Chapter 10: Organic Isomerism
Structural Isomerism: the basics

There are so many different kinds of organic functional group, that there seems to be an almost unlimited variety of organic compounds due to the presence of these functional groups alone. It turns out however, that the number of possible organic compounds is increased drastically beyond our expectations due to the existence of a phenomenon known as isomerism. In isomerism, compounds having the same chemical formulas can possess different structures, granting them different physical properties, and, often, different chemical properties as well.

A very simple example of isomerism involves the existence of two distinct compounds with the chemical formula C$_2$H$_6$O. These compounds are as follows:

- H$_3$C $\xrightarrow{\text{CH}_2}$ OH $\rightarrow$ ethanol
- H$_3$C $\xrightarrow{\text{O}}$ CH$_3$ $\rightarrow$ dimethylether

One isomer of C$_2$H$_6$O is an alcohol (the very familiar ethanol), and another is an ether. This example shows why chemists are so often reluctant to write down just the chemical formula for an organic compound, but prefer instead to write a condensed structural formula, e.g.

C$_2$H$_5$OH or CH$_3$CH$_2$OH for ethanol, and (CH$_3$)$_2$O or CH$_3$OCH$_3$ for dimethyl ether.

These formulas much more clearly delineate the differences between the two compounds.

You might argue that this example proves nothing, because these isomers are really different functional groups. No complexity is added to the situation because we already distinguish ethers from alcohols. However, the concept of isomerism also refers to differences between molecules much subtler than the above example.
Consider for example, the following two alcohols:

\[
\text{propanol (1-propanol) (propan-1-ol) (n-propyl alcohol)}
\]

\[
\text{a primary alcohol}
\]

\[
\text{2-propanol (isopropyl alcohol) (propan-2-ol) (sec-propyl alcohol)}
\]

\[
\text{a secondary alcohol}
\]

Both of these are alcohols and both are based on the same 3 carbon skeleton. Yet they have different melting points, heats of vaporization, and different human toxicities. These compounds differ only in the order and position of their constituent atoms.

To keep the ideas distinct in my mind, I refer to the kind of isomerism found in these first two pairs of molecules as structural isomerism. I have not seen this terminology used elsewhere--usually they are just referred to as isomers--but I still like to keep the label because it helps me to distinguish them from geometric and optical isomers, which we will discuss a bit later on.

Just to hammer home the point, we present two isomeric ethers, illustrating that, whatever the family of compounds, isomerism can occur without differences in the core functional group:
Another example of structural isomerism can arise from the placement of double bonds in a molecule. Consider the following two alkenes:

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{CH}_2 & \quad \text{CH} & \quad \text{CH}_2 & \quad \text{CH}_3 & \quad \text{1-butene} \\
\text{H}_3\text{C} & \quad \text{CH} & \quad \text{CH} & \quad \text{CH} & \quad \text{CH}_3 & \quad \text{2-butene}
\end{align*}
\]

Yes, we said two alkenes: These compounds differ in physical properties and also in the nature and amounts of products they yield when they undergo chemical reactions with various organic and inorganic reagents. These compounds differ only according to the position of the double bond, and yet they are still isomers under our definition because they differ from each other in the order and position of their atoms. They also act like isomers, having different chemical and physical properties, even though they have the same molecular formula, \( \text{C}_4\text{H}_8 \).

Another example of isomerism occurs between cyclic alkanes and alkenes. Examples:

\begin{align*}
\text{cyclopropane} & \\
\text{propene (propylene)}
\end{align*}
Structural Isomerism: alkanes and other hydrocarbons

Even the simplest group of organic compounds, the alkanes, can show structural isomerism. We normally think of butane as a linear four carbon chain:

\[
\begin{array}{c}
  \text{H}_3\text{C} \\
  \text{CH}_2 \\
  \text{CH}_2 \\
  \text{CH}_3
\end{array}
\]

But this is not the only possible structure for a simply hydrocarbon molecule with no double bonds:

\[
\begin{array}{c}
  \text{CH}_3 \\
  \text{H}_3\text{C} \\
  \text{CH} \\
  \text{CH}_3
\end{array}
\]

Don’t worry about the conflicting names: they represent differences of opinion about how best to name the molecule; the first name is, as always, the currently preferred name. They all represent the same 4 carbon alkane, which, like regular garden-variety butane, has a molecular formula of
C₄H₁₀, but represents a distinct chemical compound. We say (again) that butane and 2-methylpropane are isomers.

The same situation occurs with pentane, but, in this case, there are 3 isomers:

**pentane**

H₃C – CH₂ – CH₂ – CH₂ – CH₃

**2-methyl-butane**

H₃C – CH – CH₂ – CH₃

**2,2-dimethyl-propane**

H₃C – C – CH₃

Count the atoms and you will see: they are, all three of them, isomers. As the number of carbons
grows in the alkane, so does the number of isomers, and it does so dramatically. Hexane has 5 isomers and heptane has 9. There are 18 isomers of octane, 35 isomers of nonane and 75 of decane.

Since the “R” group attached to a functional group is often an alkane or a derivative of an alkane, the importance of alkane isomerism extends well beyond the alkane family itself. Consider butanol and its three isomers:
Again, don’t trouble your spirit with the multiple names: as usual the first one is the official one, we include the latter ones (in parentheses) for the sake of completeness.

We conclude this section with some isomers of $\text{C}_4\text{H}_6$. The example illustrates the incredible diversity and plenitude of isomers, even for relatively simple molecules.
Geometric Isomerism: cis/trans compounds

It is possible to have isomers in which the carbons and hydrogens, and all the functional groups are in the same place, but the geometry of the molecules are different. A good example is ethene-diol. A diol is simply a double alcohol, an alcohol with 2 –OH functionalities. We present the two isomers of ethane diol below:

\[
\text{cis - Ethene-1,2-diol} \\
\text{trans - Ethene-1,2-diol}
\]

Notice how the -OH groups are on the same side of the double bond in the cis isomer, but lie across the bond in the trans isomer (Cis and trans are latin prefixes meaning, respectively, “on the same side” and “across”).

The reason these isomers occur is the rigidity of the double bond. The molecule can’t rotate around it. Once locked in place, the -OH groups are either across from each other, or sitting together on the same side. To change this situation, we would have to destroy the double bond, which would, of course, destroy the molecule.
There is another possible isomer for this molecule, but it is structural rather than geometric, because, in this case, the –OH’s are on the same atom:

![Ethene-1,1-diol](image)

Note the distinction: this isomer is structural, because the positions of the atoms are different than in the cis and trans isomers above. Here both –OH groups are on the same carbon. In the cis/trans forms, the –OH’s are on different carbon atoms. Thus there is a difference in structure between ethene-1,1-diol and ethene-1,2-diol. But there are still two possible geometric arrangements of ethene-1,2-diol, which have the –OH’s on atoms 1 and 2 in both molecules, but which have the –OH’s configured differently in space.

It’s sort of like setting up your dorm room. You can have separated beds or bunk beds. The bed arrangement is structurally different for these two possibilities. But, if you choose to have separated beds you can have them on the same wall (cis) or on opposite walls (trans). The same wall/different wall choice still leaves you with separated beds,

You do NOT have if you only have single bonds in your molecule. The structures shown below are NOT geometric isomers because free rotation can take place about the single bond. You can twist the right hand carbon like a propeller shaft, and the –OH group will wind up on the same side of the bond as the –OH group on the next carbon.

And in fact, you yourself do not have to go to the trouble of twisting it., At room temperature these molecules rotate all by themselves. As a result, we never see cis/trans isomerism across a single bond. We frequently (but not always) DO see it across a double bond for molecules such as those discussed above.
The two molecules below, however, ARE geometric isomers and merit the separate cis trans prefixes.

![Ethane-1,2-diol](image)

The two molecules below, however, ARE geometric isomers and merit the separate cis trans prefixes.

![Ethene-1,2-diol](image)

Biomedically, cis/trans isomerism is very important in the analysis of the nutritional values of fatty acids. You may have heard some controversy about this in the news. In nature, all fatty acids are the trans isomer, but it is relatively easy to synthesize trans fatty acids.

The next page shows the structure of cis and trans oleic acid
The cis isomer has a much lower melting point. It is believed that this is because the “hairpin turn” at the double bond causes the molecule to naturally assume a “spiky” shape, and this inhibits its solidification. As a result, arterial deposits of the cis isomer are less likely to form arterial plaque than the trans isomer. Hard to say if this is true. It would be a terrible waste for OREO cookies to eliminate trans fats from their cookies were we to find out 50 years hence the the trans stuff was the good guy all along.
Optical Isomerism: the basics

A compound is said to exhibit optical isomerism when it is possible to construct a mirror image of that compound which is not superimposable on the original. The most common form of optical isomerism is found in an organic compound in which a carbon is bound to 4 different atoms or 4 different groups. Let’s look at a 3D illustration of this principle:

Compound 1 and compound 2 are mirror images. If compound 1 had eyes and could look at compound 2, it would believe it was seeing its own reflection:

The particular identity of the atoms attached to the central carbon is not a central issue. The compound will exhibit optical isomerism as long as you can construct its mirror image. If it helps, we could imagine that this compound was CHClBrI (bromo-iodo-chloro methane).

You might question this and say that if we just twist compound 2 around the up and down axis, the molecules would in fact overlap. Through the magic of computerized 3D graphics, we have done this on the next page.
As you can see, two of the atoms are in the wrong place--compound 2 can’t be superimposed on compound 1. These compounds exhibit optical isomerism.

A few definitions about terminology that also refers to this phenomenon of optical isomerism. A 50/50 mixture of two optical isomers is called a racemic mixture and the two isomers are called racemates. They are also often referred to as enantiomers, and a mixture of them is called an enantiomeric mixture.

A carbon to which 4 different substituents are affixed will exhibit optical isomerism. Such a carbon is called a chiral carbon or a chiral center, and the compound containing it is often called a chiral compound. It may also be referred to as an optically active compound.

Optically active compounds are often found in biological contexts. Consider the amino acids:

- Glycine: \( \text{H}_2\text{N} - \text{CH} - \text{C} - \text{OH} \)
- Alanine: \( \text{H}_2\text{N} - \text{C} - \text{C} - \text{OH} \)
Notice that alanine contains a chiral carbon, while glycine does not. Glycine, the simplest amino acid, does not exhibit optical activity. Alanine, and all other amino acids do exhibit optical activity (i.e. optical isomerism).

You will recall that the generic formula for an amino acid is:

\[
\begin{align*}
&\text{O} \\
&\text{C} \quad \text{OH} \\
&\text{R} \quad \text{C} \quad \text{NH}_2 \\
&\text{H}
\end{align*}
\]

You can see that this will be optically active if “R” is anything other than an H atom.

What about a carboxyl group or an amine group? The it wouldn't be an amino acid any more. But YOU SAID you could have amines or carboxylic acids as the “R” group!!! Yes I did, but this does not include a naked amine group or carboxylic acid.

The two different forms of, say, alanine have slightly different names:

\[
\begin{align*}
&\text{HO} \quad \text{C} \quad \text{C} \quad \text{NH}_2 \\
&\text{CH}_3 \\
\end{align*}
\]

\[
\begin{align*}
&\text{H}_2\text{N} \quad \text{C} \quad \text{C} \quad \text{OH} \\
&\text{CH}_3
\end{align*}
\]

L-Alanine  D-Alanine

The precise reason for using the letters “D” and “L” are unimportant for the present. The important thing is that they represent mirror images of one another (also called enantiomers). One interesting side fact: every amino acid used and produced by every organism in the world, so far as we know, uses the “D” form of the amino acid. This is the kind of insight that leads
scientists to believe that all life is related, that it somehow springs from the same source, and at the most basic cellular level, it follows the same biochemical laws.

Another important manifestation of chirality in medicine is in the optical isomerism of simple sugars. The simplest carbohydrates contain 3 carbon atoms and have the empirical formula of \( C_3H_6O_3 \). Here they are:

\[
\begin{align*}
\text{D-glyceraldehyde} & : & O \\
& & \big| \\
& & 1C \quad \big| \quad H \\
& & \big| \\
& & H \quad \big| \quad \big| \quad OH \\
& & \big| \\
& & HO \quad \big| \quad \big| \quad H \\
& & \big| \\
& & \big| \quad \big| \quad \big| \quad \big| \quad H \\
& & \big| \\
& & \big| \quad \big| \quad \big| \quad \big| \quad \big| \quad H \\
& & \big| \\
& & \big| \quad \big| \quad \big| \quad \big| \quad \big| \quad \big| \quad H \\
& & \big| \\
& & \big| \quad \big| \quad \big| \quad \big| \quad \big| \quad \big| \quad \big| \quad \big| \quad H \\
\end{align*}
\]

\[
\begin{align*}
\text{L-glyceraldehyde} & : & O \\
& & \big| \\
& & 1C \quad \big| \quad H \\
& & \big| \\
& & HO \quad \big| \quad \big| \quad H \\
& & \big| \\
& & \big| \quad \big| \quad \big| \quad \big| \quad H \\
& & \big| \\
& & \big| \quad \big| \quad \big| \quad \big| \quad \big| \quad \big| \quad H \\
& & \big| \\
& & \big| \quad \big| \quad \big| \quad \big| \quad \big| \quad \big| \quad \big| \quad \big| \quad H \\
\end{align*}
\]

\[
\begin{align*}
\text{Dihydroxyacetone} & : & H \\
& & \big| \\
& & 1C \quad \big| \quad OH \\
& & \big| \\
& & \big| \quad \big| \quad \big| \quad \big| \quad H \\
& & \big| \\
& & \big| \quad \big| \quad \big| \quad \big| \quad \big| \quad \big| \quad \big| \quad \big| \quad H \\
& & \big| \\
& & \big| \quad \big| \quad \big| \quad \big| \quad \big| \quad \big| \quad \big| \quad \big| \quad \big| \quad \big| \quad H \\
\end{align*}
\]

Note that the middle carbon is labeled as #2. It is a chiral carbon in the two glyceraldehyde molecules because it has four different groups attached to it. There are no chiral centers in dihydroxy acetone. Sugars belong to families whose name ends in –ose. We say that the two optical isomers of glyceraldehyde are ALDOSES because they have an aldehydic functional group at the end, whereas dihydroxyacetone is a ketose, because it contains a ketone functional group.

Let’s now look at some actual sugars, compounds with which we are familiar. The basic sugar used by our body, and all living things as far as we know, is glucose. The glucose molecule is drawn on the next page in both its D and L configurations.
The difference between D– and L–glucose arises from the optical arrangement around the #5 carbon. Note how we number carbons starting at the end where the carbonyl group is. As you can see there are several other chiral carbons in glucose, but they all have the same configuration in D–glucose and L–glucose. Only the next to last carbon matters. In fact, in all linear carbohydrates, the next to last carbon dictates the optical geometry of the molecule, and is named based up which of the D– and L–glyceraldehyde formulas it conforms to.

What about the other 3 carbons? They can generate a total of 23 different molecules—that’s seven more after glucose, and there are 7 other 6 carbon aldoses—we call them hexoses. We have drawn one, galactose. This is part of a larger sugar called lactose. When the body chops the lactose molecule it fragments it into 2 smaller sugars, glucose and galactose. If the body lacks the enzyme to convert galactose to glucose, the galactose acts as a poison. Young children who exhibit this enzymatic deficiency are said to have galactosemia. This is a much more serious condition than lactose intolerance, and babies so afflicted can literally be killed by their mothers’ milk. The rearrangement of a single –OH and -H on the number 4 carbon causes this malady. Sometimes nature seems almost malignantly subtle, although it can be argued that nature provides us with the mental faculties to solve the subtle problems with which it presents us.