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Encapsulated Dicopper(I): Kinetic or Thermodynamic Stabilization?

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ABSTRACT

Cyclic voltammetry of a series of air-stable dicopper(I, I) azacryptates indicates that some, including those with heterocyclic-N-donor spacers, are thermodynamically unstable towards oxidation by O_2; in this case outer-sphere oxidation by Fc^+ or Ag^+ is readily achieved.

The siting of copper in a coordination environment composed of soft donors such as sp^2 N- and/or S-ligands is a recurrent theme in bioinorganic chemistry [1]. Such an environment frequently generates a borderline Cu(I)/Cu(II) stability for utilization in enzyme-mediated redox transformations. In abiological systems, particularly where geometric constraint is absent, soft donors such as S- or P- are normally considered necessary to stabilize Cu(I) [2]. However, it has been noted [3] that ligands which favor tetrahedral coordination geometry destabilize Cu(II) even in the absence of S- or P-donors. Recent dramatic examples of geometrically constrained all-N-donor ligands which enhance Cu(I) stability include the catenanes synthesized by Sauvage [4], where tetrahedral coordination by the orthogonally disposed pairs of N2 donors is unavoidable.

A pair of copper ions ligated by 3 sp^2 N-donors constitutes a good structural model for the coupled (Type 3) sites in Hc, Tyr, and multicopper oxidases (until recently believed to be identical in structure and function): However, recent results have demonstrated important differences between these superficially similar sites [5]; significantly, the Type 3 site in the oxidase cluster is unreactive toward O_2 in the absence of the Type 2 site. This unexpected finding renews interest in the oxygenation and redox behavior of dicopper model compounds.

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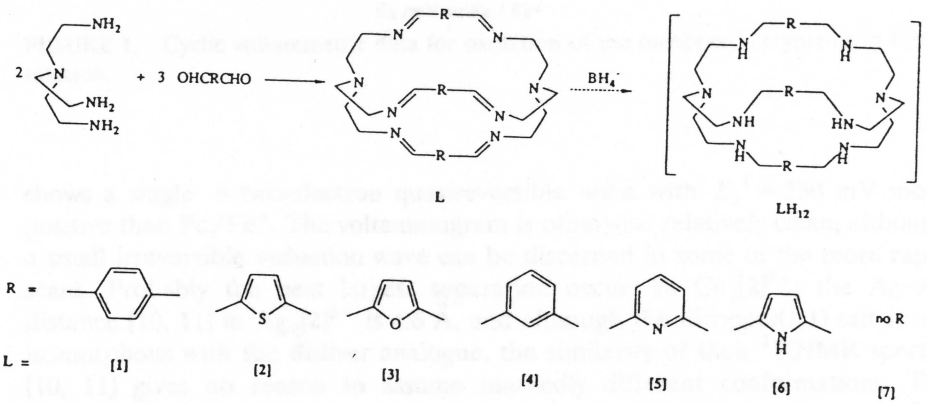
Azacryptand ligands [1]–[7] are easily generated [6] by template or nontemplate [2 + 3] condensations of *tris*-2-ethylamino amine (tren) with appropriate dicarbonyls (Scheme 1). These binucleating ligands present a pair of trigonal N3 or distorted tetrahedral N4 coordination sites depending on whether or not the bridgehead N is utilized. In some cases, there is also the possibility of coordinating one or more heteroatoms from the "spacer" groups, given favorable conformation. X-ray crystallographic structural data, available for dicopper(I, I) cryptates of [1] [7], [3] [8], and [5] [8] confirms the dominance of trigonal/distorted tetrahedral coordination geometry; in other cases structural information exists only for the free ligand [9] or the disilver cryptate [10], but gives no reason to doubt the tendency of the ligands to adopt 3-fold symmetric geometry wherever possible. Structural data also illustrate the moderately good steric protection afforded the coordination sites within the cryptand.

Scheme 1



In no case does the coordination geometry presented by the cryptand host approximate to the square-based arrangement preferred by Cu(II), so some stabilization of the +1 oxidation state is to be expected. Nonetheless, we were surprised to discover that none of the dicopper(I, I) cryptates were subject to air oxidation within a period of hours in either acetonitrile or dimethylformamide (DMF) solutions. In order to investigate whether this stability arises from thermodynamic or kinetic factors a preliminary study of the electrochemistry of the dicopper complexes was undertaken.

RESULTS AND DISCUSSION

The dicopper(I, I) cryptates (yellow-brown microcrystalline solids, readily soluble in dimethylformamide) were easily obtained upon treatment of the free ligand (where available) with the appropriate copper(I) salt[1], or alternatively, in somewhat higher yield by template condensation of triamine and dialdehyde on Cu(I). Figure 1 illustrates, in schematic form, the results obtained in cyclic voltammetric experiments (reported in more detail in Table 1).

The largest internuclear separation, 6.06 Å [7] is seen in $Cu_2[1]^{2+}$, which

[1] In the case of [1] and [2], even treatment with copper(II) salt generated the dicopper(I, I) cryptate.

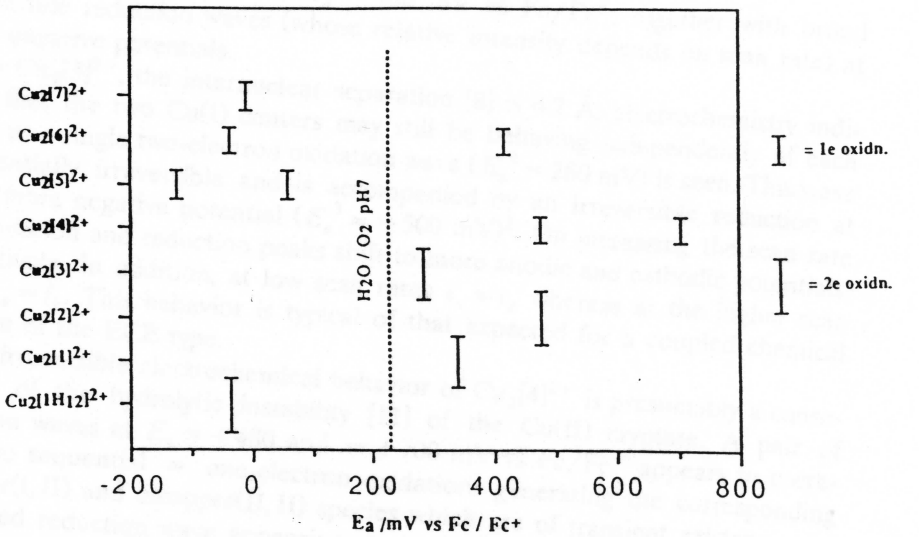


FIGURE 1. Cyclic voltammetric data for oxidation of the dicopper(I) cryptates in DMF solution.

shows a single ≈ two-electron quasireversible wave with $E_a^1 = 330$ mV more positive than Fc/Fc^+. The voltammogram is otherwise relatively clean, although a small irreversible reduction wave can be discerned in some of the more rapid scans. Probably the next largest separation occurs in $Cu_2[2]^{2+}$; the Ag–Ag distance [10, 11] in $Ag_2[2]^{2+}$ is 4.6 Å, and although the dicopper(I, I) salt is not isomorphous with the disilver analogue, the similarity of their ^{1}HNMR spectra [10, 11] gives no reason to assume markedly different conformations. The electrochemistry in this case takes the form of a single almost irreversible

TABLE 1. Cyclic Voltammetric Data[g] for Dicopper Cryptates

Cryptate	E_a^{1d}	E_c^1	ΔE	E_a^{2c}	E_c^2	ΔE	E_c^{3f}	Notes
$Cu_2[1]^{2+}$	330[a]	130[a]	200 *qr*	—	—	—	−480 w, *irr*	
$Cu_2[2]^{2+}$	480[a]	310[a,b]	170 *qr*	—	—	—	−450 br, *irr*	In some scans a broad *irr* cathodic peak −70 mV
$Cu_2[3]^{2+}$	280[a] *irr*		—	—	—	—	−510 br, *irr*	
$Cu_2[4]^{2+}$	480[d] *irr*		—	700[e] *irr*		—	−480 br	In 2nd and subsequent scans, a sharp anodic peak −380 mV
$Cu_2[5]^{2+}$	−110[d]	−190	80 *qr*	+60[e]	−20	80 *qr*	−450 br, *irr*	
$Cu_2[6]^{2+}$	−30[d]	−110	80 *r*	410[e] *irr*		—	−500 br, *irr*	+630 *irr* oxidation wave
$Cu_2[7]^{2+}$	−15[e]	−125[e]	110 *r*	—	—	—	—	
$Cu_2[1H_{12}]^{2+}$	−50[a,b]	−175[a,b]	125 *qr*	—	—	—	−800 br, *irr*	−370 mV stripping peak

[a]Only one broad two-electron wave observed; [b]reduction component weak; [c]one-electron wave *only* observed; [d]assumed $\{Cu[L]\}^{2+}$ oxidation; [e]assumed $\{Cu[L]\}^{3+}$ oxidation; [f]irreversible reduction of oxidation decomposition product; [g]scan rate 50 mV s^{-1}, DMF solution.

E_a = anodic peak potential, E_c = cathodic peak potential; $\Delta E = E_a - E_c$. *r* = reversible, *irr* = irreversible; *qr* = quasireversible.

two-electron oxidation wave, $E_a^1 = 480$ mV vs Fc/Fc^+, together with broad irreversible reduction waves (whose relative intensity depends on scan rate) at more negative potentials.

For $Cu_2[3]^{2+}$, the internuclear separation [8] is 4.2 Å; electrochemistry indicates that the two Cu(I) centers may still be behaving independently of each other, as a single two-electron oxidation wave ($E_a^1 = 280$ mV) is seen. This wave is essentially irreversible and is accompanied by an irreversible reduction at much more negative potential ($E_c^3 \approx -500$ mV)[2]. On increasing the scan rate the oxidation and reduction peaks shift to more anodic and cathodic potentials, respectively. In addition, at low scan rates $i_a > i_c$ whereas at the higher scan rates $i_a \approx i_c$. This behavior is typical of that expected for a coupled chemical reaction of the ECE type.

The irreversible electrochemical behavior of $Cu_2[4]^{2+}$ is presumably a consequence of the hydrolytic instability [11] of the Cu(II) cryptate. A pair of oxidation waves at $E_a \approx +480$ and $\approx +700$ mV vs Fc/Fc^+ appears to correspond to sequential one-electron oxidations generating the corresponding dicopper(I, II) and dicopper(II, II) species which are of transient existence. An associated reduction wave appearing at -480 mV vs Fc/Fc^+ with an anodic component at -380 mV, which may correspond to stripping, presumably results from redox transformation of the decomposition product of the oxidized form, $Cu_2[4]^{4+}$.

Two closely spaced partly reversible one-electron oxidation waves: $E_a^1 = -110$ and $E_a^2 = +60$ mV vs Fc/Fc^+ are observed for $Cu_2[5]^{2+}$, which has been structurally characterized [8], revealing a Cu–Cu distance of 3.04 Å. It is important to note the much enhanced thermodynamic stability of the +2 oxidation state in $Cu_2[5]$ versus $Cu_2[4]$. This stabilization (corresponding to a difference of some 600 mV in the potentials of the respective $Cu_2^{n+}/Cu_2^{(n+1)+}$ couples) arises from the hemicoordination [8] of one of the three heteroatom N-donors to each Cu(I) ion in [5], constituting overall a more acceptable coordination geometry for Cu(II).

For ligand [6], no structural data is as yet available[3] in either the free or complexed form. However, the appearance of a pair of one-electron oxidation waves (one, near reversible, with $E_a^1 = -30$ mV; the other irreversible, $E_a^2 =$ 410 mV) for $Cu_2[6]^{2+}$ suggests that the copper cations may be in sufficiently close proximity to interact strongly and thus generate a thermodynamically stable mixed-valence region (between around -30 and $+410$ mV). The complexity of the electrochemical behavior at potentials above 410 mV suggests electroactivity of the ligand. (In $Na[6]^+$ we observe ill-defined oxidation activity above about $+500$ mV vs Fc^+/Fc which we assign to ligand-centered processes.) Electrochemical oxidation of the ligand may result in deprotonation of the pyrolle NH in the manner well-established for porphyrin complexes, which may

[2] An irreversible reduction around this potential is a common feature of many of the voltammograms (see E^3 entries in Table 1). The occurrence of an irreversible reduction wave in DMF-solvated Cu^{2+} at similar potential suggests the possibility of dissociation in the oxidized form of the cryptate.

[3] Note added in proof: X-ray crystallographic structure determination of the dicopper cryptate of [6], how completed [16], shows a Cu–Cu separation of 3.00Å.

account for the irreversible nature of the 410 mV oxidation wave. Once deprotonation has taken place, the oxidation state of the coordinated cation may not be easily defined because of electron delocalization, as commonly observed in porphyrin complexes between metal and ligand [12].

We have already reported [13, 14] on the electrochemistry of the final dicopper(I, I) cryptate, $Cu_2[7]^{2+}$, which is included here for comparison. Stoichiometric oxidation of this dicopper(I, I) complex with Ag^+ demonstrates that the near-reversible wave with $E_a^{\,1} = -15$ mV vs Fc/Fc^+ is a one-electron process, so we have been able to use the magnitude of the peak current associated with this oxidation as calibrant for the other oxidation waves. (This calibration is necessarily only approximate when comparing waves which differ in breadth from the calibrant or which are subject to overlapping.)

The implications of the redox behavior illustrated in Figure 1 is that $Cu_2[5]^{2+}$, $Cu_2[7]^{2+}$, and $Cu_2[6]^{2+}$ are thermodynamically capable of being oxidized by atmospheric O_2. These cryptates, however, appeared stable in air, as judged by absence of color change or development of ESR spectra, on exposure to air or oxygen. As the redox potential of the O_2/H_2O couple under neutral conditions is very similar to that of Ag/Ag^+, a useful check on the existence of kinetic barriers to air-oxidation is examination of the response to Ag^+ oxidation. (It has to be remembered, however, that the fate of reduced oxygen in a dicopper cryptate may be quite different from the H_2O produced in aqueous oxidations.) Treatment of $Cu_2[7]^{2+}$ with Ag^+ instantly generates the average valence, intensely blue, $(Cu^{1.5}\text{–}Cu^{1.5}[7])^{3+}$ species [14]. Similarly, $Cu_2[5]^{2+}$ develops a greenish brown color (arising from the development of d-d absorption at 590 and 630 nm) as well as an ESR signal immediately on treatment with 1 equivalent of Ag^+ or Fc^+. The ESR signal (which integrates to $\approx 75\%$ the intensity of a $Cu(ClO_4)_2.6H_2O$ standard of the same concentration) of freshly made solutions takes the form of a simple axial 4-line ($A_{/\!/} = 120$ G) pattern in the DMF glass spectrum as typical of noninteracting Cu^{2+}, with evidence of decomposition in solutions which are more than one-half hour old. (The use of the stronger oxidizing agent, H_2O_2, generates a spectrum which contains the four-line pattern overlapped with an underlying broad $g = 2.1$ feature.) It seems that the mixed-valent form of $Cu_2[5]$, unlike that of $Cu_2[7]$, is localized on the ESR time scale at ambient temperature.

Although $Cu_2[6]^{2+}$ failed to develop an ESR signal even two days after bubbling O_2 through the DMF solution, the response to Ag^+ or Fc^+ treatment was immediate. A yellow-green color with d-d absorption at 730 nm ($\epsilon = 150$ mol^{-1} cm^2) and a complex ESR spectrum (which in this case remained unchanged over several days) developed instantly after such treatment. The fluid solution ESR spectrum of the oxidation product of $Cu_2[6]^{2+}$, however, suggests dissociation of the oxidized species, because it appears to contain the ESR signal of DMF-solvated copper(II), overlapped with other, as yet unattributed, signals centered to lower g values. This overlapping precludes any decision on the degree of delocalization in the mixed-valent species in this case.

It appears that even where thermodynamic considerations permit access to the +2 or mixed-valence state of copper encapsulated within these cryptands, kinetic factors are responsible for stabilizing the dicopper(I, I) state under aerobic conditions; in the absence of bridging anionic ligands, to the exclusion of the dicopper(II, II) state. Only where anionic ligands can be accommodated

within the sterically constrained cavities, have we been able to synthesize dicopper(II) complexes; e.g., Cu_2[**1**][NCS]$_4$ [7], Cu_2[**3**]OH^{3+}, and Cu_2[**4**]OH^{3+} [11].

Another strategy which we have used with some success to generate dicopper(II, II) complexes is the modification of the ligand by means of imine hydrogenation [13] to produce the octaamino derivatives [**1** + 12H = [$1H_{12}$], etc.] (see Scheme 1). A dicopper(I, I) cryptate of [$1H_{12}$] has been synthesized, which, somewhat to our surprise, shows no tendency to air-oxidation. The voltammogram is almost irreversible, showing a two-electron oxidation wave with only a small reduction component. The fact that the Cu^{2+}/Cu^{4+} couple for Cu_2 accommodated within [$1H_{12}$] is some 370 mV more cathodic than in the case of the unsaturated analogue [**1**] indicates enhancement of Cu(II) stability within this "harder" amino-donor ligand; however, as in the case of Cu_2[**5**]$^{2+}$, Cu_2[**6**]$^{2+}$, and Cu_2[**7**]$^{2+}$, the lack of reactivity toward atmospheric oxygen cannot be rationalized on thermodynamic grounds alone and once more testifies to kinetic stabilization of a potentially redox-active cation within the sterically protected cavity. It remains to be seen whether the lack of O_2 reactivity of the Type 2-depleted site in laccase (which, like these cryptates, is easily oxidized by H_2O_2) can similarly be attributed to kinetic factors.

EXPERIMENTAL

Complexes $Cu_2L[X]_2$ L = [**1**]–[**6**]; X = BF_4^-

The complexes were prepared by heating together, at 50°C, 2 mmole *tris*-2-ethylaminoamine (tren) and 3 mmole of the appropriate dialdehyde in ≈ 130 cm^3 of a 1:3 MeCN/EtOH solvent under nitrogen and adding $Cu(MeCN)_4BF_4$ as a solid. The volume was reduced by bubbling N_2 until orange crystals started to appear, whereupon the solution was left to stand in ice for some hours before filtering. Yields typically ≈ 60–70%. [$1H_{12}$] and [**7**] salts were obtained as previously described [13, 15].

Alternatively, 0.5 mmole ligand [**1**]–[**5**] was dissolved in 50 cm^3 CH_2Cl_2, and 50 cm^3 EtOH added and the solution deoxygenated. 1.1 mmole Cu[MeCN]$_4BF_4$ in 30 cm^3 deoxygenated MeCN was then added and volume was reduced until crystals appeared. (Analytical data supplied as supplementary material.)

Electrochemical Measurements

Cyclic voltammograms were recorded (≈ 20°C and under N_2) using an EG&G Model 264 A or 362 polarographic analyzer, and the data was analyzed using the EG&G Condecom software package (iRu compensation was not used). A glassy carbon disk and a platinum wire were employed as the working and counter electrodes, respectively. Potentials (± 10 mV) are quoted with respect to that of ferrocene/ferrocenium(1 +) couple which is arbitrarily given the value of 0 volts. Silver/silver chloride was used as the reference electrode in the cell, against which the Fc/Fc^+ couple had $E_{1/2}$ = 382 mV.

Tetraethylammonium perchlorate (0.1 M)/dimethylformamide was used as the supporting electrolyte/solvent system, and sample concentration was 4.0×10^{-3} M. Scan rate was 50 mV s^{-1}.

ESR measurements were made using a Varian E109 spectrometer equipped with Hewlett-Packard Data Acquisition system and 0.2 mm flat cells were used for fluid solution measurements.

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