Published in final edited form as:

Inorg Chem. 2019 April 15; 58(8): 4706–4711. doi:10.1021/acs.inorgchem.9b00090.

Revisiting the Synthesis and Nucleophilic Reactivity of an Anionic Copper Superoxide Complex

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Abstract

The addition of 1 equiv of KO₂ and Kryptofix222 (Krypt) in CH₃CN to a solution of LCu(CH₃CN) [L = *N,N'*-bis(2,6-diisopropylphenyl)-2,6-pyridinecarboxamide] in tetrahydrofuran at –80 °C yielded [K(Krypt)][LCuO₂], the enhanced stability of which enabled reexamination of its reactivity with 2-phenylpropionaldehyde (2-PPA). Mechanistic and product analysis studies revealed that [K(Krypt)][LCuO₂] reacts with wet 2-PPA to form [LCuOH][–], which then, deprotonates 2-PPA to yield the copper(II) enolate complex [LCu(OC=C(Me)Ph)][–]. Acetophenone was observed upon workup of this complex or mixtures of KO₂ and 2-PPA alone, in support of an alternative mechanism(s) to the one proposed previously involving an initial nucleophilic attack at the carbonyl group of 2-PPA.

Elucidating the structure and function of putative monocopper–oxygen intermediates is imperative for understanding many oxygenase enzymes¹ and abiological oxidation catalysts.² Common to all mechanistic schemes for the activation of O₂ in such systems is the initial formation of a 1:1 Cu/O₂ species, typically formulated as a copper(II) superoxide comprising a [CuO₂]⁺ core.³ Significant appreciation of the structures and spectroscopic properties of [CuO₂]⁺ cores has been achieved through studies of synthetic complexes.⁴ Some features of the reactivity of such complexes also have been examined, but many questions concerning detailed mechanisms, supporting ligand effects,⁵ and other aspects remain unanswered because of their thermal instability, challenges associated with isolating the complexes in pure form, and complicated side reactions.

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorgchem.9b00090.

Experimental details and kinetic/spectroscopic data (PDF)

Accession Codes

CCDC 1888175 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Notes

The authors declare no competing financial interest.

For example, we previously reported the preparation of $[\text{K}(18\text{-crown-6})][\text{LCuO}_2]$ [$\text{L} = N,N'$ -bis(2,6-diisopropylphen-yl)-2,6-pyridinedicarboxamide], a novel 1:1 Cu/O₂ complex because of its anionic charge, via the reaction of $\text{LCu}(\text{CH}_3\text{CN})$ with a slurry of KO_2 and 18-crown-6 in 1:1 (v/v) N,N -dimethylformamide (DMF)/tetrahydrofuran (THF) at -80°C .⁶ While identifiable by spectroscopy and chemical-trapping experiments, the complex was not isolable, required excess superoxide salt for full conversion, and decayed above -80°C in the DMF/THF solvent mixture relatively quickly ($t_{1/2} \sim 30$ min at -60°C). Because of these issues, only preliminary reactivity studies were performed, with limited results. This same complex, synthesized by 2 equiv of KO_2 in excess 18-crown-6 in a 3:1 (v/v) THF/DMF solvent, was later reported to react with acyl chlorides and 2-phenylpropionaldehyde (2-PPA).⁷ The latter process yielded acetophenone (via aldehyde deformylation), with a ^{18}O -labeled product arising when a ^{18}O -labeled superoxide was used, and a mechanism was proposed that invoked nucleophilic attack of the $[\text{CuO}_2]^+$ core at the aldehyde carbonyl,^{8,9} followed by rearrangements of intermediates comprising high-valent copper (Scheme 1). Intrigued by this report and the proposed mechanism, particularly in view of the aforementioned issues that complicate reactivity studies, we sought an improved method for synthesis of the superoxide complex $[\text{LCuO}_2]^-$ that would enhance its solubility and stability. Herein, we report success in this endeavor, which enabled reexamination of the reactivity of $[\text{LCuO}_2]^-$ with 2-PPA and provided new mechanistic insights.

We circumvented the typically low solubility and instability of superoxide salts that complicates their use in synthesis¹⁰ by use of Kryptofix222 (Krypt) as a chelator and phase-transfer reagent. Mixing equimolar amounts of KO_2 and Krypt in CH_3CN yielded homogeneous 20 mM solutions of $[\text{K}(\text{Krypt})][\text{O}_2]$, as verified by titrations monitoring the superoxide absorption by UV-vis spectroscopy ($\lambda_{\text{max}} = 256$ nm; $\epsilon = 2686 \text{ M}^{-1} \text{ cm}^{-1}$).¹¹ The addition of 1 equiv of $[\text{K}(\text{Krypt})][\text{O}_2]$ in CH_3CN to $\text{LCu}(\text{CH}_3\text{CN})$ in THF at -80°C immediately gave a deep-blue solution (Scheme 2). Analysis of the solution by UV-vis ($\lambda_{\text{max}} = 628$ nm; $\epsilon = 1400 \text{ M}^{-1} \text{ cm}^{-1}$; Figure S1), electron paramagnetic resonance (EPR; silent); and resonance Raman spectroscopy [$\nu(\text{O}-\text{O}) = 1102 \text{ cm}^{-1}$; $\lambda_{\text{ex}} = 660$ nm; Figure S2] yielded results matching those previously reported for the $[\text{LCuO}_2]^-$ unit (Table S1).⁶ Titration experiments confirmed a 1:1 reaction stoichiometry between copper and superoxide salt (Figure S1). Importantly, $[\text{K}(\text{Krypt})][\text{LCuO}_2]$ in 19:1 THF/ CH_3CN was found to be significantly more stable than the previously reported $[\text{K}(18\text{-crown-6})][\text{LCuO}_2]$ in 1:1 DMF/THF, as indicated for the former by no decay over >1 day at -80°C and $t_{1/2}$ values of ~ 12 h at -60°C , ~ 6 h at -40°C , and ~ 80 min at -20°C (Figures S3 and S4). The addition of a second equiv of $[\text{K}(\text{Krypt})][\text{O}_2]$ to a preformed solution of $[\text{K}(\text{Krypt})][\text{LCuO}_2]$ enhanced its decay ($t_{1/2} \sim 500$ s at -60°C ; Figure S5), consistent with secondary reaction of superoxide with the complex.

With the discovery that stable solutions of $[\text{LCuO}_2]^-$ could be obtained in THF/ CH_3CN mixtures in the absence of excess superoxide, studies of its reactivity could commence.¹² We chose to compare the reactivity of $[\text{K}(\text{Krypt})][\text{LCuO}_2]$ to that of the 18-crown-6 analogue (synthesized in THF/DMF) reported previously, using the same substrate, 2-PPA. The addition of neat (375 equiv) 2-PPA to a solution of $[\text{K}(\text{Krypt})][\text{LCuO}_2]$ (1 mM) at -60°C resulted in a two-phase reaction, as followed by UV-vis spectroscopy. In the first phase, the superoxide species was observed to quickly decay over 100 s to an intermediate

species (Figure 1). This intermediate then slowly reacted over the next ~1500 s to yield the final product (blue spectrum). The spectrum of the intermediate species is similar to that of $[\text{NBu}_4][\text{LCuOH}]^{13}$ and reminiscent of the final decay spectrum for the reaction of $[\text{K}(\text{crown})][\text{LCuO}_2]$ with 2-PPA described previously.⁷ Indeed, the spectrum of the intermediate species could be fit with great accuracy to a mixture of an authentic spectrum of $[\text{NBu}_4][\text{LCuOH}]$ and the final reaction product (71% and 29%, respectively; Figure S11). These data suggest that the reaction of $[\text{K}(\text{Krypt})][\text{LCuO}_2]$ and 2-PPA initially proceeds to yield $[\text{LCuOH}]^-$, which then reacts further to give the final product. In a test of this hypothesis, treatment of an independently synthesized sample of $[\text{NBu}_4][\text{LCuOH}]$ with 2-PPA yields a solution with the same EPR and UV-vis spectroscopic properties as the final product of the reaction of $[\text{K}(\text{Krypt})][\text{LCuO}_2]$ and 2-PPA (Figures S6 and S12). This conversion occurs over the same time frame (~2000 s; 20 equiv of 2-PPA; -60 °C), indicating that $[\text{LCuOH}]^-$ is kinetically competent to be the intermediate (Figure S12).

The final product of the reactions with 2-PPA was identified by EPR, UV-vis, and electrospray ionization mass spectrometry (Figures S6–S8), using samples derived from the treatment of $[\text{NBu}_4][\text{LCuOH}]$ with 2-PPA. The data for these samples matched those of X-ray-quality crystals grown from the treatment of $[\text{NBu}_4][\text{LCuOOCm}]$ (Cm = cumyl)¹⁴ with 2-PPA (Figure 2). We formulate the complex as a copper(II) enolate, $[\text{NBu}_4][\text{LCu}(\text{OC}=\text{C}(\text{Me})\text{Ph})]$, arising from deprotonation at the benzylic position of 2-PPA. Structural features indicative of the enolate formulation include an overall planarity, a C1–C2–C3 angle of 119.5(3)° indicative of C2 being a sp^2 center, a C1–C2 bond distance of 1.371(4) Å consistent with a double bond, and a C1–O1 bond distance of 1.285(3) Å that is slightly elongated relative to typical free aldehyde carbonyls. The Cu1–O1 distance of 1.865(2) Å is similar to the $\text{Cu}^{\text{II}}\text{--OH}$ distance in $[\text{LCuOH}]^-$ (1.863 Å).¹³ The complex is a rare example of a stable, structurally characterized copper(II) enolate. Long postulated as key intermediates in aldol¹⁵ and related reactions,^{16–19} copper enolates typically contain copper(I) and relatively few have been isolated, most likely because of their high reactivity.^{20–23} Also relevant to this work are the coupling of acetaldehyde by an (NHC)copper(I) hydroxide complex,²⁴ and the recently reported catalytic aldol coupling of benzaldehydes and acetone by a neutral copper(II) superoxide complex.²⁵ Exposure of $[\text{NBu}_4][\text{LCu}(\text{OC}=\text{C}(\text{Me})\text{Ph})]$ to benzaldehyde or propionaldehyde did not yield C–C-coupled products [gas chromatography (GC)/mass spectrometry (MS)], a result that we presume derives from the steric hindrance of its supporting ligand.

Returning to the reaction of $[\text{K}(\text{Krypt})][\text{LCuO}_2]$ with 2-PPA that ultimately yields the copper(II) enolate complex, we asked, how is the intermediate complex $[\text{LCuOH}]^-$ formed? The importance of water contamination was revealed by the observation of no reaction between $[\text{K}(\text{Krypt})][\text{LCuO}_2]$ and 2-PPA (100 mM; -60 °C) when extensive drying procedures were used (Figure S13). Subsequently, the purposeful addition of ROH [H_2O (5, 10, or 15 equiv based on Cu), methanol (MeOH; 10 equiv), or PhCH_2OH (10 equiv)] to the substrate solution prior to the addition to $[\text{K}(\text{Krypt})][\text{LCuO}_2]$ led to the reaction as previously observed, propagating through an intermediate²⁶ at an enhanced rate and yielding the final product $[\text{LCu}(\text{OC}=\text{C}(\text{Me})\text{Ph})]^-$ (Figure S14). When exposed to a THF solution of H_2O (5–20 equiv) in the absence of 2-PPA at -60 °C, $[\text{K}(\text{Krypt})][\text{LCuO}_2]$ does not appreciably decay, arguing against H_2O alone being a reactive species. Instead, the data

suggest that ROH additives activate 2-PPA for further reaction, potentially by nucleophilic attack under the conditions reported previously⁷ or by α -deprotonation, as we propose below.²⁷

The kinetic traces of reactions with known amounts of added water (5, 10, and 15 equiv) to anhydrous 2-PPA were best fit to the mechanism described by eqs 1 and 2 using Reactlab multiwavelength global analysis, yielding rate constants $k_1 = 6 \pm 2 \text{ M}^{-1} \text{ s}^{-1}$ and $k_2 = 0.83 \pm 0.05 \text{ M}^{-1} \text{ s}^{-1}$ and $K_{\text{eq}} = 24 \pm 5 \text{ M}^{-1}$. This mechanistic model (with A reasonably²⁸ proposed to be a hydrogen-bonded PPA/H₂O adduct) was then used to fit all data for [wet 2-PPA]₀ (5–200 mM; Figure S9), using an assumed [H₂O]₀, which resulted in a similarly fitted K_{eq} ($6.7 \pm 0.3 \text{ M}^{-1}$; Figure S16 and Table S3). Attempts to fit the kinetic data using a nucleophilic attack model without substrate activation (eq S1) were unsuccessful. Consistent with the proposed importance of deprotonation of 2-PPA, no reaction was observed upon the treatment of [K(Krypt)][LCuO₂] with pivaldehyde (20 equiv, 1 h), which lacks an acidic α -C–H bond, with or without a suitable activator such as H₂O or [K(crown)]⁺ (Figure S18).

Another mechanistic question centers on the reported observation of deformylation of 2-PPA to yield acetophenone (Scheme 1). Using the previously described workup procedure,⁷ we analyzed the organic products from the reaction of [K(Krypt)][LCuO₂] with both wet and anhydrous solutions of 2-PPA (GC/MS and NMR). As summarized in Table 1, in the reaction with [K(Krypt)][LCuO₂] and excess 2-PPA (wet), nearly quantitative production of acetophenone (based on [Cu]) was observed (entry 1). Importantly, running the independently synthesized [NBu₄][LCu(OC=C(Me)Ph)] through the same workup procedure yielded 51(2)% acetophenone (entry 2), supporting the viability of the copper(II) enolate complex as the precursor. Furthermore, when the workup of the independently synthesized [NBu₄][LCu(OC=C(Me)Ph)] was performed in the absence of O₂ (in an N₂ glovebox), no acetophenone was observed by GC/MS (entry 3). In the absence of copper, the free superoxide anion is a competent oxidant, converting 2-PPA to acetophenone under analogous conditions (entry 4). Without copper or free superoxide present (entries 5 and 6), no acetophenone was observed (with or without exposure to silica). From these results, we propose that acetophenone is produced from the aerobic oxidation of a copper-bound enolate fragment during workup in air, analogous to the proposed aerobic oxidation of metal-bound

bidentate enolates in acireductone dioxygenase or other discrete metal enolates (Scheme S4).^{29,30}

On the basis of the combined data, we propose a different reaction course (Scheme 3) than that proposed previously (Scheme 1). The pure complex $[K(\text{Krypt})][\text{LCuO}_2]$, prepared without excess KO_2 , is inert toward anhydrous 2-PPA at -60°C without a suitable activator (ROH). Instead, it decays in the presence of wet 2-PPA through deprotonation of the acidic benzylic C–H bond³¹ and decomposition of the $[\text{CuOOH}]^{2+}$ core to the intermediate $[\text{LCuOH}]^-$, which deprotonates 2-PPA to form the enolate complex $[\text{LCu}(\text{OC}=\text{C}(\text{Me})\text{Ph})]^-$. Importantly, this enolate complex undergoes aerobic oxidation during workup to acetophenone, providing one pathway for deformylation (Scheme S4). It is also possible that the excess superoxide salt used in the previous study⁷ is the oxidant responsible for acetophenone production directly from 2-PPA in that work (Table 1, entry 4); this pathway would explain the observed ^{18}O incorporation in the final product.

In conclusion, we have prepared $[K(\text{Krypt})][\text{LCuO}_2]$ without the need for excess KO_2 and in the absence of DMF solvent. Under the new conditions described herein, this complex showed enhanced stability, which facilitated the reexploration of its reactivity with 2-PPA.⁷ A new mechanistic conclusion is proposed for the reaction performed under these conditions, where $[K(\text{Krypt})][\text{LCuO}]$ acts as a base rather than a nucleophile. Instead, the decay product $[\text{LCuOH}]$ is the reactive species that activates the aldehyde substrate, forming a copper(II) enolate complex that is a viable precursor to acetophenone production.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

We thank the NIH (Grant R37GM47365 to W.B.T.) and Washington University St. Louis for financial support of this research. The X-ray diffraction experiments were performed using a diffractometer acquired through NSF-MRI Award CHE-1229400. Parts of this work were performed at the University of Minnesota.

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- (27). The addition of a potential Lewis acid catalyst, $[\text{K}-18\text{-crown-6}] [\text{OTf}]$, to anhydrous 2-PPA and $[\text{LCuO}_2]^-$ resulted in no conversion to the enolate complex (Figure S14) and slowed the self-decay of $[\text{LCuO}_2]^-$. We propose that the reactive superoxide ligand binds to potassium in this case, nullifying its reactivity.
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the Supporting Information), the acetophenone yields were 2% and 71%, respectively (GC/MS, based on Cu), indicating that the first, fast phase of the reaction does not involve 2-PPA oxidation and that acetophenone is only produced after enolate formation.

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Figure 1. UV-vis spectra as a function of time for the reaction of $[LCuO_2]^-$ (red) and 375 equiv of 2-PPA to form $[LCu(OC=C(Me)Ph)]^-$ (blue) via the intermediate (purple). Inset: Two-phase process illustrated by the absorbance at 628 nm versus time.

Figure 2.

Representation of the anionic portion of the X-ray crystal structure of $[\text{NBu}_4][\text{LCu}(\text{OC}\equiv\text{C}(\text{Me})\text{Ph})]$. All non-H atoms are shown as 50% thermal ellipsoids. Select bond distances ($\text{\AA}$) and angles (deg): Cu1–N1, 2.0197(18); Cu1–N2, 1.9221(19); Cu1–N3, 2.013(2); Cu1–O1, 1.865(2); O1–C1, 1.285(3); C1–C2, 1.371(4); C2–C3, 1.504(4); N1–Cu1–N3, 158.89(8); N1–Cu1–N2, 79.40(8); N2–Cu1–O1, 165.84(9); N2–Cu1–N3, 80.63(8); Cu1–O1–C1, 135.5(2); C1–C2–C3, 119.5(3).

Scheme 1.

Previously Proposed Mechanism for the Initial Nucleophilic Attack of [K(18-crown-6)] [LCuO₂] on Aldehydes⁷

Scheme 2.
Synthesis of [K(Krypt)][LCuO₂]

Scheme 3.

Proposed Pathway for the Formation of an Enolate Complex

Table 1.

Organic Product Analysis Results^a

entry	[LCu(Solv)] (equiv)	[O ₂] ^{•-} (equiv)	substrate	workup ^b	acetophenone % yield ^c	2-PPA % yield ^d
1	1	1	2-PPA (5 equiv)	MeOH/SiO ₂ /air	95(2) (0.95 equiv) ^{e,f}	87(4) (4.4 equiv)
2	0	0	[LCu(OC≡C(Me)Ph)] ⁻ (1 equiv)	MeOH/SiO ₂ /air	51(2) (0.51 equiv) ^e	19(2) (0.19 equiv)
3	0	0	[LCu(OC≡C(Me)Ph)] ⁻ (1 equiv)	MeOH/SiO ₂ /N ₂ ^g	<1 (0 equiv)	57 (0.57 equiv)
4	0	1	2-PPA (5 equiv)	MeOH/SiO ₂ /air	112 (1.1 equiv)	93.7 (4.7 equiv)
5	0	0	2-PPA (5 equiv)	MeOH/SiO ₂ /air	<1 (0 equiv)	111 (5.5 equiv)
6	0	0	2-PPA (5 equiv)	MeOH/air	<1 (0 equiv)	100 (5 equiv)

^a 1 equiv is the appropriate volume of a 1 mM solution. All data were from GC/MS peak integrations.^b All workups were performed at room temperature after reactions were warmed from -60 °C unless otherwise stated.^c Calculated from the acetophenone calibration curve.^d Referenced to a control (no SiO₂ workup) as 100% yield.^e Reactions run in triplicate.^f Averaged from reactions using both wet and dry 2-PPA.^g Workup, as reported in the Supporting Information, performed in an N₂ glovebox.