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Dioxygen mediated oxo-transfer to an amine and oxidative *N*-dealkylation chemistry with a dinuclear copper complex

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Reaction of dioxygen with a dinuclear copper(I) complex of a new binucleating ligand is described, wherein a peroxo–dicopper(II) (Cu_2–O_2) intermediate leads to an oxo-transfer reaction to give an *N*-oxide of an *N*-benzyl internal ligand substrate; additionally observed regioselective oxidative *N*-dealkylation chemistry occurs.

Copper(I)–dioxygen reactivity studies,[1–6] particularly those involving actual substrate oxidations, are of interest as models for metalloproteins which effect oxidative transformations,[4,5,7,8] and may serve in the development of oxidation reagents. One type of chemistry which we have extensively examined involves O_2-binding and reactivity in the dinuclear complexes where two copper(I) ions each coordinate to a bis[(2-(2-pyridyl)ethyl]amine (PY2) tridentate moiety which is linked through the alkylamino nitrogens by a $–(CH_2)_n–$ (n = 3–5) (**N*n***),[9,10] or *m*-xylyl group (**XYL**);[5,11] in the former case reversible O_2-binding occurs, while in the latter situation, the Cu_2–O_2 intermediate effects xylyl aromatic hydroxylation chemistry. In our continuing effort to investigate the behavior of Cu_2–O_2 species and their reactivities toward internal substrates, we report here the use of a new ligand analogue **D**, with similarities to **N*n*** and **XYL** ligands, but possessing an *N*-benzyl internal moiety. We describe the nature of the O_2-binding to form Cu_2–O_2 species in the dicopper(I) complex of **D**, and novel oxo-transfer and oxidative *N*-dealkylation chemistry. Such reactions occur in copper proteins (*e.g.* peptidylglycine monooxygenase, PHM)[8,12] and heme cytochrome P-450 monooxygenases.[13]

The copper(I) complex $[Cu^I_2(\mathbf{D})]^{2+}$ (**1**) was synthesized by reaction of 2 equiv. of $[Cu^I(MeCN)_4]^+$ with **D**.† An X-ray structure of **1** was obtained (Fig. 1).‡ While both copper(I) ions possess distorted tetrahedral tetracoordination, the binding is highly unsymmetrical; Cu1 ligates to its PY2 tridentate plus the central benzylamine nitrogen atom N7. The other Cu atom (Cu2) has instead as its fourth ligand a perchlorate oxygen atom O5. We have previously observed related asymmetry utilizing trinucleating ligands, either for tricopper(I)[14] or tricopper(II)[15] complexes, wherein three copper ions bind a tridentate chelate, but only one coordinates to a similarly 'central' amine nitrogen. The copper ion moieties are well separated in **1**, with Cu1···Cu2 = 5.43 Å.

At −80 °C in dichloromethane, the dicopper(I) complex $[Cu^I_2(\mathbf{D})]^{2+}$ **1** reacts with excess dioxygen to give a Cu_2O_2 species $[Cu^{II}_2(\mathbf{D})(O_2)]^{2+}$ **2** which gradually decomposes (*vide infra*). Stopped-flow kinetic results show that the reversible (k_1/k_{-1}) formation of species **2** is first order in both **1** and O_2 with k_1 = (10 ± 0.3) $M^{-1}s^{-1}$ (183 K) [$\Delta H^{\ddagger}$ = (15.8 ± 0.8) kJ mol^{-1}, $\Delta S^{\ddagger}$ = (−135 ± 4) J K^{-1} mol^{-1} (183–206 K)}. The UV–VIS spectrum of **2** [λ_{max} = 360 (ε 12 500), 514 nm (ε 1220 dm^3 mol^{-1} cm^{-1})] shows features which are very similar to the Cu_2–O_2 peroxo–dicopper(II) complexes established with **XYL**[6,16] and **N*n***[9] ligands, $[Cu_2(\mathbf{XYL})(O_2)]^{2+}$ and $[Cu_2(\mathbf{N}n)(O_2)]^{2+}$, respectively, indicating that **2** also possesses a μ-η²:η² side-on peroxodicopper(II) core.

As mentioned, an *N*-benzyl moiety was designed into **D** as a potential oxidizable site. Indeed, analysis of products obtained when O_2 is reacted with $[Cu^I_2(\mathbf{D})]^{2+}$ **1** at 0 °C reveals that the *N*-oxide **D**–**O** is obtained (Scheme 1); a labeling experiment shows that the O atom is derived from dioxygen, suggesting an oxygen atom transfer reaction has occurred.§ However, $[Cu^{II}_2(\mathbf{D})(O_2)]^{2+}$ (**2**) is not directly responsible for the formation of **D**–**O**, since if it is allowed to stand at −80 °C, whereupon decomposition occurs, no **D**–**O** forms [kinetics of decomposition: k_2 = (4.5 ± 0.9) × 10^{-4} s^{-1} at 183 K; $\Delta H^{\ddagger}$ = (44 ± 2)

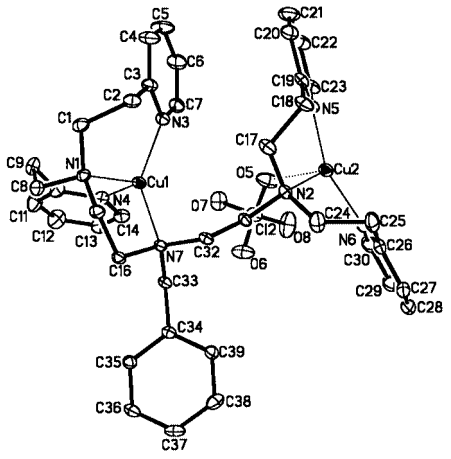
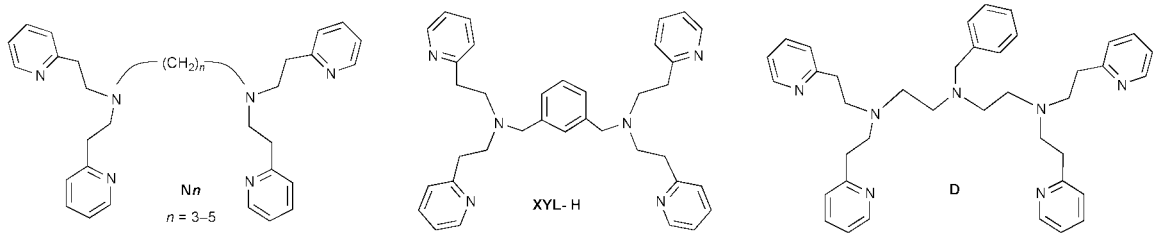
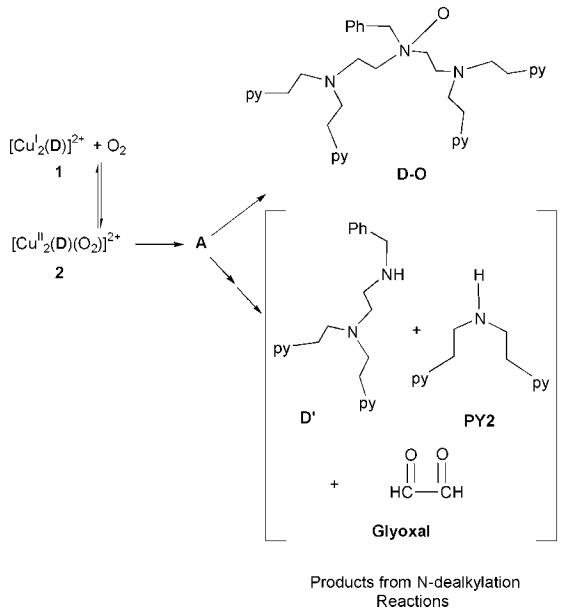


Fig. 1 ORTEP diagram of the cationic portion of complex **1**. Selected bond lengths (Å): Cu1···Cu2 5.432, Cu1–N1 2135(3), Cu1–N3 1.979(3), Cu1–N4 2.024(3), Cu1–N7 2.106(3), Cu2–N2 2.252(3), Cu2–N5 1.927(3), Cu2–N6 1.925(3), Cu2–N6 1.925(3), Cu2–O5 2.551(3).





Scheme 1

kJ mol^{-1}, $\Delta S^{\ddagger}$ = (62 ± 8) J K^{-1} mol^{-1} (198–293 K)]. We suggest that the oxo-transfer reaction, having a relatively large activation energy (*i.e.* higher temperatures are required to see **D**–**O** product), is effected by a very reactive intermediate (**A**; Scheme 1) derived from **2**, which is formed in steady state. Direct formation of the different oxidation products, *i.e.* without formation of intermediate **A**, can be ruled out by the observation that the overall rate constant k_1k_2/k_{-1} shows a perfectly linear Eyring plot between 198 and 293 K. Differentiation between the various oxidation products thus must occur after the rate determining step k_2.

When the oxygenation of [Cu$^{I}_2$(**D**)]$^{2+}$ **1** is carried out at room-temperature and for longer reaction times (> 12 h), additional products derived from oxidative *N*-dealkylation chemistry are produced. **D′** is the amine byproduct from the hydroxylation of one of the non-benzylic methylene carbons adjacent to the middle nitrogen. The other fragment expected from this *N*-dealkylation, an aldehyde, is not isolable; it is further oxidized to yield glyoxal and **PY2** (Scheme 1). Overall, **D′**, glyoxal and **PY2** form in excellent yield and material balance.¶ The fact that this chemistry requires reaction times much longer than the lifetime of the peroxo species [Cu$^{II}_2$(**D**)(O$_2$)]$^{2+}$ **2** ($t_{1/2}$ = 0.01 s at 298 K) indicates that as for the **D**–**O** formation, **2** is not responsible for the oxidative *N*-dealkylation; in another case, a Cu$_2$-O$_2$ intermediate *is* known to effect such reactivity.[17] Here, other complexes derived from the decomposition of **2**, perhaps Cu^{II}–OH–Cu^{II} or Cu^{II}–O–Cu^{II} species, may be responsible. We note that anaerobic addition of 2 [Cu(H$_2$O)$_6$](ClO$_4$)$_2$ and base to **D**, followed by heating, does lead to similar oxidative *N*-dealkylation chemistry. The oxidative *N*-dealkylation chemistry here appears to be regioselective, as benzaldehyde (which would form by oxidation at the most easily oxidizable methylene group) is formed in trace amounts only.

In conclusion, a new dicopper(I) compound, **1**, has been synthesized with a built-in substrate and dissimilar copper(I) environments. [Cu$^{I}_2$(**D**)]$^{2+}$ **1** reacts with dioxygen yielding a peroxo species [Cu$^{II}_2$(**D**)(O$_2$)]$^{2+}$ **2** which decomposes leading to two different ligand transformation reactions: (1) a reactive species, which derives from **2**, is competent to effect an oxo-transfer reaction to give the *N*-oxide **D**–**O**. This appears to be a rare known copper–dioxygen mediated amine to *N*-oxide transformation. (2) With higher temperatures and over longer time periods, the Cu$_2$–O$_2$ species transforms to copper(II) products which effect biomimetic regioselective oxidative *N*-dealkylation chemistry. Additional studies will be directed towards further structural and mechanistic understanding of the chemistry described.

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Notes and references

† Reaction of **D** with 2 equiv. of [Cu(MeCN)$_4$](ClO$_4$) gave **1**(ClO$_4$)$_2$, for which satisfactory C, H and N analyses were obtained.

‡ *Crystal data* for $C_{39}H_{47}Cl_2Cu_2N_7O_8\cdot 3CH_2Cl_2$. M = 1194.59, triclinic, $P\bar{1}$, a = 10.5816(2), b = 14.8247(2), c = 18.0045(2) Å, α = 112.4800(3), β = 97.2565(2), γ = 94.2666(2)°, V = 2565.53(6) Å^3, Z = 2, T = 173 K, $R(F)$ = 0.0469, $R(wF^2)$ = 0.1084. After accounting for the diCu cation and two ClO$_4^-$, a large void space of 644.8 Å^3 containing numerous, but chemically ill defined, difference peaks was resolved using SQUEEZE (A. Spek, PLATON library), which determined the presence of a total of 241 electrons, or *ca.* six molecules of the recrystallization solvent CH_2Cl_2 per unit cell. Due the collective nature of this treatment of solvent, the atom list does not contain individual atomic contributions. All other software was contained in the SHELXTL (5.1) library (G. Sheldrick, Bruker AXS, Madison, WI). CCDC 150146. See http://www.rsc.org/suppdata/cc/b0/b009053k/ for crystallographic data in .cif or other electronic format.

§ When the oxygenation reaction of **1** was carried out at 0 °C in CH_2Cl_2 for 10 min, **D**–**O** was isolated after workup in 47% yield. With an $^{18}O_2$ reaction, an ^{18}O atom is incorporated into **D**–^{18}**O** with 92% efficiency. *Characterization* of **D**–**O**: ^{1}H NMR ($CDCl_3$) δ 2.92 (m, 20H), 3.08 (m, 4H), 4.17 (s, 2H), 7.11–7.14 (m, 8H), 7.40–7.60 (m, 9H), 8.45 (d, 4H); positive ion FAB-MS: **D**–**O** *m/z*: 630.4 (MH$^+$), **D**–^{18}**O** *m/z*: 632.4 (MH$^+$).

¶ Organic products were isolated and characterized from the oxygenation reaction of **1** in DMF at room temperature over 12 h: **D′** (71%) ^{1}H NMR ($CDCl_3$) δ 2.54 (t, 2H), 2.73 (t, 2H), 2.88 (m, 8H), 3.58 (s, 2H), 7.05–7.12 (m, 4H), 7.26–7.36 (m, 5H), 7.50–7.53 (m, 2H), 8.43 (d, 2 H) positive ion FAB-MS *m/z*: 361 (MH$^+$); **PY2** (51%) ^{1}H NMR ($CDCl_3$) δ 2.47 (s, 1H), 3.0-3.3 (m, 8H), 7.13–7.20 (m, 4H) 7.40–7.60 (m, 2H), 8.45 (d, 2H) positive ion FAB-MS *m/z*: 228 (MH$^+$); glyoxal (51.7%, isolated and quantified as its 2,4-dinitrophenylhydrazone) ^{1}H NMR (DMSO-d$_6$) δ 7.96 (d, 2H), 8.47 (q, 2H), 8.88 (s, 2H), 11.89 (s, 2H).

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