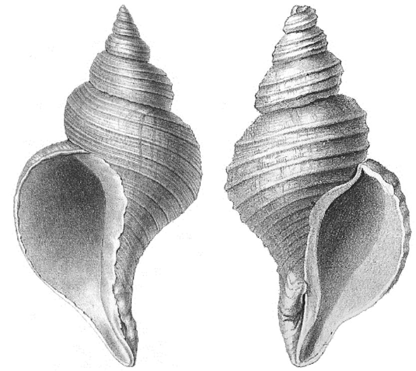
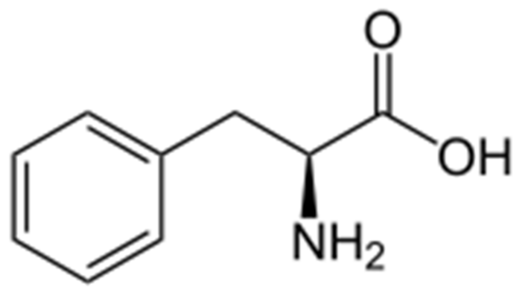
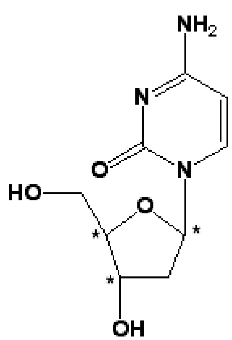
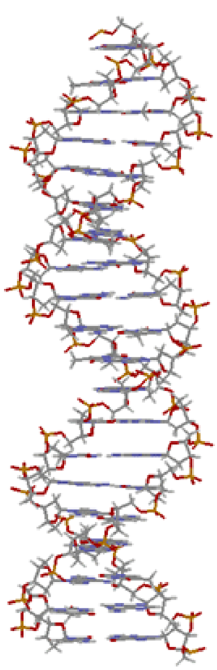
Chapter 6

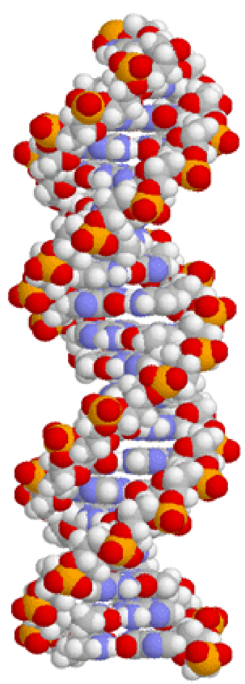


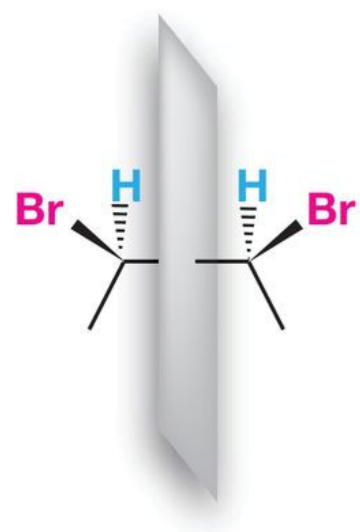
Chirality: The Handedness of Molecules











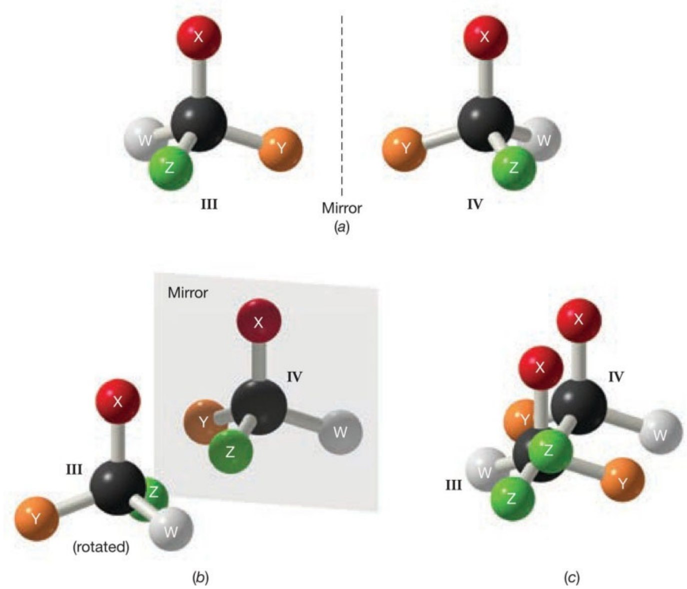


Table of Contents

In this chapter we will consider:

- How to identify, codify, and name the three-dimensional arrangement of atoms and molecules

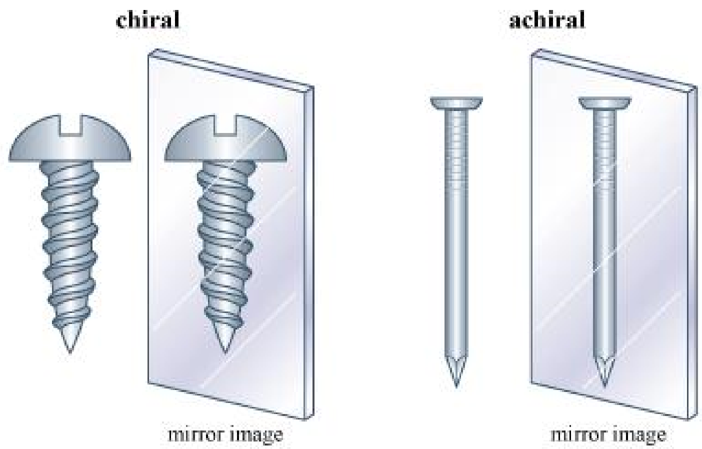
- How such arrangements can lead to unique properties and behaviors

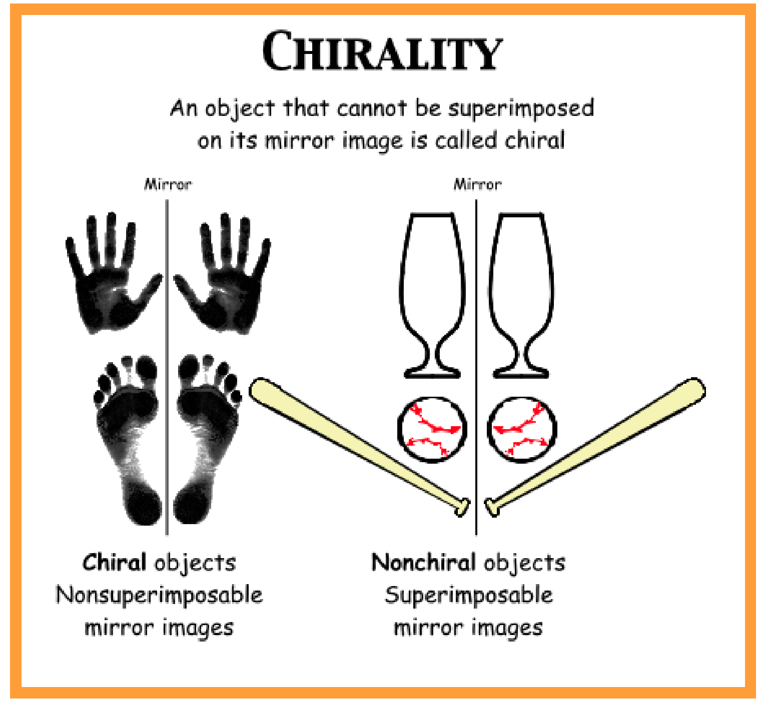
1. Chirality & Stereochemistry

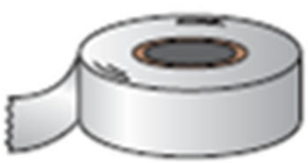
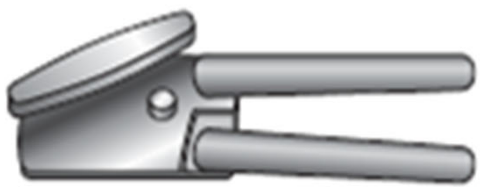
- An object is ***achiral*** (not chiral) if the object and its mirror image are identical

- A ***chiral*** object is one that cannot be superposed on its mirror image

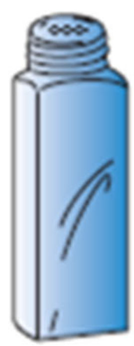
Which are chiral objects?









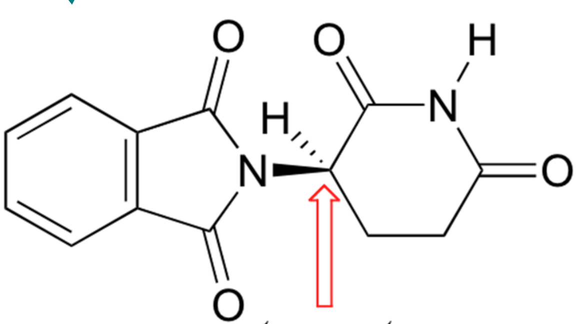

1A. The Biological Significance of Chirality

- Chiral molecules are molecules that cannot be superimposed onto their mirror images

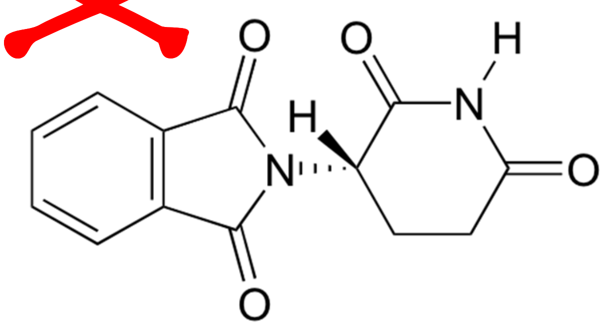
Thalomide

- One enantiomer causes birth defects, the other cures morning sickness

effective isomer

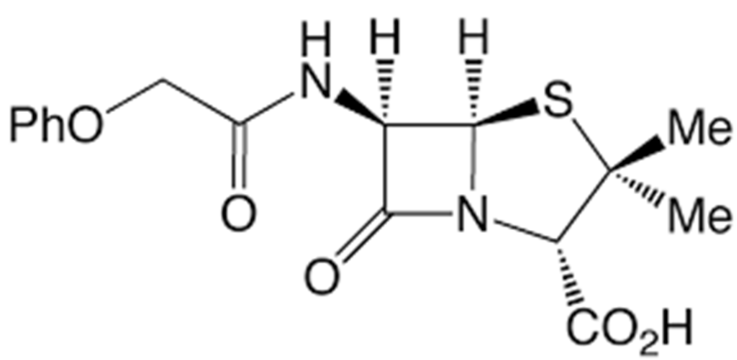


mutagenic isomer

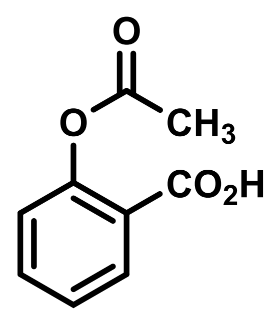


- 66% of all drugs in development are chiral, 51% are being studied as a single enantiomer

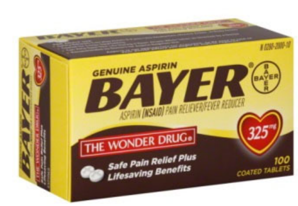
- Of the $475 billion in world-wide sales of formulated pharmaceutical products in 2008, $205 billion was attributable to single enantiomer drugs



Penicillin V (**1**)



Aspirine

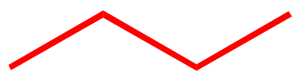
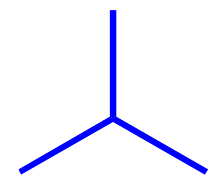
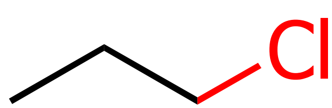
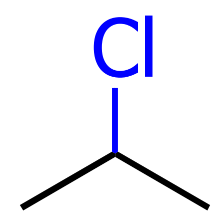


2. Isomerisom: Constitutional Isomers & Stereoisomers

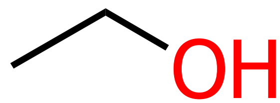
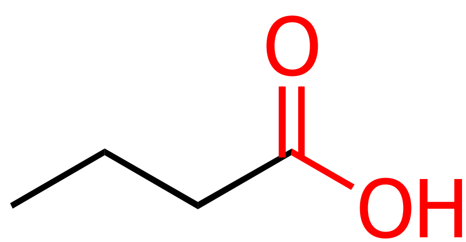
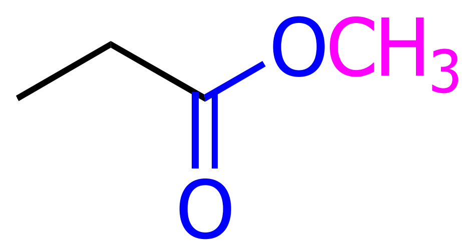
2A. Constitutional Isomers

- **Isomers**: different compounds that have the same molecular formula
  - **Constitutional isomers**: isomers that have the same molecular formula but different connectivity – their atoms are connected in a different order

❖ Examples

Molecular Formula	Constitutional Isomers		
C_4H_{10}	 Butane	and	 2-Methylpropane
C_3H_7Cl	 1-Chloropropane	and	 2-Chloropropane

❖ Examples

<u>Molecular Formula</u>	<u>Constitutional Isomers</u>		
C_2H_6O	 Ethanol	and	CH_3-O-CH_3 Methoxymethane
$C_4H_8O_2$	 Butanoic acid	and	 Methyl propanoate

2B. Stereoisomers

- Stereoisomers are **NOT** constitutional isomers

- **Stereoisomers** have their atoms connected in the same sequence but they *differ in the arrangement of their atoms in space*. The consideration of such spatial aspects of molecular structure is called ***stereochemistry***

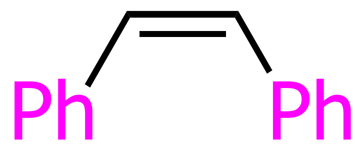
2C. Enantiomers & Diastereomers

- Stereoisomers can be subdivided into two general categories:
  enantiomers & *diasteromers*
  - **Enantiomers** – stereoisomers whose molecules are ***not superposable*** mirror images of each other
  - **Diastereomers** – stereoisomers whose molecules are not mirror images of each other

❖ Geometrical isomers (*cis* & *trans* isomers) are:

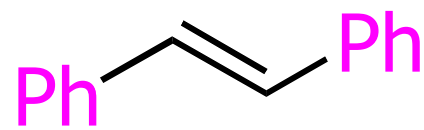
- *Diastereomers*

e.g.

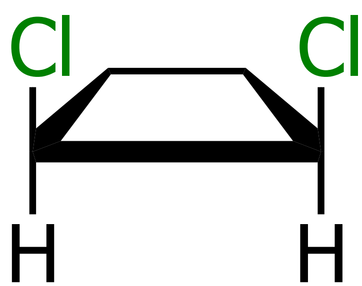


(cis)

and

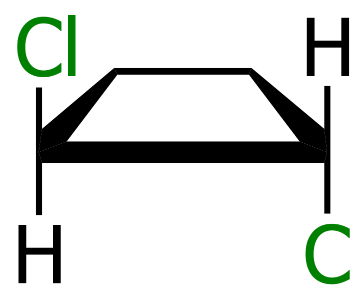


(trans)



(cis)

and



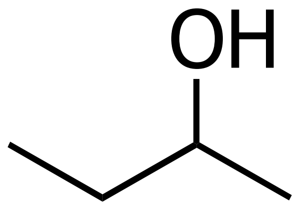
(trans)

Subdivision of Isomers

- **Isomers** (different compounds with same molecular formula)
  - **Constitutional Isomers** (isomers whose atoms have a different connectivity)
  - **Stereoisomers** (isomers that have the same connectivity but differ in spatial arrangement of their atoms)
    - **Enantiomers** (stereoisomers that are nonsuperposable mirror images of each other)
    - **Diastereomers** (stereoisomers that are NOT mirror images of each other)

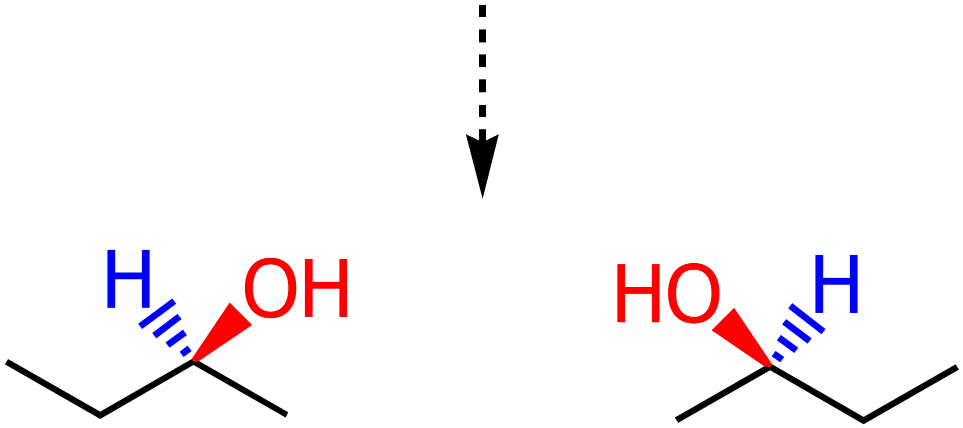
3. Enantiomers and Chiral Molecules

- Enantiomers occur only with compounds whose molecules are **chiral**
- A chiral molecule is one that is **NOT** superposable on its mirror image
- The relationship between a chiral molecule and its mirror image is one that is ***enantiomeric***. A chiral molecule and its mirror image are said to be enantiomers of each other

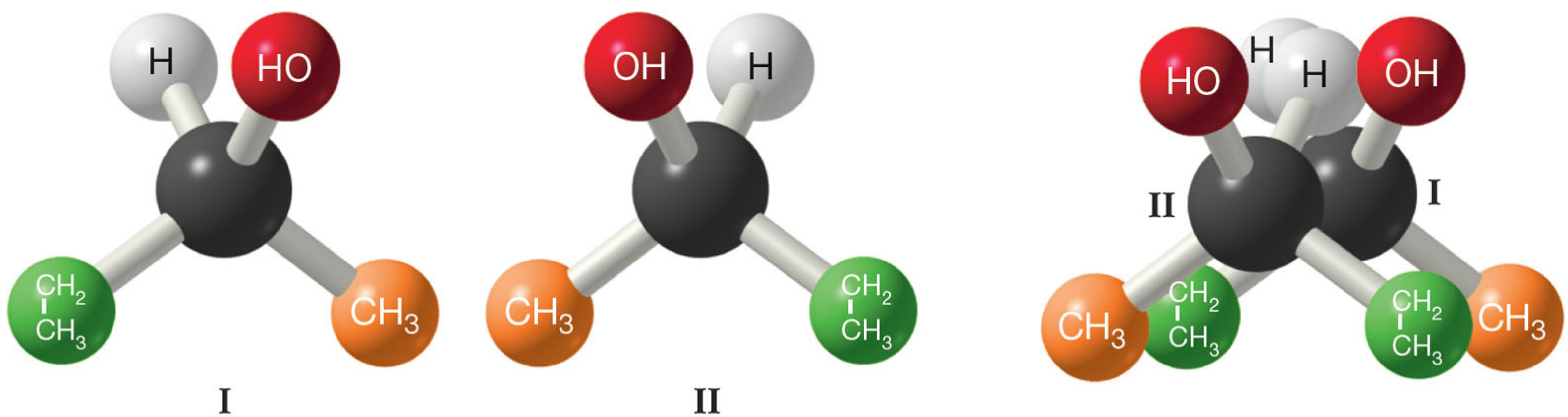


(2-Butanol)

(I) and (II) are not superposable mirror images of each other



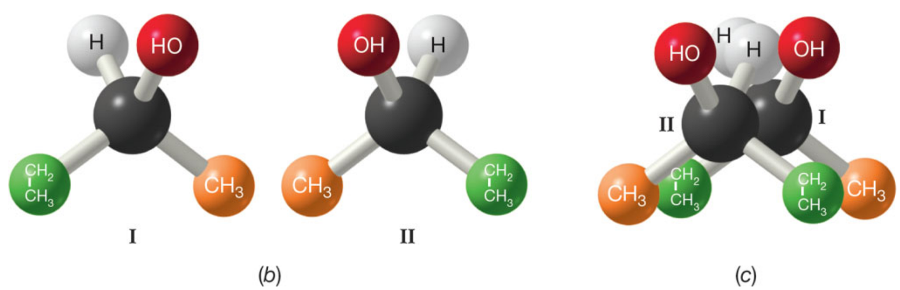
(I) (II)



(b) (c)

4. Molecules Having One Chirality Center Are Chiral

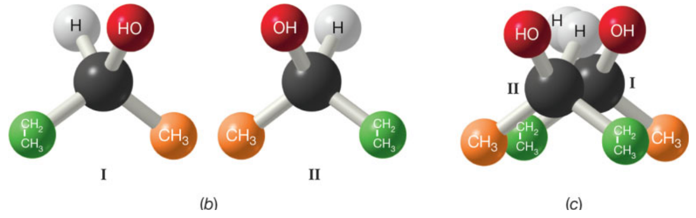
- A **chirality center** is a tetrahedral carbon atom that is bonded to <u>four different groups</u>
- Or **stereo center**…



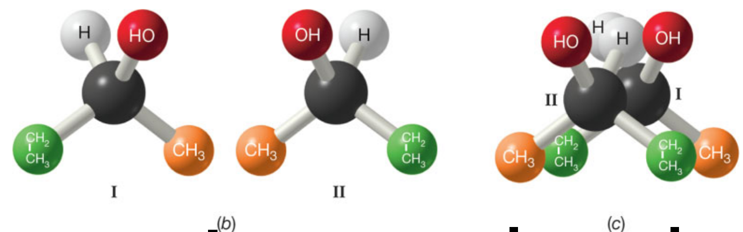
- A molecule that contains **one** chirality center is chiral and can exist as a pair of enantiomers

- The presence of a single chirality center in a molecule guarantees that the molecule is chiral and that enantiomeric forms is a possibility

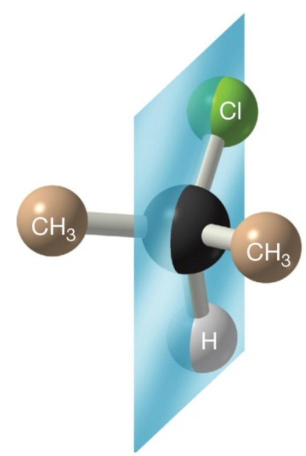
- An important property of enantiomers with a single chirality center is that *interchanging any two groups at the chirality center converts one enantiomer into the other*

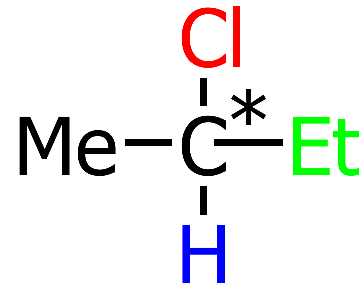


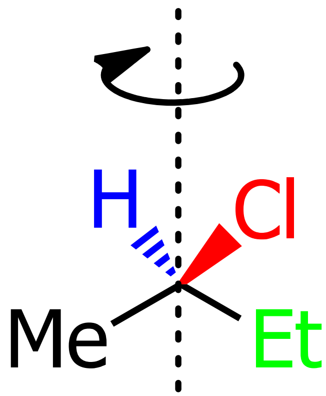
- Any atom at which an interchange of groups produces a stereoisomer is called a **stereo-genic center** (if the atom is a carbon atom it is usually called a **stereogenic carbon**, or *stereocenter* or *chiral carbon*)



- If all of the tetrahedral atoms in a molecule have two or more groups attached that *are the same*, the molecule does not have a chirality center. The molecule is superposable on its mirror image and is **achiral**

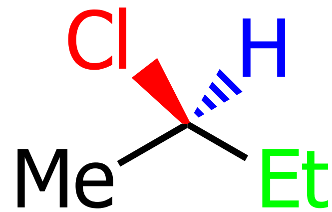




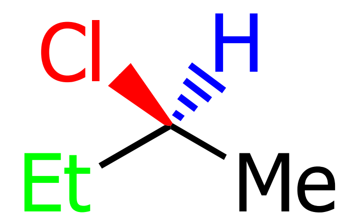


(III)

same as



mirror

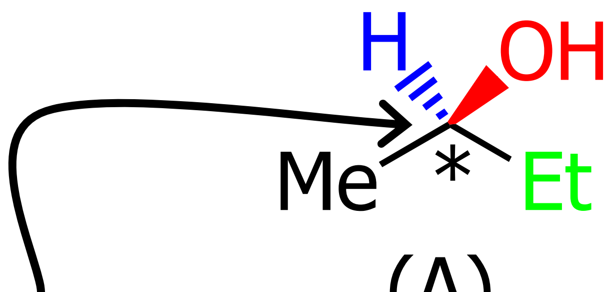


(IV)

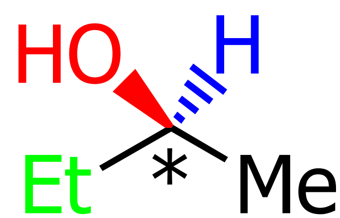
(III) and (IV) are non-superposable mirror images of each other

4A. Tetrahedral Stereogenic Centers

- Chirality centers are ***tetrahedral stereogenic*** centers



(A)



(B)

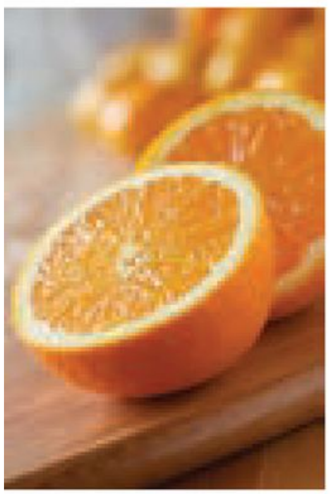
Tetrahedral stereogenic center

⇒ **chiral**

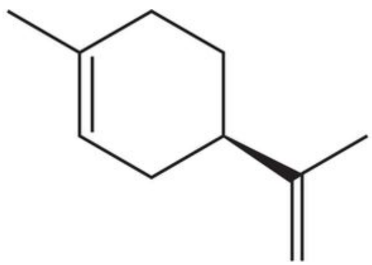
mirror

(A) & (B) are enantiomers

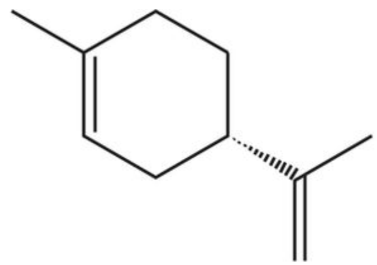
5. More about the Biological Importance of Chirality



Media Bakery



(+)-Limonene
(the enantiomer of limonene found in oranges)

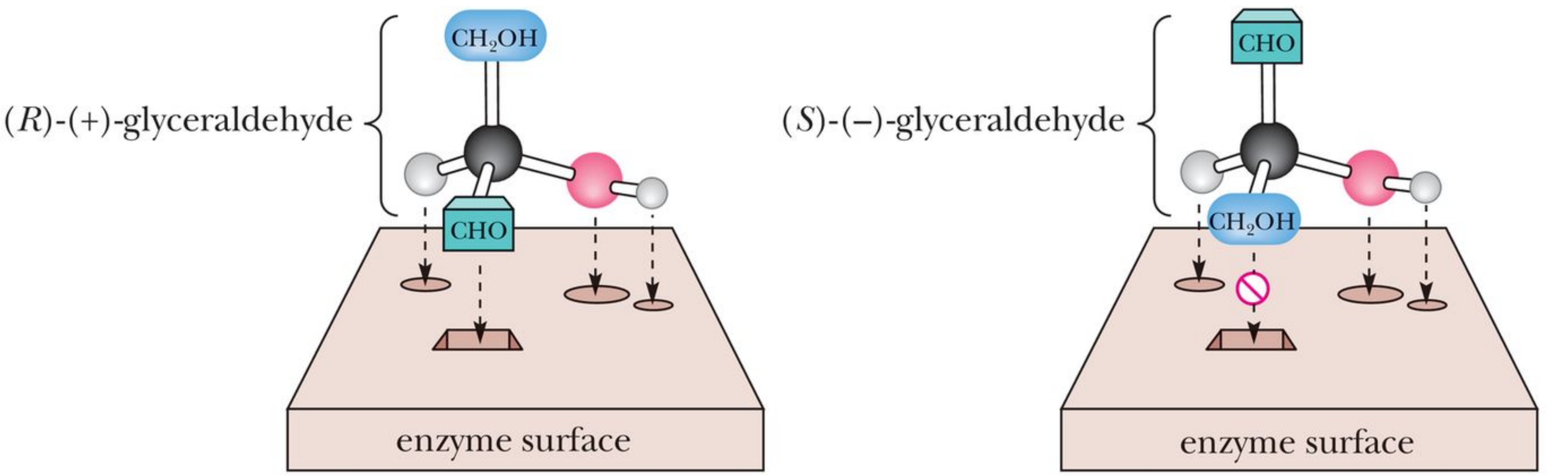


(−)-Limonene
(the enantiomer of limonene found in lemons)

Media Bakery

Chirality in Biomolecules

❖ **Figure 6.7** Schematic diagram of the surface of an enzyme capable of distinguishing between enantiomers.



This enantiomer of glyceraldehyde fits the three specific binding sites on the enzyme surface

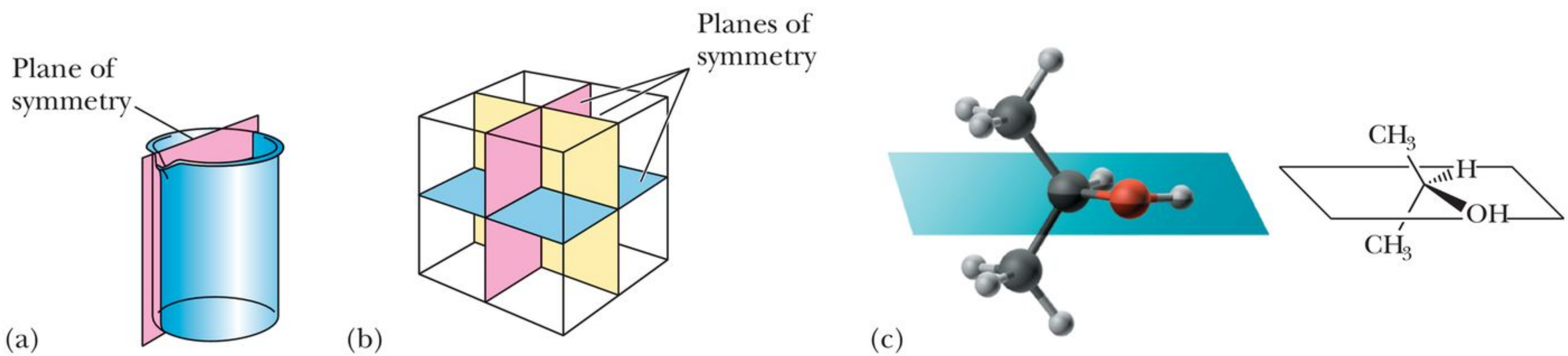
This enantiomer of glyceraldehyde does not fit the same binding sites

6. How to Test for Chirality: Planes of Symmetry

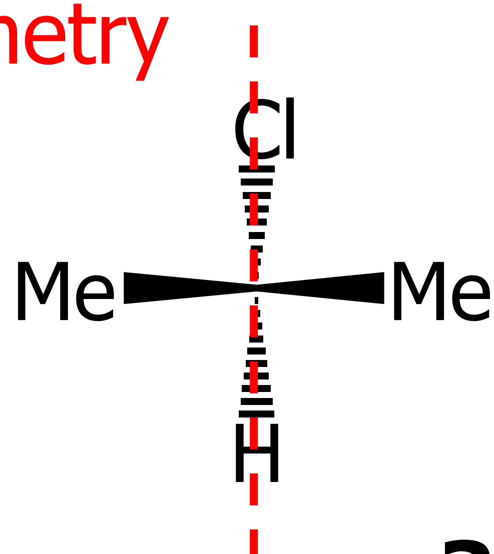
- A molecule will not be chiral if it possesses a plane of symmetry
- A plane of symmetry (mirror plane) is an imaginary plane that bisects a molecule such that *the two halves of the molecule are mirror images* of each other
- All molecules with a plane of symmetry in their most symmetric conformation are ***achiral***

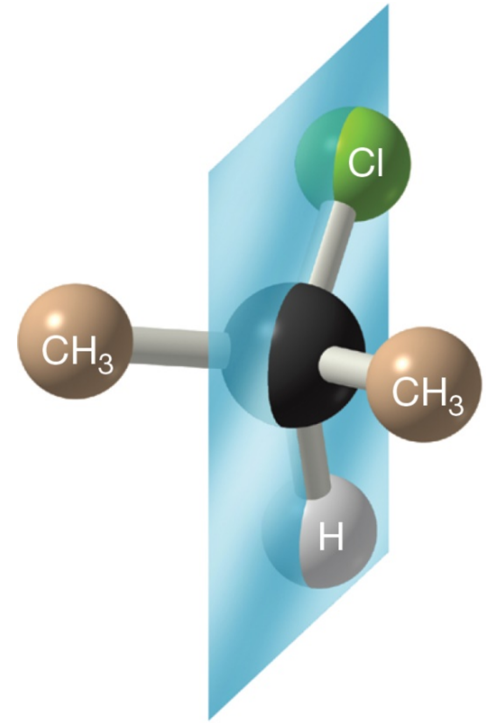
Planes of Symmetry

- **Figure 6.2 Plane of Symmetry**: An imaginary plane passing through an object and dividing it such that one half is the mirror image in of the other half.



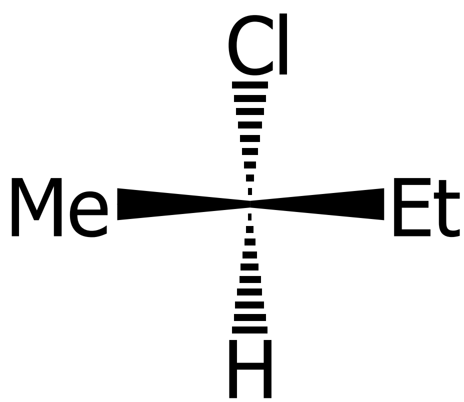
Plane of symmetry

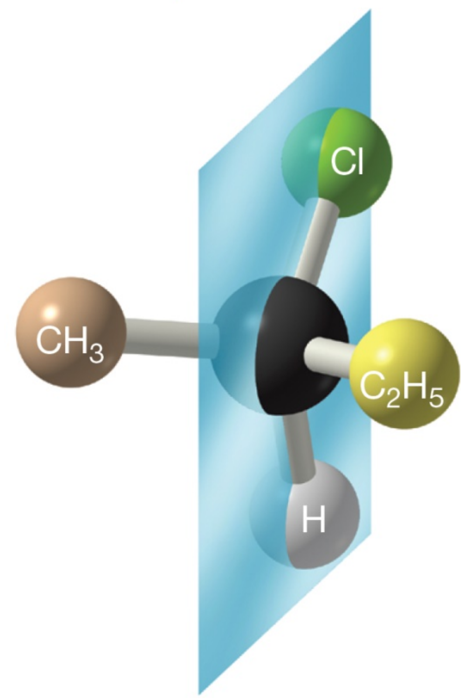




achiral

No plane of symmetry

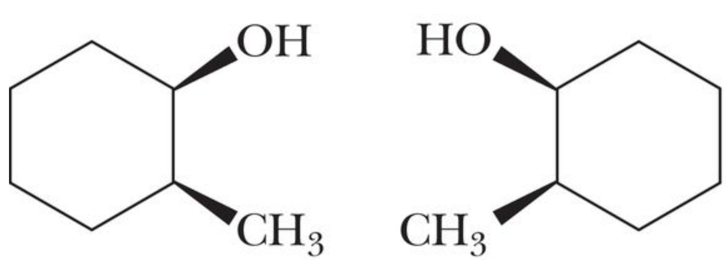




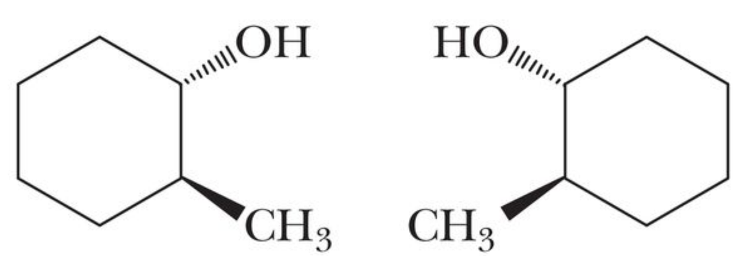
chiral

Chirality in Cyclic Molecules

- 2-Methylcyclopentanol
  - 2 stereocenters; according to the 2^n rule, a maximum of **$2^2 = 4$** stereoisomers are possible.
  - How many actually exist? Answer four; two pairs of enantiomers.



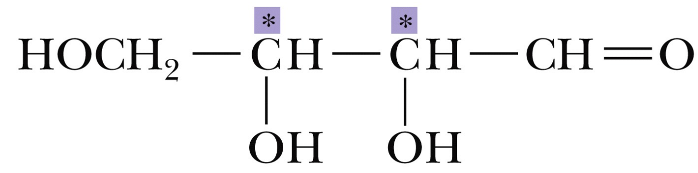
cis-2-Methylcyclohexanol
(a pair of enantiomers)



trans-2-Methylcyclohexanol
(a pair of enantiomers)

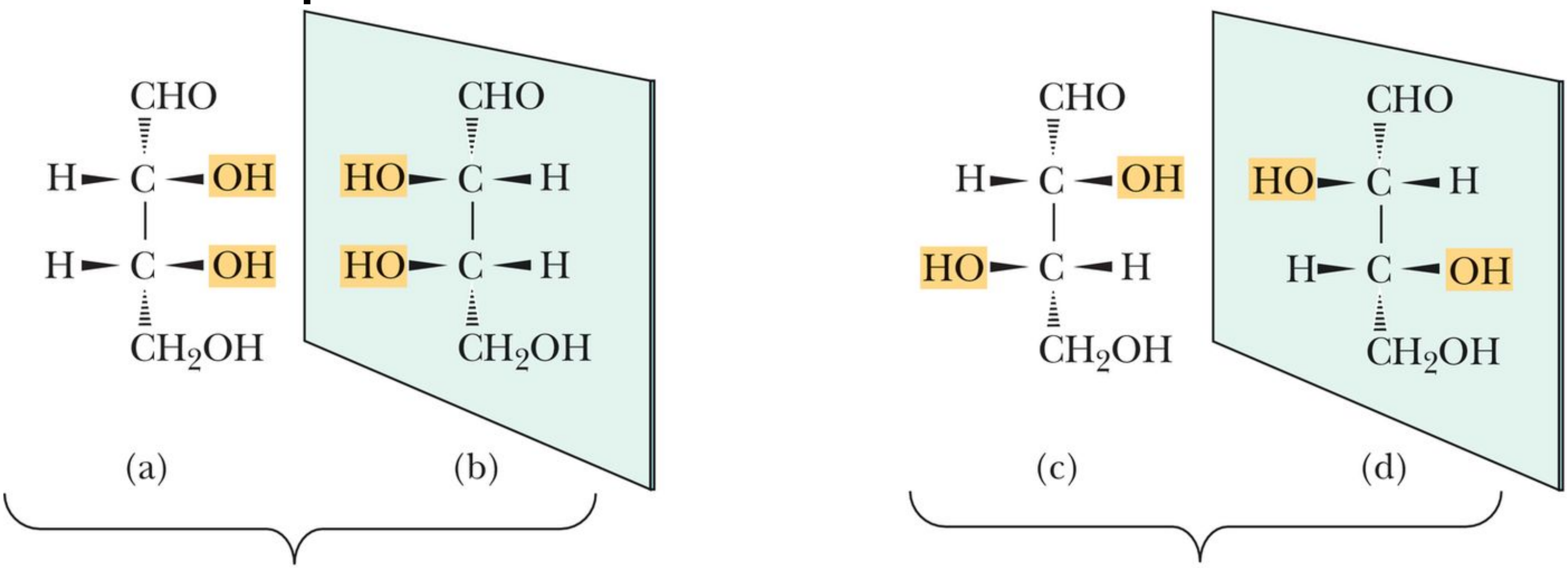
Enantiomers & Diastereomers

- 2,3,4-Trihydroxybutanal



2,3,4-Trihydroxybutanal

- **Figure 6.4** Two stereocenters; **$2^2 = 4$** stereoisomers (two pairs of enantiomers) are possible.

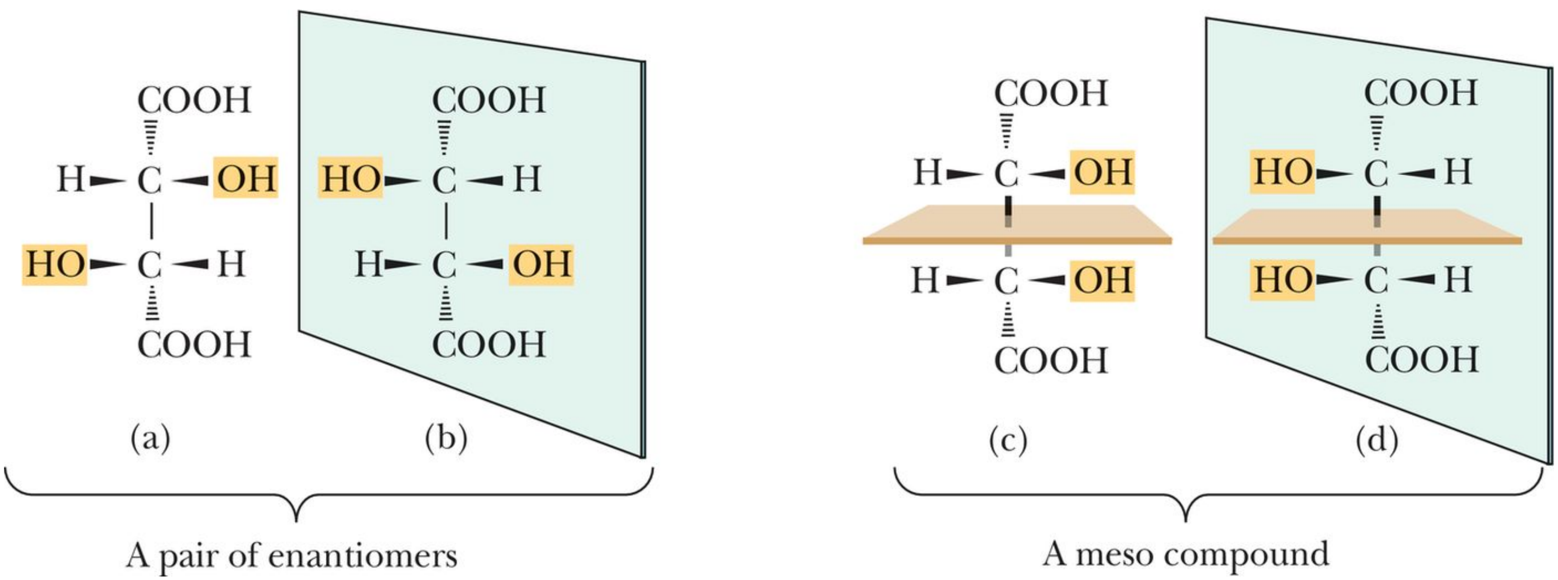


One pair of enantiomers
(Erythrose)

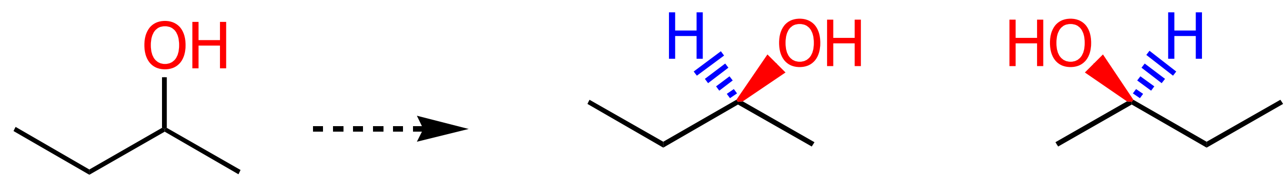
A second pair of enantiomers
(Threose)

Meso Compounds

- **Meso compound**: an achiral compound possessing two or more stereocenters.
  - Tartaric acid contains two stereocenters.
  - **Figure 6.5** Two stereocenters; $2^n = 4$, but only three stereoisomers exist, one meso compound and one pair of enantiomers.



7. Naming Enantiomers: The *R,S*-System

Recall: 

(I) (II)

- ❖ Using only the IUPAC naming that we have learned so far, these two enantiomers will have the same name:
  - **2-Butanol**
- ❖ This is undesirable because each compound must have its own distinct name

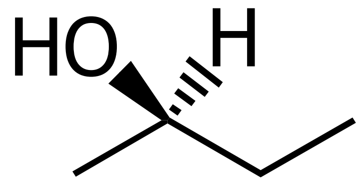
7A. How to Assign (R) and (S) Configurations

- Rule 1
  - Assign priorities to the four different groups on the stereocenter from highest to lowest (priority bases on atomic number, the higher the atomic number, the higher the priority)

- Rule 2
  - When a priority cannot be assigned on the basis of the atomic number of the atoms that are directly attached to the chirality center, then the next set of atoms in the unassigned groups is examined. This process is continued until a decision can be made.

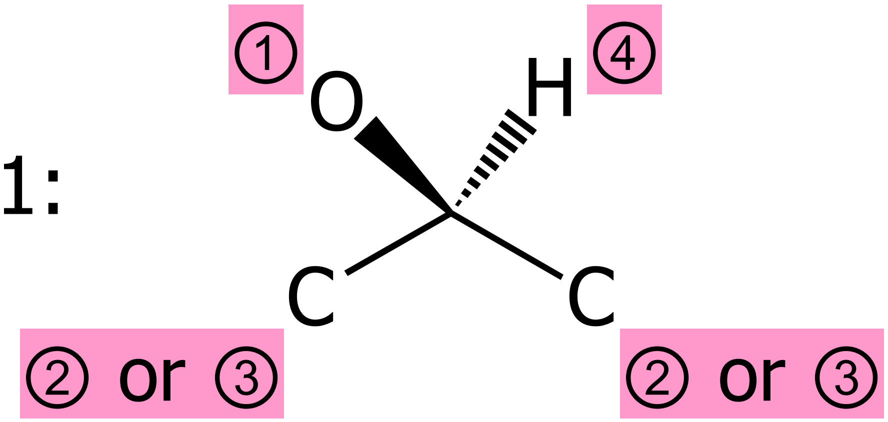
- Rule 3
  - Visualize the molecule so that the lowest priority group is directed away from you, then trace a path from highest to lowest priority. If the path is a clockwise motion, then the configuration at the asymmetric carbon is (*R*) "*Rectus*." If the path is a counter-clockwise motion, then the configuration is (*S*) "*Sinister*."

❖ Example

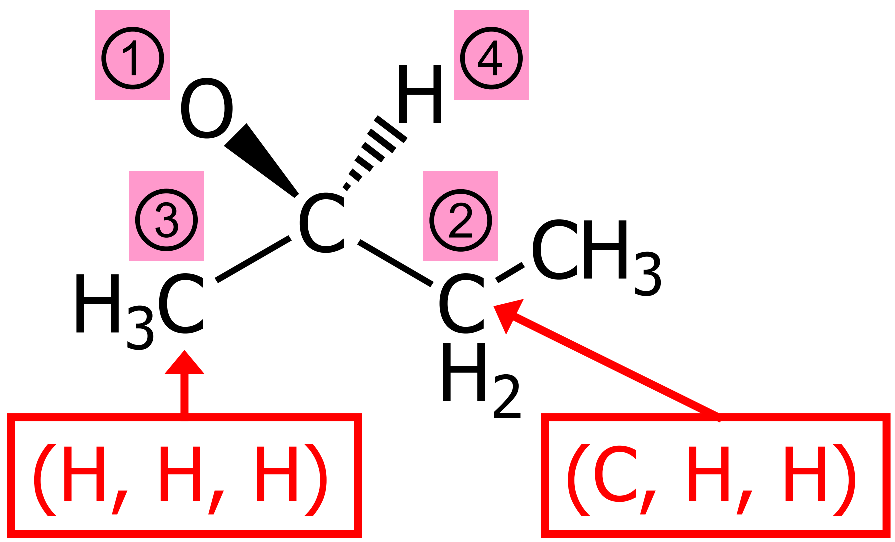


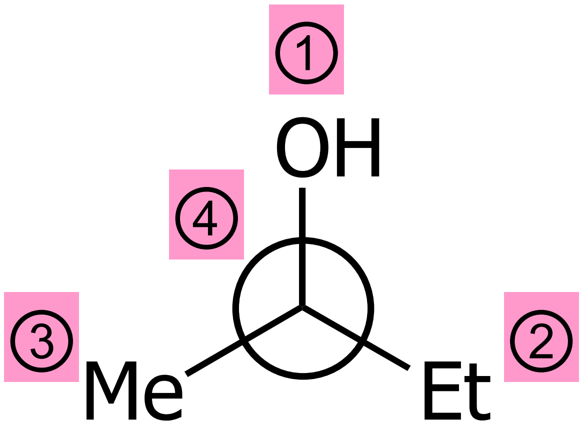
(2-Butanol)

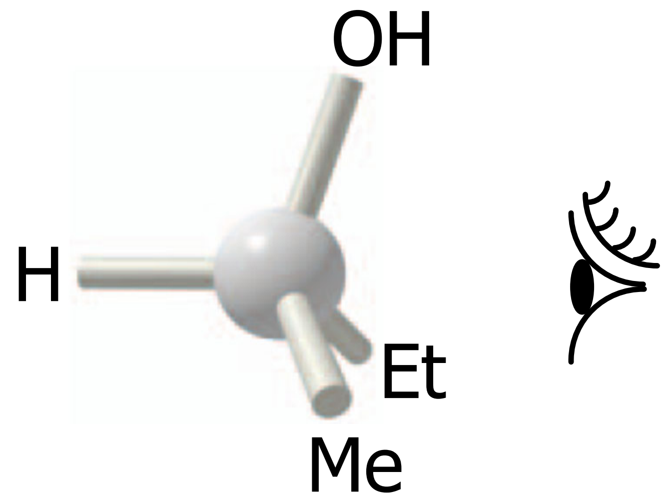
Step 1:

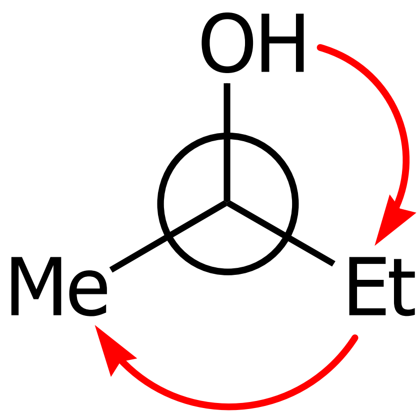


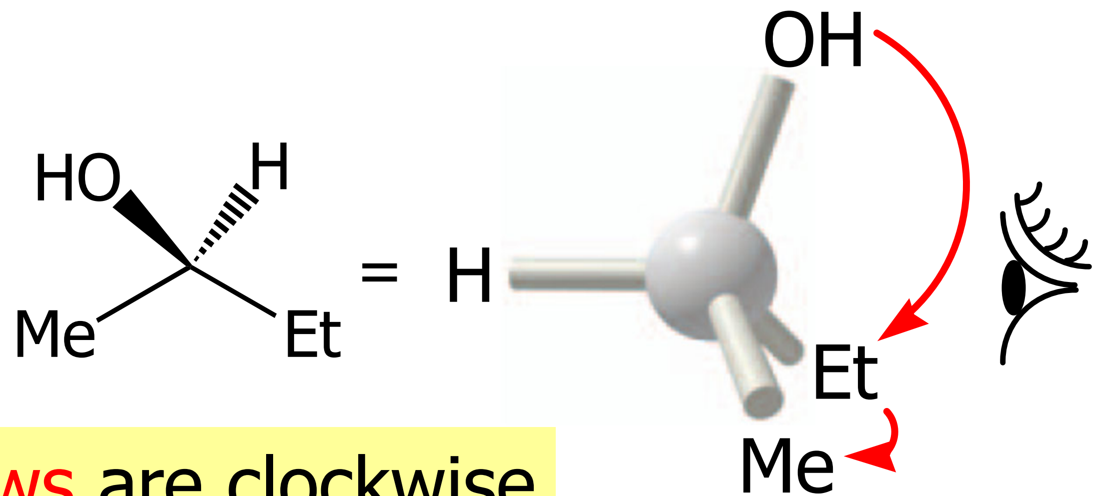
Step 2:







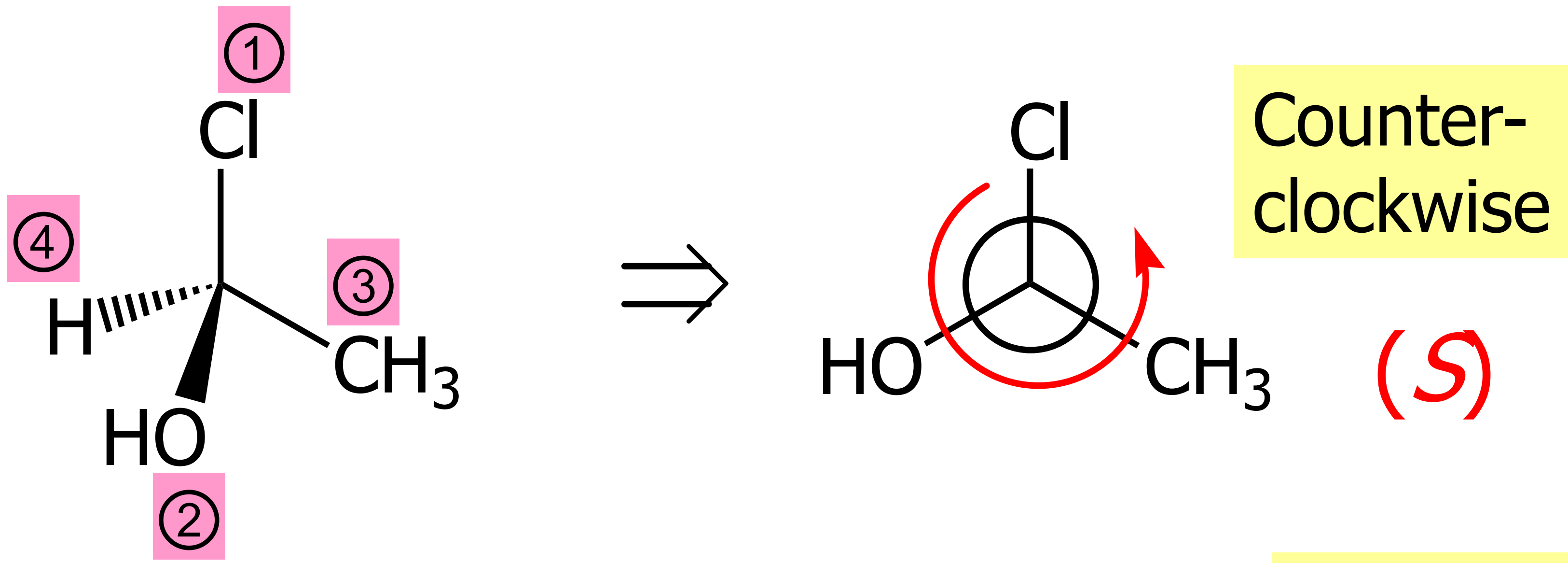


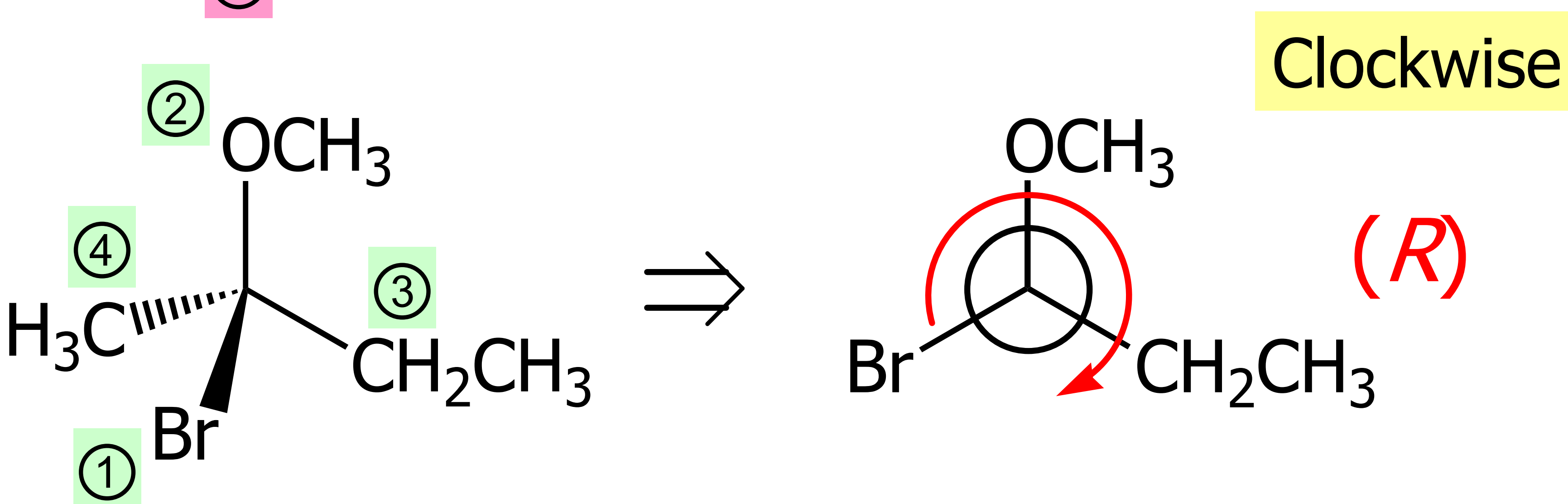


Arrows are clockwise

(*R*)-2-Butanol

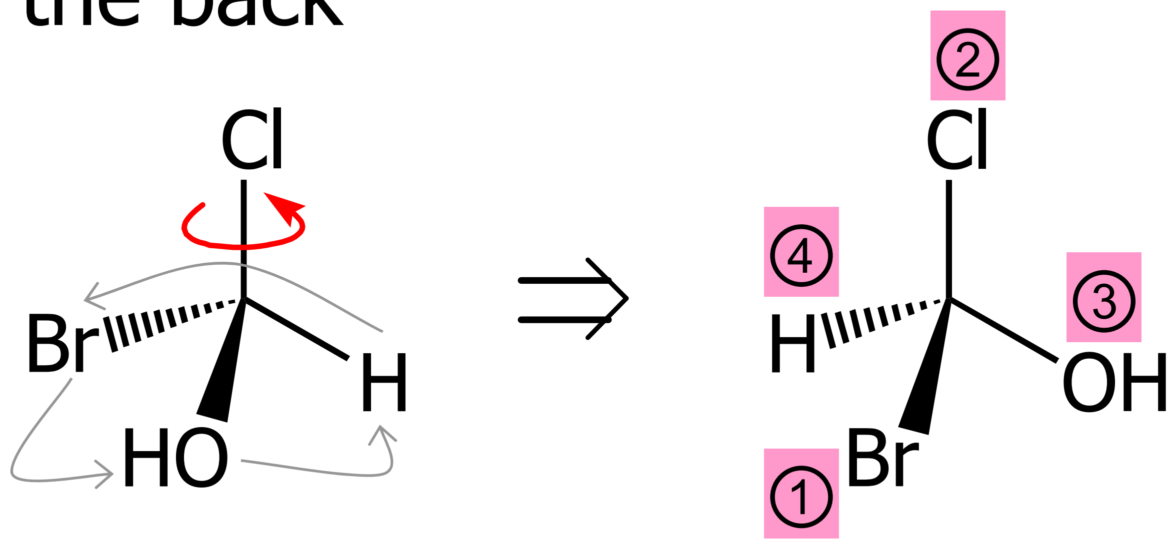
❖ Other examples



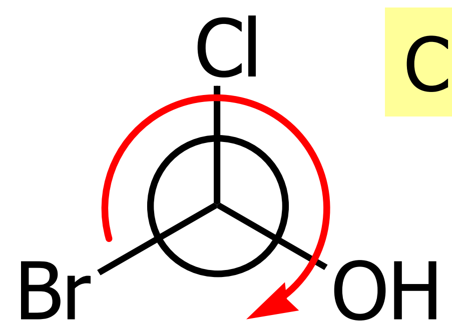


❖ Other examples

- Rotate C–Cl bond such that H is pointed to the back



⇒

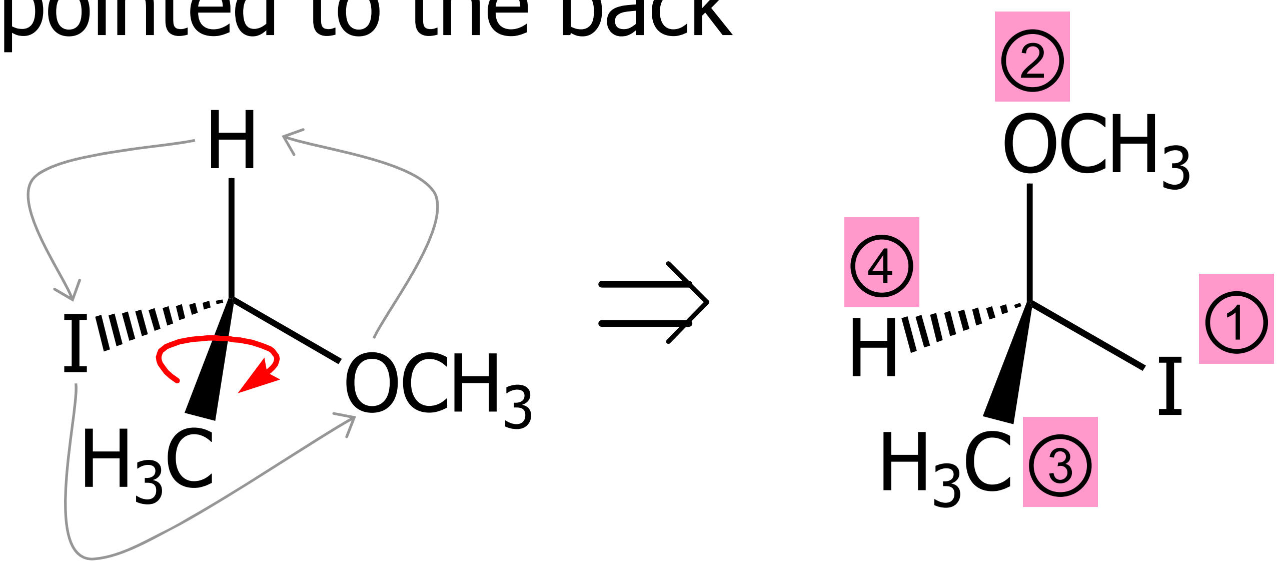


Clockwise

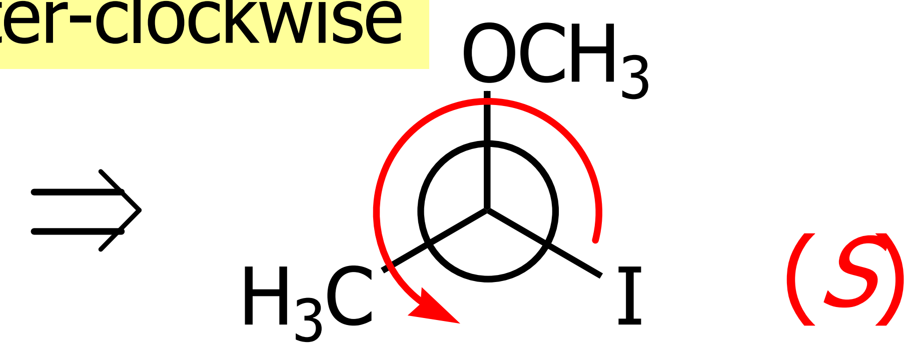
(*R*)

❖ Other examples

- Rotate C–CH_3 bond such that H is pointed to the back



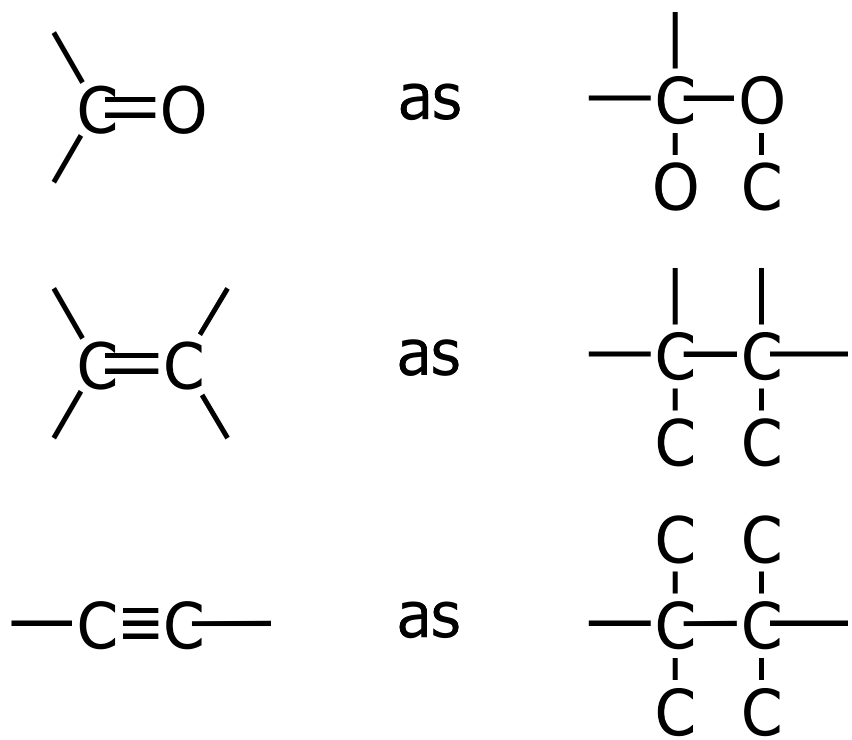
Counter-clockwise



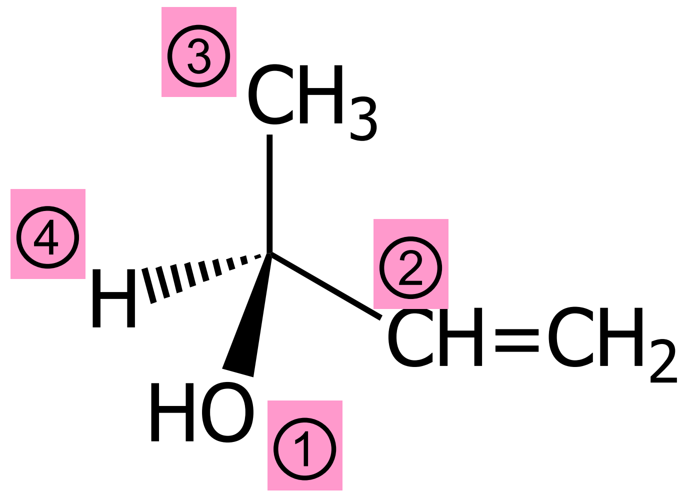
❖ Rule 4

- For groups containing double or triple bonds, assign priorities as if both atoms were duplicated or triplicated

e.g.



❖ Example



(S)

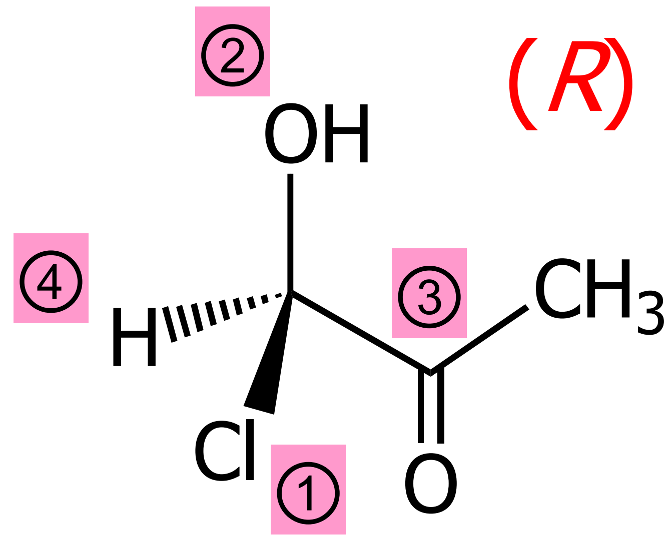
Compare $—CH_3$ & $—CH{=}CH_2$:

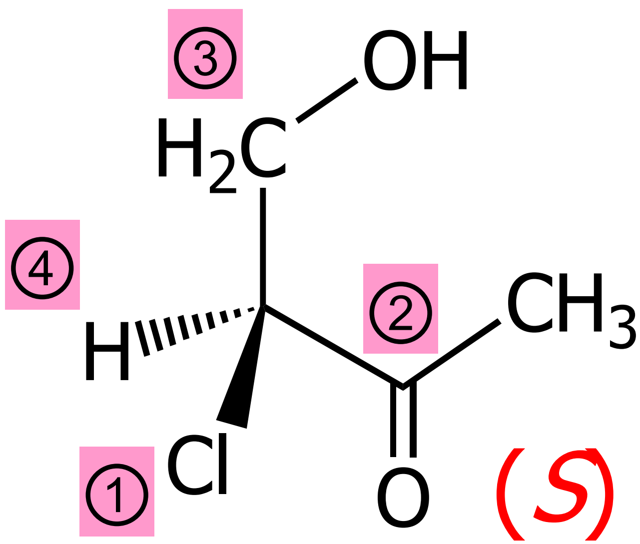
$—CH{=}CH_2$ equivalent to
$$\begin{array}{ccccc} & H & & H & \\ & | & & | & \\ — & C & — & C & — H \\ & | & & | & \\ & C & & C & \end{array}$$

Thus, $—CH_3 \Rightarrow$ (H, H, H)

$—CH{=}CH_2 \Rightarrow$ (C, C, H)

❖ Other examples



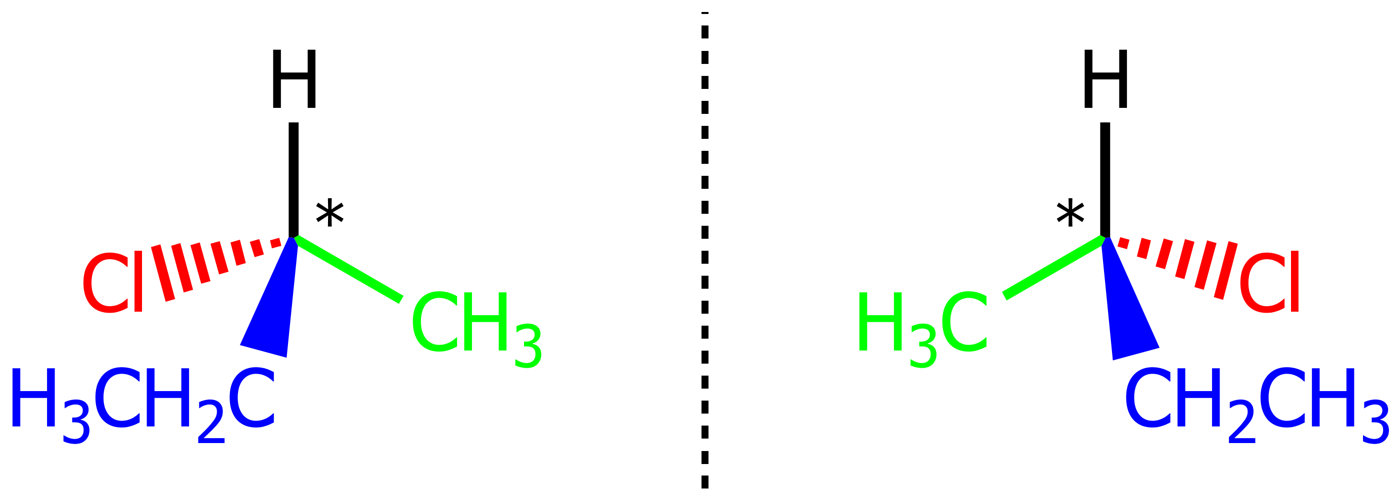


② C ⇒ (O, O, C)

③ C ⇒ (O, H, H)

8. Properties of Enantiomers: Optical Activity

- Enantiomers
  - Mirror images that are not superposable



mirror

- Enantiomers have identical physical properties (e.g. melting point, boiling point, refractive index, solubility etc.)

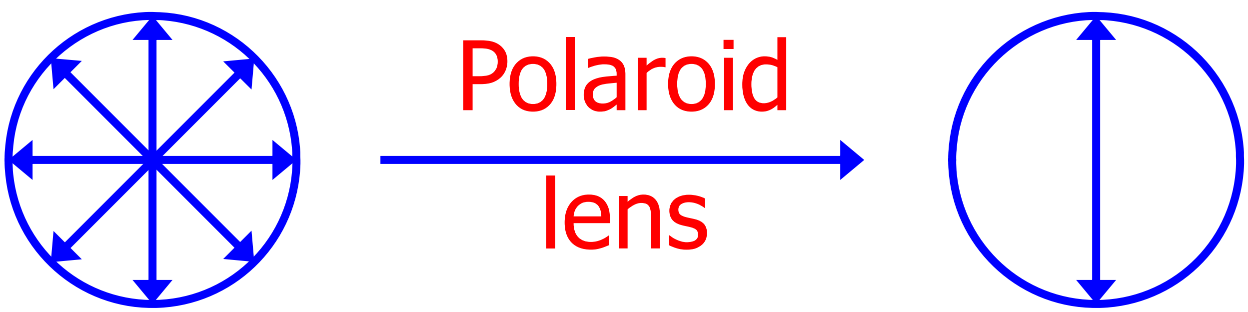
Compound	bp (^oC)	mp (^oC)
(–)-(*R*)-2-Butanol	99.5	
(+)-(*S*)-2-Butanol	99.5	
(+)-(*R,R*)-Tartaric Acid		168 – 170
(–)-(*S,S*)-Tartaric Acid		168 – 170
(+/–)-Tartaric Acid		210 – 212

- Enantiomers
  - Have the same chemical properties (except reaction/interactions with chiral substances)
  - Show different behavior only when they interact with other chiral substances
  - Rotate plane-polarized light in opposite direction

- Optical activity
  - The property possessed by chiral substances of rotating the plane of polarization of plane-polarized light

8A. Plane-Polarized Light

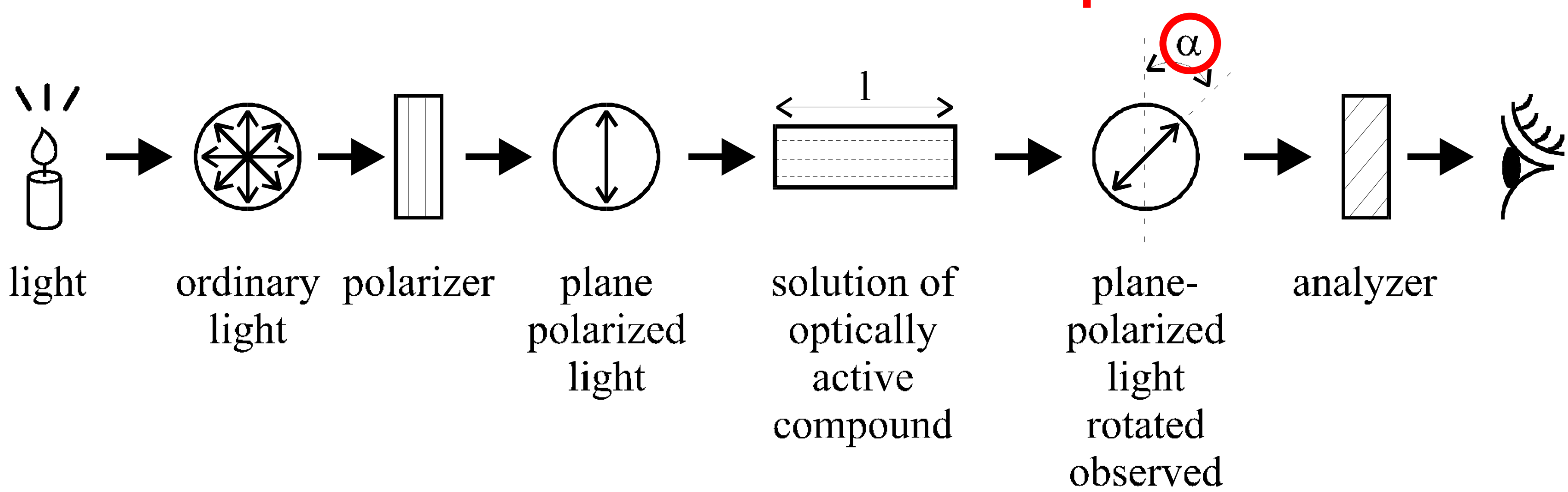
- The electric field (like the magnetic field) of light is oscillating in all possible planes
- When this light passes through a polarizer (Polaroid lens), we get plane-polarized light (oscillating in only one plane)



8B. The Polarimeter

- A device for measuring the optical activity of a chiral compound

α = observed optical rotation



8C. Specific Rotation

observed rotation

temperature

$$[\alpha]^{25}_{D} = \frac{\alpha}{c \times \ell}$$

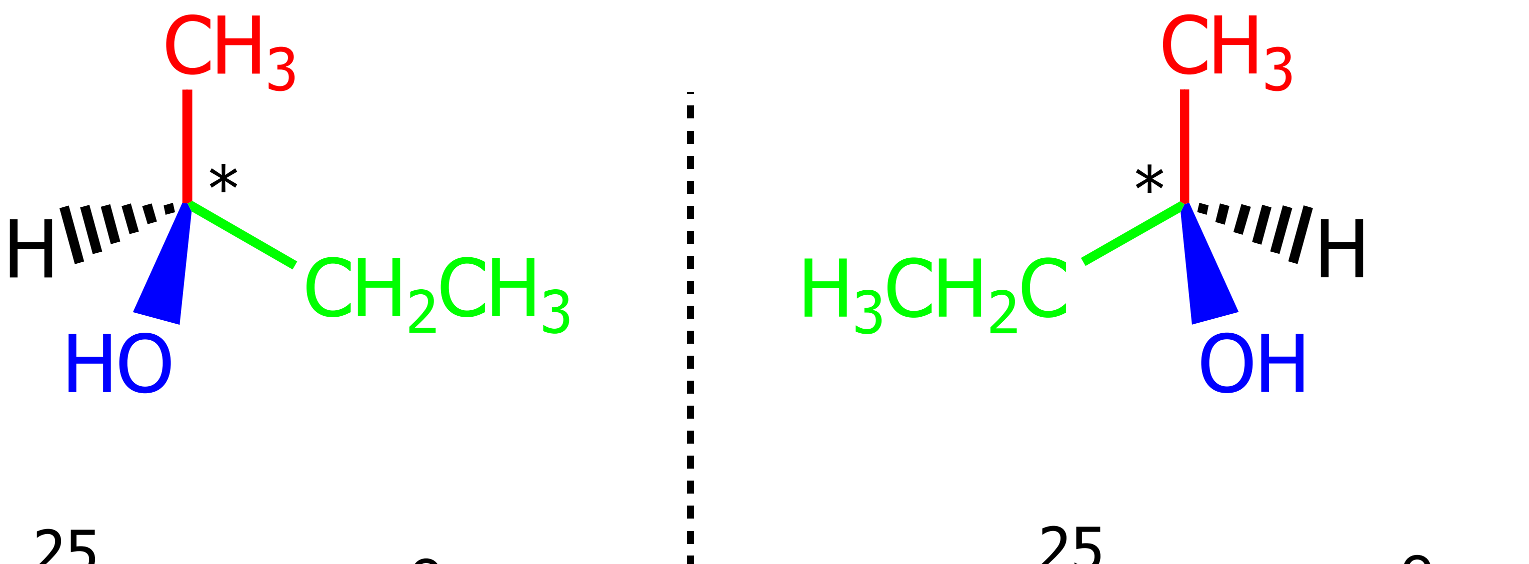
wavelength of light (e.g. D-line of Na lamp, λ=589.6 nm)

concentration of sample solution in g/mL

length of cell in dm
(1 dm = 10 cm)

- The value of α depends on the particular experiment (since there are different concentrations with each run)
  - But specific rotation $[\alpha]$ should be the same regardless of the concentration

- Two enantiomers should have the same value of specific rotation, but the signs are opposite



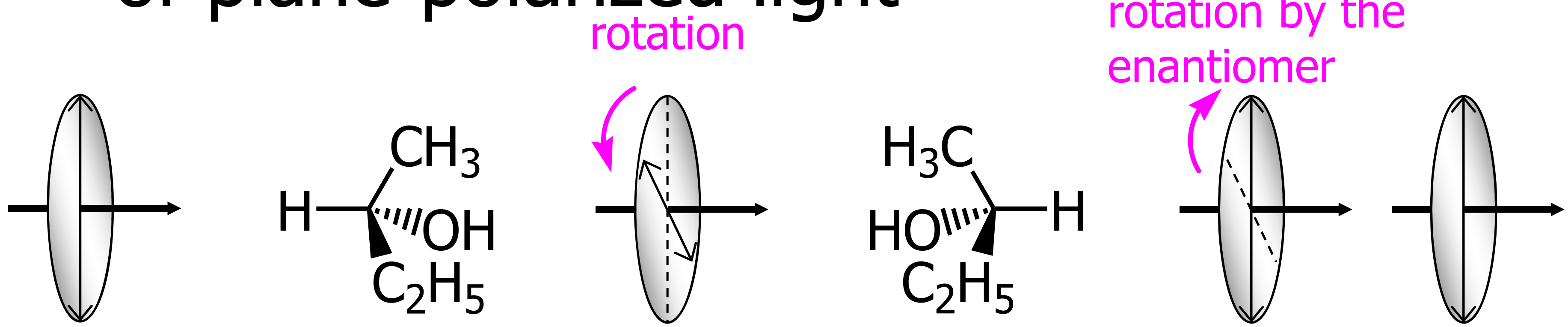
$[\alpha]_D^{25} = + 13.5^o$

mirror

$[\alpha]_D^{25} = - 13.5^o$

9. The Origin of Optical Activity
9A Racemic Forms

- An equimolar mixture of two enantiomers is called a racemic mixture (or *racemate* or *racemic form*)
- A racemic mixture causes no net rotation of plane-polarized light



(R)-2-Butanol

(S)-2-Butanol (if present)

9B. Racemic Forms and Enantiomeric Excess

- A sample of an optically active substance that consists of a single enantiomer is said to be **enantiomerically pure** or to have an **enantiomeric excess** of 100%

- An enantiomerically pure sample of (*S*)-(+)-2-butanol shows a specific rotation of +13.52

$$[\alpha]_D^{25} = +13.52$$

- A sample of (S)-(+)-2-butanol that contains less than an equimolar amount of (*R*)-(–)-2-butanol will show a specific rotation that is less than 13.52 but greater than zero
- Such a sample is said to have an *enantiomeric excess* less than 100%

❖ Enantiomeric excess (ee)

- Also known as the optical purity

$$\%\ \text{enantiomeric excess} = \frac{\begin{pmatrix}\text{moles of one}\\ \text{enantiomer}\end{pmatrix} - \begin{pmatrix}\text{moles of other}\\ \text{enantiomer}\end{pmatrix}}{\text{total moles of both enantiomers}} \times 100$$

- Can be calculated from optical rotations

$$\%\ \text{enantiomeric excess}^{*} = \frac{\text{observed specific rotation}}{\text{specific rotation of the pure enantiomers}} \times 100$$

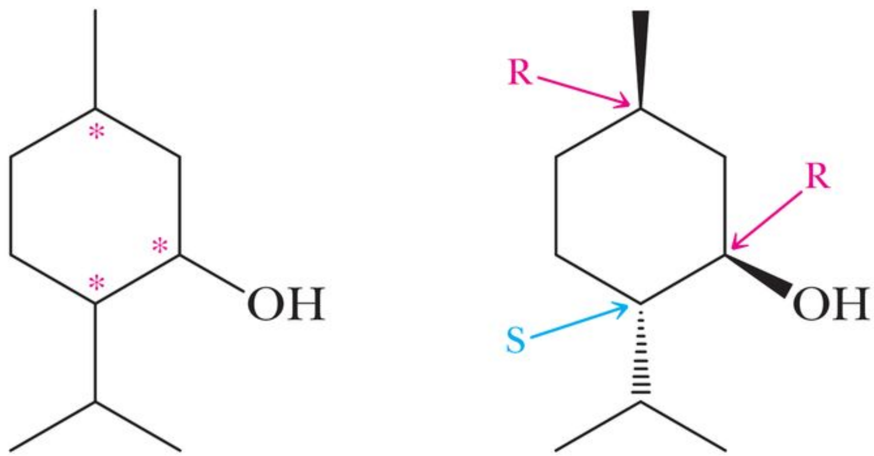
- Example
  - A mixture of the 2-butanol enantiomers showed a specific rotation of +6.76. The enantiomeric excess of the (S)-(+)-2-butanol is 50%

$$\text{\% enantiomeric excess *} = \frac{+6.76}{+13.52} \times 100 = 50\%$$

Three Or More Stereocenters

❖ **Problem**:

- How many stereocenters are present in the molecule on the left?
- How many stereoisomers are possible?
- One of the possible stereoisomers is menthol.
- Assign an R or S configuration to each stereocenter in menthol.



2-Isopropyl-5-methyl-cyclohexanol

Menthol