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Water-Soluble Crown Thia Ethers: Investigation of pH, Anion, and Steric Effects on the Equilibria and Kinetics of Aquocopper(II) Ion Reacting with Alcoholic Derivatives of a Macrocyclic Tetrathia Ether Ligand

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Water-soluble derivatives of the 14-membered macrocyclic tetrathia ether, 1,4,8,11-tetrathiacyclotetradecane ([14]aneS₄), have been synthesized by substituting a hydroxy group on the β-carbon of one or both of the propylene linkages to yield ligands designated as [14]aneS₄-ol and [14]aneS₄-diol, respectively. The latter ligand is obtained as a mixture of cis and trans isomers, which can then be separated on the basis of their differing solubilities. The aqueous stability constants of the complexes formed by aquocopper(II) ion with these ligands have been determined at 25 °C (in units of M⁻¹) in the presence of 0.10 M ClO₄⁻ yielding values of log K equal to 4.34 for [14]aneS₄, 4.69 for [14]aneS₄-ol, 3.89 for *trans*-[14]aneS₄-diol, and 3.12 for *cis*-[14]aneS₄-diol. Comparative data obtained in 0.10 M NO₃⁻ for one of these alcoholic derivatives indicate that, like that for the parent compound, the stability constants are enhanced by the formation of an adduct with the ClO₄⁻ ion. Corresponding kinetic measurements on these Cu(II) complexes at 25 °C in 0.10 M ClO₄⁻ yield formation rate constants of 13 × 10⁴, 1.4 × 10⁴, 0.60 × 10⁴, and 0.13 × 10⁴ M⁻¹ s⁻¹ for [14]aneS₄, [14]aneS₄-ol, *trans*-[14]aneS₄-diol, and *cis*-[14]aneS₄-diol, respectively. The observed effects of the hydroxy substituents upon the ligand reactivity are attributed to a combination of steric and solvation effects. All of the thermodynamic and kinetic parameters investigated appear to be independent of pH over the accessible range of pH 1-5.5.

Introduction

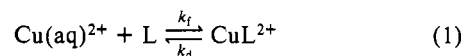
Earlier studies on macrocyclic polythia ether ligands have revealed that, of the common aquometal ions, only Cu(II), Pd(II), Ag(I), and Hg(II) [and, by analogy, Pt(II) and Au(I)] show a significant affinity for the cyclic tetrathia ether species in aqueous solution.^{2,3} As a result, these compounds represent potentially useful reagents for these specific metal ions. Moreover, due to their complete lack of protonation behavior, these ligands complex equally well at any pH, including highly acidic media.

The Cu(II) complexes formed with a variety of polythia ether ligands have also been shown to exhibit unusual spectral⁴ and

electrochemical⁵ properties and, as such, have proven useful for probing the electron-transfer behavior of the Cu(II)/Cu(I) redox couple,⁶ a matter of considerable interest in view of the biological importance of this couple. Partly for this reason, we have previously focused attention upon the thermodynamic⁷ and kinetic⁸ properties of an entire series of cyclic and open-chain aliphatic polythia ether complexes with Cu(II). However, quantitative studies on these complexes in aqueous solution have been hampered by the limited solubility of the unsubstituted polythia ethers in water.

In the current report, we direct our attention to the synthesis and characterization of two alcoholic derivatives of 1,4,8,11-tetrathiacyclotetradecane ([14]aneS₄), the macrocyclic compound previously demonstrated to form the most stable complex with Cu(II). These derivatives retain the same high level of selectivity and pH independence as the parent compound while exhibiting much higher aqueous solubility.

To compare the relative properties of these derivatized ligands, we have determined the value of their stability constants as well as the rate constants for the formation and dissociation of their Cu(II) complexes in aqueous solution (eq 1). In performing these



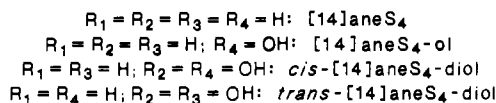
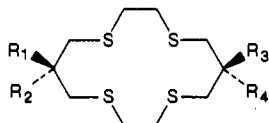
measurements, we have taken advantage of the higher ligand concentration levels attainable with these derivatized ligands to examine more fully the possible influence of pH and anion concentration on the specific kinetic parameters. In addition, in

- (1) (a) Wayne State University. (b) University of Wisconsin at Eau Claire.
 (2) (a) Young, I. R., M.S. Thesis; Wayne State University: Detroit, 1981. (b) Jones, T. E.; Sokol, L. S. W. L.; Rorabacher, D. B.; Glick, M. D. *J. Chem. Soc., Chem. Commun.* **1979**, 140-141. (c) Alcock, N. W.; Herron, N.; Moore, P. *J. Chem. Soc., Dalton Trans.* **1978**, 394-399. (d) Que, M.; Kimura, K.; Shono, T. *Anal. Chim. Acta* **1987**, *194*, 293-298 and references therein.
 (3) Due to their hydrophobic tendencies, the tetrathia ether ligands dissolve well in many organic solvents and, in fact, form stable complexes with other metal ions in solvents of lower dielectricity (e.g.: Smith, G. F.; Margerum, D. W. *J. Chem. Soc., Chem. Commun.* **1975**, 807-808). Much recent activity has also focused on the special stabilities generated by hexathia ether coordination as found for 1:1 complexes formed with 1,4,7,10,13,16-hexathiacyclooctadecane ([18]aneS₆) and bis complexes formed with 1,4,7-trithiacyclononane ([19]aneS₃), often in aqueous solution, by a variety of metal ions including the following: Co(II) and Co(III) [(a) Hartman, J. R.; Hints, E. J.; Cooper, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 1208-1214. (b) Wilson, G. S.; Swanson, D. D.; Glass, R. S. *Inorg. Chem.* **1986**, *25*, 3827-3829. (c) Küppers, H.-J.; Neves, A.; Pomp, C.; Ventur, D.; Wiegardt, K.; Nuber, B.; Weiss, J. *Inorg. Chem.* **1986**, *25*, 2400-2408]; Ni(II) [Thorne, C. M.; Rawle, S. C.; Admans, G. A.; Cooper, S. R. *Inorg. Chem.* **1986**, *25*, 3848-3850]; Cu(I) and Cu(II) [(a) Gould, R. O.; Lavery, A. J.; Schröder, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1492-1493. (b) Hartman, J. R.; Cooper, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 1202-1208]; Ru(II) [(a) Bell, M. N.; Blake, A. J.; Schröder, M.; Küppers, H.-J.; Wiegardt, K. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 250-251. (b) Rawle, S. C.; Cooper, S. R.; *J. Chem. Soc., Chem. Commun.* **1987**, 308-309]; Rh(II) [Holder, A. J.; Schröder, M.; Stephenson, T. A. *Polyhedron* **1987**, *6*, 461-463]; Pd(II) and Pd(III) [(a) Blake, A. J.; Holder, A. J.; Hyde, T. I.; Schröder, M. *J. Chem. Soc., Chem. Commun.* **1987**, 987-988. (b) Blake, A. J.; Holder, A. J.; Hyde, T. I.; Roberts, Y. V.; Lavery, A. J.; Schröder, M. *J. Organomet. Chem.* **1987**, *323*, 261-270]; Ag(I) and Ag(II) [(a) Küppers, H.-J.; Wiegardt, K.; Tsay, Y.-H.; Krüger, C.; Nuber, B.; Weiss, J. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 575-576. (b) Clarkson, J.; Yagbasan, J.; Blower, P. J.; Rawle, S. C.; Cooper, S. R. *J. Chem. Soc., Chem. Commun.* **1987**, 950-951]; Pt(II) and Pt(III) [(a) Blake, A. J.; Gould, R. O.; Lavery, A. J.; Schröder, M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 274-276. (b) Blake, A. J.; Gould, R. O.; Holder, A. J.; Holder, A. J.; Hyde, T. I.; Lavery, A. J.; Odulate, M. O.; Schröder, M. *J. Chem. Soc., Chem. Commun.* **1987**, 118-120]. Cf.: Cooper, S. R. *Acc. Chem. Res.* **1988**, *21*, 141-146.

- (4) (a) Jones, T. E.; Rorabacher, D. B.; Ochrymowycz, L. A. *J. Am. Chem. Soc.* **1975**, *97*, 7485-7486. (b) Ferris, N. S.; Woodruff, W. H.; Rorabacher, D. B.; Jones, T. E.; Ochrymowycz, L. A. *Ibid.* **1978**, *100*, 5939-5942.
 (5) (a) Dockal, E. R.; Jones, T. E.; Sokol, W. F.; Engerer, R. J.; Rorabacher, D. B.; Ochrymowycz, L. A. *J. Am. Chem. Soc.* **1976**, *98*, 4322-4324. (b) Bernardo, M. M.; Robandt, P. V.; Schroeder, R. R.; Rorabacher, D. B., submitted for publication.
 (6) (a) Martin, M. J.; Endicott, J. F.; Ochrymowycz, L. A.; Rorabacher, D. B. *Inorg. Chem.* **1987**, *26*, 3012-3022. (b) Rorabacher, D. B.; Bernardo, M. M.; Vande Linde, A. M. Q.; Leggett, G. H.; Westerby, B. C.; Martin, M. J.; Ochrymowycz, L. A. *Pure Appl. Chem.* **1988**, *60*, 501-508.
 (7) (a) Sokol, L. S. W. L.; Ochrymowycz, L. A.; Rorabacher, D. B. *Inorg. Chem.* **1981**, *20*, 3189-3195. (b) Young, I. R.; Ochrymowycz, L. A.; Rorabacher, D. B. *Ibid.* **1986**, *25*, 2576-2582.
 (8) 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.

comparing the kinetic behavior of these ligands to that of the unsubstituted parent compound, we have also attempted to interpret the effect of the added ring substituents in terms of the presumed mechanism for complex formation and dissociation.

The ligands discussed in this work include 3,6,10,13-tetrathiaacyclotetradecanol ([14]aneS₄-ol) and 3,6,10,13-tetrathiaacyclotetradecan-1,8-diol ([14]aneS₄-diol). The latter ligand exists as both *cis* and *trans* isomers, and studies on both the isomeric mixture and the separated isomers are reported.



Experimental Section

Reagents. Reagent grade Cu(NO₃)₂ (Allied Chemical Corp.) was recrystallized from hot water. Cu(ClO₄)₂ was prepared by the dropwise addition of reagent grade HClO₄ (70%, G. F. Smith Chemical Co.) to an aqueous suspension of CuCO₃ followed by recrystallization from water. Similarly, NaClO₄ was prepared by the dropwise addition of reagent grade HClO₄ to a relatively concentrated solution of NaOH followed by recrystallization from water. The stock copper solutions were standardized by titration with EDTA using murexide as the indicator. Nearly saturated stock solutions of each ligand were prepared by stirring a slurry of the solid ligand in water overnight and filtering off any undissolved material. These stock ligand solutions were standardized either spectrophotometrically (at 390 nm) as the Cu(II) complex in the presence of excess copper ion⁹ or by potentiometric titration with Hg(II).¹⁰ Borate-mannitol buffers were employed for pH control for kinetic experiments at pH 4.5 and above as these have been demonstrated not to complex with Cu(II).¹¹ All solutions were maintained at 0.1 M ionic strength by the addition of reagent grade NaNO₃ (Allied Chemical Corp.) or NaClO₄ as indicated. Distilled-deionized water of conductivity grade was used in preparing all solutions.

Ligand Syntheses. The macrocyclic polythia ether alcohols were synthesized by potassium ion templation-enhanced condensation of ω,ω-dithiols with ω,ω-bis(chlorohydrins) in basic DMF.¹² The generalized procedure involves dropwise addition of an approximately 2 M DMF solution of 1:1 reactant equivalents to an efficiently stirred 2 molar equiv suspension of finely milled anhydrous potassium carbonate in a large volume of DMF, heated under a nitrogen atmosphere at 80–100 °C. Slow addition of a single solution of reactants assures constant reactant proportions at high dilution without need for separate, difficult to synchronize addition apparatus. At room temperature no precondensation of reactants in neutral DMF was observed even after a week.

Synthesis of [14]aneS₄-ol. A mantle-heated, creased, three-necked, round-bottom, 5-L flask was fitted with a Tru-bore stirrer and two Claisen adaptors. To the adaptors were connected a nitrogen sweep, immersion thermometer, a 500-mL pressure-equalizing addition funnel, and a condenser. The whole apparatus, maintained under nitrogen for the duration, was vented through a mineral oil seal. The flask was charged with 3 L of DMF and 113.2 g (0.82 mol) of finely milled K₂CO₃ and stirred to maintain suspension. To the hot (100 °C) DMF suspension was added dropwise over 28 h a 200-mL solution containing 91.2 g (0.4

mol) of 3,7-dithianonane-1,9-dithiol (TTU)¹³ and 51.2 g (0.4 mol) of 1,3-dichloro-2-propanol (Aldrich No. 18,448-9) in DMF. After the reaction mixture was allowed to come to room temperature, salts were removed by suction filtration and DMF was removed at 80 °C/18 Torr on a rotary evaporator. The residue oil was taken up in 1.5 L of methylene chloride, heated with 3 g of charcoal, filtered, and reconcentrated on a rotary evaporator. Remaining volatiles were removed by Kugelrohr evaporation at 70 °C/0.01 Torr to yield 109.5 g of pale yellow oil, which solidified on standing overnight at room temperature.

The solid cake was dispersed in 150 mL of boiling CCl₄ and eluted on a 8 × 60 cm silica gel column with 1:10 (v/v) acetone/hexane mixed solvent. The mobile forerun components were obtained in the first liter of eluent followed by the pure (*R_f* ~0.4) component, which was completely eluted in the next 5 L to yield 44.5 g (39.2%) of concentrated solid. A single bulk recrystallization from 1.2 L of 1:10 (v/v) ether/hexane yielded 38.3 g of needle crystals, mp = 112 °C. Solution molecular weight in benzene: calcd (for C₁₀H₂₀OS₄), 284; found, 282 ± 3 (*n* = 5). IR (melt): 3450, 2050, 2895, 1422, 1265, 1205, 1070, 1025, 820, 690, 680 cm⁻¹. ¹H NMR (CDCl₃): δ 3.9 (m, 1, *J* ≈ 3 Hz), 3.15 (d, 1, *J* ≈ 3 Hz, D₂O → 0), 2.85 (three-line m overlapping adjacent t, 12), 2.68 (t, 4, *J* ≈ 7 Hz), 1.92 and 1.90 (set of q, 2, *J* ≈ 7 Hz). Anal. Calcd for C₁₀H₂₀OS₄: C, 42.21; H, 7.09; S, 45.08. Found: C, 42.24; H, 7.30; S, 44.88.

Synthesis of 1,10-Dichloro-4,7-dithiadicane-2,9-diol (DDD). Epichlorohydrin (Aldrich No. E105-5; 180.0 g (2 mol)) and 94.2 g (1 mol) of 1,2-ethandithiol (Aldrich No. E360-0) were dissolved in 1 L of absolute ethanol in a loosely stoppered, magnetically stirred, water-bath-cooled, 2-L Erlenmeyer flask. Upon addition of 4 mL of triethylamine, a vigorous reaction ensued. The temperature rose to 55 °C within 1/2 h. The reaction was allowed to stir for 6 h. The solution was heated with 8 g of activated charcoal, filtered, and concentrated with a rotary evaporator. Remaining solvent and trace elements were stripped with Kugelrohr evaporation at 60 °C/0.05 Torr to yield 266.5 g (95.8%) of TLC pure DDD as a nearly colorless oil. (A 20-g sample decomposed upon attempted vacuum Kugelrohr distillation at 140 °C/0.05 Torr with off-gassing and dark glass formation.) The oil product was consistent with high purity by spectroscopic analysis and generally consistent with theory by elemental analysis and is stable to prolonged storage at -20°.

Synthesis of [14]aneS₄-diol. The synthesis of this compound followed essentially the same procedure as that used for [14]aneS₄-ol (above). With the use of proportional solvent and base equivalents, 93.3 g (0.35 mol) of DDD and 32.9 g (0.35 mol) of 1,2-ethandiol reacted to yield 99.2 g of paste residue after charcoal treatment and volatiles evaporation by Kugelrohr. The residue, dispersed in 100 mL of boiling CCl₄, was first flash chromatographed on a 8 × 70 cm silica gel column with 1:2.5 (v/v) acetone/CCl₄ with 7 L of recycled solvent, yielding three cuts: 6 g of oil product contaminated by starting materials and forerun, 28.5 g of TLC pure solid product, and 13 g of product contaminated with higher polymers. The TLC pure cuts were recrystallized from 600 mL of 1:2 (v/v) acetone/hexane to yield an initial crop of 16.2 g (mp 106–107 °C) and a second crop of 9.3 g from 200 mL of solvent (mp 84–88 °C). High resolution showed overlapping spots indicative of two isomers in both crops. IR and ¹H NMR (60 MHz) spectroscopy and elemental analysis were indistinguishable for the crops. Crop one was estimated to contain a *trans*:*cis* ratio of 2.6:1 and crop two one of 0.7:1. The following represents data for the first crop. Solution molecular weight in benzene: calcd (for C₁₀H₂₀O₂S₄), 300; found, 302 ± 5 (*n* = 5). IR (melt): 3420, 2910, 2895, 1435, 1415, 1350, 1290, 1275, 1210, 1085, 1040, 835, 705, 690 cm⁻¹. ¹H NMR (CDCl₃): δ 4.15 (q, 2, *J* ≈ 5.5 Hz, after D₂O), 3.14 (center of ABB, seen essentially as doublet, 8, *J* ≈ 5.5), 2.93 (s, 8), 2.3 (broad s, 2, D₂O → 0). Anal. Calcd for C₁₀H₂₀O₂S₄: C, 39.96; H, 6.71; S, 42.68. Found: C, 41.14; H, 6.81; S, 42.11.

Separation of the two geometric isomers was performed by fractional crystallization, the *cis* isomer being much more soluble in both aqueous and organic media. The *trans* isomer was isolated by dissolving the *cis*/*trans* mixture in absolute ethanol on a steam bath, filtering the undissolved impurities, and slowly cooling the solution to room temperature to obtain the pure *trans* crystals. After removal of the *trans* isomer, the *cis* isomer was recrystallized several times from an 80% acetone-hexane mixture.

A tedious isolation of 30 mg of the presumed *cis* isomer as the bicyclosuccinato diester led to the appropriate assignment of the two isomers. As shown in Figure 1, these are cleanly resolved by ¹³C NMR (DMSO-*d*₆, 300 MHz): *cis* isomer, δ 69.590, 37.674, and 32.307; *trans* isomer, δ 68.385, 37.143, and 31.334. The NMR spectra indicated that each isomer was >99% pure. The pure *cis* and *trans* isomers melted at 105 and 145 °C, respectively.

- (9) In view of the effect of perchlorate ion upon the complex stability constant,⁷ the addition of ≥1 M ClO₄⁻ improves the quantitation of this method; for better accuracy, a spectrophotometric titration procedure may be carried out on the Cu(II)-polythia ether solution with Hg(II) as the titrant.
- (10) For potentiometric titrations against standard aquomercury(II) ion solutions with a mercury pool electrode, the end points are frequently sharper if the ligand is used as the titrant.
- (11) Moss, D. B.; Lin, C.-T.; Rorabacher, D. B. *J. Am. Chem. Soc.* **1973**, *95*, 5179–5185.
- (12) Kellogg and Buter have demonstrated that cesium ion provides nearly double the enhancement of cyclization to linear polymerization to that accorded by potassium ion in template syntheses of macrocyclic polythia ethers (Buter, J.; Kellogg, R. M. *J. Org. Chem.* **1981**, *46*, 4481–4485). However, we have determined that, for hydroxy-substituted macrocyclic thia ethers, cesium ion affords only about a 25% yield advantage and the sufficient potassium ion templation affords an overwhelming cost advantage, particularly in large-scale procedures.

- (13) TTU was synthesized by the method of Rosen and Busch: Rosen, W.; Busch, D. H. *J. Am. Chem. Soc.* **1969**, *91*, 4694–4697.

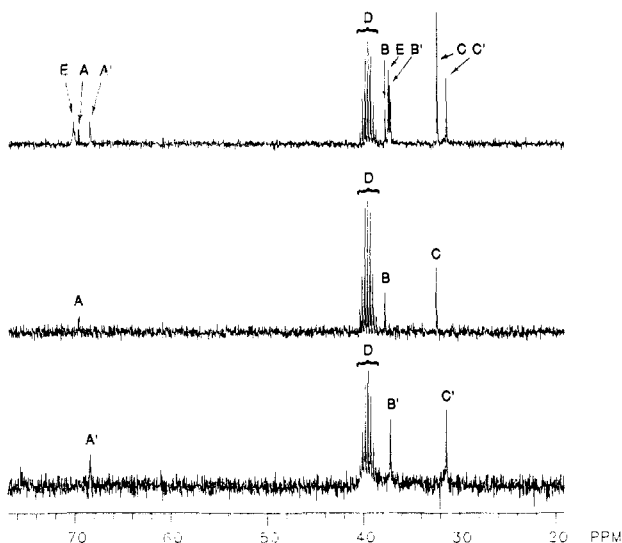


Figure 1. ^{13}C NMR spectra (300 MHz) for the *cis,trans*-[14]ane S_4 -diol mixture (top) and corresponding spectra for the purified *cis* isomer (center) and *trans* isomer (bottom). The peaks are assigned as follows: A and A' represent the β -carbons and B and B' the α -carbons in the propylene bridges, and C and C' represent the carbons in the ethylene bridges. (The septuplet labeled D is from the solvent, $\text{DMSO}-d_6$, while the two peaks labeled as E in the isomer mixture are from an unidentified impurity that was removed during the separation process.)

Stability Constant Determinations. Stability constants were determined spectrophotometrically by using a Cary Model 17D dual-beam recording spectrophotometer equipped with a thermostated cell compartment. Temperature was controlled to within $\pm 0.2^\circ$ with a circulating water bath as noted below.

Kinetic Measurements. Kinetic measurements were made by using a Durrum Model D-110 stopped-flow spectrophotometer equipped with glass and Kel-F tubing and fittings. Temperature control of $\pm 0.2^\circ\text{C}$ was maintained by the use of a Forma Scientific Model 1095 temperature bath circulating around the cell block and drive syringes. The absorbance data from the stopped-flow instrument were recorded in digital form by using a Biomation Model 810 buffered memory unit. The digital output was transmitted either to a Data General Nova 3 or a Tektronix type 564B storage oscilloscope (equipped with Type 2A63 differential amplifier and Type 2B67 time base plug-in units). The data were analyzed on a Data General Eclipse 5/130 computer. Four to seven replicate kinetic runs were performed for each set of conditions with the results statistically averaged.

All reactions were monitored at 390 nm, the absorbance maximum for the Cu(II) complexes; neither the free aquocopper(II) ion nor the free ligand absorb significantly in this region. In all cases, Cu(II) was in large excess over the ligand concentration, making it unnecessary to establish the latter value accurately.

The pH values of the reactant solutions were measured on either an Orion Model 801A digital pH meter equipped with a Markson gel-filled combination electrode or an Orion 901 Microprocessor Ionalyzer equipped with an Orion Research Ross combination pH electrode. For all pH measurements, temperature was maintained within $\pm 0.1^\circ\text{C}$ of the temperature used for the corresponding kinetics.

Results

Stability Constant Measurements. Since the Cu(II) complexes included in this study are relatively weak, the method of McConnell and Davidson¹⁴ was employed to determine the values of the conditional stability constant, $K_{\text{CuL}'}$ (eq 2), from spectro-

$$K_{\text{CuL}'} = \frac{[\text{CuL}']}{[\text{Cu}'][\text{L}']} \quad (2)$$

photometric data. In this equation, $[\text{CuL}']$, $[\text{Cu}']$, and $[\text{L}']$ represent the total concentrations of the copper complex and all species of the uncomplexed copper ion and ligand, respectively.

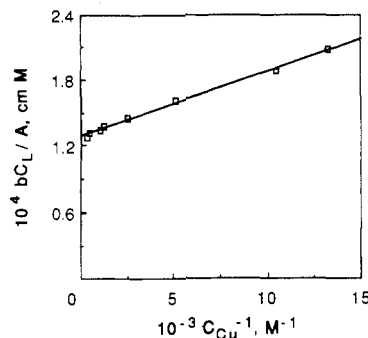


Figure 2. Typical plot of spectrophotometric data utilizing eq 3 to determine the equilibrium constant for aquocopper(II) ion reacting with [14]ane S_4 -ol in aqueous solution to yield CuL as the reciprocal of the intercept and $K_{\text{CuL}'}$ as the intercept/slope ratio. Conditions for the plot shown: $\lambda = 390\text{ nm}$, $b = 10.0\text{ cm}$, $C_L = 8.0 \times 10^{-6}\text{ M}$, pH 5.50 (borate-mannitol buffer system), 25.0°C , $\mu = 0.10\text{ M}$ (NaNO_3).

Table I. Experimental Stability Constants and Molar Absorptivity Values at Visible Peak Maxima As Determined for the Copper(II) Complexes Formed with Derivatized [14]ane S_4 Ligands at 25°C , 0.10 M (ClO_4^- or NO_3^-)^a

coordinated ligand	anion present	$10^{-3}\epsilon_{\text{CuL}}$		$10^{-3}K_{\text{CuL}'}$, M^{-1}
		390 nm	570 nm	
[14]ane S_4	ClO_4^-	8.0 ^b	1.9 ^b	21.8 ^b
	NO_3^-			11.0 ^b
[14]ane S_4 -ol	ClO_4^-	8.4 (1)	1.2 (1)	49 (2)
	NO_3^-	7.3 (1)	1.2 (1)	21.7 (6)
<i>trans</i> -[14]ane S_4 -diol	ClO_4^-	8.7 (1)	1.1 (1)	7.8 (3)
<i>cis</i> -[14]ane S_4 -diol	ClO_4^-	8.6 (0)	1.1 (1)	1.31 (4)

^a In this and the succeeding tables, the numbers in parentheses represent the standard deviation values for the final digits listed; thus, 8.4 (1) represents 8.4 ± 0.1 . ^b Reference 7.

As utilized in this study, this method involves using a series of solutions with constant ligand concentration (although this parameter could be varied) and a varying concentration of Cu(II), which was always present in large excess. The absorbance data were then plotted in the form^{7,14}

$$\frac{bC_L}{A} = \frac{1}{\epsilon_{\text{CuL}}} + \frac{1}{\epsilon_{\text{CuL}}K_{\text{CuL}'C_{\text{Cu}}}} \quad (3)$$

where b represents the path length of the spectrophotometric cell, A represents the measured absorbance, ϵ_{CuL} is the molar absorptivity of the Cu(II)-polythia ether complex, $K_{\text{CuL}'}$ is the stability constant for the $\text{Cu}^{\text{II}}\text{L}$ complex, and C_{Cu} and C_L are the analytical concentrations of Cu(II) and ligand, respectively, as represented by the relationships

$$C_{\text{Cu}} = [\text{Cu}'] + [\text{CuL}'] \quad (4)$$

$$C_L = [\text{L}'] + [\text{CuL}'] \quad (5)$$

In general, C_L values of $(1-5) \times 10^{-5}\text{ M}$ were used for the stability constant determinations with C_{Cu} in 10- to 100-fold excess.

If bC_L/A is plotted against C_{Cu}^{-1} , the value of $K_{\text{CuL}'}$ is obtained as the intercept/slope ratio as illustrated in Figure 2 for the $\text{Cu}^{\text{II}}([\text{14]aneS}_4\text{-ol})$ complex. From these plots the values determined for the stability constants of the three complexes included in this work are in the range of 10^3 - 10^4 at 25°C in the presence of 0.10 M NO_3^- and/or in 0.10 M ClO_4^- ion (Table I).

Kinetic Measurements. Due to the relatively small magnitude of the stability constants for the three complexes studied, the Cu(II) complexes were not fully formed under the conditions used for the kinetic studies. The observed reversible rate expressions are then of the form

$$\frac{d[\text{CuL}']}{dt} = k_f[\text{Cu}'][\text{L}'] - k_d[\text{CuL}'] \quad (6)$$

Since a large excess of Cu(II) was used in all cases, $C_{\text{Cu}} \approx [\text{Cu}']$ and substitution of eq 4 and 5 into eq 6 followed by integration

(14) McConnell, H.; Davison, N. *J. Am. Chem. Soc.* **1950**, *72*, 3164-3167. The spectrophotometric method described was initially reported by Benesi and Hildebrand; Benesi, H. A.; Hildebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703-2707.

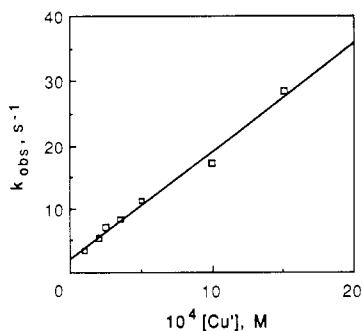


Figure 3. Typical plot of experimental pseudo-first-order kinetic data for the reaction of aquocopper(II) ion with [14]aneS₄-ol utilizing eq 9 to resolve the second-order formation rate constant, k_f , as the slope and the first-order dissociation rate constant, k_d , as the intercept. Each point represents the statistical average of about six replicate kinetic runs with standard deviations of approximately 1%. Conditions for the plot shown: pH 5.50 (borate-mannitol buffer system), 25.0 °C, $\mu = 0.10$ M (NaNO₃).

yields the linear relationship given in eq 7. This is conveniently analyzed in terms of absorbance data as shown in eq 8.

$$\ln \left[\frac{[\text{CuL}']_e}{[\text{CuL}']_e - [\text{CuL}']} \right] = k_{\text{obsd}} t \quad (7)$$

$$\ln \left[\frac{A_e}{A_e - A_t} \right] = k_{\text{obsd}} t \quad (8)$$

In the foregoing expressions, $[\text{CuL}']_e$ and $[\text{CuL}']$ represent the concentration of the copper complex at equilibrium and at any time t , respectively; A_e and A_t are the observed absorbance at equilibrium and at time t , respectively; and k_{obsd} is the observed pseudo-first-order rate constant defined by the relationship

$$k_{\text{obsd}} = k_f[\text{Cu}'] + k_d \quad (9)$$

For most of the kinetic studies, initial ligand concentrations were in the range of $(1-5) \times 10^{-5}$ M with copper concentrations varied from 10- to 100-fold in excess. A typical plot of eq 9 is shown in Figure 3 for the Cu^{II}([14]aneS₄-ol) system.

As noted in the Experimental Section, the synthesis of [14]aneS₄-diol yielded a mixture of the *cis* and *trans* isomers. When this mixture was used for kinetic studies with aquocopper(II), plots of eq 8 appeared to be linear and reproducible. Moreover, consistent values of k_f and k_d were obtained for this isomeric mixture from plots of eq 9 by using a wide variety of conditions, indicating that the kinetic behavior of the two species were too similar to be independently resolved. [Although the resolved formation rate constants for the two isomers differ by nearly a factor of 5 (vide infra), under the experimental conditions used, the contribution of the k_d values to k_{obsd} (eq 9) resulted in k_{obsd} ratios ranging from nearly unity ($C_{\text{Cu}} \approx 10^{-4}$ M) to approximately three ($C_{\text{Cu}} \approx 10^{-3}$ M). Thus, plots of eq 8 exhibited minimal curvature over the portion of the reaction used for calculating the overall k_{obsd} value (i.e., 20–90% reaction).]

In view of the fact that the *cis,trans*-[14]aneS₄-diol mixture was more readily available (compared to the purified isomers) and its kinetics appeared to be well-behaved, this mixture was used in studies surveying the pH dependence of reaction 1 and in studies on the comparative kinetic behavior of these systems in the presence of ClO₄⁻ and NO₃⁻. Similar studies were also run with pure [14]aneS₄-ol. Kinetic measurements were also made on these same two systems as a function of temperature to obtain activation parameters—although no specific significance is attributed to the activation parameters for the mixture. Finally, the reaction kinetics of the purified *cis* and *trans* isomers of [14]aneS₄-diol were studied at 25 °C at a pH of 1.5 in 0.10 M ClO₄⁻. The resolved k_f and k_d values at 25 °C for all systems studied are tabulated in Table II while the results obtained at other temperatures are listed in Table III.

Table II. Resolved Formation and Dissociation Rate Constants for the Complexes Formed between the Aquocopper(II) Ion and 14-Membered Cyclic Tetrathia Ether Ligands at 25 °C, $\mu = 0.1$ M

coordinated ligand	anion present	pH	$10^{-4}k_f$, M ⁻¹ s ⁻¹	$k_d(\text{exptl})$, s ⁻¹	$k_d(\text{calcd})$, ^a s ⁻¹
[14]aneS ₄	ClO ₄ ⁻	1.0	13 ^b	6 ^c	6
[14]aneS ₄ -ol	ClO ₄ ⁻	1.5	1.38 (8)	2.6 (6) ^d	0.3
	NO ₃ ⁻	1.5	1.32 (12)	2 (1) ^d	0.6
	NO ₃ ⁻	4.5	1.33 (9)	3.6 (7) ^d	0.6
	NO ₃ ⁻	5.5	1.67 (8)	2.1 (6) ^d	0.8
<i>trans</i> -[14]aneS ₄ -diol	ClO ₄ ⁻	1.5	0.60 (1)	0.58 (9)	0.8
<i>cis</i> -[14]aneS ₄ -diol	ClO ₄ ⁻	1.5	0.130 (3)	1.75 (2)	1.0
<i>cis,trans</i> -[14]aneS ₄ -diol (mixture)	ClO ₄ ⁻	1.5	0.39 (3)	1.4 (2)	
	ClO ₄ ⁻	4.7	0.41 (2)	0.9 (7)	
	NO ₃ ⁻	1.4	0.36 (2)	1.9 (2)	
	none ^e	3.1–3.9	0.32 (1)	1.5 (2)	
	NO ₃ ⁻	4.8	0.318 (7)	1.9 (2)	
	NO ₃ ⁻	5.1	0.36 (1)	1.5 (3)	
	NO ₃ ⁻	5.3	0.30 (2)	2.8 (6)	
	NO ₃ ⁻	5.5	0.31 (2)	2.1 (4)	
	NO ₃ ⁻	5.8	0.47 (3)	1.0 (1)	

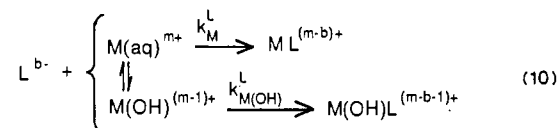
^aCalculated values of the dissociation rate constant were computed as $k_d(\text{calcd}) = k_f/K_{\text{CuL}}$. ^bExtrapolated to aqueous conditions from studies in methanol-water mixtures.⁸ ^cDetermined from measured dissociation kinetics of Cu^{II}L formed in flash photolysis experiments from the rapid oxidation of the corresponding Cu^IL complex: Martin, M. J.; Rorabacher, D. B., unpublished results as cited in ref 8. ^dThe experimentally determined values for the dissociation rate constant, $k_d(\text{exptl})$, for the [14]aneS₄-ol complex are relatively imprecise since in all cases the complexation reaction (eq 1) goes far to the right. ^eBoth nitrate and perchlorate ion present only at very low concentration levels (≤ 0.001 M).

Table III. Temperature Dependence of the Formation Rate Constants for Aquocopper(II) Ion Reacting with Selected Tetrathia Ether Ligand Systems in Aqueous Solution, $\mu = 0.10$ M (NO₃⁻)

complexed ligand	temp, °C	$10^{-3}k_f$, M ⁻¹ s ⁻¹	ΔH^\ddagger , kJ mol ⁻¹	ΔS^\ddagger , J K ⁻¹ mol ⁻¹
[14]aneS ₄ -ol	5.0	5.4 (12)	42 (3)	-23 (10)
	15.0	9.6 (10)		
	25.0	16.8 (8)		
	35.0	36 (4)		
<i>cis,trans</i> -[14]aneS ₄ -diol (mixture)	15.0	1.71 (5)	52 (7)	-15 (5)
	25.0	3.6 (2)		
	30.1	3.7 (3)		
	35.0	5.77 (8)		

Discussion

Effect of pH on Complex Formation Kinetics. For many aquometal ions, the presence of a coordinated hydroxide has been shown to labilize the remaining inner-sphere water molecules resulting in increased ligand substitution reaction rates.¹⁵ This effect is particularly pronounced for trivalent metal ions where $k_{\text{M(OH)}^L}/k_{\text{M}^L}$ ratios (eq 10) as large as 10^3 – 10^5 have been reported



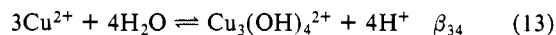
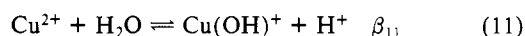
for Fe(III) after correcting for electrostatic factors.¹⁵ Although data are much more limited for divalent metal ions, a $k_{\text{M(OH)}^L}/k_{\text{M}^L}$ ratio of 10 has been reported for Ni(II) ion.¹⁶

Hydroxo species of copper(II) form more readily than with most other divalent metal ions as can be readily observed from the enhancement in the color intensity of aqueous copper(II) solutions above pH 5.3 (as a result of an increase in the visible absorption band in the vicinity of 800 nm). In fact, copper is second only to beryllium among the divalent metal ions in its ease of forming

(15) Margerum, D. W.; Cayley, G. R.; Weatherburn, D. C.; Pagenkopf, G. K. In *Coordination Chemistry*, Vol. 2, Martell, A. E., Ed.; ACS Monograph 174; American Chemical Society: Washington, DC, 1978; pp 1–220.

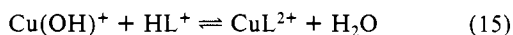
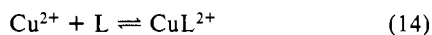
(16) Funahashi, S.; Tanaka, M. *Inorg. Chem.* 1969, 8, 2159–2165.

a monohydroxo species,¹⁷ $\text{Cu}(\text{OH})^+$; several multinuclear species with the general formula $\text{Cu}_{(n+1)}(\text{OH})_{2n}^{2+}$ are known.¹⁸ The most pertinent equilibria involving hydroxocopper(II) species are



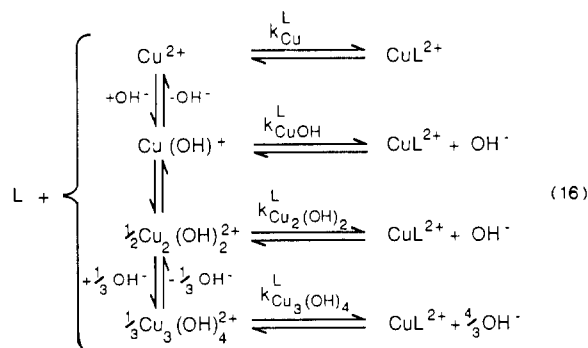
where $\beta_{11} = 1.95 \times 10^{-8} \text{ M}$, $\beta_{22} = 1.02 \times 10^{-11} \text{ M}$, and $\beta_{34} = 2.40 \times 10^{-22} \text{ M}^2$ in aqueous solution at 25 °C and $\mu = 0.10 \text{ M}$ (NO_3^-).¹⁸

Establishing the relative lability of these hydroxocopper(II) species is difficult due to the fact that most ligands studied have ionizable protons and the kinetic contribution of the individual Cu(II) species is masked by the identical pH dependence of the following two processes:



Thus, Perlmutter-Hayman and co-workers¹⁹ were unable to distinguish between the kinetic contributions of eq 14 and 15 in a study of Cu(II) ion reacting with 2-hydroxyacetophenone even though they extended their study to pH 7.5. Other workers have studied pH effects on the kinetics of metal-exchange reactions involving Cu(II) ion attacking polyamine or polyamino polycarboxylate complexes but have arrived at conflicting conclusions, some inferring that CuOH^+ exhibits a significant enhancement in kinetic lability and others attributing observed pH dependencies to other phenomena.²⁰⁻²²

In the case of the current polythia ether systems, the ligands do not protonate and any kinetic dependence on pH should be resolvable into the kinetic contributions of the various hydroxocopper(II) species according to the scheme depicted in eq 16.



Thus, the current study was carried out over as wide a pH range as possible (within the limits of the solubility of $\text{Cu}(\text{OH})_2$) for both the [14]aneS₄-ol system and the *cis,trans*-[14]aneS₄-diol mixture in an attempt to investigate the influence of inner-sphere hydroxide in these reactions.

The results in Table II indicate that there is no distinguishable change in the formation rate constant value over the range of pH from 1.5 to approximately 5.5 for either of these ligand samples reacting with aquated Cu(II). For the *cis,trans*-[14]aneS₄-diol mixture, slight variations in the resolved k_f and k_d values were noted at pH 5.8, but it is unclear whether these small differences may be attributable to experimental error caused by the onset of $\text{Cu}(\text{OH})_2$ precipitation in the stopped-flow cell.

At pH 5.5 (the upper limit of the pH range for which consistent formation and dissociation rate constants were adequately established), the maximum relative concentration of $\text{Cu}(\text{OH})^+$ in

a solution containing a total Cu(II) concentration of 10^{-3} M is 0.61%, with the multinuclear hydroxo species being present in much smaller concentrations. Thus, the upper limit for the value of k_{CuOH^+} is presumed to be less than 20 times the observed value of k_f in each of the two systems for which the pH dependence was investigated. Although this conclusion does not definitively rule out a labilization of aquocopper(II) ion by inner-sphere hydroxide ion, it does suggest that such labilization is not significantly greater than that found for Ni(II) and that complex formation studies involving aquocopper(II) ion are, in general, relatively free of hydroxide effects up to pH 5.5 or above.

Anion Effects. From the data in Table I, it is apparent that the presence of 0.10 M ClO_4^- results in stability constant values that are significantly larger than those obtained in 0.10 M NO_3^- . This is consistent with earlier studies in which it has been found that many "noncomplexing" unidentate anions enhance the apparent stability of the Cu(II)-polythia ether complexes as the result of apparent adduct formation of the type⁷



where X^- represents ClO_4^- , BF_4^- , or CF_3SO_3^- . In fact, extensive measurements involving the addition of variable ClO_4^- concentration to a variety of unsubstituted macrocyclic polythia ether systems⁷ has yielded a consistent equilibrium constant for eq 17 equal to approximately 20 M^{-1} , which predicts a 2-fold enhancement in the observed stability constant in the presence of 0.10 M ClO_4^- . By contrast, these earlier studies have shown that NO_3^- ion has no effect upon the observed stability constant. These observations are consistent with the 2-fold difference in the stability constant for $\text{Cu}^{II}(\text{[14]aneS}_4\text{-ol})$ in 0.10 M ClO_4^- and NO_3^- (Table I).

Although the kinetic parameters listed in Table II provide only limited information, it appears that, relative to solutions containing NO_3^- ion, the addition of 0.10 M ClO_4^- results in a decrease in the dissociation rate constant. This latter result is consistent with more extensive unpublished kinetic data for several Cu(II) complexes in which it has been found that the presence of increasing amounts of ClO_4^- results in small increases in the formation rate constant and much larger decreases in the dissociation rate constant.²³ The net result is an increase in the Cu(II) complex stability constants, an effect that is readily observed from thermodynamic measurements.⁷

Substituent Effects upon Complex Formation Kinetics. From the resolved values of k_f for all ligands included in this study (Table II), it is apparent that there is a significant decrease in the formation rate constant as additional hydroxy groups are substituted onto the backbone of the [14]aneS₄ ligand. For the substitution of a single -OH group, a 10-fold decrease in the formation rate constant is observed with an additional 2-fold decrease for the substitution of a second -OH group in the trans position. Interestingly, the *cis*-diol ligand shows a further 5-fold decrease in the formation rate constant relative to that observed for the corresponding *trans*-diol ligand (or an overall 100-fold decrease relative to [14]aneS₄).

In earlier kinetic studies on the unsubstituted cyclic polythia ethers reacting with Cu(II),⁸ a comparison was made with the kinetic results for aquocopper(II) ion reacting with NH_3 ²⁴ and with corresponding primary and secondary amines.¹¹ From related results with the Ni(II) ion, it was determined that the substitution of a single aliphatic chain (ethyl or longer) on a nitrogen donor atom results in a 5-fold decrease in the rate constant for initial bond formation,²⁵ and a further decrease of approximately 25-fold in this rate constant occurs upon substitution of a second aliphatic chain (ethyl or longer) on the nitrogen.²⁶ Thus, the overall

(17) Baes, C. F., Jr.; Mesmer, R. E. *The Hydrolysis of Cations*; Wiley: New York, 1976.

(18) Sylva, R. N.; Davidson, M. R. *J. Chem. Soc., Dalton Trans.* **1979**, 232-235.

(19) Eini, Y.; Perlmutter-Hayman, B.; Wolff, M. A. *J. Coord. Chem.* **1977**, 7, 27-29.

(20) Margerum, D. W.; Zabin, B. A.; Janes, D. L. *Inorg. Chem.* **1966**, 5, 250-255.

(21) Mentasti, E.; Pelizzetti, E. *Inorg. Chem.* **1978**, 17, 3133-3137.

(22) Steinhaus, R. K. *Inorg. Chem.* **1982**, 21, 4084-4088.

(23) Diaddario, L. L., Jr. Ph.D. Dissertation; Wayne State University: Detroit, MI, 1979.

(24) (a) Sokol, L. S. W. L.; Fink, T. D.; Rorabacher, D. B. *Inorg. Chem.* **1980**, 19, 1263-1266. (b) Diebler, H.; Rosen, P. *Ber. Bunsen-Ges. Phys. Chem.* **1972**, 76, 1031-1034.

(25) Rorabacher, D. B.; Melendez-Cepeda, C. A. *J. Am. Chem. Soc.* **1971**, 93, 6071-6076.

(26) Turan, T. S.; Rorabacher, D. B. *Inorg. Chem.* **1972**, 11, 288-295.

formation rate constant for the reaction of aquocopper(II) ion with a saturated disubstituted nitrogen atom is expected to be about 125-fold smaller than the rate constant for the corresponding reaction with an ammonia molecule (for which an experimental value of $2.0 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ has previously been determined).²⁴

If the same factors can be applied to sulfur atoms,²⁷ first bond formation with *any specific* thia ether sulfur donor atom would be expected to be approximately $1.6 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ at 25 °C (i.e., $(2 \times 10^8)/125$) or $6.4 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ after taking into account the fact that four donor atoms are available for initial coordinate bond formation. Since the extrapolated aqueous formation rate constant value ($1.3 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$) for aquocopper(II) ion reacting with [14]aneS₄ is 50-fold smaller than this predicted value, it was previously concluded that the rate-determining step may have shifted to the point of second-bond formation due to the relative weakness of the initial Cu–S bond formed compared to the remaining Cu(II)–solvent bonds.⁸ However, the apparent kinetic sluggishness observed for the formation of Cu^{II}([14]aneS₄) and related polythia ether complexes could also represent the effect of an unfavorable ligand conformational equilibrium (favoring the “endo” conformation) preceding the first-bond formation step, although the latter possibility was deemed unlikely in view of the facility with which [14]aneS₄ appears to adopt the “exo” configuration.²⁸

The further reduction in the formation rate constants for [14]aneS₄-ol and [14]aneS₄-diol could represent the contribution of increased steric hindrance arising from the hydroxy substituents or the greater tendency of these ligands to adopt the “endo” conformation in view of the tendency of the –OH groups to hydrogen bond to water. In this regard, it is interesting to note that the value of ΔH^\ddagger for the [14]aneS₄-ol reaction is 42 kJ mol⁻¹ (Table III) whereas the corresponding value for aquocopper(II) ion reacting with NH₃ is only 19 kJ mol⁻¹.^{24a} It is speculated that at least a portion of the difference in these two values arises from the energy required to desolvate the –OH groups in the latter macrocycle in the process of forming the “exo” conformer from the “endo” conformer. Although the activation parameters associated with the diol mixture cannot be unequivocally interpreted, the slightly larger ΔH^\ddagger value of 52 kJ mol⁻¹ associated with this mixture indicates that at least one of the components has a higher activation enthalpy, in accordance with the presence of two –OH groups.

In previous studies on similar macrocyclic tetramines reacting with Cu(OH)₃⁻ and Cu(OH)₄²⁻,²⁹ the substitution of two methyl groups on the ligand backbone (a mixture of *cis* and *trans* isomers) resulted in a 4- to 5-fold decrease in the formation rate constant as compared to the 20- to 100-fold decrease observed in this study. Although the methyl groups in the cyclic polyamine study were attached to the α - rather than the β -carbons of the propylene bridges, this difference in the position of the substituents would not be expected to alter the substituent effects by this observed

order of magnitude based on steric factors alone. Rather, we suggest that this difference in behavior provides further evidence that the hydrophilic nature of the hydroxy groups attached to the ligands included in the current work tends to increase the tendency of the [14]aneS₄-diols to adopt an “endo” conformation whereas the hydrophobic methyl groups might increase the tendency of the substituted macrocycles to exist in an “exo” conformer. Clearly, it is the “exo” conformer that promotes the initial bond formation between the metal ion and the cyclic ligand.²⁸

Finally, it is interesting to note that the substitution of one –OH group on the ligand backbone appears to bring about a relatively equal decrease in both the complex formation and dissociation rate constants for the [14]aneS₄-ol system. Consequently, the stability constant for the Cu(II) complex formed with this monoalcoholic ligand is within a factor of 2 of the constant for the parent [14]aneS₄ complex. For the substitution of a second –OH moiety in *trans*-[14]aneS₄-diol, the formation rate constant decreases slightly more than does the (calculated) dissociation rate constant, resulting in a small decrease in the stability constant. By contrast, the large decrease in the formation rate constant for Cu^{II}(*cis*-[14]aneS₄-diol) is not compensated by a similar decrease in the dissociation rate constant. Thus, although the *cis*-diol isomer is the most soluble ligand studied in this work, the nearly 40-fold greater stability constant for the [14]aneS₄-ol complex suggests that the latter ligand may be the reagent of choice for many applications.

Conclusion. The reasonable aqueous solubility of the OH-substituted cyclic tetrathia ethers studied in this work combined with the relatively similar stability constant values of their Cu(II) complexes suggests that these ligands have potential use as reagents in aqueous media. In particular, the extremely high selectivity of these ligands for copper ion over all other first-row transition metals^{2a} combined with their total lack of pH dependence suggests that ligands of this type may be very useful as scavenging agents for aquocopper(II) ion, particularly in acidic media where many other ligands are ineffectual. Since the cyclic polythia ethers are also known to be very low in toxicity,³⁰ it is suggested that water-soluble alcoholic cyclic polythia ether reagents might be exceptionally effective in the treatment of biological copper dysfunction such as that associated with Wilson's disease.³¹

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Registry No. [14]aneS₄, 24194-61-4; [14]aneS₄-ol, 74515-42-7; *cis*-[14]aneS₄-diol, 113859-51-1; *trans*-[14]aneS₄-diol, 113972-72-8; Cu, 7440-50-8.

(27) For example, see: Jones, T. E.; Cole, J. R.; Nusser, B. J. *Inorg. Chem.* **1978**, *17*, 3680–3684.

(28) DeSimone, R. E.; Glick, M. D. *J. Am. Chem. Soc.* **1976**, *98*, 762–767.

(29) Lin, C. T.; Rorabacher, D. B.; Cayley, G. R.; Margerum, D. W. *Inorg. Chem.* **1975**, *14*, 919–925.

(30) Ochrymowycz, L. A., unpublished results.

(31) (a) Sarale, D. C.; Chan, W.-Y.; Rennert, O. M. In *Metabolism of Trace Elements in Man*; Rennert, O. M.; Chan, W.-Y.; Eds.; CRC Press: Boca Raton, FL, 1984; Vol. 2, pp 53–70. (b) Owen, C. A., Jr *Physiological Aspects of Copper*; Noyes: Park Ridge, NJ, 1982.