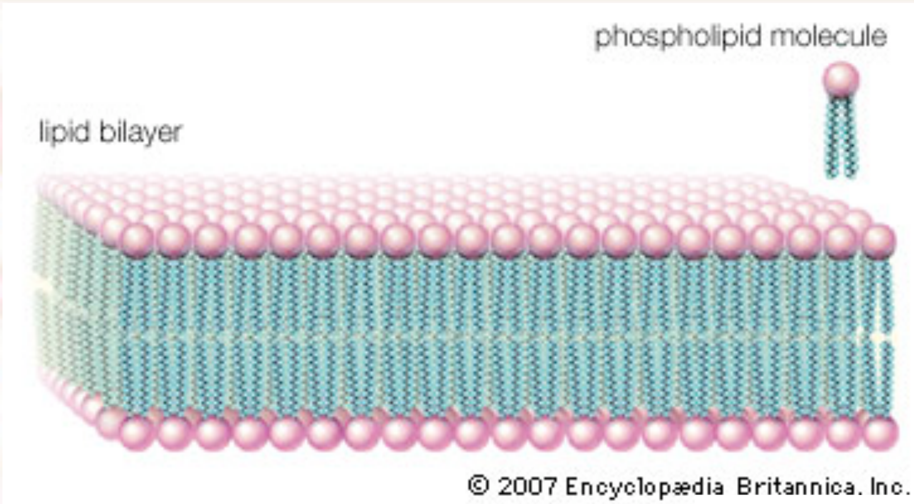
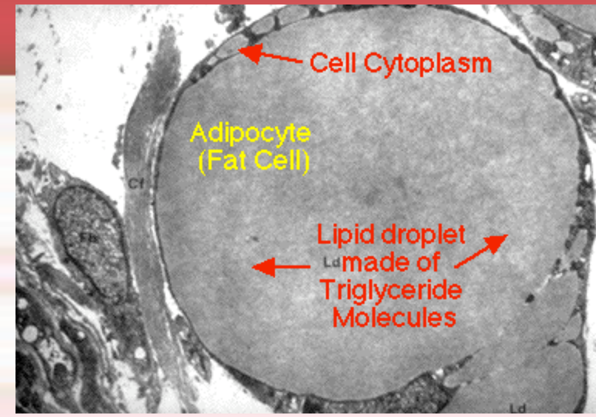
Biomolecules: lipids

Lipids: functions.

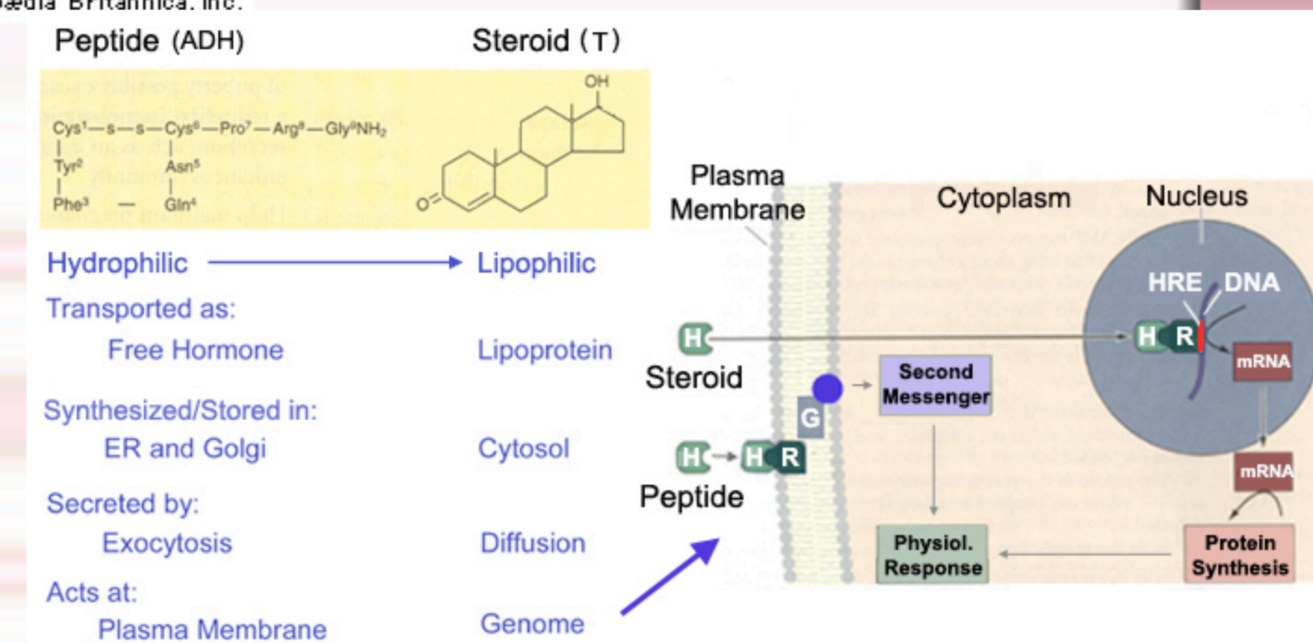
Structure





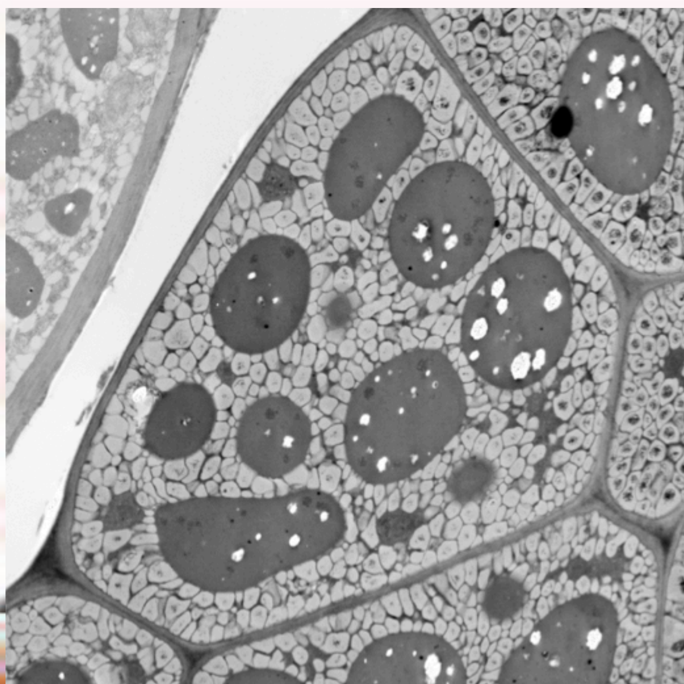
Energy storage

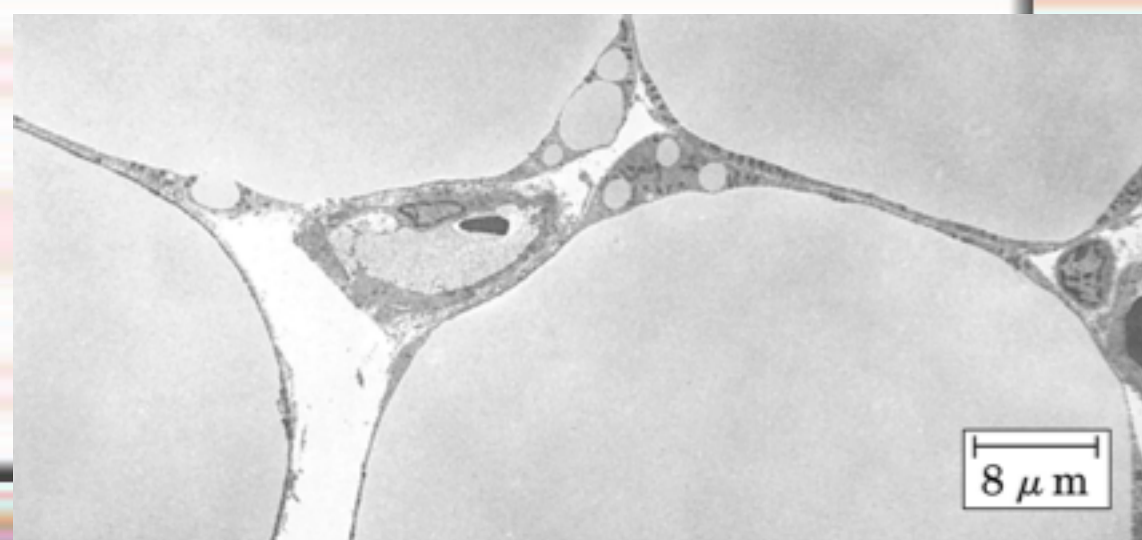
Signalling.



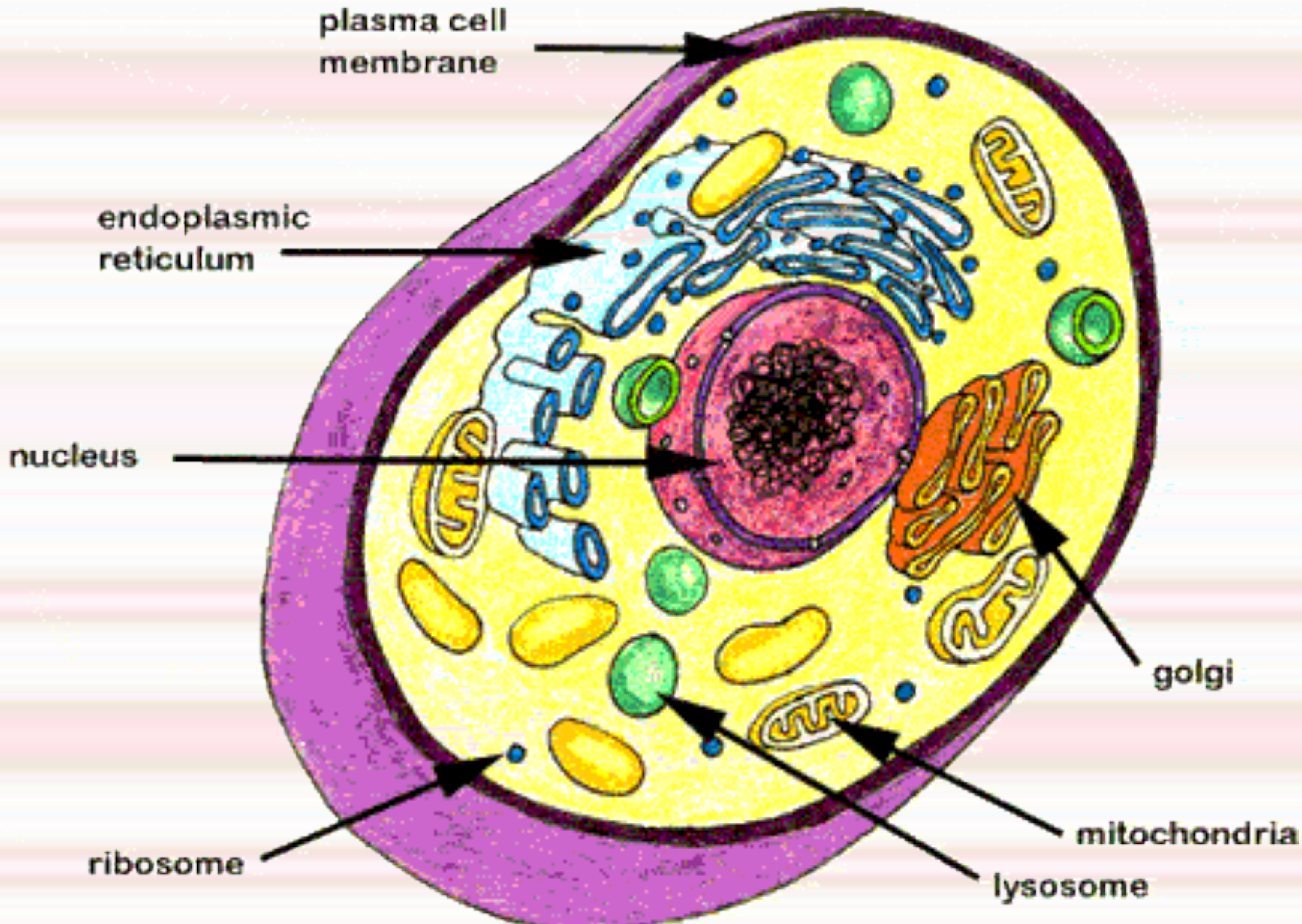
Organic biomolecules: lipids

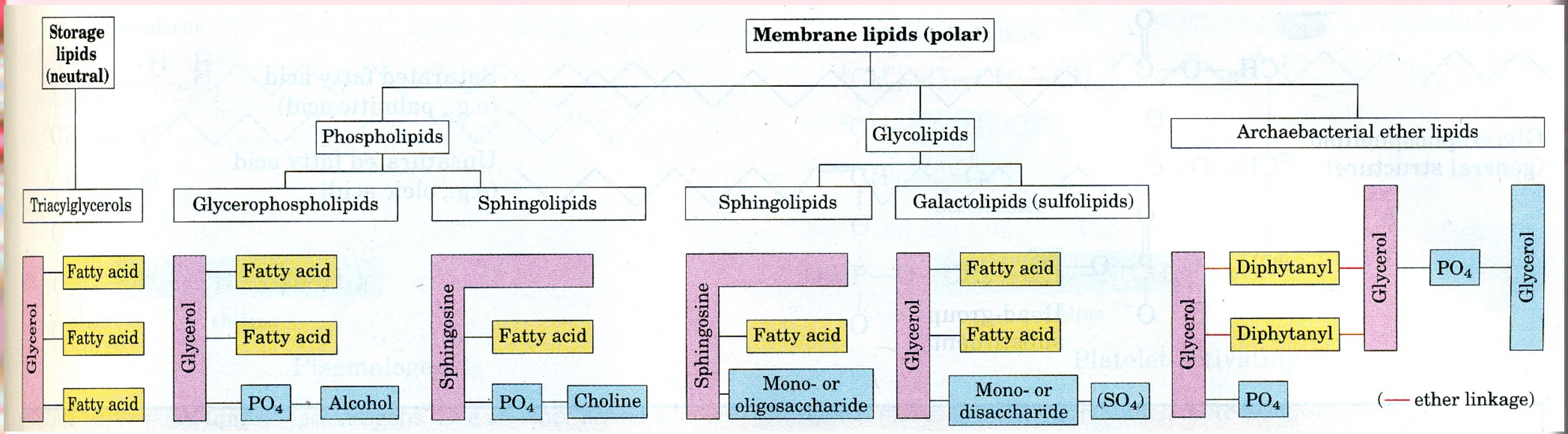
- Organic amphiphilic compounds insoluble in water
- Easily extracted from animal and vegetal cells using apolar solvents
- Fundamental to build cell's shape and organelles
- They form a heterogeneous class, difficult to classify in a simple manner





Compartmentalization is essential for a living cell





Storage lipids (neutral)
Triacylglycerols
Glycerol
Fatty acid
Fatty acid
Fatty acid
Membrane lipids (polar)
Phospholipids
Glycerophospholipids
Glycerol
Fatty acid
Fatty acid
PO4
Alcohol
Sphingolipids
Sphingosine
Fatty acid
PO4
Choline
Glycolipids
Sphingolipids
Sphingosine
Fatty acid
Mono- or oligosaccharide
Galactolipids (sulfolipids)
Glycerol
Fatty acid
Fatty acid
Mono- or disaccharide
(SO4)
Archaebacterial ether lipids
Glycerol
Diphytanyl
Diphytanyl
PO4
Glycerol
PO4
Glycerol
(— ether linkage)

A short list of lipid classes

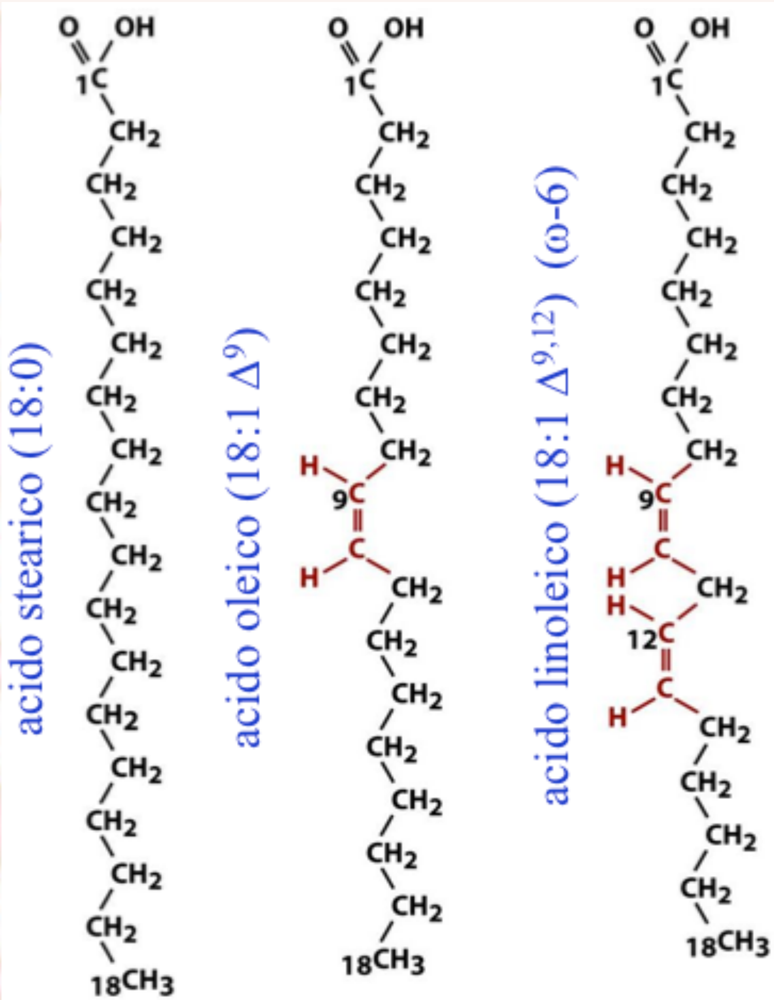
- **Fatty acids (FA)**: organic carboxylic acids with long carbon chains (C >7), saturated, unsaturated, subjected to esterification
- **Glycerides**: mono-, di-, tri-esters of fatty acids and glycerol
- **Ceramides**: esters of sphingosine and fatty acids
- **Phospholipids**: di-esters of glycerol-3-Phosphate or esters of sphingosine-phosphate
- **Cerebrosides (glycolipids)**: esters of sphingosine with 1 FA and 1 sugar with 6-C (hexose)
- **Gangliosides**: glycolipids in which the sugar moiety is complex and branched
- **Steroids:** derivatives of cholesterol **(**cicle-pentane-peri-hydro-phenanthrene**)**
- **Terpenoids**: compounds made by repetitions of isoprenes units (2-methyl-butadiene)

Heat (energy) production

Compound	Kcal/g
Methane	13.3
Octane	11.5
Stearic Acid (lipids)	9.5
Alanine (protein)	4.4
Glucose (sugars)	3.7

Lipids allow efficient energy storage, also due to the fact that they are stored in an anhydrous manner.

The most common FAs in biological membranes



In the membrane there are always FA with an even number of C.

In case there are, double bonds are always in cis configuration.

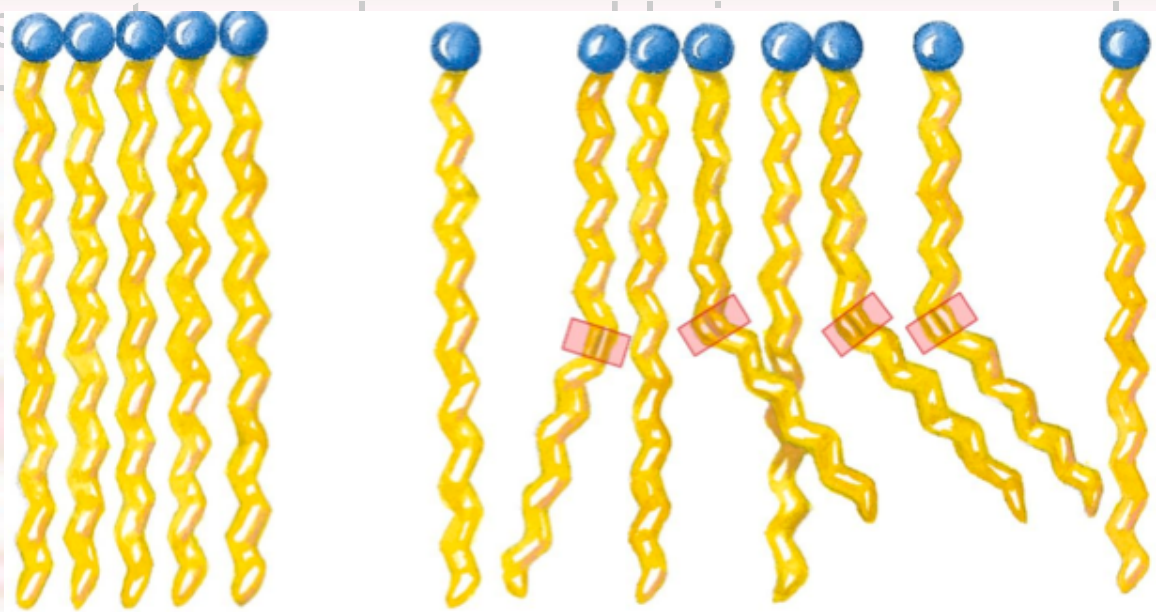
The old notation ω-3, ω-6 and ω-9 refers to the position of the first double bond, counting how many carbon atoms are left before the end

Some naturally occurring Fatty Acids

Carbon skeleton	Structure*	Systematic name[†]	Common name (derivation)	Melting point (°C)
12:0	$CH_3(CH_2)_{10}COOH$	*n*-Dodecanoic acid	Lauric acid (Latin *laurus*, "laurel plant")	44.2
14:0	$CH_3(CH_2)_{12}COOH$	*n*-Tetradecanoic acid	Myristic acid (Latin *Myristica*, nutmeg genus)	53.9
16:0	$CH_3(CH_2)_{14}COOH$	*n*-Hexadecanoic acid	Palmitic acid (Latin *palma*, "palm tree")	63.1
18:0	$CH_3(CH_2)_{16}COOH$	*n*-Octadecanoic acid	Stearic acid (Greek *stear*, "hard fat")	69.6
20:0	$CH_3(CH_2)_{18}COOH$	*n*-Eicosanoic acid	Arachidic acid (Latin *Arachis*, legume genus)	76.5
24:0	$CH_3(CH_2)_{22}COOH$	*n*-Tetracosanoic acid	Lignoceric acid (Latin *lignum*, "wood" + *cera*, "wax")	86.0
16:1(Δ^9)	$CH_3(CH_2)_5CH{=}CH(CH_2)_7COOH$	*cis*-9-Hexadecenoic acid	Palmitoleic acid	−0.5
18:1(Δ^9)	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$	*cis*-9-Octadecenoic acid	Oleic acid (Latin *oleum*, "oil")	13.4
18:2($\Delta^{9,12}$)	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$	*cis*-,*cis*-9,12-Octadecadienoic acid	Linoleic acid (Greek *linon*, "flax")	−5
18:3($\Delta^{9,12,15}$)	$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$	*cis*-,*cis*-,*cis*-9,12,15-Octadecatrienoic acid	α-Linolenic acid	−11
20:4($\Delta^{5,8,11,14}$)	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_3COOH$	*cis*-,*cis*-,*cis*-,*cis*-5,8,11,14-Icosatetraenoic acid	Arachidonic acid	−49.5

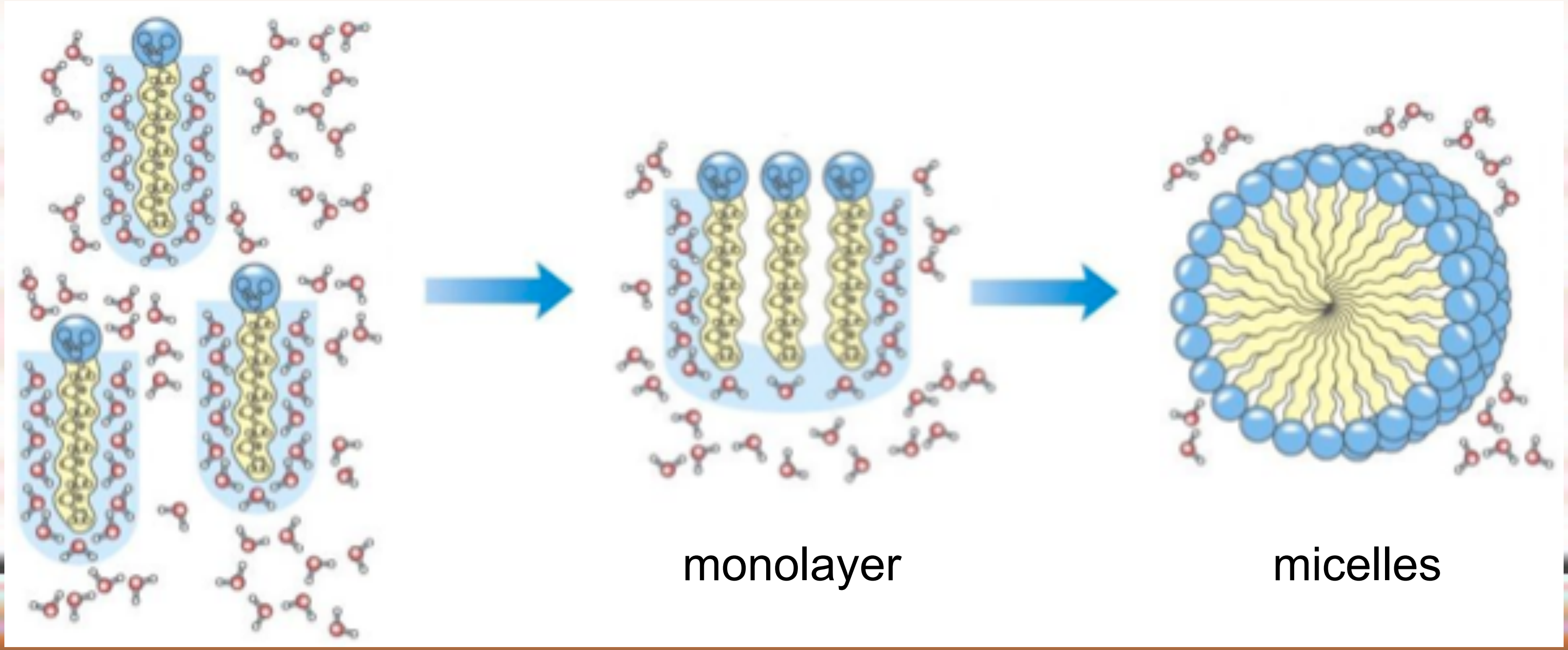
FAs packing

- 3D packing or assembly of FAs depends on the degree of unsaturation (no. of double bonds)
- The main consequence of this packing is the melting temperature: saturated FAs are solid at RT, unsaturated FAs have lower Tm)
- FAs s … tions in order … ter



FAs packing

- 3D packing or assembly of FAs depends on the degree of unsaturation (no. of double bonds)
- The main consequence of this packing is the melting temperature: saturated FAs are solid at RT, unsaturated FAs have lower Tm)
- FAs spontaneously assemble in aqueous solutions in order to decrease the hydrophobic effect of water

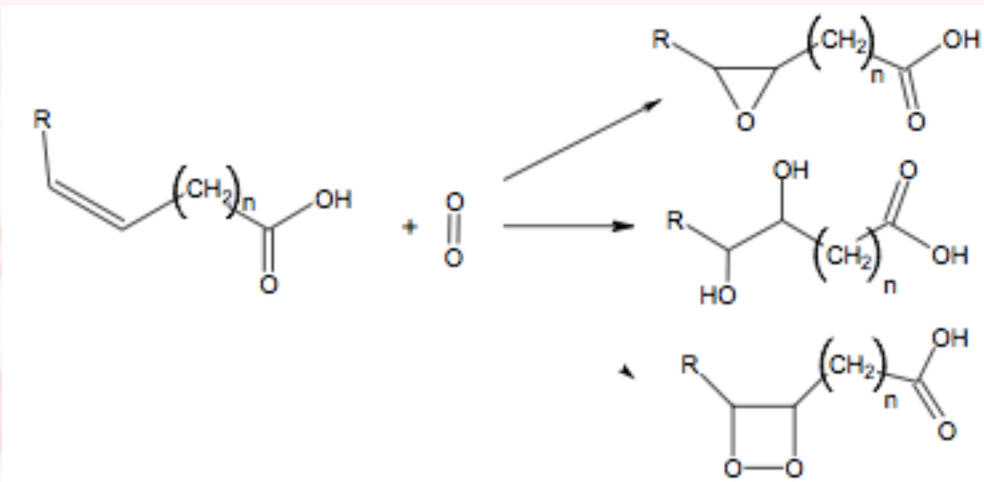


Which reactions do FAs undergo?

- They are weak acids with Ka $10^{-5} – 10^{-6}$, decreasing with increasing chain length
- They can form:
  - esters after reacting with alcohols
  - amides after reacting with amines
  - salts after reacting with a strong base (NaOH / KOH)
- They can be oxidised by enzymes to release energy (beta-oxidations)

Which reactions do FAs undergo?

- Unsaturated FAs can also be oxidised by oxygen radicals, giving rise to epoxides, di-oles, peroxides
- These byproducts are degraded into aldehydes and short chain FA, and are responsible for the bad smell/ taste of out-of-date fat

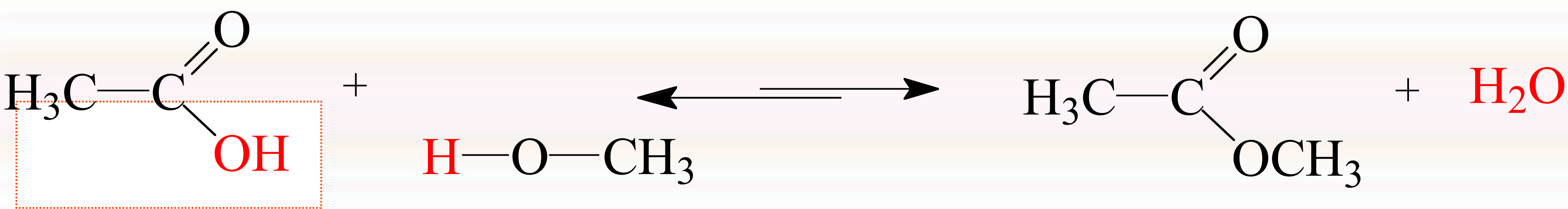


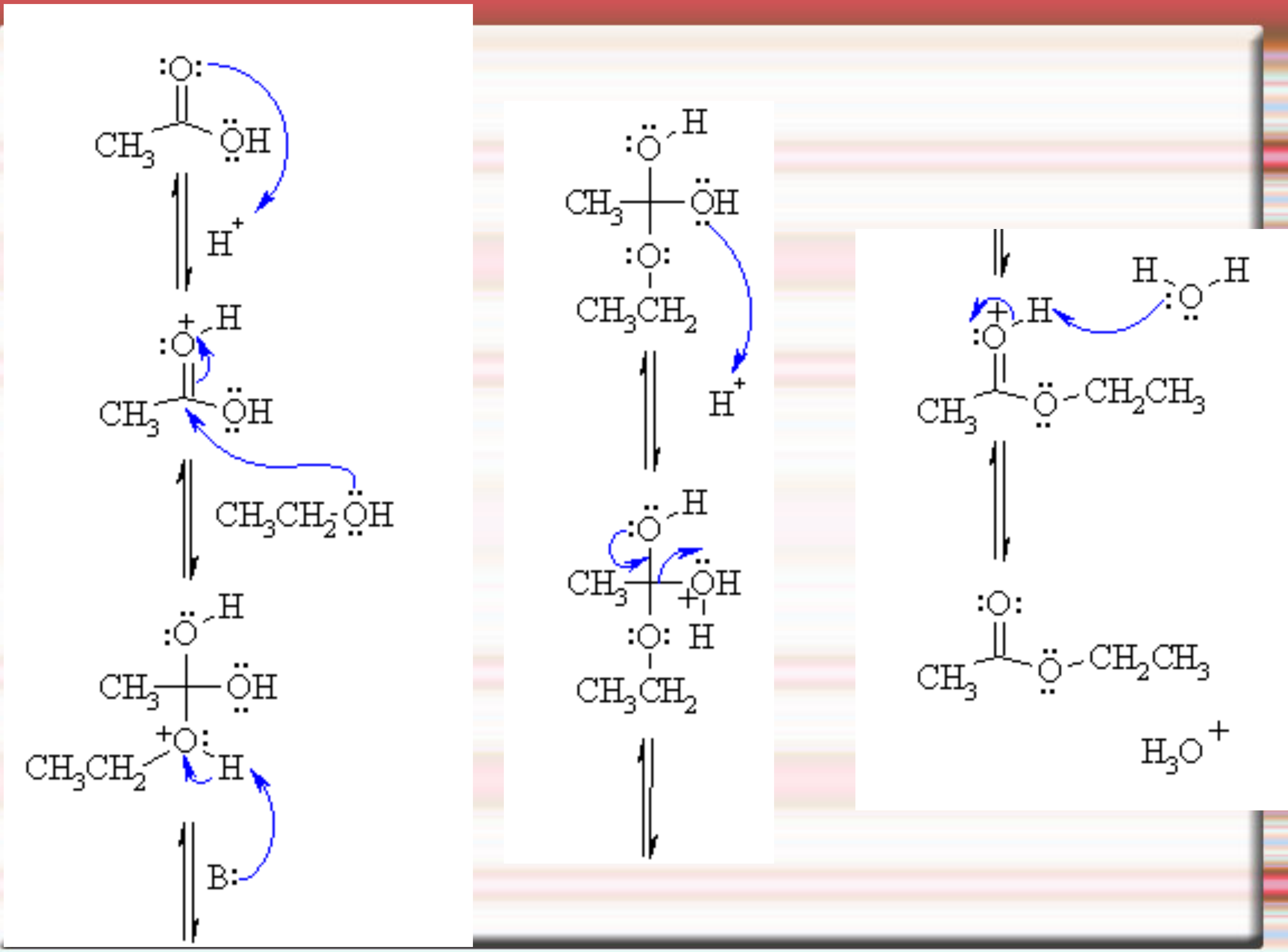
epoxide

di-ole

peroxide

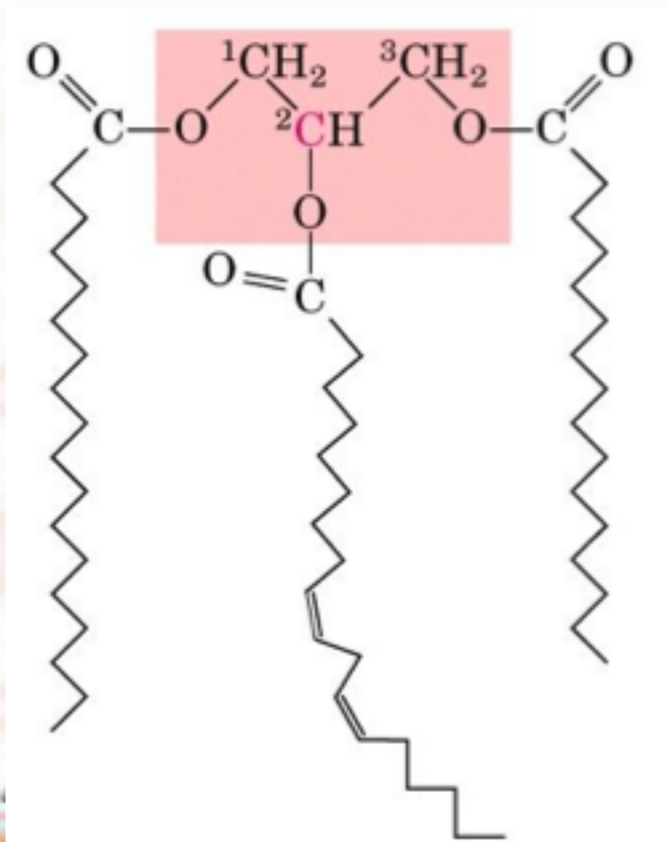
Carboxylic acid + alcohol= esther

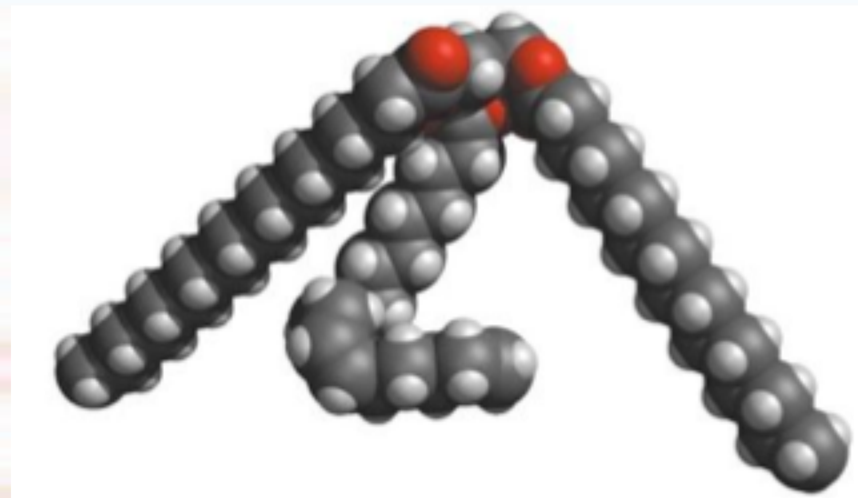




Mono-, di- and tri-glycerides

- Esters of FA(s) with glycerol (1,2,3-propan-tri-ole)
- Triglycerides are neutral lipids used for storage, they are confined in specialised vacuoles of special cells (adipose cells)

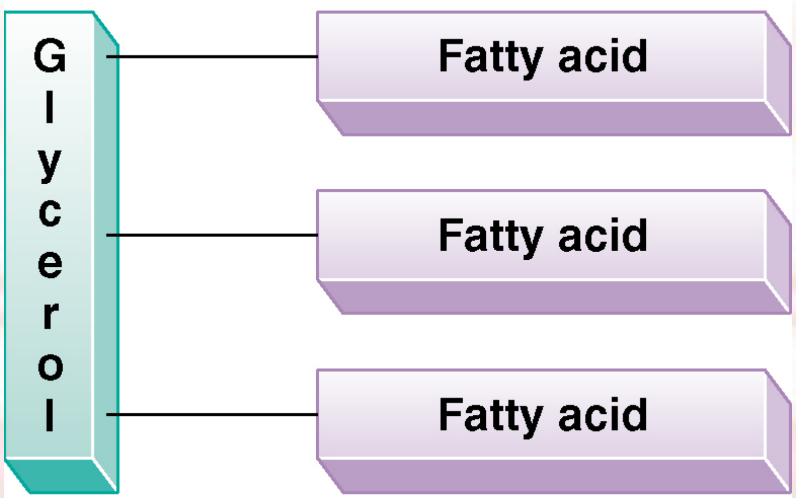




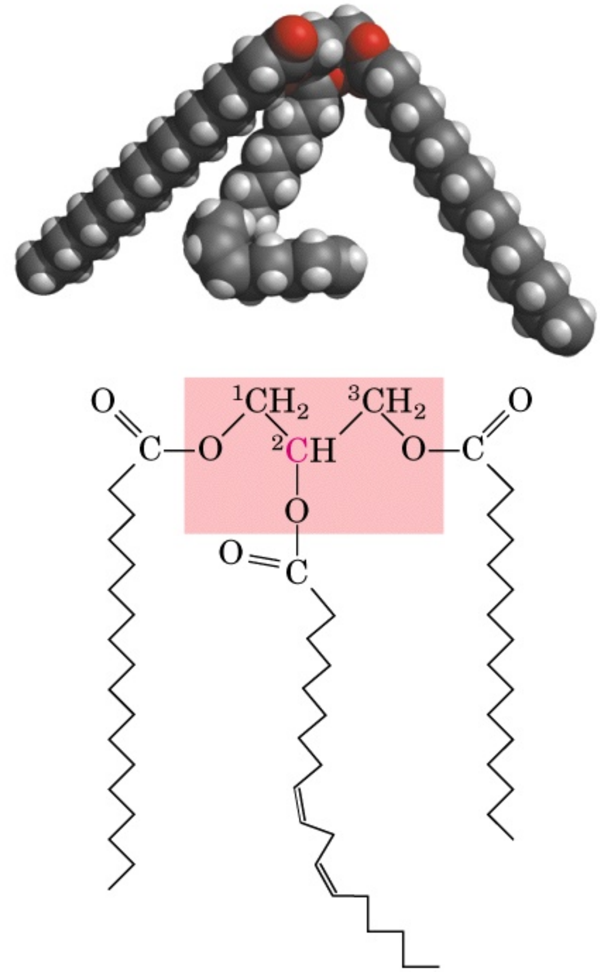
1-stearoyl-2-linoleyl-3-palmitoyl-glycerol

Triglycerides are energy storage molecules in the adipocytes.

The following diagram may help you remember the components of a triglyceride.



Glycerol

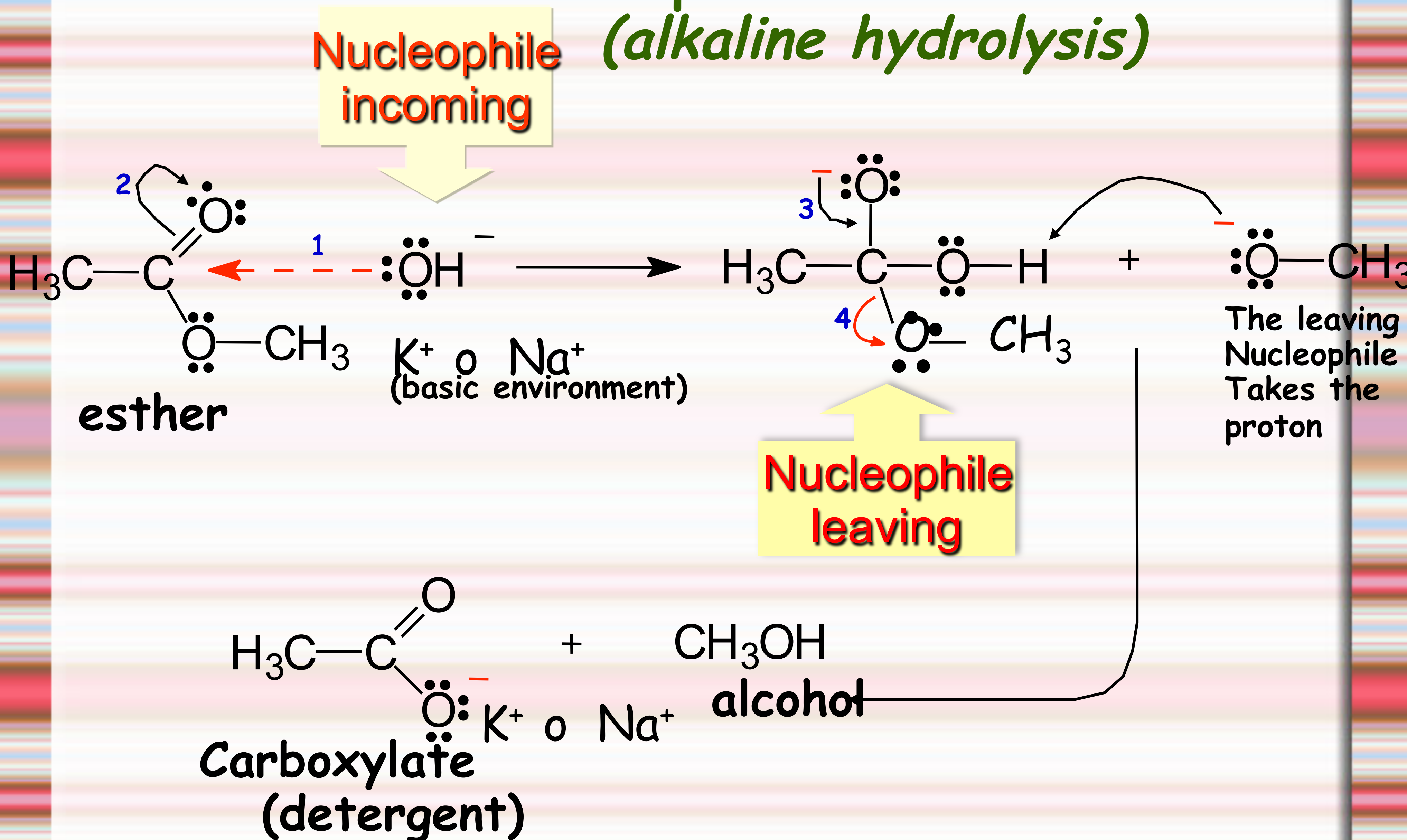


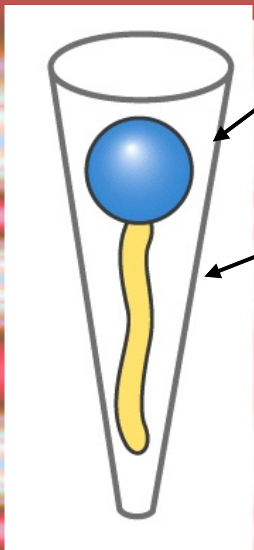
1-Stearoyl, 2-linoleoyl, 3-palmitoyl glycerol, a mixed triacylglycerol

Soap production

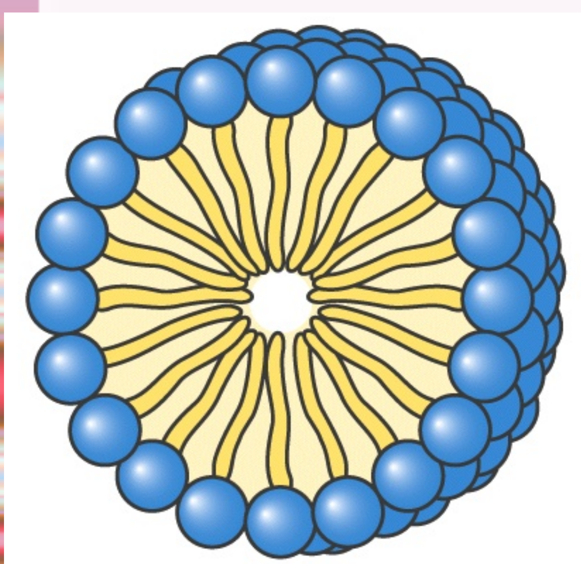
- Soap is the sodium / potassium salt of long chain FAs
- It is produced from either animal or vegetal fat
- The reaction is an alkaline hydrolysis performed at high temperature
- This reaction produces 1 mol of glycerol and 3 mol of salt per 1 mol of triglyceride
- The % of unsaturated FA and presence of additives give solid or liquid soap at room temperature

Saponification Reaction *(alkaline hydrolysis)*

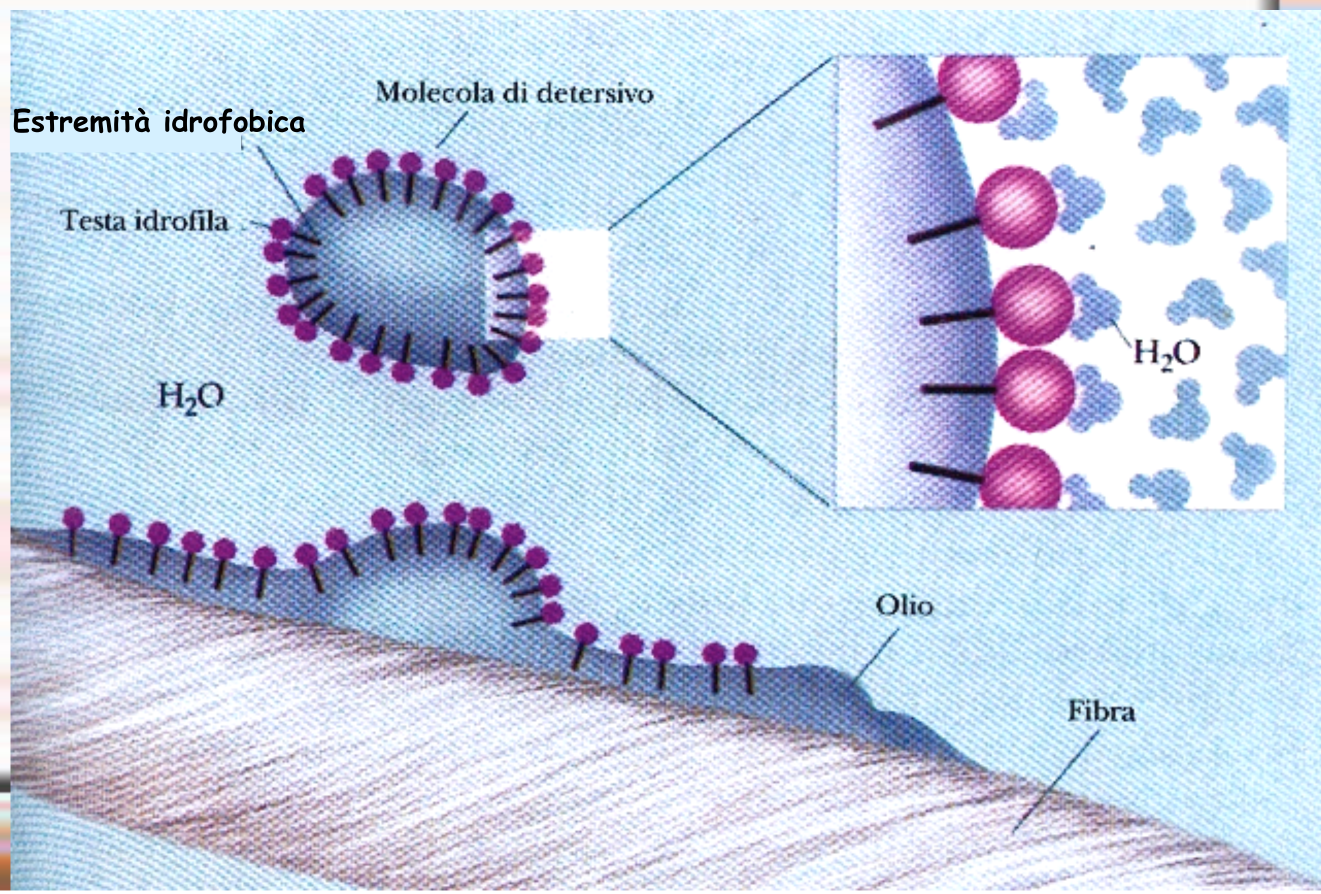




Detergent activity (soap)
(soap=fatty acid salt)



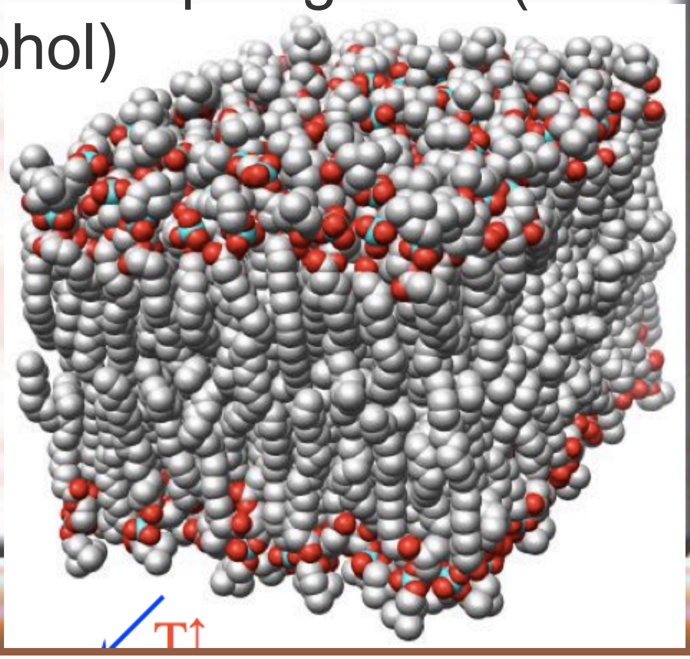
micella



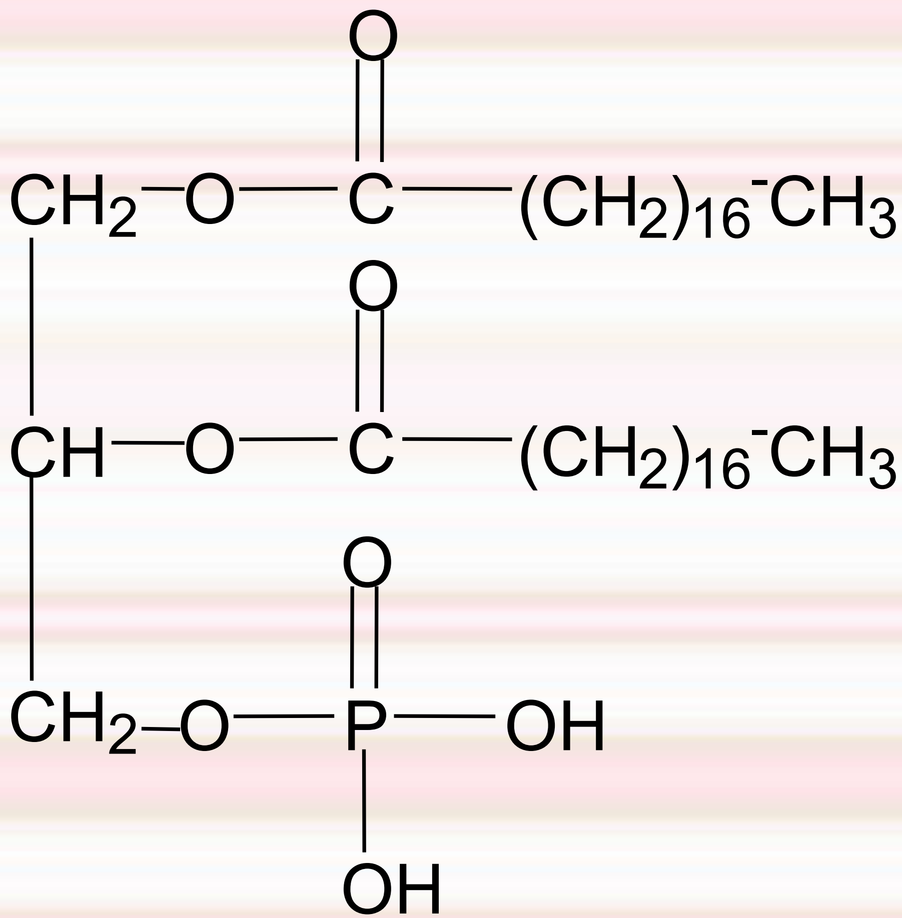
Phospholipids

- These molecules are the scaffold of the membrane lipid bilayer and contain a polar head

- The term phospholipids include two types of polar lipids present in biological membranes:
  - **Glycerol-phospholipids**, synthesized starting from glycerol-3-phosphate (G3P, an intermediate of glucose metabolism)
  - **Sphingolipids**, synthesized from sphingosine (a complex aliphatic amino-alcohol)

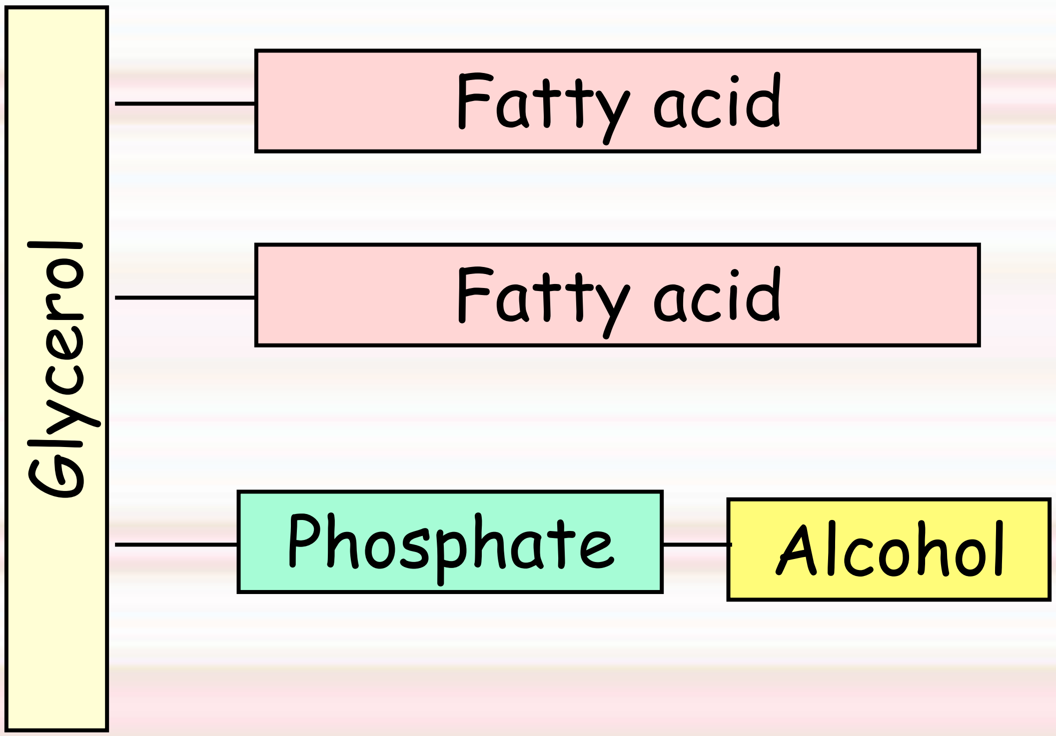


Phosphatidic acid: esther of glycerol with phosphoric acid and two fatty acids



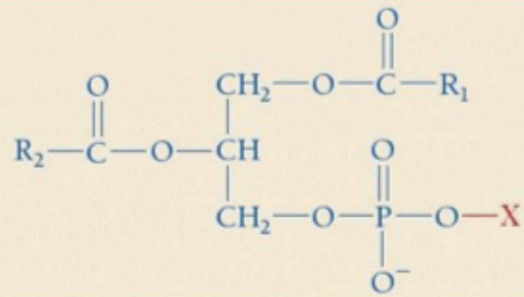
Phosphoglycerides

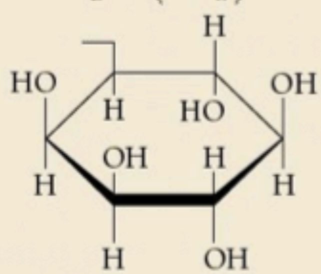
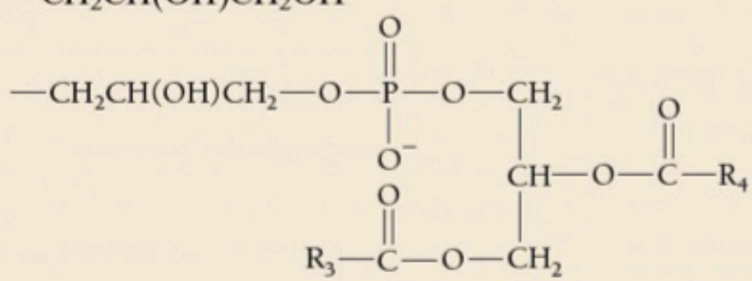
Glycerol + 2 fatty acids+ phosphate + alcohol



In phosphglycerides a fourth (polare/charged) component is bound to the phosphate..

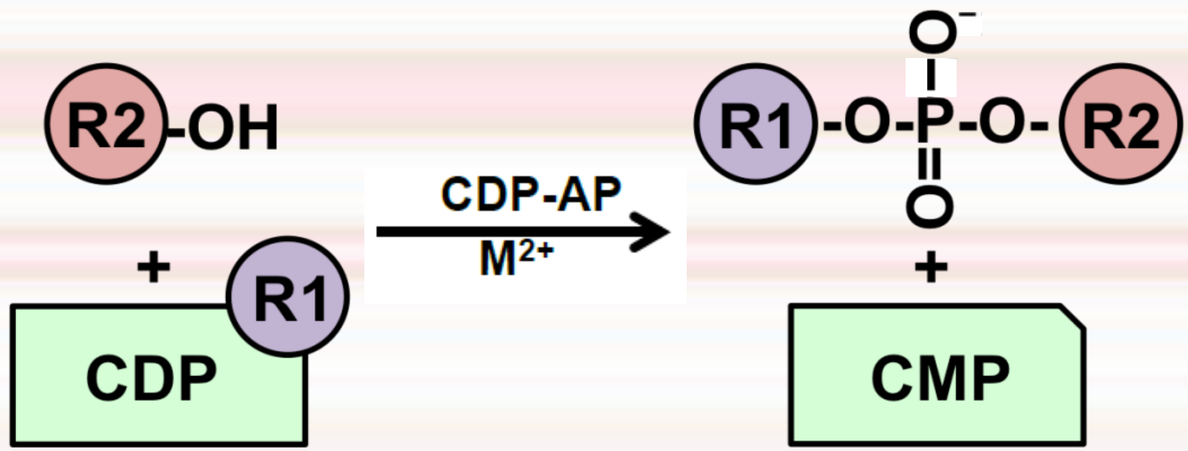
Common classes of glycerophospholipids

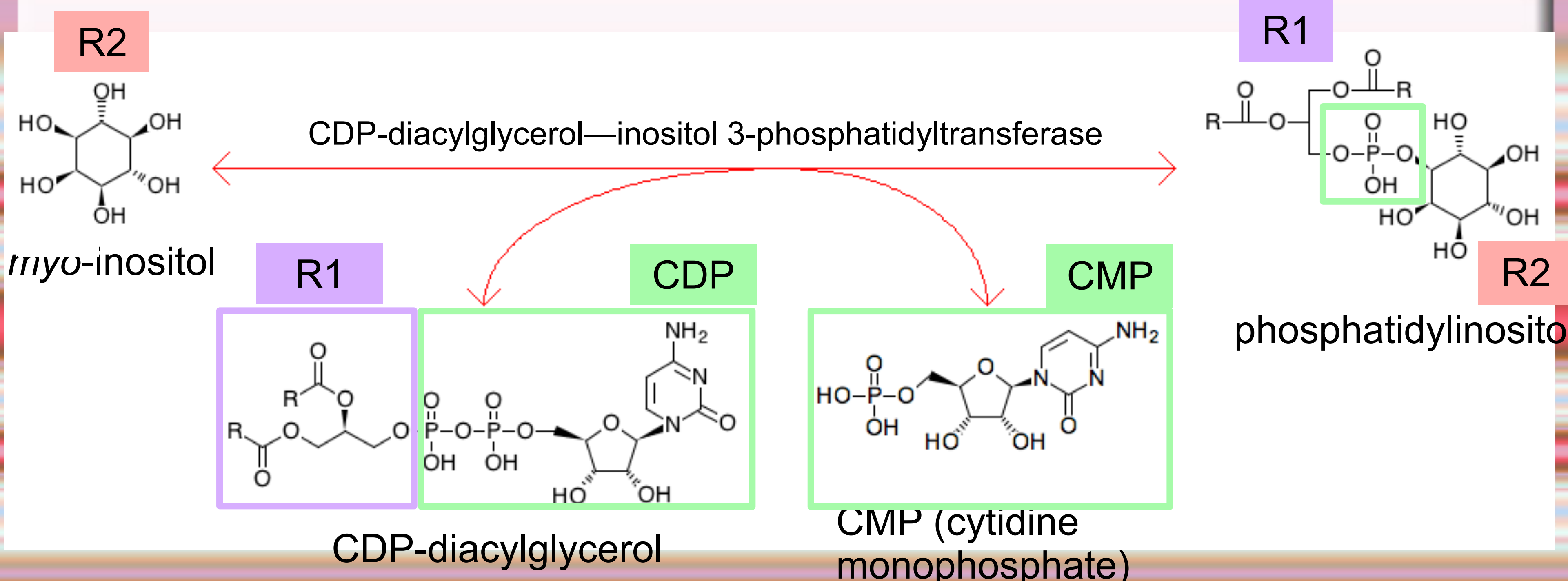


Name of X—OH	Formula of −X	Name of Phospholipid
Water	—H	Phosphatidic acid
Ethanolamine	$-CH_2CH_2NH_3^+$	Phosphatidylethanolamine
Choline	$-CH_2CH_2N(CH_3)_3^+$	Phosphatidylcholine (lecithin)
Serine	$-CH_2CH(NH_3^+)COO^-$	Phosphatidylserine
myo-Inositol		Phosphatidylinositol
Glycerol	$-CH_2CH(OH)CH_2OH$	Phosphatidylglycerol
Phosphatidylglycerol		Diphosphatidylglycerol (cardiolipin)

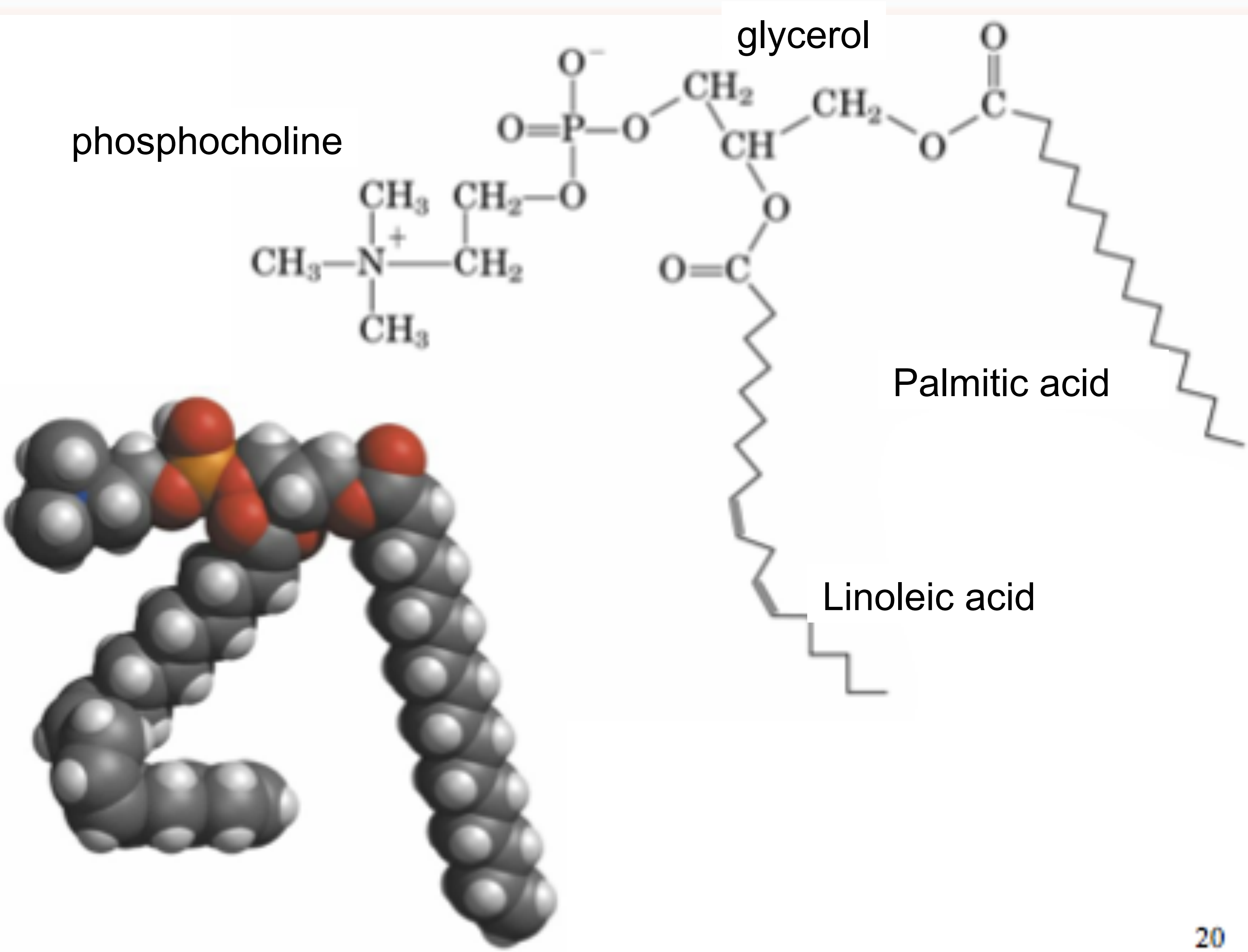
Reaction of CDP-alcohol phosphotransferases

- Transfer a substituted phosphate group from a CDP-linked donor to an alcohol acceptor molecule

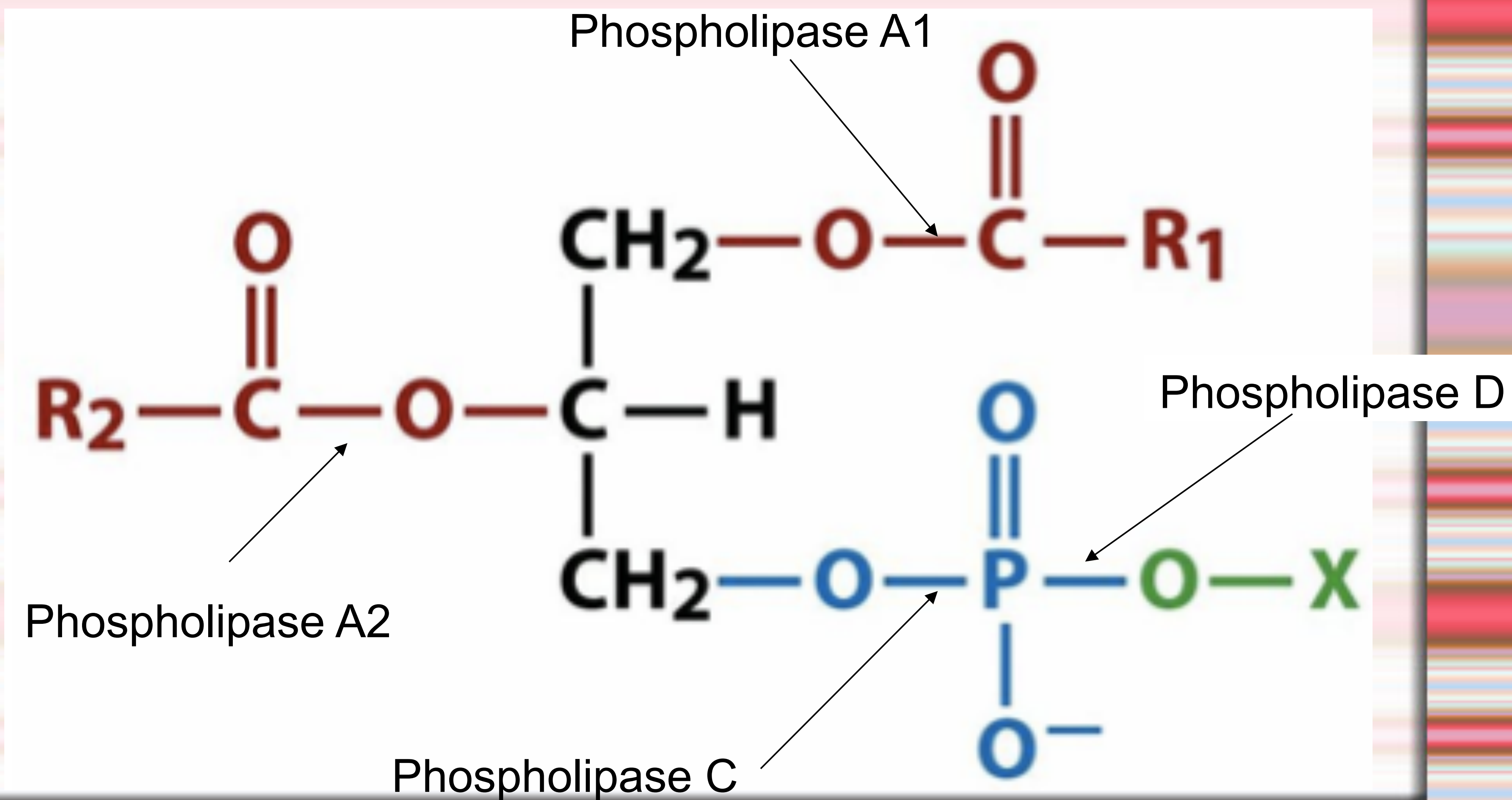




A typical mammalian phospholipid: phosphatidyl-choline (PC)



Phospholipases are enzymes specialised in the hydrolysis of single ester bonds

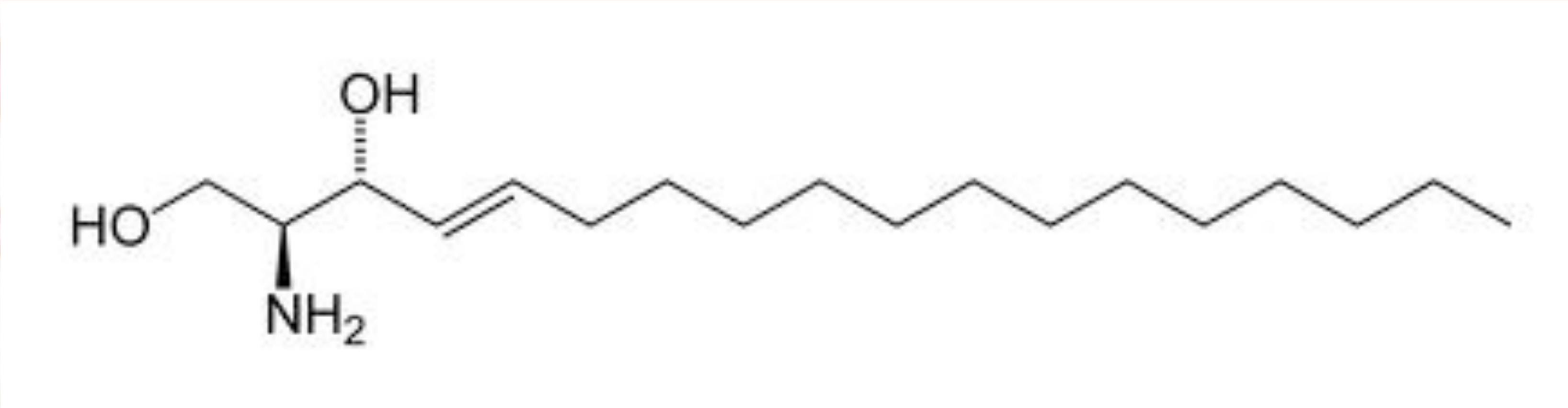


Sphingolipids

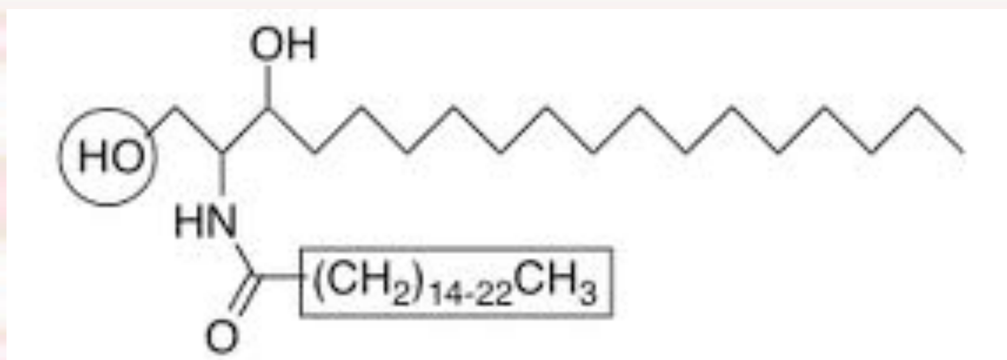
- These lipids account for 20-30% of plasma membrane, especially in cells of the central nervous system
- In this case the scaffold is the trans unsaturated 18-C amino alcohol called **sphingosine**

Sphingosine and its derivatives

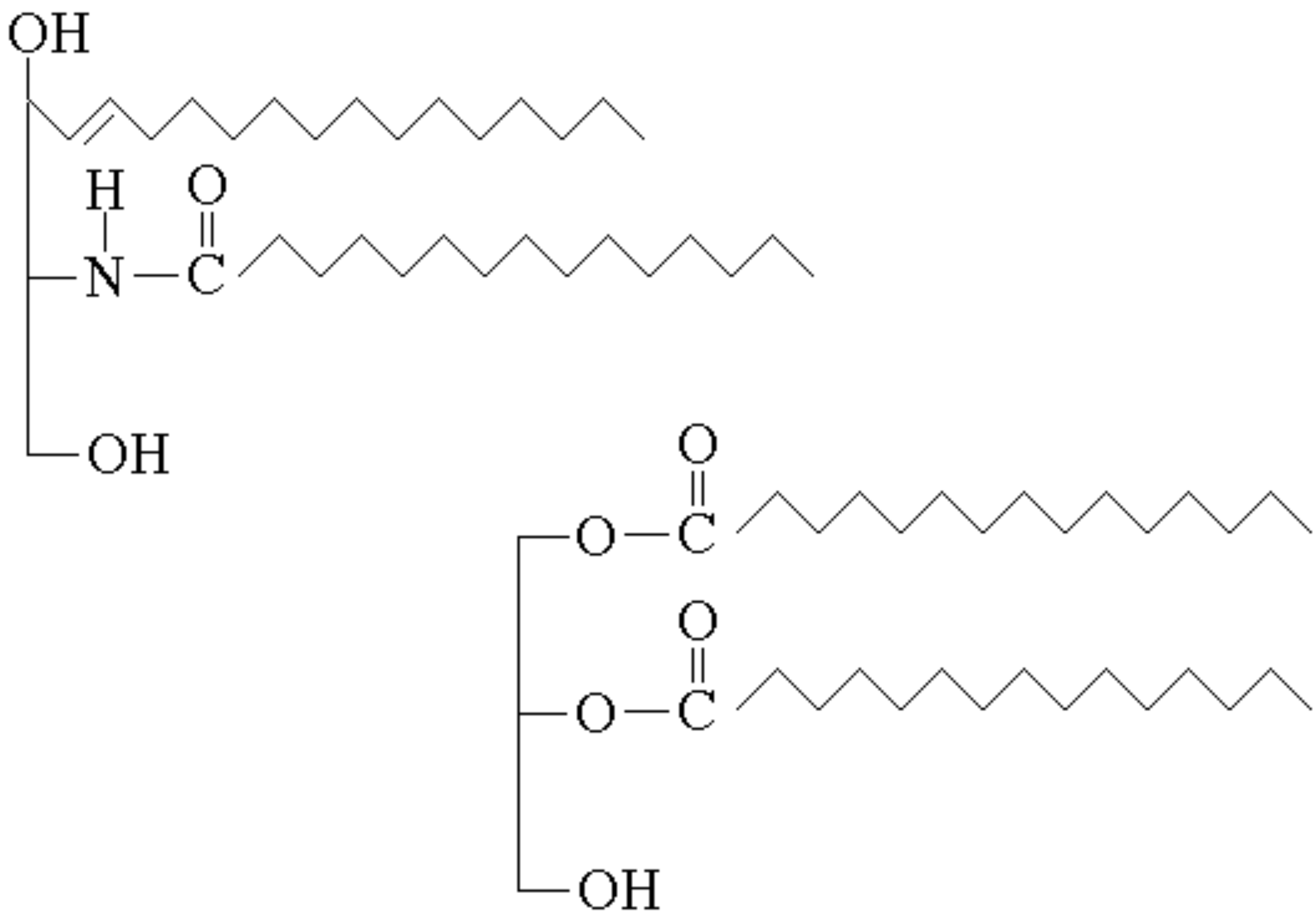
18 Carbon atons amino-alcohol



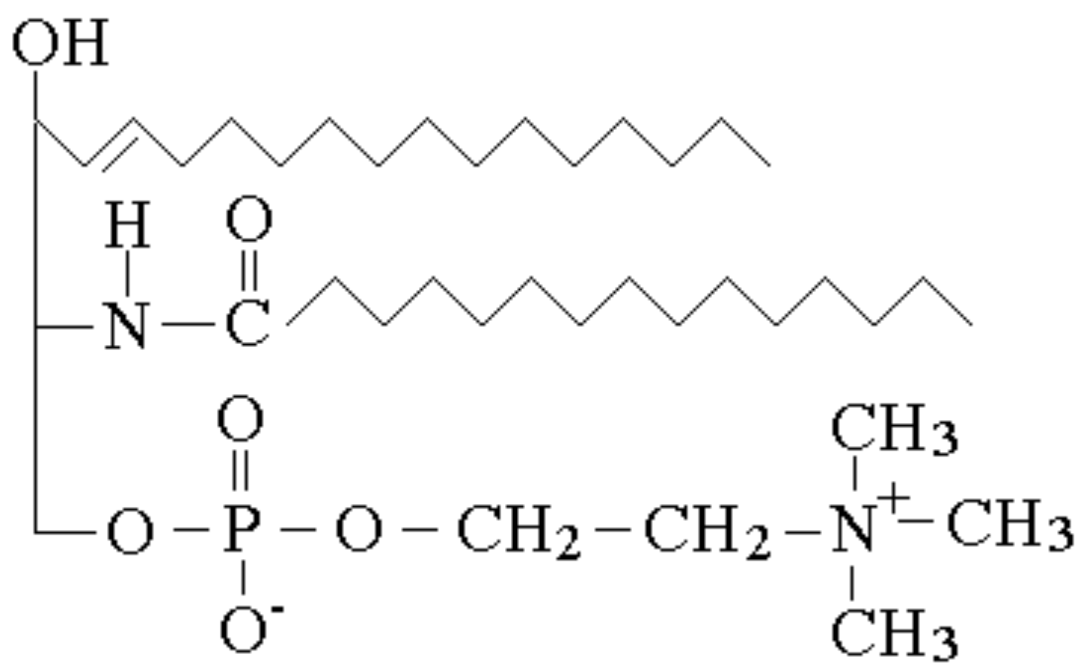
Sphingosine + fatty acid = ceramide



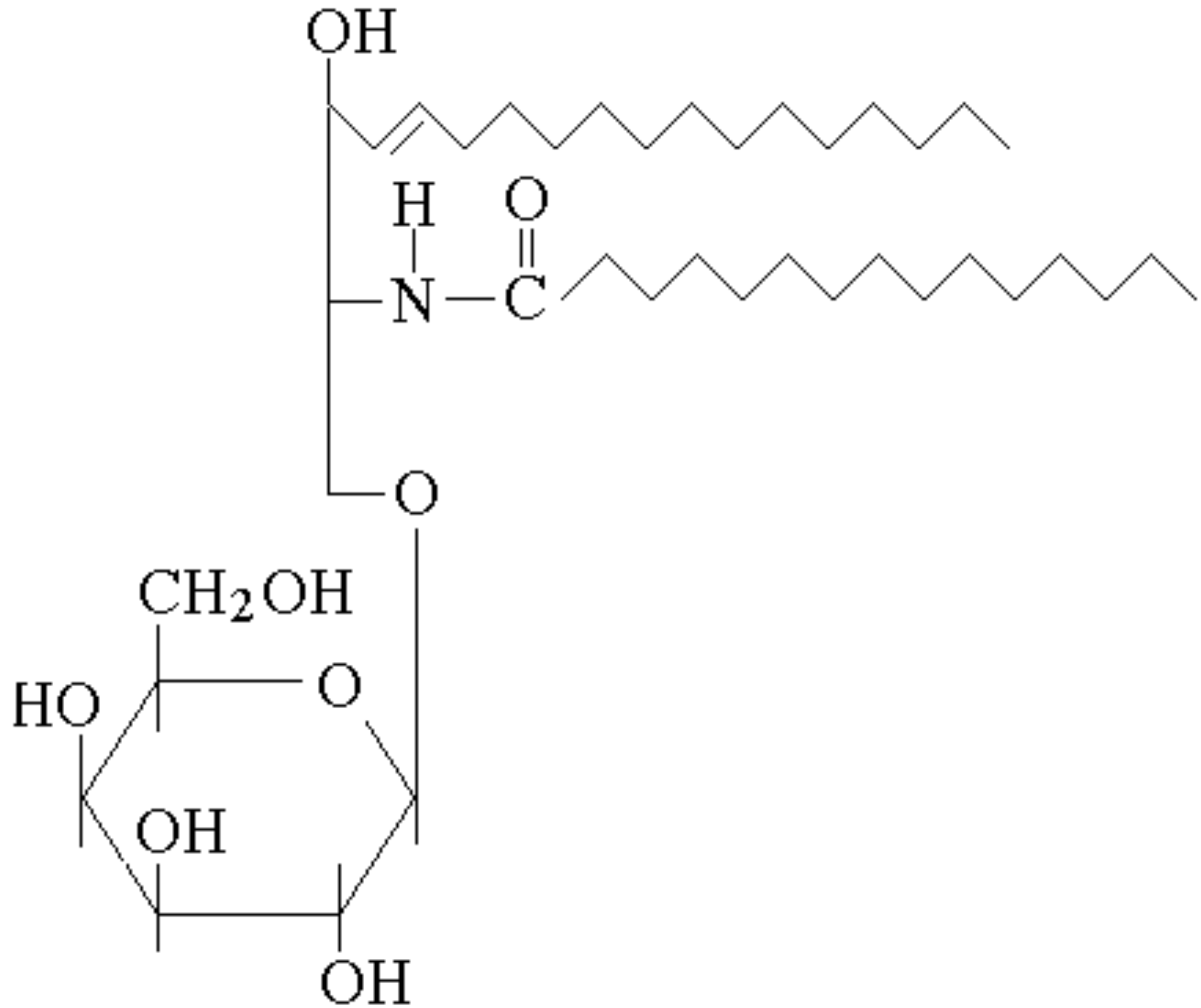
A ceramide looks like a diglyceride



Sphingomyelin looks like a phospholipid
and it is abundant in neurons

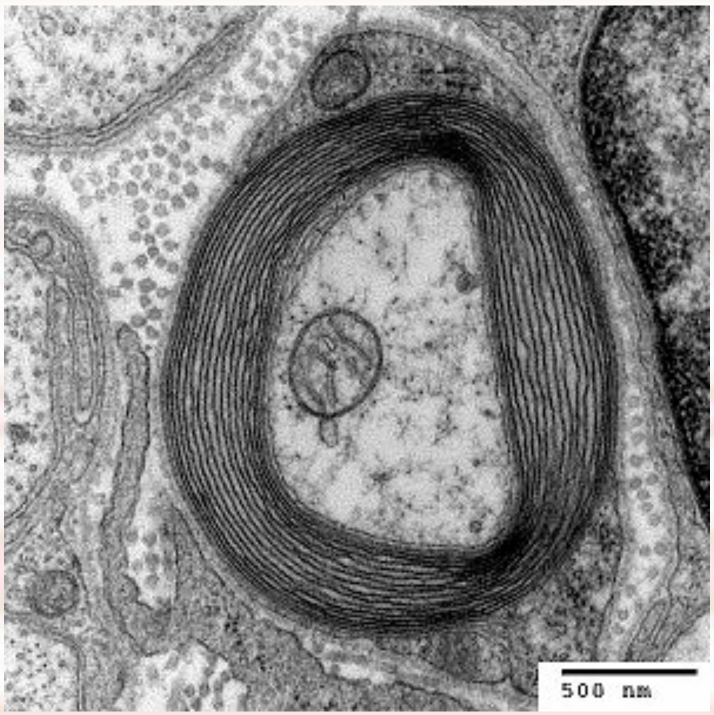


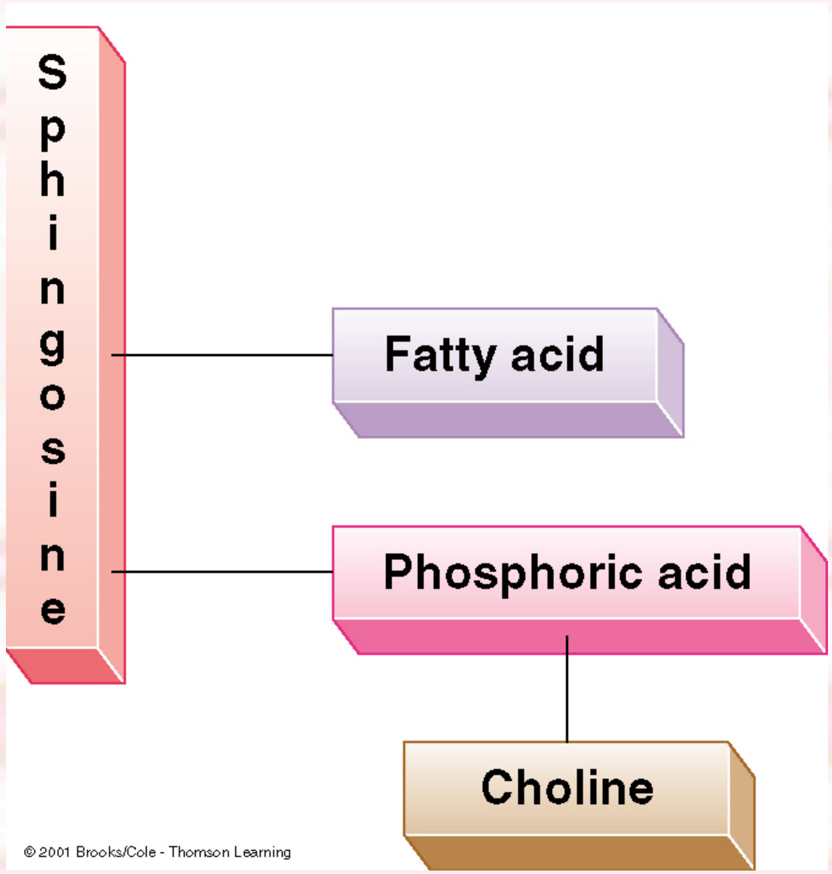
Glycosphingolipids are abundant in the SNC.



Sphingolipids

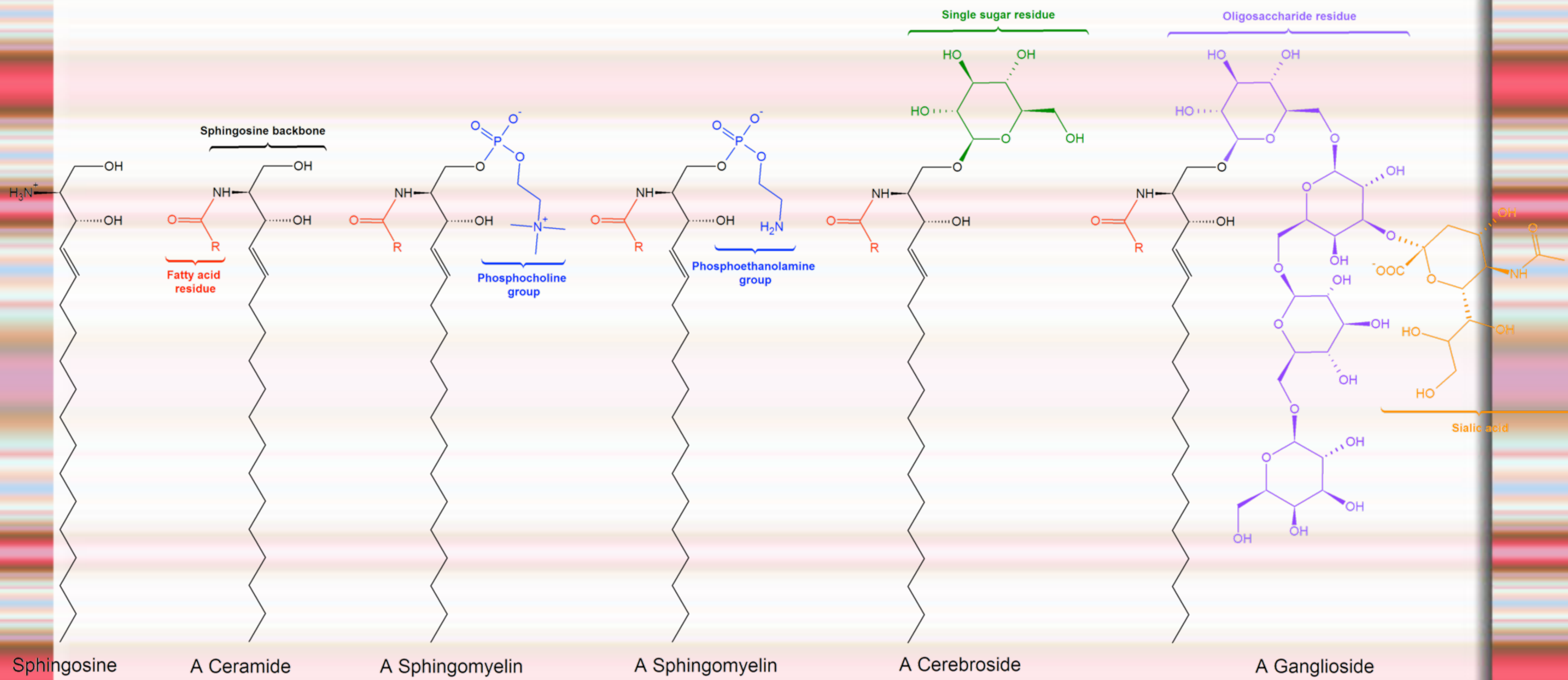
Are important components of the myeline sheath. In humans they make up to 25% of lipids.



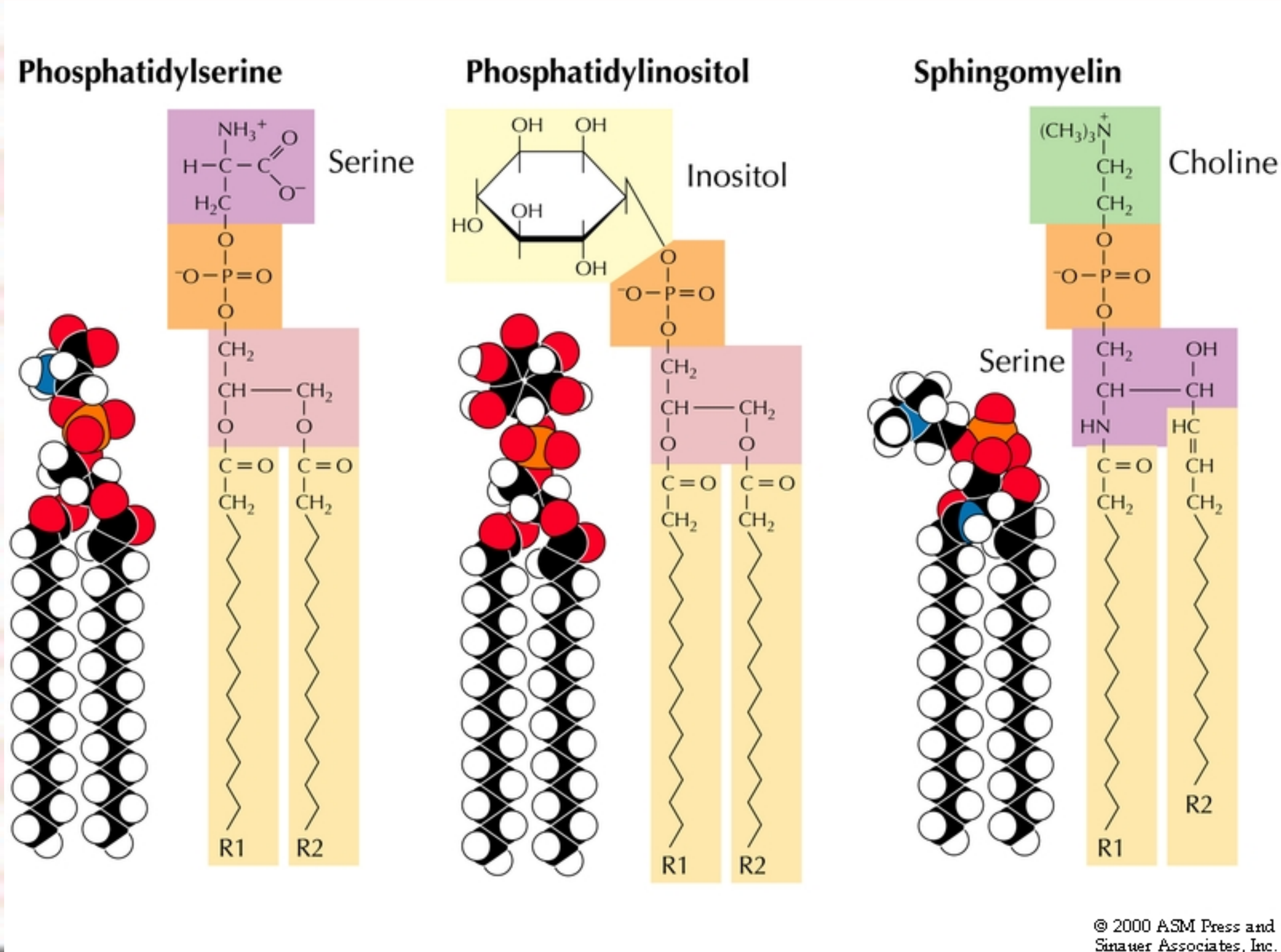


sphingomyelin

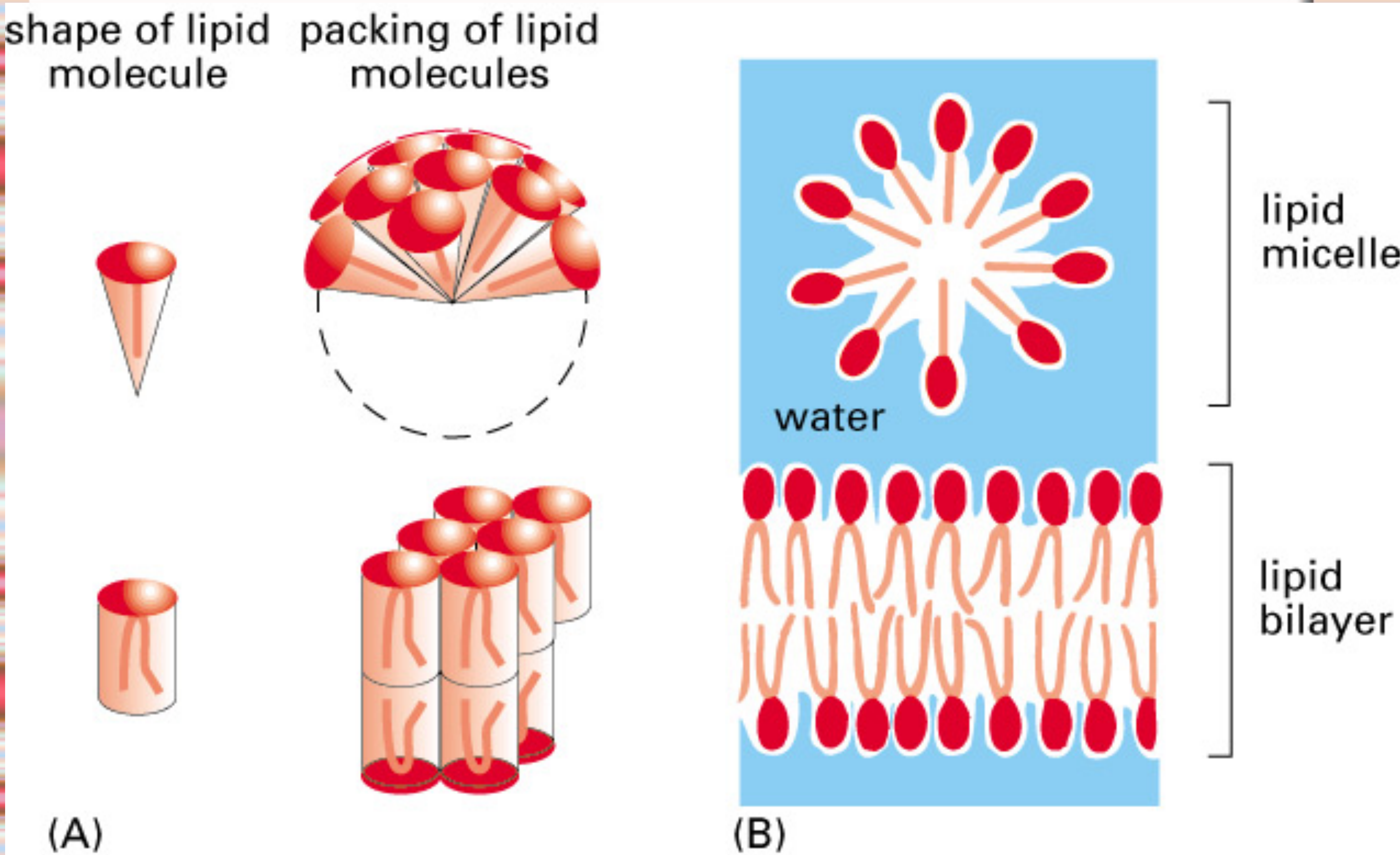
Sphingolipids



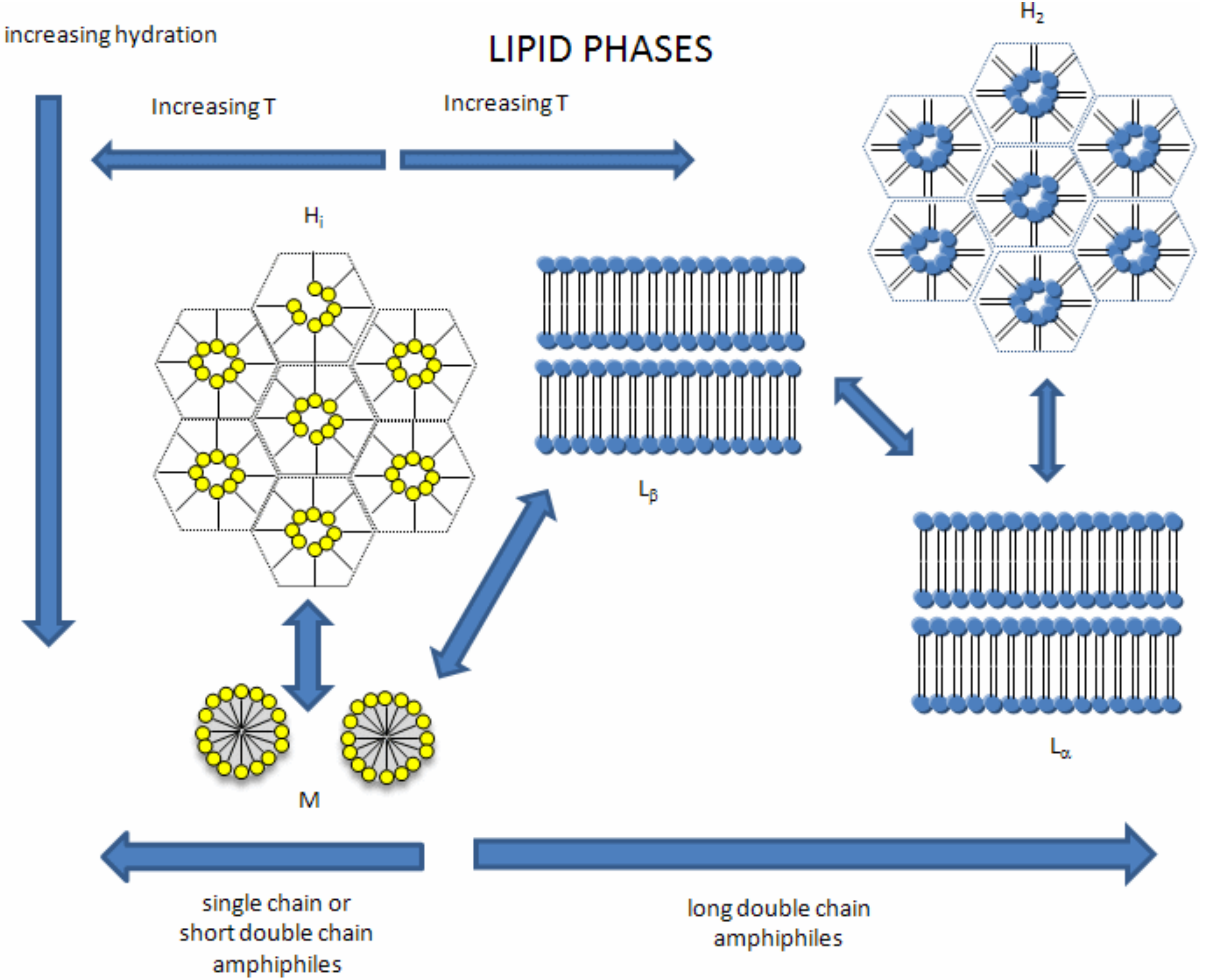
Membrane lipids are amphipathic (amphiphilic)

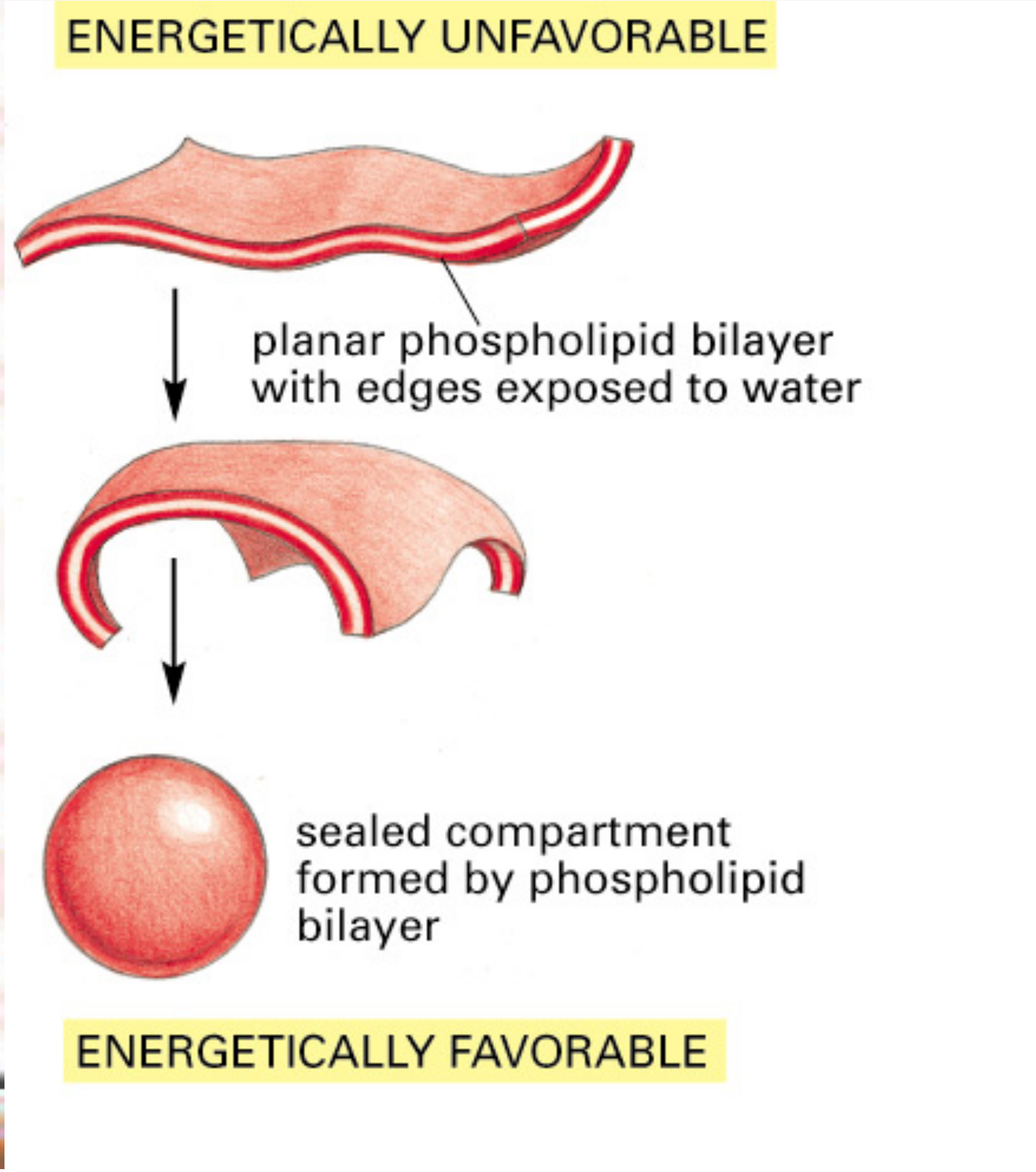


Formation of lipid bilayer: an energy minimization process



LIPID PHASES




ENERGETICALLY UNFAVORABLE
planar phospholipid bilayer with edges exposed to water
sealed compartment formed by phospholipid bilayer
ENERGETICALLY FAVORABLE

Detergents

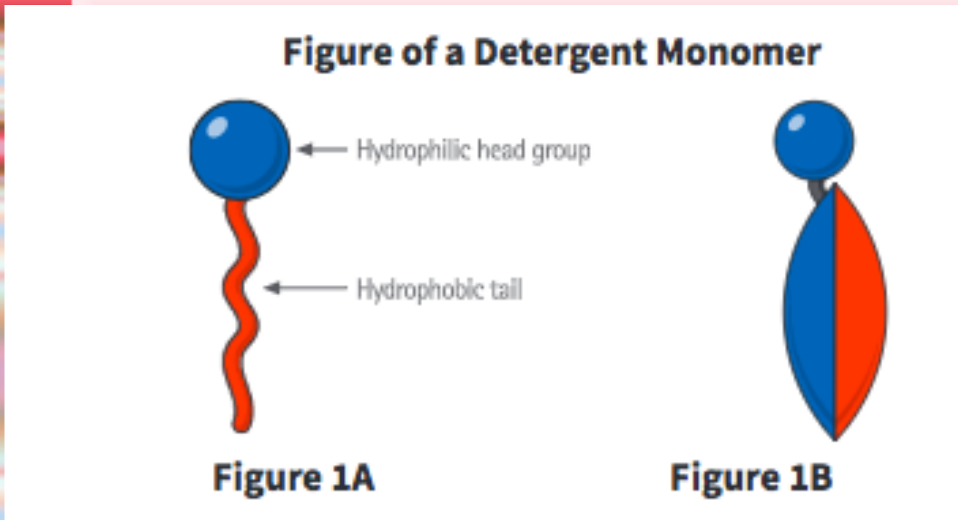
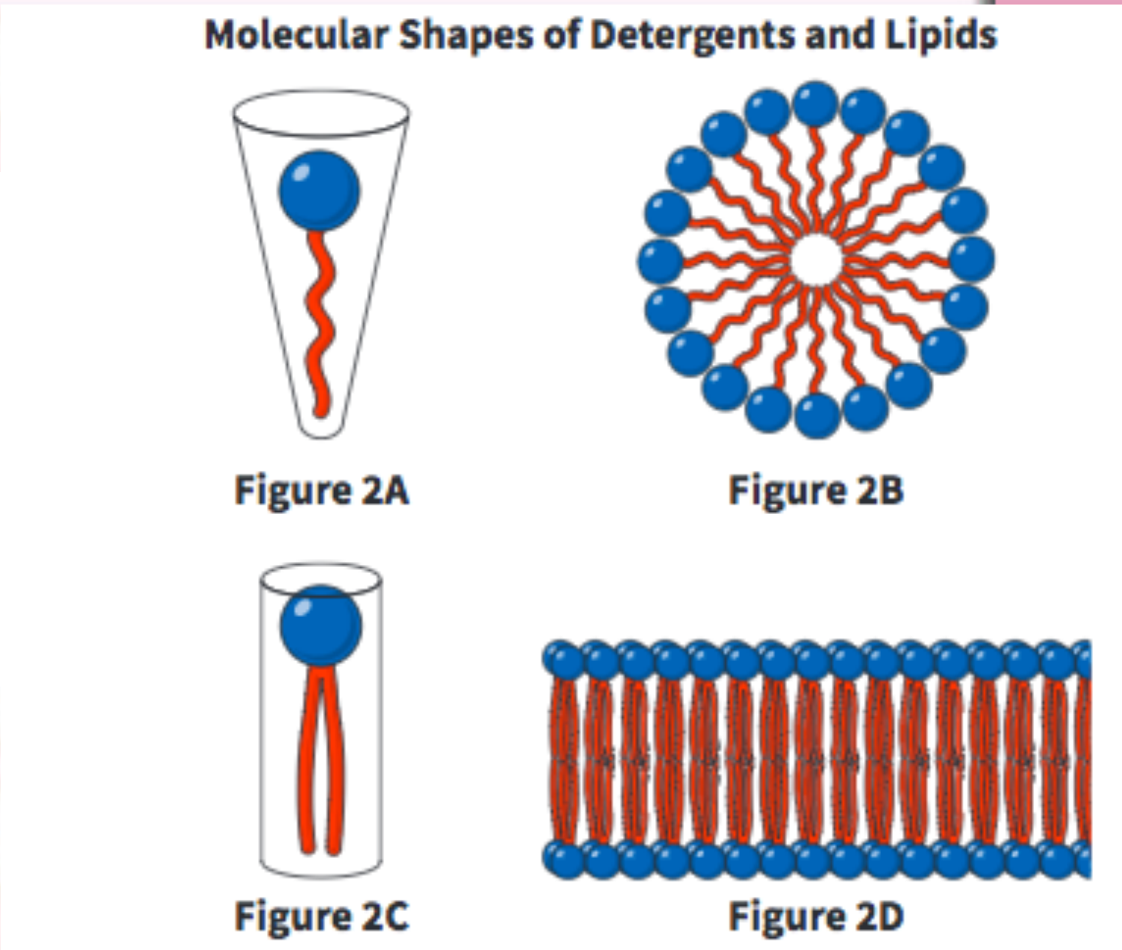


Figure of a Detergent Monomer
Hydrophilic head group
Hydrophobic tail
Figure 1A
Figure 1B



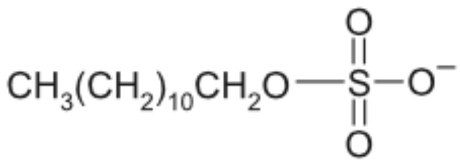
Molecular Shapes of Detergents and Lipids
Figure 2A
Figure 2B
Figure 2C
Figure 2D

Detergents

a.

Ionic detergents

Sodium dodecyl sulfate (SDS)



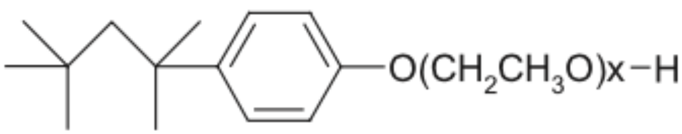
c.

Non-Ionic Detergents

R = glucose, x = 7, n-octyl-β -D-glucopyranoside
R = maltose, x = 9, decyl-β -D-maltoside
x = 11, dodecyl-β -D-maltoside

$RO(CH_2)x\text{-}CH_3$

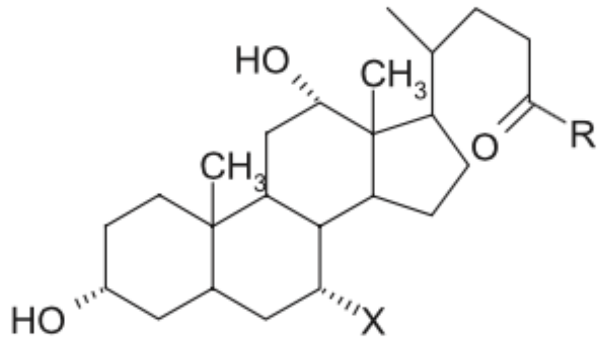
x = 9, Triton® X-100
x = 7-8, Triton® X-114



b.

Bile Acid Salts

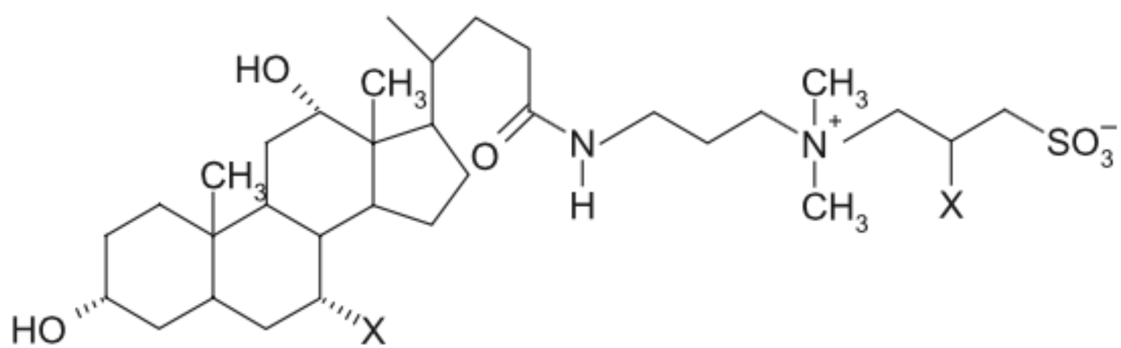
X=H, R = O-Na$^+$, sodium deoxycholate
X=OH, R = O-Na$^+$, sodium cholate



d.

Zwitterionic Detergents

x = H, CHAPS
x = OH, CHAPSO



Detergent Properties

Critical Micelle Concentration (CMC)

Critical Micelle Temperature (Krafft Temp)

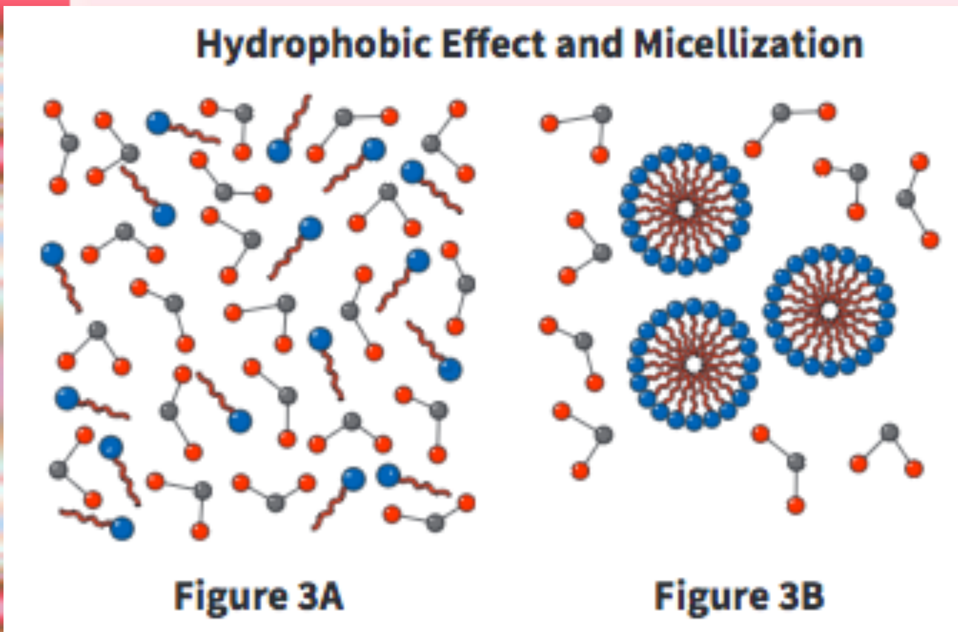
Aggregation Number

Cloud Point

Table 2
Properties[a] of various types of polar or non-ionic detergents, and of bile salts (updated from [7])

	Monomer mass (M_r)	CMC (M)	Aggregation number	$\bar{v}_D$ (cm^3/g)	Ref.[b]
Octyl-β-D-glucoside (OG)	292	$1.9–2.5\times10^{-2}$	≈90	0.859	[8,20,26,27,192]
Decyl-β-D-maltoside	483	2.2×10^{-3}	–	–	[28]
dodecyl-β-D-maltoside (DM)	511	1.8×10^{-4}	110–140	0.81–0.837	[17,20,26,29,192]
Cyclohexyl-hexyl-β-D-maltoside (CYMAL-6)	509	5.6×10^{-4}	63[f]	–	[57]
2-*O*-Lauroylsucrose	524	6.5×10^{-4}	–	–	[30]
Dodecyldimethyl-*N*-amineoxide (DDAO)	229	2.2×10^{-3}	69–73	1.128–1134	[17,31,32,199]
Lauroamido-*N*,*N*-dimethyl-3-*n*-propylamineoxide (LAPAO)	302	3.3×10^{-3}	–	1.067	[33]
Dodecyl-*N*-sulfobetaine (zwittergent 3-12)[c]	336	$1.4–4\times10^{-3}$	55–87	–	[6,20]
Tetradecyl-*N*-sulfobetaine (zwittergent 3-14)	364	$1–60\times10^{-4}$	83–130	–	[6,19]
N-dodecyl-*N*,*N*-(dimethylammmonio) butyrate (DDMAB)	300	4.3×10^{-3}	47	1.07	[34,35]
1-Myristoyl-2-hydroxy-*sn*-glycero-3-phosphocholoine ($C_{14:0}$lysoPC)	468	9×10^{-5}	–	0.97	[6,13]
1-Palmitoyl-2-hydroxy-*sn*-glycero-3-phosphocholine ($C_{16:0}$lysoPC)	496	1×10^{-5}	–	0.976	[6,13]
N-dodecylphosphocholine (DPC)	352	1.1×10^{-3}	50–60	0.937	[36,215]
1,2 Diheptanoyl-*sn*-glycero-3-phosphocholine (di-$C_{7:0}$PC)	482	$1–1.4\times10^{-3}$	42–200[g]	0.888–0.925	[5,13,58,59]
3-[(3-cholamidopropyl)-dimethylammonio]-1-propanesulfonate (CHAPS)[c]	615	$3–10\times10^{-3}$	4–14	0.81	[19,20,37]
Deoxycholic acid[d,e]	393	3×10^{-3}	22	0.778	[3,13]
Cholic acid[d,e]	409	1×10^{-2}	4	0.771	[13,38]
Taurodeoxycholic acid[d]	500	1.3×10^{-3}	20	0.75	[13,38]
Glycocholic acid[d]	466	–	6	0.77	[13,38]
Sodium dodecylsulfate[c]	288	$1.2–7.1\times10^{-3}$	62–101	0.863	[5,19,20,39]
6-*O*-(*N*-heptylcarbamoyl)-methyl-β-D-gluco-pyranoside (HECAMEG)	335	1.95×10^{-2}	92	–	[40,192]

Detergent Micelle Formation



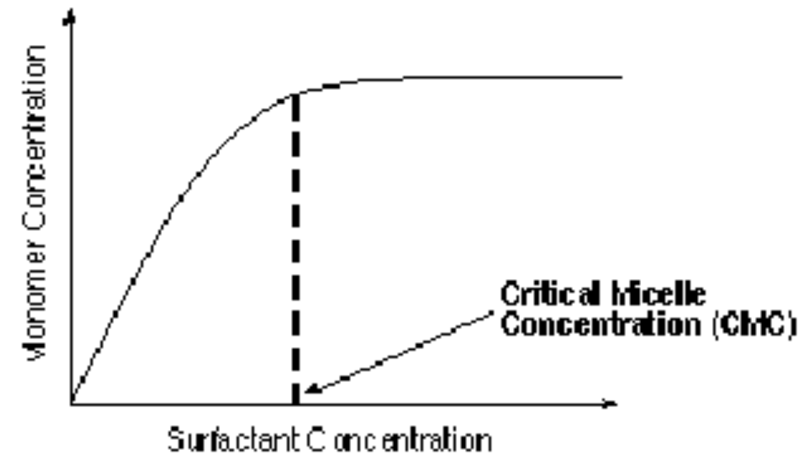
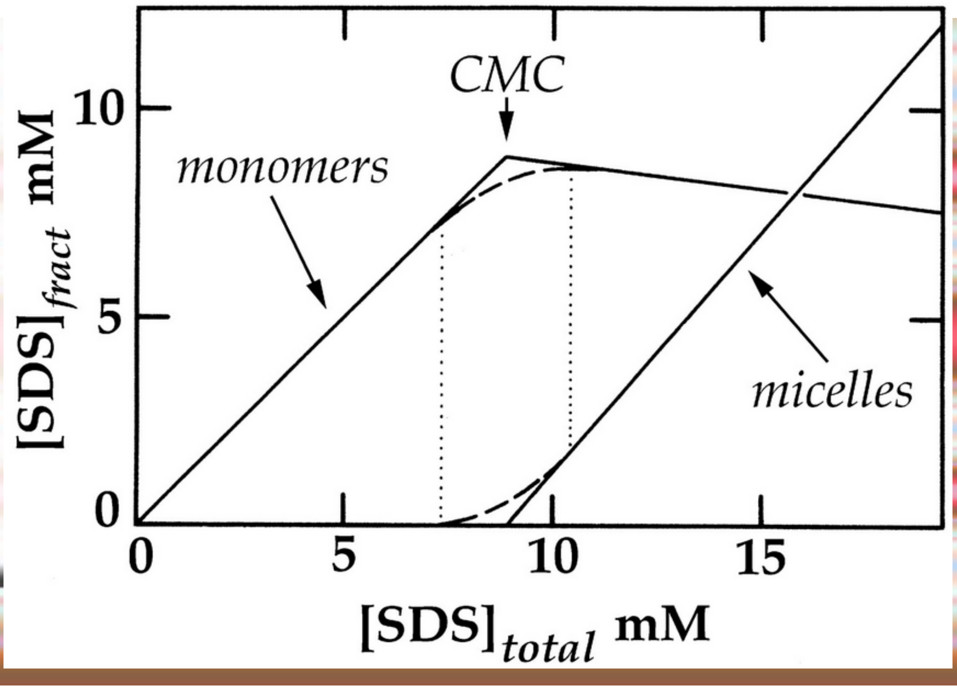
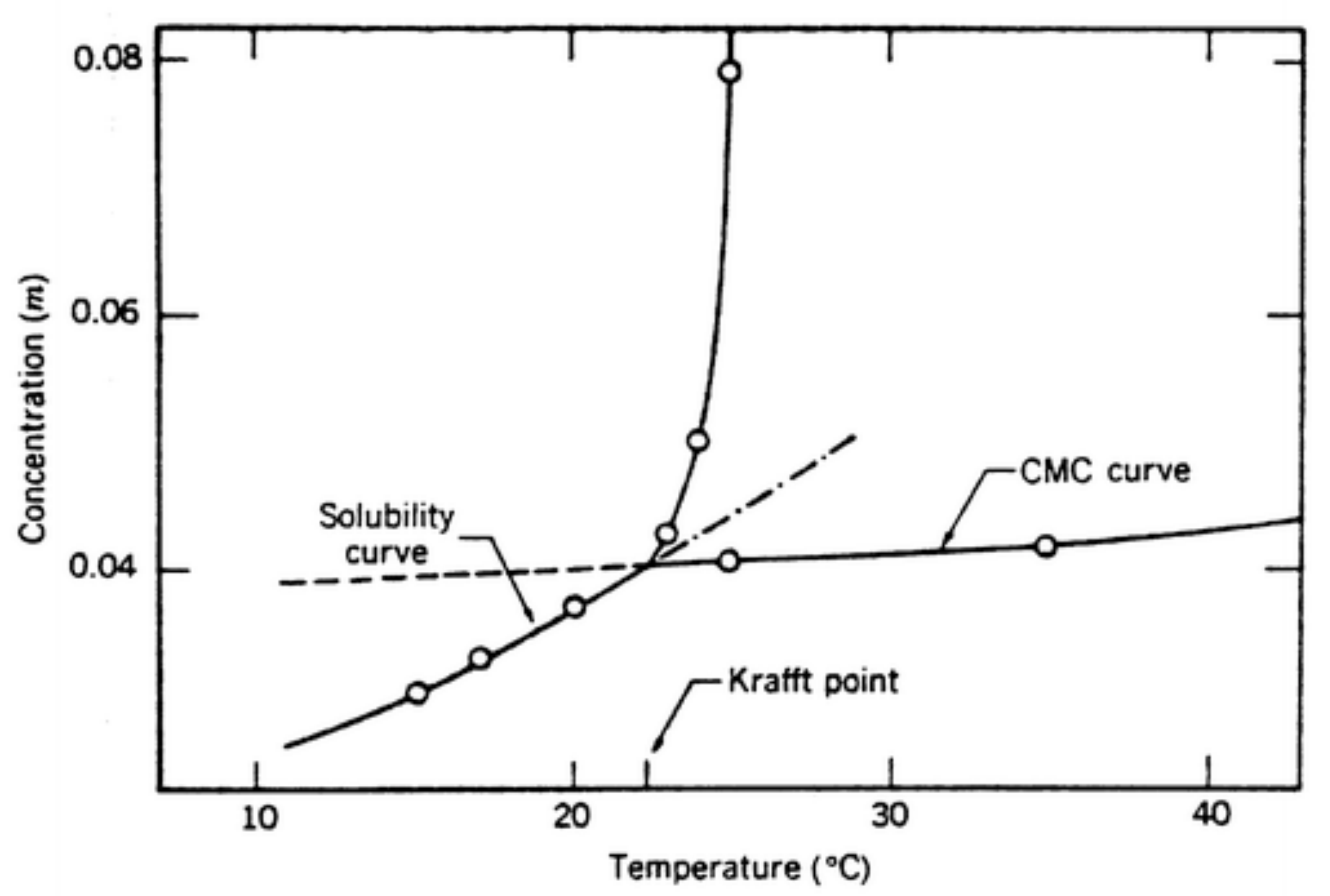


Figure 4-3
Formation of micelles at critical micelle concentration (CMC)




0.08
0.06
0.04
Concentration (m)
Solubility curve
CMC curve
Krafft point
10
20
30
40
Temperature (°C)

Thermodynamics of micelle formation

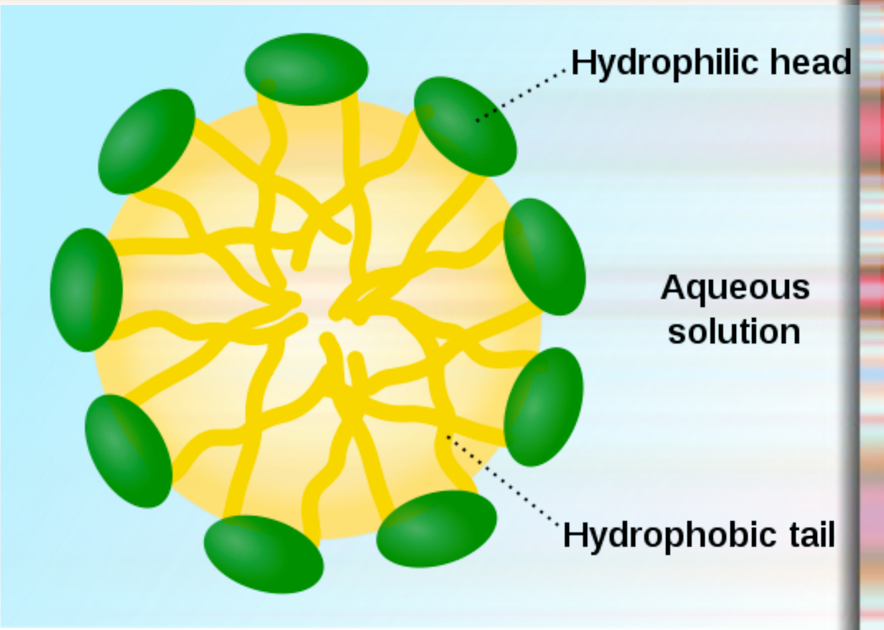
$\Delta G_{micelle} = \Delta H - T\Delta S$

$\Delta G_{micelle} = RT \times \mathit{ln}[CMC]$

$\Delta G_{micelle} = \Delta G_{HP} + \Delta G_{EL} + \Delta G_{IF}$

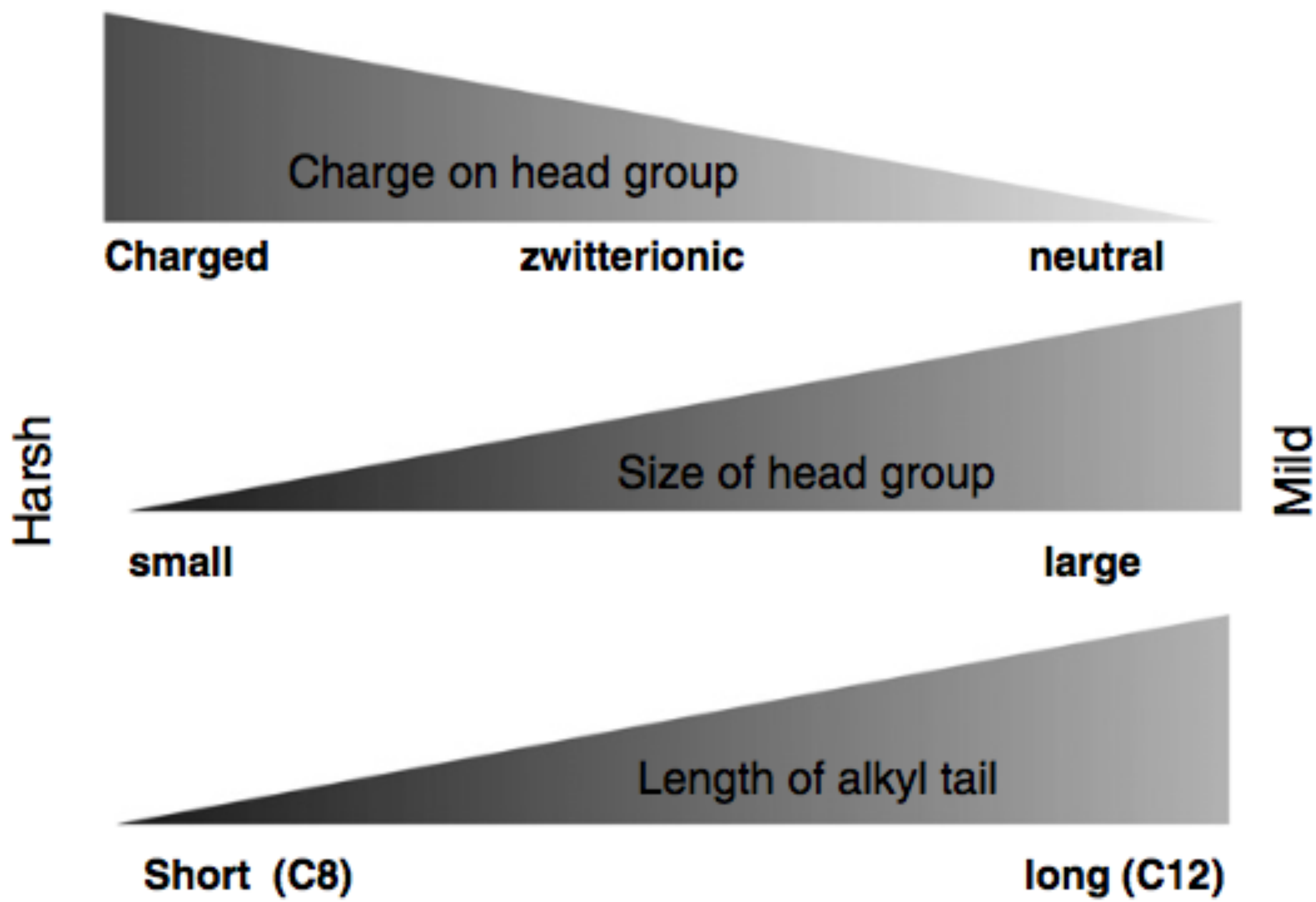
Hydrophobic – Electrostatic - Interfacial

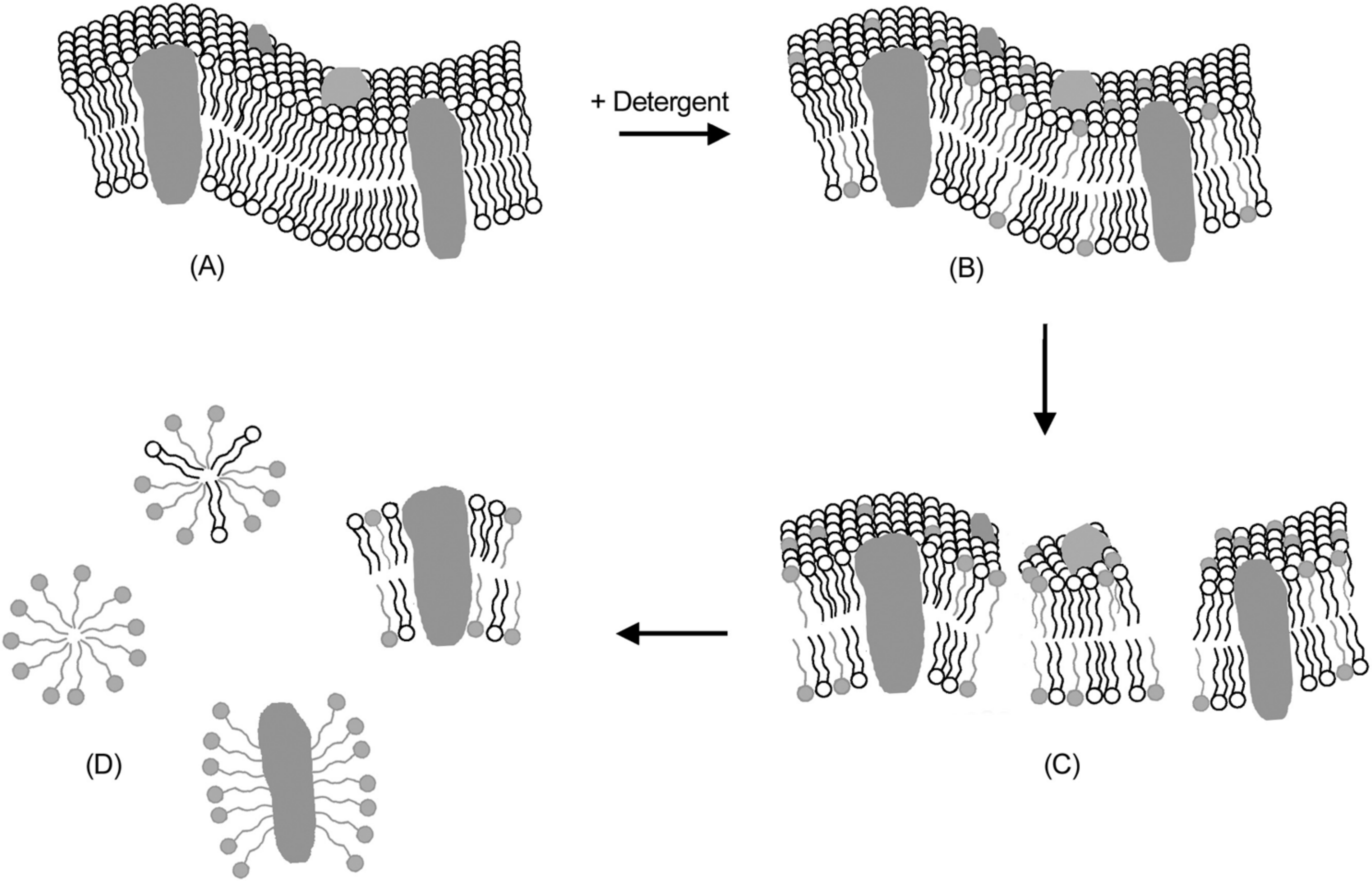
The total Gibbs energy is broken down into several components accounting for the hydrophobic tail, the electrostatic repulsion of the head groups, and the interfacial energy on the surface of the micelle.



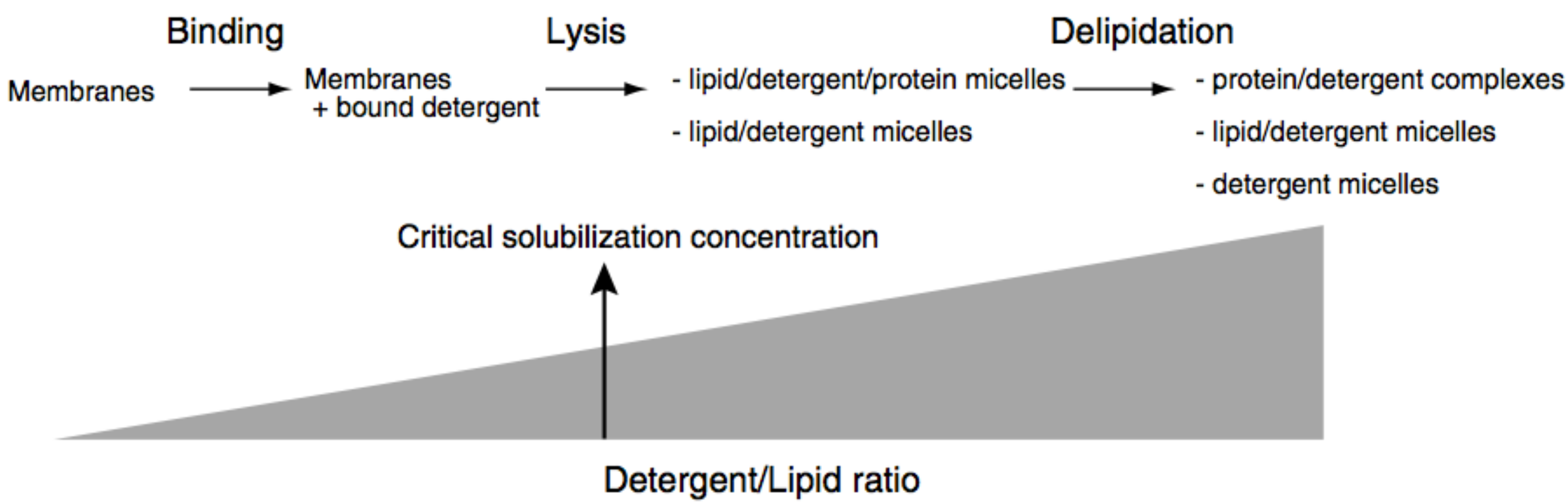
The cmc decreases with increasing tail length because the hydrophobic character increases

Harsh to mild detergents on membrane proteins




+ Detergent
(A)
(B)
(C)
(D)

Membrane protein solubilization



Malattie da accumulo di lipidi.
Malattie genticamente trasmesse in cui è carente o scarsamente attivo un enzima del metabolismo di gangliosidi o cerebroside.

La **malattia di Tay-Sachs** è una cerebrosidosi genetica ereditaria rara, provoca l'accumulo del ganglioside GM2 nel cervello. Il gene che causa la malattia si trova sul quindicesimo cromosoma (15q23).

http://www.ninds.nih.gov/disorders/lipid_storage_diseases/lipid_storage_diseases.htm

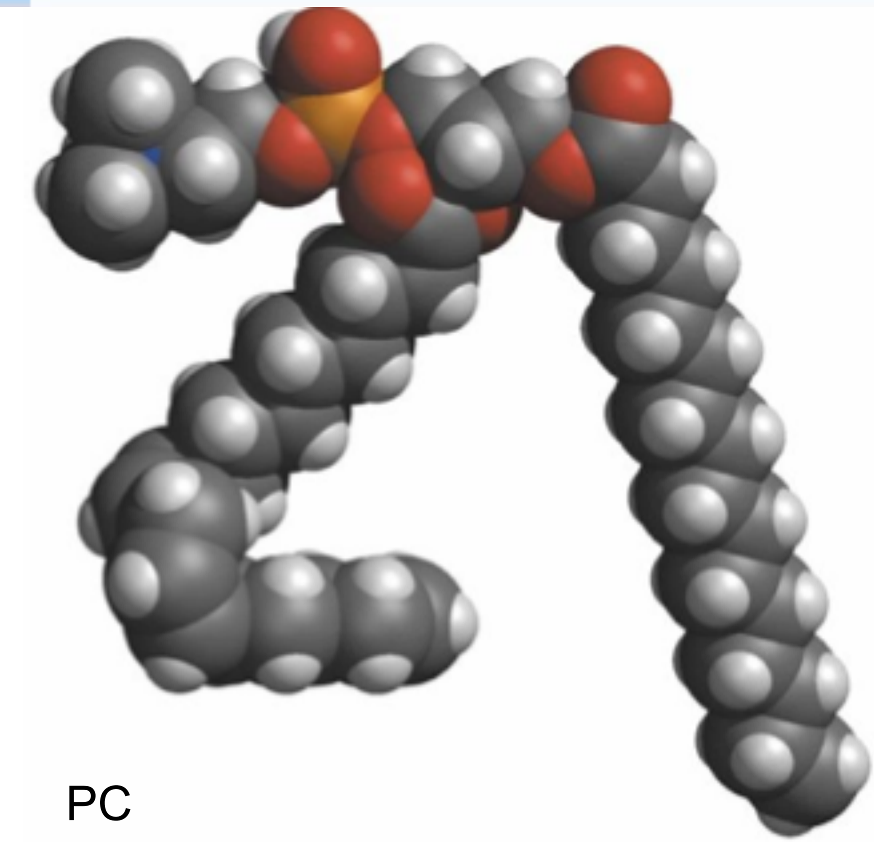
La malattia di Fabry è un'anomalia congenita del metabolismo degli sfingolipidi.

La causa è genetica, e riguarda le anomalie di un gene che si trova sul braccio lungo del cromosoma XX mappato in Xq21.33-Xq22, e sono state dimostrate più di 300 diverse mutazioni genetiche. L'enzima coinvolto partecipa al metabolismo del triesosilceramide (α-triesosilgalattosidasi lisosomiale). Terapia mediante sostituzione enzimatica (Fabrazyme).

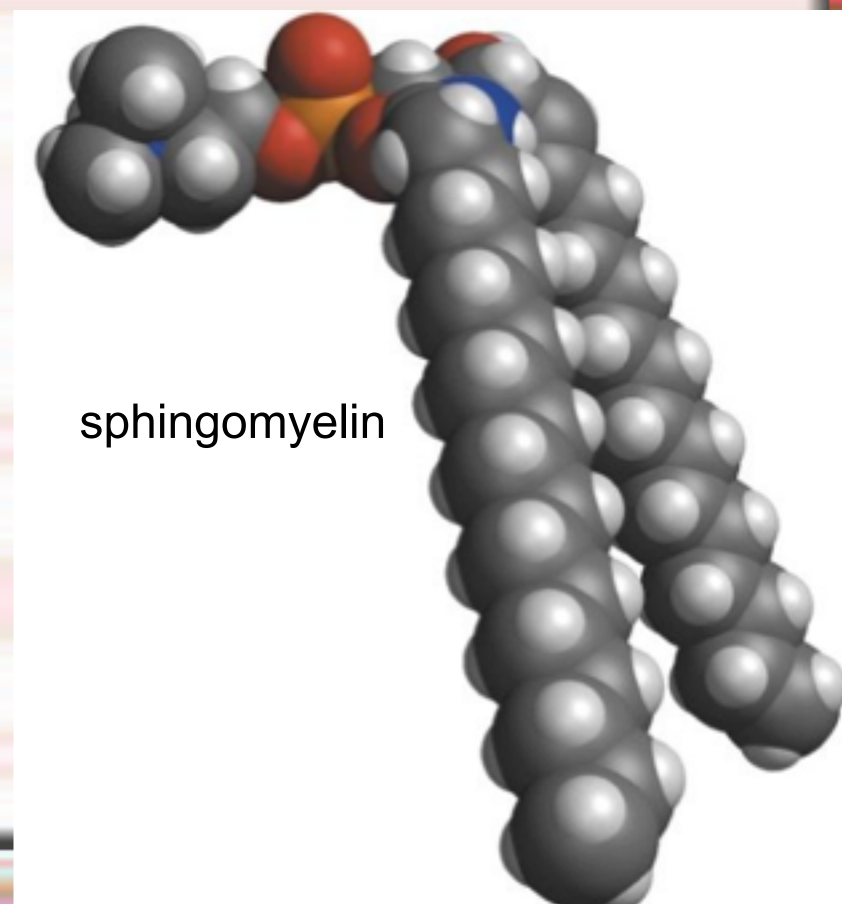
Malattia di Gaucher.
La mutazione del gene per la β-glucosidasi porta all'accumulo di glicosilceramide nei lisosomi dei macrofagi. I sintomi e i segni clinici sono frequenti emorragie, atrofia muscolare, splenomegaliaa, astenia, diarrea, osteopenia, strabismo, nelle forme più gravi (tipo III) vi sono anche casi di convulsioni, demenza e atassia.
Sostituzione enzimatica, o inibitore della sintetasi.

Glycerol-phospholipids vs sphingolipids

- Despite the different chemical origin, the two molecules have a similar 3D spatial arrangement and a similar charge (polar) distribution

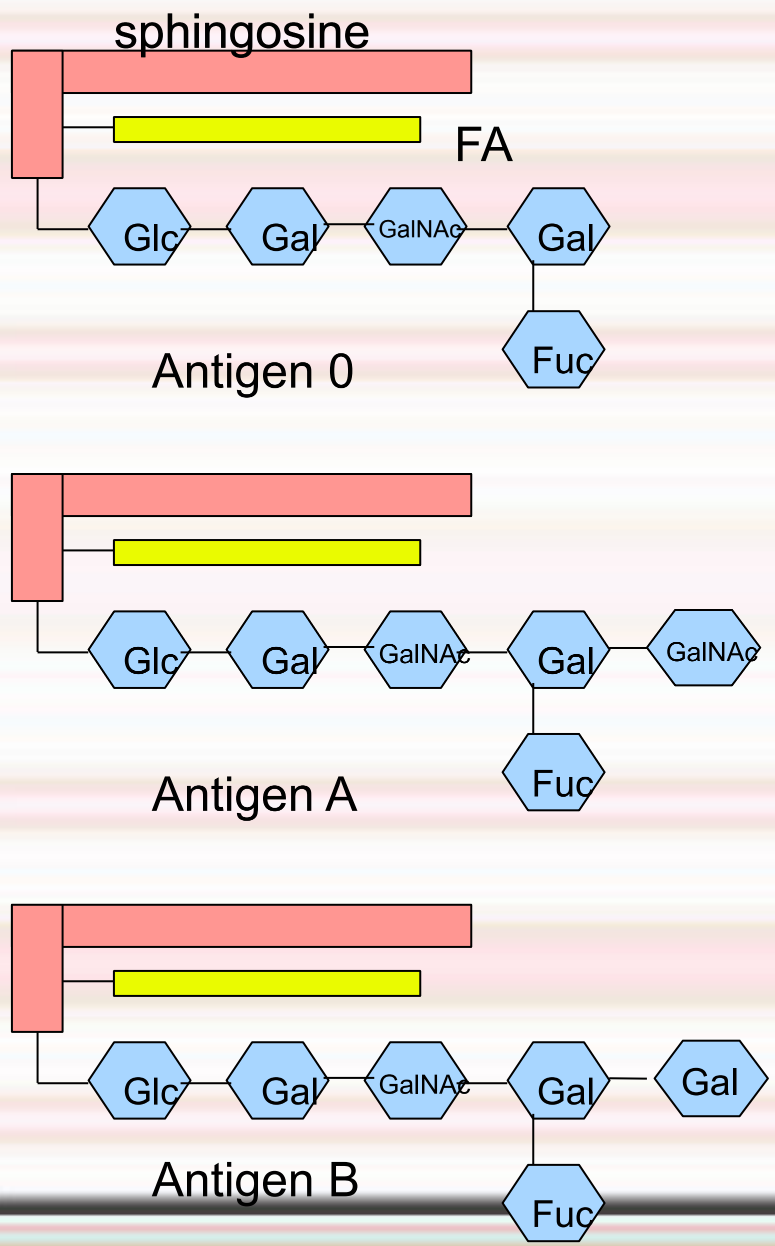


PC

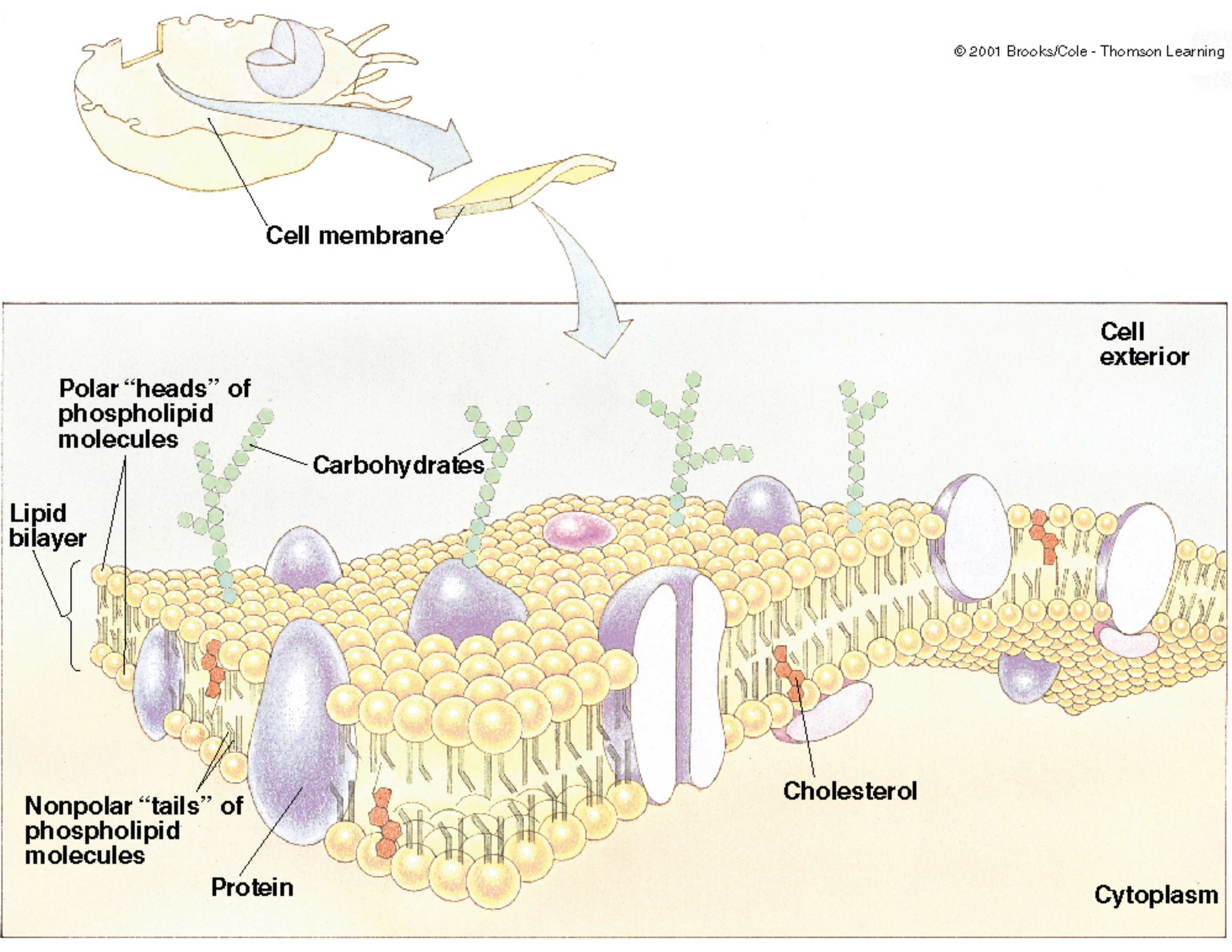


sphingomyelin

Gangliosides

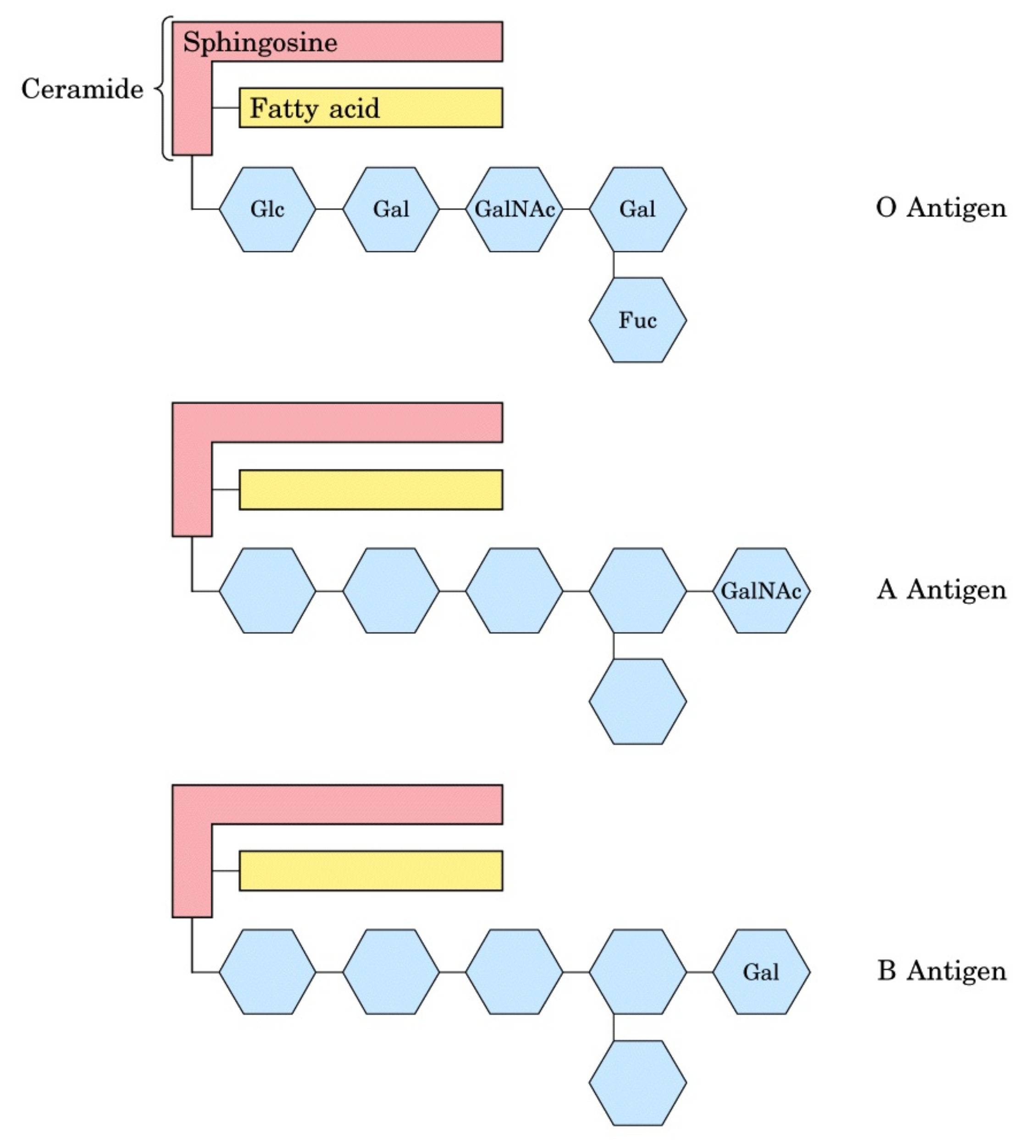


- Both Gangliosides and Cerebrosides contain sugars → they are always present only on the external leaflet of the membrane bilayer
- Gangliosides are responsible for the blood groups



© 2001 Brooks/Cole - Thomson Learning
Cell membrane
Cell exterior
Polar "heads" of phospholipid molecules
Carbohydrates
Lipid bilayer
Nonpolar "tails" of phospholipid molecules
Protein
Cholesterol
Cytoplasm

Blood Groups antigens



Glc = glucose

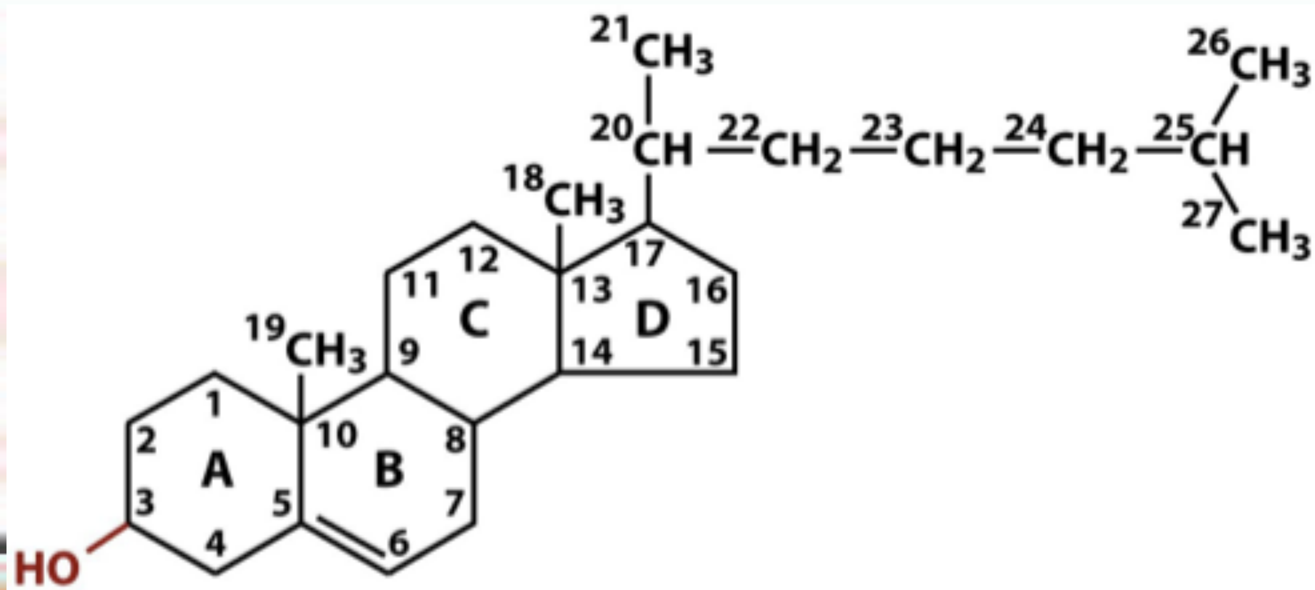
Gal = galactose

GalNAc = N-acetylgalactosamine

Fuc = fucose

Sterols

- This class is found almost exclusively in eukaryotes
- They have a common cyclic non-aromatic scaffold derived from cicle-pentane-peri-hydro-phenanthrene
- They have both structural and hormonal/signalling function
- The presence of 4 fused rings rigidifies the molecule → once inserted into the membranes it affects fluidity
- In mammals the precursor form all steroid hormones is cholesterol, whose OH group in C3 makes it slightly polar



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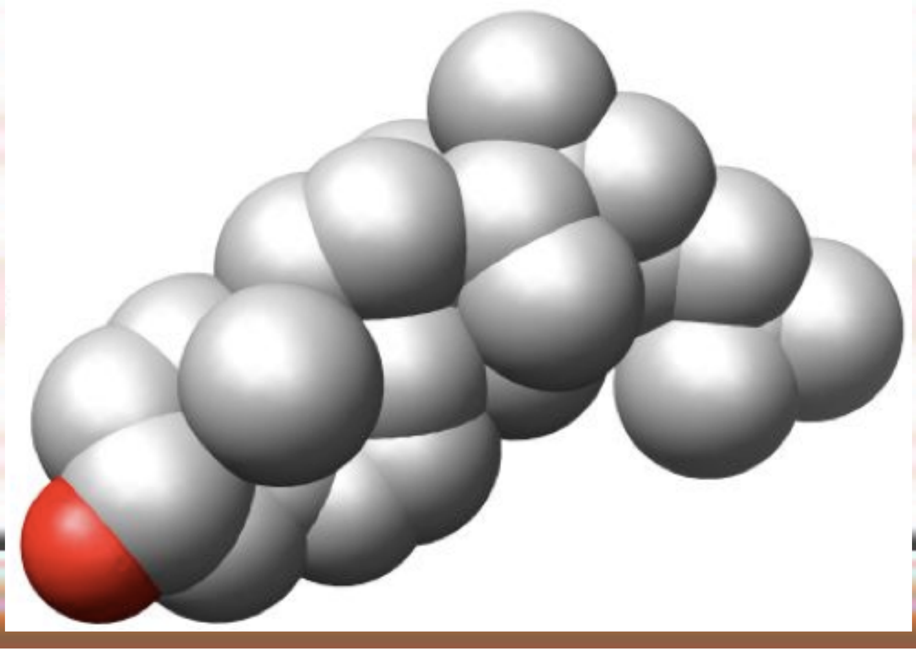
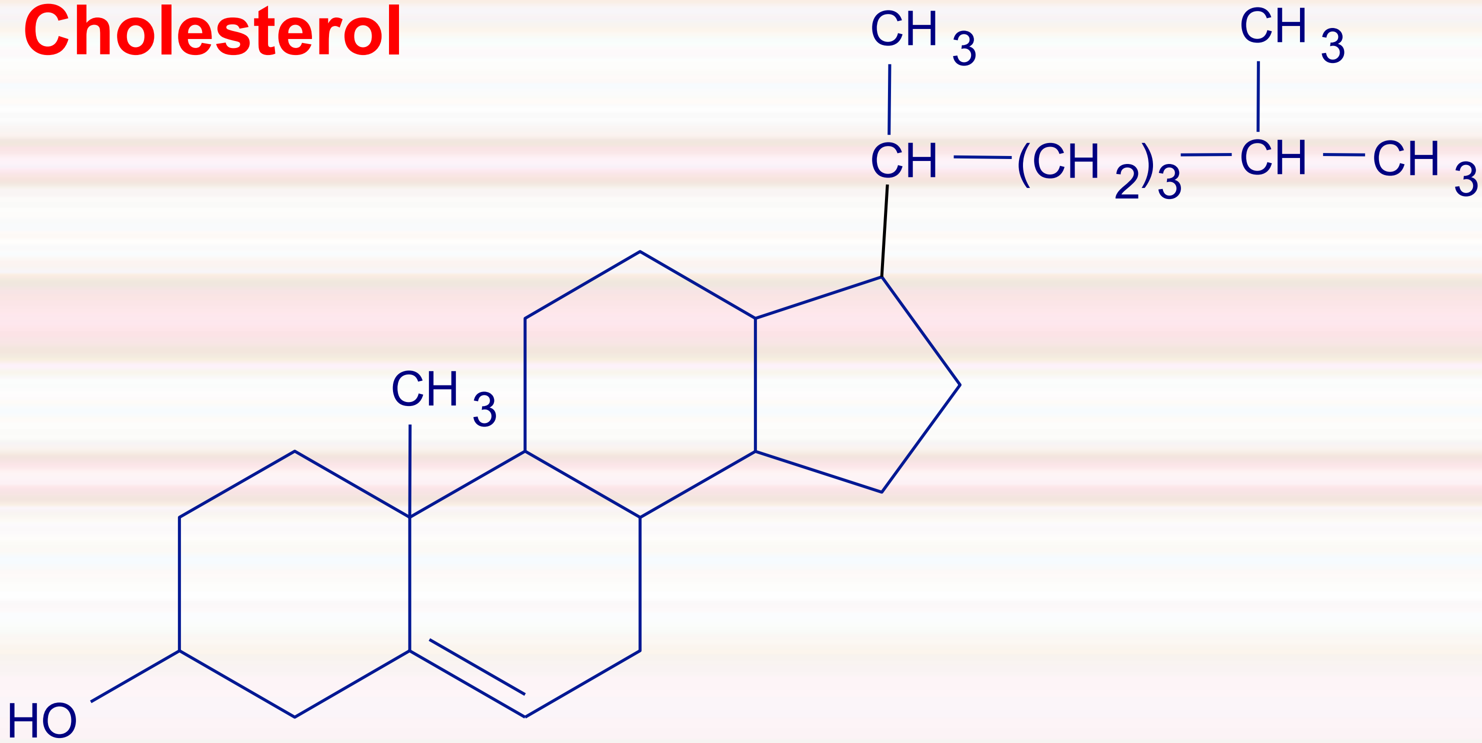


Steroid hormones

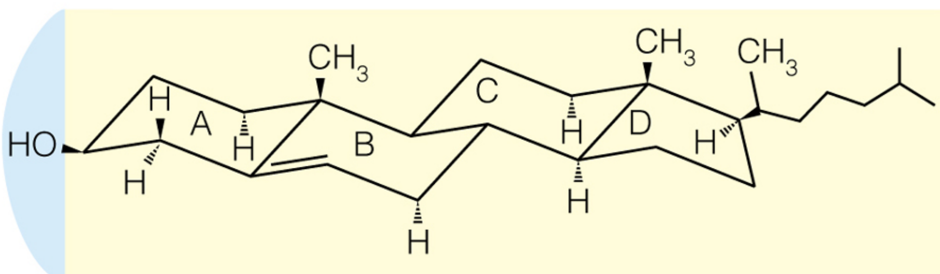
- **Glucocorticoids** (ex. Cortisol): hormones synthesised by the surrenal cortex glands, affecting the metabolism of carbohydrates, proteins and lipids. They also affect inflammatory and stress responses.
- **Mineral-corticoids** (ex. Aldosterone): hormones synthesised by the surrenal cortex glands, affecting water and salt excretion from kidneys.
- **Androgens** (ex. Testosterone) and **estrogens** (ex. beta-estradiol): crucial hormones for a correct sexual development and functionality, they are synthesised by either testes (male) or ovaries (female)
- They are all slightly more soluble than cholesterol

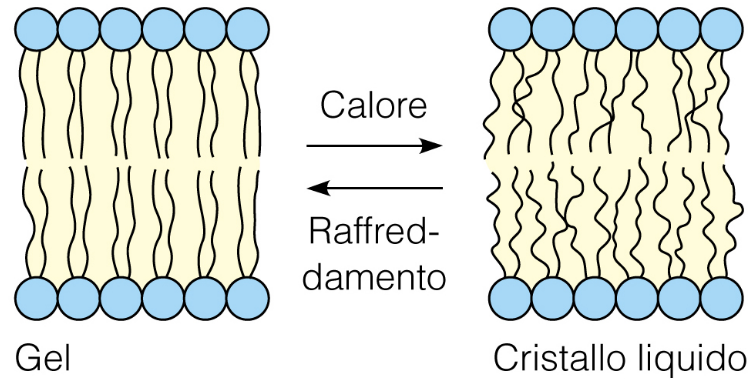
Cholesterol



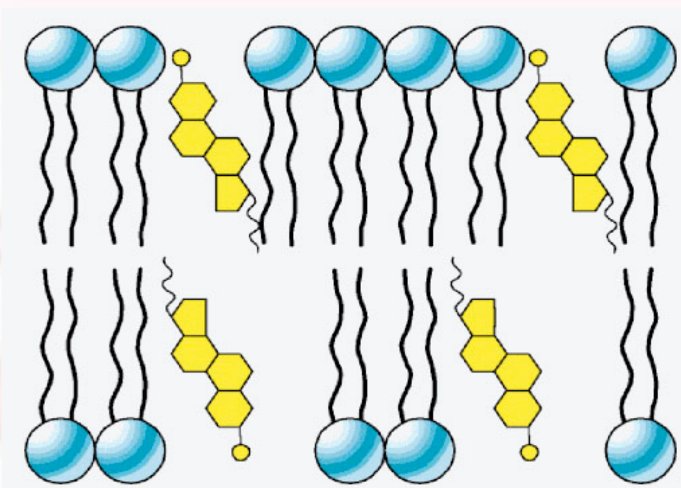
- From the diet and hepatic synthesis.
- insoluble, found in membanes.
- Steroid hormons synthesis.
- Bile salts synthesis.
- High blood levels-> cardiovascolar diseases.

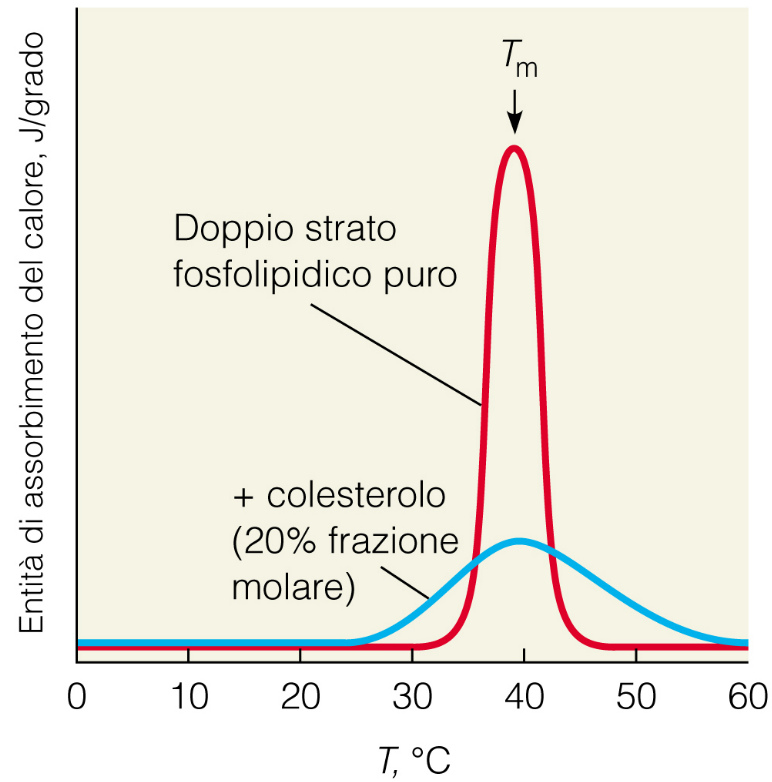
Membranes fluidity



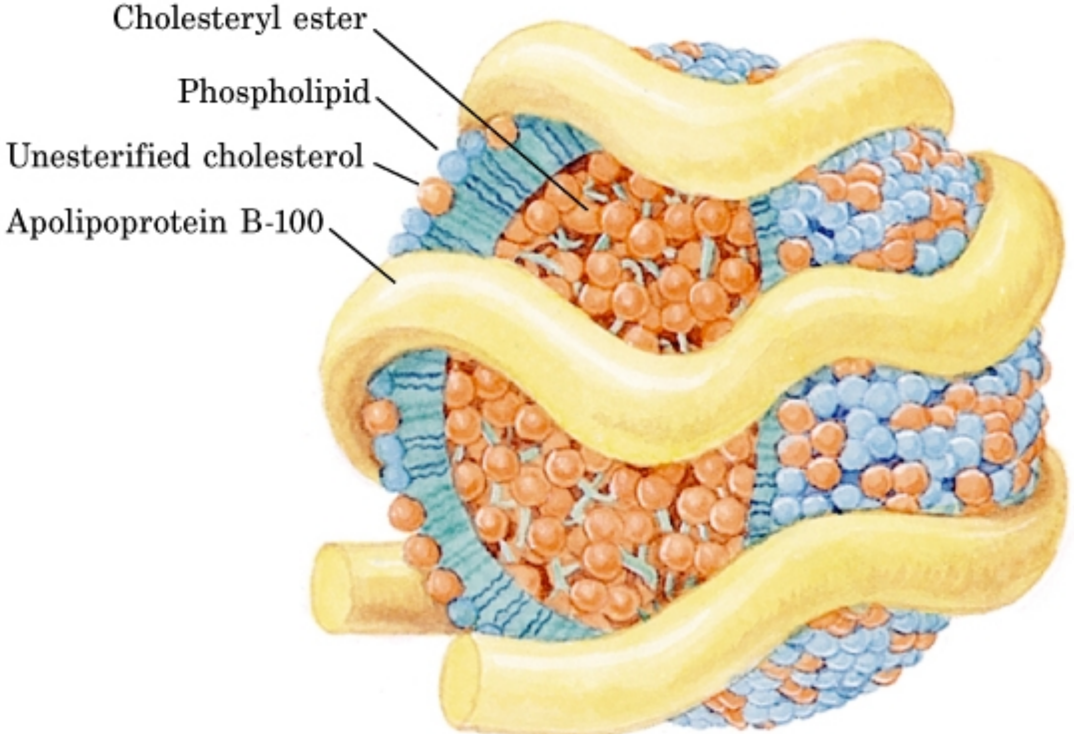


(a) Transizione





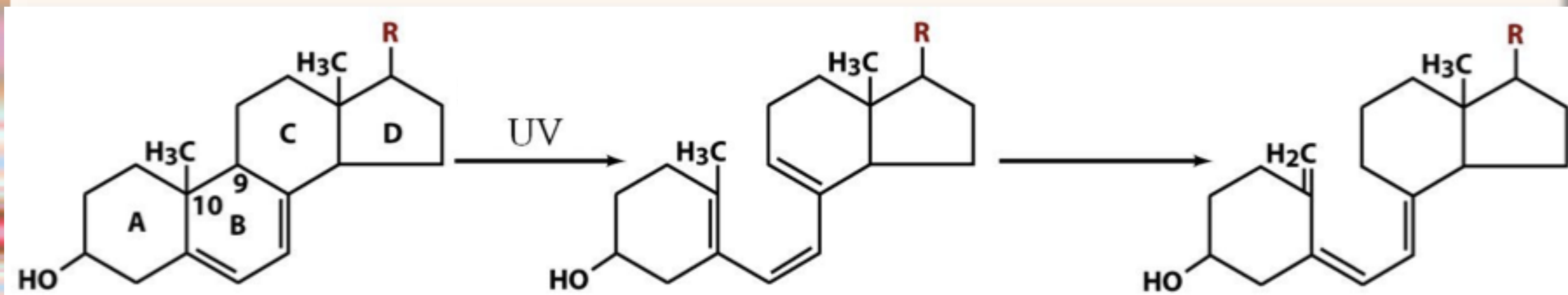
(b) Transizione con e senza colesterolo

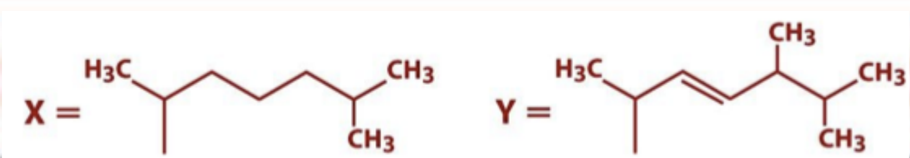


Cholesterol transportation in lipoproteic complexed (LDL)

Vitamin D

- Vitamin D is a regulator of Ca^{2+} homeostasis
- It is formed after photolysis of C9-C10 bond by UV light, followed by a spontaneous isomerization to vitamin D2 or D3
- Both these forms must be hydroxylated in the kidney (position C1) and in the liver (position C25) to give the active compound: 1-alpha-25-di-hydroxy-colecalciferol.

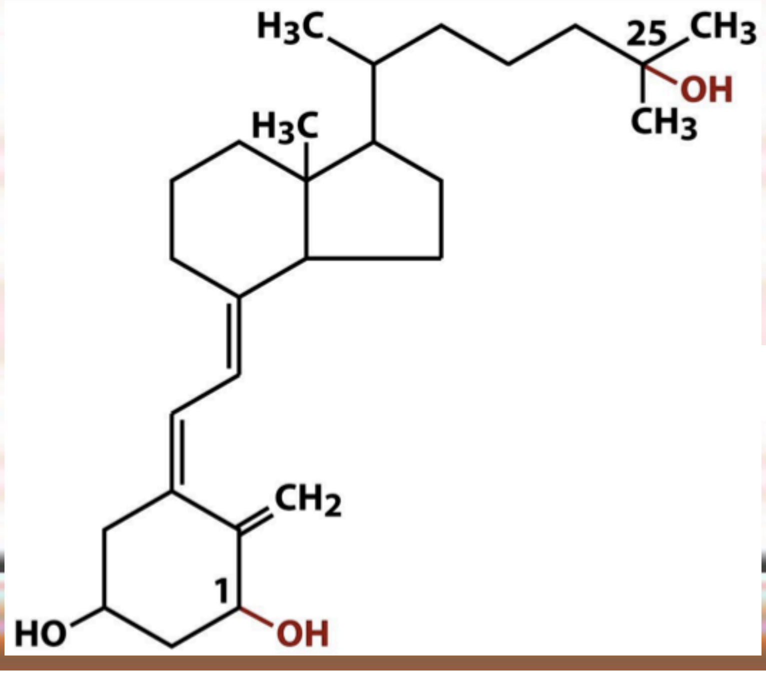




R = X vitamin D3
R = Y vitamin D2

Vitamin D

- The active form of vitamin D (1,25-dihydroxyvitamin D) induces an increase in the plasma concentration of Ca^{2+}, thus favouring its uptake by intestinal cells.
- Without vitamin D, only 10 to 15% of dietary calcium and about 60% of phosphorus is absorbed. The interaction with its receptor increases the efficiency of intestinal calcium absorption to 30 to 40% and phosphorus absorption to approximately 80%
- In this way these ions are deposited into bones and teeth.

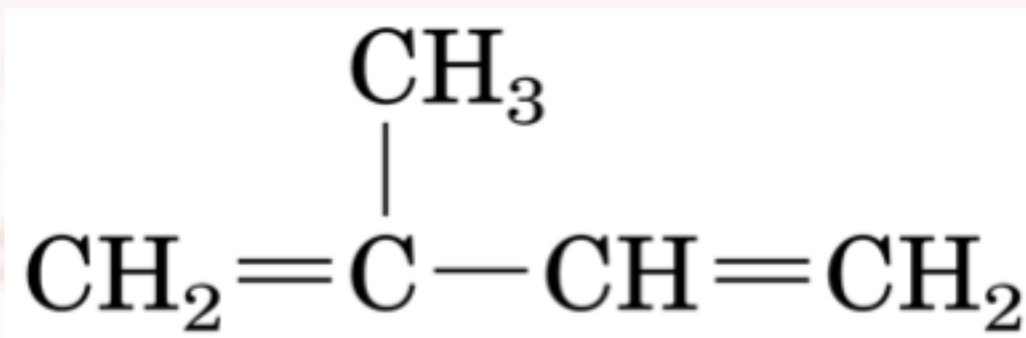


Vitamin D

- Very low levels of vitamin D, especially in pregnant women and infants, result in low level of growth and mental retardation.
- Vitamin D deficiency also causes muscle weakness. Skeletal muscles have a vitamin D receptor and require this vitamin for maximum function.
- Brain, prostate, breast, and colon tissues, among others, as well as immune cells have a vitamin D receptor. In addition, some of these tissues and cells express the 25-hydroxyvitamin D-1α-hydroxylase.
- Directly or indirectly, it controls more than 200 genes, including genes responsible for the regulation of cellular proliferation, differentiation, apoptosis, and angiogenesis.
- It decreases cellular proliferation of both normal cells and cancer cells and induces their terminal differentiation.
- One practical application is the use of 1,25-dihydroxyvitamin D3 and its active analogues for the treatment of psoriasis.

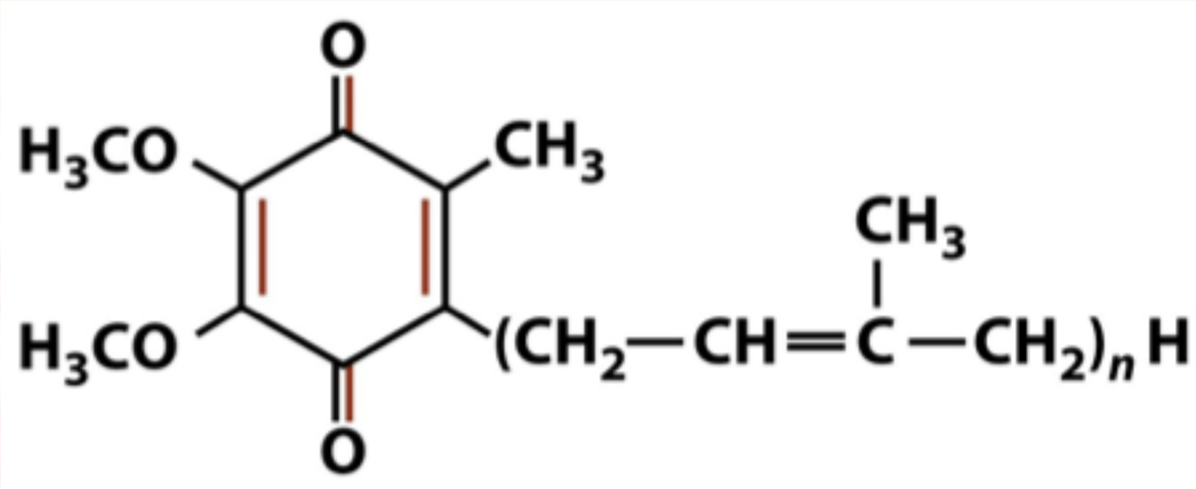
Terpenes and terpenoids

- Heterogenous class of hormones, co-enzymes, vitamins sharing only a part of the scaffold: a repeat of isoprene units



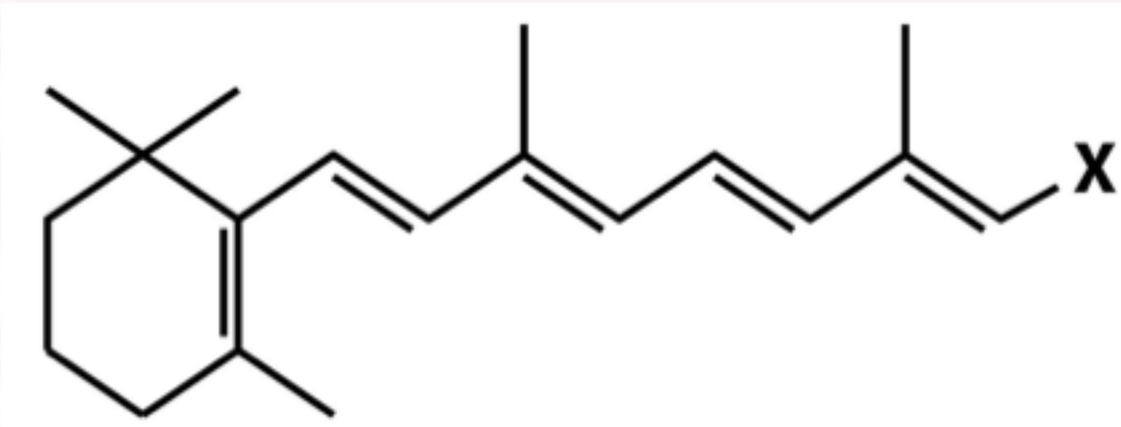
Coenzyme Q (ubiquinone)

- Shuttle of electrons in the respiratory chain in mitochondria, chloroplasts and in prokaryotes
- It is stably inserted in the membranes



Vitamin A (retinol)

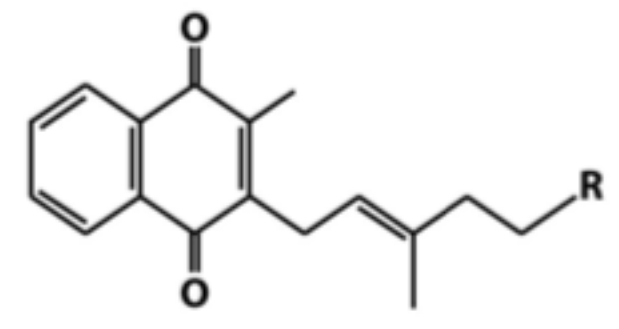
- Vitamin A is a derivative of beta-carotene, once oxidised into the aldehyde form (retinal) it is incorporated into the proteins of vision, where it helps transducing the light impulse into images
- Low levels supplied by the diet induce a reduced by-night vision
- Extremely low levels induce blindness (poverty-related blindness)

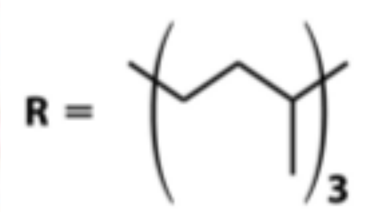


X = CH_2OH retinol
X = CHO retinal

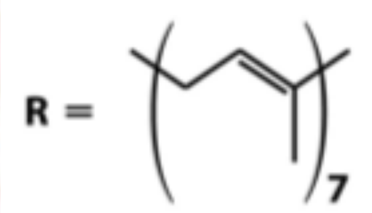
Vitamin K

- This vitamin is only produced by plants and bacteria
- In humans it is produced by the intestinal commensals
- It is crucial for a proper blood coagulation





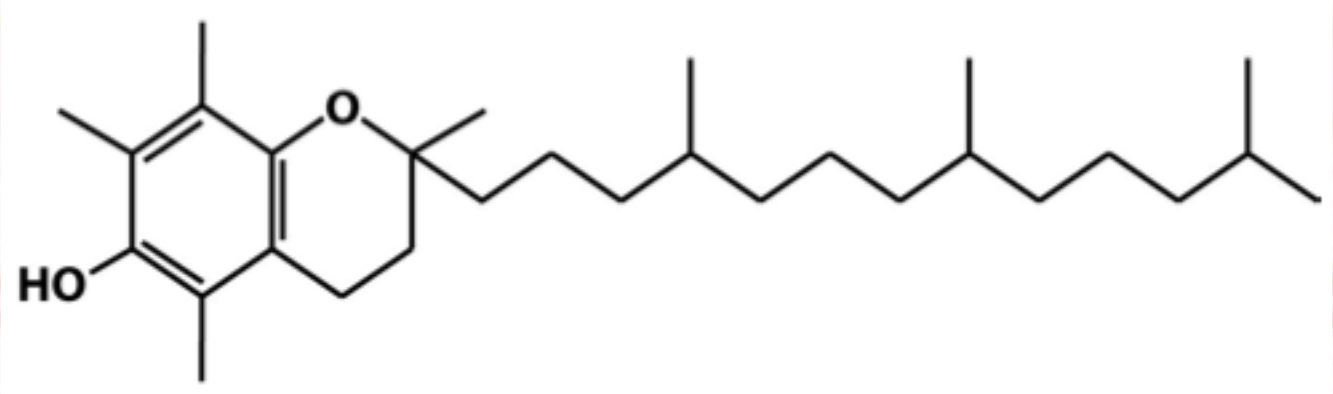
Vitamin K1 (plants)



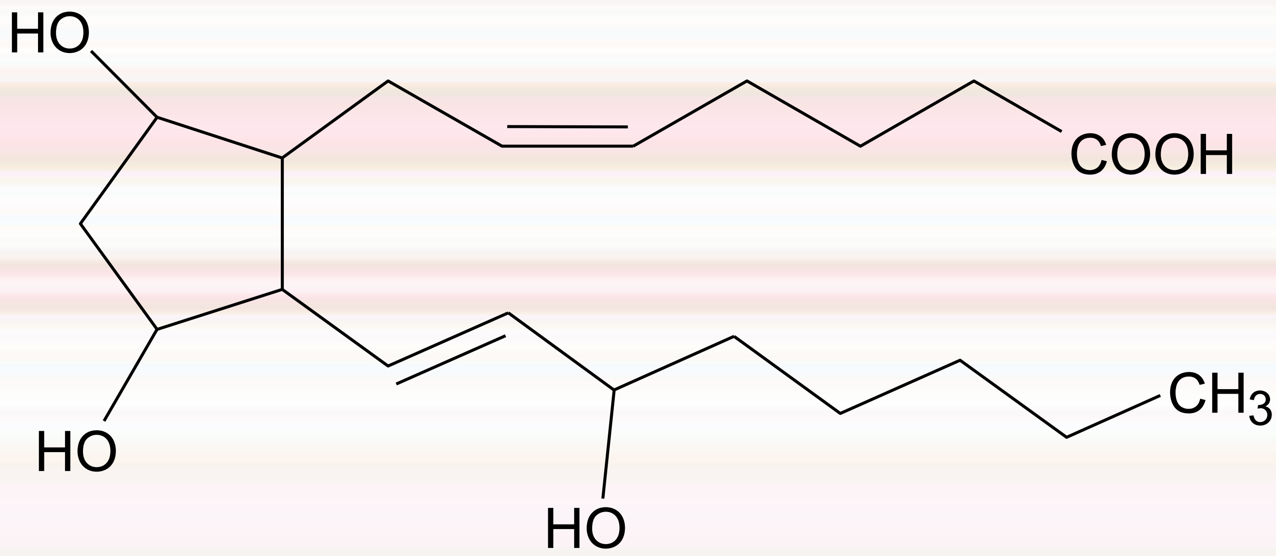
Vitamin K2 (bacteria)

Vitamin E

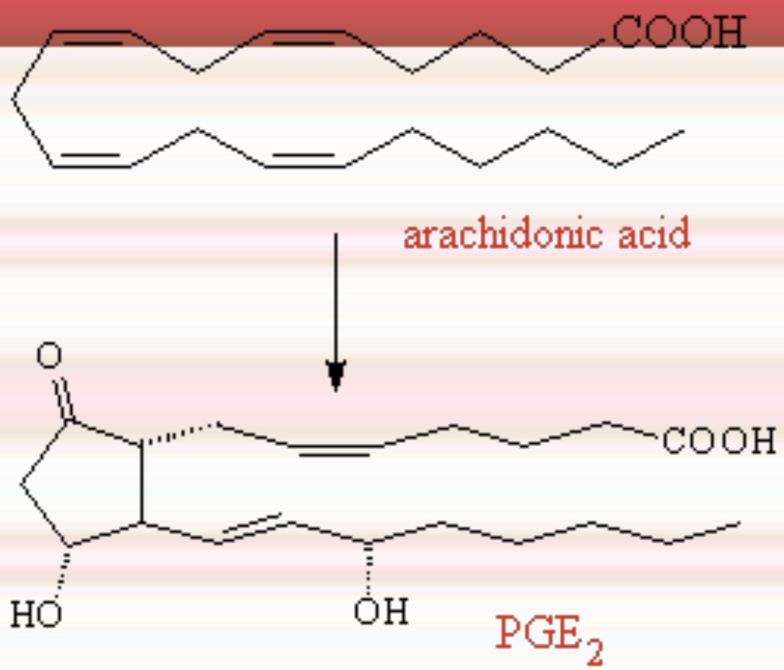
- Also known as alpha-tocopherol is an anti-oxidant, able to scavenge reactive oxygen species (ROS)
- It prevents oxidation of membranes and proteins



Prostaglandins are synthesized from arachidonic acid.



Hprmone-like effect:
Fever, contraction, inflammation, asthma…
Their synthesis is inhibited by anti-inflammatory drugs such as aspirin.



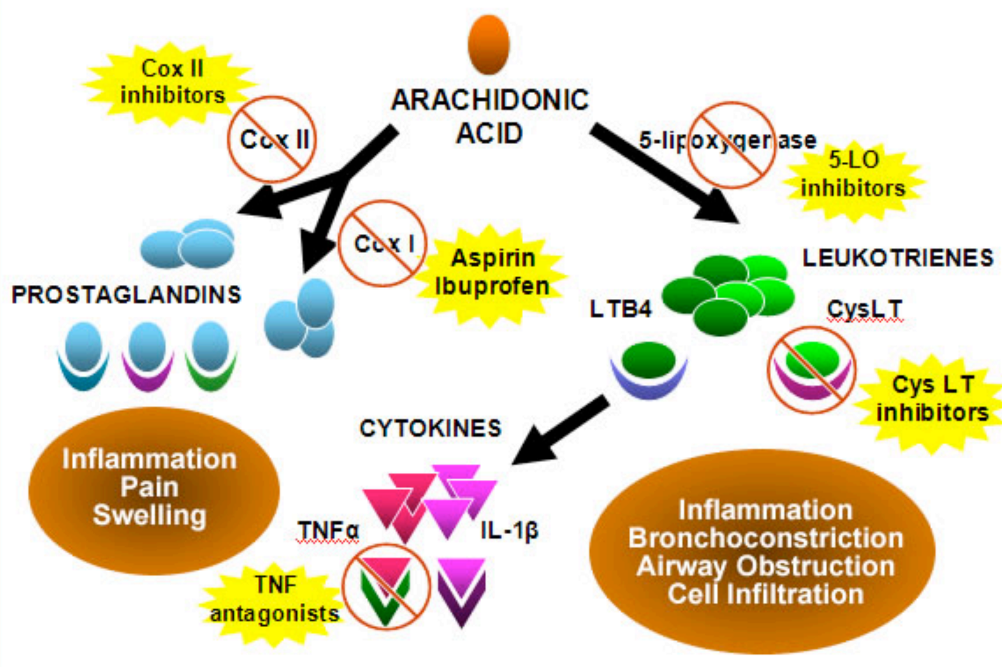


Figure 2. Arachidonic acid is metabolized to produce inflammatory mediators. Many current anti-inflammatory and pain medicines are inhibit some portion of the arachidonic acid pathways.