Type 3 Copper Model Chemistry. Dioxygen Activation by Binuclear Two-co-ordinate Copper(I) Complexes derived from L-Histidine and L-N^{τ}-Methylhistidine

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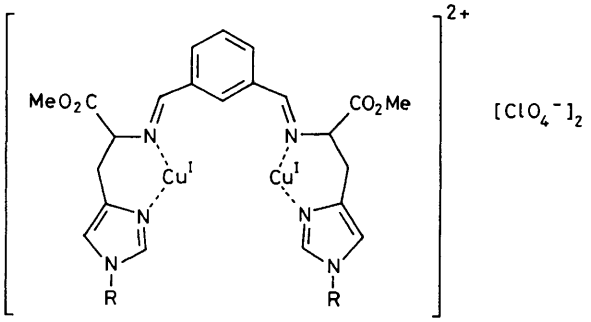
The reaction of dioxygen with the binuclear two-co-ordinate copper(I) complexes derived from the condensation of benzene-1,3-dicarbaldehyde and two molecules of L-histidine methyl ester or L-N^{τ}-methylhistidine methyl ester occurs with hydroxylation of the aromatic nucleus at position 2, producing binuclear phenoxy-bridged copper(II) complexes.

Much current interest in copper biomimetic chemistry focuses on the synthesis of copper(I) systems as mimics for the reduced state of Type 3 active sites of copper proteins.[1—5] Very little information is available on the structures of these protein copper(I) sites except for the possible involvement of imidazole groups in metal binding and the necessity of co-ordinative unsaturation of the metal ions.[6] Two-co-ordination is a likely possibility for copper(I) in these binuclear sites, although other protein ligands may become involved during activity.[6] Only a few synthetic two-co-ordinate copper(I) complexes containing nitrogen donors have been reported;[3] these display somewhat unusual behaviour, since they are apparently reluctant to react with carbon monoxide, while their reactions with dioxygen have not been understood. We report here binuclear two-co-ordinate copper(I) complexes containing L-histidine or L-N^{τ}-methylhistidine residues for which dioxygen reactivity has been characterized.

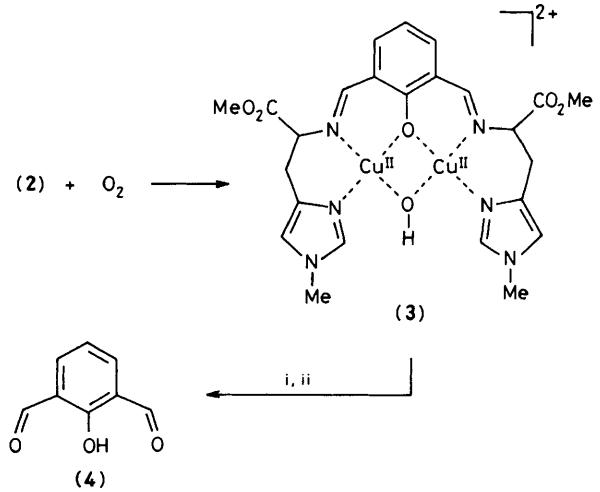
The binuclear complexes (**1**) and (**2**) were prepared by condensation of benzene-1,3-dicarbaldehyde and 2 equiv. of free L-histidine methyl ester, or L-N^{τ}-methylhistidine methyl ester (prepared according to ref. 7), respectively, in the presence of $Cu(MeCN)_4ClO_4$ (2 equiv.) in refluxing methanol under an inert atmosphere. The resulting yellow precipitates were recrystallized from methanol.† The i.r. and ^1H n.m.r. spectra of the complexes indicate that the ester groups are not co-ordinated to copper(I). The structure of the metal centres in (**1**) and (**2**) is thus assumed to be two-co-ordinate, although molecular models show that the fragments N–Cu–N cannot achieve a perfectly linear arrangement. As expected, neither (**1**) nor (**2**) form stable carbonyl adducts. Only weak CO adducts are formed in solution [ν(CO) at 2093—2096 cm^{-1}], but these readily lose CO on evaporating the solvent under vacuum.

When solutions of (**1**) or (**2**) in dry MeCN or dimethylformamide (10^{-3}—10^{-4} M) are exposed to dioxygen (1 atm; room temp.) the colour of the solution gradually turns green (~1 h). For (**1**) the electronic spectra of the oxygenated solutions show the growth of a modest, poorly defined absorption in the range 300—400 nm (ε ~1500 $dm^3\ mol^{-1}\ cm^{-1}$ for the shoulder near 360 nm) and a weak band near 650 nm (ε ~150). Bands near these wavelengths appear also in the corresponding c.d. spectra, while the frozen-solution e.s.r. spectra display only broad signals near $g = 2.1$. The near-u.v. spectral changes are indicative of the formation of imidazolate-bridged copper(II) compounds,[8] while the amount of dioxygen absorbed by the solutions, measured manometrically, corresponds to 1 O_2 molecule per 4 Cu atoms and shows that dioxygen is reduced to water or hydroxide ion rather than hydrogen peroxide. The oxygenation of (**2**) produces an intense near-u.v. absorption band near 355 nm (ε ~6000 $dm^3\ mol^{-1}\ cm^{-1}$) and a much weaker visible band near 600 nm (ε ~110); manometric measurements of dioxygen uptake correspond to 1 O_2 molecule per 2 Cu atoms. The i.r. spectrum of the product (**3**) isolated upon evaporation of the oxygenated solutions is practically superimposable on that of (**2**) but contains two additional bands near 1560 and 3500 cm^{-1}. The spectral characteristics of (**3**) are thus very similar to those of phenoxy- and hydroxy-bridged binuclear copper(II) complexes of the imines derived from 2-hydroxy-5-methylbenzene-1,3-dicarbaldehyde.[9] In particular, the near-u.v. band at ~355 nm and the i.r. band at ~1560 cm^{-1} are associated with the low-energy $\pi \rightarrow \pi^*$ electronic transition and a typical vibration, respectively, of the 2-hydroxyphenylimino chromophores,[9,10] while the i.r. band at ~3500 cm^{-1} involves formation of a hydroxy group. Therefore, the oxygenation of (**2**) occurs with hydroxylation of the aromatic nucleus according to the reaction outlined in Scheme 1. This is confirmed by the analytical data of (**3**)† and the isolation of 2-hydroxybenzene-1,3-dicarbaldehyde, (**4**), on treatment of (**3**) with



(**1**) R = H
(**2**) R = Me

† Satisfactory elemental analyses (Cu,C,H,N) were obtained for these compounds.



Scheme 1. *Reagents:* i, $HCl–H_2O$; ii, $CHCl_3$.

aqueous acid followed by extraction with chloroform.‡ Interestingly, when the oxygenation of (**1**) and (**2**) is carried out in methanol solution, the spectral features of (**3**) develop in both cases, but for (**1**) the product corresponding to (**3**) is formed either in part or at a much slower rate. Also, the amount of O_2 absorbed by (**1**) in methanol is higher than that observed in the nonprotic media and we are currently trying to establish the full distribution of the products of this reaction.

The copper-mediated hydroxylation of the aromatic ring of (**1**) and (**2**) is formally similar to that effected by copper mono-oxygenases.[6a] Although this reaction has precedent in synthetic copper systems,[1a,11] the present results show the feasibility of binuclear, two-co-ordinate copper(I) centres bound to histidine imidazole groups for the reduced state of Type 3 active sites of copper proteins.

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‡ *Spectroscopic data* for (**4**): ^{1}H n.m.r. ($CDCl_3$, 60 MHz): δ 11.6 (~s, 1 H, OH; exchanges with D_2O), 10.2 (~s, 2 H, CHO), 7.6—8.2 (m, 2 H, 4-H + 6-H), 6.7—7.2 (m, 1 H, 5-H). I.r. ($CHCl_3$): 1687; 1662 cm^{-1} [ν(C=O)]. *m/z*: 150 (M^+), 134, 133 ($M-17$), 122 ($M-28$), 121 ($M-29$).