Studies on a Model Copper Mono-oxygenase System: Peroxo–Cu^{II} Binuclear Intermediates in the Hydroxylation of an Aromatic Ring

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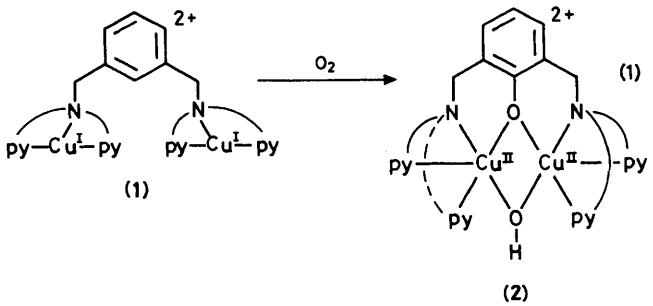
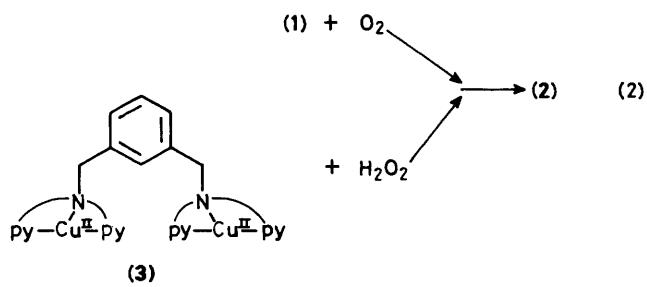
Hydrogen peroxide reacts with a Cu^{II} complex of a *m*-xylyl binucleating ligand with concomitant hydroxylation to give a phenoxo-bridged complex (previously found as the product of the reaction of dioxygen with the Cu^{I} analogue) whereas a newly synthesized mononuclear analogue is unreactive, thereby implicating μ-peroxo–Cu^{II} intermediates in the hydroxylation reaction.

The mechanism of dioxygen activation by copper containing mono-oxygenase enzymes such as tyrosinase[1] and dopamine mono-oxygenase[2] is of current interest.[3] The discovery of a model system based on a Cu^{I} complex of a *m*-xylyl (xyl) binucleating ligand, $Cu_2(m\text{-xyl})^{2+}$ (**1**), and characterization of reactants and products by *X*-ray crystallography[4] has led to a more detailed study of the mechanism of copper-mediated hydroxylation. In this reaction, (**1**) reacts with dioxygen to give specific hydroxylation of the aromatic xylyl moiety producing the phenoxo- and hydroxo-bridged binuclear Cu^{II} complex (**2**) with stoicheiometry that agrees with that of a mono-oxygenase reaction.[4b,5] In this communication, we report new developments in the chemistry represented by equation (1) which support the view that peroxo-bridged dicopper(II) intermediates are required for hydroxylation in this system.

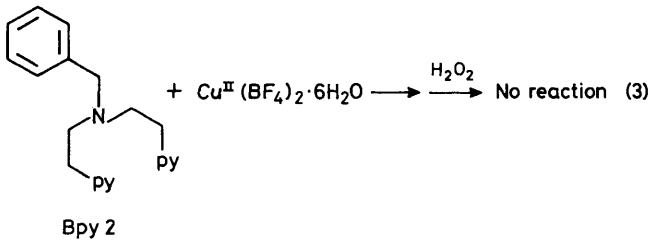
Binuclear Cu^{II} analogues, (**3**), of (**1**) were produced by the reaction of two equiv. of either $Cu(BF_4)_2\cdot 6H_2O$ or $Cu(NO_3)_2\cdot 3H_2O$ with the *m*-xyl ligand. Compounds (**3**) reacted with hydrogen peroxide to give the same hydroxylated product (**2**) [>90%, identified by i.r. and u.v.–visible spectroscopy and t.l.c. on the free ligand obtained from (**2**) by treatment with strong base]. No hydroxylation was observed



py = 2-pyridyl



Suggests a Cu^{II}–(O_2^{2-})–Cu^{II} intermediate.



in the reaction of free *m*-xyl with H_2O_2 or when (**3**) was first treated with ethylenediaminetetra-acetic acid in aqueous dimethylformamide (DMF). This result suggests that a peroxo–Cu^{II} species is a common intermediate in pathways developing either from Cu^{I}–O_2 or Cu^{II}–H_2O_2 [equation (2)].

To confirm that *two* Cu ions are required for efficient hydroxylation, we have also examined the reaction chemistry of the mononuclear complexes containing the ligand Bpy2, where an N_3 donor atom set identical to that in *m*-xyl has a similarly positioned *N*-substituted benzyl group as a potential 'substrate'. $Cu^{I}(Bpy2)PF_6$ (**4**) was synthesized by treatment of $Cu(MeCN)_4PF_6$ with Bpy2 in tetrahydrofuran and crystallized from CH_2Cl_2–Et_2O,[6] whereupon an *X*-ray crystal analysis of (**4**) was carried out.

Crystal data for (**4**): $[C_{21}H_{23}CuN_3]PF_6$, orthorhombic, space group *Pcab*, $a = 13.849(5)$, $b = 15.551(7)$, $c = 20.503(9)$ Å, $U = 4415.5$ Å^3, $Z = 8$, $D_c = 1.58$, $D_m = 1.56$ g cm^{-3}, Mo-K_α radiation ($\lambda = 0.71069$ Å). The positional parameters of the copper atom were determined by the Patterson method. The remaining atoms were located on difference-Fourier maps. A total of 1370 unique reflections [with $I > 3\sigma(I)$] were refined to $R = 0.075$ and $R_w = 0.079$.† The cation (Figure 1) displays planar co-ordination which is distorted from trigonal, analogous to that found in complex (**1**).[4]

In solution, $Cu(Bpy2)^+$ reacted rapidly with dioxygen, producing oxo- or hydroxo–Cu^{II} species,[6] but no hydroxylation of the ligand occurred. By analogy with the binuclear complexes (**3**), a monomeric Cu^{II} analogue of (**4**) was prepared from Bpy2 and $Cu(BF_4)_2$. No hydroxylation of the Bpy2 ligand occurred upon mixing of this compound with H_2O_2 in DMF–H_2O [equation (3)]. Thus, we conclude that a peroxo-bridged intermediate involving *two* Cu ions must be the precursor to oxygen atom transfer in the reaction (**1**) → (**2**). Further support for this conclusion is derived from the observation that hydroperoxides such as EtOOH and Bu^tOOH, which are not expected to form bridged species readily,[7] did not react efficiently with (**3**) to give the hydroxylated product.

The mechanism of formation of the μ-peroxo–Cu^{II} intermediate from the reaction of O_2 with (**1**) is at present under investigation. Preliminary results based on oxygen uptake kinetics in pure DMF indicate more complex behaviour than simple bimolecular reaction of O_2 with (**1**). Copper(I) co-ordinating ligands such as pyridine slow the reaction and simplify the kinetics. In 3% pyridine–DMF mixtures, a rate law $-d[O_2]/dt = k[O_2][Cu_2(m\text{-xyl})]^2$ is found. Nevertheless, clean hydroxylation ensues so that the second order dependence on binuclear copper(I) complex suggests an intermolecular reaction pathway.

† 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.

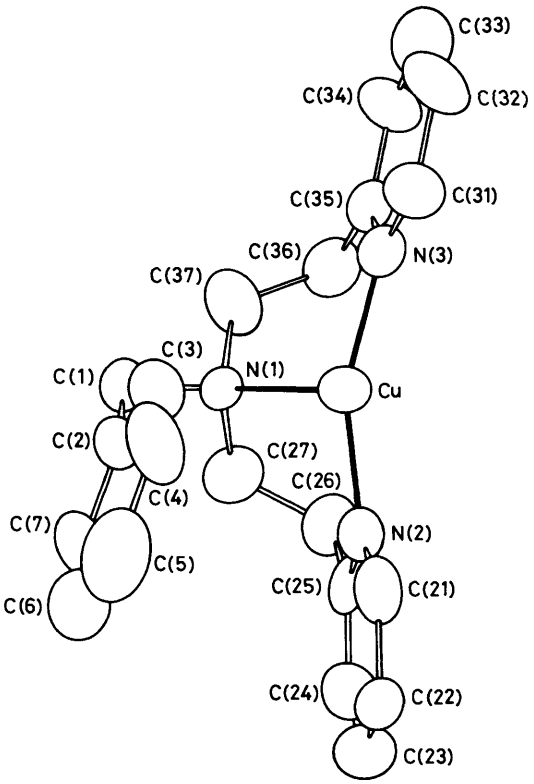


Figure 1. ORTEP Diagram of the [Cu(Bpy2)] cation of (**4**) showing the atom labelling scheme. Selected bond lengths (Å) and angles (°) are Cu–N(1) 2.216(10), Cu–N(2) 1.893(10), Cu–N(3) 1.873(9); N(1)–Cu–N(2) 99.6(4), N(1)–Cu–N(3) 98.8(4), N(2)–Cu–N(3) 158.4(4).

Thus, comparison of analogous binuclear Cu^{I}–O_2, binuclear Cu^{II}–peroxide, and monomeric Cu^{II}–peroxide systems in hydroxylation of the internal aromatic substrate has provided good evidence for the involvement of bridged peroxo–Cu^{II} intermediates. However, kinetic evidence demonstrates that different routes to these intermediates involving both intra- and inter-molecular pathways must be considered.

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