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Reactivity of Mononuclear Alkylperoxo Copper(II) Complex. O−O Bond Cleavage and C−H Bond Activation

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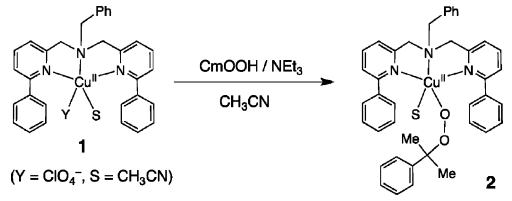
Mononuclear copper-active oxygen species play important roles as reactive intermediates in many biological and industrial catalytic oxidation processes.[1−3] For copper monooxygenases such as peptidylglycine α-amidating monooxygenase (PAM) and dopamine β-monooxygenase (DβM), a mononuclear hydroperoxo copper(II) species LCu(II)−OOH, which is formally generated by the reaction of LCu(I) and O_2 and subsequent addition of H$^\bullet$ (or $H^+ + e^-$), has been suggested as the reactive intermediate for the aliphatic hydroxylation of the substrates.[4] More recently, a mononuclear superoxo copper(II) species LCu(II)−OO$^\bullet$, initially formed intermediate of the reaction between LCu(I) and O_2, has also been proposed as a possible reactive intermediate.[5−8] Furthermore, a recent QM/MM calculation study has suggested that a copper(II)−oxyl radical species LCu(II)−O$^\bullet$, which can be generated by O−O bond homolysis of LCu(II)−OOH, is the most reactive species among the intermediates.[9] To gain insight into the dioxygen activation mechanism at the mononuclear copper active sites, a great deal of effort has been made in model chemistry to evaluate the structure, spectroscopic features, and reactivity of the mononuclear copper-active oxygen species.[1−3,10−18]

On the other hand, alkylperoxo iron(III) complexes LFe(III)−OOR have been studied extensively in model systems to provide significantly important insights into the catalytic mechanism of nonheme iron monooxygenases.[19−21] In this respect, studies of mononuclear alkylperoxo copper(II) complexes LCu(II)−OOR may also afford important information about the dioxygen activation mechanism at the mononuclear copper reaction centers. However, little is known about the reactivity of LCu(II)−OOR complexes.[22−24]

We herein report the reactivity study of a new mononuclear alkylperoxo copper(II) complex **2**, which is generated by the reaction of copper(II) starting material **1**[24] and cumene hydroperoxide (CmOOH) in CH_3CN (Scheme 1). The cumylperoxo copper-

Scheme 1



(II) complex **2** has been found to undergo homolytic cleavage of the O−O bond and induce C−H bond activation of exogenous substrates, providing important insight into the catalytic mechanism of the copper monooxygenases.

Treatment of **1** with cumene hydroperoxide in the presence of triethylamine in acetonitrile at −40 °C gave cumylperoxo copper-

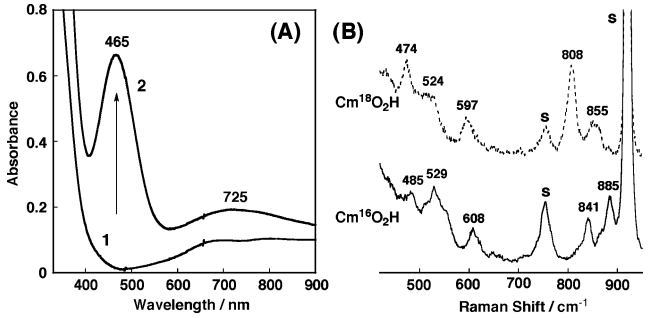


Figure 1. (A) Spectral change for the reaction of **1** (0.6 mM) with CmOOH (1.2 mM) in the presence of NEt_3 (0.6 mM) in CH_3CN at −40 °C. (B) Resonance Raman spectra of **2** generated by using Cm^{16}O^{16}OH (solid line, below) and Cm^{18}O^{18}OH (dotted line, above) obtained with $\lambda_{ex} = 488.0$ nm in CH_3CN at −40 °C; s denotes the solvent bands.

(II) complex **2**, the formation of which was confirmed by the following experimental data. Thus, complex **2** exhibited a relatively intense absorption band at 465 nm ($\epsilon = 1100$ M^{-1} cm^{-1}) due to the peroxo−to−copper(II) charge transfer transition (LMCT) together with a weak d−d band at 725 nm ($\epsilon = 320$ M^{-1} cm^{-1}) as shown in Figure 1A. Complex **2** also gave isotope-sensitive resonance Raman bands at 885, 841, 608, 529, and 485 cm^{-1}, which shifted to 855, 808, 597, 524, and 474 cm^{-1} upon ^{18}O-substitution using Cm^{18}O^{18}OH instead of Cm^{16}O^{16}OH (Figure 1B). Appearance of the multiple resonance Raman bands and their associated isotope shifts ($\Delta n = 30$, 33, 11, 5, and 11 cm^{-1}) are similar to those reported from the resonance Raman studies of the cumylperoxo copper(II) complex supported by the hydrotrispyrazolylborate ligand and the cumylperoxo iron(III) complex of 6-Me$_3$-TPA [tris(6-methyl-2-pyridylmethyl)amine].[23,25] By analogy to those detailed Raman studies, the bands in the 800 cm^{-1} region of **2** can be assigned to mixed O−O/C−O/C−C vibrations of the cumylperoxo group and the band at 608 cm^{-1} to the Cu−O stretching vibration. Then, the additional 529 and 485 cm^{-1} bands of **2** can be assigned to C−C−C and C−C−O deformation modes of the alkylperoxo moiety.[23]

The ESR spectrum of **2** (Figure S1, $g_1 = 2.250$, $g_2 = 2.065$, $g_3 = 2.030$, $A_1 = 160$, $A_2 = 7$, $A_3 = 5$ G), which is different from that of the starting material **1** (Figure S2), reflected a distorted tetragonal geometry of **2**, and its mononuclearity was confirmed by spin quantification using the ESR spectrum (99% spin remained). Unfortunately, instability of **2** precluded us from getting ESI-MS data even at the low temperature.

The cumylperoxo copper(II) complex **2** gradually decomposed, obeying first-order kinetics even at −40 °C ($k_{dec} = 2.2 \times 10^{-3}$ s^{-1}, Figure S3) to give bis(μ-hydroxo)dicopper(II) complex **4** in a 64% isolated yield, where no ligand hydroxylation took place (see Supporting Information). Notably, acetophenone (PhC(O)CH$_3$) was obtained in a 92% yield from the final reaction mixture. This clearly

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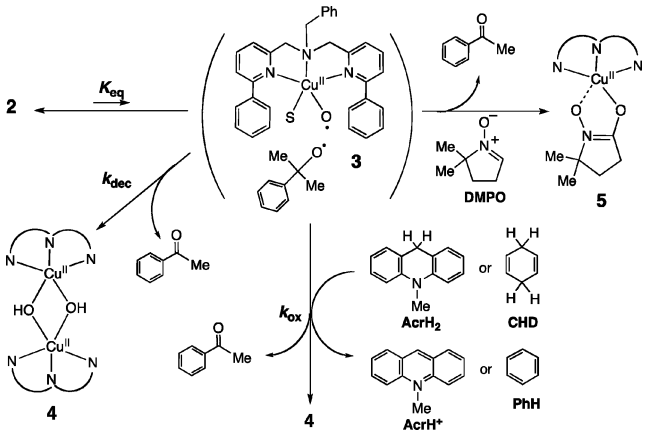
Scheme 2



demonstrates that O−O bond homolysis of the peroxo moiety of **2** occurred since it is well-known that cumyloxyl radical quickly undergoes β-scission to give acetophenone ($k = 6.3 \times 10^5$ s^{-1} at 30 °C).[26] In fact, LCu(II)−O$^\bullet$ species **3**, generated by the O−O bond homolysis of **2**, was trapped by the reaction with 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO), a well-known radical trap reagent,[16,17,27] where formation of a 1:1 adduct **5** between **3** and DMPO was confirmed by the ESI-MS and ESR measurements (a possible structure of **5** is indicated in Scheme 2).[28]

Addition of $AcrH_2$ (10-methyl-9,10-dihydroacridine) into the acetonitrile solution of **2** at −40 °C resulted in formation of $AcrH^+$ (*N*-methylacridinium ion) as an oxidation product. Figure S7 shows the spectral change for the reaction, where the characteristic absorption band at 465 nm due to **2** decreases with a concomitant increase in the absorption bands at 358, 395, 415, and 440 nm due to $AcrH^+$. From the absorption intensity at 440 nm ($\epsilon = 2150$ M^{-1} cm^{-1}),[29] the yield of $AcrH^+$ was determined as 49% based on **2**.[30] The reaction obeyed first-order kinetics in the presence of a large excess of $AcrH_2$ as shown in the inset of Figure S7. Plot of the first-order rate constant k_{obs} against the substrate concentration gave a linear line, from which the second-order rate constant k_2 ($= k_{ox}K_{eq}$) was determined as 6.7 M^{-1} s^{-1} (Figure S8).[31] In addition, a significantly large kinetic deuterium isotope effect of $k_2^H/k_2^D = 19.2$ was obtained at −40 °C when $AcrD_2$ ($AcrD_2$/9,9-dideuterated derivative) was used in place of $AcrH_2$ (Figure S8). Existence of such a large kinetic deuterium isotope effect clearly indicates that a hydrogen transfer process is involved in the rate-determining step of the C−H bond activation of $AcrH_2$ by **2**. Similarly, oxidation of 1,4-cyclohexadiene (CHD) proceeded smoothly ($k_{ox} = 0.25$ M^{-1} s^{-1}, Figures S9 and S10), and the formation of benzene product was confirmed by GC−MS.

Apparently, the oxidation of exogenous substrates ($AcrH_2$ and CHD) by **2** proceeds via the O−O bond homolysis since acetophenone was also produced in these reactions as in the case of the self-decomposition of **2** (Scheme 2). Although the mechanism involving stepwise O−O bond cleavage and C−H bond activation of the substrate (rate $= k_{ox}K_{eq}$[**2**][substrate]) and its concerted variant could not be distinguished by the kinetic data, the present results suggest a possible contribution of a mononuclear copper(II)−oxyl radical species LCu(II)−O$^\bullet$ (**3**) to the C−H bond activation process.[32] In summary, the reactivity (the O−O bond homolysis and the C−H bond activation of the exogenous substrates) of the alkylperoxo copper(II) complex has been explored for the first time to provide important insights into the catalytic mechanism of copper monooxygenases.

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Supporting Information Available: Experimental details for the synthetic procedures and additional spectroscopic and kinetic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) The ESI-MS of **5** gave a set of peaks at 632.4 with $Cm^{16}O_2H$, which shifted to 634.4 with $Cm^{18}O_2H$ (Figure S5). The mass distribution patterns and their associated isotope shift are fully consistent with the proposed structure of **5**. The ESR spectrum of **5** (Figure S6) indicated a distorted tetragonal structure of **5**, and spin quantification using the ESR technique revealed that the yield of **5** was 78%. Incorporation of ^{18}O into acetophenone was also confirmed by EI-MS using $Cm^{18}O_2H$.
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(31) The intercepts of Figure S8 (2.2×10^{-3} s^{-1}) and Figure S10 (2.2×10^{-3} s^{-1}) are identical to the self-decomposition rate (2.2×10^{-3} s^{-1}).
(32) During the course of our research, a possible contribution of LCu(II)−O$^\bullet$ has been reported in some copper-dependent oxidation reactions.[18] (a) Hong, S.; Huber, S. M.; Gagliardi, L.; Cramer, C. J.; Tolman, W. B. *J. Am. Chem. Soc*. **2007**, *129*, 14190−14193. (b) Comba, P.; Knoppe, S.; Martin, B.; Rajaraman, G.; Rolli, C.; Shapiro, B.; Stork, T. *Chem.−Eur. J*. **2008**, *14*, 344−357.

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