Kinetic Preference without Thermodynamic Stabilization in the Intra- vs Intermolecular Formation of Copper–Dioxygen Complexes

Ning Wei, Dong-Heon Lee, Narasimha N. Murthy, Zoltán Tyeklár, and Kenneth D. Karlin*

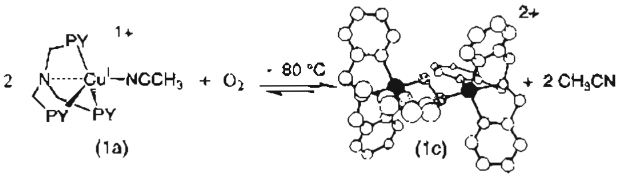
Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218

Susan Kaderli, Bernhard Jung, and Andreas D. Zuberbühler*

Institute of Inorganic Chemistry, University of Basel, CH-4056 Basel, Switzerland

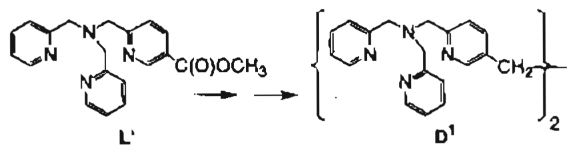
Received June 3, 1994

We have previously detailed the chemistry of the reaction between dioxygen (O_2) and the mononuclear copper(I) species $[(L)Cu(RCN)]^+$ (**1a**) (L = tris[(2-pyridyl)methyl]amine; R = Me or Et), including a kinetics/thermodynamics investigation.[1,2] In reactions with O_2, **1a** initially forms a spectroscopically detectable ($\lambda_{max} = 410$ nm, $\epsilon = 4000\ M^{-1}\ cm^{-1}$) Cu/O_2 = 1:1 adduct $[(L)Cu(O_2)]^+$ (**1b**)[1c] (formally a superoxo–copper(II) species), which further reacts rapidly with **1a** to give $[\{(L)Cu\}_2(O_2)]^{2+}$ (**1c**, $\lambda_{max} = 525$, $\epsilon = 11\,500\ M^{-1}\ cm^{-1}$; 600 (sh) nm), possessing a *trans*-μ-1,2-peroxo–dicopper(II) structure.[1b]



While **1b**,**c** can be studied at low temperatures, the room temperature stability for these (and other Cu_2O_2 complexes)[1c,2d,3] is diminished by highly unfavorable reaction entropies, i.e., for **1c** $\Delta S° = -220 \pm 11\ J\ K^{-1}\ mol^{-1}$.[1c] We have also seen that the relative stability of $Cu-O_2$ 1:1 species versus Cu_2-O_2 (i.e. peroxo-bridged) 2:1 complexes depends greatly on ligand environment and imposed metal coordination, such as when pyridyl groups in L are replaced by quinolyl[1c,4] or imidazolyl[5] donors.[6] Here, we describe the O_2-binding behavior of dicopper(I) complex $[(D^1)Cu^I_2(EtCN)_2]^{2+}$ (**2a**), where D^1 is a novel dinucleating ligand but sterically and electronically analogous to the previously studied mononucleating ligand L. The X-ray structure of **2a** is reported and details of the reaction of **2a** with O_2 are described, providing new insights into Cu(I)/O_2 reactivity patterns.

Ligand D^1 was synthesized starting with ester-substituted ligand L′,[1b] followed by reduction with $LiAlH_4$, reaction of the resulting alcohol with $SOCl_2$, and reductive coupling[7] of the chloromethyl product using $[Cu^I(CH_3CN)_4](PF_6)$. After purification, interaction of D^1 with $[Cu^I(CH_3CN)_4]ClO_4$ in EtCN led to the isolation of $[(D^1)Cu_2(EtCN)_2](ClO_4)_2$ (**2a**).[8] X-ray analysis (Figure 1)[8] confirms the ligand structure and dinuclear complex formulation, possessing an inversion center which relates the two Cu(I) ion moieties. Each Cu(I) ion is pseudopentacoordinate, with strong interactions with the propionitrile and pyridyl donor groups but with a long $Cu-N_{alkylamine}$ distance (2.423(4) Å); the Cu(I) ligation is the same as that found in $[(L')Cu(CH_3CN)]^+$.[1b] In the solid state, the Cu coordination spheres extend away from each other, Cu(I)···Cu(I) = 11.705(2) Å.



The O_2 reaction with this *dinuclear* complex $[(D^1)Cu_2(EtCN)_2](ClO_4)_2$ (**2a**) is complicated but most interesting.[9] Initial low-temperature binding of O_2 in EtCN solvent results in two types of observable intermediates (Scheme 1). These are (i) a 2:1 *open* form $[(D^1)Cu_2(O_2)(EtCN)]^{2+}$ (**2b**), formally a mixed-valence Cu^ICu^{II} complex, and (ii) a 2:2 *open* form $[(D^1)Cu_2(O_2)_2]^{2+}$ (**2b′**), where *both* copper ions have bound O_2 ligands. These $Cu-O_2$ adducts both possess the same UV–vis λ_{max} = 416 nm values, with **2b′** giving a more intense absorption ($\epsilon = 8900\ M^{-1}\ cm^{-1}$), since there are twice the absorbing chromophores. Adduct **2b** and **2b′** cannot directly be distinguished spectroscopically or kinetically, since the two O_2-binding sites are identical and behave independently. Numerical analysis was successful on the basis of the following additional assumptions/constraints: (a) The spectrum of the 2:1 open form **2b** is the arithmetic mean of the spectrum of the 2:2 complex **2b′** and the parent Cu(I) species **2a**. (b) k_1' and k_{-1}' are coupled statistically to k_1 and k_{-1}; i.e., $k_1' = 0.5k_1$ and $k_{-1}' = 2k_{-1}$. The rate and thermodynamic parameters at 183 K are $k_1 = (2.0 \pm 0.1) \times 10^4\ M^{-1}\ s^{-1}$ and $K_1 = (2.0 \pm 0.1) \times 10^3\ M^{-1}$, comparable to those observed for **1b** formation.

---

* To whom correspondence should be addressed.

(1) (a) Baldwin, M. J.; Ross, P. K.; Pate, J. E.; Tyeklár, Z.; Karlin, K. D.; Solomon, E. I. *J. Am. Chem. Soc.* **1991**, *113*, 8671–8679. (b) Tyeklár, Z.; Jacobson, R. R.; Wei, N.; Murthy, N. N.; Zubieta, J.; Karlin, K. D. *J. Am. Chem. Soc.* **1993**, *115*, 2677–2689. (c) Karlin, K. D.; Wei, N.; Jung, B.; Kaderli, S.; Zuberbühler, A. D. *J. Am. Chem. Soc.* **1993**, 9506–9514.

(2) (a) Sorrell, T. N. *Tetrahedron* **1989**, *45*, 3–68. (b) Solomon, E. I.; Baldwin, M. J.; Lowery, M. D. *Chem. Rev.* **1992**, *92*, 521–542. (c) Kitajima, N. *Adv. Inorg. Chem.* **1992**, *39*, 1–77. (d) Karlin, K. D.; Tyeklár, Z.; Zuberbühler, A. D. In *Bioinorganic Catalysis*; Reedijk, J., Ed.; Marcel Dekker, Inc.: New York, 1993; pp 261–315. (e) Kitajima, N.; Moro-oka, Y. *Chem. Rev.* **1994**, *94*, 737–757.

(3) Karlin, K. D.; Nasir, M. S.; Cohen, B. I.; Cruse, R. W.; Kaderli, S.; Zuberbühler, A. D. *J. Am. Chem. Soc.* **1994**, *116*, 1324–1336.

(4) Wei, N.; Murthy, N. N.; Chen, Q.; Zubieta, J.; Karlin, K. D. *Inorg. Chem.* **1994**, *33*, 1953–1965.

(5) Wei, N.; Murthy, N. N.; Tyeklár, Z.; Karlin, K. D. *Inorg. Chem.* **1994**, *33*, 1177–1183.

(6) The ligand environment also dramatically influences the nucleophilic versus electrophilic behavior of Cu_2-O_2 species. See: Paul, P. P.; Tyeklár, Z.; Jacobson, R. R.; Karlin, K. D. *J. Am. Chem. Soc.* **1991**, *113*, 5322–5332.

(7) Jacobson, R. R.; Tyeklár, Z.; Karlin, K. D. *Inorg. Chim. Acta* **1991**, *181*, 111–118.

(8) See supplementary material for information relating to the synthesis and X-ray structure determination of **2a**.

(9) Kinetics were followed with a diode array (359–776 nm) stopped-flow instrument and subjected to global analysis using KINFIT as described in ref 1c. Activation parameters and spectra of the dioxygen complexes were obtained from 127 measurements at 181–213 K in dry propionitrile. Concentrations of O_2 and complex were varied from 9.0×10^{-4} to 4.4×10^{-3} and 7.4×10^{-5} to 5.05×10^{-4} M, respectively.

0020-1669/94/1333-4625$04.50/0

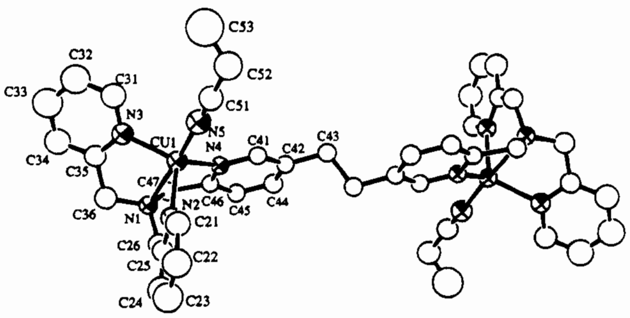
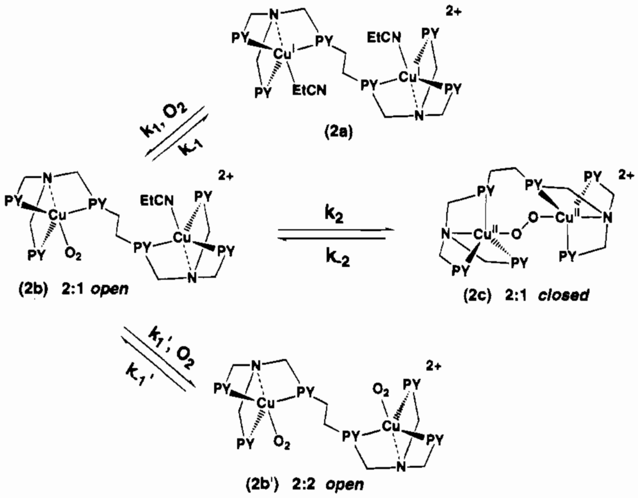


Figure 1. ORTEP diagram (30% ellipsoids) of the cationic portion of $[(D^1)Cu_2(EtCN)_2]^{2+}$ (**2a**).

Scheme 1



The ensuing product is a (μ-peroxo)dicopper(II) complex $[(D^1)Cu_2(O_2)]^{2+}$ (**2c**) (Scheme 1), as indicated by kinetics and the stoichiometry of O_2-binding ($Cu/O_2 = 2{:}1$, 183 K, manometry), as well as the UV−vis spectral similarity to **1c** (for **2c**, $\lambda_{max} = 540$, $\epsilon = 11\,100\ M^{-1}\ cm^{-1}$, 600 (sh) nm). Molecular models indicate that a *trans*-μ-peroxo-dicopper(II) structure like **1c** could form, even with the $-CH_2CH_2-$ linker in D^1. The formation of this 2:1 *closed* form product is very rapid and can be described by $k_{bim} = k_1k_2/k_{-1} = (3.3 \pm 0.1) \times 10^4\ M^{-1}\ s^{-1}$ at 183 K (bim = bimolecular)[10] and a small positive activation enthalpy of 2 ± 1 kJ mol^{-1}, quite in contrast with the results obtained for **1c** ($\Delta H^{\ddagger} = -20 \pm 2$ kJ mol^{-1}).[11] The overall formation of **2c** is faster relative to **1c**, and this is entirely due to the reduced entropy of activation ($\Delta S^{\ddagger} = -139 \pm 4$ J K^{-1} mol^{-1} for **2c** vs $\Delta S^{\ddagger} = -201 \pm 5$ J K^{-1} mol^{-1} for **1c**). However, this significantly enhanced kinetic reactivity (for **2a** → **2c**) is *not* reflected by an analogous increase in thermodynamic stability. **2c** is enthalpically *de*stabilized ($\Delta H^{\circ} = -35 \pm 1$ kJ mol^{-1}) compared to Cu_2O_2 species **1c** ($\Delta H^{\circ} = -81 \pm 3$ kJ mol^{-1}),[1c] which is formed from a mononuclear precursor; we suggest this is due to some *non*-negligible strain imposed by the $-CH_2CH_2-$ linker of dinucleating ligand D^1. However, the overall entropy for the reaction leading to **2c** ($\Delta S^{\circ} = -90 \pm 2$ J K^{-1} mol^{-1}) is significantly more positive than that which leads to **1c** (*vide supra*). This is as originally conceived in the design of the ligand, since Cu_2O_2 formation is an intramolecular, rather than bimolecular, process.[12]

In summary, the following can be stated: (a) *Intra*molecular O_2 binding by the two Cu(I) ions in $[(D^1)Cu_2(EtCN)_2]^{2+}$ (**2a**) significantly increases the kinetic reactivity leading to the intramolecular μ-peroxo complex **2c**. (b) This increased rate of formation *per se* proves insufficient for increased thermodynamic stability; relative to **1c**, Cu_2O_2 complex **2c** is enthalpically destabilized but entropically much more highly favored. (c) The D^1 dinucleating ligand system affords a "look" at several types of Cu/O_2 1:1 species, **2b** and **2b′**. Elucidation of such $LCu-O_2$ structures, spectroscopy, and subsequent chemistry are of considerable interest, since these are produced in Cu(I) autoxidation processes,[13] in reactions of Cu(II) with superoxide,[14] and evidence continues to mount for their intermediacy in the action of various copper enzymes.[15] Such intermediates have *not* yet been detected in the dinuclear copper O_2−carrier protein hemocyanin[16] and other synthetic model systems,[2,3] including our own dinuclear *m*-xylyl−copper complexes.[3,17]

In conclusion, the differences in mono- vs dinucleating copper complex chemistry observed here further attest to the great sensitivity of $Cu(I)/O_2$ binding and subsequent reactivity to detailed ligand environment variations, thus offering impetus to the continued engineering of ligands which will provide for the tuning and ultimate control of copper−dioxygen chemistry.

Acknowledgment. We thank the National Institutes of Health (K.D.K) and Swiss National Science Foundation (A.D.Z.) for support of this research. We also thank the National Science Foundation (Grant CHE-9000471) for aid in the purchase of the X-ray diffractometer.

Supplementary Material Available: Text giving analytical data for the perchlorate salt of **2a**, figures showing UV−vis spectral changes with time for the reaction of **2a** with O_2, and tables of X-ray crystal data, postional and thermal parameters, and bond distance and angle data (11 pages). This material is contained in many libraries on microfiche, immediately follows this article on the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

---

(10) Note that the order of this k_{bim} necessarily differs from that in the mononuclear complex reactions.

(11) The rate therefore increases rather than decreases with increasing temperature. Formation of **2c** is complete within instrumental limits (8 ms) for this system at 213 K.

(12) Species **2c** appears not to be the ultimate thermodynamic product; a slow as yet not fully understood further conversion occurs, probably giving intermolecular species with $\lambda_{max} = 530$ and $\epsilon \sim 10\,000$ per peroxo unit, spectral characteristics practically identical to those obtained from the mononuclear complex **1a**. Further details will be provided in a full report.

(13) Zuberbühler, A. D. In *Metal Ions in Biological Systems*; Sigel, H., Ed.; Marcel Dekker: New York, 1976; Vol. 5, pp 325−368.

(14) See for example: Goldstein, S.; Czapski, G. *Free Radical Res. Commun.* **1991**, *12−13*, 205−210.

(15) Cf. (a) Cytochrome *c* oxidase: Varotsis, C.; Zhang, Y.; Appelman, E. H.; Babcock, G. T. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 237−241. (b) Cu/Zn superoxide dismutase: Bertini, I.; Banci, L.; Piccioli, M.; Luchinat, C. *Coord. Chem. Rev.* **1990**, *100*, 67−103. (c) Amine oxidases: Dooley, D. M.; McGuirl, M. A.; Brown, D. E.; Turowski, P. N.; McIntire, W. S.; Knowles, P. F. *Nature* **1991**, *349*, 262−264. (d) Dopamine β-monooxygenase: Tian, G.; Berry, J. A.; Klinman, J. P. *Biochemistry* **1994**, *33*, 226−234.

(16) Andrew, C. R.; McKillop, K. P.; Sykes, A. G. *Biochim. Biophys. Acta* **1993**, *1162*, 105−114.

(17) In these, tridentate (and not tetradentate) pyridyl−alkylamino chelates are well separated by a *m*-xylyl spacer in the dinuclear copper(I) complexes. The reactions proceed according to $[Cu^I_2(XYL)]^{2+} + O_2 \rightarrow [Cu_2(XYL)(O_2)]^{2+}$, without the buildup of any detectable Cu/O_2 = 1:1 intermediate. See refs 2d and 3.