

Lippincott's Illustrated Reviews: Biochemistry

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The authors and publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new or infrequently employed drug.

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Structure of Amino Acids

I. OVERVIEW

Proteins are the most abundant and functionally diverse molecules in living systems. Virtually every life process depends on this class of molecules. For example, enzymes and polypeptide hormones direct and regulate metabolism in the body, whereas contractile proteins in muscle permit movement. In bone, the protein collagen forms a framework for the deposition of calcium phosphate crystals, acting like the steel cables in reinforced concrete. In the bloodstream, proteins such as hemoglobin and serum albumin shuttle molecules essential to life, whereas immunoglobulins destroy infectious bacteria and viruses. In short, proteins display an incredible diversity of functions, yet all share the common structural feature of being linear polymers of amino acids. This chapter describes the properties of amino acids; Chapter 2 explores how these simple building blocks are joined to form proteins that have unique three-dimensional structures, making them capable of performing specific biological functions.

II. STRUCTURE OF AMINO ACIDS

Although more than 100 different amino acids have been described in nature, only 20 of these species are commonly found as constituents of mammalian proteins. Each amino acid (except for proline) has a carboxyl group, an amino group, and a distinctive side chain ("R-group") bonded to the α -carbon (Figure 1.1). At physiologic pH (approximately 7.4) the carboxyl group is dissociated to form the negatively charged carboxylate ion (—COO^-), and the amino group is protonated (—NH_3^+). In proteins these carboxyl and amino groups are combined in peptide linkage and are not available for chemical reaction (except for hydrogen bonds as described on p. 17). Thus, it is the nature of the side chains that ultimately dictates the role an amino acid will play in a protein. It is therefore useful to classify the amino acids according to the polarity of their side chains, that is, whether they are nonpolar, uncharged polar, acidic, or basic (Figure 1.2).

A. Amino acids with nonpolar side chains

Glycine	=	Gly	Alanine	=	Ala
Valine	=	Val	Leucine	=	Leu

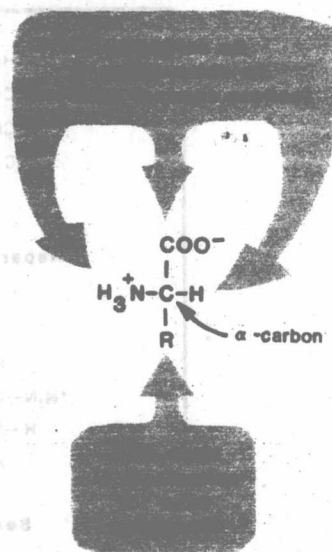
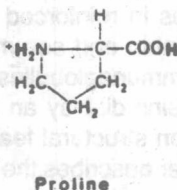
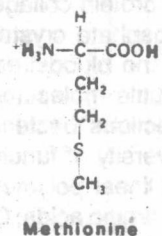
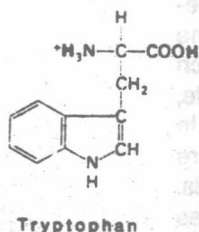
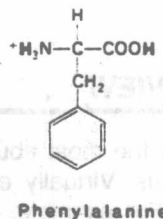
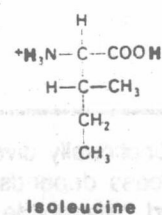
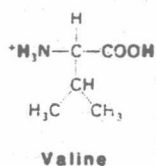
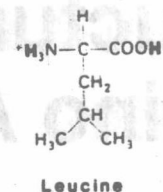
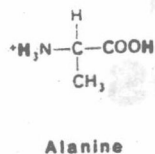
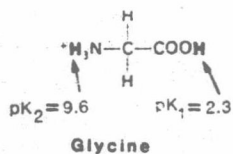
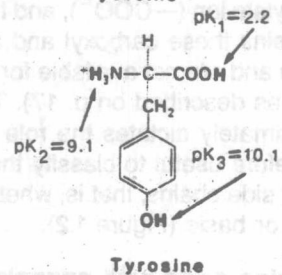
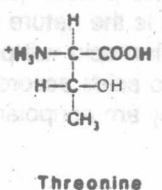
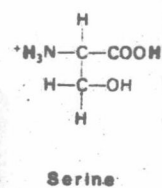
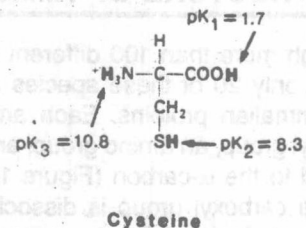
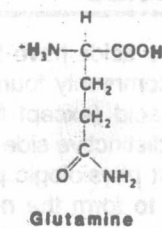
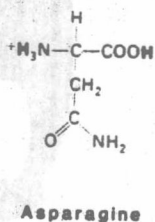


Figure 1.1
Structural features of amino acids.

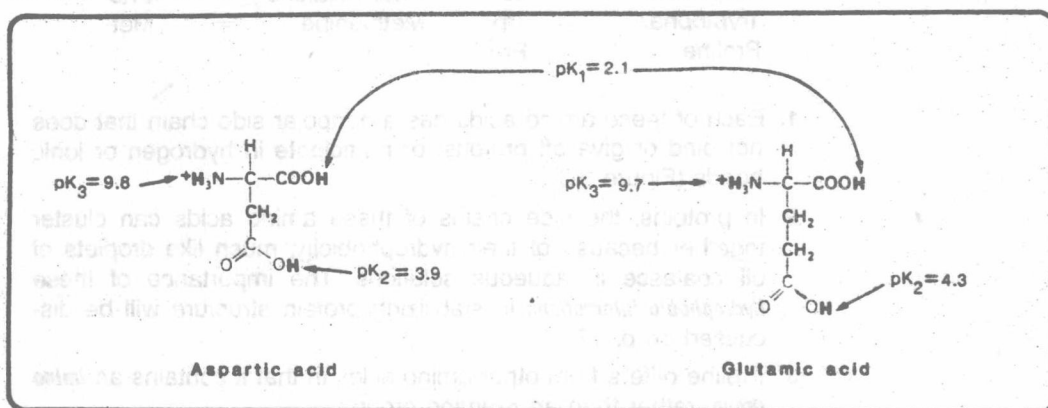
NON-POLAR SIDE CHAINS



UNCHARGED POLAR SIDE CHAINS



ACIDIC SIDE CHAINS



BASIC SIDE CHAINS

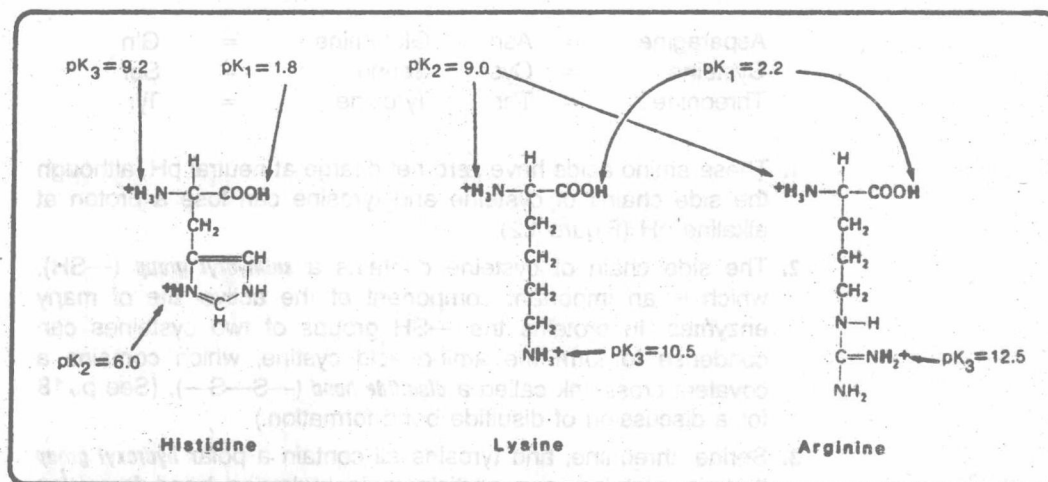
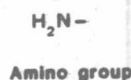


Figure 1.2

Classification of the 20 amino acids found in proteins, according to the charge and polarity of their side chains. Each amino acid is shown in its fully protonated form with dissociable hydrogen ions represented in bold print. (For convenience the protonated amino group is shown as $-\text{NH}_3^+$, with the understanding that only one hydrogen of the amino group can dissociate.) The pKa values for the α -carboxyl and α -amino groups of the nonpolar amino acids are similar to those shown for glycine.

Isoleucine	= Ile	Phenylalanine	= Phe
Tryptophan	= Trp	Methionine	= Met
Proline	= Pro		

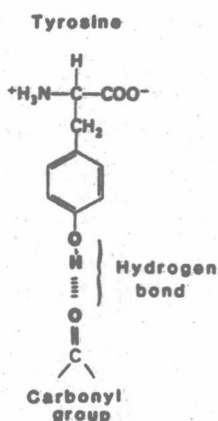
1. Each of these amino acids has a nonpolar side chain that does not bind or give off protons, or participate in hydrogen or ionic bonds (Figure 1.2).
2. In proteins, the side chains of these amino acids can cluster together because of their hydrophobicity, much like droplets of oil coalesce in aqueous solutions. The importance of these **hydrophobic interactions** in stabilizing protein structure will be discussed on p. 17.
3. Proline differs from other amino acids in that it contains an **imino group**, rather than an α -amino group.



B. Amino acids with uncharged polar side chains

Asparagine	= Asn	Glutamine	= Gln
Cysteine	= Cys	Serine	= Ser
Threonine	= Thr	Tyrosine	= Tyr

1. These amino acids have zero net charge at neutral pH, although the side chains of cysteine and tyrosine can lose a proton at alkaline pH (Figure 1.2).
2. The side chain of cysteine contains a **sulphydryl group** ($-\text{SH}$), which is an important component of the active site of many enzymes. In proteins the $-\text{SH}$ groups of two cysteines can condense to form the amino acid cystine, which contains a covalent cross-link called a **disulfide bond** ($-\text{S}-\text{S}-$). (See p. 18 for a discussion of disulfide bond formation.)
3. Serine, threonine, and tyrosine all contain a polar **hydroxyl group** that, in proteins, can participate in hydrogen bond formation (Figure 1.3) or serve as the site of attachment for a phosphate group or a carbohydrate. The side chains of asparagine and glutamine each contain a carbonyl group and an amide group, both of which can also participate in hydrogen bonds or serve as a site of attachment for carbohydrates. (See p. 17 for a discussion of hydrogen bonds.)



C. Amino acids with acidic side chains

Aspartic acid	= Asp	Glutamic acid	= Glu
---------------	-------	---------------	-------

1. The amino acids aspartic and glutamic acid are proton donors: At neutral pH the side chains of these amino acids are fully ionized and contain a **negatively charged** carboxylate group ($-\text{COO}^-$). They are therefore called aspartate or glutamate to emphasize that at physiologic pH these amino acids are negatively charged (Figure 1.2).

D. Amino acids with basic side chains

Lysine	= Lys	Arginine	= Arg
Histidine	= His		

Figure 1.3
Hydrogen bond between the phenolic hydroxyl group of tyrosine and another compound containing a carbonyl oxygen.

1. The side chains of the basic amino acids bind protons (Figure 1.2): At physiologic pH the side chains of lysine and arginine are fully ionized and *positively charged*.
2. In contrast, histidine is weakly basic and the free amino acid largely uncharged at physiologic pH. In proteins, however, the side chain of histidine can be either positively charged or neutral depending on the ionic environment provided by the polypeptide chains of the protein.

Study Questions

- Answer A if 1, 2, and 3 are correct D if only 4 is correct
 B if 1 and 3 are correct E if all are correct
 C if 2 and 4 are correct

1.1 Which of the following statements describe(s) the side chain of the amino acid serine?

1. Contains a hydroxyl group
2. Can form disulfide bonds
3. Can participate in hydrogen bonds
4. Is charged at physiologic pH

1.2 Which of the following amino acids has/have a charged side chain at physiologic pH?

1. Aspartic acid
2. Lysine
3. Glutamic acid
4. Asparagine

1.3 Glutamine

1. contains three titratable groups.
2. contains an amide group.
3. is classified as an acidic amino acid.
4. contains a side chain that can form hydrogen bonds in proteins.

1.4 Which of the following statements about amino acids is(are) true?

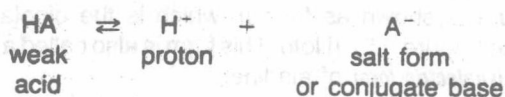
1. Glycine contains two dissociable hydrogens.
2. Tyrosine is a site of attachment of phosphate groups in proteins.
3. Cysteine is a sulfur-containing amino acid.
4. Glutamine is classified as a basic amino acid.

III. AMINO ACIDS AS BUFFERS

Amino acids contain weakly acidic α -carboxyl groups and weakly basic α -amino groups. In addition, each of the acid and basic amino acids contains an ionizable group in its side chain. Thus, both free amino acids and amino acids combined in peptide linkage can potentially act as buffers. The quantitative relation between $[H^+]$ and weak acids is described by the Henderson-Hasselbalch equation.

A. The Henderson-Hasselbalch equation

1. Consider the release of a proton by a weak acid represented by HA:



The "salt" or conjugate base, A^- , is the ionized form of a weak acid. By definition, the dissociation constant of the acid, K_a , is

$$K_a = \frac{[H^+][A^-]}{[HA]}$$

By solving for the $[H^+]$ in the above equation, taking the logarithm of both sides of the equation, multiplying both sides of the equation by -1 , and substituting $pH = -\log[H^+]$ and $pK_a = -\log K_a$, we obtain the Henderson-Hasselbalch equation:

$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$

which can also be written as

$$pH = pK_a + \log \frac{[\text{conjugate base}]}{[\text{acid form}]}$$

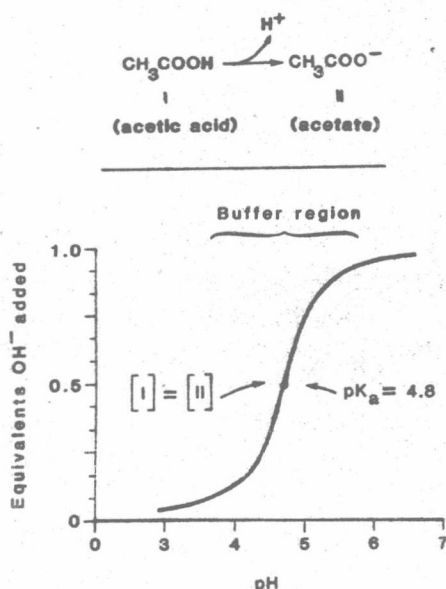


Figure 1.4
Titration curve of acetic acid.

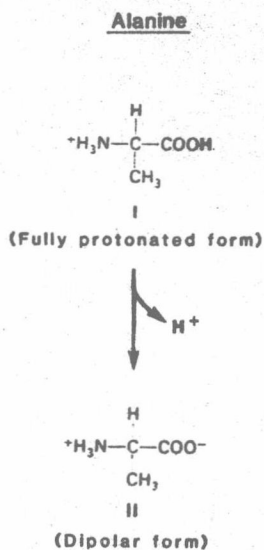


Figure 1.5
Dissociation of the carboxyl group of alanine.

2. The Henderson-Hasselbalch equation can be used to calculate the pH of a solution containing a weak acid after the addition of strong acid or base. For example, Figure 1.4 illustrates the change in pH that occurs when NaOH is added to a solution of acetic acid. This titration curve demonstrates several important concepts:

- A **buffer** is a solution that resists changes in pH following the addition of strong acid or base. A weak acid and its conjugate base, for example, acetic acid ($\text{CH}_3\text{—COOH}$) and acetate ($\text{CH}_3\text{—COO}^-$), can serve as a buffer when the pH of a solution is within ± 1 pH unit of the pK_a of the weak acid. Maximum buffering capacity occurs at the pK_a . Therefore, a solution containing the acetic acid/acetate buffer pair will resist a change in pH from pH 3.8 to 5.8, with maximum buffering at pH 4.8.
- When the pH of a solution is equal to the pK_a , the amount of the salt form is equal to the acid form. As noted above, at this pH the solution will have its maximum buffering capacity.
- At pH values less than the pK_a , the protonated acid form (e.g., $\text{CH}_3\text{—COOH}$) is the predominant species.
- At pH values greater than the pK_a , the deprotonated salt (e.g., $\text{CH}_3\text{—COO}^-$) is the predominant species in solution.

B. The titration of alanine

- The titration curve of an amino acid can be analyzed in the same way as that described above for acetic acid. For example, consider the amino acid alanine, which contains both a carboxyl and an amino group. At an acidic pH, both of these groups of alanine are protonated (shown in Figure 1.5). The —COOH group of form I can dissociate by donating a proton to the medium, where it binds to a water molecule, producing H_3O^+ . This release of a proton results in the formation of the carboxylate group, —COO^- . The structure is shown as form II, which is the dipolar form of the molecule (Figure 1.5). (Note: This form is also called a *zwitterion*, and is the *isoelectric form* of alanine.