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# $O_2$ Activation by Bis(imino)pyridine Iron(II)-Thiolate Complexes

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## Abstract

The new iron(II)-thiolate complexes [($^{i\mathrm{Pr}}$BIP)Fe$^{\mathrm{II}}$(SPh)(Cl)] (**1**) and [($^{i\mathrm{Pr}}$BIP)Fe$^{\mathrm{II}}$(SPh)(OTf)] (**2**) (BIP = bis(iminopyridine)) were prepared as models for cysteine dioxygenase (CDO), which converts Cys to Cys-$SO_2H$ at a $(His)_3Fe^{II}$ center. Reaction of **1** and **2** with $O_2$ leads to Fe-oxygenation and S-oxygenation, respectively. For **1** + $O_2$, the spectroscopic and reactivity data, including $^{18}O$ isotope studies, are consistent with an assignment of an iron(IV)-oxo complex as the product of oxygenation ([($^{i\mathrm{Pr}}$BIP)Fe$^{\mathrm{IV}}$(O)(Cl)] (**3**)). In contrast, **2** + $O_2$ results in direct S-oxygenation to give a sulfonato product ($PhSO_3^-$). The positioning of the thiolate ligand in **1** versus **2** appears to play a critical role in determining the outcome of $O_2$ activation. The thiolate ligands in **1** and **2** are essential for $O_2$ reactivity, and exhibit an important influence over the Fe$^{\mathrm{III}}$/Fe$^{\mathrm{II}}$ redox potential.

Determining the factors that govern the activation of dioxygen by both heme and nonheme iron metalloenzymes is of fundamental importance. Mononuclear nonheme iron oxygenases typically contain a 2-His-1-carboxylate ligand set bound to the catalytic iron center. An interesting exception is cysteine dioxygenase (CDO), which utilizes a $(His)_3Fe^{II}(H_2O)$ center to activate $O_2$ and oxidize cysteine to sulfinic acid ($CysSO_2H$), a key metabolic process vital for human health.[1] Despite the importance of CDO from a health perspective, little is known about the mechanism of this dioxygenase.[2] In general, the oxidation of Cys to disulfide, sulfenic acid (Cys(O)H) and other oxidized products has been implicated in oxidative stress response.[3] Thus understanding the fundamental mechanistic pathways of biologically relevant sulfur oxidations is of high current interest.[4]

Although many studies on iron(II) model complexes have yielded key insights into the reactivity of nonheme iron centers, relatively few have involved the use of $O_2$ as the oxidant, in part because of the inherent difficulties with activating and controlling $O_2$.[5] In an earlier report, we described the synthesis of an $N_3S$(thiolate)Fe$^{\mathrm{II}}$ model complex of CDO, which contains the 3 neutral N binding motif found in the enzyme, and reacts with $O_2$ selectively to yield an *S*-oxygenated sulfonato product.[6] The thiolate donor was covalently tethered to a bis(imino)pyridine (BIP) framework, in part to favor *S*-oxygenation as opposed to disulfide formation. To our knowledge, this reaction was the first example of an Fe$^{\mathrm{II}}$-thiolate complex reacting with $O_2$ to give *S*-, as opposed to Fe-oxygenation (e.g., Fe$^{\mathrm{III}}$-O-Fe$^{\mathrm{III}}$ species).[7]

Herein we report the synthesis of two new unsymmetrical Fe$^{\mathrm{II}}$-thiolate BIP complexes, [($^{i\mathrm{Pr}}$BIP)Fe$^{\mathrm{II}}$(SPh)(Cl)] (**1**) and [($^{i\mathrm{Pr}}$BIP)Fe$^{\mathrm{II}}$(SPh)(OTf)] (**2**) ($^{i\mathrm{Pr}}$BIP = 2,6-$(ArN{=}CMe)_2C_5H_3N$), Ar = 2,6-$^{i}Pr_2C_6H_3$), in which the thiolate ligands are not covalently tethered to the BIP framework. The reactivity of these complexes toward $O_2$ has been examined together with non-thiolate-ligated analogs. We show that coordination of the

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**Supporting Information Available:** Experimental procedures and characterization data for **1** – **6**. Details of the X-ray crystallography (PDF) and crystallographic information files of **1**, **2** and **7** (CIF). This material is available free of charge via the Internet at htpp://pubs.acs.org.

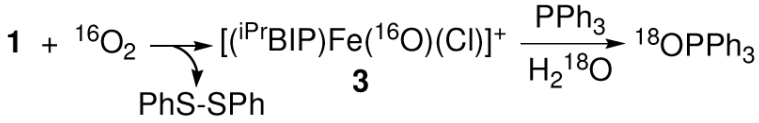
thiolate ligands is crucial for $O_2$ activation by (BIP)$Fe^{II}$. We also show that *S*-oxygenation is possible for a terminal thiolate, and furthermore that the positioning of the thiolate donor specifies the outcome of oxygenation at either sulfur or iron.

Significant efforts have gone into the synthesis and study of (BIP)Fe complexes for their use in $N_2$ activation and catalysis.[8] However, unsymmetrical derivatives of formula [(BIP)$Fe^{II}$(X)(Y)] (X ≠ Y) are scarce. Careful control of stoichiometry, together with the appropriate conditions (solvent, temperature), allowed for the isolation of the monothiolato complexes **1** and **2** (Figure 1). The molecular structures of **1** and **2** reveal 5-coordinate $Fe^{II}$ ions with the desired single terminal thiolate ligands bound to the iron. Bond distances and angles are consistent with high-spin $Fe^{II}$ BIP complexes.[8a,d,e] A distinguishing feature of the structures of **1** and **2** is the positioning of the thiolate ligand. In complex **1**, the $PhS^-$ group sits in a pseudo-axial position in relation to the $N_3Cl$ plane, *trans* to the open coordination site that subtends the obtuse N1-Fe-N3 angle (141.2°). This positioning may be aided by a π-stacking interaction between the pyridine and $PhS^-$ groups. In contrast, the $PhS^-$ ligand of **2** is bound in a pseudo-equatorial arrangement with the $^{i\mathrm{Pr}}$BIP ligand, and is *cis* to the open coordination site.

Both **1** and **2** exhibit relatively sharp, paramagnetically shifted peaks in the $^1$H NMR spectrum ($CD_2Cl_2$) typical of high-spin (BIP)$FeX_2$ complexes, and these spectra are consistent with their solid-state structures. Magnetic susceptibility for **1** measured by Evan's method in $CD_2Cl_2$ gives $\mu_{eff}$ = 5.2 $\mu_B$, close to the spin-only value for a high-spin $Fe^{II}$ (*S* = 2) ion.

Reaction of **1** (10 – 20 mM) with a slight excess of dry $O_2$ (5 equiv) leads to a color change from dark blue to green over the course of 1 h. A decrease of the $\lambda_{max}$ for **1** at 715 nm (ε ~ 4000 $M^{-1}$ $cm^{-1}$) is observed, and a new band for the green species appears at $\lambda_{max}$ 690 nm (ε ~ 1500 $M^{-1}$ $cm^{-1}$) (Figure 2; for time-dependence see Fig. S5). This spectrum is similar to that reported for a closely related bis(imino)pyridine iron(IV)-oxo complex ($\lambda_{max}$ 660 nm, ε ~ 1200 $M^{-1}$ $cm^{-1}$).[9] Analysis by laser-desorption ionization mass spectrometry (LDIMS(+)) reveals a dominant isotopic cluster at *m/z* = 588, whose isotope and fragmentation pattern (Figs. 2, S8 and S9) are consistent with an $Fe^{IV}$(O) complex, [($^{i\mathrm{Pr}}$BIP)$Fe^{IV}$(O)(Cl)]$^+$ (**3**). The thiolate ligand is oxidized to disulfide during the production of **3**, as determined by $^1$H NMR (PhS-SPh, 85%). Introduction of $^{18}O_2$ in place of $^{16}O_2$ causes a shift of two mass units for the LDIMS of **3**, giving *m/z* = 590 (80% $^{18}$O incorporation). Finally, green **3** is EPR-silent (X-band, 15 K). These data are consistent with the assignment of **3** as an $Fe^{IV}$(O) species.

If the reaction of **1** with excess $O_2$ in $CH_2Cl_2$ is carried out in the presence of $PPh_3$ (5 equiv), $OPPh_3$ is produced in good yield (70%, $^{31}$P NMR). Alternatively, formation of green **3**, followed by removal of $O_2$ under vacuum and addition of $PPh_3$ (50 – 300 equiv) under Ar, results in the smooth decay of the peak for **3** at 690 nm (Figure S6). This decay follows good pseudo-first-order behavior, and the rate constants ($k_{obs}$) thus obtained were found to increase linearly with [$PPh_3$], yielding a second-order rate constant of $k_2 = 3.6 \pm 0.3 \times 10^{-3}$ $M^{-1}$ $s^{-1}$ for oxygen-atom-transfer from **3** to $PPh_3$ (Figure S7). This relatively slow reactivity may in part be due to the steric encumbrance imposed by the 2,6-*i*$Pr_2$-$C_6H_3$ substituents. The $^{18}$O-labeled **3** produces $^{18}OPPh_3$ with modest isotopic incorporation ($^{16}$O:$^{18}$O 85:15). However, addition of excess $H_2$ $^{18}$O to the reaction of **3**-$^{16}$O and $PPh_3$ results in a significant increase in the isotopically labeled product $^{18}OPPh_3$ (50% $^{18}$O) (eq 1). These data indicate that the O atom in **3** undergoes facile exchange with exogenous $H_2O$, as seen for other iron terminal oxo species.[10] Although further spectroscopic studies are needed to definitively characterize the structure of **3**, all of the spectroscopic data and reactivity presented here strongly



(1)

support the formulation of **3** as a terminal iron-oxo complex generated from **1** + $O_2$, with the $PhS^-$ ligand undergoing concomitant oxidation to disulfide.

The formation of nonheme $Fe^{IV}(O)$ complexes from $Fe^{II}$ and $O_2$ can be induced by the addition of external co-reductants (e.g. cyclohexene or NADH).[5b,c,e] In the case of **1**, the thiolate ligand functions as a built-in co-reductant to assist in the activation of $O_2$. In comparison, the covalently-tethered thiolate complex $[Fe^{II}(N_3S(\text{thiolate}))(OTf)]$ (**4**) also serves to activate dioxygen, but in this case participation from sulfur leads to direct oxygenation of the *S* atom.[6]

To our surprise, the addition of stoichiometric amounts of $O_2$ to the triflate complex **2** follows a very different oxidation pathway than followed by the chloro analog **1**. An immediate color change from dark blue to brown is noted upon addition of $O_2$, but LDIMS reveals a cluster at *m/z* 694 corresponding to *S-oxygenated* $[Fe^{II}(^{i\text{Pr}}\text{BIP})(PhSO_3)]^+$. Attempts to crystallize $[Fe^{II}(\text{BIP})(PhSO_3)]^+$ have led thus far only to the crystallization of the known $Fe^{II}(^{i\text{Pr}}\text{BIP})(OTf)_2$ complex, but the production of benzenesulfonic acid was readily confirmed by $^1H$ NMR, and quantitation by reverse-phase HPLC after hydrolytic workup gave a yield of 30% for $PhSO_3H$ (based on total Fe). The use of labeled $^{18}O_2$ results in ~90% incorporation of $^{18}O$ into the $PhSO_3^-$ ligand. Despite the fact that the thiolate donor in **2** is not part of a chelate ring, sulfur oxygenation does occur, as seen for the covalently tethered **4**. In contrast, no evidence for $PhSO_3H$ was detected by LDIMS or HPLC for **1** + $O_2$ in control experiments.

The reactivity of the related non-thiolate-ligated complexes $Fe(^{i\text{Pr}}\text{BIP})Cl_2$ (**5**) and $Fe(^{i\text{Pr}}\text{BIP})(OTf)_2$ (**6**) was next examined for comparison with **1** and **2**. These complexes are completely inert toward $O_2$ in both solution (e.g. $CH_2Cl_2$, $CH_3CN$) and the solid-state (eq 2). Addition of $PPh_3$ to oxygenated solutions of **5** and **6** showed no formation of $OPPh_3$. The incorporation of a thiolate donor thus clearly plays a critical role in the activation of $O_2$ by these nonheme iron(II) complexes.

$$[\text{Fe(BIP)}(X)_2] \xrightarrow[CH_2Cl_2]{O_2} \text{no reaction} \qquad X=\text{Cl},\ 5;\ X=\text{OTf},\ 6 \tag{2}$$

The redox potentials of **1**, **2**, **5**, and **6** are compared in Table 1. The thiolate-ligated complexes exhibit significantly lower redox potentials than the non-thiolate analogs, correlating nicely with their relative $O_2$ reactivities. A similar correlation was made for $[Fe^{II}(\text{TMC})(OTf)_2]$ (TMC = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane), which exhibits a solvent-dependent redox potential, and reacts with $O_2$ to give an $Fe^{IV}(O)$ complex only in solvents where $E_{1/2}(Fe^{III/II}) < -0.1$ V (e.g. THF).[5a] Similarly, nonheme iron(II) complexes with more positive $E_{1/2}$ values fail to react with $O_2$ to give oxoiron(IV) species. From Table 1, an $E_{1/2}(Fe^{III/II}) < -0.1$ V appears to be a prerequisite for $O_2$ activation in nonheme iron(II) complexes, and inclusion of a single thiolate donor is sufficient to lower the redox potential of $(^{i\text{Pr}}\text{BIP})Fe^{II}$ complexes into this range. It should be noted that the $E_{1/2}$

values for **1** and **2** remain more than 1 V above the one-electron reduction potential for the $O_2/O_2^-$ couple in organic solvents,[5h] ruling out an outer-sphere mechanism of $O_2$ activation.

Given the structural and electronic similarities between the two thiolate-ligated complexes **1** and **2**, why does their reactivity with $O_2$ follow such dramatically different paths? Scrutiny of the structures of **1** and **2** appears to hold the key. The $PhS^-$ ligand in **1** is bound *trans* to the open site available for $O_2$ binding, whereas it is bound *cis* in **2**. A plausible mechanism for $O_2$ activation in **1** thus begins with coordination of $O_2$ to the open site *trans* to the thiolate donor, followed by electron-transfer from both the iron and sulfur centers to the bound $O_2$ (Scheme 1a). In this case, intramolecular attack of an Fe-$O_2$ intermediate on the sulfur donor would be strongly disfavored by the *trans* orientation of the $PhS^-$ ligand. In contrast, the analogous Fe-($O_2$) intermediate in **2** would be generated *cis* to the thiolate ligand, providing a facile pathway for intramolecular *S*-oxygenation (Scheme 1b). Similarly, the thiolate donor in the covalently-tethered **4** is also found *cis* to the open coordinate on site.

This hypothesis depends upon the feasibility of attaining a 6-coordinate structure with the sterically encumbered BIP ligand in **1** and **2**. For less bulky BIP analogs, where Ar =2,6-$Me_2$-$C_6H_3$, 6-coordinate $Fe^{II}$ complexes are known,[8d] but to our knowledge there are no examples with Ar = 2,6-$^i$Pr$_2$-$C_6H_3$. Thus we were pleased to isolate [$Fe^{II}$($^{iPr}$BIP)$(H_2O)_2(NCCH_3)$](OTf)$_2$ (**7**) as a product from reactions of **2** + $O_2$, whose molecular structure is given in Figure 3. Despite the large steric encumbrance provided by the flanking 2,6-$^i$Pr$_2$$C_6H_3$ substituents, a 6-coordinate geometry is clearly attainable in **7**.

In summary, we have demonstrated that a thiolate donor is essential for the activation of $O_2$ by nonheme iron (BIP)$Fe^{II}$ complexes, and can serve as either a co-reductant or as a site for O-capture. The relative positioning of the $PhS^-$ ligand in relation to the potential $O_2$ binding site appears to play a critical role in determining whether oxygenation occurs at iron or sulfur.[11] It is also shown that *S*-oxygenation can occur for terminal, iron-bound thiolates, contrary to established precedent. It has been proposed that the Cys substrate in CDO coordinates to the Fe center through a chelate ring involving sulfur and the amino group.[1] The findings presented here suggest that this unusual binding mode for Cys is not required for *S*-oxygenation to occur.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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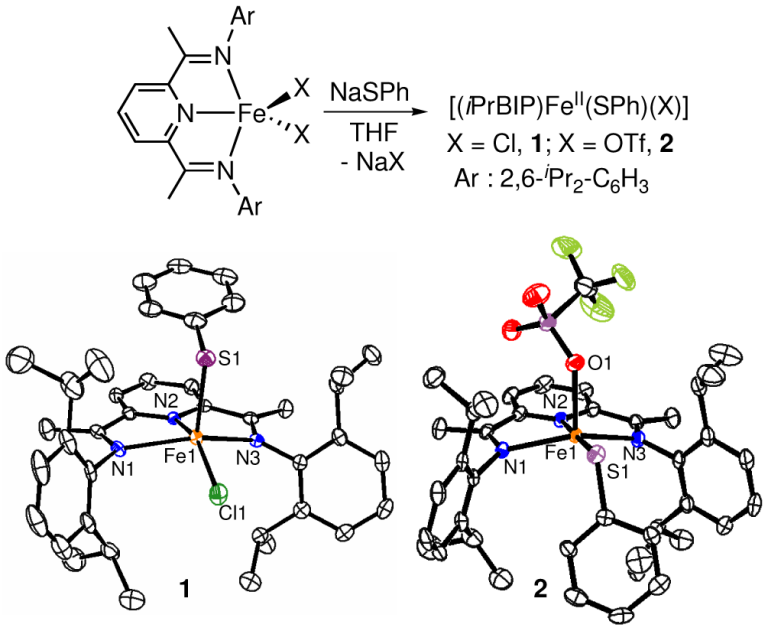



**Figure 1.**
Synthetic scheme and displacement ellipsoid plots (50% probability level) for **1** and **2** at 110 K. H atoms are omitted for clarity.

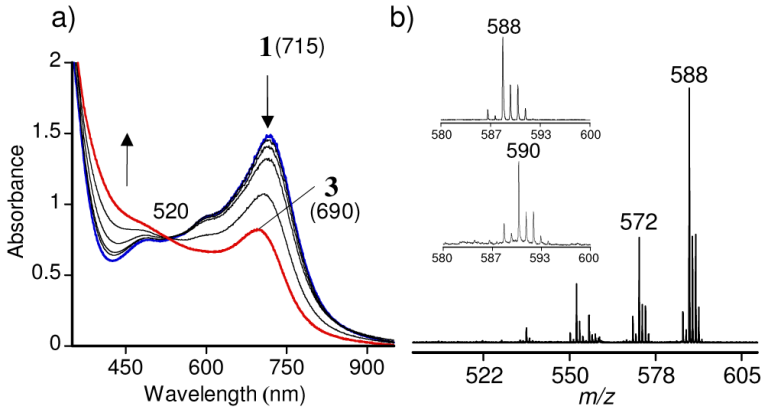



**Figure 2.**

a) UV-vis spectral changes for the reaction of **1** (715 nm, 0.370 mM) with excess $O_2$ in $CH_2Cl_2$, leading to formation of **3** (690 nm). b) LDIMS of **3** formed in the reaction of **1** + $O_2$. Peaks at *m/z* of 588 and 572 correspond to $[(^{iPr}BIP)Fe^{IV}(O)(Cl)]^+$ and $[(^{iPr}BIP)Fe^{II}(Cl)]^+$, respectively. Inset: isotopic cluster for **3** prepared from $^{16}O_2$ (top) and $^{18}O_2$ (bottom).

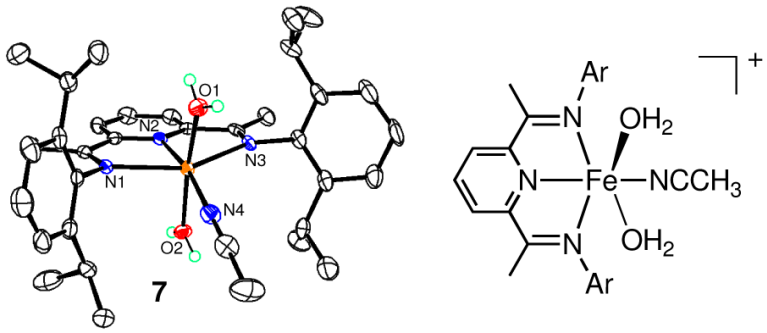
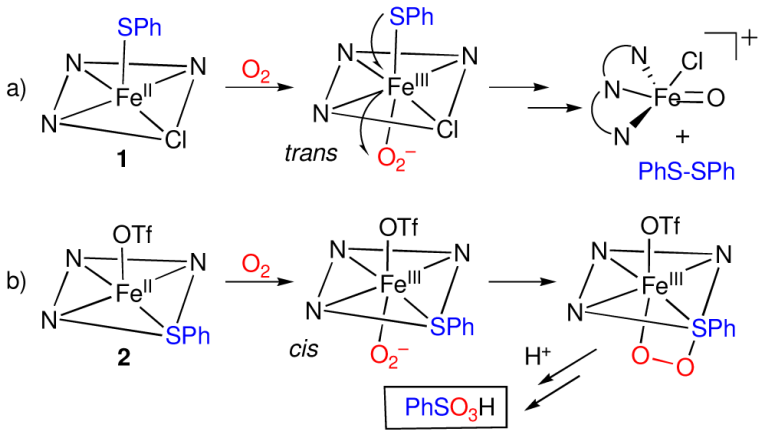



**Figure 3.**

Displacement ellipsoid plots (left, 50% probability level) and molecular structure (right) of **7**. H atoms, except for those attached to the water molecules, and the $OTf^{-}$ ions have been omitted for clarity.




**Scheme 1.**
Proposed mechanisms of $O_2$ activation by **1** and **2**.

## Table 1

Redox potentials for ($^{iPr}$BIP)Fe$^{II}$ and related nonheme Fe$^{II}$ complexes.

| Compound | $E_{1/2}$ ($\Delta E_{pp}$)[a] | $O_2$ reactivity |
|---|---|---|
| [($^{iPr}$BIP)Fe$^{II}$(SPh)(Cl)] **1** | −0.173[b] (0.114) (r) | yes |
| [($^{iPr}$BIP)Fe$^{II}$(SPh)(OTf)] **2** | −0.372[b] (0.149) (r) | yes |
| [($^{iPr}$BIP)Fe$^{II}$(Cl)$_2$] **5** | 0.025[b] (0.153) (r) | no |
| [($^{iPr}$BIP)Fe$^{II}$(OTf)$_2$] **6** | 0.613[b,c] (ir) | no |
| [(TMC)Fe$^{II}$(OTf)$_2$][d] | −0.14[e] (qr) | yes |
| [(TMC)Fe$^{II}$(OTf)$_2$][d] | 0.02[f] (r) | no |
| [(TPA)Fe$^{II}$]$^{2+}$, [d,g] | 0.36[h] (r) | no |

[a] V vs $Fc^+$/Fc; $\Delta E_{pp}$ = peak-to-peak separation; r = reversible, ir = irreversible, qr = quasi-reversible.

[b] In $CH_2Cl_2$, scan rate of 0.1 V/s.

[c] Anodic peak potential.

[d] Ref. 5a.

[e] In MeCN/THF (1:1).

[f] In MeCN/$CH_2Cl_2$ (1:1).

[g] TPA: tris(2-pyridylmethyl)amine.

[h] In neat MeCN.