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Reactivity of a Stable Copper-Dioxygen Complex

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Abstract

We report the isolation of a room temperature stable dipyrromethene Cu(O₂) complex featuring a side-on O₂ coordination. Reactivity studies highlight the unique ability of the dioxygen adduct for both hydrogen-atom abstraction and acid/base chemistry towards phenols, demonstrating that side-on superoxide species can be reactive entities.

Graphical Abstract

A stable Cu–dioxygen adduct is observed that effects both H–atom abstraction and O–atom transfer chemistry.

Activation of dioxygen by copper systems plays an essential role in both biological^{1–3} and abiological^{4–6} transformations. Studies on natural enzymes and synthetic complexes have identified structural motifs of mono-, di-, and tri-copper sites with varying degrees of dioxygen activation (superoxide, peroxide, oxo), and consequently distinct reactivity profiles.^{7–11} As such, elucidating the correlation between the initially generated 1:1 Cu(O₂) adduct and the subsequent reactivity of this intermediate towards substrates is essential for rationally designing synthetic systems competent for selective oxidation chemistry.

Among the Cu(O₂) adducts isolated to date,^{12–27} both end-on and side-on coordination of dioxygen have been observed to afford a Cu^{II}-superoxide unit that features either a triplet (end-on bound)^{12–21} or a diamagnetic (side-on bound)^{22–25, 27} ground state. Reactivity studies identified the ability of terminally bound Cu(O₂) complexes to engage in hydrogen-

atom abstraction (HAA)^{12, 14–18} from weak C–H and phenol O–H bonds or acid/base chemistry,^{14, 19} whereas no such transformations can be effected at a side-on Cu(κ^2 -O₂) complex.²³ In line with these observations, DFT investigations suggested that less electron donating ligands could increase the oxidative potency of such Cu(O₂) complexes by inducing a Cu superoxide and, therefore, electrophilic character.²³

Using weak-field dipyrromethene ligands, our group has demonstrated the stabilization of a unique ferric iminyl species that is competent for C–H amination.^{28, 29} Encouraged by these results, we set out to probe the potential of this weakly donating scaffold to similarly stabilize a dipyrin copper superoxide complex and explore its reactivity. Herein, we report the isolation of a side-on Cu(κ^2 -O₂) complex that persists at room temperature and yet manifests both HAA and acid/base chemistry towards phenolic O–H bonds.

Metalation of (^{Ar}L)Li with CuCl in tetrahydrofuran affords (^{Ar}L)Cu^I (**1**) (^{Ar}L: 5-mesityl-1,9-(2,4,6-Ph₃-C₆H₂)dipyrin²⁸). X-ray diffraction studies on single crystals obtained from a concentrated hexanes solution of **1** reveal a three-coordinate copper centre featuring an η^2 -interaction with one of the *ortho*-phenyl groups of the 2,4,6-Ph₃-C₆H₂ substituent (Fig. 1a). Treatment of **1** with strongly donating functionalities such as acetonitrile or ammonia displaces the bound arene to afford the corresponding solvento adducts (Fig. S7, ESI[†]). Upon exposure to vacuum, however, complete removal of these exogenous ligands is observed, demonstrating the inherent stability of the η^2 -coordination.

Addition of a stoichiometric amount of dioxygen to a frozen benzene solution of **1** results in immediate colour change from purple (λ_{max} 575 nm) to dark pink (λ_{max} 545 nm) upon thawing the reaction mixture, along with formation of new diamagnetic resonances in the ¹H NMR spectrum; however, full consumption of **1** is not observed (Fig. S9, ESI[†]). Diffusion of pentane into a saturated benzene solution of **1** under an atmosphere of O₂ afforded crystals suitable for X-ray diffraction, providing structural evidence for a side-on bound O₂ adduct (^{Ar}L)Cu(O₂) (**2**). The solid state molecular structure (Fig. 1b) displays an elongated O–O bond (1.383(2) Å) compared to typical superoxide moieties (1.2–1.3 Å),^{9, 23, 30–34} more in line with a doubly reduced O₂ moiety (~1.4 Å).^{9, 23, 30–34} The Cu–O bond lengths of 1.8306(11) and 1.8360(12) Å, respectively, are also indicative of a strong covalent interaction. Further, the average Cu–N_{dipyrin} bond lengths of **2** (1.878(2) Å) are significantly shorter compared to those observed in several authentic dipyrinato Cu^{II} species ((^{Ar}L)CuCl: 1.890(2) Å; (^{Ar}L)Cu(OEt): 1.919(3) Å; (^{Ar}L)Cu(OPh): 1.904(1) Å, ESI[†]). However, an anilido imine supported side-on Cu(κ^2 -O₂) species featuring an O–O bond length of 1.392(3) Å and similarly contracted Cu–O and Cu–N bond lengths²⁷ was recently reassigned as a Cu^{II} superoxide unit based on Cu K pre-edge XANES data as opposed to the originally proposed Cu^{III} peroxide formulation.³⁵ Finally, resonance Raman on **2** did not provide a definitive $\nu_{\text{O-O}}$ as the anticipated region⁸ (Fig. S12–13, ESI[†]). As such, a definitive description of **2** as either a Cu^{III} peroxide or a Cu^{II} superoxide is not possible.

[†]Electronic Supplementary Information (ESI) available: General experimental considerations and procedures, ¹H NMR data, EPR, and UV-Vis spectra, solid state molecular structures, computational details, crystallographic CIF files and crystallography data. CCDC 1557369 (**1**), 1557370 (**2**), 1557371 (**4**), 1557372 (**5**), 1557373 (**6**), 1557374 (**7**). See DOI: 10.1039/x0xx00000x

Preliminary DFT investigations³⁶ using crystallographically determined parameters identified a closed-shell singlet ground state with the lowest unoccupied molecular orbital (MO) depicting the σ^* interactions between the d_{xz} orbital and both the dipyrin ligand and the O₂ moiety. Given the weak ligand field of the dipyrin scaffold and its influence on electronic structure evidenced in our previous studies^{28, 29} as well as the multi-configurational character described for such side-on copper dioxygen species,^{22, 24} we chose to further examine the electronic structure of **2**. As discussed in literature reports,³⁵ the broken symmetry (BS) approach fails to provide a satisfactory result for these Cu(O₂) systems, and indeed, we were unable to converge to a BS solution corresponding to a cupric centre antiferromagnetically coupled to a superoxide radical. However, following a similar protocol³⁵ applied for the two crystallographically characterized side-on Cu(κ^2 -O₂) complexes,^{22,24} the use of a complete active space self-consistent field (CASSCF) method reveals the complex electronic nature of **2**. A CAS(2,2) reference space on a truncated model of **2** (see ESI[†]) identified the two $\sigma(d_{xz} + \pi^*_{O_2})$ and $\sigma^*(d_{xz} - \pi^*_{O_2})$ active MOs (Fig. S8a, Table S2, ESI[†]). Subsequent localization of these MOs (Fig. S8b, ESI[†]) and analysis of the resulting wavefunctions with respect to a valence bond description unveiled 87.1% contributions from the Cu^{II}(O₂^{•-}) configuration, with 9.4% and 3.5% participation of the Cu^I(O₂⁰) and Cu^{III}(O₂²⁻) states, respectively (Table S3, ESI[†]). These results are consistent with those calculated for the analogous β -diketiminato Cu(κ^2 -O₂) adduct³⁵ and suggest a significant Cu^{II}-superoxide character for **2**.

Complex **2** exhibits interesting properties and reactivity profile. Unlike the previously characterized Cu(O₂) species, which tend to decay above -25 °C,^{2,9,14,17,19,22–24} **2** is surprisingly persistent in solution at room temperature. However, despite the relatively strong Cu(O₂) interaction, the η^2 -arene association is still preferred; exposure of *in situ* generated **2** to vacuum results in conversion to the starting Cu^I complex **1** (Fig. S9, ESI[†]), akin to the behaviour reported for a tris(pyrazolyl)borate side-on bound Cu^{II} superoxide.²² Additionally, variable temperature ¹H NMR studies identified an equilibrium between **1** and **2**, justifying the incomplete generation of **2** at room temperature even in the presence of excess dioxygen. O₂ binding is favoured at lower temperatures, with full conversion to **2** observed *in situ* at -15 °C (Fig. S10, ESI[†]) and oxygen release noted upon warming the reaction mixture back to room temperature. Such temperature dependent reversible O₂ binding has been previously described for a tris(tetramethylguanidino)tren end-on Cu^{II} superoxide.¹²

Despite its robust nature, **2** is not inert. Heating a benzene solution of the *in situ* generated **2** at 60 °C results in full consumption of the dioxygen adduct, giving rise to a ¹H NMR spectrum with no well-defined features (Scheme 1). Notably, no ligand hydroxylation was observed. Unfortunately, structural confirmation of the final Cu complex (**3**) has been unsuccessful. A frozen toluene EPR spectrum of **3** collected at 77 K identifies an $S = 1/2$ signal consistent with a Cu^{II} formulation ($g_{Cu} = 2.24$, $A_{Cu} = 543$ MHz, Fig. S14, ESI[†]). O–O bond cleavage and decay of **2** into a copper hydroxide is possible, likely forming [(^{Ar}L)Cu(OH)]_n units, as a three-coordinate, terminal copper hydroxide would be unstable.³⁷ A tri-copper formulation would be more plausible than a dimeric motif given the cupric EPR signature of **3**. Interestingly, the same product was detected upon treatment of **1** with excess

urea hydroperoxide at 65 °C (Scheme 1 and Fig. S15, ESI[†]), suggesting that a Cu hydroperoxide species may form during the thermal decomposition of **2**. Such an intermediate would arise upon a HAA step, transformation which has been previously described for terminal Cu^{II} superoxide complexes,^{12,14–18} albeit not for side-on bound Cu(O₂) adducts.²³ Indeed, in the presence of a weak hydrogen atom source such as 2-hydroxy-2-azaadamantane **2** rapidly undergoes HAA at room temperature to afford the corresponding *N*-oxide organic radical as confirmed via EPR spectroscopy (Fig. S17, ESI[†]). Further, reaction of **2** with 1,4-cyclohexadiene (bond dissociation energy (BDE) = 77 kcal/mol)³⁸ proceeds at 45 °C, generating a Cu^{II} species with an EPR signal not well defined, but similar to that of **3** (Scheme 1 and Fig. S18, ESI[†]), suggesting that HAA from the allylic C–H bond may occur. Following a similar HAA step, exposure of **2** to 2,4-di-*tert*-butylphenol at 45 °C furnishes the expected C–C coupled dimeric product quantitatively.

Treatment of **2** with either 2,6-di-*tert*-butylphenol or 2,4,6-tri-*tert*-butylphenol at 45 °C instead allows for isolation of 2,6-di-*tert*-butyl-1,4-benzoquinone (identified via GC–MS, major organic product, ESI[†]) along with detection of the same species **3** by EPR spectroscopy (Scheme 2 and Fig. S20, ESI[†]). Oxygenation of 2,6- and 2,4,6-substituted phenols to furnish 1,4-benzoquinone derivative products has been demonstrated with several Cu superoxide complexes.^{12, 15, 16} Recent mechanistic investigations by Karlin et al.¹⁶ have proposed that the Cu superoxide is involved in both HAA and subsequent reactivity with the phenoxyl radical to effect the overall four-electron oxygenation. The reactivity of **2** is noteworthy considering that the analogous side-on bound antiferromagnetically coupled Cu^{II} superoxide complexes reported display no such chemistry. Complex **2** could potentially rearrange to a terminal O₂ binding mode *in situ* which could then undergo HAA and O-atom transfer as described. Supporting this proposal, reaction of **2** with the radical trap 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO) affords a new Cu^{II} species (Scheme 3 and Fig. S1, ESI[†]). That was identified via X-ray crystallography as the (^{Ar}L)Cu(O–DMPO) adduct (**4**) (Fig. S28, ESI[†]). Although the mechanism of O–O bond cleavage and formation of **4** is unclear at the moment, this result is in line with a superoxide character of the bound O₂ moiety in **2**.

Interestingly, despite the electrophilic character inferred from the HAA ability of **2**, the Cu/O₂ adduct can also engage in acid/base chemistry (Scheme 2). Addition of dioxygen to a benzene solution of **1** and phenol furnishes two new Cu^{II} species as indicated by EPR spectroscopy (Fig. S23, ESI[†]). No C–C coupled product is detected by ¹H NMR or GC–MS, suggesting that a phenoxyl radical is not generated during the reaction. Instead, phenol deprotonation and formation of the corresponding (^{Ar}L)Cu(OPh) (**7**) was confirmed via independent synthesis of the phenoxide complex (Figs. S4, S23, ESI[†]). Treatment of **2** with more acidic phenols such as 4-nitrophenol and 2-amino-4-*tert*-butylphenol produces a similar outcome, whereas addition of ammonium chloride furnishes the respective (^{Ar}L)CuCl (**5**) (Figs. S2, S24, ESI[†]). Both Tolman¹⁹ and Itoh¹⁴ have reported formation of copper phenoxides upon reaction of copper superoxide complexes with *para* substituted phenols. In these instances, the hypothesized mechanism involves deprotonation of the phenol unit by the superoxide moiety followed by ligand exchange to arrive at a copper phenoxide and the hydroperoxide radical which subsequently disproportionates into

hydrogen peroxide and water. Indeed, formation of hydrogen peroxide upon treatment of **2** with phenol was confirmed by iodometry (Fig. S25, ESI[†]), suggesting that the reaction likely follows an analogous mechanism as previously described.^{14,19}

The switch in the reactivity of **2** towards phenolic substrates reflects a unique property of the dipyrin Cu/O₂ complex relative to other copper dioxygen species. The similar p*K*_a values (in DMSO) for phenol and 4-methoxyphenol or 2,4,6-tri-*tert*-butylphenol (~17–19)³⁹ suggest that deprotonation over HAA is dictated by the BDE of the O–H bond. As such, **2** undergoes HAA with substrates featuring BDEs³⁸ up to 83 kcal/mol and deprotonates those phenols that necessitate higher oxidative potency for homolytic O–H cleavage, thus demonstrating both electrophilic and basic character. This is not a common feature for other mononuclear copper superoxide complexes in the literature which manifest either reactivity profile, but not both. The end-on Cu^{II} superoxide reported by Itoh is the only other example to date of a Cu/O₂ adduct engaging in acid/base chemistry with 4-*tert*-butylphenol and undergoing HAA activity from TEMPO–H (BDE ~ 70 kcal/mol),³⁸ albeit access to any stronger O–H or C–H bonds (BDE > 70 kcal/mol) was not demonstrated.¹⁴

Complementing the proton and HAA reactivity, **2** also promotes two-electron O-atom transfer chemistry to triphenylphosphine (Scheme 2). Upon addition of dioxygen to a benzene solution of **1** and substrate, regeneration of **1** was accompanied by quantitative formation of triphenylphosphine oxide as confirmed via both ³¹P NMR and GC–MS. No O-atom transfer was detected when **2** was prepared in the presence of dimethylsulfide or alkene sources (i.e., styrene, 1,3-cyclohexadiene), most likely due to the high binding affinity of the copper(I) centre for these substrates.

The foregoing results showcase the isolation of a robust dipyrromethene copper dioxygen adduct. Despite the side-on coordination of O₂, this complex manifests unique reactivity compared to previously described mononuclear Cu(O₂) species: both HAA and acid/base chemistry towards a range of phenolic substrates as well as O-atom transfer to triphenylphosphine. To account for the observed reactivity, we propose an *in situ* formation of a more reactive terminal superoxide complex may precede O-atom transfer, however, an unprecedented substrate activation at the side-on dioxygen moiety cannot be discounted. Overall, the data highlights the importance of the dipyrin platform in stabilizing such reactive entities and promoting desirable transformations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig. 1. Solid state molecular structures for (a) (ArL)Cu (**1**) and (b) (ArL)Cu(O_2) (**2**) with thermal ellipsoids at 50% probability level. Color scheme: Cu, aquamarine; N, blue; O, red. Hydrogens and solvent molecules are omitted for clarity.

Scheme 1.
Reactions leading to formation of complex **3**.

Scheme 2.
Reactivity of $(\text{ArL})\text{Cu}(\text{O}_2)$ (2).

Scheme 3.

Proposed equilibrium between side-on / end-on O₂ bound in **2** and subsequent reaction with DMPO.