Stereochemistry — Definition and Chirality

Stereochemistry is the branch of science which studies all aspects of the three-dimensional shapes of molecules. "Stereo" is Latin for "three-dimension." This article provides a fundamental explanation of the following: basic principles, terminologies, and biological significances of stereochemistry and chirality in real life.

Historical Overview

Jean-Baptiste Biot first discovered the optical activity of molecules in 1815. In 1848, Louis Pasteur, who is credited as being the first stereochemist, observed that tartaric acid salts could rotate plane polarized light (i.e., be optically active), while other salts from other sources could not. In 1874, Jacobus H. Vant Hoff and Joseph A. LeBel proposed the Theory of Organic Structure in Three-Dimensions which theorized that:

- A carbon with four attachments is tetrahedral in shape.
- A molecule comprised of a tetrahedral carbon and four different attachments may exist as a pair of isomers.

Molecular Symmetry

Molecular structures are categorized as symmetrical, dissymmetrical, or asymmetrical. The molecular structure is said to be symmetrical when it displays the elements of symmetry. For example, the derived symmetry operation transforms it into a molecule, which is then superimposable.
<table>
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<th>Symmetry elements</th>
<th>Symmetry operations</th>
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<tbody>
<tr>
<td><strong>Proper (simple) axes of rotation</strong></td>
<td>When a molecule rotates $360^\circ$ around a symmetry axis ($C_n \ n &gt; 1$), and its arrangement cannot be distinguished from the original one.</td>
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<tr>
<td><strong>Planes of symmetry</strong></td>
<td>When a mirror plane passes through the molecule and divides it into two symmetrical halves, the reflection of all the atoms through this plane creates an arrangement that cannot be distinguished from the original one.</td>
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<tr>
<td><strong>Center of symmetry (of inversion)</strong></td>
<td>Every atom has a symmetrical counterpart to this center. An inversion of all atoms relative to the center results in a molecule that is indistinguishable from the original one.</td>
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<tr>
<td><strong>Rotation-reflection axes (mirror axes, improper axes, alternating axes)</strong></td>
<td>If the molecule has an axis of rotation-reflection in which there is a $360^\circ$ rotation around this axis, followed by reflection through a mirror plane thereby giving a superimposable image, it is said to display reflection symmetry.</td>
</tr>
</tbody>
</table>

Molecular structures without reflection symmetry (no plane of symmetry) are called: **dissymmetric or chiral**. If a symmetry axis $C_n \ (n > 1)$ is also absent, the structure lacked all elements of symmetry and called: **asymmetric**.

### Chirality

Chirality (from the Greek word cheir, meaning “hand”) is the geometric property displayed by any object that is non-superimposable on its mirror image.

The main structural feature responsible for chirality is the presence of dissymmetry; as it has no plane of symmetry (as previously explained).

The best way to describe chirality is by looking at the right and left hands. They have the same number, size, and order of fingers, but their mirror images are not the same. The left hand’s mirror image cannot be placed directly on top of the right hand (hence, non-superimposable).

Image: “Two enantiomers of a generic amino acid that is chiral” by NASA, License: [Public Domain](https://creativecommons.org/licenses/publicdomain/).
**Chiral center (Stereogenic center, stereocenter)** is a carbon atom that carries four different atoms, or a group of atoms.

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**Classification of Isomers**

**Isomers**

Isomers are different compounds having the same molecular formula, but different structures. There are two types of Isomers:

1. **Constitutional (structural) isomers**: Molecules having the same molecular formula but different connectivity between their atoms.
2. **Stereoisomers**: Molecules that have the same constitution (same molecular formula and atom connectivity), but differ in the spatial arrangement of their atoms.

There is a historical distinction between the two types of stereoisomers: **conformational isomers**, which are interconvertible by rotations around single bonds, and ** configurational isomers**, which do not interconvert at room temperature and, therefore, can be separated.

**Configurational isomers** encompass two entities:

1. **Enantiomers**:

   ![Image](https://via.placeholder.com/150)

   Two stereoisomers with non-superimposable mirror images of each other.

   - This implies the molecules are dissymmetric (chiral); in which chirality is the necessary condition for the existence of enantiomers.

   They have the same physical and chemical properties except:

   A) **Direction** of rotation of plane-polarized light:

   - Compounds able to rotate plane-polarized light are considered **optically active**. Optical activity had been used to determine chirality and distinguish enantiomers, but the development of NMR and chiral chromatographic methods lessened its role.
   - A solution comprised of a mixture of enantiomers (at a ratio other than 50:50) can rotate plane-polarized light to either the:
     - Right (dextrorotatory) → designated as + or d
Note: A racemic mixture is one with equal ratios of enantiomers (a 50:50 mixture). Therefore, it is optically inactive.

B) They react differently with chiral compounds.

2. Diastereomers:

These are non-mirror image stereoisomers. The physical properties and chemical reactions of diastereomers are different. A molecule that contains two asymmetric carbons (two stereocenters) is the most common diastereomer. Ephedrine and pseudoephedrine illustrate these compounds. Each diastereomer (ephedrine and pseudoephedrine) exists as a member of an enantiomeric pair: d- and l-ephedrine, and d- and l-pseudoephedrine:

![Image: "The four diastereoisomers of ephedrine." by Wickey-nl. License: Public Domain]

Thus, diastereomeric molecules with two carbon centers are represented by four stereoisomers.

Absolute Configuration

One of the methods used in distinguishing one enantiomeric form from another is the evidence of rotation of plane-polarized light, which is shown as (+) / (-) or d / l. However, this method does not describe the spatial arrangement around the chiral center—the configuration.

A system of nomenclature has been established to represent the absolute configuration: the Cahn-Ingold-Prelog rules. These rules apply when the substituents
around the chiral center are ordered (assigned priorities) from the largest to the smallest, according to their atomic number.

![Image](image_url) "Two examples of stereocenters. The lowest substituent (number 4) is shown only by a wavy line, and is assumed to be behind the rest of the molecule. Both centers shown are S isomers." by Calvero. License: Public Domain

The lowest assigned priority group is placed towards the back. Then, the **direction (clockwise or counter-clockwise) of a line** connecting the remaining groups in descending order, from the highest priority to the lowest, is determined. Therefore:

- If the connecting line moves **clockwise** → The molecule is **R (rectus)**.
- If the connecting line moves **counter clockwise** → The molecule is **S (sinister)**.

**Note:** If one enantiomer has the R configuration, its mirror image has the S configuration.  
**Molecules with multiple chiral centers:**

- Molecules with one chiral center have two possible stereoisomers: S and R.
- Molecules with \( n \) chiral centers have \( 2 \times n \) possible stereoisomers.

**Significance of Chirality**

Nearly all of the biological environment consists of enantiomeric molecules—amino acids, nucleosides, carbohydrates, and phospholipids are all chiral molecules.

It has been shown that one enantiomer of a molecule can be much more active, pharmacologically, than another enantiomer.

In 1933, Easson and Stedman proposed that only three groups \( (b, c, d) \) out of the four \( (a,b,c,d) \) arranged on the central carbon of an enantiomer can be involved in the process of reaction. The receptor has three groups \( (b', c', d') \). The maximum physiological effect of a drug occurred when the groups \( b, c \) and \( d \) in the drug coincide, respectively, with \( b', c' \) and \( d' \) in the receptor.
The action of the enantiomers of the epinephrine supported these results. It was determined that (-)-epinephrine is 12-15 times as active as (+)-epinephrine.

Thalidomide was first introduced in Germany in 1957. It was used to alleviate morning sickness in pregnant women. However, it was soon discovered to cause birth malformations such as phocomelia, amelia and, in extreme situations, death. Re-examination of its formulaic property revealed that the two enantiomers of Thalidomide exert different effects:

1. (S)-Thalidomide → is teratogenic.
2. (R)-Thalidomide → is sedative.

This is because each one fits a different active site of a specific enzyme, producing a different biological effect.

Enzymes are chiral molecules, and can be distinguished between the two enantiomers of a chiral substrate. This is similar to the right glove fitting exactly onto the right hand, but poorly fitting the left hand.

A final example of chirality is the two enantiomers of the chemical compound carvone, in which:

1. Spearmint leaves → contain the L-enantiomer of carvone = R-(–)-carvone
2. Caraway seeds → contain the D-enantiomer of carvone = S-(+)-carvone.

Therefore, in the human body (chiral environment), two different enantiomer types can produce entirely different biological effects.
Review Questions

The answers are below the references.

1. The definition of chirality is what?
   A. The molecule is superimposable on its mirror image.
   B. The molecule is non-superimposable on its mirror image.
   C. A molecule with carbon atoms with four, different, attached groups.
   D. Molecules with the same molecular formula, but different connectivity between their atoms.

2. The molecule is considered optically active when...
   A. ...it can rotate plane-polarized light.
   B. ...it can reflect plane-polarized light.
   C. ...it has equal ratios of enantiomers (50:50 mixture).
   D. ...it contains achiral molecules.

3. Isomers that are not superimposable on their mirror images are...
   A. ...constitutional isomers.
   B. ...conformational isomers.
   C. ...diastereomers.
   D. ...enantiomers.

References

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Correct answers: 1B, 2A, 3D

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