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Thioether Sulfur Oxygenation from O_2 or H_2O_2 Reactivity of Copper Complexes with Tridentate $N_2S_{thioether}$ Ligands

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To model thioether–copper coordination chemistry including oxidative reactivity, such as occurs in the copper monooxygenases peptidylglycine α-hydroxylating monooxygenase (PHM) and dopamine β-hydroxylase (Dβ H), we have synthesized new tridentate N_2S ligands L^{SEP} and L^{SBz} [L^{SEP} = methyl(2-phenethylsulfanylpropyl)(2-pyridin-2-ylethyl)amine; L^{SBz} = (2-benzylsulfanylpropyl)methyl(2-pyridin-2-ylethyl)amine)]. Both copper(I) and copper(II) complexes have been prepared, and their respective O_2 and H_2O_2 chemistry has been studied. Under mild conditions, oxygenation of $[(L^{SEP})Cu^{I}]^+$ (**1a**) and $[(L^{SBz})Cu^{I}]^+$ (**2a**) leads to ligand sulfoxidation, thus exhibiting copper monooxygenase activity. A copper(II) complex of this sulfoxide ligand product, $[(L^{SOEP})Cu^{II}(CH_3OH)(OClO_3)_2]$, has been structurally characterized, demonstrating $Cu–O_{sulfoxide}$ ligation. The X-ray structure of $[(L^{SEP})Cu^{II}(H_2O)(OClO_3)]^+$ (**1b**) and its solution UV–visible spectral properties [$S–Cu^{II}$ LMCT band at 365 nm (MeCN solvent); $\epsilon = 4285\ M^{-1}\ cm^{-1}$] indicate the thioether sulfur atom is bound to the cupric ion in both the solid (Cu^{II}–S distance: 2.31 Å) and solution states. Reaction of **1b** with H_2O_2 leads to sulfonation via the sulfoxide; excess hydrogen peroxide gives mostly sulfone product. These results may provide some insight into recent reports concerning protein methionine oxidation, showing the potential importance of copper-mediated oxidation processes in certain biological settings.

Introduction

The investigation of sulfur atom containing ligands for copper complexes is currently of considerable interest in bioinorganic chemistry. Cysteine-thiolate−Cu ion interactions are important in electron-transfer protein centers,[1,2] and sulfide−Cu interactions as a Cu_4−S cluster occur in the enzyme nitrous oxide reductase.[3−5] Thioether methionine−copper ion interactions also occur in the type 1 "blue" electron-transfer proteins[6,7] but also at the active site of certain monooxygenases which effect substrate C−H bond activation and oxygenation chemistry.

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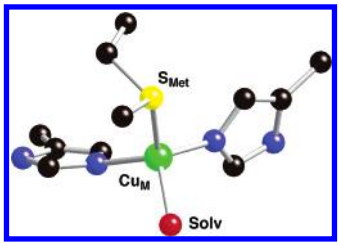


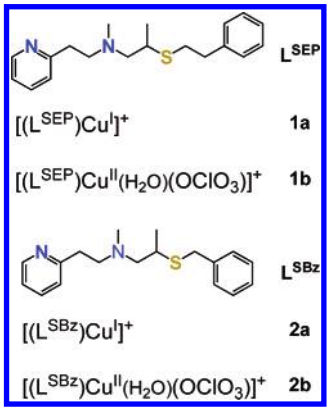
Figure 1. Representation of the X-ray structure of the Cu_M center in the PHM active site (PDB code 1PHM).[10]

Catalyzing hydroxylation reactions of substrates leading to neurotransmitters/hormones, dopamine β-hydroxylase (DβH) and a closely related enzyme, peptidylglycine α-hydroxylating monooxygenase (PHM), possess dicopper active sites, with however the two copper centers, Cu_H and Cu_M,[8] separated by ~11 Å distance.[9−12] Cu_H with $(His)_3$−Cu ligation is thought to shuttle electrons to the actual site of O_2-binding and substrate oxidation, Cu_M, which possesses a $(His)_2$(Met)−Cu coordination environment (Figure 1). Experimental[13] and computational studies[14] suggest a superoxo−copper(II) [Cu^{II}_M−(O_2^-)] moiety may be responsible for substrate hydrogen atom abstraction reaction.[15] A copper(II)−hydroperoxo moiety [Cu^{II}_M−(^-O_2H)] or higher-valent copper−oxo moiety [Cu^{III}_M−(O^{2-}) ↔ Cu^{II}_M−($O^{\bullet -}$)][16] are also considered as relevant active species. Important questions of interest which follow are (i) what is the role of the thioether ligand in stabilizing or activating a center for Cu−O_2 binding, formation of a superoxo or hydroperoxo copper(II) entity, and subsequent reactivity and (ii) how or why does the methionine not itself become oxidized irreversibly, as sulfur oxidation is relatively facile?

Further impetus for the study of oxidative processes involving methionine (Met) is the likely relevance to situations of oxidative stress,[17−19] calcium homeostasis,[20−22] and neurodegenerative disorders including Parkinson's and Alzheimer's disease.[23−29] Redox-active metals such as iron and copper will likely facilitate Met oxidation (perhaps in combination with O_2, hydrogen peroxide, or other oxidants).[27,28,30] Derived products (e.g., methionine sulfoxide) may strongly influence protein conformational changes, including either enhancing or inhibiting deposition/aggregation of protein fibrils.[31−33] There is even some discussion concerning the direct production of reactive oxygen species (ROS) as facilitated by methionine−copper chemistry.[28]

Thus, an area of research interest is to shed further light on copper redox chemistry in the presence of thioether groups (as models for protein methionine residues) directed toward oxidative chemistry, i.e., emphasizing Cu^I/O_2 or Cu^{II}/H_2O_2 reactions. Investigations in this area have been quite limited (see further discussion below). Thus, in this report, we describe copper(I) and copper(II) complexes and their oxidative chemistry with new tridentate thioether containing ligands, L^{SEP} and L^{SBz}, Chart 1. Copper(I)/O_2 chemistry with these ligands leads to stoichiometric sulfoxidations, while addition of hydrogen peroxide to copper(II) complexes of

Chart 1



(8) In DβH and PHM, the electron transfer and catalytic centers were previously designated Cu_A and Cu_B, respectively. Now, mostly commonly, they are labeled Cu_H (only His ligands) for the electron-transfer site and Cu_M (Met containing site, with two His's) for the catalytic site, to avoid confusion with copper ion center labeling in cytochrome *c* oxidase (see ref 10).

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L^{SEP} and L^{SBz} leads to sulfoxide products in both cases and additionally a sulfone for L^{SEP}. The results show how copper ion can facilitate thioether oxygenation reactions, which may be relevant to biological processes.

Experimental Section

General Methods. All reagents and solvents used for this work were commercial products and are of reagent quality unless otherwise stated. Acetonitrile, dichloromethane, diethyl ether, methanol, and tetrahydrofuran were purified and dried by passing through a double alumina column solvent purification system by Innovative Technologies, Inc. Deoxygenation of these solvents was achieved by bubbling Ar for 30 min and/or followed by three freeze/pump/thaw cycles. Air-sensitive compounds were handled under Ar atmosphere with standard Schlenk techniques or within a MBraun Labmaster 130 inert-atmosphere (N_2 atmosphere; <1 ppm O_2, <1 ppm H_2O) glovebox. $[Cu^{I}(MeCN)_4]ClO_4$ was prepared by the literature procedure.[34,35]

Warning: While we have experienced no problems in working with perchlorate compounds, they are potentially explosive and care must be taken not to work with large quantities.

^{1}H NMR and ^{13}C NMR spectra were measured on a Varian 400 MHz or Bruker 400 MHz spectrometer, and chemical shifts are reported in ppm (δ) downfield from an internal TMS reference.

Infrared spectra were recorded on a Mattson Instruments 4030 Galaxy Series FT-IR spectrometer.

Elemental analyses were performed by Desert Analytics, Tucson, AZ, for the air-sensitive samples or Quantitative Technologies Inc. (QTI), Whitehouse, NJ, for the non-air-sensitive samples.

Mass spectrometry was conducted at the mass spectrometry facility either at the Johns Hopkins University or at The Ohio State University. Chemical ionization (CI) and fast atomic bombardment (FAB) mass spectra were acquired at the Johns Hopkins University facility using a VG70S double-focusing magnetic sector mass spectrometer (VG Analytical, Manchester, U.K., now Micromass/Wasters) equipped with a Xe gas FAB gun (7.5 kV @ 1 mA) and an off-axis electron multiplier.

Cyclic voltammetry measurements were undertaken in freshly distilled acetonitrile using a BAS 100B electrochemical analyzer with a glassy carbon working electrode and a platinum wire auxiliary electrode. Potentials were recorded versus a $Ag/AgNO_3$ electrode. The voltammograms are plotted versus the $Fe(Cp)_2^{+/0}$ potential which was measured as an external standard. Scans were run at 50−500 mV/s under an argon atmosphere using ca. 0.1 M $[Bu_4N][PF_6]$ as the supporting electrolyte.

X-ray crystallography was performed at the X-ray diffraction facility either at the Johns Hopkins University or University of Delaware. A suitable blue single crystal of $[(L^{SOEP})Cu^{II}(CH_3OH)(OClO_3)_2]$ was mounted in Paratone-N oil on the end of a glass fiber and transferred to the N_2 cold stream (110 K) of an Oxford Diffraction Xcalibur3 system equipped with Enhance optics [Mo Kα radiation (λ = 0.71073 Å)] and a CCD detector. The frames were integrated, and a face-indexed absorption correction and an interframe scaling correction were also applied with the Oxford Diffraction CrysAlisRED software package (CrysAlis CCD, Oxford Diffraction Ltd.,version 1.171.27p5 beta). The structure was solved using direct methods and refined using the Bruker SHELXTL (v6.1) software package (G. M. Sheldrick, 2000). A suitable green crystal of $[(L^{SEP})Cu^{II}(H_2O)(OClO_3)](ClO_4)$ (**1b**) was mounted with epoxy cement to the tip of a glass fiber. Intensity data were collected at 150(2) K with a Bruker SMART APEX CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). An absorption correction was applied using the SADABS program (Sheldrick, G. M. *SADABS (2.01), Bruker/Siemens Area Detector Absorption Correction Program*; Bruker AXS: Madison, WI, 1998). The structure was solved using direct methods and refined using the Bruker SHELXTL (v6.1) software package (G. M. Sheldrick, 2000). The H atoms in **1b** were refined in calculated positions except the H atoms in the water molecule involved in O(1)−H(1)···O(7) hydrogen bonds which were found from the *F*-map and refined with isotropic thermal parameters. Three O atoms in one of the ClO_4 anions and the CH_2CHCH_3 group are disordered over two positions in ratios 71/29 and 56/54, respectively.

Gas chromatography was carried out and recorded using a Hewlett-Packard 5890 Series II gas chromatograph. The GC conditions for the analysis of the resulting oxidation product mixture were the following: injector port temperature, 250 °C; detector temperature, 250 °C; flow rate, 50 mL/min.

X-band electron paramagnetic resonance (EPR) spectra were recorded on a Bruker EMX CW-EPR spectrometer controlled with a Bruker ER 041 XG microwave bridge operating at X-band (~9 GHz). The low-temperature experiments were carried out via either a continuous-flow He(l) cryostat and ITC503 temperature controller made by Oxford Instruments, Inc., or N_2(l) finger dewar.

Low-temperature UV−vis spectra were obtained with either a Cary 50 Bio spectrophotometer equipped with a fiber optic coupler (Varian) and a fiber optic dip probe (Hellma: 661.302-QX-UV-2 mm-for-low-temperature) or a Hewlett-Packard model 8453 diode array spectrophotometer equipped with a custom-made quartz Dewar flask filled with methanol. A low-temperature unit (Neslab ULT-95 low-temperature circulator) is attached to the HP spectrophotometer. Air-sensitive solutions were prepared in a glovebox (N_2 filled, MBraun) and carried out in custom-made Schlenk tubes designed for the dip probe (Chemglass: JHU-0407-271MS) or Schlenk cuvettes (Quark).

Synthesis of Ligands. L^{SEP} Ligand. 2-(2-Methylaminoethyl)-pyridine (2.31 g, 17.0 mmol) and propylene sulfide (1.26 g, 17.0 mmol) were refluxed in acetonitrile (50 mL) for 4 h under Ar. After the mixture has been cooled, solvent was removed by rotary evaporator. The resulting crude yellow oil was dissolved in THF (50 mL). With vigorous stirring upon addition of sodium (0.45 g, 19.6 mmol), the yellow solution turned to a dark orange color slowly. (2-Bromoethyl)benzene (3.14 g, 17.0 mmol) was added dropwise with stirring, and then the reaction mixture was refluxed for 1 h under Ar. During this time solution color was changed to yellow. After cooling of the sample to room temperature, ethanol (10 mL) was added for deactivating the unreacted sodium and solvent was removed by rotary evaporator. The solid residue was dissolved in CH_2Cl_2 and washed with brine three times. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The oil obtained was purified by column chromatography (Al_2O_3, 9:1 hexane−ethyl acetate, R_f = 0.31). Yield: 2.6 g (8.27 mmol, 48.8%). ^{1}H NMR ($CDCl_3$): δ 8.51 (dq, J = 4, 0.8 Hz, 1H), 7.56 (td, J = 7.6, 2 Hz, 1H), ~7.2 (m, 7H), ~2.85 (m, 9H), 2.56 (dd, 1H), 2.40 (dd, 1H), 2.31 (s, 3H), 1.21 (d, J = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 161.6 (py), 150.3 (py), 141.8 (ph), 137.3 (py), 129.5 (ph), 127.3 (ph), 124.4 (py), 122.1 (py), 65.3 (NCH_2), 59.1 (NCH_2), 43.7 (NCH_3), 39.3 (CH_2-ph), 37.7 (CH), 37.1 ($pyCH_2$), 33.0 (SCH_2), 20.7 (CH_3). FAB mass spectrum: m/z 315.3 $(M + 1)^+$.

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L^{SBz} Ligand. 2-(2-Methylaminoethyl)pyridine (4.78 g, 35.1 mmol) and propylene sulfide (2.60 g, 35.1 mmol) were refluxed in acetonitrile (50 mL) for 5 h under Ar. After the mixture was cooled, solvent was removed. The crude yellow oil obtained was dissolved in THF (50 mL). With vigorous stirring upon addition of sodium (0.98 g, 42.6 mmol), slowly the yellow solution turned to dark orange color. Benzyl chloride (4.75 g, 37.5 mmol) was added dropwise with stirring, and then the mixture was refluxed for 1 h under Ar. During this time solution color was changed form black to yellow. After cooling of the sample to room temperature, ethanol (10 mL) was added for deactivating the excess sodium and solvent was removed by rotary evaporator. The product mixture was dissolved in CH_2Cl_2 and washed with brine three times. The resulting organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The oil was purified by column chromatography (Al_2O_3, 4:1 hexane−ethyl acetate, R_f = 0.45) to give a yellow oil. Yield: 5.21 g (17.35 mmol, 49.5%). ^{1}H NMR ($CDCl_3$): δ 8.40 (dt, J = 4.8, 0.8 Hz, 1H), 7.44 (tq, J = 7.6, 1.6 Hz, 1H), ∼7.1 (m, 7H), 3.65 (d, J = 4 Hz, 2H), 2.81 (t, J = 7.4 Hz, 2H), 2.65 (m, 3H), 2.44 (dd, 1H), 2.29 (dd, 1H), 2.13 (s, 3H), 1.08 (d, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 160.5 (py), 149.2 (py), 138.7 (ph), 136.1 (py), 128.8 (ph), 128.4 (ph), 126.8 (ph), 123.2 (py), 121.0 (py), 64.0 (NCH_2), 57.9 (NCH_2), 42.5 (NCH_3), 37.4 (CH), 35.9 (CH_2ph), 34.9 (pyCH_2), 19.5 (CH_3). EI-MS mass spectrum: m/z 301.2 $(M + 1)^+$.

Synthesis of Cu(I) Complexes. $[(L^{SEP})Cu^I](ClO_4)(CH_3CN)_{2/3}$. The ligand L^{SEP} (0.47 g, 1.49 mmol) and $[Cu^I(CH_3CN)_4]ClO_4$ (0.444 g, 1.36 mmol) were stirred for 1 h in O_2-free acetonitrile (5 mL) under Ar at room temperature. The complex was precipitated as a yellow solid upon addition of (oxygen free) diethyl ether into the reaction mixture. The supernatant was decanted. The resulting yellow powder was washed two times with O_2-free diethyl ether and dried under vacuum. Yield: 0.63 g (1.25 mmol, 92%). ^{1}H NMR (Acetone-d_6): δ 8.40 (d, 1H), 7.80 (td, 1H), ∼7.3 (m, 7H), 3∼2.4 (m, 14H), 1.94 (s, CH_3CN), 1.29 (d, 3H). Anal. Calcd for $C_{19}H_{26}ClCuN_2O_4S + 2/3CH_3CN$: C, 48.37; H, 5.59; N, 7.40. Found: C, 48.64; H, 5.41; N, 7.50. IR: 2019, 1602, 1316 (weak), 1090 (strong, ClO_4^-), 931 (weak), 765, 701, 623 cm^{-1}.

$[(L^{SBz})Cu^I](ClO_4)(CH_3CN)_{1/3}$. The ligand L^{SBz} (0.44 g, 1.46 mmol) and $[Cu^I(CH_3CN)_4]ClO_4$ (0.45 g, 1.37 mmol) were stirred for 1 h in O_2-free acetonitrile (5 mL) under Ar at room temperature. The complex was precipitated as a yellow solid upon addition of diethyl ether into the reaction mixture. The supernatant was decanted, and the yellow powder obtained was washed two times with diethyl ether and dried under vacuum. Yield: 0.60 g (1.26 mmol, 92%). ^{1}H NMR (CD_3NO_2): δ 8.45 (d, 1H), 7.92 (td, 1H), ∼7.3 (m, 7H), 4.0 (m, 2H), 3.44 (m, 1H), 3.18 (m, 1H), ∼2.8 (m, 4H), ∼ 2.5 (m, 4H), 2.10 (s, CH_3CN) 1.47 (d, 3H). Anal. Calcd for $C_{18}H_{24}ClCuN_2O_4S + 1/3CH_3CN$: C, 46.99; H, 5.28; N, 6.85. Found: C, 46.86; H, 5.33; N, 6.67. IR: 2015, 1603, 1316, 1248 (weak), 1083 (strong, ClO_4^-), 932 (weak), 771, 708, 623 cm^{-1}.

Dioxygen Reactivity Studies of LCu(I) Complexes. $[(L^{SEP})Cu^I]^+$ (1a) plus O_2: L^{SOEP} Formation. $[(L^{SEP})Cu^I](ClO_4)(CH_3CN)_{2/3}$ (0.35 g, 0.69 mmol) was dissolved in O_2-free acetonitrile (5 mL) under Ar. While O_2 gas was bubbling for 5 min at room temperature, the yellow solution was turning to green. The resulting green solution was stirred overnight at room temperature. Solvent was removed, and the residual green material was treated by NH_4OH/CH_2Cl_2 for demetalation.[36,37] The organic layer was separated, washed by brine three times, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The oil was purified by column chromatography (Al_2O_3, 1:5 hexane−ethyl acetate, R_f = 0.25). Yield: 0.11 g (0.33 mmol, 47%). ^{1}H NMR ($CDCl_3$): δ 8.50 (dm, J = 4, 1 Hz, 1H), 7.54 (m, 1H), ∼7.2 (m, 7H), ∼2.9 (m, 10H), 2.48 (m, J = 6 Hz, 1H), 2.32 (d, 3H), 1.20 (dd, J = 3.6, 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 160.4 (py), 149.5 (py), 139.5 (ph), 136.5 (py), 128.9 (ph), 128.8 (ph), 126.8 (ph), 123.6 (py), 121.4 (py), 59.2 (CH_2), 57.9 (CH_2N), 57.2 (CH), 51.7 (SCH_2), 42.7 (NCH_3), 36.0 (CH_2ph), 29.7 (pyCH_2), 12.2 (CH_3). CI-MS mass spectrum: m/z 331.2 $(M + 1)^+$. IR: SO (−SO−) band shows up at 1032 cm^{-1}.

$[(L^{SEP})Cu^I]^+$ (1a) plus $^{18}O_2$: $^{18}O-L^{SOEP}$ Formation. $[(L^{SEP})Cu^I](ClO_4)(CH_3CN)_{2/3}$ (0.10 g, 0.20 mmol) was dissolved in O_2-free acetonitrile (10 mL) under Ar in a 25 mL Schlenk flask connected to a three-way valve, a vacuum was applied, and an $^{18}O_2$ bulb (25 mL, 99 atom %, 1 atm from ICON, part no. IO 6393) was connected. Labeled dioxygen $^{18}O_2$ diffused into the reaction flask after breaking the seal (room temperature). The reaction solution was stirred overnight, and after the solvent was removed, the residual green material was treated with NH_4OH/CH_2Cl_2 to effect demetalation of the ligand organic.[36,37] The organic layer was separated, washed with brine (3×), dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The identity of the sulfoxide product was again confirmed by GC; subsequent mass spectrometric analysis indicated a 62% incorporation of labeled oxygen. (See Supporting Information.)

$[(L^{SBz})Cu^I]^+$ (2a) plus O_2: L^{SOBz} Formation. $[(L^{SBz})Cu^I](ClO_4)(CH_3CN)_{1/3}$ (0.30 g, 0.63 mmol) was dissolved in O_2-free acetonitrile (5 mL) under Ar. While O_2 gas was bubbling for 5 min at room temperature, the yellow solution was turning to green. The resulting green solution was stirred overnight at room temperature. Solvent was removed, and residual green material was treated by NH_4OH/CH_2Cl_2 for demetalation.[36,37] The organic layer was separated, washed by brine three times, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The resulting oil was purified by column chromatography (Al_2O_3, 1:1 hexane−ethyl acetate, R_f = 0.2). Yield: 0.06 g (0.19 mmol, 30%). ^{1}H NMR ($CDCl_3$): δ 8.51 (dm, J = 4 Hz, 1H), 7.56 (td, J = 7.2, 1.8 Hz, 1H), ∼7.3 (m, 5H), ∼7.1 (m, 2H), 3.91 (dd, 2H), ∼2.9 (m, 6H), 2.48 (dd, J = 21.2, 12.8 Hz, 1H), 2.24 (s, 3H), 1.23 (d, J = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 160.2 (py), 149.2 (py), 136.2 (py), 131.0 (ph), 129.8 (ph), 128.8 (ph), 128.0 (ph), 123.3 (py), 121.1 (py), 58.9 (NCH_2), 57.6 (CH_2N), 55.8 (CH), 51.2 (SCH_2), 42.2 (NCH_3), 35.8 (pyCH_2), 9.1 (CH_3). CI-MS mass spectrum: m/z 317.2 $(M + 1)^+$.

Synthesis of Cu(II) Complexes. $[(L^{SEP})Cu^{II}(H_2O)(OClO_3)]ClO_4 \cdot H_2O$ (1b). The ligand L^{SEP} (0.429 g, 1.36 mmol) and $Cu^{II}(ClO_4)_2 \cdot 6H_2O$ (0.485 g, 1.31 mmol) were stirred in CH_2Cl_2 (5 mL) at room temperature for 1 h. The complex was precipitated as dark green solid on addition of diethyl ether into the reaction mixture. The supernatant was decanted, and the resulting green powder was washed two times with diethyl ether and dried under vacuum. Yield: 0.622 g (1.01 mmol, 78%). UV−vis (MeCN; λ_{max}, nm; ϵ, M^{-1} cm^{-1}): 260, 7010; 365, 4285; 625, 265. Anal. Calcd for $C_{19}H_{30}Cl_2CuN_2O_{10}S$: C, 37.23; H, 4.93; N, 4.57. Found: C, 37.68; H, 4.83; N, 4.33. An EPR spectrum of $[(L^{SEP})Cu^{II}(H_2O)(OClO_3)]^+$ (**1b**) indicates a typical tetragonal copper environment. X-band spectrometer (ν = 9.186 GHz) in 2-methyltetrahydrofuran/MeCN (1:1) at 77 K: $g_{||}$ = 2.23, $A_{||}$ =170 G; $g_{\perp}$ = 2.03 (see Supporting Information). X-ray-quality dark green crystals were obtained by

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dissolving a portion of this product in CH_2Cl_2 and layering with diethyl ether.

[(L^{SOEP})Cu^{II}(CH_3OH)($OClO_3$)$_2$]. L^{SOEP} (0.360 g, 1.09 mmol) and $Cu^{II}(ClO_4)_2 \cdot 6H_2O$ (0.404 g, 1.07 mmol) were stirred in CH_3OH (5 mL) at room temperature for 1 h. The complex was precipitated as a blue powder upon addition of diethyl ether into the reaction mixture. The supernatant was decanted, and the blue powder obtained was washed two times with diethyl ether and dried under vacuum giving 0.40 g (0.64 mmol, 61%). UV−vis (MeCN; λ_{max}, nm; ϵ, M^{-1} cm^{-1}): 262, 7286; 330 (shoulder), 1946; 665, 118. Anal. Calcd for $C_{20}H_{30}Cl_2CuN_2O_{10}S$: C, 38.44; H, 4.84; N, 4.48. Found: C, 38.28; H, 4.73; N, 4.40. IR: ~3400 (weak, br), 1615, 1082 (strong), 981 (weak, br), 930 (weak), 767, 622 cm^{-1}. X-ray-quality blue single crystals were grown in from a CH_3OH/CH_2Cl_2 solution layered with diethyl ether. An EPR spectrum of [(L^{SOEP})Cu^{II}(CH_3OH)($OClO_3$)$_2$] reveals a typical tetragonal environment. X-band spectrometer (ν = 9.191 GHz) in 2-methyltetrahydrofuran/MeCN (3:1) at 8 K: $g_{\|} = 2.27$, $A_{\|} = 162$ G; $g_{\perp} = 2.04$ (see Supporting Information).

[(L^{SBz})Cu^{II}(H_2O)($OClO_3$)]ClO_4 (2b). L^{SBz} (0.31 g, 1.03 mmol) and $Cu^{II}(ClO_4)_2 \cdot 6H_2O$ (0.38 g, 1.02 mmol) were stirred in MeCN (5 mL) at room temperature for 1 h. The complex was precipitated as dark green solid on addition of diethyl ether into the reaction mixture. The supernatant was decanted, and the resulting green powder was washed two times with diethyl ether and dried under vacuum. Yield: 0.53 g (0.927 mmol, 91%). UV−vis (MeCN; λ_{max}, nm; ϵ, M^{-1} cm^{-1}): 372, 3756; 615, 334. Anal. Calcd for $C_{18}H_{24}Cl_2CuN_2O_8S \cdot 1/2H_2O$: C, 37.80; H, 4.41; N, 4.90. Found: C, 37.72; H, 4.75; N, 5.17. IR: ~3400 (weak, br, OH), 1612, 1049 (strong, ClO_4^-) cm^{-1}. An EPR spectrum of [(L^{SBz})Cu^{II}(H_2O)($OClO_3$)]$^+$ (**2b**) indicates a typical tetragonal copper environment. X-band spectrometer (ν = 9.186 GHz) in 2-methyltetrahydrofuran/MeCN (1:1) at 77 K: $g_{\|} = 2.23$, $A_{\|}$ =170 G; $g_{\perp} = 2.03$ (see Supporting Information).

Hydrogen Peroxide Reactivity Study of LCu^{II} Complexes. [(L^{SEP})Cu^{II}(H_2O)($OClO_3$)]$^+$ (1b) plus H_2O_2: L^{SO2EP} Formation. [(L^{SEP})Cu^{II}(H_2O)($OClO_3$)]$ClO_4 \cdot H_2O$ (30 mg, 0.0489 mmol) was dissolved in methanol (5 mL). A blue solution changing to green was observed upon addition of excess hydrogen peroxide (70 mg, 29.6%, 0.61 mmol) at room temperature. After the 14 h reaction time, solvent was removed and the residual green material was treated by NH_4OH/CH_2Cl_2 for demetalation.[36,37] The organic layer was separated, washed by brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The oil was purified by column chromatography (Al_2O_3, 1:1 hexane−ethyl acetate, R_f = 0.66 for the sulfone ligand). Yield of L^{SO2EP} ligand: 0.012 g (0.033 mmol, >68%). ^1H NMR ($CDCl_3$): δ 8.46 (dm, J = 4.8, 1 Hz, 1H), 7.46 (dt, J = 7.6, 1.6 Hz, 1H), ~7.2 (m, 7H), ~3.0 (m, 10H), 2.47 (dd, 1H), 2.31 (s, 3H), 1.29 (d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 160.0 (py), 149.4 (py), 138.3 (ph), 136.4 (py), 128.9 (ph), 128.6 (ph), 127.0 (ph), 123.5 (py), 121.4 (py), 58.8 (NCH_2), 57.8 (NCH_2), 55.8 (CH), 54.0 (SCH_2), 42.4 (NCH_3), 35.8 ($pyCH_2$), 27.8 (CH_2ph), 11.1 (CH_3). CI-MS: m/z = 347.2 $(M + 1)^+$. IR: SO (−SO_2−) band shows up at 1051 cm^{-1}.

Stoichiometric Hydrogen Peroxide Reactions with [(L^{SEP})-Cu^{II}(H_2O)($OClO_3$)]$^+$ (1b). [(L^{SEP})Cu^{II}(H_2O)($OClO_3$)]$ClO_4 \cdot H_2O$ (**1b**) (~100 mg scale) was dissolved in 5 mL of MeOH. The green solution turned to blue immediately upon the addition of either 1 or 2 equiv of H_2O_2 at RT (room temperature). Reactions were stopped after 18 h (1 h gives the same yield), and the solvent was removed. The metal ions were removed by treating the residual material with NH_4OH/CH_2Cl_2.[36,37] The organic layer was washed with brine solution and dried under $MgSO_4$. The oil obtained was analyzed by TLC (thin-layer chromatography), showing two more spots (R_f = 0.66, 0.22) in addition to one (R_f = 0.9) for the original ligand. After purification by column chromatography (Al_2O_3, eluent 1:1 hexane−ethyl acetate), ^1H and ^{13}C NMR spectroscopy and mass spectrometric analyses indicate that those two additional spots on the TLC correspond to a sulfoxide L^{SOEP} (R_f = 0.22) and a sulfone L^{SO2EP} (R_f = 0.66), respectively. With 1 equiv of H_2O_2, the yields determined were 34.5 mol % L^{SEP}, 48.7 mol % L^{SOEP}, and 16.8 mol % L^{SO2EP}, while with 2 equiv of H_2O_2 reaction gave 19.9 mol % L^{SEP}, 40.6 mol % L^{SOEP}, and 39.5 mol % L^{SO2EP}.

[(L^{SBz})Cu^{II}(H_2O)($OClO_3$)]$^+$ (2b) plus H_2O_2: L^{SOBz} Formation. [(L^{SBz})Cu^{II}(H_2O)($OClO_3$)]ClO_4 (49 mg, 0.0857 mmol) was dissolved in methanol (5 mL). A color change to blue from green was observed upon addition of excess hydrogen peroxide (560 mg, 29.6%, 4.8 mmol) at room temperature. After the 22 h reaction time, solvent was removed and residual green material was treated by NH_4OH/CH_2Cl_2 for demetalation.[36,37] The organic layer was separated, washed by brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The oil obtained was purified by column chromatography (Al_2O_3, 1:1 hexane−ethyl acetate, R_f = 0.7, 0.2 for L^{SBz} and sulfoxide ligand) to give 0.021 g (0.066 mmol, 77%) of product. The characterization of L^{SOBz} ligand is described above.

Results and Discussion

Ligand Design, Syntheses, and Other Systems. In the Cu_M active site of PHM and DβH, a $(His)_2(Met)$−Cu tridentate coordination environment is present (Figure 1). There previously has been considerable synthetic modeling activity on the structural, spectroscopic, and redox properties of mixed nitrogen−$S_{thioether}$ ligands,[7,38−57] including extensive studies on polythioether-containing macrocycles studied by

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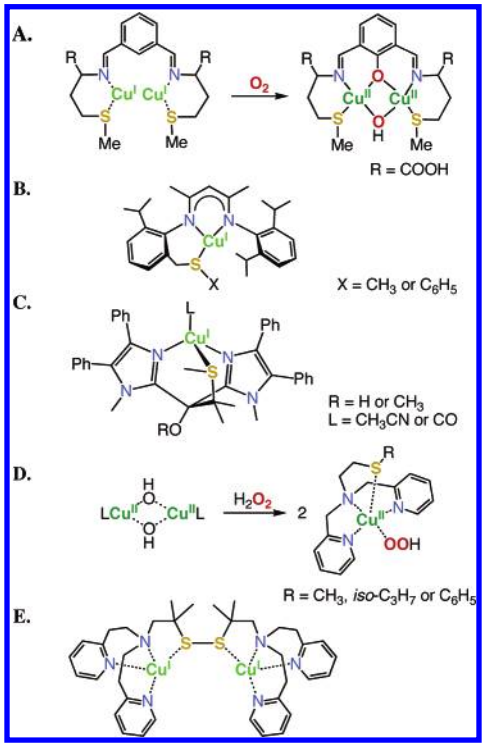
Scheme 1



Rorabacher, Ochrymowycz, and co-workers.[7,44,45] However, as stated in the Introduction, it has become of considerable interest to investigate Cu^I/O_2 and Cu^{II}/H_2O_2 chemistry of $N_2S_{thioether}$ tridentate ligands, such as L^{SEP} and L^{SBz} (Chart 1).

An early system of interest was studied by Casella and co-workers,[58] showing that C−H activation chemistry with O_2 could occur even in the presence of thioether-containing ligands. Using a xylyl-containing binucleating ligand (following our own previously studied xylyl systems with all nitrogen ligands),[36,59] aromatic hydroxylation indeed takes place (**A**, Scheme 1); only 15−20% sulfoxidation of the ligand was observed.[58] Very recently, Tolman and co-workers[60] described copper(I)/O_2 reactivity with an anionic β-diketiminate N_2S−Cu(I) complex (**B**, Scheme 1); the thioether ligand donor appears to influence the thermodynamics of O_2-binding, but it does not affect the ultimate mononuclear ligand−$Cu-O_2$ and bis(μ-oxo)dicopper(III) products, where in fact S-ligand binding to copper does not occur. Another recent report from Zhou et al.[61] revealed 20% of a sulfoxidation product derived from the oxygenation reaction of a $N_2S_{thioether}$−copper(I) complex (R = H, L = CH_3CN, **C**, Scheme 1), a product with dicopper Cu_2O_2 core for R = CH_3.

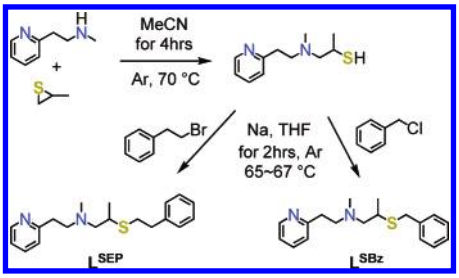


Figure 2. Synthesis of the tridentate thioether ligands L^{SEP} and L^{SBz}. See Experimental Section for further details.

Kodera and co-workers[62] demonstrated the formation of a copper hydroperoxo species via H_2O_2 reaction with a copper(II) complex of an $N_3S_{thioether}$ tetradentate ligand (**D**, Scheme 1, R = C_6H_5). However, for an alkyl thioether ligand (R = CH_3 or *iso*-C_3H_7), sulfoxide and sulfone organic products were instead detected. In a somewhat related system (with disulfide ligand), Ohta et al.[63] showed that a hydroperoxocopper(II) complex could be generated by reacting H_2O_2 with complex **E** (Scheme 1).

For our own ligand design (L^{SEP} and L^{SBz}), we chose to synthetically input ethylphenyl and benzyl groups on the thioether sulfur donor, with the thought that placement of a potential substrate, i.e., the benzylic methylene group (with C−H BDE = 85 kcal/mol), may lead to attack by a copper/O_2 derived species, thus providing a model system in which Cu(I)/O_2 chemistry in the presence of a thioether ligand might allow the study of C−H activation. As described below, this did not turn out to occur and sulfur oxidation chemistry instead ensued.

The thioether ligands L^{SEP} and L^{SBz} were synthesized from the precursor thiol (Figure 2), which was previously reported from this laboratory.[5] Introduction of sodium metal to the thiol ligand in tetrahydrofuran led to the generation of the strong thiolate nucleophile; the target ligands were then synthesized by the addition of (2-bromoethyl)benzene or benzyl chloride, respectively (Figure 2).

Copper(I) Complexes: Sulfoxidation of Thioether Ligands with Cu^I/O_2 Chemistry. Ligand−copper(I) complexes were synthesized from the addition of the thioether ligand to $[Cu^I(MeCN)_4]ClO_4$,[34,35] in acetonitrile under Ar at room temperature. Elemental analysis and ^1H NMR spectroscopy (Experimental Section) are consistent with the formulations given, $[(L^{SEP})Cu^I]^+$ (**1a**) or $[(L^{SBz})Cu^I]^+$ (**2a**) with perchlorate as counterion.

Neither copper(I) complex $[(L^{SEP})Cu^I]^+$ (**1a**) nor $[(L^{SBz})Cu^I]^+$ (**2a**) is reactive toward O_2 at −80 °C (CH_2Cl_2) or −40 °C (MeCN), as monitored by UV−vis spectroscopy. To obtain insights, the cyclic voltammetric behavior of **1a** and **2a** were measured in acetonitrile as solvent, and while the compounds turned out to be the best behaved in this solvent, irreversible oxidations peaks in the region +400−450 mV

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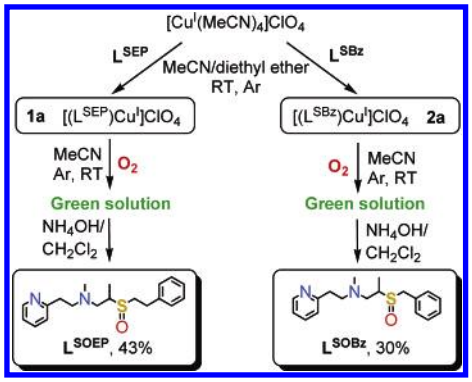

Figure 3. Synthesis of thioether ligand−copper(I) complexes and their reactivity toward O_2, producing sulfoxide products.

vs $Fe(cp)_2^{+/0}$ were observed (see Supporting Information). These characteristics, complexes with very positive oxidation potentials, are not untypical for thioether-containing ligands bound to copper ion.[7,44,64] Tridentate N_3 and tetradentate N_4 ligand−copper(I) compounds, with more negative redox potentials, are normally very reactive toward dioxygen at reduced temperatures, giving rise to peroxo- and/or bis(μ-oxo)dicopper species.[65−69]

However, following low-temperature oxygenation and warming to room temperature, solutions of $[(L^{SEP})Cu^I]^+$ (**1a**) or $[(L^{SBz})Cu^I]^+$ (**2a**) did slowly change color from yellow to green. To determine if there was a ligand transformation, reaction mixtures were treated with NH_4OH/CH_2Cl_2 to demetalate the complexes formed and allow for analysis of the organics present (see Experimental Section).[36,37] In both cases, sulfoxide products were obtained in moderately good yield (see further discussion below) (Figure 3). For the **1a**/O_2 system, isotope labeling experiments were carried out; a 62% incorporation of labeled oxygen was observed in the isolated L^{SOEP} product (see Supporting Information). This ^{18}O incorporation under theses experimental conditions is modest, but clearly the sulfoxide oxygen is derived from molecular oxygen.

It is very common in copper/dioxygen chemistry for substrate oxygenation reactions (including the copper ligands themselves) to follow a monooxygenase type reaction stoichiometry, wherein one of the two atoms of molecular oxygen is transferred from a copper−O_2-derived intermediate (e.g., a dicopper(II) peroxide or bis(μ-oxo)dicopper(III) complex)[67,70−74] where the two copper(I) ions supply the reducing equivalents necessary for reaction, formally allowing oxygen atom transfer (OAT), leaving behind two copper(II) ions and a oxide (or OH^- or H_2O) derived from O_2 (Figure 4). The expected yield of sulfoxide is thus 50% maximum. We therefore conclude that some type of monooxygenase chemistry is occurring in the present system, since our yields (vide supra) approach the range expected and the labeling study does indicate an oxygen atom from O_2 is the source of the sulfoxide oxygen.

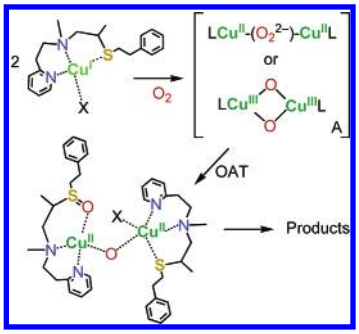

Figure 4. Possible course of reaction for ligand sulfoxidation by Cu^I/O_2 with L^{SEP}.

As mentioned above, Casella showed that Cu−O_2 chemistry can lead to ligand sulfoxidation but as a side product in his xylyl-hydroxylating system.[58] However, Itoh and coworkers[75] showed that copper−dioxygen derived binuclear products convert exogenously added sulfide substrates to the corresponding sulfoxides via an oxygen atom transfer (OAT) mechanism. In our thioether system, the soft thioether ligand donor apparently stabilizes the cuprous complex at low temperatures where we would hope to monitor Cu_n/O_2 complex formation, such as **A** (Figure 4). However, we never observed a discrete Cu^I_n/O_2-derived species even above −80 °C and must conclude that there is no buildup of such an intermediate; once formed, it reacts very rapidly with the ligand thioether substrate.

Structure of a Copper(II) Complex with L^{SOEP}. To complement the $[(L^{SEP})Cu^I]^+$ (**1a**) plus O_2 reaction chemistry, we separately added cupric perchlorate to isolated ligand sulfoxide L^{SOEP} and were able to crystallize the resulting product $[(L^{SOEP})Cu^{II}(CH_3OH)(OClO_3)_2]$. Its X-ray structure (Figure 5) reveals the sulfoxide oxygen atom as one of the equatorial ligands coordinated to the Cu(II) ion, Cu−O = 1.9407(12) Å. The sulfoxide S−O bond distance is 1.5418 Å; the latter is in accord with values known from the literature.[76] In S−O-coordinated metal complexes, average S−O bond distances are 1.492 (free), 1.527 (O-bound, including copper(II)), and 1.472 Å (S-bound; no example with copper is known). Metal−$O_{sulfoxide}$ binding reduces the S═O double bond character. The L^{SOEP} pyridine and aliphatic amine nitrogen atoms are the other equatorial ligands, along with a methanol oxygen atom, giving rise to a near planar

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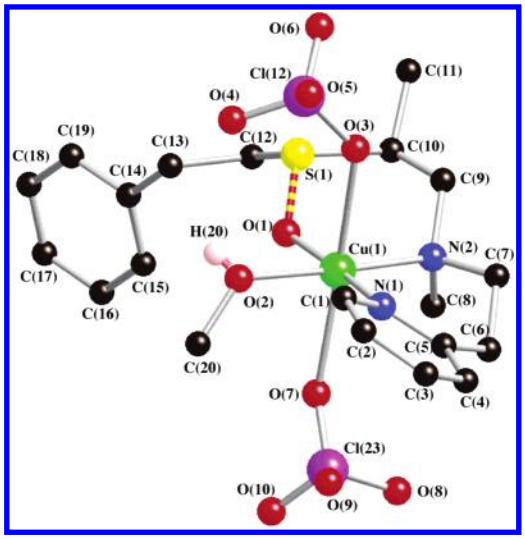

Figure 5. X-ray crystal structure of $[(L^{SOEP})Cu^{II}(CH_3OH)(OClO_3)_2]$. The hydrogen atoms have been omitted for clarity.

Table 1. Selected Bond Distances and Angles of the Crystal Structure of $[(L^{SOEP})Cu^{II}(CH_3OH)(OClO_3)_2]$

atoms	dist (Å)	atoms	angle (deg)
Cu(1)−O(1)	1.9407(12)	O(1)−Cu(1)−N(1)	173.99(5)
Cu(1)−N(1)	1.9980(14)	O(1)−Cu(1)−O(2)	84.90(5)
Cu(1)−O(2)	2.0098(13)	N(1)−Cu(1)−O(2)	89.29(6)
Cu(1)−N(2)	2.0545(14)	O(1)−Cu(1)−N(2)	87.96(5)
S(1)−O(1)	1.5418(13)	N(1)−Cu(1)−N(2)	97.86(6)
Cu(1)−O(3)	2.4740(15)	O(2)−Cu(1)−N(2)	172.86(6)
Cu(1)−O(7)	2.4684(15)		

arrangement. Two perchlorate anions coordinate weakly to the copper(II) ion as axial ligands, $Cu-O_{perchlorate} = 2.468$ and 2.474 Å, making for overall copper coordination in a distorted (axially elongated) octahedral geometry as expected for the Jahn−Teller d^9 cupric ion. Other selected bond distances and angles are listed in Table 1. This complex exhibits an infrared absorption 980 cm^{-1}, assigned as an S−O stretching vibration, in the range (862−997 cm^{-1}) for sulfoxide-O−metal complexes.[76]

Corresponding Cu^I/O_2 Chemistry with L^{SBz}. As mentioned in the Introduction, each tridentate thioether ligand L^{SEP} and L^{SBz} has a potential internal substrate for C−H oxidation/oxygenation chemistry, the ethylphenyl or benzyl group. Such groups are susceptible to oxidation via Cu^I/O_2 chemistry, as previously studied in all nitrogen-containing ligand systems.[37,73] However no carbon-based oxidation chemistry was observed, either from ligand−$Cu(I)/O_2$ or ligand−$Cu(II)/H_2O_2$ chemistry, presumably because the thioether sulfur atom is much more easily oxidized. We do note that in comparing L^{SEP} with L^{SBz} Cu^I/O_2 chemistry, the former exhibits considerably enhanced sulfoxidation (yields: $L^{SOEP} = 43\%$, $L^{SOBz} = 30\%$, Figure 3).

Thioether Copper(II) Complexes: Structure of $[(L^{SEP})Cu^{II}(H_2O)(OClO_3)]ClO_4 \cdot H_2O$. Cu(II) complexes $[(L^{SEP})Cu^{II}(H_2O)(OClO_3)]ClO_4 \cdot H_2O$ (**1b**) and $[(L^{SBz})Cu^{II}(H_2O)(OClO_3)]ClO_4$ (**2b**) were synthesized by the addition of thioether ligand (L^{SEP} or L^{SBz}) to $Cu^{II}(ClO_4)_2 \cdot 6H_2O$ in CH_2Cl_2 at room temperature. Each complex was isolated as a dark green solid (Figure 6). An X-ray crystal structure of **1b** (Figure 7) shows the thioether sulfur atom of L^{SEP} as an

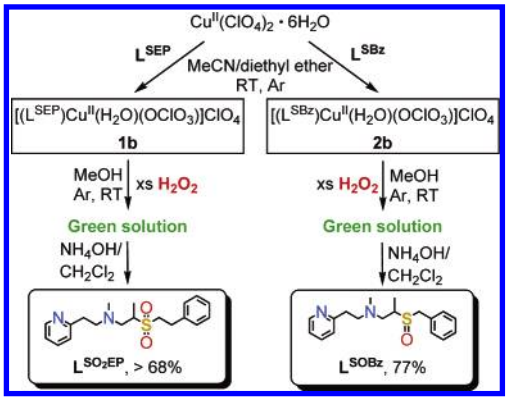

Figure 6. Synthesis of Cu(II)−thioether complexes and their reactivity with H_2O_2. Primary products with excess peroxide are the sulfone and sulfoxide, for the L^{SEP} and L^{SBz} ligand complexes, respectively. See text for more details.

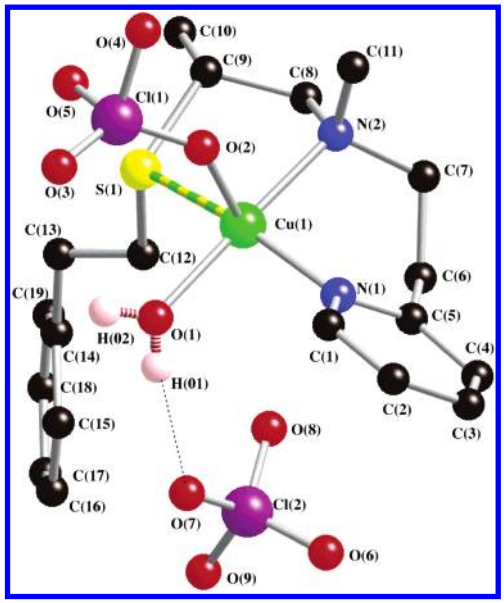

Figure 7. Crystal structure of $[(L^{SEP})Cu^{II}(H_2O)(OClO_3)](ClO_4)$ (**1b**). Hydrogen atoms are omitted for clarity.

equatorial ligand, coordinated to copper ion with Cu−S = 2.3128(10) Å. The pyridine and aliphatic amine nitrogen atoms are equatorial ligands, along with a water molecule which is hydrogen bonded to an oxygen atom of a perchlorate anion. The other perchlorate group is coordinate to the copper(II) as a unidentate axial ligand. The overall coordination geometry can be described as a distorted square pyramid ($\tau = 0.206$, where $\tau = 0.00$ for a perfect square pyramid and $\tau = 1.00$ for a trigonal bipyramidal geometry).[77] Other selected bond distances and angles are listed in Table 2.

Hydrogen Peroxide Reactivity of the Copper(II) Thioether Complexes. The UV−vis spectrum of $[(L^{SEP})Cu^{II}(H_2O)(OClO_3)]ClO_4 \cdot H_2O$ (**1b**) in MeCN solvent (Figure 8) shows a peak at 365 nm ($\epsilon = 4285\ M^{-1}\ cm^{-1}$) and a weak d−d band at 625 nm ($\epsilon = 265\ M^{-1}\ cm^{-1}$). The strong UV−absorption can be assigned as a $S_{thioether}$-to-Cu(II) LMCT band; thus, the thioether group in **1b** (and **2b**) also coordinates to the copper(II) ion in solution (and probably not as

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Table 2. Selected Bond Distances and Angles of the Crystal Structure of $[(^{L}SEP)Cu^{II}(H_2O)(OClO_3)](ClO_4)$

atoms	dist (Å)	atoms	angle (deg)
Cu(1)−O(1)	1.980(3)	O(1)−Cu(1)−N(1)	88.27(12)
Cu(1)−N(1)	1.981(3)	O(1)−Cu(1)−N(2)	177.21(14)
Cu(1)−N(2)	2.038(3)	N(1)−Cu(1)−N(2)	91.43(12)
Cu(1)−S(1)	2.3128(10)	O(1)−Cu(1)−S(1)	90.34(9)
Cu(1)−O(2)	2.332(3)	N(1)−Cu(1)−S(1)	164.83(9)
H(01)−O(7)	1.945	N(2)−Cu(1)−S(1)	89.21(9)
		O(1)−Cu(1)−O(2)	86.11(13)
		N(1)−Cu(1)−O(2)	93.40(12)
		N(2)−Cu(1)−O(2)	96.67(14)
		S(1)−Cu(1)−O(2)	101.58(8)

an axial ligand, since the observed absorptivity is quite large).[46,47,50−57,62] Addition of H_2O_2 (5 equiv) to a solution of **1b** in MeCN at −40 °C does not result in any reaction (as judged by observing no change in the UV−vis spectrum; see Supporting Information), but warming to RT causes the 365 nm absorption to disappear (Figure 8, inset), suggesting the interaction or reaction affects the Cu(II)−thioether coordination. In fact, sulfone ($RS(O)_2R'$) and/or sulfoxide (RS(O)R′) formation takes place (Figure 6), as described below.

On a synthetic scale, addition of excess hydrogen peroxide (10 equiv) to $[(L^{SEP})Cu^{II}(H_2O)(OClO_3)]ClO_4{\cdot}H_2O$ (**1b**), followed by workup and spectroscopic analysis in a manner similar to that carried out in the **1a** (and **2a**)/O_2 chemistry (vide supra), showed that the ligand L^{SEP} was mostly converted to the corresponding sulfone; only the sulfone compound L^{SO2EP} (Figure 6) was isolated and a trace of sulfoxide was detected. By contrast, the $(L^{SBz})Cu^{II}$ complex **2b** showed only ligand sulfoxidation under the same reaction conditions (Figure 6). We already mentioned (vide supra) Kodera's observation of alkyl thioether ligand sulfoxidation (**D**, Scheme 1).[62] Other groups have recently observed that certain copper(II) complexes can catalytically oxidize added sulfide substrates to corresponding sulfoxides in the presence of hydrogen peroxide.[78,79]

To try to clarify whether the sulfone forms via the sulfoxide, the reactivity of $[(L^{SEP})Cu^{II}(H_2O)(OClO_3)]ClO_4{\cdot}H_2O$ (**1b**) with various amounts of hydrogen peroxide was studied. A blue solution of **1b** in MeOH turned to green immediately upon the addition of either 1 or 2 equiv of H_2O_2. Separation from the metal ion and analysis of the mixture by column chromatography and NMR spectroscopy showed that the products included L^{SEP}, L^{SOEP}, and L^{SO2EP}. With 1 equiv of H_2O_2, the yields determined were 34.5 mol % L^{SEP}, 48.7 mol % L^{SOEP}, and 16.8 mol % L^{SO2EP}, while 2 equiv of H_2O_2 reaction gave 19.9 mol % L^{SEP}, 40.6 mol % L^{SOEP}, and 39.5 mol % L^{SO2EP}. The results suggest that the sulfoxide forms first, by either direct attack H_2O_2 on the thioether or via metal-assisted chemistry such as formation of a copper(II)−OOH species, which attacks the nearby thioether in an intramolecular fashion (Figure 9). The former explanation may be sufficient, since without any metal ion present, L^{SEP} + H_2O_2 gives the sulfoxide (100% yield). But, without copper ion present, even excess H_2O_2 plus L^{SEP} does not yield any sulfone. Thus, it seems likely that sulfone formation proceeds by H_2O_2 reaction with the copper(II)−sulfoxide. This may occur by Cu(II)−OOH formation on the metal−sulfoxide moiety (i.e., such as that found in the X-ray structure of $[(L^{SOEP})Cu^{II}(CH_3OH)(OClO_3)_2]$ (Figure 5)), or it could simply proceed by nucleophilic attack of hydrogen peroxide on the sulfoxide ligand,[80,81] with Lewis acid activation by the cupric ion, Figure 9.

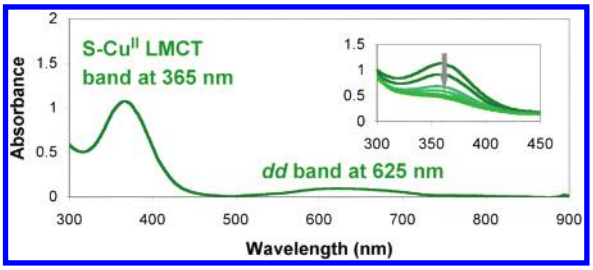

Figure 8. UV−vis spectra of $[(L^{SEP})Cu^{II}(H_2O)(OClO_3)]ClO_4{\cdot}H_2O$ in MeCN. Inset: 365 nm band decrease while the temperature is increased from −40 °C to RT after addition of H_2O_2.

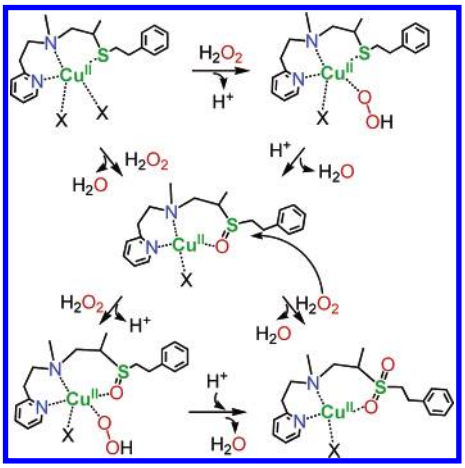

Figure 9. Proposed course of the hydrogen peroxide reactions to give sulfone product, via the initially formed copper(II)−sulfoxide complex. Metal assistance via Cu^{II}−OOH intermediates is suggested. See text.

While the $(L^{SEP})Cu^{II}$ complex (**1b**) reacts with excess H_2O_2 to give only sulfone, an interesting contrast is that the $(L^{SBz})Cu^{II}$ complex (**2b**) produces only a sulfoxide ligand product (Figure 6). At this time, we do not understand if this variation in reactivity is due to a steric or perhaps an electronic effect of the benzyl versus ethylphenyl group on the thioether sulfur.

Summary/Conclusions

The chemistry of the copper complexes with tridentate N_2S ligands, L^{SEP} and L^{SBz}, has been described. Under mild conditions, ligand sulfoxidation is observed in the reactions of ligand−Cu^{I} complexes with dioxygen. The yield of sulfoxide products are suggestive of an overall copper monooxygenase stoichiometry. No copper−dioxygen in-

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termediate or low-temperature stabilized species could be detected (by UV−vis spectroscopy), suggesting that if one forms, it very rapidly reacts with the internal sulfur-based substrate. A structure was obtained for a copper(II) complex of a separately isolated sulfoxide ligand L^{SOEP}; this exhibits sulfoxide oxygen coordination. X-ray crystallography of the cupric thioether complex $[(L^{SEP})Cu^{II}(H_2O)(OClO_3)](ClO_4)$ (**1b**) and UV−visible spectroscopy on solutions show that the thioether sulfur atom coordinates to the cupric ion in both phases. Reactions of **1b** with H_2O_2 gives both sulfoxide and sulfone product mixtures; most likely the sulfoxide is formed first, while cupric binding to this facilitates nucleophilic attack by hydrogen peroxide to give the sulfone. No C−H bond oxidation of the benzyl or ethylphenyl group on sulfur is observed in any ligand−Cu(I)/O_2 or ligand−Cu(II)/H_2O_2 reactions, presumably due to the much more facile sulfur oxygenation chemistry.

Clearly, copper ion can facilitate sulfoxide formation with either O_2 or H_2O_2, which may be relevant to various biological events (see Introduction). As for the active-site chemistry in PHM or DβH, if anything, this work just leads to even more questions about the true role of the Met thioether ligand and how Nature prevents its irreversible oxidation to sulfoxide or sulfone, as observed here.

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Supporting Information Available: Crystallographic information files (CIF) for $[(L^{SOEP})Cu^{II}(CH_3OH)(OClO_3)_2]$ and **1b**, cyclic voltammograms of **1a** and **2a**, mass spectra following $^{18}O_2$ reaction of **1a**, EPR spectra of **1b**, **2b**, and $[(L^{SOEP})Cu^{II}(CH_3OH)(OClO_3)_2]$, and UV−vis spectra for H_2O_2 reaction with **1b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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