

### Communication

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# Intramolecular Hydrogen Bonding Enhances Stability and Reactivity of Mononuclear Cupric Superoxide Complexes

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Supporting Information Placeholder

**ABSTRACT:**  $[(L)Cu^{II}(O_2^{-})]^+$  (i.e., cupric-superoxo) complexes, as the first and/or key reactive intermediates in (bio)chemical Cu-oxidative processes, including in the monooxygenases PHM and D $\beta$ M, have been systematically stabilized by intramolecular hydrogen bonding within a TMPA ligand-based framework. Also, gradual strengthening of ligand-derived H-bonding dramatically enhances the  $[(L)Cu^{II}(O_2^{-})]^+$  reactivity toward hydrogen-atom abstraction (HAA) of phenolic O–H bonds. Spectroscopic properties of the superoxo complexes and their azido analogues,  $[(L)Cu^{II}(N_3^{-})]^+$ , also systematically change as a function of ligand H-bonding capability.

The activation of molecular oxygen with copper is of considerable interest in nature, as well as in oxidative synthetic procedures and in addressing energy concerns (e.g., fuel-cell O<sub>2</sub> reduction catalysts).<sup>1</sup> Reduction of O<sub>2</sub> with Cu<sup>1</sup> leads to complexes with singly or doubly reduced dioxygen (superoxo or (hydro)peroxo, respectively); further important downstream intermediates (viz. Cu<sup>II</sup>-O') form following reductive O-O cleavage.<sup>2</sup> Various Cu<sup>1</sup>-O<sub>2</sub> derived species are suggested to initiate substrate attack leading to O-atom incorporation i.e., net hydroxylation in copper monooxygenases such as peptidylglycine- $\alpha$ -hydroxylating monooxygenase (PHM) and dopamine- $\beta$ -monooxygenase (D $\beta$ M).<sup>3</sup> For these cases, along with the dehydrogenation of RCH<sub>2</sub>OH in galactose oxidase (GO), copper amine oxidase iminosemiguinone H-atom abstraction (HAA) and in GO cofactor biogenesis (HAA from cysteine S-H),<sup>3f</sup> a mononuclear cupric superoxide (Cu<sup>ll</sup>-O<sub>2</sub><sup>--</sup>) intermediate is implicated in effecting key H-atom abstraction (HAA) chemistry.<sup>3b,3c,4</sup>

Thus there have been considerable efforts in the design of appropriate synthetic ligands to probe the factors affecting the formation, stabilization, and reactivity of these metastable  $[LCu^{II}(O_2^{-})]^+$  species.<sup>2b,c,5</sup> For example, increasing electron donation to Cu,<sup>5</sup> providing steric interactions,<sup>6</sup> controlling coordination geometry,<sup>7</sup> and employing cryogenic conditions and suitable solvents<sup>5-8</sup> have each been shown to stabilize the superoxide species and prevent its subsequent reaction with a second equiv of the Cu<sup>1</sup> precursor to yield thermodynamically favored binuclear peroxo bridged dicopper(II) complexes (Eqs. 1 & 2).<sup>9</sup>

$$LCu^{I} + O_{2} \xrightarrow{k_{1}} LCu^{II} - O_{2}^{-} K_{1} (1)$$

$$Cu^{II} - O_{2}^{-+} LCu^{I} - \frac{k_{2}}{k_{2}} LCu^{II} - O_{2}^{2} - Cu^{II} K_{2} (2)$$

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**Figure 1.**  $[(L)Cu^{II}(O_2^{-})]^+$  complexes without (**A**, L = TMPA; tris-(2-pyridyl-methyl)amine) and with internal H-bonding substituents (**B-D**, L = BA, F<sub>5</sub>BA and MPPA), corresponding resonance Raman spectra ( $\lambda_{ex} = 413.1$  nm) of complexes **A-D** in frozen 2-methyltetrahydrofuran (MeTHF) solutions prepared with  ${}^{16}O_2$  (blue) and  ${}^{18}O_2$  (red). Labels indicate the center of the Fermi doublets. See Supporting Information for tabulation of v(Cu–O) values.<sup>10</sup>

H-bonding in the secondary coordination sphere is known to stabilize binuclear  $[{(L)Cu^{II}}_2(O_2^{2^-})]^{2^+}$  and mononuclear  $[(L)Cu^{II}(OOH)]^+$  complexes with N<sub>3</sub>O

and  $N_4$  ligand architecture.<sup>11</sup> Considering extensive recent efforts in studying H-bonding influences on model complexes<sup>12</sup> and in biological systems (for example, this plays a crucial role in stabilizing and activating O<sub>2</sub>-intermediates,<sup>13</sup> effecting nitrite reduction<sup>14</sup> and facilitating neural NOS activity<sup>15</sup>), the importance of H-bonding on [(L)Cu<sup>II</sup>(O<sub>2</sub><sup>--</sup>)]<sup>+</sup> chemistries still remains a fundamental and critical area for study.

In this report, we demonstrate that the imposition of progressively enhancing H-bonding moieties in a series of TMPA-based L-Cu complexes {Figure 1; pKa's of related relevant organic groups: pentafluorobenzylamine (~7) < benzylamine (9.3)}<sup>16</sup> and note that pivalamide and other amides are more acidic than 2° amines} (i) inhibits the formation of corresponding binuclear *trans*- $\mu$ -1,2-peroxo [{(L)Cu<sup>II</sup>}<sub>2</sub>(O<sub>2</sub><sup>2-</sup>)]<sup>2+</sup> complex, in favor of monocopper [(L)Cu<sup>II</sup>(O<sub>2</sub><sup>-</sup>)]<sup>+</sup> species, while (ii) also significantly enhancing the HAA reactivity of the superoxo species toward phenolic substrates.

When a 0.4 mM solution of [(TMPA)Cu<sup>1</sup>(MeCN)]  $B(C_6F_5)_4$  in MeTHF was subjected to dioxygen bubbling at -135 °C and allowed to equilibrate for 30 min, the resulting mixture consisted of the known9 endon superoxide (i.e.,  $Cu^{II} - O - O^{-}$ ) complex A  $\{[(TMPA)Cu^{II}(O_2^{-})]^+\}$  (63% based on Cu (see Section 4.3(a) in the SI);  $\lambda_{max} = 423$  nm,  $\varepsilon = 5600 \text{ M}^{-1} \text{ cm}^{-1}$ ; 752 nm)<sup>10</sup> and the known trans-peroxide dicopper(II) complex [{(TMPA)Cu<sup>II</sup>}<sub>2</sub>(O<sub>2</sub><sup>2-</sup>)]<sup>2+</sup> (37%;  $\lambda_{max} = 525$ , 610 nm) (Figure 2).10 With its ligand derived weak Hbonding (vide infra),<sup>17</sup>  $O_2$ -bubbling of  $[(BA)Cu^{I})]^+$ significantly increased relative amounts of **B**  $\{[(BA)Cu^{II}(O_2^{-})]^+\}$  (83% (see Section 4.3(b) in the SI);  $\lambda_{\text{max}} = 418 \text{ nm}, \epsilon = 4100 \text{ M}^{-1} \text{ cm}^{-1}; 750 \text{ nm}), \text{ compared}$ to  $[\{(BA)Cu^{ll}\}_2(O_2^{2^-})]^{2^+}$  (17%;  $\lambda_{max} = 500, 605 \text{ nm}).^{11}$ However, dramatic stabilization is observed with utilization of F<sub>5</sub>BA, a new ligand capable of stronger than in BA; cupric-superoxide H-bonding  $[(F_5BA)Cu^{II}(O_2^{-})]^+$  (414 nm,  $\varepsilon = 4000 \text{ M}^{-1}\text{cm}^{-1}$ ; 748 nm) is generated exclusively.<sup>10</sup> Employing MPPA,<sup>11C,18</sup> possessing the strongest H-bonding moiety, complex **D** {[(MPPA)Cu<sup>II</sup>( $O_2^{-}$ )]<sup>+</sup>} is formed. These superoxo species, **C** and **D**, are very stable in solution (–135 °C); they are fully formed and there appears to be no hint of any peroxide analog present.<sup>10,19</sup>



**Figure 2.** UV-Vis spectra of oxygenated mixtures of ~ 0.4 mM of  $[(L)Cu^{I}]B(C_{6}F_{5})_{4}$  (L = TMPA, BA,  $F_{5}BA$  and MPPA) at -135 °C in MeTHF after 30 minutes. H-bonding stabilizes superoxide species and prevents *trans*-peroxide formation (see Figures S1-S4).<sup>10</sup>

This systematic H-bonding enhancement of  $[(L)Cu''(O_2)]^+$  stabilization is further supported by corresponding UV-Vis data obtained at [(L)Cu<sup>1</sup>]<sup>+</sup> initial concentrations of 0.1 Mm (see Figures S5-S8).<sup>10</sup> Analogous to synthetic and protein derived oxyheme adducts (formally Fe<sup>III</sup>-O<sub>2</sub> - species), the primary effect of the H-bonding (e.g., for the distal His residue in hemo- or myoglobins) is to dramatically decrease the rate of O<sub>2</sub> dissociation,<sup>20</sup> hence lowering  $k_{-1}$  thereby increasing  $K_1$  (Eq.1). With stronger Hbonding,  $[(L)Cu^{II}(O_2^{-})]^+$  species becomes systematically more stable across B-D. Without the H-bond in  $[(\text{TMPA})\text{Cu}^{\text{II}}(O_2^{\cdot})]^+(\mathbf{A}), k_{-1} \text{ is significant, more Cu(I)}$ becomes available, and  $[(L)Cu^{II}(O_2^{-})]^+$  readily reacts to yield the thermodynamic  $[\{(L)Cu^{II}\}_2(O_2^{2^-})]^{2^+}$ product (Eq. 2).

Resonance Raman (rR) spectroscopy was used to characterize the effect of H-bonding in the series of superoxide complexes A-D in frozen MeTHF solution. Laser excitation (413.1 nm) of each superoxide complex (~1 mM) revealed two sets of <sup>16/18</sup>O isotopesensitive enhanced modes at around 460 and 1120  $cm^{-1}$  (Figure 1), which are characteristic of v(Cu–O) and v(O-O), respectively (the latter appears as a Fermi doublet (Figure 1), consistent with previous observations<sup>21</sup>), of end-on cupric superoxides (see Section 5 in the SI for details).<sup>22</sup> Interestingly, a systematic trend is observed for the A-D complexes where the v(O-O) values<sup>18</sup> increased with enhancing H-bonding ability of the systematically stronger N-H dipoles present across **B-D**. Analogous to previously reported cases,<sup>18,21c</sup> we presume the observed incremental trend in v(O-O) across **B-D** is caused by enhanced structural vibrational coupling and alignment of increased O-O dipole opposite to the systematically increasing N–H dipole.  $[(TMPA)Cu''(O_2)]$ )]<sup>+</sup> (A), without any H-bonding moiety, exhibited the lowest (weakest) O-O stretch as expected.

In parallel, the doubly occupied superoxide  $\pi_{\sigma}^*$  (LMCT donor MO) undergoes more electrostatic stabilization compared to the Cu<sup>II</sup>-dz<sup>2</sup> (LMCT acceptor MO) with increasing H-bonding across the A-D [(L)Cu<sup>II</sup>(O<sub>2</sub><sup>-</sup>)]<sup>+</sup> series which increases the energy of the LMCT ( $\pi_{\sigma}^* \rightarrow Cu^{II}-dz^2$ ) transition;<sup>10</sup> hence, a systematic blue shift is observed in the higher energy LMCT absorption, ranging from 423 nm to 410 nm across A-D (Figure 2 & Table 1).

Table 1. Summary of spectroscopic features (UV-Vis, IR and rRaman) for  $[(L)Cu^{II}(O_2^{-})]^+$  and  $[(L)Cu^{II}(N_3^{-})]^+$  complexes.

	ТМРА	BA	F <sub>5</sub> BA	MPPA
rR O-O stretch $\{\Delta^{18}O_2\}$ (cm <sup>-1</sup> )	1119 {- 61}	1123 {- 64}	1126 {- 64}	1130 {- 63}
$\lambda_{max}$ Cu <sup>II</sup> -O <sub>2</sub> <sup></sup> (nm)	423	418	414	410
$\lambda_{max}$ $Cu^{II}-N_3^{-}$ (nm)	413	402	399	395
IR N≡N stretch (cm <sup>-1</sup> )	2046	2049	2052	2063

To obtain better insight into the H-bonding in these  $[(L)Cu^{II}(O_2^{-})]^+$  complexes, we examined the structures of the azido analogs,  $[(BA)Cu^{II}(N_3)]ClO_4$ ,  $[(F_5BA)-Cu^{II}(N_3)]ClO_4$ and  $[F_5BA)Cu^{II}(OClO_3)(acetone)]ClO_4$  (for syntheses, see the SI).<sup>10</sup> Azide ion bound to Cu<sup>II</sup>-complexes have been previously used to model both electronic and connectivity structural aspects for coordination of a peroxide dianion.<sup>23</sup> With respect to a cupricsuperoxide complex, a Cu<sup>II</sup>-N<sub>3</sub> moiety would be expected to have a very similar Cu<sup>II</sup>-N-N-N binding mode (e.g., bond distances and the  $\angle Cu^{II}$ -N-N angle). The crystal structure of  $[(BA)Cu^{II}(N_3)]^+$  (Figure 3) experimentally determined via single crystal X-ray crystallography revealed a weak but clearly observable H-bond found between the benzyl amino-N-H hydrogen-atom and the azido N-atom (2.17(2) Å)proximal to the Cu(II) ion. The Namino-H...Nazido distance is 2.965(2) Å with  $\angle N_{amino}$ -H... $N_{azido} = 163(2)^{\circ}$ . Similar H-bonding is observed in the F<sub>5</sub>BA analog mentioned above.<sup>10</sup> This interaction, also observed in other  $Cu^{II}$ -(X) (X =  $N_3^{-}$ , OOH or peroxo-Cu) instances with TMPA based ligands possessing internal Hbonding groups,<sup>11,24</sup> supports the notion that the Hbonding in complexes B-D occurs to the proximal Oatom, as depicted in Figure 1.

To further support our suppositions concerning the H- bonding in these  $[(L)Cu^{II}(O_2^{-})]^+$  complexes, we examined



**Figure 3**. Displacement ellipsoid plot (50% probability level) of the cationic  $[(BA)Cu^{II}(N_3^{-})]^+$  at 110(2) K. A list of relevant bond distances and angles is also provided. The H-bonding between the benzylamine and the proximal azide nitrogen is highlighted.

the antisymmetric  $N_3^-$  IR stretch (see the SI Section 7)<sup>10</sup> for the full series of complexes  $[(L)Cu^{II}(N_3^-)]^+$ . The characteristic  $v_{N-N}$  values (Table 1) increased progressively with H-bonding strength across **A-D** presumably due to increase in the triple-bond character of the azido ligand, resulting from removal of electron density from the copper-bound  $N_{azido}$ -atom, mirroring the increase in rRaman O–O stretches in **A-D**. Additionally, the azido  $\rightarrow Cu^{II}$  LMCT band shifts progressively to higher energy with increased ligand H-bonding (Table 1, also see Section 7 in the SI)<sup>10</sup>, consistent with the increasing trend in  $O_2^- \rightarrow Cu^{II}$  LMCT energy across **A-D**.

Elucidation of the oxidative capability and scope of reactivity for  $[(L)Cu^{II}(O_2^{-})]^+$  complexes is a major objective. We expected that systematic increased H-bonding to the  $O_2^-$  should stabilize its  $\pi^*$  orbital and also increase its electrophilicity. Indeed, we have found a striking difference in the reactivity toward phenols (electrophilic HAA) with varying O–H bond strengths, across the **A-D** series.

Reactions with 2,6-di-*tert*-butyl-4-methoxyphenol (DTBP) with a weak O–H bond (BDE = 82.0 kcal/mol in DMSO<sup>25</sup>) were first investigated. [(TMPA)Cu<sup>II</sup>(O<sub>2</sub><sup>--</sup>)]<sup>+</sup> (**A**) reacts with a second-order rate constant of 3.11 × 10<sup>-1</sup>M<sup>-1</sup>s<sup>-1</sup> (-135 °C, MeTHF; Figure 4) as determined by monitoring absorbance decrease at 752 nm due to **A**. [(TMPA)Cu<sup>II</sup>OOH]<sup>+</sup> (~80% yield, see Figure S42) and the corresponding phenoxyl radical were observed, demonstrating a net H-atom transfer from phenol to superoxo.<sup>5b,10</sup> Importantly the corresponding peroxodicopper(II) complex [{(TMPA)Cu<sup>II</sup>}<sub>2</sub>(O<sub>2</sub><sup>2-</sup>)]<sup>2+</sup> is observed to be completely unreactive toward phenols (see Figure S27).<sup>10</sup>

The cupric superoxo complexes possessing intramolecular H-bonds (**B-D**) react more efficiently with DTBP under the same conditions (Figure 4b), with  $k_2$ = 5.73 × 10<sup>-1</sup> M<sup>-1</sup>s<sup>-1</sup> (**B**), 11.47 × 10<sup>-1</sup> M<sup>-1</sup>s<sup>-1</sup> (**C**), and 9.88 × 10<sup>-1</sup> M<sup>-1</sup>s<sup>-1</sup> (**D**). In each case, the phenoxy radical was directly observed by both EPR (g ~ 2.0) and UV-Vis

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(407 nm) spectroscopies (see Section 9.2 in the SI).<sup>10</sup> Formation of the hydroperoxo product (86% yield) by **C** via net HAA from DTBP is also verified by spectrophotometric quatitative analysis of the amount of H<sub>2</sub>O<sub>2</sub> released upon acidification; see Section 9.3 in the SI). Although the spectroscopic data imply that **D** is the most activated in the series, it is less reactive towards DTBP than C. We presume that this apparent anomaly is due to the larger steric interaction of the *tert*-butyl group in **D**, inhibiting bulky substrate approach and decreasing the advantage D should have, with its strongest H-bonding pivalamido group. Notably, **C** could also exert  $\pi$ - $\pi$  stacking interactions with DTBP, facilitating a much favorable substrate approach compared to D, hence resulting in its slightly enhanced reaction rate.

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**Figure 4.** a) UV-Vis monitoring of the reaction of **A** and 2,6-di-*tert*-butyl-4-methoxyphenol; b) contrasting rates of oxidation by **A-D**;  $k_2$  values are given in the text; c) UV-Vis spectra of reaction of **A** with 4-methoxyphenol, showing no reaction; d) reaction of **D** with 4-methoxyphenol and (inset) kinetic trace of the decay of 741 nm band of **D**. See Section 6 in the SI for details.

Further, we tested our  $[(L)Cu^{II}(O_{2}^{-})]^{+}$  complexes **A-D** toward 4-methoxyphenol (MP), a substrate with a stronger O–H bond (BDE = 87.6 kcal/mol in DMSO<sup>25</sup>).  $[(TMPA)Cu^{II}(O_{2}^{-})]^{+}$  was completely unreactive toward 250 equiv of MP at –135 °C (Figure 4c).  $[(BA)Cu^{II}(O_{2}^{-})]^{+}$  (**B**) exhibited exceedingly slow reactivity (completion took > 6 h) and  $[(F_5BA)Cu^{II}(O_{2}^{-})]^{+}$ (**C**) reacted considerably faster.<sup>10</sup> However the kinetic behavior was complicated in these cases, and the final copper complex product could not be identified, similar to the observation by Tolman and coworkers<sup>26</sup> in MP HAA by a Cu<sup>III</sup>-hydroxide complex. The MP reaction with  $[(MPPA)Cu^{II}(O_{2}^{-})]^{+}$  (**D**) was much cleaner, and followed clear second-order decay ( $k_2 = 2.33 \times 10^{-2} \text{ M}^{-1}\text{s}^{-1}$ ). The corresponding hydroperoxo-Cu(II) product was also observed in UV-Vis spectros-copy (Figure 4d). This is the first example of a much stronger phenol being oxidized by a mononuclear cupric superoxide compared to the previously reported cases.

In conclusion, we report for the first time how Hbonding strength in the ligand secondary coordination sphere can be tuned to systematically stabilize cupric superoxide ( $[LCu^{II}-(O_2^{-})]^+$ ) species, control the superoxide-peroxide equilibrium, and concurrently activate the superoxide toward enhanced exogenous O-H substrate oxidation. This was achieved by systematically increasing the electrophilicity of  $[LCu^{II}-(O_2^{-})]^+$  via implementation of differing H-The bonding moieties. structures of the  $[(L)Cu^{II}(N_3)]^+$  analogs suggest that H-bonding occurs to the proximal O-atom in  $([LCu^{II}(O_2^{-})]^+)$  complexes. Further use of H-bonding or other ligand modifications in order to generate cupric-superoxide complexes with greater oxidative capabilities is being explored.

#### ASSOCIATED CONTENT

#### **Supporting Information**

Synthetic and analytical details (methodologies and UV-Vis, EPR, NMR and FT-IR spectra); X-ray diffraction data. This material is available free of charge via the Internet at <u>http://pubs.acs.org</u>.

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#### Notes

The authors declare no competing financial interest.

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## TOC Graphic

