Inorganic Chemistry

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Redox Properties of a Mononuclear Copper(II)-Superoxide Complex

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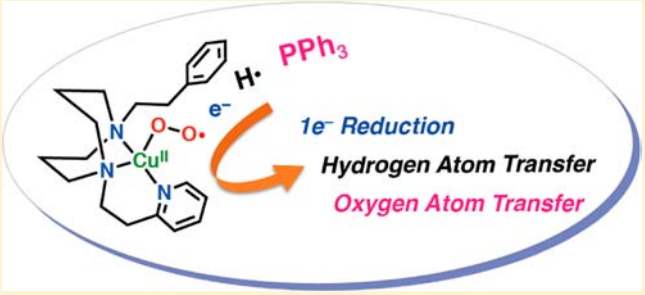
Supporting Information

ABSTRACT: Redox properties of a mononuclear copper(II) superoxide complex, (L)Cu^{II}–$OO^{\bullet}$, supported by a tridentate ligand (L = 1-(2-phenethyl)-5-[2-(2-pyridyl)ethyl]-1,5-diazacyclooctane) have been examined as a model compound of the putative reactive intermediate of peptidylglycine α-hydroxylating monooxygenase (PHM) and dopamine β-monooxygenase (DβM) (Kunishita et al. *J. Am. Chem. Soc.* **2009**, *131*, 2788–2789; *Inorg. Chem.* **2012**, *51*, 9465–9480). On the basis of the reactivity toward a series of one-electron reductants, the reduction potential of (L)Cu^{II}–$OO^{\bullet}$ was estimated to be 0.19 ± 0.07 V vs SCE in acetone at 298 K (cf. Tahsini et al. *Chem.—Eur. J.* **2012**, *18*, 1084–1093). In the reaction of TEMPO-H (2,2,6,6-tetramethylpiperidine-*N*-hydroxide), a simple HAT (hydrogen atom transfer) reaction took place to give the corresponding hydroperoxide complex LCu^{II}–OOH, whereas the reaction with phenol derivatives (^{X}ArOH) gave the corresponding phenolate adducts, LCu^{II}–O^{X}Ar, presumably via an acid–base reaction between the superoxide ligand and the phenols. The reaction of (L)Cu^{II}–$OO^{\bullet}$ with a series of triphenylphosphine derivatives gave the corresponding triphenylphosphine oxides via an electrophilic ionic substitution mechanism with a Hammett ρ value as −4.3, whereas the reaction with thioanisole (sulfide) only gave a copper(I) complex. These reactivities of (L)Cu^{II}–$OO^{\bullet}$ are different from those of a similar end-on superoxide copper(II) complex supported by a tetradentate TMG_3tren ligand (1,1,1-Tris{2-[N^2-(1,1,3,3-tetramethylguanidino)]ethyl}amine (Maiti et al. *Angew. Chem., Int. Ed.* **2008**, *47*, 82–85).

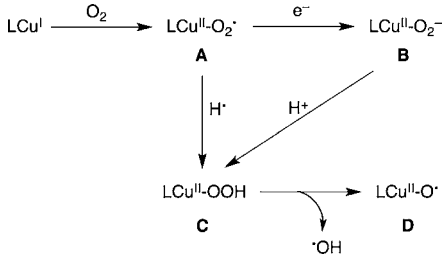


INTRODUCTION

Mononuclear copper active-oxygen species are the important reactive intermediates in biological oxygenation reactions.[1−12] Copper monooxygenases such as peptidylglycine α-hydroxylating monooxygenase (PHM), dopamine β-monooxygenase (DβM), and tyramine β-monooxygenase (TβM) have been demonstrated to catalyze aliphatic C–H bond hydroxylation of their respective substrates (dopamine, peptide hormones, and tyramine, respectively) using molecular oxygen (O_2) at a mononuclear copper active site.[1,13−16] It has also been suggested that bacterial depolymerization of polysaccharides is initiated by a class of copper oxygenases (GH61 and CBM33), in which O_2-activation is taking place at a mononuclear copper reaction center for the substrate oxygenation.[17−21] So far, the series of mononuclear copper active-oxygen species such as superoxide (**A**), peroxide (**B**), hydroperoxide (**C**), and oxyl radical (**D**) complexes have been proposed as the key reactive intermediate for the direct aliphatic C–H bond activation from both enzymatic and computational studies.[1,4,13,15,22−31]

In principle, the reaction of a mononuclear copper(I) complex and O_2 gives a mononuclear copper(II)-superoxide complex **A**, from which a copper(II)-hydroperoxide complex **C** can be generated by the one-electron reduction of **A** and subsequent protonation of a copper(II)-peroxide complex **B** or direct hydrogen atom transfer to **A** from a substrate. Furthermore, O–O bond homolysis of the hydroperoxide complex **C** may occur to provide a mononuclear copper(II)-oxyl radical species **D** (Scheme 1). In synthetic modeling systems, however, copper(II)-superoxide complex **A** tends to react with another molecule of copper(I) starting material to give a dinuclear copper(II)-peroxide complex (not shown in

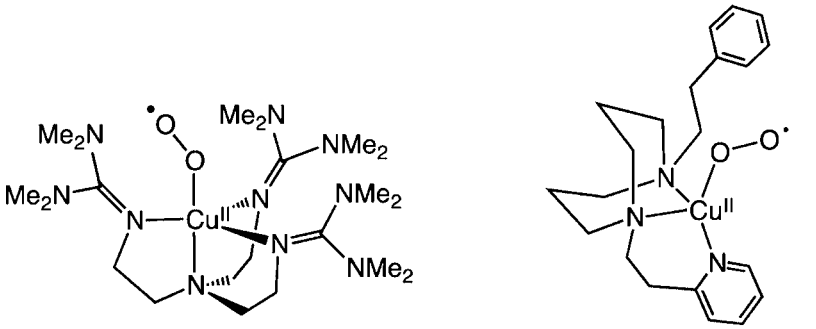
Scheme 1



Received: May 21, 2013
Published: September 5, 2013

   dx.doi.org/10.1021/ic401261z | *Inorg. Chem.* 2013, 52, 10431–10437

Chart 1



$(TMG_3tren)Cu^{II}$-OO• $(L)Cu^{II}$-OO• ($\mathbf{2}^{O_2}$)

Scheme 1), making it difficult to isolate and characterize the mononuclear copper active-oxygen complexes in the reaction of copper(I) complexes and O_2.[2,3,12] Nonetheless, a couple of mononuclear copper(II) end-on superoxide complexes have recently been characterized,[32,33] and one of them, $(TMG_3tren)Cu^{II}$–OO•, has been successfully isolated by using the tetramethylguanidine derivative of tripodal *tetradentate* tren ligand (tris(2-aminoethyl)amine) (Chart 1),[34] providing important insights into the structure and chemical properties of the proposed reaction intermediate of the mononuclear copper oxygenases.[35−37] We have also studied the reactivity of the end-on superoxide copper(II) complex $\mathbf{2}^{O_2}$ generated by using a *tridentate* ligand L (Chart 1) to demonstrate that $\mathbf{2}^{O_2}$ can directly induce aliphatic hydroxylation at the benzylic position of the ligand side arm, providing important insight into the catalytic mechanism of PHM and DβM.[38,39] In this study, we have examined the redox properties of $\mathbf{2}^{O_2}$ toward several types of external substrates to get further insights into the intrinsic reactivity of the end-on superoxide copper(II) complex and to see how the supporting ligand affects the reactivity of the superoxide complexes. We have also tried to see the formation of possible mononuclear copper active oxygen species such as peroxide (one-electron reduced product **B**), hydroperoxide (hydrogen atom adduct **C**), and oxyl radical (**D**) complexes, which could be derived from $\mathbf{2}^{O_2}$ in the reactions with external substrates (see Scheme 1).

EXPERIMENTAL SECTION

Materials and Methods. The reagents and the solvents 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, if necessary.[40] The ligand 1-(2-phenethyl)-5-[2-(2-pyridyl)ethyl]-1,5-diazacyclooctane (**L**) and its copper(I) complex $[(L)Cu^{I}]PF_6$ (**1**) were prepared according to the reported procedures.[38] FT-IR spectra were recorded on a Jasco FTIR-4100, and UV−visible spectra were taken on a Hewlett-Packard 8453 photo diode array spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL LMN−ECP300WB, a JEOL ECP400, a JEOL ECS400, or a Varian UNITY INOVA 600 MHz spectrometer. ESI-MS (electrospray ionization mass spectra) measurements were performed on a PerSeptive Biosystems Mariner Biospectrometry workstation. Elemental analyses were performed on a Perkin-Elmer or a Fisons instruments EA1108 Elemental Analyzer.

Synthesis. *$[Cu^{II}(L)(OAc)](BF_4)$ ($\mathbf{2}^{OAc}$).* Ligand **L** (20 mg, 62 μmol) was treated with an equimolar amount of $Cu^{II}(CH_3COO)_2{\cdot}H_2O$ (12 mg, 62 μmol) in CH_2Cl_2 (5.0 mL). After stirring the mixture for 5 min at room temperature, $NaBF_4$ (6.8 mg, 62 μmol) was added to the solution. Insoluble material was then removed by filtration. Addition of *n*-hexane (100 mL) to the filtrate gave a blue powder that was precipitated by standing in the mixture for several minutes. The supernatant was then removed by decantation, and the remained blue solid was washed with *n*-hexane three times and dried to give $\mathbf{2}^{OAc}$ in 71%. FT-IR (KBr) 1610 and 1578 cm^{-1} (OAc^-), 1083 cm^{-1} (BF_4^-); HR-MS (FAB, pos) m/z = 445.1798, calcd for $C_{23}H_{32}N_3O_2Cu$ = 445.1791; Anal. Calcd for $[Cu^{II}(OAc)](BF_4){\cdot}1.5H_2O{\cdot}0.1C_6H_{14}$ ($C_{23.6}H_{36.4}BCuF_4N_3O_{3.5}$): C, 49.86; H, 6.45; N, 7.39. Found: C, 49.65; H, 6.39; N, 7.13.

EPR Measurements. The EPR spectrum of the final reaction mixture of copper(II) superoxide complex $\mathbf{2}^{O_2}$ and TEMPO-H were recorded on a JEOL X-band spectrometer (JES-RE1XE) with an attached variable temperature apparatus. The EPR spectrum was measured in frozen acetone at 77 K. The magnitude of modulation was chosen to optimize the resolution and the signal-to-noise (S/N) ratio of the observed spectra under nonsaturating microwave conditions. The *g* values and the hyperfine coupling constants were calibrated with a Mn^{2+} marker.

Resonance Raman Spectrum. Resonance Raman scattering was excited at 406.7 nm from Kr^+ laser (Spectra Physics, BeamLok 2060). Resonance Raman scattering was dispersed by a single polychromator (Ritsu Oyo Kogaku, MC-100) and was detected by a liquid nitrogen cooled CCD detector (Roper Scientific, LNCCD-1100-PB). The resonance Raman measurements were carried out using a rotated cylindrical cell thermostatted at −70 to −90 °C by flashing cold liquid nitrogen gas.

Kinetic Measurements. Kinetic measurements for the reactions of copper(II) superoxide complex $\mathbf{2}^{O_2}$ with external substrates were performed using a Hewlett-Packard 8453 photo diode array spectrophotometer with a Unisoku thermostatted cell holder designed for low temperature measurements (USP-203, a desired temperature can be fixed within ±0.5 °C) in an appropriate solvent (3.0 mL) at a low temperature. For the preparation of the copper(II) superoxide complex $\mathbf{2}^{O_2}$, O_2 gas was rapidly introduced to a solution of the copper(I) complex $[(L)Cu^{I}]PF_6$ in a UV cell (1.0 cm path length) through a silicon rubber cap by using a gastight syringe, and the increase of the absorption band due to $\mathbf{2}^{O_2}$ was monitored. Then, an excess O_2 was removed by flashing Ar gas through a needle for about 5 min, and the substrate was added to start the reaction. The reaction was followed by monitoring the decrease in the ligand-to-metal charge transfer (LMCT) absorption band due to $\mathbf{2}^{O_2}$. The pseudo-first-order rate constants for the decay of $\mathbf{2}^{O_2}$ were determined from the plots of $\ln(\Delta A)$ vs time based on the time course of the absorption change at λ_{max} due to $\mathbf{2}^{O_2}$.

Quantification of H_2O_2. Amount of H_2O_2 was determined by iodometry as follows. A final reaction mixture of $\mathbf{2}^{O_2}$ and a substrate was quenched by adding an acetone solution of HPF_6 (2 equiv). Then, the diluted acetone solution (1/10) was treated with an excess NaI. The amount of I_3^- formed was then quantified using its visible spectrum (λ_{max} = 361 nm, ε = 2.5 × 10^4 M^{-1} cm^{-1}).[41]

dx.doi.org/10.1021/ic401261z | Inorg. Chem. 2013, 52, 10431−10437

RESULTS AND DISCUSSION

Electron-Transfer Reduction of 2^{O_2}. As shown in Scheme 1 in the Introduction, one-electron reduction of the copper(II)-superoxide complex 2^{O_2} may afford a copper(II)-peroxide complex **B**. Thus, the reactions of 2^{O_2} with a series of one-electron reductants were examined to search such a possibility. Figure 1 shows a typical example of the spectral change for the

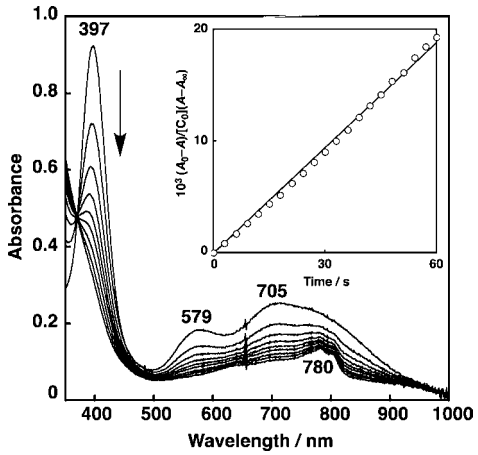


Figure 1. UV−vis spectral change for the reaction of 2^{O_2} (0.2 mM) and decamethylferrocene (0.2 mM) in acetone at −85 °C. Inset: Second-order plot based on the absorption change at 397 nm.

reaction of 2^{O_2} (0.2 mM) with an equimolar amount of decamethylferrocene ($Me_{10}Fc$) at −85 °C in acetone. The LMCT band at 397 nm due to 2^{O_2} gradually decreased with a concomitant increase of the absorption band due to the ferrocenium cation ($Me_{10}Fc^+$). The yield of $Me_{10}Fc^+$ was estimated to be 88% based on the initial concentration of 2^{O_2} using the intensity of the absorption band due to $Me_{10}Fc^+$ itself ($\varepsilon = 8.0 \times 10^2$ M^{-1} cm^{-1} at λ_{max} = 780 nm). This is consistent with a one-electron reduction of the superoxide species. In fact, nearly quantitative formation of H_2O_2 (81% based on 2^{O_2}, 92% based on $Me_{10}Fc^+$ formed) was confirmed by iodometry as shown in Supporting Information, Figure S1A, and quantitative generation of a copper(II) complex was detected by the EPR spectrum (Supporting Information, Figure S1B). However, all our efforts to isolate the reduced product (type **B** in Scheme 1) have been unsuccessful because of its thermal instability, and a complicated mixture of products was obtained, when the reaction mixture was warmed to room temperature.

The decay of 2^{O_2} obeyed second-order kinetics in the presence of the equimolar amount of $Me_{10}Fc$, and the second-order rate constant (k_2) was obtained as 320 ± 2 M^{-1} s^{-1} from the slope of the linear line of the second-order plot shown in the inset of Figure 1. The reduction of 2^{O_2} also proceeded with octamethylferrocene (Me_8Fc) and *N,N,N′N′*-tetramethylphenylenediamine (TMPD), and the second-order rate constants were determined as 56 ± 0.4 M^{-1} s^{-1} and 9.4 ± 0.06 M^{-1} s^{-1}, respectively, as shown in Supporting Information, Figures S2 and S3, respectively (the data are listed in Table 1). On the other hand, no reaction took place when weaker reductants such as dimethylferrocene (Me_2Fc) and ferrocene (Fc) were employed under the same experimental conditions (Table 1). On the basis of the one-electron oxidation potentials of TMPD (E_{ox} = 0.12 V vs SCE) and Me_2Fc (E_{ox} = 0.26 V vs SCE),[42] the one-electron reduction potential of 2^{O_2} was estimated as E_{red} = (0.19 V ± 0.07) vs SCE. However, the reduction of 2^{O_2} was

Table 1. One-Electron Oxidation Potential of the Reductants and the Second-Order Rate Constants for the Reduction of 2^{O_2} in Acetone at −85 °C

	$Me_{10}Fc$	Me_8Fc	TMPD	Me_2Fc	Fc
E^0_{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.[42] [b]No reaction.

irreversible because of the thermal instability of the reduced product; addition of an oxidant such as ferrocenium cation Fc^+ to the final reaction mixture did not reproduce the original superoxide complex 2^{O_2}. Thus, the estimated E_{red} value is not a true reduction potential.

Reaction with TEMPO-H (Hydrogen-Atom Donor). Figure 2 (left) shows a spectral change for the reaction of 2^{O_2} with 2,2,6,6-tetramethylpiperidine-*N*-hydroxide (TEMPO-H) under anaerobic conditions (excess O_2 was removed by flushing Ar gas before the reaction), where the absorption bands due to 2^{O_2} decrease to give new absorption bands at 375 nm (ε = 1650 M^{-1} cm^{-1}) and 620 nm (309). The final spectrum is similar to those of copper(II)-hydroperoxide complexes that so far have been reported,[43] suggesting the formation of a similar type of copper(II)-hydroperoxide complex 2^{OOH} (Scheme 2), even though resonance Raman data of sufficient quality has yet to be obtained; there is only a very weak Raman band at 831 cm^{-1}, which shifted to 788 cm^{-1}, when the reaction was carried out with ^{18}O-substituted 2^{O_2} (see, Figure S4). The reaction obeyed first-order kinetics in the presence of an excess amount of TEMPO-H (Figure 2 (left), Inset), and a plot of the observed pseudofirst-order rate constants against the concentration of TEMPO-H gave a straight line passing through the origin, from which the second rate constant was determined as k_2 = 2.4 ± 0.05 M^{-1} s^{-1} at −85 °C (Figure 2, right).

The EPR spectrum of the final reaction mixture shown in Supporting Information, Figure S5 exhibited the typical signal due to TEMPO• free-radical (g = 2.004) (Supporting Information, Figure S5B), which is overlapped with a EPR signal of a copper(II) species (Supporting Information, Figure S5A). The spin quantification by double integration of the whole EPR signals confirms the existence of two S = 1/2 species corresponding to TEMPO• and copper(II)-hydroperoxide species 2^{OOH}.

2^{OOH} was relatively stable at −85 °C, but gradually decomposed at room temperature to give a copper(II) complex having a weak d-d band at 640 nm (ε = 210 M^{-1} cm^{-1}) (Supporting Information, Figure S6). In addition, quantitative formation of H_2O_2 (93% based on the copper complex) was confirmed by iodometry after quenching the final reaction mixture with HPF_6 (Supporting Information, Figure S7). It should be noted that no ligand hydroxylation product was detected from the final reaction mixture by ESI-MS (Supporting Information, Figure S8), and the original ligand was recovered quantitatively by the ordinary workup treatment (demetalation) of the final reaction mixture using NH_4OH (aq) (Scheme 3a). This result is in sharp contrast to the $(TMG_3tren)Cu^{II}$−$OO^•$ system, where a ligand hydroxylation took place only after the reaction with hydrogen atom donor such as TEMPO-H or phenols (Scheme 3b).[36] The authors concluded that $(TMG_3tren)Cu^{II}$−$OO^•$ (type **A** in Scheme 1) was not the direct oxidant, but that $(TMG_3tren)Cu^{II}$−$O^•$ (type **D**) generated by O−O bond homolysis of $(TMG_3tren)Cu^{II}$−

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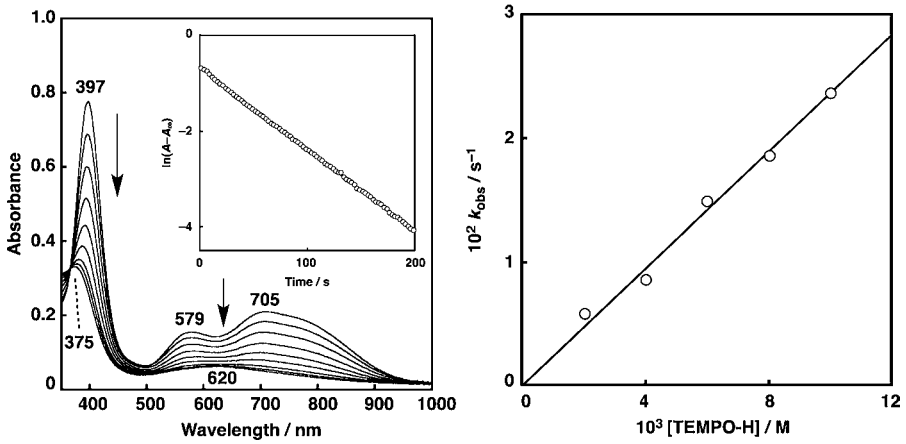
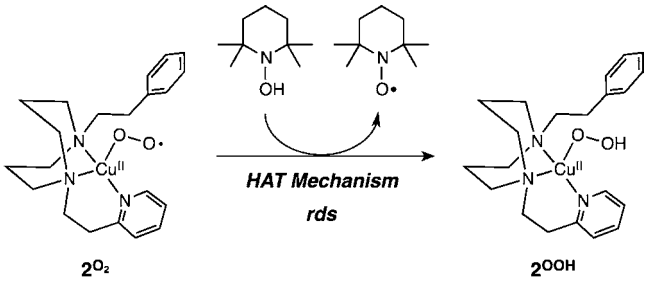


Figure 2. Left: UV−vis spectral change for the reaction of 2^{O_2} (0.2 mM) and TEMPO-H (4.0 mM) in acetone at −85 °C. Inset: Pseudo-first-order plot based on the absorption change at 397 nm. Right: Plot of k_{obs} against the substrate concentration for the reaction of 2^{O_2}.

Scheme 2



OOH (type **C**), generated by the reaction of **A** and the hydrogen atom donor, might be the reactive intermediate that induced the ligand methyl hydroxylation.[36] On the other hand, our results clearly indicated that the superoxide complex 2^{O_2} (Type **A**), but not the hydroperoxide complex 2^{OOH} (type **C**), directly participates in the aliphatic ligand hydroxylation (Scheme 3a).[38,39] Such a difference in reactivity between 2^{O_2} and $(TMG_3tren)Cu^{II}$−$OO^{\bullet}$ could be attributed in part to the difference in the coordination number and geometry (four-coordinate/tetrahedral vs five-coordinate/trigonal bipyramidal) as well as to the difference in the kind of donor atoms (alkylamine and pyridine nitrogen atoms vs imine (guanidine) nitrogen atoms). It is interesting to note that the proposed geometry (distorted tetrahedral)[38] and observed reactivity (direct C−H bond activation)[38] of 2^{O_2} are closer to those of the putative reactive intermediate in the enzymes.[44,45]

Reaction with Phenol Derivatives. Karlin, Schindler, Sundermeyer, and co-workers reported that the reaction of $(TMG_3tren)Cu^{II}$−$OO^{\bullet}$ and phenols (ArOH) induced hydrogen atom transfer to provide $(TMG_3tren)Cu^{II}$−OOH and phenoxyl radical species ($ArO^{\bullet}$), from which the ligand hydroxylation product (Scheme 3b) and several phenol oxidation/oxygenation products were produced.[36] Thus, we also investigated the reaction of 2^{O_2} with phenol derivatives to compare the reactivity between 2^{O_2} and $(TMG_3tren)Cu^{II}$−$OO^{\bullet}$. Figure 3 shows a spectral change for the reaction of 2^{O_2}

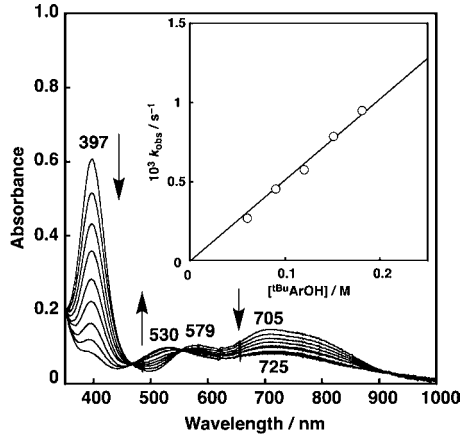
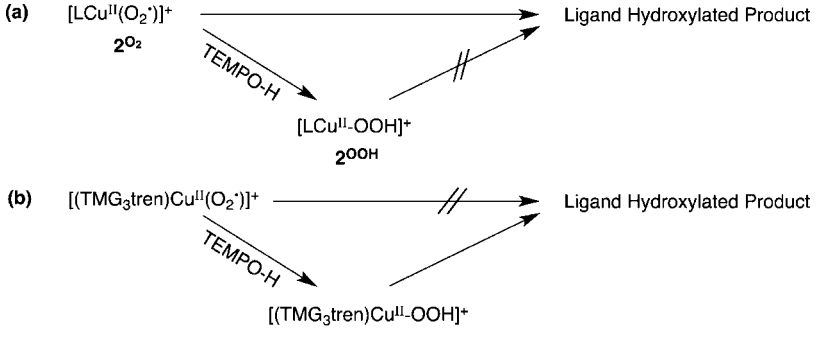


Figure 3. UV−vis spectral change for the reaction of 2^{O_2} (0.2 mM) with *p-tert*-butylphenol (180 mM) in acetone at −85 °C. Each spectrum was taken at 500 s intervals. Inset: Plot of k_{obs} against the substrate concentration.

Scheme 3



dx.doi.org/10.1021/ic401261z | *Inorg. Chem.* 2013, 52, 10431−10437

with *p-tert*-butylphenol (^{tBu}ArOH) as a typical example, where the LMCT bands due to $\mathbf{2}^{O_2}$ decrease obeying first-order kinetics in the presence of an excess amount of ^{tBu}ArOH.

A plot of the pseudo-first-order rate constants (k_{obs}) against the substrate concentration gave a straight line passing through the origin, from which the second-order rate constant k_2 was determined to be $(0.68 \pm 0.01) \times 10^{-2}$ M^{-1} s^{-1} from the slope (Figure 3, Inset). In this case, the spectrum of the final reaction mixture exhibiting weak absorption bands at 530 nm (ε = 485 M^{-1} cm^{-1}) and 725 nm (ε = 405 M^{-1} cm^{-1}), which was different from that of $\mathbf{2}^{OOH}$ (see, Figure 2) but identical to that of the copper(II)-phenolate complex ($\mathbf{2}^{OAr(tBu)}$) prepared by the reaction of a copper(II) complex $[Cu^{II}(L)(OCOCH_3)]^+$ ($\mathbf{2}^{OAc}$) and lithium *p-tert*-butylphenolate under the same experimental conditions (Supporting Information, Figure S9).[46] Thus, the product was not the copper(II)-hydroperoxide complex $\mathbf{2}^{OOH}$, but a copper(II)-phenolate complex $\mathbf{2}^{OAr(tBu)}$. Furthermore, no phenol coupling dimer product was obtained, when the final reaction mixture was quenched with HPF_6 at the low temperature (−85 °C).

The reactions of $\mathbf{2}^{O_2}$ with a series of *p*-substituted phenols (^{X}ArOH; X = OPh, Me, H, F, Cl) were also examined under the same experimental conditions to give the corresponding copper(II)-phenolate complexes ($\mathbf{2}^{OAr(X)}$) (Supporting Information, Figure S10−S15), and the second-order rate constants k_2 for the reactions were determined in the same manner as $(0.51 \pm 0.01) \times 10^{-2}$ M^{-1} s^{-1}, $(0.22 \pm 0.01) \times 10^{-2}$ M^{-1} s^{-1}, $(0.37 \pm 0.3) \times 10^{-2}$ M^{-1} s^{-1}, $(0.42 \pm 0.02) \times 10^{-2}$ M^{-1} s^{-1}, $(0.42 \pm 0.01) \times 10^{-2}$ M^{-1} s^{-1}, and $(2.0 \pm 0.1) \times 10^{-3}$ M^{-1} s^{-1}, respectively, at −85 °C (Supporting Information, Figure S10−S15). When C_6D_5OD (fully deuterated phenol) was employed instead of C_6H_5OH, there was an appreciable amount of kinetic deuterium isotope effect (KIE = 2.2); $k_{obs(H)} = 9.2 \times 10^{-4}$ s^{-1} vs $k_{obs(D)} = 4.2 \times 10^{-4}$ s^{-1} (Supporting Information, Figure S16).

Formation of the copper(II)-phenolate complexes suggests that the reaction involves a simple acid−base reaction between the phenol substrate ^{X}ArOH and the superoxide ligand ($O_2^{\bullet-}$) in $\mathbf{2}^{O_2}$ to generate the copper(II)-phenolate complex, ^{X}ArO-Cu^{II}, and $HO_2^{\bullet}$, the latter of which may rapidly disproportionate into $(1/2)O_2$ and $(1/2)H_2O_2$ (Scheme 4, R = ^{X}Ar). This was confirmed by iodometric detection of H_2O_2 in a 49% yield based on $\mathbf{2}^{O_2}$ (Supporting Information, Figure S17).

Scheme 4

$$\underset{\mathbf{2}^{O_2}}{[LCu^{II}(O_2^{\bullet})]^+} + ROH \xrightarrow[(R = {}^{X}Ar \text{ or } Ac)]{} \underset{\mathbf{2}^{OR}}{[LCu^{II}OR)]^+} + HO_2^{\bullet}$$

$$HO_2^{\bullet} \longrightarrow 1/2\ O_2 + 1/2\ H_2O_2$$

If the proton transfer from the phenol substrate to the superoxide ligand occurs via a simple bimolecular reaction, the rate constant k_2 should increase as the pK_a of phenols decreases (as the acidity of phenols increases). Such a rate-dependence on the pK_a values was actually observed as shown in Supporting Information, Figure S18, although the correlation is not so good. In support of this mechasnim, addition of a stronger acid such as acetic acid (AcOH) to the superoxide complex $\mathbf{2}^{O_2}$ rapidly afforded the copper(II)-acetate complex $\mathbf{2}^{OAc}$ and H_2O_2 (~50%) (Scheme 4, R = Ac). Furthermore, a largely negative $\Delta S^{\ddagger}$ value (-143 ± 3 J K^{-1} mol^{-1}) was obtained in the Eyring plot analysis shown in Figure 4, which also supports the bimolecular reaction.

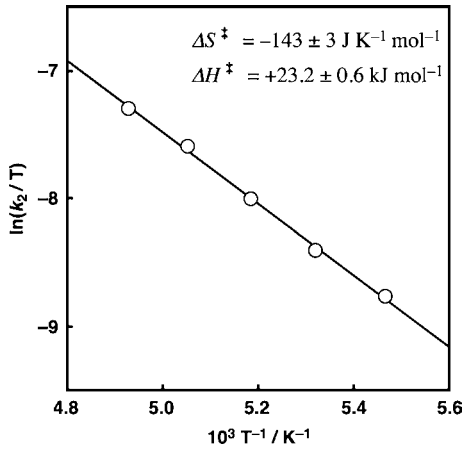


Figure 4. Eyring plot for the reaction of $\mathbf{2}^{O_2}$ (0.2 mM) with ^{MeO}ArOH in acetone.

A simple hydrogen atom transfer (HAT) mechanism from the phenol substrate by the superoxide complex may be ruled out, since the putative copper(II)-hydroperoxide complex $\mathbf{2}^{OOH}$ was not detected during the course of the reaction, and no phenoxyl radical coupling dimer product was obtained after the reaction (vide ante).

Reaction with Phosphine and Sulfide. The reaction of $\mathbf{2}^{O_2}$ with triphenylphosphine derivatives was studied to examine the oxo-transfer ability of the superoxide complex. Figure 5

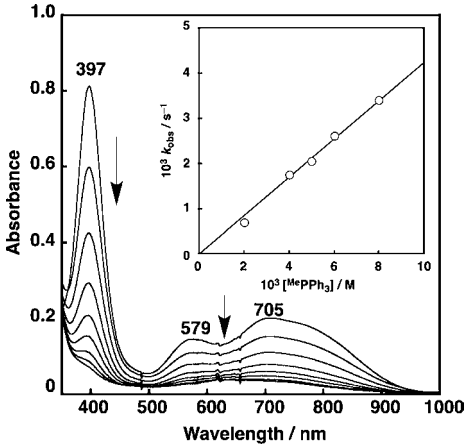


Figure 5. UV−vis spectral change for the reaction of $\mathbf{2}^{O_2}$ (0.2 mM) with $P(Ar^{Me})_3$ (4.0 mM) in acetone at −85 °C. Each spectrum was taken at 200 s intervals. Inset: Plot of k_{obs} against the substrate concentration.

shows a spectrum change for the reaction of $\mathbf{2}^{O_2}$ with tris(4-methylphenyl)phosphine $P(Ar^{Me})_3$ as a typical example, where the decrease of the LMCT bands due to $\mathbf{2}^{O_2}$ obeys first-order kinetics in the presence of a large excess of the substrate.

A plot of the observed first-order rate constants against the substrate concentration gave a straight line passing through the origin, from which the second-order rate constant was determined from the slope (Figure 5, Inset, Table 2). In the preparative-scale reaction, the corresponding phosphine oxide was obtained in a 86% yield based on $\mathbf{2}^{O_2}$ (^{1}H NMR yield). The reactions of a series of *p*-substituted-triphenylphosphine derivatives $P(Ar^{Y})_3$ (Y = OMe, H, F, and Cl) were also examined to get insight into the reaction mechanism as shown in Supporting Information, Figure S19−S22, and the second-

dx.doi.org/10.1021/ic401261z | Inorg. Chem. 2013, 52, 10431−10437

Table 2. Second-Order Rate Constants for the Reaction of 2^{O_2} with $P(Ar^Y)_3$ in Acetone at −85 °C

p-substituent	OMe	Me	H	F	Cl
$10^2\ k_2/M^{-1}\ s^{-1}$	64 ± 1	42 ± 0.8	7.2 ± 0.1	1.5 ± 0.9	0.67 ± 0.004

order rate constants thus obtained are listed in Table 2. In this case, the plot of log k_2 against the Hammett constant σ_p provides a linear correlation with a negative slope (ρ = −4.3, Figure 6). This suggests that the superoxide complex also has an electrophilic character in nature.

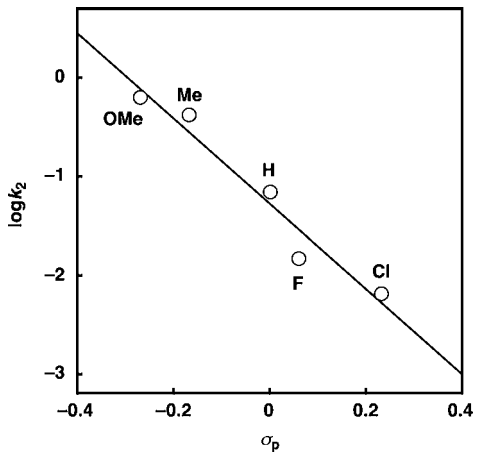
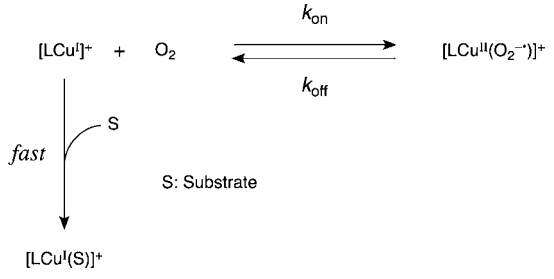


Figure 6. Hammett plot for the reaction of 2^{O_2} with $P(Ar^Y)_3$ in acetone at −85 °C.

Recently, Nam and co-workers reported the oxygen atom transfer (OAT) reaction from a chromium(III)-superoxide complex supported by a macrocyclic TMC ligand, $[Cr^{III}(O_2^{\bullet})(TMC)(Cl)]^+$, to triphenylphosphine, where they confirmed generation of $[Cr^{IV}(O)(TMC)(Cl)]^+$ together with triphenylphosphine oxide as the products.[47] These products may be produced by homolytic O−O bond cleavage from a $(TMC)(Cl)Cr^{III}-O-O-^{\bullet+}PPh_3$ adduct intermediate.[47] If the OAT reaction from 2^{O_2} to $P(Ar^Y)_3$ proceeds in a similar manner, a $Cu^{II}-O^{\bullet}$ intermediate (Type **D** in Scheme 1) might be generated. However, such a reactive intermediate could not be detected in the present reaction.

The reaction of 2^{O_2} with thioanisole (PhSMe) was also examined. In this case, however, no oxygenation product (Ph(Me)SO) was obtained, but 2^{O_2} was converted to the copper(I) stating material as shown in Supporting Information, Figure S23. The result can be explained by the mechanism shown in Scheme 5. The O_2-bindng to the copper(I) complex **1** is reversible as demonstrated in our previous study,[39] and addition of PhSMe to LCu^I competes with the O_2-binding. A similar phenomenon was observed in the reaction of a superoxide copper(II) complex supported by $HIPT_3$tren and PhSMe.[48]

Scheme 5



CONCLUSION

In this study, the reactions of 2^{O_2} with a series of external substrates were examined to evaluate the intrinsic reactivity of the superoxide complex supported by the tridentate ligand L (Chart 1). On the basis of the reactivity of 2^{O_2} with a series of one-electron reductants with various E_{ox}, the reduction potential of 2^{O_2} was estimated to be E_{red} = (0.19 ± 0.07) V vs SCE. In the reaction with a hydrogen atom donor such as TEMPO-H, a simple HAT (hydrogen atom transfer) reaction proceeded to give the corresponding hydroperoxide complex $LCu^{II}-OOH$ (2^{OOH}). In this case, intramolecular ligand hydroxylation did not proceed. On the other hand, the reaction with phenols (^{X}ArOH) gave the corresponding phenolate adducts $LCu^{II}-O^XAr$ instead of 2^{OOH}. Kinetic analysis has suggested an acid−base reaction between 2^{O_2} and ^{X}ArOH. The reaction of 2^{O_2} with a series of triphenylphosphine derivatives gave the corresponding triphenylphosphine oxides via an electrophilic adduct formation mechanism with a Hammett value ρ = −4.3. In this case, $Cu^{II}-O^{\bullet}$ type intermediate may be generated by the O−O bond homolysis from a putative $Cu^{II}-O-O-^{\bullet+}PPh_3$ adduct intermediate.

It is interesting to note that the reactivity of 2^{O_2} is quite different from that of $(TMG_3tren)Cu^{II}-OO^{\bullet}$. The superoxide complex 2^{O_2} itself can induce intramolecular aliphatic ligand hydroxylation, whereas no ligand hydroxylation product is obtained from the hydroperoxide complex 2^{OOH} (Scheme 3a). On the other hand, the superoxide complex $(TMG_3tren)Cu^{II}-OO^{\bullet}$ does not give any ligand hydroxylation products, but the hydroperoxide complex $(TMG_3tren)Cu^{II}-OOH$ does (Scheme 3b). Furthermore, the reaction of $(TMG_3tren)Cu^{II}-OO^{\bullet}$ with phenol derivatives causes a HAT reaction to provide several oxidation/oxygenation products from the phenol substrates in addition to the ligand hydroxylation product.[36] On the other hand, the reaction of 2^{O_2} and phenols simply affords the phenolate adducts 2^{OAr}. These differences in reactivity between 2^{O_2} and $(TMG_3tren)Cu^{II}-OO^{\bullet}$ could be attributed in part to the difference in the coordination number and geometry (four-coordinate/tetrahedral vs five-coordinate/trigonal bipyramidal) as well as to the difference in the kind of donor atoms (alkylamine and pyridine nitrogen atoms vs imine (guanidine) nitrogen atoms). Such ligand effects on the reactivity of the superoxide complexes should be considered in the mechanistic studies of the copper monooxygenases.

ASSOCIATED CONTENT

Supporting Information

Further details are given in Figures S1−S23. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The present work was financially supported by Grant-in-Aids for Scientific Research on Innovative Areas "Molecular Activation Directed toward Straightforward Synthesis" (No. 22105007) and "Stimuli-responsive Chemical Species" (No. 24109015) and a Grant-in-Aid for Exploratory Research (No. 25620044) from the Ministry of Education, Culture, Sports, Science and Technology, Japan. The authors thank Dr. Kei Ohkubo and Prof. Shunichi Fukuzumi for their help in the measurements of EPR spectra.

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