J|A|C|S
COMMUNICATIONS

A 1:1 Copper−Dioxygen Adduct is an End-on Bound Superoxo Copper(II) Complex which Undergoes Oxygenation Reactions with Phenols

Debabrata Maiti,† H. Christopher Fry,† Julia S. Woertink,‡ Michael A. Vance,‡
Edward I. Solomon,‡ and Kenneth D. Karlin*,†
Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218, and
Department of Chemistry, Stanford University, Stanford, California 94305

Received October 16, 2006; E-mail: karlin@jhu.edu

Reactive intermediates derived from binding and activation of dioxygen by a single copper ion site play a central role in the mechanism of biologically significant metalloenzymes, including amine oxidases, peptidylglycine-α-hydroxylating monooxygenase (PHM), and dopamine-β monooxygenases (DβM).[1−3] This enzyme chemistry, in particular, for PHM/DβM, has spurred continued emphasis on the development of mononuclear Cu−oxygen-derived chemistry,[1] for example, $Cu^{II}-O_2^-$,[3−5] $Cu^{II}-OOH$,[1,6] and $Cu^{II}-O\bullet$ species,[1,7−9] along with interrogation of their structures (e.g., end-on vs side-on), electronic nature/spectroscopy and reactivity.

Herein, we conclusively identify and prove *end-on* η^1-O_2^- ligation for a low-temperature stable cupric superoxide $Cu^{II}(O_2^-)$ species and for the first time describe exogenous substrate oxygenative reactivity. In a recent X-ray structure of PHM,[10] this 1:1 Cu^I/O_2 adduct has been observed and it has been suggested by some that such an entity would effect H-atom abstraction.[3−5] The end-on bound $Cu^{II}(O_2^-)$ moiety has been previously suggested to occur in a number of synthetically derived copper complex systems,[11−16] typically stopped-flow kinetic transients or low-temperature and sterically or electronically stabilized species. With a highly basic tripodal tetradentate N_4 ligand, Schindler and Sundermeyer recently obtained the first X-ray structure for a complex in this $Cu^{II}(O_2^-)$ class (∠Cu−O−O = 123.5°, Cu−O = 1.927 Å, O−O = 1.280 Å).[16]

The generation of superoxo−Cu(II) complex **1** starts with the colorless carbonyl complex $[Cu^I(NMe_2-TMPA)(CO)]^+$ (**2**),[17] in CO-saturated THF at −85 °C [λ_{max}= 350 nm (ϵ = 2500 M^{-1} cm^{-1}, Figure 1)]. Bubbling O_2 directly through the solution for 1 min (slowly displacing CO)[18] results in a color change to a brilliant green, giving an EPR silent complex formulated as $[Cu^{II}(NMe_2-TMPA)(O_2^-)]^+$ (**1**), λ_{max} = 418 nm (ϵ = 4300 M^{-1} cm^{-1}), 615 nm (ϵ= 1100 M^{-1} cm^{-1}), and 767 nm (ϵ = 840 M^{-1} cm^{-1}) (Figure 1), features which are identical to those observed in a stopped-flow spectroscopic $[Cu^I(NMe_2-TMPA)]^+/O_2$ reactivity study.[17] The UV−vis features also match the data extracted for the parent compound $Cu^{II}(O_2^-)$ species, $[Cu^{II}(TMPA)(O_2^-)]^+$ [λ_{max} = 410 nm (ϵ = 4000 M^{-1} cm^{-1}), 747 nm (ϵ = 1000 M^{-1} cm^{-1})].[11] The superoxide complex decays very slowly ($t_{1/2}$ ≥ 4 h) and without formation of the bridging binuclear peroxo species. The electron-rich nature of the NMe_2-TMPA ligand and the procedures/conditions used here lead to severely diminished (and not detectable) formation of the binuclear μ-1,2-bridged peroxo species $[\{Cu^{II}(NMe_2-TMPA)\}_2(O_2^{2-})]^{2+}$.[17] The X-ray structure and properties of the parent TMPA peroxo−dicopper(II) complex have been previously established.[19−22] Attack of the primary Cu^I/O_2 1:1 adduct by a second copper(I) ion is generally favorable in this and many other systems, making it normally difficult to characterize initial 1:1 Cu^I/O_2 (i.e., $Cu^{II}-O_2^-$) adducts.[1,21,23]

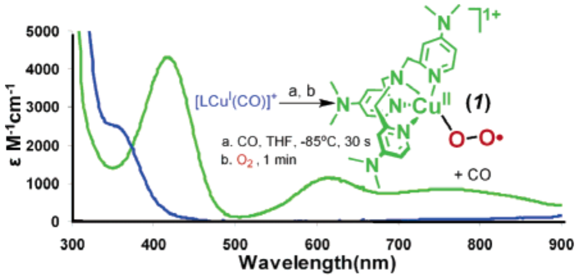


Figure 1. UV−visible spectra of $[Cu^I(NMe_2-TMPA)(CO)]^+$ (**2**) in CO-saturated THF at −85 °C, λ_{max} = 350 nm (blue) and after addition of O_2, producing $[Cu^{II}(NMe_2-TMPA)(O_2^-)]^+$ (**1**), λ_{max} = 418, 615, 767 nm (green).

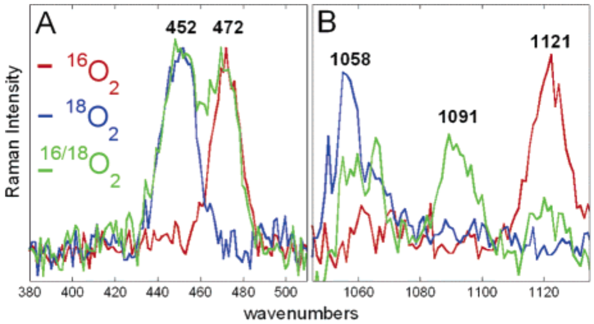


Figure 2. Solvent-subtracted rR spectra of THF solutions of $[Cu^{II}(NMe_2-TMPA)(O_2^-)]^+$ (**1**) (λ_{ex} = 413.1 nm). (A) Detail of the ν_{Cu-O} region. (B) Detail of the ν_{O-O} region. red, $^{16}O_2$; blue, $^{18}O_2$; green, $^{16-18}O_2$.[24]

The resonance Raman (rR) spectrum (λ_{ex}= 413.1 nm, 77 K) of $[Cu^{II}(NMe_2-TMPA)(O_2^-)]^+$ (**1**) in THF shows an O−O stretch at 1121 cm^{-1} which shifts to 1058 cm^{-1} upon $^{18}O_2$ isotopic substitution (Figure 2B). This stretching frequency is consistent with a bound superoxo species.[1,15,25] A Cu−O stretch was observed for the complex at 472 cm^{-1} and shifted to 452 cm^{-1} upon $^{18}O_2$ isotopic substitution. Upon substitution with a mixed isotope gas containing a 1:2:1 stoichiometric mixture of $^{18}O_2/^{16/18}O_2/^{18}O_2$ ($^{16/18}O_2$), a new intermediate O−O stretch at 1091 cm^{-1} appears (Figure 2B) as expected. For this mixed isotope sample, two equal intensity Cu−O stretches were resolved at 472 and 452 cm^{-1}, overlaying the pure isotope stretches (Figure 2A). This Cu−O splitting pattern is only consistent with an end-on, η^1 superoxo−Cu binding mode, as a symmetrically bound η^2 superoxo−Cu complex would be expected to show an additional ν(Cu−O) vibration at an averaged frequency position.[26]

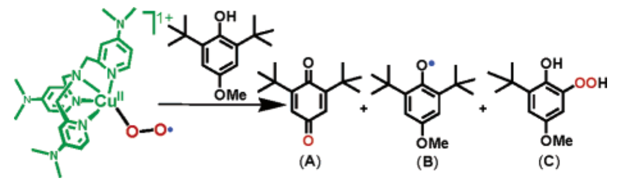
The reactivity of $[Cu^{II}(NMe_2-TMPA)(O_2^-)]^+$ (**1**) toward substituted phenols as potential H-atom donors was probed; there is considerable practical interest in such oxidations (with Cu),[27] and there is relevant literature with Co superoxo complexes,[28−34] along with examples involving Fe,[34,35] Mn,[34] as well as Cr and Rh.[36]

When *p*-MeO-2,6-DTBP[37] is added to a −85 °C THF solution of $[Cu^{II}(NMe_2-TMPA)(O_2^-)]^+$ (**1**) (excess O_2 removed), decom-

---

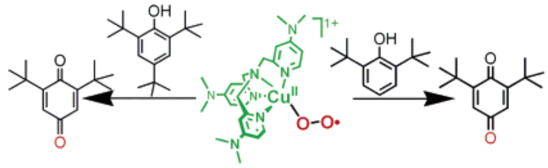
† The Johns Hopkins University.
‡ Stanford University.

10.1021/ja067411l CCC: $37.00 © 2007 American Chemical Society



position of **1** occurs over ∼30 min, as observed by UV−vis spectroscopy. A sharp strong peak is observed at ∼405 nm in the absorption spectrum along with $g \sim 2$ signal in EPR spectroscopy, indicating the formation of the stabilized phenoxyl radical (**B**, 40% yield, diagram).[18] Other products identified in this **1**/*p*-MeO-2,6-DTBP reaction are the 1,4-benzoquinone **A** (∼24% yield) and the arylhydroperoxide **C**, as identified by GC and GC−MS.[38] With an $^{18}O_2$ source, GC−MS reveals ^{18}O-incorporation (∼80% insertion into **A** and ∼90% into **C**).[18]

Unlike *p*-MeO-2,6-DTBP, the reaction of $[Cu^{II}(NMe_2{-}TMPA)(O_2^-)]^+$ (**1**) with 2,6-DTBP and 2,4,6-TTBP[37] produces only 2,6-di-*tert*-butyl-1,4-benzoquinonone (diagram), confirmed by GC and GC−MS after low-temperature reaction,[38] warming, and workup. With $^{18}O_2$ labeled **1**, ∼70% ^{18}O-atom incorporation occurs.[18]



Thus, the reactivity of $[Cu^{II}(NMe_2{-}TMPA)(O_2^-)]^+$ (**1**) appears to parallel that known for other M−superoxo species.[28−33,36] The superoxo complex **1** is able to effect hydroxylation and hydroperoxylation of phenols, with incorporated oxygen atoms derived from the $Cu^{II}{-}O_2^-$ moiety. In M = Co^{III}, Cr^{III}, and Rh^{III} or other M−superoxo complex mediated phenol reactions, initial H-atom abstraction (i.e., $M{-}O_2^- + ArOH \rightarrow M{-}OOH + ArO\bullet$) is implicated (however, it may not be rate-limiting[28]). The quinone and hydroperoxide products observed can be explained from reactions of initially formed ArO• and its further interactions with a $M{-}O_2^-$ complex. However, a number of mechanisms have been suggested, including those that do not derive from initial $M{-}O_2^-$/ArOH H-atom abstraction chemistry.[31,33,39−41] Thus, detailed mechanistic work on the chemistry described here is needed and planned. In addition, we will survey the reactivity of $[Cu^{II}(NMe_2{-}TMPA)(O_2^-)]^+$ (**1**) with other kinds of C−H, O−H, and N−H containing substrates.

In summary, the present work provides evidence for our early supposition[12] that a tripodal tetradentate TMPA-type ligand copper(I) complex O_2 reaction may lead to a terminally bound end-on superoxide−copper(II) species that was further hypothesized by Suzuki for tripodal tetradentate ligands,[14] demonstrated recently in the coordination complex (with an X-ray structure) of Schindler and Sundermeyer,[16] and has been seen in an X-ray structure of PHM.[10] The further significant advance is the demonstration of substrate oxidations starting from a superoxo−copper(II) complex; the observed phenol oxygenation reactions likely involve initial H-atom abstraction chemistry directly parallel to that known for other metal−superoxides, especially cobalt. Further investigations of the reactivity and complementary studies aiming toward O−O cleavage reactions (leading to $Cu^{II}{-}O\bullet$?) will provide a firmer basis for understanding chemical and biological copper-promoted oxidative processes with 1:1 Cu^I/O_2-derived species.

Acknowledgment. This work was supported by grants from the National Institutes of Health (K.D.K., GM28962; E.I.S, DK31450).

Supporting Information Available: Synthetic details, descriptions of reactions, and product analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Itoh, S. *Curr. Opin. Chem. Biol.* **2006**, *10*, 115.
(2) Gherman, B.; Heppner, D.; Tolman, W.; Cramer, C. *J Biol. Inorg. Chem.* **2006**, *11*, 197.
(3) Chen, P.; Solomon, E. I. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 13105−13110.
(4) Klinman, J. P. *J. Biol. Chem.* **2006**, *281*, 3013−3016.
(5) Chen, P.; Solomon, E. I. *J. Am Chem. Soc.* **2004**, *126*, 4991−5000.
(6) Kodera, M.; Kita, T.; Miura, I.; Nakayama, N.; Kawata, T.; Kano, K.; Hirota, S. *J. Am. Chem. Soc.* **2001**, *123*, 7715−7716.
(7) Crespo, A.; Marti, M. A.; Roitberg, A. E.; Amzel, L. M.; Estrin, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 12817−12828.
(8) Yoshizawa, K.; Kihara, N.; Kamachi, T.; Shiota, Y. *Inorg. Chem.* **2006**, *45*, 3034−3041.
(9) Decker, A.; Solomon, E. I. *Curr. Opin. Chem. Biol.* **2005**, *9*, 152−163.
(10) Prigge, S. T.; Eipper, B.; Mains, R.; Amzel, L. M. *Science* **2004**, *304*, 864−867.
(11) Karlin, K. D.; Wei, N.; Jung, B.; Kaderli, S.; Niklaus, P.; Zuberbühler, A. D. *J. Am Chem. Soc.* **1993**, *115*, 9506−9514.
(12) Lee, D.-H.; Wei, N.; Murthy, N. N.; Tyeklár, Z.; Karlin, K. D.; Kaderli, S.; Jung, B.; Zuberbühler, A. D. *J. Am. Chem. Soc.* **1995**, *117*, 12498−12513.
(13) Chaudhuri, P.; Hess, H.; Weyhermüller, T.; Wieghardt, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 1095−1098.
(14) Komiyama, K.; Furutachi, H.; Nagatomo, S.; Hashimoto, A.; Hayashi, H.; Fujinami, S.; Suzuki, M.; Kitagawa, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 59−72.
(15) Schatz, M.; Raab, V.; Foxon, S. P.; Brehm, G.; Schneider, S.; Reiher, M.; Holthausen, M. C.; Sundermeyer, J.; Schindler, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 4360−4363.
(16) Würtele, C.; Gaoutchenova, E.; Harms, K.; Holthausen, M. C.; Sundermeyer, J.; Schindler, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 3867−3869.
(17) Zhang, C. X.; Kaderli, S.; Costas, M.; Kim, E.-i.; Neuhold, Y.-M.; Karlin, K. D.; Zuberbühler, A. D. *Inorg. Chem.* **2003**, *42*, 1807−1824.
(18) See Supporting Information.
(19) Tyeklár, Z.; Jacobson, R. R.; Wei, N.; Murthy, N. N.; Zubieta, J.; Karlin, K. D. *J. Am. Chem. Soc.* **1993**, *115*, 2677−2689.
(20) Baldwin, M. J.; Ross, P. K.; Pate, J. E.; Tyeklár, Z.; Karlin, K. D.; Solomon, E. I. *J. Am. Chem. Soc.* **1991**, *113*, 8671−8679.
(21) Mirica, L. M.; Ottenwaelder, X.; Stack, T. D. P. *Chem. Rev.* **2004**, *104*, 1013−1045.
(22) Quant Hatcher, L.; Karlin, K. D. *J. Biol. Inorg. Chem.* **2004**, *9*, 669−683.
(23) Lewis, E. A.; Tolman, W. B. *Chem. Rev.* **2004**, *104*, 1047−1076.
(24) The noise in the 1058 cm^{-1} peak is higher due to overlap and subsequent subtraction with a large solvent peak.
(25) Cramer, C. J.; Tolman, W. B.; Theopold, K. H.; Rheingold, A. L. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 3635−3640.
(26) Pate, J. E.; Cruse, R. W.; Karlin, K. D.; Solomon, E. I. *J. Am. Chem. Soc.* **1987**, *109*, 2624−2630.
(27) Guieu, S. J. A.; Lanfredi, A. M. M.; Massera, C.; Pachon, L. D.; Gamez, P.; Reedijk, J. *Catal. Today* **2004**, *96*, 259−264.
(28) Zombeck, A.; Drago, R. S.; Corden, B. B.; Gaul, J. H. *J. Am. Chem. Soc.* **1981**, *103*, 7580−7585.
(29) Nishinaga, A.; Shimizu, T.; Matsuura, T. *Tetrahedron Lett.* **1981**, *22*, 5293−5296.
(30) Nishinaga, A.; Tomita, H.; Nishizawa, K.; Matsuura, T.; Ooi, S.; Hirotsu, K. *J. Chem. Soc., Dalton Trans.* **1981**, 1504−1514.
(31) Deng, Y. P.; Busch, D. H. *Inorg. Chem.* **1995**, *34*, 6380−6386.
(32) Musie, G. T.; Wei, M.; Subramaniam, B.; Busch, D. H. *Inorg. Chem.* **2001**, *40*, 3336−3341.
(33) Knaudt, J.; Forster, S.; Bartsch, U.; Rieker, A.; Jager, E. G. *Z. Naturforsch. B* **2000**, *55*, 86−93.
(34) Simandi, T. M.; May, Z.; Szigyarto, I. C.; Simandi, L. I. *Dalton Trans.* **2005**, 365−368.
(35) Shan, X. P.; Que, L. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 5340−5345.
(36) Bakac, A. *Coord. Chem. Rev.* **2006**, *250*, 2046−2058.
(37) Abbreviations: 2,4,6-TTBP = 2,4,6-tri-*tert*-butylphenol; 2,6-DTBP = 2,6-di-*tert*-butylphenol; *p*-MeO-2,6-DTBP = 2,6-di-*tert*-butyl-4-methoxyphenol.
(38) For product **A**, we detected formaldehyde[18] as a product derived from the −OMe substituent, but we have not yet elucidated products derived from the *t*-Bu substituent loss in formation of **C** or reaction of 2,4,6-TTBP.
(39) Gupta, M.; Upadhyay, S. K.; Sridhar, M. A.; Mathur, P. *Inorg. Chim. Acta* **2006**, *359*, 4360−4366.
(40) Fecenko, C. J.; Meyer, T. J.; Thorp, H. H. *J. Am. Chem. Soc.* **2006**, *128*, 11020−11021.
(41) Sun, H. J.; Harms, K.; Sundermeyer, J. *J. Am. Chem. Soc.* **2004**, *126*, 9550−9551.

JA067411L