

Amino Acids and Peptides

CHAPTER 3

3.1 Amino Acids Exist in a Three-Dimensional World

Why is it important to specify the three-dimensional structure of amino acids?

Among all the possible amino acids, only 20 are usually found in proteins. The general structure of amino acids includes an **amino group** and a **carboxyl group**, both of which are bonded to the α -carbon (the one next to the carboxyl group). The α -carbon is also bonded to a hydrogen and to the **side chain group**, which is represented by the letter R. The R group determines the identity of the particular amino acid (Figure 3.1). The two-dimensional formula shown here can only partially convey the common structure of amino acids because one of the most important properties of these compounds is their three-dimensional shape, or **stereochemistry**.

Every object has a mirror image. Many pairs of objects that are mirror images can be superimposed on each other; two identical solid-colored coffee mugs are an example. In other cases, the mirror-image objects cannot be superimposed on one another but are related to each other as the right hand is to the left. Such nonsuperimposable mirror images are said to be **chiral** (from the Greek *cheir*, “hand”); many important biomolecules are chiral. A frequently encountered chiral center in biomolecules is a carbon atom with four different groups bonded to it (Figure 3.1). Such a center occurs in all amino acids except glycine. Glycine has two hydrogen atoms bonded to the α -carbon; in other words, the side chain (R group) of glycine is hydrogen. Glycine is not chiral (or, alternatively, is **achiral**) because of this symmetry. In all the other commonly occurring amino acids, the α -carbon has four different groups bonded to it, giving rise to two nonsuperimposable mirror-image forms. Figure 3.2 shows perspective drawings of these two possibilities, or **stereoisomers**, for alanine, where the R group is $-\text{CH}_3$. The dashed wedges represent bonds directed away from the observer, and the solid triangles represent bonds directed out of the plane of the paper in the direction of the observer.

The two possible stereoisomers of another chiral compound, L- and D-glyceraldehyde, are shown for comparison with the corresponding forms of alanine. These two forms of glyceraldehyde are the basis of the classification of amino acids into L and D forms. The terminology comes from the Latin *laevus* and *dexter*, meaning “left” and “right,” respectively, which comes from the ability of optically active compounds to rotate polarized light to the left or the right. The two stereoisomers of each amino acid are designated as **L- and D-amino acids** on the basis of their similarity to the glyceraldehyde standard. When drawn in a certain orientation, the L form of glyceraldehyde has the hydroxyl group on the left side of the molecule, and the D form has it on the right side, as shown in perspective in Figure 3.2 (a Fischer projection). To determine the L or D designation



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A protein supplement available in a health food store. The label lists the amino acid content and points out the essential amino acids.

Chapter Outline

3.1 Amino Acids Exist in a Three-Dimensional World

- Why is it important to specify the three-dimensional structure of amino acids?

3.2 Individual Amino Acids: Their Structures and Properties

- Why are amino acid side chains so important?
- Which amino acids have nonpolar side chains? (Group 1)
- Which amino acids have electrically neutral polar side chains? (Group 2)
- Which amino acids have carboxyl groups in their side chains? (Group 3)
- Which amino acids have basic side chains? (Group 4)
- Which amino acids are found less commonly in proteins?

3.3 Amino Acids Can Act as Both Acids and Bases

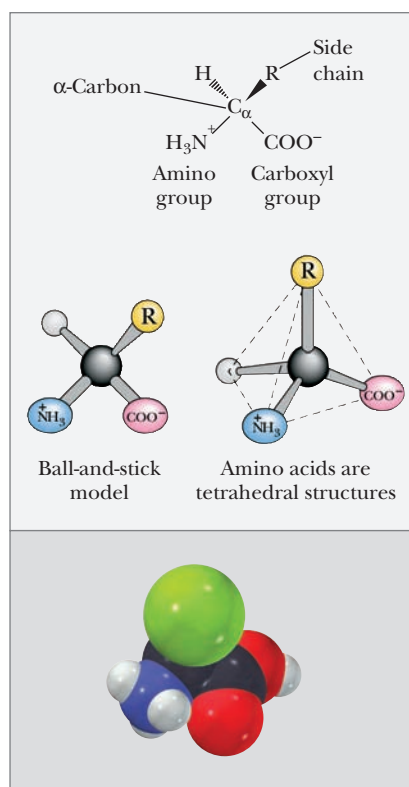
- What happens when we titrate an amino acid?

3.4 The Peptide Bond

- Which groups on amino acids react to form a peptide bond?

3.5 Small Peptides with Physiological Activity

- What are some biological functions of small peptides?



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■ ANIMATED FIGURE 3.1

The general formula of amino acids, showing the ionic forms that predominate at pH 7. Sign in at www.thomsonedu.com/login to see an animated version of this figure.

for an amino acid, it is drawn as shown. The position of the amino group on the left or right side of the α -carbon determines the L or D designation. The amino acids that occur in proteins are all of the L form. Although D-amino acids occur in nature, most often in bacterial cell walls and in some antibiotics, they are not found in proteins.

Section 3.1 Summary

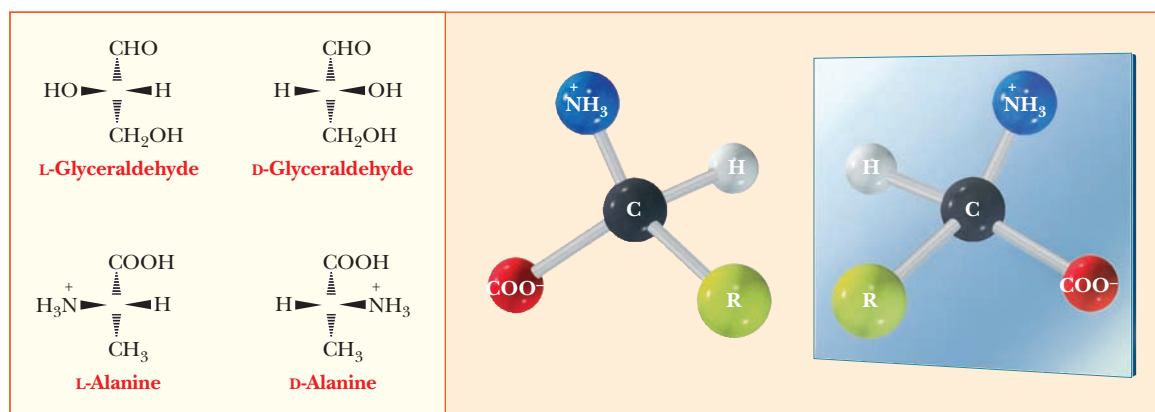
- The amino acids that occur in proteins consist of an amino group and a carboxyl group bonded to the same carbon atom. The other two bonds of the carbon are to a hydrogen and to a side chain group, shown as R in diagrams.
- The amino acids found in proteins are not superimposable on their mirror images (with the exception of glycine). The mirror images known as L-amino acids are found in proteins; the D-amino acid mirror image molecules are not.

3.2 Individual Amino Acids: Their Structures and Properties

Why are amino acid side chains so important?

The R groups, and thus the individual amino acids, are classified according to several criteria, two of which are particularly important. The first of these is the polar or nonpolar nature of the side chain. The second depends on the presence of an acidic or basic group in the side chain. Other useful criteria include the presence of functional groups other than acidic or basic ones in the side chains and the nature of those groups.

As mentioned, the side chain of the simplest amino acid, glycine, is a hydrogen atom, and in this case alone two hydrogen atoms are bonded to the α -carbon. In all other amino acids, the side chain is larger and more complex (Figure 3.3). Side-chain carbon atoms are designated with letters of the Greek alphabet, counting from the α -carbon. These carbon atoms are, in turn, the β -, γ -, δ -, and ϵ -carbons (see lysine in Figure 3.3); a terminal carbon atom is referred to as the ω -carbon, from the name of the last letter of the Greek alphabet. We frequently refer to amino acids by three-letter or one-letter abbrevia-



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■ **ANIMATED FIGURE 3.2** Stereochemistry of alanine and glycine. The amino acids found in proteins have the same chirality as L-glyceraldehyde, which is opposite to that of D-glyceraldehyde. Sign in at www.thomsonedu.com/login to see an animated version of this figure.

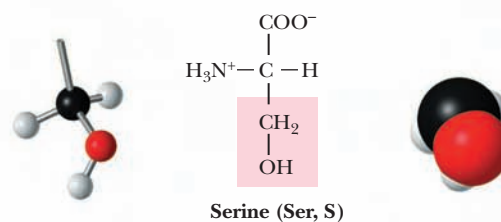
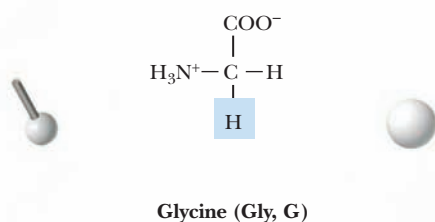
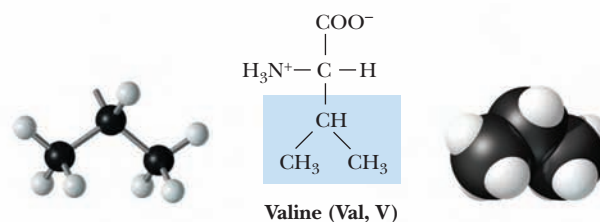
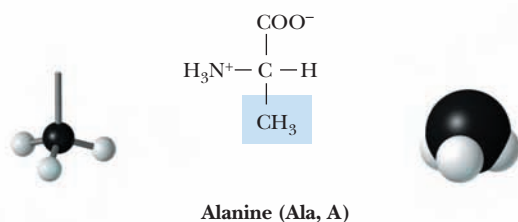
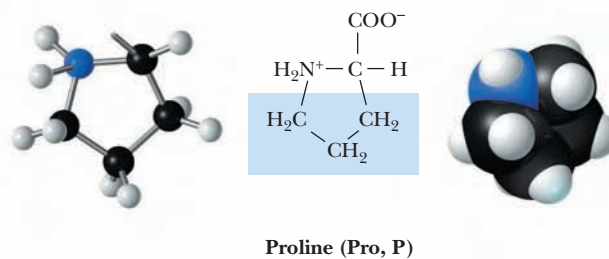
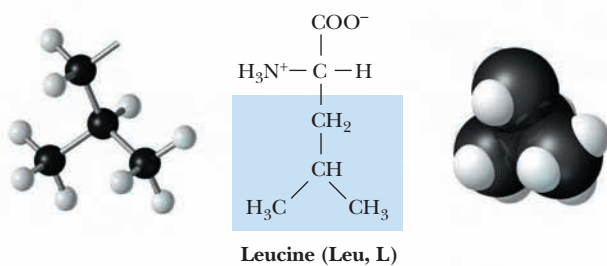
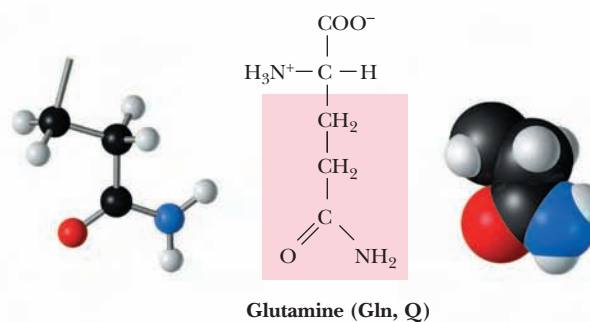
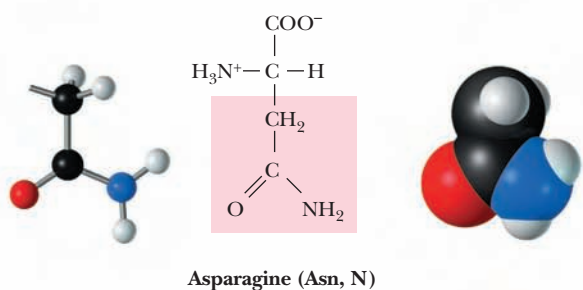
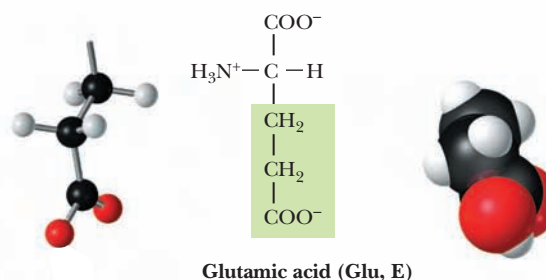
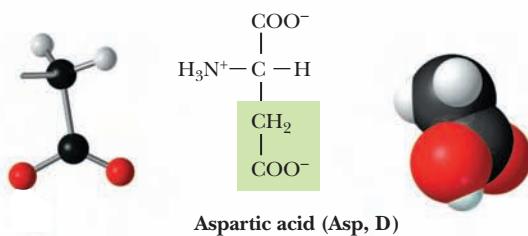
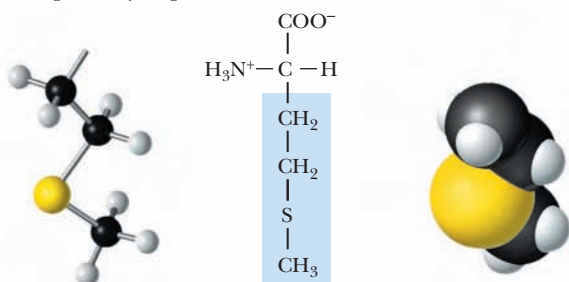
A Non-polar (hydrophobic)**B** Polar, uncharged**C** Acidic

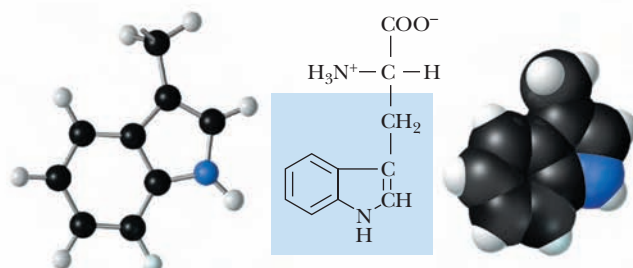
FIGURE 3.3 Structures of the amino acids commonly found in proteins. The 20 amino acids that are the building blocks of proteins can be classified as (a) nonpolar (hydrophobic), (b) polar, (c) acidic, or (d) basic. Also shown are the one-letter and three-letter codes used to denote amino acids. For each amino acid, the ball-and-stick model (left) and the space-filling model (right) show only the side chain. (Illustration, Irving Geis. Rights owned by Howard Hughes Medical Institute. Not to be reproduced without permission.)

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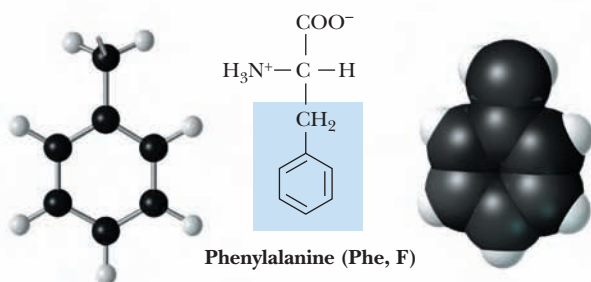
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A Non-polar (hydrophobic)

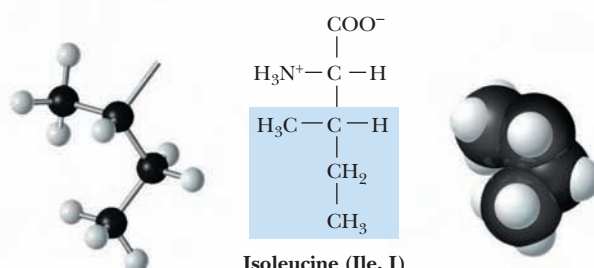
Methionine (Met, M)



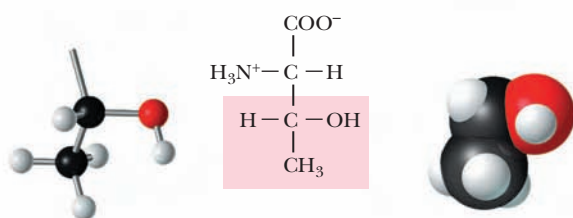
Tryptophan (Trp, W)



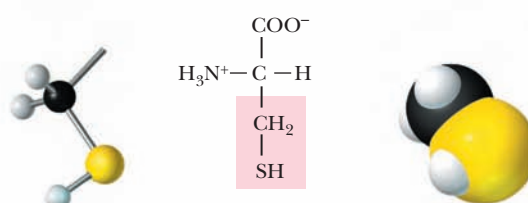
Phenylalanine (Phe, F)



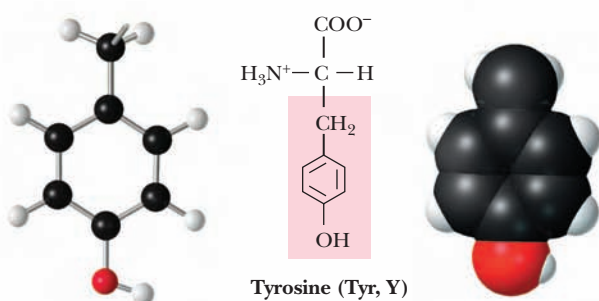
Isoleucine (Ile, I)

B Polar, uncharged

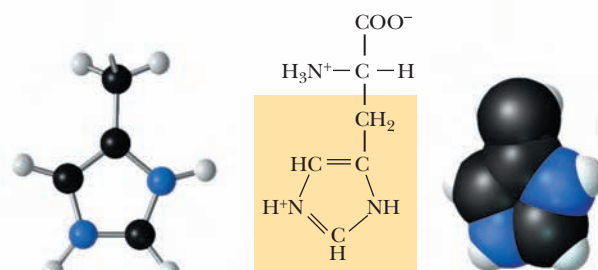
Threonine (Thr, T)



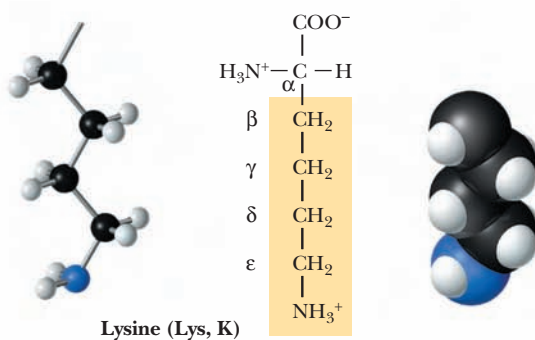
Cysteine (Cys, C)



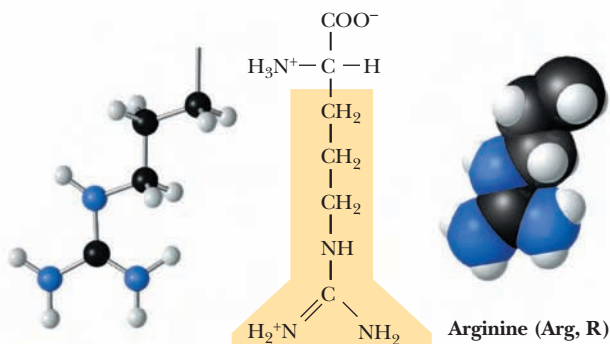
Tyrosine (Tyr, Y)



Histidine (His, H)

D Basic

Lysine (Lys, K)



Arginine (Arg, R)

tions of their names, with the one-letter designations becoming much more prevalent these days; Table 3.1 lists these abbreviations.

Which amino acids have nonpolar side chains? (Group 1)

One group of amino acids has nonpolar side chains. This group consists of glycine, alanine, valine, leucine, isoleucine, proline, phenylalanine, tryptophan, and methionine. In several members of this group—namely alanine, valine, leucine, and isoleucine—each side chain is an aliphatic hydrocarbon group. (In organic chemistry, the term *aliphatic* refers to the absence of a benzene ring or related structure.) Proline has an aliphatic cyclic structure, and the nitrogen is bonded to two carbon atoms. In the terminology of organic chemistry, the amino group of proline is a secondary amine, and proline is often called an *imino acid*. In contrast, the amino groups of all the other common amino acids are primary amines. In phenylalanine, the hydrocarbon group is aromatic (it contains a cyclic group similar to a benzene ring) rather than aliphatic. In tryptophan, the side chain contains an indole ring, which is also aromatic. In methionine, the side chain contains a sulfur atom in addition to aliphatic hydrocarbon groupings. (See Figure 3.3.)

Which amino acids have electrically neutral polar side chains? (Group 2)

Another group of amino acids has polar side chains that are electrically neutral (uncharged) at neutral pH. This group includes serine, threonine, tyrosine,

Table 3.1

Names and Abbreviations of the Common Amino Acids

Amino Acid	Three-Letter Abbreviation	One-Letter Abbreviation
Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartic acid	Asp	D
Cysteine	Cys	C
Glutamic acid	Glu	E
Glutamine	Gln	Q
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	Thr	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V

Note: One-letter abbreviations start with the same letter as the name of the amino acid where this is possible. When the names of several amino acids start with the same letter, phonetic names (occasionally facetious ones) are used, such as Rginine, asparDic, Fenylalanine, tWryptophan. Where two or more amino acids start with the same letter, it is the smallest one whose one-letter abbreviation matches its first letter.

cysteine, glutamine, and asparagine. Glycine is sometimes included here for convenience because it lacks a nonpolar side chain.

In serine and threonine, the polar group is a hydroxyl (—OH) bonded to aliphatic hydrocarbon groups. The hydroxyl group in tyrosine is bonded to an aromatic hydrocarbon group, which eventually loses a proton at higher pH. (The hydroxyl group in tyrosine is a phenol, which is a stronger acid than an aliphatic alcohol. As a result, the side chain of tyrosine can lose a proton in a titration, whereas those of serine and threonine would require such a high pH that pK_a values are not normally listed for these side chains.) In cysteine, the polar side chain consists of a thiol group (—SH), which can react with other cysteine thiol groups to form disulfide (—S—S—) bridges in proteins in an oxidation reaction (Section 1.9). The thiol group can also lose a proton. The amino acids glutamine and asparagine have amide groups, which are derived from carboxyl groups, in their side chains. Amide bonds do not ionize in the range of pH usually encountered in biochemistry. Glutamine and asparagine can be considered derivatives of the Group 3 amino acids, glutamic acid and aspartic acid, respectively; those two amino acids have carboxyl groups in their side chains.

Which amino acids have carboxyl groups in their side chains? (Group 3)

Two amino acids, glutamic acid and aspartic acid, have carboxyl groups in their side chains in addition to the one present in all amino acids. A carboxyl group can lose a proton, forming the corresponding carboxylate anion (Section 2.5)—glutamate and aspartate, respectively, in the case of these two amino acids. Because of the presence of the carboxylate, the side chain of each of these two amino acids is negatively charged at neutral pH.

Which amino acids have basic side chains? (Group 4)

Three amino acids—histidine, lysine, and arginine—have basic side chains, and the side chain in all three is positively charged at or near neutral pH. In lysine, the side-chain amino group is attached to an aliphatic hydrocarbon tail. In arginine, the side-chain basic group, the guanidino group, is more complex in structure than the amino group, but it is also bonded to an aliphatic hydrocarbon tail. In free histidine, the pK_a of the side-chain imidazole group is 6.0, which is not far from physiological pH. The pK_a values for amino acids depend on the environment and can change significantly within the confines of a protein. Histidine can be found in the protonated or unprotonated forms in proteins, and the properties of many proteins depend on whether individual histidine residues are or are not charged.

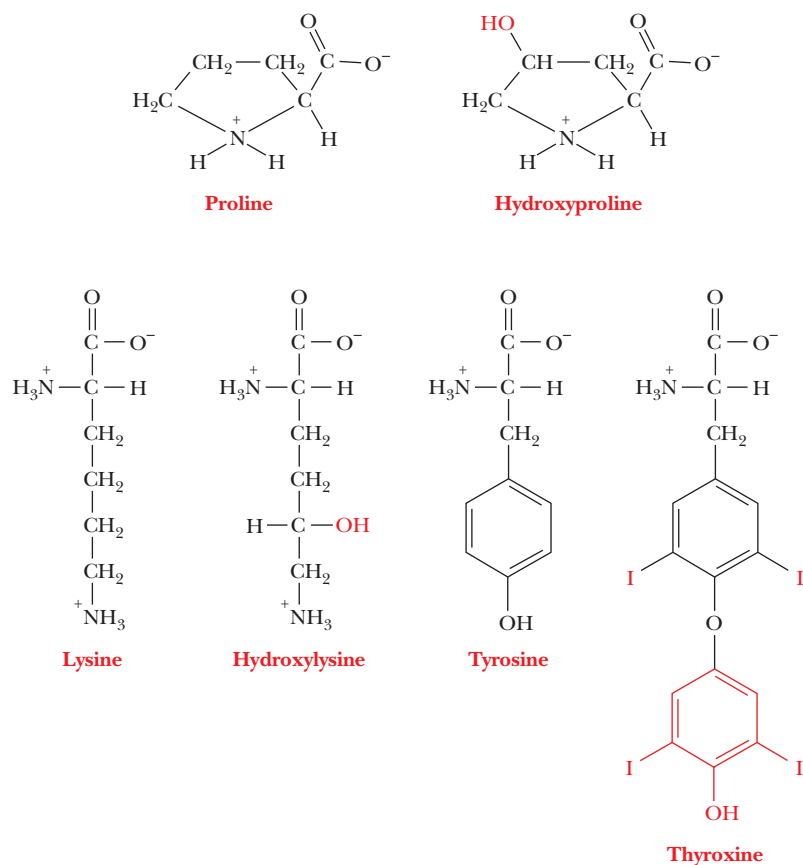
Uncommon Amino Acids

Which amino acids are found less commonly in proteins?

Many other amino acids, in addition to the ones listed here, are known to exist. They occur in some, but by no means all, proteins. Figure 3.4 shows some examples of the many possibilities. They are derived from the common amino acids and are produced by modification of the parent amino acid after the protein is synthesized by the organism in a process called posttranslational modification. Hydroxyproline and hydroxylysine differ from the parent amino acids in that they have hydroxyl groups on their side chains; they are found only in a few connective-tissue proteins, such as collagen. Thyroxine differs from tyrosine in that it has an extra iodine-containing aromatic group on the side

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■ **FIGURE 3.4** Structures of hydroxyproline, hydroxylysine, and thyroxine. The structures of the parent amino acids—proline for hydroxyproline, lysine for hydroxylysine, and tyrosine for thyroxine—are shown for comparison. All amino acids are shown in their predominant ionic forms at pH 7.

chain; it is produced only in the thyroid gland, formed by posttranslational modification of tyrosine residues in the protein thyroglobulin. Thyroxine is then released as a hormone by proteolysis of thyroglobulin.

Apply Your Knowledge

Amino Acids, Their Structures and Properties

1. In the following group, identify the amino acids with nonpolar side chains and those with basic side chains: alanine, serine, arginine, lysine, leucine, and phenylalanine.
2. The pK_a of the side-chain imidazole group of histidine is 6.0. What is the ratio of uncharged to charged side chains at pH 7.0?

Solution

Notice that in the first part of this exercise in applying your knowledge, you are asked to do a fact check on material from this chapter, and in the second part you are asked to recall and apply concepts from an earlier chapter.

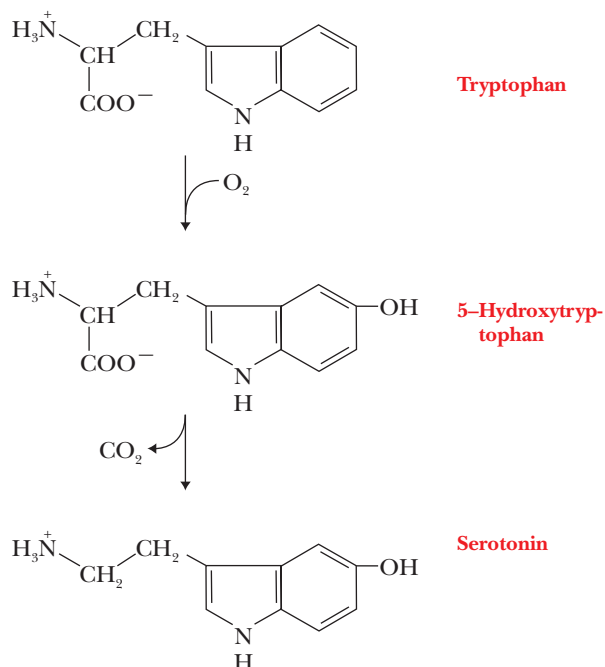
1. See Figure 3.3. Nonpolar: alanine, leucine, and phenylalanine; basic: arginine and lysine. Serine is not in either category because it has a polar side chain.
2. The ratio is 10:1 because the pH is one unit higher than the pK_a .

Amino Acids to Calm Down and Pep Up

Two amino acids deserve some special notice because both are key precursors to many hormones and neurotransmitters (substances involved in the transmission of nerve impulses). The study of neurotransmitters is work in progress, but we do recognize that certain key molecules appear to be involved. Because many neurotransmitters have very short biological half-lives and function at very low concentrations, we also recognize that other derivatives of these molecules may be the actual biologically active forms.

Two of the neurotransmitter classes are simple derivatives of the two amino acids **tyrosine** and **tryptophan**. The active products are monoamine derivatives, which are themselves degraded or deactivated by monoamine oxidases (MAOs).

Tryptophan is converted to serotonin, more properly called 5-hydroxytryptamine.

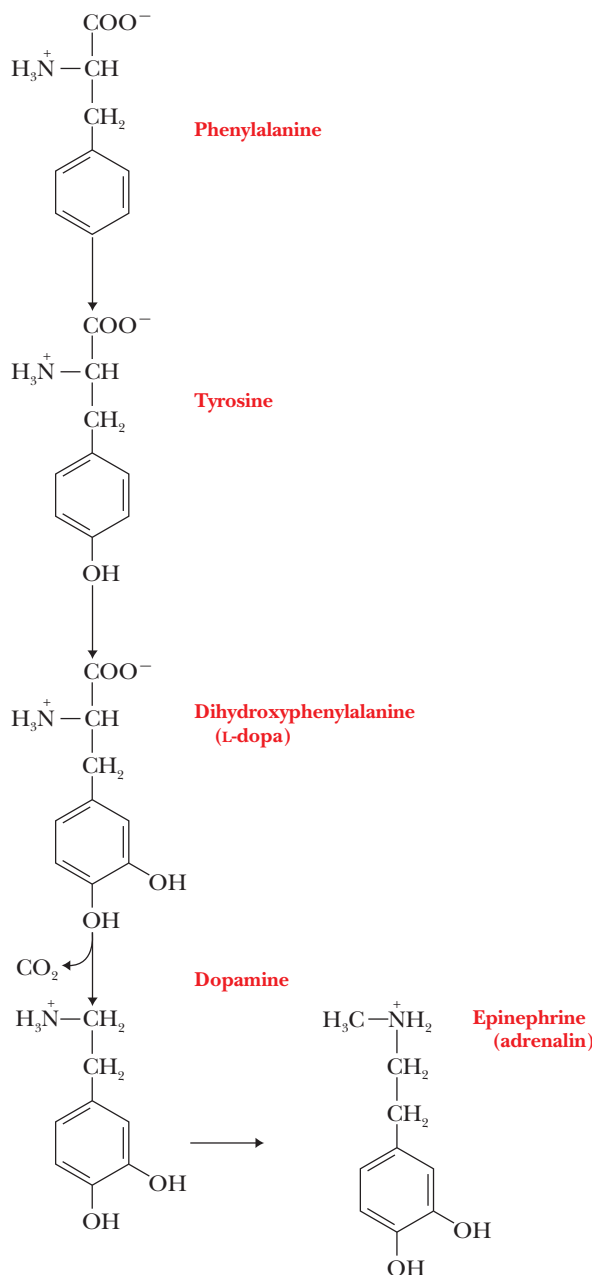


Tyrosine, itself normally derived from phenylalanine, is converted to the class called catecholamines, which includes epinephrine, commonly known by its proprietary name, **adrenalin**.

Note that L-dihydroxyphenylalanine (L-dopa) is an intermediate in the conversion of tyrosine. Lower-than-normal levels of L-dopa are involved in Parkinson's disease. Tyrosine or phenylalanine supplements might increase the levels of dopamine, though L-dopa, the immediate precursor, is usually prescribed because L-dopa passes into the brain quickly through the blood-brain barrier.

Tyrosine and phenylalanine are precursors to norepinephrine and epinephrine, both of which are stimulatory. Epinephrine is commonly known as the "flight or fight" hormone. It causes the release of glucose and other nutrients into the blood and also stimulates brain function. People taking MAO inhibitors stay in a relatively high mental state, sometimes too high, because the epinephrine is not metabolized rapidly. Tryptophan is a precursor to serotonin, which has a sedative effect, giving a pleasant feeling. Very low levels of serotonin are associated with depression, while extremely high levels actually produce a manic state. Manic-depressive illness (also called bipolar disorder) can be managed by controlling the levels of serotonin and its further metabolites.

It has been suggested that tyrosine and phenylalanine may have unexpected effects in some people. For example, there is increasing evidence that some people get headaches from the phenylala-



nine in aspartame (a low-calorie sweetener), which is described in more detail in the Biochemical Connections box on page 80. It is also likely that many illegal psychedelic drugs, such as mescaline and psilocine, mimic and interfere with the effects of neurotransmitters. A recent Oscar-winning film, *A Beautiful Mind*, focused on the disturbing problems associated with schizophrenia. Until recently, the neurotransmitter dopamine was a major focus in the study of schizophrenia. More recently, it has been suggested that irregularities in the metabolism of glutamate, a neurotransmitter, can lead to the disease. (See the article by Javitt and Coyle cited in the bibliography at the end of this chapter.)

Some people insist that supplements of tyrosine give them a morning lift and that tryptophan helps them sleep at night. Milk proteins have high levels of tryptophan; a glass of warm milk before bed is widely believed to be an aid in inducing sleep. Cheese and red wines contain high amounts of tyramine, which mimics epinephrine; for many people a cheese omelet in the morning is a favorite way to start the day.

Section 3.2 Summary

- Amino acids are classified according to two major criteria: the polarity of the side chains and the presence of an acidic or basic group in the side chain.
- Four groups of amino acids are found in proteins: first, those with non-polar side chains; second, those with electrically neutral polar side chains; third, those with carboxyl groups in their side chains; fourth, those with basic side chains.

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3.3 Amino Acids Can Act as Both Acids and Bases

In a free amino acid, the carboxyl group and amino group of the general structure are charged at neutral pH—the carboxylate portion negatively and the amino group positively. Amino acids without charged groups on their side chains exist in neutral solution as zwitterions with no net charge. A zwitterion has equal positive and negative charges; in solution, it is electrically neutral.

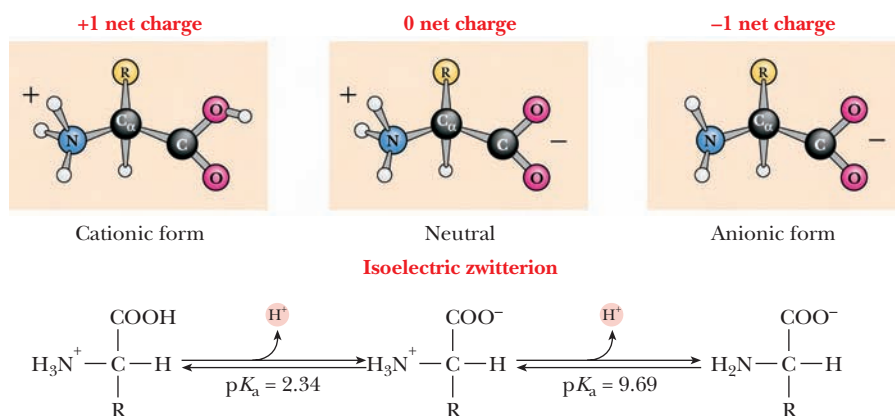
Neutral amino acids do not exist in the form $\text{NH}_2\text{—CHR—COOH}$ (that is, without charged groups).

What happens when we titrate an amino acid?

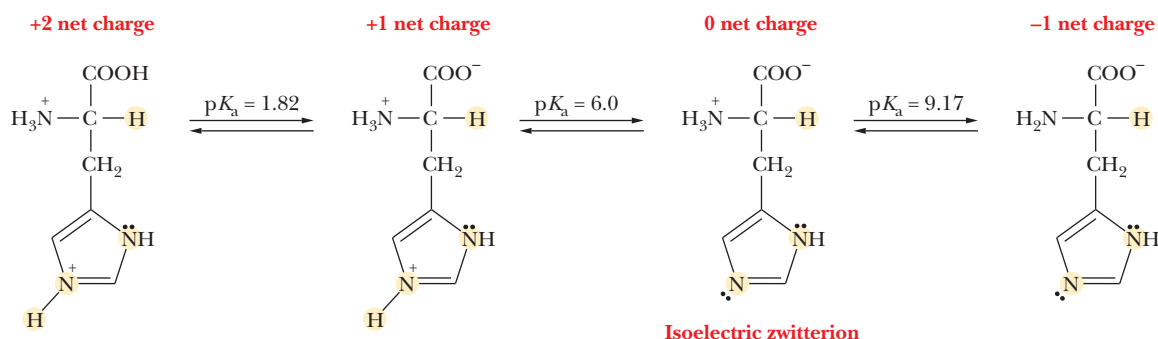
When an amino acid is titrated, its titration curve indicates the reaction of each functional group with hydrogen ion. In alanine, the carboxyl and amino groups are the two titratable groups. At very low pH, alanine has a protonated (and thus uncharged) carboxyl group and a positively charged amino group that is also protonated. Under these conditions, the alanine has a net positive charge of 1. As base is added, the carboxyl group loses its proton to become a negatively charged carboxylate group (Figure 3.5a), and the pH of the solution increases. Alanine now has no net charge. As the pH increases still further with addition of more base, the protonated amino group (a weak acid) loses its proton, and the alanine molecule now has a negative charge of 1. The titration curve of alanine is that of a diprotic acid (Figure 3.6).

In histidine, the imidazole side chain also contributes a titratable group. At very low pH values, the histidine molecule has a net positive charge of 2 because both the imidazole and amino groups have positive charges. As base is added and the pH increases, the carboxyl group loses a proton to become a carboxylate as before, and the histidine now has a positive charge of 1 (Figure 3.5b). As still more base is added, the charged imidazole group loses its proton, and this is the point at which the histidine has no net charge. At still higher values of pH, the amino group loses its proton, as was the case with alanine, and the histidine molecule now has a negative charge of 1. The titration curve of histidine is that of a triprotic acid (Figure 3.7).

Like the acids we discussed in Chapter 2, the titratable groups of each of the amino acids have characteristic $\text{p}K_a$ values. The $\text{p}K_a$ values of α -carboxyl groups are fairly low, around 2. The $\text{p}K_a$ values of amino groups are much higher, with values ranging from 9 to 10.5. The $\text{p}K_a$ values of side-chain groups, including side-chain carboxyl and amino groups, depend on the groups' chemical nature. Table 3.2 lists the $\text{p}K_a$ values of the titratable groups of the amino acids. The classification of an amino acid as acidic or basic depends on the $\text{p}K_a$ of the side chain as well as the chemical nature of the group. Histidine, lysine, and arginine are considered basic amino acids because each of their side chains has a nitrogen-containing group that can exist in either a protonated or deprotonated form. However, histidine has a $\text{p}K_a$ in the acidic range. Aspartic acid and glutamic acid are considered acidic because each has a carboxylic acid side chain with a low $\text{p}K_a$.



A The ionic forms of the amino acids, shown without consideration of any ionizations on the side chain. The cationic form is the low-pH form, and the titration of the cationic species with base yields the zwitterions and finally the anionic form.



B The ionization of histidine (an amino acid with a titratable side chain).

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ANIMATED FIGURE 3.5 The ionization of amino acids.
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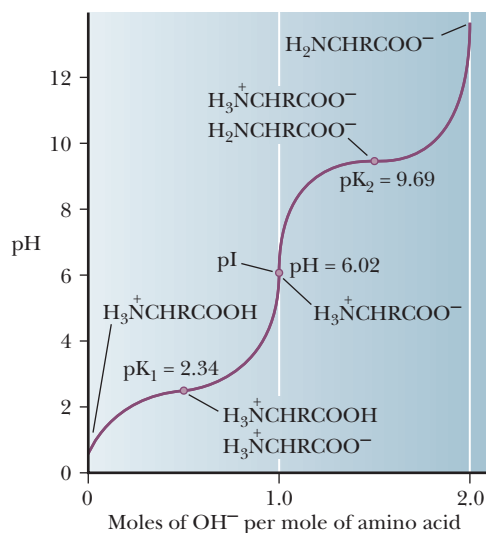
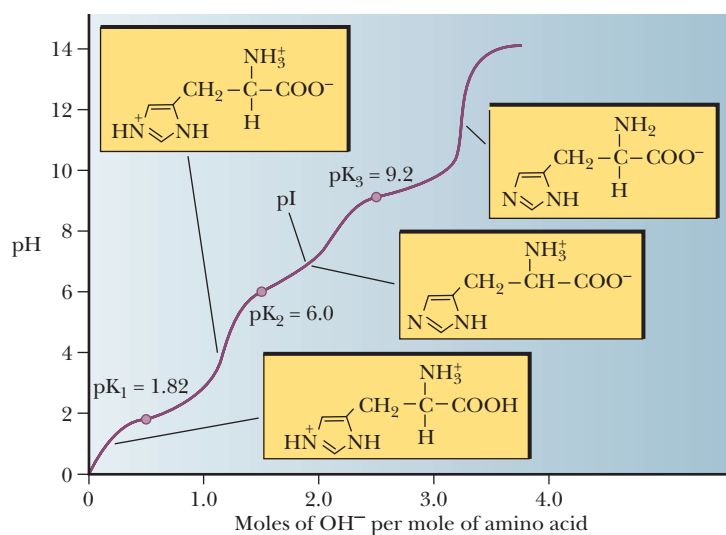


FIGURE 3.6 The titration curve of alanine.

value. These groups can still be titrated after the amino acid is incorporated into a peptide or protein, but the $\text{p}K_a$ of the titratable group on the side chain is not necessarily the same in a protein as it is in a free amino acid. In fact, it can be very different. For example, a $\text{p}K_a$ of 9 has been reported for an aspartate side chain in the protein thioredoxin. (For more information, see the article by Wilson et al. cited in the bibliography at the end of this chapter.)

The fact that amino acids, peptides, and proteins have different $\text{p}K_a$ values gives rise to the possibility that they can have different charges at a given pH. Alanine and histidine, for example, both have net charges of -1 at high pH, above 10; the only charged group is the carboxylate anion. At lower pH, around 5, alanine is a zwitterion with no net charge, but histidine has a net charge of 1 at this pH because the imidazole group is protonated. This property is useful in **electrophoresis**, a common method for separating molecules in an electric field. This method is extremely useful in determining the important properties of proteins and nucleic acids. We shall see the applications to proteins in Chapter 5 and to nucleic acids in Chapter 14. The pH at which a molecule has no net charge is called the **isoelectric pH**, or isoelectric point (given the symbol **pI**). At its isoelectric pH, a molecule will not migrate in an electric field. This



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■ **ACTIVE FIGURE 3.7** The titration curve of histidine. The isoelectric pH (pI) is the value at which positive and negative charges are the same. The molecule has no net charge. **Sign in at www.thomsonedu.com/login to explore an interactive version of this figure.**

Table 3.2

pK_a Values of Common Amino Acids

Acid	α-COOH	α-NH ₃ ⁺	RH or RH ⁺
Gly	2.34	9.60	
Ala	2.34	9.69	
Val	2.32	9.62	
Leu	2.36	9.68	
Ile	2.36	9.68	
Ser	2.21	9.15	
Thr	2.63	10.43	
Met	2.28	9.21	
Phe	1.83	9.13	
Trp	2.38	9.39	
Asn	2.02	8.80	
Gln	2.17	9.13	
Pro	1.99	10.6	
Asp	2.09	9.82	3.86*
Glu	2.19	9.67	4.25*
His	1.82	9.17	6.0*
Cys	1.71	10.78	8.33*
Tyr	2.20	9.11	10.07
Lys	2.18	8.95	10.53
Arg	2.17	9.04	12.48

*For these amino acids, the R group ionization occurs before the α-NH₃⁺ ionization.

property can be put to use in separation methods. The pI of an amino acid can be calculated by the following equation:

$$\text{pI} = \frac{\text{pK}_{\text{a1}} + \text{pK}_{\text{a2}}}{2}$$

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Most of the amino acids have only two pK_a values, so this equation is easily used to calculate the pI. For the acidic and basic amino acids, however, we must be sure to average the correct pK_a values. The pK_{a1} is for the functional group that has dissociated at its isoelectric point. If two groups are dissociated at isoelectric pH, the pK_{a1} is the higher pK_a of the two. Therefore, pK_{a2} is for the group that has not dissociated at isoelectric pH. If there are two groups that are not dissociated, the one with the lower pK_a is used. See the following apply your knowledge exercise.

Apply Your Knowledge

Amino Acid Titrations

1. Which of the following amino acids has a net charge of +2 at low pH? Which has a net charge of -2 at high pH? Aspartic acid, alanine, arginine, glutamic acid, leucine, lysine.
2. What is the pI for histidine?

Solution

Notice that the first part of this exercise deals only with the qualitative description of the successive loss of protons by the titratable groups on the individual amino acids. In the second part, you need to refer to the titration curve as well to do a numerical calculation of pH values.

1. Arginine and lysine have net charges of +2 at low pH because of their basic side chains; aspartic acid and glutamic acid have net charges of -2 at high pH because of their carboxylic acid side chains. Alanine and leucine do not fall into either category because they do not have titratable side chains.
2. Draw or picture histidine at very low pH. It will have the formula shown in Figure 3.5b on the far left side. This form has a net charge of +2. To arrive at the isoelectric point, we must add some negative charge or remove some positive charge. This will happen in solution in order of increasing pK_a . Therefore, we begin by taking off the hydrogen from the carboxyl group because it has the lowest pK_a (1.82). This leaves us with the form shown second from the left in Figure 3.5b. This form has a charge of +1, so we must remove yet another hydrogen to arrive at the isoelectric form. This hydrogen would come from the imidazole side chain because it has the next highest pK_a (6.0); this is the isoelectric form (second from right). Now we average the pK_a from the highest pK_a group that lost a hydrogen with that of the lowest pK_a group that still retains its hydrogen. In the case of histidine, the numbers to substitute in the equation for the pI are 6.0 [pK_{a1}] and 9.17 [pK_{a2}], which gives a pI of 7.58.

Section 3.3 Summary

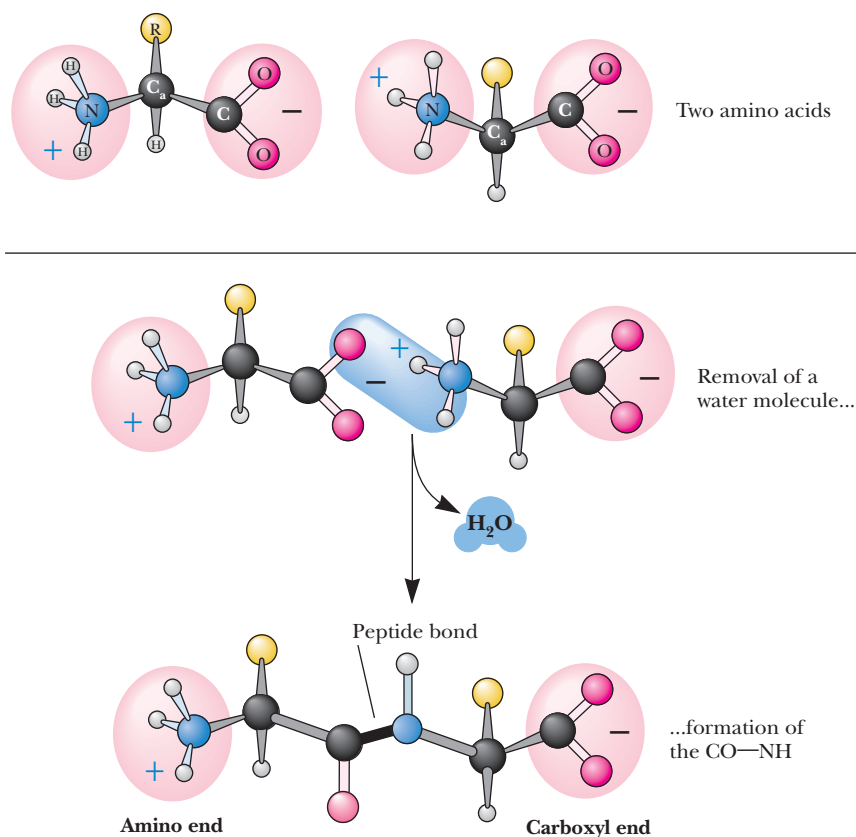
- The carboxyl group of every amino acid is acidic, and the amino group is basic. The carboxylate group is the conjugate base of the carboxyl group, and the protonated amino group is the conjugate acid of the amino group. In addition, a number of side chains have groups with acid-base properties.
- Titration curves can be obtained for amino acids, just as they can for any diprotic or multiprotic acid. It is possible to determine the charge on amino acids at any given pH.

3.4 The Peptide Bond

Which groups on amino acids react to form a peptide bond?

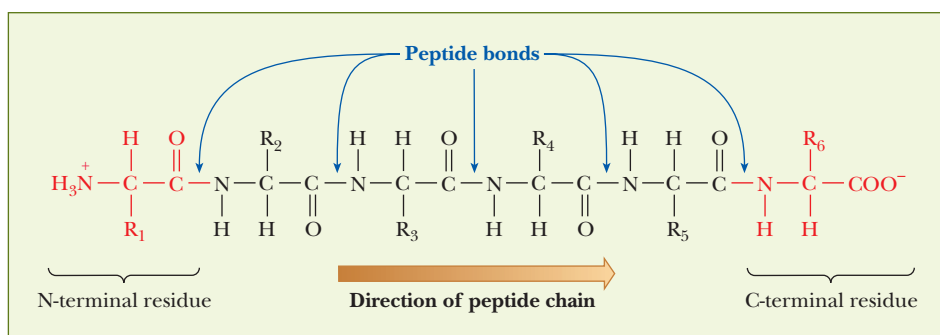
Individual amino acids can be linked by forming covalent bonds. The bond is formed between the α -carboxyl group of one amino acid and the α -amino group of the next one. Water is eliminated in the process, and the linked amino acid **residues** remain after water is eliminated (Figure 3.8). A bond formed in this way is called a **peptide bond**. **Peptides** are compounds formed by linking small numbers of amino acids, ranging from two to several dozen. In a protein, many amino acids (usually more than a hundred) are linked by peptide bonds to form a **polypeptide chain** (Figure 3.9). Another name for a compound formed by the reaction between an amino group and a carboxyl group is an *amide*.

The carbon–nitrogen bond formed when two amino acids are linked in a peptide bond is usually written as a single bond, with one pair of electrons shared between the two atoms. With a simple shift in the position of a pair of electrons, it is quite possible to write this bond as a double bond. This shifting of electrons is well known in organic chemistry and results in **resonance structures**, structures that differ from one another only in the positioning of electrons. The positions of double and single bonds in one resonance structure are different from their positions in another resonance structure of the same compound. No single resonance structure actually represents the bonding in the compound; instead all resonance structures contribute to the bonding situation.



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■ **ANIMATED FIGURE 3.8** Formation of the peptide bond. (Illustration, Irving Geis. Rights owned by Howard Hughes Medical Institute. Not to be reproduced without permission.) Sign in at www.thomsonedu.com/login to see an animated version of this figure.



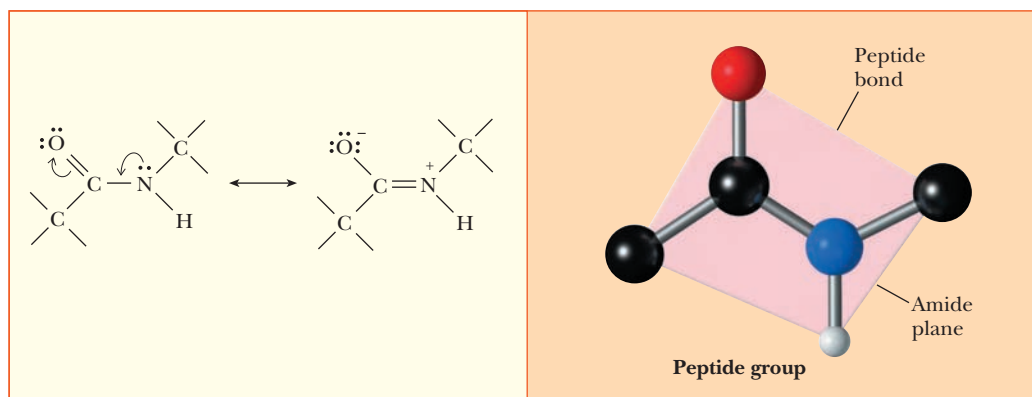
■ **FIGURE 3.9** A small peptide showing the direction of the peptide chain (N-terminal to C-terminal).

The peptide bond can be written as a resonance hybrid of two structures (Figure 3.10), one with a single bond between the carbon and nitrogen and the other with a double bond between the carbon and nitrogen. The peptide bond has partial double bond character. As a result, the peptide group that forms the link between the two amino acids is planar. The peptide bond is also stronger than an ordinary single bond because of this resonance stabilization.

This structural feature has important implications for the three-dimensional conformations of peptides and proteins. There is free rotation around the bonds between the α -carbon of a given amino acid residue and the amino nitrogen and carbonyl carbon of that residue, but there is no significant rotation around the peptide bond. This stereochemical constraint plays an important role in determining how the protein backbone can fold.

Section 3.4 Summary

- When the carboxyl group of one amino acid reacts with the amino group of another to give an amide linkage and eliminate water, a peptide bond is formed. In a protein, upward of a hundred amino acids are so joined to form a polypeptide chain.
- The peptide group is planar as a result of resonance stabilization. This stereochemical feature determines a number of features of the three-dimensional structure of proteins.



A Resonance structures of the peptide group.

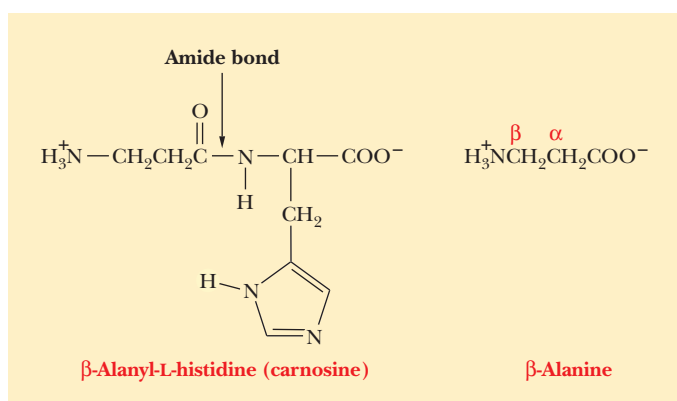
B The planar peptide group.

■ **FIGURE 3.10** The resonance structures of the peptide bond lead to a planar group. (Illustration, Irving Geis. Rights owned by Howard Hughes Medical Institute. Not to be reproduced without permission.)

3.5 Small Peptides with Physiological Activity

What are some biological functions of small peptides?

The simplest possible covalently bonded combination of amino acids is a dipeptide, in which two amino acid residues are linked by a peptide bond. An example of a naturally occurring dipeptide is carnosine, which is found in muscle tissue. This compound, which has the alternative name β -alanyl-L-histidine, has an interesting structural feature. (In the systematic nomenclature of peptides, the **N-terminal** amino acid residue—the one with the free amino group—is given first; then other residues are given as they occur in sequence. The **C-terminal** amino acid residue—the one with the free carboxyl group—is given last.) The N-terminal amino acid residue, β -alanine, is structurally different from the α -amino acids we have seen up to now. As the name implies, the amino group is bonded to the third or β -carbon of the alanine (Figure 3.11).



■ **FIGURE 3.11** Structures of carnosine and its component amino acid β -alanine.

Biochemical Connections *ORGANIC CHEMISTRY*

Amino Acids Go Many Different Places

Why Are Amino Acids Featured in Health Food Stores?

Amino acids have biological functions other than as parts of proteins and oligopeptides. The following examples illustrate some of these functions for a few of the amino acids.

Branched-Chain Amino Acids

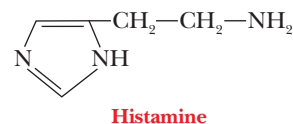
Some products sold in health food stores feature the presence of the branched-chain amino acids isoleucine, leucine, and valine. These are *essential* amino acids in the sense that the body cannot synthesize them. Under normal circumstances, a diet with adequate protein intake provides enough of all the essential amino acids. Athletes involved in intensive training want to prevent muscle loss and to increase muscle mass. As a result, they take protein supplements and pay particular attention to branched-chain amino acids. (These three amino acids are by no means the only essential ones, but they are mentioned specifically here.)

Glutamic Acid

Monosodium glutamate, or MSG, is a derivative of glutamic acid that finds wide use as a flavor enhancer. MSG causes a physiological reaction in some people, with chills, headaches, and dizziness resulting. Because many Asian foods contain significant amounts of MSG, this problem is often referred to as *Chinese restaurant syndrome*.

Histidine

If the acid group of histidine is removed, it is converted to histamine, which is a potent vasodilator, increasing the diameter of blood vessels. Histamine, which is released as part of the immune response, increases the localized blood volume for white blood cells. This results in the swelling and stuffiness that are associated with a cold. Most cold medications contain antihistamines to overcome this stuffiness.



Apply Your Knowledge

Sequence of Peptides

Write an equation with structures for the formation of a dipeptide when alanine reacts with glycine to form a peptide bond. Is there more than one possible product for this reaction?

Solution

The main point here is to be aware of the possibility that amino acids can be linked together in more than one order when they form peptide bonds. Thus, there are two possible products when alanine and glycine react: alanylglycine, in which alanine is at the N-terminal end and glycine is at the C-terminal end, and glycylalanine, in which glycine is at the N-terminal end and alanine is at the C-terminal end.

Glutathione is a commonly occurring tripeptide; it has considerable physiological importance because it is a scavenger for oxidizing agents. Recall from Section 1.9 that oxidation is the loss of electrons; an oxidizing agent causes another substance to lose electrons. (It is thought that some oxidizing agents are harmful to organisms and play a role in the development of cancer.) In terms of its amino acid composition and bonding order, it is γ -glutamyl-L-cysteinylglycine (Figure 3.12a). The letter γ (gamma) is the third letter in the Greek alphabet; in this notation, it refers to the third carbon atom in the molecule, counting the one bonded to the amino group as the first. Once again, the N-terminal amino acid is given first. In this case, the γ -carboxyl group (the side-chain carboxyl group) of the glutamic acid is involved in the peptide bond; the

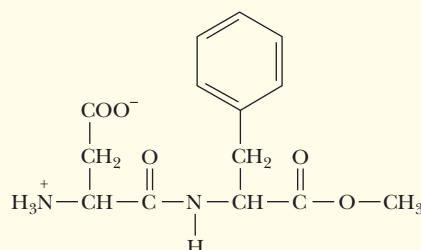
Biochemical Connections *NUTRITION*

Aspartame, the Sweet Peptide

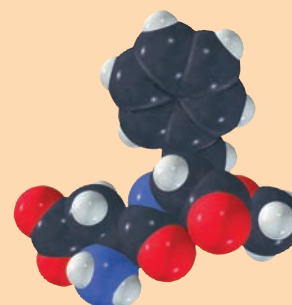
The dipeptide L-aspartyl-L-phenylalanine is of considerable commercial importance. The aspartyl residue has a free α -amino group, the N-terminal end of the molecule, and the phenylalanyl residue has a free carboxyl group, the C-terminal end. This dipeptide is about 200 times sweeter than sugar. A methyl ester derivative of this dipeptide is of even greater commercial importance than the dipeptide itself. The derivative has a methyl group at the C-terminal end in an ester linkage to the carboxyl group. The methyl ester derivative is called *aspartame* and is marketed as a sugar substitute under the trade name NutraSweet.

The consumption of common table sugar in the United States is about 100 pounds per person per year. Many people want to curtail their sugar intake in the interest of fighting obesity. Others must limit their sugar intake because of diabetes. One of the most common ways of doing so is by drinking diet soft drinks. The soft-drink industry is one of the largest markets for aspartame. The use of this sweetener was approved by the U.S. Food and Drug Administration in 1981 after extensive testing, although there is still considerable controversy about its safety. Diet

soft drinks sweetened with aspartame carry warning labels about the presence of phenylalanine. This information is of vital importance to people who have phenylketonuria, a genetic disease of phenylalanine metabolism. (See the Biochemical Connections box on page 82). Note that both amino acids have the L configuration. If a D-amino acid is substituted for either amino acid or for both of them, the resulting derivative is bitter rather than sweet.

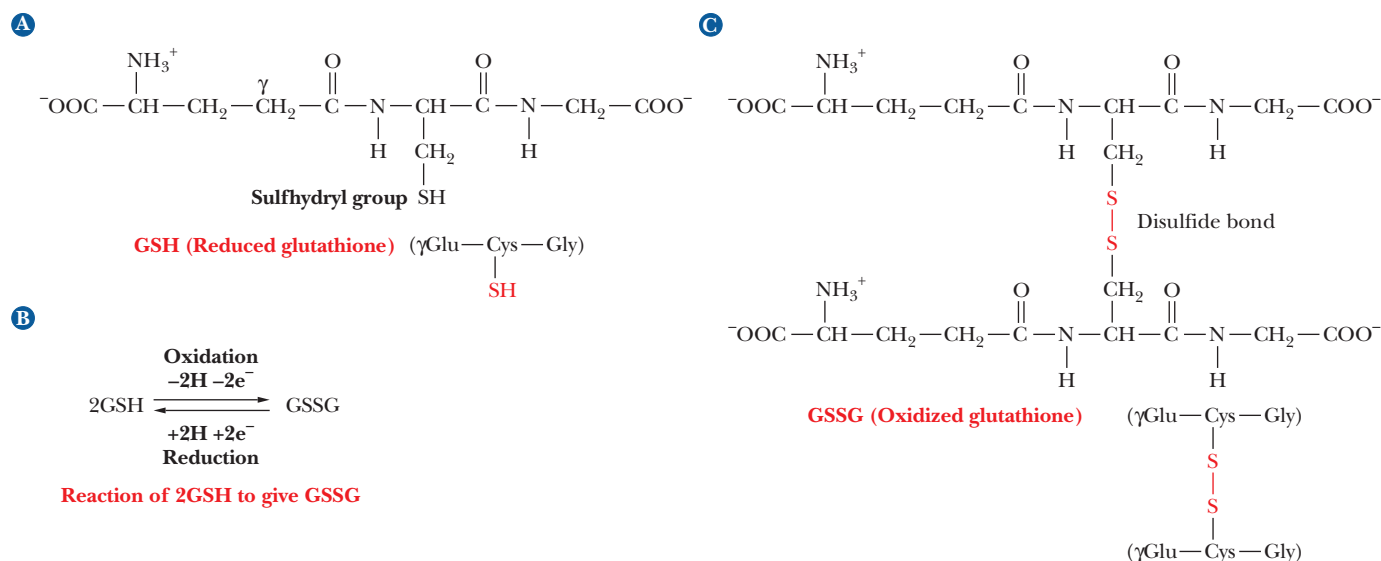


L-Aspartyl-L-phenylalanine (methyl ester)



A Structure of aspartame.

B Space-filling model of aspartame.



■ **FIGURE 3.12** The oxidation and reduction of glutathione. (a) The structure of reduced glutathione. (b) A schematic representation of the oxidation–reduction reaction. (c) The structure of oxidized glutathione.

amino group of the cysteine is bonded to it. The carboxyl group of the cysteine is bonded, in turn, to the amino group of the glycine. The carboxyl group of the glycine forms the other end of the molecule, the C-terminal end. The glutathione molecule shown in Figure 3.12a is the reduced form. It scavenges oxidizing agents by reacting with them. The oxidized form of glutathione is generated from two molecules of the reduced peptide by forming a disulfide bond between the —SH groups of the two cysteine residues (Figure 3.12b). The full structure of oxidized glutathione is shown in Figure 3.12c.

Two pentapeptides found in the brain are known as enkephalins, naturally occurring analgesics (pain relievers). For molecules of this size, abbreviations for the amino acids are more convenient than structural formulas. The same notation is used for the amino acid sequence, with the N-terminal amino acid listed first and the C-terminal listed last. The two peptides in question, leucine enkephalin and methionine enkephalin, differ only in their C-terminal amino acids.

Tyr—Gly—Gly—Phe—Leu (three-letter abbreviations)

Y—G—G—F—L (one-letter abbreviations)

Leucine enkephalin

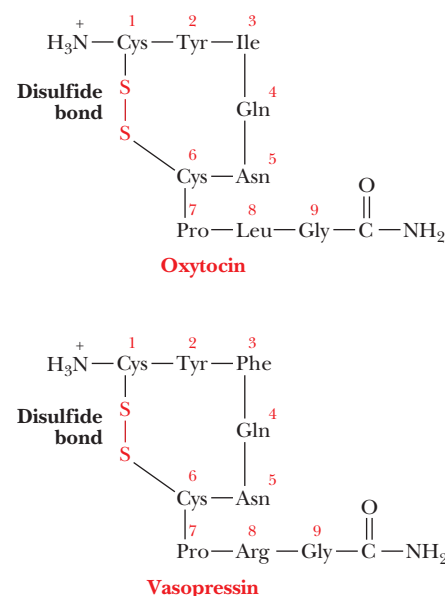
Tyr—Gly—Gly—Phe—Met

Y—G—G—F—M

Methionine enkephalin

It is thought that the aromatic side chains of tyrosine and phenylalanine in these peptides play a role in their activities. It is also thought that there are similarities between the three-dimensional structures of opiates, such as morphine, and those of the enkephalins. As a result of these structural similarities, opiates bind to the receptors in the brain intended for the enkephalins and thus produce their physiological activities.

Some important peptides have cyclic structures. Two well-known examples with many structural features in common are oxytocin and vasopressin (Figure 3.13). In each, there is an —S—S— bond similar to that in the oxidized form



■ **FIGURE 3.13** Structures of oxytocin and vasopressin.

of glutathione. The disulfide bond is responsible for the cyclic structure. Each of these peptides contains nine amino acid residues, each has an amide group (rather than a free carboxyl group) at the C-terminal end, and each has a disulfide link between cysteine residues at positions 1 and 6. The difference between these two peptides is that oxytocin has an isoleucine residue at position 3 and a leucine residue at position 8, and vasopressin has a phenylalanine residue at position 3 and an arginine residue at position 8. Both of these peptides have considerable physiological importance as hormones (see the following Biochemical Connections box).

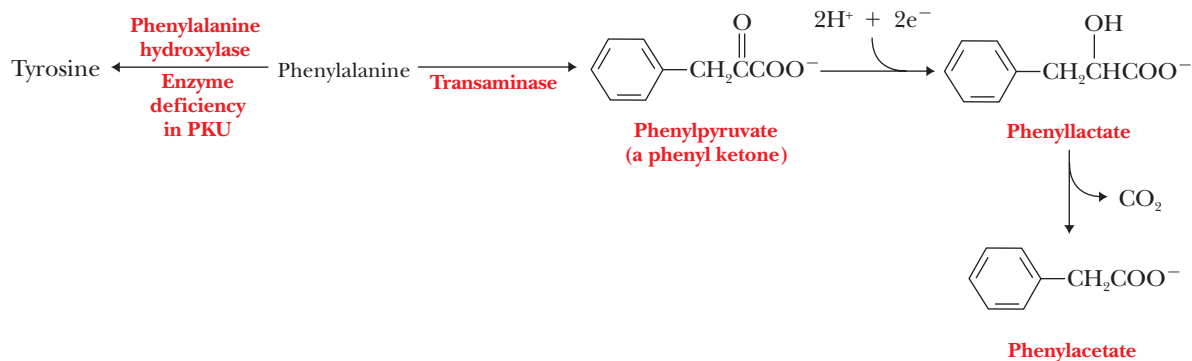
In some other peptides, the cyclic structure is formed by the peptide bonds themselves. Two cyclic decapeptides (peptides containing 10 amino acid residues) produced by the bacterium *Bacillus brevis* are interesting examples. Both of these peptides, gramicidin S and tyrocidine A, are antibiotics, and both contain D-amino acids as well as the more usual L-amino acids (Figure 3.14). In addition, both contain the amino acid ornithine (Orn), which does not occur in proteins, but which does play a role as a metabolic intermediate in several common pathways (Section 23.6).

Biochemical Connections ALLIED HEALTH

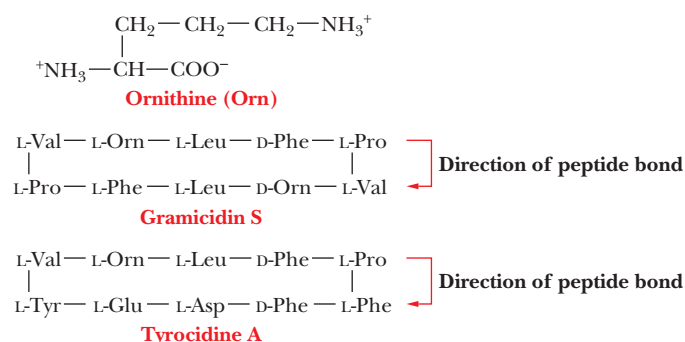
Phenylketonuria—Little Molecules Have Big Effects

Mutations leading to deficiencies in enzymes are usually referred to as “inborn errors of metabolism,” because they involve defects in the DNA of the affected individual. Errors in enzymes that catalyze reactions of amino acids frequently have disastrous consequences, many of them leading to severe forms of mental retardation. Phenylketonuria (PKU) is a well-known example. In this condition, phenylalanine, phenylpyruvate, phenyllactate, and phenylacetate all accumulate in the blood and urine. Available evidence suggests that phenylpyruvate, which is a phenylketone, causes mental retardation by interfering with the conversion of pyruvate to acetyl-CoA (an important intermediate in many biochemical reactions) in the brain. It is also likely that the accumulation of these products in the brain cells results in an osmotic imbalance in which water flows into the brain cells. These cells expand in size until they crush each other in the developing brain. In either case, the brain is not able to develop normally.

Fortunately, PKU can be easily detected in newborns, and all 50 states and the District of Columbia mandate that such a test be performed because it is cheaper to treat the disease with a modified diet than to cope with the costs of a mentally retarded individual who is usually institutionalized for life. The dietary changes are relatively simple. Phenylalanine must be limited to the amount needed for protein synthesis, and tyrosine must now be supplemented, because phenylalanine is no longer a source. You may have noticed that foods containing aspartame carry a warning about the phenylalanine portion of that artificial sweetener. A substitute for aspartame, which carries the trade name *Alatame*, contains alanine rather than phenylalanine. It has been introduced to retain the benefits of aspartame without the dangers associated with phenylalanine.



- Reactions involved in the development of phenylketonuria (PKU). A deficiency in the enzyme that catalyzes the conversion of phenylalanine to tyrosine leads to the accumulation of phenylpyruvate, a phenyl ketone.



■ **FIGURE 3.14** Structures of ornithine, gramicidin S, and tyrocidine A.

Section 3.5 Summary

- Small peptides play many roles in organisms. Some, such as oxytocin and vasopressin, are important hormones. Others, like glutathione, regulate oxidation–reduction reactions. Still others, such as enkephalins, are naturally occurring painkillers.

Biochemical Connections *ALLIED HEALTH*

Peptide Hormones—More Small Molecules with Big Effects

Both oxytocin and vasopressin are peptide hormones. Oxytocin induces labor in pregnant women and controls contraction of uterine muscle. During pregnancy, the number of receptors for oxytocin in the uterine wall increases. At term, the number of receptors for oxytocin is great enough to cause contraction of the smooth muscle of the uterus in the presence of small amounts of oxytocin produced by the body toward the end of pregnancy. The fetus moves toward the cervix of the uterus because of the strength and frequency of the uterine contractions. The cervix stretches, sending nerve impulses to the hypothalamus. When the impulses reach this part of the brain, positive feedback leads to the release of still more oxytocin by the posterior pituitary gland. The presence of more oxytocin leads to stronger contractions of the uterus so that the fetus is forced through the cervix and the baby is born. Oxytocin also plays a role in stimulating the flow of milk in a nursing mother. The process of suckling sends nerve signals to the hypothalamus of the mother's brain. Oxytocin is released and carried by the blood to the mammary glands. The presence of oxytocin causes the smooth muscle in the mammary glands to contract, forcing out the milk that is in them. As suckling continues, more hormone is released, producing still more milk.

Vasopressin plays a role in the control of blood pressure by regulating contraction of smooth muscle. Like oxytocin, vasopressin is released by the action of the hypothalamus on the posterior pituitary and is transported by the blood to specific receptors. Vasopressin stimulates reabsorption of water by the kidney, thus having an antidiuretic effect. More water is retained, and the blood pressure increases.



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- Nursing stimulates the release of oxytocin, producing more milk.

Summary

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Why is it important to specify the three-dimensional structure of amino acids?

The amino acids that are the monomer units of proteins have a general structure in common, with an amino group and a carboxyl group bonded to the same carbon atom. The nature of the side chains, which are referred to as R groups, is the basis of the differences among amino acids. Except for glycine, amino acids can exist in two forms, designated L and D. These two stereoisomers are nonsuperimposable mirror images of each other. The amino acids found in proteins are of the L form, but some D-amino acids occur in nature.

Why are amino acid side chains so important? A classification scheme for amino acids can be based on the properties of their side chains. Two particularly important criteria are the polar or nonpolar nature of the side chain and the presence of an acidic or basic group in the side chain.

Which amino acids have nonpolar side chains?

(Group 1) One group of amino acids has nonpolar side chains. The side chains are mostly aliphatic or aromatic hydrocarbons or their derivatives.

Which amino acids have electrically neutral polar side chains?

(Group 2) A second group of amino acids has side chains that contain electronegative atoms such as oxygen, nitrogen, and sulfur.

Which amino acids have carboxyl groups in their side chains?

(Group 3) Two amino acids, glutamic acid and aspartic acid, have carboxyl groups in their side chains.

Which amino acids have basic side chains?

(Group 4) Three amino acids—histidine, lysine, and arginine—have basic side chains.

Which amino acids are found less commonly in proteins?

Some amino acids are found only in a few proteins. They are formed from the common ones after the protein has been synthesized in the cell.

What happens when we titrate an amino acid?

In free amino acids at neutral pH, the carboxylate group is negatively charged and the amino group is positively charged. Amino acids without charged groups on their side chains exist in neutral solution as zwitterions, with no net charge. Titration curves of amino acids indicate the pH ranges in which titratable groups gain or lose a proton. Side chains of amino acids can also contribute titratable groups; the charge (if any) on the side chain must be taken into consideration in determining the net charge on the amino acid.

Which groups on amino acids react to form a peptide bond?

Peptides are formed by linking the carboxyl group of one amino acid to the amino group of another amino acid in a covalent (amide) bond. Proteins consist of polypeptide chains; the number of amino acids in a protein is usually 100 or more. The peptide group is planar; this stereochemical constraint plays an important role in determining the three-dimensional structures of peptides and proteins.

What are some biological functions of small peptides?

Small peptides, containing two to several dozen amino acid residues, can have marked physiological effects in organisms.

Review Exercises

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3.1 Amino Acids Exist in a Three-Dimensional World

- Recall** How do D-amino acids differ from L-amino acids? What biological roles are played by peptides that contain D-amino acids?

3.2 Individual Amino Acids: Their Structures and Properties

- Recall** Which amino acid is technically *not* an amino acid? Which amino acid contains no chiral carbon atoms?

- Recall** For each of the following, name an amino acid in which the R group contains it: a hydroxyl group, a sulfur atom, a second chiral carbon atom, an amino group, an amide group, an acid group, an aromatic ring, and a branched side chain.
- Recall** Identify the polar amino acids, the aromatic amino acids, and the sulfur-containing amino acids, given a peptide with the following amino acid sequence:

Val—Met—Ser—Ile—Phe—Arg—Cys—Tyr—Leu

5. **Recall** Identify the nonpolar amino acids and the acidic amino acids in the following peptide:

Glu—Thr—Val—Asp—Ile—Ser—Ala

6. **Recall** Are amino acids other than the usual 20 amino acids found in proteins? If so, how are such amino acids incorporated into proteins? Give an example of such an amino acid and a protein in which it occurs.

3.3 Amino Acids Can Act as Both Acids and Bases

7. **Mathematical** Predict the predominant ionized forms of the following amino acids at pH 7: glutamic acid, leucine, threonine, histidine, and arginine.
8. **Mathematical** Draw structures of the following amino acids, indicating the charged form that exists at pH 4: histidine, asparagine, tryptophan, proline, and tyrosine.
9. **Mathematical** Predict the predominant forms of the amino acids from Question 8 at pH 10.
10. **Mathematical** Calculate the isoelectric point of each of the following amino acids: glutamic acid, serine, histidine, lysine, tyrosine, and arginine.
11. **Mathematical** Sketch a titration curve for the amino acid cysteine, and indicate the pK_a values for all titratable groups. Also indicate the pH at which this amino acid has no net charge.
12. **Mathematical** Sketch a titration curve for the amino acid lysine, and indicate the pK_a values for all titratable groups. Also indicate the pH at which the amino acid has no net charge.
13. **Mathematical** An organic chemist is generally happy with 95% yields. If you synthesized a polypeptide and realized a 95% yield with each amino acid residue added, what would be your overall yield after adding 10 residues (to the first amino acid)? After adding 50 residues? After 100 residues? Would these low yields be biochemically “satisfactory”? How are low yields avoided, biochemically?
14. **Mathematical** Sketch a titration curve for aspartic acid, and indicate the pK_a values of all titratable groups. Also indicate the pH range in which the conjugate acid–base pair +1 Asp and 0 Asp will act as a buffer.
15. **Reflect and Apply** Suggest a reason why amino acids are usually more soluble at pH extremes than they are at neutral pH. (Note that this does not mean that they are insoluble at neutral pH.)
16. **Reflect and Apply** Write equations to show the ionic dissociation reactions of the following amino acids: aspartic acid, valine, histidine, serine, and lysine.
17. **Reflect and Apply** Based on the information in Table 3.2, is there any amino acid that could serve as a buffer at pH 8? If so, which one?
18. **Reflect and Apply** If you were to have a mythical amino acid based on glutamic acid, but one in which the hydrogen that is attached to the γ -carbon were replaced by another amino group, what would be the predominant form of this amino acid at pH 4, 7, and 10, if the pK_a value were 10 for the unique amino group?
19. **Reflect and Apply** What would be the pI for the mythical amino acid described in Question 18?
20. **Reflect and Apply** Identify the charged groups in the peptide shown in Question 4 at pH 1 and at pH 7. What is the net charge of this peptide at these two pH values?
21. **Reflect and Apply** Consider the following peptides: Phe—Glu—Ser—Met and Val—Trp—Cys—Leu. Do these peptides have different net charges at pH 1? At pH 7? Indicate the charges at both pH values.
22. **Reflect and Apply** In each of the following two groups of amino acids, which amino acid would be the easiest to distinguish from the other two amino acids in the group, based on a titration?
 - (a) gly, leu, lys
 - (b) glu, asp, ser

23. **Reflect and Apply** Could the amino acid glycine serve as the basis of a buffer system? If so, in what pH range would it be useful?

3.4 The Peptide Bond

24. **Recall** Sketch resonance structures for the peptide group.
25. **Recall** How do the resonance structures of the peptide group contribute to the planar arrangement of this group of atoms?
26. **Biochemical Connections** Which amino acids or their derivatives are neurotransmitters?
27. **Biochemical Connections** What is a monoamine oxidase, and what function does it serve?
28. **Reflect and Apply** Consider the peptides Ser—Glu—Gly—His—Ala and Gly—His—Ala—Glu—Ser. How do these two peptides differ?
29. **Reflect and Apply** Would you expect the titration curves of the two peptides in Question 28 to differ? Why or why not?
30. **Reflect and Apply** What are the sequences of all the possible tripeptides that contain the amino acids aspartic acid, leucine, and phenylalanine? Use the three-letter abbreviations to express your answer.
31. **Reflect and Apply** Answer Question 30 using one-letter designations for the amino acids.
32. **Reflect and Apply** Most proteins contain more than 100 amino acid residues. If you decided to synthesize a “100-mer,” with 20 different amino acids available for each position, how many different molecules could you make?
33. **Biochemical Connections** What is the stereochemical basis of the observation that D-aspartyl-D-phenylalanine has a bitter taste, whereas L-aspartyl-L-phenylalanine is significantly sweeter than sugar?
34. **Biochemical Connections** Why might a glass of warm milk help you sleep at night?
35. **Biochemical Connections** Which would be better to eat before an exam, a glass of milk or a piece of cheese? Why?
36. **Reflect and Apply** What might you infer (or know) about the stability of amino acids, when compared with that of other building-block units of biopolymers (sugars, nucleotides, fatty acids, etc.)?
37. **Reflect and Apply** If you knew everything about the properties of the 20 common (proteinous) amino acids, would you be able to predict the properties of a protein (or large peptide) made from them?
38. **Reflect and Apply** Suggest a reason why the amino acids thyroxine and hydroxyproline are produced by posttranslational modification of the amino acids tyrosine and proline, respectively.
39. **Reflect and Apply** Consider the peptides Gly—Pro—Ser—Glu—Thr (open chain) and Gly—Pro—Ser—Glu—Thr with a peptide bond linking the threonine and the glycine. Are these peptides chemically the same?
40. **Reflect and Apply** Can you expect to separate the peptides in Question 39 by electrophoresis?
41. **Reflect and Apply** Suggest a reason why biosynthesis of amino acids and of proteins would eventually cease in an organism with carbohydrates as its only food source.
42. **Reflect and Apply** You are studying with a friend who draws the structure of alanine at pH 7. It has a carboxyl group ($-\text{COOH}$) and an amino group ($-\text{NH}_2$). What suggestions would you make?
43. **Reflect and Apply** Suggest a reason (or reasons) why amino acids polymerize to form proteins that have comparatively few covalent crosslinks in the polypeptide chain.
44. **Reflect and Apply** Suggest the effect on the structure of peptides if the peptide group were not planar.
45. **Reflect and Apply** Speculate on the properties of proteins and peptides if none of the common amino acids contained sulfur.
46. **Reflect and Apply** Speculate on the properties of proteins that would be formed if amino acids were not chiral.

3.5 Small Peptides with Physiological Activity

47. **Recall** What are the structural differences between the peptide hormones oxytocin and vasopressin? How do they differ in function?
48. **Recall** How do the oxidized and reduced forms of glutathione differ from each other?

49. **Recall** What is an enkephalin?

50. **Reflect and Apply** The enzyme D-amino acid oxidase, which converts D-amino acids to their α -keto form, is one of the most potent enzymes in the human body. Suggest a reason why this enzyme should have such a high rate of activity.

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