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Asymmetric Oxygenation of a Ruthenium Dithiolate Mimics the Mixed Sulfenato/Sulfinato Donor Sets of Nitrile Hydratase and Thiocyanate Hydrolase

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The dithiolate complex (bmmp-TASN)RuPPh$_3$ reacts with O_2 under limiting conditions to yield the mixed sulfenato/sulfinato product (bmmp-O_3-TASN)RuPPh$_3$ in 82% yield. Isotopic labeling studies confirm O_2 as the sole source of O atoms in the product complex. X-ray crystallographic studies reveal decreases in the Ru−S bond distances of 0.026(1) and 0.151(1) Å for the sulfenato and sulfinato donors, respectively, and a 0.088(1) Å increase in the Ru−PPh$_3$ bond distance upon oxygenation.

The active sites of nitrile hydratase (NHase)[1,2] and thiocyanate hydrolase (SCNase)[3] share a common asymmetric sulfenato (RSO^-)/sulfinato (RSO_2^-) donor set that results from sulfur oxygenation of metal-coordinated cysteine thiolates under aerobic conditions. Small-molecule studies provide numerous examples of metal sulfinates prepared upon O_2 oxidation, but metal sulfenates are scarce because they tend to oxidize further. Consequently, only three mixed sulfenato/sulfinato complexes have been structurally reported.[4−6] Of these, the only one isolated from aerobic oxidation is a sulfenic acid (RSOH)/sulfinate derivative of $[Ru(DPPBT)_3]^-$ (DPPBT = 2-diphenylphosphinobenzenethiolate) for which no yield is reported.[5] A more biologically relevant (N_3S_2)Co example reported by Kovacs et al. is readily isolated by H_2O_2 oxidation of the sulfinato precursor due to η^2-coordination of the sulfenate, which prevents further reactivity but does not mimic coordination of the active sites.[4] Herein, we report oxygenation of the ruthenium(II) complex (bmmp-TASN)-RuPPh$_3$ (**1**) under limiting O_2 conditions to directly yield a sulfenato/sulfinato derivative with η^1-S-coordination of the oxygenated ligands (**2**; Scheme 1).

Previously, we reported (bmmp-TASN)FeCl and its derivatives as synthetic models of NHase.[7,8] These complexes display spin-state-dependent oxygen sensitivity with the high-spin chloro derivative degrading to disulfide and iron−oxo clusters, while the low-spin cyano complex undergoes sulfur oxygenation, yielding an insoluble disulfonate ($(RSO_3^-)_2$) product.[9,10] As such, we prepared the low-spin ruthenium(II) derivative **1** and explored its O_2 sensitivity.

Complex **1** is isolated from $RuCl_2(PPh_3)_3$ and H_2(bmmp-TASN) upon deprotonation of the ligand in tetrahydrofuran as an air- and water-stable orange solid. In a O_2-saturated solution, **1** reacts within 96 h to yield an intractable brown product with an FT-IR spectrum (Figure S2 in the Supporting Information) reminiscent of our previously reported iron disulfonate derivative.[9] Repeated attempts to isolate analytically pure samples from this product mixture were unsuccessful. This "overoxygenated" product can be avoided by limiting the quantity of O_2 and the reaction time.

In the O_2 limited reactions, ~5 equiv of O_2 were added to a solution of **1** under an argon atmosphere. After 12 h, the solvent was removed under vacuum. The solid residue was dissolved in methanol, which yielded crystals of the sulfenato/sulfinato derivative **2** in 82% yield upon slow evaporation under air-free conditions. Additional air or O_2 exposure results in complex degradation. While limiting the quantity of O-atom-transfer reagents is a common tactic in attempts to obtain partially sulfur-oxygenated derivatives of metal thiolates,[6] intentionally limiting the O_2 supply for their controlled oxygenation has not been exploited. The importance of limiting O_2/metal thiolate interactions to achieve partial oxygenation was suggested by the results with $[Ru(DPPBT)_3]^-$. When suspensions of $[Ru(DPPBT)_3]^-$ as the poorly soluble $HNEt_3^+$ salt were exposed to air, the mixed sulfenic acid/sulfinato product was obtained.[5] However,

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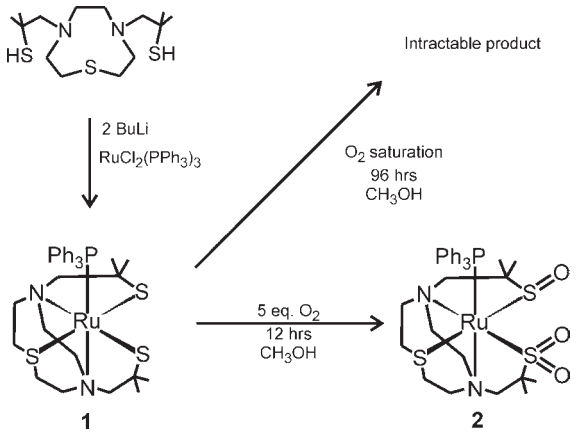
Scheme 1. Synthetic Pathways for **1** and **2**



homogeneous solutions of the complex as the PPN^+ salt reproducibly yield the disulfinato derivative.[11] As an additional example, the product distribution of singlet oxygen addition to an (N_2S_2)Ni complex shifts toward the sulfenato/sulfinato derivative as the complex concentration increases and the relative O_2 concentration decreases.[12]

Isotopic labeling studies employing $^{18}O_2$ confirm O_2 as the O-atom source in the conversion of **1** to **2**. The difference IR spectrum of **1** and **2** prepared with $^{16}O_2$ (Figure 1a) displays intense bands at 1140 and 1020 cm^{-1} attributed to the asymmetric and symmetric S=O stretches of the sulfinato donor. These bands shift by 45 and 38 cm^{-1} to 1095 and 982 cm^{-1}, respectively, for samples of **2** prepared with $^{18}O_2$ (Figure 1b). The isotopic shifts are larger than those observed for ^{34}S-labeled NHase[13] but consistent with a simple harmonic oscillator approximation and other ^{18}O-labeled metal sulfinates.[14,15] The weak sulfenato S=O stretch of **2** cannot be assigned. The sulfenato stretching band was also not able to be discerned in ^{34}S-labeled NHase. Our IR studies clearly show O_2 as the source of the sulfinato O atoms. To confirm O_2 as the source of all of the O atoms in **2**, (+)ESI-MS was recorded (Figure S4 in the Supporting Information).

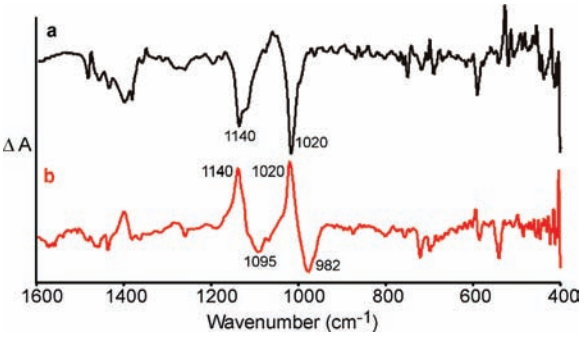


Figure 1. FT-IR difference spectra highlighting the $^{18}O_2$-sensitive sulfinato stretching frequencies of (a) **1** and **2** prepared under $^{16}O_2$ (black line) and (b) **2** prepared under $^{16}O_2$ and $^{18}O_2$ (red line).

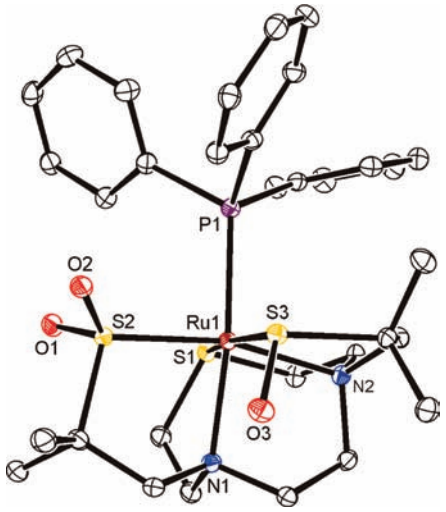


Figure 2. ORTEP representation of **2** showing 40% probability ellipsoids. H atoms and methanol solvates have been omitted to clearly illustrate the asymmetric oxygenation of S2 and S3. Selected bond distances are provided in Table 1.

Samples of **2** prepared with $^{16}O_2$ display a parent peak at m/z 731.1138 that shifts to m/z 737.1267 in samples prepared with $^{18}O_2$.

X-ray crystallographic analyses of **1** and **2** reveal similar $(N_2S_3)RuPPh_3$ donor environments.[16] As shown in the ORTEP representations of **1** and **2** (Figure S5 in the Supporting Information and Figure 2, respectively), both complexes display a facially coordinated TASN ring (N1, N2, and S1), two pendant sulfur donors (S2 and S3), and triphenylphosphine (P1). The two O atoms O1 and O2 of the sulfinato donor (S2) of **2** are directed roughly along the S1−Ru−S3 bond axis with torsion angles of −12.63(12) and +35.55(13)° for O1−S2−Ru1−S1 and O2−S2−Ru1−S3, respectively. The sulfenato oxygen (O3) is oriented toward N1 along the P1−Ru−N1 axis with an O3−S3−Ru1−N1 torsion angle of −16.47(14)°. As shown in Figure 3, the triphenylphosphine donor restricts access to the remaining potential oxygenation site on S3, which may retard the rate of further oxygenation under limited O_2.

Sulfur oxygenation significantly influences bond distances in the first coordination sphere of ruthenium (Table 1). The Ru−S bond distances to the oxygenated sulfur donors S2 and S3 are shorter in **2** than in **1**. The $Ru-S_{sulfinate}$, Ru−S2, bond distance decreases by 0.151(1) Å, while the $Ru-S_{sulfenate}$ bond distance, Ru−S3, shortens by only 0.026(1) Å.

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(16) Crystal data for **1**: orange block, monoclinic, space group $P2_1/n$, a = 11.085(4) Å, b = 16.885(6) Å, c = 16.110(6) Å, α = 90°, β = 95.848(6)°, γ = 90°, V = 2999.7(19) $Å^3$, ρ_{calcd} = 1.514 Mg/m^3, Z = 4. Data were collected on a Bruker SMART APEX CCD using Mo Kα radiation. For all 6966 unique reflections [R(int) = 0.0319], the final anisotropic full-matrix least-squares refinement on F^2 for 356 variables converged at R1 = 0.0490, wR2 = 0.0738 with a GOF of 1.058. Crystal data for **2**: yellow plate, triclinic, space group $P\bar{1}$, a = 9.0426(5) Å, b = 10.4315(6) Å, c = 19.8314(11) Å, α = 80.6320(10)°, β = 88.2470(10)°, γ = 70.8840(10)°, V = 1743.41(17) $Å^3$, ρ_{calcd} = 1.509 Mg/m^3, Z = 2. Data were collected on a Bruker SMART APEX CCD using Mo Kα radiation. For all 7795 unique reflections [R(int) = 0.0327], the final anisotropic full-matrix least-squares refinement on F^2 for 427 variables converged at R1 = 0.0605, wR2 = 0.1139 with a GOF of 1.074. CCDC 767263 for **1** and CCDC 767264 for **2** contain the supplementary crystallographic data for this paper. Data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request.cif.

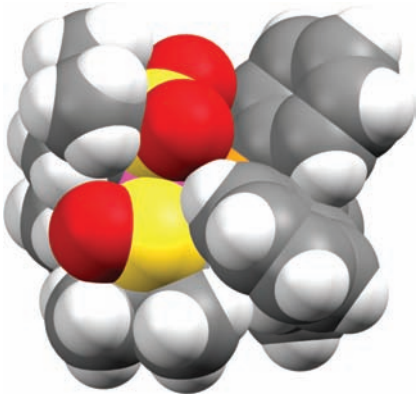

Figure 3. Space-filling representation of **2** illustrating the steric crowding imposed by the phenyl substituents around the sulfenato sulfur, S3.

The decrease in the M−S bond distance has previously been attributed to the elimination of a four-electron dπ−pπ antibonding interaction as the thiolate S atoms lose their π-donating electrons upon oxygenation.[6,17,18] Consistent with this explanation, **2** displays significantly longer bond distances to its π-accepting ligands than **1**. The Ru−P1 bond distance to the triphenylphosphine increases by 0.088(1) Å, and the $Ru-S_{thioether}$, Ru−S1, bond distance similarly increases by 0.072(1) Å. This is similar to a recent theoretical prediction by Mascharak et al. of a 0.023 Å increase in the Fe−NO bond distance upon sulfur oxygenation of a dithiolatoiron nitrosyl.[25] The average S−O distance for the sulfinate, S2, of 1.48 Å falls in the usual range (1.42−1.48 Å).[4,14,19] The sulfenato S−O bond is more polarized, resulting in a longer S−O distance of 1.556(3) Å, which also lies in the typical range (1.50−1.60 Å)[4,14,20,21]

The polarized S−O bond of the sulfenate has been suggested as a nucleophile for nitrile hydrolysis.[18] Previously, Chottard et al. reported the slow, catalytic (18 turnovers after 17 h) hydrolysis of acetonitrile by a coordinately saturated, exchange-inert cobalt(III) sulfenate.[22] Attempts to hydrolyze acetonitrile with **2** following the same protocol yielded no quantifiable acetamide. This may be attributed to steric influences of the PPh_3 ligand or the reduced Lewis acidity of ruthenium(II) in **2** as compared to cobalt(III) in the Chottard system.

Table 1. Selected Bond Distances (Å) for **1** and **2**

	1	**2**
Ru1−S1	2.2900(10)	2.3622(9)
Ru1−S2	2.4057(9)	2.2548(9)
Ru1−S3	2.3754(10)	2.3493(9)
Ru1−P1	2.2911(10)	2.3790(9)
Ru1−N1	2.198(2)	2.178(3)
Ru1−N2	2.178(2)	2.192(3)
S2−O1		1.489(3)
S2−O2		1.471(3)
S3−O3		1.556(3)

The present work offers insight into the controlled sulfur oxygenation of metal thiolates and the resulting changes in the electronic structure. Our previous hypothesis that "t_{2g}-rich" low-spin complexes favor sulfur oxygenation is supported by the reactivity of **1** with O_2. Further, partial sulfur oxygenation is achievable using limited O_2 conditions, as demonstrated by **2** and other reported sulfenato/sulfinato complexes. In **1**, the steric bulk of PPh_3 slows oxygenation beyond **2** but does not prevent it, as demonstrated under excess O_2 conditions. These results suggest that asymmetric oxygenation of nitrile hydratase and thiocyanate hydrolase may also be facilitated by limited O_2 at the active site without the necessity for single O-atom-transfer reagents. Finally, sulfur oxygenation shortens the M−S bond while lengthening the metal−ligand bonds to π acceptors. In combination with the previously documented labilizing effect of the *trans*-thiolate,[23,24] sulfur oxygenation may promote ligand exchange. As demonstrated by Mascharak, sulfur oxygenation facilitates photodissociation of NO.[25] It is also expected to enhance coordination of π donors, such as HO^-, and may help to discriminate substrate coordination. Further studies to exchange the triphenylphosphine of **2** with more biologically significant donors are underway.

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Supporting Information Available: X-ray structural data in CIF format (CCDC 767263 and 767264), experimental procedures, crystallographic details, FT-IR and mass spectra of **1** and **2**, ORTEP of **1**, and a space filling diagram of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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