Kinetic and Thermodynamic Measurements on Branched Amino Polythiaether Ligands: A Family of Complexing Agents Analogous to EDTA and NTA Exhibiting Enhanced Selectivity for Copper(II)

Thomas H. Cooper,[1a] **Michael J. Mayer,**[1b] **Kwan-Hang Leung,**[1b] **L. A. Ochrymowycz,***[1b] **and D. B. Rorabacher***[1a]

Departments of Chemistry, Wayne State University, Detroit, Michigan 48202, and University of Wisconsin—Eau Claire, Eau Claire, Wisconsin 54701

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A series of branched amino polythiaether multidentate ligands has been synthesized involving one or two tertiary amine nitrogen donor atoms to which are appended alkyl chains containing thiaether sulfur donors. The resulting compounds are analogous to the amino polycarboxylate reagents EDTA and NTA. Ligand protonation constants, Cu(II) complex stability constants, and Cu(II) complex formation rate constants have been determined for three of these amino polythiaethers including the EDTA analogue, *N,N,N',N'*-tetrakis((ethylthio)ethyl)ethylenediamine (TEMEED) and two NTA analogues, tris((ethylthio)ethyl)amine (TEMEA) and tris((methylthio)ethyl)amine (TMMEA). Due to limitated aqueous solubility, the first two ligand systems were studied in 80% methanol while the last system was successfully studied in aqueous solution. For all three ligands, it is concluded that the mechanism for Cu(II) complex formation involves the initial formation of a Cu–S bond followed by Cu–N bond formation (to complete the first chelate ring) as the rate-determining step. The mixed-mode ligand protonation constants ($K_{H_n}{}^{m}$), Cu(II) complex stability constants (K_{CuL}), and Cu(II) complex formation rate constants with the unprotonated ($k_{Cu}{}^{L}$) and (where appropriate) protonated ligand species ($k_{Cu}{}^{HL}$), all at 25 °C, are as follows (the first two ligand systems in 80% methanol, the last in water): TEMEED, $\log K_{H1}{}^{m} = 7.45 \pm 0.05$, $\log K_{H2}{}^{m} = 3.0 \pm 0.1$, $\log K_{CuL} = 10.0 \pm 0.1$, $k_{Cu}{}^{L} = (1.6 \pm 0.5) \times 10^6\ M^{-1}\ s^{-1}$, $k_{Cu}{}^{HL} = (1.1 \pm 0.2) \times 10^4\ M^{-1}\ s^{-1}$; TEMEA, $\log K_{H1}{}^{m} = 6.34 \pm 0.05$, $\log K_{CuL} = 6.82 \pm 0.06$, $k_{Cu}{}^{L} = (1.22 \pm 0.06) \times 10^6\ M^{-1}\ s^{-1}$; TMMEA, $\log K_{H1}{}^{m} = 8.22 \pm 0.03$, $\log K_{CuL} = 6.02 \pm 0.06$, $k_{Cu}{}^{L} = (5.3 \pm 0.3) \times 10^6\ M^{-1}\ s^{-1}$. Similar static and kinetic measurements for the CuL^{2+} formation reactions were conducted in the presence of large excess amounts of other first-row transition metal ions, including Mn(II), Co(II), Ni(II), and Zn(II). With the possible exception of Ni(II), none show any indication of weak complex formation. It is concluded that these amino polythiaether ligands should serve as highly selective reagents for Cu(II) among the divalent first-row transition metal ions. By analogy to other polythiaethers, these ligands should also function as excellent reagents for Pd(II), Pt(II), Ag(I), Au(I), and Hg(II).

Introduction

In extensive studies on macrocyclic polythiaether ligands conducted in our laboratory over the past several years,[2-4] it has become apparent that thiaether sulfur donor atoms tend to be selective for only a few elements *as they exist in their common oxidation states in aqueous solution*: Cu(II), Pd(II), Ag(I), Pt(II), Au(I), and Hg(II). A similar observation was made a number of years ago by the late Gerold Schwarzenbach, pioneer in the development of EDTA applications,[5] who noted the high selectivity of thiaether sulfurs for metal ions in this portion of the periodic table which he called the "copper triangle".[6] This observation implies that, in mixtures of first-row transition metal ions, the macrocyclic polythiaethers could be used as highly selective reagents for Cu(II). However, even with the most favorable macrocyclic polythiaether ligands investigated to date, the Cu(II) complexes are relatively weak, with stability constants of 10^2–$10^5\ M^{-1}$,[3,4] making it difficult to achieve quantitative conditions.

In view of the foregoing observation, it seemed appropriate to investigate the possible exploitation of ligands containing thiaether sulfur donor atoms in combination with stronger donor atoms as selective reagents for Cu(II). The introduction of nitrogen donor atoms into the cyclic polythiaethers has been shown to increase the Cu(II) complex stability constants significantly.[7] At the same time, however, such substitutions greatly reduce ligand selectivity.

In considering the possible alternatives for exploiting thiaether selectivity for Cu(II), we decided to incorporate thiaether donor atoms into ligand structures in which the "stronger" donor atoms were sterically blocked relative to initial attack by external metal ions. This approach was suggested by studies conducted in our laboratory a number of years ago in which it was demonstrated that ligands containing tertiary amine nitrogens *in which all alkyl substituents are ethyl groups or larger*, such as in *N,N,N',N'*-tetraethylethylenediamine (TEEN, Figure 1), are seemingly incapable of coordinating to solvated metal ions due to problems associated with steric hindrance.[8] Nonetheless, when even

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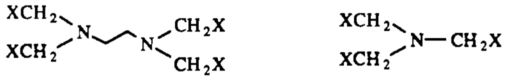


EDTA:	X = HOOC-	NTA:	X = HOOC-
Penten:	X = H_2NCH_2-	Tren:	X = H_2NCH_2-
TKED:	X = $HOCH_2$-	TEA:	X = $HOCH_2$-
TEMEED:	X = $CH_3CH_2SCH_2$-	TMMEA:	X = CH_3SCH_2-
		TEMEA:	X = $CH_3CH_2SCH_2$-
TEEN:	X = H_3C-	TMMPA:	X = $CH_3SCH_2CH_2$-
		TEMPA:	X = $CH_3CH_2SCH_2CH_2$-

Figure 1. Ligands discussed in this work.

relatively weak donor atoms, such as alcoholic oxygens, are substituted on the ends of such alkyl groups (e.g., TKED and TEA, Figure 1), complexation is facilitated since initial bonding can occur with the terminal donor atoms.[9,10] This observation is also consistent with independent studies, particularly by Margerum and co-workers,[11,12] in which it has been concluded that, in the reaction of metal ions with branched complexing agents such as ethylenediamine-*N,N,N′,N′*-tetraacetate (EDTA, Figure 1), initial bonding occurs with the carboxylate oxygens, after which coordination to the tertiary nitrogens is facilitated. It is presumed that the same principle should be applicable to a variety of branched ligand structures in which tertiary nitrogen donor atoms are surrounded by aliphatic chains containing weak donor atoms near the ends of the pendant arms. A survey of the available literature indicates that this strategy of combining strongly bonding, but sterically blocked, interior donor atoms with weak, but highly selective, peripheral donor atoms does not appear to have been exploited previously in any rigorous manner.[13]

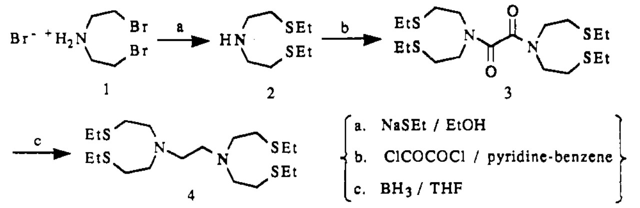
In the current investigation, we have synthesized and studied the branched amino polythiaether ligands designated as TEMEED [*N,N,N′,N′*-tetrakis(2-(ethylthio)ethyl)ethylenediamine], TEMEA [tris(2-(ethylthio)ethyl)amine], and TMMEA [tris(2-(methylthio)ethyl)amine] (Figure 1). Both the protonation constants of these ligands and the stability constants of their Cu(II) complexes have been measured as well as the kinetics of their reactions with Cu(II). Whereas the studies with TMMEA have been conducted in aqueous media, all measurements involving TEMEED and TEMEA have been carried out in 80% methanol–20% water (w/w) to circumvent their limited solubility in water. The ligands designated as TEMPA [tris(3-(ethylthio)propyl)amine] and TMMPA [tris(3-(methylthio)propyl)amine], containing trimethylene bridging groups, have also been synthesized but do not form complexes having measurable stability with the Cu(II) ion in aqueous and methanolic solvents. For these last two ligands, only the protonation constant determination for TMMPA has been included in this work.

The stability and kinetics of Cu(II) complex formation with TEMEED and TEMEA have also been studied in the presence of a large excess of several other transition metal ions to examine the ability of the latter ions to react with these specific ligands. The results suggest that, among the divalent first-row transition metal ions, this class of ligands is, indeed, highly selective for the Cu(II) ion.

Experimental Section

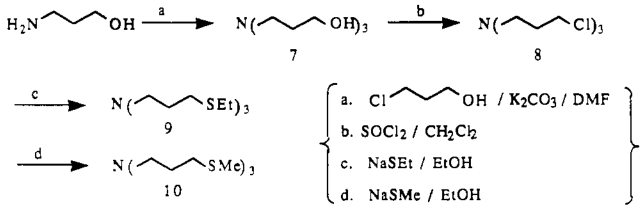
Ligand Syntheses. The specific details for all ligand syntheses are given in the supplementary material with only brief outlines provided here. The synthetic approach used for TEMEED is illustrated in Scheme I in which literature methods[14] were used to prepare bis(2-bromoethyl)ammonium bromide (**1**). [*Caution*: This is a potent vesicant!] This material was then condensed at low temperature under nitrogen atmosphere with ethanethiol [*Caution, stench*! Use a well-functioning fume hood!] to yield bis(2-(ethylthio)ethyl)amine (**2**). The latter compound was further condensed with oxalyl chloride in a 3:4 v/v mixture of pyridine/benzene to yield *N,N,N′,N′*-tetrakis(2-(ethylthio)ethyl)oxalamide (**3**), which was then reduced to TEMEED (**4**) using borane/THF in an adaptation of the general amide reduction of Brown and Heim.[15] The final product was obtained as a colorless oil and characterized as follows: IR (neat) ν_{max}, 2983, 2944, 2815, 2762, 1660, 1461, 1430, 1388, 1294, 1255, 1178, 1162, 1071, 994, 990, 763 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ 2.4–2.8 (m, 8 H), 1.21 (t, 3 H, J = 7.8 Hz); ^{13}C-NMR ($CDCl_3$), δ 55.33, 51.60, 34.05, 23.17, 15.45. (NOTE: Spectral characterization of all intermediate compounds and elemental analyses for all final products are provided in the supplementary material.)

Scheme I



a. NaSEt / EtOH
b. ClCOCOCl / pyridine-benzene
c. BH_3 / THF

Scheme II



a. Cl⁀⁀OH / K_2CO_3 / DMF
b. $SOCl_2$ / CH_2Cl_2
c. NaSEt / EtOH
d. NaSMe / EtOH

The tripodal ligands TMMEA (**5**) and TEMEA (**6**) were prepared by the general approach described for TMMEA by Morassi and Sacconi.[16] The final product for TEMEA was isolated by consecutive distillation to yield a colorless oil (bp 188–122 °C at 1 Torr) with the following characteristics: IR (neat) ν_{max}, 2976, 2945, 2870, 2818, 1675, 1444, 1372, 1266, 1113, 1061, 978, 752 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ 2.55 (m, 6 H), 1.18 (t, 3 H, J = 7.8 Hz); ^{13}C-NMR ($CDCl_3$), δ 47.62, 33.75, 24.68, 14.95.

Samples of TEMPA (**9**) and TMMPA (**10**) were prepared by the general method outlined in Scheme II in which 3-amino-1-propanol was condensed under nitrogen atmosphere with 3-chloro-1-propanol in basic DMF to yield tris(3-hydroxypropyl)amine (**7**). This material was then reacted with thionyl chloride in CH_2Cl_2 to generate tris(3-chloropropyl)amine (**8**). The latter compound was then reacted with ethanethiol or methanethiol in an ice cold solution of sodium ethoxide in ethanol to yield the desired TEMPA or TMMPA, each of which was purified by two successive distillations. For TEMPA: IR (neat) ν_{max}, 2952, 2933, 2840, 2801, 1705, 1456, 1375, 1258, 1160, 1103, 941, 755 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ 2.47 (m, 6 H), 1.67 (q, 2 H, J = 7.0 Hz), 1.23 (t, 3 H, J = 7.3 Hz); ^{13}C-NMR ($CDCl_3$), δ 53.07, 29.62, 27.31, 26.02, 14.83. For TMMPA: IR (neat) ν_{max}, 2945, 2918, 2847, 2805, 1705, 1433, 1360, 1278, 1235, 1111, 1053, 1005, 954, 760 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ 2.42 and 2.38 (overlapping t's, 4 H), 1.98 (s, 3 H), 1.60 (q, 2 H, J = 7.0 Hz); ^{13}C-NMR ($CDCl_3$), δ 52.87, 32.12, 26.81, 15.49.

Buffers and Solvents. To buffer the solutions for the kinetic and stability constant measurements, the sterically hindered diamine TEEN (*N,N,N′,N′*-tetraethylethylenediamine) (Figure 1) and the corresponding methylene bridged diamine TEMN (*N,N,N′,N′*-tetraethylmethylenediamine) were used, these ligands having been shown to be too sterically hindered to react with the solvated Cu(II) ion.[8,17] The sample of TEMN (particularly useful for buffering in the region of pH 3–4) was obtained (Alfa Products) as a distinctly orange-colored liquid, indicative of the presence of

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impurities, and was vacuum distilled to obtain a clear liquid. The TEEN was obtained (Eastman or Alfa Products) in 99% purity as a nearly colorless liquid and was also vacuum distilled. Methanol (Mallinckrodt, >99%) was used without further purification, the primary contaminant being water. Conductivity grade distilled–deionized water was used in the preparation of all solutions.

Metal Salts. Perchlorate salts of Na(I), Mn(II), Co(II), Ni(II), Cu(II), and Zn(II) were prepared by the slow addition of 70% $HClO_4$ (G. F. Smith Chemical Co.) to the reagent grade solid metal carbonates, following which the salts were recrystallized twice from water and air dried. (*Warning! Metal perchlorate salts may be explosive if heated to dryness!*) All transition metal ion solutions were standardized by EDTA titration. Ligand solutions were standardized potentiometrically by pH titration of the protonated ligand with standard NaOH solution. For this purpose, solutions of carbonate-free NaOH were prepared from saturated NaOH and standardized against primary standard potassium acid phthalate. New solutions were prepared shortly before use, and solution containers were sealed tightly to minimize contamination by CO_2.

Instrumentation. NMR spectra for all compounds were obtained on a Bruker NR/80 FT-NMR spectrometer. Infrared spectra were obtained on a Nicolet 5DXC FT-IR spectrometer. Solution molecular weights were obtained in $CHCl_3$ using a Hitachi-Perkin-Elmer 115 vapor phase osmometer. For column chromatography, Baker Analyzed Reagent silica gel (60–200 mesh) was utilized while TLC analyses were performed on Whatman MK6F, 60A, 1 × 3 in., 250-μm layer plates.

All pH measurements were made with an Orion 901 Microprocessor Ionalyzer standardized with aqueous buffers. For aqueous measurements, an Orion Research Ross Combination pH electrode was filled with 3 M NaCl (rather than KCl) to prevent possible precipitation of $KClO_4$ at the liquid junction. For pH measurements in 80% methanol/20% water (w/w), a conical pH sensing electrode was utilized in conjunction with an Orion double-junction reference electrode with removable sleeve, the outer chamber being filled with 0.1 M $NaClO_4$ in 80% methanol. Before nonaqueous pH measurements were made, the meter was first standardized with aqueous buffers and the electrodes were then conditioned by soaking in 80% methanol for 15–30 min. The meter readings were corrected to pH* values (referenced to infinite dilution in 80% methanol) by utilizing deLigny's published correction factor, δ, to account for differences in the liquid junction potential and medium effects:[18]

$$\mathrm{pH}^* = \mathrm{pH} - \delta$$

For 80% methanol, a value of $\delta = -0.08$ was used. (In subsequent sections, pH* is generally referred to simply as pH regardless of the solvent composition; in all cases, however, pH values are referenced to the standard state at infinite dilution in the solvent used.)

Protonation constants for all branched amino polythiaether ligands were determined by potentiometric titration of the protonated ligands with carbonate-free standardized NaOH solution. Solubility problems at higher pH values for TEMEED (pH > 2) and TEMEA (pH > 4) precluded titration of these ligands in aqueous media, and studies were restricted to 80% methanol/20% water. (In contrast, TMMEA is exceptionally soluble in water—up to 1 M.) Both water and methanol were boiled prior to use to eliminate dissolved CO_2 and were stored under nitrogen. The potentiometric pH titrations were also carried out under a stream of humidified nitrogen to minimize CO_2 absorption, and the temperature was maintained at 25.0 ± 0.1 °C by immersing the titration vessel in a thermostated holder through which water was circulated from a temperature bath. Ionic strength was maintained at 0.1 M with $NaClO_4$. At the concentration levels used (3–9 mM in ligand), the charge reduction upon neutralization did not result in a significant change in the ionic strength.

All kinetic measurements were carried out on a Durrum Model D-110 stopped-flow spectrophotometer equipped with glass and Kel-F tubing and fittings, and the temperature was controlled at 25.0 ± 0.2 °C with a circulating bath. The absorbance data were recorded in 8-bit resolution using a Biomation Model 810 buffered memory unit and analyzed in batch form on a Data General Eclipse S/130 computer.

Results

Ligand Protonation Constants. The ligand protonation equilibria may be written as

$$\mathrm{L} + \mathrm{H}^+ \rightleftharpoons \mathrm{HL}^+ \qquad (1)$$

$$\mathrm{HL}^+ + \mathrm{H}^+ \rightleftharpoons \mathrm{H_2L}^{2+} \qquad (2)$$

where L represents the unprotonated ligand species, the second reaction applying only for TEMEED. The corresponding equilibrium constants were treated as mixed-mode values in the form

$$K_{\mathrm{H1}}{}^{\mathrm{m}} = [\mathrm{HL}^+]/a_{\mathrm{H}}[\mathrm{L}] \qquad (3)$$

$$K_{\mathrm{H2}}{}^{\mathrm{m}} = [\mathrm{H_2L}^{2+}]/a_{\mathrm{H}}[\mathrm{HL}^+] \qquad (4)$$

where the terms in brackets represent molar concentrations and $a_H = 10^{-pH}$ is the apparent activity of the hydrogen ion. The pH data were collected manually and converted to $\bar{n}_H$ values as defined by Bjerrum[19]

$$\bar{n}_{\mathrm{H}} = \frac{[\mathrm{HL}^+] + 2[\mathrm{H_2L}^{2+}]}{[\mathrm{L}']} = \frac{C_{\mathrm{H}} - C_{\mathrm{OH}} + [\mathrm{OH}^-] - [\mathrm{H}^+]}{[\mathrm{L}']} \qquad (5)$$

where [L′] represents the total concentration of all protonated and unprotonated ligand species in solution ($[L] + [HL^+] + [H_2L^{2+}]$), and C_H and C_{OH} represent the total amount of strong acid (including protons initially on the ligand when starting with the ligand–HCl salts as well as added $HClO_4$) and strong base (NaOH) added, respectively, both terms being corrected for dilution at each point in the titration. The hydroxide and hydrogen ion concentrations were determined directly from the pH readings according to the relationships:[20]

$$[\mathrm{H}^+] = 10^{-\mathrm{pH}} d/\gamma_{\mathrm{H}}$$

$$[\mathrm{OH}^-] = K_{\mathrm{s}} d/(10^{-\mathrm{pH}} \gamma_{\mathrm{OH}})$$

In these expressions, d represents the solvent density (1.00 for H_2O, 0.8483 for 80% methanol),[20] K_s represents the solvent autoprotolysis constant at 25 °C ($10^{-14.00}$ for water, $10^{-14.42}$ for 80% methanol),[20] and γ_H and γ_{OH} represent the activity coefficients for hydrogen and hydroxide ions, respectively, as calculated from the extended Debye–Hückel equation at 25 °C and $\mu = 0.10$ M ($\gamma_H \approx \gamma_{OH} \approx \gamma_\pm = 0.825$ for water, 0.590 for 80% methanol).

For the monobasic ligands, the value of $K_{H1}{}^m$ was calculated for each point in the titration

$$K_{\mathrm{H1}}{}^{\mathrm{m}} = \bar{n}_{\mathrm{H}}/[a_{\mathrm{H}}(1 - \bar{n}_{\mathrm{H}})] \qquad (6)$$

utilizing all data in the region $0.2 \leq \bar{n}_H \leq 0.8$. In the case of TEMEED, it was anticipated that a more sophisticated treatment would be needed due to the presence of two K_H values.[7] However, it was found that the two K_H values differed by more than 10^4 so that $K_{H2}{}^m$ could be obtained for this latter ligand by applying an expression parallel to eq 6 {i.e., $K_{H2}{}^m = (\bar{n}_H - 1)/(a_H(2 - \bar{n}_H))$} to the data in the interval $1.2 \leq \bar{n}_H \leq 1.8$ with no loss in accuracy. The resulting protonation constants for all four ligands studied are listed in Table I.

Copper Complex Stability Constants. With the exception of TMMPA and TEMPA, each of the amino polythiaether ligands studied forms a 1:1 complex with Cu(II):

$$\mathrm{Cu}^{2+} + \mathrm{L} \rightleftharpoons \mathrm{CuL}^{2+} \quad K_{\mathrm{CuL}} \qquad (7)$$

for which the stability constant can be expressed in terms of molar concentrations. The strong Cu(II)–S charge-transfer bands

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Table I. Protonation Constants and Copper(II) Complex Stability Constants for the Branched Amino Polythiaether Ligands Studied in This Work in 80% Methanol or Aqueous Solution at 25 °C and μ = 0.10 M ($NaClO_4$)[a]

ligand	$\log K_{H1}{}^{m}$ [b]	$\log K_{H2}{}^{m}$ [b]	$\log K_{CuL}$	$10^{-3}\,\epsilon_{CuL}$, $M^{-1}\,cm^{-1}$
		80% Methanol		
TEMEED	7.45 (5)	3.0 (1)	10.0 (1)	6.73 (5)[c]
TEMEA	6.34 (5)		6.82 (6)	3.23 (4)[d]
TMMPA	7.86 (1)		very small	
		Aqueous		
TMMEA	8.22 (3)		6.02 (6)	6.8 (8)[e]

[a] In Tables I–V, values in parentheses represent standard deviations relative to the last significant figure listed (e.g., 7.45 (5) represents 7.45 ± 0.05). [b] Ligand concentrations used for protonation constant determinations (prior to dilution corrections) were as follows: TEMEED, 3.06 mM; TEMEA, 2.67 mM; TMMPA, 9.53 mM; TMMEA, 6.64 mM. [c] 404 nm, pH* 1.58, C_{Cu} = 0.16–2.00 mM, C_L = 0.00835 mM. [d] 372 nm, pH* 3.08, C_{Cu} = 0.56–3.20 mM, C_L = 0.0591 mM. [e] 375 nm, pH 5.00, C_{Cu} = 0.567–4.71 mM, C_L = 0.0332 mM.

in the visible spectrum made it possible to utilize the spectrophotometric approach of McConnell and Davidson,[21] which we have applied previously to the macrocyclic polythiaether complexes.[3,4] In the pH range accessible to aquacopper(II) ion, the ligands included in this work are extensively protonated so that the measurements made at a specific pH value are more readily evaluated in terms of the conditional stability constant values, designated as K_{CuL}',

$$K_{CuL}' = [CuL]/[Cu^{2+}][L'] = K_{CuL}/\alpha_L \qquad (8)$$

where (using Ringbom's convention)[22] α_L represents the reciprocal of the fractional concentration of free ligand which is in the unprotonated form as defined by the relationship

$$\alpha_L = [L']/[L] = 1 + K_{H1}{}^{m}a_H + K_{H1}K_{H2}{}^{m}a_H{}^2 \qquad (9)$$

Experimental values of K_{CuL}' at a specific pH value were determined by preparing a series of solutions containing a constant concentration of total ligand and variable concentrations of Cu(II) ion (in large excess). The absorbance values of these solutions were then measured spectrophotometrically at a selected wavelength, the latter values being plotted according to the expression (applicable for conditions where $C_{Cu} \gg C_L$)[3,4,21]

$$\frac{bC_L}{A} = \frac{1}{\epsilon_{CuL}} + \frac{1}{\epsilon_{CuL}K_{CuL}'C_{Cu}} \qquad (10)$$

where b represents the cell pathlength, A is the measured absorbance value, ϵ_{CuL} is the molar absorptivity of the CuL^{2+} complex, and C_L and C_{Cu} are the analytical concentrations of ligand and copper(II) ion (including both complexed and uncomplexed forms) in solution, respectively.

A typical plot of eq 10 is shown for the $Cu(TEMEED)^{2+}$ complex in Figure 2 from which the K_{CuL}' value is obtained as the intercept/slope ratio. The thermodynamic stability constant, K_{CuL}, was then calculated using the relationship in eq 8. The resultant values for all complexes included in this study are listed in Table I.

Copper(II) Complexation Kinetics. The kinetics for the reactions of Cu(II) with the various ligands were studied in aqueous solution for TMMEA and in 80% methanol for TEMEA and TEMEED. In all cases the kinetics conformed to the reversible rate equation

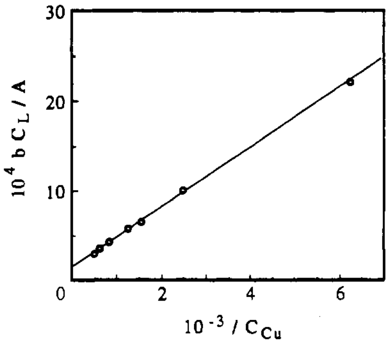

Figure 2. McConnell–Davidson plot (eq 12) for Cu^{II}(TEMEED) in 80% methanol at pH* 1.58, 25 °C, and μ = 0.10 M ($NaClO_4$). Absorbance data were obtained at 404 nm using a 5-cm cell. All solutions contained 8.35 μM TEMEED.

$$d[CuL^{2+}]/dt = k_f[Cu^{2+}][L'] - k_d[CuL^{2+}] \qquad (11)$$

where k_f and k_d represent, respectively, the formation and dissociation rate constants of the CuL^{2+} complex at the specific pH under investigation. Measurements were made under conditions where $C_{Cu} \gg C_L$ so that the observed kinetic behavior could be fitted to the pseudo-first-order expression

$$d[CuL^{2+}]/dt = k_{obs}[L'] \qquad (12)$$

which was conveniently plotted in the following integrated form:[23]

$$\ln\left\{\frac{[CuL^{2+}]_e}{[CuL^{2+}]_e - [CuL^{2+}]}\right\} = \ln\left\{\frac{A_e}{A_e - A_t}\right\} = k_{obs}t \qquad (13)$$

In eq 13, $[CuL^{2+}]_e$ and $[CuL^{2+}]$ represent the concentrations of the copper complex at equilibrium and at any time t, respectively, and A_e and A_t are the corresponding measured absorbance values.

A series of kinetic runs was made at each selected pH value involving five to eight different values of C_{Cu} spanning an approximately 10-fold range (with $C_{Cu} \geq 10\,C_L$). For each set of conditions, five to eight replicate measurements were made and the results statistically averaged. The mean values of k_{obs} were then plotted against $[Cu^{2+}]$ ($\approx C_{Cu}$) according to eq 14 to

$$k_f[Cu^{2+}] + k_d = k_{obs} \qquad (14)$$

yield k_f as the slope and k_d as the intercept. This was repeated for several pH values, generally covering at least one full pH unit or more. Statistically significant k_d values were obtained only in the case of the aqueous studies on TMMEA. The resulting k_f (and k_d) values for all three systems studied are tabulated in Tables II and III. [The individual k_{obs} data for all ligand systems (including the results of over 1000 individual kinetic runs) are available from the authors upon request.]

Competitive Thermodynamic Studies Involving Other Divalent Metal Ions. As a sensitive means of determining the extent of competition by other first-row transition metal ions for the amino polythiaether ligands, solutions containing the CuL^{2+} complexes were mixed with ≥100-fold excesses of Mn^{2+}, Co^{2+}, Ni^{2+}, and Zn^{2+} and allowed to equilibrate for several hours. The measured spectrophotometric absorbance of these solutions, using the CuL^{2+} absorbance peaks, showed no significant decrease in the amount of CuL^{2+} formed. These measurements indicated that Cu(II) ion formed much stronger complexes with these ligands than did any of the other metal ions tested, but the results did not preclude the possibility that some of these metal ions might form weak complexes in the absence of Cu(II) competition.

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(21) McConnell, H.; Davidson, N. *J. Am. Chem. Soc.* **1950**, *72*, 3164–3167. Potentiometric pH titrations in the absence and presence of added Cu(II) (Bjerrum's $\bar{n}_L$ method[19]), frequently utilized for systems of this type, were not suitable for obtaining accurate stability constant values for the complexes in the current study as the K_{CuL} values approach or exceed the maximum value ($K_{ML} \leq 10^7$) for which this method is useful.

(22) Ringbom, A. *Complexation in Analytical Chemistry*; Wiley-Interscience: New York, 1963.

(23) Pett, V. B.; Leggett, G. H.; Cooper, T. H.; Reed, P. R.; Situmeang, D.; Ochrymowycz, L. A.; Rorabacher, D. B. *Inorg. Chem.* **1988**, *27*, 2164–2169.

Table II. Second-Order Formation Rate Constants for the Reaction of Solvated Cu^{2+} Ion with the Amino Polythiaether Ligands TEMEED and TEMEA as a Function of pH in 80% Methanol at 25 °C and μ = 0.1 M ($NaClO_4$)

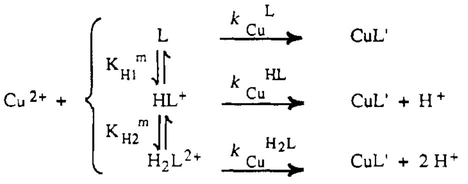
pH	$10^{-3}k_f$, M^{-1} s^{-1}	pH	$10^{-3}k_f$, M^{-1} s^{-1}
	TEMEED		
2.98	5.84 (6)	4.68	15.6 (9)
3.10	4.7 (1)	4.88	14.3 (3), 22.2 (3)
3.74	6.0 (2)	5.08	14.2 (3), 22.8 (7)
4.28	10.6 (4)	5.28	17.8 (9), 21 (1)
4.48	13 (1)		
	TEMEA		
3.10	0.74 (8)	4.68	35 (2)
3.82	5.4 (2)	4.88	42 (2), 51 (3)
4.11	9 (1)	5.08	71 (3)
4.28	18.1 (7)	5.28	87 (6)
4.48	25 (1)	5.28	130 (10)

Competitive Metal Complex Kinetic Studies. In an attempt to determine whether the foregoing divalent metal ions might form even very weak complexes with the branched amino polythiaether ligands, the kinetics of copper(II) reacting with TEMEED and TEMEA were remeasured in the presence of the same competing metal ions. In these experiments, the ligand was first mixed with a very large excess of the test metal ion and allowed to equilibrate for several hours to achieve thermodynamic equilibrium. The resulting equilibrated solution was then reacted with Cu^{2+} in the stopped-flow spectrophotometer. The resulting formation kinetics for CuL^{2+} were compared with the corresponding kinetic behavior in the absence of a second metal ion.

These latter kinetic measurements were undertaken on the basis of the presumption that the displacement of the second metal ion from the ligand by Cu(II) would be measurably slower than the reaction of Cu(II) with the free ligand, regardless of whether the Cu(II) ion formed a mixed metal ion intermediate, $MLCu^{4+}$, or reacted directly with the free ligand following ML^{2+} dissociation. The kinetic data were treated in a manner identical to that used in the previous studies in which no second metal ion was present. Most of these studies were carried out at pH 5.28 with a few measurements made at other pH values as specified. A summary of the resolved second-order formation rate constants, designated as k_f, for Cu(II) reacting with both TEMEED and TEMEA in the presence of Mn(II), Co(II), Ni(II), and Zn(II), is presented in Table IV.

Discussion

Resolution of Specific Formation Rate Constant Values. For each of the copper–amino polythiaether complexes included in this work, both the unprotonated and protonated species can conceivably contribute to the observed complexation kinetics.



On the basis of this scheme, it is apparent that the resolved second-order formation rate constant at each pH value, k_f, is a combination of the contributions of the individual ligand species, i.e.

$$k_f[L'] = k_{Cu}{}^{L}[L] + k_{Cu}{}^{HL}[HL^+] + k_{Cu}{}^{H_2L}[H_2L^{2+}] \qquad (15)$$

Table III. Second-Order Formation Rate Constants and First-Order Dissociation Rate Constants for the Reaction of Cu^{2+} with TMMEA as a Function of pH in Aqueous Solution at 25 °C and μ = 0.1 M ($NaClO_4$)

pH	$10^{-3}k_f$, M^{-1} s^{-1}	k_d, s^{-1}
4.90	2.6 (3)	5.1 (4)
5.00	2.72 (6)	5.2 (1)
5.10	3.2 (3)	5.4 (5)
5.30	6.5 (3)	4.6 (4)
5.40	7.1 (3)	4.5 (4)
5.50	10.1 (6)	5.2 (9)
5.60	11.4 (4)	4.1 (5)
5.70	16 (1)	4 (2)

Table IV. Experimental Formation Rate Constant Data for the Reaction of Solvated Cu(II) Ion with TEMEED and TEMEA in the Presence of Large Excesses of Mn(II), Co(II), Ni(II), and Zn(II) in 80% Methanol at 25 °C and μ = 0.10 M ($NaClO_4$)[a]

added metal ion	C_M, M	pH	experimental $10^{-3}k_f'$, M^{-1} s^{-1}	theoretical $10^{-3}k_f$, M^{-1} s^{-1} [b]
			TEMEED	
Mn^{2+}	0.03	5.28	20.0 (9)	21
Co^{2+}	0.015	4.88	14.4 (2)	15
	0.03	5.28	22.7 (4)	21
Ni^{2+}	0.0014	2.98	4.3 (5)	5
	0.0014	5.08	13.8 (5)	18
	0.0055	5.28	17.1 (3)	21
	0.011	5.28	16.0 (4)	21
Zn^{2+}	0.03	5.28	21.7 (5)	21
			TEMEA	
Mn^{2+}	0.03	5.28	110.5 (8)	98
Co^{2+}	0.015	4.88	44 (1)	41
Ni^{2+}	0.0014	5.28	69 (5)	98
Zn^{2+}	0.015	5.28	84 (2)	98

[a] For all competitive studies, $C_L \approx 0.014$ mM while C_{Cu} was varied over the range 0.14–1.4 mM. [b] Theoretical values were calculated using eq 20′ and the resolved $k_{Cu}{}^{L}$ and $k_{Cu}{}^{HL}$ values from Table V.

Equation 15 can be converted to a variety of expressions involving the dependence of the experimental formation rate constant on hydrogen ion activity, of which the two most useful are

$$k_f\alpha_L = k_{Cu}{}^{L} + k_{Cu}{}^{HL}K_{H1}{}^{m}a_{H+} + k_{Cu}{}^{H_2L}K_{H1}{}^{m}K_{H2}{}^{m}(a_{H+})^2 \qquad (16)$$

$$k_f\alpha_{HL} = k_{Cu}{}^{L}(K_{H1}{}^{m}a_{H+})^{-1} + k_{Cu}{}^{HL} + k_{Cu}{}^{H_2L}K_{H2}{}^{m}a_{H+} \qquad (17)$$

In the latter expression, α_{HL} represents the reciprocal mole fraction of the monoprotonated ligand species at any specific pH (cf., eq 9):

$$\alpha_{HL} = [L']/[HL^+] = (K_{H1}{}^{m}a_{H+})^{-1} + 1 + K_{H2}{}^{m}a_{H+} \qquad (18)$$

In eqs 16 and 17, the last term, representing the kinetic contribution of the diprotonated ligand species, is feasible only in the case of TEMEED, and even for that system, there was no evidence for a significant contribution of the H_2L^{2+} species to the overall kinetics of complex formation. In resolving the specific rate constants for each ligand species, therefore, the $k_{Cu}{}^{H_2L}$ term was omitted for all systems to yield the simplified linear relationships:

$$k_f\alpha_L = k_{Cu}{}^{L} + k_{Cu}{}^{HL}K_{H1}{}^{m}a_{H+} \qquad (16a)$$

$$k_f\alpha_{HL} = \frac{k_{Cu}{}^{L}}{K_{H1}{}^{m}a_{H+}} + k_{Cu}{}^{HL} \qquad (17a)$$

The formation rate constant data for all three ligand systems were plotted using both eqs 16a and 17a. As represented in Figures 3 and 4, eq 17a is the more advantageous expression for the TEMEA and TMMEA systems since the protonated species of these two ligands do not contribute significantly to the overall kinetics. As illustrated in Figure 5, plotting the TEMEED data

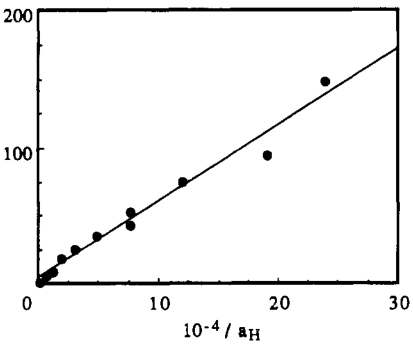


Figure 3. Resolution of the specific formation rate constants for Cu^{2+} reacting with TEMEA in 80% methanol at 25 °C and μ = 0.10 M ($NaClO_4$). Data were plotted using eq 17a.

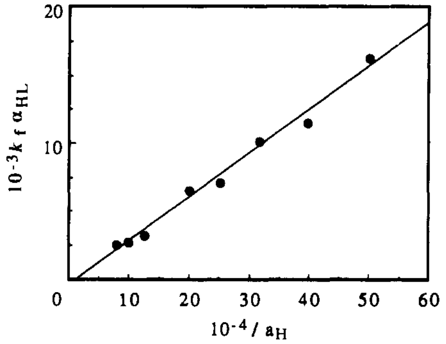


Figure 4. Resolution of the specific formation rate constants for Cu^{2+} reacting with TMMEA in aqueous solution at 25 °C and μ = 0.10 M ($NaClO_4$). Data were plotted using eq 17a.

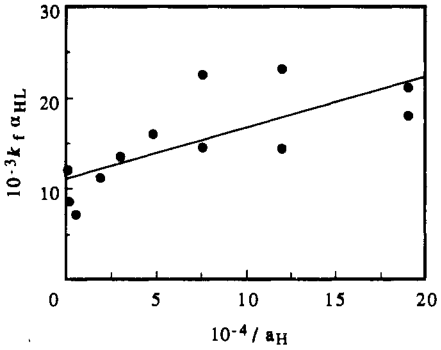


Figure 5. Resolution of the specific formation rate constants for Cu^{2+} reacting with TEMEED in 80% methanol at 25 °C and μ = 0.10 M ($NaClO_4$). Data were plotted using eq 17a. The larger scatter reflects the poor reproducibility of the experimental kinetic data at higher pH values and results in a large standard deviation for the $k_{Cu}{}^{L}$ value as determined from the slope.

utilizing eq 17a results in extensive scatter, although the resultant estimates of both $k_{Cu}{}^{L}$ and $k_{Cu}{}^{HL}$ are statistically significant. A similar value of the $k_{Cu}{}^{HL}$ value is obtained using eq 16a; however, the data at low pH dominate this plot and do not provide a statistically significant value for $k_{Cu}{}^{L}$. The difficulty in obtaining a precise value for $k_{Cu}{}^{L}$ with this system is largely attributable to the lack of reproducible data obtained for replicate studies at each of the higher pH values as noted in Table II, and it is in the higher pH region where the relative contribution of the unprotonated ligand to the overall kinetics is the most significant. However, the studies in the presence of the other transition metal ions serve to confirm the reported specific rate constants (vide infra). Optimal values of the resolved specific rate constants for all three ligand systems are tabulated in Table V.

Table V. Resolved Specific Rate Constant Values for Cu(II) Reacting with TEMEED, TEMEA, and TMMEA in 80% Methanol or Aqueous Solution at 25 °C and μ = 0.10 M ($NaClO_4$)

ligand	$10^{-6}k_{Cu}{}^{L}$, $M^{-1}\,s^{-1}$	$10^{-4}k_{Cu}{}^{HL}$, $M^{-1}\,s^{-1}$	k^{CuL}, s^{-1}
	80% Methanol		
TEMEED	1.6 (5)[a]	1.1 (2)	
TEMEA	1.22 (6)	$\ll 1$[b]	
	Aqueous		
TMMEA	5.3 (3)	$\ll 0.1$[b]	4.3 (3)
TEMEED	≈ 8[c]		
TEMEA	≈ 6[c]		
TKED	35[d]	5.4[d]	
TEA	30[d]		5.0×10^{3}[d]

[a] The value of $k_{Cu}{}^{L}$ is not well established; even at the highest pH studied, less than 50% of the observed k_f value is attributable to the unprotonated ligand species. [b] Linear regression analysis yielded statistically meaningless values for the specific formation rate constant involving the monoprotonated ligand species: TEMEA, $k_{Cu}{}^{HL} = 4.4\ (\pm 3.3) \times 10^{3}$ $M^{-1}\,s^{-1}$; TMMEA, $k_{Cu}{}^{HL} = -4.3\ (\pm 4.4) \times 10^{3}$ $M^{-1}\,s^{-1}$. [c] Estimates of $k_{Cu}{}^{L}$ for aqueous conditions are based on previous studies of Cu(II) reacting with macrocyclic polythiaether ligands in which it was found that the estimated $k_{Cu}{}^{L}$ values in aqueous solution were approximately 5 times larger than the values obtained in 80% methanol.[24] [d] Reference 25.

In a similar manner, two specific dissociation rate constants can be considered for the TMMEA system from the experimental k_d values

$$k_d = k^{CuL} + k_H{}^{CuL}a_{H+} \tag{19}$$

where k^{CuL} and $k_H{}^{CuL}$ represent the unaided and proton-aided complex dissociation processes, respectively. Applying this expression to the k_d data in Table III yields $k^{CuL} = 4.3\ (\pm 0.3)$ s^{-1} (Table V) while the value for $k_H{}^{CuL} = 8.9\ (\pm 3.9) \times 10^{4}$ M^{-1} s^{-1} is not statistically significant at the 99% confidence level. Thus, we can draw no conclusions regarding the magnitude of the latter constant. With regards to the former constant, however, it is worth noting that the ratio $k_{Cu}{}^{L}/k^{CuL} = 1.2 \times 10^{6}$ for TMMEA is in excellent agreement with the stability constant value obtained experimentally ($K_{CuL} = 1.0 \times 10^{6}$) from direct equilibrium measurements (Table I).

Interpretation of the Specific Rate Constant Values. Previous studies on the kinetics of solvated Cu(II) ion reacting with macrocyclic and acyclic polythiaether ligands in methanol/water mixtures led us to conclude that the $k_{Cu}{}^{L}$ values obtained in 80% methanol were consistently 0.19 times the value obtained for aqueous solution.[24] This was attributed to the decreased reactivity of the various mixed-solvated Cu(II) species, of the general formula $Cu(CH_3OH)_n(H_2O)_{6-n}{}^{2+}$, compared to the more reactive hexaaqua species, $Cu(H_2O)_6{}^{2+}$, as a result of a reduction in Jahn–Teller distortion (and a corresponding delabilization of axial solvent molecules) upon removing d-orbital degeneracy when all donor atoms in the inner-coordination sphere are not identical. If the same ratio of reactivity can be presumed to apply to the amino polythiaether ligands studied in this work, we can obtain reasonable estimates of $k_{Cu}{}^{L}$ for both TEMEED and TEMEA in aqueous solution. These aqueous estimates are included in Table V.

As noted in the Introduction, the direct reaction of solvated metal ions with tertiary nitrogens, in which all of the appended substituents are ethyl or larger, does not appear to be sterically feasible.[8] As a result, the first bond formation between Cu^{2+} and the amino polythiaethers must involve bond formation with one of the sulfur donor atoms. The proposed step-by-step mechanism for the complexation reaction, as illustrated in Figure 6, is identical with that which we have discussed in our previous investigations on the alcoholic analogues of the branched amino polythiaethers TEA and TKED[25] (depicted in Figure 1). From those earlier studies we concluded that the terminal alcoholic oxygens were

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(24) 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 (Table V).

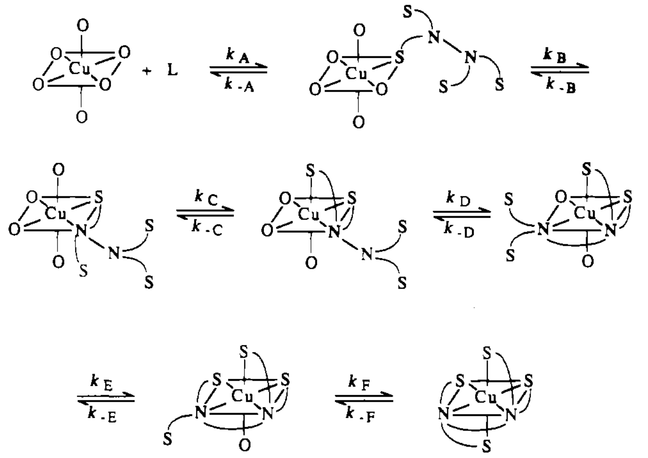

Figure 6. Schematic representation of the stepwise mechanism for Cu^{2+} complexation by TEMEED (each "O" represents a coordinated solvent molecule). Although all four sulfur donor atoms are shown as coordinated in the final product, it is likely that only two sulfurs are actually bonded to the Cu(II) ion on a time-averaged basis.

involved in the first bond formation step. We also proposed that the initial Cu–O bonds dissociate readily so that the rate-determining step is represented by the second-bond formation involving the proximal nitrogen donor to close the first chelate ring (equivalent to step k_B in Figure 6). As outlined below, a similar argument can be developed for the amino polythiaether ligands in the current study.

On the basis of a number of kinetic studies involving solvated Cu^{2+} reacting with simple ligands in solution, it is estimated that first-bond formation should occur with a second-order rate constant of about 2×10^8 M^{-1} s^{-1} in aqueous solution at 25 °C in the absence of steric and electrostatic effects.[25-27] The steric effects associated with bonding to an atom substituted by two groups which are ethyl or larger (as is the case with the sulfur donor atoms in TEMEA and TEMEED) is estimated to be approximately 50-fold based on studies with secondary amine nitrogens.[8] For ligands with multiple donor atoms, the rate constant may be increased statistically by the number of donor atoms available for first bond formation. This line of reasoning suggests that $k_A \approx (1\text{–}2) \times 10^7$ M^{-1} s^{-1} (i.e., $2 \times 10^8 \div 50 \times 4$) might be anticipated in aqueous solution. It is noted that the experimental k_{Cu}^{L} values generated are within a factor of 2 of this value. However, we believe that this estimate may be off by as much as an order of magnitude since the same steric factors may not apply to the larger sulfur donor atoms, containing two lone electron pairs, as were previously determined for amine nitrogens. Therefore, other factors need to be considered.

The apparent absence of any kinetic contribution for the protonated ligand species for both TMMEA and TEMEA indicates that the nitrogen donor atom must be unprotonated at the time of the rate-determining step. This observation is particularly noteworthy in the case of TMMEA where the large protonation constant results in a ratio of $[HL^+]/[L] > 10^3$ for the lowest pH values studied. Only in the case of TEMEED, where two nitrogen donor atoms are available for complexation, does the monoprotonated ligand species show evidence of competitive reactivity. Since we cannot account for the observed formation rate constants in terms of a mechanism in which Cu^{2+} bonds directly to the nitrogens, we infer that the initial bond formation must involve a sulfur donor atom (step k_A) and that subsequent coordination to the proximal nitrogen (step k_B) to complete the first chelate ring is the rate-determining step (see Figure 6).

Comparison of the aqueous k_{Cu}^{L} value obtained directly for TMMEA with the estimated aqueous values generated for the other two ligand systems (Table V) reveals that there is no significant difference in the reactivity of the three unprotonated ligands. This is somewhat surprising since one might expect that the terminal ethyl substituents on TEMEED and TEMEA would provide a greater degree of steric hindrance relative to the initial bond formation process than would the terminal methyl groups on TMMEA. However, any such differences are apparently smaller than the error inherent in extrapolating the k_{Cu}^{L} values for TEMEED and TEMEA to aqueous conditions. The absence of an accelerative kinetic effect for the diamine TEMEED ligand also implies that this ligand is not sufficiently basic to promote hydrogen bonding between the second nitrogen and a coordinated water molecule at the time of the rate-determining step—the so-called internal conjugate base (ICB) effect—as has been observed with more basic diamine ligands.[8-10]

If the initial bond formation to the donor atoms in the branches represents a prior equilibrium (i.e., $K_A = k_A/k_{-A}$ in Figure 6) preceding the rate-determining step, then the 10-fold decrease in the k_{Cu}^{L} values observed in the case of the branched amino polythiaether ligands relative to TEA and TKED (Table V) must represent a combination of the greater steric hindrance associated with first bond formation in the amino polythiaether complexes and the differences in the bond strength for the initially formed Cu–S bonds relative to the Cu–O bonds initially formed with the amino polyalcohols. Previous studies in our laboratories have suggested that, for copper(II) ion bonding to amine nitrogens, the rate constant for primary amines is about 10 times faster than that for secondary amines (where the substituent groups are ethyl or larger). If the same ratio applies to sulfur donor atoms, the entire difference in the k_{Cu}^{L} values for TKED relative to TEMEED and for TEA relative to TEMEA could be ascribed to differences in the rate constant for the first-bond formation step (k_A in Figure 6), indicating that the dissociation rate constant for the first Cu(II)–thiaether sulfur bond (k_{-A} in Figure 6) is on the same order of magnitude as the corresponding constant for the Cu(II)–alcoholic oxygen bond.

Copper(II) Selectivity Relative to Other Transition Metal Ions. As noted in the Introduction, thiaether sulfur donor atoms appear to be highly selective for only a few metal ions in their commonly occurring oxidation states in aqueous solution. In particular, it was proposed that the branched structure represented by the current series of ligands might result in complexes of measurable stability being formed only with Cu(II) among the divalent first-row transition metal ions, since the other metal ions of this series might not be expected to gain a sufficient "toehold" on the sulfur atom prior to completing the first chelate ring as the rate-determining step.

As noted in the Results section, competitive thermodynamic studies were conducted involving solutions containing a branched amino polythiaether ligand, Cu(II) ion, and a competing divalent first-row transition metal ion (Mn^{2+}, Co^{2+}, Ni^{2+} or Zn^{2+}), the latter being present in 100-fold excess over Cu^{2+}. In each case, no decrease was observed in the absorbance value of the intense CuL^{2+} peak in the 372–404-nm region (Table I). These observations led us to conclude that these ligands are, indeed, highly selective for Cu^{2+}. Moreover, these results permit us to establish an upper limit for the stability constants of the ML complexes based on the ratio of the two stability constant

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[25] Moss, D. B.; Lin, C.-T.; Rorabacher, D. B. *J. Am. Chem. Soc.* **1973**, *95*, 5179–5185.

[26] Sokol, L. S. W. L.; Fink, T. D.; Rorabacher, D. B. *Inorg. Chem.* **1980**, *19*, 1263–1266.

[27] (a) Maass, G. *Z. Phys. Chem.* (*Frankfurt*) **1968**, *60*, 138–151. (b) Pearlmutter, A. F.; Stuehr, J. *J. Am. Chem. Soc.* **1968**, *90*, 858–862. (c) Eisenstadt, M.; Friedman, H. L. *J. Chem. Phys.* **1968**, *48*, 4445–4448. (d) Harada, S.; Tsuji, Y.; Yasunaga, T. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1930–1931. (e) Diebler, H.; Rosen, Ph. *Ber. Bunsen-Ges. Phys. Chem.* **1972**, *76*, 1031–1034.

expressions as represented by the relationship

$$K_{ML} = \left(\frac{[ML^{2+}][Cu^{2+}]}{[CuL^{2+}][M^{2+}]}\right)K_{CuL} \qquad (20)$$

Since a change in absorbance of 1% or more should have been observable, we presume that $[ML^{2+}] \leq 0.01\,[CuL^{2+}]$. Moreover, in all experiments, $[M^{2+}] \approx 100\,[Cu^{2+}]$. Thus, based on eq 20, we conclude that, in all cases, $K_{ML} \leq 1 \times 10^{-4}K_{CuL}$. Whereas, this places an upper limit on the metal complex stability constant values, it does not preclude the possibility that some degree of ML complex formation could occur in the absence of competing Cu(II).

In the subsequent kinetic studies, both the ligand and M^{2+} were mixed together and allowed to sit for several hours to assure the attainment of thermodynamic equilibrium. These solutions were then combined with Cu^{2+} in the stopped-flow spectrophotometer and the resulting kinetic measurements were used to determine whether any measurable complexation was taking place with these other metal ions. This approach is illustrated by

$$Cu^{2+} + \left\{\begin{array}{lcl} M^{2+} + L & \xrightarrow{k_{Cu}{}^{L}} & CuL^{2+} + M^{2+} \\ K_{ML} \downarrow\!\uparrow & & \\ \quad ML^{2+} & \xrightarrow{k_{Cu}{}^{ML}} & CuL^{2+} + M^{2+} \end{array}\right.$$

If ML^{2+} complexes are formed to any significant extent, it was reasoned that the effect should be observed as a marked perturbation in the CuL^{2+} complexation kinetics regardless of whether the subsequent reaction with Cu^{2+} occurred by a direct displacement (as represented by the rate constant $k_{Cu}{}^{ML}$) or by dissociation of the ML^{2+} complex followed by rapid reaction of the ligand with Cu^{2+}.[28] In all cases the second metal ion was present at concentration levels 100–3000 times larger than the ligand concentration and up to 30 times greater than the amount of added Cu^{2+} (see Table VI).

If the conditional stability constants under the experimental conditions used were $K_{ML}' \geq 10^2$, the presence of 10^{-2} M excess M^{2+} should result in at least 50% complexation of the ligand at the time of mixing with Cu^{2+} and would presumably affect the observed formation kinetics for CuL^{2+} unless ML^{2+} dissociation (or $MLCu^{4+}$ formation) were extremely rapid. In estimating the magnitude of the anticipated effect of ML^{2+}, we note that the rate constant for ML^{2+} dissociation can be estimated from the relationship $k_d{}^{ML} = k_M{}^{L}/K_{ML}$ where, at maximum, the $k_M{}^{L}$ values should be from 10^2 to 10^5 smaller than the corresponding values for Cu^{2+}.[29] Under these circumstances, the respective estimates of $k_d{}^{ML}$ for Mn^{2+}, Co^{2+}, Ni^{2+}, and Zn^{2+} are ≤ 1, 10^{-3}, 10^{-4}, and 1 s^{-1},[29] which would cause dramatic effects on the observed CuL^{2+} formation kinetics if ML^{2+} dissociation were a factor. Moreover, since Cu(II)–thiaether sulfur bonds are quite weak, a mixed $MLCu^{4+}$ species, particularly in the case of TEMEA, would not be expected to lead to much faster displacement kinetics.

Table VI. Comparative Stability Constants of Complexes Formed by Related Branched Ligands with Mn(II), Co(II), Ni(II), Cu(II), and Zn(II)[a]

ligand	log K_{H1}	log K_{H2}	log K_{MnL}	log K_{CoL}	log K_{NiL}	log K_{CuL}	log K_{ZnL}
			Sexadentate Ligands				
EDTA	10.26^b	6.16^b	14.04^b	16.31^b	18.62^b	18.80^b (13.3)^c	16.50^b
Penten	10.20^d	9.70^d	9.37^d	15.75^d	19.30^d	22.44^d (6.8)^c	16.24^d
TKED	8.38^e	4.37^e	?	4.8^f	6.5^e	8.52^g (5.6)^c	4.74^g
TEMEED	7.45^{h,i}	3.0^h	<4^{h,j}	<4^{h,j}	<4^{h,j}	10.0^{h,k} (8.0)^c	<4^{h,j}
			Quadridentate (Tripodal) Ligands				
NTA	9.73^l	2.49^l	7.44^m	10.4^l	11.54^l	12.96^l	10.66^l
Tren	10.29^n	9.59^n	5.8^n	12.8^n	14.8^n	18.8^n	14.6^n
TEA	7.70^o		?	2.25^p	2.76^p	4.07^p	2.05^p
TEMEA	6.34^{h,i}		<3^{h,j}	<3^{h,j}	<3^{h,j}	6.8^{h,k}	<3^{h,j}

[a] Unless otherwise specified, all values are for aqueous solution at 25 °C and μ = 0.1 M. [b] 20 °C (log K_{H3} = 2.67, log K_{H4} = 2.00): Schwarzenbach, G.; Gut, R.; Anderegg, G. *Helv. Chim. Acta* **1954**, *37*, 937–957. [c] Conditional stability constant (log K_{CuL}') at pH 5.5. [d] 20 °C (log K_{H3} = 9.14, log K_{H4} = 8.56): Schwarzenbach, G.; Moser, P. *Helv. Chim. Acta* **1953**, *36*, 581–597. [e] Reference 9. [f] Reference 10. [g] μ = 0.5 M: Hall, J. L.; Dean, W. E.; Pacofsky, E. A. *J. Am. Chem. Soc.* **1960**, *82*, 3303–3308. [h] 80% methanol: This work. [i] By analogy to TKED and other substituted amines, the aqueous values should be log $K_{H1} \approx 8.2$ for TEMEED, ≈ 7.1 for TEMEA.[20] [j] Maximum stability constants for TEMEA are based on both competitive thermodynamic studies and kinetic Cu(II) "displacement" studies in this work; for TEMEED, the maximum values listed are those obtained from kinetic displacement studies, the thermodynamic maxima being 2 orders of magnitude higher at log $K_{ML} \leq 6$ (see text). [k] By analogy to Cu(II)–polythiaether complexes, the aqueous value should be log $K_{CuL} \geq 11.0$ for TEMEED, ≥ 7.8 for TEMEA: (a) Reference 24. (b) Nazarenko, A. Y.; Izatt, R. M.; Lamb, J. D.; Desper, J. M.; Matysik, B. E.; Gellman, S. H. Submitted for publication in *Inorg. Chem.* [l] 20 °C (log K_{H3} = 1.89): Schwarzenbach, G.; Gut, R. *Helv. Chim. Acta* **1956**, *34*, 1589–1599. [m] 20 °C: Schwarzenbach, G.; Freitag, E. *Helv. Chim. Acta* **1951**, *34*, 1492–1508. [n] 20 °C (log K_{H3} = 8.56): Prue, J. E.; Schwarzenbach, G. *Helv. Chim. Acta* **1950**, *33*, 963–974. [o] Bates, R. G.; Allen, G. F. *J. Res. Natl. Bur Std.* **1960**, *64A*, 343–346. [p] Hancock, R. D.; Nakani, B. S. *J. Coord. Chem.* **1984**, *13*, 309–314.

As indicated by the data in the fourth and fifth columns in Table IV, the CuL^{2+} formation rate constants obtained in the presence of Mn^{2+}, Co^{2+} and Zn^{2+}, designated as k_f', are clearly within experimental error of the theoretical values predicted in the absence of these metal ions as calculated using eq 16a (applying the $k_{Cu}{}^{L}$ and $k_{Cu}{}^{HL}$ values listed in Table V). In the presence of Ni^{2+} ion, the k_f' values for both TEMEED and TEMEA average about 10–20% smaller than the values obtained in the absence of competing metal ions. This is still within the presumed experimental error. Moreover, for TEMEED the observed decrease is reasonably consistent over the pH range 2.98–5.28 and does not appear to be significantly dependent upon the total Ni^{2+} concentration over the range of conditions tested. These observations are inconsistent with Cu^{2+} displacement of Ni^{2+} from NiL^{2+} since the latter complex should be decreased in stability by over 2 orders of magnitude at pH 2.98 relative to 5.28, and increasing the value of $[Ni^{2+}]$ should decrease the dissociation rate. Thus, the kinetic results for Ni^{2+} are not consistent with NiL^{2+} formation and must be ascribed to experimental error. In fact, we conclude that the conditional stability constants with all four competing metal ions must be well below 10^2 at pH 5.28 for both TEMEA and TEMEED. On the basis of the α_L values at this pH, the maximum values of the thermodynamic stability constants for these other metal ions are then estimated to be $\leq 10^3$ for TEMEA and $\leq 10^4$ for TEMEED. Whereas these maximum values for K_{ML} are essentially identical to our estimates based on the competitive thermodynamic studies in the case of TEMEA, the maximum K_{ML} values for TEMEED

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(28) Since complex formation reactions involving Cu^{2+} are generally much faster than similar reactions of any of the other metal ions listed, it is assumed that CuL^{2+} formation should not be the rate-determining step (cf. Diaddario, L. L., Jr.; Ochrymowycz, L. A.; Rorabacher, D. B. *Inorg. Chem.* **1992**, *31*, 2347–2353).

(29) For simple complex formation reactions, in which first-bond formation is the rate-determining step, the rate constants for the various divalent metal ions are expected to be in the ratio of their observed rate constants for water loss (ref 12). On the basis of this premise, Mn^{2+}, Co^{2+}, Ni^{2+}, and Zn^{2+} should exhibit values which are 10^{-2}, 10^{-4}, 10^{-5}, and 10^{-2} times those of Cu^{2+}, respectively, at a comparable pH leading to maximum k_f values with TEMEED of about 10^2, 1, 0.1, and 10^2 $M^{-1}\,s^{-1}$, respectively, at pH 5.28 and 25 °C. (On the basis of the assumption that the second-bond formation step is rate determining, and the fact that these other metal ions appear to form much weaker bonds with thiaether sulfurs than does Cu(II), these ratios should be even smaller.) If the *conditional* stability constants, K_{ML}', were $\geq 10^2$ for these metal ions under these conditions, the resultant estimated k_d values would be ≤ 1, 10^{-3}, 10^{-4}, and 1 s^{-1}, respectively.

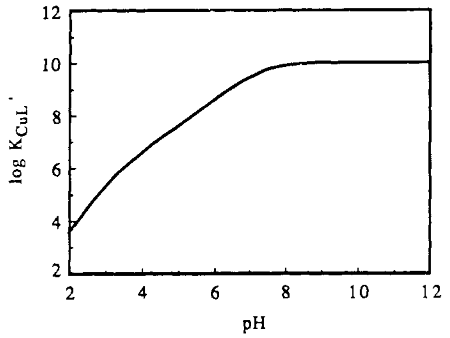


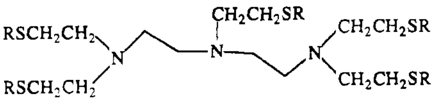
Figure 7. Plot of the conditional stability constant for Cu^{II}(TEMEED) as a function of pH* in 80% methanol.

are reduced by 2 orders of magnitude. These estimated maximum K_{ML} values are included in Table VI.

Conclusions. The strategy of placing highly selective (though weakly bonding) thiaether sulfur donor atoms on the ligand periphery while embedding strongly bonding nitrogen donor atoms in the ligand interior in a series of branched amino polythiaethers has proved to be successful in generating ligands with a high degree of selectivity for Cu(II). As illustrated by the comparative stability constant values in Table VI, the relative preference of TEMEED for Cu(II) is markedly enhanced compared to the case of closely related ligands. For quadridentate (tripodal) ligands, only Tren comes close to the amino polythiaether ligands in its preference for Cu(II) over Ni(II).

Although the CuL^{2+} stability constants with the amino polythiaethers are not extremely large, the ligand protonation constants are sufficiently small that quantitative complexation of Cu(II) can be achieved at pH values below the point where solvated Cu(II) normally precipitates as the hydroxide. A plot of the conditional stability constant as a function of pH* in 80% methanol is illustrated for the Cu(II)–TEMEED system in Figure 7, which shows that a value of $K_{CuL}' = 10^8$ is achieved at pH 5.5. Thus, a 0.01 M solution of Cu(II) can be 99.9% complexed by a stoichiometric quantity of ligand under these conditions. The comparative K_{CuL}' values at pH 5.5 for the other sexadentate branched ligands are included (in parentheses) in Table VI. It will be noted that, under these conditions, only EDTA is as effective a complexing agent for Cu(II) at this pH and its level of selectivity is very poor.

The high selectivity of the branched poly(amino thiaether) ligands for Cu(II) suggests their possible application as therapeutic agents for Wilson's disease. Due to the low solubility of the TEMEED and TEMEA ligands in aqueous solution, these latter two ligands may also be useful as selective extraction agents for Cu(II). For applications in which greater solubility in water is desired, it is suggested that methanolic groups could be substituted in place of the terminal ethyl groups (i.e., X = $HOCH_2SCH_2$– in Figure 1) without significantly altering the other properties associated with these ligands. We suggest that it may also be possible to increase the magnitude of the Cu(II) complex stability constants, while preserving the selective character of these ligands, by inserting another sterically hindered amine nitrogen donor atom into the ligand to produce a substituted diethylenetriamine structure of the type



Although the current studies have shown measurable complex stabilities only with Cu^{2+}, it is clear from a number of studies on related ligands that the branched amino polythiaether ligands should also be excellent complexing agents for second- and third-row metal ions within the "copper triangle", specifically Pd(II), Pt(II), Ag(I), Au(I), and Hg(II).

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Supplementary Material Available: Text giving detailed synthetic procedures for all ligands described in this work (4 pages). Ordering information is given on any current masthead page.