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Communication

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Generation, Characterization, and Reactivity of a Cu^{II}-alkylperoxide/anilino-radical Complex: Insight into the O–O Bond Cleavage Mechanism

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Supporting Information Placeholder

ABSTRACT: The reaction of $[Cu^{I}(TIPT_3tren)(CH_3CN)]ClO_4$ (**1**) and cumene hydroperoxide ($C_6H_5C(CH_3)_2OOH$, ROOH) at –60°C in CH_2Cl_2 gave a Cu^{II}-alkylperoxide/anilino-radical complex **2**, the formation of which was confirmed by UV-vis, resonance Raman, EPR, and CSI-mass spectroscopy. The mechanism of formation of **2** as well as its reactivity has been explored.

Copper–active-oxygen species play versatile roles in a variety of biological and chemical oxidation/oxygenation reactions.[1-3] So far, several types of supporting ligands have been developed to examine copper(I)/dioxygen reactivity as well as copper(II)/peroxide reactivity, providing important information about the structure, physical properties, and reactivity of the reactive intermediates involved in those reactions.[4-6] However, little attention has been focused on non-innocent supporting ligands in the oxygen-activation chemistry by copper complexes.

In this study, we have developed a mononuclear copper(I) complex **1** supported by an N_4-tetradentate ligand, $TIPT_3tren$, consisting with three bulky substituents TIPT (3,5-bis(2,6-diisopropylphenyl)phenyl) and tren (tris(2-aminoethyl)amine) (Figure 1). The reaction of **1** with cumene hydroperoxide (ROOH) at a low temperature gave an unprecedented Cu^{II}-alkylperoxide/anilino-radical complex **2** (Scheme 1), where the non-innocent aniline moiety of the ligand played crucial roles. The mechanism of formation of **2** as well as its reactivity is reported in this *Communication*.

Copper(I)-complex **1** was synthesized by mixing an equimolar amount of ligand $TIPT_3tren$ and $[Cu^{I}(CH_3CN)_4]ClO_4$ in acetone. Single crystals of **1** suitable for X-ray diffraction analysis were obtained as a BF_4^- salt (for synthetic procedures and characterizations, see Experimental Section and Figures S1–S8 in Supporting Information).

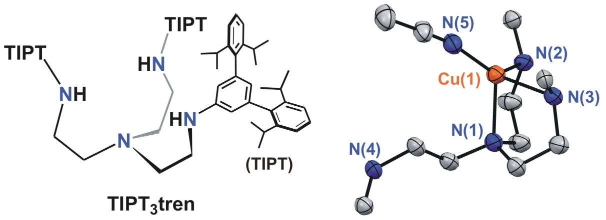


Figure 1. ChemDraw structure of $TIPT_3tren$ ligand (left) and ORTEP drawing of the crystal structure of the core domain of complex **1** (right), where only the carbon atoms connected to the aniline nitrogen atoms, N(2), N(3), and N(4), of the TIPT substituents are shown. All hydrogen atoms and counter anion are also omitted for clarity. For the whole structure, see Supporting Information.

Scheme 1. Reaction of Complex 1 with Cumene Hydroperoxide

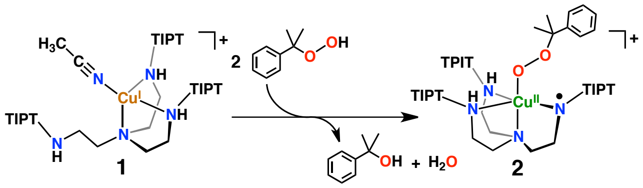


Figure 1 shows the crystal structure of **1**, where copper(I) center exhibits a distorted tetrahedral geometry ligated by three nitrogen atoms, N(1), N(2), and N(3), of the ligand and one nitrogen atom, N(5), of acetonitrile molecule ($\tau_4 = 0.73$, $\tau_4 = [(360° - (\alpha + \beta))/141°]$, where α and β are the two largest bond angles of four-coordinate structure. For an ideal tetrahedral geometry, $\tau_4 = 1$, and for a perfect square planer geometry, $\tau_4 = 0$).[7] Thus, one of the ligand arms, N(4), is detached from the copper ion. The FAB-mass spectrum of the complex showed a molecular ion peak cluster at m/z = 1397.98, which matched with a molecular composition of $[(\mathrm{TIPT_3tren})\mathrm{Cu}]^+$ (Figure S7).

The reaction of **1** with cumene hydroperoxide ($C_6H_5C(CH_3)_2OOH$ = ROOH) was then examined. Addition of an excess amount of ROOH to **1** at –60 °C in CH_2Cl_2 under anaerobic conditions resulted in formation of a metastable intermediate **2** exhibiting intense absorption bands at 396 nm (ε = 5400 M^{-1} cm^{-1}), 465 nm (6000 M^{-1} cm^{-1}), and 748 nm (6600 M^{-1} cm^{-1}) (Figure 2). The reaction obeyed pseudo-first-order kinetics, and from a linear plot of k_{obs} vs [ROOH] was obtained a second order rate constant k_2 = 1.67 $\pm$ 0.06 M^{-1} s^{-1} (Figure S9).

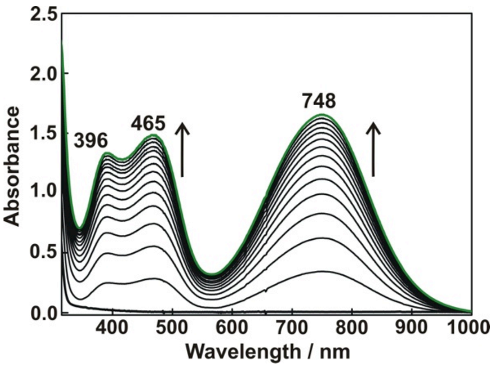


Figure 2. UV-vis spectral changes observed upon addition of ROOH (10 equiv) to **1** (0.25 mM) in CH_2Cl_2 at –60°C under anaerobic conditions.

Product analysis of organic compounds by HPLC (Figure S10) after quenching the reaction at –60°C revealed nearly quantitative formation of cumyl alcohol ($C_6H_5C(CH_3)_2OH$) (98% based on **1**) together with a trace amount of acetophenone ($C_6H_5C(O)CH_3$). The quantitative formation of cumyl alcohol (ROH) indicated that the reaction formally involved a heterolytic O–O bond cleavage of the alkylperoxide moiety.[8]

The X-band EPR spectrum of the reaction solution indicated that most of the species in the solution were EPR silent, although a small amount of Cu^{II} signal (~20 %) was observed (Figure S11) probably due to a decomposition product of copper complex intermediate.

The resonance Raman spectrum obtained with 488 nm excitation laser light gave isotope sensitive Raman bands at 831 (Fermi doublet), 604, 569, and 541 cm^{-1}, which shifted to 788, 589, 558, and 531 cm^{-1} ($\Delta\nu$ = 43, 15, 11, and 10 cm^{-1}), respectively, upon using isotope labeled cumene hydroperoxide ($C_6H_5C(CH_3)_2(^{18}O)_2H$, $R(^{18}O)_2H$) (Figures 3a and 3b). Based on the analogy of the resonance Raman features with those of reported Cu^{II}-alkylperoxide complexes,[8-11] a similar type of alkylperoxide complex may be generated in the present reaction. Thus, the band at 831 cm^{-1} is assigned to the O–O stretching vibrations, whereas the band at 604 cm^{-1} is due to the Cu–O stretching vibration. Furthermore, the bands around the lower frequency region are attributable to the carbon skeleton deformation (C–C–C/O–C–C) to the carbon skeleton deformation (C–C–C/O–C–C) modes. The isotope shifts of these two bands (569 to 558 and 541 to 531 cm^{-1}) observed by using $R(^{18}O)_2H$ indicate the presence of significant coupling of the C–C–C/O–C–C deformation modes with the Cu–O stretching mode.[9]

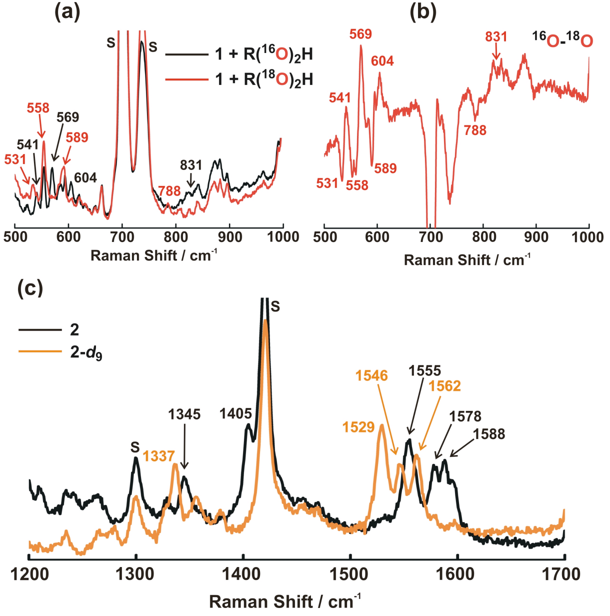


Figure 3. Resonance Raman spectra of (a) **2** (black) and its ^{18}O-derivative (red), (b) a difference spectrum (^{16}O – ^{18}O), and (c) **2** (black) and its ligand-deuterated derivative **2-*d*₉** (orange).

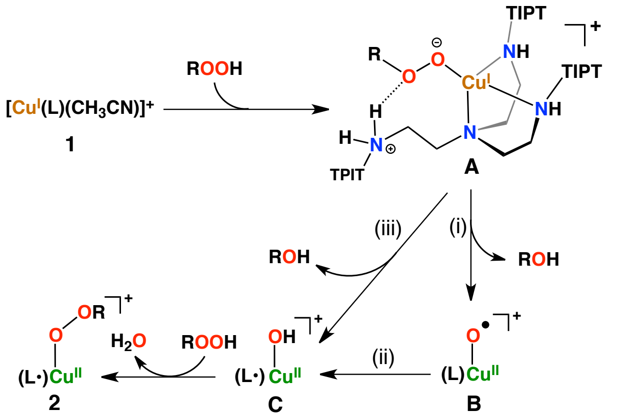
Inspection of the resonance Raman spectrum at the higher frequency region revealed the presence of several bands between 1300–1600 cm^{-1} (1588, 1578, 1555, 1405, and 1345 cm^{-1}; Figure 3c, black line spectrum). Importantly, no ^{18}O-isotope shift was observed in the ^{18}O-isotope labeled intermediate **2** (Figure S12),clearly indicating that the origin of these bands is not the Cu^{II}-alkylperoxide moiety. Notably, these Raman bands are very similar to those reported for metal-bound anilino radical species, where the bands have been assigned to the C–C and C–N stretching vibrations of the anilino radical moiety.[12,13] In order to confirm this possibility, we have prepared a deuterated ligand at the 2,4,6-positions of the aniline rings of all the TIPT substituents, referred to as $\mathrm{TIPT_3tren}$-d_9 (Figures S5, S6, S7 and S8), and examined the resonance Raman spectrum (Figure 3c, orange line spectrum) of the ROOH adduct intermediate. In this case, we observed prominent peak shifts to 1562, 1546, 1529, and 1337 cm^{-1}, respectively. The result confirmed that the bands at the higher frequency region were due to the anilino ligand radical bound to the Cu^{II} ion. Considering the resonance structure of the anilino radical moiety, the band at 1588 cm^{-1}, which shifted to 1562 cm^{-1} in the deuterated derivative **2-*d*$_9$**, can be assigned to the C_{ortho}–C_{meta} (ν_{8a}) stretching vibration. The other band at 1578 cm^{-1} (shifted to 1546 cm^{-1}) was tentatively assigned to the ν_{19a} vibration mode. Then, the most intense band at 1555 cm^{-1} has been assigned to C–N stretching vibration (ν_{7a}), which shifted to 1529 cm^{-1} in the deuterated derivative. The band at 1405 cm^{-1} disappeared in the deuterated derivative, suggesting that the band has significant contribution to C–H bending motion, thus assigned to the Wilson ν_{14} mode.[14] The vibration at 1345 cm^{-1} could be assigned to the non-totally symmetric ν_{19b} mode, which shifted to 1337 cm^{-1} in the deuterated intermediate.[14,15] These assignments of the Raman data were well supported by the DFT calculations (Figure S25, Table S3). It was also noted that the O–O/Cu–O stretching modes at 831 and 604 cm^{-1} slightly shifted to 828 and 606 cm^{-1}, respectively, in the deuterated intermediate **2-*d*$_9$**, suggesting a direct interaction between the anilino radical and Cu^{II}-OOR moieties (Figures S13a and S13b).

All these results are consistent with the assignment of compound **2** as a Cu^{II}-alkylperoxide/anilino-radical complex as illustrated in Scheme 1. The intense absorption bands in the visible to near-IR region shown in Figure 2 can be assigned to $\pi \rightarrow \pi^*$ transitions of the metal bound organic radical and an anilino radical to Cu^{II} as well as an alkylperoxide to Cu^{II} charge transfer transitions. The EPR silence of **2** may be due to antiferromagnetic coupling between Cu^{II} and anilino radical as in the case of the oxidized-form of galactose oxidase, in which there is a strong antiferromagnetic coupling between Cu^{II} and coordinating phenoxyl radical species, thus being EPR silent.[16,17]

In support of this assignment, the CSI (cold electrospray ionization)-mass spectrum of intermediate **2** measured in CH_2Cl_2 at –60°C showed a peak cluster at m/z = 1550, the isotope distribution pattern of which is consistent with the molecular component of [Cu + TIPT$_3$tren + $C_6H_5C(CH_3)_2OOH$] (Figure S14). Upon using the isotope labeled cumene hydroperoxide ($R(^{18}O)_2H$), the peak cluster was shifted by four mass unit (Figure S15), clearly demonstrating that **2** is an alkylperoxide-adduct.

A possible mechanism for the formation of **2** is presented in Scheme 2. Addition of ROOH to complex **1** initially forms a peroxide adduct **A** by replacing the coordinating CH_3CN by ROOH. In this step, the non-coordinating ligand arm of **1** (N(4) in Figure 1) may act as a base to accept proton from ROOH to promote its coordination to Cu^{I}. The resulting ammonium group (TIPT–NH_2^+–) may stabilize the alkylperoxide adduct **A** *via* an intramolecular hydrogen bonding interaction. Then, the heterolytic O–O bond cleavage takes place to give (L)Cu^{II}–O• (intermediate **B**) and ROH (path i), which may be assisted by the ammonium group (TIPT–NH_2^+–) as a general acid catalyst. In fact, the reaction did not occur at all in the presence of base such as triethylamine or 2,6-lutidine. The added base may abstract proton from the ammonium group to prevent the intramolecular hydrogen bonding interaction and the intramolecular general acid catalysis. The generated intermediate **B** immediately abstracts one of the hydrogen atoms of the aniline moieties to give (L$^•$)Cu^{II}–OH (intermediate **C**), where L$^•$ denotes the ligand anilino radical (path ii). A concerted mechanism is also possible for the generation of **C** from **A** directly (path iii). Intermediate **C** undergoes ligand exchange reaction of the -OH group with another equivalent of ROOH to give the final product **2**. In fact, almost two equivalent of ROOH is needed to get a quantitative formation of complex **2** (Scheme 1). The reaction of an M–OH complex with alkyl/acyl peroxide is well known in the literature.[18,19] Although an iron(IV)-oxo intermediate supported by a ligand radical is known for the porphyrin system,[20] and Peters et al. have recently reported a mononuclear Cu(I)-radical complex,[21] compound **2** represents a unique example of a metastable peroxide-complex supported by a non-porphyrin organic radical.

Scheme 2. Proposed Mechanism for the Formation of 2

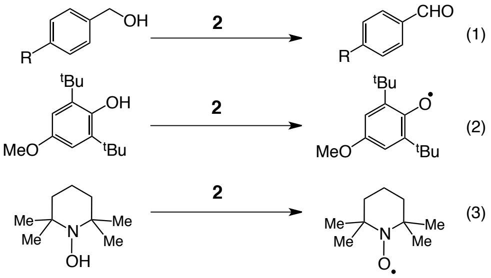


Reactivity of the copper(II)-alkylperoxide/anilino radical complex **2** toward alcohols was examined, since **2** has a similar structural motif with that of the active form of galactose oxidase as mentioned above. Complex **2** readily reacted with an excess amount (20 equiv) of 4-methylbenzyl alcohol at –45°C (Figure S18a) to give 4-methylbenzaldehyde (Scheme 3-1) together with cumyl alcohol as confirmed by HPLC and ^{1}H-HNR spectroscopy (Figure S19 and S20).

The decay of absorption bands due to **2** obeyed pseudo-first-order kinetics as shown in Figure S18b, and plot of the pseudo-first-order rate constants k_{obs} against the substrate concentration [$ArCH_2OH$] gave a linear correlation, from which the second-order rate constant k_2 = 0.57 ± 0.03 M^{-1} s^{-1} was obtained from the slope (Figure S18c). The Hammett analysis (plot of log k_2 vs Hammett constant σ_p^+) using a series of p-substituted benzyl alcohols (-OCH_3, -CH_3, -F, -Cl) gave a Hammett ρ value as –0.42 ± 0.08 as indicated in

Figure S21. Notably, the Hammett ρ value of the present reaction is very close to that of the oxidation of benzyl alcohol derivatives by galactose oxidase ($\rho = -0.09 \pm 0.32$),[22] suggesting that the mechanism of the present reaction is similar to that of galactose oxidase.[22] Namely, the alcohol substrate initially replaces the alkylperoxide ligand (ROO) to give an alkoxide adduct (Scheme S1). Then, inner sphere electron transfer takes place from the coordinated alkoxide to Cu^{II}, generating an alkoxyl radical intermediate, from which benzylic hydrogen atom is abstracted by the anilino radical moiety to give the aldehyde product. This event produces starting copper(I) complex **1**, from which **2** is regenerated according to the reaction pathways shown in Scheme 2. In fact, the reaction proceeded in a catalytic manner to give 4-methylbenzaldehyde in a 350% yield based on the copper complex after a prolonged reaction time (1 h) at 25°C.

Scheme 3. Reactivity of Complex 2 toward External Substrates.



Complex **2** also reacted with typical hydrogen atom donors such as 2,6-di-*tert*-butyl-4-methoxyphenol (Scheme 3-2) and 2,2,6,6-tetramethylpiperidine-1-ol (TEMPOH, Scheme 3-3) at a low temperature to give 2,6-di-*tert*-butyl-4-methoxyphenoxyl radical and TEMPO$^\bullet$, respectively, as confirmed by UV-vis and/or EPR spectroscopy, respectively (Figures S22 and S23), further demonstrating the radical character of **2**. It should be noted that the three absorption bands due to **2** (λ_{max} = 396, 465, and 748 nm) decayed in the same rate in each reaction (Eq 1-3, see Figures S18b, S22b, and S23b). The results clearly indicate that the three absorption bands shown in Figure 2 arise from one species, that is complex **2**, but not from a mixture of multiple compounds.

In summary, we have developed a novel Cu^{II}-alkylperoxide/anilino-radical complex **2**, which represents the first example of a metal-alkylperoxide species supported by a non-innocent ligand radical. For the formation of **2**, the bulky TIPT substituents prohibit undesirable dimerization reaction and one of the alkylamine arms is dissociated from the copper ion to dictate acid-base catalysis for the formation of Cu^{I}–OOR and following O–O bond heterolytic cleavage (Scheme 2). Complex **2** induces catalytic oxidation of benzyl alcohol derivatives, presumably through a similar mechanism of galactose oxidase. Further studies are now being undertaken to explore the in-depth reactivity of this novel intermediate.

ASSOCIATED CONTENT

Supporting Information

All experimental details and additional data mentioned in the text. This material is available free of cost *via* the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(17) In a parallel-EPR spectrum taken at 4K, there was no signal around g ~ 4. All the ^{1}H and ^{2}H signals appeared in the diamagnetic region for **2** and **2-d_9** in the ^{1}H- and ^{2}H-NMR spectra (Figure S16 and Figures S17). All these results were consistent with the assignment of **2** as a singlet species ($S = 0$). However, a preriminaly DFT caluculation of complex **2** suggested that the triplet state is more stable than the singlet state by 3.3 kcal mol^{-1} (see SI). Thus, further detailed studies are needed to clarify the presice electronic structure of **2**.

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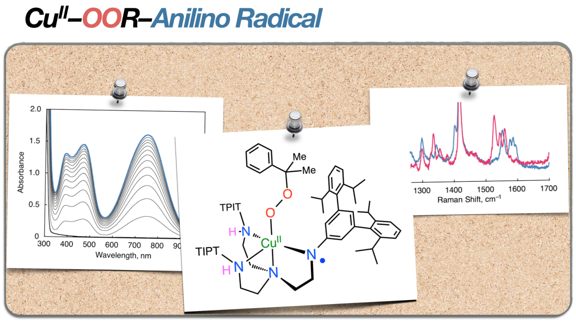
Cu^{II}–OOR–Anilino Radical
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Absorbance
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90
Wavelength, nm
Me
Me
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Cu^{II}
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