

Biochemistry

for Medical Sciences

Preface

The primary goal of this book is to present the biochemical foundation necessary to students of medicine and related fields. More specifically, the aim is to introduce the reader to the basic aspects of normal metabolism that are required for an understanding of the causes and consequences of various disorders. As such, this text should also be useful to biologists and clinicians who wish to keep abreast of ongoing developments and current hypotheses.

A major portion of the book deals with intermediary metabolism and its relationship to the overall functioning of mammalian organisms. In order to maintain the emphasis on these subjects, digressions into historical developments are avoided, and descriptions of experimental methodologies are kept to a minimum. In conformance with the primary objective, attention is centered on the reactions or pathways that regulate metabolism and the disorders that result from disturbances or deficiencies in those processes.

The basic principles and the structural chemistry required for the description of intermediary metabolism are discussed in the first two chapters. More specific details of molecular structures and enzyme characteristics are presented in conjunction with their application to metabolism. For example, only the general aspects of lipid structure are described in Chapter 1, whereas the individual structures are given when lipid metabolism is discussed in Chapters 3 and 5. Similarly, the principles of enzyme catalysis are described in Chapter 2, but the features of allosteric enzymes are defined in connection with isocitrate dehydrogenase (Chapter 3) and aspartate transcarbamoylase (Chapter 9).

Chapters 3, 4, and 5 deal with the metabolism of lipids and carbohydrates. The interrelationships of the metabolism of these materials, their transport in the circulatory system, and their disposition in different tissues are discussed in Chapter 6. Various control mechanisms and disorders of lipid and carbohydrate metabolism are also outlined in this chapter.

Chapter 7 discusses the reactions that are common to most amino acids and their relationship to carbohydrate and lipid metabolism. This discussion is followed by an outline of the metabolism of each amino acid (Chapter 8). The biosynthesis and degradation of nucleotides and porphyrins are then described in Chapters 9 and 10, respectively. Chapter 11 focuses on the general field of molecular biology, i.e., synthesis of nucleic acids and proteins. If one desires, the material covered in Chapter 11 may be inserted in the teaching sequence before the discussions of intermediary metabolism.

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Blood, respiration, and electrolyte balance are the subjects of Chapters 12 and 13. Although some material introduced in those chapters overlaps topics that are treated in physiology courses, the chemical aspects are extremely important to medical students and are, therefore, covered in this text.

Chapter 14 is concerned with the structure and function of specialized tissues, and Chapter 15 deals with various aspects of nutrition. In addition to the basic importance of nutrition, discussions of this subject also serve to integrate various aspects of metabolism described in earlier chapters.

The Suggested Reading lists include articles that expand on the subject matter in each chapter, as well as papers involving clinical applications.

As a research science, the field of biochemistry has become so vast and diverse that its specific boundaries cannot always be defined. Therefore, in writing a book on this subject, one is faced with the prospect of preparing an encyclopedic compendium but still not including all the important topics. In this textbook I have attempted to restrict myself to material that can be covered within the amount of time assigned to biochemistry in most medical schools. It includes the core subject matter required for clinical medicine and for comprehension of the current literature. Conceivably, there will be some objections regarding subjects that were omitted. It is hoped there will not be too many.

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I. D.

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1. Fundamentals

1.1. Scope of Biochemistry

The aim of biochemistry is to define the chemical or molecular properties of living entities. This involves characterization of the structural components of cells as well as elucidation of the chemical reactions that occur within the organism. Living systems are unique in several respects. Cells can utilize materials from the environment to maintain their functional capabilities and structural integrity. They also contain the machinery for self-repair and reproduction. Additionally, higher organisms undergo regulated growth and develop tissues with specialized functions. Biochemistry deals with the molecular structures and transformations that give rise to these distinctive manifestations of life.

The maintenance of life involves numerous dynamic systems of sequential and concurrent reactions. Most of the subject matter of biochemistry is concerned with these processes. Before this material can be considered, however, it is necessary to describe some of the structural features and chemical properties of the principal cellular and tissue components. This chapter deals with the basic concepts and structures required for understanding biochemistry. Details of some of the more complex molecular structures will be described in conjunction with discussions of their metabolism.

1.2. Chemistry of Cellular Components

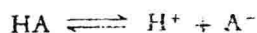
A. WATER AND ELECTROLYTES

Water constitutes about 80% of the weight of animal tissues. It also serves as the medium in which tissue components are dissolved or suspended. Substances that dissociate in water to yield ions are called *electrolytes*. These include acids, bases, and salts. *Acids* are defined as electrolytes that release hydrogen ions, or protons. *Bases* are substances that combine with hydrogen ions. Acids are classified further according to their degree of ionization or dissociation: those that are completely dissociated (or ionized) are termed *strong acids*, and those that are partially dissociated (or ionized) are called *weak acids*.

When a weak acid is dissolved in water, the solution contains a mixture of undissociated acid, hydrogen ions, and anions. Thus, for such an acid

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(HA), the dissociation can be expressed as a reversible reaction:*

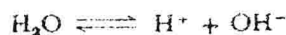


The concentrations of these components when the process reaches equilibrium are governed by the equation:

$$K_a = \frac{[\text{H}^+][\text{A}^-]}{[\text{HA}]} \quad (1-1)$$

In this relationship, the square brackets indicate that the concentrations of H^+ , A^- , and HA are in moles per liter. The term K_a is the *ionization constant*, or the dissociation constant, of the acid, and it has a specific value for a given temperature. The ionization constant for acetic acid (CH_3COOH) at 25°C , for example, is 1.86×10^{-5} . From the relatively low value of this ionization constant, we know that only a very small fraction of acetic acid is dissociated.

Water itself dissociates to a minute but significant extent, and this process can also be defined by an equilibrium constant:



$$K_a = \frac{[\text{H}^+][\text{OH}^-]}{[\text{H}_2\text{O}]} = 1.8 \times 10^{-16} \text{ at } 25^\circ\text{C}$$

Since the molar concentration of undissociated water (1000/18) is not affected significantly by the amount that is ionized, this equation may be written as:

$$K_a = \frac{[\text{H}^+][\text{OH}^-]}{55.5} = 1.8 \times 10^{-16}$$

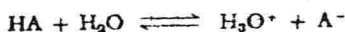
A new constant, K_w , the *ion-product of water*, is thus obtained:

$$K_w = [\text{H}^+][\text{OH}^-] = 1 \times 10^{-14} \quad (1-2)$$

In pure water, $[\text{H}^+]$ is equal to $[\text{OH}^-]$, and the concentrations of the hydrogen ions and of the hydroxyl ions are equal to 10^{-7} molar.

Upon addition of acid to water, the hydrogen-ion concentration is in-

* The dissociation of acids in aqueous solutions yields hydronium ions rather than protons:



However, since this does not affect the ensuing discussions or calculations, H^+ will be employed for simplification.

Table 1-1. Relationship Between $[H^+]$, $[OH^-]$, and pH

Molarity of H^+	Molarity of OH^-	pH
1.0	10^{-14}	0
0.01 (10^{-2})	10^{-12}	2
10^{-4}	10^{-10}	4
10^{-6}	10^{-8}	6
10^{-7}	10^{-7}	7
10^{-8}	10^{-6}	8
10^{-10}	10^{-4}	10
10^{-12}	10^{-2}	12

creased. However, since the ion-product of water is a constant, the hydroxyl-ion concentration must be decreased to a value less than 10^{-7} M. The hydrogen-ion concentration of an aqueous solution can be expressed in terms of pH. The pH is defined as the negative logarithm of the hydrogen-ion concentration:

$$pH = -\log [H^+] = \log \frac{1}{[H^+]} \quad (1-3)$$

Thus, for neutral solutions, when $[H^+]$ is 10^{-7} , the pH is 7. Acidic solutions have a hydrogen-ion concentration greater than 10^{-7} ; hence, their pH is below 7. The relationship between pH and hydrogen-ion concentration is shown in Table 1-1.

The ionization constants of acids can also be expressed in a manner analogous to the pH scale. Thus, the pK_a of an acid is the negative logarithm of the ionization constant of the acid:

$$pK_a = -\log K_a = \log \frac{1}{K_a} \quad (1-4)$$

In this system, an acid with an ionization constant of 10^{-6} has a pK_a of 6, one with K_a of 10^{-3} has a pK_a of 3, and so on. From this consideration, it should be obvious that the magnitude of the pK_a is related inversely to the strength of the acid, i.e., a strong acid will have a low pK_a value and a weak acid a high one.

Problem 1 If the hydrogen-ion concentration of a solution is 3.2×10^{-5} moles per liter, what is the pH?

$$\begin{aligned} \text{Answer} \quad pH &= -\log [H^+] = -\log (3.2 \times 10^{-5}) \\ &= -\log 3.2 + 5 \\ &= -0.505 + 5 = 4.49 \end{aligned}$$

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Problem 2 If $[H^+]$ is 6.4×10^{-5} M, what is the pH?

Answer $pH = -\log(6.4 \times 10^{-5}) = -0.806 + 5.0 = 4.19$
(Note in Problem 2 that the $[H^+]$ is double that in Problem 1, but the difference in pH is only 0.3. This is because a change of one in the pH scale represents a 10-fold change in the hydrogen-ion concentration.)

Problem 3 What is the hydrogen-ion concentration of a solution with pH 4.23?

Answer $-\log[H^+] = 4.23$
 $\log[H^+] = -4.23$
 $[H^+] = 10^{-4.23} = 10^{0.77} \times 10^{-5}$
 $= 5.9 \times 10^{-5}$ M

Problem 4 What is the hydroxyl-ion concentration in the solution discussed in Problem 3?

Answer $[H^+][OH^-] = K_w = 1 \times 10^{-14}$
 $(5.9 \times 10^{-5})[OH^-] = 1 \times 10^{-14}$
 $[OH^-] = \frac{1 \times 10^{-14}}{5.9 \times 10^{-5}} = 0.169 \times 10^{-9}$
 $= 1.69 \times 10^{-10}$ M

Problem 5 An acid has a K_a of 3.4×10^{-5} . What is the pK_a ?

Answer $pK_a = -\log K_a$
 $pK_a = -\log(3.4 \times 10^{-5}) = -0.5315 + 5 = 4.47$

A strong acid is completely dissociated when dissolved in water. The hydrogen-ion concentration of such an acid, therefore, is essentially the same as the normality of the acid. Thus, for example, the hydrogen-ion concentration of 0.01 M HCl is 10^{-2} and that of 0.01 M H_2SO_4 is 2×10^{-2} . This is not the case, however, with weak acids, which dissociate to a very limited extent. With solutions of these acids, the concentration of hydrogen ions depends on the K_a of the acid and on its concentration.

When protons are released during the dissociation of a monoprotic acid, an equal number of anions (A^-) are generated. Thus, equation 1-1 for K_a may be written as:

$$K_a = \frac{[H^+]^2}{[HA]}$$

The hydrogen-ion concentration for a solution of a weak acid is thus:

$$[H^+] = \sqrt{[HA]K_a}$$

Hence, the information required for ascertaining the hydrogen-ion concentration of a solution of weak acid is the K_a and the molar concentration of the undissociated acid. Since a fraction of the acid is dissociated, the amount of undissociated acid in solution is actually less than the total that was added. However, the degree of dissociation of weak acids is extremely small, so only a minimal error is introduced if the value for the total acid is used for the concentration of undissociated acid, $[HA]$, in the calculation of hydrogen-ion concentration. The equation for the hydrogen-ion concentration of solutions of weak acids can therefore be expressed as:

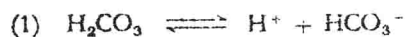
$$[H^+] = \sqrt{K_a C_a} \quad (1-5)$$

where C_a = normality of acid. (It should be noted that when the degree of dissociation of an acid in solution is greater than 5%, the effect of dissociation on the concentration of undissociated acid becomes significant and $[H^+]$ must be determined by alternative procedures.)

Problem 6 The K_a for acetic acid is 1.86×10^{-5} . What is the hydrogen-ion concentration of a 0.015 M solution of acetic acid? What is its pH?

$$\begin{aligned} \text{Answer} \quad [H^+] &= \sqrt{0.015 \times 1.86 \times 10^{-5}} \\ &= 5.28 \times 10^{-4} \\ \text{pH} &= 3.28 \end{aligned}$$

Certain acids contain more than one ionizable hydrogen. These are called *polyprotic* or *polybasic* acids. The ionization of these acids proceeds in discrete steps; for example, carbonic acid, a *dibasic* (or *diprotic*) acid, dissociates in the following sequence:



The degree of each dissociation is governed by a specific ionization constant. The constant for the release of a proton and bicarbonate ion from carbonic acid is termed the first ionization constant, K_1 . The second step, i.e., the

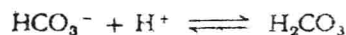
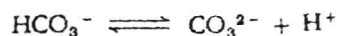
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formation of carbonate ions and the concomitant release of the second proton, is governed by the second ionization constant, K_2 . Both the constants and the molar ratios that they define are expressed as follows:

$$K_1 = \frac{[\text{H}^+][\text{HCO}_3^-]}{[\text{H}_2\text{CO}_3]} = 1.70 \times 10^{-4}$$

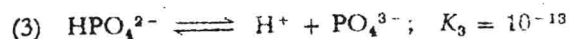
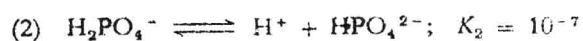
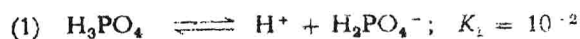
$$K_2 = \frac{[\text{H}^+][\text{CO}_3^{2-}]}{[\text{HCO}_3^-]} = 6.31 \times 10^{-11}$$

It may be noted that HCO_3^- functions both as an acid and as a base:



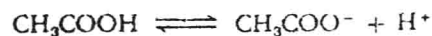
Such substances, which can act as both proton donors and proton acceptors, are called *amphoterics* materials.

Another important example of a polyprotic acid is phosphoric acid, H_3PO_4 . The sequence for its ionization is represented by the following equations:



It can be seen from both of these examples that the first ionization occurs to a considerably greater extent than the subsequent release of additional hydrogens.

The interrelationship between acids and bases can be expressed in terms of the ionization reaction of the acid. The dissociation of acetic acid yields protons and acetate ions:



Since the acetate ion can accept a proton to form acetic acid, it can be categorized as a base. Acetate ion is therefore called the *conjugate base* of acetic acid. Similar relationships can be defined for all acid-base pairs, as shown in Table 1-2.