

## Chapter 2

# Introduction to Biomolecules

The complexity of even the simplest of life forms, the single cell, cannot be overstated. Nevertheless, from a chemical perspective, cellular components can be segregated into macromolecules (DNA, RNA, proteins, etc.), relatively simple molecules (amino acids, monosaccharides, and lipids), and their precursors:  $\text{CO}_2$ ,  $\text{H}_2\text{O}$ , and  $\text{NH}_3$ . In general, the macromolecules tend to be polymers of small biomolecules; however, each of these molecules, whether simple or complex, is involved in a myriad of intricate metabolic reactions. A case in point is the monosaccharide glucose which is synthesized from  $\text{H}_2\text{O}$  and  $\text{CO}_2$ . When degraded to its precursors, it provides the cell with its energy requirements for such diverse processes as macroscopic movement as well as the synthesis of complex macromolecules. In addition, glucose is the fundamental building block of macromolecules such as starch and cellulose. This basic theme, in which the cell uses a simple small molecule in a multitude of processes, is typical of how relatively small biomolecules are used in living systems.

In this chapter we will consider the chemistry and properties of four small biomolecules: amino acids, carbohydrates, lipids, and nucleotides and their roles in metabolism.

## 2.1 Amino Acids

Amino acids are the most versatile small biomolecules. They fulfill a number of extremely important roles in biology. These include: building blocks of proteins which are polymers of amino acids, precursors of hormones, and precursors of molecules with specialized physiological functions, e.g., the neurotransmitter dopamine and the hormone thyroxine are both derivatives of the amino acid tyrosine.

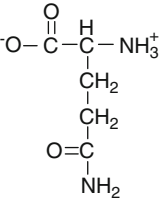
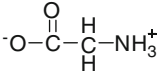
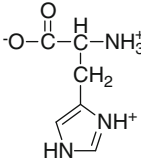
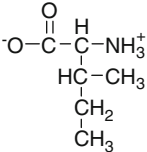
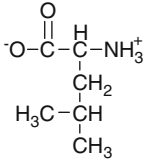
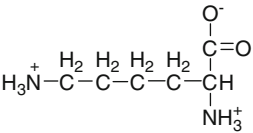
As the name implies, amino acids contain amino and carboxyl groups. They can be divided into groups based on acidic, basic, and neutral properties when dissolved in water. They are also classified according to solubility, e.g., hydrophilic and hydrophobic.

**Table 2.1** Amino acid structures, names and acid–base properties

Amino acid	Abbreviations	Structure	Acid and basic properties		
			p <i>K</i> <sub>1</sub>	p <i>K</i> <sub>2</sub>	p <i>K</i> <sub>3</sub>
		$\begin{array}{c} \text{O} \\ \parallel \\ ^-\text{O}-\text{C}-\text{C}-\text{NH}_3^+ \\   \\ \text{CH}_3 \end{array}$			
Alanine	Ala, A		2.35	9.87	
		$\begin{array}{ccccccc} & & \text{NH}_2^+ & & & & \text{O}^- \\ & &    & & & &   \\ \text{H}_2\text{N}-\text{C}- & \text{N}-\text{C}- & \text{H}_2-\text{C}- & \text{H}_2-\text{C}- & \text{H}-\text{C}- & \text{C}=\text{O} \\ & & & & &   \\ & & & & & \text{NH}_3^+ \end{array}$			
Arginine	Arg, R		1.82	8.99	12.5
		$\begin{array}{c} \text{O} \\ \parallel \\ ^-\text{O}-\text{C}-\text{C}-\text{NH}_3^+ \\   \\ \text{CH}_2 \\   \\ \text{O}=\text{C} \\   \\ \text{NH}_2 \end{array}$			
Asparagine	Asn, N		2.14	8.72	
		$\begin{array}{c} \text{O} \\ \parallel \\ ^-\text{O}-\text{C}-\text{C}-\text{NH}_3^+ \\   \\ \text{CH}_2 \\   \\ \text{O}=\text{C} \\   \\ \text{O}^- \end{array}$			
Aspartic acid	Asp, D		1.99	3.90	9.90
		$\begin{array}{c} \text{O} \\ \parallel \\ ^-\text{O}-\text{C}-\text{C}-\text{NH}_3^+ \\   \\ \text{CH}_2 \\   \\ \text{SH} \end{array}$			
Cysteine	Cys, C		1.92	8.37(SH)	10.7
		$\begin{array}{c} \text{O} \\ \parallel \\ ^-\text{O}-\text{C}-\text{C}-\text{NH}_3^+ \\   \\ \text{CH}_2 \\   \\ \text{CH}_2 \\   \\ \text{O}=\text{C} \\   \\ \text{O}^- \end{array}$			
Glutamic acid	Glu, E		2.10	4.07	9.47

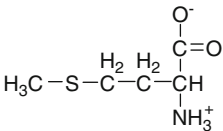
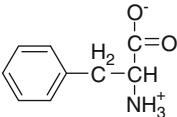
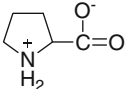
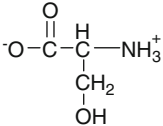
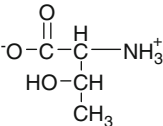
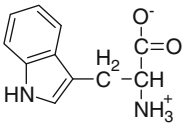
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Table 2.1 (continued)

Amino acid	Abbreviations	Structure	Acid and basic properties		
			p <i>K</i> <sub>1</sub>	p <i>K</i> <sub>2</sub>	p <i>K</i> <sub>3</sub>
Glutamine	Gln, Q		2.17	9.13	
Glycine	Gly, G		2.35	9.78	
Histidine	His, H		1.80	6.04	9.33
Isoleucine	Ile, I		2.32	9.76	
Leucine	Leu, L		2.33	9.74	
Lysine	Lys, K		2.16	9.06 (α-NH <sub>3</sub> <sup>+</sup> )	10.5

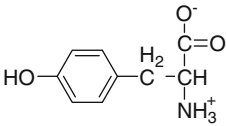
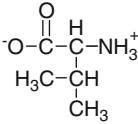
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**Table 2.1** (continued)

Amino acid	Abbreviations	Structure	Acid and basic properties		
			p <i>K</i> <sub>1</sub>	p <i>K</i> <sub>2</sub>	p <i>K</i> <sub>3</sub>
Methionine	Met, M		2.13	9.28	
Phenylalanine	Phe, F		2.20	9.31	
Proline	Pro, P		1.95	10.6	
Serine	Ser, S		2.19	9.23	
Threonine	Thr, T		2.09	9.10	
Tryptophan	Trp, W		2.46	9.41	

(continued)

Table 2.1 (continued)

Amino acid	Abbreviations	Structure	Acid and basic properties		
			p <i>K</i> <sub>1</sub>	p <i>K</i> <sub>2</sub>	p <i>K</i> <sub>3</sub>
Tyrosine	Tyr, Y		2.20	9.21	10.5 (phenol)
Valine	Val, V		2.29	9.74	

There are 20 so-called amino acids in proteins; however, one of these, proline, is in fact an imino acid. Nineteen of the 20 amino acids are optically active, i.e., they are capable of rotating plane polarized light either to the right (*dextrorotary*) or left (*levorotary*). All 19 amino acids have an amino group at the α-position (C-2). Similarly, all amino acids have a carboxyl group in the 1-position.

Table 2.1 illustrates the amino acids found in proteins along with the p*K* values for the various functional groups associated with these molecules. Also included in the table are the one- and three-letter abbreviations for the individual amino acids.

2.1.1 Essential Amino Acids

Of the 20 amino acids found in proteins, 8 are said to be *essential amino acids*. These amino acids are: Met, Val, Leu, Ile, Lys, Phe, Thr, and Trp. Essential amino acids, as opposed to nonessential amino acids, are required in the diet for maintenance and sustenance. The elimination of a single essential amino acid from the diet will lead ultimately to death even on an otherwise nutritionally adequate ration. Children need two additional amino acids in their diets; His and Arg. The nutritionally essential nature of certain amino acids was determined by feeding healthy volunteer students synthetic diets lacking a single amino acid and measuring their nitrogen balance (*N<sub>B</sub>*) which is equal to dietary nitrogen intake minus nitrogen excretion in the urine and feces. Thus

$$N_B = N_{\text{Intake}} - N_{\text{Excretion}},$$

in so-called normal human beings  $N_B$  equals 0, whereas it is positive in growing individuals and negative in the case of wasting diseases. Plants have the ability to synthesize all amino acids from  $\text{CO}_2$ ,  $\text{H}_2\text{O}$ ,  $\text{NH}_3$ , and inorganic salts including sulfate.

Bacteria, such as *Escherichia coli* are similar to plants in their nutritional requirements but also require an organic carbon source such as glucose.

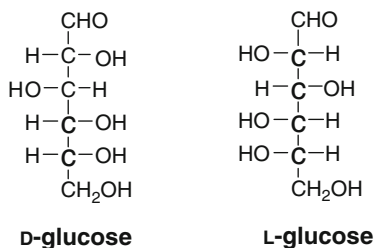
### 2.1.2 Optical Properties

In 1874 Jacobus van't Hoff, who is referred to as the “father of stereochemistry” suggested that a carbon atom with four bound substituents exhibits tetrahedral geometry [1]. In addition, he surmised that if these substituents were different entities, two different stereoisomers (*enantiomers*) of this compound could exist. These enantiomers would also have different optical properties. Shortly after van't Hoff's discovery was made, the French chemist J.A. Le Bel came to the same conclusion independently. Although Le Bel did not win the Nobel Prize for his work (see below) he did share the Davey Medal with van't Hoff.

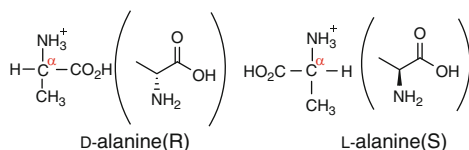
With the exception of glycine (amino acetic acid), all of the amino acids are optically active. Because the  $\alpha$ -carbon atom of amino acids is a chiral center, with the exception of glycine whose  $\alpha$ -carbon is bound to two hydrogen atoms, amino acids can exist as enantiomers (nonsuperimposable mirror images). Both isoleucine (2S,3S) and threonine (2S,3R) are diastereomers because they contain two chiral carbon centers. R and S nomenclature is rarely used in reference to amino acids; trivial names and D and L being the designations most frequently encountered.

As one may recall from organic chemistry, the D and L designations were first proposed by Emil Fischer using D- and L-glucose as examples (Fig. 2.1) [2]. In fact, his fundamental research on sugars proved, experimentally, the proposal of van't Hoff for the tetrahedral geometry of the carbon atom. Both van't Hoff and Fischer received the first and second Nobel prizes in chemistry, respectively.

These compounds are by definition enantiomers. By analogy with these aldohexose sugars, amino acids use identical nomenclature for enantiomers, e.g., alanine (Fig. 2.2).



**Fig. 2.1** The structures of the enantiomers, D- and L-glucose, as proposed by Emil Fischer

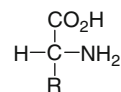


**Fig. 2.2** The structures of D and L-alanine with carbon 2 designated the  $\alpha$ -carbon atom. By placing the amino group up and the carboxyl group either to the right (D) or left (L) these structures are analogous to the D and L forms of sugars. In terms of R,S stereochemical nomenclature, D corresponds to (R) and L to (S). Abbreviated amino acids structures are shown in parenthesis.

It is important to note that although both D- and L-amino acids exist in nature, proteins are made up exclusively of L-amino acids.

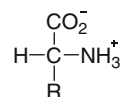
Because of the  $pK$  values of amino and carboxyl groups, amino acids will always carry a charge, i.e., the uncharged form of amino acids *cannot* exist, e.g., the structure shown in Fig. 2.3.

**Fig. 2.3** The structure of an uncharged amino acid

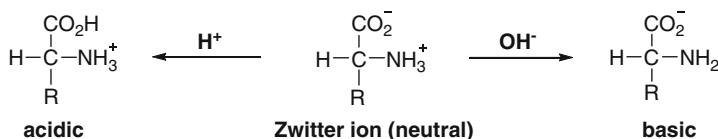


On the other hand, amino acids although charged, may not exhibit a net charge, e.g., in Fig. 2.4.

**Fig. 2.4** The structure of an amino acid with no net charge



If we consider this structure, referred to as the *Zwitter ion* form, it is clear that amino acids can exist in net acid and net basic states (Fig. 2.5).



**Fig. 2.5** The effect of acids and bases on the amino and carboxyl groups of an amino acid

The *Zwitter ion* form is said to be at the amino acid's *isoelectric point* ( $pI$ ), i.e., it will not migrate in an electrical field. Depending upon the pH, the amino acid may be above (negative) or below (positive) its  $pI$ .

Obviously an amino acid below its  $pI$  will migrate to the cathode, and that above its  $pI$  will migrate to the anode when exposed to an electrical field. It is important to

note that the  $pK$  values for amino acids in solution may be markedly different for analogous functional groups in proteins where the dielectric constants are very different from that of water.

When a neutral amino acid such as glycine is placed in water, the resulting pH is 6.1. The equation used to calculate the pH of neutral amino acids in solution is:

$$\text{pH} = \frac{pK_1 + pK_2}{2} = \frac{2.4 + 9.8}{2} = 6.1.$$

For a diacidic amino acid such as glutamate,  $pK_3$ , the  $pK$  of the amino group is not a factor

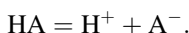
$$\text{pH} = \frac{pK_1 + pK_2}{2},$$

in the calculation because the amount of the charged amino group ( $\text{NH}_3^+$ ) is extremely small and does not contribute significantly to the solution pH.

In the case of dibasic amino acids in solution, the pH is:

$$\text{pH} = \frac{pK_2 + pK_3}{2}.$$

Amino acids, because they are *weak* acids and bases, can act as *buffers*. Buffers are defined as weak acids or bases and their conjugate salts that resist changes in pH upon the addition of acids ( $\text{H}^+$ ) or bases ( $\text{OH}^-$ ). The rationale for the action of an acidic buffer (HA) and its salt ( $\text{A}^-$ ) is as follows:



When an acid ( $\text{H}^+$ ) is added to the buffer, it combines with the salt ( $\text{A}^-$ ), thus effectively removing the added  $\text{H}^+$  from solution, and the pH of the solution remains unchanged. When a base ( $\text{OH}^-$ ) is added to the buffer, a proton ( $\text{H}^+$ ) reacts with the added base ( $\text{OH}^-$ ), and HA dissociates to maintain the equilibrium and  $\text{H}^+$  concentration constant.

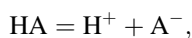
As a rule, buffers are effective when the [salt]/[acid] ratio is greater than 1/10 or less than 10/1. Buffering capacity decreases when these values are exceeded.

A very useful equation, when preparing a buffer, is the *Henderson–Hasselbach* equation:

$$\text{pH} = \text{p}K_a + \log \frac{[\text{salt}]}{[\text{acid}]}.$$



The derivation of the Henderson–Hasselback equation is relatively straight forward:



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

Taking logs of both sides of this equation gives:

$$\log K_a = \log \text{H}^+ + \log \text{A}^- - \log \text{HA}.$$

Multiplying both sides of this equation by  $-1$  and rearranging, gives the Henderson–Hasselbach equation.

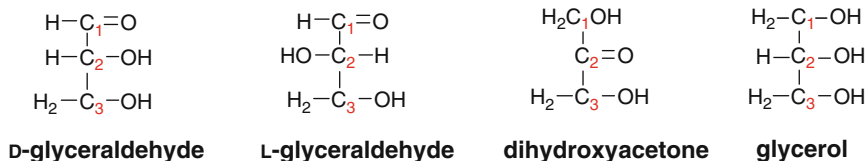
## 2.2 Carbohydrates

Carbohydrates, also known as sugars or saccharides, are defined as polyhydroxy aldehydes and ketones and/or their derivatives. They are the most abundant molecules found in nature and are involved in both dynamic and structural roles, e.g., they are focal points in energy metabolism and are major intermediates in plant structure and metabolism. They may exist in nature as carbohydrates per se, but they may also be associated chemically with lipids and proteins.

Simple carbohydrates are called sugars, whereas complex carbohydrates are referred to as glycoconjugates, i.e., glycolipids and glycoproteins.

### 2.2.1 Monosaccharides

1. By definition the simplest monosaccharides are the trioses; two glyceraldehydes, dihydroxyacetone, and glycerol (Fig. 2.6).
2. It is clear from these triose structures that monosaccharides can exist either as *aldo* or *keto sugars*.
3. The aldo and keto sugar carbons are numbered as illustrated for the trioses.



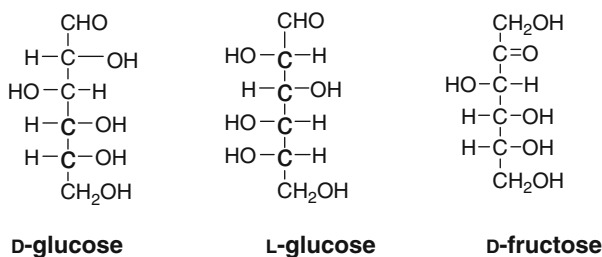
**Fig. 2.6** The structures of the trioses glyceraldehyde and dihydroxyacetone and the numbering of their carbon atoms. D- and L-glyceraldehyde are enantiomers – nonsuperimposable mirror images

### 2.2.1.1 D and L Designation of Monosaccharides

The designation D or L has nothing to do with rotational properties of plane polarized light when it passes through a sugar solution, e.g., D-glucose rotates plane polarized light to the right whereas D-fructose rotates plane polarized light to the left, i.e., D-glucose is dextrorotary and D-fructose is levorotary.

The secondary hydroxyl group *farthest* from the aldo or keto group determines whether the sugar is D or L. If it is on the right-hand side, the sugar is D; on the left side, it is L. Examples are D- and L-glucose and D-fructose (Fig. 2.7).

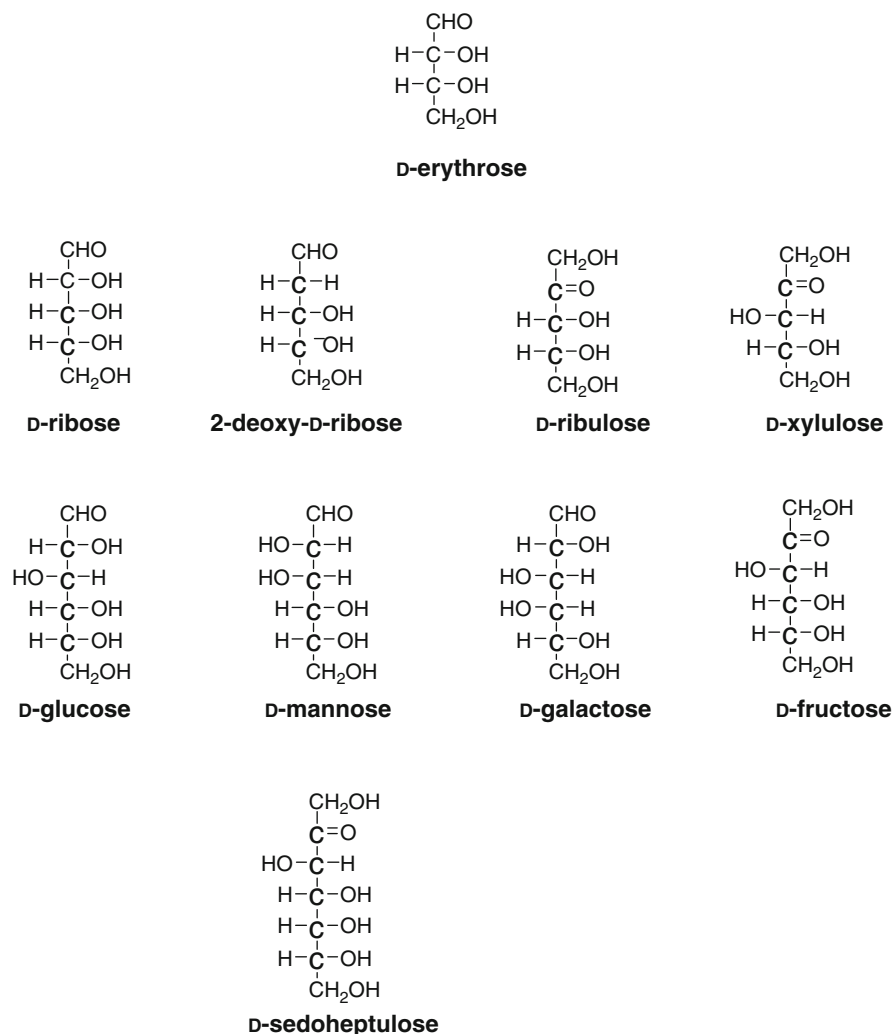
Note that D-glucose is the mirror image of L-glucose. The D-sugars are the principal carbohydrates that occur naturally.



**Fig. 2.7** Structures of the aldohexoses, D- and L-glucose and the ketohexose D-fructose

### 2.2.1.2 Monosaccharides that Play Important Roles in Metabolism

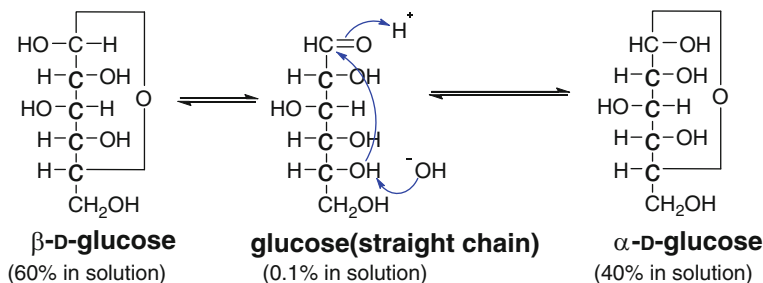
Three, four, five, six, and seven carbon monosaccharides and their derivatives play important roles in metabolism. Figure 2.6 illustrates the structures of important triose sugars. Other sugars that play significant metabolic roles are shown in Fig. 2.8.



**Fig. 2.8** The structures of biologically important four, five, six, and seven carbon sugars

### 2.2.1.3 Mutarotation: A Form of Tautomerization

If one views the straight chain form of glucose, it is clear that there are four chiral carbon centers. From the equation  $n^2$  where  $n$  equals the number of chiral centers, there should be 16 isomers of glucose; however, there are 32 isomers of glucose. This was recognized by Emil Fischer [3] and is a result of mutarotation, which is base-catalyzed (Fig. 2.9).



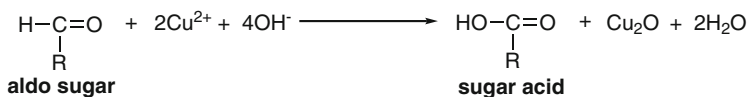
**Fig. 2.9** Mechanism for the mutarotation of D-glucose in basic solution

The  $\alpha$  and  $\beta$  forms of glucose are referred to as *anomers* and the C-1 carbons are called *anomeric carbons*. Both forms of glucose are *hemiacetals*. If the hydrogen atom of the C-1 hydroxyl is replaced by an R-group, the compound is an *acetal*.

### 2.2.1.4 Reducing Sugars

Sugars such as glucose form acids when exposed to strong bases and certain metal ions (Fig. 2.10).

In the case of Fehling's solution or Benedict's reagent, the  $\text{Cu}^{2+}$  is reduced to  $\text{Cu}^{1+}$  and the reddish color of copper oxide is observed. Such sugars are referred to as *reducing sugars*. It is important to note that the oxidation occurs at the anomeric carbon atom of the reducing sugar.



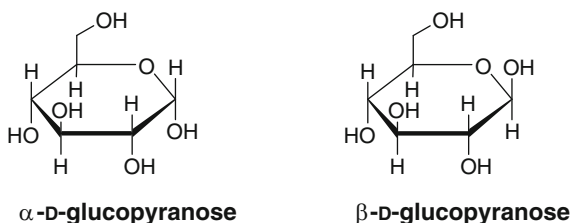
**Fig. 2.10** The oxidation of an aldo sugar to a sugar acid by an alkaline solution of  $\text{Cu}^{2+}$

### 2.2.1.5 Pyranoses and Furanoses

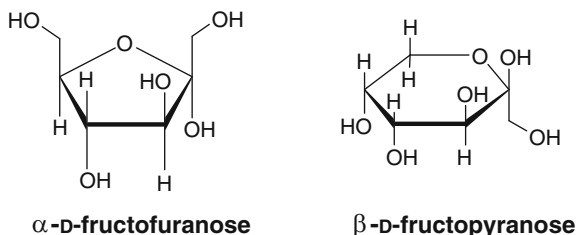
In solution, the straight chain forms of aldo and ketopentoses and hexoses represent a very small fraction of the sugars. Haworth used the pyranose and furanose rings to more correctly describe the structures of the sugars. The following glucose structures,  $\alpha$  and  $\beta$  pyranoses, are illustrated by *Haworth projections* (Fig. 2.11). In the case of D-fructose, the Haworth projections are shown in Fig. 2.12.

The primary forms of D-fructose are pyranoses, unless the C-6 hydroxyl is substituted with a phosphoryl group. When the C-1 OH of glucopyranose or the C-2 OH of fructofuranose reacts with alcohols, the products are the acetals; glucopyranosides, and fructofuranosides, respectively.

**Fig. 2.11**  $\beta$ -D-Glucopyranose, the primary structure of D-glucose in solution



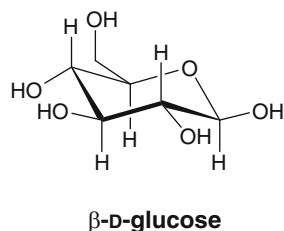
**Fig. 2.12** The pyranose and furanose forms of D-fructose, showing the hemiketal hydroxyl group in the  $\alpha$  and  $\beta$  positions



The Haworth projections, as useful as they are, do not accurately depict the bond angles and structures of the sugars and therefore their conformations. Illustrated here is the C-1, or normal conformation of  $\beta$ -D-glucopyranose which is much more faithful to the true structure of D-glucose than the other projections. In this structure all of the hydroxyl groups are in the equatorial position (parallel to the nonadjacent side of the ring), whereas all of the hydrogen atoms are in the axial position (perpendicular to the ring's axis of symmetry) (Fig. 2.13).

Biochemists tend to use both Haworth projections and chair forms of sugars interchangeably, and this practice will be continued in this text.

**Fig. 2.13** The C-1, or normal conformation of  $\beta$ -D-glucopyranose. All of the hydroxyl groups, associated with the ring, are equatorial and all the hydrogens axial

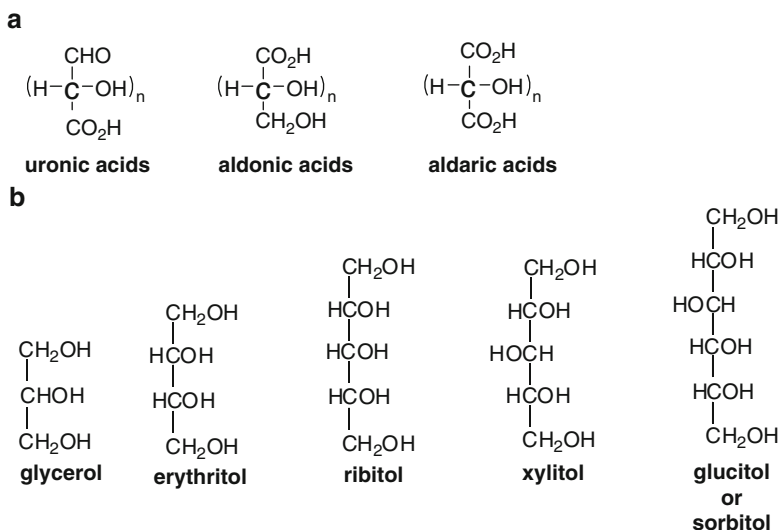


### 2.2.1.6 Sugar Acids and Alcohols

Sugars can be oxidized either chemically or enzymatically. The nomenclature used to describe these acids is shown in Fig. 2.14(a):

In the case of glucose, the acids would be glucuronic, gluconic, and glucaric (saccharic) acids based on the general structures above. Sugars also form alcohols

when reduced either chemically or enzymatically. Some of the common sugar alcohols are illustrated in Fig. 2.14(b).

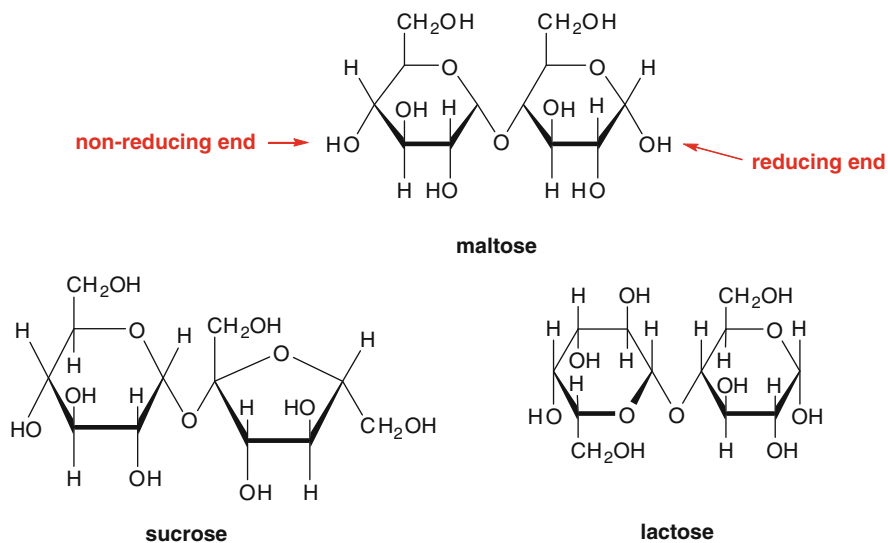


**Fig. 2.14** The monocarboxylic and dicarboxylic forms of sugar acids (a) and some common sugar alcohols (b)

## 2.2.2 Disaccharides

Disaccharides are sugars containing two monosaccharides linked covalently through a glycosidic linkage. There are three disaccharides whose metabolism will be considered under the chapter on carbohydrate metabolism (Chap. 11): maltose, lactose, and sucrose. Their structures are illustrated in Fig. 2.15. Maltose and lactose contain acetal structures and have hemiacetal hydroxyl groups at their reducing ends. When these hemiacetal groups react with an alcohol, the product is referred to as a *glycoside*. Maltose is composed of two glucosyl units connected by an  $\alpha 1 \rightarrow 4$  glycosidic linkage. The OH group at the reducing end of sugars, as illustrated for maltose and lactose, is not an alcohol but a hemiacetal (Fig. 2.15). In the case of sucrose, the linkage between the sugars is a glycosidic bond which is an acetal-ketal linkage. With no free hemiketal or hemiacetal hydroxyl group, sucrose is a nonreducing sugar.

Other oligo and polysaccharides have both reducing and non-reducing ends. This distinction will become important when carbohydrate metabolism is considered.

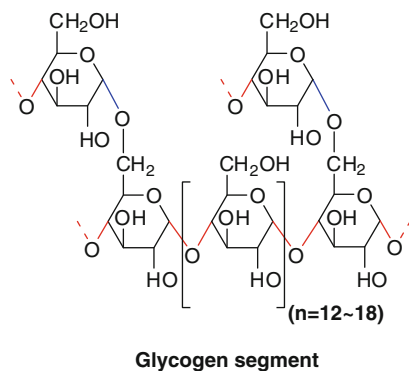


**Fig. 2.15** The disaccharide maltose illustrating the reducing and nonreducing ends of the molecule. Also shown are the reducing sugar lactose and the non-reducing sugar sucrose

## 2.2.3 Polysaccharides

### 2.2.3.1 Glycogen

Glycogen is the storage form of glucose in animals. It is made up of a polymer of glucose units connected by glycosidic linkages. The glycosidic bonds are  $\alpha$ -1  $\rightarrow$  4, which produces a linear chain; however, a branch point ( $\alpha$ -1  $\rightarrow$  6) occurs approximately every 12–18 glucopyranosyl units. The end result is a branched chain between the linear polysaccharide chains (Fig. 2.16).



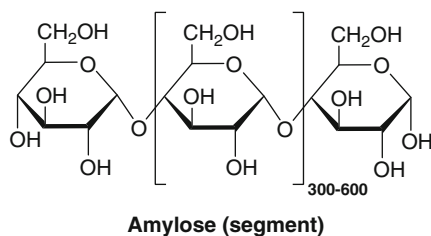
**Fig. 2.16** A glycogen segment:  $\alpha$ 1  $\rightarrow$  4 (red) and  $\alpha$ 1  $\rightarrow$  6 (blue) glycosidic linkages in glycogen

### 2.2.3.2 Starch

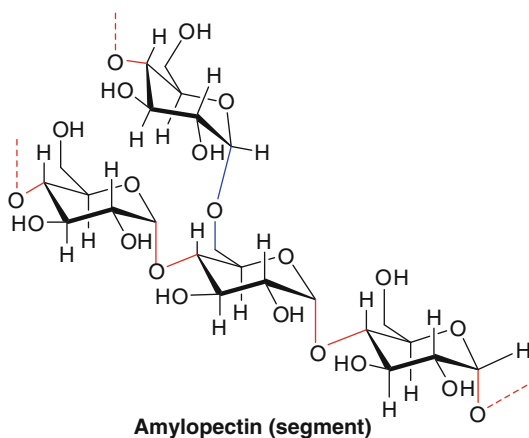
Starch is the storage form of glucose in plants. Most starches are made up of two distinctly different molecules, *amylose* and *amylopectin*. Segments of amylose and amylopectin are illustrated in Figs. 2.17 and 2.18, respectively.

- Amylose is a linear molecule composed of glucopyranosyl units connected by  $\alpha 1 \rightarrow 4$  glycosidic linkages.
- Amylopectin is similar to glycogen; however, the branch points ( $\alpha 1 \rightarrow 6$ ) occur much less frequently. Most starches are composed of approximately 20%-25% amylose and 75%-80% amylopectin; however, waxy rice and waxy maize are devoid of amylose and contain 100% amylopectin. The characteristics of starches vary depending upon the amylose to amylopectin ratio.

**Fig. 2.17** A segment of amylose:  $\alpha 1 \rightarrow 4$  glycosidic linkages in a portion of amylose



**Fig. 2.18** A segment of amylopectin illustrating  $\alpha 1 \rightarrow 4$  (red) and  $\alpha 1 \rightarrow 6$  (blue) linkages

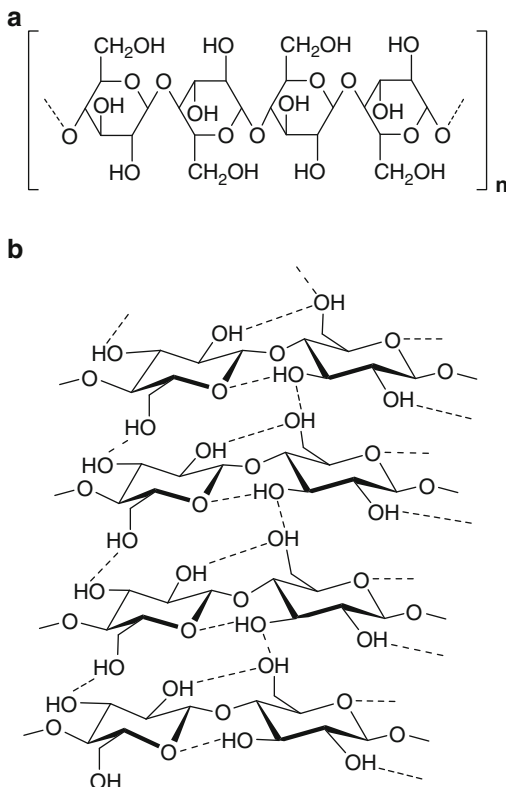


### 2.2.3.3 Cellulose

Cellulose is present in plants as a structural element. It is the most abundant molecule in nature. Wood and most plant cell walls are approximately 50% cellulose. Because of its highly hydrogen-bonded structure, cellulose is extremely



**Fig. 2.19** Segments of a cellulose structure. A segment of cellulose: (a)  $\beta \rightarrow 1,4$  linkages between glucose units. (b) Interchain hydrogen bonding network between cellulose chains. Chains are not held together by 1,6-glycosidic linkages, but by interchain hydrogen bonding



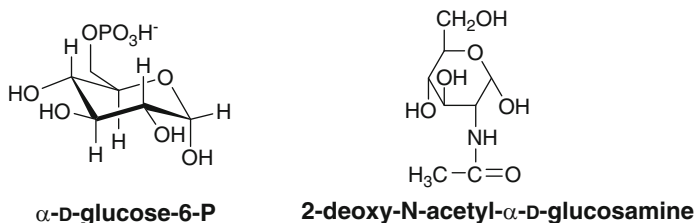
difficulty to degrade either chemically or enzymatically to glucose. It is a linear chain of glucopyranosyl units joined by  $\beta 1 \rightarrow 4$  glycosidic linkages. Cellulose chains are held together intermolecularly by hydrogen bonds between adjacent chains. The chains are believed to be among the tightest helices found in nature, called a twofold screw axis helix. The properties of the various celluloses are determined to a large degree by the number of glucose units in the linear chain. Segments of a cellulose structure are shown in Fig. 2.19.

#### 2.2.3.4 Derived Carbohydrates

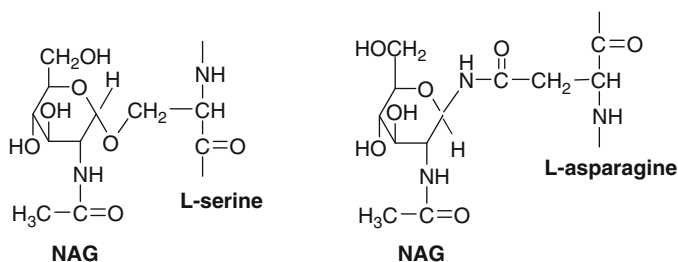
A large number of important biological molecules are *derived sugars*. Examples are D-glucose-6-P and 2-deoxy-N-acetyl-D-glucosamine (NAG) (Fig. 2.20).

Many membrane proteins are covalently bound to sugars through alcohol groups of L-serine (see Fig. 2.21) and L-threonine residues and the amide nitrogen of L-asparagine.

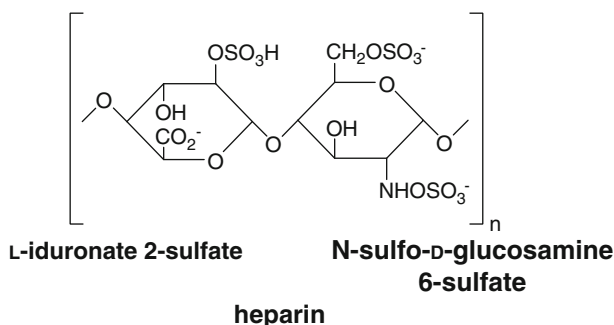
*Heparin* is a derived polysaccharide that is a powerful blood anticoagulant. Its structure is depicted in Fig. 2.22.



**Fig. 2.20** Examples of derived sugars:  $\alpha$ -D-glucose-6-P and 2-deoxy-N-acetyl- $\alpha$ -D-glucosamine (NAG)



**Fig. 2.21** NAG bound to a serine residue in a protein and through the amide group of an asparagine residue



**Fig. 2.22** The basic repeating unit in the heparin molecule

## 2.3 Lipids

Lipids, also known as fats, are biomolecules that are soluble in organic solvents but insoluble in aqueous solutions. They play essential roles in biological membranes in which they are the major components. All organelles from mitochondria to nuclei are surrounded by lipid membranes. They also play prominent roles in energy metabolism as components of adipose tissue. Finally, as hormones, they are essential to physiological regulation of cell metabolism.

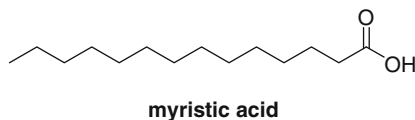
There are a variety of compounds that fall into the lipid category. These include:

- (a) Fatty acids
- (b) Triacylglycerols
- (c) Sphingolipids
- (d) Phospholipids
- (e) Glycolipids
- (f) Lipoproteins
- (g) Steroids and sterols
- (h) Prostaglandins

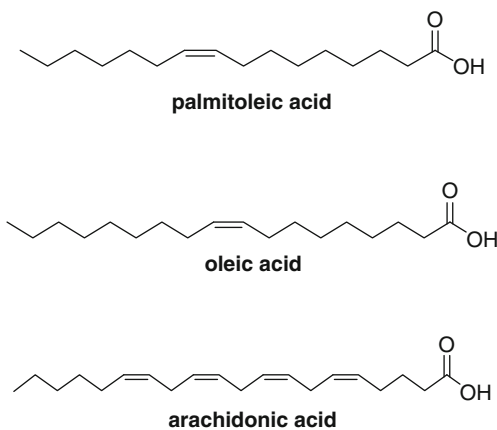
### 2.3.1 Fatty Acids

Fatty acids are composed of a polar head (a carboxyl group) and a nonpolar aliphatic tail. Compounds that exhibit both polar and nonpolar properties are considered to be *amphiphathic*. There is essentially no free fatty acid in the cell; they exist either associated with other molecules, e.g., lipoproteins, or are short-lived metabolic intermediates. Fatty acids fall into two categories: saturated and unsaturated. Using 12 carbon atoms as the smallest fatty acid and 20 carbons as the largest, they are *lauric* (C<sub>12</sub>), *myristic* (C<sub>14</sub>), *palmitic* (C<sub>16</sub>), *stearic* (C<sub>18</sub>), and *arachidic* (C<sub>20</sub>) (Fig. 2.23).

**Fig. 2.23** Structure  
the saturated fatty acid  
myristic acid



Unsaturated fatty acids of physiological importance are *palmitoleic* (C<sub>16</sub>; 16:1 *cis*  $\Delta^9$ ), *oleic* (C<sub>18</sub>; 18:1 *cis*  $\Delta^9$ ), and *arachidonic* (C<sub>20</sub>; 20:1 all *cis*  $\Delta^5, \Delta^8, \Delta^{11}, \Delta^{14}$ ). The nomenclature in parenthesis is self-evident, i.e., it lists the numbers of carbons in the fatty acid, the number and position of the double bonds, and the stereochemical relationship of the hydrogen atoms at the double bond (Fig. 2.24).

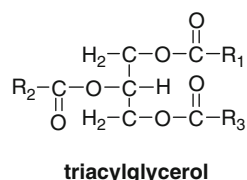


**Fig. 2.24** Chemical  
structures of unsaturated  
fatty acids

### 2.3.2 Triacylglycerols

Triacylglycerols, also known as triglycerides and depot fats and stored as such in adipose tissue, are fatty acid esters of glycerol. A typical triacylglycerol is shown in Fig. 2.25

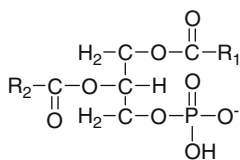
Note that C<sub>2</sub> of the substituted glycerol is chiral. The enantiomer illustrated is the prevalent form found in nature.



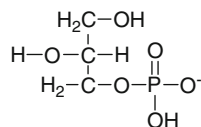
**Fig. 2.25** The structure of triacylglycerol

### 2.3.3 Phosphoacylglycerols

Phosphoglycerols are glycerol esters of phosphoric acid. Examples of phosphoglycerols are shown in Fig. 2.26.



**Phosphatidic Acid**



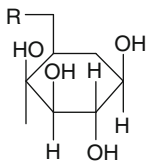
**sn-glycerol-3-phosphate**

**Fig. 2.26** The structures of two phospholipids: phosphatidic acid and (2R)-2,3-dihydroxypropyl phosphate (*sn*-glycerol-3-P)

These molecules, like other phosphoglycerides, have a polar head and a hydrophobic tail. A number of important biological compounds are derivatives of *phosphatidic acid*.

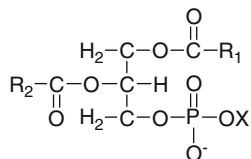
These are represented by the structure in Fig. 2.27, where X is:

- (a) Glycerol:  $-\text{CH}_2-\text{CHOH}-\text{CH}_2\text{OH}$
- (b) Ethanolamine:  $-\text{CH}_2-\text{CH}_2-\text{N}^+\text{H}_3$
- (c) Choline:  $-\text{CH}_2-\text{CH}_2-\text{N}^+(\text{CH}_3)_3$
- (d) Serine:  $-\text{CH}_2-(\text{CH}-\text{N}^+\text{H}_3, \text{CO}_2\text{H})$
- (e) Inositol:



These compounds are referred to as phosphatidylglycerol, phosphatidylethanolamine, etc.

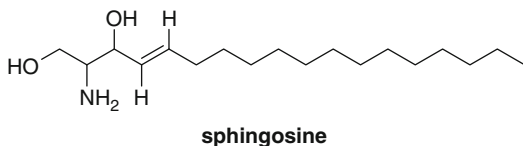
**Fig. 2.27** Phosphatidic acid is where  $X = H$ . A variety of derivatives of phosphatic acid exist in nature



### 2.3.4 Sphingolipids

Sphingolipids are found in membranes and are derivatives of the base *sphingosine*. Note that the hydrogen atoms are *trans* at the double bond in sphingosine (Fig. 2.28).

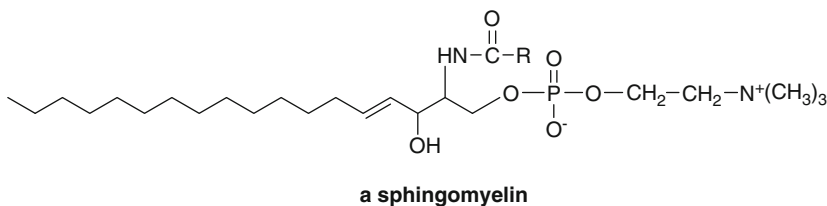
Esterification of the hydroxyl group can occur to yield the compound *ceramide*, in which the R group of the fatty acid can vary from  $C_{16}$  to  $C_{20}$ . The concentration of ceramides in the cell is very low; they are precursors of other sphingolipids.



**Fig. 2.28** The structure of the base sphingosine

#### 2.3.4.1 Sphingomyelin

Note that the fatty acid is linked to the (Fig. 2.29) base in an amide linkage and also that sphingomyelin is a phospholipid.

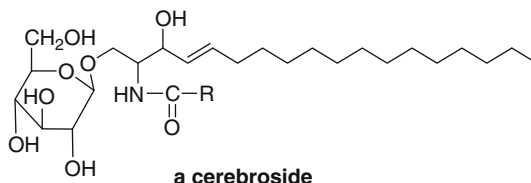


**Fig. 2.29** Sphingomyelins are derivatives of sphingosine that contain a fatty acid and a phosphate ester

### 2.3.4.2 Cerebrosides

Cerebrosides are sphingolipids that contain sugars such as D-glucose or D-galactose (Fig. 2.30).

**Fig. 2.30** Cerebrosides are derivatives of sphingosine that contain a fatty acid and a sugar



### 2.3.4.3 Gangliosides

Gangliosides are sphingolipids that contain oligosaccharides rather than the monosaccharide as illustrated in the case of glucocerebrosides. They also contain *sialic acid*. The oligosaccharide portion of these molecules extends into the cytosol of the cell from the membrane anchor provided by the lipid moiety of the ganglioside and functions as hormone receptors.

## 2.3.5 Waxes

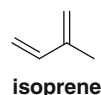
Waxes are esters of long-chain fatty acids and long-chain alcohols. Although the head of the wax is a polar (ester) group, it represents a small fraction of the remainder of the wax molecule which is hydrophobic. Waxes tend not to be permeable to water.

## 2.3.6 Terpenes

Terpenes are lipids formed by condensation of 2-methyl-1,3-butadiene (isoprene) resulting in long-chain unsaturated molecules (Fig. 2.31).

In the case of *cholesterol*, a linear terpene chain cyclizes to form a precursor of cholesterol. Cholesterol, a component of cell membranes in animals, is not found in plants.

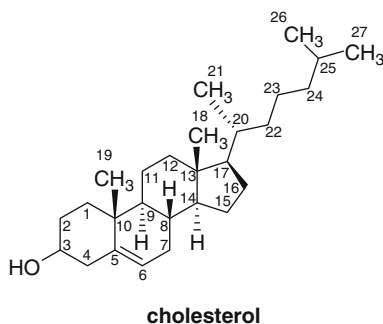
**Fig. 2.31** The structure of isoprene, the precursor of sterol and steroid structures



### 2.3.7 Sterols

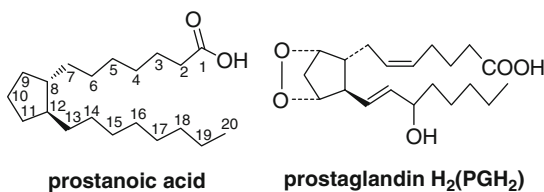
Cholesterol is only one of the lipid compounds derived from terpenes. Others include testosterone (male sex hormone), estradiol (female sex hormone), cortisone (important in regulation of metabolism), and other sterols and steroids. Cholesterol is the precursor of many cellular sterols and steroids (Fig. 2.32).

**Fig. 2.32** The structure of the sterol cholesterol and its numbering system



### 2.3.8 Prostaglandins

Prostaglandins are hormone-like lipids that have a variety of physiological functions. But unlike hormones, which are transported throughout the body, prostaglandins function in the cells where they are synthesized. They were discovered by the Swedish scientist Ulf von Euler in the 1930s who believed that they originated in the prostate gland; hence the name prostaglandin. Their physiological roles involve control of blood pressure, smooth muscle contraction, and induction of inflammation. It is of interest that aspirin inhibits their biosynthesis. Prostaglandins are derivatives of the lipid prostanoic acid. They are synthesized *in vivo* from arachidonic acid. The structures of prostanoic acid and the prostaglandin  $\text{PGH}_2$  are illustrated in Fig. 2.33.



**Fig. 2.33** Structures of prostanoic acid and prostaglandin  $\text{H}_2$

### 2.3.9 Membranes

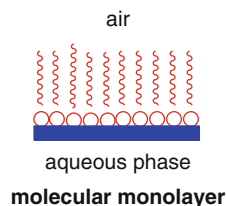
Lipids by definition are water insoluble; however, under certain conditions lipids and water are in fact miscible. Consider a typical water-insoluble fatty acid. At elevated

pH values, the fatty acid forms *soaps* with ions such as  $\text{Na}^+$  and  $\text{K}^+$ . Fatty acids consist of a polar head and a hydrocarbon or nonpolar tail. Thus, salts of fatty acids are soluble in both polar and nonpolar solvents. These types of substances are called *amphiphatic* compounds, i.e., compounds with both polar and nonpolar components.

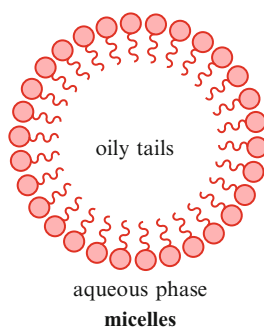
Amphiphatic substances form a number of different structures. Some of these structures are *monolayers*, *micells*, and *bilayers*.

1. A monolayer of lipid may form at the water–lipid interface (Fig. 2.34)
2. *Soaps* and *detergents* may form structures known as *micelles* when they reach a defined concentration in solution. This concentration of amphiphatic compound, known as the *critical micelle concentration* (CMC), is required before micelle formation can occur. The compounds that form micelles are made up of fatty acids with a single hydrophobic tail (Fig. 2.35)
3. *Lipid bilayers* may form from lipids that typically contain two hydrophobic tails. The most prominent members of this class are the sphingolipids and glycerophospholipids (Fig. 2.36).

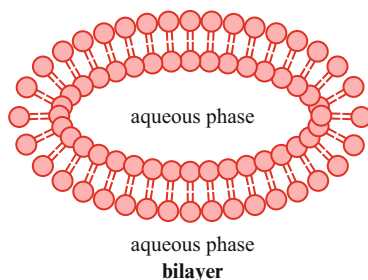
**Fig. 2.34** Lipid monolayer illustrating the distribution of the fatty acids between the aqueous and gas (air) phases



**Fig. 2.35** The structure of a typical micelle illustrating the relationship between the fatty acids and the aqueous solution



**Fig. 2.36** The structure of a synthetic bilayer

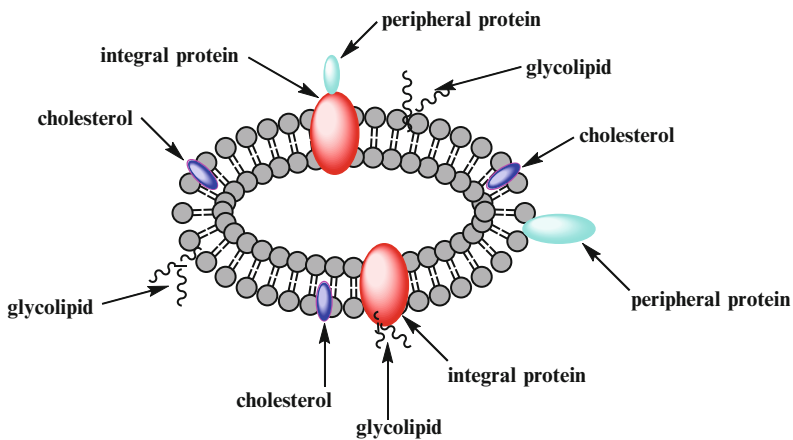




Studies have indicated that the bilayer thickness is approximately  $60 \text{ \AA}$ .

Lipid bilayers are structurally very similar to *biological membranes* and thus their properties have been studied extensively. Experimental bilayers, known as *liposomes*, have been prepared from phospholipids and sphingolipids by sonication.

4. Biological membranes will not be discussed in detail; however, simply stated, they are similar to liposomes in that they contain a lipid bilayer, but unlike liposomes they contain two types of proteins. One, the *integral proteins*, are embedded in the bilayer and the other, the *peripheral proteins*, are associated either with the surface of the bilayer or with the integral protein itself. Miscellaneous lipids such as cholesterol are also components of biological membranes and affect its fluidity (Fig. 2.37).



**Fig. 2.37** Cartoon of a cell membrane and its many components. The basic structure of the cell membrane is the lipid bilayer

## 2.4 Nucleotides

Like amino acids which are the building blocks of proteins, nucleotides are the building blocks of the nucleic acids, RNA and DNA. Aside from these major biological roles, nucleotides are important players in energy metabolism, coenzymes, and intermediary metabolism.

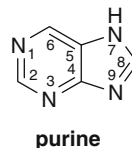
Nucleotides are composed of a *nitrogenous base*, a *sugar*, and a *phosphoryl group*. Removal of phosphoryl group results in a compound known as a *nucleoside*.

There are two types of bases found in nucleotides, *purines* and *pyrimidines*. The sugars are either *D-ribose* or *2-deoxy-D-ribose*.

## 2.4.1 The Bases

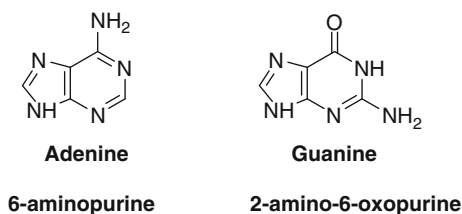
### 2.4.1.1 Purines

**Fig. 2.38** Purine and its numbering system



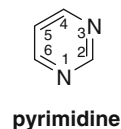
There are two purine bases, *adenine*(A) and *guanine*(G) (Fig. 2.39).

**Fig. 2.39** Guanine and adenine are both derivatives of the base purine

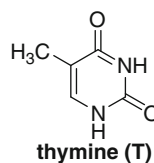
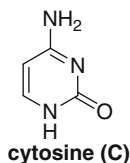
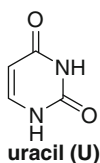


### 2.4.1.2 Pyrimidines

**Fig. 2.40** The structure of pyrimidine along with its numbered atoms



There are three pyrimidine bases, *uracil*(U), *cytosine*(C), and *thymine*(T).



2,4-dioxo pyrimidine

2-oxo-4-amino pyrimidine

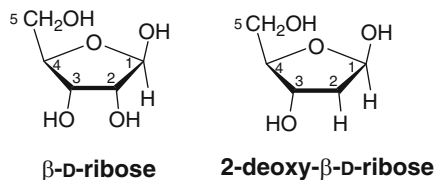
2,4-dioxo-5-methyl pyrimidine

**Fig. 2.41** The pyrimidine bases, uracil, cytosine, and uridine are derivatives of pyrimidine

## 2.4.2 The Sugars

The sugars found in nucleotides are *D-ribose* and *2-deoxy-D-ribose* (Fig. 2.42).

**Fig. 2.42** The structures of D-ribose and 2-deoxy-D-ribose and their numbering systems

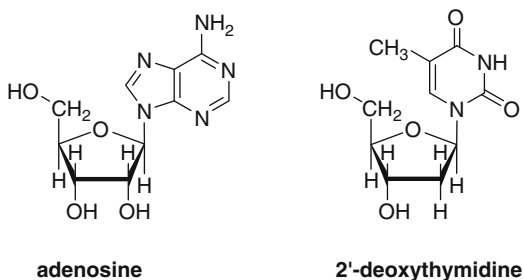


### 2.4.3 The Nucleosides

Examples of nucleosides which consist of either a purine or pyrimidine base and a sugar are illustrated in Fig. 2.43.

#### 2.4.3.1 Structures

**Fig. 2.43** The nucleosides, adenosine and thymidine. Note that besides the two different bases the sugars are also different



#### 2.4.3.2 Nomenclature and Numbering the Bases and Sugars

The bases are numbered as illustrated in Figs. 2.38 and 2.40; however, the sugars when part of nucleosides or nucleotides have primed numbers, e.g., 5'.

Base	Nucleoside
Adenine(A)	Adenosine
Guanine(G)	Guanosine
Uracil (G)*	Uridine
Cytosine(C)	Cytidine
Thymine(T)**	Thymidine

\*Uracil is found exclusively in RNA

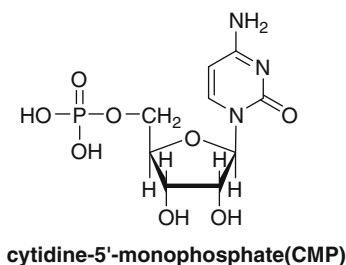
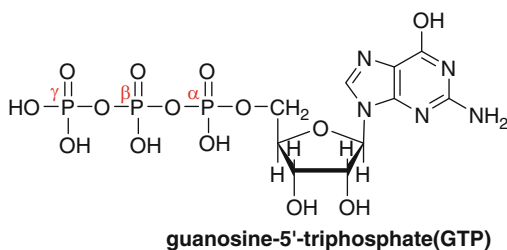
\*\*Thymine is found exclusively in DNA

### 2.4.4 The Nucleotides

Abbreviations are used to describe the various nucleotides, e.g., guanosine-5'-monophosphate, -diphosphate, and -triphosphate are referred to as GMP, GDP and GTP, respectively. Analogous deoxyribonucleotides are dGMP, dGDP, and dGTP.

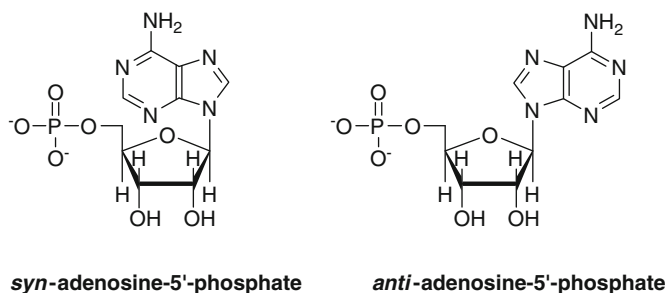
Note that the linkage between the sugars and the purine bases is  $\beta 1' \rightarrow 9$ , and between the pyrimidine bases and the sugar,  $\beta 1' \rightarrow 1$ . The phosphoryl groups, in the case of a nucleoside-5'-triphosphate such as GTP, are labeled  $\alpha$ ,  $\beta$ , and  $\gamma$ . The  $\gamma$  phosphoryl is farthest from the ribose and the  $\alpha$ , closest to the sugar (See Fig. 2.44).

**Fig. 2.44** The structures of the nucleotides GTP and CMP along with the numbering of the phosphoryl groups



#### 2.4.4.1 *Syn* and *Anti* Conformations of Nucleosides and Nucleotides

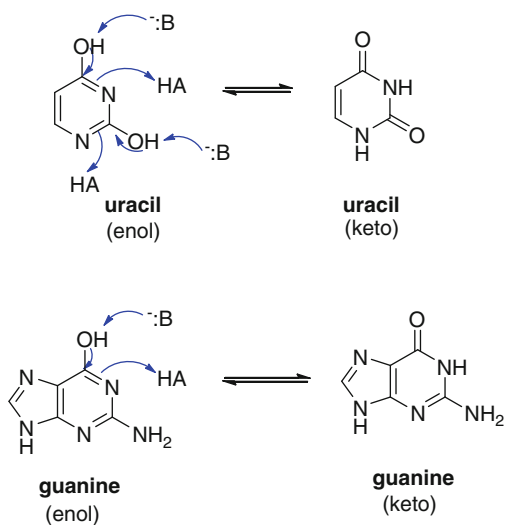
Nucleosides and nucleotides can exist in one of two conformational states with the nitrogenous bases relative to the sugars. Although not at all clear in two-dimensional drawings, there is steric hindrance to free rotation around the bond connecting the sugars and the bases. These two conformations are *syn* and *anti* and are depicted in Fig. 2.45. In the *syn* conformation the base lies directly above the sugar, whereas in the *anti* conformation, positions 1, 2, and 6 of the purine ring are away from the sugar. Similarly, in the *anti* conformation, positions 2 and 3 of the pyrimidine ring lies away from the sugar.



**Fig. 2.45** The *syn* and *anti* forms of AMP

#### 2.4.4.2 Tautomerism

The nitrogenous bases in nucleosides and nucleotides, with the exception of adenine and adenosine, undergo enol–keto tautomerism. Studies have shown that the predominant species in solution is the keto form. Examples are uracil and guanine (Fig. 2.46).



**Fig. 2.46** Examples of tautomerism that occur with purines and pyrimidines. HA and B represent an acid and a base, respectively

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