Published in final edited form as:

Chemistry. 2015 June 15; 21(25): 9256–9260. doi:10.1002/chem.201500152.

Protonation and Proton-Coupled Electron Transfer at S-Ligated [4Fe-4S] Clusters

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Abstract

Biological [Fe-S] clusters are increasingly recognized to undergo proton-coupled electron transfer (PCET), but the site of protonation, mechanism, and role for PCET remains largely unknown. Here we explore this reactivity with synthetic model clusters. Protonation of the arylthiolate-ligated [4Fe-4S] cluster $[\text{Fe}_4\text{S}_4(\text{SAr})_4]^{2-}$ (**1**, SAr = S-2,4,6-(ⁱPr)₃C₆H₂) leads to thiol dissociation, reversibly forming $[\text{Fe}_4\text{S}_4(\text{SAr})_3\text{L}]^{1-}$ (**2**) + ArSH (L = solvent, and/or conjugate base). Solutions of **2** + ArSH react with the nitroxyl radical TEMPO to give $[\text{Fe}_4\text{S}_4(\text{SAr})_4]^{1-}$ (**1_{ox}**) and TEMPOH. This reaction involves PCET coupled to thiolate association and may proceed via the unobserved protonated cluster $[\text{Fe}_4\text{S}_4(\text{SAr})_3(\text{HSAr})]^{1-}$ (**1-H**). Similar reactions with this and related clusters proceed comparably. An understanding of the PCET thermochemistry of this cluster system has been developed, encompassing three different redox levels and two protonation states.

Keywords

PCET; [Fe-S] cluster; enzyme mechanism; iron; thiol

Introduction

Iron-sulphur ([Fe-S]) clusters are ubiquitous as electron-transfer (ET) cofactors in biology, and recent studies indicate that they can engage in proton-coupled electron transfer (PCET).^{[1],[2],[3],[4]} This is most noted in His-ligated clusters such as those in Rieske and mitoNEET proteins,^[1] but has also been shown to occur at the all S-ligated [3Fe-4S] ferredoxin from *Azotobacter vinelandii*.^[2a] PCET from the nitrogenase FeMo-co cluster inevitably plays a role in reducing N₂ to NH₃, though the mechanism and site(s) of protonation are still uncertain.^[5] Synthetic S-ligated [4Fe-4S] can mediate several multi-

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e^-/H^+ transformations,^[6] including the reduction of CO_2 to formate,^[7] H^+ to H_2 ,^[6b, 8] acetylene to ethylene,^[6b, 9] and nitrobenzene to aniline.^[10] Related reactivity is known for chalcogels incorporating [4Fe-4S] clusters.^[11] Similar to the biological cases, little is known about the site of protonation in synthetic systems, and mechanistic advances have been made primarily through analyses of kinetic data.^[6b, 12] Herein we describe a spectroscopic and thermochemical study of PCET and proton transfer (PT) reactions of synthetic [4Fe-4S] clusters, which begin to establish the nature of such reactions at [4Fe-4S] clusters. This has implications to understanding metalloenzyme mechanisms as well as catalytic synthetic [4Fe-4S] systems.

Results and Discussion

Cluster Protonation

O'Sullivan and Millar's [4Fe-4S] cluster $[Fe_4S_4(SAr)_4]^{2-}$ (**1**), where SAr is the bulky thiolate ligand $SC_6H_2-2,4,6-(iPr)_3$ (ArSH),^[13] has good stability for these studies. The $1-e^-$ oxidized and reduced congeners, $[Fe_4S_4(SAr)_4]^{1-}$ (**1_{ox}**) and $[Fe_4S_4(SAr)_4]^{3-}$ (**1_{red}**) were prepared by addition of a suitable oxidant or reductant to **1**, respectively.^[13-14] Thus, the redox states for both high-potential [Fe-S] proteins and ferredoxins can be modelled by this cluster system.

(1)

Protonation of cluster **1** in d_3 -MeCN with 1 equivalent of the strong acid $[(OEt)_2H]BARF_{24}$ ($BARF_{24}$ = tetrakis(3,5-trifluoromethyl)phenylborate) was monitored by 1H NMR spectroscopy (eq 1). A shift of the ligand resonances was observed; for instance, the *m*-H resonance of **1** shifted and broadened from 8.05 ppm to 8.25 ppm (see ESI Section V.1). In addition, a new set of resonances appeared in the spectrum, corresponding to free thiol, ArSH, confirmed by addition of ArSH to the sample. From the 3:1 integration of bound ligand to free ArSH, the new cluster is assigned as $[Fe_4S_4(SAr)_3L]^{1-}$ (**2**) in which the thiolate has been replaced by solvent or the conjugate base of the added acid (L). These results parallel Holm and co-workers' report that additions of electrophiles to $[Fe_4S_4(SR)_4]^{2-}$ clusters result in thiolate release; in their studies there is only limited discussion on the reaction with acid due to instability.^[15] Addition of the strong base $tBuNP(pyr)_3$ (pyrr = pyrrolidine) to solutions of **2** + ArSH, causes **1** to be regenerated quantitatively (by 1H NMR spectroscopy). The same reactivity is observed for this cluster in CD_2Cl_2 , and for the related less bulky arylthiolate clusters $[Fe_4S_4(SC_6H_4^tBu)_4]^{2-}$ and $[Fe_4S_4(SC_6H_4CF_3)_4]^{2-}$ in d_3 -MeCN. With these latter clusters, however, competitive ArS-SAr formation limits the reversibility (see ESI V.2). The dissociation of ArSH shows that protonation eventually occurs at a thiolate, likely a thiolate ligand of the [4Fe-4S] cluster, but our results do not rule out initial protonation at a bridging sulfide.^[2a, 12]

Cluster **2** shows little degradation over ~ 20 minutes at room temperature, but a black precipitate forms over the course of hours. Protonation of synthetic [Fe-S] clusters is known to facilitate ligand exchange and degradation.^[12, 14-15] ¹H NMR spectra of *d*₃-MeCN solutions of **2** + ArSH show no broadening in the thiol resonances, so chemical exchange between the thiolate ligands and free thiol is slow on the NMR timescale.

The identity of L in [Fe₄S₄(SAr)₃L]¹⁻ (**2**) was probed by generating it with a variety of acids in *d*₃-MeCN. The resulting ¹H NMR spectra of **2** are similar when [DMF-H]OTf, [py-H]OTf (py = pyridine), and [H(OEt₂)₂]BARF₂₄ are used, suggesting that L is not the conjugate base or the counteranion (ESI V.1). The reaction of **1** with [NH₄]OTf (p*K*_a = 16.46),^[16] forms an equilibrium mixture of **1** and **2** (eq 2), with *K*₂ = 3.4 × 10⁻⁴ M (ESI VIII). This equilibrium

does not shift upon addition of 1 or 10 equiv of [ⁿBu₄N]OTf, further indicating that triflate coordination is not significant. However, when **1** is treated with [py-H]OTf or [DMF-H]OTf, py and DMF are only observed by NMR spectroscopy upon addition of base ^tBuNP(pyr)₃, which suggests reversible coordination of the py and DMF. We conclude that L is likely a coordinating solvent such as *d*₃-MeCN, but that it can be the conjugate base of the acid in some cases (ESI V.1).

Reactions 1 and 2 provide an upper limit for the p*K*_a of the unobserved protonated cluster, [Fe₄S₄(SAr)₃(ArSH)]¹⁻ (**1-H**) of 14.4 in *d*₃-MeCN. This is a firm upper bound because **1-H** would have been observed in reaction 2 if it were lower in energy than **1** + NH₄⁺ (see the discussion in ESI VIII. and the free energy diagrams in Figure S29). The estimated p*K*_a indicates that **1-H** is a stronger acid than ArSH by 9.8 p*K*_a units. This is consistent with the prior report that C₂H₅SH coordination to (NH₃)₅Ru^{x+} increases its acidity by 2.8 and 19 p*K*_a units for x = 2 and 3, respectively.^[17] This result that p*K*_a(**1-H**) < 14.4 contrasts with very recent conclusions by Dance and Henderson, from computational and experimental (kinetic) studies, that there is complete initial protonation of a thiolate ligand [Fe₄S₄(SR)₄]²⁻ (R = Et, Ph) by Et₃NH⁺, also in MeCN.^[18] Since the p*K*_a of Et₃NH⁺ in MeCN is 18.9, their study implies p*K*_a values for the protonated clusters of >18.9. This discrepancy could be due to the different thiolate ligands used (SPh vs. SC₆H₂ⁱPr₃), although the >5.5 unit p*K*_a difference seems large for a change of three alkyl substituents. Complex **1-H** has not been observed so we have no information about its structure, but thiolate protonation seems likely given the Dance and Henderson results and the final formation of free thiol. Protonation at a bridging sulphide cannot be excluded, and if the formation of **1-H** involves bond cleavage (*e.g.*, change from a μ³-S to a μ²-SH), then our estimate would be an apparent p*K*_a rather than 'true' p*K*_a.

Protonation of the reduced cluster **1_{red}** by [(OEt₂)₂H]BARF₂₄ in *d*₃-MeCN gives, after ~ 20 min, free thiol (1 equiv per **1_{red}**) and the *oxidized* cluster **1** (~ 65% yield) by ¹H NMR spectroscopy. No other cluster resonances are observed. Similar results are obtained with other acids such as [NH₄]OTf and [py-H]OTf. The presence of both **1** and thiol suggests at least two reactions are occurring in the presence of acid. The related cluster,

$[\text{Fe}_4\text{S}_4(\text{SPh})_4]^{3-}$, is known to oxidize and liberate H_2 upon addition of acid.^[6] Though our experiments were not done at sufficient concentration to detect H_2 by ^1H NMR spectroscopy, this seems like a plausible reaction to occur and account for the presence of **1**. The formation of thiol likely occurs from successive protonation/ligand exchange in the reduced cluster, akin to what Holm has noted for the di-ferric/di-ferrous clusters in the presence of excess electrophiles.^[15]

PCET Studies

Mixtures of **2** + ArSH (from addition of 1 equiv [py-H]OTf to **1**) react with 1 equiv of the nitroxyl radical TEMPO to generate **1_{ox}** (~ 30%) and TEMPOH (27%), as ascertained by ^1H NMR spectroscopy (Scheme 1). The **2** + ArSH mixture also reacts with 2,4,6-tri-*t*-butylphenoxyl radical, $^t\text{Bu}_3\text{ArO}^\bullet$, (1 equiv) or 2,5-di- ^tBu -*p*-benzoquinone ($^t\text{Bu}_2\text{Q}$, 0.5 equiv) to give **1_{ox}** and $^t\text{Bu}_3\text{ArOH}$ or the hydroquinone, $^t\text{Bu}_2\text{H}_2\text{Q}$, respectively. For all reactions, an immediate color change from brown to red is observed upon addition of the oxidant, and the reactions are complete within ~ 5 min (when NMR spectra are collected). The modest yields of **1_{ox}** in these reactions is likely due to the instability of **1_{ox}** in MeCN.^[19] Addition of an oxidant such as ferrocenium to solutions of **1** in d_3 -MeCN does not cleanly generate **1_{ox}**, but rather gives mixtures of **1**, **1_{ox}**, thiol, and other unidentifiable resonances, many of which are present in the PCET reactions. Though the observed yields of **1_{ox}** are modest, the yields of $^t\text{Bu}_3\text{ArOH}$ (90 %) and $^t\text{Bu}_2\text{H}_2\text{Q}$ (90 %) are high, suggesting that **1_{ox}** degradation occurs after the PCET reaction.

Competing reactions may also affect the observed yields. The control reactions of ArSH + TEMPO ($\pm$ [py-H]OTf) gives < 5 % TEMPOH, even after monitoring for 24 h. The reaction of **1** + ArSH + TEMPO gives TEMPOH (12% yield after 15 min) (see ESI). Thus, these side reactions are not the primary path to TEMPOH. ArSH also reacts with $^t\text{Bu}_3\text{ArO}^\bullet$ within minutes to give ~ 40% $^t\text{Bu}_3\text{ArOH}$, which again cannot account for the high yields of phenol observed.

The heightened instability of oxidized clusters with less bulky thiolate ligands precluded related PCET studies from $[\text{Fe}_4\text{S}_4(\text{SC}_6\text{H}_4^t\text{Bu})_4]^{2-}$ and $[\text{Fe}_4\text{S}_4(\text{SC}_6\text{H}_4\text{CF}_3)_4]^{2-}$.

Mixtures of the trianionic cluster, **1_{red}**, and 1 equiv [(OEt)₂H]BARF₂₄ (d_3 -MeCN) also reduces H-atom acceptors. Addition of TEMPO, $^t\text{Bu}_2\text{Q}$ or $^t\text{Bu}_3\text{ArO}^\bullet$ ~ 10 s after protonation, results in formation of **1** and TEMPOH, $^t\text{Bu}_2\text{H}_2\text{Q}$, or $^t\text{Bu}_3\text{ArOH}$, respectively (Scheme 2). The yields for these PCET reactions increase with less electron-rich/bulky clusters (Scheme 2 and ESI V.3). For all reactions that commence with a trianionic cluster, such as **1_{red}**, the cluster yields more closely mirror those of the oxidant than was found in the reactions of **1**. This is likely due to **1_{red}** being oxidized to the more stable dianionic **1**, oxidation of **1** forms the less stable **1_{ox}**.

The aforementioned reactions are net PCET and ligand association; to our knowledge, they are the first examples of PCET at synthetic S-ligated [Fe-S] clusters. Thus, net PCET from S-ligated [4Fe-4S] clusters can occur from two oxidation states, which correspond to that of ferredoxins and high-potential proteins.

Thermochemical Considerations

The free energy changes for interconversion of the more oxidized clusters are summarized in Scheme 3. This includes an upper limit for the bond dissociation free energy (BDFE) of **1-H**, 64.1 kcal mol⁻¹. Though this cluster is not observed, this limit can be obtained from the reduction potential of **1_{ox}** and the upper estimate for the pK_a of **1-H**. [BDFE = 23.06E_{1/2}(**1_{ox}**/**1**) + 1.37 pK_a(**1-H**) + C_G; C_G = 54.9 ± 1.0 kcal mol⁻¹ in MeCN^[20]]. By contrast, the G° is 75.6 kcal mol⁻¹ for the conversion of **2** + ArSH, to **2_{ox}** + ArS⁻ + H[•], which can be termed an “effective BDFE.”^[20] This is determined from the pK_a of ArSH, and the reduction potential of [Fe₄S₄(SC₆H₂(ⁱPr)₃)L] (**2_{ox}**) (bottom of Scheme 3 and ESI IV., VII.).^[15] Thus, donation of H[•] from **2** + ArSH without thiolate association is 11.5 kcal mol⁻¹ *less favorable* than H[•] donation from **1-H**. This difference is due to the different oxidized products, as PCET from **1-H** gives **1_{ox}** while PCET from **2** + ArSH gives **2_{ox}** + ArS⁻. The 11.5 kcal mol⁻¹ corresponds to the difference in free energy change associated with ligand exchange (i.e.), $G_{l.e.}^\circ (G_{l.e.}^\circ = G_{l.e.}^\circ(\mathbf{2} - \mathbf{1-H}) - G_{l.e.}^\circ(\mathbf{1_{ox}} - \mathbf{2_{ox}})$; Figure 1 and ESI VIII.).

The reaction of **2** + ArSH + TEMPO to give **1_{ox}** + TEMPOH corresponds to PCET and ligand exchange. It is overall exergonic by at least -4.3 kcal mol⁻¹ (Figure 1, top). If PCET precedes ligand exchange, the initial termolecular step is **2** + ArSH + TEMPO → **2_{ox}** + ArS⁻ + TEMPOH, uphill by 9.1 kcal mol⁻¹ (from the difference in BDFEs, step i. in Figure 1). In this step, the H⁺ transferred comes from ArSH and the e⁻ originates from **2** (an example of multiple-site PCET; ms-PCET). By Hess's law, the subsequent ligand exchange to give the observed **1_{ox}** is then downhill by > -13.4 kcal mol⁻¹ (step ii., Figure 1). Alternatively, ligand exchange could precede PCET, via pre-equilibrium binding of ArSH to give **1-H** (step iii., Figure 1, $G^\circ < -1.9$ kcal mol⁻¹). Then **1-H** could transfer H⁺/e⁻ by concerted bimolecular PCET to give **1_{ox}** ($G^\circ < -2.4$ kcal mol⁻¹, step iv., Figure 1). This analysis shows that **1-H** is a reasonable intermediate in the PCET reactions in Scheme 1, both energetically and in terms of avoiding termolecular steps. A similar analysis for the reaction of **2** + ArSH + ^tBu₃ArO[•] to give **1_{ox}** + ^tBu₃ArOH is shown in Figure 1 (bottom).

A similar thermochemical discussion is not possible for the interconversion of **2_{red}** with **1**, due to the limited stability of the relevant cluster congeners. However, an upper limit of the “effective BDFE” of “**1_{red}** + DMAP-H⁺” can be obtained from the reactions in Scheme 4. The [2Fe-2S] cluster [Fe₂S₂(^{Pr}bbim)₂]²⁻ (**3**) is a weak H-atom acceptor, as the corresponding [Fe₂S₂(^{Pr}bbim)(^{Pr}bbimH)]²⁻ species (**3_{red-H}**) has a BDFE of 60.5 kcal mol⁻¹.^[20, 22] Addition of stoichiometric [DMAP-H]OTf to a *d*₃-MeCN solution containing equimolar **1_{red}** and **3** results in complete reduction and protonation of **3** to **3_{red-H}** and oxidation of **1_{red}** to **1**, as ascertained by NMR spectroscopy. The formation of NMR-silent **3_{red-H}** was confirmed by addition of TEMPO to this solution to give **3** and TEMPOH in ~93% yield, as previously described.^[22] Also, mixing **3_{red-H}** (generated from **3** + DMAP-H⁺) and **1** gives no net reaction. This shows that the BDFE of “**1_{red}** + DMAP-H⁺” is less than 60.5 kcal mol⁻¹.

Conclusions

In sum, we have shown that S-ligated [4Fe-4S] clusters can undergo PCET reactions from two distinct oxidation states, which correspond to those found in ferredoxins and high-potential proteins. Protonation of **1** results in loss of ArSH, suggesting that protonation occurs at a thiolate (akin to a Cys residue) rather than at a bridging sulfide. The unobserved cluster **1-H** is $11.5 \text{ kcal mol}^{-1}$ more reducing — a stronger $\text{H}^\bullet$ (H^+/e^-) donor — than mixtures of **2** and ArSH (which donate H^+/e^- to give **2_{ox}** + ArS^-). This suggests that PCET at biological [Fe-S] clusters may modulate the “effective BDFE” by binding of the acidic species to the cluster. This effective BDFE is the key energetic parameter for a PCET active site.^[15] Related ligand exchange/protonation upon reduction of the nitrogenase P-cluster has been proposed to help control the flux of e^-/H^+ to the active-site.^[23] Despite **1-H** not being observed, thermochemical considerations indicate that it is a reasonable intermediate in the PCET reaction of **2** + ArSH with TEMPO. To our knowledge, these are the first examples of PCET at S-ligated [Fe-S] clusters. These findings suggest that biological S-ligated [Fe-S] clusters may facilitate PCET, and that this reactivity should be considered in mechanistic hypotheses for enzymes that feature these clusters.

Experimental Section

See Supporting Information for full details. The clusters were prepared following literature procedures.^[13-14]

Protonation and PCET Studies (NMR Spectroscopy)

In a typical experiment, in the glove-box, d_3 -MeCN solutions of cluster (1-5 mM) were prepared with $\sim 1 \text{ mM}$ hexamethyldisilazane (HMDS) as an internal standard. d_3 -MeCN solutions of acid and base were also prepared (15-60 mM). 400-500 μL of the cluster solution was aliquoted out into separate NMR tubes. Unless noted, 1 equiv. of acid was then added via syringe or pipettor, the tube capped, inverted twice, immediately removed from the glovebox, parafilm added to the cap, and frozen with liquid nitrogen. If base (to show reversibility) or an oxidant (to show PCET reactivity) was added, this was done in the glove-box after inversion and prior to removal. The NMR samples were thawed at the probe, and allowed to temperature equilibrate ~ 5 minutes prior to collection of spectra. Spectra of the cluster (with internal standard) were also obtained to quantify yields.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors gratefully acknowledge the U.S. National Institute of Health, GM50422 to JM and 1F32GM099316 to CS, for financial support.

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21. For the purposes of this Figure, we assume L is a molecule of solvent. Under the reaction conditions of millimolar reagents, the $2 + \text{ArSH} \rightleftharpoons 1\text{-H} + \text{L}$ equilibrium lies strongly to the left. The reason that the minimum energy of the $1\text{-H} + \text{L}$ state is still placed lower than $2 + \text{ArSH}$ in Figure 1 (top) is that the diagram shows the energies at standard state (1 M concentrations). This equilibrium involves two molecules going to one (the solvent L not being included in the equilibrium expression), so the $2 + \text{ArSH}$ side is more favored at lower concentrations. This leads to the minimum value of $G^\circ_{\text{L.e.}}$ of $-1.9 \text{ kcal mol}^{-1}$ based on the observation that $K_{\text{L.e.}} \ll 1$.
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Scheme 1.

Reactions of **2** + ArSH with H-atom acceptors (d_3 -MeCN). L is a neutral (e.g., solvent) ligand; see text.

Scheme 2.

Reactions of **1_{red}** with acid then H-atom acceptors. Yields for reactions with analogous clusters are indicated below.

Scheme 3.

Square scheme for $[\text{Fe}_4\text{S}_4(\text{SAr})_{4-x}(\text{HSAr})_x]^n$ showing the thermochemical values that interconvert the cluster congeners and thiol/thiolate in MeCN. The clusters shown in grey have not been observed. Potentials refer to $E_{1/2}$ (see ESI IV). See ESI (VIII) for calculation of the upper limit for $G^\circ(1-\text{H} \rightarrow 2 + \text{ArSH})$.

Figure 1.

(top) Free energy diagram for the reaction of **2** + ArSH + TEMPO to **1_{ox}** + TEMPOH, showing two possible intermediates. The thick grey arrow indicates that the $G^\circ(\mathbf{1-H} + \text{L} + \text{TEMPO})$ is a lower limit. (Step i): multiple-site(ms) PCET (ET from **2**, PT from ArSH). (ii): L/ArS⁻ ligand exchange in **2_{ox}**/**1_{ox}**. The G° is from Hess' law and is similar to the $G^\circ = 13.9 \text{ kcal mol}^{-1}$ for L/ArS⁻ ligand exchange in **2/1** (from K_2 , see ESI VIII). (iii): L/ArSH ligand exchange in **2/1** (see ESI VIII).^[21] (iv): PCET from **1-H** to TEMPO; G° is an upper limit. (bottom) Free energy diagram for the reaction of **2** + ArSH + ^tBu₃ArO• to **1_{ox}** + ^tBu₃ArOH, showing two possible intermediates. The steps are analogous to those in the reaction with TEMPO. The energy of the intermediate **1-H** + L + ^tBu₃ArO• is a lower limit.

Scheme 4.

Equilibration studies to determine the “effective BDFE” for **1_{red}** + DMAP-H⁺.

N⁺N=Pr_{bbim}.