

Notes on Isomers

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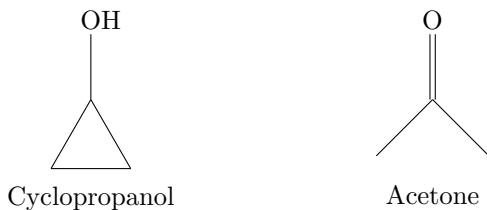
October 8, 2013

1 Introduction

Many organic compounds can have their atoms rearranged in various ways; these rearrangements are isomers of the molecule. These notes cover the classification, nomenclature, and enumeration of isomers.

2 Constitutional or Structural Isomers

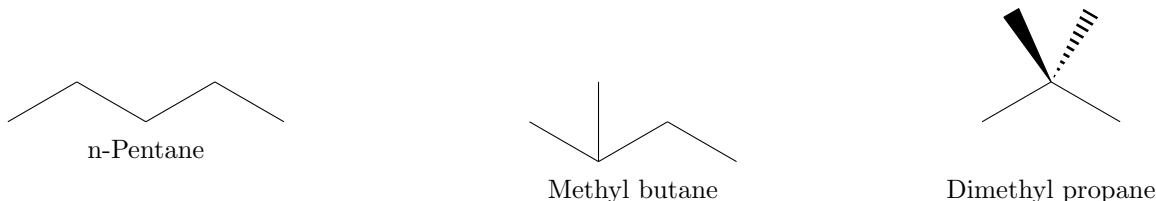
If two isomers have different connectivity, they are called constitutional isomers. For example, cyclopropanol and acetone (shown below) are constitutional isomers, because they have the same molecular formulas (C_3H_6O) but different connectivities.



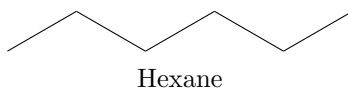
Constitutional isomerism can be subdivided into three basic types. Understanding these types is helpful when trying to enumerate all of the constitutional isomers of a compound.

2.1 Chain Isomerism

When members of the carbon chain are rearranged to form distinct isomers, chain isomers are formed. A good example is the 3 isomers of pentane, in which the carbon skeleton are arranged in three unique ways:

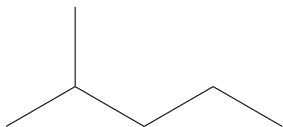


The five¹ isomers of hexane can be found similarly, by removing carbons from the main chain and inserting them as alkyl groups. To do this methodically, it may be beneficial to work through different numbers and types of alkyl groups as separate cases. For the example of hexane, we start by finding all isomers which have no alkyl groups. This is clearly just straight-chain hexane:

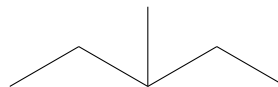


¹There is a sequence of these numbers available at <http://oeis.org/A000602>.

Next, we consider all isomers which contain a single methyl group. After removing a carbon from the chain, 5 carbons remain. We cannot place the methyl group on either of the terminal carbons, because the resulting molecule would be identical to straight-chain hexane. Therefore, we can place it on any of the three middle carbons. Two of those possibilities would be superimposable mirror images, so we are left with two isomers:

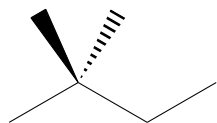


2-methyl pentane

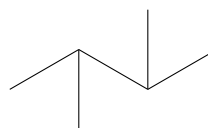


3-methyl pentane

Naturally, we next consider isomers with 2 methyl groups. The main chain will be left with only 4 carbons, and because we cannot place the methyl groups on the terminal carbons, there are two places to put each one. Removing superimposable mirror images from the count, we are left with 2 more isomers:



2,2-methyl butane

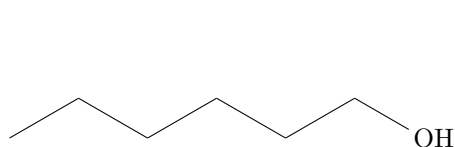


2,3-methyl butane

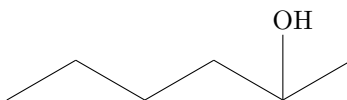
Thus, we have found all 5 isomers. There are no isomers of hexane containing ethyl groups, because they would all be identical to one of the aforementioned isomers.

2.2 Position Isomerism

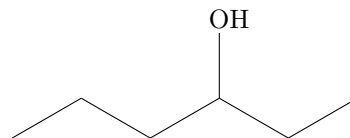
In addition to rearranging carbon chains, we can also rearrange functional groups. The isomers of hexane which fell into the same cases in the above enumeration may be considered examples of position isomerism. Hexanol also provides a good example, because of the hydroxyl group which can be shifted:



1-Hexanol



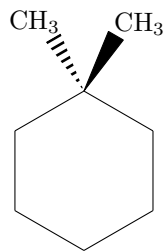
2-Hexanol



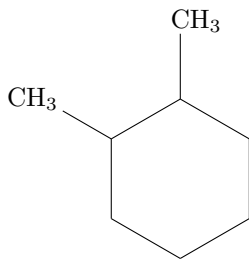
3-Hexanol

There are, of course, more isomers of hexanol; any of the isomers of hexane above can be transformed into hexanol by attaching a hydroxyl group.

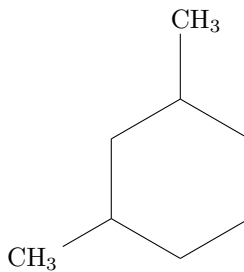
Position isomerism is also present in cyclic compounds. Dimethyl cyclohexane displays position isomerism:



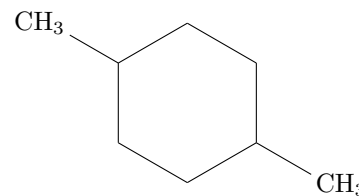
1,1-dimethyl cyclohexane



1,2-dimethyl cyclohexane



1,3-dimethyl cyclohexane



1,4-dimethyl cyclohexane

2.3 Functional Group Isomerism

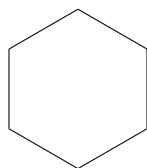
The most complex variety of structural isomerism is functional group isomerism. Functional group isomers have their atoms arranged so that the molecule possesses different functional groups. When working with functional group isomerism, it is very advantageous to know the degree of unsaturation (DOU) of the molecule in question. This can be determined easily from the chemical formula by the following relation:

$$\text{DOU} = \frac{2C + 2 + N - H - X}{2}$$

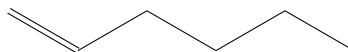
Where C is the number of carbons, N is the number of nitrogens, H is the number of hydrogens, and X is the number of halogens. Note that oxygen is not present in this formula. Here is a table of examples:

Formula	DOU
C_4H_{10}	0
C_3H_7	1
C_2H_2	2
C_6H_6	4
C_6H_5OH	4
C_2H_3Cl	2
HCN	2

The reason this quantity is useful is because it corresponds to the number of structural unsaturation features in a molecule. Each double bond and each ring is equivalent to one degree of saturation; a triple bond is equivalent to two degrees of saturation. You can verify by drawing structures for the molecules in the above table that this rule holds. This provides a simple way of finding isomers: change the number of multiple bonds and rings while keeping the DOU constant. For example, cyclohexane can be transformed into 1-hexene:



Cyclohexane

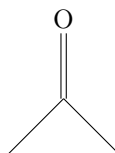


1-hexene

Another example, from the beginning of this section, is acetone and cyclopropanol. The double bond in acetone becomes a ring in cyclopropanol, keeping the DOU constant.



Cyclopropanol

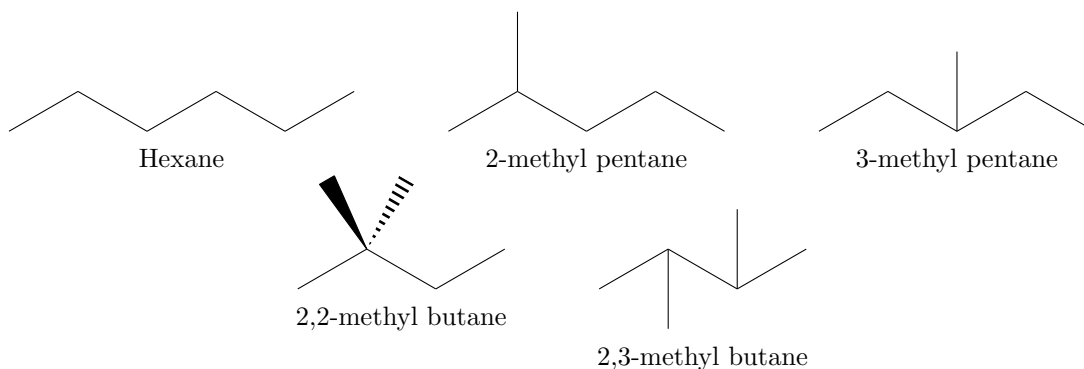


Acetone

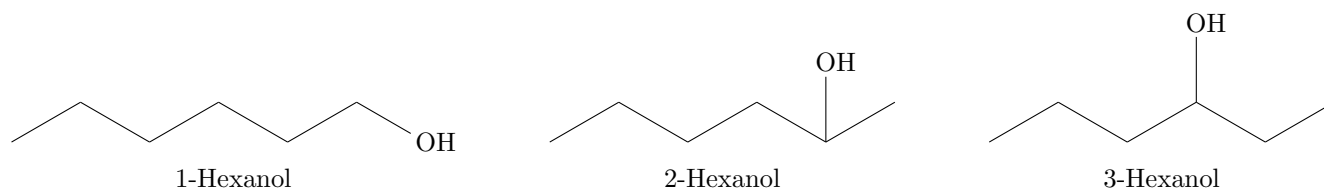
Functional group isomerism can lead to many different isomers. For example, acetone has 7 more isomers, most of which could be considered functional group isomers. It's possible that you'll encounter a test question which says something like "find all the isomers of this alcohol which are themselves alcohols." In that case, functional group isomerism is not important, because isomers which change the functional group are not being considered.

2.4 Isomer Counting

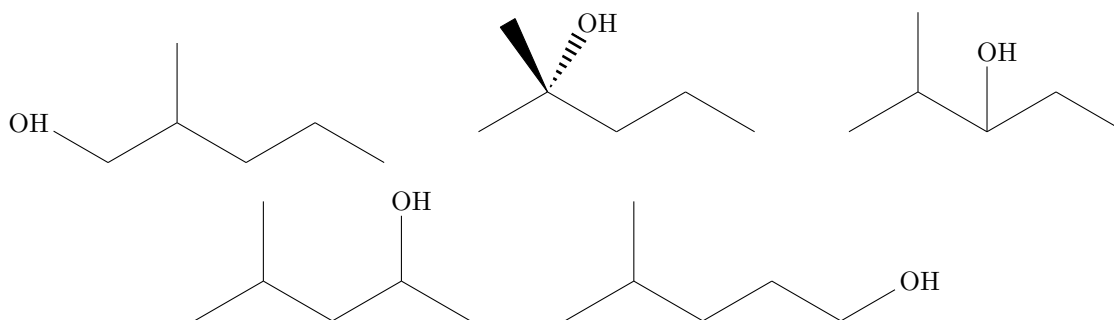
Counting the number of isomers of a molecule is a very challenging problem in combinatorics. Even for simple alkanes, more math than is practical to do by hand is required. However, the sheer quantity of isomers one can find for even mildly complex molecules will limit test questions. For example, something as small as C_8H_8NBr has no less than 649,000 constitutional isomers. A more practical case is hexanol. We've already done much of the work for hexanol, by finding the chain isomers of hexane:



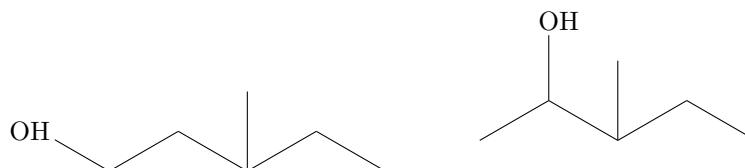
Now we just need to place hydroxyl groups on these. Again, we've already done the work for the first case:

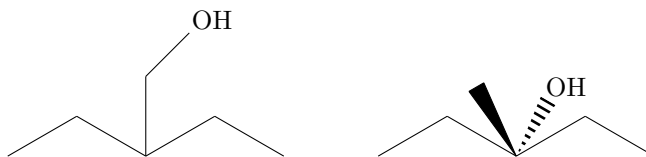


The asymmetry of 2-methyl pentane leads to many possible isomers. Note that attaching a hydroxyl to the methyl group is not an option, because that would be identical to the first isomer shown.

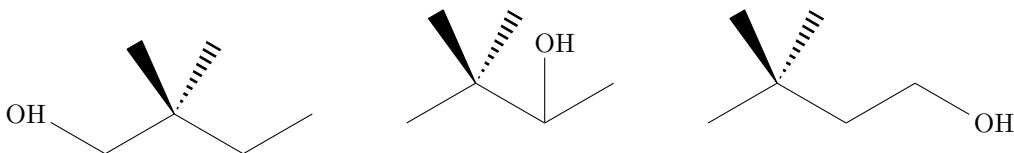


Next comes 3-methyl pentane, which is fairly straightforward:

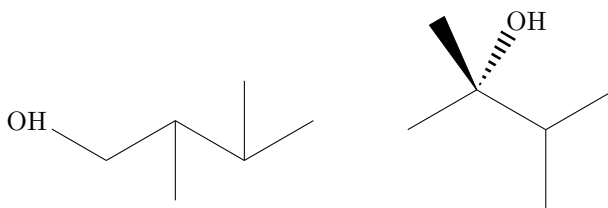




The next case, 2,2-dimethyl butane, is also asymmetric:



And, finally, 2,3-dimethyl-butane, with only 2 isomers:



In total, that's 17 different isomers - and that's not including functional group isomers. You may see other places where hydroxyl groups could be attached, but all of those possibilities (assuming I haven't made an error) would be identical to an isomer already identified. Justifying that to yourself may be good practice.

3 Stereoisomers

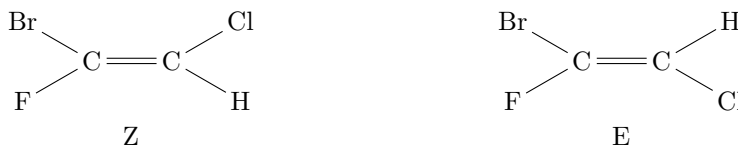
When isomers have the same connectivity, then they are stereoisomers. Stereoisomers can be either diastereomers or enantiomers.

3.1 Diastereomers

Diastereomers are stereoisomers that are not mirror images of each other. The most important examples are geometric isomers. A good example is 2-butene, which has a cis and a trans form:

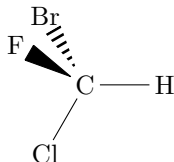


This naming system is fairly easy to remember: *trans* means across, and trans isomers have identical groups across from each other. However, when there are more than 2 different groups in question, which isomer is cis and which is trans becomes unclear. In these cases, we use E/Z naming instead. The first step in E/Z naming is to assign each group a priority; this is done through the CIP system. It's often just the atomic number, but in the case where that ties, the complete rules are at the end. Once each group is assigned a priority, we look and see if the higher-priority groups are on the same side of the double bond. If so, then the molecule is the Z isomer; otherwise, it is the E isomer. Here's a simple example:

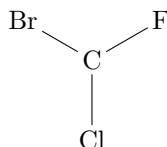


3.2 Enantiomers

Enantiomers, also known as optical isomers, are non-superimposable mirror images of each other. The simplest and most common example is a carbon atom with 4 different groups attached. Here's a simple example using the same atoms as the diastereomer example:



Enantiomers are most often named using the R/S system. To use this system, we first orient the molecule so that the lowest priority group (hydrogen, in this case) faces away from the viewer:

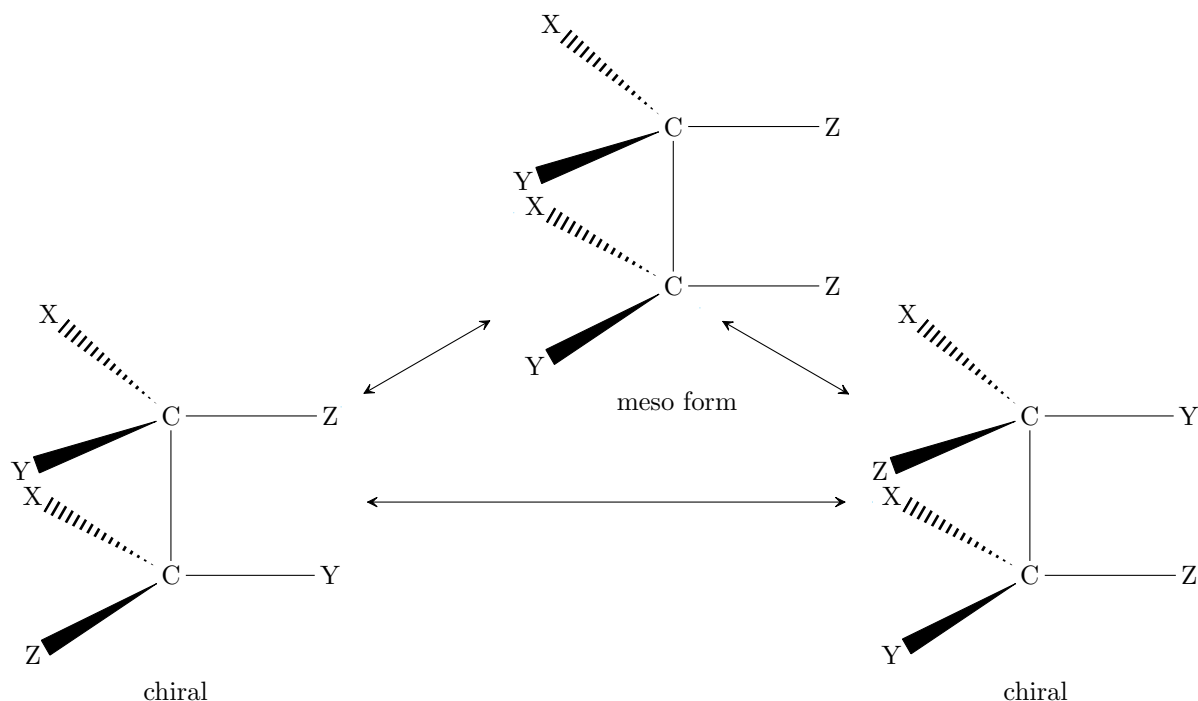


We then observe that the groups, ordered by decreasing priority, are oriented counter-clockwise. Therefore, this is the S (for *sinister*, Latin for left) isomer. If instead the groups were oriented clockwise, it would be the R (for *rectus*, Latin for right) isomer.

Another naming system, the +/- system, uses the optical properties of enantiomers. Given a pair of enantiomers, one will rotate the plane of polarized light clockwise, and the other will rotate it counter-clockwise. The one which rotates the plane clockwise is labeled +, and called dextrorotatory. The one which rotates it counter-clockwise is labeled -, and called levorotatory. There is no direct relationship between the R/S system and the +/- system.

3.3 Stereochemistry with Two Singly-bonded Carbons

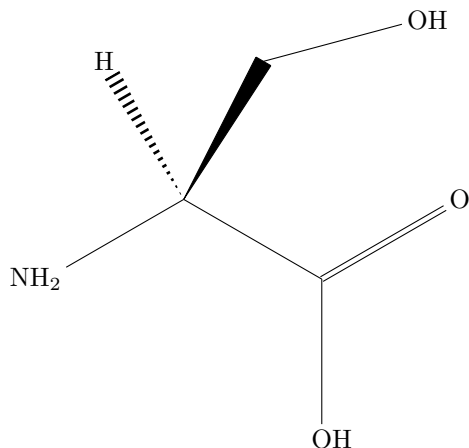
With two singly-bonded carbons, each with the same three other groups attached, a molecule can have a meso form. This is the structure which possesses a plane of symmetry perpendicular to the carbon-carbon bond. The same molecule has two other optical isomers. Each of these isomers are diastereomers with the meso form, and enantiomers with each other. The following diagram illustrates this concept, by labeling the three groups X, Y, and Z for clarity.



4 CIP Priority

The CIP system is a means of assigning relative priorities to groups in a stereoisomer. The first and most common way is to look at the atomic numbers of the atoms bonded directly to the stereocenter. In a case where this results in a tie between two groups, we look at the atoms 2 bonds away from the stereocenter. Both sets of such atoms are arranged in decreasing order of atomic number. When the sets are placed side-by-side, the group with the higher atomic number at the first discrepancy is given the higher priority. If these sets happen to be identical, proceed to the atoms 3 bonds away from the stereocenter, and so on until a priority can be assigned.

The amino acid serine is a good example. Serine has the following structure:



The amine group is assigned highest priority, because nitrogen has the highest atomic number. Likewise, the hydrogen is assigned lowest priority, because it has the lowest atomic number. Between the two carbons, we must examine the atoms of distance 2 from the stereocenter. The carbon on the methyl alcohol group has 1 oxygen, and 2 hydrogens bonded to it. The carbon on the carboxyl group has 2 oxygens bonded to it.

Arranging these atoms in decreasing order of atomic number, we see that at the second position, carboxyl has an oxygen where methyl alcohol has a hydrogen. Therefore, carboxyl gets the higher priority.