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Terminal Hydride in [FeFe]-Hydrogenase Model Has Lower Potential for H₂ Production Than the Isomeric Bridging Hydride

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Abstract

Protonation of the symmetrical tetraphosphine complexes Fe₂(S₂C_nH_{2n})(CO)₂(dppv)₂ afforded the corresponding terminal hydrides, establishing that even symmetrical diiron(I) dithiolates undergo protonation at terminal sites. The terminal hydride [HFe₂(S₂C₃H₆)(CO)₂(dppv)₂]⁺ was found to catalyze proton reduction at potentials 200 mV milder than the isomeric bridging hydride, thereby establishing a thermodynamic advantage for catalysis operating via terminal hydride. The azadithiolate protonates to afford, [Fe₂[(SCH₂)₂NH₂](CO)₂(dppv)₂]⁺, [HFe₂[(SCH₂)₂NH](CO)₂-(dppv)₂]⁺, and [HFe₂[(SCH₂)₂NH₂](CO)₂(dppv)₂]²⁺, depending on conditions.

Recent research has significantly advanced our understanding of nature's most efficient catalysts for hydrogen production, the [FeFe]-hydrogenases (Figure 1).¹ First, the mixed-valence H_{ox} state has been replicated with synthetic models providing a coordinatively unsaturated model featuring a vacant coordination site on the distal iron, approximately trans to the Fe–Fe vector.^{2,3} Second, unsymmetrically substituted diiron dithiolatotetracarbonyls have been shown to protonate at a single Fe site to afford *terminal* hydrides that have been characterized by ¹H NMR spectroscopy at low temperatures (~–75 °C).⁴ The protonation at a single Fe center conforms to a mechanism whereby proton reduction, hydrogen oxidation, and CO inhibition all occur via substrate binding at a single site on the distal Fe. In this paper, we describe results that support the single-site hypothesis for hydrogenogenesis by examining factors that influence the stability and reactivity of terminal hydrides.

Our starting complexes are the recently described diiron(I) dithiolates Fe₂(S₂C_nH_{2n})(CO)₂(dppv)₂ [*n* = 2 (**1**), 3 (**2**); dppv = *cis*-1,2-bis(diphenylphosphino)ethene].⁵ With four phosphine ligands, these diiron dithiolato complexes are basic in both Lewis and, as we show, Brønsted senses. The Fe₂ complexes are protonated by HBF₄ · Et₂O at room temperature to afford the expected bridging hydrides [Fe₂(S₂C_nH_{2n})(μ-H)(CO)₂(dppv)₂]⁺, [1μH]⁺ and [2μH]⁺. One isomer of the propanedithiolato derivative, [2μH]BF₄, was characterized crystallographically, which established the location of the μ-hydrido ligand (Supporting Information).

When **1** and **2** were protonated at low temperatures, we observed high-field ¹H NMR signals characteristic of hydrides (for [1H]BF₄, δ –6.1, t, J_{PH} = 74 Hz; for [2H]BF₄, δ –3.5, t, J_{PH} = 78 Hz).^{4,6} These kinetic products were observed to isomerize to the μ-hydrido isomers upon warming. The ethanedithiolate, [1H]⁺, isomerized in minutes even at –20 °C to [1μH]⁺, whereas the propanedithiolate [2H]⁺, derivative proved more stable (t_{1/2} ~ 10 min at 20 °C). The slower isomerization of the propanedithiolate (pdt) derivative is ascribable to the steric

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clash between dppv and the middle methylene group of pdt, which inhibits rotation of the FeH(CO)(dppv) site (eq 1).⁷

The isomerization of the terminal $[2H]^+$ to the bridging $[2\mu]^+$ hydride proceeds via a first-order pathway ($k = 1 \times 10^{-3} \text{ s}^{-1}$, 25°C) and was unaffected by solvent polarity or the presence of CO. These findings are indicative of an intramolecular process, consistent with isomerization kinetics previously reported.⁶ The temperature dependence of the rates indicate $\Delta H^\ddagger = 80 \text{ kJ/mol}$ and $\Delta S^\ddagger = -23 \text{ J/mol K}$, also consistent with an intramolecular process that proceeds without ligand dissociation.

In light of the lability of the tetracarbonyl hydrides recently described by Schollhammer et al.,⁴ our results suggest that the stability of the terminal hydride (vs the bridging hydride) depends mainly on the basicity of the Fe_2 center. The electronic asymmetry of the Fe_2 unit also plays a role because terminal hydrides have been detected for the protonation of unsymmetrical $\text{Fe}_2(\text{S}_2\text{C}_3\text{H}_6)(\text{CO})_4(\text{PR}_3)_2$ isomers but not yet for the corresponding symmetrical isomers.

Methylene chloride solutions of $[2H]^+$ are unreactive toward HOTf, showing no tendency to evolve H_2 , nor did the FeH group exchange with CD_3OD over the course of 3 h. In contrast, the more basic trimethylphosphine derivative $[\text{HFe}_2(\text{S}_2\text{C}_2\text{H}_4)(\mu\text{-CO})(\text{CO})(\text{PMe}_3)_4]^+$ ($\nu_{\text{CO}} = 1940$ and 1874 cm^{-1} in CH_3CN solution) reacts with HBF_4 in CH_3CN to afford H_2 .⁶ On the basis of ν_{CO} , $[2H]\text{BF}_4$ is the better spectroscopic model for the H_{red} state of the enzyme (observed: 1964 (s) and 1905 (m) cm^{-1} vs H_{red} for *D.d.*:⁸ 1965 , 1916 , and 1894 cm^{-1}).

Cyclic voltammetric (CV) studies (CH_2Cl_2 solution, 0°C , vs Ag/AgCl) show that the terminal hydride $[2H]\text{BF}_4$ reduces at $\sim 200 \text{ mV}$ milder than the isomeric bridging hydride $[2\mu H]\text{BF}_4$ (Figure 2). The reduction current ($i_{p,c}$) for $[2H]\text{BF}_4$ in a CH_2Cl_2 solution displayed a first-order dependence on $[\text{HBF}_4]$, indicative of proton reduction catalysis. For catalytic proton reduction involving $[2H]\text{BF}_4$, we propose the catalytic cycle depicted in Figure 3. Reduction of $[2H]\text{BF}_4$ is a $1e^-$ process as indicated by the similarity of the dependence of i_p vs $\nu^{1/2}$ for both $[2H]\text{BF}_4$ and its conjugate base **2**, which we have established undergoes a $1e^-$ oxidation to **2**⁺ (the recently described model of H_{ox}).⁹ At 0°C , the $[2H]^{+/0}$ couple is reversible even at scan rates as slow as 25 mV/s , which implies that the reduced hydride has a half-life of at least several seconds at this temperature. The pathway for hydrogenogenesis therefore entails protonation of the mixed-valence hydride $[2H]^0$. We can estimate the $\text{p}K_a$ of $[2H]^0$ by the strength of the acids that render the $[2H]^{+/0}$ couple irreversible. For these CV titrations, we used phosphonium acids, for which Morris has established a $\text{p}K_a$ scale for CD_2Cl_2 solutions.¹⁰ In the presence of $[\text{HPPH}_2\text{Me}]\text{BF}_4$ ($\text{p}K^{\text{CD}_2\text{Cl}_2} = 3.3$), the $[2H]^{+/0}$ couple was reversible; however, the couple became irreversible with the slightly stronger acid $[\text{HPPH}_3]\text{BF}_4$ ($\text{p}K^{\text{CD}_2\text{Cl}_2} \sim 1.6$). These experiments show that reduction of $[2H]^+$ increases the basicity of the iron hydride by at least five $\text{p}K^{\text{CD}_2\text{Cl}_2}$ units ($[2H]^+$ is unreactive toward HBF_4 , $\text{p}K^{\text{CD}_2\text{Cl}_2} \sim -4.7$). Tilset et al. have reported that redox-state changes can change the acidity of hydrides by more than 20 $\text{p}K_a$ units in monometallic complexes.¹¹

According to our proposed mechanism, the reduced species $[2H]^0$ undergoes protonation to release H_2 , affording **2**⁺. Under the conditions of the experiment, **2**⁺ would be reduced to **2**,

completing the cycle.³ The isomeric bridging hydride $[2\mu\text{H}]^+$ also catalyzes proton reduction catalysis but at potentials more negative by 200 mV.

The azadithiolate $\text{Fe}_2[(\text{SCH}_2)_2\text{NH}](\text{CO})_2(\text{dppv})_2$ (**3**) also undergoes protonation at -40°C to give a terminal hydride $[3\text{H}]^+$ ($\delta -4.2$, t, $J_{\text{PH}} = 73$ Hz). The stereochemistry of the protonation, indicated by the ^1H and ^{31}P NMR data, again places the hydride in an apical site adjacent to the amine and cis to the phosphine ligands. For the related systems, $\text{Fe}_2[(\text{SCH}_2)_2\text{NAr}](\text{CO})_{6-x}(\text{PR}_3)_x$, *N*-protonation occurs rapidly,¹² which suggests that $[3\text{H}]^+$ arises via migration of the proton from N to Fe.

Compound $[3\text{H}]^+$ isomerized to the bridging hydride in seconds at 0°C , faster than $[2\text{H}]^+$ but more slowly than $[1\text{H}]^+$. As for $[2\text{H}]^+$, CD_2Cl_2 solutions of $[3\text{H}]^+$ do not exchange with CD_3OD during the course of the isomerization. Double protonation of **3** with $\text{H}(\text{Et}_2\text{O})_2\text{BAR}^{\text{F}}_4$ (selected because it can be accurately weighed) occurred readily to give the terminal hydride bearing an adjacent ammonium center, $[3\text{H}_2][\text{BAR}^{\text{F}}_4]_2$. This species was characterized by ^1H NMR (high field), ^{31}P NMR, and IR (ν_{CO} region) spectroscopies. The protonated derivatives of **3** can be accessed by selective deprotonation of $[3\text{H}_2]^{2+}$ (Figure 4).

Monoiron hydrides exchange intramolecularly with adjacent ammonium centers,¹³ but the rate depends on the relative basicities of the amine and the FeH centers. In $[3\text{H}_2][\text{BAR}^{\text{F}}_4]_2$, the ammonium center is highly acidic, being deprotonated even by MeOD. The ammonium hydride $[3\text{H}_2]^{2+}$ is stable in a CH_2Cl_2 solution but released H_2 when the protonation was conducted in a MeCN solution. The acid–base properties of **3** are clearly sensitive to the medium¹⁴ and will be explored more fully in a future report. Preliminary CV experiments indicate that $[3\text{H}]^+$ is a better catalyst than $[2\text{H}]^+$, in terms of both kinetics and thermodynamics, but its thermal lability complicates the electrochemical measurements.

In summary, this work supports the following mechanistic features for the production of H_2 by these models for $[\text{FeFe}]$ -hydrogenases:

- i. The protonation of diiron dithiolato complexes can occur at a single Fe site, even for symmetrical $(\text{Fe}^{\text{I}})_2$ compounds.
- ii. The terminal hydride is thermodynamically more easily reduced than the isomeric μ -hydride.
- iii. Isomerization of the terminal hydride is inhibited both by the basicity of the Fe_2 complex as well as by the steric size of the dithiolate in the models. In the enzyme, terminal-bridge isomerization may also be inhibited by hydrogen bonding between $\text{CN}_{\text{distal}}$ and a ϵ -ammonium center of a nearby, highly conserved lysine residue (358 in Cpl and 237 in DdH).¹⁵
- iv. Even though terminal hydrides are more readily protonated than their isomeric bridging hydrides,¹⁶ diferrous terminal hydrides are not necessarily poised for hydrogenogenesis. Their hydridic character is, however, enhanced by several $\text{p}K_{\text{a}}$ units upon 1e^- reduction.

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Figure 1. Structure of the [FeFe]-hydrogenase active site (Fe^p = proximal iron center and Fe^d = distal iron center).

Figure 2. Cyclic voltammetry (200 mV/s, 0 °C) of a 1 mM solution of $[\text{HFe}_2(\text{S}_2\text{C}_3\text{H}_6)(\text{CO})_2(\text{dppv})_2][\text{BF}_4]$ as a mixture of terminal and bridging isomers (a) and the same solution scanned after isomerization (b).

Figure 3.
Proposed mechanism of hydrogenogenesis by $[2H]^+$.

Figure 4.
Protonation of $\text{Fe}_2[(\text{SCH}_2)_2\text{NH}](\text{CO})_2(\text{dppv})_2$.