Communication

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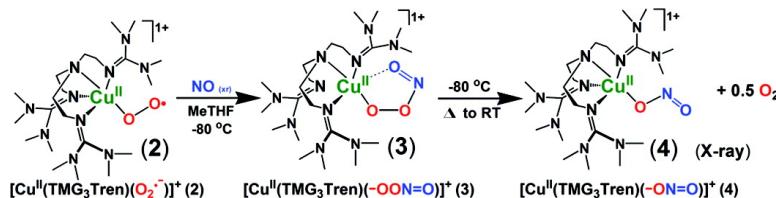
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Reaction of a Copper−Dioxygen Complex with Nitrogen Monoxide (•NO) Leads to a Copper(II)−Peroxynitrite Species

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Peroxynitrite (oxoperoxonitrate (1−), $^-OON{=}O$) is a reactive agent generated by the near diffusion controlled combination of •NO (often called nitric oxide) and the superoxide anion ($O_2^{•-}$) and is considered as a likely mediator of nitric oxide biochemistry and oxidative/nitrative stress injury.[1,2] Metal ions in biological systems may be important in $^-OON{=}O$ generation, stabilization, thermal transformation reactions (e.g., isomerization to nitrate (NO_3^-) or production of nitrite ($+1/2O_2$)), or activation toward substrate oxidation/nitration.[2–4] Heme proteins have been recently well-studied with respect to their mediation of peroxynitrite formation and subsequent transformation to nitrate;[1a,2,5] NO dioxygenases convert NO to nitrate using O_2, putatively via peroxynitrite intermediates.[6] Metal complexes with Fe, heme, Mn, and Cu act as peroxynitrite decomposition (i.e., to nitrate) catalysts and may possess therapeutic applications.[1,7] Discrete metal−peroxynitrite complexes are rare[2] but are suggested to form as transients from metal−NO + $O_{2(g)}$ or metal−O_2 + •NO$_{(g)}$ reactions.[3,8]

Following our interest in Cu oxidative chemistries, we note that the literature solution chemistry of copper ion with peroxynitrite is limited;[4,9] no discrete copper−peroxynitrite species have been described. Here, we report the reaction of •NO$_{(g)}$ with a Cu^I/O_2 adduct, $[(TMG_3tren)Cu^{II}(O_2^{•-})]^+$ (**2**), with end-on bound superoxo ligand, $\angle Cu{-}O{-}O = 123.5°$, $O{-}O = 1.280$ Å.[10] The product is a discrete peroxynitrite−Cu^{II} complex, formulated as $[(TMG_3tren)Cu^{II}(^-OON{=}O)]^+$ (**3**) (Scheme 1). This undergoes a thermal transformation to give a nitrite complex, $[(TMG_3tren)Cu^{II}(^-ONO)]^+$ (**4**), plus dioxygen. The results suggest the viability of biological $Cu^I/O_2/(•NO)$ peroxynitrite formation, that is, *not* coming from free superoxide plus •NO reaction (vide supra) and as perhaps already observed for CuZn superoxide dismutase (SOD)[11] and cytochrome *c* oxidase.[12] Peroxynitrite has been discussed with respect to CuZn−SOD, a vector for disease states; might mutant SODs not abrogate ^-OONO toxicity (i.e., downstream oxidative or nitrative stress) or even produce peroxynitrite?[11,13]

Bubbling $O_{2(g)}$ through a colorless solution of $[(TMG_3tren)-Cu^I]B(C_6F_5)_4$ (**1**) in 2-methyltetrahydrofuran (MeTHF) at −80 °C leads to the EPR silent light green colored complex $[(TMG_3tren)Cu^{II}(O_2^{•-})]B(C_6F_5)_4$ (**2**) $[\lambda_{max} = 447, 680, 780$ nm (Figure S1)].[14,15] With excess O_2 removed by vacuum/purging$_{(Ar)}$, bubbling **2** with •NO$_{(g)}$ (−80 °C; subsequent excess NO$_{(g)}$ removed) gives a yellowish green complex, formulated as the peroxynitrite species $[(TMG_3tren)Cu^{II}(^-OON{=}O)]B(C_6F_5)_4$ (**3**) (Figure S1, $\lambda_{max} = 314$ nm, $\varepsilon = 6900$ M^{-1} cm^{-1}).[15] Direct evidence for the formation of **3** comes from electrospray ionization mass spectrometry (ESI-MS).[15] Injection of −80 °C MeTHF solutions of **3** gives rise to a parent peak cluster with $m/z = 565.15$ and expected ^{63,65}Cu pattern for the $[(TMG_3tren)Cu^{II}(^-OON{=}O)]^+$ cation (Figure 1a).[15] When $^{18}O_{2(g)}$ is used for the generation of **2**, subsequent addition of •NO$_{(g)}$ reveals

Scheme 1
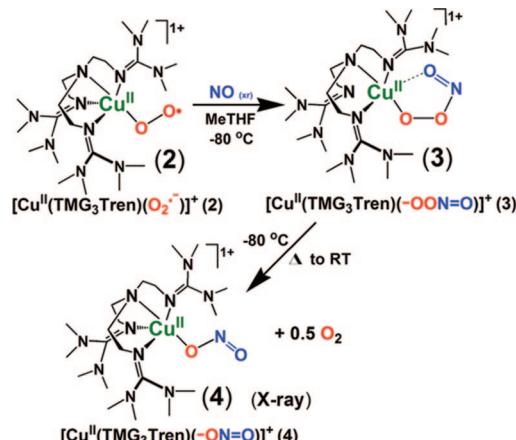
that the peroxynitrite−Cu^{II} peak shifted (by 4 mass units) to m/z 569.34 [Figure 1b; 65% incorporation (also with appropriate ^{63,65}Cu isotope pattern)], indicating that $[(TMG_3tren)Cu^{II}(^{-18}O^{18}ON{=}O)]^+$ has formed;[15] the adjacent peroxo oxygen atoms are derived from O_2 (Scheme 1).[16]

As mentioned, X-ray structures are not known for peroxynitrite−metal species.[2] For the one known isolated complex from Koppenol and co-workers, a k^1-O-OONO binding in $[(NC)_5Co(^-OONO)]^{3-}$ is expected.[2,17] O- and N-bound ^-OONO ligation in various geometries has been considered, especially for iron porphyrinate adducts.[5b,18] DFT calculations, using B3LYP and a mixed triple-ζ basis set, suggest two possible structures for $[(TMG_3tren)Cu^{II}(^-OON{=}O)]^+$ (**3**), a lower energy (by 9.3 kcal/mol in THF) form with monodentate k^1-O-OONO ligation in an overall trigonal bipyramidal (TBP) coordination (d_{z^2} ground state), and a more square pyramidal (SP) form ($d_{x^2-y^2}$ ground
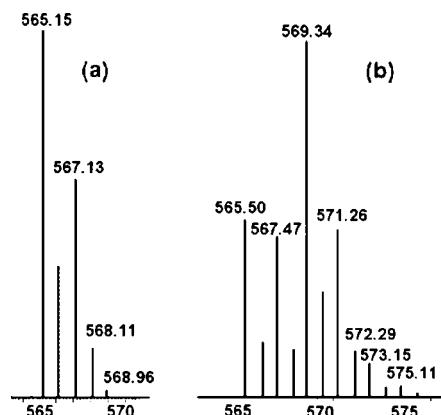
Figure 1. ESI-MS spectra: (a) $[Cu^{II}(TMG_3tren)(^-OON{=}O)]^+$ (**3**) at m/z = 565.15; (b) $[Cu^{II}(TMG_3tren)(^{-18}O^{18}ONO)]^+$ (**3**), m/z = 569.34.

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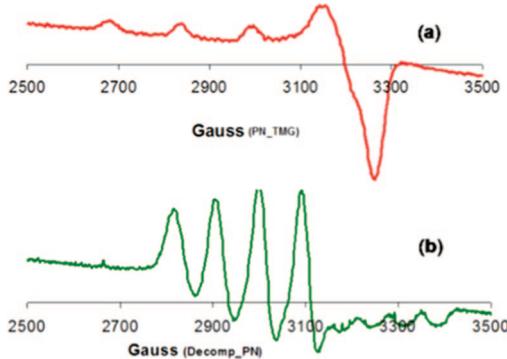
Figure 2. EPR spectrum of (a) **3** (red) and (b) **4** (green).

state) possessing a cyclic bidentate k^2-O,O'-OONO peroxynitrite moiety, with one short equatorial and one long axial Cu—O distance (1.95 and 2.58 Å, respectively).[15] One (TMG$_3$tren) guanidine arm functionality in the SP form is dangling, that is, not ligated, and this arm is replaced by the long Cu—O in the axial position. See Supporting Information for structural diagrams.[15] The EPR spectrum of **3** is distinctly tetragonal with a d$_{x^2-y^2}$ ground state (Figure 2a), thus consistent with the latter (SP) and not the former (TBP) structure. In support of a pentacoordinate SP-type structure for **3** are a number of literature observations: (i) displacement of one arm of the tris(2-aminoethyl)amine (tren) derivative five-coordinate Cu(II) complexes in solution is well-established;[19] (ii) the solid-state structure of [(TMG$_3$tren)—Mo(CO)$_3$] reveals one ligand arm to be uncoordinated;[20] and (iii) SP geometries for many pentacoordinate Cu(II) with tridentate analogues of tren (i.e., [(N$_3$)Cu^{II}X$_2$]$^{n+}$) and bidentate analogues of TMG$_3$tren are documented via X-ray crystallography.[21]

The thermal transformation properties of [(TMG$_3$tren)Cu^{II}-($^-$OON=O)]$^+$ (**3**) support its formulation and provide insights into the observed peroxynitrite chemistry. Prolonged storage of $-$80 °C solutions of **3**, or warming to room temperature leads to >90% yields of the green Cu^{II}—nitrite (NO$_2^-$) complex [(TMG$_3$tren)-Cu^{II}($^-$ONO)]B(C$_6$F$_5$)$_4$ (**4**) [λ_{max} = 350 (sh) (3200), 610 (700) nm, Figure S1], accompanied by the evolution of dioxygen (30$-$35% yield, 50% theoretical), as determined by trapping with a known Cu-based O$_2$ carrier.[15] The structure of **4** was determined by X-ray crystallography,[15] revealing an η^1-O-nitrito bound to Cu(II) ion in an overall trigonal bipyramidal environment. DFT calculations[15] on this structure show that it possesses a d$_{z^2}$ ground state (Figure S12), and an EPR spectrum of **4** (Figure 2b) reveals the reverse axial spectrum expected.[22] The dramatic EPR spectroscopic differences between $^-$OONO (peroxynitrito) complex **3** and ONO$^-$ (nitrito) compound **4** (Figure 2) highlight the distinctly different nature of these species.

The identification of nitrite complex **4** and O$_2$, along with their yields (vide supra), further confirms the Scheme 1 stoichiometry and formulation of peroxynitrite complex **3**. We find no evidence for Cu(II)—nitrate (NO$_3^-$) formation, that is, peroxynitrite isomerization.[15,23]

For **4**, m/z = 549.45,[15] but when the reaction sequence (Scheme 1) is carried out with ^{18}O$_{2(g)}$, this shifts to m/z = 551.12 (78% incorporation, based on an expectation of one of the two O$_2$-derived atoms being incorporated),[15] indicating that [(TMG$_3$tren)Cu^{II}-($^{-18}$ONO)]$^+$ (**4**) has formed. Clearly, an O—O cleavage reaction has occurred. An extensive literature[1a,24,25] known for HOONO conversion to nitrite and O$_2$ may apply; further studies are needed. In fact, related copper(aq) chemistry has been described.[4,9c]

In summary, we have described here the formation, spectroscopic features, and thermal transformation chemistry of the first discrete Cu(II)—peroxynitrite complex. Further studies will focus on the reactivity of this peroxynitrite complex, likely involving peroxynitrite O—O cleavage chemistry. The work described here suggests that copper ion in biological media may facilitate Cu/O$_2$/•NO and thus peroxynitrite chemistry, that is, oxidation and/or nitration.

Supporting Information Available: Details of synthesis; reactivity, product analyses, ESI-MS findings, DFT calculations, and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA801540E