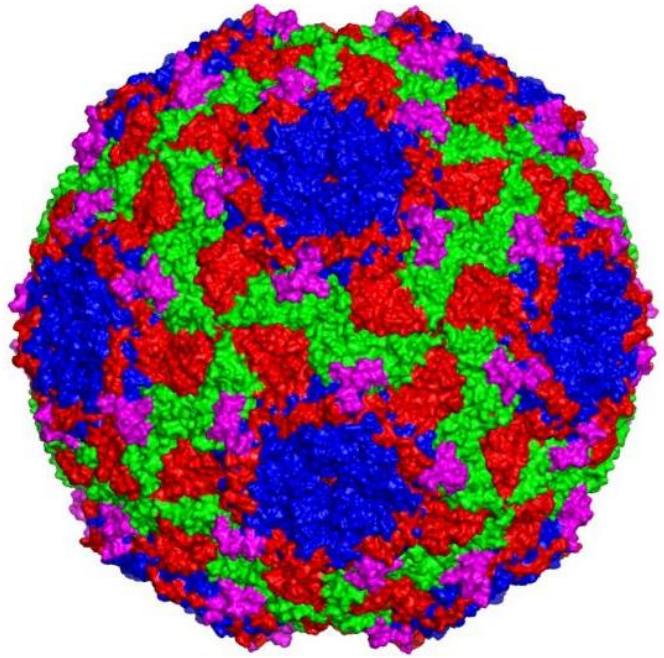
MUNI PHARM

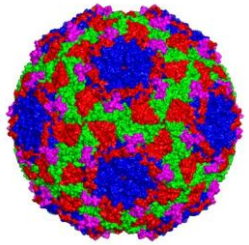
Department of Natural Drugs

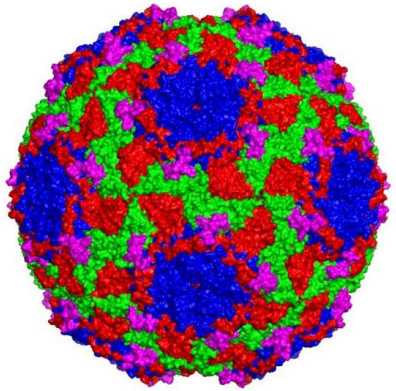


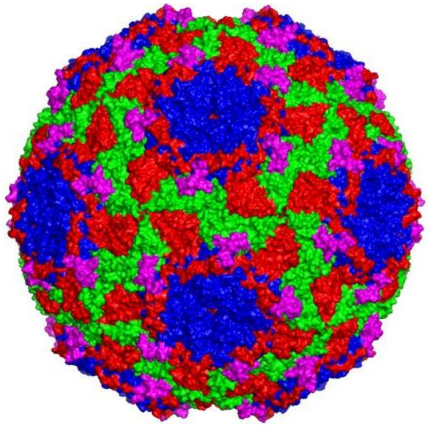
# Supramolecular Pharmacy

## 5. The supramolecular chemistry of life

**Ondřej Jurček**





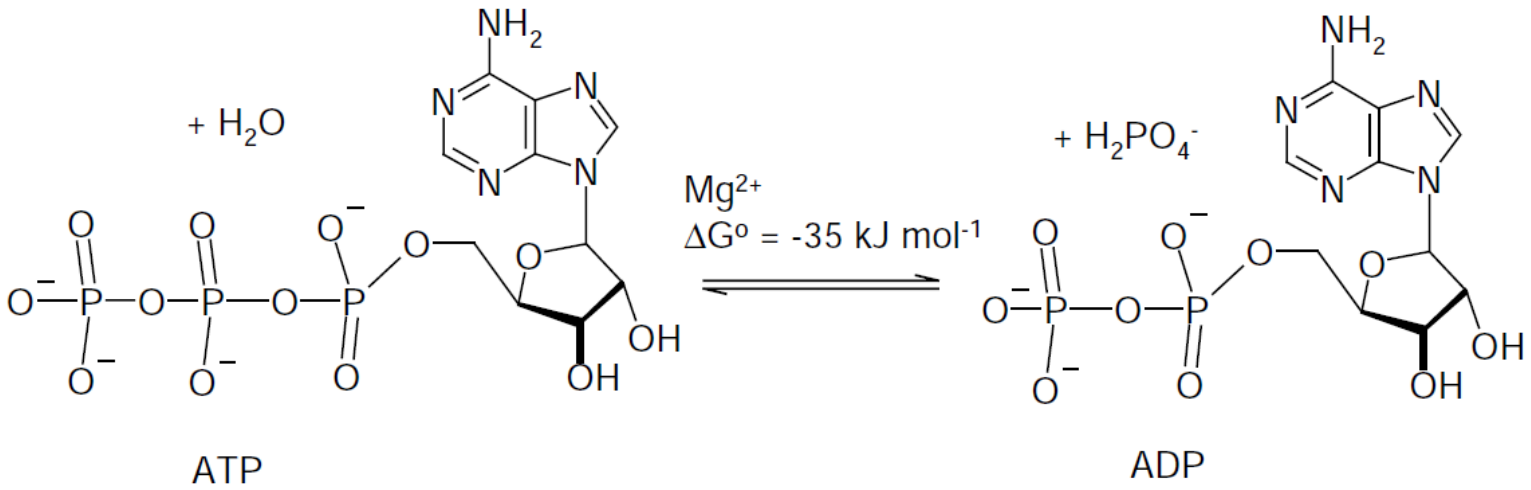


# Supramolecular chemistry is inspired by Nature

- Nature has evolved highly specific, hierarchical, selective, and cooperative chemistry
- Supramolecular hosts are the receptor sites of enzymes, genes, antibodies of the immune system, and ionophores or ion channels
- Guests are substrates, inhibitors, co-factors, drugs, antigens
- These components exhibit supramolecular behavior such as molecular recognition, self-assembly, self-organization, self-replication and kinetic and thermodynamic complementarity
- The vast majority is mediated via coordination (ion-dipole) bonds, hydrogen bonds, π-π stacking
- The greatest supramolecular chemist is Nature
- Insight has been gained into biochemistry by the study of supramolecular compounds
- Synthetic and model systems mimic these biological processes

# Alkali metal cations in biochemistry

- Energy is vital to life: plants use light (photosynthesis), humans eat food – energy from food is transformed and stored as the chemical bond energy of ATP (adenosine triphosphate)
- ATP anion is 4- balanced by alkaline and alkaline earth metal cations
- Energy is released by enzymes ATPases, mainly the transmembrane enzyme $Na^+/K^+$-ATPase (1 mole ATP = 35 kJ of energy)
- Muscle contraction – consumes ATP, transport of $Na^+$ from the inside out and $K^+$ from the outside in against gradient



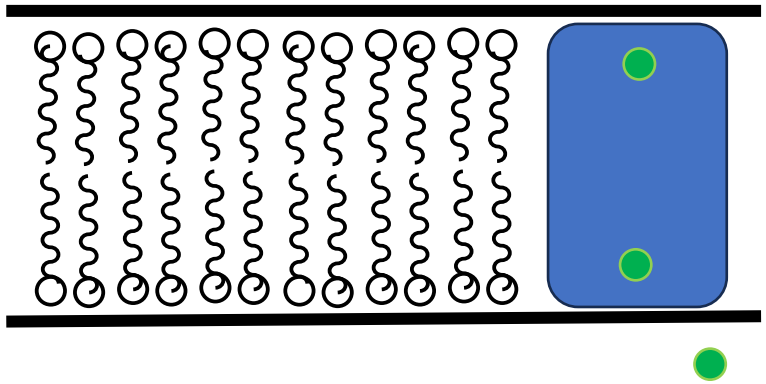
# Alkali metal cations in biochemistry

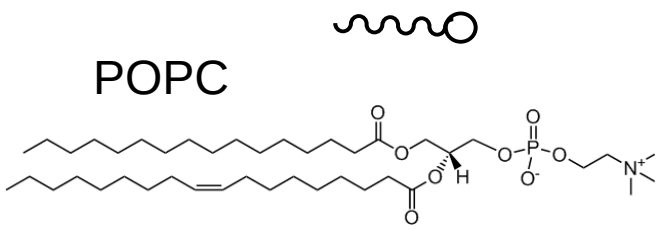
- In the intracellular fluid there is a high concentration of $K^+$, outside there is a high concentration of $Na^+$
- Uneven distribution of alkali metal cations across the cell membrane is a highly important and results in a transmembrane electrical potential
- Very important feature in many processes, e.g., transfer of neural signal

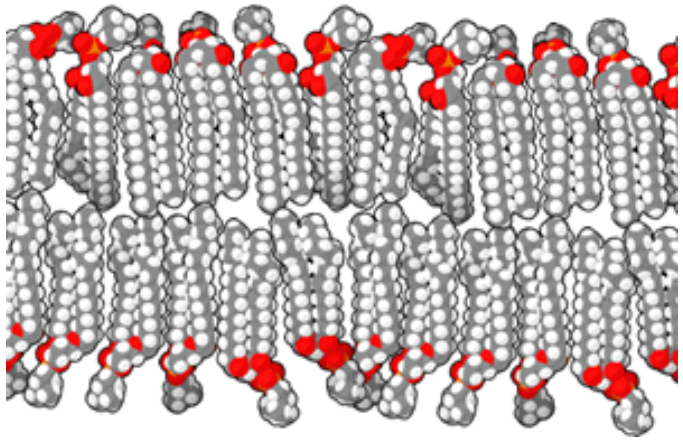
| | Concentration/mmol $kg^{-1}$ | |
|---|---|---|
| Location | $K^+$ | $Na^+$ |
| Human intracellular fluid (*e.g.* erythrocytes) | 92 | 11 |
| Human extracellular fluid (*e.g.* blood plasma) | 5 | 152 |
| Squid nerve (inside) | 300 | 10 |
| Squid nerve (outside) | 22 | 440 |

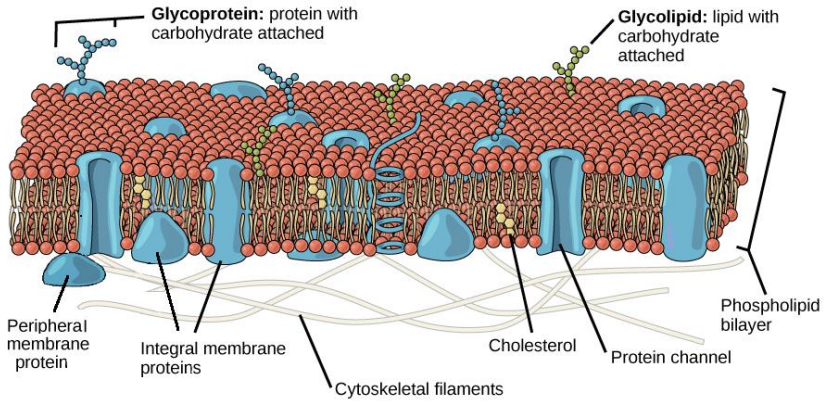
# Membrane transport

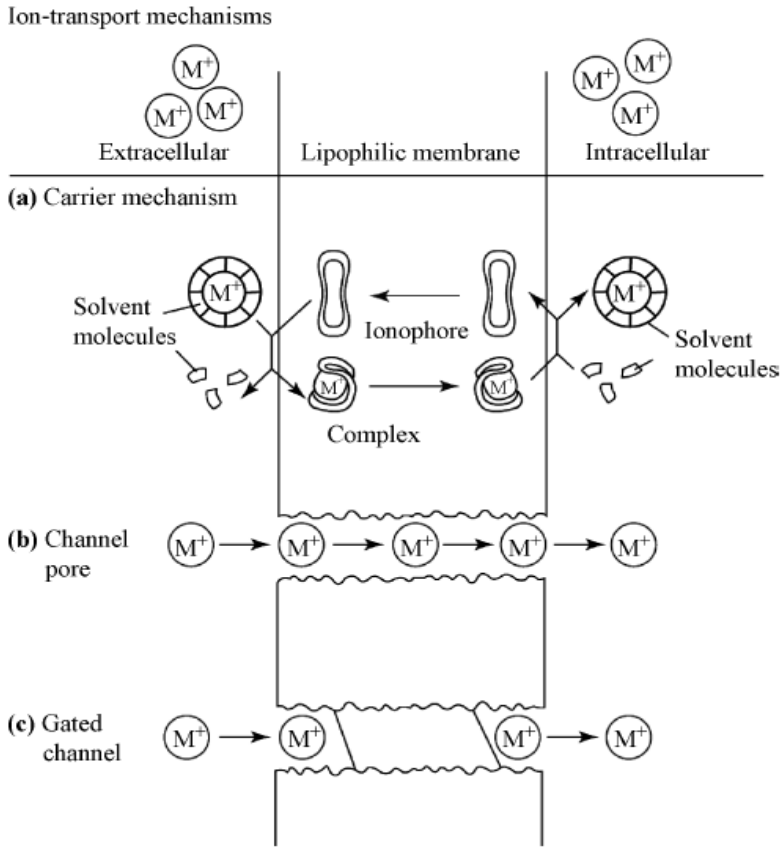
- Chemistry of cell membrane
- Cation does not penetrate itself, needs lipophilic coat or hydrophilic channel
- Ionophores, e.g., valinomycin





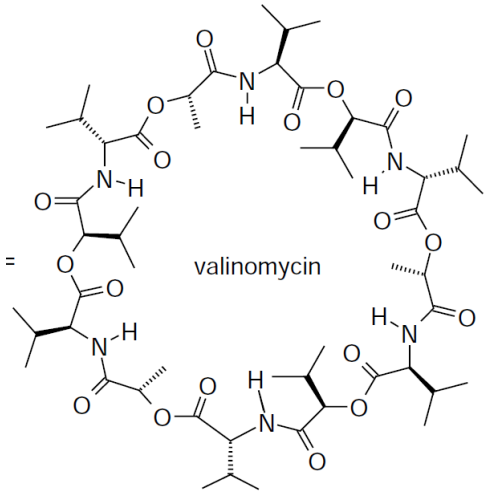





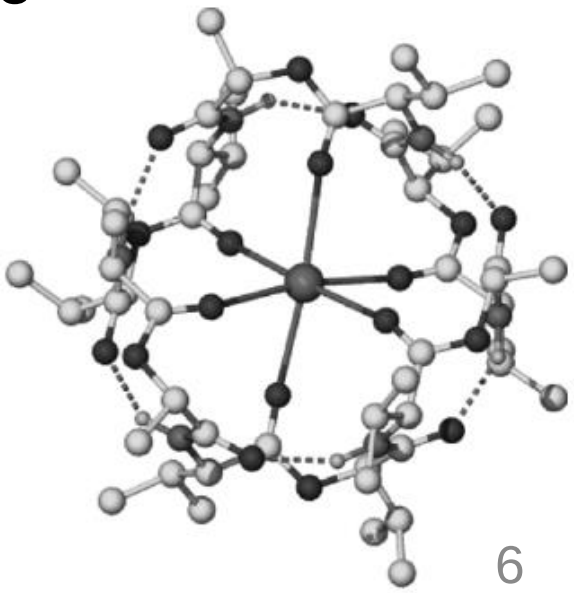
# Valinomycin

- Isolated from *Streptomyces fulvissimus* in 1955
- Exchange of $K^+$ and $H^+$ across the membrane of mitochondria *via* carrier mechanism
- N–H···O=C to both ester and amide carbonyl groups plays an important role in the conformation of valinomycin, where it helps the peptide chain wrap around the metal cation
- Selectivity to $K^+$ because of octahedral array of hard carbonyl oxygens
- Potential antibiotic because of the potential to disturb the balance of ions in bacteria



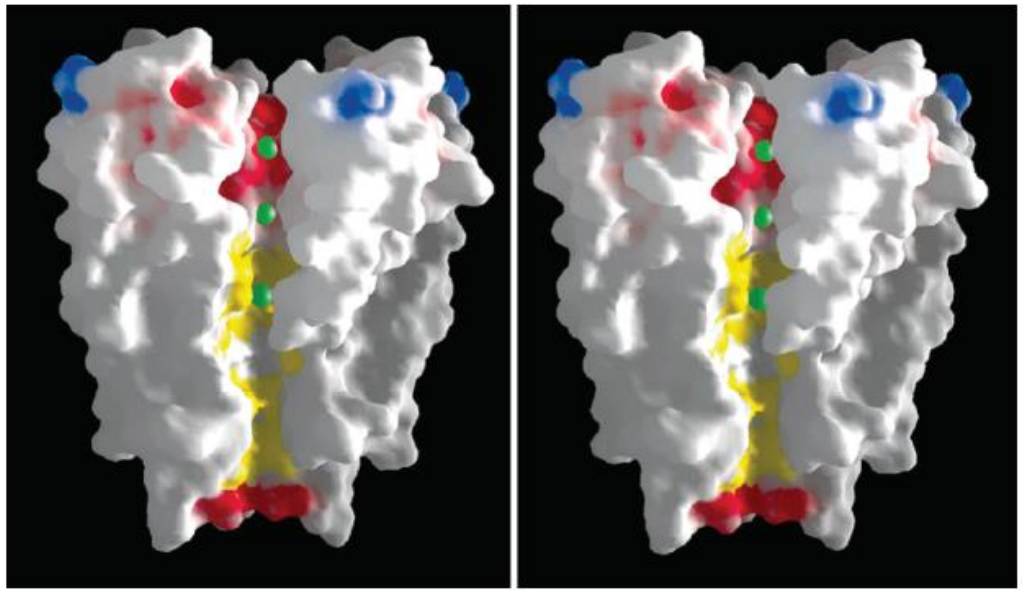

*Log K in MeOH at 25 °C*

| Ligand | $Li^+$ | $Na^+$ | $K^+$ | $Rb^+$ | $Cs^+$ |
|---|---|---|---|---|---|
| Valinomycin | <0.7 | 0.67 | 4.90 | 5.26 | 4.42 |
| Monactin | <0.3 | 2.60 | 4.38 | 4.38 | 3.30 |
| Enniatin B | 1.28 | 2.42 | 2.92 | 2.74 | 2.34 |
| Nigericin | – | 4.7 | 5.6 | 5.0 | – |
| Monensin | 3.6 | 6.5 | 5.0 | 4.3 | 3.6 |



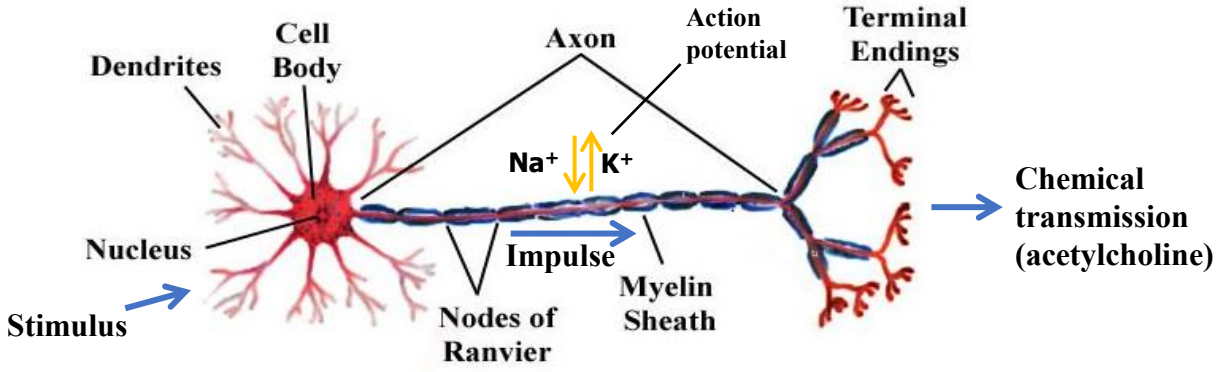
# Ion channels

- Sequential desolvation–complexation–transport–decomplexation mechanism of ionophore-mediated cation transport is far too slow for effective use in the generation of nerve impulses
- Passage of ions through ion channels results in transport close to the diffusion limits (about $10^8$ ions per channel per second)
- K+ channel from *Streptomyces lividans* possesses ion throughput rate and the vital $10^5$-fold selectivity of the channel for $K^+$ over $Na^+$



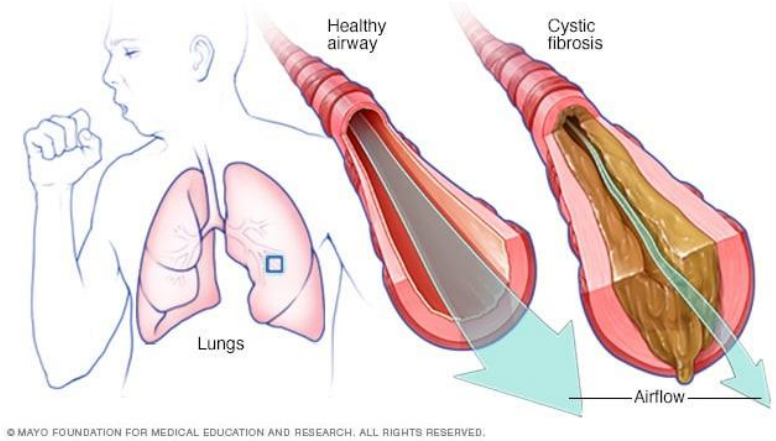
# Alkali metal cations in biochemistry

- In the intracellular fluid there is a high concentration of $K^+$ outside there is a high concentration of $Na^+$
- Uneven distribution of alkali metal cations across the cell membrane is a highly important and results in a transmembrane electrical potential
- Very important feature in many processes, e.g., transfer of neural signal
    - multiple sclerosis
    - dalfampridine (4-aminopyridine) (FDA, 2010)



# Anion channels

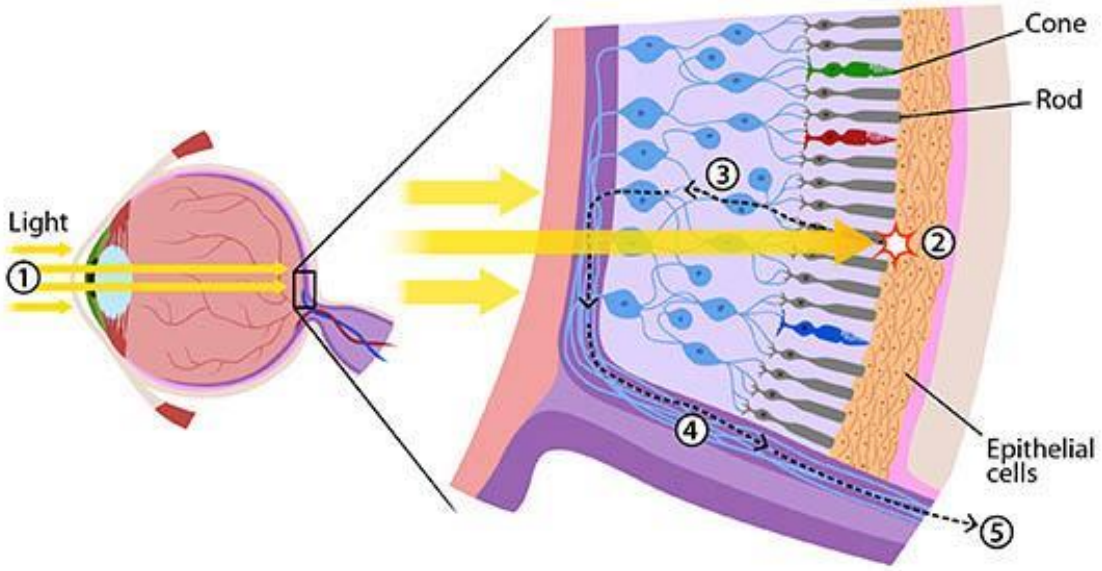
- Chloride maintains regulation of pH, volume homeostasis, organic solute transport, cell migration, cell proliferation and differentiation
- CIC chloride channel - *Salmonella typhimurium,* the 2003 Nobel prize in chemistry for Roderick MacKinnon
- Cystic fibrosis transmembrane conductance regulator (CFTR) – coding gene mutations cause cystic fibrosis (CZ 1:4000 live births, over 54 000 cases across Europe)
- movement of $Na^+$ ions in the same direction to balance the charge ($Na^+/Cl^-$ symport)

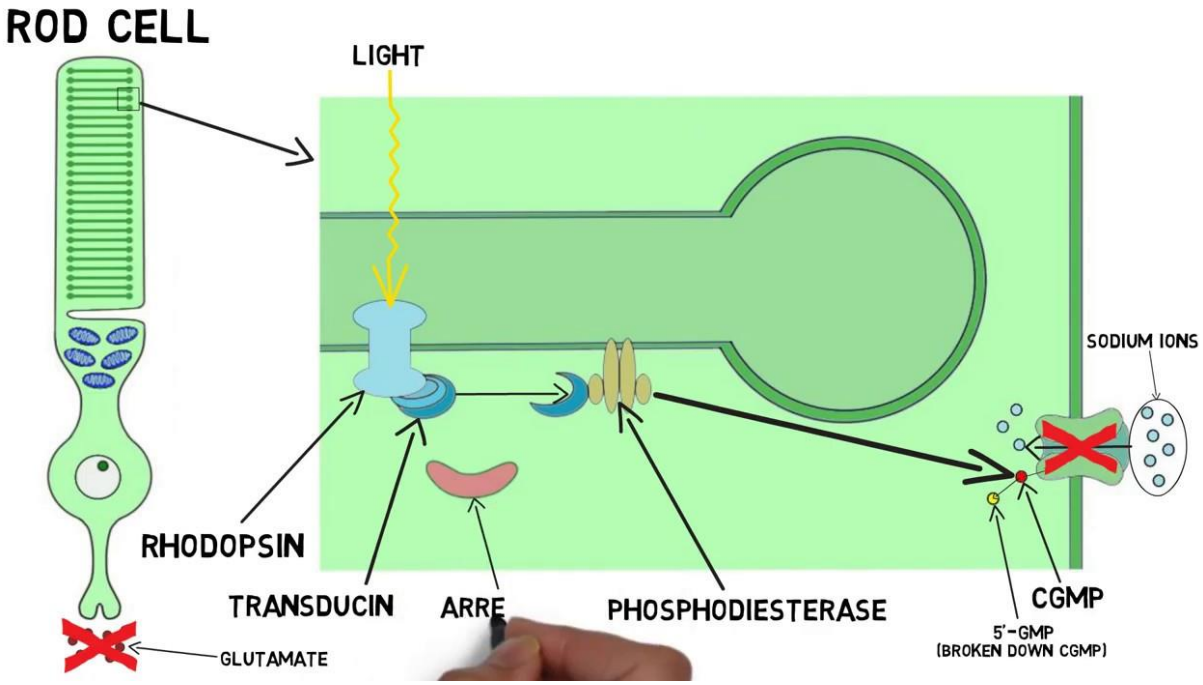



https://www.mayoclinic.org/diseases-conditions/cystic-fibrosis/symptoms-causes/syc-20353700

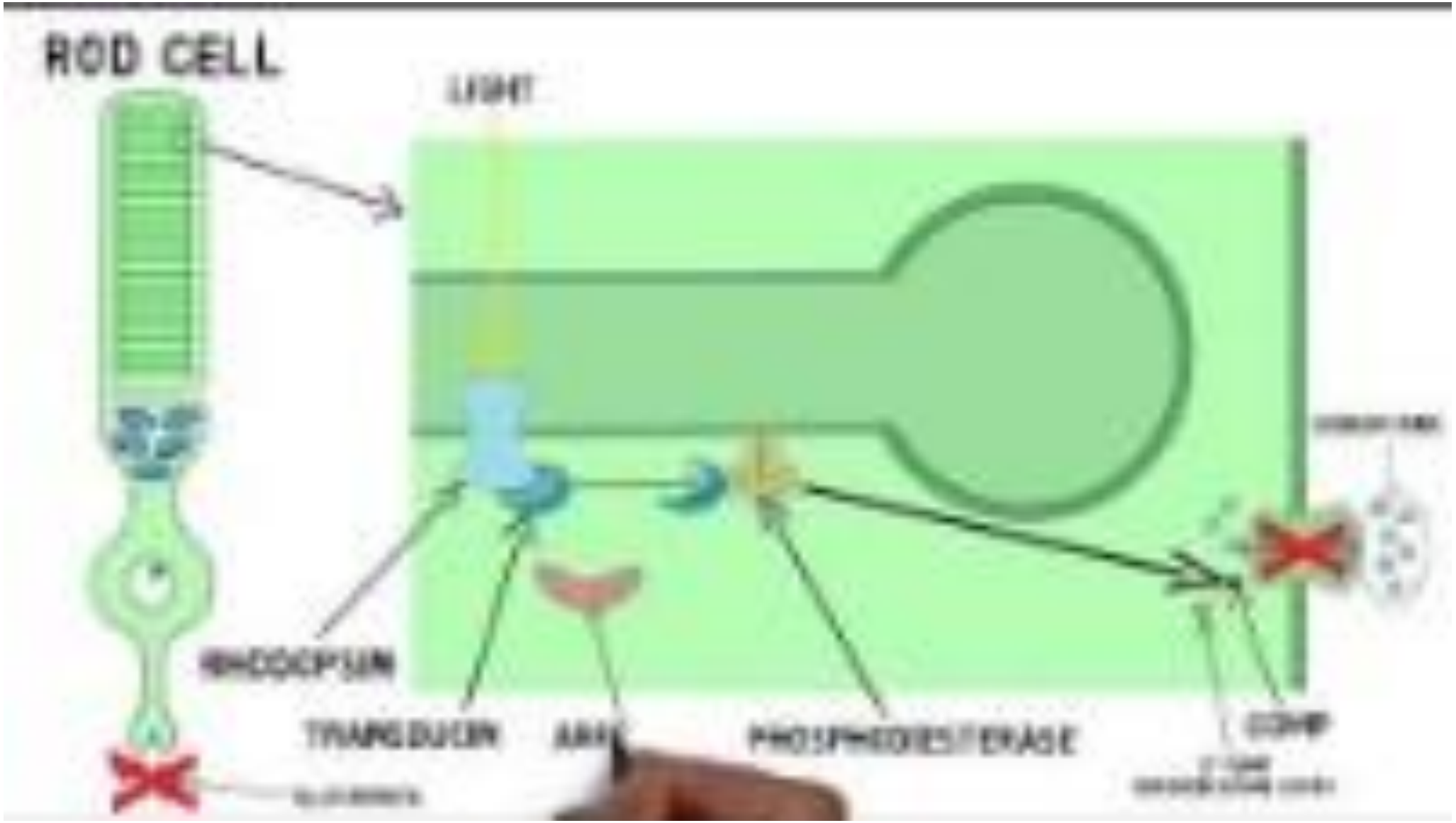
# Rhodopsin

- alkali metal cation transport is also of importance in the stimulation by visible light of rod and cone cells in the retina of the eye



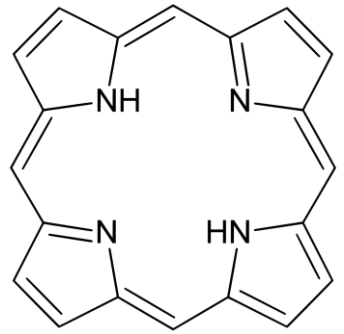
# Rhodopsin



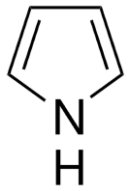

https://www.youtube.com/watch?v=dhd2fja0LZ4

# Porphyrins and tetrapyrrole macrocycles

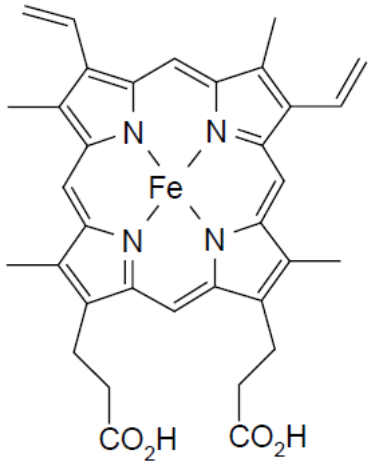
- Macrocyclic compounds able to bind metals via chelate and macrocyclic effect
- Tetrapyrrols have extensive redox chemistry because of conjugated ring net
- Chlorophylls ($Mg^{2+}$) energy harvesting system of photosynthesis
- Cobalamins – active form of vitamin $B_{12}$ (corrin system)



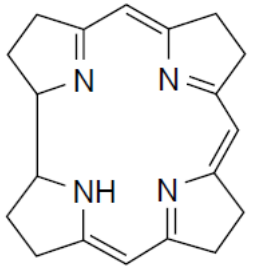

porphyrin



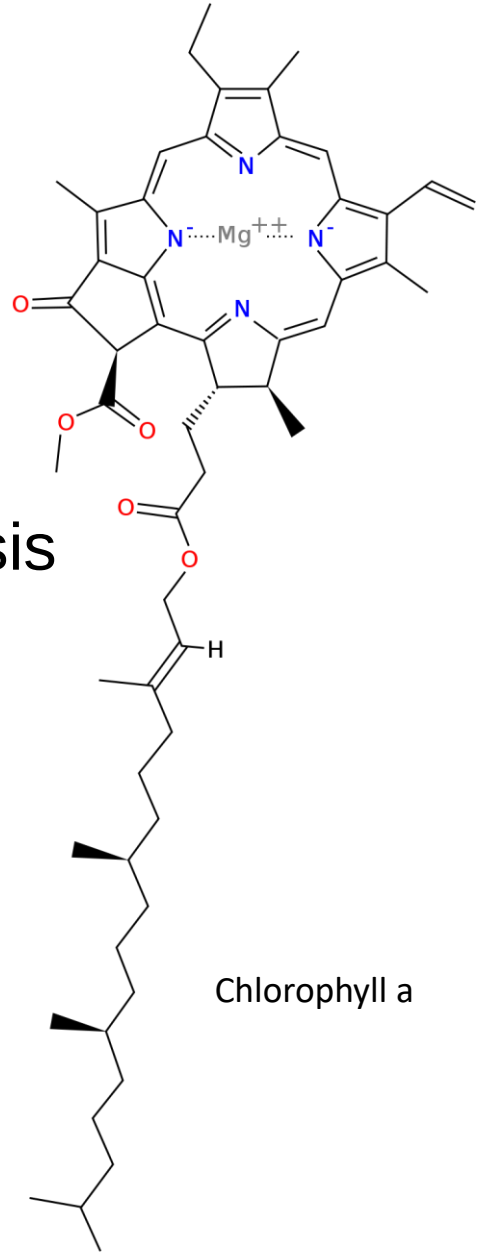

pyrrole




Heme
(Fe-protoporphyrin IX)



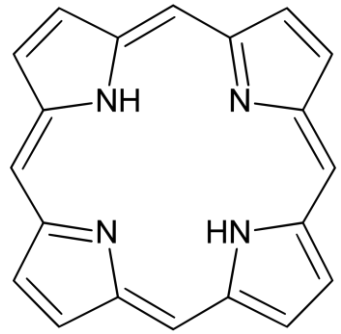

Corrin



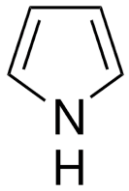

Chlorophyll a

# Porphyrins and tetrapyrrole macrocycles

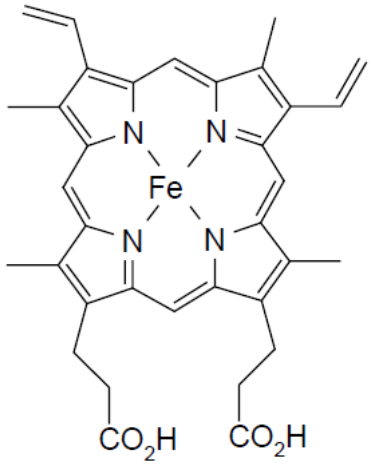
- Hem complexes having iron center – binding site for $O_2$ in hemoglobin




porphyrin




pyrrole

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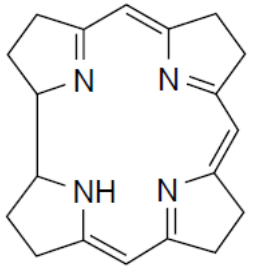
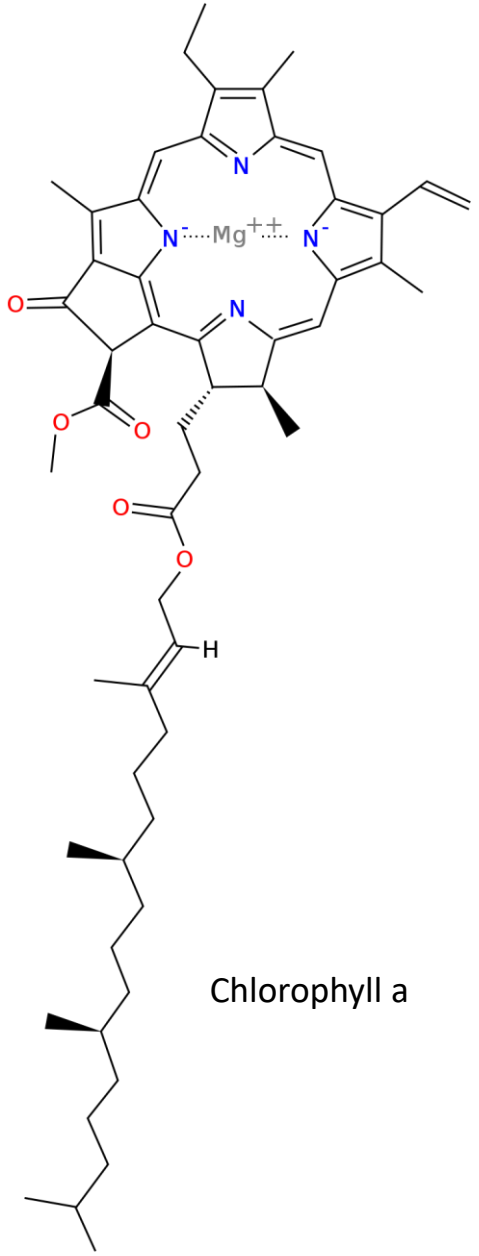


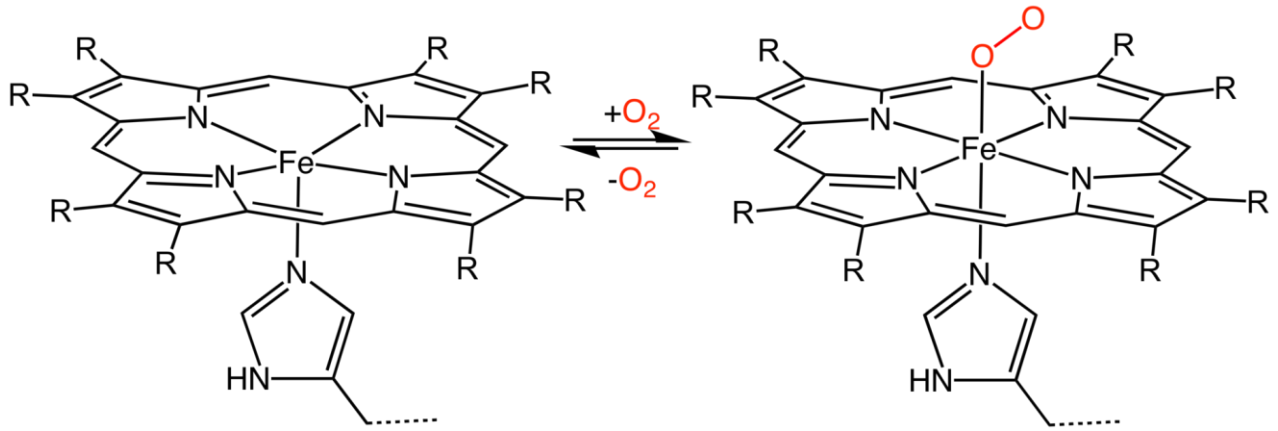

Corrin




Chlorophyll a

# Properties of tetrapyrrole macrocycles

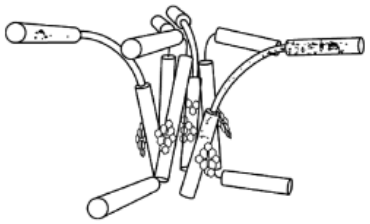
- The near planar ring system is very stable
- The tetrapyrrole ring can bind even highly labile metal cations
- Highly selective because of the cycle rigidity - preorganization
- Most contain conjugated π-system (colored)
- Macrocycle contains four coordinating atoms in a planar arrangement, leaving two available sites on an octahedral metal centre available to bind the substrate and a regulating ligand

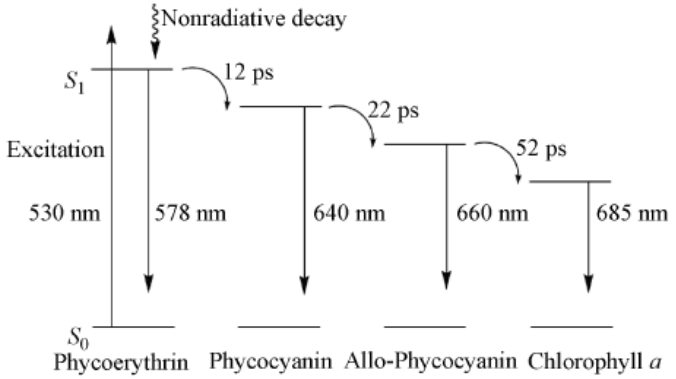


# Photosynthesis

$$H_2O + CO_2 \underset{\text{respiration (downhill catalysis)}}{\overset{\text{photosynthesis (uphill catalysis)}}{\rightleftharpoons}} 1/n(CH_2O)_n + {}^3O_2 \quad \Delta H = +470\,\text{kJ mol}^{-1}$$

- Green plants = about 1 g of glucose per hour per 1 $m^2$ of leaf surface area
- Chlorophylls contain a fully conjugated tetrapyrrole π-system (18 π electrons) with a low-energy π−π* transition
- The complementary colours blue (after short-wavelength absorption) and yellow (after long-wavelength absorption) combine to give the characteristic green colour of fresh leaves ($\lambda_{max}$ 455 and 630 nm)





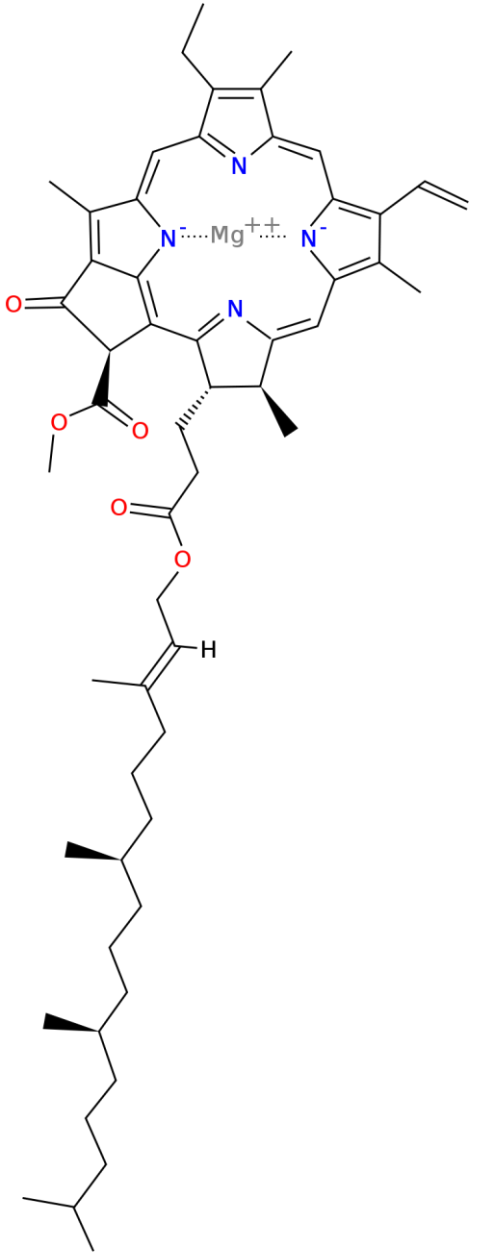
# Why Mg?

- High natural abundance
- Lack of redox activity
- Strong tendency for penta- or hexacoordination
- Suitable ionic radius

- Contributes to the arrangement of the pigments in photosynthetic membrane by binding to polypeptide

- Electron is promoted to an excited state and used to effect a chemical reaction (production of $O_2$ from $H_2O$)

„Dark“ reaction (Calvin cycle)

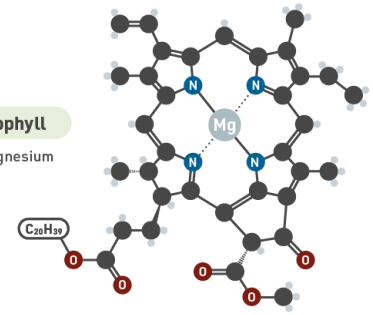



$$4e^- + 4H^+ + CO_2 \longrightarrow 1/n\,(CH_2O)_n + H_2O$$

# The Chemistry of Autumn Leaf Colours

COMPOUND INTEREST

## Chlorophyll



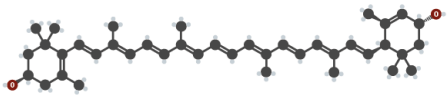

**Chlorophyll**

Mg = magnesium

KEY: Carbon O Oxygen N Nitrogen Hydrogen

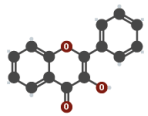
Chlorophyll gives plant leaves their green colour. Plants require warm temperatures and sunlight to produce chlorophyll. In autumn, the amount produced begins to decrease and existing chlorophyll is slowly broken down, diminishing the green colour of the leaves.

## Carotenoids and flavonoids



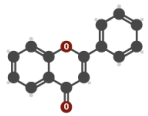
**Lutein (a carotenoid)**

Carotenoids and flavonoid pigments are always present in leaves, but as chlorophyll is broken down in the autumn their colours come to the fore. Xanthophylls, a subclass of carotenoids, are responsible for the yellows of autumn leaves. A major xanthophyll, lutein, is also the compound that contributes towards the yellow colour of egg yolks.



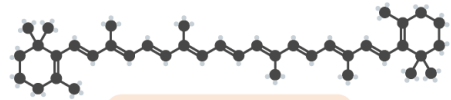
**Flavonol**

**Flavone**



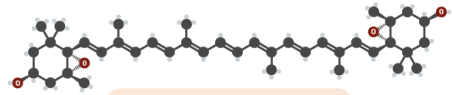
General structures shown

## Carotenoids



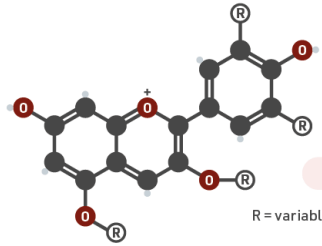
**β-carotene (a carotenoid)**

Carotenoids also contribute orange colours. Beta-carotene is one of the most common carotenoids in plants, and absorbs green and blue light strongly, reflecting red and yellow light and causing its orange appearance. It is also responsible for the colour of carrots. Carotenoids in leaves start degrading at the same time as chlorophyll, but they do so at a much slower rate. Some fallen leaves can still contain measurable amounts.



**Violaxanthin (a carotenoid)**

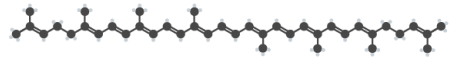
## Anthocyanins & carotenoids




**Anthocyanin**

R = variable parts of molecule

Anthocyanin synthesis is kick-started by the onset of autumn. As sugar concentration in the leaves increases, sunlight initiates anthocyanin production. The purpose anthocyanins serve isn't clear, but it is suggested that they may play a light-protective role. It was thought they might delay leaf fall, but this has been discounted.



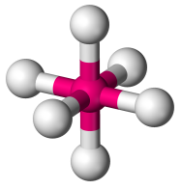
**Lycopene (a carotenoid)**

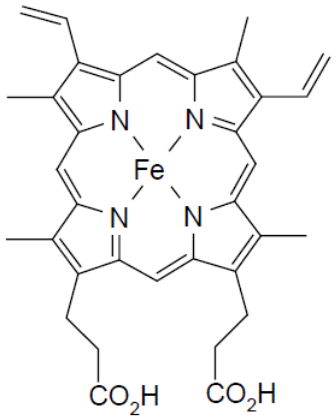
# Hemoglobin

- Oxygen is used to metabolically oxidize sugars (glucose, sucrose) to release energy, which is used in ATP synthesis

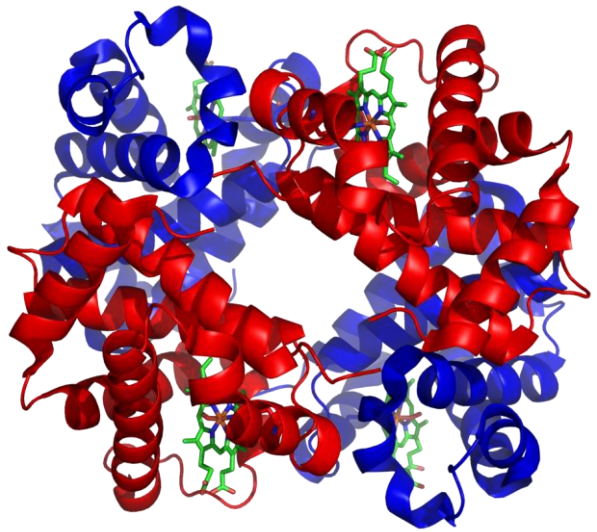
$$C_6H_{12}O_6 + 6O_2 \longrightarrow 6CO_2 + 6H_2O + \text{Energy}$$

- Hemoglobin is tetrameric protein containing four myoglobins, each has iron-porphyrin complex protein by a coordination interaction between an axial site of the octahedral Fe(II) centre and a nitrogen atom from the proximal protein histidine residue
- Iron binds the oxygen (water)



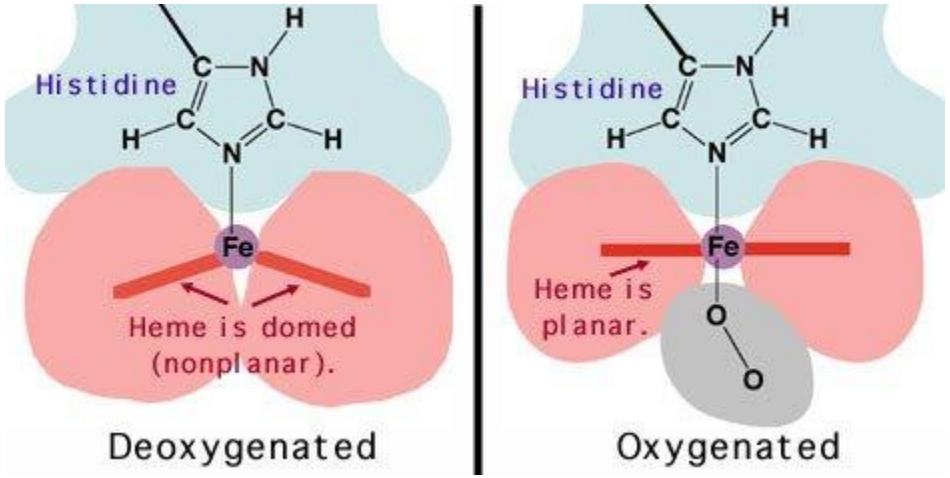


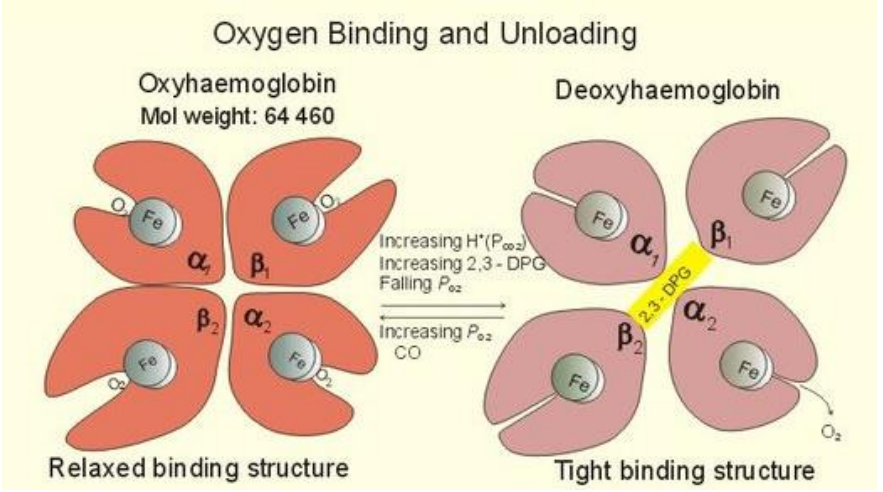
Heme
(Fe-protoporphyrin IX)



# Hemoglobin

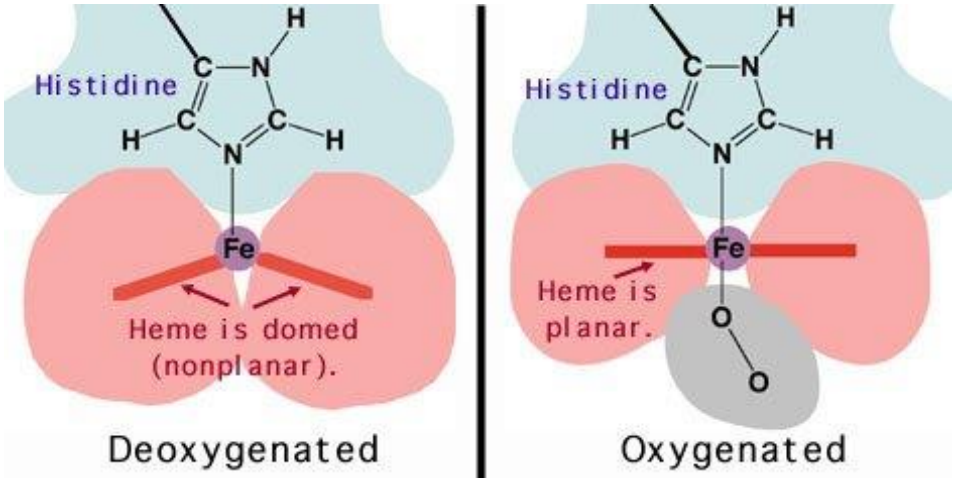
- $O_2$ is binding reversibly, its complexation and release occur rapidly and at the correct controlled concentrations
- $O_2$ binding must occur selectively amongst other atmospheric components such as water, $N_2$, $CO_2$ and even excellent ligands for Fe(II) such as CO
- Haemoglobin is an excellent example of a functional and selective supramolecular receptor

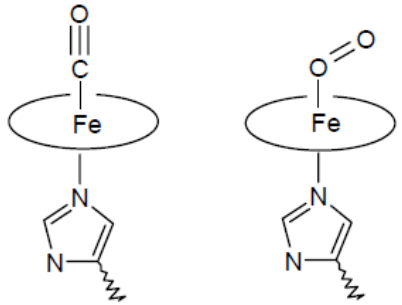


# Hemoglobin

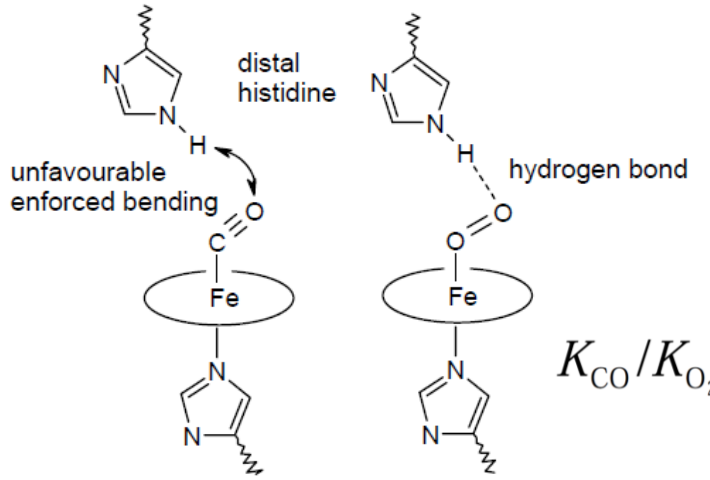
- Single electron transfer from $O_2$ to Fe(II) leads to Fe(III) formation
- Smaller ionic radius for Fe(III), better fit in porphyrin, no doming
- CO or readily adsorbed salts such as $CN^-$ are extremely toxic as they are binding irreversibly to the Fe in haemoglobin preventing oxygen transport and resulting in rapid suffocation




$K_{CO}/K_{O_2} = 25\,000$

(a) free heme complexes

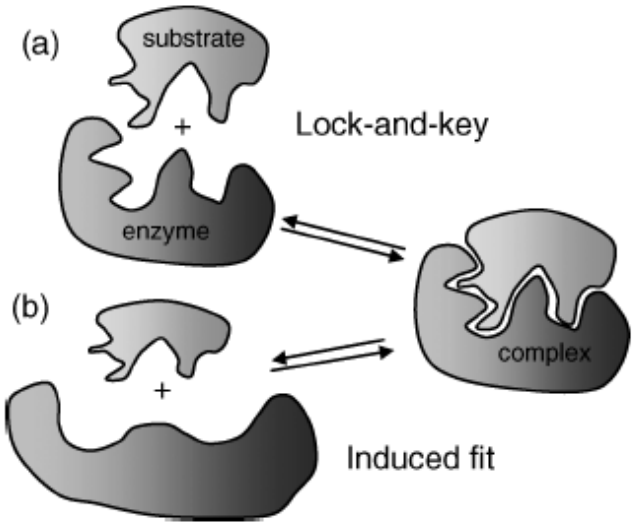



$K_{CO}/K_{O_2} = 200$

(b) myoglobin, haemoglobin

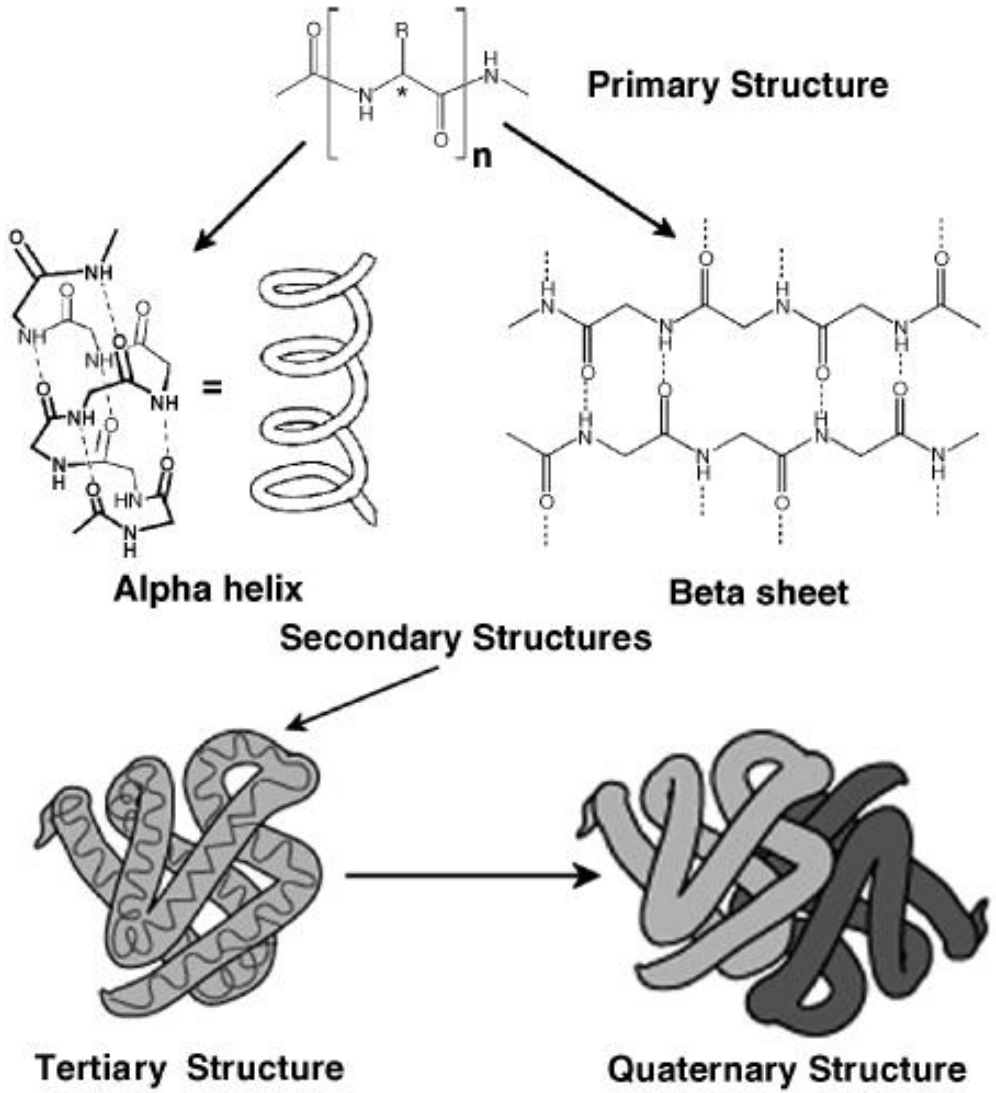
# Enzymes and coenzymes

- Enzymes catalyze all biological processes – great inspiration for supramolecular chemists
- Polypeptide chains > 10000 Da
- Polypeptide chains are folded into a unique conformation giving a globular structure incorporating surface clefts and crevices
- Active sites lie in these clefts and often contain a metal ion
- Binding involves hydrophobic effects, hydrogen bonding, salt bridges (ion–ion) and other forms of intermolecular interaction
- Extremely fast chemical conversion of substrates
- Enzyme structure may be divided into primary, secondary, tertiary and quaternary features



# Enzymes and coenzymes

- Enzyme tertiary and quaternary structure is responsible for the organisation of the binding site(s)
- Enzymes are generally named according to the reaction they carry out with the suffix -ase being added to the name of the substrate
- $Na^+/K^+$-ATPase, DNA polymerase, lactace, esterase…



# Mechanism of enzymatic catalysis

- Linus Pauling stated in 1948 that ‘enzymes are molecules that are complementary in structure to the transition states of the reactions they catalyze’

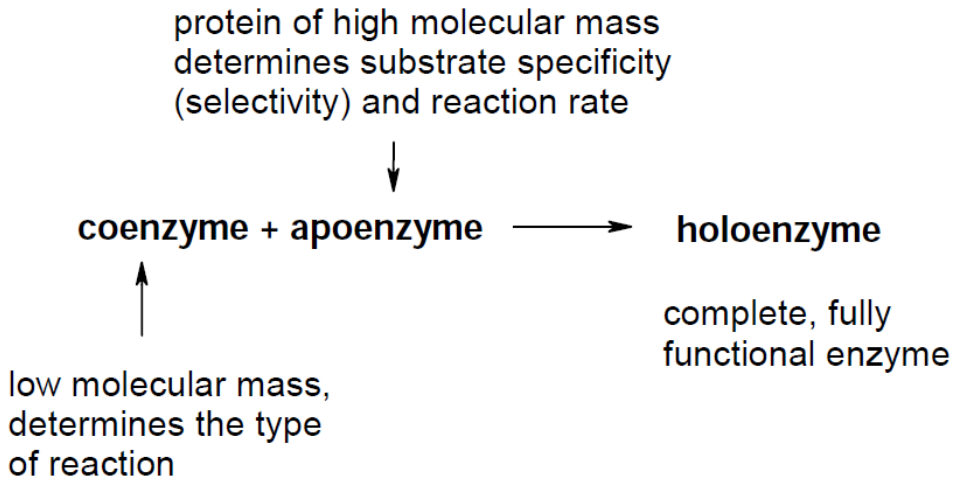
$$\mathrm{E} + \mathrm{S} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{ES} \xrightarrow{k_{\mathrm{cat}}} \mathrm{P} + \mathrm{E}$$

$$k_1 / k_{-1} = K_{11}$$

- Non-covalent forces involved in substrate binding should be sufficient to distort the substrate such that it becomes more like a transition state, lowering activation energy required to form [ES]
- Effective concentration, desolvation of the bound state
- Both, enzyme and substrate, undergo conformational change

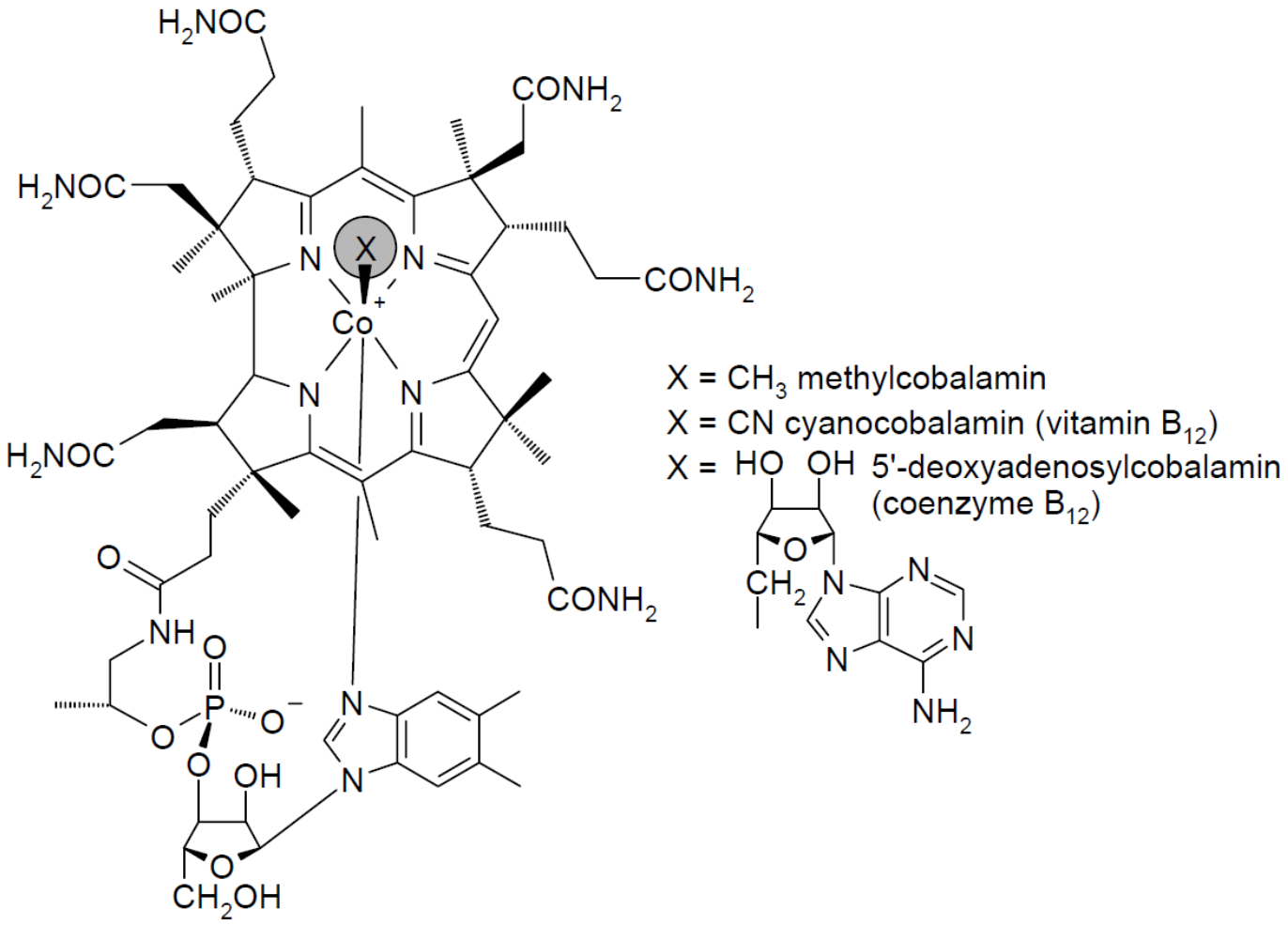
# Coenzymes

- Coenzyme is a non-enzyme ‘helper molecule’ that forms one constituent of a biological catalytic system (e.g., ATP, or vitamins)
- Full system requires the coenzyme, an apoenzyme and a substrate
- The nature of the coenzyme determines the type of the reaction, while the nature of the apoenzyme determines the selectivity of the reaction in terms of the substrate and the regiospecificity



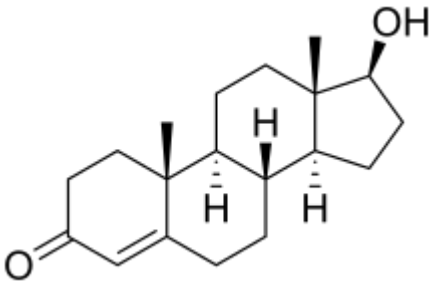
# Coenzyme $B_{12}$, cobalamin, vitamin $B_{12}$

- Can be used with various apoenzymes
- Alkylation
- Required for amino acid metabolism in the liver and its absence, as a result of genetic defects, is lethal (pernicious anemia)
- The X-ray crystal structure earned the 1964 Nobel Prize in Chemistry for Dorothy Crowfoot-Hodgkin



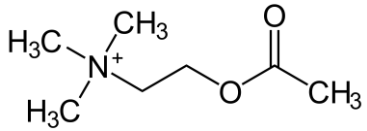
# Neurotransmitters and hormones

- messengers and activating agents
- E.g., sex hormones (testosteron, estrogen, progesteron), or neurotransmitters such as dopamine, acetylcholine



testosterone

***Acetylcholine***

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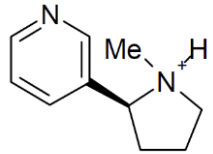
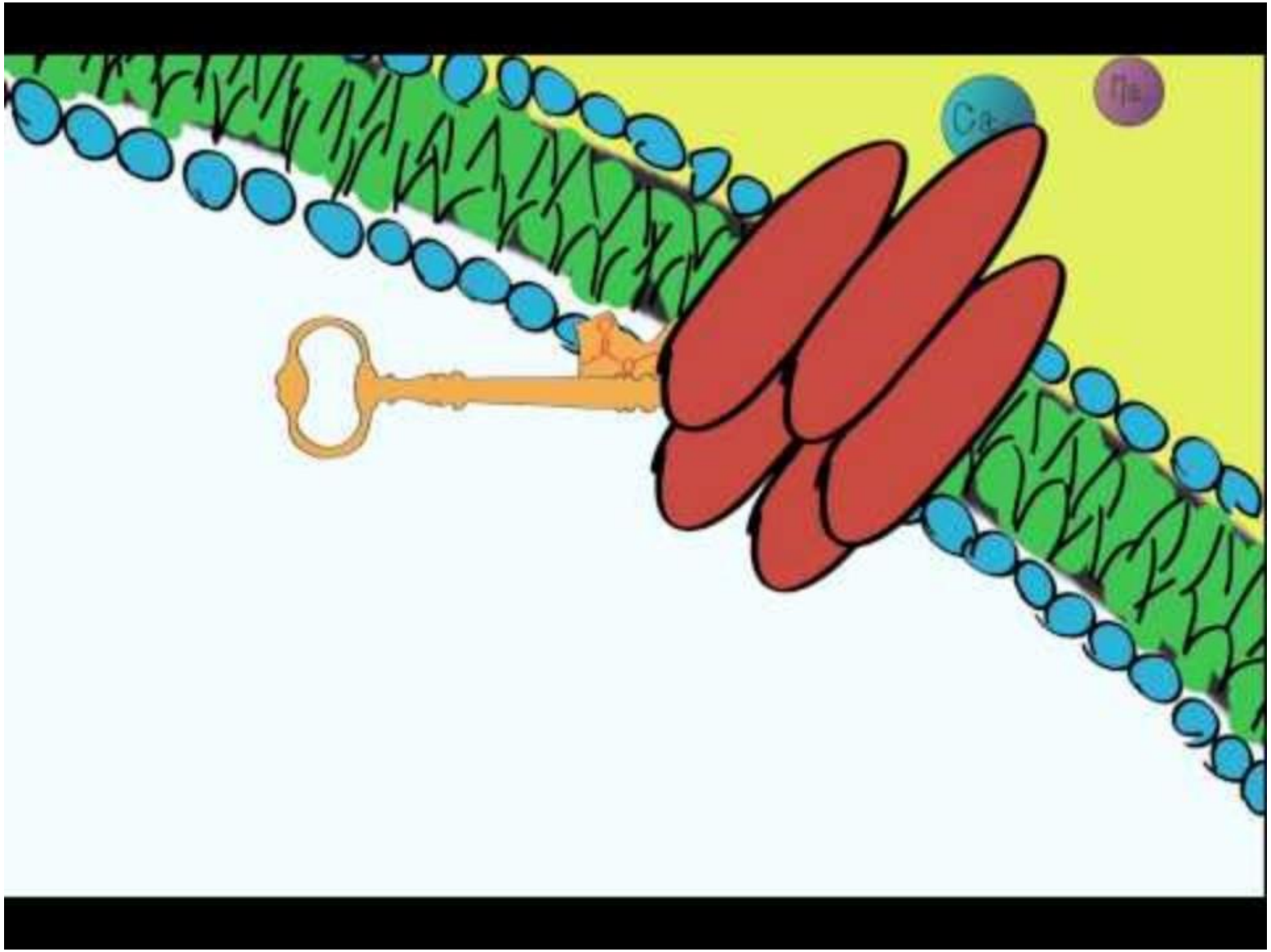


nicotine

lower selectivity

- Nerve pulses are passed among neurons across synapses (gaps between nerve cells, 30–40 nm thick) by transfer of acetylcholine (highly selective binding involves cation-π interactions) – ligand-gated ion channel
- This opens $Na^+$ channels, part of the nicotinic acetylcholine receptor protein (nAChR), $Na^+$ flows into the cell in concentration gradient, current flow
- Then acetylcholine esterase hydrolyses the ester functionality preventing the molecule from further binding to nAChR, closing the $Na^+$ channel
- Nicotine × acetylcholine

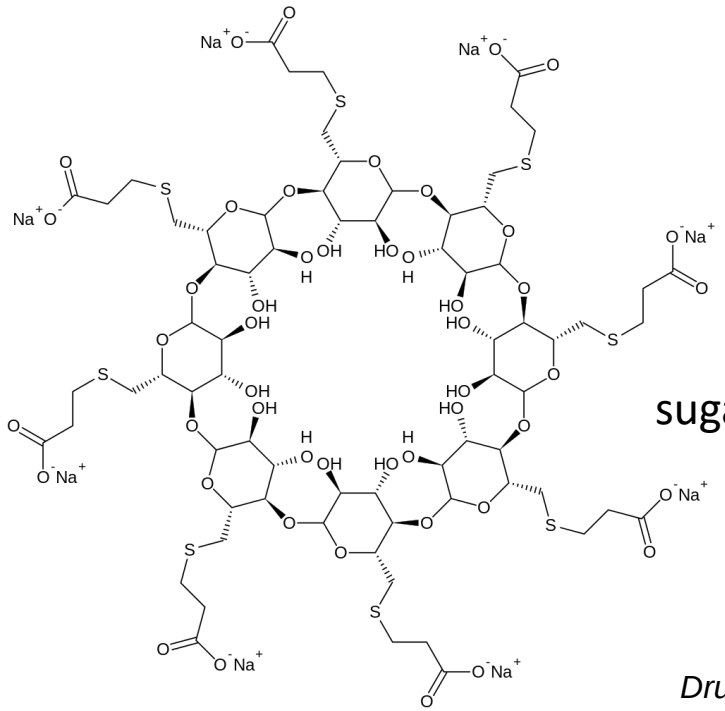
# Acetylcholine and nAChR




https://www.youtube.com/watch?v=P7pEUF3-IXI

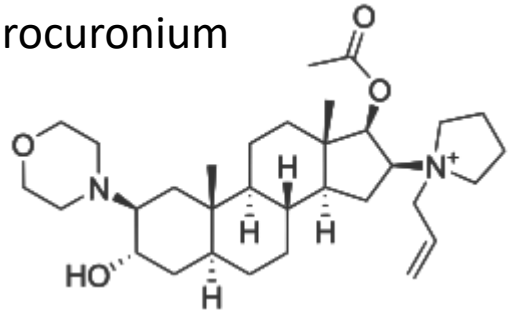
# Rocuronium, acetylcholin, sugammadex

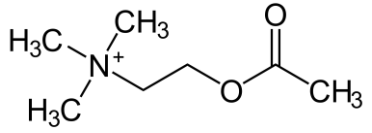
- **In general, many drugs used utilize the low selectivity of various receptors**
- Sugammadex – used as reversal of neuromuscular blockade induced by rocuronium and vecuronium in general anaesthesia (by competing for the cholinoceptors at the motor end plate, thereby exerting its muscle-relaxing properties, which are used adjunctively to general anesthesia)



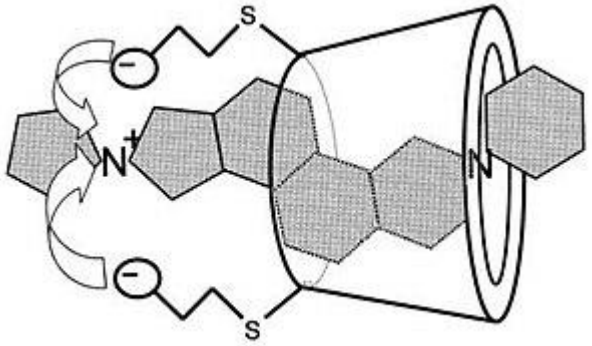
sugammadex

rocuronium



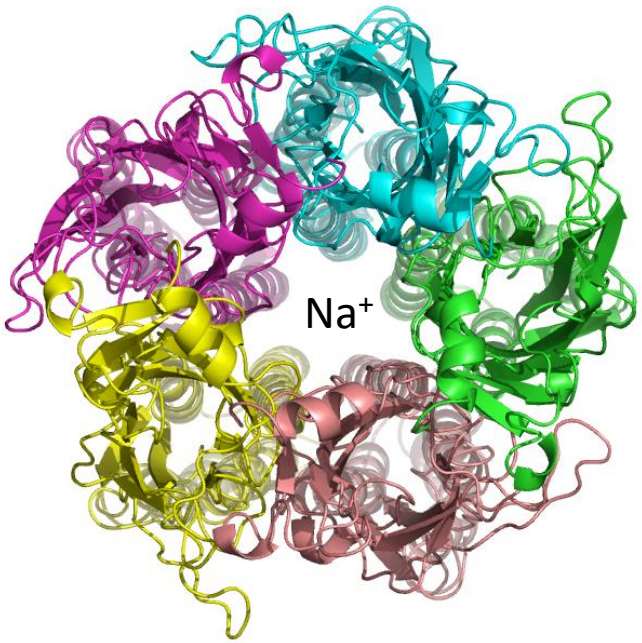


acetylcholin



HG-complex

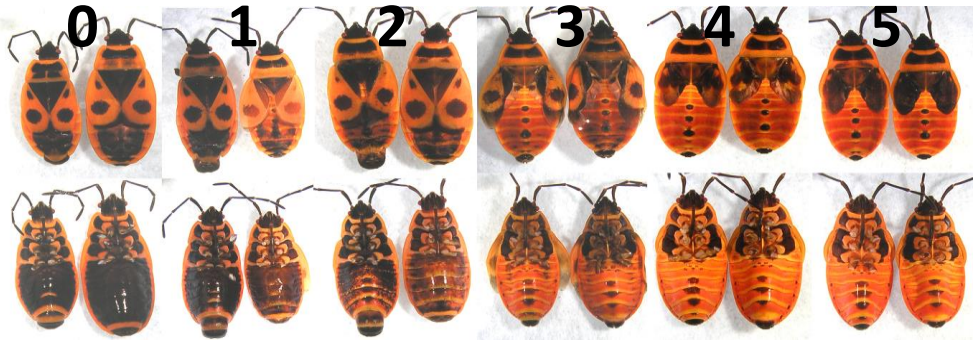
acetylcholin receptor

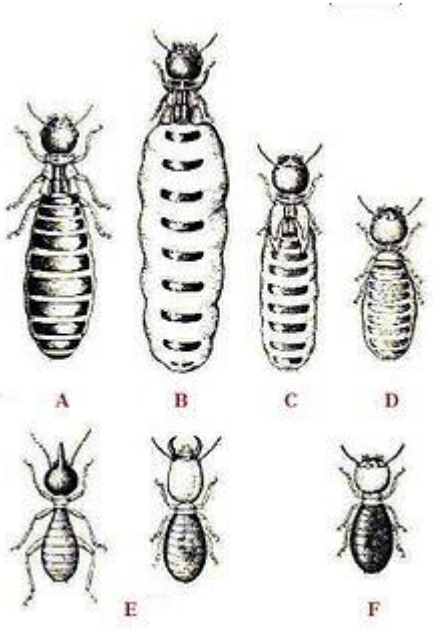


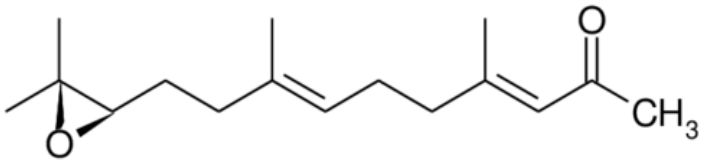

*Drugs 2009, 69, 919–942*

# Insect juvenile hormones and analogues (insecticides)

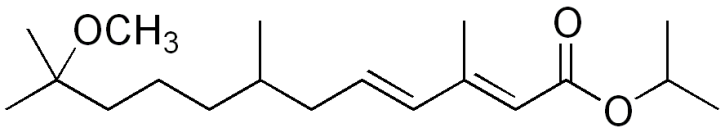
- Juvenile hormones (JH) regulate development, reproduction, diapause, and polyphenisms in insect
- Juvenile hormone receptors are less selective
- JH analogues can have insecticidal properties – block development and metamorphosis of insect (mosquitoes, termites)
- Juvabion – paper factor
- Juvenoids, juvenogens
- Very low general toxicity



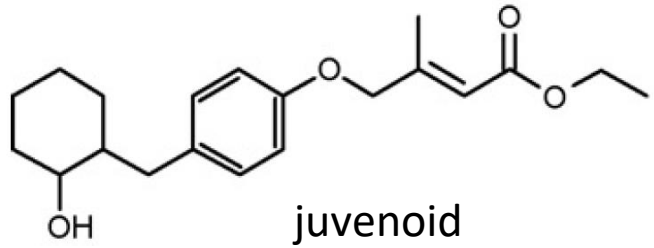




juvenile hormone III




methoprene – JH analogue used




juvenoid

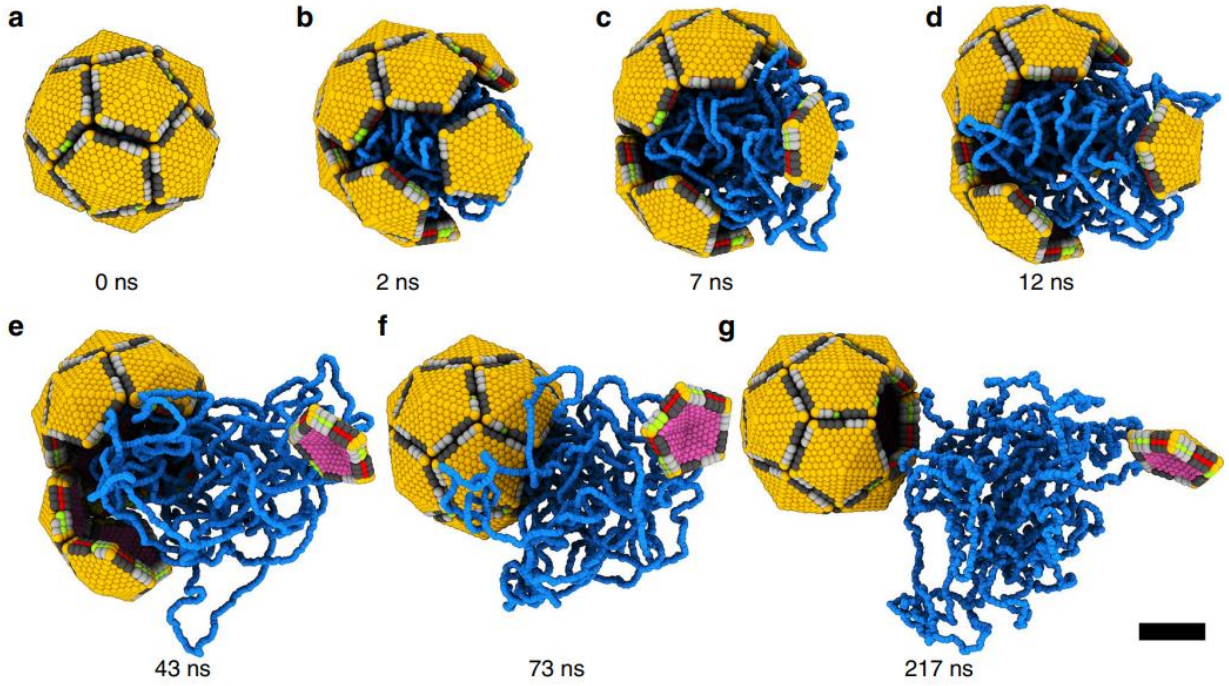


Jurček *et al*. *Steroids* 2009, *74*, 779 / *J. Agric. Food Chem.* 2009, *57*, 10852 / J. Agric. Food Chem. 2007, 55, 7387.

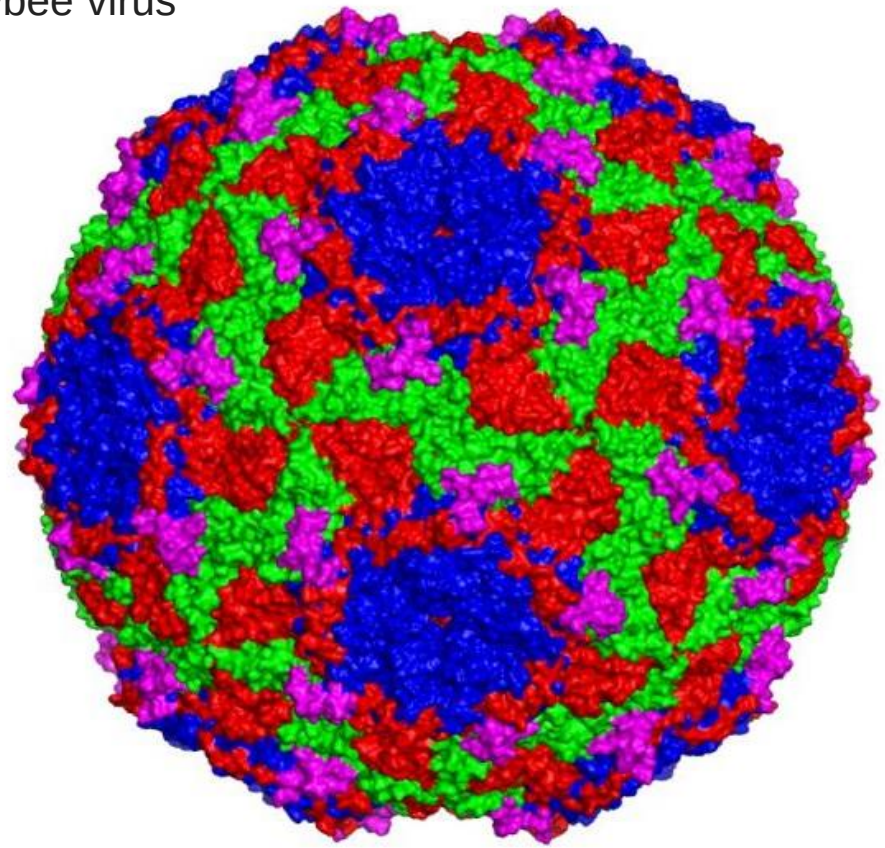
# Biochemical self-assembly

- Viruses are built of numerous protein sub-units, encoded by viral RNA, which self-assemble reversibly to form protective hollow coatings termed capsids

enterovirus



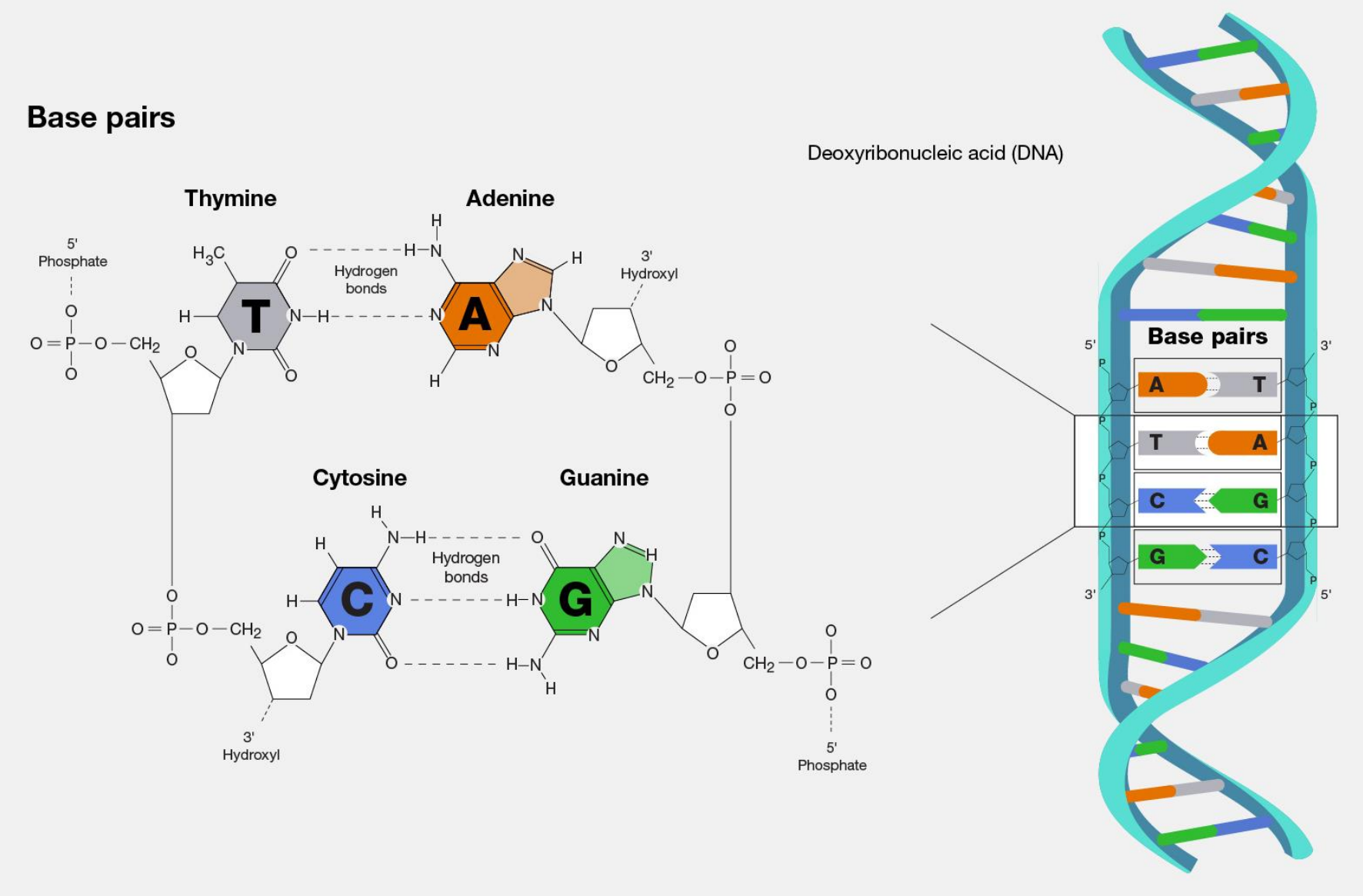

sacbrood honeybee virus



Plevka et al. NATURE COMMUNICATIONS | (2019) 10:1138

Plevka *et al.* PNAS 2018, 115 (30) 7759-7764.

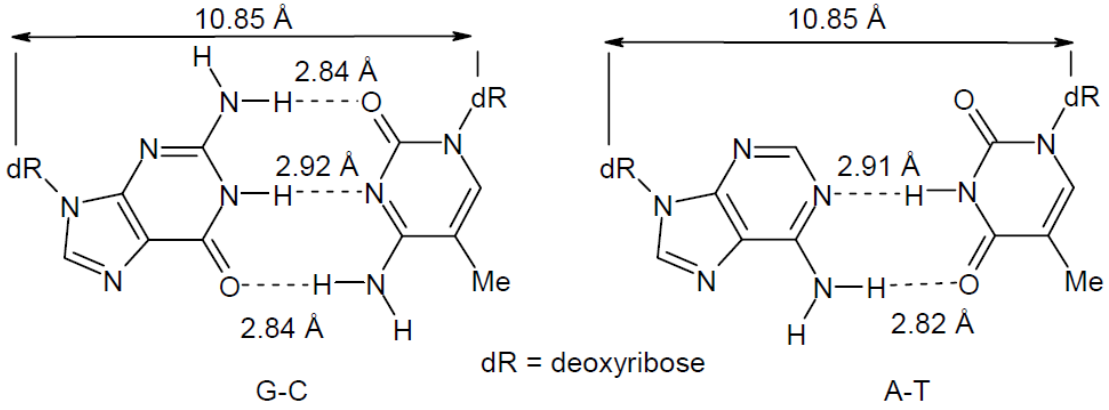
# DNA




https://en.wikipedia.org/wiki/Base_pair#/media/File:DNA_base-pair_diagram.jpg

# DNA

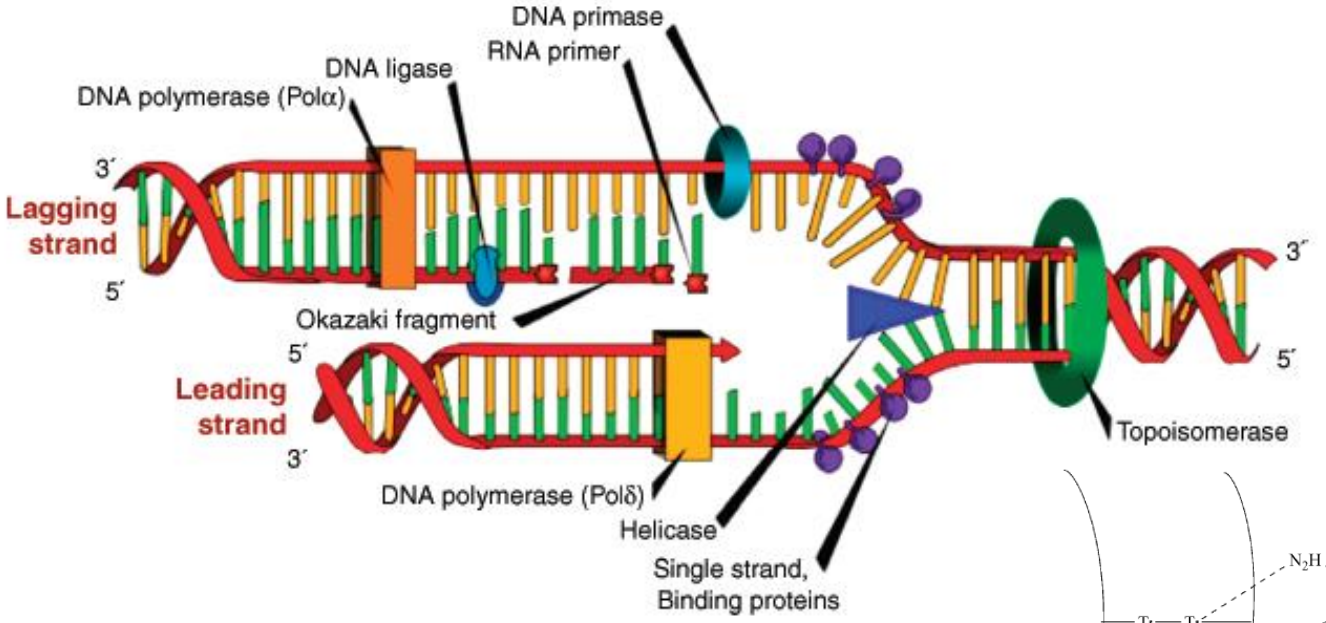
- Molecule that bears all of the genetic information necessary to construct and operate a living organism
- Held together in double helix through hydrogen bonding and π–π stacking interactions (each cell has about 3 cm long and $2 \cdot 10^{-9}$ m thin)
- Nucleotides, molecules that contain a nucleobase (either adenine (A), thymine (T), cytosine (C) or guanine (G)) attached to a sugar and a phosphate tail
- Genetic information on DNA is stored as a large number of three letter codons = triplets of nucleobases (*e.g.*, GCC, CAG, ATC etc.). Each codon is translated biochemically into one of the 20 amino acids building proteins

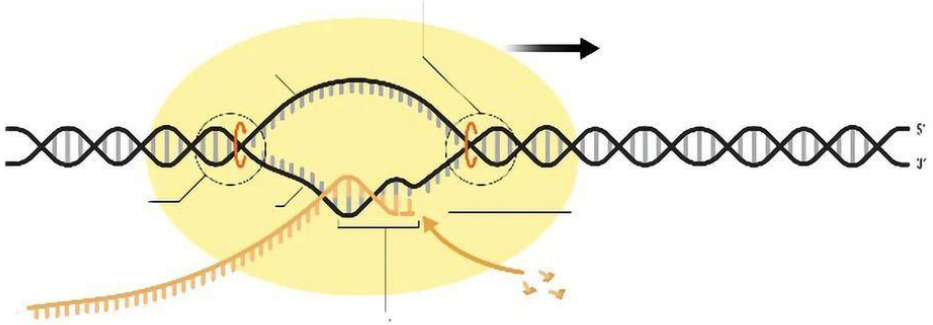


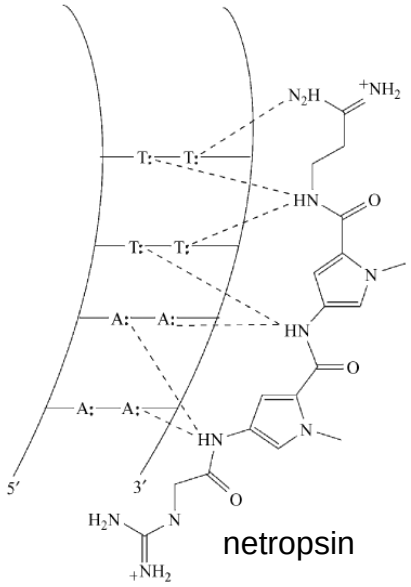

Watson–Crick base pairing

# Binding to DNA

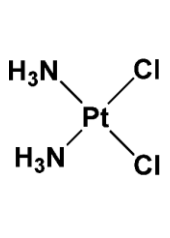
- Pairing enables DNA to replicate itself as well as passing on its encoded genetic information to messenger RNA



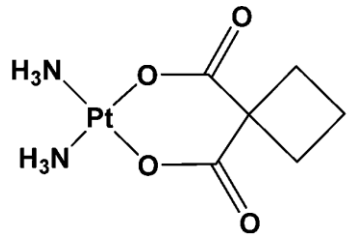





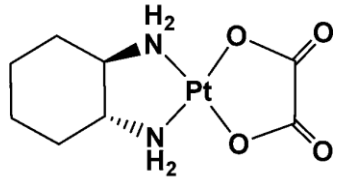
netropsin



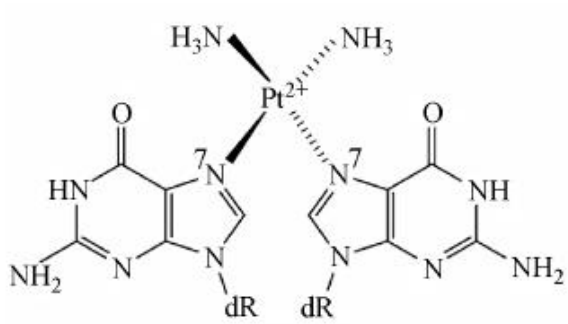
cisplatin



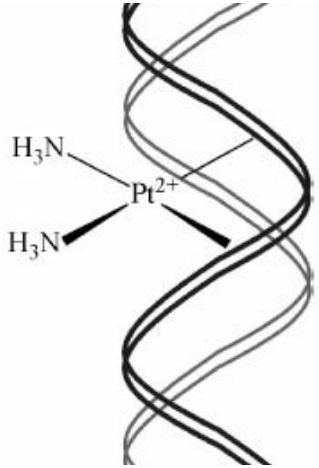
carboplatin

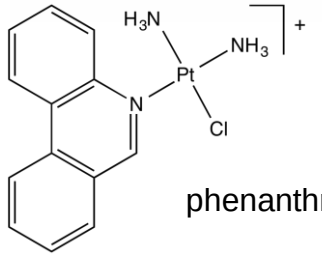


oxaliplatin



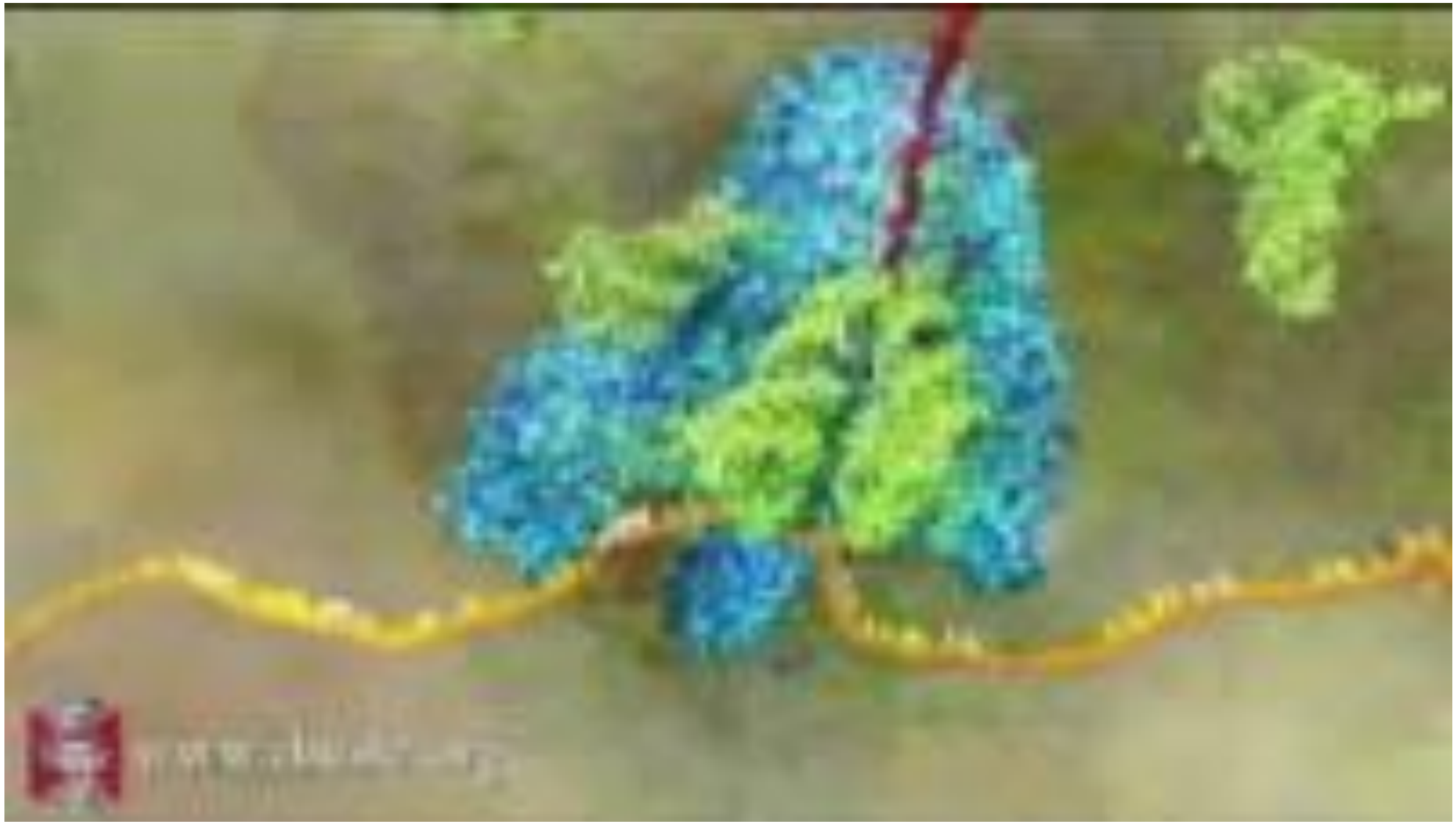
guanosine binding





phenanthriplatin

# Ribosomes as supramolecular molecular machines



https://www.youtube.com/watch?v=TfYf_rPWUdY&t=2s

# In the next class…

## Gels and metallogels

# Thank you for your attention!

With thanks to Jonathan W. Steed, Jerry L. Atwood for Supramolecular Chemistry, ISBN: 978-1-119-58251-9 and Wikipedia for several lovely images.