



Dedicated to Academician Cristian Silvestru  
on the occasion of his 70<sup>th</sup> anniversary

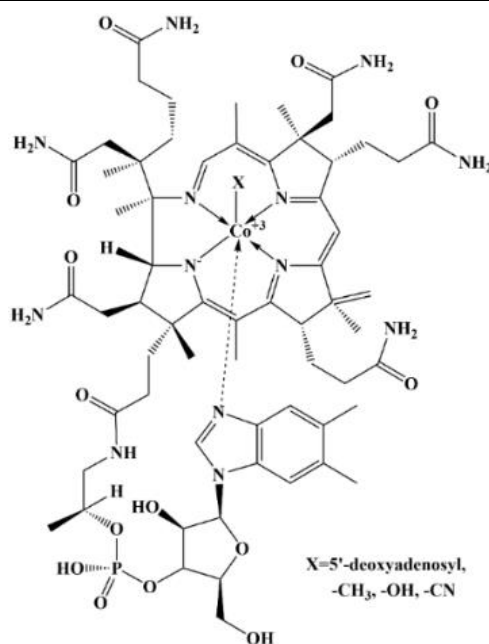
## BIOORGANOMETALLIC CHEMISTRY AND SUPER-REDUCED BIOLOGICAL METAL CENTERS

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Bioinorganic centers such as cobalamin (B<sub>12</sub>), hydrogenases (H<sub>2</sub>-ase) or nitrogenases (N<sub>2</sub>-ase) achieve reactions unusual for biochemistry, involving unusually reduced metal oxidation or ligation states (*e.g.*, Fe(I), Co(I) and/or unusual (for biology) metal complexation – with -carbon and metal-hydrogen bonds. In this, they overlap with the relatively narrow field of bioorganometallic chemistry – *i.e.*, organometallic chemistry in biological environments and/or with biological relevance. Their mechanistic details are still a matter of exploration. Examples of challenging questions in these fields include (1) the nature/properties of metal-hydride complexes known to be relevant for N<sub>2</sub>-ase and H<sub>2</sub>-ase, but also suggested in B<sub>12</sub>; in the case of N<sub>2</sub>-ase and to some degree H<sub>2</sub>-ase this also entails isomerism insofar as the location of the hydride, but also possibly redox isomerism; (2) the role of low-valent states (*e.g.*, Fe(I)) in such bioinorganic centers; (3) the mechanisms and reasons whereby such low-valent centers become available; for instance, in the case of N<sub>2</sub>-ase (especially the Fe-only N<sub>2</sub>-ase) the coordination sphere is dominantly sulfur-based similarly to ferredoxins; (4) to what extent does the choice of a given transition metal for these bioinorganic centers rely on environmental/evolutionary availability, and to what extent on other factors (*e.g.*, a comparison of ferribalamin *vs.* B<sub>12</sub>, or a comparison of other transition metals instead of iron in N<sub>2</sub>-ase, or instead of Fe/Ni in H<sub>2</sub>-ase)?



### INTRODUCTION

At odds with a traditional association with standard aqueous aerobic organic and coordination chemistry, living organisms do at times offer examples of spectacularly exotic reactions. This is the case of bioorganometallic centers – where

metal-carbon bonds and biologically-unusual metal oxidation states are seen at work far away from the carefully-controlled (often anhydrous and anaerobic) chemical laboratory conditions typical of organometallic chemistry.<sup>1</sup> In the case of transition metals, where multiple oxidation states are accessible, specific to the organometallic chemistry

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is often the fact that the metal-carbon bond entails metals in lower oxidation states. In fact, these oxidation states are often below the realm typically accessible to biological aqueous environments. As such, the field of bioorganometallic chemistry overlaps (though does not coincide) with the field of super-reduced biological metal centers. By super-reduced, from the biochemical point of view, we define oxidation states below those typically accessible in biological molecules and environments;  $\text{Fe}^+$ ,  $\text{Ni}^+$ , and  $\text{Co}^+$  are the most cited examples of super-reduced centers in biological molecules under biologically-relevant conditions.

In biologically relevant systems, organometallic complexes often feature transition metals

coordinated by ligands such as porphyrins or iron-sulfur clusters, which modulate their redox properties and geometric structure. Figure 1 shows representative examples of such biological metal centers involved in exotic reactivities. Breaking some of the most stable bonds such as those in molecular hydrogen or nitrogen requires intricate mechanistic pathways supported by exotic structures the likes of those in Fig. 1. In the world of biological organometallic chemistry an interstitial carbon bound through six bonds is not peculiar, but rather essential in supporting the catalytic role of nitrogenase.

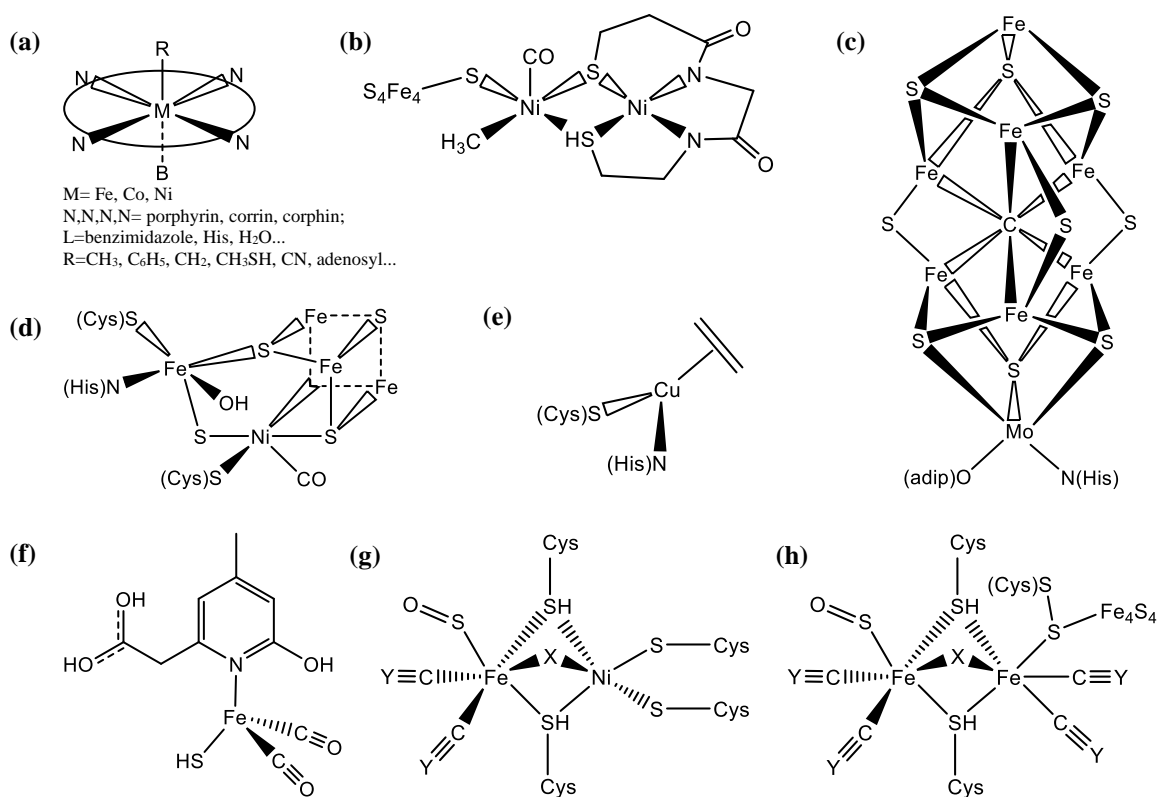


Fig. 1 – Representative exotic metalloenzyme sites: a) cobalamin/cobinamide/F430/heme; b) acetyl CoA synthase; c) nitrogenase; d) CO dehydrogenase; e) ETR1; f) [Fe] hydrogenase; g) [FeNi] hydrogenase; h) [FeFe] hydrogenase.

## COBALAMIN AND SUPER-REDUCED COBALT

Cobalamin (Cbl) is arguably the quintessential example of bioorganometallic center, with its cobalt coordinated equatorially by a corrin macrocycle and then axially by ligands (X in Fig. 2) which may include methyl, adenosyl, and other carbon-based ligands. Trans to X, one may find a side-chain extending from the edge of the corrin with a benzimidazole ligand to the cobalt;

alternatively, the benzimidazole may be replaced by any number of ligands – especially in cobalamin congeners such as cobinamide, where the benzimidazole-containing side-chain is missing from the corrin. Cobalamin is seen at the catalytic sites of enzymes typically involved in methyl unit transfers (Fig. 3) or carbon-carbon rearrangements/isomerizations (Fig. 4) – where homo- or heterolysis of the Co-C bond is central to the mechanism, and where the less usual Co(I) formal oxidation state may be invoked.<sup>2</sup>

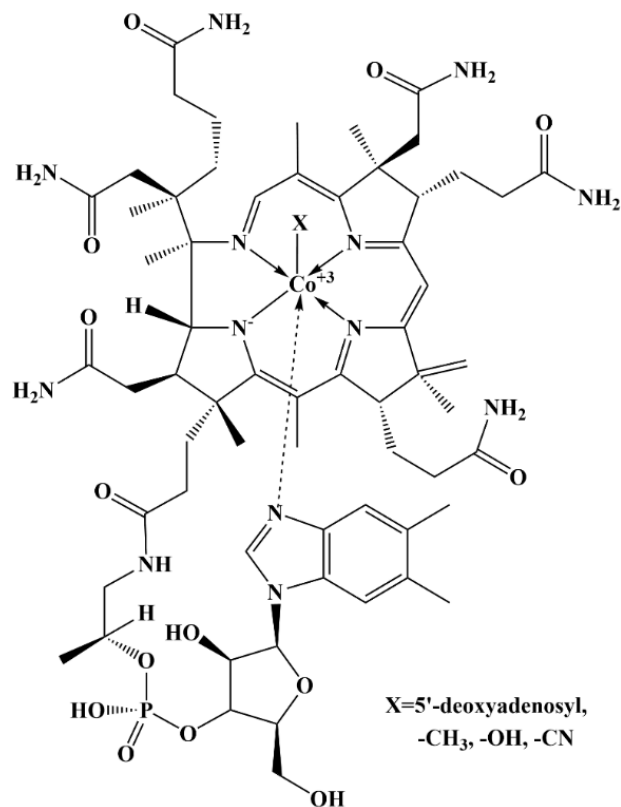


Fig. 2 – The structure of cobalamin. Among the possible ligands ("X"), cyanide has no biological relevance, appearing only at purification as an impurity resulting from activated carbon.

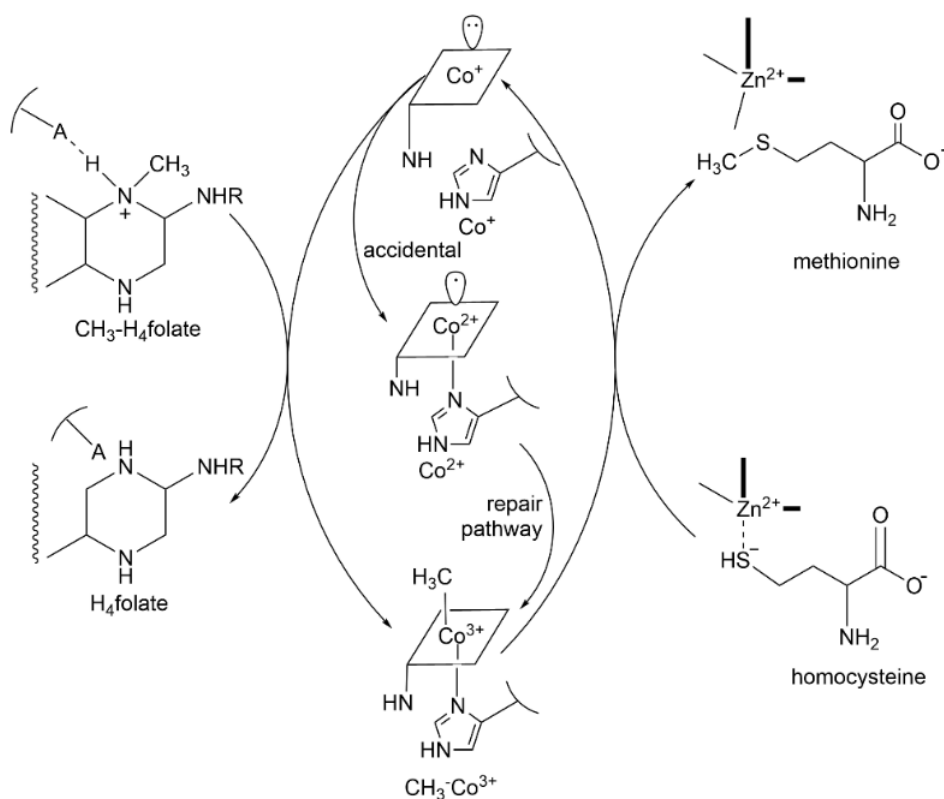


Fig. 3 – Mechanism of methionine synthase, an example of a B<sub>12</sub>-dependent enzyme that involves heterolysis of the carbon-cobalt bond. It involves Co<sup>+</sup> and Co<sup>3+</sup>; the Co<sup>2+</sup> form can occur accidentally, and the figure illustrates that there are enzymatic mechanisms to return the metal to an oxidation state within the catalytic cycle.

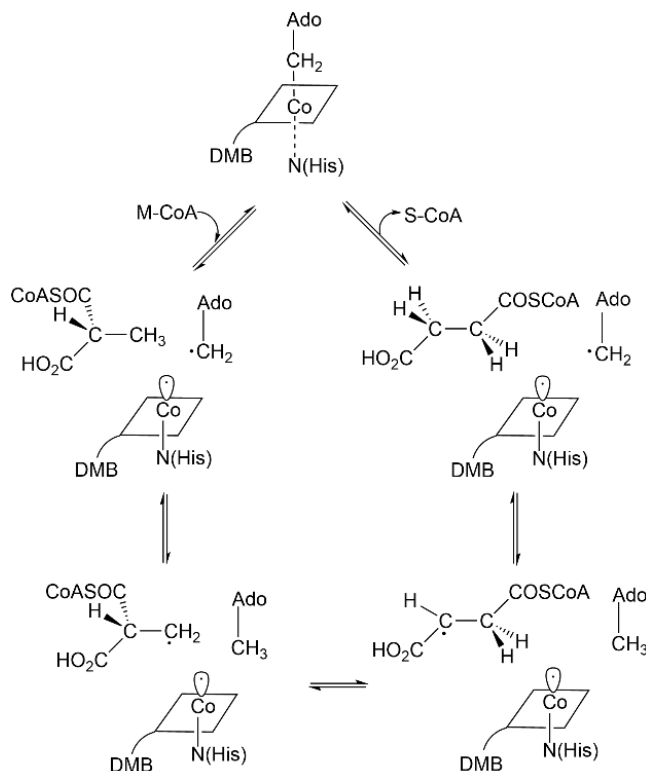


Fig. 4 – The mechanism of methylmalonyl coenzyme A mutase, an example where heterolytic cleavage of a carbon-cobalt bond is essential.

Cobalamin and its related compounds also offer interesting chemistry beyond Co-methyl/adenosyl compounds. Such related compounds include ferribalamin (where Co has been replaced by iron in the center of the corrin ring), on which there are scarce reports.<sup>3</sup> Also of note is cobinamide, obtained by removing the benzimidazole pendant arm from cobalamin.<sup>2,4,5</sup> To some extent, Co complexes with related macrocycles (porphyrazine, porphyrin, or phthalocyanine) may also be regarded as relevant in this context.<sup>6–8</sup>

Examples of interesting reactivity in cobalamin and in its related complexes may include a recently-described reversible/stable complex with hydrogen peroxide.<sup>9</sup> This complex can be easily overlooked since its UV-Vis spectrum is very similar to that of aqua and of hydroxo Cbl. However, it has been found that more complex spectroscopic methods (especially NMR, but also resonance Raman) can clearly identify this new complex. These observations not only open the way towards a new class of previously unexplored/ignored Cbl complexes, but also point to a need to expand experimental methodology in order to more extensively focus on NMR spectroscopy, and also to a need to more closely examine the nature of the Cbl UV-Vis spectra (with potentially key contributions from computational analyses such as

TD-DFT), where the corrin  $\pi/\pi^*$  orbitals appear very resilient to influences of axial ligands to the extent that the influence of the latter can be very subtle and often overlooked experimentally. Indeed, it was later found that some organic peroxides as well as chlorite and hypochlorite also afford complexes with cobalamin.<sup>10–13</sup>

On the other hand, the super-reduced states of cobalamin and of related complexes have been implicated in such exotic processes as proton activation/reduction via hydride complexes (hence related to processes in hydrogenases and nitrogenases, see below), or carbon dioxide activation.<sup>8,14–19</sup>

Last but not least, cobalamin and related macrocyclic complexes also offer an opportunity to explore linkage isomerism – with possible case studies involving nitrite and other oxides, oxyanions of or other derivatives of main-group elements (*e.g.*, sulfur, selenium, halides).<sup>2,5,6,20–22</sup>

## COENZYME F430 AND SUPER-REDUCED NICKEL

While corrin may to some extent be seen as a reduced (and one-carbon-shorter) version of a porphyrin, with only 6 double bonds left compared

to ~double this number in porphyrin, the corphin is even further reduced, with only 5 double bonds left. Coenzyme F<sub>430</sub> consists of a Ni<sup>2+</sup> center complexed by a corphin, and is known to be involved in the final step of methane-generating reactions in anaerobic methanotrophic archaea.

At the heart of this process is the nickel ion within coenzyme F<sub>430</sub>, which cycles between oxidation states to drive the reaction. In its active unusual Ni<sup>+</sup> state, the nickel ion presumably donates an electron to the methyl group of methyl-coenzyme M, facilitating the cleavage of the carbon-sulfur bond and the formation of a methyl radical. This radical then abstracts a hydrogen atom from coenzyme B, resulting in the production of methane and the formation of a thiyl radical on coenzyme B. Subsequently, the thiyl radical reacts with the thiolate of coenzyme M to form the heterodisulfide product, regenerating the Ni<sup>+</sup> state of the cofactor and completing the catalytic cycle. This mechanism underscores the unique role of the Ni<sup>+</sup>/Ni<sup>2+</sup> redox cycling in biological systems, particularly in facilitating radical-based transformations under anaerobic conditions. The intricate coordination chemistry of coenzyme F<sub>430</sub> not only stabilizes these reactive intermediates but also ensures the specificity and efficiency of methane production in methanogenic pathways.

### Copper organometallic centers

The plant ethylene receptor ETR1 (Ethylene Response 1) from *Arabidopsis thaliana* features a Cu<sup>+</sup> cofactor that is essential for high-affinity ethylene binding. This copper ion is coordinated within the transmembrane domain of the receptor. The presence of copper enables the receptor to interact effectively with ethylene, facilitating signal transduction that influences various physiological processes in plants.<sup>23</sup>

### Nitrogenases super-reduced iron centers

Nitrogenase is one of the newer members of the bioorganometallic club. It is now generally accepted that at the core of its iron-sulfur-molybdenum active cofactor (FeMoCo) one finds a carbon atom in what one may call “inverse coordination”<sup>24</sup> by six iron

centers (Figs. 1 and 5). The nature of the interstitial atom was a hot topic in the early 2000s, when X-ray crystallography (1.16 Å resolution) revealed an electron density at the center of the FeMoCo cofactor consistent with a light atom. Based on common sense chemistry, this density was assigned to a nitrogen atom. However, subsequent investigations employing advanced spectroscopic techniques and higher-resolution crystallographic data challenged this initial assignment. Electron spin echo envelope modulation (ESEEM) and electron-nuclear double resonance (ENDOR) spectroscopy, combined with isotope labeling (<sup>13</sup>C, <sup>15</sup>N, <sup>17</sup>O),<sup>25</sup> provided compelling evidence against the nitrogen hypothesis. Further confirmation came from X-ray emission spectroscopy (XES) studies, which conclusively identified the interstitial atom as a carbon species. This discovery corrected the earlier misassignment and has significant implications for understanding the structure and function of the FeMoCo in nitrogenase.<sup>26</sup>

Nitrogenase's catalytic cycle involves binding a nitrogen molecule – a task essentially incompatible with Fe<sup>2+,3+</sup> or Mo<sup>4+,6+</sup> centers such as hitherto reported in FeMoCo. While it is still unclear exactly how and where N<sub>2</sub> coordinates to FeMoCo, there is an added complexity in the fact that six protons need to sequentially bind to FeMoCo and then get transferred onto N<sub>2</sub> in order to generate ammonia. For N<sub>2</sub> as well as for H<sup>+</sup> binding, iron cannot be excluded as the site of choice – which would be in contrast to the known chemistry of iron-sulfur clusters or of Fe<sup>2+,3+</sup> in general. The recently discovered super-reduced Mo<sup>3+</sup> states (i.e., of unusually low valence for biological environments) further complicate the picture. Of interest may also be the fact that alternative nitrogenase sites are known, featuring a super-reduced vanadium instead of molybdenum and possibly even with iron as the only metal.<sup>1,27–31</sup> The formation of iron-hydride complexes is not only perplexing in itself by comparison with the known chemistry of other biological iron-sulfur clusters, but also appears counterintuitive in a mechanism where the N<sub>2</sub> molecule would be reduced stepwise and then protonated: if protonation is needed, then why produce metal-hydride complexes? A possible hypothesis is that N<sub>2</sub> binding requires super-

reduced  $\text{Fe}^+$  and that access to such a state is facilitated by iron-hydride formation. A role for the central carbon atom in facilitating this process

(and hence further discussion on the choice of this central atom *vs.* sulfide, nitride or others) may also warrant further investigation.

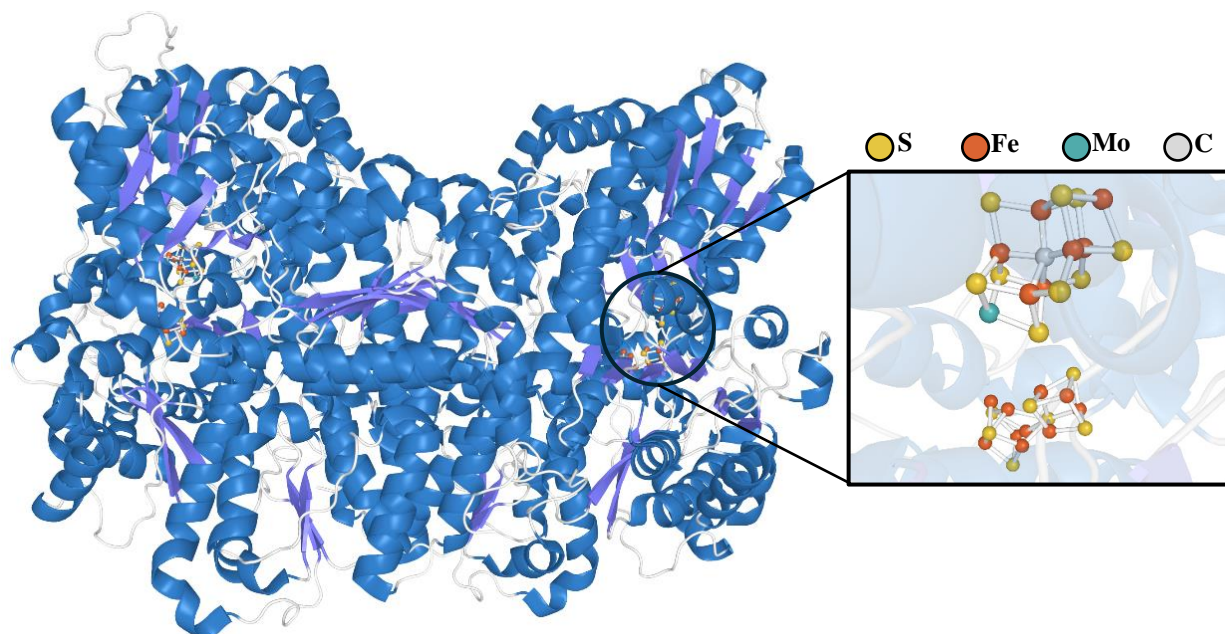


Fig. 5 – Structural representation of a nitrogenase (PDB code: 3U7Q), with a close-up view of the 7Fe-9S-Mo-C cluster from its active site.

### Hydrogenases and reduced iron and nickel centers

Hydrogenases are metalloenzymes that catalyze the reversible oxidation of molecular hydrogen ( $\text{H}_2$ ), playing a central role in microbial energy metabolism. These enzymes are classified into three main types based on the metal composition of their active sites: [NiFe], [FeFe], and [Fe] hydrogenases, where  $\text{H}_2$  and  $\text{H}^+$  are interconverted. The catalytic requirement to bind protons to the metal has been correlated with the fact that nitrogenases feature unusual coordination spheres (with CO and CN as proposed though unexpected *physiological* ligands to the metal), increasing the electron density at the iron or nickel possibly to the point where low-valent  $\text{Fe}^+$  or  $\text{Ni}^+$  states can be reached.<sup>32–47</sup>

The [NiFe] hydrogenases (Fig. 6) possess a bimetallic active site comprising nickel and iron atoms, coordinated by ligands such as carbon monoxide (CO) and cyanide ( $\text{CN}^-$ ), thereby the organometallic character. These enzymes are primarily involved in hydrogen oxidation and are found in a variety of microorganisms, including bacteria and archaea. Notably, some [NiFe] hydrogenases exhibit oxygen tolerance.

The [FeFe] hydrogenases (Fig. 6) feature a diiron active site known as the H-cluster, which includes iron atoms coordinated by CO and  $\text{CN}^-$  ligands and linked to a [4Fe-4S] cluster. They are highly efficient in catalyzing hydrogen evolution and are predominantly found in anaerobic bacteria.

The [Fe] hydrogenases, also referred to as Hmd hydrogenases, contain a mononuclear iron center without accompanying iron-sulfur clusters. These enzymes are unique to certain methanogenic archaea and are involved in the reversible reduction of methenyl-tetrahydromethanopterin using hydrogen.

The catalytic process typically begins with the heterolytic cleavage of  $\text{H}_2$  at the active site, resulting in a proton ( $\text{H}^+$ ) and a hydride ( $\text{H}^-$ ). This reaction is facilitated by the unique coordination environment of the metal centers and surrounding amino acid residues, which stabilize the transition states and intermediates. The electrons and protons generated are then transferred through a series of pathways within the enzyme to external acceptors or donors, depending on whether the enzyme is catalyzing hydrogen oxidation or production. The efficiency of this process is attributed to the precise arrangement of redox-active centers and proton transfer pathways within the enzyme structure.<sup>48</sup>

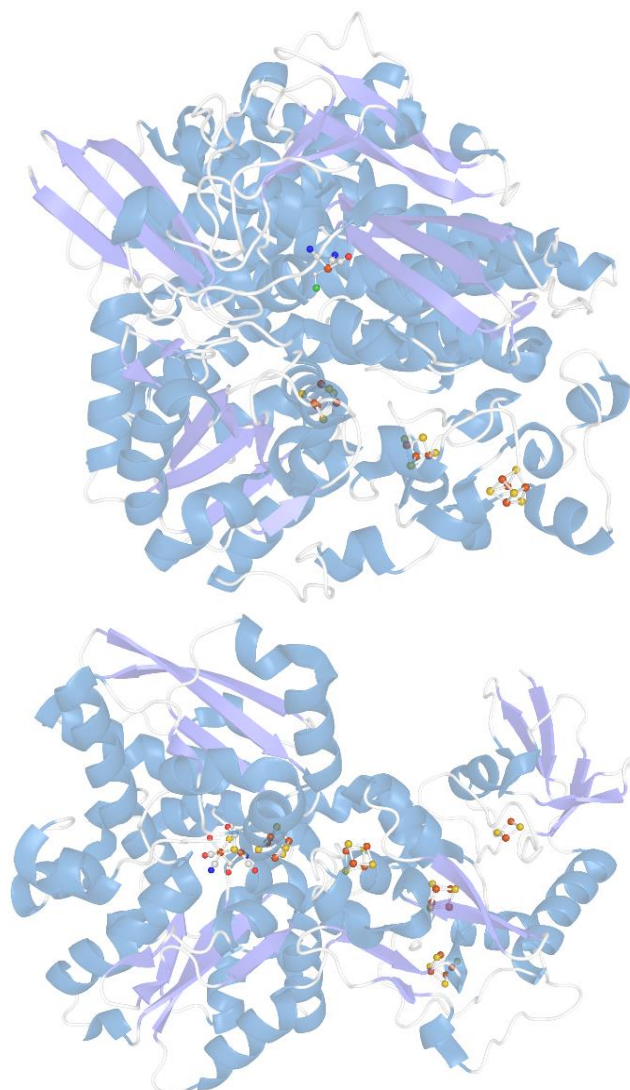


Fig. 6 – Structural representation of NiFe-hydrogenase (4U9H) and FeFe-hydrogenase (3C8Y) (See also Fig. 1).

### Acetyl CoA synthase and CO dehydrogenase<sup>1</sup>

Acetyl-CoA synthase (ACS) is a key enzyme in the Wood–Ljungdahl pathway, facilitating the synthesis of acetyl-CoA from carbon monoxide (CO), a methyl group, and coenzyme A (CoA). Central to its function is the A-cluster, a unique metallocluster comprising two nickel atoms and a [4Fe-4S] cluster. The proximal nickel plays a pivotal role in the enzyme's catalytic mechanism, undergoing various organometallic transformations. The catalytic cycle begins with the transfer of a methyl group from a methylated corrinoid iron-sulfur protein (CFeSP) to Ni, forming a Ni–CH<sub>3</sub> intermediate. Subsequently, CO, produced by the associated carbon monoxide dehydrogenase (CODH) enzyme, binds to Ni, leading to the formation of a Ni–CO complex. These two ligands then undergo a condensation reaction at the nickel

center, resulting in an acetyl–Ni intermediate. Finally, CoA attacks this intermediate, displacing the acetyl group to form acetyl-CoA and regenerating the active Ni site. This sequence of organometallic intermediates—Ni–CH<sub>3</sub>, Ni–CO, and acetyl–Ni—highlights the enzyme's intricate coordination chemistry and its reliance on nickel's versatile redox and bonding capabilities.<sup>49</sup> Recent spectroscopic and computational studies have provided deeper insights into these intermediates, confirming their structures and roles within the catalytic cycle. For instance, advanced techniques have been used to characterize the nickel-methyl and nickel-acetyl species, shedding light on the enzyme's mechanism and the dynamic nature of its active site.<sup>50</sup>

Carbon monoxide dehydrogenases (CODHs) are metalloenzymes that catalyze the reversible oxidation of carbon monoxide (CO) to carbon

dioxide (CO<sub>2</sub>). Central to their function is the C-cluster, a unique metallocluster comprising nickel and iron-sulfur components. In the catalytic cycle, CO binds to the nickel center of the C-cluster, forming a Ni–CO intermediate. This binding is a critical step, as it activates the CO molecule for subsequent oxidation. Structural studies have revealed that the C-cluster consists of a [Ni-4Fe-5S] core, with the nickel atom coordinated in a distorted square-planar geometry. The iron-sulfur components facilitate electron transfer during the catalytic process. Spectroscopic analyses, including electron paramagnetic resonance (EPR) and infrared (IR) spectroscopy, have provided insights into the nature of the Ni–CO bond. These studies have identified a Ni<sup>+</sup>–CO species as a key intermediate, characterized by specific g-values in EPR spectra and distinct CO stretching frequencies in IR spectra. The formation and decay of this intermediate occur at rates consistent with the enzyme's catalytic turnover, underscoring its relevance in the mechanism. The catalytic

mechanism proceeds with the nucleophilic attack of a hydroxide ion on the carbon atom of the Ni–CO complex, leading to the formation of a Ni–carboxylate intermediate. This intermediate subsequently decomposes to release CO<sub>2</sub>, regenerating the active site for another catalytic cycle.<sup>51</sup>

### Bioorganometallic chemistry beyond the naturally-occurring functions of metalloproteins and protein cofactors

#### Hemes and hemoproteins

Iron-porphyrins (hemes) are known to engage in metal-carbon bond formation, with a wide range of hemoprotein iron-aryl and iron-alk(en)yl complexes characterized experimentally in small synthetic compounds as well as in a wide range of heme proteins (including at least one protein crystal structure cf. Fig. 7). These can be formed by reaction with alkyl and aryl halogen derivatives.<sup>51</sup>

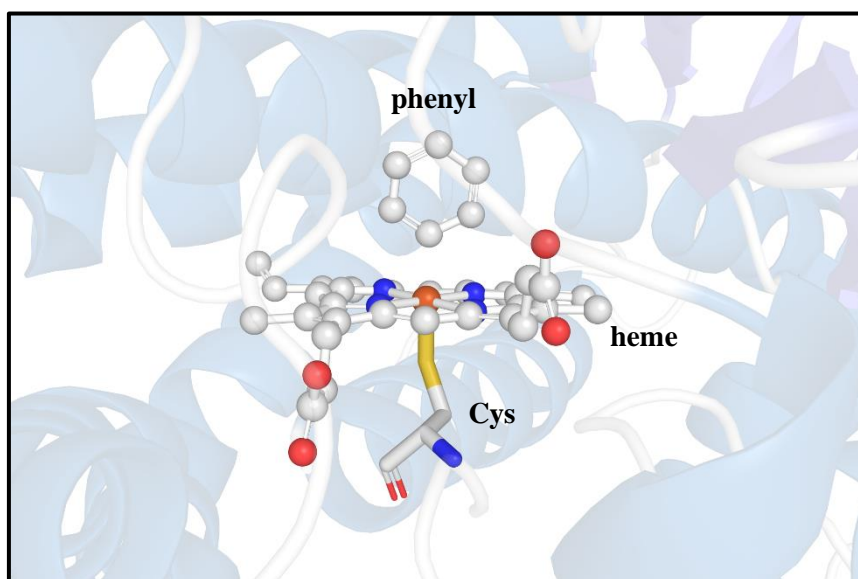


Fig. 7 – A bioorganometallic adduct that does not involve vitamin B<sub>12</sub>: cytochrome P450 complexed with phenyl (PDB code: 1CP4).

Super-reduced states of the metal in heme and related complexes (*i.e.*, iron or cobalt complexed with porphyrin, porphyrazine and phthalocyanine, or cobalamin and related complexes) can be obtained under physiologically relevant conditions with sulfur-based reducing agents (primarily sulfoxylate) or with borohydride – to the stage of Fe(I)/Co(I) or even further to (formally) Fe(0) or Co(0). However, especially for the latter, doubts exist as to whether the extra electrons are located on the metal or if in fact

they are located on the macrocycle in the form of an anion radical.<sup>2,8,14,22,52–55</sup>

#### Synthetic chemistry

Organometallic compounds sufficiently stable under biologically-relevant conditions have afforded exquisite tools for mechanistic investigations, development of new functionalities on biological molecules, or development of new therapeutic agents. These fields, while vast (see *e.g.* <sup>56–62</sup>), are beyond the scope of the present review.

## CONCLUDING REMARKS AND OUTLOOK

The above-mentioned centers, their reactivity, and their potential applications are all of notable interest. Nitrogenases and hydrogenases offer the opportunity of accessing valuable chemical raw materials from essentially cost-less raw materials (protons and air, respectively). Cobalamins and CO dehydrogenase offer routes into useful chemical compounds. Centers such as CO dehydrogenase and the methane-forming  $F_{430}$  are linked to greenhouse gases/pollutants which on the other hand may also constitute useful chemical feedstock. There is also medical potential, with cobinamide an efficient antidote for poisoning with cyanide and perhaps with a range of other small molecules/ions (*e.g.*, hydrogen sulfide).<sup>2</sup> It is in this context that one may seek to understand the details of the mechanisms for these exotic bioinorganic reactions – and realize that they are generally far from clear. Intermediate states in the catalytic cycles of nitrogenases and hydrogenases have been detected and characterized – but the exact location of ligand binding in the critical steps, and the exact distribution of electron density therein (hence, including issues of linkage and redox isomerism), are still a matter of debate and exploration – as are the above-discussed questions about the reasons why such choices for metals and of reaction intermediates are made. Among the open questions at this point, one can propose:

1. What makes a good nitrogenase catalyst? What are the general defining features, in terms of oxidation state, spin state, HSAB properties, electron density, ligation state etc?

2. Where exactly does  $N_2$  bind to FeMoCo, and what is the exact electronic structure of the cluster at that point? Likewise, for  $H^+$  binding at FeMoCo. How do nitrogenases work in cases where the Mo in FeMoCo is replaced by V or even by Fe – and why only these metals?

3. What makes a good hydrogenase (proton-reducing) catalyst? What are the general defining features, in terms of oxidation state, spin state, HSAB properties, electron density, ligation state etc? Where exactly do protons and  $H_2$  bind to the hydrogenase active sites, and what is the exact electronic structure of the cluster at that point?

4. What makes a good CO and  $CO_2$  activator (for reduction and/or coupling) in biology, under chemically-mild conditions? Super-reduced metal states may play a role in this as well.

5. How common, and how important, are unusual metal oxidation states in bioorganometallic centers?

6. How common, and how important, are redox and linkage isomerism in bioorganometallic centers?

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