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Rates of Electron Transfer and Redox Potentials of some Copper(II) Thioether Complexes

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Introduction

Understanding the functional consequences of the unusual structure of the 'blue' or Type I copper enzymes is a challenging problem. Recent crystallographic investigations [1] have confirmed that the coordination sphere of the copper in the enzymes is indeed unusual, in that both copper(II) and copper(I) states have a distorted tetrahedral arrangement of two histidine nitrogens, a methionine sulfur and a cysteine sulfur.

Two features of this arrangement have been assigned a role in the function of the enzymes. The sulfur atoms, particularly the methionine, are thought to be necessary for the high redox potentials reported for the enzymes. We challenge this view, on the basis, in part, of our measurements of standard redox potentials for some copper thioether complexes. Though other redox potential studies of such complexes have been published [2–4], comparison to the enzymes has been restricted by the use of non-standard potentials derived from irreversible polarography in non-aqueous solvents. The present results allow a more confident assessment of the factors contributing to the redox potentials of the enzymes.

The four coordinate, distorted stereochemistry of the enzyme has been assigned [5] a functional role in facilitating electron transfer to and from the copper center [5]. It is argued, without experimental support, that a large Franck Condon barrier will exist for small copper complexes because of stereochemical changes necessary to reduce 'normal' six coordinate, tetragonal, copper(II) complexes to four coordinate, tetrahedral copper(I) complexes. Thus the enzyme needs to adopt the unusual copper(I) and copper(II) stereochemistries to minimize this structural barrier. We have recently [6] shown for the copper complexes of some N and O donor ligands, that electron transfer is indeed slow. In this paper we extend these results to include some complexes of thioether ligands, and examine an

TABLE I. Copper(II)–Copper(I) Redox Potentials in Water.

Complex	Types of Donor Atom[a]	E°_{obsd}[b] (mV *vs.* N.H.E.)	E°_{calc}[c]
Cupdto	$2N_H$, 2S	594[d]	600
Cupma	N_H, N_S, 2S	400[d]	380
$Cudadt^{2+}$	$2N_S$, 2S	274[d]	260
$Cumta^{2+}$	N_S, S	187[e]	205
$Cu(mta)_2^{2+}$	$2N_S$, S	243[e]	260
Cuta	$2CO_2^-$, S	190[d]	185
Cu2-dta	$2CO_2^-$, 2S	300[d]	300
Cu3-dta	$2CO_2^-$, 2S	310[d]	300
$Cu14\text{-ane-}S_4^{2+}$	4S	611[d]	610
$Cupyridine^{2+}$	N_H	197[e]	210
$Cu(pyridine)_2^{2+}$	$2N_H$	270[e]	260
$Cu(imidazole)_2$	$2N_H$	317[f]	270

[a]Donor atoms thought to be coordinated in both oxidation states, excluding water molecules. Both oxidation states are complexed to the same number of the ligands as specified in the table. N_H-heterocyclic nitrogen, N_S-Saturated nitrogen, S-thioether Sulfur, CO_2^--carboxylate oxygen. [b]All data at 25 °C, and ionic strength = 0.1 (nitrate). [c]Calculated from E° (calc) = $E^\circ(Cu^{2+/+}) + n_L\Delta E^\circ(L)$, with the following values: $E^\circ(Cu^{2+/+})$ = 150 mV; $E^\circ(N_H)$ = +60 mV; $E^\circ(N_S)$ = −60 mV; $E^\circ(S)$ = 115 mV; and $E^\circ(CO_2^-)$ = −40 mV. [d]This work. [e]Reference 14. [f]Reference 15.

TABLE II. Kinetic Data on Copper(II)–Copper(I) Electron Transfer and Exchange.

Copper(II) Complex	k_{12} [a,b] M^{-1} s^{-1}	k_{22} [a,c] M^{-1} s^{-1}	ΔG_{int} kJ mol^{-1}
$Cu(phen)_2^{2+}$ [d]	2.7 x 10	4.3 x 10	34
$Cu(nitrophen)_2^{2+}$ [d]	1.6 x 10^2	8.6 x 10	32
$Cu(bpy)_2^{2+}$ [d]	1.4 x 10	1.4 x 10^2	30
Cupdto^{2+} [e]	1.7 x 10^4	4.6	36
Cupma^{2+} [e]	1.7 x 10^3	4.6 x 10	29
Cuta [e]	1.7 x 10^2	2.6 x 10^2	25
Cu2dta [e]	5.1 x 10^3	5.5 x 10^3	19
Cu3dta [e]	3.6 x 10	2.0 x 10	33
Cu14-ane-S_4^{2+} [e]	2.4 x 10^6	7.6 x 10^4	11

[a] All data at 25 °C, ionic strength 0.1 (nitrate), and pH 6. [b] Rate constant for $Cu(II)L_n$ + cyt c(II) ⇌ $Cu(I)L_n$ + cyt c(III). [c] Rate constant for $Cu(II)L_n$ + $Cu(I)L_n$ ⇌ $Cu(I)L_n$ + $Cu(II)L_n$. [d] Reference 6. [e] This work.

alternative proposition that the sulfur donor atoms in the proteins are essential for rapid electron transfer.

Results and Discussion

Redox Potentials

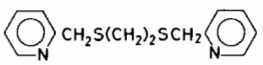
Standard redox potentials (*vs.* NHE) are given in Table I for a number of copper(II) thioether complexes. These were obtained by potentiometric titration. The potentials are fitted surprisingly well by the equation:

$$E^\circ = E^\circ(Cu^{2+/+}) + n_L E^\circ(L) \quad (1)$$

where n_L is the number of donor atoms of type L and $E^\circ(L)$ is the change in the redox potential induced by the donor atom L. Values of $E^\circ(L)$ are given in Table I.

Though the good correlation with eqn. (1) is probably to some extent fortuitous, it nevertheless increases our confidence in our ability to isolate the factors that contribute to the redox potentials of the enzymes. For the best available model of the type I centers (2S, 2 heterocyclic N), eqn. (1) predicts a redox potential of 600 mV. This should be increased by a further 50 to 200 mV [8] by the low dielectric constant of the protein outside the first coordination sphere of the enzyme, and by a further 300 to 700 mV by imposition of tetrahedral coordination [9] in the copper(II) state. Thus, for a protein with this donor set and stereochemistry, redox potentials greater than 900 mV are anticipated. Even for four heterocyclic nitrogen donors, redox potentials greater than 800 mV are predicted on this basis.

Redox potentials reported for the type I enzymes vary widely from 184 mV to 785 mV [10]. In the light of the predictions based on the model systems it is obviously simplistic to ascribe the presence of



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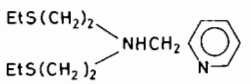

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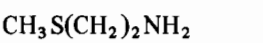
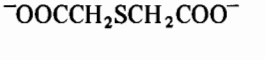
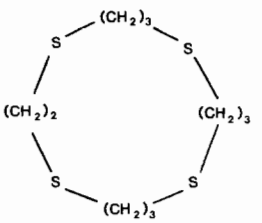


mta



ta

n = 2, 2dta;
n = 3, 3dta



14-ane-S_4

Fig. 1. The ligands in the Tables.

methionine in the enzymes simply to the need to attain a high redox potential. High redox potentials may be readily achieved without thioether donors. Furthermore, substitution of histidine by methionine is only expected to raise the redox potential by 55 mV.

This is clearly not enough to rationalise the range of the experimental values, or, in particular, the difference between stellacyanin and rustocyanin (500 mV) as suggested by Reinhammar [10]. The problem it now appears, is to explain the lower values reported

for the enzymes. Though the presence of coordinated cysteine may contribute to a lower potential, the stereochemical constraints on the enzymes are likely to be more important. Specifically, distortion of the copper(I) coordination sphere from its preferred configuration will lower the redox potential. This may be the case with Cu(II)-plastocyanin since it is not tetrahedral.

Kinetics of Electron Transfer

Rates of electron transfer between the copper(II) complexes of the ligands in Fig. 1 (and Tables I and II) and reduced horse cytochrome c were found to be first order in both reactant concentrations. Second order rate constants (k_{12}) are given in Table II, along with rate constants for Cu(II)–Cu(I) electron exchange (k_{22}) derived from the Marcus cross relationship. The validity of this relationship has been questioned in some studies of cytochrome c [11], but we have shown [4] that it holds well for the reduction of copper(II) phenanthrolines by a number of reductants including cytochrome c. For the present series of complexes, we have confirmed that the exchange values in Table II are realistic from reaction with other reductants. Thus, a k_{22} value of 35 M^{-1} s^{-1} was derived from the reaction of $Cupma^{2+}$ with $[Co(tripyridine)_2]^{2+}$, (*cf.* 46 in Table II).

Table II also includes values for the contribution of the inner sphere rearrangement to the activation free energy. These were calculated by subtraction of the outer sphere and work terms from the total energy, as described by Brown and Sutin [12].

From data for copper–phenanthroline [6] and other copper(II) complexes [13] it appears that 'normal' copper complexes exhibit exchange rates in the range 1 to 10^3 M^{-1} s^{-1} and ΔG_{int} values of 25 to 35 kJ mol^{-1}. The results for the mixed nitrogen and sulfur donor ligands, $Cupdto^{2+}$ and $Cupma^{2+}$, fall at the lower end of this range. *We conclude that these complexes do not have abnormally low structural barriers to electron transfer and therefore that up to two thioether ligands do not appreciably enhance rates of electron transfer.*

Rates of electron exchange are faster and the internal rearrangement barriers are lower than anticipated for some of the mixed thioether carboxylate complexes. We cannot at present eliminate the possibility that the enhancement is related to the carboxylate groups rather than the thioether atoms. More surprising was the very low value for the internal rearrangement term for the cyclic tetrathioether. Further information is obviously required to ascertain whether this is a function of the pure thioether coordination (not including solvent) or a consequence of the macrocyclic ligand.

The relatively slow electron exchange values, which reflect a substantial structural barrier to electron transfer for 'normal' copper complexes imply that for rapid electron exchange ($>10^4$ M^{-1} s^{-1}) the copper enzymes will require a special coordination environment; especially if, as expected, the protein envelope further decreases the rate by reducing accessibility of the copper center. (By both reducing the surface available for attack, and by reducing the probability of electron transfer in the transition state, *i.e.* non adiabatic effects.) Sulfur coordination *per se* might have contributed to enhanced electron transfer in the enzyme, *but it is clear from our data that one or two thioether ligands do not effect electron transfer significantly.*

It seems likely that similar stereochemistry in both oxidation states, as in plastocyanin, is necessary for rapid electron transfer. Sulfur donor ligands may be important in stabilizing this configuration.

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