Isomers

Isomers are molecules with the same molecular formula but different structural or spatial arrangements of atoms. Due to this isomers can have differences in properties, reactions, and biological effects. Isomerism is broadly classified into structural and stereoisomerism.

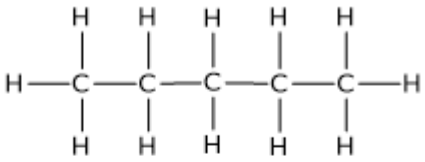
Structural isomers can be split into chain isomers, positional isomers, and functional group isomers.

Structural Isomerism

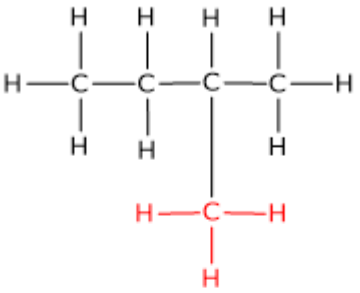
Structural isomers differ in their connectivity, while stereoisomers have the same connectivity but differ in their spatial arrangement.

Chain isomerism

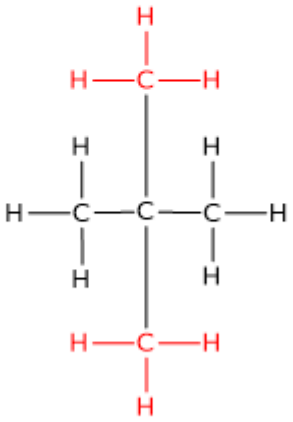
Chain isomers can also be called structural or skeletal isomers, are compounds that share the same molecular formula but have different arrangements of carbon atoms in their main chains. This difference in carbon skeleton results in branching or variations in the length of the carbon chain.



n-Pentano



2-Metilbutano



2,2-Dimetilpropano

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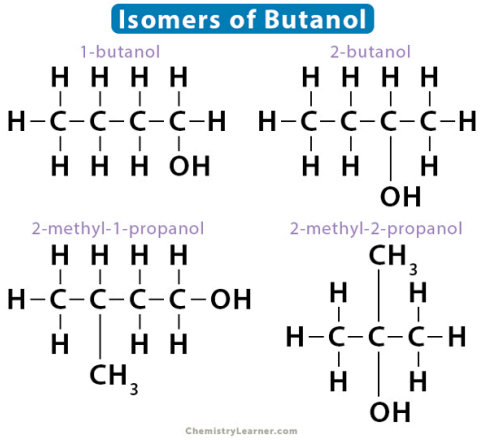
Properties of Isomers:

Chain isomers and positional isomers can have different boiling points due to varying intermolecular forces.

Positional Isomers:
Molecules with the same carbon skeleton and functional group but differing in the position of the functional group (e.g., propan-1-ol and propan-2-ol).



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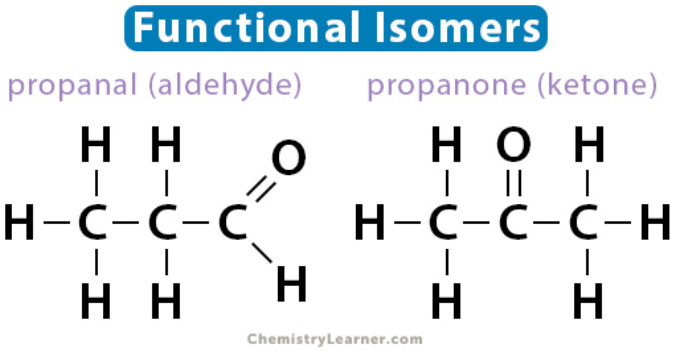
Functional Group Isomers:

Functional group isomers are compounds that share the same molecular formula but differ in the type of functional groups they contain, leading to different chemical and physical properties. This type of isomerism is a subset of structural isomerism.



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Molecules with the same molecular formula but different functional groups leading to different chemical and physical properties.
They have the same number and types of atoms. The arrangement of these atoms results in different functional groups (e.g., alcohol vs. ether, aldehyde vs. ketone). Due to the distinct functional groups, they exhibit varying reactivity and physical characteristics. E.g. formula C2H6O can be alcohols and ethers, formula C3H6O can be aldehydes that have a -CHO group - propanal or a ketones C=O group- propanone. This demonstrates that different arrangement of atoms create molecules with distinct functional groups with distinct chemical properties.

Properties of Isomers:

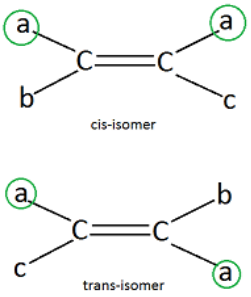
Functional group isomers can react differently due to the presence of different functional groups (e.g., aldehydes vs. ketones).

Stereoisomerism

Geometric (cis/trans or E/Z) Isomerism

These isomers occur when there is a double bond which restricts rotation around a double bond or a ring. This leads to different spatial arrangements of substituents.

Cis - trans isomers:



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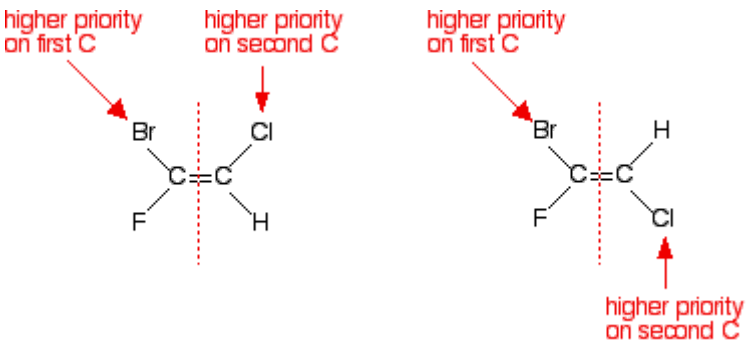
Cis indicates substituents are on the same side, while trans indicates they are on opposite sides.

E/Z Isomerism:

This is a more general system for naming geometric isomers, particularly useful when there are multiple different atoms or groups on the double bond. In this German system E= entgegen-meaning opposite indicates that the higher-priority groups are on opposite sides of the double bond and Z= zusammen - meaning together indicates they are on the same side.



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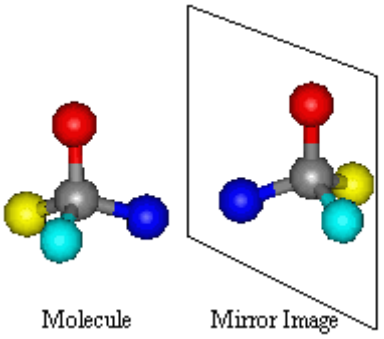
- Note from the diagram above that atomic mass of H=1, F=9, Cl= 17, Br=35

- On the left hand side of the double bond Br has the highest atomic mass and therefore the highest priority
- On the left hand side the Cl has the highest atomic mass and therefore the highest priority
- If the two groups with the higher priorities are on the same side of the double bond, that is described as the (Z)- isomer
- If the two groups with the higher priorities are on the opposite side of the double bond, that is described as the (E)- isomer

Properties of Isomers: Z (cis) isomers often have lower melting points than E (trans) isomers due to their packing efficiency.

Optical Isomerism

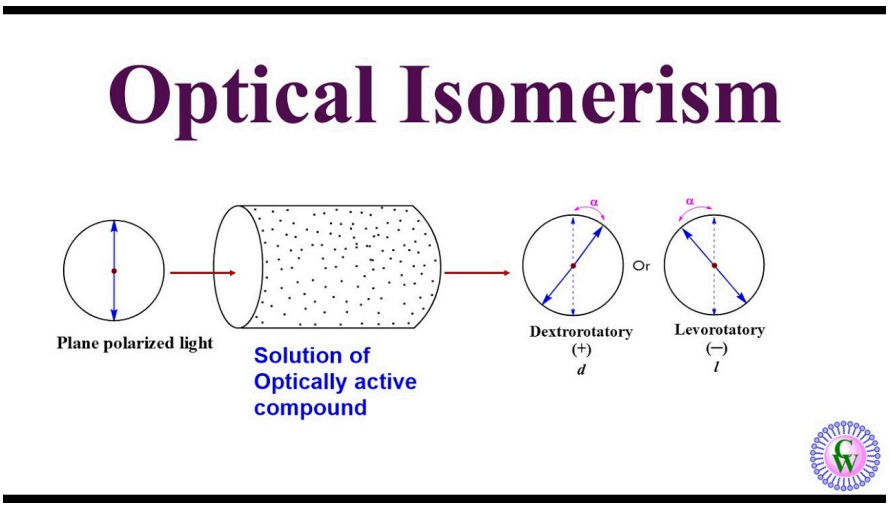
Molecules that are non-superimposable mirror images of each other (enantiomers). These isomers exhibit different optical activity and can have distinct biological effects (e.g., sugars, amino acids).



https://www.chm.bris.ac.uk/motm/thalidomide/opticaliso.html

An example of this type of isomerism can be found in thalidomide. With optical isomerism, there is no difference in way the atoms are connected eg by double bonds. The isomerism is to do with the arrangement of the atoms in space. This type of isomerism must have a '***Chiral Centre***'. With four different groups attached to the central carbon atom. Optical isomers are ***non superimposable, mirror Images*** of each other. These are called ***enantiomers***.

To change one isomer into another you would have to break the bonds. They have mostly identical physical properties and can usually be told apart by their **optical activity.**



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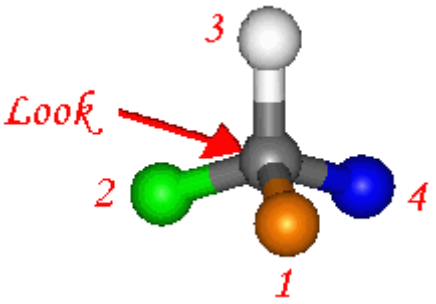
Working out optical properties of isomers (enantiomers)

- Plane polarized light- The light source produces light that only vibrates in one -plane and the polarizing filter only allies light vibrating in one plane.
- The pale polarized light pass through the sample
- If the substance is optically active it will rotate the plane polarized light
- The degree of rotation of the light can be measured. If light is rotated to the **right** it is called **dextrorotatory** if light is rotated to the **left** it is called **levorotatory**

Naming optical isomers:

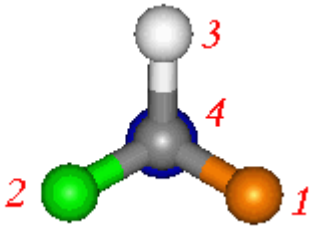
Naming the optical isomers



https://www.chm.bris.ac.uk/motm/thalidomide/opticaliso.html

There are a few simple steps which allow us to assign either 'D' or 'L' configuration to chiral atoms. These configurations are then included in the name to enable differentiation.

- Firstly assign priority to the substituents by molecular mass around the chiral centre.

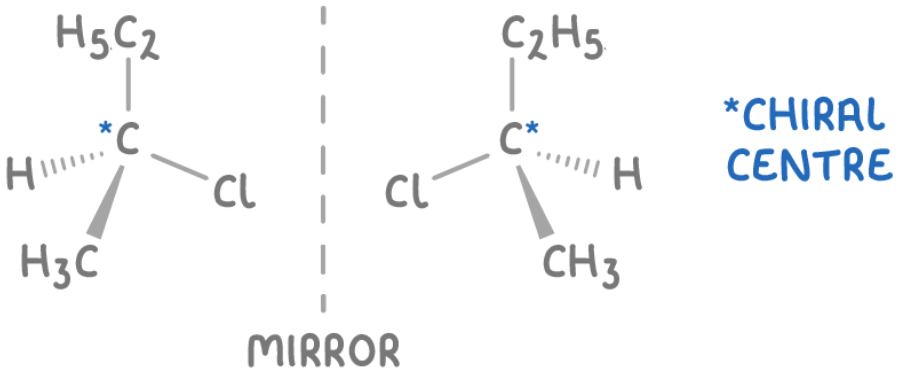


https://www.chm.bris.ac.uk/motm/thalidomide/opticaliso.html

Now we look at the molecule from the direction which puts the lowest priority group (often hydrogen), in line with, and behind, the chiral atom.

- Group 4 has been enlarged so it can be seen behind the chiral atom.
- If the priority order of the groups (1-2-3) is now clockwise the molecule is named as the 'D' isomer.
- If the priority order of the groups (1-2-3) is anti-clockwise the molecule is named as the 'L' isomer.
- Here the order is clockwise and so the isomer would be named 'D'.

Three-Dimensional Structures and Representations



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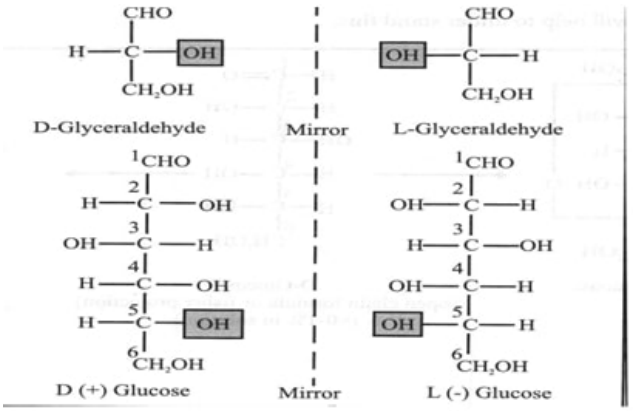
- Representations like wedge-dash notation help visualize and understand the three-dimensional structures of isomers. Dash = in the plane of the paper, dotted dash = going behind the plane of the paper and a wedge means pointing out of the plane of the paper.

Examples of isomers in Nature

Cis/Trans isomers

Cis and trans isomers occur in fats and oils, and trans fats are generally considered less healthy due to their impact on cholesterol levels.

Optical Isomers of Sugars



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Most naturally occurring sugars like glucose are of the D-configuration. This means that the stereochemistry at the chiral carbon farthest from the carbonyl group (the hemiacetal carbon) is the same as that of D-glyceraldehyde. For example, glucose, a primary sugar, is predominantly found as the D-isomer.

Glucose

Glucose, a common sugar, has four chiral carbon atoms, leading to 16 possible optical isomers (2^4). While many of these isomers exist in the laboratory, only D-glucose is naturally abundant.

D- vs. L-Sugars:

The distinction between D and L sugars is crucial in biological systems. Most naturally occurring sugars are of the D-configuration, and enzymes are often specific for one enantiomer over the other.

Optical Isomers of Amino Acids

Almost all amino acids found in proteins are of the L-configuration. This means that the stereochemistry at the chiral carbon (the alpha carbon) is the same as that of L-glyceraldehyde. The exception to this is glycine, which is not optically active because it lacks a chiral carbon.

Difference between starch and cellulose.

Starch is a carbohydrate composed of glucose monomers, used for energy storage in plants. Starch and cellulose are both polysaccharides (complex carbohydrates) made up of glucose molecules, but they differ in their structure and function. Starch is primarily used for energy storage in plants, while cellulose provides structural support in plant cell walls. The key difference lies in

the type of glucose linkage: starch uses alpha-glucose and has a branched structure, while cellulose uses beta-glucose and has a linear, unbranched structure.

Starch function: energy storage in plants.

Starches glucose type: Alpha-glucose.

Starch-linkage: Alpha-1,4 glycosidic bonds (amylose) and alpha-1,6 glycosidic bonds (amylopectin for branching).

Structure: has a branched, coiled structure

Humans have enzymes to digest starch, making it an important food source.

Cellulose function: structural support in plant cell walls (e.g., wood, cotton).

Glucose type in cellulose: Beta-glucose.

Cellulose linkage: Beta-1,4 glycosidic bonds.

Cellulose structure: Linear, unbranched, and rigid.

Humans lack the necessary enzymes to digest cellulose, so it's considered fiber.

Chirality and Function in enzyme activity in humans

Enzymes are protein molecules which catalyse reactions in the cell. Enzymes, which are highly specific for their substrates, are often designed to interact with only one enantiomer of a molecule. The right "fit" of a chiral molecule into an enzyme's active site is critical for proper biological processes. For example, enzymes that synthesize proteins will only incorporate L-amino acids. Similarly, enzymes that metabolize sugars will only interact with D-sugars.

Compare the different types of isomers and their industrial importance

Many pharmaceuticals are designed to be enantiomers, with one isomer being active and the other inactive or even harmful. The ability to isolate and produce specific enantiomers is crucial in drug development.

In the food industry isomers play a role in the flavor and sweetness of food products. For example, different isomers of sugars can have different sweetness levels. E.g. aspartame has two isomers, but only one of them has a sweet taste.

In materials Science isomers can be used to tailor the properties of materials. E.g. different isomers of polymers can have different physical properties like melting point and solubility.

In chemical Industry isomers are important intermediates in many chemical reactions and processes.

Different therapeutic effects of optical isomers of drugs

Different optical isomers of drugs can have different therapeutic effects, sometimes with one isomer being significantly more effective or less harmful than the other.

Optical isomers (enantiomers) of the same drug molecule can exhibit very different therapeutic effects due to their distinct spatial arrangements and interactions with biological targets. One isomer might be effective, while the other could be inactive, produce side effects, or even be toxic. This difference in activity arises from how the isomers interact with enzymes, receptors, or other biological molecules within the body.

Receptor Binding
Enantiomers can bind to different receptors or bind to the same receptor with varying degrees. One isomer might be a strong activator for certain receptors to get a strong biological effect while the other enantiomer may be a weak activator for certain receptors to get a weak or no biological effect .

Enzyme Activity
One enantiomer might be a substrate for an enzyme, while the other might not, or, they might interact with the same enzyme but with different rates or efficiencies.

Metabolism
Enantiomers can be metabolized differently, leading to different metabolites with different activities. One isomer might be rapidly metabolized and inactive, while the other is more stable and active.

Different Therapeutic Effects in pharmaceuticals

Thalidomide has two isomers where one isomer was effective as a sedative, while the other caused birth defects. In the late 1950s and early 1960s, thalidomide was widely prescribed for nausea and insomnia, particularly in pregnant women. It was soon discovered that thalidomide caused severe birth defects, including limb deformities, in thousands of children. The drug was withdrawn from the market in many countries.

Later, it was found to be effective in treating certain cancers and other conditions, leading to its re-emergence as a therapeutic agent. Thalidomide is used in combination with dexamethasone to treat multiple myeloma, a type of cancer that can now be prescribed. It is also used to treat erythema nodosum leprosum (ENL), a skin manifestation of leprosy with the precaution that it is not used in pregnancy.

Naproxen has two optical isomers both are therapeutic, the S-isomer (S-naproxen) is more effective and generally preferred for pain and anti-inflammatory effects. The R-isomer can have different and potentially less desirable effects, including a higher risk of liver damage. While both R-naproxen and S-naproxen are active as NSAIDs, their pharmacological properties and therapeutic effects can differ. S-naproxen is generally considered more active and is the preferred isomer. It has shown greater efficacy in animal models of inflammation and in inhibiting platelet aggregation, indicating a stronger anti-inflammatory and analgesic effect. Due to its superior activity and fewer side effects, the S-enantiomer of naproxen is increasingly favored in pharmaceutical formulations, either as a single-enantiomer formulation or as a high-enantiomeric excess (e.g., 97%) preparation.

R-naproxen, while still active, may be less potent and could have undesirable side effects. Some studies suggest that R-naproxen may be less effective at inhibiting platelet aggregation and may be associated with a higher risk of liver damage.

Ethambutol is a bacteriostatic drug that inhibits cell wall synthesis and is used to manage and treat tuberculosis (TB). One isomer is effective against tuberculosis, while the other causes blindness. Ethambutol has enantiomers, the chiral drug can have very different effects on the body.

One enantiomer of Ethambutol-induced optic neuritis can result in loss of red-green color discrimination, decreased visual acuity, and visual field defects. Studies have indicated that ethambutol-induced optic neuropathy (EON) is an adverse effect that depends on both the dosage and duration of treatment.

Ketamine in two enantiomeric forms -R-ketamine, otherwise called arketamine and S-ketamine, also known as esketamine. The two are mirror images of each other. Arketamine rotates polarized light clockwise, while esketamine spins it in the opposite direction. One isomer causes fewer emergence reactions and psychosis compared to the other. The L- isomer is used to treat Parkinson's disease, while the other D-isomer can cause white blood cell deficiency.

Implications for Drug Development

To improve efficacy it is advised in using a single enantiomer that has the greatest potency and is an effective drug.

Reduced Side Effects can be done by eliminating the inactive or harmful isomer, side effects can be minimized by separating the enantiomer (optical isomers) from its racemic mixture.

Using only the active isomer in a smaller dosage

Scientists are increasingly using asymmetric synthesis to produce single enantiomers of drugs.