# Model Monooxygenase Reactivity by Binuclear Two-coordinate Copper(I) Complexes extends to New Ligand Systems Containing Nitrogen and Sulphur Donors

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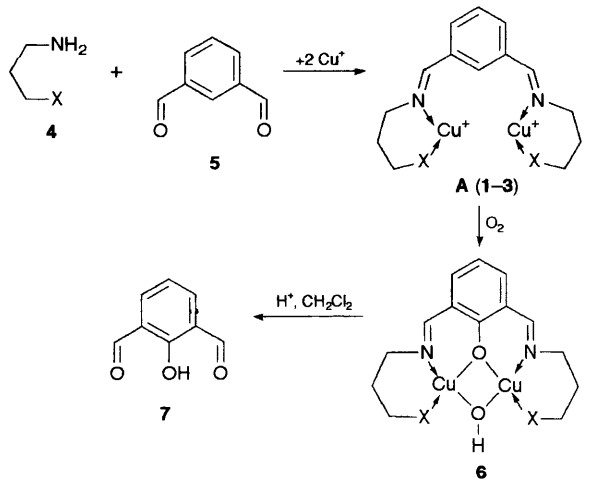
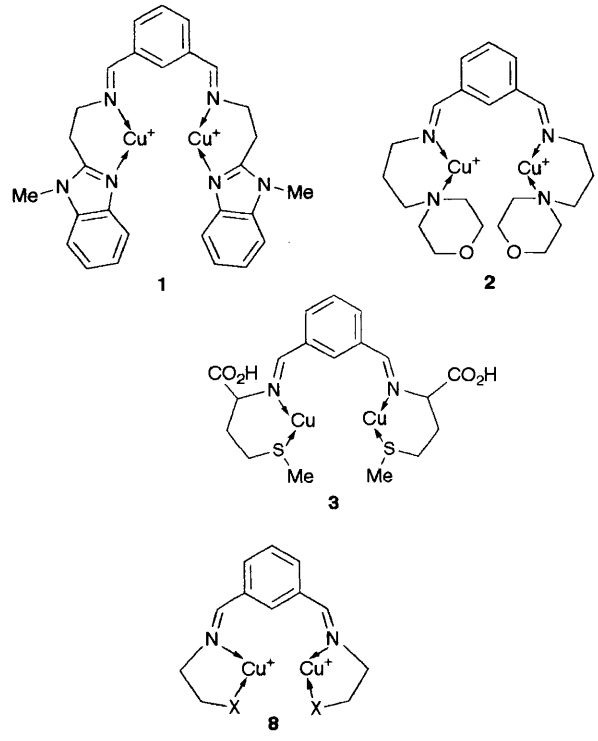
The oxygen insertion reaction exhibited by binuclear two-coordinate copper(I) complexes derived from bis-imine ligands extends to systems containing additional benzimidazole, tertiary amine and thioether donor groups; an inverse correlation has been found between the rate of the reaction and the basicity of the donor group.

Biomimetic investigations of copper-mediated monooxygenase reactions have produced a few binuclear copper(I) complexes with nitrogen donors which react with dioxygen mimicking the aromatic hydroxylation reaction catalysed by tyrosinase.[1] The structure of this enzyme is not known, but it is thought[2] to be closely related to that of the dioxygen carrier protein hemocyanin,[3a] which contains two copper ions in close proximity (~3.6 Å) in the active site, each bound to three imidazole groups.[3b,c] One of these imidazoles is bound more weakly, though,[4] and may be less important for activity. The first synthetic model for tyrosinase was reported by Karlin *et al.*;[5] it consists of a binuclear copper(I) complex in which a *m*-phenylenedimethyl bridging ligand provides two pyridine and one tertiary amine nitrogen donors to each copper(I) ion.




**Scheme 1** Preparation of complexes **1–3**







Subsequently, we reported simpler model systems in which a Schiff base binucleating ligand provides only one imine and one imidazole nitrogen donors per copper(I).[6] Replacement of the imidazole groups by pyridine donors in these systems was shown later not to alter the reactivity to dioxygen.[7]† The activity of Karlin's model system seems to depend strictly on the presence of the pyridine donors; replacement of these groups with other nitrogen heterocycles leads, in fact, to complete inhibition of the oxygen insertion reaction.[1c,8] By contrast, we report here that the monooxygenase reactivity of the binuclear copper(I) complexes derived from the bis-imine ligands can be extended to a range of systems containing nitrogen and even sulphur donor atoms.

The binuclear copper(I) complexes **1–3** were prepared by metal template condensation of the amines **4**‡ with benzene-1,3-dicarbaldehyde **5** in the presence of $Cu(MeCN)_4ClO_4$, under an inert atmosphere, as described previously[6b] for the imidazole-containing analogues (Scheme 1). The yellow dicopper(I) complexes were obtained in 30–60% yield; **1** and **2** contain a bound acetonitrile molecule per copper(I).§ Complexes **1–3** form weak carbonyl adducts in solution, with ν(CO) near 2100 $cm^{-1}$. The presence of six-membered chelate rings seems crucial for the stability of binuclear copper(I) complexes **1–3** since all attempts to prepare complexes of type **8** containing five-membered chelate rings were unsuccessful.

When dilute solutions ($10^{-3}$–$10^{-4}$ mol $dm^{-3}$) of **1–3** in methanol are exposed to dioxygen a rapid colour change from yellow to green takes place. The reactions are complete in a few minutes and the spectral properties of the resulting solutions, with prominent near-UV bands near 360 nm, are clearly indicative of the presence of the phenoxo-bridged binuclear copper(II) complexes **6**.[6b] The oxygenation is accompanied by simple oxidation of copper(I), though. The relative importance of the oxygenation and oxidation pathways for **1–3** can be established by the ratio between 2-hydroxybenzene-1,3-dicarbaldehyde **7**, and benzene-1,3-dicarbaldehyde **5**, isolated as mixtures upon treatment of the product residues, after evaporation of the solvent, with mineral acids and extraction with dichloromethane. The molar ratio of **7** to **5**, established by $^1H$ NMR spectroscopy, corresponds to 70 : 30 for **1**, 40 : 60 for **2**, and 50 : 50 for **3** when $10^{-3}$ mol $dm^{-3}$ solutions of the copper(I) complexes in methanol are exposed to dioxygen at 20 °C.¶

Although a detailed kinetic analysis of the reaction systems is complicated by the presence of competitive oxygenation and oxidation pathways, comparative experiments including the copper(I) complexes **A** with X = *N*-methylimidazole[6a,b] and pyridine[7] show that the rate of growth of the 360 nm band of **6** is inversely correlated with the basicity of the nitrogen donor group (Scheme 2).

The slower reactivity of the methionine complex **3** is probably due to the stabilization of the copper(I) state by the thioether ligand. When carefully dried acetonitrile is used as solvent the oxygenation is largely to completely depressed in favour of simple copper(I) oxidation. These results suggest that an electrophilic copper–peroxo or copper–hydroperoxo complex may represent the active species in the hydroxylation process.

† A related ligand hydroxylation system reported by Menif and Martell[1e] contains three-coordinate copper(I) centres.

‡ Methionine and 4-(2-aminoethyl)morpholine were commercially available products. 1-Methyl-2-(2-aminoethyl)-benzimidazole was obtained as the dihydrochloride salt by refluxing a mixture of *N*-methyl-*o*-diaminobenzene (25.6 mmol), β-alanine (38.4 mmol) and 6 mol $dm^{-3}$ hydrochloric acid (30 $cm^3$) for 100 h. After cooling, the solvent was removed carefully under vacuum, the residue was dissolved in a minimum amount of water and precipitated by addition of ethanol. The crude product was collected by filtration and crystallized from ethanol, giving a white crystalline solid (yield 70%): $^1H$ NMR ($D_2O$): δ 3.69 (m, 4H), 4.07 (s, 3H) and 7.6–7.9 (m, 4H).

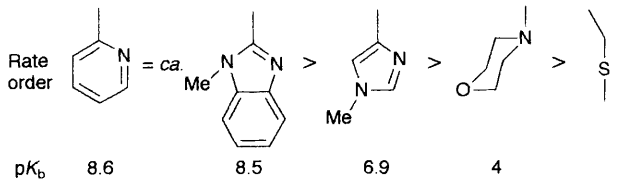
Satisfactory elemental analyses were obtained for all new compounds.

§ *Selected data* for **1**: IR (Nujol mull, ν/$cm^{-1}$): 2250w [ν(C≡N)], 1630s [ν(C=N)], 1100vs, br and 623m [ν($ClO_4$)]; $^1H$ NMR ($CD_3CN$): δ 2.89 (t, 4H, C–$CH_2$–C), 3.41 (s, 6H, $CH_3$), 4.19 (t, 4H, $CH_2$–N=), 7.0–7.5 (m), 8.40 (s) (12H) (Ph-H) and 8.05 (s, 2H, CH=N). The carbonyl adduct in methanol solution exhibits ν(CO) at 2096 $cm^{-1}$.

*Selected data* for **2**: IR (Nujol mull, ν/$cm^{-1}$): 2278w (ν(C≡N)], 1634s [ν(C=N)], 1095vs, br and 621 [ν($ClO_4$)]; $^1H$ NMR ($CD_3CN$): δ 2.3–2.8 (m, 16H, C–$CH_2$–C + C–$CH_2$–N), 3.7–4.0 (m, 12H, $CH_2$–O + $CH_2$–N=); 7.67 (t, 1H), 7.98 (d, 2H) and 8.37 (s, 1H) (Ph–H), and 8.45 (s, 2H, CH=N). The carbonyl adduct in methanol solution exhibits ν(CO) at 2102 $cm^{-1}$.

*Selected data* for **3**: IR (Nujol mull, ν/$cm^{-1}$): 3400br [ν(OH)], 1700m [ν(C=O)], 1634s [ν(C=N)], 1100vs, br and 621m [ν($ClO_4$]. The compound is not sufficiently soluble for reliable NMR spectra to be recorded. The carbonyl adduct in methanol solution exhibits ν(CO) at 2108 $cm^{-1}$.

¶ Under the same conditions we obtained a ratio of 7 to **5** corresponding to 100 : 0 in the oxygenation of the copper(I) complexes **A** with X = $N^1$-methylimidazole,[6b] 50 : 50 for the complex with X = imidazole,[6b] and 88 : 12 for the complex with X = pyridine.[7]




**Scheme 2** Rate of formation of **6** and basicity of donor group X in **A**

The present results show that for simple systems of type **1–3** the nature of the donor group X has influence *only* on the relative rate of the oxygenation and oxidation pathways that the reaction with dioxygen can take. Particularly important is the reactivity of the methionine complex **3** because this amino acid residue has received scarce consideration as a potential donor group for copper in proteins binding and activating dioxygen.[9] A recent report suggests that a conserved methionine may be a copper ligand in molluscan hemocyanins,[10] while the presence of a sulphur atom in the copper coordination sphere of the monoxygenase dopamine β-hydroxylase, proposed on the basis of EXAFS results,[11] has been more recently questioned on reexamination of the spectroscopic data.[12] As we see here, however, methionine bonding to copper(I) does not *per se* prevent the binding of dioxygen and the potential monooxygenase activity of copper sites.

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