Stereochemistry: an introduction

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Stereochemistry of Tetrahedral Carbons

We need:

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

For example:

\[
\begin{align*}
\text{2D drawing} & \quad \text{Not appropriate for Stereochem} \\
\text{3D drawing} & \quad \text{Appropriate for Stereochem}
\end{align*}
\]
Let’s consider some molecules......

First pair

\[
\begin{align*}
\text{A} & \quad \text{B} \\
H & \quad \text{Br} \\
\text{H} & \quad \text{Cl} \\
\text{Br} & \quad \text{H} \\
\end{align*}
\]

- same molecular formula \((\text{CH}_2\text{BrCl})\)
- same atom connectivity
- superposable

\[\rightarrow \text{identical (same compound)}\]

Second pair

\[
\begin{align*}
\text{C} & \quad \text{D} \\
F & \quad \text{Br} \\
H & \quad \text{H} \\
\text{F} & \quad \text{Br} \\
\text{Cl} & \quad \text{Cl} \\
\end{align*}
\]

- same molecular formula \((\text{CHFBrCl})\)
- same atom connectivity
- nonsuperposable

\[\rightarrow \text{stereoisomers (two different compounds)}\]
Thus, we can define.......... 

**Stereoisomers:** isomers that have same formula and connectivity but 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:

- Normal light (nonpolarized)
- Horizontally polarized light
- Light completely blocked
- Direction of light
- Horizontal filter
- Vertical filter
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).
**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.

![Chemical structures of (-)-Nicotine and (+)-Methamphetamine]

(-)-Nicotine

(+)-Methamphetamine
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:

**Historical perspective**

plane polarized light → **IN** → tube containing solution of **Tartaric Acid (TA)** → **OUT** → 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:

- RA is not optically active

![Chemical structure of Racemic Acid](image-url)
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:

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

$[\alpha]_D = -12.7^\circ$ (-)-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 different attachments may exist as a pair of isomers.
**Stereoisomers**: isomers that differ only in the position of atoms in space, and that cannot be interconverted by rotation around a single bond.

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

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**: stereo-isomers 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)

Carbon with 4 attachments is **Tetrahedral**.

A molecule having a tetrahedral carbon with 4 different attachments may exist as a pair of isomers.

**Mesotartaric Acid** could not be separated into (+) crystals and (-) crystals.
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 space.”

In 1901 van’t Hoff received the first Nobel Prize in Chemistry.
**Take-home problem**

**Stereoisomers of 2-chlorobutane**

Enantiomers: stereoisomers that are nonsuperposable mirror images.

Racemic mixture: a 1:1 (equimolar) mixture of two 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 the same formula and connectivity but 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:

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

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

The figure shows the molecular structure of Ibuprofen with labels indicating the stereocenters. The R enantiomer and S enantiomer are highlighted. The notation indicates that the second carbon (C2) is the stereocenter, with the * symbol indicating the chirality. The CO2H group is shown at position 1, and the CH3 group at position 4. The text notes that the first and fourth carbons are not stereocenters.
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 $\rightarrow$ 4 possible stereoisomers

Mirror

Enantiomers

Diastereomers

Diastereomers
Remember

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

**Diastereomers**: stereoisomers that are not mirror images.

For example:

\[
\begin{align*}
(S, S)\text{-Tartaric acid} & & (S, R)\text{-Tartaric acid} \\
\text{not mirror image} & & \text{mirror image}
\end{align*}
\]
(R, S)-Tartaric acid \[\rightarrow\] (S, R)-Tartaric acid

Enantiomers
Why not Enantiomers?

Enantiomers:

- same molecular formula
- same connectivity
- mirror images
- 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)**

![Enantiomers of Epinephrine](image)

\[[\alpha]_D = + 53.3^\circ\]  
\[[\alpha]_D = -53.3^\circ\]

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

\[
\begin{align*}
\text{smells like caraway} & \quad [\alpha]_D = + 62.5 \\
\end{align*}
\]

(-)-carvone

\[
\begin{align*}
\text{smells like spearmint} & \quad [\alpha]_D = - 62.5 \\
\end{align*}
\]

**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

\[
\begin{align*}
\text{[α]_D} & : -12.7 \\
\text{Melting p. (°C)} & : 171-174 \\
\text{Density (g/cm}^3\text{)} & : 1.7598 \\
\text{Solubility in H}_2\text{O} & : 139
\end{align*}
\]

Mesotartaric Acid

\[
\begin{align*}
\text{[α]_D} & : 0 \text{ (achiral)} \\
\text{Melting p. (°C)} & : 146-148 \\
\text{Density (g/cm}^3\text{)} & : 1.660 \\
\text{Solubility in H}_2\text{O} & : 125
\end{align*}
\]
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:

Drug $\rightarrow$ Enzyme

Tight Binding $\rightarrow$ Weak Binding

Enantiomers
Biological Significance of Chirality

**Enantiomers of Epinephrine**

- **(-)-Epinephrine**
  - Anionic site:
    - Not Occupied
  - Flat area:
    - Occupied

- **(+)-Epinephrine**
  - Anionic site:
    - Occupied
  - Flat area:
    - Not Occupied

**Poorer Fit** → **Less Active**

**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
Sedative (to calm nervousness)

R-thalidomide
Teratogen (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…….

- **Enantiomers** (same properties)
- **Diastereomers** (different properties) i.e. different boiling points

**R-thalidomide** + **S-thalidomide**

Add a chiral reagent (**C***)

**C*** = 1 or more stereocenters

**R-C*** + **S-C***

Separate by distillation

**R-C*** → **R-Thalidomide**

**S-C*** → **S-Thalidomide**

Cleave off the chiral reagent

Separated enantiomers
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.