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Mild Redox Complementation Enables H₂ Activation by [FeFe]-Hydrogenase Models

James M. Camara and Thomas B. Rauchfuss*

School of Chemical Sciences, University of Illinois, Urbana, IL 61801

Abstract

Mild oxidants such as [Fe(C₅Me₅)₂]⁺ accelerate the activation of H₂ by [Fe₂[(SCH₂)₂NBn](CO)₃(dppv)(PMe₃)]⁺ ([1]⁺). The reaction is first order in [1]⁺ and [H₂] but is independent of the E_{1/2} and concentration of the oxidant. The analogous reaction occurs with D₂ and proceeds with an inverse isotope effect of 0.75(8). The activation of H₂ is further enhanced with the tetracarbonyl [Fe₂[(SCH₂)₂NBn](CO)₄(dppn)]⁺ ([2]⁺), the first crystallographically characterized H_{ox} model containing an amine cofactor. These studies point to rate-determining binding of H₂ followed by proton-coupled electron-transfer (PCET). In comparison with [1]⁺, the rate of H₂ activation by [2]⁺/Fc⁺ is enhanced by 10⁴ (25 °C).

The hydrogenases (H₂ases) are attractive targets for synthetic modeling because they catalyze the redox of H₂/H⁺, an important and topical reaction.¹ The [FeFe]- (and [NiFe]-) hydrogenases operate by the combined action of acid-base and electron-transfer. As has been previously shown by both biophysical studies² and synthetic modeling,³ the catalytic properties of the active site of the [FeFe] enzyme are enabled by the juxtaposition of functional groups dedicated to substrate binding, specifically the azadithiolate cofactor and the distal Fe center. This active site also features two redox-active components, the Fe₂(SR)₂ and the Fe₄S₄ subsites, each of which provides 1e⁻ required for the two-electron H₂/2H⁺ couple. In recent years, the advantageous cooperative reactivity of the amine cofactor and one Fe center has been demonstrated in models,⁴ which enables highly active proton-reduction catalysts. *Unsolved* in previous models is the ability of the same enzyme to activate H₂, an excellent substrate for the enzyme.^{2b,2c}

The activation of H₂ by diiron models requires that the Fe₂ center be (i) sufficiently electrophilic to attract H₂ but (ii) not so electrophilic to induce binding of the amine to Fe.⁵ For a variety of ligands, the mixed-valence complexes of the type [Fe₂[(SCH₂)₂NR](CO)_{3-x}(PR₃)_x]⁺ almost satisfy these criteria, but such models are very slow to activate H₂, requiring high pressures and many hours. In this report we show that rapid H₂ activation by these H_{ox} models can be achieved by the addition of a mild and fast oxidant.

Previously, we showed that the H_{ox} model [Fe₂[(SCH₂)₂NBn](CO)₃(dppv)(PMe₃)]⁺ ([1]⁺, dppv = *cis*-C₂H₂(PPh₂)₂, Figure 1) reacts with H₂ only slowly (>26 h, 25 °C, 1800 psi H₂).⁶ We have now discovered that the same complex in the presence of 1 equiv of the mild oxidant [Fe(C₅Me₅)₂]BAr^F₄ (Ar^F = 3,5-C₆H₃(CF₃)₂) reacts with 2 atm of H₂ quantitatively at 25 °C in hours to give the diferrous hydride product. The nearly isosteric complex that lacks the amine cofactor, [Fe₂(S₂C₃H₆)(CO)₃(dppv)(PMe₃)]⁺,⁵ is *unreactive* toward H₂ under the same conditions.

Corresponding Author: rauchfuz@illinois.edu.

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To simplify the analysis of the reaction by proton was trapped as $[\text{HP}(o\text{-tol})_3]^+$. Heterolytic cleavage in the presence of $\text{P}(o\text{-tol})_3$ produced known hydride $[\text{1H}]^+$ and $[\text{HP}(o\text{-tol})_3]^+$, which undergoes slow proton transfer on the NMR timescale and displays distinctive ^1H and ^{31}P NMR signals. ^2H NMR analysis of the same reaction in CH_2Cl_2 solution using D_2 showed equal deuterium incorporation into $[\text{1D}]^+$ and coproduct $[\text{DP}(o\text{-tol})_3]^+$ (Supplementary Information). H_2 activation is proposed to initially produce the diferrous ammonium hydride complex $[\text{1HH}]^{2+}$. Subsequent deprotonation and rearrangement of the incipient terminal hydride complex leads to the final product that contains a bridging hydride, $[\text{1H}]^+$ (Scheme 1).

To investigate the role of the oxidant, we carried out reactions with various ferrocenium-derivatives,⁷ $[\text{Me}_n\text{Fc}]\text{BAr}^{\text{F}}_4$ ($[\text{Me}_n\text{Fc}]^+ = [\text{Fe}(\text{C}_5\text{Me}_5)_2]^+$, $[\text{Fe}(\text{C}_5\text{Me}_4\text{H})_2]^+$, $[\text{Fe}(\text{C}_5\text{Me}_5)(\text{C}_5\text{H}_5)]^+$, Table 1. Monitoring product formation by ^1H NMR spectroscopy, we found that the rate of reaction was independent of oxidant strength (for the $\text{BAr}^{\text{F}}_4^-$ salts: -593 to -313 mV vs $\text{Fc}/\text{FcBAr}^{\text{F}}_4$)⁸. Furthermore the rate is unaffected by the concentration of the oxidant. These findings imply that electron transfer does not occur in or before the rate-determining step.

Having observed that oxidant did not affect the rate of H_2 oxidation, we probed the effect of hydrogen pressure. When one equiv of oxidant was used, the appearance of product $[\text{1H}]^+$ was strictly first order. Under these conditions, H_2 dissolves quickly and was present in large excess. As a result, $[\text{H}_2]$ remains constant over the course of each experiment. A plot of k_{obs} vs $[\text{H}_2]$ was linear, verifying a first order dependence on $[\text{H}_2]$. These observations imply a rate law that only includes terms in $[\text{H}_2]$ and $[\text{Fe}_2]$.

$$d[\text{1H}^+]/dt = k_{\text{obs}}[\text{H}_2][\text{1}^+] \quad (1)$$

The experimental rate law in eq 1 is consistent with two kinetic situations (Scheme 2). The first involves rate-determining binding of H_2 followed by rapid oxidation and/or heterolysis. In the second mechanism, fast H_2 binding is followed by rate-determining heterolysis to form the mixed-valence hydride, which is rapidly oxidized in a subsequent step. The acidity of transition metal dihydrogen complexes is well established.⁹ The favorability of H_2 cleavage is expected to depend on the hydride-acceptor ability of the Fe_2^+ fragment. Also, numerous precedents show that the electrophilicity of metal centers correlates with their affinity for H_2 .^{9d} Thus, more electrophilic diiron models should result in a faster reaction. An obvious choice of an electrophilic diiron center would be $[\text{Fe}_2(\text{SCH}_2)_2\text{NBn}(\text{CO})_4(\text{dppv})]^+$, a tetracarbonyl relative of $[\text{1}]^+$.¹⁰ This mixed-valence compound was found to be unstable, probably owing to disproportionation caused by amine binding.⁵ We discovered however that a more rigid bulky diphosphine allowed isolation of the sought-for electrophilic, amine-containing H_{ox} model. Specifically $[\text{Fe}_2((\text{SCH}_2)_2\text{NBn})(\text{CO})_4(\text{dppn})]^+$ ($[\text{2}]^+$) (dppn = 1,8-bis(diphenylphosphino)naphthalene) was accessed in two steps from $\text{Fe}_2((\text{SCH}_2)_2\text{NBn})(\text{CO})_6$. According to cyclic voltammetric measurements on CH_2Cl_2 solutions (Figure S4), the $[\text{2}]^{+/0}$ couple occurs at -254 mV, 390 mV more positive than the $[\text{1}]^{+/0}$ couple.

Treatment of a CH_2Cl_2 solution of **2** with 1 equiv of $[\text{Fc}]\text{BAr}^{\text{F}}_4$ gave the mixed-valence salt $[\text{2}]\text{BAr}^{\text{F}}_4$, solutions of which remained unchanged for up to 24 h at room temperature. The stability of this mixed-valence amine allowed us to obtain single crystals. Crystallographic analysis shows that the amine (proton acceptor) is poised over the electrophilic Fe center (hydride acceptor) only 3.2 Å away. The high stability of this organometallic frustrated Lewis pair¹¹ is attributed to the steric shielding provided by a pair of phenyl rings that project axially from the dppn ligand (Figure 2). IR spectra in the ν_{CO} region show that $[\text{2}]^+$

is far more electrophilic than is $[1]^{+}:\nu_{\text{CO}} = 1896, 2022, 2078$ vs $1870, 1965, 2017$ cm^{-1} respectively (Figure 3).

The EPR spectrum of $[2]\text{BAr}^{\text{F}}_4$ features an axial pattern and exhibits triplets indicative of large hyperfine coupling to ^{31}P . This suggests the assignment of $[2]^{+}$ as formally $[(\text{dppn})(\text{CO})\text{Fe}^{\text{I}}(\mu\text{-SR})_2\text{Fe}^{\text{II}}(\text{CO})_3]^{+}$. The spectrum is similar to that reported for related cations such as $[\text{Fe}_2(\text{S}_2\text{C}_3\text{H}_6)(\text{CO})_4(\text{dppv})]^{+}$. It is likely that, as previously reported for $[1]^{+}$, the electrophilic site is the iron center formally assigned as $\text{Fe}(\text{I})$.¹²

Gratifyingly, in the presence of one equiv of $[\text{Fc}]\text{BAr}^{\text{F}}_4$, $[2]^{+}$ was found to rapidly react with 1 atm H_2 ($t_{1/2} < 13$ min at 20 °C). Monitoring the reaction by IR and ^1H NMR spectroscopies confirmed the formation of the same ammonium hydride produced by treatment of **2** with 2 equiv of $[\text{H}(\text{OEt}_2)_2]\text{BAr}^{\text{F}}_4$. Rate measurements showed H_2 activation by $[2]^{+}/[\text{Fc}]^{+}$ to be $10\times$ faster than by $[1]^{+}/[\text{Fc}]^{+}$ and $10^4\times$ faster than $[1]^{+}$ in the absence of a supplemental oxidant.

We measured the rates of reaction of a 1:1 mixture of $[2]\text{BAr}^{\text{F}}_4$ and $[\text{Fc}]\text{BAr}^{\text{F}}_4$ with H_2 and D_2 using UV-vis spectroscopy at 20 °C. The kinetic isotope effect was found to be $k_{\text{H}}/k_{\text{D}} = 0.71(5)$. Reactions in which H_2 cleavage is known to be rate determining typically exhibit *normal* kinetic isotope effect (eg $k_{\text{H}}/k_{\text{D}} \sim 2.0$).^{9d} Although few reports describe kinetic isotope effects for H_2 binding,¹³ an inverse kinetic isotope effect has been observed for H_2 binding to $\text{Ir}(\text{H})_2\text{Cl}(\text{PBU}^t_2\text{Me})_2$.¹⁴ The inverse isotope effect measured for our reaction is inconsistent with rate-determining heterolytic cleavage of H_2 .

An enigmatic aspect of the present results is the observation that $[1]^{+}$ and $[2]^{+}$ do not serve as oxidants for the oxidation of H_2 by a second equiv of the same cations. This finding may be explicable if the activation of H_2 occurs via a *concerted* proton-coupled electron transfer (PCET), whereby intramolecular heterolysis of the H_2 ligand depends on the rate of the electron-transfer.¹⁵ Proton-transfer associated with the intramolecular heterolysis of the H_2 adducts is expected to be extremely rapid,¹⁶ requiring a rapid oxidant. The rate of self-exchange for $\text{Fc}^{+/0}$ is indeed fast ($5 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$),¹⁷ but we propose that self-exchange for $[1]^{+/0}$ and $[2]^{+/0}$ are probably far slower owing to the substantial structural changes that accompany this redox process.¹⁸ Further work is required on these self-exchange rates.

We have shown H_2 activation by the organometallic radical $[\text{Fe}_2[(\text{SCH}_2)_2\text{NR}](\text{CO})_x\text{L}_{6-x}]^{+}$ requires the addition of an oxidant. It is intriguing that for heterolysis the oxidant must be both mild and fast. Kinetic measurements show that H_2 binding is rate-determining. The present results point to the important role of PCET for the heterolytic activation of dihydrogen in this class of enzyme mimics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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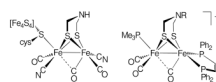


Figure 1. Active site of the H_{0x} state of [FeFe]-hydrogenase (left) and the model [1]⁺ (right, R = CH₂Ph).

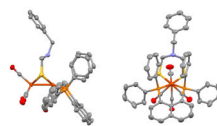


Figure 2.
Structure of the cation in $[\text{Fe}_2(\text{SCH}_2)_2\text{NBn}](\text{CO})_4(\text{dppn})]\text{BARF}_4$. Selected bond lengths:
(Fe-N) = 3.234(3), (Fe-Fe) = 2.568(1), (Fe-P) = 2.231(1) Å.

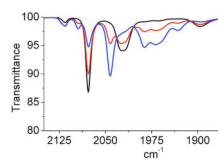


Figure 3. IR spectra of a CH₂Cl₂ solution of [2]BAr^F₄ and [Fc]BAr^F₄ before (black) and 5 (red) and 14 min. (blue) after introducing H (1 atm).

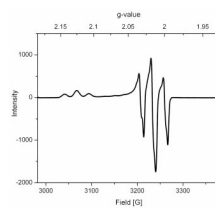
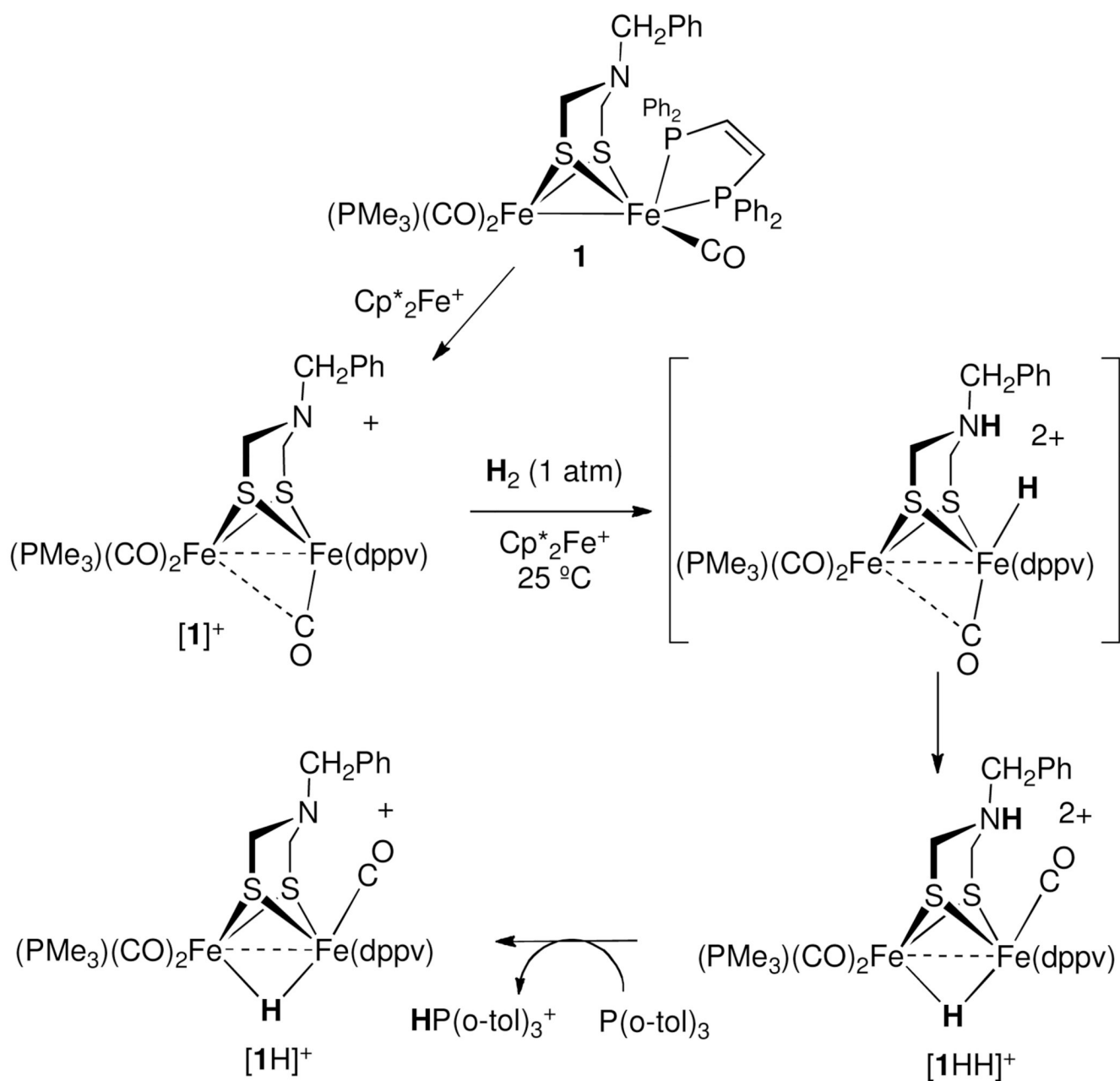
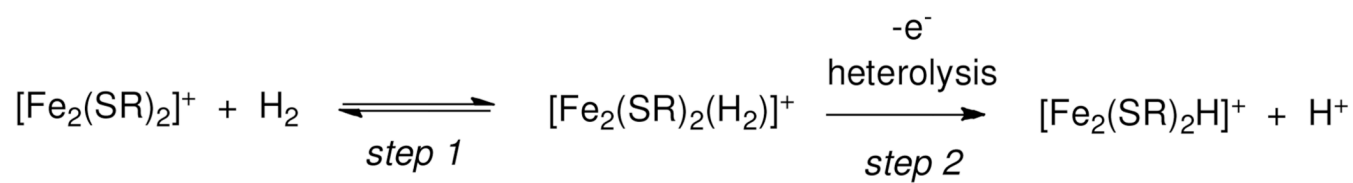


Figure 4.
X-Band EPR spectrum of [2]BARF₄ (110 K, 1:1 CH₂Cl₂:toluene frozen solution).
Parameters: $g_z = 2.1260$ with $A_z(^{31}\text{P}) = 78$ MHz, $g_x \approx g_y = 2.0165$ with $A_x(^{31}\text{P}) \approx A_y(^{31}\text{P}) = 79$ MHz.



Scheme 1.
Activation of H_2 by $[1]^+$ and Cp^*_2Fe^+ to form $[1\text{H}]^+$.

**Scheme 2.**

The rate law for oxidation of H₂ by [1]⁺ and ferrocenium is consistent with the rate determining step being H₂ addition (step 1) or redox/heterolysis of the H₂ complex (step 2).

Table 1

Observed Pseudo First-Order Rate Constants for the Conversion of **1** to **[1]⁺** with Various Ferrocenium Oxidants. *Conditions:* 2 atm H₂, 0 °C, CD₂Cl₂ solution, **[1]₀** = **[P(o-tol)₃]** = 4.67 mM.

Oxidant	equiv Me _n Fc ⁺	$E(\text{Me}_n\text{Fc}^{+/0})$ vs $E(\text{Fc}^{+/0})$	k_{obs} (s ⁻¹)× 10 ⁵	Conversion
[Me ₁₀ Fc] ⁺	2	-593 mV	2.2(3)	100%
[Me ₁₀ Fc] ⁺	2*	-593 mV	2.2(4)	100%
[Me ₁₀ Fc] ⁺	4	-593 mV	2.7(3)	100%
[Me ₈ Fc] ⁺	2	-512 mV	4.2(6)	>75%
[Me ₈ Fc] ⁺	4	-512 mV	4.2(5)	>75%
[Me ₅ Fc] ⁺	2	-313 mV	3.3(8)	>50%

* P(o-tol)₃ omitted from reaction.