
OpenCourseWare (2023)

CHEMISTRY II

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STEREOCHEMISTRY



1. ISOMERISM

Isomers are compounds that share the same types and quantities of atoms but exhibit differences in their atomic arrangement. *Isomerism* comes in two main forms: constitutional (also known as structural) and spatial.

Constitutional isomerism describes compounds that possess identical molecular formulas but display variations in how individual atoms are interconnected. Constitutional isomers may exhibit differences in their carbon skeletons, such as in the case of 2-methylpropane and butane, or in their functional groups, as seen in ethanol and dimethylether. Another possibility is variations in the placement of a functional group along the molecular chain, for instance, in isopropylamine and propylamine. Regardless of the specific cause of isomerism, constitutional isomers are distinct compounds with differing properties, yet they share the same chemical formula.

Spatial isomerism, also referred to as **stereoisomerism**, involves compounds with identical atom connectivity but differing spatial orientations. These spatial variations can be classified into two categories: geometric isomers and optical isomers (enantiomers):

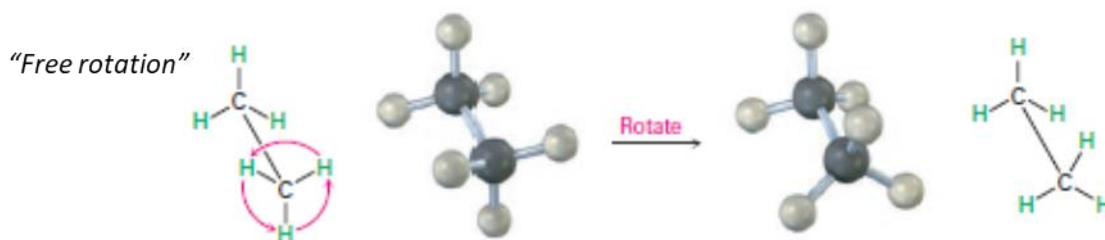
- Geometric isomers include relatively stable and isolatable *cis-trans isomers*, where substituents can be on the same side or opposite sides of a double bond or a ring. In contrast, conformational isomers, another type of stereoisomerism, are rapidly interconverting and usually not isolable.
- *Enantiomers*, a subset of optical isomers, exhibit mirror-image stereoisomerism and are said to possess "handedness." Just as your left hand cannot be superimposed onto your right hand, enantiomers cannot be superimposed onto each other. This property of handedness is significant in nature, especially in the context of biologically relevant compounds, as left- and right-handed molecules react differently with each other. Molecules exhibiting this property are termed *chiral*, deriving from the Greek word "cheir," meaning hand. Chiral molecules generally contain an atom connected to four distinct groups, often denoted by an asterisk, and are referred to as asymmetric atoms (e.g., asymmetric carbon) or stereocenters. Molecules with one stereocenter are always chiral.

2. CONFORMATIONAL ISOMERISM

Conformational isomerism is a type of stereoisomerism where isomers can be transformed exclusively through rotations about formally single bonds. These isomers are commonly referred to as *conformational isomers* or *conformers*, and more specifically as rotamers.

For instance, when constructing a molecular model of ethane, it becomes evident that the two methyl groups can be rotated with respect to each other (Figure 1). The energy required to facilitate the movement of hydrogen atoms past each other, known as the barrier to rotation, is only 2.9 Kcal/mol. This

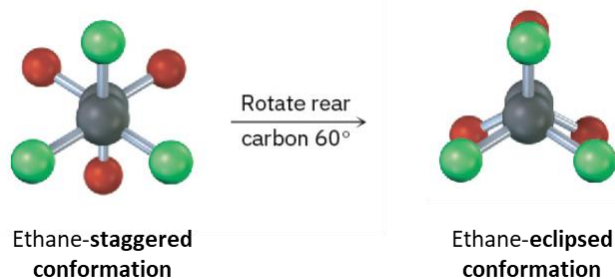
low energy barrier results in what chemists' term "free rotation" of the methyl groups, which generally occurs for all single bonds at room temperature.



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Figure 1. Rotation takes place around the C-C single bond in ethane.

To illustrate this concept, consider the figure that demonstrates the rotational motion in ethane using hashed-wedged line structures (Figure 2). There are two extreme ways to depict the conformation of ethane: the *staggered* conformation and the *eclipsed* conformation. When viewed along the C-C axis in the staggered conformation, each hydrogen atom on the first carbon is perfectly positioned between two hydrogen atoms on the second carbon. In contrast, the eclipsed conformation is derived from the staggered conformation by a 60° rotation of one of the methyl groups about the C-C bond. When viewed along the C-C axis in the eclipsed conformation, all hydrogen atoms on the first carbon are directly opposite those on the second, resulting in an eclipsing of the two sets of hydrogen atoms. A further 60° turn converts the eclipsed form into a new but equivalent staggered arrangement. Between these two extremes, the rotation of the methyl group leads to numerous intermediate positions, collectively referred to as skew conformations.



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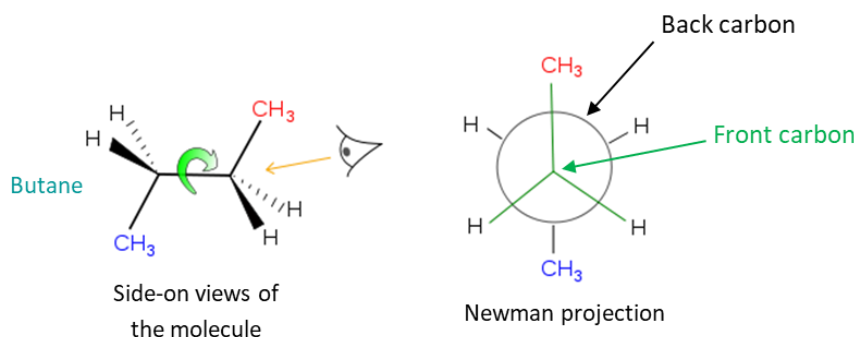
Figure 2. Rotation of ethane.

The various forms of ethane (and similar compounds, including substituted analogs) generated through these rotations are termed conformations, or conformers. Importantly, all of these conformations rapidly interconvert at room temperature. The study of their thermodynamic and kinetic properties is known as *conformational analysis*.

2.1. Newman Projections

A Newman projection provides a direct, head-on view of the carbon-carbon bond, using a circular representation for the two carbon atoms. The bonds attached to the front carbon are depicted as lines converging at the center of the circle, while those attached to the rear carbon extend outwards from the edge of the circle. To create a Newman projection from the molecular structure displayed in a hashed-wedged line diagram, we rotate the molecule out of the plane of the page towards us and align it along the C-C axis, as shown in the Figure 3. This representation may obscure the rear carbon but offers clear visibility of the bonds extending from both carbons.

The front carbon is symbolized as the meeting point of the three bonds attached to it, with one typically drawn vertically and pointing upwards. In contrast, the rear carbon is denoted by a circle, and its bonds radiate from the outer edge of this circle. To enhance the visibility of the three rear hydrogen atoms in eclipsed conformations, they are slightly rotated from the perfectly eclipsed position.

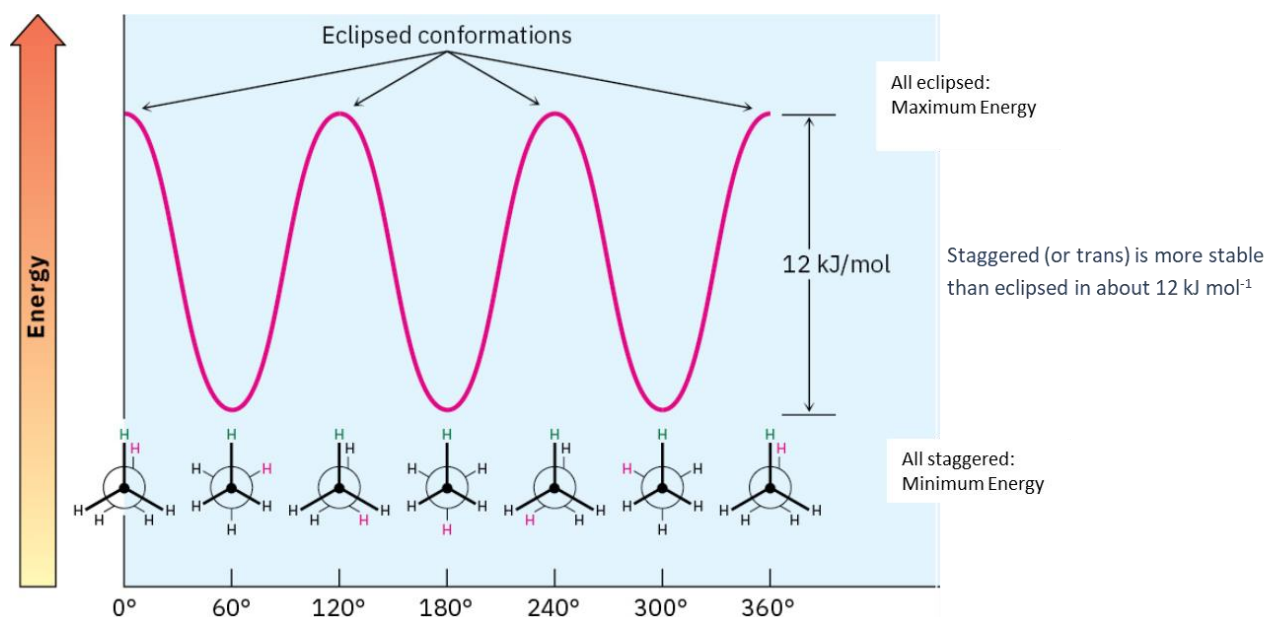


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Figure 3. Newman representation of butane.

2.2. Conformational Analysis

Intramolecular forces govern the positioning of substituents on neighboring and bonded carbon atoms. In ethane, the relatively stable staggered conformations transition through higher-energy states in which hydrogen atoms become eclipsed. Because the energy barrier for this motion is quite low, rotation happens swiftly at typical temperatures. A potential-energy diagram is a useful tool for illustrating the energetic aspects of C-C bond rotation. It is employed to visualize the energy changes associated with bond rotation. In the case of ethane's rotation (Figure 4), the x-axis represents degrees of rotation, often referred to as the torsional angle. The diagram designates 0° as the energy minimum corresponding to the staggered conformation, which is the most stable arrangement for the ethane molecule. It's important to note that the eclipsed conformation occurs at the highest point on the energy curve. However, it has an extremely brief existence (less than 10^{-12} seconds) and serves as a transitional state between rapidly equilibrating staggered arrangements. The 2.9 Kcal/mol energy difference between the staggered and eclipsed conformations corresponds to the activation energy required for the rotational process.

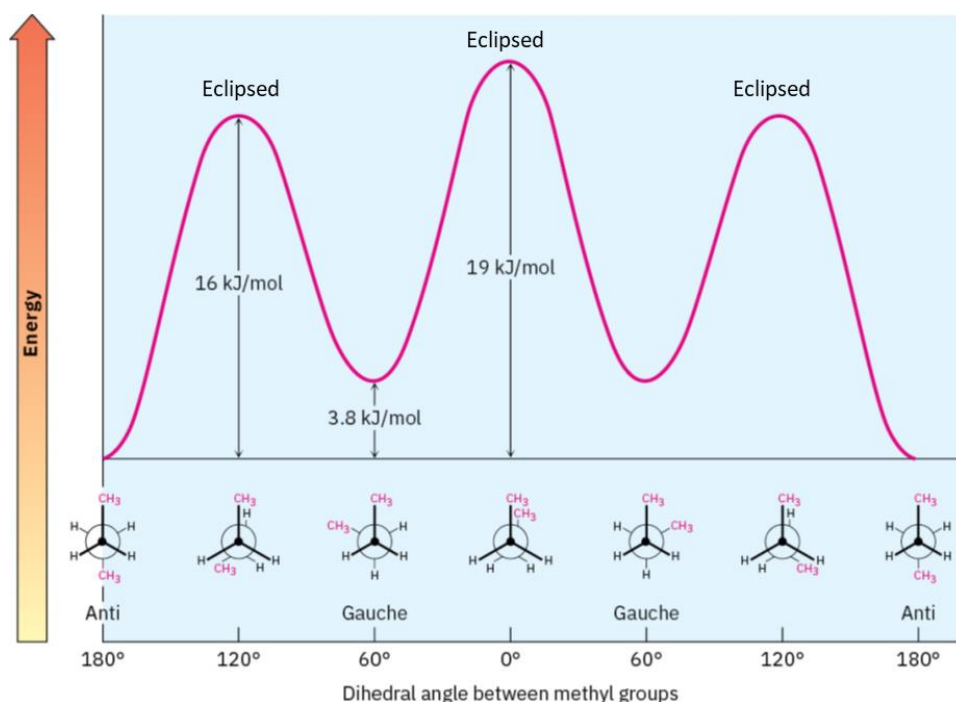


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Figure 4. Potential-energy diagram of the rotational isomerism in ethane.

When we examine the rotation about the central C-C bond in butane, we discover that there are more conformations than just one staggered and one eclipsed (as shown in the Figure 5). Let's explore these conformations:

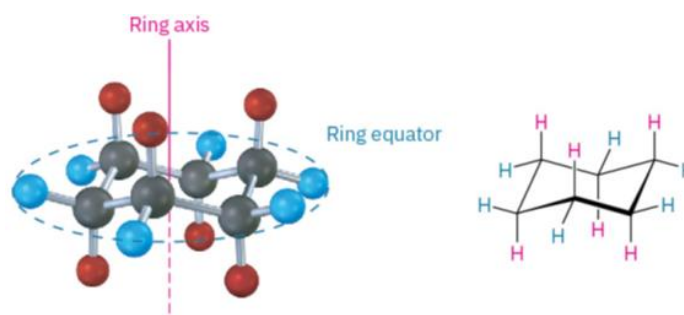
- **Anti Conformation:** In this staggered conformer, the two methyl groups are positioned as far apart from each other as possible, resulting in the most stable arrangement with zero energy (0 kJ/mol). The term "anti" signifies their opposed orientation.
- **Eclipsed Conformation:** Rotating the rear carbon in the Newman projections, either clockwise or counterclockwise, leads to an eclipsed conformation where two CH₃-H interactions occur. This conformer is less stable, being 16 kJ/mol higher in energy than the anti conformation.
- **Gauche Conformation:** Further rotation results in a new staggered structure known as "gauche." In this conformation, the two methyl groups are closer together than in the anti conformation, but it is less stable due to steric hindrance, being approximately 3.8 kJ/mol higher in energy than the anti conformation. This energy difference arises from the repulsive interaction between the hydrogen atoms of the methyl groups, known as steric strain.
- **Eclipsed Conformation with Methyl Groups Superposed:** More rotation leads to an eclipsed arrangement where the two methyl groups overlap, making it the highest in energy among the conformers, with a 19 kJ/mol difference from the most stable anti structure.



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Figure 5. Potential-energy diagram of rotation about either C-C bond in butane.

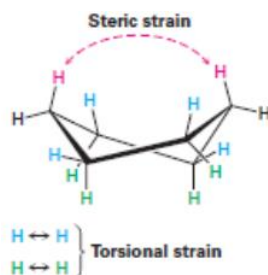
Cyclohexane exhibits a strain-free, three-dimensional structure referred to as a "chair conformation" due to its resemblance to a lounge chair, complete with a back, seat, and footrest. In this chair conformation, there is an absence of both angle strain and torsional strain. All the C-C-C bond angles closely approximate the ideal tetrahedral angle of 109.5 degrees, and the arrangement ensures that all neighboring C-H bonds are staggered, contributing to its overall stability. In cyclohexane, there are distinct positions for bonds and substituents (Figure 6), which play a significant role in its stability and conformational preferences: *Axial Bonds*: Cyclohexane has six axial bonds, one on each carbon. These axial bonds are oriented perpendicular to the ring and run parallel to the ring's central axis. They alternate in an up-down fashion. *Equatorial Bonds*: Similarly, there are six equatorial bonds in cyclohexane, one on each carbon. These equatorial bonds are arranged in three sets of two parallel lines. Each set is also parallel to two adjacent ring bonds. The equatorial bonds alternate between the two sides of the ring.



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Figure 6. Axial and equatorial positions in chair conformation of cyclohexane.

Cyclohexane predominantly adopts the "chair conformation," which is highly stable because it minimizes both angle strain and torsional strain. In this conformation, all C-C-C bond angles closely approximate the ideal tetrahedral angle of 109.5 degrees, and neighboring C-H bonds are staggered, ensuring a strain-free, three-dimensional structure. However, there is an alternative conformation known as the "twist-boat conformation", which is nearly free of angle strain but has both steric and torsional strain (Figure 7). The twist-boat conformation is energetically less favorable, being approximately 23 kJ/mol higher in energy than the chair conformation. As a result, molecules adopt the twist-boat geometry only under specific conditions or when constrained to do so.



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Figure 7. Twist-boat conformation.

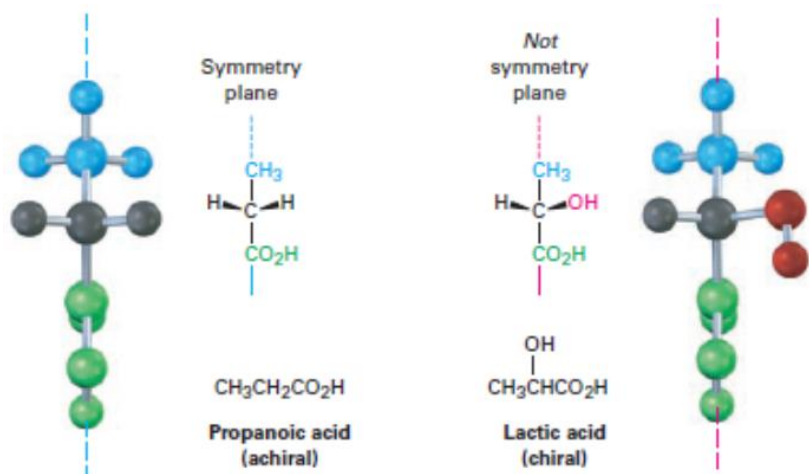
3. ENANTIOMERS

Stereoisomerism is a concept that describes isomers with the same atoms connected in the same order but differing in their spatial arrangement. It plays a significant role in various aspects of chemistry and biology. Many drugs and virtually all molecules in living organisms, including amino acids, carbohydrates, and nucleic acids, exhibit *handedness*. In organic and biological chemistry, handedness is essential. It results primarily from the tetrahedral stereochemistry of sp^3 -hybridized carbon atoms. To illustrate stereochemistry, consider the example of three molecules alongside their mirror images. CH_3X and CH_2XY molecules are identical to their mirror images and are therefore not handed. You can create molecular models of each molecule and its mirror image, superimpose them, and align all atoms. However, the $CHXYZ$ molecule is different from its mirror image. You cannot superimpose the model of this molecule on the model of its mirror image, just as you can't place a left hand over a right hand because they are not the same. Molecules that are not identical to their mirror images are known as *enantiomers*, derived from the Greek word "enantio," meaning "opposite". Enantiomers occur whenever a tetrahedral carbon atom is bonded to four different substituents.

3.1. Chirality. The Symmetry in Molecules

Chirality is a concept in chemistry that refers to the property of certain molecules and objects that are non-superimposable on their mirror images. In other words, a chiral molecule or object cannot be exactly aligned with its mirror image, just like your left and right hands cannot be superimposed. Predicting whether a given molecule is chiral or achiral involves examining its structural symmetry and the presence of stereocenters, specifically asymmetric carbon atoms.

To predict whether a molecule is chiral or achiral, you need to examine its structural symmetry, the presence of planes of symmetry, and the existence of stereocenters (asymmetric atoms). A molecule is achiral if it possesses a plane of symmetry. A plane of symmetry is a plane that cuts through the molecule in such a way that one half of the molecule is a mirror image of the other half. If a molecule has a plane of symmetry in any conformation, it must be identical to its mirror image and is therefore achiral. For example, propanoic acid ($\text{CH}_3\text{CH}_2\text{CO}_2\text{H}$) has a plane of symmetry in a specific conformation and is achiral and lactic acid ($\text{CH}_3\text{CH}(\text{OH})\text{CO}_2\text{H}$) has no plane of symmetry in any conformation and is thus chiral (Figure 8).

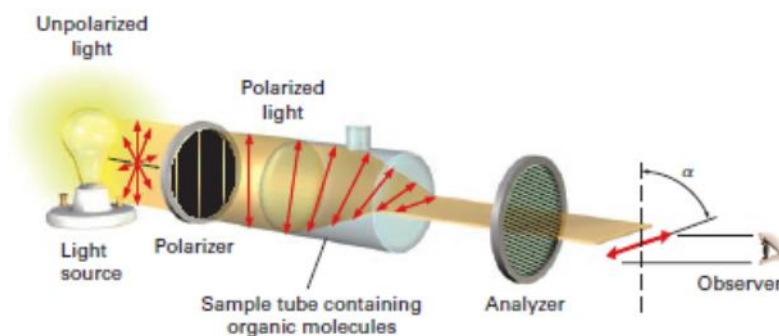


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Figure 8. Example of chiral and achiral molecules.

3.2. Optical Activity

In the case of chiral molecules, if we were to isolate each enantiomer in its pure form, we would discover that their physical properties, such as boiling points, melting points, and densities, are indistinguishable. This outcome might not be surprising since their chemical bonds are identical, as are their energy contents. However, a remarkable distinction emerges when we introduce a special type of light known as plane-polarized light. This light is produced when a beam of ordinary light passes through a device called a polarizer, allowing only light waves oscillating in a single plane to pass through while blocking out light waves in all other planes. When we pass plane-polarized light through a sample of one of the enantiomers, the plane of polarization of the incoming light undergoes a rotation, either clockwise or counterclockwise. When we repeat this experiment with the other enantiomer, the plane of the polarized light also rotates by the exact same angle but in the opposite direction. The angle of rotation can be quantified with a device called *polarimeter*.



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Figure 9. Schematic representation of a polarimeter.

An enantiomer that causes a clockwise rotation of the plane of light when viewed from the light source is referred to as "dextrorotatory" (from the Latin "dexter", meaning "right"), and it is designated as the "(+)" enantiomer. Consequently, the other enantiomer, which induces counterclockwise rotation, is termed "levorotatory" (from the Latin "laevus", meaning "left") and is labeled the "(-)" enantiomer. This interaction with light is known as *optical activity*, and enantiomers are often referred to as "optical isomers".

The magnitude of rotation observed in a polarimetry experiment depends on the number of optically active molecules encountered by the light beam. This number is influenced by the sample's concentration and the path length of the sample. If the sample concentration is doubled, the observed rotation also doubles. Likewise, if the concentration remains constant but the length of the sample tube is doubled, the observed rotation doubles. Additionally, the angle of rotation is influenced by the wavelength of the light used. The "specific rotation", denoted as $[\alpha]_D$, of a compound is defined as the observed rotation when light with a wavelength of 589.6 nanometers is employed, with a sample path length (l) of 1 decimeter and a sample concentration (c) of 1 g/cm^3 . This choice of conditions ensures consistent reporting of specific rotations, $[\alpha]$, for various compounds, as it is influenced by factors such as concentration, molecular structure, path length, wavelength, solvent, and temperature. To eliminate ambiguity, chemists have agreed upon a standard value of the specific rotation, $[\alpha]$, for each compound, though it is important to note that this value can be solvent-dependent.

$$[\alpha]_{\lambda}^{t_0} = \frac{\alpha}{l \times c}$$

3.3. Absolute Configuration: R, S Sequence Rules

Establishing the structure of one pure enantiomer of a chiral compound and providing an unambiguous name for it, while distinguishing it from its mirror image, is achieved using a systematic nomenclature system known as the Cahn-Ingold-Prelog (CIP) rules. These rules provide a clear method for designating the configuration or handedness of chiral molecules. The CIP rules are as follows:

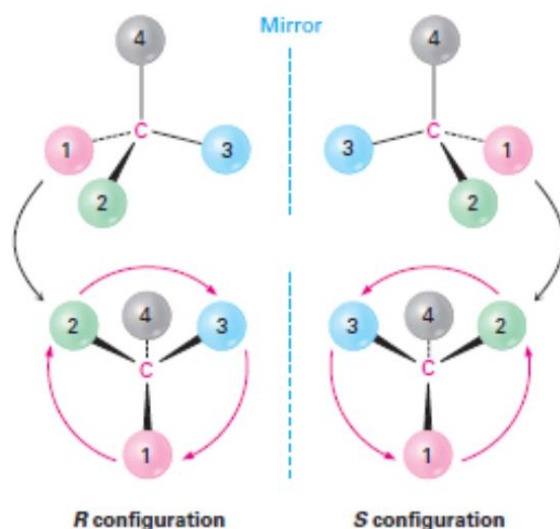
- **Rule 1: Rank by Atomic Number.** Examine the four atoms directly attached to the chirality center (the carbon atom with four different substituents). Rank these four atoms according to their atomic numbers, with the atom having the highest atomic number assigned the

highest rank (first), and the atom with the lowest atomic number, usually hydrogen, assigned the lowest rank (fourth). In cases where isotopes of the same element are involved, such as deuterium (^2H) and protium (^1H), the heavier isotope ranks higher than the lighter isotope.

- **Rule 2: Resolve Ties.** If the first atoms in the substituents are not sufficient to decide (i.e., there is a tie in atomic numbers), move to the second, third, or fourth atoms away from the chirality center. Continue ranking these atoms until the first point of difference is found. For example, consider a $-\text{CH}_2\text{CH}_3$ substituent and a $-\text{CH}_3$ substituent. Both have carbon as the first atom (by Rule 1), but by Rule 2, ethyl ($-\text{CH}_2\text{CH}_3$) ranks higher than methyl ($-\text{CH}_3$) because ethyl has a carbon as its second atom, while methyl has only hydrogen as its second atom.
- **Rule 3: Handling Multiple Bonds.** Multiple-bonded atoms are considered equivalent to the same number of single-bonded atoms. For instance, an aldehyde substituent ($-\text{CH}=\text{O}$), where a carbon atom is doubly bonded to one oxygen atom, is equivalent to a substituent with a carbon atom singly bonded to two oxygen atoms.

By applying the CIP rules, chemists can systematically determine the configuration of chiral molecules and provide an unambiguous designation that distinguishes one enantiomer from its mirror image. The resulting nomenclature helps convey the exact spatial arrangement of atoms in chiral compounds, allowing for precise communication and characterization of their properties and reactivity. This system is crucial in the fields of chemistry and biochemistry, particularly in the study of chiral molecules in pharmaceuticals, natural products, and other areas of chemical research.

1. After ranking the four groups attached to a chiral carbon using the CIP rules, we describe the stereochemical configuration around the carbon by following these steps:
2. Orient the Molecule: Position the molecule so that the group with the lowest ranking (4) points directly away from us in the background.
3. Examine the Remaining Substituents: Focus on the three remaining substituents, which now appear to radiate toward us in the foreground.
4. Clockwise or Counterclockwise?: Imagine a curved arrow drawn from the highest-ranked (1) substituent to the second-highest-ranked (2) to the third-highest-ranked (3) substituent (1 - 2 - 3).
5. Assign Configuration: If the direction of this imaginary arrow (1 - 2 - 3) is clockwise (rightward), we designate the chirality center as having the *R configuration*. The term "R" is derived from the Latin word "rectus", meaning "right." If the direction of the arrow (1 - 2 - 3) is counterclockwise (leftward), we assign the chirality center the *S configuration*. The term "S" is derived from the Latin word "sinister", meaning "left".



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Figure 10. Assigning configuration to a chirality center.

This systematic approach to assigning stereochemical configurations (*R* and *S*) ensures a standardized and unambiguous way of describing the spatial arrangement of substituents around a chiral center, facilitating clear communication in the field of organic chemistry.

3.4. Fischer Projections

To represent the stereochemistry of carbohydrates and other molecules with multiple chirality centers efficiently, Emil Fischer, a German chemist, introduced a method in 1891 known as the *Fischer projection*. Fischer projections are widely used for depicting stereochemistry at chirality centers, particularly in carbohydrate chemistry.

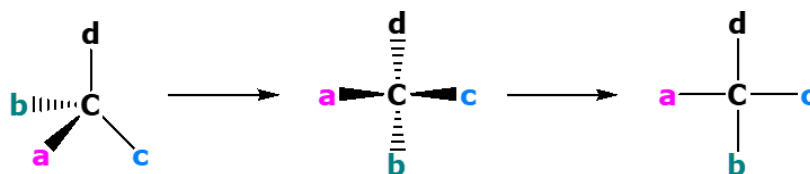
Fischer projections simplify the representation of tetrahedral carbon atoms and their substituents in two dimensions. The central carbon atom is placed at the intersection of horizontal and vertical lines, forming a cross-like structure. Horizontal lines represent bonds directed toward the viewer, while vertical lines represent bonds pointing away from the viewer. To convert other structural representations, such as hashed-wedged line structures, into Fischer projections, you may need to rearrange the groups accordingly. Since there are multiple ways to draw a chiral molecule, comparing Fischer projections can help determine whether they represent the same or different enantiomers.

The steps to assign *R* or *S* configuration using Fischer projections (Figure 11) are as follow:

Step 1: Begin by ranking the four substituents attached to the chirality center in the usual way, following the Cahn-Ingold-Prelog (CIP) rules for assigning priorities based on atomic numbers.

Step 2: Place the substituent with the lowest rank (typically hydrogen, H) at the top of the Fischer projection by utilizing one of the allowed motions. This arrangement ensures that the lowest-ranked group is oriented away from the viewer, consistent with configuration assignment requirements.

Step 3: Determine the direction of rotation when moving from the highest-ranked (1) substituent to the second-highest-ranked (2) to the third-highest-ranked (3) substituent, which corresponds to the 1 - 2 - 3 sequence. Based on the direction of this sequence (clockwise or counterclockwise), assign either *R* or *S* configuration to the chirality center.



Source: Image made by the authors.

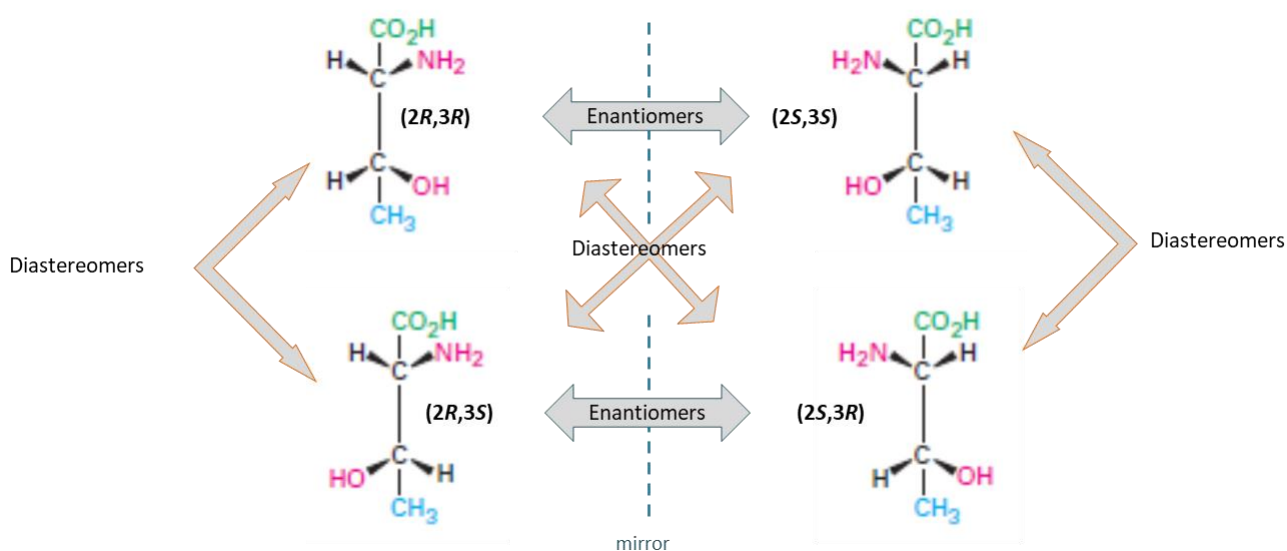
Figure 11. Conversion of hashed-wedged line structures into Fischer Projections.

By following these steps, Fischer projections offer a straightforward and standardized way to represent the stereochemistry of chiral molecules, especially those with multiple chirality centers. This notation simplifies the comparison of different structural representations and facilitates clear communication in the field of organic chemistry, particularly in the study of carbohydrates and other complex molecules.

4. DIASTEREOMERS

Molecules like lactic acid, alanine, and glyceraldehyde are relatively simple because each has only one chirality center, leading to just two possible stereoisomers. However, the complexity increases when dealing with molecules that have more than one chirality center. As a general rule, a molecule with n chirality centers can potentially have up to 2^n stereoisomers, although it may have fewer due to specific structural constraints.

Diastereomers are a category of stereoisomers that are not mirror images of each other. They have opposite configurations at some (one or more) chirality centers but maintain the same configuration at others. Understanding the concept of diastereomers is valuable when dealing with complex molecules that possess multiple chirality centers, as it helps in distinguishing between different stereoisomers that do not share a mirror-image relationship. For example, consider the four stereoisomers of 2-amino-3-hydroxybutanoic acid (Figure 12). They can be grouped into two pairs of enantiomers: the $2R,3R$ stereoisomer is the mirror image of the $2S,3S$ stereoisomer, and the $2R,3S$ stereoisomer is the mirror image of the $2S,3R$ stereoisomer. However, the $2R,3R$ isomer and the $2R,3S$ isomer are stereoisomers, but they are not enantiomers. They are diastereomers.



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Figure 12. The four stereoisomers of 2-amino-3-hydroxybutanoic acid.