Copper dioxygen complexes stable at ambient temperature: optimization of ligand design and solvent

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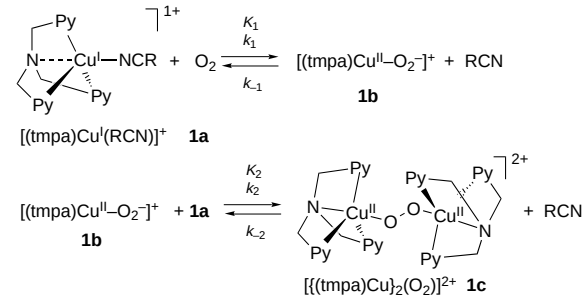
Entropic destabilization of low-molecular mass μ-peroxo-dicopper(II) complexes are overcome using a new binucleating open-chain ligand by the combination of an optimized linking unit with a less competing solvent; complete formation and satisfactory stability at room temperature are thus obtained.

As with efforts by synthetic chemists to design systems which mimic the O_2-binding of haemoglobin/myoglobin using modified iron porphyrinates, there has been considerable recent interest in studies of O_2-binding by copper complexes,[1,2] relevant to the arthropodal and molluscan haemolymph O_2-carrier haemocyanins.[3] In the deoxygenated state, these possess a dinuclear copper(I) centre; oxygenation proceeds *via* oxidative addition, producing a side-on bound μ-η²:η²-peroxo-dicopper(II) species (Cu···Cu 3.6 Å). Using tridentate nitrogen-containing ligands, synthetic models with this structure and accompanying spectroscopic properties have been generated and characterized at reduced temperatures (either in solution or as isolated solids).[1,2,4]

With tetradentate ligands such as tris(2-pyridylmethyl)amine (tmpa), divergent copper–dioxygen structure–spectroscopic types form. Kinetic/spectroscopic studies[5–7] reveal that copper(I) complexes with tmpa, its quinolyl substituted analogues, and binucleating version L^2, form sequentially both $Cu:O_2 = 1:1$ [superoxocopper(II)] and 2:1 [peroxodicopper(II)] products, stable only at reduced temperatures (*i.e.* −80 °C); X-ray structure analysis[8] establishes [{(tmpa)Cu}$_2$(O$_2$)]$^{2+}$ **1c** (Scheme 1) to possess a *trans*-μ-1,2-peroxo ligation. The quinolyl[5] and dinucleating ligand[6] variations measurably affect Cu^I_n/O_2 stoichiometric preferences, reaction rates, and Cu_n–O_2 structural distortions or strain.[6,7] Here, however, we report dramatic effects upon reaction rates and copper–dioxygen complex stability, elicited by ligand synthetic modification or alteration of reaction solvent. In fact, the long sought goal of generating a fully formed and reasonably stable copper–dioxygen complex at room temperature in solution, has been achieved.

Kinetic–spectroscopic monitoring of [(tmpa)Cu^I(RCN)]$^+$ **1a** reacted with O_2 in EtCN at −90 °C typically reveals initial {*t ca*. 50 ms, [**1a**] = 0.4 mm; [O_2] = 4.5 mm} growth of the band at λ_{max} = 410 nm, associated with a 1:1 intermediate adduct [(tmpa)Cu^{II}(O$_2^-$)]$^+$ **1b** ($k_1 = 1.8 \times 10^4$ m^{-1} s^{-1}). The final peroxo product [{(tmpa)Cu^{II}}$_2$(O$_2^{2-}$)]$^{2+}$ **1c** (λ_{max} = 525 nm) subsequently builds up at the expense of **1b** (and **1a**; Scheme 1) such that at *t ca*. 10 s at this temperature, **1b** mostly disappears and **1c** is nearly fully formed. The room-temperature stability of **1c** (and other copper–dioxygen complexes in general)[6,7] is precluded by a highly unfavoured reaction entropy ($\Delta S_{on}° = -220 \pm 11$ J K^{-1} mol^{-1}),[6] and the 525 nm absorption essentially disappears, either in favour of Cu^I (short times) or Cu^{II} decomposition products.

These results stand in marked contrast to reactions now carried out in acetone as solvent. At −90 °C, [{(tmpa)Cu^{II}}-(O$_2^-$)]$^+$ **1b** fully forms within the mixing time of the stopped-flow apparatus (< 2 ms), Fig. 1(*a*), providing a lower limit $k_1 \geqslant 10^6$ m^{-1} s^{-1}. This O_2-binding to [{(tmpa)Cu^I}(Me$_2$CO?)]$^+$ **1a′** at −90 °C is at least comparable with the room-temperature reaction of O_2 with deoxyhaemocyanin (k_{on} *ca*. 10^7 m^{-1} s^{-1}).[9] Thus, with the right ligand and medium, there is little, if any, restriction to O_2-binding to Cu^I, and these observations point to



Scheme 1

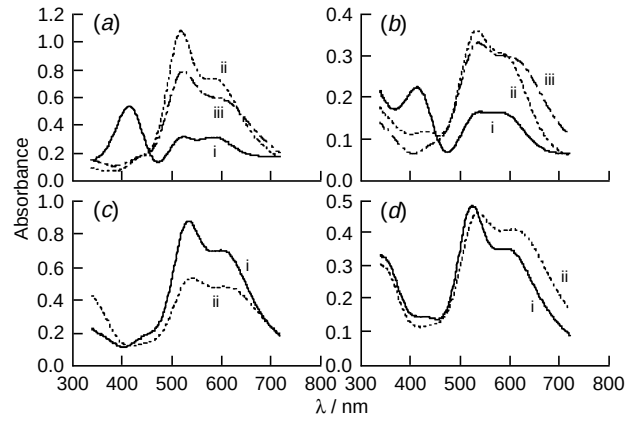
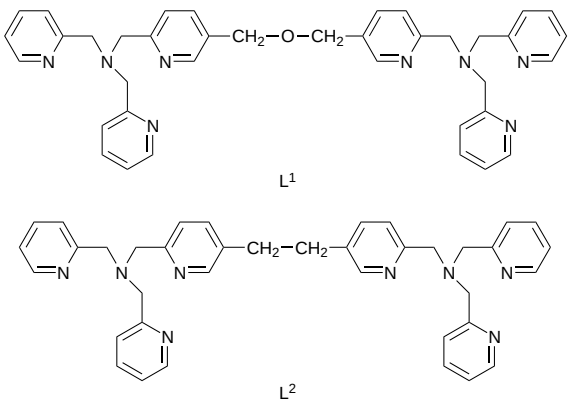


Fig. 1 Stopped-flow spectral monitoring of the reaction in acetone of O_2 (5.1 mm) with (*a*) [(tmpa)Cu^I(RCN)]$^+$ (**1a**, 0.9 mm) and (*b*) [L^{2}Cu$_2$(EtCN)$_2$]$^{2+}$ (**2a**, 0.26 mm). Superoxo formation with some admixture of peroxo complex (2.6 ms after mixing) (i, superoxo −90 °C; ii, peroxo −90 °C; iii, peroxo +20 °C). Reaction of O_2 (5.1 mm) with [L^{1}Cu$_2$(EtCN)$_2$)]$^{2+}$ (**3a**, 0.55 mm) in (*c*) propionitrile or (*d*) acetone (0.28 mm) (i, peroxo −90 °C; ii, peroxo +20 °C).



nitrile coordination and rate-limiting dissociation being critical in the chemistry of tripod copper(i) complexes detailed for EtCN solutions.[5–7] The stability of $[\{(tmpa)Cu^{II}\}_2(O_2^{2-})]^{2+}$ **1c** [λ_{max} = 525 nm, shoulders at *ca*. 430 and 600 nm; Fig. 1(*a*)][10]† is increased even more dramatically, with $\beta_2 = K_1K_2 \geqslant 5 \times 10^5$ m^{-2} (5×10^2 m^{-2} in EtCN) at room temperature. Formation of 70% **1c** is obtained within the mixing time (EtCN: not observable, calculated formation 0.2%). At 20 °C, **1c** decomposes with $t_{1/2}$(decomp.) *ca*. 45 s.

We previously showed that $[L^2Cu_2(EtCN)_2]^{2+}$ **2a** reacts with O_2 in EtCN giving both Cu : O_2 = 1 : 1 and 2 : 1 intermediates; $[L^2(Cu^ICu^{II})(O_2^-)(EtCN)]^{2+}$ **2b** reacts intramolecularly giving closed peroxo species $[L^2Cu_2(O_2)]^{2+}$ **2c** (Scheme 2).[6] The dinucleating nature of L^2 (compared to tmpa) results in considerable reduction of the entropic handicap found for formation of $[\{(tmpa)Cu\}_2(O_2)]^{2+}$ **1c**, by 130–140 J K^{-1} mol^{-1}. However comparison of the $\Delta H_{on}°$ for **1c** *vs*. **2c** formation (−81 *vs*. −35 kJ mol^{-1})[6] revealed the latter to be significantly strained, resulting in rearrangement to trimeric $[L^2Cu_2(O_2)]_3^{6+}$. In acetone, **2a** reaction with O_2 again results in enhanced stability of copper–dioxygen adducts. As with tmpa, 1 : 1 complex adduct formation occurs within the stopped-flow mixing time even at −90 °C, giving the characteristic λ_{max} = 414 nm absorption [Fig. 1(*b*)], assigned to a bis-superoxocopper(ii) species $[L^2Cu_2(O_2)_2]^{2+}$ **2b′**. Formation of peroxo complex $[L^2Cu_2(O_2)]^{2+}$ **2c** is essentially complete even at 20 °C [Fig. 1(*b*)], yielding $K_1K_2 > 4 \times 10^3$ m^{-1} (27 m^{-1} in EtCN),[6] but precluding calculation of thermodynamic parameters $\Delta H°$ and $\Delta S°$. Enhanced decomposition of **2c** [$t_{1/2}$(decomp.) *ca*. 4 s] *vs*. $t_{1/2}$(decomp.) *ca*. 40 s for **1c** may reflect the still considerably strained nature of adduct $[L^2Cu_2(O_2)]^{2+}$.

In combination, the new ligand L^1,‡ a modification designed to relieve the strain in **2c**, [11] is the most successful in giving a pseudoreversible Cu_2–O_2 complex stable at room temperature. Curiously, for both EtCN and acetone solvents, there is no spectral indication of any 1 : 1 adducts (*e.g*. **3b**, Scheme 2) upon reaction of dicopper(i) precursor $[L^1Cu_2(MeCN)_2]^{2+}$ **3a**‡ with O_2.§ Their formation appears to be inhibited and slow relative to the subsequent reactions leading to peroxo complex $[L^1Cu_2(O_2)]^{2+}$ **3c** (λ_{max} = 535 nm). However, in EtCN, formation of **3c** is complete within the experimental mixing time even at −60 °C. Theoretical calculations[11] and preliminary analyses of the present kinetic data suggest that the longer linker arm in L^1 indeed relieves the strain observed for $[L^2Cu_2(O_2)]^{2+}$ **2c**, significantly enhancing adduct formation at room temperature to 60% [K_1K_2 = 300 m^{-1} *vs*. 27 m^{-1} for L^2, Fig. 1(*c*),† with $t_{1/2}$(decomp.) increased to 20 s]. L^1 seems to afford significant entropic advantage for formation of $[L^1Cu_2(O_2)]^{2+}$ **3c** compared to $[\{(tmpa)Cu\}_2(O_2)]^{2+}$ **1c**, with little enthalpic loss.

Acetone once more confers additional stability to **3c**. Peroxo formation is immediate and complete within experimental error at room temperature, thus precluding quantitative determination of K_1K_2, but we may safely assume that thermodynamic stability is still increased relative to L^2 in acetone. In line with this, enhanced persistence of the characteristic $[L^1Cu_2(O_2)]^{2+}$ **3c** spectrum [Fig. 1(*d*); $t_{1/2}$(decomp.) *ca*. 60 s] may be indicative of released strain and leads to the most stable of all copper–dioxygen complexes thus far studied by us.[7]¶

The results further demonstrate the importance in ligand design/modification, here shown to confer solution room-temperature stability to Cu_2–O_2 complexes. L^1 utilizes a dinucleating design which appears to be strain minimized. Acetone is shown to be a remarkable solvent for enhancing rates of formation and thermal stability of Cu_n–O_2 species, probably by virtue of its poor ability to ligate to Cu^I. Further analyses and investigations are aimed at further detailing of factors which can be controlled *via* ligand design (*i.e*. steric, electronic and medium effects), and which are critical to Cu_n–O_2 formation, structure, stability and reactivity.

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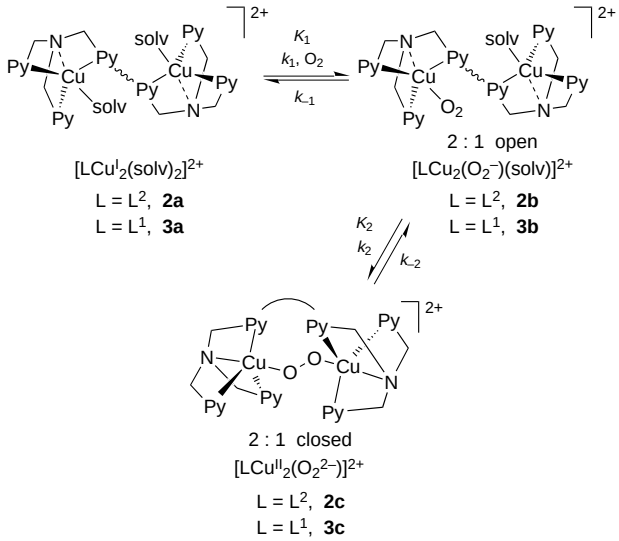

Scheme 2

Footnotes

† Solution spectral broadening and intensity diminution is expected with increase in temperature. See S. F. Rice, R. B. Wilson and E. I. Solomon, *Inorg. Chem*., 1980, **19**, 3425.

‡ Ether L^1 was synthesized by condensation of previously described hydroxymethyl and chloromethyl precursors.[6] Reaction of L^1 with 2 equiv. of $[Cu(MeCN)_4]ClO_4$ gave **3a**$(ClO_4)_2$, for which satisfactory C, H and N analyses were obtained.

§ We are investigating the hypothesis that **3a** in solution exists as a tight dinuclear complex (with pyridyl ligand stacking), altering the more typical and previously observed process of Cu–O_2 1 : 1 complex formation. See L. F. Newcomb and S. H. Gellman, *J. Am. Chem. Soc*., 1994, **116**, 4993, for examples of solution stacking of aromatics connected with a propylene spacer.

¶ A recent report describes the use of a macrocycle dicopper complex which (irreversibly) binds dioxygen at room temp. See J. E. Bol, W. L. Driessen, R. Y. N. Ho, B. Moase, L. Que, Jr. and J. Reedyk, *Angew. Chem., Int. Ed. Engl*., in the press.

References

1 N. Kitajima and Y. Moro-oka, *Chem. Rev*., 1994, **94**, 737.
2 S. Fox and K. D. Karlin, in *Dioxygen Reactivity in Copper Proteins and Complexes*, ed. J. S. Valentine, C. S. Foote, A. Greenberg and J. F. Liebman, Glasgow, 1995; K. D. Karlin and Z. Tyeklár, *Adv. Inorg. Biochem*., 1994, **9**, 123.
3 K. A. Magnus, H. Ton-That and J. E. Carpenter, *Chem. Rev*., 1994, **94**, 727; E. I. Solomon, U. M. Sundaram and T. E. Machonkin, *Chem. Rev*., 1996, **96**, 2536.
4 W. E. Lynch, D. M. Kurtz, Jr., S. Wang and R. A. Scott, *J. Am. Chem. Soc*., 1994, **116**, 11030; T. N. Sorrell, W. E. Allen and P. S. White, *Inorg. Chem*., 1995, **34**, 952; J. A. Halfen, S. Mahapatra, E. C. Wilkinson, S. Kaderli, V. G. Young, Jr., L. Que, Jr., A. D. Zuberbühler and W. B. Tolman, *Science*, 1996, **271**, 1397.
5 K. D. Karlin, N. Wei, B. Jung, S. Kaderli, P. Niklaus and A. D. Zuberbühler, *J. Am. Chem. Soc*., 1993, **115**, 9506.
6 D.-H. Lee, N. Wei, N. N. Murthy, Z. Tyeklár, K. D. Karlin, S. Kaderli, B. Jung and A. D. Zuberbühler, *J. Am. Chem. Soc*., 1995, **117**, 12498.
7 K. D. Karlin, S. Kaderli and A. D. Zuberbühler, *Acc. Chem. Res*., 1997, in the press.
8 Z. Tyeklár, R. R. Jacobson, N. Wei, N. N. Murthy, J. Zubieta and K. D. Karlin, *J. Am. Chem. Soc*., 1993, **115**, 2677.
9 C. R. Andrew, K. P. McKillop and A. G. Sykes, *Biochim. Biophys. Acta*, 1993, **1162**, 105.
10 M. J. Baldwin, P. K. Ross, J. E. Pate, Z. Tyeklár, K. D. Karlin and E. I. Solomon, *J. Am. Chem. Soc*., 1991, **113**, 8671.
11 P. Comba, P. Hilfenhaus and K. D. Karlin, *Inorg. Chem*., submitted for publication.

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