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Kinetics and Mechanism of Copper(II) Complex Formation with Tripodal Aminopolythiaether and Aminopolypyridyl Ligands in Aqueous Solution

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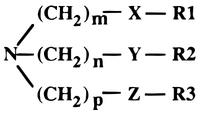
The complex formation kinetics of aquated copper(II) ion reacting with 12 related tripodal ligands have been studied in aqueous solution at 25 °C, $\mu = 0.10$ M ($NaClO_4$). For most of the ligands studied, specific formation rate constants have been resolved for both the unprotonated and monoprotonated ligand species. All of the tripodal ligands included in this study contain a bridgehead amine nitrogen with the three legs consisting of 2-methylthioethyl or 2-ethylthioethyl and/or 2-pyridylethyl or 2-pyridylmethyl. Since the bridgehead nitrogen is too sterically hindered to participate in initial coordinate bond formation, the first bond must involve a thiaether sulfur or a pyridine nitrogen on one of the pendant legs followed by coordination to the bridgehead nitrogen to complete the first chelate ring. All kinetic data are interpreted in terms of this presumed sequence in the bond formation steps. For the two ligands in which all three pendant legs contain thiaether sulfur donor atoms, the rate-determining step appears to be at the point of second bond formation (chelate ring closure), although the distinction is not well defined. For all other unprotonated ligands, the kinetic behavior is consistent with the first-bond formation being rate-determining. Upon protonation, the rate-determining step appears to shift to the point of proton loss associated with second-bond formation in several cases. A particularly interesting observation is that the tripodal ligand tris(ethylthioethyl)amine (TEMEA) exhibits specific Cu(II) complex formation rate constants that are virtually identical to those for a closely related macrocyclic ligand, 1,4,8-trithia-11-azacyclotetradecane ([14]aneNS$_3$), but the calculated $Cu^{II}L$ dissociation rate constants differ by a factor of 1000. A further comparison of the calculated dissociation rate constants for Cu(II)−tripodal ligand complexes indicates that a Cu(II)−N(pyridine) bond is approximately 10^4 times stronger than a Cu(II)−SR_2 bond. This leads to the conclusion that a 1:1 Cu(II)−SR_2 complex would have a predicted stability constant of about 0.04 M^{-1} in aqueous solution—the first estimate obtained for the strength of a single Cu(II)−S(thiaether) bond.

Introduction

Tripodal ligands represent a unique class of complexing agents in which each of three legs, containing at least one donor atom (X, Y, Z), is connected to a bridgehead atom. If the



bridgehead atom is nitrogen and *m, n, p* = 2 or 3, the ligands tend to be quadridentate. The terminal groups (R1, R2, R3) may be hydrogens, alkyl groups, aromatic groups, or other substituents.

Because of structural constraints, quadridentate tripodal ligands cannot coordinate in a planar fashion but tend to be well suited for tetrahedral coordination.[2] When octahedral complexes are generated, the two remaining donor sites must be cis. In the specific case of Cu(II), tripodal ligands with identical pendant legs, in which $m = n = p = 2$, have been shown to form trigonal bipyramidal complexes in which the fifth coordination site, opposite the nitrogen bridgehead, is occupied by a solvent molecule or other unidentate ligand.[2] Slow inner-sphere exchange at this site—and a switch from a dissociative interchange to an associative interchange mechanism—has recently been reported by van Eldik, Merbach, and co-workers for the Cu(II) complex with tris(2-aminoethyl)amine (tren; see Figure 1) and related derivatives.[3,4] By contrast, Debreczeni and Nagypál reported very rapid exchange at the fifth site in Cu(II)−nitrilotriacetate (NTA).[5] Other workers have shown that the catalytic properties of copper−tripodal ligand complexes depend on both the Cu(II/I) redox potential and the steric access of substrates to the remaining inner-sphere site.[6] Karlin and co-workers have utilized the unique properties of Cu(II/I)−tripodal ligand complexes to develop biomimetic dicopper sites that coordinate dioxygen.[7−9]

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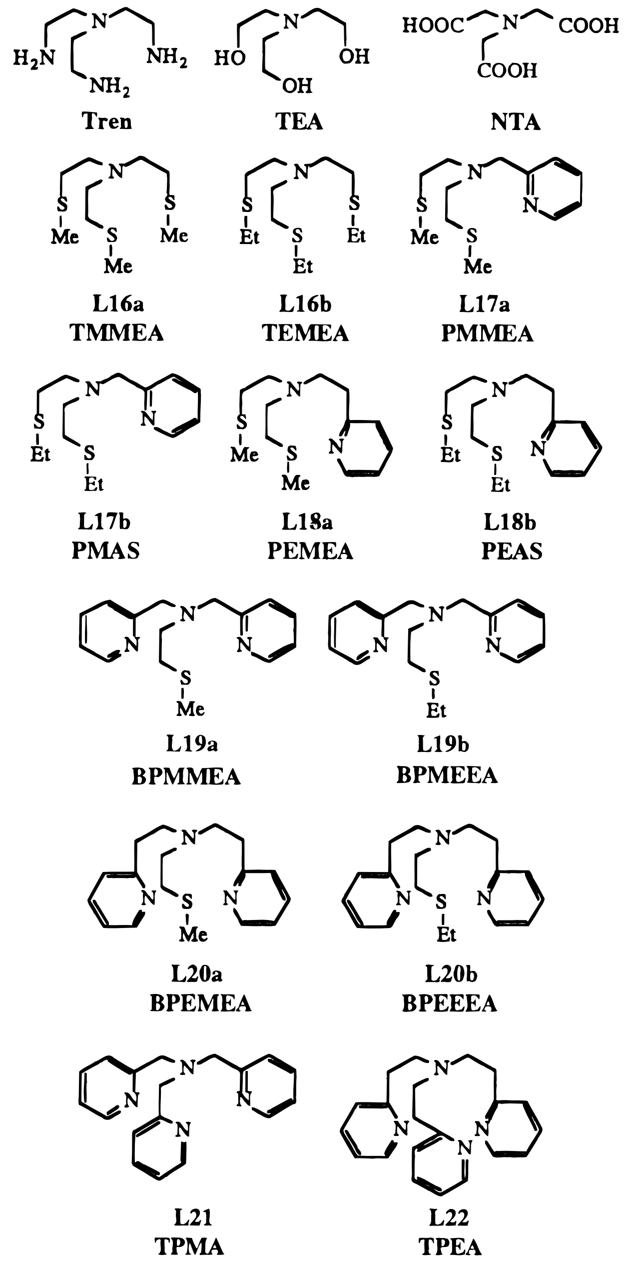

Figure 1. Tripodal ligands discussed in the current work. Numbers assigned to the individual ligands are consistent with ref 2.

Despite the high level of interest in the chemistry of copper–tripodal ligand complexes, most studies have been limited to a determination of their redox potentials and structures. In conjunction with an ongoing study of the effect of tripodal ligands on Cu(II/I) electron transfer, we recently expanded the available data by determining the (i) ligand protonation constants, (ii) $Cu^{II}L$ stability constants, and (iii) $Cu^{II/I}L$ potentials for 12 tripodal ligands containing pendant thiaether sulfurs and/or pyridine nitrogens (Figure 1).[2] Structures of eight of these $Cu^{II}L$ complexes (L16a,[2] L16b,[10] L17a,[11] L17b,[12] L18b,[13] L19a,[11] L21,[14] and L22[15]) are also known. In a further effort to examine the effects of coordinative constraints associated with tripodal ligands, we now report the results of kinetic studies of their reactions with $Cu(H_2O)_6^{2+}$.

Mechanistic Considerations. Earlier work has shown that bridgehead nitrogens are too sterically hindered to promote initial coordinate bond formation to an aquated metal ion.[16–21] Therefore, the first coordinate bond must involve a donor atom in one of the pendant legs followed by coordination to the bridgehead donor atom to complete the first chelate ring. As a result, the mechanistic sequence of complex formation is presumed to be more predictable for tripodal ligands than for corresponding linear or macrocyclic quadridentate ligands. However, only six kinetic studies have previously appeared in the literature involving aquametal ions reacting with tripodal ligands, and each of these was limited to a single ligand:[22] triethanolamine (TEA) reacting with Cu(II)[19] and Ni(II);[23] nitrilotriacetate (NTA) reacting with Cu(II)[24] and with Zn(II), Cd(II), and Pb(II);[25] Fe(II) reacting with an analogue of NTA (H_3muia) in which one of the pendant carboxylate legs is replaced by a substituted phenol;[26] and tris(methylthioethyl)amine (TMMEA) reacting with Cu(II).[20] With the exception of H_3muia, all of these ligands are shown in Figure 1.

In the current work, a detailed comparison is made of the relative Cu(II) complexation kinetics with closely related ligands. This has permitted us to generate specific conclusions about the position of the rate-determining step and the lability of the initially formed coordinate bonds, including an estimate of the strength of a single Cu–S(thiaether) bond in aqueous solution.

Experimental Section

Reagents. The synthetic and purification procedures for each of the 12 ligands used in this work have recently been described.[2] Preparation of pure $Cu(ClO_4)_2$ and $NaClO_4$ has also been reported.[27] Distilled–

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Table 1. Major Visible Spectral Peaks and Protonation Constants for the Copper(II)−Tripodal Ligand Complexes Included in This Work As Determined at 25 °C, $\mu = 0.10$ ($\mathrm{ClO_4}^-$)[a]

coordinated ligand	$\lambda_{\max}$, nm	$\epsilon_{\mathrm{CuL}} \times 10^{-3}$, $\mathrm{M^{-1}\,cm^{-1}}$	log $K_{\mathrm{H1}}{}^m$	log $K_{\mathrm{H2}}{}^m$	log $K_{\mathrm{H3}}{}^m$
NTA			9.73[b]	2.49[b]	1.89[b]
TEA			7.9[c]		
TMMEA (L16a)	374	4.76	8.36		
TEMEA (L16b)	380	4.73	8.32		
PMMEA (L17a)	338	2.98	6.53	<2	
PMAS (L17b)	340	3.14	6.56	<2	
PEMEA (L18a)	350	3.19	7.33	3.26	
PEAS (L18b)	349	3.20	7.35	3.21	
BPMMEA (L19a)	254[d]	11.4	6.29	3.60	<2
BPMEEA (L19b)	255[d]	10.6	6.23	3.50	<2
BPEMEA (L20a)	340	3.42	7.66	3.74	2.38
BPEEEA (L20b)	348	3.26	7.78	3.81	2.58
TPMA (L21)	256	18.3	6.24	4.41	2.57
TPEA (L22)	259	19.5	8.21	3.94	3.51

[a] Except as noted, all data are from ref 2. [b] At 20 °C, $\mu = 0.10$ (KCl). Schwarzenbach, G.; Ackermann, H.; Ruckstuhl, P. *Helv. Chim. Acta* **1949**, *32*, 1175−1186. [c] At 25 °C, $\mu = 0.5$ ($\mathrm{KNO_3}$). Bjerrum, J.; Refn, S. *Suom. Kemistil. B* **1956**, *29*, 68−74. [d] The absence of a S → Cu charge transfer peak in the region of 350 nm indicates that the thiaether sulfur donor atom is not significantly coordinated.

deionized water was used for all reagent solutions. Concentrations of $\mathrm{Cu(ClO_4)_2}$ solutions were determined by EDTA titration using murexide indicator. Ligand solutions were standardized using Cu(II) mole ratio plots with spectrophotometric monitoring.

Kinetics. A Durrum D-110 stopped−flow spectrophotometer, thermostated at 25.0 ± 0.2 °C, was used for all kinetic measurements. The data were resolved with an interfaced computer using software developed in house. Each reaction was studied by following the absorption change at the major UV or visible peak characteristic for the Cu(II) complex utilizing the molar absorptivity value previously determined (Table 1).[2] In all cases, ligand concentrations were 7−70 μM with Cu(II) in 10- to 100-fold excess. The ionic strength was maintained at 0.10 M using $\mathrm{NaClO_4}$, and the reaction kinetics were determined as a function of pH using sterically hindered tertiary amine buffers (5 mM) recently developed to avoid complexation with Cu(II) ion.[21] The relevant pK_a values (25 °C) for the buffers used are[28] PIPES (*N*,*N*′-bis(2-sulfonatoethyl)piperazine), 2.67; PIPPS (*N*,*N*′-bis(3-sulfonatopropyl)piperazine), 3.79; PIPBS (*N*,*N*′-bis(4-sulfonatobutyl)-piperazine), 4.29; DEPP (*N*,*N*′-diethylpiperazine), 4.48; and MES (*N*-(2-sulfonatoethyl)morpholine), 6.06. To avoid any possible complications arising from the formation of hydroxycopper(II) ion,[29] no studies were carried out above pH 5.7.

Results

Copper(II) Complex Formation Kinetics. The observed reaction between hexaaquacopper(II) ion and each of the 12 tripodal ligands included in this study can be represented as

$$\mathrm{Cu_{aq}}^{2+} + \mathrm{L}' \underset{k_{\mathrm{d}}}{\overset{k_{\mathrm{f}}}{\rightleftharpoons}} \mathrm{CuL}^{2+} + n\mathrm{H}^+ \tag{1}$$

where L′ represents the sum of all unprotonated and protonated forms of the ligand: L, HL^+, $\mathrm{H_2L}^{2+}$, etc. At a specific pH value, the reaction kinetics can be represented by the expression

$$\frac{\mathrm{d}[\mathrm{Cu^{II}L'}]}{\mathrm{d}t} = k_{\mathrm{f}}[\mathrm{Cu}^{2+}][\mathrm{L'}] - k_{\mathrm{d}}[\mathrm{CuL}^{2+}] \tag{2}$$

All reactions were studied at several pH values—generally over a range of two pH units—under conditions where the total Cu(II) concentration was in 10- to 100-fold excess over the total ligand concentration. Under the experimental conditions utilized, $[\mathrm{CuL}^{2+}] = 0$ at $t = 0$ so that the kinetics corresponded to the pseudo-first-order rate expression[30]

$$\frac{\mathrm{d}[\mathrm{Cu^{II}L'}]}{\mathrm{d}t} = k_{\mathrm{obs}}[\mathrm{L'}] \tag{3}$$

where

$$k_{\mathrm{obs}} = k_{\mathrm{f}}[\mathrm{Cu}^{2+}] + k_{\mathrm{d}} \tag{4}$$

In all cases, plots of k_{obs} versus $[\mathrm{Cu}^{2+}]$ at a constant pH were linear with zero intercepts even at the lowest pH values studied (i.e., all reactions proceeded to virtual completion).

For each reaction, k_{f} can be expressed as

$$k_{\mathrm{f}}[\mathrm{L'}] = k_{\mathrm{Cu}}{}^{\mathrm{L}}[\mathrm{L}] + k_{\mathrm{Cu}}{}^{\mathrm{HL}}[\mathrm{HL}^+] + k_{\mathrm{Cu}}{}^{\mathrm{H_2L}}[\mathrm{H_2L}^{2+}] + \ldots \tag{5}$$

where $k_{\mathrm{Cu}}{}^{\mathrm{L}}$, $k_{\mathrm{Cu}}{}^{\mathrm{HL}}$, and $k_{\mathrm{Cu}}{}^{\mathrm{H_2L}}$ represent the specific formation rate constants for Cu(II) reacting with L, HL^+, and $\mathrm{H_2L}^{2+}$, respectively. Equation 5 can then be rearranged to the form

$$k_{\mathrm{f}}/\alpha_{\mathrm{L}} = k_{\mathrm{Cu}}{}^{\mathrm{L}} + k_{\mathrm{Cu}}{}^{\mathrm{HL}}K_{\mathrm{H1}}{}^{m}a_{\mathrm{H^+}} + k_{\mathrm{Cu}}{}^{\mathrm{H_2L}}K_{\mathrm{H1}}{}^{m}K_{\mathrm{H2}}{}^{m}(a_{\mathrm{H^+}})^2 + \ldots \tag{6}$$

where $a_{\mathrm{H^+}}$ represents the activity of hydrogen ion; $K_{\mathrm{H1}}{}^m$, $K_{\mathrm{H2}}{}^m$, etc. represent the successive mixed-mode protonation constants for each ligand (see Table 1);[2]

$$K_{\mathrm{H}n}{}^{m} = \frac{[\mathrm{H}_n\mathrm{L}^{n+}]}{[\mathrm{H}_{n-1}\mathrm{L}^{(n-1)+}]a_{\mathrm{H^+}}} \tag{7}$$

and α_{L} represents the fractional concentration of the uncomplexed ligand in the unprotonated form:

$$\alpha_{\mathrm{L}} = \frac{[\mathrm{L}]}{[\mathrm{L'}]} = \frac{1}{1 + K_{\mathrm{H1}}{}^{m}a_{\mathrm{H^+}} + K_{\mathrm{H1}}{}^{m}K_{\mathrm{H2}}{}^{m}(a_{\mathrm{H^+}})^2 + K_{\mathrm{H1}}{}^{m}K_{\mathrm{H2}}{}^{m}K_{\mathrm{H3}}{}^{m}(a_{\mathrm{H^+}})^3} \tag{8}$$

With the exception of TPMA, plots of $k_{\mathrm{f}}/\alpha_{\mathrm{L}}$ versus $a_{\mathrm{H^+}}$ were linear, indicating that only L and HL^+ contributed significantly to the observed formation kinetics over the pH range studied. For BPMMEA (L19a) and BPMEEA (L19b), the intercepts of such plots were not statistically significant so that the kinetic contribution of the unprotonated ligand could not be resolved. In the specific case of TPMA, a plot of $k_{\mathrm{f}}/\alpha_{\mathrm{L}}$ versus $a_{\mathrm{H^+}}$ showed positive deviations at high $a_{\mathrm{H^+}}$ and a zero intercept, making it evident that the species contributing to the observed reaction kinetics were HL^+ and $\mathrm{H_2L}^{2+}$. This was confirmed by the essential linearity of a plot of $k_{\mathrm{f}}/\alpha_{\mathrm{HL}}$ versus $a_{\mathrm{H^+}}$:

$$k_{\mathrm{f}}/\alpha_{\mathrm{HL}} = k_{\mathrm{f}}/(\alpha_{\mathrm{L}}K_{\mathrm{H1}}a_{\mathrm{H^+}}) = k_{\mathrm{Cu}}{}^{\mathrm{HL}} + k_{\mathrm{Cu}}{}^{\mathrm{H_2L}}K_{\mathrm{H2}}{}^{m}a_{\mathrm{H^+}} \tag{9}$$

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Table 2. Specific Rate Constants for Hexaaquacopper(II) Ion Reacting with Unprotonated and Monoprotonated Tripodal Ligands in Aqueous Solution at 25 °C, $\mu = 0.10$ ($NaClO_4$)

ligand	pH range studied	$10^{-6}k_{Cu}{}^{L}$,[a] $M^{-1}\,s^{-1}$	$10^{-6}k_{Cu}{}^{HL}$,[a] $M^{-1}\,s^{-1}$	k^{Cu-L}, s^{-1}, calcd	$\rho\,(k_{Cu}{}^{L})$,[b] calcd	$\rho\,(k_{Cu}{}^{L})$,[c] ref
NH_3		230			0.4	1.0
F^-		500			0.15	1.0
NTA	2.1−6.0	7000(1000)[d]		0.0014[e]	0.8	1.2
TEA	4.5−5.3	30(3)[f]		5000[f]	0.06	0.6
TMMEA (L16a)	4.0−5.7	7.0(2)	0.00022(3)	3.6	0.01	>0.06
TEMEA (L16b)	4.0−5.3	5.22(7)	0.00017(3)	2.3	0.008	>0.018
PMMEA (L17a)	2.4−4.3	28.2(4)	0.0027(2)	0.00025	0.05	0.02
PMAS (L17b)	2.4−4.0	28.6(2)	0.00187(5)	0.00095	0.05	0.02
PEMEA (L18a)	3.0−5.0	15.2(7)	0.0055(2)	0.20	0.03	0.02
PEAS (L18b)	3.0−5.0	18.9(2)	0.0032(4)	0.25	0.03	0.02
BPMMEA (L19a)	2.0−3.4		1.95(8)			
BPMEEA (L19b)	2.1−3.7		1.6(2)			
BPEMEA (L20a)	2.6−5.6	38(6)	0.31(2)	0.003	0.07	0.04
BPEEEA (L20b)	3.0−5.6	59(3)	0.34(1)	0.0037	0.11	0.04
TPMA (L21)	2.0−3.0		≈20[g]			
TPEA (L22)	4.1−5.5	≈300	0.71(5)	≈0.1	0.6	0.06
related macrocyclic ligands						
[14]aneNS_3		3.2(2)[h]	0.00014(3)[h]	0.0018[h]	0.006	
[14]aneS_4		0.19[i]		18[i]	0.0003	>0.024

[a] Values in parentheses represent the standard deviation relative to the last digit listed; thus, 7.0(2) and 0.00022(3) represent 7.0 ± 0.2 and 0.00022 ± 0.00003, respectively. [b] Calculated using eq 13. [c] Reference 46. [d] Resolved by applying eq 6 to data shown in Figure 1 of ref 24 ($\mu = 0.05$). [e] Based on a Cu^{II}(NTA) stability constant value of $5 \times 10^{12}\ M^{-1}$ (20 °C). Schwarzenbach, G.; Freitag, E. *Helv. Chim. Acta* **1951**, *34*, 1492−1502. [f] Reference 19. [g] An approximate value of $k_{Cu}{}^{H_2L} = 2 \times 10^5\ M^{-1}\ s^{-1}$ was obtained for the diprotonated species of TPEA. [h] Reference 61. [i] Reference 27 (cf., ref 39 of ref 27).

The precision of the TPMA data was poor for the limited pH range studied, and only approximate values of $k_{Cu}{}^{HL}$ and $k_{Cu}{}^{H_2L}$ are reported. This lack of precision is largely attributable to the fact that the spectrum of the Cu^{II}(TPMA) complex differs only slightly from that of the uncomplexed ligand, thereby limiting the sensitivity of the data. For all ligands studied, the resolved values for $k_{Cu}{}^{L}$, $k_{Cu}{}^{HL}$, and $k_{Cu}{}^{H_2L}$ (the latter for TPMA only) are given in Table 2.

Discussion

Stepwise Complex Formation Mechanism. Since substitution reactions involving hexaaquacopper(II) ion occur by dissociative interchange,[31,32] all reactions under discussion can be interpreted in terms of the Eigen−Wilkins mechanism[31,33] in which $Cu(H_2O)_6{}^{2+}$ and the ligand initially form an outer-sphere (nearest-neighbor) complex, after which a $Cu-OH_2$ bond dissociates to permit the rapid insertion of a ligand donor atom into an inner-sphere site. Formation of subsequent coordinate bonds is perceived to occur in a sequence of similar steps.

As noted in the Introduction, previous research has indicated that the tertiary nitrogen, which serves as the bridgehead in all tripodal ligands included in this investigation, is too sterically hindered to promote initial bond formation.[16−21] Therefore, as illustrated schematically in Figure 2 for TMMEA, a pendant donor atom must form the first coordinate bond to Cu(II) followed by coordination to the bridgehead nitrogen to complete the first chelate ring. The same sequence should apply to all ligands in this study. Interpretation of the mechanistic behavior is facilitated by comparing the experimental rate constants for the various ligands with the stepwise parameters.

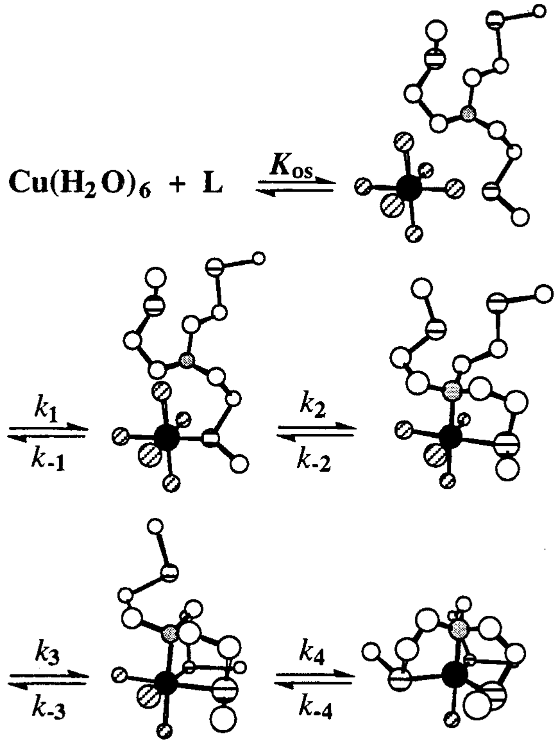

Figure 2. Schematic representation of the stepwise mechanism for $Cu(H_2O)_6{}^{2+}$ reacting with TMMEA (and related tripodal ligands). The solid atom represents copper, the diagonally striped atoms represent oxygens from coordinated water molecules, the shaded atoms represent nitrogens, the horizontally striped atoms represent sulfurs, and the open atoms are carbons. Hydrogen atoms have been omitted for clarity. The initial equilibrium constant, K_{os}, represents the equilibrium for outer-sphere complex (nearest neighbor) formation, and the successive rate constants in the forward direction represent the rate constant for $Cu-OH_2$ bond rupture modified by any steric factors and rotational barriers required to bring the next donor atom to a bonding site.

Outer-Sphere Equilibrium Constant. In Figure 2, K_{os} represents the equilibrium constant for outer-sphere complex

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formation as approximated from the modified Fuoss equation,[31,34]

$$K_{OS} = (^4/_3)\pi a^3 N_A 10^{-3} e^{-\delta} \tag{10}$$

where a represents the center-to-center distance of closest approach (in cm) between the solvated metal ion and the ligand, N_A represents Avogadro's number, and $e^{-\delta}$ represents the electrostatic interaction between the two reacting partners.[16,35] For all *unprotonated* ligand species in this study, $e^{-\delta} = 1$ (i.e., $\delta = 0$), since the ligands are uncharged. As has been argued previously, analysis of complex formation is facilitated by treating the donor atom involved in the initial bond formation as a "donor atom with a tail".[35] On the basis of this concept, $a \approx 4.0 \times 10^{-8}$ cm for the approach of $Cu(H_2O)_6^{2+}$ to an unhindered nitrogen atom (as in NH_3)[36] and about 4.4×10^{-8} cm for a corresponding sulfur atom yielding, respectively, $K_{os} \approx 0.16$ and 0.21 M^{-1}.

Stepwise Rate Constants. For multidentate ligand reactions, the rate-determining step is generally at the point of either first-bond formation, k_1, or second-bond formation, k_2.[31,37] Application of the steady-state approximation to the singly bonded complex yields

$$k_{Cu}{}^{L} = K_{OS}\left(\frac{k_1 k_2}{k_{-1} + k_2}\right) \tag{11}$$

Thus, the relative magnitudes of k_{-1} and k_2 are of primary importance in determining the position of the rate-determining step. If $k_2 \gg k_{-1}$, the first-bond formation step is rate-determining,

$$k_{Cu}{}^{L} = K_{os} k_1 \tag{11a}$$

whereas if $k_2 \ll k_{-1}$, the rate-determining step is shifted to the point of second-bond formation,

$$k_{Cu}{}^{L} = K_{os} k_1 k_2 / k_{-1} = K_{os} K_1 k_2 \tag{11b}$$

For $Cu(H_2O)_6^{2+}$, k_1 is exceptionally large because of the elongation of the Cu−OH_2 bonds along one axis (Jahn−Teller distortion) where as a result all six inner-sphere water molecules are assumed to be equally labile because of rapid Jahn−Teller inversion.[19,32,38] Substitution of a single unique donor atom into the inner-coordination sphere should remove the electronic degeneracy, thereby diminishing (or eliminating) Jahn−Teller distortion.[19,39] As a result, both k_{-1} and k_2 may be smaller than k_1, but their values cannot be estimated from available experimental data as a means of establishing the likely position of the rate-determining step. Thus, we have taken the approach of comparing the experimental complex formation rate constants to the values predicted by eq 11a for first-bond formation. When the differences appear too large to be attributed to steric and statistical effects, we infer that the rate-determining step has switched to the point of second-bond formation (i.e., closure of the first chelate ring).

Comparison of Experimental and Theoretical Formation Rate Constants. For a dissociative interchange mechanism, k_1 should be related to the rate of exchange of bulk water molecules per inner-coordination sphere site for which the most reliable value is $k_{ex} = 4.4 \times 10^9$ s^{-1} at 25 °C.[32] As suggested by Neely and Connick, $k_1 = (^3/_4)k_{ex}$ when considering solvent−ligand exchange on octahedral aquometal ions.[40] Thus, for reactions involving unhindered donor atoms in which first-bond formation is the rate-determining step,

$$k_{Cu}{}^{L} = K_{os}(^3/_4)k_{ex} \tag{12}$$

For $Cu(H_2O)_6^{2+}$ reacting with the two simplest unidentate ligands for which experimental kinetic data are available—namely, NH_3 and F^-—the foregoing considerations yield predicted theoretical formation rate constant values (at 25 °C) as follows:

$$k_{Cu}{}^{NH_3} = (0.16\ M^{-1})(^3/_4)(4.4 \times 10^9\ s^{-1}) = 5.3 \times 10^8\ M^{-1}\ s^{-1}$$

$$k_{Cu}{}^{F} = (1.0\ M^{-1})(^3/_4)(4.4 \times 10^9\ s^{-1}) = 3.3 \times 10^9\ M^{-1}\ s^{-1} \qquad (\mu = 0.5)$$

where $e^{-\delta} = 6.4$ (25 °C, $\mu = 0.5$ M) in the latter case. The experimental values are $k_{Cu}{}^{NH_3} = 2.3 \times 10^8$ (25 °C)[38,41] and $k_{Cu}{}^{F} = 5 \times 10^8$ M^{-1} s^{-1} (25 °C, $\mu = 0.5$ M),[42] which differ from prediction by 2.3- and 6.6-fold, respectively. The latter discrepancy suggests that $k_{Cu}{}^{F}$, as estimated from literature data,[42] is likely in error. This conclusion is supported by the data for Cu(II) reacting with acetate and chloroacetate (both of which are more sterically hindered monoanions) for which $k_{Cu}{}^{L} = 1.5 \times 10^9$ (20 °C, variable μ)[43] and 8.5×10^8 M^{-1} s^{-1} (25 °C, $\mu = 1.0$),[44] respectively.

Steric Effects. On the basis of our "donor atom with a tail" model, the theoretical formation rate constant values for larger ligands must be modified to account for the fact that donor atoms within 4 Å of the solvated metal ion in the outer-sphere complex may either be sterically hindered or be oriented in such a way as to be unavailable for inner-sphere insertion at the time a Cu−OH_2 bond dissociates.[35] The availability of multiple accessible donor atoms per molecule will also increase the number of

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(34) Fuoss, R. M. *J. Am. Chem. Soc.* **1958**, *80*, 5059−5061. Eigen, M.; Kruse, W.; Maass, G.; DeMaeyer, L. *Prog. React. Kinet.* **1964**, *2*, 285−318.

(35) Lin, C.-T.; Rorabacher, D. B. *Inorg. Chem.* **1973**, *12*, 2402−2410. For the "donor atom with a tail" concept, see p 2406, column 2, paragraph 3.

(36) Rorabacher, D. B. *Inorg. Chem.* **1966**, *5*, 1891−1899.

(37) Margerum, D. W.; Rorabacher, D. B.; Clarke, J. F. G., Jr. *Inorg. Chem.* **1963**, *2*, 667−677. See p 675.

(38) Sokol, L. S. W. L.; Fink, T. D.; Rorabacher, D. B. *Inorg. Chem.* **1980**, *19*, 1263−1266 and references therein.

(39) Diaddario, L. L.; Zimmer, L. L.; Jones, T. E.; Sokol, L. S. W. L.; Cruz, R. B.; Yee, E. L.; Ochrymowycz, L. A.; Rorabacher, D. B. *J. Am. Chem. Soc.* **1979**, *101*, 3511−3520.

(40) The outer-sphere model assumes that the outer-sphere ligands are situated over the faces of the octahedrally solvated metal ions and must compete with outer-sphere solvent molecules over the adjacent faces whenever an inner-sphere solvent molecule dissociates. The fact that each face is adjacent to three inner-sphere sites and that each inner-sphere site is adjacent to four faces leads to the statistical probability that an outer-sphere ligand has a $^3/_4$ statistical probability of inserting into a vacated inner-sphere site. Neely, J.; Connick, R. *J. Am. Chem. Soc.* **1970**, *92*, 3476−3478 (cf., ref 38).

(41) Diebler, H.; Rosen, P. *Ber. Bunsen-Ges. Phys. Chem.* **1972**, *76*, 1031−1034.

(42) The experimental dissociation rate constant for CuF^+ is reported to be $k^{Cu-F} = 1 \times 10^8$ s^{-1} at 25 °C, $\mu = 0.5$ M [Eisenstadt, M.; Friedman, H. L. *J. Chem. Phys.* **1968**, *48*, 4445−4458.]. The best value for the stability constant of the 1:1 complex under these same conditions is $K_{CuF} = 5$ M^{-1} [(a) Sillen, L. G.; Martell, A. E. *Stability Constants of Metal-Ion Complexes*; Special Publication No. 17; The Chemical Society, Burlington House: London, 1964. (b) Smith, R. M.; Martell, A. E. *Critical Stability Constants*; Plenum: New York, 1976.]. Thus, $k_{Cu}{}^{F} = k^{Cu-F}K_{CuF} = 5 \times 10^8$ M^{-1} s^{-1}.

(43) Maass, G. *Z. Phys. Chem. (Frankfurt)* **1968**, *60*, 138−151.

(44) Harada, S.; Tsuji, Y.; Yasunaga, T. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1930−1931.

reactive encounters accordingly (e.g., any one of the three sulfurs in TMMEA are presumed to be accessible for first-bond formation). These steric and statistical corrections can be combined in an empirical steric correction factor, ρ.[45] For complex formation reactions involving first-bond formation as the rate-determining step, eq 12 should then be modified to the form

$$k_{\mathrm{Cu}}{}^{\mathrm{L}} = K_{\mathrm{os}}(^{3}/_{4})k_{\mathrm{ex}}\rho \qquad (13)$$

Thus, estimates of ρ can then be generated as follows:

$$\rho \approx \frac{k_{\mathrm{Cu}}{}^{\mathrm{L}}(\mathrm{exptl})}{K_{\mathrm{OS}}(0.75)(4.4 \times 10^{9})} \qquad (13a)$$

For the unprotonated ligands in the current study, ρ values calculated using eq 13a are listed in Table 2 adjacent to reference ρ values based on rate constant comparisons between specific amine ligands involving similar steric groups.[46] A large discrepancy between the calculated and reference ρ values suggests the likelihood of a switch in the position of the rate-determining step.

NTA, TEA, TMMEA, and TEMEA. Among the tripodal ligands for which $k_{\mathrm{Cu}}{}^{\mathrm{L}}$ values have been determined experimentally, NTA, TEA, TMMEA, and TEMEA (Figure 1) are of particular interest, since each contains three identical legs. The complex formation rate constant for $\mathrm{Cu(H_2O)_6}^{2+}$ reacting with TEA was previously determined in our laboratory[19] and is included in Table 2. Maguire[24] studied the kinetics of Cu(II) reacting with NTA but did not resolve specific rate constant values, since he observed an unexplained increase in the apparent formation rate constant below pH 4. However, application of eq 6 to Maguire's data (as shown in his Figure 1)[24] indicates that only the unprotonated ligand is contributing to the formation rate constant at pH $\geq$ 5 from which we calculate $k_{\mathrm{Cu}}{}^{\mathrm{NTA}} = (7 \pm 1) \times 10^{9}\ \mathrm{M^{-1}\ s^{-1}}$ at 25 °C, $\mu = 0.05$ using his data. (At this ionic strength, $K_{\mathrm{os}} \approx 2.4$ for the donor atom with a tail model.)

On the basis of earlier studies of sterically hindered mono- and diamines,[16,35,47,48] we estimate that for a terminal carboxylic oxygen (NTA) or alcoholic oxygen (TEA), $\rho \approx 0.2$ per donor atom.[46] Since there are six available pendant donor atoms in NTA (each carboxylate group having two available oxygens) and three in TEA, the overall reference ρ values should be 1.2 and 0.6, respectively.[49] For $\mathrm{Cu^{II}}$(NTA), the calculated and reference ρ values (Table 2) are within experimental error with no evidence of outer-sphere hydrogen-bond formation (ICB effect) as expected for this very basic ligand.[16,36,50] However, this agreement could be fortuitous, since the experimental $k_{\mathrm{Cu}}{}^{\mathrm{NTA}}$ value is close to the theoretical diffusion limit.[51] In the case of TEA, the calculated ρ value is 1 order of magnitude smaller than the reference value, implying that the rate-determining step is at the point of second-bond formation, as concluded in earlier work.[19]

For nitrogen atoms attached to both a methyl and an ethyl (or larger) group or to two ethyl (or larger) groups, $\rho \approx 0.02$ and 0.006 per donor atom, respectively,[46,49] or 0.06 and 0.018 for tripodal ligands containing three pendant donor atoms. The corresponding ρ values for substituted sulfur donor atoms, as in TMMEA and TEMEA, should be somewhat larger, since the sulfur atoms are both larger and have two unshared electron pairs. To account for this, the reference ρ values based on substituted nitrogen ligands are listed as *lower limits* for TMMEA and TEMEA in Table 2. The calculated ρ values for these two ligand reactions are 6 and 2 times smaller, respectively, than the limiting reference ρ values. This suggests that the rate-determining step for these ligand reactions may also have switched to the point of second-bond formation as concluded in an earlier study,[20] although the distinction is not totally clear in this case.

PMMEA, PMAS, PEMEA, and PEAS. The $k_{\mathrm{Cu}}{}^{\mathrm{L}}$ values for PMMEA and PMAS are 4−5 times larger than for TMMEA and TEMEA. Thus, substitution of a pyridine nitrogen for one thiaether sulfur accelerates the reaction. Molecular models suggest that the steric hindrance associated with pyridine nitrogens is similar to that for thiaether sulfurs substituted by two ethyl groups so that the rate increase is not readily attributed to an increase in ρ. However, unsaturated nitrogens are better nucleophiles than thiaether sulfurs so that initial bond formation to a pyridine nitrogen should decrease k_{-1} relative to the value for an initial thiaether sulfur bond, thereby increasing the likelihood that the first-bond formation step may be rate-determining. Accordingly, the reference ρ value listed in Table 2 for PMMEA and PMAS presumes that only the nitrogen is effective in first-bond formation. (Although both remaining thiaether sulfurs are also available for first-bond formation, the fraction of reaction in which a pyridine nitrogen bonds first is presumed to lead to faster complex formation.) This premise is consistent with the fact that comparable $k_{\mathrm{Cu}}{}^{\mathrm{L}}$ values are obtained for both PMMEA and PMAS despite differences in the sulfur steric factors. Identical values should be obtained for PEMEA and PEAS if first-bond formation is rate-determining. The decrease in $k_{\mathrm{Cu}}{}^{\mathrm{L}}$ values for the latter two ligands suggests the possibility that the rate-determining step may shift to the point of second-bond formation because of the difficulty of closing a six-membered chelate ring, but the difference is too small to justify definitive conclusions.

BPMMEA, BPMEEA, BPEMEA, BPEEEA, TPMA, and TPEA. If initial bond formation to a pyridine nitrogen dominates

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(45) It should be noted that the steric factor represented as ρ in this document is equivalent to the "reduction in the solid angle [of approach] corresponding to reactive encounters" as defined by Kowalak et al. Kowalak, A.; Kustin, K.; Pasternack, R. F.; Petrucci, S. *J. Am. Chem. Soc.* **1967**, *89*, 3126−3130.

(46) The reference ρ value for a monoalkyl-substituted donor atom (alkyl = ethyl or larger) relative to an unsubstituted donor atom is presumed to be equal to the ratio of formation rate constants for $\mathrm{Ni(H_2O)_6}^{2+}$ reacting with ethylamine compared to $\mathrm{NH_3}$; i.e., $\rho = 0.2$ [ref 47]. In the current discussion, this value is applied to each donor atom in TEA and NTA. For donor atoms substituted by two alkyl groups, the additional steric effect imposed by a second alkyl group on a donor atom is assumed to be equal to the ratio of formation rate constants for $\mathrm{Ni(H_2O)_6}^{2+}$ reacting with *N*,*N*,*N*-trimethylethylenediamine ($\mathrm{tmen^{+}}$) [ref 35] and the monoprotonated species of *N*,*N*′-dimethylethylenediamine [ref 48] (for terminal methyl groups) and *N*,*N*′-diethylethylenediamine [ref 16] (for terminal ethyl groups), viz., 0.02 and 0.006 per available donor atom.

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(49) Kulatilleke, C. P.; Goldie, S. N.; Ochrymowycz, L. A.; Rorabacher, D. B. *Inorg. Chem.*, in press.

(50) Taylor, R. W.; Stepien, H. K.; Rorabacher, D. B. *Inorg. Chem.* **1974**, *13*, 1282−1289.

(51) The rate constant for the formation of the outer-sphere complex between $\mathrm{Cu(H_2O)_6}^{2+}$ and NTA can be estimated as $k_0 = 4\pi a D_{\mathrm{AB}} N_{\mathrm{A}}(10^{-3})\{\delta/(1 - e^{-\delta})\} \approx 1.6 \times 10^{10}\ \mathrm{M^{-1}\ s^{-1}}$ (25 °C, $\mu = 0.1$, $a = 4.0 \times 10^{-8}$ cm, $Z_{\mathrm{A}}Z_{\mathrm{B}} = -2$), which is within a factor of 2 of the estimated experimental value. In this latter expression, $D_{\mathrm{AB}} \approx 2 \times 10^{-5}\ \mathrm{cm^2\ s^{-1}}$ represents the sum of the diffusion constants for the two reactants, and $Z_{\mathrm{A}}Z_{\mathrm{B}}$ is the charge product of the Cu(II) ion and the proximal carboxylate oxygen in the outer-sphere complex [Eigen, M.; Kruse, W.; Maass, G.; De Maeyer, L. *Prog. React. Kinet.* **1964**, *2*, 285−318.].

the formation kinetics, as inferred above, the presence of two (or three) pyridine groups should double (or triple) k_{Cu}^{L} relative to corresponding monopyridyl ligands. This appears to be the case for BPEMEA and BPEEEA within the precision of the data obtained. Unfortunately, no conclusions can be drawn for BPMMEA, BPMEEA, or TPMA, since their k_{Cu}^{L} values were not resolved. For TPEA, k_{Cu}^{L} is about 4 times larger than anticipated if pyridine bond formation is rate-determining. However, this discrepancy may be attributable to the ICB effect (outer-sphere H-bonding), since a ligand with log $K_{H1} = 8.2$ should exhibit a rate constant enhancement of about 2-fold.[48,52]

Protonated Ligand Rate Constants. For all *monoprotonated* ligand species in the current study, the proton is expected to reside predominantly on the bridgehead nitrogen as the most basic site available.[53] For the "donor atom with a tail" model, the *charge* center-to-center distance (i.e., the distance from the center of $Cu(H_2O)_6^{2+}$ to a protonated bridgehead nitrogen on the ligand) in the outer-sphere complex is $\sim 6.5 \times 10^{-8}$ cm.[35] This yields $e^{-\delta} \approx 0.27$; that is, the K_{os} value will decrease by a factor of 4 relative to a corresponding unprotonated ligand.

For TMMEA, TEMEA, PMMEA, and PEAS, the kinetic contribution of the HL^+ species never becomes dominant within the pH range studied, but it does contribute sufficiently to permit the resolution of k_{Cu}^{HL} with reasonable accuracy. This implies that the proton is still involved at the time of the rate-determining step. Since the bridgehead nitrogen is the *only* protonatable donor atom available in TMMEA and TEMEA—and it must be involved in second-bond formation—the appearance of a k_{Cu}^{HL} term might normally be taken as evidence that first-bond formation is rate-determining. However, the k_{Cu}^{HL} values for these two ligands are four and one-half orders of magnitude smaller than k_{Cu}^{L}. This cannot be explained in simple electrostatic and steric terms[54] nor can it be attributed to internal hydrogen bonding because in these ligands only the bridgehead nitrogen could bond to a hydrogen ion to any significant degree.

In early studies on multidentate ligand reactions, it was noted that if the second coordinate-bond formation involves a protonated donor atom, the loss of the proton prior to second-bond formation can itself become rate-limiting.[37,55] This hypothesis was invoked by Rabenstein and Kula[25] to justify their observation that $k_M^{L}/k_M^{HL} \approx 10^4$ for Cd(II) and Zn(II) reacting with NTA. A similar approach has been used to account for the relative reactivity of Cu(II) reacting with bidentate ligand species such as ethylenediamine (2×10^4) [56] and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (1×10^5).[19] Our similar ratio of $k_{Cu}^{L}/k_{Cu}^{HL} \approx 3 \times 10^4$ in the case of TMMEA and TEMEA is consistent with this behavior.

For monoprotonated PMMEA and PMAS, we also obtain $k_{Cu}^{L}/k_{Cu}^{HL} \approx 10^4$, which again implies that proton loss is the rate-determining step. As the distance between the pendant pyridine nitrogen and the protonated nitrogen bridgehead is increased in monoprotonated PEMEA and PEAS, K_{os} should increase slightly, which could account for the 2-fold increase in k_{Cu}^{HL} for these latter ligands.[54] Since the bonding sequence for these tripodal ligands should be identical to that for monoprotonated 2-aminomethylpyridine (AMP), it is particularly noteworthy that the k_{Cu}^{HL} values for all four monopyridine tripodal ligands are within a factor of 3 or 4 of the AMP value, $k_{Cu}^{HL} = 8.6 \times 10^3$ M^{-1} s^{-1}.[57] Voss and Jordan[58] subsequently proposed that the buffer could catalyze rate-determining proton loss in Cu^{II}(AMP) formation, but even at low pH they observed less than a 2-fold increase in k_f with buffer concentrations of 0.2 M. No kinetic effect was observed in our studies for buffer concentrations in the range 1−10 mM at pH 4.0.

The incorporation of a second pyridine leg in BPMMEA and BPMEEA causes k_{Cu}^{HL} to increase by an additional two and one-half to three orders of magnitude, which implies a change in the reaction mechanism. We attribute this to the fact that a significant fraction of these ligands has the proton residing on one of the pyridine nitrogens rather than on the bridgehead nitrogen.[59] This would then permit the second pyridine nitrogen to form the first bond as the rate-determining step followed by chelate ring closure—without requiring proton loss. The 15-fold difference in these k_{Cu}^{HL} values compared to the k_{Cu}^{L} values for PMMEA and PMAS suggests that 7% of monoprotonated BPMMEA and BPMEEA have the proton on a pyridine. A similar phenomenon is presumed to account for the unexpectedly large k_{Cu}^{HL} value obtained for TPMA, although the latter value is not well established. The further observation that the k_{Cu}^{HL} values for BPEMEA and BPEEEA decrease by about 5-fold relative to BPMMEA and BPMEEA may then reflect the smaller percentage of the HL^+ species in which the proton resides on a pyridine nitrogen as expected from the much larger difference between the K_{H1} and K_{H2} values.[59] Thus, although the overall complex formation rate constants for the various *monoprotonated* ligand species cannot be described in purely quantitative terms, the results appear to be internally consistent.

Dissociation Rate Constants. The rate constants for the dissociation of the Cu(II) complexes are also of interest, since

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(52) As noted in Table 1, the only other tripodal ligands with a sufficiently basic nitrogen atom to promote significant hydrogen bond formation in the outer-sphere complex (log $K_{H1} > 8$) [ref 48] are NTA, TMMEA, and TEMEA. As noted in the text, the reaction of NTA may be diffusion-controlled. In the case of TMMEA and TEMEA, if the rate-determining step is at the point of second-bond formation, any hydrogen bond formed initially between the bridgehead nitrogen and a coordinated water molecule in the outer-sphere complex would be required to rupture prior to the rate-determining step, thereby canceling out any accelerative effect.

(53) In an equilibrium study involving a trisphenolate-substituted derivative of tren, Caravan and Orvig have stated that the bridgehead nitrogen is very acidic (pK_a < 1.5) [Caravan, P.; Orvig, C. *Inorg. Chem.* **1997**, *36*, 236−248. Caravan, P.; Hedlund, T.; Liu, S.; Sjöberg, S.; Orvig, C. *J. Am. Chem. Soc.* **1995**, *117*, 11230−11238.]. This conclusion is inconsistent with the normal basicity of amine nitrogens and is in conflict with the experimental protonation constants for TEA, TMMEA, and TEMEA (see Table 1) for which the only protonatable donor atom is the bridgehead nitrogen.

(54) The rate constant for $Ni(H_2O)_6^{2+}$ reacting with NH_3 in aqueous solution at 25 °C, $\mu = 0.10$, is 4×10^3 M^{-1} s^{-1} (ref 36), while that for the unidentate ligand *N*,*N*,*N*-trimethylethylenediammonium ion (corresponding to monoprotonated ethylenediamine) is about 5×10^2 M^{-1} s^{-1} (ref 35)—an overall decrease of about 10-fold. If one assumes that the steric factor slows the latter reaction by a factor of about 5, as is the case for ethylamine (ref 47), the electrostatic effect alone is presumed to decrease the formation rate constant by a factor of only 2.

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(59) The log K_{H1} and K_{H2} values for BPMMEA and BPMEEA differ by about 2.5. If the fraction of HL^+ species in which the proton resides on a pyridine nitrogen is about 7%, and one considers the fact that there are two pyridine nitrogens to one amine nitrogen, electrostatic repulsion between the two hydrogens combined with solvation effects would have to account for about 1 order of magnitude difference in the two K_H values. This appears to be reasonable when compared to reference ligands containing two similar donor atoms in proximity. In the case of BPEMEA and BPEEEA, the first two K_H values differ by nearly 4 orders of magnitude so that the fraction of HL^+ species in which the proton resides on a pyridine nitrogen must be substantially decreased. As an alternative, but related, mechanism, the proton on a bridgehead nitrogen could be internally hydrogen-bonded to a pendant pyridine, which would then facilitate the rapid migration of the proton to the pyridine nitrogen prior to chelate ring closure to the bridgehead nitrogen.

they relate to the strengths of the individual donor atom bonds as well as to the internal strains induced in the complexed ligand. Since proton-aided dissociation is generally very ambiguous, because of the effect of donor atom protonation on the several equilibria that precede the rate-determining step, it is preferable to compare proton-independent dissociation rate constants.

As noted earlier, all formation reactions in this study proceeded to completion under the experimental conditions used so that no dissociation rate constants were obtained directly. However, if there is no buildup of intermediates prior to the rate-determining step in the formation reactions, the rate constants for copper–ligand dissociation can be calculated as

$$k^{\mathrm{Cu-L}} = k_{\mathrm{Cu}}{}^{\mathrm{L}}/K_{\mathrm{Cu^{II}L}} \tag{14}$$

using the $K_{\mathrm{Cu^{II}L}}$ values recently determined.[2] These calculated $k^{\mathrm{Cu-L}}$ values are listed in Table 2.

Since the $k_{\mathrm{Cu}}{}^{\mathrm{L}}$ values indicate that the rate-determining step for complex formation is at or near the point of first-bond formation, the rupture of the last coordinate bond must be at or near the point of the rate-determining step for the (proton-unaided) dissociation process. It is particularly interesting to note that the $k^{\mathrm{Cu-L}}$ values for TMMEA and TEMEA are 4 orders of magnitude larger than for PMMEA and PMAS. This difference implies that a Cu(II) bond to a pyridine nitrogen dissociates 10^4 more slowly than a corresponding thiaether sulfur bond; that is, the Cu(II)–N(pyridine) bond is about 10^4 stronger than a Cu(II)–S(thiaether) bond. On the basis of the reported stability constant for $\mathrm{Cu(py)(H_2O)_5}^{2+}$ (400 $\mathrm{M^{-1}}$ at 25 °C, $\mu = 1.0$),[60] the stability constant for $\mathrm{Cu(R_2S)(H_2O)_5}^{2+}$ is then expected to be $\sim 0.04\ \mathrm{M^{-1}}$. As a result, a $\mathrm{Cu^{II}(R_2S)(H_2O)_5}^{2+}$ species is too weak to be detectable in aqueous solution, in agreement with observations.

Estimate of k_{-1} for Cu(II)–SR$_2$ Bonds. From the foregoing rationale, it is possible to obtain a crude estimate of the value of k_{-1} for a tripodal ligand in which the first-coordinate bond involves a thiaether sulfur, as in TMMEA and TEMEA. On the basis of methylethyl sulfide as a model, the stability constant can be expressed as

$$K_{\mathrm{Cu(MeSEt)}} = \frac{k_{\mathrm{Cu}}{}^{\mathrm{L}}}{k^{\mathrm{Cu-L}}} = \frac{K_{\mathrm{OS}}k_1}{k_{-1}} \tag{15}$$

Substitution of eq 13 into eq 15, where $\rho \geq 0.02$,[46] yields the following estimate:

$$k_{-1} = \frac{K_{\mathrm{OS}}k_{\mathrm{ex}}(^3/_4)\rho}{K_{\mathrm{Cu(MeSEt)}}} \approx \frac{(0.21\ \mathrm{M^{-1}})(4.4 \times 10^9\ \mathrm{s^{-1}})(^3/_4)(\geq 0.02)}{0.04\ \mathrm{M^{-1}}} \geq 3.6 \times 10^8\ \mathrm{s^{-1}}$$

The value of k_2 in eq 11 should depend on the rupture of a second Cu–H$_2$O bond, which is expected to be significantly smaller than $4.4 \times 10^9\ \mathrm{M^{-1}\ s^{-1}}$, since coordination of a single thiaether sulfur atom should remove the orbital degeneracy of d^9 Cu(II), thereby lowering Jahn–Teller distortion[19] (as observed previously when a methanol replaces an inner-sphere water molecule in solvated Cu(II)).[39] The value of k_2 should be reduced further by the energy barrier required to rotate the nitrogen donor atom into position for chelate ring closure. Thus, it is anticipated that $k_2 < 3.6 \times 10^8\ \mathrm{s^{-1}}$, consistent with our earlier conclusion that the rate-determining step in the reactions with TMMEA and TEMEA has likely shifted to the point of second-bond formation.

For PEMEA and PEAS, the $k^{\mathrm{Cu-L}}$ values are approximately 10^3 larger than for PMMEA and PMAS (Table 2). Inasmuch as the rate constant for rupturing the final Cu–N bond should be essentially identical for both pairs of ligands, the larger $k^{\mathrm{Cu-L}}$ values for PEMEA and PEAS must reflect the decreased stability (i.e., greater strain) in the six-membered chelate ring as a prior equilibrium preceding the rate-determining step. This strain should also be manifested in a decrease in the k_2 value for ligands with six-membered chelate rings, which suggests that the rate-determining step can more readily be shifted to the point of second-bond formation (e.g., by protonation) when six-membered rings are involved.

Comparative Kinetic Behavior of a Related Macrocyclic Ligand. An interesting comparison can be made between the kinetics of Cu(II) reacting with TEMEA and with the macrocycle [14]aneNS$_3$ (1,4,8-trithia-11-azacyclotetradecane).[61] Both ligands contain an amine nitrogen and three thiaether sulfurs, and the steric hindrance for bond formation to the sulfurs is approximately the same in both cases (although the macrocyclic structure restricts conformational flexibility). As shown in Table 2, $k_{\mathrm{Cu}}{}^{\mathrm{L}}$ and $k_{\mathrm{Cu}}{}^{\mathrm{HL}}$ are nearly identical for these two ligands. Since initial Cu–N bond formation could be rate-determining with [14]aneNS$_3$, the similarity in the $k_{\mathrm{Cu}}{}^{\mathrm{L}}$ values for these two ligands lends support to our conclusion that the rate-determining step for TMMEA and TEMEA is close to the point of first-bond formation. By contrast, the fact that the dissociation rate constant, $k^{\mathrm{Cu-L}}$, for Cu$^{\mathrm{II}}$([14]aneNS$_3$) is more than 1000 times smaller than for Cu$^{\mathrm{II}}$(TEMEA) reflects the greatly enhanced stability of the macrocyclic complex.

It is also interesting to contrast the formation rate constants for TMMEA and TEMEA with the corresponding value for [14]aneS$_4$ (1,4,8,11-tetrathiacyclotetradecane) for which we have concluded that the rate-determining step is at the point of second-bond formation.[20,39] Both ligands involve a Cu(II)–S(thiaether) bond in the first-bond formation step. Yet $k_{\mathrm{Cu}}{}^{\mathrm{L}}$ for [14]aneS$_4$ is about 30 times smaller than the values for TMMEA, TEMEA, and [14]aneNS$_3$. The difference in behavior is attributed to the fact that the rotational barrier for closing the first chelate ring is substantially larger for the macrocycle, whereas the k_{-1} values remain nearly constant.

Conclusions

The $k_{\mathrm{Cu}}{}^{\mathrm{L}}$ values have been determined for nine of the tripodal ligands included in this study. When the first bond formed involves a pyridine nitrogen, the rate-determining step appears to be at the point of first-bond formation. However, when first-bond formation involves a more weakly coordinating thiaether sulfur donor atom, the rate-determining step may shift to the point of second bond formation (but just barely). In the case of the *monoprotonated* species of TMMEA and TEMEA and all four ligands containing a single pyridine moiety, the rate-determining step appears to involve proton loss. This is particularly notable for tripodal ligands, since the bridgehead nitrogen must be involved in chelate ring closure.

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With the exception of TPEA, the formation rate constants involving the unprotonated ligands are all within an order of magnitude. The large differences in the Cu(II) complex stability constants for the tripodal ligands included in this study are primarily reflected in the dissociation rate constants. These clearly demonstrate the relative weakness of Cu(II)−S(thiaether) bonds compared to Cu(II)−N(pyridine) bonds for which we have estimated a difference in bond strength of approximately 10^4-fold. The kinetic behavior for all 12 ligand systems considered in the current study—plus the earlier data for Cu(II) reacting with NTA and TEA—appears to be internally consistent and enhances our general understanding of both tripodal ligand behavior and $Cu(H_2O)_6^{2+}$ substitution.

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Supporting Information Available: Tables listing rate constant data for all 12 complex formation reactions as a function of pH. This material is available free of charge via the Internet at http://pubs.acs.org.

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