

## 1-1 Amino Acids

### The chemical characters of the amino-acid side chains have important consequences for the way they participate in the folding and functions of proteins

The amino-acid **side chains** (Figure 1-3) have different tendencies to participate in interactions with each other and with water. These differences profoundly influence their contributions to protein stability and to protein function.

**Hydrophobic** amino-acid **residues** engage in *van der Waals* interactions only. Their tendency to avoid contact with water and pack against each other is the basis for the *hydrophobic effect*. Alanine and leucine are strong helix-favoring residues, while proline is rarely found in helices because its backbone nitrogen is not available for the hydrogen bonding required for helix formation. The aromatic side chain of phenylalanine can sometimes participate in weakly polar interactions.

**Hydrophilic** amino-acid residues are able to make *hydrogen bonds* to one another, to the peptide backbone, to polar organic molecules, and to water. This tendency dominates the interactions in which they participate. Some of them can change their charge state depending on their pH or the microenvironment. Aspartic acid and glutamic acid have  $pK_a$  values near 5 in aqueous solution, so they are usually unprotonated and negatively charged at pH 7. But in the hydrophobic interior of a protein molecule their  $pK_a$  may shift to 7 or even higher (the same effect occurs if a negative charge is placed nearby), allowing them to function as proton donors at physiological pH. The same considerations apply to the behavior of lysine, which has a  $pK_a$  greater than 10 in water and so is usually depicted as positively charged. But in a nonpolar environment, or in the presence of a neighboring positive charge, its  $pK_a$  can shift to less than 6, and the resulting neutral species can be a proton acceptor. Histidine is perhaps the most versatile of all the amino acids in this regard, which explains why it is also the residue most often found in enzyme active sites. It has two titratable  $-N-H$  groups, each with  $pK_a$  values around 6. When one of these  $-N-H$  groups loses a proton, however, the  $pK_a$  of the other one becomes much greater than 10. When both are protonated, the residue as a whole is positively charged. When only one is protonated (usually it is the one farthest from the main chain of the protein) the side chain is neutral and has the ability both to donate and to accept a proton. The fully deprotonated form is negatively charged, and occurs rarely. Arginine is always completely protonated at neutral pH; its positive charge is localized primarily at the carbon atom of the guanidium head. Serine, threonine, glutamine and asparagine do not ionize but are able both to donate and to accept hydrogen bonds simultaneously. Cysteine, like histidine, is commonly found in enzyme active sites, because the thiolate anion is the most powerful *nucleophile* available from the naturally occurring amino acids.

**Amphipathic** residues have both polar and nonpolar character, making them ideal for forming interfaces. It may seem surprising to consider the charged side chain of lysine as amphipathic, but its long hydrophobic region is often involved in *van der Waals* interactions with hydrophobic side chains. Tyrosine does not usually ionize at physiological pH (its  $pK_a$  is about 9) but in some enzyme active sites it can participate in acid-base reactions because the environment can lower this  $pK_a$ . The  $-O-H$  group is able both to donate and to accept hydrogen bonds, and the aromatic ring can form weakly polar interactions. Tryptophan behaves similarly, but the indole  $-N-H$  group does not ionize. Methionine is the least polar of the amphipathic amino acids, but the thioether sulfur is an excellent ligand for many metal ions.

#### Definitions

**amphipathic:** having both polar and nonpolar character and therefore a tendency to form interfaces between **hydrophobic** and **hydrophilic** molecules.

**hydrophilic:** tending to interact with water. Hydrophilic molecules are polar or charged and, as a consequence, are very soluble in water. In polymers, hydrophilic **side chains** tend to associate with other hydrophilic side chains, or with water molecules, usually by means of hydrogen bonds.

**hydrophobic:** tending to avoid water. Hydrophobic molecules are nonpolar and uncharged and, as a consequence, are relatively insoluble in water. In polymers, hydrophobic **side chains** tend to associate with each other to minimize their contact with water or polar side chains.

**residue:** the basic building block of a polymer; the fragment that is released when the bonds that hold the polymer segments together are broken. In proteins, the residues are the amino acids.

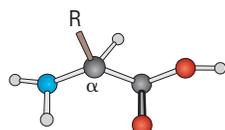
**side chain:** a chemical group in a polymer that protrudes

from the repeating backbone. In proteins, the side chain, which is bonded to the alpha carbon of the backbone, gives each of the 20 amino acids its particular chemical identity.

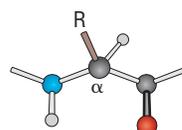
#### References

Creighton, T.E.: *Proteins: Structure and Molecular Properties* 2nd ed. Chapter 1 (Freeman, New York, 1993).

A website summarizing the physical-chemical properties of the standard amino acids may be found at: <http://prowl.rockefeller.edu/aainfo/contents.htm>



The chemical structure of an amino acid. The backbone is the same for all amino acids and consists of the amino group (NH<sub>2</sub>), the alpha carbon and the carboxylic acid group (COOH). Different amino acids are distinguished by their different side chains, R. The neutral form of an amino acid is shown: in solution at pH 7 the amino and carboxylic acid groups ionize, to NH<sub>3</sub><sup>+</sup> and COO<sup>-</sup>. Except for glycine, where R=H, amino acids are chiral (that is, they have a left-right asymmetry). The form shown is the L-configuration, which is most common.

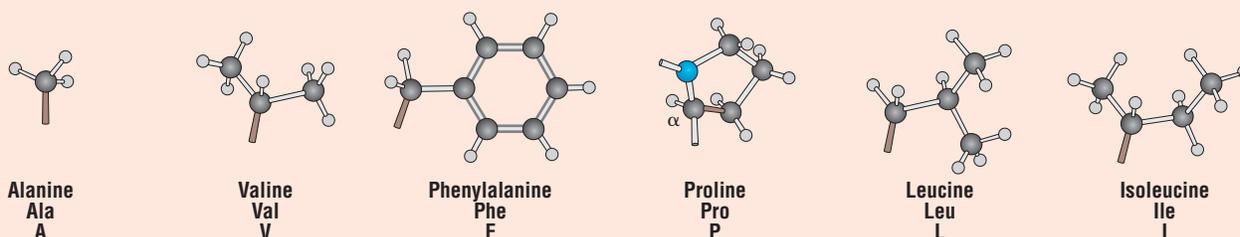


An amino-acid residue as it is incorporated into a polypeptide chain. The R group is the side chain. The 20 different side chains that occur in proteins are depicted below. For proline, the side chain is fused back to the nitrogen of the backbone. The configuration about the alpha carbon is L for most amino acids in proteins.

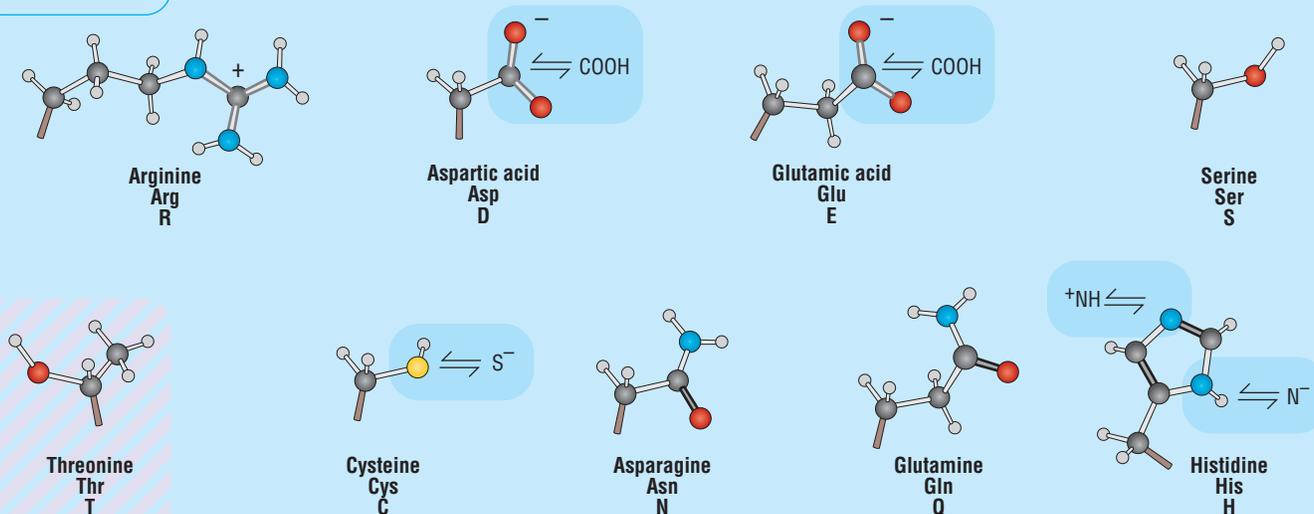
○ Hydrogen ● Carbon ● Oxygen ● Sulfur ● Nitrogen | bond to functional group (R) || double bond || partial double bond | single bond



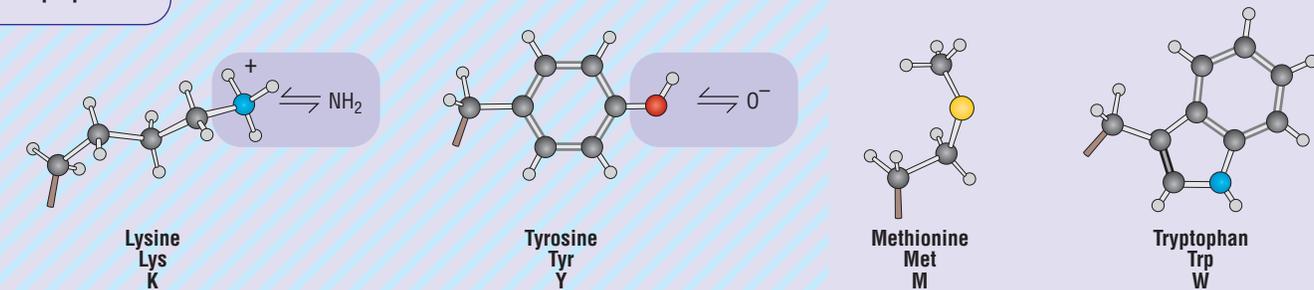
**Hydrophobic**



**Hydrophilic**



**Amphipathic**



**Figure 1-3 Amino-acid structure and the chemical characters of the amino-acid side chains** Charged side chains are shown in the form that predominates at pH 7. For proline, the nitrogen and alpha carbon are shown because the side chain is joined to the nitrogen atom to form a ring that includes these atoms.