# TOPIC 4. STEREOCHEMISTRY

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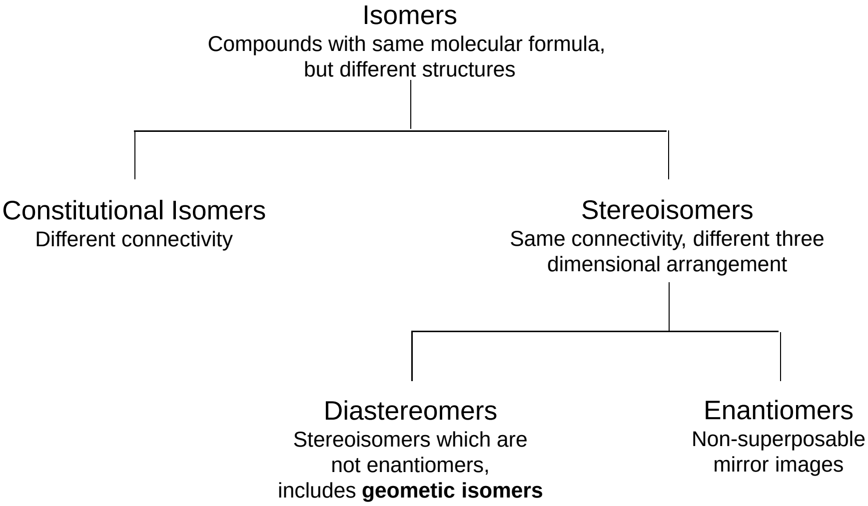
## OBJECTIVES

1. Discuss the three-dimensional structure of organic molecules
2. Recognize enantiomers, diastereomers, meso compounds
3. Provide *R/S* designations of stereocenters
4. Calculate optical rotations, enantiomeric excesses
5. Use molecular models to determine the 3D arrangement of atoms in chiral molecules

# RECOGNIZING ISOMERS



- Isomers
  Compounds with same molecular formula, but different structures
  - Constitutional Isomers
    Different connectivity
  - Stereoisomers
    Same connectivity, different three dimensional arrangement
    - Diastereomers
      Stereoisomers which are not enantiomers, includes **geometic isomers**
    - Enantiomers
      Non-superposable mirror images

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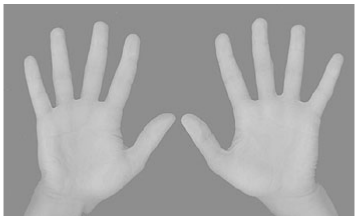
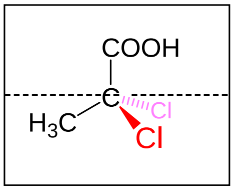
# CHIRALITY: ENANTIOMERS

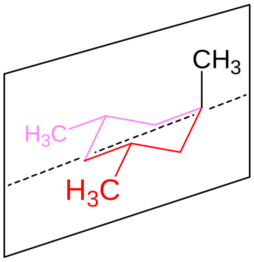
An object (molecule) which has a non-superposable* mirror image is chiral (the opposite of chiral is “achiral”).



## Symmetry: Mirror Planes and Centers of Inversion

Another test for chirality is to assess whether the object itself has a mirror plane of symmetry or point of symmetry (point of inversion). Objects (molecules) with mirror planes or centers of inversion are achiral (NOT chiral)



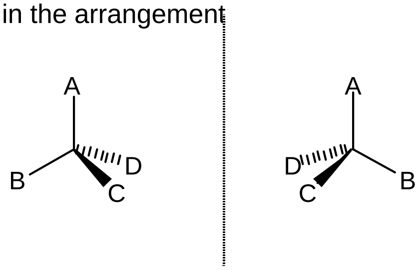


Objects (molecules) without a mirror plane or point of inversion are chiral. They are non-superposable on their mirror images.

## Enantiomers

Molecules can be *chiral*. Pairs of molecules which are non-superposable mirror images of one another are called *enantiomers*. Enantiomers are examples of *stereoisomers*: molecules which differ only in the spatial arrangement of atoms.

Molecules with a single carbon atom bearing *four different* substituents can exist as a pair of enantiomers which differ in the arrangement ("configuration") of these substituents.

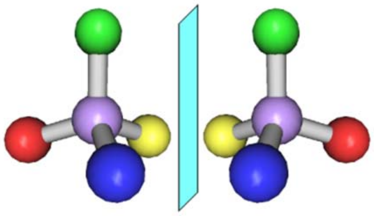


The carbon is *stereogenic*

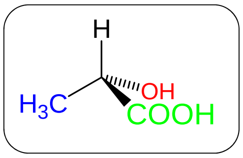
The carbon is a *stereocenter*

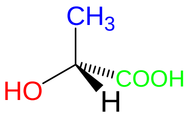
A 1:1 mixture of enantiomers is called a racemic mixture

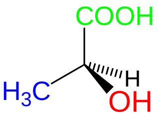
You must be able to recognize when pairs of molecules are identical (superposable) or entaniomers (non-superposable mirror images)



*Problem:* Which of the following are identical to the first structure?







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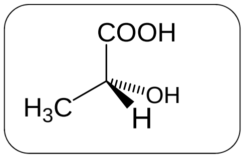

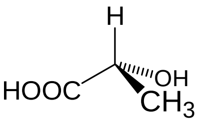

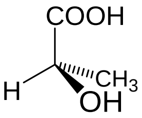

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## Designating Configuration

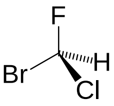
Stereocenters are designated as having either *R*- or *S*-configurations….

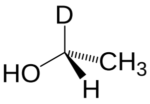
- Assign priorities to the substituents using the *Cahn-Ingold-Prelog system* (briefly, atoms are ranked in order of atomic number (if isotopes are present, the heavier isotope has higher priority); if two atoms are identical, the next set of attached atoms is considered).
- View the molecule with the lowest priority (d) substituent pointing away from you.
- Trace from highest priority (a) to second priority (b), to third (c)….

Clockwise = *R*

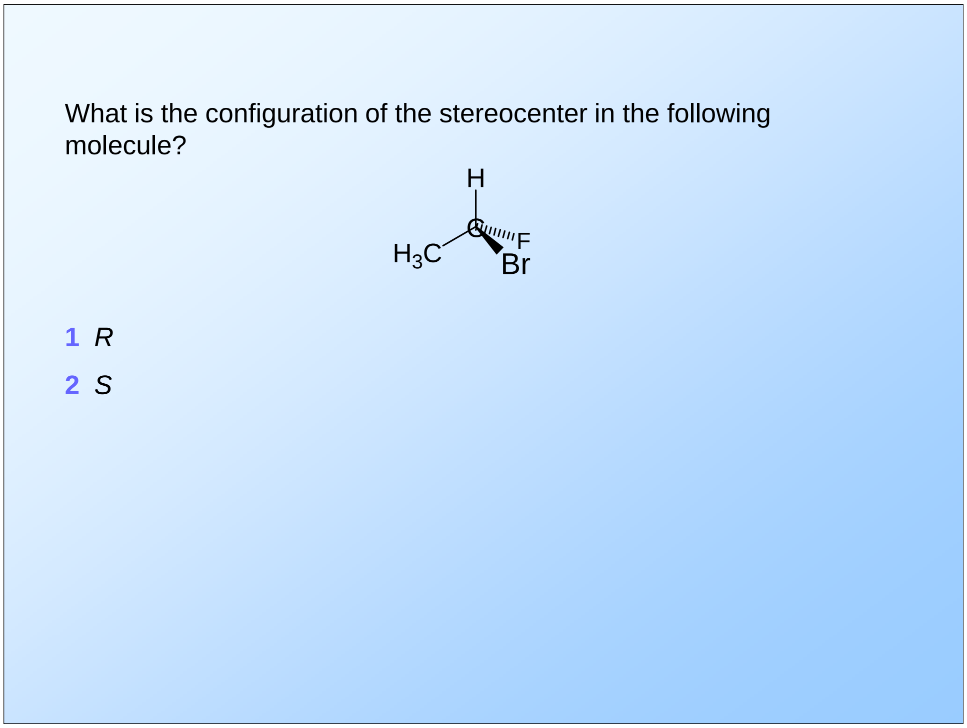
Counterclockwise = *S*

*e.g.*,





D = deuterium = $^2$H;
D > H



What is the configuration of the stereocenter in the following molecule?

1 *R*

2 *S*

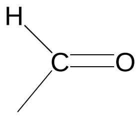
## Ranking Substituents

If the atoms joined to the chiral center are identical, you must consider the set of three atoms connected to them:

$-C(CH_3)_3$ ||| C(C,C,C) > $-CH(CH_3)_2$ ||| C(C,C,H) > $-CH_2CH_3$ ||| C(C,H,H) > $-CH_3$ ||| C(H,H,H)

$-CH_2OH$ C(O,H,H) > $-C(CH_3)_3$ C(C,C,C)

A double bond is considered to be two bonds to the next atom:



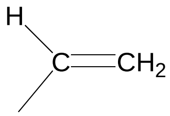
C(O,O,H)

>

$-CH_2OH$

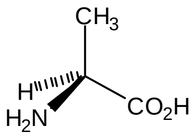
C(O,H,H)

>

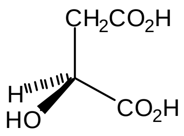


C(C,C,H)

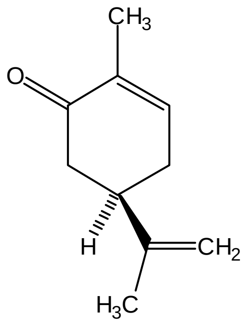
# Examples of Chiral Molecules



*S*-alanine
(an α-amino acid)

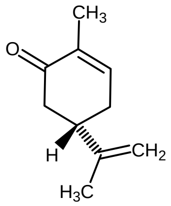


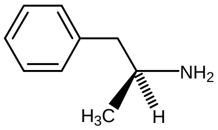
*S*-malic acid
(from apples)

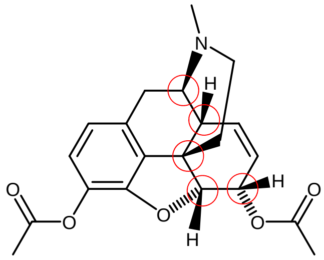


*R*-carvone
(spearmint)

*Problem:* What is the configuration of each stereocenter (chiral carbon atom) in each of the following compounds?

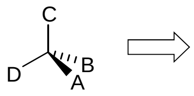


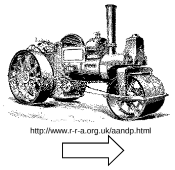




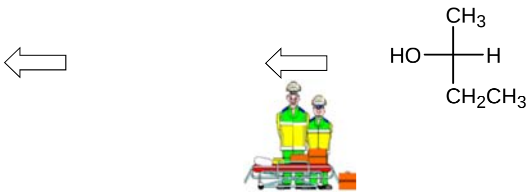
# FISCHER PROJECTIONS

Orient the molecule so that *substituents oriented up and down are pointing away from you* and then apply a steamroller.




http://www.r-r-a.org.uk/aandp.html

Converting a Fischer projection back into a 3D tetrahedral representation.



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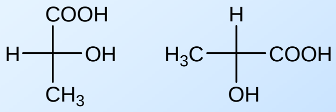
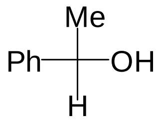
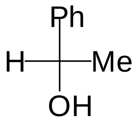
What is the configuration of the following two molecules?

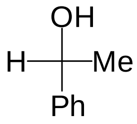


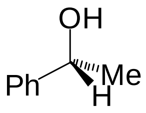
**1** *R* and *R*
**2** *R* and *S*
**3** *S* and *R*
**4** *S* and *S*

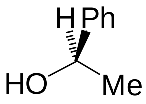
*Problem*: Which of the following represent the *S*-enantiomer of 2-phenyl-1-ethanol, which ones are *R*?







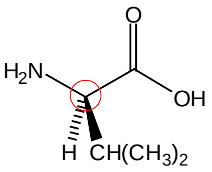




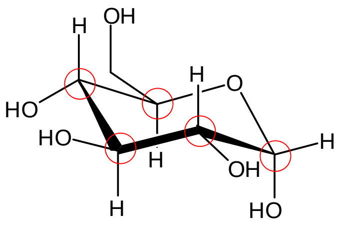
## WHY IS STEREOCHEMISTRY IMPORTANT?

### Chirality in Nature

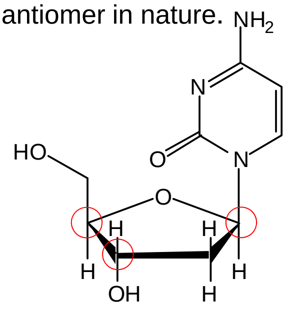
Most biomolecules are chiral and only exist as one enantiomer in nature.



Amino acids
(in proteins)
*e.g.*, valine



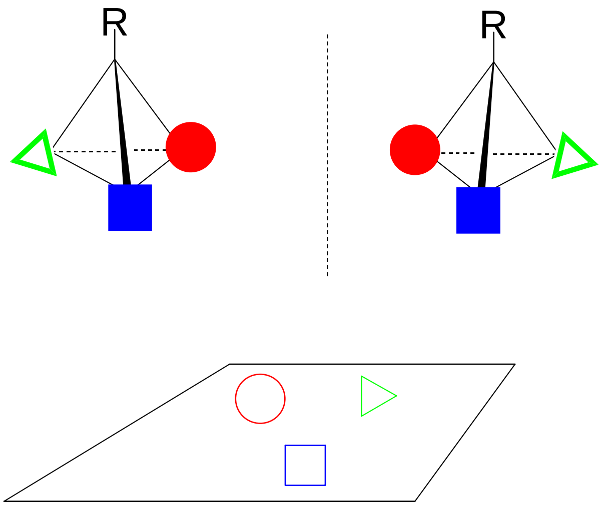
Carbohydrates
(sugars)
*e.g.*, glucose



Nucleotides
(in DNA)
*e.g.*, cytosine

*Problem:* What is the configuration of each stereocenter (chiral carbon atom) in each of the above compounds?

## Interaction between the Body (Receptors) and Chiral Drugs



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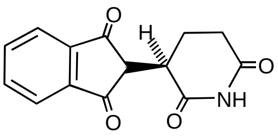
## Chiral Pharmaceuticals: Thalidomide

The racemate of thalidomide was marketed in Europe in early 1960s for treatment of morning sickness. One enantiomer is a sedative. However, the other causes birth defects.

Today, both enantiomers of any pharmaceutical must be tested for efficacy and side effects. Recent studies have shown that thalidomide may be effective against HIV, cancer, leprosy and other inflammatory disorders.

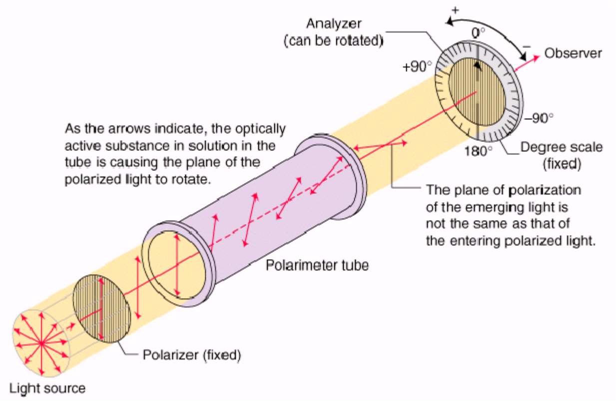


*Problem:* Which enantiomer of thalidomide is shown above?

# ROTATION OF PLANE-POLARIZED LIGHT

Enantiomers have identical physical and chemical properties in the absence of other chiral molecules, except for their influence on plane-polarized light.

## Polarimetry



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## Optical Rotation

The observed rotation is: $\alpha$

The observed specific rotation is: $[\alpha] = \alpha / c\cdot l$

where $c$ = concentration of solution (in g/mL) and $l$ = pathlength in dm (1 dm = 10 cm = $10^{-1}$ m)

$\alpha$ and $[\alpha]$ depend on solvent, temperature and wavelength of the polarized light. Generally the sodium D line is used for the light source and the experiment is done at room temperature, 25 °C.

The specific rotation is then noted as

$$[\alpha]^{25}_{D} \text{ (conc./solvent)}$$

The specific rotation of an optical pure chiral compound is a “property” (like melting point or boiling point)

The specific rotation, $[\alpha]$,of a given sample depends on its “optical purity”. Only the excess of one enantiomer over the other gives rise to a rotation.

## Optical Purity

*The rotation of enantiomers are equal but opposite.* If the [α] of the *R*-enantiomer of compound **A** is +100°, the [α] of the *S*-enantiomer is _____

The [α] of a equal mixture of the *R*- and *S*-enantiomers (racemic mixture) is _____

The % excess amount of one enantiomer over the other is called the *enantiomeric excess* (ee). *e.g.*,

100% *R*, 0% *S*: *ee* = ____
50% *R*, 50% *S*: *ee* = ____
70% *R*, 30% *S*: *ee* = ____

*Problem*: The [α] of the *R*-enantiomer of compound **A** is +100°. The [α] of a certain mixture of *R*- and *S*-enantiomers of compound **A** is -50°. What is the ee of this mixture? What is the % *R*-enantiomer in this mixture?

## Other Terminology

*Review:* The terminology "*R*-enantiomer of compound **A**" refers to its absolute configuration using the Cahn-Ingold-Prelog system

*<u>If</u>* the [α] of (*R*)-**A**, is (+) we can also refer to it as (+)-**A** or (*d* )-**A**, where *d* stands for dextrorotatory (clockwise).

*<u>In this case</u>*, the [α] of (*S*)-**A**, would be (-) and we can also refer to it as (-)-**A** or (*l* )-**A**, where *l* stands for levotrorotatory (counterclockwise).

Thus, (+) = (*d*), and (-) = (*l*)

An equal mixture of the *R*- and *S*-enantiomers of compound **A**, is called a *racemic mixture* and is noted as (*R*/*S*)-**A**, or (±)-**A** or (*d*,*l* )-**A**.

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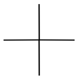
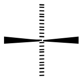
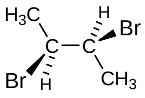
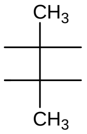
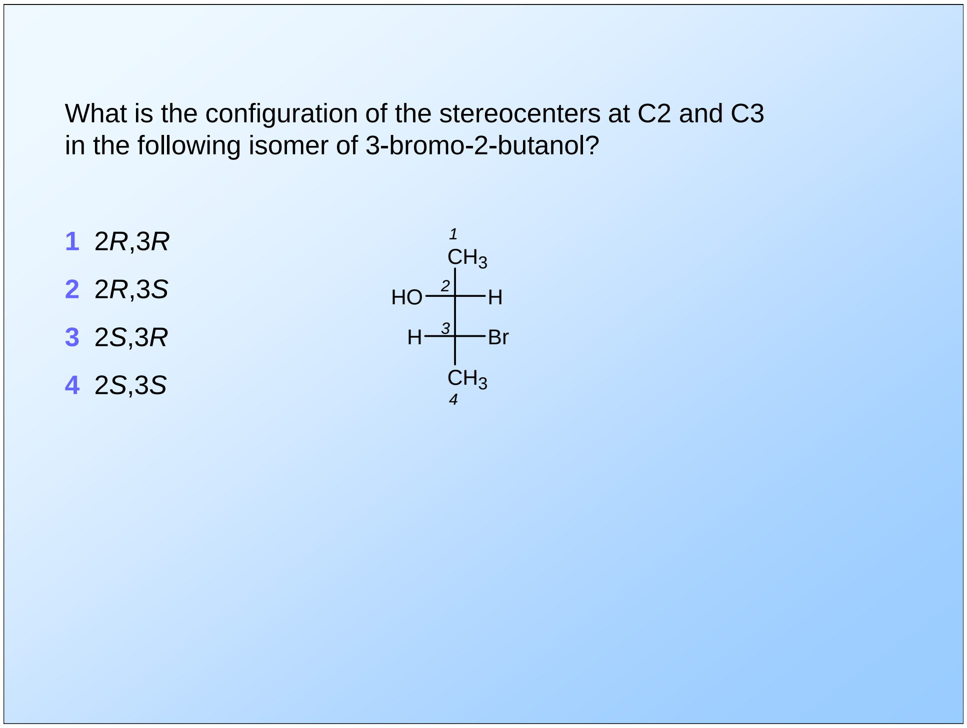
## STEREOISOMERS WITH MORE THAN ONE STEREOCENTER

For Fischer projections of compounds with more than one stereocenter, remember that each  represents  *and <u>consider each stereocenter</u> <u>one at a time</u>*

*Problem:* Complete the Fischer projection on the right to represent the molecule on the left. *Consider the configuration of the two carbon atoms independent of one another.* Provide a complete name for this compound (including stereochemistry!) Is this compound chiral?







What is the configuration of the stereocenters at C2 and C3 in the following isomer of 3-bromo-2-butanol?

1 2*R*,3*R*
2 2*R*,3*S*
3 2*S*,3*R*
4 2*S*,3*S*

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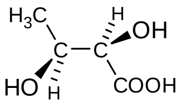
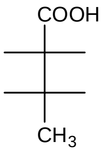
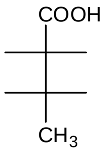
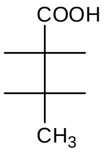
## Diastereomers

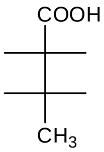
*Problem:* Draw all the stereoisomers of $CH_3CH(OH)CH(OH)COOH$:









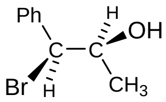


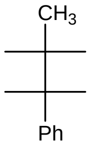
If the <u>sets of substituents</u> on stereogenic centers are different there will be $2^n$ stereoisomers.

Stereoisomers which are not mirror images of each other are called *diastereomers*.

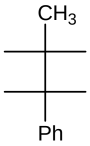
Diastereomers have *different* properties from each other (e.g., solubility, mp, bp, polarity). They can be separated by recrystallization, distillation or chromatography.

*Problem:* Complete the Fischer projection of the following compound

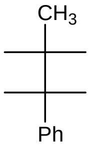


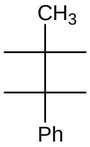


*Problem:* Draw the enantiomer of the compound shown above



*Problem:* Draw *two* diastereomers of the molecule shown above.





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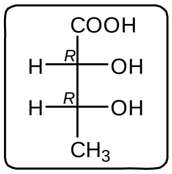
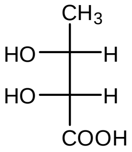
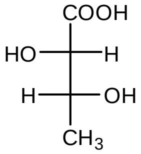
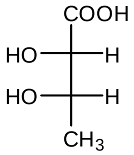
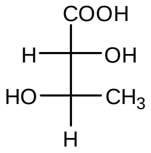
*Problem*: What is the relationship between the first structure and each of the others (identical, enantiomers, diastereomers)?





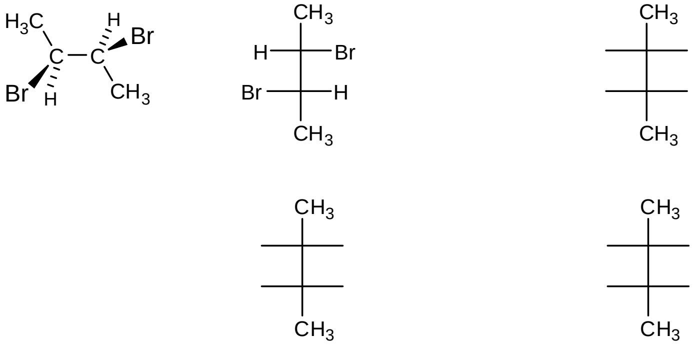






## Meso Compounds

If the <u>sets of substituents</u> on stereogenic centers are identical there will be fewer than $2^n$ stereoisomers.



Compounds with stereogenic centers which are *not* chiral are called *meso compounds.*

*Meso* compounds possess a point or plane of symmetry (in at least one conformation)

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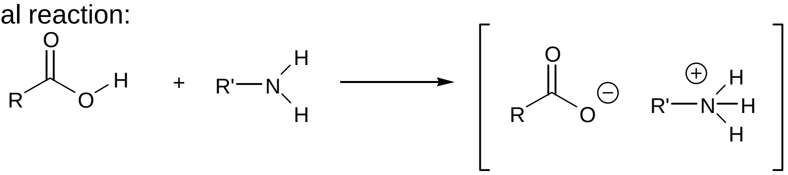
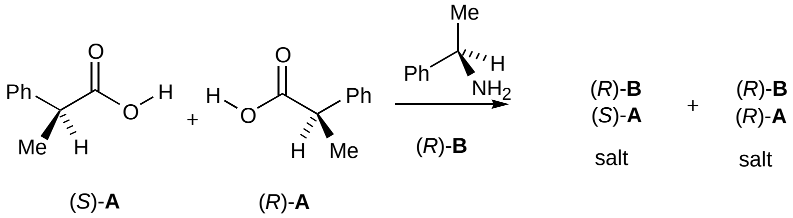
# SEPARATION OF ENANTIOMERS

Enantiomers have identical physical properties. Racemic mixtures of carboxylic acids can be treated with a pure enantiomer of an amine to form a pair of *diastereomeric* ammonium carboxylates which has different properties

general reaction:

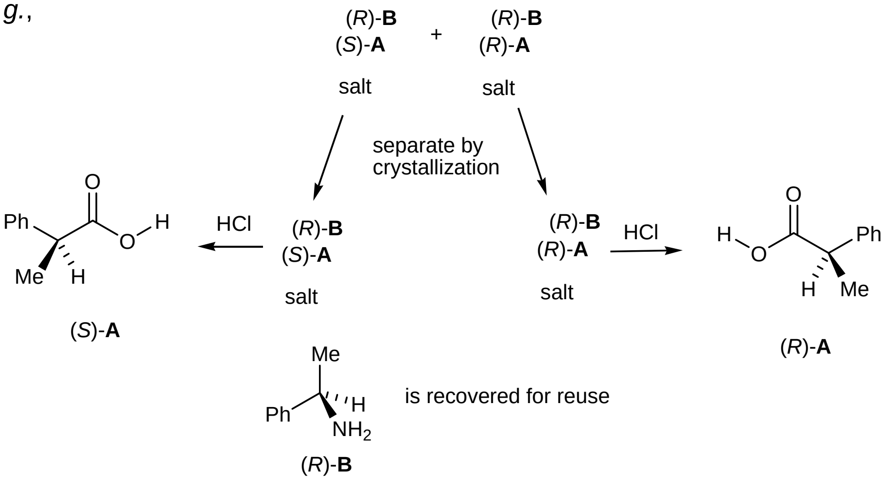


*e.g.*,



The pair of *diastereomeric* ammonium carboxylates can usually be separated by recrystallization (with hard work and luck) and the two acids (and the amine) recovered.

*e.g.*,



*acid-base chemistry to convert diastereomeric ammonuim carboxylate to carboxylic acid:*

$RCOO^- \ R'NH_3^+ + HCl \qquad RCOOH + R'NH_3^+Cl^-$

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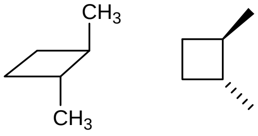
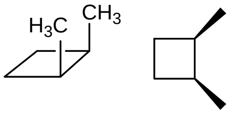
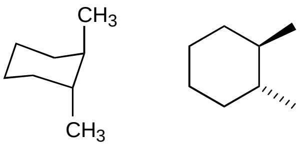
# CYCLIC COMPOUNDS

*e.g., trans- and cis-1,2-dimethylcyclobutane*



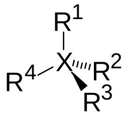


*e.g., trans-1,2-dimethylcyclohexane*

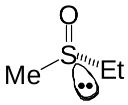


# OTHER CHIRAL COMPOUNDS

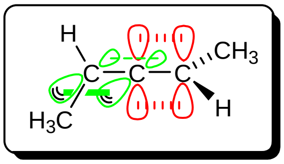
## Non-Carbon Stereocenters

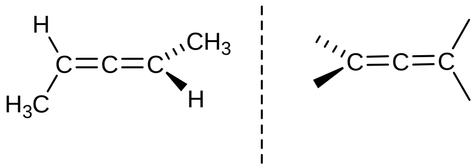


X = Si, $N^+$, $P^+$, etc

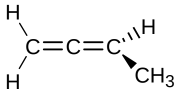


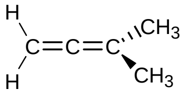
## Chiral molecules without stereocenters: Allenes (C=C=C)

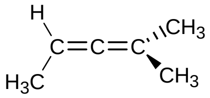




*Problem*: Which of the following are chiral?







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# TOPIC 4

## Key Concepts

- Recognize enantiomers, diastereomers, meso compounds
- Provide R/S designations of stereocenters
- Calculate optical rotations, enantiomeric excesses