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Some Aspects of Aprotic Copper(I)-Dioxygen Systems

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Some Aspects of Aprotic Copper(I)–Dioxygen Systems

There has been considerable progress in understanding the stoichiometry, products and kinetics of aprotic copper(I)-dioxygen reactions, which are an integral part of all copper–catalyzed dioxygen systems. Attention is focused on the effects of ligands on the reaction stoichiometry and on the stability of the products. The great tendency for complete aprotic dioxygen reduction appears to have both kinetic and thermodynamic origins. It is suggested that immobilization of copper(I) sites is necessary to prevent complete aprotic reduction of dioxygen.

INTRODUCTION

Progress in understanding the stoichiometry, products and thermodynamics of aprotic reactions of low molecular weight transition metal complexes with dioxygen has been dramatic over the last decade, particularly for cobalt[1] and iron.[2,3] A primary interest in all of this work is the simulation (and perhaps improvement) of the oxygen-carrying and catalytic properties of biochemical systems.

Copper also plays an important role in oxygen-carrying and in catalytic processes involving dioxygen[4] but our understanding of the products of aprotic copper(I)–dioxygen reactions is still very incomplete. Thus, although it is now felt that *two* copper(I) centers per dioxygen molecule are necessary to impart dioxygen-carrying properties, there is no completely reversible model copper–dioxygen system presently known (although we are close[5]) and hard evidence for peroxocopper species (which are still only stable at low temperatures) is only very recent.[6,19]

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Although copper(II) has a wide and varied coordination chemistry,[7] the corresponding chemistry of copper(I) is only now being developed, in part because of experimental difficulties connected with the dioxygen sensitivity of copper(I) complexes.[8] The copper(I)/copper(II) couple differs from other known dioxygen-sensitive couples in that one of the oxidation states involved has a completely filled *d*-orbital. This undoubtedly sets copper apart from the other systems, and it will be some while before the structural, kinetic and thermodynamic relationships between these two catalytically important oxidation states are fully recognized.

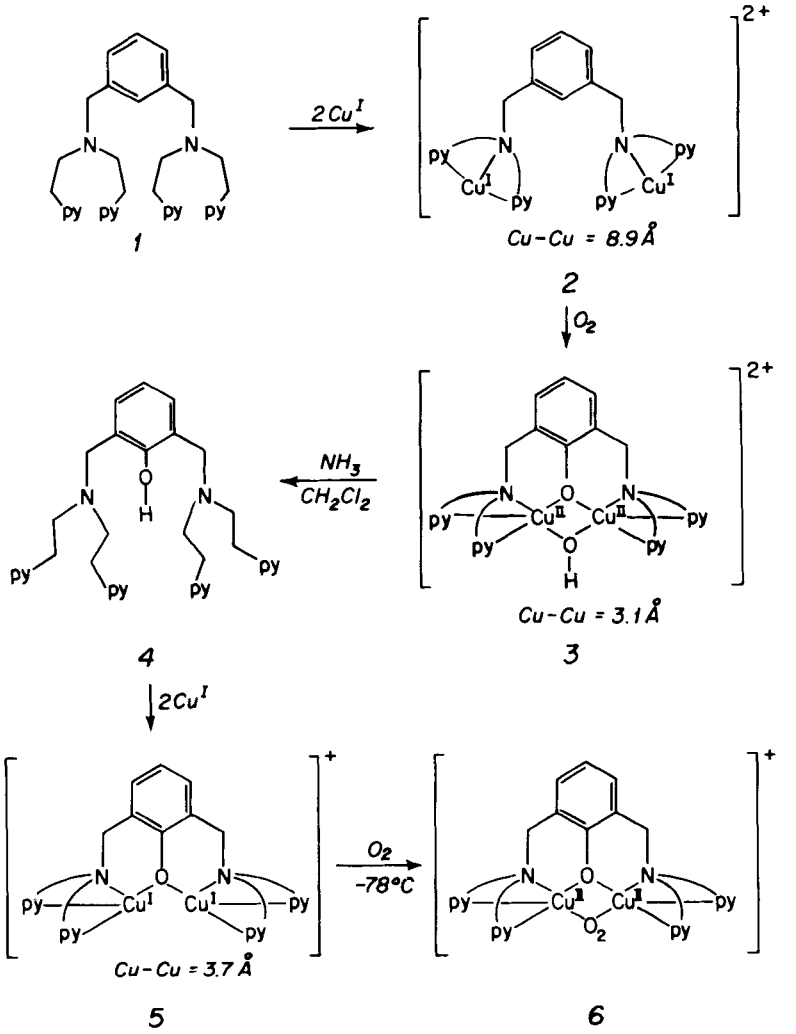
There are three other major impediments to advancing our knowledge of dioxygen systems which depend on a copper(I)–dioxygen interaction. The first has an evolutionary origin that leaves copper centers in flexible and oxidatively vulnerable ligand systems in plants and lower animals[4,9] rather than in the robust, rigid porphyrin ligand systems utilized by iron.[2] The second is the great tendency of low molecular weight copper(I) systems to completely reduce dioxygen under aprotic conditions.[10]

An important driving force for complete dioxygen reduction is the formation of strong *oxo*-copper(II) bonds. The consequence of complete dioxygen reduction is, of course, that oxygen can now only act as a base rather than as an oxidant or reductant for a substrate. Unfortunately, no detailed structure of any simple oxocopper(II) species is presently known, largely due to difficulties of crystallization in the absence of disproportionation.[10,11] Structural information may ultimately come from studies of the products of direct transmetalation of oxocopper(II) species in which copper centers have been stoichiometrically replaced with other metals.[12]

Complete dioxygen reduction in iron systems is sterically prevented or impeded by the well-known "picket fence" and "capped" porphyrin ligands and, as a result, highly reversible iron(II)–dioxygen systems have been developed at room temperature.[2a]

The third impediment is the tendency of the products of aprotic oxidation of low molecular weight copper(I) complexes to catalyze the oxidation of their own ligands,[13] leading to model systems which are constantly changing in the presence of excess dioxygen. This property has been turned to advantage in building a moderately stable peroxocopper(II) complex in very recent work (Scheme I).[14]

At the present time the ligands at the active sites of hemocyanin and tyrosinase are known with some certainty.[4b,4c] However, those sites have not yet been chemically simulated in structurally charac-



SCHEME I Reactions observed by Karlin and co-workers (Refs. 6 and 14) in m-xylyl ligand systems. Here py represents 2-pyridyl. Known copper–copper distances are indicated.

terized model complexes that are stable as dioxygen carriers or oxidative catalysts under ambient conditions.[5,14]

The main purpose of this Comment is to present what we believe is the minimum list of ligand requirements for the characterization of such species. It is based on stoichiometric and kinetic data for the

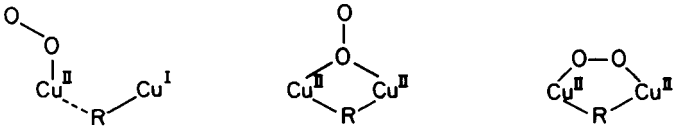
aprotic oxidation of low molecular weight copper(I) complexes by dioxygen which will be summarized after the list has been presented.

LIGAND REQUIREMENTS

1. *Coordination of copper centers.* The molecular integrity of the metal site through redox cycles must be maintained by tightly held ligands.[5,6,14] Polydentate ligands maintain this situation in dilute catalytic systems. The total conformation of the active site will determine substrate specificity in biochemical systems.[4,9,18]

2. *Promotion of copper(I) oxidation by dioxygen and compatibility with coordination of reduced oxygen.* Although ligand variations are useful in tuning a metal couple to a particular potential,[5a,15] a crucial factor is their effect in determining the stoichiometry and thermodynamics of the reduced oxygen coordination: this is a natural consequence in aprotic systems because anionic oxygen species are nucleophilic and copper(I) oxidation often induces an increase in coordination number.[10]

3. *Determination of the number and geometric relationship of the metals at the site and the final form of reduced dioxygen.* When the geometric and thermodynamic requirements are met all the copper(I) centers at the site will be oxidized by dioxygen. The ligand should be able to respond to the requirements for coordination of reduced dioxygen. Three possible geometries for dioxygen coordination at dimeric copper centers are shown in Fig. 1. Structures I–III have yet to be characterized. It appears that a copper–copper distance of 3.5–



I *II* *III*

FIGURE 1 Alternative structures for the products of aprotic reaction of dimeric copper(I) sites with dioxygen. The dotted line in structure I indicates a potential R-bridging interaction. Structure II, with its inequivalent O atoms, is anticipated at Cu–Cu fixed at < 3 Å and is apparently of low stability (Ref. 10). Structure III has been established spectrally in oxyhemocyanin (Ref. 4b).

4.0 Å (preferably set by a second ligand bridge)[4,14] is a requirement for formation of what is presumably the most stable structure, III.[4,14] Kinetic evidence indicates that alternative structure II, which would be expected at shorter copper–copper distances, is not stable as such under ambient conditions even in the presence of additional (halo) bridges.[10] Structure I seems least likely to be found in copper(I)–dioxygen systems on the basis of available evidence (see below). The ligand system may be able to conform well to the geometric and electronic requirements of copper(II) and stabilize products through hydrogen bonding[12] (but see Ref. 5a). A catalytic oxidizing system will result if the ligand destabilizes copper(II) relative to copper(I)[15] and does not hydrogen bond with reduced dioxygen. Between these extremes is the reversible dioxygen-carrying system.

4. *Resist oxidation.* Even if the ligand system is only weakly protic, the catalytic site will slowly be destroyed in the presence of excess dioxygen or by substrate deficit.[13] There is some evidence that such ligand oxidation can create a desirable geometry for dioxygen reactions in model copper systems[14] (Scheme I).

5. *Prevent active site interactions.* In a system where copper(I) can donate only one or two electrons to dioxygen to create a catalytic product, the ligands must prevent further dioxygen reduction by unoxygenated, mobile copper(I) sites or must physically isolate those sites.[10d]

6. *Create a strongly hydrophobic site* so that only the substrate can donate protons.[4]

We claim no originality for the list and offer it solely as guidelines for those who would build models for active sites in copper–dioxygen systems.

STOICHIOMETRY AND KINETICS IN APROTIC COPPER(I)–DIOXYGEN SYSTEMS

The goal of synthesizing dioxygen carriers or catalytically active species from aprotic copper(I)–dioxygen reactions which are stable at room temperature can, of course, only be achieved if simple, fixed reaction stoichiometries are observed, Eqs. (1)–(3) for monomeric, dimeric and tetrameric reaction centers, respectively.[13]

$$Cu^{I} + O_2 \rightarrow CuO_2 \quad (1)$$

$$Cu^{I}_2 + O_2 \rightarrow Cu_2O_2 \quad (2)$$

$$Cu^{I}_4 + O_2 \rightarrow Cu_4O_2 \quad (3)$$

To our knowledge, reaction (1) has never been observed in aprotic copper(I)–dioxygen systems. Stoichiometry (2) has been established in some ligand systems (Scheme I and Fig. 2), some of which have partially reversible dioxygen-carrying ability but whose structural constitutions have proven very difficult to establish. We might expect the rate law for primary reactions of the copper(I) complexes in Fig. 2 to be Eq. (4) if evidence for ready dioxygen reduction by

$$d[\text{product}]/dt = k[Cu^{I}]^2[O_2] \quad (4)$$

copper(I) centers in similar ligand systems is a reliable guide.[10] The

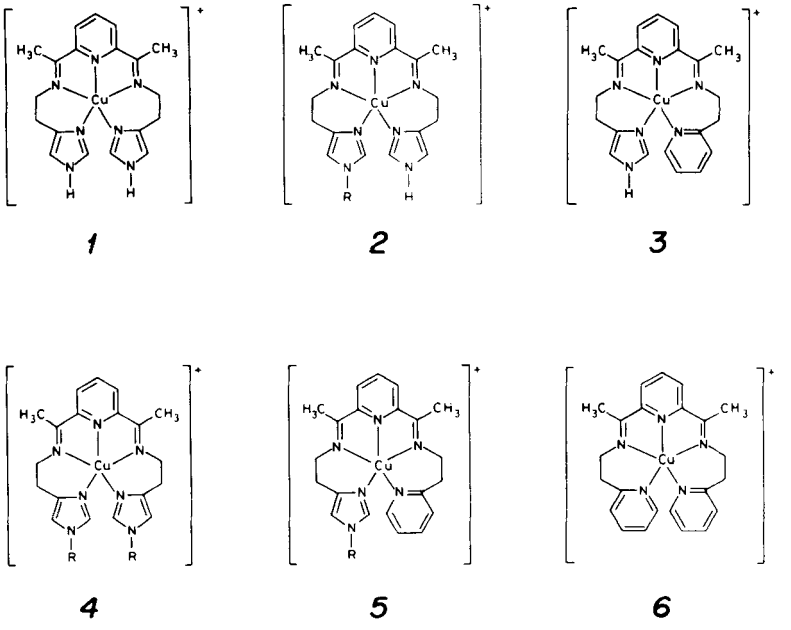


FIGURE 2 Ligand systems employed by Wilson and coworkers (Ref. 5a) to establish reversible dioxygen-carrying by copper(I) centers. The systems are arranged in order of decreasing reversibility.

establishment of this rate law would confirm the tendency for stoichiometric dioxygen reduction in systems where reaction (5) is sterically impossible.[10]

$$Cu_2O_2 + 2Cu^I \rightarrow 2Cu_2O \tag{5}$$

Reaction (6) is by far the most prevalent situation in aprotic

$$2Cu_2^I + O_2 \rightarrow Cu_4O_2 \quad \text{or} \quad 2Cu_2O \tag{6}$$

dimeric copper(I)–dioxygen systems and corresponds to complete dioxygen reduction. This tendency is so great in low molecular weight copper(I) complexes that the rate laws for reactions (3) and (6) are Eqs. (7) and (8), respectively, and are a direct reflection of reactant molecularity.[10]

$$d[\text{product}]/dt = k_T[Cu_4^I][O_2] \tag{7}$$

$$d[\text{product}]/dt = k_D[Cu_2^I]^2[O_2] \tag{8}$$

TABLE I
Kinetic parameters for oxidation of $[LCuX]_2$ (X = Cl, Br) by dioxygen in nitrobenzene (Refs. 10a, 10b, 10d)

Complex	$10^{-3}k_D$[a]	$\Delta H_D^{\neq}$[b]	$-\Delta S_D^{\neq}$[c]
$[TMEDCuCl]_2$	857	3.2	21
$[TMEDCuBr]_2$	44	10.3	3
$[TEEDCuCl]_2$	195	6.9	12
$[TEEDCuBr]_2$[d]	0.55	12.9	3
$[TPEDCuCl]_2$	4.8	12.7	−1
$[TPEDCuBr]_2$	0.48	15.2	−5
$[TAEDCuCl]_2$	112	4.3	21
$[TAEDCuBr]_2$	43.6	8.3	10
$[TMPDCuCl]_2$	1360	4.8	14
$[TMPDCuBr]_2$	123	7.4	10
$[ENCA_2CuCl]_2$[e]	3.1	1.4	38
$[Py_2CuCl]_2$[f]	15.7	0.0	39

Ligand abbreviations: (a) ethylenediamine ligands L = $R_2N(CH_2)_2NR_2$: R = Me, TMED; R = Et, TEED; R = C_3H_7, TPED; R = C_5H_{11}, TAED; (b) $Me_2N(CH_2)_3NMe_2$ = TMPD.

[a]Units are M^{-2} s^{-1} at 25 °C in Eq. (8); typical error is ±5%.

[b]Units are kcal $mole^{-1}$; typical error = ±0.4 kcal $mole^{-1}$.

[c]Units are cal deg^{-1} $mole^{-1}$ at 25 °C; typical error is ±3 cal deg^{-1} $mole^{-1}$.

[d]Data from Ref. 10b.

[e]ENCA = ethylnicotinate, data from Ref. 10a.

[f]Py = pyridine, data from Ref. 10a.

The kinetic data for aprotic oxidation of dimeric halo(tetraalkyldiamine)copper(I) complexes $LCu(X,X)CuL$[10,16] in Table I refer to rate law (8); in no case is reaction (6) (to give $L_2Cu_2X_2O$ species) sterically prevented.[10b,10d]

BASIC THERMODYNAMIC AND KINETIC FACTORS DETERMINING THE STABILITY AND REACTIVITY OF THE PRODUCTS OF DIMERIC COPPER(I)–DIOXYGEN INTERACTIONS

As pointed out in the Introduction, our understanding of the thermodynamics of reactions of iron(II) and cobalt(II) centers with dioxygen is quite advanced.[1-3] The reason for this is that the primary products are sufficiently stable to be characterized.

We have observed that there is a strong tendency for complete dioxygen reduction by low molecular weight dimeric copper (I) complexes in solution. We can think about this in two ways. If Eqs. (1) and (2) are rapid and have large equilibrium constants then there will be little excess copper(I) left to reduce the products. Since reactions (1) and (2) will have negative ΔS, the enthalpy of reaction must be moderate and negative to compensate at room temperature.[1] The second factor is the relative rates of reaction pairs (2) and (5). The latter must have much the smaller rate if any peroxocopper(II) product is to survive.

Nature has the best answer to stabilizing superoxo- and peroxocopper(II) species. The latter are stabilized by physical isolation of dimeric active sites in hemocyanins and tyrosinases,[4] which prevents their reduction by copper(I) despite comparatively low equilibrium constants for oxygenation. It seems that the building of stable models for oxyhemocyanins and oxytyrosinases will only result from the oxygenation of dilute dimeric copper(I) sites in functionalized polymeric systems. It should be possible to work with more concentrated sites than found in the metalloproteins, which will hopefully simplify characterization of the products. Fortunately, there is a considerable amount of data available for the kinds of ligands which are likely to suit the purpose.[17]

Figure 3 depicts three possible enthalpy profiles for formation of a putative peroxocopper(II) species, P, from a mobile copper(I) dimer

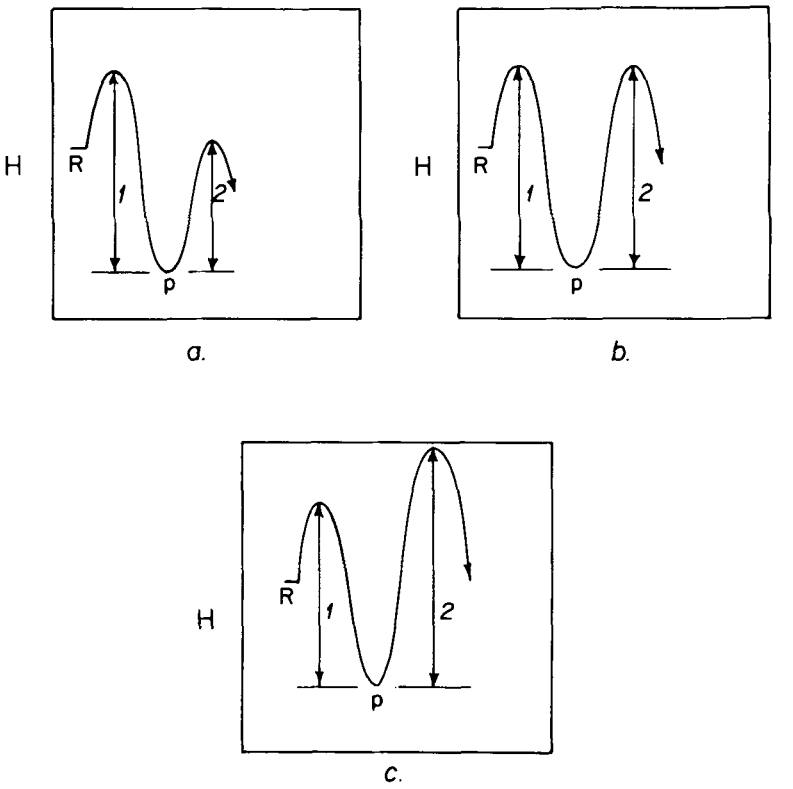


FIGURE 3 Enthalpic alternatives for dimeric copper(I)–dioxygen interactions.

and a molecule of dioxygen as reactants, R, in solution. The enthalpy change for this reaction, ΔH_1, will, of course, be ligand dependent, but we have made it a constant, negative quantity in Fig. 3 to simplify discussion. The enthalpy of activation for the process P → R, $\Delta H^{\neq}_1$, is also kept constant. Significant kinetic reversibility between R and P requires that ΔH_1 and $\Delta H^{\neq}_1$ be near zero (for instance, approximately −2 and +4 kcal mole^{-1}, respectively).[1]

Processes that can complete with reversible oxygenation of copper(I) are represented by barrier heights (2) and include the following:

1. Reaction with excess dimeric copper(I). Note that the appearance of oxocopper(II) products through rate law (8) makes reaction (5), with a small equilibrium constant for reaction (2),[10b] the rate-deter-

mining process in this case. This situation is eliminated in oxyhemocyanin and oxytyrosinase by physical isolation of the copper sites and we hope that it can be simulated in functionalized polymeric systems (see above). We will neglect it in discussion of other possibilities.

2. Aprotic disproportionation of P, for example, through $O_2^{2-} \rightarrow O^{2-} + O$ in P.[6] Such a process would perhaps be favored by structure II (Fig. 1) or allowed by the existence of two different ligand environments for copper in structure III; the latter situation would make the two oxygen atoms of that structure electronically inequivalent.[18] In either case, disproportionation results in oxygenase activity, as found in step **2** → **3** of Scheme I[6] or in the *o*-hydroxylation of a protic, phenolic substrate. The possibility that the ligand system or substrate induces disproportionation by protonation is worth considering,[4b,18] although we see no obvious reason for particularly basic oxygen sites in structure III and the C–H bond into which O is inserted in the ligand in the first reaction of Scheme I is not notably acidic. Since the copper centers in Scheme I remain stereochemically equivalent throughout, this raises the question as to whether the putative peroxocopper(II) intermediate in the first reaction has structure II of Fig. 1.

Hemocyanins are reversible dioxygen carriers which do not *o*-hydroxylate phenols, whereas tyrosinases catalyze this process. Since structure III is assigned to the oxy-form of both metalloenzymes,[4b,4c] could it be that the active sites of tyrosinases are sufficiently different that proton-assisted disproportionation is possible or is it just a matter of substrate accessibility?[4b,18]

The three enthalpic alternatives in Fig. 3 are presented to emphasize the kinetic and thermodynamic relationships which will determine the fate of peroxocopper(II) species, given that the basic requirements for a stabilizing ligand system have been met (see above). Figure 3a represents the situation where peroxocopper(II) is an intermediate in the irreversible formation of other products by ligand oxidation. Figure 3b refers to a partially reversible dioxygen carrier.[5a] If $\Delta H_2^{\neq}$ is sufficiently large relative to $\Delta H_1^{\neq}$, and ΔH_1 is sufficiently negative to give a significant equilibrium constant for reaction (2), then a reversible dimeric copper(I) dioxygen-carrying system with significant dioxygen capacity[1-3] will result (Fig. 3c).

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Note Added in Proof. Solomon and co-workers have concluded from the spectra of oxytyrosinase–carboxylate inhibitor complexes that coordination of a substrate analogue does indeed cause the two copper(II) centers at the active site to become inequivalent, favoring peroxide disproportionation. Thompson[19] has reported the reversible formation of epr-silent, blue $[L_2Cu_2(O_2)(H_2O)](ClO_4)_2$ (L = TEED), which contains bridging peroxo and water ligands. The solid is quite stable at room temperature, but decomposes to $[L_2Cu_2(OH)_2](ClO_4)_2$ under dinitrogen in methanol even at low temperatures. Ligand oxidation takes place in the presence of O_2.

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