

# Chapter 6: Stereochemistry

Stereochemistry - The study of stereoisomers

stereoisomers → molecules that have the same connectivity but differ in the way the atoms are arranged in space.

CHIRAL OBJECT → any object that is NOT superimposable on its mirror image

- example of a chiral object - YOUR HANDS (each is chiral)



⇒ if you hold your right hand in front of a mirror, you see an image of your left hand (vice versa)

⇒ your right and left hands are related to each other as mirror images <sup>BUT</sup> your hands are NOT superimposable on each other (They are CHIRAL)

- If an object IS superimposable on its mirror image it is ACHIRAL

example:



a Chair

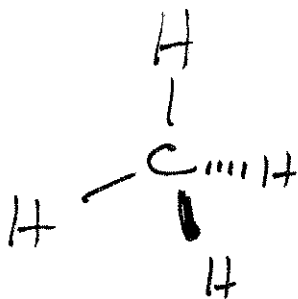
achiral object

(6-1)

# Molecular Examples

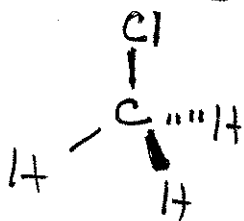
CHIRAL or  
ACHIRAL?

methane

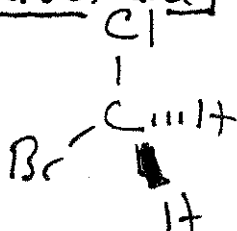


mirror image

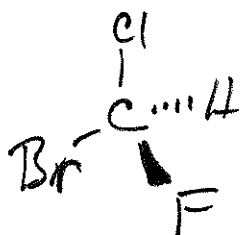
chloromethane



bromochloroethane



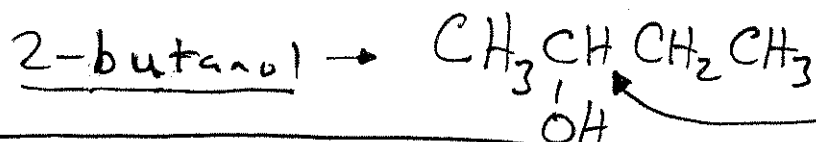
bromochlorofluoromethane



- Non superimposable (or nonidentical) mirror images referred to as **ENANTIOMERS**
- Carbon atom in bromochlorofluoromethane is Asymmetrical → it has 4-different substituents attached

- Any compound with 1 (and only 1) asymmetric carbon atom will always be chiral

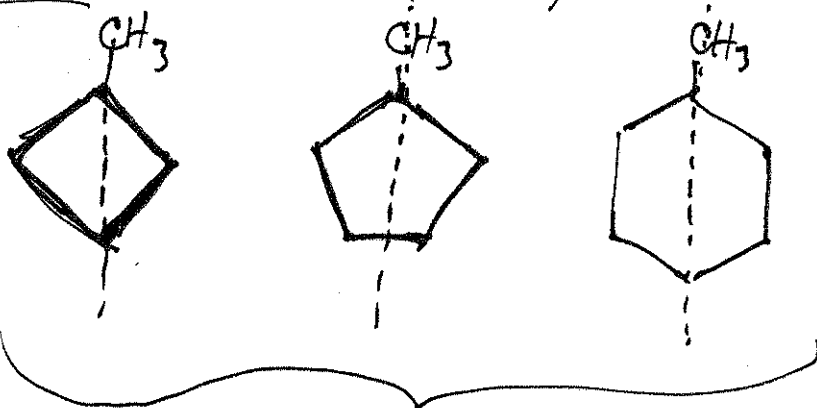
→ A chiral carbon atom is referred to as a stereocenter



4 different groups bonded to this carbon  
→ an asymmetric carbon (a stereocenter)  
Molecule is CHIRAL

## Chirality in Cycloalkane Derivatives

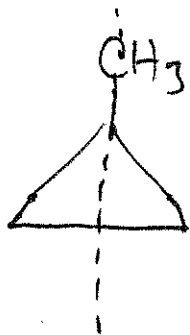
- Monosubstituted Cycloalkanes - ACHIRAL



Unless substituent attached has an asymmetric carbon

All achiral

- each possesses an internal plane of symmetry

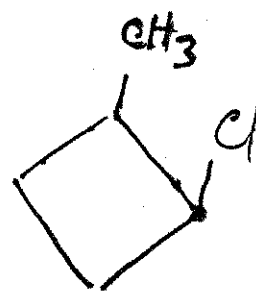
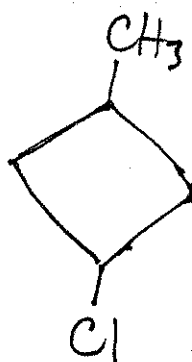
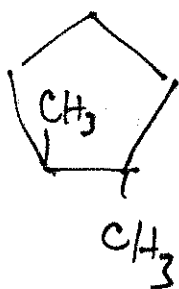
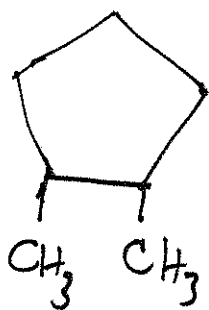


← ACHIRAL as well

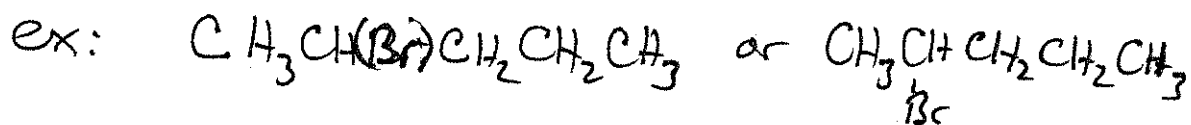
a molecule can not be chiral if an internal plane of symmetry is present

• Chiral Cycloalkanes are possible → depends on substitution

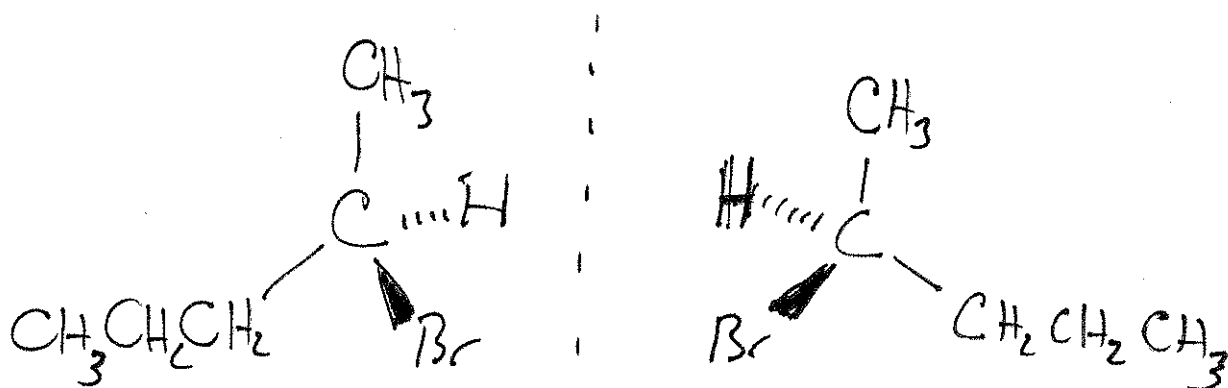
\* Determine whether the following pattern disubstituted cycloalkanes are Chiral or achiral.



• One cannot distinguish stereoisomers by looking at their condensed formula



→ need to show stereochemistry (line, wedge dash drawing)



no internal plane of symmetry

Pair of Enantiomers

non-superimposable mirror images (6-4)

# Physical Properties of Enantiomers

→ Many are exactly the same:

1. Melting Points
2. Boiling Points
3. Solubility Characteristics
4. Density
5. Spectra (IR, NMR, UV-vis, MS, .. etc)
6. Chemical reactivity towards Achiral reagents

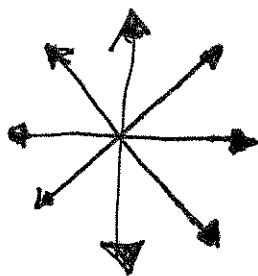
\* Only two sets of properties are different for a pair of enantiomers

1. Reactivity with other chiral reagents (ex: enzymes)

2. Interaction with plane polarized light  
↗ (also called OPTICAL ACTIVITY)

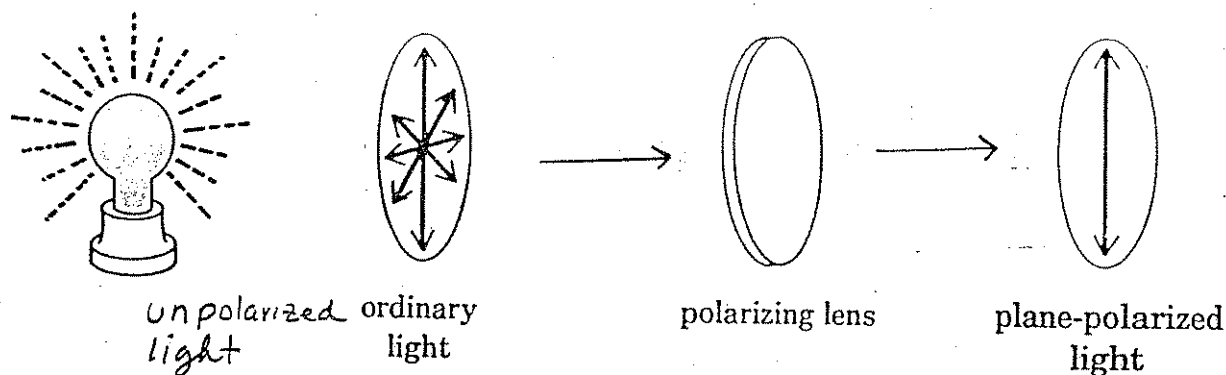
Allows us to physically distinguish enantiomers

• Ordinary Light: has magnetic + electric field vectors



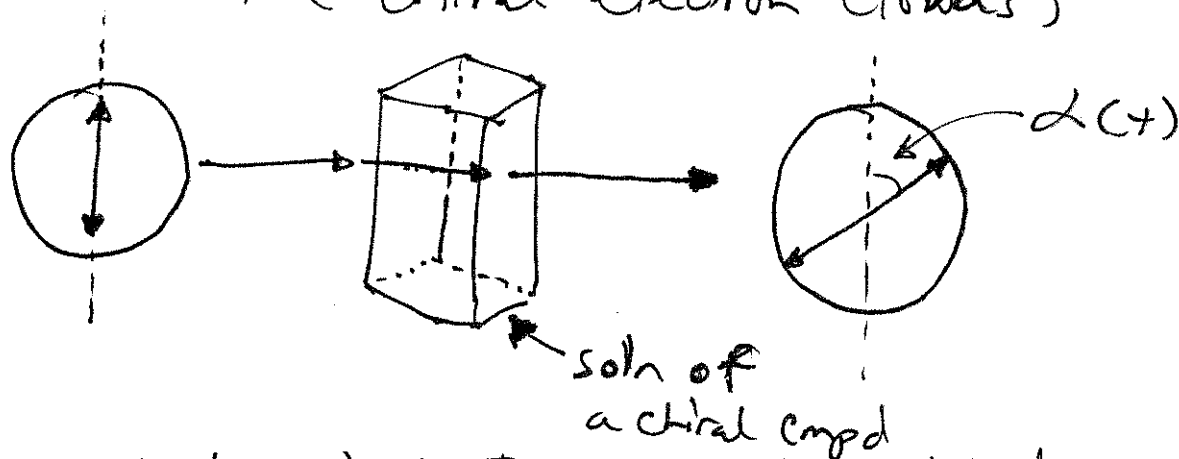
oriented in all possible directions

- Pass light Through a polarizer; light is filtered such that all vectors are in the same plane



- When the plane polarized light is passed through a solution containing a chiral molecule, the plane of light will be rotated.

(Rotation is due to the interaction with the chiral electron clouds)



- amount by which the light is rotated =  $\alpha$  (in degrees)
- $\alpha (+)$  = clockwise (dextrarotatory)
- $\alpha (-)$  = counterclockwise (levorotatory)

$\alpha$  varies  $\rightarrow$  depends on:

- 1) Concentration of the chiral molecule in solution
- 2) length of the sample tube

So, report:

Specific Rotation  $\leftarrow$  is a specific physical property of a chiral compound

$$[\alpha]_D^t = \frac{\alpha}{l \cdot c}$$

$t$  = temp in  $^{\circ}\text{C}$

$D$  = light wavelength  
(Na D line)  
5890 Å

$l$  = tube length  
(usually 1 dm)

$c$  = conc. in  $\frac{\text{g}}{\text{mL}}$

ex: sucrose solution: 0.10  $\frac{\text{g}}{\text{mL}}$   
 $\alpha = +6.65$  at the Na D  
line in a 10 cm cell ( $= 1 \text{ dm}$ )

$$[\alpha]_D = \frac{+6.65}{1 \times 0.1} = +66.5$$

$\leftarrow$  (in magnitude)

Enantiomers: 1) have exactly equal, but opposite optical rotations  
 $\leftarrow$  (in sign)

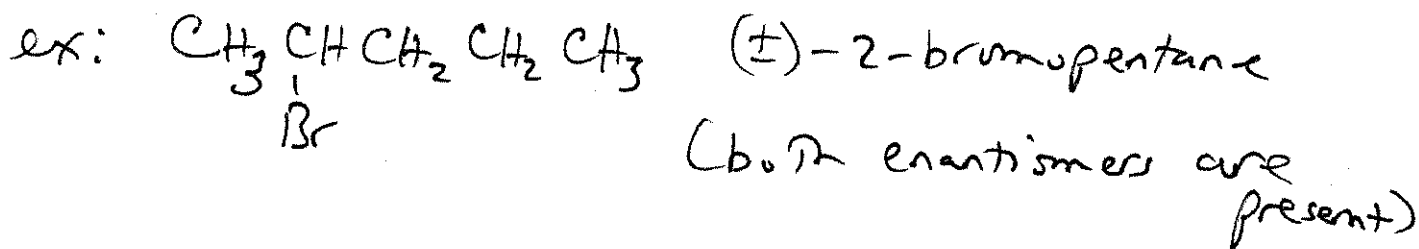
(have to determine (+) or (-) experimentally)  $\rightarrow$  2) The sign (+) or (-) DOES NOT correspond to whether the enantiomer is R or S

3) An equimolar mixture of enantiomers gives a NET rotation of ZERO

(6-7)

- An equimolar mixture of enantiomers is called a **Racemic Mixture** (Racemate)

→ designated by (±) - Compound name



- Can't separate enantiomers by ordinary physical means. Why?

## Optical Purity

**Enantiomeric excess = % ee** ⇒ tells us about the excess of one enantiomer over another

$$\% ee = \frac{\text{observed spec. rotation of mixture}}{\text{Spec. rotation of pure enantiomer}} \times 100$$

ex: impure sample of 2-iodobutane  
found  $[\alpha]_D = +12.7$

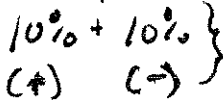
$$= \frac{+12.7}{+15.9} \times 100 = 80\% = \% ee$$

} 90% dextra rotatory  
} 10% leura rotatory

known spec. rotation of pure (+)-2-iodobutane

$$80\% + 20\% = 100\%$$

$$\uparrow \quad \downarrow$$



→ This portion gives a zero rotation (rotations cancel each other out)

The excess (+) enantiomer gives the net (+) rotation

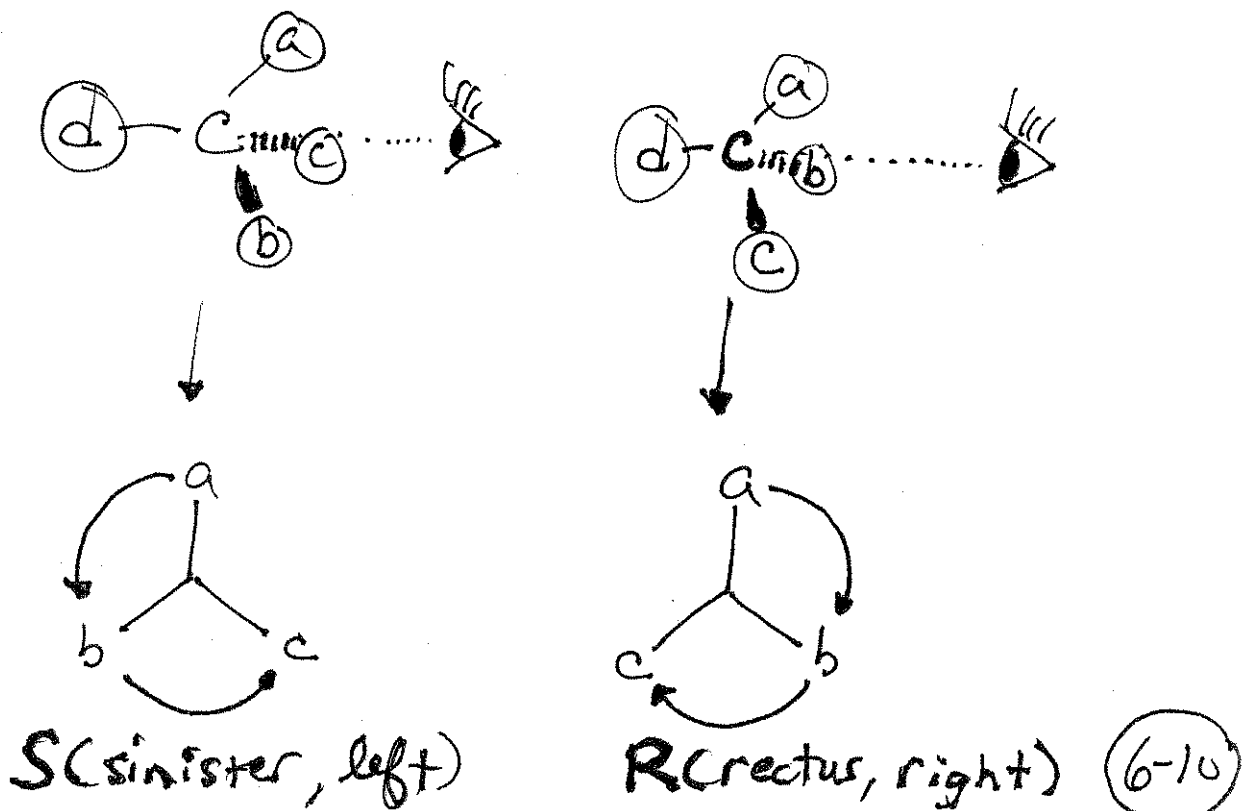
$$80\% (+) + 10\% (+) = 90\% \alpha (+) \quad 10\% \alpha (-)$$



- For The assignment of The Absolute Configuration of a chiral center use the

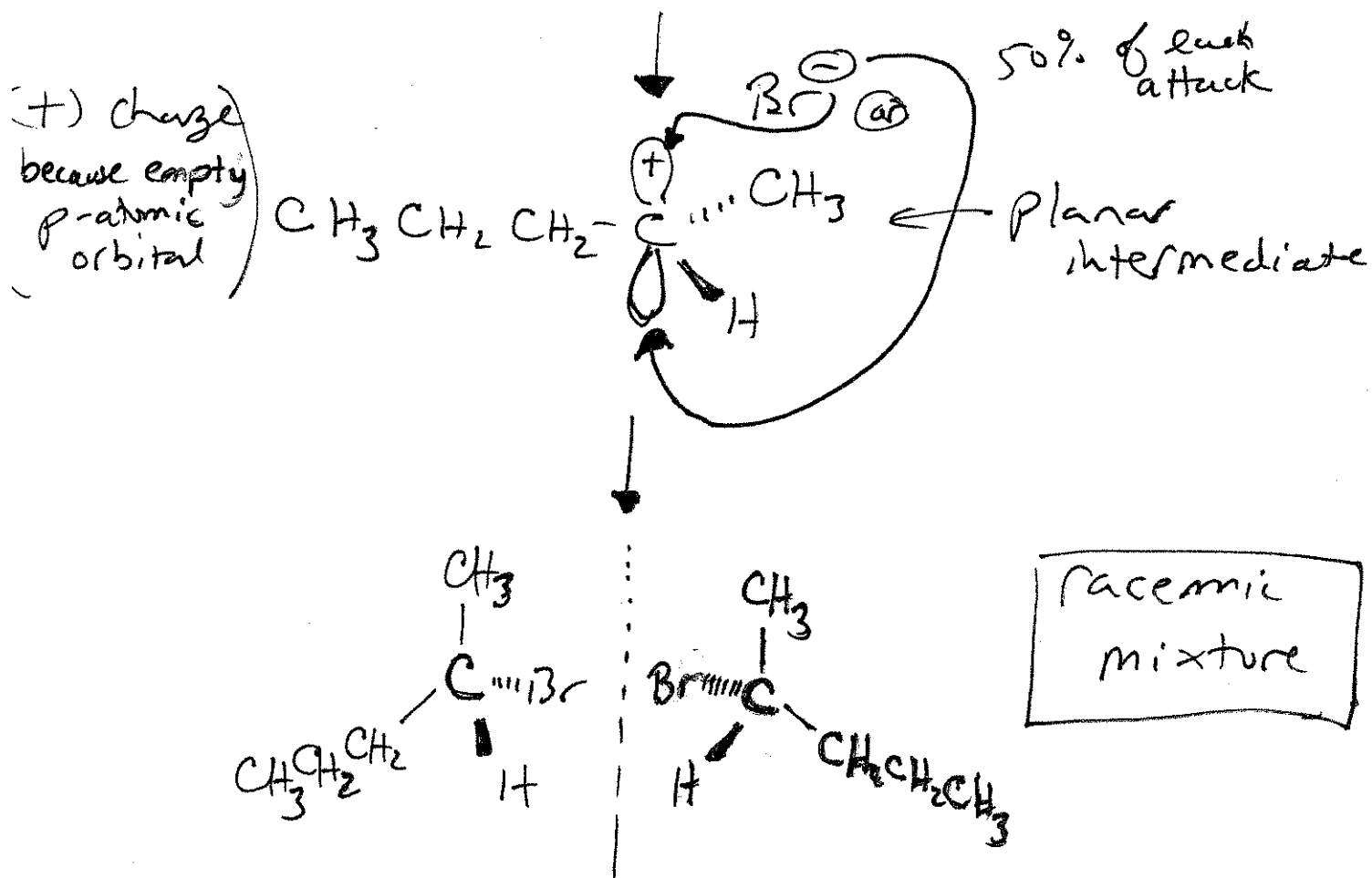
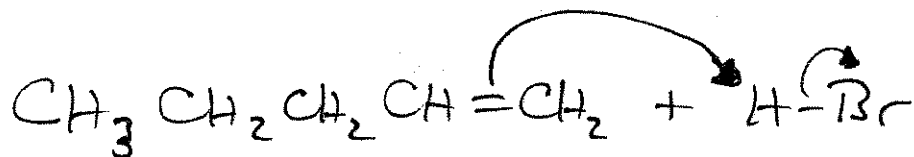
R, S System of Nomenclature

- Identify The 4 substituents attached to an asymmetric carbon and assign each a priority (a, b, c, d) using The Sequence rules such That  $a > b > c > d$  (will explain later)
- Orient The molecule in space such That you view The bond from carbon (c) to The substituent of LOWEST priority.



# Addition of H-Br to 1-pentene

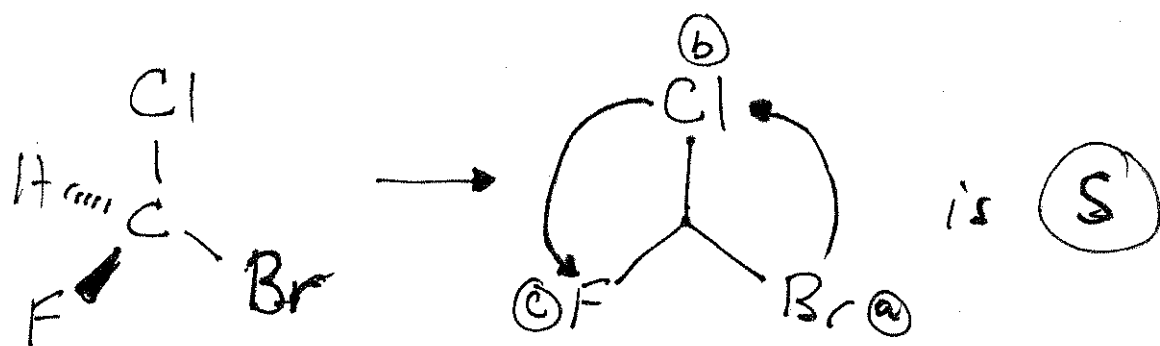
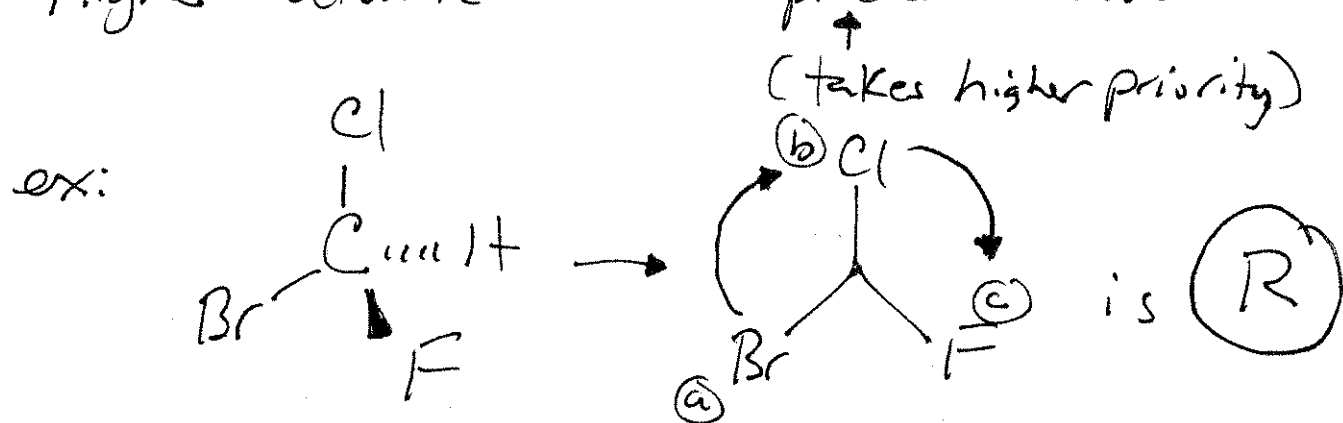
→ example of a reaction that forms a racemic mixture



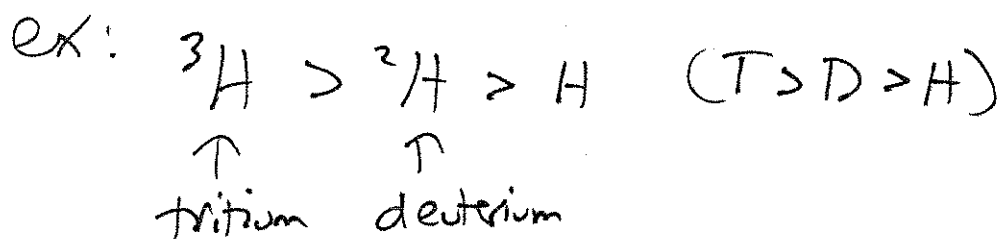
- The bromide ion,  $\text{Br}^-$ , can attack the planar carbocation intermediate from either face (above or below the plane)
  - There is an equal probability to attack either side

The **SEQUENCE RULES**: method whereby  
 The 4-substituents are assigned priorities

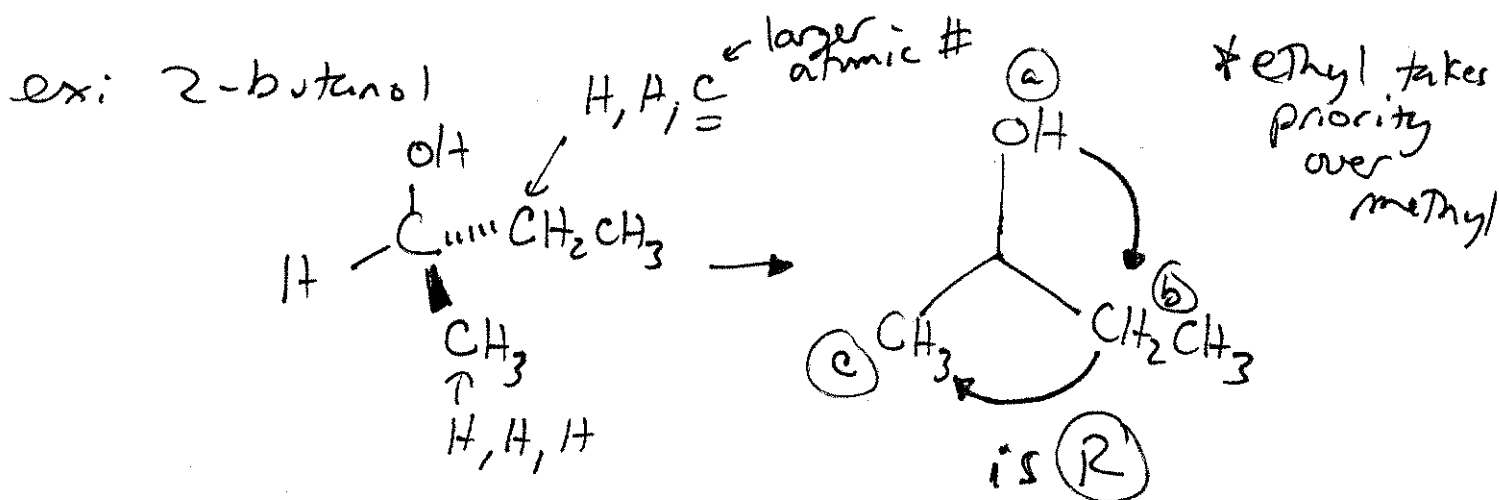
1. For The 4-atoms bonded to The carbon,  
 higher atomic number precedes lower



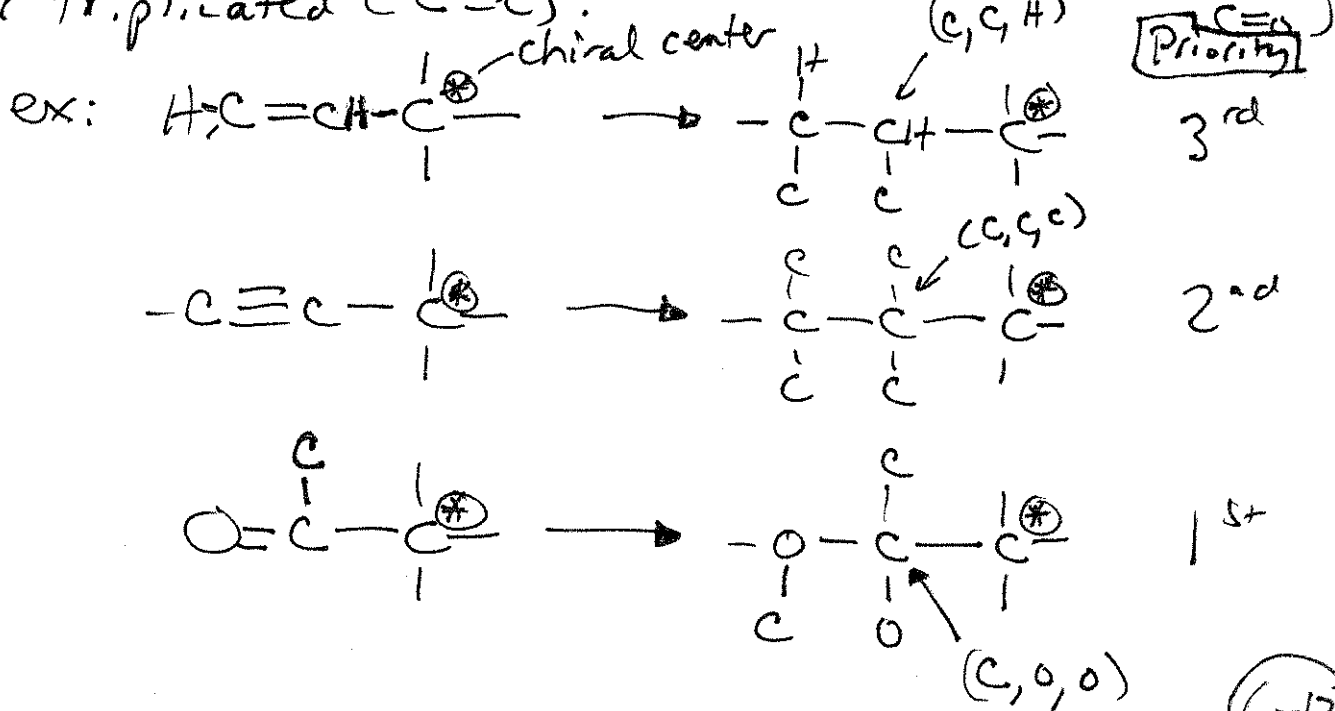
2. If The two atoms attached are  
 isotopes of each other, higher atomic  
 mass precedes lower.



3. If The two atoms directly attached to The asymmetrical carbon are The same, work outward along The two chains until a point of difference is reached. Priorities are assigned at The 1<sup>st</sup> point of difference

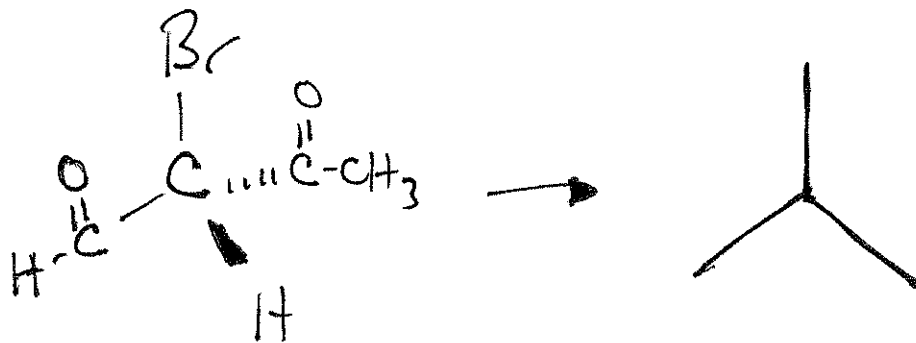
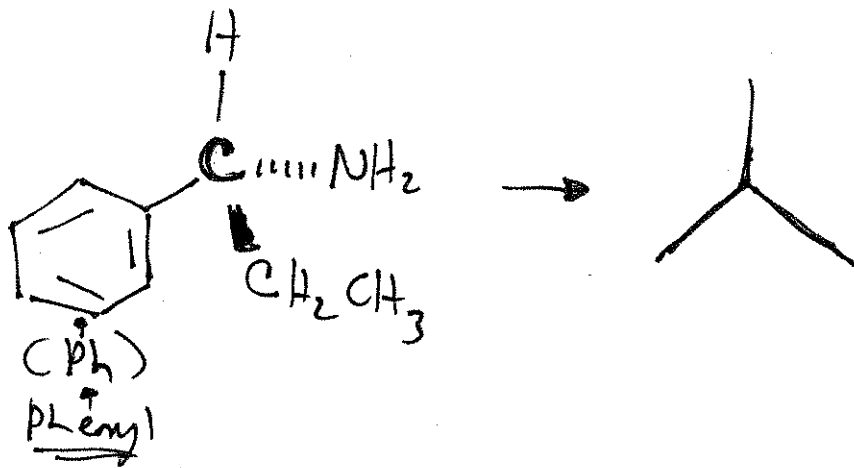
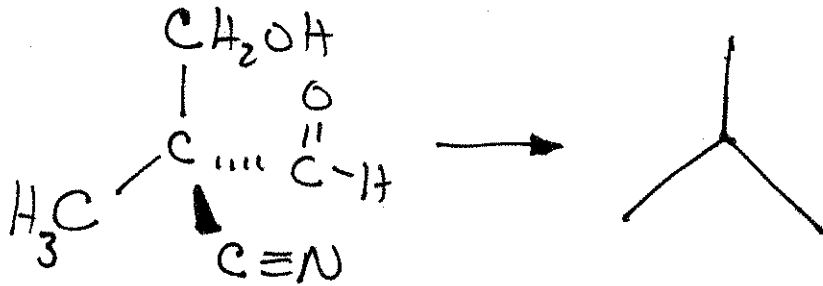
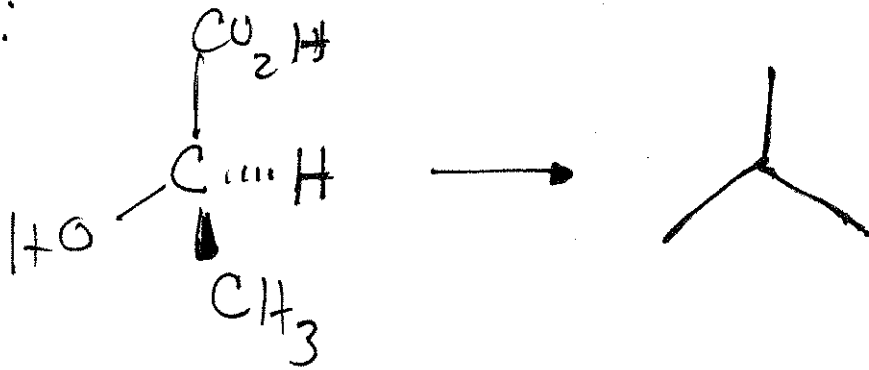


4. Double bonds and Triple Bonds are treated by assuming that each bonded atom is duplicated or triplicated ( $\text{C} \equiv \text{C}$ ).



R or S?

ex:



# Dia stereoisomers

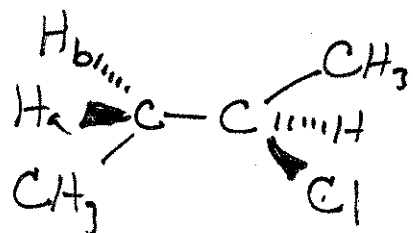
→ stereoisomers that are NOT enantiomers

(not mirror images of each other)

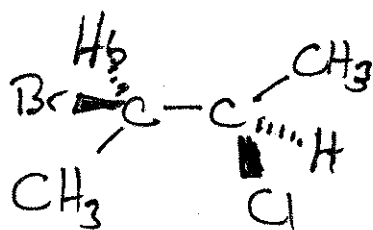
→ some diastereomers have 2 or more stereocenters

ex:

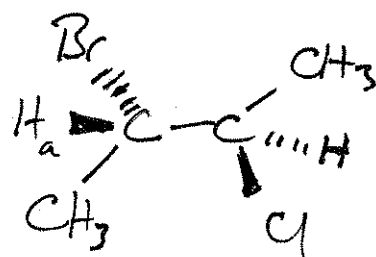
## 2-chlorobutane



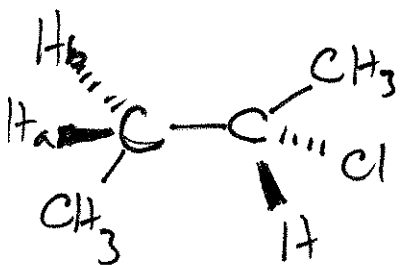
R-2-chlorobutane



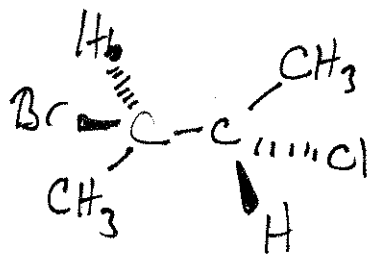
Replacement of  
Ha w/ Bromine



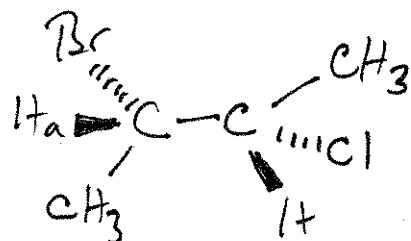
Replacement of  
Hb w/ Bromine



S-2-chlorobutane

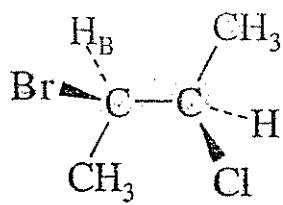


Replacement of  
Ha w/ Bromine

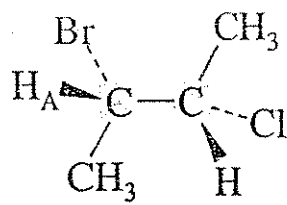


Replacement of  
Hb w/ Bromine

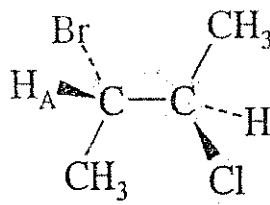
- The original stereocenter (the carbon with the chlorine) has been left undisturbed.
- Now have a compound with 2 stereocenters



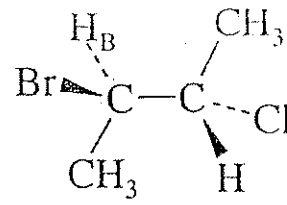
(2R,3R)-2-bromo-3-chlorobutane



(2S,3S)-2-bromo-3-chlorobutane



(2S,3R)-2-bromo-3-chlorobutane



(2R,3S)-2-bromo-3-chlorobutane

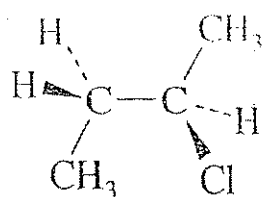
enantiomers of each other

diastereomers of the compounds to the right

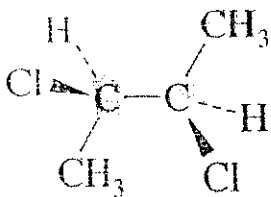
enantiomers of each other

diastereomers of the compounds to the left

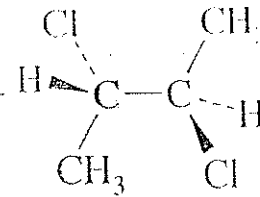
- The maximum number of stereoisomers for a compound with  $n$  stereocenters is  $2^n$ .



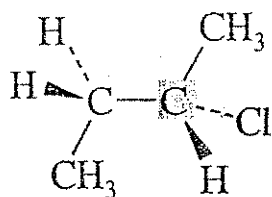
(R)-2-chlorobutane



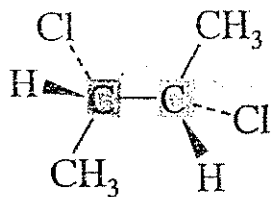
(2R,3R)-2,3-dichlorobutane



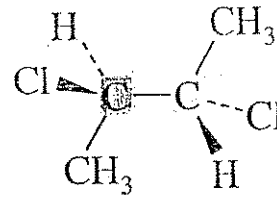
(2R,3S)-2,3-dichlorobutane



(S)-2-chlorobutane



(2S,3S)-2,3-dichlorobutane



(2S,3R)-2,3-dichlorobutane

enantiomer of (2R,3R)-2,3-dichlorobutane

apparent enantiomer of (2R,3S)-2,3-dichlorobutane

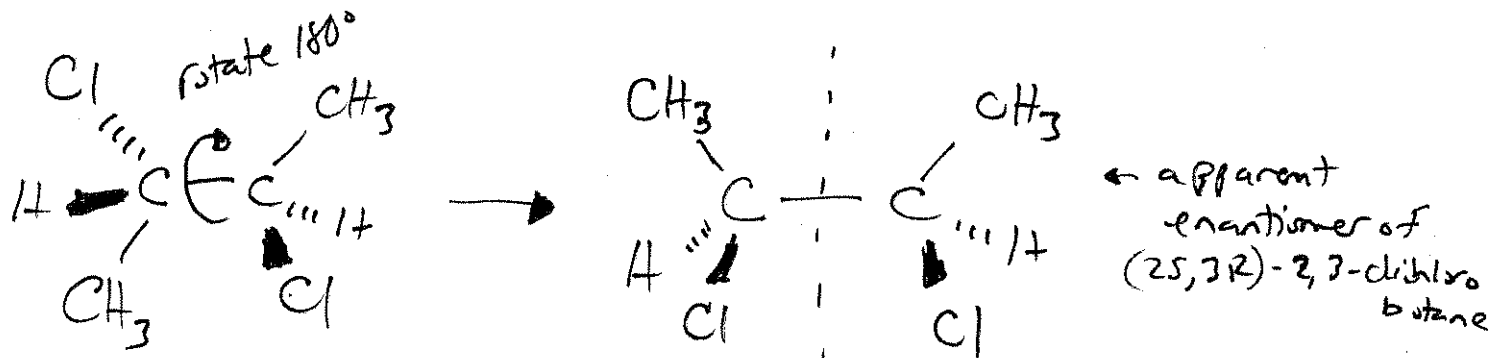
## Meso Compound

→ a compound with

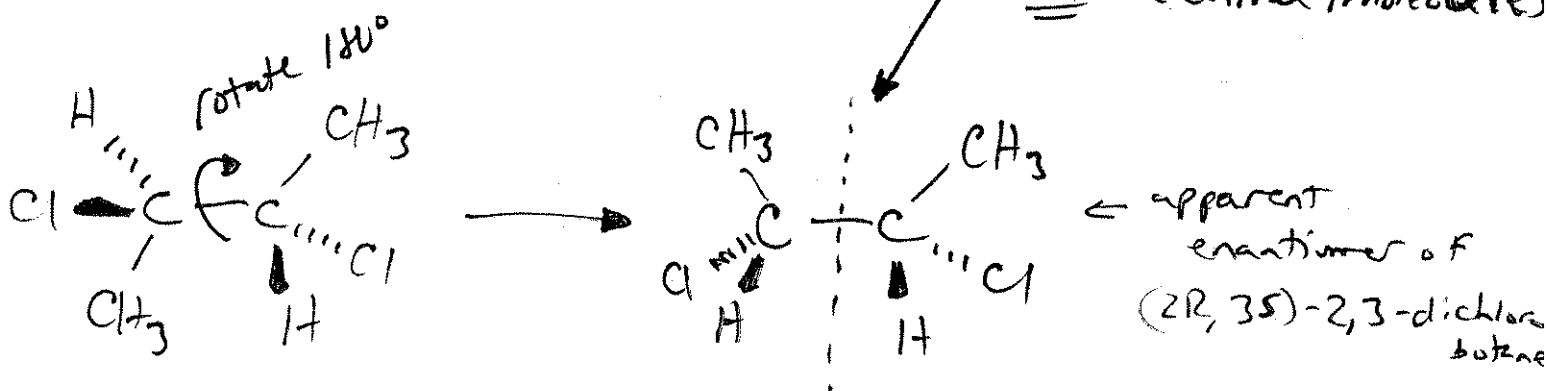
2 or more chiral centers yet it has an internal plane of symmetry (so compd not chiral no optical activity)

6-15

# (2R, 3S)-2,3-dichlorobutane



# (2S, 3R)-2,3-dichlorobutane



- Rotate (2S, 3R)-2,3-dichlorobutane 180° (left to right) (flip over)  
Is this molecule the same or different from (2R, 3S)-2,3-dichlorobutane?

→ Apparent enantiomer (2S, 3R)-2,3-dichlorobutane  
can be superimposed on (2R, 3S)-2,3-dichlorobutane  
(They are the same compound)

**A MESO COMPOUND**



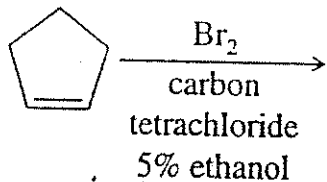
# Stereoisomerism in Cyclic Compounds

one way to draw

- Addition of Br<sub>2</sub> to cyclopentene

gives a

racemic mixture  
(50%/50% of each enantiomer) - 8 °C

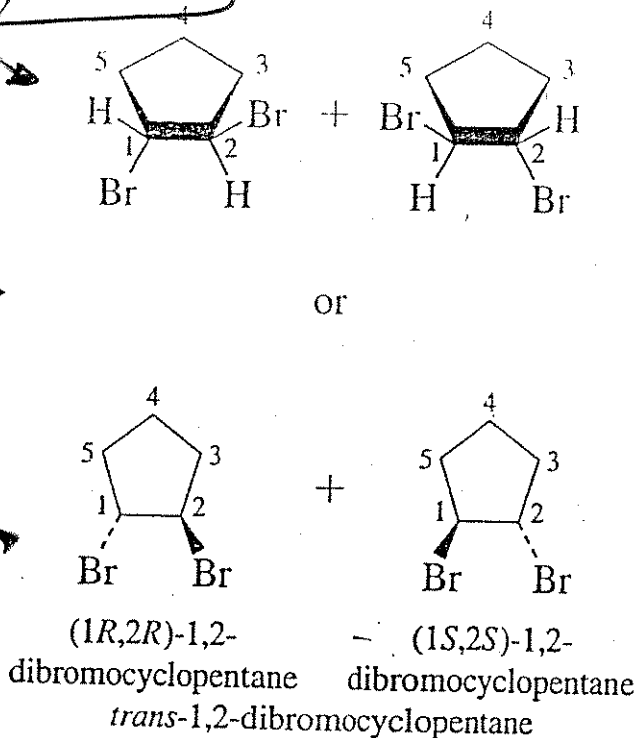


or

of trans-1,2-dibromocyclopentane

Bromines on the opposite face of ring

another way to draw

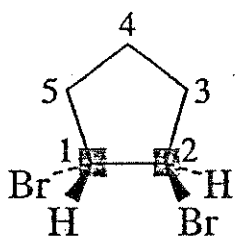
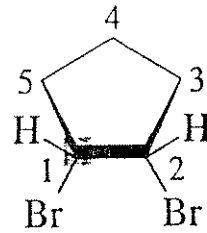
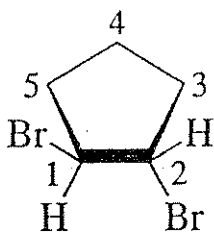
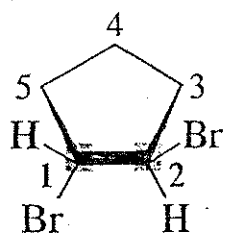


- It's also possible to have cis-1,2-dibromocyclopentane

Bromines on the same face of the ring

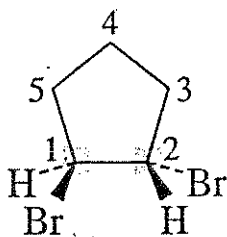
Fig. 6.9 intext

mirror



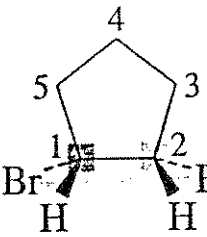
(1R,2R)-1,2-dibromocyclopentane

trans-1,2-dibromocyclopentane



(1S,2S)-1,2-dibromocyclopentane

trans-1,2-dibromocyclopentane



(1R,2S)-1,2-dibromocyclopentane

cis-1,2-dibromocyclopentane

Is this compound chiral or achiral?

Will this compound rotate plane polarized light? **6-17**

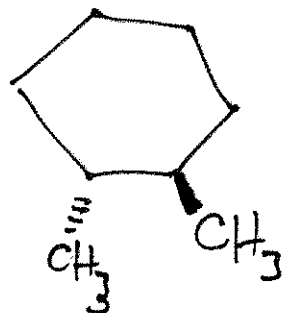
preferred convention

diastereomers

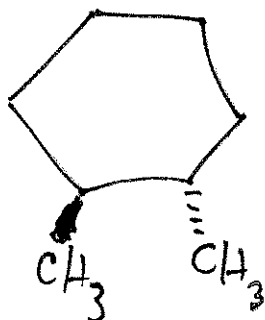
these are enantiomers!

# Configuration and Conformation of Disubstituted Cyclohexanes

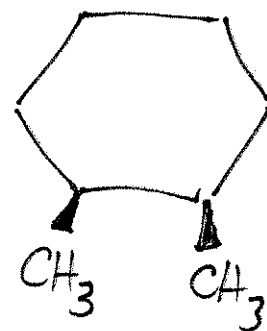
## 1,2-disubstituted cyclohexanes



(1R, 2R)-1,2-dimethylcyclohexane



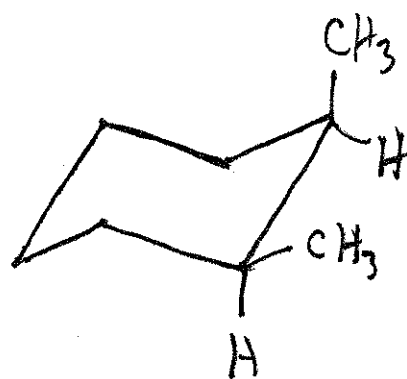
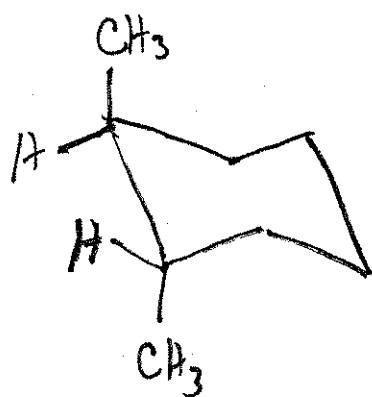
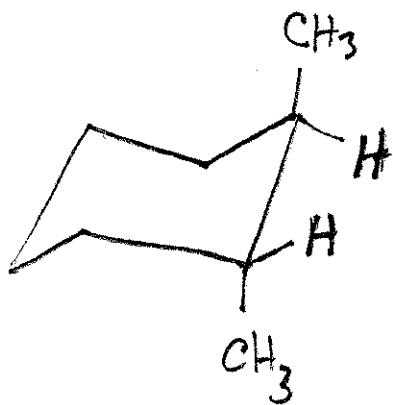
(1S, 2S)-1,2-dimethylcyclohexane



(1S, 2R)-1,2-dimethylcyclohexane

trans-1,2-dimethylcyclohexane

cis

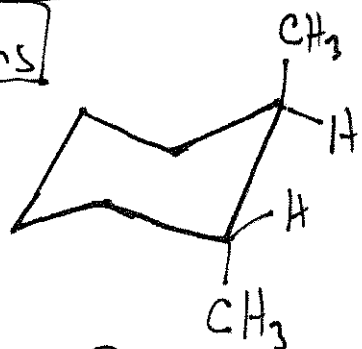


• Which are:

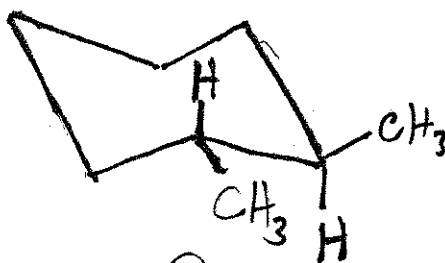
- enantiomers?
- diastereomers?
- a meso compound?

# Disubstituted Cyclohexanes - 2 chair conformations

Trans



(A)

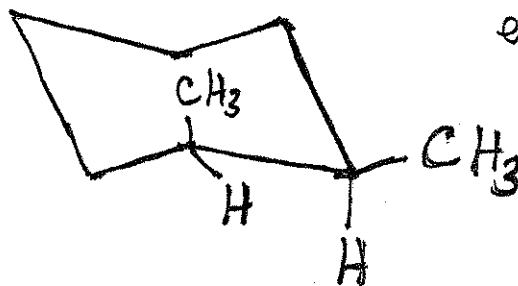
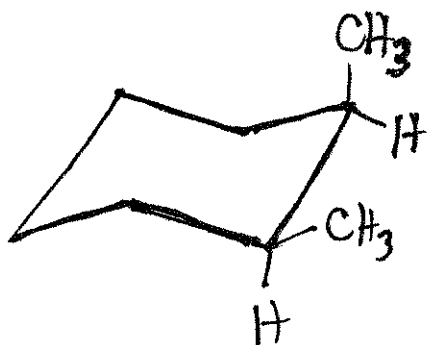


(B)

Which Conformation is more stable?

Why?

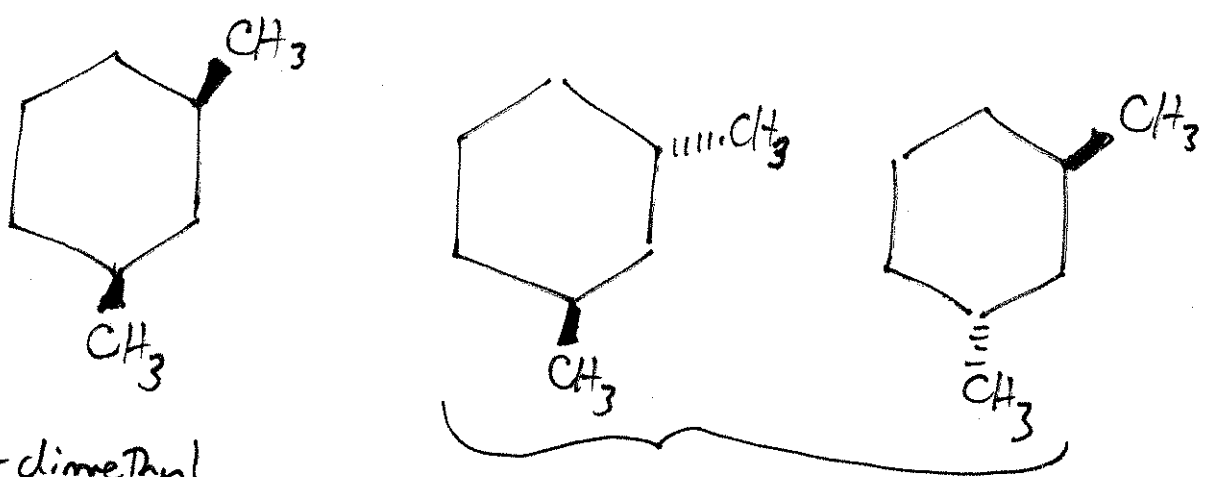
- Conformational changes do NOT change the Configuration at stereocenters
- For cis-1,2-dimethylcyclohexane 1-methyl group must always be axial + 2 equatorial



Which conformer is lower energy?

\* Draw both chair conformers of trans-1,2-dichlorocyclohexane.

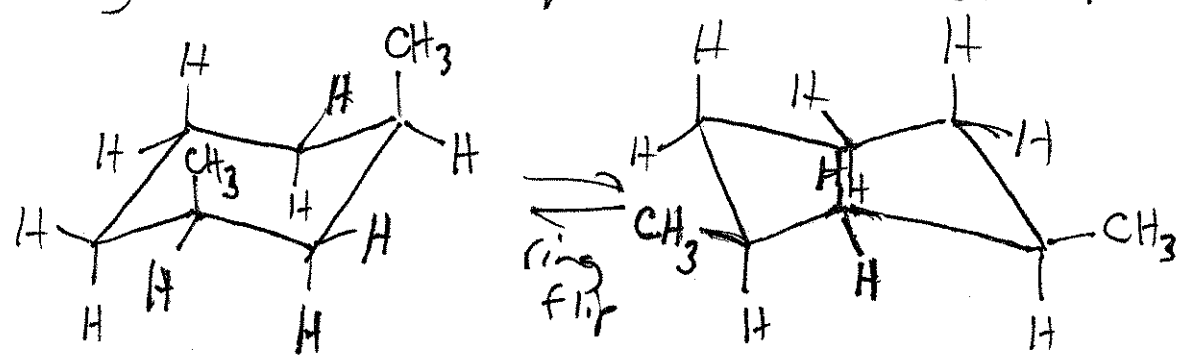
# 1,3-disubstituted cyclohexanes



Cis-1,3-dimethylcyclohexane

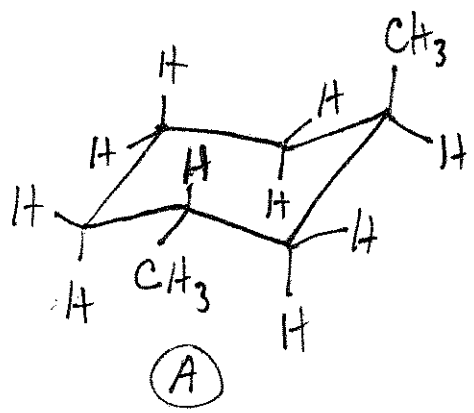
Trans-1,3-dimethylcyclohexane

- Are any of these compounds a *meso* compound?
- Are any of these compounds the same? (superimposable?)

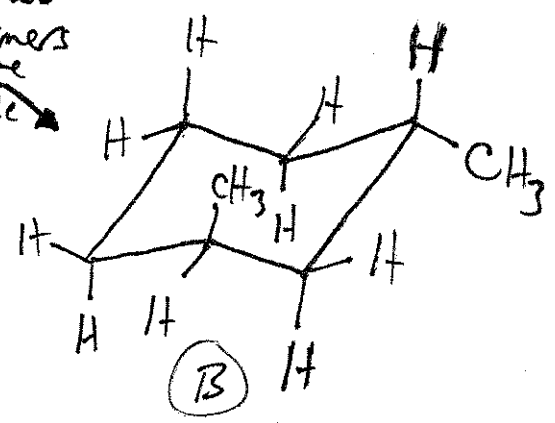


• Cis or trans compound?

• Which conformer is most stable?



NOT two conformers of same molecule

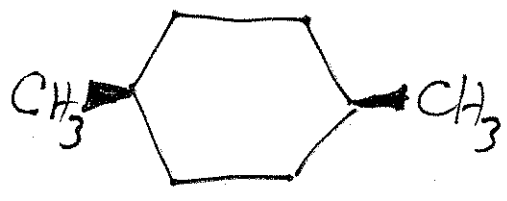


• Cis or trans compounds?

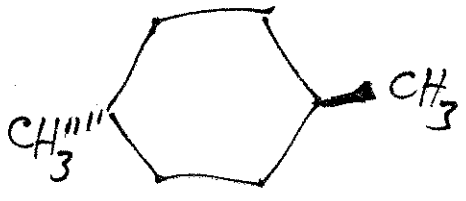
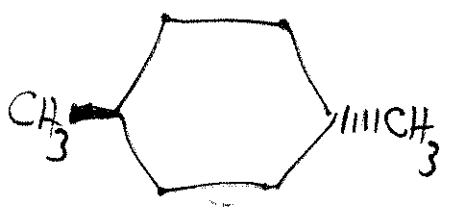
• Which chair drawing

corresponds to drawings on top of page? (6-20)

# 1,4-disubstituted cyclohexanes



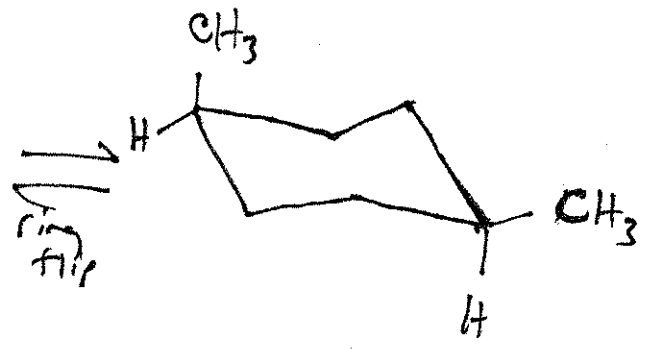
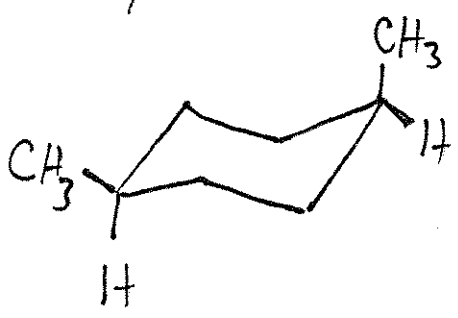
cis



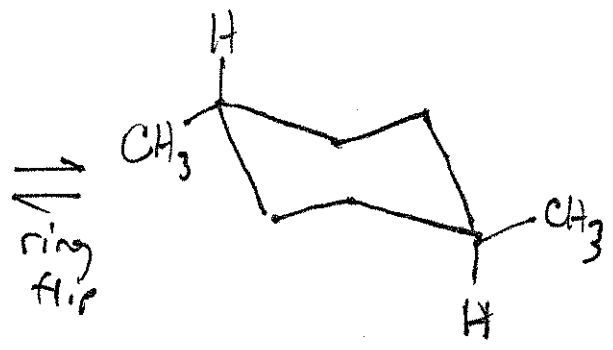
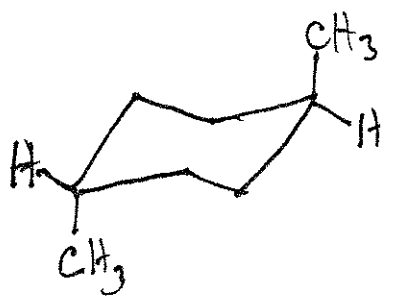
trans

- Are any of these compounds the same?
- Do any of these compounds have <sup>an</sup> internal plane of symmetry? If so, which ones?
- Do any of these compounds have stereocenters?
- Are any of these compounds optically active?
- Are any of these compounds a meso compound?

CIS



TRANS



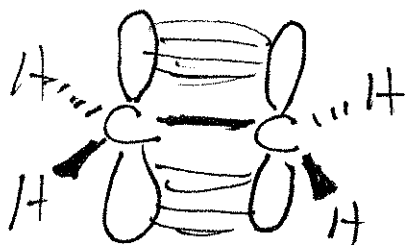
Which conformer is most stable?

# Alkene Stereoisomerism

- called geometric (cis-trans) isomerism

- Not all bonds allow free rotation → double bonds are rigid and cannot be twisted

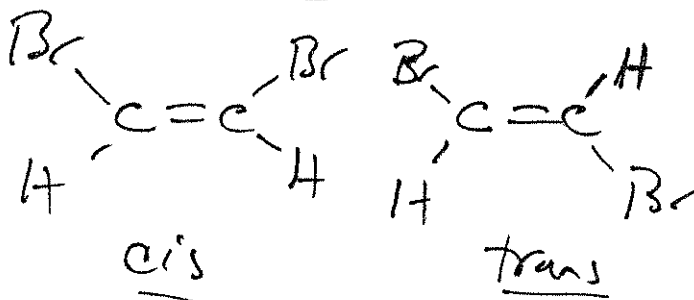
ex: ethylene (ethene)



- rotation destroys the overlap necessary to form a  $\pi$ -bond

→ The rigidity of double bonds gives rise to stereoisomers ⇒ geometric (cis-trans) isomers

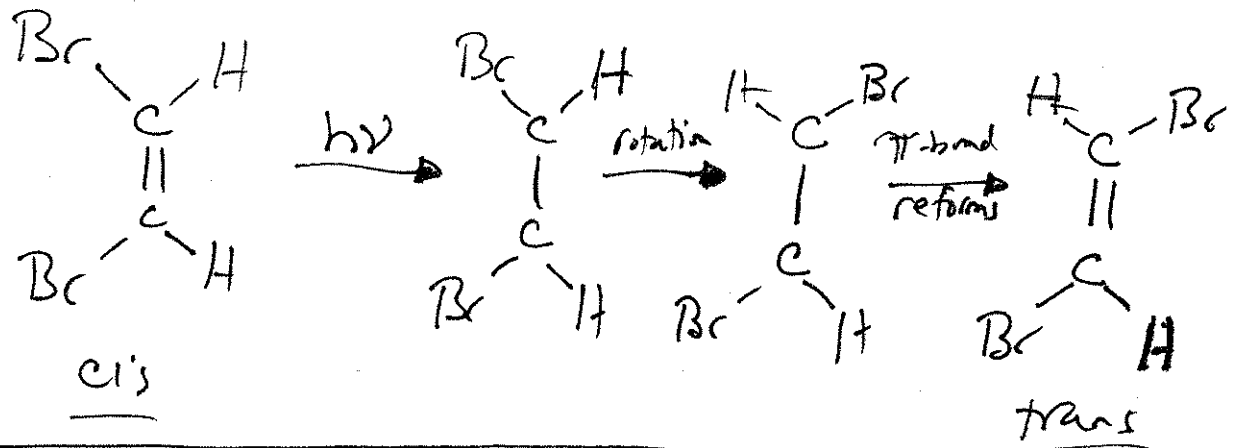
ex: 1,2-dibromoethene



- cis + trans 1,2-dibromoethene are related as diastereomers

- two different compounds
- not interconvertible by bond rotation
- both cis + trans 1,2-dibromoethene have a plane of symmetry; they are both achiral

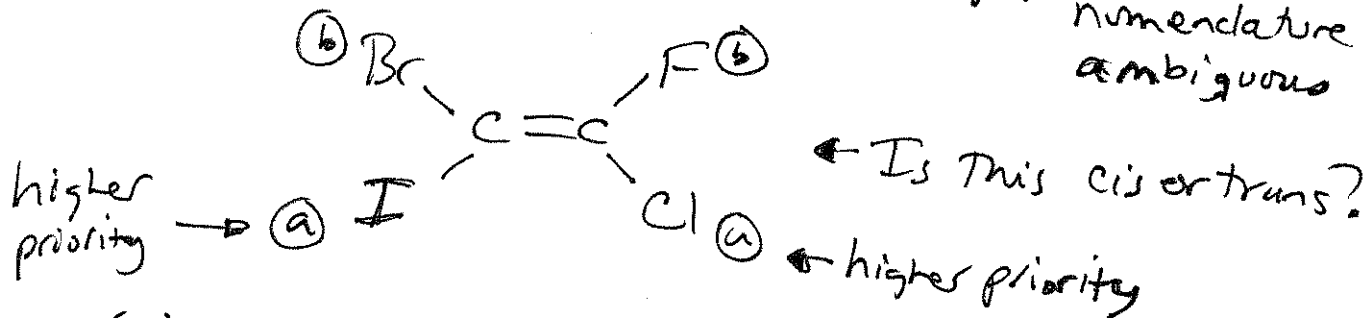
- But, if there is enough energy, can break the  $\pi$ -bond and interconvert the cis isomer to the trans isomer. ( $\Delta H \approx 65 \frac{\text{kcal}}{\text{mol}}$ )



## Nomenclature of Stereoisomeric Alkenes

→ Use Cahn-Ingold-Prelog Rules (Sequence Rules) to prioritize groups in assigning names of more complex alkenes

ex: If have 3 or 4 different groups, cis-trans nomenclature is ambiguous



(E)-1-bromo-2-chloro-2-fluoro-1-iodoethene

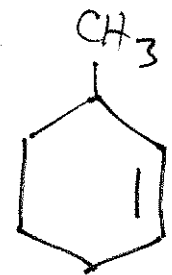
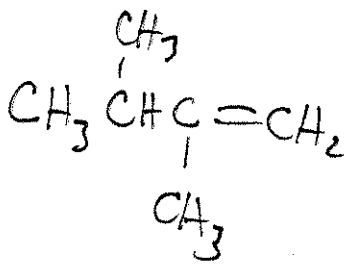
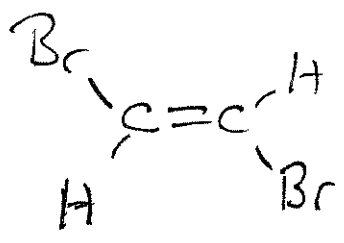
• A (Z) configuration is assigned if the two groups of higher priority are on the SAME SIDE

• An (E) configuration is assigned if the two groups of higher priority are on opposite sides. (6-23)

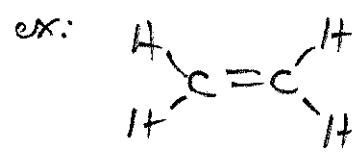
# Z are on Zee Zame Zide

- Alkene names are derived from the corresponding alkane → "ane" is changed to "ene"
- The carbon chain is numbered to give carbon atoms joined by the double bond the lowest possible number. (Position of double bond given by <sup>o</sup>n number before base name)

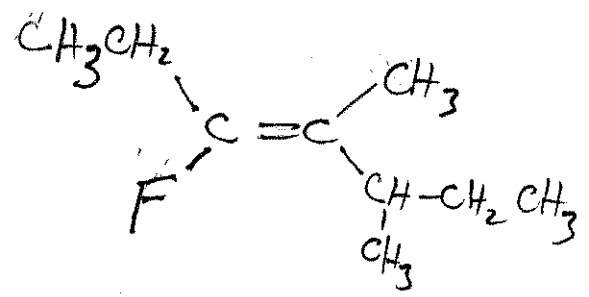
✶ Name the following alkenes, using E, Z prefixes when necessary.



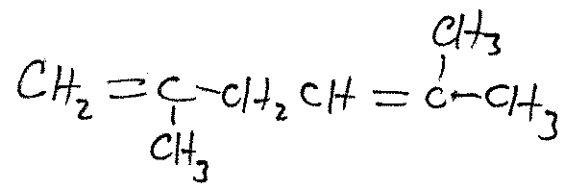
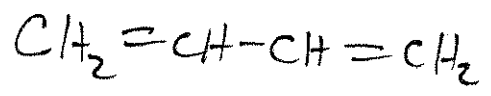
- Some simple alkenes have common + IUPAC names



IUPAC  
ethene  
Common  
ethylene



- If two double bonds are present replace "ene" w/ "diene"



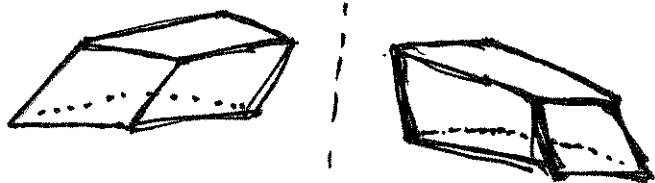


# Resolution of Racemic Mixtures

Enantiomers - have basically the same chemical and physical properties. Therefore, they can't be separated by ordinary means.

In text - Pasteur was able to separate enantiomers of tartaric acid using a microscope and a pair of tweezers. Why could he do this?

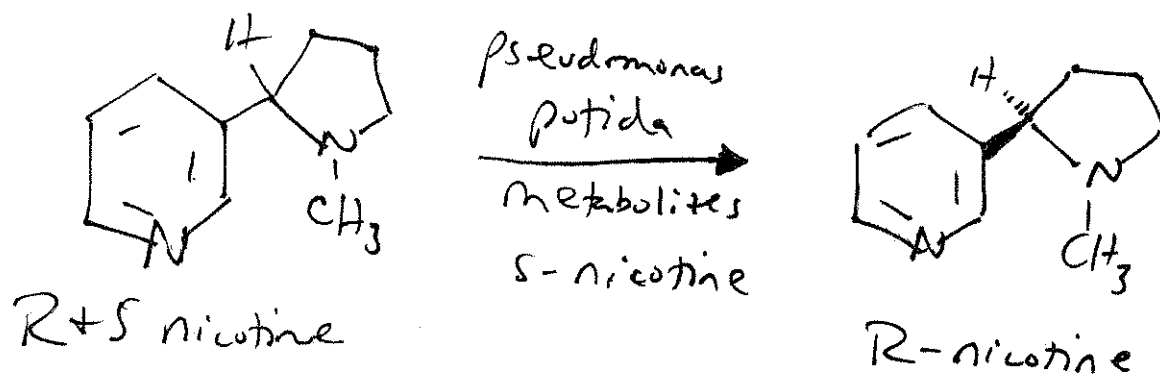
→ Enantiomers of tartaric acid form mirror image crystals when crystallized from solution. (This is not the case for most other enantiomeric pairs)



→ This technique is not widely useful + VERY tedious

\* Another way to RESOLVE a racemic mixture (or at least isolate one pure enantiomer) is to treat the mixture with a microorganism which will consume only one of the two enantiomers (6-25)

ex: (from text)

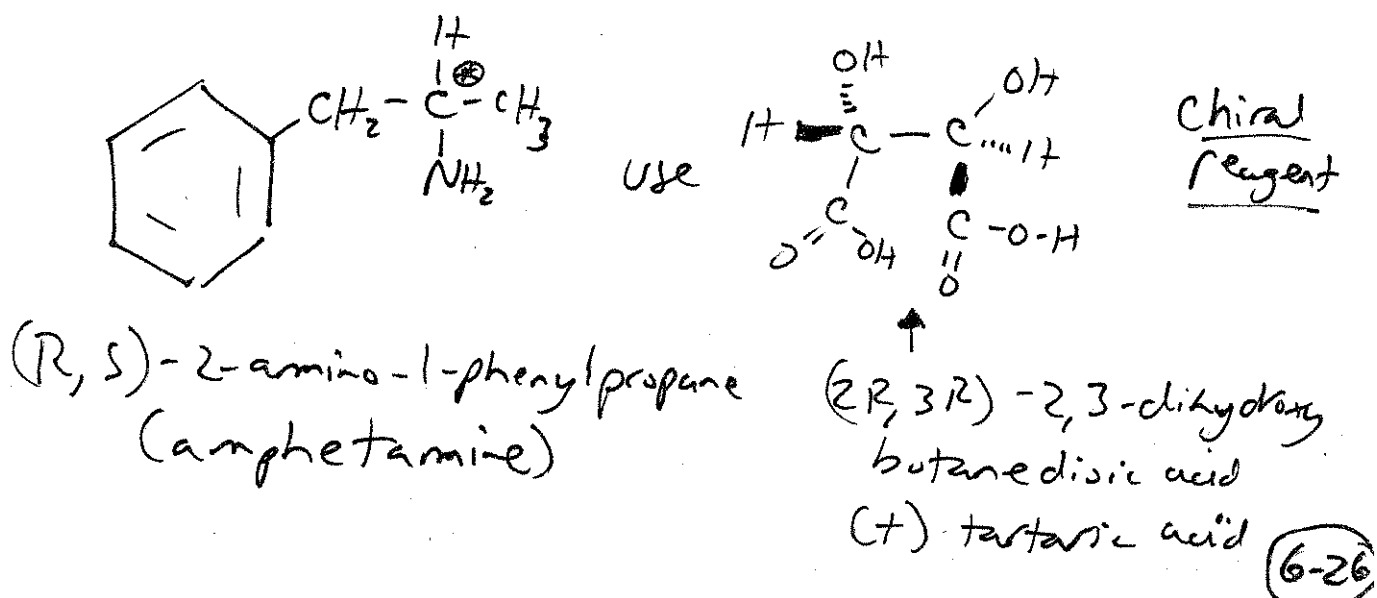


- Another resolution technique: subject a pair of enantiomers to a reaction using a **CHIRAL REAGENT** to obtain a pair of diastereomers

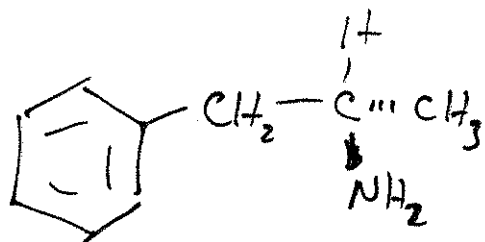
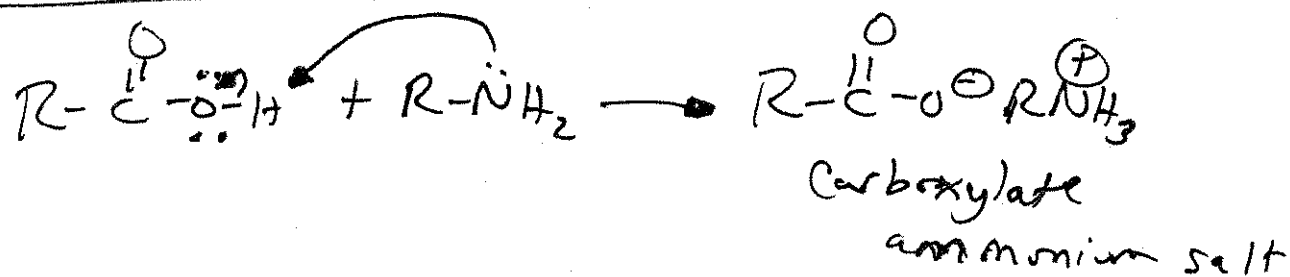
→ Can separate diastereomers by physical means

→ Most general method

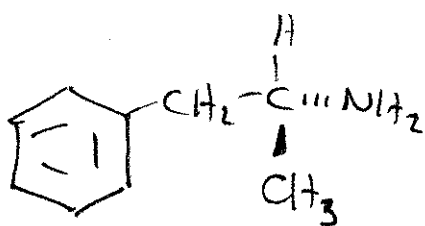
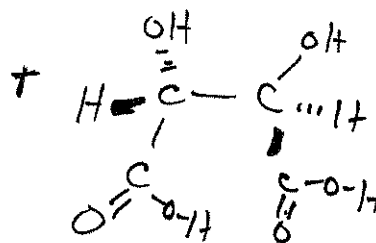
Ex: Want to separate the following enantiomers



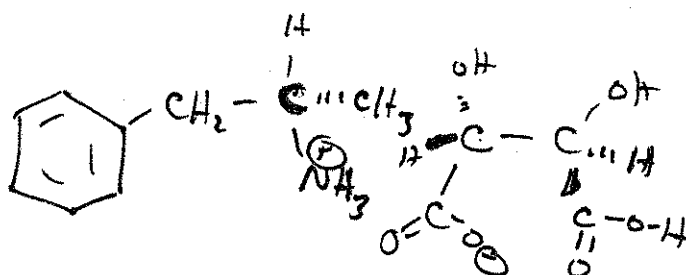
# General Rxn:



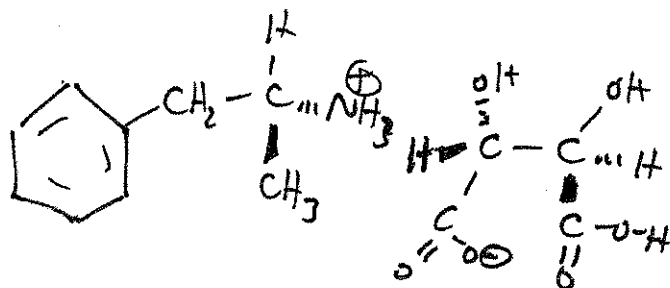
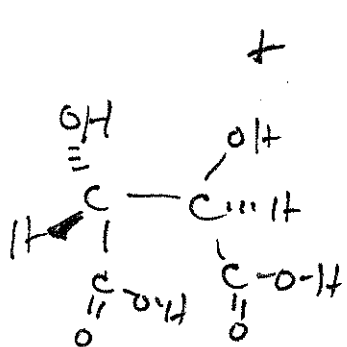
(S)-enantiomer



(R)-enantiomer



(S, R, R) salt



(R, R, R) salt

- Z-Diastereomeric salts - have different properties
  - in this case the solubility is very different (allows these salts to be separated)