



Focused review

Metal–metal bonds in biology

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ABSTRACT

Nickel-containing carbon monoxide dehydrogenases, acetyl-CoA synthases, nickel–iron hydrogenases, and diron hydrogenases are distinct metalloenzymes yet they share a number of important characteristics. All are O₂-sensitive, with active-sites composed of iron and/or nickel ions coordinated primarily by sulfur ligands. In each case, two metals are juxtaposed at the “heart” of the active site, within range of forming metal–metal bonds. These active-site clusters exhibit multielectron redox abilities and must be reductively activated for catalysis. Reduction potentials are milder than expected based on formal oxidation state changes. When reductively activated, each cluster attacks an electrophilic substrate via an oxidative addition reaction. This affords a two-electron-reduced substrate bound to one or both metals of an oxidized cluster. M–M bonds have been established in hydrogenases where they serve to initiate the oxidative addition of protons and perhaps stabilize active sites in multiple redox states. The same may be true of the CODH and ACS active sites—Ni–Fe and Ni–Ni bonds in these sites may play critical roles in catalysis, stabilizing low-valence states and initiating oxidative addition of CO₂ and methyl group cations, respectively. In this article, the structural and functional commonalities of these metalloenzyme active sites are described, and the case is made for the formation and use of metal–metal bonds in each enzyme mentioned. As a post-script, the importance of Fe–Fe bonds in the nitrogenase FeMoco active site is discussed.

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1. Introduction

Nickel-containing carbon monoxide dehydrogenases (CODHs [1]), acetyl-CoA synthases (ACSs [2]), diiron hydrogenases ([FeFe] Hases [3]) and nickel-and-iron hydrogenases ([NiFe] Hases [4]) are distinct, genetically unrelated, metalloenzymes, yet they share a remarkable number of structural and functional properties. When these properties are viewed collectively, a pattern emerges that suggests the formation of metal–metal (M–M) bonds during catalysis and the functional importance of such bonds. The purpose of this article is to highlight these properties and the possible functions of M–M bonds in catalysis.

All four metalloenzymes are O₂-sensitive and are found in anaerobic bacteria and archaea. Hases and CODHs catalyze redox reactions involving low reduction potentials; Hases catalyze the reversible reduction of protons to H₂, while CODHs catalyze the reversible reduction of CO₂ to CO. Once reductively activated, ACSs catalyze an overall *non*-redox reaction, namely the synthesis of acetyl-coenzyme A from CO, CoA, and a methyl cation transferred from a corrinoid–iron–sulfur protein.

The active sites of these enzymes are clusters of iron, sulfur and, except for [FeFe] Hases, nickel ions. [FeFe] and [NiFe] Hases contain

binuclear clusters (Fig. 1) bridged by thiolate groups and coordinated by CO and CN[−] ligands [5–8]. The [NiFe] active site is located near to an [Fe₄S₄] cluster while the active-site *H*-cluster of [FeFe] Hases is coordinated directly to such a cluster. The CODH *C*-cluster has the Fe/S cluster “built-in” so to speak; it consists of a NiFe₄S₄ cluster in which a unique iron (Fe_u, Fig. 1) is juxtaposed to the Ni [9–13]. Fe_u and Ni form a substrate-binding subsite while the remaining iron and sulfide ions form a [Fe₃S₄] sub-cluster that supports the [Ni Fe_u] subsite structurally and functionally. The ACS *A*-cluster consists of a Ni–Ni binuclear site (Fig. 1) coordinated to an [Fe₄S₄] cluster [11,14].

All of these binuclear metal–sulfur clusters are activated for catalysis when they are reduced relative to an oxidized state. In their activated states, they react with substrates via oxidative addition reactions in which substrates become reduced and bound to a site on the cluster. Hase clusters attack protons to generate metal-bound hydrides [3,4], the *C*-cluster reacts with CO₂ to generate a bound carboxylate group [13], and the *A*-cluster reacts with what is essentially a methyl cation to afford a methyl-bound intermediate [15].

1.1. The hypothesis

The active-site structures in Fig. 1 correspond to inactive *oxidized* states. Current research problems on these enzymes involve characterizing the activated *reduced* state of these sites, and understanding, on the electronic level, the mechanism by which these sites react with substrates. The hypothesis to be considered here is that *reduced states of all*

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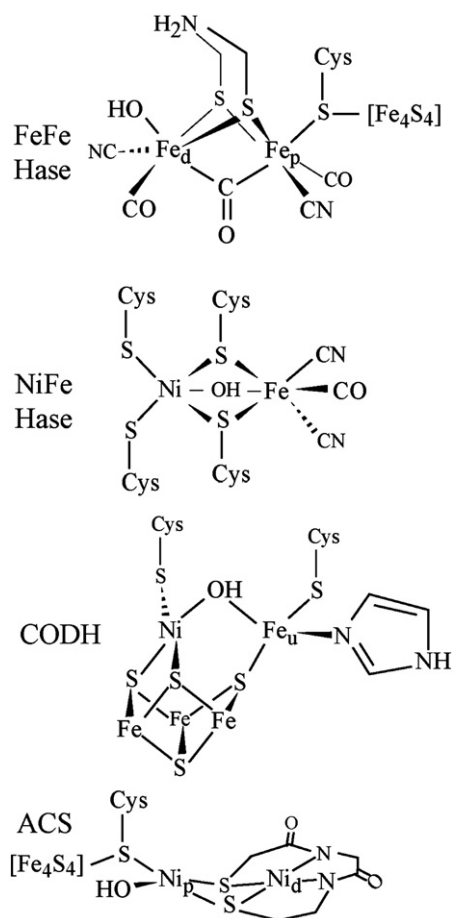


Fig. 1. Structures of oxidized active sites that are hypothesized to possess M–M bonds when reduced.

four enzymes involve metal–metal bonds (either transiently or stably) and that such bonds play critical roles in catalysis. These bonds would stabilize multiple electronic states of these centers, including low-valence states, and they would promote oxidative addition reactions with substrates. These bonds may be covalent, polar covalent, or dative in character. Their strength can vary from weak interactions that can barely be viewed as a bond to strong covalent bonds.

1.2. Characteristics of metal–metal bonds

Polar covalent and dative bonding interactions arise when different metals are used and/or with different ligand environments [16]. Given the different metals involved in the sites considered here, and the asymmetries in ligand coordination spheres, it seems likely that the M–M bonds in these protein-bound clusters will have some polar or dative character. Describing the polarity and dative character of metal–metal bonds in quantitative terms is beyond the scope of

this article. However, even minor differences in coordination environment appear sufficient for a M–M bond to have some polar/dative character. For example, the M–M bond in $[\text{CH}_3\text{N}(\text{PF}_2)_2]_3 \text{M}_2$ (M = Fe, Co, Ni) is covalent whereas the bond in the same base compound augmented by one CO coordinated to one of the metal atoms is sufficient to be viewed as dative [17].

Another aspect that suggests polar or dative bond character is that in each of the binuclear centers to be considered, one of the metal ions appears to be redox active while the other appears to be redox inactive. In the example of Fig. 2, the two neighboring metals in the oxidized state are assumed to be divalent $\text{M}_\text{D}^{\text{II}}$ (donor) and $\text{M}_\text{A}^{\text{II}}$ (acceptor) and non-interacting [18]. $\text{M}_\text{A}^{\text{II}}$ is redox-inactive and perhaps electron-deficient. $\text{M}_\text{D}^{\text{II}}$ has a softer ligand environment and is redox-active. In the presence of a sufficiently powerful reductant, $\text{M}_\text{D}^{\text{II}}$ accepts two electrons and becomes electron-rich. The same ligand environment would not support such a reduction in an equivalent mononuclear complex, but in the binuclear setting, interactions between the two metal ions stabilize the reduction. The formally $\text{M}_\text{D}^{\text{II}}$ species shares its newly acquired electrons with $\text{M}_\text{A}^{\text{II}}$, affording a $\text{M}_\text{D}^{\text{0}} \rightarrow \text{M}_\text{A}^{\text{II}}$ dative bond. A loosely bound ligand (water in this example) dissociates as the bond forms. Dative bond formation is reversible, as required for enzyme-catalyzed reactions. The $\text{M}_\text{D}^{\text{II}} \rightarrow \text{M}_\text{A}^{\text{II}}$ bond stabilizes the system, as it relieves the electron richness of the donor and the electron deficiency of the acceptor. Thus, oxidation states that would otherwise be thermodynamically unattainable (or attainable only with non-biological organometallic ligands) become attainable using biological ligands. Relative to covalent M–M bonds, dative bonds are dominated by dispersive (London) and electrostatic forces between the metals; relativistic effects are important [18]. The polarized anisotropic electronic nature of $\text{M}_\text{D} \rightarrow \text{M}_\text{A}$ bonds may facilitate small molecule activation and allow multielectron reductions [19,20]. Systems containing dative bonds react readily with electrophiles, forming oxidative addition products.

$\text{M}_\text{D} \rightarrow \text{M}_\text{A}$ bonds have been characterized in numerous inorganic systems. Thomas and coworkers [19] examined the effects of dative bond formation on the redox properties of $[\text{Co} \dots \text{Zr}]$ complexes. Formation of a dative bond causes the Co–Zr distance to shorten and allows multielectron reduction of the Co ion at unusually mild potentials. More recently, Thomas demonstrated oxidative addition of CH_3I across Co–Zr bonds in dinuclear complexes with phosphinoamide ligands [21]. Mashima et al. [20] prepared a number of $\text{Pt}^{\text{0}} \rightarrow \text{Mo}^{\text{II}} - \text{Mo}^{\text{II}} \leftarrow \text{Pt}^{\text{0}}$ compounds with trigonal-planar ligand geometry at each Pt. These compounds undergo 1,4-oxidative additions with diaryl disulfides to generate $\text{ArS}-\text{Pt}^{\text{I}}-\text{Mo}^{\text{II}} = \text{Mo}^{\text{II}}-\text{Pt}^{\text{I}}-\text{SAr}$ (dithiolate Pt^{I} complexes). E^{0} corresponding to the formation of these bonds is ca. -500 mV vs. NHE, a shift of about 1 V toward milder potentials, relative to related systems lacking such bonds. White and Stephan [22] characterized the complex $[\text{Cp}_2\text{Ti}(\text{SCH}_2\text{CH}_2\text{CH}_2\text{PPh}_2)_2\text{Ni}]$ in which there is a 2.852 \AA $\text{Ni}^{\text{0}} \rightarrow \text{Ti}^{\text{IV}}$ dative bond. The complex undergoes two reversible $n = 1$ oxidations to afford the Ni^{I} and Ni^{II} states; the Ti^{IV} ion is redox inactive. Similar mononuclear Ni^{0} complexes with P_2S_2 (thioether) coordination showed either irreversible oxidation [23] or a substantially larger spread in reduction potentials corresponding to the $\text{Ni}^{\text{II}}/\text{Ni}^{\text{I}}$ and $\text{Ni}^{\text{I}}/\text{Ni}^{\text{0}}$ couples [24].

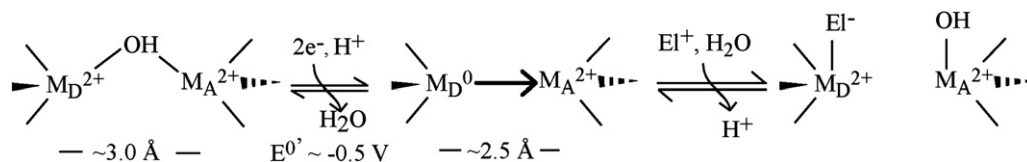


Fig. 2. Formation of M \rightarrow M dative bonds. In this hypothetical example, a divalent donor metal is located near to the acceptor metal. The ligand environment supports redox-activity of the donor but not the acceptor. A two electron reduction is coupled to the formation of a dative bond. The two metals move together slightly and a water/hydroxide that had bridged the two metal ions dissociates. Once formed, the dative bond can initiate oxidative addition chemistry by reacting with an electrophile. After reacting, the reduced electrophile is bound to the donor metal which has become reoxidized, and a hydroxide ion coordinates the other site. In other cases, the electrophile might bridge the metals.

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