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Diiron Azadithiolates as Models for the [FeFe]-Hydrogenase Active Site and Paradigm for the Role of the Second Coordination Sphere

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CONSPECTUS

The [FeFe] hydrogenases (H₂ases) catalyze the redox reaction that interconverts protons and H₂. This area of biocatalysis has attracted attention because the metal-based chemistry is unusual, and the reactions have practical implications. The active site consists of a [4Fe–4S] cluster bridged to a [Fe₂(μ-dithiolate)(CN)₂(CO)₃]^z center (z = 1– and 2–). The dithiolate cofactor is [HN(CH₂S)₂]^{2–}, called the azadithiolate ([adt^H]^{2–}). Although many derivatives of Fe₂(SR)₂(CO)_{6–x}L_x are electrocatalysts for the hydrogen evolution reaction (HER), most operate by slow nonbiomimetic pathways. Biomimetic hydrogenogenesis is thought to involve intermediates, wherein the hydride substrate is adjacent to the amine of the adt^H, being bonded to only one Fe center.

Formation of terminal hydride complexes is favored when the diiron carbonyl models contain azadithiolate. Although unstable in the free state, the adt cofactor is stable once it is affixed to the Fe₂ center. It can be prepared by alkylation of Fe₂(SH)₂(CO)₆ with formaldehyde in the presence of ammonia (to give adt^H derivatives) or amines (to give adt^R derivatives). Weak acids protonate Fe₂(adt^R)(CO)₂(PR₃)₄ to give terminal hydrido (term-H) complexes. In contrast, protonation of the related 1,3-propanedithiolate (pdt^{2–}) complexes Fe₂(pdt)(CO)₂(PR₃)₄ requires strong acids. The amine in the azadithiolate is a kinetically fast base, relaying protons to and from the iron, which is a kinetically slow base. The crystal structure of the doubly protonated model [(term-H)Fe₂(Hadt^H)(CO)₂(dppv)₂]²⁺ confirms the presence of both ammonium and terminal hydrido centers, which interact through a dihydrogen bond (dppv = *cis*-C₂H₂(PPh₂)₂). DFT calculations indicate that this H---H interaction is sensitive to the counterions and is strengthened upon reduction of the diiron center. For the monoprotonated models, the hydride [(term-H)Fe₂(adt^H)(CO)₂(dppv)₂]⁺ exists in equilibrium with the ammonium tautomer [Fe₂(Hadt^H)(CO)₂(dppv)₂]⁺. Both [(term-H)Fe₂(Hadt^H)(CO)₂(dppv)₂]²⁺ and [(term-H)Fe₂(adt^H)(CO)₂(dppv)₂]⁺ are highly active electrocatalysts for HER. Catalysis is initiated by reduction of the diferrous center, which

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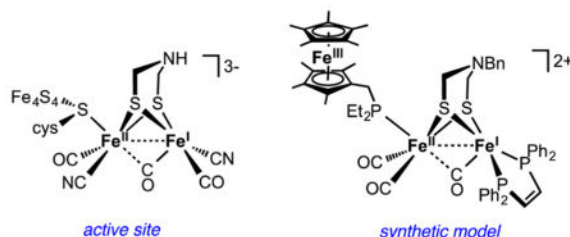
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This paper published ASAP on June 16, 2015. Reference 58 was added in the captions of Scheme 6 and Figure 5, and the revised version reposted on July 2, 2015.

induces coupling of the protic ammonium center and the hydride ligand. In contrast, the propanedithiolate $[(\text{term-H})\text{Fe}_2(\text{pdt})(\text{CO})_2(\text{dppv})_2]^+$ is a poor electrocatalyst for HER.

Oxidation of H_2 has been demonstrated, starting with models for the oxidized state (“ H_{ox} ”), for example, $[\text{Fe}_2(\text{adt}^{\text{H}})(\text{CO})_3(\text{dppv})(\text{PMe}_3)]^+$. Featuring a distorted $\text{Fe}(\text{II})\text{Fe}(\text{I})$ center, this H_{ox} model reacts slowly with high pressures of H_2 to give $[(\mu\text{-H})\text{Fe}_2(\text{adt}^{\text{H}})(\text{CO})_3(\text{dppv})(\text{PMe}_3)]^+$. Highlighting the role of the proton relay, the propanedithiolate $[\text{Fe}_2(\text{pdt})(\text{CO})_3(\text{dppv})(\text{PMe}_3)]^+$ is unreactive toward H_2 . The H_{ox} -model + H_2 reaction is accelerated in the presence of ferrocenium salts, which simulate the role of the attached $[\text{4Fe-4S}]$ cluster. The redox-complemented complex $[\text{Fe}_2(\text{adt}^{\text{Bn}})(\text{CO})_3(\text{dppv})-(\text{FcP}^*)]^{2+}$ catalyzes both proton reduction and hydrogen oxidation ($\text{FcP}^* = (\text{C}_5\text{Me}_5)\text{Fe}(\text{C}_5\text{Me}_4\text{CH}_2\text{PEt}_2)$).

Graphical abstract



1. INTRODUCTION TO THE $[\text{FeFe}]\text{-H}_2$ ases

The crystallographic characterization¹ of the $[\text{FeFe}]\text{-hydrogenases}$ (H_2 ases) from *Desulfovibrio desulfuricans* and *Clostridium pasteurianum* coincided roughly with a surge of interest in the “hydrogen economy.” These two developments led to intense scrutiny of these unusual enzymes by many scientific communities, including geneticists, biophysicists, organometallic chemists, and computational scientists.^{2–4} This Account presents an organometallic chemist’s perspective on this area, emphasizing contributions from the author’s laboratory. We have focused on replicating the structure and function of the active site, especially the role of the cofactors and hydride-containing intermediates.

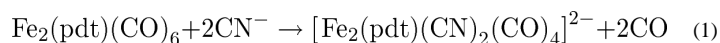
To the eyes of an organometallic chemist, the active site of the $[\text{FeFe}]\text{-H}_2$ ases combines the familiar and unfamiliar. The presence of Fe-Fe bonds as well as CO and CN^- ligands are conventional motifs. Unusual are the geometry of the Fe_2 site, a $1e\text{-redox}$ active catalytic center, and a cofactor (azadithiolate ligand) that modulates catalysis at Fe . The active site consists of a Fe_6 entity called the H-cluster , wherein a $[\text{4Fe-4S}]$ cubane is linked via a cysteinyl thiolate to an $\text{Fe}_2(\text{SR})_2(\text{CN})_2(\text{CO})_3$ core with a $\text{Fe}\cdots\text{Fe}$ distance of 2.60 \AA . Typical $[\text{FeFe}]\text{-H}_2$ ases, although notably not that from the alga *Chlamydomonas reinhardtii*, feature several auxiliary Fe-S clusters, whose presence not only underscores the mechanistic importance of electron-transfer but also complicates their study.³ The nature of the dithiolate cofactor that bridges the Fe_2 subunit has posed the greatest challenge to the definition of the active site. The dithiolate cofactor was eventually identified by reconstitution experiments using synthetic models developed in our laboratory, as described below.

The [FeFe]-, [FeNi]-, and [Fe]-H₂ases all feature Fe-CO-SR centers at their active sites.² Because no evolutionary relationship exists between these three enzymes, one must conclude that the Fe-SR-CO ensemble is particularly well suited for the activation of H₂.³ The reducing and oxidizing equivalents that drive H₂ases are supplied by [4Fe-4S] clusters, so the question naturally arises, why do [4Fe-4S]-containing proteins *not* function as H₂ases? The answer is that, compared to high-spin alternatives (cf. [4Fe-4S] clusters), low-spin Fe centers (cf. iron carbonyls) better stabilize metal-hydrides, as is usually required to interconvert H₂ and protons.

The [FeFe]-H₂ases can be isolated in two active states (Scheme 1), H_{ox} and H_{red}. With one unpaired electron, H_{ox} is especially well characterized spectroscopically. It features a Lewis acidic Fe(I) center poised to bind H₂. H_{red} is the reduced state with an *S* = 0 ground state (i.e., all electrons are paired). Available data support two descriptions for H_{red}: Fe(II)Fe(0) and Fe(I)Fe(I). Protonation of H_{red} or H₂ activation at H_{ox} (concomitant with electron transfer) would give a diferrous hydride Fe(II)Fe(II)-H⁻, a presumed catalytic intermediate.⁵ A catalytically relevant super-reduced state has also been identified in the enzyme from *C. reinhardtii*, featuring a reduced [4Fe-4S]⁺ cluster and possibly an Fe-H bond.^{2,6}

2. ACID-BASE REACTIONS OF Fe₂(SR)₂(CO)_{6-x}L_x

The similarity of the two-iron subunit of the [FeFe]-H₂ases and classical organoiron complexes⁷ sparked the development of synthetic models.⁸ Species like Fe₂(SEt)₂(CO)₆, which have been known for decades, resist protonation⁹ and undergo redox reluctantly. In contrast, the active site of the [FeFe]-H₂ases exhibits *both* acid-base and redox reactivity. The basicity of classical diiron(I) dithiolate carbonyls can be elevated upon replacement of some CO ligands with better Lewis bases, for example, cyanide, which can be introduced according to eq 1.¹⁰



The resulting complex remains electron-precise (i.e., satisfying the 18e rule as does its precursor), but the diiron dicyanide center is far more electron-rich, as indicated by ν_{CO} , the intense C-O vibrational bands observed by FT-IR spectroscopy. Thus, $(\nu_{\text{CO}})_{\text{avg}}$ for [Fe₂(pdt)(CN)₂(CO)₄]²⁻ is 1924 vs 2015 cm⁻¹ for Fe₂(pdt)(CO)₆ (ligand abbreviations in Scheme 2).

Being more basic, substituted (i.e., electron-rich) diiron(I) dithiolates readily protonate to give hydrido derivatives. The process entails formal oxidation of Fe(I)Fe(I) to Fe(II)Fe(II)-H⁻, as indicated by an increase in ν_{CO} by ~90 cm⁻¹. Spanning the Fe-Fe bond is a *bridging* hydride, which is labeled μ -H. The complex [(μ -H)Fe₂(pdt)(CN)₂(CO)₄]⁻ has a $\text{p}K_{\text{a}}^{\text{MeCN}}$ of 16, indicating that it is less acidic than a typical pyridinium ($\text{p}K_{\text{a}}^{\text{MeCN}} = 12.3$) and more acidic than a tertiary ammonium salt ($\text{p}K_{\text{a}}^{\text{MeCN}} = 18.8$). The Fe₂ center of the reduced active site might be expected to have a $\text{p}K_{\text{a}}$ near that of neutral water, its source of protons. Typical for low-spin ferrous (*d*⁶) complexes, the diferrous hydrido complexes are stereochemically more rigid than their [Fe(I)]₂ precursors. Thus, three isomers of [(μ -H)Fe₂(pdt)(CN)₂(CO)₄]⁻ are distinguishable by NMR spectroscopy.¹¹

For mechanistic analysis, most fruitful synthetic models contain organophosphorus ligands, not cyanide. The complexes $\text{Fe}_2(\text{pdt})(\text{CO})_{6-x}(\text{PR}_3)_x$ form well-behaved hydrides for $x \geq 2$. Studies on these phosphine derivatives uncovered the first evidence for *terminal* hydrides. In these species, the hydride ligand (i.e., substrate) occupies a coordination site *cis* to both sulfur ligands. Terminal hydrides are of particular interest because they are implicated in the catalytic cycle by biophysical^{5,12} and computational studies.¹³ The more prevalent μ -hydrides are also competent electrocatalysts for hydrogen evolution,¹⁴ but they probably do not utilize biomimetic mechanisms,^{7,15} although the matter is debated.¹⁶

Models with terminal hydrides can be stabilized by steric congestion, which slows their inevitable isomerization to the μ -hydride.¹⁷ The terminal hydrides $[(\textit{term}\text{-H})\text{Fe}_2(\text{pdt})(\text{CO})_2(\text{dppv})_2]^+$ and $[(\textit{term}\text{-H})\text{Fe}_2(\text{pdt})(\text{CO})_2(\text{PMe}_3)_4]^+$ have half-lives of minutes at room temperature.^{18,19} In contrast, $[(\textit{term}\text{-H})\text{Fe}_2(\text{pdt})(\text{CO})_4(\text{dppv})]^+$ isomerizes in seconds at -80°C , and $[(\textit{term}\text{-H})\text{Fe}_2(\text{pdt})(\text{CO})_4(\text{PMe}_3)_2]^+$ has never been detected despite strenuous efforts.²⁰ In Nature, terminal-to-bridge isomerization is prevented by strong hydrogen bonding between the protein and at least one of the FeCN sites.²¹ Although Fe–H species are likely intermediates in the biological mechanism,^{5,16} they have not been confirmed in native enzymes.

The protonation of $\text{Fe}_2(\text{pdt})(\text{CO})_2(\text{PR}_3)_4$ has been studied in depth. Sulfur is implicated as the kinetic site of protonation by strong acids. The resulting SH-containing intermediate rearranges to Fe–H species.²² The recurring pattern is that protonation of metal complexes and clusters occurs first at nonmetal sites, even weakly basic ones, followed by more basic metal centers.²³

Studies on $\text{Fe}_2(\text{dithiolate})(\text{CO})_2(\text{PMe}_3)_4$ ($[\text{dithiolate}]^{2-} = [\text{edt}]^{2-}$ and $[\text{pdt}]^{2-}$) also provide insights into the formation of μ -hydrides. Although a nuisance for modeling the [FeFe]- H_2 ase, μ -hydrides are important because they are pervasive in multimetallic clusters. Bridging hydride ligands occur in [NiFe]- H_2 ases, and perhaps other bioorganometallic centers,²⁴ including the FeMoco cluster in nitrogenase.²⁵ In the diiron dithiolates, a major pathway to μ -hydrides entails intramolecular rearrangement of terminal hydrides (Scheme 3). The isomerization of the terminal to μ -hydride is far faster for the edt derivatives, indicating the influence of steric bulk of the dithiolate on the behavior of the underlying diiron center.^{26,27} Isomerization of *term*-H to μ -H follows first order kinetics. H/D exchange is not observed when the isomerization is conducted in the presence of D_2O . Computational analysis suggests that the isomerization proceeds via intermediates with trigonal prismatic geometry at the FeH center.²⁸ This isomerization is probably impossible for the enzyme owing to the strong interaction of the distal FeCN center with the protein.²¹

A second pathway to μ -hydrides was detected for $\text{Fe}_2(\text{dithiolate})(\text{CO})_2(\text{PMe}_3)_4$ ($[\text{dithiolate}]^{2-} = [\text{edt}]^{2-}$, $[\text{pdt}]^{2-}$). The main finding is that in concentrated solutions μ -hydrides appear at temperatures too low for intramolecular isomerization. Analysis of the reaction kinetics suggests that the S-protonated species $[\text{Fe}_2(\text{Hdithiolate})(\text{CO})_2(\text{PMe}_3)_4]^+$ *intermolecularly* protonates the Fe–Fe bond of $[\text{Fe}_2(\text{dithiolate})(\text{CO})_2(\text{PMe}_3)_4]$.¹⁹

3. REDOX REACTIONS OF $\text{Fe}_2(\text{SR})_2(\text{CO})_{6-x}\text{L}_x$ AND DERIVED HYDRIDES

In addition to exhibiting acid–base reactivity, the diiron subunit of the H-cluster is redox active. The classical diiron dithiolato carbonyls $\text{Fe}_2(\text{SR})_2(\text{CO})_6$ resist oxidation, although they can be reduced to Fe(0)–Fe(I) derivatives. Such reduced diiron complexes exhibit fascinating chemistry,^{7,15} but they are probably not relevant to the enzyme. Diiron dithiolates with mild and biological plausible redox couples result from replacement of some of the CO ligands in $\text{Fe}_2(\text{SR})_2(\text{CO})_6$ by stronger bases (Figure 1). These substituted species undergo at least quasi-reversible one-electron oxidation, the glaring exception being the cyanide derivatives, which oxidize at mild potentials but always irreversibly.²⁹ It is this irreversibility that forced modeling efforts to refocus on phosphine-based complexes.

Protonation at these electron-rich diiron complexes strongly impacts the redox properties. The hydrido complexes exhibit highly negative reduction potentials (Figure 1). For the couple $[(\text{term-H})\text{Fe}_2(\text{pdt})(\text{CO})_2(\text{dppv})_2]^{+/0}$, the site of reduction can avoid the FeH center,³⁰ and thus, this couple is 200 mV milder than the isomeric $[(\mu\text{-H})\text{Fe}_2(\text{pdt})(\text{CO})_2(\text{dppv})_2]^{+/0}$.¹⁷

4. DIIRON AZADITHIOLATES $\text{Fe}_2(\text{adt}^{\text{R}})(\text{CO})_{6-x}\text{L}_x$

Traditionally, $\text{Fe}_2(\text{SR})_2(\text{CO})_6$ compounds arise from thermal reactions of iron(0) carbonyls with thiols, although sometimes disulfides or even thioethers are employed.⁷ Synthesis of azadithiolato complexes $\text{Fe}_2(\text{adt}^{\text{R}})(\text{CO})_6$, however, require specialized methods (Scheme 4). Free azadithiols ($\text{RN}(\text{CH}_2\text{SH})_2$) and azadithiolates ($[\text{RN}(\text{CH}_2\text{S})_2]^{2-}$) are unstable,³¹ so these azadithiolates must be constructed on the diiron framework.

A widely used route entails the four-component reaction of $\text{Fe}_2(\text{SH})_2(\text{CO})_6$ with formaldehyde and an amine. This kind of S-centered reactivity has long been a topic of our research.³² In terms of its mechanism, this reaction proceeds by the condensation of FeSH and CH_2O groups to give $\text{Fe}_2(\text{SCH}_2\text{OH})_2(\text{CO})_6$, which has been crystallized.³³ Treatment of $\text{Fe}_2(\text{SCH}_2\text{OH})_2(\text{CO})_6$ with ammonia and primary amines gives $\text{Fe}_2(\text{adt}^{\text{R}})(\text{CO})_6$. The N-substituted derivatives $\text{Fe}_2(\text{adt}^{\text{R}})(\text{CO})_6$ are also readily prepared by alkylation of $\text{Li}_2\text{Fe}_2\text{S}_2(\text{CO})_6$ with bis(chloromethyl)amines, for example, $\text{MeN}(\text{CH}_2\text{Cl})_2$.³⁴ These N-substituted derivatives also arise from the condensation of $\text{Fe}_2(\text{SH})_2(\text{CO})_6$ and imine trimers $(\text{RNCH}_2)_3$.

In terms of structure, the two $\text{Fe}(\text{CO})_3$ centers in $\text{Fe}_2(\text{adt}^{\text{H}})(\text{CO})_6$ are nonequivalent because of the folded conformation of the adt. An analogous situation applies to the pdt derivatives. The flipping occurs with a barrier of about 10 kcal/mol, although it appears that the adt^{R} derivatives are slightly more rigid than analogous pdt complexes. Two isomers are possible for $\text{Fe}_2(\text{adt}^{\text{H}})(\text{CO})_6$, depending on the orientation of the NH group (Scheme 5). In the axial isomer, the N-substituent projects toward the Fe-center, whereas in the equatorial isomer, the lone pair projects toward the diiron subsite. DFT calculations predict that the equatorial isomer is stabilized by 5.7 kcal/mol by an anomeric interaction between the lone pair orbital on nitrogen and the C–S σ^* orbitals. With N-alkyl derivatives, the substituents are typically axial for hexacarbonyls but often equatorial when the diiron center bears bulky ligands in an apical site. The amine is planar when the substituent R can participate in π -bonding (R = aryl groups,³⁵ acyls, alkynyl).

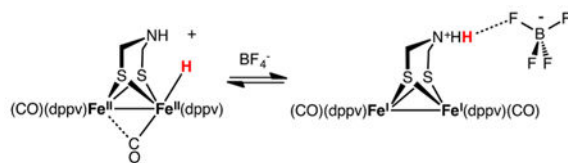
Just like other diiron dithiolates, $\text{Fe}_2(\text{adt}^{\text{H}})(\text{CO})_6$ undergoes CO substitution by donor ligands. For example, treatment with cyanide salts gives $[\text{Fe}_2(\text{adt}^{\text{H}})(\text{CN})_2(\text{CO})_4]^{2-}$.³⁶ This species can be incorporated in the apo- H_2 ase from *C. reinhardtii* to give fully active enzyme. This “artificial maturation” experiment can be extended to many analogous but these derivatives are far less catalytically active.³⁷ These elegant experiments verified that *azadithiolate* is the dithiolate cofactor in the active site.

The acid–base behavior of the diiron dithiolato complexes is obviously enriched by the presence of the $[\text{adt}^{\text{R}}]^{2-}$ ligand. The parent $\text{Fe}_2(\text{adt}^{\text{H}})(\text{CO})_6$ undergoes reversible protonation at nitrogen, signaled by a ν_{CO} shift of $\sim 15 \text{ cm}^{-1}$ (vs $\sim 65 \text{ cm}^{-1}$ for protonation at Fe).³⁸ The basicity of the amine, $\text{p}K_{\text{a}}^{\text{MeCN}} = 8$,³⁹ is much greater than that of the Fe centers, $\text{p}K_{\text{a}}^{\text{MeCN}}$ for which is < 2.6 ($\text{p}K_{\text{a}}^{\text{MeCN}}$ of $\text{CF}_3\text{SO}_3\text{H}$). The relative basicity of the Fe vs amine is strongly affected by substitution of the CO ligands. For $\text{Fe}_2(\text{adt}^{\text{H}})(\text{CO})_4(\text{PMe}_3)_2$, the $\text{p}K_{\text{a}}^{\text{MeCN}}$ of the amine has increased to 10.2, but the Fe–Fe bond is still more basic, having increased by about 12 units. Protonation of complexes of the type $\text{Fe}_2(\text{adt}^{\text{R}})(\text{CO})_4(\text{PR}_3)_2$ first gives the ammonium species, which subsequently converts to the μ -hydride.⁴⁰ These experiments establish that the amine, not the Fe centers, is the superior kinetic base, reflecting the small reorganizational penalties for their protonation.²³ The $\text{p}K_{\text{a}}^{\text{MeCN}}$ value of $[(\text{term-H})\text{Fe}_2(\text{pdt})(\text{CO})_2(\text{PR}_3)_4]^+$ and $[(\mu\text{-H})\text{Fe}_2(\text{pdt})(\text{CO})_2(\text{PR}_3)_4]^+$ are estimated respectively at 16 and > 19 . At equilibrium, the terminal hydride complex is never observed in any model complex.

5. HYDROGEN EVOLUTION CATALYZED BY $\text{Fe}_2(\text{adt}^{\text{R}})(\text{CO})_2(\text{dppv})_2$

With respect to catalytic hydrogen evolution, an informative catalyst is $\text{Fe}_2(\text{adt}^{\text{H}})(\text{CO})_2(\text{dppv})_2$. This greenish-brown, air-sensitive solid is conveniently soluble in organic solvents. In terms of spectroscopic (IR and variable temperature ^{31}P NMR) and redox properties, this adt^{H} complex and the pdt analogue are very similar as are the corresponding hydrides. Since the electronic structures of the pdt and adt^{H} systems are so similar,⁴¹ the thermodynamics for their protonations are the same and differences can be attributed to kinetic factors. Overall, the pdt complex allows for perfect control experiments in studying the role of the second coordination sphere because the first coordination spheres are identical.

The Fe sites in $\text{Fe}_2(\text{adt}^{\text{H}})(\text{CO})_2(\text{dppv})_2$ are more basic than the amine. In CH_2Cl_2 solution, the equilibrium is delicately balanced, as indicated by the finding that the addition of BF_4^- , a weak hydrogen-bond acceptor, shifts the equilibrium toward the ammonium tautomer (eq 2). With the use of $\text{BAR}^{\text{F}_4^-}$ counterions ($\text{BAR}^{\text{F}_4^-} = \text{B}(3,5\text{-C}_6\text{H}_3(\text{CF}_3)_2)_4^-$), this complication is absent, and the hydride is the exclusive species.



Treatment of $\text{Fe}_2(\text{adt}^{\text{H}})(\text{CO})_2(\text{dppv})_2$ with 2 equiv of $\text{HBF}_4 \cdot \text{Et}_2\text{O}$ gives the *doubly* protonated species $[(\text{term-H})\text{Fe}_2(\text{Hadt}^{\text{H}})(\text{CO})_2(\text{dppv})_2](\text{BF}_4)_2$ wherein one Fe and amine are protonated (Figure 2). Crystals were of sufficient quality that the NH and FeH centers were located and refined. The NH---HFe distance of 1.88(7) Å indicates dihydrogen bonding.⁴² Careful analysis of this dication by DFT revealed that the experimental H---H distance is affected by the interaction of the N–H centers with two BF_4^- anions. Upon removal these anions in silico, the H---H separation contracts to 1.40 Å, consistent with a strong dihydrogen bond.⁴³

The ammonium-hydrides $[(\text{term-H})\text{Fe}_2(\text{Hadt}^{\text{H}})(\text{CO})_2\text{L}_4]^{2+}$ ($\text{L}_4 = (\text{dppv})_2$ and $(\text{PMe}_3)_4$) do *not* eliminate H_2 .^{19,38} The nonreactivity is understandable: loss of H_2 would generate a highly unsaturated dication, which electrochemical measurements confirm are high energy species.^{44,45} In contrast to the stability of $[(\text{term-H})\text{Fe}_2(\text{Hadt}^{\text{H}})(\text{CO})_2\text{L}_4]^{2+}$, the ammonium hydrides of nickel(II) $[\text{HNi}(\text{P}_2\text{N}_2)(\text{HP}_2\text{N}_2)]^{2+}$ eliminate H_2 spontaneously ($\text{P}_2\text{N}_2 =$ diaminodiphosphine).⁴⁶ Protonation of $[(\text{term-H})\text{Fe}_2(\text{edt})(\text{CO})_2(\text{PMe}_3)_4]^+$ does give H_2 , but this reaction requires the presence of MeCN, which enables formation of $[\text{Fe}_2(\text{edt})(\text{CO})_2(\text{NCMe})(\text{PMe}_3)_4]^{2+}$.¹⁸

Although the diferrous adt-hydrides are thermally stable, they release H_2 upon reduction. Cyclic voltammetry studies established the irreversibility of the couple $[(\text{term-H})\text{Fe}_2(\text{adt}^{\text{H}})(\text{CO})_2(\text{dppv})_2]^{+/0}$. This irreversibility is attributed to hydrogen release, following rapid proton transfer. Computational studies indicate reduction (i) is localized on the proximal (nonhydride-bearing) iron center and (ii) induces coupling of the $\text{N-H}^{\delta+}$ and $\text{Fe-H}^{\delta-}$ centers to give an intermediate corresponding to the weakly bound H_2 adduct of the H_{ox} state.⁴⁷ In contrast, the $[(\mu\text{-H})\text{Fe}_2(\text{adt}^{\text{H}})(\text{CO})_2(\text{dppv})_2]^{+/0}$ and the $[(\text{term-H})\text{Fe}_2(\text{pdt})(\text{CO})_2(\text{dppv})_2]^{+/0}$ couples are at least quasi-reversible, as are the analogous $(\text{PMe}_3)_4$ complexes.

The complex $[(\text{term-H})\text{Fe}_2(\text{Hadt}^{\text{H}})(\text{CO})_2\text{s}(\text{dppv})_2]^{2+}$ is a very fast electrocatalyst. In the presence of strong acids such as $\text{HBF}_4 \cdot \text{Et}_2\text{O}$ or trifluoroacetic acid, a catalytic wave appears at -1.22 V associated with a turnover frequency of $58\,000\text{ s}^{-1}$ (Figure 3). In stark contrast, the isomeric bridging hydrido complexes $[(\mu\text{-H})\text{Fe}_2(\text{adt}^{\text{H}})(\text{CO})_2(\text{dppv})_2]^+$, are slow catalysts ($\sim 20\text{ s}^{-1}$) and operate at even higher overpotentials (Table 2).

6. MODELS FOR THE H_{ox} STATE: H_2 OXIDATION

The H_{ox} state is a well-characterized, almost iconic state of the $[\text{FeFe}]\text{-H}_2$ ases (Scheme 1). With a mixed valence Fe(II)–Fe(I) core, H_{ox} is 1e-oxidized relative to the usual diiron(I) dithiolates. In models and the proteins alike, the Fe(I) center features a vacant coordination site adjacent to the adt cofactor (Figure 4). As the oxidized state, H_{ox} is poised for activation of H_2 . Models for this state are of the type $[\text{Fe}_2(\text{dithiolate})(\text{CO})_{4-x}\text{L}_x]^+$, where $\text{L} = \text{PR}_3$ or carbene ligand, and $x = 2, 3, 4$.⁴⁹

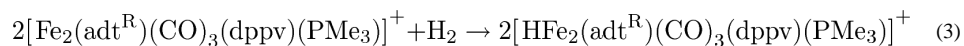
Initial experiments on the oxidation of H_2 entailed studies on the hydrogenation of $[\text{Fe}_2(\text{dithiolate})(\text{CO})_3(\text{dppv})(\text{PMe}_3)]^+$, where $[\text{dithiolate}]^{2-} = [\text{pdt}]^{2-}$ and $[\text{adt}^{\text{H}}]^{2-}$. Consistent with their electrophilicity, these cations are labile in solution as their BF_4^- salts, but the corresponding $\text{BAr}^{\text{F}}_4^-$ salts give stable CH_2Cl_2 solutions. The salt $[\text{Fe}_2(\text{adt}^{\text{H}})$

(CO)₃(dppv)(PMe₃)]-BAr^F₄ reacts with H₂, but slowly (18h, 1800 psi, 25 °C). The product is [(μ-H)Fe₂(adt^H)(CO)₃(dppv)(PMe₃)]⁺, as expected since [(*term*-H)Fe₂(adt)(CO)₃(dppv)(PMe₃)]⁺, the anticipated kinetic product, isomerizes extremely rapidly near room temperature.²⁶ In contrast to the efficient hydrogenation of the adt^H complex, the propanedithiolate [Fe₂(pdt)(CO)₃(dppv)-(PMe₃)]BAr^F₄ was recovered unchanged after prolonged treatment with high pressures of hydrogen. These experiments established that adt^R assists in the activation of H₂.⁵⁰

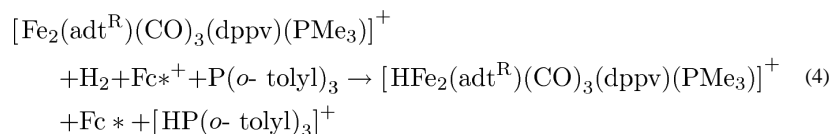
The slowness of the reaction between H_{ox} models and H₂ can be rationalized in terms of thermodynamics and electron counting. To activate H₂, the catalytic center must compensate for the 76 kcal/mol (in MeCN solution⁴⁶) required to cleave H₂ into H⁺ and H⁻. This energetic price is paid in two ways:⁴⁶ the protonation of the amine of the adt and the coordination of the hydride at Fe. The contribution from deprotonation by the amine is 1.35(pK_a), which translates to ~20 kcal/mol. So the major contributor to heterolysis of H₂ derives from the affinity of the diiron center for H⁻, i.e. its hydricity, which must be around 55 kcal/mol. Such hydricity is achievable for ferrous complexes,⁵¹ but unlikely for weakly electrophilic Fe(I) centers as exist in simple models for H_{ox}. From the perspective of traditional electron counting, the coordination of H⁻ to the 17e⁻ Fe(I) center is unfavorable. On the other hand, oxidation of such H_{ox} models to the diferrous state induces coordination of the amine to Fe, saturating its coordination sphere and thus ruining any chance of heterolysis.⁴⁴

The above considerations led to proposition that H₂ *heterolysis is synchronized with oxidation* of the diiron center.⁵² According to this hypothesis, the distal Fe center “turns on” its electrophilicity only in the presence of substrate H₂. The hypothesized coupling of H₂ activation and redox is supported by the observation that [Fe₂(adt^R)(CO)₃(dppv)(PMe₃)]⁺ activates 1 atm H₂ at room temperature in the presence of decamethylferrocenium (Fc^{*+}), a mild oxidant, and P(*o*-tolyl)₃, a weak non-nucleophilic base. Note that Fc^{*+} does not oxidize [Fe₂(adt^R)(CO)₃(dppv)(PMe₃)]⁺; instead, it intercepts a diiron hydrido intermediate. The rate of hydrogen oxidation is first order both in H₂ and in the H_{ox} model. No reaction occurs when the adt^R is replaced by pdt (eqs 3–5).⁵²

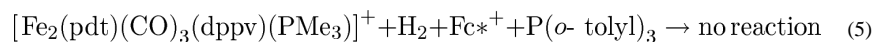
slow:



fast:



control:



To achieve *catalytic* oxidation of H₂, the model requires complementation by a redox cofactor. To fulfill this function, the diiron center was fitted with phosphine ligand linked to decamethylferrocene. Called FcP*, the ligand (C₅Me₅)Fe-(C₅Me₄CH₂PET₂) is a rough functional approximation of an [4Fe-4S] cluster, although about 700 mV less reducing (Figure 1).⁵³ Oxidation of Fe₂(adt^{Bn})(CO)₃(dppv)(FcP*) occurs first at the FeFe site ($\nu_{\text{CO}} \sim 60 \text{ cm}^{-1}$) and second at FcP* ($\nu_{\text{CO}} \sim 5 \text{ cm}^{-1}$).⁵⁴ Incidentally, the dication [Fe₂(adt^{Bn})(CO)₃(dppv)(FcP*)]²⁺ (as well as H_{ox}) is a rare example of species with iron in three different oxidation states (Fe(III), Fe(II), and Fe(I)). In the presence of excess P(*o*-tolyl)₃ and Fc⁺, the dication catalyzes the oxidation H₂ (1 atm), before it deactivates to [(μ -H)Fe₂(adt^{Bn})(CO)₃(dppv)(FcP*)]⁺.

Design of catalysts for H₂ oxidation was guided by the fact that the H₂/H⁺ couple requires *two* redox equivalents, only one of which can be provided by the diiron center (the H_{ox}/H_{red} couple, Scheme 1). In our models, the second redox equivalent is supplied by ferrocenium reagents, whereas in the protein the [4Fe-4S] cluster serves this role. The same principles apply to hydrogen evolution (next section). These results underscore the functional role of the [4Fe-4S] component of the H-cluster.⁶

Although H₂ oxidation proceeds, the rates are modest, being a few turnovers per hour vs thousands per second for the enzyme. The problem is attributed to the low affinity of the H_{ox} models for H₂, which correlates with their low affinity for CO,⁴⁹ a potent inhibitor of these enzymes. Some mono-Fe complexes are faster catalysts for H₂ oxidation, with rates of 2 s⁻¹,⁴³ suggesting that this performance gap can be closed.

7. BIDIRECTIONAL CATALYSIS

While H₂ases are expressed for either the production or oxidation of hydrogen, these enzymes characteristically mediate both reactions.³ Thus, far this Account describes complexes that are electrocatalysts for H₂ production and others that oxidize H₂. It turns out that the H₂-oxidizing catalysts are also active for hydrogen evolution, thereby establishing bidirectionality in these models.

Analogous to other Fe₂(dithiolate)(CO)₃(PR₃)₃ complexes, Fe₂(adt^{Bn})(CO)₃(dppv)(FcP*) reacts with one equiv of [H(OEt₂)₂]BAR^F₄ to give [(μ -H)Fe₂(adt^{Bn})(CO)₃(dppv)-(FcP*)]⁺. Curiously, when the acid is added rapidly, H₂ is produced (Scheme 6). Furthermore, when excess [H(OEt₂)₂]-BAR^F₄ is added to a mixture of the model complex *and* the electron donor Fc*, H₂ is produced catalytically according to the stoichiometry 2Fc* + 2H⁺ → 2Fc⁺⁺ + H₂. Subsequent to H₂ evolution, the main organometallic product is [Fe₂(Hadt^{Bn})(CO)₃(dppv)(FcP*)]²⁺. EPR and FT-IR spectroscopic evidence indicates that this dication contains a ferrocenium group and a Fe(I)Fe(I) core. This species is conveniently slow to rearrange to the μ -hydride because its ferrocenium substituent lowers the basicity of the diiron subunit. In the ammonium species [Fe₂(Hadt^{Bn})(CO)₃(dppv)(FcP*)]⁺, the FcP* group is more reducing than the Fe₂ center. In other words, N-protonation induces the electron hole to shift from the FeFe core to FcP* (Figure 5). Electron-transfer is fast and so does not require covalent attachment of the electron donor to the catalytic center. Thus, Fe₂(adt^{Bn})(CO)₃(dppv)(PMe₃) also catalyzes the reduction of acids by Fc* to H₂, provided that the acid is added to a

performed solution of the catalyst and the electron donor Fc^* . The order of addition is important, lest μ -hydrides form irreversibly.⁵⁸

The adt^{R} cofactor in the redox-complemented H_2 evolution catalyst does *not* relay a proton to the Fe(I)Fe(I) site. The individual Fe sites (not the Fe–Fe bond!) in $\text{Fe}_2(\text{adt}^{\text{R}})(\text{CO})_3(\text{PR}_3)_3$ are less basic than the amine (see Table 1). For this reason, the rate-determining step in H_2 evolution is probably protonation of the weakly basic Fe center of $[\text{Fe}_2(\text{Hadt}^{\text{R}})(\text{CO})_3(\text{PR}_3)_3]^+$, hence the requirement for strong acids. Upon formation of the ammonium diferrous hydride, electron transfer from the FcP^* center would induce heterolytic coupling of the $\text{N-H}^{\delta+}$ and $\text{Fe-H}^{\delta-}$ centers to give H_2 . This electron transfer outcompetes the isomerization of the *term*-hydride to μ -hydride, which occurs in seconds even at $-90\text{ }^\circ\text{C}$.²⁶

8. SUMMARY AND CLOSING COMMENTS

The catalysts described above utilize bioinspired motifs to mediate the interconversion of H^+ and H_2 . The observed reactivity can be attributed to the combined effect of these factors:

- i. The adt cofactor, which compensates for otherwise slow rates of proton transfer at metals.²³
- ii. A low-spin, redox-active $\text{Fe}_2(\text{SR})_2$ core sufficiently basic to form Fe–H species. To enhance the basicity of the diiron center, Nature employs cyanide, whereas synthetic models often rely on phosphine ligands.
- iii. A source of redox equivalents to complement the $[\text{Fe}_2(\text{SR})_2(\text{CO})_{6-x}\text{L}_x]^{+/0}$ couple. Redox equivalents can be supplied by electrodes or artificial electron donors/acceptors.
- iv. Prevention of μ -hydride formation. Model complexes rely on steric congestion to slow isomerization, but Nature exploits the embrace of the protein.²¹

Further work on FeFe- H_2 ase modeling would naturally focus on catalysts that operate faster and at lower overpotentials. These goals might be met in part with models featuring preorganized catalytic centers. Indeed, chemists are learning how to control the geometry at the substrate-bearing Fe center⁵⁵ and to fine-tune proton relays.^{5,56} Finally, these exquisitely multifunctional complexes⁵⁷ could in principle be repurposed to effect other reactions, such as hydrogenation and atom-transfer processes.

Acknowledgments

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Biography

Thomas B. Rauchfuss studied at the University of Puget Sound, Washington State University, and the Australian National University, before starting his independent career at the University of Illinois at Urbana–Champaign where he is Larry Faulkner Professor of Chemistry. His research interests are synthetic inorganic and organometallic chemistry.

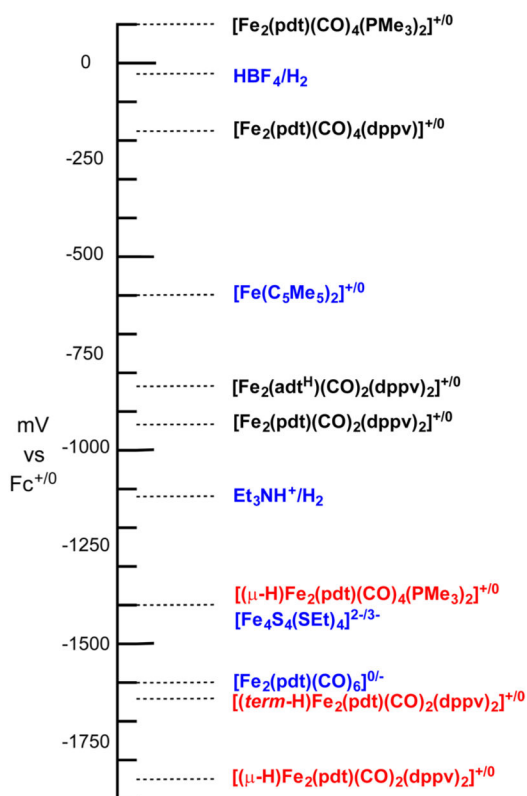


Figure 1.

Redox potentials of diiron hydrides (red), Fe(I)Fe(I) complexes (black), and selected reference compounds (blue). Redox couples are at least quasi-reversible, recorded in CH₂Cl₂ or MeCN solution with quaternary ammonium salts of BF₄⁻ or BAr₄^{F-4-} as electrolytes.

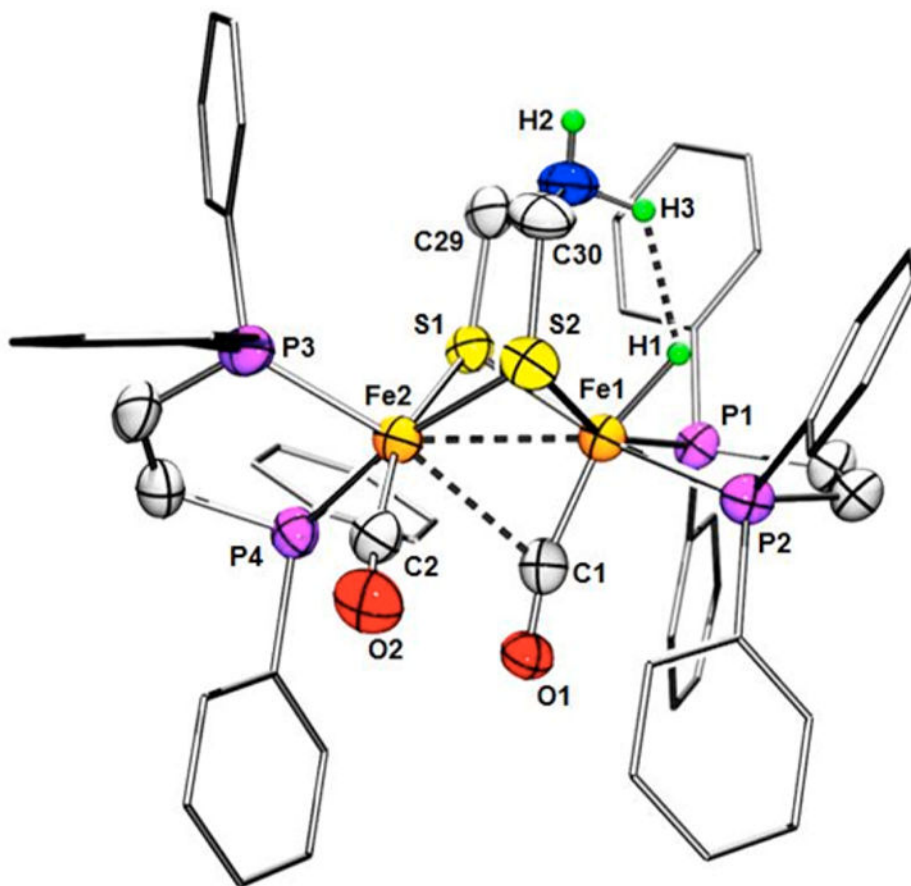


Figure 2.
Structure of the dication $[(term-H)Fe_2(Hadt^H)-(CO)_2(dppv)_2]^{2+}$.

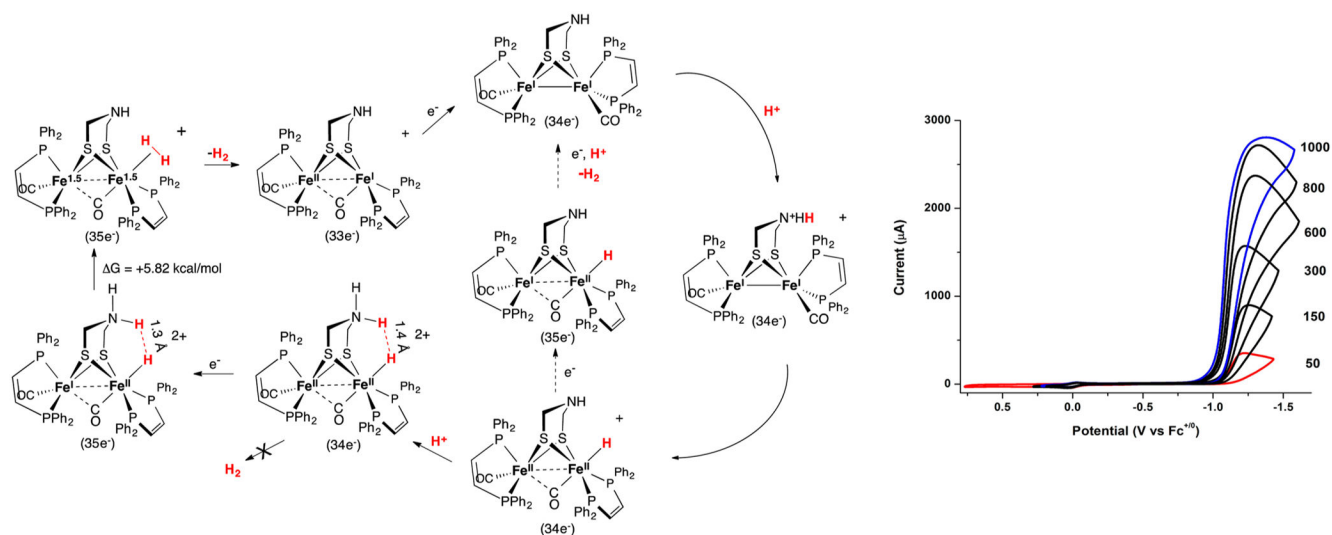


Figure 3.

Left: Mechanisms for H₂ production with strong (solid lines, characterized by DFT calculations) and weak acids (dashed lines). (Reproduced with permission from ref 47. Copyright 2014 American Chemical Society.) Right: Cyclic voltammograms of a 0.5 mM solution of [(*term*-H)Fe₂(adt^H)(CO)₂(dppv)₂]⁺ (0 °C, 0.125 M [Bu₄N]BAR^F₄, CH₂Cl₂, scan rate = 1.0 V/s, glassy carbon working electrode, Pt counter electrode, Ag wire pseudo reference electrode, Fc internal standard) recorded with increasing equivalents of CF₃CO₂H.

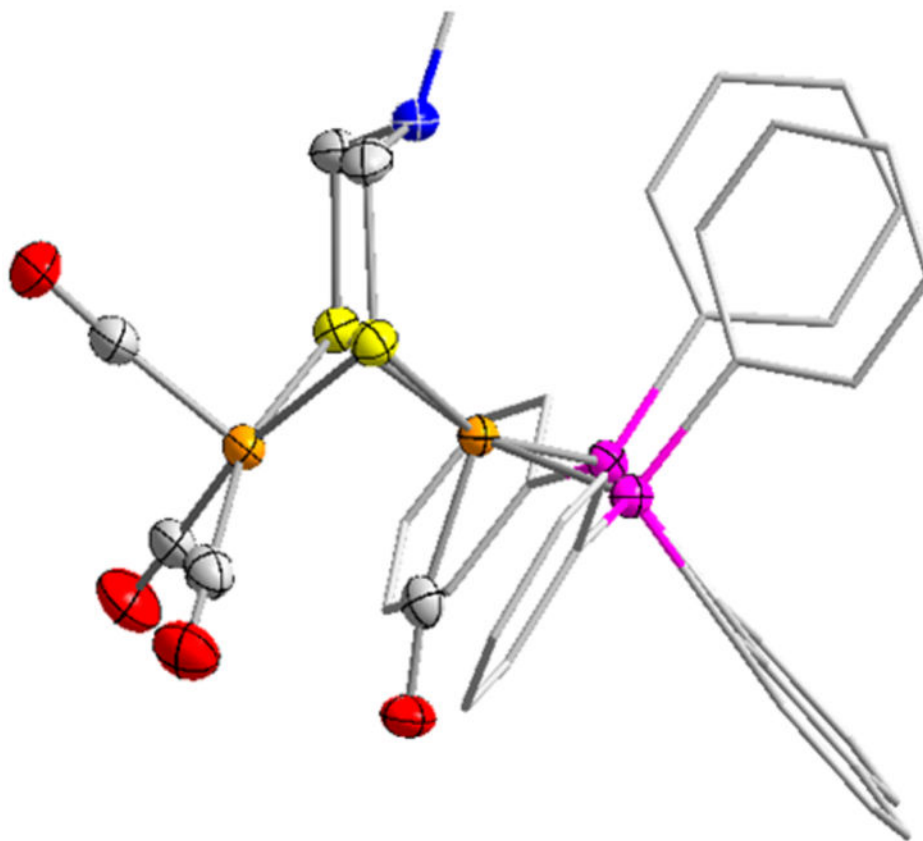


Figure 4. Structure of $[\text{Fe}_2(\text{adt}^{\text{Bn}})(\text{CO})_4(\text{naphthalene-1,8-(PPh}_2)_2)]^+$, a synthetic model for the diiron subunit in the H_{ox} state (Ph on adt omitted).

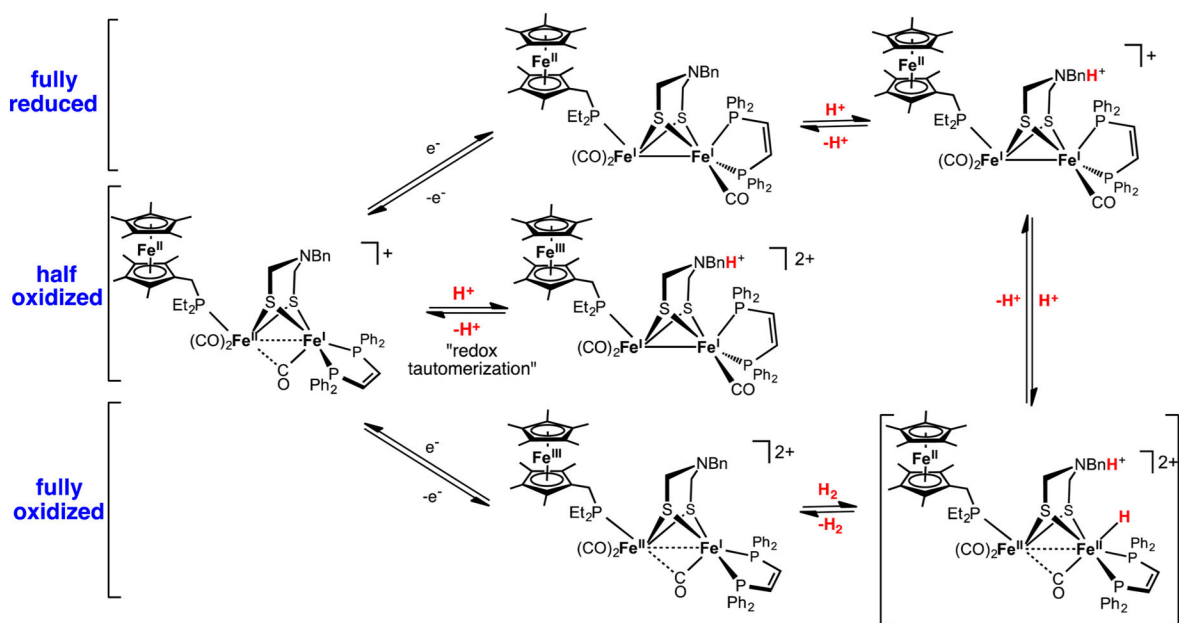
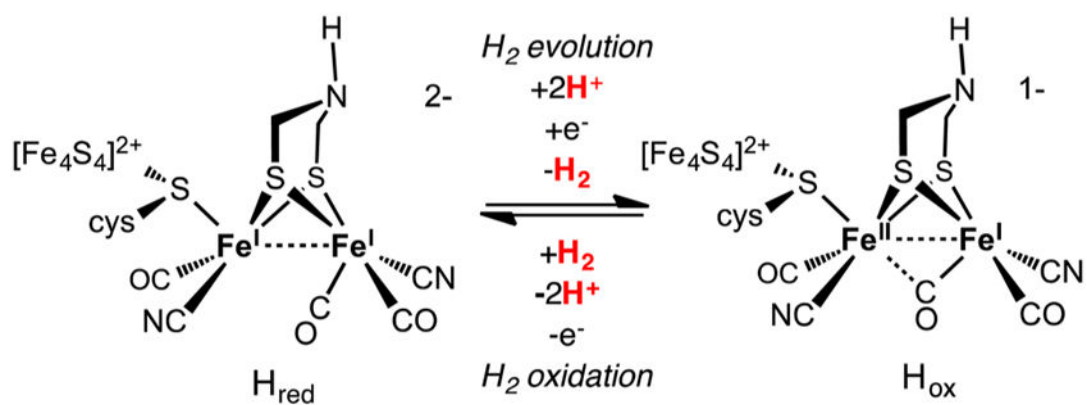
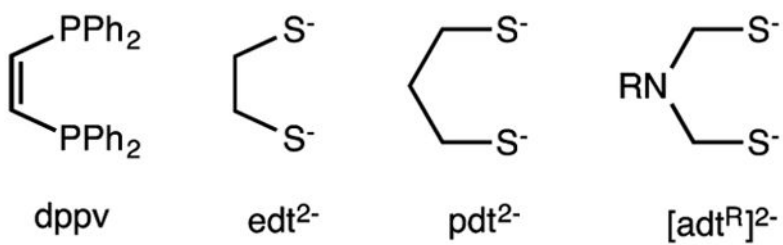


Figure 5. Catalytic cycle for H₂ oxidation and production by models containing the redox complement (FcP*) and proton relay (adt^{Bn}). The central species, a resting state, arises by comproportionation.⁵⁸

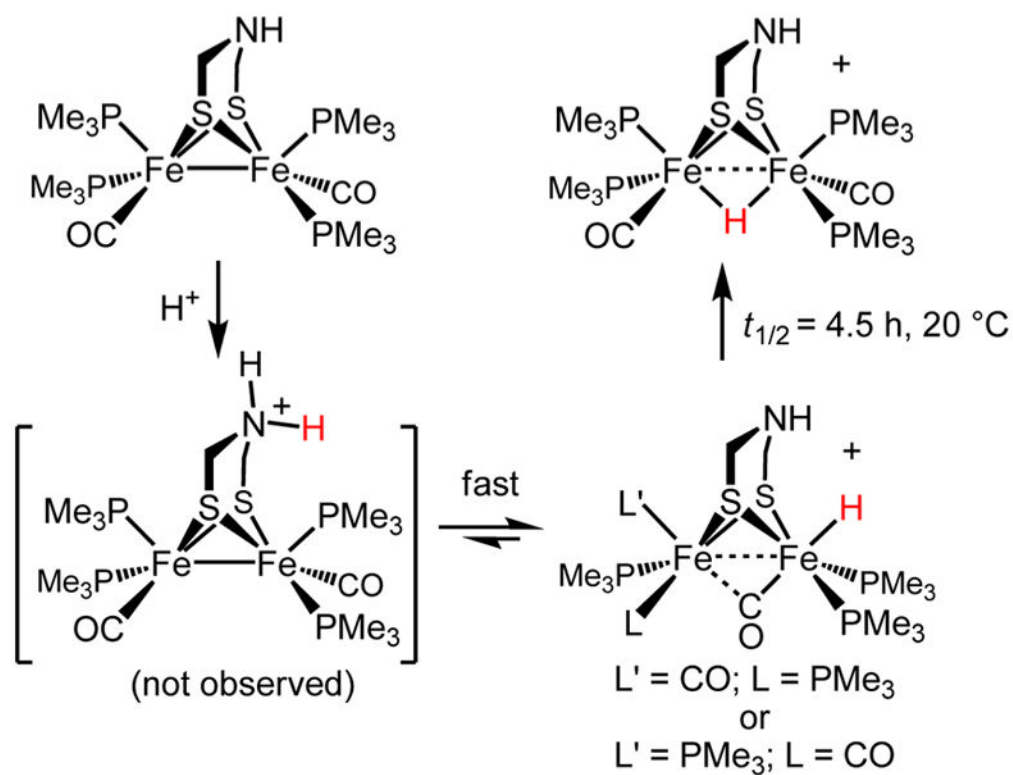


Scheme 1. Active Site of [FeFe]-H₂ase in Two Catalytically Significant States^a

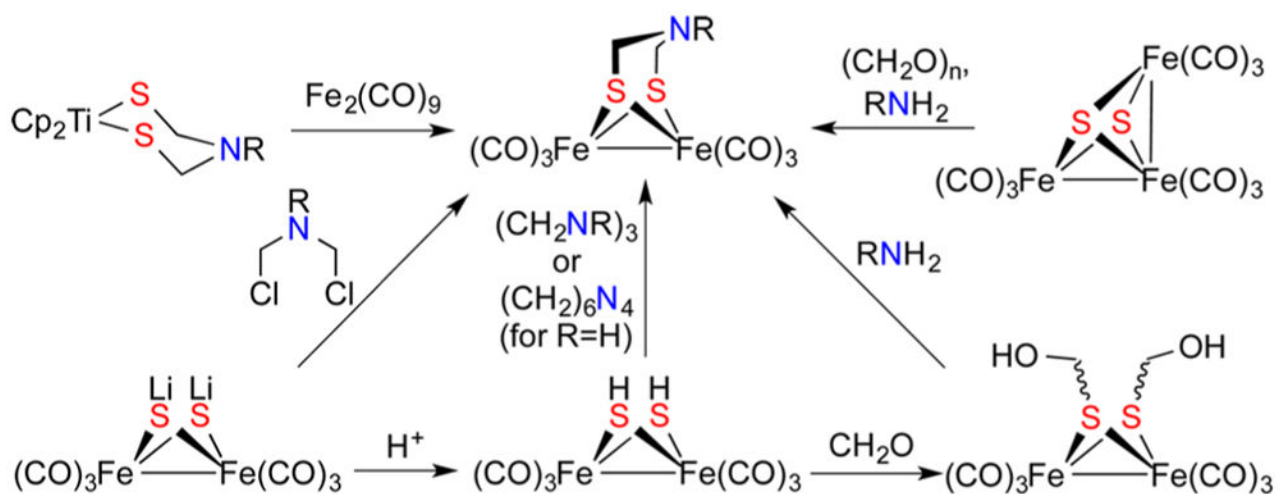
^aThe charges of the complexes ignore the [4Fe-4S] site.

**Scheme 2.**

Abbreviations for Some Ligands Used in Synthetic Models

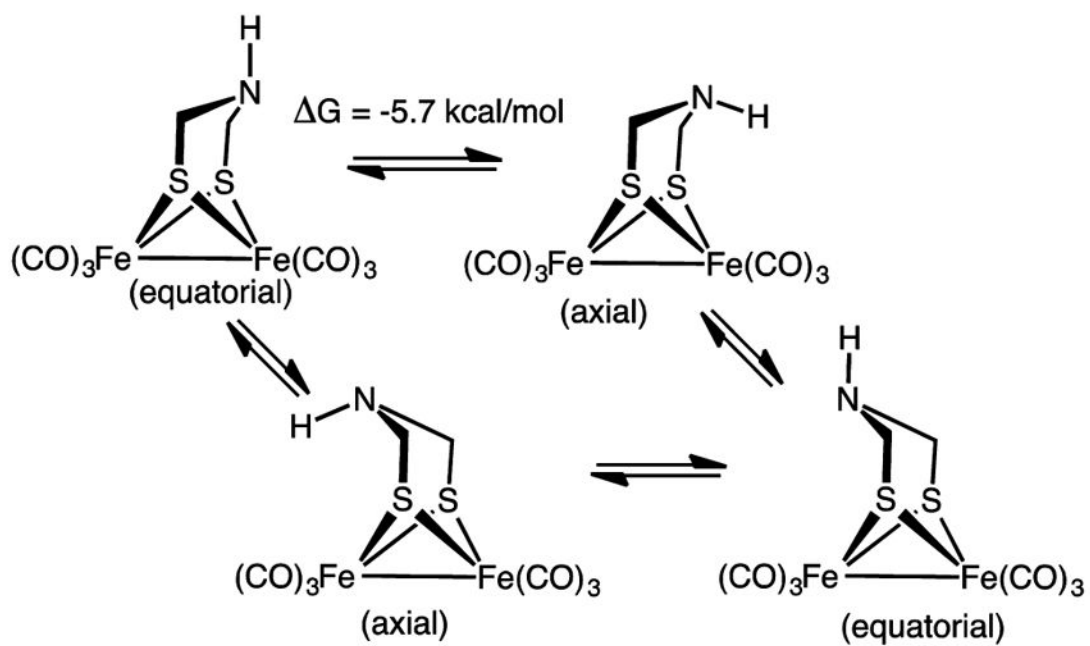
**Scheme 3.**

Protonation of $\text{Fe}_2(\text{adt}^{\text{H}})(\text{CO})_2(\text{PMe}_3)_4$ and Isomerization of the Resulting Hydrido Cations

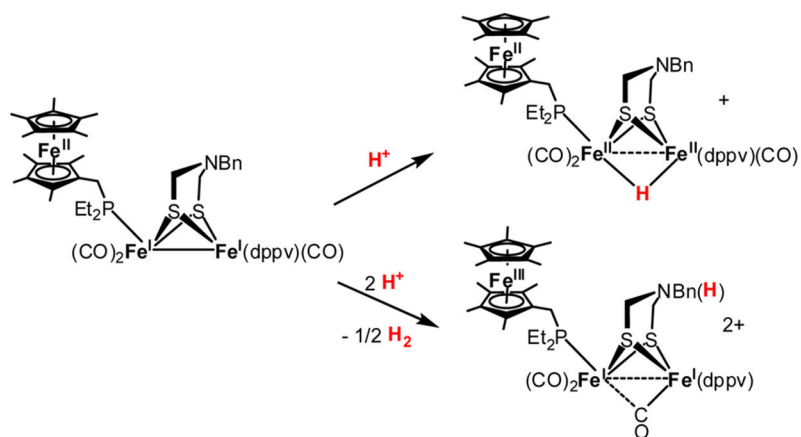
**Scheme 4.**

Routes to Diiron Azadithiolates ($\text{adt}^{\text{R}'\text{s}}$) (Reproduced with permission from ref 31.

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Scheme 5.
Stereodynamics of $\text{Fe}_2(\text{adt}^{\text{H}})(\text{CO})_6$



Scheme 6.
Competition between μ -Hydride Formation and H_2 Evolution in the Protonation of $\text{Fe}_2(\text{adt}^{\text{Bn}})(\text{CO})_3(\text{dppv})(\text{FcP}^*)$ ⁵⁸

Table 1

Effect of Coligands on the Relative Basicities of the Three Basic Sites in adt-Containing Diiron Carbonyls. Terminal hydrides are only detected for the (PR₃)₄ case.

reaction: H ⁺ +	relative basicities of three sites
Fe ₂ (adt ^H)(CO) ₆	N > Fe-Fe > Fe _{term}
Fe ₂ (adt ^H)(CO) ₄ (PR ₃) ₂	Fe-Fe > N > Fe _{term}
Fe ₂ (adt ^H)(CO) ₃ (PR ₃) ₃	Fe-Fe > N > Fe _{term}
Fe ₂ (adt ^H)(CO) ₂ (PR ₃) ₄	Fe-Fe > Fe _{term} ~ N
[Fe ₂ (adt ^H)(CN) ₂ (CO) ₄] ²⁻	Fe-Fe > Fe _{term} ~ N

Table 2Selected Electrocatalytic Properties of Fe₂(adt^H)- and Fe₂(pdt)-Based Models

catalyst	acid	<i>k</i> (s ⁻¹)	overpotential (V) ^a
[(<i>term</i> -H)Fe ₂ (adt ^H)(CO) ₂ (dppv) ₂] ⁺	ClCH ₂ CO ₂ H	5000	0.71
[(<i>term</i> -H)Fe ₂ (Had ^H)(CO) ₂ (dppv) ₂] ²⁺	CF ₃ CO ₂ H	58 000	0.51
[(<i>μ</i> -H)Fe ₂ (adt ^H)(CO) ₂ (dppv) ₂] ⁺	ClCH ₂ CO ₂ H	20	0.90
[(<i>term</i> -H)Fe ₂ (pdt)(CO) ₂ (dppv) ₂] ⁺	HBF ₄ ·Et ₂ O	5	1.32
[(<i>μ</i> -H)Fe ₂ (pdt)(CO) ₂ (dppv) ₂] ⁺	ClCH ₂ CO ₂ H	3	0.95

^a Overpotential = $E^{\circ}\text{HA}/\text{H}_2 - E_{\text{cat}}$, where $E^{\circ}\text{HA}/\text{H}_2$ is the standard reduction potential of the acid.⁴⁸