Advanced Stereochemistry

Presented By

Dr. Sujata Deo
Associate Professor
Department of Chemistry
Govt. Institute of science, Nagpur

Syllabus

ORGANIC CHEMISTRY SPECIALIZATION

CH-401: Paper XIII (Special I-Organic Chemistry)

Unit III: 15 h

A] Advanced Stereochemistry:

- **Conformation of sugars, monosaccharides, disaccharides, mutorotation,**
- **Recapitulation of Stereochemical concepts- enantiomers, diastereomers, homotopic and heterotopic ligands, Chemo-, regio-, diastereo-and enantio-controlled approaches;**
- **Chirality transfer,**
- **Stereoselective addition of nucleophiles to carbonyl group:**

Re-Si face concepts,

Models:Cram's rule, Felkin Anh rule, Houk model, Cram's chelate model.

Asymmetric synthesis use of chiral auxiliaries,

asymmetric hydrogenation,

asymmetric epoxidation

asymmetric dihydroxylation,

Unit 3 – Stereochemistry

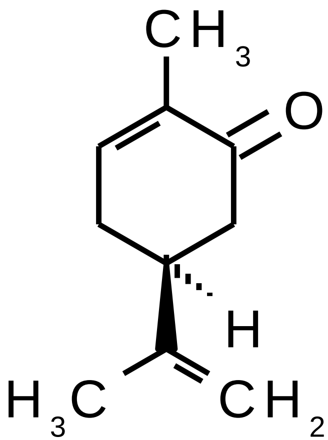
- Stereoisomers
- Chirality
- (R) and (S) Nomenclature
- Depicting Asymmetric Carbons
- Diastereomers
- Fischer Projections
- Stereochemical Relationships
- Optical Activity
- Resolution of Enantiomers

Stereochemistry

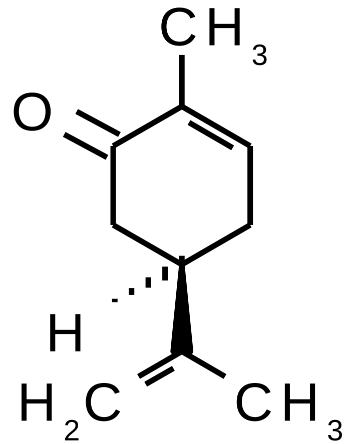
- Stereochemistry:
  - The study of the three-dimensional structure of molecules
- Structural (constitutional) isomers:
  - same molecular formula but different bonding sequence
- Stereoisomers:
  - same molecular formula, same bonding sequence, different spatial orientation

Stereochemistry

- **Stereochemistry plays an important role in determining the properties and reactions of organic compounds:**



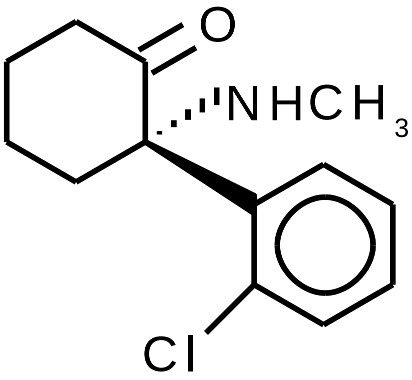
Caraway seed

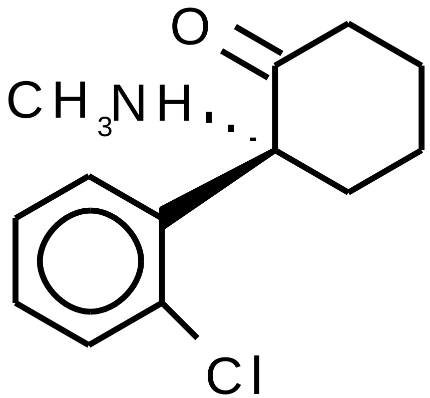


spearmint

Stereochemistry

- The properties of many drugs depends on their stereochemistry:





(S)-ketamine

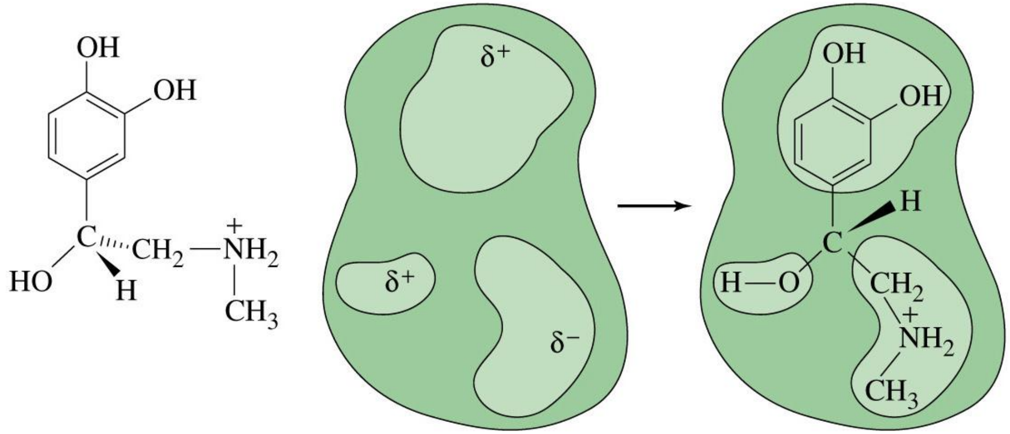
anesthetic

(R)-ketamine

hallucinogen

Stereochemistry

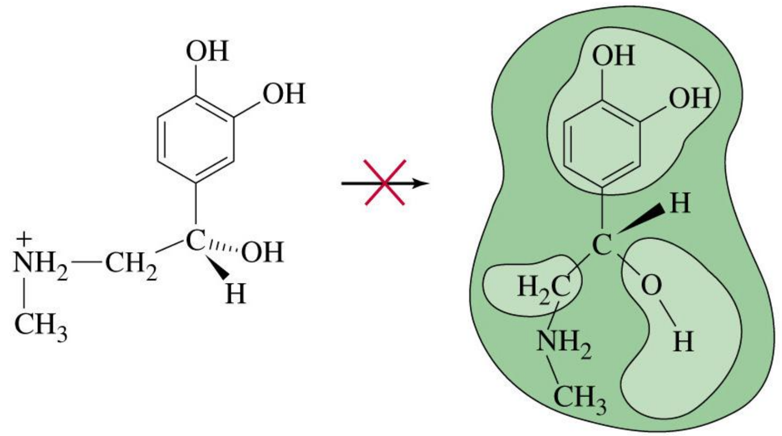
- **Enzymes are capable of distinguishing between stereoisomers:**



(*R*)-(–)-epinephrine natural epinephrine

enzyme active site

enzyme–substrate complex



(*S*)-(+)-epinephrine unnatural epinephrine

does not fit the enzyme's active site

Types of Stereoisomers

- Two types of stereoisomers:
  - enantiomers
    - two compounds that are nonsuperimposable mirror images of each other
  - diastereomers
    - Two stereoisomers that are not mirror images of each other
    - Geometric isomers (cis-trans isomers) are one type of diastereomer.

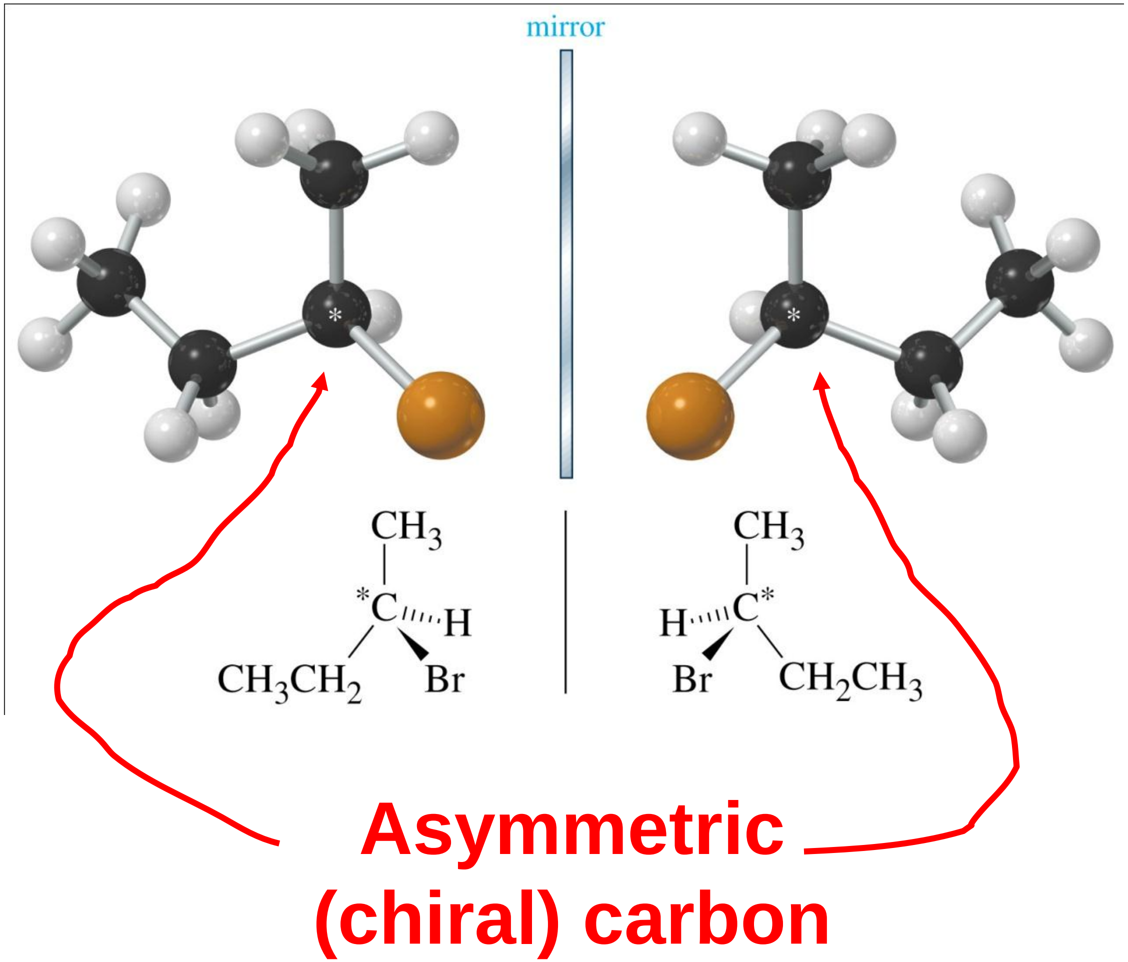
Chiral

- Enantiomers are chiral:
  - Chiral:
    - Not superimposable on its mirror image
- Many natural and man-made objects are chiral:
  - hands
  - scissors
  - screws (left-handed vs. right-handed threads)

Right hand threads slope up to the right.

Chiral

- Some molecules are chiral:



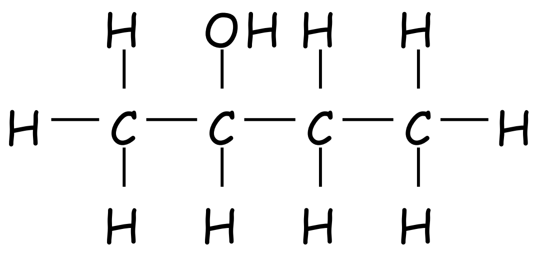
Asymmetric Carbons

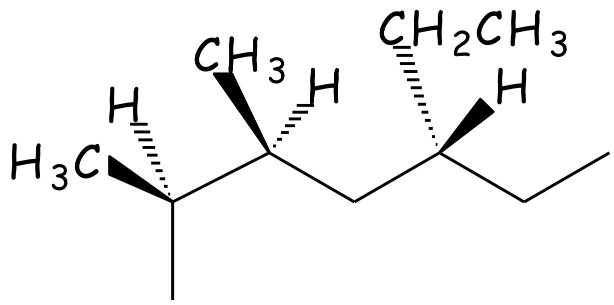
- The most common feature that leads to chirality in organic compounds is the presence of an asymmetric (or chiral) carbon atom.
  - A carbon atom that is bonded to four different groups

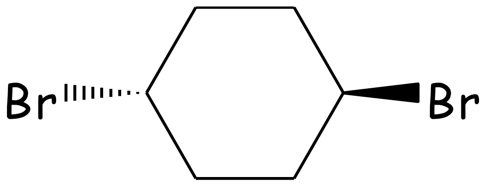
- In general:
  - no asymmetric C → usually achiral
  - 1 asymmetric C → always chiral
  - $\geq$ 2 asymmetric C → may or may not be chiral

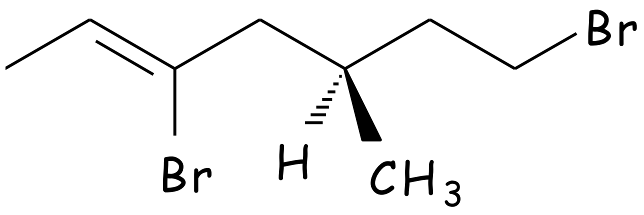
Asymmetric Carbons

Example: Identify all asymmetric carbons present in the following compounds.



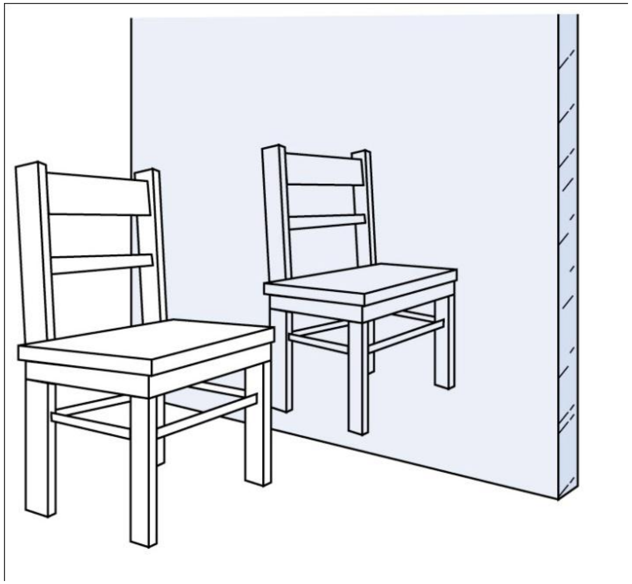


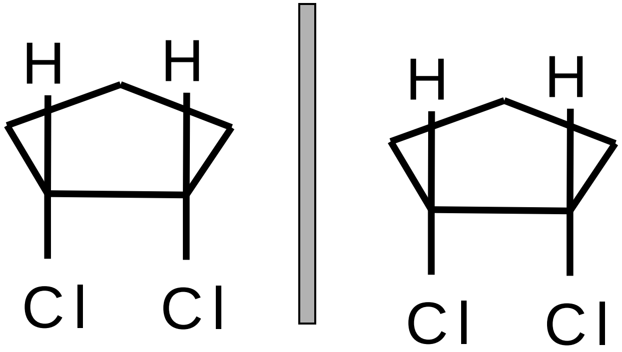




Achiral

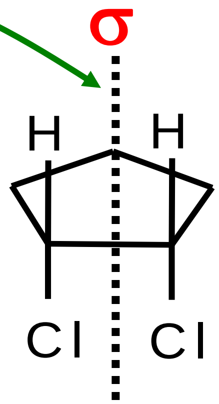
- Many molecules and objects are achiral:
  - identical to its mirror image
  - not chiral





Internal Plane of Symmetry

- Cis-1,2-dichlorocyclopentane contains two asymmetric carbons but is achiral.
  - contains an internal mirror plane of symmetry



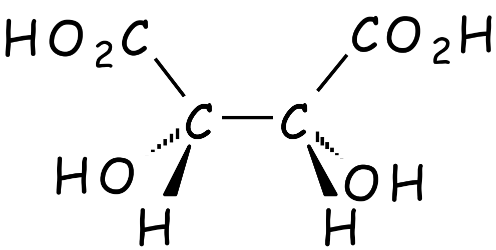
- Any molecule that has an internal mirror plane of symmetry is achiral even if it contains asymmetric carbon atoms.

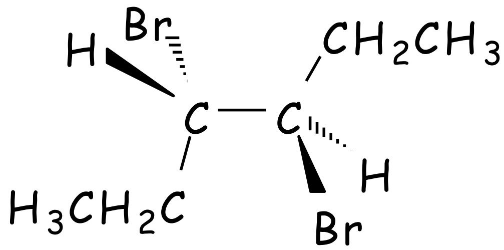
Internal Plane of Symmetry

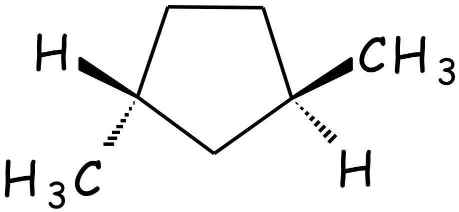
- Cis-1,2-dichlorocyclopentane is a meso compound:
  - an achiral compound that contains chiral centers
  - often contains an internal mirror plane of symmetry

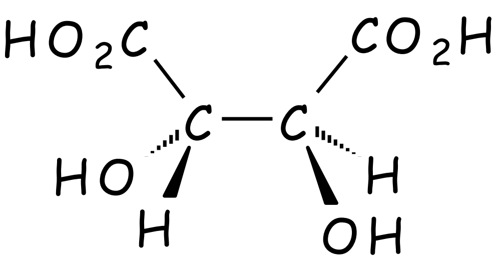
Internal Plane of Symmetry

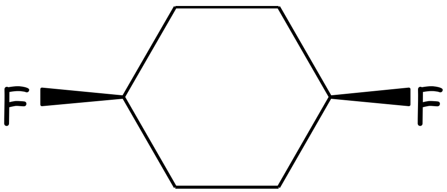
Example: **Which of the following compounds contain an internal mirror plane of symmetry?**

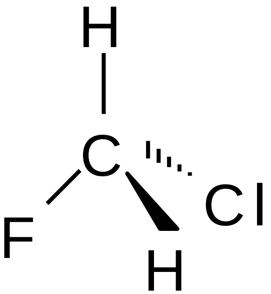












Chiral vs. Achiral

- To determine if a compound is chiral:
  - 0 asymmetric carbons: → Usually achiral
  - 1 asymmetric carbon: → Always chiral
  - 2 asymmetric carbons: → Chiral or achiral
    - Does the compound have an internal plane of symmetry?
      - Yes: → achiral
      - No:
        - If mirror image is non-superimposable, then it's chiral.
        - If mirror image is superimposable, then it's achiral.

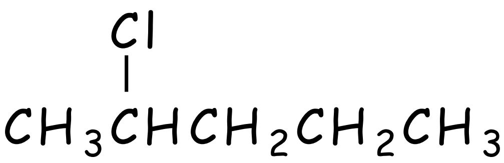
Conformationally Mobile Systems

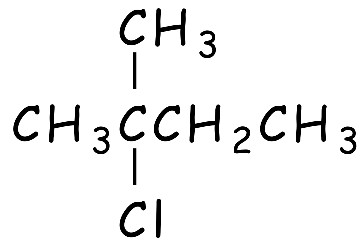
- Alkanes and cycloalkanes are conformationally mobile.
  - rapidly converting from one conformation to another

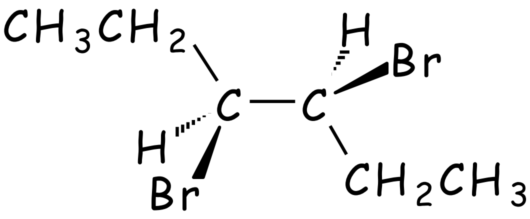
- In order to determine whether a cycloalkane is chiral, draw its most symmetrical conformation (a flat ring).

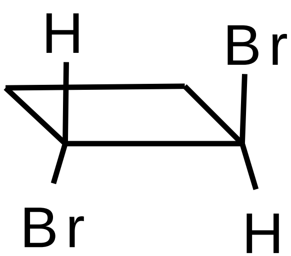
Chiral vs. Achiral

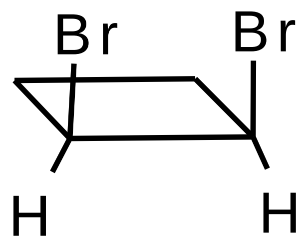
Example: **Identify the following molecules as chiral or achiral.**











trans-1,3-dibromocyclohexane

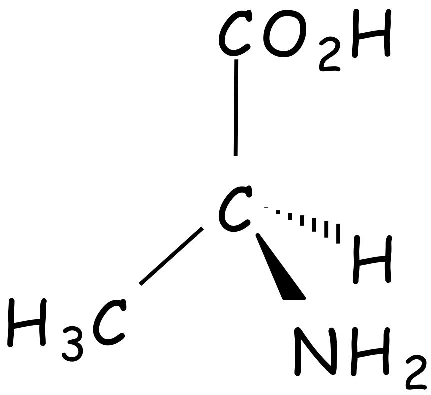
ethylcyclohexane

(R) And (S) Nomenclature

- Stereoisomers are different compounds and often have different properties.
- Each stereoisomer must have a unique name.
- The Cahn-Ingold-Prelog convention is used to identify the configuration of each asymmetric carbon atom present in a stereoisomer.
  - (R) and (S) configuration

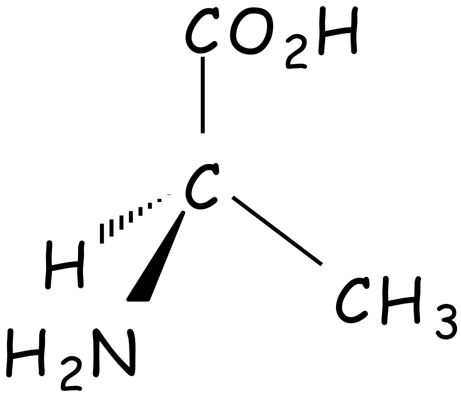
(R) and (S) Nomenclature

- The two enantiomers of alanine are:



Natural alanine

(S)-alanine



Unnatural alanine

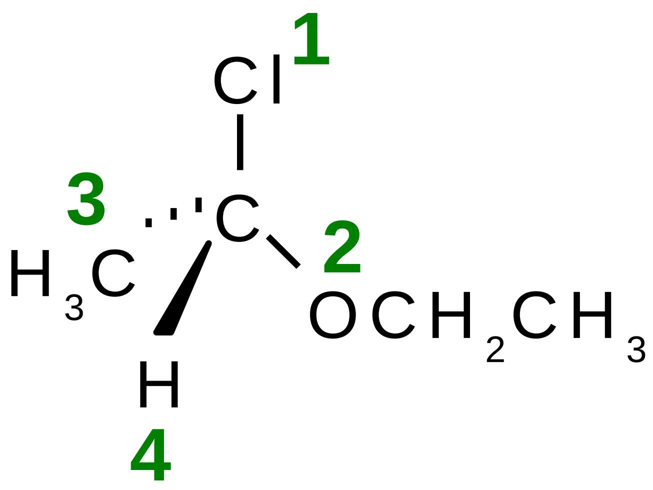
(R)-alanine

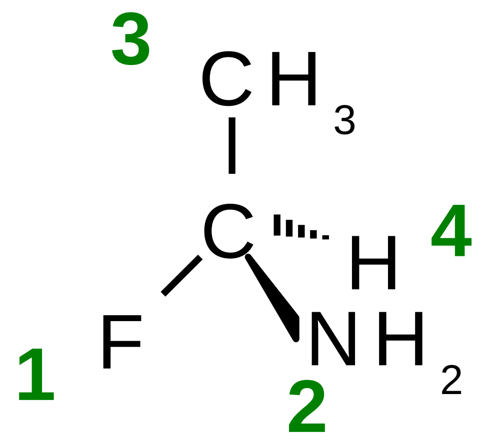
(R) and (S) Nomenclature

- Assign a numerical priority to each group bonded to the asymmetric carbon:
  - group 1 = highest priority
  - group 4 = lowest priority

- Rules for assigning priorities:
  - Compare the first atom in each group (i.e. the atom directly bonded to the asymmetric carbon)
    - Atoms with higher atomic numbers have higher priority

(R) and (S) Nomenclature



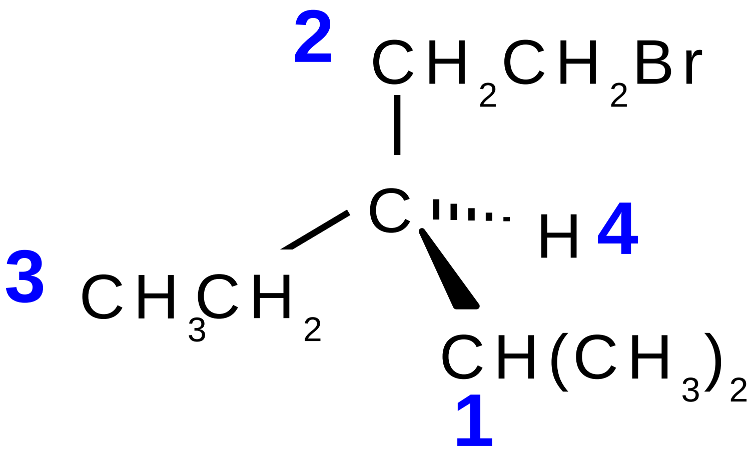


Example priorities:

I > Br > Cl > S > F > O > N > ^{13}C > ^{12}C > ^{3}H > ^{2}H > ^{1}H

(R) and (S) Nomenclature

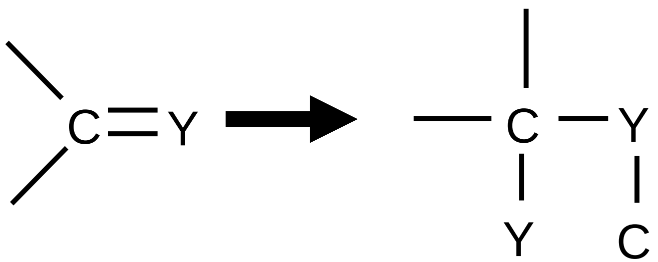
- In case of ties, use the next atoms along the chain as tiebreakers.

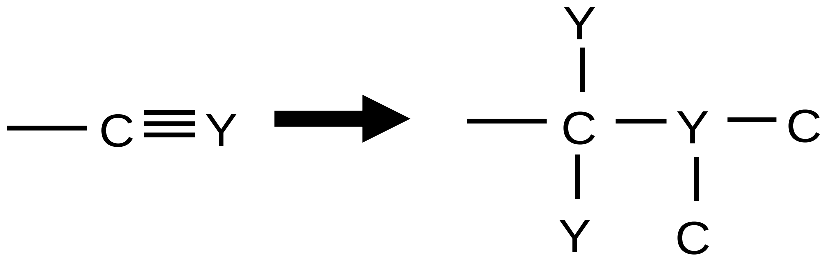


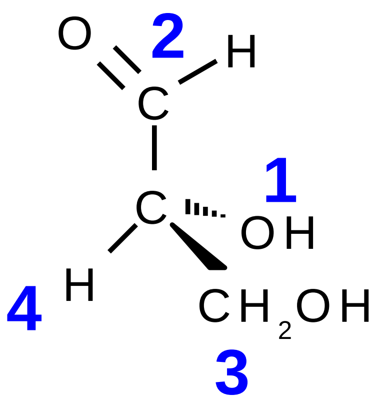
$CH(CH_3)_2$ > CH_2CH_2Br > CH_3CH_2

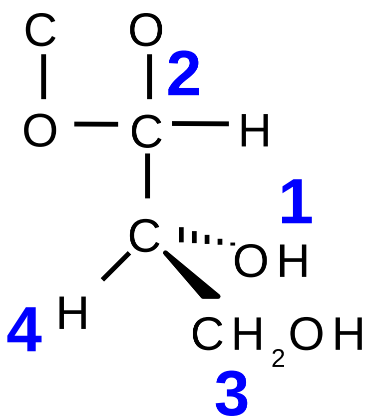
(R) and (S) Nomenclature

- Treat double and triple bonds as if both atoms in the bond were duplicated or triplicated:







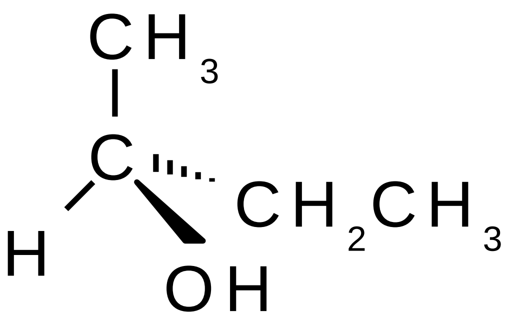


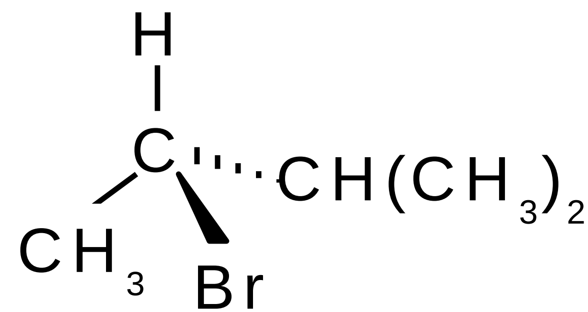
(R) and (S) Nomenclature

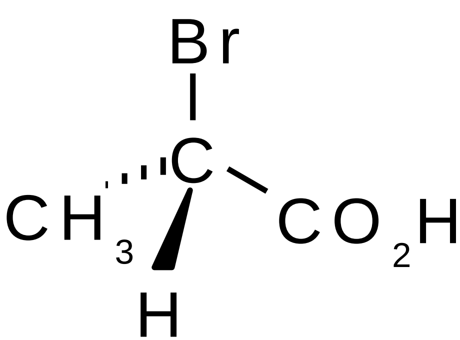
- Using a 3-D drawing or model, put the 4th priority group in back.
- Look at the molecule along the bond between the asymmetric carbon and the 4th priority group.
- Draw an arrow from the 1st priority group to the 2nd group to the 3rd group.
  - Clockwise arrow → (R) configuration
  - Counterclockwise arrow → (S) configuration

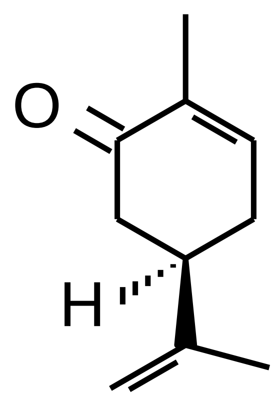
(R) and (S) Nomenclature

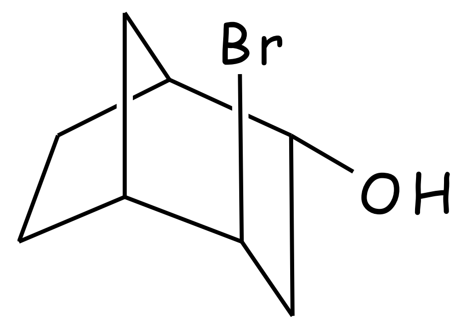
Example: Identify the asymmetric carbon(s) in each of the following compounds and determine whether it has the (R) or (S) configuration.





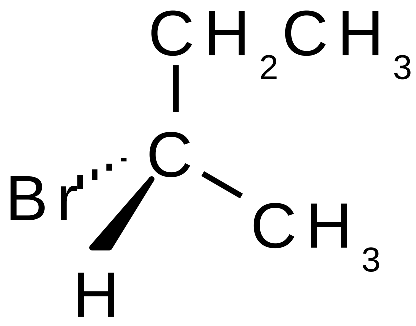


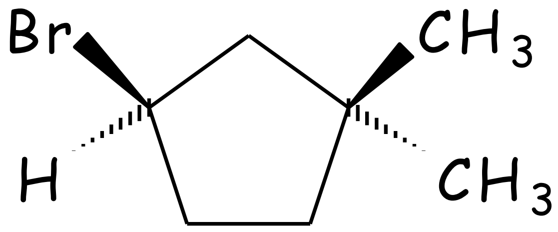




(R) and (S) Nomenclature

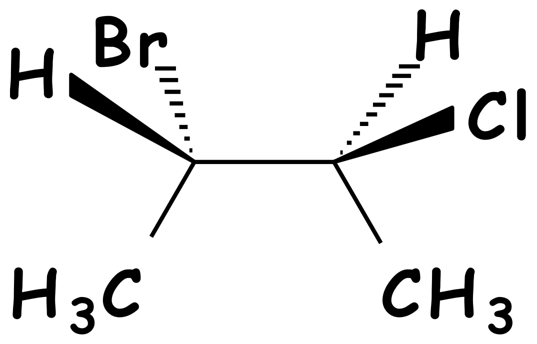
Example: Name the following compounds.





(R) and (S) Nomenclature

- When naming compounds containing multiple chiral atoms, you must give the configuration around each chiral atom:
  - position number and configuration of each chiral atom in numerical order, separated by commas, all in ( ) at the start of the compound name

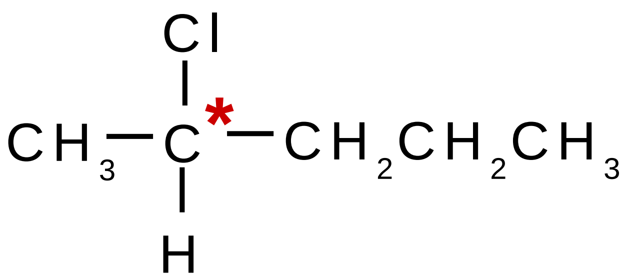


(2S, 3S)-2-bromo-3-chlorobutane

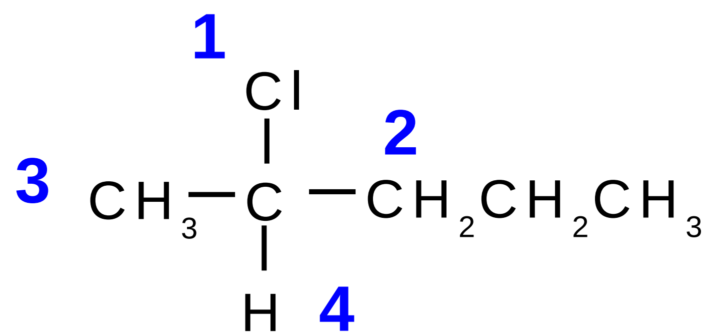
Depicting Structures with Asymmetric Carbons

Example: Draw a 3-dimensional formula for (R)-2-chloropentane.

Step 1: Identify the asymmetric carbon.

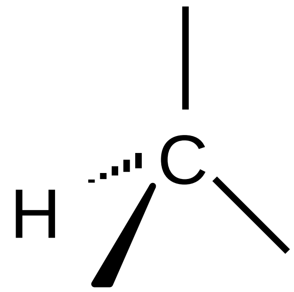


Step 2: Assign priorities to each group attached to the asymmetric carbon.

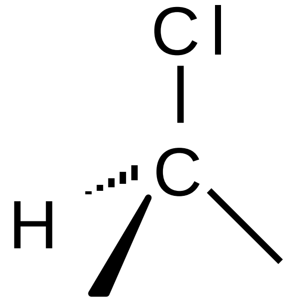


Depicting Structures with Asymmetric Carbons

Step 3: Draw a "skeleton" with the asymmetric carbon in the center and the lowest priority group attached to the "dashed" wedge (i.e. pointing away from you).

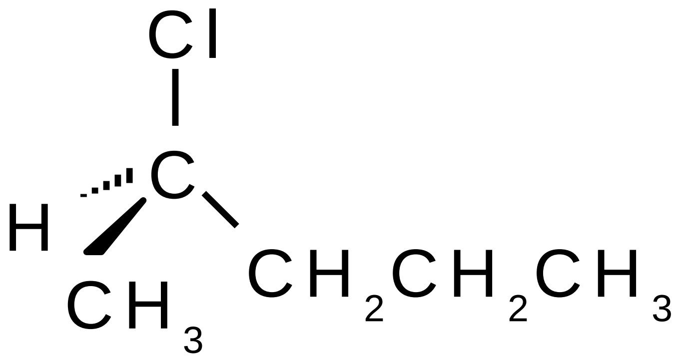


Step 4: Place the highest priority group at the top.



Depicting Structures with Asymmetric Carbons

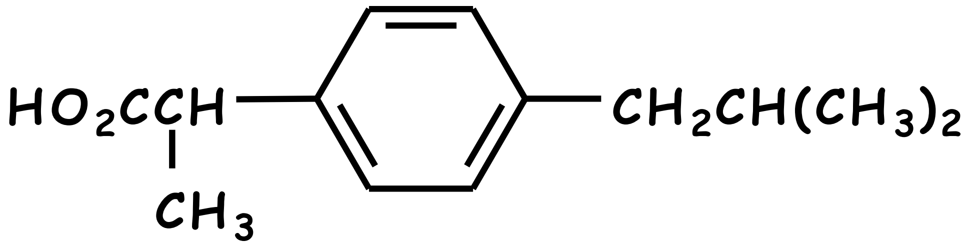
Step 5: For (R) configuration, place the 2nd and 3rd priority groups around the asymmetric carbon in a clockwise direction.



Step 6: Double-check your structure to make sure that it has the right groups and the right configuration.

Depicting Structures with Asymmetric Carbons

Example: The R-enantiomer of ibuprofen is not biologically active but is rapidly converted to the active (S) enantiomer by the body. Draw the structure of the R-enantiomer.



Depicting Structures with Asymmetric Carbons

Example: Captopril, used to treat high blood pressure, has two asymmetric carbons, both with the S configuration. Draw its structure.