1: Amino Acids and the Role of pH

Overview

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

Structure

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Although more than 300 different amino acids have been described in nature, only 20 are commonly found as constituents of mammalian proteins. These 20 standard amino acids are the only amino acids that are encoded by DNA, the genetic material in the cell. Nonstandard amino acids are produced by chemical modification of standard amino acids. Each amino acid has a carboxyl group, a primary amino group (except for proline, which has a secondary amino group), and a distinctive side chain or R group bonded to the α-carbon atom.

At physiologic pH (~7.4), the carboxyl group of an amino acid is dissociated, forming the negatively charged carboxylate ion ($-COO^-$), and the amino group is protonated ($-NH_3^+$) (Fig. 1.1A). In proteins, almost all of these carboxyl and amino groups are combined through peptide linkage and, in general, are not available for chemical reaction except for hydrogen bond or ionic bond formation (Fig. 1.1B). Amino acids within proteins are referred to as *residues* in reference to the residual structure remaining after peptide bond formation between consecutive amino acids within a peptide chain. It is the nature of the side chains that ultimately dictates the role an amino acid plays in a protein. Therefore, it is useful to classify the amino acids according to the properties of their side chains, that is, whether they are nonpolar, with an even distribution of electrons, or polar with an uneven distribution of electrons, such as acids and bases (Figs. 1.2 and 1.3).

FIGURE 1.1

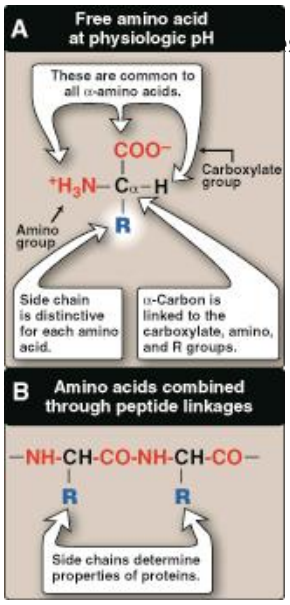

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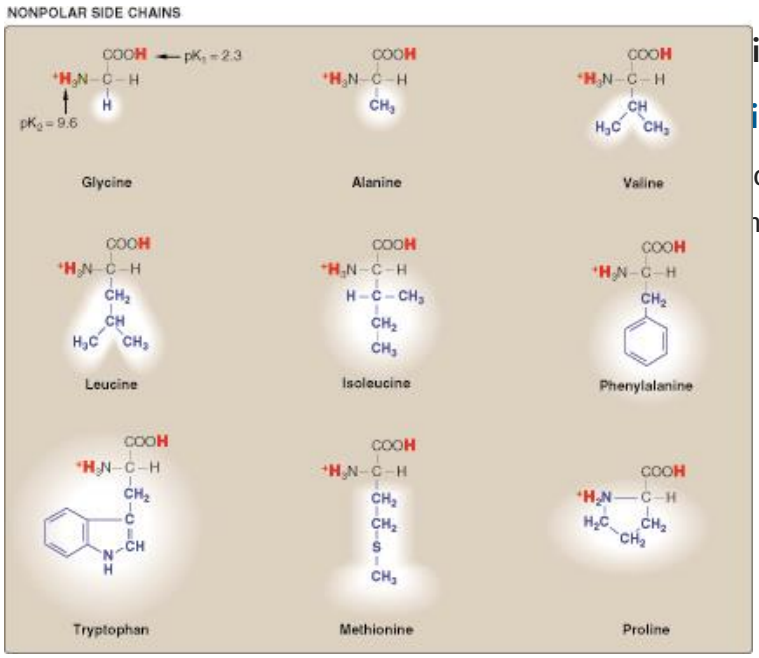
FIGURE 1.2



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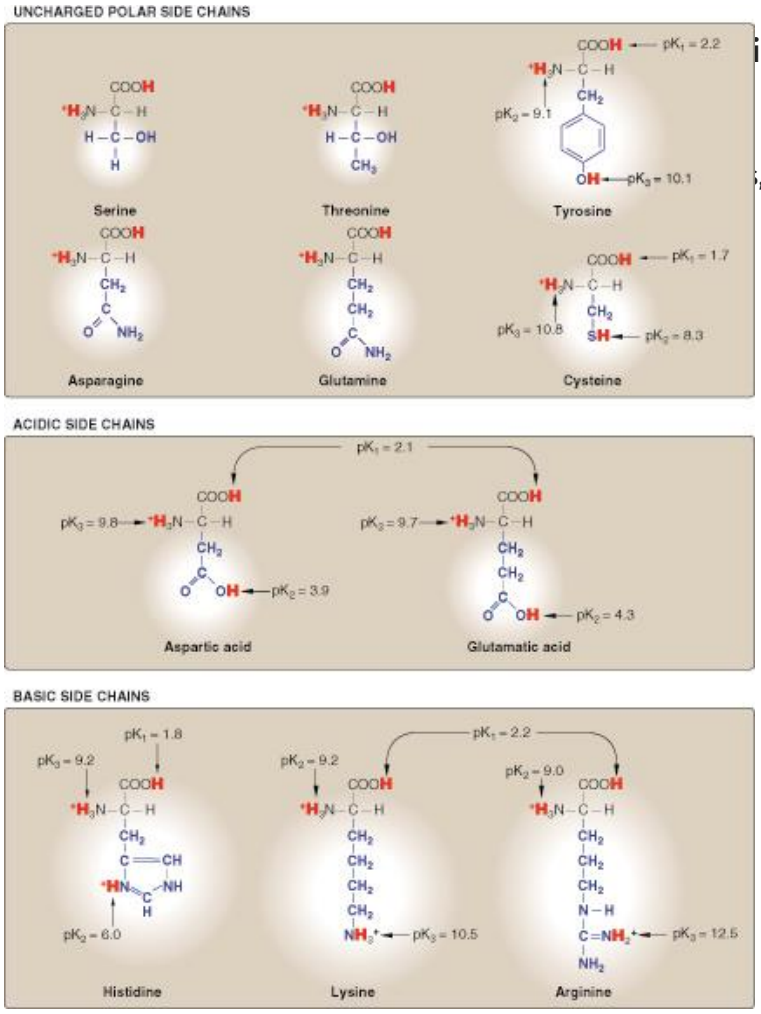
igure 1.3.

dissociable hydrogen ions represented in *red*. The

npolar amino acids are similar to those shown for

FIGURE 1.3



ing to the charge and polarity of their side

, the acidic side chains, and the side chain of free

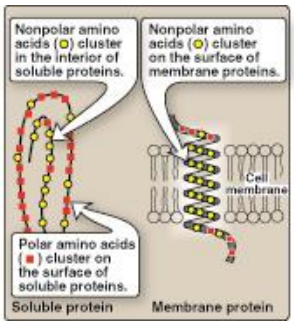
Amino acids with nonpolar side chains

Each of the amino acids in this category has a side chain that does not gain or lose protons or participate in hydrogen or ionic bonds (see Fig. 1.2). The side chains of these amino acids can be thought of as “oily” or lipid like, a property that promotes hydrophobic interactions (see Fig. 2.10).

Location in proteins

In proteins found in polar environments such as aqueous solutions, the side chains of nonpolar amino acids tend to cluster together in the interior of the protein (Fig. 1.4). This phenomenon is known as the hydrophobic effect and is the result of the hydrophobicity of the nonpolar R groups, which act much like droplets of oil that coalesce in an aqueous environment. By occupying the interior of the folded protein, these nonpolar R groups help give proteins their three-dimensional shape.

FIGURE 1.4



amino acids in soluble and membrane proteins.

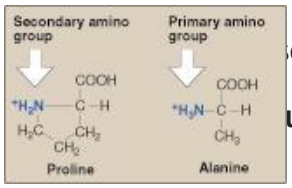
For proteins located in a hydrophobic environment, such as within the hydrophobic core of a phospholipid membrane, nonpolar R groups are found on the outside surface of the protein, interacting with the lipid environment (see Fig. 1.4). The importance of these hydrophobic interactions in stabilizing protein structure is discussed in Chapter 2.

Sickle cell anemia, a disease that causes red blood cells to become sickle shaped rather than disc shaped, results from the replacement of polar glutamate with nonpolar valine at the sixth position in the β subunit of hemoglobin A (see Chapter 4).

Unique features of proline

Proline differs from other amino acids in that its side chain and α-amino nitrogen form a rigid, five-membered ring structure (Fig. 1.5). Proline, then, has a secondary (rather than a primary) amino group and is frequently referred to as an "imino acid." The unique geometry of proline contributes to the formation of the extended fibrous structure of collagen (see Chapter 4, II Collagen B. Structure), but it interrupts the α-helices found in more compact globular proteins (see Chapter 2, III Secondary structure).

FIGURE 1.5



econdary amino group found in proline with the primary amino group found in uch as alanine.

Amino acids with uncharged polar side chains

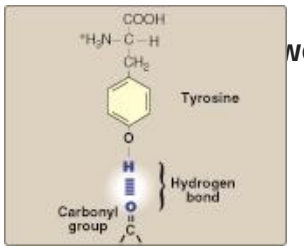
These amino acids have zero net charge at physiologic pH of approximately 7.4, although the side chains of cysteine and tyrosine can lose a proton at an alkaline pH (see Fig. 1.3). Serine, threonine, and tyrosine each contain a polar hydroxyl group that can participate in hydrogen bond formation (Fig. 1.6). The side chains of asparagine and glutamine each contain a carbonyl group and an amide group, both of which can also participate in hydrogen bonds.

Disulfide bond formation

The side chain of cysteine contains a sulfhydryl (thiol) group (–SH), which is an important component within the active site of many enzymes. In proteins, the –SH groups of two cysteines can be oxidized to form a covalent cross-link called a disulfide bond (–S–S–). Two cysteine residues that form a disulfide bond are referred to as cystine. (See Chapter 2 Section IV. B. for a further discussion of disulfide bond formation.)

Many extracellular proteins are stabilized by disulfide bonds. Albumin, a protein that functions in the transport of a variety of molecules in the blood, is one example. Fibrinogen, a blood protein converted to fibrin to stabilize blood clots, is another example.

FIGURE 1.6



ween the phenolic hydroxyl group of tyrosine and another molecule containing

Side chains as attachment sites for other compounds

The polar hydroxyl group of serine, threonine, and tyrosine can serve as a site of attachment for phosphate groups. Kinases are enzymes that catalyze phosphorylation reactions. Phosphatases are enzymes that remove the phosphate group. The changes in phosphorylation status of proteins (whether phosphorylated or not), especially of enzymes, alters their activation status; some enzymes are more active when phosphorylated while others are less active. In addition, the amide group of asparagine, as well as the hydroxyl group of serine or threonine, can serve as a site of attachment for oligosaccharide chains in glycoproteins (see also Chapter 14 Section VII.).

Amino acids with acidic side chains

The amino acids aspartic acid and glutamic acid are proton donors. At physiologic pH, the side chains of these amino acids are fully ionized, containing a negatively charged carboxylate group ($-COO^-$). The fully ionized forms are called aspartate and glutamate.

Amino acids with basic side chains

The side chains of the basic amino acids accept protons (see Fig. 1.3). At physiologic pH, the R groups of lysine and arginine are fully ionized and positively charged. In contrast, the free amino acid histidine is weakly basic and largely uncharged at physiologic pH. However, when histidine is incorporated into a protein, its R group can be either positively charged (protonated) or neutral, depending on the ionic environment provided by the protein. This important property of histidine contributes to the buffering role it plays in the functioning of proteins including hemoglobin (see Chapter 3). Histidine is the only amino acid with a side chain that can ionize within the physiologic pH range (7.35 to 7.45).

CLINICAL APPLICATION 1.1

Slower, Longer-Acting Insulin Created by Substituting Amino Acids

Insulin glargine was first approved for use in the United States in the year 2000. It is a slower-acting form of insulin created in the laboratory by replacing the asparagine normally at position 21 on the A chain of insulin with glycine, and extending the carboxy terminus by two additional arginine residues. The result of these changes is a less water-soluble form of insulin with a net charge of +0.2, which is closer to 0, causing a slower absorption of insulin glargine from the site of injection. The glycine substitution prevents deamidation of the asparagine at acidic pH in the neutral, subcutaneous space. The additional arginine residues shift the isoelectric point from pH 5.4 to pH 6.7, making the molecule more soluble at acidic pH and less soluble at neutral pH. Insulin glargine is therefore a form of insulin that acts slowly, has longer activity, and requires less frequent injection. This form of insulin can be useful in the treatment of diabetes mellitus and help patients achieve better glycemic control. (See Chapter 23 for the structure of insulin.)

Abbreviations and symbols for commonly occurring amino acids

Each amino acid has an associated three-letter abbreviation and a one-letter symbol (Fig. 1.7). The one-letter codes are determined by the following rules:

Unique first letter

If only one amino acid begins with a given letter, then that letter is used as its symbol. For example, V = valine.

Most commonly occurring amino acids have priority

If more than one amino acid begins with a particular letter, the most common of these amino acids receives this letter as its symbol. For example, glycine is more common than glutamate, so G = glycine.

Similar sounding names

Some one-letter symbols sound like the amino acid they represent. For example, F = phenylalanine.

Letter close to initial letter

For the remaining amino acids, a one-letter symbol is assigned that is close in the alphabet as possible to the initial letter of the amino acid, for example, K = lysine. Furthermore, B is assigned to Asx, signifying either aspartic acid or asparagine; Z is assigned to Glx, signifying either glutamic acid or glutamine; W is used for tryptophan and X is used to represent an unidentified amino acid.

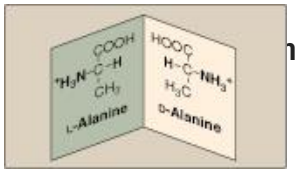
FIGURE 1.7

mbols for the standard amino acids.

Amino acid isomers

Because the α-carbon of an amino acid is attached to four different chemical groups, it is an asymmetric or chiral atom. Glycine is the exception because its α-carbon has two hydrogen substituents. Amino acids with a chiral α-carbon exist in two different isomeric forms, designated D and L, which are enantiomers, or mirror images (Fig. 1.8). (Note: Enantiomers are optically active. If an isomer, either D or L, causes the plane of polarized light to rotate clockwise, it is designated the [+] form.) All amino acids found in mammalian proteins are of the L configuration. However, D-amino acids are found in some antibiotics and in bacterial cell walls. (Note: Racemases enzymatically interconvert the D- and L-isomers of free amino acids.)

FIGURE 1.8



nine are mirror images (enantiomers).

Acidic and Basic Properties

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Amino acids in an aqueous solution contain weakly acidic α-carboxyl groups and weakly basic α-amino groups. In addition, each of the acidic and basic amino acids contains an ionizable group in its side chain. Thus, both free amino acids and some amino acids combined in peptide linkages can act as buffers. Acids may be defined as proton donors and bases as proton acceptors. Acids (or bases) described as weak ionize to only a limited extent.

pH

The concentration of protons ($[H^+]$) in aqueous solution is expressed as pH.

$$pH = \log 1/ [H^+] \text{ or } -\log [H^+]$$

Dissociation constants

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

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

The larger the K_a, the stronger the acid, because most of the HA has dissociated into H^+ and A^-. Conversely, the smaller the K_a, the less acid has dissociated and, therefore, the weaker the acid.

Henderson–Hasselbalch equation

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

$$pH = pKa + \log [A–] / [HA]$$

This equation demonstrates the quantitative relationship between the pH of the solution and concentration of a weak acid (HA) and its conjugate base (A^-).

Buffers

A buffer is a solution that resists a change in pH following the addition of an acid or base and can be created by mixing a weak acid (HA) with its conjugate base (A^-). If an acid is added to a buffer, A^- can neutralize it, being converted to HA in the process. If a base is added, HA can likewise neutralize it, being converted to A^- in the process.

Maximum buffering capacity occurs at a pH equal to the pK_a, but a conjugate acid–base pair can still serve as an effective buffer when the pH of a solution is within approximately ±1 pH unit of the pK_a. If the amounts of HA and A^- are equal, the pH is equal to the pK_a. As shown in Figure 1.9, a solution containing acetic acid (HA = $CH_3 – COOH$) and acetate (A^- = $CH_3 – COO^-$) with a pKa of 4.8 resists a change in pH from 3.8 to 5.8, with maximum buffering at pH 4.8. At pH values less than the pKa, the protonated acid form ($CH_3 – COOH$) is the predominant species in solution. At pH greater than the pK_a, the deprotonated base form ($CH_3 – COO^-$) is the predominant species.

Dissociation of the carboxyl group

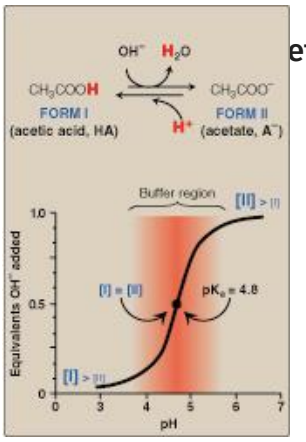
The dissociation constant of the carboxyl group of an amino acid is called K_1, rather than K_a, because the molecule contains a second titratable group. The Henderson–Hasselbalch equation can be used to analyze the dissociation of the carboxyl group of alanine:

$$K_1 = [H^+] [II] / [I]$$

where I is the fully protonated form of alanine and II is the isoelectric form of alanine (Fig. 1.10). This equation can be rearranged and converted to its logarithmic form to yield:

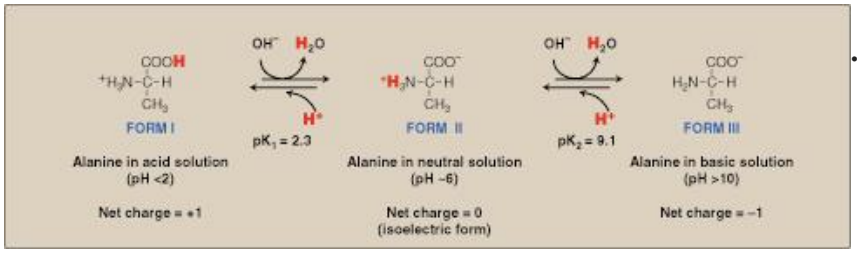
$$pH = pK_1 + \log [II] / [I]$$

FIGURE 1.9



etic acid.

FIGURE 1.10



Amino group dissociation

The second titratable group of alanine is the amino ($-NH_3^+$) group. Because this is a much weaker acid than the –COOH group, it has a much smaller dissociation constant, K_2. (Note: Its pK_a is, therefore, larger.) Release of a H^+ from the protonated amino group of form II results in the fully deprotonated form of alanine, form III.

pKs and sequential dissociation

The sequential dissociation of H^+ from the carboxyl and amino groups is summarized in Figure 1.10 using alanine as an example. Each titratable group has a pK_a that is numerically equal to the pH at which exactly one half of the H^+ have been removed from that group. The pK_a for the most acidic group (–COOH) is pK_1, whereas the pK_a for the next most acidic group ($-NH_3^+$) is pK_2. (Note: The pK_a of the α-carboxyl group of amino acids is ~2, whereas the pK_a of the α-amino group is ~9.)

By applying the Henderson–Hasselbalch equation to each dissociable acid group, it is possible to calculate the complete titration curve of a weak acid. Figure 1.11 shows the change in pH that occurs during the addition of base to the fully protonated form of alanine (I) to produce the fully deprotonated form (III).

Buffer pairs

The $-COOH/-COO^-$ pair can serve as a buffer in the pH region around pK_1, and the $-NH_3^+/-NH_2$ pair can buffer in the region around pK_2.

When pH = pK

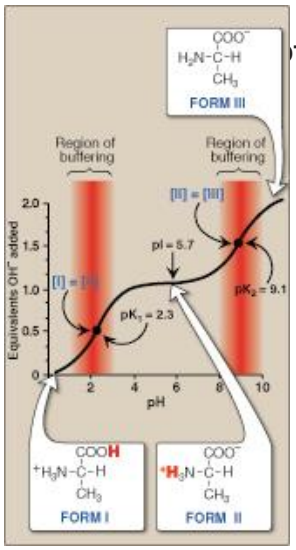
When the pH is equal to pK_1 (2.3), equal amounts of forms I and II of alanine exist in solution. When the pH is equal to pK_2 (9.1), equal amounts of forms II and III are present in solution.

Isoelectric point pI

At neutral pH, alanine exists predominantly as the dipolar form II in which the amino and carboxyl groups are ionized, but the net charge is zero. The isoelectric point (pI) is the pH at which an amino acid is electrically neutral, that is, when the sum of the positive charges equals the sum of the negative charges. For alanine, with only two dissociable hydrogens (one from the α-carboxyl and one from the α-amino group), the pI is the average of pK_1 and pK_2 (pI = [2.3 + 9.1]/2 = 5.7) as shown in Figure 1.11. The pI is, thus, midway between pK_1 (2.3) and pK_2 (9.1). pI corresponds to the pH at which the form II (with a net charge of zero) predominates and at which there are also equal amounts of forms I (net charge of +1) and III (net charge of –1).

In the laboratory, separation of plasma proteins by charge is typically done at a pH above the pI of the major proteins. Therefore, at a high pH (alkaline) the charge on the proteins is negative. In an electric field, the proteins will move toward the positive electrode at a rate determined by their net negative charge. Variations in the mobility pattern are suggestive of certain diseases.

FIGURE 1.11



f alanine.

Net charge at neutral pH

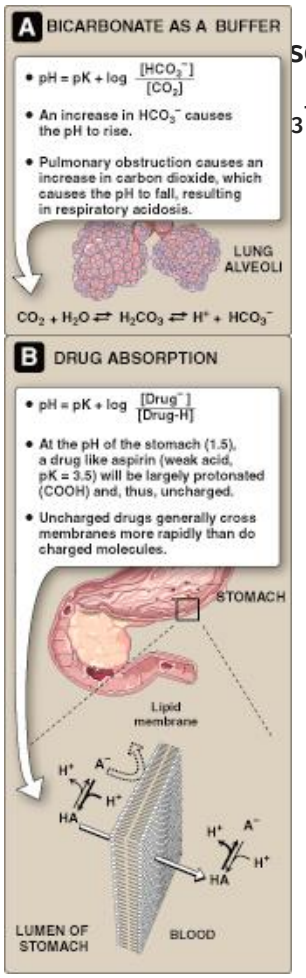
At physiologic pH, amino acids have a negatively charged group ($-COO^-$) and a positively charged group ($-NH_3^+$), both attached to the α-carbon. Glutamate, aspartate, histidine, arginine, and lysine have additional potentially charged groups in their side chains. Substances such as amino acids that can act either as an acid or a base are described as amphoteric.

Buffering the blood, the bicarbonate buffer system

The pH within our blood is maintained in the slightly alkaline range of 7.35 to 7.45 by the bicarbonate buffer system. Most proteins function optimally at this physiologic pH and their amino acid constituents exist in the chemical form; exceptions include some digestive enzymes that function at acidic pH of the stomach between pH 1.5 and 3.5. Lysosomal enzymes also function at an acidic pH range between pH 4.5 and 5.0. Maintaining arterial pH at 7.40 ± 0.5 is important for health; normally the bicarbonate buffer system is able to keep pH within the acceptable range.

The bicarbonate ion concentration, $[HCO_3^-]$, and the carbon dioxide concentration $[CO_2]$ influence the pH of the blood, as depicted in Figure 1.12A. The need for a buffering system can be appreciated by considering that organic acids (e.g., lactic acid) are generated during metabolism and that glucose and fatty acid oxidation generate CO_2, the anhydrous form of H_2CO_3 (carbonic acid). The relatively water-insoluble CO_2 is converted by the enzyme carbonic anhydrase to the water-soluble HCO_3^- (bicarbonate), which is carried through the blood to the lungs where dissolved CO_2 is exhaled. Therefore, lungs regulate the loss and retention of CO_2 by altering the breathing rate. The kidneys are also important in regulating acid–base balance. Kidneys retain or excrete bicarbonate, H^+, ammonia, and other acids/bases that may appear in the blood.

FIGURE 1.12



selbalch equation is used to predict: (A) changes in pH as the concentrations $_3^-$) or carbon dioxide (CO_2) are altered and (B) the ionic forms of drugs.

pH and drug absorption

Many drugs are administered orally and must be transported across intestinal epithelial cells in order to be absorbed into the blood. Most drugs are either weak acids or weak bases. Acid drugs (HA) release a H^+, causing a charged anion (A^-) to form. Weak bases (BH^+) can also release a H^+; however, the protonated form of basic drugs is usually charged and the loss of a proton produces the uncharged base (B).

$$HA \leftarrow \rightarrow H^+ + A^-$$
$$BH^+ \leftarrow \rightarrow B + H^+$$

Drugs are best absorbed at a pH where dissociation of their side chains results in the most neutral molecule. The effective concentration of the permeable form of each drug at its absorption site is determined by the relative concentrations of the charged and uncharged forms. (Fig. 1.12B). It is believed that the transport of drugs occurs via transport proteins and often occurs through active transport, although the systems are not well characterized.[1]

Blood gases and pH

As a consequence of certain disease processes or poisons, blood pH can become abnormal. Acidemia is defined as an arterial pH <7.35 and alkalemia is defined as an arterial pH >7.45. In the bicarbonate buffer system, CO_2 is an acid and bicarbonate is a base. Because the bicarbonate buffer is an open system and CO_2 is released in the breath, changes in breathing can impact the acid–base balance in the body. Hyperventilation can cause release of too much acid, causing alkalosis; on the other hand, generation of excess metabolic acids (e.g., lactic acidosis or ketoacidosis that can accompany type 1 diabetes mellitus) can cause acidosis. Loss of excess acid through vomiting can cause an acid–base disturbance as well. Neither renal compensation nor compensation by breathing rate changes (respiratory compensation) will bring pH back toward normal physiologic range if excess metabolic acids have been generated. It should be noted that neither the lungs nor the kidneys can fully compensate or overcompensate for pH imbalances. Measuring CO_2 and bicarbonate along with pH can help to determine the acid–base imbalance that may be present in a patient (Table 1.1).

TABLE 1.1

Disturbances in Acid–Base Balance

pH	$[H^+]$	Initial Issue	Response	Disorder
Decreased	Increased	Hypoventilation; increased retention of CO_2 (more acid)	Increased renal retention of HCO_3^- (more base)	Respiratory acidosis; lungs not excreting enough acid as CO_2, as in COPD
Increased	Decreased	Hyperventilation; increased release of CO_2 (less acid)	Decreased renal retention of HCO_3^- (less base)	Respiratory alkalosis; lungs excreting too much acid as CO_2, as in hyperventilation and asthma
Decreased	Increased	More acid generated	Less CO_2 released in breath (hypoventilation); HCO_3^- will be low to attempt to buffer the acid	Metabolic acidosis; body generates acid that cannot be excreted by lungs, as in lactic acidosis, diabetic ketoacidosis, ingestion of acid
Increased	Decreased	HCO_3^- increases	More CO_2 released in breath (hyperventilation); renal excretion of HCO_3^-	Metabolic alkalosis; when blood is alkaline and not caused by respiratory imbalance, as in excess loss of acid in vomiting or ingestion of a base

[1]For further discussion of drug transport, see *LIR Cell and Molecular Biology*, 2nd Edition, Chapter 16.

Chapter Summary

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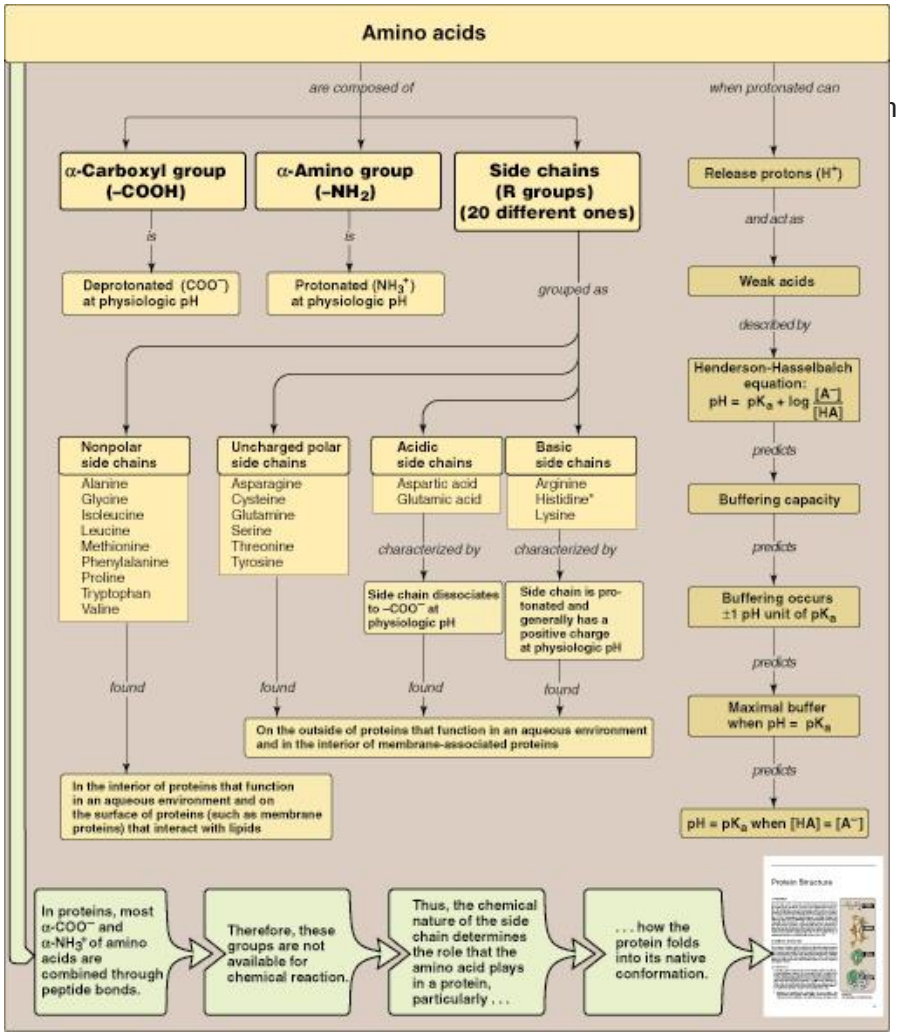
- Each amino acid has an **α-carboxyl group** and a primary **α-amino group** (except for **proline**, which has a **secondary amino group**) (Fig. 1.13).

FIGURE 1.13



…hen incorporated into a protein, it can

- Because the α-carbon of each amino acid (except glycine) is attached to four different chemical groups, it is asymmetric (**chiral**), and amino acids exist in D- and L-isomeric forms that are optically active mirror images (**enantiomers**). The L-form of amino acids is found in proteins synthesized by the human body.
- At physiologic pH, the α-carboxyl group is dissociated, forming the negatively charged carboxylate ion ($-COO^-$), and the α-amino group is protonated ($-NH_3^+$).
- Each amino acid also contains one of 20 distinctive **side chains** attached to the α-carbon atom.
- The chemical nature of this **R group** determines the function of an amino acid in a protein and provides the basis for classification of the amino acids as **nonpolar**, **uncharged polar**, **acidic** (**polar negative**), or **basic** (**polar positive**).
- All free amino acids, plus charged amino acids in peptide chains, can serve as **buffers**.
- The quantitative relationship between the pH of a solution and the concentration of a weak acid (HA) and its conjugate base (A^-) is described by the **Henderson–Hasselbalch equation**. Buffering occurs within ±1 pH unit of the pK_a and is maximal when pH = pK_a, at which $[A^-] = [HA]$.

- The pH within blood is maintained in the slightly alkaline range of 7.4 ± 0.5 by the bicarbonate buffer system; the lungs regulate the acid CO_2 by altering breathing rate and the kidneys retain or release acids and base.

Study Questions

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Choose the ONE best answer.

1.1. The peptide Val-Cys-Glu-Ser-Asp-Arg-Cys:

A. Contains asparagine.

B. Contains a side chain with a secondary amino group.

C. Contains a side chain that can be phosphorylated.

D. Cannot form an internal disulfide bond.

E. Cannot move toward the cathode during electrophoresis at pH 5.

Correct answer = C. The hydroxyl group of serine can accept a phosphate group. Asp is aspartate, not asparagine. Proline contains a secondary amino group and is not within this peptide. The two cysteine residues can, under oxidizing conditions, form a disulfide bond. The net charge on the peptide at pH 5 is negative, and it would move to the anode.

1.2. An amino acid has a secondary amino group that is geometrically incompatible with a right-handed spiral of an alpha helix. It is observed to insert a kink in the amino acid chain and to interfere with the normally smooth, helical structure of the alpha helix, and is found in high concentration in collagen. The amino acid described is:

A. Ala

B. Cys

C. Gly

D. Pro

E. Ser

Correct answer = D. Proline differs from other amino acids in that its side chain and a-amino nitrogen form a rigid, 5-membered ring structure and therefore contains a secondary amino group. It interrupts α helices in globular proteins, contributes to the structure of collagen, and is found in high concentration in collagen. None of the other amino acids have these properties.

1.3. An amino acid that may have its side chain phosphorylated by the action of a kinase is:

A. Arg

B. Cys

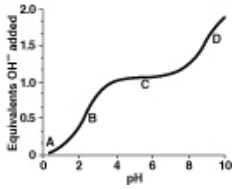
C. Gly

D. Thr

E. Val

Correct answer = D. The polar hydroxyl group found within Ser, Thr, and Tyr can serve as a site of attachment for phosphate groups. Kinases are enzymes that catalyze phosphorylation reactions. None of the other amino acids contain a hydroxyl group susceptible to phosphorylation by a kinase.

1.4. Concerning the titration curve for a nonpolar amino acid where the letters A through D designate certain regions on the curve below,



A. Point A represents the region where the amino acid is deprotonated.

B. Point B represents a region of minimal buffering.

C. Point C represents the region where the net charge on the amino acid is zero.

D. Point D represents the pK of the amino acid's carboxyl group.

E. The amino acid could be lysine.

Correct answer = C. Point C represents the isoelectric point, or pI, and as such is midway between pK_1 and pK_2 for a nonpolar amino acid. The amino acid is fully protonated at Point A. Point B represents a region of maximum buffering, as does Point D. Lysine is a basic amino acid, and free lysine has an ionizable side chain in addition to the ionizable α-amino and α-carboxyl groups.

1.5. An 18-year-old female with a 15-year history of type 1 diabetes mellitus is brought to the Emergency Department for evaluation of nausea, vomiting, and altered consciousness. Her blood glucose is 560 mg/dl (reference range for random glucose, <200 mg/dl). Her arterial blood pH is 7.15 (reference range is 7.35 to 7.45) and bicarbonate is 12 mEq/l (reference range, 22 to 28 mEq/l). Which of the following is the expected type of compensation in her body in response to this acid–base imbalance?

A. Increased respiration

B. Increased renal release of acid

C. Increased renal retention of base

D. Decreased respiration

E. Decreased renal release of acid

Correct answer = A. In response to a metabolic acidosis, compensation is respiratory. Increased respiration removes acid in the form of CO_2 from the body. Since the acid is being generated metabolically (diabetic ketoacidosis suspected) altered renal release of acid or retention of base would not be compensatory.