Iron–Sulfur Proteins

Many metals coordinate to their binding sites in proteins and nucleic acids as simple ions.
. **Zn(II)** binds to carboxypeptidase and to zinc-fingers domains
. **Cu(I/II)** binds plastocyanin

Sometimes a more complex metal-containing unit is required.

Two examples: **Iron-Sulfur clusters**
Polyiron Oxo Clusters and Biomineralization

Based on **Spontaneous *Self-Assembly* of Metal Clusters**

The majority of the ubiquitous Fe/S centers in proteins are involved in electron transfer at typically negative redox potentials

Fe/S centers have essential functions in:

. Photosynthesis

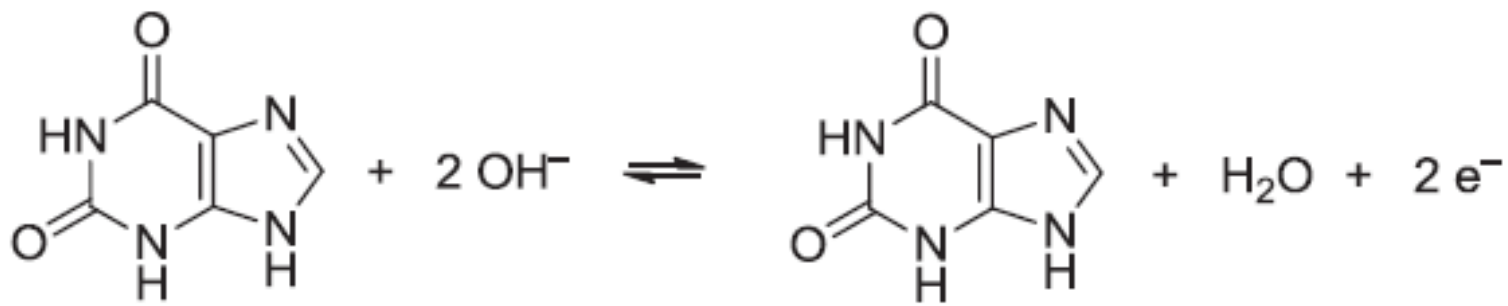
. Nitrogen fixation

. Metabolism of H_2, NO_2^-, SO_3^{2-}

In addition to the electron-transfer function, Fe/S centers have been recognized as sites for redox and non-redox catalysis; examples include the exclusively Fe/S-dependent hydrogenases and nitrogenases, as well as (de)hydrolase/isomerase enzymes of the aconitase type

Approximately 1% of the iron content of mammals is present in the form of Fe/S proteins

Some reactions catalyzed by Fe/S center-containing redox enzymes.

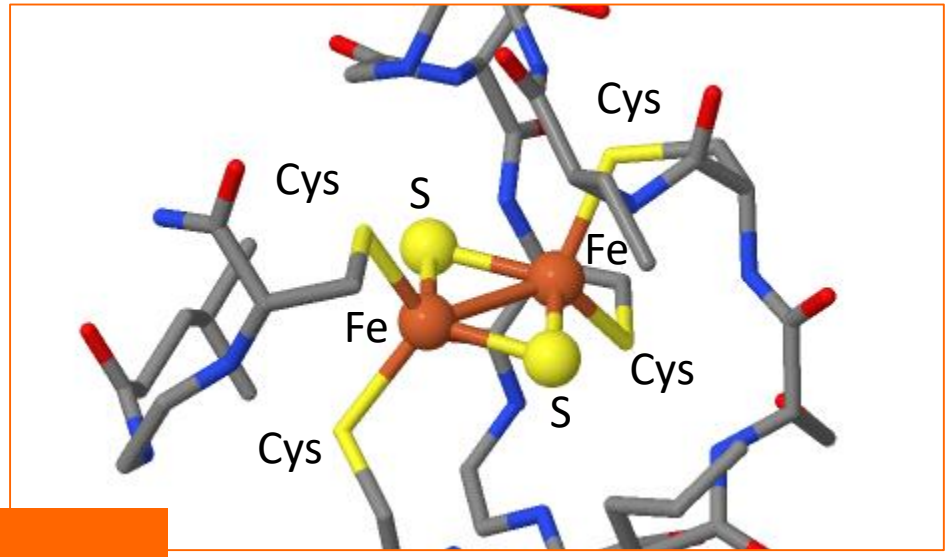
Enzymes	Catalyzed reaction
hydrogenases	$2\,H^+ + 2\,e^- \rightleftharpoons H_2$
nitrogenases	$N_2 + 10\,H^+ + 8\,e^- \rightleftharpoons NH_4^+ + H_2$
sulfite reductase	$SO_3^{2-} + 7\,H^+ + 6\,e^- \rightleftharpoons HS^- + 3\,H_2O$
aldehyde oxidase	$R\text{-}CHO + 2\,OH^- \rightleftharpoons R\text{-}COOH + H_2O + 2e^-$
xanthine oxidase	
NADP oxidoreductase	$NADP^+ + H^+ + 2\,e^- \rightleftharpoons NADPH$

Redox potentials of representative Fe/S proteins

Protein	Typical origin	Type of Fe/S center	Molecular mass (kDa)	E (mV)
rubredoxin	*Clostridium pasteurianum*	$[Rd]^{2+;3+}$	6	−60
2Fe ferredoxin	spinach	$[2Fe\text{-}2S]^{1+;2+}$	10.5	−420
adrenodoxin	adrenal mitochondria	$[2Fe\text{-}2S]^{1+;2+}$	12	−270
Rieske center	adrenal mitochondria	$[2Fe\text{-}2S]^{1+;2+}$	250 (bc_1 complex)	+280
4Fe ferredoxin	*Bacillus stearothermophilus*	$[4Fe\text{-}4S]^{1+;2+}$	9.1	−280
8Fe ferredoxin	*Cl. pasteurianum*	$2[4Fe\text{-}4S]^{1+;2+}$	6	−400
High-potential iron–sulfur protein (HiPIP)	*Chromatium vinosum*	$[4Fe\text{-}4S]^{2+;3+}$	9.5	+350
ferredoxin II	*Desulfovibrio gigas*	$[3Fe\text{-}4S]^{n+}$	24	−130
ferredoxin I	*Azotobacter vinelandii*	$[3Fe\text{-}4S]^{n+}$		
		$[4Fe\text{-}4S]^{n+}$	14	−460

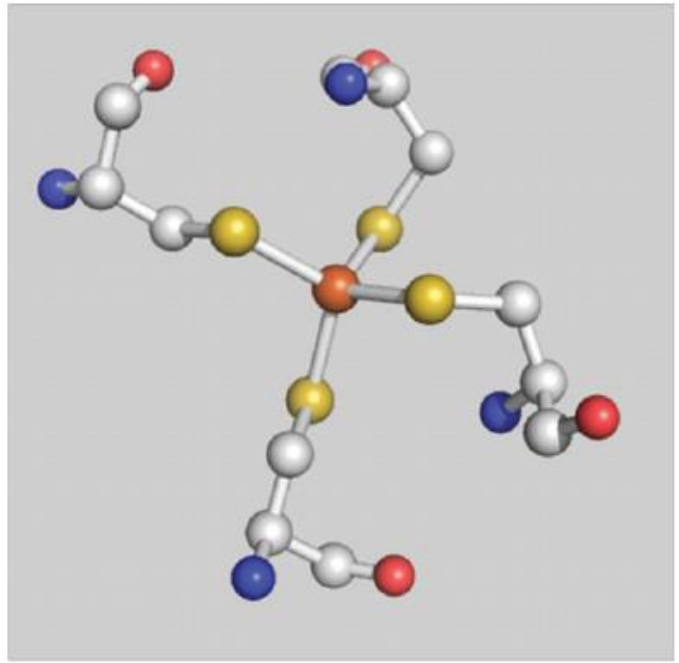
Fe/S centers in proteins occur as:

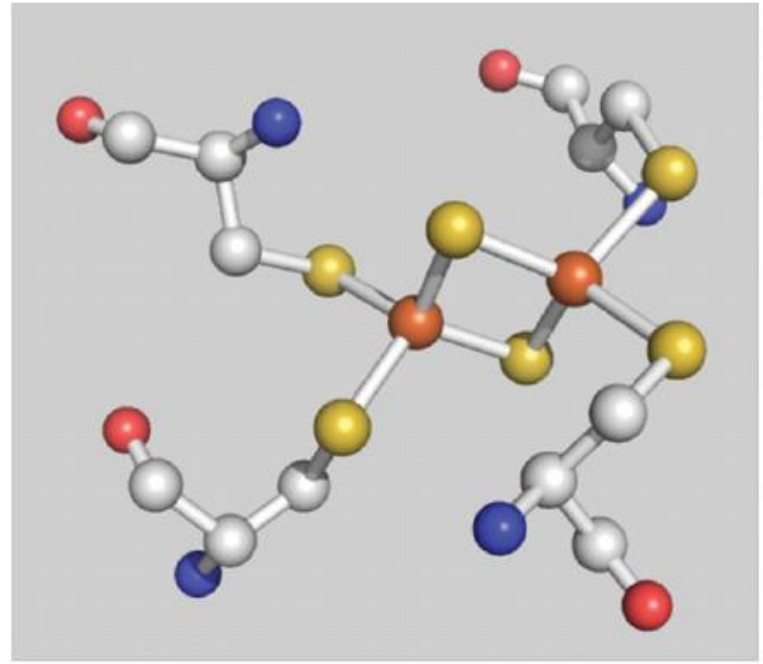
- isolated clusters, for example in the small, electron-transferring “ferredoxins”
- in interaction with other prosthetic groups such as other metal centers (Ni, Mo, V, heme-Fe) and flavins
- in Fe/S proteins happens the coordination of iron ions with protein-bound cysteinate sulfur (RS^-) (rubredoxins)
- also in polynuclear Fe/S centers, with “inorganic” acid-labile sulfide, (S^{2-}).



PDB = 1A70
SPINACH FERREDOXIN

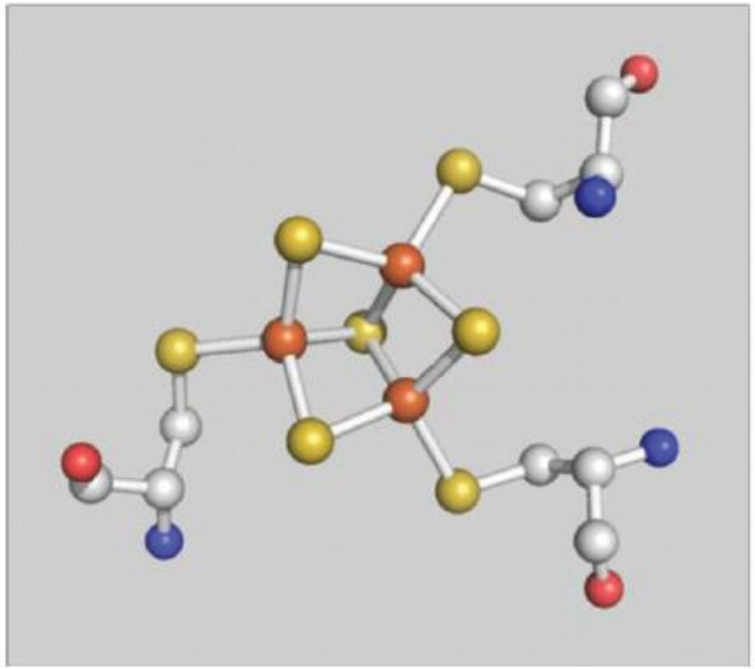
$[Rd]^{3+;2+}$

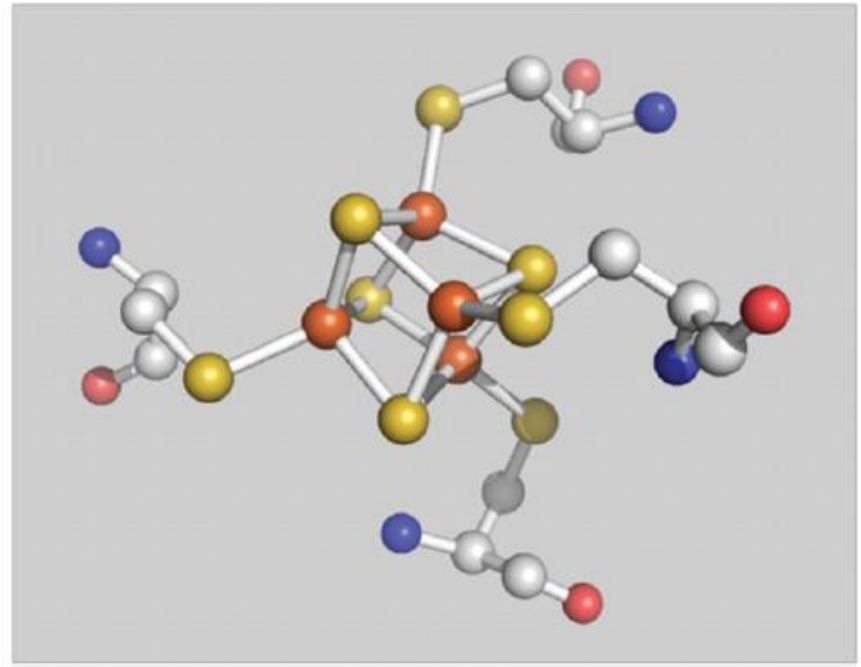




$[2Fe\text{-}2S]^{2+;+}$

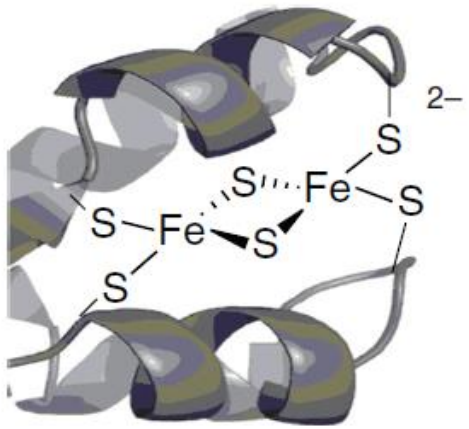
$[3Fe\text{-}4S]^{+;0}$





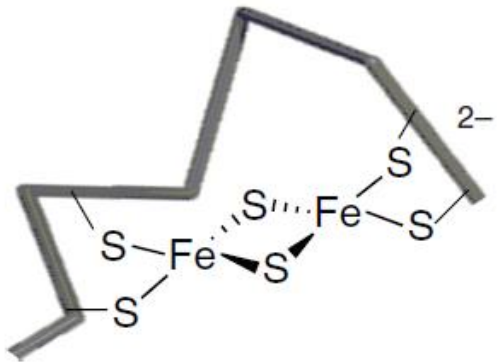
$[4Fe\text{-}4S]^{3+;2+;+}$

Sulfide and iron ions are often extractable and in many cases the remaining apoenzymes can be reconstituted with external S^{2-} and $Fe^{2+/3+}$ ions.

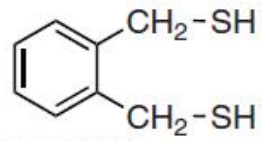


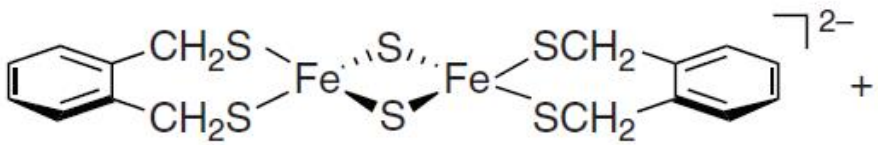
Fe/S protein

+ solvent
(denaturing)



+ 2 S^{2-} + 2 Fe^{3+}
(reconstitution)

+ 2 
(extraction)



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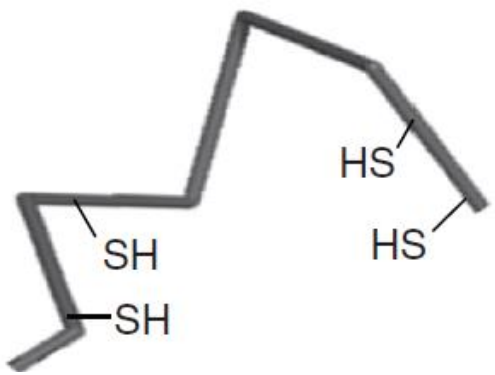
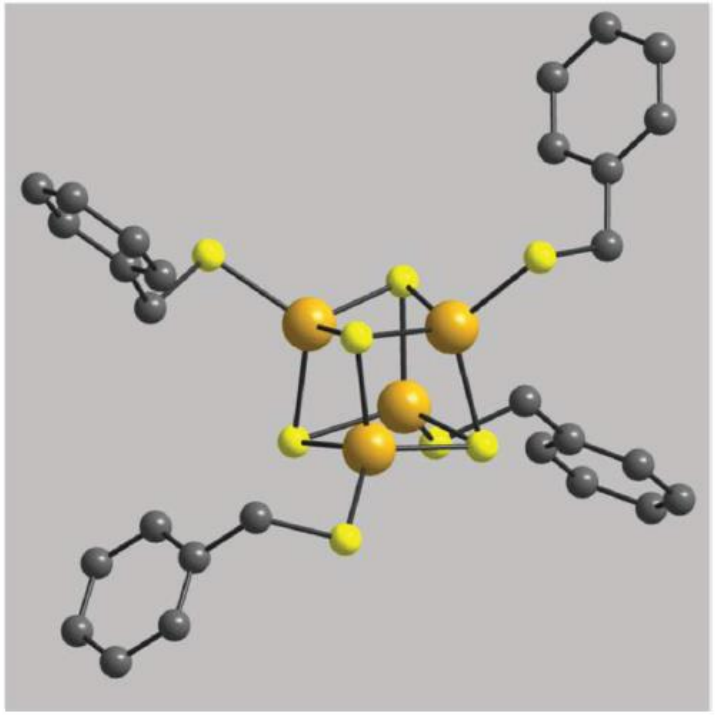


Several model complexes for Fe/S centers in proteins can be prepared via
“spontaneous self-assembly” reactions

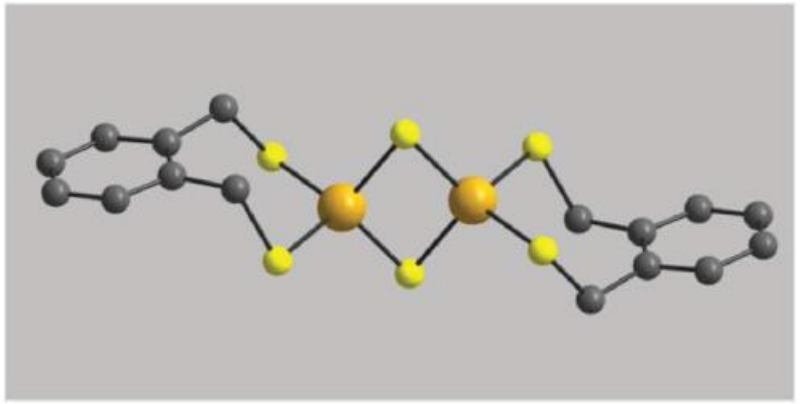
$$6\,RSH + 4\,NaHS + 4\,FeCl_3 + 10\,NaOR \longrightarrow Na_2[Fe_4S_4(RS)_4] + 10\,ROH + 12\,NaCl + RSSR$$

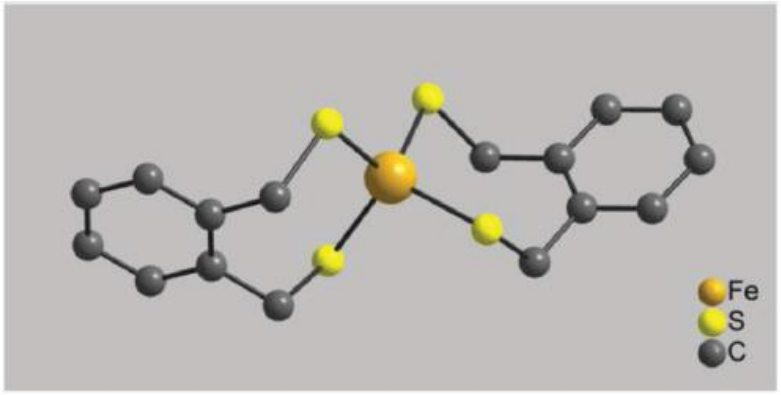
reducing conditions in polar aprotic solvents such as dimethylsulfoxide

[4Fe-4S] systems are typically formed with sterically unhindered thiols as model ligands for cysteine



conformational constraints imposed by preferentially chelate-forming dithiols (*o*-xylene-α,α’-dithiol) lead to models of **[2Fe-2S]** dimers or, in the absence of sulfide, models of **rubredoxin**





Advantages: **facile formation and thermal robustness**

Distribution in evolutionary «old» species with remarkable conservation of critical a.a. sequences

Also, occurrence in highly temperature resistant
(>100C) “hyperthermophilic” microorganisms and general oxygen sensitivity of the reduced states

important role very early in evolution => reducing atmosphere

Theory:

inorganic iron sulfides (FeS) or the disulfide (S_2^{2-})-containing pyrite (FeS_2) might have been involved in the beginning of chemoautotrophic metabolism through reduction of CO_2, according to the following reaction schemes and thus possibly in the evolution of life.

$$H_2S + 2\,FeS + CO_2 \longrightarrow 2\,FeS_2 + HCOOH$$

$$H_2O + 2\,FeS + CO_2 \xrightarrow{h\nu} 2\,FeO + 1/2\,(CHOH)_n + 2\,S$$

Off topic side note

“bacterial leaching” or “biomining” in geobiotechnology

Uses Robust “chemolithotrophic” sulfur bacteria, which obtain their energy from the transformation of inorganic compounds. The pH optimum (2–3) of reaction, the temperature resistance and the tolerance of thiobacilli with respect to heavy-metal concentrations are remarkable.

Ex.: the ubiquitous bacteria *Thiobacillus thiooxidans* and *T. ferrooxidans* can leach hardly soluble sulfides such as CuS and $CuFeS_2$ and oxides such as UO_2 which become transformed into soluble sulfates, at the same time releasing enclosed noble metals such as gold.

$$S + 3/2\ O_2 + H_2O \xrightarrow{T.\ thiooxidans} H_2SO_4$$

$$2\ FeSO_4 + 1/2\ O_2 + H_2SO_4 \xrightarrow{T.\ ferrioxidans} Fe_2(SO_4)_3 + H_2O$$

$$MS + Fe_2(SO_4)_3 \longrightarrow MSO_4 + 2\ FeSO_4 + S$$

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overall reaction:

$$MS\ (insoluble) + 2\ O_2 \longrightarrow MSO_4\ (soluble)$$

M: e.g. Cu, Zn, Ni, Co

Worldwide, about 15% of all copper produced is obtained via microbially supported leaching (50 tons per day)

[1Fe – 0S] Rubredoxins

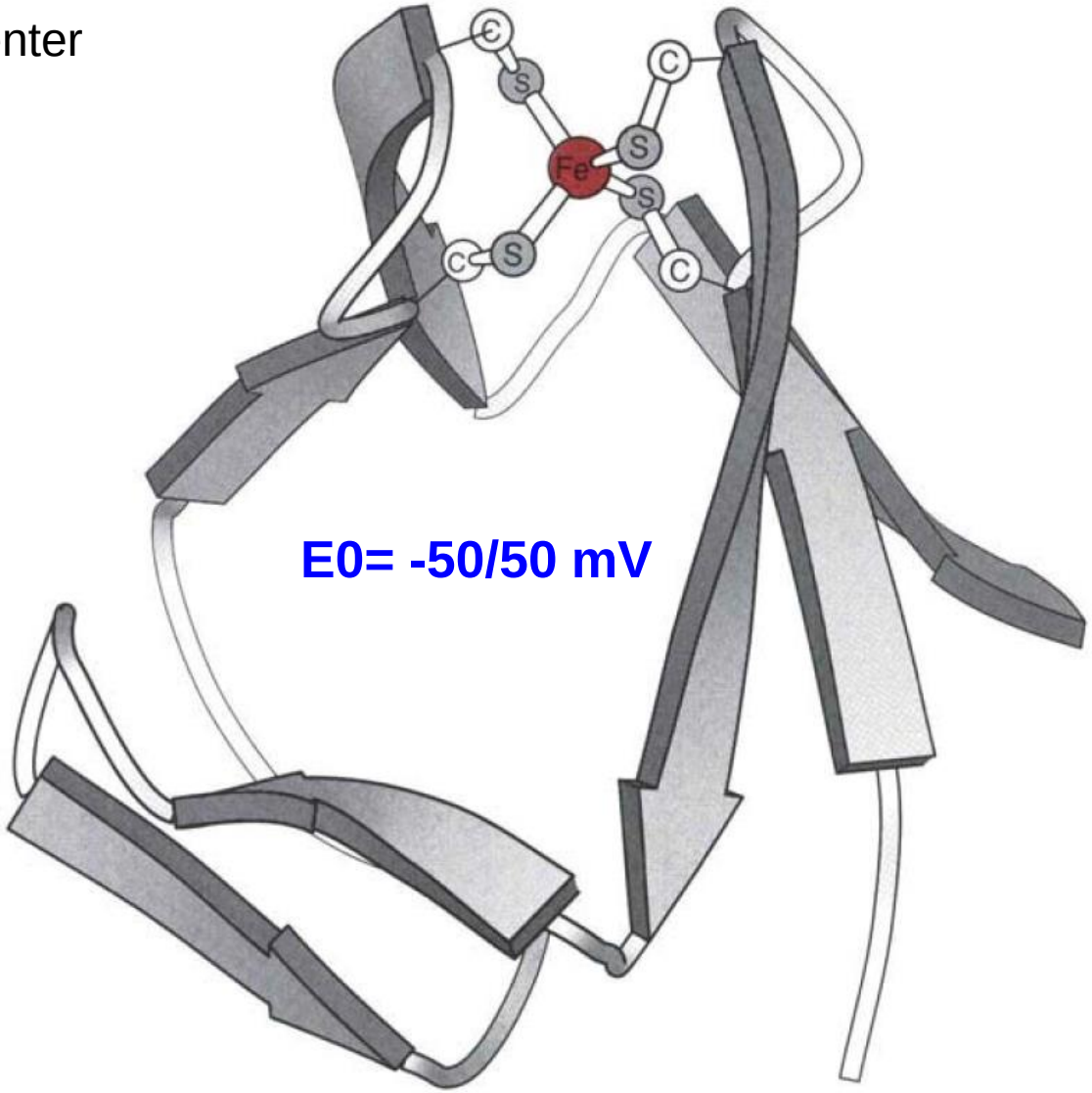
EPR and Mossbauer spectroscopy => high-spin Fe^{II}/Fe^{III}

Small redox proteins occurring in bacteria just **one iron** center

Four cysteinate ligands from two amino acid sequences

-Cys(6)-X-X-Cys(9)-Gly / -Cys(39)-X-X-Cys(42)-Gly,

The transition between the nearly colorless iron(II) state (*S* = 2) and the red iron(III) form occurs without a major change in Fe–S distances



E0= -50/50 mV

The red color of the oxidized form of Rb derives from a S -> Fe charge-transfer band at 490 nm

$$Fe^{III}(^{-}S-R) \xrightarrow{h\nu} [Fe^{II}(^{\bullet}S-R)]^{*}$$

*represents the excited state

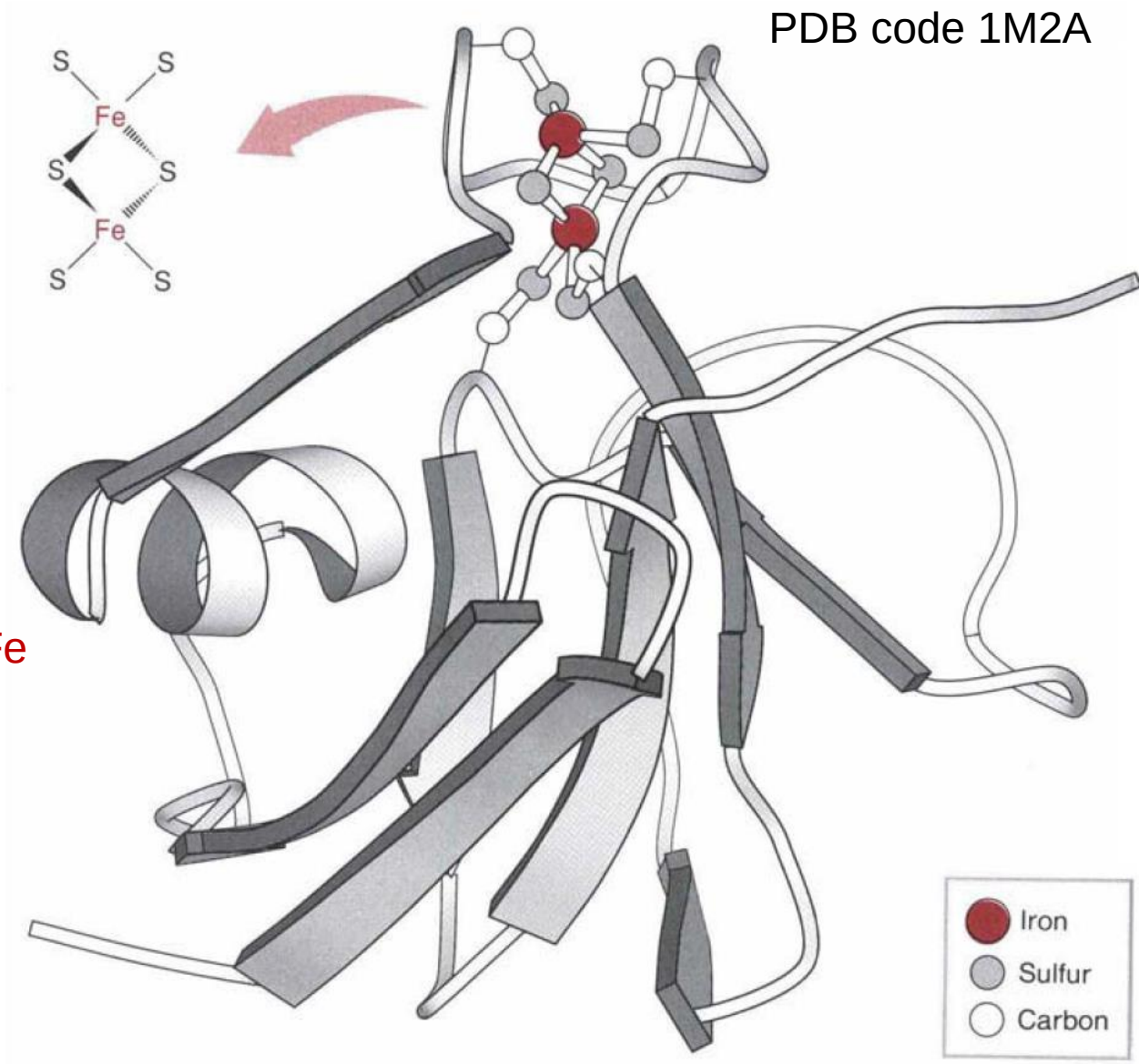
PDB = 2DSX

[2Fe – 2S] 2Fe ferredoxins

PDB code 1M2A

Presents **two iron centers each coordinated by two cysteinate side chains** of the protein and by two shared (i.e. bridging) (μ-)sulfide dianions.

The [2Fe-2S] centers are particularly common in chloroplasts, the 2Fe ferredoxin obtained from spinach leaves(in figure) having become especially well known.



The iron-iron distance is 2.70 **A** with Fe-S-Fe angles near 75", reflecting the presence of significant metal-metal bonding

Iron centers four-coordinate =weak crystal-field splitting

the metals are high-spin in both oxidized and reduced forms.

The presence of the bridging sulfur atoms provides a pathway for antiferromagnetic exchange coupling such that the ground state of the oxidized, diiron(III) form of the proteins is diamagnetic *(S = 0)*

The charge on the $[2Fe\text{-}2S2]^{n+}$ core can, in principle, vary from 0 $[Fe^{II}Fe^{II}]$ to **+I $[Fe^{II}Fe^{III}]$** mixed-valence form to **+2 $[Fe^{III}Fe^{III}]$**

These latter two forms exist in the proteins

Due to different **protein environment** and resulting electrostatic and structural asymmetry the **two iron centers are not equivalent**;

What about their redox behavior?

Mossbauer spectroscopy and other physical methods showed a **localized description with fixed valences Fe^{II} and Fe^{III}** for reduced [2Fe-2S] centers

The reduction potentials for proteins containing these two iron sites are more negative than the mononuclear centers and range from - 280 to - 490 mV.

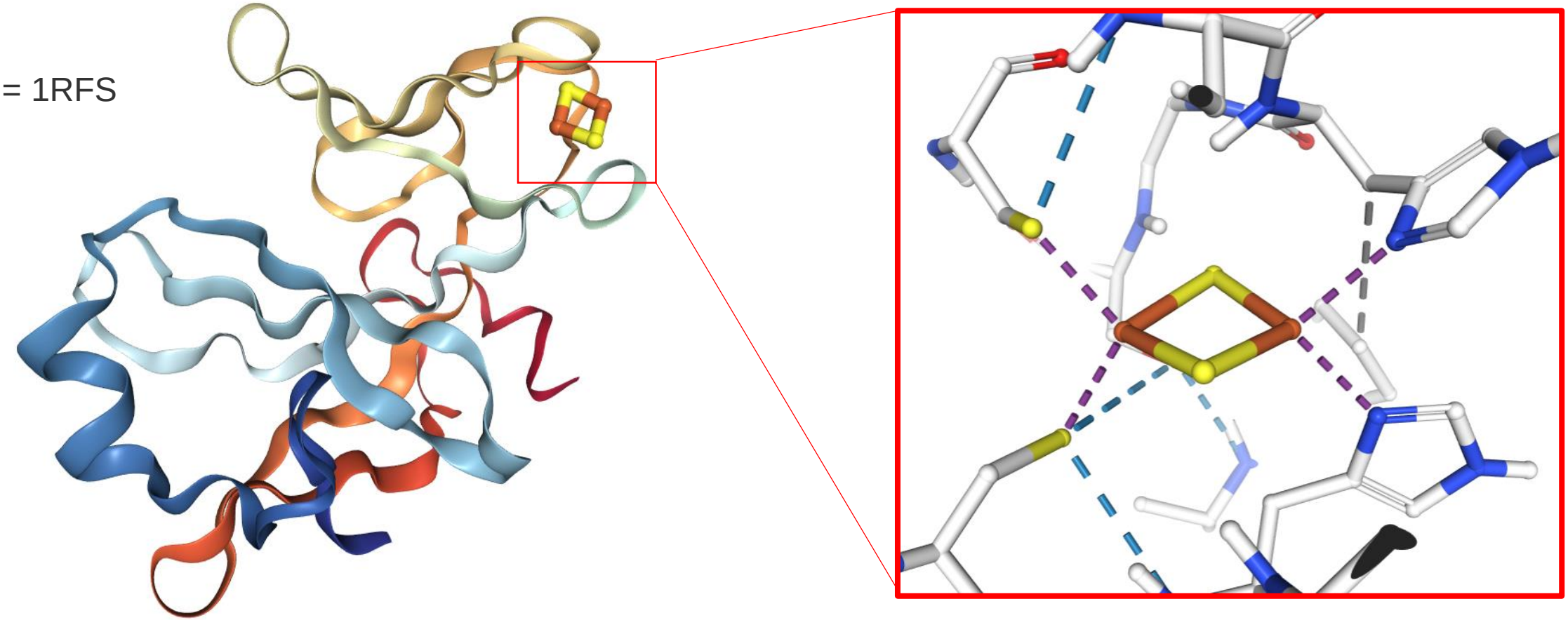
Some [2Fe-2S] proteins contain centers with unusual spectroscopic properties and relatively high redox potentials.

“Rieske centers”

found in the cytochromecontaining membrane protein complexes of mitochondria (bc1) and in chloroplasts (b6f).

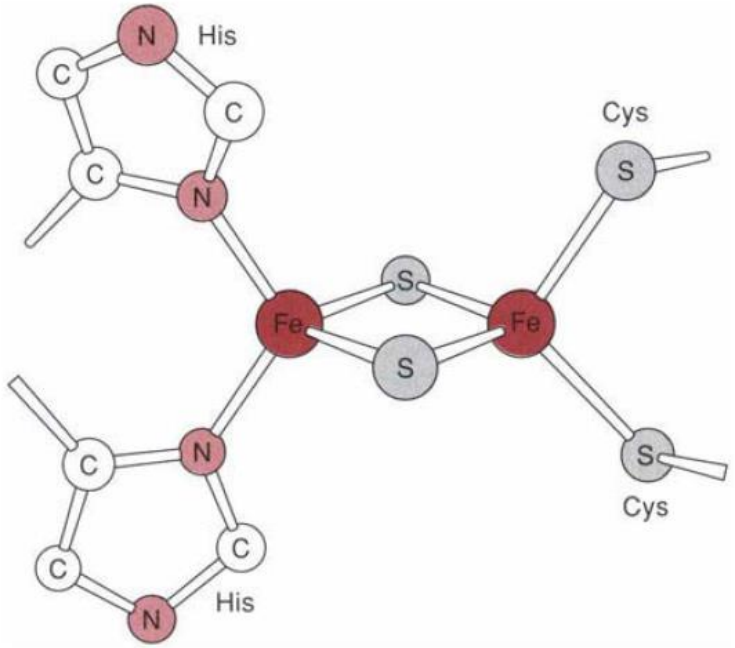
The Rieske proteins contain **two markedly different iron centers**, due to an unsymmetrical coordination involving the neutral ***non*-sulfur ligand histidine**

PDB = 1RFS



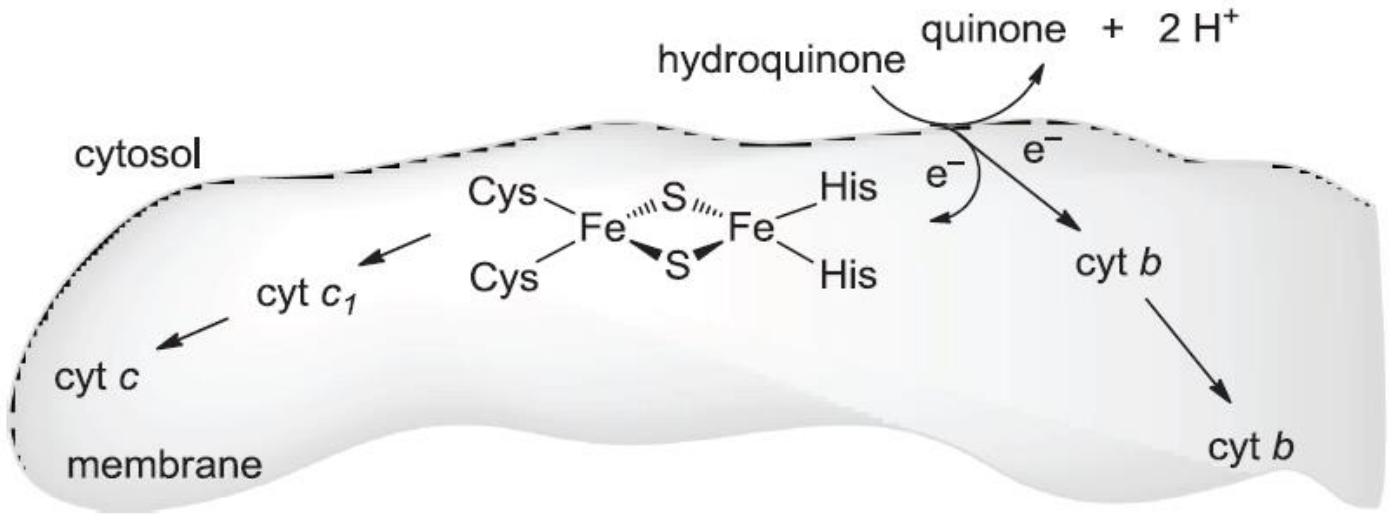
These centers have much higher redox potentials, falling in the **-150 to +350 mV range** generally closer to the higher value

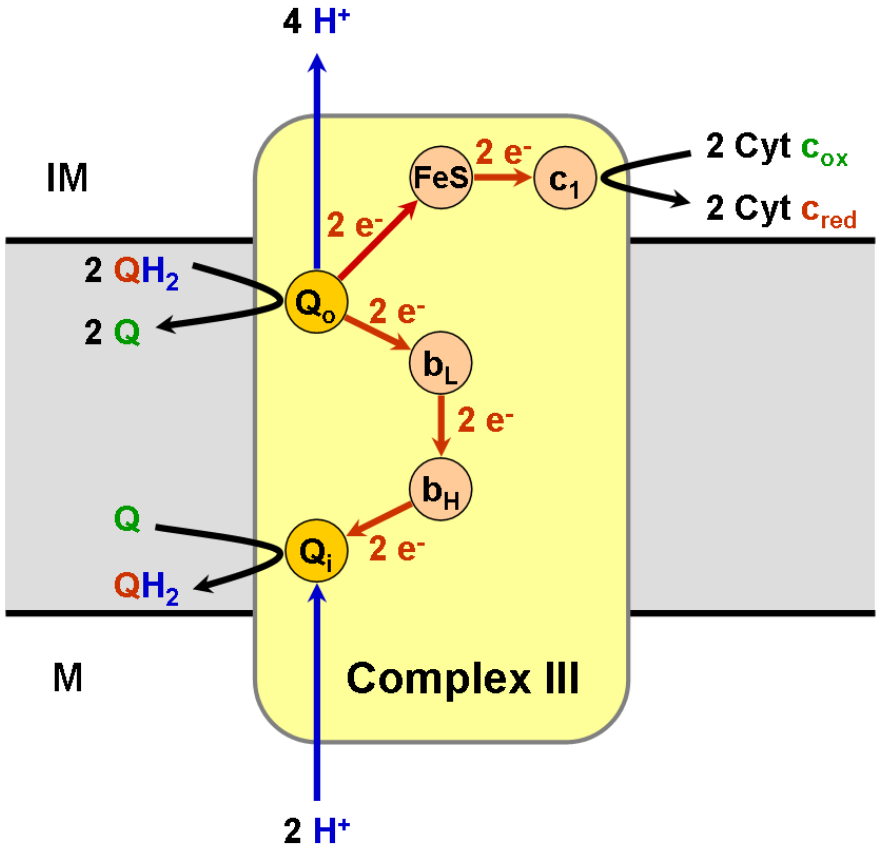
The presence of the two histidine ligands accounts for the higher redox potentials observed for the 2Fe2S, core in the Rieske center; **nitrogen-donor ligands stabilize the Fe(II),** compared with the Fe(III), oxidation level, and **the diminished charge on the histidine coordinated center** further **stabilizes the lower oxidation state**.



In combination with a cytochrome *b*, the function of the Rieske centers is to guarantee a splitting of the electron flow in the intramembrane electron transport chain: starting from the two-electron-donating hydroquinones, there is one electron pathway ***along*** **the membrane at high potential** and another ***across*** **the membrane at low potential**

Generation of a proton gradient

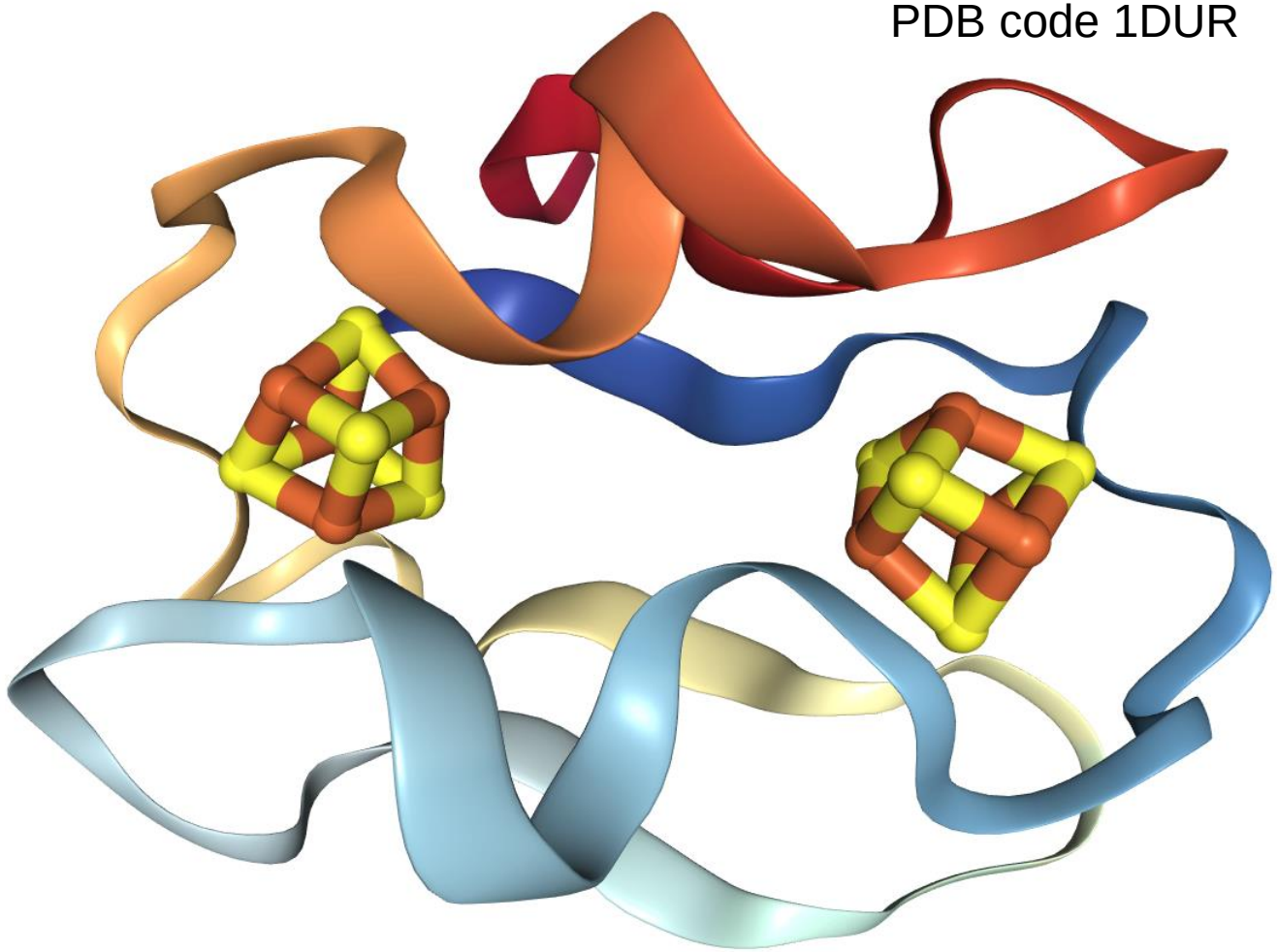




[4Fe – 4S] 7(8)Fe/8S ferredoxins

8Fe/8S protein
Peptostreptococcus asaccharolyticus FERREDOXIN

PDB code 1DUR



These clusters can be visualized as a dimer of two [2Fe-2S] units
the sulfido groups now bridge three rather than two iron centers.

This structure has been observed in several different proteins, either alone or in the presence of other prosthetic groups

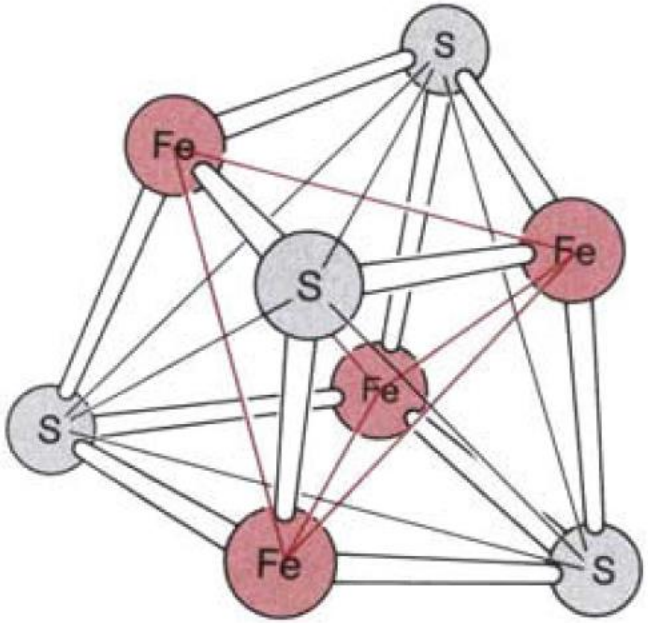
[4Fe-4S] centers
participate in nearly all complex biological redox reactions (**photosynthesis, respiration and N_2 fixation**)
they act mainly as electron-transfer centers at negative potentials.

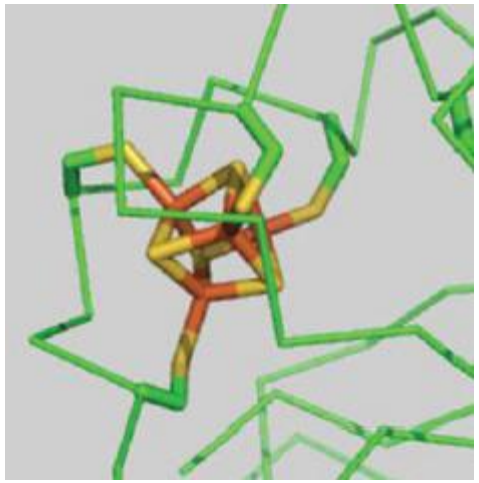
However, they may also have non-redox catalytic or noncatalytic functions

The basic structure is a distorted cube with alternating Fe and S atoms at the corners.

The result is two interpenetrating concentric tetrahedra of four iron and four sulfide atoms

Fe . . .Fe	S . . . S	distances
2.75 Å	3.55 Å	





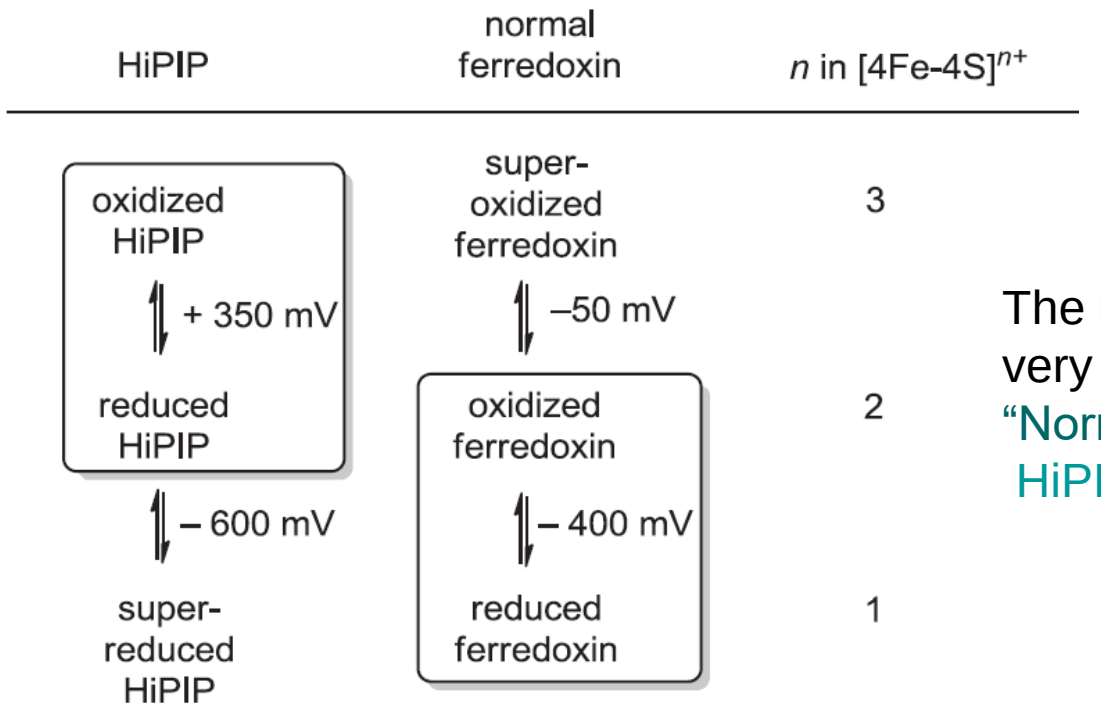
These centers are connected to the proteine by interaction of the Fe atoms with 4 cysteinate residues

!!it can exist in three rather than two oxidation levels!!

Influence of protein environment on oxidation states

P. asaccharolyticus ferredoxin contains two [4Fe-4S] clusters
oxidized state $[4Fe\text{-}4S]^{2+}$ two Fe(III) ions and two Fe(II) ions
reduced state $[4Fe\text{-}4S]^{+}$ one Fe(III) and three Fe(II) ions

Chromatium ferredoxin (formerly called the high-potential iron protein or HiPIP)
oxidized state $[4Fe\text{-}4S]^{3+}$ three Fe(III) ions and one Fe(II) ions
reduced state $[4Fe\text{-}4S]^{2+}$ two Fe(III) ions and two Fe(II) ions



The redox potentials of proteins containing [4Fe-4S] units span a very wide range because of the accessibility of three oxidation levels.
"Normal" [4Fe-4S] potentials range from -650 to -280 mV
HiPIP potential near +350 mV

The amino acid sequence determines whether a HiPIP center or the “normal” ferredoxin form of the [4Fe-4S] system occurs

also responsible for deciding whether a 4Fe or a 2Fe ferredoxin is formed from a cysteine-containing protein and enzymatically introduced iron and sulfide

Fe/S center	typical amino acid sequence
[Rd]	: - Cys - X_2 - Cys - X_n - Cys - X_2 - Cys -
[2Fe-2S]	: - Cys - X_4 - Cys - X_2 - Cys - X_{29} - Cys -
[3Fe-3S]	: - Cys - $X_{5,7}$ - Cys - X_n - Cys -
[4Fe-4S] or "normal Fd"	: - Cys - X_2 - Cys - X_2 - Cys - X_n - Cys -
HiPIP	: - Cys - X_2 - Cys - X_{16} - Cys - X_{13} - Cys -
nonredox active (endonuclease III)	: - Cys - X_6 - Cys - X_2 - Cys - X_5 - Cys -
nitrogenase Fe protein (dimer)	: - Cys - X_{34} - Cys - - Cys - X_{34} - Cys -

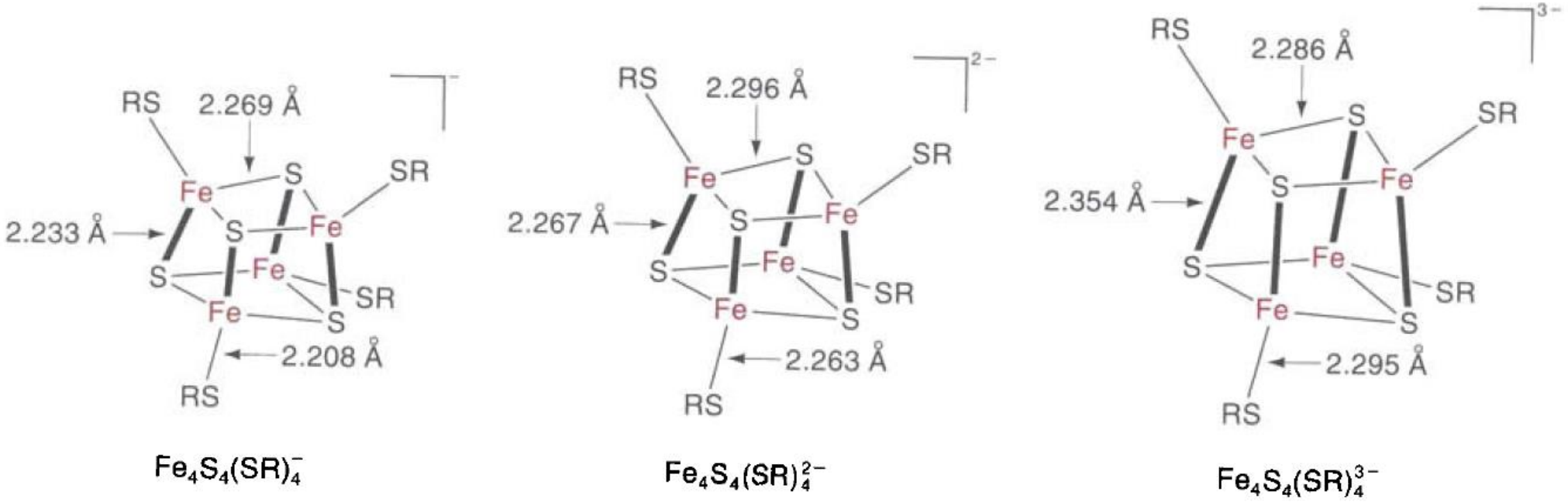
Although it is possible to obtain the respective **unphysiological “super-reduced” or “super-oxidized” states** under denaturation of the protein, the protein environments of the intact species allow only the biologically intended redox behavior.

The system is actually electronically delocalized
[4Fe-4S]$^{2+}$ shows four equivalent iron centers of average **oxidation state +2.5**.

The higher degree of delocalization (resonance) found in the [4Fe-4S]$^{n+}$ clusters can be attributed to the structurally determined **orthogonality of metal orbitals** that interact via superexchanging sulfide bridges.

Following theoretical analyses, this favors parallel spin–spin interactions with higher resonance energies according to Hund's rule.
The electron delocalization as such is less susceptible to perturbation from external asymmetries induced from the protein (in contrast to what happens in [2Fe-2S] centers).

Also the cysteinate ligands participate in the accommodation of additional electrons
- strengthening of hydrogen bond interactions X–H. . .−S(Cys), suggesting an increase of effective negative charge at the cysteinate sulfur centers-



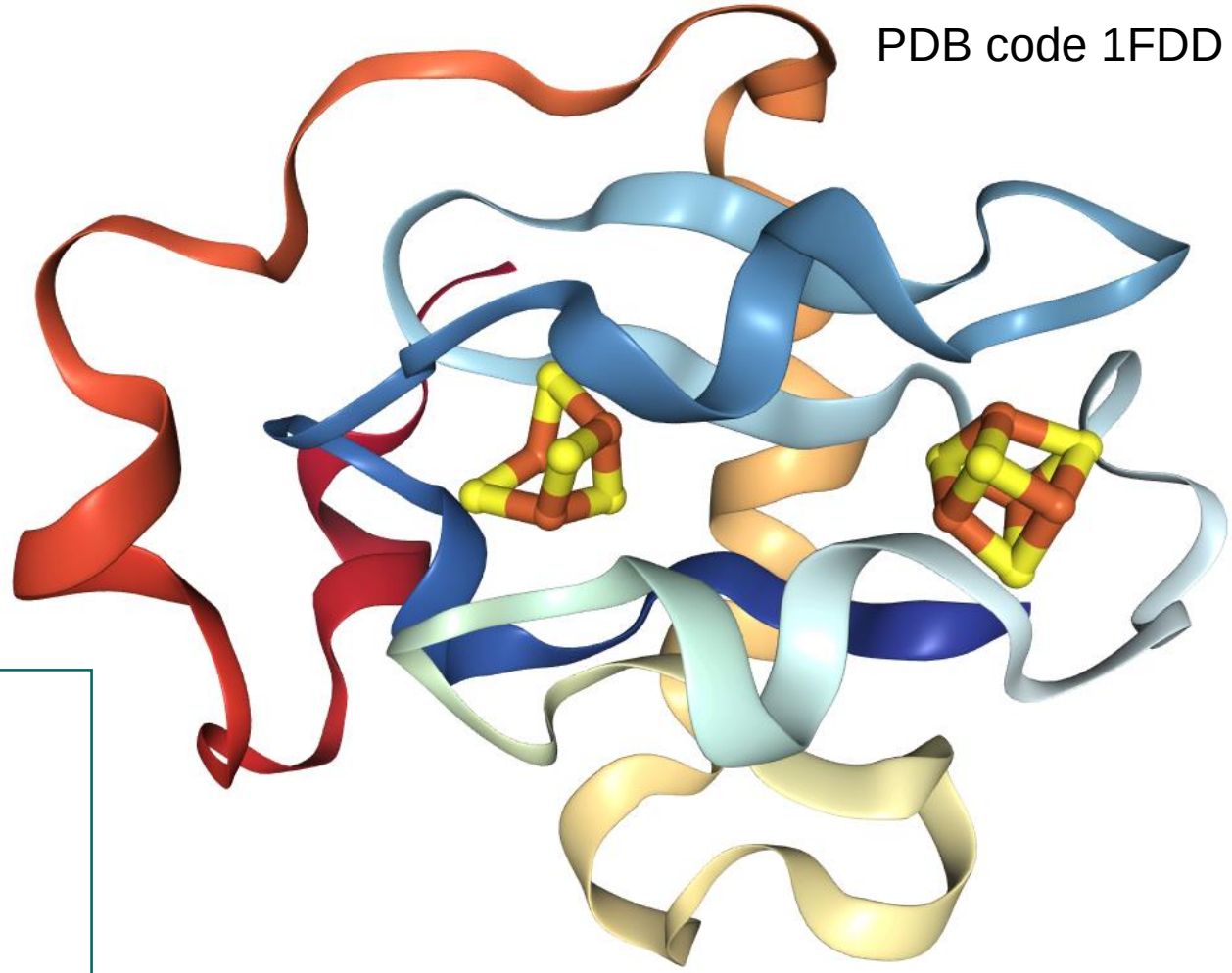
Studies of the bimolecular, outer-sphere rate constants of $[Fe_4S_4(SR)_4]^{n-}$ (R = aryl) showed rate constants in the 10^6 to 10^7 $M^{-1}s^{-1}$ range, making electron transfer for the [4Fe-4S] cubes among the **faster known self-exchange processes in inorganic chemistry**.

These values are 10^3 larger than the fastest known electron-transfer rate constants for $[4Fe\text{-}4S]^{n-}$ proteins undergoing the $n = 2$ to $n = 3$ transition.

The rates of electron transfer are faster in model clusters, consistent with minimal cluster reorganizational energy. **Actual rates of electron transfer from the proteins are therefore controlled by factors extrinsic to their iron-sulfur cores.**

[3Fe – 4S] 7Fe/8S ferredoxins

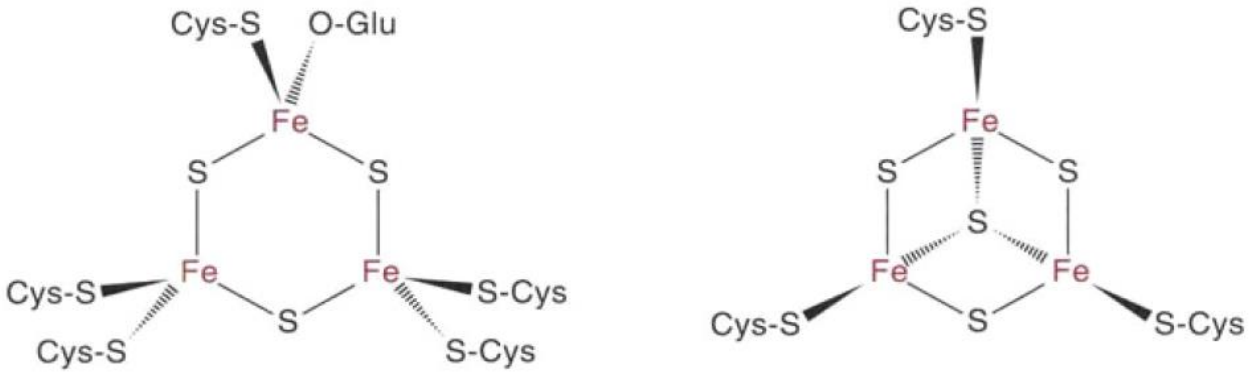
Different amino acid sequences are responsible for the formation of a special kinds of Fe/S proteins, which, in addition to [4Fe-4S] moieties, contain **[3Fe-4S]** centers (3Fe and 7Fe ferredoxins).



PDB code 1FDD

7Fe/8S protein
AZOTOBACTER VINELANDII FERREDOXIN I

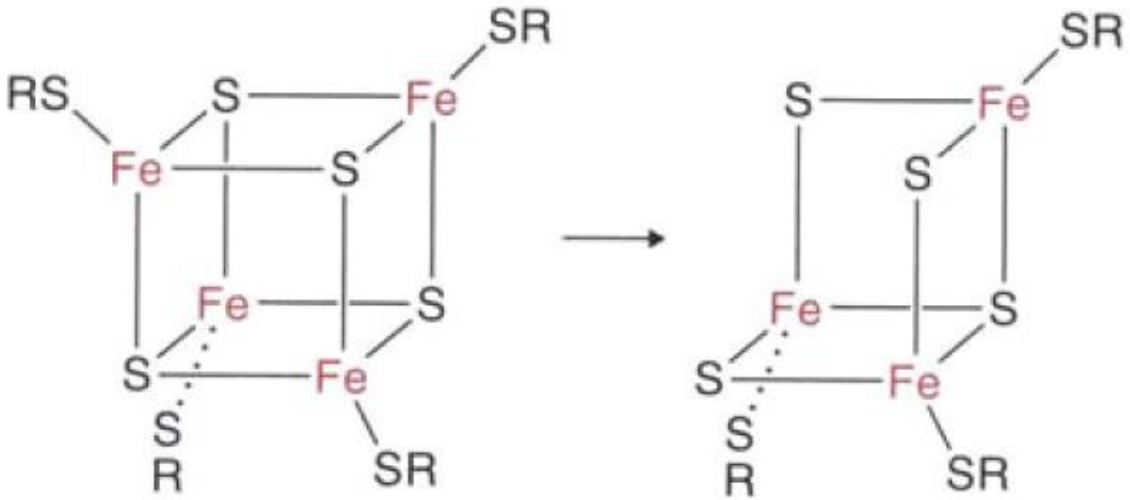
Scheme showing the original planar (left) and corrected non-planar (right) [3Fe-4S] cluster in *A. vinelandii* ferredoxin



False attribution based on crystal structure!

After suitable modification, these [3Fe-4S] centers may be converted to [4Fe-4S] centers.

Structurally, they can be derived from [4Fe-4S] analogues by removal of **a labile, *non-cysteinate-coordinated* iron atom**

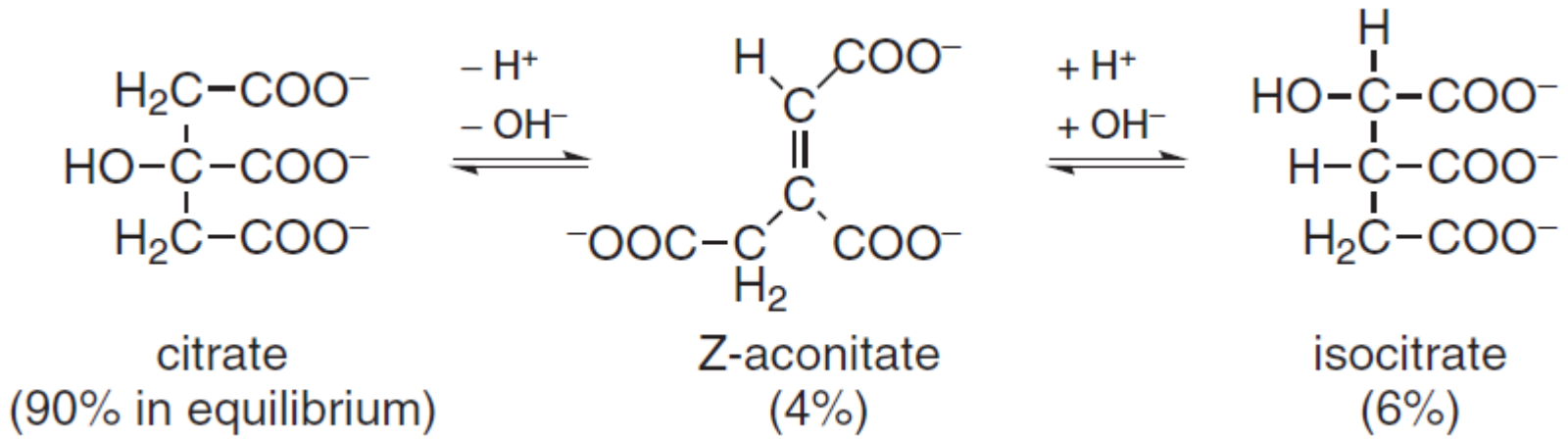


In some cases, excited spin states are readily accessible.
According to their “open”, coordinatively unsaturated structure, the [3Fe-4S] centers are **well fitted for chemical catalytic activity**, including iron sensor functions

Aconitate hydratase/isomerase

the [3Fe-4S] systems have been found in equilibrium with a labile [4Fe-4S] form as a component of the enzyme aconitase (aconitate hydratase/isomerase) in mitochondria

The enzyme catalyzes the following equilibrium within the Calvin cycle:



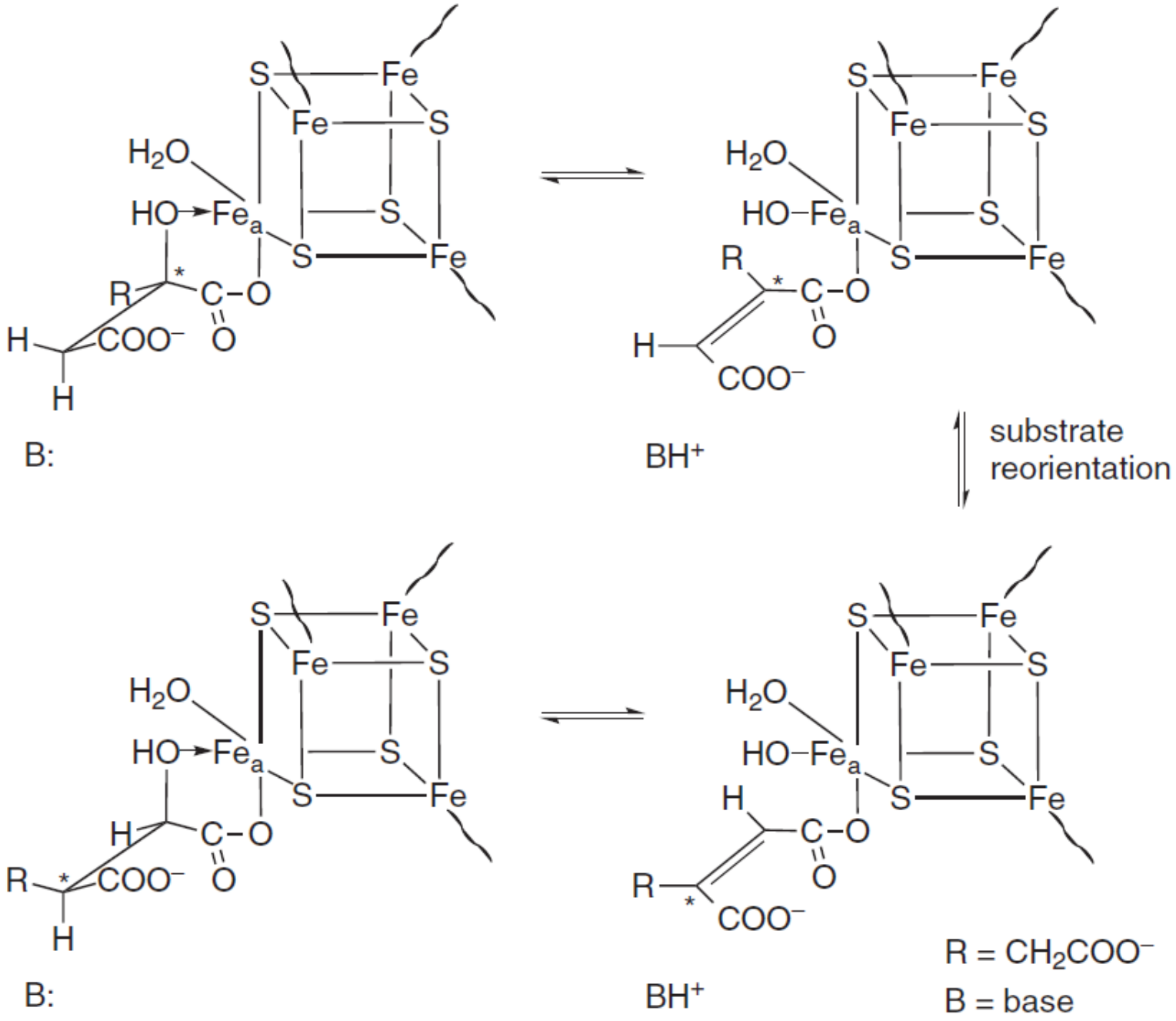
citrate
(90% in equilibrium)

Z-aconitate
(4%)

isocitrate
(6%)

In the active state, the labile iron center, Fe_a, of the [4Fe-4S] form of aconitase is **not coordinated by cysteinate but by water molecules**.

After substitution of H_2O and coordination of the chelating substrate (five-membered chelate ring, coordination number 5 or 6 at Fe_a), a sequence **of non-redox steps** leads to a rapid equilibration



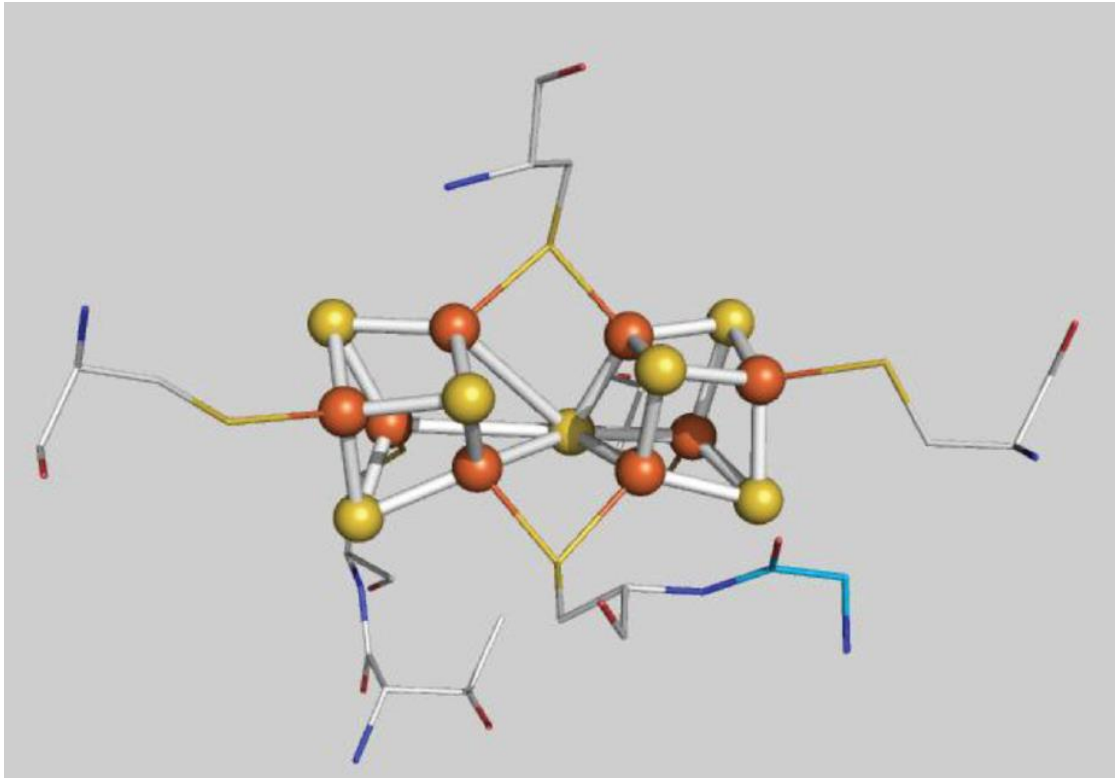
Going beyond

Possibiulity to have **more complex [xFe-yS] centers**

Examples:

- the sulfide-bridged double-cubane “P-clusters” in nitrogenase (showed in figure) => very negative redox potential of −470mV

- the (6Fe) “H clusters” in nickel-free hydrogenases, which catalyze the equilibrium $2H^+ + 2\ e^- = H_2$



Copper-containing ET proteins: Blue Copper Proteins

But first,

An Introduction to Copper-containing Proteins

Alternative to Biological Iron

For many iron-containing proteins, there are “parallel” copper-dependent analogues with comparable functions

Function	Fe protein	Cu protein
O_2 transport	hemoglobin (*h*) hemerythrin (*nh*)	hemocyanin
oxygenation	cytochrome P-450 (*h*) methane monooxygenase (*nh*) catechol dioxygenase (*nh*)	tyrosinase quercetinase (dioxygenase)
oxidase activity	peroxidases (*h*) peroxidases (*nh*)	amine oxidases laccase
electron transfer	cytochromes (*h*)	blue Cu proteins
antioxidative function	peroxidases (*h*) bacterial superoxide dismutases (*nh*)	superoxide dismutase (Cu, Zn) from erythrocytes
NO_2^- reduction	heme-containing nitrite reductase (*h*)	Cu-containing nitrite reductase

h, heme system; *nh*, non-heme system.

Besides the function similarities there are several differences:

- Unlike iron in heme, biological copper **does not occur in the form of tetrapyrrole coordination compounds.** Imine-nitrogen atom in the imidazole ring of histidine is able to form strong and kinetically inert bonds to copper in both relevant oxidation states, (+I) and (+II).

- As a general rule, the **redox potentials for Cu(I/II) transitions are higher** than those for Fe(II/III) redox pairs. Copper proteins such as ceruloplasmin are thus able to catalyze the oxidation of Fe(II) to Fe(III) (ferroxidase reactivity).

- In neutral aqueous solution and in sea water, the *oxidized* form Cu^{2+} is more soluble than Cu^{+}, which forms insoluble compounds with halide and sulfide; in contrast, the oxidized form is *less* soluble in the Fe(II/III) system

- Due to its later appearance and bioavailability in evolution, copper is often found in the extracellular space, whereas iron occurs mainly within cells.

Copper definciency symptoms

- Wilson's disease involves a hereditary dysfunction of the primary copper storage capability of the body (protein ceruloplasmin). The metal ion is then accumulated in liver and brain, leading to dementia, liver failure and ultimately death → administration of Cu-specific chelate ligands such as D-penicillamine

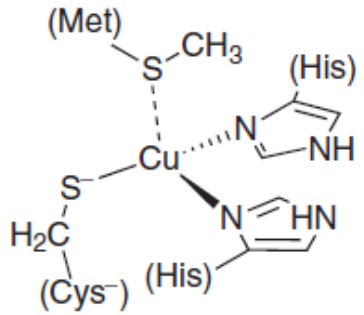
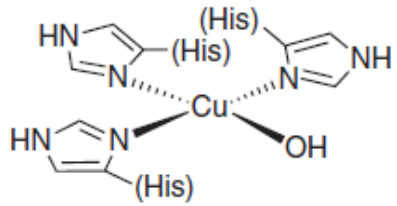
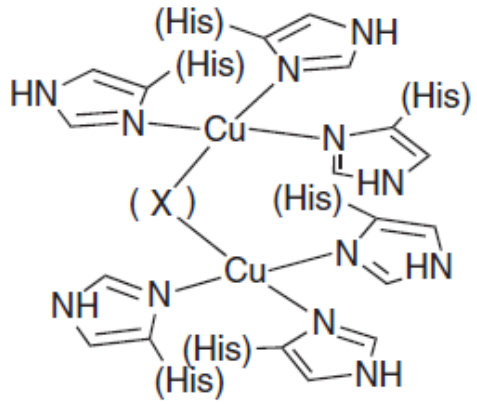
- Acute copper deficiency may occur in newborn infants, since the complex metal transport stabilizes only several months after birth. This deficiency can cause an insufficient oxygen utilization in the brain.
- Infants are sensitive to excessive supply of copper; usually high saturation concentration in the liver directly after birth. Corresponding childhood cirrhosis in copper-exposed parts of the world (India, Tyrol, parts of Germany).

- Menke's "kinky hair" syndrome is based on a hereditary dysfunction of intracellular copper transport. The resulting copper deficiency symptoms in infants include severe disturbances in mental and physical development accompanied by the occurrence of kinky hair (therapy = intravenously administered copper).

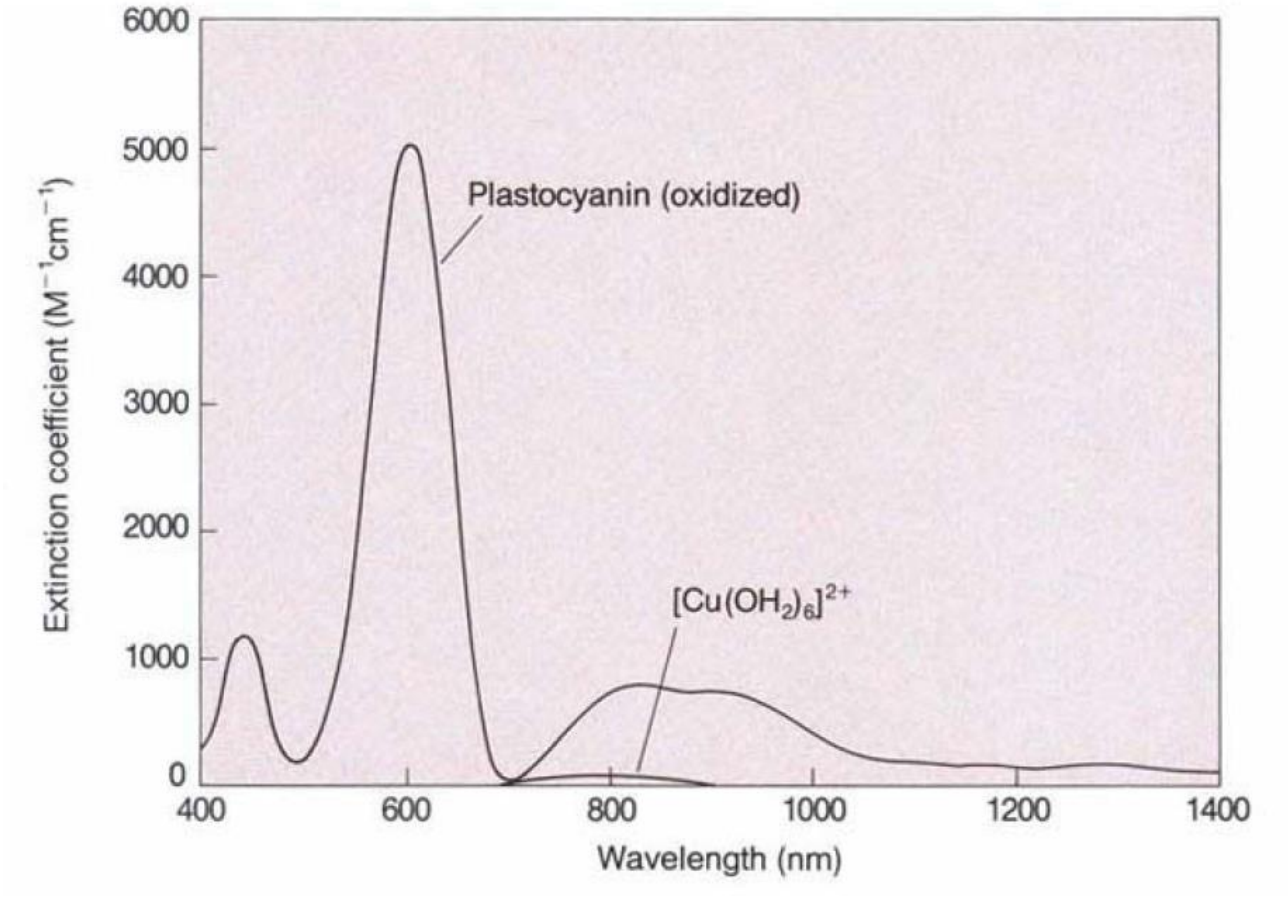
- Defects (mutations) in the copper-dependent superoxide dismutase (SOD) are responsible for a neurodegenerative (paralytic) disorder known as familial amylotrophic lateral sclerosis (ALS)

- Copper has also received much attention for its involvement in other neurodegenerative diseases, such as Parkinson's and Alzheimer's diseases and prion-based disorders

Classification of copper centers based on structural and spectroscopic point of view

Generalized coordination geometry	Function, structure, characteristics
type 1 	**type 1:** "blue" copper centers function: reversible electron transfer $Cu^{II} + e^- \rightleftarrows Cu^{I}$ structure: strongly distorted, (3 + 1) coordination absorption of the copper(II) form at about 600 nm, molar extinction coefficient $\varepsilon > 2000\ M^{-1}\ cm^{-1}$, LMCT transition S(Cys) → Cu^{II} EPR/ENDOR of the oxidized form: small $^{63,65}Cu$ hyperfine coupling and *g* anisotropy, interaction of the electron spin with -**S-CH**$_2$-; Cu^{II} → S(Cys) spin delocalization
type 2 	**type 2:** normal, "non-blue" copper function: O_2 activation from the Cu^{I} state in cooperation with organic coenzymes structure: essentially planar with weak additional coordination (Jahn–Teller effect for Cu^{II}), typically weak absorptions of Cu^{II}, $\varepsilon < 1000\ M^{-1}\ cm^{-1}$, ligand–field transitions (d → d) normal Cu^{II} EPR
type 3 	**type 3:** copper dimers function: O_2 uptake from the Cu^{I}–Cu^{I} state structure: (bridged) dimer, Cu–Cu distance about 360 pm after O_2 uptake, intense absorptions around 350 and 600 nm, $\varepsilon = 20\,000$ and $1000\ M^{-1}\ cm^{-1}$, LMCT transitions O_2^{2-} → Cu^{II} EPR-inactive Cu^{II} form (antiferromagnetically coupled d^9 centers)

Back to Blue Copper Proteins (type 1 copper proteins)



Comparison of the electronic spectra of oxidized plastocyanin and hexaaquacopper(II) ion.

The type 1 copper centers
named after *weird intense* blue color of the corresponding Cu^{II} proteins

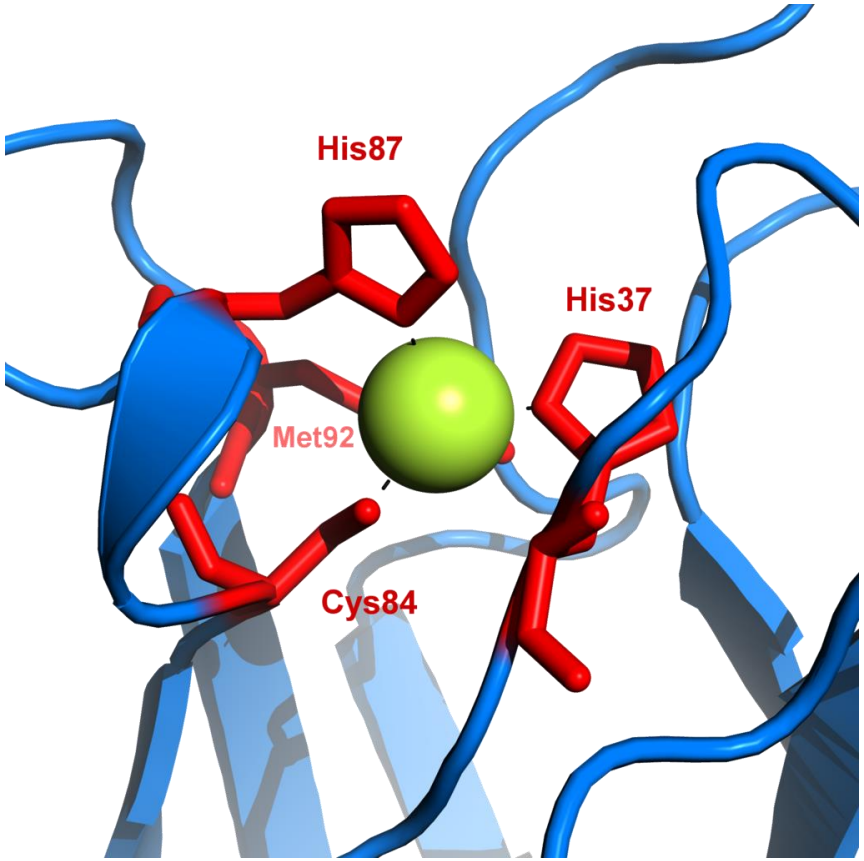
names such as “azurin” and “plastocyanin”

the comparatively pale blue color of normal Cu^{2+}, as in crystalline copper(II)sulfate pentahydrate results from “forbidden” electronic transitions between d orbitals of different symmetries

What about blue copper proteins?

Structure

Two histidine residues and one hydrogen bond-forming cysteinate ligand are strongly bound in an approximately trigonal planar arrangement, while weakly bound methionine (or glutamine as in stellacyanin) and, in some instances, a very weakly coordinating oxygen atom from a peptide bond complete the coordination environment



As in the case of **oxidized rubredoxin**, the intense absorption of the oxidized form is attributed to a **ligand-to-metal charge transfer (LMCT) transition**, that is, an electronic charge is transferred from the electron-rich thiolate ligand to the electron-poor Cu^{II} center via light excitation

$$(R\text{-}CH_2\text{-}S^-)Cu^{II}(His)_2(Met) \xrightarrow[LMCT]{h\nu} (R\text{-}CH_2\text{-}S^\bullet)Cu^{I}(His)_2(Met)^*$$

Crystal structure analyses of several “blue” copper proteins have shown that the metal centers feature **very irregular “distorted” coordination**

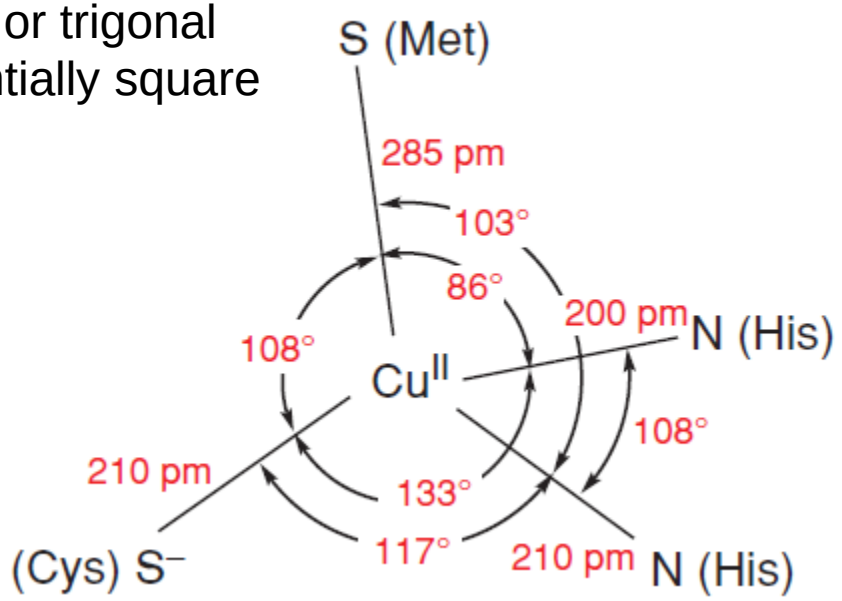
The strong geometrical distortion is a consequence of the incorporation of the coordinating amino acid ligands in well-conserved sequences His-Xk-Cys-Xn-His-Xm-Met (n, m = 2–4; large k).

Just like the mixture of donor centers (two N, two S), this strongly distorted arrangement represents a compromise between Cu^{I} = d10, with its preferred tetrahedral or trigonal coordination through “soft” (e.g. sulfur) ligands, and Cu^{II} = d9, with preferentially square planar or square pyramidal geometry and N ligand coordination.

The irregular high-energy arrangement at the metal largely resembles the transition-state geometry between the tetrahedral and the square planar equilibrium configurations of the two involved oxidation states,

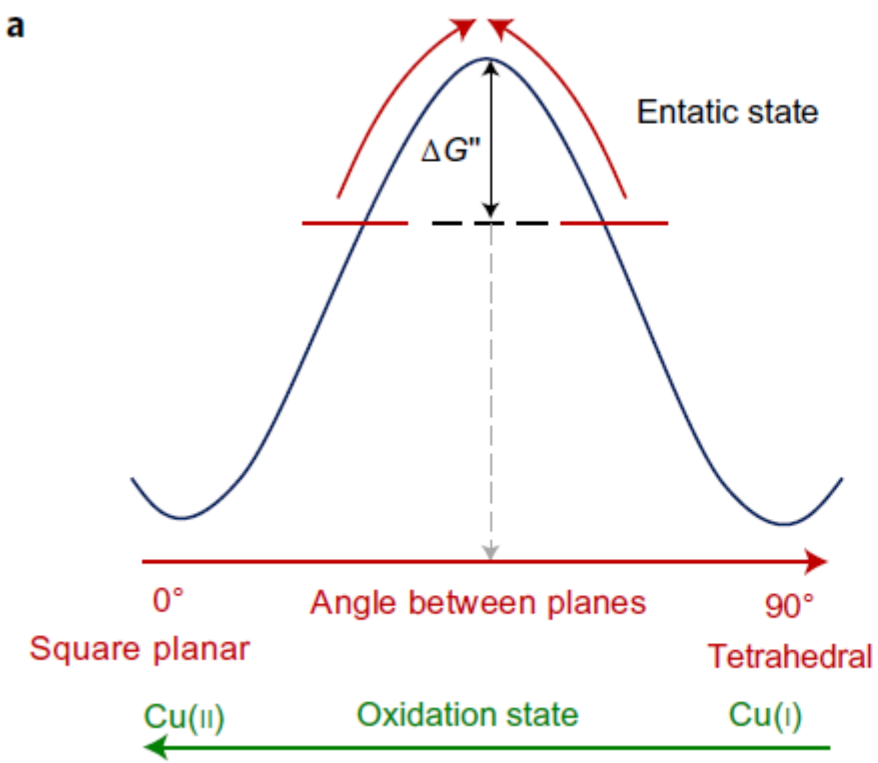
⇓

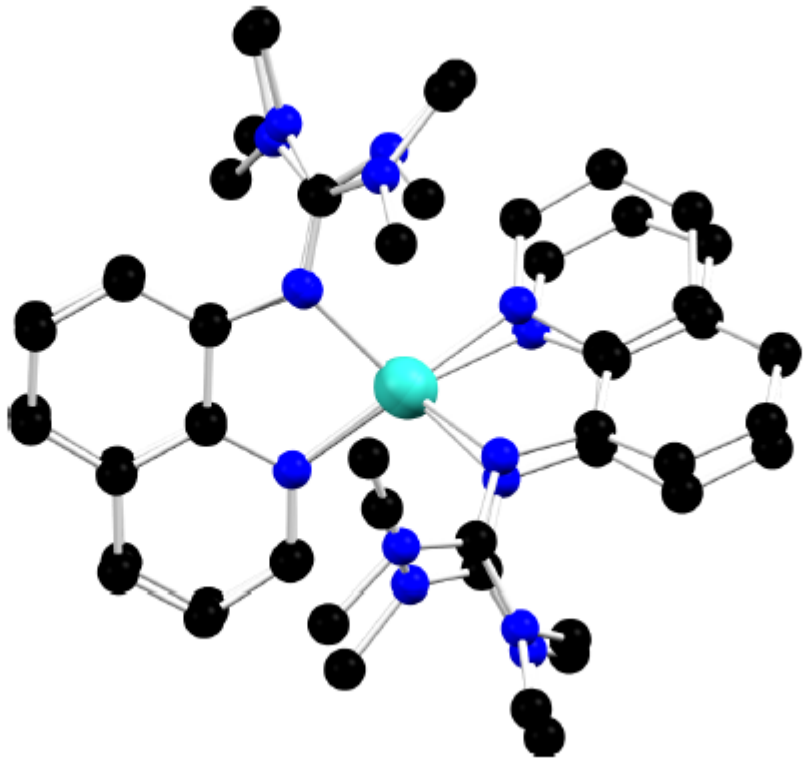
higher rate of electron transfer

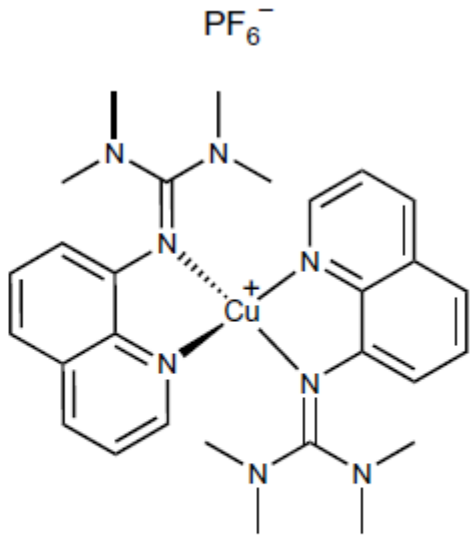


The potential range for proteins with type 1 copper centers runs from 0.18V (stellacyanin, with **Gln instead of Met** as axial ligand) to 0.68V (rusticyanin).

Model example







$[Cu^{I}(TMGqu)_2]PF_6$ **(1)**