

Addition of Dioxygen to an N₄S(thiolate) Iron(II) Cysteine Dioxygenase Model Gives a Structurally Characterized Sulfinato–Iron(II) Complex

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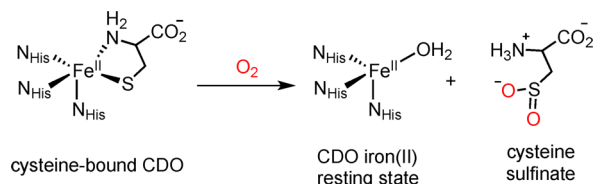
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S Supporting Information

ABSTRACT: The non-heme iron enzyme cysteine dioxygenase (CDO) catalyzes the S-oxygenation of cysteine by O₂ to give cysteine sulfinic acid. The synthesis of a new structural and functional model of the cysteine-bound CDO active site, [Fe^{II}(N3PyS)(CH₃CN)]BF₄ (**1**) is reported. This complex was prepared with a new facially chelating 4N/1S(thiolate) pentadentate ligand. The reaction of **1** with O₂ resulted in oxygenation of the thiolate donor to afford the doubly oxygenated sulfinato product [Fe^{II}(N3PySO₂)(NCS)] (**2**), which was crystallographically characterized. The thiolate donor provided by the new N3PyS ligand has a dramatic influence on the redox potential and O₂ 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 O₂ for substrate oxidation. These non-heme iron oxygenases form a class of enzymes that utilize O₂ 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 O₂ to

Scheme 1. Sulfur Oxygenation of Cysteine with O₂ by CDO



catalyze the S-oxygenation of cysteine to cysteine sulfinic acid (Cys-SO₂H), 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 O₂ 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 NH₂ donors.^{1e,3c}

Mononuclear non-heme iron model complexes have proven beneficial for addressing questions regarding enzyme mechanism, but the use of biologically relevant O₂ as oxidant with these models remains quite rare.⁴ We previously described the syntheses of two N₃S(thiolate)Fe^{II} model complexes of CDO that react with O₂ to yield sulfinato products.⁵ In one case, the thiolate donor was covalently tethered to the N₃ platform (Figure 1a), whereas in the other, an exogenous arylthiolate

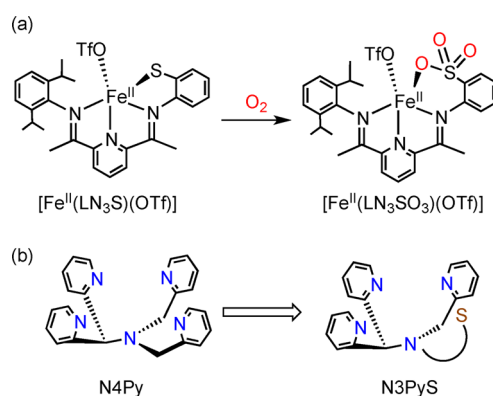


Figure 1. (a) S-oxygenation of a previous CDO model containing a covalently tethered phenylthiolate donor and (b) design of the N3PyS ligand.

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 O₂ 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 sulfinato

Received: March 2, 2012

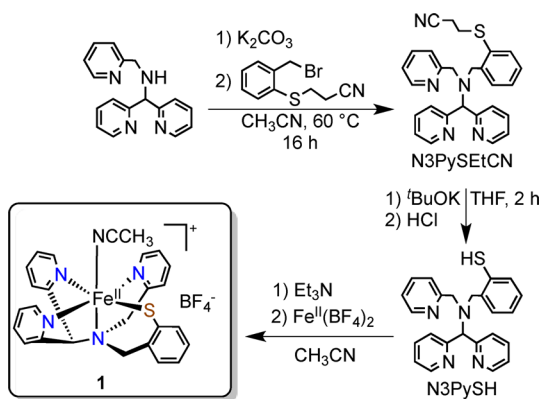
Published: May 11, 2012



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

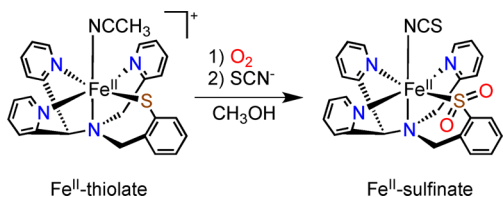
To improve our model design, we set out to prepare a pentadentate N₄S ligand that would be constrained to provide three neutral N donors in a *facial* arrangement along with a fourth N donor to mimic the amino coordination from Cys and a single S donor held cis to the putative O₂ binding site at the 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 N₄S 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)(CH₃CN)]BF₄ (**1**) (Scheme 2). We

Scheme 2. Synthesis of N3PySH and **1**



also show that **1** reacts with O₂ via sulfur oxygenation to generate the doubly oxygenated sulfinato complex, [Fe^{II}(N3PySO₂)]⁺ (Scheme 3). Thus, **1** is a close structural

Scheme 3. O₂ Reactivity of [Fe^{II}(N3PyS)(CH₃CN)]⁺ in CH₃OH



and functional model of CDO and provides a rare example of the reaction of an Fe^{II}–thiolate complex with O₂ 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 (BrCH₂PhSEtCN)⁸ with *N*–[di(2-pyridinyl)methyl]–*N*–(2-pyridinylmethyl)amine^{7c} in the presence of K₂CO₃ at 60 °C in CH₃CN afforded the protected pentadentate ligand N3PySEtCN (Scheme 2). Addition of ^tBuOK in THF yielded the deprotected ligand N3PySH in moderate yield (43%) after workup. Addition of

Fe^{II}(BF₄)₂ to N3PySH in CH₃CN in the presence of 1 equiv of Et₃N afforded the dark-red Fe^{II} complex [Fe^{II}(N3PyS)(CH₃CN)]BF₄ (**1**). X-ray quality crystals were grown by vapor diffusion of Et₂O into a solution of **1** in CH₃CN. 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 CH₃CN ligand (Figure 2). The four neutral N plus one thiolate donor motif corresponds closely to the cysteine-bound active site of CDO.

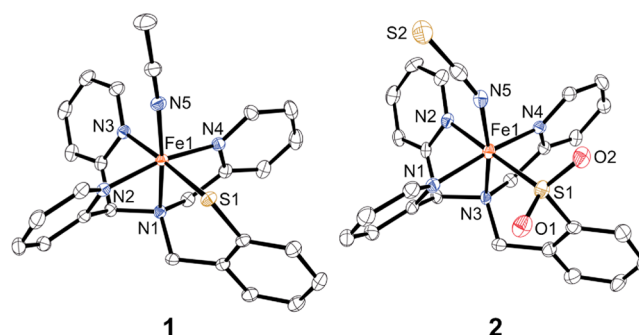


Figure 2. Displacement ellipsoid plots (50% probability level) of the cation of **1** and complex **2**. H atoms have been omitted for clarity.

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 ¹H NMR spectrum in CD₃CN is characteristic of ls-Fe^{II}. In CH₃CN, 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 CH₃OH, 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 CH₃OH, a relatively weak-field ligand, likely displaces CH₃CN 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 O₂ 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 *i*Pr₂O 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 sulfinato product and a thiocyanate anion has replaced the CH₃CN 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-

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 CH₃CN 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 CH₃CN. 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 O₂ 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 O₂ reactivity: **1** reacts with O₂ without the use of added reductants, whereas [Fe^{II}(N4Py)]²⁺ reacts with O₂ 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 O₂ reactivity is $E_{1/2}(\text{Fe}^{\text{III/II}}) < -0.1$ V vs Fc⁺/Fc.^{5b} Cyclic voltammetry of **1** in CH₃CN 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 CH₃CN).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 CH₃OH, where two quasi-reversible waves at $E_{1/2}$ = −233 and −583 mV vs Fc⁺/Fc were found. The former is assigned to some CH₃CN-bound **1** that remains in equilibrium with the methanol complex, and the latter is assigned to the Fe^{III/II} couple of the *hs* CH₃OH-bound **1**, which clearly falls well within the previously noted range for O₂ 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 ¹⁸O₂ were conducted to gain insight into the mechanism of the reaction of **1** with O₂. Analysis of reaction mixtures with natural-abundance O₂ 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}(N3PyS¹⁶O₂)(NCS))]⁺ ([M + K]⁺; Figure 3). When the reaction was run with ¹⁸O₂ (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 (S¹⁶O¹⁸O), while ~2% of the product was labeled in both O positions

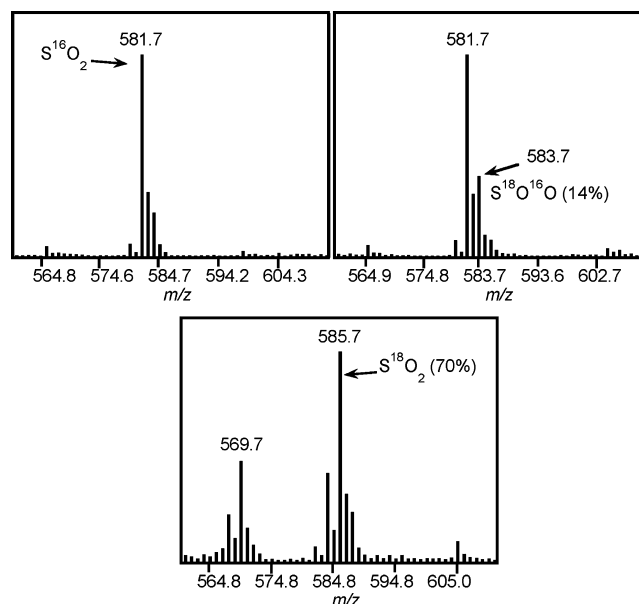
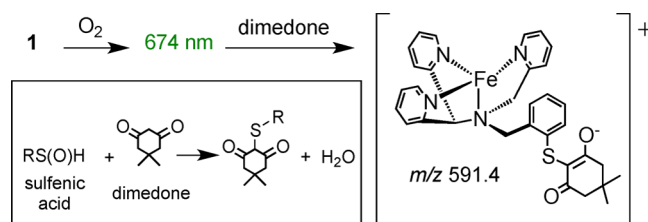


Figure 3. ESI-MS spectra after the reaction of **1** with (top left) O₂, (top right) ¹⁸O₂, and (bottom) O₂/H₂¹⁸O.

(S¹⁸O₂). These results suggest that O₂ is a source of O atoms for the S-oxygenation but that significant exchange with exogenous H₂O during the course of the reaction is likely. To test this idea, the reaction was carried out using H₂¹⁸O (50 μL). Subsequent ESI-MS analysis revealed 70% S¹⁸O₂ and 28% S¹⁶O¹⁸O, suggesting that the O atoms in the sulfinate complex are susceptible to exchange during S-oxygenation. However, independent experiments with pure **2** and H₂¹⁸O revealed that the O atoms of the *ls* Fe^{II}–sulfinate complex are *not exchangeable* with H₂¹⁸O 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 H₂O. 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 H₂O.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 PR₃.¹⁷ Anaerobic addition of PPh₃ (2 equiv) to the green intermediate resulted in a color change to brown and the production of OPPh₃ (50%,

Scheme 4. Reaction of Dimedone with the Green Species



^{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 $[\text{Fe}^{\text{II}}(\text{N3PyS})]^+$, 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>.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The NIH (GM62309) is gratefully acknowledged for financial support, and Y.J. is grateful for the Ernest M. Marks Fellowship.

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