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

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## Abstract


The dithiolate cofactor for the [FeFe]-hydrogenase models, $Fe_2(xdt)(CO)_2(dppv)_2$ (where xdt = 1,3-propanedithiolate (pdt), azadithiolate (adt), $(SCH_2)_2NH$, and oxadithiolate (odt), $(SCH_2)_2O$; dppv = *cis*-1,2-bis-(diphenylphosphino)ethylene) have been probed for their functionality as proton relays enabling formation and deprotonation of terminal hydrides. Compared to the propanedithiolate derivative, the azadithiolate and oxaditiholate show enhanced rates of proton transfer between solution and the terminal site on one Fe center. The results are consistent with the heteroatom of the dithiolate serving a gating role for both protonation and deprotonation. The $pK_a$ of the transiently formed ammonium ($pK^{CD_2Cl_2}$ 5.7–8.2) or oxonium ($pK^{CD_2Cl_2}$ –4.7–1.6) regulates the proton transfer. As consequence, only the azadithiolate is capable of yielding the terminal hydride from weak acids. The aza- and oxadithiolates manifested the advantages of proton relays: the odt derivative proved to be a faster catalyst for hydrogen evolution than the pdt derivative as indicated from cyclic voltammetry plots of $i_c/i_p$ vs. $[H^+]$. The adt derivative was capable of proton reduction from the weak acid $[HPMe_2Ph]BF_4$ ($pK^{CD_2Cl_2} = 5.7$). The proton relay function does not apply to the isomeric bridged-hydrides $[Fe_2(xdt)(\mu\text{-}H)(CO)_2(dppv)_2]^+$, where the hydride is too distant and too basic to interact to be affected by the heteroatomic relay site. None of these μ-H species can be deprotonated.

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 $H_2$/mol 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]

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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]

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 ($t_{1/2}$ ~ 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).

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, $[\mathbf{3}(\mu\text{-}H)]BAr^F{}_4$ ($2.6 \times 10^{-4}$ $s^{-1}$, −10 °C), a process following unimolecular kinetics. The isomerization rate is similar to that for $[\mathbf{2}(t\text{-}H)]BAr^F{}_4$ ($1.4 \times 10^{-4}$ $s^{-1}$) but is faster than $[\mathbf{1}(t\text{-}H)]BAr^F{}_4$ ($2.5 \times 10^{-5}$ $s^{-1}$).

## 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 concentration of the base as well as its p$K_a$, as indicated by deprotonations with both strong and weak bases, respectively tetramethylguanidine ($TMGH^+$, p$K_a$ ~23) and $PPh_3$ ($[HPPh_3]BF_4$, p$K$ $^{CD_2Cl_2}$ = 1.6).[16] In contrast, $[\mathbf{1}(t\text{-}H)]BAr^F{}_4$ cannot be deprotonated by any base, even at room temperature, where isomerization to $[\mathbf{1}(\mu\text{-}H)]^+$ eventually occurs. Deprotonation of $[\mathbf{2}(t\text{-}H)]BAr^F{}_4$ is however immediate with $PBu_3$ ($[HPBu_3]BF_4$, p$K$ $^{CD_2Cl_2}$ = 8.2) even at −90 °C, *exclusively* providing **2**. The close similarity of the IR spectra in the $\nu_{CO}$ region for $[\mathbf{1}(t\text{-}H)]BAr^F{}_4$, $[\mathbf{2}(t\text{-}H)]BAr^F{}_4$, and $[3(t\text{-}H)]BAr^F{}_4$ 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, $[\mathbf{1}(\mu\text{-}H)]^+$, $[\mathbf{2}(\mu\text{-}H)]^+$, and $[\mathbf{3}(\mu\text{-}H)]^+$ 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 $[2H]^+$ 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 $[\mathbf{2}H]^+$ are comparable is supported by the previously reported finding that the ratio of the ammonium and hydride tautomers can be shifted by the solvent: MeOH favors the ammonium tautomer, $CH_2Cl_2$ the hydride tautomer.[18]

These results are consistent with a mechanism whereby hydride formation is regulated by the basicity of the heteroatom in the dithiolate: the ammonium center in **2** is easily protonated and then quickly relays protons to Fe. In contrast for complexes with weakly basic oxadithiolate ($pK^{CD_2Cl_2}(R_2OH^+)$ ~−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 −40 °C, where these terminal hydrides are stable, the hydrides $[\mathbf{1}(t\text{-H})]BF_4$, $[\mathbf{2}(t\text{-H})]BF_4$, and $[\mathbf{3}(t\text{-H})]BF_4$ all catalyze hydrogen evolution at about 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, $[\mathbf{2}(t\text{-H})]BF_4$ is catalytically active, but $[\mathbf{1}(t\text{-H})]BF_4$ and $[\mathbf{3}(t\text{-H})]BF_4$ 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 $[\mathbf{2}(t\text{-H})]BF_4$ with strong acids is complicated because protonation occurs at both the amine and terminally at Fe.[7,10,18] Interestingly, for strong acids, $[\mathbf{3}(t\text{-H})]BF_4$ is a significantly faster catalyst for hydrogen evolution than is $[\mathbf{1}(t\text{-H})]BF_4$, which suggests that even the weakly basic ether group assists in proton relay (Figure 1).

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.[19]

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

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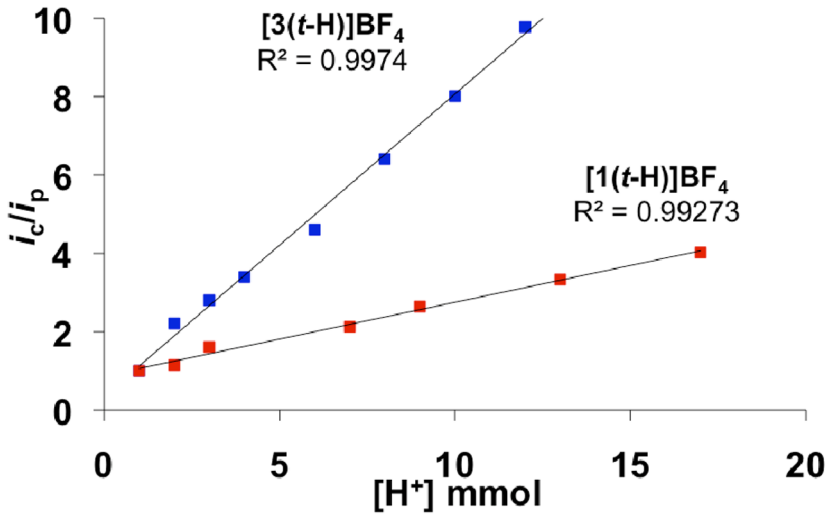
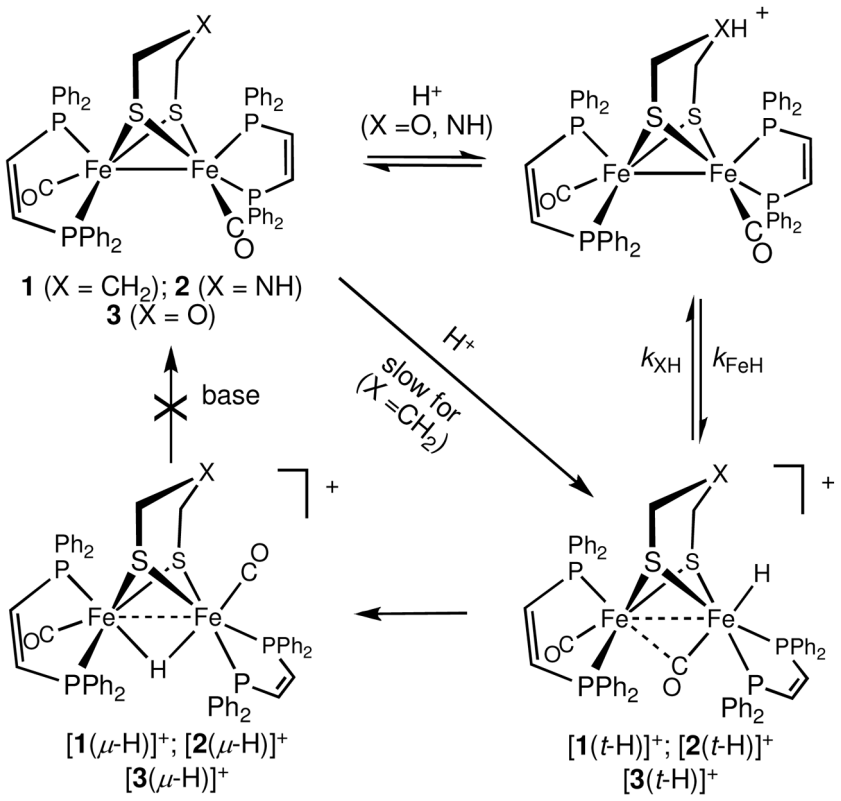



**Figure 1.**

Dependence of current ($i_c/i_p$) vs of [$HBF_4$·$Et_2O$] for [**1**(*t*-H)]$BF_4$ and [**3**(*t*-H)]$BF_4$ (−40 °C, 1 mM catalyst), where $i_c$ is peak catalytic current and $i_p$ is the peak current in the absence of acid.




**Scheme 1.**
Acid-base reactions of **1**–**3**.