Modeling Copper-Dioxygen Reactivity in Proteins: Aliphatic C-H Bond Activation by a New Dicopper(II)-Peroxo Complex

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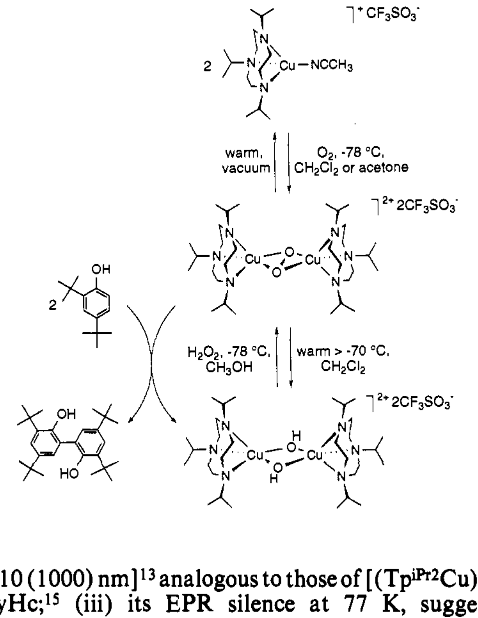
The central role of the binding and/or activation of dioxygen by copper(I) ions in a wide range of important processes in biology and catalysis has led to intense interest in the synthesis, characterization, and examination of the reactivity of Cu_nO_2 complexes.[1] Relatively few such complexes have been definitively identified, however, and only two, $[((TMPA)Cu)_2(O_2)](PF_6)_2$[2,3] and $[(Tp^{iPr2}Cu)_2(O_2)]$,[2,4] have been characterized structurally by X-ray crystallography. The former complex contains a *trans*-μ-1,2-peroxo ligand, while the latter has a planar dicopper(II)-μ-η^2:η^2-peroxo core that accurately models the dioxygen adduct of hemocyanin (Hc).[5] Despite extensive studies of the reaction pathways followed by these and other less well-defined Cu/O_2 adducts in synthetic and biological systems, our understanding of the relationship between their structural features and their reactivity with substrates remains rudimentary.[1,6] In particular, insight into the mechanistic details of aliphatic hydrocarbon oxidations that involve Cu/O_2 species in proteins, such as those catalyzed by dopamine β-monooxygenase (DβM),[7] peptidylglycine α-amidating enzyme (PAM),[8] and particulate methane monooxygenase (pMMO),[9] has been limited by the relatively small number of synthetic copper-dioxygen complexes available for study and their general lack of reactivity with aliphatic C-H bonds. Here we report the preparation of a new dicopper(II)-μ-η^2:η^2-peroxo complex and demonstrate unequivocally the cleavage of an sp^3 C-H(D)bond by the Cu_2O_2 unit.[10]

Treatment of solutions of $[LCu(CH_3CN)]CF_3SO_3$ (L = 1,4,7-triisopropyl-1,4,7-triazacyclononane)[11,12] in CH_2Cl_2 or acetone with dry O_2 at -78 °C resulted in the formation of red-brown $[(LCu)_2(O_2)](CF_3SO_3)_2$ (Scheme 1). The adduct was not perturbed by an N_2 purge or application of vacuum at -78 °C, suggesting that O_2 binding is essentially irreversible at this temperature. Assignment of a dicopper(II)-μ-η^2:η^2-peroxo structure to the product is based on (i) manometric data [Cu:O_2 = 2.2(2):1]; (ii) its UV-vis spectrum, which contains $O_2^{2-} \rightarrow$ Cu(II) charge transfer bands [Figure 1; λ_{max} = 365 ($\epsilon \sim$ 11 000 M^{-1} cm^{-1}), 510 (1000) nm][13] analogous to those of $[(Tp^{iPr2}Cu)_2(O_2)]$[14] and oxyHc;[15] (iii) its EPR silence at 77 K, suggestive of antiferromagnetic coupling between Cu(II) ions; and (iv) its resonance Raman spectrum, which contains ν_{O-O} at 722 cm^{-1} [$\nu_{O-O}(^{18}O_2)$ = 680 cm^{-1}; $\Delta\nu(^{16}O_2-^{18}O_2)$ = 42 cm^{-1} = $\Delta\nu_{calc}$]. This low ν_{O-O} value is consistent with a weak O-O bond[6,15] and is similar to those of $[(Tp^{R2}Cu)_2(O_2)]$ (R = Ph, 759 cm^{-1}; R = iPr, 741 cm^{-1}; R = Me, 731 cm^{-1})[4] and oxyHc (750 cm^{-1}).[16] Additional evidence in favor of the presence of a peroxo ligand in the O_2 adduct includes (i) identification of H_2O_2 (77% yield) by iodometric titration after addition of excess $HBF_4 \cdot Et_2O$ to the complex and (ii) generation of a UV-vis spectrum identical to that obtained upon addition of O_2 to the Cu(I) starting material

Scheme 1



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[2] Abbreviations used: TMPA, tris(2-pyridylmethyl)amine; Tp^{iPr2}, tris-(3,5-diisopropylpyrazolyl)hydroborate.

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[12] $[LCu(CH_3CN)]CF_3SO_3$: ^1H NMR (CD_3CN, 300 MHz) δ 3.07 (septet, *J* = 6.6 Hz, 3H), 2.84-2.74 (m, 6H), 2.50-2.59 (m, 6H) 1.96 (s, 3H), 1.20 (d, *J* = 6.6 Hz, 18H). Anal. Calcd. for $C_{18}H_{36}CuF_3N_4O_3S$: C, 42.47; H, 7.13; N, 11.00. Found: C, 42.86; H, 7.43; N, 10.18. $[(LCu)_2(OH)_2]$-$(CF_3SO_3)_2$: FTIR (KBr, cm^{-1}) 3590 (ν_{OH}; 2653, ν_{OD}), 3440 (H_2O), 2977, 2879, 1626 (H_2O), 1498, 1471, 1390, 1370, 1351, 1260, 1224 ($CF_3SO_3^-$), 1149 ($CF_3SO_3^-$), 1074, 1030 ($CF_3SO_3^-$), 967, 765, 720, 637 ($CF_3SO_3^-$), 572, 517; UV-vis (CH_2Cl_2) [λ_{max}, nm (ϵ, M^{-1} cm^{-1})] 360 (2540), 664 (200); EPR (9.1 GHz, 77 K) silent; electrospray MS (CH_2Cl_2) *m/z* (relative abundance) 821.2 ($[(LCu)_2(OH)_2(CF_3SO_3)]^+$, 100), 335.1 ($[LCu(OH)]^+$, 40). Anal. Calcd for $C_{32}H_{68}Cu_2F_6N_6O_8S_2$: C, 39.62; H, 7.07; N, 8.66. Found: C, 38.88; H, 7.01; N, 8.44. The complex as isolated is extremely hygroscopic; inclusion of one water molecule, the presence of which is supported by the IR spectrum, significantly improves the elemental analysis. Anal. Calcd for $C_{32}H_{70}Cu_2F_6N_6O_9S_2$: C, 38.90; H, 7.14; N, 8.50.

[13] The low ratio of ϵ values for the charge transfer bands (~11:1 vs ~20:1 in oxyHc) has been observed for other proposed Cu_2O_2 adducts. See: (a) Sorrell, T. N.; Garrity, M. L.; Richards, J. L.; White, P. S. *Inorg. Chim. Acta* **1994**, *218*, 103-108. (b) Nasir, M. S.; Karlin, K. D.; McGowty, D.; Zubieta, J. *J. Am. Chem. Soc.* **1991**, *113*, 698-700.

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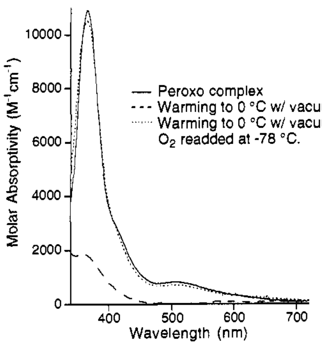


Figure 1. UV-vis spectrum of $[(LCu)_2(O_2)](CF_3SO_3)_2$ and spectroscopic demonstration of the reversible nature of O_2 binding.

by adding aqueous H_2O_2 to a solution of the dicopper(II)-bis-(μ-hydroxo) complex $[(LCu)_2(OH)_2](CF_3SO_3)_2$[12] in CH_3OH at -78 °C.

Although it appears on the basis of the data collected so far that $[(LCu)_2(O_2)](CF_3SO_3)_2$ and $[(Tp^{R2}Cu)_2(O_2)]$ contain structurally similar μ-η^2:η^2-peroxo units, key aspects of their reactivity differ. For example, in contrast to the Tp^{R2} peroxo complexes,[17] O_2 binding to $[LCu(CH_3CN)](CF_3SO_3)$ is reversible upon warming under vacuum, as shown by the UV-vis cycling data shown in Figure 1. In addition, quantitative radical coupling of 2,4-di-*tert*-butylphenol was effected by the peroxo compound at -78 °C in the absence of uncoordinated O_2 to cleanly afford $[(LCu)_2(OH)_2](CF_3SO_3)_2$ (Scheme 1). This efficient radical generation and coupling differs from the reactivity observed for $[(Tp^{Me2}Cu)_2(O_2)]$, which yields diphenoquinones under similar conditions,[17] but is analogous to that reported for a putative "bent" μ-η^2:η^2-peroxo complex.[18]

Most intriguing were the results of experiments in which $[(LCu)_2(O_2)](CF_3SO_3)_2$ was warmed without application of vacuum in the absence of external reagents, conditions which led to the formation of the hydroxo-bridged compound $[(LCu)_2(OH)_2](CF_3SO_3)_2$ as the major product (85% yield, Scheme 1).[19] Decomposition of the peroxo complex perdeuterated at the isopropyl substituents yielded OD-bridged product (FTIR; ν_{OD} = 2653 cm^{-1}, ν_{OH}/ν_{OD} = 1.35; calcd = 1.37), demonstrating conclusively that the H(D) atoms of the bridges are derived from the isopropyl groups of the triazacyclononane ligand. Analysis of kinetic data obtained by monitoring the decrease of the 510 nm band of the dicopper(II)-peroxo complexes containing H- and D-substituted isopropyl groups as a function of time over the temperature range 223-263 K revealed that the reaction to form $[(LCu)_2(OH)_2](CF_3SO_3)_2$ was first-order with respect to the peroxo complex and that it exhibited a large primary isotope effect [k_H/k_D = 18(1) at 298 K][20] with a minor temperature dependence described by $\Delta H^‡_H$ = 13.5(5) kcal mol^{-1}, $\Delta S^‡_H$ = -12(1) eu, $\Delta H^‡_D$ = 14.0(5) kcal mol^{-1}, and $\Delta S^‡_D$ = -16(1) eu (Figure 2). These data conclusively demonstrate that the rate-determining step in the decomposition of the peroxo species involves cleavage of a C-H(D) bond of the isopropyl group(s), a transformation relevant to C-H activation processes mediated by Cu/O_2 species in proteins (cf. DβM, PAM, and pMMO) that, to our knowledge, has not been demonstrated previously for a synthetic copper-peroxo complex.[21] Reinaud and Theopold observed similar attack at the ligand isopropyl groups of a dicobalt-peroxo complex $[(Tp^{iPr2}Co)_2(O_2)]$[22] but with significantly different kinetic parameters [$\Delta H^‡_H$ = 16.4(5) kcal mol^{-1}, $\Delta S^‡_H$ = -12(1) eu, $\Delta H^‡_D$ = 19.2(5) kcal mol^{-1}, and $\Delta S^‡_D$ = -8(1) eu]. These kinetic data were interpreted to indicate a substantial tunneling contribution to the reaction rate that is not evident in our system.[23] Nonetheless, a rate-determining step involving peroxo O-O bond cleavage in concert with (*not* prior to)[24] two intramolecular H atom abstractions analogous to that proposed for the $Tp^{iPr2}Co$ case (cf. transition state **A**) is consistent with the large k_H/k_D and negative $\Delta S^‡$ values we have measured.[25] Subsequent rapid trapping of the resulting tertiary alkyl radicals by solvent or CH_3CN hydrogen atoms would account for the final product isolated.

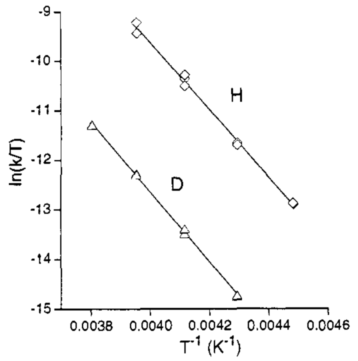
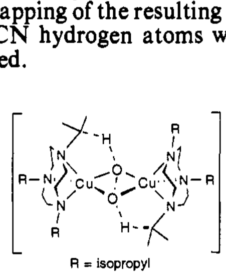


Figure 2. Eyring plot for the decompositions of $[(LCu)_2(O_2)](CF_3SO_3)_2$ (**H**) and $[(d_{21}\text{-}LCu)_2(O_2)](CF_3SO_3)_2$ (**D**) in CH_2Cl_2 (see text for derived activation parameters).



A

Important aspects of biological copper-dioxygen chemistry are modeled by the work described here. Both structural and functional mimicry of Hc are demonstrated by the reversible binding of O_2 to yield a dicopper(II)-μ-η^2:η^2-peroxo species. Most significantly, the definitive characterization of an aliphatic C-H bond activation reaction by the Cu_2O_2 unit suggests that such moieties (or related species) in biological systems may be capable of directly attacking nonaromatic hydrocarbons, a mechanistic possibility for copper protein-catalyzed oxidations that should be considered in future synthetic and biochemical research.

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Supplementary Material Available: Representative first-order kinetic plot (233 K) for the peroxo complex decompositon reactions (1 page). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(19) Another minor (<15%) coproduct is formed that will be discussed in a future report.

(20) Calculated at this temperature from the activation parameters.

(21) Hydroxylation of one ethyl group of *N,N,N',N'*-tetraethylethylenediamine ligated to Cu(I) in the presence of excess O_2 has been reported, but the direct involvement of a copper-peroxo complex as the oxidant in this reaction was not verified. See: Thompson, J. S. *J. Am. Chem. Soc.* **1984**, *106*, 8308-8309 and references therein.

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(24) In contrast, the pathway proposed for the decomposition of $[(Tp^{Me2}Cu)_2(O_2)]$ involves rate-determining peroxo cleavage to monomeric $Tp^{Me2}CuO^•$ species that are subsequently trapped (e.g., by a $Tp^{Me2}Cu(I)$ fragment to yield $[(Tp^{Me2}Cu)_2O]$).[17]

(25) A reviewer has suggested that **A** "is extremely ordered and is in many ways similar to a ternary complex if one considers the two isopropyl hydrogens independently. Such a ternary complex is usually formed via two sequential binary events and the intermediate complex *AB* is stabilized pending its interaction with *C*. A possible pathway here might be such a sequential reaction where the peroxide undergoes a slow one-electron event followed by a fast radical abstraction at the second isopropyl group. The kinetics of such a process would be indistinguishable from the current proposal." We concur, as long as the "slow one-electron event" involves C-H(D) bond breaking (to explain the kinetic isotope effect).