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Controlled nitrene transfer from a tyrosinase-like arylnitroso-copper complex[†]

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The reaction between *p*-nitrosonitrobenzene and the tetramethylpropylenediamine–copper(i) complex yields a dinuclear complex that is structurally and electronically similar to side-on peroxo species known in Cu/O_2 chemistry. The complex reacts with di-*tert*butylphenolate *via* nitrene transfer, as observed through an intermediate and the aminophenol product obtained upon reductive work-up.

Transition metal complexes of non-innocent ligands have attracted much attention recently due to their application in catalysis and molecular switches.^{1,2} In the case of the wellstudied Cu/O₂ chemistry, the extent of dioxygen reduction by electron-rich Cu^I species to the superoxo ($O_2^{\bullet-}$) or peroxo (O_2^{2-}) ligand, as well as the nuclearity of the ensuing Cu/O₂ complex, are controlled by the geometric and electronic properties of the supporting ligands (Scheme 1a).^{3,4} One Cu/O₂ species of interest is the μ - η^2 : η^2 -peroxodicopper(π), **P**, because it is the active oxidant in the ubiquitous enzyme tyrosinase, which promotes oxygen-atom transfer to convert a phenol into a versatile *ortho*quinone (Scheme 1b).^{3–5} But for a few exceptions,^{6,7} the vast majority of Cu/O₂ species characterized outside a protein pocket are typically stable only at low temperatures (-80 °C), which makes them impractical to carry out oxygenation reactions.

Arylnitroso compounds can be used as surrogates for O₂ in reactions with Cu^I and the adducts are stable at room temperature.^{8–10} For example, the electron-rich Cu^I complex with tetradentate ligand Me₆tren reduces nitrosobenzene by one electron to the radical anion, forming [(Me₆tren)Cu^{II}(κ O-PhNO^{•-})]⁺ complexes. These species are structural and electronic mimics of end-on Cu^{II}-superoxo species that are otherwise too transient

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Scheme 1 (a) Typical Cu^{I}/O_{2} reactivity with a bidentate ligand L. (b) Tyrosinase-catalyzed oxygenation of ι -tyrosine during melanogenesis. (c) Synthesis of **1** via redox-controlled self-assembly.

to be isolated. In similar fashion, the one-electron reduction of nitrosobenzene upon binding to low-valent complexes further demonstrates the versatility of arylnitroso species for inner-sphere electron-transfer reactions.^{11,12}

Here, we focus on the bidentate N,N,N',N'-tetramethylpropylenediamine (TMPD) ligand, which, in the case of Cu/O₂ chemistry, stabilizes the bis(μ -oxo)dicopper(III) **O** isomer (Scheme 1a).¹³ The combination of the TMPD–Cu^I complex and an electron-poor arylnitroso substrate yields a **P** mimic that displays tyrosinaselike reactivity (Scheme 1c).

Slow addition in THF at 25 °C of *p*-nitrosonitrobenzene (ArNO) to the TMPD–Cu(I) complex, formed from a 1:1 TMPD–[(MeCN)₄Cu](TfO) mixture,¹³ results in the formation of a deep green complex, **1**, which remains stable for days under inert conditions. Clean samples of **1** are prepared *via* slow addition of a [(MeCN)₄Cu](TfO) solution to a solution of TMPD and ArNO in THF at 25 °C, then precipitated with

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Fig. 1 ORTEP representation of the solid-state structures of the monocations (a) **1** and (b) **2** at 50% ellipsoid probability (hydrogen atoms, noncoordinated TfO-anions and crystallization solvent molecules removed for clarity). Selected bond lengths (Å) and angles (°) for **1**: N1–O1, 1.457(9); Cu1–N1, 1.970(6); Cu1–O1, 1.926(6); Cu2–N1, 1.980(6); Cu2–O1, 1.916(6); Cu1–O2, 2.357(6); Cu2–O3, 2.359(6); Cu1–N2, 1.983(7); Cu1–N3, 1.991(7); Cu2–N4, 1.992(7); Cu2–N5, 2.006(8); N1–C1, 1.447(11); O1–N1–C1, 108.0(6); for **2**: Cu1–N1, 1.889(3); Cu1–O1, 2.165(2); Cu1–N3, 1.989(3); Cu1–N4, 2.018(3); O1–C12, 1.250(4); N1–C7, 1.333(4); C7–C8, 1.419(4); C8–C9, 1.363(5); C9–C10, 1.446(4); C10–C11, 1.360(5); C11–C12, 1.460(4); C7–C12, 1.486(5); N3–Cu1–N4, 102.94(12); N1–Cu1–N3, 139.86(12); N1–Cu1–N4, 115.88(11); N1–Cu1–O1, 79.95(10).

pentane. ¹H NMR spectra of **1** indicate a diamagnetic species with a 2:1 TMPD-ArNO stoichiometry. Crystallization of **1** by slow diffusion of pentane into the reaction mixture at -30 °C afforded crystals that were suitable for X-diffraction analysis. The solid-state structure of **1** (as its TfO⁻ salt, Fig. 1a) is consistent with the solution stoichiometry and shows a dinuclear species in which the NO moiety is bonded side-on to the two Cu centers (μ - η^2 : η^2), along with one of the two triflate ions bridging at axial positions. This coordination mode is reminiscent of the well-known side-on **P** species (Scheme 1).³⁻⁵

As with **P** species in which the O₂ molecule is reduced by two electrons to form the peroxide O_2^{2-} , we propose that the N=O bond of ArNO undergoes 2-electron reduction by the Cu^I precursors to a hydroxylamine dianion in 1. This proposal is based on the significantly lengthened N-O bond in 1 at 1.457(9) Å compared with 1.244(7)-1.253(7) Å in the organic ArNO dimer, ArN(O)N(O)Ar,¹⁴ or other uncoordinated arylnitroso molecules (1.131(11)-1.343(47) Å).15 This bond length matches well with N-O single bond in Diels-Alder adducts of ArNO (N-O = 1.463(5) and 1.4571(16) Å).¹⁶ In addition, the square-pyramidal geometry of the Cu centers is consistent with a Cu^{II} oxidation state. The overall Cu2NO diamond core exhibits a butterfly distortion (38° angle between the two CuNO planes), and the Cu…Cu distance (3.416 Å) is between that for butterfly-distorted P dimers (3.2-3.4 Å)¹⁷ and P species supported by mononucleating ligands (3.45-3.6 Å).³ Quite remarkably, 1 is one of the few crystallographically characterized complexes exhibiting a μ - η^2 : η^2 bonded C-nitroso/hydroxylamine core.9,18,19

The degree of reduction of the ArNO moiety in 1 was further probed by vibrational analysis. Thus, IR spectra of solid 1 and its analogue with an Ar¹⁵NO moiety reveal the presence of

several isotope-sensitive bands (Fig. S6, ESI[†]). Although the bands appear in the fingerprint region and many seem to undergo Fermi splitting, a clear feature is observed at ca. 875 $(\Delta \nu \approx 15)$ cm⁻¹, which we assign to the N–O stretch based on computational investigation (Fig. S6 and S7, ESI†). This value is much lower than for the delocalized double N=O bond in the organic ArNO dimer, ArN(O)N(O)Ar (1238 ($\Delta \nu = 20$) cm⁻¹, Fig. S4, ESI⁺),¹⁵ and lower than in the mononuclear Cu^{II}(η^2 -PhNO^{•-}) species by Warren *et al.* (1113 ($\Delta \nu = 20$) cm⁻¹).⁹ This N–O stretch in 1 is comparable to that of the single N-O bond in primary hydroxylamines (910–920 cm⁻¹),²⁰ mononuclear η^2 -PhNO²⁻ complexes (900 cm⁻¹ range),¹¹ and the analogous μ - η^{2} : η^{2} -PhNO²⁻ Ni^{II} dimer (915 ($\Delta \nu = 14$) cm⁻¹),⁹ with the even lower wavenumber in 1 likely influenced by the p-NO₂ group. The vibrational analysis of 1 thus concurs with the structural analysis, confirming the 2-electron reduction of ArNO into a side-on hydroxylamine dianion that mimics the side-on peroxide in **P** species.

Complex 1 is also similar to P species in terms of electronic structure. Broken-symmetry DFT calculations indicate that 1 is a strongly antiferromagnetically coupled Cu^{II} dimer (1798 cm⁻¹ between the ground singlet and excited triplet states), consistent with the experimentally observed diamagnetism. The calculated and experimental structures of 1 are within a 0.338 rms deviation (0.175 when only considering the first coordination sphere) and reveals a butterfly distorted Cu₂NO core (59° angle between the two CuNO planes). The two UCOs (unrestricted corresponding orbitals) of **1** are each involving the $d(x^2 - y^2)$ of one Cu atom in antibonding fashion with the in-plane π_{σ}^* of the ArNO moiety (Fig. S10, ESI⁺), which is reminiscent of the SOMOs of P species.^{4,21–23} Likewise, the HOMO and LUMO of **1** are involving the out-of-plane π_v^* and the in-plane π_σ^* orbitals of the ArNO moiety, respectively (Fig. 2d and e), as in known P species and the calculated peroxo analogue of 1 (Fig. S14-S16, ESI⁺).



Fig. 2 (a) UV-visible spectrum of 1 (CH₂Cl₂, 25 °C). (b, c) TD-DFTcalculated transitions as difference electron densities (yellow = negative, red = positive). (d) LUMO of 1. (e) HOMO of 1.



Scheme 2 Top: 1:1 reaction of **1** with 2,4-di-*tert*-butylphenolate and reductive work-up to **3**; L = TMPD; (i) CH₂Cl₂, N₂, 25 °C; (ii) saturated aqueous Na₂S₂O₄ work-up, N₂. Bottom: the comparable reaction with a **P** species requires careful protonation to release the **SQ** species; L' = N,N'-di-*tert*-butylethylenediamine; (iii) THF, -80 °C. 1 equiv. H⁺ per phenolate.

The UV-vis spectrum of **1** (Fig. 2), with an intense band at 346 nm ($\varepsilon = 19.4 \text{ mM}^{-1} \text{ cm}^{-1}$) and several features in the visible region, resembles closely the spectra of **P** species,³ particularly when a butterfly distortion is present.¹⁷ TD-DFT calculations reproduce the spectrum accurately (Fig. S12, ESI[†]). The 346 and 640 nm bands correspond to MLCT transitions involving the π_{σ}^* of the nitroso moiety, consistent with the descent in symmetry from a C_{2h} or C_{2v} **P** to C_s in **1**.¹⁷

The electronic structure similarity between 1 and P species portends similar reactivities. Thus, reaction of 1 with 1.0 equivalent of sodium 2,4-di-tert-butylphenolate in CH2Cl2 at 25 °C leads to the fast formation of a deep blue solution, from which diamagnetic complex 2 can be isolated in 76% yield by slow diffusion of pentane at -30 °C (Scheme 2, top). The crystal structure of 2 reveals a TMPD-Cu^I-iminoquinone complex in which the nitrene of *p*-nitroaniline (*p*-NO₂-C₆H₄-N fragment) has formally replaced a hydrogen atom ortho to the phenol. The short C12–O1 (1.250(4) Å) and C7–N1 (1.333(4) Å) bonds and the quinoid C-C bond distribution on the chelating aromatic ring are strong indicators that the new ligand is an iminoquinone, in line with Wieghardt's comprehensive appraisal of such ligands (C-O of 1.24, 1.30, 1.35 and C-N of 1.30, 1.35, 1.37 Å for iminoquinone, iminosemiquinone and aminophenolate ligands, respectively).²⁴⁻³¹ In addition, the trigonal-monopyramidal coordination geometry of Cu in 2 is standard for a Cu^I oxidation state. The dihedral angle between the CuNN_{TMPD} and CuNO_{iminoquinone} planes of 84° strongly contrasts with reported Cu^{II}-iminosemiquinone complexes for which minimal tetrahedral distortion (up to 26°) from square-planarity is consistent with a Cu^{II} oxidation state.³¹ The electronic assignment of 2 is further confirmed by DFT calculations conducted on both singlet (Cu^I-iminoquinone) and triplet (Cu^{II}-semiquinone) forms of 2. Comparison of the optimized structures with X-ray data shows that 2 is compatible with a singlet Cu^I-iminoquinone species (Fig. S18, ESI⁺). Energy analysis indicates that the singlet is stabilized by 11 kcal mol^{-1} over the triplet form (Fig. S12, ESI[†]) and TD-DFT-predicted UV-vis parameters for the singlet do match the features of the experimental spectrum (Fig. S20, ESI⁺).

Reductive work-up of the reaction mixture containing 2 with a saturated $Na_2S_2O_4$ aqueous solution under inert atmosphere

provides novel 2-aminophenol **3** in 80% yield with respect to the phenolate (Scheme 2, top). Noteworthy, the corresponding iminoquinone was too reactive to be isolated, but its Cu^I complex **2** was stable indefinitely in the glovebox. We assign this stability to Cu^I-to-iminoquinone backbonding (Fig. S21, ESI[†]), which diminishes the electrophilicity of organic fragment.

The C-H bond amination of the phenolate into 2 parallels the reaction carried by tyrosinase and its models whereby a P species transfers an oxygen atom to the phenolate via electrophilic aromatic substitution to yield a dinuclear catecholate species C (Scheme 2, bottom).^{5,32} In stoichiometric models of tyrosinase, usually at -80 °C, this catecholate liberates the catechol upon acidic quench. $^{33-37}$ In one instance, C was shown to cleave into a mononuclear Cu^{II}-semiquinone species SQ upon careful acidification, which then liberates a mix of the corresponding catechol and ortho-quinone.³⁸ Complex 2 is similar to SO except for the different valences of Cu and the ring, the iminoquinone being less electron-poor than the quinone. We propose that cleavage of a dimeric C-type intermediate into monomeric 2 does occur. This hypothesis is based on indirect evidence for the formation of [TMPD-Cu^I-OH]⁺ through the products of its disproportionation: the classic $\left[TMPD-Cu^{II}(\mu\text{-}OH)_2Cu^{II}TMPD\right]^{2+}$ species as a precipitate and Cu^0 on the flask walls (while 2 is in solution). In our case, cleavage of the C-type dimer proceeds readily at 25 °C whereas it requires addition of an external acid in the case of Cu/O2 reactions at -80 °C (Scheme 2). We were unable to observe any intermediate between 1 and 2 at temperatures ranging from 25 to -80 °C. The insolubility of the sodium phenolate in CH2Cl2 seems to be important for the cleanliness of the reaction and, at the same time, prevents accumulation of intermediates. Performing the reaction in THF with a soluble phenolate led to intractable mixtures of products, highlighting the sensitivity of oxidant 1 to reaction conditions. Notwithstanding, 1 is selective for nitrogen transfer to the phenolate, and not its oxygen atom (only trace amounts of 3,5di-tert-butyl-o-quinone were observed), a feature which will be the topic of a more in-depth study of 1 and analogous species.

Arylnitroso compounds have long been known to transiently generate nitrenes in their many unwanted side reactions leading to azoxy and azo compounds. Similarly, our control experiments for the phenolate reaction with *p*-nitrosonitrobenzene in the absence of Cu led to a intractable mixture of decomposition products. The clean reactivity of **1** with the phenolate is likely indicative of an inner-sphere mechanism similar to tyrosinaselike oxygenations.^{38,39} Thus, phenolate would first bind to the Cu complex and then intramolecular nitrene transfer would occur. This reactivity contrasts with Cu-catalyzed allylic aminations (nitroso–ene reactions) in which C–N bond formation is thought to occur prior to N–O bond cleavage.^{40–42}

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