Properties of Enantiomers

Achiral Properties

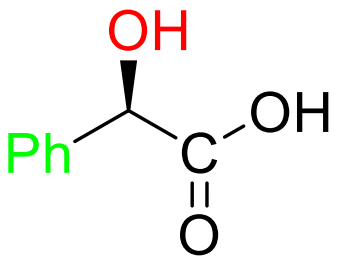
Any pair of enantiomers are physically and chemically indistinguishable by most techniques in achiral environments.

Enantiomers have identical achiral properties such as:

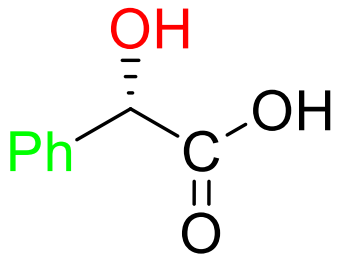
- melting point,
- boiling point,
- density,
- solubility in water,
- spectroscopic properties (NMR, IR, UV)
- same rate of reaction with achiral reagents

Properties of Enantiomers

Achiral Properties of Mandelic Acid



(R)



(S)

133°C	Melting Point	133°C
15 g per 100 mL	Solubility in water	15 g per 100 mL
1.3 g/cm^3	Density	1.3 g/cm^3

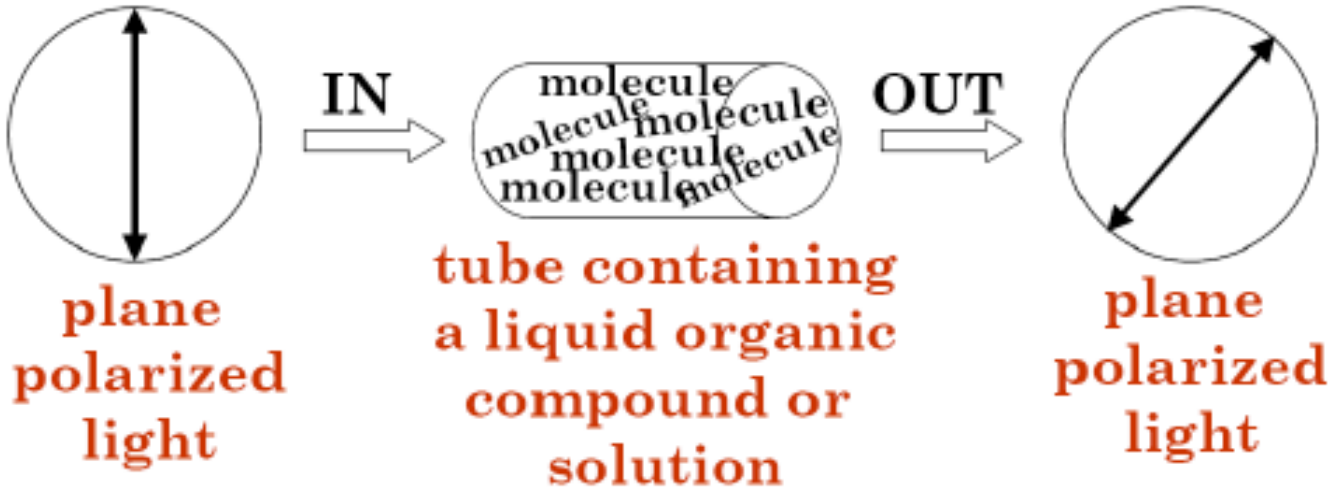
Mandelic acid is isolated from sweet and bitter almonds

Enantiomers

Chiral Properties: Optical Activity

Chiral molecules rotate plane-polarised monochromatic light either clockwise or counterclockwise. This phenomenon is called optical activity.

This property is inherent in the interaction between light and the individual molecules through which it passes.

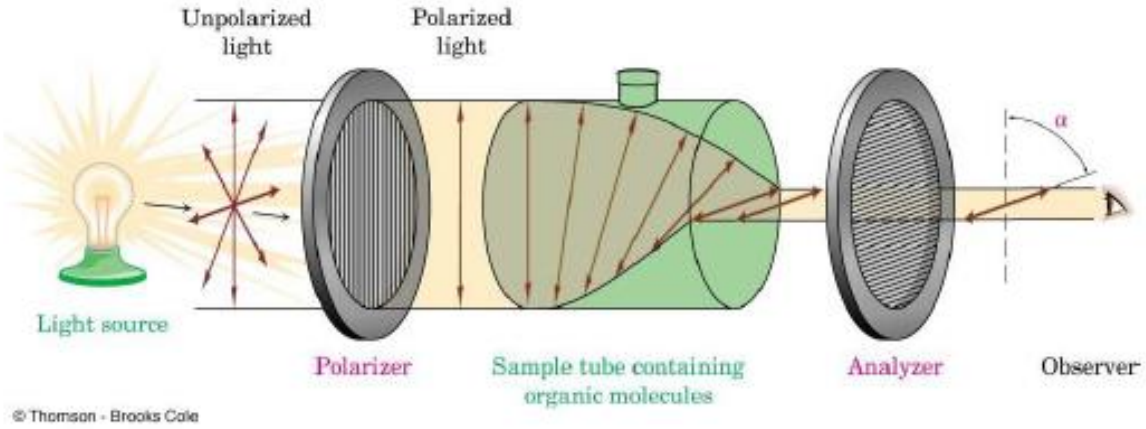


Chiral molecules are thus optically active.

Enantiomers

Measurement of Optical Activity: Optical Rotation

The optical activity of a substrate is usually assessed as the optical rotation in degrees. The degree of rotation of plane-polarized light is measured using a *polarimeter.*



The source light passes through a *polarizer* and then is detected at an analyzer.

The angle between the entrance and exit planes is the optical rotation, α.

Enantiomers

Measurement of Optical Rotation

Optical rotation α is measured in degrees.

A clockwise rotation is called **dextrorotatory or (+)**, while a counterclockwise rotation is **levorotatory or (-)**.

The optical rotation α is not very useful for direct comparative purposes since it depends on the path length the light traverses, the concentration of the analyte, the analyte itself and the wavelength of the light.

The more useful property is the specific rotation $[\alpha]_D$ that is standardized for concentration and path length.

Enantiomers

Calculation of Specific Rotation

Specific rotation [α] is a standardized physical constant for the degree that a solution rotates plane-polarized light.

$$\text{specific rotation} = [\alpha] = \frac{\alpha}{l \times c}$$

α = observed rotation (°)
l = length of sample tube (dm)
c = concentration (g/mL)

[dm = decimeter
1 dm = 10 cm]

Specific rotation is the optical rotation observed for 1 g/mL of an analyte in solution in a cell of 10 cm (1 dm) path length using light of the sodium D line of wavelength 589 nm.

The temperature is maintained at 25 °C

Enantiomers

Sample Calculation of Specific Rotation

The optical rotation of a solution of 0.497 g of valine dissolved in 5 ml of ethanol measured in a cell of path length 2 decimeter is +6.58°.

Calculate the specific rotation, $[\alpha]_D$, of the amino acid valine .

Remember to include its sign (+ or -).

Specific Rotation = Observed Rotation / (conc,g/ml) x (length of sample tube, decimeters)

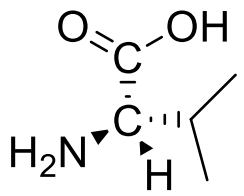
0.497g / 5 mL = 0.0994 g/mL

+6.58 / (0.0994 g/mL x 2 dm) = +33.1°

Enantiomers

Stereochemical Terminology vs Optical Activity

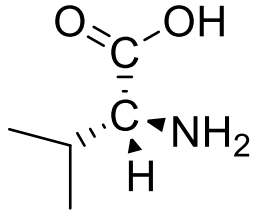
Dextrorotatory: an optically active compound that rotates plane polarized light in a clockwise direction. Usually represented with **(+)** or (***d***) (lower case).



S-(+)-Valine

[α] = +27.5° (6M HCl)

L-(+)-Valine



R-(-)-Valine

[α] = -27.5° (6M HCl)

D-(-)-Valine

Levorotatory: an optically active compound that rotates plane polarized light in a counterclockwise direction. Usually represented with **(-)** or (***l***) (lower case).

Enantiomers

Stereochemical Terminology vs Optical Activity

D/L vs d/l Notations

The D/L notation is unrelated to (+)/(−) or d/l; it does not indicate which enantiomer is dextrorotatory and which is levorotatory.

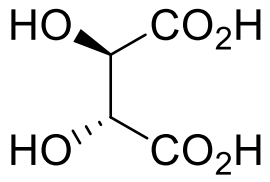
$[\alpha] = +27.5^{o}$ (6M HCl)	$[\alpha] = -27.5^{o}$ (6M HCl)
L-(+)-Valine	D-(-)-Valine
L-(d)-Valine	D-(l)-Valine

The D/L notation simply indicates that a compound's stereochemistry is related to either the dextrorotatory or levorotatory enantiomer of glyceraldehyde. It is just mere coincidence that the D-stereoisomer of glyceraldehyde is dextrorotatory.

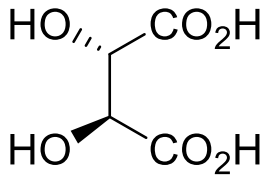
Enantiomers

Stereochemical Terminology vs Optical Activity

Enantiomerically pure or enantiopure: A substance or system comprising of exclusively one enantiomer.



or



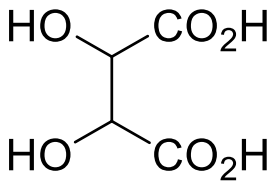
Dextrorotatory

+12.7°

Levorotatory

-12.7°

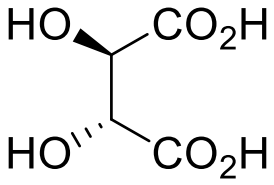
Racemic mixture: A substance or system comprising of an equal mixture of enantiomers.



Racemic Tartaric Acid

Specific rotation = 0°

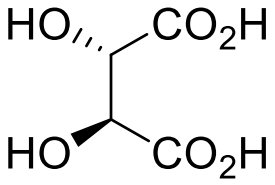
=



Dextrorotatory

(50%)

+



Levorotatory

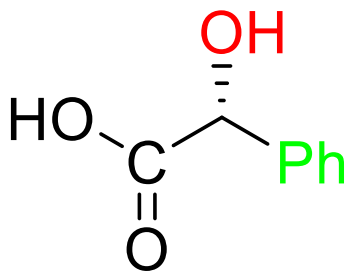
(50%)

Enantiomers

Chiral Properties: Optical Activity

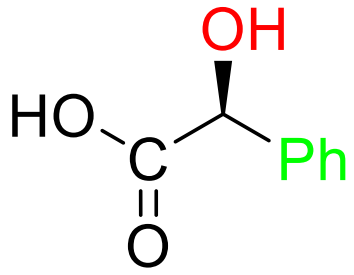
Enantiomers differ only in the properties that are chiral:

- direction of rotation of plane polarized light,
- their rate of reaction with chiral reagents,
- biological activity and taste.



(R)

Mandelic Acid



(S)

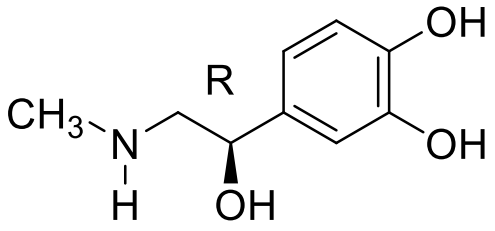
-154° Specific Rotation +154°

Isolated from Sweet and Bitter almonds

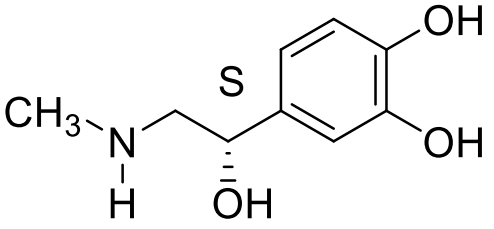
Enantiomers

Chiral Properties: Optical Activity and Aroma

Enantiomers of Adrenaline (Epinephrine)

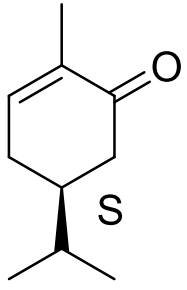


[α] = +53.3°



[α] = -53.3°

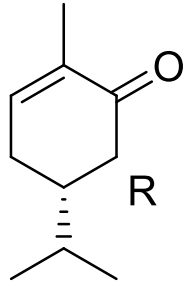
Enantiomers of Carvone



(+)-Carvone

Caraway aroma

[α] = +62.5°



(-)-Carvone

Spearmint aroma

[α] = -62.5°

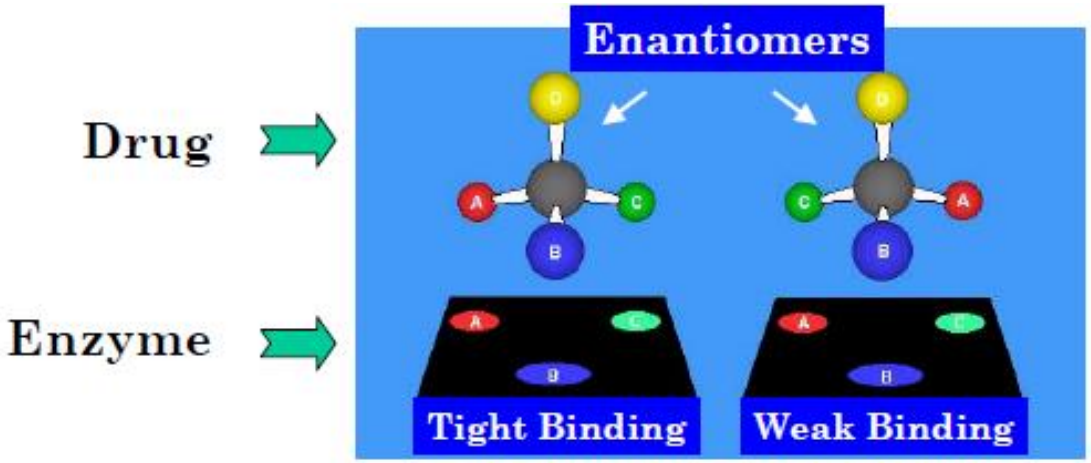
Enantiomers

Chiral Properties: Biological Activity

Differences in biological activity are based on the recognition that biological receptors are chiral and biochemical reactions or interactions are **stereospecific**.

Receptors on cells interact favorably with molecules with specific spatial arrangements. Other configurations of the same molecule may be less favorable or be toxic.

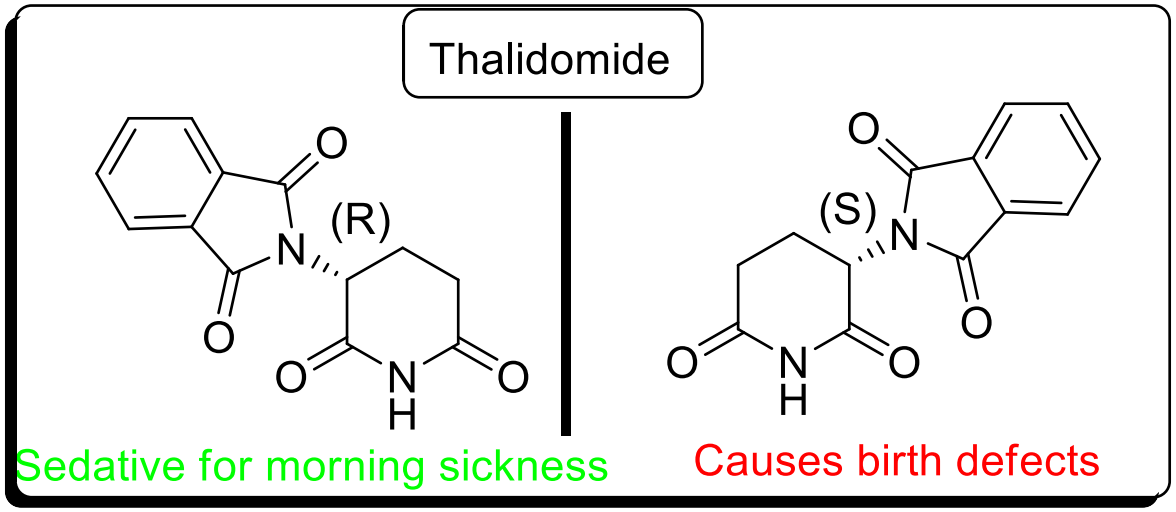
Enantiomers interact with a receptor as depicted below.



Enantiomers

Biological Activity: The Tragic Case of Thalidomide

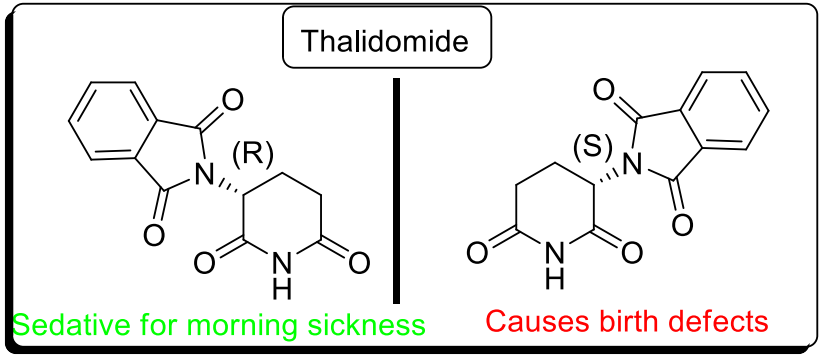
Thalidomide was once hailed as a "wonder drug" that provided a "safe, sound sleep". It was considered an effective sedative for pregnant women to combat many of the symptoms associated with morning sickness.



However, thalidomide later became notorious as the killer and disabler of thousands of babies.

Enantiomers

Biological Activity: The Tragic Case of Thalidomide



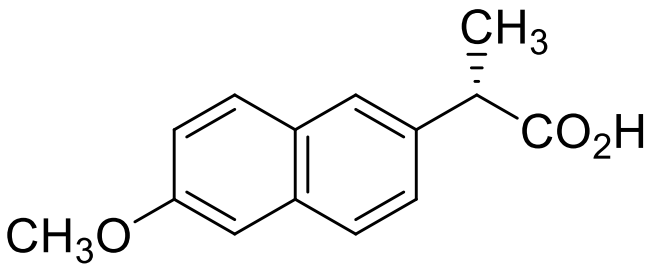
*T*he R-enantiomer fits the active site of a specific enzyme (like a “key” for a specific “lock”) producing the desired sedative effect.

The S-enantiomer cannot interact with the same site due to the different arrangement in space (3D shape) at the chiral centre. Instead, it fits the active pocket of a different enzyme triggering a different biological effect (toxic).

Enantiomers

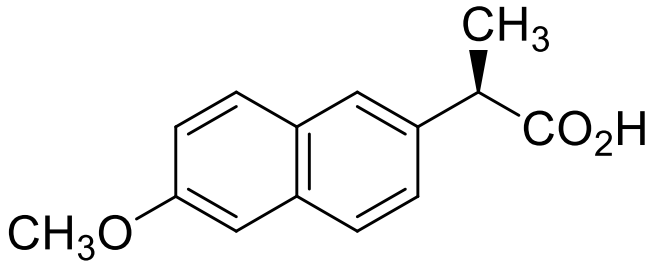
Chiral Properties: Chemotherapy

- Many drugs are chiral and interact with a chiral receptor or enzyme to elicit its efficacy. One enantiomer of a drug may effectively treat a disease *w*hereas its antipode may be ineffective or toxic.



(S)-Naproxen

Anti-inflammatory



(R)-Naproxen

Liver toxin

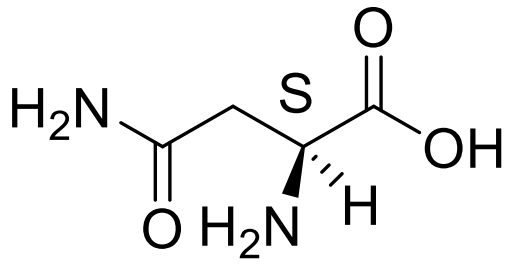
- As a regulatory requirement, for safe application, the (S)-Naproxen should be in excess of 97% pure.

Enantiomers

Chiral Properties: Taste

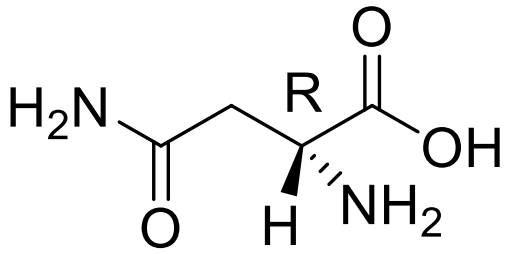
Although there are individual variations between enantiomers, there are now well-recognized taste differences between enantiomers of many compounds.

For example, D-asparagine has a sweet taste, while the natural L-asparagine is tasteless.



Natural

Tasteless



Asparagine

Unnatural

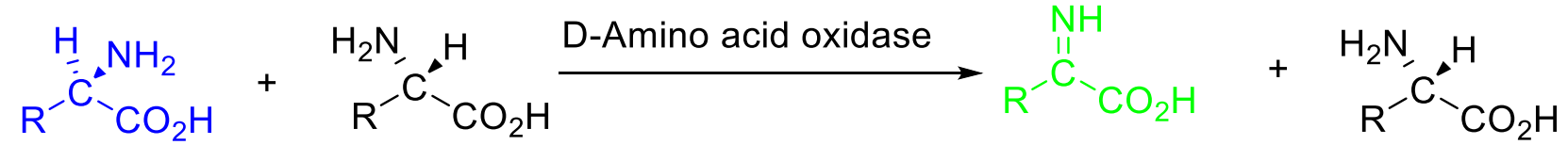
Sweet

Enantiomers

Chiral Properties: Kinetics of Enantiomers

Enantiomers react at different rates with chiral reagents. Enzymes being chiral, the enzyme D-amino acid oxidase catalyzes only the reaction of the R-enantiomer (D-amino acid) and leaves the S-enantiomer (L-amino acid) unchanged.

The enzyme typically binds only one enantiomer since as expected “only the right hand fits the right-hand glove”.



R-Enantiomer S-Enantiomer Oxidized R-Enantiomer S-Enantiomer

Molecular Structure Relationships

The Roadmap

After the enantiomers, the next set of stereoisomers to discus are the diastereomers. Refer to the family tree below as a reminder of these relationships.