Integrative Medical Biochemistry

Examination and Board Review

Michael W. King

Mc Graw Hill Education

LANGE®

Integrative Medical Biochemistry Examination and Board Review

NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

Integrative Medical Biochemistry Examination and Board Review

MICHAEL W. KING, PHD

Professor
Indiana University School of Medicine and
Center for Regenerative Biology and Medicine
Terre Haute, Indiana

Mc Graw Hill Education | Medical

New York Chicago San Francisco Athens London Madrid Mexico City
Milan New Delhi Singapore Sydney Toronto

ISBN: 978-0-07-183275-5

MHID: 0-07-183275-0

The material in this eBook also appears in the print version of this title: ISBN: 978-0-07-178612-6,
MHID: 0-07-178612-0.

eBook conversion by codeMantra
Version 2.0

Contents

Preface

This book has been designed with the intention of preparing students, particularly those in medical school, for both regular course exams in biochemistry and medical biochemistry as well as medical board exams, namely the USMLE Step 1 exam taken by all US medical students at the completion of their second year of education. To accomplish this goal, there are 1100 multiple choice questions throughout all of the chapters with 50% being formatted in the current USMLE Step 1 format.

In addition to the general content and questions, a major focus of this book is on the integration of medical biochemistry with physiology, pathophysiology, pathology, and anatomy. This focus has been undertaken with this book to ensure that it serves that critical audience of current and future medical student, exposed to the shifting medical school curriculum, which is to use a more integrated content approach.

This review book is divided into four broad sections. The first section covers the basics of the major building blocks of all cells and tissues. The second section, and by far the major bulk of any medical biochemistry text, covers metabolic biochemistry with a strong emphasis on clinical correlations and clinical disorders related to these all-important pathways. The third section covers the cellular and molecular biology topics associated with medical biochemistry, physiology, and pathology. The fourth section includes 10 chapters dealing with high-yield integrative topics that are beneficial to not only medical students but to all students of the discipline.

Each chapter begins with an outline listing the major topics covered in the content. This is followed by a list of high-yield terms related to the included content. Each chapter includes numerous explanatory figures and tables aimed at allowing for increased understanding of and focus on the critical content. Most chapters include detailed Clinical Boxes that describe and discuss the high-yield information concerning diseases and disorders related to defects in the pathways being discussed. Although each chapter does not warrant one or more Clinical Boxes, there are over 90 such high-yield topics throughout the book. Each chapter content section is followed by a series of multiple choice questions, which also include explanatory answers for each and every question. Finally, at the end of each chapter is a Checklist designed to refocus the reader to the most important and high-yield concepts covered by each chapter. If a student finds concepts and/or content confusing or unclear when completing any chapter, it is highly recommended that for further detailed information they go to http://themedicalbiochemistrypage.org. This is the most complete resource for a more comprehensive study of the material reviewed in this book.

I would like to acknowledge the invaluable contributions provided by the McGraw-Hill editorial team of Michael Weitz, Karen Edmonson, Thomas DiPierro, Anthony Landi, and Laura Libretti. I give great thanks to the graphic design students, Matt Wilson, Janine Phelps, and Austin Woodall (at IUSM-Terre Haute host campus, Indiana State University) who were instrumental in preparing much of the artwork for this text. I would also like to acknowledge my students from the Indiana University School of Medicine-Terre Haute, class of 2017, for their willingness to serve as test subjects for many of the clinical vignette questions in this book. Finally, I would like to thank my colleagues for their support and encouragement throughout the process of completing this book.

This page intentionally left blank

PART I Biological Building Blocks of Cells and Tissues

CHAPTER 1

Amino Acids, Carbohydrates, Lipids, Nucleic Acids

CHAPTER OUTLINE

High-Yield Terms

pH: defined as the negative logarithm of the hydrogen ion (H^+) concentration of any given solution

pK_a: represents a relationship between pH and the equilibrium constant (K_a) for the dissociation of weak acids and bases in solution. Like pH, pK_a is the negative logarithm of K_a

Isoelectric point: defines the pH at which a molecule or substance carries no net electric charge

Hendersen-Hasselbalch equation: defines the relationship between pH and pK_a for any dissociation reaction of a weak acid or base such that when the concentration of any conjugate base (A^-) and its acid (HA) are equal, the pK_a for that dissociation is equivalent to the pH of the solution

Buffering: relates to the property that when the pH of a solution is close to the pK_a of a weak acid or base, the addition of more acid or base will not result in appreciable change in the pH

Amino Acids: Building Blocks for Protein

Chemical Nature of the Amino Acids

All peptides and polypeptides are polymers of α-amino acids. There are 20 α-amino acids relevant to the makeup of mammalian proteins (see later). Several other amino acids found in the body are in free or combined states (ie, not associated with peptides or proteins). These non–protein-associated amino acids perform specialized functions. Several of the amino acids found in proteins also serve functions distinct from the formation of peptides and proteins, for example, tyrosine in the formation of thyroid hormones or glutamate acting as a neurotransmitter.

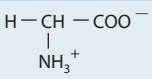
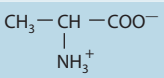
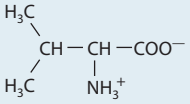
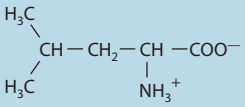
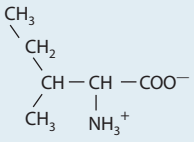
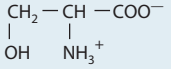
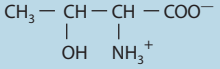
The α-amino acids in peptides and proteins (excluding proline) consist of a carboxylic acid (–COOH) and an amino ($–NH_2$) functional group attached to the same tetrahedral carbon atom. This carbon is the α-carbon. Distinct R groups, that distinguish one amino acid from another, are also attached to the α-carbon (except in the case of glycine where the R group is hydrogen). The fourth substitution on the tetrahedral α-carbon of amino acids is hydrogen.

Classification of Amino Acids

Each of the 20 α-amino acids found in proteins can be distinguished by the R group substitution on the α-carbon atom. There are 2 broad classes of amino acids based upon whether the R group is hydrophobic or hydrophilic (Table 1-1).

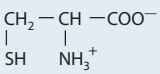
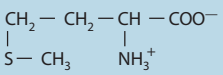
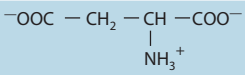
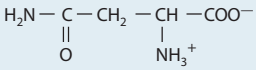
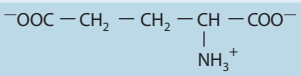
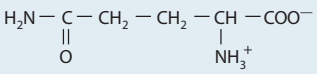
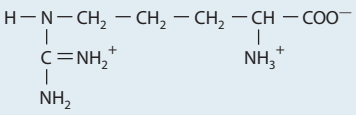
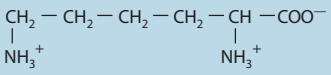
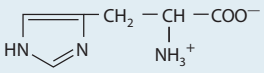
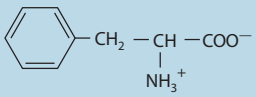
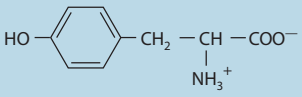
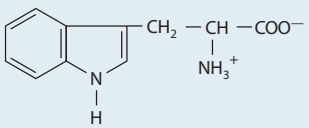
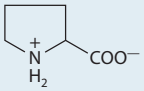
The hydrophobic amino acids tend to repel the aqueous environment and, therefore, reside predominantly in the interior of proteins. This class of amino acids does not ionize nor participate in the formation of H-bonds. The hydrophilic amino acids tend to interact with the aqueous environment, are often involved

TABLE 1-1: L-α-Amino Acids Present in Proteins

Name	*Symbol*	*Structural Formula*	*pK_1* α-COOH	*pK_2* α-NH_3^+	*pK_3* R Group
With Aliphatic Side Chains					
Glycine	Gly [G]		2.4	9.8	
Alanine	Ala [A]		2.4	9.9	
Valine	Val [V]		2.2	9.7	
Leucine	Leu [L]		2.3	9.7	
Isoleucine	Ile [I]		2.3	9.8	
With Side Chains Containing Hydroxylic (OH) Groups					
Serine	Ser [S]		2.2	9.2	About 13
Threonine	Thr [T]		2.1	9.1	About 13
Tyrosine	Tyr [Y]	See below.			

(*continued*)

TABLE 1-1: L-α-Amino Acids Present in Proteins (*continued*)

Name	*Symbol*	*Structural Formula*	pK_1 α-COOH	pK_2 α-NH_3^+	pK_3 R Group
With Side Chains Containing Sulfur Atoms					
Cysteine	Cys [C]		1.9	10.8	8.3
Methionine	Met [M]		2.1	9.3	
With Side Chains Containing Acidic Groups or Their Amides					
Aspartic acid	Asp [D]		2.1	9.9	3.9
Asparagine	Asn [N]		2.1	8.8	
Glutamic acid	Glu [E]		2.1	9.5	4.1
Glutamine	Gln [Q]		2.2	9.1	
With Side Chains Containing Basic Groups					
Arginine	Arg [R]		1.8	9.0	12.5
Lysine	Lys [K]		2.2	9.2	10.8
Histidine	His [H]		1.8	9.3	6.0
Containing Aromatic Rings					
Histidine	His [H]	See above.			
Phenylalanine	Phe [F]		2.2	9.2	
Tyrosine	Tyr [Y]		2.2	9.1	10.1
Tryptophan	Trp [W]		2.4	9.4	
Imino Acid					
Proline	Pro [P]		2.0	10.6	

Source: Murray RK, Bender DA, Botham KM, Kennelly PJ, Rodwell VW, Weil PA. *Harper's Illustrated Biochemistry*, 29th ed. New York, NY: McGraw-Hill; 2012.

High-Yield Concept

An amino acid with no ionizable R group would be electrically neutral at this pH and is termed a *zwitterion*. The term zwitterion defines an electrically neutral molecule with one positive and one negative charge at different sites within that molecule.

in the formation of H-bonds, and are predominantly found on the exterior surfaces of proteins or in the reactive centers of enzymes.

Acid–Base Properties of the Amino Acids

The α-COOH and α-NH_2 groups in amino acids are capable of donating or accepting protons (as are the acidic and basic R groups of the amino acids). As a result of their ionizing, the following ionic equilibrium reactions may be written in the basic form:

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

The equilibrium constant, K_a, for a reaction of this type is defined as:

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

For the α-COOH and α-NH_2 groups of the amino acids, these equilibrium reactions would be:

$$R\text{-}COOH \leftrightarrow R\text{-}COO^- + H^+$$

$$R\text{-}NH_3^+ \leftrightarrow R\text{-}NH_2 + H^+$$

The equilibrium reactions, as written, demonstrate that amino acids contain at least 2 weakly acidic groups. However, the carboxyl group is a far stronger acid than the amino group. At physiological pH (~7.4) the carboxyl group will be unprotonated and the amino group will be protonated.

Like typical organic acids, the acidic strength of the carboxyl, amino, and ionizable R groups in amino acids can be defined by the association or equilibrium constant, K_a, or more commonly the negative logarithm of K_a ($-\log K_a$), the pK_a. This value is determined for any given acid or base from the Hendersen-Hasselbalch equation:

$$pH = pK_a + \log\frac{[A^-]}{[HA]}$$

The net charge (the algebraic sum of all the charged groups present) of any amino acid, peptide, or protein will depend upon the pH of the surrounding aqueous environment. As the pH of a solution of an amino acid or protein changes so too does the net charge. This phenomenon can be observed during the titration of any amino acid or protein (Figure 1-1). When the net charge of an amino acid or protein is zero, the pH will be equivalent to the isoelectric point (pI).

Functional Significance of Amino Acid R Groups

In solution, it is the nature of the amino acid R groups that dictate structure–function relationships of peptides and proteins. The hydrophobic amino acids will generally be encountered in the interior of proteins shielded from direct contact with water. Conversely, the hydrophilic amino acids are generally found on the exterior of proteins as well as in the active centers of enzymatically active proteins. Indeed, it is the very nature of certain amino acid R groups that allow enzyme reactions to occur.

The imidazole ring of histidine allows it to act as either a proton donor or acceptor at physiological pH. Hence, it is frequently found in the reactive center of enzymes. Equally important is the ability of histidines

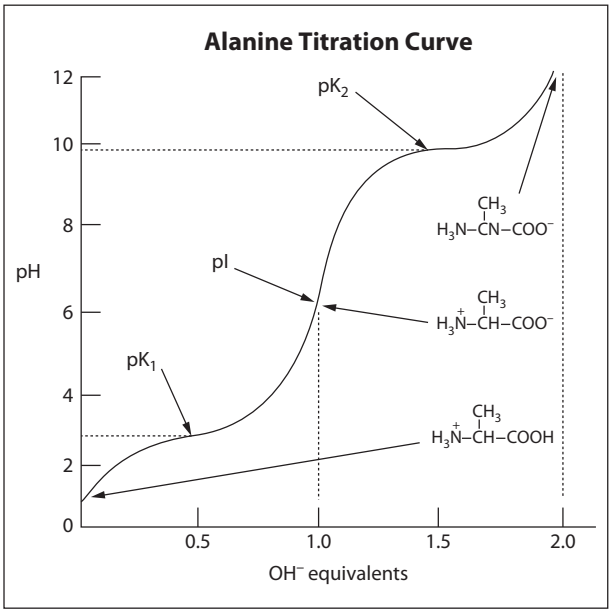


FIGURE 1-1: Titration of alanine. Reproduced with permission of themedicalbiochemistrypage, LLC.

in hemoglobin to buffer the H^+ ions from carbonic acid ionization in red blood cells. It is this property of hemoglobin that allows it to exchange O_2 and CO_2 at the tissues or lungs, respectively.

The primary alcohol of serine and threonine as well as the thiol (–SH) of cysteine allow these amino acids to act as nucleophiles during enzymatic catalysis. Additionally, the thiol of cysteine is able to form a disulfide bond with other cysteines:

Cysteine-SH + HS-Cysteine ↔ Cysteine-S-S-Cysteine

This simple disulfide is identified as *cystine*. The formation of disulfide bonds between cysteines present within proteins is important to the formation of active structural domains in a large number of proteins. Disulfide bonding between cysteines in different polypeptide chains of oligomeric proteins plays a crucial role in ordering the structure of complex proteins, for example, the insulin receptor.

Optical Properties of the Amino Acids

A tetrahedral carbon atom with 4 distinct constituents is said to be chiral. The one amino acid not exhibiting chirality is glycine since its R group is a hydrogen atom. **Chirality** describes the handedness of a molecule that is observable by the ability of a molecule to rotate the plane of polarized light either to the right (dextrorotatory) or to the left (levorotatory). All of the amino acids in proteins exhibit the same absolute steric configuration as L-glyceraldehyde. Therefore, they are all L-α-amino acids. D-amino acids are never found in proteins, although they exist in nature.

The aromatic R groups in amino acids absorb ultraviolet light with an absorbance maximum in the range of 280 nm. The ability of proteins to absorb ultraviolet light is predominantly due to the presence of the tryptophan, which strongly absorbs ultraviolet light.

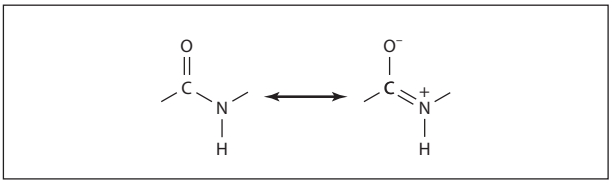


FIGURE 1-2: Resonance stabilization forms of the peptide bond. Murray RK, Bender DA, Botham KM, Kennelly PJ, Rodwell VW, Weil PA. *Harper's Illustrated Biochemistry*, 29th ed. New York, NY: McGraw-Hill; 2012.

The Peptide Bond

Peptide bond formation is a condensation reaction leading to the polymerization of amino acids into peptides and proteins. *Peptide* is the term used to define a small compound consisting of only a few amino acids. A number of hormones and neurotransmitters are peptides. Additionally, several antibiotics and antitumor agents are peptides. Proteins are polypeptides of greatly divergent length. The simplest peptide, a dipeptide, contains a single peptide bond formed by the condensation of the carboxyl group of one amino acid with the amino group of the second with the concomitant elimination of water. The presence of the carbonyl group in a peptide bond allows electron resonance stabilization to occur such that the peptide bond exhibits rigidity not unlike the typical –C=C– double bond. The peptide bond is, therefore, said to have partial double-bond character (Figure 1-2).

REVIEW QUESTIONS

1. Which of the following correctly defines the term pK_a?

A. equilibrium constant for the dissociation of HA to A^- and H^+
B. ion constant of water
C. negative log of the concentration of H^+
D. pH at which a molecule is neutrally charged
E. pH at which an equivalent distribution of acid and conjugate base exist in solution

Answer E: The logarithmic measure of the acid dissociation constant of an acid or base, termed pK_a, is defined as the pH at which the protonated and unprotonated molecular species are at equal concentrations. With respect to this question the protonated species can be represented as HA while the unprotonated species would be A^-.

2. Which of the following correctly defines the isoelectric point (pI) of an amino acid or protein?

A. the equilibrium constant for the ionization of the substance
B. the ion constant of water
C. negative log of the concentration of H^+
D. pH at which a molecule is electrically neutral
E. pH at which an equivalent distribution of acid and conjugate base exists in solution

Answer D: The **isoelectric point** is that pH at which a substance exhibits no net charge. In other

words, all the negative and positive charges, say for instance in a protein, are equal in number such that the molecule is electrically neutral.

3. The blood contains many compounds that serve to buffer the pH of the fluid such as bicarbonate and phosphate ions. Which of the following most correctly defines the meaning of the term buffering?
- **A.** a solution containing a large concentration of a base such that the pH will not change significantly when an acid is added
- **B.** a solution containing a large concentration of an acid such that the pH will not change significantly when more acid is added
- **C.** a solution or substance which resists changes in pH when small quantities of an acid or base are added to it
- **D.** pH at which a molecule or solution is neutrally charged
- **E.** pH at which an equivalent distribution of acid and conjugate base exists in solution

Answer C: A *buffer* is a molecule that tends to either bind or release hydrogen ions in order to maintain a particular pH. More precisely, a **buffer** is defined as a mixture of a conjugate acid–base pair that can resist changes in pH when small amounts of strong acids or bases are added to it.

4. Which of the following best describes the characteristics of polar amino acids?
- **A.** ionizable in water
- **B.** more likely to be exposed to water than to be found in the interior of a folded protein
- **C.** partially charged due to the oxygen atom in their carboxyl group
- **D.** partially charged due to fairly consistent sharing of electrons among atoms in their R group
- **E.** positively charged

Answer B: **Polar amino acids** are defined as those whose R groups are capable of forming hydrogen bonds with water. Due to this property they are also said to be hydrophilic (water loving) and, therefore, are most often found exposed to the aqueous environment on the surface of proteins as opposed to buried in the interior.

5. Which one of the following amino acids may be considered a hydrophobic amino acid at physiological pH of 7.4?
- **A.** arginine
- **B.** aspartic acid
- **C.** glycine
- **D.** isoleucine
- **E.** threonine

Answer D: Hydrophobic amino acids are those with side chains that do not like to reside in an aqueous environment. For this reason, these amino acids are more often found buried within the hydrophobic core of a protein, or within the lipid portion of a membrane.

6. The greatest buffering capacity at physiological pH would be provided by a protein rich in which of the following amino acids?
- **A.** alanine
- **B.** cysteine
- **C.** histidine
- **D.** proline
- **E.** tyrosine

Answer C: Histidine contains an imidazole ring as its R group. The nitrogen in this ring possesses a pK_a around 6.0, thus it is able to accept or donate a proton at physiological pH. This fact makes the amino acid an ideal buffering component of a protein containing several histidine residues.

Checklist

- ✓ All amino acids found in human proteins exist as L-α-amino acids, although D-amino acids are found in nature.
- ✓ All amino acids contain at least 2 weakly acidic groups, the α-NH_2 and the α-COOH groups. Many amino acids also contain weakly acidic function groups designated as the R group.
- ✓ The R groups of the amino acids determines their classification, for example, acidic or basic.

- ✓ The association constant, pK_a, can be determined for H^+ dissociation from any of the ionizable groups of each amino acid.
- ✓ As with all acids and bases, when titrating amino acids the pH at which the net charge on the molecule is neutral is referred to as the isoelectric point, pI.
- ✓ Amino acids form peptide bonds creating polymers called peptides and proteins. Due to resonance stabilization of electrons about the peptide bond, there is limited mobility leading to restricted protein conformations.

CHAPTER 2

Biological Building Blocks: Carbohydrates

CHAPTER OUTLINE

High-Yield Terms

Carbohydrate: any organic molecule composed exclusively of carbon, hydrogen, and oxygen where the hydrogen-to-oxygen ratio is usually 2:1, biological synonym is saccharide, commonly called sugars

Saccharide: synonym for carbohydrate in biological systems, lay terminology is sugar

Aldose: a monosaccharide that contains only one aldehyde (–CH=O) group per molecule

Ketose: a monosaccharide that contains only one ketone (–C=O) group per molecule

Enantiomer: one of 2 stereoisomers that are mirror images of each other, which cannot be superimposed

Anomeric carbon: the carbon of a carbohydrate bearing the reactive carbonyl about which free rotation into 2 distinct configurations (termed α and β) can occur when in the cyclic form

Glycosidic bond: any of the type of covalent bond that joins a carbohydrate molecule to another group

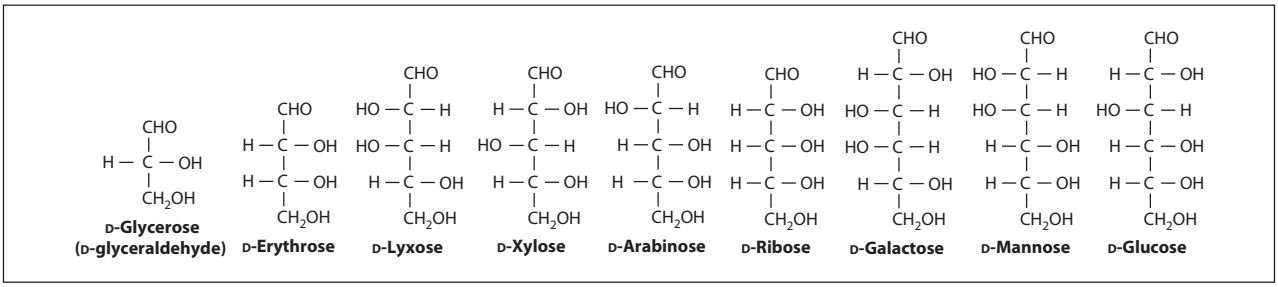


FIGURE 2-1: Examples of aldoses of physiologic significance. Murray RK, Bender DA, Botham KM, Kennelly PJ, Rodwell VW, Weil PA. *Harper's Illustrated Biochemistry*, 29th ed. New York, NY: McGraw-Hill; 2012.

Simple carbohydrates are biological compounds composed solely of carbon, oxygen, and hydrogen that generally contain large quantities of hydroxyl groups (–OH). In biochemistry, carbohydrate is synonymous with saccharide and the more common term, sugar. The simplest carbohydrates also contain either an aldehyde moiety and are termed *polyhydroxyaldehydes*, commonly called *aldoses* (Figure 2-1), or a ketone moiety and are termed *polyhydroxyketones*, commonly called *ketoses* (Figure 2-2).

All carbohydrates can be classified as either **monosaccharides**, **oligosaccharides**, or **polysaccharides**. Anywhere from 2 to 10 monosaccharide units, linked by glycosidic bonds, make up an oligosaccharide. Polysaccharides are much larger, generally containing hundreds of monosaccharide units. The presence of the hydroxyl groups allows carbohydrates to interact with the aqueous environment and to participate in hydrogen bonding, both within and between chains. Derivatives of the carbohydrates can contain nitrogen, phosphates, and sulfur compounds. Carbohydrates can also combine with lipid to form glycolipids (see Chapter 21) or with protein to form glycoproteins (see Chapter 38).

Carbohydrate Structure and Nomenclature

The predominant carbohydrates encountered in the body are structurally related to the aldotriose **glyceraldehyde** and to the ketotriose **dihydroxyacetone**. All carbohydrates contain at least one asymmetrical (chiral) carbon and are, therefore, optically active. In addition, carbohydrates can exist in either of the 2 conformations, as determined by the orientation of the hydroxyl group about the asymmetric carbon farthest from the carbonyl. With a few exceptions, those carbohydrates that are of physiological significance exist in the D-conformation. The mirror-image conformations, called **enantiomers**, are in the L-conformation (Figure 2-3).

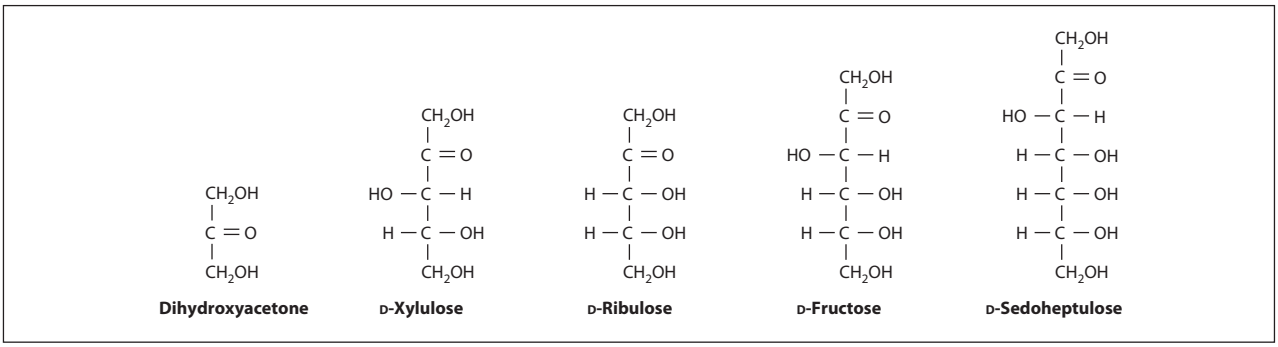


FIGURE 2-2: Examples of ketoses of physiologic significance. Murray RK, Bender DA, Botham KM, Kennelly PJ, Rodwell VW, Weil PA. *Harper's Illustrated Biochemistry*, 29th ed. New York, NY: McGraw-Hill; 2012.