Introduction to Lipids

Lipids are biological molecules characterized by limited solubility in water and solubility in non-polar organic solvents. Their intermolecular interactions are dominated by the hydrophobic effect and van der Waals interactions. Many lipids are, however, amphipathic molecules, which interact with other molecules and with aqueous solvents via hydrogen bonding and electrostatic interactions.

Importance

Lipids are major components of **cell membranes**, and are responsible for most of the permeability filter functions of membranes. Membranes act as barriers to separate compartments within eukaryotic cells, and to separate all cells from their surroundings.

Lipids are also used as **metabolic fuels**. Adipose tissue fat stores contain ~9 kcal/gram (= ~37 kJ/g) of dry weight lipid. This compares to ~4 kcal/g for protein or carbohydrate. In addition, lipid aggregates contain very little water; most lipid stores contain about 8 kcal/g of wet weight lipid. This contrasts to about 1 kcal/g for protein or carbohydrate (which are heavily hydrated under physiological conditions). As a result, physiological fat stores have roughly 8-fold higher energy density than other forms of energy storage molecules. Note, however, that lipids are much more limited as biosynthetic precursors than other energy storage molecules because the primary breakdown product of most lipids is acetyl-CoA. In animals, acetyl-CoA cannot be converted to any gluconeogenic substrate; as a result, in animals few lipids can be used to synthesize carbohydrates or amino acids. Lipids include the **vitamins** A, D, E, and K, and include some non-vitamin enzyme cofactors. Lipids include a number of **hormones**, of which the most important are steroids and prostaglandins. Lipids act as **insulation**, and play a role in **physical appearance** of animals. Finally, lipids play roles in a variety of **pathological conditions**, including heart disease and some genetic disorders related to lipid metabolism.

Most lipids are **amphipathic**: they have both polar and non-polar characteristics. The polar regions of lipids are capable of forming favorable interactions with water, while the non-polar regions tend to aggregate with other non-polar molecules. This differential polarity is critical for their structural role in membranes, as well as in a number of functional roles.

Fatty Acids

Fatty acids consist of a long carbon chain (also called an **acyl chain**) with a carboxylic acid at one end. The vast majority of fatty acids are unbranched linear molecules. The carboxylic acid is ionized at physiological pH (the carboxyl group is deprotonated and therefore negatively charged).

Fatty acids in most biological systems are synthesized by serial addition of two-carbon units. As a result, fatty acids usually contain an even number of carbons, especially in animals, which synthesize even-chain fatty acids almost exclusively.

Biological fatty acids usually contain 14 to 20 carbons, although small amounts of 22 and 24 carbon compounds are found in some tissues.

The fatty acid acyl chain has a tendency to adopt an extended structure, because this results in the least steric hindrance; however, the chain is very flexible, and will adopt a large variety of conformations. The reason for this flexibility is that each carbon-carbon bond can (more or less) freely rotate, and all fatty acids have many carbon-carbon bonds.

Saturated fat and unsaturated fat
Many fatty acids contain double bonds. Fatty acids that do not contain carbon-carbon double bonds are considered to be **saturated**. When producing unsaturated fatty acids, the biosynthetic machinery incorporates nearly exclusively *cis* configuration double bonds. Some food products, such as margarine, may contain *trans* double bonds because of manipulations during food processing; some evidence suggests that fatty acids containing *trans* double bond cannot be metabolized properly, and that food products without *trans* fatty acids are therefore healthier. **Monounsaturated** fatty acids contain a single double bond, while **polyunsaturated** fatty acids contain more than one site of unsaturation. The *cis* bond causes a kink in the fatty acid acyl chain (recall that, unlike single bonds, double bonds do **not** allow free rotation).

"**Partially hydrogenated vegetable oil**" is a term often found on food ingredient labels. It means that some of the fatty acids in the oil were "hydrogenated" (reduced, so that the double bonds were converted to single bonds). Saturated fat and monounsaturated fat form solids at room temperature. Polyunsaturated fat is (usually) liquid at room temperature. Mixing fatty acids of varying saturation is a way of regulating consistency of food, and also of regulating the consistency of biological systems. This is because, in membranes or in bulk lipid, *cis* double bonds alter packing density, and therefore decrease the number of favorable van der Waals contacts. The presence of *cis* double bonds therefore results in lower melting temperature because the double bonds result in less regular and less stable structures. The table below shows the effect of chain length and number of *cis* double bonds on melting temperature. Longer chains result in higher melting temperatures; increasing numbers of double bonds decreases melting temperature for fatty acids of a given length.

| Saturated Fatty Acids		Effect of Unsaturation on Fatty Acids		
Number of Carbons	Melting point (°C)	Number of Carbons	Number of double bonds	Melting point (°C)
10	32	18	0	70
12	44	18	1	13
14	54	18	2	−5
16	63	18	3	−11
18	70			
20	77			
22	82			
24	86			

Nomenclature

Fatty acids are named using both historical labels and symbols. Both types of nomenclature uniquely define molecules with specific lengths and number and position of double bonds. The table (below) gives the name and symbol for some of the common physiological fatty acids.

Number of Carbons	Name	Symbol	Structure
12	Lauric acid (dodecanoic acid)	12:0	
14	Myristic acid	14:0	
16	Palmitic acid	16:0	
18	Stearic acid	18:0	
16	Palmitoleic acid	$16:1^{\Delta 9}$	
18	Oleic acid	$18:1^{\Delta 9}$	
18	Linoleic acid	$18:2^{\Delta 9,12}$	
18	α-Linolenic acid	$18:3^{\Delta 9,12,15}$	
18	γ-Linolenic acid	$18:3^{\Delta 6,9,12}$	
20	Arachidonic acid	$20:4^{\Delta 5,8,11,14}$	

Palmitoleic acid (16:1 Δ^9)
ω^9 fatty acid

Oleic acid (18:1 Δ^9)
ω^9 fatty acid

Linoleic acid (18:2 $\Delta^{9,12}$)
ω^6 fatty acid

α-Linolenic acid (18:3 $\Delta^{9,12,15}$)
ω^3 fatty acid

γ-Linolenic acid (18:3 $\Delta^{6,9,12}$)
ω^6 fatty acid

Arachidonic acid (20:4 $\Delta^{5,8,11,14}$)
ω^6 fatty acid

Palmitic, oleic (>40%), and linoleic acids are the main fatty acids present in fat stores in animals. Palmitic, oleic, stearic, and arachidonic acids are the main fatty acids found in animal membranes.

Δ nomenclature

The vast majority of fatty acids are linear molecules with carboxylic acids are one end. The only differences between fatty acid molecules are therefore the number of carbons and the number and position of double bonds. Thus 18:0 uniquely defines stearic acid, which is a fully-saturated (*i.e.* no double bonds) 18-carbon fatty acid. Fatty acids that contain double bonds could have the double bonds in different places. The symbol "Δ" is used to indicate the presence and position of the double bond. A "Δ^9" fatty acid contains a double bond between the 9 and 10 carbons. Biological fatty acids should be assumed to contain *cis* double bonds unless the double bond is explicitly stated to be *trans*. Oleic acid can therefore be identified as $18:1^{\Delta 9}$ (*i.e.* an 18 carbon fatty acid with one double bond between the 9 and 10 carbons).

Stearic acid (18:0)

Oleic acid (18:1 Δ^9)
ω^9 fatty acid

Linoleic acid (18:2 $\Delta^{9,12}$)
ω^6 fatty acid
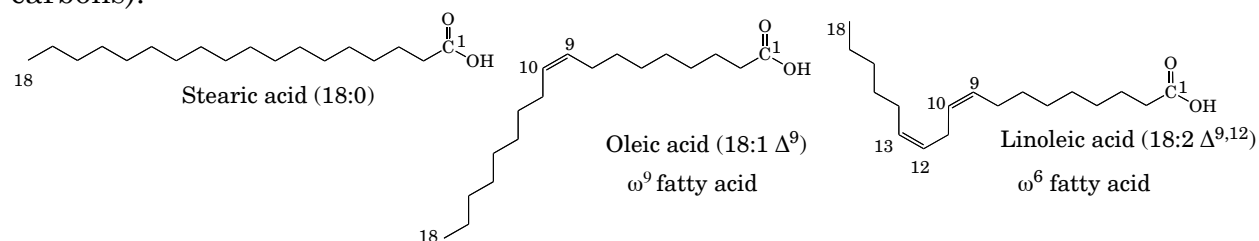
ω nomenclature

Physiological unsaturated fatty acids all have double bonds three carbons apart. This allows the first or the last carbon present as a double bond to be used in identifying the compound. It is possible therefore to count from the methyl-group end of the fatty acid; the Greek letter ω (the last letter in the Greek alphabet) is used to refer to the position of the double bond counting from the terminal methyl group.

Using this nomenclature, oleic acid is an ω^9 fatty acid, and linoleic acid is an ω^6 fatty acid containing two double bonds. Humans can synthesize ω^9 fatty acids; plants and some animals (especially fish and Arctic mammals) can synthesize ω^6 and ω^3 fatty acids as well. For incompletely understood reasons having to do with regulation of plasma lipid levels, high levels of dietary ω^6 and ω^3 fatty acids are related to reduced risk of heart disease.

Structures of Lipids

Simple lipids are lipids comprised of a single type of lipid molecule. Fatty acids are one class of simple lipids. Another major class of simple lipids are **terpenes**, which are molecules formed from repeating isoprene (2-methyl-1,3-butadiene) units. Terpene is comprised of two isoprene molecules; molecules containing one or more terpene units are called terpenes.

Isoprene
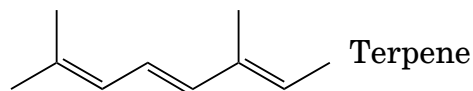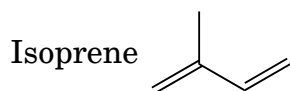
Terpene

| Designation	Number of Terpene Units	Number of Carbons
Monoterpene	1	10
Sesquiterpene	1.5	15
Diterpene	2	20
Triterpene	3	30

Examples of terpenes include the diterpene retinol (vitamin A) and the plant compound β-carotene, a tetraterpene that can act as a precursor of retinol.


Retinol
(Vitamin A)

β-Carotene
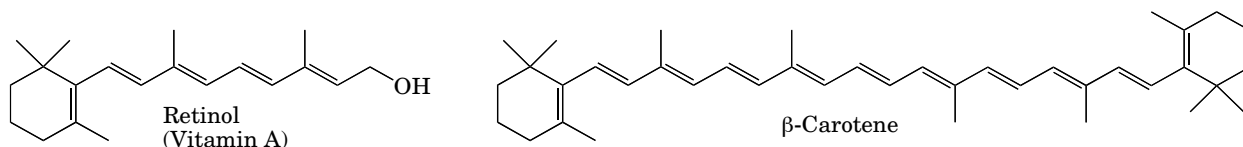
Dolichol is formed from 14-24 isoprene units, corresponding to 70-120 carbons; dolichol phosphate is used as enzyme co-factor in carbohydrate addition to proteins and other molecules.
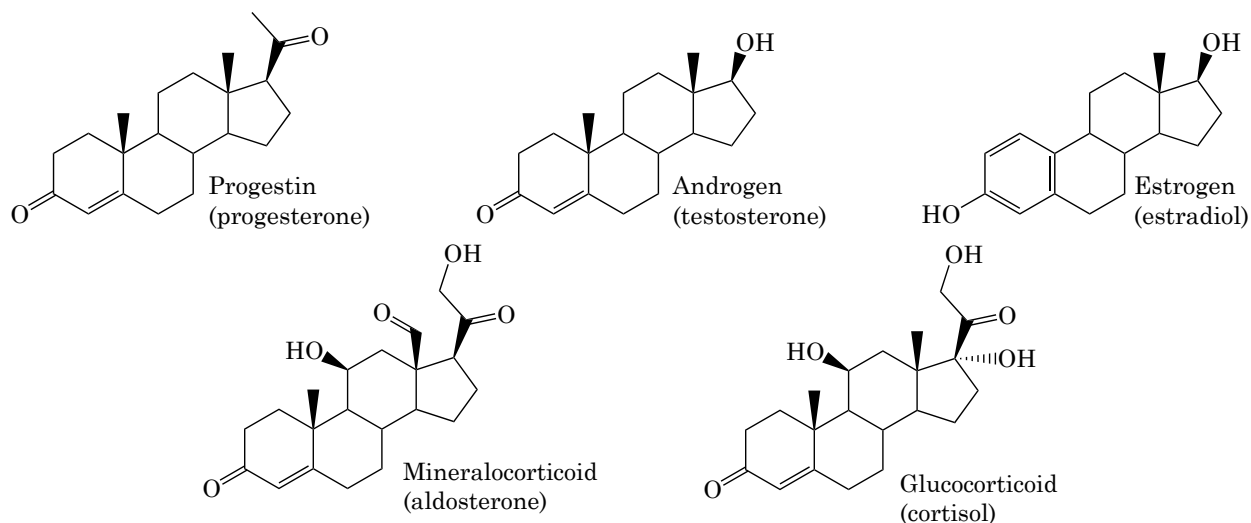

Dolichol
(n = 14 - 24)
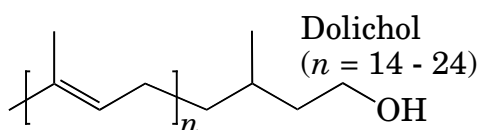
Squalene is a triterpene (30 carbons) compound formed from 2 sesquiterpenes linked tail to tail.
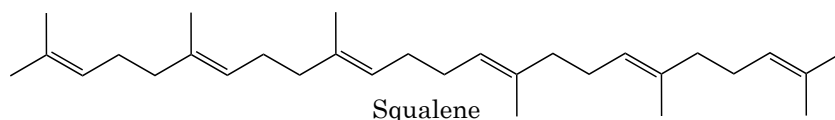

Squalene

Squalene acts as a precursor of cholesterol. Cholesterol is therefore a 27-carbon terpene derivative (the synthesis of cholesterol involves the removal of three of the carbons from the original squalene, among a considerable number of other reactions). Cholesterol itself is important molecule required for proper membrane structure in animals; it also used as starting material for bile acid synthesis.
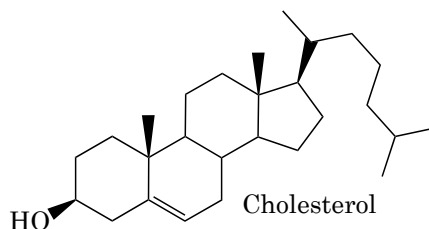

Cholesterol

In addition, cholesterol is the precursor for a wide variety of steroid hormones, including the sex steroids (androgens, estrogens, and progestins) and the glucocorticoids and mineralocorticoids.

Progestin
(progesterone)

Androgen
(testosterone)

Estrogen
(estradiol)

HO

Mineralocorticoid
(aldosterone)

Glucocorticoid
(cortisol)

Finally, cholesterol is the precursor for the secosteroid vitamin D and its hormone derivative, 1α,25-dihydroxyvitamin D.

Cholecalciferol
(Vitamin D$_3$)

HO

1α,25-Dihydroxy-
vitamin D$_3$

OH

HO

OH
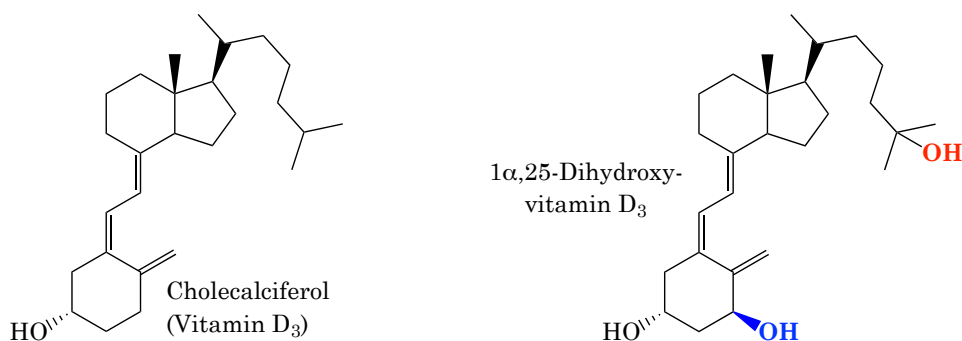
Another class of simple lipid is a family of compounds called **prostaglandins**. Prostaglandins act as signaling molecules. Prostaglandins are derived from 20-carbon polyunsaturated fatty acids. The most commonly used of these fatty acids is arachidonic acid, although ω^3 20:5 fatty acids can also be used. Some examples of arachidonic acid derivative prostaglandins are shown below.

PGE$_2$

HO   OH

PGF$_{2\alpha}$

HO   OH

PGI$_2$
(Prostacyclin)

HO   OH
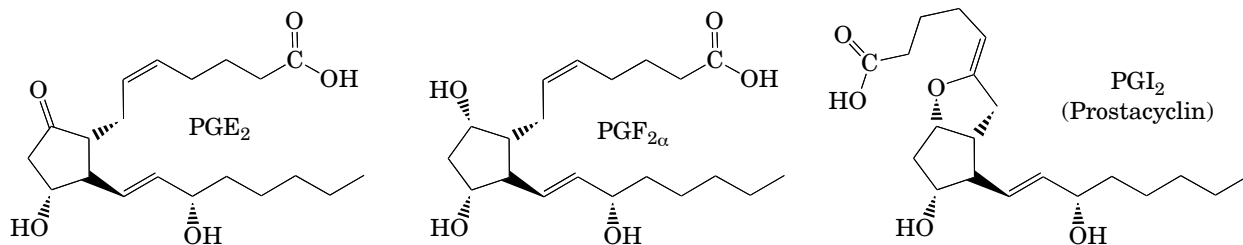
Complex Lipids

A complex lipid is a compound produced by forming a covalent bond between one lipid molecule and another. Complex lipids exhibit a large variety of structural and functional roles, including energy storage, barrier formation, and lipid transport. An

example of the last is a **cholesteryl ester**, which is formed by an ester link of a fatty acid to cholesterol. Cholesteryl esters are extremely hydrophobic, and are used for storage and transport of cholesterol. A **wax** is a type of barrier molecule comprised of a long chain alcohol with an ester link to a fatty acid. Waxes are extremely hydrophobic. Waxes are used for water-repellent coatings of skin, fur, feathers . . . and also for cosmetics, automobiles, and candles.

Cholesteryl palmitate

An example of a wax
(**9-*cis*-octadecenoyl stearoate**)
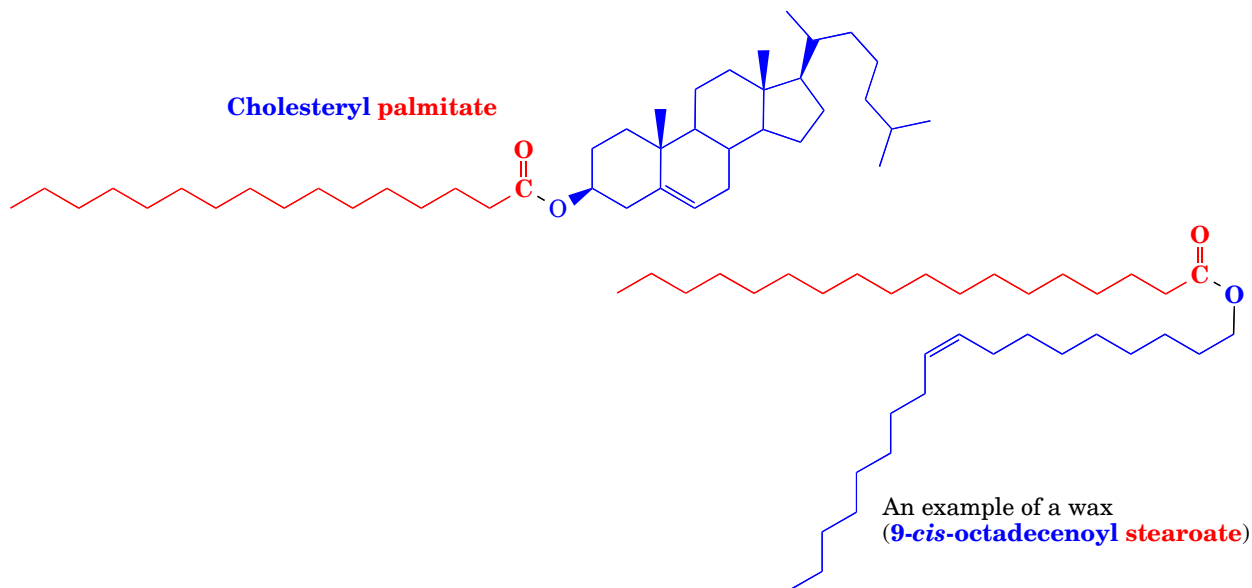
Triacylglycerols

Triacylglycerols (formerly called triglycerides) are complex lipids. Triacylglycerols act as energy storage molecules, especially in adipose tissue; triacylglycerols are also found in lipoproteins. Triacylglycerols are **not** found in membranes, because they are essentially entirely non-polar. Triacylglycerols consist of three fatty acid molecules forming ester links to glycerol. A triacylglycerol molecule can be comprised of different fatty acids, or of three identical fatty acids.

Glycerol

CH_2-CH–CH_2
OH OH OH

Triacylglycerol

CH_2 CH-CH_2
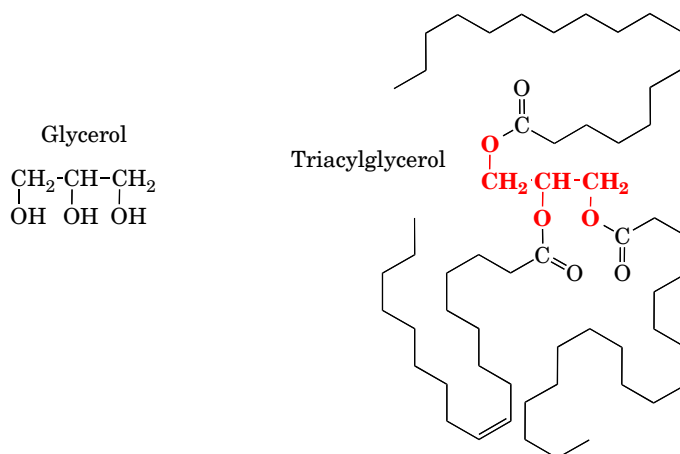
Glycerophospholipids

Glycerophospholipids are the major component of biological membranes. As with triacylglycerols, glycerophospholipids are composed of a glycerol backbone forming ester linkages to fatty acids. However, the third position is a phosphate ester,

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rather than a fatty acyl ester. This makes the glycerophospholipid molecule considerably more polar, because the phosphate group is charged under physiological conditions.

In animal membranes, the fatty acyl chain attached at the 2 position is usually unsaturated. The example shown below is 1-stearoyl, 2-oleoyl phosphatidic acid. Note that the fatty acyl chains can vary considerably, and these are merely examples.
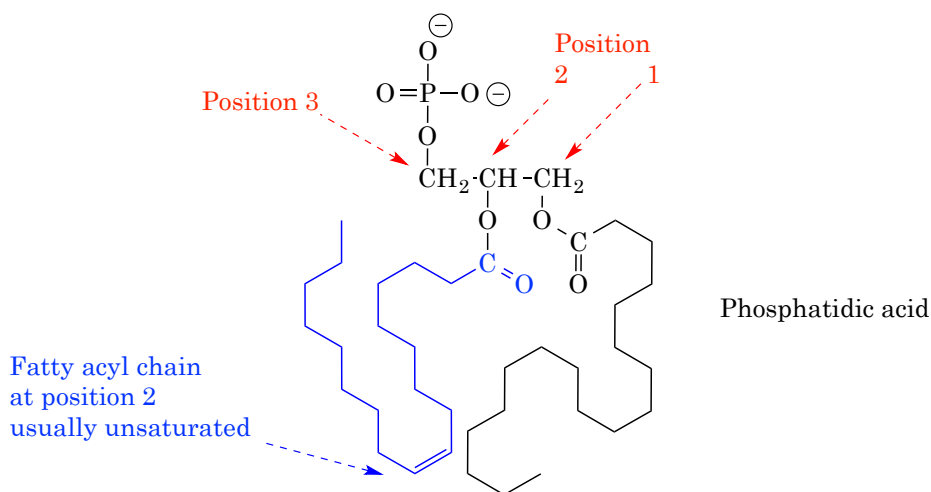

Phosphatidic acid

Phosphatidic acid is not a major membrane component, although it does act as a precursor for some glycerophospholipids. Some common membrane glycero-phospholipids are shown below. Note that each is based on the phosphatidic acid structure, with an additional compound esterified to the phosphate. The phosphate and this additional compound are collectively called the **head group** of the phospholipid. Note that in each case, the head group is a polar molecule.


Phosphatidylethanolamine

Phosphatidylcholine

Phosphatidylserine
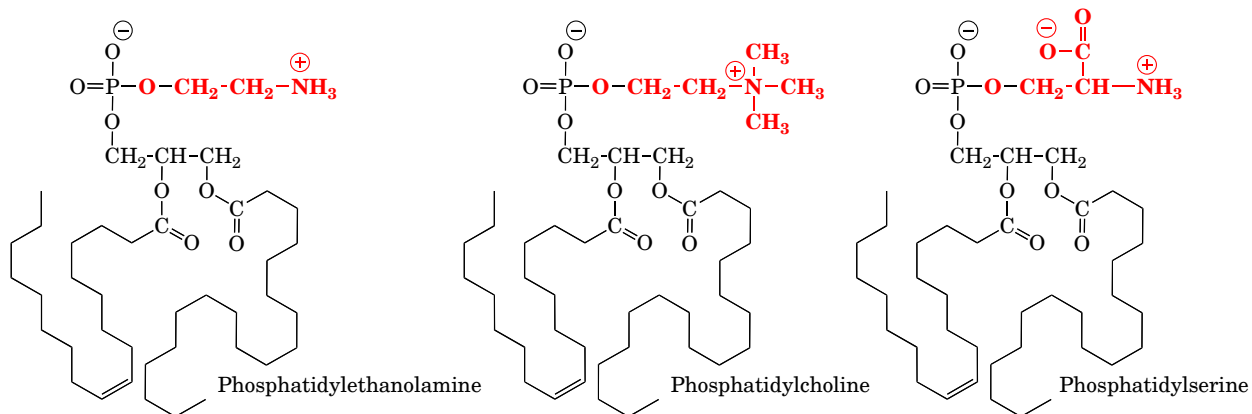
Lipids as intracellular signaling molecules

Phosphatidylinositol is another type of glycerophospholipid that is normally found in animal membranes. It is important because it can be cleaved to release several important signaling molecules. The ring structure that comprises part of the head group is **inositol**. Note that inositol is not actually a carbohydrate (the ring atoms are all carbons). The ring hydroxyls can be phosphorylated varying numbers of times to produce phosphatidylinositol bisphosphate and related compounds, and the increased charge that results can alter membrane structure.


Phosphatidyl inositol
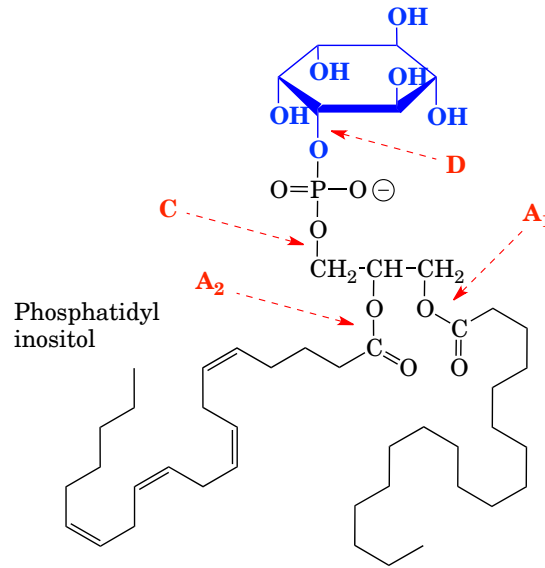
More importantly, enzymes called phospholipases can specifically hydrolyze the ester bonds in the molecule. The cleavage positions of each type of phospholipase are shown on the diagram above. **Phospholipase A$_2$** removes the 2-position acyl chain (this is usually arachidonic acid; the released arachidonic acid can then be converted to prostaglandins or other compounds). **Phospholipase C** removes the phosphate (and attached compounds), which leaves **diacylglycerol**. Diacylglycerol is much less polar than the parent glycerophospholipid, and its production can alter membrane structure. Diacylglycerol can also activate the family protein kinase C family of enzymes, and these kinases, by phosphorylating cellular enzymes, can alter cellular behavior.

In addition to diacylglycerol release, the action of phospholipase C results in release of inositol phosphates. These molecules are then capable of influencing cellular functions. The most studied of these is **inositol trisphosphate**, which acts to release calcium ions from stores in the endoplasmic reticulum. We will return to these concepts when we discuss signal transduction.

Inositol 1,4,5-trisphosphate (IP$_3$)
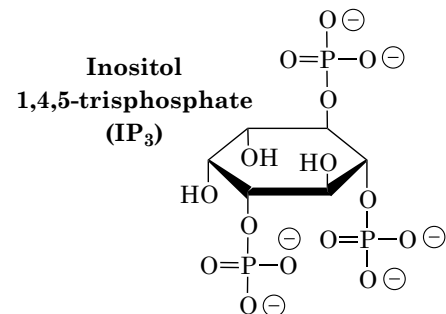
Ether Glycerophospholipids

Another membrane component is closely related to the glycerophospholipids. In the case of **ether glycerophospholipids** (these compounds are also called **plasmalogens**), the 1-position chain is formed from a long chain alcohol, rather than a fatty acid. The result is an ether linkage to the glycerol backbone. As with the standard glycerophospholipids, ether glycerophospholipids can have a variety of head groups (choline is shown in the example below). Ether glycerophospholipids are relatively minor membrane components, and are much less common than the glycerophospholipids discussed above.

Ether phosphatidylcholine
(1-octadecyl, 2-oleoyl phosphatidylcholine)
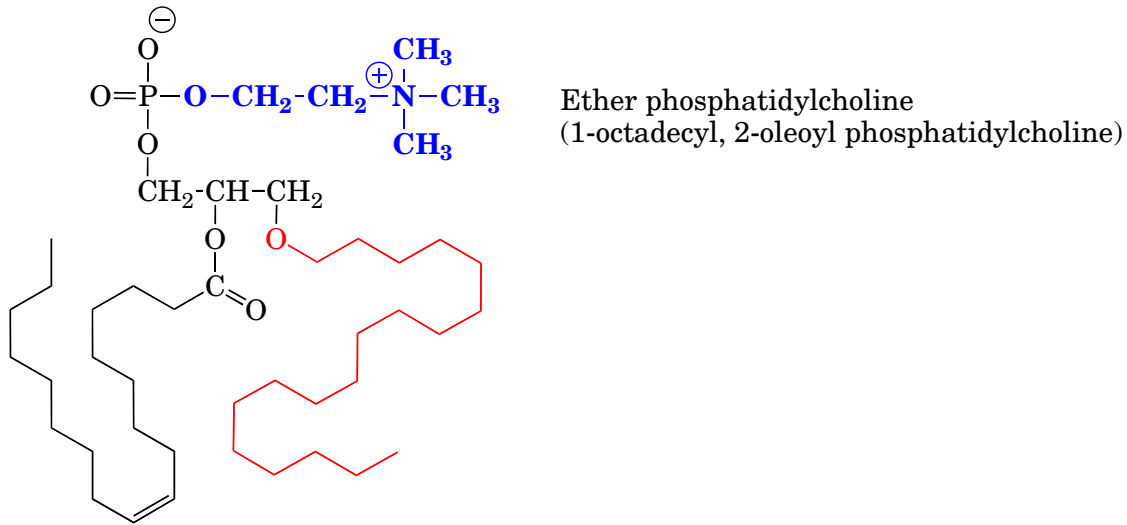
Sphingolipids

Another minor but important class of membrane lipids is comprised of the sphingolipids. Sphingolipids are not based on glycerol, but instead are derivatives of **sphingosine**, an 18-carbon amino alcohol. Note that sphingosine contains a *trans* double bond. Sphingolipids are important in plasma membranes, especially in those of neurons.
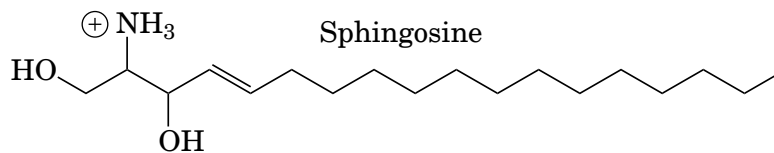
Sphingosine

The simplest sphingolipid is **ceramide**, which is formed from sphingosine in an amide linkage to a fatty acid.
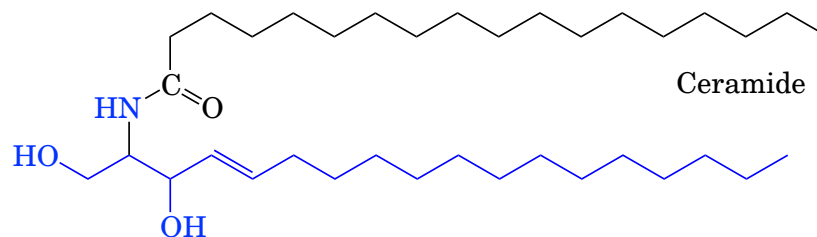
Ceramide

More important, and more commonly observed than ceramide, are **sphingomyelins**, which are ceramide derivatives. Sphingomyelins are phosphate esters of ceramide, and like the other phospholipids, usually have an additional group attached to the phosphate. The possible other groups are also similar to those found in the other phospholipids, and include choline (part of the head group of the sphingomyelin shown below) and ethanolamine.

Sphingomyelin
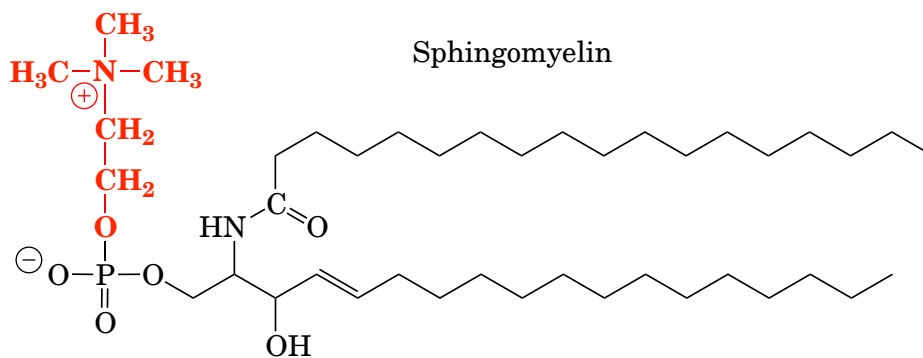
Cerebrosides are ceramide derivatives linked to a carbohydrate by an ether link to the 1-position alcohol of the sphingosine backbone. (Recall that "oside" indicates linked to carbohydrate.) Most cerebrosides contain either β-D-glucose or β-D-galactose (a cerebroside with β-D-galactose is shown below). Note that cerebrosides lack phosphate, and are typically non-ionic compounds, although some variants contain ionizable groups attached to the carbohydrate group of the cerebroside.
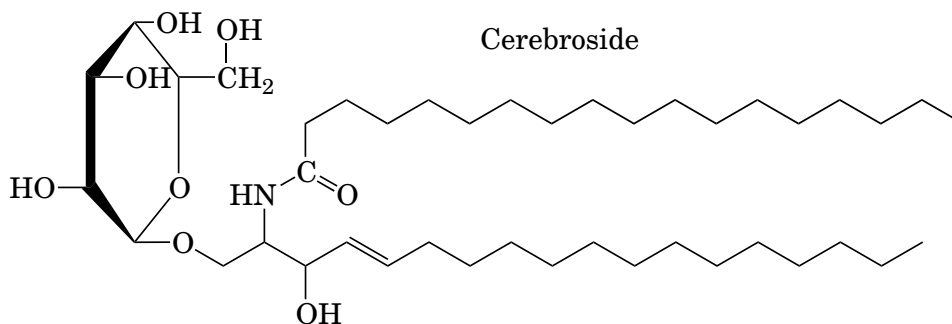
Cerebroside

Gangliosides are related to cerebrosides, but are more complex. Gangliosides contain three or more sugar residues, with N-acetyl-neuraminic acid, a more complicated monosaccharide derivative, at the end of the chain. Gangliosides are important components of nerve cells (the term is derived from the word ganglion, which is another name for the nerve terminal). Cerebrosides and related glycosphingolipids are thought to be important in mediating cell-cell recognition.

Neuronal tissues must contain the **correct** amount of these compounds: too much causes severe, and often fatal, problems. For example, lack of the enzyme hexosaminidase A, part of a ganglioside degradation pathway, results in Tay-Sachs disease, which is a genetic neurological disorder fatal early in life due to accumulation of ganglioside G_{M2}.

Ganglioside G$_{M2}$

Hexosaminidase A

Ganglioside G$_{M1}$

+

N-acetyl-Galactosamine

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