Published in final edited form as:

Angew Chem Int Ed Engl. 2014 May 5; 53(19): 4935–4939. doi:10.1002/anie.201402166.

Observation of a $\text{Cu(II)}_2(\mu\text{-}1,2\text{-peroxo})/\text{Cu(III)}_2(\mu\text{-oxo})_2$ Equilibrium and its Implications for Copper-Dioxygen Reactivity**

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Abstract

Synthesis of small molecule Cu_2O_2 adducts has provided insight into the related biological systems and their reactivity patterns including the interconversion of the $\text{Cu}^{\text{II}}_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-peroxo})$ and $\text{Cu}^{\text{III}}_2(\mu\text{-oxo})_2$ isomers. In this study, absorption spectroscopy, kinetics, and resonance Raman

**These studies were supported by the NIH (DK031450 to EIS; GM60353 to KDK; Postdoctoral fellowship GM085914 to MKE).

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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

data show that the oxygenated product of $[(\text{BQPA})\text{Cu}^{\text{I}}]^+$ initially yields an “end-on peroxo” species, that subsequently converts to the thermodynamically more stable “bis- μ -oxo” isomer ($K_{\text{eq}} = 3.2$ at -90°C). Calibration of density functional theory calculations to these experimental data suggest that the electrophilic reactivity previously ascribed to end-on peroxo species is in fact a result of an accessible bis- μ -oxo isomer, an electrophilic Cu_2O_2 isomer in contrast to the nucleophilic reactivity of binuclear Cu^{II} end-on peroxo species. This study is the first report of the interconversion of an end-on peroxo to bis- μ -oxo species in transition metal-dioxygen chemistry.

Keywords

structure/function; tyrosinase; copper; dioxygen ligands; Raman spectroscopy

Dioxygen binding and activation by hemocyanin, catechol oxidase, tyrosinase, and hydroxy-anilinase^[1] have inspired exploration of the preparative chemistry and structure-function correlations of small molecule Cu_2O_2 adducts.^[2] Only the “side-on peroxo” ($\text{Cu}^{\text{II}}_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-peroxo})$) binding motif has been observed in these enzymes,^[1] while two additional structural types are commonly found in small molecule adducts: “end-on peroxo” ($\text{Cu}^{\text{II}}_2(\mu\text{-}1,2\text{-peroxo})$) and “bis- μ -oxo” ($\text{Cu}^{\text{II}}_2(\mu\text{-oxo})_2$) isomers (Figure 1).^[2] The side-on peroxo and bis- μ -oxo species have been found to be in equilibrium, suggesting the possibility of either functioning as the electrophile in tyrosinase that *o*-hydroxylates phenol during catalysis. Indeed, both mechanistic possibilities are supported by model studies^[3] In contrast, the end-on peroxo species typically behaves as a nucleophile.^[2d, 4]

Thus, we were intrigued by a recent report of phenolate *ortho*-hydroxylation by an end-on peroxo adduct,^[5] a reaction otherwise believed to proceed via electrophilic aromatic substitution.^[3a, 3d] This led us to consider the possible involvement of an unobserved bis- μ -oxo species that possesses the electrophilic character needed to affect a phenol-to-catechol conversion. Depar

Presented here is a reevaluation of the chemistry of a binuclear $\text{Cu}_2(\text{O}_2)$ complex that employs the tripodal amine scaffold, bis(2-quinolylmethyl)-(2-pyridylmethyl)amine (BQPA, Figure 2),^[7] that explicitly demonstrates, for the first time, an end-on peroxo to bis- μ -oxo equilibrium, deduced from UV/Vis and resonance Raman (rR) spectroscopies. The calibration of density functional theory (DFT) calculations to experimental thermodynamic data support involvement of a bis- μ -oxo rather than an end-on peroxo species as the electrophile in the reported^[5] phenolate hydroxylation.

Following earlier investigations into the O_2 -reactivity of $[(\text{BQPA})\text{Cu}^{\text{I}}]\text{PF}_6$ in EtCN,^[7–8] Figure 3 illustrates the UV-Vis spectroscopic progression of the reaction of $[(\text{BQPA})\text{Cu}^{\text{I}}]\text{B}(\text{C}_6\text{F}_5)_4$ **1** with O_2 in THF. Initially, complex **2** with 545 and 620 (sh) nm features forms rapidly and has a similar absorption spectrum to those of previously characterized end-on peroxo species.^[9] Within a few seconds, **2** begins converting to species **3** with an intense 380 nm band. However the transformation is not complete, but rather approaches an equilibrium mixture of **2** and **3** in approximately a 1:3 ratio.

The structure of the oxygenated species **2** and **3** were further probed by rR spectroscopy. Excitation of a solution that contains mostly **2** with 568 nm laser radiation resulted in the observation of four apparent oxygen isotope sensitive features clustered in two distinct regions, 835 cm⁻¹ and 821 cm⁻¹ (¹⁸O₂: 793 cm⁻¹ and 777 cm⁻¹) and 542 cm⁻¹ and 504 cm⁻¹ (¹⁸O₂: 521 cm⁻¹ and 488 cm⁻¹, Figure 4). The former region is consistent with the intraperoxide stretch (νO—O) and the latter is consistent with metal-ligand stretch (νCu—O) of an end-on peroxide core.^[9–10] Excitation of a frozen solution of mostly **3** with 380 nm laser light enhanced an oxygen isotope sensitive feature at 584 cm⁻¹ (¹⁸O₂: 560 cm⁻¹) (Figure 5).

Based on its energy and isotope shift, this feature is assigned as the symmetric νCu—O breathing mode of a bis-μ-oxo species; a similar rR spectrum was observed for the crystallographically characterized [(Me₂tpa)Cu^{III}]₂(μ-O)₂]²⁺ (Figure 2).^[11] These results indicate that the two oxygenated products of [(BQPA)Cu^I]⁺ that are in equilibrium are an end-on peroxo (**2**) and a bis-μ-oxo species (**3**) (Figure 6).^[12]

The detailed assignment of the rR spectra of **2** is complicated by the observation of two νO—O features. This suggested the presence of two peroxo adducts, attributed to the non-symmetric BQPA ligand that would lead to two possible orientations of the pyridyl substituent in the interdigitated dimer (Figure 6), *C_I* symmetric “syn” (**2^{syn}**) and overall *C_i* symmetric “anti” (**2^{anti}**) that contains a *C_{2h}* Cu₂O₂ core. DFT calculations on these two isomers indicate that **2^{anti}** is favored by ~3 kcal (Supporting Information, Table S9). Group theory considerations predict that in the effective

C_{2h} symmetry (**2^{anti}**), only the νCu—O_{sym} vibration transforms as *A_g* and would be allowed, whereas in *C_I* symmetry (**2^{syn}**) both νCu—O_{sym} and νCu—O_{antisym} transform as *A* leading to a total of three expected features in the metal ligand stretching region. For the Cu—O region, two transitions with comparable intensity are observed (Figure 4). In other end-on peroxo complexes, two metal-ligand features are observed and are assigned as dimer νCu—O_{sym} and dimer νCu—O_{antisym} bands at higher and lower energy respectively, with the symmetric stretch enhanced relative to the weaker antisymmetric stretch.^[6a, 13] In the rR spectrum of **2**, the lower energy metal-ligand feature is more intense than the higher energy feature, inconsistent with a simple assignment as the νCu—O_{antisym} stretch. Bandshape analysis of the oxygen isotope sensitive features in the metal ligand stretching region are best fit by three bands with the same bandwidth at 542 cm⁻¹, 512 cm⁻¹ and 491 cm⁻¹ giving an intensity ratio of 1.0:1.0:0.8. Analytical frequency calculations from the DFT structures (see Supporting Information) indicate that the 835 cm⁻¹ and 542 cm⁻¹ features correspond to **2^{anti}** (the νO—O and νCu—O_{sym}, respectively) while the 821 cm⁻¹, 512 cm⁻¹, and 491 cm⁻¹ features arise from **2^{syn}** (the νO—O, νCu—O_{sym}, and νCu—O_{antisym}, respectively).

Additional quantitative information on the nature of the end-on peroxo/bis-μ-oxo equilibrium was determined from modeling stopped-flow kinetics data of the reaction of [(BQPA)Cu^I]B(C₆F₅)₄ with dioxygen.^[14] Fitting the observed spectral changes (Figure 1) to the simplest, sequential model of **1** ⇌ **2** ⇌ **3** (Scheme S1) yields spectra that are inconsistent with the absorption spectra of a pure trans-peroxo or bis-μ-oxo species (Figure S1). Inclusion of an additional pathway where **1** can also convert directly to **3** in a parallel

kinetic model (Scheme 1) remedies the kinetically derived spectra (Figure S1). While both species form simultaneously at the very early stages of the reaction, the formation of the trans-peroxo is preferred by an order of magnitude (i.e., $k_1 > k_2$) and at equilibrium roughly 85% of **3** is formed from **2**. As indicated in Scheme 1 and substantiated by the corresponding Eyring plots with varying initial concentrations of $[(\text{BQPA})\text{Cu}^{\text{I}}]^+$ (**1**) and O_2 (Figures S2), these initial reactions are second order in **1** and first order in O_2 for both the formation of **2** and **3**. Subsequently, **2** is converted in a first order reaction (k_3) to the more thermodynamically stable bis- μ -oxo species **3**; this transformation is zero order in $[(\text{BQPA})\text{Cu}^{\text{I}}]^+$. The same is true for the back reaction k_{-3} from **3** to **2** ($K_{\text{EQ}} = k_3/k_{-3} = 3.2$ at $-90\text{ }^\circ\text{C}$; Table 1). Further, thermodynamic parameters for the parallel kinetic model (Scheme 1) were determined indicating that the formation of the bis- μ -oxo from the trans-peroxo is slightly exergonic ($\Delta H = -0.64 \pm 0.07\text{ kcal/mol}$, $\Delta S = 5.7 \pm 0.3\text{ cal/mol}\cdot\text{K}$).

We sought to computationally model these thermodynamic results by surveying the functional dependence of the end-on peroxo/bis- μ -oxo equilibrium. We also included a series of related copper-dioxygen adducts in the modeling, since TMPA and BPQA yield trans-peroxo species as the thermodynamic product while Me_2tpa (like BQPA) yields a bis- μ -oxo as the thermodynamic product (Figure 2).^[8–9, 11] Of the tested methods, BLYP, BP86, mPWPW91, PBE, and TPSSh correctly predicted Me_2tpa and BQPA to form bis- μ -oxo species and for BPQA and TMPA, end-on peroxo adducts were energetically favored.

This calibrated computational methodology was then applied to the binuclear “end-on” copper-dioxygen complex $[\text{Cu}_2(\text{O}_2)(m\text{-Xyl}^{\text{N}_3\text{N}_4})]^{2+}$ (**4**) (Figure 2) that was recently reported to perform the *ortho*-hydroxylation of 4-methyl-phenolate.^[5] Attribution of this electrophilic reactivity to an end-on peroxo core is significant because it contradicts a sizeable pool of literature that suggests this structural type displays nucleophilic reactivity.^[2d, 4] These calibrated computational methods indicate that a bis- μ -oxo isomer of **4** is in fact energetically accessible. This is in contrast to the DFT calculations reported in reference [5] which suggested that a bis- μ -oxo isomer was $\sim 40\text{ kcal}$ higher in energy. Our calculations differed from the previous report in two major respects. First, using the computational methodology reported in reference [5], we found an alternative structure of the putative bis- μ -oxo species that was $\sim 15\text{ kcal}$ more favorable due to equatorial coordination of the amine ligand (Table S10). Second, the experimentally calibrated methodology developed in this report indicates that the bis- μ -oxo isomer of **4** is within $\sim 2\text{ kcal/mol}$ of the end-on peroxo isomer (Table S12). This is in contrast to the DFT methodology in reference [5] that predicts that the bis- μ -oxo is 25 kcal/mol higher than the end-on peroxo. Thus while experimental data in reference [5] indicate that **4** is an end-on peroxo, the calibrated DFT calculations presented here indicate that a bis- μ -oxo isomer is energetically accessible.^[15] The reaction coordinate for electrophilic aromatic substitution of 4-methyl-phenolate was thus reevaluated using the improved ligand geometries and calibrated method (TPSSh is shown in Figure 7). The bis- μ -oxo was found to have both a larger driving force and a lower barrier to *ortho*-hydroxylation than the end-on peroxo despite being slightly higher in energy in the absence of an interaction with 4-methylphenolate (2 kcal/mol). Our present experimental findings with BQPA provide precedent that the end-on species **4** can convert to a bis- μ -oxo species,

which is computationally capable of performing the electrophilic aromatic substitution observed experimentally for the *m*-Xyl^{N3N4} system.

In conclusion, analysis of the oxygenation of [(BQPA)Cu^I]⁺, utilizing rR spectroscopy, kinetics analyses, and DFT calculations has led to the observation of an end-on peroxo/bis-μ-oxo equilibrium, featuring formation of the end-on peroxo isomer followed by its conversion to the thermodynamically more stable bis-μ-oxo species (Scheme 1, $K_{eq} = 3.2$ at $-90\text{ }^{\circ}\text{C}$); a first in transition metal-dioxygen chemistry. This equilibrium sheds light into the reactivity patterns in Cu₂O₂ chemistry, and strongly suggests that the nucleophilic reactivity pattern of end-on peroxo species holds, in contrast to the recent literature wherein electrophilic reactivity has been proposed.

Experimental Section

BQPA was synthesized as previously reported^[7] and metalated with [Cu^I(CH₃CN)₄](BC₆F₅)₄ to form [Cu^I(BQPA)](BC₆F₅)₄ (See Supporting Information). Low temperature stopped-flow kinetics were carried out as previously described and for numerical analysis, all data were pretreated by factor analysis and concentration profiles were calculated by numerical integration.^[8, 16] rR samples were prepared by adding dioxygen to solutions of [Cu^I(BQPA)](BC₆F₅)₄ in dry, degassed THF (See Supporting Information for details). DFT calculations were performed using Gaussian03.^[17] Molecular structures were optimized using the B3LYP functional within the spin-unrestricted formalism on an ultrafine integration grid. The basis sets employed on Cu, O, and N were of triple-ζ quality with polarization (6–311g*). A double-ζ quality, split-valence basis was used on all other atoms (6–31g*). The functional dependence of the end-on peroxo/bis-μ-oxo equilibrium was determined from solvated single point energies (PCM model in THF) for the tested functionals (BLYP, BP86, mPWPW91, PBE, TPSSH, B3LYP, BMK, M06, M06-L, mPW1PW91, τHCTH, TPSS, VSXC) with the same basis set and B3LYP thermal correction at $-80\text{ }^{\circ}\text{C}$.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. a) Solomon EI, et al. Chem Rev. 2014;10.1021/cr400327tb) Ginsbach JW, Kieber-Emmons MT, Nomoto R, Noguchi A, Ohnishi Y, Solomon EI. Proceedings of the National Academy of Sciences. 2012; 109:10793–10797.
2. a) Kitajima N, Moro-oka Y. Chem Rev. 1994; 94:737–757. b) Mirica LM, Ottenwaelder X, Stack TDP. Chem Rev. 2004; 104:1013–1045. [PubMed: 14871148] c) Lewis EA, Tolman WB. Chem Rev. 2004; 104:1047–1076. [PubMed: 14871149] d) Hatcher LQ, Karlin KD. J Biol Inorg Chem. 2004; 9:669–683. [PubMed: 15311336]
3. a) Nasir MS, Cohen BI, Karlin KD. J Am Chem Soc. 1992; 114:2482–2494. b) Pidcock E, Obias HV, Zhang CX, Karlin KD, Solomon EI. J Am Chem Soc. 1998; 120:7841–7847. c) Holland PL, Rodgers KR, Tolman WB. Angew Chem Int Ed Engl. 1999; 38:1139–1142. d) Mirica LM, Vance MA, Rudd DJ, Hedman B, Hodgson KO, Solomon EI, Stack TDP. Science. 2005; 308:1890–1892. [PubMed: 15976297] e) Company A, Palavicini S, Garcia-Bosch I, Mas-Balleste R, Que L, Rybak-Akimova EV, Casella L, Ribas X, Costas M. Chem-Eur J. 2008; 14:3535–3538. [PubMed: 18611111]

- 18348133] f) Qayyum MF, Sarangi R, Fujisawa K, Stack TDP, Karlin KD, Hodgson KO, Hedman B, Solomon EI. *J Am Chem Soc.* 2013; 135:17417–17431. [PubMed: 24102191]
4. Paul PP, Tyeklár Z, Jacobson RR, Karlin KD. *J Am Chem Soc.* 1991; 113:5322–5332.
5. Garcia-Bosch I, et al. *Angew Chem Int Ed Engl.* 2010; 49:2406–2409. [PubMed: 20191646]
6. a) Maiti D, Woertink JS, Narducci Sarjeant AA, Solomon EI, Karlin KD. *Inorg Chem.* 2008; 47:3787–3800. [PubMed: 18396862] b) Lucas HR, Li L, Sarjeant AAN, Vance MA, Solomon EI, Karlin KD. *J Am Chem Soc.* 2009; 131:3230–3245. [PubMed: 19216527]
7. Wei N, Murthy NN, Chen Q, Zubieta J, Karlin KD. *Inorg Chem.* 1994; 33:1953–1965.
8. Karlin KD, Wei N, Jung B, Kaderli S, Niklaus P, Zuberbühler AD. *J Am Chem Soc.* 1993; 115:9506–9514.
9. Jacobson RR, Tyeklar Z, Farooq A, Karlin KD, Liu S, Zubieta J. *J Am Chem Soc.* 1988; 110:3690–3692.
10. a) Tyeklar Z, Jacobson RR, Wei N, Murthy NN, Zubieta J, Karlin KD. *J Am Chem Soc.* 1993; 115:2677–2689. b) Baldwin MJ, Ross PK, Pate JE, Tyeklar Z, Karlin KD, Solomon EI. *J Am Chem Soc.* 1991; 113:8671–8679.
11. Hayashi H, Fujinami S, Nagatomo S, Ogo S, Suzuki M, Uehara A, Watanabe Y, Kitagawa T. *J Am Chem Soc.* 2000; 122:2124–2125.
12. In an earlier kinetic analysis^[8], it was suggested that a cupric superoxo species was formed following the end-on peroxo species. At this time, a $\text{Cu}^{\text{III}}_2(\mu\text{-oxo})_2$ species had not been discovered.
13. a) Lee Y, et al. *Inorg Chem.* 2009; 48:11297–11309. [PubMed: 19886646] b) Lee Y, et al. *Inorg Chem.* 2010; 49:8873–8885. [PubMed: 20822156]
14. An initial report on the solution kinetics and the equilibrium was published in a meeting abstract, see Wick PK, Karlin KD, Suzuki M, Zuberbühler AD. *Micron.* 2004; 35:137–139. [PubMed: 15036318]
15. While one might expect that an energetically accessible bis- μ -oxo isomer in 4 would oxygenate thioanisole, no reaction was previously observed.^[5] This lack of this reactivity may be complicated by the coordination of thioanisole in the open coordination site in 4, stabilizing the end-on peroxo isomer relative to the bis- μ -oxo.
16. a) Karlin KD, Nasir MS, Cohen BI, Cruse RW, Kaderli S, Zuberbühler AD. *J Am Chem Soc.* 1994; 116:1324–1336. b) Zhang CX, Kaderli S, Costas M, Kim E, Neuhold YM, Karlin KD, Zuberbühler AD. *Inorg Chem.* 2003; 42:1807–1824. [PubMed: 12639113] c) Karlin KD, Zhang CX, Rheingold AL, Galliker B, Kaderli S, Zuberbühler AD. *Inorg Chim Acta.* 2012; 389:138–150.
17. Frisch, MJ., et al. Gaussian 03, revision E.01. Gaussian, Inc; Wallingford, CT: 2004.

Figure 1.
 Cu_2O_2 isomers.

Figure 2.
Ligand scaffolds.

Figure 3.

Time-dependent UV-vis spectra (207 s) for the oxygenation of $[(\text{BQPA})\text{Cu}^{\text{I}}]^+$ **1** in THF at -98.6°C and absorbance–time traces at 380 nm and 550 nm (insert). Initially, the 370 nm band of **1** decays as the spectral features of **2** forms (—) followed by the decay of **2** and the growth of **3** (– –).

Figure 4.

Resonance Raman spectra of **2**, prepared with natural abundance O_2 (—) and $^{18}\text{O}_2$ (---) with 568 nm excitation in THF. Inset: Spectrum scaled 5X

Figure 5.
Resonance Raman spectra of **3** prepared with natural abundance O_2 (—) and $^{18}\text{O}_2$ (—) with 380 nm excitation in THF.

Figure 6.
End-on peroxo/Bis-μ-oxo isomerization.

Figure 7. Computational evaluation of electrophilic aromatic substitution by an end-on peroxo (—) and bis-μ-oxo (---) of **4**.

Scheme 1.
Parallel kinetic model.

Table 1

Rates and thermodynamic parameters for the reactions in Scheme 1.

	k (-90 °C)	$H^\ddagger$ (kcal/mol)	$S^\ddagger$ (cal/mol·K)
k_1 ($M^{-2}s^{-1}$)	$(4.3 \pm 0.4) \times 10^5$	-1.4 ± 0.1	-39.4 ± 0.5
k_2 ($M^{-2}s^{-1}$)	$(5.9 \pm 0.2) \times 10^4$	-1.9 ± 0.2	-46 ± 1
k_{-2} (s^{-1})	$(3 \pm 2) \times 10^{-5}$	17.0 ± 0.5	15 ± 3
k_3 (s^{-1})	$(1.6 \pm 0.1) \times 10^{-1}$	10.94 ± 0.05	-1.4 ± 0.2
k_{-3} (s^{-1})	$(5.0 \pm 0.2) \times 10^{-2}$	10.29 ± 0.05	-7.2 ± 0.2