

Basics of Bioinorganic Chemistry

Handout

Lorenz Kienle

Max-Planck-Institut für
Festkörperforschung
Stuttgart



Outline

1. Very important terms of coordination chemistry
2. General aspects of bioinorganic chemistry
3. Coordination for uptake, transport and storage (Fe)
4. Hard ions: Na^+ , K^+ , Mg^{2+} , Ca^{2+}
5. Cobalamines
6. Metals in Photosynthesis
7. Fe in bio systems

Resources

Text books

- W. Kaim, B. Schwederski: **Bioinorganic Chemistry: Inorganic Elements in the Chemistry of Life**, Wiley 1994, German edition: Teubner 1995
- S. J. Lippard, J. M. Berg: **Bioanorganische Chemie**, Spektrum- Akademischer Verlag
- D. Shriver, P. Atkins: **Inorganic Chemistry**, Freeman and Comp. 1999 (Chapter 19)

Internet resources

- Lectures of Prof. Rehder (University Hamburg), doc-files (german)
- Internet resources, e. g. Uni Siegen (KomplexMaster7Sem.ppt, etc.)
- Bonding: <http://wwwchem.uwimona.edu.jm:1104/courses/CFT.html>
- Lectures of Prof. Klüfers (LMU, see homepage)

Papers

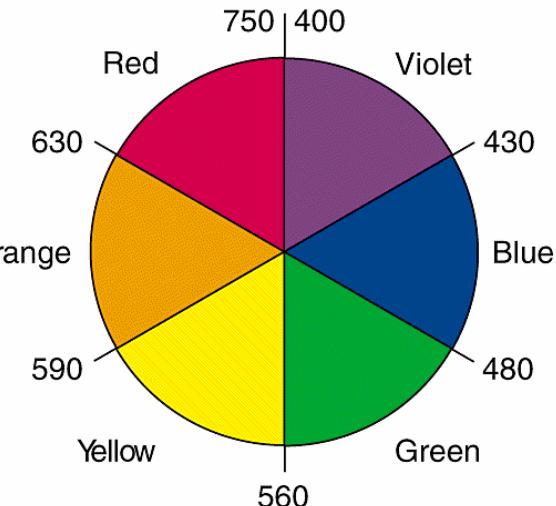
- S. Busch et al., **Eur. J. Inorg. Chem.** 1999, 1643
- E. Bäuerlein, **Angew. Chem. Int. Ed.** 2003, 42, 614

1.

Very important terms of coordination chemistry

Coordination compound (complex)- basics

- Central atom is bound to unexpectedly large number of ligands (CN)
- Usually discrete species in solution and solid
- Examples: $K_4[Fe(CN)_6]$, $CoCl_2 \cdot 6 H_2O$
- Properties of central atoms (transition metals):
 - Large charge/radius ratio
 - Variable oxidation states (d-electrons available)
 - (Meta)stable high oxidation states, s- electrons are removed first
 - Compounds are often paramagnetic (unpaired electrons)
 - Formation of colored ions and compounds
 - Compounds with profound catalytic activity
 - Formation of stable complexes (Lewis acids, see HSAB)
 - Trend to metal-metal bonding (clusters, not important in biology)
- Properties of ligands
 - Monodentate or polydentate ligand
 - Ambidentate ligands (nitro-, nitrito)



Electron configurations of transition metals

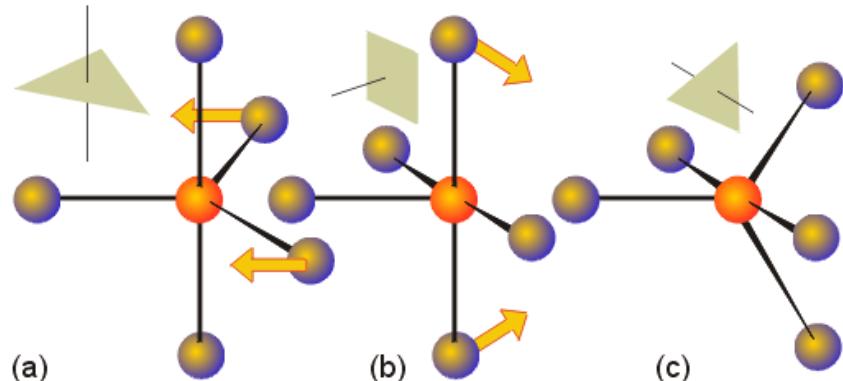
- Prerequisite: basic knowledge of periodic table
- Co: [Ar] 4s² 3d⁷, Co²⁺: [Ar] 3d⁷, Co³⁺: [Ar] 3d⁶

Group	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18				
Period																						
1	1 H																2 He					
2	3 Li	4 Be															5 B	6 C	7 N	8 O	9 F	10 Ne
3	11 Na	12 Mg															13 Al	14 Si	15 P	16 S	17 Cl	18 Ar
4	19 K	20 Ca	21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr				
5	37 Rb	38 Sr	39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe				
6	55 Cs	56 Ba	*	71 Lu	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn			
7	87 Fr	88 Ra	**	103 Lr	104 Rf	105 Db	106 Sg	107 Bh	108 Hs	109 Mt	110 Uun	111 Uuu	112 Uub	113 Uut	114 Uuq	115 Uup	116 Uuh	117 Uus	118 Uuo			
*Lanthanoids		*	57 La	58 Ce	59 Pr	60 Nd	61 Pm	62 Sm	63 Eu	64 Gd	65 Tb	66 Dy	67 Ho	68 Er	69 Tm	70 Yb						
**Actinoids		**	89 Ac	90 Th	91 Pa	92 U	93 Np	94 Pu	95 Am	96 Cm	97 Bk	98 Cf	99 Es	100 Fm	101 Md	102 No						

Geometrical features

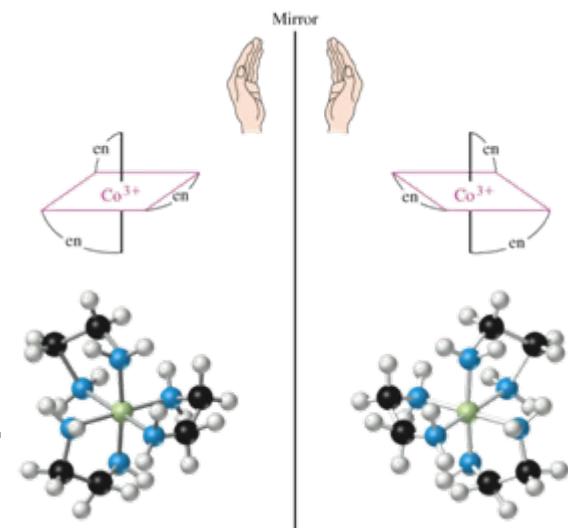
Pseudorotation

- Exchange of a- and e-ligand, see MgATPase
- $[\text{Ni}(\text{CN})_5]^{3-}$: b) and a) in crystal structure
- $\text{Fe}(\text{CO})_5$: fast pseudorotation in solution



Isomerism

- Molecules have the same molecular formula but the atoms are arranged differently
- The structures of isomers are not super imposable
- Isomers have different physical (color) and/or chemical properties.



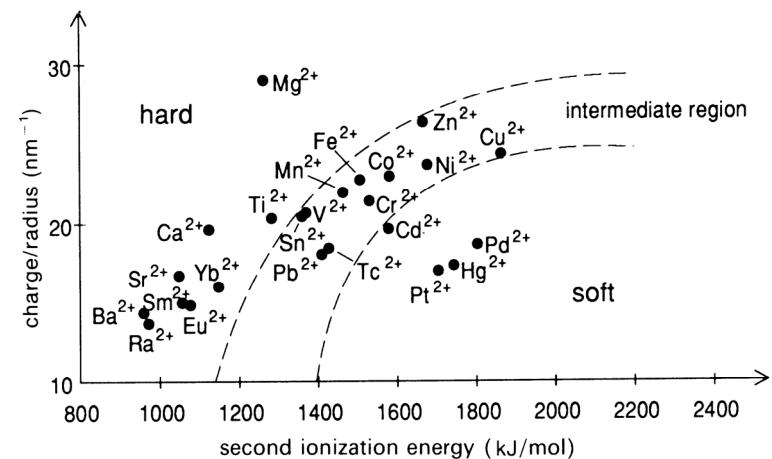
HSAB concept

- Pearson's concept, 1963

- Lewis concept: metal ions are acids because they accept electrons
ligands are bases because they donate electrons

- Hard acids tend to form complexes with hard bases (ionic bonds)
- Soft acids tend to form complexes with soft bases (covalent bonds)

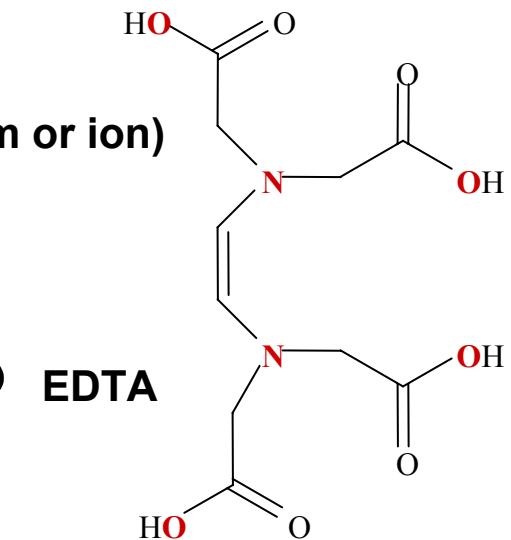
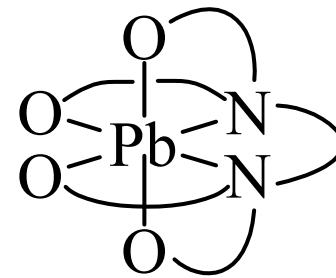
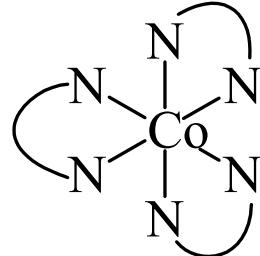
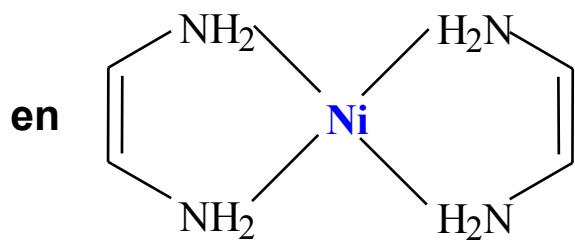
- Hard acids: H^+ , Li^+ ($> \text{Na}^+ \dots$), Cr^{6+} ($> \text{Cr}^{3+}$)
- Intermediate acids: Fe^{2+} , Mn^{2+} , Cu^{2+} , Zn^{2+}
- Soft acids: Au^+ ($> \text{Ag}^+$, Cu^+), Hg^{2+} , Pt^{2+}
- Hard bases: F^- , OH^- , NH_3 , PO_4^{3-} ($> \text{HPO}_4^{2-}$), MoO_4^{2-}
- Intermediate bases: Cl^-
- Soft bases: I^- ($> \text{Br}^- \dots$), S^{2-} ($> \text{HS}^-$, $> \text{H}_2\text{S}$), AsS_2^-



Chelates

- **Structure**

- Multidentate ligands (more than one bond with the central atom or ion)
- Ring structures



- **Properties**

- Multidentate ligands are much stronger complex formers than monodentate ligands
- Chelates remain stable even at very dilute concentrations (less dissociation)
- Chelate effect: Increase of entropy

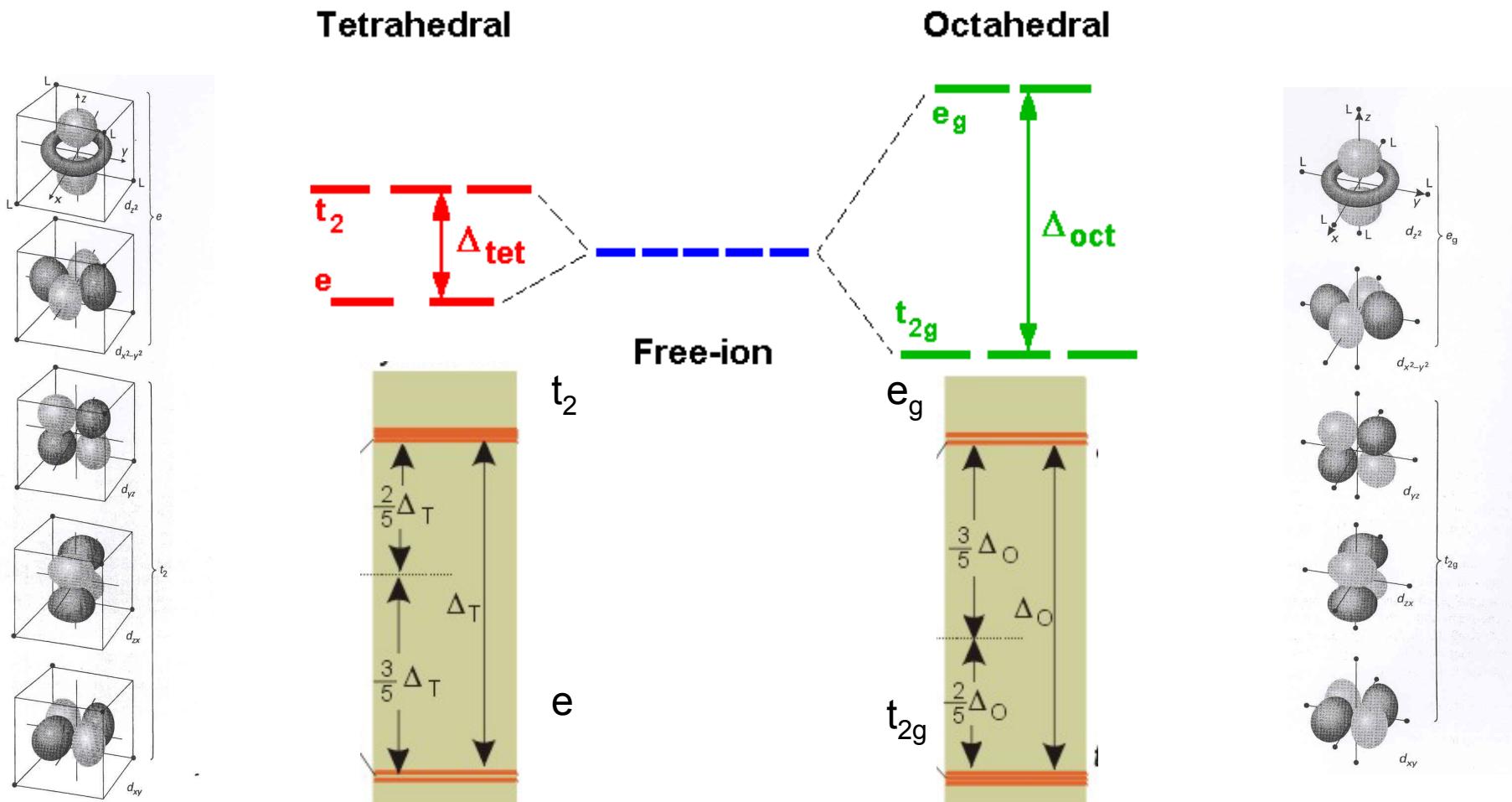
$$\Delta G = \Delta H - T\Delta S, \Delta H \sim \text{for multi- and mono-dentate complexes}$$



- Chelate therapy (detoxification)

Bonding in complexes- CTF

- Crystal Field Theory (Electrostatic guide to splitting of d-levels)
- Ligands regarded as point charges, ligand field splitting Δ_0
- LFSE (Ligand Field Stabilization Energy)



Bonding in complexes- CTF

- Spectrochemical series:



- Metal: Δ_0 increases with increasing oxidation number and down a group



- Electronic configuration (h.s., l.s.) depend on LFSE and P (pairing energy)

- Trends for l.s:

- ligands: right end of spectrochemical series
- central atoms: 4d, 5d metals
- geometry: octahedral coordination

} large Δ_0

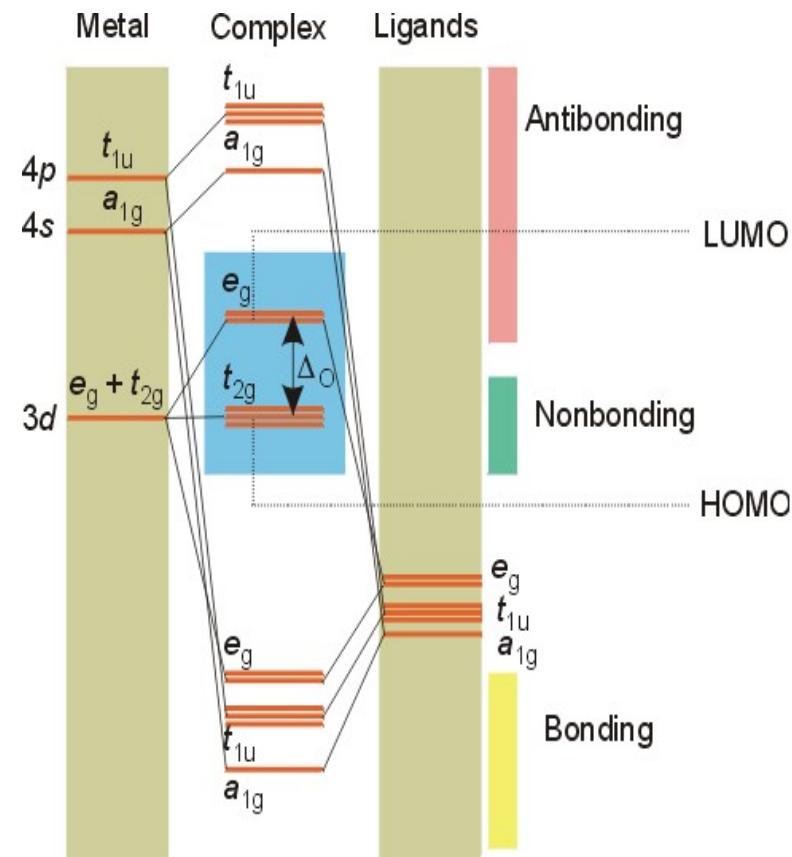
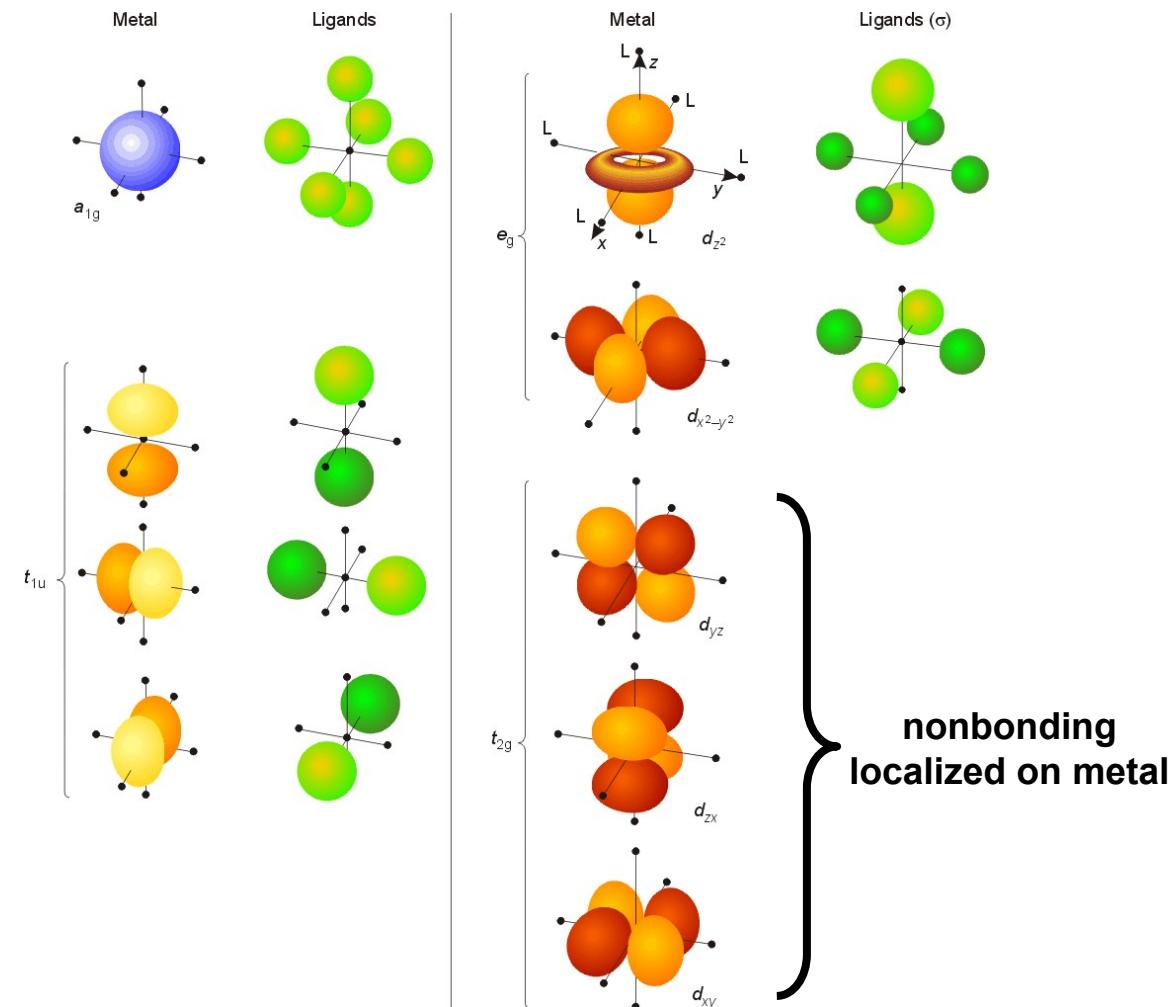
- Jahn-Teller distortion: remove of degeneracy, increase of LFSE

- Splitting e_g (d_{z2} lower energy) and t_{2g} (d_{xy} higher energy)

- Square coordination: d_{xy} higher energy than d_{z2}

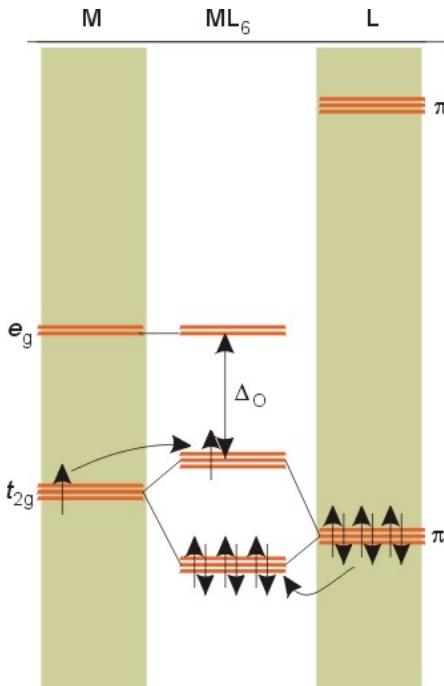
Bonding in complexes- LFT (σ -bonding)

- Ligand field theory (Interaction in terms of atomic and molecular orbitals)
- Overlap atomic orbitals of similar symmetry to form molecular orbitals

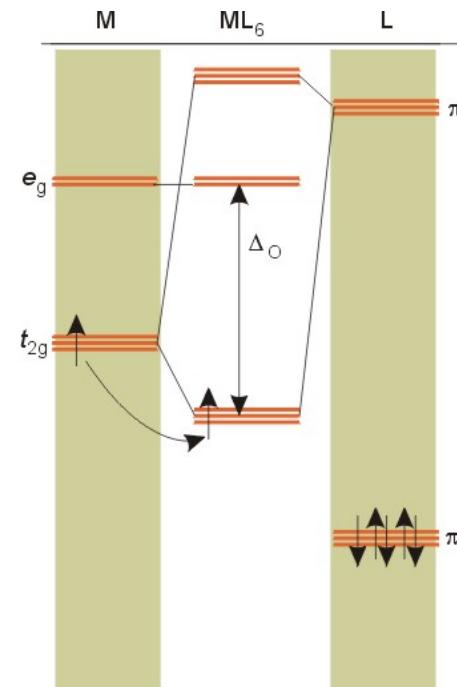


Bonding in complexes- LFT (π -bonding)

- SALC of metal t_{2g} and π -orbitals of the ligand
- Non-bonding t_{2g} become antibonding (π -donor)
- Non-bonding t_{2g} become bonding (π -acceptor)



π -donor ligand: completely filled low-energy π -orbitals:
 Δ_0 is reduced



π -acceptor ligand: incompletely filled low-energy π -orbitals:
 Δ_0 is increased

2.

General aspects of bioinorganic chemistry

“Bioinorganic Chemistry” – a contradiction?

- **Organic chemistry:** restricted to carbon compounds
- **Biochemistry:** chemical components of living systems
- **Inorganic chemistry:** no covalent carbon components (?)
- **Bioinorganic chemistry:** biochemical function of “inorganic elements”
- **Consequence:** interdisciplinary research!
- **Profit from Bioinorganic Chemistry:** learning from nature
- Nature: optimized system by evolution
- Efficient collection, conversion and storage of energy
- Moderate conditions during catalytic processes supported by metal proteins
- Stereoselective synthesis
- **Three main fields of research**
- Enzymes, biological relevant complexes: biochemistry and coordination chemistry
- Biominerization: biochemistry and solid state (materials) chemistry
- Synthesis and characterization (NMR, XRD, TEM, ...) of model systems

Periodic table of life

H																				He
Li	Be														B	C	N	O	F	Ne
Na	Mg														Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr			
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In		Sn	Sb	Te	I	Xe		
Cs	Ba	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn			
Fr	Ra	Ac																		

Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr

Metals

Essential elements for humans (daily requirement: 25 mg)

Non metals

Presumably essential elements

- Symptoms of deficiency: Mg (muscle cramps), Fe (anemia), Mn (infertility)
- Toxic effects in case of high doses (therapeutic width)
- Occurrence of non essential elements (e.g. Rb: 1.1 g / 70 kg) and of contaminations (e.g. Hg)

Metal content of a human body (70 kg)

Ca	1000 g	Sn	20 mg
K	140 g	V	20 mg
Na	100 g	Cr	14 mg
Mg	25 g	Mn	12 mg
Fe	4.2 g	Mo	5 mg
Zn	2.3 g	Co	3 mg
Cu	72 mg	Ni	1 mg

Low concentration: use for catalysis

Non metals: O (45500 g), C (12600 g), H (7000 g), N (2100 g), P (700 g)

Metal content of a human body (70 kg)

Earth's Crust		Human Body	
Element	%	Element	%
O	47	O	63
Si	28	C	25.5
Al	7.9	H	9.5
Fe	4.5	N	1.4
Ca	3.5	Ca	0.31
Na	2.5	P	0.22
K	2.5	K	0.08
Mg	2.2	S	0.06

- Week correlation to distribution of the elements in the earth's crust (there: O > Si > Al > Fe...)
- Consequence: optimized mechanisms for uptake and storage of the inorganic elements
- Good correlation to distribution of the elements in sea water

Functions of “inorg. elements” – summary

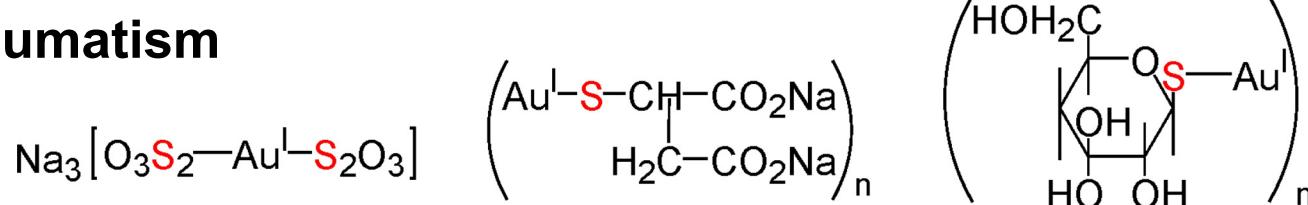
- Assembly of structures (DNA, biomineralization), endo- and exoskeletons. **Ca, Mg, Zn, Si**
- Information carriers (muscle contractions, nerve function). **Na, K, Ca, Mg**
- Activation of enzymes. **Mg, Ca**
- Formation, metabolism and degradagation of organic compounds by Lewis acid/base catalysis. **Zn, Mg**
- Transfer of electrons (energy conversion), **FeI/FeIII/FeIV**, stable due to bioligands
- Uptake, transport, storage and conversion of small molecules
 - $^3\text{O}_2$: Fe, Cu (conversion), Mn (generation)
 - N_2 : Fe, Mo, V (conversion to ammonia)
 - CO_2 : Ni, Fe (reduction to methane)

Most prominent “bioelements”

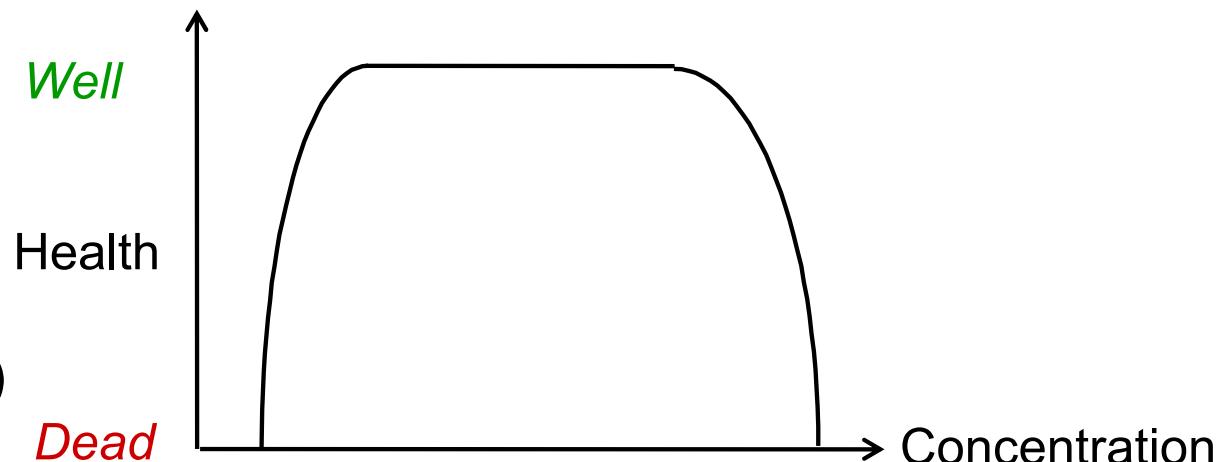
- Na^+ , K^+ : Electrolytes
- Mg^{2+} : Chlorophyll, energy production ($\text{ATP} \rightarrow \text{ADP}$), skeleton
- Ca^{2+} : muscle functions, Hydroxylapatite $\text{Ca}_5(\text{PO}_4)_3(\text{OH})$, CaCO_3
- $\text{V}^{\text{IV}/\text{V}}$, $\text{Mo}^{\text{IV}/\text{VI}}$, $\text{W}^{\text{IV}/\text{VI}}$, $\text{Mn}^{\text{II}/\text{III}/\text{IV}}$, $\text{Fe}^{\text{II}/\text{III}}$, $\text{Ni}^{\text{II}/\text{III}}$, $\text{Cu}^{\text{I}/\text{II}}$: electron transfer
- Fe and Cu: transport and storage of oxygen
- Fe^{II} , Fe^{III} : Magnetite (Fe_3O_4)
- Co: Cobalamin, e.g. Vitamin-B₁₂
- Zn^{2+} : Enzymes, zincfinger (gen. transcription), stabilization of proteins
- Si^{IV} : bones; SiO_2 /silicagel
- P^{V} : Hydroxyapatite, ATP, cell membrane, DNA
- $\text{Se}^{\text{-II}}$: Selenocysteine
- F^- : Fluorapatit ($\text{Ca}_5(\text{PO}_4)_3\text{F}$) teeth; Cl^- : besides HCO_3^- most important free anion, I^- : hormones of the thyroid, radiation therapy

Application of metals in medicine 1

- Li^+ : Treatment of depression (Li_2CO_3 , low doses)
- Gd^{3+} : Contrast agent (NMR)
- BaSO_4 : Contrast agent (radiography)
- ${}^{99}\text{mTc}$: radio diagnostics (thyroid)
- Au(I) : Rheumatism

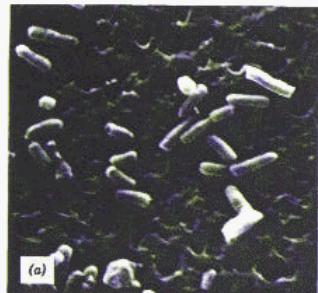
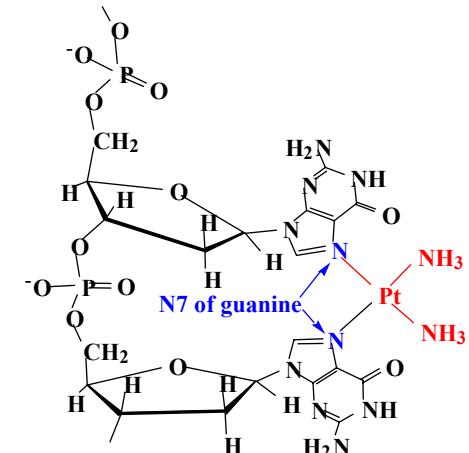
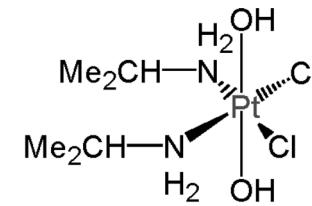
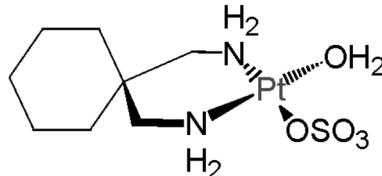
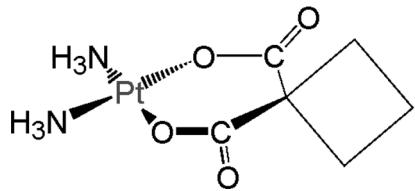


- Sb(III) : Eczema
- Bi(III) : Gastric ulcer
- Cd(II) : Carboanhydrase
(*Thalassiosira weissflogii*)



Application of metals in medicine 2

- Pt(II): Cisplatin (*cis*-[Pt(NH₃)₂Cl₂]), chemotherapy
(inhibition of cell division, no inhibition of cell growth)



Filamentous growth of bacteria



Treated on day 8, tumour completely regressed by day 14.
Died of old age 3 years later.

Untreated
died day 21
tumour 3 g.

Terms related to bioinorganic chemistry

- Active center: Location in an enzyme where the specific reaction takes place
- Apo-enzyme: An enzyme that lacks its metal center
- ATP: Adenosine 5'-triphosphate
- Biomembrane: Sheet like assemblies of proteins and lipids (bilayer)
- Charge-transfer complex: An aggregate of two or more molecules in which charge is transferred from a donor to an acceptor.
- Chlorophyll: Magnesium complex of a porphyrin in which a double bond in one of the pyrrole rings (17-18) has been reduced. A fused cyclopentanone ring is also present
- Cluster: Metal centers grouped close together which can have direct metal bonding or through a bridging ligand, e.g. ferredoxin
- Cobalamin: Vitamin B12, substituted corrin-Co(III) complex
- Coenzyme: A low-molecular-weight, non-protein organic compound (often a nucleotide) participating in enzymatic reactions
- Cofactor: An organic molecule or ion (usually a metal ion) that is required by an enzyme for its activity. It may be attached either loosely (coenzyme) or tightly (prosthetic group).
- Cooperativity: The phenomenon that binding of an effector molecule to a biological system either enhances or diminishes the binding of a successive molecules, e.g. hemoglobin

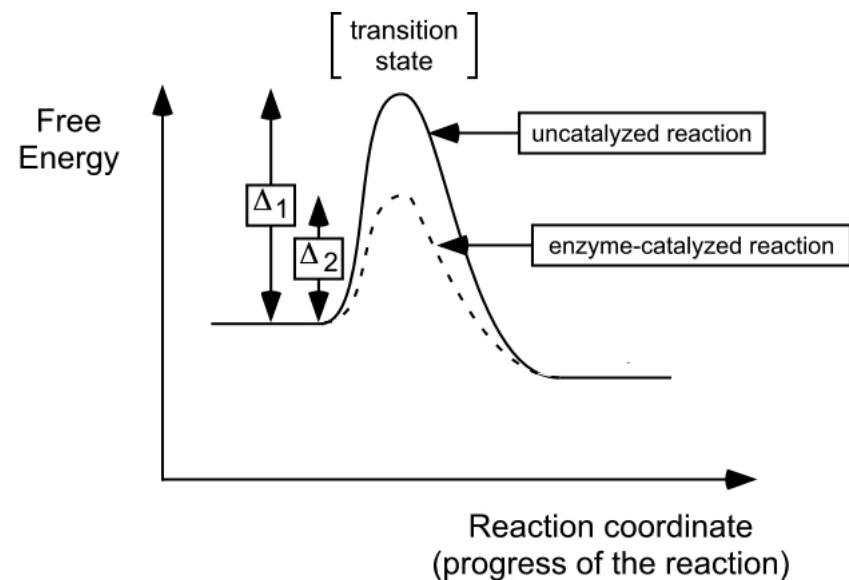
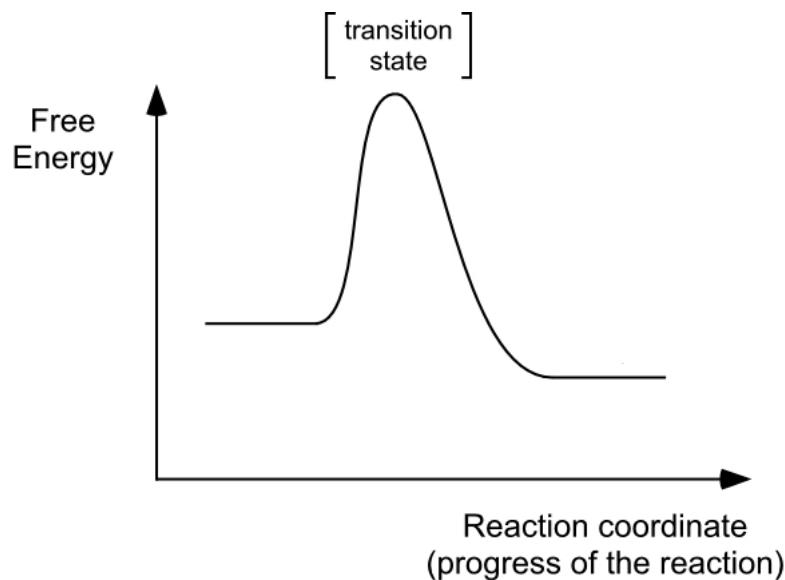
Terms related to bioinorganic chemistry

- **Entatic state:** A state of an atom or group which has its geometric or electronic condition adapted for function. Derived from entasis (Greek) meaning tension
- **Enzyme:** A macromolecule that functions as a biocatalyst by increasing the reaction rate
- **Heme:** A near-planar coordination complex obtained from iron and dianionic porphyrin
- **Hemoglobin:** A dioxygen-carrying heme protein of red blood cells
- **Holoenzyme:** An enzyme containing its characteristic prosthetic group(s) and/or metal(s)
- **Ion channel:** Enable ions to flow rapidly through membranes in a thermodynamically downhill direction after an electrical or chemical impulse.
- **Ionophore:** A compound which can carry specific ions through membranes
- **Ion pumps:** Enable ions to flow through membranes in a thermodynamically uphill direction by the use of an energy source. They open and close upon the binding and subsequent hydrolysis of ATP, usually transporting more than one ion towards the outside or the inside of the membrane
- **Photosynthesis:** A metabolic process in plants and certain bacteria, using light energy absorbed by chlorophyll and other photosynthetic pigments for the reduction of CO₂, followed by the formation of organic compounds
- **Substrates:** A compound that is transformed under the influence of a catalyst

Basics of enzyme reactions (catalysis)

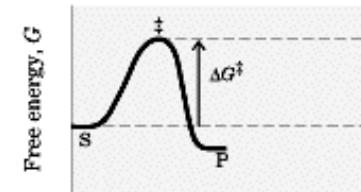
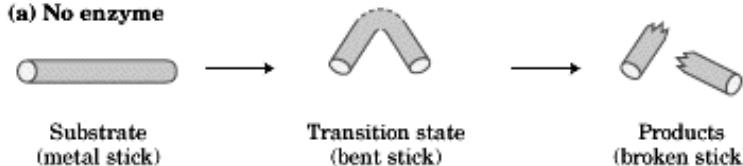
Catalysts...

- Accelerate chemical reactions (rate enhancement)
- Participate in reactions but are not consumed
- Stabilize the transition state (lower activation energy)
- DO NOT alter the chemical equilibrium, $\Delta \Delta(E) \sim \text{reaction rate}$
- Reduce the amount of time required to attain the equilibrium

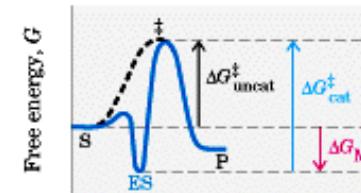
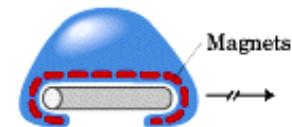


Catalysis- principle of complementarity

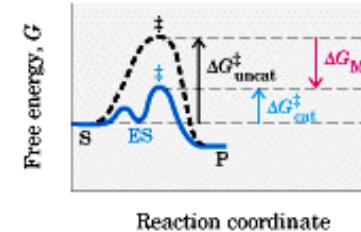
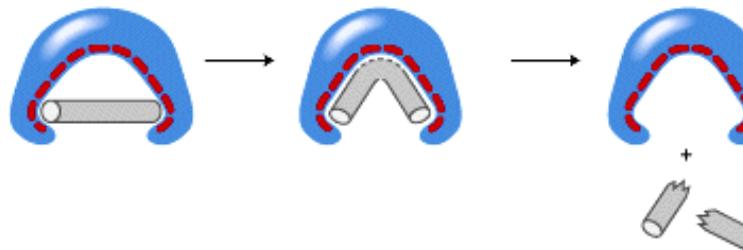
(a) No enzyme



(b) Enzyme complementary to substrate



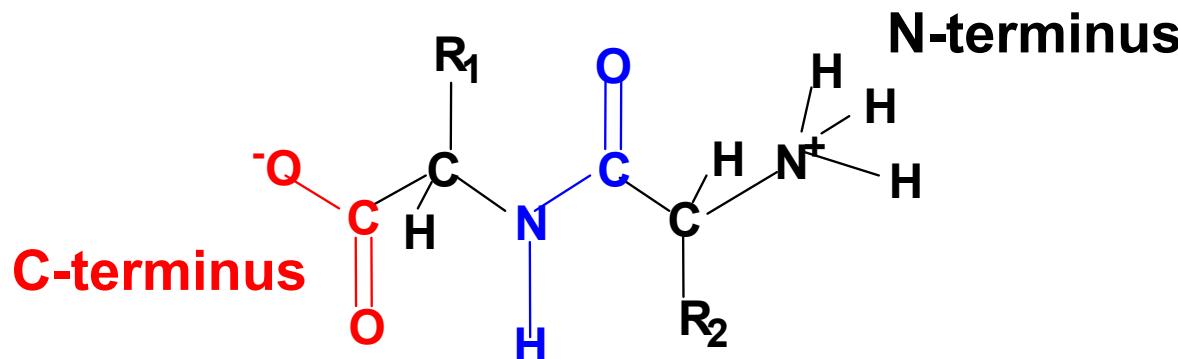
(c) Enzyme complementary to transition state



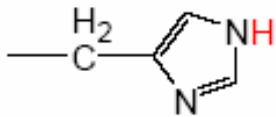
- The active sites of enzymes tend to be more complementary to the transition states than they are to the actual substrates
- Preformation of the transition state by strained enzyme (entatic state)
- Energy aspect: small activation energy, statistical aspect: more productive encounters between reaction partners, kinetic aspect: faster reaction

Ligands- Proteins

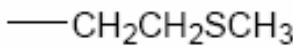
- Proteins consist of α -amino acids, connected via peptide bonds



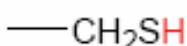
- Metal coordination by functional groups in the side chain (R)



Histidine (both N atoms available, metal-metal bridging possible, pKa ~6)



Methionine



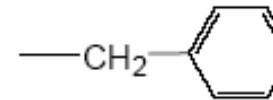
Cysteine

(metal-metal bridging, pKa ~ 8)

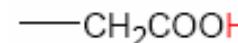


Selenocysteine

("non-innocent ligand")



Tyrosine
("non-innocent ligand")

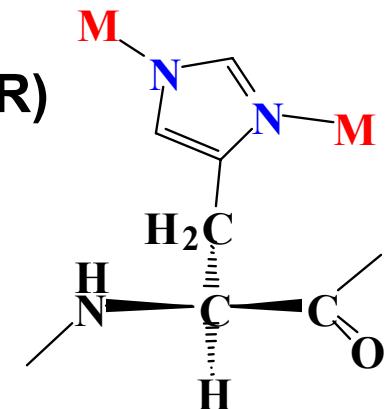


Aspartic acid



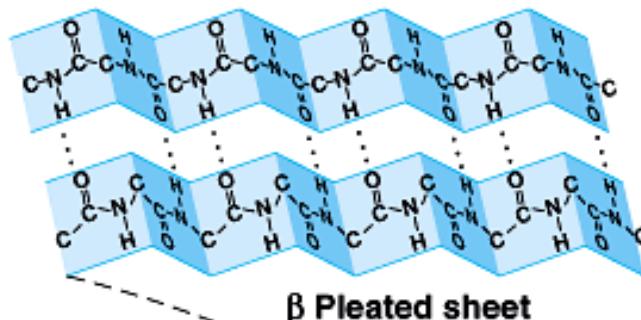
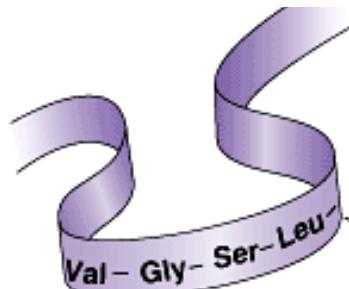
Glutamic acid

pKa ~ 4

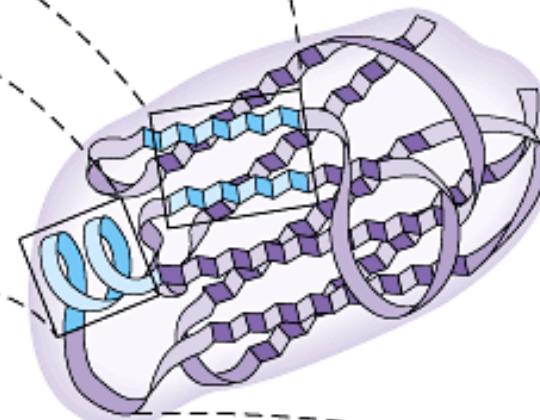


Proteins- Structure

Primary structure:
Sequence of amino acids



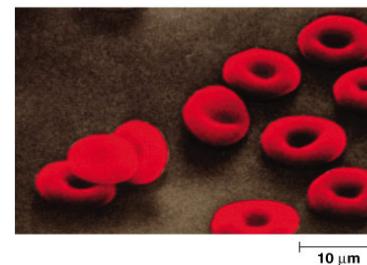
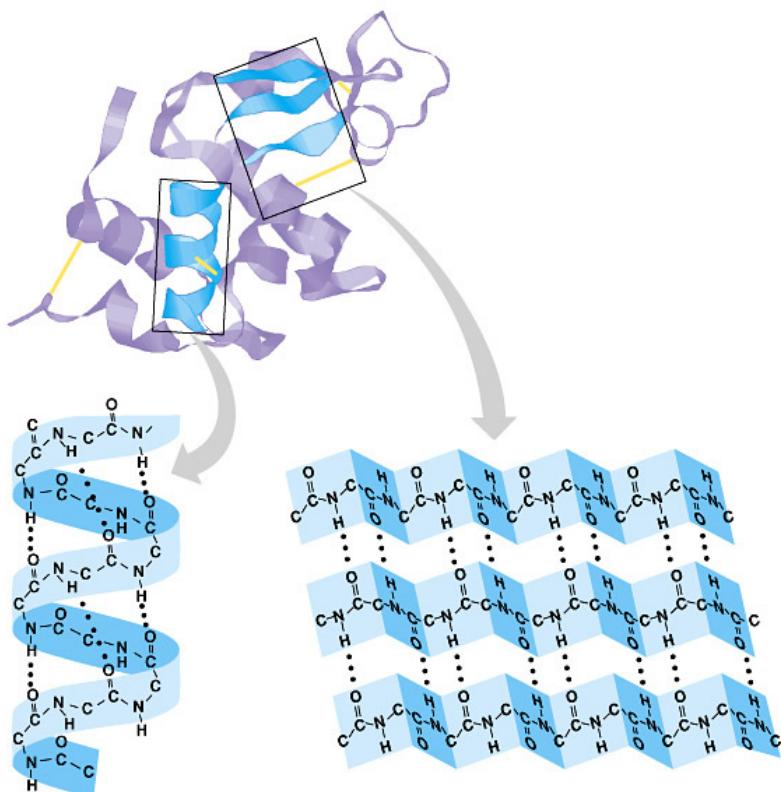
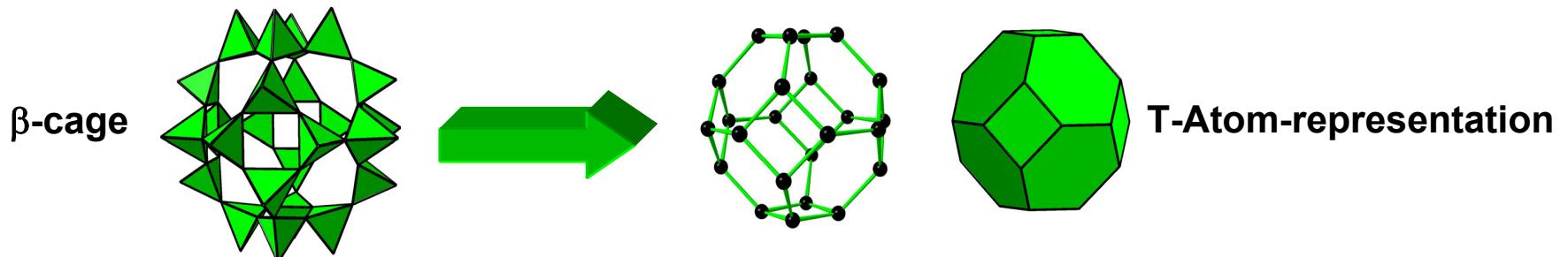
Tertiary structure:
Shape of entire protein



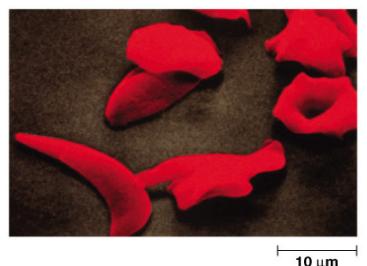
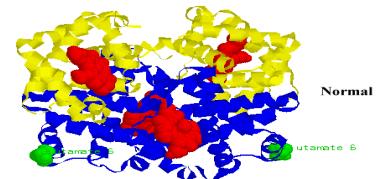
Secondary structure:
Shapes formed within regions of the protein

Quaternary structure:
Structures formed by interaction of several subunit

Proteins- Structure representation



(a) Normal red blood cells and the primary structure of normal hemoglobin

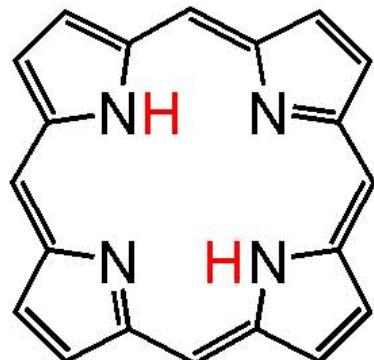


(b) Sickled red blood cells and the primary structure of sickle-cell hemoglobin



Cyclic ligands- Porphyrin complexes

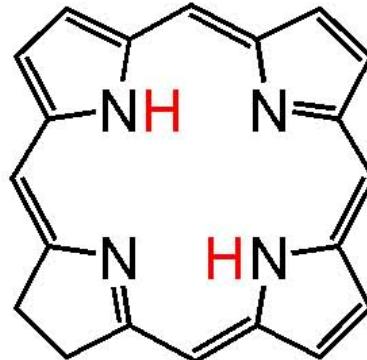
- Unsaturated tetradeятate macrocyclic ligands
- Coordination of otherwise labile divalent metal ions
- Porphyrin complexes: chelate-effect and size selective as host
- Porphyrin: very stable, Hückel-aromatic ($18 \text{ el} = 4n + 2$), colored



Porphyrin

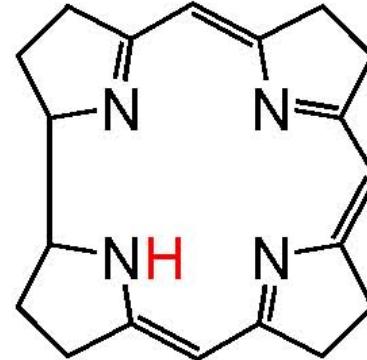
Hemoglobin
Myoglobin
Peroxidases

} Fe



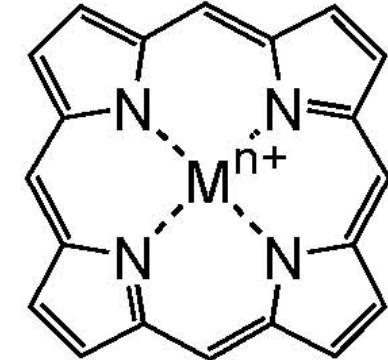
Chlorin

Chlorophyll (Mg^{2+})
Tunichlorine (Ni^{2+})



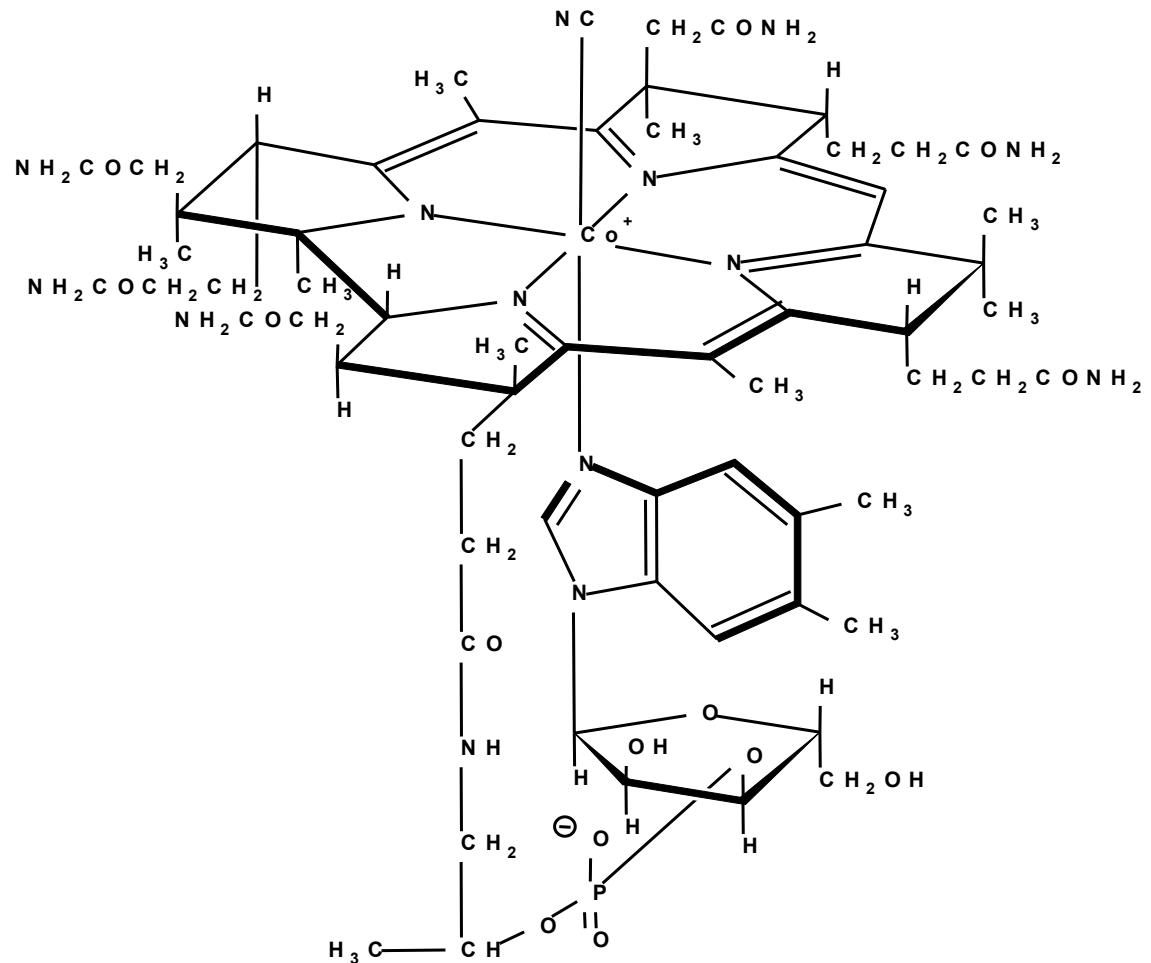
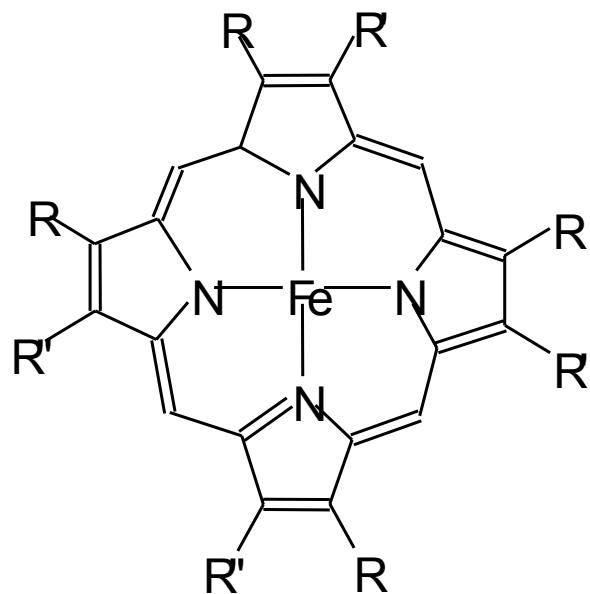
Corrin

Cobalamin (Co^{2+})



Metallaporphyrin
complex

Cyclic ligands- Porphyrin complexes

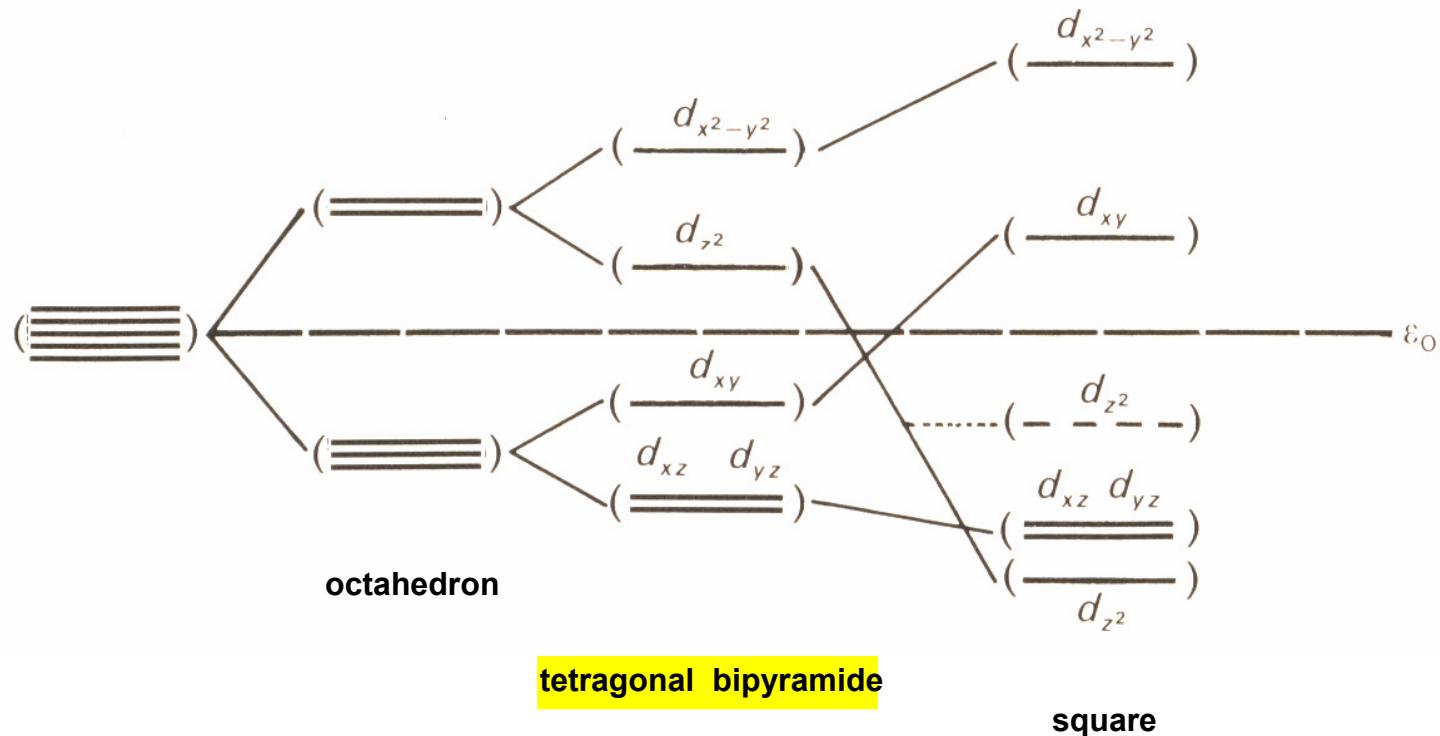


Vitamine B₁₂

Cyclic ligands- Porphyrin complexes

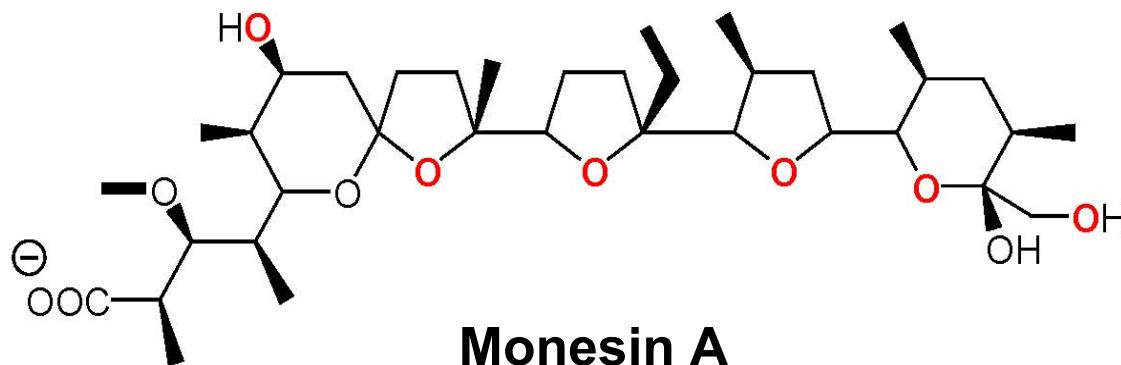
Bonding

- Most complexes are (nearly) planar → two open coordination sites (e.g. substrate...)
- Usually low spin complexes → Fe(II) high spin in deoxy-hemoglobin out-of-plane position
- Fine tuning of electronic configuration by conformation and axial ligands
- Splitting of d orbitals (CFT):



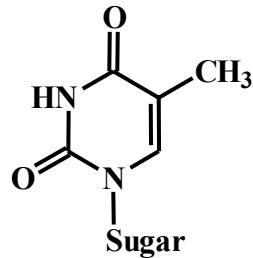
Cyclic ligands- Ionophores

- Bonding of hard cations by macrocycles or quasi-macrocycles
- Coordination by O, N
- Production of a lipophilic shell around hard cations
- Size, charge selective

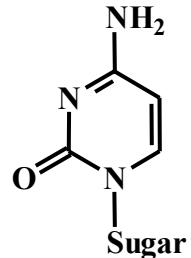


Nucleobases- building units of DNA, RNA

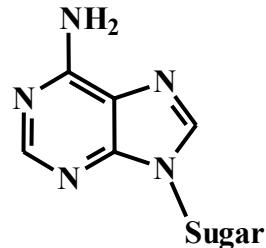
- DNA, RNA: macromolecules consisting of nucleotides as building units
- Nucleotides: Pentose, pyrimidine- or purine base, phosphate group (1:1:1)
- Information carriers as ligands (oligo- and polynucleotides)
- Coordination by nucleobases or by phosphate groups (Zn^{2+} , Mg^{2+})



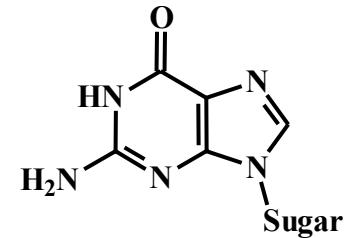
Thymine



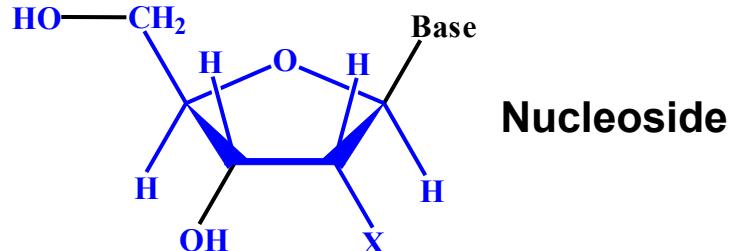
Cytosine



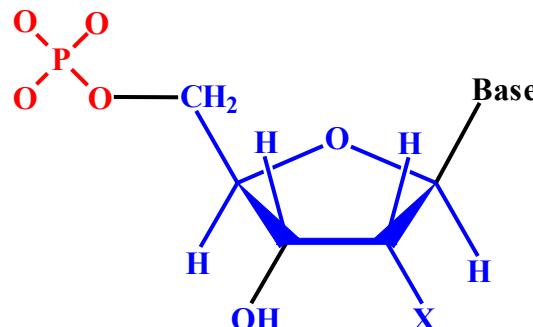
Adenine



Guanine



Nucleoside



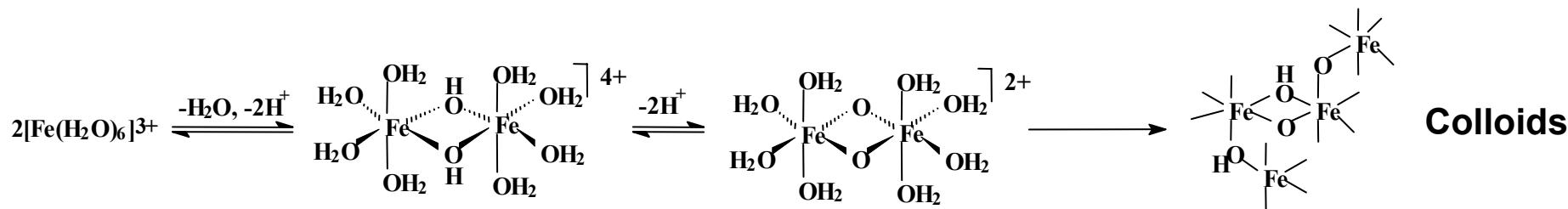
Nucleotide
 $X = \text{OH}$: Ribose
 $X = \text{H}$ Desoxiribose

3.

Coordination for uptake,
transport and storage (Fe)

Some basic properties of Fe

- Usually oxidation of Fe(II)aq to Fe(III)aq under in-vivo conditions
- Insalubrious function of Fe(II) high spin: formation of radicals, e.g. Fe(II) h.s. + ${}^3\text{O}_2 \rightarrow \text{Fe(III)} + \text{O}_2^-$
- Fe(III) non soluble at pH ~7, coordination of Fe(III) by complexing agents unambiguous
- Condensation to clusters and colloids

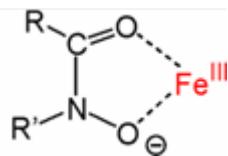


- Related affinity to different ligands (S, O, N)
- Switching from high- to low spin configuration (medium strength of ligand)
- Complexation interconnected with electron and proton transfer:

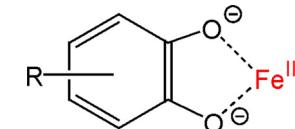


Siderophores (microorganisms)

- Two groups of chelating agents



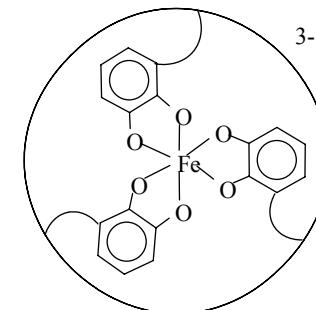
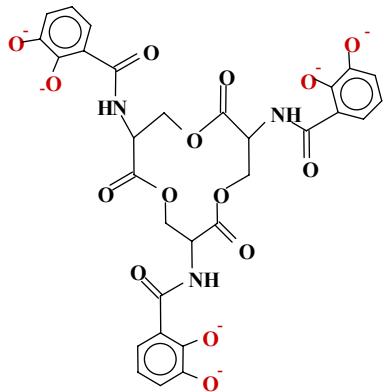
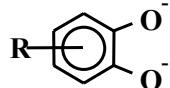
Hydroxamate



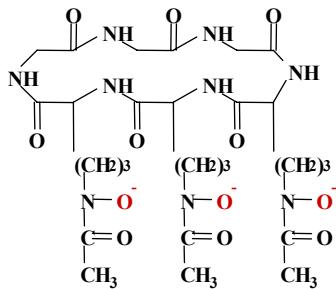
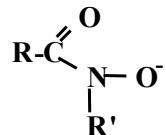
Catecholate

- Antibiotic function, highly active (!), octahedral coordination of Fe(III)

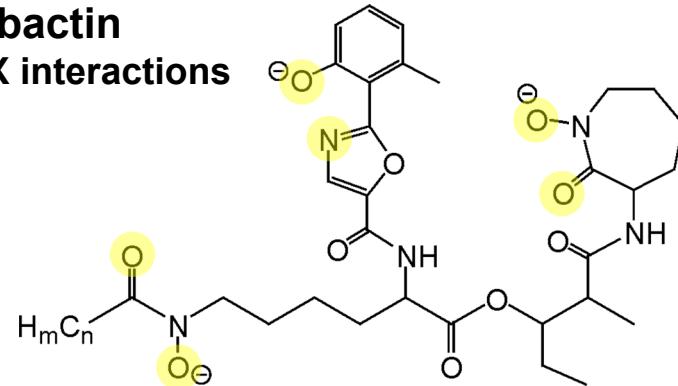
Catecholate



Hydroxamate

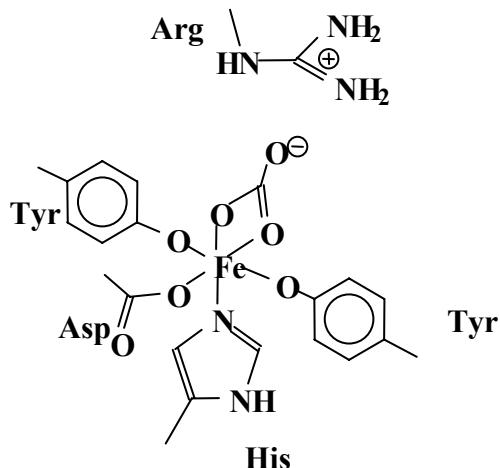


Mycobactin
Different M-X interactions



Proteins (complex organisms)

Transport: Transferrin

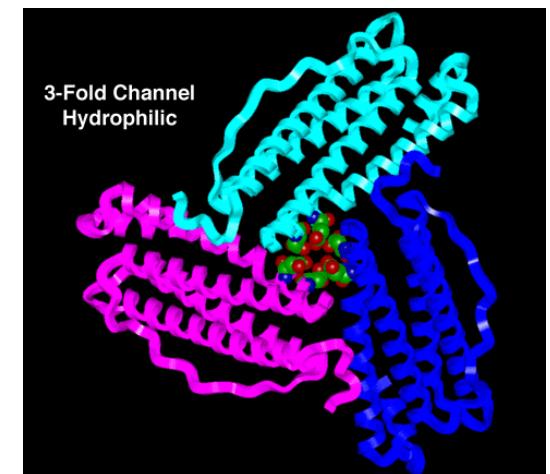
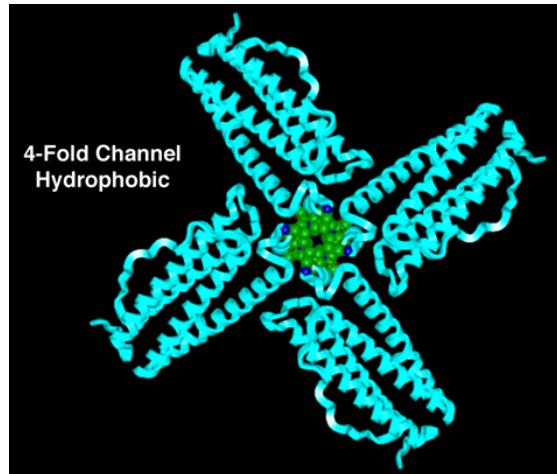
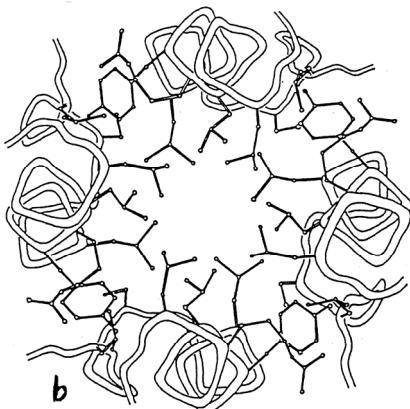


Characteristics

- Coordination of Fe by carboxy- and phenolate groups of residues
- Uptake of two Fe(III) and one HCO_3^-
- Stability of complexes decrease with decreasing pH
- High affinity of Apotransferrin, protection against infections
- Not very specific (Cr^{3+} , Al^{3+} , Cu^{2+} , Mn^{2+} ...)
- Release of Fe(III): Reduction to Fe(II) and binding by porphyrine

Proteins (complex organisms)

Ferritin (Storage)



Characteristics

- High symmetry of Apoferritin: *F*432
- Hollow sphere built from proteins (inner dia.: ~ 7 nm, outer dia. ~ 13 nm)
- Capacity: up to 4500 Fe³⁺, biomineralization (?)
- Carboxylate groups for Fe(III) binding, core-structure related to Ferrihydrite ($\text{Fe}_{10}\text{O}_6(\text{OH})_{18}$)
- Exchange via channels (dia. 1nm), tuning of hydrophilic/hydrophobic character via residues
- Release of Fe as Fe(II) via hydrophilic channels

4.

Hard ions: Na^+ , K^+ ,

Mg^{2+} , Ca^{2+}

Basic characteristics

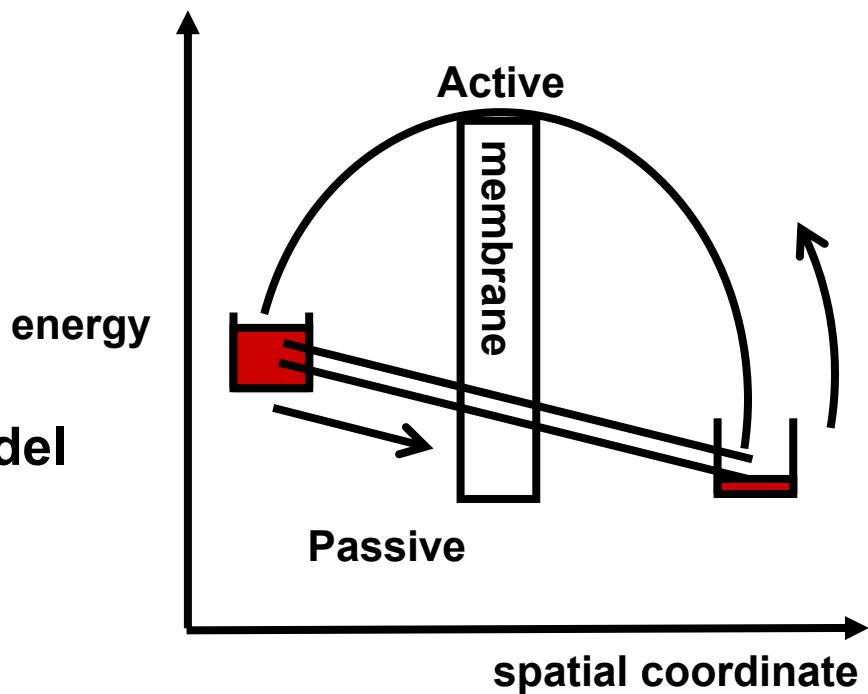
	Na ⁺	K ⁺	Mg ²⁺	Ca ²⁺
Ionic radius, Å	1.16	1.52	0.86	1.14
Charge/radius ratio	0.86	0.66	2.32	1.75
Coordination number	6	6-8	6	6-8
Preferred donors	O	O	N,O	O
	multidentate chelates		bidentate chelates	
Concentration (mmol/kg)				
Intracellular	11	92	2.5	0.1
Extracellular	152	5	1.5	2.5

Labile bonding in solution, fast diffusion along a concentration gradient

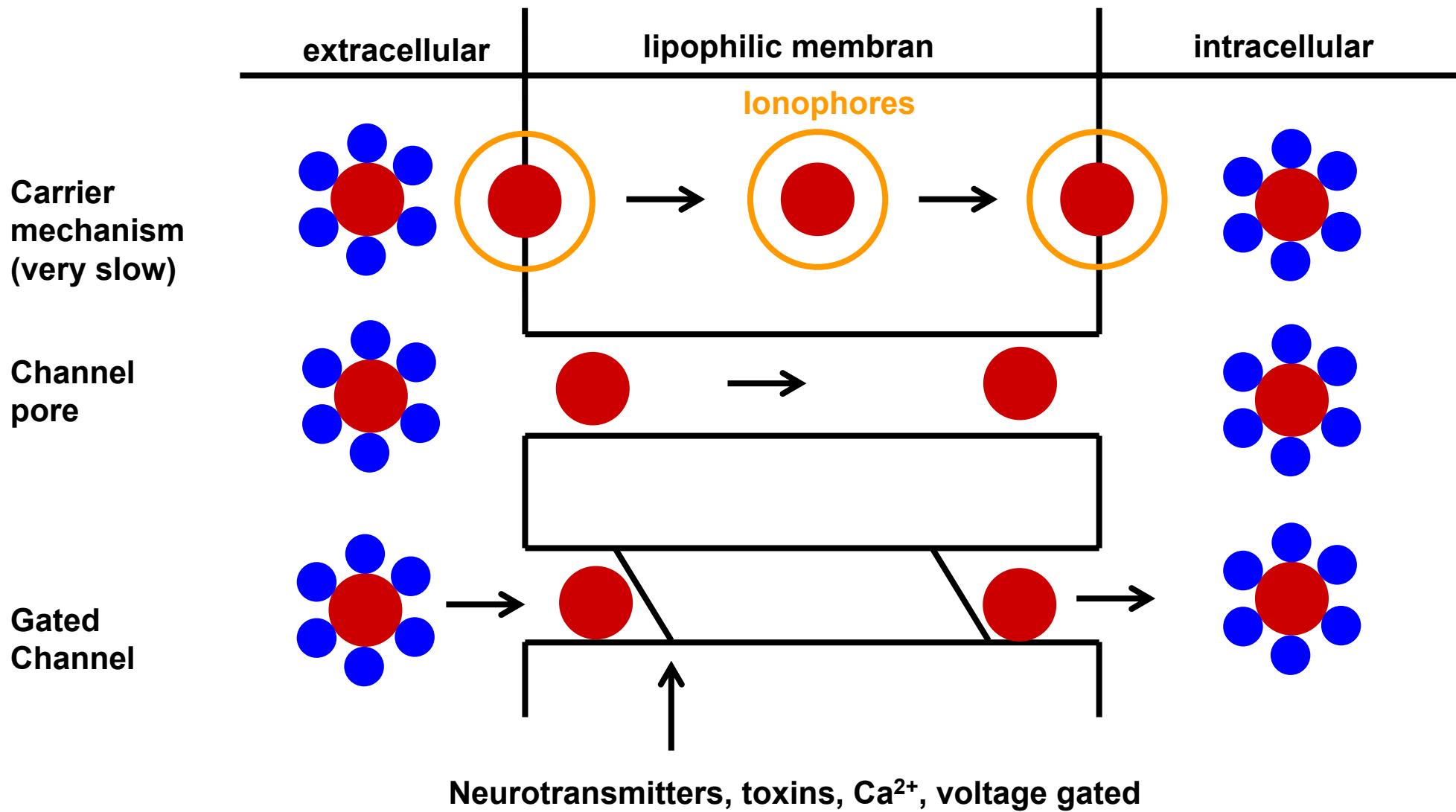
Na, K: Inhom. distributed electrolytes

- Function
 - Stabilization (membrane, nucleotides, enzymes)
 - Fast information transfer by diffusion (highly volatile, diffusion control)
 - Maintenance of the concentration gradient
 - Pump storage model
 - Active Transport:
Ion pumps, proteins triggered by enzymes
 - Passive transport:
Ionophores, chelating ligands
Ion channels, proteins

Pump-storage model

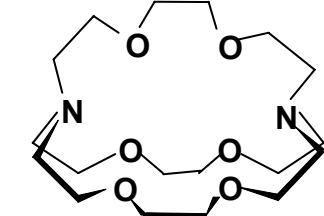
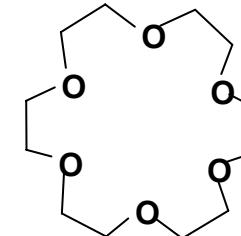


Passive Ion transport- summary

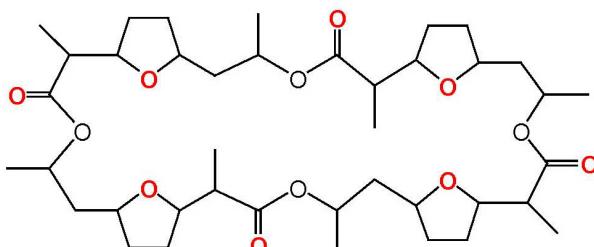


Passive transport: Ionophores

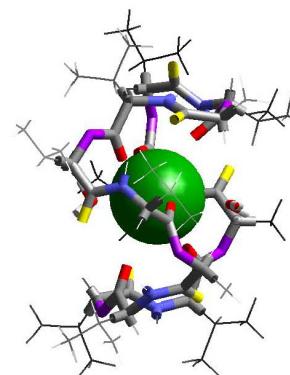
- Analogs from the lab: crown ethers, cryptands (macrocycles)
- Chelate effect (thermodyn. and kinet. stable)
- Size/charge selectivity
- Distinct polarity inside / outside the complex
- Template effect of alkali metal (conformational change of ionophore)
- Selectivity depending on number of coordination centers of ligand
- Selectivity adjusted by optimum conformation
- Natural ionophores act as antibiotics
- Transport of alkali metal through biological membranes (carrier mechanism)
- Perturbation of electrolyte level in bacteria



Higher selectivity



Nonactin



K-Valinomycin
3d coordination by folding

Passive transport: Ion channels

Transmembrane protein with tube structure

Gramicidin A: a simple example

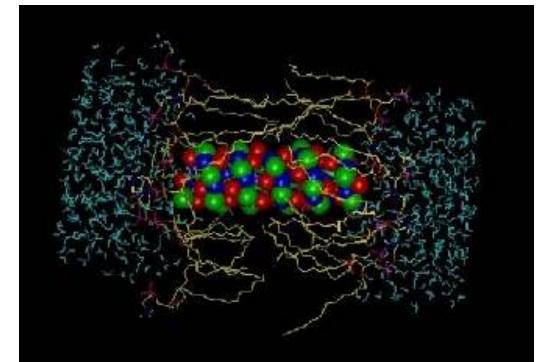
- Formed from integral membrane proteins
- Length 3 nm, two tubes in a row can perorate a membrane

More complex channels

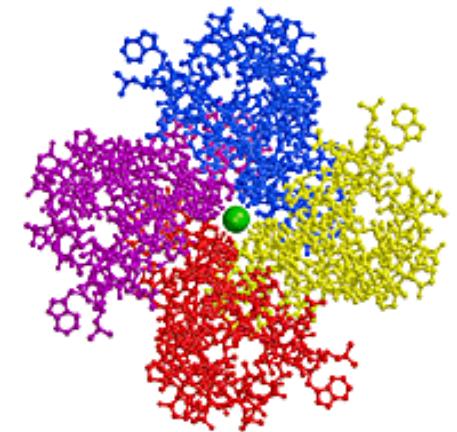
- Building units: 4-5 homologous membrane proteins (helices)
- Immediate lining contains polar groups (fixed charges)
- Specific due to diameter, and chemistry inside the channel

Gates of the channels

- Gate functioning important subject of pharmaceutical research
- Opening by neurotransmitters, Ca^{2+} , electrical pulses...
- Blocking as important biological function,
e.g. blocking of K^+ channels by H^+ → sensing of “sour”



antiparallel helical
aggregate of proteins



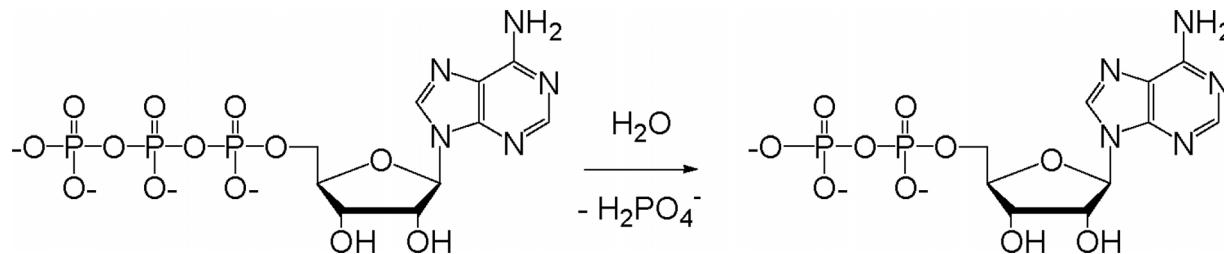
K^+ channel,
NP 2003 to Mc Kinnon

Active transport: Ion pumps- overview

Transmembrane protein acting against concentration gradient

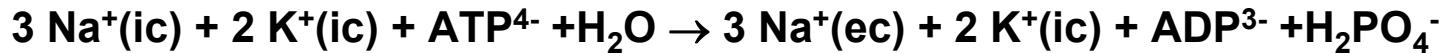
Structure, function:

- Carboxylate groups (hydrophilic) for binding the active species
- Selectivity by formation of E1 and E2 which are produced via (de)phosphorylation
- Energy-consuming ion transport mechanism, energy production by hydrolysis of ATP



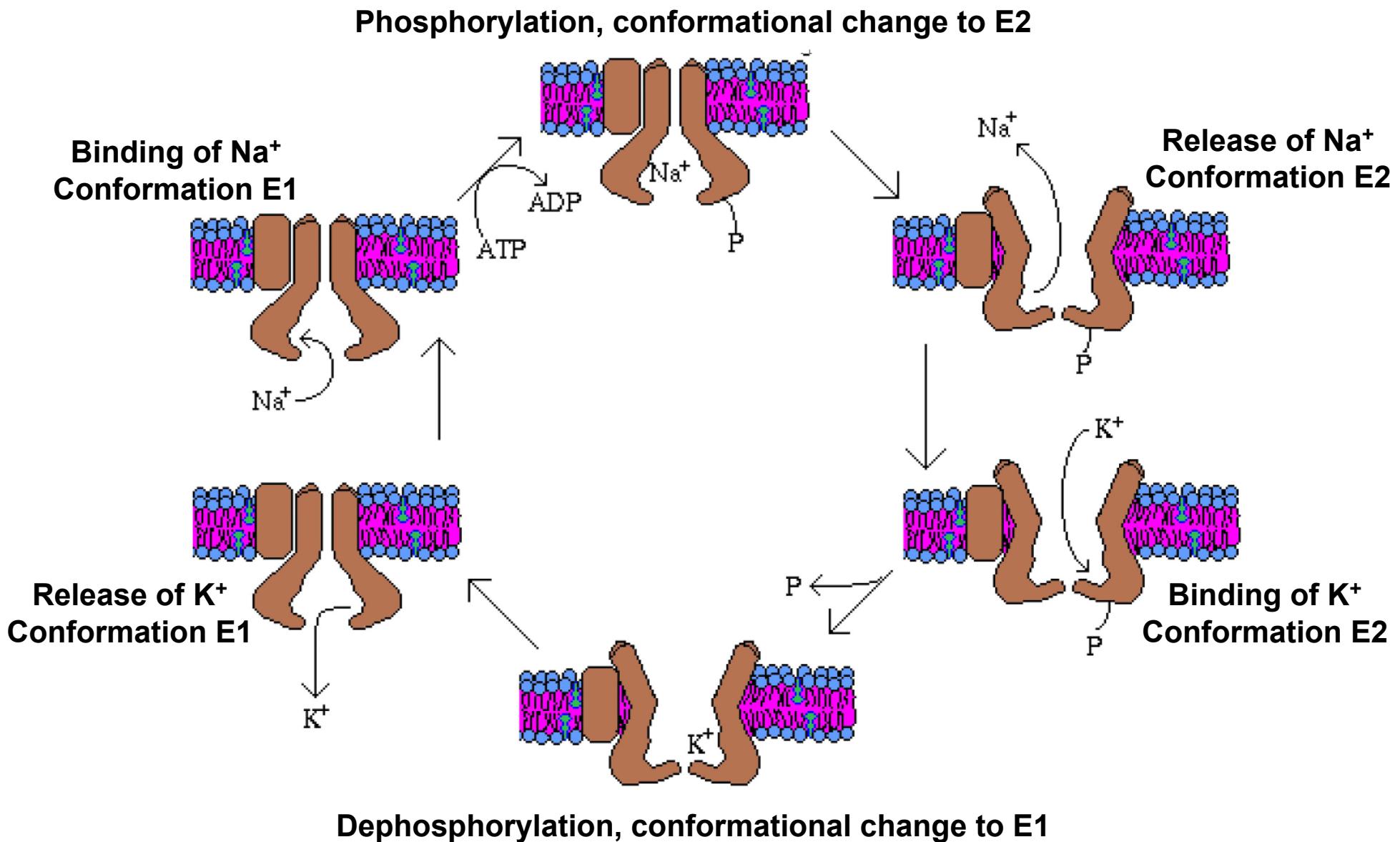
- Symport: simultaneous transport of anions and cations (K^+/Cl^-) in same direction
- Antiport: transport of ions of the same charge in opposite direction (H^+/K^+)

Example: $Na^+/K^+/MgATPase$ (Mg^{2+} -catalysis)



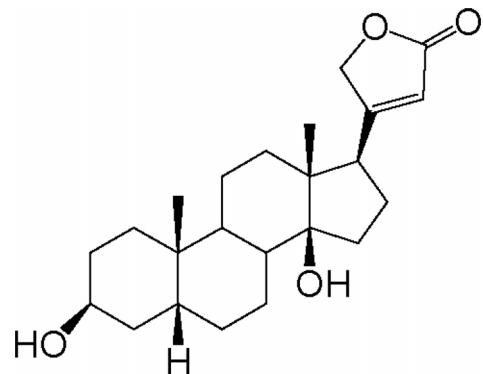
ic: intracellular, ec: extracellular

$\text{Na}^+/\text{K}^+/\text{MgATPase}$: Flip-Flop-mechanism



Toxins affecting ion transport (examples)

Digitoxigenine (Foxglove) Blocking of Na^+/K^+ /ATPase



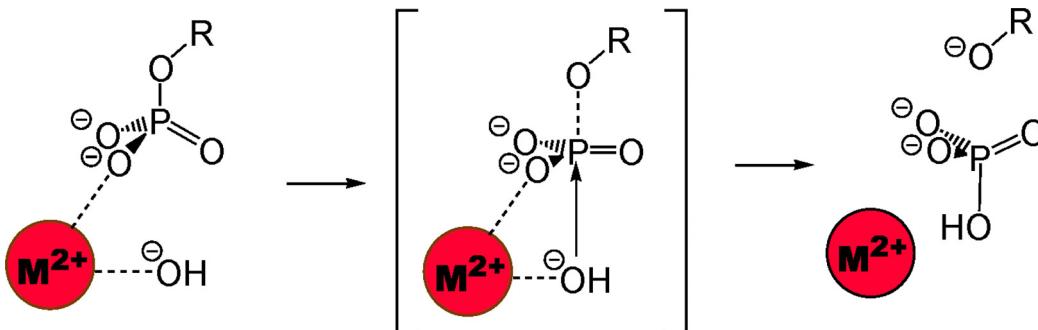
- Inhibition of dephosphorylization
- Increase of Na^+ and Ca^{2+} due to antiport system
- Consequence: Muscle contraction (heart!)



Fugu fish (Tetrodotoxin) Blocking of Na^+ channels

Mg: Catalysis of phosphate transfer

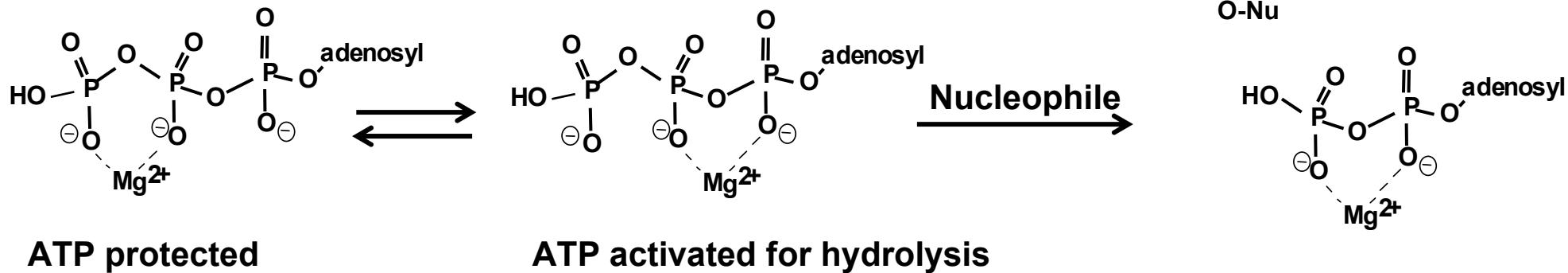
- Mg²⁺: very hard, CN = 6, prefers multiple charged ligands (phosphates)
- Functions:
- Charge compensation, e.g. ATP (reduction of the high concentration of negative charges)
- Polarization, increase of nucleophilic character: Mg²⁺ + OH₂ → [Mg...OH]⁺ + H⁺
- Fixation of the reactants
- Mechanism: S_N2 with pseudorotation
 - Conformational changes during Na/K pumping



On the average a human adult synthesizes and uses an amount of ATP per day which corresponds to the body weight!

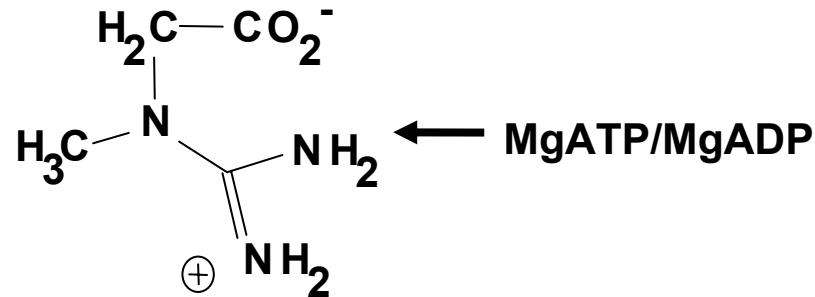
Mg: phosphate transfer- examples

Hydrolysis of ATP (Na/K/ATPase pump)



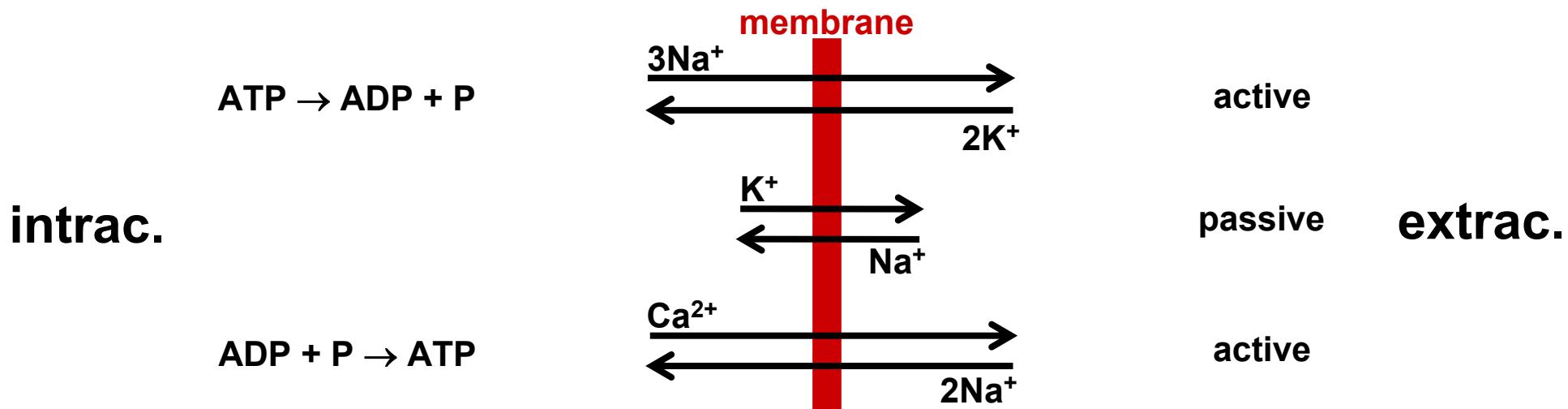
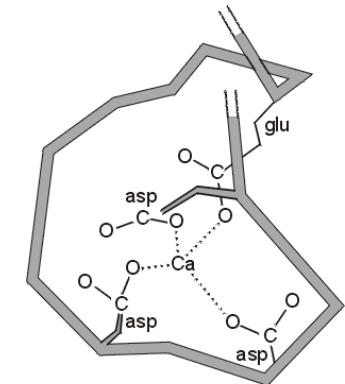
Phosphate transfer to creatine via MgATP

Phosphate transfer to glycerate (formation of 2-phosphoglycerate)



Ca: great variety of functions

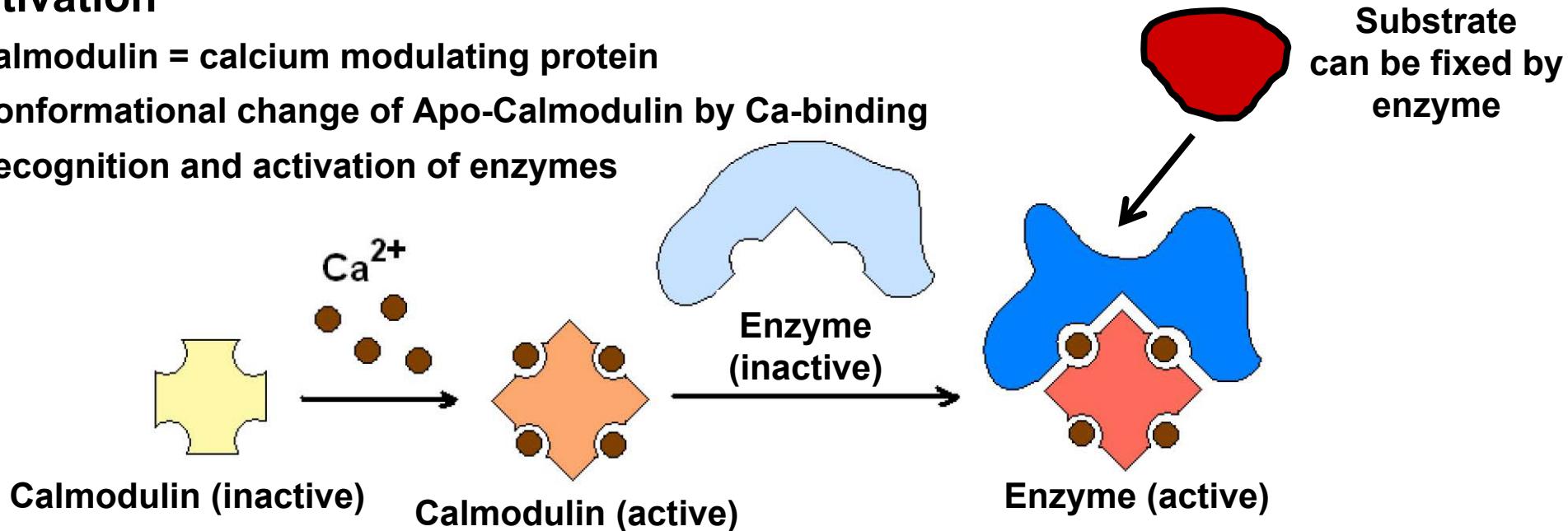
- Structural function
- Biominerization (1 kg), 10g/70kg in non-solid form
- Strong influence on protein folding
- Second messenger-, trigger-, activation funftion
- Binding to acidic μ^2 -carboxy groups of proteins
- High coordination numbers (7, 8), irregular coordination geometry
- Lability of complexes allows fast structural changes
- High concentration gradient (Ca^{2+} pumps in sarcoplasmic reticulum)
- Interconnections of electrolyte transport



Ca: Activation of enzymes, energetic processes

Activation

- Calmodulin = calcium modulating protein
- Conformational change of Apo-Calmodulin by Ca-binding
- Recognition and activation of enzymes



Muscle contraction (Translation of electrical stimulus into chemical stimulus)

- Depolarization of membrane, opening of Na-channels
- Release of Ca^{2+} from acidic storage protein: Calsequestrin
- Calsequestrin contains up to 50 Ca-binding sites, carboxylate groups (Glu, Asp)
- Uptake of Ca^{2+} by Troponin C, coupling with ATP Hydrolysis...

Biomineralization: CaCO_3 - Modifications

- Occurrence e.g. in shells, otholiths...
- Control of morphology and orientation by organic component
- Carboxy-groups of peptide side chains (Asp, Glu...)
- Oxidized carbohydrates...
- Lab-examples:
 - Spindel-shaped calcite crystals in presence of malonic acid
 - Presence of stearic acid supports the formation of disc shaped Vaterite crystals
- Four important modifications of CaCO_3

Calcite, Calcite, {104}

stable, structural relation to rock salt
{104} frequently at the surface of shells

Aragonite

metastable, otholithes of fishes,
coral reef, pearls

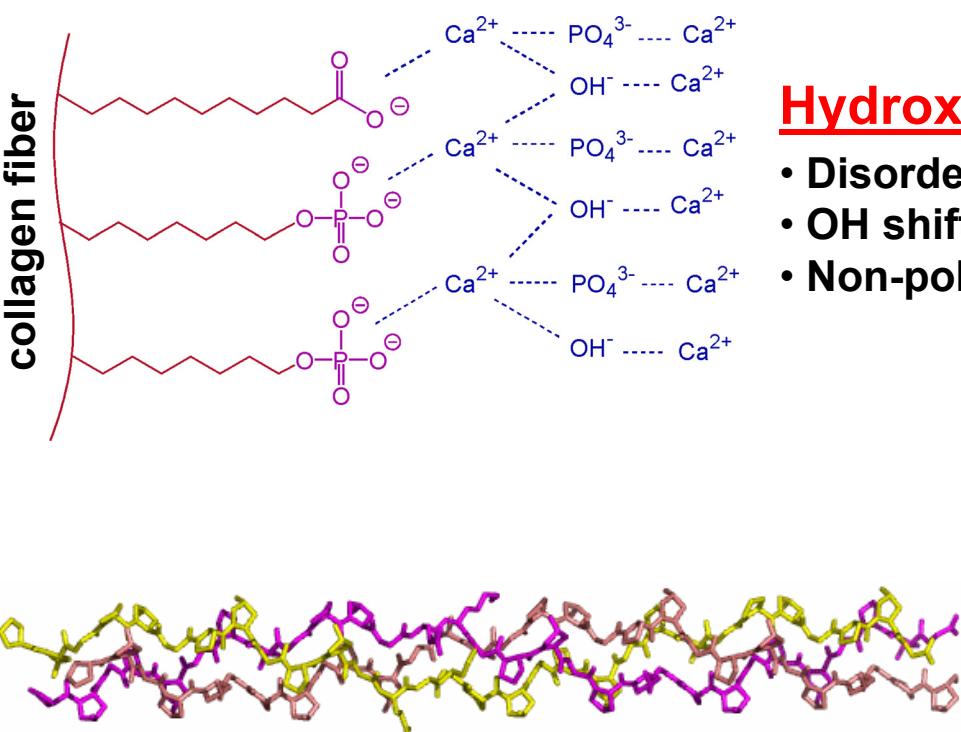
Vaterit

metastable, disordered (?), rare
formation of spherolithes

Amorphous CaCO_3 , formation of spherolites

Biomineralization: Apatite $\text{Ca}_5(\text{PO}_4)_3\text{X}$

- Occurrence e.g. in bones and teeth (enamel: larger crystals, F-substituted)
- Highly effective mechanisms for Ca-transport (humans: 0.7g/day)
- Collagen: template function, serves for defined orientation of apatite crystals
- Binding of Ca via carboxy groups of osteocalcin or via phospho-proteins (?)

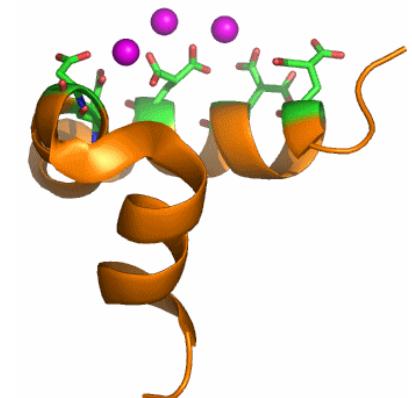


Hydroxyapatite

- Disordered structure
- OH shifted from mirror plane
- Non-polar structure ($P6_3/m$)

Osteocalcin

- Perfect match with apatite



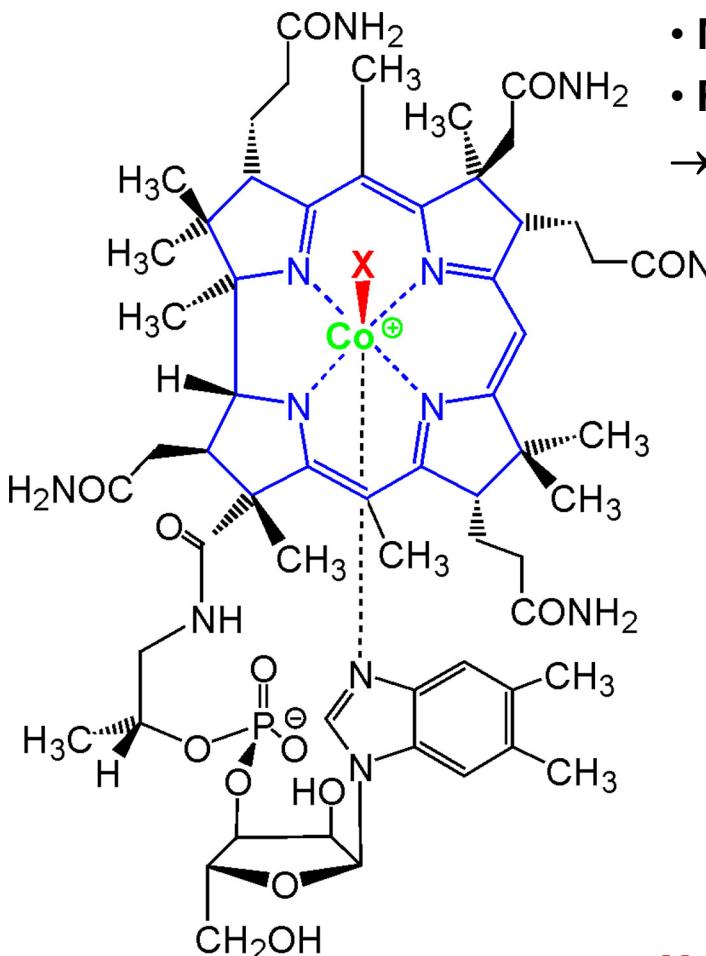
Collagen

- Three left handed helices combined to one right handed super helix
- [001](Apatite) parallel to collagen helices
- Composite material, no binding sites for Ca

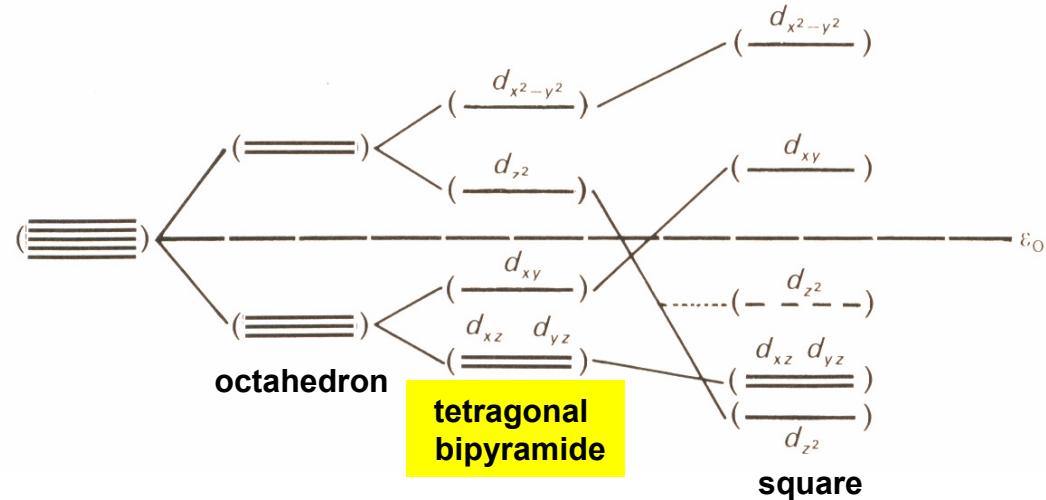
5.

Cobalamines

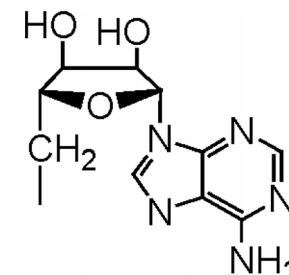
Basic molecular features



- Organometallic compound, low-spin configuration of Co^{3+}
- Macrocycle: Corrin (small, butterfly) + 5,6 Dimethylbenzimidazole
- Reduction: population of d_{z^2} ($\sigma^*(\text{Co}-\text{CH}_2-)$)
→ Decrease of axial coordination

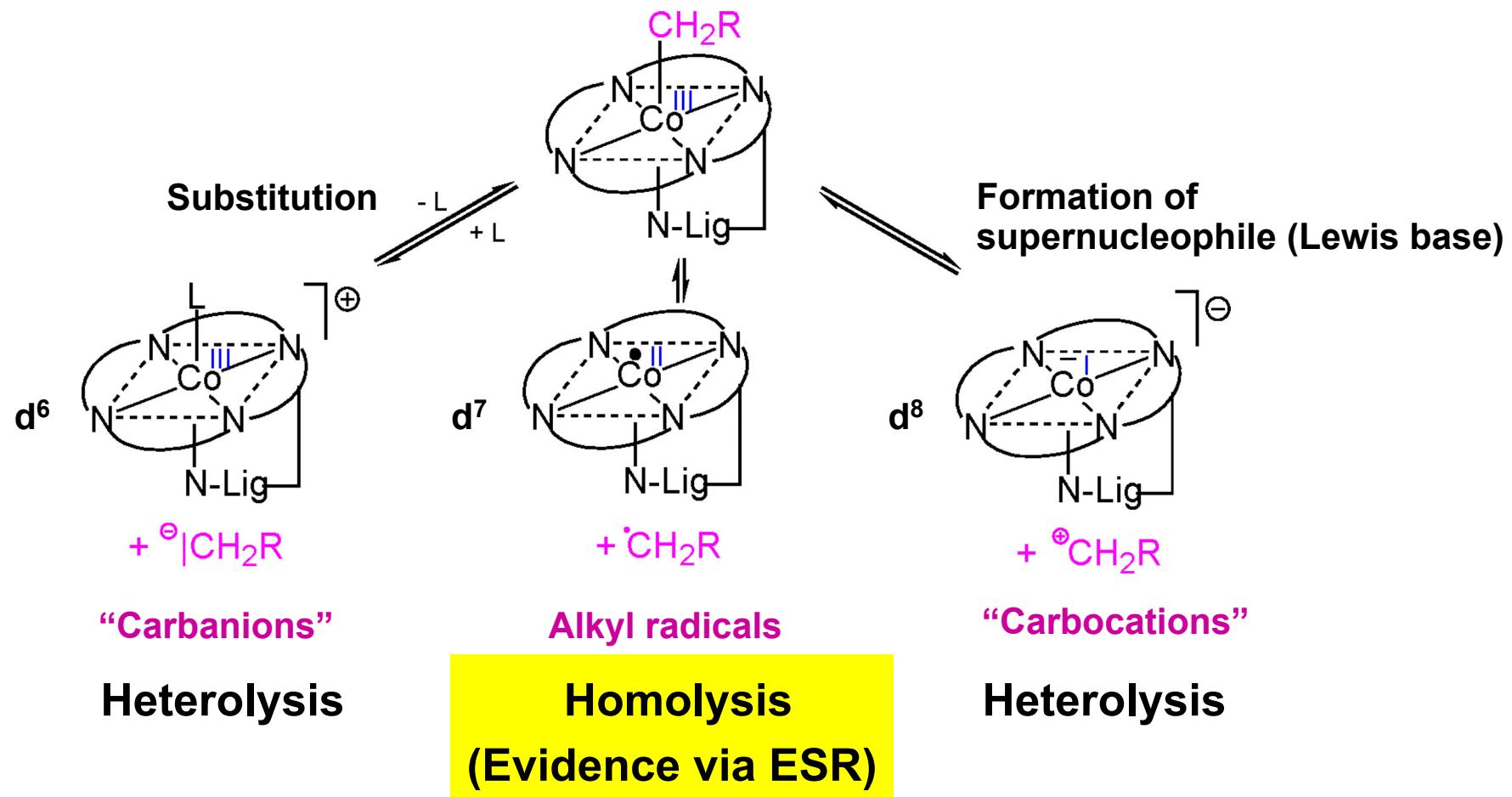


X = CH_3 , OH, CN (vitamin B₁₂),



5' deoxyadenosine
(Coenzyme B₁₂)

Reactions- types of Co-C bond cleavages

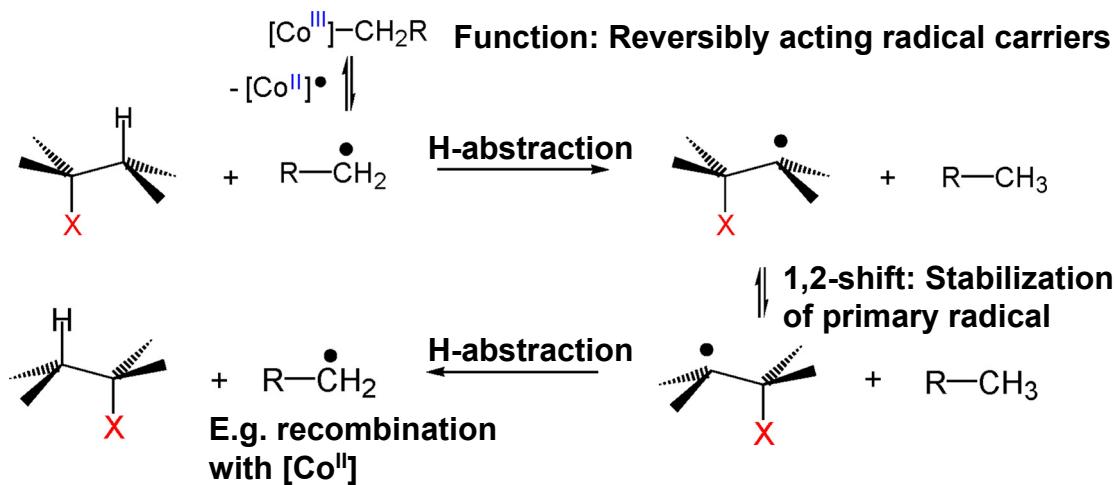


Determination of reaction pathway: N-ligand, Substrate, redox potential

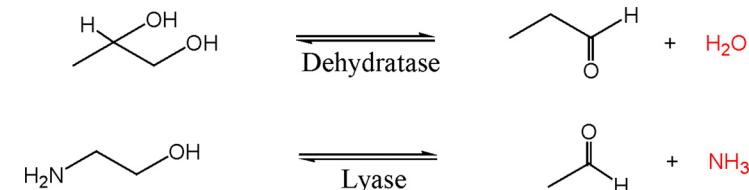
Reactions

- **Mutase activity:**

- 1,2-shift at saturated hydrocarbon centers (rearrangement)
- Function of apoenzyme: Decrease of Co-C bonding (el. transfer?), Protection of pr. radical
- Less amount of byproducts, stereoselectivity

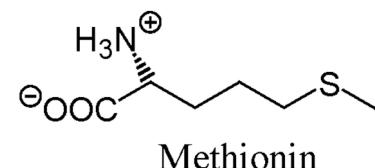


Examples:



- **Alkylation:**

- Alkylation of electrophilic substrates by carbanions, e. g. methylation of Hg²⁺ ((CH₃)Hg⁺)
- Methylation of homocysteine to methionine



6.

Metals in Photosynthesis

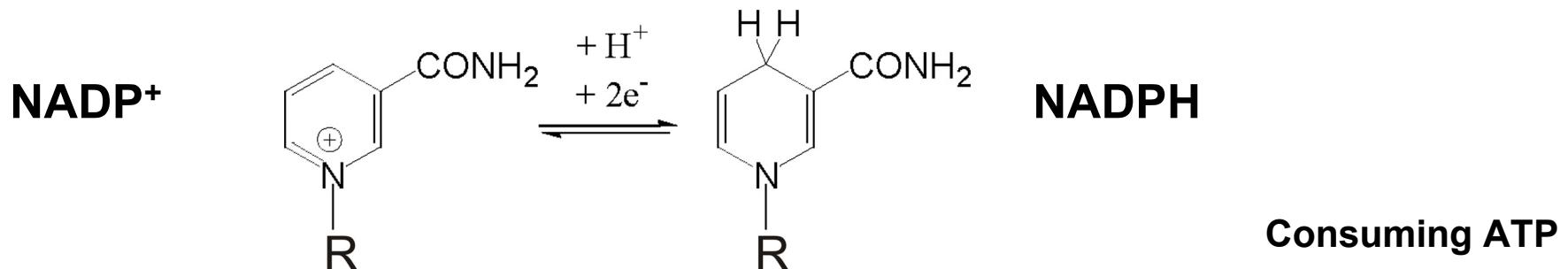
Mg, Mn, (Fe), (Cu), (Ca)

Fundamental aspects

- Photosynthesis: production of organic material and oxygen
- “Uphill-Catalysis” ($\Delta H = +470 \text{ kJ/mol}$), 200 billion tons of $(\text{CH}_2\text{O})_n$ / year



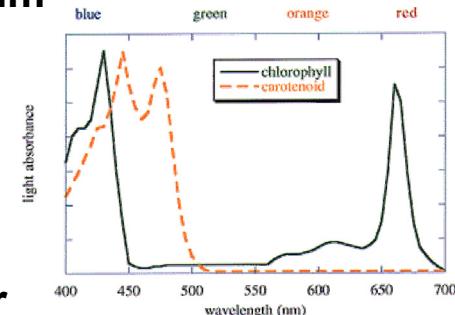
- Light induced charge separation, reduction of CO_2 , oxidation of H_2O
- Light harvesting by antenna pigments light harvesting
- Light reactions
- One PS for bacteria (~ PS II), two PS (PS I (P_{700}) and PS II (P_{680})) for green plants and algae
- Oxidation of water, oxidation of H_2S , $\text{H}_2\text{...}$, at least synthesis of ATP, production of H^+ gradient
- Dark reaction: $2(\text{NADPH} + \text{H}^+) + \text{CO}_2 \rightarrow 1/n (\text{CH}_2\text{O})_n + 2 \text{ NADP}^+ + \text{H}_2\text{O}$



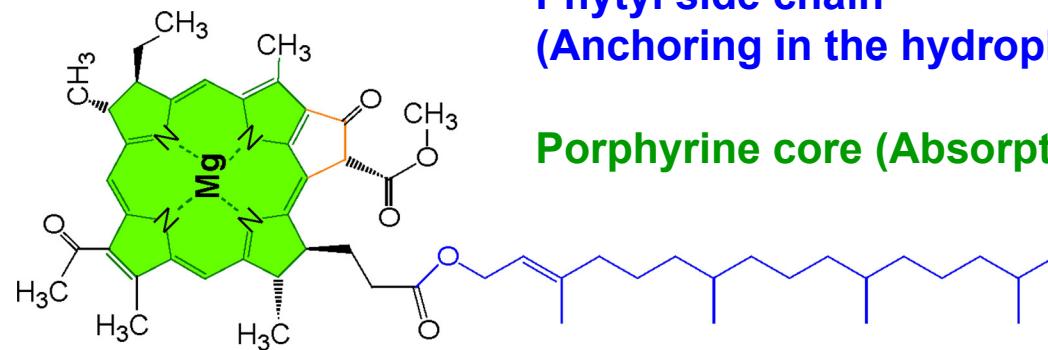
Compounds

Chromophors for light harvesting: chlorophylls, carotenoids (300!)

- Chlorophyll: absorption at short and long wavelength end of vis. spectrum
- $\pi(\text{HOMO}), \pi^*(\text{LUMO})$ -transition, Q-band (blue) and Soret-band (red)
- Broad spectral absorption range with high absorptivity
- Exciton transport: highly efficient and orientated transfer of energy
- Spectral overlap of optical bands of exciton source and exciton acceptor
- Anchoring of molecules by phytol side-chains and by peptide/Mg coordination (three point fixation, spatial organization)
- Mg as light element favorable for high efficiency (small spin-orbit coupling)



Bacteriochlorophyll a,
partially hydrogenated
Chlorine



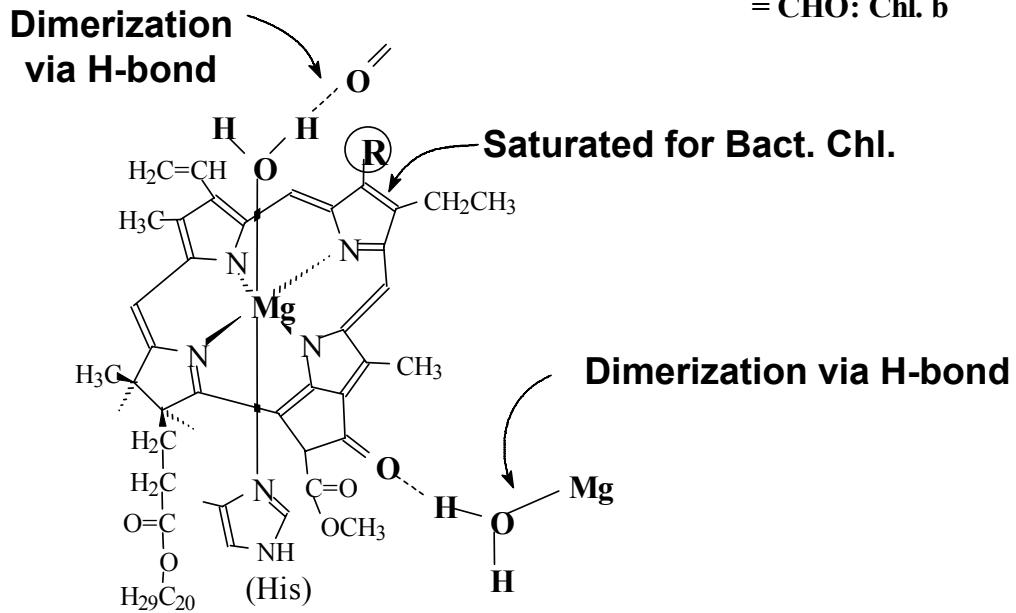
Phytol side chain
(Anchoring in the hydrophobic membrane)

Porphyrine core (Absorption of light)

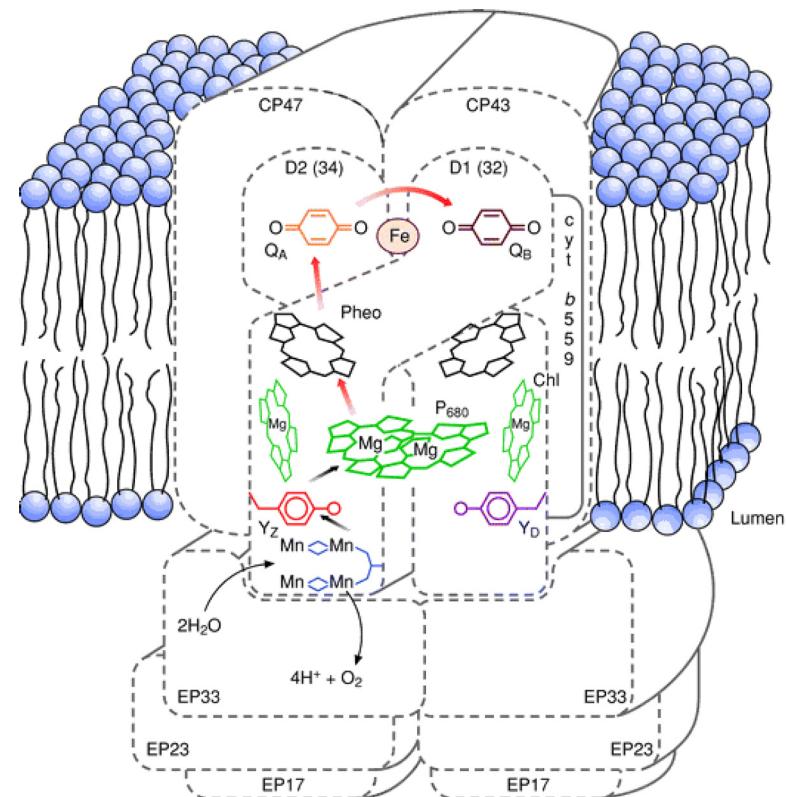
Compounds

Compounds for electron and proton transfer:

- Special pairs of chlorophyll (electron donor), single chlorophyll (BC, first acceptor)
 - Bacteriopheophytin (BP, secondary acceptor in PS II, BC without metal)
 - Quinones (third acceptor), Fe(His)₄Glu center (?) located on C₂
 - Fe,S-cluster compounds, Fe-Heme-proteins
 - Plastocyanine (Cu)
 - OEC (Mn, Ca)
- } Purple bacteria one PS



④ = CH₃: Chl. a
= CHO: Chl. b

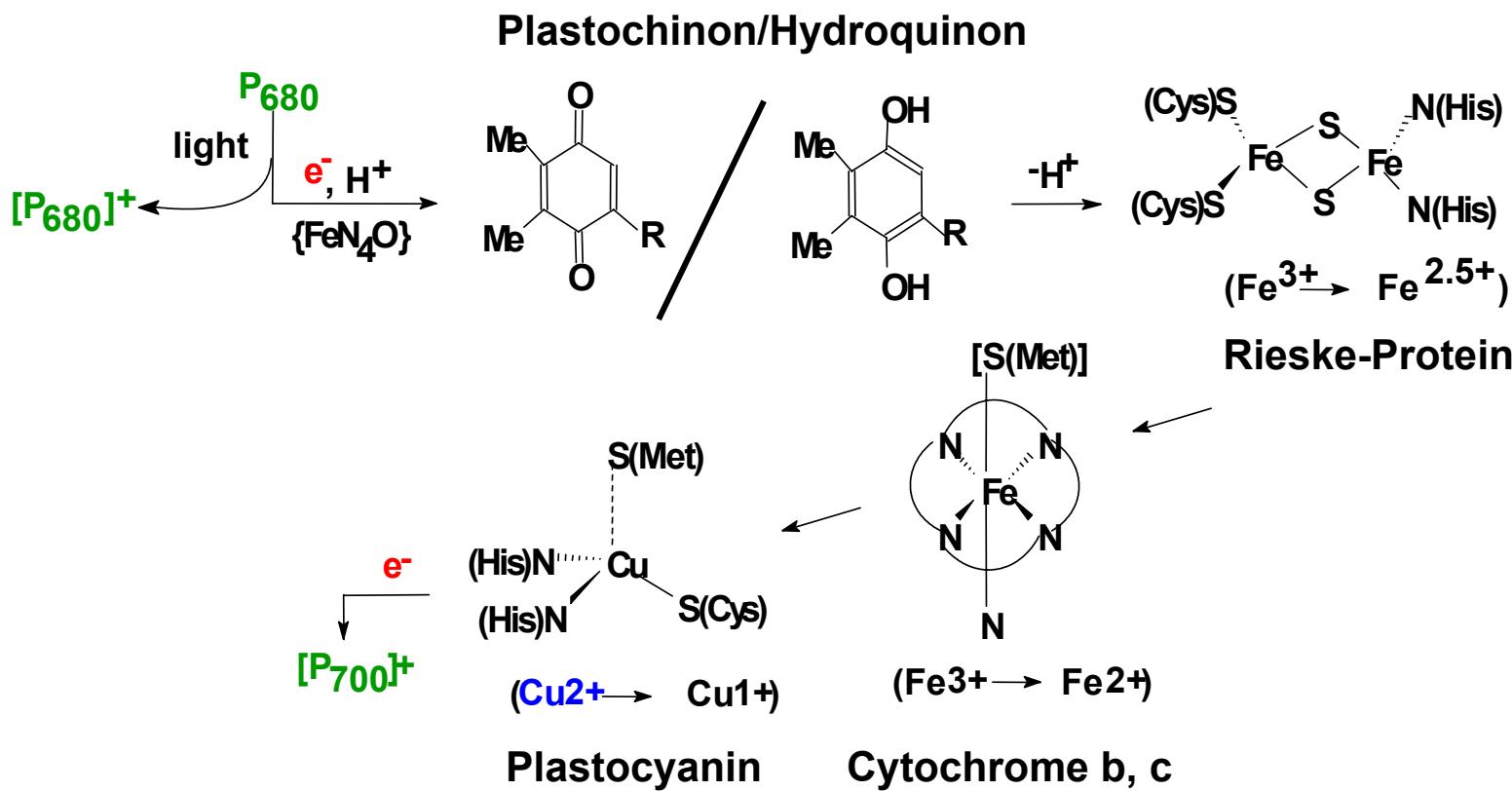


Electron transfer in light reactions



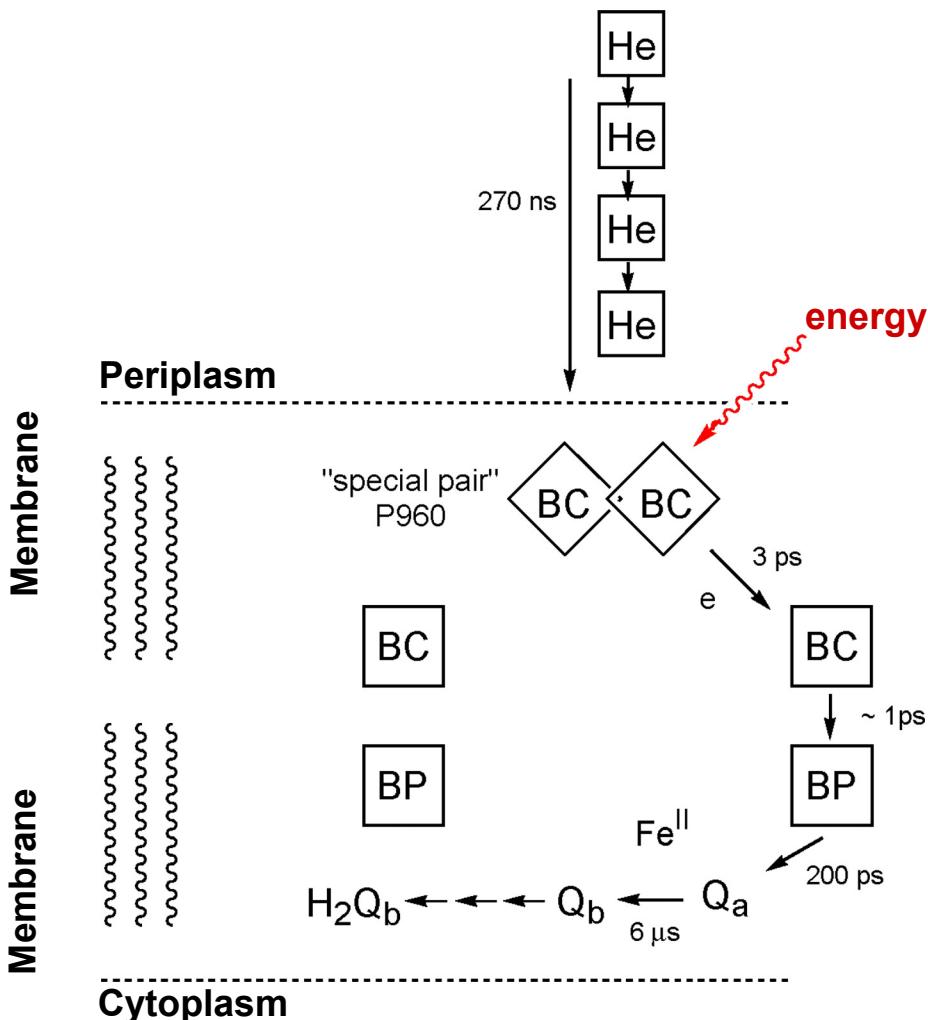
Light: $P_{680} \rightarrow P_{680}^+ + e^-$
 $2P_{680}^+ + H_2O \rightarrow 2P_{680} + \frac{1}{2}O_2 + 2H^+$ (cat. OEC)

Light: $P_{700} \rightarrow P_{700}^+ + e^-$,
 $P_{700}^+ + e^- \rightarrow P_{700}$
 $NADP^+ + 2e^- + 2H^+ \rightarrow NADPH + H^+$



PS II: Production of H⁺ and electrons

Special pair: dimer of porphyrines which acts as electron donor
(determined for reaction center of a bacteriochlorophyll)



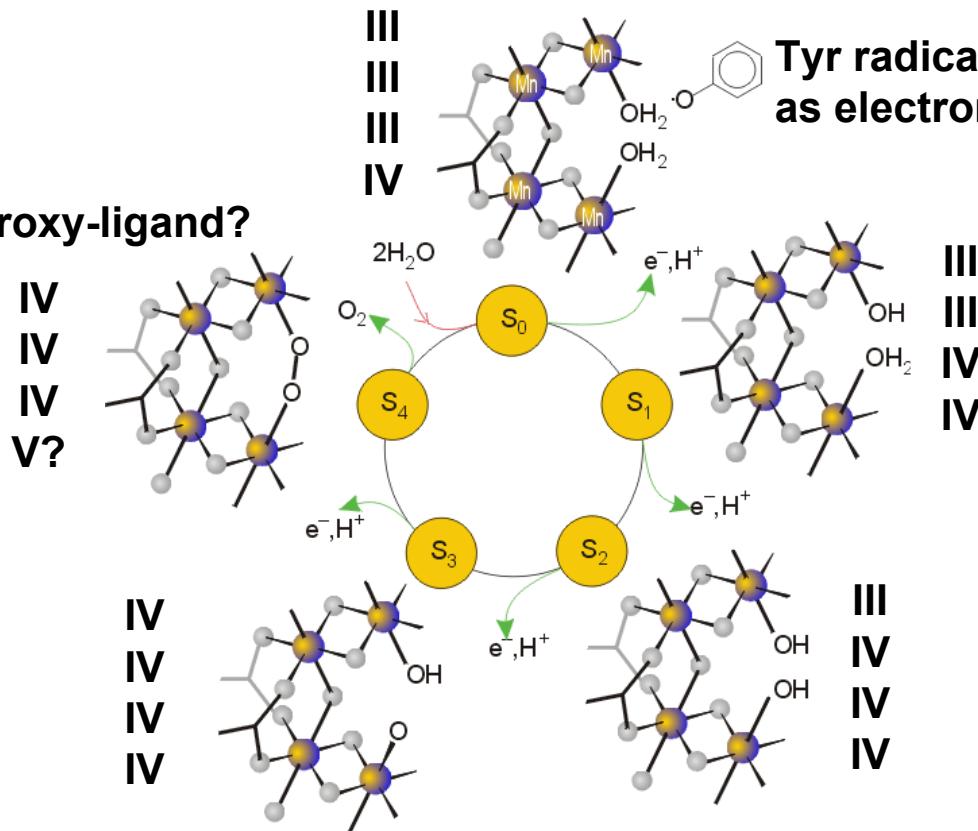
SP: Special pair
HE: Heme systems
BC: Bacteriochlorophyll
BP: Bacteriopheophytin (no metal)
Q: Quinones

1. Excited state of BC
2. Transfer of el. from SP to BC
3. Transfer of el. from BC to BP
4. Transfer of el. to Q
5. Release of H⁺ and el. in cytoplasma
(ADP → ATP and NADP+ → NADPH)
6. Reconstruction of SP via He (donor)

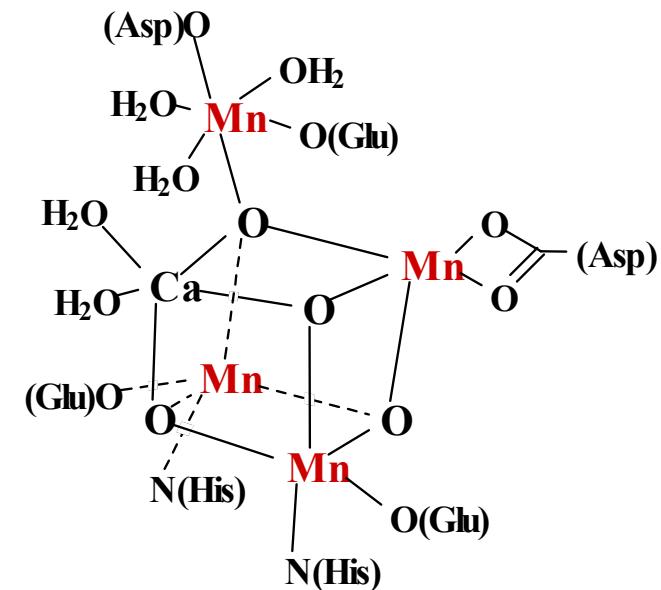
PS II: Production of byproduct O₂

- Direct production of oxygen via SP not possible
- Coupling with OEC (Oxygen Evolving Complex)
- Essential component: oxygen-bridged Mn-clusters (C-cluster, dimer of dimers)
- Combination of oxidation and deprotonation
- Important property of Mn: high flexibility of oxidation states, no complexation of ³O₂

Peroxy-ligand?



Tyr radical
as electron acceptor



Model of OEC

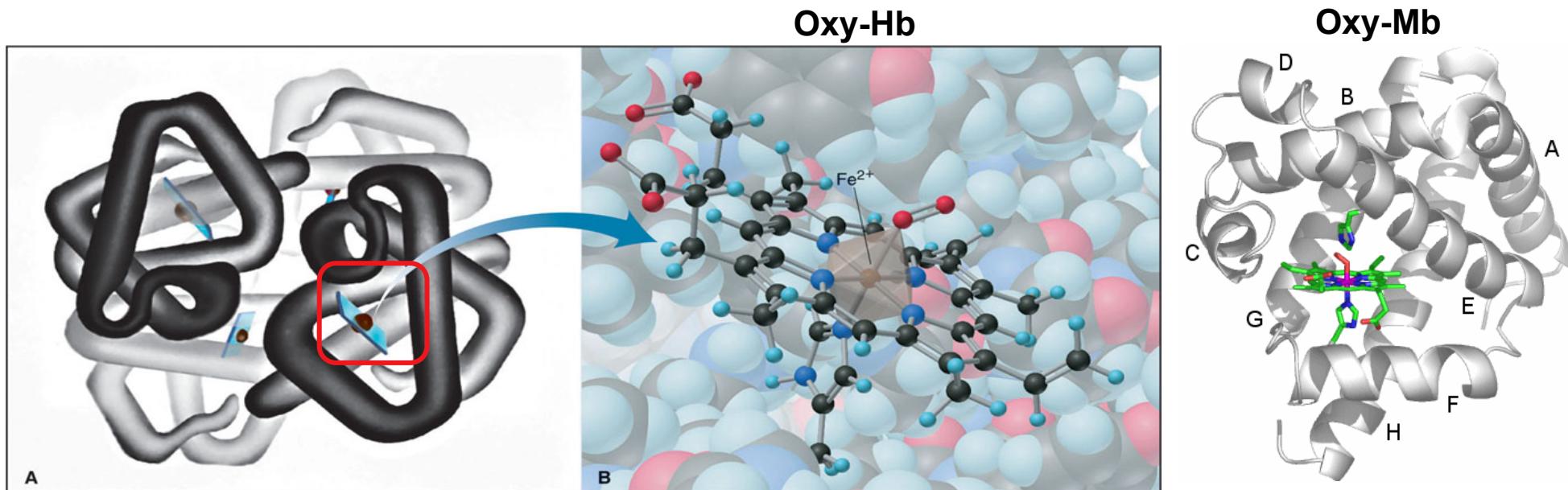
7.

Fe in bio systems

Uptake, transport and storage of O₂

Compounds

- 4g Fe in humans (most common transition metal)
- Heme-proteins with Fe porphyrin complex, stoichiometric function, e.g.:
 - Hemoglobin (Hb) for oxygen transport, tetrameric
 - Myoglobin (Mb) for oxygen storage, monomeric



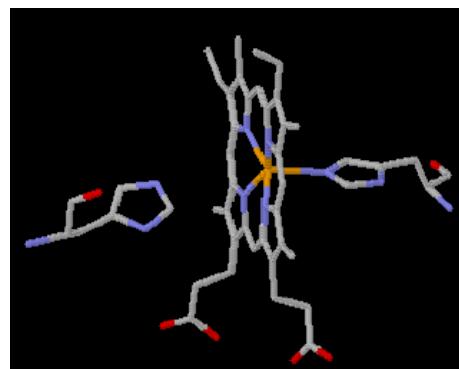
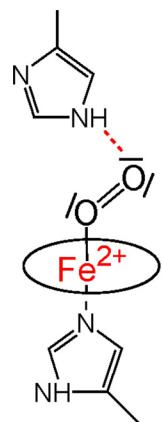
- Binding of ${}^3\text{O}_2$ via end-on coord. (less reactive as the two forms of ${}^1\text{O}_2$)

Function of protein

Function of the protein ligands:

- Inhibition of irreversible oxidation (Fe(III)- μ -peroxo dimer)
- Proximal His (conformational changes of quart. structure)
- Distal His (binding of O₂ via H-bonds)
- Cooperativity: Increase of affinity to oxygen during uptake by Hb (sigmoid)
T (tense, low O₂ affinity) and R (relaxed, high O₂ affinity)
- Binding of CO₂

distal His



proximal His
 σ -donor directs π -acceptor
in trans position

Configuration of Fe

- Desoxy-Mb and -Hb: High-spin Fe(II) with $S = 2$, out-of-plane position
- Two different theories for oxy-Mb and -Hb:

1) Pauling:

low-spin Fe(II) + $^1\text{O}_2$ (both diamagnetic, bonding via σ , π -interactions)

2) Weiss:

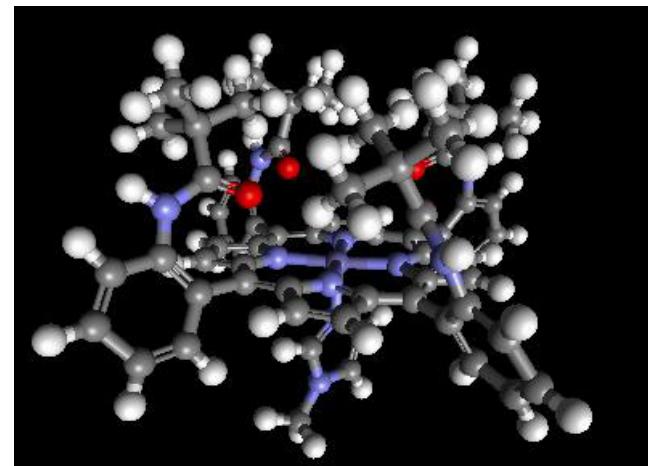
low-spin Fe(III) + Superoxide radical anion (O_2^-). Both paramagnetic

→ Strong paramagnetic coupling for explanation of diamagnetism

→ Spectroscopical data ($\nu_{\text{O-O}}$ consistent with superoxide)

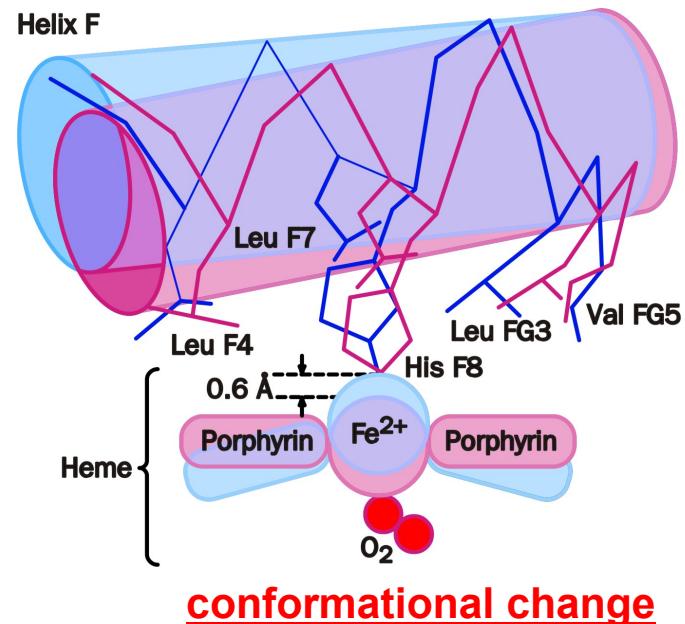
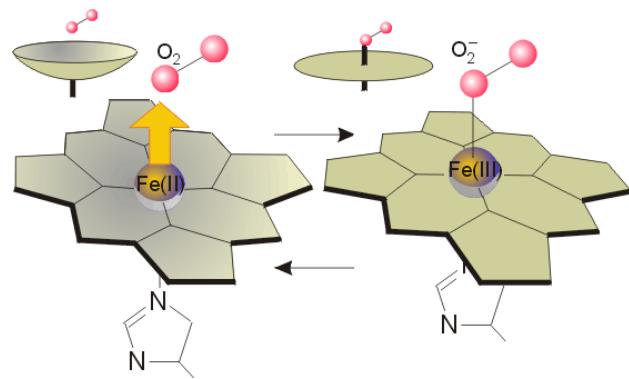
→ Charact. exchange reaction of O_2^- (e.g. by Cl^-)

- Model systems: Protection of Fe(II),
e.g. picket fence molecules

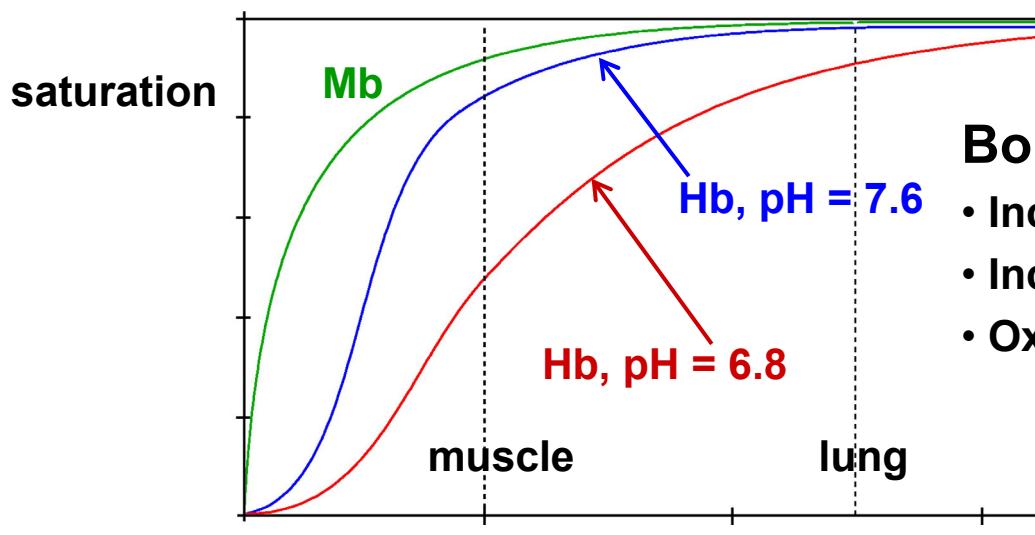


Cooperative binding

Domed and planar coordination of porphyrin
Fe(II) high spin too large for in-plane position

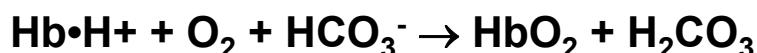


Sigmoid characteristics of Hb (T- and R-form)



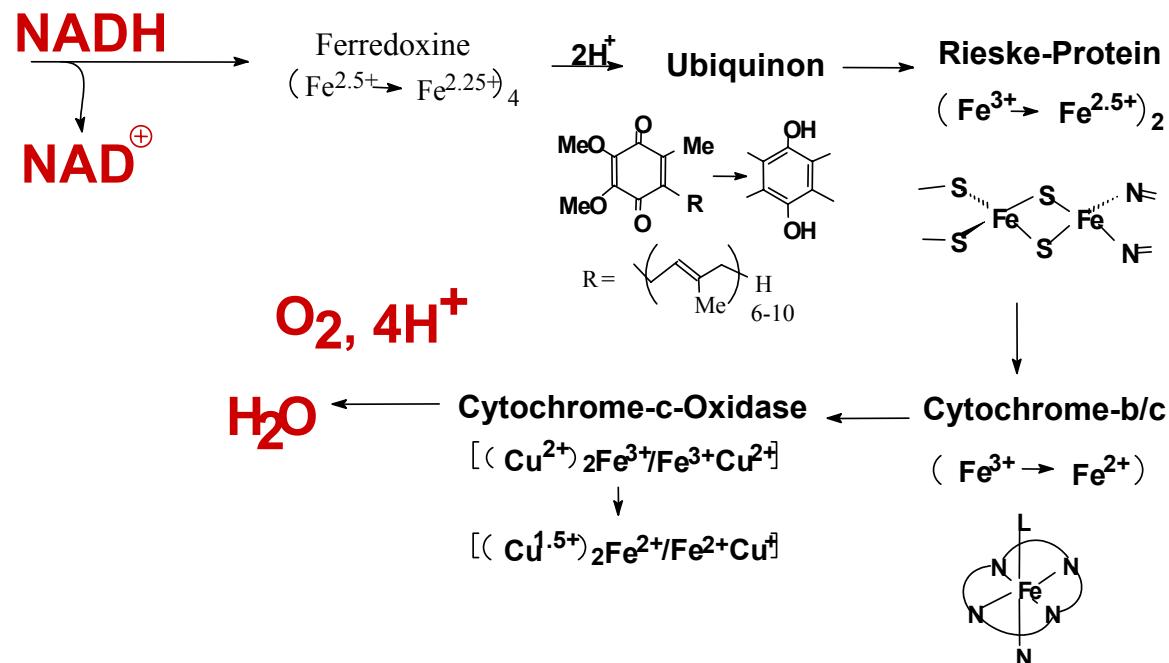
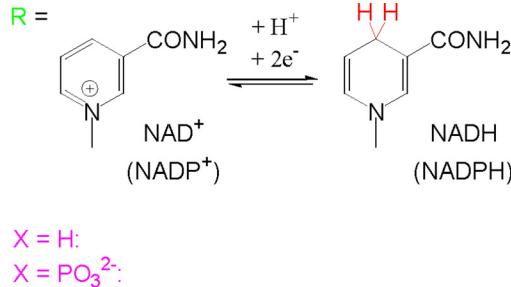
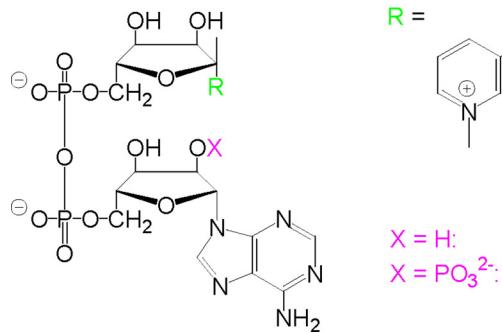
Bohr effect

- Increasing O₂ storage in Hb with increasing pH
- Increasing affinity of Hb to O₂ with increasing pH
- Oxy-Hb is a stronger acid than Desoxy-Hb:



Conversion of O₂ to water

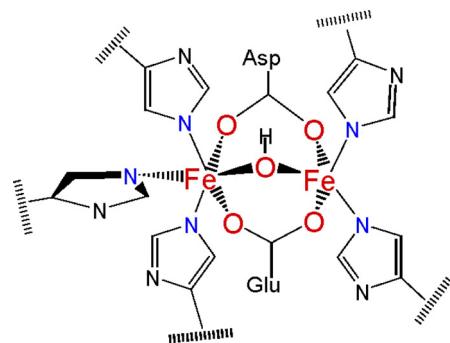
Brutto reaction: O₂ + 2(NADH + H⁺) → 2 H₂O + 2 NAD⁺ (mitochondria)



Stepwise electron transfer

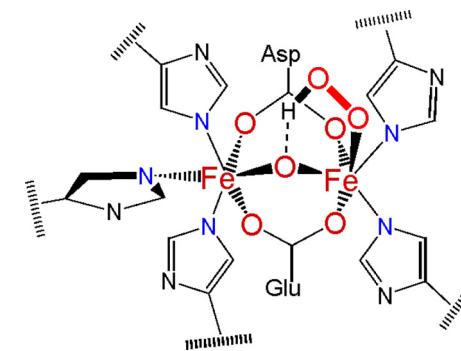
- one el. transfer to Ferredoxin
- two el. transfer to Ubiquinon
- one el. transfer to rieske protein
- one el. transfer to Cytochrome b/c
- four el. transfer to Cyt.-c-oxidaze

Alternatives: Hemerythrin and Hemocyanine



Hemerythrin

Deoxyhemerythrin, h.s. Fe(II), CN = 5, 6



Oxyhemerythrin, Fe(III) with superexchange

- Non-porphinoid metal proteins for reversible O_2 uptake (spiders, etc.)
- Attachment of 3O_2 at Fe with CN = 5,
- Oxidation of both Fe (Fe(III)), reduction of 3O_2 to peroxide (oxo-bridge via H-transport to peroxide)

Hemocyanine

- Proteins with two Cu-centers
- Reversible oxidative addition:
 $O_2 \rightarrow O_2^{2-}$, $Cu^+ \rightarrow Cu^{2+}$
- Side-on bridging coordination

