Chapter 9 Lipids

Lipids are vital components of all cells. Unlike nucleic acids, proteins, and carbohydrates, lipids do not have unifying structural features. They are defined operationally as a diverse group of nonpolar substances. They are therefore poorly or not at all water-soluble but dissolve readily in many organic solvents. Lipids are essential constituents of biological membranes. In addition, the acyl chains of lipids serve as energy sources. Finally, a number of cell signaling processes involve lipids. This chapter focuses on the structures and physical characteristics of lipids, as well as on the properties of the lipid bilayer. These subjects serve as an introduction to Chapter 10, in which biological membranes and protein–lipid interactions are considered.

Essential Concepts

Lipid Classification

1. Fatty acids are common components of other lipids, where they occur in ester or amide linkages. They are straight-chain carboxylic acids, usually having between 14 and 22 carbons. Eukaryotic fatty acids usually possess an even number of carbon atoms and may contain one or more double bonds. Although the systematic names of fatty acids reveal their structures, many fatty acids also have common names.

2. Saturated fatty acids, of which the most common are palmitic acid (C_{16}; hexadecanoic acid) and stearic acid (C_{18}; octadecanoic acid), contain no double bonds and are highly flexible molecules that tend to assume a fully extended conformation. In the pure compound, neighboring saturated fatty acyl chains pack together tightly. The resulting van der Waals interactions cause fatty acid melting points to increase as chain length increases.

3. The double bonds of unsaturated fatty acids nearly always have the cis configuration, which introduces a 30° bend in the acyl chain. This prevents unsaturated fatty acids from packing together as closely as saturated fatty acids. As a result, the melting point of an unsaturated fatty acid is always lower than the melting point for a saturated fatty acid with the same number of carbons.

4. Most fatty acid groups in eukaryotic lipids are unsaturated. The most common fatty acid with one double bond is oleic acid (C_{18}; 9-octadecenoic acid). Fatty acids with two or more double bonds are termed polyunsaturated.

5. Triacylglycerols, which contain three fatty acids esterified to the hydroxyl groups of D-glycerol, serve as energy reserves in plants and animals. A triacylglycerol generally contains more than one type of fatty acyl group. Mixtures of triacylglycerols may be fats (which are solid at room temperature) or oils (which are liquid at room temperature), depending on the properties of their component fatty acyl groups.

6. The highly reduced nature of triacylglycerols makes them an efficient metabolic energy store. Adipocytes are cells specialized for the biosynthesis, storage, and breakdown of triacylglycerols. Adipose tissue also provides thermal insulation.

7. The major lipid constituents of biological membranes are glycerophospholipids. These substances are composed of D-glycerol with fatty acids esterified to C1 and C2 and a phosphate group esterified to C3. The phosphate is almost always also esterified to a hydrophilic moiety. Thus, glycerophospholipids are amphipathic molecules with a polar head group and a nonpolar tail. Glycerophospholipids frequently contain saturated or monounsaturated acyl groups at C1 of glycerol and more highly unsaturated acyl moieties at C2.

8. Phospholipases are enzymes that hydrolyze glycerophospholipids. For example, phospholipase A_2, which occurs in bee and snake venoms, specifically cleaves the C2 ester linkage to yield a free fatty acid and a lysophospholipid. Several phospholipase-catalyzed hydrolysis products of glycerolipids play roles in cell signaling processes. These include 1,2-diacylglycerol and lysophosphatidic acid.

9. Plasmalogens are glycerophospholipids in which a fatty acyl group is linked to C1 via an α,β-unsaturated ether bond.

10. Sphingolipids all contain a long-chain nitrogen-containing alcohol, sphingosine. Ceramides have a fatty acyl group linked to the primary amino group of sphingosine and can be regarded as the basic building block of more complex sphingolipids. Among these are (a) sphingomyelin, in which ceramide is esterified to a phosphocholine or phosphoethanolamine head group; (b) cerebrosides, in which ceramide forms a glycosidic bond with either glucose or galactose; and (c) gangliosides, in which oligosaccharides containing one or more *N*-acetylneuraminic acid groups form the ceramide head group. Cerebrosides and gangliosides are therefore glycosphingolipids. On hydrolysis, sphingolipids, like glycerophospholipids, give rise to products that have signaling activity.

11. Steroids are derivatives of the cyclopentaneperhydrophenanthrene fused-ring system. Cholesterol, the most abundant animal steroid, is weakly amphiphilic because it has a hydroxyl group at C3 (it is therefore classified as a sterol). It is a major component of biological membranes in animals. In a cholesteryl ester, the hydroxyl group of cholesterol is esterified to a fatty acid.

12. Cholesterol is the precursor of steroid hormones, which include (a) glucocorticoids (e.g., cortisol), which modulate metabolic processes, inflammatory reactions, and stress responses; (b) mineralocorticoids (e.g., aldosterone), which regulate salt and water excretion; and (c) androgens and estrogens, which influence sexual development and reproductive functions.

13. Vitamins D_2 and D_3 are produced from steroid precursors through photolysis by ultraviolet light. These two vitamins are then converted to active forms by enzymatic hydroxylation.

Active vitamin D promotes absorption of dietary Ca^{2+} and enhances the release of Ca^{2+} from bone into the blood.

14. Eicosanoids are derived from the highly unsaturated C_{20} lipid arachidonic acid after its release from membrane glycerophospholipids by phospholipase A_2. The eicosanoids include prostaglandins, thromboxanes, and leukotrienes, all of which are biologically active at extremely low concentrations. They are produced in a tissue-specific manner and play roles in inflammatory reactions, the regulation of the cardiovascular system, and reproduction.

15. The effectiveness of aspirin, ibuprofen, and acetaminophen as anti-inflammatory drugs is due to their ability to inhibit an enzyme required for prostaglandin synthesis.

Lipid Bilayers

16. The physical properties of lipids in aqueous solution cause them to aggregate. Water tends to exclude the hydrophobic portions of amphiphilic lipids, whereas the polar head groups remain in contact with the aqueous environment. Amphiphiles with a single nonpolar tail, such as soaps, many detergents, and lysophospholipids, form globular micelles. Amphiphiles with two hydrocarbon tails, such as glycerophospholipids, instead form disklike micelles that are actually lipid bilayers. A bilayer of phospholipids in an aqueous milieu may form a vesicle with a solvent-filled interior, called a liposome. Liposomes are useful as models of biological membranes and as water-soluble drug delivery vehicles.

17. The movement of an amphiphilic lipid across a lipid bilayer, a process called transverse diffusion or a flip-flop, occurs infrequently, because the passage of a polar head group through the hydrophobic interior of the bilayer is thermodynamically unfavorable. In contrast, lipids readily diffuse laterally in the plane of the bilayer, indicating that the hydrocarbon core of the bilayer is highly fluid. The motion of the acyl chains is greatest in the center of the bilayer and decreases markedly near the polar head groups.

18. Bilayer fluidity is a function of temperature. At high temperatures, the lipids form a highly mobile liquid-crystal state, and at low temperatures, they form a gel-like solid as the hydrocarbon tails tightly associate. The transition temperature, the temperature at which the phase changes, depends on bilayer composition and increases with increasing acyl chain length and decreasing unsaturation of the component lipids. The presence of cholesterol also reduces a bilayer's transition temperature. Living organisms alter their membrane composition in order to maintain constant fluidity as the ambient temperature varies.

19. Cholesterol stabilizes the bilayer over a range of temperatures: At high temperatures, its rigid ring system interferes with fatty acyl chain mobility and thereby decreases membrane fluidity. At low temperatures, cholesterol prevents tight packing of adjacent hydrocarbon tails and thereby promotes membrane fluidity.

Guide to Study Exercises (text p. 237)

1. Lipids differ from the three other major classes of biological molecules primarily in their hydrophobicity. Because this property—rather than a common structure—unites lipids, they exhibit greater structural variety than do other classes of biological molecules. Lipids, unlike amino acids, carbohydrates, or nucleotides, do not form extended polymers.

2. The degree of unsaturation of a fatty acid is correlated with its melting point and overall fluidity: The greater the unsaturation, the lower the melting point and the more fluid the fatty acid. Consequently, unsaturated fatty acids and triacylglycerols that contain unsaturated fatty acid residues pack together less efficiently. (Section 9-1A)

3. The structures of triacylglycerols, glycerophospholipids, and sphingolipids are shown on pages 222, 223, and 226, respectively. The triacylglycerols are the simplest, with three fatty acyl groups esterified to a glycerol backbone. Glycerophospholipids consist of two fatty acyl groups esterified to a glycerol backbone whose C3 position is linked to a phosphate that is, in turn, linked to a polar group. Sphingolipids are similar to glycerophospholipids in overall shape since they contain two hydrocarbon tails and a phosphate derivative or carbohydrate as a head group.

   The physical properties of these three types of lipids depend on the length and saturation of their fatty acyl chains and on the identity of their head group. Triacylglycerols, which have no head group, are entirely nonpolar. Glycerolipids and sphingolipids that have phosphate derivatives as head groups are amphipathic molecules with nonpolar tails and polar or charged head groups. The sphingolipids known as gangliosides are attached to oligosaccharides whose large nonionic head groups dominate their structure. (Sections 9-1B, C, and D)

4. Steroids in the form of cholesterol are important components of animal cell membranes. In mammals, steroid hormones include the glucocorticoids (which regulate metabolism and stress responses), mineralocorticoids (which regulate water and salt balance), and the sex hormones (androgens and estrogens). Vitamin D, which is ultimately derived from the plant sterol ergosterol or the closely related 7-dehdyrocholesterol, regulates Ca^{2+} metabolism. Eicosanoids, which are derivatives of arachidonic acid, regulate pain, fever, vasoconstriction, and other physiological processes. Both steroid hormones and eicosanoids are synthesized in a tissue-specific manner, but eicosanoids usually act close to their site of synthesis, whereas steroids travel throughout the body. (Sections 9-1E and F)

5. Lateral diffusion of lipids in a membrane is faster than transverse diffusion because the trans-bilayer movement of a membrane lipid requires that its hydrated head group pass through the hydrophobic interior of the bilayer, an energetically unfavorable process. (Section 11-2B)

Questions

Lipid Classification

1. Draw structures for the following fatty acids:

   (a) 18:0 octadecanoic acid
   (b) 20:4 5,8,11,14-eicosatetraenoic acid
   (c) 22:6 4,7,10,13,16,19-docosahexaenoic acid
   (d) 13-(2-cyclopentenyl)-tridecanoic acid (a cyclic fatty acid)

2. How do the following alterations in the structures of fatty acids affect their physical properties?
   (a) Increasing the chain lengths of saturated fatty acids
   (b) Increasing the number of double bonds in unsaturated fatty acids
   (c) Changing a *cis* double bond in a fatty acid to a *trans* double bond

3. Draw and name a typical triacylglycerol.

4. List the two major functions of triacylglycerols.

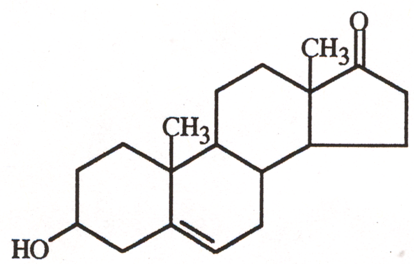
5. Why are glycerophospholipids considered amphiphilic molecules?

6. Draw the structures of the following lipids:
   (a) 1-palmitoyl-2-oleoyl-3-glycerophosphatidylethanolamine
   (b) 1-stearoyl-2-arachidonoyl-3-glycerophosphatidylinositol

7. What distinguishes a plasmalogen from other glycerophospholipids?

8. What chemical moieties do sphingomyelin and gangliosides have in common and which are unique to each?

9. The compound shown below has been advertised as a dietary supplement that purportedly prevents obesity, heart disease, and the ill effects of aging. Based on its structure, what physiological function is it most likely to actually perform?



10. Why are eicosanoids called local mediators rather than hormones?

11. Arachidonic acid can arise from phospholipid precursors by the action of:
    (a) Phospholipase A_1
    (a) Phospholipase A_2
    (b) Phospholipase C
    (c) Phospholipase D

12. In arachidonate metabolism, the production of ________, ________, and ________ is blocked by the drug ________, which inhibits the reaction catalyzed by ________.

Lipid Bilayers

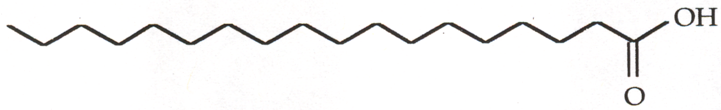
13. Explain why single-tailed amphiphiles tend to form micelles whereas two-tailed amphiphiles tend to form bilayers.

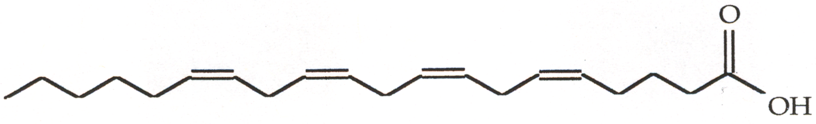
14. Why is a polar solute unlikely to penetrate a lipid bilayer?

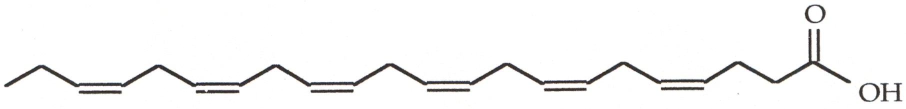
15. Describe the structural changes that occur when a pure phospholipid bilayer is warmed and passes through its transition temperature. Explain what would happen if the bilayer contained a significant amount of cholesterol.

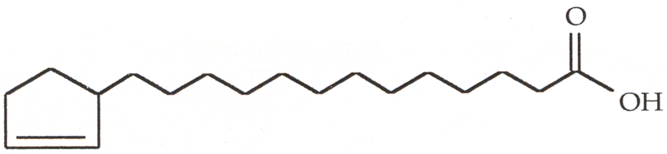
Answers to Questions

1.

(a) 

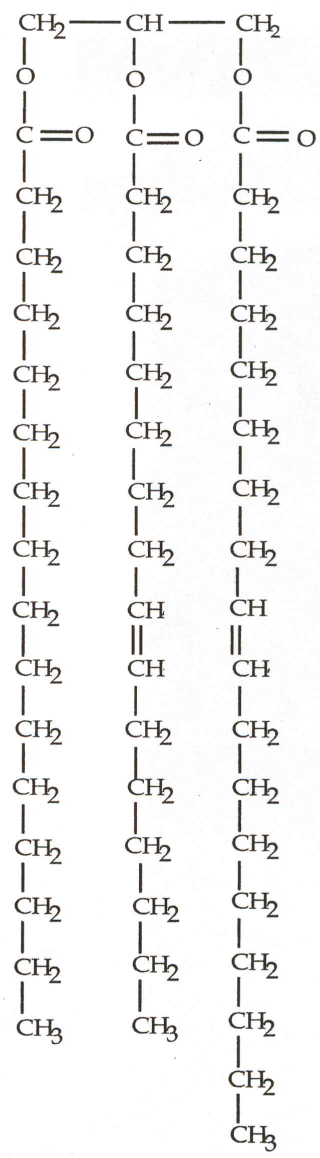
(b) 

(c) 

(d) 

2. (a) The melting point increases with increasing hydrocarbon chain length. Fully saturated hydrocarbon chains have the least amount of steric hindrance and thus can pack together closely.
   (b) The melting point decreases with an increasing number of double bonds.
   (c) Fatty acid residues that have a cis double bond exhibit a 30° bend in their hydrocarbon chain that interferes with close packing. In contrast, trans double bonds distort the acyl chain conformation much less, allowing closer packing of molecules. Hence a fatty acid with trans double bonds has a higher melting point than the corresponding cis fatty acid of the same chain length and with the same number of double bonds.

3. For example, 1-palmitoyl-2-palmitoleoyl-3-oleoyl-glycerol

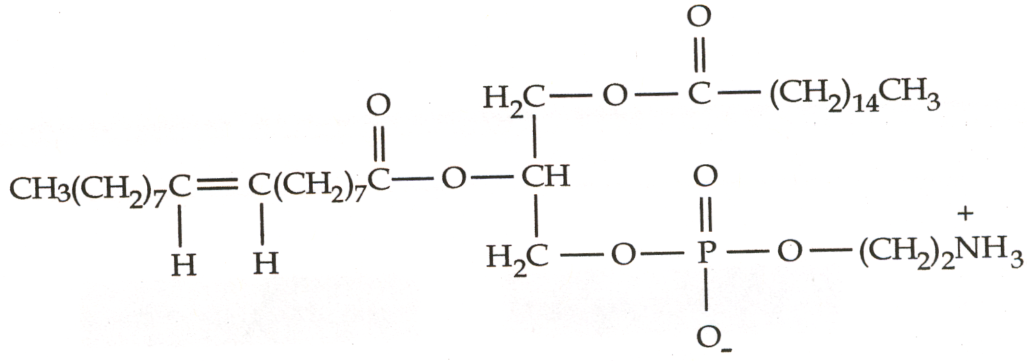


4. Triacylglycerols serve as metabolic energy sources and thermal insulators.

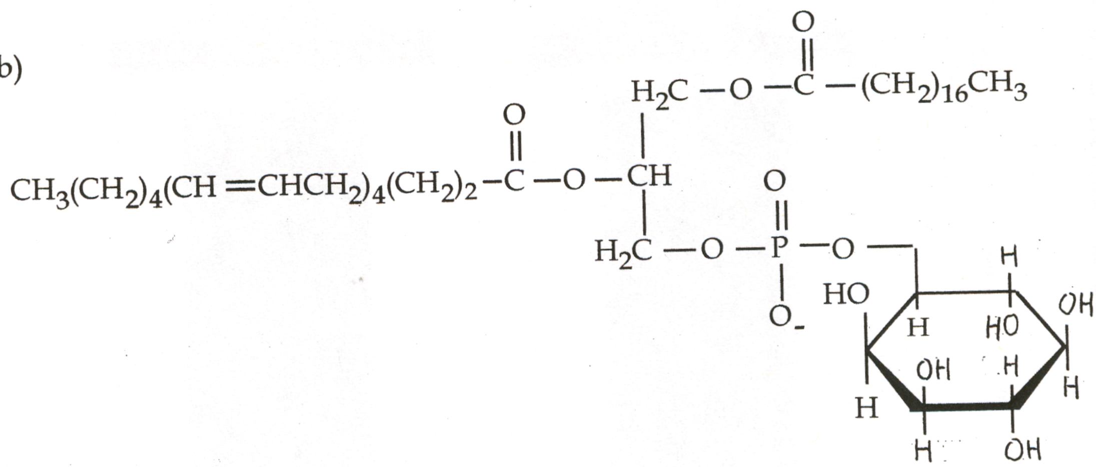
5. Glycerophospholipids are amphiphilic because they are composed of a hydrophobic diacylglycerol "tail" attached to a hydrophilic phosphoryl derivative "head."

6.

(a)



(b)



7. A plasmalogen differs from a diacylglycerophospholipid in that a hydrocarbon chain is attached to the C1 position of glycerol via an α,β-unsaturated ether bond in the cis configuration instead of an ester bond.

8. Sphingomyelin and gangliosides both contain a sphingosine moiety to which is attached a fatty acyl group in an amide linkage. They differ in that sphingomyelin has a phosphocholine (or less commonly a phosphoethanolamine) head group, whereas the ganglioside head group is an oligosaccharide that includes one or more sialic acid residues.

9. This compound is a sterol that closely resembles testosterone and estradiol (shown in Figure 9-11). It is most likely to exert its effects by influencing physiological processes that depend on the sex hormones. In fact, it is dehydroepiandrosterone (DHEA), a metabolic precursor of androgens and estrogens.

10. Although eicosanoids, like hormones, are synthesized by a variety of cells and exert their effects on other cells, they are considered local mediators rather than hormones because they act near their sites of synthesis rather than being carried throughout the body via the bloodstream, and because they decompose quickly.

11. (b)

12. In arachidonate metabolism, the production of prostacyclins, prostaglandins, and thromboxanes is blocked by the drug aspirin, which inhibits the reaction catalyzed by PGH_2 synthase.

13. The difference arises from geometrical considerations. Single-tailed amphiphiles, such as fatty acid anions, form micelles because of their tapered shape. Their hydrated head groups are wider than their tails, enabling them to pack efficiently into a spheroidal micelle. The cylindrical shape of two-tailed amphiphiles, such as glycerophospholipids, prevents their packing into a spheroidal micelle. Instead they pack together to form disklike micelles, which are really extended bilayers.

14. In order for a polar solute to enter a lipid bilayer, its interactions with surrounding water molecules must first be disrupted (i.e., it must lose its hydration shell), and new interactions with the hydrophobic bilayer constituents would have to form. This would require an increase in free energy for the system; that is, the process is unfavorable.

15. When a pure phospholipid bilayer in an orderly gel-like state is warmed, it is converted (at its transition temperature) to a liquid crystal form that is more fluid. The presence of cholesterol in a phospholipid bilayer both decreases its fluidity and broadens the transition temperature range. These effects occur because the sterically rigid cholesterol molecules insert between the fatty acyl chains of the phospholipids and thus restrict their motion.