

## Stereochemistry II

**Reading:** Wade chapter 5, sections 5-8- 5-16

**Study Problems:** 5-28, 5-29, 5-30, 5-31, 5-35

### Key Concepts and Skills:

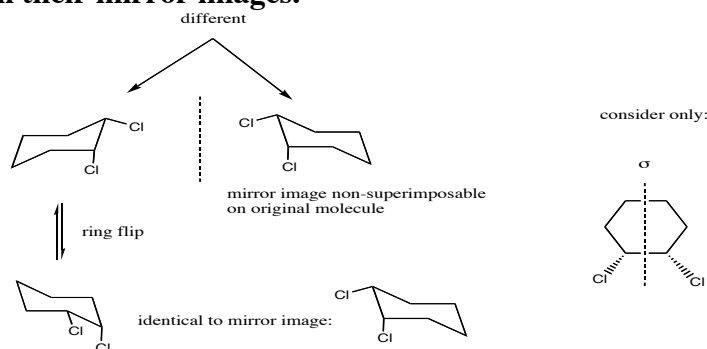
- Draw all stereoisomers of a given structure.
- Identify enantiomers, diastereomers, and meso compounds; draw correct Fischer projections of asymmetric carbon atoms.
- Explain how the physical properties differ for different types of stereoisomers, and suggest how to separate different types of stereoisomers

### Lecture Topics:

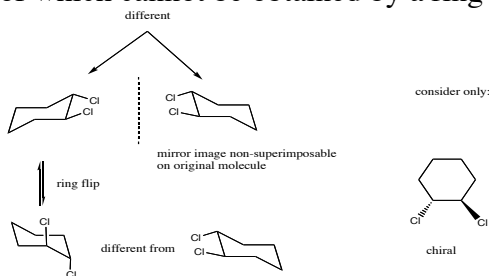
#### I. Conformational isomerism

Consider cis-1,2-dichlorocyclohexane; each chair conformation is chiral, but a ring flip will convert one stereoisomer to its mirror image. Since chair-chair interconversions are rapid at room temperature.

**A molecule cannot be optically active if its chiral conformations are in rapid equilibrium with their mirror images.**

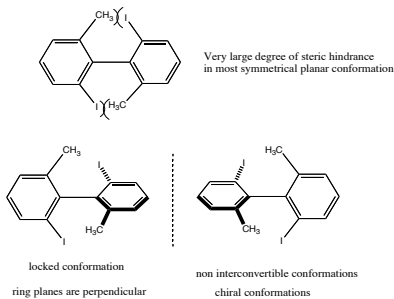


**A correct prediction about whether a molecule is chiral or achiral can be made by analyzing the most symmetrical conformation (in the case of a cyclic molecule, it is the “flat” conformation)** Note that trans 1,2-dibromo cyclohexane has chiral chair forms, the mirror images of which cannot be obtained by a ring flip:

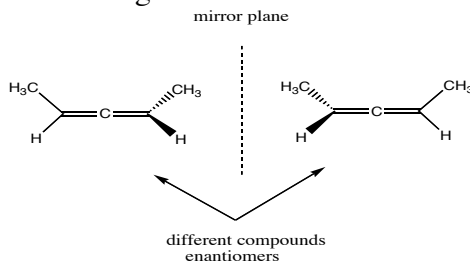


- Some molecules have no asymmetric carbon atoms (no centers of chirality) yet they are chiral. This is due to locked conformations of a molecule which are chiral and cannot interconvert because of steric hindrance: “axial chirality”
- An example is 2,2,2,2’-substituted biphenyls, in which the most symmetrical “flat” conformation cannot be obtained because of a very large degree of steric hindrance to rotation about the central C-C bond: a very high energy is required to rotate past the point

of planarity. The molecular conformations are thus locked with the two rings perpendicular to each other. The two conformations are enantiomeric; their mirror images cannot be superimposed.



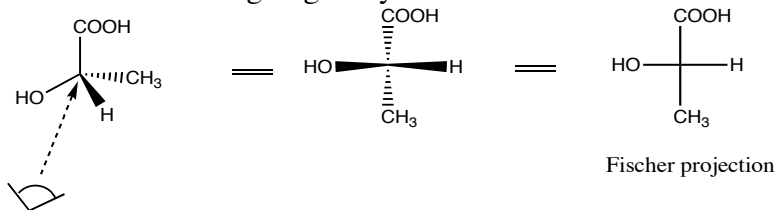
• **Allene** is a molecule with one sp-hybridized carbon and two sp<sup>2</sup>-hybridized carbon atoms. Because of the perpendicular p-orbitals on the central sp-hybridized carbon which overlap to form the pi orbitals, the pi orbitals are also perpendicular, and thus the end groups on the molecule are perpendicular. Substituted allenes are thus chiral molecules with non-superimposable mirror images:



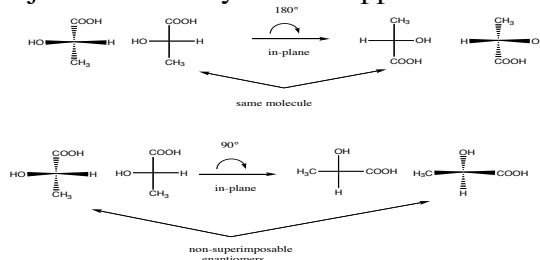
## II. Fischer Projections

Fischer Projections are a shorthand method of drawing stereoisomers to facilitate their comparison when there are multiple asymmetric carbon atoms within a molecule.

• Fischer projections are drawn in cross form with the horizontal bonds coming toward the viewer and the vertical bonds going away from the viewer. For S-lactic acid:

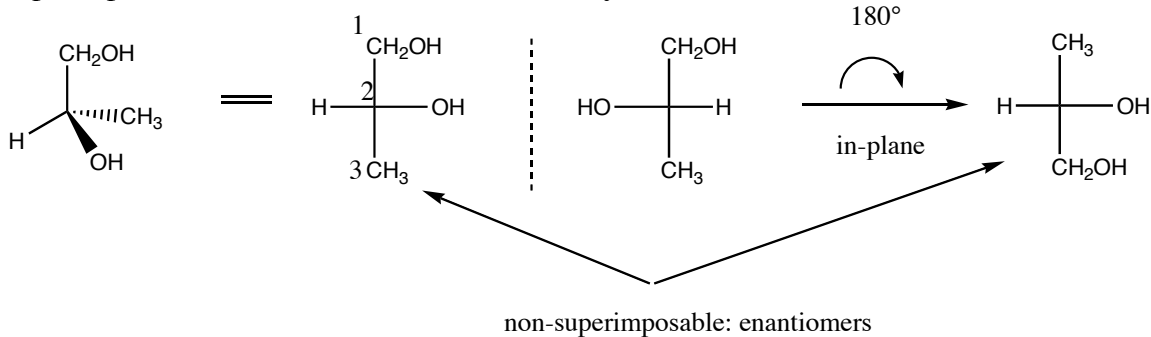


• Fischer projections that differ by 180° are the same molecule. A 90° rotation, however, is not allowed. Fischer projections also may not be flipped over: they must be kept in-plane.

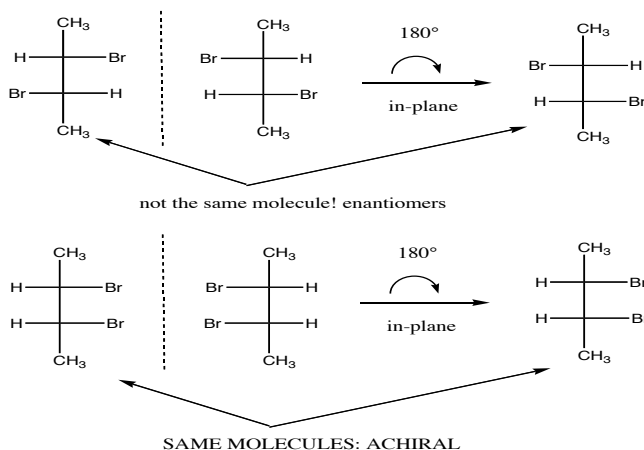


- A carbon chain must be drawn along the vertical line of the projection and given IUPAC numbering from top to bottom

- When looking **at the mirror image** of a Fischer projection, any groups that fail to superimpose after a 180° turn indicates chirality and the two molecules are enantiomers.

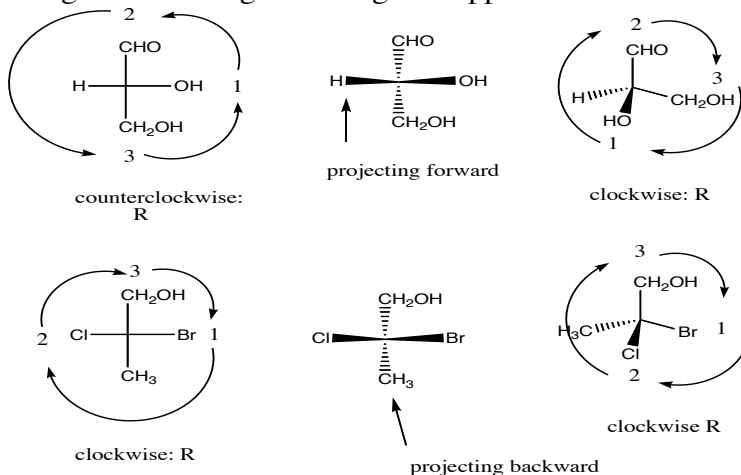


ALSO:



### Assigning R and S configurations to Fischer Projections

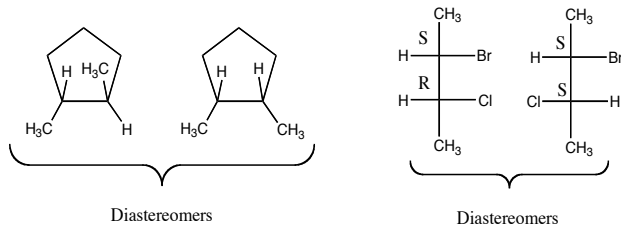
- Same rules apply, but if the low priority group (H) is projecting forward (on a horizontal bond), a counterclockwise rotation indicates R configuration and a clockwise rotation indicates S configuration; if the low priority group is projecting backward (on a vertical bond) the regular Cahn-Ingold Prelog rule applies:



### III. Diastereomers

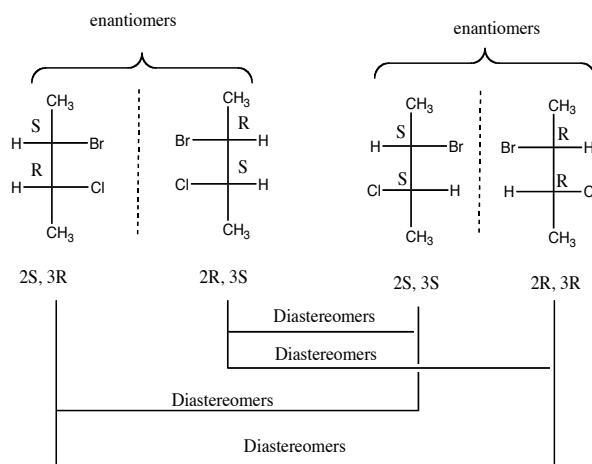
**Diastereomers** are stereoisomers that are not mirror images; they are geometric isomers (like cis-trans isomers about a double bond) and usually compounds containing at least two centers of chirality.

Examples:



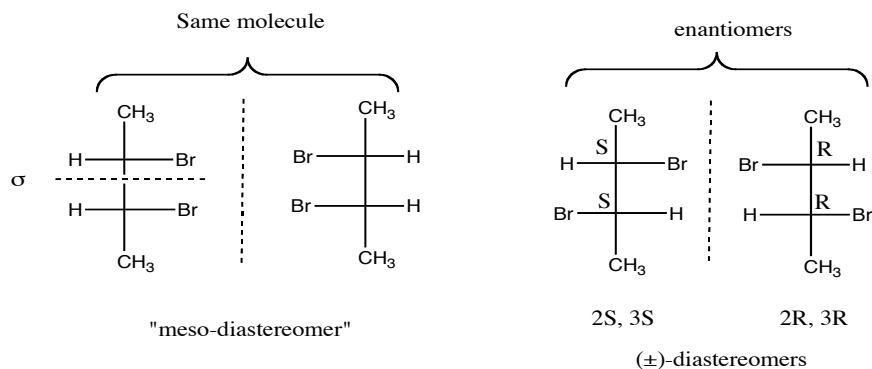
Stereoisomers but not  
enantiomers

Relationships:



• If the number of stereogenic carbon atoms in a molecule is  $n$ , there are a maximum of  $2^n$  possible stereoisomers. Thus, for two stereogenic carbon atoms, there are a maximum of  $2^2$  or 4 possible stereoisomers. There are many cases where less than the maximum number of stereoisomers may be found, especially in symmetrical molecules.

Example:



2-stereogenic carbon atoms;  
a total of 3 stereoisomers for 2,3-dibromobutane!

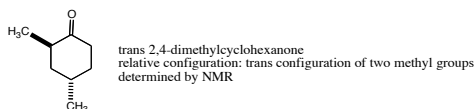
• A **meso compound** is one that is achiral despite having centers of chirality: it usually has some element of symmetry, like an internal mirror plane

## IV. Absolute and Relative Configuration

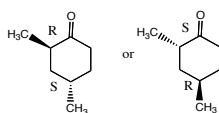
**Absolute configuration** is the detailed stereochemical picture of a molecule, specifying how the atoms are arranged in space through designating R or S configurations at each chirality center.

**Relative configuration** is the experimentally determined relationship between the configuration of two molecules or two stereogenic carbon atoms within a molecule, even though we may not know the absolute configuration of either.

Example:



however, we don't know absolute stereochemistry:



## V. Physical Properties of diastereomers

- Diastereomers, unlike enantiomers, have different physical properties: melting points, boiling points, etc. Diastereomers can thus be separated by ordinary means: chromatography, distillation, crystallization, etc.

- Enantiomers, which are mirror-image molecules, have virtually identical physical properties and are thus very difficult to separate..

- Pure enantiomers of optically active compounds are often obtained by isolation from natural sources. Examples: carbohydrates (D-(+)-glucose) and amino acids (L-(+)-alanine)

- Many chemical reactions involve achiral reagents and thus can yield racemic mixtures as products. How can one separate (resolve) enantiomers of a given molecule?

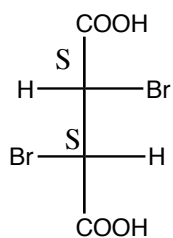
### Resolution of Enantiomers

- Column Chromatography can be employed using a chiral stationary phase as an adsorbent: different enantiomers form diastereomeric complexes with the chiral column packing and move through the column at different rates. In this way separation can be achieved without chemical modification of a racemic mixture.

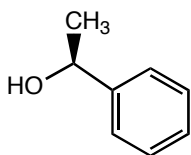
- A racemic mixture can also be resolved by reacting the mixture of enantiomers with a chiral **resolving agent**, which generates diastereomers that are easily separated. The pure enantiomers can then be obtained by hydrolysis of the respective diastereomers.

We illustrate this process for the formation of diastereomeric esters by reaction of a racemic diacid with a chiral alcohol:

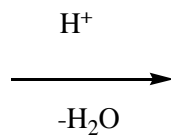
inseparable  
Racemic mixture



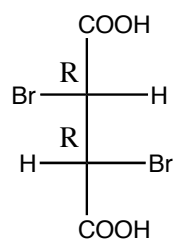
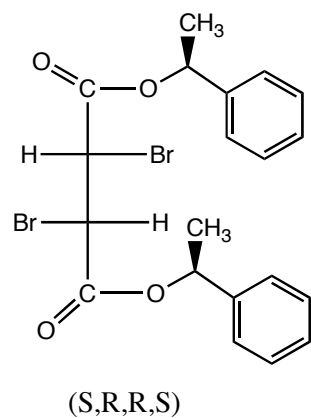
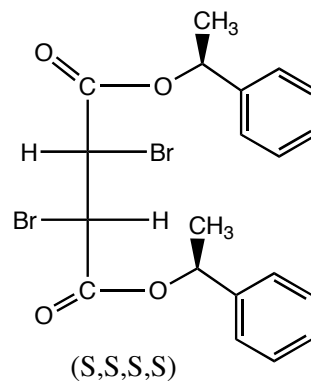
Resolving agent



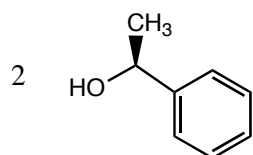
S-phenyl ethanol



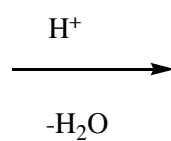
separable  
Diastereomers



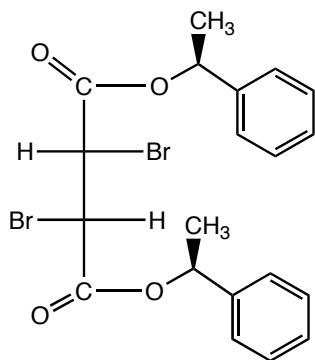
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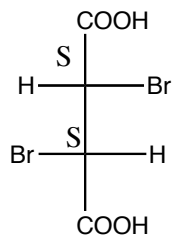
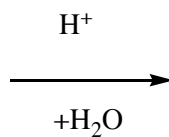
S-phenyl ethanol



hydrolysis:



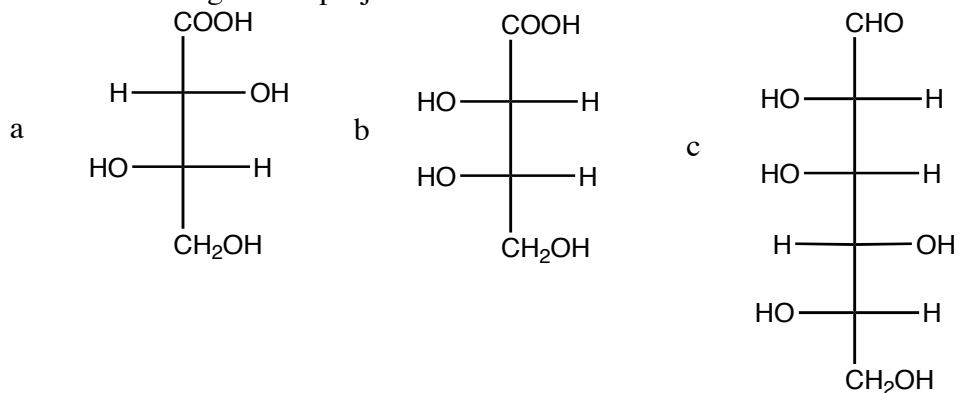
(S,S,S,S)



pure enantiomer

Additional Problems for practice:

- 1.) Draw a three-dimensional picture that corresponds to each of the following Fisher projections:



- 2.) State the relationship between each of the following pairs of structures (identical, enantiomers, diastereomers, constitutional (structural) isomers, or different compounds that are not isomeric)

