is not ruled out that the entering nucleophile is already weakly coordinated to the complex ion in the ground state and that the substitution process follows an interchange path as described by an I_a mechanism. Similar data[9] have previously been considered as evidence for an I_a mechanism in the substitution reactions of $[Pt(dien)X]^+$ complexes, where dien = diethylenetriamine and $X^- = Br^-$, Cl^-, I^-, and N_3^-.

To sum up, we conclude that the isomerization reaction of *cis*-$[Pt(PEt_3)_2(2,4,6\text{-}Me_3C_6H_2)Br]$ and the substitution reactions (k_1 and k_2 paths) of *cis*- and *trans*-$[Pt(PEt_3)_2(2,4,6\text{-}Me_3C_6H_2)Br]$ all proceed via an associative type of mechanism. A definite conclusion as to whether the mechanisms are of the A or I_a type cannot be made, although it is hoped that the results of the solvent dependence study presently in progress will provide more detail on the intimate mechanism involved.

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Registry No. *cis*-$[Pt(PEt_3)_2(2,4,6\text{-}Me_3C_6H_2)Br]$, 22289-37-8; *trans*-$[Pt(PEt_3)_2(2,4,6\text{-}Me_3C_6H_2)Br]$, 68681-91-4; I^-, 20461-54-5; thiourea, 62-56-6.

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Rates of Electron-Transfer Reactions of Some Copper(II)–Phenanthroline Complexes with Cytochrome *c*(II) and Tris(phenanthroline)cobalt(II) Ion

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Rate constants for the one-electron oxidation of horse heart cytochrome *c*(II) (ferrocytochrome *c*) by aquated bis(1,10-phenanthroline)copper(II) ion, bis(2,9-dimethyl-1,10-phenanthroline)copper(II) ion, and bis(5-nitro-1,10-phenanthroline)copper(II) ion were found to be $(2.72 \pm 0.26) \times 10^1$ M^{-1} s^{-1}, $(1.00 \pm 0.04) \times 10^6$ M^{-1} s^{-1}, and $(1.57 \pm 0.06) \times 10^2$ M^{-1} s^{-1}, respectively, in aqueous solution at pH 6.1, at 25 °C, and at an ionic strength of 0.1 M. Activation enthalpies, $\Delta H^\ddagger$ = 55, 16, and 46 kJ mol^{-1}, and activation entropies, $\Delta S^\ddagger$ = −33, −77, and −50 J mol^{-1} K^{-1}, were also measured for the same reactions. The rate constant and activation parameters for the one-electron oxidation of tris(1,10-phenanthroline)cobalt(II) ion by bis(2,9-dimethyl-1,10-phenanthroline)copper(II) ion were found to be $(8.8 \pm 0.3) \times 10^4$ M^{-1} s^{-1}, $\Delta H^\ddagger$ = 43 kJ mol^{-1}, and $\Delta S^\ddagger$ = −6 J mol^{-1} K^{-1} under the same conditions. These results are discussed in terms of a "structural barrier" to electron transfer, which is a consequence of the difference in coordination number and stereochemistry between the copper(II) reactants and the copper(I) products.

Introduction

Copper(II)–copper(I) redox reactions are unusual in that, at least for "simple" copper complexes, the coordination number and stereochemistry of the two oxidation states differ. Copper(II) complexes in aqueous solution are usually thought to be six-coordinate and tetragonal, whereas copper(I) complexes prefer four-coordinate, tetrahedral coordination. This may be an oversimplification since in the solid state Cu(II) is frequently found to be five-coordinate[1] and Cu(I) exhibits some tendency toward linear two-coordination. In any event, in water, Cu(II) complexes are likely to have a higher coodination number (including solvent ligands). A classic manifestation of this difference was reported by James and Williams[2] in 1961. They found that the methyl substituents in 2,9-dimethyl-1,10-phenanthroline (dmphen) greatly decreased the stability of the $Cu(dmphen)_2^{2+}$ but increased

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the stability of $Cu(dmphen)_2^+$ relative to the unsubstituted phenanthroline complexes. This observation is well explained by the supposition that little repulsive steric interaction occurs between the methyl groups in the tetrahedral copper(I) complexes but that they destabilize the copper(II) complex through steric interaction with one another or with coordinated water molecules. As a result the coordination number of $Cu(dmphen)_2^{2+}$ is likely to be less than 6 even in water.

Structural differences between the two oxidation states can easily be seen, through the application of the Franck–Condon principle, to increase the potential barrier to electron transfer. Such a *structural barrier* will contribute to the internal rearrangement term in the Marcus–Hush treatment of the rates of electron-transfer reactions.[3]

This discussion is closely related to an argument of Valee and Williams[4] about "blue" copper proteins. They suggested, as an example of an "entatic" state, that the coordination geometry of the metal in these enzymes would be found to be intermediate between square planar and tetrahedral, thus facilitating electron transfer by lowering the internal rearrangement barrier compared to that for simple copper complexes. This approach emphasizes the stereochemical differences between copper(II) and copper(I) complexes. We consider that it needs to be extended to include all the structural differences between the two oxidation states, in particular, the difference in coordination number since this is likely to make the greatest contribution to the overall structural barrier. This paper reports our initial attempts to assess the magnitude of the structural barrier. The choice of copper complexes was dictated by the expectation that the distorted $Cu(dmphen)_2^{2+}$ complex would require less structural rearrangement during reduction than the other less sterically hindered phenanthroline complexes and therefore that the differences in their rates of electron transfer might reflect differences in the size of the structural rearrangement barrier.

Until recently, no studies of simple outer-sphere electron transfer between copper(II) and copper(I) appear to have been published, apart perhaps from a study[5] of electron exchange in concentrated hydrochloric acid. Two papers related to this work have been published, however, while this paper was in preparation. Al-Shatti et al.,[6] who investigated the rate of reduction of a copper(II) macrocyclic complex, concluded that this complex was "extremely reluctant" to undergo outer-sphere electron transfer. Yoneda, Blackmer, and Holwerda[7] deduced that the electron-exchange rates for copper phenanthroline and bipyridyl complexes were quite fast from a study of rate of oxidation of $Cu(phen)_2^+$ and $Cu(bpy)_2^+$ by $CoEDTA^-$. This conclusion conflicts with ours. Some other electron-transfer kinetic studies,[8,9] most notably those of Espenson and co-workers on the aquo ions, have been reported but are thought to be inner-sphere reactions.

Cytochrome *c* (cyt *c*), a low molecular weight heme protein, was used as a reductant in these studies partly because of our interest[10] in its electron-transfer properties particularly in relation to its biological role as a member of the mitochondrial electron-transport chain. Cyt *c* was also chosen because of the pertinence of copper–heme electron transfer to the biochemistry of cytochrome oxidase.[11] In this multicentered metalloprotein, electron transfer between copper and heme centers occurs internally. Electron transfer from cyt *c* to the oxidase may also occur through one of the copper atoms of the oxidase, as suggested in a recent review.[11] The authors also noted the paucity of information on electron-exchange interactions between copper and heme. We hope that this work and our continuing studies of related reactions will increase our understanding of such systems.

Experimental Section

Reagents. Horse heart cytochrome *c* (Sigma type III or type VI) was used without further purification. Reduced cyt *c* was prepared by dithionite reduction of an approximately 10^{-3} M solution of cyt *c*(III), which was buffered at pH 6, was deoxygenated with argon, and contained 0.1 M sodium nitrate. The reduced cytochrome was separated from the low molecular weight material by gel filtration (Sephadex G 25—20 × 1 cm column) and stored under argon. Copper–phenanthroline complexes were generally prepared in solution by mixing the appropriate amounts of stock solutions of copper nitrate and the required phenanthroline. The stock copper solution was standardized with EDTA to a spectrophotometric end point.[12] In early work $Cu(dmphen)_2^{2+}$ solutions were prepared by dissolving the required amount of the solid complex prepared according to the method of Hall, Marchant, and Plowman.[13] No significant difference in behavior was found between these solutions and solutions prepared from the metal and ligand separately. Where dissociation of the complexes was significant, the concentrations of the reactant species were calculated from the published stability constant and pK_a values.[2] All reactant solutions were maintained at a pH of 6.15 with 10^{-2} M MES (2-(*N*-morpholino)ethanesulfonic acid) buffer[14] and at an ionic strength of 0.1 M with sodium nitrate, unless otherwise specified. MES does not bind appreciably to Cu(II) under our conditions;[14] the visible spectra of aqueous solutions of copper nitrate are unaltered by up to at least 0.1 M MES. When necessary, solutions were deoxygenated by bubbling with purified nitrogen or argon (O_2 removed with BASF R 311 catalyst). $Co(phen)_3^{2+}$ solutions were prepared by mixing standardized solutions of cobalt(II) nitrate and 1,10-phenanthroline in appropriate concentrations. $Cu(dmpen)_2^{2+}$ solutions used in the oxidation of $Co(phen)_3^{2+}$ contained a constant concentration of dimethylphenanthroline (2×10^{-4} M)—only the copper concentration was varied.

Equilibrium Constants. Solutions of the copper phenanthroline complex were deoxygenated in a 1-cm spectrophotometer cell fitted with a Suba seal. Ferrocytochrome *c* was introduced with a microsyringe, and the approach to equilibrium was monitored spectrophotometrically at 549 nm. Initial rates in the absence of oxygen were derived from this data. The absorbance of the solutions was measured at 549 nm after reaching equilibrium and again after the addition of approximately 10^{-4} L of an oxygen-free, saturated solution of EDTA. The equilibrium constant could then be calculated from (i) the total concentration of cyt *c* (determined from the absorbance coefficients at the isosbestic points at 541, 525, and 504 nm), (ii) the reduced cyt *c* concentration at equilibrium (calculated from the absorbance at 549 nm), and (iii) the Cu(I) concentration (determined from the difference in the reduced cyt *c* concentration at equilibrium and after the addition of EDTA). EDTA forms copper complexes with a low redox potential which completely reverses the original reaction resulting in the reoxidation of the Cu(I) and formation of an equal amount of cyt *c*(II).

Kinetics. The rates of the cyt *c* reactions were monitored by the decrease in absorbance of the reduced cytochrome at 420 or 549 nm on either a Varian 635 UV–visible spectrophotometer or a stopped-flow apparatus of conventional design[15] incorporating two Durrum-Gibson mixing chambers. $Co(phen)_3^{2+}$ oxidation was followed on the stopped-flow apparatus at 455 nm where $Cu(dmp)_2^+$ absorbs strongly.[16] All reactions were carried out with a greater than tenfold excess of the copper complex over the cyt *c*(II) or a greater than tenfold excess of $Co(phen)_3^{2+}$ over the $Cu(dmphen)_2^{2+}$. Pseudo-first-order rate constants were obtained from the gradients of the usual log plots which were linear over at least 3 half-lives. Rate constants were reproducible to better than 10%. Errors in the second-order rate constants in the tables represent the mean deviation of the results from the mean of five or six individual rate constants obtained at the specified concentration. Errors on the average k_2 values express approximately 90% confidence limits within the random errors. Systematic errors estimated to be less than 10% have not been included. Energies of activation were obtained from weighted linear regression analyses of the temperature dependence of the rate constants. The quoted error is the standard error resulting from this analysis. Again systematic errors as a result of volume changes, partial dissociation of the complexes, etc. have not been included but are likely to be small relative to the random error. No significant differences were detected in the kinetic or equilibrium behavior between solutions of type III and type VI cytochrome.

Results

$Cu(dmphen)_2^{2+}$ Oxidation of Ferrocytochrome *c*. Rapid

Table I. Rate Constants for the Oxidation of Cytochrome *c*(II) by $Cu(dmphen)_2^{2+}$ [a]

$10^5 \times [Cu(II)]_{tot}$, M	$10^5 \times [dmphen]_{tot}$, M	$10^5 \times [Cu(dmphen)_2^{2+}]$, M	$10^{-6}k_2$, M^{-1} s^{-1}
0.89	1.78	0.53	1.1 ± 0.1
1.9	3.8	1.3	1.02 ± 0.1
2.5	5.0	1.83	1.08 ± 0.1
2.9	5.8	2.17	1.08 ± 0.08
6.1	12.2	5.0	1.07 ± 0.06
7.45	14.9	6.23	1.07
9.6	19.2	8.18	0.95 ± 0.03
10.0[b]	20.0	8.56	0.99 ± 0.08
5.1	20.4	5.1	0.92 ± 0.06
4.9[c]	9.8	3.68	1.02 ± 0.11
5.3[d]	10.6	4.44	0.88 ± 0.11

[a] All data at 25 °C ionic strength 0.1 M (sodium chloride), pH 6.15, and initial [cyt *c*(II)] (1.5–6) × 10^{-6} M. [b] [cyt *c*(II)] = 13 × 10^{-6} M. [c] pH 4.2. [d] pH 8.0.

(5–200 ms) visible spectral changes occur on mixing solutions of cytochrome *c*(II) with an excess of bis(2,9-dimethylphenanthroline)copper(2+)–*n*-water ion ($Cu(dmphen)_2^{2+}$) in water. The spectral changes are consistent with the complete oxidation of cyt *c*(II) and concomitant formation of $Cu(dmphen)_2^{+}$. ($Cu(dmphen)_2^{+}$ is not oxidized by molecular oxygen nor does it disproportionate into Cu(II) and Cu, but in water under our conditions some precipitation occurs at a rate that does not interfere with the reaction of interest.) These observations are consistent with the simple electron-transfer reaction (1). Complete oxidation is anticipated from the

$$Cu(dmphen)_2^{2+} + \text{cyt } c(II) \rightleftharpoons Cu(dmphen)_2^{+} + \text{cyt } c(III) \quad (1)$$

known redox potentials ($Cu(dmphen)_2^{2+/+}$, E° = 0.603 V;[2] cyt *c*(III)/(II), E° = 0.26 V[17]) which require an equilibrium constant of 6.2 × 10^5 for reaction 1. The rate of change of absorbance at 420 nm was found to be first order over a 12-fold range in concentration of the copper complex and over a 10-fold range in concentration of the cytochrome. Rate constants (Table I) derived from the observed pseudo-first-order rates are consistent with the simple second-order rate equation (2). The mean value of k_2 at 25 °C was found to

$$d[\text{cyt } c(III)]/dt = k_2[Cu(dmphen)_2^{2+}][\text{cyt } c(II)] \quad (2)$$

be (1.00 ± 0.04) × 10^6 M^{-1} s^{-1}. k_2 values at pH 4.2 and 8.0 were found to be within experimental error of the value at pH 6.1 (Table I). Excess dmphen had no significant effect on the rate of reaction, as expected since appreciable concentrations of $Cu(dmphen)_3^{2+}$ are not formed. This result also demonstrates that neither $Cu(dmphen)^{2+}$ nor Cu^{2+} is a kinetically important intermediate in the reaction. Copper(II) aquo ion has also been shown to be less reactive in separate experiments. Activation parameters based on the temperature dependence data in Table II are given in Table III.

$Cu(phen)_2^{2+}$ and $Cu(nitrophen)_2^{2+}$ Oxidation of Ferrocytochrome *c*. Equilibria. In the absence of oxygen, visible absorption spectra of cyt *c* indicated that bis(1,10-phenanthroline)copper(2+)–*n*-water ions ($Cu(phen)_2^{2+}$), as with $Cu(dmphen)_2^{2+}$ ions, oxidize cyt *c*(II) to cyt *c*(III) but that the reaction is not complete in the concentration range investigated. Equilibrium constant values (mean: 0.052[18]) found for the simple electron-transfer reaction (3) are within ex-

$$Cu(phen)_2^{2+} + \text{cyt } c(II) \rightleftharpoons Cu(phen)_2^{+} + \text{cyt } c(III) \quad (3)$$

perimental error of the equilibrium constant calculated from the published[2] redox potentials (0.035). Similarly, the measured equilibrium constant (0.81) for the oxidation of cyt *c*(II) by bis(5-nitro-1,10-phenanthroline)copper(2+)–*n*-water ions ($Cu(nitrophen)_2^{2+}$) satisfactorily agrees with the calculated value of 0.89, based on E° = 0.257 V for $Cu(nitrophen)_2^{2+/+}$ couple in water. (E° is derived from the reported value[2] for dioxane–water by addition of difference between the E° values found for the $Cu(phen)_2^{2+}$ couple in water and in dioxane–water.[2])

Table II. Temperature Dependence of the Rate Constant for Reduction of $Cu(dmphen)_2^{2+}$ [a] by Cytochrome *c*(II) and by $Co(phen)_3^{2+}$

t, °C	cyt *c*(II)[b] $10^{-6}k_2$, M^{-1} s^{-1}	$Co(phen)_3^{2+}$ [c] $10^{-3}k_2$, M^{-1} s^{-1}
5		22.9 ± 0.8
10	0.65 ± 0.04	34.4 ± 1.4
15	0.75 ± 0.09	46.4 ± 1.4
20	0.88 ± 0.02	61.2 ± 1.9
25	1.02 ± 0.04	93.2 ± 4.4
30	1.12 ± 0.02	
35	1.29 ± 0.05	

[a] All data at pH 6.15, ionic strength 0.1 M (sodium nitrate). [b] Total [Cu(II)] = 1.94 × 10^{-5} M, total [dmphen] = 1.0 × 10^{-4} M, [$Cu(dmphen)_2^{2+}$] = 1.87 × 10^{-5} M, and [cyt *c*(II)] = (1.2–2.9) × 10^{-6} M. [c] [$Co(phen)_3^{2+}$] = 1.0 × 10^{-3} M, total [Cu(II)] = 0.5 × 10^{-4} M, and total [dmphen] = 2.0 × 10^{-4} M.

Table III. Activation Parameters for the Reduction of Copper(II)–Phenanthroline Complexes by Cytochrome *c*(II) and $Co(phen)_3^{2+}$

	$\Delta H^{\ddagger}$, kJ mol^{-1}	$\Delta S^{\ddagger}$, J mol^{-1} K^{-1}
$Cu(dmphen)_2^{2+}$ [a]	15.8 ± 1.7	−77 ± 7
$Cu(nitrophen)_2^{2+}$ [a]	45.6 ± 3.7	−50 ± 15
$Cu(phen)_2^{2+}$ [a]	55.2 ± 4.5	−33 ± 16
$Cu(dmphen)_2^{2+}$ [b]	43.1 ± 2.6	−6 ± 9

[a] Cyt *c*(II) as reductant. [b] $Co(phen)_3^{2+}$ as reductant.

In the presence of oxygen, oxidation was found to go to completion, through the regeneration of the copper(II) species from the copper(I) ions by oxidation of molecular oxygen which is known to be a rapid process.[19] We have shown[18] that the resultant catalytic cycle is common to a range of copper complex catalyzed autoxidation reactions of ferrocytochrome *c*.

Kinetics. The rate of oxidation of cyt *c*(II) in air in the presence of either the nitrophenanthroline or the phenanthroline complexes exhibited simple second-order behavior as in eq 2. Rate constants, k_2, for $Cu(phen)_2^{2+}$ oxidation are listed in Table IV. The mean value is given in Table VII. Without oxygen, when the cyt *c*(II) is only partially oxidized, full kinetic analysis is not feasible, but initial rates of oxidation were in good agreement with the rates observed in solutions containing oxygen.[18] Saturation of the reactant solution with oxygen rather than air made no significant difference to the rate of reaction with $Cu(phen)_2^{2+}$ but appeared to slightly increase the rate of the $Cu(nitrophen)_2^{2+}$ catalyzed oxidation (Table V) from a mean value of 141 ± 5 to 157 ± 6 M^{-1} s^{-1}.

Although the bis complexes predominate in all the solutions investigated above, it is possible that low concentrations of other species such as $Cu(phen)_3^{2+}$ or $Cu(phen)^{2+}$ were nevertheless kinetically significant. However, decreasing rates of electron transfer were found with increasing concentrations of phenanthroline and nitrophenanthroline when the concentration of these ligands was more than twice the copper concentration. This observation indicates that the bis complexes were the kinetically dominant species in such solutions and that k_2 values for oxidation by $Cu(phen)_3^{2+}$ (and $Cu(bpy)_3^{2+}$ [18]) were less than 0.2 M^{-1} s^{-1}. Solutions in which the mono complexes were the main copper ions present oxidized reduced cyt *c* at slower rates than solutions with comparable

Table IV. Rate Constants for the Oxidation of Cytochrome *c*(II) by $Cu(phen)_2^{2+}$ [a]

$10^3 \times [Cu(II)]_{tot}$, M	$10^3 \times [phen]_{tot}$, M	$10^3 \times [Cu(phen)_2^{2+}]$, M	k_2, M^{-1} s^{-1}
0.13[b]	0.236	0.105	27.3 ± 1.4
0.26	0.473	0.211	22.3 ± 3.4
0.26[c]	0.473	0.211	29.2 ± 1.4
0.52	0.946	0.42	28.4 ± 2.5
0.78	1.42	0.63	24.4 ± 1.2
1.04	1.89	0.84	28.4 ± 5
1.04	1.98	0.92	30.7 ± 3.9
1.04	2.08	0.99	28.8 ± 3.6
2.08	3.78	1.69	26.5 ± 0.7
2.08[d]	3.78	1.69	27.4 ± 2.9
1.04[e]	1.89	0.84	30.0 ± 3
1.04[f]	1.89	0.84	23.2 ± 2.3

[a] All data in air at 25 °C, ionic strength 0.1 M (sodium nitrate), pH 6.15, and initial [cyt *c*(II)] in the range (2–5) × 10^{-6} M. [b] Initial [cyt *c*(II)] = 0.76 × 10^{-6} M. [c] Initial [cyt *c*(II)] = 14 × 10^{-6} M. [d] Initial [cyt *c*(II)] = 30 × 10^{-6} M. [e] pH 5.0. [f] pH 7.1.

Table V. Rate Constants for the Oxidation of Cytochrome *c*(II) by $Cu(nitrophen)_2^{2+}$ [a]

$10^3[Cu(nitrophen)_2^{2+}]$, M	k_2, M^{-1} s^{-1}	$10^3[Cu(nitrophen)_2^{2+}]$, M	k_2, M^{-1} s^{-1}
0.021[b]	138 ± 7	0.52[d]	163 ± 6
0.26	138 ± 14	0.78[d]	156 ± 6
0.52	153 ± 8	0.26[e]	198 ± 15
0.52[c]	140 ± 12	0.26[f]	152 ± 9
0.78	136 ± 30	0.26[g]	80 ± 4
1.04	139 ± 7	0.26[d,f]	149 ± 9
0.104[d]	147 ± 10	0.26[d,g]	85 ± 9
0.26[d]	163 ± 3		

[a] All data in air at 25 °C, ionic strength 0.1 M (sodium nitrate), total [nitrophen] = 2[Cu(II)]$_{tot}$, initial [cyt *c*(II)] in the range (5–25) × 10^{-6} M, and pH 6.15. [b] Initial [cyt *c*(II)] = 2.2 × 10^{-6} M. [c] Initial [cyt *c*(II)] = 30 × 10^{-6} M. [d] Solutions saturated with oxygen. [e] pH 5.0. [f] pH 7.0. [g] pH 8.0.

$Cu(phen)_2^{2+}$ concentrations. Precise determination of k_2 for $Cu(phen)^{2+}$ was not attempted because the Cu^{2+} present also contributes to the rate of reaction, but k_2 is approximately 4 M^{-1} s^{-1}. (This value was used to make small corrections to the results for the bis complex in Table IV.)

The effect of temperature and pH on the rates of reaction is recorded in Tables IV–VI. Activation parameters derived from these data may be found in Table III. Finally, the effect of propan-1-ol on the rate of autoxidation of cyt *c*(II) was measured in the presence and absence of $Cu(phen)_2^{2+}$. Propan-1-ol (5.4 M) increased the $Cu(phen)_2^{2+}$-catalyzed rate by a factor of 5 (from 28 to 120 M^{-1} s^{-1}) but increased the uncatalyzed rate by a factor of 250.

$Cu(dmphen)_2^{2+}$ Oxidation of $Co(phen)_3^{2+}$. Cobalt(III) and cobalt(II) tris(phenanthroline) complexes are well-characterized ions whose electron-transfer properties have been extensively investigated. The cobalt(III) complex is extremely inert, whereas the cobalt(II) species is only marginally inert exhibiting substitution rates of the order of 0.1 s^{-1}.[20] Mixing solutions of $Co(phen)_3^{2+}$ and $Cu(dmphen)_2^{2+}$ resulted in a rapid (<1 s) increase in the absorbance at 455 nm as a result of the formation of $Cu(dmphen)_2^{+}$. This was followed by a slower ($t_{1/2}$ > 1 s) increase in absorbance which also occurred when $Co(phen)_3^{2+}$ was mixed with dimethylphenanthroline alone. For this reason and because the reaction rate observed was close to that reported for similar species, the slow absorbance change was assigned to the substitution of $Co(phen)_3^{2+}$ by the excess dimethylphenanthroline. At 25 °C this substitution reaction restricted the range of concentrations that could be quantatively studied so that the order of the electron-transfer reaction had to be established at a lower temperature. The results listed in Table VII are consistent with simple second-order kinetics, first order in the concentration of each reactant. Mean values of the second-order rate constant, k_2, are given in Table II and the resulting activation parameters in Table III. That $Co(phen)_3^{2+}$ is the active species in solution and not some Co(II) species with less than three coordinated phenanthrolines was shown by the small decrease in rate observed when cobalt(II) solutions which were deficient in phenanthroline were used. The decrease in rate was consistent with the decrease in the concentration of the $Co(phen)_3^{2+}$. Excess phenanthroline over that required to completely form the cobalt(II) tris complex eliminated the electron-transfer reaction because of the rapid formation of copper(II)–phenanthroline complexes through substitution of $Cu(dmphen)_2^{2+}$ by the excess phenanthroline.

Table VI. Temperature Dependence of the Rate Constants for the Oxidation of Cytochrome *c*(II) by $Cu(phen)_2^{2+}$ and $Cu(nitrophen)_2^{2+}$ [a]

t, °C	$Cu(phen)_2^{2+}$ [b] k_2, M^{-1} s^{-1}	$Cu(nitrophen)_2^{2+}$ [c] k_2, M^{-1} s^{-1}
20	18.3 ± 0.8	109 ± 5
25	27.3 ± 0.9	157 ± 6
30	41.9 ± 1.1	201 ± 8
35	53.5 ± 2.9	295 ± 14

[a] All data at pH 6.15 (25 °C) and at ionic strength 0.1 M (sodium nitrate). [b] Total [Cu(II)] = 0.52 × 10^{-3} M, total [phen] = 1.1 × 10^{-3} M, $[Cu(phen)_2^{2+}]$ = 0.48 × 10^{-3} M, and initial [cyt *c*(II)] in the range (0.5–0.7) × 10^{-6} M. [c] $[Cu(nitrophen)_2^{2+}]$ = 0.26 × 10^{-3} M, initial [cyt *c*(II)] in the range (0.5–1.4) × 10^{-6} M.

Table VII. Rate Constants for the Oxidation of $Co(phen)_3^{2+}$ by $Cu(dmphen)_2^{2+}$ [a]

$10^3[Co(phen)_3^{2+}]$, M	$10^{-4}k_2$, M^{-1} s^{-1}	
	15 °C	25 °C
0.199	4.79 ± 0.16[b]	
0.397	4.98 ± 0.25[c]	
0.496	4.60 ± 0.13[c]	8.63 ± 0.12[c]
0.794	4.90 ± 0.22[b]	8.81 ± 0.28[c]
0.794	4.82 ± 0.14[c]	
0.993	4.70 ± 0.14[c]	9.38 ± 0.45[c]
1.99	4.61 ± 0.26[c]	

[a] All data at an ionic strength of 0.1 M (sodium nitrate), pH 6.15, total [dmphen] = 2.0 × 10^{-4} M. [b] Total [Cu(II)] = 0.25 × 10^{-4} M. [c] Total [Cu(II)] = 0.5 × 10^{-4} M.

Discussion

Mechanism of the Reactions. All the results for the oxidation of cyt *c*(II) in the presence of copper–phenanthroline complexes as well as other complexes are consistent with a mechanism in which the first step is electron transfer from copper to iron, followed, whenever possible, by the reoxidation of the resultant Cu(I) complexes by molecular oxygen.[18] This reoxidation does not occur with $Cu(dmphen)_2^{+}$ since it is stable in the presence of oxygen. In the $Cu(phen)_2^{2+}$-catalyzed reaction, the absence of any kinetic effect of increased oxygen concentration, the simple second-order kinetic behavior, and the observation of identical rates in the presence and absence of oxygen demonstrate that the rate-determining step is the electron-transfer reaction. With $Cu(nitrophen)_2^{2+}$ the small increase in rate in pure oxygen relative to that in air suggests that in air there may be a vestige of competition between the reoxidation of Cu(I) by molecular oxygen and by cyt *c*(III). Initial rates in the absence of oxygen and the second-order kinetics are still consistent with a rate-controlling electron-transfer reaction. Thus the kinetic results presented in this

Table VIII. Rate and Equilibrium Constants for Electron Transfer between Cytochrome *c* or $Co(phen)_3^{2+}$ and Some Copper Complexes[a]

	K_{12}	k_{12}, M^{-1} s^{-1}	k_{22},[b] M^{-1} s^{-1}	k_{22}^{cor},[c] M^{-1} s^{-1}
$Cu(dmphen)_2^{2+}$ [d]	6.2×10^5 [e]	$(1.00 \pm 0.04) \times 10^6$	1.9×10^4	1.7×10^4
$Cu(dmphen)_2^{2+}$ [f]	8.6×10^3 [e]	$(8.81 \pm 0.3) \times 10^4$	4.9×10^4	4.4×10^4
$Cu(phen)_2^{2+}$ [d]	$(5.2 \pm 1.2) \times 10^{-2}$	$(2.72 \pm 0.26) \times 10$	5.0×10	4.6×10
	3.5×10^{-2} [g]		7.5×10	6.8×10
$Cu(nitrophen)_2^{2+}$ [d]	0.81 ± 0.1	$(1.57 \pm 0.06) \times 10^2$	1.01×10^2	9.3×10
$Cu(bpy)_2^{2+}$ [d,h]	$(2.9 \pm 0.5) \times 10^{-3}$	$(1.39 \pm 0.1) \times 10$	2.5×10^2	2.8×10^2
	4.3×10^{-3} [g]		1.8×10^2	1.6×10^2

[a] All data at 25 °C and ionic strength 0.1 M (sodium nitrate). [b] Calculated from the Marcus cross relationship assuming $k_{11} = 3 \times 10^2$ M^{-1} s^{-1} (ref 43). [c] Corrected for effect of reactant charge (see ref 23). [d] Cyt *c*(II) as reductant. [e] Calculated assuming $E^\circ = 0.603$ V for $Cu(dmphen)_2^{2+/1+}$ (ref 2) and $E^\circ = 0.260$ V for cyt *c*(III)/(II) (ref 13) or $E^\circ = 0.370$ V for $Co(phen)_3^{3+/2+}$ (ref 23). [f] $Co(phen)_3^{2+}$ as reductant. [g] Calculated from the E° values given in ref 2. [h] Reference 18.

paper are assumed to apply to the rate of the forward reaction in eq 1 and 3, that is, to the rate of electron transfer from cyt *c*(II) to the Cu(II) complexes.

Mechanism of the Electron Transfer between Cytochrome *c* and the Copper Complexes. Two pathways have been reported for the reduction of ferricytochrome *c* by low molecular weight reductants. Reduction by chromium(II) aquo ion[10] and dithionite ion[21] is thought to occur by direct electron transfer from the reductant to the iron in cyt *c* following exposure of the iron atom through a rapid preequilibrium dissociation of the axial iron–methionine bond (inner-sphere mechanism). However, for most reductants[22,23] including $Ru(NH_3)_6^{2+}$, $Fe(EDTA)_6^{4-}$, and reduced cytochromes the most plausible mechanism appears to involve electron transfer to the intact cyt *c* through the edge of the heme porphyrin that is exposed to the bulk solvent and is therefore accessible to solutes.[24] Heme edge electron transfer is also likely for the oxidation of reduced cyt *c* by such species as $Co(phen)_3^{3+}$ [25] and ferricyanide. Heme edge electron transfer is likely in the reactions of cyt *c*(II) with the copper complexes, even though inner-sphere behavior has been proposed in some other reactions of copper complexes.[8,9] Our reasons for preferring heme edge transfer include (i) the greater stability of the reduced cytochrome to dissociation of the methionine 80 from the heme iron, compared to that of oxidized cytochrome,[26–29] (ii) the high rate of reaction found in the oxidation by $Cu(dmphen)_2^{2+}$, (iii) the relatively small effect of the chaotropic reagent[29] propan-1-ol on the rate of oxidation by $Cu(phen)_2^{2+}$, and (iv) the small effect of pH on the rates of reaction.

For these reasons electron transfer through the porphyrin edge that is accessible to the copper complexes in the native cytochrome appears to be the most probable pathway from cyt *c* to copper. This general proposition still permits in principle an inner-sphere electron transfer with respect to the copper, in which the copper is directly bound to porphyrin edge in the transition state. We nevertheless favor an outer-sphere mechanism without a bridging ligand, because of the absence of any suitable binding sites for the copper, apart, perhaps, from the heme carboxylate group which is likely to be too isolated electronically from the heme to be useful for electron transfer. The mechanism of the $Co(phen)_3^{2+}$–$Cu(dmphen)_2^{2+}$ reaction is taken to be outer sphere because electron transfer is faster than substitution of $Co(phen)_3^{2+}$.

Negative entropies of activation have been commonly found[26,30] for outer-sphere electron-transfer reactions between ions of like charge. Our values are therefore not exceptional. It is also worth noting that the difference between the rate constants for the dmphen complexes and the other complexes resides entirely in the enthalpy term—in fact the entropy term is counteractive.

Structural Barriers to Electron Transfer. As argued in the Introduction, it is reasonable, a priori, to suppose that an internal rearrangement barrier will exist for electron exchange between two oxidation states with substantially different coordination-sphere geometries. It was further argued that such a structural barrier will be significant for the one-electron reduction of most "simple" copper(II) complexes such as $Cu(phen)_2^{2+}$ but will be smaller for the reduction of $Cu(dmphen)_2^{2+}$ because of the distortion produced by the steric interactions of the methyl substituents. The slow rate of reduction of the unsubstituted phenanthroline complex and the 10^6-fold greater rate of reduction of the dimethylphenanthroline complex are gratifyingly in accord with these proposals. However, the simple comparison of rates of reduction may be misleading because of the effects of differences in redox potential of the copper complexes. We have therefore calculated electron-exchange rates from the Marcus cross relationship: $k_{12} = (k_{11}k_{22}K_{12}f)^{1/2}$ (Table VIII). Chou, Creutz, and Sutin[31] have recently examined the validity of this equation in general and Wherland, Gray, and Holwerda[32,23] have discussed its application to electron-transfer proteins including cytochromes. Chou, Creutz, and Sutin conclude that the cross relationship is reliable to within a factor of 10 for complexes other than the aquo ions, provided that the system is not initially far from equilibrium ($K < 10^6$). Exchange rates were underestimated when this latter condition was not met. The cross relationship also assumes that the work terms in the Marcus treatment are identical for all the reactions in the relationship. This is not obviously true for the copper–cyt *c* reactions, though all the complexes are positively charged and the higher charge on the cytochrome (+6 to +7) compared to that of the copper complexes will in part be compensated for by the larger radius of the cytochrome. Calculation of the work terms for such large molecules is difficult principally because the usual approximation of uniformly charged spheres may not be acceptable. Wherland and Gray[23] have nonetheless attempted to make corrections for the effects of work terms on the calculated rates of exchange of proteins including cyt *c*. Although we have reservations about the reliability of this approach, we have still subjected our results to their treatment (see Table VIII). The corrections are very small in all cases.

We are confident that our calculated exchange rate constants are reliable to within 1 order of magnitude and that *relatively* they are considerably more reliable. Most importantly also we feel that the use of cyt *c* as a reductant does not result in anomalous rate constants for exchange. Both of these statements are strongly supported by the results derived from the oxidation of $Co(phen)_3^{2+}$. Even though this is chemically a very different reductant to cyt *c*, the rate constant deduced for $Cu(dmphen)_2^{2+}/Cu(dmphen)_2^{+}$ exchange is in superb agreement with that derived from the cytochrome data.

These observations must, however, be contrasted with those of Yoneda, Blackmer, and Holwerda[7] based on the rate of oxidation of $Cu(phen)_2^{+}$ and $Cu(bpy)_2^{+}$ by $Co(EDTA)^-$. They calculated from the Marcus cross relationship rate constants for electron exchange between the Cu(II) and copper(I)–phenanthroline and –bipyridyl complexes of 5×10^7 and 4×10^6 M^{-1} s^{-1}, respectively. Even though these values would be

reduced substantially if corrected for the effects of opposite charge by the Wherland and Gray procedure, they would still be 4 orders of magnitude greater than our numbers. It is evident that the use of the Marcus cross relationship is not valid either in their work or in ours. However, the consistency of our results with two very different reducing agents strongly supports our conclusions. Further confidence in the slowness of the exchange reactions has been gained from our observations on the rate of the pseudo-electron-exchange reactions between $Cu(bpy)_2^+$ and $Cu(phen)_2^{2+}$. On mixing copper(I)–bipyridyl and copper(II)–phenanthroline solutions, we observed a rapid increase in visible absorption occurs in the range 400–450 nm. This observation is consistent with electron transfer from the Cu(I) complex to the Cu(II) complex. The rate of the reaction is close (within a factor of 5) to that predicted from our calculated exchange rate constants. If the exchange rate constants reported by Yoneda et al. were correct, then the rate constant for this reaction should have been ca. 10^7 M^{-1} s^{-1}. Similar conclusions can be drawn from our preliminary studies on the reduction of $Cu(phen)_2^{2+}$ and $Cu(nitrophen)_2^{2+}$ by $Ru(NH_3)_6^{2+}$. Again the rate of reaction observed is consistent with our exchange rate constants but more than 10^3 slower than expected from the higher values determined by Yoneda et al. Rate constants in the range (2–4) $\times$ 10^5 M^{-1} s^{-1} have also been measured for the reaction of $Cu(dmphen)_2^{2+}$ and $Cu(bpy)_2^+$. These values are approximately a factor of 10 less than predicted on our exchange values but a factor of 1000 less than expected from the $Cu(bpy)_2^{2+/1+}$ value of Yoneda et al.

Do the rate constants for exchange in Table VII also support the proposed structural rearrangement barrier to electron transfer between copper(II) and copper(I)? We believe that they do or at least that this is the most consistent interpretation.

First, the rates of electron transfer and electron exchange are slow compared to those of other metal complexes and in particular other phenanthroline complexes.[31] $Fe(phen)_3^{3+}$–$Fe(phen)_3^{2+}$ exchange, $k = 3 \times 10^8$ M^{-1} s^{-1},[33] $Ru(bpy)_3^{3+}$–$Ru(bpy)_3^{2+}$ exchange, $k = 2 \times 10^9$ M^{-1} s^{-1},[34] and $Cr(bpy)_3^{3+}$–$Cr(bpy)_3^{2+}$ exchange, $k = 10^7$–10^9 M^{-1} s^{-1},[25] are all much faster than exchange for the copper complexes. These rapid rates imply that the internal reorganization barrier is negligible for these complexes. By contrast, $Co(phen)_3^{3+}$–$Co(phen)_3^{2+}$ exchange, in common with other Co(III)–Co(II) electron-transfer reactions, is relatively slow with a rate constant, $k = 45$ M^{-1} s^{-1},[35] similar to that of the $Cu(phen)_2^{2+}$–$Cu(phen)_2^+$ exchange. The slowness of both exchange rates suggests a large internal energy barrier to electron exchange compared to that for the more rapid exchange reactions. This large barrier probably arises from structural differences between the two oxidation states, which, we propose, result mainly from differences in coordination number and stereochemistry between copper(II) and copper(I), rather than differences in metal–ligand bond lengths as is likely in the $Co(phen)_3^{3+/2+}$ system. Crystal structure studies, which might help to confirm such differences, are not available for either the cobalt or the copper complexes. However, studies of some copper complexes with macrocyclic sulfur donor ligands did not reveal any significant difference in the copper–sulfur distances between the Cu(II) and Cu(I) species, despite a change in coordination number. A second argument in support of a structural barrier is based on the observation that the rate of exchange of the dmphen complexes is more than 100 times greater than the rate of exchange of the copper–phenanthroline complexes. Steric interference between the methyl substituents of dmphen and the other ligands bound to the copper (water or another dmphen) is expected[13] to distort the coordination sphere of $Cu(dmphen)_2^{2+}$. That such steric strain exists in $Cu(dmphen)_2^{2+}$ (but not in $Cu(dmphen)_2^+$) is evident from the low stability constants[10] for the formation of this complex. The nature of the distortion is not, however, clear, partly because of the few relevant crystal structure studies available.[36–38] It is nevertheless likely that the copper–water interaction is weakened by the steric crowding—thus forcing the structure toward the expected copper(I) structure. The faster rate of exchange is consistent with such changes.

Comparison of the rate constants for electron exchange of the copper–phenanthroline complexes with those of some ostensibly four-coordinate copper(II) complexes also bolsters the concept of a structural barrier. A rate constant of 5×10^7 M^{-1} s^{-1} was reported[5] by McConnell and Weaver for exchange between the copper complexes present in concentrated hydrochloric acid. In this medium the copper(II) complexes are probably four-coordinate.[40] Consequently the structural barrier should be low and the electron exchange rapid, as reported. Published studies[32] on the "blue" copper proteins also indicate that relatively rapid exchange between copper(II) and copper(I) occurs with these proteins, at least when the active site is "kinetically accessible". We again ascribe the fast exchange to a relatively low structural barrier in these rigid[14] four-coordinate[42] copper systems. It should be admitted, however, that the unusual environment of the copper, as reflected by the unusual spectroscopic properties of the blue copper center, may also differ from low molecular weight, "normal" copper complexes in other kinetically important ways. Foremost of these might be the sulfur donor atoms present in the coordination sphere. Whatever factors contribute to the faster rates of the "blue" copper proteins, our results suggest that the unusual nature of the copper coordination sphere is needed to meet the functional requirements of fast electron transfer and high redox potential.

It is instructive to briefly consider the origins of the slow rate of electron transfer from cyt *c*(II) to $Cu(phen)_3^{2+}$ and $Cu(bpy)_3^{2+}$. Reduction of these species clearly requires a change in coordination number. It is then apparent, a priori, that such reactions are likely to be slow. If electron transfer occurs prior to the loss of a phenanthroline, that is with the initial formation of $Cu(phen)_3^+$, it will be thermodynamically impeded to an extent related to the stability of the Cu(I) complex relative to that of the copper(II) complex. If, on the other hand, dissociation of the third ligand occurs prior to the electron transfer, then the rate of electron transfer will be restricted by the low concentration of the four-coordinate copper(II) intermediate in equilibrium with the reactant. Major structural differences between the coordination spheres of metal ions in two oxidation states also occurs, of course, with metals other than copper. In all such cases the rate of electron transfer is likely to be less than that for similar systems without structural differences. For example, the alkaline (pK_a = 9.4) form of ferricytochrome is reduced more slowly than the native form,[27] since ferrocytochrome retains the native configuration up to pH 12.

From the viewpoint of the cytochrome the reactions with the copper complexes do not obviously exhibit any new features. The results are therefore consistent with the developing picture of the electron-transfer behavior of cyt *c*, viz., that it is not outstandingly different to the behavior of low molecular weight metal complexes, apart from the effects of the obvious differences in size and charge.

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Registry No. Cytochrome *c*(II), 9007-43-6; $Cu(dmphen)_2^{2+}$, 14875-91-3; $Co(phen)_3^{2+}$, 16788-34-4; $Cu(nitrophen)_2^{2+}$, 47758-31-6; $Cu(phen)_2^{2+}$, 15823-71-9.

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Cation Radicals of Phenothiazines. Electron Transfer with Aquoiron(II) and -(III) and Hexacyanoferrate(II) and -(III)

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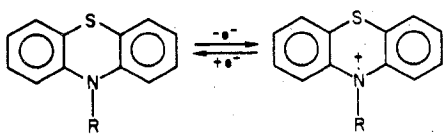
The rates of electron transfer of three different groups of reactions involving *N*-alkylphenothiazines (PTZ) have been obtained in aqueous perchloric acid medium by means of stopped-flow and *T*-jump spectrophotometric techniques: (1) the electron transfer between the cation radical and different PTZ derivatives; (2) the oxidation of PTZ by $Fe(H_2O)_6^{3+}$; (3) the oxidation of PTZ by $Fe(CN)_6^{3-}$. Electron transfers involving $Fe(CN)_6^{3-}$ are in agreement with the Marcus theory, while oxidation by Fe(III) shows an expected dependence of activation free energy on overall free energy change, although the calculated values are 300–500 times higher than the experimental ones.

Increasing interest has been recently devoted to the chemistry of organic cation radicals.[1] These species are intermediates in several oxidation processes; therefore it is useful to know some of their characteristic parameters such as the reduction potentials and the self-electron-exchange rates in solution as well as if their reaction kinetics can be treated in the light of most currently adopted electron-transfer theories,[2] particularly the Marcus theory,[3] which is one of the most frequently applied, since its form is conducive to experimental evaluation.

Cation radicals of *N*-alkylphenothiazines are known to be generated in solution by removal of one electron from their parent molecules,[4] according to



and to be long-lived in aqueous acidic medium. Almost all *N*-alkylphenothiazines are antipsychotic drugs, and their redox activity was related to the pharmaceutical properties (free radicals were in fact discovered as metabolites of phenothiazine-like drugs).[5a]

Unsubstituted phenothiazine attracted large interest also in photoionization studies performed for solar energy conversion purposes.[6] These investigations were performed in alcoholic solution or micellar phase owing to the poor solubility in water of phenothiazine (all of the present *N*-alkyl derivatives are, however, water soluble).

Besides, the photogalvanic effect of the thionine (a diamino derivative of phenothiazine)–iron system[7] is one of the most extensively studied because of the possibility of its use in the construction of photogalvanic cell.[8]

In this paper we present the results of our studies on the kinetics and mechanism of electron transfer between a series of *N*-alkylphenothiazines and $Fe(H_2O)_6^{3+/2+}$ and $Fe(CN)_6^{3-/4-}$ in acidic aqueous solution.

Experimental Section

Reagents. The *N*-alkylphenothiazines (later referred to as PTZ) in Chart I, obtained from Rhône-Poulenc, were investigated. The purity of the compounds was checked by elemental analysis as well

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