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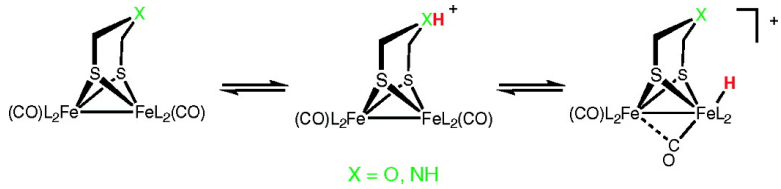

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Aza- and Oxadithiolates Are Probable Proton Relays in Functional Models for the [FeFe]-Hydrogenases

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The [FeFe]-hydrogenases are among the very best catalysts known for the reduction of protons to dihydrogen, with turnover frequencies estimated to be ~6000 mol of H_2/mol of enzyme per second operating at nearly Nerstian potentials.[1] The question about why the [FeFe]-hydrogenases are so efficient is topical,[2] and the answer is likely related to the incompletely characterized dithiolate cofactor that bridges the diiron subunit. In 2001, Nicolet et al. proposed that this dithiolate is the azadithiolate (adt, $(SCH_2)_2NH$), wherein the amine functionality could relay protons to and from the apical site on the distal Fe center.[3] It is known that, unlike typical amine bases, transition metals can be slow to protonate.[4] The adt hypothesis is attractive because it potentially shows how to couple the kinetic facility of amine protonation with the redox abilities of iron hydrides. Indeed, DuBois has demonstrated that amine bases constrained within diphosphine ligands greatly accelerate both H_2 uptake and production for mononuclear iron and nickel phosphine complexes.[5] A recent DFT investigation suggests that the dithiolate cofactor is the oxadithiolate (odt, $(SCH_2)_2O$), which also merits evaluation since protein crystallography cannot distinguish between C, N, and O.[6]

Efforts to understand and exploit the possible presence of the adt cofactor have been underway for several years. The amine can be protonated independently of the diiron site.[7,8] However, *N*-protonation has little effect on proton reduction by the catalysts of the general type $Fe_2(\mu\text{-H})(SR)_2L_6$, where μ-H indicates that the hydride bridges the two Fe centers.[9,10]

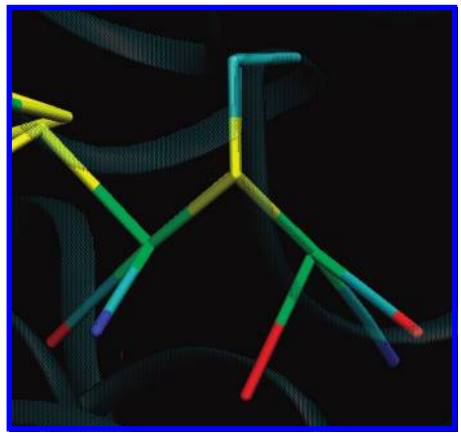
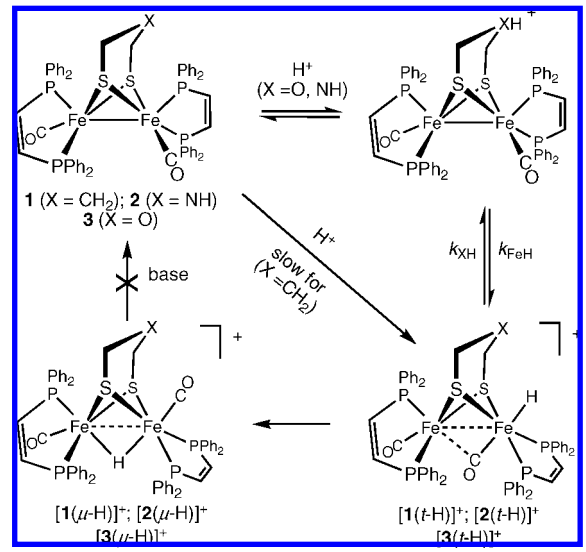


Figure 1. Structure of diiron active site of the enzyme from *D. desulfuricans* showing the dithiolate cofactor (turquoise/yellow).

The recent discovery that diiron(I) dithiolates initially protonate to give terminal, not bridging, hydrides opens a new and potentially significant phase in elucidating the role of the dithiolate cofactor in the catalysis.[11] Terminal hydride ligands[12] would be directly adjacent to the heteroatom in the dithiolate, which is therefore well positioned as a site for proton relay. We recently demonstrated that protonations of the electronically symmetrical $Fe_2(pdt)(CO)_2(dppv)_2$ (**1**) and $Fe_2(adt)(CO)_2(dppv)_2$ (**2**) yield relatively stable ($t_{1/2} \approx$ minutes at 25 °C), terminal hydride derivatives (dppv = *cis*-1,2-bis(diphenylphosphino)ethylene; pdt = 1,3-propanedithiolate; adt = 2-azapropane-1,3-dithiolate). These terminal hydrides undergo reduction at a milder potential than the isomeric bridging hydride species, are catalytically competent, and are sufficiently robust to study in detail.[13] The crucial unanswered question is whether a heteroatom in the dithiolate participates in proton transfer to and from the terminal hydride. To address this question, we report results that demonstrate a functional role of oxa- and azadithiolates as proton relays. These experiments are benchmarked relative to the third crystallographically feasible dithiolate, propanedithiolate. We prepared $Fe_2(odt)(CO)_2(dppv)_2$ from the hexacarbonyl[14] and confirmed spectroscopically (odt = 2-oxopropane-1,3-dithiolate).

Scheme 1. Acid−Base Reactions of **1**−**3**



Protonation of $Fe_2(odt)(CO)_2(dppv)_2$ (**3**) at −78 °C with the strong acid $[H(Et_2O)_2]BAr^F{}_4$ afforded the terminal hydride $[\mathbf{3}(t\text{-H})]BAr^F{}_4$. ^1H and ^{31}P NMR analysis confirmed that protonation occurred at a single Fe center, characteristic of related derivatives.[15] This terminal hydride was found to isomerize upon warming to give the μ-hydride complex, $[\mathbf{3}(\mu\text{-H})]BAr^F{}_4$ (2.6×10^{-4} s^{-1}, −10 °C), a process following unimolecular kinetics. The isomerization rate is similar to that for $[\mathbf{2}(t\text{-H})]BAr^F{}_4$ (1.4×10^{-4} s^{-1}) but is faster than $[\mathbf{1}(t\text{-H})]BAr^F{}_4$ (2.5×10^{-5} s^{-1}).

Odt and Adt Accelerate Deprotonation of $[HFe_2(xdt)(CO)_2(diphosphine)_2]^+$. We first compared the facility with which a CD_2Cl_2 solution of $[\mathbf{3}(t\text{-H})]BAr^F{}_4$ deprotonates. At −78 °C, $[\mathbf{3}(t\text{-H})]BAr^F{}_4$ is unreactive toward base, but upon warming to ~0 °C, two products form, $[\mathbf{3}(\mu\text{-H})]BAr^F{}_4$ and **3**, as assayed by ^1H and ^{31}P NMR spectroscopy. The ratio of these two products was unaffected by the concentration of the base as well as its pK_a, as indicated by deprotonations with both strong and weak bases, respectively, tetramethylguanidine ($TMGH^+$, pK_a ~23) and PPh_3 ($[HPPh_3]BF_4$, $pK^{CD_2Cl_2} = 1.6$).[16] In contrast, $[\mathbf{1}(t\text{-H})]BAr^F{}_4$ cannot be deprotonated by any organic base, even at room temperature, where isomerization to $[\mathbf{1}(\mu\text{-H})]^+$ eventually occurs.

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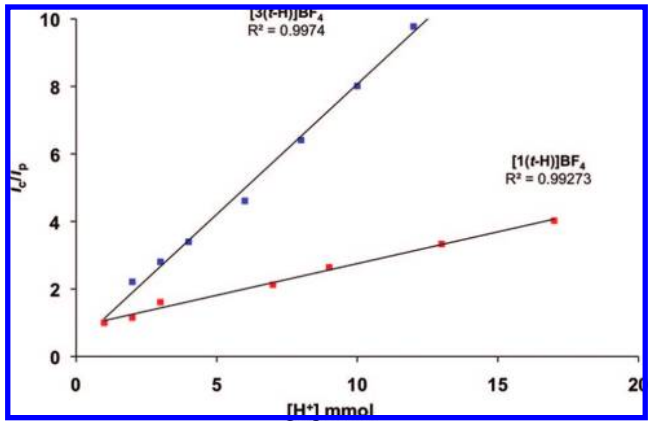

Figure 2. Dependence of current (i_c/i_p) vs [HBF_4.Et_2O] for [**1**(*t*-H)]BF_4 and [**3**(*t*-H)]BF_4 (−20 °C, 1 mM catalyst), where i_c is peak catalytic current and i_p is the peak current in the absence of acid.

Deprotonation of [**2**(*t*-H)]BAr^F_4 is however immediate with PBu_3 ([$HPBu_3$]BF_4, $pK^{CD_2Cl_2} = 8.2$) even at −90 °C, *exclusively* providing **2**. The close similarity of the IR spectra in the ν_{CO} region for [**1**(*t*-H)]BAr^F_4, [**2**(*t*-H)]BAr^F_4, and [**3**(*t*-H)]BAr^F_4 suggests that these terminal hydrides should have similar thermodynamic acidities.[17] The similar thermodynamic acidities of these three hydrides indicate that the rate of deprotonation is strongly influenced by the presence of a heteroatom in the dithiolate (Scheme 1). Not only is deprotonation of the terminal hydrides strongly affected by the identity of the dithiolate ligand, the stereochemistry of the hydride also has a profound effect. The three bridging hydrides, [**1**(μ-H)]$^+$, [**2**(μ-H)]$^+$, and [**3**(μ-H)]$^+$, are not deprotonated by NEt_3 at room temperature.

Heteroatom in the Dithiolate Strongly Affects the Protonation of $Fe_2(xdt)(CO)_2(diphosphine)_2$. The presence of a heteroatom was found to strongly affect the rate of protonation at iron. The strong acid [$H(Et_2O)_2$]BAr^F_4 protonated **1**, **2**, and **3** quickly at −90 °C, but the *billion-fold* weaker acid [$HPMe_2Ph$]BF_4 ($pK^{CD_2Cl_2} = 5.7$) protonated only **2** (−90 °C), not **1** or **3**.[16] The pK_a of [**2**H]$^+$ is bracketed by the finding that **2** is not protonated by [$HPBu_3$]BF_4. The implication that the acidity of the ammonium and terminal hydride tautomers of [**2**H]$^+$ are comparable is supported by the previously reported finding that the ratio of the ammonium and terminal hydride tautomers can be shifted by the solvent: MeOH favors the ammonium tautomer, CH_2Cl_2 the hydride tautomer.[13] Indicative of the facile tautomerization, FT-IR measurements show that addition of [NBu_4]BF_4 to a CH_2Cl_2 solution of [**2**H]BAr^F_4 partially converts the terminal hydride to the ammonium tautomer.

These results are consistent with a mechanism whereby hydride formation is regulated by the basicity of the heteroatom in the dithiolate: the amine center in **2** is easily protonated and then quickly relays protons to Fe. In contrast for complexes with weakly basic oxadithiolate ($pK^{CD_2Cl_2}(R_2OH^+) \sim -4.7$ to 1.6) or nonbasic propanedithiolate, the Fe site can only be protonated by strong acids, even though the basicities of these diiron centers are very similar.

Heteroatom-Containing Dithiolates Enhance Proton Reduction Catalysis. As the azadithiolate exhibits enhanced rates of protonation, this enhancement could be manifested in catalysis by accelerating the rate of proton reduction. At −20 °C, where these terminal hydrides are stable, the hydrides [**1**(*t*-H)]BF_4, [**2**(*t*-H)]BF_4, and [**3**(*t*-H)]BF_4 all catalyze hydrogen evolution at approximately the same potentials, ∼−1.5 V vs Fc/Fc^+ (∼−0.8 V vs NHE). Using [$HPMe_2Ph$]BF_4 ($pK^{CD_2Cl_2} = 5.7$), however, [**2**(*t*-H)]BF_4 is catalytically active, but [**1**(*t*-H)]BF_4 and [**3**(*t*-H)]BF_4 are not. The $pK^{CD_2Cl_2}$ of [$HPMe_2Ph$]BF_4 has been estimated to correspond to an aqueous pK_a of 6.8.[16] Catalysis by the amine [**2**(*t*-H)]BF_4 with strong acids is complicated because protonation occurs at both the amine and terminally at Fe.[7,10,13] Interestingly, for strong acids, [**3**(*t*-H)]BF_4 is a significantly faster catalyst for hydrogen evolution than is [**1**(*t*-H)]BF_4, which suggests that even the weakly basic ether group assists in proton relay (Figure 2).

The results presented in this paper indicate that the presence of a heteroatom in the dithiolate bridge strongly facilitates proton transfer to and from the apical site on Fe, but only to the extent that the acid can protonate the bridgehead atom. Although both azadithiolate (in **2**) and oxadithiolate (in **3**) exhibit relay-like behavior, indicated by enhanced rates of proton reduction catalysis by **2** and **3**, only the azadithiolate **2** enables hydride formation from weak acids, which is relevant to catalysis at low overpotentials.[18]

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

References

(1) (a) Vincent, K. A.; Parkin, A.; Armstrong, F. A. *Chem. Rev* **2007**, *107*, 4366–4413. (b) Fontecilla-Camps, J. C.; Volbeda, A.; Cavazza, C.; Nicolet, Y. *Chem. Rev.* **2007**, *107*, 4273–4303.
(2) Lewis, N. S.; Nocera, D. G. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 15729–15735.
(3) Nicolet, Y.; de Lacey, A. L.; Vernede, X.; Fernandez, V. M.; Hatchikian, E. C.; Fontecilla-Camps, J. C. *J. Am. Chem. Soc.* **2001**, *123*, 1596–1601.
(4) Kramarz, K. W.; Norton, J. R. *Prog. Inorg. Chem.* **1994**, *42*, 1–65.
(5) (a) Henry, R. M.; Shoemaker, R. K.; DuBois, D. L.; Rakowski DuBois, M. *J. Am. Chem. Soc.* **2006**, *128*, 3002–3010. (b) Wilson, A. D.; Shoemaker, R. K.; Miedaner, A.; Muckerman, J. T.; DuBois, D. L.; Rakowski Dubois, M. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 6951–6956.
(6) Pandey, A. S.; Harris, T. V.; Giles, L. J.; Peters, J. W.; Szilagyi, R. K. *J. Am. Chem. Soc.* **2008**, *130*, 4533–4540.
(7) Eilers, G.; Schwartz, L.; Stein, M.; Zampella, G.; de Gioia, L.; Ott, S.; Lomoth, R. *Chem.—Eur. J.* **2007**, *13*, 7075–7084.
(8) (a) Wang, F.; Wang, M.; Liu, X.; Jin, K.; Dong, W.; Li, G.; Åkermark, B.; Sun, L. *Chem. Commun.* **2005**, *322*, 1–3223. (b) Stanley, J. L.; Heiden, Z. M.; Rauchfuss, T. B.; Wilson, S. R.; De Gioia, L.; Zampella, G. *Organometallics* **2007**, *27*, 119–125.
(9) (a) Jiang, S.; Liu, J.; Shi, Y.; Wang, Z.; Åkermark, B.; Sun, L. *Dalton Trans.* **2007**, *89*, 6–902. (b) Wang, Z.; Liu, J.-H.; He, C.-J.; Jiang, S.; Åkermark, B.; Sun, L.-C. *J. Organomet. Chem.* **2007**, *692*, 5501–5507.
(10) Wang, F.; Wang, M.; Liu, X.; Jin, K.; Dong, W.; Sun, L. *Dalton Trans.* **2007**, 3812–3819.
(11) Capon, J.-F.; Ezzaher, S.; Gloaguen, F.; Petillon, F. Y.; Schollhammer, P.; Talarmin, J. *Chem.—Eur. J.* **2007**, *14*, 1954–1964.
(12) van der Vlugt, J. I.; Rauchfuss, T. B.; Whaley, C. M.; Wilson, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 16012–16013.
(13) Barton, B. E.; Rauchfuss, T. B. *Inorg. Chem.* **2008**, *47*, 2261–2263.
(14) (a) Li, H.; Rauchfuss, T. B. *J. Am. Chem. Soc.* **2002**, *124*, 726–727. (b) Song, L.-C.; Yang, Z.-Y.; Bian, H.-Z.; Hu, Q.-M. *Organometallics* **2004**, *23*, 3082–3084.
(15) 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.
(16) Li, T.; Lough, A. J.; Morris, R. H. *Chem.—Eur. J.* **2007**, *13*, 3796–3803.
(17) Landau, S. E.; Morris, R. H.; Lough, A. J. *Inorg. Chem.* **1999**, *38*, 6060–6068.
(18) (a) Felton, G. A. N.; Glass, R. S.; Lichtenberger, D. L.; Evans, D. H. *Inorg. Chem.* **2006**, *45*, 9181–9184. (b) Felton, G. A. N.; Vannucci, A. K.; Chen, J.; Lockett, L. T.; Okumura, N.; Petro, B. J.; Zakai, U. I.; Evans, D. H.; Glass, R. S.; Lichtenberger, D. L. *J. Am. Chem. Soc.* **2007**, *129*, 12521–12530. (c) Hu, X. L.; Brunschwig, B. S.; Peters, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 8988–8998.

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