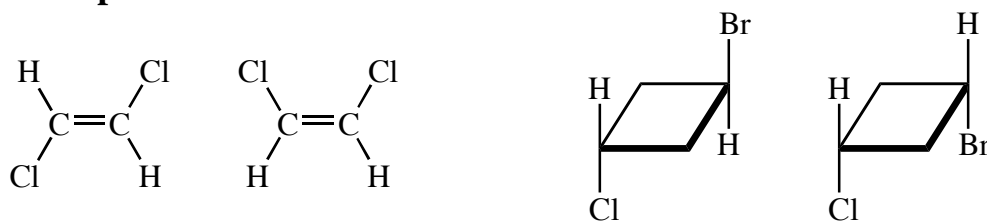


Lecture Notes
Chem 51A
S. King

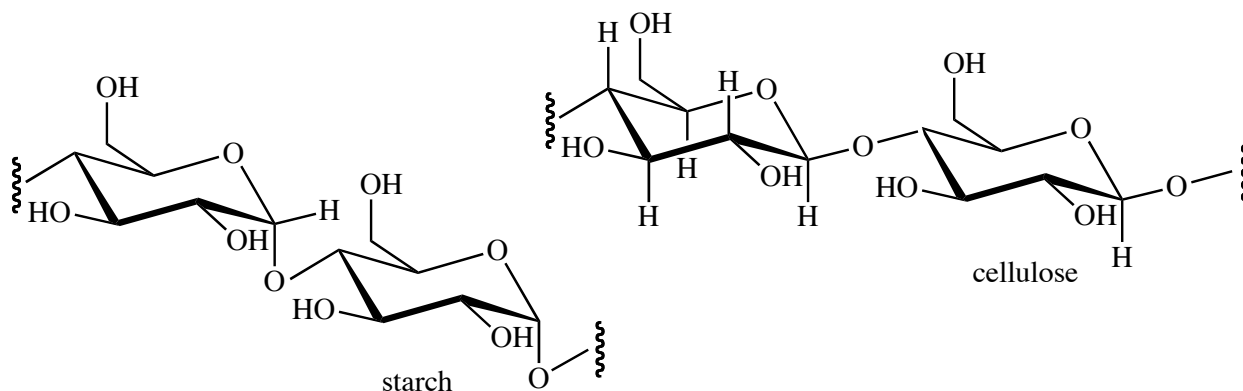
Chapter 5 Stereochemistry

Stereoisomers are compounds that have the same atom connectivity but a different arrangement of atoms in space.

Example:



Starch and cellulose are two more examples of molecules that have the same connectivity, but different 3-D arrangement of atoms. They are both composed of the same repeating unit, glucose, joined by an oxygen atom. The only difference is one ring carbon. In cellulose, it is equatorial, and in starch, it is axial.



How the six-membered rings are joined together has an enormous effect on the shape and properties of these carbohydrate molecules.

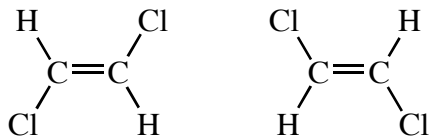
Cellulose: Composed of long chains held together by intermolecular hydrogen bonds, thus forming sheets that stack in an extensive 3-D network.

Starch: The axial C-O bond causes the starch molecule to fold into a helix

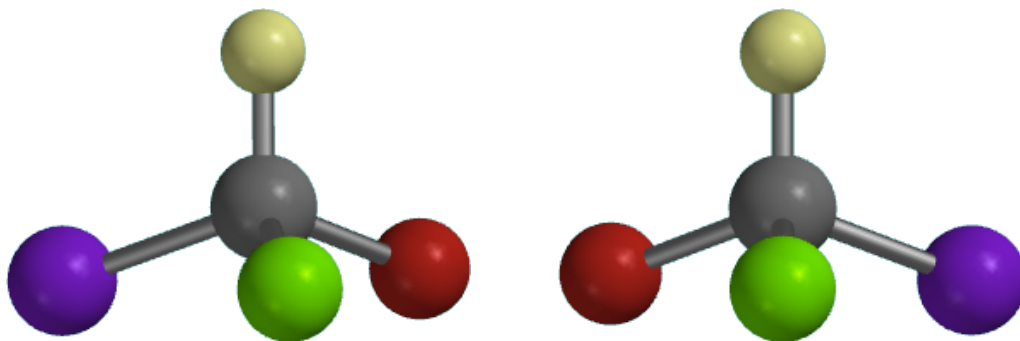
I. Enantiomers & Chirality, and Symmetry

Any molecule - indeed any object - has a mirror image. Some molecules are superimposable on their mirror images, that is, all atoms and bonds in a molecule can be simultaneously aligned with identical atoms and bonds in its mirror image. When this is the case, the molecule and its mirror image are *identical*.

Example:



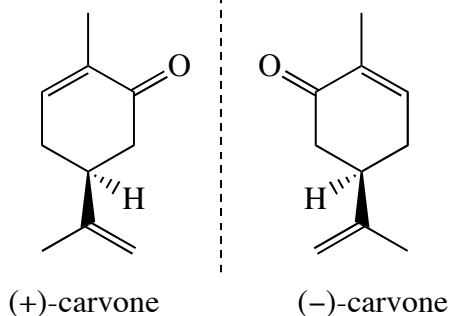
Some molecules are *not* superimposable on their mirror images. When a molecule and its mirror image are not congruent (superimposable), they are *different* molecules. Any molecule or object that cannot be superimposed on its mirror image is *chiral*. A chiral molecule and its mirror image are *enantiomers*.



☛ See handout *Drawing Stereoisomers* for correct and incorrect ways to draw 3D dash/wedge structures.

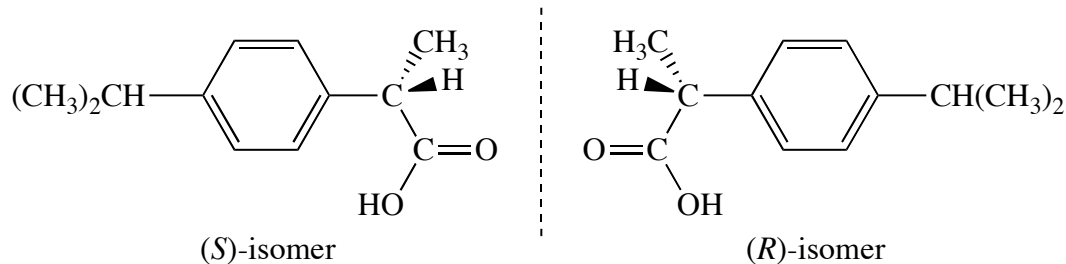
- Enantiomeric molecules have the same relationship as right and left hands. Enantiomers and hands are **chiral** (*they possess the property of chirality*)
- Molecules (or other objects) that are not chiral are said to be **achiral** (*without chirality.*)

Our noses can distinguish enantiomers:

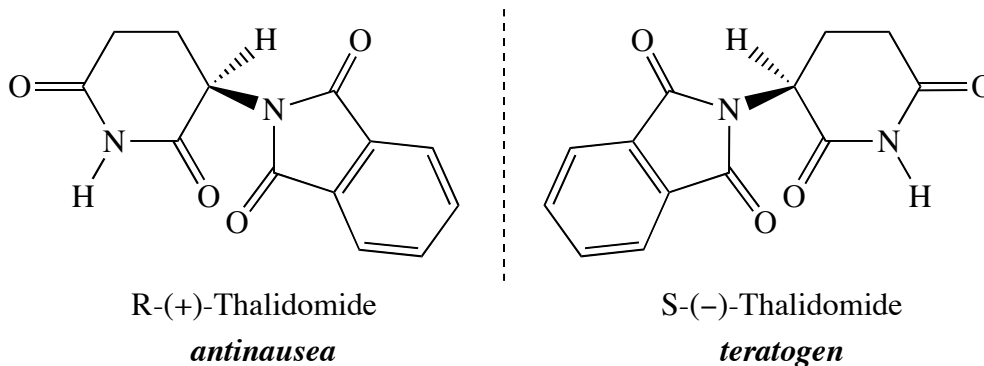


Receptor sites for the sense of smell are chiral, just as the active sites in most enzymes are chiral.

Ibuprofen



Thalidomide

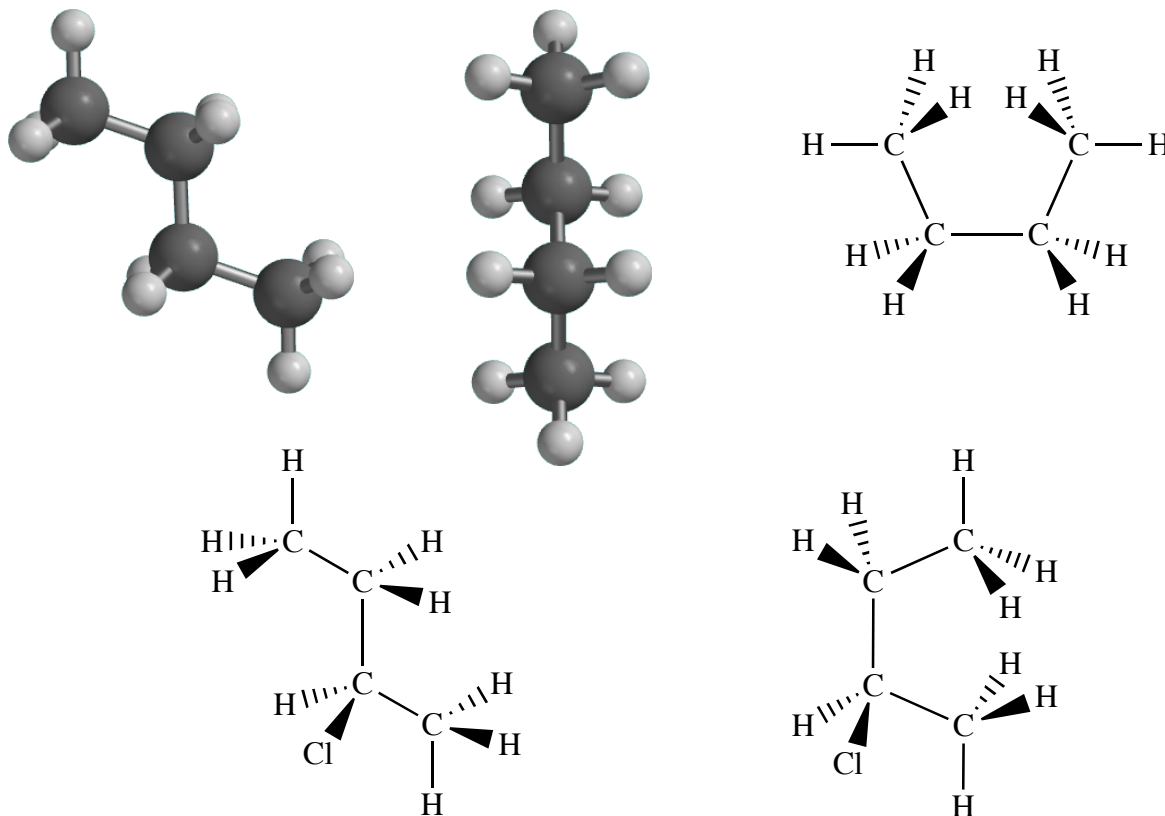


Q. How can we tell if a molecule is chiral?

A. There are two things to look for:

1. Look for a plane of symmetry

A plane of symmetry divides an object or molecule into two equal halves that are mirror images of each other. An object that has a plane of symmetry is superimposable on its mirror image and is **achiral**. A chiral molecule **DOES NOT** have a plane of symmetry.

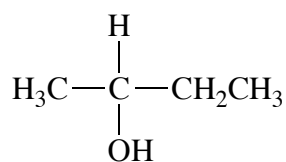


2. Look for a tetrahedral atom with 4 different substituents

A tetrahedral atom that is bonded to 4 different substituents constitutes a **stereocenter** (AKA: **chiral center** or **stereogenic center**).

If there is:

- one chiral center only:



2-butanol

3-D formulas:

- to change from one enantiomer of 2-butanol to the other enantiomer, with models, you have to ***physically remove two bonds and switch them!***

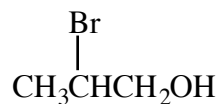
If there are:

- two or more chiral centers:

II. Drawing Enantiomers

Enantiomers can be drawn using 3-D (*dash-wedge*) formula.

Example: Draw enantiomers of the following compound using 3-D formulas:



III. Properties of Enantiomers: Optical Activity

Enantiomers have *identical*: b.p.'s, m.p.'s, solubilities, index of refraction, IR, NMR in achiral solvent, etc.

Enantiomers *differ*

- when they interact with other chiral substances
- when they interact with plane polarized light

Enantiomers rotate the plane of polarized light by exactly the same amount but in the opposite direction.

Device used to measure optical rotation: *polarimeter*

The specific rotation of a compound is calculated using the following formula:

$$\left[\alpha \right]_D^T = \frac{\alpha}{cl} \quad (\text{concentration, solvent})$$

$$\left[\alpha \right]_D^T = \begin{array}{l} \text{specific rotation @T}^\circ\text{C} \\ \text{using line from D line} \\ \text{visible spectrum of sodium} \\ \text{(wavelength: 589 nm)} \end{array}$$

α = measured \angle of rotation

l = length of sample tube (dm) (1 dm = 10 cm)

c = concentration of sample (g/ml)

(- = counterclockwise = levorotatory)

(+ = clockwise = dextrorotatory)

- There is no obvious correlation between the configuration of enantiomers and the direction in which they rotate plane polarized light.
- A sample of pure chiral compound uncontaminated by its enantiomer is said to be *enantiomerically pure*.
- An equimolar pair of enantiomers is called a *racemic mixture*. A *racemic mixture* has an optical rotation of zero.

☛ **THIS DOES NOT MEAN THAT A RACEMIC MIXTURE IS ACHIRAL!**

Chirality is a property of individual molecules or objects. A chiral molecule has this property whether it's mixed with its enantiomer or not. Optical activity is a physical property - chirality is a structural attribute.

A. Enantiomeric Excess

A pure sample of a single enantiomer is said to be *enantiomerically pure* or have an *enantiomeric excess* (%ee) of 100%. If the sample is contaminated with the other enantiomer, the mixture will show an optical rotation corresponding to the % of the species present in excess (%ee will be less than 100%.)

$$\%ee = \frac{\text{measured specific rotation of mixture}}{\text{specific rotation for the pure enantiomer}} \times 100\%$$

Example 1: A sample of 2-bromobutane has $[\alpha]_D^{22} = +11.55^\circ$. The specific rotation of (+)-2-bromobutane @ 22°C is +23.1°. What is the enantiomeric excess of (+)-2-bromobutane in this sample?

Example 2: What is the stereoisomeric composition of a mixture of 2-bromobutanes, with 50%ee of (+)-2-bromobutane?

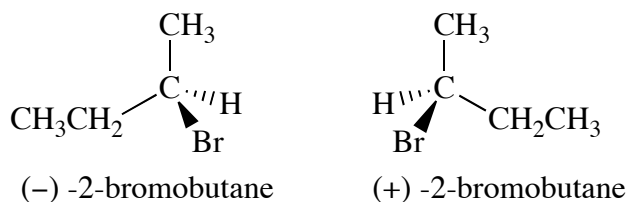
IV. Configuration, Representation, and Nomenclature of Stereoisomers

Sample of: (-)-2-bromobutane

Sample of: (+)-2-bromobutane

- These two samples have the opposite *relative configuration*.
- The optical rotation tells us nothing about the *absolute configuration* (the *actual* orientation in space of the groups around a stereocenter).

What is the **absolute configuration** of (-)-2-bromobutane and (+)-2-bromobutane?

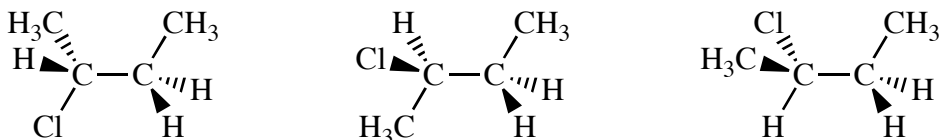


*****DON'T confuse Configuration with Conformation!**

The *configuration* of a compound is unchanged unless at least one bond at the stereocenter is broken.

The *conformation* of a molecule changes continuously @ room temperature as a result of rotation about single bonds and the flipping of rings in molecules

- A stereoisomer has a single configuration, but may exist in a number of conformations, depending on solvent and temperature.



Absolute configuration is specified by using the R,S (Cahn-Ingold-Prelog Rules)

R - from *rectus* (or right-handed), **clockwise**

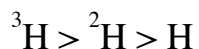
S - from *sinister* (or left-handed), **counterclockwise**

Step 1: Assign priorities (1, 2, 3 or 4) to the atoms directly bound to the stereocenter.

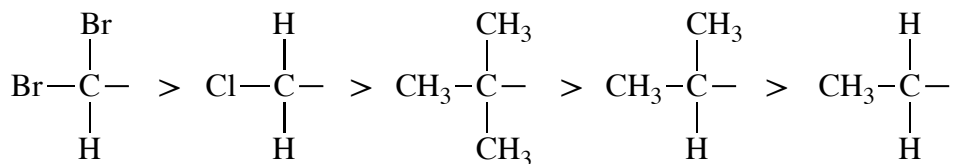
- Higher atomic numbers receive higher priority



- Isotopes: higher atomic mass takes priority

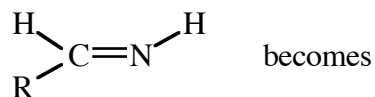
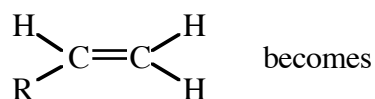


- In case of ties, next atom in chain is used as a tiebreaker.



☛ **Important:** a priority decision is made at the *first point of difference!!*

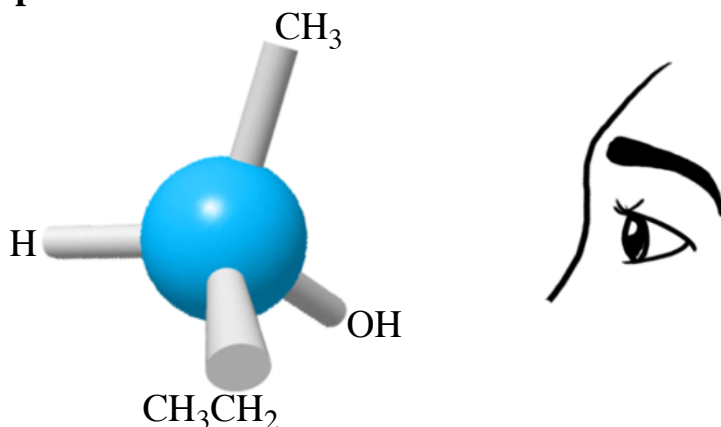
- Double and triple bonds are treated as if each bond were a bond to a separate atom.



Step 2: View chiral carbon with lowest priority substituent away from viewer.
Trace a path from **1st** priority to **2nd** to **3rd** priority:

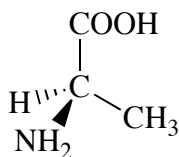
- if clockwise, configuration is **R**.
- if counterclockwise, configuration is **S**.

Example 1:



***** Designation of a compound as R or S has nothing to do with the sign of rotation!**

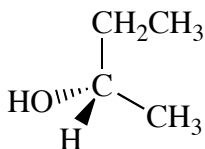
Example 2: Assign (*R*) or (*S*) configuration to the following amino acid alanine.



Q. What if the lowest priority substituent is not drawn going back?

A. Approach #1:

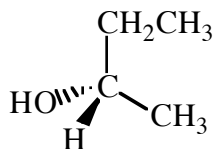
*Assign (*R*) or (*S*) configuration with lowest priority substituent towards you, then switch.*



Approach #2:

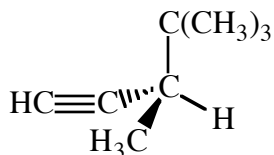
Recognize that exchanging two groups at the stereocenter inverts the configuration of that carbon atom and converts a structure with only one stereocenter into its enantiomer.

(Exchange H & OH so that H is going back, determine (*R*) or (*S*) configuration, then switch.)

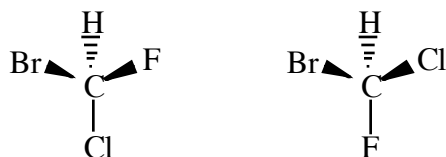


Example 3: Assign R or S configuration to the following molecule:

(**NEVER** try to assign configuration when H (*or lowest priority substituent*) is in the plane of the paper!)



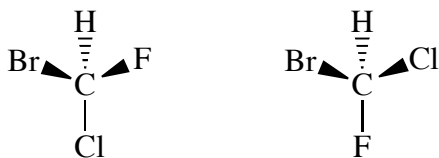
Example 4: Tell whether the two structures in the following pair represent enantiomers or conformers (same molecule, different orientation).



Ways to approach this problem:

1. Make 2 models and compare (*can be time consuming*).
2. Designate (R) or (S) configuration for each and compare.

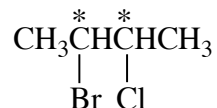
3. See if any groups have been exchanged:



V. Molecules with More than One Stereocenter

Many organic compounds have more than one chirality center. The more chirality centers a molecule has, the more stereoisomers are possible for the compound.

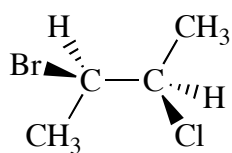
Look at 2-Bromo-3-chlorobutane:



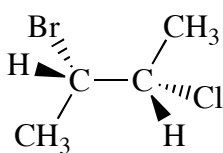
Q. There are two stereocenters. How many stereoisomers can we draw?

A.

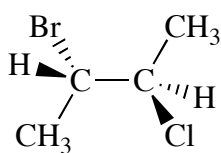
The total number of stereoisomers will not exceed 2^n , where n is equal to the number of tetrahedral stereocenters.



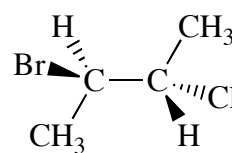
1



2



3



4

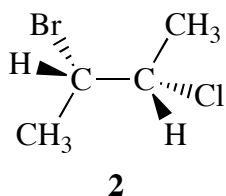
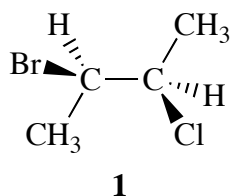
Molecules 1 & 3 are not identical, and they are not mirror images. Molecules with two or more stereocenters that are not mirror images of each other are *diastereomers*. Diastereomers have different physical properties (b.p.'s, m.p.'s, solubilities, etc)

NOTE:

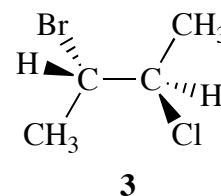
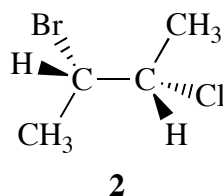
- The enantiomeric pairs have *opposite* configurations at each of the stereocenters

- The diastereomeric pairs have the *same* configuration at one of the two stereocenters, and *opposite* configuration at the other.

Look at the enantiomeric pair #1 & #2:



Look at the diastereomeric pair #2 & #3:

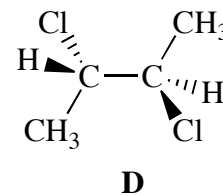
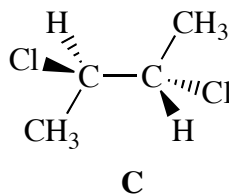
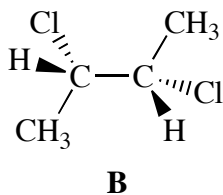
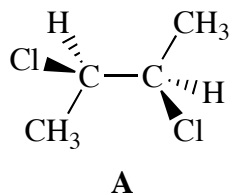


Meso Compounds:

If we followed the same procedure above for drawing the stereoisomers of 2,3-dichlorobutane, there would be only 3 stereoisomers rather than 4.

Q. Why?

A.



meso compound: a compound that has stereocenters but no chirality due to internal symmetry.

Enantiomeric Pairs:

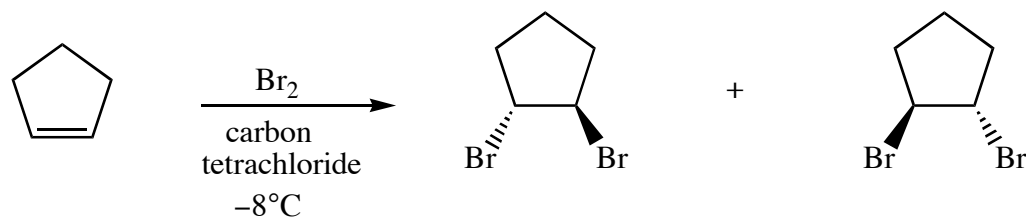
Diastereomeric pairs:

Q. How do you know whether a molecule possesses a *meso* stereoisomer?

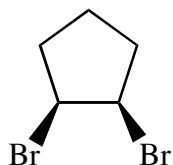
A. A meso compound is possible only when a molecule can be divided into structurally identical halves

VI. Stereoisomerism in Cyclic Compounds:

A. Disubstituted Cyclopentane Rings

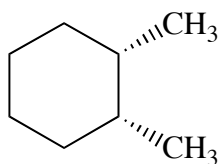


- *cis*-1,2-dibromocyclopentane is a **diastereomer** of the two *trans* compounds and a *meso* compound.

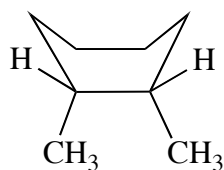
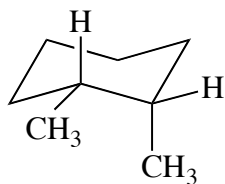


B. Disubstituted Cyclohexane Rings

Consider 1,2-dimethylcyclohexane:



Problem: Cyclohexane is not flat!

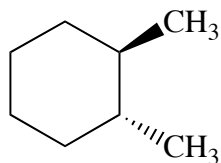


Q. Is the *cis* isomer optically active? The chair conformation has no plane of symmetry. But the boat conformation has a plane of symmetry!

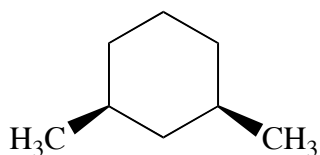
A.

∴ The *cis* isomer is **achiral** and is a **meso** compound.

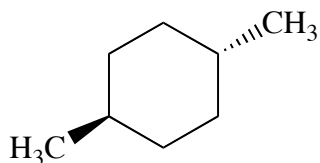
Is trans-1,2-dimethylcyclohexane chiral?



What about cis-1,3-dimethylcyclohexane? Is it chiral?



Is trans-1,4-dimethylcyclohexane chiral?



VII. Enantiomeric Resolution

Enantiomers are not separable by normal techniques used to separate constitutional isomers and diastereomers (fractional distillation, chromatography, recrystallization).

- Louis Pasteur separated right and left-handed crystals of tartaric acid using a microscope and a pair of tweezers.

- Enzyme systems: Perform resolutions when they metabolize one enantiomer and reject another.
- In the lab, resolutions are performed using a **resolving agent**, a chiral agent that bonds to the enantiomeric pair, resulting in a pair of diastereomers. This type of resolution capitalizes on the fact that *diastereomers, unlike enantiomers, have different physical properties.*

racemic mixture + chiral resolving agent → diastereomers → separate via conventional techniques → release enantiomer

Example: