5 Structures of the Major Compounds of the Body

The body contains compounds of great structural diversity, ranging from relatively simple sugars and amino acids to enormously complex polymers such as proteins and nucleic acids. Many of these compounds have common structural features related to their names, their solubility in water, the pathways in which they participate, or their physiologic function. Thus, learning the terminology used to describe individual compounds and classes of compounds can greatly facilitate learning biochemistry.

In this chapter, we describe the major classes of carbohydrates and lipids and some of the classes of nitrogen-containing compounds. The structures of amino acids, proteins, the nucleic acids, and vitamins are covered in more detail in subsequent chapters.

Functional Groups on Molecules. Organic molecules are composed principally of carbon and hydrogen. However, their unique characteristics are related to structures termed functional groups involving oxygen, nitrogen, phosphorus, or sulfur.

Carbohydrates. Carbohydrates, commonly known as sugars, can be classified by their carbonyl group (aldo- or ketosugars), the number of carbons they contain (e.g., pentoses, hexoses), or the positions of the hydroxyl groups on their asymmetric carbon atoms (**D- or L-sugars, stereoisomers**, or epimers). They can also be categorized according to their substitutents (e.g., amino sugars), or the number of monosaccharides (such as glucose) joined through glycosidic bonds (disaccharides, oligosaccharides, and polysaccharides.). Glycoproteins and proteoglycans have sugars attached to their protein components.

Lipids. Lipids are a group of structurally diverse compounds defined by their hydrophobicity; they are not very soluble in water. The major lipids of the human body are the **fatty acids**, which are esterified to **glycerol** to form **triacylglycerols** (triglycerides) or **phosphoacylglycerols** (phosphoglycerides). In the **sphingolipids**, a fatty acid is attached to sphingosine, which is derived from serine and another fatty acid. Glycolipids contain sugars attached to a lipid hydroxyl group. Specific polyunsaturated fatty acids are precursors of eicosanoids. The lipid cholesterol is a component of membranes, and the precursor of other compounds that contain the steroid nucleus, such as the **bile salts** and **steroid hormones**. Cholesterol is one of the compounds synthesized from a 5-carbon precursor called the isoprene unit.

Nitrogen-containing compounds. Nitrogen in amino groups or heterocyclic ring structures often carries a positive charge at neutral pH. Amino acids contain a carboxyl group, an amino group, and one or more additional carbons. **Purines**, pyrimidines, and pyridines have heterocyclic nitrogen-containing ring structures. Nucleosides comprise one of these ring structures attached to a sugar. The addition of a phosphate produces a nucleotide.



CH₃OH

CH₃CH₂OH Ethanol Methanol

The names of chemical groups are often incorporated into the common name of a compound, and denote important differences in chemical structure. For example, in the name ethanol, the "eth" denotes the ethyl group (CH_3CH_2 -), the "ol" denotes the alcohol group (OH), and the "an" denotes the single bonds between the carbon atoms. Methanol contains a methyl group (CH₃) instead of the ethyl group. Methanol (also called wood alcohol) is much more toxic to humans than ethanol, the alcohol in alcoholic beverages. Ingestion of methanol results in visual disturbances, bradycardia, coma, and seizures.



Hydrophobic molecules are transported in the blood bound to carrier proteins or incorporated into lipoprotein complexes that have a hydrophobic lipid core and a more polar surface.



THE WAITING ROOM

Di Abietes recovered from her bout of diabetic ketoacidosis and was discharged from the hospital (see Chapter 4). She has returned for a followup visit as an outpatient. She reports that she has been compliant with her recommended diet and that she faithfully gives herself insulin by subcutaneous injection twice daily. Her serum glucose levels are monitored in the hospital laboratory approximately every 2 weeks, and she self-monitors her blood glucose levels every other day.



Lotta Topaigne is a 47-year-old woman who came to the physician's office complaining of a severe throbbing pain in the right great toe that began 8 hours earlier. The toe has suffered no trauma but appears red and swollen. It is warmer than the surrounding tissue and is exquisitely tender to even light pressure. Ms. Topaigne is unable to voluntarily flex or extend the joints of the

FUNCTIONAL GROUPS ON BIOLOGIC COMPOUNDS I.

digit, and passive motion of the joints causes great pain.

A. Biologic Compounds

The organic molecules of the body consist principally of carbon, hydrogen, oxygen, nitrogen, sulfur, and phosphorus joined by covalent bonds. The key element is carbon, which forms four covalent bonds with other atoms. Carbon atoms are joined through double or single bonds to form the carbon backbone for structures of varying size and complexity (Fig. 5.1). Groups containing 1, 2, 3, 4, and 5 carbons plus hydrogen are referred to as methyl, ethyl, propionyl, butyl, and pentanyl groups, respectively. If the carbon chain is branched, the prefix "iso" is used. If the compound contains a double bond, "ene" is sometimes incorporated into the name. Carbon structures that are straight or branched with single or double bonds, but do not contain a ring, are called aliphatic.

Carbon-containing rings are found in a number of biologic compounds. One of the most common is the six-membered carbon-containing benzene ring, sometimes called a phenyl group (see Fig. 5.1). This ring has three double bonds, but the electrons are shared equally by all six carbons and delocalized in planes above and below the ring. Compounds containing the benzene ring, or a similar ring structure with benzene-like properties, are called aromatic.

B. Functional Groups

Biochemical molecules are defined both by their carbon skeleton and by structures called functional groups that usually involve bonds between carbon and oxygen, carbon and nitrogen, carbon and sulfur, and carbon and phosphate groups (Fig. 5.2). In carbon-carbon and carbon-hydrogen bonds, the electrons are shared equally between atoms, and the bonds are nonpolar and relatively unreactive. In carbon-oxygen and carbon-nitrogen bonds, the electrons are shared unequally, and the bonds are polar and more reactive. Thus, the properties of the functional groups usually determine the types of reactions that occur and the physiologic role of the molecule.

Functional group names are often incorporated into the common name of a compound. For example, a ketone might have a name that ends in "one" like acetone, and the name of a compound that contains a hydroxyl (alcohol or OH group) might end in "ol" (e.g., ethanol). The acyl group is the portion of the molecule that provides



Di Abietes had a metabolic acidosis resulting from an increased hepatic production of ketone bodies. Her response to therapy was followed with screening tests for ketone bodies in her urine that employed a paper strip containing nitroprusside, a compound that reacts with keto groups. Her blood glucose was measured with an enzymatic assay that is specific for the sugar D-glucose and will not react with other sugars.

> Α Single Double bond bond CH₂ Aliphatic isopentenyl group В



Fig. 5.1. Examples of aliphatic and aromatic compounds. A. An isoprene group, which is an aliphatic group. The "iso" prefix denotes branching, and the "ene" denotes a double bond. B. A benzene ring (or phenyl group), which is an aromatic group.

The ketone bodies synthesized in the liver are β -hydroxybutyrate and acetoacetate. A third ketone body, acetone, is formed by the nonenzymatic decarboxylation of acetoacetate.

OH
I
$$CH_3 - CH - CH_2 - COO^-$$

 β -Hydroxybutyrate

$$\begin{array}{cccc}
O & O & O \\
II & II & II \\
CH_3 - C - CH_2 - C - O^- \rightarrow CH_3 - C - CH_3 + CO_2 \\
Acetoacetate & Acetone
\end{array}$$

Acetone is volatile and accounts for the sweet mousy odor in the breath of patients such as Di Abietes when they have a ketoacidosis. What functional groups are present in each of these ketone bodies?



Fig. 5.2. Major types of functional groups found in biochemical compounds of the human body.



Which compound is glycerol, and which is glyceraldehyde?



Judging from the structures shown in the question on page 55 which compound is more oxidized, β -

hydroxybutyrate or acetoacetate? Which is more reduced?



 β -hydroxybutyrate and acetoacetate are carboxylates (dissociated carboxylic acids). Acetoacetate and

acetone contain keto/ketone groups. Because β -hydroxybutyrate contains an alcohol (hydroxyl) group and not a keto group, the general name of ketone bodies for these compounds is really a misnomer.

the carbonyl (-C=O) group in an ester or amide linkage. It is denoted in a name by an "yl" ending. For example, the fat stores of the body are tri**acyl**glycerols. Three acyl (fatty acid) groups are esterified to glycerol, a compound containing three alcohol groups. In the remainder of this chapter, we will bold the portions of names of compounds that refer to a class of compounds or a structural feature.

1. OXIDIZED AND REDUCED GROUPS

The carbon–carbon and carbon–oxygen groups are described as "oxidized" or "reduced" according to the number of electrons around the carbon atom. Oxidation is the loss of electrons and results in the loss of hydrogen atoms together with one or two electrons, or the gain of an oxygen atom or hydroxyl group. Reduction is the gain of electrons and results in the gain of hydrogen atoms or loss of an oxygen atom. Thus, the carbon becomes progressively more oxidized (and less reduced) as we go from an alcohol to an aldehyde or a ketone to a carboxyl group (see Fig. 5.2). Carbon–carbon double bonds are more oxidized (and less reduced) than carbon–carbon single bonds.

2. GROUPS THAT CARRY A CHARGE

Acidic groups contain a proton that can dissociate, usually leaving the remainder of the molecule as an anion with a negative charge (see Chapter 4). In biomolecules, the major anionic substituents are carboxylate groups, phosphate groups, or sulfate groups (the "ate" suffix denotes a negative charge) (Fig. 5.3). Phosphate groups attached to metabolites are often abbreviated as P with a circle around it, or just as "P", as in glucose-6-P.

Compounds containing nitrogen are usually basic and can acquire a positive charge (Fig. 5.4). Nitrogen has five electrons in its valence shell. If only three of these electrons form covalent bonds with other atoms, the nitrogen has no charge. If the remaining two electrons form a bond with a hydrogen ion or a carbon atom, the nitrogen carries a positive charge. Amines consist of nitrogen attached through single bonds to hydrogen atoms and to one or more carbon atoms. Primary amines,

such as dop**amine**, have one carbon–nitrogen bond. These amines are weak acids with a pK_a of approximately 9, so that at pH 7.4 they carry a positive charge. Secondary, tertiary, and quarternary amines have 2, 3, and 4 nitrogen–carbon bonds, respectively (see Fig. 5.4).

C. Polarity of Bonds and Partial Charges

Polar bonds are covalent bonds in which the electron cloud is denser around one atom (the atom with the greater electronegativity) than the other. Oxygen is more electronegative than carbon, and a carbon–oxygen bond is therefore polar, with the oxygen atom carrying a partial negative charge and the carbon atom carrying a partial positive charge (Fig. 5.5). In nonpolar carbon–carbon bonds and carbon–hydrogen bonds, the two electrons in the covalent bond are shared almost equally. Nitrogen, when it has only three covalent bonds, also carries a partial negative charge relative to carbon, and the carbon–nitrogen bond is polarized. Sulfur can carry a slight partial negative charge.

1. SOLUBILITY

Water is a dipolar molecule in which the oxygen atom carries a partial negative charge and the hydrogen atoms carry partial positive charges (see Chapter 4). For molecules to be soluble in water, they must contain charged or polar groups that can associate with the partial positive and negative charges of water. Thus, the solubility of organic molecules in water is determined by both the proportion of polar to nonpolar groups attached to the carbon–hydrogen skeleton and to their relative positions in the molecule. Polar groups or molecules are called hydrophilic (water-loving), and nonpolar groups or molecules are hydrophobic (water-fearing). Sugars such as glucose 6-phosphate, for example, contain so many polar groups that they are very hydrophilic and almost infinitely water-soluble (Fig. 5.6). The water molecules interacting with a polar or ionic compound form a hydration shell around the compound.

Compounds that have large nonpolar regions are relatively water insoluble. They tend to cluster together in an aqueous environment and form weak associations through van der Waals forces, often termed hydrophobic bonds. Hydrophobic compounds are essentially pushed together as the water molecules maximize the number of energetically favorable hydrogen bonds they can form with each other in the water lattice. Thus, lipids form droplets or separate layers in an aqueous environment (e.g., vegetable oils in a salad dressing).

2. REACTIVITY

Another consequence of bond polarity is that atoms that carry a partial (or full) negative charge are attracted to atoms that carry a partial (or full) positive charge and vice versa. These partial or full charges dictate the course of biochemical reactions which follow the same principles of electrophilic and nucleophilic attack characteristic of organic reactions in general. The partial positive charge on the carboxyl carbon attracts more negatively charged groups and accounts for many of the reactions of carboxylic acids. An ester is formed when a carboxylic acid and an alcohol combine, splitting out water (Fig. 5.7). Similarly, a thioester is formed when an acid combines with a sulfhydryl group, and an amide is formed when an acid combines with an amine. Similar reactions result in the formation of a phosphoester from phosphoric acid and an alcohol and in the formation of an anhydride from two acids.

D. Nomenclature

Biochemists use two systems for the identification of the carbons in a chain. In the first system, the carbons in a compound are numbered, starting with the carbon in



Carboxylate group



Phosphate group

Sulfate group

Fig. 5.3. Examples of anions formed by dissociation of acidic groups. At physiologic pH, carboxylic acids, phosphoric acid, and sulfuric acid are dissociated into hydrogen ions and negatively charged anions.



Testosterone

In medicine and biochemistry, the common or trivial names of compounds are used rather than the systematic nomenclature favored by chemists. Sometimes such names reflect functional groups, classes of compounds or the source from which the compound was first isolated. The compound testosterone provides an example. It was first isolated from monkey testis, the "ster" in its name denotes the steroid ring structure, and the "one" denotes a ketone group.

"A" contains three **alcohol** groups and is called glycerol. Compound B contains an **aldehyde group**, and is called glycer**aldehyde**.

Acetoacetate is more oxidized than β -hydroxybutyrate. The carbon in the keto group contains one less hydrogen than the carbon to which the OH group is attached. It has lost an electron.

the most oxidized group (e.g., the carboxyl group). In the second system, the carbons are given Greek letters, starting with the carbon next to the most oxidized group. Hence, the compound shown in Figure 5.8 is known as 3-hydroxybutyrate or β-hydroxybutyrate.

CARBOHYDRATES П.

Α. Monosaccharides

Acid

Acid

Acid

acid

 $R_1 - C$

HO-

OH

Acid

OH

-ОН

OH

Simple monosaccharides consist of a linear chain of three or more carbon atoms, one of which forms a carbonyl group through a double bond with oxygen (Fig. 5.9). The other carbons of an unmodified monosaccharide contain hydroxyl groups, resulting in the general formula for an unmodified sugar of C_nH_{2n}O_n. The suffix "ose" is used for the names of sugars. If the carbonyl group is an aldehyde, the sugar is an aldose; if the carbonyl group is a ketone, the sugar is a ketose. Monosaccharides are also classified according to their number of carbons: Sugars containing 3, 4, 5, 6, and 7 carbons are called trioses, tetroses, pentoses, hexoses, and heptoses, respectively. Fructose is therefore a ketohexose (see Fig. 5.9), and glucose is an aldohexose (see Fig. 5.6).

Alcohol

HSR/

Sulfhydryl

 R_2

Amine

HOR



Dopamine (a primary amine)



Choline (a quaternary amine)

Fig. 5.4. Examples of amines. At physiologic pH, many amines carry positive charges.



Fig. 5.5. Partial charges on carbon-oxygen, carbon-nitrogen, and carbon-sulfur bonds.



Glucose 6-phosphate

Fig. 5.6. Glucose 6-phosphate, a very polar and water-soluble molecule.



P-OR

O II C – OR

Ester

Thioester

. C

Amide

Fig. 5.7. Formation of esters, thioesters, amides, phosphoesters and anhydrides.



Fig. 5.8. Two systems for identifying the carbon atoms in a compound. This compound is called 3-hydroxybutyrate or β -hydroxybutyrate.



Fig. 5.9. Fructose is a ketohexose.

The stereospecificity of D-glucose is still frequently denoted in medicine by the use of its old name, dextrose. A solution used for intravenous infusions in patients is a 5% (5 g/100 mL) solution of dextrose.



Are D-mannose and D-galactose stereoisomers? Are they epimers of each other? (see Fig. 5.12)



D-Glyceraldehyde L-Glyceraldehyde



Fig. 5.10. D- and L-Glyceraldehyde. The carbon in the center contains four different substituent groups arranged around it in a tetrahedron. A different arrangement creates an isomer that is a nonsuperimposable mirror image. If you rotate the mirror image structure so that groups 1 and 2 align, group 3 will be in the position of group 4, and group 4 will be in position 3.

1. D- AND L-SUGARS

A carbon atom that contains four different chemical groups forms an asymmetric (or chiral) center (Fig. 5.10). The groups attached to the asymmetric carbon atom can be arranged to form two different isomers that are mirror images of each other and not superimposable. Monosaccharide stereoisomers are designated D or L based on whether the position of the hydroxyl group furthest from the carbonyl carbon matches D or L glyceraldehyde (Fig. 5.11). Although a more sophisticated system of nomenclature using the designations of (R) and (S) is generally used to describe the positions of groups on complex molecules such as drugs, the D and L designation is still used in medicine for describing sugars and amino acids. Because glucose (the major sugar in human blood) and most other sugars in human tissues belong to the D series, sugars are assumed to be D unless L is specifically added to the name.

2. STEREOISOMERS AND EPIMERS

Stereoisomers have the same chemical formula but differ in the position of the hydroxyl group on one or more of their asymmetric carbons (Fig. 5.12). A sugar with n asymmetric centers has 2^n stereoisomers unless it has a plane of symmetry. Epimers are stereoisomers that differ in the position of the hydroxyl group at only one of their asymmetric carbons. D-glucose and D-galactose are epimers of each other, differing only at position 4, and can be interconverted in human cells by enzymes called epimerases. D-mannose and D-glucose are also epimers of each other.

3. RING STRUCTURES

Monosaccharides exist in solution mainly as ring structures in which the carbonyl (aldehyde or ketone) group has reacted with a hydroxyl group in the same molecule to form a five- or six-membered ring (Fig. 5.13). The oxygen that was on the hydroxyl group is now part of the ring, and the original carbonyl carbon, which now contains a –OH group, has become the anomeric carbon atom. An hydroxyl group on the anomeric carbon drawn down below the ring is in the α -position; drawn up above the ring, it is in the β position. In the actual three-dimensional structure, the ring is not planar but usually takes a "chair" conformation in which the hydroxyl groups are located at a maximal distance from each other.

In solution, the hydroxyl group on the anomeric carbon spontaneously (nonenzymatically) changes from the α to the β position through a process called mutarotation. When the ring opens, the straight chain aldehyde or ketone is formed. When the ring closes, the hydroxyl group may be in either the α or the β position (Fig. 5.14). This process occurs more rapidly in the presence of cellular enzymes called mutarotases. However, if the anomeric carbon forms a bond with another molecule, that bond is fixed in the α or β position, and the sugar cannot mutarotate. Enzymes are specific for α or β bonds between sugars and other molecules, and react with only one type.

4. SUBSTITUTED SUGARS

Sugars frequently contain phosphate groups, amino groups, sulfate groups or N-acetyl groups. Most of the free monosaccharides within cells are phosphorylated at their terminal carbons, which prevents their transport out of the cell (see glucose 6-phosphate in Fig. 5.6). Amino sugars such as galactos**amine** and glucos**amine** contain an amino group instead of a hydroxyl group on one of the carbon atoms, usually carbon 2 (Fig. 5.15). Frequently this amino group has been acetylated to form an *N*-acetylated sugar. In complex molecules termed proteoglycans, many of



Fig. 5.11. D-Glyceraldehyde and D-glucose. These sugars have the same configuration at the asymmetric carbon atom farthest from the carbonyl group. Both belong to the D series. Asymmetric carbons are shown in blue.



Fig. 5.12. Examples of stereoisomers. These compounds have the same chemical formula (C₆H₁₂O₆) but differ in the positions of the hydroxyl groups on their asymmetric carbons (in blue).



They are stereoisomers, but not epimers of each other. They have the same chemical formula, but differ in the position of two hydroxyl groups.



Fig. 5.13. Pyranose and furanose rings formed from glucose and fructose. The anomeric carbons are highlighted.



Fig. 5.14. Mutarotation of glucose in solution, with percentages of each form at equilibrium.

the *N*-acetylated sugars also contain negatively charged sulfate groups attached to a hydroxyl group on the sugar.

5. OXIDIZED AND REDUCED SUGARS

Sugars can be oxidized at the aldehyde carbon to form an acid. Technically the compound is no longer a sugar, and the ending on its name is changed from "-ose" to "onic acid" or "onate" (e.g., gluc**onic** acid, Fig. 5.16). If the carbon containing the terminal hydroxyl group is oxidized, the sugar is called a uronic acid (e.g., gluc**uronic** acid).

If the aldehyde of a sugar is reduced, all of the carbon atoms contain alcohol (hydroxyl) groups, and the sugar is a polyol (e.g., sorbitol)(see Fig. 5.16). If one of

Oxidized sugars



β-D-Glucuronate



N–Acetyl–β–D–glucosamine

Fig. 5.15. An *N*-acetylated amino sugar. The *N*-denotes the amino group to which the acetyl group is attached, shown in the blue box.

Proteoglycans contain many long unbranched polysaccharide chains attached to a core protein. The polysaccharide chains, called glycosaminoglycans, are composed of repeating disaccharide units containing oxidized acid sugars (such as glucuronic acid), sulfated sugars, and N-acetylated amino sugars. The large number of negative charges causes the glycosaminoglycan chains to radiate out from the protein so that the overall structure resembles a bottlebrush. The proteoglycans are essential parts of the extracellular matrix, the aqueous humor of the eye, secretions of mucus-producing cells, and cartilage.

Reduced sugars





Fig. 5.16. Oxidized and reduced sugars. The affected group is shown in blue. Gluconic acid (D-gluconate) is formed by oxidation of the glucose aldehyde carbon. Glucuronic acid is formed by oxidation of the glucose terminal OH group. Sorbitol, a sugar alcohol, is formed by reduction of the glucose aldehyde group. Deoxyribose is formed by reduction of ribose.

the hydroxyl groups of a sugar is reduced so that the carbon contains only hydrogen, the sugar is a deoxysugar, such as the **deoxy**ribose in DNA.

B. Glycosides

1. N- AND O-GLYCOSIDIC BONDS

The hydroxyl group on the anomeric carbon of a monosaccharide can react with an -OH or an -NH group of another compound to form a glyc**osidic** bond. The linkage may be either α or β , depending on the position of the atom attached to the anomeric carbon of the sugar. *N*-glycosidic bonds are found in nucle**osides** and nucle**otides**. For example, in the adenosine moiety of ATP, the nitrogenous base adenine is linked to the sugar ribose through a β -*N*-glycosidic bond (Fig. 5.17). In contrast, *O*-glycosidic bonds, such as those found in lactose, join sugars to each other or attach sugars to the hydroxyl group of an amino acid on a protein.

2. DISACCHARIDES, OLIGOSACCHARIDES, AND POLYSACCHARIDES

A disaccharide contains two monosaccharides joined by an *O*-glycosidic bond. Lactose, which is the sugar in milk, consists of galactose and glucose linked through a $\beta(1\rightarrow 4)$ bond formed between the β –OH group of the anomeric carbon of galactose and the hydroxyl group on carbon 4 of glucose (see Fig. 5.17). Oligosaccharides contain from 3 to roughly 12 monosaccharides linked together. They are often found



Fig. 5.17. *N*- and *O*-glycosidic bonds. Adenosine triphosphate (ATP) contains a β , *N*-glycosidic bond. Lactose contains an *O*-glycosidic $\beta(1 \rightarrow 4)$ bond. Glycogen contains α -1,4 and α -1,6 *O*-glycosidic bonds.

attached through *N*- or *O*-glycosidic bonds to proteins to form **glyco**proteins (see Chapter 6). Polysaccharides contain tens to thousands of monosaccharides joined by glycosidic bonds to form linear chains or branched structures. Amylopectin (a form of starch) and glycogen (the storage form of glucose in human cells) are branched polymers of glucosyl residues linked through $\alpha(1 \rightarrow 4)$ and $\alpha(1 \rightarrow 6)$ bonds.

III. LIPIDS

A. Fatty Acids

Fatty acids are usually straight aliphatic chains with a methyl group at one end (called the ω -carbon) and a carboxyl group at the other end (Fig. 5.18). Most fatty acids in the human have an even number of carbon atoms, usually between 16 and 20. Saturated fatty acids have single bonds between the carbons in the chain, and unsaturated fatty acids contain one or more double bonds. The most common saturated fatty acids present in the cell are palmitic acid (C16) and stearic acid (C18). Although these two fatty acids are generally called by their common names, shorter fatty acids are often called by the Latin word for the number of carbons, such as octanoic acid (8 carbons) and decanoic acid (10 carbons).

Monunsaturated fatty acids contain one double bond, and polyunsaturated fatty acids contain two or more double bonds (see Fig. 5.18). The position of a double bond is designated by the number of the carbon in the double bond that is closest to the carboxyl group. For example, oleic acid, which contains 18 carbons and a double bond between position 9 and 10, is designated 18:1, Δ^9 . The number 18 denotes the number of carbon atoms, 1 (one) denotes the number of double bonds, and Δ^9

The melting point of a fatty acid increases with chain length and decreases with the degree of saturation. Thus, fatty acids with many double bonds, such as those in vegetable oils, are liquid at room temperature and saturated fatty acids, such as those in butterfat, are solids. Lipids with lower melting points are more fluid at body temperature and contribute to the fluidity of our cellular membranes.



Fig. 5.18. Saturated fatty acids and unsaturated fatty acids. In stearic acid, the saturated fatty acid at the top of the figure, all the atoms are shown. A more common way of depicting the same structure is shown below. The carbons are either numbered starting with the carboxyl group or given Greek letters starting with the carbon next to the carboxyl group. The methyl (or ω) carbon at the end of the chain is always called the ω -carbon regardless of the chain length. 18:0 refers to the number of carbon atoms (18) and the number of double bonds (0). In the unsaturated fatty acids shown, not all of the carbons are numbered, but note that the double bonds are *cis* and spaced at three-carbon intervals. Both ω 3 and ω 6 fatty acids are required in the diet.



The eicosanoids are a group of hormone-like compounds produced by many cells in the body.

They are derived from polyunsaturated fatty acids such as arachidonic acid that contain 20 carbons (eicosa) and have 3, 4, or 5 double bonds. The prostaglandins, thromboxanes, and leukotrienes belong to this group of compounds.



Palmitoleic acid, oleic acid, and arachidonic acid are the most common unsaturated fatty acids in the cell. Palmitoleic acid is a 16:1, Δ^9

fatty acid. How would you name it as an ω fatty acid?



Fig. 5.19. *Cis* and *trans* double bonds in fatty acid side chains. Note that the *cis* double bond causes the chain to bend.



Triacyl-sn-glycerol

Fig. 5.20. A triacylglycerol. Note that carbons 1 and 3 of the glycerol moiety are not identical. The broad end of each arrowhead is closer to the reader than the narrow, pointed end.

denotes the position of the double bond between the 9th and 10th carbon atoms. Oleic acid can also be designated 18:1(9), without the Δ . Fatty acids are also classified by the distance of the double bond closest to the ω end (the methyl group at the end farthest from the carboxyl group). Thus oleic acid is an ω 9 fatty acid, and linolenic acid is an ω 3 fatty acid. Arachidonic acid, a polyunsaturated fatty acid with 20 carbons and 4 double bonds, is an ω 6 fatty acid that is completely described as 20:4, $\Delta^{5,8,11,14}$.

The double bonds in most naturally occurring fatty acids are in the *cis* configuration (Fig. 5.19). The designation *cis* means that the hydrogens are on the same side of the double bond and the acyl chains on the other side. In *trans* fatty acids, the acyl chains are on opposite sides of the double bond. Margarine and the fat used in preparing French fries are probably the major sources of *trans* fatty acids found in humans. Trans fatty acids are produced by the chemical hydrogenation of polyunsaturated fatty acids in vegetable oils and are not a natural food product.

C. Acylglycerols

An **acyl**glycerol comprises glycerol with one or more fatty acids (the **acyl** group) attached through ester linkages (Fig. 5.20). Monoacylglycerols, diacylglycerols, and triacylglycerols contain 1, 2, or 3 fatty acids esterified to glycerol, respectively. Tri**acyl**glycerols rarely contain the same fatty acid at all three positions and are therefore called mixed triacylglycerols. Unsaturated fatty acids, when present, are most often esterified to carbon 2. In the three-dimensional configuration of glycerol, carbons 1 and 3 are not identical, and enzymes are specific for one or the other carbon.

D. Phosphoacylglycerols

Phosphoacylglycerols contain fatty acids esterified to position 1 and 2 of glycerol and a phosphate (alone or with a substituent) attached to carbon 3. If only a phosphate group is attached to carbon 3, the compound is **phospha**tidic acid (see Fig. 5.21). Phosphatidic acid is a precursor for the synthesis of the other phosphoacyl-glycerols.

Phosphatidylcholine is one of the major phosphoacylglycerols found in membranes (see Fig. 5.21). The amine is positively charged at neutral pH, and the phosphate negatively charged. Thus, the molecule is amphipathic; it contains large polar and nonpolar regions. Phosphatidylcholine is also called lecithin. Removal of a fatty acyl group from a phosphoacyl glycerol leads to a lyso-lipid. For example, removing the fatty acyl group from lecithin forms lysolecithin.

E. Sphingolipids

Sphingolipids do not have a glycerol backbone; they are formed from sphingosine. (Fig. 5.22). Shingosine is derived from serine and a specific fatty acid, palmitate. Ceramides are amides formed from sphingosine by attaching a fatty acid to the



Fig. 5.21. Phosphoacylglycerols. Phospholipids found in membranes, such as phosphatidylcholine, have a polar group attached to the phosphate.





Fig. 5.22. Sphingolipids, derivatives of ceramide. The structure of ceramide is shown at the bottom of the figure. The portion of ceramide shown in blue is sphingosine. The NH and OH were contributed by serine. Different groups are added to the hydroxyl group of ceramide to form sphingomyelin, galactocerebrosides, and gangliosides. NANA = N-acetylneuraminic acid, also called sialic acid; Glc = glucose; Gal = galactose; GalNAc = N-acetylgalactosamine.

amino group. Various sphingolipids are then formed by attaching different groups to the hydroxyl group on ceramide. As reflected in the names for cerebrosides and gangliosides, these sphingolipids contain sugars attached to the hydroxyl group of ceramide through glycosidic bonds. They are glycolipids (more specifically, glycosphingolipids). Sphingomyelin, which contains a phophorylcholine group attached to ceramide, is a component of cell membranes and the myelin sheath around neurons.

Е. **Steroids**

Steroids contain a four-ring structure called the steroid nucleus (Fig. 5.23). Cholesterol is the steroid precursor in human cells from which all of the steroid hormones are synthesized by modifications to the ring or C20 side chain. Although cholesterol is not very water soluble, it is converted to amphipathic water-soluble bile salts such as cholic acid. Bile salts line the surfaces of lipid droplets called micelles in the lumen of the intestine, where they keep the droplets emulsified in the aqueous environment.

Cholesterol is one of the compounds synthesized in the human from branched 5carbon units with one double bond called an isoprenyl unit (see Fig. 5.1A). Isoprenyl



Palmitoleic acid is an ω7 fatty acid. It has one double bond between the 9th and 10th carbons. It has 16 carbons, like palmitic acid, so the double bond must be at the 7th carbon from the $\boldsymbol{\omega}$ end.



Fig. 5.23. Cholesterol and its derivatives. The steroid nucleus is shown in blue. The bile salt, cholic acid, and the steroid hormone 17β-estradiol are derived from cholesterol and contain the steroid ring structure.

What structural features account for the differences in the solubility of cholesterol, estradiol and cholic acid in the body? (see Fig. 5.23)

coenzyme Q in humans and vitamin A in plants.

units are combined in long chains to form other structures, such as the side chains of

IV. NITROGEN-CONTAINING COMPOUNDS

Nitrogen, as described in Section IB2, is an electronegative atom with two unshared electrons in its outer valence shell. At neutral pH, the nitrogen in amino groups is usually bonded to four other atoms and carries a positive charge. However, the presence of nitrogen atom in an organic compound will increase its solubility in water, whether the nitrogen is charged or uncharged.

A. Amino Acids

Amino acids are compounds that contain an amino group and a carboxylic acid group. In proteins, the amino acids are always $L-\alpha$ amino acids (the amino group is attached to the α carbon in the L-configuration) (Fig. 5.24). These same amino acids also serve as precursors of nitrogen-containing compounds in the body, such as phosphatidylcholine (see Fig. 5.21) and are the basis of most human amino acid metabolism. However, our metabolic reactions occasionally produce an amino acid that has a β or γ amino group, such as the neurotransmitter γ -aminobutyric acid (see Fig. 5.24). However, only α amino acids are incorporated into proteins.

B. Nitrogen-Containing Ring Structures

PURINES, PYRIMIDINES AND PYRIDINES 1.

Nitrogen is also a component of ring structures referred to as heterocyclic rings or nitrogenous bases. The three most common types of nitrogen-containing rings in the



Fig. 5.24. The structure of amino acids.



Although D-amino acids are not usually incorporated into proteins in living organisms, they serve many other functions in bacteria, such as

synthesis of cross-links in cell walls.

body are purines (e.g., adenine), pyrimidines (e.g., thymine), and pyridines (e.g., the vitamins nicotinic acid, also called niacin, and pyridoxine, also called vitamin B_6) (Fig.5.25). The suffix "ine" denotes the presence of nitrogen (amine) in the ring. The pyrimidine uracil is an exception to this general type of nomenclature. The utility of these nitrogen-containing ring structures lies in the ability of the nitrogen to form hydrogen bonds and to accept and donate electrons while still part of the ring. In contrast, the unsubstituted aromatic benzene ring, in which electrons are distributed equally among all six carbons (see Fig. 5.1), is nonpolar, hydrophobic, and relatively unreactive.

2. NUCLEOSIDES AND NUCLEOTIDES

Nitrogenous bases form nucleosides and nucleotides. A nucleoside consists of a nitrogenous base joined to a sugar, usually ribose or deoxyribose, through an *N*-gly-cosidic bond (see Fig. 5.17). If phosphate groups are attached to the sugar, the compound becomes a nucleotide. In the name of the nucleotide adenosine triphosphate (ATP), the addition of the ribose is indicated by the name change from adenine to aden**osine** (for the glyc**osidic** bond). Monophosphate, diphosphate, or triphosphate are added to the name to indicate the presence of 1, 2, or 3 phosphate groups in the nucleotide. The structures of the nucleotides that serve as precursors of DNA and RNA are discussed in more detail in Section Three, Chapter 12.

3. TAUTOMERS

In many of the nitrogen-containing rings, the hydrogen can shift to produce a tautomer, a compound in which the hydrogen and double bonds have changed position (i.e., $-N=C-OH \rightarrow -NH-C=O$) (Fig. 5.26). Tautomers are considered the same compound, and the structure may be represented either way. Generally one tautomeric form is more reactive than the other. For example, in the two tautomeric forms of uric acid, a proton can dissociate from the enol form to produce urate.

V. FREE RADICALS

Radicals are compounds that have a single electron, usually in an outer orbital. Free radicals are radicals that exist independently in solution or in a lipid environment.

(Keto form)

Compounds that cannot be oxidized as fuels in the human are often excreted in the urine. Chemical modifications often occur in the liver, kidney, or other tissues that inactivate or detoxify the chemicals, make them more water-soluble, or otherwise target such molecules for excretion. Uric acid, the basis of Lotta Topaigne's pain, is excreted in the urine (see Fig. 5.26). Judging from the similarity in structure, do you think it is derived from the degradation of purines, pyrimidines, or pyridines?

Cholesterol is composed almost entirely of CH₂ groups and is therefore water-insoluble. Estradiol is likewise relatively water-insoluble. However, cholic acid contains a hydrophilic carboxyl group, and three hydroxyl groups. As shown by the dashed lines, the three hydroxyl groups all lie on one side of the molecule, thus creating a hydrophilic surface.

Lotta Topaigne's gout is caused by depositions of monosodium urate crystals in the joint of her big toe. At a blood pH of 7.4, all of the uric acid has dissociated a proton to form urate, which is not very water-soluble and forms crystals of the Na⁺ salt. In the more acidic urine generated by the kidney, the acidic form, uric acid, may precipitate to form kidney stones.



Fig. 5.26. Tautomers of uric acid. The tautomeric form affects the reactivity. The enol form dissociates a proton to form urate.

(Enol form)



Free radicals are not just esoteric reactants; they are the agents of cell death and destruction. They are

involved in all chronic disease states (e.g., coronary artery disease, diabetes mellitus, arthritis, and emphysema) as well as acute injury (e.g., radiation, strokes, myocardial infarction, and spinal cord injury). Through free radical defense mechanisms in our cells, we can often restrict the damage attributed to the "normal" aging process.



Uric acid contains two rings and is similar to the purines adenine and guanine (adenine is shown in Fig. 5.25). In fact, it is the urinary excretion product formed from the oxidation of these two purine bases. It is not very soluble in water, particularly if the pH is near the pK_a of its acidic OH group. If present in excess amounts, Na⁺ urate tends to precipitate in joints, causing the severe pain of gout experienced by Ms. Topaigne.



The reducing sugar test. The reducing sugar test was used for detection of sugar in the urine long before specific enzymatic assays for glucose and galac-

tose became available. In this test, the aldehyde group of a sugar is oxidized as it donates electrons to copper; the copper becomes reduced and produces a blue color. In alkaline solution, keto sugars (e.g., fructose) also react in this test because they form tautomers that are aldehydes. Ring structures of sugars will also react, but only if the ring can open (i.e., it is not attached to another compound through a glycosidic bond). Until a specific test for fructose becomes available, a congenital disease resulting in the presence of fructose in the urine is indicated by a positive reducing sugar test and negative results in the specific enzymatic assays for glucose or galactose.



Fig. 5.27. Glucose oxidase.

Although many enzymes generate radicals as intermediates in reactions, these are not usually released into the cell to become free radicals.

Many of the compounds in the body are capable of being converted to free radicals by natural events that remove one of their electrons, or by radiation. Radiation, for example, dissociates water into the hydrogen atom and the hydroxyl radical:

$$H_2O \leftrightarrow H \bullet + OH \bullet$$

In contrast, water normally dissociates into a proton and the negatively charged hydroxyl ion. The hydroxyl radical forms organic radicals by taking one electron (as H•) from a compound such as an unsaturated membrane lipid, which then has a single unpaired electron and is a new radical.

Compounds that are radicals may be written with, or without, the radical showing. For example, nitrogen dioxide, a potent, reactive, toxic radical present in smog and cigarette smoke, may be designated in medical and lay literature as NO₂ rather than NO₂•. Superoxide, a radical produced in the cell and that is the source of much destruction, is correctly written as the superoxide anion, O_2^{-} . However, to emphasize its free radical nature, the same compound is sometimes written as O_2^{-} . If a compound is designated as a radical in the medical literature, you can be certain that it is a reactive radical, and that its radical nature is important for the pathophysiology under discussion. (Reactive oxygen and nitrogen-containing free radicals are discussed in more detail in Chapter 24).

CLINICAL COMMENTS

Dianne Abietes. The severity of clinical signs and symptoms in patients with diabetic ketoacidosis (DKA), such as Di Abietes, is directly correlated with the concentration of ketone bodies in the blood. Direct quantitative methods for measuring acetoacetate and β -hydroxybutyrate are not routinely available. As a result, clinicians usually rely on semiquantitative reagent strips (Ketostix, Bayer Diagnostics, Mishawaha, IN) or tablets (Acetest, Bayer Diagnostics, Mishawaha, IN) to estimate the level of acetoacetate in the blood and the urine. The nitroprusside on the strips and in the tablets reacts with acetoacetate and to a lesser degree with acetone (both of which have ketone groups), but does not react with β -hydroxybutyrate (which does not have a ketone group). β -hydroxybutyrate is the predominant ketone body present in the blood of a patient in DKA, and its concentration could decline at a disproportionately rapid rate compared with that of acetoacetate and acetone. Therefore, tests employing the nitroprusside reaction to monitor the success of therapy in such a patient may be misleading.

In contrast to the difficulty of ketone body measurements, diabetic patients can self-monitor blood glucose levels at home, thereby markedly decreasing the time and expense of the many blood glucose determinations they need. Blood obtained from a finger prick is placed on the pad of a plastic strip. The strip has been impregnated with an enzyme (usually the bacterial enzyme glucose oxidase) that specifically converts the glucose in the blood to a compound (hydrogen peroxide, H_2O_2) that reacts with a dye to produce a color (Fig. 5.27). The intensity of the color, which is directly proportionate to the concentration of glucose in the patient's blood, is read on an instrument called a blood glucose monitor.

Lotta Topaigne. Ms. Topaigne has acute gouty arthritis (podagra) involving her right great toe. Polarized light microscopy of the fluid aspirated from the joint space showed crystals of monosodium urate phagocytosed by white blood cells. The presence of the relatively insoluble urate crystals within the joint space activates an inflammatory cascade leading to the classic components of joint inflammation (pain, redness, warmth, swelling, and limitation of joint motion).

BIOCHEMICAL COMMENTS



Chlorinated Aromatic Hydrocarbon Environmental Toxins. As a result of human endeavor, toxic compounds containing

chlorinated benzene rings have been widely distributed in the environment. The pesticide DDT and the class of chemicals called dioxins provide examples of chlorinated aromatic hydrocarbons and structurally related compounds that are very hydrophobic and poorly biodegraded (Fig. 5.28). As a consequence of their persistence and lipophilicity, these chemicals are concentrated in the adipose tissue of fish, fish-eating birds, and carnivorous mammals, including humans.

DDT, a chlorinated biphenyl, was widely used in the United States as an herbicide between the 1940s and 1960s (see Fig. 5.28). Although it has not been used in this country since 1972, the chlorinated benzene rings are resistant to biodegradation, and U.S. soil and water are still contaminated with small amounts. DDT is still used in other parts of the world. Because this highly lipophilic molecule is stored in the fat of animals, organisms accumulate progressively greater amounts of DDT at each successive stage of the food chain. Fish-eating birds, one of the organisms at the top of the food chain, have declined in population because of the effect of DDT on the thickness of their eggshells. DDT is not nearly as toxic in the human, although long-term exposure or exposure to high doses may cause reversible neurologic symptoms, hepatotoxic effects, or cancer.

Dioxins, specifically chlorinated dibenzo-p-dioxins (CDDs), constitute another class of environmental toxins that are currently of great concern (see Fig. 5.28). They have been measured at what is termed background levels in the blood, adipose tissue, and breast milk of all humans tested. CDDs are formed as a byproduct during the production of other chlorinated compounds and herbicides, and from the chlorine bleaching process used by pulp and paper mills. They are released during the incineration of industrial, municipal, and domestic waste, and during the combustion of fossil fuels, and are found in cigarette smoke and the exhaust from gasoline and diesel fuels. They can also be formed from the combustion of organic matter during forest fires. They enter the atmosphere as particulate matter, are vaporized, and can spread large distances to enter soil and water.

As humans at the top of the food chain, we have acquired our background levels of dioxins principally through the consumption of food, primarily meat, dairy products,





Fig. 5.28. Environmental toxins. Dichlorodiphenyl trichlorethane (DDT) is a member of a class of aromatic hydrocarbons that contain two chlorinated benzene (phenyl) rings joined by a chlorinated ethane molecule. Chlorodibenzo-p-dioxin's (CDDs) are a related class of more than 75 chlorinated hydrocarbons that all contain a dibenzo-p-dioxin (DD) molecule comprising two benzene rings joined via two oxygen bridges at adjacent carbons on each of the benzene rings. 2,3,7,8 Tetrachlorodibenzo-p-dioxin, shown above, is one of the most toxic and the most extensively studied. Chlorinated dibenzofurans (CDF) are structurally and toxicologically related.



Most of this chapter has dealt with the names and structures of compounds that are nutrients for the human or metabolites that can be produced from reactions in the human body. However, our health is also affected by naturally occurring and man-made xenobiotic compounds (compounds that have no nutrient value and are not produced in the human) that we ingest, inhale, or absorb through our skin. DDT and dioxins provide examples of chlorinated aromatic hydrocarbons, an important class of manmade chemicals present in the environment.

The accumulation of DDT in adipose tissue may be protective in the human because it decreases the amount of DDT available to pass through nonpolar lipid membranes to reach neurons in the brain, or pass through placental membranes to reach the fetus. Eventually we convert DDT to more polar metabolites that are excreted in the urine. However, some may pass with lipid into the breast milk of nursing mothers.

Most of what is known about the toxicity of dioxins in the human comes from individuals exposed incidentally or chronically to higher levels (e.g., industrial accidents or presence in areas sprayed with Agent Orange or other herbicides contaminated with dioxins.). The lowest dose effects are probably associated with thymic atrophy and decreased immune response, chloracne and related skin lesions, and neoplasia (cancer). Dioxins can cross into the placenta to cause developmental and reproductive effects, decreased prenatal growth, and prenatal mortality.

and fish. Once in the human body, dioxins are stored in human fat and adipose tissue, and have an average half-life of approximately 5 to 15 years. They are unreactive, poorly degraded, and not readily converted to more water-soluble compounds that can be excreted in the urine. They are slowly excreted in the bile and feces, and together with lipids enter the breast milk of nursing mothers.

Suggested References

- Nomenclature of chemical compounds. Most undergraduate organic textbooks provide a more detailed account of the nomenclature used for organic molecules, including the R,S nomenclature for chiral centers
- Environmental toxins. Good literature reviews for many environmental toxins are published by the U.S. Department of Health and Human Services: Public Health Service Agency for Toxic Substances and Disease Registry, including: Toxicological Profile for Chlorinated Dibenzo-p-dioxins, 1998, and the Toxicological Profile for 4,4'-DDT, 4,4'-DDE, 4,4'-DDD (Update), 1994.



REVIEW QUESTIONS-CHAPTER 5

Directions: Select the single best answer for each of the questions below. Base your answers on your knowledge of nomenclature. You need not recognize any of the structures shown to answer the questions.

- 1. Which of the following is a universal characteristic of water-soluble organic compounds?
 - (A) They are composed of carbon and hydrogen atoms.
 - (B) They must contain a group that has a full negative charge.
 - (C) They must contain a group that has a full positive charge.
 - (D) They contain polar groups that can hydrogen bond with water.
 - (E) They contain aromatic groups.

2. CH₂OH–CH₂–CH₂–COO⁻

A patient was admitted to the hospital emergency room in a coma. Laboratory tests found high levels of the compound shown above in her blood. On the basis of its structure (and your knowledge of the nomenclature of functional groups), you identify the compound as

- (A) methanol (wood alcohol).
- (B) ethanol (alcohol).
- (C) ethylene glycol (antifreeze).
- (D) β -hydroxybutyrate (a ketone body).
- (E) γ -hydroxybutyrate (the "date rape" drug).
- 3. A patient was diagnosed with a deficiency of the lysosomal enzyme α -glycosidase. The name of the deficient enzyme suggests that it hydrolyzes a glycosidic bond, which is a bond formed
 - (A) through multiple hydrogen bonds between two sugar molecules.
 - (B) between the anomeric carbon of a sugar and an O-H (or N) of another molecule.
 - (C) between two anomeric carbons in polysaccharides.
 - (D) internally between the anomeric carbon of a monosaccharide and its own 5th carbon hydroxyl group.
 - (E) between the carbon containing the aldol or keto group and the α carbon.

- 4. A patient was diagnosed with a hypertriglyceridemia. This condition is named for the high blood levels of lipids composed of
 - (A) 3 fatty acyl groups attached to a glycerol backbone.
 - (B) a glycerol lipid containing a phosporylcholine group.
 - (C) a sphingolipid containing three fatty acyl groups.
 - (D) three glycerol moieties attached to a fatty acid.
 - (E) three glyceraldehyde moieties attached to a fatty acid.
- 5. A patient was diagnosed with a sphingolipidoses, which are congenital diseases involving the inability to degrade sphingolipids. All sphingolipids have in common
 - (A) a glycerol backbone.
 - (B) ceramide.
 - (C) phosphorylcholine.
 - (D) N-acetylneuraminic acid (NANA).
 - (E) a steroid ring structure to which sphingosine is attached.