JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

A $N_3S_{(thioether)}$-Ligated Cu^{II}-Superoxo with Enhanced Reactivity

Sunghee Kim,[†] Jung Yoon Lee,[†] Ryan E. Cowley,[‡] Jake W. Ginsbach,[‡] Maxime A. Siegler,[†] Edward I. Solomon,*[,‡] and Kenneth D. Karlin*[,†]

[†]Department of Chemistry, Johns Hopkins University, Baltimore, Maryland 21218, United States
[‡]Department of Chemistry, Stanford University, Stanford, California 94305, United States

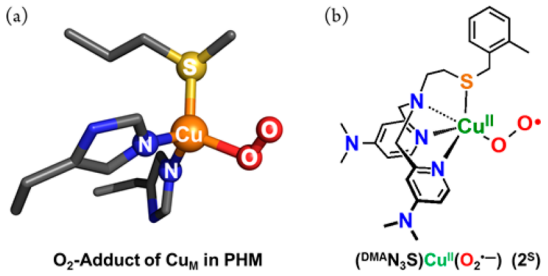
Supporting Information

ABSTRACT: Previous efforts to synthesize a cupric superoxide complex possessing a thioether donor have resulted in the formation of an end-on *trans*-peroxo-dicopper(II) species, $[\{(Ligand)Cu^{II}\}_2(\mu\text{-}1,2\text{-}O_2^{2-})]^{2+}$. Redesign/modification of previous N_3S tetradentate ligands has now allowed for the stabilization of the monomeric, superoxide product possessing a $S_{(thioether)}$ ligation, $[(^{DMA}N_3S)Cu^{II}(O_2^{\bullet-})]^+$ ($\mathbf{2^S}$), as characterized by UV−vis and resonance Raman spectroscopies. This complex mimics the putative $Cu^{II}(O_2^{\bullet-})$ active species of the copper monooxygenase PHM and exhibits enhanced reactivity toward both O−H and C−H substrates in comparison to close analogues $[(L)Cu^{II}(O_2^{\bullet-})]^+$, where L contains only nitrogen donor atoms. Also, comparisons of $[(L)Cu^{II/I}]^{n+}$ compound reduction potentials (L = various N_4 vs $^{DMA}N_3S$ ligands) provide evidence that $^{DMA}N_3S$ is a weaker donor to copper ion than is found for any N_4 ligand-complex.

The copper monooxygenases peptidylglycine-α-hydroxylating monooxygenase (PHM) and dopamine-β-monooxygenase (DβM) possess a dicopper active site, but it is "noncoupled"; the two copper ions are about 11 Å apart.[1] Extensive biochemical and biophysical research has shown that one copper ion (designated Cu_H or Cu_A) receives and passes electron reducing equivalents to the His_2Met $N_2S_{(thioether)}$ ligated Cu_M (or Cu_B) center, where O_2 and substrate binding occur. Recent computational analyses[2] lead to the hypothesis that an initial O_2-adduct, a Cu_M centered cupric superoxide $\{Cu^{II}(O_2^{\bullet-})\}$ moiety, forms from oxygenation of the fully reduced ($Cu^I\cdots Cu^I$) enzyme. This species performs the H-atom abstraction of the peptide prohormone substrate (in PHM) leading to C−H hydroxylation and formation of the product hormone. Reaction mechanisms suggesting other possible reactive intermediates being responsible for substrate C−H attack have been proposed.[3] In support of the importance of the $Cu^{II}(O_2^{\bullet-})$ reaction intermediate's involvement, a crystal structure obtained by Amzel and co-workers in the presence of a substrate inhibitor reveals dioxygen bound to Cu_M in an end-on fashion,[1b] as depicted in Scheme 1a.

Undoubtedly, the thioether ligand plays a critical role in determining the electronic structure and functions of Cu_M site leading to C−H bond activation.[2] However, the precise role of Met coordination and the actual PHM reaction mechanism have yet to be fully elucidated.

Scheme 1



Within the subfield of copper-dioxygen synthetic bioinorganic chemistry, one long-standing goal has been to produce $Cu^{II}(O_2^{\bullet-})$ species that can be studied in detail, and to this end several cupric superoxo complexes have been reported with ligands containing either three or four N-atoms.[4] In an attempt to mimic the active site donors of PHM and DβM, considerable effort has been devoted toward generating thioether containing tridentate or tetradentate ligands to study their Cu^I/O_2 reactivity.[5] In our own efforts we have been able to generate binuclear peroxo-dicopper complexes with $S_{(thioether)}$ ligation,[6] but there has been no report of a mononuclear $Cu^{II}(O_2^{\bullet-})$ species coordinated by a $S_{(thioether)}$ donor. Herein, for the first time we present the spectroscopic evidence and reactivity of the new mononuclear cupric superoxo complex, $[(^{DMA}N_3S)Cu^{II}(O_2^{\bullet-})]^+$ ($\mathbf{2^S}$) (Scheme 1b) possessing thioether S-ligation that exhibits enhanced reactivity toward both O−H and C−H substrates.

This new ligand, $^{DMA}N_3S$,[7] differs from our previously reported N_3S ligands in two important ways. First, it possesses highly electron-rich dimethylamino (DMA)[8] groups at the *para* position of the two pyridyl donors; this ligand design approach is the same previously employed to stabilize a mononuclear $Cu^{II}(O_2^{\bullet-})$ complex containing a N_4 tripodal tetradentate ligand.[4c,h,9] Second, the thioether moiety is capped with a bulkier *o*-methyl benzyl substituent to slow dimerization relative to previous designs.[6d] Treatment of $^{DMA}N_3S$ with $[Cu^I(CH_3CN)_4]B(C_6F_5)_4$ in THF, followed by pentane addition leads to the isolation of bright yellow powders with formula $[(^{DMA}N_3S)Cu^I]B(C_6F_5)_4$ (**1**).[7] Single crystals could be grown from 2-methyltetrahydrofuran (MeTHF)/pentane at room temperature under Ar. As shown in Figure 1a, the cuprous complex is a four-coordinate monomer ligated by two

Received: November 8, 2014
Published: February 20, 2015

DOI: 10.1021/ja511504n
J. Am. Chem. Soc. 2015, 137, 2796−2799

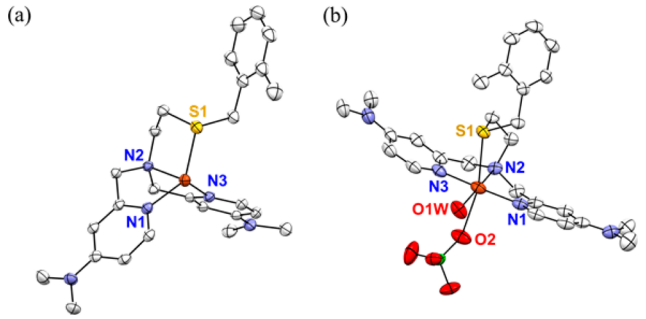


Figure 1. Displacement ellipsoid plots of the cations: (a) $[(^{DMA}N_3S)Cu^{I}]^+$ (**1**) and (b) $[(^{DMA}N_3S)Cu^{II}(H_2O)(ClO_4)]^+$ (**3**). Hydrogen atoms were removed for clarity.

pyridyls, one tertiary amine, and one thioether atom in a distorted pyramidal geometry providing an open site for potential dioxygen binding. The Cu−S bond length in **1** (2.2327(5) Å) falls in the usual range (2.2−2.44 Å) for Cu^{I}−$S_{(thioether)}$ complexes.[6] Many previously studied $N_3S_{(thioether)}$−Cu^{I} complexes form dimers in the solid state,[6d] and the incorporation of the larger *o*-methylbenzyl group in this study may disfavor their formation.

Furthermore, the copper(II) complex $[(^{DMA}N_3S)Cu^{II}(H_2O)(ClO_4)](ClO_4)$ (**3**) (Figure 1b) was generated and structurally characterized.[7] A slightly distorted octahedral coordination is observed. The thioether donor group is found in an axial position with Cu−S bond distance of 2.6974(6) Å. Electron paramagnetic resonance (EPR) measurement on **3** reveals a standard axial spectrum of copper(II) complex.[7]

Bubbling O_2 into a MeTHF solution of **1** at −135 °C led to the immediate formation of a new species (λ_{max} = 425 nm) that rapidly (~50 s) converted to the thermodynamically more stable end-on *trans*-peroxo-dicopper(II) species $[\{(^{DMA}N_3S)Cu^{II}\}_2(\mu\text{-}1,2\text{-}O_2^{2-})]^{2+}$ (**2**^{P}) (Figure 2, top) exhibiting strong UV−vis absorptions at λ_{max} = 534 (6500 M^{-1} cm^{-1}) and 604 (6600 M^{-1} cm^{-1}) nm (Figure 2, bottom) consistent with the feature of previously synthesized $S_{(thioether)}$-ligated (μ-1,2-peroxo)Cu^{II}_2.[6] The formulation of **2**^{P} is confirmed by

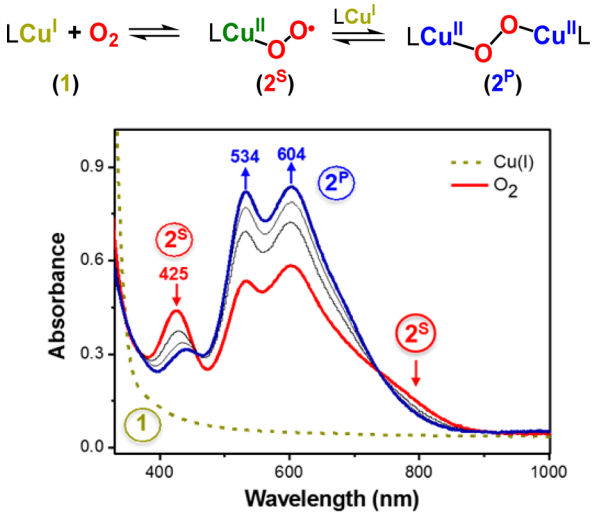


Figure 2. Low-temperature UV−vis absorption spectra of the reaction of **1** with O_2 at −135 °C in MeTHF (0.2 mM). The superoxo product **2**^{S} is observed immediately upon O_2 addition (red) and converted to the peroxo **2**^{P} (t = 50 s, blue).

resonance Raman (rR) spectroscopy (ν_{O-O} = 821 cm^{-1}, ν_{Cu-O} = 547 cm^{-1}).[7] Although the initially formed species has a short lifetime, the characteristic λ_{max} value of 425 nm and the transformation to a more stable (μ-1,2-peroxo)Cu^{II}_2 strongly suggest it is the S-ligated cupric superoxo species $[(^{DMA}N_3S)Cu^{II}(O_2^{\bullet-})]^+$ (**2**^{S}).

Interestingly, when polar or potentially hydrogen-bonding solvents such as acetone, ethanol, methanol, or trifluoroethanol (TFE) are mixed with MeTHF, $[(^{DMA}N_3S)Cu^{II}(O_2^{\bullet-})]^+$ (**2**^{S}) is much more persistent than is found in MeTHF only (Figure 3a; λ_{max} = 418, 605, 743 nm). There appears to be a shift of the

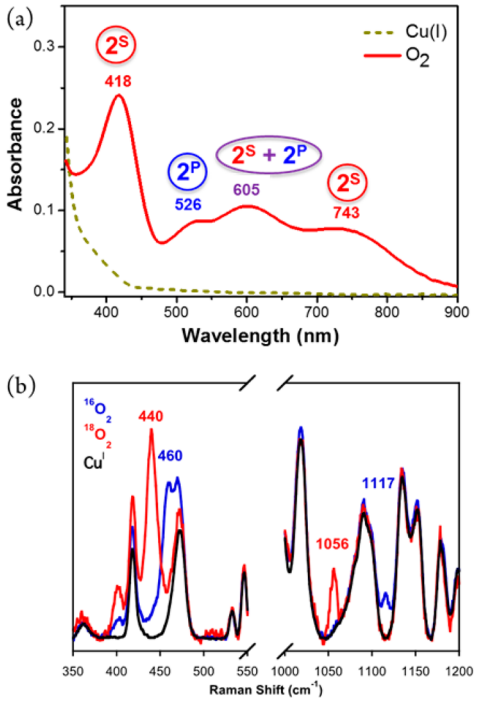


Figure 3. (a) Low-temperature (−135 °C) UV−vis absorption spectrum of **2**^{S} (containing ~11% **2**^{P}, λ_{max} = 526 nm, ε = 6500)[12] as recorded ~40 s after bubbling O_2 into a MeTHF:TFE (4:1) solution of **1** (0.098 mM). (b) rR spectra of frozen **2**^{S} (0.62 mM, λ_{ex} = 413 nm, 77 K) in MeTHF:TFE (4:1).[7]

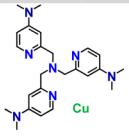
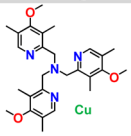
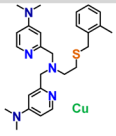
equilibrium constant to the mononuclear superoxide over the binuclear *trans*-peroxo complex. This result could be due to the formation of a hydrogen bond between an O-atom of the superoxide ligand and the TFE solvent, as observed in a "classical" cobalt(III)-superoxo complex with TFE.[10]

The rR spectra of **2**^{S} (λ_{ex} = 413 nm) reveal two dioxygen isotope sensitive vibrations (Figure 3b). An O−O stretch is observed at 1117 cm^{-1} which shifts to 1056 cm^{-1} upon $^{18}O_2$ substitution ($\Delta^{18}O_2$ = −61 cm^{-1}) and a Cu−O stretch at 460 cm^{-1} ($\Delta^{18}O_2$ = −20 cm^{-1}). The energy and isotope shifts of these vibrations confirm the assignment of **2**^{S} as an end-on superoxide species. In fact, these parameters closely match those for previously described cupric-superoxo complexes with tripodal tetradentate N_4 ligands (^{DMA}tmpa and ^{DMM}tmpa) (Table 1), both having ν_{O-O} = 1121 cm^{-1}.[4c,h] The species **2**^{S} is assigned as having an S = 1 (triplet) ground state based on literature precedent.[7,11]

In MeTHF:TFE (4:1 v:v), an approximately 4:1 (mol/mol) equilibrium mixture of (**2**^{S})/(**2**^{P})[12] forms within ~150 s following oxygenation of $[(^{DMA}N_3S)Cu^{I}]^+$ (**1**) at −135 °C. This mixture shows minimal decomposition over 1 h; thus, we could

DOI: 10.1021/ja511504n
J. Am. Chem. Soc. 2015, 137, 2796−2799

Table 1. Comparison of LCu^{II}/LCu^{I} Redox Potentials and Reactivity of Derived $[(L)Cu^{II}(O_2^{\bullet-})]^+$ Complexes

	^{DMA}tmpa[4c]	^{DMM}tmpa[4h]	$^{DMA}N_3S$
			
p-OMe-DTBP [a]	No [b]	No [b]	**Yes**
$AcrH_2$ [a]	No [b]	No [b]	**Yes**
$E_{1/2}$, mV [c]	−700	−570	−470

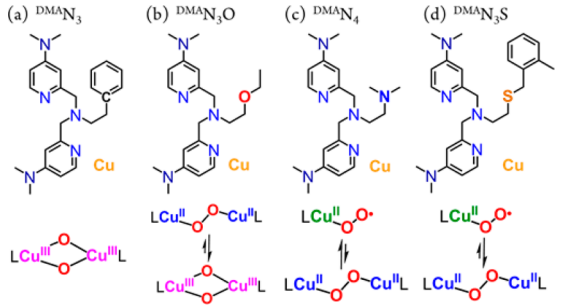
[a]Reaction comparisons of $[(L)Cu^{II}(O_2^{\bullet-})]^+$ complexes (MeTHF:TFE (4:1) at −135 °C) toward substrates. [b]Reactions do occur, but only above −100 °C. [c]$E_{1/2}$ (vs Fc^+/Fc) for $[(L)Cu^{II}(solvent)](ClO_4)_2$ complexes as determined by cyclic voltammetry.[7]

carry out reactivity studies of $\mathbf{2^S}$ with the O−H and C−H substrates, 2,6-di-*tert*-butyl-4-methoxyphenol (*p*-OMe-DTBP) and *N*-methyl-9,10-dihydroacridine ($AcrH_2$). Pseudo-first-order kinetic behavior was observed upon addition of *p*-OMe-DTBP (with $t_{1/2}$ = 3 min) or $AcrH_2$ ($t_{1/2}$ = 2 min) as monitored by the disappearance of the 418 nm UV−vis band of $\mathbf{2^S}$. Following workup at room temperature the products were analyzed as 2,6-di-*tert*-butyl-1,4-benzoquinone and 10-methyl-9-acridone, respectively.[7] Independent observations demonstrate that the complex $\mathbf{2^P}$ is unreactive toward these substrates. Warming up the $\mathbf{2^S}$ solution does not lead to sulfur oxygenation which can occur in bis(μ-oxo)Cu^{III}_2 species.[6d]

To assess the effect of the thioether donor in $\mathbf{2^S}$, we compared the reactivity of $(L)Cu^{II}(O_2^{\bullet-})$ complexes (L = ^{DMA}tmpa or ^{DMM}tmpa) toward the same substrates.[4c,h] Notably, both cupric superoxide complexes showed no reactivity under identical conditions (Table 1), although they do react above −100 °C. Thus, $\mathbf{2^S}$ with $S_{(thioether)}$-ligation is more reactive than the closely related N_4 superoxide compounds. The difference in reactivity is rationalized by the different donor strengths of the corresponding ligands. The substitution of a $S_{(thioether)}$ for a $N_{(pyridine)}$ donor decreases the ligand field strength, consistent with the $Cu^{II/I}$ redox potentials for the separately isolated Cu^{II} complexes in which thioether coordination raises the reduction potential by 230 mV (Table 1).[7] As a result, we hypothesize that $\mathbf{2^S}$ is more electrophilic and hence better able to accept an H-atom from either an O−H or C−H substrate, as compared to the N_4 complexes.

The influence of the Cu−S interaction on the oxygenated products was further probed by comparing Cu/O_2 species with different donor atoms binding Cu. Three structurally analogous ligands were synthesized replacing the sulfur site with carbon, oxygen, and nitrogen (Scheme 2).[7] The isolated Cu^I complex with tridentate $^{DMA}N_3$ ligand exhibits a distinctive 382 nm absorption band[7] upon O_2 addition at −135 °C in MeTHF. This absorption spectrum is consistent with a bis(μ-oxo)Cu^{III}_2 complex, which is known for many other products from low-temperature oxygenation of Cu^I-N_3 precursors.[6d,14] Under identical reaction conditions, oxygenation of the $Cu^I(^{DMA}N_3O)$, possessing three N-donors and an ether O-atom, leads to the initial formation of a (μ-1,2-peroxo)Cu^{II}_2 which rapidly (~1 min) converts to a bis(μ-oxo)Cu^{III}_2 species with very similar UV−vis spectrum as for the case with $^{DMA}N_3$.[6d,15] Thus, as seen before,[6d,16] the oxygen atom of the ether arm in $^{DMA}N_3O$ has an extremely weak to nonexistent interaction with the copper ion in the oxygenated product. We find that for $Cu^I(^{DMA}N_4)$ in

Scheme 2. Oxygenated Products of Ligand-Cu^I Complexes[13]



MeTHF (Scheme 2c), both Cu^{II}-superoxo and (μ-1,2-peroxo)-Cu^{II}_2 complexes are generated,[7] as in the case of $^{DMA}N_3S$. This strongly suggests that the $S_{(thioether)}$-atom donor of $^{DMA}N_3S$ ligand is coordinated in both Cu^{II}-superoxo/μ-1,2-peroxo complexes, $\mathbf{2^S}$ and $\mathbf{2^P}$. If it were not, a bis(μ-oxo)Cu^{III}_2 complex would prominently form.[17]

In summary, $[(^{DMA}N_3S)Cu^{II}(O_2^{\bullet-})]^+$ ($\mathbf{2^S}$) is the first reported example of a cupric superoxo species supported by a $S_{(thioether)}$ donor. This advance allowed us to determine that a superoxide species from an N_3S donor was more reactive toward O−H and C−H bonds than the corresponding N_4 complex. These results indicate that one role of the Met ligand in PHM and DβM is to activate the superoxide species for reaction by increasing its electrophilicity. The synthesis of this species will also allow us to further consider the role of thioether ligation on critical downstream O_2-reduced (and protonated) derivatives, such as Cu^{II}-hydroperoxo and to perform detailed kinetic analysis of the preliminary reactivity study presented here.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Details concerning X-ray crystallography analyses, including CIF files, NMR, UV−vis, EPR, and rR spectroscopies, cyclic voltammetry, ESI mass spectrometry, and procedures for carrying out the reactivity studies. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*edward.solomon@stanford.edu
*karlin@jhu.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors acknowledge support of this research from the National Institutes of Health (GM28962 to K.D.K., DK31450 to E.I.S., and Ruth L. Kirschstein National Research Service Award F32-GM105288 to R.E.C.).

■ REFERENCES

(1) (a) Klinman, J. P. *Chem. Rev.* **1996**, *96*, 2541. (b) Prigge, S. T.; Eipper, B.; Mains, R.; Amzel, L. M. *Science* **2004**, *304*, 864. (c) Klinman, J. P. *J. Biol. Chem.* **2006**, *281*, 3013. (d) Solomon, E. I.; Heppner, D. E.; Johnston, E. M.; Ginsbach, J. W.; Cirera, J.; Qayyum, M.; Kieber-Emmons, M. T.; Kjaergaard, C. H.; Hadt, R. G.; Tian, L. *Chem. Rev.* **2014**, *114*, 3659.

DOI: 10.1021/ja511504n
J. Am. Chem. Soc. 2015, 137, 2796−2799

(2) (a) Chen, P.; Solomon, E. I. *J. Am. Chem. Soc.* **2004**, *126*, 4991. (b) Chen, P.; Bell, J.; Eipper, B. A.; Solomon, E. I. *Biochemistry* **2004**, *43*, 5735.
(3) (a) Crespo, A.; Marti, M. A.; Roitberg, A. E.; Amzel, L. M.; Estrin, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 12817. (b) Yoshizawa, K.; Kihara, N.; Kamachi, T.; Shiota, Y. *Inorg. Chem.* **2006**, *45*, 3034. (c) Abad, E.; Rommel, J. B.; Kaestner, J. *J. Biol. Chem.* **2014**, *289*, 13726.
(4) (a) Fujisawa, K.; Tanaka, M.; Morooka, Y.; Kitajima, N. *J. Am. Chem. Soc.* **1994**, *116*, 12079. (b) Würtele, C.; Gaoutchenova, E.; Harms, K.; Holthausen, M. C.; Sundermeyer, J.; Schindler, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 3867. (c) Maiti, D.; Fry, H. C.; Woertink, J. S.; Vance, M. A.; Solomon, E. I.; Karlin, K. D. *J. Am. Chem. Soc.* **2007**, *129*, 264. (d) Kunishita, A.; Kubo, M.; Sugimoto, H.; Ogura, T.; Sato, K.; Takui, T.; Itoh, S. *J. Am. Chem. Soc.* **2009**, *131*, 2788. (e) Donoghue, P. J.; Gupta, A. K.; Boyce, D. W.; Cramer, C. J.; Tolman, W. B. *J. Am. Chem. Soc.* **2010**, *132*, 15869. (f) Peterson, R. L.; Himes, R. A.; Kotani, H.; Suenobu, T.; Tian, L.; Siegler, M. A.; Solomon, E. I.; Fukuzumi, S.; Karlin, K. D. *J. Am. Chem. Soc.* **2011**, *133*, 1702. (g) Pirovano, P.; Magherusan, A. M.; McGlynn, C.; Ure, A.; Lynes, A.; McDonald, A. R. *Angew. Chem., Int. Ed.* **2014**, *53*, 5946. (h) Lee, J. Y.; Peterson, R. L.; Ohkubo, K.; Garcia-Bosch, I.; Himes, R. A.; Woertink, J.; Moore, C. D.; Solomon, E. I.; Fukuzumi, S.; Karlin, K. D. *J. Am. Chem. Soc.* **2014**, *136*, 9925.
(5) (a) Kodera, M.; Kita, T.; Miura, I.; Nakayama, N.; Kawata, T.; Kano, K.; Hirota, S. *J. Am. Chem. Soc.* **2001**, *123*, 7715. (b) Zhou, L.; Nicholas, K. M. *Inorg. Chem.* **2008**, *47*, 4356. (c) Aboelella, N. W.; Gherman, B. F.; Hill, L. M. R.; York, J. T.; Holm, N.; Young, V. G.; Cramer, C. J.; Tolman, W. B. *J. Am. Chem. Soc.* **2006**, *128*, 3445. (d) Martínez-Alanis, P. R.; Sánchez Eguía, B. N.; Ugalde-Saldívar, V. M.; Regla, I.; Demare, P.; Aullón, G.; Castillo, I. *Chem.—Eur. J.* **2013**, *19*, 6067. (e) Hoppe, T.; Josephs, P.; Kempf, N.; Wölper, C.; Schindler, S.; Neuba, A.; Henkel, G. *Z. Anorg. Allg. Chem.* **2013**, *639*, 1504. (f) Tano, T.; Mieda, K.; Sugimoto, H.; Ogura, T.; Itoh, S. *Dalton Trans.* **2014**, *43*, 4871.
(6) (a) Hatcher, L. Q.; Lee, D.-H.; Vance, M. A.; Milligan, A. E.; Sarangi, R.; Hodgson, K. O.; Hedman, B.; Solomon, E. I.; Karlin, K. D. *Inorg. Chem.* **2006**, *45*, 10055. (b) Lee, Y.; Lee, D.-H.; Park, G. Y.; Lucas, H. R.; Narducci Sarjeant, A. A.; Kieber-Emmons, M. T.; Vance, M. A.; Milligan, A. E.; Solomon, E. I.; Karlin, K. D. *Inorg. Chem.* **2010**, *49*, 8873. (c) Park, G. Y.; Lee, Y.; Lee, D.-H.; Woertink, J. S.; Sarjeant, A. A. N.; Solomon, E. I.; Karlin, K. D. *Chem. Commun.* **2010**, *46*, 91. (d) Kim, S.; Ginsbach, J. W.; Billah, A. I.; Siegler, M. A.; Moore, C. D.; Solomon, E. I.; Karlin, K. D. *J. Am. Chem. Soc.* **2014**, *136*, 8063.
(7) See Supporting Information.
(8) Zhang, C. X.; Kaderli, S.; Costas, M.; Kim, E.-i.; Neuhold, Y.-M.; Karlin, K. D.; Zuberbühler, A. D. *Inorg. Chem.* **2003**, *42*, 1807.
(9) We believe the increased stability comes about as a result of a larger rate (constant) for formation of a $Cu^{II}(O_2^{\bullet-})$ complex, due to the nature of the ligand donor group; the rate of reaction of $Cu^{II}(O_2^{\bullet-})$ with a second ligand-Cu^{I} species is not as enhanced a reaction.
(10) Drago, R. S.; Cannady, J. P.; Leslie, K. A. *J. Am. Chem. Soc.* **1980**, *102*, 6014.
(11) Ginsbach, J. W.; Peterson, R. L.; Cowley, R. E.; Karlin, K. D.; Solomon, E. I. *Inorg. Chem.* **2013**, *52*, 12872.
(12) The ratio or relative amount of superoxo complex $\mathbf{2}^{\mathbf{S}}$ to *trans*-peroxo complex $\mathbf{2}^{\mathbf{P}}$ was determined by first finding and calculating the molar absorptivity (ε) for a solution of pure $\mathbf{2}^{\mathbf{P}}$ in MeTHF at −135 °C. Note: as described, initial oxygenation of a solution of a known concentration of **1** gives the $\mathbf{2}^{\mathbf{S}}/\mathbf{2}^{\mathbf{P}}$ mixture, but waiting 5 min leads to complete conversion to $\mathbf{2}^{\mathbf{P}}$.
(13) See the Supporting Information for cyclic voltammograms and redox potential values for the Cu^{II}/Cu^{I} complex couples for the $^{DMA}N_3$, $^{DMA}N_3O$, and $^{DMA}N_4$ ligands.
(14) (a) Mirica, L. M.; Ottenwaelder, X.; Stack, T. D. P. *Chem. Rev.* **2004**, *104*, 1013. (b) Hatcher, L. Q.; Karlin, K. D. *J. Biol. Inorg. Chem.* **2004**, *9*, 669.
(15) Kieber-Emmons, M. T.; Ginsbach, J. W.; Wick, P. K.; Lucas, H. R.; Helton, M. E.; Lucchese, B.; Suzuki, M.; Zuberbühler, A. D.; Karlin, K. D.; Solomon, E. I. *Angew. Chem., Int. Ed.* **2014**, *53*, 4935.
(16) Lucas, H. R.; Li, L.; Sarjeant, A. A. N.; Vance, M. A.; Solomon, E. I.; Karlin, K. D. *J. Am. Chem. Soc.* **2009**, *131*, 3230.
(17) More direct confirmation of a $Cu-S_{(thioether)}$ bond, such as by X-ray absorption spectroscopy (XAS), is not possible here due to the short lifetime of $\mathbf{2}^{\mathbf{S}}$ and the related fact that at the higher concentrations needed for XAS, transformation of $\mathbf{2}^{\mathbf{S}}$ to $\mathbf{2}^{\mathbf{P}}$ occurs.

DOI: 10.1021/ja511504n
J. Am. Chem. Soc. 2015, 137, 2796−2799