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Addition of Dioxygen to an N_4S(thiolate) Iron(II) Cysteine Dioxygenase Model Gives a Structurally Characterized Sulfinato–Iron(II) Complex

Alison C. McQuilken, Yunbo Jiang, Maxime A. Siegler, and David P. Goldberg*

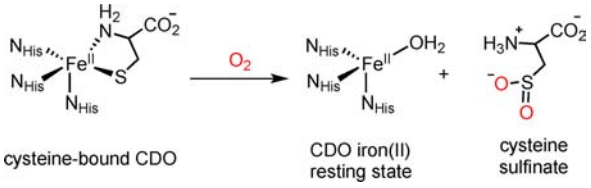
Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland, 21218, United States

Supporting Information

ABSTRACT: The non-heme iron enzyme cysteine dioxygenase (CDO) catalyzes the S-oxygenation of cysteine by O_2 to give cysteine sulfinic acid. The synthesis of a new structural and functional model of the cysteine-bound CDO active site, $[Fe^{II}(N3PyS)(CH_3CN)]BF_4$ (**1**) is reported. This complex was prepared with a new facially chelating 4N/1S(thiolate) pentadentate ligand. The reaction of **1** with O_2 resulted in oxygenation of the thiolate donor to afford the doubly oxygenated sulfinate product $[Fe^{II}(N3PySO_2)(NCS)]$ (**2**), which was crystallographically characterized. The thiolate donor provided by the new N3PyS ligand has a dramatic influence on the redox potential and O_2 reactivity of this Fe^{II} model complex.

Metalloenzymes containing mononuclear non-heme iron centers have been implicated in a variety of biological roles, including the activation of O_2 for substrate oxidation. These non-heme iron oxygenases form a class of enzymes that utilize O_2 for catalytic oxidations and typically consist of a 2-His-1-carboxylate donor set bound to the iron center. Cysteine dioxygenase (CDO), on the other hand, differs from the norm in that its active site consists of a mononuclear high-spin (hs) Fe^{II} center with three His residues bound in a "facial triad" (Scheme 1).[1] Upon substrate binding,[2] CDO utilizes O_2 to catalyze the S-oxygenation of cysteine to cysteine sulfinic acid ($Cys\text{-}SO_2H$), which is essential for the biosynthesis of pyruvate and taurine. This enzyme is also vital for the maintenance of healthy levels of cysteine in the body. While information on the mechanism of O_2 activation in CDO is just emerging,[3a,b] several key X-ray crystal structures of CDO have been determined, including a substrate-bound form in which the Cys is coordinated in a bidentate fashion through the S and NH_2 donors.[1e,3c]

Scheme 1. Sulfur Oxygenation of Cysteine with O_2 by CDO



Mononuclear non-heme iron model complexes have proven beneficial for addressing questions regarding enzyme mechanism, but the use of biologically relevant O_2 as oxidant with these models remains quite rare.[4] We previously described the syntheses of two N_3S(thiolate)Fe^{II} model complexes of CDO that react with O_2 to yield sulfonato products.[5] In one case, the thiolate donor was covalently tethered to the N_3 platform (Figure 1a), whereas in the other, an exogenous arylthiolate ligand was employed. In each of these models, an hs-Fe^{II} center is ligated by three planar N donors from a bis(imino)pyridine (BIP) framework in a distorted square-pyramidal geometry, with a triflate anion occupying the axial position. One finding to result from these studies was that there appears to be a requirement for the S donor to be positioned cis to the potential binding site for O_2 to obtain S-oxygenation. These analogues contain only three N donors bound to the Fe^{II} center, unlike the four N donors ligated in the Cys-bound form of the enzyme.[1e] The three N ligands are also constricted to one plane by the BIP framework, leading to a meridional configuration, unlike the facial arrangement of the three His donors found in CDO. Furthermore, while there was some indirect evidence that S-oxygenation gave sulfinato intermediates in these model systems, the final, isolated S-oxygenated iron complexes were found to be triply oxygenated sulfonato

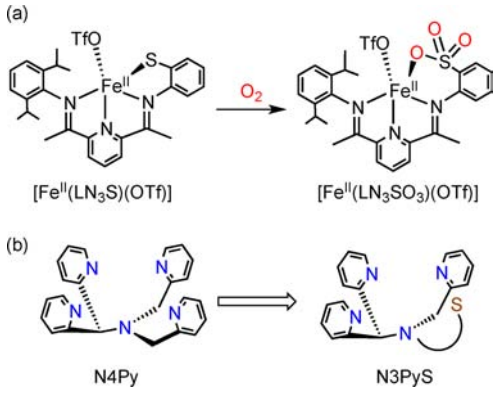


Figure 1. (a) S-oxygenation of a previous CDO model containing a covalently tethered phenylthiolate donor and (b) design of the N3PyS ligand.

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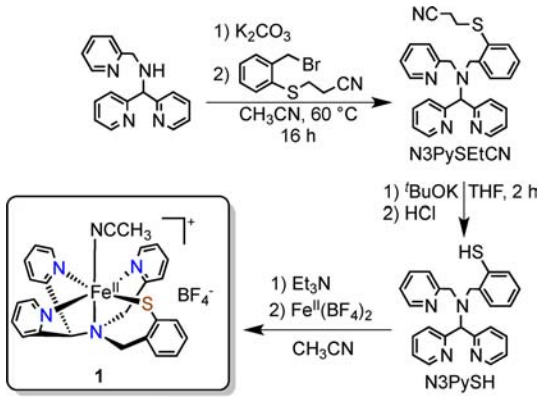
products, reaching a level of oxygenation beyond that observed in the biochemical reaction.

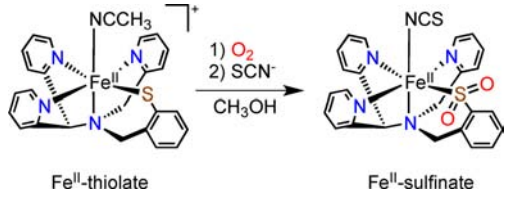
To improve our model design, we set out to prepare a pentadentate N_4S ligand that would be constrained to provide three neutral N donors in a *facial* arrangement along with a fourth N donor to mimic the amino coordination from Cys and a single S donor held cis to the putative O_2 binding site at the metal center. The N4Py ligand established previously for non-heme iron models (Figure 1b)[6] appeared to be an ideal scaffold for building the desired N_4S system. The pentadentate N4Py ligand has a rigid structure that binds Fe^{II} in a square-pyramidal fashion, and it has allowed for the characterization and isolation of several key Fe−O [e.g., Fe═O, Fe−OO(H)] intermediates. These beneficial properties have provided motivation for the synthesis of derivatives of the N4Py ligand by several groups, but to date none of these efforts has led to the incorporation of a thiolato donor.[7] Herein we report the synthesis of a new pentadentate ligand, N3PySH, and its corresponding Fe^{II} complex $[Fe^{II}(N3PyS)(CH_3CN)]BF_4$ (**1**) (Scheme 2). We

Scheme 2. Synthesis of N3PySH and 1



also show that **1** reacts with O_2 via sulfur oxygenation to generate the doubly oxygenated sulfinato complex, $[Fe^{II}(N3PySO_2)]^+$ (Scheme 3). Thus, **1** is a close structural

Scheme 3. O_2 Reactivity of $[Fe^{II}(N3PyS)(CH_3CN)]^+$ in CH_3OH



and functional model of CDO and provides a rare example of the reaction of an Fe^{II}−thiolate complex with O_2 to give a sulfinato complex. This product was characterized by X-ray crystallography and is to our knowledge the first example of a structurally characterized mononuclear Fe^{II}−sulfinate complex.

Reaction of the protected phenylthiolate 3-(2-bromomethylphenylsulfanyl)propionitrile ($BrCH_2PhSEtCN$)[8] with *N*-[di(2-pyridinyl)methyl]-*N*-(2-pyridinylmethyl)amine[7c] in the presence of K_2CO_3 at 60 °C in CH_3CN afforded the protected pentadentate ligand N3PySEtCN (Scheme 2). Addition of ^{t}BuOK in THF yielded the deprotected ligand N3PySH in moderate yield (43%) after workup. Addition of $Fe^{II}(BF_4)_2$ to N3PySH in CH_3CN in the presence of 1 equiv of Et_3N afforded the dark-red Fe^{II} complex $[Fe^{II}(N3PyS)(CH_3CN)]BF_4$ (**1**). X-ray quality crystals were grown by vapor diffusion of Et_2O into a solution of **1** in CH_3CN. The X-ray structure of **1** reveals that the pentadentate ligand is bound in a pseudo-square-pyramidal geometry about the Fe^{II} center as designed, with the phenylthiolate donor held cis to the sixth site occupied by a labile CH_3CN ligand (Figure 2). The four neutral N plus one thiolate donor motif corresponds closely to the cysteine-bound active site of CDO.

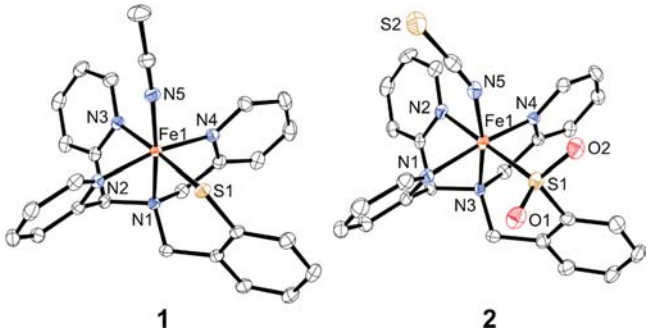


Figure 2. Displacement ellipsoid plots (50% probability level) of the cation of **1** and complex **2**. H atoms have been omitted for clarity.

The Fe−N bond distances [av Fe−N_{py} = 1.9594(13) Å] in **1** are consistent with those in low-spin (ls) Fe^{II} complexes utilizing pyridyl ligands.[6a,9] Likewise, the Fe−S distance [2.3018(4) Å] is consistent with those in other Fe^{II}−thiolate complexes.[5a,b,10] The diamagnetic ^{1}H NMR spectrum in CD_3CN is characteristic of ls-Fe^{II}. In CH_3CN, intense UV−vis features at 325, 418, and 493 nm (ε = 4475, 4550, and 4820 M^{-1} cm^{-1}, respectively) were observed (Figure S1a in the Supporting Information). In CH_3OH, however, **1** is converted to an hs-Fe^{II} complex, as indicated by the solution-state magnetic moment (μ_{eff} = 4.5 μ_B, Evans method) and less-intense UV−vis bands (Figure S1b). We conclude that CH_3OH, a relatively weak-field ligand, likely displaces CH_3CN in the labile site of **1**, providing a convenient switch for accessing the biologically relevant hs-Fe^{II} state that mimics resting CDO.

Addition of excess O_2 to a methanolic solution of hs-**1** results in an immediate color change from the dark-brown of **1** (470 nm, 1000 M^{-1} cm^{-1}) to a new deep-green (674 nm, 1300 M^{-1} cm^{-1}) (Figure S3). Efforts to obtain X-ray quality crystals of this green species for characterization have to date been unsuccessful. However, preliminary experiments suggested that this species may be an S-oxygenated intermediate (see below). To isolate a crystalline product, SCN^- was added as a potentially good ligand for the labile site on the iron product. Immediately upon addition of 1 equiv of KSCN, the green solution turned brown. Vapor diffusion of iPr_2O resulted in the isolation of orange-red crystals of **2** in 6 days. Determination of the structure of **2** by X-ray crystallography (Figure 2) revealed an ls-Fe^{II} complex wherein the chelated S atom has been doubly oxygenated to give the sulfinate product and a thiocyanate anion has replaced the CH_3CN ligand in **1**.

The average Fe−N distance in **2** [1.971(3) Å] is consistent with those in other ls-Fe^{II} complexes and only slightly larger than that in **1**. The Fe−S bond distance [2.1812(9) Å] decreased upon S-oxygenation, consistent with the decrease in other metal−sulfur (M−S) bond lengths observed upon S-

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oxygenation.[11a−e] The reduction in the M−S bond length in going from the thiolate to the sulfinate donor corresponds to both the contraction in the size of the S atom in the sulfinate due to the increase in the formal oxidation state and the elimination of the repulsive interaction between the metal's filled d orbitals and the S lone pairs on the thiolate donor. The S−O distances [S1−O1 = 1.488(2) Å, S1−O2 = 1.476(2) Å] match other sulfinate bond lengths.[11] Spectroscopic characterization of crystalline **2** in CH_3CN showed two intense UV−vis bands at 380 and 451 nm (ε = 4600 and 4200 M^{-1} cm^{-1}, respectively; Figure S2), similar to the spectrum of **1** in CH_3CN. The attenuated total reflectance IR spectrum of neat **2** revealed two prominent peaks at 1129 and 1012 cm^{-1}, which fall in the observed range for metal−sulfinate complexes,[11] and we assign these bands to the asymmetric and symmetric S−O stretching modes. Thus, addition of O_2 to CDO model **1** led to the isolation and characterization of an Fe^{II}−sulfinate complex wherein the thiolate donor was doubly oxygenated in a manner parallel with the enzymatic chemistry. Although there are a few examples of structurally characterized Fe^{III}−sulfinate complexes,[11f,12] **2** is to our knowledge the first example of a crystallographically characterized mononuclear Fe^{II}−sulfinate complex.

The influence of the thiolate donor on non-heme iron active sites is of fundamental interest, and the N3PySH ligand provided us with an ideal system to address this issue by comparison with the all-nitrogen N4Py analogue. Complex **1** and $[Fe^{II}(N4Py)]^{2+}$ show a dramatic difference in O_2 reactivity: **1** reacts with O_2 without the use of added reductants, whereas $[Fe^{II}(N4Py)]^{2+}$ reacts with O_2 only in the presence of 1-benzyl-1,4-dihydronicotinamide (BNAH) to give $[(N4Py)Fe^{III}(OOH)]^{2+}$.[13] As we have reported, a prerequisite for O_2 reactivity is $E_{1/2}(Fe^{III/II}) < -0.1$ V vs Fc^+/Fc.[5b] Cyclic voltammetry of **1** in CH_3CN showed a single quasi-reversible wave at −0.226 V vs Fc^+/Fc (Figure S4a), which we assign to the $Fe^{III/II}$ couple. This potential is shifted significantly more negative relative to the same couple for the non-thiolate analogue $[Fe^{II}(N4Py)]^{2+}$ ($E_{1/2}$ = +0.61 V vs Fc^+/Fc in CH_3CN).[14] These results show that replacement of a pyridyl donor with a single thiolate ligand causes a dramatic cathodic shift of over 800 mV relative to N4Py. The redox potential of **1** was also measured in CH_3OH, where two quasi-reversible waves at $E_{1/2}$ = −233 and −583 mV vs Fc^+/Fc were found. The former is assigned to some CH_3CN-bound **1** that remains in equilibrium with the methanol complex, and the latter is assigned to the $Fe^{III/II}$ couple of the hs CH_3OH-bound **1**, which clearly falls well within the previously noted range for O_2 reactivity. As expected, the redox potential for **2** (−0.001 V; Figure S4b) is shifted more positive than **1** by 225 mV, consistent with less electron donation from the S-bound sulfinate group. However, the $E_{1/2}$ value for S-bound **2** remains significantly more negative than that for $[Fe^{II}(N4Py)]^{2+}$.

Isotope labeling studies with $^{18}O_2$ were conducted to gain insight into the mechanism of the reaction of **1** with O_2. Analysis of reaction mixtures with natural-abundance O_2 by electrospray ionization mass spectrometry (ESI-MS) revealed a prominent isotopic cluster centered at m/z 581.7 that can be assigned to $[(K)(Fe^{II}(N3PyS^{16}O_2)(NCS))]^+$ ($[M + K]^+$; Figure 3). When the reaction was run with $^{18}O_2$ (98% isotope-enriched), a shift in the isotopic pattern was observed. Simulations of this pattern indicated that 14% of the Fe^{II}−sulfinate complex contained one labeled O atom ($S^{16}O^{18}O$), while ∼2% of the product was labeled in both O positions

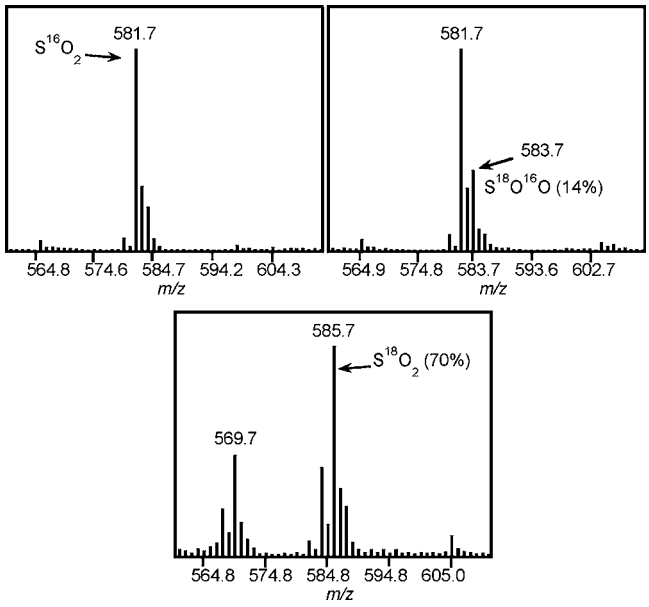
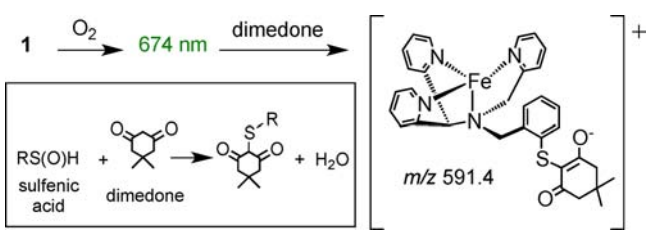


Figure 3. ESI-MS spectra after the reaction of **1** with (top left) O_2, (top right) $^{18}O_2$, and (bottom) $O_2/H_2{}^{18}O$.

($S^{18}O_2$). These results suggest that O_2 is a source of O atoms for the S-oxygenation but that significant exchange with exogenous H_2O during the course of the reaction is likely. To test this idea, the reaction was carried out using $H_2{}^{18}O$ (50 μL). Subsequent ESI-MS analysis revealed 70% $S^{18}O_2$ and 28% $S^{16}O^{18}O$, suggesting that the O atoms in the sulfinate complex are susceptible to exchange during S-oxygenation. However, independent experiments with pure **2** and $H_2{}^{18}O$ revealed that the O atoms of the ls Fe^{II}−sulfinate complex are *not exchangeable* with $H_2{}^{18}O$ under the same conditions (data not shown). Thus, the isotope labeling results implicate one or more intermediates in the S-oxygenation pathway that undergo facile O exchange with H_2O. One such intermediate could be a monooxygenated sulfenato−iron species. Sulfenato−metal [RS(O)−M] complexes are rare but have been shown to undergo facile O-atom exchange with H_2O.[15]

Given these results, we speculated that the green intermediate (674 nm) may contain a singly oxygenated sulfenate donor. In previous studies, it has been shown that dimedone reacts selectively with sulfenic acids but not thiols or sulfinic acids.[16] Addition of dimedone (50 equiv) caused the complete decay of the band at 674 nm over 2 h. MS analysis revealed a major peak at m/z 591.4, corresponding to [Fe−N3PyS−dimedone − H]$^+$, the product expected from the reaction of dimedone with a sulfenic acid group (Scheme 4). Metal sulfenates are also known to react with PR_3.[17] Anaerobic addition of PPh_3 (2 equiv) to the green intermediate resulted in a color change to brown and the production of $OPPh_3$ (50%,

Scheme 4. Reaction of Dimedone with the Green Species



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^{31}P NMR, based on total Fe). Addition of $H_2{}^{18}O$ to the green intermediate followed by reaction with PPh_3 led to 49% ^{18}O-labeled $OPPh_3$. In contrast, sulfinato complex **2** did not react with either dimedone or PPh_3 under the same conditions. These data are consistent with the presence of a sulfenato−iron intermediate containing an exchangeable O atom, although the presence of other intermediates at this stage, including doubly oxygenated sulfinato species, cannot be ruled out.

In summary, we have reported the synthesis of a novel N_4S(thiolate) ligand that functions as designed to give $[Fe^{II}(N3PyS)]^+$, a structural analogue of substrate-bound CDO. The incorporation of a single thiolate donor into the coordination sphere to mimic the Cys sulfur ligation in the enzyme was critical for the reactivity of the Fe^{II} complex with O_2. In contrast, the all-N analogue N4Py is completely inert to O_2 in the absence of coreductants. The present findings, in comparison with those for our previous CDO model complexes, suggest that a *facial* arrangement of the N donors about the Fe^{II} center biases the O_2 reactivity toward production of the biologically relevant sulfinato product. Although more work is needed to understand the mechanism of S-oxygenation of **1**, the preliminary data suggest that the O_2 addition proceeds through monooxygenase-like steps, as indicated by calculations for the CDO mechanism.[3b]

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, spectra, electrochemical data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

dpg@jhu.edu

Notes

The authors declare no competing financial interest.

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