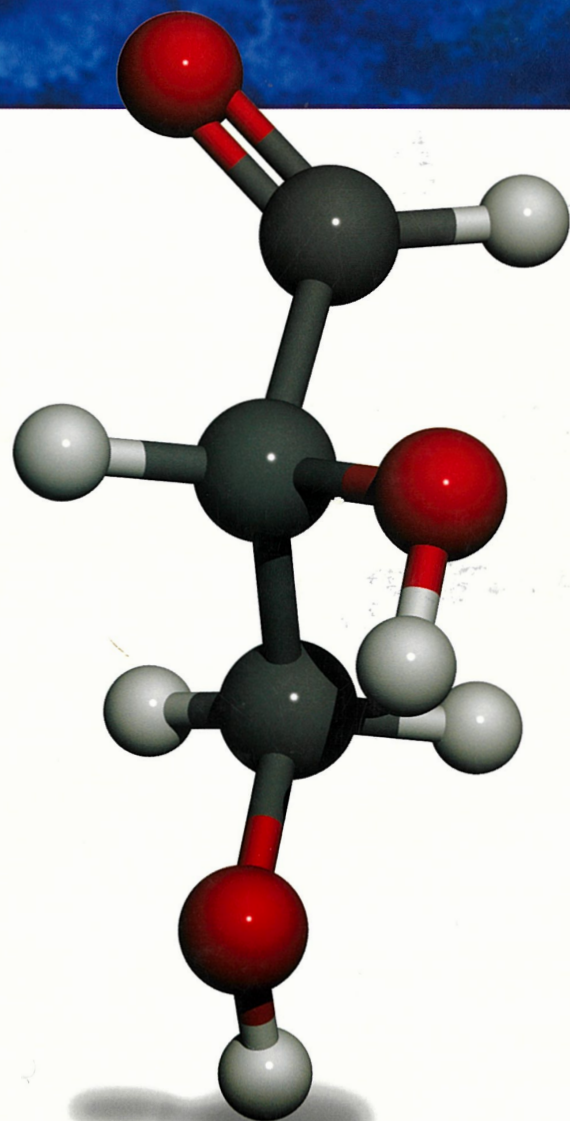
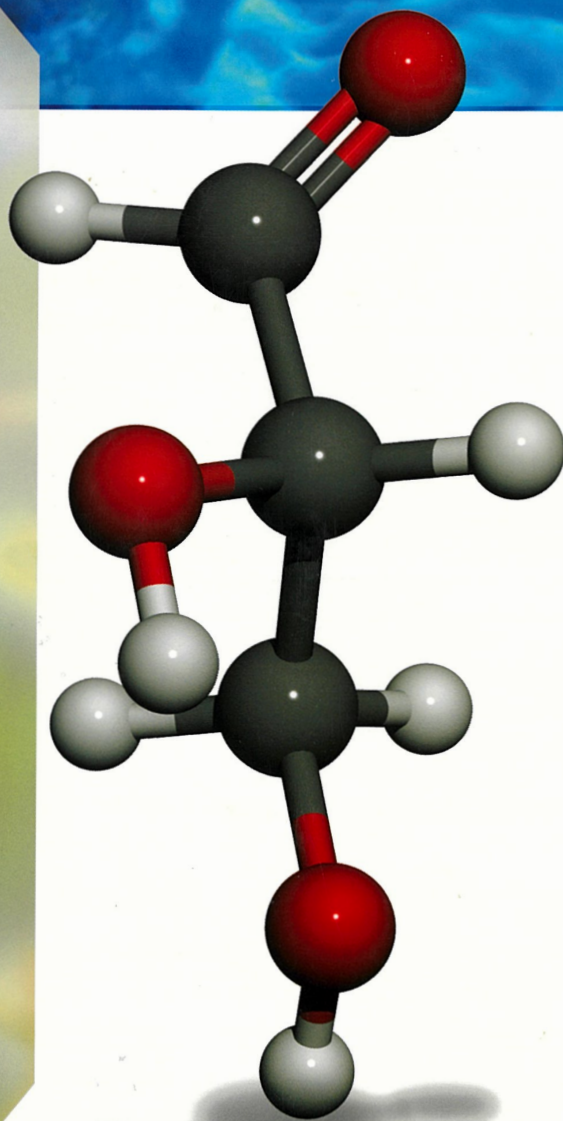


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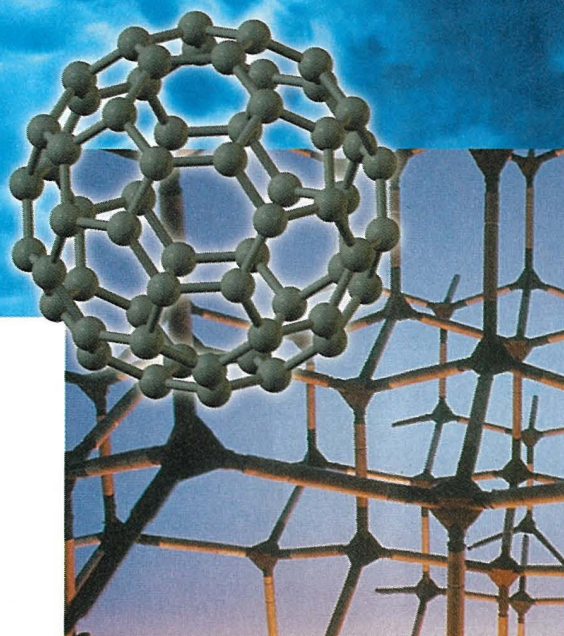
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Beloit College

Christopher S. Foote

University of California, Los Angeles

Brent L. Iverson

University of Texas, Austin

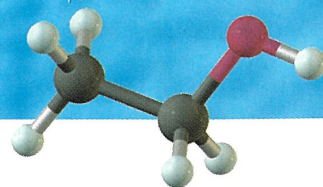
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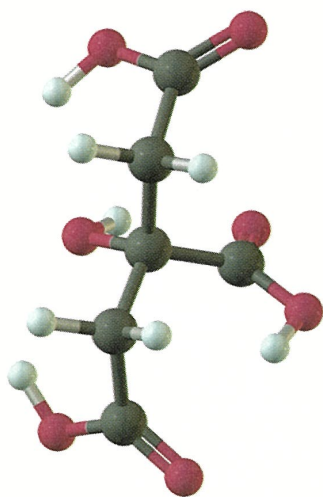
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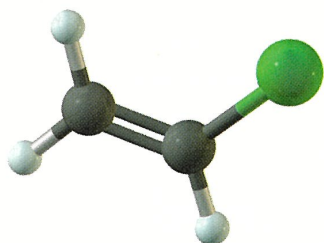
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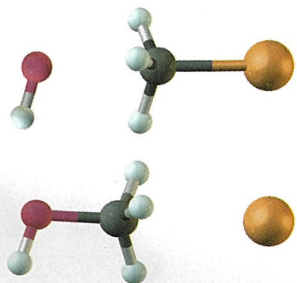
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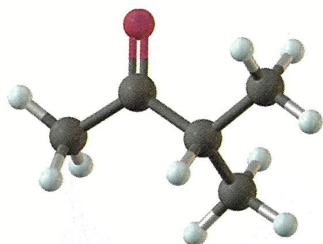
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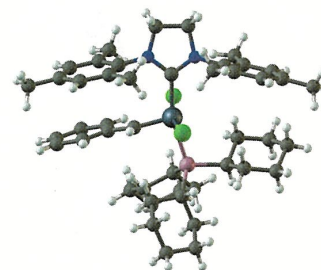
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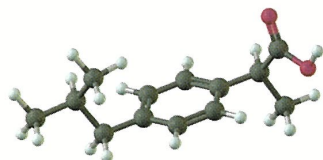
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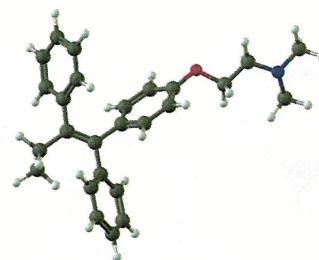
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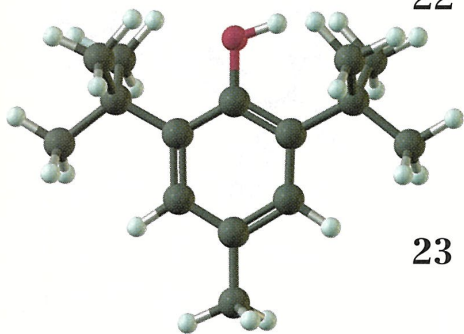
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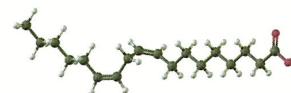
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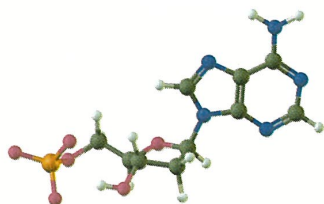
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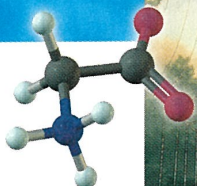
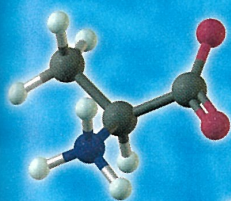
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Amino Acids and Proteins

We begin this chapter with a study of amino acids, compounds whose chemistry is built on amines (Chapter 23) and carboxylic acids (Chapter 17). We concentrate in particular on the acid-base properties of amino acids because these properties are so important in determining many of the properties of proteins, including the catalytic functions of enzymes. With this understanding of the chemistry of amino acids, we then examine the structure of proteins themselves.

27.1 Amino Acids

A. Structure

An **amino acid** is a compound that contains both a carboxyl group and an amino group. Although many types of amino acids are known, the **α -amino acids** are the most significant in the biological world because they are the monomers from which proteins are constructed. We have already introduced amino acids (see Connections to Biological Chemistry: “Amino Acids” in Chapter 3). A general structural formula of an α -amino acid is shown in Figure 27.1.

Spider silk is a fibrous protein that exhibits unmatched strength and toughness. Insert: Alanine and Glycine are major components of the fibrous protein of spider silk. See Chemical Connections: “Spider Silk.”

Outline

- 27.1 Amino Acids
- 27.2 Acid-Base Properties of Amino Acids
- 27.3 Polypeptides and Proteins
- 27.4 Primary Structure of Polypeptides and Proteins
- 27.5 Synthesis of Polypeptides
- 27.6 Three-Dimensional Shapes of Polypeptides and Proteins

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Amino acid A compound that contains both an amino group and a carboxyl group.

α -Amino acid An amino acid in which the amino group is on the carbon adjacent to the carboxyl group.

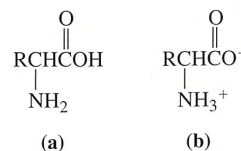
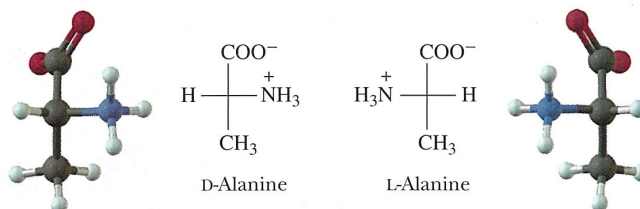


Figure 27.1

An α -amino acid. (a) Un-ionized form and (b) internal salt (zwitterion) form.

Figure 27.2

The enantiomers of alanine. The vast majority of α -amino acids in the biological world have the L configuration at the α -carbon.



Although Figure 27.1(a) is a common way of writing structural formulas for amino acids, it is not accurate because it shows an acid (—COOH) and a base (—NH_2) within the same molecule. These acidic and basic groups react with each other to form a dipolar ion or internal salt [Figure 27.1(b)]. The internal salt of an amino acid is given the special name **zwitterion**. Note that a zwitterion has no net charge; it contains one positive charge and one negative charge.

Zwitterion An internal salt of an amino acid; the carboxylate anion is negatively charged, and the ammonium group is positively charged.

Because they exist as zwitterions, amino acids have many of the properties associated with salts. They are crystalline solids with high melting points and are fairly soluble in water but insoluble in nonpolar organic solvents such as ether and hydrocarbon solvents.

B. Chirality

To review, with the exception of glycine, $\text{H}_2\text{NCH}_2\text{COOH}$, all protein-derived amino acids have at least one chiral center and, therefore, are chiral. Figure 27.2 shows Fischer projection formulas for the enantiomers of alanine. The vast majority of carbohydrates in the biological world are of the D-series, whereas the vast majority of α -amino acids in the biological world are of the L-series.

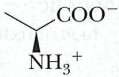
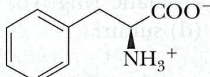
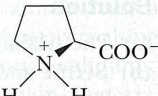
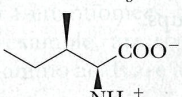
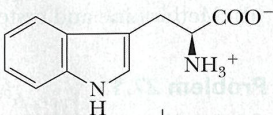
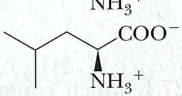
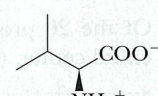
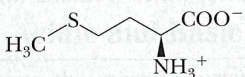
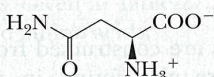
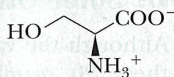
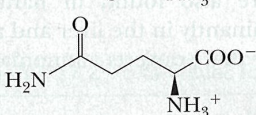
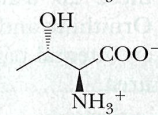
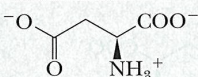
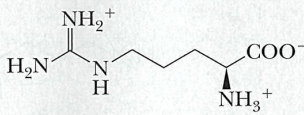
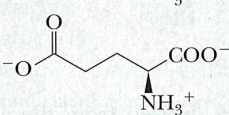
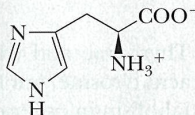
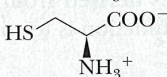
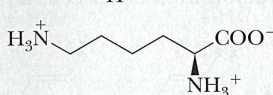
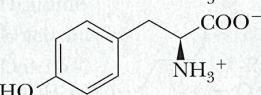
The alternative R,S convention is also used to specify the configurations of amino acids. According to this convention, L-alanine is designated (S)-alanine. Because D- and L- are used more commonly to describe the configuration of amino acids, we use this convention throughout the remainder of the chapter.

C. Protein-Derived Amino Acids

Table 27.1 gives common names, structural formulas, and standard three-letter and one-letter abbreviations for the 20 common L-amino acids found in proteins. The amino acids in this table are divided into four categories: those with nonpolar side chains, polar but un-ionized side chains, acidic side chains, and basic side chains. The following structural features of these amino acids should be noted.

1. All 20 of these protein-derived amino acids are α -amino acids, meaning that the amino group is located on the carbon alpha to the carboxyl group.
2. For 19 of the 20 amino acids, the α -amino group is primary. Proline is different; its α -amino group is secondary.
3. With the exception of glycine, the α -carbon of each amino acid is a chiral center. Although not shown in this table, all 19 chiral amino acids have the same relative configuration at the α -carbon. In the D,L convention, all are L-amino acids. According to the R,S convention, amino acid α -carbons, with the exception of cysteine, have the S configuration. Because of priority rules, the presence of the sulfhydryl group on the side chain of L-cysteine gives the chiral center the R configuration.

Table 27.1 The 20 Common Amino Acids Found in Proteins

Nonpolar Side Chains			
	Alanine (Ala, A)		Phenylalanine (Phe, F)
	Glycine (Gly, G)		Proline (Pro, P)
	Isoleucine (Ile, I)		Tryptophan (Trp, W)
	Leucine (Leu, L)		Valine (Val, V)
	Methionine (Met, M)		
Polar Side Chains			
	Asparagine (Asn, N)		Serine (Ser, S)
	Glutamine (Gln, Q)		Threonine (Thr, T)
Acidic Side Chains		Basic Side Chains	
	Aspartic acid (Asp, D)		Arginine (Arg, R)
	Glutamic acid (Glu, E)		Histidine (His, H)
	Cysteine (Cys, C)		Lysine (Lys, K)
	Tyrosine (Tyr, Y)		

* Each ionizable group is shown in the form present in highest concentration at pH 7.0.

- Isoleucine and threonine contain a second chiral center. Four stereoisomers are possible for each amino acid, but only one is found in proteins.
- The sulfhydryl group of cysteine, the imidazole group of histidine, and the phenolic hydroxyl of tyrosine are partially ionized at pH 7.0, but the ionic form is not the major form present at this pH.

Example 27.1

Of the 20 protein-derived amino acids shown in Table 27.1, how many contain: (a) an aromatic ring, (b) a side-chain hydroxyl group, (c) a phenolic —OH group, and (d) sulfur?

Solution

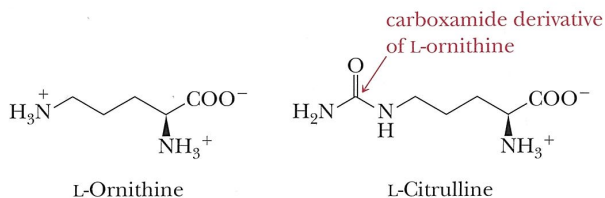
- (a) Phenylalanine, tryptophan, tyrosine, and histidine contain aromatic rings.
- (b) Serine and threonine contain side-chain hydroxyl groups.
- (c) Tyrosine contains a phenolic —OH group.
- (d) Methionine and cysteine contain sulfur.

Problem 27.1

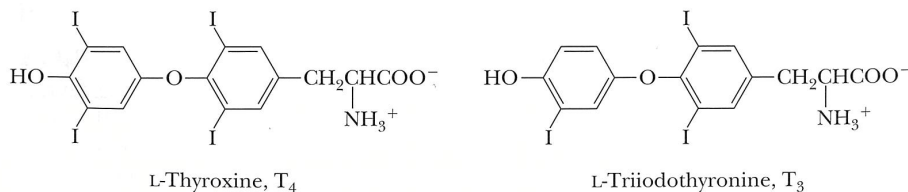
Of the 20 protein-derived amino acids shown in Table 27.1, which contain (a) no chiral center, (b) two chiral centers?

D. Some Other Common L-Amino Acids

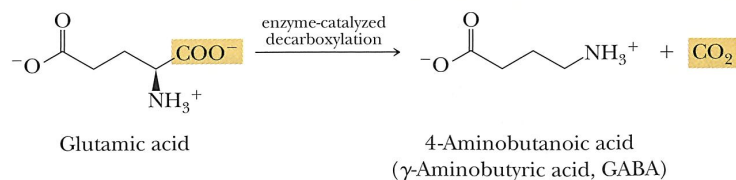
Although the vast majority of plant and animal proteins are constructed from just these 20 α -amino acids, many other amino acids are also found in nature. Ornithine and citrulline, for example, are found predominantly in the liver and are an integral part of the urea cycle, the metabolic pathway that converts ammonia to urea.



Thyroxine and triiodothyronine, two of several hormones derived from the amino acid tyrosine, are found in thyroid tissue. Their principal function is to stimulate metabolism in other cells and tissues.



4-Aminobutanoic acid is found in high concentration (0.8 mM) in the brain but in no significant amounts in any other mammalian tissue. It is synthesized in neural tissue by decarboxylation of the α -carboxyl group of glutamic acid and is a neurotransmitter in the central nervous system of invertebrates and in humans as well.



Only L-amino acids are found in proteins, and only rarely are D-amino acids a part of the metabolism of higher organisms. Several D-amino acids, however, along with their L-enantiomers, are found in lower forms of life. D-Alanine and D-glutamic acid, for example, are structural components of the cell walls of certain bacteria. Several D-amino acids are also found in peptide antibiotics.

27.2 Acid-Base Properties of Amino Acids

A. Acidic and Basic Groups of Amino Acids

Among the most important chemical properties of amino acids are their acid-base properties; all are weak polyprotic acids because of their —COOH and —NH^+ groups. Given in Table 27.2 are pK_a values for each ionizable group of the 20 protein-derived amino acids.

Table 27.2 pK_a Values for Ionizable Groups of Amino Acids

Amino Acid	pK_a of $\alpha\text{—COOH}$	pK_a of $\alpha\text{—NH}_3^+$	pK_a of Side Chain	Isoelectric Point (pI)
Alanine	2.35	9.87	—	6.11
Arginine	2.01	9.04	12.48	10.76
Asparagine	2.02	8.80	—	5.41
Aspartic acid	2.10	9.82	3.86	2.98
Cysteine	2.05	10.25	8.00	5.02
Glutamic acid	2.10	9.47	4.07	3.08
Glutamine	2.17	9.13	—	5.65
Glycine	2.35	9.78	—	6.06
Histidine	1.77	9.18	6.10	7.64
Isoleucine	2.32	9.76	—	6.04
Leucine	2.33	9.74	—	6.04
Lysine	2.18	8.95	10.53	9.74
Methionine	2.28	9.21	—	5.74
Phenylalanine	2.58	9.24	—	5.91
Proline	2.00	10.60	—	6.30
Serine	2.21	9.15	—	5.68
Threonine	2.09	9.10	—	5.60
Tryptophan	2.38	9.39	—	5.88
Tyrosine	2.20	9.11	10.07	5.63
Valine	2.29	9.72	—	6.00

Acidity of α -Carboxyl Groups

The average value of pK_a for an α -carboxyl group of a protonated amino acid is 2.19. Thus, the α -carboxyl group is a considerably stronger acid than acetic acid (pK_a 4.76) and other low-molecular-weight aliphatic carboxylic acids. This greater acidity is accounted for by the electron-withdrawing inductive effect of the adjacent $-\text{NH}_3^+$ group. Recall that we used similar reasoning in Section 17.4A to account for the relative acidities of acetic acid and its mono-, di-, and trichloroderivatives.

The ammonium group has an electron-withdrawing inductive effect.

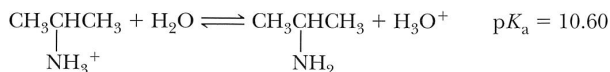


Acidity of Side-Chain Carboxyl Groups

Owing to the electron-withdrawing inductive effect of the α - NH_3^+ group, the side-chain carboxyl groups of protonated aspartic and glutamic acids are also stronger acids than acetic acid (pK_a 4.76). Notice that this acid-strengthening inductive effect decreases with increasing distance of the $-\text{COOH}$ from the $-\text{NH}_3^+$. Compare the acidities of the α - COOH of alanine (pK_a 2.35), the β - COOH of aspartic acid (pK_a 3.86), and the γ - COOH of glutamic acid (pK_a 4.07).

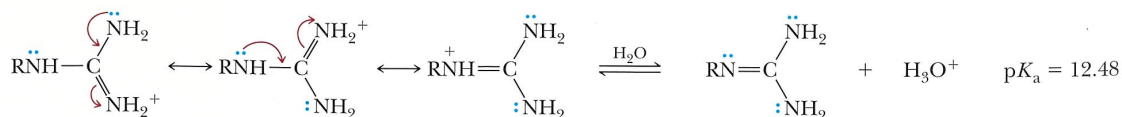
Acidity of α -Ammonium Groups

The average value of pK_a for an α -ammonium group, $-\text{NH}_3^+$, is 9.47 compared with an average value of 10.60 for primary aliphatic ammonium ions (Section 23.5A). Thus, the α -ammonium group of an amino acid is a slightly stronger acid than a primary aliphatic ammonium ion. Conversely, an α -amino group is a slightly weaker base than a primary aliphatic amine.



Basicity of the Guanidine Group of Arginine

The side-chain guanidine group of arginine is a considerably stronger base than an aliphatic amine. As we saw in Section 23.5D, guanidine (pK_a 13.6) is the strongest base of any neutral organic compound. The remarkable basicity of the guanidine group of arginine is attributed to the large resonance stabilization of the protonated form relative to the neutral form.

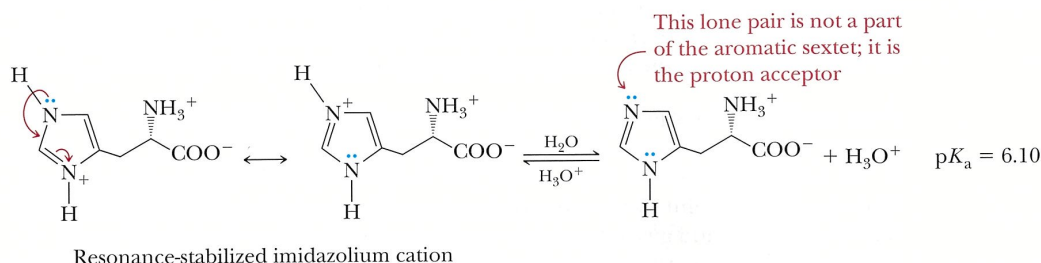


The guanidinium ion side chain of arginine is a hybrid of three contributing structures

No resonance stabilization without charge separation

Basicity of the Imidazole Group of Histidine

Because the imidazole group on the side chain of histidine contains six π electrons in a planar, fully conjugated ring, imidazole is classified as a heterocyclic aromatic amine (Section 21.2D). The unshared pair of electrons on one nitrogen is a part of the aromatic sextet, whereas that on the other nitrogen is not. The pair of electrons that is not part of the aromatic sextet is responsible for the basic properties of the imidazole ring. Protonation of this nitrogen produces a resonance-stabilized cation.



B. Titration of Amino Acids

Values of pK_a for the ionizable groups of amino acids are most commonly obtained by acid-base titration and by measuring the pH of the solution as a function of added base (or added acid, depending on how the titration is done). To illustrate this experimental procedure, consider a solution containing 1.00 mol of glycine to which has been added enough strong acid that both the amino and carboxyl groups are fully protonated. Next, this solution is titrated with 1.00 M NaOH; the volume of base added and the pH of the resulting solution are recorded and then plotted as shown in Figure 27.3.

The most acidic group and the one to react first with added sodium hydroxide is the carboxyl group. When exactly 0.50 mol of NaOH has been added, the carboxyl group is half neutralized. At this point, the concentration of the zwitterion equals that of the positively charged ion, and the pH of 2.35 equals the pK_a of the carboxyl group (pK_{a1}).

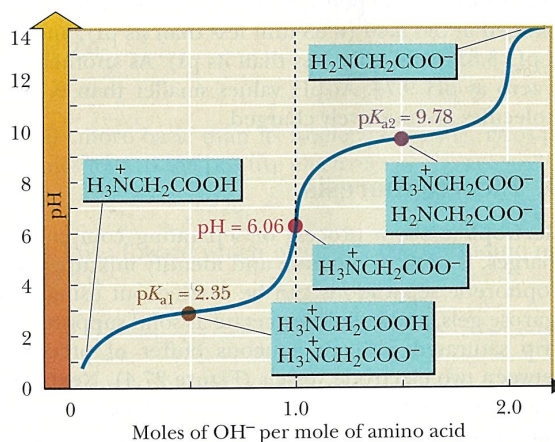


Figure 27.3
Titration of glycine with sodium hydroxide.



The end point of the first part of the titration is reached when 1.00 mol of NaOH has been added. At this point, the predominant species present is the zwitterion, and the observed pH of the solution is 6.06.

The next section of the curve represents titration of the —NH_3^+ group. When another 0.50 mole of NaOH has been added (bringing the total to 1.50 mol), half of the —NH_3^+ groups are neutralized and converted to —NH_2 . At this point, the concentrations of the zwitterion and negatively charged ion are equal, and the observed pH is 9.78, the $\text{p}K_a$ of the amino group of glycine ($\text{p}K_{a2}$).



The second end point of the titration is reached when a total of 2.00 mol of NaOH have been added and glycine is converted entirely to an anion.

C. Isoelectric Point

Titration curves such as that for glycine permit us to determine $\text{p}K_a$ values for the ionizable groups of an amino acid. They also permit us to determine another important property: isoelectric point. **Isoelectric point, pI**, for an amino acid is the pH at which the majority of molecules in solution have a net charge of zero (they are zwitterions). By examining the titration curve, you can see that the isoelectric point for glycine falls half way between the $\text{p}K_a$ values for the carboxyl and amino groups.

$$\begin{aligned} \text{pI} &= \frac{1}{2}(\text{p}K_a \alpha\text{—COOH} + \text{p}K_a \alpha\text{—NH}_3^+) \\ &= \frac{1}{2}(2.35 + 9.78) = 6.06 \end{aligned}$$

At pH 6.06, the predominant form of glycine molecules is the dipolar ion; furthermore, at this pH, the concentration of positively charged glycine molecules equals the concentration of negatively charged glycine molecules.

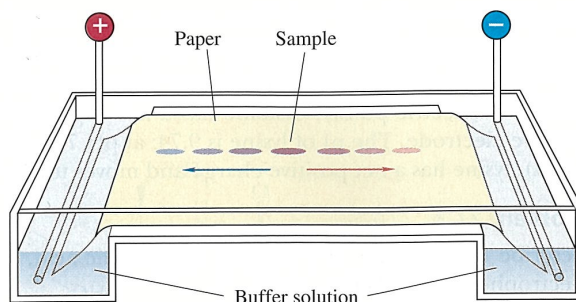
Given a value for the isoelectric point of an amino acid, it is possible to estimate the charge on that amino acid at any pH. For example, the charge on tyrosine at pH 5.63, its isoelectric point, is zero. A small fraction of tyrosine molecules are positively charged at pH 5.00 (0.63 unit less than its pI), and virtually all are positively charged at pH 3.63 (2.00 units less than its pI). As another example, the net charge on lysine is zero at pH 9.74. At pH values smaller than 9.74, an increasing fraction of lysine molecules are positively charged.

D. Electrophoresis

Electrophoresis, a process of separating compounds on the basis of their electric charges, is used to separate and identify mixtures of amino acids and proteins. Electrophoretic separations can be carried out using paper, starch, polyacrylamide and agarose gels, and cellulose acetate as solid supports. In paper electrophoresis, a paper strip saturated with an aqueous buffer of predetermined pH serves as a bridge between two electrode vessels (Figure 27.4). Next, a sample of amino acids is applied as a spot on the paper strip. When an electrical potential is then applied to the electrode vessels, amino acids migrate toward the electrode carrying the charge opposite

Isoelectric point (pI) The pH at which an amino acid, polypeptide, or protein has no net charge.

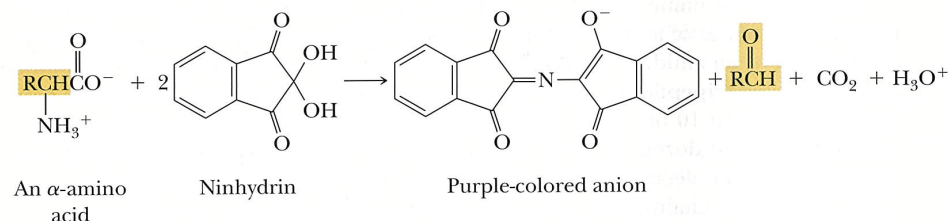
Electrophoresis The process of separating compounds on the basis of their electric charge.

**Figure 27.4**

An apparatus for electrophoresis of a mixture of amino acids. Those with a negative charge move toward the positive electrode; those with a positive charge move toward the negative electrode; those with no charge remain at the origin.

to their own. Molecules having a high charge density move more rapidly than those with a lower charge density. Any molecule already at its isoelectric point remains at the origin. After separation is complete, the strip is dried and sprayed with a dye to make the separated components visible.

A dye commonly used to detect amino acids is ninhydrin (1,2,3-indanetrione monohydrate). Ninhydrin reacts with α -amino acids to produce an aldehyde, carbon dioxide, and a purple-colored anion. This reaction is used very commonly in both qualitative and quantitative analysis of amino acids.



Nineteen of the 20 protein-derived α -amino acids have primary amino groups and give the same purple-colored ninhydrin-derived anion. Proline, a secondary amine, gives a different, orange-colored compound.

Example 27.2

The isoelectric point of tyrosine is 5.63. Toward which electrode does tyrosine migrate on paper electrophoresis at pH 7.0?

Solution

On paper electrophoresis at pH 7.0 (more basic than its isoelectric point), tyrosine has a net negative charge and migrates toward the positive electrode.

Problem 27.2

The isoelectric point of histidine is 7.64. Toward which electrode does histidine migrate on paper electrophoresis at pH 7.0?

Example 27.3

Electrophoresis of a mixture of lysine, histidine, and cysteine is carried out at pH 7.64. Describe the behavior of each amino acid under these conditions.

Solution

The isoelectric point of histidine is 7.64. At this pH, histidine has a net charge of zero and does not move from the origin. The pI of cysteine is 5.02; at pH 7.64 (more basic than its isoelectric point), cysteine has a net negative charge and moves toward the positive electrode. The pI of lysine is 9.74; at pH 7.64 (more acidic than its isoelectric point), lysine has a net positive charge and moves toward the negative electrode.

Problem 27.3

Describe the behavior of a mixture of glutamic acid, arginine, and valine on paper electrophoresis at pH 6.0.

27.3 Polypeptides and Proteins

Peptide bond The special name given to the amide bond formed between the α -amino group of one amino acid and the α -carboxyl group of another amino acid.

Dipeptide A molecule containing two amino acid units joined by a peptide bond.

Tripeptide A molecule containing three amino acid units, each joined to the next by a peptide bond.

Polypeptide A macromolecule containing many amino acid units, each joined to the next by a peptide bond.

In 1902, Emil Fischer proposed that proteins are long chains of amino acids joined together by amide bonds between the α -carboxyl group of one amino acid and the α -amino group of another. For these amide bonds, Fischer proposed the special name **peptide bond**. Figure 27.5 shows the peptide bond formed between serine and alanine in the dipeptide serylalanine.

Peptide is the name given to a short polymer of amino acids. Peptides are classified by the number of amino acid units in the chain. A molecule containing 2 amino acids joined by an amide bond is called a **dipeptide**. Those containing 3 to 10 amino acids are called **tripeptides**, **tetrapeptides**, **pentapeptides**, and so on. Molecules containing more than 10 but fewer than 20 amino acids are called **oligopeptides**. Those containing several dozen or more amino acids are called **polypeptides**. **Proteins** are biological macromolecules of molecular weight 5000 or greater, consisting of one or more polypeptide chains. The distinctions in this terminology are not precise.

By convention, polypeptides are written from the left, beginning with the amino acid having the free —NH_3^+ group and proceeding to the right toward the amino

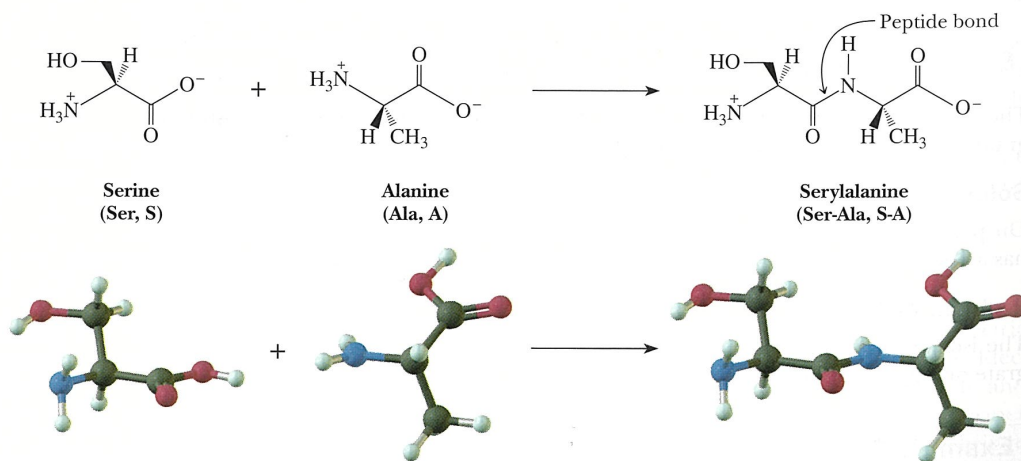
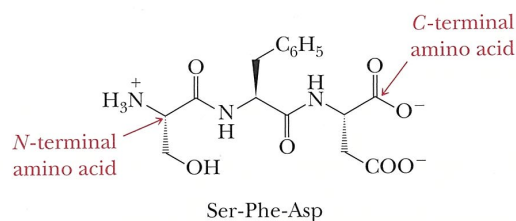


Figure 27.5

The peptide bond in serylalanine.

acid with the free —COO^- group. The amino acid with the free —NH_3^+ group is called the **N-terminal amino acid** and that with the free —COO^- group is called the **C-terminal amino acid**. Notice the repeating pattern in the peptide chain of $\text{N—}\alpha\text{-carbon—carbonyl}$, etc.



N-Terminal amino acid The amino acid at the end of a polypeptide chain having the free —NH_2 group.

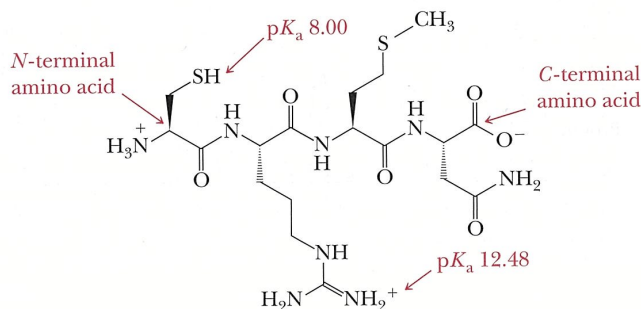
C-Terminal amino acid The amino acid at the end of a polypeptide chain having the free —COOH group.

Example 27.4

Draw a structural formula for Cys-Arg-Met-Asn. Label the N-terminal amino acid and the C-terminal amino acid. What is the net charge on this tetrapeptide at pH 6.0?

Solution

The backbone of this tetrapeptide is a repeating sequence of nitrogen— α -carbon—carbonyl. The net charge on this tetrapeptide at pH 6.0 is +1.



Problem 27.4

Draw a structural formula for Lys-Phe-Ala. Label the N-terminal amino acid and the C-terminal amino acid. What is the net charge on this tripeptide at pH 6.0?

27.4 Primary Structure of Polypeptides and Proteins

The **primary** (1°) **structure** of a polypeptide or protein refers to the sequence of amino acids in its polypeptide chain. In this sense, primary structure is a complete description of all covalent bonding in a polypeptide or protein.

In 1953, Frederick Sanger of Cambridge University, England, reported the primary structure of the two polypeptide chains of the hormone insulin. Not only was

Primary structure of proteins

The sequence of amino acids in the polypeptide chain, read from the N-terminal amino acid to the C-terminal amino acid.

this a remarkable achievement in analytical chemistry, but it also clearly established that the molecules of a given protein all have the same amino acid composition and the same amino acid sequence. Today, the amino acid sequences of over 20,000 different proteins are known.

A. Amino Acid Analysis

The first step for determining the primary structure of a polypeptide is hydrolysis and quantitative analysis of its amino acid composition. Recall from Section 18.4D that amide bonds are very resistant to hydrolysis. Typically, samples of protein are hydrolyzed in 6 M HCl in sealed glass vials at 110°C for 24 to 72 hours. This hydrolysis can be done in a microwave oven in a shorter time. After the polypeptide is hydrolyzed, the resulting mixture of amino acids is analyzed by ion-exchange chromatography.

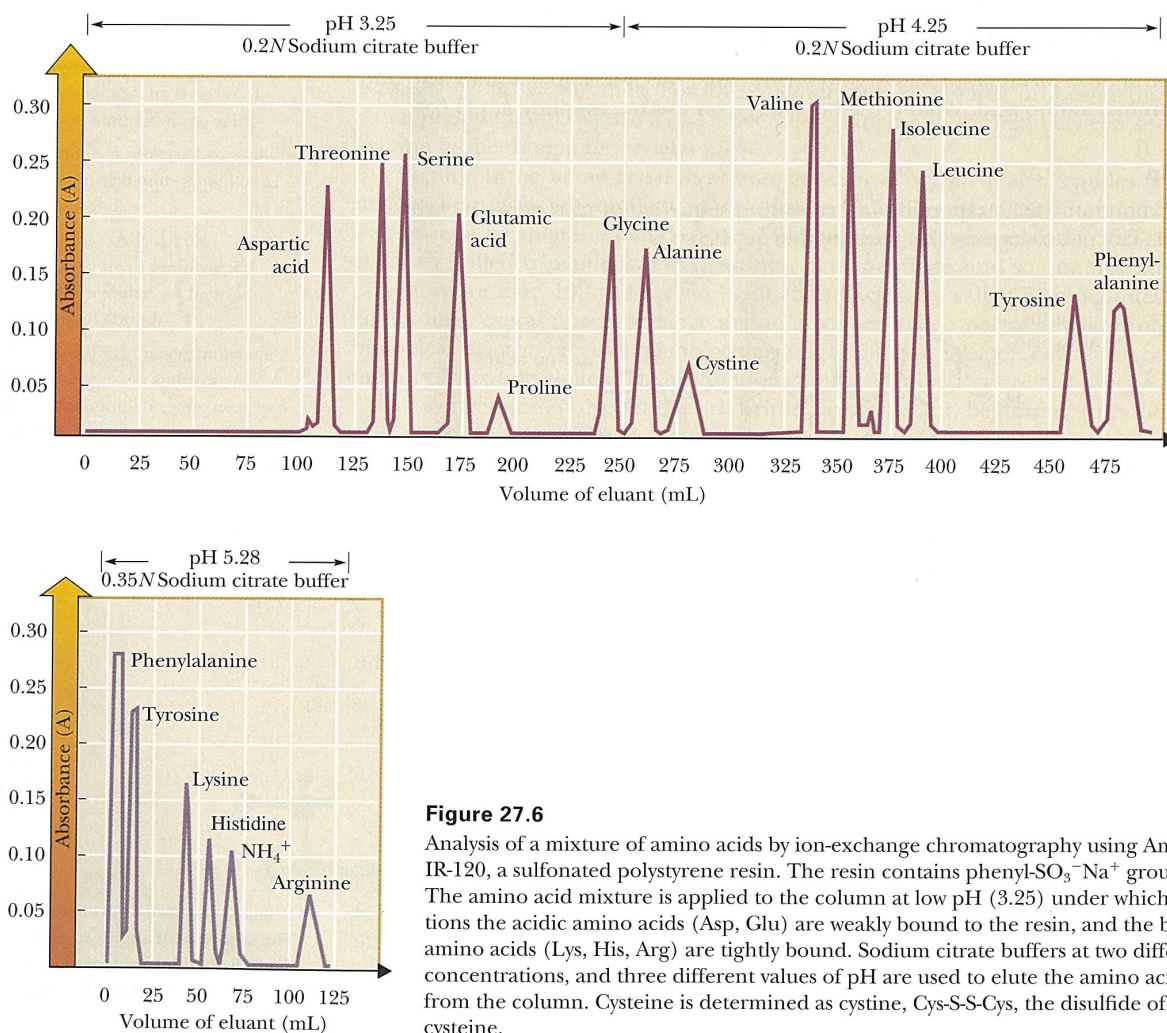


Figure 27.6

Analysis of a mixture of amino acids by ion-exchange chromatography using Amberlite IR-120, a sulfonated polystyrene resin. The resin contains $\text{phenyl-SO}_3^-\text{Na}^+$ groups. The amino acid mixture is applied to the column at low pH (3.25) under which conditions the acidic amino acids (Asp, Glu) are weakly bound to the resin, and the basic amino acids (Lys, His, Arg) are tightly bound. Sodium citrate buffers at two different concentrations, and three different values of pH are used to elute the amino acids from the column. Cysteine is determined as cystine, Cys-S-S-Cys, the disulfide of cysteine.