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Technical Note

# Structure of Isomers

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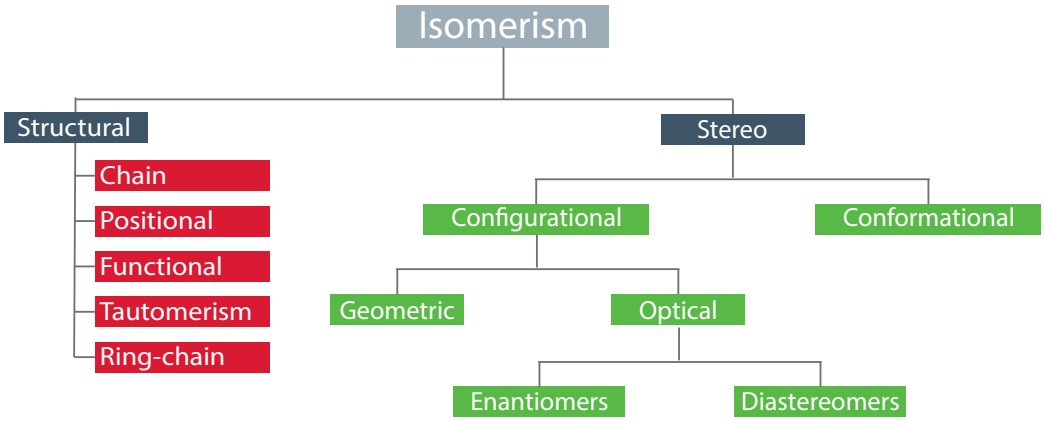
Isomers are molecules that have the same molecular formula but contain different arrangements of atoms. Depending on how differently the atoms are arranged, isomers can display similar or vastly different properties.

Isomers are organized into two main groups depending on how they differ. Structural isomers are those that have their atoms connected to each other in different ways. In contrast, stereo isomers have the same arrangement of atoms, but occupy 3-dimensional space differently.

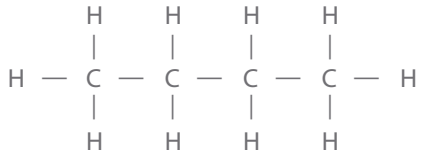



## I. Structural Isomers

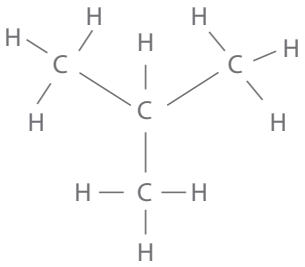
There are five general ways in which molecules can contain different structures:

1. **Chain isomers**: In this category, the focus is on the carbon backbone of the molecule. For example, four of the carbon atoms of n-Butane form one single chain, while in isobutane, the chain is only three atoms long, with a fourth carbon attached to the central carbon.

n-Butane:

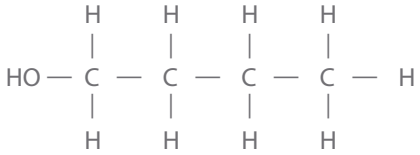


Isobutane:

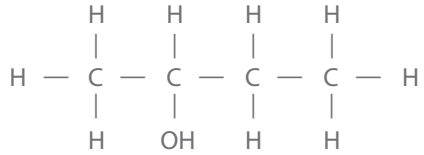


2. **Positional isomers**: In this category, the molecules contain the same carbon chain, but have their functional substituents in different positions. For example, 1-butanol is a primary alcohol with the hydroxyl group on carbon #1, and 2-butanol is a secondary alcohol with the hydroxyl on carbon #2. Positional isomers usually have different chemical properties. For example, primary alcohols tend to have higher boiling points than secondary alcohols, because their hydroxyl groups are more available for inter-molecular hydrogen boiling.

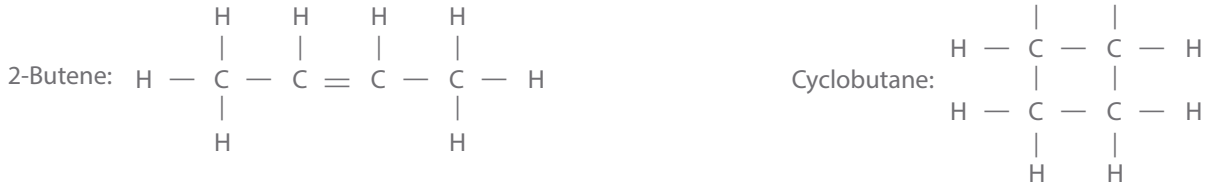
1-Butanol:



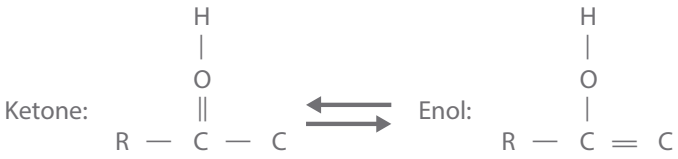
2-Butanol:



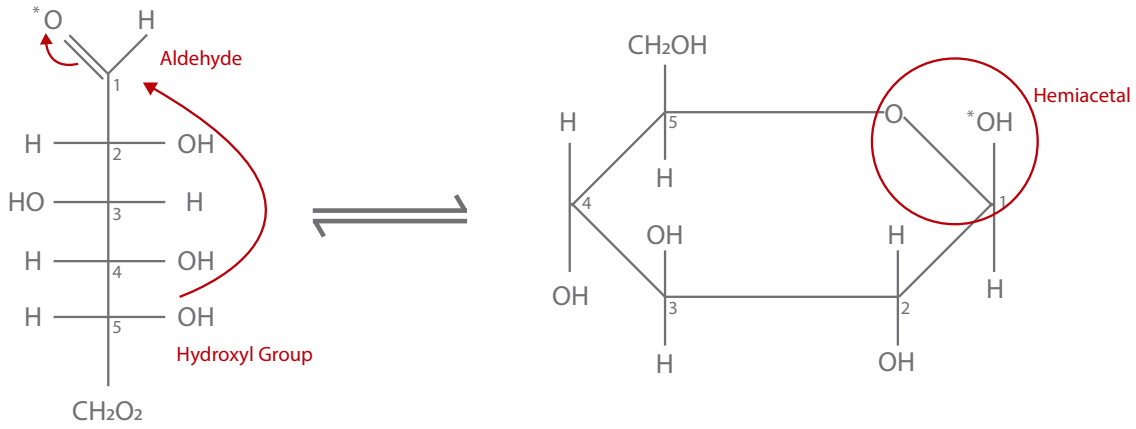
3. **Functional isomers**: In this class of isomers, the atoms are arranged in such a way that different chemical functionality results. A simple example is the difference between 2-butene and cyclobutene. The former is a straight chain olefin, and the latter is a cyclic, saturated hydrocarbon.




4. **Tautomers**: These are a special case of functional group isomerism in which there is a dynamic equilibrium between two isomers. A frequently encountered example are ketones, that rapidly coexist in the ketone and enol forms.




5. **Ring chain isomers:** Isomers that have a cyclic and an open-chain form especially when the two forms are tautomeric. Sugars, for example, exist in a dynamic mixture of the open and ring forms. The hydroxyl at position 5 of the open chain isomer interacts with the aldehyde to form a 6-membered ring, with a hemiacetal formed in the process.




Glucose Glucopyranose

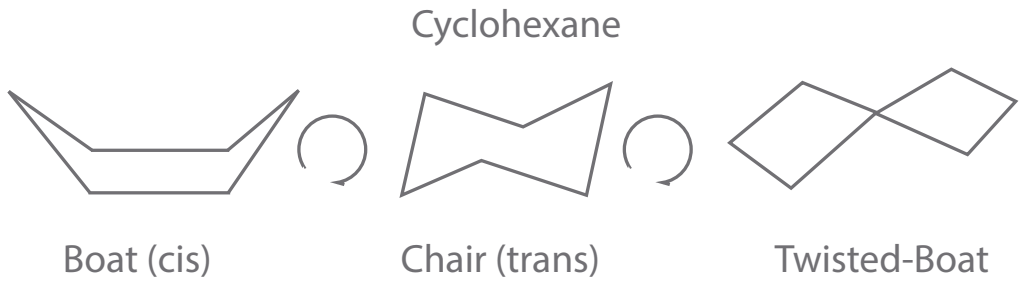
* Identifies the oxygen involved in the formation of the ring

## II. Stereoisomers

Unlike structural isomers, these isomers have all of the same atomic connections, but are arranged differently in 3-dimensional space. Much of this is due to the geometrical nature of the carbon atom. This group of isomers can be divided into two general categories: Conformational and Configurational.

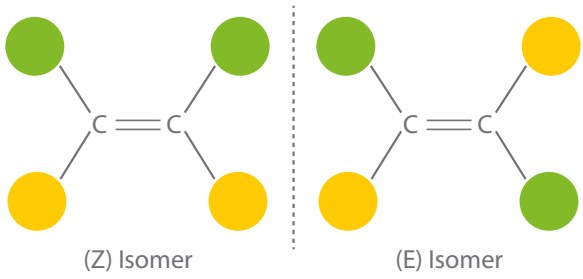
1. **Conformational isomers**: They are exactly the same atomic structure, but differ in the way their bonds are rotated.

   - All flexible molecules exist in a number of different conformations. The relative stability of each conformation determines the relative amounts of these isomers in existence.
   - The solvent can also affect the relative distribution of these isomers. For example, in a polar solvent, the polar functional groups will all be exposed. In a non-polar solvent, the same functional groups become relatively hidden.
   - A classic example of a conformational isomer is cyclohexane which exists in a dynamic mixture of chair, boat and twist boat conformations. The chair conformation is the most stable.




2. **Configurational isomers**: They are similar to positional and functional isomers in that atoms are in different positions in the two isomers. However, in these cases, the isomerization reflects different arrangements to these chemical groups. This class of isomers can be divided into two groups: geometric or optical.

   a. **Geometric isomerism**: The most commonly encountered isomers in this category are due to the arrangement of functional groups around carbon-carbon double bonds. Unlike single bonds, rotation around C=C bonds does not occur under normal conditions. If the two largest substituents are on the same side of the double bond, they are defined as cis (or Z). If they are on the opposite sides of the isomer, they are called trans (or E). The letters E and Z are from the German Entgegen (opposite) and Zusammen (together). The term 'cis' is Latin for 'this side of', while trans means 'other side of' or 'opposite'.



(Z) Isomer (E) Isomer

   b. **Optical stereoisomers** - This is a result of the tetrahedral nature of the saturated carbon atom. When all four different atoms (or functional groups) are attached to the same carbon atom, that atom is called a chiral center.

      i. **Enantiomers** - The two different possible molecular arrangements around a chiral center are called enantiomers. Enantiomers have the same physical properties and cannot be separated by standard methods.

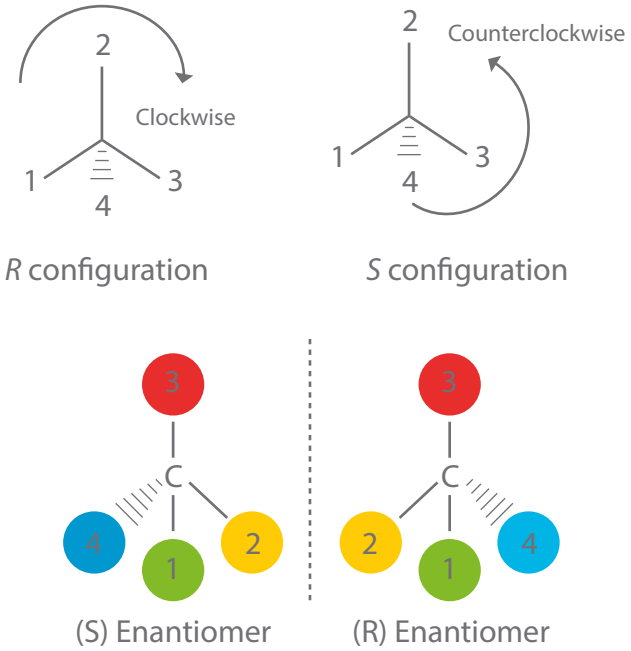
Enantiomers can only be separated in a chiral environment, such as a chiral column.

Enantiomers possess the interesting property that they cause polarized light to rotate when it passes through them. One enantiomer rotates light in the opposite direction compared to the other one.

This type of isomerization is analogous to the difference between a right and left hand. Although they are constructed the same way, the right hand cannot be superimposed on top of the left hand. They are mirror images of each other, as are pairs of enantiomers.

Enantiomers are designated by the priority of the groups attached to the chiral carbon. If one looks down the axis defined by the carbon and the lowest priority group, the remaining three groups can be seen decreasing in priority in a clockwise, or counterclockwise sense.

The S-isomer (from sinister (Latin) for left) and the R-isomer (from recuts (Latin) for right) are designated in this way.




ii. Diastereomers - By definition, diastereomers are optical isomers that do not fit into the enantiomer category. Typically, this includes all of the molecules that contain more than one chiral center.

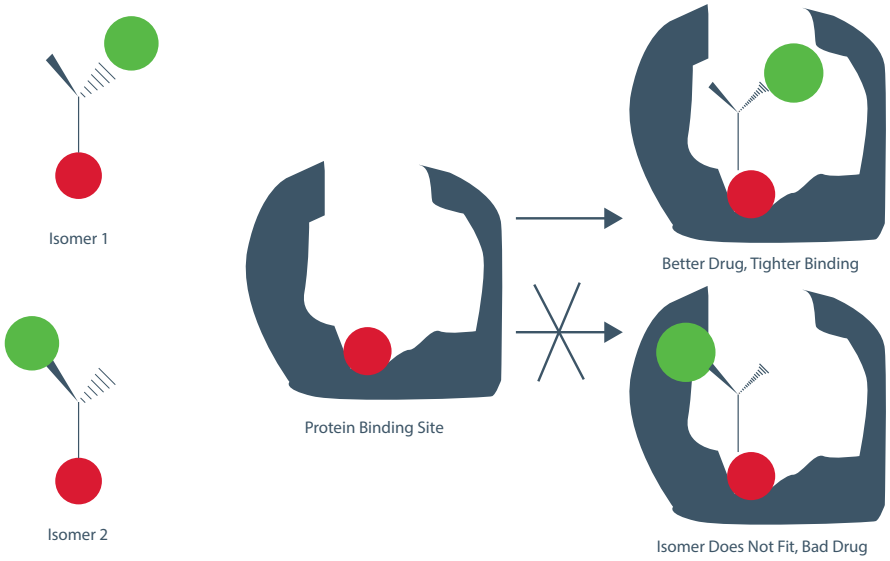
Compounds that contain two or more chiral centers are not mirror images of the other. Diastereomers tend to have different physical and chemical properties and can be separated, as long as the substituents around each chiral center are different enough.

## Biological Activity and Chemical Isomerization

The biological activity of a molecule is closely related to its stereochemistry. Most drug-like molecules contain at least one chiral center. Because proteins in biological systems are made exclusively with the L-enantiomer of amino acids, protein binding sites have a stereochemical bias.

Biological specificity is due to sensitive physical requirements of the protein active sites that biologically active molecules interact with. This interaction is analogous to a key fitting into its lock. Small changes in molecular structure can make it impossible for a drug to perform its action, while other changes make it fit better.

When medicinal chemists design new drugs, they carry our structure-activity studies in which they evaluate small changes in a series of related chemical analogs. In the following figure, two mirror image isomers of a potential drug interact with the binding site of a protein. The red substituent on each isomer interacts with the red binding region inside the protein. As a result, in isomer 1 the bulky group (green circle) is on the right side, which is nicely accommodated by the right side of the site. In isomer 2, the bulky group is on the left side, and it cannot fit in the binding site. Chemists study the 3-dimensional structure of proteins to design the ideal shape for a potential drug molecule.




The most infamous example of this phenomena was uncovered in the 1960s when Thalidomide was used as an anti-anxiety drug for pregnant women. Severe birth defects started to appear, and it became clear that it was due to Thalidomide.

Thalidomide is a chiral molecule, and the R-isomer is known to have the desired biological activity, however, it was later discovered that the S-isomer caused the birth defects.

The FDA now requires drug companies to prove that the inactive stereoisomer does not cause side effects. Otherwise, the company must go through the expensive process of manufacturing only the safe isomer.

There are many examples of enantiomers and diastereomers possessing significantly different biological activity profiles. Structural isomers can also possess great differences in biological activity. For example, the pesticide dimethomorph is found as two isomers (Z and E). The E-dimethomorph is inactive while the Z-dimethomorph is active. The sweetener asparagine also has two forms (R and S), the R form is sweet while the S-form is bitter.

## Conclusion

There is a vast array of molecules that carbon atoms can form in combination with hydrogen and various heteroatoms. This results in the rich and diverse field of organic chemistry. This richness is greatly deepened by the ability of organic molecules of the same formula to form different 3-dimensional structures. In some cases, these isomers can have very different structures with significant variations in chemical and physical properties. In other cases, such as enantiomers, these mirror image isomers have essentially the same properties, except for in a chiral environment, such as biological systems. One enantiomer can be an effective, safe drug, while the other enantiomer can be inactive, or even toxic.

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