Inorg. Chem. **2008**, *47*, 2261−2263

Inorganic Chemistry
Communication

Terminal Hydride in [FeFe]-Hydrogenase Model Has Lower Potential for H_2 Production Than the Isomeric Bridging Hydride

Bryan E. Barton and Thomas B. Rauchfuss*

Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801

Received January 8, 2008

Protonation of the symmetrical tetraphosphine complexes $Fe_2(S_2C_nH_{2n})(CO)_2(dppv)_2$ afforded the corresponding terminal hydrides, establishing that even symmetrical diiron(I) dithiolates undergo protonation at terminal sites. The terminal hydride $[HFe_2(S_2C_3H_6)(CO)_2(dppv)_2]^+$ 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, $[Fe_2[(SCH_2)_2NH_2](CO)_2(dppv)_2]^+$, $[HFe_2[(SCH_2)_2NH](CO)_2(dppv)_2]^+$, and $[HFe_2[(SCH_2)_2NH_2](CO)_2(dppv)_2]^{2+}$, 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 ^{1}H 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 $Fe_2(S_2C_nH_{2n})(CO)_2(dppv)_2$ [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 Fe_2 complexes are protonated by $HBF_4 \cdot Et_2O$ at room temperature to afford the expected bridging hydrides $[Fe_2(S_2C_nH_{2n})(\mu\text{-H})(CO)_2(dppv)_2]^+$, $[\mathbf{1}\mu\mathrm{H}]^+$ and $[\mathbf{2}\mu\mathrm{H}]^+$. One isomer of the propanedithiolato derivative, $[\mathbf{2}\mu\mathrm{H}]BF_4$, was characterized crystallographically, which established the location of the μ-hydrido ligand (Supporting Information).

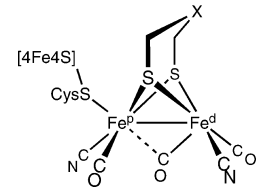


Figure 1. Structure of the [FeFe]-hydrogenase active site (Fe^p = proximal iron center and Fe^d = distal iron center).

When **1** and **2** were protonated at low temperatures, we observed high-field ^{1}H NMR signals characteristic of hydrides (for $[\mathbf{1}\mathrm{H}]BF_4$, δ −6.1, t, J_{PH} = 74 Hz; for $[\mathbf{2}\mathrm{H}]BF_4$, 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, $[\mathbf{1}\mathrm{H}]^+$, isomerized in minutes even at −20 °C to $[\mathbf{1}\mu\mathrm{H}]^+$, whereas the propanedithiolate $[\mathbf{2}\mathrm{H}]^+$, 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 clash between dppv and the middle methylene group of pdt, which inhibits rotation of the FeH(CO)(dppv) site (eq 1).[7]

* To whom correspondence should be addressed. E-mail: rauchfuz@uiuc.edu.

(1) (a) Fontecilla-Camps, J. C.; Volbeda, A.; Cavazza, C.; Nicolet, Y. *Chem. Rev.* **2007**, *107*, 4273–4303. (b) Siegbahn, P. E. M.; Tye, J. W.; Hall, M. B. *Chem. Rev.* **2007**, *107*, 4414–4435. (c) Vignais, P. M.; Billoud, B. *Chem. Rev.* **2007**, *107*, 4206–4272.

(2) Liu, T.; Darensbourg, M. Y. *J. Am. Chem. Soc.* **2007**, *129*, 7008–7009.

(3) Justice, A. K.; Rauchfuss, T. B.; Wilson, S. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 6152–6154.

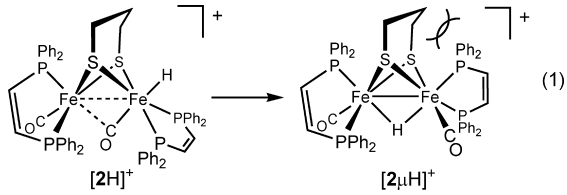
(4) (a) Ezzaher, S.; Capon, J.-F.; Gloaguen, F.; Pétillon, F. Y.; Schollhammer, P.; Talarmin, J.; Pichon, R.; Kervarec, N. *Inorg. Chem.* **2007**, *46*, 3426–3428. (b) Morvan, D.; Capon, J.-F.; Gloaguen, F.; Le Goff, A.; Marchivie, M.; Michaud, F.; Schollhammer, P.; Talarmin, J.; Yaouanc, J.-J. *Organometallics* **2007**, *26*, 2042–2052. (c) Orain, P.-Y.; Capon, J.-F.; Kervarec, N.; Gloaguen, F.; Pétillon, F.; Pichon, R.; Schollhammer, P.; Talarmin, J. *Dalton Trans.* **2007**, 3754–3756.

(5) Justice, A. K.; Zampella, G.; De Gioia, L.; Rauchfuss, T. B. *Chem. Commun.* **2007**, 2019–2021.

(6) van der Vlugt, J. I.; Rauchfuss, T. B.; Whaley, C. M.; Wilson, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 16012–16013.

(7) Justice, A. K.; Zampella, G.; De Gioia, L.; Rauchfuss, T. B.; van der Vlugt, J. I.; Wilson, S. R. *Inorg. Chem.* **2007**, *46*, 1655–1664.

10.1021/ic800030y CCC: $40.75
Published on Web 03/12/2008



(1)

The isomerization of the terminal $[\mathbf{2}H]^+$ to the bridging $[\mathbf{2}\mu]^+$ hydride proceeds via a first-order pathway ($k = 1 \times 10^{-3}$ 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 $\Delta H^{\ddagger} = 80$ kJ/mol and $\Delta S^{\ddagger} = -23$ 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 $Fe_2(S_2C_3H_6)(CO)_4(PR_3)_2$ isomers but not yet for the corresponding symmetrical isomers.

Methylene chloride solutions of $[\mathbf{2}H]^+$ 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 $[HFe_2(S_2C_2H_4)(\mu\text{-CO})(CO)(PMe_3)_4]^+$ ($\nu_{CO} = 1940$ 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}, $[\mathbf{2}H]BF_4$ 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 $[\mathbf{2}H]BF_4$ reduces at ~200 mV milder than the isomeric bridging hydride $[\mathbf{2}\mu H]BF_4$ (Figure 2). The reduction current ($i_{p,c}$) for $[\mathbf{2}H]BF_4$ in a CH_2Cl_2 solution displayed a first-order dependence on $[HBF_4]$, indicative of proton reduction catalysis. For catalytic proton reduction involving $[2H]BF_4$, we propose the catalytic cycle depicted in Figure 3. Reduction of $[\mathbf{2}H]BF_4$ is a 1e$^-$ process as indicated by the similarity of the dependence of i_p vs $v^{1/2}$ for both $[\mathbf{2}H]BF_4$ and its conjugate base **2**, which we have established undergoes a 1e$^-$ oxidation to $\mathbf{2}^+$ (the recently described model of H_{ox}).[9] At 0 °C, the $[\mathbf{2}H]^{+/0}$ 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 $[\mathbf{2}H]^0$. We can estimate the pK_a of $[\mathbf{2}H]^0$ by the strength of the acids that render the $[\mathbf{2}H]^{+/0}$ couple irreversible. For these CV titrations, we used phosphonium acids, for which Morris has established a pK_a scale for

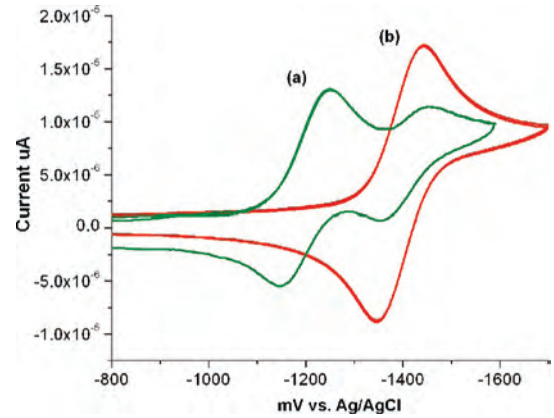


Figure 2. Cyclic voltammetry (200 mV/s, 0 °C) of a 1 mM solution of $[HFe_2(S_2C_3H_6)(CO)_2(dppv)_2][BF_4]$ as a mixture of terminal and bridging isomers (a) and the same solution scanned after isomerization (b).

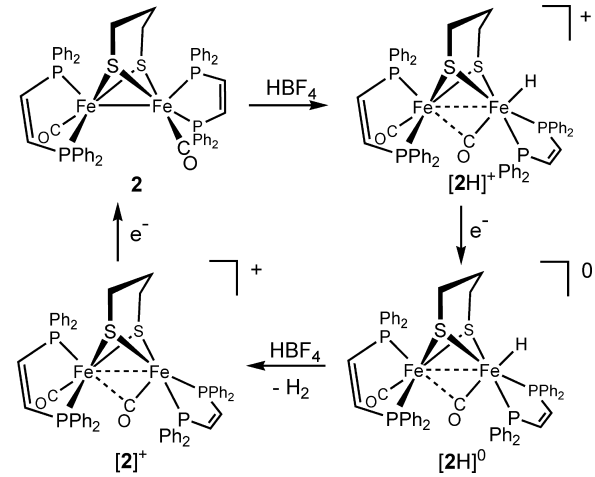


Figure 3. Proposed mechanism of hydrogenogenesis by $[\mathbf{2}H]^+$.

CD_2Cl_2 solutions.[10] In the presence of $[HPPh_2Me]BF_4$ ($pK^{CD_2Cl_2} = 3.3$), the $[\mathbf{2}H]^{+/0}$ couple was reversible; however, the couple became irreversible with the slightly stronger acid $[HPPh_3]BF_4$ ($pK^{CD_2Cl_2} \sim 1.6$). These experiments show that reduction of $[\mathbf{2}H]^+$ increases the basicity of the iron hydride by at least five p$K^{CD_2Cl_2}$ units ($[\mathbf{2}H]^+$ is unreactive toward HBF_4, p$K^{CD_2Cl_2} \sim -4.7$). Tilset et al. have reported that redox-state changes can change the acidity of hydrides by more than 20 pK_a units in monometallic complexes.[11]

According to our proposed mechanism, the reduced species $[\mathbf{2}H]^0$ undergoes protonation to release H_2, affording $\mathbf{2}^+$. Under the conditions of the experiment, $\mathbf{2}^+$ would be reduced to **2**, completing the cycle.[3] The isomeric bridging hydride $[\mathbf{2}\mu H]^+$ also catalyzes proton reduction catalysis but *at potentials more negative by 200 mV*.

The azadithiolate $Fe_2[(SCH_2)_2NH](CO)_2(dppv)_2$ (**3**) also undergoes protonation at −40 °C to give a terminal hydride $[\mathbf{3}H]^+$ (δ −4.2, t, $J_{PH} = 73$ Hz). The stereochemistry of the protonation, indicated by the ^{1}H and ^{31}P NMR data, again places the hydride in an apical site adjacent to the amine

(8) De Lacey, A. L.; Fernández, V. M.; Rousset, M.; Cammack, R. *Chem. Rev.* **2007**, *107*, 4304–4330.
(9) Justice, A. K.; Nilges, M.; Rauchfuss, T. B.; Wilson, S. R.; De Gioia, L.; Zampella, G. *J. Am. Chem. Soc.* **2008**, *130*, in press.
(10) Li, T.; Lough, A. J.; Morris, R. H. *Chem.—Eur. J.* **2007**, *13*, 3796–3803.
(11) Ryan, O. B.; Tilset, M.; Parker, V. D. *J. Am. Chem. Soc.* **1990**, *112*, 2618–2626.

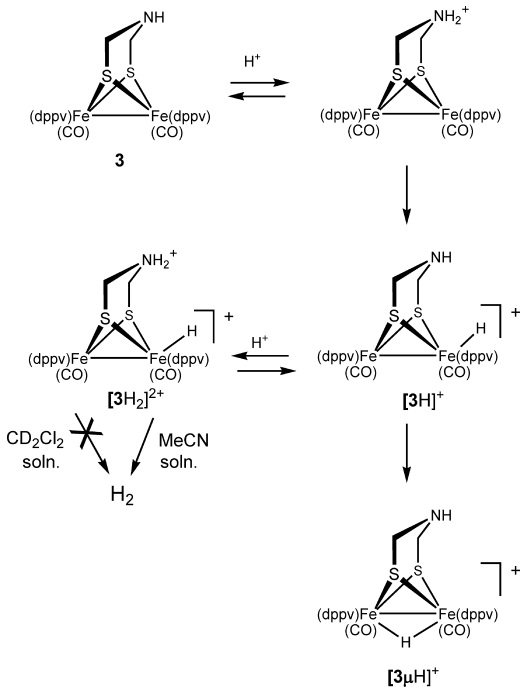


Figure 4. Protonation of $Fe_2[(SCH_2)_2NH](CO)_2(dppv)_2$.

and cis to the phosphine ligands. For the related systems, $Fe_2[(SCH_2)_2NAr](CO)_{6-x}(PR_3)_x$, *N*-protonation occurs rapidly,[12] which suggests that $[\mathbf{3}H]^+$ arises via migration of the proton from N to Fe.

Compound $[\mathbf{3}H]^+$ isomerized to the bridging hydride in seconds at 0 °C, faster than $[\mathbf{2}H]^+$ but more slowly than $[\mathbf{1}H]^+$. As for $[\mathbf{2}H]^+$, CD_2Cl_2 solutions of $[\mathbf{3}H]^+$ do not exchange with CD_3OD during the course of the isomerization. *Double* protonation of **3** with $H(Et_2O)_2BAr^F{}_4$ (selected because it can be accurately weighed) occurred readily to give the terminal hydride bearing an adjacent ammonium center, $[\mathbf{3}H_2][BAr^F{}_4]_2$. 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 $[\mathbf{3}H_2]^{2+}$ (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 $[\mathbf{3}H_2][BAr^F{}_4]_2$, the ammonium center is highly acidic, being deprotonated even by MeOD. The ammonium hydride $[\mathbf{3}H_2]^{2+}$ 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 medium[14] and will be explored more fully in a future report. Preliminary CV experiments indicate that $[\mathbf{3}H]^+$ is a better catalyst than $[\mathbf{2}H]^+$, 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 [FeFe]-hydrogenases:

(i) The protonation of diiron dithiolato complexes can occur at a single Fe site, even for symmetrical $(Fe^I)_2$ 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 CN_{distal} and a ϵ-ammonium center of a nearby, highly conserved lysine residue (358 in CpI 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 pK_a units upon $1e^-$ reduction.

Acknowledgment. This research was supported by the National Institutes of Health and the Petroleum Research Fund.

Supporting Information Available: Experimental methods, spectra, and voltammograms and CIF for the crystal structure. This material is available free of charge via the Internet at http://pubs.acs.org.

IC800030Y

(12) (a) Eilers, G.; Schwartz, L.; Stein, M.; Zampella, G.; De Gioia, L.; Ott, S.; Lomoth, R. *Chem.—Eur. J.* **2007**, *13*, 7075–7084. (b) Wang, F.; Wang, M.; Liu, X.; Jin, K.; Dong, W.; Li, G.; Åkermark, B.; Sun, L. *Chem. Commun.* **2005**, 3221–3223. (c) Stanley, J. L.; Heiden, Z. M.; Rauchfuss, T. B.; Wilson, S. R.; De Gioia, L.; Zampella, G. *Organometallics* **2007**, *27*, 119–125.

(13) Jacobsen, G. M.; Shoemaker, R. K.; Rakowski DuBois, M.; DuBois, D. L. *Organometallics* **2007**, *26*, 4964–4971.

(14) Curtis, C. J.; Miedaner, A.; Ciancanelli, R.; Ellis, W. W.; Noll, B. C.; Rakowski DuBois, M.; DuBois, D. L. *Inorg. Chem.* **2003**, *42*, 216–227.

(15) Nicolet, Y.; Lemon, B. J.; Fontecilla-Camps, J. C.; Peters, J. W. *Trends Biochem. Sci.* **2000**, *25*, 138–143.

(16) Justice, A. K.; Linck, R. C.; Rauchfuss, T. B.; Wilson, S. R. *J. Am. Chem. Soc.* **2004**, *126*, 13214–13215.