Stereochemistry | yrtsimehcoeretS

Chirality

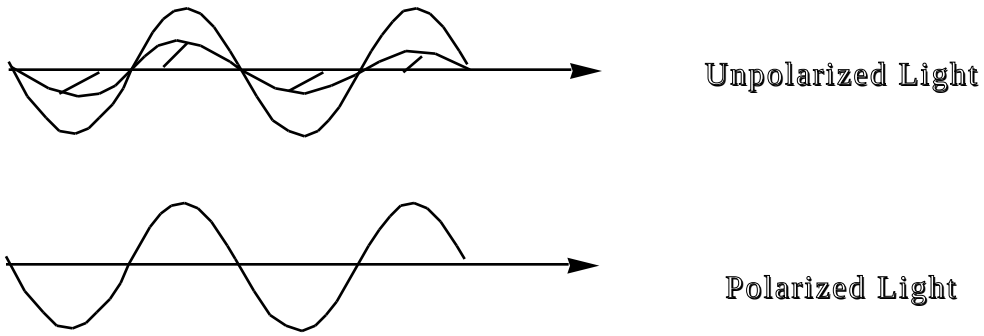
Explain “handedness” considering hands. Mirror images of each other. Any object is **chiral** if it cannot be superimposed with its mirror image. **Chiral** versus **achiral**. Molecules that are **chiral** occur in pairs of **enantiomers**. A mixture of equal amounts of enantiomers is called a **racemate**.

The simplest cases of chirality in chemistry occur for molecules with a **chiral carbon**. A chiral carbon (also called an asymmetric carbon) has four different substituents connected to it. Example: CBrClFI and its mirror image. (Models)

Optical Activity - Rotation of Plane Polarized Light

The optical activity is the only difference between enantiomers. Optical activity is used to characterize the enantiomers.

Light waves (electro-magnetic waves) have electric field amplitudes perpendicular to the direction of travel. Light interacts with materials by way of "electric" interactions (in contrast to magnetic). Using special filters (e.g. calcite $CaCO_3$) light can be polarized such that the amplitude in only one direction remains - polarized light.



Chiral molecules **turn the plane** of the polarized light. Enantiomers turn the plane of the polarized light in **different** directions. That is the only difference between enantiomers.

Optical Activity - Definitions

Optical rotation is the physical effect that causes the change in the plane of the polarized light. We need not be concerned with the physical origin of this effect.

Optical isomers are isomeric molecules that turn the light in different directions. If these isomers are enantiomers, then they rotate the light plane by the same amount.

Optically active molecules turn the plane of the light. Chiral molecules may or may not turn the light. Chirality is a necessary but not a sufficient condition for optical activity.

Polarimeters are devices that let you measure the angle of rotation of polarized light. They are essentially just another filter of polarized light. The light comes only through if this filter is aligned with the plane of polarization of the polarized and rotated light. (See overhead)

Specific Rotation

A characteristic value for an optically active material.

$$[\alpha]_D^{20} = \beta / l \cdot c$$

β = measured optical rotation

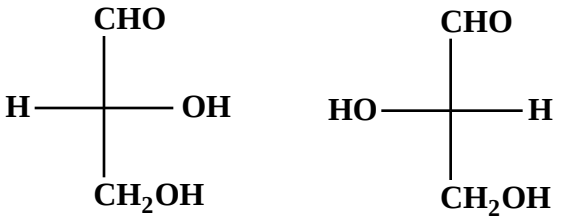
l = length of cell, 1dm

c = conc. in g/ml

Measurement is temperature dependent. (Typical 20˚C.)
Measurement depends on the wave length of the light used. (Often the sodium D-line of yellow light is used.)

Sign of the Rotation

The terms **dextrorotatory (+)** and **levorotatory (-)** are used to describe the optical rotation. The terms D and L will be explained later. Note that there is no relation between D and (+) and L and (-). It just so happens that D glycerine-aldehyde turns right.



D (+) 8.7 L (-) -8.7

Enantiomeric Excess & Optical Purity

Optical Purity is defined as the ratio between the rotation of a mixture that contains x mol of one enantiomer and y mole of the other enantiomer as compared to the pure enantiomer.

$$o.p. = \frac{\text{observed specific rotation of mixture}}{\text{specific rotation of pure enantiomer}} \times 100\%$$

Example 1: 75% S and 25% R. Observed rotation?
25% S and 25% R cancel each other. Observed rotation will be 50% of what it would be if the sample were pure.

The optical purity therefore tells you about **the excess of one enantiomer over the other**. In terms of the enantiomer concentration, we can write:

$$o.p. = e.e. = \frac{|R - S|}{R + S} \times 100\%$$

Example 2: 90% S and 10% R. O.p. and e.e.?
o.p. = e.e. = 80 %

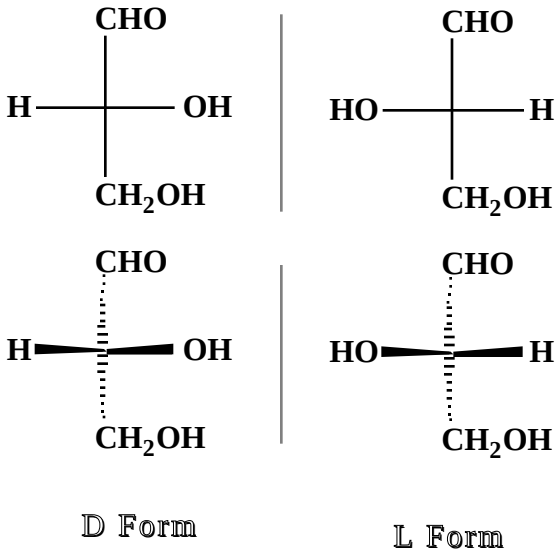
Fischer Projections - The First Nomenclature for Chiral Molecules

The FPs were originally used by **Emil Fischer** for sugars. They are still in use and we need to learn them. A more general nomenclature will be discussed below.

The Fischer Projection rules are:

(a) The main chain vertical
(b) The highest oxidized group on top
(c) All vertical bonds behind the paper plane
(d) All horizontal bonds in front of the paper plane.
(e1) If the "key" substituent is on the right ==> D for dexter (right)
(e2) If the "key" substituent is on the left ==> L for laevus (left)

The Classical Example:
Glycerinealdehyde



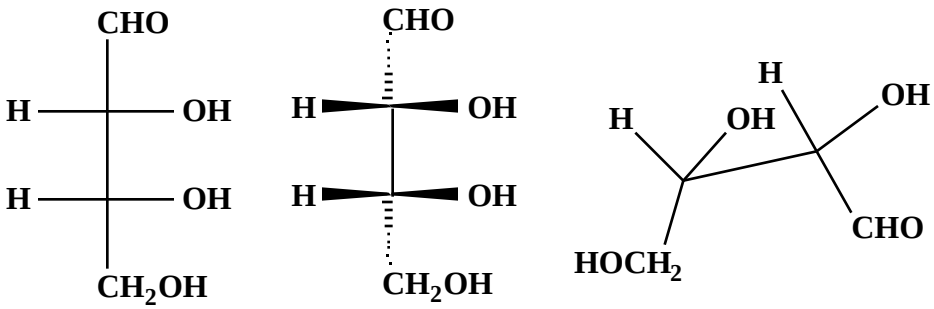
More Rules

(f) Fischer Projections may be rotated by 180° without loss of the stereochemistry.

(g) Fischer projections may not be rotated by 90°. This would change the D to L and *vice versa*.

Fischer Projections and Conformation

FPs do **not** represent the molecules in the best conformations. The molecule is drawn in an *all-cis* fashion! No conclusions regarding conformation can be drawn! Example: D-erythrose



No good conformation

The Cahn-Ingold-Prelog System to Establish Priority of Substituents

The basic rule is very simple:

The higher the atomic number of the directly attached atom, the higher the priority of that substituent

Note that
(a) isotopes with higher mass get higher priority (e.g. D > H)
(b) lone pairs have the lowest priority.

If the directly attached atom is the same for several substituents, then we need another rule:

The Sequence Rule: :[Look at the priorities of the attached atoms]: until a difference in priorities becomes apparent.

(a) Order the attached atoms in the order of highest priority
(b) If a multiple bond is attached, count that attached atom **once for each bond**.

Example 1: Methyl *versus* ethyl
C(HHH) has a lower priority than C(CHH)
"The next neighbors decide"

More Examples of the Sequence Rules

Example 2: Ethyl *versus* propyl
For the directly attached methylene groups, C(**C**HH), the priorities are the same; the next neighbors do not decide. In this case, one needs to look at the groups attached to them.
The ethyl **C** is that of a methyl group attached: **C**(HHH).
The propyl **C** is that of an attached ethyl group: **C**(CHH).
"Propyl wins in the third round"

Example 3: Ethyl *versus* hydroxymethyl groups
C(CHH) is less than C(OHH); priority of O is larger than of C.
"O wins in the second round"

Example 4: Hydroxymethyl *versus* formyl
C(OHH) is less than C(OOH). Note that the C=O shows as two Os; one for each bond. The first O makes no difference; the second O wins against H.

Example 5: Ester *versus* nitrile
C(OOO) is higher than C(NNN). First O wins against first N.

Example 6: Nitrile *versus* hydroxmethyl
C(OHH) versus C(NNN). O wins! The first difference matters!

The R/S System of Nomenclature

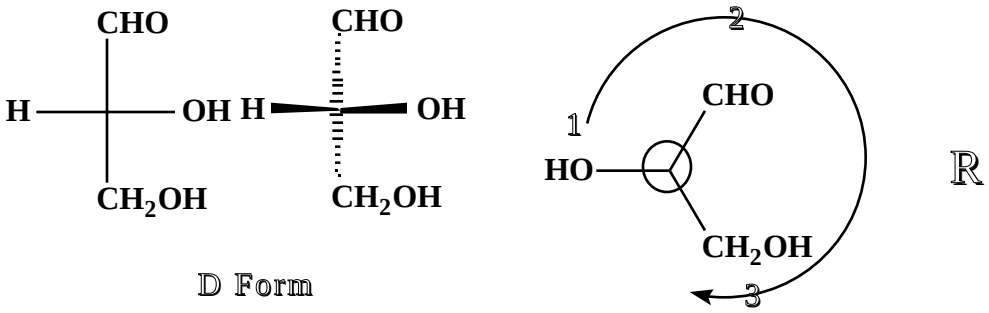
This is done for each chiral atom in a molecule using the Cahn-Ingold-Prelog system to establish priorities of substituents:

(a) Priorities of the four groups

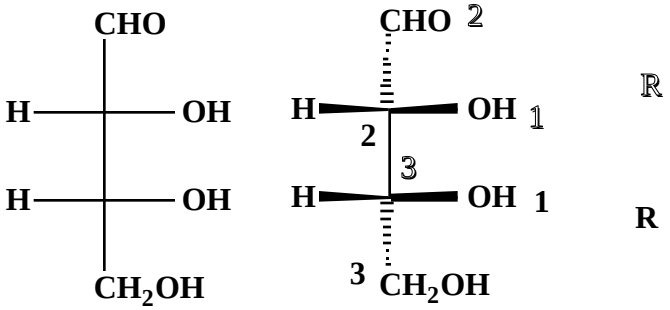
(b) Look in the direction C-LPS (lowest-priority-substituent)

(c) Clockwise decrease of priorities is R, S otherwise.

Example 1: Glycerinealdehyde - one chiral center



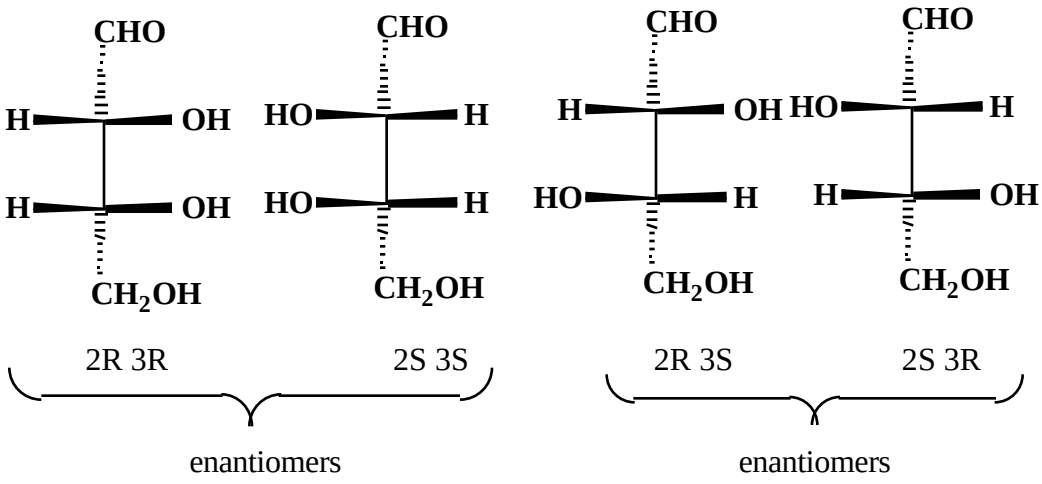
Example 2: Erythrose - 2 chiral centers



Diastereoisomers

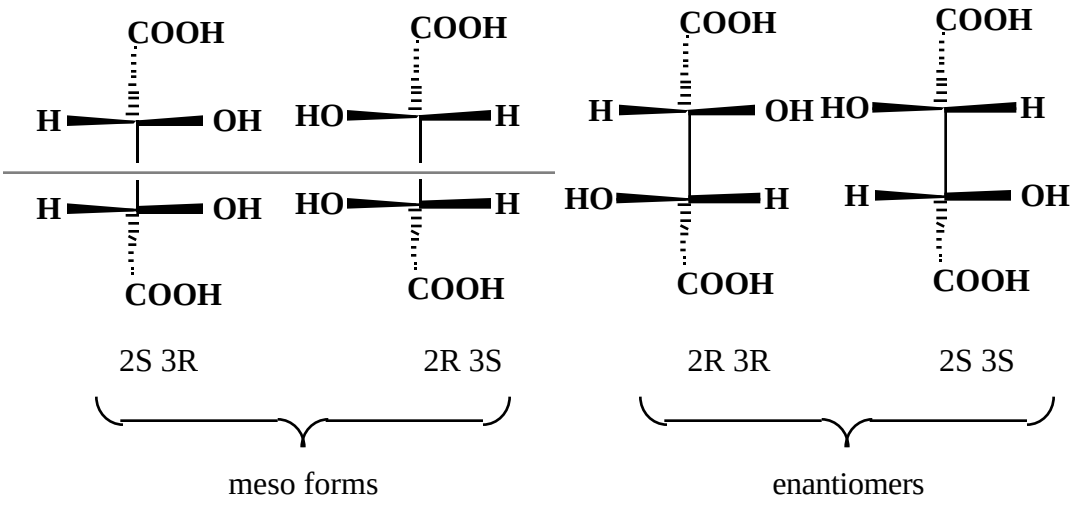
These are stereoisomers that are not enantiomers. They can occur if there are **several chiral carbons** in the molecule. For example, if there are 2 chiral carbons, then there are the possibilities RR, SS, RS and SR. Enantiomers have opposite configurations at all centers. Diastereoisomers differ at least in the configuration of one chiral center but not all.

Example 1: Erythrose yet again.

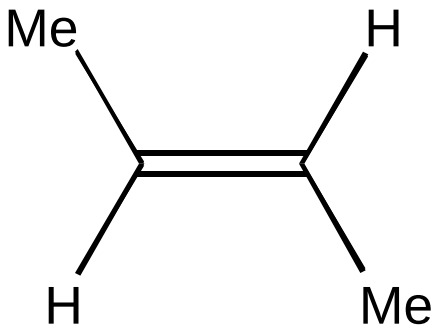


Example 2: Tartaric Acid - *Meso* Forms.

Remember that we can rotate FPs by 180 degrees. For tartaric acid, it turns out that (2S,3R) and (2R,3S) are one and the same structure! The presence of 2 chiral centers results in a nonchiral structure - the *meso* form. These are easily recognized because they have a plane of symmetry (dashed below) that is horizontal in the FPs. In this case there are only 3 stereoisomers!

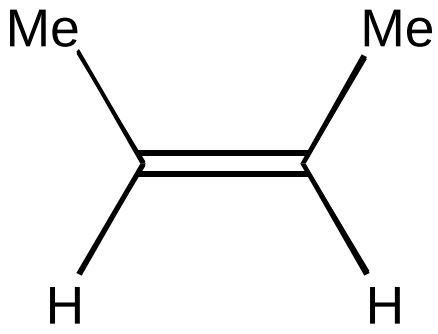


Diastereoisomers in Molecules without Chirality Centers



Trans butene
(*E*) Butene

μ = 0 Debye
bp = 0.9˚ Celsius



Cis butene
(*Z*) Butene

μ = 0.33 Debye
bp = 3.7˚ Celsius

Chiral Compounds Without Chirality Centers
Chirality and Symmetry Elements

Step 1: You learn about the chiral carbon **causing** chirality.
Step 2: Several chiral Cs **may** or **may not** cause chirality.
Step 3: Chirality occurs even if there are **no chiral carbons**.
Confusing?

The much better way to determine whether a molecule is chiral or not is by way of examining whether certain "symmetry elements" exist in a molecule. The "symmetry elements" are

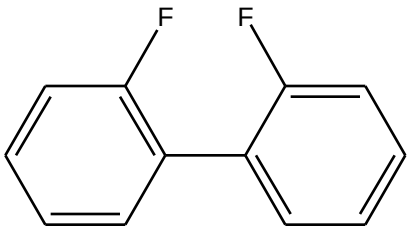
I, inversion center
C_n, rotational axis (rotate by 360/n degrees)
σ, symmetry plane

With these terms, we can state that a molecule is chiral if has no symmetry elements other than a C_n rotational axis. In other words, if a molecule has an inversion center, then it is not chiral. If a molecule has a plane of symmetry, then it is not chiral. A molecule may still have a rotational axis (but nothing else) and still be chiral.

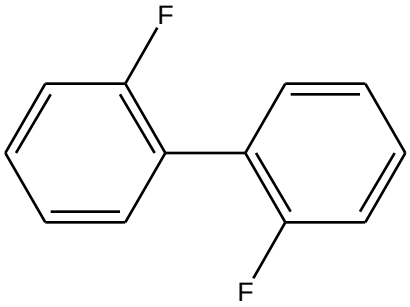
Let's look at some molecules that have no chiral carbon atoms, but that are chiral because they have no inversion centers and symmetry planes.

Chiral Compounds Without Chiral Carbon Atoms

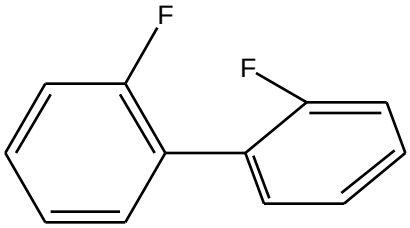
1. Twisted Biphenyl



If the molecule were planar with the F on the same side, there would symmetry planes and a C_2 rotational axis. Not chiral!



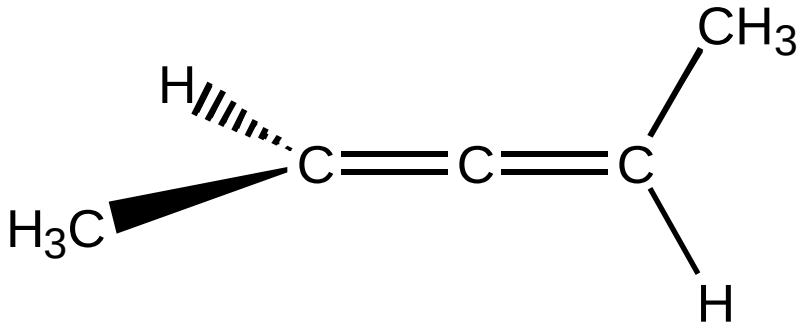
If the molecule were planar with the F on opposite sides, there would symmetry planes, an inversion center, and a C_2 rotational axis. Not chiral.



With the twist, all that is left is one C_2 rotational axis. Chiral!

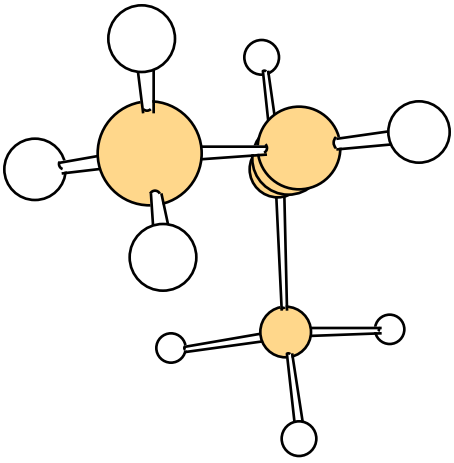
Chiral Compounds Without Chiral Carbon Atoms

2. Substituted Allenes

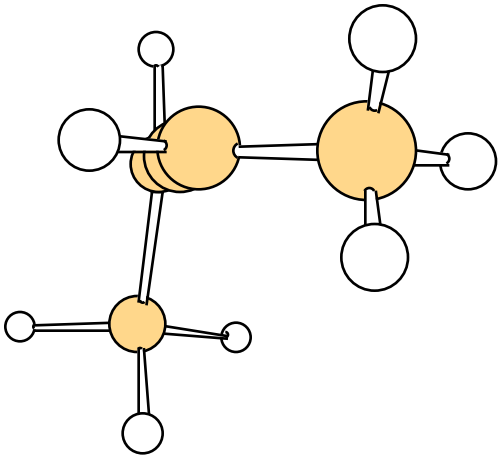


The methylene groups in this molecule are perpendicular with each other. There is no plane of symmetry. There is no inversion center. There is only one C_2 rotational axis. Chiral!

Enantiomer 1

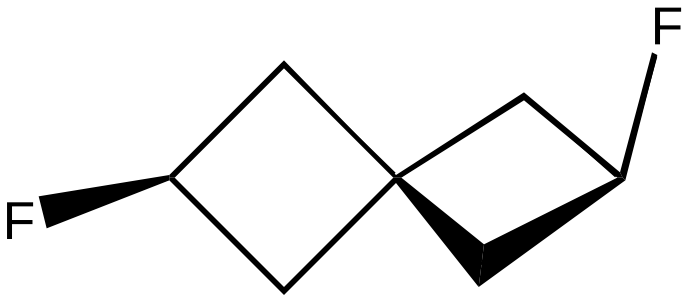


Enantiomer 2



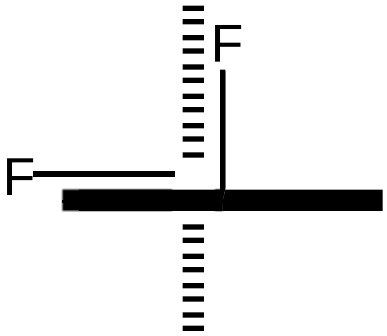
Chiral Compounds Without Chiral Carbon Atoms

3. Substituted Spiro Compounds

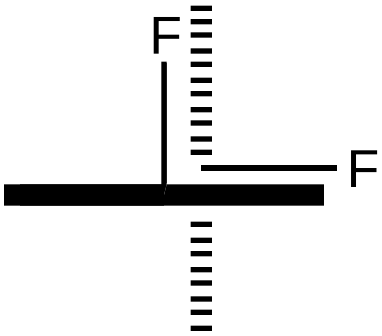


The methylene groups that carry the F-atoms in this molecule are perpendicular with each other. There is no plane of symmetry. There is no inversion center. There is only one C_2 rotational axis. Chiral!

Enantiomer 1



Enantiomer 2



Resolution of Racemic Mixtures

The facts are

(a) enantiomers do have the same physical properties and

(b) diastereoisomers do not have the same physical properties.

Thus: We cannot separate enantiomers by physical means, but we can separate diastereoisomers that way.

The Key Idea: React enantiomers with a molecule that does have one chiral center with one defined configuration. This reaction makes a pair of diastereoisomers out of a pair of enantiomers. Then separate. Then "undo the reaction".

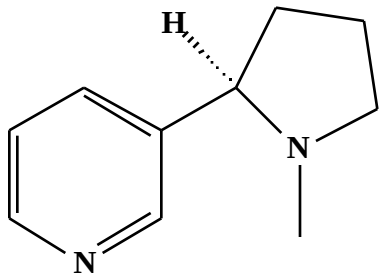
Start with mixture of enantiomers	R R S R S S R S
Add pure S-reagent to make diastereoisomers	Plus S
Obtain diastereoisomers (different physical properties)	RS SS RS SS SS RS RS SS

Example 1: Acid Base Reaction.
Have racemic acid, react with one pure enantiomer of a chiral base. Get diastereoisomeric salts. Separate by crystallization. Add strong acid to undo the reaction.

Typical chiral bases used include **amphetamine** and **strychnine** (both of which are not used in laboratory courses!). Amphetamine is Ph-CH_2-C*HMe-NH_2.

Example 2: Acid Base Reaction.
Have racemic base, react with one pure enantiomer of a chiral acid. Get diasteroisomeric salts. Separate by crystallization. Add acid to undo the reaction.

Example 3: Use enzyme reactions.
Some microorganisms recognize enantiomers. For example, *P. putitda* will metabolize the S form of nicotine but not the R form. So, adding the racemic mixture will eventually result in the consumption of S; R will be left over.



ℝ

On Overhead:

Example 4: Recognition of epinephrine by an active site.

Example 5: Resolution of 2-butanol with tartartic acid.

Example 6: Chromatographic Resolution of Enantiomers.

Chirality in Cycloalkanes

To find out whether cyclic compounds are chiral or not, we proceed just like with the acyclic compounds:

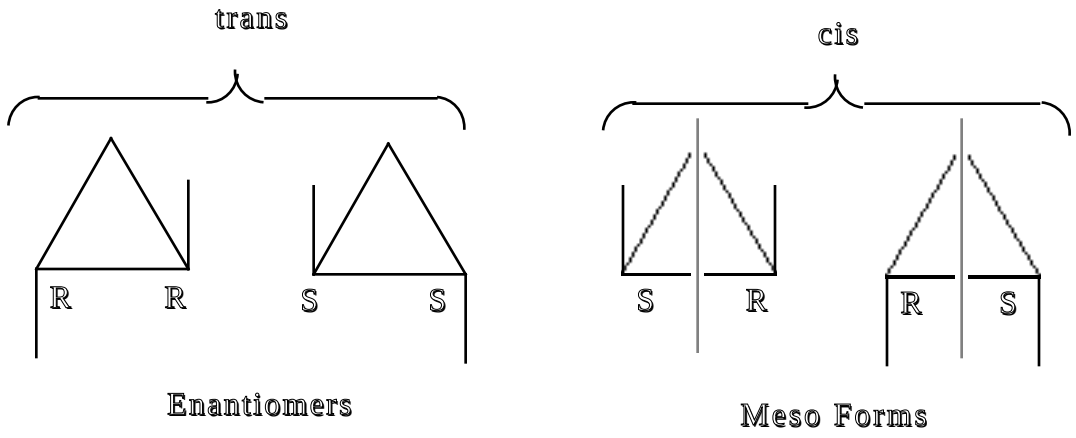
(a) Any chiral carbons?

(b) Any symmetry planes that cause *meso* forms?

(c) R/S nomenclature as with the acyclic molecules.

1. Conformationally Rigid Molecules

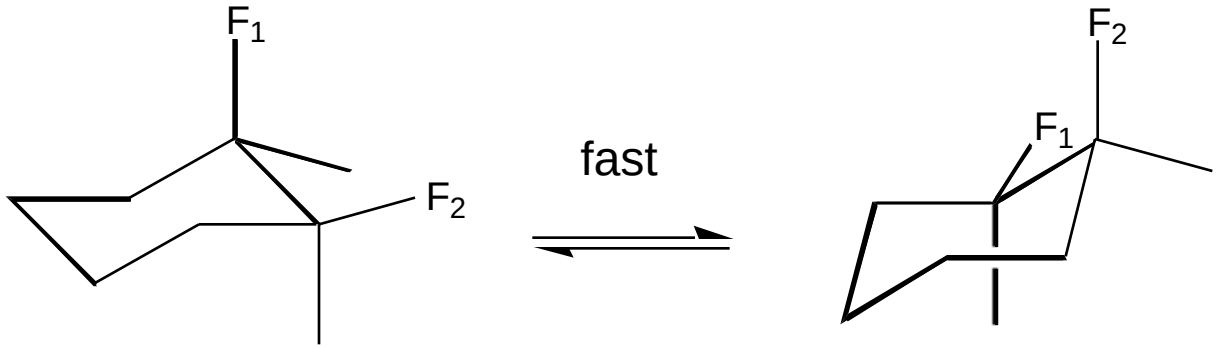
Example 1: Dimethylcyclopropane.



Examples 2 at Home: Take your model set and make two molecules of cyclobutane. Produce 1,2- and 1,3-disubstituted molecules. For each molecule built the "image" and the "mirror image". Try to superimpose. How many isomers are there? *(Rumor has it that we will get back to this problem in a future test).*

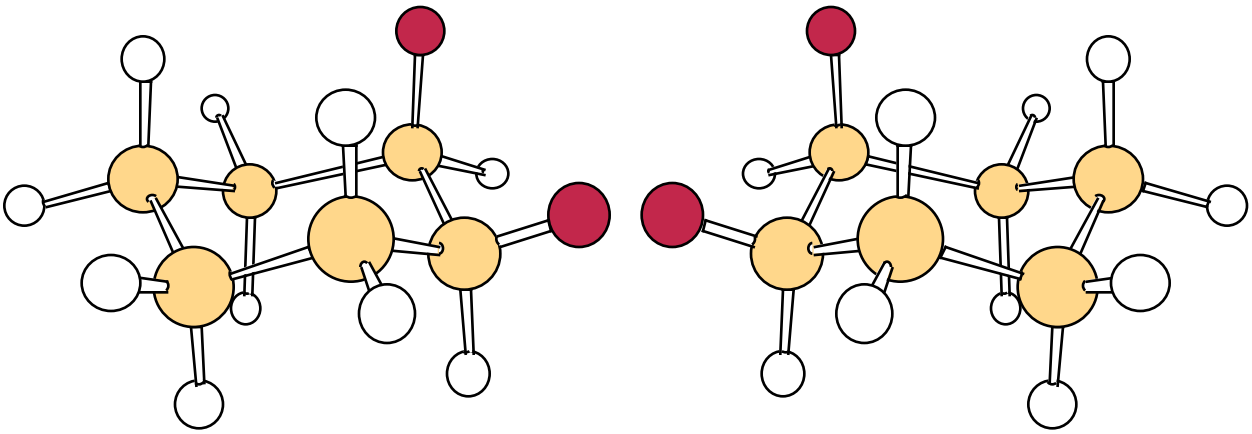
2. Conformationally Flexible Molecules

Example 3: *Cis* 1,2-Difluorocyclohexane

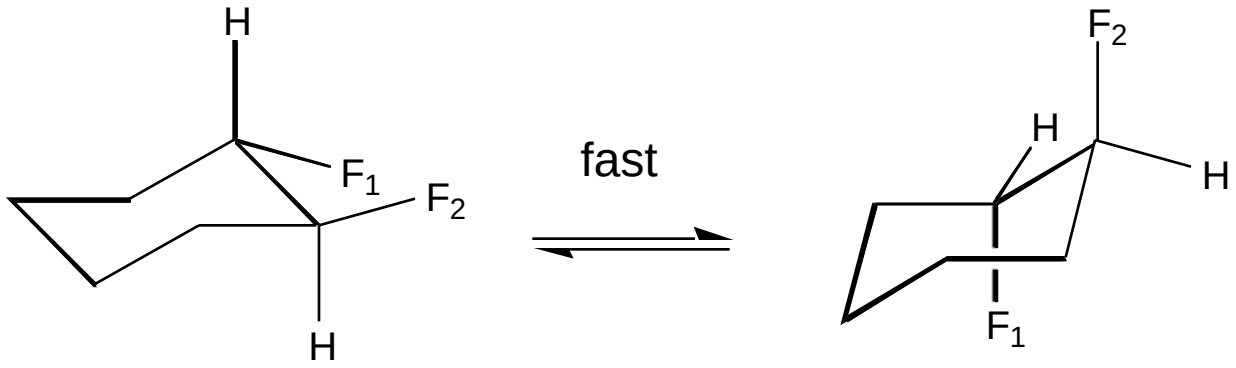


The chair form is chiral. There is no plane of symmetry and there is no inversion center. In the older approach, we can say that there are two chiral carbons and the molecule is not a *meso* form since there is no symmetry plane. No matter how you look at it: The chair is chiral. HOWEVER: There is no optical activity since the enantiomers interconvert into eachother fast and they cannot be separated.

Enantiomer 1 Enantiomer 2



Example 4: *Trans* 1,2-Difluorocyclohexane



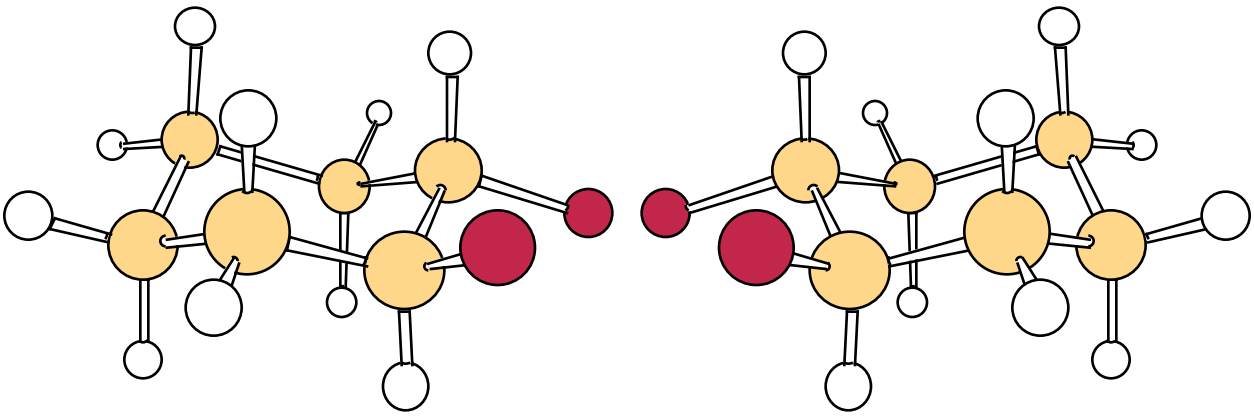
Each chair form is chiral. There is no plane of symmetry and there is no inversion center. In the older approach, we can say that there are two chiral carbons and the molecule is not a *meso* form since there is no symmetry plane. No matter how you look at it: Both chairs are chiral.

NOTE 1: The structure does **not** flip into its enantiomer!

NOTE 2: Only the e,e-structure on the left matters!

NOTE 3: The e,e-structure comes in two enantiomers.

Enantiomer 1 Enantiomer 2



Stereochemistry in Reactions

Stereochemistry is an essential aspect of chemistry and the value of every reaction depends on its ability to produce desired stereochemical outcomes. For every reaction we will be studying in future, we will looking at

Connectivity. What bonds are formed/broken?
Regiochemistry. Where does the molecule react?
Stereochemistry. What stereoisomers are formed?

Racemization Reaction (Not desirable! Avoid!)
A reaction in which a stereoisomer is converted into a racemic mixture of products. (Example: SN1 reaction.)

Stereospecific Reaction
A reaction in which one stereoisomer reacts to give one specific stereoisomer. (Example: Walden Inversion.)

Stereoselective Reaction
A reaction in which several stereoisomers are formed in unequal amounts. (Example: Asymmetric induction.)

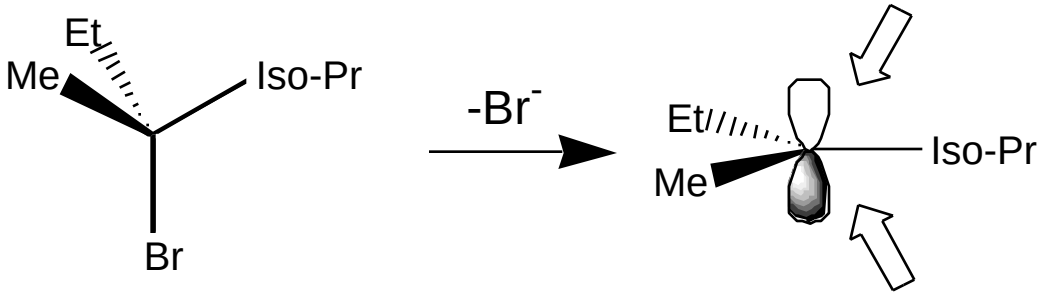
Racemization Reactions

1. SN1 Reaction

Chirality lost.

The reaction goes through a planar intermediate, the carbenium ion, which can be attacked by a nucleophile from either side with equal probability. Racemic product.

Example: Hydrolysis of tertiary halide.

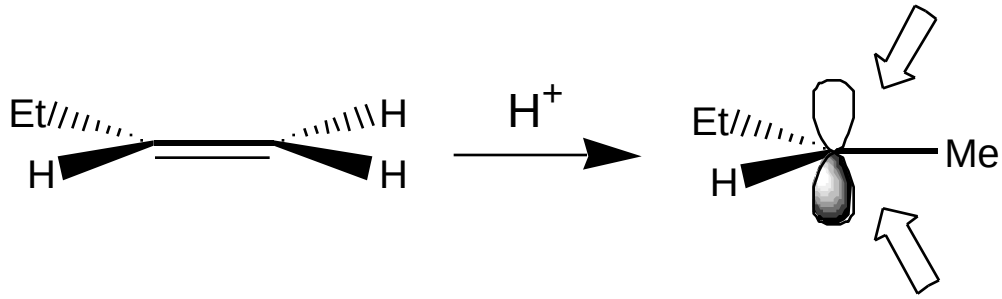


2. Addition of HBr to Alkenes

No chirality lost - no overall chirality generated.

The reaction goes through a planar intermediate, the carbenium ion, which can be attacked by the Br from either side with equal probability. Racemic product.

Example: 1-butene reacts with HBr in ether.



3. Hydrogenation of Butanone

No chirality lost - no overall chirality generated.

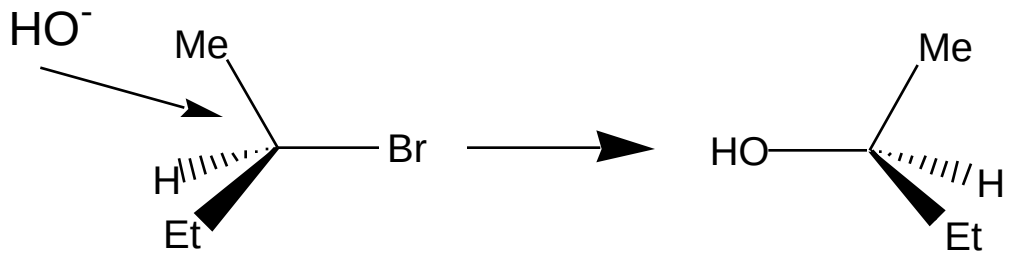
The nonchiral starting material can be reduced from either side and a racemic mixture of chiral butanols is obtained.

(Transparency)

Stereospecific Reaction

1. SN2 Reaction

Example: Base-catalyzed hydrolysis of a secondary bromide, (*R*) to (*S*).

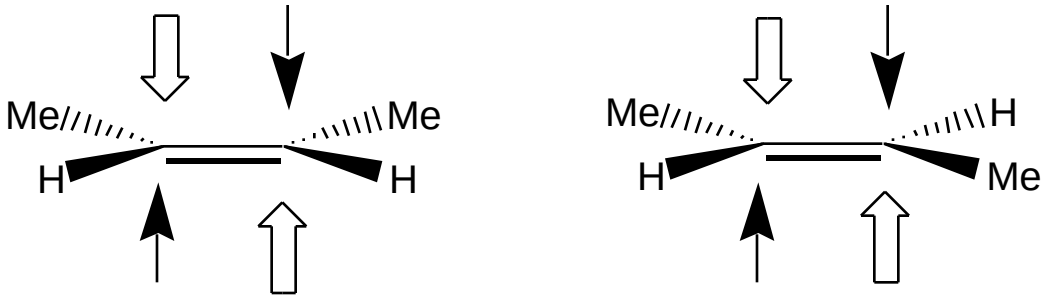


This is an example of a Walden inversion.

Stereoselective Reaction

1. Addition of Br_2 to Alkene

Two chiral carbons are formed and therefore there are in principle four possible distereoisomers. Are they all formed? No, the reaction is stereoselective because the addition is *trans*.



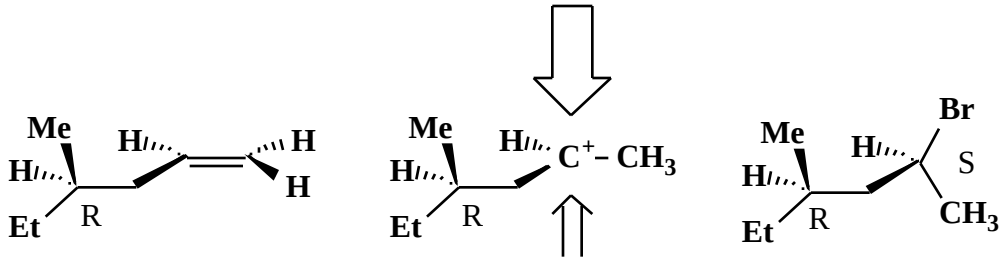
The *cis*-2-butene yields only the enantiomers (2S,3S) and (2R,3R) dibromobutane. These enantiomers are formed as a racemate.

The *trans*-2-butene yields only one product - the *meso* form (2R,3S).

2. **Hydrogenation of a Chiral Alkene - Chiral Induction** (Transparency)

Heterogeneous hydrogenation of 2-methylcyclopentanone. Because of the methyl group, one way of absorption of the ketone on the surface is greatly preferred over the other. Consequently, the hydrogenation will result in the preferential formation of one diastereoisomer. Unequal amounts of diastereoisomers will be formed. This reaction is **diasteroselective**.

3. **Addition of HBr to a Chiral Alkene - Chiral Induction**
Consider the HBr addition to the *pure enantiomer of R-4-methylhexene*. Protonate and form a carbenium ion.



Again, the carbenium carbon will be planar **but the two faces of the carbenium ion will no longer be the same!** Attack of the bromine from one face will be preferred and at the carbenium carbon one configuration will be formed preferentially. Unequal amounts of diastereoisomers will be formed. This reaction is **diasteroselective**.

The transition states for the formation of the diastereoisomeric products are diastereoisomeric. It is this difference in the TS energies that causes the chiral induction.