Synthesis of a Phenoxy-bridged Copper(I) Dimer and its Reaction with Dioxygen: Implications for the Reversible Binding of O_2 by Hemocyanin

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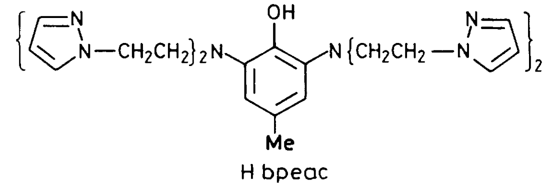
The first copper(I) dimer having only a single phenolate bridge has been prepared and structurally characterized; its irreversible oxidation suggests the importance of site isolation in type III copper proteins.

Oxygen transport in several species of marine organisms utilizes the binuclear copper protein hemocyanin.[1] Model studies for that protein have focused on mimicking the spectroscopic and magnetic properties of the oxidized forms of the protein,[2] but little attention has been paid to preparing structural models for the oxygen-reactive deoxy state, principally because the spectroscopic data for the active site, which contains two Cu^I ions, have been insufficient to define its structure unambiguously.[3] One possible structural element in deoxyhemocyanin is a single phenolate bridge from a tyrosine residue, and we report here the first such synthetic complex and its reaction with dioxygen.†

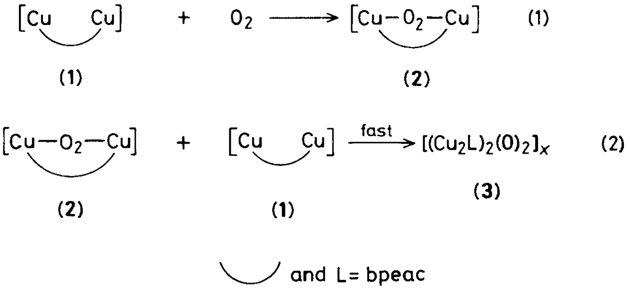
The bimetallic copper(I) complex $[Cu_2(bpeac)][BF_4]$, (**1**) was prepared by stirring the potassium salt of 2,6-bis{*N*,*N*-[2-(2-pyrazolyl)ethyl]amino}-*p*-cresol (Hbpeac)[4] with $Cu(MeCN)_4BF_4$ in methanol under an inert atmosphere. The resulting off-white precipitate was recrystallized from acetonitrile and tetrahydrofuran.

Crystal data: $C_{27}H_{33}BCu_2F_4N_{10}O$, $M = 727.5$, crystal dimensions $0.50 \times 0.25 \times 0.20$ mm, orthorhombic, $a = 20.412(8)$, $b = 23.563(7)$, $c = 12.614(4)$ Å, $U = 6066.7$ Å^3, $Z = 8$, space group *Pbca*, Mo-K_α radiation ($\lambda = 0.71069$ Å), μ(Mo-K_α) = 15.27 cm^{-1}. Intensity data were collected on an Enraf-Nonius CAD-4 diffractometer using graphite monochromated Mo-K_α radiation and the ω—2θ scan method in the range $2 < 2\theta < 50°$. 5319 Reflections were collected and corrected for Lorentz–polarization effects and for absorption. 1817 Unique reflections for which $I > 2\sigma(I)$ were used for the structure determination. The copper atoms were located by the Patterson function; the remaining non-hydrogen atoms were located from difference Fourier maps and refined by full-matrix least squares methods. Hydrogen atoms were included at calculated positions (C–H 0.95 Å). The refinement converged at $R = 0.070$, $R_w = 0.054$, with the copper atoms and the atoms in the inner co-ordination sphere, the pyrazole rings, and the BF_4 anion anisotropic; the function minimized was $\Sigma w(|F_o| - |F_c|)^2$ where $|F_o|$ and $|F_c|$ are the observed and calculated structure factor amplitudes and the weight, *w*, is $4F_o^2/\sigma^2(F_o^2)$.‡

The structure of the cation portion of (**1**) is shown in Figure 1. Each copper ion resides in a distorted tetrahedral environment with Cu–N(pyrazolyl) bond distances between 1.93 and 2.00 Å. The Cu–O bond lengths are much longer than those observed for similar copper(II) species,[2] reflecting the weaker interaction expected.



H bpeac



There are only two types of μ-phenolato copper(I) dimers known, and each requires an additional bridging group for stability. In one, the copper ions are chelated by a macrocyclic ligand that provides two phenolate bridges;[5] and in the other, the copper ions are bridged additionally by a pyrazolate ion[6] to prevent disproportionation or the co-ordination of only a single copper.[7] While several factors may add to the stability of (**1**), the presence of two pyrazole donors probably compensates for the destabilizing influence of the harder phenolate ligand. The isolation of (**1**) demonstrates the viability of phenolate bridging in the deoxy form of the protein.

Ideally, the cavity between the two copper atoms in (**1**) should provide an environment for binding small molecules such as O_2. When (**1**) is treated with dioxygen in acetonitrile or dichloromethane at 238 K, the initially colourless solution turns dark green. However, manometric uptake at 238 K indicates the stoicheiometry of the reaction to be two molecules of (**1**) per oxygen molecule. Since clean isosbestic behaviour is observed by electronic spectroscopy, we believe that the data are consistent with formation of a dioxygen adduct (equation 1) followed by a fast reaction of a second dimer unit with the initially formed dioxygen adduct (equation 2).

The observed four-electron reduction of dioxygen is similar to a reaction of an unrelated binuclear copper complex reported recently by Nelson.[8] In the latter system, the possibility of a μ-1,1-peroxo bridge was suggested. However, in the reaction of (**1**) with O_2, formation of such an adduct is impossible because it would lead to severe cross-bridge contacts between phenolate and peroxide;[3] therefore, a 1,2-peroxy bridge is more likely in this case. The product (**3**), which has so far resisted attempts at isolation, is probably a dimeric or oligomeric μ-oxo species. Since outer-sphere electron transfer would most likely generate the complex $[Cu_2(bpeac)(MeCN)_2]^{3+}$ (**4**), we can rule out outer-sphere

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† *Note added in proof:* After this manuscript was submitted, Karlin *et al.* published an example of a monophenoxy-bridged Cu^I dimer which reacts with dioxygen to form a Cu^{II} peroxide species (K. D. Karlin, R. W. Cruse, Y. Gultneh, J. C. Hayes, and J. Zubieta, *J. Am. Chem. Soc.*, 1984, **106**, 3372).

‡ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

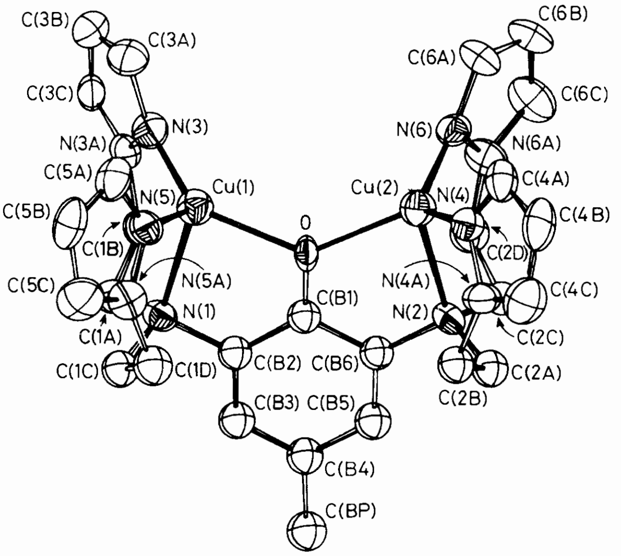

Figure 1. Structure of the Cu_2(bpeac)$^+$ cation showing 40% probability thermal elipsoids. Selected bond lengths (Å) and angles (°): Cu(1)–Cu(2) 3.825(3), Cu(1)–O 2.077(8), Cu(1)–N(1) 2.191(10), Cu(1)–N(3) 1.927(12), Cu(1)–N(5) 2.001(13), Cu(2)–O 2.093(8), Cu(2)–N(2) 2.199(10), Cu(2)–N(4) 1.987(13), Cu(2)–N(6) 1.959(12); Cu(1)–O–Cu(2) 133.0(4), O–Cu(1)–N(1) 82.1(4), O–Cu(1)–N(3) 122.6(4), O–Cu(1)–N(5) 115.9(4), N(1)–Cu(1)–N(3) 101.4(5), N(1)–Cu(1)–N(5) 99.2(5), N(3)–Cu(1)–N(5) 119.8(5), O–Cu(2)–N(2) 81.1(4), O–Cu(2)–N(4) 117.6(4), O–Cu(2)–N(6) 117.2(4), N(2)–Cu(2)–N(4) 99.7(5), N(2)–Cu(2)–N(4) 102.9(5), N(4)–Cu(2)–N(6) 123.0(5).

processes on the basis of the dissimilarity between the electronic spectra for (**3**) and (**4**), generated from Hbpeac and $Cu(MeCN)_4(BF_4)_2$[9] in acetonitrile; treatment of (**3**) with HBF_4 generates a species with the same spectrum as that for (**4**).

This work demonstrates two important points: first, copper(I) dimers with a single phenolate bridge can be isolated as stable entities; therefore, any proposed structure for deoxyhemocyanin must consider the possibility of μ-phenoxy co-ordination. Secondly, this work suggests that as in the case of oxyhemoglobin,[10] oxyhemocyanin must owe its stability to site isolation by the protein milieu which prevents the bimolecular, four-electron reduction of dioxygen. Thus, a sterically hindered analogue of (**1**) should inhibit reaction (2), a hypothesis that we are currently exploring.

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