5.12 Lecture 6

V. Alkanes

H. Cyclohexane

- ✓ The "Chair"
- 2. Ring Flipping
- 3. Monosubstituted
- 4. Disubstituted

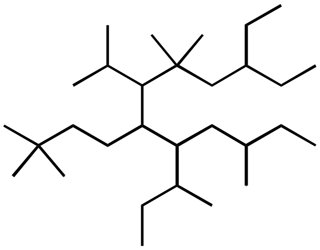
I. Polycyclic systems

VI. Stereochemistry

- A. Classification
- B. Chirality
- C. Optical Activity
- D. Chirality at Other Atoms
- E. Prochirality

Stereochemistry
Suggested Reading: 9.1-9.5, 6.6, 9.6-9.11, 9.15-9.17
Suggested Problems: 9.1-9.4, 9.6-9.19, 9.24-9.26, 9.32-9.57, 9.70-9.74, 9.79-9.83

Name That Molecule!



8-*sec*-butyl-3-ethyl-6-isopropyl-5,5,10-trimethyl-7-neohexyldodecane

or

8-*sec*-butyl- 7-(3,3-dimethylbutyl)-3-ethyl-6-(1-methylethyl)-5,5,10-trimethyldodecane

VI. Stereochemistry

A. Classification of Stereoisomers
  1. Conformational
    a. Bond rotation
    b. Ring flip
    c. Nitrogen inversion
  2. Configurational
    a. Cis-trans
    b. 4 different subst. on carbon
    c. Subclasses of a) and b)
      i. Enantiomers
      ii. Diastereomers

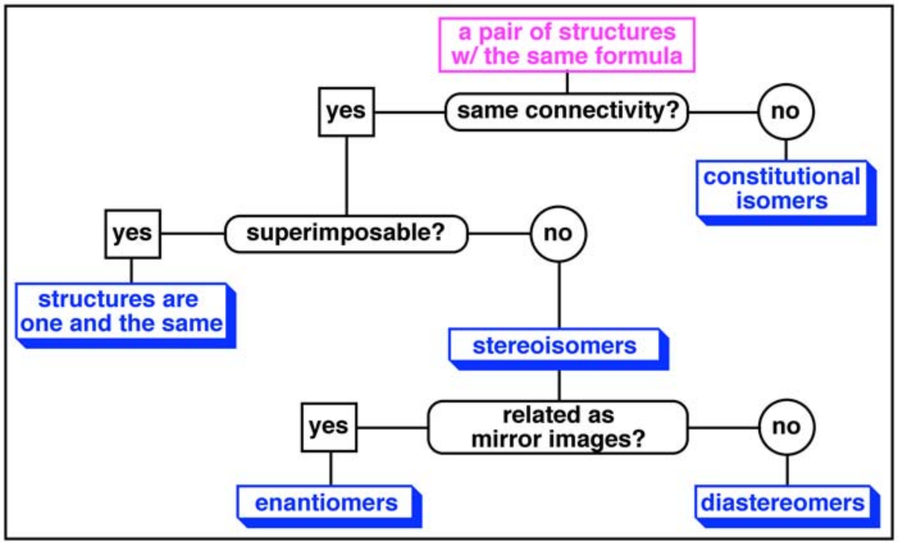
B. Chirality
  1. Definition
  2. Determining chirality
  3. Origins of chirality
    a. Carbon with 4 diff. subst.
    b. Axial chirality
    c. Meso compounds
  4. Facts about Chirality

C. Optical Activity

D. Chirality at Other Atoms

E. Prochirality

Classifying Stereoisomers



a pair of structures w/ the same formula

same connectivity?

yes

no

constitutional isomers

superimposable?

yes

structures are one and the same

no

stereoisomers

related as mirror images?

yes

enantiomers

no

diastereomers

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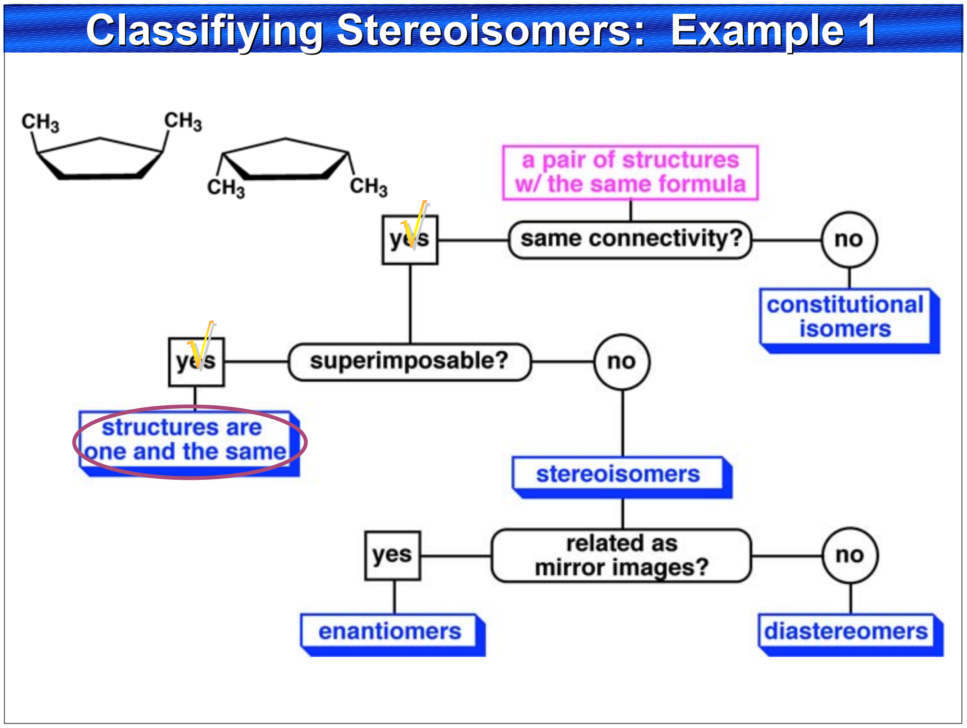

Classifiying Stereoisomers: Example 1

a pair of structures w/ the same formula

same connectivity?

[✓ yes]

no

constitutional isomers

superimposable?

[✓ yes]

no

[✓ structures are one and the same]

stereoisomers

related as mirror images?

yes

no

enantiomers

diastereomers

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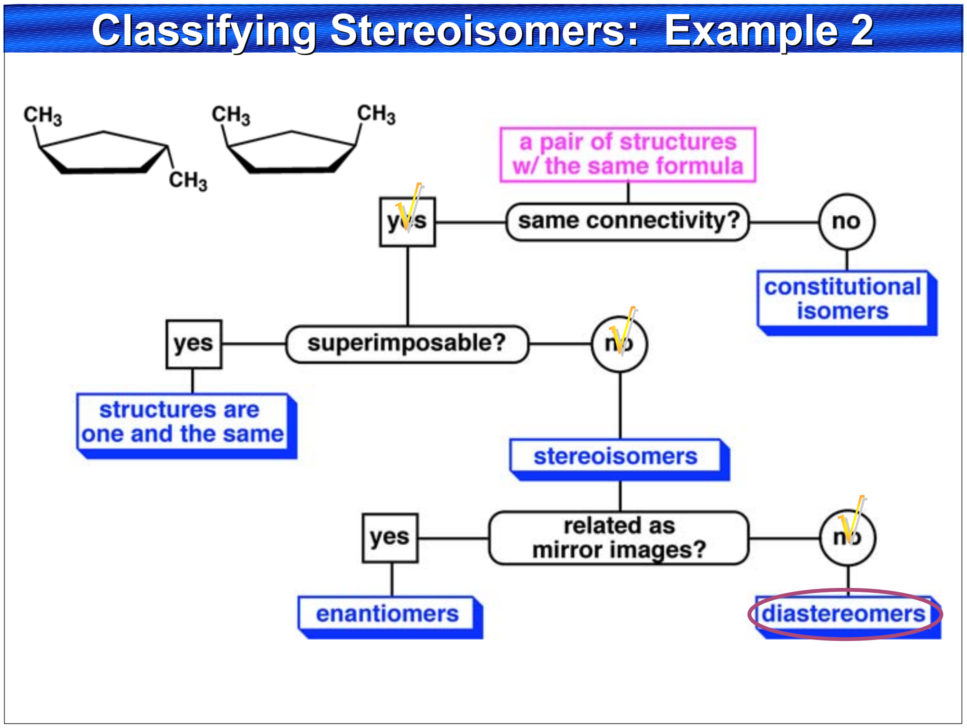

Classifiying Stereoisomers: Example 2

a pair of structures w/ the same formula

same connectivity?

[✓ yes]

no

constitutional isomers

superimposable?

yes

[✓ no]

structures are one and the same

stereoisomers

related as mirror images?

yes

[✓ no]

enantiomers

[✓ diastereomers]

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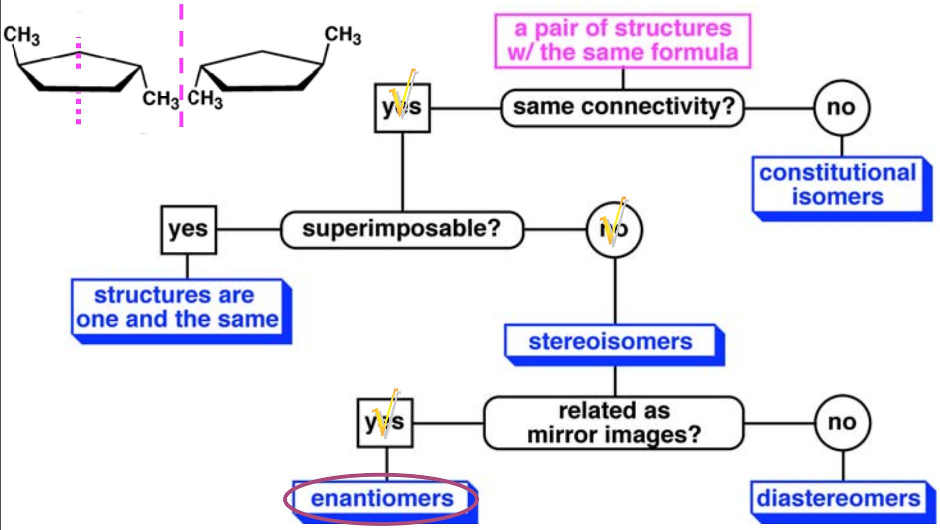
Classifying Stereoisomers: Example 3



a pair of structures w/ the same formula

same connectivity?

yes ✓

no

constitutional isomers

superimposable?

yes

structures are one and the same

no ✓

stereoisomers

related as mirror images?

yes ✓

enantiomers

no

diastereomers

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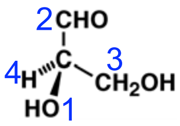
Prioritize Using Cahn-Ingold-Prelog Rules

1. Look at atoms directly attached to chirality center
   - a) higher atomic number = higher priority
   - b) heavier isotopes = higher priority
2. If no difference at first attached atom, move along the chain until the first point of difference.
3. Multiple-bonded atoms are equivalent to the same number of single-bonded atoms.

Assigning Chirality Center Configuration

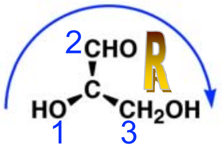
The configuration of chirality centers can be assigned using “R,S” descriptors.

1. Prioritize substituents with #’s 1-4 following Cahn-Ingold-Prelog Rules



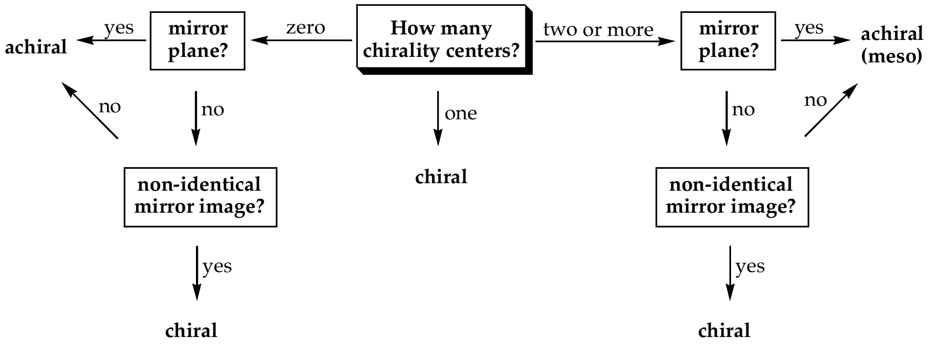
2. Orient molecule so substituent of lowest priority (4) is directed back

3. Starting from highest priority substituent (1) move to the second highest (2), then to third highest (3)

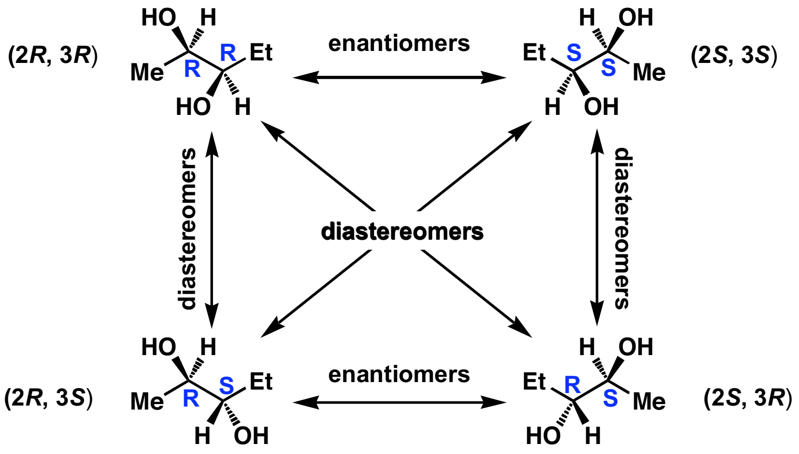


Clockwise movement: R
Counterclockwise movement: S

Determining Chirality Flow Chart



Enantiomers and Diastereomers



(2*R*, 3*R*)

enantiomers

(2*S*, 3*S*)

diastereomers

diastereomers

diastereomers

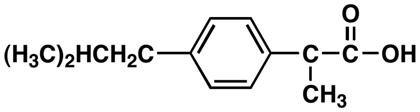
(2*R*, 3*S*)

enantiomers

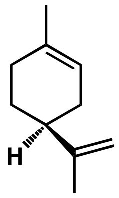
(2*S*, 3*R*)

Importance of Chirality

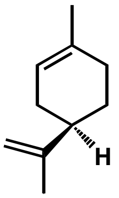
half of all pharmaceuticals are chiral compounds!



(*S*)-Ibuprofen (responsible for pain relief)



(*S*)-Limonene
Lemon smell

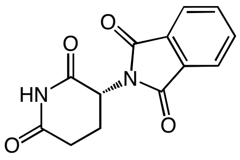


(*R*)-Limonene
Orange smell

Thalidomide

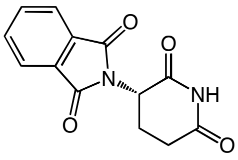
Thalidomide

- "Wonder drug" synthesized in 1953 & given to pregnant women to treat morning sickness
- Available in 46 countries until 1961/1962 (Not USA!)



(R)-**Thalidomide**

sedative



(S)-**Thalidomide**

teratogen

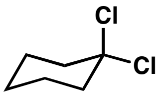
teratogen: causes birth defects

phocomelia: arrests limb formation

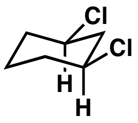
- ***(R)***-**Thalidomide racemizes under biological conditions (H^+)**

Chirality and Disubstituted Cyclohexane

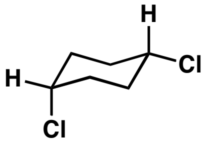
Achiral:



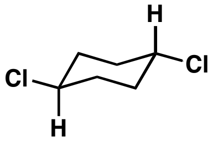
1,1
(plane of symmetry through C-1 and C-4)



***cis*-1,3**
(plane of symmetry through C-2 and C-5)

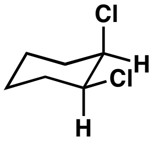


***cis*-1,4**
(plane of symmetry through C-1 and C-4)

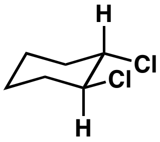


***trans*-1,4**
(plane of symmetry through C-1 and C-4)

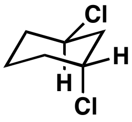
Chiral:



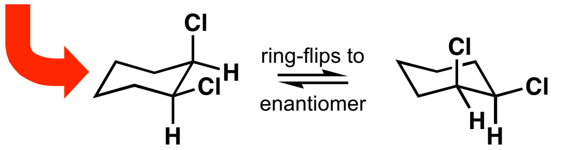
***cis*-1,2**



***trans*-1,2**



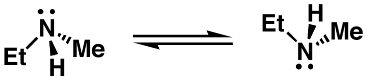
***trans*-1,3**



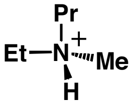
ring-flips to
enantiomer

D. Chirality at Other sp^3 Atoms

All tetrahedral atoms have the possibility of being chiral (Si, N, P, S)



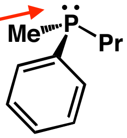
rapid inversion
low energy barrier
achiral



high energy barrier
for inversion
chiral

R

Lone pairs are lowest priority

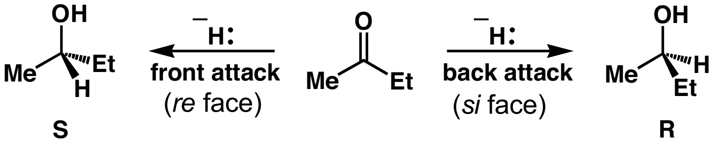


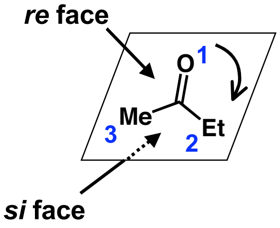
high energy barrier
for inversion
chiral

R

E1. Prochirality at Planar sp^2 Carbon

Prochiral - can be converted from achiral to chiral in a single chemical step (one step removed from chirality)

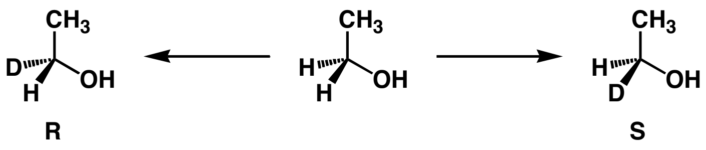


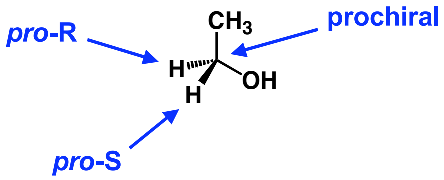


1. Assign priorities to three substituents.
2. If clockwise, assign face as *re*
3. If counterclockwise, assign face as *si*

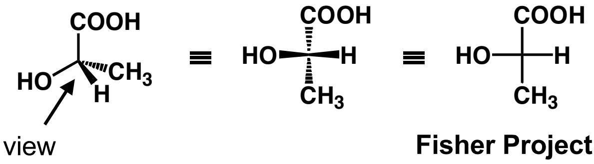
E2. Prochirality at Achiral sp^3 Carbon

Can become chiral by changing one of its attached groups





Fisher Projections (Common in Biology)



Fisher Projection

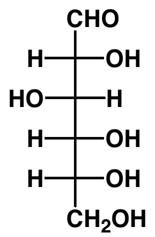
Vertical lines go into the paper
Horizontal lines come out of the paper

Dos and Don'ts of Fisher Projections

1. Do place atom with the IUPAC numbering of 1 at the top
2. Don't rotate 90 degrees, changes molecule into enantiomer
3. Do rotate 180 degrees to see different perspective
4. Do hold one atom constant and then rotate the other three clockwise or counterclockwise to put lowest priority on horizontal axis, or in back

Advantages of Fisher Projections

1. Simplifies drawing of molecules with multiple stereogenic centers (see D-glucose)
2. Easy to test if molecule is meso
3. Easy to determine R/S
4. Easy to test for enantiomerism



D-glucose

Important Definitions

stereocenter (stereogenic atom): any atom at which the interchange of two groups results in a stereoisomer; usually either a chiral carbon atom or a double-bonded carbon in a cis/trans alkene

chirality center: atom holding a set of ligands in a spatial arrangement that is not superimposable on its mirror image; one type of stereocenter

chiral atom (asymmetric atom): atom that is bonded to four different groups; a chiral carbon atom is the most common example of a chirality center

internal mirror plane: plane that divides molecule in such a way that two halves are identical

chiral (optically active): possessing a non-identical mirror image (an enantiomer)

achiral: superimposable on its mirror image

enantiomers: stereoisomers that are non-identical mirror images (same physical properties)

diastereomers: stereoisomers that are not enantiomers (different physical properties)

meso compound: achiral molecule that has chirality centers

Using the Lingo

an atom:
- that gives rise to stereoisomers when its substituents are interchanged is a **stereocenter**
- holding a set of ligands in an arrangement that is not superimposable on its mirror image is a **chirality center** (one type of stereocenter)
- with four **different** substituents attached is a **chiral atom** (one type of chirality center)
- that is chiral uses the **R/S descriptors** to assign absolute configuration

a molecule:
- must be either **achiral** (optically inactive) or **chiral** (optically active)
- that is achiral but contains chirality centers is called a **meso compound**
- that is optically active can be labelled **(+/–)** or **(*d/l*)**

related molecules:
- **enantiomers** (non-identical mirror images)
- **diastereomers** (any stereoisomers that are not enantiomers)

samples of molecules:
- **optically pure** (only one enantiomer present in sample)
- **racemate** or racemic mixture (mixture containing equal amounts of each enantiomer), not optically active
- mixtures in between optically pure and racemic are described by their **optical purity** (only 1 enantiomer present) or **enantiomeric excess** (1 enantiomer is in excess)

Note: Do not to confuse experimentally derived labels (+/– or d/l) with structurally derived labels (R/S). **They are not related!**