Organic Chemistry II

Stereochemistry

Part 1

Lecture 5

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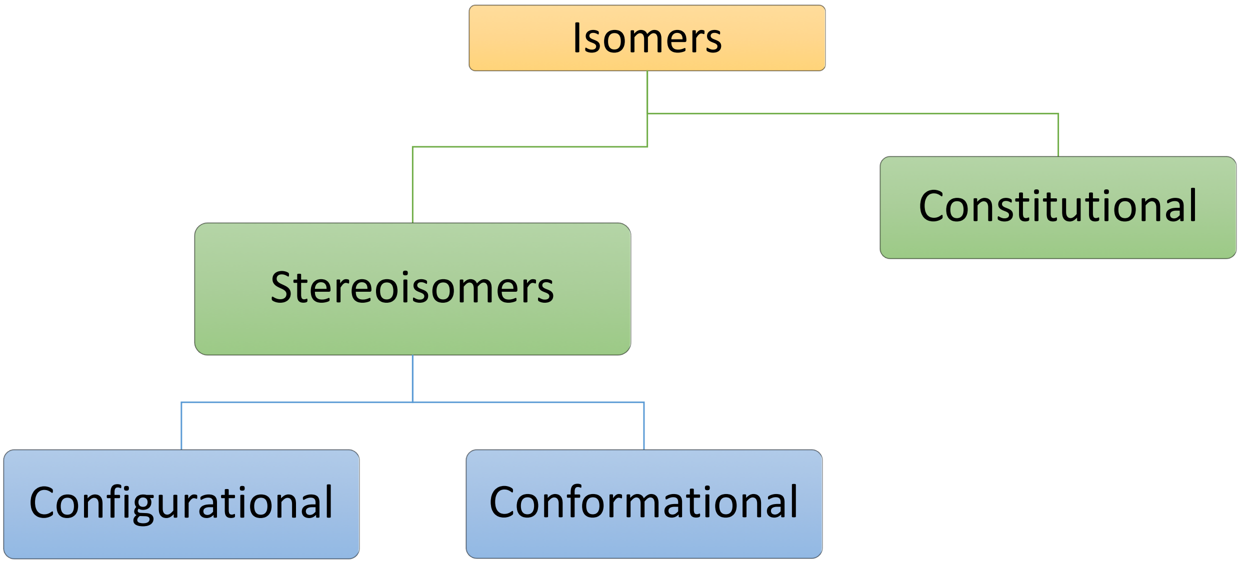
Stereochemistry

- A Types of isomers
- B Configurational isomers

A Types of isomers



Isomers

Stereoisomers

Constitutional

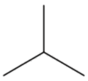
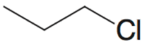
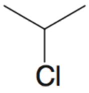
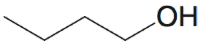
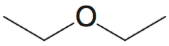
Configurational

Conformational

Isomers are different compounds that have the same molecular formula.

Constitutional isomers have the same molecular formula but different connectivity, meaning that 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**
$C_4H_{10}O$	 **1-Butanol**	and	 **Diethyl ether**

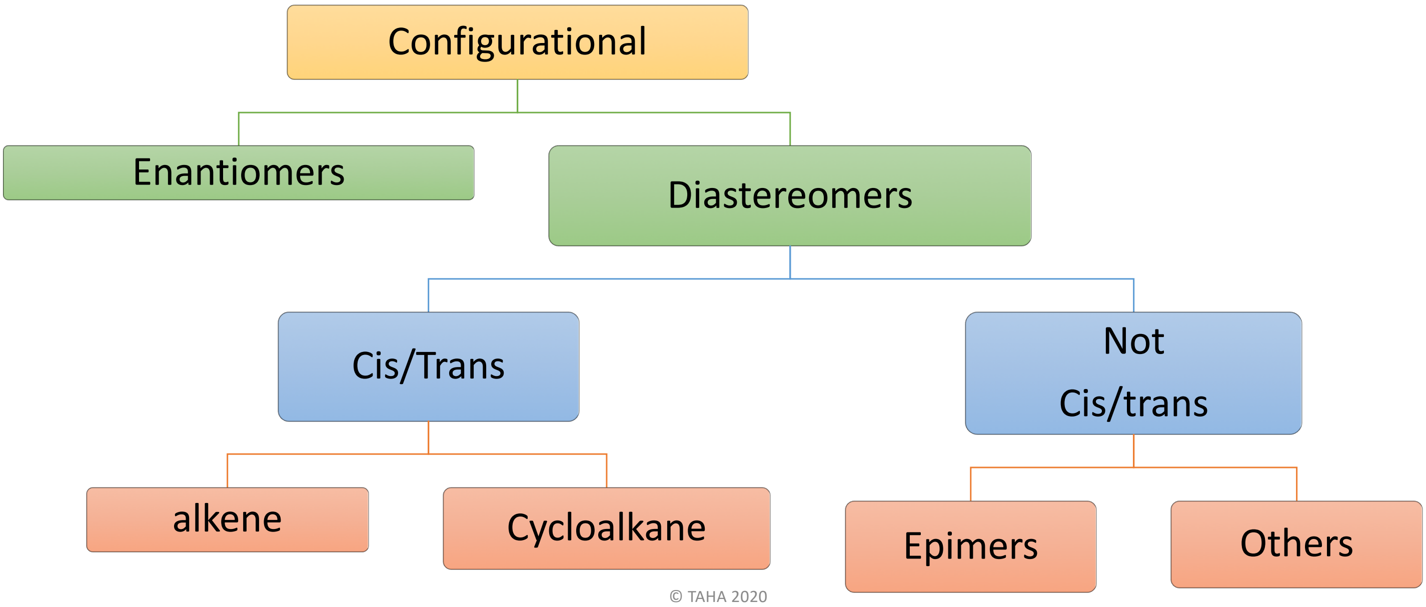
- Stereoisomers are not constitutional isomers.
- Stereoisomers have their atoms connected in the same sequence (the same constitution), but they differ in the arrangement of their atoms in space.
- The consideration of such spatial aspects of molecular structure is called stereochemistry.
- Stereoisomers can be subdivided into two general categories:

a) those that are enantiomers of each other, and
b) those that are diastereomers of each other.

B Configurational isomers

1. Types & classes
2. Nomenclature
3. Optical activity
4. Separation
5. Application

B Configurational isomers Types



- Configurational
  - Enantiomers
  - Diastereomers
    - Cis/Trans
      - alkene
      - Cycloalkane
    - Not Cis/trans
      - Epimers
      - Others

Enantiomers

Enantiomers are stereoisomers whose molecules are nonsuperposable mirror images of each other.

Enantiomers occur only with compounds whose molecules are chiral.

A chiral molecule is one that is not superposable on its mirror image.

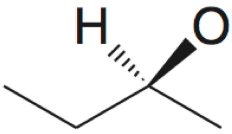
A chiral molecule and its mirror image are called a pair of enantiomers. The relationship between them is enantiomeric.

Stereochemistry

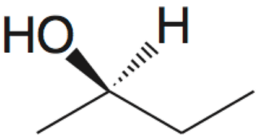
A chiral object is one that cannot be superposed on its mirror image

Stereochemistry

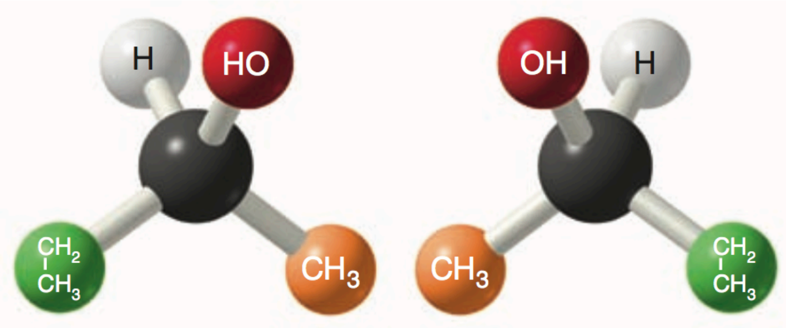
A chiral molecule is one that cannot be superposed on its mirror image



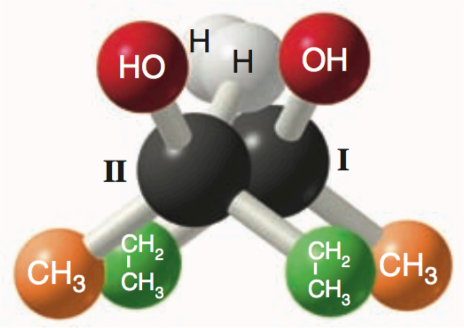
I



II

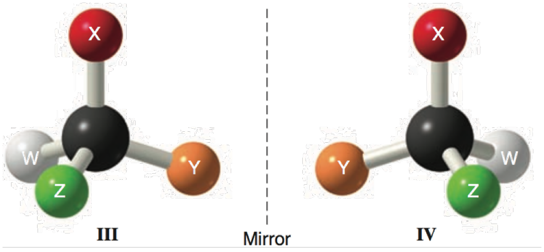


I **II**

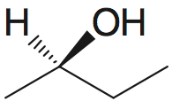


Stereochemistry

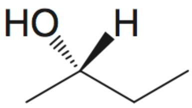
- A chirality center is a tetrahedral carbon atom that is bonded to four different groups.



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



(*R*)-2-Butanol



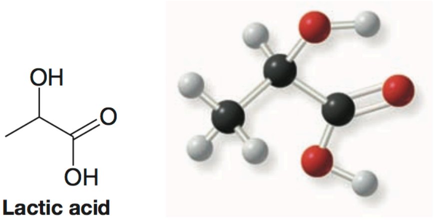
(*S*)-2-Butanol

- An equimolar mixture of two enantiomers is called a racemic mixture.

Quiz (1)

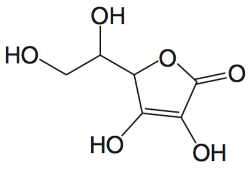
PRACTICE PROBLEM 5.6 Which atoms in each of the following molecules are chirality centers?

(a)



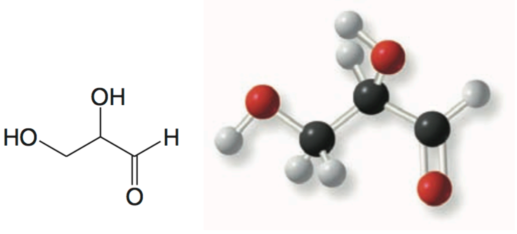
Lactic acid

(c)



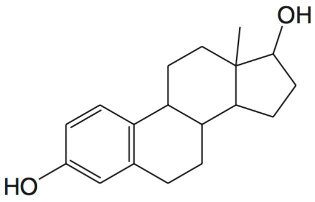
Ascorbic acid (vitamin C)

(b)



Glyceraldehyde

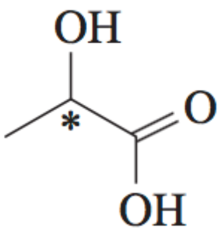
(d)



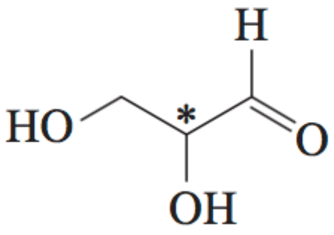
Estradiol (an estrogen)

Answer (1)

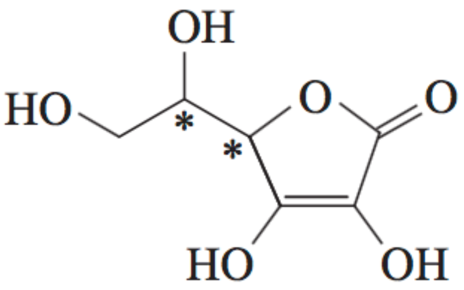
(a)



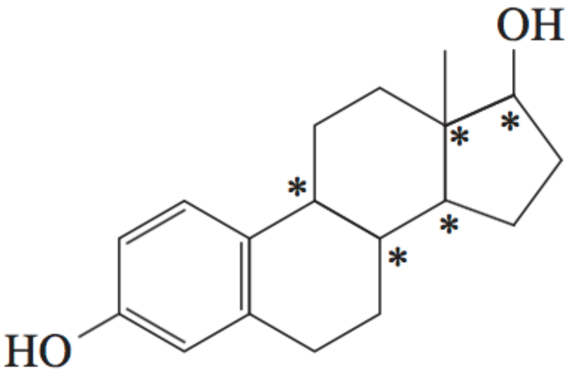
(b)



(c)

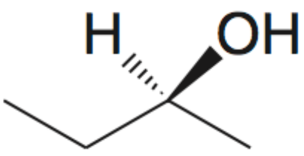


(d)

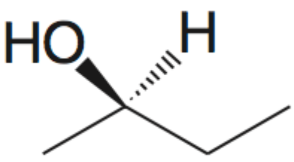


NAMING ENANTIOMERS:

The two enantiomers of 2-butanol are the following:



I



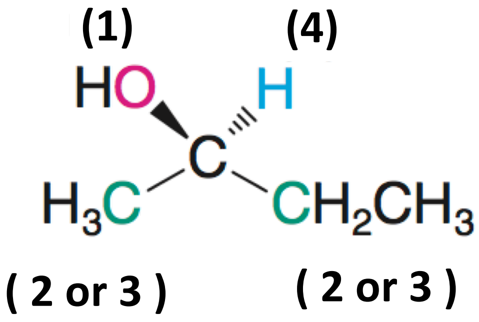
II

Name: 2-butanol 2-butanol

THE *R*,*S*-SYSTEM

HOW TO Assign (*R*) and (*S*) Configurations

1- Priority (atomic number)



One of the 2-butanol enantiomers

^{1}H

^{6}C ^{7}N ^{8}O ^{9}F

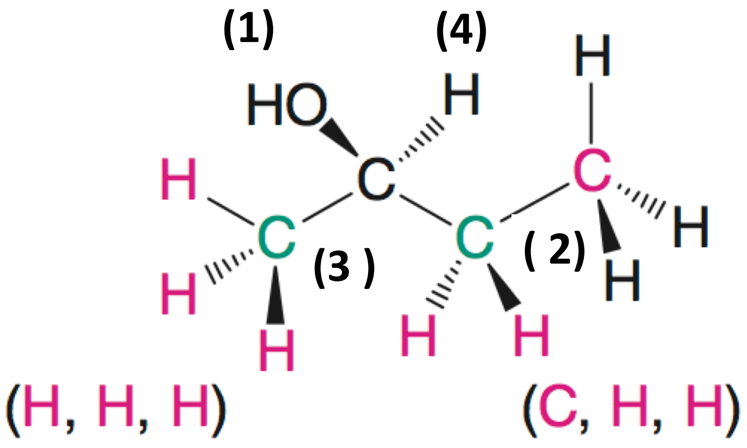
^{15}P ^{16}S ^{17}Cl

^{35}Br

^{53}I

HOW TO Assign (*R*) and (*S*) Configurations

2-



^{1}H

^{6}C ^{7}N ^{8}O ^{9}F

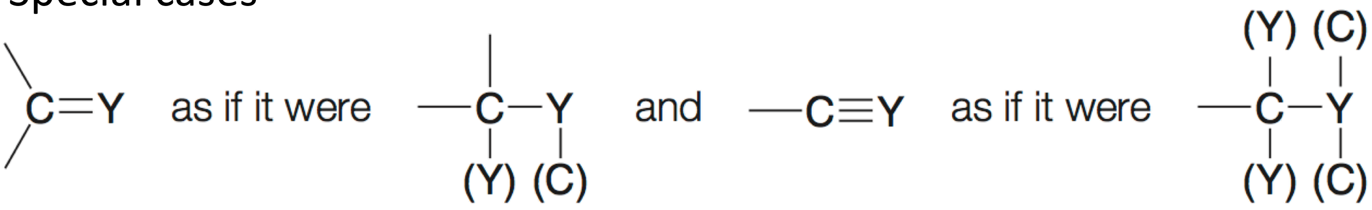
^{15}P ^{16}S ^{17}Cl

^{35}Br

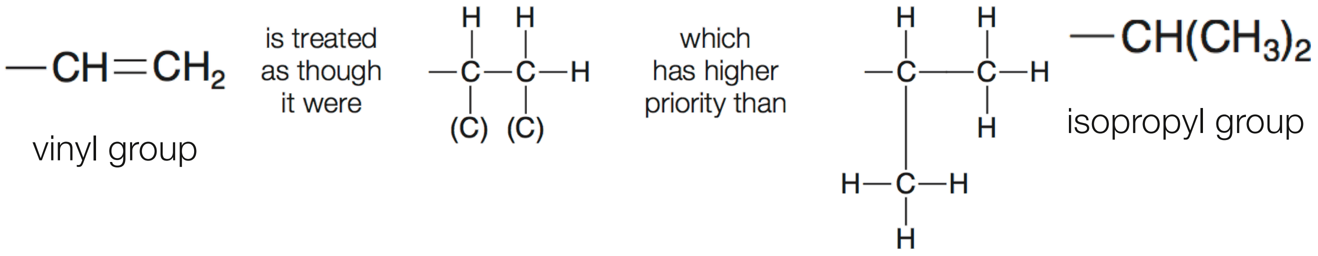
^{53}I

HOW TO Assign (*R*) and (*S*) Configurations

Special cases



Example:



Quiz (2)

List the substituents in each of the following sets in order of priority, from highest to lowest:

(a) $-Cl$, $-OH$, $-SH$, $-H$

(b) $-CH_3$, $-CH_2Br$, $-CH_2Cl$, $-CH_2OH$

(c) $-H$, $-OH$, $-CHO$, $-CH_3$

(d) $-CH(CH_3)_2$, $-C(CH_3)_3$, $-H$, $-CH{=}CH_2$

(e) $-H$, $-N(CH_3)_2$, $-OCH_3$, $-CH_3$

(f) $-OH$, $-OPO_3H_2$, $-H$, $-CHO$

Answer (2)

(a) $-\text{Cl} > -\text{SH} > -\text{OH} > -\text{H}$

(b) $-\text{CH}_2\text{Br} > -\text{CH}_2\text{Cl} > -\text{CH}_2\text{OH} > -\text{CH}_3$

(c) $-\text{OH} > -\text{CHO} > -\text{CH}_3 > -\text{H}$

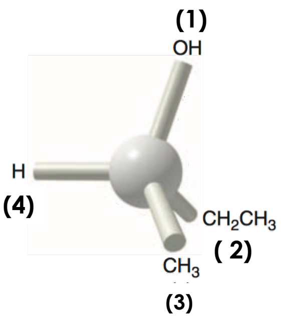
(d) $-\text{C(CH}_3)_3 > -\text{CH}{=}\text{CH}_2 > -\text{CH(CH}_3)_2 > -\text{H}$

(e) $-\text{OCH}_3 > -\text{N(CH}_3)_2 > -\text{CH}_3 > -\text{H}$

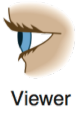
(f) $-\text{OPO}_3\text{H}_2 > -\text{OH} > -\text{CHO} > -\text{H}$

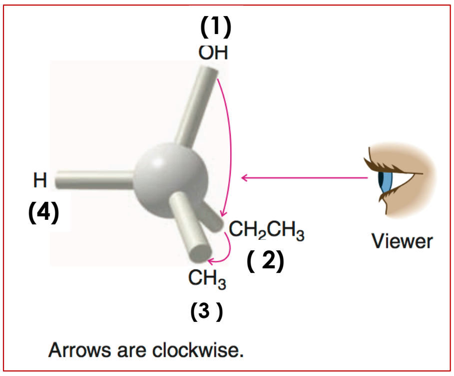
HOW TO Assign (*R*) and (*S*) Configurations

3. We now rotate the formula (or model) so that the group with lowest priority (4) is directed away from us:



One of the 2-butanol enantiomers





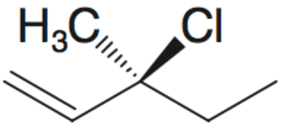
Arrows are clockwise.

(R)-2-butanol

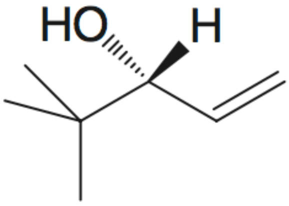
Quiz (3)

Assign (*R*) or (*S*) designations to each of the following compounds:

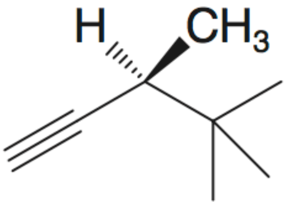
(a)



(b)



(c)



Answer (3)

(a) (*S*)

(b) (*R*)

(c) (*S*)

Diastereomers

- They are stereoisomers whose molecules are not mirror images of each other.
- Diastereomers have different physical properties—different melting points and boiling points, different solubilities, and so forth.

There are four types of diastereomers

a) cis-/trans- (E/Z) of alkenes,

b) cis-/trans- of cycloalkanes,

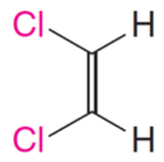
c) diastereomers that are not cis and trans isomers of each other.

d) epimers.

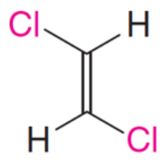
Diastereomers

Four Types

a) cis-/trans- (E/Z) of alkenes



***cis*-1,2-Dichloroethene**
($C_2H_2Cl_2$)



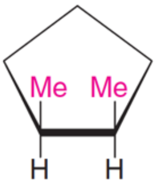
***trans*-1,2-Dichloroethene**
($C_2H_2Cl_2$)

Cis and trans alkene isomers are diastereomers.

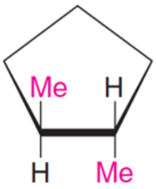
Diastereomers

Four Types

b) cis-/trans- of cycloalkanes



cis-1,2-Dimethylcyclopentane
(C_7H_{14})



trans-1,2-Dimethylcyclopentane
(C_7H_{14})

Cis and trans cycloalkane isomers are diastereomers.

Diastereomers

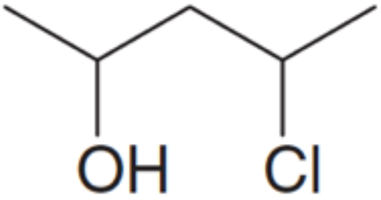
Four Types

c) diastereomers that are not cis and trans isomers of each other.

All other Stereoisomers

Quiz (4)

- Write three-dimensional formulas for all of the stereoisomers of the following compound. Label pairs of enantiomers and label Diastereomers.



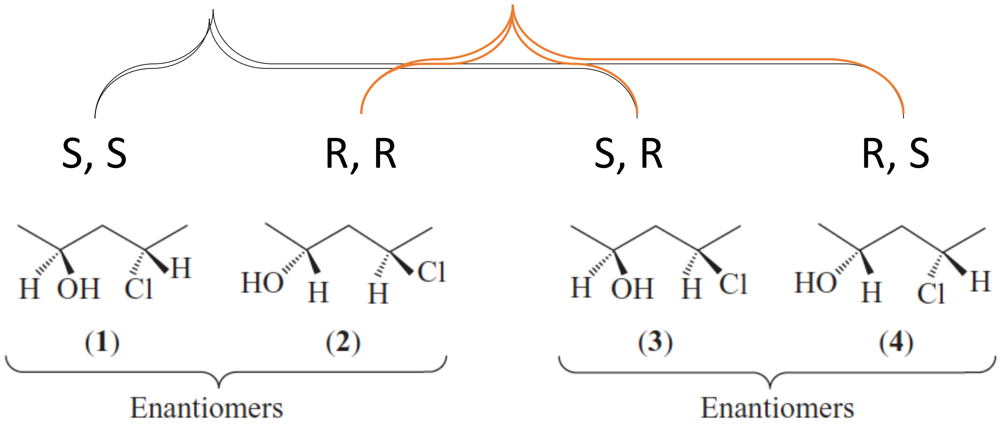
Answer (4_a)

- First: find the chiral centers = assign * to each chiral center
- Second: count the number of chiral centers = n = 2
- Third: calculate the number of possible isomers = $2^n = 2^2 = 4$ isomers
- Fourth: draw the 3D structures of all possible isomer using dash-wedge
- Fifth: label pairs of enantiomers and label Diastereomers.

Answer (4_b)

Diastereomers [1&3] and [1&4]

Diastereomers [2&3] and [2&4]



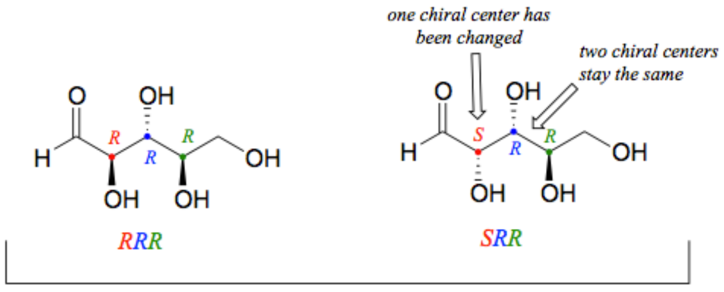
Diastereomers

Four Types

d) epimers.

They are diastereomers which differ at only a single chiral center.

For example,



one chiral center has been changed

two chiral centers stay the same

RRR

SRR

diastereomers
(epimers)

Fischer Projections Nomenclature

A. Formal nomenclature [R & S] system.

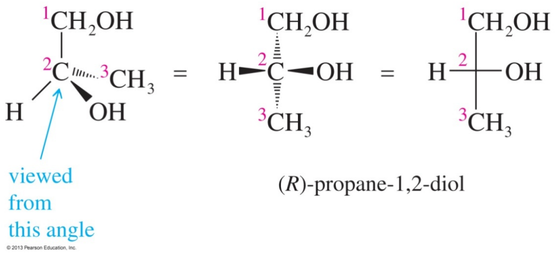
B. Informal nomenclature

1. Erythro & Threo system
2. D & L system

A. Formal nomenclature [R & S] system.

Fischer Projections

- Flat representation of a 3-D molecule.
- A chiral carbon is at the intersection of horizontal and vertical lines.
- Horizontal lines are forward, out of plane.
- Vertical lines are behind the plane.



(*R*)-propane-1,2-diol

Fischer Rules

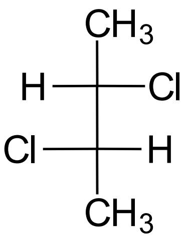
- Carbon chain is on the vertical line.
- Highest oxidized carbon is at top.
- Rotation of 180° in plane doesn't change molecule.
- Rotation of 90° is NOT allowed.

HINT

When naming (*R*) and (*S*) from Fischer projections with the hydrogen on a horizontal bond (toward you instead of away from you), just apply the normal rules backward.

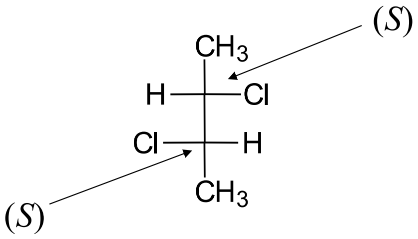
Fischer Mirror Images

- Fisher projections are easy to draw and make it easier to find enantiomers and internal mirror planes when the molecule has two or more chiral centers.



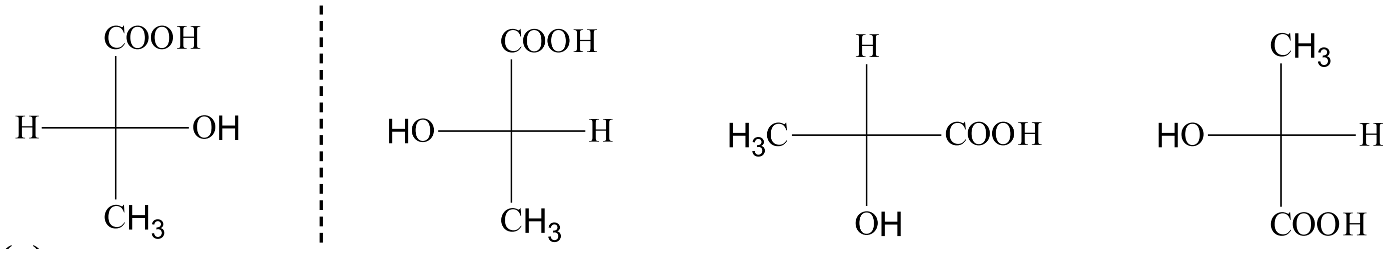
Fischer (*R*) and (*S*)

- Lowest priority (usually H) comes forward, so assignment rules are backward!
- Clockwise 1-2-3 is (*S*) and counterclockwise 1-2-3 is (*R*).
- Example:



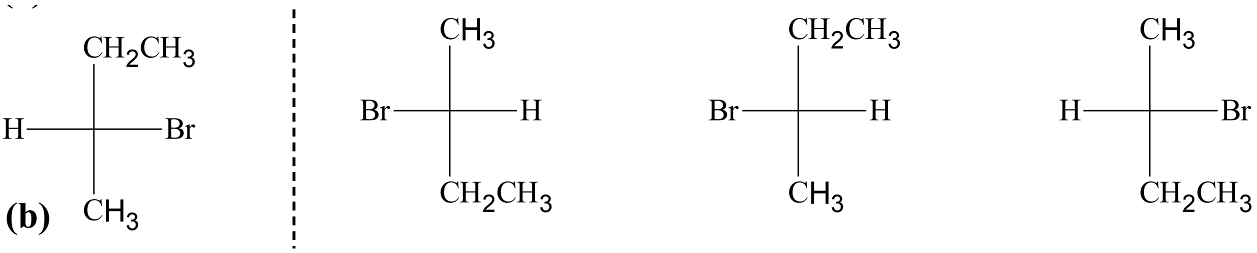
Quiz (5A)

For each set of examples, make a model of the first structure and tell the relationship of each of the other structures to the first structure. Examples of relationships: same compound, enantiomer, structural isomer.



Quiz (5B)

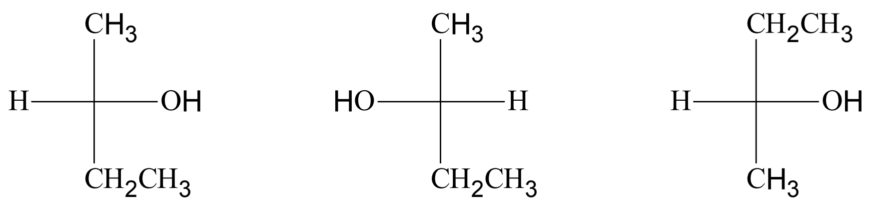
For each set of examples, make a model of the first structure and tell the relationship of each of the other structures to the first structure. Examples of relationships: same compound, enantiomer, structural isomer.



Quiz (5C)

For each set of examples, make a model of the first structure and tell the relationship of each of the other structures to the first structure. Examples of relationships: same compound, enantiomer, structural isomer.

(c) (R)-2-butanol



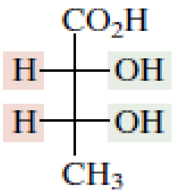
Fischer Projections Nomenclature (Continued)

B. Informal nomenclature

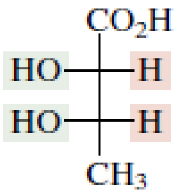
1. Erythro & Threo system
2. D & L system

1. Erythro & Threo system_A

- When the carbon chain is vertical and like substituents are on the same side of the Fischer projection, the molecule is described as the erythro diastereomer.



I
erythro



II
erythro

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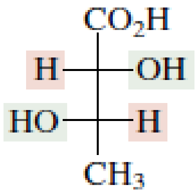
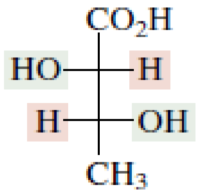
1. Erythro & Threo system_B

- When the carbon chain is vertical and like substituents are on the opposite side of the Fischer projection, the molecule is described as the threo diastereomer.



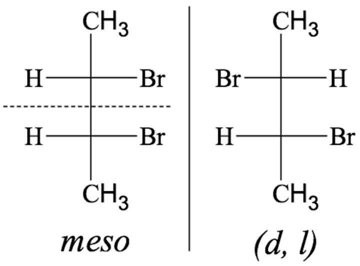
III
threo



IV
threo

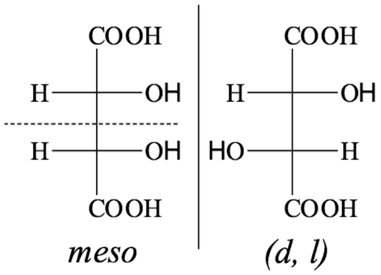
1. Erythro & Threo system_C

- Important note:
  - ✓ The terms erythro and threo are generally used only with molecules that do not have symmetric ends.
- Example:
  - ✓ In symmetric molecules such as 2,3-dibromobutane and tartaric acid, the terms meso and (*d*, *l*) are preferred.



meso *(d, l)*

2,3-dibromobutane

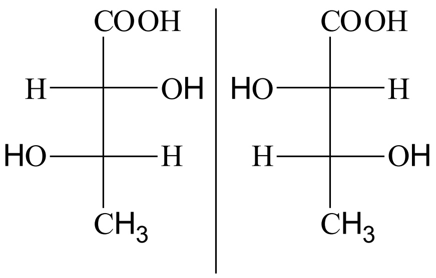


meso *(d, l)*

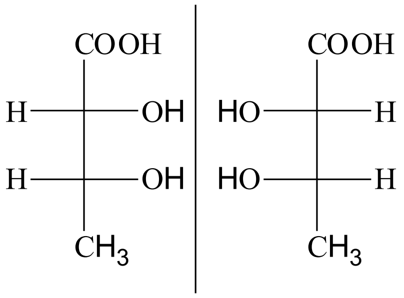
tartaric acid

Quiz (6)

- Indicate whether the following compounds are Erythro or Threo.



Threo Threo

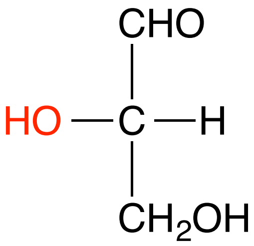


Erythro Erythro

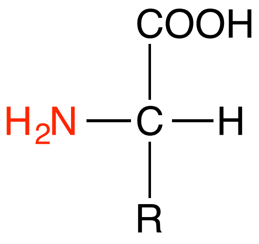
2. D & L system_ A

- **The configurations of sugars and amino acids were related to the enantiomers of glyceraldehyde.**

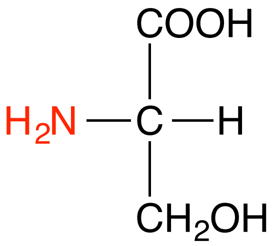
1. **Compounds with the same relative configuration as (-) glyceraldehyde were assigned the L prefix.**



L (-) glyceraldehyde



L aminoacid

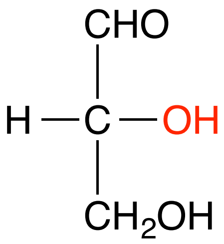


L (-) serine

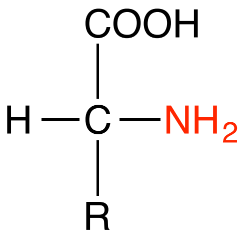
---

2. D & L system_ B

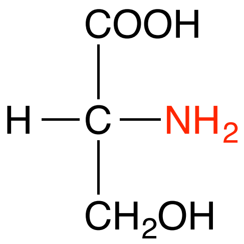
2. **Compounds with the same relative configuration as (+) glyceraldehyde were assigned the D prefix.**



D (+) glyceraldehyde



D aminoacid



D (+) serine

Thank You

MINIA UNIVERSITY

Organic Chemistry II
Stereochemistry
Part 2

Lecture 5

Dr Taha Ali, taha.ali@mu.edu.eg
Assistant professor,
Minia University

B Configurational isomers

1. Types & classes
2. Nomenclature
3. Optical activity
4. Separation
5. Application

Different Classes of ***Chiral*** Molecules

1. Chiral molecules with <u>one</u> chiral center.
2. Chiral molecules with <u>more</u> than one chiral center.
3. Chiral molecules <u>without</u> chiral center.
4. Chiral molecules with chiral center other than <u>carbon</u>.
5. Chiral molecules become <u>achiral</u> due to the "Plan of symmetry".

1- Chiral molecules with one chiral center

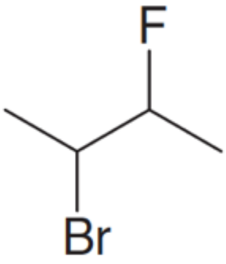
- A chirality center is a tetrahedral carbon atom that is bonded to four different groups.
- Chirality centers are often designated with an asterisk (*).
- A molecule that contains one chirality center is chiral and can exist as a pair of enantiomers.
- For examples, see Quiz 1, Lecture 1.

2- Chiral molecules with more than one chiral center.

- Molecules with more than one chirality center can exist as enantiomers or diastereomers.
- For examples, see Quiz 6, Lecture 4.
- Next slide, I will give one more example.

Quiz (7)

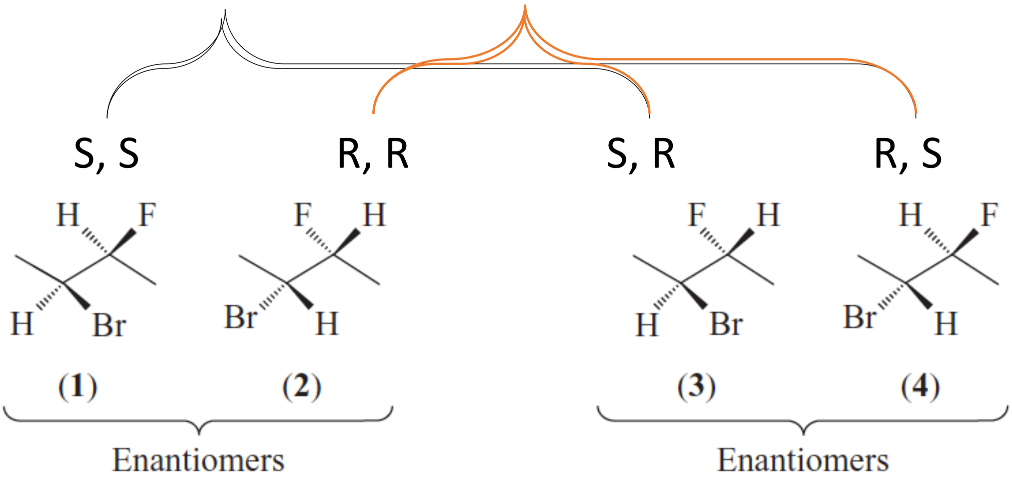
- Write three-dimensional formulas for all of the stereoisomers of the following compound. Label pairs of enantiomers and label Diastereomers.



Answer (7_a)

- First: find the chiral centers = assign * to each chiral center
- Second: count the number of chiral centers = n = 2
- Third: calculate the number of possible isomers = $2^n = 2^2 = 4$ isomers
- Fourth: draw the 3D structures of all possible isomer using dash-wedge
- Fifth: label pairs of enantiomers and label Diastereomers.

Answer (7_b)



Diastereomers [1&3] and [1&4]

Diastereomers [2&3] and [2&4]

S, S

R, R

S, R

R, S

(1) **(2)** **(3)** **(4)**

Enantiomers

Enantiomers

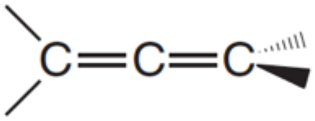
3- Chiral molecules <u>without</u> chiral center.

- ➢ A molecule is chiral if it is not superposable on its mirror image.
- ➢ Because they contain chiral axis which divide molecules into two halves perpendicular to each other.
- ➢They are named atropeisomers and involve the following types:
  - a. Allenes
  - b. Spiranes
  - *c. Ortho*-substituted biphenyl

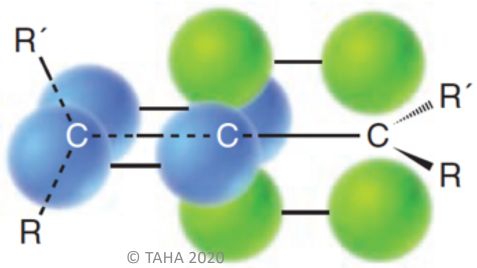
3- Chiral molecules without chiral center.

a. Allenes_1

- Allenes are molecules that contain the following double-bond sequence:



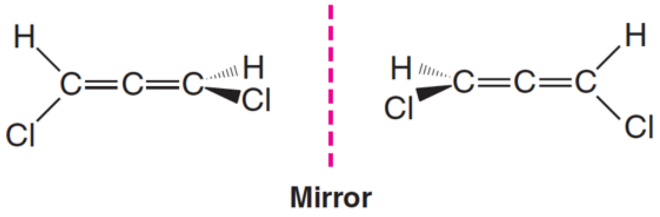
- The planes of the π bonds of allenes are perpendicular to each other:



3- Chiral molecules without chiral center.

a. Allenes_2

- This geometry of the π bonds causes the groups attached to the end carbon atoms to lie in perpendicular planes, and, because of this, allenes with different substituents on the end carbon atoms are chiral



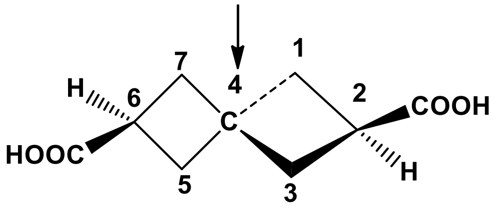
- Allenes do n erism

3- Chiral molecules without chiral center.

b. Spiranes

- They are bicyclic structure which is linked at one saturated carbon atom (spiro carbon).

hybridization of common carbon is SP3



The chilarity of this spirane is due to:

a) Restriction of rotation due to cyclic structure.

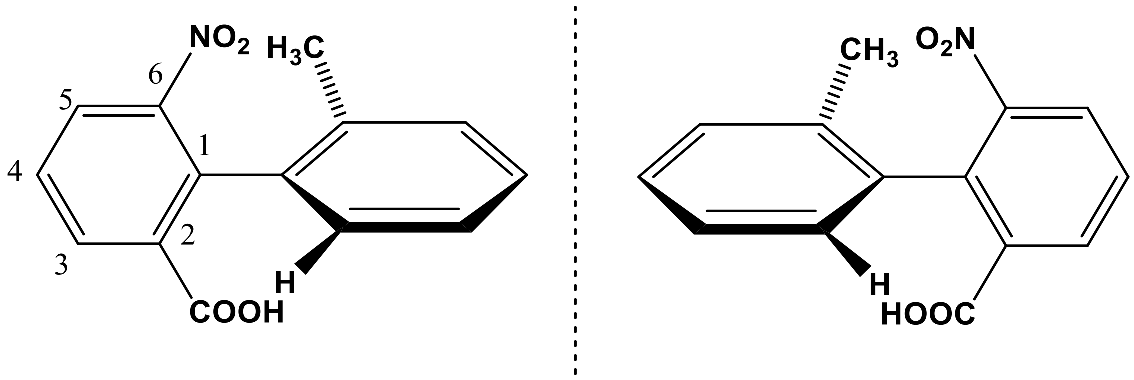
b) Two rings are perpendicular to each other.

c) Two different substitutions at each ring.

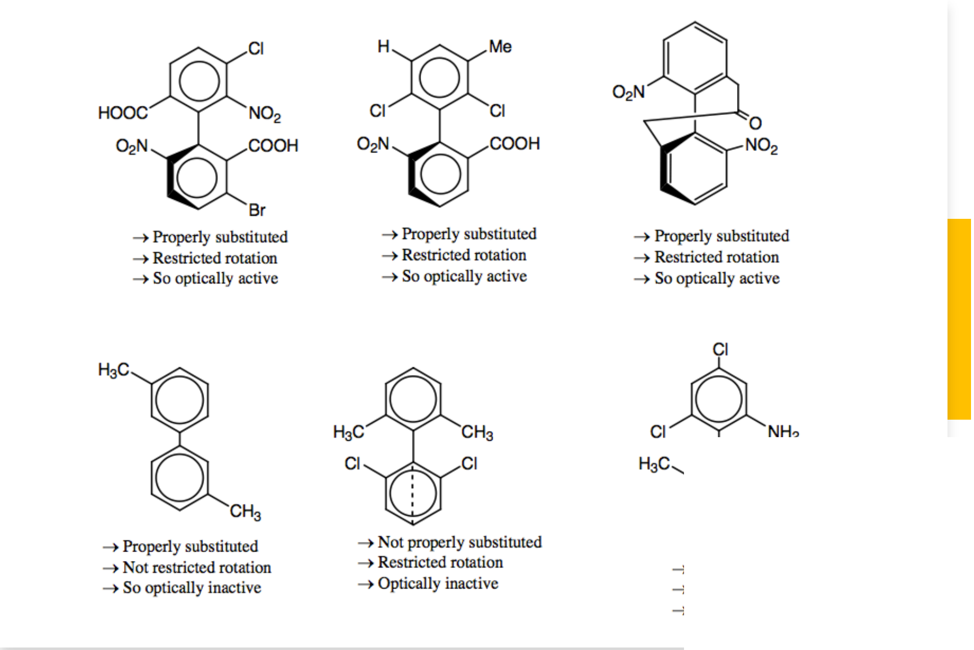
Spiro[3,3]heptane-2,6-dicarboxylic acid (chiral)

3- Chiral molecules without chiral center.

c. Ortho-substituted biphenyl



2'-methyl-6-nitrobiphenyl-2-carboxylic acid



→ Properly substituted
→ Restricted rotation
→ So optically active

→ Properly substituted
→ Restricted rotation
→ So optically active

→ Properly substituted
→ Restricted rotation
→ So optically active

→ Properly substituted
→ Not restricted rotation
→ So optically inactive

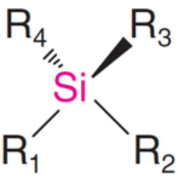
→ Not properly substituted
→ Restricted rotation
→ Optically inactive

More examples of o-substituted biphenyl molecules

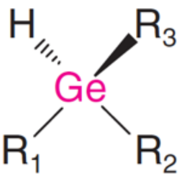
4- Chiral molecules **with chiral center other than** <u>carbon</u>.

- A chirality center is a **tetrahedral** <u>carbon</u> atom that is bonded to four different groups.
- Any **tetrahedral** <u>atom</u> with four different groups attached to it is a chirality center.

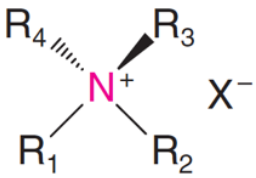
Examples



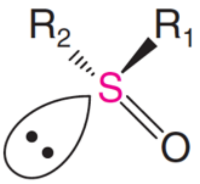
Silicon



Germanium



Nitrogen



Sulfoxides

5- Chiral molecules become achiral due to the "Plan of symmetry" .

- A structure with two chirality centers does not always have four possible stereoisomers.
- Sometimes there are only three.
- Some molecules are achiral even though they contain chirality centers.

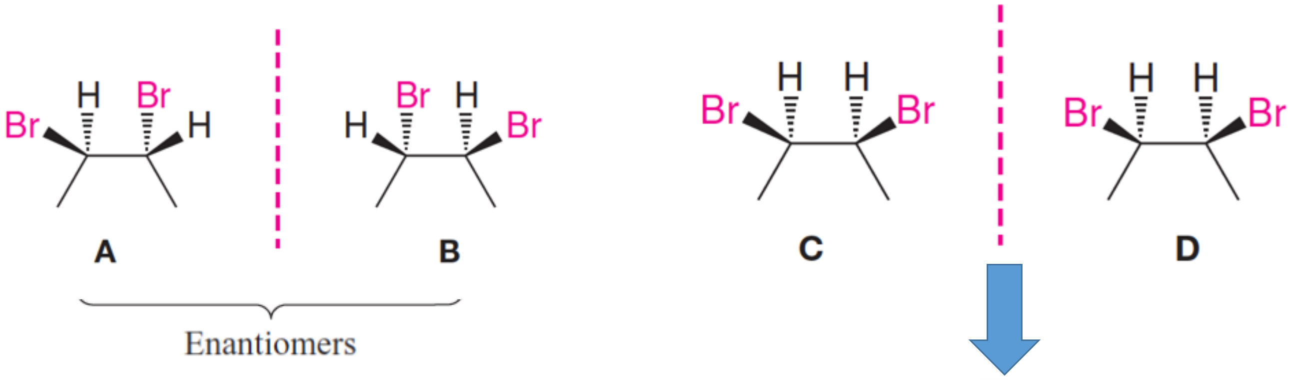
Quiz (8)

- Write three-dimensional formulas for all of the stereoisomers of 2,3-dibromobutane
- Label pairs of enantiomers and label Diastereomers and meso compounds.

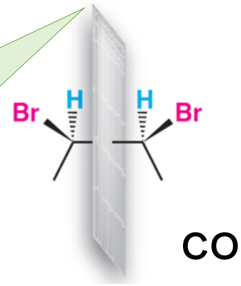
Answer (8_a)

- First: find the chiral centers = assign * to each chiral center
- Second: count the number of chiral centers = n = 2
- Third: calculate the number of possible isomers = $2^n = 2^2 = 4$ isomers
- Fourth: draw the 3D structures of all possible isomer using dash-wedge
- Fifth: label pairs of enantiomers and label Diastereomers.

Answer (8_b)



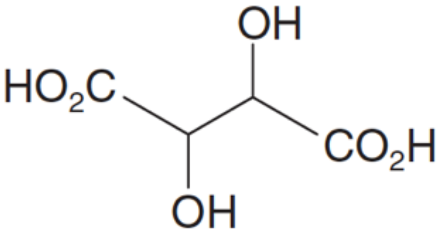
- The plane of symmetry of meso-2,3-dibromobutane.
- This plane divides the molecule into halves that are mirror images of each other.
- The compound become achiral & optically inactive.



Meso compound

Quiz (9)

- Write three-dimensional formulas for all of the stereoisomers of the following compound. Label pairs of enantiomers and label Diastereomers and meso compounds.

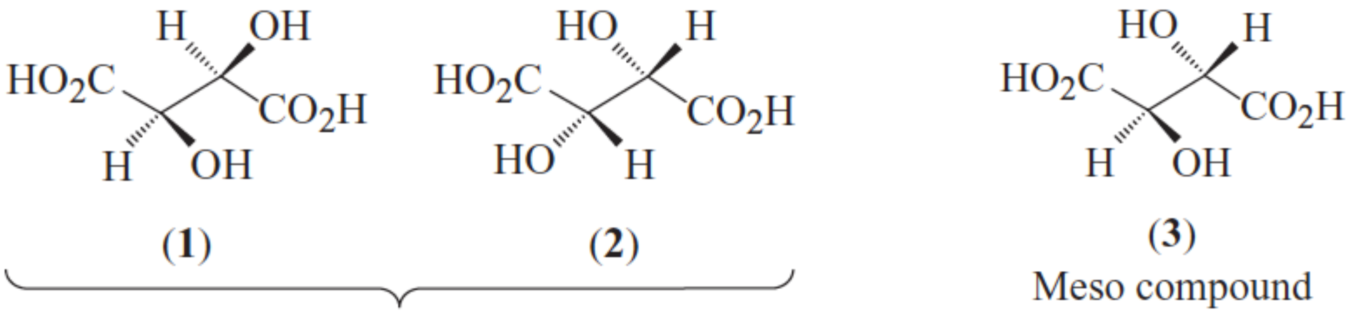


Tartaric acid

Answer (9_a)

- First: find the chiral centers = assign * to each chiral center
- Second: count the number of chiral centers = n = 2
- Third: calculate the number of possible isomers = $2^n = 2^2 = 4$ isomers
- Fourth: draw the 3D structures of all possible isomer using dash-wedge
- Fifth: label pairs of enantiomers and label Diastereomers.

Answer (9_b)



Enantiomers

Meso compound

3

Optical activity of Configurational isomers

a. Polarimeter

b. Enantiomers

c. Racemic Forms

The Polarimeter

A device used for measuring the effect of optically active compounds on plane-polarized light

A substance that rotates plane-polarized light in the clockwise direction is also said to be dextrorotatory, and one that rotates plane-polarized light in a counterclockwise direction is said to be levorotatory (Latin: *dexter*, right, and *laevus*, left).

✓ No correlation exists between the (R) and (S) designation and the direction of rotation of plane-polarized light.

Properties of Enantiomers: Optical Activity

- Pure enantiomers have identical melting and boiling points.
- Enantiomers show different behavior only when they interact with other chiral substances.
- One easily observable way in which enantiomers differ is in their behavior toward plane-polarized light.
- When a beam of plane-polarized light passes through an enantiomer, the plane of polarization rotates.
- Separate enantiomers are said to be optically active compounds. Because of their effect on plane-polarized light.

Racemic Forms

- A molecule that contains one chirality center is chiral and can exist as a pair of enantiomers.
- Separate enantiomers rotate the plane of plane-polarized light equal amounts but in opposite directions.

✓ Example: The specific rotations of (R)-2-butanol and (S)-2-butanol

(*R*)-2-Butanol
$[\alpha]_D^{25} = -13.52$

(*S*)-2-Butanol
$[\alpha]_D^{25} = +13.52$

4

Separation of Configurational isomers

a. Traditional
b. HPLC

Background

- The process of separating a racemic mixture into its enantiomers is called **resolution**.
- Enantiomers have **identical** solubilities in ordinary solvents, and they have identical boiling points.
- Consequently, the **conventional methods** for separating organic compounds, such as crystallization and distillation, **fail** when applied to a racemic form.

---

a) Traditional method_1

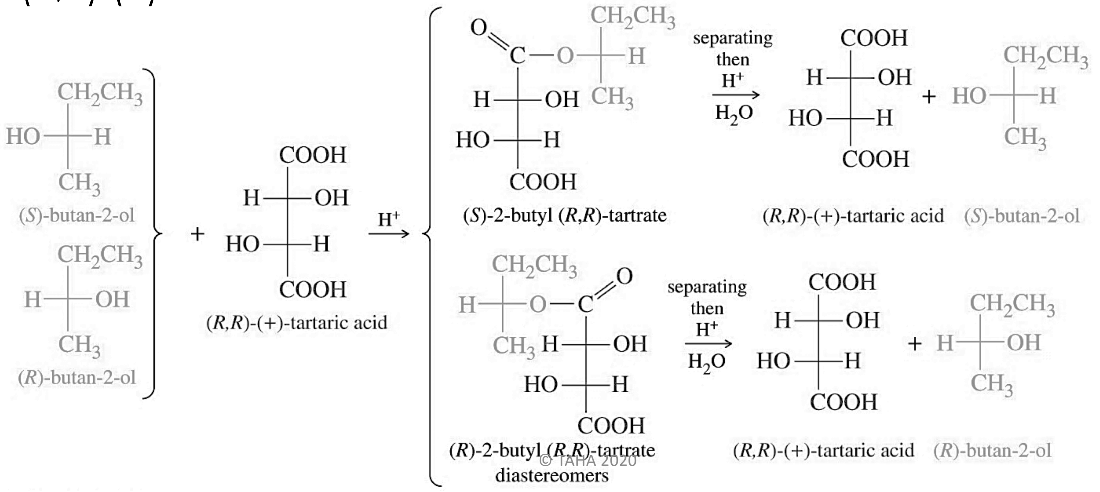
- **What?**
  this method depends on conversion of enantiomers into diastereomers.
- **Why?**
  because diastereomers have different melting points, boiling points, and solubilities, can be separated by conventional means.
- **How?**
  when a racemic mixture reacts with a single enantiomer of another compound, a mixture of diastereomers results.
- **Example:**
  resolution of (S)-(+)-2-butanol and (R)-(-)-2-butanol by reacting with (R,R)-(+)-tartaric acid.

Separation of Configurational isomers

a) Traditional method_2

- **Example:**

  resolution of (S)-(+)-2-butanol and (R)-(-)-2-butanol by reacting with (R,R)-(+)-tartaric acid.



Separation of Configurational isomers

b) HPLC method

- ✓ **What?**

  this method depends on Chromatography using chiral media.
- ✓ **Why?**

  interactions between molecules of the racemic mixture and the chiral chromatography medium cause enantiomers of the racemate to move through the chromatography apparatus at different rates
- ✓ **How?**

  the enantiomers are then collected separately as they elute from the chromatography device.
- ✓ **Example:**

  resolution of (S)-(+)-2-butanol and (R)-(-)-2-butanol by using high-performance liquid chromatography (HPLC) with chiral column.

5

Applications of Configurational isomers

a. Drug synthesis

b. Drug action

---

a) Drug synthesis **Stereoselective reactions_1**

✓ Types of reactions from stereochemistry point of view?

1. **Stereoselective reactions**:

Definition: They are reactions that lead to a preferential formation of one stereoisomer over other stereoisomers that could possibly be formed.

Types: a) **enantioselective reaction**: It is a reaction that produces preferentially one enantiomer over its mirror image.

b) **diastereoselective reaction**: It is a reaction that produces one diastereomer over others that are possible.

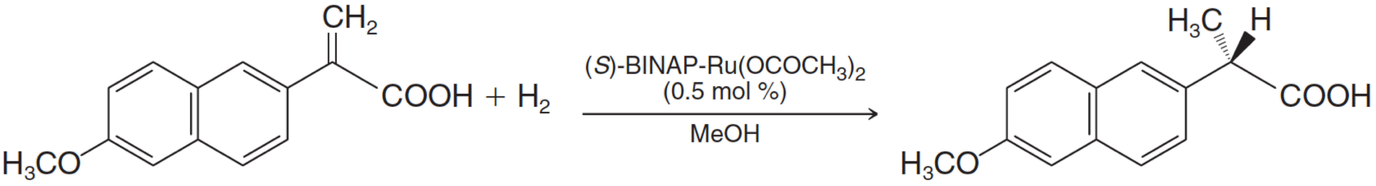
Note: For a reaction to be either enantioselective or diastereoselective, a **chiral** reagent, catalyst, or solvent must assert an influence on the path of the reaction.

Examples: Next slides

Applications of Configurational isomers

a) Drug synthesis **Stereoselective reactions_2**

Example: **enantio**selective synthesis of the anti-inflammatory agent Naproxen (the S enantiomer is an anti-inflammatory agent, while the R enantiomer is a liver toxin) involving a stereoselective catalytic hydrogenation reaction:



(S)-Naproxen
(an anti-inflammatory agent)
(92% yield, 97% ee)

Applications of Configurational isomers

a) Drug synthesis **Non-stereoselective reactions**

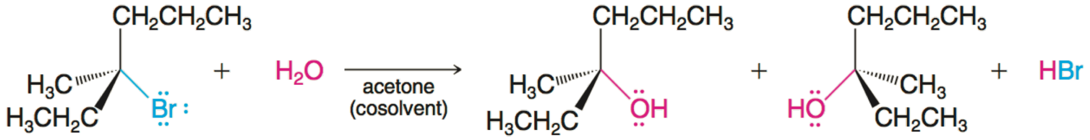
✓ Types of reactions from stereochemistry point of view?

2. Non-stereoselective reactions:

Definition: They are reactions that produce the chiral product as a 50:50 mixture of enantiomers (racemic mixture).

Note: For a reaction to be non-stereoselective, the reaction must be carried out in the absence of any chiral influence from a catalyst, reagent, or solvent.

Example_1: Hydrolysis of (S)-3-bromo-3-methylhexane by SN1 mechanism.



(S)-3-bromo-3-methylhexane

(S)-3-methylhexan-3-ol
50%

(R)-3-methylhexan-3-ol
50%

Applications of Configurational isomers

a) Drug action

Background_1

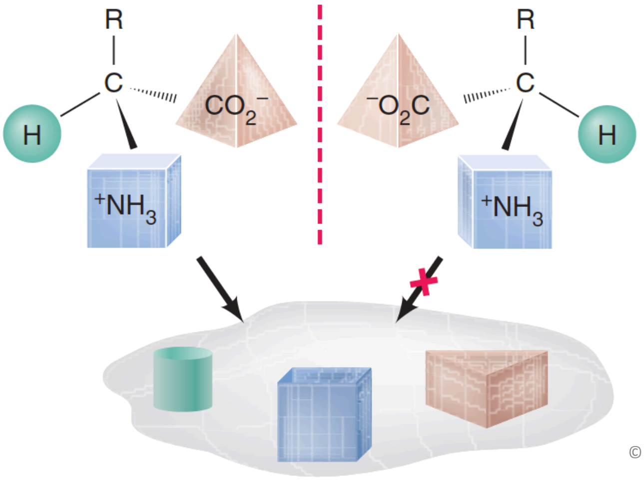
- The origin of biological properties relating to chirality is often likened to the specificity of our hands for their respective gloves; the binding specificity for a chiral molecule (like a hand) at a chiral receptor site (a glove) is only favorable in one way.
- If either the molecule or the biological receptor site had the wrong handedness, the natural physiological response (e.g., neural impulse, reaction catalysis) would not occur.
- A diagram showing how only one amino acid in a pair of enantiomers can interact in an optimal way with a hypothetical binding site (e.g., in an enzyme) is shown in the following figure.

Applications of Configurational isomers

a) Drug action

Background_2

- Because of the chirality center of the amino acid, three-point binding can occur with proper alignment for only one of the two enantiomers.



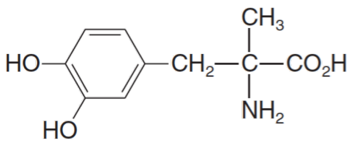
✓ Only one of the two amino acid enantiomers shown (the left-hand one) can achieve three-point binding with the hypothetical binding site (e.g., in an enzyme).

Applications of Configurational isomers

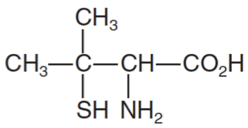
a) Drug action

Example

- The U.S. Food and Drug Administration and the pharmaceutical industry are very interested in the production of chiral drugs—that is, drugs that contain a single enantiomer rather than a racemate.
- The antihypertensive drug **methyldopa** (Aldomet), for example, owes its effect exclusively to the (S) isomer. In the case of **penicillamine**, the (S) isomer is a highly potent therapeutic agent for primary chronic arthritis, while the (R) isomer has no therapeutic action and is highly toxic.



Methyldopa



$CH_3-\overset{CH_3}{\underset{SH}{C}}-\underset{NH_2}{CH}-CO_2H$

Penicillamine

Thank You