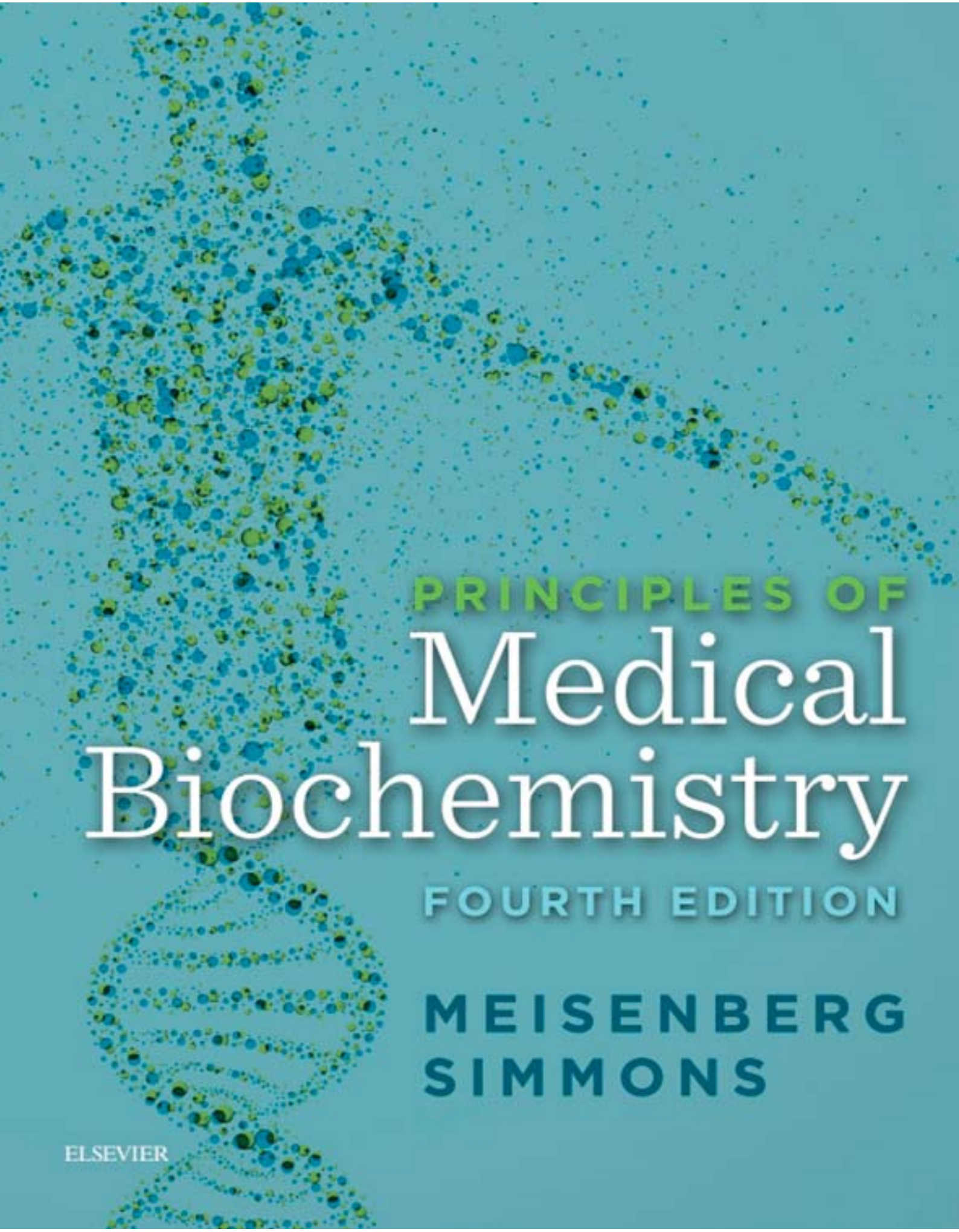
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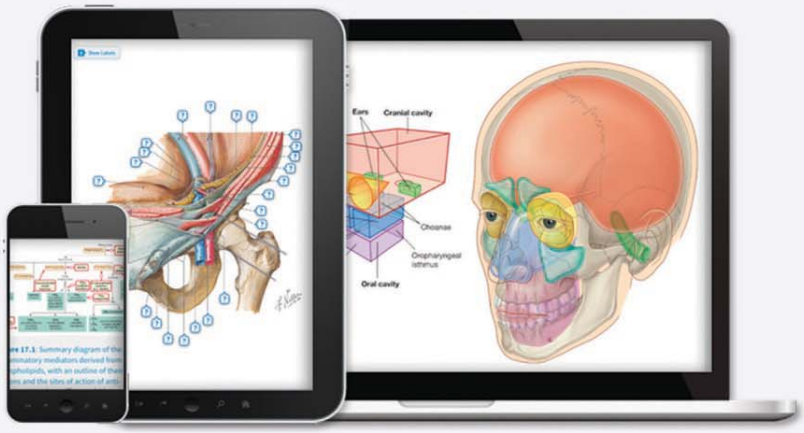

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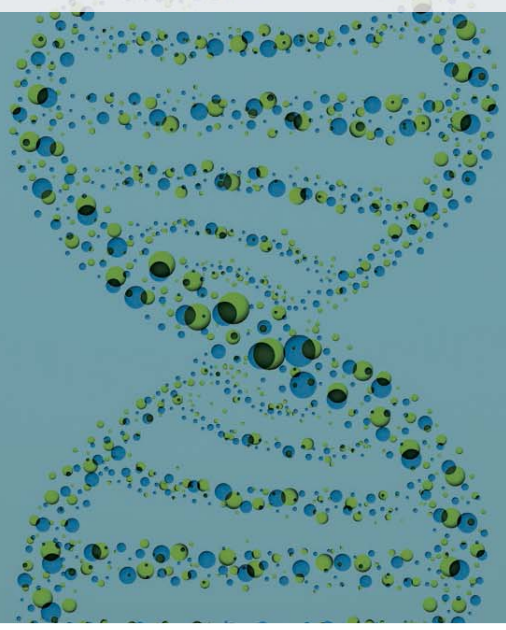

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PREFACE

It is rumored that among students embarking on a course of study in the medical sciences, biochemistry is the most common cause of pretraumatic stress disorder: the state of mind into which people fall in anticipation of unbearable stress and frustration. No other part of their preclinical curriculum seems as abstract, shapeless, unintelligible, and littered with irrelevant detail as does biochemistry. This prejudice is understandable. Biochemistry is less intuitive than most other medical sciences. Even worse, it is a vast field with an ever-expanding frontier. From embryonic development to carcinogenesis and drug action, biochemistry is becoming the ultimate level of explanation.

This fourth edition of *Principles of Medical Biochemistry* is yet another attempt to impose structure and meaning on the blooming, buzzing confusion of this runaway science. This text is designed for first-year medical students as well as veterinary, dental, and pharmacy students and students in undergraduate premedical programs. Therefore, its aim goes beyond the communication of basic biochemical facts and concepts. Of equal importance is the link between basic principles and medical applications. To achieve this aim, we enhanced this edition with numerous clinical examples embedded in the chapters that illustrate the importance of biochemistry in medicine.

Although biochemistry advances at a faster rate than most other medical sciences, we did not match the increased volume of knowledge by an increased size of the book. The day has only 24 hours, the cerebral cortex has only 30 billion neurons, and students have to learn many other subjects in addition to biochemistry. Rather, we tried to be more selective and more concise. The book is still comprehensive in the sense that it covers most aspects of biochemistry that have significant medical applications. However, it is intended for day-to-day use by students. It is not a reference work for students, professors, or physicians. It does not contain "all a physician ever needs to know" about biochemistry. This is impossible to achieve because the rapidly expanding science requires new learning (and unlearning) of received wisdom on a continuous basis.

This book is evidently a compromise between the two conflicting demands of comprehensiveness and brevity. This compromise was possible because medical biochemistry is not a random cross-section of the general biochemistry that is taught in undergraduate courses and PhD programs. Biochemistry for the medical professions is "physiological" chemistry: the chemistry needed to understand the structure and functions of the body and their malfunction in disease. Therefore, we pay little attention to topics of abstract theoretical interest, such as three-dimensional protein structures and enzymatic reaction mechanisms, but we give thorough treatments of medically important topics such as lipoprotein metabolism, mutagenesis and genetic diseases, the molecular basis of cancer, nutritional disorders, and the hormonal regulation of metabolic pathways.

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Gerhard Meisenberg, PhD
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ANSWERS TO CASE STUDIES

Part ONE

PRINCIPLES OF MOLECULAR STRUCTURE AND FUNCTION

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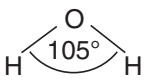
Chapter 1
INTRODUCTION TO BIOMOLECULES

Biochemistry is concerned with the molecular workings of the body, and the first question we must ask is about the molecular composition of the normal human body. *Table 1.1* lists the approximate composition of the proverbial 75-kg textbook adult. Next to water, **proteins** and **triglycerides** are most abundant. Triglyceride (aka fat) is the major storage form of metabolic energy, found mainly in adipose tissue. Proteins are of more general importance. They form the structural backbone of cells and tissues and are responsible for enzymatic catalysis, membrane transport, and cell motility. **Carbohydrates,** in the form of glucose and the storage polysaccharide glycogen, are substrates for the generation of metabolic energy. They also are covalently linked components of glycoproteins and glycolipids. Soluble **inorganic salts** are present in all intracellular and extracellular fluids, and insoluble salts, most of which are related to calcium phosphate, give strength and rigidity to the bones.

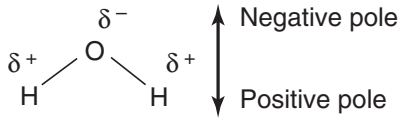
This chapter introduces the principles of molecular structure, the types of noncovalent interactions between biomolecules, and the structural features of the major classes of biomolecules.

WATER IS THE SOLVENT OF LIFE

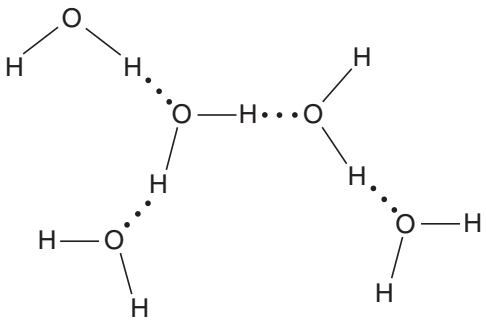
Charles Darwin speculated that life originated in a warm little pond. Perhaps it really was a big warm ocean, but one thing is certain: We are appallingly watery creatures. Almost two-thirds of the adult human body is water (see *Table 1.1*). The structure of water is simple, with two hydrogen atoms bonded to an oxygen atom at an angle of 105 degrees:



Water is a lopsided molecule, with its binding electron pairs displaced toward the oxygen atom. Thus the oxygen atom has a high electron density, and the hydrogen atoms are electron deficient. The oxygen atom has a partial negative charge (δ^-), and the hydrogen atoms have partial positive charges (δ^+). Therefore the water molecule forms an electrical **dipole:**



Unlike charges attract each other. Therefore the hydrogen atoms of a water molecule are attracted by the oxygen atoms of other water molecules, forming **hydrogen bonds:**



The hydrogen bonds are weak. Only 29 kJ/mol (7 kcal/mol)[1] are needed to break a hydrogen bond in water, but 450 kJ/mol (110 kcal/mol) are required to break a covalent oxygen-hydrogen bond in the water molecule itself. Breaking the hydrogen bonds requires no more than heating the water to 100 °C. *The hydrogen bonds determine the physical properties of water,* including its boiling point.

All body fluids contain inorganic **cations** (positively charged ions) such as sodium and potassium, and **anions** (negatively charged ions) such as chloride and phosphate. *Table 1.2* lists the typical ionic compositions of intracellular (cytoplasmic) and extracellular (interstitial) fluids. Interestingly, the extracellular fluid has an ionic composition similar to seawater. We carry a warm little pond with us, a replica of the environment in which our ancestors originated.

Predictably, the cations are attracted to the oxygen atom of the water molecule, and the anions are attracted to the hydrogen atoms. The **ion-dipole interactions** thus formed are the forces that keep the components of soluble salts in solution, as in the case of sodium chloride (table salt):

[1] 1 kcal = 4.18 kJ.

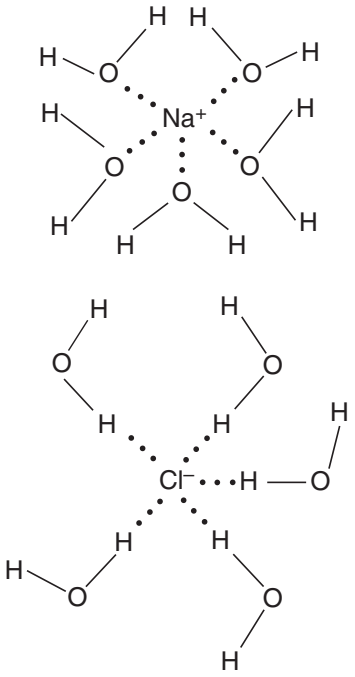


Table 1.1 Approximate Composition of a 75-kg Adult

Substance	Content (%)
Water	60
Inorganic salt, soluble	0.7
Inorganic salt, insoluble*	5.5
Protein	16
Triglyceride (fat)†	13
Membrane lipids	2.5
Carbohydrates	1.5
Nucleic acids	0.2

* In bones.

† In adipose tissue.

Table 1.2 Typical Ionic Compositions of Extracellular (Interstitial) and Intracellular (Cytoplasmic) Fluids

	Concentration (mmol/L)	
Ion	Extracellular Fluid	Cytoplasm
Na^+	137	10
K^+	4.7	141
Ca^{2+}	2.4	10^{-4}*
Mg^{2+}	1.4	31
Cl^-	113	4
$HPO_4^{2-}/H_2PO_4^-$	2	11
HCO_3^-	28†	10†
Organic acids, phosphate esters	1.8	100
pH	7.4	6.5–7.5

* Cytoplasmic concentration. Concentrations in mitochondria and endoplasmic reticulum are much higher.

† The lower HCO_3^- concentration in the intracellular space is caused by the lower intracellular pH, which affects the equilibrium:

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

The calcium phosphates in human bones are not soluble because the **electrostatic interactions** (**"salt bonds"**) between the anions and cations in the crystal structure are stronger than their ion-dipole interactions with water.

WATER CONTAINS HYDRONIUM IONS AND HYDROXYL IONS

Water molecules dissociate reversibly into hydroxyl ions and hydronium ions:

$$(1)\quad \underset{\text{Hydronium ion}}{H_3O^+} + \underset{\text{Hydroxyl ion}}{OH^-} \quad \text{from} \quad H_2O + H_2O \rightleftharpoons$$

In pure water, only about 1 in 280 million molecules is in the H_3O^+ or OH^- form:

$$(2)\quad [H_3O^+] = [OH^-] = 10^{-7}\ \text{mol/L}$$

The brackets indicate molar concentrations (mol/L or M). *One mole of a substance is its molecular weight in grams.* Water has a molecular weight close to 18; therefore 18 g of water is 1 mol. The hydronium ion concentration $[H_3O^+]$ is usually expressed as the **proton concentration** or the **hydrogen ion concentration** $[H^+]$, regardless of the fact that the proton is actually riding on the free electron pair of a water molecule.

In aqueous solutions, the product of proton (hydronium ion) concentration and hydroxyl ion concentration is a constant:

$$(3)\quad [H^+] \times [OH^-] = 10^{-14}\ \text{mol}^2/\text{L}^2$$

The proton concentration $[H^+]$, otherwise measured in moles per liter (mol/L, or M), is more commonly expressed as the **pH value,** defined as the negative logarithm of the hydrogen ion concentration:

$$(4)\quad pH = -\log[H^+]$$

With Equations (3) and (4), the H^+ and OH^- concentrations can be predicted at any given pH value (***Table 1.3***).

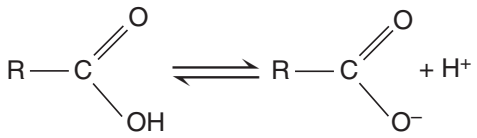
The pH value of an aqueous solution depends on the presence of **acids** and **bases.** According to the **Brønsted definition,** in aqueous solutions, *an acid is a substance that releases a proton, and a base is a substance that binds a proton.* The prototypical acidic group is the

Table 1.3 Relationship among pH, $[H^+]$, and $[OH^-]$

pH	$[H^+]$*	$[OH^-]$*
4	10^{-4}	10^{-10}
5	10^{-5}	10^{-9}
6	10^{-6}	10^{-8}
7	10^{-7}	10^{-7}
8	10^{-8}	10^{-6}
9	10^{-9}	10^{-5}
10	10^{-10}	10^{-4}

* $[H^+]$ and $[OH^-]$ are measured in mol/L (M).

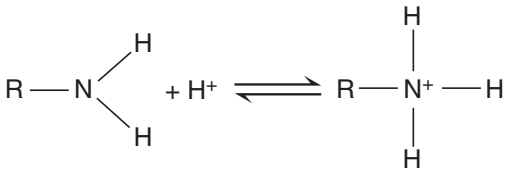
carboxyl group, which is the distinguishing feature of the organic acids:



Carboxylic acid (protonated form) — Carboxylate anion (deprotonated form)

The protonation-deprotonation reaction is reversible; therefore the carboxylate anion fits the definition of a Brønsted base. It is called the **conjugate base** of the acid.

Amino groups are the major basic groups in biomolecules. In this case the amine is the base, and the ammonium salt is the conjugate acid:



Amine (deprotonated form) — Ammonium salt (protonated form)

Carboxyl groups, phosphate esters, and **phosphodiesters** are the most important acidic groups in biomolecules. They are mainly deprotonated and negatively charged at pH 7. Aliphatic (nonaromatic) **amino groups,** including the primary, secondary, and tertiary amines, are the most important basic groups. They are mainly protonated and positively charged at pH 7.

IONIZABLE GROUPS ARE CHARACTERIZED BY THEIR p*K* VALUES

The equilibrium of a protonation-deprotonation reaction is described by the **dissociation constant** (K_D). For the reaction:

$$R—COOH \rightleftharpoons R—COO^- + H^+$$

the dissociation constant K_D is defined as:

$$(5) \quad K_D = \frac{[R—COO^-] \times [H^+]}{[R—COOH]}$$

This can be rearranged to:

$$(6) \quad [H^+] = K_D \times \frac{[R—COOH]}{[R—COO^-]}$$

The molar concentrations in this equation are the concentrations observed at equilibrium. Because the hydrogen ion concentration $[H^+]$ is most conveniently expressed as the pH value, **Equation** (6) can be transformed into the negative logarithm:

$$(7) \quad pH = pK - \log \frac{[R—COOH]}{[R—COO^-]}$$

$$= pK + \log \frac{[R—COO^-]}{[R—COOH]}$$

This is the **Henderson-Hasselbalch equation,** and *the* p*K value is defined as the negative logarithm of the dissociation constant.* The p*K* value is a property of an ionizable group. If a molecule has more than one ionizable group, then it has more than one p*K* value.

In the Henderson-Hasselbalch equation, p*K* is a constant, whereas $[R—COOH]/[R—COO^-]$ changes with the pH. When the pH value equals the p*K* value, $\log[R—COOH]/[R—COO^-]$ must equal zero. Therefore $[R—COOH]/[R—COO^-]$ must equal one: *The* p*K value indicates the pH value at which the ionizable group is half-protonated.* At pH values below their p*K* (high $[H^+]$, high acidity), ionizable groups are mainly protonated. At pH values above their p*K* (low $[H^+]$, high alkalinity), ionizable groups are mainly deprotonated (*Table 1.4*).

THE BLOOD pH IS TIGHTLY REGULATED

Most biomolecules contain ionizable groups that are subject to protonation and deprotonation. The protonation states of these groups are important for the structures of the molecules, their interactions with other molecules, and their biological functions. Consequently, *all important biological processes are pH dependent, and a constant pH therefore has to be maintained in body fluids and cells.* The pH of blood plasma is approximately 7.40 in arterial blood and 7.35 in venous blood. The difference is caused by the

Table 1.4 Protonation State of a Carboxyl Group and an Amino Group at Different pH Values

	Carboxyl Group		Amino Group	
pH	Percent of Group Protonated (R—COOH)	Percent of Group Deprotonated ($R—COO^-$)	Percent of Group Protonated ($R—NH_3^+$)	Percent of Group Deprotonated ($R—NH_2$)
p*K*+3	0.1	99.9	0.1	99.9
p*K*+2	1	99	1	99
p*K*+1	10	90	10	90
p*K*	50	50	50	50
p*K*−1	90	10	90	10
p*K*−2	99	1	99	1
p*K*−3	99.9	0.1	99.9	0.1

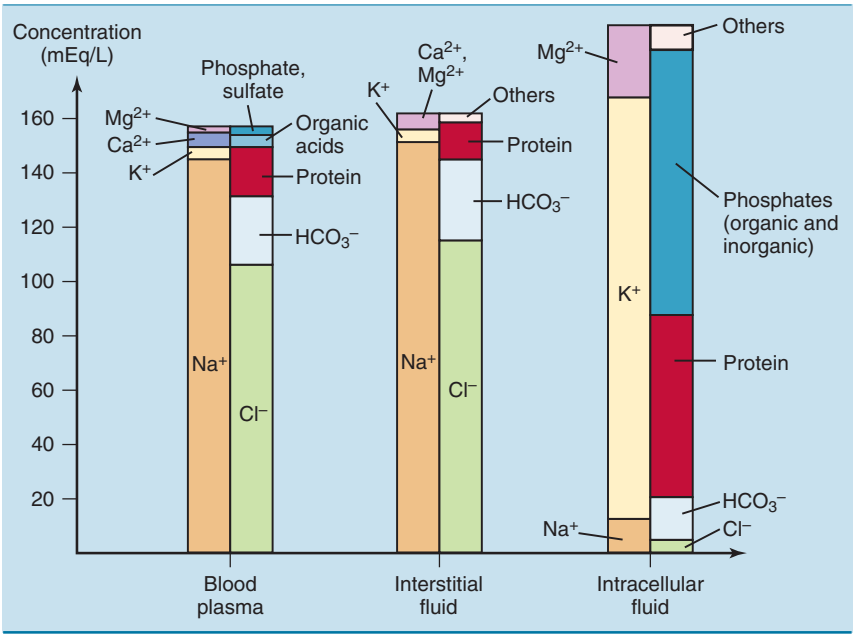


Fig. 1.1 Ionic compositions of blood plasma, interstitial fluid, and intracellular fluid.

higher concentration of **carbonic acid** in venous blood. Carbonic acid forms from carbon dioxide and water, either spontaneously or catalyzed by the enzyme **carbonic anhydrase:**

$$CO_2 + H_2O \underset{}{\overset{\text{Carbonic anhydrase}}{\rightleftharpoons}} H_2CO_3 \overset{\text{Spontaneous}}{\rightleftharpoons} HCO_3^- + H^+$$

At 37°C and pH7.4, there are approximately 800 molecules of dissolved CO_2 and 16,000 molecules of HCO_3^- for every molecule of H_2CO_3. The apparent p*K* for the overall reaction $CO_2 + H_2O \rightarrow HCO_3^- + H^+$ is 6.1.

The importance of the equilibrium between H_2CO_3, HCO_3^-, and H^+ is evident when the pH of the solution is disturbed. When acid (H^+) is added while HCO_3^- is present, most of the H^+ will be absorbed by the HCO_3^-, forming first H_2CO_3 and then CO_2. Conversely, when alkali is added (H^+ removed) H_2CO_3 releases H^+ to the surrounding water while being regenerated from CO_2 and H_2O. Thus the presence of the weak acid H_2CO_3 and the weak base HCO_3^- stabilizes the pH of the solution.

Substances that stabilize the pH are called **buffers.** *All weak acids and weak bases buffer the pH of the solution at pH values close to the pK values of their ionizable groups.* Ionizable groups in proteins participate in the maintenance of a constant pH in cells and body fluids. However, *carbonic acid/bicarbonate is the most important physiological buffer system in the body.* It is important because CO_2 and HCO_3^- are present in high concentrations in the interstitial and intracellular compartments as well as in the plasma (***Fig. 1.1***). In addition, *the CO_2 level can be regulated by the lungs and the HCO_3^- level by the kidneys.*

Phosphate groups provide an additional buffer system:

$$H_3PO_4 \overset{H^+}{\rightleftharpoons} H_2PO_4^- \overset{H^+}{\underset{pK = 6.9}{\rightleftharpoons}} HPO_4^{2-} \overset{H^+}{\rightleftharpoons} PO_4^{3-}$$

The phosphate buffer is important only in the intracellular compartments, in which both inorganic phosphate and organically bound phosphate are plentiful.

ACIDOSIS AND ALKALOSIS ARE COMMON IN CLINICAL PRACTICE

Even small deviations from the normal blood pH lead to severe disturbances. An arterial pH lower than 7.35 is called **acidemia,** and an arterial pH exceeding 7.45 is called **alkalemia.** The pathological states leading to these outcomes are called **acidosis** and **alkalosis,** respectively.

Respiratory acidosis is caused by the abnormal retention of CO_2, and **respiratory alkalosis** is caused by hyperventilation. For example, a doubling in the rate of alveolar ventilation raises the blood pH from 7.40 to 7.62, and a 50% reduction in alveolar ventilation lowers the blood pH from 7.40 to 7.12 (***Fig. 1.2***).

Metabolic acidosis can be caused by the overproduction of an organic acid, for example:

$$\text{Glucose} \rightarrow \text{Lactic acid}$$

$$\text{Triglyceride (fat)} \rightarrow \beta\text{-hydroxybutyric acid}$$

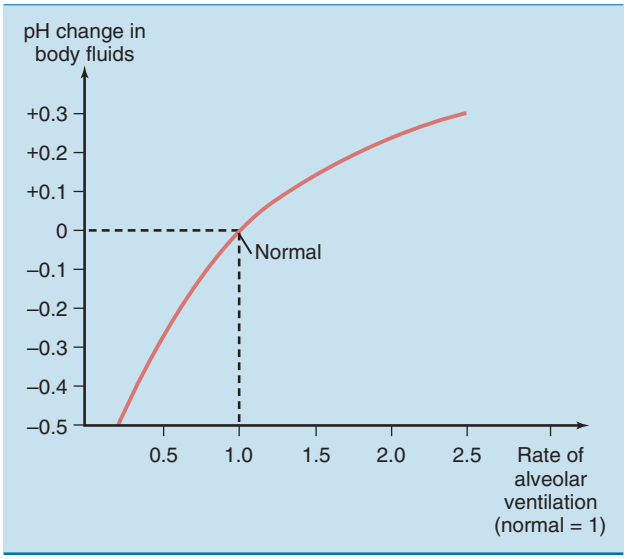


Fig. 1.2 pH change in plasma and extracellular fluids in response to changes in alveolar ventilation.

Some toxins are converted into acids in the human body, causing acidosis. For example:

$$\text{Methanol} \rightarrow \text{Formic acid}$$

Other causes of metabolic acidosis include failure to convert a metabolic acid to a nonacidic product or failure of the kidneys to excrete excess acid. The normal urinary pH varies between 4.0 and 7.0, depending on the need to excrete excess protons. Conversely, **metabolic alkalosis** is caused by the abnormal loss of acids from the body (e.g., as a result of excessive vomiting).

Whenever the blood pH is abnormal, the body uses three lines of defense in an attempt to restore a normal blood pH:

1. *The buffer systems act immediately to prevent excessive fluctuations of the blood pH.*
2. *Alveolar ventilation increases in acidosis and decreases in alkalosis.* The respiratory center in the medulla oblongata of the brain responds to pH and CO_2 within minutes. In consequence, hyperventilation is a manifestation of metabolic acidosis.
3. *The kidneys excrete excess H^+ in acidosis and excess HCO_3^- in alkalosis.* This is a long-term mechanism that acts on a time scale of hours to days.

Measurement of the plasma total carbon dioxide ($CO_2 + H_2CO_3 + HCO_3^-$) distinguishes between metabolic and respiratory acidosis. In respiratory acidosis, the total carbon dioxide is elevated because CO_2 retention is, by definition, the cause of the acidosis. In metabolic acidosis, it is reduced because the patient hyperventilates in an attempt to eliminate excess carbonic acid. The converse applies to alkalosis.

BONDS ARE FORMED BY REACTIONS BETWEEN FUNCTIONAL GROUPS

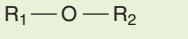
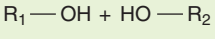
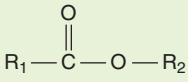
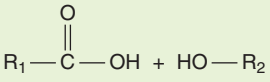
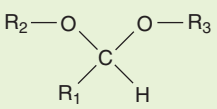
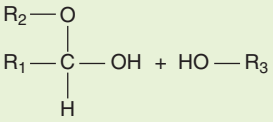
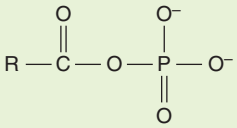
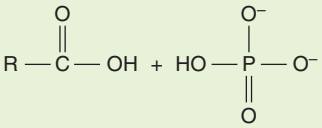
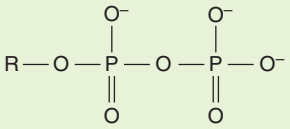
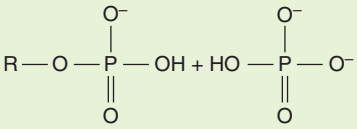
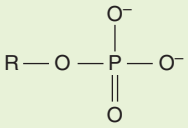
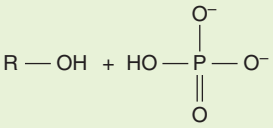
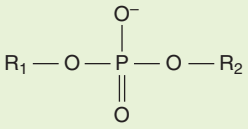
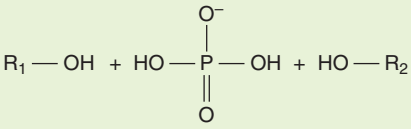
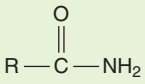
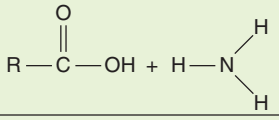
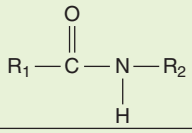
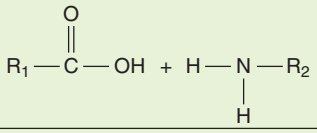
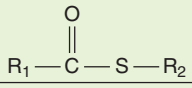
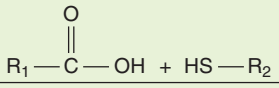
Most biomolecules contain only three to six different elements out of the 92 that are listed in the periodic table. Carbon (C), hydrogen (H), and oxygen (O) are always present. Nitrogen (N) is present in many biomolecules, and sulfur (S) and phosphorus (P) are present in some. These elements form a limited number of **functional groups,** which determine the physical properties and chemical reactivities of the molecules (***Table 1.5***). Many of these functional groups can form bonds through **condensation reactions,** in which two groups join with the release of water (***Table 1.6***). This type of reaction links small molecules into large, polymeric structures (macromolecules). Bond formation is an endergonic (energy-requiring) process. Therefore *the synthesis of macromolecules from small molecules requires metabolic energy.*

Cleavage of these bonds by the addition of water is called **hydrolysis.** It is an exergonic (energy-releasing) process that occurs spontaneously, provided it is catalyzed by acids, bases, or enzymes. For example, the digestive enzymes, which catalyze hydrolytic bond cleavages (see Chapter 20), work perfectly well in the

Table 1.5 Functional Groups in Biomolecules

1. Hydrocarbon Groups		
—CH_3	Methyl	
—CH_2—CH_3	Ethyl	
—CH_2—	Methylene	
—CH=	Methine	
2. Oxygen-Containing Groups		
R—OH	Hydroxyl (alcoholic)	
⟩—OH	Hydroxyl (phenolic)	
C=O	Keto	Carbonyl
—C(H)=O	Aldehyde	Carbonyl
—C(=O)—OH	Carboxyl	
3. Nitrogen-Containing Groups		
—NH_2	Primary amine	
NH	Secondary amine	
N—	Tertiary amine	
—N^+—	Quaternary ammonium salt	
4. Sulfur-Containing Group		
—SH	Sulfhydryl group	

Table 1.6 Important Bonds in Biomolecules

Bond	Structure	Formed from	Occurs in
Ether			Methyl ethers, some membrane lipids
Carboxylic ester			Triglycerides, other lipids
Acetal			Disaccharides, oligosaccharides, and polysaccharides (glycosidic bonds)
Mixed anhydride*			Some metabolic intermediates
Phosphoanhydride*			Nucleotides; most important: ATP
Phosphate ester			Many metabolic intermediates, phosphoproteins
Phosphodiester			Nucleic acids, phospholipids
Unsubstituted amide			Asparagine, glutamine
Substituted amide			Polypeptides (peptide bond)
Thioester*			Acetyl-CoA, other "activated" acids
Thioether	$R_1—S—R_2$	$R_1—SH + HO—R_2$	Methionine

ATP, adenosine triphosphate; *CoA*, coenzyme A.

* "Energy-rich" bonds.

lumen of the gastrointestinal tract, where neither adenosine triphosphate (ATP) nor other usable energy sources are available.

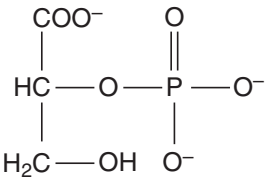
Some bonds contain more energy than others. Most ester, ether, acetal, and amide bonds require between 4 and 20 kJ/mol (1 and 5 kcal/mol) for their formation, and the same amount of energy is released during their hydrolysis. Anhydride bonds and thioester bonds, however, have free energy contents greater than 20 kJ/mol. They are classified, rather arbitrarily, as **energy-rich bonds.**

ISOMERIC FORMS ARE COMMON IN BIOMOLECULES

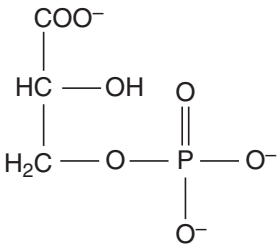
The biological properties of molecules are determined not only by their composition but by their geometry. **Isomers** are chemically different molecules with identical

composition but different geometry. The three different types of isomers are as follows:

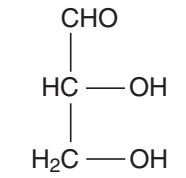
1. **Positional isomers** differ in the positions of functional groups within the molecule. Examples include the following:



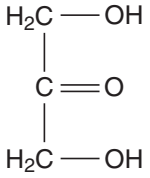
2-Phosphoglycerate



3-Phosphoglycerate

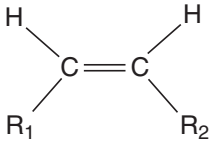


Glyceraldehyde

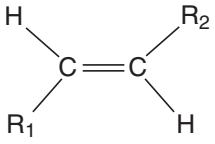


Dihydroxyacetone

2. **Geometric isomers** differ in the arrangement of substituents at a rigid portion of the molecule. A typical example involves the *cis-trans* isomers of carbon-carbon double bonds:



cis double bond



trans double bond

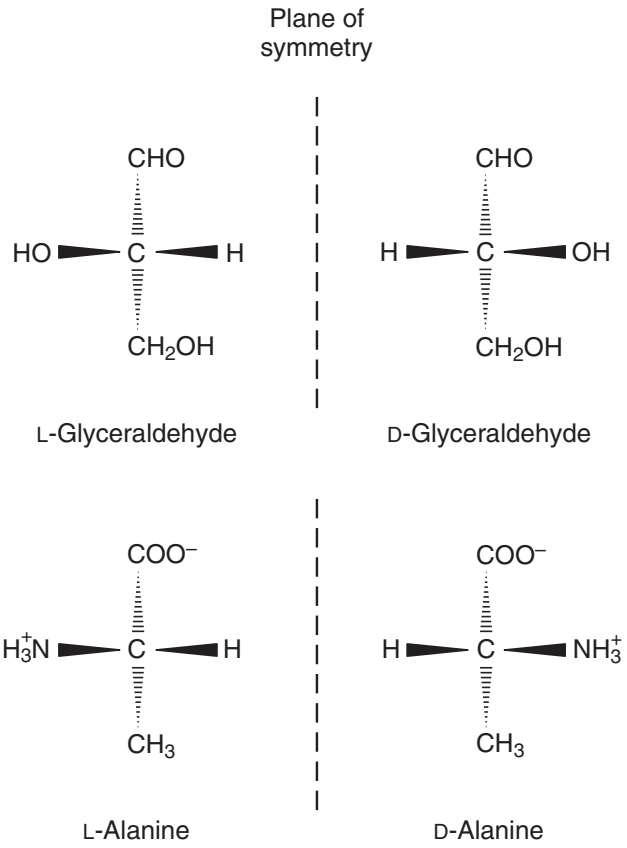
The two forms are not interconvertible because there is no rotation around the double bond. All substituents (H, R_1, and R_2) are fixed in the same plane. Also ring systems show geometrical isomerism, with substituents protruding over one or the other surface of the ring. Geometrical isomers are called **diastereomers.**

3. **Optical isomers** differ in the orientation of substituents around an **asymmetric carbon:** a carbon with four *different* substituents. If the molecule has only one asymmetric carbon, the isomers are mirror images. These mirror-image molecules are called **enantiomers.** They are related to each other in the same way as the left hand and the right hand; therefore optical isomerism is also called **chirality** (from Greek χειρ meaning "hand").

Unlike positional and geometric isomers, which differ in their melting points, boiling points, solubilities, and crystal structures, *enantiomers have identical physical and chemical properties*. They can be distinguished only by the direction in which they turn the plane of polarized light. They do, however, differ in their biological properties.

If more than one asymmetric carbon is present in the molecule, isomers at a single asymmetric carbon are not mirror images (enantiomers) but are geometric isomers (diastereomers) with different physical and chemical properties.

In the **Fischer projection,** the substituents above and below the asymmetric carbon face behind the plane of the paper, and those on the left and right face the front. The asymmetric carbon is in the center of a tetrahedron whose corners are formed by the four substituents. For example,



PROPERTIES OF BIOMOLECULES ARE DETERMINED BY THEIR NONCOVALENT INTERACTIONS

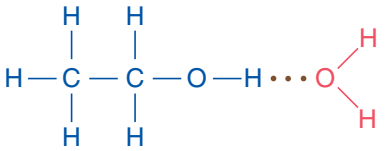
The functions of biomolecules require interactions with other molecules. Molecules communicate with

one another, and being incapable of speech, they have to communicate by touch. The surfaces of interacting molecules must be complementary, and noncovalent interactions must be formed between them. These interactions are weak. They break and re-form continuously; therefore *noncovalent binding is always reversible*. We can distinguish five types of noncovalent interactions:

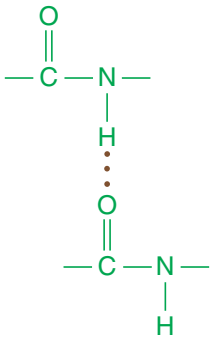
1. **Dipole-dipole interactions** usually come in the form of hydrogen bonds, similar to those between water molecules. They are formed when a hydrogen atom that is covalently bound to an electronegative atom such as oxygen or nitrogen associates noncovalently with another electronegative atom, either in the same or a different molecule. **Electronegativity** is the tendency of an atom to attract electrons. For the atoms commonly encountered in biomolecules, the rank order of electronegativity is as follows:

$$O > N > S \geq C \geq H$$

Examples:

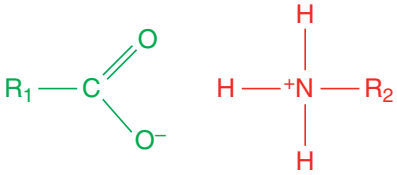


Hydrogen bond between ethanol and water

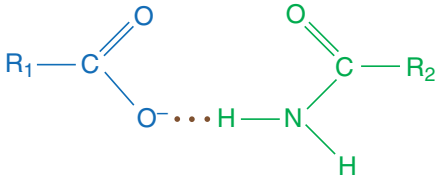


Hydrogen bond between two peptide bonds

2. **Electrostatic interactions,** or **salt bonds,** are formed between oppositely charged groups:



3. **Ion-dipole interactions** are formed between a charged group and a polarized bond, as in the case of a carboxylate anion and a carboxamide:



4. **Hydrophobic interactions** hold nonpolar molecules, or nonpolar portions of molecules, together. There is no strong attractive force between such groups. However, an interface between a nonpolar structure and water is thermodynamically unfavorable because it limits the ability of water molecules to form hydrogen bonds with their neighbors. The water molecules are forced to reorient themselves in order to maximize their hydrogen bonds with neighboring water molecules, thereby attaining a more ordered and energetically less favored state. *By clustering together, nonpolar groups minimize their area of contact with water.*
5. **van der Waals forces** appear whenever two molecules approach each other (***Fig. 1.3***). A weak attractive force, caused by induced dipoles in the molecules, prevails at moderate distances. However, when the molecules come too close, electrostatic repulsion between the electron shells of the approaching groups overwhelms the attractive force. There is an optimal contact distance at which the attractive force is canceled by the repulsive force. *Because of van der Waals forces, molecules whose surfaces have complementary shapes tend to bind each other.*

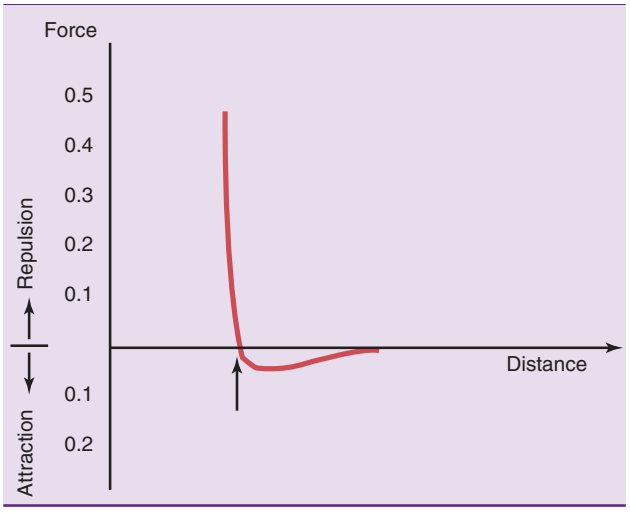


Fig. 1.3 Attractive and repulsive van der Waals forces. At the van der Waals contact distance *(arrow),* the opposing forces cancel each other.