

Use of macrocyclic polythiaether ligands in structure-reactivity studies of copper(II)/(I)

D. B. Rorabacher,* M. M. Bernardo, A. M. Q. Vande Linde, G. H. Leggett, B. C. Westerby, M. J. Martin, and L. A. Ochrymowycz

Departments of Chemistry, Wayne State University, Detroit, Michigan 48202, and University of Wisconsin-Eau Claire, Eau Claire, Wisconsin 54701, U.S.A.

Abstract - In studying the relationship between structure and reactivity in the electron-transfer behavior of Cu(II)/(I), macrocyclic polythiaether ligands have been used to generate relatively high Cu(II)/(I) redox potentials while, at the same time, exerting a degree of control upon the coordination geometry of the copper atom. Electrochemical studies over a wide variety of conditions have provided evidence that both the Cu^{II}L and Cu^IL species exist in at least two conformational states. It is proposed that, depending upon the conditions used, conformational rearrangement may either precede or succeed the electron-transfer step resulting in the generation of a "square" mechanistic scheme. Stopped-flow kinetic studies on homogeneous electron-transfer reactions with selected cross reagents can also be interpreted in terms of the same type of "square" scheme. This hypothesis can then be used to explain the discrepancies in apparent self-exchange rate constants which normally arise from applying the Marcus relationship to Cu(II)/(I) electron-transfer processes. Preliminary determinations of Cu(II)/(I) self-exchange rate constants from nmr measurements appear to be reasonably consistent with this hypothesis.

INTRODUCTION

The relationship between structure and reactivity is of central interest in all aspects of chemistry. In the area of metal coordination chemistry, inferences regarding the dependence of metal ion reactivity upon structure are limited by the degree to which the coordination environment surrounding the central metal ion can be controlled and/or varied by introducing steric constraints into the ligand architecture. In this respect, macrocyclic ligands are particularly well suited for such studies because of their inherent control of the cavity size. The introduction of substituents upon the ligand backbone, bridging groups, or internal multiple bonds can be used to enhance further the steric restrictions and rigidity of the coordination environment.

Metalloenzymes represent one of the most significant manifestations of structural control on reactivity. Nearly two decades ago, Vallee and Williams formulated an "entatic state" hypothesis (ref. 1) in which they proposed that the unusually high reactivity of all enzymes was attributable to the geometric constraints imposed upon the reactive center by the surrounding protein matrix. These constraints are conceived to minimize the atomic rearrangements required at the active site of the enzymes during the course of the reaction, thereby lowering the required activation energy and increasing the observed rate constants. Incorporated into this hypothesis was the suggestion that the geometry of the active site in resting enzymes approximates that of the transition state of similar unconstrained systems.

In discussing this hypothesis, Williams (ref. 1b) focused attention upon redox enzymes involving iron and copper centers (the most common metals found in biological electron-transfer systems). He noted that the geometric rearrangements normally occurring upon converting Fe(II) to Fe(III) in inorganic complexes involve a shortening of the iron-donor atom bonds. This led him to propose, therefore, that in iron enzymes the protein matrix may be presumed to constrain the iron-donor bonds to a length intermediate between that preferred by Fe(II) and by Fe(III).

For Cu(II)/(I) systems, larger rearrangements of the inner-coordination sphere are generally anticipated since Cu(II) tends to prefer distorted octahedral (i.e., tetragonal) or square pyramidal geometries whereas Cu(I) shows a strong preference for a tetrahedral environment. This implies that, in an unconstrained environment, one or two coordinate bonds must be ruptured in reducing Cu(II) to Cu(I). In addition, a significant alteration in bond angles must also occur.

In the "blue electron carriers" (a special class of blue copper proteins containing a single type 1 copper ion), crystal structure determinations have revealed that the active copper site is indeed in a distorted tetrahedral (or elongated trigonal pyramidal) geometry (ref. 2). This geometric arrangement has been credited both for the high redox potentials and for the large observed self-exchange electron-transfer rate constants which have been observed for this class of metalloproteins. However, this presumed structural influence upon the redox behavior of copper has never been thoroughly tested. Although some attempts have been made previously to examine the correlation between copper coordination geometry and the resultant redox potentials (ref. 3), no systematic examination of the influence of coordination geometry upon Cu(II)/(I) self-exchange rate constants has previously been reported. For the most part, in fact, nearly all studies on the electron-transfer kinetics of copper complexes have involved the reduction of Cu(II) to

Cu(I) (ref. 4) since the tendency for most Cu(I) species to undergo disproportionation generally makes it difficult to study the oxidation process.

In pursuing studies on the properties of macrocyclic polythiaether complexes with Cu(II), we have long been intrigued by the similarities in behavior between these latter complexes and the type 1 copper site in the simple blue copper proteins. These similar properties include the very strong visible absorption bands which give rise to the intense color of both the blue copper proteins and the copper polythiaethers (ref. 5a) and their relatively high Cu(II)/(I) redox potentials (ref. 5b) (see Table 1). In fact, of the unique properties exhibited by the type 1 copper centers, only the unusual A_{11} values of the latter species, which are attributable to the distorted coordination geometry, are not mimicked by the polythiaether complexes.

TABLE 1. Apparent formal Cu(II)/(I) potential values, major visible absorption peaks, and molar absorptivity values for Cu(II) polythiaether complexes and representative blue electron carrier proteins.

Coordinated Ligand	E^f , V (vs. NHE)	$\lambda_{\max(1)}$, nm	$\epsilon \times 10^{-3}$ at $\lambda_{\max(1)}$	$\lambda_{\max(2)}$, nm	$\epsilon \times 10^{-3}$ at $\lambda_{\max(2)}$
Inorganic Complexes					
[12]aneS ₄	0.64	387	6.9	675	2.0
[13]aneS ₄	0.52	390	6.1	625	1.8
[14]aneS ₄	0.60	390	8.2	570	1.9
[15]aneS ₄	0.64	414	8.0	565	1.1
[16]aneS ₄	0.69	440	6.1	603	0.8
Me ₂ -2,3,2-S ₄	0.81	407	7.9	610	~1.2
Et ₂ -2,3,2-S ₄	0.81	410	6.8	612	1.1
[15]aneS ₅	0.70	414	6.2	565	~2
Type 1 Copper Proteins: Blue Electron Carriers					
Plastocyanin	0.36	460	1.2	597	9.8
Azurin	0.33	467	0.2	625	3.5
Stellacyanin	0.18	448	0.6	604	3.8
Rusticyanin	0.67			597	2.2

In view of the striking similarities between the low molecular weight inorganic copper polythiaethers and the blue electron carriers, a comparative study of their electron-transfer kinetics seemed most appropriate. By exploiting the differences in the copper coordination geometry induced by varying the macrocyclic ring size and the number of donor atoms, it was hoped that such studies might shed light on the degree to which the coordination geometry influences the actual rate of electron transfer to and from the copper site.

Of the limited number of electron-transfer studies which have previously been carried out on the Cu(II)/(I) couple in low molecular weight complexes, most have involved either unsaturated nitrogen donor atoms or a combination of unsaturated nitrogens and sulfur donors (refs. 4, 7-9). By focusing our studies on systems involving principally thiaether sulfur donor atoms, we have profited from several advantages including (i) the presence of a single type of donor atom (other than solvent molecules) in the inner-coordination sphere, (ii) a complete lack of observable ligand protonation phenomena, and (iii) the generation of the highest Cu(II)/(I) potential values ever observed in aqueous or mixed aqueous solvents (ref. 6).

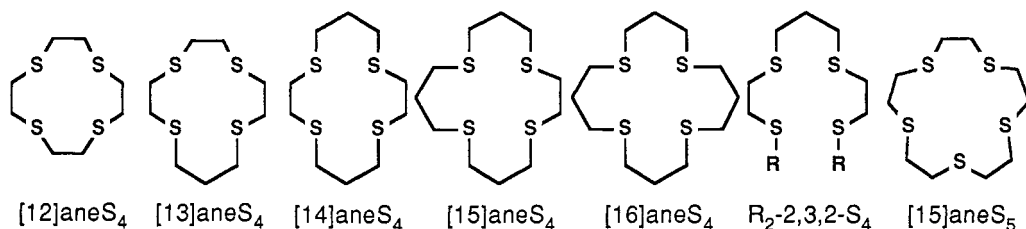


Fig.1. Polythiaether ligands discussed in this work.

In general, the stability constants for the Cu(II) complexes formed with open-chain polythiaether ligands are extremely small in aqueous solution. By utilizing macrocyclic ligands, however, these values may be enhanced by about 100-fold (ref. 6) as illustrated in Table 2. [Since the apparent stabilities of most of the Cu(II)-polythiaether complexes are known to increase with increasing concentration of anion (ClO_4^- , BF_4^- , or CF_3SO_3^-), it is necessary to distinguish

between the thermodynamic stability constant values, K_{CuL}^0 , and the conditional stability constant values for specific anion concentrations, K_{CuL}' (quoted in Table 2 for 0.1 M ClO_4^-).

TABLE 2. Logarithmic stability constants and related thermodynamic parameters for Cu(II)-polythiaether complexes in aqueous solution at 25° (ClO_4^- media).

Coordinated Ligand	$\log K_{CuL}'$ ($\mu = 0.1 M$)	$\log K_{CuL}^0$ ($\mu = 0$)	ΔH_{CuL}^0 kJ mol ⁻¹	ΔS_{CuL}^0 J K ⁻¹ mol ⁻¹
[12]aneS ₄	3.48	3.27	-2.6	54
[13]aneS ₄	3.41	3.15	-6.2	39
[14]aneS ₄	4.34	4.04	-13.0	34
[15]aneS ₄	3.17			
[16]aneS ₄	~2.2	~1.9		
Me ₂ -2,3,2-S ₄	2.0			
Et ₂ -2,3,2-S ₄	2.2			
[15]aneS ₅	4.07	4.01	-12.2	36

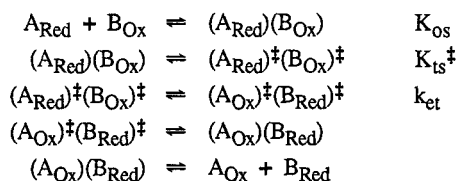
THEORETICAL CONSIDERATIONS

For any homogeneous oxidation-reduction process (eq 1),



the reacting oxidant and reductant must diffuse together to achieve sufficient orbital overlap to promote electron transfer. In the case of an outer-sphere electron-transfer mechanism (to which the current discussion will be limited), the two reactants are conceived to diffuse to a point of surface-to-surface contact with no interactions other than coulombic forces being of significance. Since the movement of electrons is much more rapid than the movement of atoms (Franck-Condon Principle), it is presumed that the atoms must rearrange to the configuration of the transition state prior to the electron-transfer step in order for net transfer to occur. This stepwise mechanism is shown in Scheme 1:

Scheme 1



In this mechanism, K_{Os} represents the equilibrium constant for the formation of the precursor outer-sphere complex, $(A_{Red})(B_{Ox})$, (i.e., the contact pair); K_{ts}^\ddagger represents the equilibrium constant for the formation of the transition state configuration; k_{et} is the rate constant for the actual electron-transfer step; $(A_{Red})^\ddagger(B_{Ox})^\ddagger$ and $(A_{Ox})^\ddagger(B_{Red})^\ddagger$ represent the rearranged (transition-state) configurations of the outer-sphere complex before and after the electron-transfer step, respectively; and $(A_{Ox})(B_{Red})$ represents the successor outer-sphere complex. Based on this mechanism, the overall cross-exchange electron-transfer rate constant can be expressed as:

$$k_{12} = K_{Os} K_{ts}^\ddagger k_{et} \quad (2)$$

Of the terms in eq 2, it is presumed that the value of K_{ts}^\ddagger , which involves the free energy contributions for rearranging both the inner-coordination sphere of the metal ion and the surrounding solvent shell, is most sensitive to structural variations at the active site.

Using the foregoing premises, Marcus (ref. 10) and Hush (ref. 11) independently developed theoretical equations correlating the rate constants of "cross-reaction" electron-transfer processes between differing reaction partners (eq 1) to the rate constants for the corresponding "self-exchange" reactions (eqs 3 and 4):



The resulting relationship as generated by Marcus may be expressed as:

$$k_{12} = \left[k_{11} k_{22} K_{12} f_{12} \right]^{\frac{1}{2}} W_{12} \quad (5)$$

where K_{12} is the equilibrium constant for the overall reaction (dependent upon the potential values of the two component redox couples),

$$K_{12} = \exp \left[\frac{(E_{11}^f - E_{22}^f) nF}{RT} \right] \quad (6)$$

f_{12} is a non-linear correction term, and W_{12} is the so-called work term to correct for differences in coulombic interactions between the two component self-exchange reactions and the cross reaction (see, e.g., ref. 12).

Most of the published studies on Cu(II)/(I) systems have involved the reduction of Cu(II) complexes since the corresponding Cu(I) species are frequently unstable relative to disproportionation and, therefore, more difficult to work with as starting reagents. For the few cases in which kinetic studies have been reported for both the oxidation and reduction of the same copper complexes, a huge discrepancy exists between the k_{11} values resolved from the two processes (see e.g., ref. 4). In calling attention to this discrepancy, Lee and Anson (ref. 13) have suggested that eq 5 does not apply to Cu(II)/(I) systems since the rupturing of inner-sphere coordinate bonds, which accompanies the reduction of Cu(II) to Cu(I) in most known inorganic copper complexes, may invalidate the harmonic oscillator model which forms the basis for the Marcus cross relationship.

SYSTEMATIC STUDIES OF COPPER(II)/(I) SYSTEMS

As noted in the Introduction, we have utilized a variety of macrocyclic polythiaether complexes to investigate the electron-transfer properties of Cu(II)/(I) systems. In order to characterize these systems fully, we have applied a series of electrochemical and kinetic techniques including:

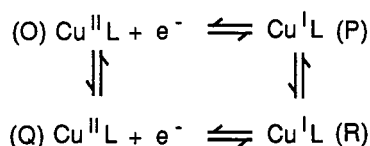
- (i) Cyclic voltammetric measurements to diagnose the mechanisms of the heterogeneous electron-transfer reactions.
- (ii) Potentiostatic measurements with spectrophotometric monitoring to establish the formal potentials for the thermodynamically stable species.
- (iii) Stopped-flow kinetic measurements to determine the rate constants for cross reactions between Cu(I) or Cu(II) with other selected reagents (eq 1).
- (iv) Line-broadening nmr measurements to determine the rate constants and activation parameters for Cu(II)/(I) self-exchange reactions (eq 3).

Cyclic voltammetric studies. Cyclic voltammetric studies on the various Cu(II)/(I) polythiaether systems have yielded a variety of patterns of behavior (ref. 14). For several systems (e.g., Cu([15]aneS₄)^{2+/+} and Cu([15]aneS₅)^{2+/+}), reversible behavior has been observed, both in water and in methanol-water mixtures, in which a single reduction and a single oxidation peak are observed at all attainable sweep rates and temperatures. For a number of other systems, however, the emergence of a second oxidation peak is observed with increasing sweep rate and/or at lower temperature. This phenomenon is illustrated for Cu([14]aneS₄)^{2+/+} in Figs. 2 and 3.

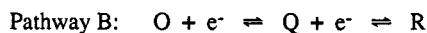
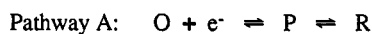
In systems where a second oxidation peak is observed, the relative heights of the two observed peaks are dependent on both the sweep rate and the temperature. In order to characterize this behavior, extensive studies have been conducted using both Cu^IL and Cu^{II}L solutions under a variety of conditions. The observed behavior has been shown to be consistent with the existence of two alternate conformers of the Cu^IL complex, the less stable species being re-oxidized to Cu^{II}L at a more positive potential. The reduction peak corresponding to this second oxidation peak is never well developed and, therefore, can not be thoroughly investigated.

The overall electrochemical behavior of the Cu(II)/(I)-polythiaether systems is consistent with a "square" scheme of the type treated theoretically by Laviron and Roullier (ref. 15). As applied to Cu(II)/(I), the transfer of an electron to or from the copper center can be considered as a step which is distinctly separated from the reorganization of the inner-coordination sphere. As depicted in Scheme 2, species "O" and "R" represent the stable conformers of Cu^{II}L and Cu^IL, respectively, while "Q" and "P" are less stable intermediate species. Within the context of this scheme, it is presumed that species "P" represents a Cu^IL conformer having a coordination geometry more closely approximating the stable conformation of Cu^{II}L; similarly, species "Q" is presumed to represent a Cu^{II}L conformer possessing a coordination geometry approximating that of the stable conformation of Cu^IL.

Scheme 2



Based on this square scheme, the reduction of $\text{Cu}^{\text{II}}\text{L}$ to $\text{Cu}^{\text{I}}\text{L}$ may take place by either of two reversible pathways:



The dominant pathway for any $\text{Cu}^{\text{II}}\text{L}/\text{Cu}^{\text{I}}\text{L}$ system under a specific set of conditions will depend upon the applied potential sweep rate and the relative rate constants for the interconversion of $\text{P} \rightleftharpoons \text{R}$ and $\text{O} \rightleftharpoons \text{Q}$.

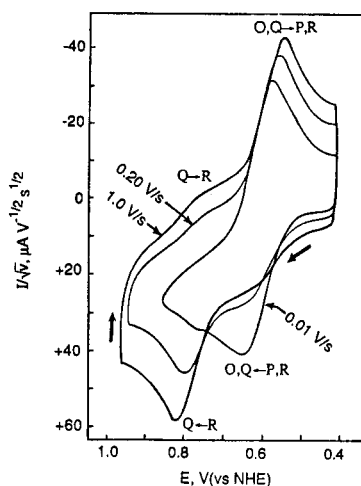


Fig. 2. Cyclic voltammometric behavior for $\text{Cu}^{\text{I}}([\text{14}] \text{aneS}_4)$ as a function of sweep rate showing the development of a second oxidation peak (labeled Q-R) representing the oxidation of R to Q (see Scheme 2): 80% CH_3OH , 25° , $\mu = 1.0$.

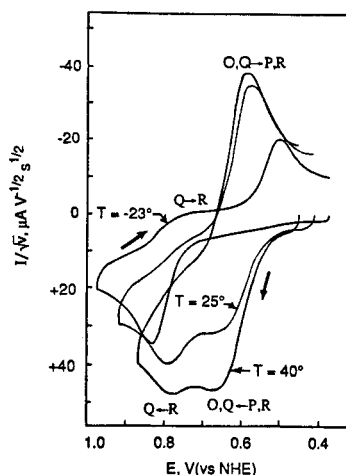


Fig. 3. Cyclic voltammometric behavior for $\text{Cu}^{\text{I}}([\text{14}] \text{aneS}_4)$ as a function of temperature showing the development of the second oxidation peak (Q-R) as the temperature is lowered from 40° to -23°C : 80% CH_3OH , $\mu = 1.0$, $v = 0.05 \text{ V s}^{-1}$.

Potentiostatic measurements. At very slow sweep rates, species P and R as well as species O and Q should be in complete equilibrium at all times. Therefore, the $E_{1/2}$ values obtained from cyclic voltammometric measurements under slow scan conditions should approximate the thermodynamic formal potentials of these redox pairs. In order to establish that our slow scan cv data represented equilibrium conditions, a series of potentiostatic measurements were performed in which the potential was held constant until the current diminished to negligible values (requiring 20-30 minutes) at which time the visible spectrum was recorded. This process was repeated several times at 10-20 mV increments, bracketing the E^f value of the $\text{Cu}(\text{II})/(\text{I})$ redox couple. From the $\text{Cu}^{\text{II}}\text{L}$ absorption peaks, the value of $\ln\{[\text{Cu}^{\text{II}}\text{L}]/[\text{Cu}^{\text{I}}\text{L}]\}$ was calculated and plotted against the applied potential to obtain a line with a slope equal to RT/F and an intercept of E^f . Values obtained in this manner were within experimental error of the potentials obtained from the slow scan cv measurements (Table 1).

Cross-reaction kinetic studies. Having established the electrochemical behavior of the $\text{Cu}(\text{II})/(\text{I})$ polythiaether systems, including the measurement of their formal potential values, it has become possible to apply the Marcus cross relationship (eq 5) to the kinetic rate constants obtained from selected cross reactions and examine the consistency of the resulting calculated self-exchange rate constants for these same systems. Extensive kinetic data have been obtained for the following cross reactions involving the entire series of copper polythiaethers:



In these reactions, Z represents 1,10-phenanthroline or substituted derivatives thereof (particularly 4,7-dimethyl-1,10-phenanthroline) and N_4 represents the unsaturated macrocyclic tetramine 2,3,9,10-tetramethyl-1,4,8,11-tetraazacyclo-

tetradeca-1,3,8,10-tetraene (often referred to as Me₄[14]tetraeneN₄). (The CoN₄ complex also contains two axially coordinated water molecules.) In a few cases, the reduction kinetics were cross-checked with Ru(II).

By utilizing available literature values for the potentials and self-exchange rate constants of the FeZ₃ and CoN₄ reagents in the Marcus cross relationship (eq 5) and applying appropriate work term corrections, it has been possible to calculate the apparent self-exchange rate constants (i.e., k_{11}) for each of the copper complexes from cross-reaction rate constants (ref. 12). These comparative k_{11} values are tabulated in Table 3. By way of comparison, the k_{11} values reported for the blue electron carriers are primarily in the range of 10^4 - 10^7 (refs. cited in ref. 12).

TABLE 3. Comparison of logarithmic self-exchange rate constants for Cu(II)/Cu(I) polythiaether systems calculated from cross-reaction kinetics for reactions 7 ($k_{11(\text{Ox})}$) and 8 ($k_{11(\text{Red})}$) using the Marcus relationship (eq 5). All rate constants are reported in units of $\text{M}^{-1} \text{s}^{-1}$ in aqueous solution at 25°, 0.1 M ClO₄⁻.

Coordinated Ligand	log $k_{11(\text{Red})}$ calcd.	log $k_{11(\text{Ox})}$ calcd.	$\Delta \log k_{11}$ calcd	log k_{11} nmr
[12]aneS ₄	5.6	-2.0	7.6	
[13]aneS ₄	5.0	-1.3	6.3	
[14]aneS ₄	3.2(3.5)	0.2	3.0	5.3
[15]aneS ₄	3.7	1.0	2.7	
[16]aneS ₄	3.6	1.3	2.3	
Me ₂ -2,3,2-S ₄	5.2	-1.2	6.4	
[15]aneS ₅	5.5	3.9	1.6	4.4
[15]aneNS ₄	5.1			5.1

As has been noted in earlier studies, there is a large discrepancy between the k_{11} values which we have obtained from reactions in which Cu(II) is being reduced ($k_{11(\text{Red})}$) as compared to those in which Cu(I) is being oxidized ($k_{11(\text{Ox})}$). In contrast to prior comparisons (refs. 4, 13), however, where $k_{11(\text{Ox})} \gg k_{11(\text{Red})}$, the reverse trend is apparent in our studies. As noted in Table 3, the most extreme disagreements in the calculated k_{11} values are obtained for the smallest macrocyclic ligand systems (involving [12]- and [13]aneS₄) and for the open-chain ligand complex where variations in the k_{11} values are on the order of 10^6 to $>10^7$. The disagreement between $k_{11(\text{Red})}$ and $k_{11(\text{Ox})}$ for the larger ring systems is on the order of 10^1 to 10^3 for the two types of processes. Although this is still outside the level of anticipated agreement (i.e., about 10^1) which is normally expected in using this approach, part of this difference may be attributable to errors in the published parameters for the cross reagents utilized.

In discussing the earlier discrepancies in Cu^{II}L/Cu^IL self-exchange rate constants, Lee and Anson (ref. 13) have suggested that such disagreements may be inherent in all Cu(II)/(I) systems as a result of unequal reorganizational barriers for the two oxidation states of copper in attaining the transition state geometry. They suggested, therefore, that the "true" self-exchange rate constants for Cu(II)/(I) systems might actually be the geometric mean of the $k_{11(\text{Red})}$ and $k_{11(\text{Ox})}$ values obtained using the Marcus equation. Subsequently, these workers attempted to determine the corresponding self-exchange rate constant for the copper-phenanthroline system in a more direct manner by measuring the heterogeneous electron-transfer kinetics at an electrode surface (ref. 16). They concluded that these results supported their hypothesis.

Our interpretation of the electrochemical behavior of the copper-polythiaether complexes (Scheme 2) suggests that the observed discrepancies in the $k_{11(\text{Red})}$ and $k_{11(\text{Ox})}$ values may arise, instead, from the fact that one process (e.g., Cu(II) reduction) is proceeding by Pathway A while the other process (e.g., Cu(I) oxidation) is represented by Pathway B. In either case, the dominant pathway is determined by the overall potential driving force for a particular cross reaction and the relative magnitude of individual rate constants for each of the steps in the overall process. To illustrate this alternative hypothesis, Scheme 2 can be rewritten in terms of a generalized cross reaction process as represented in Scheme 3.

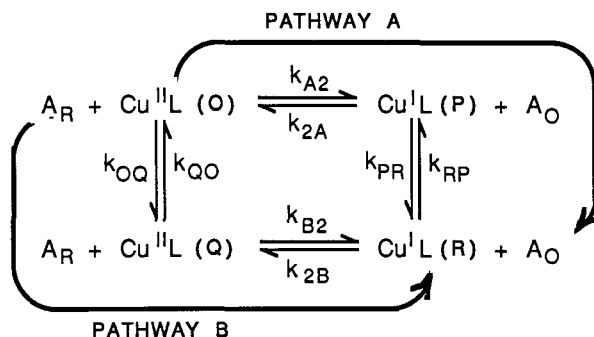
Based on the mechanism in Scheme 3, the *limiting* second-order values for $k_{11(\text{Red})}$ and $k_{11(\text{Ox})}$ should correspond to one of the following pairs of expressions, depending upon the prevailing conditions:

$$\begin{aligned} \text{Pathway A:} \quad & k_{11(\text{Red})} = k_{A2} \\ & k_{11(\text{Ox})} = (k_{\text{RP}}/k_{\text{PR}})k_{2A} \\ \text{Pathway B:} \quad & k_{11(\text{Red})} = (k_{\text{OQ}}/k_{\text{QO}})k_{B2} \\ & k_{11(\text{Ox})} = k_{2B} \end{aligned}$$

Thus, the apparent discrepancy between the observed $k_{11(\text{Red})}$ and $k_{11(\text{Ox})}$ values listed in Table 3 may represent a shift in the dominant mechanistic pathway in reactions 7 and 8 under the reaction conditions used in this work.

This suggestion is supported by very recent kinetic studies in our laboratory on $\text{Cu}([\text{13}] \text{aneS}_4)^{2+/+}$ in which the copper has been both oxidized and reduced with $\text{Ru}(\text{NH}_3)_4(\text{bpy})^{3+/2+}$. In these reactions, which exhibit a very small driving potential, the value obtained for $k_{11(\text{Red})}$ is identical to the previous value (10^5) while the newly resolved $k_{11(\text{Ox})}$ value is about 10^3 . Thus, the values of $k_{11(\text{Red})}$ and $k_{11(\text{Ox})}$ obtained in this manner appear to be within two orders of magnitude, the same level of agreement found earlier for the larger macrocyclic complexes (Table 3).

Scheme 3



Direct determination of self-exchange rate constants via nmr. In attempting to establish the validity of the foregoing conclusion, we have undertaken the task of determining the value of the self-exchange rate constants for several copper-polythiaether systems directly using nmr line-broadening techniques. Only one such k_{11} value has previously been determined in this manner for a $\text{Cu}^{\text{II}}\text{L}/\text{Cu}^{\text{I}}\text{L}$ system similar to those reported here (ref. 17) and the authors of that study questioned whether their system might involve an inner-sphere mechanism. In applying this technique we have used the approach pioneered by McConnell and Berger and by Wahl (ref. 18) in which the ^1H nmr spectrum of the $\text{Cu}^{\text{I}}\text{L}$ species is monitored and the peak width at half height of a selected peak is measured as it is broadened by small incremental additions of the paramagnetic $\text{Cu}^{\text{II}}\text{L}$ species. In most of our systems, this requires a deconvolution of overlapping peaks. Nonetheless, reasonably precise results have been obtained to date by this method for three systems which appear to represent solely outer-sphere electron transfer.

The resultant k_{11} values determined by the nmr approach are included in Table 3. For the two 15-membered ring systems, the latter values are within an order of magnitude of the $k_{11(\text{Red})}$ values determined from the cross reactions. In the remaining system ($\text{Cu}([\text{14}] \text{aneS}_4)^{2+/+}$), the nmr k_{11} value is considerably larger than both the $k_{11(\text{Red})}$ and $k_{11(\text{Ox})}$ values obtained from the cross exchange studies. No evidence of inner-sphere behavior was found.

CONCLUSIONS

Presumably, the $\text{Cu}^{\text{II}}\text{L}/\text{Cu}^{\text{I}}\text{L}$ self-exchange rate constants obtained by nmr represent exchange by the most favorable pathway under conditions of zero driving potential. If pathway A is dominant under these conditions, for example, it would be expected that $k_{11(\text{Red})}$ would agree with the nmr k_{11} value. The $k_{11(\text{Ox})}$ value might also be in agreement at low driving potentials. However, under conditions of high driving potentials, the rate constant for the electron-transfer step may become very fast relative to the rate constant for conformational change (k_{RP}). This switch in behavior could first be manifested in an observed first-order rate constant for the cross reaction. At still larger driving potentials, a second-order rate constant might begin to be observed which would represent the alternate electron-transfer pathway (i.e., pathway B).

For two of the blue electron carriers, rusticyanin (ref. 19) and azurin (ref. 20), observations of both second- and first-order kinetic behavior have, in fact, been observed directly. Although none of the mechanistic interpretations have incorporated all of Scheme 3, investigators have suggested that the observed electron-transfer behavior for these two enzymes results from the existence of two conformers of one of the oxidation states of copper. Moreover, for both of these blue copper proteins independent spectral evidence supports the existence of two stable or metastable conformers of the copper site (ref. 19, 21).

In our low molecular weight copper complexes, the difference in behavior for the small cyclic and open-chain ligand complexes compared to the larger macrocyclic species may reflect changes in the relative kinetics of the two alternate pathways. Thus, the switch from one pathway to another may be more readily achieved in the small macrocycles where structural evidence suggests that one Cu-S bond must be ruptured upon reducing $\text{Cu}^{\text{II}}\text{L}$ to $\text{Cu}^{\text{I}}\text{L}$ (ref 22).

If Scheme 3 represents an accurate portrayal of the generalized mechanism for electron transfer in $\text{Cu}^{\text{II}}\text{L}/\text{Cu}^{\text{I}}\text{L}$ systems, it is conceivable that the copper enzymes take advantage of this mechanism as a means of "switching off" reverse electron-transfer processes after a desired oxidation or reduction has taken place. Such switching mechanisms resulting from conformational changes are known in other types of proteins, but rarely has it been possible to mimic this behavior with low molecular weight species.

The use of macrocyclic ligands in this work has allowed us some degree of control of the geometry at the copper site. By generating ligands which impose a greater variety of constraints upon the copper site, it should be possible to induce unique reactive behavior to Cu(II)/(I) systems.

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REFERENCES

1. (a) B. L. Vallee and R. J. P. Williams, *Proc. Natl. Acad. Sci., USA* **59**, 498-505 (1968); (b) R. J. P. Williams, *Inorg. Chim. Acta Rev.* **5**, 137-155 (1971).
2. (a) P. M. Colman, H. C. Freeman, J. M. Guss, M. Murata, V. A. Norris, J. A. M. Ramshaw, and M. P. Venkatappa, *Nature* **272**, 319-324 (1978); (b) H. C. Freeman in *Coordination Chemistry*, pp 29-51, J. P. Laurent, Ed., Pergamon Press, Oxford (1981); (c) E. T. Adman, R. E. Stenkamp, L. C. Sieker, and L. H. Jensen, *J. Mol. Biol.* **123**, 35-47 (1978); (d) G. E. Norris, B. F. Anderson, and E. N. Baker, *J. Mol. Biol.* **165**, 501-521 (1983).
3. (a) G. S. Patterson and R. H. Holm, *Bioinorganic Chem.* **4**, 257-275, (1975); (b) U. Sakaguchi and A. W. Addison, *J. Chem. Soc., Dalton Trans.* 600-608 (1979).
4. J. K. Yandell in *Copper Coordination Chemistry: Biochemical and Inorganic Perspectives*, pp 157-166, K. D. Karlin and J. Zubieta, Eds., Adenine Press, Guilderland, New York (1983); and references therein.
5. (a) T. E. Jones, D. B. Rorabacher, and L. A. Ochrymowycz, *J. Am. Chem. Soc.* **97**, 7485-7486 (1975); (b) E. R. Dockal, T. E. Jones, W. F. Sokol, R. J. Engerer, D. B. Rorabacher, and L. A. Ochrymowycz, *J. Am. Chem. Soc.* **98**, 4322-4324 (1976).
6. (a) L. S. W. L. Sokol, L. A. Ochrymowycz, and D. B. Rorabacher, *Inorg. Chem.* **20**, 3189-3195 (1981); (b) I. R. Young, L. A. Ochrymowycz, and D. B. Rorabacher, *Inorg. Chem.* **25**, 2576-2582 (1986).
7. (a) N. Aoi, G. Matsubayashi, and T. Tanaka, *J. Chem. Soc., Dalton Trans.* 1059-1066 (1983); (b) K. M. Davies, *Inorg. Chem.* **22**, 615-619 (1983).
8. (a) N. Al-Shatti, A. G. Lappin, and A. G. Sykes, *Inorg. Chem.* **20**, 1466-1469 (1981); (b) P. Leupin, N. Al-Shatti, and A. G. Sykes, *J. Chem. Soc., Dalton Trans.* 927-930 (1982).
9. (a) J. D. Clemmer, G. K. Hogaboom, and R. A. Holwerda, *Inorg. Chem.* **18**, 2567-2572 (1979); (b) R. A. Holwerda, *Inorg. Chem.* **21**, 2107-2109 (1982).
10. (a) R. A. Marcus, *J. Chem. Phys.* **43**, 679-701 (1965); (b) R. A. Marcus and N. Sutin, *Biochim. Biophys. Acta* **811**, 265-322 (1985).
11. N. S. Hush, *Trans. Faraday Soc.* **57**, 557-580 (1961).
12. M. J. Martin, J. F. Endicott, L. A. Ochrymowycz, and D. B. Rorabacher, *Inorg. Chem.* **26**, in press.(1987).
13. C. W. Lee and F. C. Anson, *J. Phys. Chem.* **87**, 3360-3362 (1983).
14. D. B. Rorabacher, R. R. Schroeder, and M. M. Bernardo, XXIV International Chemistry Coordination Chemistry Conference, Abstract D1-693, Athens (1986).
15. E. Laviron and L. Roullier, *J. Electroanal. Chem.* **186**, 1-15 (1985).
16. C. W. Lee and F. C. Anson, *Inorg. Chem.* **23**, 837-844 (1984).
17. E. J. Pulliam and D. R. McMillan, *Inorg. Chem.* **23**, 1172-1175 (1984).
18. (a) H. M. McConnell and S. B. Berger, *J. Chem. Phys.* **27**, 230-234 (1957); (b) M. W. Dietrich and A. C. Wahl, *J. Chem. Phys.* **38**, 1591-1596 (1963); (c) M. S. Chan and A. C. Wahl, *J. Phys. Chem.* **82**, 2542-2549, (1978).
19. A. G. Lappin, C. A. Lewis, and W. J. Ingledew, *Inorg. Chem.* **24**, 1446-1450 (1985).
20. (a) M. C. Silvestrini, M. Brunori, M. T. Wilson, and V. M. Darley-Usmar, *J. Inorg. Biochem.* **14**, 327-338 (1981); (b) P. Rosen and I. Pecht, *Biochemistry* **15**, 775-786 (1976).
21. A. G. Szabo, T. M. Stepanik, D. M. Wayner, and N. M. Young, *Biophys. J.* **41**, 233-244 (1983).
22. (a) L. L. Diaddario, E. R. Dockal, M. D. Glick, L. A. Ochrymowycz, and D. B. Rorabacher, *Inorg. Chem.* **24**, 356-363 (1985); (b) P. W. R. Corfield, C. Ceccarelli, M. D. Glick, I. W.-Y. Moy, L. A. Ochrymowycz, and D. B. Rorabacher, *J. Am. Chem. Soc.* **107**, 2399-2404 (1985); (c) V. B. Pett, L. L. Diaddario, E. R. Dockal, P. W. R. Corfield, C. Ceccarelli, M. D. Glick, L. A. Ochrymowycz, and D. B. Rorabacher, *Inorg. Chem.* **24**, 3661-3670 (1983).