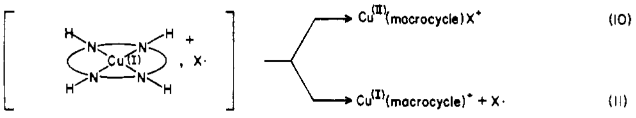
generated under experimental conditions where the photolytes are mainly in the form of pentacoordinated species (Cu(macrocycle)X$^+$ with X = Cl$^-$, Br$^-$, or SCN$^-$). Hence, the photoreactivity of these complexes can be described by means of two primary photoprocesses. One process is the reduction of the complex to Cu(macrocycle)$^+$ with the simultaneous oxidation of the acido ligand X$^-$ (eq 2), and the other is the photooxidation of the macrocycle ligand (eq 1). Moreover the secondary formation and decay of the copper(III) macrocycles is described in eq 2 and 10–14.



$$X\cdot + X^- \rightleftharpoons X_2^- \qquad (12)$$

$$2X_2^- \longrightarrow X_2 + 2X^- \qquad (13)$$

$$(X\cdot)\ X_2^- + Cu^{(II)}(macrocycle)X^+ \longrightarrow Cu^{(III)}(macrocycle)X_2^+ \dashrightarrow products \qquad (14)$$

The photooxidations of the acido and macrocycle ligands, in two distinct photoprocesses, have different threshold energies, namely, $E_{th}{}^{Cl} \approx 102$ kcal and $E_{th}{}^{N} \leq 92$ kcal. These energies and the action spectra (Figure 2) suggest that the two photoprocesses have different precursors, namely, two different charge-transfer to metal states. The photooxidation of the macrocycle ligand must be attributed to the population of a charge-transfer ligand to metal state that involves the electronic density of the tetraaza macrocycle, e.g., CTTM$_{N\to Cu}$ in eq 1. In addition, the photooxidation of the acido ligand is more likely the result of the population of an acido to copper(II) charge-transfer state, namely, a CTTM$_{X\to Cu}$ in eq 2. The presence of these states CTTM$_{N\to Cu}$ and CTTM$_{X\to Cu}$ can be justified by means of the optical electronegativities.[29] Indeed, the position of the charge-transfer maxima in the spectra of the copper(II) polyamine complexes yield an optical electronegativity $X \simeq 2.98$ for nitrogen orbitals with σ symmetry.[30] The value of the optical electronegativity for an amino ligand is close to the optical electronegativities of halides and pseudohalides.[30] This suggests that vertical transitions, CTTM$_{N\to Cu}$ and CTTM$_{X\to Cu}$, must occur at similar energies. However, the charge-transfer transitions that involve the electronic density of the axially coordinated ligand are orbitally forbidden and must have a low intensity. Changes in the charge-transfer spectra, induced by pentacoordination, can be the result of the introduction of new, low-intensity, charge-transfer transitions and modifications of the overall ligand field strength.[31]

Acknowledgment. The research described herein was supported by the Office of Basic Energy Sciences of the Department of Energy. This is Document No. NDRL-2168 from the Notre Dame Radiation Laboratory. We are also indebted to Professor J. F. Endicott for helpful discussions.

Registry No. Cu(*dl*-Me$_6$[14]aneN$_4$)$^{2+}$, 24830-76-0; Cu(*rac*-Me$_6$[14]aneN$_4$)$^{2+}$, 53447-11-3; Cu(*rac*-Me$_6$[14]aneN$_4$)(CH$_3$CN)$^{2+}$, 77357-89-2; Cu(*rac*-Me$_6$[14]aneN$_4$)F$^+$, 72477-18-0; Cu(*rac*-Me$_6$[14]aneN$_4$)Cl$^+$, 66139-47-7; Cu(*rac*-Me$_6$[14]aneN$_4$)Br$^+$, 66139-48-8; Cu(*rac*-Me$_6$[14]aneN$_4$)I$^+$, 70024-13-4; Cu(*rac*-Me$_6$[14]aneN$_4$)py^{2+}, 77357-90-5; Cu(*rac*-Me$_6$[14]aneN$_4$)N$_3{}^+$, 73384-35-7; Cu(*rac*-Me$_6$[14]aneN$_4$)SCN$^+$, 73384-34-6; Cu(*rac*-Me$_6$[14]aneN$_4$)NO$_2{}^+$, 73384-33-5; Cu(*rac*-Me$_6$[14]aneN$_4$)CN$^+$, 47249-07-0.

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(29) Notice that similar assignments have been made by Lever et al. in the charge-transfer spectrum of copper(II) ethylenediamines.[5]

(30) For a definition and tabulations of optical electronegativities see: Lever, A. B. P. "Inorganic Electronic Spectroscopy"; Elsevier: "Concepts in Inorganic Photochemistry"; Adamson, A., Fleischauer, P. D., Eds.; Wiley: 1975; Chapter 3.

(31) Such modifications of the overall ligand field strength are suggested by the dependence of the dd-band positions and of the half-wave potentials on axial ligand.

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Determination of the Self-Exchange Electron-Transfer Rate Constant for a Copper(III/II) Tripeptide Complex by ^{1}H NMR Line Broadening

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The electron-transfer self-exchange rate constant k_{11} between the +3 and +2 oxidation states of the copper complex of tri-α-aminoisobutyric acid has been determined by ^{1}H NMR line broadening. At 298 K $k_{11} = 5.5 \times 10^4$ M^{-1} s^{-1} with $\Delta H^{\ddagger} = +7.0$ kcal mol^{-1} and $\Delta S^{\ddagger} = -13$ cal deg^{-1} mol^{-1}. Cross reactions between copper tri- and tetrapeptide complexes indicate that this value of k_{11} is appropriate for many Cu(III)/Cu(II) oligopeptide redox couples. Chloride and hydroxide ions do not accelerate the Cu(III)/Cu(II) electron-transfer processes, which suggests an outer-sphere mechanism, although bridging by an axially bound water molecule is a possibility. Cross reactions with IrCl$_6{}^{3-,2-}$ appear to proceed via inner-sphere pathways.

Introduction

The Marcus correlation equation[1]

$$k_{12} = (k_{11}k_{22}K_{12}f)^{1/2} \qquad (1)$$

where

$$\log f = (\log K_{12})^2/[4 \log (k_{11}k_{22}/Z^2)] \qquad (2)$$

has been used extensively to interpret the kinetics of a variety of electron-transfer reactions.[2,3] Values of the self-exchange rate constants k_{11} and k_{22} are usually difficult to measure directly due to lack of experimental observables or the necessity for rapid separation techniques. Often when values of k_{11} for new redox systems cannot be measured directly, k_{11} is calculated, with use of eq 1, by measuring cross-reaction rate constants, k_{12}, for reactions involving redox couples where k_{22} is known. This procedure can result in large errors. Even for

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(1) Marcus, R. A. *J. Phys. Chem.* **1963**, *67*, 853; *J. Chem. Phys.* **1965**, *43*, 679.

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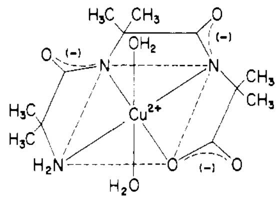
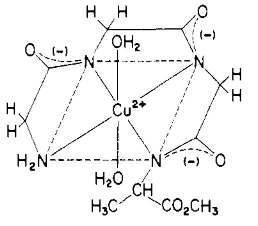
0020-1669/81/1320-2311$01.25/0

systems where k_{11} and k_{22} are known, k_{12}^{calcd} and k_{12}^{obsd} often differ by 1 order of magnitude.[4] Due to the mathematical form of eq 1, any systematic error in k_{12}^{obsd} for a cross reaction will result in that error squared in a calculated value of k_{11}. Therefore, directly measured values of k_{11} provide a basis that allows use of the Marcus correlation with increased confidence.

Tri- and tetrapeptides react with Cu^{2+} in basic media to form complexes in which the peptide ligand supplies four donor atoms in a square-planar arrangement.[5] Structures I and II give the geometries for two of the complexes used in the present study. Freeman[5] found that crystal structures of some peptide complexes had tetragonally distorted octahedral and square-pyramidal geometries as well as square-planar geometries. He postulated that a trigylcine complex such as $Cu^{II}(H_{-2}G_3)^-$, which has one axial water in the crystal, might have two more distant axial waters in solution. He initially postulated[5] that square-planar complexes such as that of tetraglycine, $Cu^{II}(H_{-3}G_4)^{2-}$, remain square planar in solution. However, magnetic resonance studies by Falk and Freeman et al.[6] led to the conclusion that $Cu^{II}(H_{-3}G_4)^{2-}$ has one or two waters coordinated axially in solution.



I. $Cu^{II}(H_{-2}Aib_3)^-$



II. $Cu^{II}(G_3AOCH_3)^-$

The copper peptide complexes can be reversibly oxidized to the Cu(III) state with formal reduction potentials ranging from greater than +1.0 to less than +0.5 V vs. the normal hydrogen electrode.[7,8] Bossu et al.[8] have shown that these reduction potentials can be empirically correlated with a variety of factors associated with the peptide ligand such as the number of deprotonated nitrogen donors and the nature of the R groups on the α-carbons. Recent studies[9] of the temperature dependence of the electrode potentials lead to the conclusion that the copper(III) peptide complexes are not axially solvated in contrast to the copper(II) peptide complexes. Hence electron-transfer reactions also involve changes in coordination number, but the equatorial geometries with respect to the peptide coordination are similar. Considering the large change of $E°$ values with various peptides, it is not obvious that there should be a single self-exchange rate constant for a series of different peptide complexes. On the other hand the donor atoms in all the complexes are hard σ donors. Consequently the energy required for bond-length changes and coordination changes prior to the electron-transfer step would be expected to be similar for all complexes, which implies similar values of k_{11}. In any case the present study does indicate a constant value for k_{11}. A series of redox couples with a wide range of reduction potentials and similar self-exchange rates constitutes a powerful probe for investigation of other redox systems.

The direct determination of k_{11} generally requires the existence of a set of solution conditions where both halves of the redox couple are stable. Unfortunately, the Cu(II)–oligopeptide complexes rapidly dissociate in acid,[10] and the Cu(III)–oligopeptide complexes decompose via intramolecular redox processes that are catalyzed by acid, base, and visible light.[11-13] Three previous studies have examined the electron-transfer reactions of a series of Cu(III)–peptide complexes with hexachloroiridate(III),[14] tris(1,10-phenanthroline)cobalt(II),[15] and bis(2,9-dimethyl-1,10-phenanthroline)copper(I).[16] In each case plots of log $(k_{12}/f^{1/2})$ vs. log K_{12} were linear, which is consistent with a constant value of k_{11} for the Cu(III)/Cu(II) redox couples. Numerical evaluation of k_{11} was ambiguous however. In the study with $IrCl_6^{3-}$ a value of 7×10^7 M^{-1} s^{-1} was calculated for k_{11}, but the possibility of an inner-sphere mechanism could not be excluded. While the rate of reaction of Cu(III)-peptide complexes with $Co(phen)_3^{2+}$ was related to the free energy change, the relationship was not as predicted by eq 1. The slope of the Marcus plot, log k_{12} vs. log K_{12}, was 0.34 instead of 0.5. This is typical for reactions involving Co(III)/Co(II) redox couples. Values of k_{11} equal to 7×10^7 or 3×10^5 M^{-1} s^{-1} could be calculated by using alternate theoretical interpretations.[15] In the third study,[16] the self-exchange rate for $Cu^{II,I}(dmp)_2^{2+,+}$ had not been measured directly; therefore the intercept of the Marcus plot yielded only the product $k_{11}k_{22}$.

Recently, Kirksey et al. reported the synthesis of an unusually stable Cu(III)–tripeptide complex derived from α-aminoisobutyric acid, $Cu^{III}(H_{-2}Aib_3)$.[17] The remarkable stability of this complex allows the direct determination of the self-exchange rate constant and activation parameters for the Cu(III)/Cu(II) couple using ^1H NMR line boadening. In the present work we report the results of the line-broadening study as well as rate constants for a variety of cross reactions involving copper tri- and tetrapeptide complexes. The rate constants for the reactions of $Cu^{III}(H_{-2}Aib_3)$ with $Co(phen)_3^{2+}$ and $Cu(dmp)_2^+$ and for the reaction of $Cu^{II}(H_{-2}Aib_3)^-$ with $Ir^{IV}Cl_6^{2-}$ are also reported in order to provide a comparison with the earlier studies.[14-16]

Experimental Section

Reagents and Materials. The tripeptide $Aib_3 \cdot H_2O$ was synthesized from α-aminoisobutyric acid.[17,18] The other oligopeptides were obtained (Biosynthetika or Cyclo Chemical Co.) and were used without further purification. Other chemicals and solvents were reagent grade.

Potentiometric Titrations. Potentiometric titrations were performed by using an Orion Research Model 701A Digital Ionalyzer equipped with a Sargent-Welch S30050-15C glass electrode. A sodium chloride saturated calomel electrode was connected to the cell via a salt bridge containing 0.1 M $NaClO_4$. All solutions were freshly prepared from a standardized $Cu(ClO_4)_2$ solution, solid $Aib_3 \cdot H_2O$, standardized $HClO_4$, and carbonate-free water and were blanketed with water-saturated argon during the course of the titrations. The titrant was 0.1 M NaOH delivered from a calibrated micrometer syringe of 2-mL capacity. Potentiometric data were recorded in millivolts vs. volume of titrant added. Periodic titrations of standard $HClO_4$ solutions provided the means for conversion of potential (mV) readings to $[H^+]$ and calculation of K_w.[19] Solutions were maintained at an ionic strength

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of 0.1 with $NaClO_4$. Equilibrium constants were calculated from the potentiometric data with use of a modified version of the computer program SCOGS.[20,21]

Preparation of Solutions of Copper Peptide Complexes for NMR Experiments. Solid $Cu^{III}(H_{-2}Aib_3)$ was prepared by the method described by Kirksey[17] and purified by recrystallization from water. Solutions of this material contained small concentrations of $Cu^{II}(H_{-2}Aib_3)^-$ as judged by their NMR spectra at pH >7, which were broader than spectra of solutions containing only $Cu^{III}(H_{-2}Aib_3)$. Solutions free of $Cu^{II}(H_{-2}Aib_3)^-$ could be obtained by lowering the pH to less than 4, where any residual $Cu^{II}(H_{-2}Aib_3)^-$ is dissociated. The rapid dissociation of $Cu^{II}(H_{-2}Aib_3)^-$ in acid combined with the substitutional inertness of the Cu(III) complex permitted the selective removal of the small concentrations of Cu^{2+} using the following procedure. Solid $Cu^{III}(H_{-2}Aib_3)$ was dissolved in 4 mL of D_2O, and ~1 g of Chelex-100 resin (Bio-Rad), which had been washed with dilute $HClO_4$ and D_2O, was added. The suspension was stirred for 1–3 h before the resin was removed by filtration through a coarse sintered-glass frit and a 0.22-μm Millipore filter. The remaining solution was then combined with various reagents in order to attain the desired pH and ionic conditions (see Table IV). Most of the solutions were adjusted to a similar set of conditions that provided buffer capacity and ionic-strength control. In this procedure a 2.3-mL volume of the solution was combined with 0.1 mL of a concentrated buffer solution and 0.1 mL of a concentrated salt solution. The buffer solution was 0.25 M KH_2PO_4 in D_2O, adjusted to pH 6.7 with NaOD. The salt solution was $NaClO_4$ in D_2O at the concentration required for a total ionic strength of 0.1 for a given pH. Finally the 2.5 mL of solution was adjusted to the desired pH with microliter volumes of concentrated NaOD. Two milliliters of this solution was transferred to an 8-mm NMR tube. The concentration of $Cu^{III}(H_{-2}Aib_3)$ was determined by diluting a 0.1-mL volume of the solution and checking the absorbance at 395 nm ($\epsilon = 5300\ cm^{-1}\ M^{-1}$).[17] All manipulations of Cu(III) solutions were conducted in light that was passed through a Kodak 1A filter ($\lambda > 580$ nm) to avoid photodecomposition. Solutions of $Cu^{III}(H_{-2}Aib_3)$ prepared in this manner gave NMR spectra with narrow peaks.

The solutions of $Cu^{II}(H_{-2}Aib_3)^-$ used in the NMR experiment were prepared by diluting a standardized aqueous solution of $Cu(ClO_4)_2$ (0.1 M) with D_2O. A 10% excess of Aib_3 was added and the pH adjusted to 8–9 with NaOD. Only microliter volumes of the $Cu^{II}(H_{-2}Aib_3)^-$ solutions were used in the NMR experiments, and contamination by H_2O or undesired pH changes were not a problem.

NMR Spectra. The NMR spectra used for the assignment of chemical shifts were recorded on a Perkin-Elmer R32 NMR spectrometer (90 MHz) and a Nicolet NTC360 NMR spectrometer. The solutions were contained in 5-mm tubes. Solutions of $Cu^{II}(H_{-2}Aib_3)^-$ contained in 12-mm tubes were examined with a Nicolet 150-MHz NMR spectrometer.

All NMR spectra for the line-broadening experiments were recorded with use of a Varian XL-100 NMR spectrometer in the continuous-wave mode using the signal from HOD as an internal lock. Each solution was contained in an 8-mm tube, which in turn was positioned in a 12-mm tube with a Teflon adapter. The volume between the tubes was filled with CCl_4. The temperature of the probe was measured periodically by inserting a methanol sample and recording the difference in chemical shift for the proton resonances.[22] The standard deviation for these measurements was ±0.5 K.

Each determination of the self-exchange rate constant consisted of measuring the change in peak width after additions of the $Cu^{II}(H_{-2}Aib_3)^-$ solution to the $Cu^{III}(H_{-2}Aib_3)$ solution. Peak widths are defined by their full widths at half-maximum, fwhm.[23] The change in peak width is fwhm − $fwhm_0$, where $fwhm_0$ is the peak width for solutions containing only diamagnetic material. Five to eight additions were made for each determination. In order to ensure that the field homogeneity contribution to the line width remained constant, we added ~2 μL of acetone or 1,4-dioxane to each solution. The width of the signal due to the acetone or dioxane was constant to within ±0.2 Hz throughout the course of each determination. Each spectrum was recorded twice to ensure reproducibility. The scanning rate was 0.1 Hz s^{-1}.

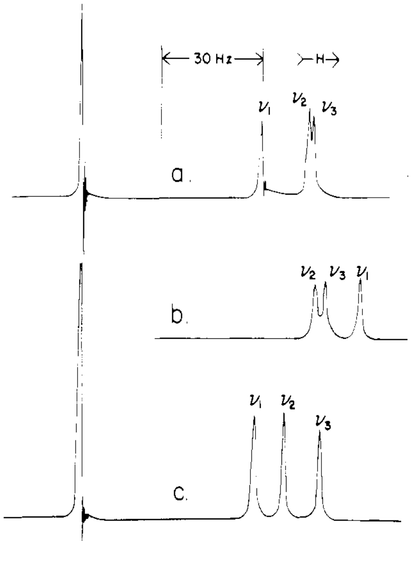

Figure 1. ^1H NMR spectra (90 MHz) of the free and complexed ligand Aib_3 in D_2O: curve a, $H_2Aib_3^+$ (pD ~2); curve b, Aib_3^- (pD ~12); curve c, $Cu^{III}(H_{-2}Aib_3)$ at pH ~4. The downfield resonance is due to added acetone.

Values of fwhm were measured directly from the spectral chart by averaging the values for each resonance for the two scans. Simulated spectra were obtained by adding computer-generated Lorentzian peaks of specified linewidth. The two methods of line width determination agreed within 0.1 Hz. When the fwhm exceeded 2 Hz, significant overlap of the three signals occurred. In these cases the upfield and downfield resonances, ν_1 and ν_3 in Figure 1, were bisected vertically and fwhm was taken as twice the value in the upfield and downfield directions, respectively. When fwhm values approached 4 Hz, this procedure also became unreliable, as judged by comparison with computer fits, and such data were ignored. Each value of fwhm − $fwhm_0$ used in the Results represents an average of the three peaks or only ν_1 and ν_3 if fwhm > 2 Hz.

Analysis of Line Broadening.[24–26] The electron-transfer reaction (eq 3) can be treated as a two-site exchange process. The two sites

$$Cu^{*III}(H_{-2}Aib_3) + Cu^{II}(H_{-2}Aib_3)^- \underset{k_{11}}{\overset{k_{11}}{\rightleftharpoons}} Cu^{*II}(H_{-2}Aib_3)^- + Cu^{III}(H_{-2}Aib_3) \quad (3)$$

are distinguished by their proton relaxation times. The observed changes in line width have been analyzed to obtain the kinetics of exchange by using eq 4 derived from the method of Wahl,[25] where

$$k_{11} = \frac{1}{[Cu^{II}(H_{-2}Aib_3)^-]}\left(\frac{1}{(T_2)_{DP}} - \frac{1}{(T_2)_D}\right) = \frac{\pi}{[Cu^{II}(H_{-2}Aib_3)^-]}(fwhm_{DP} - fwhm_D) \quad (4)$$

the subscript D refers to the solutions containing the diamagnetic complex $Cu^{III}(H_{-2}Aib_3)$ and the subscript DP refers to solutions containing mixtures of Cu(III) and the paramagnetic Cu(II) complex. The use of this equation depends on several assumptions concerning relative relaxation times and lifetimes of species. The electron-spin–lattice relaxation time, T_{1e}, for $Cu^{II}(H_{-2}Aib_3)^-$ must be short with respect to the lifetime, τ_P, for the electron-exchange process in

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(23) Abbreviations used: fwhm, full width at half-maximum; $fwhm_0$, fwhm of pure diamagnetic material; G_3, triglycine; A_3, trialanine; L_3, triglycinamide; G_2Aa, diglycylalanylamide; G_4, tetraglycine; Aib_3, tri-α-aminoisobutyric acid; phen, 1,10-phenanthroline; dmp, 2,9-dimethyl-1,10-phenanthroline.

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eq 3. The value of T_{1e} for Cu(II) is of the order of 10^{-9} s, and τ_P is equal to $([\mathrm{Cu^{III}(H_{-2}Aib_3)}]k_{11})^{-}$. For 10^{-2} M concentrations of Cu(III) the approximation will be valid provided $k_{11} < 10^9$ M^{-1} s^{-1}. Further, τ_P must be much longer than the spin-spin relaxation time $(T_2)_P$ for the protons in the $\mathrm{Cu^{II}(H_{-2}Aib_3)^-}$ complex. An attempt was made to measure $(T_2)_P$ directly from a proton spectrum at 150 MHz with use of a solution of $\mathrm{Cu^{II}(H_{-2}Aib_3)^-}$ in D_2O. No signal apart from HOD was detectable. A crude estimate gives an upper limit of 5×10^{-3} s for $(T_2)_P$ from the Solomon-Bloembergen equations[27] if we assumed a Cu-H distance of 4 Å, a correlation time of 3×10^{-11} s, and the free-electron *g* value for Cu(II). The observed line-broadening dependences indicate that the actual value of $(T_2)_P$ must be substantially less than 10^{-3} s. The upper limit for the exchange to be studied by line broadening also requires that τ_P be less than $(T_2)_D$. This condition is clearly met as broadening is observed. Use of eq 4 is justified if determined values of k_{11} are independent of $[\mathrm{Cu^{III}(H_{-2}Aib_3)}]$ and if the temperature dependence of k_{11} demonstrates Arrhenius behavior.

Stopped-Flow and Pulsed-Flow Measurements. The experimental conditions for the reactions of $\mathrm{Cu^{III}(H_{-2}Aib_3)}$ with $\mathrm{Co^{II}(phen)_3^{2+}}$ and $\mathrm{Cu^I(dmp)_2^+}$ have been previously described.[15,16] The reaction of $\mathrm{Cu^{II}(H_{-2}Aib_3)^-}$ with $\mathrm{IrCl_6^{2-}}$ was monitored by using a recently developed pulsed-flow instrument.[28] The experimental conditions using the pulsed-flow method are described in a separate publication dealing with the kinetics of the reaction of $\mathrm{IrCl_6^{2-}}$ with a series of Cu(II)-peptide complexes.[29]

Solutions for the reactions between copper tripeptide complexes and copper tetrapeptide or tripeptide amide complexes were prepared from a standardized $\mathrm{Cu(ClO_4)_2}$ solution and 5-10% excesses of the appropriate oligopeptide. In each of the reactions the Cu(II) complex was the reagent in excess. These solutions were buffered with $\mathrm{Na_2B_4O_7}$, except for the reaction of $\mathrm{Cu^{II}(H_{-2}Aib_3)^-}$ and $\mathrm{Cu^{III}(H_{-3}G_3AOCH_3)}$ where a phosphate buffer was used. Ionic strength was maintained at 0.1 with $\mathrm{NaClO_4}$ unless otherwise stated. Solutions of the Cu(III) complexes were prepared by oxidation of solutions of the Cu(II) complexes using an electrochemical flow system comprised of graphite powder packed in a porous-glass column, wrapped externally with a platinum wire.[30] The solutions of the Cu(III) complexes were then diluted to the desired concentration with 0.1 M $\mathrm{NaClO_4}$. Reactions were followed by monitoring the absorbance increase at 365 nm for at least 3 half-lives with a Durrum stopped-flow spectrometer interfaced to a Hewlett-Packard Model 2115A general-purpose computer. This wavelength is the absorbance maximum for Cu(III) complexes that contain three deprotonated nitrogen donors, i.e., tetrapeptide complexes. Complexes containing two deprotonated nitrogen donors adsorb less strongly at 365 nm ($\lambda_{\max}$ =395 nm). Reactions were carried out under pseudo-first-order conditions, and reaction orders with respect to the excess reagent were checked by constructing order plots, which invariably indicated an order of 1. Absorbance vs. time data were collected and ensemble averaged for three kinetic runs. The data for each set of runs were subjected to linear and nonlinear analysis, which gave pseudo-first-order rate constants k_{obsd}. Three values of k_{obsd} were averaged for each set of experimental conditions.

Results

Formation Constants for Cu^{2+} and Aib$_3$. Preliminary studies indicated that the rate of thermal decomposition of $\mathrm{Cu^{III}(H_{-2}Aib_3)}$ to give $\mathrm{Cu^{II}(H_{-2}Aib_3)^-}$ and other products increased with increasing temperature and pH. Long-term stability could only be achieved at pH values less than 7.5 where the fully deprotonated complex $\mathrm{Cu^{II}(H_{-2}Aib_3)^-}$ is not the only Cu(II) species. In order that the $[\mathrm{Cu^{II}(H_{-2}Aib_3)^-}]$ could be known accurately, formation constants for Cu^{2+} and Aib$_3$ were determined by potentiometric titration at 15, 25, and 40 °C. The conditions for the various titrations are listed in Table I. The data were analyzed with use of a modified version of the computer program SCOGS.[20] The formation constants so derived are tabulated in Table II.

Table I. Summary of Conditions Used for Potentiometric Titrations at 10, 25, and 40 °C

T, °C	initial concn, M × 10^{-3} $[\mathrm{Cu^{2+}}]_T$	$[\mathrm{Aib_3}]_T$	$[\mathrm{HClO_4}]$	$-\log [\mathrm{H^+}]$	no. of data points
10	0	1.990	2.119	3.2-10.7	66
	0	1.990	2.119	3.2-10.7	68
	0.876	0.984	1.049	3.4-10.7	63
	0.876	1.990	2.168	3.2-10.7	79
	1.770	1.990	2.242	3.2-10.7	87
25	0	1.970	2.134	3.2-10.5	67
	0	1.970	2.134	3.2-10.5	73
	0.876	0.976	0.990	3.4-10.5	71
	0.876	1.970	2.179	3.2-10.5	76
	1.770	1.970	2.230	3.2-10.5	74
40	0	1.990	2.174	3.2-10.5	79
	0	1.990	2.124	3.2-10.5	79
	0.876	0.984	1.071	3.4-10.6	76
	0.876	1.990	2.124	3.2-10.5	84
	1.770	1.990	2.189	3.2-10.5	84

The equilibria typically used to define the complexation of a tripeptide ligand, L, with Cu^{2+} are[21]

$$\beta_2 = \frac{[\mathrm{H_2L^+}]}{[\mathrm{H^+}]^2[\mathrm{L^-}]} \qquad \beta_1 = \frac{[\mathrm{HL}]}{[\mathrm{H^+}][\mathrm{L^-}]} \qquad \beta_0 = \frac{[\mathrm{CuL^+}]}{[\mathrm{Cu^{2+}}][\mathrm{L^-}]}$$

$$\beta_{-1} = \frac{[\mathrm{CuH_{-1}L}][\mathrm{H^+}]}{[\mathrm{Cu^{2+}}][\mathrm{L^-}]} \qquad \beta_{-2} = \frac{[\mathrm{CuH_{-2}L^-}][\mathrm{H^+}]^2}{[\mathrm{Cu^{2+}}][\mathrm{L^-}]}$$

Analysis of the Cu^{2+}/Aib$_3$ system using these equilibria was complicated by the inability of the program to converge on values for β_0. Indeed acceptable and equally good fits were obtained by ignoring the formation of $\mathrm{CuAib_3^+}$. This behavior can be qualitatively explained by comparison with the Cu^{2+}/triglycine system. Formation constants for Cu^{2+}/triglycine were measured by Hauer et al.[21] at 25 °C with μ = 0.1, and the β values are included in Table II. For the $\mathrm{CuG_3^+}$ complex the first peptide nitrogen deprotonation occurs with a pK_{a1} value of 5.11 where $K_{a1} = \beta_{-1}/\beta_0 = ([\mathrm{CuH_{-1}L}][\mathrm{H^+}])/[\mathrm{CuL^+}]$. The assumption of a similar value of log β_0 for $\mathrm{CuAib_3^+}$ implies that p$K_{a1} \simeq 5 - 1 \simeq 4$ for the Aib$_3$ complex. If the first amide deprotonation occurs at this low pH for the Cu^{2+}/Aib$_3$ system, then the $\mathrm{CuAib_3^+}$ complex near becomes a dominant species over the course of the titration. Indeed, the SCOGS analysis allows an upper limit, log $\beta_0 \leq 5$, to be assigned for the Cu^{2+}/Aib$_3$ system. Arbitrary assignment of log $\beta_0 > 5$ caused the standard deviations of titer (sdt), which were typically less than 6 μL, to increase dramatically. Assignment of log $\beta_0 \leq 5$ caused little effect in sdt, and the program would not converge.

Regardless of the value of β_0, values of $K_{a2} = \beta_{-2}/\beta_{-1} = ([\mathrm{CuH_{-2}L^-}][\mathrm{H^+}])/[\mathrm{CuH_{-1}L}]$ were determined at three temperatures (Table II). In the pH range 6.5-7.5 essentially all of the copper is present either as $\mathrm{Cu^{II}(H_{-2}Aib_3)^-}$ or as $\mathrm{Cu^{II}(H_{-1}Aib_3)}$, and eq 5 can be used to calculate the concentrations.

$$[\mathrm{Cu^{II}(H_{-2}Aib_3)^-}] = [\mathrm{Cu^{2+}}]_T/(1 + [\mathrm{H^+}]/K_{a2}) \qquad (5)$$

Since $[\mathrm{Cu^{2+}}]_T$, $[\mathrm{H^+}]$, and K_{a2} were known, the $[\mathrm{Cu^{II}(H_{-2}Aib_3)^-}]$ could be calculated for the conditions of the NMR experiments. The fraction $[\mathrm{Cu^{II}(H_{-2}Aib_3)^-}]/[\mathrm{Cu^{2+}}]_T$ ranged from 0.78 to 0.91. Assuming a value of log $\beta_0 \leq 5$ implies that the fraction $[\mathrm{Cu^{II}(Aib_3)^+}]/[\mathrm{Cu^{2+}}]_T$ is less than 0.003, which justifies the assumption that the concentration of $\mathrm{Cu^{II}(Aib_3)^+}$ is negligible.

The fact that the overall formation constant β_{-2} for Cu^{2+}/Aib$_3$ is more than 50 times larger than β_{-2} for Cu^{2+}/G$_3$ is somewhat surprising. The electron-donating ability of the methyl groups should increase the basicity of the nitrogen atoms, but this has a relatively small effect on the basicity of

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Table II. Equilibrium Constants for Cu^{2+}/Aib_3[a,b] and Cu^{2+}/G_3[c]

tripeptide	T, °C	log β_2	log β_1	log β_0[d]	log β_{-1}	log β_{-2}	pK_{a2}
Aib_3	10.0	12.00 ± 0.01	8.33 ± 0.01		1.02 ± 0.02	−5.43 ± 0.01	6.45
Aib_3	25.0	11.62 ± 0.01	7.97 ± 0.01		1.00 ± 0.01	−5.05 ± 0.02	6.05
Aib_3	40.0	11.36 ± 0.02	7.73 ± 0.01		1.02 ± 0.01	−4.77 ± 0.01	5.79
G_3	25.0	11.00 ± 0.04	7.88 ± 0.01	5.12 ± 0.01	0.01 ± 0.01	−6.67 ± 0.01	6.68

[a] For definition of β, see text. [b] Precision equals one standard deviation. [c] Reference 21. [d] Not determined; see text.

Table III. Chemical Shifts for Aib_3 and $Cu^{III}(H_{-2}Aib_3)$ in D_2O[a]

compd, pD	ν_1	ν_2	ν_3
Aib_3, 1.2	1.44	1.28	1.27
Aib_3, 6.8	1.45	1.28	1.26
Aib_3, 10.2	1.12	1.27	1.24
$Cu^{III}(H_{-2}Aib_3)$, 3.8	1.47	1.37	1.25

[a] Chemical shift in ppm with the assumption of acetone at 2.05 ppm, relative to Me_4Si.

the terminal amine groups as seen by the β_1 values in Table II. Nevertheless, inductive effects apparently lead to stronger Cu(II)–deprotonated peptide bonds in the α-substituted systems.

^1H NMR Spectra of Aib_3, $Cu^{III}(H_{-2}Aib_3)$, and $Cu^{II}(H_{-2}Aib_3)^-$. The tripeptide ligand Aib_3 contains three nonequivalent pairs of methyl groups. The ^1H NMR spectra of Aib_3 in D_2O under acidic or neutral conditions and under basic conditions are presented in Figure 1, parts a and b, respectively. In each case the spectrum contains one well-resolved singlet and two overlapping singlets. The chemical shifts are listed in Table III for three values of pD. The large change in chemical shift of ν_1 that occurs upon changing from neutral or acidic to basic conditions allows assignment of ν_1 to the methyl groups on the amine residue. The presence of a proton at the carboxylate end of the tripeptide has too small an effect to allow assignment of ν_2 and ν_3.

The ^1H NMR spectrum of $Cu^{III}(H_{-2}Aib_3)$, shown in Figure 1c, also consists of three singlets, however, the three resonances are cleanly resolved in the complex. The chemical shifts (Table III) are similar to those of the uncomplexed tripeptide, indicating that the Cu(III) atom affects the electron-donating ability of the amide nitrogens to a similar degree as protons. As expected, ν_1, ν_2, and ν_3 have equal integrated intensities; however, ν_3 has a smaller amplitude and correspondingly greater $fwhm_0$ than do ν_1 and ν_2. Spectra of $Cu^{III}(H_{-2}Aib_3)$ were recorded at variable temperature (10–60 °C) on the 90-MHz instrument and at ambient temperature on the 360-MHz spectrometer. The changes in temperature and field strength did not affect the chemical shifts or the differences in peak shapes. The variable-temperature experiments indicate that the system is not complicated by a dynamic equilibrium involving the conformation of the ligand or an intramolecular electron transfer; i.e., $Cu^{III}(H_{-2}Aib_3) \rightleftarrows Cu^{II}(H_{-2}Aib_3^+)$. Similarly, the larger $fwhm_0$ of ν_3 does not appear to be caused by overlapping resonances because two peaks are not resolved at higher field strength. The broadening is probably caused by an unresolved long-range coupling.

Attempts to locate proton signals attributable to $Cu^{II}(H_{-2}Aib_3)^-$ using a Nicolet 150-MHz NMR spectrometer in the FT mode were unsuccessful, indicating that fwhm for these resonances are greater than 3 ppm and that $(T_2)_P$ is less than 3 ms.

Determination of the Self-Exchange Rate for $Cu^{III,II}(H_{-2}Aib_3)^{0,-}$. Qualitatively, Figure 2 depicts the changes in the NMR spectrum of $Cu^{III}(H_{-2}Aib_3)$ that result when small concentrations of $Cu^{II}(H_{-2}Aib_3)^-$ are present. If eq 4 accurately describes the kinetics of the exchange process, plots of π (fwhm − $fwhm_0$) vs. $[Cu^{II}(H_{-2}Aib_3)^-]$ should be linear with a slope equal to k_{11} and a zero y-intercept. Furthermore, the slope should be independent of $[Cu^{III}(H_{-2}Aib_3)]$. Data taken from three series of spectra with different initial concentrations of $Cu^{III}(H_{-2}Aib_3)$ are presented graphically in Figure 3. As eq 4 predicts, the plots are linear with nearly zero intercepts and identical slopes. Indentical experiments were performed at 10 and 35.5 °C for two initial concentrations of $Cu^{III}(H_{-2}Aib_3)$. The data yielded plots similar to those in Figure 3. The rate constants and conditions are summarized in Table IV.

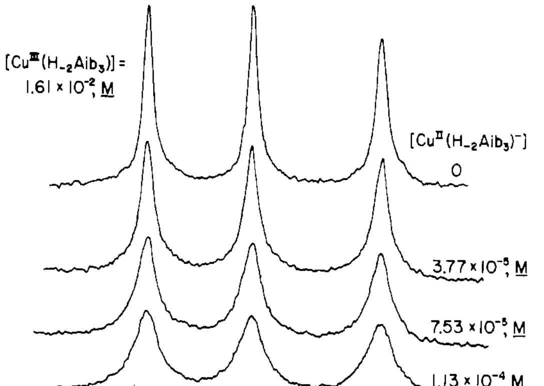


Figure 2. ^1H NMR spectra (100 MHz) of a solution of $Cu^{III}(H_{-2}Aib_3)$ at 25 °C with various concentrations of $Cu^{II}(H_{-2}Aib_3)^-$.

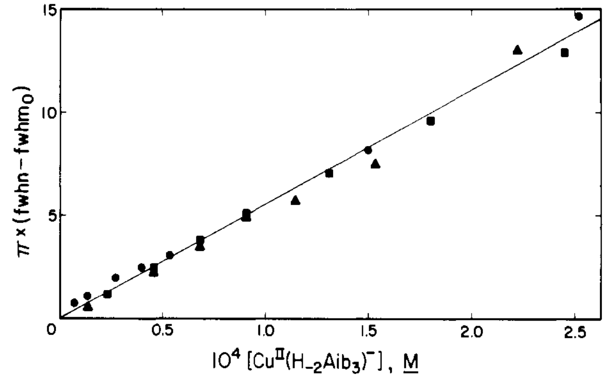


Figure 3. Plot of peak width vs. concentration of $Cu^{II}(H_{-2}Aib_3)^-$ at different initial concentrations of $Cu^{III}(H_{-2}Aib_3)$: ●, 10.7 mM; ▲, 4.74 mM; ■, 26.1 mM.

If the line broadening is due to a chemical process, i.e., electron-exchange, the self-exchange constant should exhibit Arrhenius behavior. A plot of log (k_{11}/T) vs. $1/T$ for the data in Table IV is linear, allowing activation parameter of $\Delta H^{\ddagger}$ = 7.0 ± 0.5 kcal mol^{-1} and $\Delta S^{\ddagger}$ = −13 ± 2 cal deg^{-1} mol^{-1} to be calculated.

Cross Reactions between Copper Tripeptides and Tetrapeptides or Tripeptide Amide Complexes. So that it could be ascertained whether the measured value of k_{11} for $Cu^{III,II}(H_{-2}Aib_3)^{0,-}$ is appropriate for other peptide couples, the rate constants for a group of cross reactions between copper tripeptide and tetrapeptide or tripeptide amide complexes were determined. Cross reactions between two copper complexes with different tripeptide ligands are difficult to monitor spectrophotometrically because of the similarity of the elec-

Table IV. Conditions and Results for Line-Broadening Experiments

T, °C	conditions	$[Cu^{III}(H_{-2}Aib_3)]_i$, mM	no. of additions		$10^{-4}k_{11}$, M^{-1} s^{-1}
10 ± 0.5	pH 7.5[a]	14.9	6		2.82 ± 0.001
10 ± 0.5	pH 7.5[a]	9.4	6		2.83 ± 0.004
				av	2.82 ± 0.005
25 ± 0.5	pH 7.0, $[PO_4]_T < 0.01$ M, $\mu \leqslant 0.05$	4.7, 10.7, 24.0	7, 7, 7		5.5 ± 0.1
25 ± 0.5	pH 7.0[a]	16.1	5		5.63 ± 0.008
25 ± 0.5	pH 7.0, $\mu = 0.1$ with KH_2PO_4	11.0	6		5.38 ± 0.004
				av	5.5 ± 0.1
25 ± 0.5	pH 7.0, $\mu = 0.1$ with NaCl[b]	16.3	6		5.90 ± 0.005
35.5 ± 0.5	pH 6.5[a]	11.4	5		8.6 ± 0.1
35.5 ± 0.5	pH 6.5[a]	16.1	4		8.8 ± 0.2
				av	8.7 ± 0.2

[a] $[PO_4]_T = 0.01$ M, $\mu = 0.1$ with $NaClO_4$. [b] See text.

Table V. Rate Constants for Cu(III)/Cu(II) Cross Reactions[a]

Cu(III) tripeptide	Cu(II) tetrapeptide or tripeptide amide	K_{12}	$10^{-5}k_{12}^{obsd}$, M^{-1} s^{-1}
A_3	G_3AOCH_3	107	3.2 ± 0.1
A_3	G_3a	752	13 ± 1
A_3	G_2Aa	3580	19 ± 2
L_3	G_3AOCH_3	22.6	3.5 ± 0.1
L_3	G_3a	158	13 ± 1
L_3	G_2Aa	752	16 ± 3
Aib_3	G_3AOCH_3	0.3	0.20 ± 0.01[b]
Aib_3	G_3a	2.2	0.34 ± 0.01
Aib_3	G_2Aa	10.4	0.78 ± 0.01

[a] Reference 21. [b] $k_{12} = k_{12}^{obsd}K_{12}$.

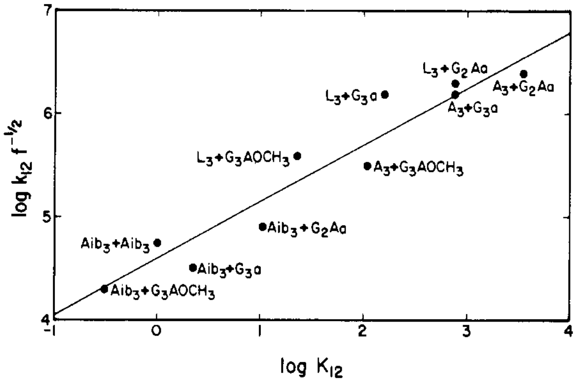


Figure 4. Marcus plot for the Cu(III)/Cu(II) cross reactions listed in Table V; slope = 0.55 ± 0.6.

tronic spectra of the Cu(III) species. Three tripeptides, a tetrapeptide, and two tripeptide amide complexes were chosen in order to permit the electron exchange to be observed and to give some variation in the K_{12} values as summarized in Table V. In each case the cross reaction was examined in the thermodynamically favored direction with sufficient excess of the Cu(II) complex to drive the reaction to completion, yielding first-order kinetic traces.

A plot of $\log k_{12}/f^{1/2}$ vs. $\log K_{12}$ using the data in Table V is presented in Figure 4. Linear regression yields a slope of 0.55 ± 0.06, which is in satisfactory agreement with the slope of 0.5 predicted by eq 1. The intercept of the plot is 4.6 ± 0.1. If the self-exchange rate constants for the different complexes are equal, then $k_{11} = k_{22} = (4.0 \pm 1.0) \times 10^4$ M^{-1} s^{-1}. This value is in reasonable agreement with the value of (5.5×10^4) M^{-1} s^{-1} determined by NMR.

Cross Reactions with $Ir^{IV}Cl_6^{2-}$, $Co^{II}(phen)_3^{2+}$, and $Cu(dmp)_2^+$. In order to compare the reactivity of $Cu(H_{-2}Aib_3)^{0,-}$ to other oligopeptide complexes and to compare the directly determined value of k_{11} to values estimated with use of the Marcus theory, we determined the rate constants for several cross reactions using stopped-flow and pulsed-flow methods. The rate constants for the reactions are given in Table VI.

Table VI. Cross Reactions of $Cu^{III,II}(H_{-2}Aib_3)^{0,-}$ with $Ir^{IV}Cl_6^{2-}$, $Co^{II}(phen)_3^{2+}$, and $Cu^I(dmp)_2$•

reaction	K_{12}	k_{12}^{obsd}, M^{-1} s^{-1}	ref
$Cu^{III}(H_{-2}Aib_3) + Co^{II}(phen)_3^{2+}$	5.5×10^4	5.0×10^4	15
$Cu^{III}(H_{-2}Aib_3) + Cu^I(dmp)_2^+$	5.7	6.1×10^4	16
$Cu^{II}(H_{-2}Aib_3)^- + Ir^{IV}Cl_6^{2-}$	8.4×10^3	5.8×10^8	29

Table VII. Anion, Ionic Strength, and pH Effects

$Cu^{III}(H_{-3}G_3AOCH_3) + Cu^{II}(H_{-2}Aib_3)^-$

μ[a]	$10^{-4}k_{12}$, M^{-1} s^{-1}	pH[b]	$10^{-4}k_{12}$, M^{-1} s^{-1}
0.1 ($NaClO_4$)	6.5	8.2	6.9
0.1 (NaCl)	7.3	8.7	6.5
1.0 ($NaClO_4$)	5.5	9.2	6.3
1.0 (NaCl)	6.4		

$Cu^{III}(H_{-2}Aib_3) + Cu^{II}(H_{-3}G_3a)^-$

pH[b]	$10^{-4}k_{12}$, M^{-1} s^{-1}
9.7	3.4
10.0	3.4
10.5	3.1

[a] pH 8.7. [b] $\mu = 0.1$ with $NaClO_4$.

Anion and pH Effects. Since copper peptide complexes display square-planar geometry as Cu(III) and contain labile water molecules as Cu(II), mechanisms involving axial bridging ligands were considered. In the NMR determination of the $Cu^{III,II}(H_{-2}Aib_3)^{0,-}$ self-exchange rate constant (Table IV), use of $H_2PO_4^-/HPO_4^{2-}$ instead of ClO_4^- to maintain ionic strength had little effect on the rate. Use of Cl^- instead of ClO_4^-, however, caused a 7% increase in k_{11}. In order to further explore this effect, we measured the rate of the reaction of $Cu^{III}(H_{-3}G_3AOCH_3)$ and $Cu^{II}(H_{-2}Aib_3)^-$ at ionic strength 0.1 and 1.0 in Cl^- and ClO_4^- media. The results are tabulated in Table VII. As in the case of the NMR experiments, the rates measured in chloride media are slightly faster than those measured in perchlorate media. A 10-fold increase in the concentrations of these anions, however, only causes the rate increase to change from 12% to 16%. If bridging by Cl^- were occurring, a much greater effect would be expected, which indicates that the differences in the Cl^- and ClO_4^- rates are probably due to other factors. The observed slight decrease in k_{12} that occurs when the ionic strength is changed from 0.1 to 1.0 is not expected, since $Cu^{III}(H_{-3}G_3AOCH_3)$ is uncharged.

The thermal instability of $Cu^{III}(H_{-2}Aib_3)$ required the NMR experiments to be run at slightly different pH values at the three temperatures. In order to show that the self-exchange rate does not depend on the pH, the rates of the reactions of $Cu^{III}(H_{-2}Aib_3)$ + $Cu^{II}(H_{-3}G_3a)^-$ and $Cu^{III}(H_{-3}G_3AOCH_3)$ + $Cu^{II}(H_{-2}Aib_3)^-$ were measured at several pH values. These data are listed in Table VII. Neither reaction rate constant has a dramatic pH dependence despite a 10-fold change in $[H^+]$. The small trend that is observed is opposite to what would be expected if OH^- entered into the mechanism. This observation is further evidence against anion bridging.

Discussion

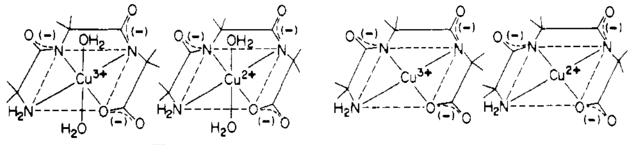
Mechanism of the Self-Exchange Reaction. The rate constants for the $Cu(H_{-2}Aib_3)^{0,-}$ self-exchange reaction and the copper tri- and tetrapeptide cross reactions (Table V) support the hypothesis that many Cu(III)/Cu(II) peptide couples undergo electron self-exchange processes at a similar rate. Although k_{11} is approximately 5×10^4 M^{-1} s^{-1} instead of the 10^8 M^{-1} s^{-1} value suggested previously[13] from the hexachloroiridate reactions, the electron exchange is still a facile process. With a relatively low activation enthalpy, $\Delta H^{\ddagger} = 7.0$ kcal/mol.

When a single-pathway outer-sphere electron-transfer process is considered for self-exchange reactions, the Franck–Condon principle and the principle of microscopic reversibility require that axial coordinations be identical for both oxidation states in the activated complex. The rate of axial substitution itself is certainly not rate limiting. For $Cu(H_2O)_6^{2+}$, the water-exchange rate constant[31] is 2×10^9 s^{-1} and the substitution rate for tetragonally distorted water molecules in the Cu(II)–peptide complexes should be at least as rapid. It is likely, however, that loss or gain of axial water molecules during formation of the activated complex will dominate the entropy of activation.

According to the Marcus theory of electron transfer, the experimentally measured activation entropy, $\Delta S^{\ddagger}$, can be separated into a series of terms:[32]

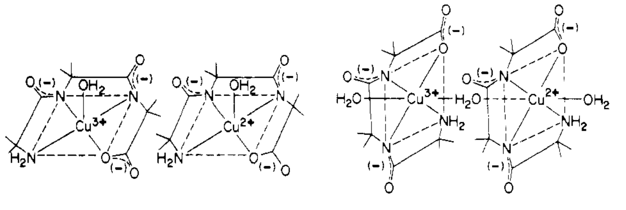
$$\Delta S^{\ddagger} = \Delta S_C^{\ddagger} + \Delta S_o^{\ddagger} + \Delta S_i^{\ddagger} + R \ln (hZ/\bar{k}T) - \tfrac{1}{2}R \qquad (6)$$

In this expression $\Delta S_C^{\ddagger}$, $\Delta S_o^{\ddagger}$, and $\Delta S_i^{\ddagger}$ are the Coulombic, outer-sphere, and inner-sphere contributions and h, Z, $\bar{k}$, and R have their usual meanings. If we assume that $T = 298$ K and $Z = 10^{11}$ M^{-1} s^{-1}, the last two terms in eq 4 contribute −9.2 cal K^{-1} mol^{-1}. Furthermore, for a one-electron self-exchange $\Delta S_o^{\ddagger}$ is small, ~0.6 eu, and, since one of the reactants in each of the Cu(III)/Cu(II) reactions is uncharged, $\Delta S_C^{\ddagger} = 0$. For substitutionally inert octahedral complexes, $\Delta S_i^{\ddagger}$ is also equal to zero, but in the present case where coordination numbers for the two oxidation states can differ, this term can be nonzero.



(a) Solvation of Cu^{III}
$\Delta S^{\ddagger} = -8.6 - 7.3(2) = -23.2$

(b) Desolvation of Cu^{II}
$\Delta S^{\ddagger} = -8.6 - 7.3(-2) = +6.0$



(c) Five - coordinate
$\Delta S^{\ddagger} = -8.6 - 7.3(0) = -8.6$

(d) Bridging Water
$\Delta S^{\ddagger} = -8.6 - 7.3(+1) = -15.9$

Figure 5. Possible activated complexes for the Cu^{III}/Cu^{II} self-exchange reactions and the value of $\Delta S^{\ddagger}$ (cal deg^{-1} mol^{-1}) estimated from eq 9. Oxidation state values are for the reactants: (a) solvation of Cu(III) to give electron transfer with six-coordinate species; predicted $\Delta S^{\ddagger} = -23$; (b) desolvation of Cu(II) to give electron transfer with four-coordinate species; predicted $\Delta S^{\ddagger} = +6$; (c) addition of one H_2O to Cu(III) and loss of one H_2O from Cu(II) to give electron transfer with five-coordinate species; predicted $\Delta S^{\ddagger} = -9$; (d) bridging H_2O with another H_2O added to Cu(III) to give weak inner-sphere electron transfer; predicted $\Delta S^{\ddagger} = -16$.

The change in the number of coordinated water molecules for the Cu(III)/Cu(II) and Ni(III)/Ni(II) peptide redox couples has been assigned by Youngblood and Margerum via measurement of reaction entropies, $S_{II}° - S_{III}°$, using a nonisothermal electrochemical cell.[9] The signs and magnitudes of the reaction entropies indicate that the redox reactions are described by eq 7 and 8. Loss of a single coordinated water

$$\begin{gathered} Cu^{III}(H_{-x}L) + 2H_2O + e^- \rightleftarrows Cu^{II}(H_{-x}L)(H_2O)_2 \\ S_{II}° - S_{III}° = -14 \pm 1 \text{ cal mol}^{-1} \text{ deg}^{-1} \end{gathered} \qquad (7)$$

$$\begin{gathered} Ni^{III}(H_{-x}L)(H_2O)_2 + e^- \rightleftarrows Ni^{II}(H_{-x}L) + 2H_2O \\ S_{II}° - S_{III}° = +13 \pm 2 \text{ cal mol}^{-1} \text{ deg}^{-1} \end{gathered} \qquad (8)$$

molecule has been estimated[33] thermodynamically to yield a gain in entropy of 7.3 cal mol^{-1} deg^{-1}, a value which is consistent with other experimental results from equilibria involving square-planar and octahedral geometries.[34] On the assumption that the change in the number of coordinated water molecules, Δn, is the dominant contribution to $\Delta S_i^{\ddagger}$, activation entropies for the formation of activated complexes can be esimated with eq 9, where Δn is positive for a gain of water

$$\Delta S^{\ddagger} \text{ (cal mol}^{-1} \text{ deg}^{-1}) = -8.6 + \Delta S_i^{\ddagger} = -8.6 - 7.3(\Delta n) \qquad (9)$$

and is negative for a loss of water in the activated complexes. Such estimates for several possible activated complexes are shown in Figure 5. In Figure 5a the Cu(III) complex adds two axial waters prior to the electron-exchange reaction with the axially coordinated Cu(II) complex. This requires a much more negative $\Delta S^{\ddagger}$ value than is found. On the other hand, in Figure 5b axial desolvation of the Cu(II) complex prior to electron transfer requires a positive $\Delta S^{\ddagger}$ value. Neither mechanism appears likely. In Figure 5c Cu(III) adds one H_2O and Cu(II) loses one H_2O to give five-coordinate activated complexes with a predicted $\Delta S^{\ddagger}$ value closer to the experimental value. A bridging mechanism is shown in Figure 5d with the net addition of one H_2O, and this gives the best agreement between the predicted and experimental $\Delta S^{\ddagger}$. However, the assumptions and approximations used in these models do not permit a conclusive assignment of the activated complex.

Although the bridging-water model has the best agreement in $\Delta S^{\ddagger}$, this activated complex constitutes an inner-sphere mechanism. Lack of a significant dependence of the rate on chloride or hydroxide concentration in the Cu(III)/Cu(II) peptide reactions argues against a bridging-water mechanism, since anions are generally better bridging ligands than water. The five-coordinate mechanism is supported by the fact that this is a common geometry for Cu(II) complexes.[6] Hence, the mechanisms in Figure 5c and 5d must both be considered as possibilities.

Cross Reactions with $IrCl_6^{2-,3-}$, $Co(phen)_3^{3+,2+}$, and $Cu(dmp)_2^{2+,+}$. It is important to discern whether the value of $k_{11}^{Cu(III,II)}$ can be used to predict rates for various cross re-

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actions with use of eq 1. Even if the self-exchange process is an outer-sphere process, axial bridging to other molecules is possible. For example, the reaction between $IrCl_6^{2-}$ and $Cu^{II}(H_{-2}Aib_3)^-$ is much faster than predicted by eq 1. If $k_{11} = 5.5 \times 10^4$ M^{-1} s^{-1}, $k_{12}^{calcd} = 6.8 \times 10^6$ M^{-1} s^{-1} while $k_{12}^{obsd} = 5.8 \times 10^8$ M^{-1} s^{-1}. An apparent value of 7×10^7 M^{-1} s^{-1} for k_{11} was originally proposed[14] on the basis of a series of reactions involving $IrCl_6^{3-}$ and Cu(III)–peptide complexes. The fact that the directly measured value is 3 orders of magnitude smaller than this indicates that the reactions with $IrCl_6^{2-}$ or $IrCl_6^{3-}$ proceed via an inner-sphere pathway. Even though an inner-sphere mechanism is likely, plots of log $(k_{12}/f^{1/2})$ vs. log K_{12} for either uphill[14] or downhill[29] reactions between copper peptide complexes and $IrCl_6^{3-,2-}$ have nearly the slope of 0.5 that is predicted by eq 1. This phenomenon has been observed for several other inner-sphere electron-transfer reactions.[35-37] Despite the observation of a slope of 0.5 in the Marcus plot, separation of the intercept into values of k_{11} and k_{22} led to an apparent k_{11} value that is more than 2 orders of magnitude larger than the directly measured value.

In its reaction with $IrCl_6^{2-,3-}$, $Cu^{II}(H_{-2}Aib_3)^-$ behaves as many other Cu(II)–peptide complexes. In reactions with $Co(phen)_3^{2+}$ and $Cu(dmp)_2^+$, $Cu^{III}(H_{-2}Aib_3)$ reacts significantly slower than do Cu(III) complexes derived from peptide ligands that do not contain R groups in place of every α-hydrogen. If the values of $k_{12}^{obsd}/f^{1/2}$ for $Cu^{III}(H_{-2}Aib_3)$ are placed on the plots in ref 14 (Figure 4) and 15 (Figure 2), they fall respectively ~1 and ~1.75 log units below the least-squares lines. Since it appears that the copper peptide complexes do have similar self-exchange rates (Table VI), the more sterically blocked complex may be reacting nonadiabatically.

Taken separately, the rates of the reactions of $Cu^{III}(H_{-2}Aib_3)$ with $Co(phen)_3^{2+}$ and $Cu(dmp)_2^+$ are quite consistent with eq 1. For the reaction with $Co(phen)_3^{2+}$, $k_{12}^{calcd} = 1.9 \times 10^5$ M^{-1} s^{-1} while the observed value is 5.0×10^4 M^{-1} s^{-1}. The self-exchange rate for $Cu(dmp)_2^{2+,+}$ has not been directly determined. Using $k_{11} = 5.5 \times 10^4$ M^{-1} s^{-1} and $k_{12}^{obsd} = 6.1 \times 10^4$ M^{-1} s^{-1} yields a calculated value $k_{22} = 9.7 \times 10^3$ M^{-1} s^{-1}. For $Cu(dmp)_2^{2+,+}$ this value can be compared to values of 1.7×10^4 and 4.4×10^4 M^{-1} s^{-1} calculated from cross reactions with $Co(phen)_3^{2+}$ and cytochrome *c*.[38] Considering the difference in reactivity displayed by $Cu^{III}(H_{-2}Aib_3)$ compared to the other Cu^{III}–peptide complexes, this apparent agreement with eq 1 is probably a fortuitous result. Reactions between Cu^{III}–peptide complexes and $Ru(NH_3)_6^{2+}$ and $Ru(NH_3)_5(py)^{2+}$, which should proceed by outer-sphere mechanisms, are currently being examined.

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Registry No. $Cu^{III}(H_{-2}Aib_3)$, 69990-31-4; $Cu^{II}(H_{-2}Aib_3)(H_2O)_2^-$, 77341-99-2; $Cu^{III}(H_{-2}A_3)$, 69042-71-3; $Cu^{III}(H_{-2}L_3)$, 69042-72-4; $Cu^{III}(H_{-3}G_3AOCH_3)$, 69042-73-5; $Cu^{II}(H_{-3}G_3AOCH_3)(H_2O)_2^-$, 77342-00-8; $Cu^{II}(H_{-3}G_3a)(H_2O)_2^-$, 77342-01-9; $Cu^{II}(H_{-3}G_2Aa)(H_2O)_2^-$, 77357-33-6; $Co^{II}(phen)_3^{2+}$, 16788-34-4; $Cu^I(dmp)_2^+$, 21710-12-3; $Ir^{IV}Cl_6^{2-}$, 16918-91-5; $HAib_3$, 50348-89-5.

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