

Aromatic Hydroxylation Reactivity of a Mononuclear Cu(II)–Alkylperoxy Complex

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The reactions of copper(II) complexes and hydrogen peroxide (H_2O_2) have been studied extensively in order to gain insight into reactive intermediates involved in copper monooxygenases and copper oxidases as well as copper-catalyzed oxidation reactions.^{1–19} Several types of mononuclear and dinuclear copper/active-oxygen complexes have been reported, and their structures and physico-chemical properties have been explored in detail.^{1–19} However, less is known about the intrinsic reactivity of the generated copper/active-oxygen complexes.

We herein report a new copper(II)–alkylperoxy species 2^{X} [2-hydroxy-2-hydroperoxypropane (HHPP) adduct], which is generated by the reaction of H_2O_2 and copper(II) complex 1^{X} supported by the bis(pyridylmethyl)amine tridentate ligand containing *m*-substituted phenyl groups at the 6-positions of the pyridine rings (L^{X}) in acetone in the presence of triethylamine (NEt_3) (Scheme 1). The alkylperoxy intermediate 2^{X} undergoes an efficient aromatic ligand hydroxylation reaction, producing phenolate complex 4^{X} via another intermediate 3^{X} . Kinetic studies on the aromatic hydroxylation process are reported here together with spectral characterization of 2^{X} .

Starting mononuclear copper(II) complexes 1^{X} supported by ligand L^{X} ($\text{X} = \text{NO}_2, \text{Cl}, \text{H}, \text{Me}, \text{OMe}$; $\text{Y} = \text{ClO}_4^-$ or H_2O ; $\text{S} = \text{CH}_3\text{CN}$ or H_2O) were prepared by mixing the ligands and $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ in acetone or acetonitrile (Figures S1–S4).²⁰ The reaction of 1^{X} and H_2O_2 (1 equiv) was then examined in acetone at -70°C in the presence of triethylamine (1 equiv). Figure 1A shows a spectral change for the reaction of 1^{NO_2} as a typical example, where intermediate 2^{NO_2} exhibiting a characteristic absorption band at 420 nm ($\epsilon = 1350 \text{ M}^{-1} \text{ cm}^{-1}$) together with a weak d–d band at 630 nm ($\epsilon = 200 \text{ M}^{-1} \text{ cm}^{-1}$) becomes apparent. Spectroscopic titration for the generation of 2^{NO_2} established that the stoichiometry of 1^{NO_2} to H_2O_2 was 1:1 (Figure S5). Similar spectral changes were obtained with other ligand systems (Figures S6–S9). A more detailed characterization of intermediate 2^{X} was carried out for 2^{NO_2} since it showed higher stability than any other (as discussed further below).

Intermediate 2^{NO_2} generated with $\text{H}_2^{16}\text{O}_2$ showed isotope sensitive Raman bands at 855, 823, 792, and 545 cm^{-1} when an acetone- d_6 (CD_3COCD_3) solution of 2^{NO_2} was excited with a 441.6 nm laser light (Figure S10). These Raman bands shifted to 825, 803, 785, and 525 cm^{-1} , respectively, when $\text{H}_2^{18}\text{O}_2$ was used (Figure S10). The appearance of multiple Raman bands in the 800 cm^{-1} region and their associated isotope shifts ($\Delta\nu = 30, 20, \text{ and } 7 \text{ cm}^{-1}$) as well as their intensity patterns are similar to those reported from

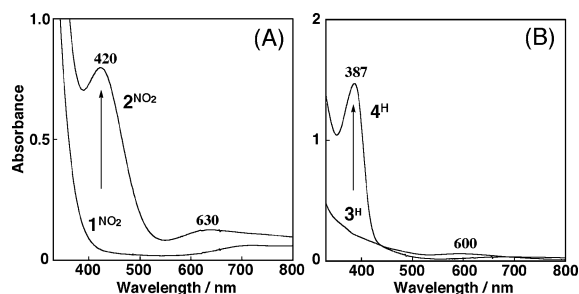
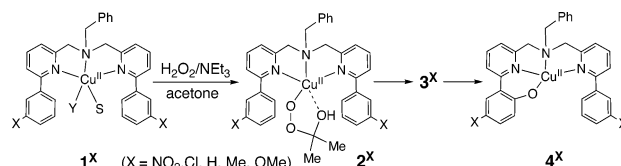


Figure 1. (A) UV–vis spectra of 1^{NO_2} (0.6 mM) and 2^{NO_2} from the reaction of 1^{NO_2} and H_2O_2 (0.6 mM) in the presence of NEt_3 (0.6 mM) in acetone at -70°C . (B) UV–vis spectra of 3^{H} and 4^{H} generated by decomposition of 2^{H} in acetone.

Scheme 1



resonance Raman studies of copper(II)–alkylperoxy ($\text{Cu}^{\text{II}}\text{–OOR}$) and iron(III)–alkylperoxy ($\text{Fe}^{\text{III}}\text{–OOR}$) complexes ($\text{R} = \textit{tert}$ -butyl and cumyl), where such bands have been assigned as mixed O–O/C–O/C–C vibrations.^{9,21,22} An additional Raman band of 2^{NO_2} at 545 cm^{-1} ($^{18}\Delta\nu = 20 \text{ cm}^{-1}$) can be assigned to a Cu–O stretching vibration (Figure S10). These Raman features are consistent with the formation of a copper(II)–alkylperoxy type species. If 2^{NO_2} were instead to be a copper(II)–hydroperoxy species, $\text{Cu}(\text{II})\text{–OOH}$, the Raman spectrum should be much simpler, showing only one peak near 800 cm^{-1} due to the O–O bond stretching vibration.^{1–19}

A plausible structure of copper(II)–alkylperoxy complex 2^{NO_2} is a 2-hydroxy-2-hydroperoxypropane (HHPP) adduct as indicated in Scheme 1. A similar HHPP adduct of iron(III) has recently been reported by Que and co-workers in the reaction of $\text{Fe}^{\text{II}}(\text{TPA})$ and H_2O_2 in acetone.^{23,24} The proposed structure of 2^{NO_2} is consistent with the sensitivity of the resonance Raman bands at 855 and 823 cm^{-1} using acetone- d_6 versus acetone- h_6 (CH_3COCH_3 ; other peaks observed in acetone- d_6 were masked by the large solvent vibration peaks in acetone- h_6 ; Figure S11), which provides evidence for the incorporation of an acetone molecule into 2^{NO_2} . In addition, the ESI-MS of 2^{NO_2} showed a set of peaks at 685.1 which shifted to 689.1 upon $\text{H}_2^{18}\text{O}_2$ substitution (Figure S12). The mass distribution patterns and the isotope shift are fully consistent with the proposed structure of 2^{NO_2} . The ESR spectrum of 2^{NO_2} (Figure S14, $g_1 = 2.315$, $g_2 = 2.110$, $g_3 = 2.035$, $A_1 = 135$, $A_2 = 25$, $A_3 = 30 \text{ G}$), which is different from that of starting material 1^{NO_2} (Figure S13,

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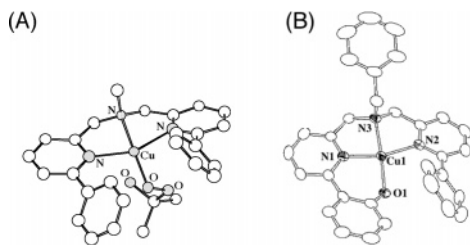


Figure 2. (A) Computed B98 structure for 2^H (*N*-benzyl group is replaced with a methyl group for simplicity) and (B) ORTEP drawing of 4^H showing 50% probability thermal ellipsoids. The counteranion and the hydrogen atoms are omitted for clarity.

$g_1 = 2.310$, $g_2 = 2.100$, $g_3 = 2.030$, $A_1 = 140$, $A_2 = 22$, $A_3 = 24$ G), indicates a distorted tetragonal structure. Moreover, double integration of the ESR spectrum of 2^{NO_2} indicated that 99% of spin remained, confirming the mononuclearity of 2^{NO_2} . Finally, B98 density functional calculations predict a stationary structure for 2^{NO_2} (Figure 2A) whose spectral characteristics are in good accord with experiment.²⁵

The HHPP adduct 2^X gradually decomposed at -70 °C, resulting in the formation of another intermediate 3^X having a featureless UV/vis spectrum (Figure 1B; the spectrum of 3^H is presented as a typical example). The reaction of 2^H to 3^H obeyed first-order kinetics (Figure S15), and from the temperature dependence of the decay rate, we obtained the activation parameters $\Delta H^\ddagger = 24.9 \pm 1.2$ kJ mol⁻¹ and $\Delta S^\ddagger = -162.9 \pm 5.5$ J K⁻¹ mol⁻¹ (Figure S16). Furthermore, Hammett analysis (plot of log k_{obs} vs σ^+) gave $\rho = -2.2$ ($r^2 = 0.99$) (Figure S17), which is very close to the ρ values reported for aromatic hydroxylation reactions of dicopper(II)–peroxo complexes (-1.8 to -2.2).^{26–28} In addition, no kinetic deuterium isotope effect (KIE = 1.0) was obtained with perdeuterated ligand L^H-*d*₁₀ (replacing all protons of the 6-phenyl groups). These kinetic results suggest that the reaction of 2^X to 3^X involves an electrophilic aromatic substitution mechanism.

Intermediate 3^X further reacted at higher temperature to give the final product 4^X exhibiting an intense absorption band at ~ 380 nm (the spectrum of 4^H is shown in Figure 1B, and those of other 4^X are presented in Figures S19–S22). The ESI-MS of the final reaction mixture with H₂¹⁶O₂ and H₂¹⁸O₂ (Figure S23) showed, respectively, increments of 15 and 17 mass units relative to 1^H , demonstrating incorporation of one oxygen atom into the product. Aromatic ligand hydroxylation was unambiguously confirmed by single-crystal X-ray structural analysis of the isolated copper(II)–phenolate complex 4^H (Figure 2B) and by ¹H NMR analysis on the modified ligands L^X–OH isolated by demetalation of the final products 4^X . The yields of ligand hydroxylation were 99, 98, 85, 99, and 53% for X = OMe, Me, H, Cl, and NO₂, respectively.

In summary, we have demonstrated a unique reactivity of copper(II) complexes 1^X with H₂O₂ in acetone via the intermediacy of a new copper(II)–alkylperoxo complex 2^X . The alkylperoxo complex 2^X is electrophilic in nature ($\rho = -2.2$) and accomplishes aromatic ligand hydroxylation. In other solvent systems such as propionitrile, by contrast, we observed formation of copper(II)–hydroperoxo species, Cu^{II}–OOH (360 nm, $\epsilon = 3150$ M⁻¹ cm⁻¹), from which no aromatic ligand hydroxylation took place. Thus, the present study offers important insights into solvent effects on the reactivity of copper(II) complexes when mixed with H₂O₂. The structure of intermediate 3^X and the mechanism for its formation is now under investigation by experiment and computation.²⁹

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Supporting Information Available: Experimental details for the synthetic procedures, computational methods, crystal structures of 1^X and 4^H (ORTEP drawings and CIF data), 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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- ESR data for 3^H are presented in Figure S18. The acquisition of a resonance Raman spectrum has not yet proven possible.

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