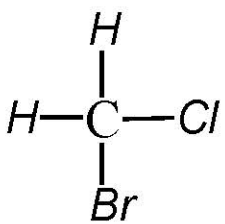
Stereochemistry: an introduction

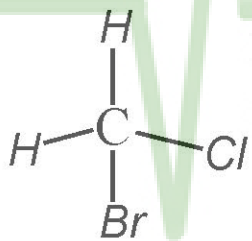
Stereochemistry of Tetrahedral Carbons

We need:

- ***one Carbon sp^3-hybridized, at least***
- ***to represent molecules as 3D objects***

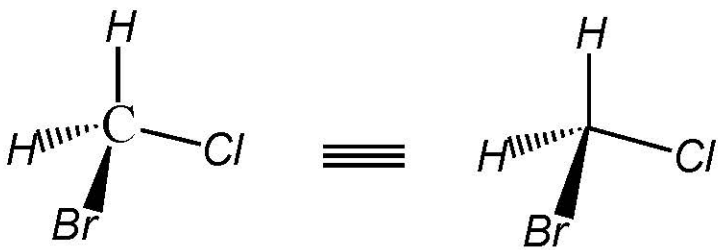
For example:





2D drawing

Not appropriate for Stereochem

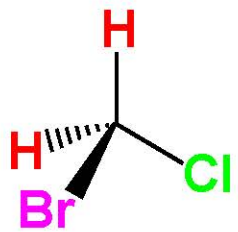


3D drawing

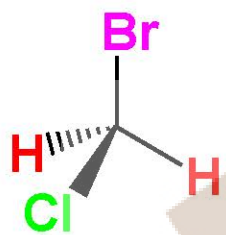
Appropriate for Stereochem

Let's consider some molecules……

First pair



A

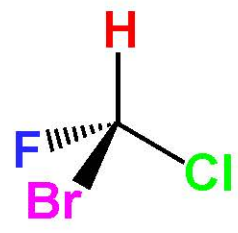


B

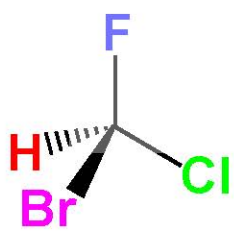
- same molecular formula (CH_2BrCl)
- same atom connectivity
- superposable

⇒ **identical (same compound)**

Second pair



C



D

- same molecular formula (CHFBrCl)
- same atom connectivity
- nonsuperposable

⇒ **stereoisomers**
(two different compounds)

Thus, we can define……

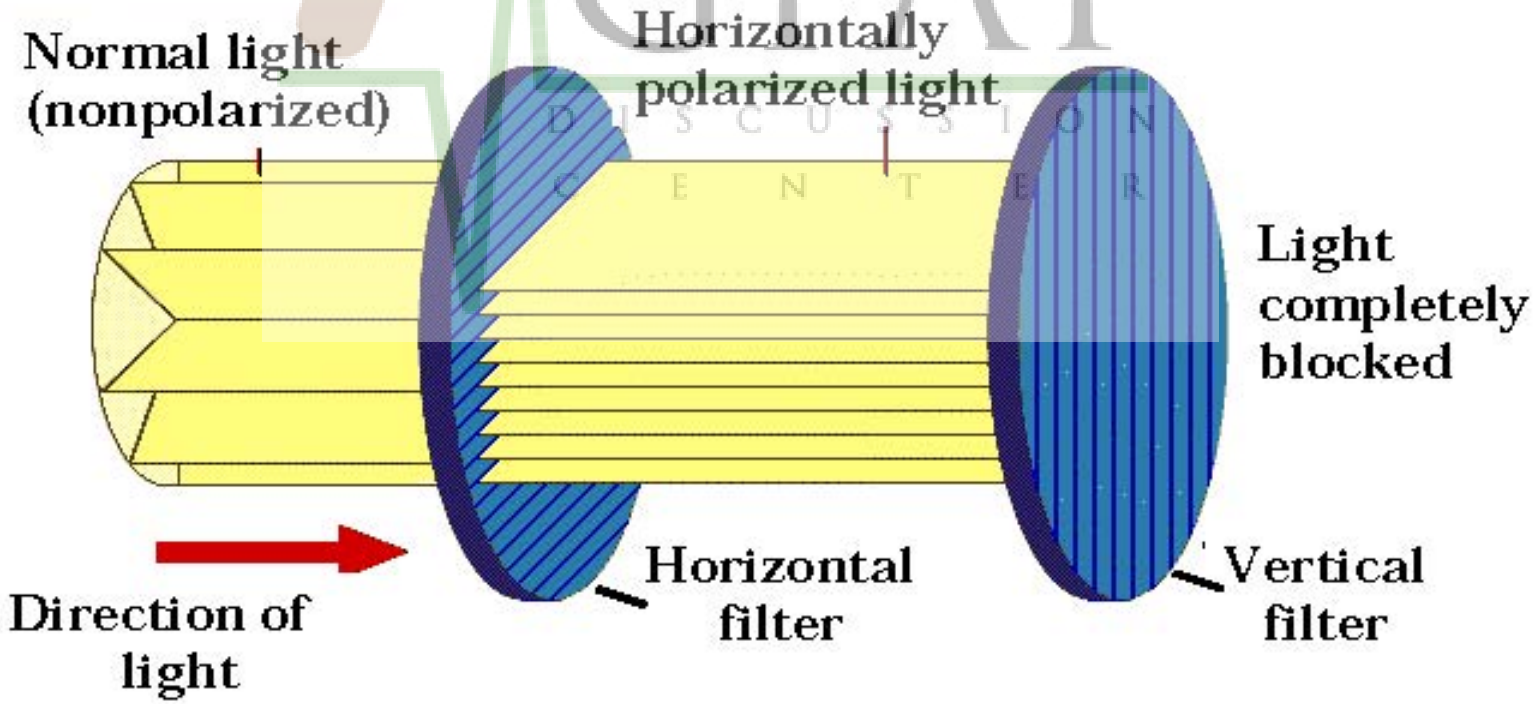
- ***Stereoisomers**: isomers that have same formula and connectivity <u>but</u> differ in the position of the atoms in space*

- ***Stereochemistry**: chemistry that studies the properties of stereoisomers*

Historical perspective

Christiaan Huygens

(1629-1695). Dutch astronomer, mathematician, and physicist. He discovers plane polarized light:

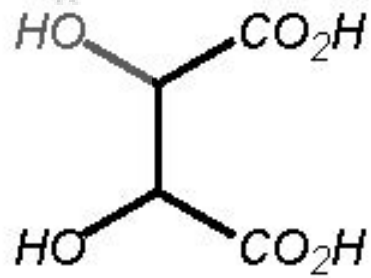


Historical perspective

Carl Wilhelm Scheele (1742-1786)

"Oh, how happy I am! No care for eating or drinking or dwelling, no care for my pharmaceutical business, for this is mere play to me. But to watch new phenomena this is all my care, and how glad is the enquirer when discovery rewards his diligence; then his heart rejoices"

In 1769, he discovers Tartaric Acid from tartar (the potassium salt of tartaric acid, deposited on barrels and corks during fermentation of grape juice).

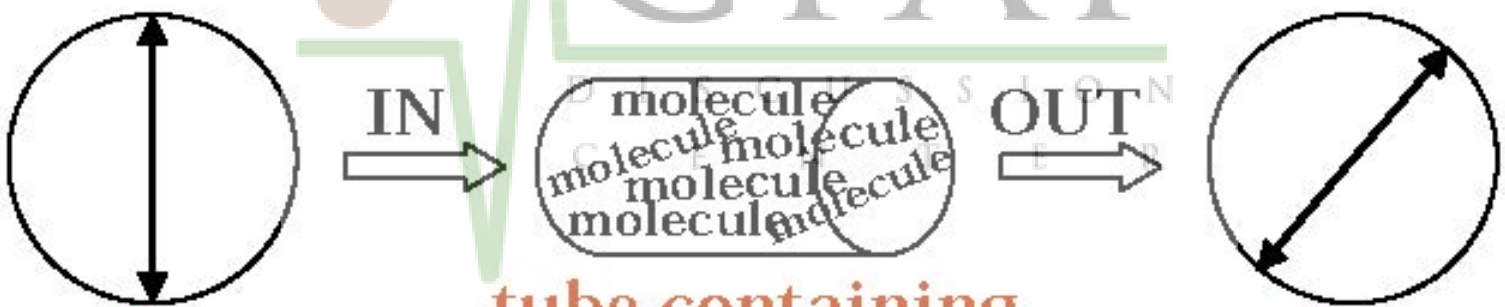


Tartaric Acid

Historical perspective

Jean Baptiste Biot (1774-1862)

In 1815, he notes that certain natural organic compounds (liquids or solutions) rotate plane polarized light (Optical Activity).



plane polarized light

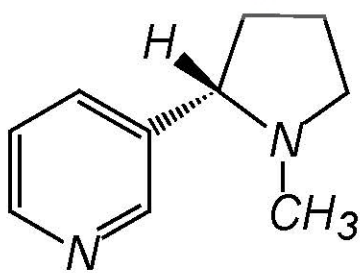
tube containing a liquid organic compound or solution

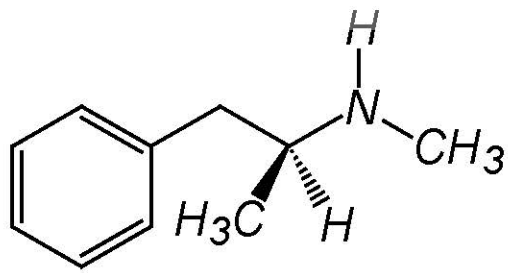
plane polarized light

Definitions

- ***Optically Active**: the ability of some compounds to rotate plane polarized light.*
- ***Dextrorotatory (+)**: an optically active compound that rotates plane polarized light in a clockwise direction.*
- ***Levorotatory (-)**: an optically active compound that rotates plane polarized light in a counterclockwise direction.*

(-)-Nicotine

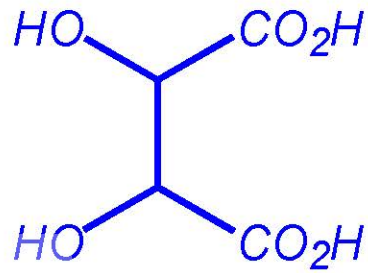




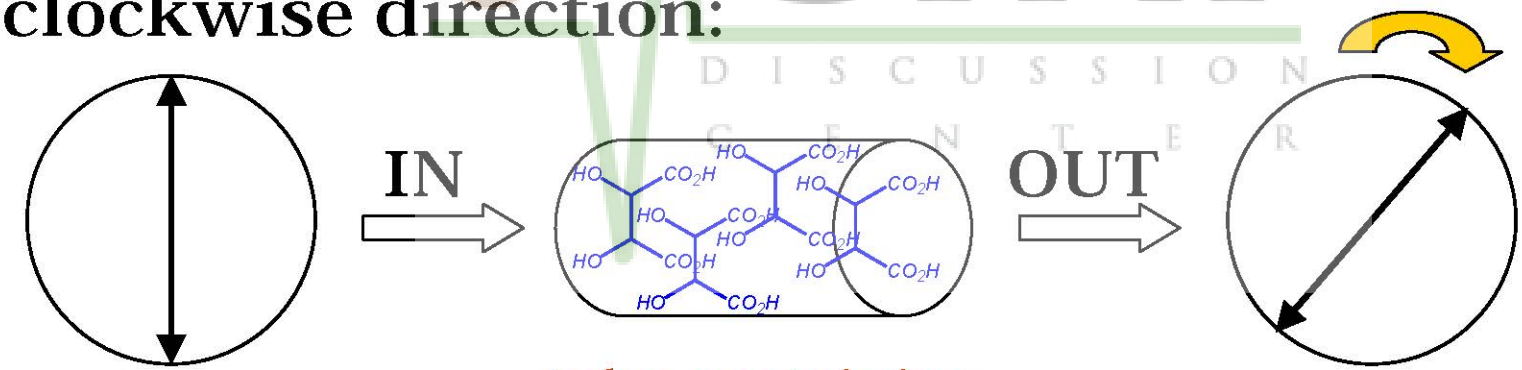
(+)-Methamphetamine

Historical perspective

In 1819, Racemic Acid was discovered. Later shown to have the same formula as Tartaric Acid.



In 1832, Biot notes that Tartaric Acid from grape juice fermentation rotates plane polarized light in a clockwise direction:



plane polarized light

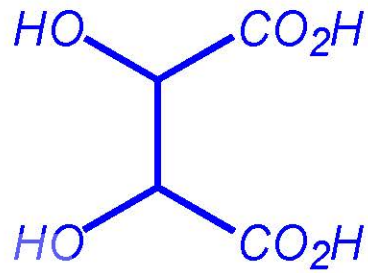
tube containing solution of Tartaric Acid (TA)

plane polarized light, rotated clockwise

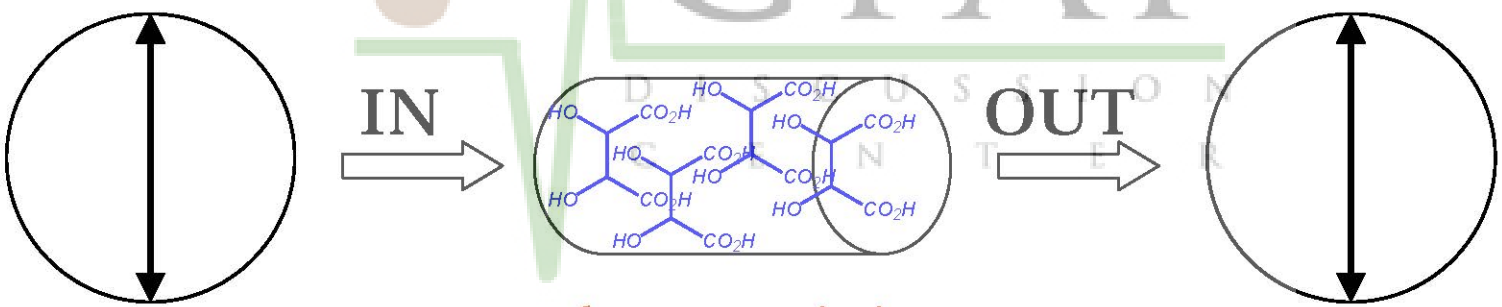
TA is dextrorotatory

Historical perspective

In 1819, Racemic Acid was discovered. Later shown to have the same formula as Tartaric Acid.



In 1838, Biot notes that Racemic Acid does not rotate plane polarized light:



plane polarized light

tube containing solution of Racemic Acid (RA)

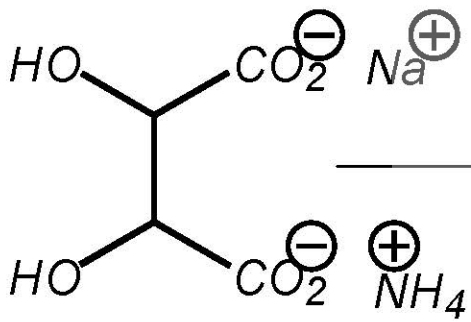
plane polarized light, unchanged

RA is not optically active

Historical perspective

Louis Pasteur (1822-1895)

In 1847, he repeats earlier work on Racemic Acid. Crystallization of sodium ammonium salt gives mirror image crystals that he separated by hand. Equimolar solutions of separated crystals have equal but opposite optical activity:



Racemic acid salt

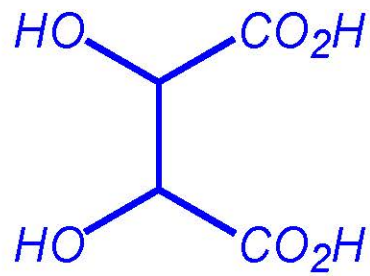
separate crystals

$[\alpha]_D$= +12.7° (+)-Tartaric Acid (dextrorotatory, natural)

$[\alpha]_D$= -12.7° (-)-Tartaric Acid (levorotatory, unnatural)

Historical perspective

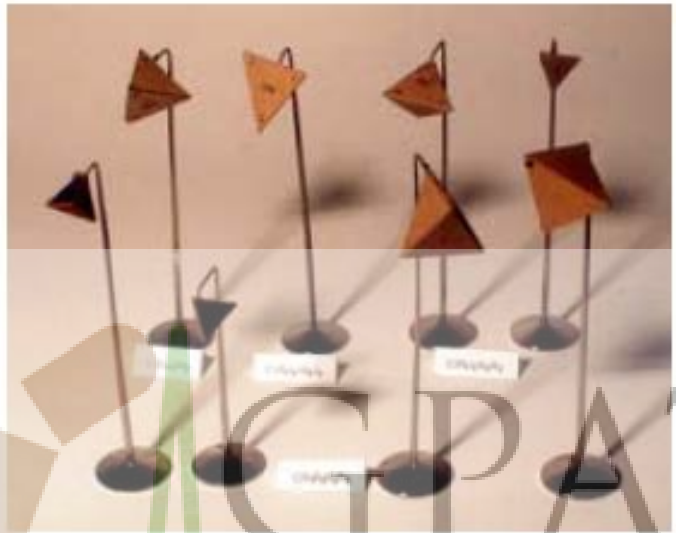
In 1853, Pasteur studies Mesotartaric Acid (same formula as Racemic and Tartaric Acid) but fails to separate into (+) and (-) crystals.



In 1854, he notes that certain plant mold metabolizes (+)-tartaric acid but not (-)-tartaric acid.

Historical perspective

Joseph A. LeBel (1847-1930)



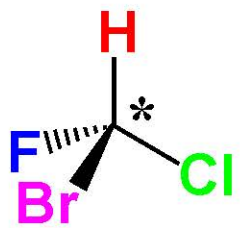
Jacobus H. van't Hoff (1852-1930)

In 1874, they propose:

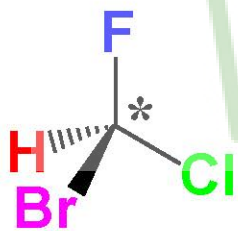
- Carbon with 4 attachments is Tetrahedral.
- A molecule having a tetrahedral carbon with 4 <u>different</u> attachments may exist as a pair of isomers.

Therefore…..

- ***Stereoisomers**: isomers that differ only in the position of atoms in space, and that <u>cannot</u> be interconverted by rotation around a single bond.*
- ***Stereocenter**: a carbon atom bearing 4 different atoms or group of atoms.*



C

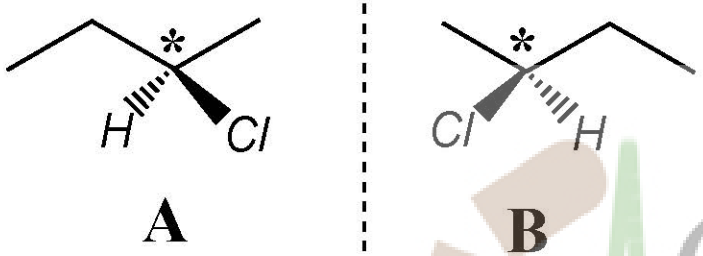


D

C,D are a pair of stereoisomers
Carbon * is a stereocenter

…..another example

Stereoisomers of 2-chlorobutane



A,B are stereoisomers

Carbons * are stereocenters

A,B are nonsuperposable mirror images

Enantiomers

Enantiomers: stereoisomers that are nonsuperposable mirror images.

Chiral: any molecule that is nonsuperposable with its mirror image (i.e. A and B are chiral).

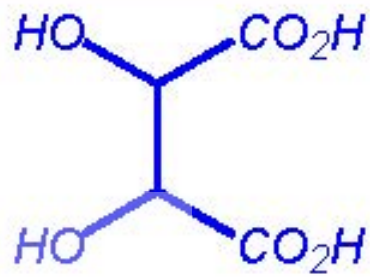
Achiral: any molecule that is not chiral.

Racemic mixture: a 1:1 (equimolar) mixture of two enantiomers.

Unsolved Issues

Joseph A. LeBel
(1847-1930)

Jacobus H. van't Hoff
(1852-1930)



Mesotartaric Acid
could not be separated into (+) crystals and (-) crystals

- Carbon with 4 attachments is Tetrahedral.
- A molecule having a tetrahedral carbon with 4 <u>different</u> attachments may exist as a pair of isomers.

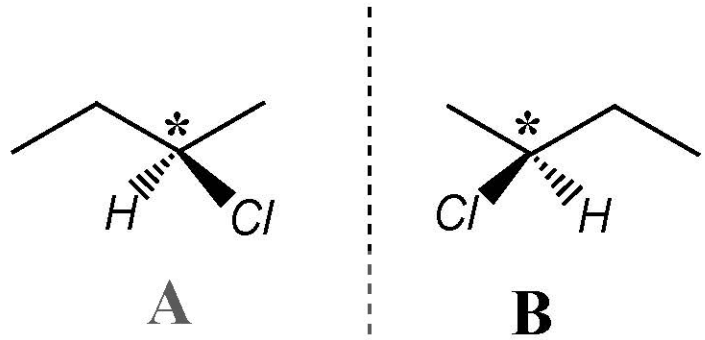
In 1877, Hermann Kolbe, one of the best organic chemist of the time wrote:

"Not long ago, I expressed the view that the lack of general education and of through training in chemistry was one of the reasons of the causes of the deterioration of chemical research in Germany.....Will anyone to whom my worries seem exaggerated please read, if he can, a recent memoir by a Herr van't Hoff on "The Arrangement of Atoms in Space", a document crammed to the hilt with the outpouring of childish fantasy...This Dr. J. H. van't Hoff, employed by the Veterinary College at Utrecht, has, so it seems, no taste for accurate chemical research. He finds it more convenient to mount his Pegasus (evidently taken from the stables of the Veterinary College) and to announce how, on his bold flight to Mount Parnassus, he saw the atoms arranged in in space."

In 1901 van't Hoff received the first Nobel Prize in Chemistry.

Take-home problem

Stereoisomers of 2-chlorobutane



Enantiomers

- ***Remember:***

  Enantiomers: stereoisomers that are nonsuperposable mirror images.

  Racemic mixture: a 1:1 (equimolar) mixture of two enantiomers.

- ***Explain why:***

  - **A and B cannot be physically separated.**
  - **a racemic mixture of A and B has no optical activity (no rotation of plane polarized light).**

Summary

***Stereoisomers**: isomers that have same formula and connectivity <u>but</u> differ in the position of the atoms in space. They possess one or more stereocenters.*

***Stereocenter**: a carbon atom bearing 4 different atoms or group of atoms.*

***Chiral**: any molecule that is nonsuperposable with its mirror image.*

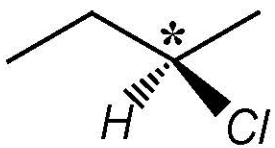
***Enantiomers**: stereoisomers that are non superposable mirror images.*

***Racemic mixture**: a 1:1 (equimolar) mixture of two enantiomers.*

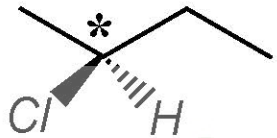
***Optically Active**: the ability of some compounds to rotate plane polarized light.*

Configuration of Stereocenters

Enantiomers of 2-chlorobutane:



A

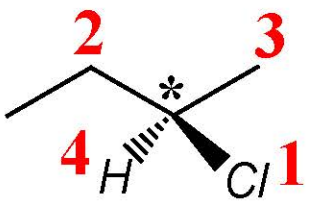


B

The Cahn-Ingold-Prelog (CIP) rule assigns R or S configuration to the two enantiomers.

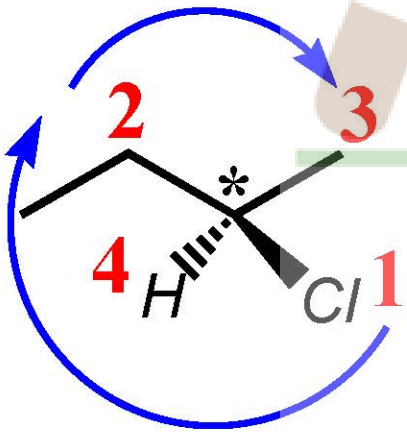
1) Assign the priorities to the groups attached to the stereocenter. Priority is based on the atomic number, i.e. H has lower priority than Cl.
But methyl and ethyl both are attached to the stereocenter through carbon! In these cases, priority assignments proceed outward, to the next atoms. The Methyl carbon has 3 Hs attached while the Ethyl carbon has 2Hs and and a carbon (the terminal methyl group). Therefore, the latter gets higher priority.

Configuration of Stereocenters



A

2) Orient the molecule so that the group of priority four (lowest priority) points away from the observer.

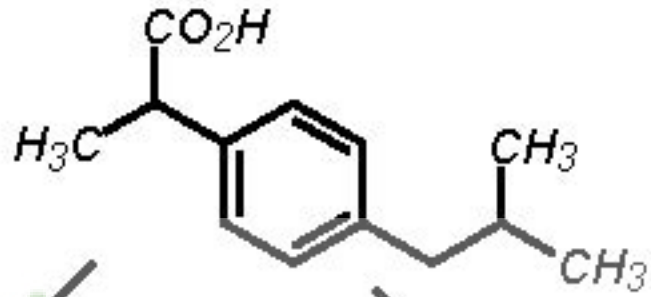


3) Draw a circular arrow from the group of first priority to the group of second priority.

4) If this circular motion is clockwise, the enantiomer is the R enantiomer. If it is counterclockwise, it is the S enantiomer. Thus, A is the R enantiomer of 2-chlorobutane.

Configuration of Stereocenters

Ibuprofen, an antiinflammatory agent

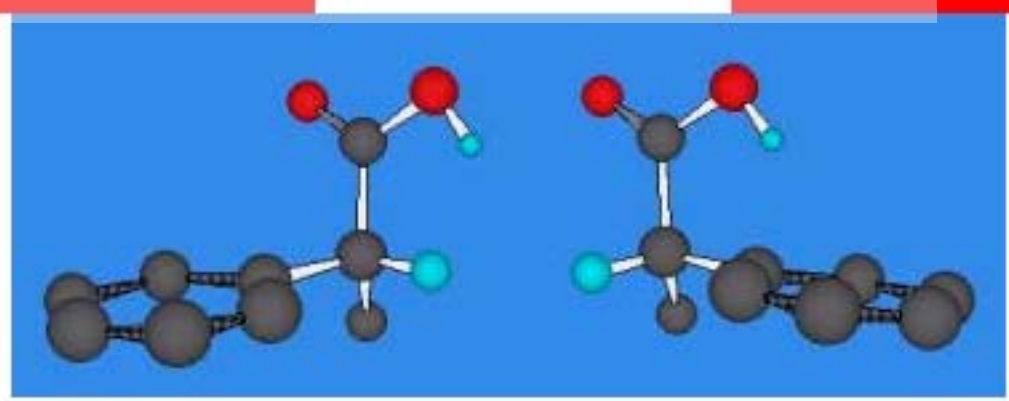


Not a Stereocenter!

Not a Stereocenter!

R enantiomer

S enantiomer

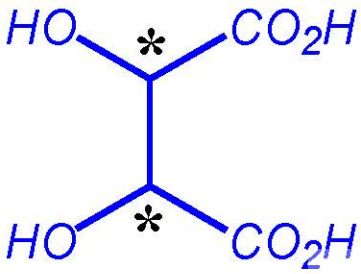


Molecules with multiple stereocenters

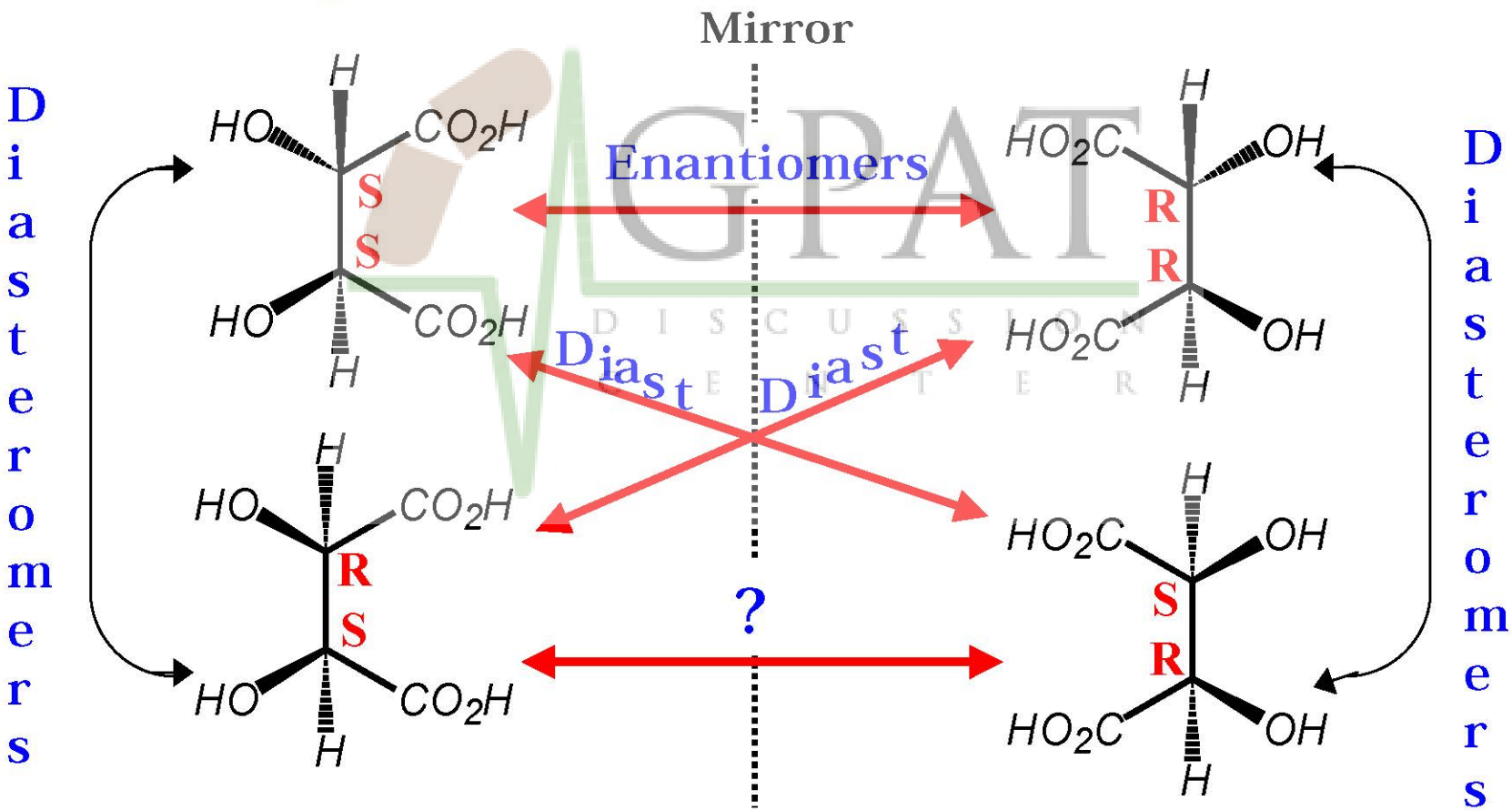
Molecules with 1 stereocenter can be R or S → 2 possible stereoisomers

Molecules with *n* stereocenters can have all the possible combinations of R and S for each stereocenter → 2^n possible stereoisomers

Tartaric Acid



2 stereocenters ⇒ **4 possible stereoisomers**

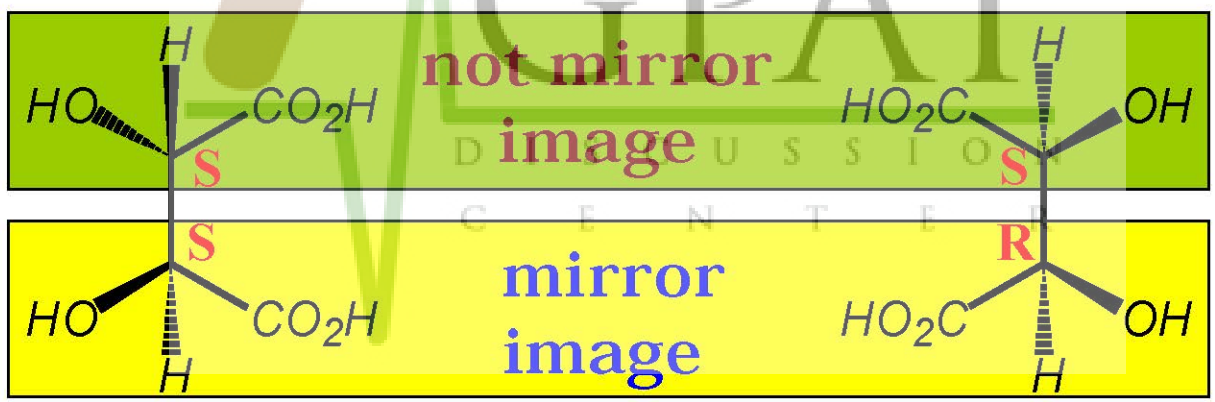


Remember

Enantiomers: stereoisomers that are non superposable mirror images.

Diastereomers: stereoisomers that are not mirror images.

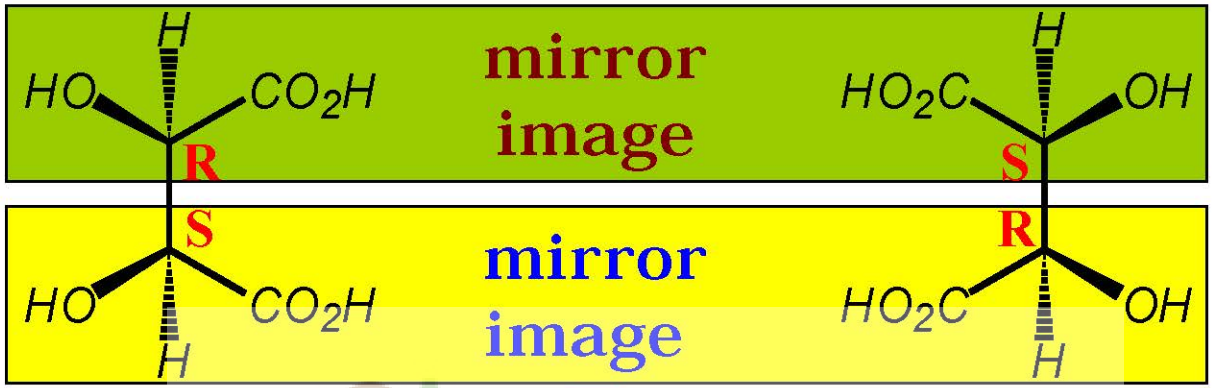
For example:



(S, S)-Tartaric acid

(S, R)-Tartaric acid

DIASTEREOMERS

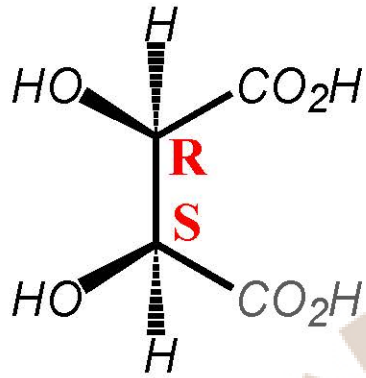


(R, S)-Tartaric acid ⇩ (S, R)-Tartaric acid

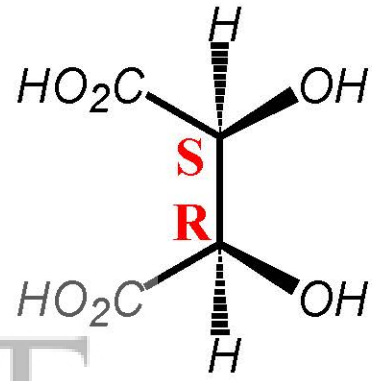
Enantiomers

?

Why not Enantiomers?



Same compound!!!!



Enantiomers:

√ same molecular formula

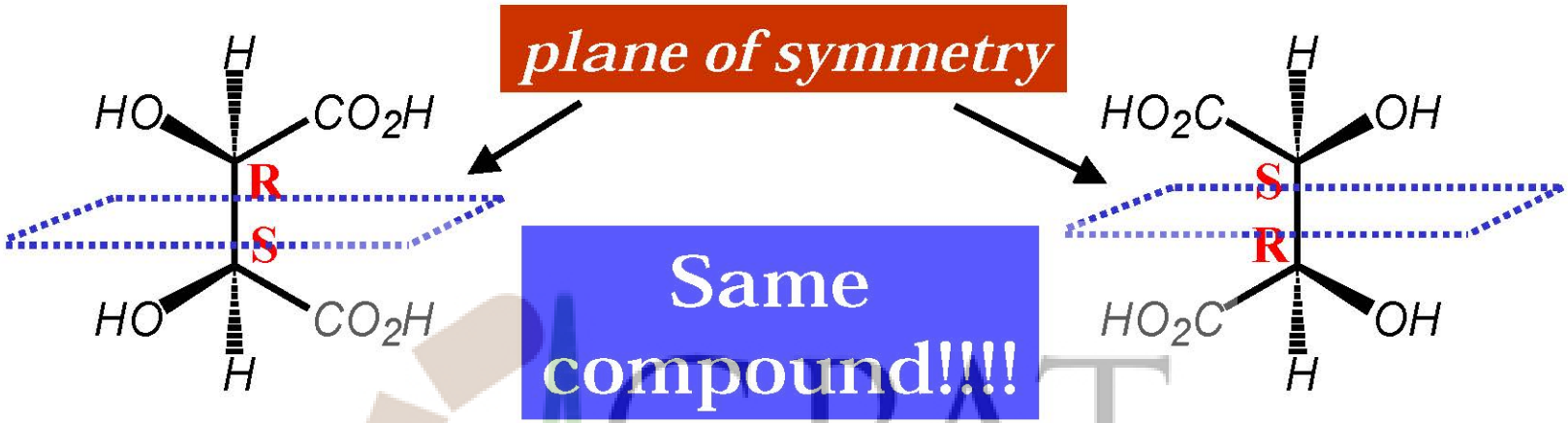
√ same connectivity

√ mirror images

X nonsuperposable ➡ Superposable

Achiral compound

Why not Enantiomers?



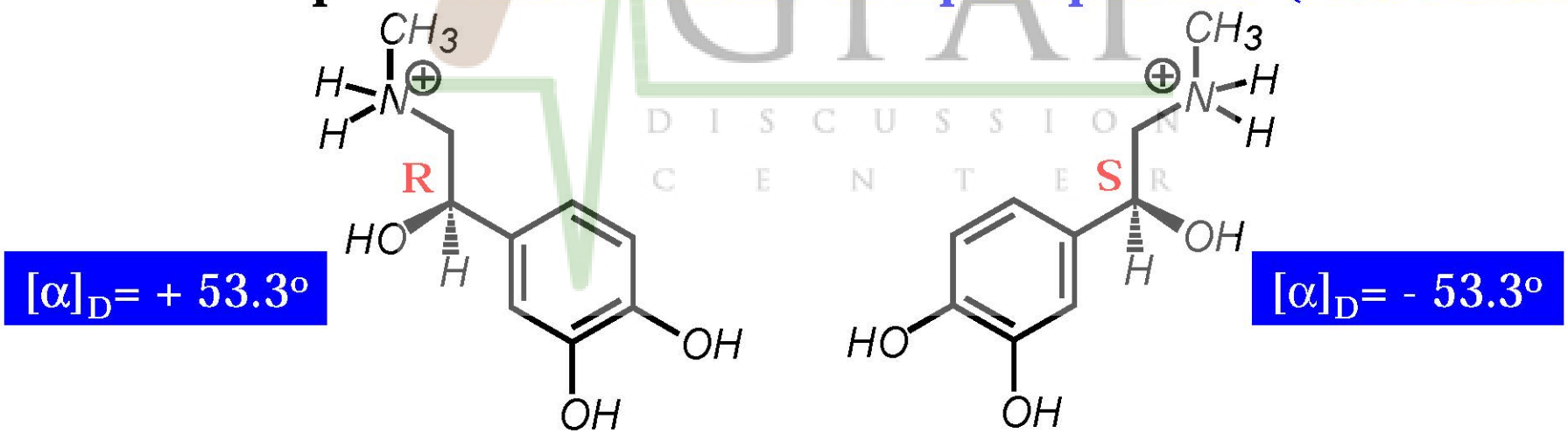
Meso compound

A compound with at least 2 stereocenters that is achiral due to the presence of a plane of symmetry

Properties of Stereoisomers

Enantiomers: have same chemical and physical properties in an **achiral** environment but they differ on the sign of rotation of plane polarized light.

For example: Enantiomers of Epinephrine (Adrenaline)



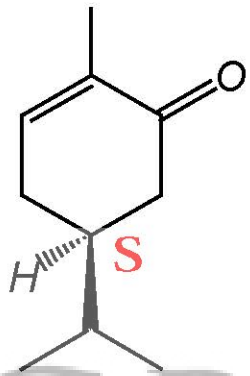
$[\alpha]_D$= + 53.3°

$[\alpha]_D$= - 53.3°

Same melting/boiling point, same rate of reaction with achiral reagents, same degree of rotation of plane polarized light……thus difficult to separate!

Properties of Stereoisomers

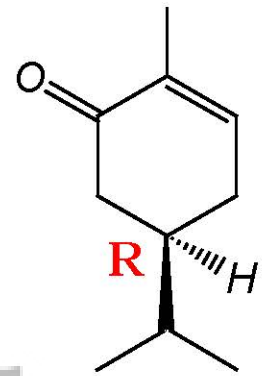
Carvone exists as a pair of enantiomers:



(+)-carvone

smells like caraway

$[\alpha]_D = +62.5$



(-)-carvone

smells like spearmint

$[\alpha]_D = -62.5$

Note:

- No relationship exists between the S/R configuration and the sign or the magnitude of rotation of plane polarized light.
- A 1:1 mixture of enantiomers (racemic mixture) has always no optical activity (rotation equal to zero) because the rotation of 50% of one enantiomer is cancelled out by the rotation (equal but opposite) of 50% of the other enantiomer.

Properties of Stereoisomers

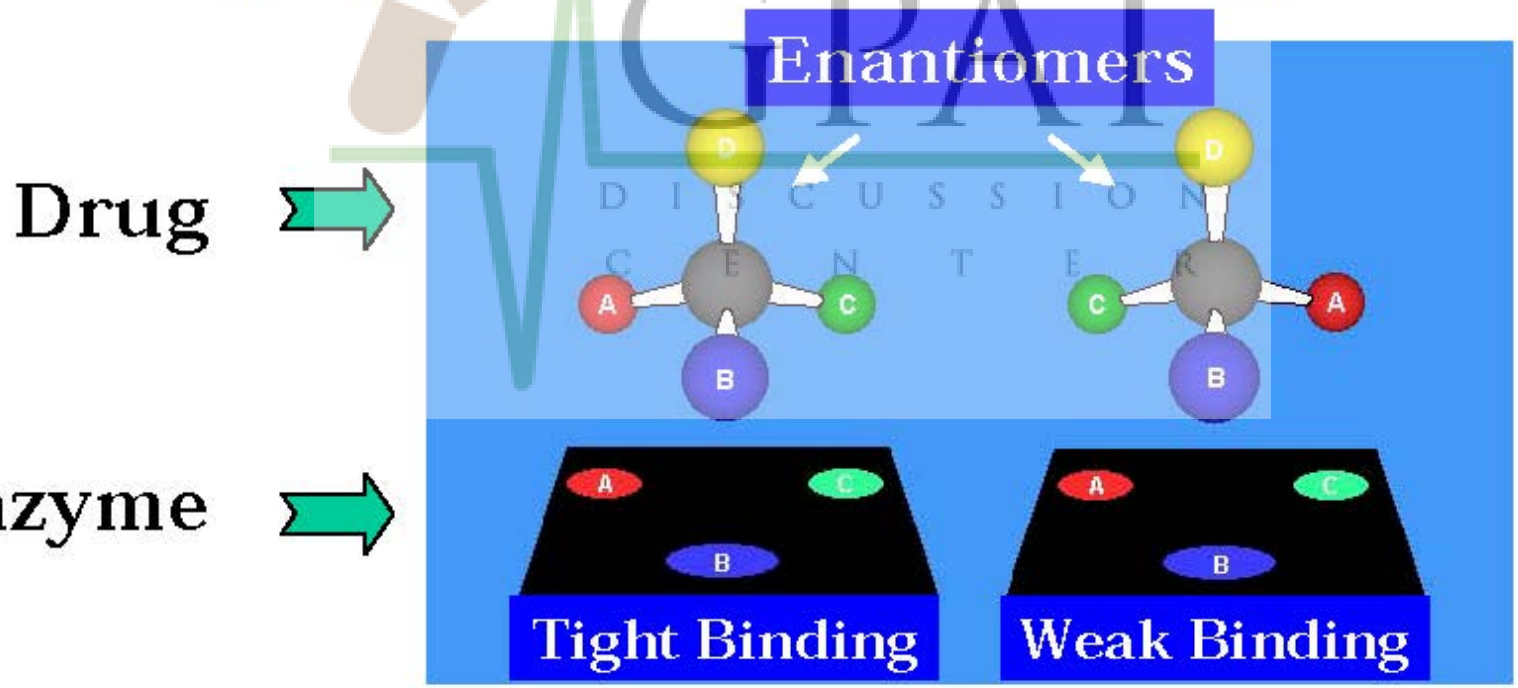
Diastereomers: have different chemical and physical properties in any type of environment.

(S,S)-Tartaric Acid Mesotartaric Acid

$[\alpha]_D$	- 12.7	0 (achiral)
Melting p. (°C)	171-174	146-148
Density (g/cm^3)	1.7598	1.660
Solubility in H_2O	139	125

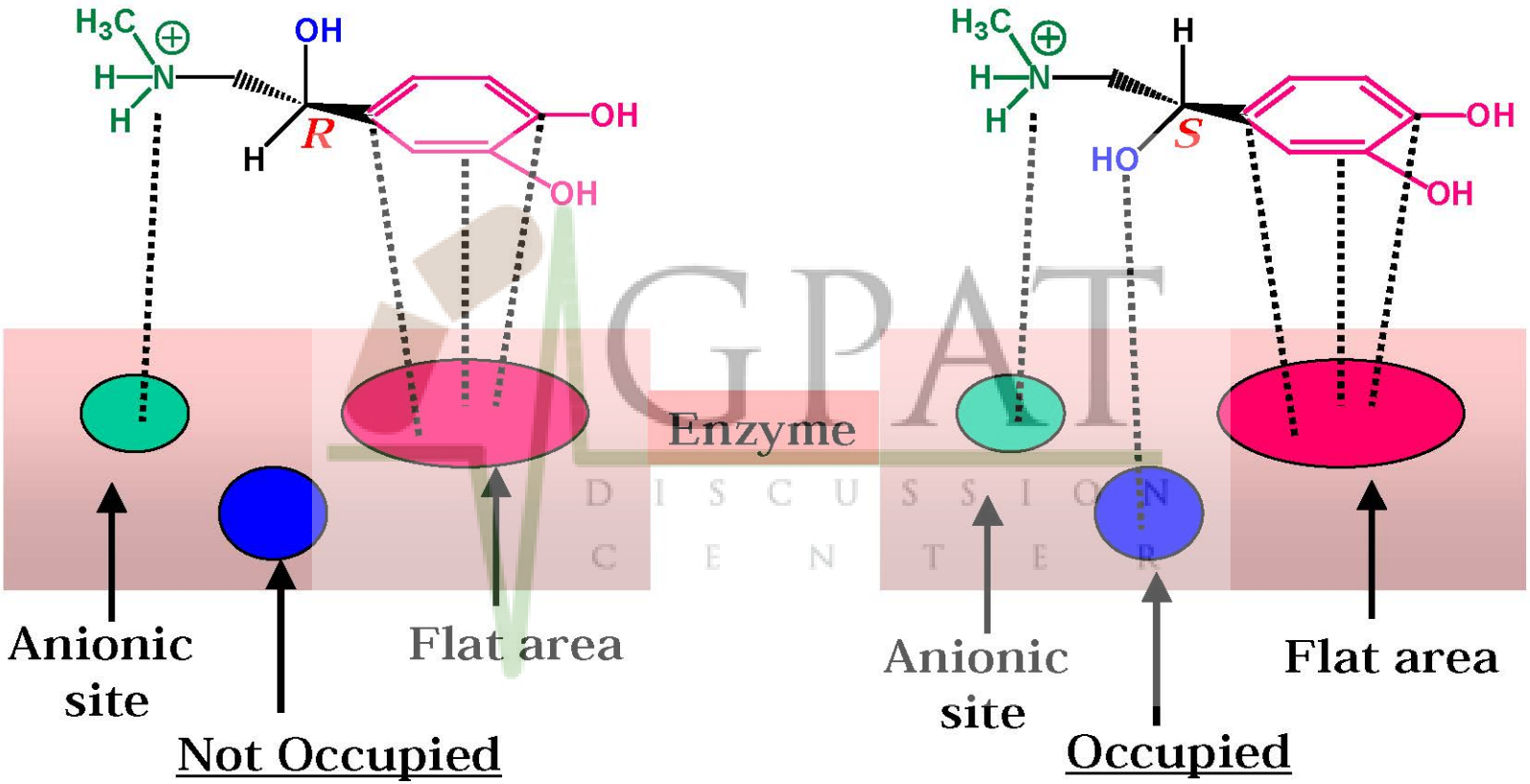
Biological Significance of Chirality

Since most of the natural (biological) environment consists of enantiomeric molecules (amino acids, nucleosides, carbohydrates and phospholipids are chiral molecules), then enantiomers will display different properties. Then, in our body:



Biological Significance of Chirality

Enantiomers of Epinephrine



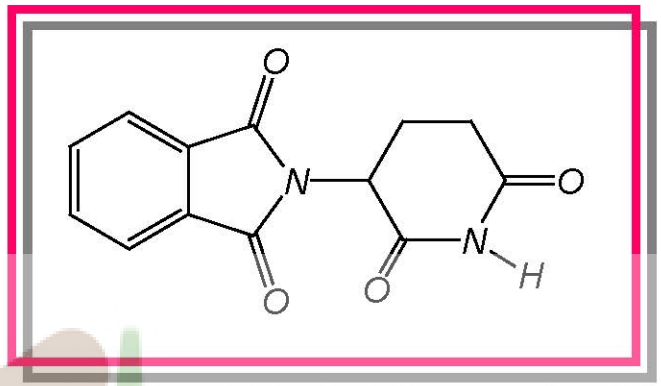
(+)-Epinephrine

Poorer Fit ⇨ Less Active

(-)-Epinephrine

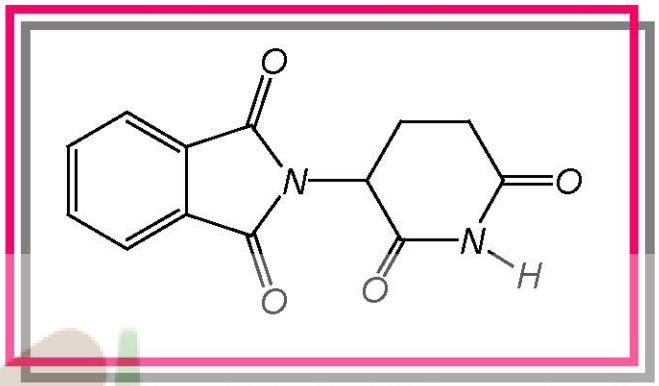
Better Fit ⇨ More Active

The case of Thalidomide



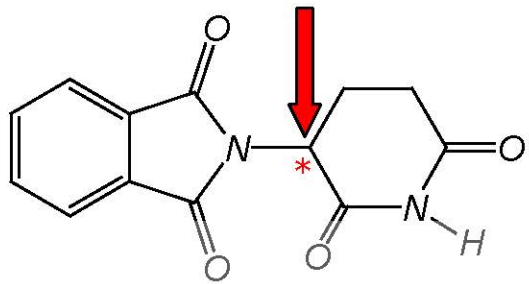
Thalidomide was synthesized in West Germany in 1953 by Chemie Grünenthal. It was marketed (available to patients) from **October 1, 1957** *(West Germany) into the early 1960's. Sold in at least 46 countries (US not included), Thalidomide was hailed as a "wonder drug" that provided a "safe, sound sleep". It was a sedative that was found to be effective when given to pregnant women to combat many of the symptoms associated with morning sickness. No clinical testing was available to show that Thalidomide molecules could cross the placental wall affecting the fetus until it was too late.*

The case of Thalidomide

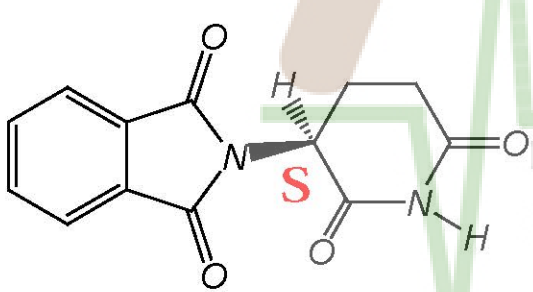


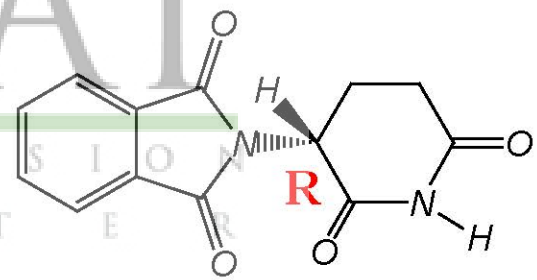
Thalidomide was a catastrophic drug with tragic side effects. Not only did a percentage of the population experience the effects of peripheral neuritis, a devastating and sometimes irreversible side effect, but Thalidomide became notorious as the killer and disabler of thousands of babies. When Thalidomide was taken during pregnancy (particularly during a specific window of time in the first trimester), it caused startling birth malformations, and death to babies. Any part of the fetus that was in development at the time of ingestion could be affected.

The case of Thalidomide



1 stereocenter = 2 stereoisomers





S-thalidomide

R-thalidomide

Sedative

Teratogen

(to calm nervousness)

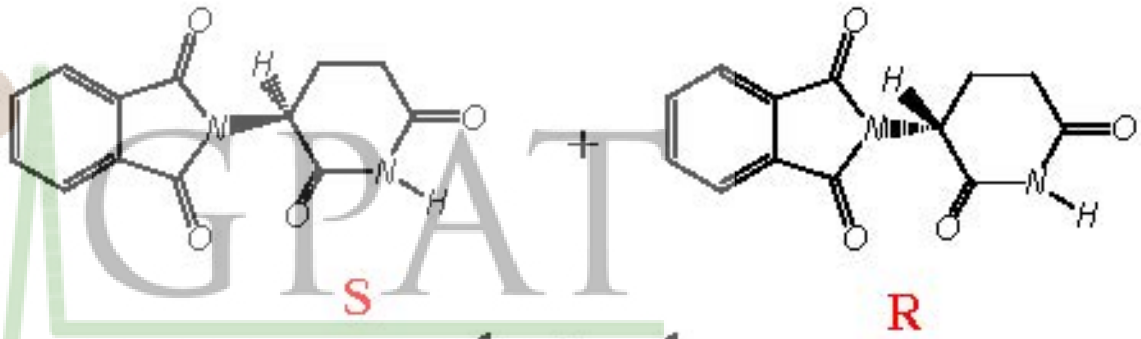
(to cause birth defects)

Why did the two enantiomers display different biological activity?

Enantiomers differ in the arrangement of atoms in space. Therefore, the S enantiomer of Thalidomide can fit the active site of a specific enzyme (like a "key" for a specific "lock") producing the desired effect (sedative). On the other hand, the R enantiomer cannot interact with the same site due to a different arrangement of atoms (3D shape). As consequence, it fits a different enzyme active pocket triggering a different biological effect (toxic).

How to solve this problem?

Chemical synthesis of Thalidomide from achiral starting materials



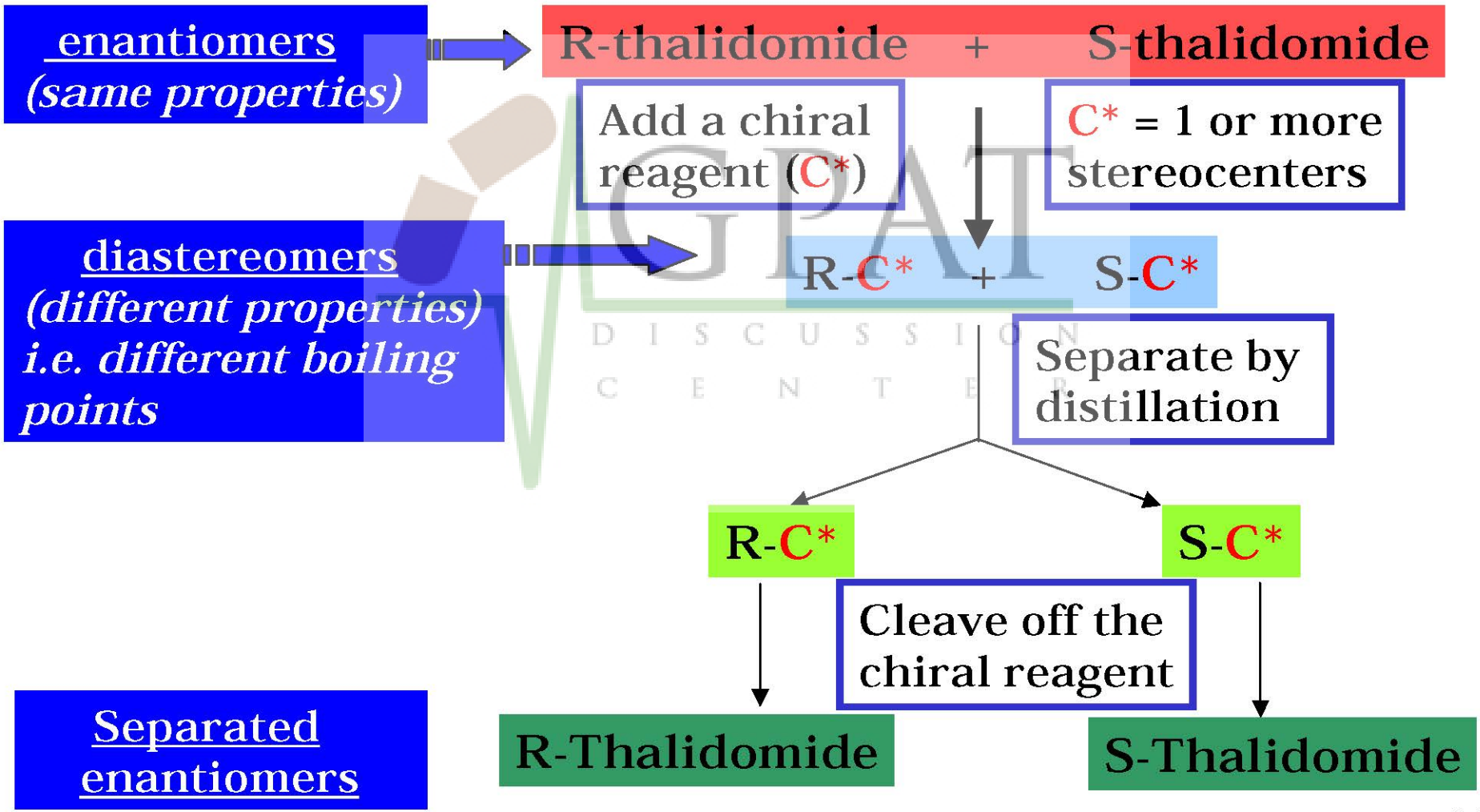
1 : 1

(racemic mixture)

Separate enantiomers (Resolution)

Resolution of Enantiomers

Enantiomers are temporarily converted into a pair of **diastereomers** by adding a chiral reagent…….



Conclusions

- Some organic molecules possess one or more (n) stereocenters, thus several (2^n) stereoisomers are possible.
- Enantiomers and diastereomers differ only in the position of atoms in space.
- Unlike Diastereomers, Enantiomers display the same chemical/physical properties in an achiral environment.
- In the human body (chiral environment) two enantiomers can be discriminated producing different biological responses.