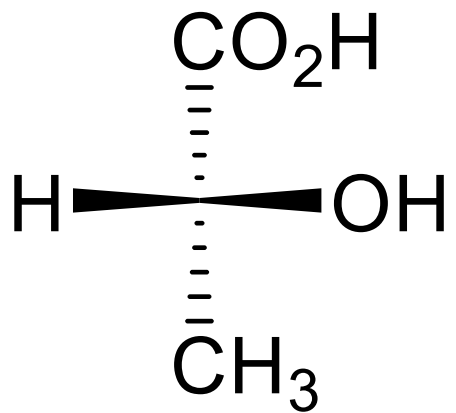
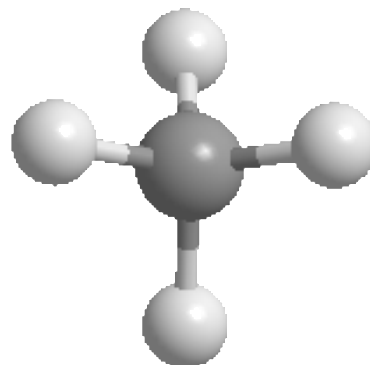
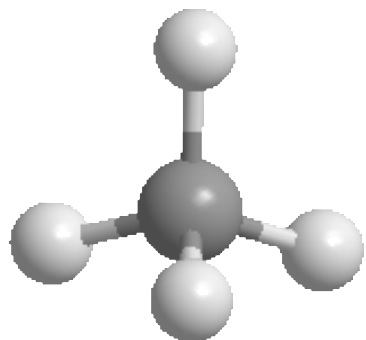
Configuration: R/S Nomenclature

Examples:

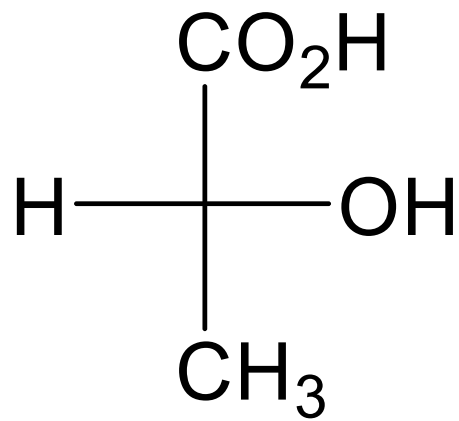


Fisher Projections

Fisher projections are a stylized way of conveying 3D info in a 2D drawing. They are very common in biochemistry. The convention is a cross where the horizontal arms are coming out of the page towards you and the vertical arms are going back into the page. For 2 adjacent chiral centers the middle vertical bond is in the plane of the page, i.e.

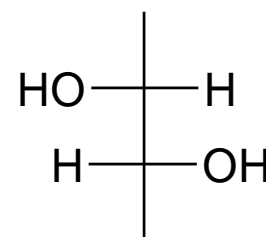
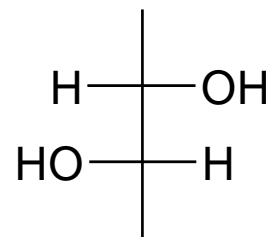
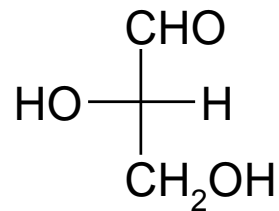
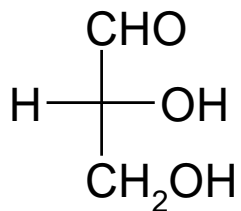
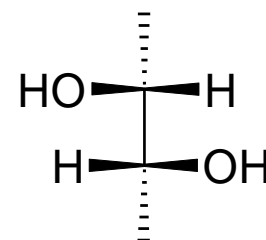
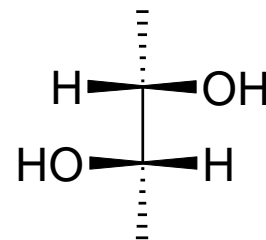
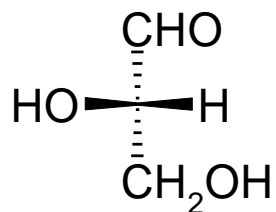
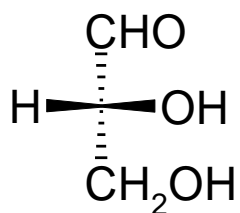


=



Fisher Projections

Examples:



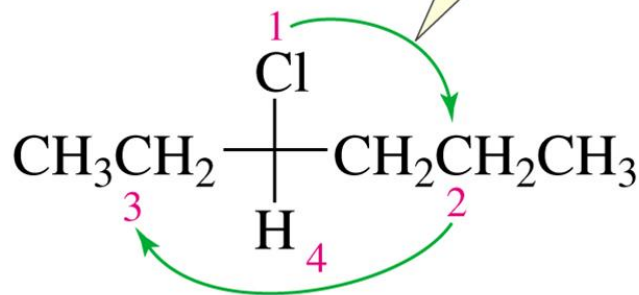
Fisher Projections

Manipulating Fisher diagrams:

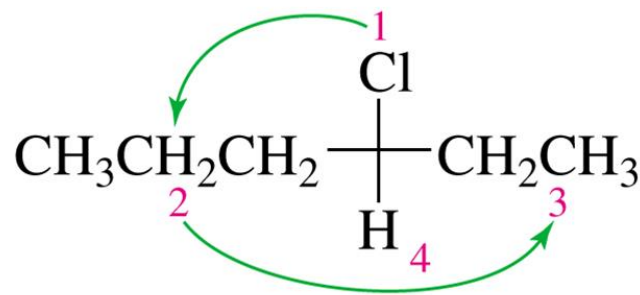
- Entire diagram: Rotation by 180° but not 90° (90° inverts the configuration)
- Three groups: can be rotated by any amount
- Two groups: exchange of any two groups inverts the configuration

Naming Enantiomers

clockwise signifies *R*, because H is on a vertical bond



(*R*)-3-chlorohexane



(*S*)-3-chlorohexane

If the lowest priority group is on a **vertical bond**, then

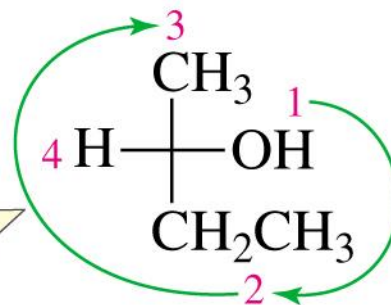
clockwise = *R*

and

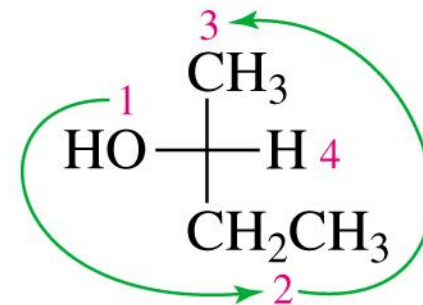
counterclockwise = *S*

Naming Enantiomers

clockwise signifies *S*,
because H is on a horizontal bond



(*S*)-2-butanol



(*R*)-2-butanol

If the lowest priority group is on a **horizontal bond**, then

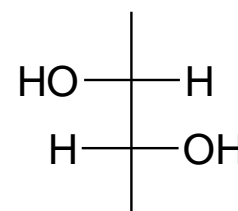
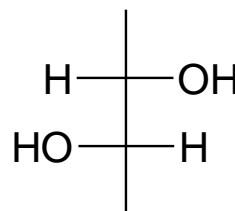
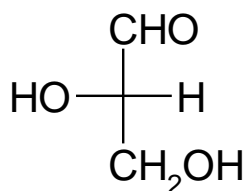
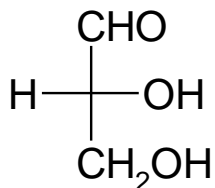
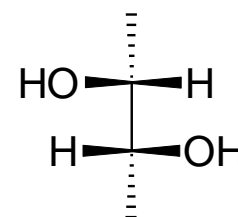
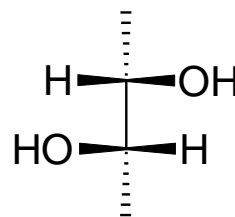
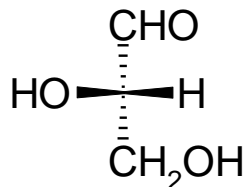
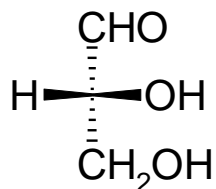
counterclockwise = *R*

and

clockwise = *S*

Fisher Projections

Assign the following stereochemistry



D-glyceraldehyde

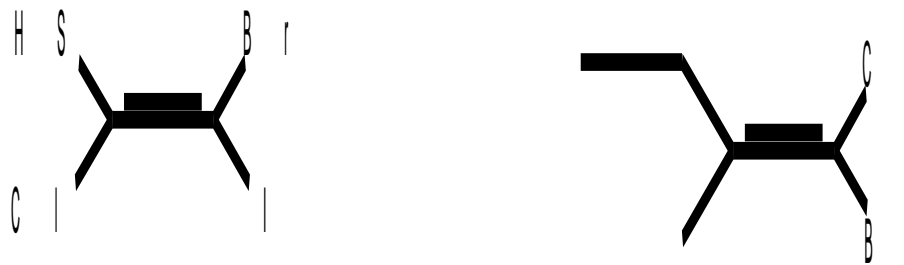
L-glyceraldehyde

S,S-butane-2,3-diol

R,R-butane-2,3-diol

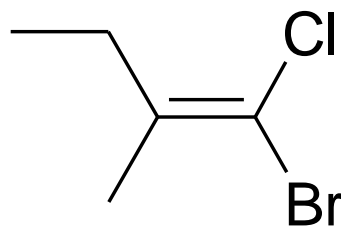
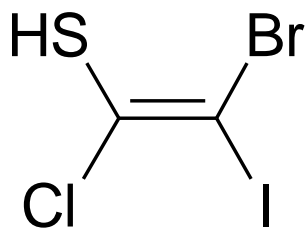
5.4: Configuration: E/Z Nomenclature

We have already seen geometric isomers when we discussed cyclic alkanes, the cis-/trans-isomers. Generally cis & trans only refer to hydrocarbons, what happens for other non C & H systems?



Configuration: E/Z Nomenclature

In this case we can use the same rules for chiral centers to assign a priority to each group on the double bond. When the two high priority groups are on the same side of the double bond: Z (zusammen (together)), on opposite sides: E (entgegen (opposite)).



(E)-1-bromo-1-chloro-2-methylbut-1-ene

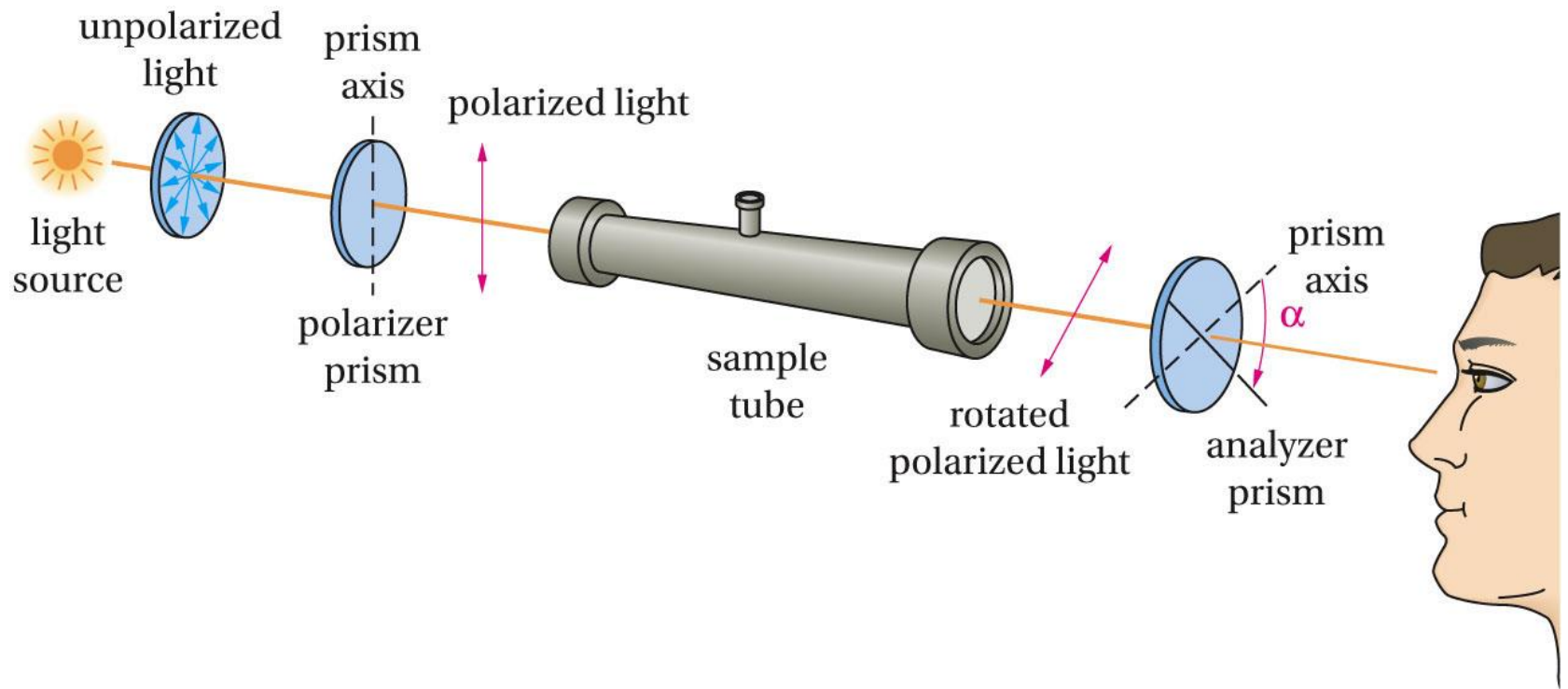
Enantiomers

Definition: non-superimposable mirror images.

- Identical non-chiral properties, i.e. MP or BP, interaction with other non-chiral objects/molecules
- Different chiral properties, i.e. optical activity, interactions with other chiral objects/molecules

Optical Activity

The experiment is performed using a polarimeter.



Optical Activity

Optical activity refers to a molecule's ability to interact with plane polarized light (PPL).

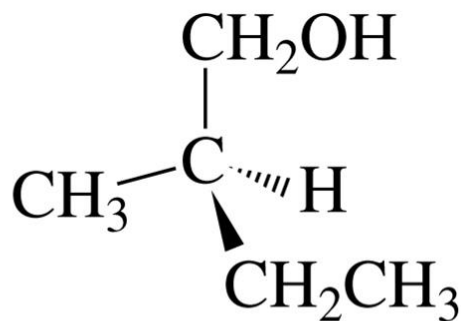
Optically active compounds will rotate PPL due to the electron distribution in the molecule either clockwise (dextrorotatory (+)) or counterclockwise (levorotatory (-)).

Optical Activity

The polarimeter measures the observed rotation (α , degrees), but since the rotation is dependent on the concentration, temperature, wavelength of light and device it is more common to report the *specific rotation*, where l is the pathlength through the polarimeter and c is the concentration.

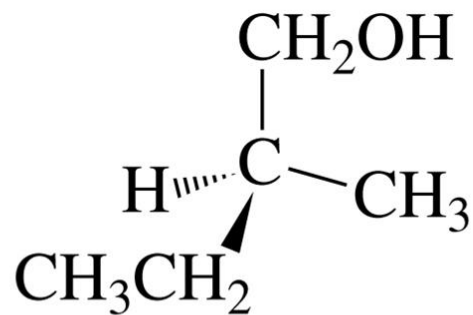
$$[\alpha]_{\lambda}^T = \frac{\alpha}{lc}$$

If One Enantiomer is (+), the Other is (-)



(R)-2-methyl-1-butanol

$$[\alpha]_{\text{D}}^{20\text{ }^{\circ}\text{C}} = +5.75$$



(S)-2-methyl-1-butanol

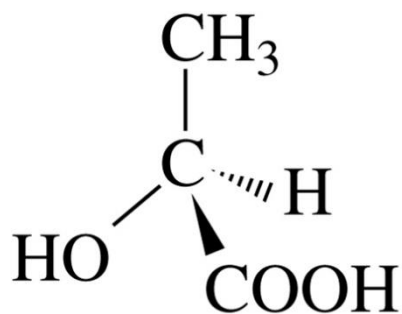
$$[\alpha]_{\text{D}}^{20\text{ }^{\circ}\text{C}} = -5.75$$

R and *S* versus (+) and (-)

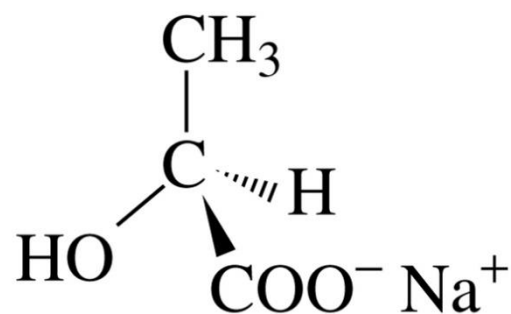
There is no relationship between (R/S) and (+/-)

Some *R* enantiomers are (+) and some are (-).

Some *S* enantiomers are (+) and some are (-).



(S)-(+)-lactic acid



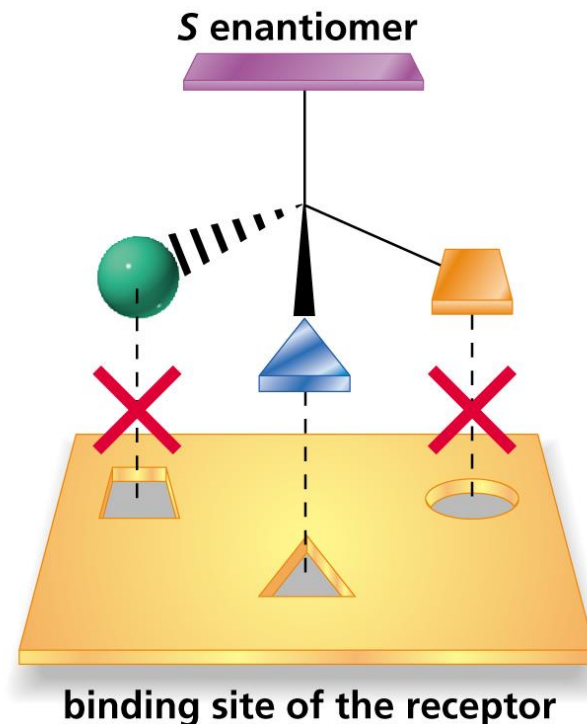
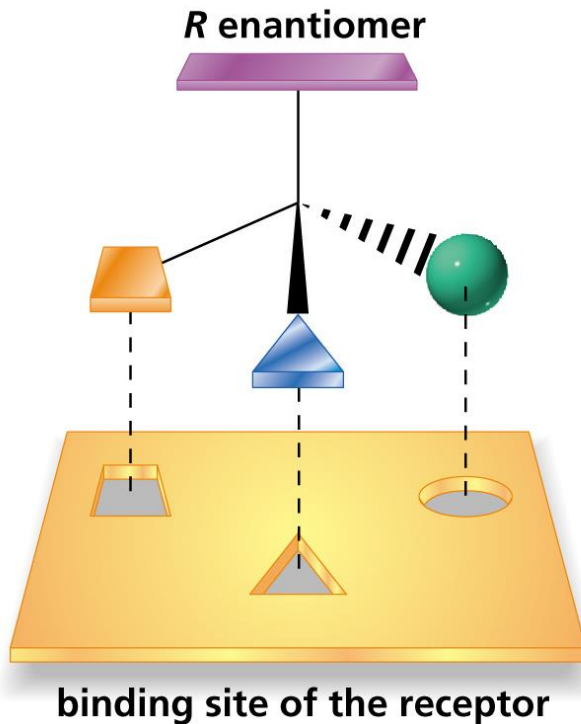
(S)-(-)-sodium lactate

Biological properties of enantiomers

A Receptor is a Protein Proteins are Chiral Molecules

Because a receptor is chiral, it binds **one enantiomer**.

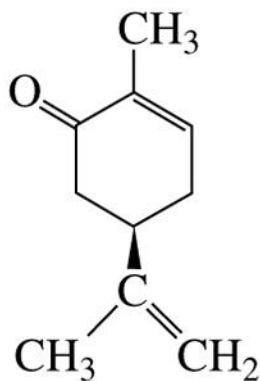
A **right-handed glove** fits only a **right hand**.



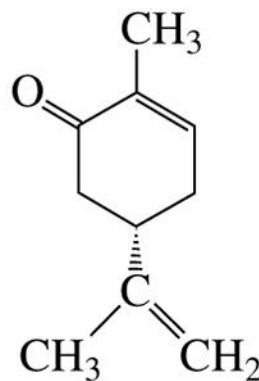
A Receptor Binds One Enantiomer



(R)-(-)-carvone
smells like
spearmint



(R)-(-)-carvone
 $[\alpha]_D^{20\text{ }^\circ\text{C}} = -62.5$



(S)-(+)-carvone
 $[\alpha]_D^{20\text{ }^\circ\text{C}} = +62.5$

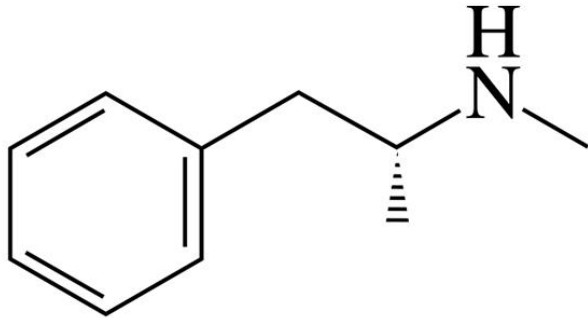


(S)-(+)-carvone
smells like
caraway seeds

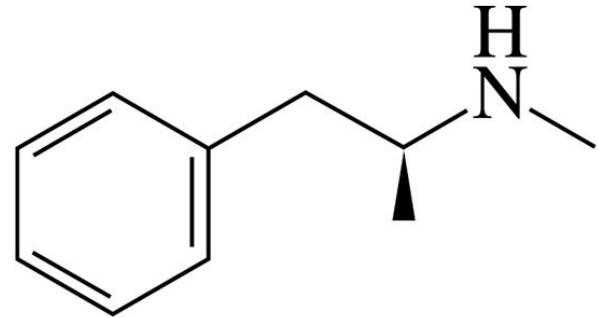
Each **enantiomer** binds to a **different receptor** in the nose.

Physiological Properties of Enantiomers

Enantiomers can have **very different** physiological properties.



**the active ingredient
in Vicks Vapor Inhaler®**



**methamphetamine
"meth"**

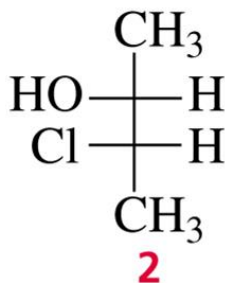
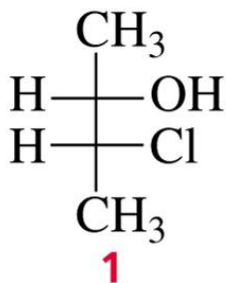
Compounds with Two Asymmetric Centers



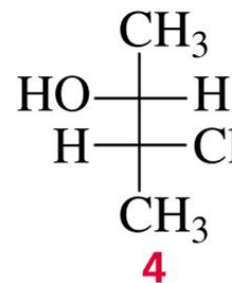
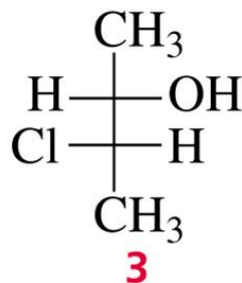
maximum # of stereoisomers = 2^n

(n = # of asymmetric centers)

3-chloro-2-butanol



erythro enantiomers



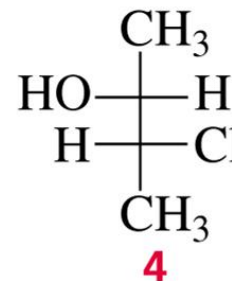
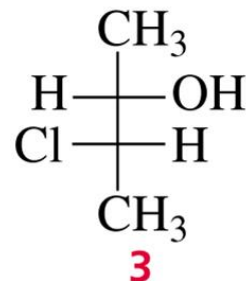
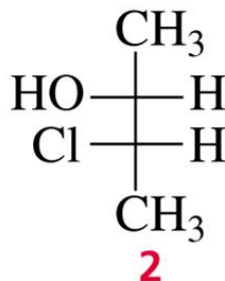
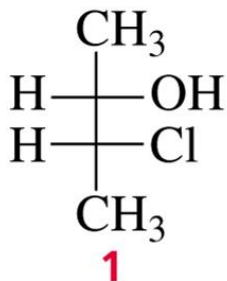
threo enantiomers

Fischer projections of the stereoisomers of 3-chloro-2-butanol (eclipsed)

1 and **2** are enantiomers.

3 and **4** are enantiomers.

Diastereomers



erythro enantiomers

threo enantiomers

Fischer projections of the stereoisomers of 3-chloro-2-butanol (eclipsed)

1 and **2** are enantiomers.

3 and **4** are enantiomers.

Diastereomers are stereoisomers that are not enantiomers.

1 and **3** are diastereomers.

2 and **3** are diastereomers.

1 and **4** are diastereomers.

2 and **4** are diastereomers.

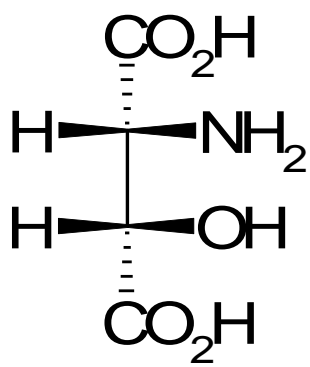
Diastereomers have different physical and chemical properties.

Diastereomers

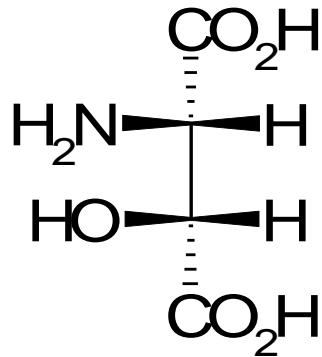
Diastereomers are an additional class of stereoisomers. In contrast to enantiomers (non-superimposable mirror images) diastereomers are non-superimposable non-mirror images. This means they need to have two or more chiral centers (and/or geometric (E/Z) isomeric centers).

Diastereomers

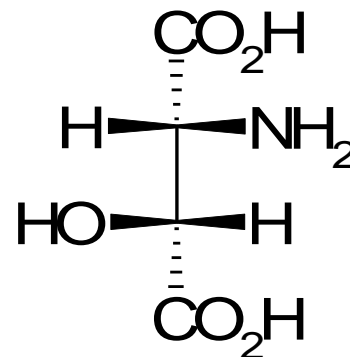
Nonequivalent stereogenic centers:



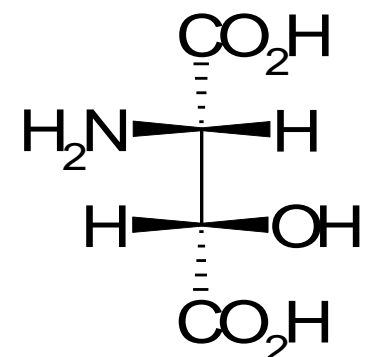
2R,3R



2S,3S



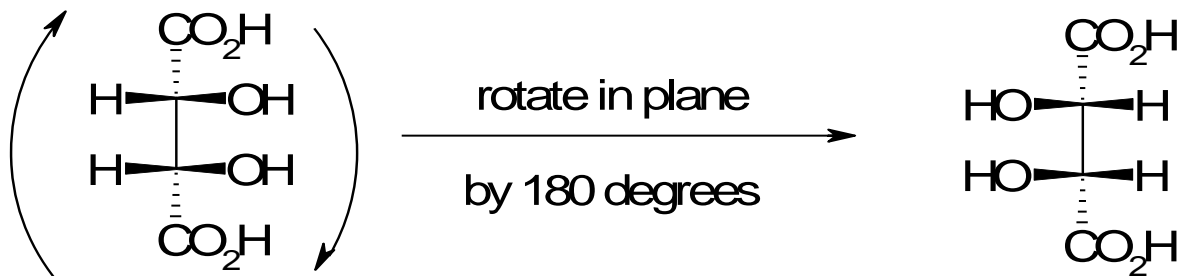
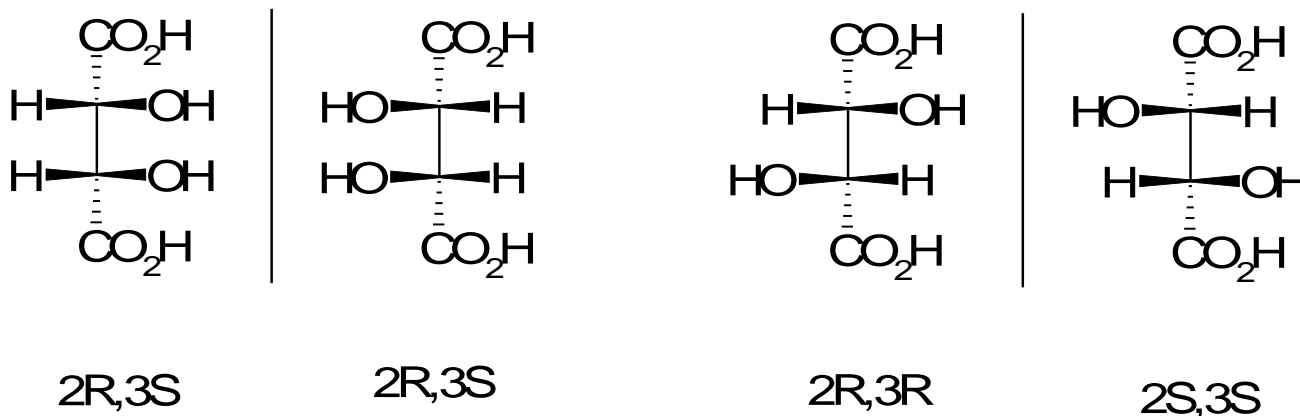
2R,3S



2S,3R

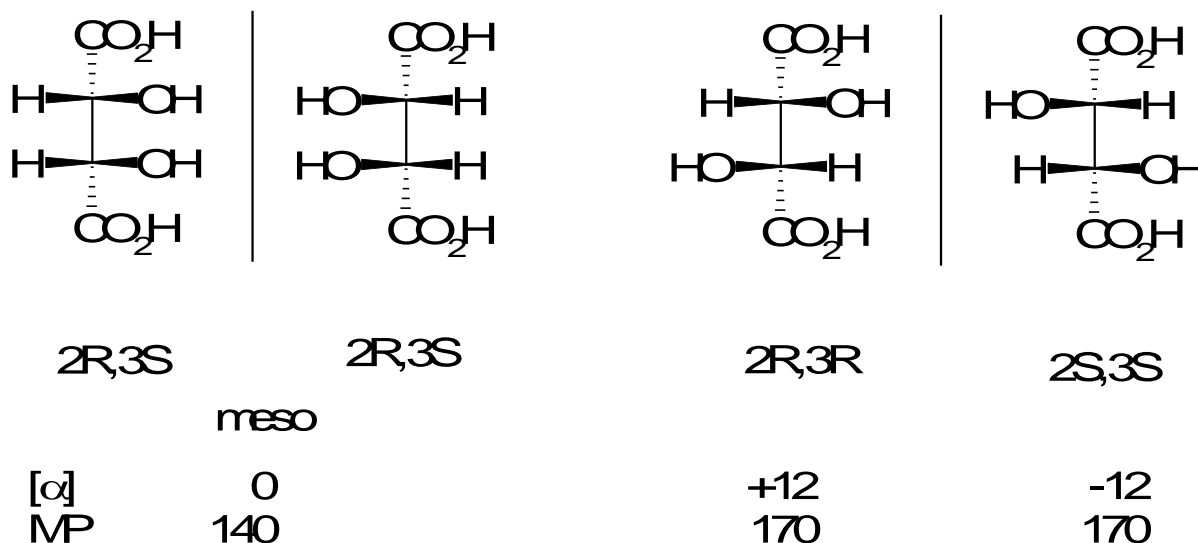
Diastereomers: Meso compounds

Equivalent stereogenic centers:



Diastereomers: Meso compounds

Equivalent stereogenic centers: meso compounds, although they contain multiple chiral centers, there are two configurations that are mirror images and superimposable, This results from the fact they contain a plane of symmetry



Diastereomers

The physical and chemical properties of diastereomers are different.

For meso compounds two isomers are actually enantiomeric so they will have the same non-chiral properties but different chiral properties. The meso isomers will have different physical and chemical properties to the other isomers.

Stereochemistry in Chemical Reactions

Stereochemistry is very important in chemistry as you are normally only interested in one of the stereoisomers.

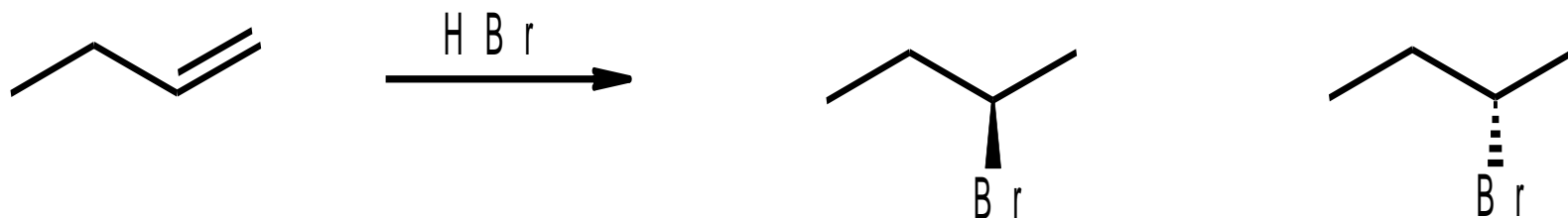
There are two possibilities:

1. Chiral products from achiral reagents
2. Chiral products from chiral reagents

Stereochemistry in Chemical Reactions

Chiral products from achiral reagents:

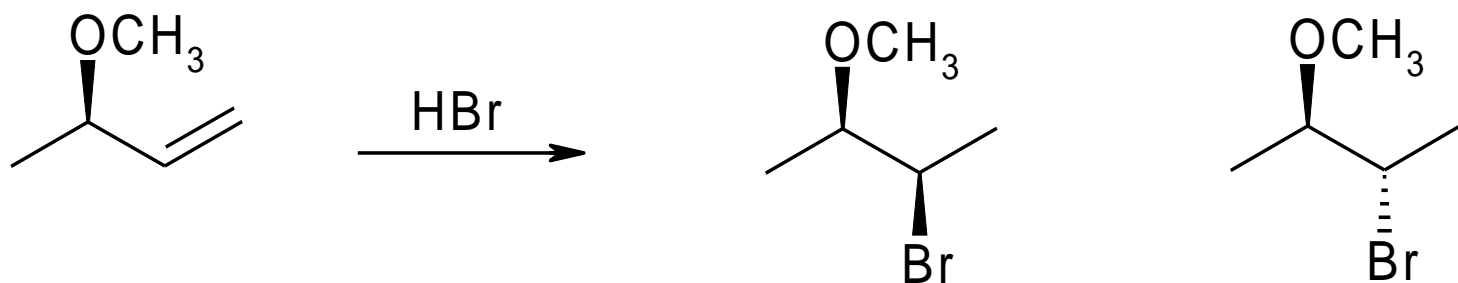
This commonly results from addition type reactions that go through a carbocation intermediate, equal chance of reacting with either side of the carbocation. Usually results in a racemic mixture (50:50) of both enantiomers, i.e.



Stereochemistry in Chemical Reactions

Chiral products from chiral reagents:

Since the chiral reagents react with each other at different rates this results in the production of diastereomers in unequal amounts. i.e.



50:50 **mixture** of two enantiomers

Racemic Mixtures

optically inactive

Chiral Resolution

A common problem is how to separate enantiomeric products from a reaction. This can be difficult as many of the common techniques to separate compounds rely on physical properties that are the same for enantiomers.

The solution? Change them into diastereomers using a chiral resolving agent. These can be easily separated as their physical properties are now different.

Chiral Resolution

i.e.



The two new products are easily separated.

This technique work best when the chiral resolving agent is easy to add and then remove, i.e.

