Chapter 6: Chirality: The Handedness of Molecules

6.1. Chirality and Stereochemistry

What does chirality mean?

Chiral objects are not superimposable on their mirror images

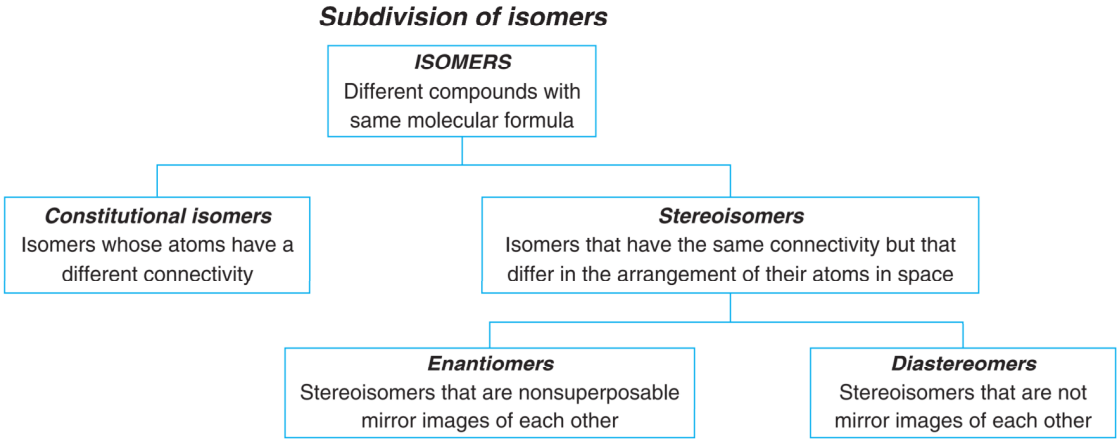
Achiral objects contain a plane of symmetry (mirror plane) and are superimposable on their mirror image

Are the following objects chiral or achiral?

A G H J L E

W Q Y B P T

6.2 The Relationship Between Different Isomers

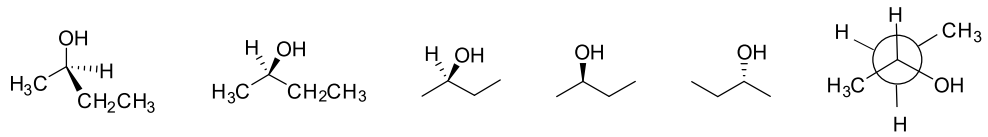


Achiral molecules are optically inactive and have a plane of symmetry (mirror plane) which makes their mirror image superimposable with the original

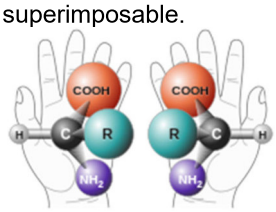
Chiral molecules are **optically active** molecules and contain either a stereogenic center or another chiral element which makes their mirror image non-superimposable with the original

Stereocenter (Stereogenic center): carbon with 4 different groups attached = chiral center

Graphical representation of stereogenic centers



Enantiomers – A pair of ***chiral*** molecules which behave like image and mirror image and are not superimposable.

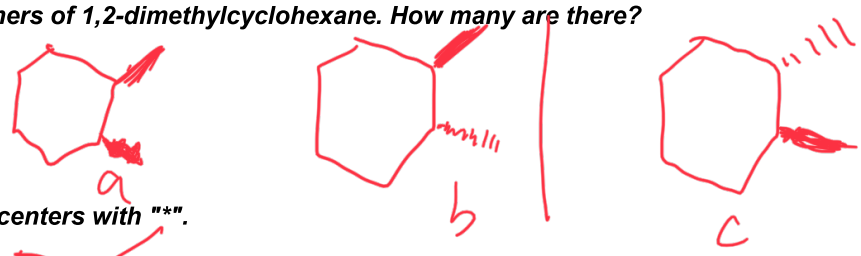


- Identical physical properties (except when in chiral environment)
- Opposite rotation of plane-polarized light ("optically active")

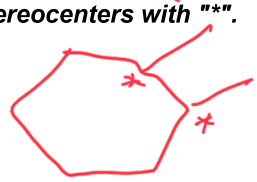
Diastereomers – Stereoisomers which are not enantiomers.
Molecules with the same connectivity which ***do not*** behave like image and mirror image and are not superimposable. They have different physical properties.

Exercise

1. Draw all stereoisomers of 1,2-dimethylcyclohexane. How many are there?



2. Label all the stereocenters with "*".



3. Which molecules are chiral, which are achiral?

a b+c

4. Which molecules are enantiomers?

bc

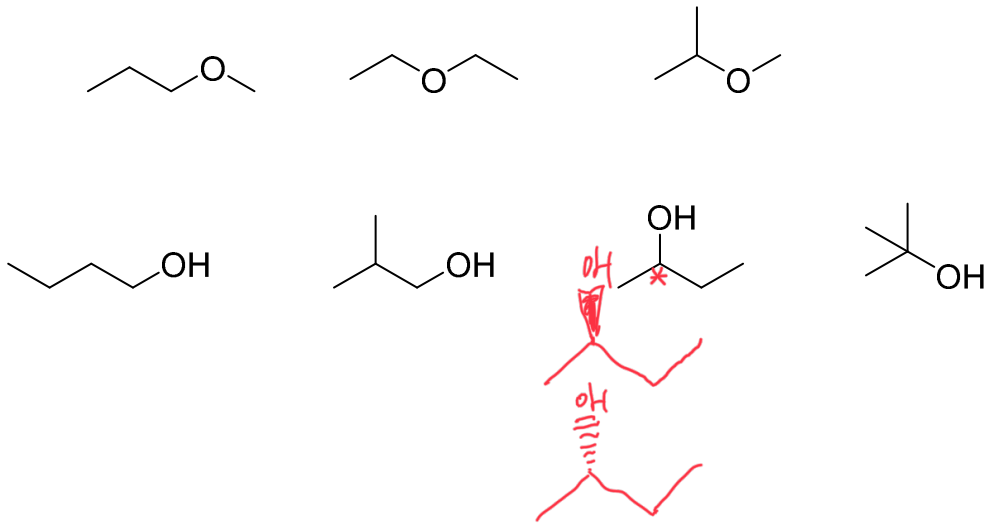
5. Which molecules are diastereomers?

a+b

a+c

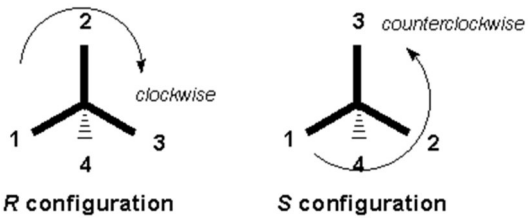
6.3 Molecules with one Stereogenic Center: Enantiomers

C_4H_{10}



The R,S-System for Naming Stereocenters
(Cahn-Ingold-Prelog Sequence Rules)

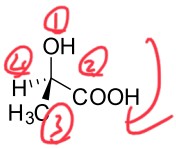
1. Determine the priority of the substituents (see below)
2. Turn the lowest priority group away
3. Trace the three remaining groups from Rank 1 to Rank 2 to Rank 3



Priority: 1>2>3>4 (4: lowest priority, in the back)

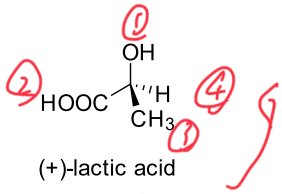
How to determine priority

1. Atomic numbers
2. Isotopes
3. Multiple Bonds
4. If 1st sphere no difference, then 2nd sphere, etc.



(-)-lactic acid

R



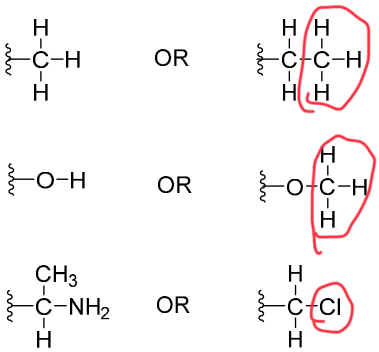
(+)-lactic acid

S

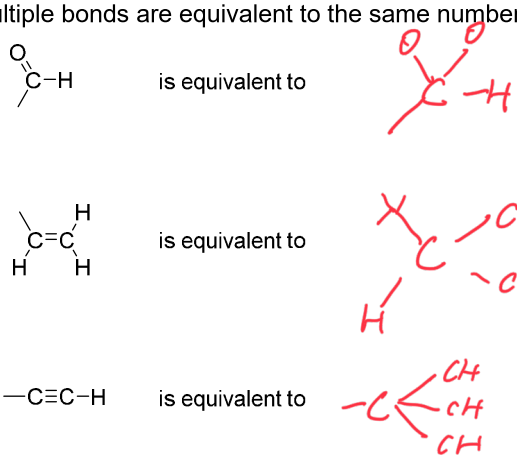
Note: There is **no** connection between R/S and +/-

Which substituent has the higher priority?

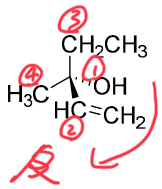
Stereocenter →

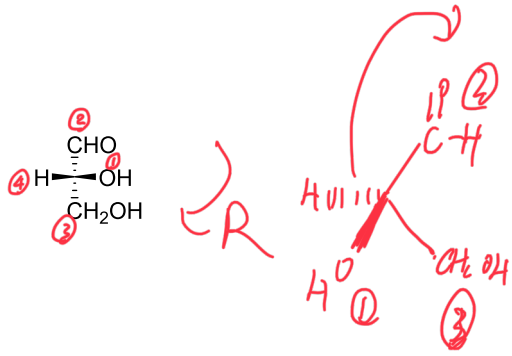


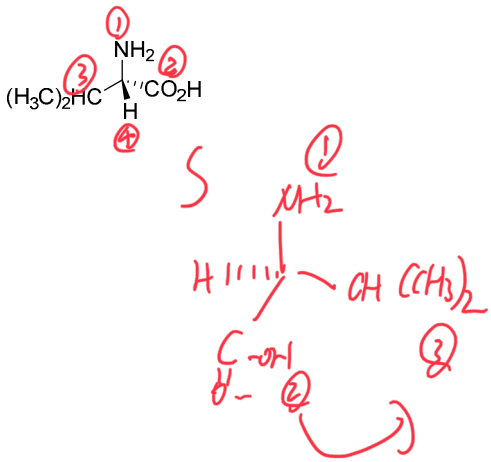
Multiple bonds are equivalent to the same number of single bonded atoms.



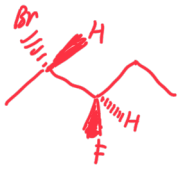
Examples: Assign (R) and (S) configurations to all stereogenic centers







(2S,3R)-2-bromo-3-fluorobutane



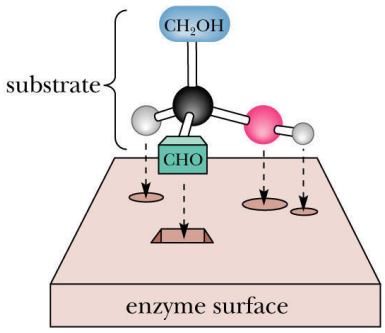
6.4 Biological Significance of Chirality and Asymmetric Synthesis

Interactions between molecules in living systems take place in a chiral environment, a molecule and its enantiomer or one of its diastereomers elicit different physiological responses.

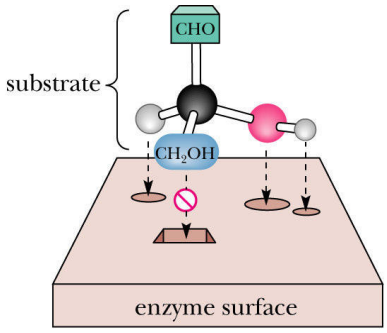
Enzymes (catalytic proteins) are made up of individual amino acids which all have a chiral center (except glycine).

- Chymotrypsin has 251 stereocenters and exists as one single stereoisomer
- the maximum number of stereoisomers possible is

Because enzymes are chiral substances; most either produce or react with only substances that match their stereochemical requirements.



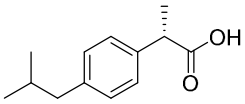
This enantiomer of glyceraldehyde fits the three specific binding sites on the enzyme surface



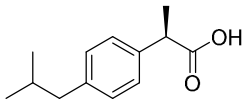
This enantiomer of glyceraldehyde does not fit the same binding sites

Chiral drugs

- (*S*)-ibuprofen is a pain and fever reliever, its R enantiomer is inactive.

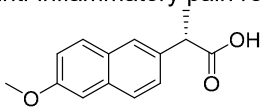


(S) enantiomer

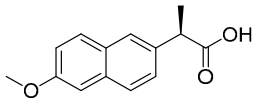


(R) enantiomer

- (S)-naproxen is an anti-inflammatory pain reliever; its R enantiomer is a liver toxin.

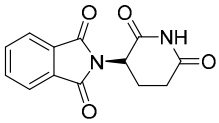


(S) enantiomer

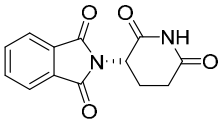


(R) enantiomer

- (R)-thalidomide is a sedative; its S enantiomer is tetragenic



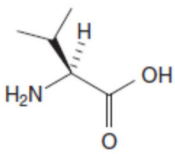
(R) enantiomer



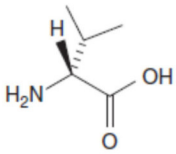
(S) enantiomer

6.5 Properties of Chiral Molecules: Optical Activity

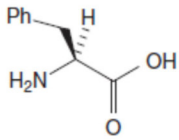
Pure enantiomers have identical physical and chemical properties unless they are in an asymmetric environment where they interact with chiral substances. Two sets of enantiomerically pure amino acids demonstrate this:



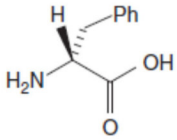
(*S*)-(+)-valine
[L-valine]
m.p. 295–300 °C
(sublimes)
$[\alpha]_D^{20}$ +27.5°



(*R*)-(–)-valine
[D-valine]
m.p. 295–300 °C
(sublimes)
$[\alpha]_D^{20}$ –27.5°



(*S*)-(–)-phenylalanine
[L-phenylalanine]
m.p. 273–276 °C
$[\alpha]_D^{25}$ –35°



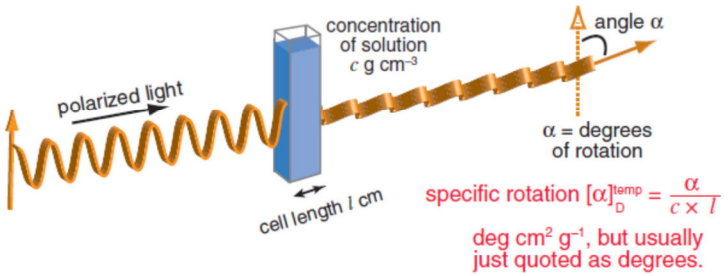
(*R*)-(+)-phenylalanine
[D-phenylalanine]
m.p. 273–276 °C
$[\alpha]_D^{25}$ +35°

One way to distinguish pure enantiomers is to measure their optical rotation. Enantiomers rotate plane-polarized light by equal amounts but in opposite directions.

Levorotatory (L or -) – rotation to the left
Dextrorotatory (D or +) – rotation to the right

Optical activity of enantiomers

The rotation of plane-polarized light is measured using an instrument known as a *polarimeter*, which is illustrated schematically below.



Specific Rotation: observed rotation when the wavelength (λ) of light used is 589.6 nm
How far the plane rotates depends on the structure of the molecules and the concentration of the sample:

$$[\alpha]_D = \frac{observed\ rotation\ (°)}{path\ length\ (dm) \times conc\ (^{g}/_{mL})} = \frac{\alpha}{\ell \times C}$$

A 1.20 g sample of cocaine, $[\alpha]_D$ = -16°, was dissolved in 7.50 mL of chloroform and placed in a sample tube having a path length of 5.00 cm. What was the observed rotation?

Enantiomeric Excess *(also called optical purity)*
For <u>known</u> compounds (with known specific rotations) we can calculate how much of each enantiomer is present in a mixture.

Enantiomeric excess (e.e.) is defined as:

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

$$\%\ \text{Enantiomeric excess} = \frac{\text{observed specific rotation}}{\text{specific rotation of the pure enantiomer}} \times 100$$

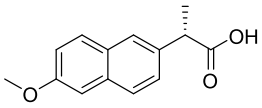
A racemic mixture (a racemate) is a 50:50 mixture of enantiomers.
Because enantiomers rotate plane polarized light by equal amount but in opposite directions, a racemic mixture exhibits no optical activity

Examples:

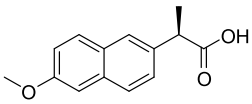
- A sample of D-phenylalanine ((*R*)-(+)-phenylalanine) has an optical purity of 98%. How much of the D- and L-enantiomers are present?

- For a sample of D-phenylalanine ((*R*)-(+)-phenylalanine, $[\alpha]_D$ = +35°) a rotation of 30º is observed. What is the enantiomeric excess?

How to determine enantiomeric excess of (new) compounds.
Example from earlier: (S)-naproxen is an anti-inflammatory pain reliever; its R enantiomer is a liver toxin.



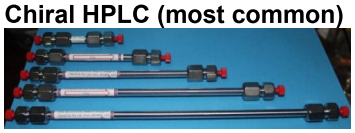
(S) enantiomer



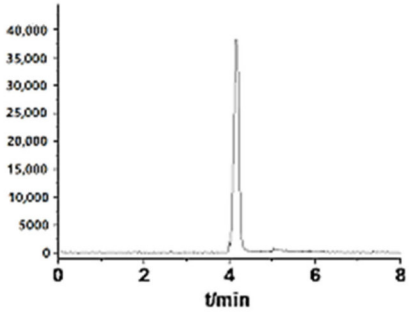
(R) enantiomer

How do pharma companies ensure that only the S-enantiomer is present?

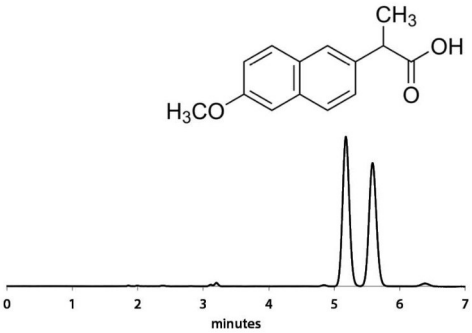
Chiral HPLC (most common)



HPLC with a normal (achiral) column:



HPLC with a chiral column:

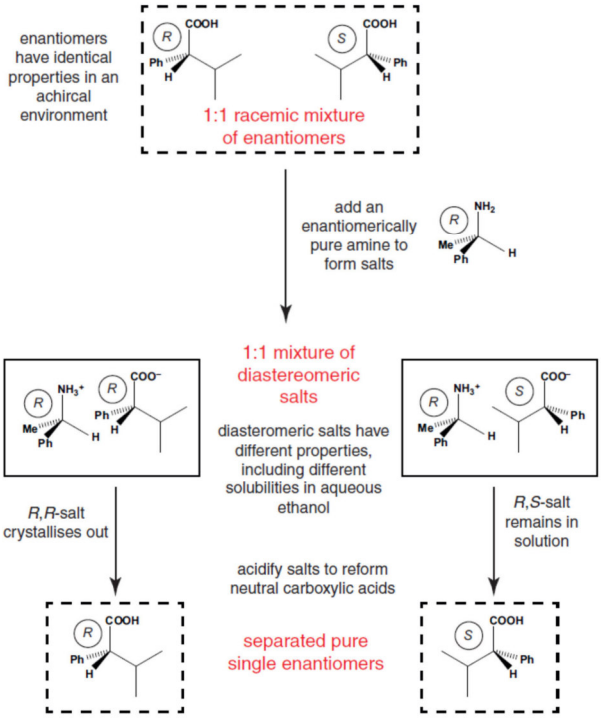


6.6 Racemic Forms and Resolution of Enantiomers

A racemic mixture (a racemate) is a 50:50 mixture of enantiomers.

Resolution of enantiomers:
Separation of a racemic mixture

Reaction of a racemic mixture with a (enantiopure) chiral molecule converts the enantiomers into diastereomers

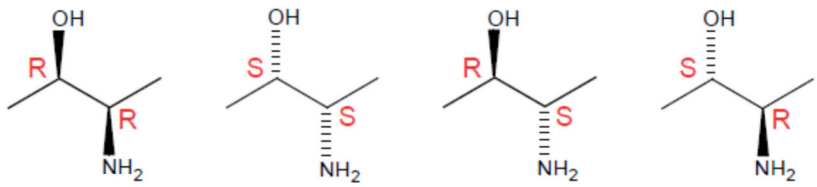


6.7 Molecules with Two or More Stereogenic Centers
Diastereomers, Enantiomers, Meso Compounds

The number of stereocenters dictates how many stereoisomers *may* occur.

- 2^n stereoisomers are possible for *n* stereocenters.
- some may be too strained to actually exist
- some may lead to meso compounds

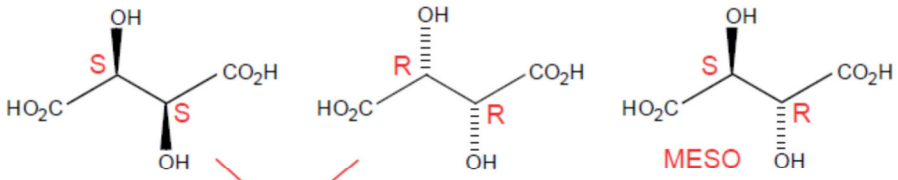
Example: Stereoisomers of 3-amino-butan-2-ol



mp / °C	15-16	15-16	49.2-49.3	49.2-49.3
α ^{25}D (neat) / degrees	−16	+16	+0.8	−0.8

It is not necessary for all diastereomers to be optically active.

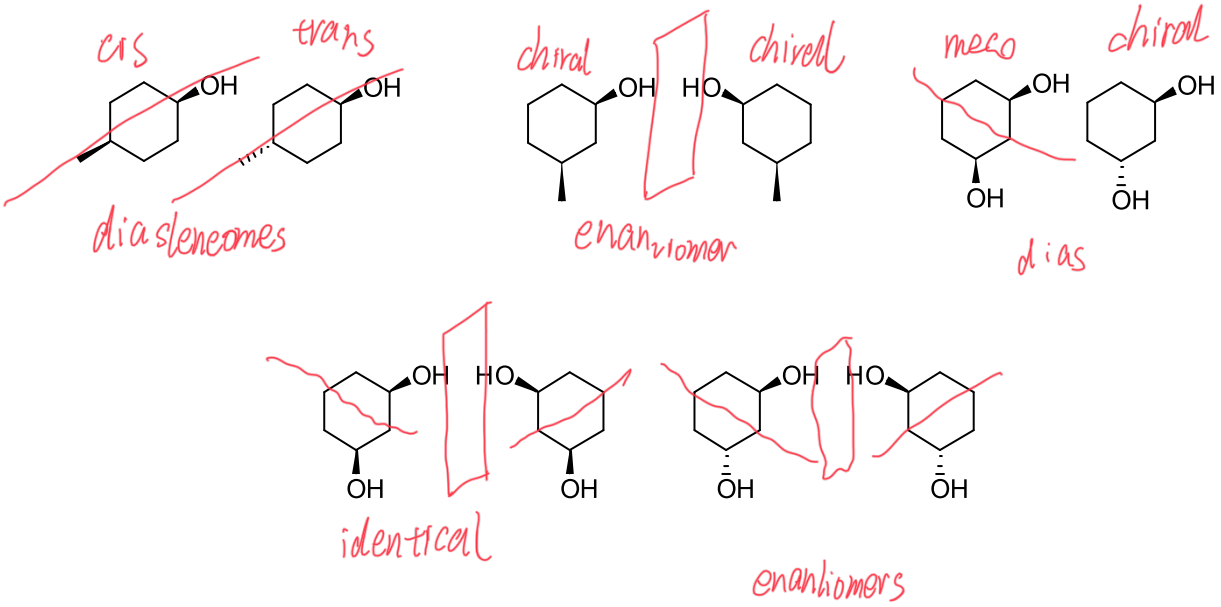
Example: Tartaric acid only has three diastereomers.



mp / °C	170	205 (racemate)	170	140
$[\alpha]_D^{20}$	−12°	0°	+12°	0°

Why is R,S-tartaric acid not optically active?

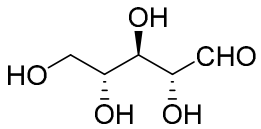
Exercise: Which molecules are chiral? Which are meso-structures?
What is the relationship between each pair of molecules?



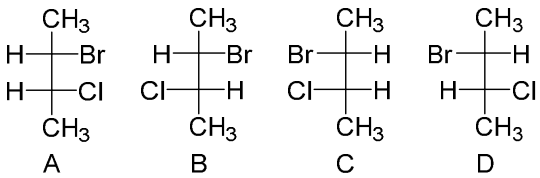
6.8 Fischer Projections

Often used in Biochemistry, e.g. representation of sugars.

Example: (D)-ribose



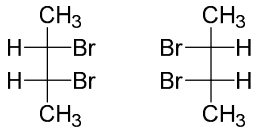
- 2-bromo-3-chlorobutane has 2 stereogenic centers and exists as 4 different stereoisomers:
-



What is the relationship between these stereoisomers?
A+B dia
A+C en
A+D dia
B+C dia
B+D en
C+D dia

2,3-dibromobutane only has 3 stereoisomers:

Meso Compounds are easily identified in Fischer projections:



Meso compounds:
- Contain 2 or more stereocenters and a plane of symmetry
- Because of the plane of symmetry, they are identical and achiral.
- Are optically inactive.

6.9 Revision of Definitions

Isomers: different compounds with the same molecular formula.

Constitutional Isomers: isomers with different order of attachment (connectivity).

Conformers: same connectivity and are interconvertible by rotation about single bonds.

Stereoisomers: isomers with same order of attachment but different 3-D orientations of atoms in space.

Chiral: mirror image not superimposable on itself.

Achiral: molecule and mirror image are identical.

Enantiomers: mirror images; have opposite configuration at all stereocenters.

Diastereomers: stereoisomers but not mirror images; have same configuration at 1 or more stereocenters, but differ at remaining stereocenters.

Meso compound: mirror images (with at least 2 stereocenters) that are identical due to a plane of symmetry (mirror plane).

Racemic mixture: 1:1 mixture of enantiomers.