

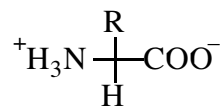
Biochemistry: The Chemistry of Life - The principles learned in general and organic chemistry are relevant to everyday life. However, only a fraction of the reactions studied actually play a role in how we function. Biochemistry is the study of the chemical processes and principles as applied to living systems. Indeed, without biochemistry, we could not live!

The difference between organic chemistry and biochemistry is subtle. In the former, all the experimental conditions that govern how a reaction occurs are in the control of the experimenter. In biochemistry, on the other hand, all the processes studied occur under pre-set conditions. When studying biochemistry in a lab, one tries to emulate the "natural" conditions to get the full picture. It is helpful to study the reactions using traditional organic chemistry methods, but in the end, the details are only understood in terms of the biological environment.

In the discussion that follows, the chemical principles of biochemistry will be introduced and eventually applied to the biological system. However, it is assumed that the "details" of the cellular structure of the organs in the body are already known. This information falls under the category of biology and is not part of this course.

Amino Acids - The "normal" organic acids are the Carboxylic acids, and the "normal" organic bases are the Amines. What do you get when you have both moieties in the same molecule? If the two groups are separated by 1 carbon, the resulting molecule is referred to as a normal **amino acid**. More specifically, if the intervening carbon has at least one hydrogen bound to it, the amino acid is said to be an ordinary one. The terms "ordinary" and "normal" are not generally used; rather, when the molecule is different from the common, normal amino acid, special attention is made to make that "unusual-ness" be known.

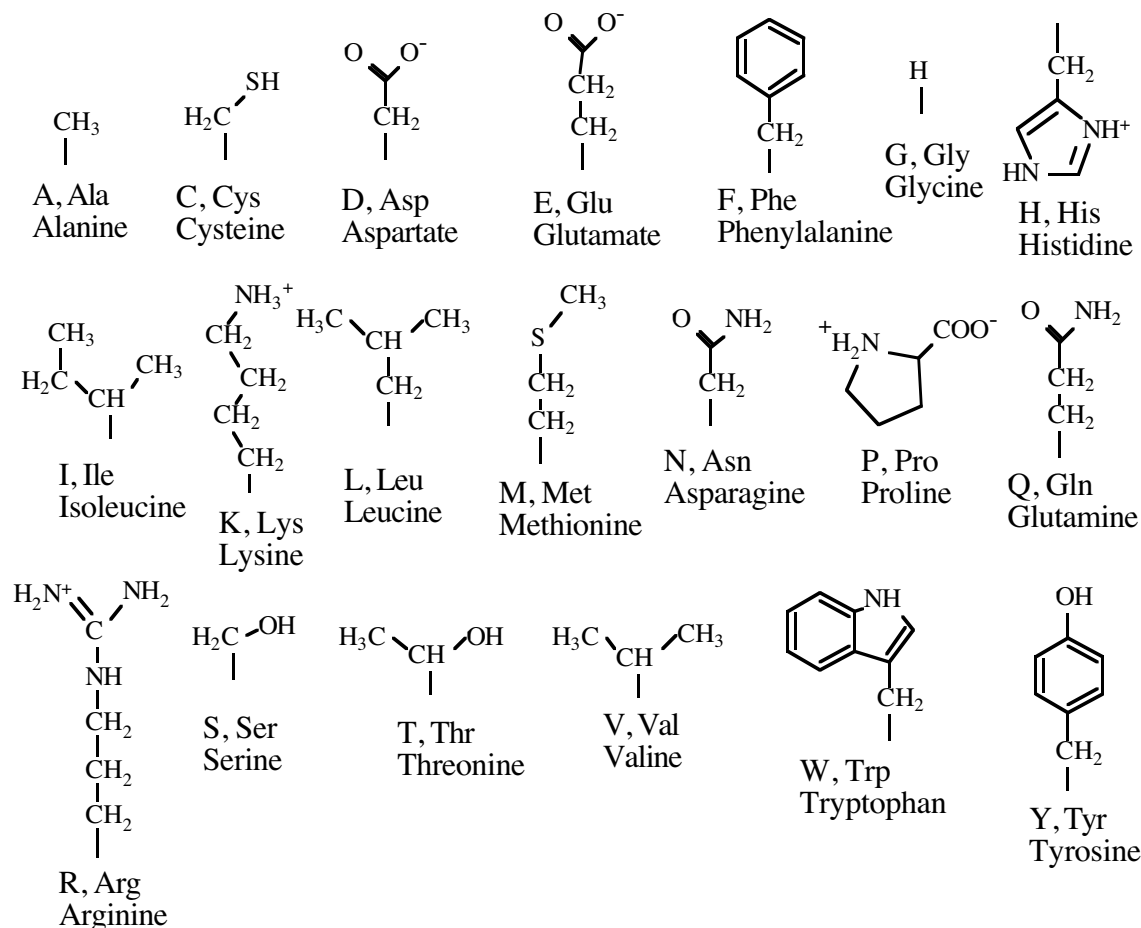
There are 20 naturally occurring amino acids that appear commonly, and a few not-so-common ones (that are generally due to external sources). These amino acids all follow the general formula:



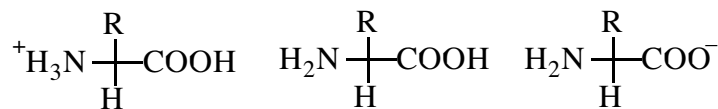
Where the R side chain can be one of 20 different "groups" or moieties. Below is the list of the side chains with the name of the amino acid below the structure. The letters appearing immediately above the names are the **one-letter** and **three-letter codes** that people use to refer to the amino acids. As we will see, this is a great time saver when it comes to describing the amino acid content of proteins.

Of all the amino acids listed, the "simplest" one is **glycine**, where the side chain is just a hydrogen atom. The most "complicated" one is **proline**, because the "amino" portion of the amino acid is part of the side chain. This unusual character will be discussed later when we talk about protein structures.

It is not absolutely necessary for you to memorize the structures, but it is helpful if you have a working knowledge of them. The details of their structures plays an important role in the way they behave. Generally, we group these amino acids based on the general characteristics of the side chains. The four groupings are: (1) non-polar, (2) polar, (3) acidic, (4) basic. In a future section, we will discuss the members of the groups and why they are in their respective groups. But first, there are a few general properties we need to discuss.



Zwitterion - The skeleton structure of the amino acid drawn above is doubly charged. The carboxylic group is deprotonated (to give the carboxylate ion) and the amine group is protonated (to give the ammonium ion). Is this the appropriate structure? Or, should we maybe draw the amino acid neutral, or positively charged, or negatively charged? i.e., are any of the following appropriate?



The answer is "it depends on the pH". At low pH, the carboxylic acid group will not lose its proton, since the solution already has a lot of H⁺ (think of LeChâtelier's principle), but

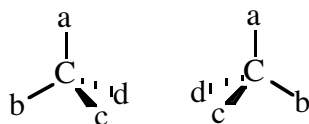
the amine group, since it is a base, will pick up an H^+ , and the net charge on the molecule will be positive (Note: we are ignoring the effect of the side chain for now). Similarly, at high pH, the OH^- in the solution will abstract the H^+ from both the $-COOH$ and the NH_3^+ , leaving the molecule negatively charged.

What about the completely neutral structure and the doubly charged structure (which is also neutral overall)? When the pH of the solution is just right, the $-COOH$ can lose its H^+ and the $-NH_2$ can pick up an H^+ . The resulting structure is the doubly charged **zwitterion** (this comes from the German word for hermaphrodite), which is what was drawn at the beginning of the discussion. The pH at which this occurs is called the **isoelectric point**, and it is dependent on the side chain, since it is the point where the net positive charge and net negative charge of the molecule cancel out. We will discuss this in more detail shortly.

So, what about that unionized neutral form? When does that occur? The answer is "only in the gas phase"! For all practical purposes, this is not a useful structure to consider.

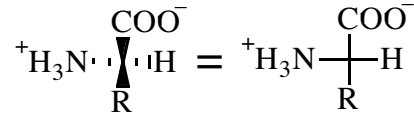
Chirality - The notion of mirror images was briefly touched upon in organic chemistry. It is a very important chemical concept, but an even more important biochemical one. So, we will reintroduce the concept, and use the amino acids as examples of **chiral** compounds (i.e. compounds that exhibit this mirror image property known as **optical activity**).

When a carbon atom has 4 different things bound to it, there are two unique ways to place the objects:



Why are these unique? The answer is that there is no way of superimposing the two molecules so that all the 4 groups overlap without breaking 2 bonds and making two bonds. These two isomers are said to be **enantiomers**. The physical property that differentiates them is the way they interact with polarized light. One of them will cause the light to rotate to the left (called **levorotation**), and the other rotates it to the right (called **dextrorotation**). From looking at the structure, there is no straightforward way of deciding which is which. The only way to know for sure is to do an experiment. But, we can arbitrarily call one "left" and the other "right", as long as we always use the same rules consistently.

As it turns out, all naturally occurring amino acids have the levorotatory property (with the exception of glycine), and are called **L-amino acids**. The chiral center to which we are referring is the carbon between the amino and carboxylic groups. To represent them as such, we draw them:



If the orientation is inconvenient, we can rotate the molecule, but we must always be aware that the R and COO⁻ are coming out of the page and the NH₃⁺ and H are going into the page.

Side Chain Characteristics - As mentioned above, the side chains are generally grouped into four categories. Using the 3-letter codes, the groups are:

Non-Polar: Gly, Ala, Val, Leu, Ile, Pro, Phe, Met
 Polar: Ser, Thr, Asn, Gln, Trp, Cys*, Tyr**
 Acidic: Asp, Glu
 Basic: His, Lys, Arg, *, **

The nonpolar groups are essentially alkyl chains (and, in the case of methionine, a thio-ether), and are generally **hydrophobic** - i.e. water fearing - in nature. This property is important in protein structure.

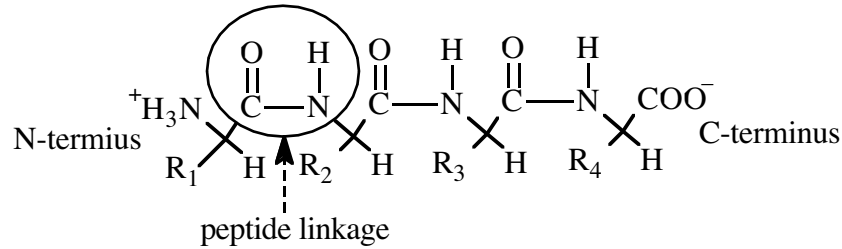
The polar groups are amides, alcohols, an amine, and a thiol. These groups are somewhat **hydrophilic** - water loving - but, more importantly, they can form hydrogen bonds with each other (and, in the case of cysteine, a covalent **disulfide bridge**) . The amino acids marked with asterisks fall into either the basic or polar families, but are generally considered polar because they are uncharged at neutral pH.

The acidic groups both have carboxylic moieties, and the basic groups have amino moieties. At neutral pH, these groups are charged (acids are negative and bases are positive), and are very hydrophilic. Due to their opposite charges, acid groups and base groups often interact with each other to form an ionic bond called a **salt bridge**.

The charged nature of the acidic and basic groups, and the ability for some of the polar groups to form H-bonds with water, affect the isoelectric points of the amino acids. The isoelectric point is the pH at which the entire amino acid is neutral, not just the **backbone** groups (i.e. the ⁺H₃N-C-COO⁻). Therefore, the isoelectric points of the acidic groups tend to be lower than the non-polar groups (need more H⁺ to neutralize the side chain carboxylate), and the basic groups have higher isoelectric points (need more OH⁻ to remove the H⁺ from the side chain ammonium group).

Peptides - Amino acids have the tendency to bind to each other via backbone amide bonds. The carboxylic acid of one amino acid binds to the amine of another. The amide bond in this situation is called a **peptide** linkage, and the resulting molecule is a **di-peptide**. If a third amino acid is added, the molecule is a **tripeptide**. In general, the molecules are called **polypeptides**.

The amino acid that supplies the first carboxyl group to the first amide still has a free amine. This end of the molecule is, therefore, called the **N-terminus**. The last amino acid added has a free carboxylic acid group. This end is called the **C-terminus**:



The order in which the amino acids are connected, from the N-terminus to the C-terminus (left to right), is called the **sequence** or the **primary structure** of the polypeptide. But this does not tell the whole story. The free rotation about the peptide linkages allows many different conformations of the polypeptide. And, the side chains often have the ability to rotate as well, making the conformation quite confusing. Luckily, the side chains can interact with each other, and the backbone carbonyls and amines can interact (form H-bonds) with each other. Each of these types of interactions cause the polypeptide to take on a preferred structure. We will look at the interactions to get a better idea of what the structures might be.