JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Mild Redox Complementation Enables H_2 Activation by [FeFe]-Hydrogenase Models

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Supporting Information

ABSTRACT: Mild oxidants such as $[Fe(C_5Me_5)_2]^+$ accelerate the activation of H_2 by $[Fe_2[(SCH_2)_2NBn](CO)_3(dppv)(PMe_3)]^+$ ($[\mathbf{1}]^+$), despite the fact that the ferrocenium cation is incapable of oxidizing $[\mathbf{1}]^+$. The reaction is first-order in $[\mathbf{1}]^+$ and $[H_2]$ but independent of the $E_{1/2}$ and concentration of the oxidant. The analogous reaction occurs with D_2 and proceeds with an inverse kinetic isotope effect of 0.75(8). The activation of H_2 is further enhanced with the tetracarbonyl $[Fe_2[(SCH_2)_2NBn](CO)_4(dppn)]^+$ ($[\mathbf{2}]^+$), the first crystallographically characterized model for the H_{ox} state of the active site containing an amine cofactor. These studies point to rate-determining binding of H_2 followed by proton-coupled electron transfer. Relative to that by $[\mathbf{1}]^+$, the rate of H_2 activation by $[\mathbf{2}]^+/Fc^+$ is enhanced by a factor of 10^4 at 25 °C.

Hydrogenases (H_2ases) are attractive targets for synthetic modeling because they catalyze the redox of H_2/H^+, an important and topical reaction.[1] The [FeFe]- (and [NiFe]-) hydrogenases operate by the combined action of acid−base and electron-transfer processes. As has been previously shown by both biophysical studies[2] and synthetic modeling,[3] the catalytic properties of the active site in 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 $Fe_2(SR)_2$ and Fe_4S_4 subsites, each of which provides one of the two electrons required for the $H_2/2H^+$ couple. In recent years, the advantageous cooperative reactivity of the amine cofactor and one Fe center has been demonstrated in models,[4] and this reactivity enables the enzyme to serve as a highly active proton-reduction catalyst. *Unsolved* in previous models is the ability of the same enzyme to activate H_2, which is an excellent substrate for the enzyme.[2b,c]

The activation of H_2 by diiron models requires that the Fe_2 center be (i) sufficiently electrophilic to bind H_2 but (ii) not electrophilic enough to induce binding of the amine to Fe.[5] For a variety of ligands, mixed-valence complexes of the type $[Fe_2[(SCH_2)_2NR](CO)_{6-x}(PR_3)_x]^+$ almost satisfy these criteria, but such models are very slow to activate H_2, requiring high pressures and many hours. In this report, we show that rapid H_2 activation by these models can be achieved by the addition of a mild and fast oxidant.

We previously showed that $[Fe_2[(SCH_2)_2NBn](CO)_3(dppv)(PMe_3)]^+$ ($[\mathbf{1}]^+$; dppv = *cis*-$C_2H_2(PPh_2)_2$; Figure 1) reacts with H_2 only slowly (>26 h, 25 °C, 1800 psi H_2).[6] We have now discovered that the same complex in the presence of 1 equiv of the mild oxidant $[Fe(C_5Me_5)_2]BAr^F{}_4$ [Ar^F = 3,5-$C_6H_3(CF_3)_2$] reacts with 2 atm H_2 quantitatively at 25 °C in hours to give the diferrous hydride product. The nearly isosteric complex that lacks the amine cofactor, $[Fe_2(S_2C_3H_6)(CO)_3(dppv)(PMe_3)]^+$,[5] is *un*reactive toward H_2 under the same conditions.

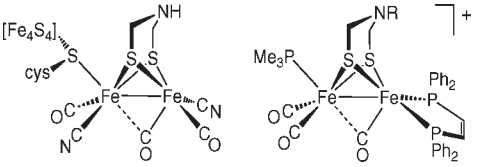


Figure 1. Active site of (left) the H_{ox} state of [FeFe]-hydrogenase and (right) model $[\mathbf{1}]^+$ (R = CH_2Ph).

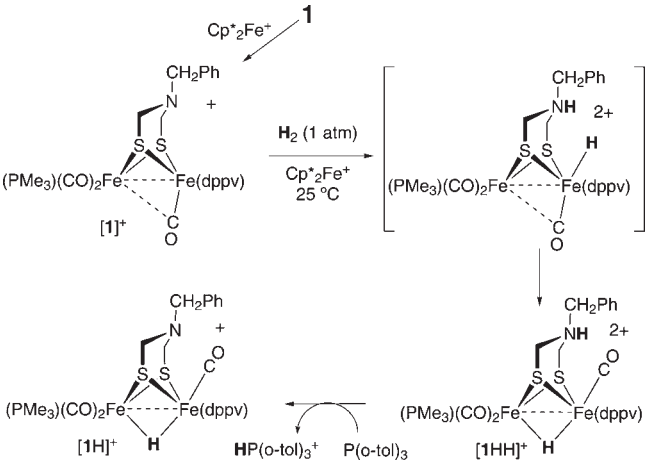
To simplify the analysis of the heterolytic activation of dihydrogen, the proton was trapped as $[HP(o\text{-tol})_3]^+$. Heterolytic cleavage in the presence of $P(o\text{-tol})_3$ produced the known hydride $[\mathbf{1}H]^+$ and $[HP(o\text{-tol})_3]^+$, which undergoes slow proton transfer on the NMR time scale 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 $[\mathbf{1}D]^+$ and the coproduct $[DP(o\text{-tol})_3]^+$ (see the Supporting Information). It is proposed that H_2 activation initially produces the diferrous ammonium hydride complex $[\mathbf{1}HH]^{2+}$. Subsequent deprotonation and rearrangement of the incipient terminal hydride complex leads to the final product, $[\mathbf{1}H]^+$, which contains a bridging hydride (Scheme 1).

To investigate the role of the oxidant, we carried out reactions with various ferrocenium derivatives[7] $[Me_nFc]BAr^F{}_4$ (n = 10, 8, 5; $[Me_{10}Fc]^+ = [Fe(C_5Me_5)_2]^+$, $[Me_8Fc]^+ = [Fe(C_5Me_4H)_2]^+$, $[Me_5Fc]^+ = [Fe(C_5Me_5)(C_5H_5)]^+$) (Table 1). Monitoring product formation by ^1H NMR spectroscopy, we found that the rate of reaction was independent of the oxidant strength (for the $BAr^F{}_4^-$ salts, E = −593 to −313 mV vs $Fc/FcBAr^F{}_4$).[8] Furthermore, the rate was unaffected by the concentration of the oxidant. These findings imply that electron transfer does not occur in or before the rate-determining step.

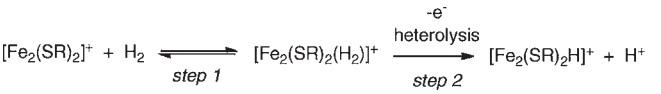
Having observed that the oxidant did not affect the rate of H_2 oxidation, we probed the effect of hydrogen pressure. When 1 equiv of oxidant was used, the appearance of the product $[\mathbf{1}H]^+$ was strictly first-order. Under these conditions, H_2 dissolved quickly and was present in large excess. As a result, $[H_2]$ remained constant over the course of each experiment. A plot of k_{obs} vs $[H_2]$ was linear, verifying a first-order dependence

Received: February 24, 2011
Published: May 06, 2011

Scheme 1. Activation of H_2 by $[1]^+$ and $Cp^*_2Fe^+$ To Form $[1H]^+$



Scheme 2. Two Possible Kinetic Scenarios for H_2 Oxidation by $[1]^+$ and Ferrocenium (Terminal Ligands Have Been Omitted for Clarity).



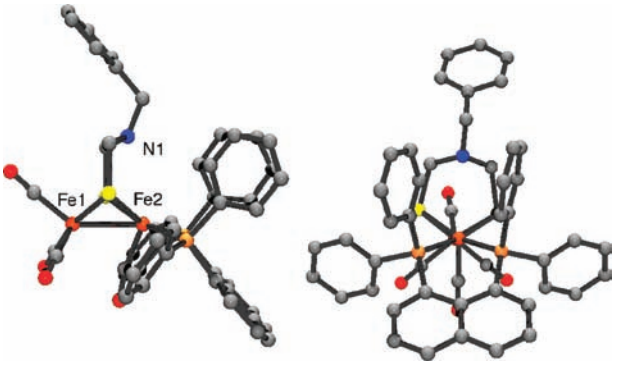


Figure 2. Structure of the cation in $[Fe_2[(SCH_2)_2NBn](CO)_4(dppn)]BAr^F_4$. Selected bond lengths (Å): Fe2−N1, 3.234(3); Fe1−Fe2, 2.568(1); $[Fe2-P]_{ave}$, 2.231(1).

Table 1. Observed Pseudo-First-Order Rate Constants for the Conversion of 1 to $[1]^+$ with Various Ferrocenium Oxidants[a]

oxidant	equiv of Me_nFc^+	$E(Me_nFc^{+/0})$ [mV vs $E(Fc^{+/0})$]	$10^5 k_{obs}$ (s^{-1})	conv. (%)
$[Me_{10}Fc]^+$	2	−593	2.2(3)	100
$[Me_{10}Fc]^+$	2[b]	−593	2.2(4)	100
$[Me_{10}Fc]^+$	4	−593	2.7(3)	100
$[Me_8Fc]^+$	2	−512	4.2(6)	>75
$[Me_8Fc]^+$	4	−512	4.2(5)	>75
$[Me_5Fc]^+$	2	−313	3.3(8)	>50

[a] Conditions: 2 atm H_2, 0 °C, CD_2Cl_2 solution, $[1]_o = [P(o\text{-tol})_3] = 4.67$ mM. [b] $P(o\text{-tol})_3$ was omitted from the reaction.

on $[H_2]$. These observations imply a rate law that includes only terms in $[H_2]$ and $[1^+]$:

$$\frac{d[1H^+]}{dt} = k_{obs}[H_2][1^+] \quad (1)$$

The experimental rate law in eq 1 is consistent with two kinetic situations (Scheme 2). The first involves rate-determining binding of H_2 (Step 1, Scheme 2) followed by rapid oxidation and/or heterolysis. In the second kinetic scenario, fast H_2 binding is followed by rate-determining heterolysis to form the mixed-valence hydride (Step 2, Scheme 2), which is rapidly oxidized in a subsequent step. In either scenario, the rate of reaction can be improved rationally on the basis of well-established principles.[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 for an electrophilic diiron center was $[Fe_2[(SCH_2)_2NBn](CO)_4(dppv)]^+$, a *tetra*carbonyl relative of $[1]^+$.[10] This mixed-valence compound was found to be unstable, probably because of disproportionation caused by amine binding.[5] We discovered, however, that the use of a more rigid diphosphine allowed the sought-for electrophilic, amine-containing cation to be isolated. Specifically, $[Fe_2[(SCH_2)_2NBn](CO)_4(dppn)]^+$ ($[2]^+$) [dppn = 1,8-bis(diphenylphosphino)naphthalene] was accessed in two steps from $Fe_2[(SCH_2)_2NBn](CO)_6$. According to cyclic voltammetric measurements on CH_2Cl_2 solutions, the $[2]^{+/0}$ couple occurs at −254 mV, which is 390 mV more positive than the $[1]^{+/0}$ couple.

Treatment of a CH_2Cl_2 solution of **2** with 1 equiv of $[Fc]BAr^F_4$ gave the mixed-valence salt $[2]BAr^F_4$, solutions of which remained unchanged for up to 24 h at room temperature. The stability of this mixed-valence cation allowed us to obtain single crystals. Crystallographic analysis showed that the amine (proton acceptor) is poised over the electrophilic Fe center (hydride acceptor) at a distance of only 3.2 Å. The high stability of this organometallic frustrated Lewis pair[11] 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 showed that $[2]^+$ is far more electrophilic than $[1]^+$: ν_{CO} = 1896, 2022, 2078 vs 1870, 1965, 2017 cm^{-1}, respectively.

The EPR spectrum of $[2]BAr^F_4$ (Figure 3) features an axial pattern and exhibits triplets indicative of large hyperfine coupling to ^{31}P, consistent with the assignment of $[2]^+$ as $[(dppn)(CO)Fe^I(\mu\text{-}SR)_2Fe^{II}(CO)_3]^+$. The spectrum is similar to that reported for related cations such as $[Fe_2(S_2C_3H_6)(CO)_4(dppv)]^+$. It is likely that, as previously reported for $[1]^+$, the electrophilic site is the iron center formally assigned as Fe(I).[12]

Gratifyingly, in the presence of 1 equiv of $[Fc]BAr^F_4$, $[2]^+$ was found to react rapidly with 1 atm H_2 ($t_{1/2}$ < 13 min at 20 °C). Monitoring of the reaction by IR (Figure 4) and ^1H NMR spectroscopies confirmed the formation of the same ammonium hydride produced by treatment of **2** with 2 equiv of $[H(OEt_2)_2]BAr^F_4$. Rate measurements showed H_2 activation by $[2]^+/[Fc]^+$ to be 10-fold faster than that by $[1]^+/[Fc]^+$ and 10^4-fold faster than that by $[1]^+$ in the absence of a supplemental oxidant.

dx.doi.org/10.1021/ja201731q | J. Am. Chem. Soc. 2011, 133, 8098–8101

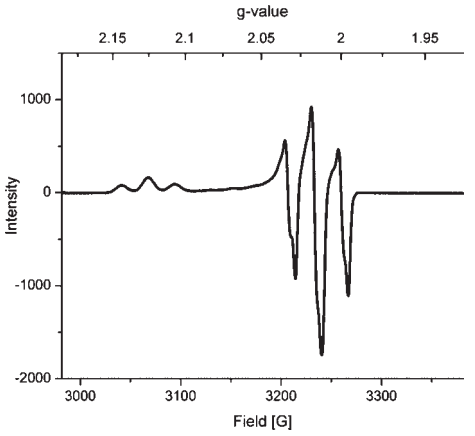


Figure 3. X-band EPR spectrum of $[\mathbf{2}]BAr^{F}_{4}$ (110 K, 1:1 CH_2Cl_2/toluene glass). Parameters: $g_z = 2.1260$ with $A_z(^{31}P) = 78$ MHz; $g_x \approx g_y = 2.0165$ with $A_x(^{31}P) \approx A_y(^{31}P) = 79$ MHz.

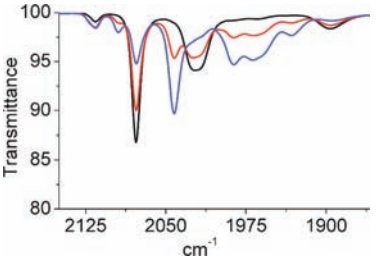


Figure 4. IR spectra of a CH_2Cl_2 solution of $[\mathbf{2}]BAr^{F}_{4}$ and $[Fc]BAr^{F}_{4}$ before (black) and 5 min (red) and 14 min (blue) after introduction of H_2 (1 atm).

We measured the rates of reaction for a 1:1 mixture of $[\mathbf{2}]BAr^{F}_{4}$ and $[Fc]BAr^{F}_{4}$ with H_2 and D_2 using UV−vis spectroscopy at 20 °C. The kinetic isotope effect (KIE) was found to be $k_H/k_D = 0.71(8)$. Reactions in which H_2 cleavage is known to be rate-determining typically exhibit a *normal* KIE (e.g., $k_H/k_D \sim 2.0$).[9d] Although few reports have described KIEs for H_2 binding,[13] an inverse KIE has been observed for H_2 binding to $Ir(H)_2Cl(PBu^{t}_{2}Me)_2$.[14] The inverse KIE measured for our reaction is inconsistent with rate-determining heterolytic cleavage of H_2 and suggests that H_2 binding is rate-determining.

An enigmatic aspect of the present results is the observation that $[\mathbf{1}]^+$ and $[\mathbf{2}]^+$ do not serve as oxidants for the oxidation of H_2 by a second equivalent of the same cations. This finding may be explicable if the activation of H_2 occurs via *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 $Fc^{+/0}$ is indeed high ($k = 5 \times 10^6$ M^{-1} s^{-1}),[17] but we propose that self-exchange for $[\mathbf{1}]^{+/0}$ and $[\mathbf{2}]^{+/0}$ are probably far slower because of the substantial structural changes that accompany this redox process.[18] Further work on these self-exchange rates is required.

We have shown that H_2 activation by the organometallic radicals $[Fe_2[(SCH_2)_2NR](CO)_{6-x}L_x]^+$ requires the addition of an oxidant, which simulates the role of the 4Fe−4S cluster in the protein. It is intriguing that for heterolysis the oxidant must be both mild and fast. Kinetic measurements suggest that H_2 binding is rate-determining. The present results point to the important role of PCET in the heterolytic activation of dihydrogen in this class of enzyme mimics.

■ ASSOCIATED CONTENT

Supporting Information. Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

This research was supported by the NIH. We thank Danielle Gray for solving the structure of $[\mathbf{2}]BAr^{F}_{4}$, Mark Nilges for assistance with EPR measurements, and Matthew Olsen for advice.

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