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Developing Mononuclear Copper–Active-Oxygen Complexes Relevant to Reactive Intermediates of Biological Oxidation Reactions

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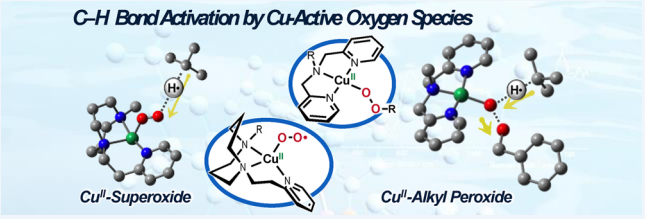
CONSPECTUS: Active-oxygen species generated on a copper complex play vital roles in several biological and chemical oxidation reactions. Recent attention has been focused on the reactive intermediates generated at the mononuclear copper active sites of copper monooxygenases such as dopamine β-monooxygenase (DβM), tyramine β-monooxygenase (TβM), peptidylglycine-α-hydroxylating monooxygenase (PHM), and polysaccharide monooxygenases (PMO). In a simple model system, reaction of O_2 and a reduced copper(I) complex affords a mononuclear copper(II)–superoxide complex or a copper(III)–peroxide complex, and subsequent $H^{\bullet}$ or e^-/H^+ transfer, which gives a copper(II)–hydroperoxide complex. A more reactive species such as a copper(II)–oxyl radical type species could be generated via O–O bond cleavage of the peroxide complex. However, little had been explored about the chemical properties and reactivity of the mononuclear copper–active-oxygen complexes due to the lack of appropriate model compounds. Thus, a great deal of effort has recently been made to develop efficient ligands that can stabilize such reactive active-oxygen complexes in synthetic modeling studies.



In this Account, I describe our recent achievements of the development of a mononuclear copper(II)–(end-on)superoxide complex using a simple tridentate ligand consisting of an eight-membered cyclic diamine with a pyridylethyl donor group. The superoxide complex exhibits a similar structure (four-coordinate tetrahedral geometry) and reactivity (aliphatic hydroxylation) to those of a proposed reactive intermediate of copper monooxygenases. Systematic studies based on the crystal structures of copper(I) and copper(II) complexes of the related tridentate supporting ligands have indicated that the rigid eight-membered cyclic diamine framework is crucial for controlling the geometry and the redox potential, which are prerequisites for the generation of such a unique mononuclear copper(II)–(end-on)superoxide complex.

Reactivity of a mononuclear copper(II)–alkylperoxide complex has also been examined to get insights into the intrinsic reactivity of copper(II)–peroxide species, which is usually considered as a sluggish oxidant or just a precursor of copper–oxyl radical type reactive species. However, our studies have unambiguously demonstrated that copper(II)–alkylperoxide complex can be a direct oxidant for C–H bond activation of organic substrates, when the C–H bond activation is coupled with O–O bond cleavage (concerted mechanism). The reactivity studies of these mononuclear copper(II) active-oxygen species (superoxide and alkylperoxide) will provide significantly important insights into the catalytic mechanism of copper monooxygenases as well as copper-catalyzed oxidation reactions in synthetic organic chemistry.

INTRODUCTION

Copper complexes of the active-oxygen species such as superoxide, peroxide, and oxide have been invoked as the key reactive intermediates not only in a variety of biological oxidation and oxygenation reactions catalyzed by copper enzymes but also in several types of copper-catalyzed oxidation reactions in synthetic organic chemistry and catalytic oxidation chemistry.[1−5] In Scheme 1 are shown the possible reaction pathways for the generation of the series of copper–active-oxygen complexes in a simple model system. The reaction of a copper(I) complex and O_2 provides a mononuclear copper–dioxygen adduct such as copper(II)–(side-on)superoxide (**CuS^S**), copper(II)–(end-on)superoxide (**CuS^E**), or copper(III)–(side-on)peroxide (**CuP^S**) complex, the structure of which depends largely on the supporting ligand features (L) (*vide infra*).[2,3,6,7] In many cases, the mononuclear copper–dioxygen adducts are easily trapped by another molecule of the copper(I) starting material existing in the solution to give a μ-peroxide dicopper(II) complex with a side-on or an end-on binding mode, **Cu$_2$P^S** or **Cu$_2$P^E**.[2,3] The μ-peroxide complexes can be further converted to a bis(μ-oxido)dicopper(III) complex, **Cu$_2$O$_2$**, when the supporting ligand can stabilize the higher oxidation state of copper(III). In this case, two more electrons are injected to the peroxide moiety from each copper(II) ion to induce the O–O bond homolysis.[2,3,8] Moreover, **Cu$_2$O$_2$** supported by a sterically less hindered bidentate ligand further reacts with another molecule of

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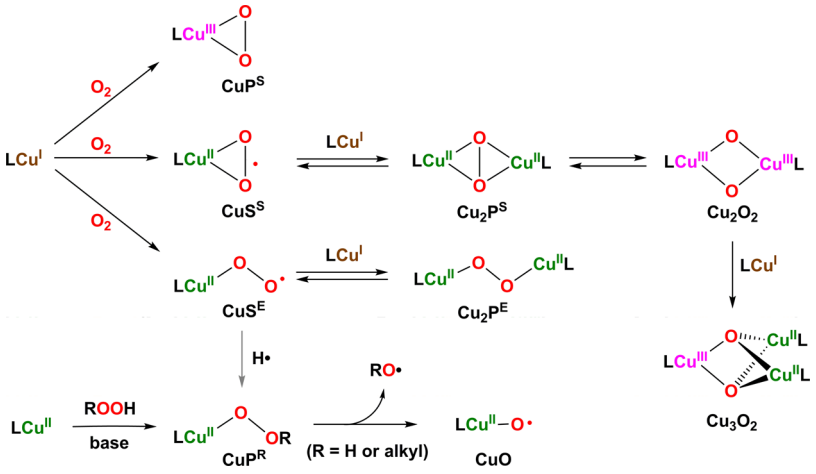
Scheme 1. Possible Reaction Pathways for Generation of Copper−Active-Oxygen Complexes



copper(I) starting complex to give a mixed-valent trinuclear copper(II,II,III) complex, **Cu$_3$O$_2$**.[9,10]

Mononuclear copper(II)−hydroperoxide complex, **CuP^H**, could be generated, if one could trap the mononuclear copper(II)−superoxide complex by adding an efficient hydrogen atom donor. However, only few examples have been reported for such a reaction.[11,12] Instead, mononuclear copper(II)−hydroperoxide, **CuP^H**, and copper(II)−alkylperoxide, **CuP^R**, complexes have been synthesized by the reaction of copper(II) complexes with hydrogen peroxide (H_2O_2) or alkylhydroperoxide (ROOH) in the presence of a base (so-called shunt pathway). Theoretically, O−O bond homolysis of **CuP^R** might provide a mononuclear copper(II)−oxyl radical type species, **CuO**, which is also a putative reactive intermediate of mononuclear copper monooxygenases. However, **CuO** has yet to be detected directly, neither in the synthetic modeling reactions nor in the enzymatic reactions.

Compared with the extensive studies of the dinuclear copper−active-oxygen complexes such as **Cu$_2$P^S**, **Cu$_2$P^E**, and **Cu$_2$O$_2$**, chemistry of the mononuclear copper−active-oxygen complexes had been much less explored until recently due to the lack of sufficient model compounds. In this Account, I summarize the recent advances in our reactivity studies of biologically relevant mononuclear copper−active-oxygen complexes such as **CuS^E** and **CuP^R**, the putative reactive intermediates of copper monooxygenases.

FORMATION OF MONONUCLEAR COPPER(II)−SUPEROXIDE COMPLEXES

Mononuclear copper(II)−superoxide complexes are receiving much recent attention as the key reactive intermediate of copper monooxygenases such as dopamine β-monooxygenase (DβM), tyramine β-monooxygenase (TβM), and peptidylglycine-α-hydroxylating monooxygenase (PHM).[13−15] These enzymes catalyze the stereoselective hydroxylation at the benzylic position of dopamine and tyramine, the biologically important hormone and monoamine neurotransmitter (DβM and TβM), and the initial step of amidation of the C-terminus of peptide hormones and neuropeptides (PHM).[16] Amzel and co-workers succeeded in determining the crystal structure of the oxy-form of PHM using a slow substrate (inhibitor), to demonstrate existence of a mononuclear copper active center having an end-on bound O_2 with a distorted tetrahedral geometry (Figure 1).[17] Recently, polysaccharide monooxygenases have also been shown to have a simple mononuclear copper reaction center for the oxidative degradation of stable polysaccharides such as cellulose and chitin,[18,19] for which a mononuclear copper(II)−superoxide species is also suggested to be involved as a key intermeidtae.[20] However, little is known about the physicochemical properties and reactivity of such species involved in the enzymatic reactions.

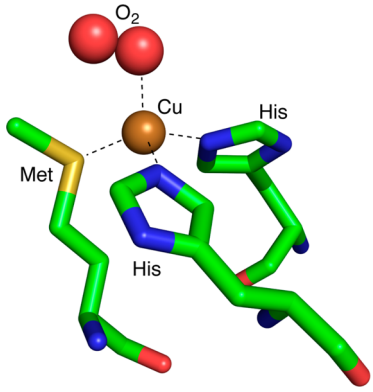


Figure 1. Crystal structure of the Cu$_M$ active site of oxy-PHM.[17]

To stabilize the mononuclear copper−active-oxygen species, supporting ligands having bulky or strongly electron donating substituents have been usually employed to prevent dimerization reactions.[2,3,6,21] For instance, Kitajima and co-workers succeeded to obtain the first crystal structure of **CuS^S** using monoanionic hydrotrispyrazolylborate tridentate ligand **Tp** having bulky alkyl substituents such as *tert*-butyl or adamantyl (Chart 1).[22,23] Tolman and co-workers reported a similar type of mononuclear copper−dioxygen adduct in a side-on fashion that was prepared by using a monoanionic β-diketiminate

Chart 1. Ligands Used for the Synthesis of Mononuclear Copper−O$_2$ Adduct Complexes

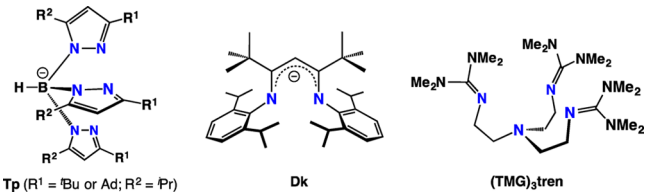


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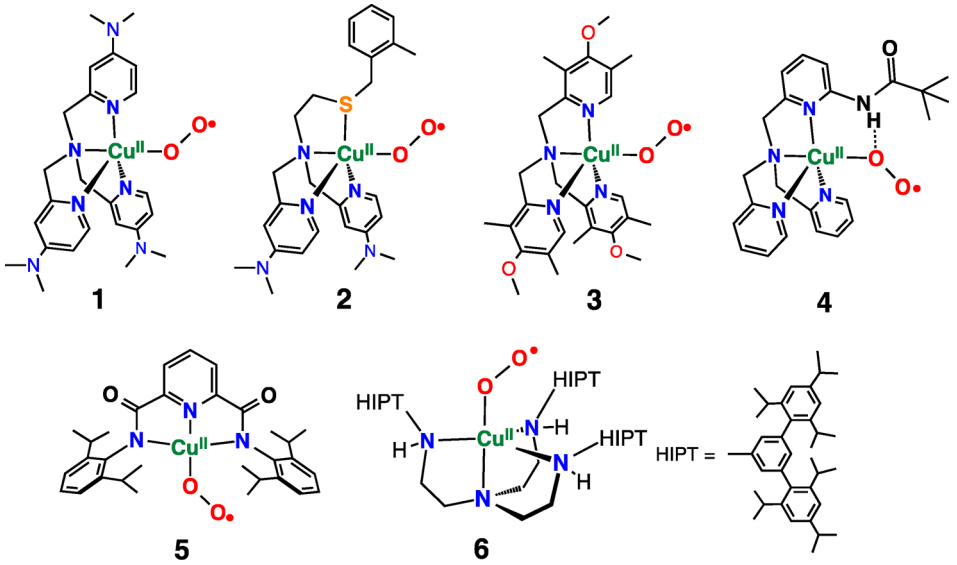
Chart 2. Well Characterized Copper(II) End-on Superoxide Complexes, CuS^E

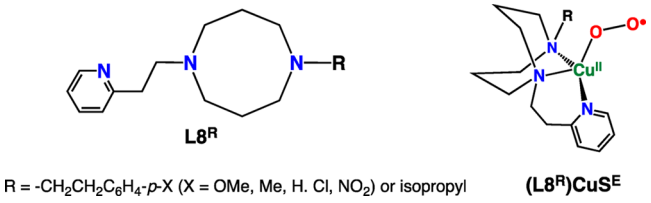


bidentate ligand also having bulky substituents, **Dk** (Chart 1). In this case, the electronic configuration has been shown to be copper(III)−peroxide, CuP^S, due to the strong electron-donating ability of the monoanionic bidentate ligand, which may be able to stabilize the higher oxidation state of copper(III) with a square planar structure.[7,24,25] Schindler and co-workers reported the first crystal structure of an end-on superoxide−copper(II) complex, CuS^E, which was generated by using a tripodal tetradentate tren ligand having a bulky and strongly electron-donating substituent, tetramethylguanidine, $(TMG)_3$**tren** (Chart 1).[26]

After Schindler's report, a couple of well-characterized mononuclear copper(II)−(end-on)superoxide complexes, CuS^E, have been developed also by using supporting ligands containing strongly electron-donating groups (**1**, **2**, **3**, and **5** in Chart 2), hydrogen bonding interaction (**4** in Chart 2), or sterically bulky substituents (**6** in Chart 2) stabilizing the superoxide moiety.[27−32] However, these superoxide complexes have a five-coordinate trigonal bipyramidal structure (**1**−**4** and **6**) or a square planar structure (**5**), which are different from the four-coordinate tetrahedral geometry found in the enzymatic system (Figure 1).

In this respect, we have succeeded to develop a mononuclear copper(II)−superoxide complex exhibiting a four-coordinate tetrahedral geometry and aliphatic hydroxylation reactivity similar to those of the proposed reactive intermediate of copper monooxygenases (Figure 1), by using simple tridentate ligands $L8^R$ (Chart 3).[33] The ligand consists of a 1,5-diazacyclooctane with a 2-(pyridyn-2-yl)ethyl donor group but involves neither a sterically bulky substituent nor a strongly electron-donating substituent. Thus, the stabilization mechanism of CuS^E in this particular ligand system might be different from that of the others listed in Charts 1 and 2 (*vide infra*).

Chart 3. Ligand $L8^R$ and Copper(II)−Superoxide Complex $(L8^R)CuS^E$



Reaction of the copper(I) complexes supported by $L8^R$ ($(L8^R)Cu$) and O_2 gave mononuclear copper(II)−(end-on)superoxide complexes $(L8^R)CuS^E$, exhibiting a LMCT band around 400 nm together with the broad absorption bands in the visible-to-near IR region.[33] A typical spectral change for the generation of $(L8^R)CuS^E$ is shown in Figure 2A, where R = $-CH_2CH_2Ph$.[33] The superoxide complex exhibited O−O and Cu−O stretching vibrations in the resonance Raman spectrum (λ_{ex} = 406.7 nm) at 1033 and 457 cm^{-1}, respectively, which shifted to 968 and 442 cm^{-1} upon $^{18}O_2$-substitution.[33] The EPR study using a parallel excitation mode (Figure 2B) has indicated that $(L8^R)CuS^E$ has a spin triplet ground state (S = 1),[33] the assignment of which was supported by DFT calculations.[34]

The O_2-binding process is reversible at low temperature (eq 1), and the k_{on} and k_{off} as well as K_{eq} values have been determined kinetically (eqs 2 and 3). From the temperature dependence of k_{on}, k_{off}, and K_{eq} values ($\ln(k_{on}/T)$, $\ln(k_{off}/T)$, and $\ln K_{eq}$ against $1/T$), the kinetic and thermodynamic parameters (ΔH and ΔS) for the formation of $(L8^R)CuS^E$ (R = isopropyl, Chart 3) have been determined and compared with those of the other ligand systems.[34]

$$(L8^R)Cu + O_2 \underset{k_{off}}{\overset{k_{on}}{\rightleftarrows}} (L8^R)CuS^E \quad (1)$$

$$k_{obs} = k_{on}[O_2] + k_{off} \quad (2)$$

$$K_{eq} = k_{on}/k_{off} \quad (3)$$

REACTIVITY OF SUPEROXIDE COMPLEX, $(L8^R)CUS^E$

Copper(II)−superoxide complex $(L8^R)CuS^E$ (R = $-CH_2CH_2Ph$) further reacted at a low temperature (−65 °C) to induce an aliphatic ligand hydroxylation at its benzylic position of substituent R to give a copper(II)−alcoholate complex $(L8^{R-O})Cu$ (Scheme 2) in ∼35% yield based on the starting copper complex (the maximum yield is 50% based on the copper(I) starting complex, since the ligand hydroxylation

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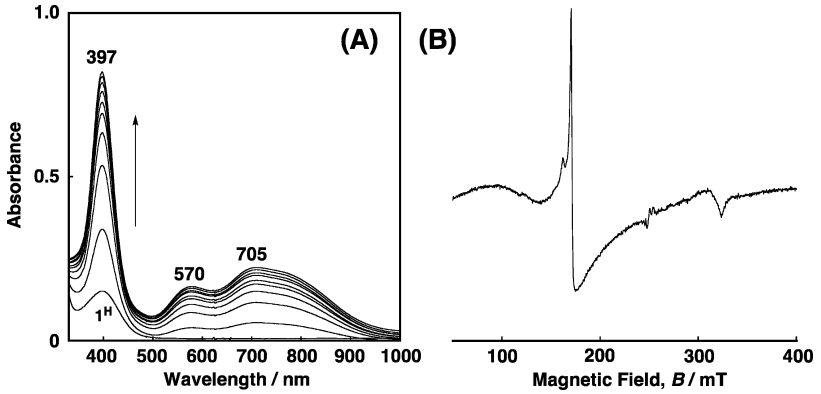
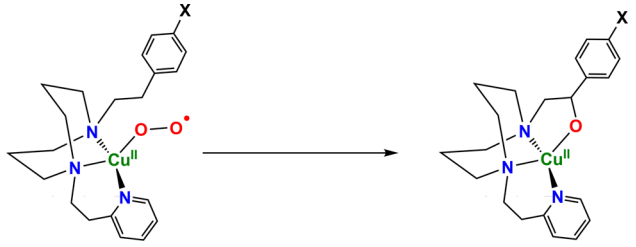


Figure 2. (A) Spectral change for the reaction of copper(I) complex of $\mathbf{L8^R}$ (0.2 mM) with O_2 in acetone−CH_3CN (9:1) at −85 °C. (B) X-band fine-structure ESR spectrum of $\mathbf{(L8^R)CuS^E}$ observed in the microwave parallel excitation mode ($\mathbf{B_0}\|\mathbf{B_1}$) in acetone−$CH_3CN$ (9:1) at 3 K.[33]

Scheme 2. Aliphatic Ligand Hydroxylation in $\mathbf{(L8^R)CuS^E}$



is a two-electron oxidation process).[33] Isotope labeling experiments using $^{18}O_2$ confirmed that the oxygen atom in the product was originated from O_2.[33] This is the unique example of the functional model of the copper monooxygenases (DβM and TβM), exhibiting the aliphatic C−H bond hydroxylation reactivity.[35]

The reaction obeyed first-order kinetics, suggesting that the ligand hydroxylation reaction is an intramolecular process.[34] In the reaction of perdeuterated phenetyl derivative $\mathbf{L8^R}$-d_4 (R = $-CD_2CD_2Ph$) an appreciable KIE value (4.1) was obtained.[34] The activation parameters for the ligand hydroxylation process were also determined as $\Delta H^{\ddagger}$ = 19 ± 0.1 kJ mol^{-1} and $\Delta S^{\ddagger}$= −223 ± 0.6 J K^{-1} mol^{-1},[34] which are close to those of the intramolecular aliphatic ligand hydroxylation reactions in the other copper−active oxygen complexes.[3] Electronic effects of the *p*-substituent (X) on the hydroxylation reaction were also examined using a series of *p*-substituted phenetyl derivatives, $\mathbf{(L8^R)CuS^E}$ (X = OMe, Me, H, Cl, NO_2, see Scheme 2), to give a negative small Hammett ρ value (−0.63), suggesting that the reactive species acts as a weakly nucleophilic radical in nature. Based on these results, we have concluded that the ligand hydroxylation reaction involves hydrogen atom abstraction and oxygen rebound mechanism, which was also supported by DFT calculations.[34] It should be noted that the Hammett ρ value of −0.63 in our model reaction is nearly identical to that of the benzylic hydroxylation of phenethylamine derivatives by DβM (ρ = −0.4),[36] suggesting that the enzymatic reaction also involves a similar mechanism, that is, C−H bond activation of the substrate by a copper(II)−(end-on)superoxide intermediate as proposed by Klinman et al.[13]

$\mathbf{(L8^R)CuS^E}$ could be reduced by electron-transfer reductants such as decamethylferrocene ($Me_{10}Fc$), octamethylferrocene (Me_8Fc), and *N*,*N*,*N*′,*N*′-tetramethylphenylenediamine (TMPD) at −85 °C in acetone (Table 1).[12] Quantitative formation of H_2O_2 (by iodometric titration) and a copper(II) complex product (by ESR spectrum) was confirmed, suggesting the reduction of superoxide to peroxide.[12] On the other hand, weaker reductants such as dimethylferrocene (Me_2Fc) and ferrocene itself (Fc) did not react with $\mathbf{(L8^R)CuS^E}$ under the same conditions (Table 1). From these results, the reduction potential of $\mathbf{(L8^R)CuS^E}$ is estimated to be close to that of TMPD (~0.12 V vs SCE).

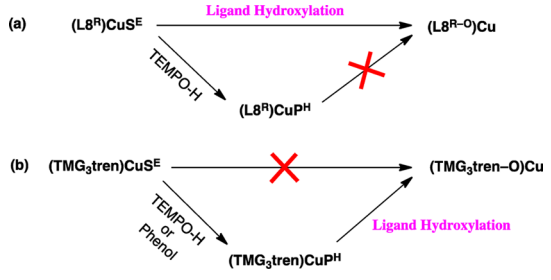
Table 1. One-Electron Oxidation Potential of the Reductants and the Second-Order Rate Constants for the Reduction of $\mathbf{(L8^R)CuS^E}$ (R = $-CH_2Ch_2Ph$) in Acetone at −85 °C

	$Me_{10}Fc$	Me_8Fc	TMPD	Me_2Fc	Fc
E°_{ox}, V vs SCE[a]	−0.08	−0.04	0.12	0.26	0.37
k_2, M^{-1} s^{-1}	320 ± 2	56 ± 0.4	9.4 ± 0.06	NR[b]	NR[b]

[a]The data are taken from the literature.[37] [b]No reaction.

$\mathbf{(L8^R)CuS^E}$ reacted with a typical hydrogen atom donor such as 2,2,6,6-tetramethylpiperidine-*N*-hydroxide (TEMPO-H) to give a copper(II)−hydroperoxide $\mathbf{(L8^R)CuP^H}$ (Scheme 1) and TEMPO$^{\bullet}$ quantitatively at a low temperature (−85 °C).[12] Even though, the hydroperoxide complex was not stable enough to be characterized in detail, quantitative formation of H_2O_2 was also confirmed by iodometric titration.[12] It should be noted that no ligand hydroxylation product was obtained from the final reaction mixture of the decomposition of $\mathbf{(L8^R)CuP^H}$ (Scheme 3a). This result is in sharp contrast to the $\mathbf{(TMG_3tren)CuS^E}$ system (see Chart 1), where a ligand hydroxylation took place at one of the methyl groups of the TMG substituent only after the reaction with the hydrogen

Scheme 3. Reactivity of $\mathbf{CuS^E}$ and $\mathbf{CuP^H}$ in the $\mathbf{L8^R}$ and $\mathbf{TMG_3tren}$ Ligand Systems



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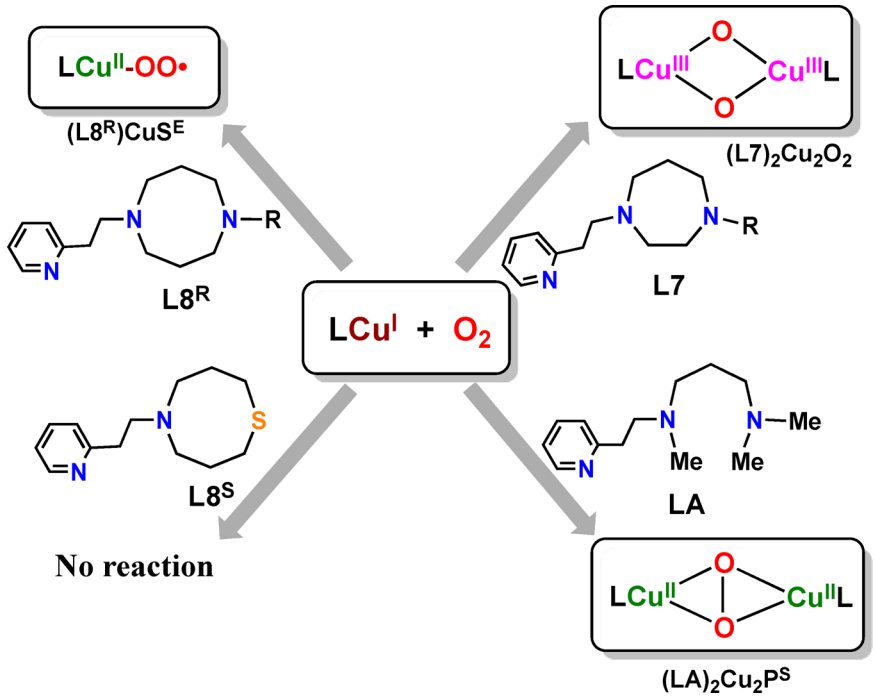
Scheme 4. Ligand Effects on Copper(I)−O_2 Reactivity (R = $-CH_2CH_2Ph$)



atom donor (Scheme 3b).[38] Thus, it was concluded that **(TMG$_3$tren)CuS^E** was not the direct oxidant for the ligand hydroxylation reaction, but that **(TMG$_3$tren)CuO** (**Cu−O$^•$**, see Scheme 1) generated by O−O bond homolysis of **(TMG$_3$tren)CuP^H**, which may be produced by the reaction of **(TMG$_3$tren)CuS^E** and the hydrogen atom donor, might be the reactive intermediate that induced the ligand hydroxylation.[38] However, no direct evidence was provided for the involvement of **(TMG$_3$tren)CuO** as the real active species. On the other hand, our results clearly indicated that the superoxide complex **(L8^R)CuS^E**, but not the hydroperoxide complex **(L8^R)CuP^H**, directly participates in the aliphatic ligand hydroxylation (Scheme 3a).[33,34] It should be noted that the tetrahedral geometry[33] of **(L8^R)CuS^E** is similar to those of the putative reactive intermediates of the copper monooxygenases,[17,39] suggesting that such a geometry of **CuS^E** is important for dictating the aliphatic hydroxylation reactivity.

LIGAND EFFECTS

As described above, **(L8^R)CuS^E** is a unique example as an end-on superoxide−copper(II) complex, exhibiting a similar structure and reactivity to those of a putative reactive intermediate of the enzymatic reactions (Figure 1). To address the ligand effects, related tridentate ligands containing seven-membered cyclic diamine (1,4-diazacycloheptane), **L7**, and an acyclic diamine (1,3-propanediamine), **LA**, as well as a sulfur version, **L8^S**, have been examined in the copper(I)−O_2 reactivity (Scheme 4).[40]

Notably, oxygenation of the copper(I) complex of **L7** having the smaller cyclic diamine moiety gave a bis(μ-oxido)dicopper(III) complex, **(L7)$_2$Cu$_2$O$_2$**,[40] whereas the same reaction of the copper(I) complex of **LA** containing the acyclic diamine moiety gave a (μ−η^2:η^2-peroxido)dicopper(II), **(LA)$_2$Cu$_2$P^S**, as a major product.[40] On the other hand, no O_2 reactivity was observed with the copper(I) complex of **L8^S** under the same conditions.[41] To get insights into the ligand effects, crystal structures of the copper(I) and copper(II) complexes have been examined in detail (Figures 3 and 4).

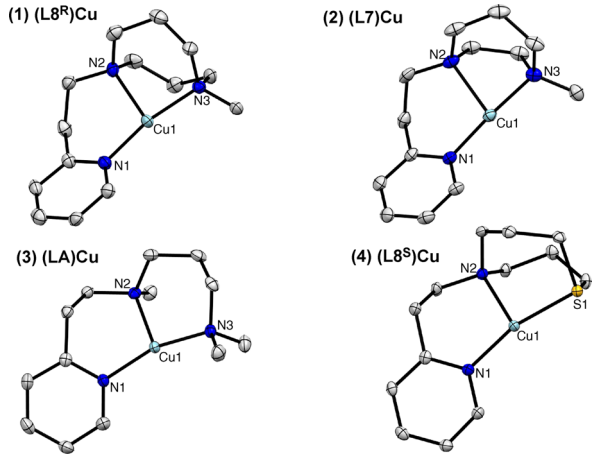


Figure 3. Crystal structures of the cationic part of the copper(I) complexes: (1) [Cu^I(**L8^R**)]PF$_6$ ((**L8^R**)**Cu**), (2) [Cu^I(**L7**)]PF$_6$ ((**L7**)**Cu**), (3) [Cu^I(**LA**)]PF$_6$ ((**LA**)**Cu**), and (4) [Cu^I(**L8^S**)]PF$_6$ ((**L8^S**)**Cu**). Hydrogen atoms are omitted, and only the methylene carbon connected to N3 in [Cu^I(**L8^R**)]PF$_6$ and [Cu^I(**L7**)]PF$_6$ is shown for simplicity.

All of the copper(I) complexes exhibit a similar three-coordinate T-shape structure (Figure 3).[33,34,40,41] However, detailed inspection of the crystal structures has pointed out a notable difference in the geometry around the metal center among the series of N$_3$-tridentate ligand systems (**L8^R** vs **L7** vs **LA**).[40] Namely, the bond angle N(2)−Cu(1)−N(3) at the diamine moiety decreases in going from (**LA**)**Cu** (105.57°) to (**L8^R**)**Cu** (90.30°) to (**L7**)**Cu** (80.56°), even though the Cu(1)−N(2) and Cu(1)−N(3) distances are fairly constant among the three complexes as 2.166−2.198 and 1.965−1.979 Å, respectively. Such structural features are reflected in the

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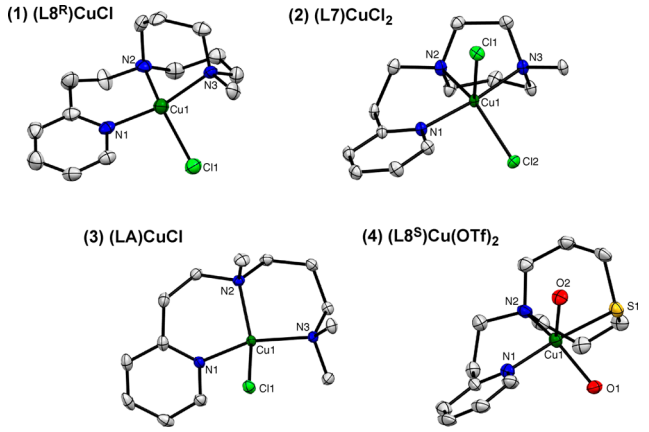

Figure 4. Crystal structures (1) $[Cu^{II}(\mathbf{L8^R})(Cl)]PF_6$ ($(\mathbf{L8^R})\mathbf{CuCl}$), (2) $[Cu^{II}(\mathbf{L7})(Cl)_2]$ ($(\mathbf{L7})\mathbf{CuCl_2}$), (3) $[Cu^{II}(\mathbf{LA})(Cl)]PF_6$ ($(\mathbf{LA})$-$\mathbf{CuCl}$), and (4) $[Cu^{II}(\mathbf{L8^S})(OTf)_2]$ ($(\mathbf{L8^S})\mathbf{Cu(OTf)_2}$). Hydrogen atoms and noncoordinating counteranion (PF_6) are omitted, and only methylene carbon connected to N3 in $(\mathbf{L8^R})\mathbf{CuCl}$ and $(\mathbf{L7})\mathbf{CuCl_2}$ is shown for simplicity.

difference in the oxidation potential, E^{ox}, of the copper(I) complexes, 0.49 V vs SCE for $(\mathbf{LA})\mathbf{Cu}$, 0.40 V for $(\mathbf{L8^R})\mathbf{Cu}$, and 0.18 V for $(\mathbf{L7})\mathbf{Cu}$.[40] In the case of $(\mathbf{L8^S})\mathbf{Cu}$, the oxidation potential is even higher at 0.52 V vs SCE, which is mainly due to the sulfur coordination, stabilizing the lower oxidation state of copper(I) through back electron donation from the d-orbital of copper(I) to the empty d-orbitals of the sulfur atom.[41]

More prominent differences are found in the crystal structures of the copper(II) complexes.[33,34,40] Namely, $(\mathbf{L8^R})\mathbf{CuCl}$ and $(\mathbf{LA})\mathbf{CuCl}$ exhibit a *four-coordinate distorted tetrahedral* geometry with the N_3Cl donor set (Figure 4, structures 1 and 3), whereas $(\mathbf{L7})\mathbf{CuCl_2}$ shows *five-coordinate distorted trigonal bipyramidal* geometry with the N_3Cl_2 donor set (Figure 4, structure 2). As in the case of the copper(I) complexes, the bond angles of N(2)−Cu(1)−N(3) at the cyclic diamine moiety decrease in going from $(\mathbf{LA})\mathbf{CuCl}$ (97.82°) to $(\mathbf{L8^R})\mathbf{CuCl}$ (89.5°) to $(\mathbf{L7})\mathbf{CuCl_2}$ (78.93°), whereas the bond angle at the pyridylethylamine moiety N(1)−Cu(1)−N(2) is fairly similar among the three complexes (95.97°, 98.8°, and 94.93°, respectively). As a result, the **L7** complex can provide enough space at the opposite side of N(2) to accommodate two chloride anions giving the five-coordinate structures, whereas the **LA** and $\mathbf{L8^R}$ complexes can accommodate only one chloride anion due to the limited space, providing the four-coordinate structure in the solid. $(\mathbf{L8^S})\mathbf{Cu(OTf)_2}$ also shows a five-coordinate structure, but its geometry is closer to square pyramidal structure, where N(1), N(2), S(1), and O(1) constitute the basal plane and O(2) occupies the axial position (Figure 4, structure 4).

Regarding the geometric effects of supporting ligands, the most important factor may be rigidity or flexibility of the diamine moiety of $\mathbf{L8^R}$, **L7**, and **LA**. Due to the rigid cyclic diamine framework, the diatomic distances of N(2)−N(3) in the $\mathbf{L8^R}$ complex and in the **L7** complex are fairly constant regardless of the oxidation state of copper ion. Namely, the N(2)−N(3) distances are similar around 2.9 Å between the copper(I) and copper(II) complexes of $\mathbf{L8^R}$, and both the copper(I) and copper(II) complexes of **L7** exhibit the N(2)−N(3) distance around 2.65 Å. The N(2)−N(3) distances of the **L7** complexes are nearly the same as the N_{eq}−N_{eq} distance of the reported bis(μ-oxido)dicopper(III) complexes ($\mathbf{Cu_2O_2}$), that is, 2.75 ± 0.04 Å, where N_{eq} is the equatorial nitrogen donor atom of N_2-bidentate and N_3-tridentate supporting ligands.[42−44] Thus, the **L7** ligand is inherently suited to fit the structural requirement for the formation of $\mathbf{Cu_2O_2}$. The higher coordination number (five-coordinate) of the **L7** complex in the higher oxidation state (see Figure 4) is also favorable for the formation of dimeric $\mathbf{Cu_2O_2}$, where two μ-oxide bridges occupy the *cis*-positions of each copper ion. On the other hand, the N(2)−N(3) distance (~2.9 Å) of the $\mathbf{L8^R}$ ligand system is too long for the formation of $\mathbf{Cu_2O_2}$, whereas the lower coordination number (four-coordinate) of the $\mathbf{L8^R}$ complex is favorable for the formation of $(\mathbf{L8^R})\mathbf{CuS^E}$ with a four-coordinate tetrahedral geometry. In the case of acyclic diamine ligand **LA**, on the other hand, the N(2)−N(3) distance changes significantly depending on the oxidation state of copper ion: 3.298 Å in the copper(I) complex and 3.067 Å in the copper(II) complex. Thus, the flexible **LA** ligand can adopt the structural change required for the formation of $(\mathbf{LA})_2\mathbf{Cu_2P^S}$ (Scheme 4).

Oxidation potential of the copper(I) complexes might also be an important factor in copper(I)−O_2 chemistry. The reduction potential of the copper(II)−superoxide complex $(\mathbf{L8^R})\mathbf{CuS^E}$ is estimated as ~0.12 V vs SCE (Table 1), which is lower than the oxidation potential of copper(I) complex $(\mathbf{L8^R})\mathbf{Cu}$ (E^{ox} = 0.40 V). Therefore, the reduction of $(\mathbf{L8^R})\mathbf{CuS^E}$ by $(\mathbf{L8^R})\mathbf{Cu}$ is energetically disfavored, even though the bond-formation energy gained by the reaction between these complexes is not clear. Thus, the mononuclear copper(II)−superoxide species $(\mathbf{L8^R})\mathbf{CuS^E}$ may be stabilized in the $\mathbf{L8^R}$ system. On the other hand, the oxidation potential of copper(I) complex $(\mathbf{L7})\mathbf{Cu}$ is much lower at E^{ox} = 0.18 V vs SCE. Thus, $(\mathbf{L7})\mathbf{Cu}$ may be able to reduce a superoxide complex generated in situ to give $(\mathbf{L7})_2\mathbf{Cu_2O_2}$ as experimentally observed. In this respect, O_2 reactivity of $(\mathbf{LA})\mathbf{Cu}$ having the higher E^{ox} value (0.49 V) might be low as in the case of $(\mathbf{L8^S})\mathbf{Cu}$ having a similar E^{ox} (0.52 V). However, the structural flexibility of **LA** may allow the complex to gain larger bond formation energy in the O_2 adduct formation reaction, thus providing $(\mathbf{LA})_2\mathbf{Cu_2P^S}$.

REACTIVITY OF COPPER(II)−ALKYLPEROXIDE COMPLEXES, $\mathbf{CuP^R}$

The mononuclear copper(II)−hydroperoxide, $\mathbf{CuP^H}$, and copper(II)−alkylperoxide, $\mathbf{CuP^R}$, complexes are also important copper−active-oxygen intermediates involved in several biological and chemical oxidation reactions (Scheme 1). These species themselves might be an active species or a precursor of copper(II)−oxyl-radical species (**CuO** in Scheme 1). To examine such possibilities, reactivity of $\mathbf{CuP^R}$ complexes has been examined using a variety of tridentate and tetradentate supporting ligands.[41,45−49]

For instance, a copper(II)−alkylperoxide complex $(\mathbf{bpa})$-$\mathbf{CuP^R}$ generated in situ by the reaction of copper(II) precursor complex $[Cu^{II}(bpa)(CH_3CN)_2](ClO_4)_2$ (for **bpa**, see Scheme 5) and cumene hydroperoxide ($PhC(Me)_2OOH$) gradually decomposed at 60 °C to give acetophenone (PhCOMe) as the major product (76%) together with cumyl alcohol ($PhC(Me)_2OH$) as the minor one (15%).[46] It has been reported that the products obtained from a cumylperoxide complex largely depend on the O−O bond cleavage manner. If homolytic O−O bond cleavage occurs, PhCOMe is produced from cumyloxyl radical ($PhC(Me)_2O^{\bullet}$) via β-scission releasing $CH_3^{\bullet}$. In contrast, heterolytic O−O bond cleavage gives $PhC(Me)_2OH$ after oxyanion protonation.[50] Thus, formation of PhCOMe as

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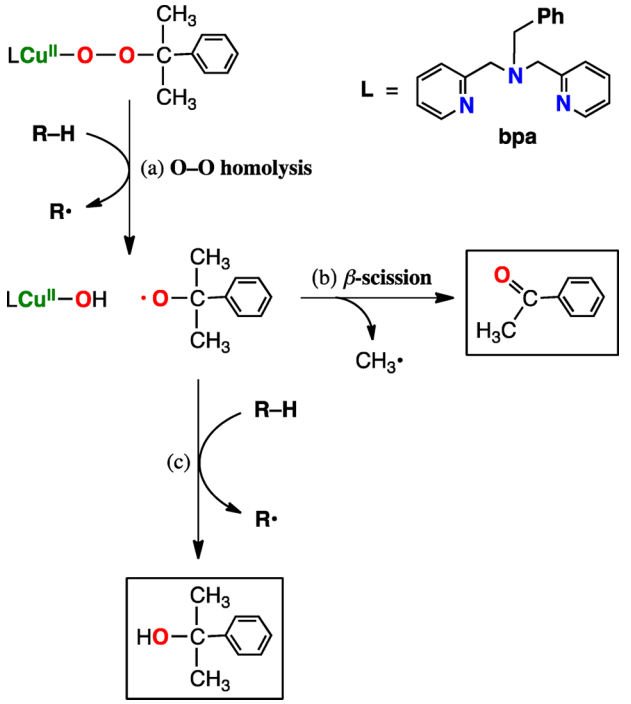
Scheme 5. Possible Decay Process of (bpa)CuP^{R}[a]



[a]For self-decomposition, R–H is acetonitrile (solvent). In the presence of CHD, R–H is CHD.

the major product (76%) suggests that self-decomposition of **(bpa)CuP^{R}** formally involves O–O bond homolysis, which may be associated with C–H bond activation of the solvent, path a, where **R–H** is CH_3CN (Scheme 5). In support of this notion, the decay process of **(bpa)CuP^{R}** exhibits a distinct solvent kinetic deuterium isotope effect of 2.9, when the reaction was carried out in CD_3CN.[46] The minor product $PhC(Me)_2OH$ may be produced from $PhC(Me)_2O^{\bullet}$ via hydrogen atom abstraction from the solvent (path c), which may compete with the β-scission of $CH_3^{\bullet}$ (path b). Generated solvent radical $^{\bullet}CH_2CN$ may be trapped by the generated $LCu^{II}–OH$ to give $LCu^{II}–OCH_2CN$, which is further converted to $[Cu^{II}(bpa)(CN)]^{+}$, which is detected by ESI-MS from the final reaction mixture.[46]

The first-order decay rate (k_{obs}) of **(bpa)CuP^{R}** is significantly accelerated when 1,4-cyclohexadiene (CHD) is added into the acetonitrile solution of **(bpa)CuP^{R}**,[46] obeying the kinetic equation of $k_{obs} = k_2[CHD]$, where $k_2 = 4.9 \times 10^{-2}$ M^{-1} s^{-1} at 30 °C. At this temperature, self-decomposition rate was negligibly slow. Thus, in the presence of CHD, the O–O bond cleavage of **(bpa)CuP^{R}** may be associated with the C–H bond activation of CHD (**R–H**), path a in Scheme 5. Quantitative formation of benzene as the oxidation product of CHD was confirmed by HPLC (98% based on **(bpa)CuP^{R}**). In this case, $PhC(Me)_2OH$ became a major product (64%), whereas PhCOMe was a minor one (32%). This is because, the C–H bond dissociation energy of CHD (76 kcal/mol) is much lower than that of acetonitrile (97 kcal/mol), enhancing step c compared with step b in Scheme 5. Were the O–O bond homolysis to be the only component of the rate-limiting step, with hydrogen atom abstraction occurring after complete O–O bond homolysis, the rate constant k_2 would perforce be the same as the self-decomposition rate and be independent of the CHD concentration. However, this is not the case for the present reaction, where k_2 was much faster than the self-decomposition and showed a first-order dependence on CHD concentration. Thus, it can be concluded that the O–O bond homolysis of **(bpa)CuP^{R}** occurs concomitantly with the hydrogen atom abstraction (concerted mechanism) as mentioned above. This conclusion is supported by DFT calculations.[46]

SUMMARY

A mononuclear copper(II)–(end-on)superoxide complex exhibiting similar structural features as well as reactivity to those of a putative reactive intermediate of the copper monooxygenases have been developed using a simple N_3-tridentate ligand consisting of a rigid eight-membered cyclic-diamine and pyridylethyl donor groups **L8^{R}** (Chart 3). The notable feature of this complex is the reactivity for aliphatic hydroxylation (Scheme 2), which is a unique example of a functional model of copper monooxygenases so far reported. This clearly indicates that the superoxide complex having a distorted tetrahedral geometry in the enzyme active site (Figure 1) could be the reactive species for the aliphatic C–H bond activation (Scheme 3) as proposed by Klinman et al.[13] In fact, the Hammett ρ value of the enzymatic reaction is nearly identical to that of the model reaction. Systematic studies using related supporting ligands have indicated that the rigid eight-membered cyclic diamine framework is critical for the formation of such a mononuclear copper(II)–(end-on)-superoxide complex. We intended to generate a more biologically relevant copper–active-oxygen complex supported by N_2S donor set as found in the enzyme active site (Figure 1) by using **L8^{S}**. However, the copper(I) complex of **L8^{S}** does not show O_2 reactivity. In this respect, Karlin and co-workers recently reported a mononuclear copper(II)–(end-on)-superoxide complex **2** supported by a N_2S-tridentate ligand, which exhibits higher reactivity compared with the one supported by a similar N_3-tridentate ligand **1** (Chart 2).[32] Apparently, a subtle change of the coordination sphere greatly influences the reactivity of **CuS^{E}** species.

So far, copper(II)–hydroperoxide **CuP^{H}** and copper(II)–alkylperoxide **CuP^{R}** complexes themselves have been considered as sluggish oxidants for C–H bond activation reaction. In this study, we have unambiguously demonstrated that **CuP^{R}** can be a direct oxidant for C–H bond activation of organic substrates, where C–H bond activation occurs concomitantly with O–O bond homolysis (concerted mechanism). Theoretical studies have suggested that **CuO** is a much stronger oxidant compared with **CuP**. It might be true, but our result suggested that **CuP** could also be an oxidant, once the O–O bond cleavage is associated with the C–H bond activation. Obviously, one of the next targets in the mononuclear copper/dioxygen chemistry is direct characterization of the **CuO** species.

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Notes

The authors declare no competing financial interest.

Biography

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