医学整合课程系列教材·原版影印

Integrated Biochemistry

整合生物化学

（第2版）

JOHN W. PELLEY

北京大学医学出版社

医学整合课程系列教材

整合生物化学

Integrated Biochemistry

（第2版）

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出版说明

知识整合是当前医学教育改革的一项重要内容。目前国内基础医学各门课程的教材基本上是以学科为单位单独编写的，缺乏学科之间知识的联系。为了推动医学教育改革，借鉴国外医学教材的编写模式，北京大学医学出版社经过充分调研，引进出版了世界著名医学出版集团Elsevier公司的“Integrated”系列教材。

在编写上，该系列书最大的特色就是在保持本学科知识体系完整的同时插入大量的“整合框”。这些“整合框”出现在需要链接到其他学科相关知识的位置，每个学科都有独特的标识。例如在《病理学》的细胞损伤一节，讲述缺氧时，会插入一个“生物化学整合框”，介绍生物化学中糖酵解的知识；在感染一节，出现NK细胞的时候，会插入一个“免疫学整合框”，介绍免疫学中NK细胞的知识；在凝血一节，则是插入一个“临床医学整合框”，介绍临床上凝血的实验室评估方面的知识……这些分布在各本书中的“整合框”，把各学科之间知识点连接起来，不但方便了读者学习，更是体现了学科整合的理念。

该系列书包括：

●整合生理学　●整合病理学

●整合药理学　●整合生物化学

●整合遗传学　●整合免疫学与微生物学

该系列书可作为国内医学生整合课程教材、双语教学教材及来华留学生教材，也有利于医学教师拓展知识，方便备课；同时也是美国医师执照考试的优秀参考用书。

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Series Preface

How to Use This Book

The idea for Elsevier's Integrated Series came about at a seminar on the USMLE Step 1 Exam at an American Medical Student Association (AMSA) meeting. We noticed that the discussion between faculty and students focused on how the exams were becoming increasingly integrated—with case scenarios and questions often combining two or three science disciplines. The students were clearly concerned about how they could best integrate their basic science knowledge.

One faculty member gave some interesting advice: "read through your textbook in, say, biochemistry, and every time you come across a section that mentions a concept or piece of information relating to another basic science—for example, immunology—highlight that section in the book. Then go to your immunology textbook and look up this information, and make sure you have a good understanding of it. When you have, go back to your biochemistry textbook and carry on reading."

This was a great suggestion—if only students had the time, and all of the books necessary at hand, to do it! At Elsevier we thought long and hard about a way of simplifying this process, and eventually the idea for Elsevier's Integrated Series was born.

The series centers on the concept of the integration box. These boxes occur throughout the text whenever a link to another basic science is relevant. They're easy to spot in the text—with their color-coded headings and logos. Each box contains a title for the integration topic and then a brief summary of the topic. The information is complete in itself—you probably won't have to go to any other sources—and you have the basic knowledge to use as a foundation if you want to expand your knowledge of the topic.

You can use this book in two ways. First, as a review book . . .

When you are using the book for review, the integration boxes will jog your memory on topics you have already covered. You'll be able to reassure yourself that you can identify the link, and you can quickly compare your knowledge of the topic with the summary in the box. The integration boxes might highlight gaps in your knowledge, and then you can use them to determine what topics you need to cover in more detail.

Second, the book can be used as a short text to have at hand while you are taking your course . . .

You may come across an integration box that deals with a topic you haven't covered yet, and this will ensure that you're one step ahead in identifying the links to other subjects (especially useful if you're working on a PBL exercise). On a simpler level, the links in the boxes to other sciences and to clinical medicine will help you see clearly the relevance of the basic science topic you are studying. You may already be confident in the subject matter of many of the integration boxes, so they will serve as helpful reminders.

At the back of the book we have included case study questions relating to each chapter so that you can test yourself as you work your way through the book.

Online Version

An online version of the book is available on our Student Consult site. Use of this site is free to anyone who has bought the printed book. Please see the inside front cover for full details on Student Consult and how to access the electronic version of this book.

In addition to containing USMLE test questions, fully searchable text, and an image bank, the Student Consult site offers additional integration links, both to the other books in Elsevier's Integrated Series and to other key Elsevier textbooks.

Books in Elsevier's Integrated Series

The nine books in the series cover all of the basic sciences. The more books you buy in the series, the more links that are made accessible across the series, both in print and online.


Anatomy and Embryology


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Biochemistry


Physiology


Pathology


Immunology and Microbiology


Pharmacology


Genetics

Preface

I wrote this book to make biochemistry easier to learn and easier to remember. Learning and remembering do not always go together, since any new material can be learned but forgotten quickly. It is only through integrative learning that long-term memory is built. Even if you have never had a biochemistry course or if you have taken biochemistry but forgotten much of it, you will find this innovative approach helpful.

To make learning easier, I have given careful attention to the sequence and organization of each chapter so that each topic builds on previous topics. Also, within each chapter, the material is presented in a way that suggests how it should be learned. For example, each metabolic pathway has five consistent organizing aspects: pathway components, regulation points, intersection with other pathways, unique features, and clinical features. Hence all chapters on metabolism, for example, have the same headings, allowing easy comparison and quicker integrative learning. An additional aid to easier learning is the minimal inclusion of chemical structures, thus shifting the learning emphasis in a more physiologic direction.

Information in biochemistry is easier to remember when it is integrated with information from other basic science disciplines. This approach can be seen in the clinical vignette case studies at the end of the text, which contain questions about other basic science disciplines in addition to biochemistry. Such integrative thinking will be needed in the clinic, where patients present with symptoms that cross the boundaries of traditional disciplines. Integration across disciplines is further enhanced throughout each chapter by the Integration Boxes.

This book is written as concisely, clearly, and completely as possible. I hope that it brings you the same helpful assistance that I try to bring to my students here at the Texas Tech School of Medicine.

John W. Pelley, PhD

Acknowledgments

My wife, MJ, has always seen more in me than I have. Her love, encouragement, and patience were essential to the organization and composition of this book. It is also important to acknowledge the many intelligent students whom I have taught at Texas Tech. They probably do not realize how much their questions have taught me. Alex Stibbe deserves a substantial acknowledgment for her skill in bringing such a diverse group of authors together and creating the early integration between us that was so essential to the first edition of an innovative series such as this. Kate Dimock has been a tremendous help in continuing this integrative authorship, making the refinements that have led to a significant upgrade for this second edition. And, finally, a note of appreciation to Andy Hall, for his continuing support and perfect balance of professionalism and a great sense of humor.

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Acid-Base Concepts 1

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WATER AND ELECTROLYTES

An understanding of the properties of water underlies an understanding of the properties of all biologic molecules. Water molecules have the ability to form hydrogen bonds with each other (intramolecular) and also with molecules that they solubilize (intermolecular). If water could not form extensive intramolecular hydrogen bonds, it would be a gas like other small molecules (e.g., CO_2, CH_4, NH_3, O_2, and N_2).

Hydrogen bonds are weak (and therefore reversible) chemical bonds that are formed between molecules that can either donate or accept a partially charged hydrogen atom (Fig. 1-1). Since water can serve both functions, its intramolecular bonds create tetrahedral structures that dynamically break and re-form. The hydrogen bonding forces that hold water molecules together also indirectly determine the shape of the biomolecules that they surround. Hydrogen bonds can also pull electrolytes apart to create charged ions and then can associate with those ions to neutralize their charges.

Hydrophobic and Hydrophilic Molecules

Hydrophilic molecules derive their solubility by forming hydrogen bonds with water. Molecules that can form many hydrogen bonds with water have higher solubility. Solubility decreases as size increases owing to the disruption of water structure. Therefore, large molecules such as proteins, polysaccharides, and nucleic acids are able to maintain their solubility by forming a very large number of hydrogen bonds with water.

Hydrophobic molecules have low solubility in water because they form few or no hydrogen bonds with water. This causes them to aggregate to minimize the disruption of water structure, as illustrated by the coalescence of oil droplets floating on a water surface. The process of forcing hydrophobic molecules together by water plays a major role in determining the three-dimensional structure of macromolecules and biologic membranes.

Electrolytes

Electrolytes dissociate into cations (positive charge) and anions (negative charge) when added to water; this permits water to conduct an electric current. Strong electrolytes such as HCl and NaCl dissociate completely in water. Weak electrolytes do not dissociate completely. Instead they establish an equilibrium between an undissociated form (the conjugate acid or protonated form, HA) and a dissociated form (conjugate base, A^-).

$$HA \leftrightarrow H^+ + A^-$$

Weak electrolytes are generally organic acids; phosphoric acid and carbonic acids are also in this category.

$$H_2CO_3 \rightleftharpoons H^+ + HCO_3^- \rightleftharpoons H^+ + CO_3^{--}$$

$$H_3PO_4 \rightleftharpoons H^+ + H_2PO_4^-$$

$$\rightleftharpoons H^+ + HPO_4^{--} \rightleftharpoons H^+ + PO_4^{---}$$

The hydrogen ion (proton) concentration in a solution of a weak acid is dependent on the equilibrium constant (K_{eq}) for the dissociation reaction:

$$HA \rightleftharpoons H^+ + A^-$$

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

The K_{eq} is unique for each conjugate pair (Table 1-1). Conjugate pairs make good buffers (i.e., solutes that act to resist change in pH), since they always try to reestablish equilibrium when adding either acid or base. Increasing acidity (adding protons) "pushes" the equilibrium toward the undissociated form (HA) to reduce the proton concentration. Similarly, decreasing acidity (adding base, or OH^-) "pulls" the equilibrium away from the HA form to restore the proton concentration.

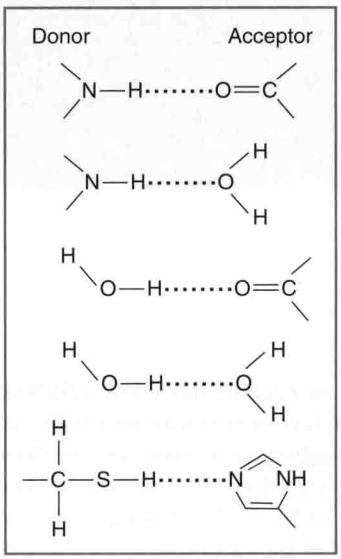

Figure 1-1. Hydrogen bonding between common donors and acceptors.

Water itself is also a weak electrolyte and is in a dissociation equilibrium, with one proton and one hydroxyl ion produced for each water molecule that dissociates (see Table 1-1).

PHARMACOLOGY

Aspirin Absorption

Aspirin must be in the uncharged protonated form on the left in order to diffuse through the cell membrane of the stomach mucosal lining. The stomach pH of around 2 is well below the carboxylic acid group pK of about 4, shifting the equilibrium to the necessary protonated form. The stomach mucosal intracellular pH around 6.8 to 7.1 is above the aspirin pK, shifting the equilibrium to the ionized form on the right, which then prevents the aspirin from crossing back into the stomach. The absorbed aspirin then crosses into the bloodstream, where it reaches its target.

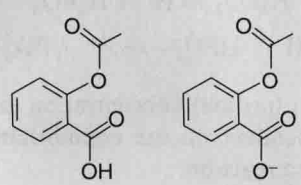

TABLE 1-1. Conjugate Pairs and Their Equilibrium Constants

CONJUGATE PAIR	K_{eq}
$H_2O \rightleftharpoons H^+ + OH^-$	1.0×10^{-14}
$H_2PO_4^- \rightleftharpoons HPO_4^{--} + H^+$	2.0×10^{-7}
Acetic acid $\rightleftharpoons$ Acetate $+ H^+$	1.74×10^{-5}
Lactic acid $\rightleftharpoons$ Lactate $+ H^+$	1.38×10^{-4}

KEY POINTS ABOUT WATER AND ELECTROLYTES

- Intermolecular hydrogen bonds confer a "structure" to water that is disrupted when it dissolves other molecules.
- Hydrophilic molecules form many hydrogen bonds with water; hydrophobic molecules form few to no hydrogen bonds with water.
- Weak electrolytes are generally weak acids that form a dissociation equilibrium.

ACIDS AND BASES

Acidic solutions have more protons than are produced by the ionization of water. Likewise, alkaline (basic) solutions have fewer protons (and more hydroxide ions) than are produced by ionization of water. The ionization of water allows it to participate in the equilibria of weak acids. For example, when the strong electrolyte sodium acetate (reaction 1) is added to water, it dissociates completely. The acetate anion that is produced enters into equilibrium with the protons produced by water, thus reducing the proton concentration below that of pure water and producing a slightly alkaline solution (reactions 2 and 3).

1. $\underset{\text{Na acetate}}{CH_3COONa} \rightarrow \underset{\text{Acetate ion}}{CH_3COO^-} + Na^+$
2. $H_2O \rightleftharpoons H^+ + OH^-$
3. $H^+ + \underset{\text{Acetic acid}}{CH_3COO^-} \rightleftharpoons CH_3COOH$

- The functional group giving up (releasing) a free proton is "acting as" an acid.
- The functional group accepting (binding) a free proton is "acting as" a base.
- Thus acids are proton donors and bases are proton acceptors. In the above example, acetate is considered the conjugate base of acetic acid.

pH—An Expression of Acidity

pH is a convenient way to express proton concentration (i.e., representation as a positive whole number rather than a negative exponent of 10). pH is defined as the negative logarithm of the proton concentration.

$$pH = -\log[H^+]$$

This relationship produces pH units that are exponents of 10 and are, therefore, not directly but logarithmically related to acidity. This produces a reciprocal relationship between pH and acidity so that an increase in pH is equivalent to a decrease in acidity (Fig. 1-2).

The pK value for a reaction is the negative logarithm of the equilibrium constant. The pK of an electrolyte is always a constant, whereas pH can change with physiologic conditions.

The equilibrium constant for dissociation of a weak acid is often termed the Ka, and similarly the pK for an acid is defined as the pKa.

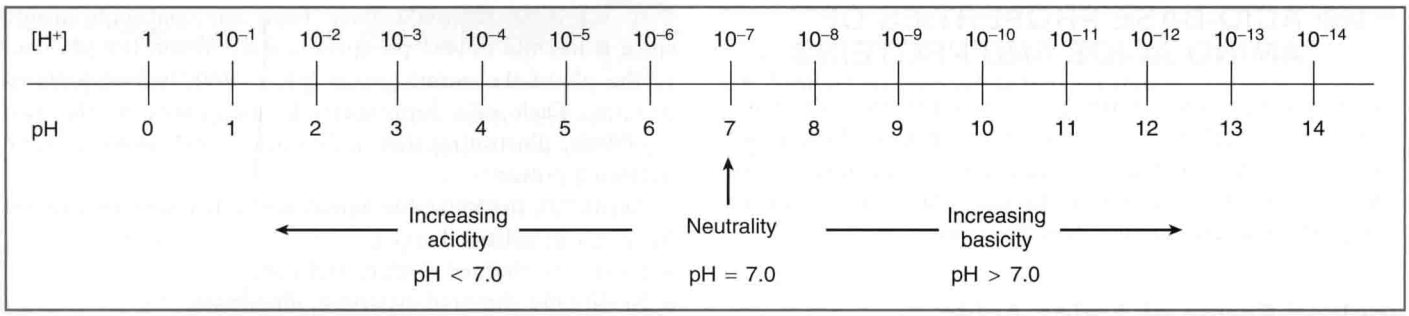

Figure 1-2. Relationship of pH to proton concentration.

- An acidic functional group is defined as having a pKa value less than 7.
- A basic functional group is defined as having a pKa value greater than 7.

Henderson-Hasselbalch Equation

When physiologic solutes, such as blood gases or metabolites, cause the pH of a solution to change, the new equilibrium changes the ratio of all conjugate acids (HA) to conjugate bases (A^-). The quantitative relationship between the pH and the ratio of conjugate acid to conjugate base is described by the Henderson-Hasselbalch equation:

$$pH = \frac{pKa + \log(\text{conjugate base})}{(\text{conjugate acid})}$$

or

$$pH = \frac{pKa + \log(A^-)}{(HA)}$$

- Note: For pH problems, always set up the Henderson-Hasselbalch equation first, then fill in the known values and solve for the unknown value.
- Note: Remember that $\log (A^-)/(HA) = \log A^- - \log HA$.

Buffers and Titration Curves

Buffers are conjugate pairs that resist changes in pH. The effect of buffering on the change in pH is best illustrated by a titration curve (Fig. 1-3). The titration curve is a plot of the change in pH when a strong base, such as sodium hydroxide (NaOH), is added. pH is usually plotted from low to high pH values, and an inflection point is apparent in the region of effective buffering (resistance to pH change). The midpoint of the inflection in the curve (arrow in Fig. 1-3) is the point at which the pH equals the pKa. This part of the curve reveals the smallest change in pH for a given amount of base added. The best buffering range is at the pK ± 1 pH unit.

Carbonic Acid Conjugate Pair—A Special Case

Carbonic acid (H_2CO_3) is a major acid-base buffer in blood. It establishes an equilibrium with both a volatile gas, CO_2, and its conjugate base, bicarbonate ion (HCO_3^-).

$$H_2O + CO_2 \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

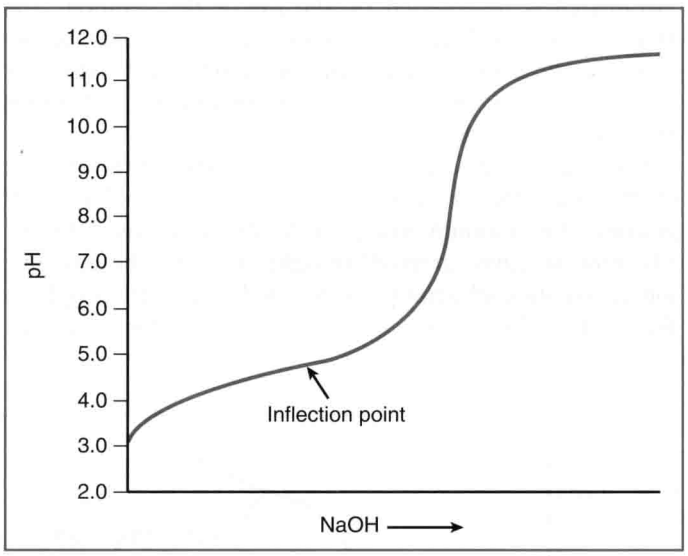

Figure 1-3. Titration curve showing buffering by acetic acid.

Because it is never present in significant amounts, carbonic acid is not included in the Henderson-Hasselbalch equation. It either rapidly breaks down to bicarbonate or is immediately converted to CO_2 by the enzyme carbonic anhydrase.

$$pH = pKa + \log$$

The overall equilibrium between bicarbonate and CO_2 is influenced by the rate of production of CO_2 in the tissues and its rate of elimination in the lungs. Thus the lungs play a major role in regulation of blood pH. Inability to eliminate CO_2 because of lung disease may lead to the acidification of blood, which is called respiratory acidosis.

KEY POINTS ABOUT ACIDS AND BASES

- Dissociation of a weak acid into a conjugate pair (acid plus anion) is at the midpoint when the pH equals the pK and provides maximum buffering.
- The Henderson-Hasselbalch equation relates the conjugate base-to-acid ratio to the pH.
- Titration curves have an inflection point for every ionizable functional group.
- The carbonic acid conjugate pair is in equilibrium with a volatile gas, CO_2.

ACID-BASE PROPERTIES OF AMINO ACIDS AND PROTEINS

Proteins acquire their charge properties from the side chains of the amino acids that comprise them. Several of these side chains can ionize and act as weak acids. Depending on the pK of the functional group in the side chain, this ionization can produce a positive or a negative charge.

Ionized Forms of Amino Acids

Whether or not a given functional group is dissociated or protonated is determined by the pH of the solution. The Henderson-Hasselbalch equation describes the amount of ionization (ratio of dissociated to protonated) for each individual functional group, since each has its own pKa value and ionizes independently of the others.

The titration curve for alanine (Fig. 1-4) gives an illustration of the independent dissociation of both of its functional groups: the α-amino group and the α-carboxyl group. The titration curve from left to right illustrates the changing ionization state of alanine as depicted from left to right in Figure 1-5. As protons are removed from the molecule, they are first removed only from the carboxyl group, since it has the lowest pK (pKa = 2.3). When the pH rises to the pK of the amino group (pK = 9.9), it then loses its protons. Each pKa represents the midpoints of the two equilibria, illustrating that amino acids (and proteins) have buffering power.

At pH 7.0, the ionizable amino acid side chains in proteins have characteristic charges:

- Positively charged: lysine, arginine.
- Negatively charged: aspartate, glutamate.
- Histidine becomes positively charged if pH drops below 6.0.
- Cysteine becomes negatively charged if pH rises above 8.0.

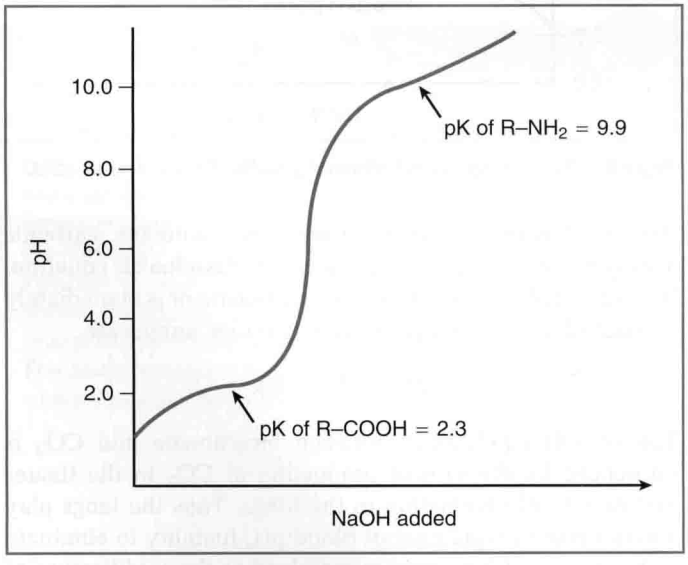

Figure 1-4. Titration curve for alanine.

PHYSIOLOGY

Metabolic Acidosis

When acid accumulates in the blood (acidemia) and lowers the pH of blood (acidosis), it depletes serum bicarbonate by shifting the equilibrium toward carbonic acid. Carbonic anhydrase quickly converts the carbonic acid to CO_2 plus water, and the CO_2 is then exhaled by the lungs. If the acidosis is due to a metabolite (metabolic acidosis [e.g., ketoacidosis, lactic acidosis, or methylmalonic acidemia]), then the anion gap [$Na^+ - (Cl^- + HCO_3^-)$] is increased (normal anion gap, 10 to 16 mmol/L).

Note: Always check for bicarbonate depletion to diagnose metabolic acidosis.

Isoelectric pH

The net charge on an amino acid or a protein is equal to the sum of all charges on each amino acid side chain. The pH value that produces a net zero (neutral) charge on the molecule is the isoelectric pH, or pI.

- For pH > pI, the net charge on the amino acid (or protein) is negative.
- For pH < pI, the net charge on the amino acid (or protein) is positive.

Proteins do not migrate in an electrical field when the pH of the buffer is equal to their isoelectric point, since they have no net charge to attract them to either the cathode or the anode.

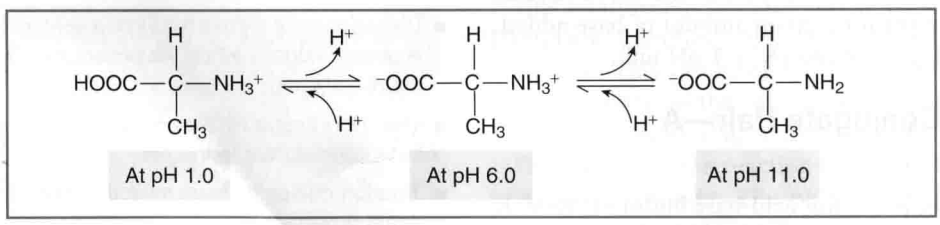

Figure 1-5. Ionization states of alanine.

PHYSIOLOGY

Metabolic Alkalosis

When protons are lost from the blood, the carbonic acid equilibrium with CO_2 is shifted toward carbonic acid, which is then converted to bicarbonate and restores the lost protons. This results in the accumulation of bicarbonate in the blood. Metabolic alkalosis is less common than metabolic acidosis and is precipitated by persistent vomiting, diuretics, large intake of alkaline substances, Cushing syndrome, and primary aldosteronism.

Note: Always check for bicarbonate accumulation to diagnose metabolic alkalosis.

KEY POINTS ABOUT ACID-BASE PROPERTIES OF AMINO ACIDS AND PROTEINS

- The side chains of the amino acids asp, glu, lys, arg, cys, and his act as weak acids at physiologic pH and confer charge properties to proteins that contain them.
- The isoelectric point for either an amino acid or a protein is that pH where the net sum of all charges is zero.

Self-assessment questions can be accessed at www.StudentConsult.com.