

# Basics of Bioinorganic Chemistry

## Handout- part 1

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# 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:  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+}$**
5. **Cobalamines**
6. **Metals in Photosynthesis**
7. **Fe in bio systems**
8. **Function of Zn**
9. **Fixation of nitrogen**

# 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 (KomplexeMaster7Sem.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**

# Quiz

- What is the function of an enzyme?
- What is a coenzyme, what are vitamins?
- Describe the function of Hb and Mb
- Do you know any Zn-containing enzyme?
- Is there any metal-organic compound in-vivo?
- Can you describe the effect of  $\pi$ -bonding on  $\Delta_0$ ?
- Describe the function of Mn in photosynthesis
- What are cytochromes?
- Do you know any redox-active cluster compound?
- Describe the biological nitrogen fixation

**1.**

**Very important terms  
of coordination chemistry**

# Coordination compound (complex)- basics

- **Central atom is bound to unexpectedly large number of ligands**
- **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)**

# Coordination number- examples

## Higher CN's are favoured:

- Complexes containing central atoms of the periods 5 and 6, small ligands (size)
- Single bonds metal-ligand (see  $\text{MnO}_4^-$ ...)
- On the left of a row of the d-block (size and small number of d-electrons)
- Central atoms with a high oxidation number (size and small number of d-electrons)

- CN 2: linear ( $\text{Cu}^+$ ,  $\text{Ag}^+$ ,  $\text{Au}^+$ ,  $\text{Hg}$ )

- CN 3: trigonal planar ( $\text{HgI}_3^-$ ,  $[\text{Pt}(\text{P}\{\text{C}_6\text{H}_5\}_3)_3]$ ,  
trigonal pyramid

- CN 4: tetrahedron ( $[\text{Al}(\text{OH})_4]^-$ ,  $[\text{Cd}(\text{CN})_4]^{2-}$ )

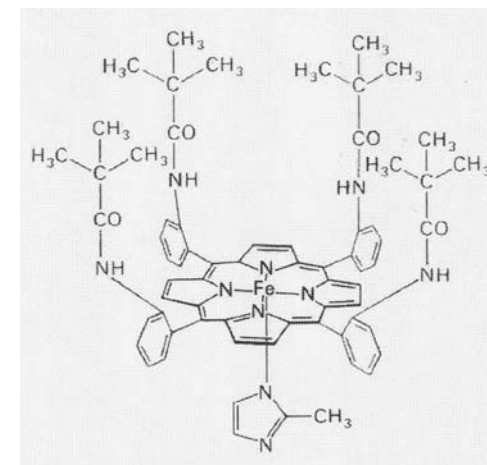
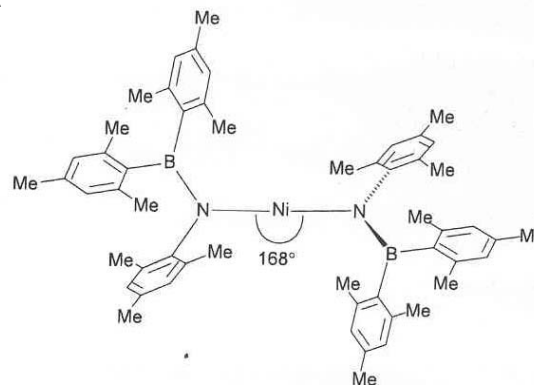
square planar ( $d^8$ ,  $[\text{PtCl}_4]^{2-}$ ,  $[\text{AuF}_4]^-$ )

bisphenoidal ( $\psi$ -trigonal bipyramid,  $[\text{AsF}_4]^-$   $[\text{SbCl}_4]^-$ )

tetragonal pyramid ( $\psi$ -octahedron)

- CN 5: trigonal bipyramid ( $\text{Fe}(\text{CO})_5$ ,  $[\text{SnCl}_5]^-$ )

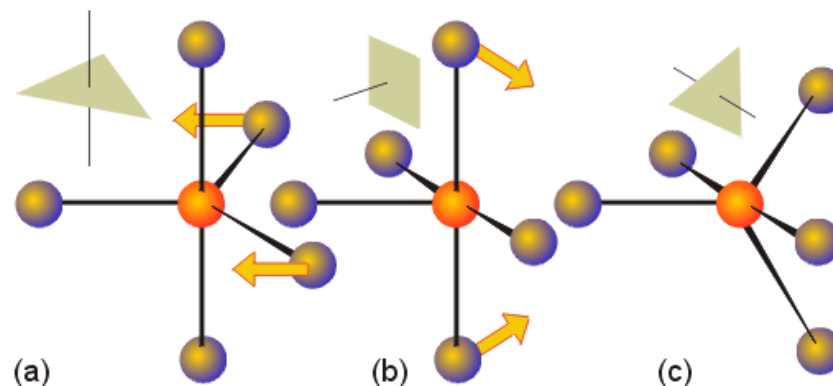
tetragonal pyramid



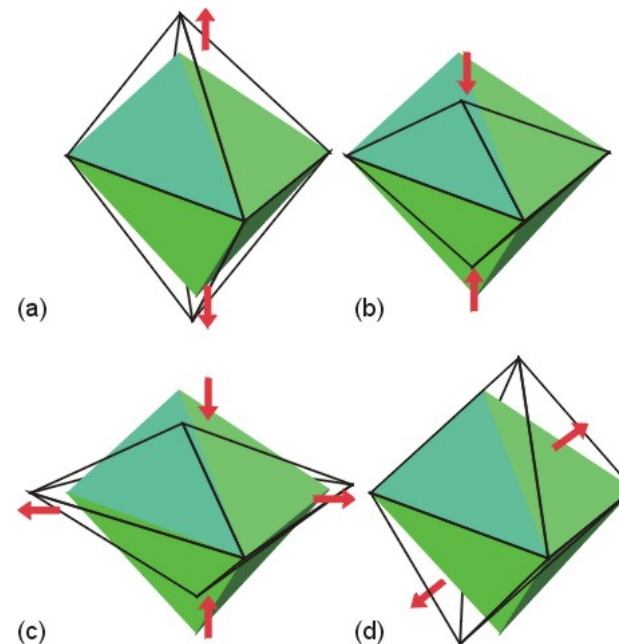
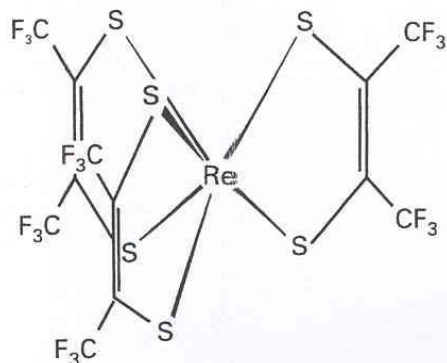
# Coordination number- examples

## 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



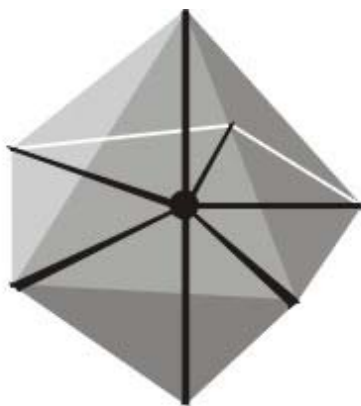
- CN 6: octahedron ( $[\text{Cr}(\text{H}_2\text{O})_6]^{3+}$ ,  $[\text{Fe}(\text{CN})_6]^{3-}$ )  
distorted octahedron  
trigonal prism



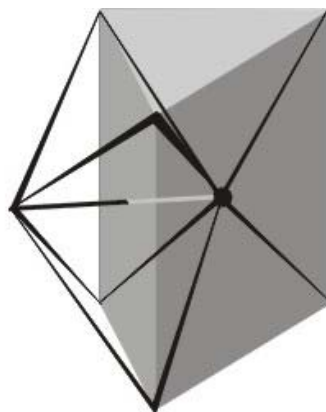


# Coordination number- examples

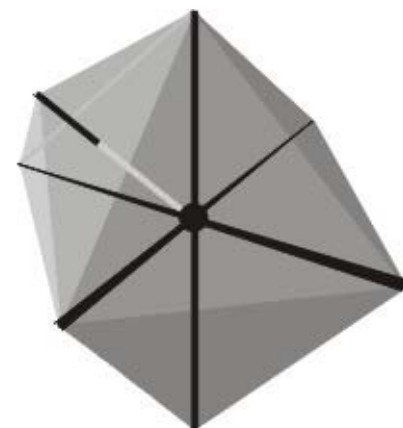
- CN 7:



pentagonal bipyramid  
 $[\text{UO}_2\text{F}_5]^{3-}$ ,  $[\text{HfF}_7]^{3-}$



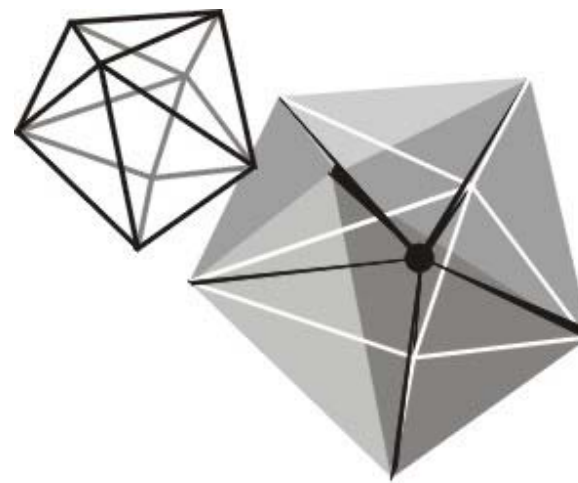
monocapped trigonal prism  
 $[\text{TaF}_7]^{3-}$



monocapped octahedron  
 $[\text{IF}_6]^-$ ,  $[\text{NbOF}_6]^{3-}$

- CN 8: cube ( $[\text{UF}_8]^{3-}$ )

square antiprism  
 $[\text{TaF}_8]^{3-}$ ,  $[\text{ReF}_8]^{3-}$



dodecahedron  
 $[\text{Mo}(\text{CN})_8]^{4-}$

# Isomerism

- Two or more molecules or ions 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.

## Stereoisomerism

- Optical isomerism: Enantiomers
- Geometrical isomerism:  
cis-, trans; meridional, facial

## Structural isomerism

- Ionization isomerism ( $[\text{CoCl}(\text{NH}_3)_5]\text{SO}_4$  /  $[\text{CoSO}_4(\text{NH}_3)_5]\text{Cl}$ )
- Coordination isomerism ( $[\text{Co}(\text{NH}_3)_6][\text{Cr}(\text{CN})_6]$  /  $[\text{Cr}(\text{NH}_3)_6][\text{Co}(\text{CN})_6]$ )
- Linkage isomerism (cyano / isocyano)

# HSAB concept

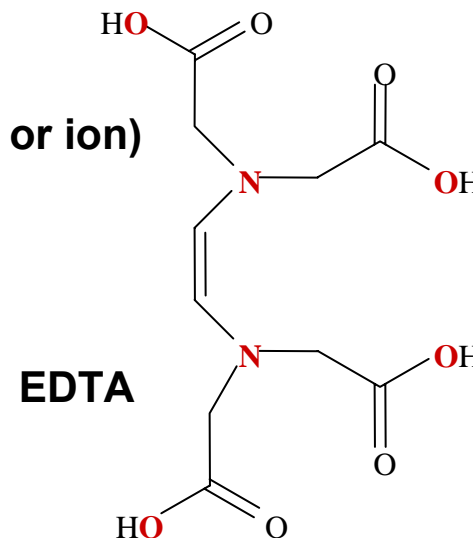
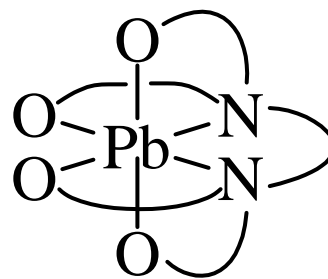
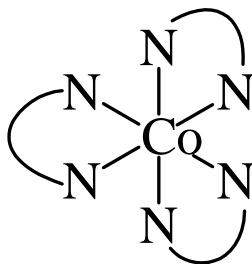
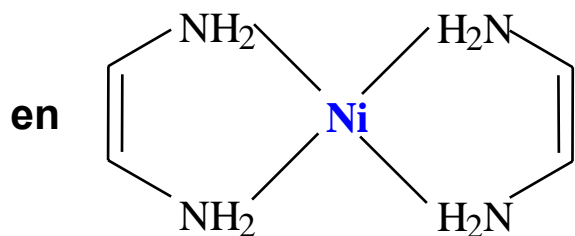
- **Pearson's concept, 1963**

- **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:  $H^+$ ,  $Li^+$  ( $> Na^+ \dots$ ),  $Cr^{6+}$  ( $> Cr^{3+}$ )**
- **Intermediate acids:  $Fe^{2+}$ ,  $Mn^{2+}$ ,  $Cu^{2+}$ ,  $Zn^{2+}$**
- **Soft acids:  $Au^+$  ( $> Ag^+$ ,  $Cu^+$ ),  $Hg^{2+}$ ,  $Pt^{2+}$**
- **Hard bases:  $F^-$ ,  $OH^-$ ,  $NH_3$ ,  $PO_4^{3-}$  ( $> HPO_4^{2-}$ ),  $MoO_4^{2-}$**
- **Intermediate bases:  $Cl^-$**
- **Soft bases:  $I^-$  ( $> Br^- \dots$ ),  $S^{2-}$  ( $> HS^-$ ,  $> H_2S$ ),  $AsS_2^-$**

# Chelates

- **Structure**

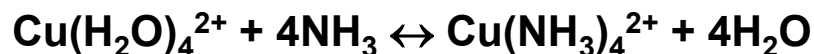
- Multidentate ligands (more than one bond with the central atom or ion)
- Ring structures



- **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

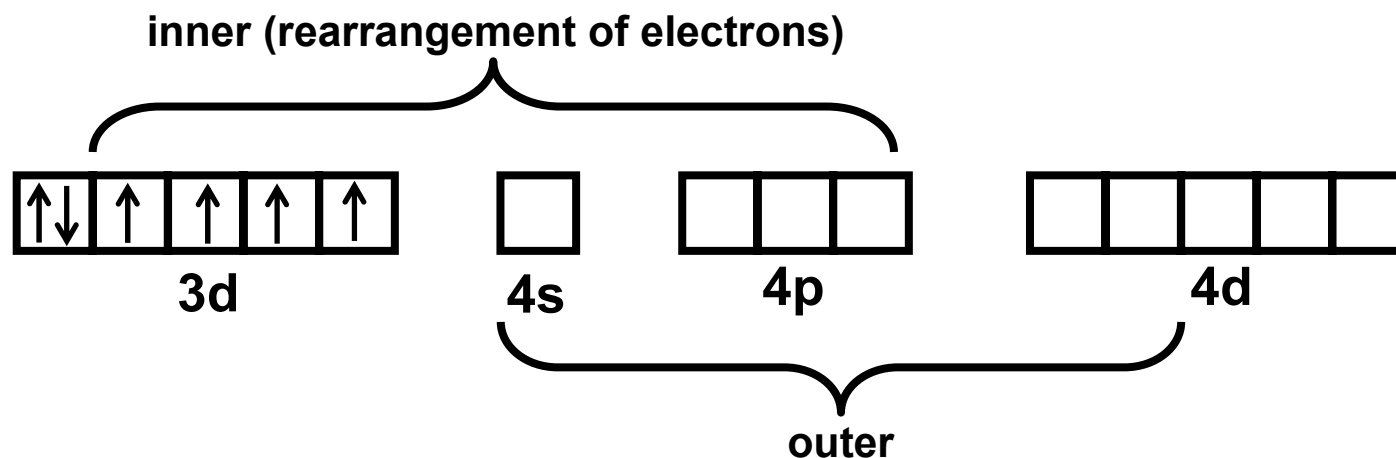
$$\Delta G = \Delta H - T\Delta S, \Delta H \sim \text{for multi- and mono-dentate complexes}$$



- Chelate therapy (detoxification)

# Bonding in coordination compounds

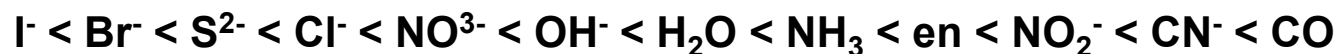
- Simple electrostatic model (problem: square complexes)
- 18 Val. el.-rule (problem: no information about geometry, magnetism...)
- Related to octet rule, no. of el. on metal ion = number of el. on a noble gas, [Ar] + 18 Val. el
- $[\text{Co}(\text{NO}_2)_6]^{3-}$ , but  $[\text{Cr}(\text{NH}_3)_6]^{3+}$ , carbonyls obey EAN ( $\text{Fe}(\text{CO})_5$ ,  $\text{Ni}(\text{CO})_4$ )
- Valence Bond Theory (Pauling)
- Hybridization of the metals orbitals,  $\sigma$ -bond with ligand orbitals
- $\text{sp}^3$  (tetrahedral),  $\text{d}^2\text{sp}^3$  (octahedral),  $\text{dsp}^3$  (trigonal bipyramid),  $\text{dsp}^2$  (square planar)
- inner- and outer orbital complexes, e. g.  $\text{Co}^{3+}$  (consequences for magnetism)



# Bonding in complexes- CTF

- Crystal Field Theory (Electrostatic guide to splitting of d-levels)
- Ligand field splitting  $\Delta_0$ , LFSE (Ligand Field Stabilization Energy)

- Spectrochemical series:



- Metal:  $\Delta_0$  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  $\Delta_0$

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

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

- Square coordination:  $d_{xy}$  higher energy than  $d_{z^2}$

# Bonding in complexes- LFT

- **$\sigma$ -bonding**
- Ligand field theory (Interaction in terms of atomic and molecular orbitals)
- Overlap atomic orbitals of similar symmetry to form molecular orbitals
  
- **$\pi$ -bonding**
- SALC of metal  $t_{2g}$  and  $\pi$ -orbitals of the ligand
- Non-bonding  $t_{2g}$  become antibonding ( $\pi$  -donor)
- Non-bonding  $t_{2g}$  become bonding ( $\pi$  -acceptor)
  
- **Interconnection CFT-LFT**

**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, synthesis and analysis of “model systems”**
- **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**
- **Biom mineralization: biochemistry and solid state (materials) chemistry**
- **Synthesis and characterization of model systems**

# Methods for characterization

- **Diffraction methods (3d structure)**
- **Problem: crystallization of proteins**
- **Complex structures, “high” resolution (ca. 0.2 nm), no identification of hydrogen atoms**
- **NMR (local structure and dynamical properties of species )**
- **Electron microscopy (3d structure with medium resolution)**
- **ESR (electronic properties of species containing unpaired electrons)**
- **Mössbauer spectroscopy (identification of species with quadrupol moment)**
- **Optical spectroscopy (color, electronic properties)**
- **X-ray absorption techniques (local structure)**
- **SQUID (characterization of magnetic materials)**
- **Cyclovoltammetry (characterization of electron transfer)**
- **...**

# Periodic table of life

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

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

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)

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

- 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

- **Weak correlation to distribution of the elements in the earth's crust (there: O > Si > Al > Fe...)**
- **Good correlation to distribution of the elements in sea water**

# Functions of “inorg. elements” – summary

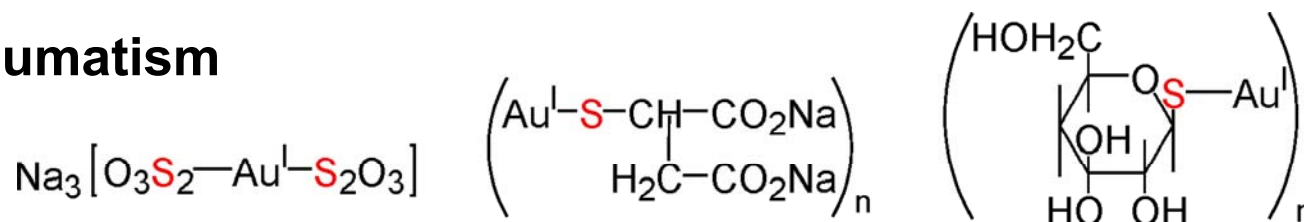
- Assembly of structures (DNA, biomineralization), endo- and exoskeletons. **Ca, Mg, Zn, Si**
- Information carriers (muscle contractions, nerve function). **Na, K, Ca, Mg**
- Activation of enzymes. **Mg, Ca**
- Formation, metabolism and degradation of organic compounds by Lewis acid/base catalysis.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

# Most prominent “bioelements”

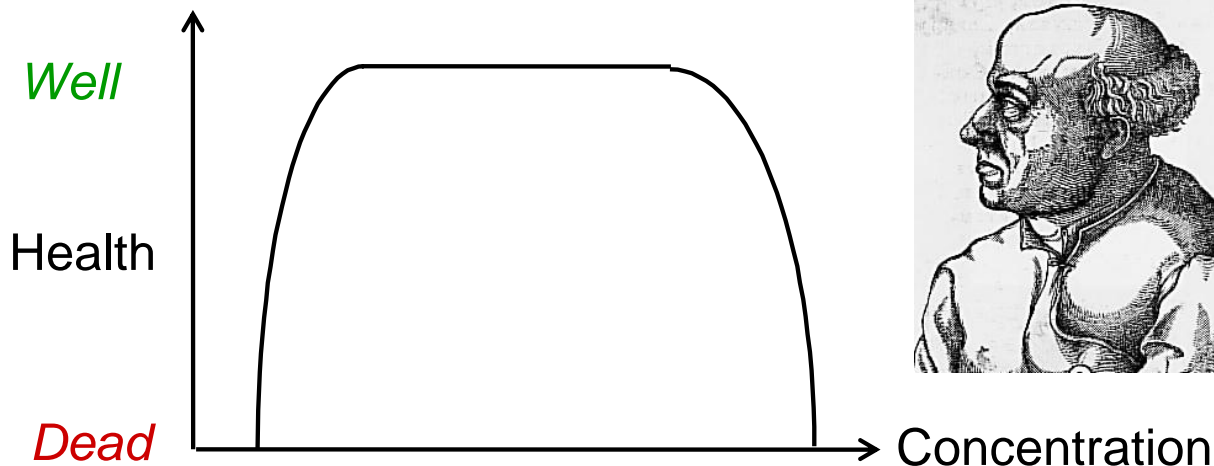
- **Na<sup>+</sup>, K<sup>+</sup>: Electrolytes**
- **Mg<sup>2+</sup>: Chlorophyll, energy production (ATP → ADP), skeleton**
- **Ca<sup>2+</sup>: muscle functions, Hydroxylapatite Ca<sub>5</sub>(PO<sub>4</sub>)<sub>3</sub>(OH), CaCO<sub>3</sub>**
- **V<sup>IV/V</sup>, Mo<sup>IV/VI</sup>, W<sup>IV/VI</sup>, Mn<sup>II/III/IV</sup>, Fe<sup>II/III</sup>, Ni<sup>I/II/III</sup>, Cu<sup>I/II</sup>: electron transfer**
- **Fe and Cu: transport and storage of oxygen**
- **Fe<sup>II</sup>, Fe<sup>III</sup>: Magnetite (Fe<sub>3</sub>O<sub>4</sub>)**
- **Co: Cobalamine, e.g. Vitamin-B<sub>12</sub>**
- **Zn<sup>2+</sup>: Enzymes, zincfinger (gen. transcription), stabilization of proteins**
- **Si<sup>IV</sup>: bones; SiO<sub>2</sub>/silicagel**
- **P<sup>V</sup>: Hydroxylapatite, ATP, cell membrane, DNA**
- **Se<sup>-II</sup>: Selenocysteine**
- **F<sup>-</sup>: Fluorapatit (Ca<sub>5</sub>(PO<sub>4</sub>)<sub>3</sub>F) teeth; Cl<sup>-</sup>: besides HCO<sub>3</sub><sup>-</sup> most important free anion, I<sup>-</sup>: hormones of the thyroid, radiation therapy**

# Application of metals in medicine

- $\text{Li}^+$ : Treatment of depression ( $\text{Li}_2\text{CO}_3$ , low doses)
- $\text{Gd}^{3+}$ : Contrast agent (NMR)
- $\text{BaSO}_4$ : Contrast agent (radiography)
- $^{99\text{m}}\text{Tc}$ : radio diagnostics (thyroid)
- $\text{Au(I)}$ : Rheumatism



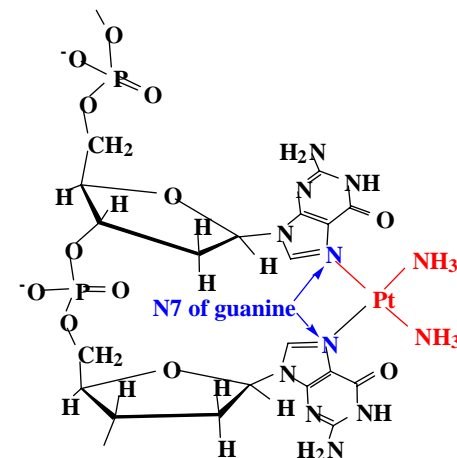
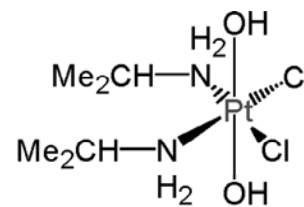
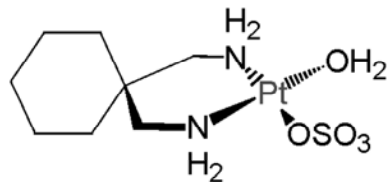
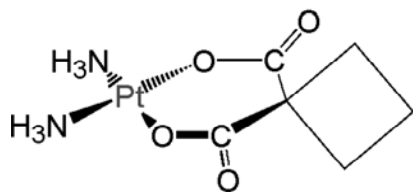
- $\text{Sb(III)}$ : Eczema
- $\text{Bi(III)}$ : Gastric ulcer
- $\text{Cd}$ : Carboanhydrase (*Thalassiosira weissflogii*)





# Application of metals in medicine

- Pt(II): Cisplatin ( $cis$ -[Pt(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>]), chemotherapy (inhibition of cell division, not cell growth)



- Filamentous growth of bacteria

# Terms related to bioinorganic chemistry

- See: <http://www.chem.qmul.ac.uk/iupac/bioinorg/>: glossary terms
- **Active center:** Location in an enzyme where the specific reaction takes place
- **Allosteric enzyme:** Can bind a small regulatory molecule that influences catalytic activity
- **Apo-enzyme:** An enzyme that lacks its metal center or prosthetic groups
- **ATP:** Adenosine 5'-triphosphate
- **Biomembrane:** Sheet like assemblies of proteins and lipids (bilayer)
- **Calmodulin:** Ca binding protein involved in metabolic regulation
- **Carboanhydrase:** Zn-containing enzyme that catalyzes the reversible decomposition of carbonic acid to carbon dioxide and water
- **Charge-transfer complex:** An aggregate of two or more molecules in which charge is transferred from a donor to an acceptor.
- **Chlorin:** 2,3-Dihydroporphyrin, reduced porphyrin with two non-fused saturated carbon atoms (C-2, C-3) in one of the pyrrole rings.
- **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
- **Cisplatin:** Cis-diamminedichloroplatinum(II), antitumor drug. Of major importance in the antitumor activity of this drug is its interaction with the nucleic acid bases of DNA

# Terms related to bioinorganic chemistry

- **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
- **Corrin:** Ring-contracted porphyrin derivative that is missing a carbon
- **Cytochrome:** Heme protein that transfers electrons, and exhibits intense absorption bands. The iron undergoes oxidation-reduction between oxidation states Fe(II) and Fe(III).
- **Cytochrome-c oxidase:** The major respiratory protein of animal and plant mitochondria. It catalyzes the oxidation of Fe(II)-cytochrome c, and the reduction of dioxygen to water. Contains two hemes and three copper atoms, arranged in three centers.

# Terms related to bioinorganic chemistry

- **Cytochrome P-450:** General term for a group of heme-containing monooxygenases The reaction with dioxygen appears to involve higher oxidation states of iron, such as  $\text{Fe(IV)=O}$
- **Cytoplasm:** The part of protoplasm in a cell outside of and surrounding the nucleus
- **Dehydrogenase:** An oxidoreductase which catalyzes the removal of hydrogen
- **Desferrioxamine (dfo):** Chelating agent used world-wide in the treatment of iron overload conditions, such as hemochromatosis and thalassemia.
- **Dismutase:** Enzyme that catalyzes a disproportionation reaction
- **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
- **FeMo-cofactor:** An inorganic cluster found in the FeMo protein of the molybdenum-nitrogenase, essential for the catalytic reduction of  $\text{N}_2$  to ammonia
- **Ferredoxin:** A protein containing more than one iron and acid-labile sulfur, that displays electron-transferactivity but not classical enzyme function
- **Ferritin:** An iron storage protein consisting of a shell of 24 protein subunits, encapsulating up to 4500 iron atoms in the form of a hydrated iron(III) oxide.

# Terms related to bioinorganic chemistry

- **Heme:** A near-planar coordination complex obtained from iron and dianionic porphyrin
- **Hemerythrin:** A dioxygen-carrying protein from marine invertebrates, containing an oxo-bridged dinuclear iron center
- **Hemocyanin:** A dioxygen-carrying protein (from invertebrates, e.g. arthropods and molluscs), containing dinuclear type 3 copper sites
- **Hemoglobin:** A dioxygen-carrying heme protein of red blood cells
- **HiPIP:** High-Potential Iron-sulfur Protein (ferredoxin). Cluster which undergoes oxidation-reduction between the  $[4\text{Fe-4S}]^{2+}$  and  $[4\text{Fe-4S}]^{3+}$  states
- **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. Their structures usually consist of 4-6 membrane-spanning domains. This number determines the size of the pore and thus the size of the ion to be transported
- **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

# Terms related to bioinorganic chemistry

- **Metalloenzyme:** An enzyme that, in the active state, contains one or more metal ions
- **Mitochondria:** Cytoplasmic organelles, produce ATP by oxidative phosphorylation
- **Model:** A synthetic coordination entity that closely approaches the properties of a metal ion in a protein and yields useful information concerning biological structure and function
- **Myoglobin:** A monomeric dioxygen-binding hemeprotein of muscle tissue, structurally similar to a subunit of hemoglobin
- **Nucleic acids:** Macromolecules composed of sequences of nucleotides that perform several functions in living cells, e.g. the storage of genetic information
- **Nucleosides:** Compounds in which a purine or pyrimidine base is beta-N-glycosidically bound to C-1 of either 2-deoxy-D-ribose or of D-ribose, but without any phosphate groups
- **Nucleotides:** Nucleosides with one or more phosphate groups esterified mainly to the 3'- or the 5'- position of the sugar moiety
- **OEC:** Oxygen-Evolving Complex
- **Photosynthesis:** A metabolic process in plants and certain bacteria, using light energy absorbed by chlorophyll and other photosynthetic pigments for the reduction of CO<sub>2</sub>, followed by the formation of organic compounds

# Terms related to bioinorganic chemistry

- **Plastocyanin:** An electron transfer protein, containing a type 1 copper site, involved in plant and cyanobacterial photosynthesis, which transfers electrons to Photosystem 1
- **Rieske protein:** An iron-sulfur protein of the mitochondrial respiratory chain, containing a [2Fe-2S] cluster
- **Rubredoxin:** A single iron-sulfur protein, function as an electron carrier
- **SOD:** See superoxide dismutase, catalysis of disproportionation of superoxide
- **Soret band:** Strong absorption band in the blue region of the optical absorption spectrum of a heme protein
- **Substrates:** A compound that is transformed under the influence of a catalyst
- **Trace elements:** Elements required for physiological functions in very small amounts, e.g. Co, Cu, F, Fe, I, Mn, Mo, Ni, Se, V, W, and Zn
- **Type 1,2,3 copper:** Different classes of copper-binding sites in proteins, classified by their spectroscopic properties as Cu(II). Type 1, or blue copper centers the copper is coordinated to at least two imidazole nitrogens from His and one sulfur from Cys. In type 2, or non-blue copper sites, the copper is mainly bound to imidazole nitrogens from His. Type 3 copper centers comprise two spin-coupled copper ions, bound to imidazole nitrogens
- **Zinc finger:** A domain, found in certain DNA-binding proteins, comprising a helix-loop structure in which a zinc ion is coordinated to 2 - 4 Cys sulfurs, the remaining ligands being His

# 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,  $\Delta \Delta(E) \sim$  reaction rate
- Reduce the amount of time required to attain the equilibrium

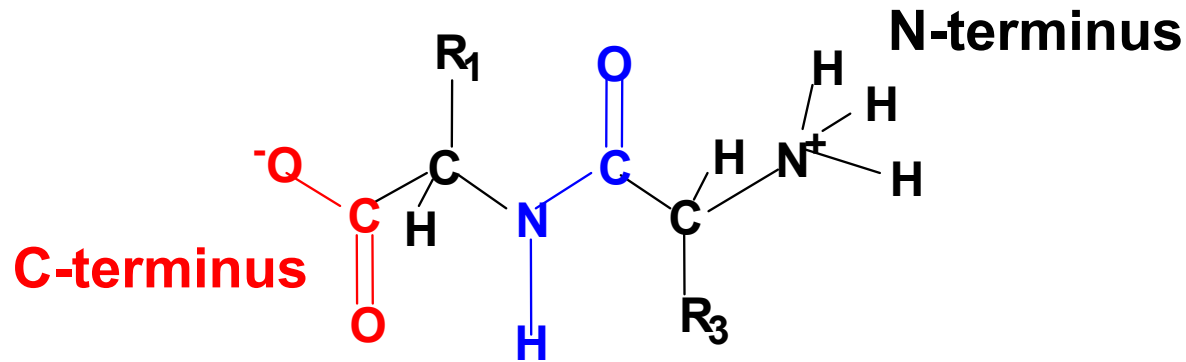
## Principle of complementarity

- 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

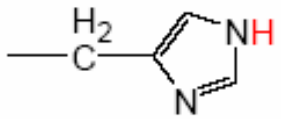


# Ligands- Proteins

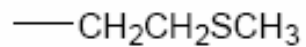
- Proteins consist of  $\alpha$ -amino acids, connected via **peptide bonds**



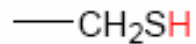
- Metal coordination by functional groups in the side chain (R)



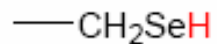
**Histidine** (both N atoms available, metal-metal bridging possible, pKa ~6)



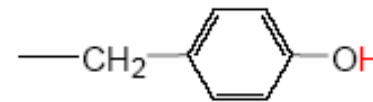
**Methionine**



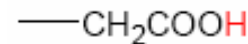
**Cysteine**  
(metal-metal bridging, pKa ~ 8)



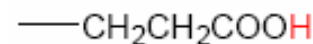
**Selenocysteine**  
(“non-innocent ligand”)



**Tyrosine**  
(“non-innocent ligand”)

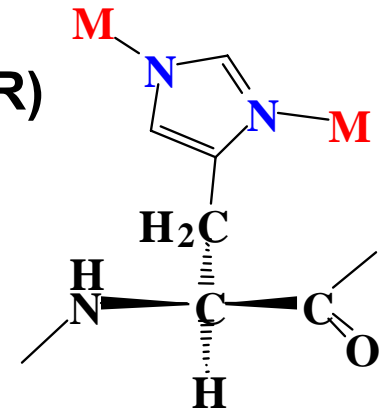


**Aspartic acid**



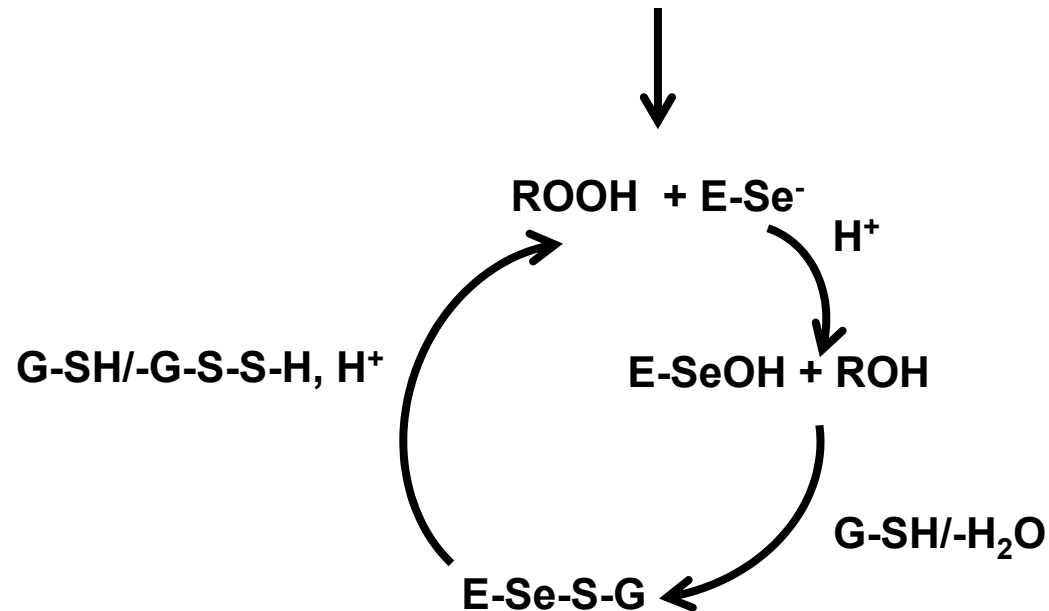
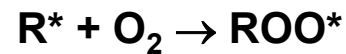
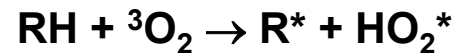
**Glutamic acid**

} pKa ~ 4



# Excursus: biochemistry of Se

- Related to S-containing biomolecules
- More reactive, function as antioxidant (“anti-aging”)
- Deactivation of radicals and lipohydroperoxides



# Ligands- Proteins

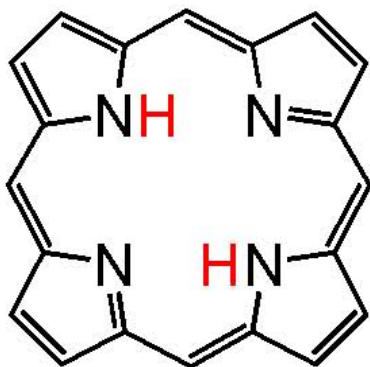
- Coordination of metals by carboxylates:  $\eta^1$  (syn and anti),  $\eta^2$ , bridging
- Characteristic affinities of R to defined oxidation states of metals

	bond stability	CN	R	typical coordn. geometry
Zn(II)	high	3	His, Cys <sup>-</sup>	dis. tetrahedron
Cu(I)	high	3,4	His, Cys <sup>-</sup> , Met	dis. tetrahedron
Cu(II)	high	3,4	His	dis. square
Fe(II), Ni(II), Co(II), Mg(II)	low	4-6	His, Glu <sup>-</sup> , Asp <sup>-</sup>	dis. octahedron
Fe(III)	high	4-6	Glu, Asp <sup>-</sup> , Tyr <sup>-</sup> , Cys <sup>-</sup>	dis. octahedron

- Metal centers are undersaturated (bonding of substrate)
- Coordination geometry frequently distorted (entatic state theory)
- Structure of Proteins
  - Primary structure: Sequence of amino acids
  - Secondary structure: Shapes formed within regions of the protein
  - Tertiary structure: Shape of entire protein
  - Quaternary structure: Structures formed by interaction of several subunit

# Cyclic ligands- Porphyrin complexes

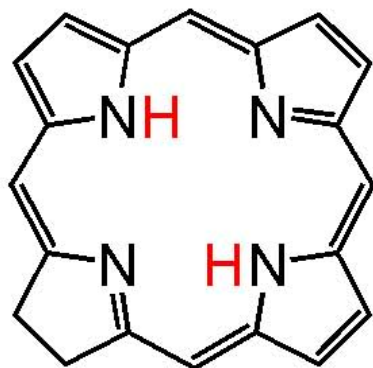
- Unsaturated tetradentate macrocyclic ligands
- Coordination of otherwise labile divalent metal ions
- Porphyrin complexes: chelate-effect and size selective as host
- Porphyrin: very stable, Hückel-aromatic ( $18 \text{ el} = 4n + 2$ ), colored



Porphyrin

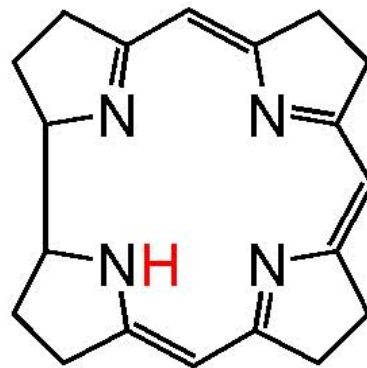
Hemoglobin  
Myoglobin  
Peroxidases

} Fe



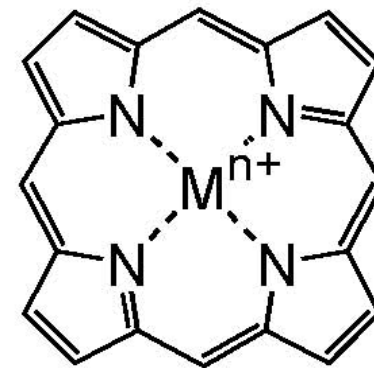
Chlorin

Chlorophyll ( $\text{Mg}^{2+}$ )  
Tunichlorine ( $\text{Ni}^{2+}$ )



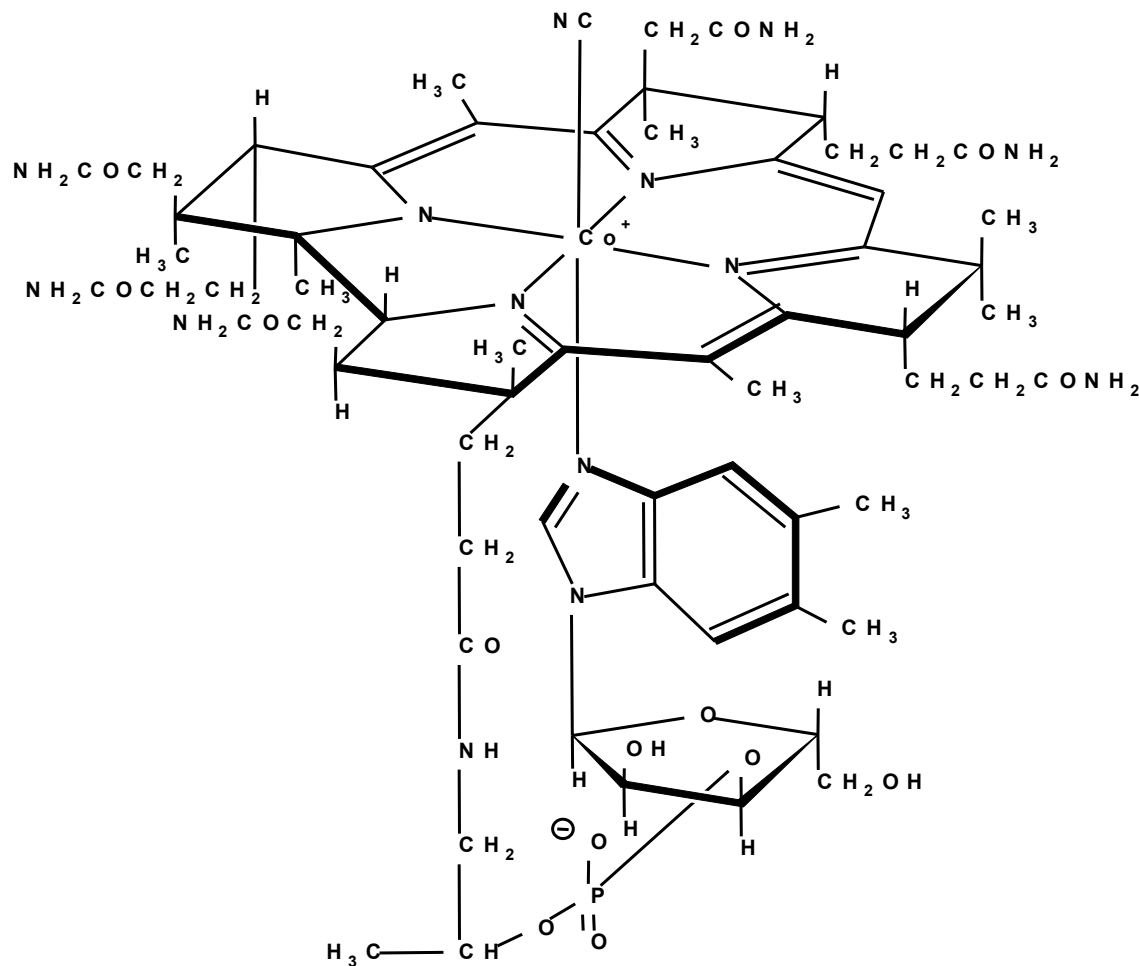
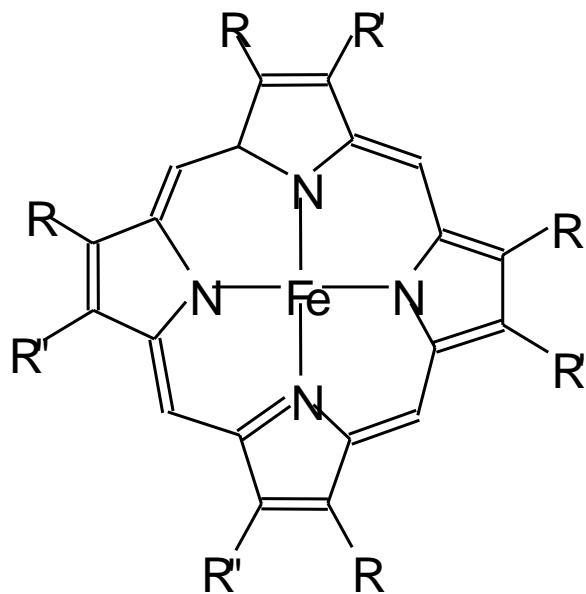
Corrin

Cobalamin ( $\text{Co}^{2+}$ )



Metallaporphyrin  
complex

# Cyclic ligands- Porphyrin complexes

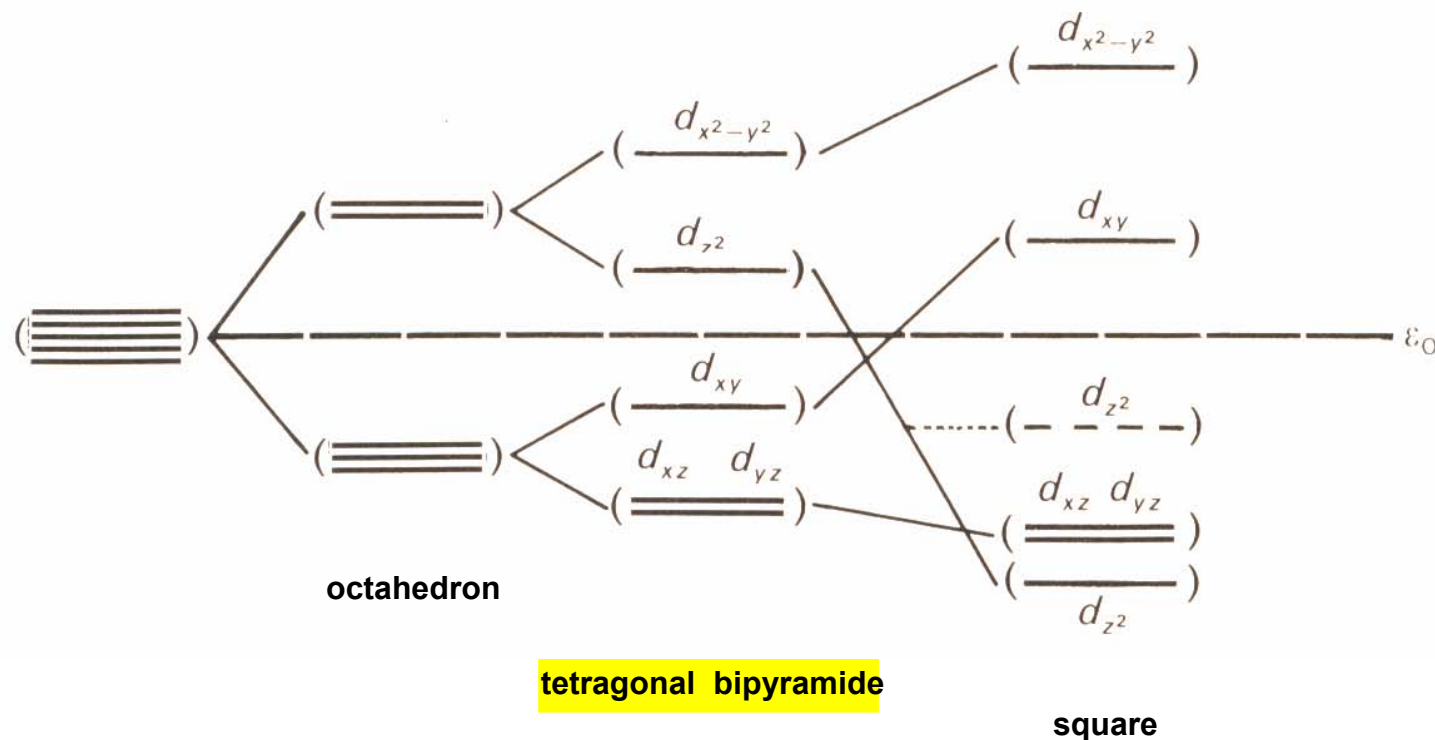


Vitamine B<sub>12</sub>

# Cyclic ligands- Porphyrin complexes

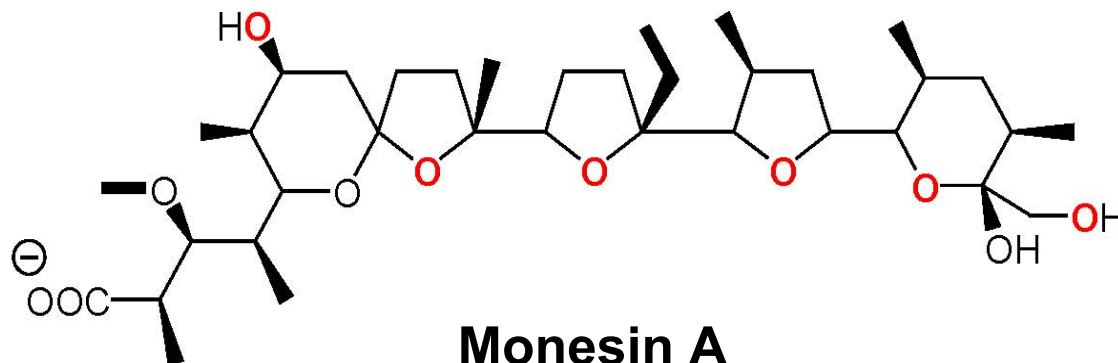
## Bonding

- 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):



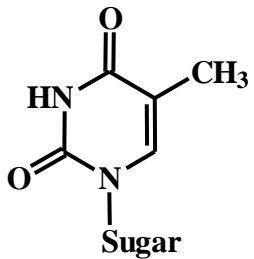
# Cyclic ligands- Ionophores

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

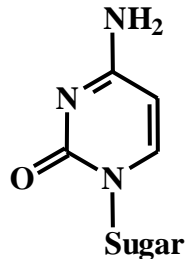


# Nucleobases- building units of DNA, RNA

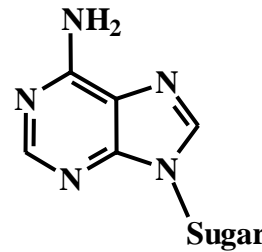
- DNA, RNA: macromolecules consisting of nucleotides as building units
- Nucleotides: Pentose, pyrimidine- or purine base, phosphate group (1:1:1)
- Information carriers as ligands (oligo- and polynucleotides)
- Coordination by nucleobases or by phosphate groups ( $Zn^{2+}$ ,  $Mg^{2+}$ )



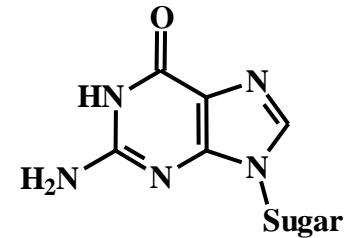
Thymine



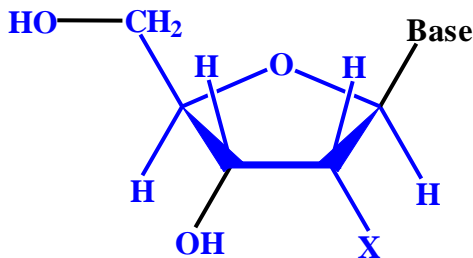
Cytosine



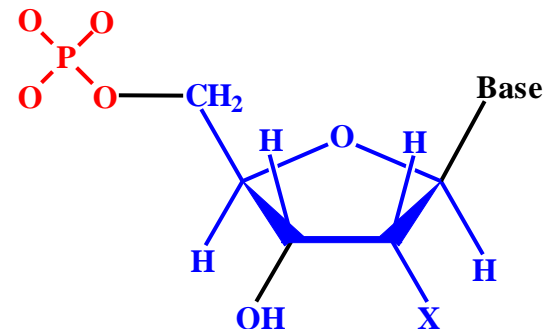
Adenine



Guanine



Nucleoside



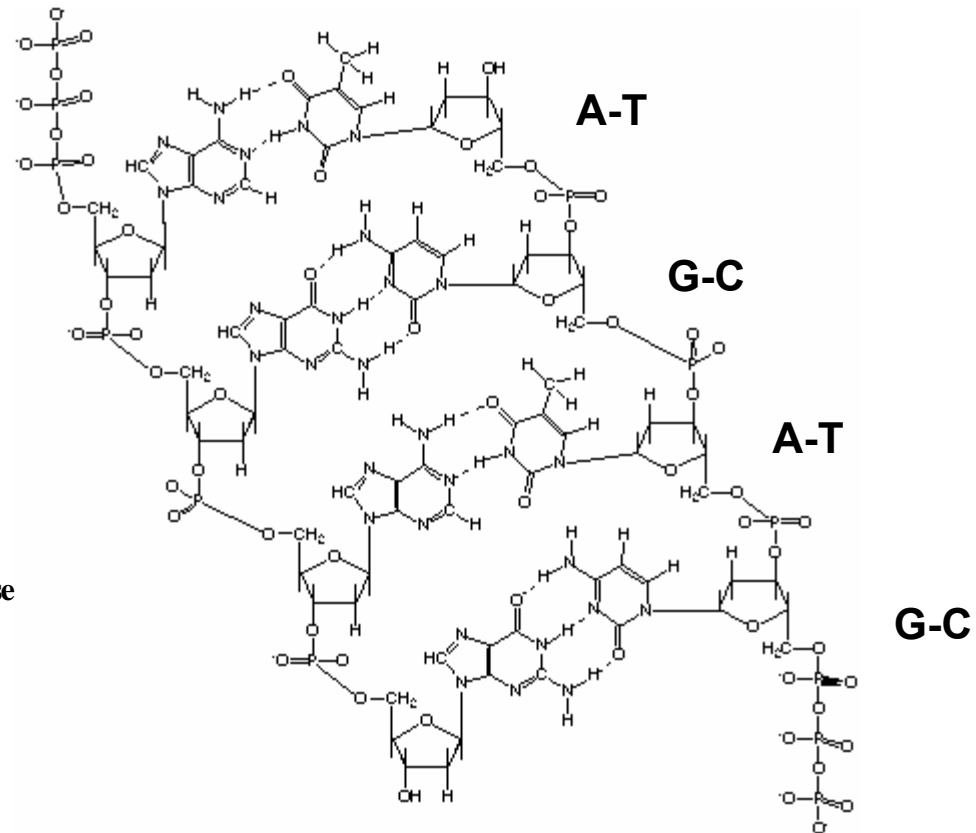
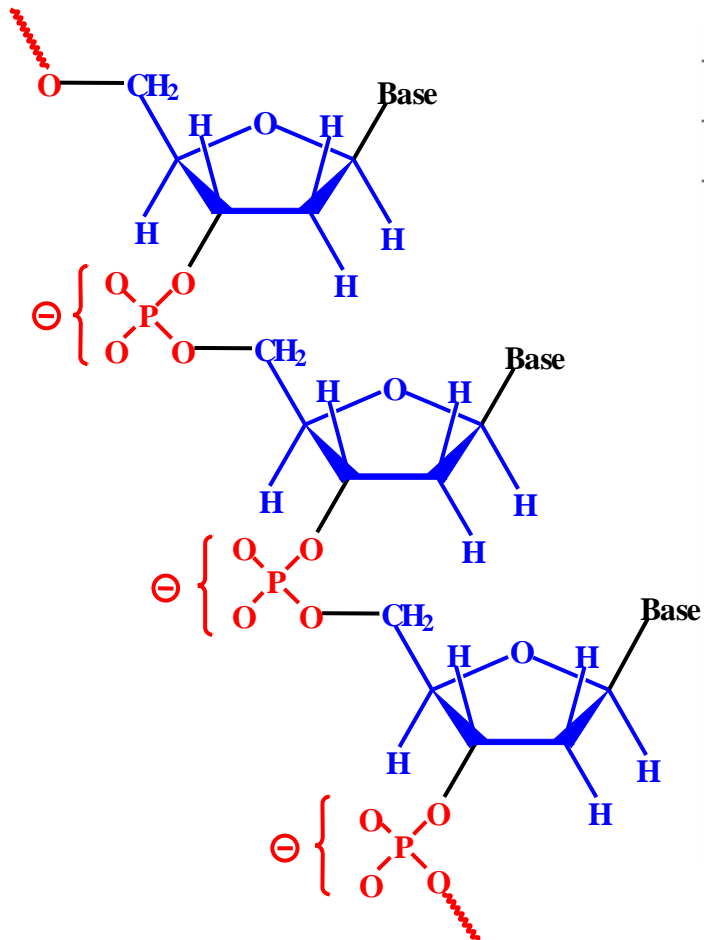
Nucleotide  
X = OH: Ribose  
X = H Desoxiribose



# Nucleobases – pairing

## Metals influence pairing of nucleic acid polymers (H-bonding)

- Pairing of nucleobases inside DNA, complementarity of A-T and G-C
- Metal atoms: Mispairing possible (carcinogenic effect), e.g. T-G

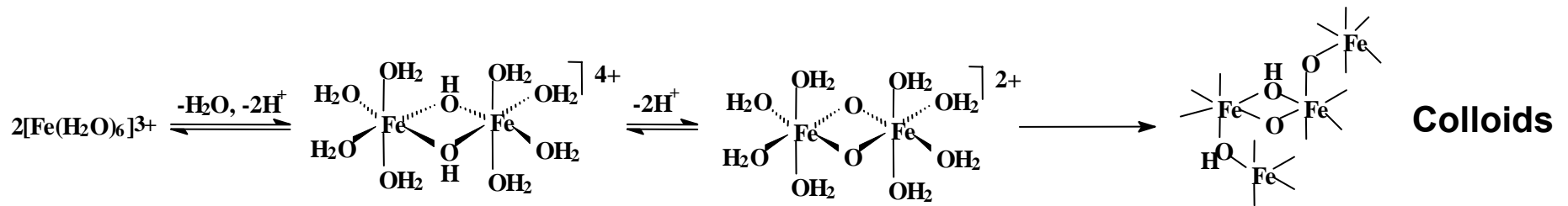


**3.**

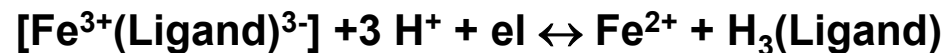
**Coordination for uptake,  
transport and storage (Fe)**

# Some basic properties of Fe

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

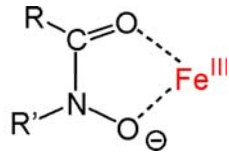


- Related affinity to different ligands (S, O, N)
- Switching from high- to low spin configuration (medium strength of ligand)
- Complexation interconnected with electron and proton transfer:

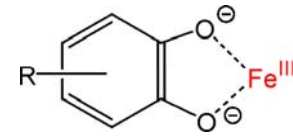


# Siderophores (microorganisms)

- Two groups of chelating agents



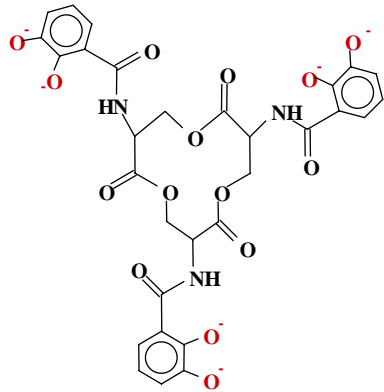
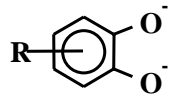
Hydroxamate



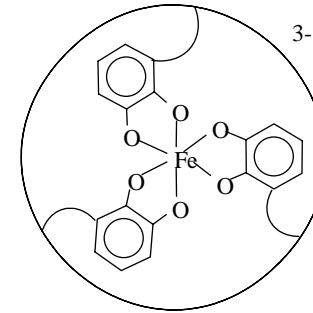
Catecholate

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

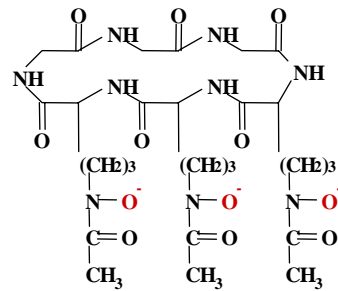
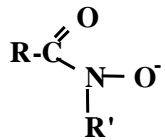
Catecholate



Apoenterobactin

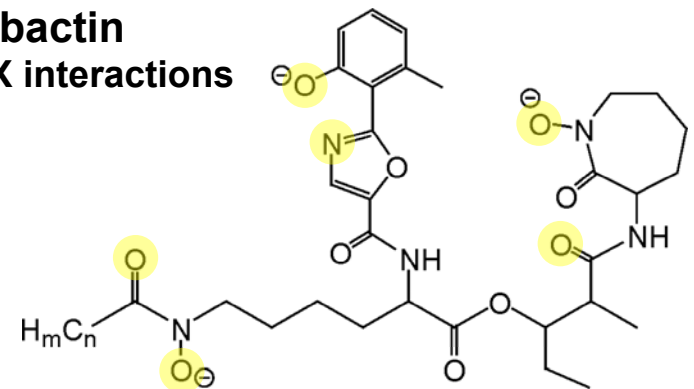


Hydroxamate



Ferrichrome

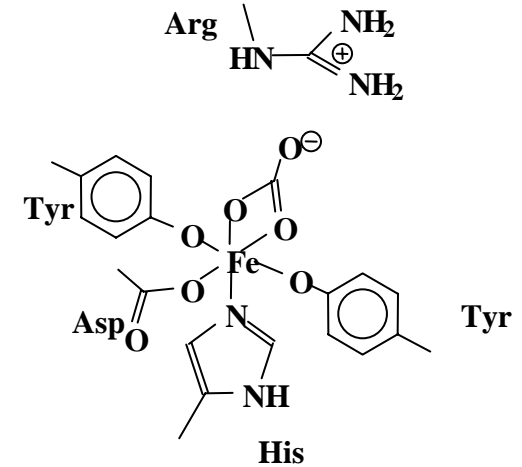
Mycobactin  
Different M-X interactions



# Proteins (complex organisms)

## Transport: Transferrin

- Coordination of Fe by carboxy- and phenolate groups of residues
- Uptake of two Fe(III) and one  $\text{HCO}_3^-$
- Stability of complexes decrease with decreasing pH
- High affinity of Apotransferrin, protection against infections
- Not very specific ( $\text{Cr}^{3+}$ ,  $\text{Al}^{3+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Mn}^{2+}$ ...)
- Release of Fe(III): Reduction to Fe(II) and binding by porphyrine



## Storage: Ferritin

- High symmetry of Apoferritin:  $F_{432}$
- Hollow sphere built from proteins (inner dia.: ~ 7 nm, outer dia. ~ 13 nm)
- Capacity: up to 4500  $\text{Fe}^{3+}$ , 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

# Basics of Bioinorganic Chemistry

## Handout- part 2

**Lorenz Kienle**

**Max-Planck-Institut für  
Festkörperforschung  
Stuttgart**







**4.**

**Hard ions: Na<sup>+</sup>, K<sup>+</sup>,**

**Mg<sup>2+</sup>, Ca<sup>2+</sup>**

# Basic characteristics

	Na <sup>+</sup>	K <sup>+</sup>	Mg <sup>2+</sup>	Ca <sup>2+</sup>
				
	<b>Antagonism</b>			
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

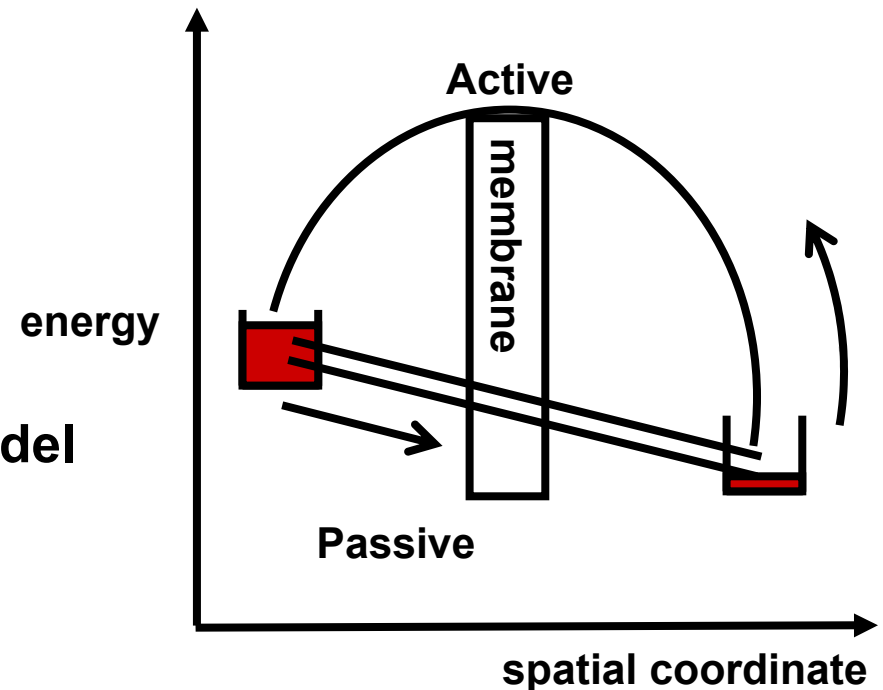
**Labile bonding in solution, fast diffusion along a concentration gradient**



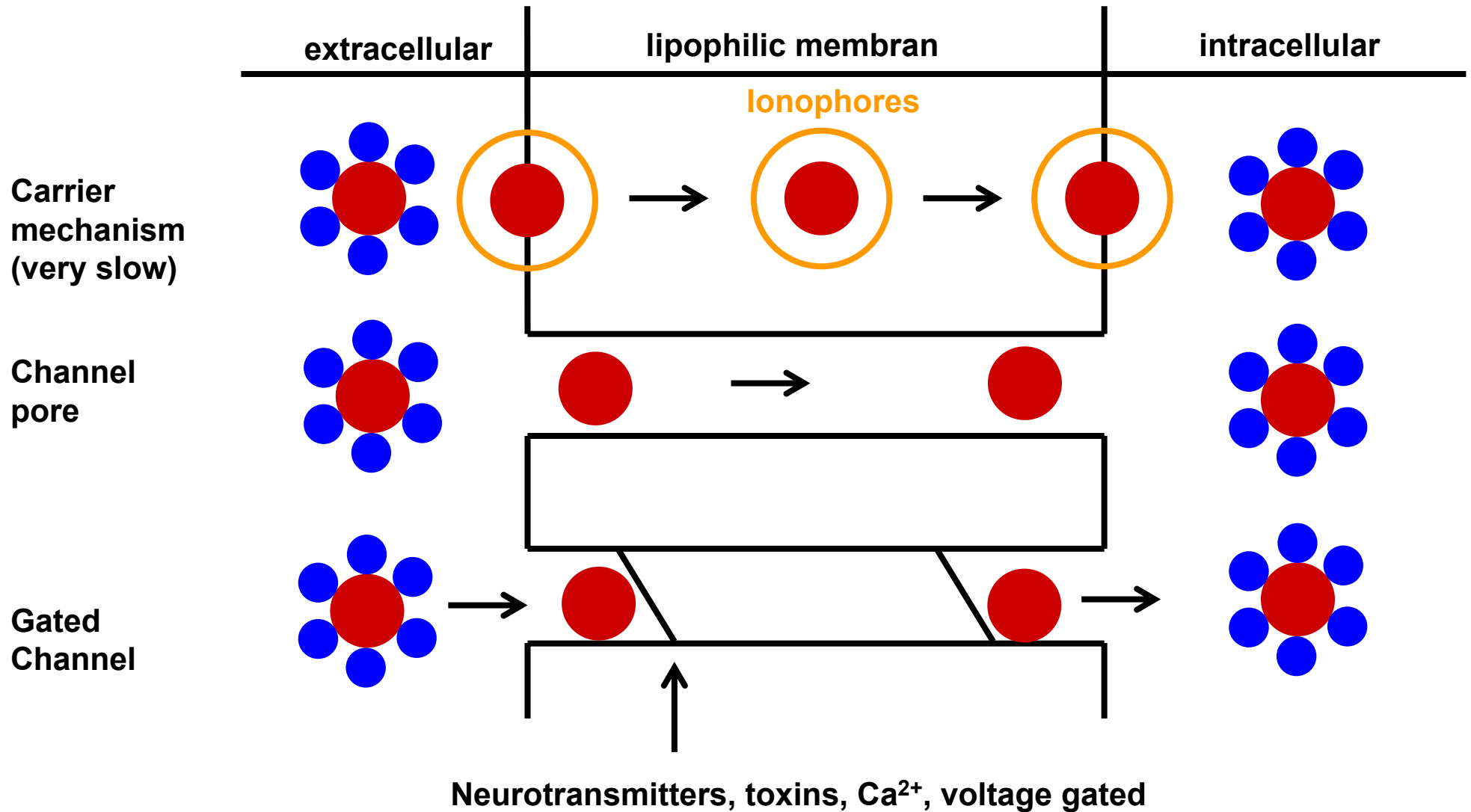
# Na, K: Inhom. distributed electrolytes

- **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

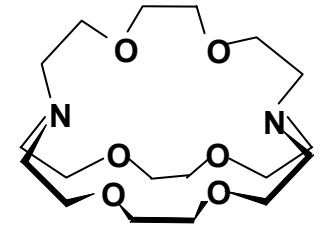
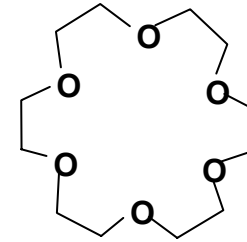


# Passive Ion transport- summary

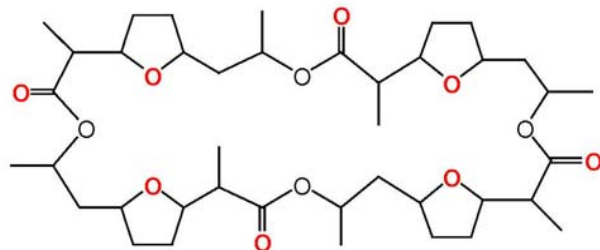


# Passive transport: Ionophores

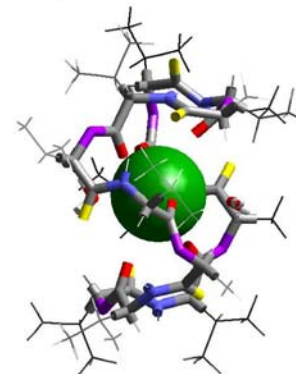
- **Analogs from the lab: crown ethers, cryptands (macrocycles)**
- **Chelate effect (thermodyn. and kinet. stable)**
- **Size/charge selectivity**
- **Distinct polarity inside / outside the complex**
- **Template effect of alkali metal (conformational change of ionophore)**
- **Selectivity depending 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 perforate a membrane
- Antiparallel helical aggregate of proteins

### 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

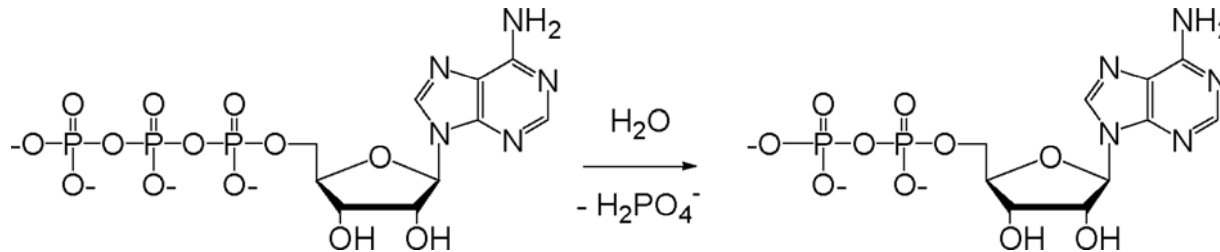
- Gate functioning important subject of pharmaceutical research
- Opening by neurotransmitters,  $\text{Ca}^{2+}$ , electrical pulses...
- Blocking as important biological function, e.g. blocking of  $\text{K}^+$  channels by  $\text{H}^+$  → sensing of “sour”

# Active transport: Ion pumps- overview

Transmembrane protein acting against concentration gradient

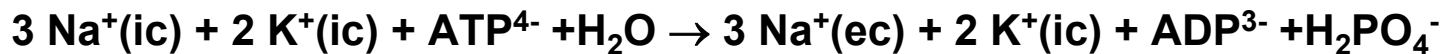
## Structure, function:

- 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<sup>+</sup>/Cl<sup>-</sup>) in same direction
- Antiport: transport of ions of the same charge in opposite direction (H<sup>+</sup>/K<sup>+</sup>)

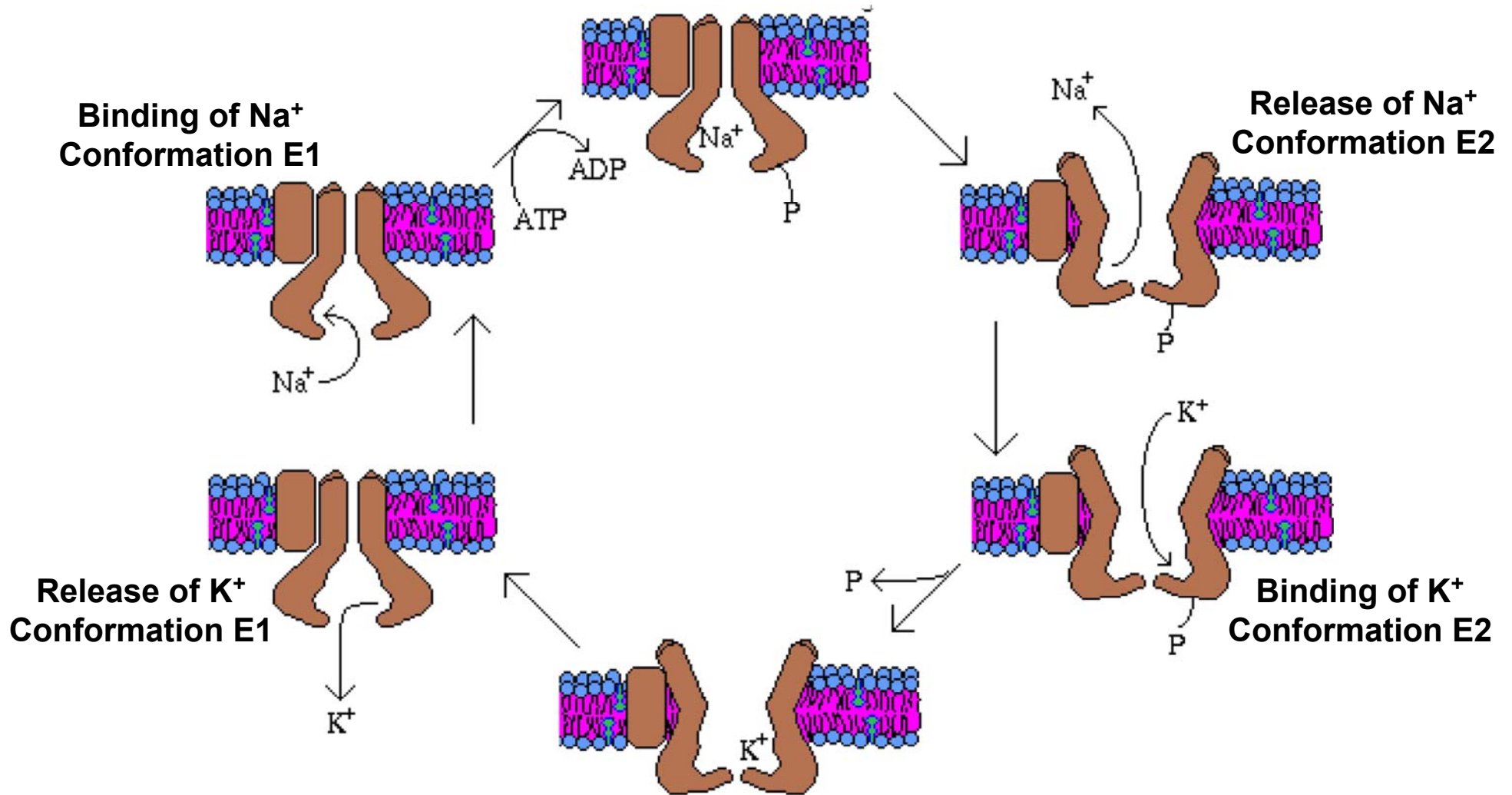
## Example: Na<sup>+</sup>/K<sup>+</sup>/MgATPase (Mg<sup>2+</sup>-catalysis)



ic: intracellular, ec: extracellular

# Na<sup>+</sup>/K<sup>+</sup>/MgATPase: Flip-Flop-mechanism

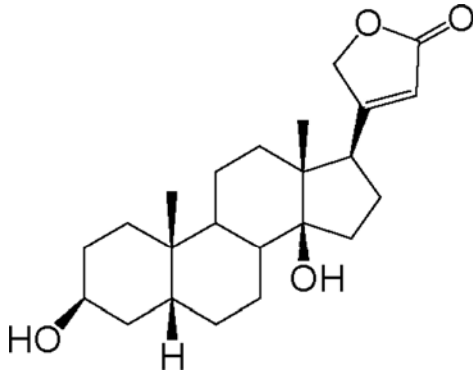
Phosphorylation, conformational change to E2



Dephosphorylation, conformational change to E1

# Toxins affecting ion transport (examples)

- **Digitoxigenine (Foxglove): Blocking of Na<sup>+</sup>/K<sup>+</sup>/ATPase**

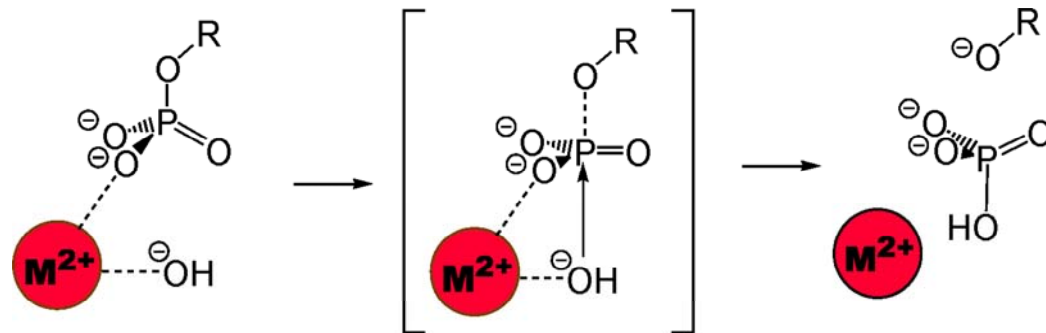


- Inhibition of dephosphorylation
- Increase of Na<sup>+</sup> and Ca<sup>2+</sup> due to antiport system
- Consequence: Muscle contraction (heart!)

- **Poison of Fugu fish (Tetrodotoxin): Blocking of Na<sup>+</sup> channels**

# Mg: Catalysis of phosphate transfer

- $\text{Mg}^{2+}$ : 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:  $\text{Mg}^{2+} + \text{OH}_2 \rightarrow [\text{Mg}\cdots\text{OH}]^+ + \text{H}^+$
  - Fixation of the reactants
- Mechanism:  $\text{S}_{\text{N}}2$  with pseudorotation
  - Conformational changes during Na/K pumping

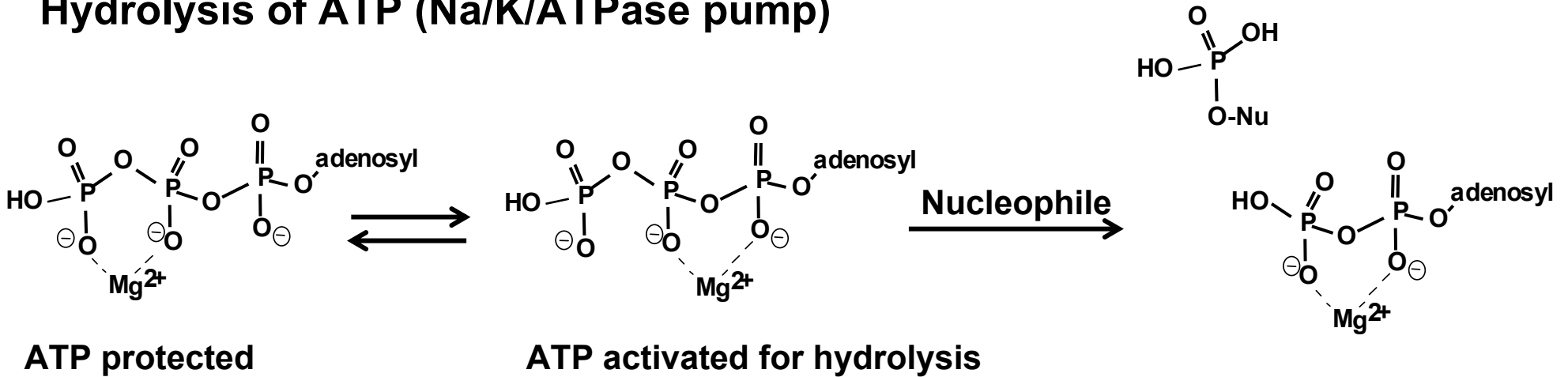


On the average a human adult synthesizes and uses an amount of ATP per day which corresponds to the body weight!



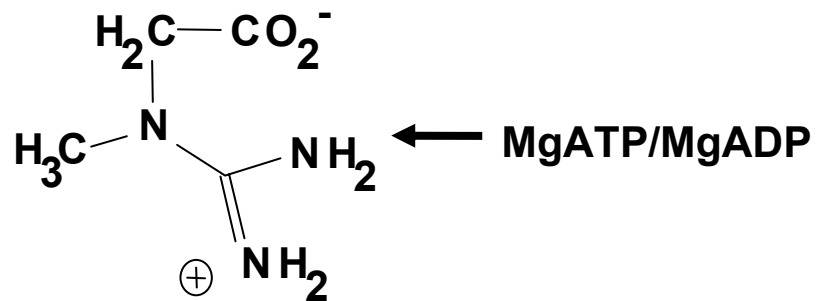
# Mg: phosphate transfer- examples

## Hydrolysis of ATP (Na/K/ATPase pump)



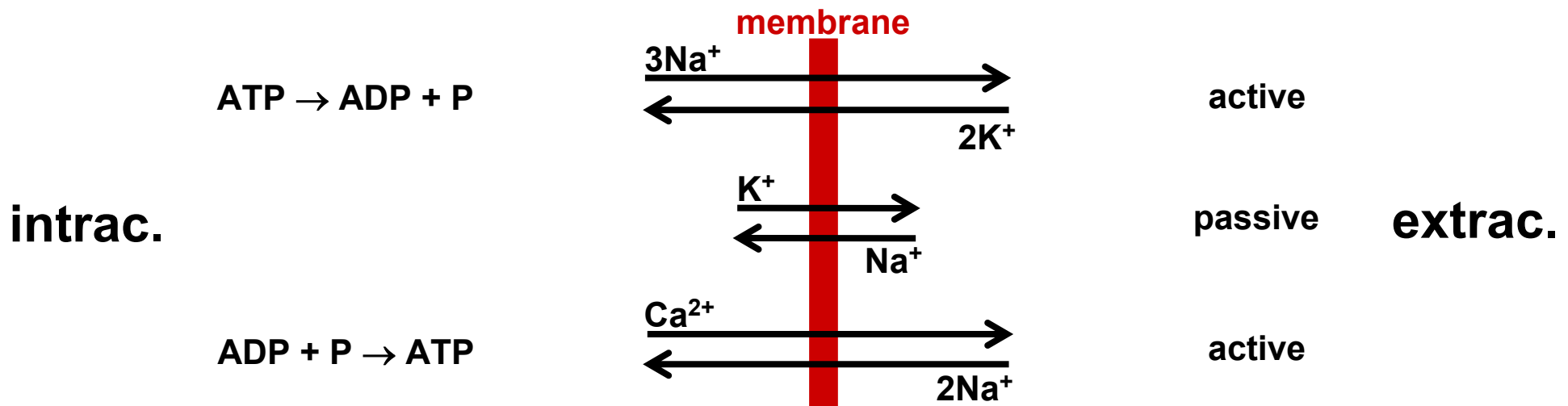
## Phosphate transfer to creatine via MgATP

## Phosphate transfer to glycerate (formation of 2-phosphoglycerate)



# Ca: great variety of functions

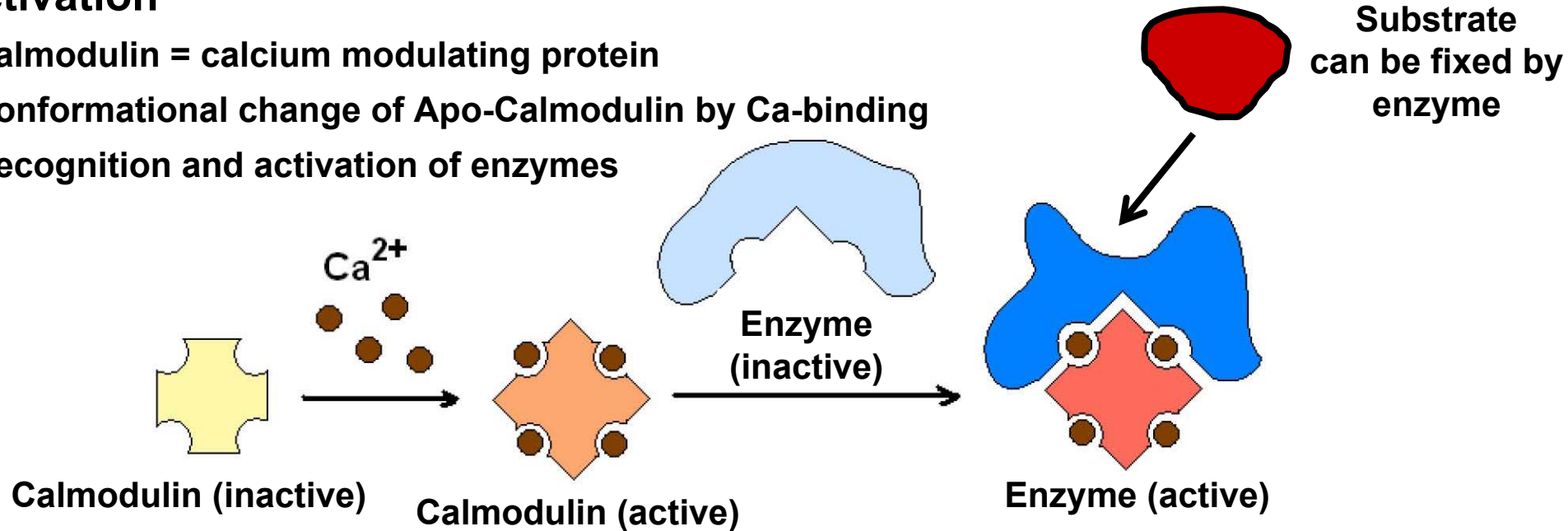
- **Structural function**
  - Biomineralization (1 kg), 10g/70kg in non-solid form
  - Strong influence on protein folding
- **Second messenger-, trigger-, activation function**
  - Binding to acidic  $\mu^2$ -carboxy groups of proteins
  - High coordination numbers (7, 8), irregular coordination geometry
  - Lability of complexes allows fast structural changes
  - High concentration gradient ( $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  from acidic storage protein: Calsequestrin
- Calsequestrin contains up to 50 Ca-binding sites, carboxylate groups (Glu, Asp)
- Uptake of  $\text{Ca}^{2+}$  by Troponin C, coupling with ATP Hydrolysis...

# Biom mineralization: $\text{CaCO}_3$ - 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  $\text{CaCO}_3$

## Calcite, Calcite, {104}

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

## Aragonite

metastable, otholithes of fishes,  
coral reef, pearls

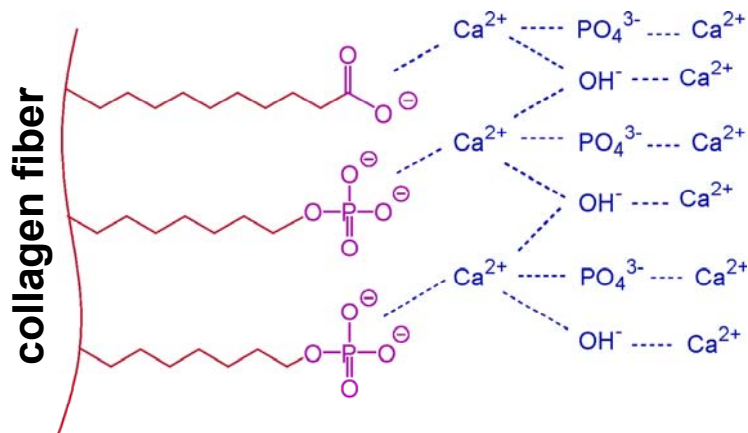
## Vaterit

metastable, disordered (?), rare  
formation of sperolithes

**Amorphous  $\text{CaCO}_3$**   
formation of spherolites

# Biom mineralization: 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 (?)

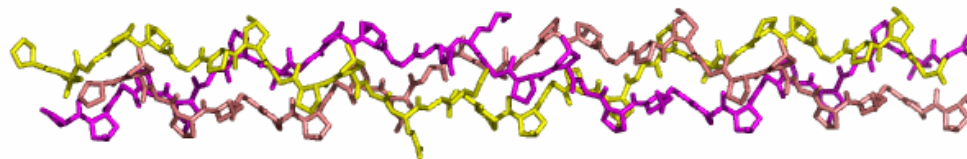
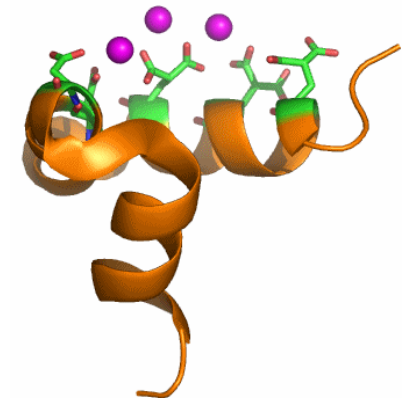


## Hydroxyapatite

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

## Osteocalcin

- Perfect match with apatite

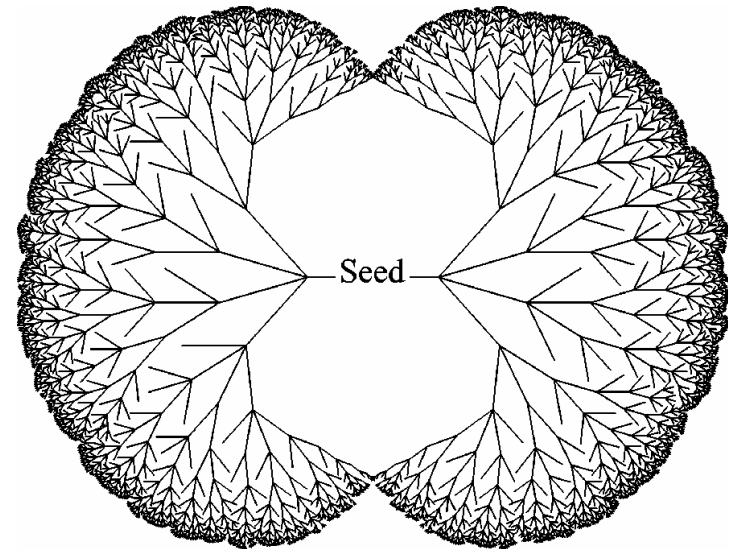


## Collagen

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

# Biomimetic morphogenesis (S. Busch)

- **Growth of apatite on gelatine in the lab**
- **Observations:**
  - Formation of a hexagonal seed (no crystal)
  - Formation of dumbbell
  - Formation of closed spheres
- **Principles of crystal growth**
  - Fractal growth with self-similarity
  - Maximum aperture:  $(45 \pm 5)^\circ$ , down scaling by 0.7
  - Discussion of internal electrical fields
  - Switch to polar space group (?), ordering of OH-groups (?)



**Umbrella tree model**

# Biom mineralization: $\text{SiO}_2$ - diatoms

- Polymers of silicid acid  $\text{SiO}_n(\text{OH})_{4-2n}$ , no silicates, related to opal
- Aggregation of silicid acid in SVD (silica deposition vesicles)
- Inhibition of spontaneous polycondensation by ionophores (?)
- Polycondensation via Proteins, e.g. silaffines: engaged condensation
- Intermediates: D6R, D4R (see zeolites)
- Formation of nanospheres, micro-morphogenesis