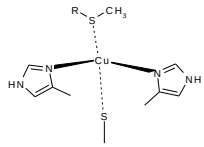
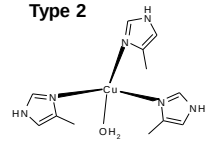
4) Metals in biological systems III, Copper proteins (1)

- Copper is an essential trace element
- components in redox systems
- biological alternative to Fe proteine (but completely different coordination environment)
-Coordination via histidin and cystein

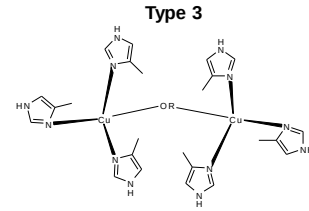
Type 1



Type 2



Type 3



Type 1	Type 2	Type 3
- ‚blue' copper proteins - $Cu^{2+} + e^- \rightleftarrows Cu^+$ - strongly distorted tetrahedron - EPR with small Cu couplings (e^- in ligand orbitals)	-‚non-blue' copper proteins - O_2 activation - almost square- planar coordination - EPR with well-resolved Cu couplings	- oxygen-bridged dimer - O_2 uptake and transport - EPR inactive - antiferromagnetic coupling of the unpaired electrons

4) Metals in biological systems III, Copper proteins (2)

Iron and copper proteins with similar functions

Function	**Fe-Protein** (h: Hem-system) (nh: Non-hem-system)	**Cu-Protein**
O_2 Transport	Haemoglobin (h) Haemerythrin (nh)	Hemocyanin
Oxygenation	Cytochrome P-450 (h) Methan monooxygenase (nh) Catechol dioxygenase (nh)	Tyrosinase Quercetinase (Dioxygenase)
Oxidase-Activity	Peroxidases (h) Peroxidases (nh)	Amin-Oxidases Laccase
Electron Transfer	Cytochromes (h)	Blue (Type 1) Cu-Proteins
Antioxidizing function	Peroxidases (h) Bacterial Superoxide Dismutases (nh)	Superoxide Dismutase (Cu, Zn) from erythrozytes
NO_2^--Reduction	Hem-containing Nitrite reductase (h)	Cu-containing Nitrite reductase

4) Metals in biological systems III, Zinc proteins (3)

- Two principally different functions are common for zinc in biological systems

Structural function
(Coordinative bonds as parts of protein skeleton)

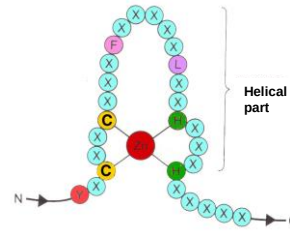
Enzymatic function
(Biocatalysis)

Structural function	**Catalytical function**
- completely coordinated Zn centers (frequently tetrahedral) - Coordination by two or more histidin ligands (with this, the increase of the coordination numer is highly unprobable) -Typical Coordination spheres: $[Zn(Cys)_4]$, $[Zn(Cys)_3(His)]$, $[Zn(Cys)_2(His)_2]$	- Molecules possess incomplete coodination sphere of the metal (in inactice form frequently occupied by OH^- or H_2O) - Coordination numbers 5 or 6 are - possible -Typical Coordination spheres: $[Zn(His)_2(Glu)(H_2O]$, $[Zn(His)_3(H_2O)]$, $[Zn(Cys)_2(His)(H_2O)]$

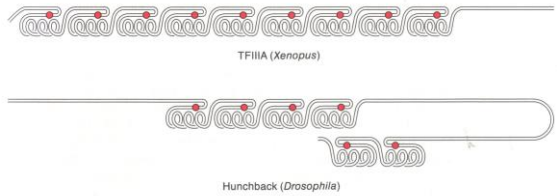
4) Metals in biological systems III, Zinc proteins (4)

Structural function of zinc in proteins

- Typical structural unit → 'zinc finger'
- finger-like bonding motif in many proteins
- frequently used to fix 3D-structure of reactive centers



Arrangement of zinc finger domains in proteins



4) Metals in biological systems III, Zinc proteins (5)

Structural function of zinc in proteins

Typical representatives of proteins with zinc in structure-determining role:

Zinc protein	M (kDa)	Ligands	Function
Gen transscription Factors	TF IIIA: 40	2 His n x 2 Cys	Structur funktion: formation of specifically folded domains
	Gal4: 17	2 x 4 Cys	
Insulin hexamer	6 x 6	3 His n x 3 H_2O	Structure function: stabilization of oligomers
Metalothionein	6	≤ 7 x 4 Cys	transport and storage of metals

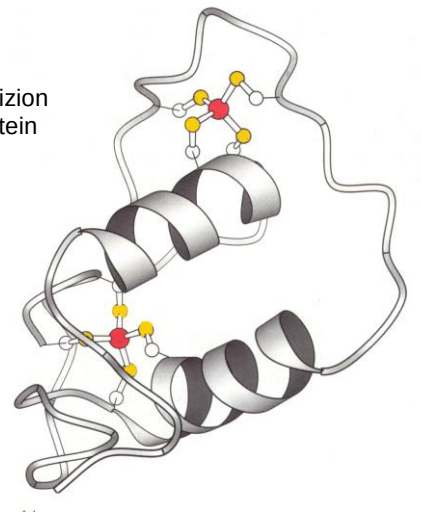
Zn-binding domains in nucleic acid forming proteins:
- Structural role of Zn centers
- Zn is essential for the function of the proteins
- modular design of the proteins are governed by Zn

4) Metals in biological systems III, Zinc proteins (6)

Structural function of zinc in proteins

Steroid receptors:

- Small domains of 66 amino acids
- 9 conserved cystein residues
- Zn has no influence on DNA recognizion
- Zn promotes dimerization of the protein

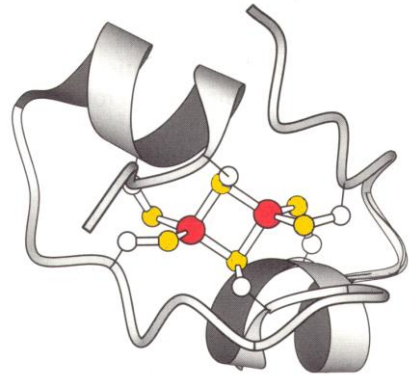


4) Metals in biological systems III, Zinc proteins (7)

Structural function of zinc in proteins

GAL4 protein:

- gen-regulating protein
- Zn centers are essential for the function of the protein
- $[Zn_2(Cys)_6]$ centers

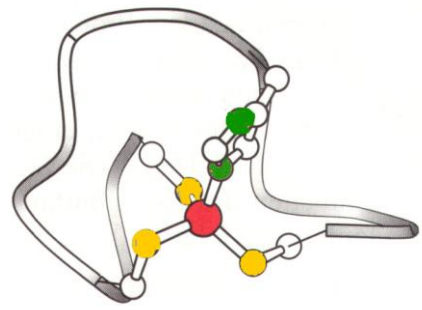


4) Metals in biological systems III, Zinc proteins (8)

Structural function of zinc in proteins

Retrovirus shell protein:

- Zn coordinated by 3 x cystein and 1 x histidine
- Zn is essential for the functionality of the protein
- The small units are copied many times in retroviruses, which results in unusually high Zn concentrations (up to 1 mmol/L)



4) Metals in biological systems III, Zinc proteins (9)

Catalytical function of zinc in proteins

Typical examples for Zn catalysis:

Zinc protein	M (kDa)	Ligands /domain	Function
Carboanhydrase (CA)	30	3 His, 1 H_2O	Hydrolysis
Carboxypeptidase (CPA)	34	2 His, 1 η^2-Glu,1 H_2O	Hydrolysis
Thermolysin	35	2 His, 1 η^1-Glu, 1 H_2O	Hydrolysis
Alkaline phosphatases	2 x 47	3 His, 2 H_2O	(Phosphate) hydrolysis
		1 His, 2 Asp, 1 Ser	
		2 Asp, 1Glu, 1 Thr	
Alcohol dehydrogenase (ADH)	2 x 40	2 Cys, 1 His, 1 H_2O	Oxidation of 1- or 2-Alkoholen by means of NAD^+
Glyoxalase	2 x 23	2 His, Glu, 2 H_2O	Reduction of α-Diketones by means of glutathione
Superoxid dismutase (SOD)	2 x 16	2 His, 1 His^-,1 Asp	Disproportionation of $O_2^{\bullet-}$

4) Metals in biological systems III, Zinc proteins (10)

Catalytical function of zinc in proteins

Carboanhydrase:

Process:

$$H_2O + CO_2 \underset{}{\overset{K_1}{\rightleftharpoons}} H^+ + HCO_3^-$$

$$K_2 \quad K_3$$

$$H_2CO_3$$

$$OH^- + CO_2 \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} HCO_3^-$$

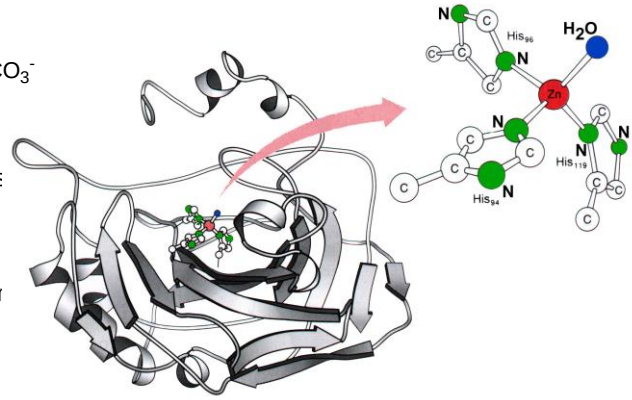
Equilibrium constants:

$K_1 = 4.44 \times 10^{-7}$

$K_2 = 1.72 \times 10^4\ M^{-1}$

$K_3 = 2.58 \times 10^3\ M^{-1}$

- Protein of medium size
- M (30 kD, 259 amino acids
- Zn coordinated by 3 x His
- Additional H_2O/OH^- ligand takes part in reaction
- Acceleration of the reaction **by a factor of 10^8 !!**
- Strongly pH dependent

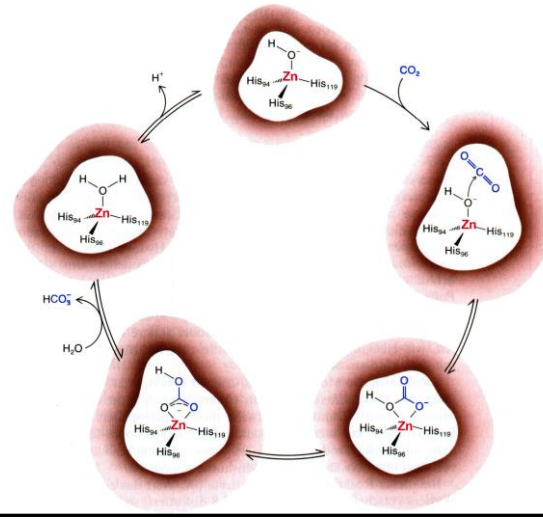


4) Metals in biological systems III, Zinc proteins (11)

Catalytical function of zinc in proteins

Carboanhydrase:

Simplified mechanism:



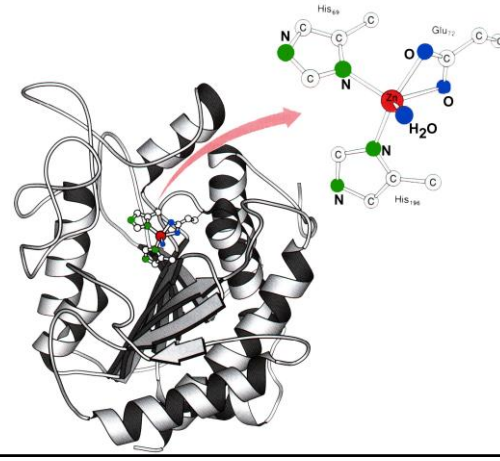
4) Metals in biological systems III, Zinc proteins (12)

Catalytical function of zinc in proteins

Carbopeptidase:

-Catalyzed reactions: cleavage of peptide bonds

- Zn is coordinated by 2 x His, 1 x chelated carboxylate and 1 x H_2O
- Carboxylate becomes monodentate, when substrate is bonded

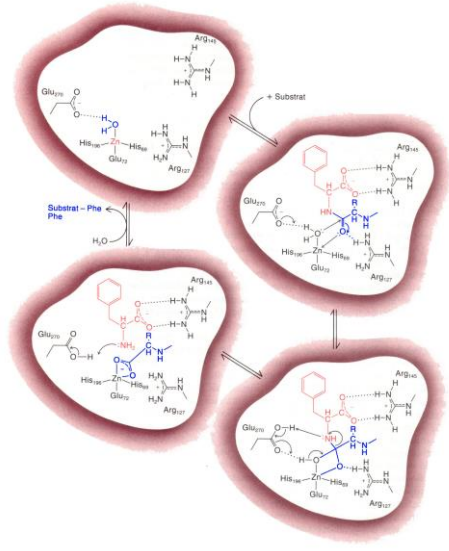


4) Metals in biological systems III, Zinc proteins (13)

Catalytical function of zinc in proteins

Carbopeptidase:

Assumed mechanism:



4) Metals in biological systems III, Vanadium (14)

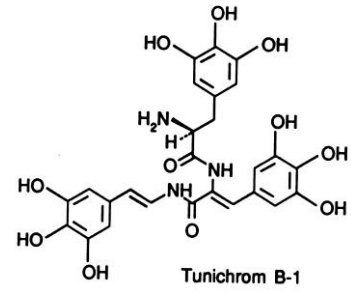
Vanadium extraction by biological systems

Tunichrome B:

Enrichment of vanadium from sea water by a factor of **10^7 !!!:**

Sea squirt

Ligand system



Tunichrom B-1

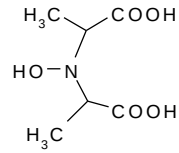
4) Metals in biological systems III, Vanadium (15)

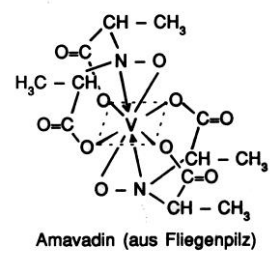
Vanadium extraction by biological systems

Amavadin:

Stable complex allows concentration of vanadium from soil up to 200 ppm **!!!:**

Fly agaric | Ligand system | Complex





Amavadin (aus Fliegenpilz)

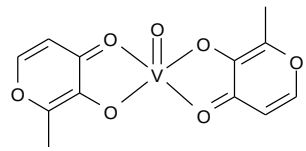
4) Metals in biological systems III, Vanadium (16)

Vanadium extraction by biological systems

Vanadium in medicine (glucose metabolism):

- Vanadium stimulates glucose metabolism

Bis(maltolato)oxovanadium(IV):



- 4 x more effective than $VO(SO_4)$
- Rapid autoxidation to V(V) compounds

- The development of new V-containing drugs is an important work to be done during the coming years

- Also other biologically active compounds are under investigation (cancerostatic activity has been detected for some compounds)