Lipids and Steroids

Types of lipids

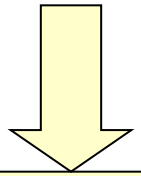
see Med.Chem. II App. 4

Simple

- triacylglycerols
- waxes
- ceramides
- **non-polar**
- insoluble in water
- soluble in lipophilic solvents

Complex

- glycerophospholipids
- sphingophospholipids
- glycosphingolipids
- **polar and non-polar**



have the character of tenside

concentrate on phase interface

Lipophilic solvents are very toxic

- trichloroethene $Cl_2C=CHCl$ (hepatotoxic)
- tetrachloroethene $Cl_2C=CCl_2$ (hepatotoxic)
- chloroform $CHCl_3$ (hepatotoxic)
- tetrachloromethane CCl_4 (☠ extremely hepatotoxic!!)
- benzene C_6H_6 (☠ carcinogen!!)
- toluene C_6H_5-CH_3 (lung damages, addictive inhalant)
- nitrobenzene C_6H_5-NO_2 (☠ methemoglobinemia)
- carbon disulfide CS_2 (☠ neurotoxic)

Fatty acids (FA)

Number of carbons and double bonds		Common name	Systematic name
Saturated fatty acids			
4:0		Butyric	butanoic
6:0		Caproic	hexanoic
8:0		Caprylic	octanoic
10:0		Capric	decanoic
12:0		Lauric	dodecanoic
14:0		Myristic	tetradecanoic
16:0		**Palmitic**	hexadecanoic
18:0		**Stearic**	octadecanoic
20:0		Arachidic	eicosanoic
22:0		Behenic	docosanoic
24:0		Lignoceric	tetracosanoic
Unsaturated fatty acids			
16:1(9)		Palmitoleic	*cis*-hexadec- 9-enoic
18:1(9)	(*n*–9)	Oleic	*cis*-octadec-9-enoic
18:2(9,12)	(*n*–6)	Linoleic	*cis,cis*-octadeca-9,12-dienoic
18:3(6,9,12)	(*n*–6)	γ-Linolenic	*cis*,*cis*-octadeca-6,9,12-trienoic
18:3(9,12,15)	(*n*–3)	α-Linolenic	all-*cis*-octadeca-9,12,15-trienoic
20:4(5,8,11,14)	(*n*–6)	Arachidonic	all-*cis*-eicosa-5,8,11,14-tetraenoic
20:4(5,8,11,14,17)	(*n*–3)	(Timnodonic)	all-*cis*-eiscosa-5,8,11,14,17-pentaenoic

The three features of „fatty“

1. Non-polar

= hydrophobic

= insoluble in water

= lipophilic

= soluble in organic solvents
($CHCl_3$, CCl_4, benzene)

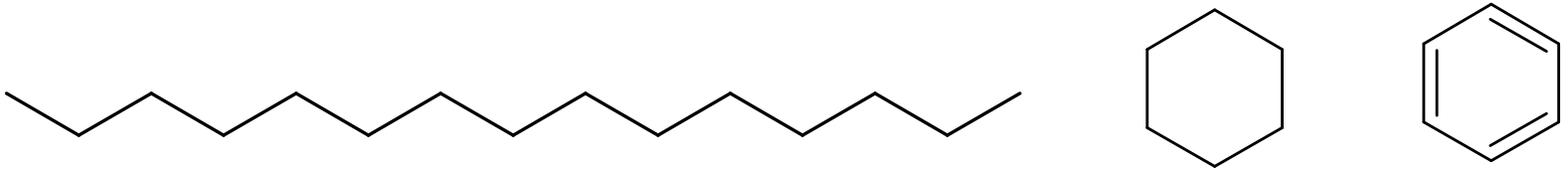
2. Lighter than water

= density < 1 g/cm^3

= floats on water surface

= makes upper liquid phase

3. Contains long C-H chains and/or cycles



any fatty substance
(oil, hydrocarbon)
makes the upper phase

water

Three types of fatty acids

SAFA saturated fatty acids

MUFA monounsaturated fatty acids

PUFA polyunsaturated fatty acids

- aliphatic, monocarboxylic acid
- **even** number of C atoms, biosynthesis from acetyl-CoA (2C)
- saturated or unsaturated (configuration ***cis***)
- free FA are **non-polar** compouds, insoluble in water
- very weak acids ($pK_A \sim 10$)

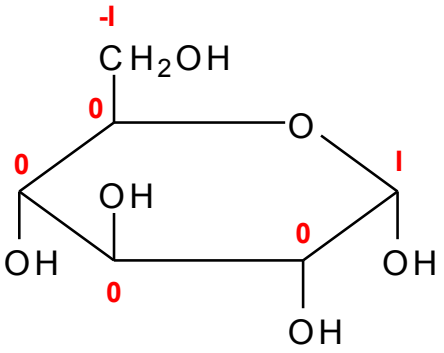
Three groups of SAFA

C	Acid	Occurence	Commentary
4 6 8 10	butyric caproic caprylic capric	butter butter butter butter	easily digestible, absorbed directly to blood metabolic fuel for enterocytes and liver Lat. *butyrum, i, n.* butter Lat. *capra, ae, f.* goat
12 14 16	lauric myristic palmitic	coconut fat coconut fat animal fats	**atherogenic**, increase blood cholesterol coconut fat is used to make ice cream etc.
18	stearic	animal fats cocoa butter	does not elevate blood cholesterol

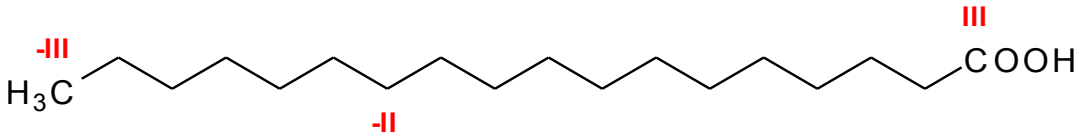
Biochemical role of SAFA

- **source of energy**, for most tissues (not for brain)
- excessive intakes leads to obesity, atherosclerosis (especially FA C12, C14, C16), increase total and LDL-cholesterol in blood
- it is recommended to reduce the intake of SAFA
- occurence: lard, butter, fatty meat, hardened fats, coconut fat
- **exception:** cocoa butter – contains mainly C18, stearic acid does not harm, in addition cocoa is very rich in antioxidants

Fatty acids possess the highest energy from nutrients

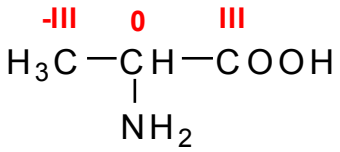


Average ox. num. C = 0.0



Average ox. num. C = -1.8

$\Rightarrow$ C is the most reduced

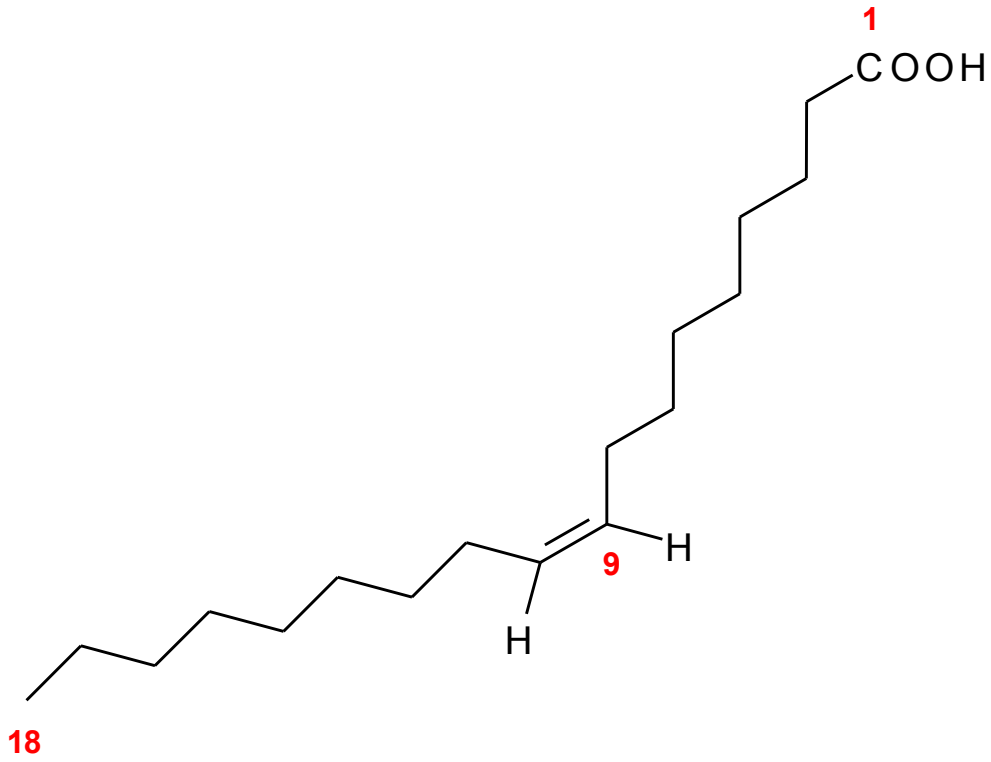


Average ox. num. C = 0.0

Lipids	38	kJ/g
Saccharides	17	kJ/g
Proteins	17	kJ/g

MUFA prevail in olive and rape seed oils

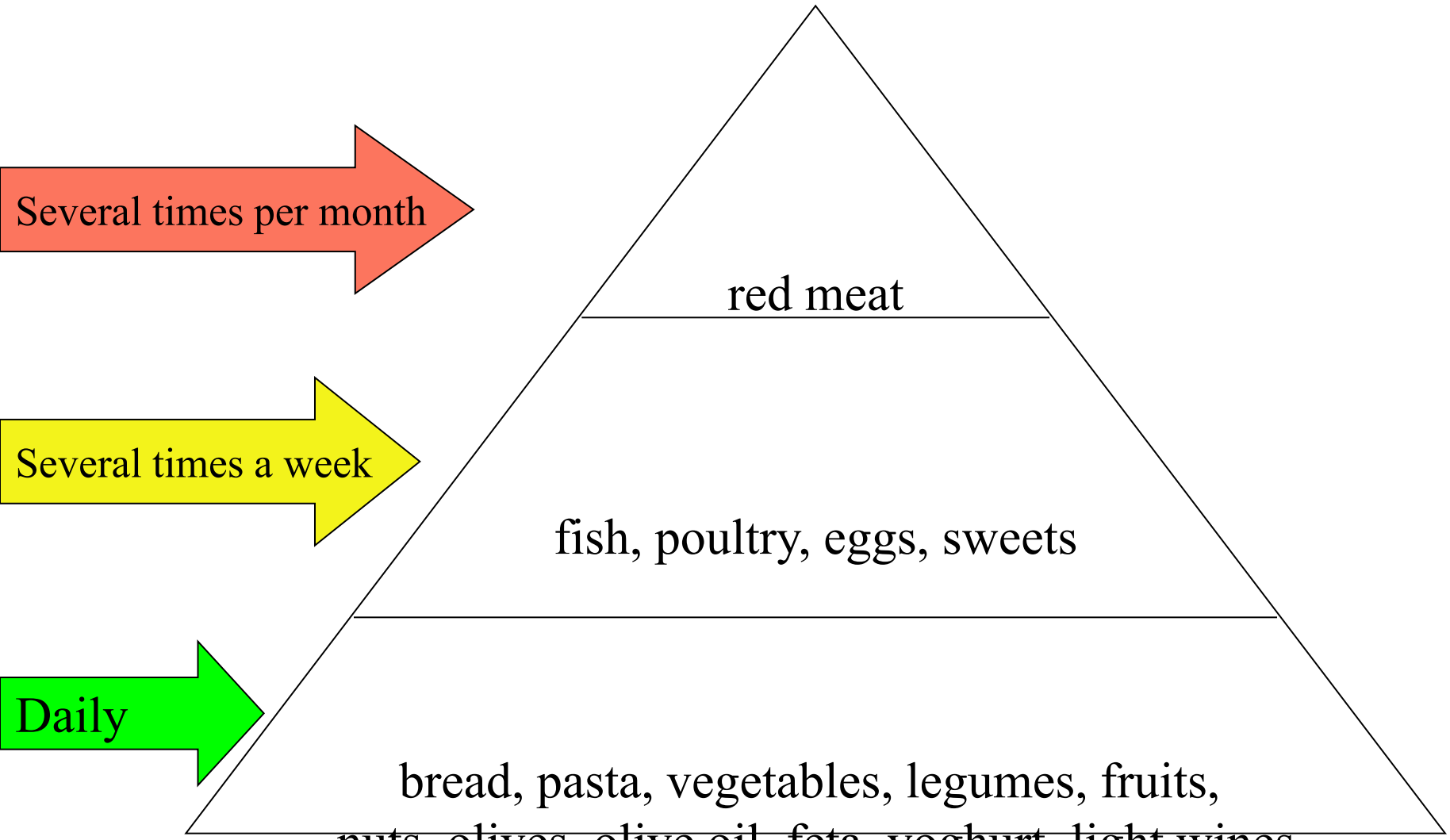
- 16:1(9) palmitoleic
- 18:1(9) oleic



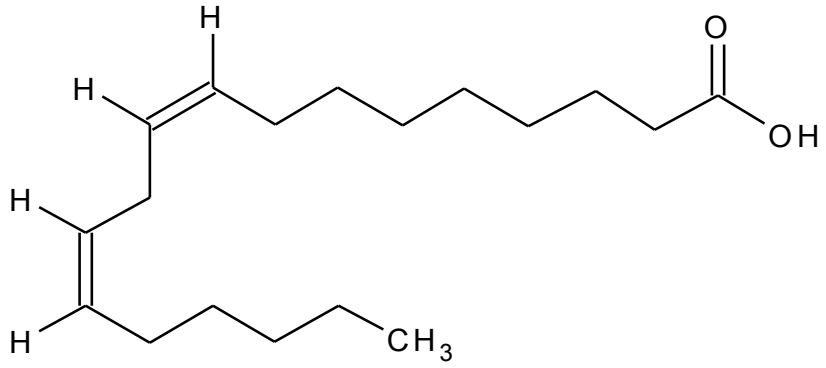
Biochemical role of MUFA

- mainly oleic acid, **source of energy**
- beneficial influence on blood lipids, decreases LDL-cholesterol, lipoproteins rich in MUFA are more resistent to lipoperoxidation
- phenolic compounds in extra virgin olive oil increase antioxidant capacity of LDL
- **Mediterranean diet** – low occurence of cardiovascular and cancer diseases
- sufficient intake of MUFA is recommended
- occurence: triacylglycerols of olive and rape seed oil

Pyramid of Mediterranean diet



PUFA



- 18:2 (9,12) linoleic **n-6** **essential**
- 18:3 (9,12,15) α-linolenic **n-3** **essential**
- 20:4 (5,8,11,14) arachidonic **n-6**
- 20:5 (5,8,11,14,17) eicosapentaenoic (EPA) **n-3**
- 22:6 (4,7,10,13,16,19) docosahexaenoic (DHA) **n-3**

Nomenclature of PUFA

Example: *all-cis*-octadeca-9,12,15-trienoic acid (systematic name)

Linolenic acid (neutral compound), Linolenate (anion)

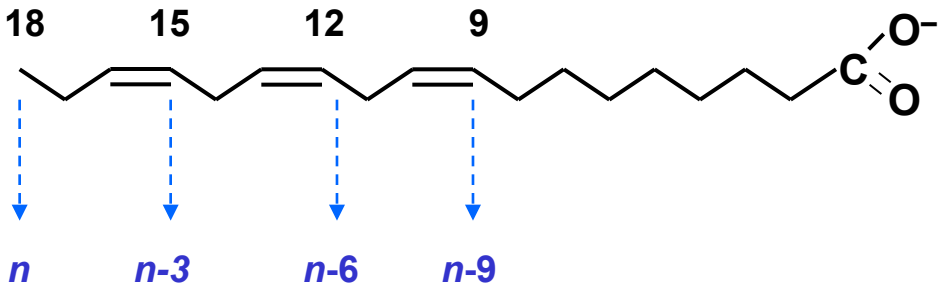
18 : 3 (9,12,15)

positions of double bonds

number of double bonds

total number of carbon atoms

18:3 (*n*–3) or ω-3



Linguistic analysis: octadeca - tri - en - oic acid

Name component	Explanation
octadeca	18 (from Greek) = the number of C atoms
tri	3 = the number of double bonds
en	infix, indicates a double bond
oic acid	suffix, indicates a compound type (carboxylic acid)

Essential fatty acids:
linoleic acid (LA), α-linolenic acid (ALA)

- cannot be created in the body, we do not have enzymes for corresponding desaturations
- desaturation in human body proceeds **only from C1 to C9**
- n-3 and n-6 desaturations occur only in plants
- essential FA must be supplied by food
- recommended intake of total PUFA: around 20 g
- optimal ratio LA : ALA = 1:1, not higher than 5:1

Biochemical roles of PUFA

- **structural components of membrane phospholipids**
- **the precursors of eicosanoids**
- primarily not source of energy
- beneficial influence on blood cholesterol
- **CAUTION:** excessive intake of PUFA is harmful, they are sensitive to lipoperoxidation
- excess of LA-derived eicosanoids exhibit unfavourable health effects (increased blood coagulation etc.)
- PUFA occurence: sunflower oil and soybean oil (ω-6),
  fish oil, nuts, linseed oil (ω-3)

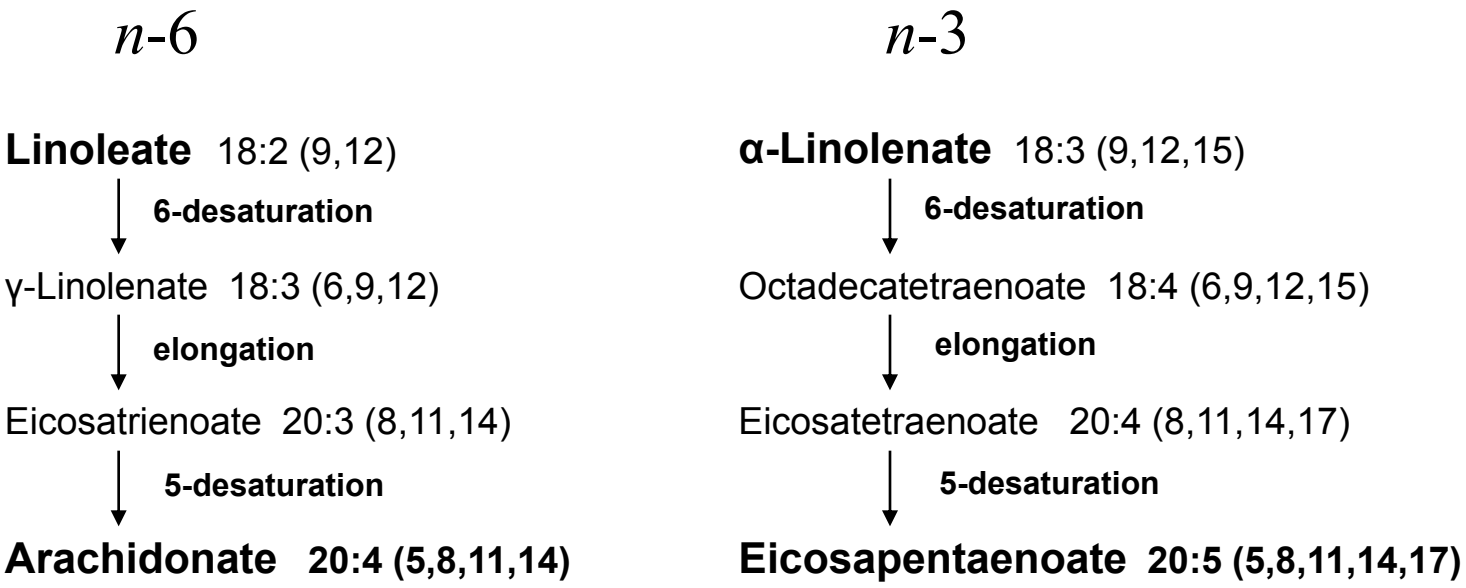
Physiological effects of n-6 and n-3 PUFA are not the same.

They are given by the opposite effects of corresponding eicosanoids

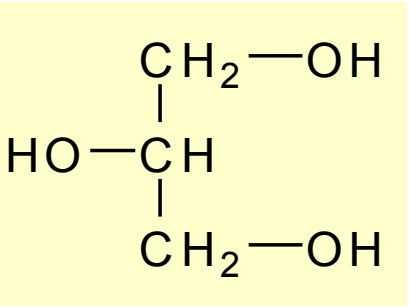
n-6	n-3
Decrease blood cholesterol	Decrease blood TAG
Increase blood coagulation (platelet aggregation)	Decrease blood coagulation (platelet aggregation)
Inflammatory effect	Anti-inflammatory effect
	Necessary for the development of brain in children

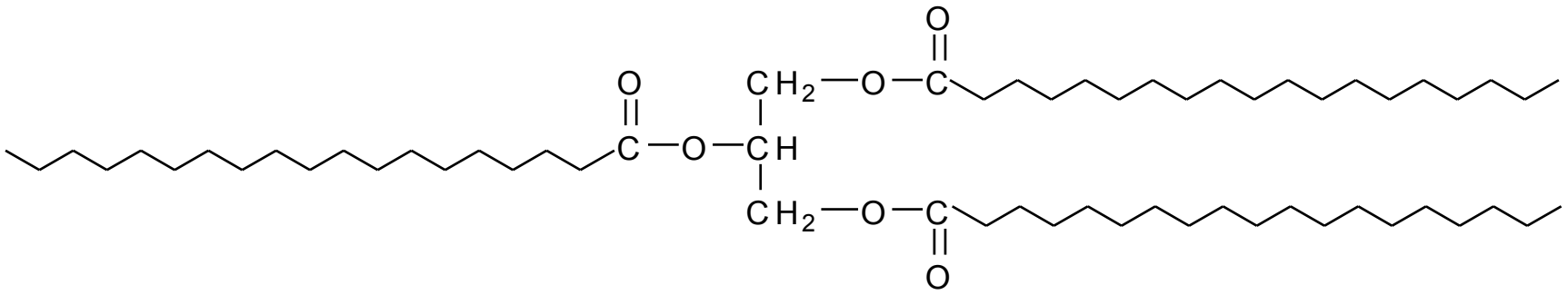
Essential FA are the substrates for desaturations and elongations

PUFA with double bonds beyond C9 (*n*-6 and *n*-3) are synthesized by plants. If dietary intake is sufficient, **linoleate** and **α-linolenate** are precursors of other PUFA such as **arachidonate** (*n*-6) and **eicosapentaenoate** (*n*-3), from which eicosanoids are formed.



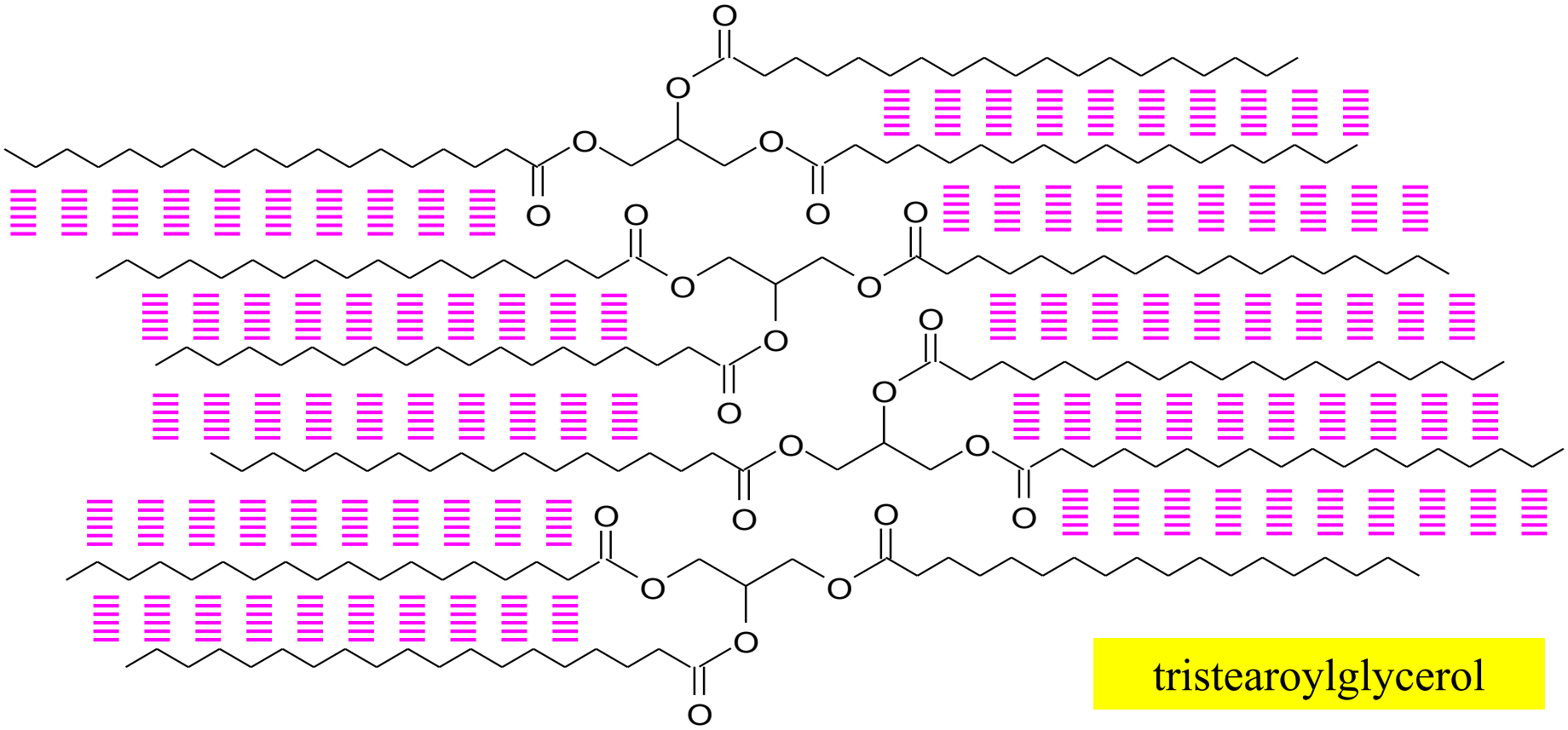
Simple lipids are triesters of glycerol





saturated triacylglycerol (TAG)

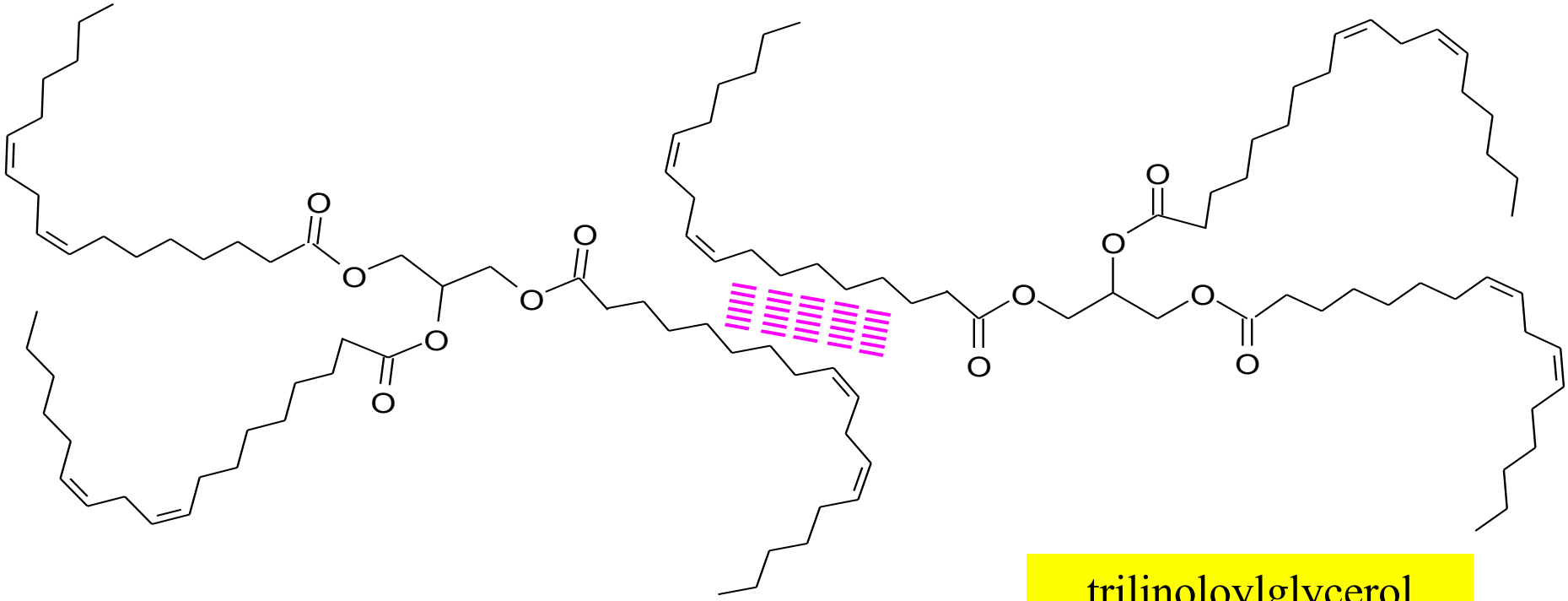
Dispersion interactions between saturated TAG (linear molecules) are very extensive



tristearoylglycerol

Higher melting point – solid fats

Dispersion interactions between unsaturated TAG (spherical molecules) are limited



trilinoloylglycerol

➡ Lower m.p. – liquid fats (oils)

Chemical conversion of lipids

- hydrogenation (*in vitro*)
- re-esterification (*in vitro*)

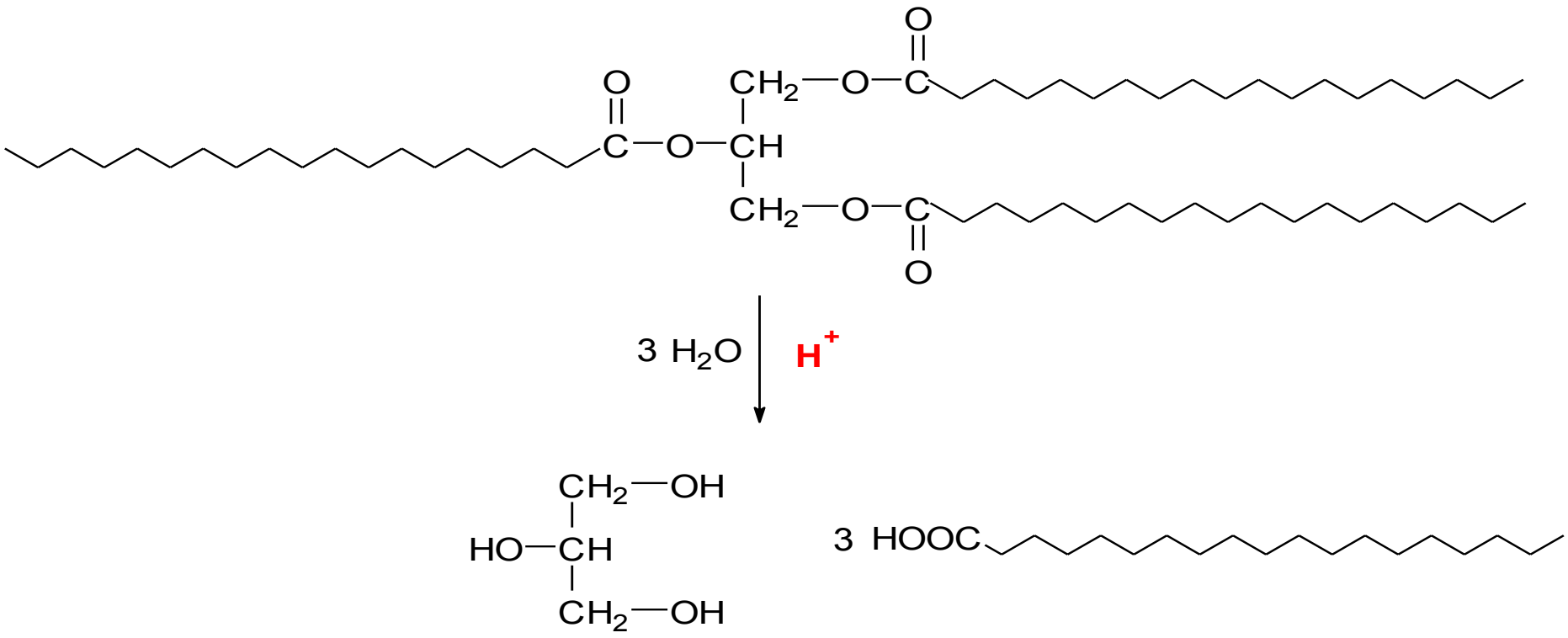
} fat hardening

- **hydrolysis** (*in vitro*, ***in vivo***)
- **lipoperoxidation** (*in vitro*, ***in vivo***)
- rancidification (*in vitro*)

Hydrolysis of triacylglycerols

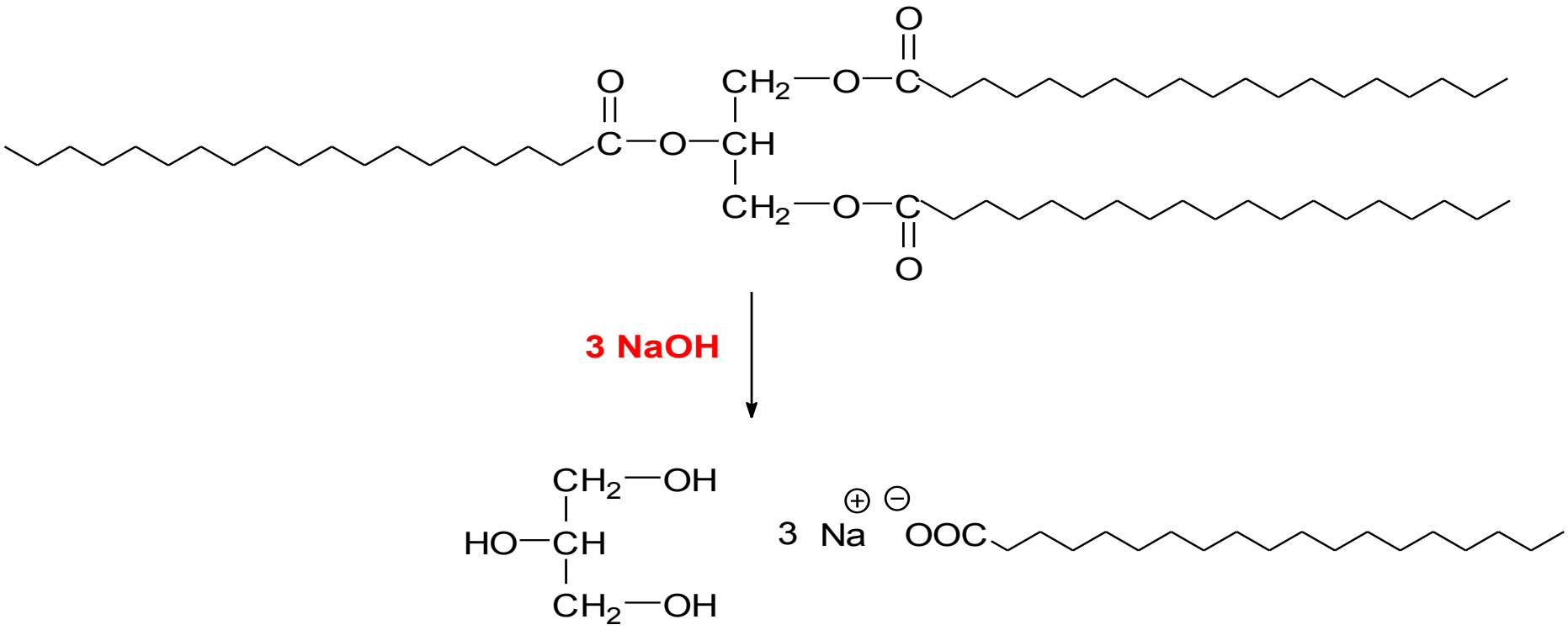
- **acidic** $\rightarrow$ glycerol + 3 FA
- **alkaline** $\rightarrow$ glycerol + 3 salts of FA
- **enzymatic:** lipase action (see later)

Acidic hydrolysis provides free FA



Alkaline hydrolysis provides soap

linguistic paradox



Soap (sodium salt of fatty acid) is anionic surfactant

Composition of soap

Aqua, Sodium Tallowate, Sodium Lardate, Sodium Cocoate, Perfume, Glycerine, Almond Extract, Sodium Chloride, Titanium Dioxide, EDTA, CI 15510

tallow = fat obtained from beef cattle and sheep
lard = pig fat
coconut fat = fat obtained from the flesh of coconut fruit

See Seminars, p. 24

Lipoperoxidation *in vivo*

- Reaction of PUFA with free radicals (•OH, •OR, •OOR)
- Chain reaction, non-specific
- Products: higher aldehydes, alkanes

  malondialdehyde (MDA) O=CH-CH_2-CH=O

- MDA attacks proteins and other biomolecules

Lipids in food: Various aspects

Pure (100%) plant oils, lard, hardened kitchen fats	**Emulsified with water** butter, margarins
Obvious (explicit) see above	**Hidden (latent)** meat products, cheese, ice cream, cookies etc.
Atherogenic SAFA, especially C12, C14, C16 most animal fats, coconut fat	**Anti-atherogenic** MUFA, PUFA olive oil, rape seed oil, nuts, sea fish
Suitable for frying resistent to oxidation (SAFA, MUFA) cholesterol-free	**Unsuitable for frying** containing: higher portion of PUFA / cholesterol / water

Average content of FA in selected kitchen fats (%)

Fat	SAFA	MUFA	ω-3 PUFA	ω-6 PUFA
Rape seed oil	10	60	10	20
Sunflower oil	10	25	1	64
Soybean oil	16	24	7	53
Olive oil	15	75	1	9
Coconut fat	90	7	0	3
Lard	43	48	1	8
Butter*	67	28	0	2
Poultry fat	42	37	1	20
Fish oil	28	52	15	5
Cocoa butter	60	38	0	2

* The difference to 100 % is made by 3 % of *trans*-FA.

Nutritional recommendations about fats

- 2/3 plant oils, 1/3 animal fat
- avoid fats with SAFA (mostly contain cholesterol)
- prefer olive oil, rape seed oil, and sea fish
- be careful with sunflower oil and soybean oil
- prefer margarins to butter
- avoid *trans*-FA
- avoid dead-burn fats and fried meals

Fat content in meat varies in the big range

Type of meat	Fat content (%)
Long-life salamis	40-60
Sausages, wursts, hot dogs etc.	20-50
Pork	40
Goose, duck	20-40
Pork lean	20
Sea fish (herring, mackerel, salmon)	10-20
Sardines	7-9
Rabbit	7
Chicken, turkey	5-6
Beef lean	3
Carp (fish)	3
Venison	1
Codfish	0,6
Chicken brest	0,5
Zander (fish)	0,4
Pangasius (fish)	0,4
Turkey breast	0,3

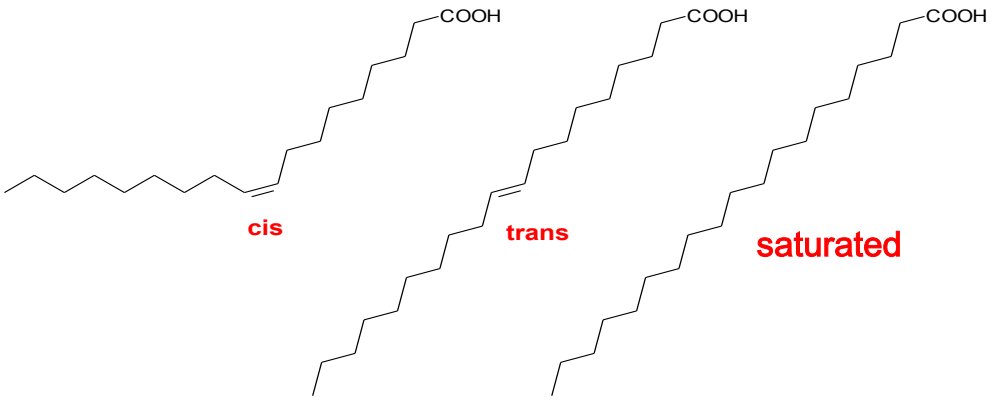
trans-Fatty acids contribute to coronary heart disease

Natural occurence

- tallow (3-7 %)
- butter (3 %)

Synthetic origin

- kitchen fats hardened by hydrogenation
- food products containg hardened fats (cookies etc.)



Other lipid-like substances

- lipophilic vitamins

  (retinol, tocopherol, calciol, phylloquinone)
- terpenes, antioxidants etc.
- cholesterol, phytosterols

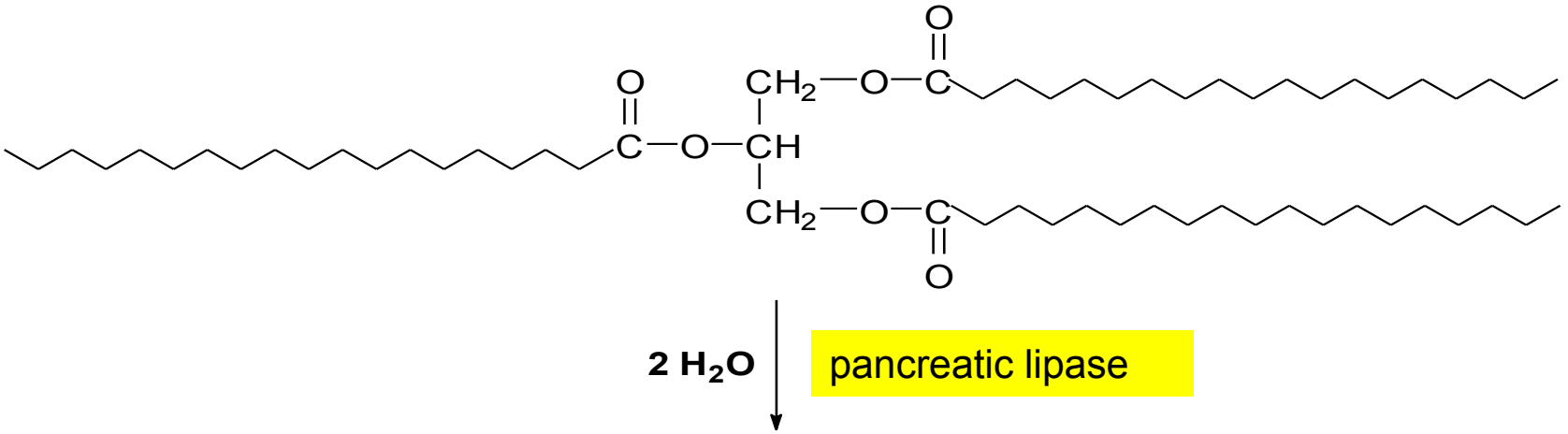
Severe lipid-free diets lead to the deficit of lipophilic vitamins, antioxidants, and essential FA.

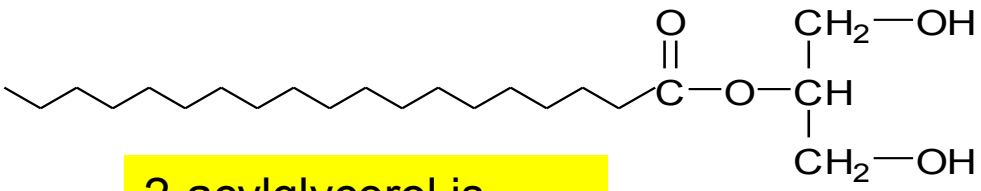
Lipophilic vitamins and antioxidants

Compound	Structure type	Main food sources
Retinol	isoprene	butter, egg yolk, liver, vegetables
Carotenoids	isoprene	colored vegetables and fruits
Phylloquinone	naphtoquinone	green vegetables, **made in intestine**
Tocopherol	chroman	nuts, seeds, cold pressed plant oils
Calciol	cholesterol	fish oil, butter, **made in skin (UV)**

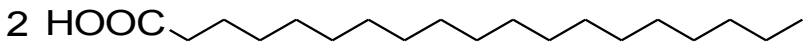
Biochemical conversions of lipids

Enzymatic hydrolysis in small intestine





2-acylglycerol is
non-ionic surfactant



free FA dissociates
and makes anionic surfactant

pH of pancreatic juice 7.5-8.8

Natural tensides in fat digestion

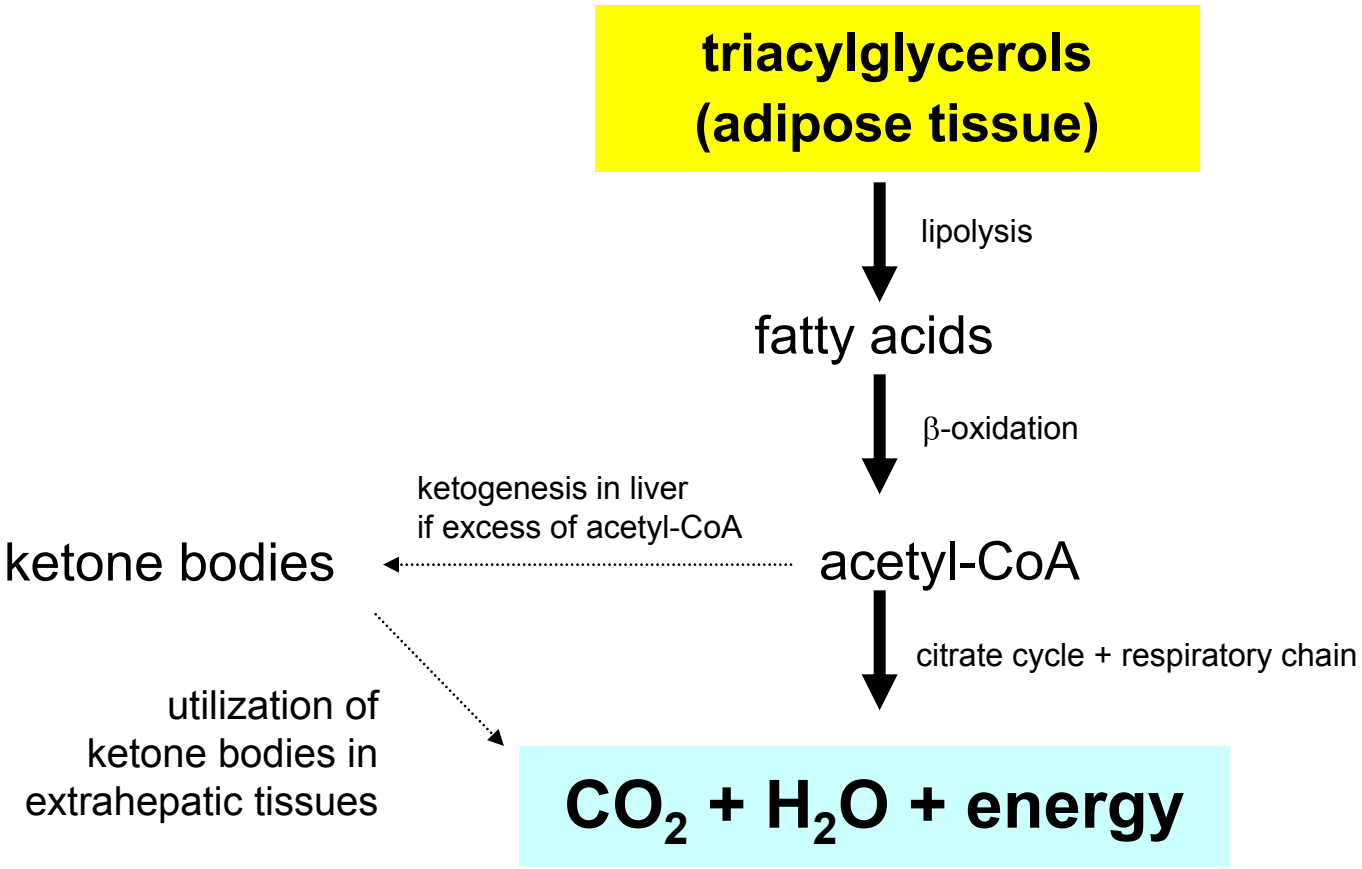
Tenside	Type	Origin
Bile acids	anionic	from cholesterol in liver
2-Acylglycerol	non-ionic	TAG hydrolysis in gut
FA anions	anionic	TAG hydrolysis in gut
Phospholipids	amphoteric	food

They all together make a mixed micelle which enters enterocyte

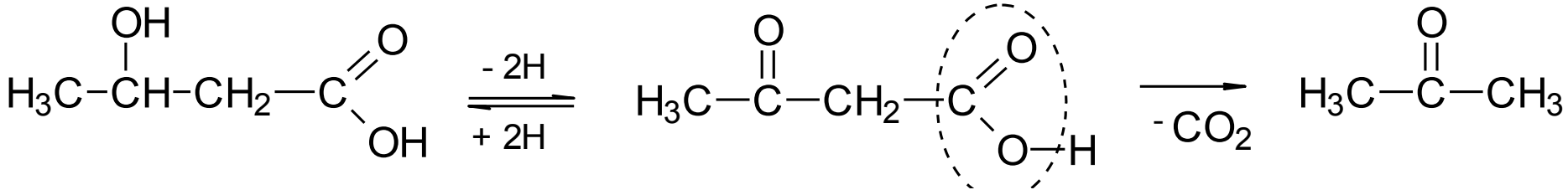
Lipases in human body

Lipase	Substrate	Organ location
Pancreatic lipase	exogenous TAG	small intestine
Hormon-sensitive lipase (HSL)	endogenous TAG	adipose tissue
Lipoprotein lipase (LPL)	TAG of chylomicrons and VLDL	capillaries of peripheral tissues (muscles etc.)
Hepatic lipase (HL)	TAG of HDL	liver sinusoids

Catabolic pathway of lipids

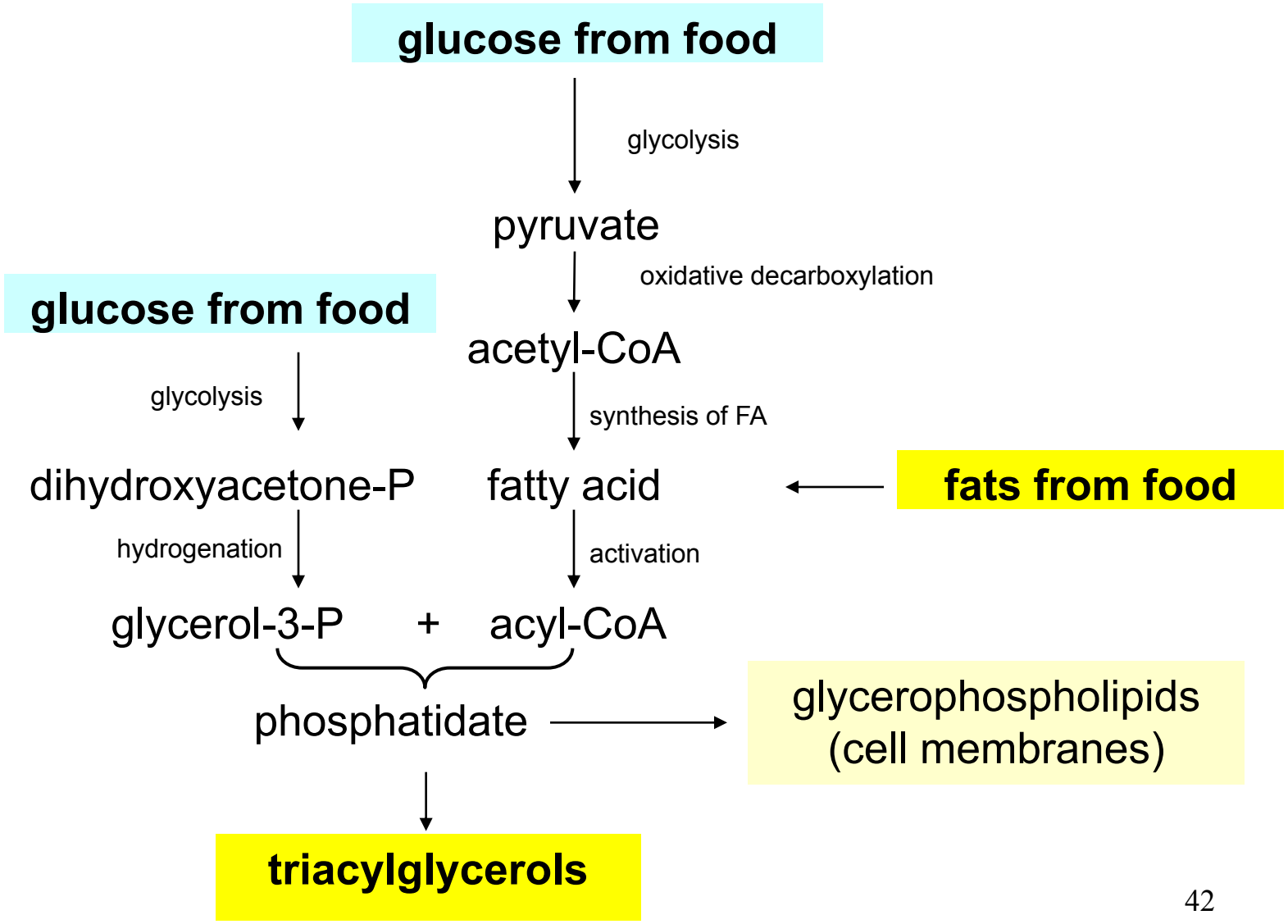


Ketone bodies



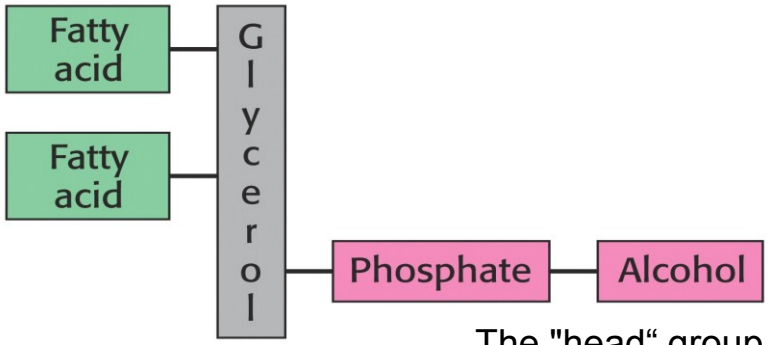
beta-hydroxybutyrate acetoacetate acetone

Anabolic pathway- biosynthesis of lipids



Schematic diagrams of complex lipids

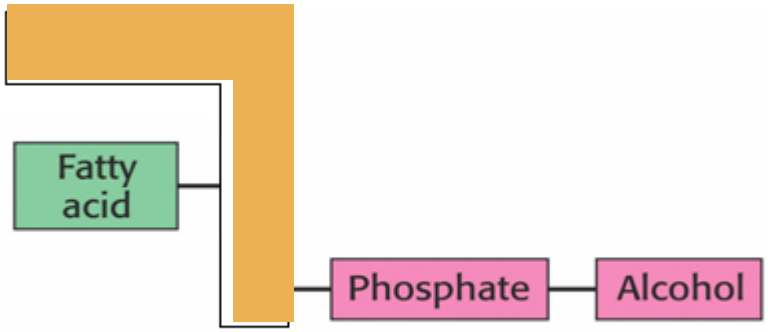
Glycerophospholipids



The "head“ group

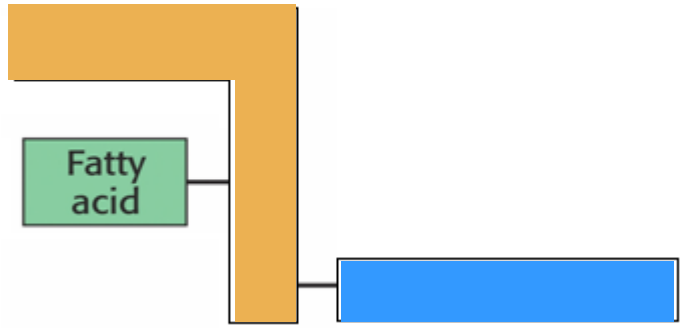
see MCH II App. 4

Sphingophospholipids

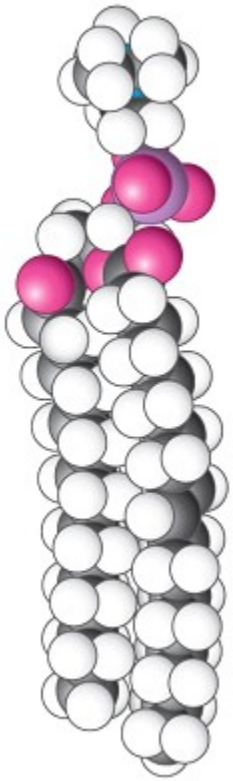


The "head“ group

Glycolipids

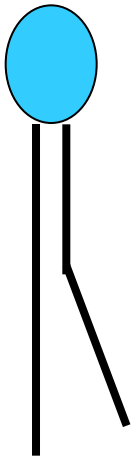


Complex lipids are tensides



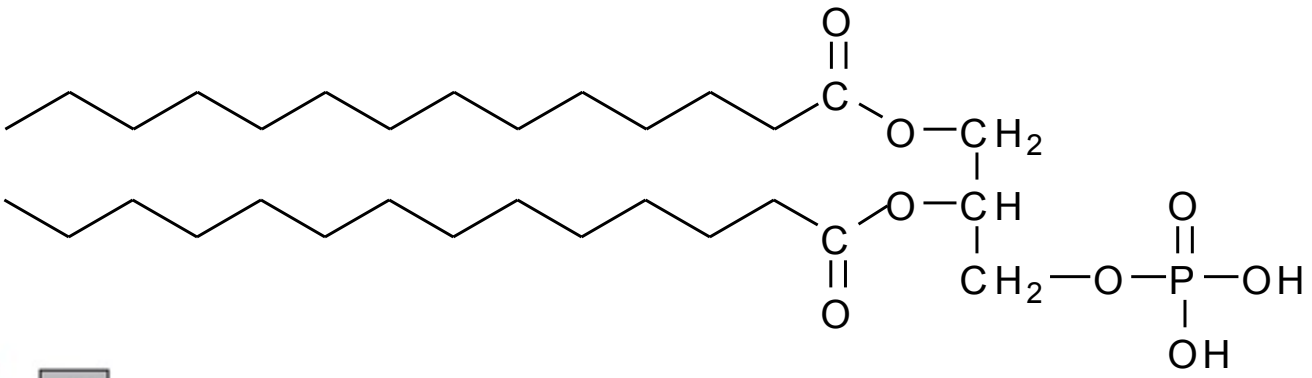
glycerophospholipid

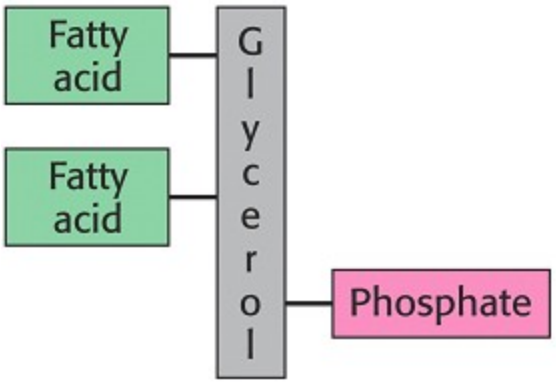
sphingophospholipid



Phosphatidic acid is the main structure of glycerophospholipids

1,2-diacylglycerol-3-phosphoric acid

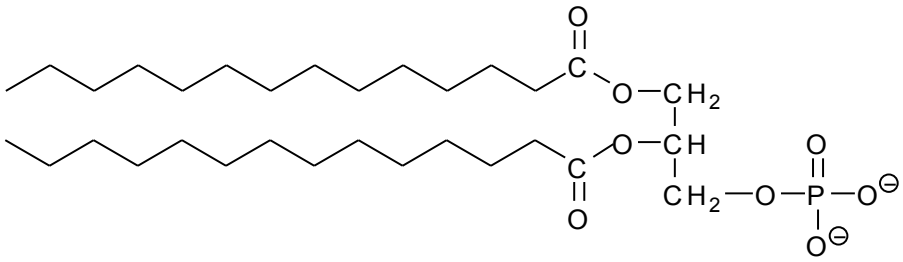




Distinguish

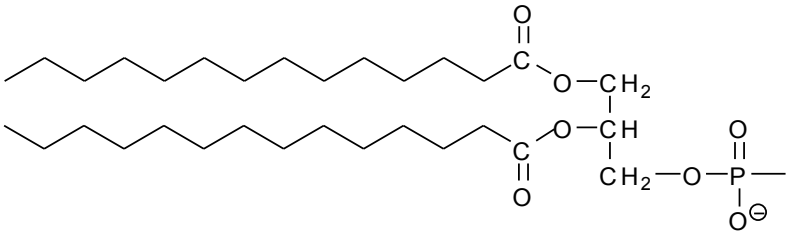
- **Phosphatidate** = anion of phosphatidic acid

  (after removing H^+)

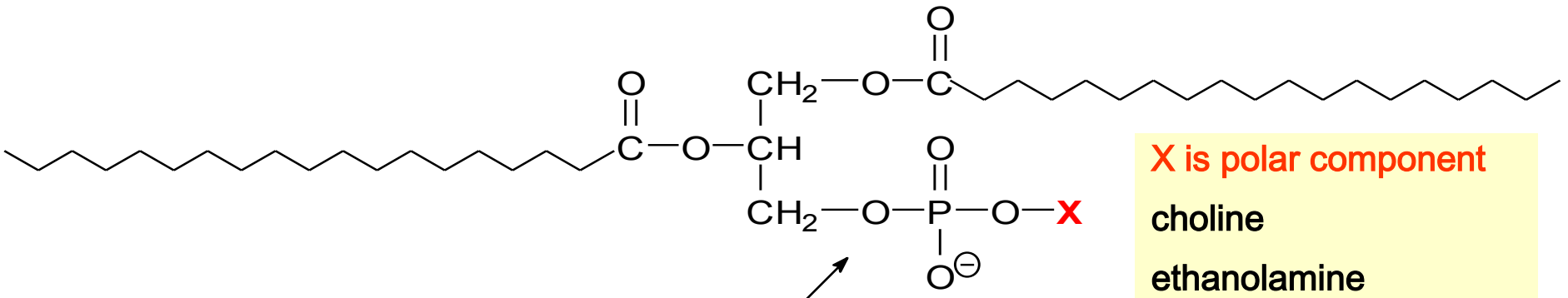


- **Phosphatidyl** = acyl of phosphatidic acid

  (after removing –OH group)



Glycerophospholipids



diester of phosphoric acid

dissociated – negative charge

X is polar component

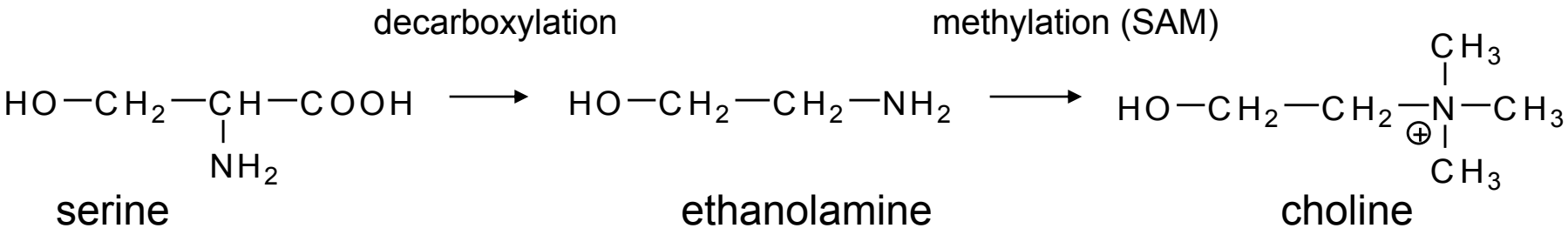
choline

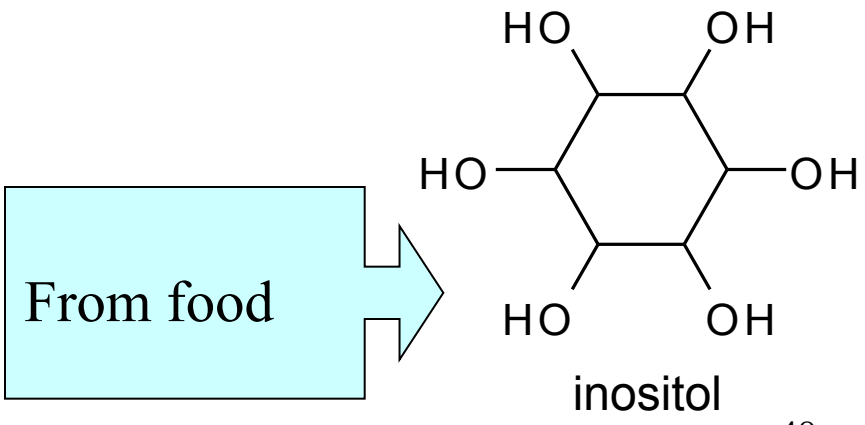
ethanolamine

serine

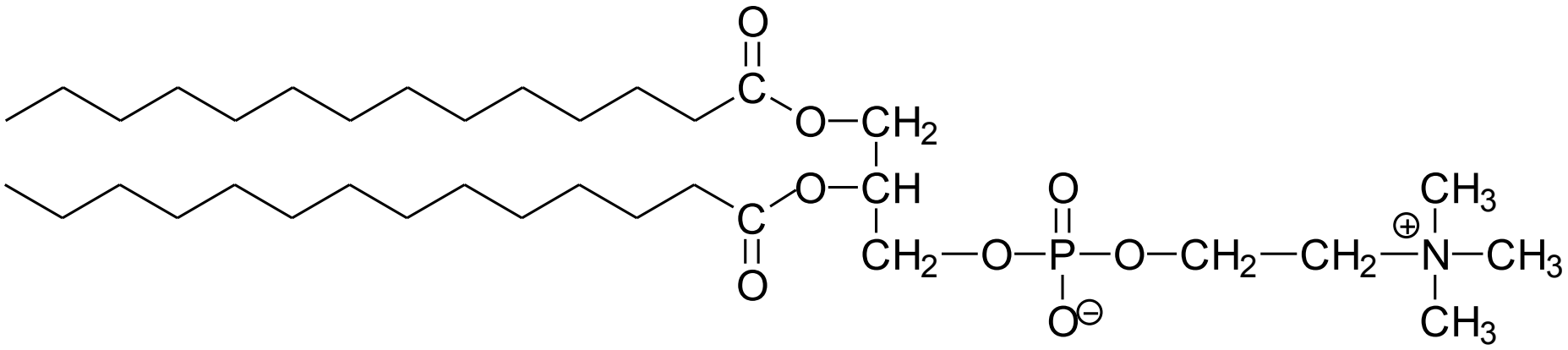
inositol

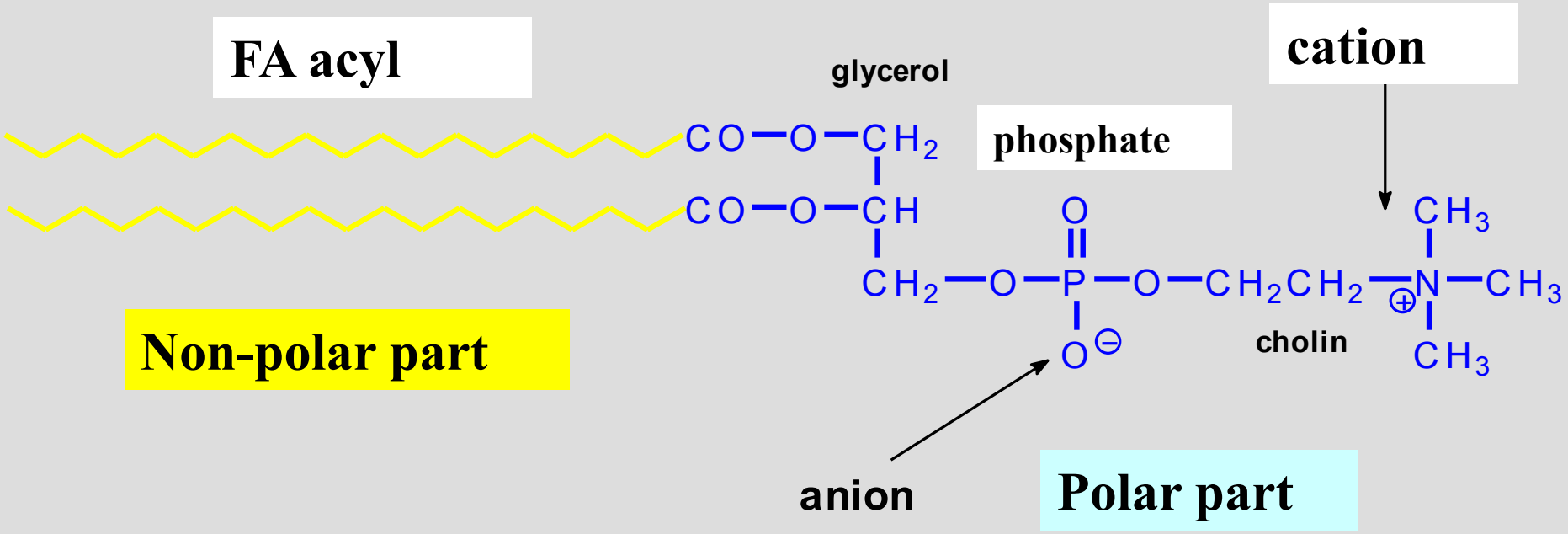
Polar components – Metabolic origin



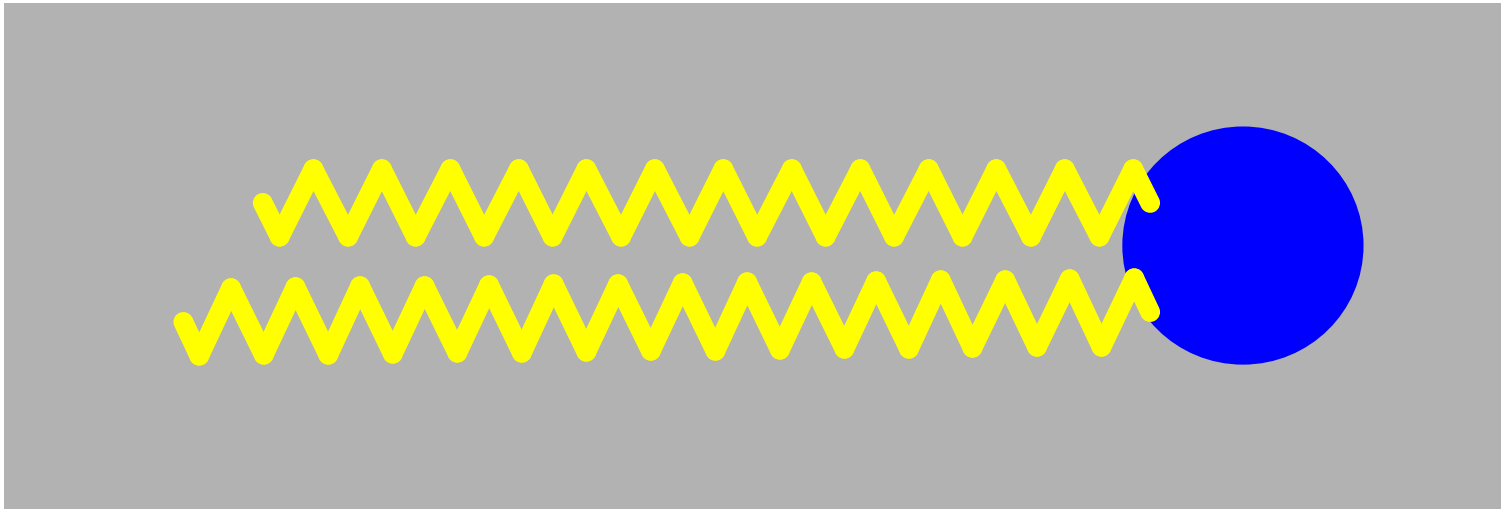


Phosphatidylcholine is amphoteric tenside

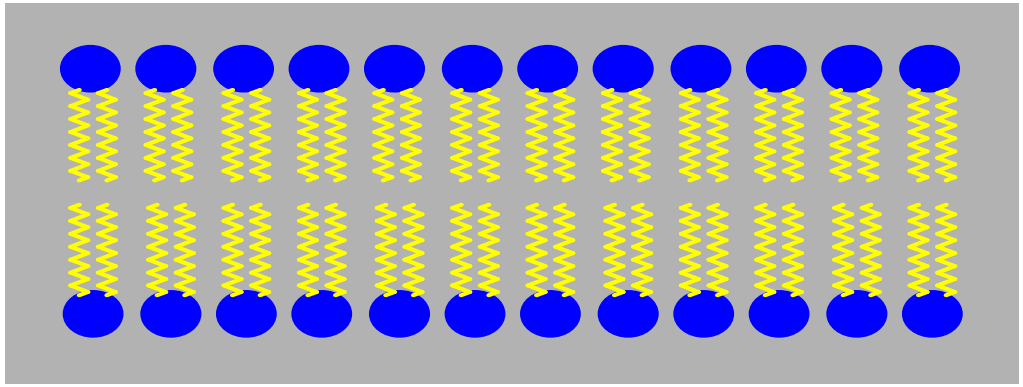



FA acyl
glycerol
cation
phosphate
Non-polar part
cholin
anion
Polar part

A pictogram of phospholipid shows <u>one</u> polar head and <u>two</u> non-polar tails



Phospholipids make a bilayer of cell membranes

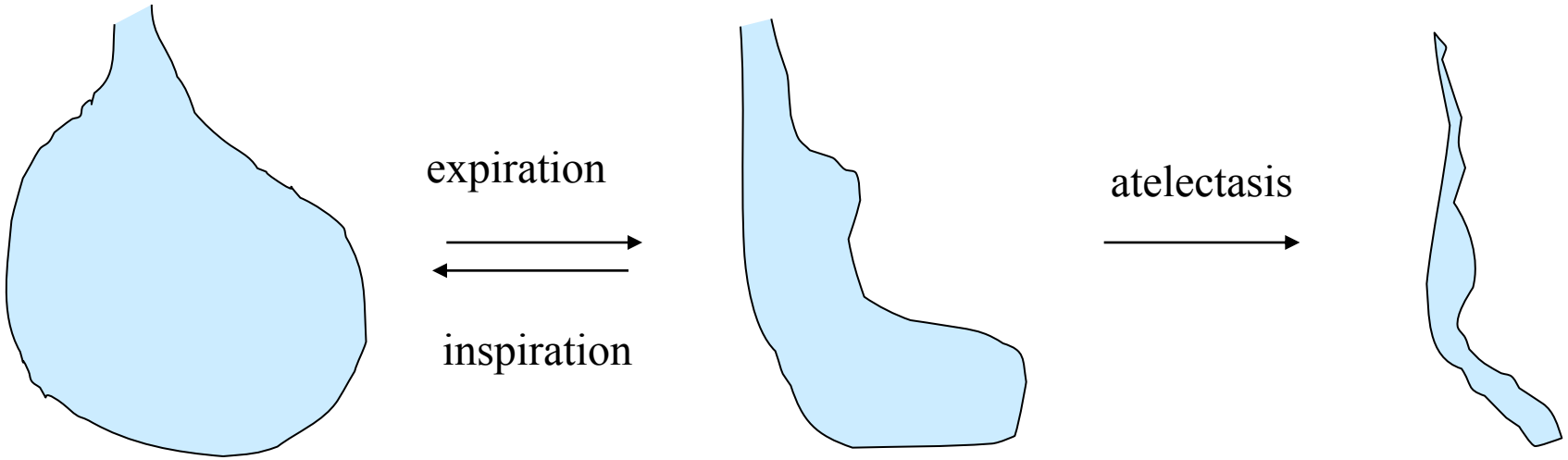


Cell mebrane is predominantly non-polar system.

Non-polar substances penetrate easily (O_2, CO_2, some toxins and drugs).

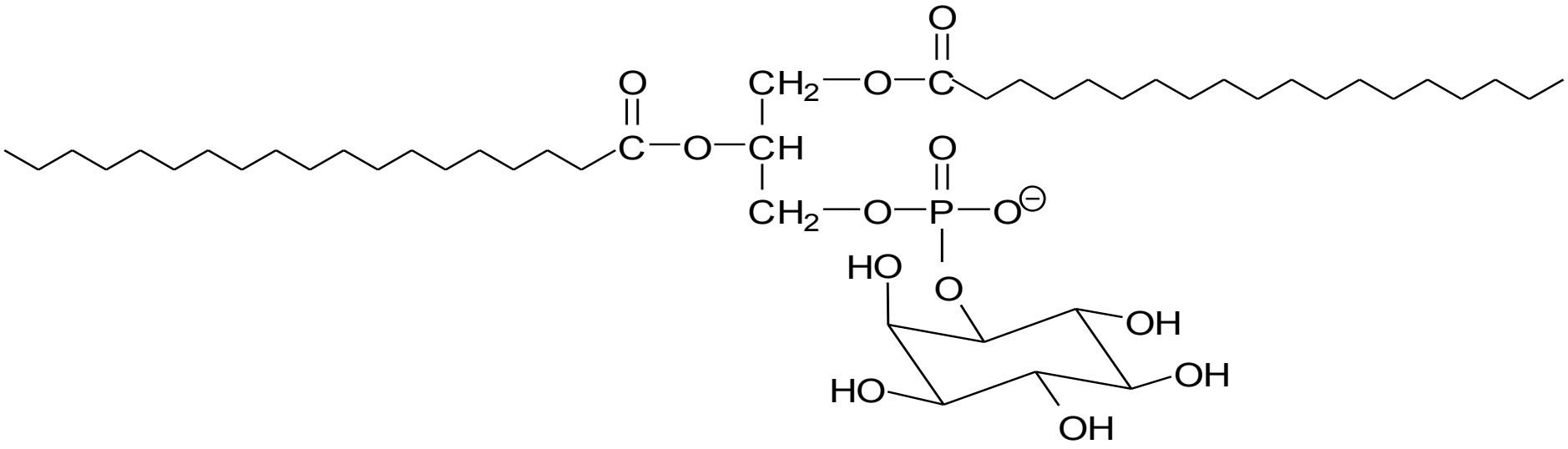
Polar (glucose) and ionic species (Na^+, Ca^{2+}) require specific transporters.

Dipalmitoylphosphatidylcholine is the main component of pulmonary surfactant



- decreases surface tension of alveoli
- prevents the collapse of lungs during expiration
- facilitates the opening of alveoli during inspiration
- lack of surfactant $\Rightarrow$ respiratory distress (atelectasis)

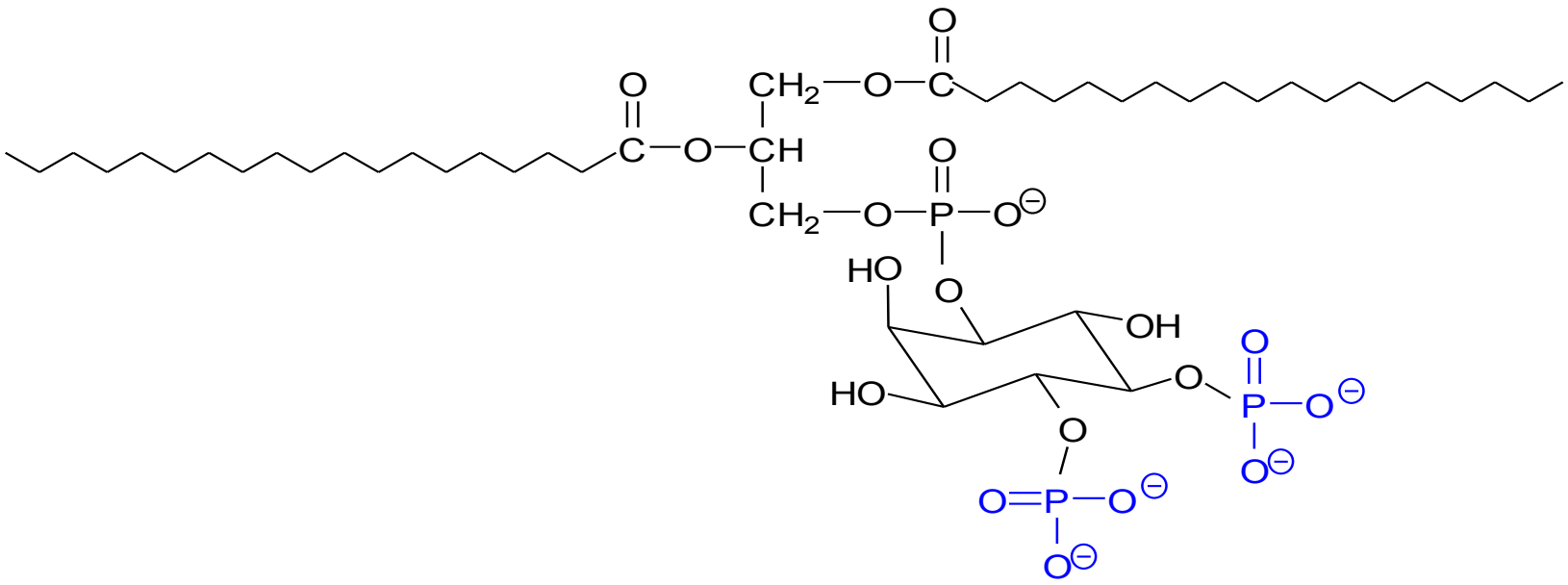
Phosphatidylinositol



It makes up to 20 % of phospholipids in cell membranes.

PIP_2 is a precursor of the second messenger

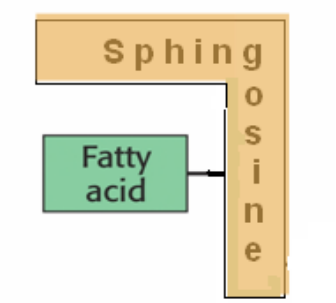
phosphatidylinositol-4,5-bisphosphate (PIP_2)



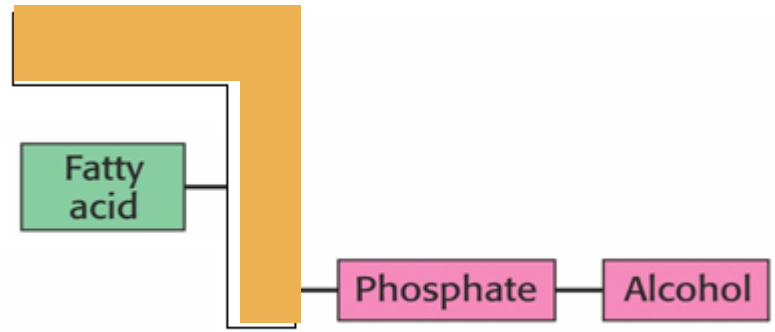
Second messengers: inositol trisphosphate (IP_3) and diacylglycerol (DAG) are released after hydrolysis of PIP_2

Sphingolipids – Schematic diagrams

Ceramide
N-Acylsphingosine

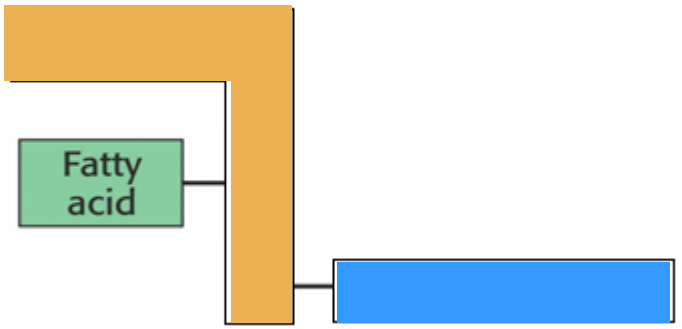


Sphingophospholipids



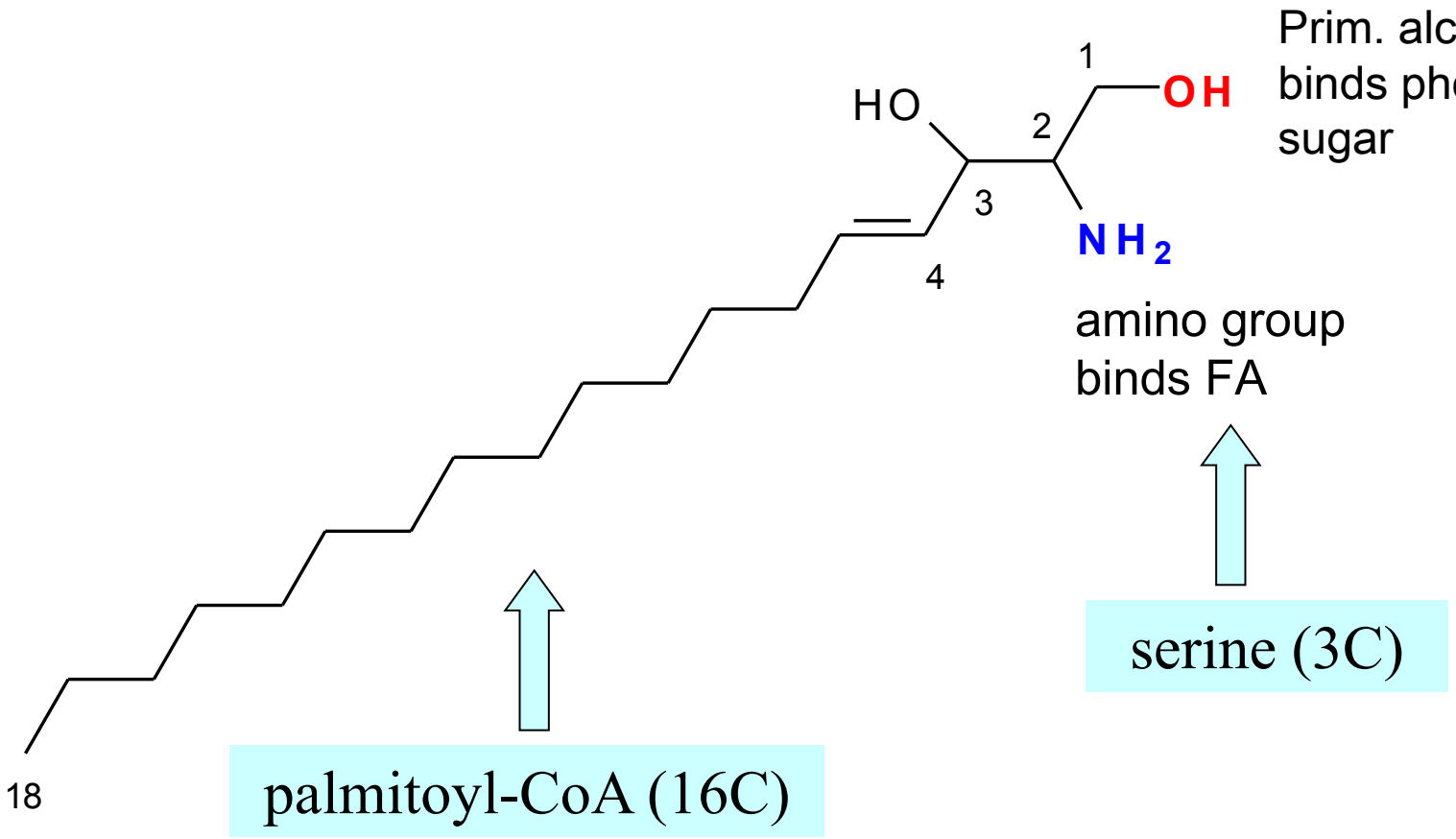
The "head“ group

Glycolipids

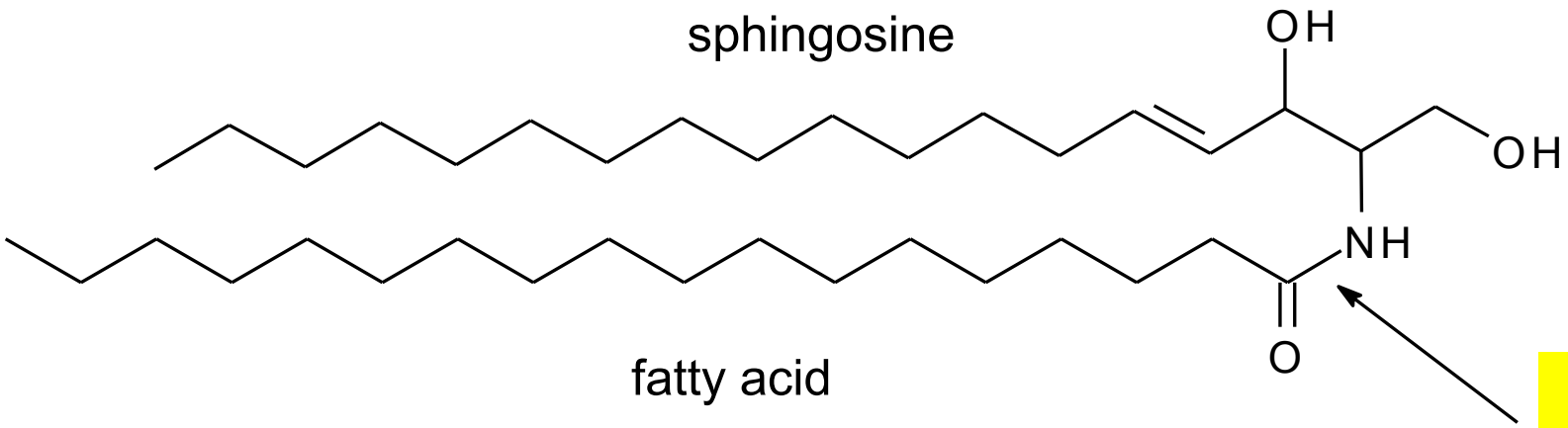


Sphingosine has 18 carbons

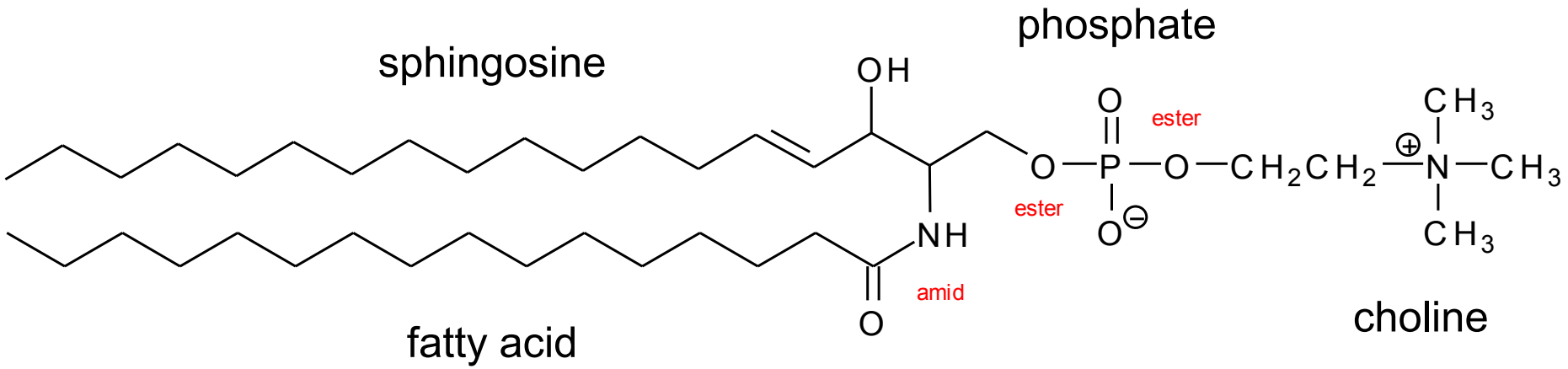
(16 from palmitic acid, 2 from serine)



Ceramides are amides



Sphingomyelines



FA – lignoceric 24:0 and nervonic 24:1(15)

Glycosphingolipids

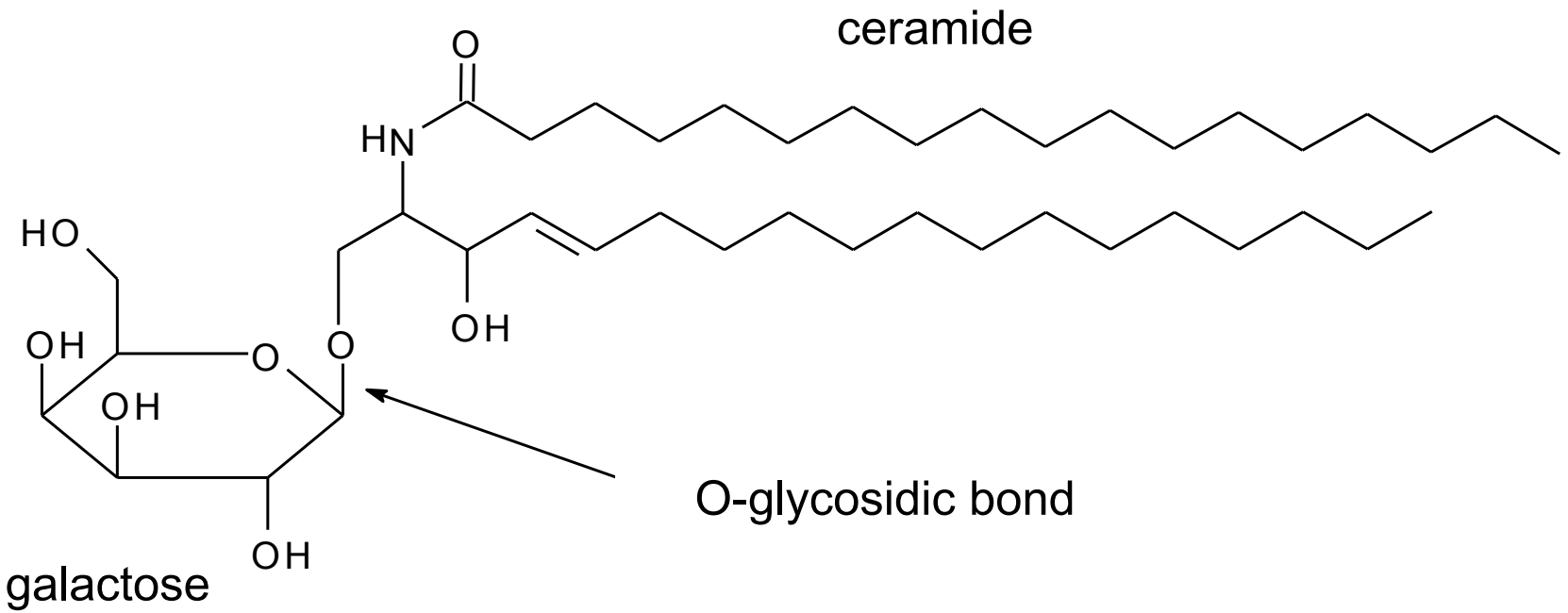
Neutral

- **cerebrosides**
  (monoglycosylceramides)
- **oligoglycosylceramides**
- contain galactose (Gal)
  and/or glucose (Glc)
- attached by *O*-glycosidic bond

Acidic

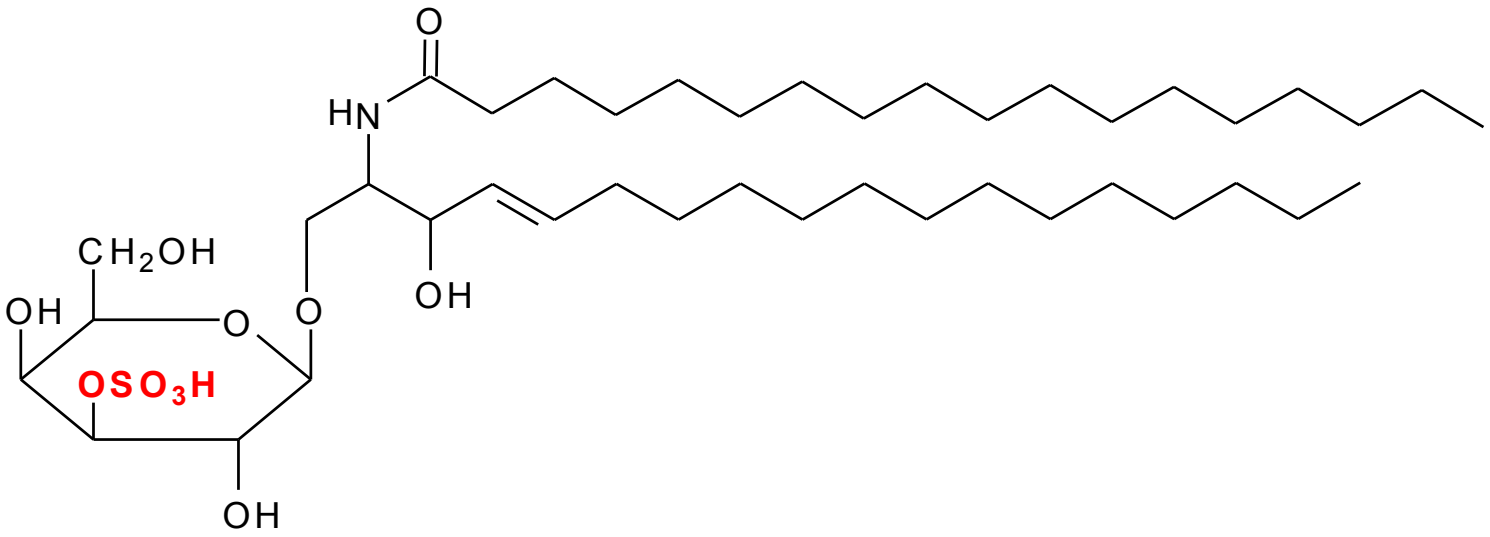
- **sulfoglycosphingolipids**
  (esters of sulfuric acid)
- **gangliosides**
  (contain sialic acid)

Cerebroside (monoglycosylceramide)



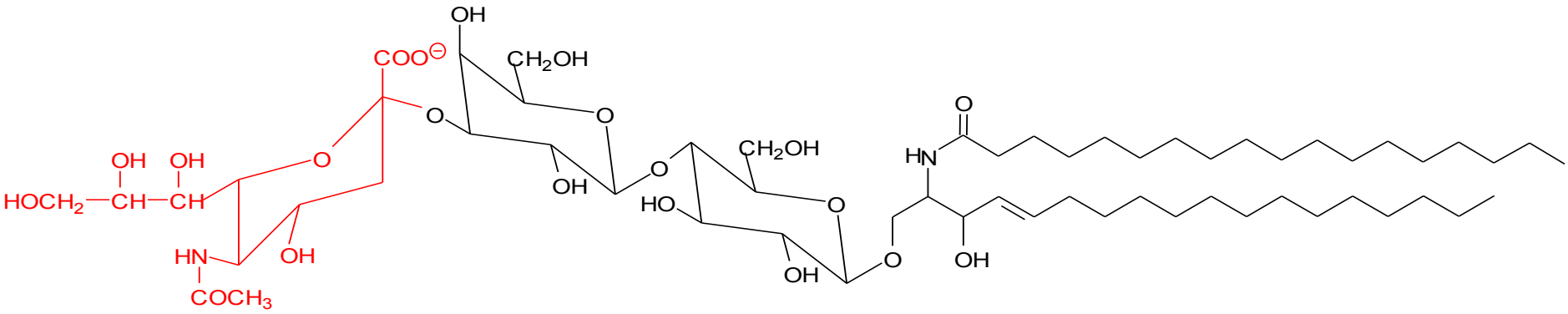
galactosylceramide

Glycolipids can be sulfated



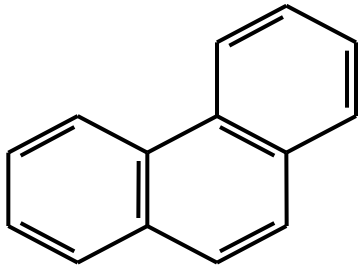
C3 hydroxyl of galactose is esterified by sulfuric acid

Gangliosides (sialoglycosphingolipids)

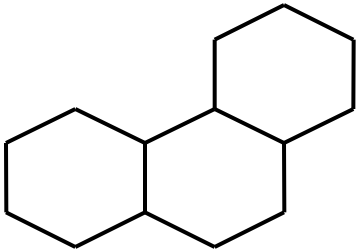


Sialic acid is attached in terminal position to oligosaccharide

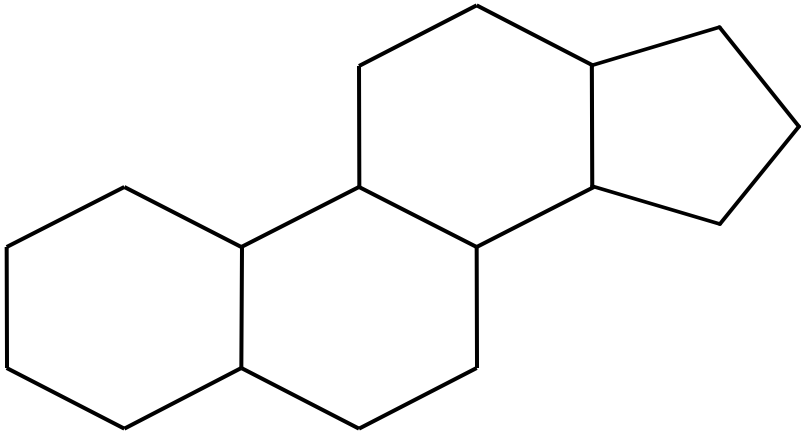
Steroids



phenanthrene
(fused aromatic benzene rings)

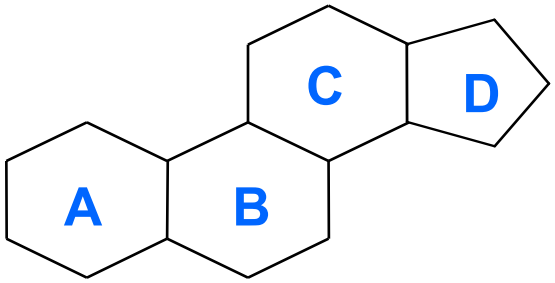


perhydrophenanthrene
(fused cyclohexane rings)

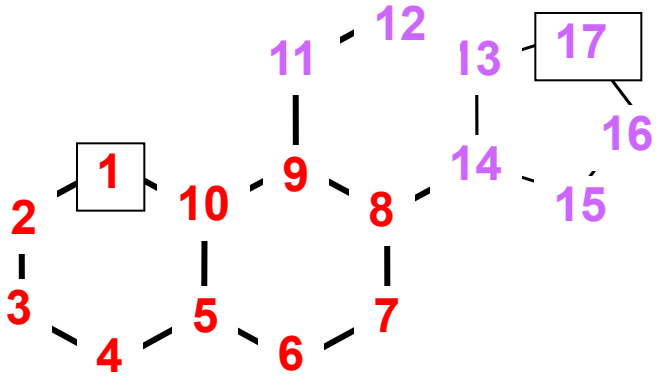


cyclopentanoperhydrophenanthrene
(**sterane**)

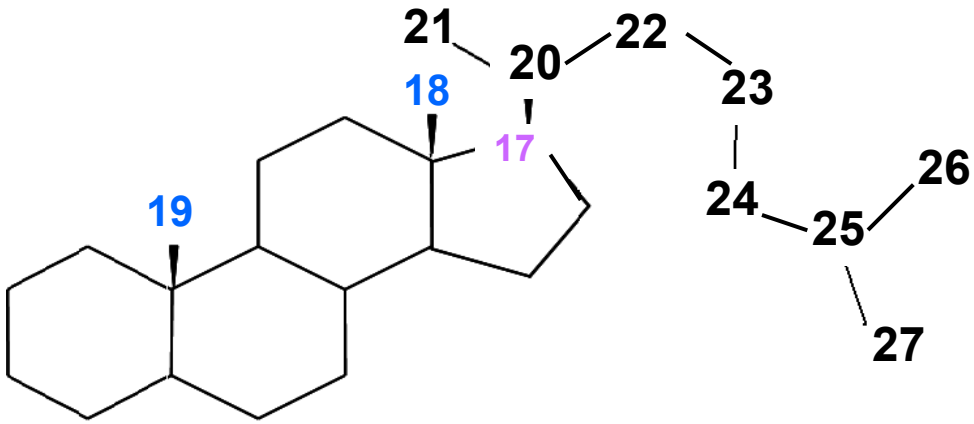
The rings in steroids are denoted by the letters A, B, C, and D:



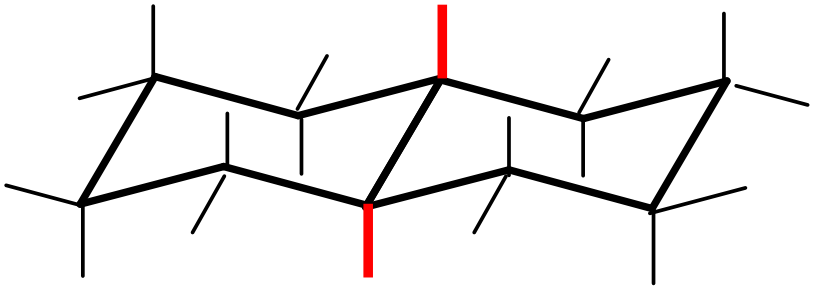
Carbon atoms in steroids are numbered:



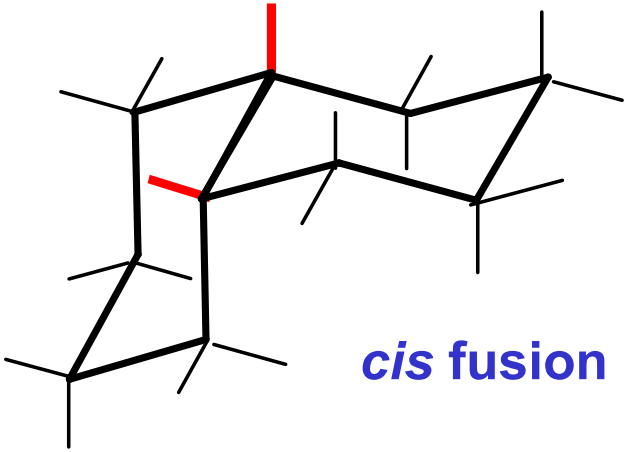
Carbons outside the rings:



The two fused cyclohexane rings in chair conformations

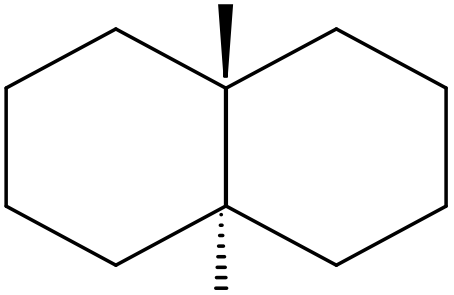


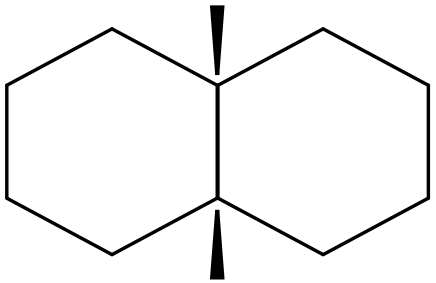
***trans* fusion**



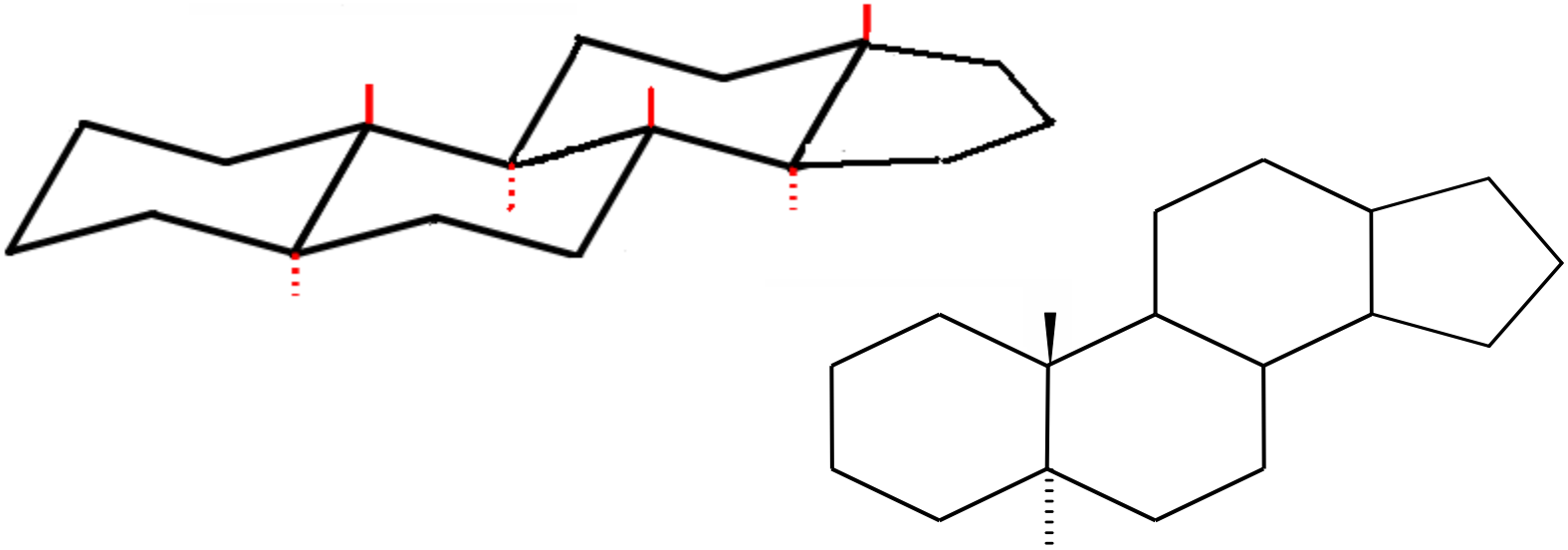
***cis* fusion**

A ***trans*** fusion yields a nearly planar structure, whereas a ***cis*** fusion gives a buckled structure.



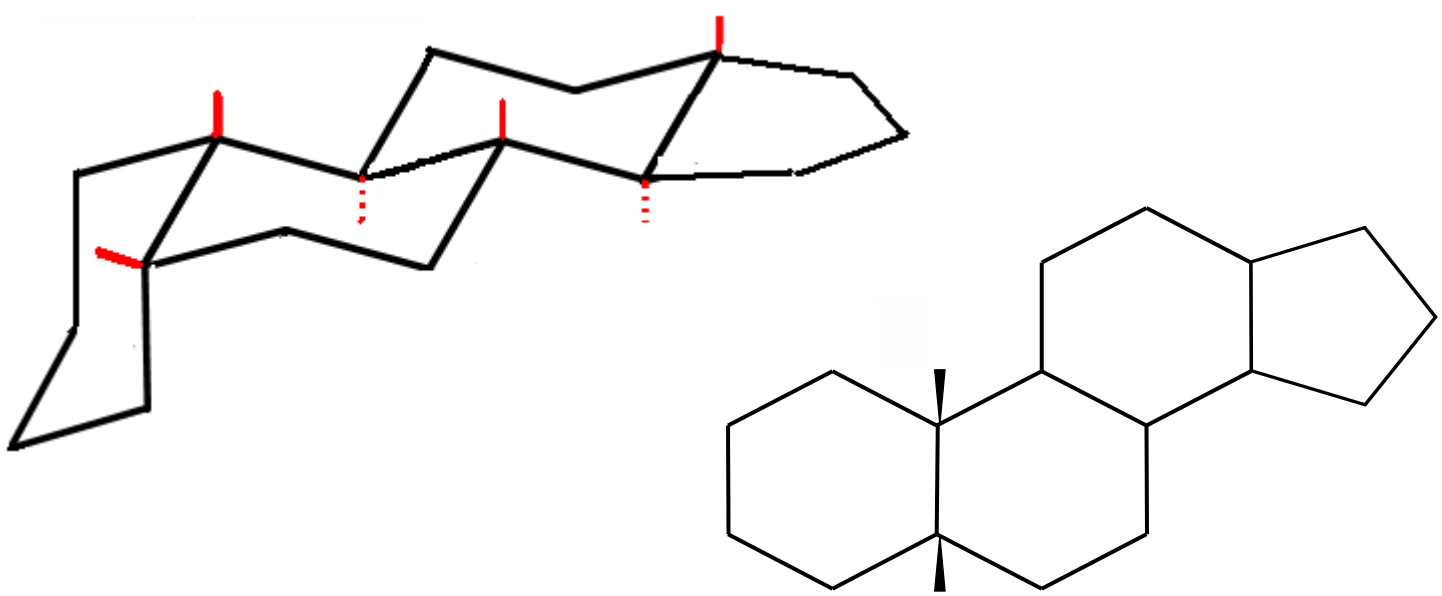


From the eight stereoisomers of sterane, two are named **gonanes**:
The fusion of the steroid rings B ands C as well as C and D is *trans,*
the fusion of the rings A and B is either *trans* (so called 5α-)
or *cis* (5β-configuration).
In nearly all natural steroids the atoms attached to C-10, C-8, C-13 lie **above** the plane containing the four rings – they **are β-oriented.**
The atoms (substituents) that are **below** the plane **are α-oriented.**



5α-Gonane

The *cis* fusion of the rings A and B (characteristic for the bile acids, with the buckled structure) occurs rarely.



5β-Gonane

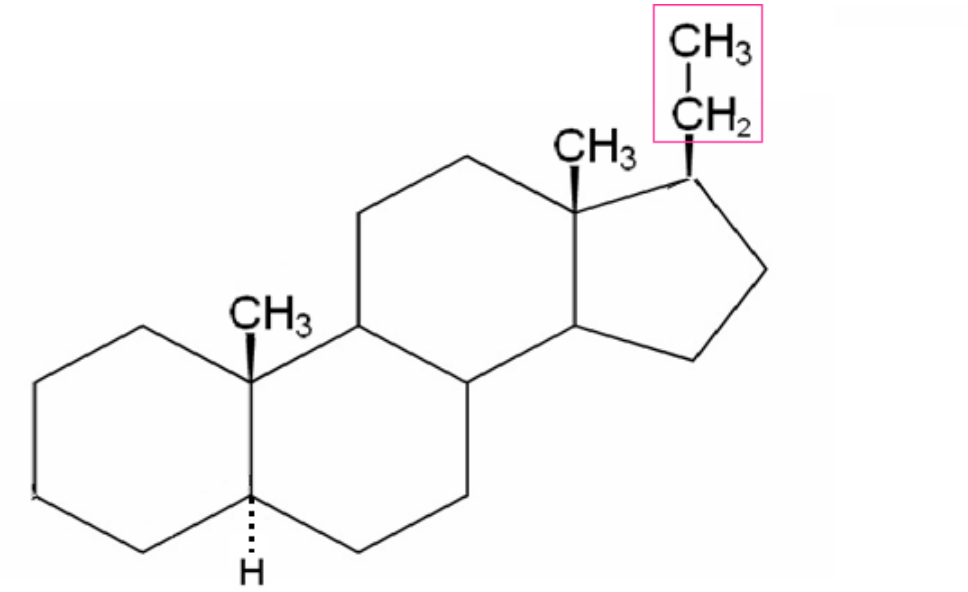
Steroidal hydrocarbons

Name	No. of C	Substituent	17β -Substituent
Gonane	17	-	-
Estrane	18	13-methyl	-
Androstane	19	10,13-dimethyl	-
Pregnane	21	10,13-dimethyl	ethyl
Cholane	24	10,13-dimethyl	pentan-2-yl
Cholestane	27	10,13-dimethyl	6-methylheptan-2-yl

C_{21}

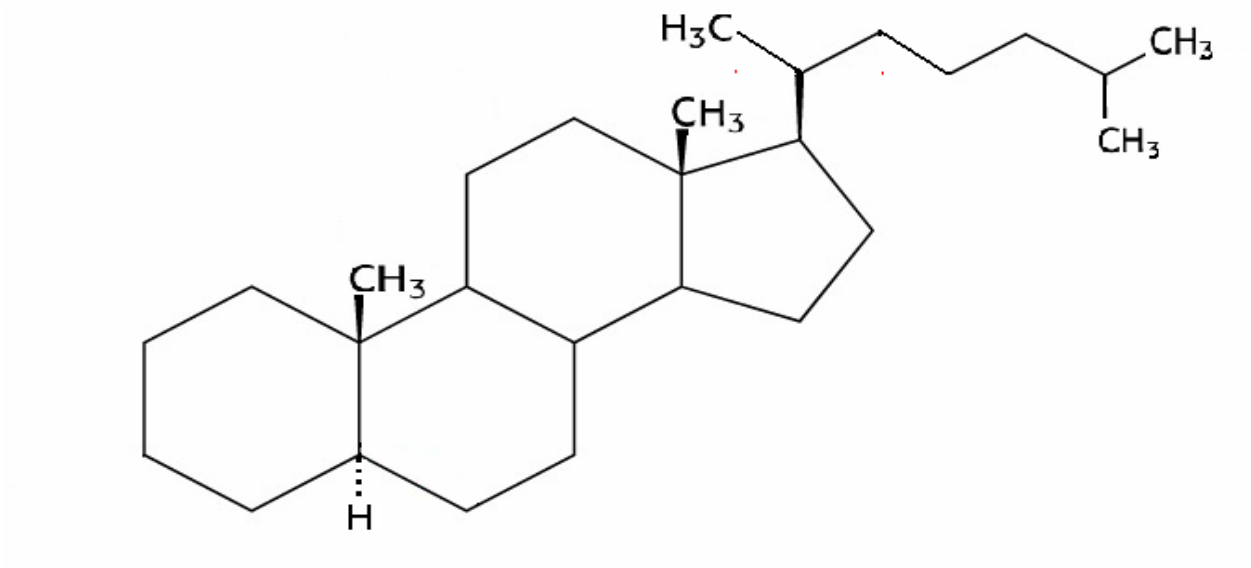
17β-Ethyl-5α-androstane

5α-Pregnane

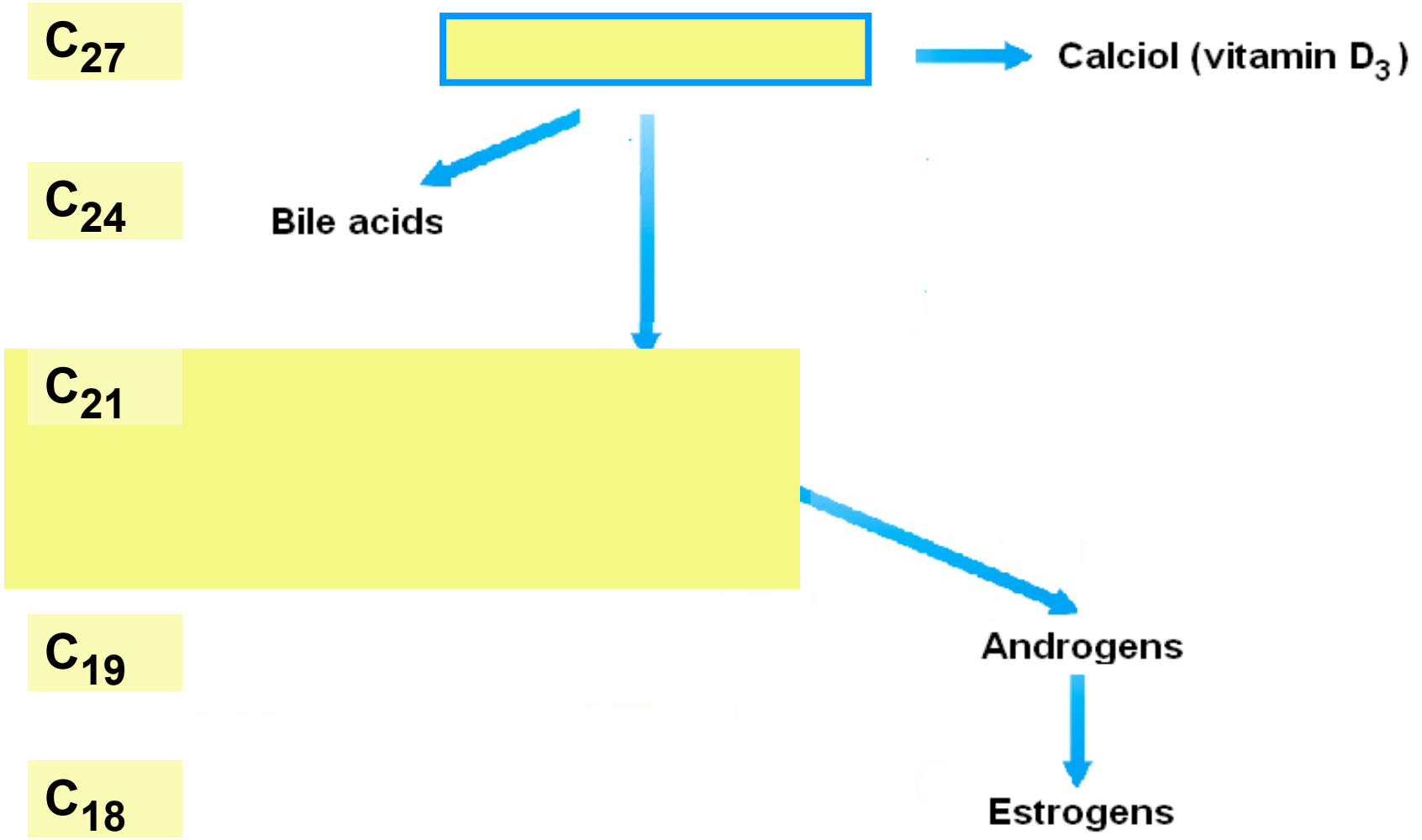


C_{27} 5α-Cholestane

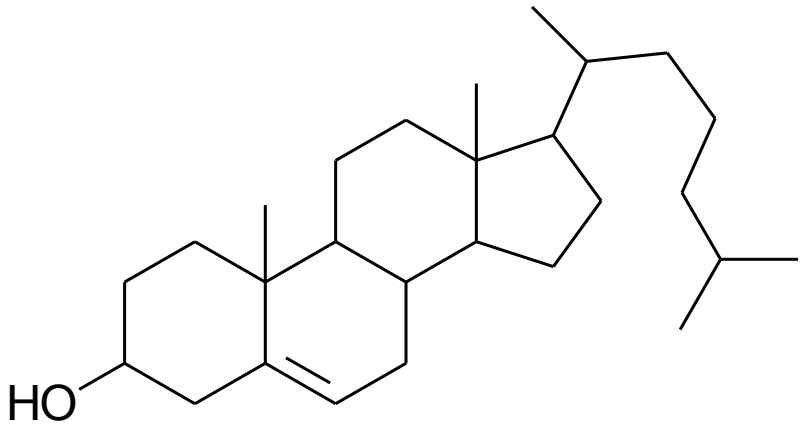
Eight-carbon branched side chain at C-17



Cholesterol is the precursor for other steroids



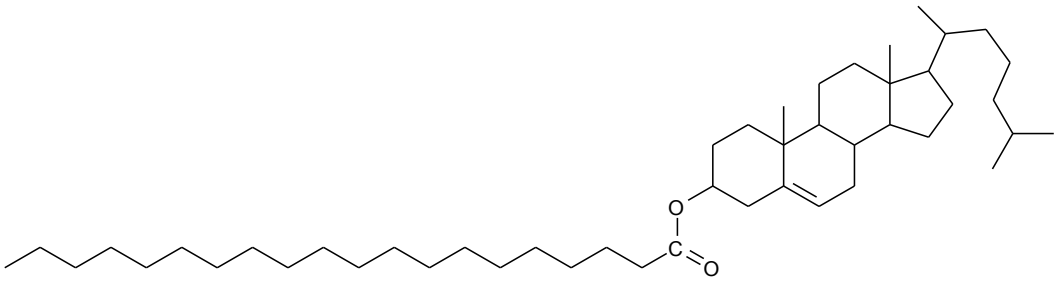
Cholesterol free and esterified



27 carbon atoms

1 hydroxyl (C3)

1 double bond (C5)



the only polar group

In blood, cholesterol occurs in lipoproteins

Class	Density (g/ml)	Proteins (%)	Cholesterol (%)	TAG (%)
CM	0.90	2	5	**84**
VLDL	0.95	9	15	54
LDL	1.05	21	**50**	11
HDL	1.20	50	22	4

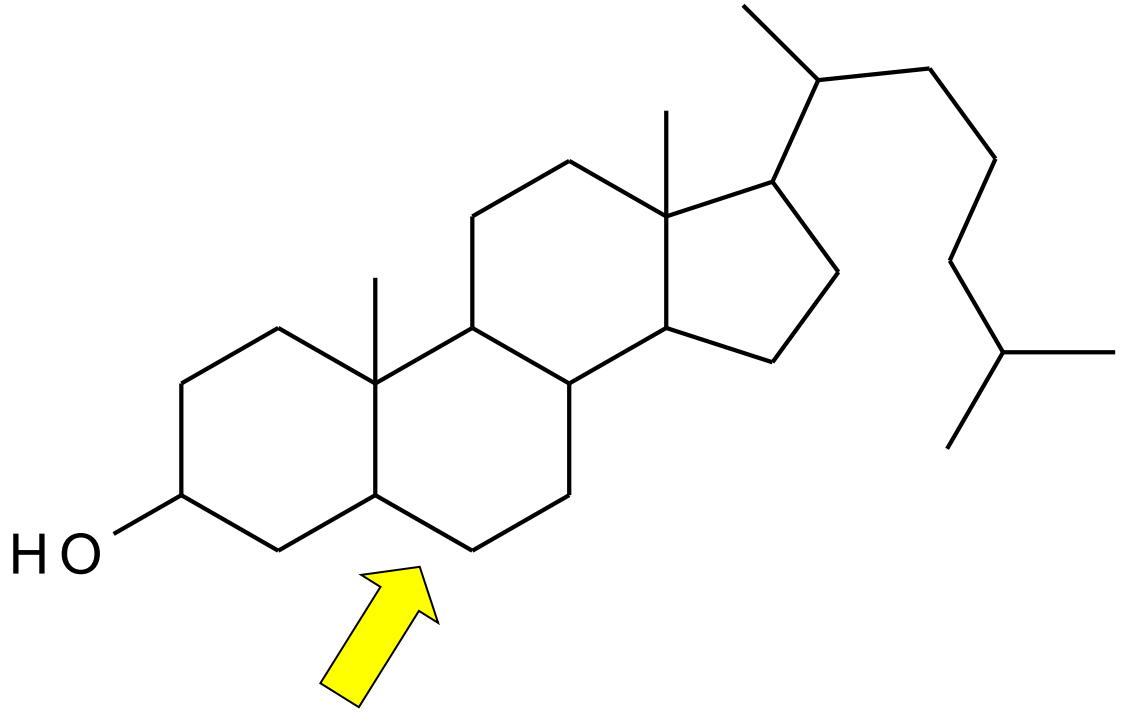
CM – chylomicrons

VLDL – very low density lipoprotein

LDL - low density lipoprotein

HDL - high density lipoprotein

Coprostanol is hydrogenated cholesterol



The product of bacterial reduction of cholesterol in intestine.

The balance of cholesterol in human body

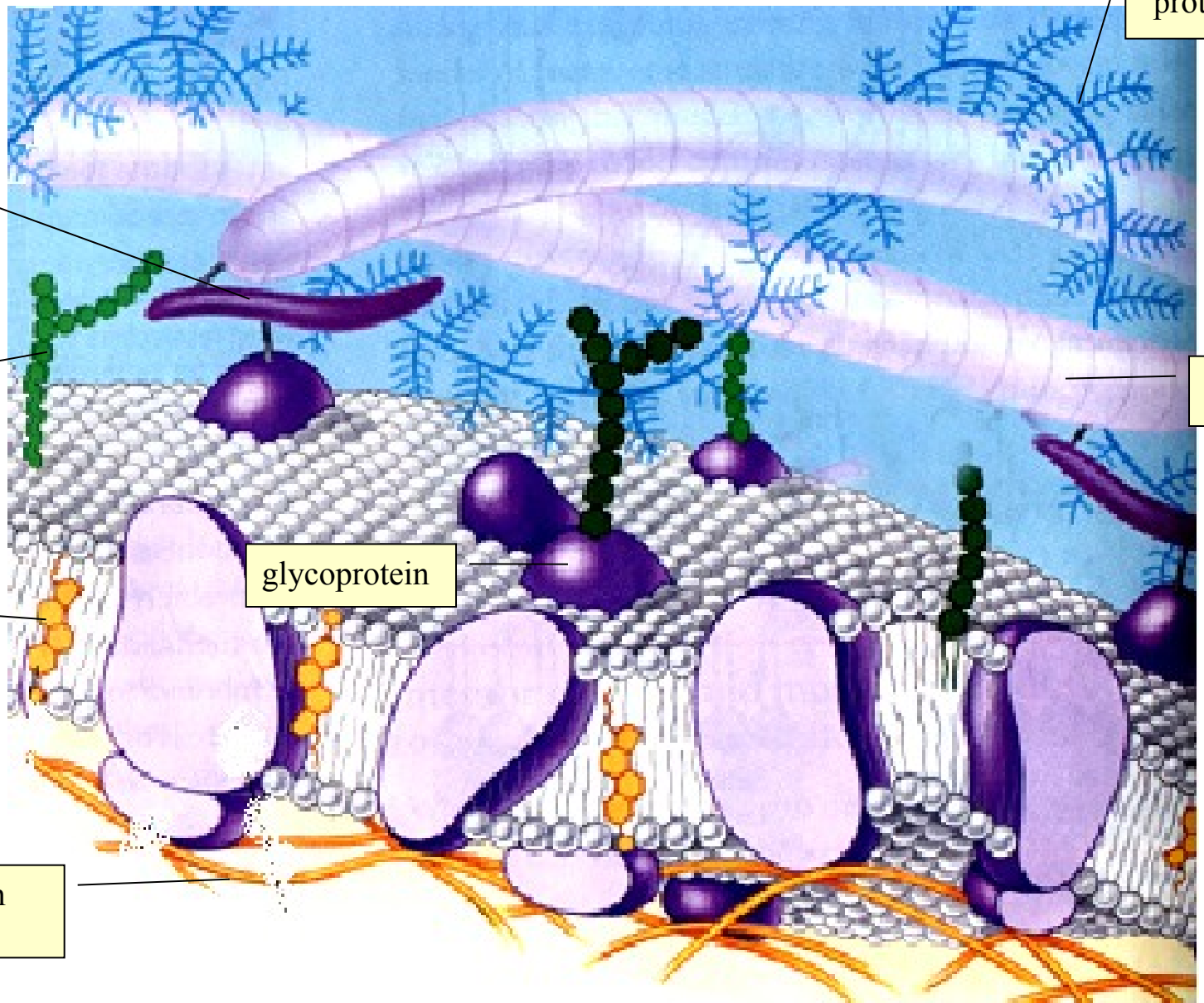
Input into body	g/day	Output from body	g/day
food	0.5 g	coprostanol (stool)	0.8 g
biosynthesis in body	1.0 g	bile acids (stool)	0.5 g
		sebum/desquamated cells	0.2 g
Total:	**1.5 g**	**Total:**	**1.5 g**

cholesterol in food

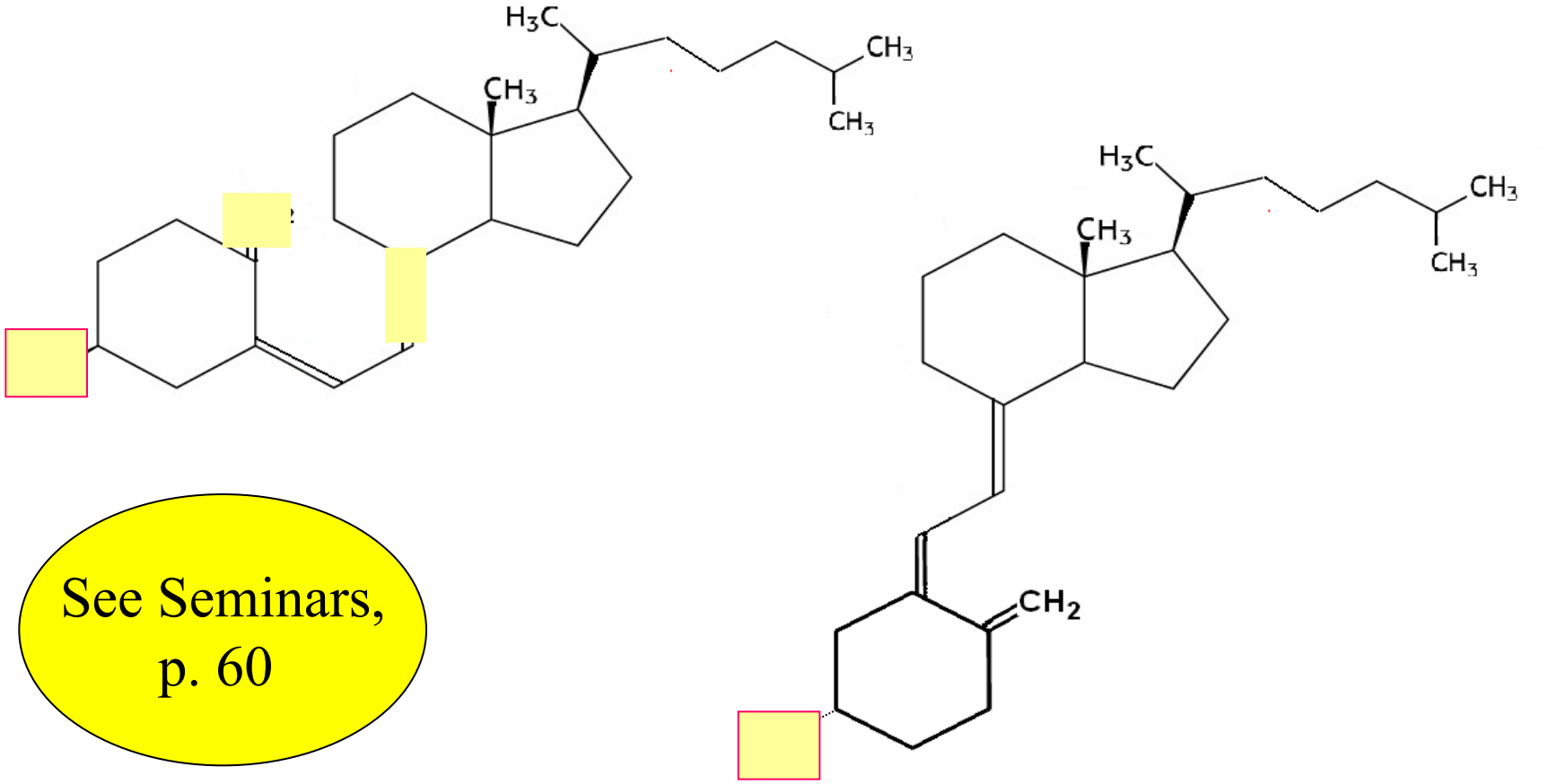
only animal fats (including fish):

lard, butter, bacon, egg yolk, mayonnaise, fat meat, fat cheese

Cell membranes contain phospholipids, glycoproteins, and cholesterol



C_{27} **Calciol** (cholecalciferol, vitamin D_3) is synthesized from 7-dehydrocholesterol by photolysis that leads to opening the ring B:



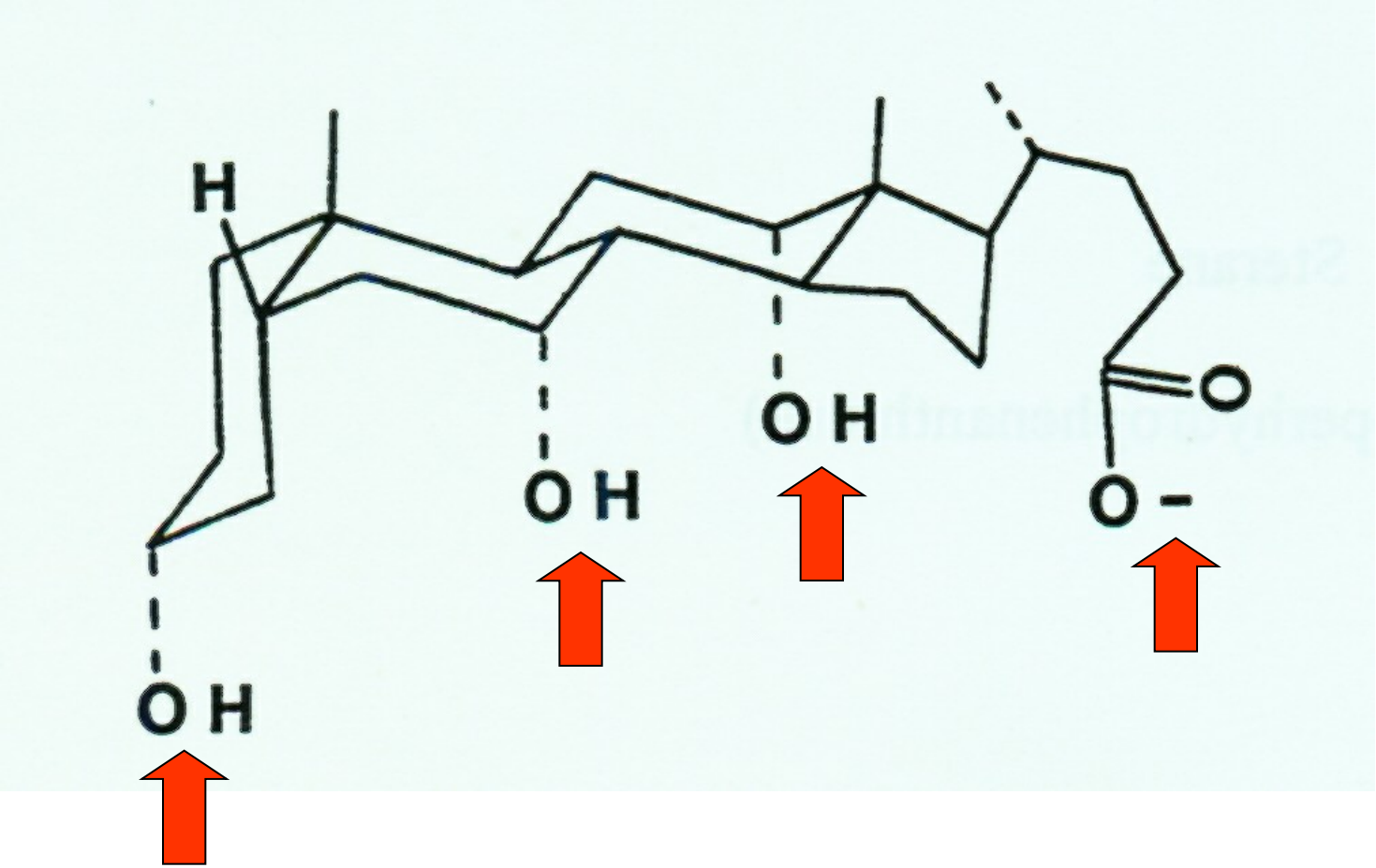
See Seminars, p. 60

The effects of calciol

- Calciol is made in skin (UV light)
- Calciol is metabolized to calcitriol – active hormone
- Regulates calcium and phosphate homeostasis
- Stimulates intestinal absorption of calcium

- Deficit of calciol – rickets in children, osteomalacia in adults

Bile acids are anionic surfactants



all polar groups are oriented on one side of molecule

Steroid hormones

Glucocorticoids

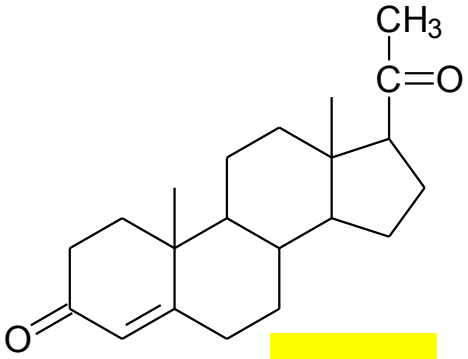
Mineralocorticoids

Androgens

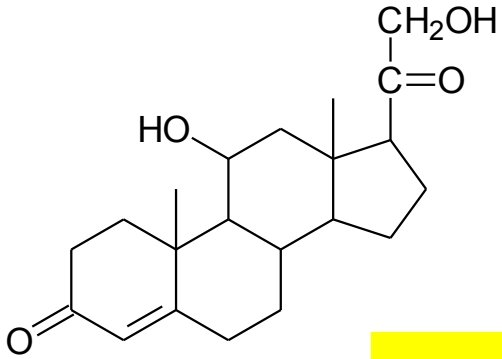
Estrogens

Gestagen

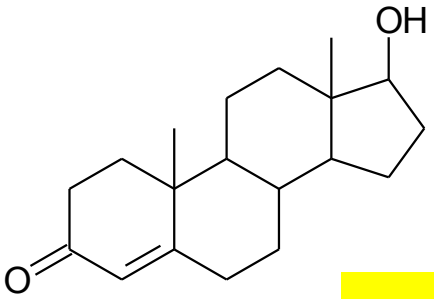
Steroid hormones



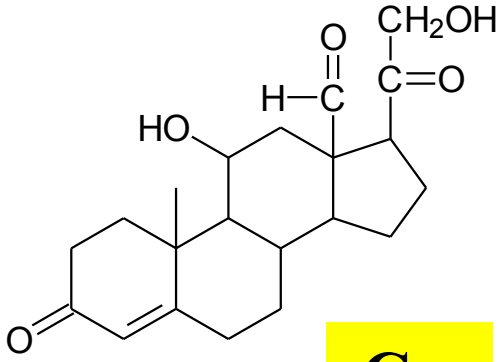
progesteron **C_{21}**



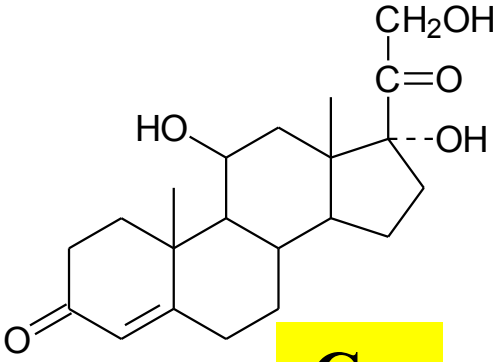
corticosterone **C_{21}**



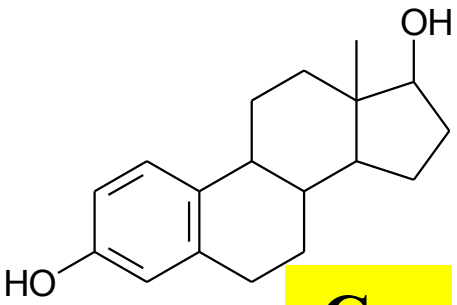
testosterone **C_{19}**



aldosterone **C_{21}**



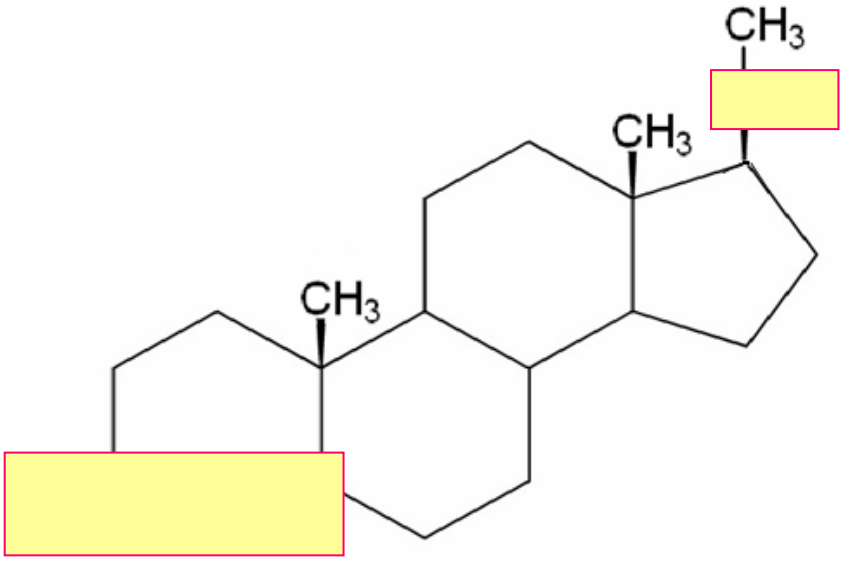
cortisol **C_{21}**



estradiol **C_{18}**

C_{21}

Progesteron is a **gestagen**: it prepares the lining of the uterus for implantation of an ovum and is also essential for the maintenance of pregnancy.



C_{21}

Corticoids are hormones produced in the adrenal cortex.

Glucocorticoids (such as **cortisol**) promote gluconeogenesis and the formation of glycogen, enhance the degradation of proteins and fat, and inhibit the inflammatory response. They enable animals to respond to stress.

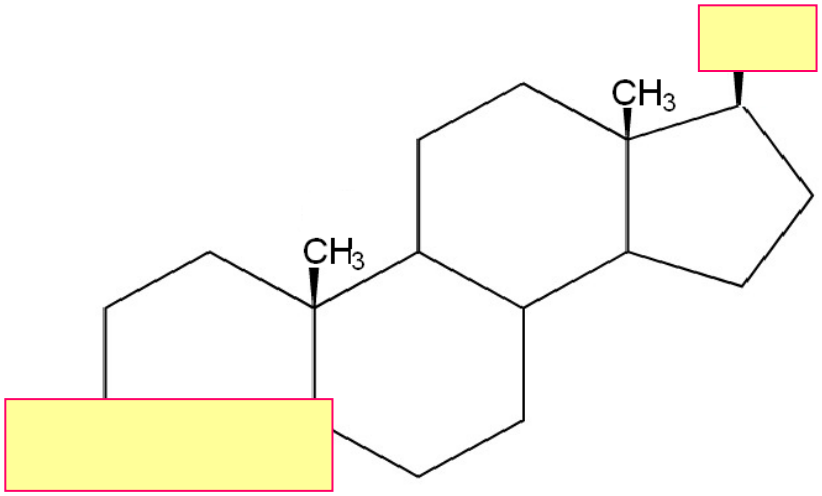
Mineralocorticoids (primarily **aldosterone**) act on the kidney to increase the reabsorption of Na^+ and the excretion of K^+, which leads to an increase in blood volume and blood pressure.

C_{19}

Androgens are responsible for the development of male secondary sex characteristics.

Testosterone

17β-Hydroxyandrost-4-ene-3-one



C_{18}

Estrogens are required for the development of female secondary sex characteristics and, along with progesterone, also participate in the ovarian cycle.

Estradiol

Estra-1,3,5(10)-triene-3,17β-diol