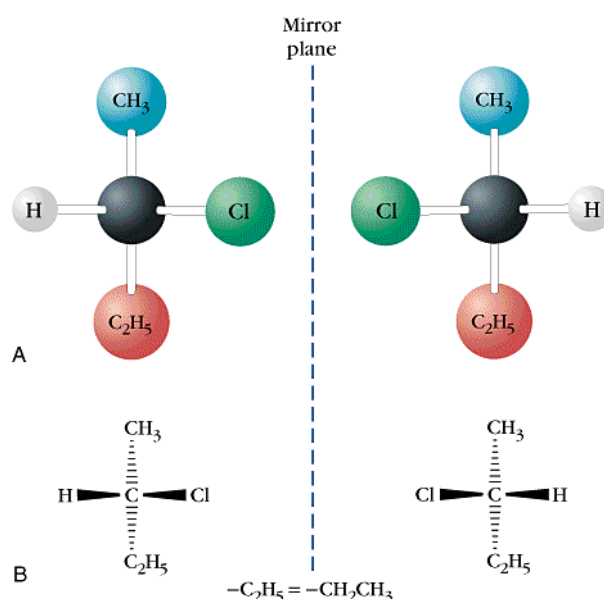


## 6. Chirality (text 6.1 – 6.11)

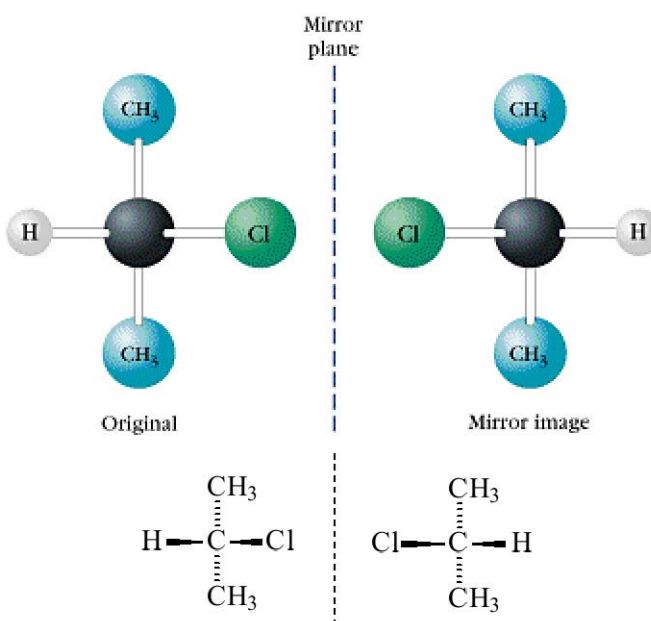
### A. Review of Chirality and R/S Configuration

- Chiral objects do not have a plane of symmetry, so they *are not* superimposable on their mirror images. Achiral (non-chiral) objects have a plane of symmetry and *are* superimposable on their mirror images.

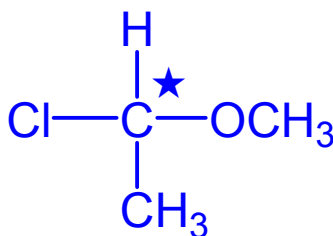
- 2-Chlorobutane is chiral and not superimposable on its mirror image. The two structures are **enantiomers**.
- Carbon #2 is bonded to four different substituents (H, Cl, CH<sub>3</sub>, and CH<sub>2</sub>CH<sub>3</sub>)



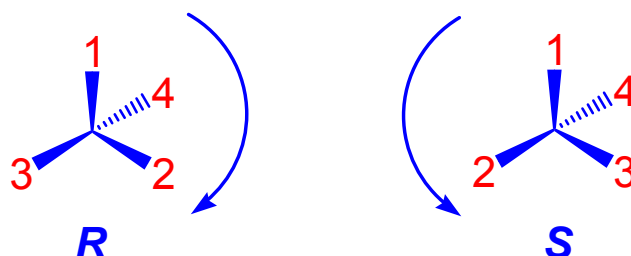
- 2-Chloropropane is achiral and superimposable on its mirror image. *i.e.* its mirror image is identical.
- Carbon #2 is bonded to four substituents, two of which are identical (CH<sub>3</sub>).



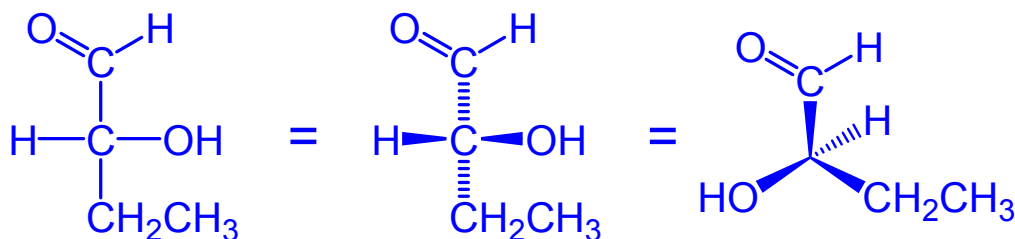
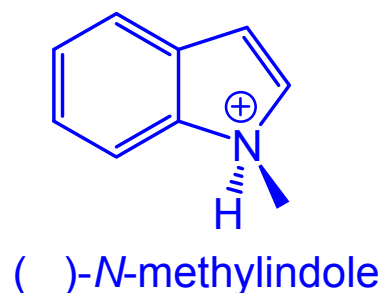
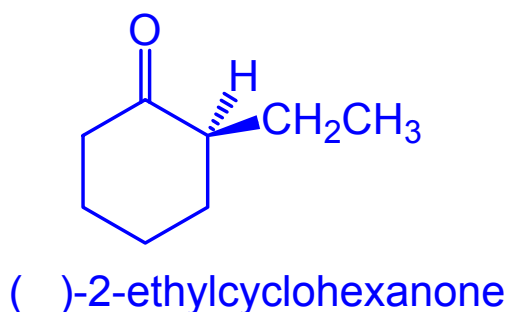
- The most common source of chirality in a molecule is a stereocentre (chiral centre), usually an atom bonded to four different groups (substituents).
- Enantiomers are isomers that do not interconvert at room temperature. They are different compounds. Because they share the same bonding sequence, the same formula, and the same number and type of functional groups, **their chemistry is exactly the same**, EXCEPT:
  - The two enantiomers have different effects on the rotation of plane-polarized light.
  - They react differently with other chiral compounds (this is the very important in biochemistry).
- We use the *R* and *S* convention to specify the absolute 3D configuration of stereocentres, which are commonly marked in structures as ★.
- The convention assigns a priority order to the substituents on the stereocentre according the same priority rules we examined when looking that the *E/Z* convention in alkenes.
- Example on assigning priorities:



- Using the priority assignments, we can assign an *R* or *S* configuration label to the molecule as follows:
  1. Draw or place the molecule with the lowest-priority group (#4) behind the plane.
  2. Draw an arrow going from the highest priority group (#1) to the second-highest (#2), and the third-highest (#3).
    - Clockwise = absolute configuration is *R*
    - Counterclockwise = absolute configuration is *S*

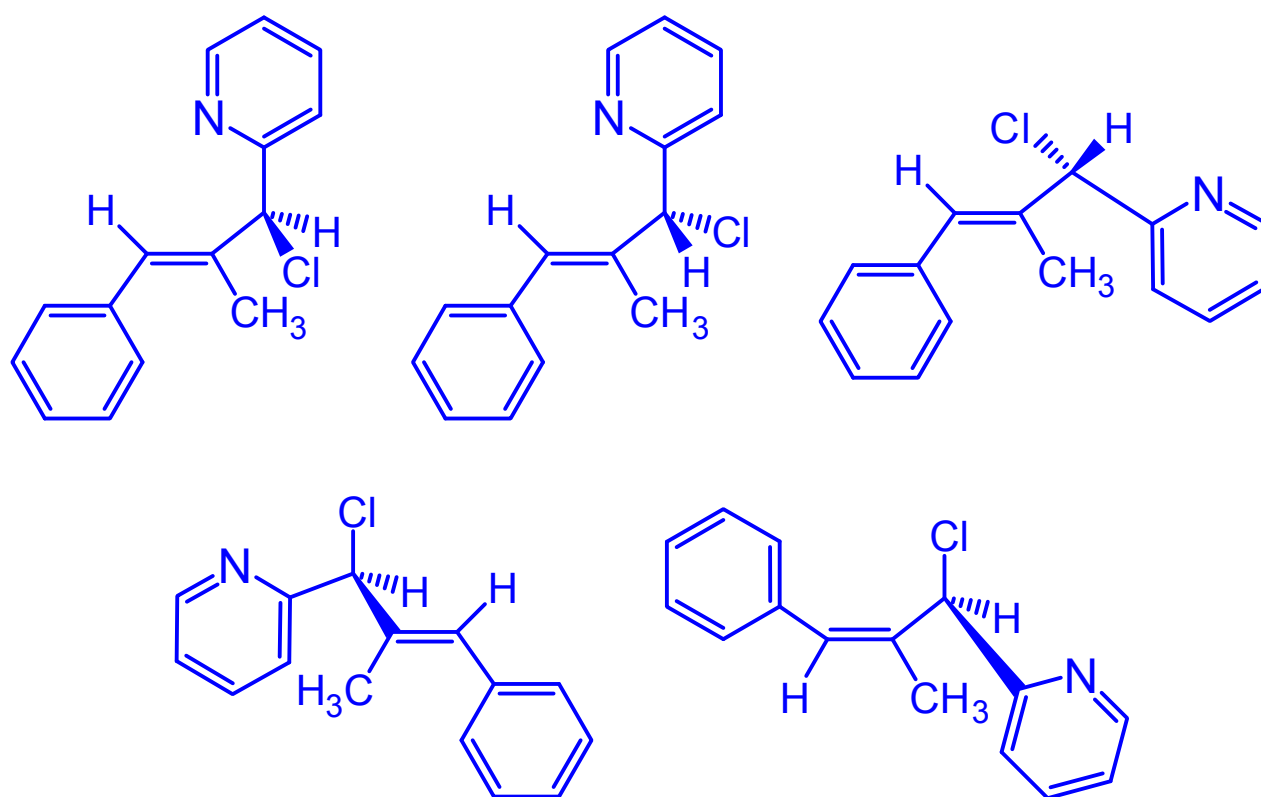


- What are the *R* and *S* configurations of the following?



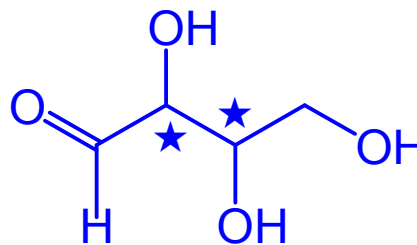
Fischer projection

- Summary up to now
  - Pages 142 – 150, Q. 16, 17, 18, 20, 23, 24, 26, 28.
  - 2005: 23 – 25                      2006: 20, 25 – 28
  - 2007: 18, 22, 26, 28      2008: 24, 25, 27
- Past test question: Which one is an *E,R* stereoisomer?

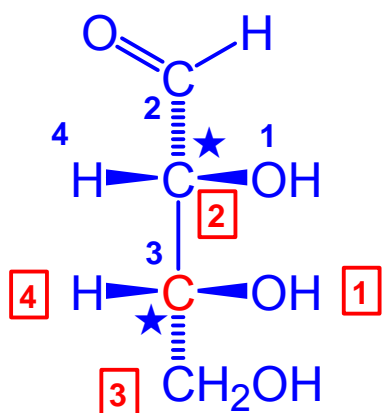


## B. Molecules with Two or More Stereocentres

- A molecule with 2 stereocentres will have **up to**  $2^2 = 4$  potential stereoisomers, e.g. 2,3,4-hydroxybutanal.



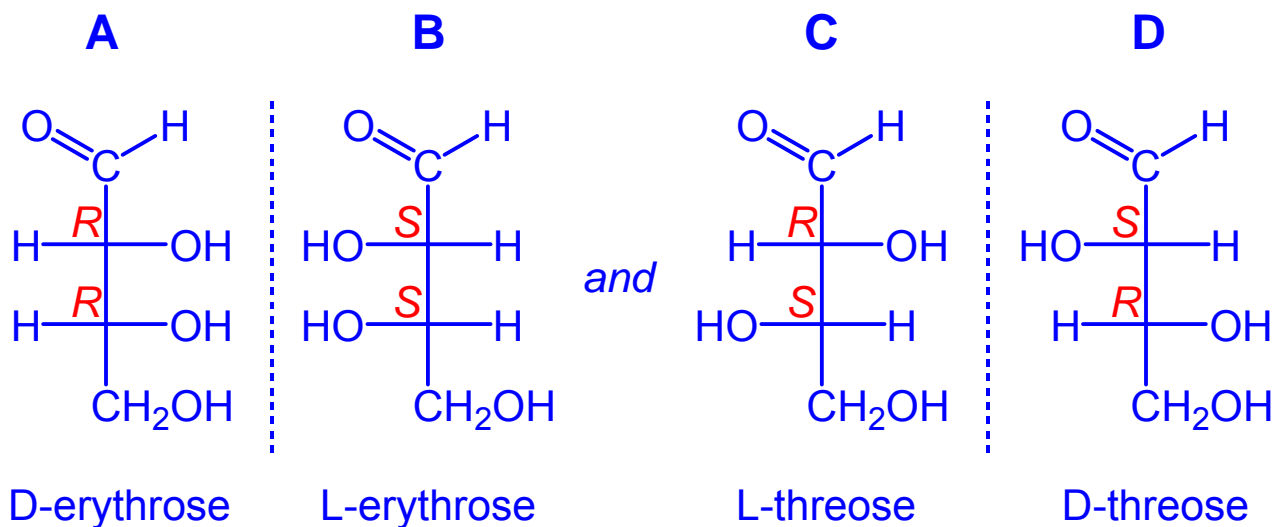
- Such noncyclic molecules with  $> 1$  chiral centre are usually drawn as Fischer projections.



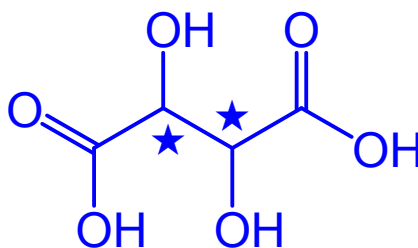
# = group priority around top C

[#] = group priority around lower C

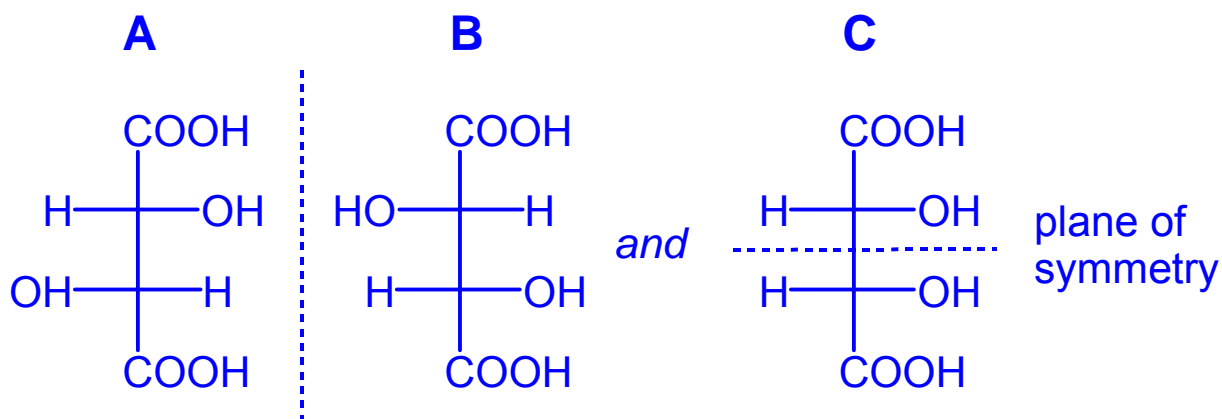
- The four stereoisomers of 2,3,4-hydroxybutanal are:



- The four stereoisomers are naturally occurring sugars (carbohydrates). We'll learn about D/L convention later.
- Since **A** and **B** are mirror images of another, they are enantiomers. **C** and **D** are also enantiomers.
- How about the relationship between **A** & **C**, or **A** & **D**, or **B** & **C**, or **B** & **D**? These are called **diastereomers**.
  - Diastereomers are stereoisomers of a chiral compound that are NOT enantiomers.
- **Note:** The easiest way to distinguish enantiomers and diastereomers is to realize that enantiomers have a different (opposite) configuration at every stereocentre. Whereas, diastereomers have at least one stereocentre in common.
- Although enantiomers have identical chemical properties (except for light rotation and reactions with chiral reagents), **diastereomers have different properties**, such as their melting points or solubilities in solvents.
- Molecules with two or more stereocentres can exist in their non-chiral form if they contain an internal plane of symmetry. In this case, the number of stereoisomers is less than the  $2^n$  theoretical maximum. e.g. tartaric acid, found in many natural products including wine, fruit, vegetables, etc.

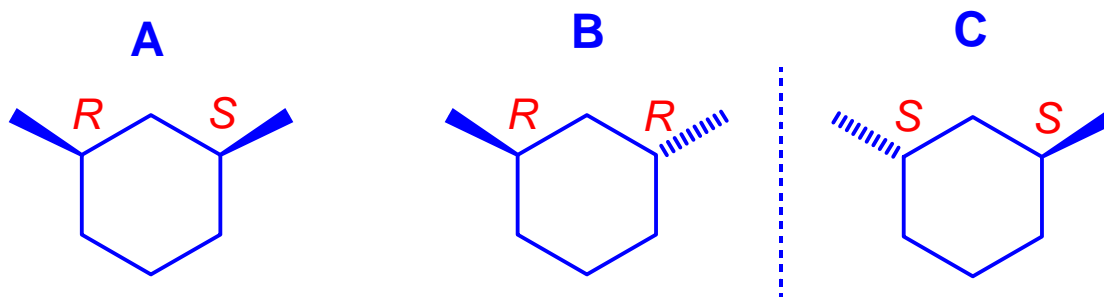


- There are only 3 possible stereoisomers of tartaric acid:



- Because C has a plane of symmetry, it can be superimposed on its mirror image, *i.e.* it is achiral.
- Achiral compounds containing two or more stereocentres are termed *meso*.
- So, the structures of tartaric acid are related as follows:
  - A and B are enantiomers
  - A and C are diastereomers, as are B and C
  - C is a *meso* compound
- Make sure you understand the structural basis of enantiomers and diastereomers, including the achiral diastereomers known as *meso* compounds.

- For cyclic compounds, the stereoisomers can be drawn while depicting the ring as a flat polygon, *i.e.*, the cyclohexane ring does not need to be drawn as a chair. This simplification is allowed because the changes from one conformation to another do not affect the *R* and *S* configurations at the stereocentres.
- Note: the stereoisomers that arise from stereocentres in a ring can be described as *cis* or *trans* isomers if one only wishes to focus on the *relative* location of two substituents (same side or opposite side). If one wishes to give definitive structural information, *R* and *S* are more appropriate for *absolute* configuration.
- For example, the three stereoisomers of 1,3-dimethylcyclohexane are:

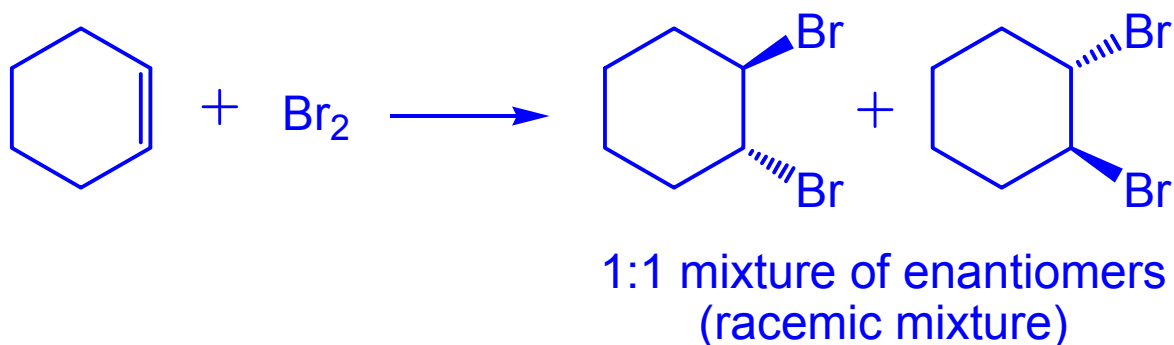


- A is a *cis* compound, and is *meso*
- B and C are *trans* isomers, and are enantiomers
- A and B (or A and C) are *cis/trans* pairs, and are diastereomers

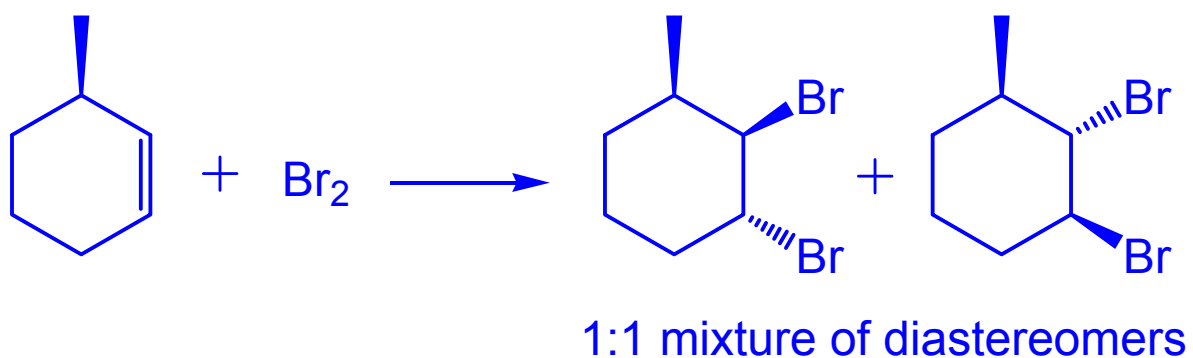


## C. Reactions Producing Stereoisomers

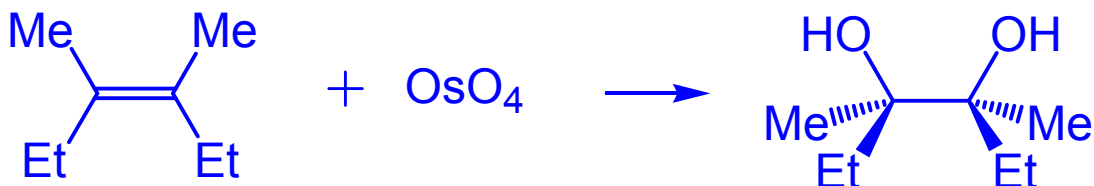
- Many reactions, such as those that add to alkenes in a *syn* or *anti* manner in the previous chapter, give specific stereoisomers as products.
- Example: alkene bromination (*anti* addition)



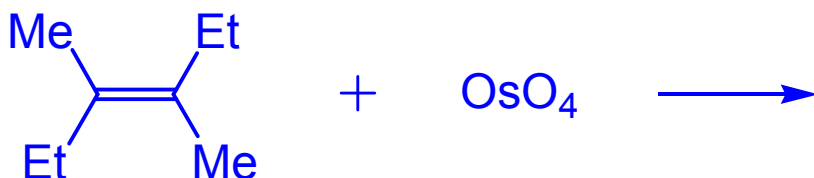
- Both products above are *trans*, but they have different absolute configuration.
- Realize that the stereochemistry of the products depends on that of the starting material



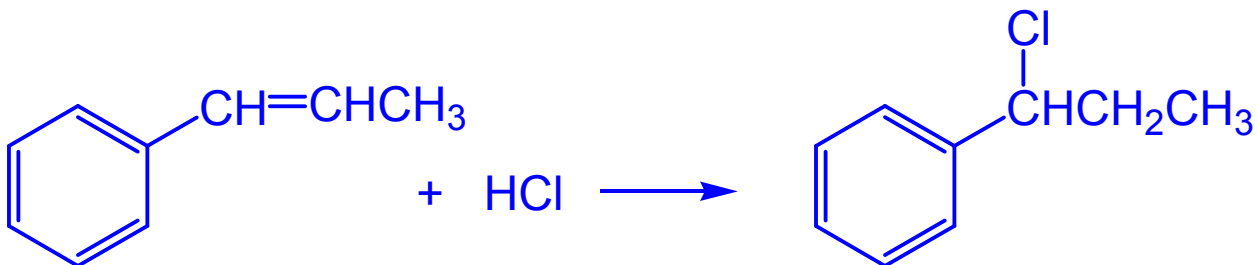
- Example: alkene oxidation (*syn* addition)



- In the above, addition to the *cis* alkene results in a *meso* product. What is formed if the *trans* alkene were used?

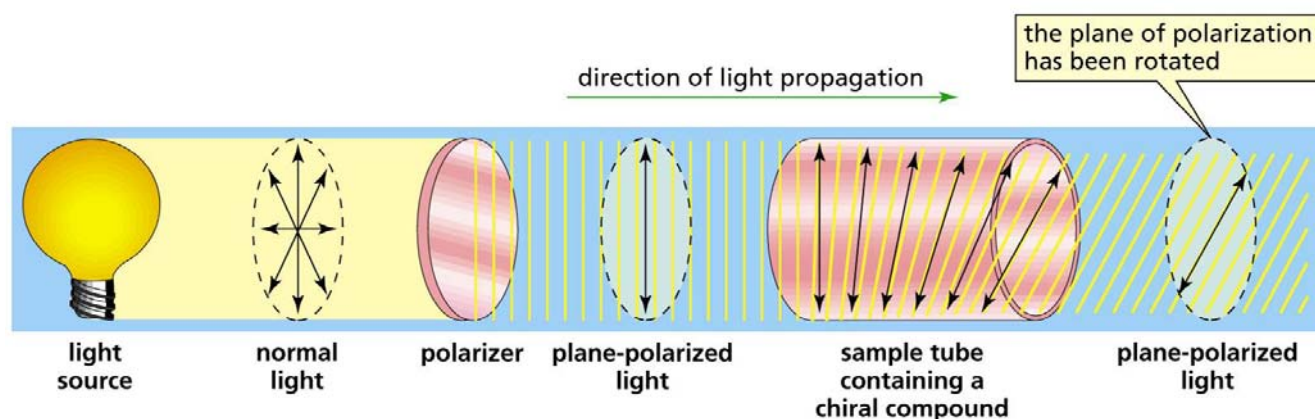


- A pair of enantiomers (a racemic mixture) can be formed if the reaction involves a carbocation intermediate.

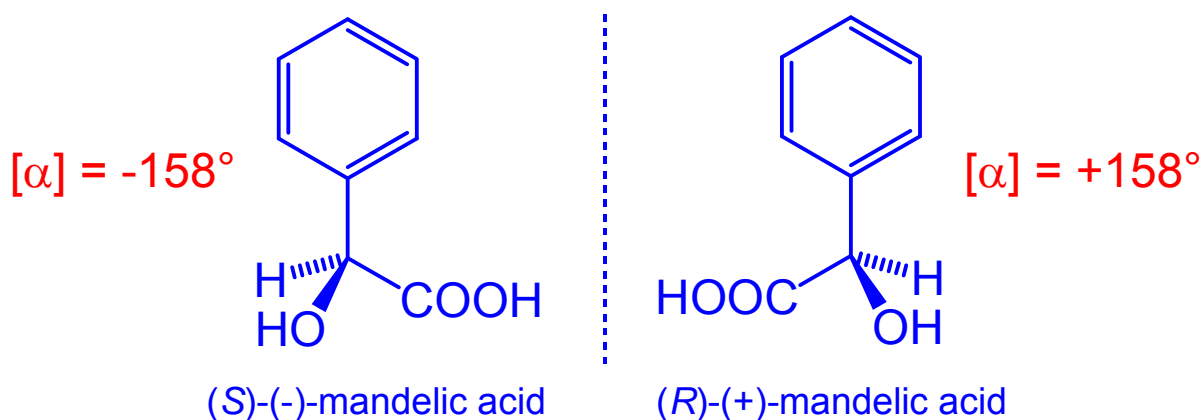


## D. Plane-Polarized Light and Optical Activity

- If normal light or sunlight is passed through a plane-polarizing filter, the light rays all vibrate in the same plane.
- In the 19<sup>th</sup> century, it was discovered that when light is passed through a solution of pure enantiomer, the plane of polarization was rotated to the right by one enantiomer, and to the left by the other enantiomer.
- The enantiomer rotating light to the right was termed the D (dextrarotatory) enantiomer, designated as a “+” rotation. Similarly, the one rotating light to the left was termed the L (levorotatory) enantiomer, designated as a “–” rotation.
- The amount of light rotation can be measured using a polarimeter, which determines an enantiomer’s **specific rotation**  $[\alpha]$ , an angle value, under standard conditions.



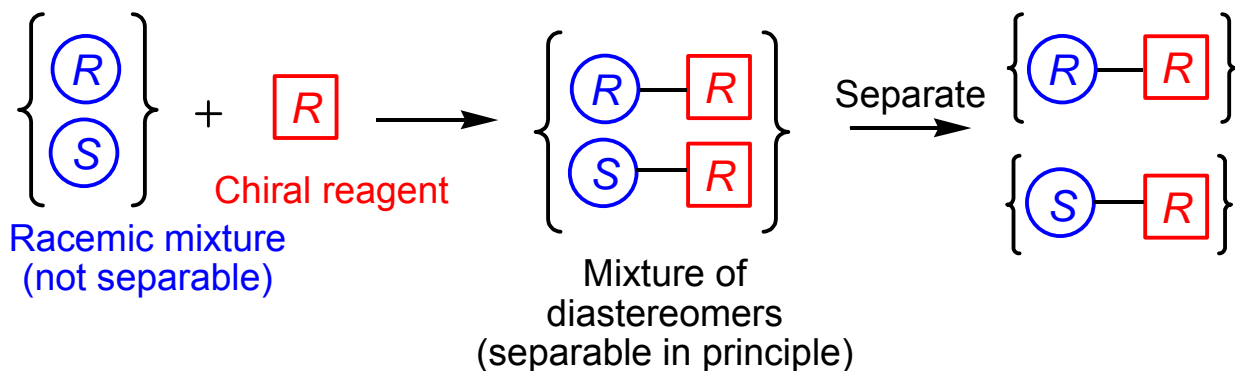
- The specific rotation of an enantiomer is a fixed physical property of a chiral molecule and is experimentally found, just like a molecule's melting point. The specific rotations of a pair of enantiomers are equal, but opposite in sign.



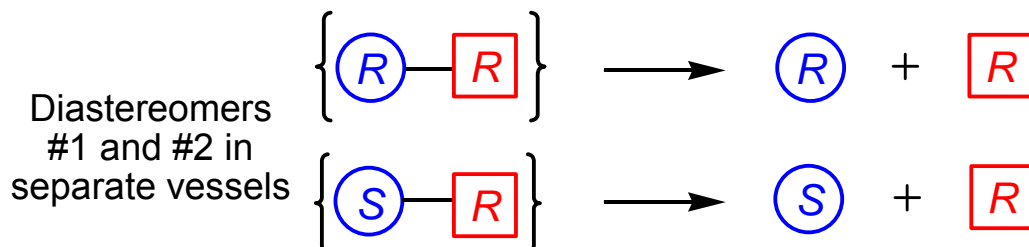
- Thus, if we have a **racemic mixture** (a 1:1 mixture of enantiomers), the net rotation is zero, and it is said to be *optically inactive*. The rotation of light by one enantiomer is cancelled out by the other.
- Note: Most laboratory syntheses prepare chiral compounds in racemic mixtures. However, biological reactions almost always result in one single enantiomer.
- Recognize that D and L (+ and -) have absolutely no relationship with R and S. This is why both the configuration and direction of light rotation are specified.
- NOTE:** *meso* and achiral compounds are optically inactive.

## E. Chemical Separation of Enantiomers - Resolution

- Recall that enantiomers have identical properties, except for plane-polarized light rotation. They cannot be separated by normal methods, e.g. distillation, crystallization, etc.
- However, diastereomers *do* have different properties, and in principle, they can be separated.
- Thus, it is possible to separate enantiomers by temporarily converting the racemic mixture to diastereomers using a chiral reagent that is commercially available in an enantiomerically pure form (usually something natural). This reagent can be *R* or *S*, but must be enantiomerically pure.



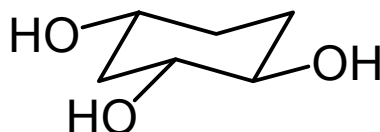
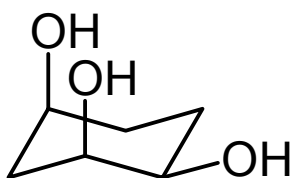
- Once the diastereomers have been separated, the reaction needs to be reversed to recover the chiral reagent and the pure enantiomers.



- This gives the *R* and *S* enantiomers in separate vessels. The whole process is called the *resolution of a racemate*, and the chiral reagent is the *resolving agent*.
- One technique used is the preparation of a mixture of diastereomeric salts from a racemic mixture and a resolving agent. After the salts are separated (e.g. recrystallization), regeneration of the enantiomerically pure acid or base is usually easy.

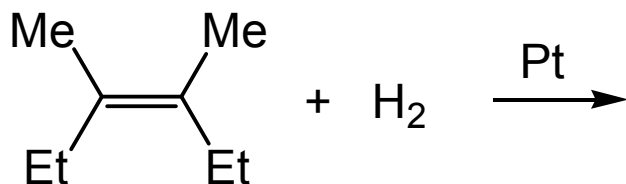
## Summary

- Chapter 6, pages 150 – 163. #30, 32, 34, 36, 37, 40, 42-46.
- 2005: 26 – 32                      2006: 26 – 31  
 2007: 25, 27, 29, 30, 31      2008: 26, 28 – 31
- What term describes the relationship between these two compounds?



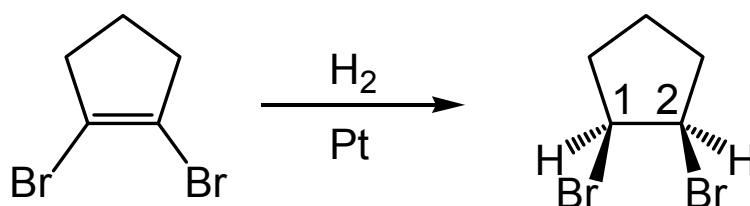
Conformations	Identical	Enantiomers
Diastereoisomers	Structural isomers	

- How many different stereoisomers are formed by the following reaction?



1    2    3    4    5

- MCAT: Refer to the reduction of 1,2-dibromopentene below to answer the subsequent questions



- What is the absolute configuration at C-1 and C-2, respectively? A) *R,R* B) *R,S* C) *S,R* D) *S,S*
- In what direction will the product rotate light?
  - A. Clockwise      B. Counterclockwise
  - C. Cannot be determined without measurement
  - D. The product will not rotate light
- What is the relationship between the product molecule and this molecule?
  - A. Diastereomers      B. Enantiomers
  - C. Structural isomers      D. Not stereoisomers

