BME 2901-BIOCHEMISTRY

Lipids

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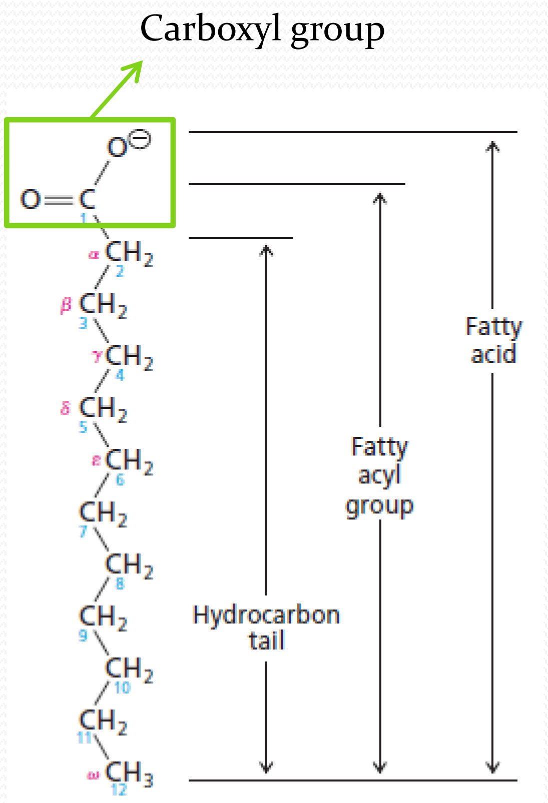
LIPIDS

- Biological lipids are a chemically diverse group of compounds which are insoluble in water.
- Fats and oils are the principal stored forms of energy in many organisms.
- Phospholipids and sterols are major structural elements of biological membranes.
- Other lipids, although present in relatively small quantities, play crucial roles as enzyme cofactors, electron carriers, light absorbing pigments, hydrophobic anchors for proteins, “chaperones” to help membrane proteins fold, emulsifying agents in the digestive tract, hormones, and intracellular messengers.

Storage Lipids

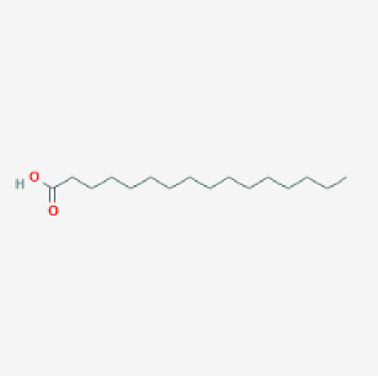
- The fats and oils used almost universally as stored forms of energy in living organisms are derivatives of **fatty acids** which are hydrocarbon derivatives.
- They have the general formula R-COOH, where R represents a hydrocarbon chain composed of various lengths of -CH2 (methylene) units.
- Fatty acids are carboxylic acids with hydrocarbon chains ranging from 4 to 36 carbons long (C4 to C36).
- Fatty acids differ from one another in the length of their hydrocarbon tails, the number of carbon–carbon double bonds, the positions of the double bonds in the chains, and the number of branches.



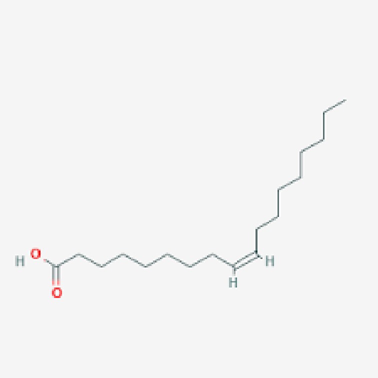
- All fatty acids have a carboxyl group (—COOH) at their “head.” This is why they are acids.
- The p*K*a of this group is about 4.5 to 5.0 so it is ionized at physiological pH ($-COO^{-}$).
- Fatty acids are a form of detergent because they have a long hydrophobic tail and a polar head.
- As expected, the concentration of *free* fatty acid in cells is quite low because high concentrations of free fatty acids could disrupt membranes.
- Most fatty acids are components of more complex lipids. They are joined to other molecules by an ester linkage at the terminal carboxyl group.

Fatty Acid Nomenclature

- A simplified nomenclature for these compounds specifies the chain length and number of double bonds, separated by a colon; for example, the 16-carbon saturated palmitic acid is abbreviated 16:0, and the 18-carbon oleic acid, with one double bond, is 18:1.



- The positions of any double bonds are specified by superscript numbers following Δ(delta); a 20-carbon fatty acid with one double bond between C-9 and C-10 (C-1 being the carboxyl carbon) and another between C-12 and C-13 is designated 20:2($\Delta^{9,12}$).

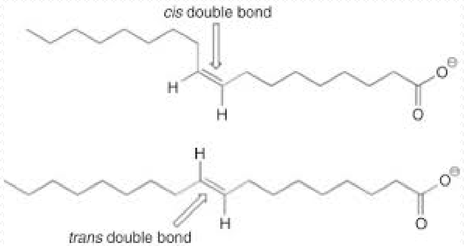


- The most commonly occurring fatty acids have even numbers of carbon atoms in an unbranched chain of 12 to 24 carbons fatty acids are synthesized by the sequential addition of two-carbon units..
- There is also a common pattern in the location of double bonds; in most monounsaturated fatty acids the double bond is between C-9 and C-10 (9), and the other double bonds of polyunsaturated fatty acids are generally 12 and 15.

- The physical properties of the fatty acids, and of compounds that contain them, are largely determined by the length and degree of unsaturation of the hydrocarbon chain.
- The nonpolar hydrocarbon chain accounts for the poor solubility of fatty acids in water.
- The longer the fatty acyl chain and the fewer the double bonds, the lower is the solubility in water.
- The carboxylic acid group is polar (and ionized at neutral pH) and accounts for the slight solubility of short-chain fatty acids in water.

- Melting points are also strongly influenced by the length and degree of unsaturation of the hydrocarbon chain.
- At room temperature (25°C), the saturated fatty acids from 12:0 to 24:0 have a waxy consistency, whereas unsaturated fatty acids of these lengths are oily liquids.
- This difference in melting points is due to different degrees of packing of the fatty acid molecules.

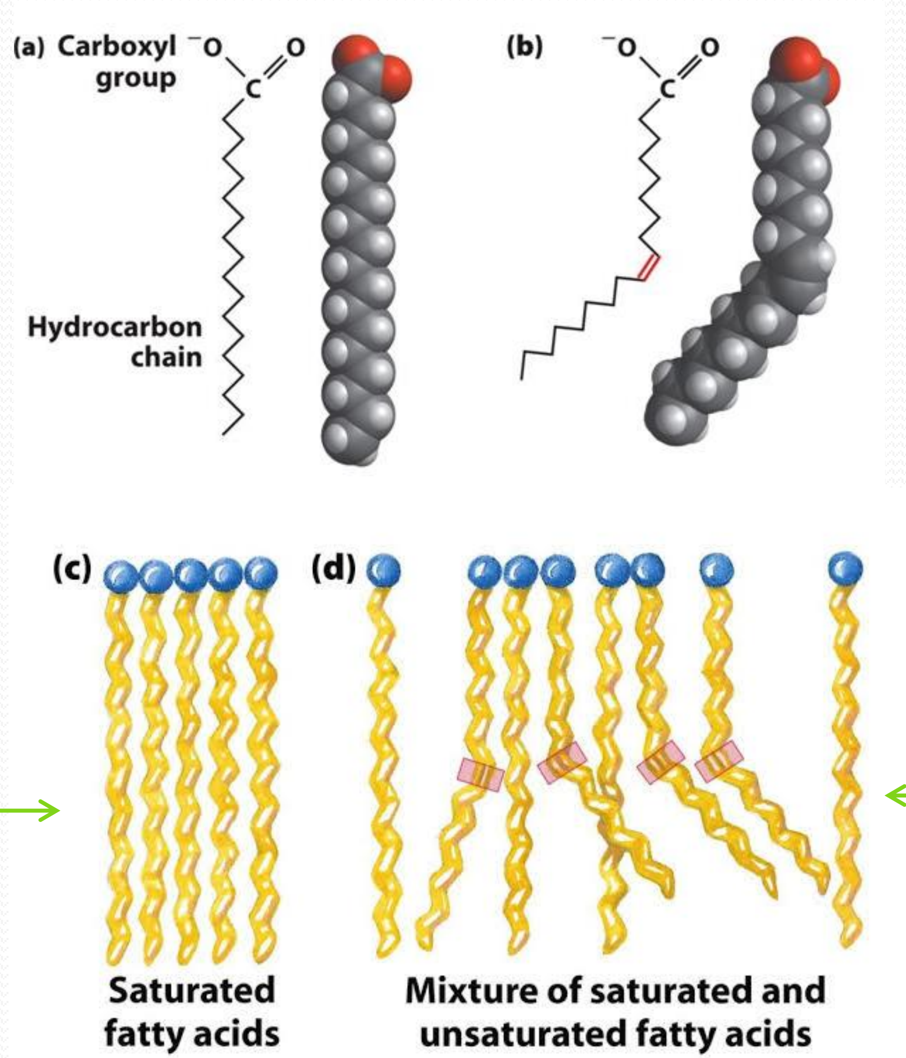
- The double bonds of polyunsaturated fatty acids are almost never conjugated (alternating single and double bonds, as in —CH=CH—CH=CH —), but are separated by a methylene group: — CH=CH — CH_2 — CH=CH —.
- In nearly all naturally occurring unsaturated fatty acids, the double bonds are in the cis configuration.
- Trans fatty acids are produced by fermentation in the rumen of dairy animals and are obtained from dairy products and meat.
- They are also produced during hydrogenation of fish or vegetable oils.
- Because diets high in trans fatty acids correlate with increased blood levels of LDL (bad cholesterol) and decreased HDL (good cholesterol), it is generally recommended to avoid large amounts of these fatty acids.



cis and *trans* fatty acids

- In the fully saturated compounds, free rotation around each carbon–carbon bond gives the hydrocarbon chain great flexibility; the most stable conformation is the fully extended form, in which the steric hindrance of neighboring atoms is minimized. These molecules can pack together tightly in nearly crystalline arrays, with atoms all along their lengths in van der Waals contact with the atoms of neighboring molecules.
- In unsaturated fatty acids, a cis double bond forces a kink in the hydrocarbon chain. Fatty acids with one or several such kinks cannot pack together as tightly as fully saturated fatty acids, and their interactions with each other are therefore weaker.
- Because it takes less thermal energy to disorder these poorly ordered arrays of unsaturated fatty acids, they have markedly lower melting points than saturated fatty acids of the same chain length.
- In vertebrates, free fatty acids (unesterified fatty acids, with a free carboxylate group) circulate in the blood bound noncovalently to a protein carrier, **serum albumin**.
- However, fatty acids are present in blood plasma mostly as carboxylic acid derivatives such as esters or amides. Lacking the charged carboxylate group, these fatty acid derivatives are generally even less soluble in water than are the free fatty acids.

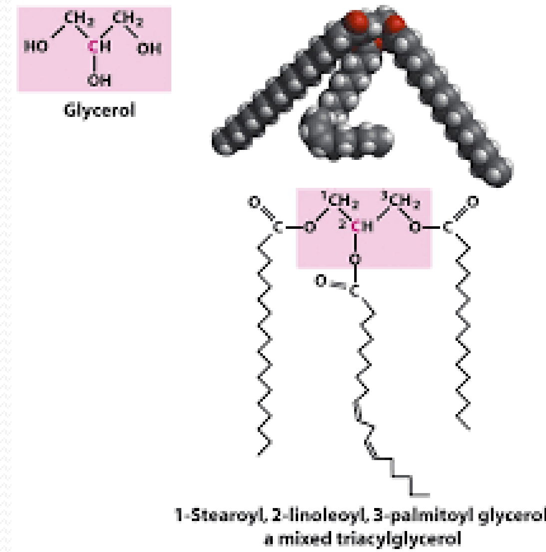
Higher melting point, thus, generally solid at room temperature

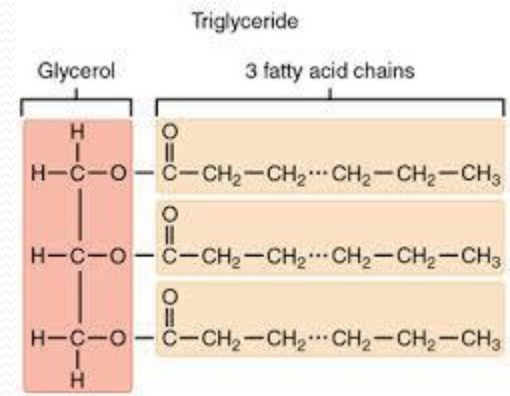


Lower melting point, thus, generally liquid at room temperature

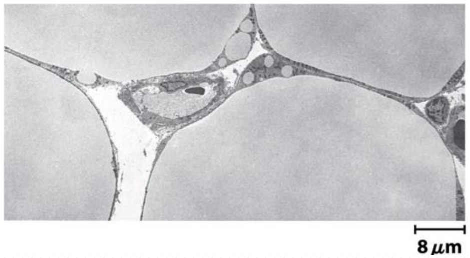
Triacylglycerols

- The simplest lipids constructed from fatty acids are the **triacylglycerols,** also referred to as triglycerides, fats, or neutral fats.
- Triacylglycerols are composed of three fatty acids each in ester linkage with a single glycerol. Those containing the same kind of fatty acid in all three positions are called simple triacylglycerols and are named after the fatty acid they contain.
- Because the polar hydroxyls of glycerol and the polar carboxylates of the fatty acids are bound in ester linkages, triacylglycerols are nonpolar, hydrophobic molecules, essentially insoluble in water.

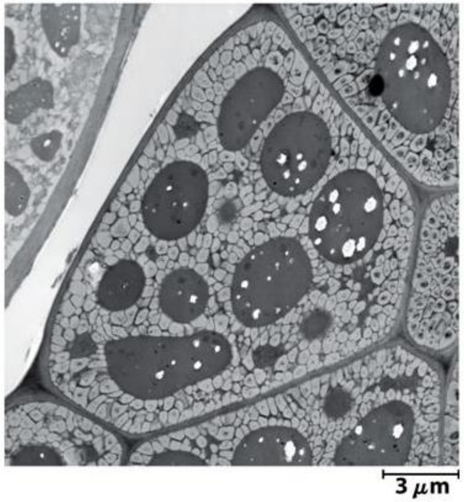




- In most eukaryotic cells, triacylglycerols form a separate phase of microscopic, oily droplets in the aqueous cytosol, serving as depots of metabolic fuel. In vertebrates, specialized cells called adipocytes, or fat cells, store large amounts of triacylglycerols as fat droplets that nearly fill the cell.



- Triacylglycerols are also stored as oils in the seeds of many types of plants, providing energy and biosynthetic precursors during seed germination. Adipocytes and germinating seeds contain **lipases**, enzymes that catalyze the hydrolysis of stored triacylglycerols, releasing fatty acids for export to sites where they are required as fuel.



Fatty Acid or Carbohydrate as Stored Fuels?

- There are two significant advantages to using triacylglycerols as stored fuels, rather than polysaccharides such as glycogen and starch.
  - First, because the carbon atoms of fatty acids are more reduced than those of sugars, oxidation of triacylglycerols yields more than twice as much energy, gram for gram, as the oxidation of carbohydrates.
  - Second, because triacylglycerols are hydrophobic and therefore unhydrated, the organism that carries fat as fuel does not have to carry the extra weight of water of hydration that is associated with stored polysaccharides (2 g per gram of polysaccharide).
- Carbohydrates such as glucose and glycogen do offer certain advantages as quick sources of metabolic energy, one of which is their ready solubility in water.

- In some animals, triacylglycerols stored under the skin serve not only as energy stores but as insulation against low temperatures.
- Seals, walruses, penguins, and other warm-blooded polar animals are amply padded with triacylglycerols.
- In hibernating animals (bears, for example), the huge fat reserves accumulated before hibernation serve the dual purposes of insulation and energy storage.
- The low density of triacylglycerols is the basis for another remarkable function of these compounds.
- In sperm whales, a store of triacylglycerols and waxes allows the animals to match the buoyancy of their bodies to that of their surroundings during deep dives in cold water.

- Most natural fats, such as those in vegetable oils, dairy products, and animal fat, are complex mixtures of simple and mixed triacylglycerols.
- These contain a variety of fatty acids differing in chain length and degree of saturation.
- Vegetable oils such as corn (maize) and olive oil are composed largely of triacylglycerols with unsaturated fatty acids and thus are liquids at room temperature.
- They are converted industrially into solid fats by catalytic hydrogenation, which reduces some of their double bonds to single bonds and converts others to trans double bonds.
- Triacylglycerols containing only saturated fatty acids, such as tristearin, the major component of beef fat, are white, greasy solids at room temperature.

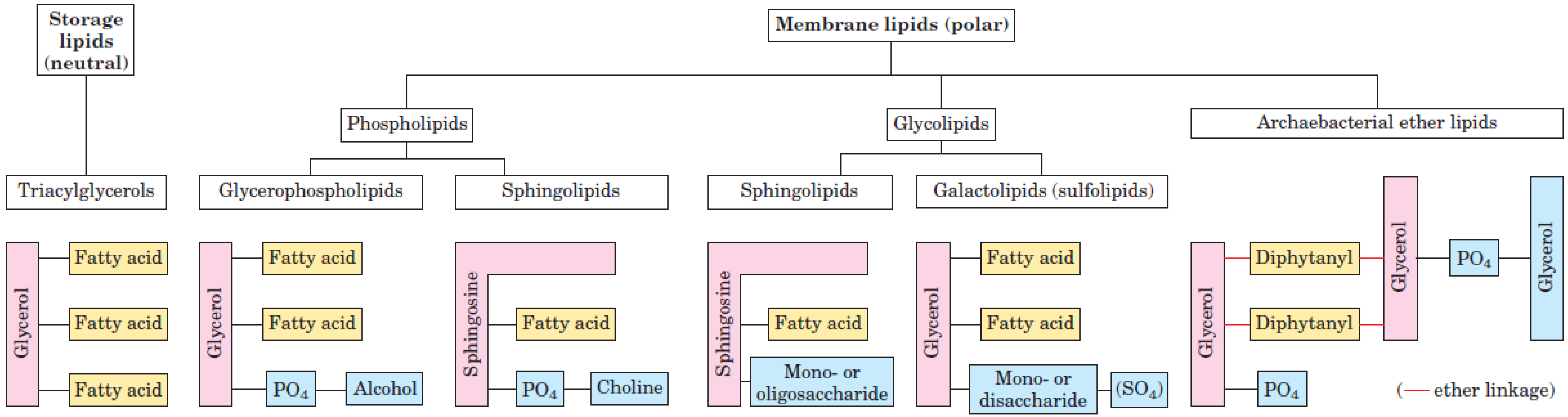
Waxes

- Biological waxes are esters of long-chain (C_{14} to C_{36}) saturated and unsaturated fatty acids with long-chain (C_{16} to C_{30}) alcohols.
- Their melting points (60 to 100°C) are generally higher than those of triacylglycerols.
- In plankton, the free-floating microorganisms at the bottom of the food chain for marine animals, waxes are the chief storage form of metabolic fuel.
- Waxes also serve a diversity of other functions related to their water-repellent properties and their firm consistency.
- Certain skin glands of vertebrates secrete waxes to protect hair and skin and keep it pliable, lubricated, and waterproof.
- Birds, particularly waterfowl, secrete waxes from their preen glands to keep their feathers water-repellent.
- The shiny leaves of many tropical plants are coated with a thick layer of waxes, which prevents excessive evaporation of water and protects against parasites.

Structural Lipids

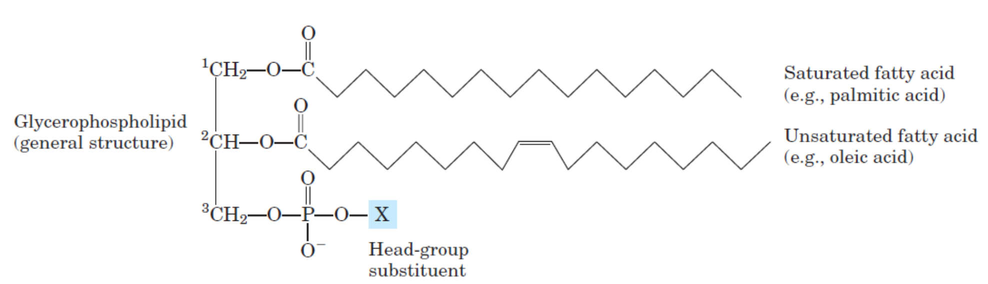
- The central architectural feature of biological membranes is a double layer of lipids, which acts as a barrier to the passage of polar molecules and ions.
- Membrane lipids are amphipathic: one end of the molecule is hydrophobic, the other hydrophilic.
- Their hydrophobic interactions with each other and their hydrophilic interactions with water direct their packing into sheets called membrane bilayers.
- There are five general types of membrane lipids:
  - **Glycerophospholipids**, in which the hydrophobic regions are composed of two fatty acids joined to glycerol
  - **Galactolipids and sulfolipids**, which also contain two fatty acids esterifiedn to glycerol, but lack the characteristic phosphate of phospholipids
  - **Ether lipids,** in which one of the two acyl chains is attached to glycerol in ether, rather than ester, linkage
  - **Sphingolipids**, in which a single fatty acid is joined to a fatty amine, sphingosine
  - **Sterols**, compounds characterized by a rigid system of four fused hydrocarbon rings.

- The hydrophilic moieties in these amphipathic compounds may be as simple as a single -OH group at one end of the sterol ring system, or they may be much more complex.
- In glycerophospholipids and some sphingolipids, a polar head group is joined to the hydrophobic moiety by a phosphodiester linkage; these are the **phospholipids.**
- Other sphingolipids lack phosphate but have a simple sugar or complex oligosaccharide at their polar ends; these are the **glycolipids**.
- Within these groups of membrane lipids, enormous diversity results from various combinations of fatty acid “tails” and polar “heads.”


Storage lipids (neutral)
Membrane lipids (polar)
Phospholipids
Glycolipids
Archaebacterial ether lipids
Triacylglycerols
Glycerophospholipids
Sphingolipids
Sphingolipids
Galactolipids (sulfolipids)
Glycerol
Fatty acid
Fatty acid
Fatty acid
Glycerol
Fatty acid
Fatty acid
PO_4
Alcohol
Sphingosine
Fatty acid
PO_4
Choline
Sphingosine
Fatty acid
Mono- or oligosaccharide
Glycerol
Fatty acid
Fatty acid
Mono- or disaccharide
(SO_4)
Glycerol
Diphytanyl
Diphytanyl
Glycerol
PO_4
Glycerol
PO_4
(— ether linkage)

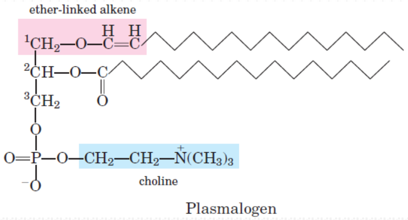
Glycerophospholipids

- **Glycerophospholipids**, also called phosphoglycerides, are membrane lipids in which two fatty acids are attached in ester linkage to the first and second carbons of glycerol, and a highly polar or charged group is attached through a phosphodiester linkage to the third carbon.
- Glycerophospholipids are named as derivatives of the parent compound, phosphatidic acid, according to the polar alcohol in the head group. Phosphatidylcholine and phosphatidylethanolamine have choline and ethanolamine in their polar head groups, for example.
- The head group is joined to glycerol through a phosphodiester bond, in which the phosphate group bears a negative charge at neutral pH.
- The polar alcohol may be negatively charged (as in phosphatidylinositol 4,5-bisphosphate), neutral (phosphatidylserine), or positively charged (phosphatidylcholine, phosphatidylethanolamine).
- These charges contribute greatly to the surface properties of membranes.
- In general, glycerophospholipids contain a C16 or C18 saturated fatty acid at C-1 and a C18 to C20 unsaturated fatty acid at C-2.

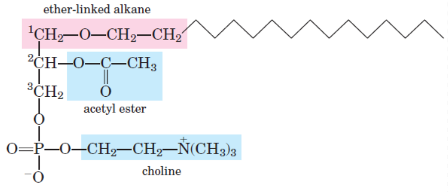


Ether Lipids

- Some animal tissues and some unicellular organisms are rich in **ether lipids,** in which one of the two acyl chains is attached to glycerol in ether, rather than ester, linkage.
- The ether-linked chain may be saturated, as in the alkyl ether lipids, or may contain a double bond between C-1 and C-2, as in **plasmalogens** .
- Vertebrate heart tissue is uniquely enriched in ether lipids; about half of the heart phospholipids are plasmalogens.
- The membranes of halophilic bacteria, ciliated protists, and certain invertebrates also contain high proportions of ether lipids.
- The functional significance of ether lipids in these membranes is unknown; perhaps their resistance to the phospholipases that cleave ester-linked fatty acids from membrane lipids is important in some roles.
- At least one ether lipid, **platelet-activating factor,** is a potent molecular signal. It is released from leukocytes called basophils and stimulates platelet aggregation and the release of serotonin (a vasoconstrictor) from platelets. It also exerts a variety of effects on liver, smooth muscle, heart, uterine, and lung tissues and plays an important role in inflammation and the allergic response.



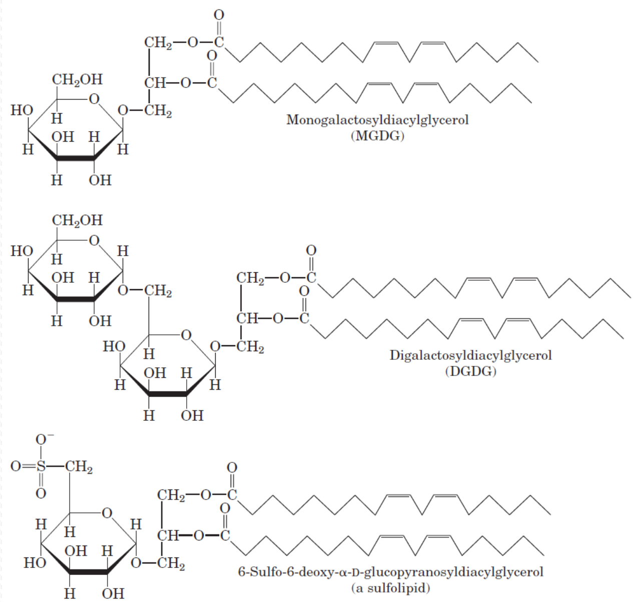
Plasmalogen



Platelet-activating factor

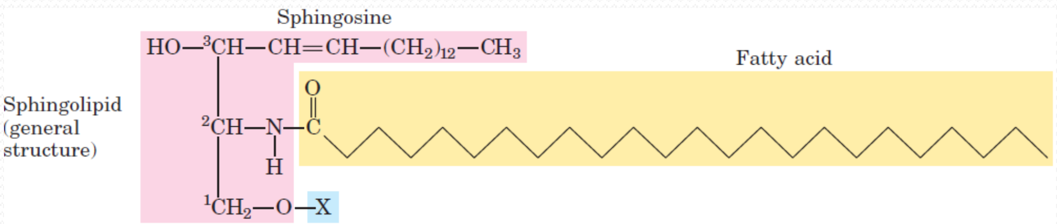
Galactolipids

- The second group of membrane lipids are those that predominate in plant cells: the **galactolipids,** in which one or two galactose residues are connected by a glycosidic linkage to C-3 of a 1,2-diacylglycerol.
- Galactolipids are localized in the thylakoid membranes (internal membranes) of chloroplasts; they make up 70% to 80% of the total membrane lipids of a vascular plant.
- They are probably the most abundant membrane lipids in the biosphere. Phosphate is often the limiting plant nutrient in soil, and perhaps the evolutionary pressure to conserve phosphate for more critical roles favored plants that made phosphatefree lipids.
- Plant membranes also contain sulfolipids, in which a sulfonated glucose residue is joined to a diacylglycerol in glycosidic linkage.
- In sulfolipids, the sulfonate on the head group bears a fixed negative charge like that of the phosphate group in phospholipids.



Sphingolipids

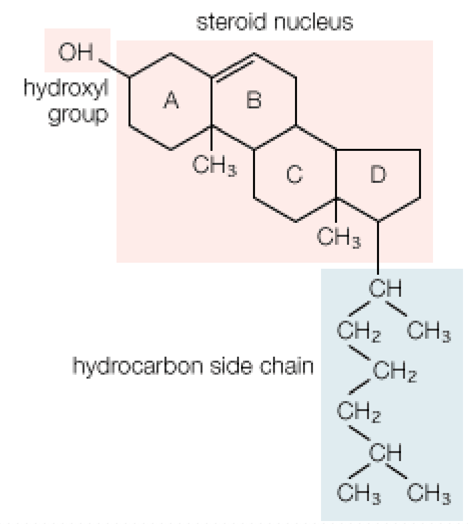
- **Sphingolipids,** the fourth large class of membrane lipids, also have a polar head group and two nonpolar tails, but unlike glycerophospholipids and galactolipids they contain no glycerol.
- Sphingolipids are composed of one molecule of the long-chain amino alcohol sphingosine (also called 4-sphingenine) or one of its derivatives, one molecule of a long-chain fatty acid, and a polar head group that is joined by a glycosidic linkage in some cases and by a phosphodiester in others.
- There are three subclasses of sphingolipids, all derivatives of ceramide but differing in their head groups: **sphingomyelins**, **neutral (uncharged) glycolipids**, and **gangliosides**.

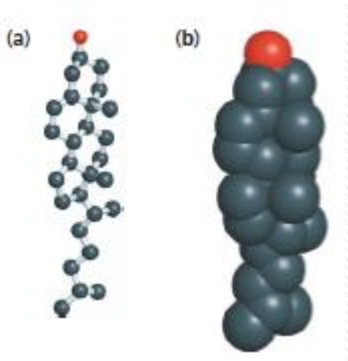


- In humans, at least 60 different sphingolipids have been identified in cellular membranes. Many of these are especially prominent in the plasma membranes of neurons, and some are clearly recognition sites on the cell surface.
- The carbohydrate moieties of certain sphingolipids define the **human blood groups** and therefore determine the type of blood that individuals can safely receive in blood transfusions.
- Gangliosides are concentrated in the outer surface of cells, where they present points of recognition for extracellular molecules or surfaces of neighboring cells.

Sterols

- **Sterols** are structural lipids present in the membranes of most eukaryotic cells. The characteristic structure of this fifth group of membrane lipids is the steroid nucleus, consisting of four fused rings, three with six carbons and one with five.
- The steroid nucleus is almost planar and is relatively rigid; the fused rings do not allow rotation about C-C bonds.
- **Cholesterol**, the major sterol in animal tissues, is amphipathic, with a polar head group (the hydroxyl group at C-3) and a nonpolar hydrocarbon body (the steroid nucleus and the hydrocarbon side chain at C-17), about as long as a 16- carbon fatty acid in its extended form.

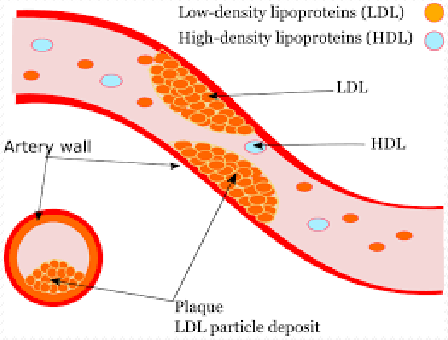




- In addition to their roles as membrane constituents, the sterols serve as precursors for a variety of products with specific biological activities.
- Steroid hormones, for example, are potent biological signals that regulate gene expression.
- Bile acids are polar derivatives of cholesterol that act as detergents in the intestine, emulsifying dietary fats to make them more readily accessible to digestive lipases.

HDL and LDL

- **Lipoproteins** are complex aggregates of lipids and proteins that render the hydrophobic lipids compatible with the aqueous environment of body fluids and enable their transport throughout the body.
- Lipoproteins are synthesised mainly in the intestines and liver and carry insoluble fatty acids, triacylglycerols, phopholipids and cholesterol in blood.
- Low-density lipoproteins (**LDL**) and high-density lipoproteins (**HDL**), are two of those lipoproteins which are based on the relative densities of the aggregates on ultracentrifugation.
- LDL, known publicly as 'bad cholesterol', contributes to fatty buildups in arteries (atherosclerosis) which narrow the arteries raising the risk for heart attack and stroke.
- HDL, known publicly as 'good cholesterol', acts as a scavenger, carrying LDL cholesterol away from the arteries and high levels of blood HDL is correlated with a *decrease* in the risk of having a heart attack.



Lipids as Signals, Cofactors, and Pigments

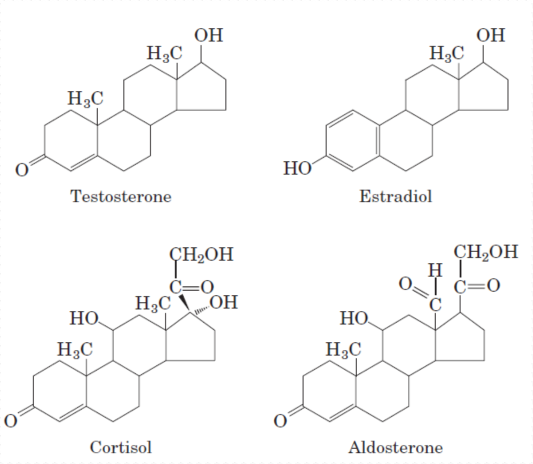
- Lipids, present in much smaller amounts, have *active* roles in the metabolic traffic as metabolites and messengers.
- Some serve as potent signals—as hormones, carried in the blood from one tissue to another, or as intracellular messengers generated in response to an extracellular signal (hormone or growth factor).
- Others function as enzyme cofactors in electron-transfer reactions in chloroplasts and mitochondria, or in the transfer of sugar moieties in a variety of glycosylation (addition of sugar) reactions.
- A third group consists of lipids with a system of conjugated double bonds: pigment molecules that absorb visible light. Some of these act as light-capturing pigments in vision and photosynthesis; others produce natural colorations.
- They are derived from lipids of the plasma membrane or from the fat-soluble vitamins A, D, E, and K.

Some Carries Messages to Nearby Cells

- Prostaglandins, for example, are paracrine hormones which sre fatty acid derivatives and act only on cells near the point of hormone synthesis instead of being transported in the blood to act on cells in other tissues or organs.
- They act in many tissues by regulating the synthesis of the intracellular messenger 3,5-cyclic AMP (cAMP). Because cAMP mediates the action of diverse hormones, the prostaglandins affect a wide range of cellular and tissue functions.
- Some prostaglandins stimulate contraction of the smooth muscle of the uterus during menstruation and labor.
- Others affect blood flow to specific organs, the wake-sleep cycle, and the responsiveness of certain tissues to hormones such as epinephrine and glucagon.
- Prostaglandins in a third group elevate body temperature (producing fever) and cause inflammation and pain.

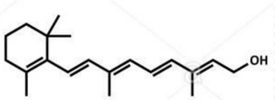
Some Carries Messages between Tissues

- Steroids are oxidized derivatives of sterols; they have the sterol nucleus but lack the alkyl chain attached to ring D of cholesterol, and they are more polar than cholesterol.
- Steroid hormones move through the bloodstream (on protein carriers) from their site of production to target tissues, where they enter cells, bind to highly specific receptor proteins in the nucleus, and trigger changes in gene expression and metabolism.
- The major groups of steroid hormones are the male and female sex hormones and the hormones produced by the adrenal cortex, cortisol and aldosterone.

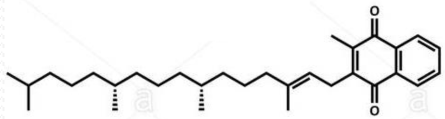


Some are used as cofactors

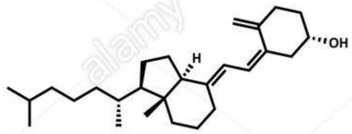
- **Vitamin D** and **Vitamin A** serve as hormone precursors.
- **Vitamin E is a** biological antioxidant.
- The aromatic ring of vitamin E reacts with and destroys the most reactive forms of oxygen radicals and other free radicals, protecting unsaturated fatty acids from oxidation and preventing oxidative damage to membrane lipids, which can cause cell fragility.
- The aromatic ring of **vitamin K** undergoes a cycle of oxidation and reduction during the formation of active prothrombin, a blood plasma protein essential in blood clot formation.



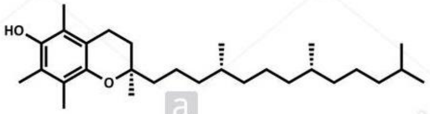
Vitamin A



Vitamin K1



Vitamin D3



Vitamin E

Studying Lipids

- Because lipids are insoluble in water, their extraction and subsequent fractionation require the use of organic solvents and some techniques not commonly used in the purification of water-soluble molecules such as proteins and carbohydrates.
- In general, complex mixtures of lipids are separated by differences in the polarity or solubility of the components in nonpolar solvents.

- Neutral lipids are readily extracted from tissues with ethyl ether, chloroform, or benzene, solvents that do not permit lipid clustering driven by hydrophobic interactions.
- Membrane lipids are more effectively extracted by more polar organic solvents, such as ethanol or methanol, which reduce the hydrophobic interactions among lipid molecules while also weakening the hydrogen bonds and electrostatic interactions that bind membrane lipids to membrane proteins.
- In the determination of lipid composition, the lipids are first extracted from tissues with organic solvents and separated by thin-layer, gas chromatography, or high-performance liquid chromatography (HPLC).