Mechanistic Studies of Aliphatic Ligand Hydroxylation of a Copper Complex by Dioxygen: A Model Reaction for Copper Monooxygenases

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Abstract: Mechanistic studies on the aliphatic ligand hydroxylation in a copper complex of tridentate ligand **1a** {*N*,*N*-bis[2-(2-pyridyl)ethyl]-2-phenylethylamine} by O_2 have been performed in order to shed light on the structure and reactivity of the active oxygen species of our functional model for copper monooxygenases (Itoh, S.; et al. *J. Am. Chem. Soc.* **1995**, *117*, 4714). When the copper complex $[Cu^{II}(\mathbf{1a})(ClO_4)_2]$ was treated with an equimolar amount of benzoin and triethylamine in CH_2Cl_2 under O_2 atmosphere, efficient hydroxylation occurred selectively at the benzylic position of the ligand to provide oxygenated product **2a** {*N*,*N*-bis[2-(2-pyridyl)ethyl]-2-phenyl-2-hydroxyethylamine} quantitatively. An isotope labeling experiment using $^{18}O_2$ confirms that the oxygen atom of the OH group in **2a** originates from molecular oxygen. Spectroscopic analyses using UV−vis, resonance Raman, and ESR on the reaction of $[Cu^{I}(\mathbf{1a})]^+$ and O_2 at low temperature show that a μ-η^2:η^2-peroxodicopper(II) complex is an initially formed intermediate. Kinetic analysis on the peroxo complex formation indicates that the reaction of the Cu(I) complex and the monomeric superoxocopper(II) species is rate-determining for the formation of the μ-η^2:η^2-peroxodicopper(II) intermediate. When ligand **1a** is replaced by 1,1,2,2-tetradeuterated phenethylamine derivative **1a**-d_4, a relatively small kinetic deuterium isotope effect (k_H/k_D = 1.8 at −40 °C) is observed for the ligand hydroxylation step. The rate of the hydroxylation step is rather insensitive to the *p*-substituent of the ligand $[(PyCH_2CH_2)_2NCH_2CH_2Ar$, **1a** Ar = C_6H_5; **1b** Ar = *p*-$CH_3C_6H_4$, **1c** Ar = *p*-ClC_6H_4, and **1d** Ar = *p*-$NO_2C_6H_4)]$, but it varies depending on the solvent (THF > acetone > CH_3OH > CH_2Cl_2). The *p*-substituent, the solvent, and the kinetic deuterium isotope effects suggest that O−O bond homolysis of the μ-η^2:η^2-peroxodicopper(II) intermediate is involved as a rate-determining step in the aliphatic ligand hydroxylation process. Based on the results of the kinetics and the crossover experiments, we propose a mechanism involving intramolecular C−H bond activation in a bis-μ-oxodicopper(III) type intermediate for the ligand hydroxylation reaction.

Introduction

There has been considerable interest in O_2-binding and -activation by non-heme metalloenzymes.[1−5] Several types of mono- and multinuclear iron/copper centers of O_2 carrier enzymes and oxygenases have been characterized by extensive spectroscopic studies, and some of their deoxy and oxy forms have been structurally identified by recent X-ray crystallographic investigations.[6] Model studies on O_2-binding and activation using simple metal complexes have been also performed to provide valuable insight into the O_2-binding mode and its activation mechanism at several metal centers not only in the enzymatic systems but also in catalytic processes of organic synthesis.

During the past decade, there has been much progress in Cu/O_2 chemistry. Karlin and co-workers reported the first example of *aromatic ligand hydroxylation* in a dinuclear copper(I) complex by O_2 (Scheme 1), opening the current research field of Cu/O_2 bioinorganic chemistry.[1a,4,7,8] Reversible O_2-binding

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Scheme 1

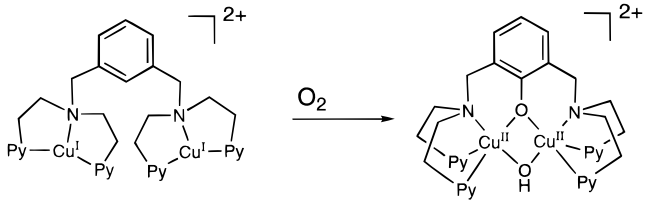
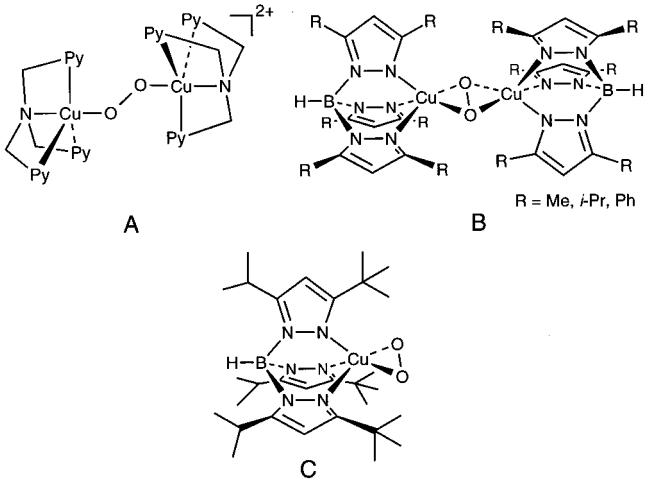


Chart 1



to a series of dinuclear copper(I) complexes[9] and the first crystal structure of *trans*-μ-1,2-peroxodicopper(II) complex **A** (in Chart 1)[10] have attracted many researchers in the related area.

Kitajima and Moro-oka's group reported another type of μ-peroxodicopper(II) complex having a μ-η^2:η^2 core (**B**)[11] that is finally concluded to exist in the enzyme active site of oxyhemocyanin.[12] Introduction of a sterically hindered substituent such as the *tert*-butyl group into the ligand face of the O_2-binding pocket made it possible to isolate a monomeric superoxocopper(II) species in a similar side-on fashion (**C**).[13,14]

Tolman and co-workers have further extended the Cu/O_2 chemistry to provide valuable information about the O_2-activation mechanism at copper ion centers (Scheme 2).[15−18] They also observed formation of a μ-η^2:η^2-peroxodicopper(II) species (**D**) in the reaction of $[(i\text{-}Pr_3TACN)Cu(CH_3CN)]^+$ (i-Pr_3TACN = 1,4,7-triisopropyl-1,4,7-triazacyclononane) with O_2

Scheme 2

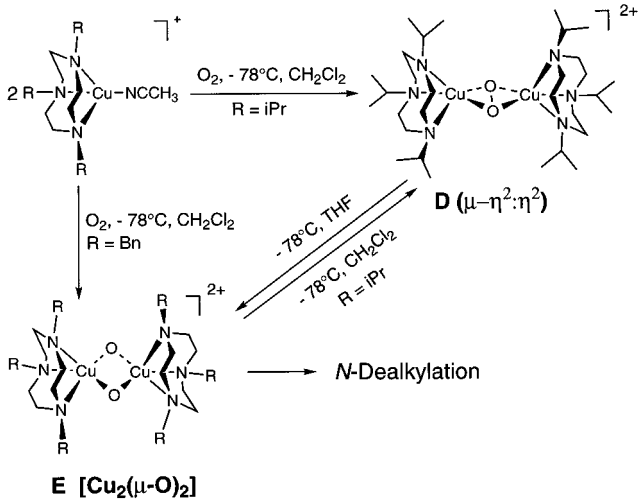
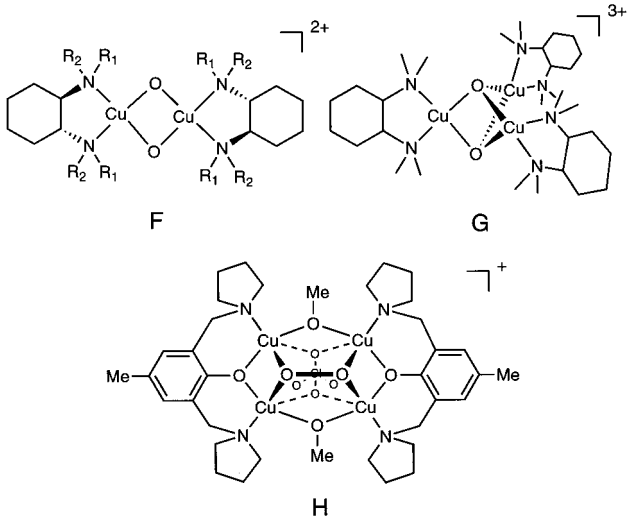


Chart 2



in CH_2Cl_2 at −80 °C, where a hydrogen atom abstraction occurs only from the methine carbon of the isopropyl substituent with a little amount of *N*-dealkylation (<15%).[15] When the substituent of the TACN ligand is replaced by benzyl group, O−O bond homolysis takes place to afford bis-μ-oxodicopper(III) intermediate **E** under the same experimental conditions.[16] More interestingly, interconversion between the μ-η^2:η^2-peroxodicopper(II) species and the bis-μ-oxodicopper(III) species is observed just by changing the solvent between CH_2Cl_2 and THF, where the oxidative *N*-dealkylation occurs efficiently from the bis-μ-oxodicopper(III) intermediate.[17,18] Stack and co-workers have recently demonstrated that a similar bis-μ-oxodicopper(III) species (**F**) can be generated by starting with a copper(I) complex with a bidentate ligand such as ethylenediamine derivatives (Chart 2).[19a,b] In this case, a novel trinuclear Cu-

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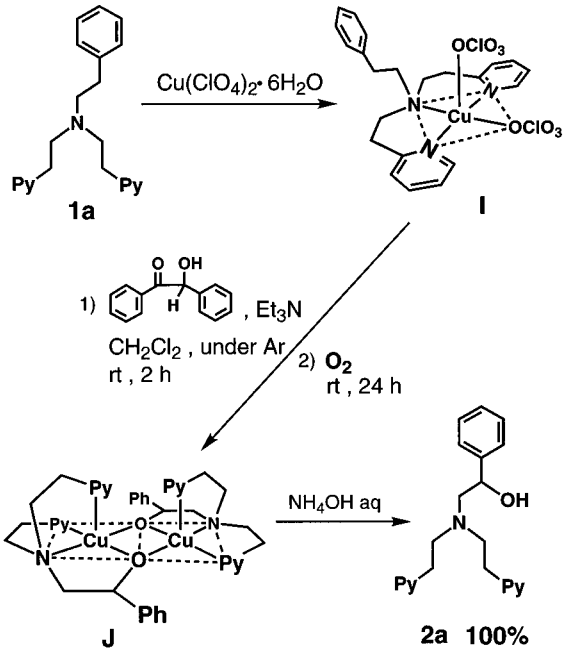
(II)Cu(II)Cu(III) mixed valence complex with two μ_3-oxo bridges (**G**) is also formed, probably due to the reaction between the bis-μ-oxodicopper(III) intermediate and another Cu(I) species.[19c] Krebs and co-worker reported another type of tetranuclear Cu(II)$_4$ μ_4-peroxo species **H** which was produced by the treatment of Cu(II) ion and the bidentate phenolate diamine ligand with 3,5-di-*tert*-butyl catecolate (reductant) under aerobic conditions.[19d]

In contrast to the quantitative aromatic ligand hydroxylation reaction observed in a series of dinuclear copper(I) complex−O_2 systems,[8,20] *quantitative aliphatic ligand hydroxylation* is still very rare.[18,19a,21] In this context, we have recently found that quantitative ligand hydroxylation occurs selectively at the benzylic position of the substrate moiety of the ligand, when [Cu^{II}(**1a**)(ClO$_4$)$_2$] (**I**, **1a** = *N*,*N*-bis[2-(2-pyridyl)ethyl]-2-phenylethylamine) is treated with an equimolar amount of benzoin and triethylamine under O_2 atmosphere (Scheme 3).[22] Such a system can be regarded as a *functional model* for copper monooxygenases catalyzing alkane hydroxylation reactions such as particulate methane monooxygenase (pMMO), dopamine β-hydroxylase (DβH), or peptidylglycine α-amidating monooxygenase (PAM). Here, we have performed mechanistic studies of the aliphatic ligand hydroxylation reaction (Scheme 3) to demonstrate that the benzylic hydroxylation occurs via a rate-determining O−O bond homolysis of a μ-η^2:η^2-peroxodicopper(II) complex formed from [Cu^{I}(**1a**)]$^+$ and O_2 during the course of the reaction. Mechanisms of the hydroxylation process are discussed on the basis of the results of kinetics and product analyses of the crossover experiments.

Results and Discussion

Aliphatic Ligand Hydroxylation (Product Analysis and Stoichiometry). During the course of O_2-activation process in enzymatic systems, electrons are injected into O_2 at a metal center from an external electron donor, such as ascorbate in DβH and PAM.[23] To mimic such a process, we first tried to examine the reaction of the Cu(II) complex of tridentate ligand **1a** and O_2 in the presence of a reductant (Scheme 3). The Cu(II) complex [Cu^{II}(**1a**)(ClO$_4$)$_2$] (**I** in Scheme 3)[24] was treated with an equimolar amount of the 1,2-enediolate derived from benzoin and triethylamine, which is used as a model of

Scheme 3



ascorbate,[25] in CH_2Cl_2 at room temperature for 2 h under Ar. The mixture was then stirred under an atmospheric pressure of O_2 for 24 h. The hydroxylated ligand **2a** was isolated quantitatively (100%) after an ordinary workup treatment of the reaction mixture with aqueous NH_4OH and following extraction by CH_2Cl_2 (Scheme 3).[24]

The mass spectroscopic analysis of the modified ligand **2a** obtained in the same reaction with $^{18}O_2$ (96% content) clearly showed that the oxygen atom of the OH group came from molecular oxygen (more than 95% of ^{18}O was incorporated; peak height of M^+:(M^+ + 2) = 11:100). The stoichiometry of O_2 to Cu(II) in this reaction was determined as 1:1 by a manometric measurement. The ligand hydroxylation was only observed in the presence of all reaction components together, i.e., benzoin, triethylamine, and O_2 in addition to the copper complex.

The same reaction as shown in Scheme 3 occurred when [Cu^{I}(**1a**)]PF$_6$ was treated with O_2 in CH_2Cl_2. In this case, however, the yield of hydroxylation was not more than 50% based on the Cu ion, and the stoichiometry of Cu:O_2 became 2:1. Such a stoichiometry indicates clearly that 2 equiv of electrons and 1 equiv of O_2 are required for the single ligand hydroxylation process (50% conversion). Starting from Cu(I), the isolated yield of the hydroxylated ligand reached the maximum value (50%) in about 5 h, while starting from Cu(II) in the presence of benzoin and triethylamine, it took about 24 h to reach completion. When hydroquinone (1 equiv), a more powerful reductant than benzoin, was used as an electron donor, the rate of the reaction became as fast as that starting from Cu(I). The yield of hydroxylation was lower (62%), however, probably because hydroquinone itself reacted with O_2 to be oxidized to benzoquinone under the present reaction conditions. These results indicate that the reduction of Cu(II) to Cu(I) is the rate-determining step in the benzoin/triethylamine system at room temperature.

Reaction Intermediate. The hydroxylated ligand **2a** was also obtained in 33% yield when [Cu^{II}(**1a**)(ClO$_4$)$_2$] was treated with H_2O_2 (10 equiv) in CH_3OH for 18 h under Ar. On the

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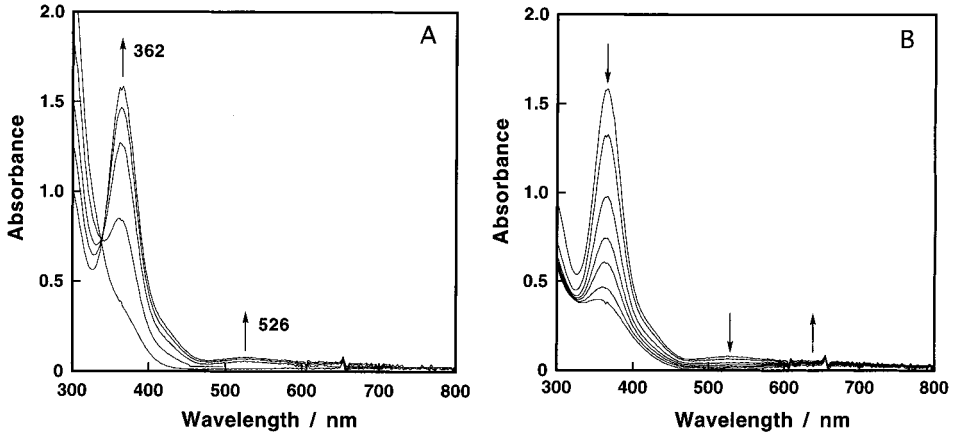


Figure 1. Spectral change observed upon introduction of O_2 gas into the THF solution of $[Cu^{I}(\mathbf{1})]PF_6$ (2.5×10^{-3} M) at −80 °C in a 1 mm path length UV cell: (A) O_2-adduct formation, 30 s interval; (B) ligand hydroxylation, 5 min interval.

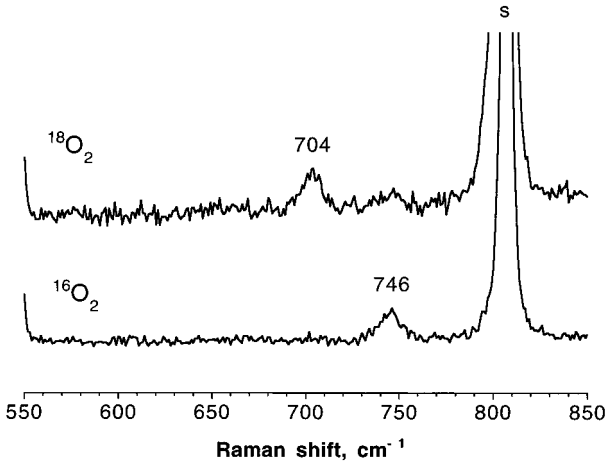


Figure 2. Resonance Raman spectra obtained with 514.5 nm excitation on frozen (77 K) acetone solutions of (A) $[Cu^{II}_2(\mu\text{-}^{16}O_2)(\mathbf{1a}\text{-}d_4)_2](PF_6)_2$ and (B) $[Cu^{II}_2(\mu\text{-}^{18}O_2)(\mathbf{1a}\text{-}d_4)_2](PF_6)_2$.

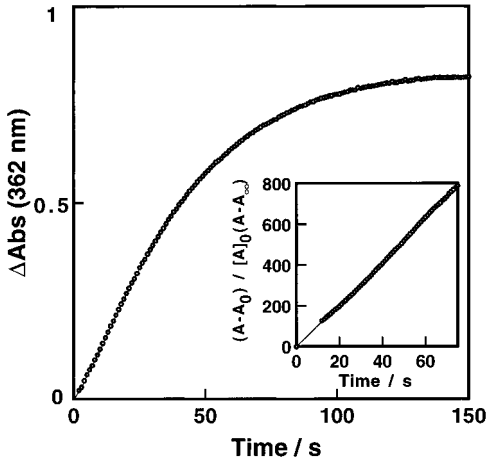


Figure 3. Time course of the absorption change at 362 nm in the reaction of $[Cu^{I}(\mathbf{1})]PF_6$ (2.5×10^{-3} M) and O_2 in THF at −80 °C. Inset: second-order plot based on the absorbance change at 362 nm.

other hand, the reaction with *tert*-butyl hydroperoxide, cumene hydroperoxide, or *m*-chloroperoxybenzoic acid (*m*-CPBA) gave no hydroxylation product under the same experimental conditions as those with H_2O_2.[26] These results together with the stoichiometry mentioned above (Cu(I):O_2 = 2:1) indicate that a μ-peroxodicopper(II) species is involved as a reaction intermediate.

Figure 1 shows the spectral change observed upon introduction of O_2 gas into a THF solution of $[Cu^{I}(\mathbf{1a})]PF_6$ at −80 °C. The Cu(I) complex itself has no characteristic absorption in the visible region, but introduction of O_2 gas into the solution causes a drastic spectral change. After a few minutes, we obtained a spectrum with a strong absorption at 362 nm together with a small one around 526 nm (Figure 1A). The final spectrum shown in Figure 1A is very close to that reported for μ-η^2:η^2-species **B** in Chart 1 and **D** in Scheme 2. Essentially the same spectrum was obtained independently in the reaction of $[Cu^{II}(\mathbf{1a})(ClO_4)_2]$ and H_2O_2 (10 equiv) in the presence of a base such as triethylamine. Furthermore, this species was ESR silent, indicating that there is a strong anti-ferromagnetic interaction between the two cupric ions as seen in the case of other μ-η^2:η^2 core systems.[11,15]

Resonance Raman spectra of the intermediate provided a further evidence of the μ-η^2:η^2-peroxodicopper(II) core structure. Figure 2 shows the resonance Raman spectrum obtained with 514.5 nm excitation on a frozen (77 K) acetone solution of $[Cu^{II}_2(\mu\text{-}^{16}O_2)(\mathbf{1a}\text{-}d_4)_2](PF_6)_2$ (**1a**-d_4 = *N*,*N*-bis[2-(2-pyridyl)-ethyl]-1,1,2,2-tetradeuterio-2-phenylethylamine). A characteristic absorption is observed at 746 cm^{-1} that shifts to 704 cm^{-1} upon $^{18}O_2$ substitution.[27] The observed ν_{O-O} value at 746 cm^{-1} and the isotopic shift ($\Delta\nu$ = 42 cm^{-1}) are very close to those reported for the structurally characterized μ-η^2:η^2-peroxodicopper(II) complex by Kitajima et al.[11] and other related systems,[15,28] confirming that μ-peroxodicopper(II) complex formed in the present system has a μ-η^2:η^2 core. There is, however, no evidence for formation of the bis-μ-oxodicopper(III) intermediate at around 600 cm^{-1}.

At the prolonged reaction time, the characteristic spectrum of the μ-η^2:η^2-peroxodicopper(II) species gradually decreases even at the low temperature as shown in Figure 1B, which corresponds to the ligand hydroxylation reaction as discussed below.

O_2-Binding Process. Figure 3 shows the time course of the absorption change due to formation of the μ-η^2:η^2-peroxodicopper(II) complex at the low temperature in THF. In order to keep the O_2 concentration constant, dioxygen gas was continu-

(26) Réglier et al. reported that the ligand hydroxylation occurs only at the *o*-position of one pyridine nucleus in the reaction of Cu(I) complex of the same ligand **1a** with iodosylbenzene: Réglier, M.; Amadeï, E.; Tadayoni, R.; Waegell, B. *J. Chem. Soc., Chem. Commun.* **1989**, 447.

(27) High reactivity of the μ-peroxodicopper(II) complex has precluded getting a solution resonance Raman spectrum at −80 °C: Itoh, S.; Nakao, H.; Fukuzumi, S.; Mukai, M.; Kitagawa, T. Unpublished results.

(28) Sorrell, T. N.; Allen, W. E.; White, P. S. *Inorg. Chem.* **1995**, *34*, 952.

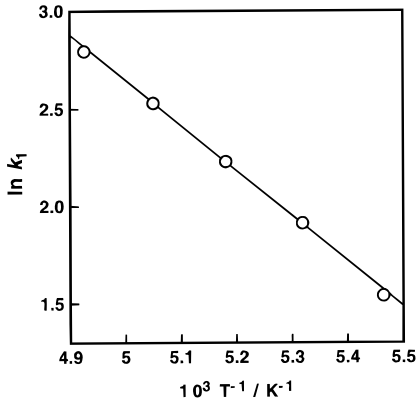


Figure 4. Eyring plot for the formation of the μ-η^2:η^2-peroxodicopper(II) intermediate in THF.

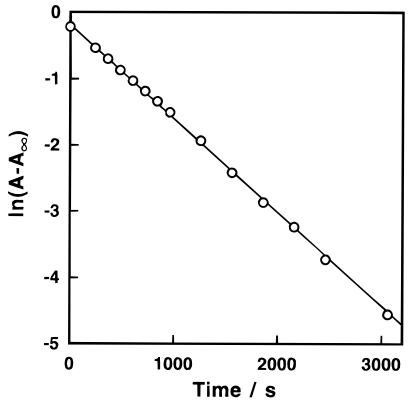
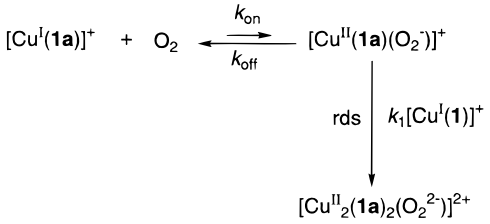


Figure 5. First-order plot for the ligand hydroxylation process in THF at −80 °C.

Scheme 4



ously supplied by gentle bubbling. Although there is a small lag phase at the very beginning of the reaction due to the time required for O_2-saturation into the solution,[29] the time course after the lag phase can be fitted by second-order kinetics. The second-order rate constant was obtained as the slope of the linear line of the second-order plot shown in the inset of Figure 3. The observed second-order rate constant was essentially constant (11 ± 1 M^{-1}s^{-1}) within a wide range of the initial concentrations of the Cu(I) complex from 0.45 to 5.9 mM. Thus, it can be concluded that the bimolecular reaction between the monomeric superoxocopper(II) complex [Cu^{II}(**1a**)(O$_2^-$)]$^+$ and another Cu(I) complex is rate-determining (Scheme 4), although direct detection of such a monomeric superoxo species has not been successful yet.[29] From the dependence of the rate constants on the reaction temperature shown as an Eyring plot in Figure 4 were obtained the activation enthalpy ($\Delta H^{\ddagger}$) of 19.3 ± 0.4 kJ mol^{-1} and the activation entropy ($\Delta S^{\ddagger}$) of -91.6 ± 2.0 J K^{-1} mol^{-1} for the μ-η^2:η^2-peroxodicopper(II) complex formation.

In the Karlin's system shown in Scheme 1, reversible dioxygen binding to the dinuclear Cu(I) site occurs in a single observable step with the low activation enthalpy ($\Delta H^{\ddagger} = 8.2 \pm 0.1$ kJ mol^{-1}) and the largely negative activation entropy ($\Delta S^{\ddagger} = -146 \pm 1$ JK^{-1} mol^{-1}).[30] They suggested that the μ-peroxo intermediate had a bent μ-η^2:η^2 core that underwent the aromatic ligand hydroxylation reaction in Scheme 1. They also investigated the reversible formation of *trans*-μ-1,2-peroxodicopper(II) complex using the monomeric Cu(I) complex with a tetradentate ligand (see **A** in Chart 1), where they detected a monomeric superoxocopper(II) intermediate. In such a case, the second step, the reaction between the monomeric superoxocopper(II) intermediate and another Cu(I), is rate-determining. The activation parameters for the formation of the monomeric superoxocopper(II) intermediate (the first step) and the formation of the *trans*-μ-1,2-peroxodicopper(II) complex (the second step) were reported as $\Delta H^{\ddagger} = 32 \pm 4$ kJ mol^{-1}, $\Delta S^{\ddagger} = 14 \pm 18$ JK^{-1} mol^{-1} and $\Delta H^{\ddagger} = 14 \pm 1$ kJ mol^{-1}, $\Delta S^{\ddagger} = -78 \pm 2$ J K^{-1} mol^{-1}, respectively.[31] In the case of *i*-Pr$_3$TACN ligand system (see, Scheme 2), superoxocopper(II) complex formation (the first step) is the rate-determining step and the activation parameters are $\Delta H^{\ddagger} = 37.2 \pm 0.5$ kJ mol^{-1} and $\Delta S^{\ddagger} = -62 \pm 2$ J K^{-1} mol^{-1}.[17a] These values are close to those of the superoxocopper(II) complex formation with sterically more hindered BQPA [bis(2-quinolyl)(2-pyridyl)methylamine] ligand.[31b] Thus, the present system is closer to that of the Karlin's system with regard to the O_2-binding,[30] although the overall O_2-binding process is irreversible at the low temperature. When the solution of the μ-η^2:η^2-peroxodicopper(II) complex of the present system was subjected to vacuum at the low temperatures (from −80 to −60 °C), there was no spectral change due to the dissociation of O_2 from the peroxo intermediate.[32] Several factors such as steric hindrance, hydrophobicity in the O_2-binding pocket, and the redox potential of the copper center may be responsible for such differences in reactivity of the Cu(I) complexes toward O_2.

Kinetics of the Benzylic Ligand Hydroxylation. In contrast to the bimolecular O_2-binding process, the ligand hydroxylation reaction (the second-phase process, Figure 1B) obeys first-order kinetics with respect to the peroxo complex as indicated in Figure 5. The activation parameters are determined as $\Delta H^{\ddagger} = 28.1 \pm 1.0$ kJ mol^{-1} and $\Delta S^{\ddagger} = -155 \pm 5$ J K^{-1} mol^{-1} by the Eyring plot shown in Figure 6 (line H). Such a large negative $\Delta S^{\ddagger}$ value suggests that the rate-determining step of the hydroxylation reaction requires a highly constrained transition state as discussed below.

Kinetic deuterium isotope effect on the ligand hydroxylation process was examined using **1a**-d_4 as a ligand. As in the case of **1a**, only the benzylic position of the phenethylamine sidearm was hydroxylated in a 50% yield, when [Cu^{I}(**1a**-d_4)]PF$_6$ was treated with O_2 in CH_2Cl_2 at room temperature for 24 h. The ^{1}H NMR spectrum of the organic product obtained in a similar workup treatment clearly showed that the ethylene group of the pyridine sidearms remained intact and that all proton peaks of

(29) Direct injection of a *concentrated solution* of the Cu(I) starting materials into the solvent saturated with dioxygen at the low temperature may remove the lag phase observed in Figure 3, enabling us to detect the initially formed Cu(I)−superoxo intermediate (Scheme 4). However, the limited solubility of the Cu(I) starting materials in THF has precluded doing this experiment.

(30) (a) Cruse, R. W.; Kaderli, S.; Karlin, K. D.; Zuberbühler, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 6882. (b) Karlin, K. D.; Nasir, M. S.; Cohen, B. I.; Cruse, R. W.; Kaderli, S.; Zuberbühler, A. D. *J. Am. Chem. Soc.* **1994**, *116*, 1324.

(31) (a) Karlin, K. D.; Wei, N.; Jung, B.; Kaderli, S.; Zuberbühler, A. D. *J. Am. Chem. Soc.* **1991**, *113*, 5868. (b) Karlin, K. D.; Wei, N.; Jung, B.; Kaderli, S.; Niklaus, P.; Zuberbühler, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 9506.

(32) The follow-up reaction (ligand hydroxylation) prevents us from examining the reversibility of the O_2-binding at higher temperature (> −40 °C).

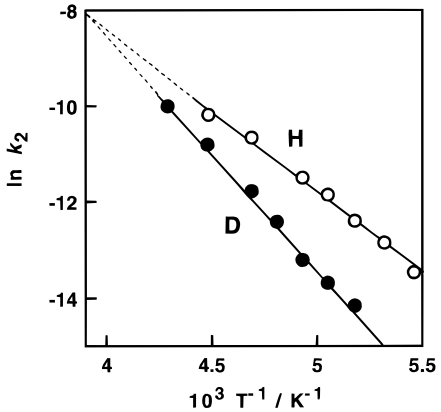


Figure 6. Eyring plot for the ligand hydroxylation of (H) [Cu^I(**1a**)]-PF_6 and (D) [Cu^I(**1a**-d_4)]PF_6 by O_2 in THF.

the hydroxylated ligand from **1a**-d_4 were identical to those of **2a**. An Eyring plot for the ligand hydroxylation reaction of [Cu^I(**1a**-d_4)]PF_6 by O_2 is also shown in Figure 6 (line D). The kinetic isotope effect (KIE) for the ligand hydroxylation process was 5.9 at −80 °C in THF, but the KIE value decreases to 1.8 at −40 °C. The small KIE value shows a sharp contrast with the case of $[Cu_2(\mu\text{-}O)_2(L)_2]^{2+}$ (Scheme 2 and Chart 2), where significant kinetic deuterium isotope effects were observed: $k_H/k_D = 26$ for L = *i*-Pr_3-TACN and $k_H/k_D = 40$ for L = Bn_3-TACN at −40 °C in THF and $k_H/k_D = 3.0$ for L = *N*,*N*,*N*′,*N*′-tetraethylcyclohexanediamine at 20 °C for the oxidative *N*-dealkylation process (C−H bond cleavage).[18,19a,33] Similarly, Que et al. recently reported a very large kinetic deuterium isotope effect of $k_H/k_D = 20$ at −40 °C for the hydrocarbon hydroxylation by a high-valent $[Fe_2(\mu\text{-}O)_2(TAP)_2]^{3+}$ species [TAP = tris(2-pyridylmethyl)amine].[34] From the Eyring plot shown in Figure 6 are determined the activation parameters as $\Delta H_D^{\ddagger} = 40.3 \pm 1.3$ kJ mol^{-1} and $\Delta S_D^{\ddagger} = -107 \pm 6$ J K^{-1} mol^{-1}. The extrapolation of the Eyring plots gives the KIE value being unity at −16 °C, when the rate-determining step may be a process that precedes the hydrogen transfer.[35] Thus, the O−O bond cleavage may be involved as a rate-determining step which is followed by the facile hydrogen transfer at the higher temperature (> −16 °C) as discussed in more detail below.

Solvent and counteranion effects of the reaction of [Cu^I(**1a**)]$^+$ and O_2 at −80 °C are summarized in Table 1. The spectrum of active oxygen intermediate obtained in each solvent system (THF, acetone, CH_3OH, and CH_2Cl_2) has essentially the same feature having a λ_{max} at 362 nm due to the μ-η^2:η^2 core. Interconversion between the μ-η^2:η^2-peroxodicopper(II) species and the bis-μ-oxodicopper(III) species (Scheme 2) is not observed by changing the solvent in the present system, since the absorption ratio between 362 and 430 nm in each solvent is nearly constant ($A_{362}/A_{430} = 10 \pm 0.4$). This is consistent with the resonance Raman spectrum of the frozen acetone solution (Figure 2), where no feature due to bis-μ-oxodicopper(III) species around 600 cm^{-1} can be seen.[16] The rate constants for

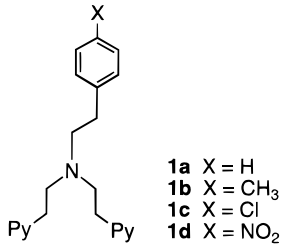
Table 1. Solvent and Counteranion Effects on the UV−Vis Spectrum and the Formation and Decay Rate Constants (k_1 and k_2) of the μ-η^2:η^2-Peroxodicopper(II) Complex at −80 °C

run	solvent	counteranion[a]	λ_{max}[b]	k_1 (M^{-1} s^{-1})	$10^4 k_2$ (s^{-1})
1	THF	PF_6^-	362	10.0	8.1
2	acetone	PF_6^-	362	2.0	4.8
3	CH_3OH	PF_6^-	362	2.0	3.1
4	CH_2Cl_2	PF_6^-	362	0.14	0.86
5	CH_3OH	ClO_4^-	362	2.1	3.2
6	CH_3OH	$CF_3SO_3^-$	360	0.61	3.0
7	CH_3OH	BPh_4^-	362	1.9	2.8

[a] The counteranion effect was investigated mainly in CH_3OH because of the low solubility of the ClO_4^- and BPh_4^- salts in THF. [b] Although the ϵ_{max} value could not be determined directly because of the subsequent ligand hydroxylation reaction (k_2 process), the ϵ_{max} values were estimated to be $(1.56 \pm 0.06) \times 10^4$ M^{-1} cm^{-1} by computer curve fitting of the second-order plot for the k_1 process.

formation of the μ-η^2:η^2-peroxodicopper(II) complex (k_1) and the ligand hydroxylation step (k_2) were then determined in each solvent system. It is obvious that both k_1 and k_2 values vary significantly depending on the solvent. Although both of the rate constants have no relation with dielectric constant (ϵ) or dipole moment of the solvents, a solvent having an oxygen donor ability such as THF enhances both processes. Interestingly, the ligand hydroxylation (k_2 process) proceeds most efficiently in THF (run 1) which is the most favorable solvent for the formation of bis-μ-oxodicopper(III) species in the reaction of [(*i*-Pr_3TACN)Cu(CH_3CN)]$^+$ and O_2 (Scheme 2), while it proceeds most slowly in CH_2Cl_2 (run 4) in which μ-η^2:η^2-peroxodicopper(II) complex is a major component in the *i*-Pr_3-TACN system.

Counteranions have been also demonstrated to affect the ratio of μ-η^2:η^2-peroxodicopper(II) to bis-μ-oxodicopper(III) species.[16b] Tolman et al. reported that ClO_4^- and PF_6^- gave only bis-μ-oxo species in THF but that $CF_3SO_3^-$ and BPh_4^- gave a 4:1 mixture of μ-η^2:η^2-peroxodicopper(II) complex and bis-μ-oxodicopper(III) complex. As seen in Table 1 (compare runs 3 and 5−7), the major species formed in the present system is always μ-η^2:η^2-peroxodicopper(II) complex, and the absorption ratio A_{362}/A_{430} is almost constant within the experimental error (10 ± 0.5). The counteranion effects on both the O_2-adduct formation process (k_1) and the ligand hydroxylation reaction (k_2) were, however, relatively small as compared to the solvent effects mentioned above.



Electronic effects of the *p*-substituents (X = H, CH_3, Cl, NO_2) on the benzene ring of the ligand (**1a**−**d**) have been also examined both on the k_1 and k_2 processes as summarized in Table 2. Because of the low solubility of [Cu^I(**1d**)]PF_6 in CH_3-OH, the substituent effect of the nitro group was examined in acetone by comparing the reactivity of [Cu^I(**1d**)]PF_6 to that of [Cu^I(**1a**)]PF_6 under the same experimental conditions (runs 4 and 5). While the electron-donating substituent retards the O_2-adduct formation process (k_1),[36] the electronic effect on the ligand hydroxylation process (k_2) is negligible. Little effect of the *p*-substituent on the k_2 process also suggests that the benzylic

(33) For the electrophilic aromatic hydroxylation reaction in the dinuclear Cu(I) complex shown in Scheme 1, Karlin et al. reported the absence of kinetic deuterium isotope effect.[30a] This is reasonable since the electrophilic attack of the peroxo species upon the proximate aromatic substrate is the rate-determining step in their system: Nasir, M. S.; Cohen, B. I.; Karlin, K. D. *J. Am. Chem. Soc.* **1992**, *114*, 2482.

(34) Kim, C.; Dong, Y.; Que, L., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 3635.

(35) The direct hydrogen abstraction mechanism in the μ-η^2:η^2-peroxodicopper(II) core can be ruled out, since a large kinetic isotope effect ($k_H/k_D = 18$ at 25 °C) was detected in the direct C−H bond cleavage in the μ-η^2:η^2 core of $[Cu_2(\mu\text{-}O_2)(i\text{-}Pr_3\text{-}TACN)_2]^{2+}$ in CH_2Cl_2.[15]

Table 2. *p*-Substituent Effects on the Formation and Decay Rate Constants (k_1 and k_2) of the μ-η^2:η^2-Peroxodicopper(II) Complex at −80 °C[a]

run	X (ligand)	solvent	λ_{max}	k_1 (M^{-1} s^{-1})	10^4k_2 (s^{-1})
1	CH_3 (**1b**)	CH_3OH	360	0.39	3.1
2	H (**1a**)	CH_3OH	362	2.0	3.1
3	Cl (**1c**)	CH_3OH	362	4.1	3.7
4	H (**1a**)	acetone	362	1.8	4.8
5	NO_2 (**1d**)	acetone	362	7.1	5.1

[a] Counteranion: PF_6^-.

hydrogen transfer is not involved in the rate-determining step of the benzylic hydroxylation process.

Crossover Experiment. The oxidative *N*-dealkylation reaction in the Tolman bis-μ-oxodicopper(III) system (Scheme 2) has been shown to be an intramolecular process in its diamond core.[18] On the other hand, Kitajima and co-workers reported that μ-η^2:η^2-peroxodicopper(II) complex [Cu[HB(3,5-Me_2pz$_3$]]$_2$-$(O)_2$ (**B** in Chart 1; R = Me) spontaneously decomposes into the corresponding μ-oxodicopper(II) complex via rate-determining O−O bond homolysis of the μ-peroxo species. In the later case, they proposed that the O−O bond homolysis resulted in formation of a monomeric Cu(II)−O$^\bullet$ species, which would react rapidly with the remained Cu(I) species via an intermolecular pathway to provide the final μ-oxodicopper(II) product.[37] Thus, to determine whether the present ligand hydroxylation reaction proceeds via an intramolecular pathway through a bis-μ-oxodicopper(III)-type intermediate or via the C−H bond activation involving an intermolecular process with a monomeric Cu(II)−O$^\bullet$ species, we performed a double-labeling experiment by mixing CH_2Cl_2 solutions of [Cu^{II}_2(**1a**)$_2$(μ-$^{18}O_2$)]$^{2+}$ and [Cu^{II}_2-(**1c**)$_2$(μ-$^{16}O_2$)]$^{2+}$ as has been done in the R_3TACN system.[18] Only **2a**(^{18}OH) and **2c**(^{16}OH) in 1:1 ratio would be obtained if the reaction occurs solely via the intramolecular pathway, whereas a mixture comprised of equivalent amounts of **2a**(^{18}-OH), **2a**(^{16}OH), **2c**(^{16}OH), and **2c**(^{18}OH) would be produced if the hydroxylation reaction proceeds via the intermolecular process.

The double-labeling experiment using [Cu^{II}_2(**1a**)$_2$(μ-$^{18}O_2$)]$^{2+}$ and [Cu^{II}_2(**1c**)$_2$(μ-$^{16}O_2$)]$^{2+}$ at −80 °C gave us a mixture of **2a**(^{18}-OH), **2c**(^{16}OH), **2a**(^{16}OH), and **2c**(^{18}OH) in a 0.87:1:0.36:0.37 ratio. The two peroxo complexes prepared separately were mixed after removal of excess amounts of $^{18}O_2$ and $^{16}O_2$ by placing the reaction vessel under vacuum. Formation of **2a**(^{18}-OH) and **2c**(^{16}OH) in nearly 1:1 ratio as the major products indicates that the intramolecular process is the major pathway for the ligand hydroxylation reaction. On the other hand, mixing of a CH_2Cl_2 solution of [Cu^{II}(**1a**)(ClO_4)$_2$]$^{2+}$ and an equimolar amount of [Cu^{II}_2(**1c**)$_2$(μ-$^{16}O_2$)]$^{2+}$ in CH_2Cl_2 at −80 °C gave us only **2c**(^{16}OH) as the oxygenated product. This result suggests that neither exchange of $^{18}O_2$ and $^{16}O_2$ at the peroxo stage nor the intermolecular ligand hydroxylation occurs. Thus, we assume that the ligand hydroxylation reaction proceeds intramolecularly in a bis-μ-oxo diamond core intermediate and the isotope scrambling products **2a**(^{16}OH) and **2c**(^{18}OH) are produced by isotope exchange between ^{16}O and ^{18}O through the monomeric Cu(II)−O$^\bullet$ species[38] as discussed below.

Mechanistic Consideration. On the basis of all the results described above, we propose a mechanism for the aliphatic ligand hydroxylation reaction, as illustrated in Scheme 5. Formation of the μ-η^2:η^2-peroxodicopper(II) complex (**K**) as an initial O_2-adduct is evident from the stoichiometry of Cu:O_2 = 2:1 and the spectroscopic characterization using UV−vis, resonance Raman, and ESR. Generation of an identical UV−vis spectrum in the reaction of [Cu^{II}(**1a**)(ClO_4)$_2$] and H_2O_2 to that obtained in the reaction between [Cu^{I}(**1a**)]PF_6 and O_2 is also an evidence for the formation of the μ-η^2:η^2-peroxodicopper(II) complex. Involvement of the following O−O bond homolysis of the peroxo intermediate prior to the ligand hydroxylation reaction is implicated by (i) the small KIE values (k_D/k_H = 1.8 at −40 °C and the extrapolated value of 1.0 above −16 °C) and (ii) no *p*-substituent effect (Table 2) on the k_2 process. The solvent effects (THF > acetone > CH_3OH > CH_2-Cl_2) on the k_2 process shown in Table 1 also suggest a significant contribution of the O−O bond homolysis of the peroxo intermediate as demonstrated in the Tolman *i*-Pr_3TACN ligand system.[17] In other words, μ-η^2:η^2-peroxodicopper(II) complex (**K**) is not a real active species for the C−H bond activation. The O−O bond homolysis of the μ-η^2:η^2 core will produce a bis-μ-oxodicopper(III)-type intermediate (**L**)[39] and/or a monomeric Cu(II)−O$^\bullet$ species (**M**). However, the largely negative activation entropy ($\Delta S^\ddagger$ = −155 ± 5 J K^{-1} mol^{-1}) observed on the k_2 process may rule out the direct formation of the monomeric Cu(II)−O$^\bullet$ species from the μ-η^2:η^2-peroxodicopper-(II) complex (**K**), since such a process is entropically favorable, producing a positive $\Delta S^\ddagger$ value. Formation of the isotope scrambling products, **2a**(^{16}OH) and **2c**(^{18}OH), in the double-labeling experiment, however, indicates that the monomeric Cu-(II)−O$^\bullet$ species (**M**) is also involved somewhere in the mechanism of the ligand hydroxylation reaction. We assume that the monomeric Cu(II)−O$^\bullet$ species (**M**) is formed from the bis-μ-oxodicopper(III) intermediate (**L**), and **M** is in equilibrium with **L**. The isotope scrambling between ^{16}O and ^{18}O may occur in this stage. The hydrogen abstraction from the benzylic position of the ligand sidearm producing **N** and **O** or concerted oxygen atom insertion producing **P** and **O** occurs from intermediate **L** intramolecularly.[40] No ligand scrambling in the crossover experiment between [Cu^{II}(**1a**)(ClO_4)$_2$]$^{2+}$ and [Cu^{II}_2-(**1c**)$_2$(μ-$^{16}O_2$)]$^{2+}$ may rule out the intermolecular attack by bis-μ-oxo species **L** or by monomeric Cu(II)−O$^\bullet$ species **M** on the ligand sidearm of another molecule. Thus, the intramolecular process in the bis-μ-oxodicopper(III) type intermediate (**L**) is the only pathway for the benzylic ligand hydroxylation, and we propose that the monomeric Cu(II)−O$^\bullet$ species (**M**) is contributed only in the isotope scrambling between ^{16}O and ^{18}O.

(36) The electron-donating substituent would increase the d−π interaction between the copper center and the benzene ring, which may prevent the interaction of the copper center with dioxygen by a steric hindrance. Details about such interaction in the copper complexes will be reported elsewhere.

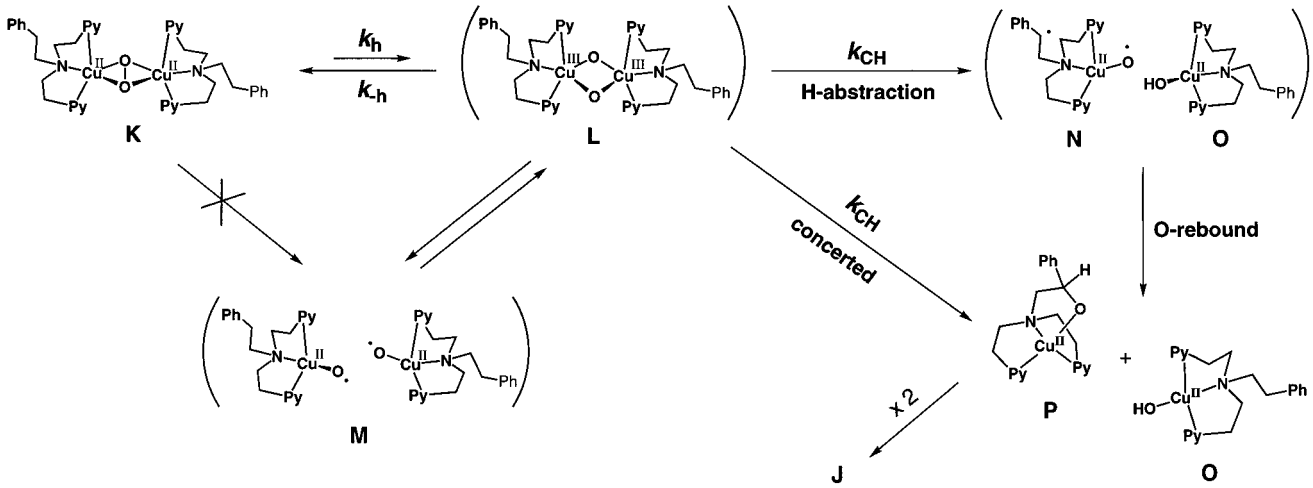
(37) Kitajima, N.; Koda, T.; Iwata, Y.; Moro-oka, Y. *J. Am. Chem. Soc.* **1990**, *112*, 8833.

(38) In this paper, the monomeric species formed from the peroxo intermediate by O−O bond homolysis is described as Cu(II)−O$^\bullet$, although another canonical form Cu(III)═O is also possible. In the present system, however, we could not characterize such a monomeric copper−oxygen species, since it is just a transient reactive intermediate, if it is formed.

(39) When [Cu^{I}(Py$_2$$CH_2CH_2CH_2$Ph)]($ClO_4$) (Py$_2$$CH_2CH_2CH_2$Ph = *N*,*N*-bis[2-(2-pyridyl)ethyl]-3-phenylpropylamine) was used instead of [Cu^{I}(**1a**)]-(ClO_4), the k_2 process significantly slowed (k_2 = 5.1 × 10^{-5} s^{-1} in CH_3OH at −80 °C) and the absorption ratio between 358 nm vs 430 nm became smaller (A_{358}/A_{430} = 5.8) as compared to that of [Cu^{II}_2(**1a**)$_2$(μ-O_2)](ClO_4)$_2$ (A_{362}/A_{430} = 10). These results suggest that bis-μ-oxodicopper(III) intermediate (λ_{max} = ca. 430 nm) can be accumulated to some extent when the ligand hydroxylation process becomes slow. Our attempt to detect the bis-μ-oxodicopper(III) intermediate in this system by resonance Raman spectrum was not successful though (Berreau, L. M.; Tolman, W. B.; Que, L., Jr. Unpublished result). The low-temperature (−80 °C) UV−vis examination on the reactions of [Cu^{I}(L)]$^+$ and O_2 in THF {L = Py$_2$$CH_2$Ph (*N*,*N*-bis[2-(2-pyridyl)ethyl]benzylamine) and Py$_2$$CH_2CH_2CH_2CH_3$ (*N*,*N*-bis[2-(2-pyridyl)ethyl]butylamine)} also showed the predominant formation of the μ-η^2:η^2-peroxodicopper(II) species.

(40) With regard to the mechanism of the ligand hydroxylation process in the bis-μ-oxodicopper(III) core, Tolman et al. have proposed that both the "hydrogen abstraction−oxygen rebound" and "direct oxygen insertion" mechanisms are possible.[18]

Scheme 5



If the O−O bond homolysis is solely the rate-determining step in the ligand hydroxylation process, the KIE value would be 1.0. The observed small KIE values in the present system suggest that the O−O bond homolysis (k_h) is much slower than the back reaction (k_{-h}) which competes with the facile C−H bond activation (k_{CH}). In such a case, the observed rate constant (k_2) is given by eq 1.

$$k_2 = k_h k_{CH}/(k_{-h} + k_{CH}) \quad (1)$$

The O−O bond homolysis may be largely the rate-determining step, i.e., $k_{CH} \gg k_{-h}$, but the ligand perdeuteration may result in a significant decrease in the rate of the C−D cleavage (k_{CD}), which becomes partially rate-determining. Little *p*-substituent effect observed on the k_2 process is also consistent with the proposed mechanism where the ligand hydroxylation process is not a rate-determining step.

The oxygenated product **P** dimerizes to from a thermodynamically stable product **J** as has been demonstrated by the X-ray analysis.[22] For the [Cu^{II}(**1a**)(ClO_4)$_2$]/benzoin/triethylamine system, the Cu^{II}−OH complex (**O**) is reduced to a cuprous state by the reductant that may participate in the hydroxylation reaction again until all the ligand is hydroxylated. According to this mechanism, the stoichiometry of **1a**:O_2:benzoin is 1:1:1, agreeing with the experimental results. The autoxidation mechanism (reaction between the carbon center radical and external O_2 to generate an alkylsuperperoxo species which undergoes radical chain reactions) has been ruled out since the benzylic hydroxylation reaction occurs in the same yield (50%) when the solution of μ-η^2:η^2-peroxodicopper(II) complex (**I**) is allowed to stand at −80 °C after removal of the excess amount of O_2 under vacuum.

In summary, we have demonstrated that the efficient benzylic hydroxylation of the copper complex proceeds via the rate-determining O−O bond homolysis of the μ-η^2:η^2-peroxodicopper(II) intermediate (**K**) which is formed from the Cu(I) complex and O_2 or from the Cu(II) complex with H_2O_2. We propose the intramolecular hydrogen atom abstraction and oxygen rebound or direct oxygen insertion mechanism through the bis-μ-oxodicopper(III) type intermediate (**L**) for the efficient benzylic hydroxylation reaction,[40] although such an intermediate could not be detected directly in our system probably because of its high reactivity and/or instability. We believe that the lower electron donor ability of the aromatic nitrogens as compared to that of the aliphatic amine nitrogens is one of the critical points for such a difference in reactivity of the Cu/O_2 species between our system and the Tolman or Stack systems. In fact, Kitajima's hydrotris(pyrazolyl)borate ligands afford only μ-η^2:η^2-peroxodicopper(II) species and the O−O bond homolysis becomes the rate-determining step in its decomposition process.[37] Recent ligand modification experiments also demonstrated that sterically less hindered amine ligands stabilized bis-μ-oxo dicopper(III) species.[16d,19a] Thus, this steric factor must also be taken into account for the difference in reactivity of the Cu/O_2 species between our system and others. Nonetheless, all of our kinetic results including kinetic deuterium isotope effect, solvent effects, and *p*-substituents effects as well as the product analyses of the crossover experiments support our proposed mechanism.

Very recently, Que and co-workers have reported that intermediate Q of sMMO (soluble methane monooxygenase) has an Fe^{IV}−(μ-O)$_2$−Fe^{IV} diamond core structure.[41] Chan et al. have also proposed that a bis-μ-oxo-Cu(II)Cu(III) core corresponds to the methane hydroxylation in pMMO (particulate methane monooxygenase),[42] suggesting the mechanistic viability of the bis-μ-oxo high-valent dimetallic diamond core for the dioxygen activation and hydrocarbon oxygenation.

Experimental Section

All chemicals used in this study except the ligands and the copper complexes were commercial products of the highest available purity and were further purified by the standard methods.[43] IR spectra were recorded with a Hitachi 270−30 spectrophotometer or a Shimadzu FTIR-8200PC. UV−vis spectra were measured using a Hewlett-Packard HP8452A diode array spectrophotometer with a Unisoku thermostated cell holder designed for low-temperature experiments. Mass spectra were recorded with a JEOL JNX-DX303 HF mass spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL FT-NMR EX-270 spectrometer. ESR measurements were performed on a JEOL JES-ME−2X spectrometer at −196 °C (liquid N_2 temperature).

Synthesis of Ligands. All ligands used in this study were prepared according to the established procedures using benzylamine, phenethylamine, or *p*-substituted phenethylamines (X = CH_3, Cl, NO_2) and vinylpyridine in methanol containing acetic acid and purified by flash column chromatography (SiO_2).[44] The structures of the products were confirmed by the following analytical data.

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***N,N*-Bis[2-(2-pyridyl)ethyl]-2-phenylethylamine (1a):** pale yellow oil; IR (neat, cm^{-1}) 3150−2800 (aromatic and aliphatic C−H), 1594, 1572, 1496, 1478 (aromatic C═C and C═N), 750, and 700 (C−H); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.71−3.01 (12 H, m, $-CH_2-CH_2-$), 7.00−7.28 (9 H, m, C_6H_5, H_{py-3}, and H_{py-5}), 7.53 (2 H, dt, J = 2.0 and 7.6 Hz, H_{py-4}), 8.52 (2 H, d, J = 4.0 Hz, H_{py-6}); MS [EI (pos), *m*/*z*] 332 ($M^+ + 1$). Anal. Calcd for $C_{22}H_{25}N_3$: C, 79.72; H, 7.60; N, 12.68. Found: C, 79.54; H, 7.72; N, 12.60.

The 1,1,2,2-tetradeuterated derivative (**1a**-d_4) was prepared with $PhCD_2CD_2NH_2$ instead of $PhCH_2CH_2NH_2$, and its purity (> 99%) was confirmed by the ^{1}H NMR and mass spectra.

***N,N*-Bis[2-(2-pyridyl)ethyl]-2-(*p*-tolyl)ethylamine (1b):** pale yellow oil; IR (neat, cm^{-1}) 3090−2770 (aromatic and aliphatic C−H), 1591, 1473, 1435 (aromatic C═C and C═N), and 752 (C−H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (3H, s, CH_3), 2.66−2.82 (4 H, m, $-CH_2-CH_2-$), 2.90−3.02 (8 H, m, $-CH_2-CH_2-$), 7.00−7.11 (8 H, m, H_o, H_m, H_{py-3}, and H_{py-5}), 7.53 (2 H, dt, J = 2.0 and 7.6 Hz, H_{py-4}), 8.52 (2 H, d, J = 4.0 Hz, H_{py-6}); MS (EI, *m*/*z*) 346 ($M^+ + 1$).

***N,N*-Bis[2-(2-pyridyl)ethyl]-2-(*p*-chlorophenyl)ethylamine (1c):** pale yellow oil; IR (neat, cm^{-1}) 3090−2770 (aromatic and aliphatic C−H), 1590, 1568, 1491, 1474, 1435 (aromatic C═C and C═N), 1091 (C−Cl), and 748 (C−H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64−2.79 (4 H, m, $-CH_2-CH_2-$), 2.87−3.00 (8 H, m, $-CH_2-CH_2-$), 6.97−7.01 (4 H, m, H_{py-5}, H_m), 7.10 (2 H, ddd, J = 1.2, 4.8, and 7.6 Hz, H_{py-3}), 7.18 (2 H, d, J = 8.4 Hz, H_o), 7.53 (2 H, dt, J = 2.0 and 7.6 HZ, H_{py-4}), 8.52 (2 H, ddd, J = 0.8, 2.0, and 4.8 Hz, H_{py-6}); MS (EI, *m*/*z*) 365 (M^+).

***N,N*-Bis[2-(2-pyridyl)ethyl]-2-(*p*-nitrophenyl)ethylamine (1d):** yellow oil; IR (neat, cm^{-1}) 3100−2770 (aromatic and aliphatic C−H), 1592, 1473, 1436 (aromatic C═C and C═N), 1517, 1344, 857 (NO_2), and 748 (C−H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75−2.85 (4 H, m, $-CH_2-CH_2-$), 2.86−3.01 (8 H, m, $-CH_2-CH_2-$), 6.98 (2 H, d, J = 7.9 Hz, H_{py-3}), 7.11 (2 H, ddd, J = 0.8, 4.9, and 7.9 Hz, H_{py-5}), 7.17 (2 H, d, J = 8.6 Hz, H_m), 7.53 (2 H, dt, J = 1.4 and 7.9 Hz, H_{py-4}), 8.04 (2 H, d, J = 8.6 Hz, H_o), 8.52 (2 H, dd, J = 1.4 and 4.9 Hz, H_{py-6}); MS (EI, *m*/*z*) 376 (M^+).

Synthesis of Copper Complexes. [Cu^{II}(1a)(ClO_4)$_2$]. To a CH_3OH solution (6 mL) of ligand **1a** (1.19 g, 3.58 mmol) was added an equimolar amount of $Cu(ClO_4)_2 \cdot 6H_2O$, and the mixture was stirred for 15 min. The mixture was then poured into a large amount of Et_2O. The resulting oily blue material was separated and dissolved in 600 mL of CH_2Cl_2. Addition of Et_2O (300 mL) into the CH_2Cl_2 solution gave a blue solid which was collected by filtration and washed with Et_2O several times (1.50 g, 71%): UV−vis [CH_2Cl_2, λ_{max}, nm (ϵ, M^{-1} cm^{-1})] 266 (15 400), 664 (234); FTIR (KBr, cm^{-1}); 1123, 1090, and 625 (ClO_4^-). Anal. ([Cu^{II}(**1a**)(ClO_4)$_2$]). Calcd for $C_{22}H_{25}Cl_2CuN_3O_8$: C, 44.49; H, 4.24; N, 7.08. Found: C, 44.33; H, 4.23; N, 7.00.[24]

[Cu^{I}(1a)]PF_6 was prepared according to the reported procedures[45] as follows. To a deaerated CH_2Cl_2 solution (6 mL) of ligand **1a** (99 mg, 0.33 mmol) was added [$Cu^{I}(CH_3CN)_4$]PF_6[46] (112 mg, 0.3 mmol) under Ar atmosphere. After 15 min of stirring at room temperature, addition of deaerated ether (50 mL) with a syringe gave a pale yellow Cu(I) complex which was precipitated by standing the mixture for several minutes. The supernatant was then sucked up with a syringe, and the remained pale yellow solid was washed with deaerated ether three times under anaerobic conditions and dried under vacuum (79% yield): ^{1}H NMR (270 MHz, CD_3CN) δ 2.80−3.08 (12 H, m, $-CH_2-CH_2-$), 7.17−7.38 (9 H, m, C_6H_5, H_{py-3}, and H_{py-5}), 7.83 (2 H, t, J = 7.3 Hz, H_{py-4}), 8.47 (2 H, d, J = 7.3 Hz, H_{py-6}); FTIR (KBr, cm^{-1}) 839 (PF_6^-). Anal. ([Cu^{I}(**1**)]$PF_6 \cdot 0.75CH_2Cl_2$). Calcd for $C_{22.75}H_{26.5}Cl_{1.5}CuN_3PF_6$: C, 45.26; H, 4.42; N, 6.96. Found: C, 45.62; H, 4.45; N, 7.27.

[Cu^{I}(1a)]ClO_4 was obtained in a similar manner using [$Cu^{I}(CH_3CN)_4$]ClO_4[46] instead of [$Cu^{I}(CH_3CN)_4$]PF_6 in 71% as a pale yellow powder: ^{1}H NMR (400 MHz, CD_3CN) δ 2.85−3.05 (12 H, m, $-CH_2-CH_2-$), 7.21−7.36 (9 H, m, C_6H_5, H_{py-3}, and H_{py-5}), 7.82 (2 H, t, J = 7.0 Hz, H_{py-4}), 8.46 (2 H, br s, H_{py-6}); FTIR (KBr, cm^{-1}) 1090 and 623 (ClO_4^-). Anal. for ([Cu^{I}(**1a**)]ClO_4). Calcd for $C_{22}H_{25}O_4ClCuN_3$: C, 53.44; H, 5.10; N, 8.50. Found: C, 53.41; H, 5.22; N, 8.20.

[Cu^{I}(1a)]CF_3SO_3 was prepared in a similar manner using [$Cu^{I}(CH_3CN)_4$]CF_3SO_3[46] instead of [$Cu^{I}(CH_3CN)_4$]PF_6. However, the Cu(I) complex could be obtained only as an oily pale yellow material. Thus, after the treatment of [$Cu^{I}(CH_3CN)_4$]CF_3SO_3 with exactly the same amount of ligand **1a** in deaerated CH_2Cl_2 for 15 min, the solvent was removed under a reduced pressure. The purity of the complex was checked by ^{1}H NMR [(400 MHz, CD_3CN) δ 2.89−3.02 (12 H, m, $-CH_2-CH_2-$), 7.21−7.35 (9 H, m, C_6H_5, H_{py-3}, and H_{py-5}), 7.83 (2 H, t, J = 7.8 Hz, H_{py-4}), 8.43 (2 H, br s, H_{py-6})] and FTIR [(KBr, cm^{-1}): 1225, 1153, 1030, and 640 ($CF_3SO_3^-$)].

[Cu^{I}(1a)]BPh_4 was prepared according to the reported procedure[16b] and was obtained as an oily pale yellow material. The purity of the complex was checked by ^{1}H NMR [(270 MHz, CD_3CN) δ 2.86−3.02 (12 H, m, $-CH_2-CH_2-$), 6.83 (4 H, t, J = 7.2 Hz), 6.98 (8 H, t, J = 7.2 Hz), 6.18−7.37 (17 H, m), 7.81 (2 H, dt, J = 1.8 and 7.8 Hz, H_{py-4}), 8.46 (2 H, d, J = 3.5 Hz, H_{py-6}) and FTIR [(KBr, cm^{-1}) 735 and 704 (BPh_4^-)].

[Cu^{I}(1b)]PF_6 was obtained in a manner similar to that for the synthesis of [Cu^{I}(**1a**)]PF_6 using ligand **1b** instead of ligand **1a** in 60% as a pale yellow powder: ^{1}H NMR (270 MHz, CD_3CN) δ 2.29 (3 H, s, CH_3), 2.89−3.03 (12 H, m, $-CH_2-CH_2-$), 7.11 (4 H, br s, C_6H_4), 7.34−7.36 (4 H, m, H_{py-3} and H_{py-5}), 7.83 (2 H, t, J = 7.0 Hz, H_{py-4}), 8.47 (2 H, d, J = 4.3 Hz, H_{py-6}); FTIR (KBr, cm^{-1}): 837 (PF_6^-). Anal. ([Cu^{I}(**1b**)]$PF_6 \cdot H_2O$). Calcd for $C_{23}H_{29}CuF_6N_3OP$: C, 48.30; H, 5.11; N, 7.35. Found: C, 48.72; H, 4.88; N, 7.51.

[Cu^{I}(1c)]PF_6 was obtained in a manner similar to that for the synthesis of [Cu^{I}(**1a**)]PF_6 using ligand **1c** instead of ligand **1a** in 55% as a pale yellow powder: ^{1}H NMR (270 MHz, CD_3CN) δ 2.88−3.05 (12 H, m, $-CH_2-CH_2-$), 7.20−7.38 (8 H, m, C_6H_4, H_{py-3}, and H_{py-5}), 7.84 (2 H, dt, J = 1.6 and 7.8 Hz, H_{py-4}), 8.49 (2 H, dd, J = 1.6 and 5.1 Hz, H_{py-6}); FTIR (KBr, cm^{-1}): 1086 (C−Cl) and 841 (PF_6^-). Anal. ([Cu^{I}(**1c**)]PF_6). Calcd for $C_{22}H_{24}ClCuF_6N_3P$: C, 46.00; H, 4.21; N, 7.32. Found: C, 45.31; H, 4.16; N, 7.28.

[Cu^{I}(1d)]PF_6 was obtained in a manner similar to that for the synthesis of [Cu^{I}(**1a**)]PF_6 using ligand **1d** instead of ligand **1a** in 87% as a pale orange powder: ^{1}H NMR (270 MHz, CD_3CN) δ 2.90 (8 H, br s, $-CH_2-CH_2-$), 3.06 (4 H, br s, $-CH_2-CH_2-$), 7.34−7.38 (4 H, m, H_{py-3}, and H_{py-5}), 7.45 (2 H, d, J = 8.8 Hz, H_m), 7.83 (2 H, dt, J = 1.4 and 7.4 Hz, H_{py-4}), 8.15 (2 H, d, J = 8.8 Hz, H_o), 8.49 (2 H, d, J = 4.1 Hz, H_{py-6}); FTIR (KBr, cm^{-1}) 1515, 1344 (NO_2), and 843 (PF_6^-). Anal. ([Cu^{I}(**1d**)]PF_6). Calcd for $C_{22}H_{24}CuF_6N_4O_2P$: C, 45.17; H, 4.14; N, 9.58. Found: C, 44.83; H, 4.18; N, 9.14.

Ligand Hydroxylation Reaction. [Cu^{II}(1a)]$^{2+}$/Benzoin/Triethylamine/O_2 System. The Cu(II) complex [Cu^{II}(**1a**)(ClO_4)$_2$] (84 μmol) was treated with an equimolar amount of benzoin and triethylamine in CH_2Cl_2 (5 mL) at room temperature for 2 h under Ar, and then the mixture was stirred under an atmospheric pressure of O_2 for several hours. The modified ligand **2a** was isolated quantitatively after an ordinary workup treatment of the reaction mixture with NH_4OH aq and following extraction by CH_2Cl_2: ^{1}H NMR (270 MHz, $CDCl_3$, δ, TMS) 2.57−3.16 (m, 10 H, $-CH_2-$ × 5), 4.60 (dd, J = 3.5 and 9.7 Hz, 1 H, −CHOH−), 7.02 (d, J = 7.7 Hz, 2 H, py-H_3), 7.10 (dd, J = 4.8, 7.7 Hz, 2 H, py-H_5), 7.22−7.38 (m, 5 H, −Ph), 7.54 (dt, J = 1.7, 7.7 Hz, 2 H, py-H_4), 8.52 (d, J = 4.8 Hz, 2 H, py-H_6); IR (neat, cm^{-1}) 3396 (OH); MS (CI, *m*/*z*) 348 ($M^+ + 1$).

[Cu^{I}(L)]$^+$/O_2 System (L = 1a−d). Typically, [Cu^{I}(**1a**)]PF_6 (61 mg, 0.10 mmol) was dissolved into deaerated CH_2Cl_2 (5 mL) under anaerobic conditions, and the solution was cooled to − 78 °C using a dry ice/acetone bath. O_2 gas was introduced into the solution by bubbling for 1 h, when the color of the solution turned dark brown due to the formation of the μ-peroxodicopper(II) complex. Then the excess amount of O_2 gas was replaced with Ar by letting the system under reduced pressure and flashing Ar gas (three cycles) at the low temperature. The reaction temperature was then gradually increased to room temperature, and the mixture was stirred for additional 3 h. A mixture of **1a** and **2a** was obtained after an ordinary workup treatment of the reaction mixture with NH_4OH aq and following extraction by CH_2Cl_2. Yield of **2a** was determined as 47% by using an integral ratio

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in the ^{1}H NMR spectrum between the methine proton (−CHOH−) at δ 4.60 of **2a** and the pyridine protons at the 6-position (py-H_6, δ 8.52) from both **1a** and **2a** (py-H_6s of **1a** and **2a** are overlapped); (−CHOH−):(py−H_6) = 0.47:2.00.

The reactions of the copper(I) complexes of other ligands (**1b**−**d**) were carried out in a similar manner, and the yields of the ligand hydroxylation were determined as 49%, 48%, and 47% for **2b**, **2c**, and **2d**, respectively: for **2b**, [−CHOH−, δ 4.57 (dd, J = 3.8 and 9.4 Hz)]:[py-H_6, δ 8.52 (d, J = 4.6 Hz)] = 0.49:2.00; for **2c**, [−CHOH−, δ 4.58 (dd, J = 3.0 and 9.7 Hz)]:[py-H_6, δ 8.51 (d, J = 4.6 Hz)] = 0.48:2.00; for **2d**, [−CHOH−, δ 4.72 (dd, J = 3.8 and 9.4 Hz)]:[py-H_6, δ 8.52 (d, J = 4.7 Hz)] = 0.47:2.00. In all the cases, there is no byproduct other than the benzyl hydroxylated ligand (**2b**−**d**).

O_2-Uptake Measurements were carried out according to the reported procedure using CH_2Cl_2 as a solvent at 21 °C.[47] The volume of O_2 consumed during the oxygenation reaction was obtained as a difference of the O_2 consumption between the ligand hydroxylation reaction and the blank solution without the reactants under exactly the same conditions. For the reaction system of [Cu^{II}(**1**)(ClO_4)$_2$]/benzoin/NEt_3, Cu:O_2 was 1:0.96 ± 0.1, and for the reaction with [Cu^{I}(**1**)]PF_6, Cu:O_2 was 2:0.97 ± 0.1.

Resonance Raman Measurements. The $^{16}O_2$ sample was prepared via bubbling of dry dioxygen into an acetone solution of [Cu^{I}(**1a**-d_4)]-PF_6 (0.02 M) at −80 °C. The $^{18}O_2$ analogue was prepared via condensation of $^{18}O_2$ into a previously evacuated Schlenk flask containing a frozen acetone solution (77 K) of [Cu^{I}(**1a**-d_4)]PF_6 (0.02 M). The flask was then allowed to warm to −80 °C and was maintained at this temperature for about 30 min to allow for complete formation of the dioxygen complex. Resonance Raman spectra were collected on a SPEX 1403 spectrometer interfaced with a DM3000 data collection system using a Spectra-Physics Model 2030-15 argon ion laser (514.5 nm). The spectra were obtained at 77 K using a backscattering geometry. The samples were frozen onto a gold-plated copper coldfinger in thermal contact with a dewar containing liquid nitrogen for data collection. Raman frequencies were referenced to the intense feature at 806 cm^{-1} from frozen acetone.

Kinetic Measurements. The reaction of the copper(I) complex and O_2 was carried out in a 1 mm path length UV−vis cell that was held in a Unisoku thermostated cell holder designed for low-temperature experiments (a desired temperature can be fixed within ± 0.5 °C). After the deaerated solution of the copper(I) complex (2.5×10^{-3} M) in the cell was kept at the desired temperature for several minutes, dry dioxygen gas was continuously supplied by gentle bubbling from a thin needle. The formation and decay of the μ-peroxodicopper complex intermediate were monitored by following the increase and decrease in the absorption at 362 nm.

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