(7) (a) G. A. Ozin and H. Huber, *Inorg. Chem.*, **17**, 155 (1978); (b) M. Moskovits and J. E. Hulse, *J. Chem Phys.*, **67**, 4271 (1977).
(8) K. A. Gingerich, *J. Cryst. Growth*, **9**, 31 (1971).
(9) (a) C. R. Hare, T. P. Sleight, W. Cooper, and G. A. Clarke, *Inorg. Chem.*, **7**, 669 (1968); (b) R. C. Baetzold, *J. Chem. Phys.*, **55**, 4355 (1971); (c) A. B. Anderson, *ibid.*, **68**, 1744 (1978).
(10) (a) W. Klotzbucher, G. A. Ozin, J. G. Norman, Jr., and H. J. Kolari, *Inorg. Chem.*, **16**, 2871 (1977); (b) J. G. Norman, Jr., and H. J. Kolari, *J. Am. Chem. Soc.*, **100**, 791 (1978).
(11) E. P. Kundig, M. Moskovits, and G. A. Ozin, *J. Mol. Struct.*, **14**, 137 (1972).
(12) M. Moskovits and G. A. Ozin, *Appl. Spectrosc.*, **26**, 487 (1972).
(13) K. Schwarz, *Phys. Rev. B*, **5**, 2466 (1972); *Theor. Chim. Acta*, **34**, 225 (1974).
(14) J. G. Norman, Jr., *J. Chem. Phys.*, **61**, 4630 (1974); *Mol. Phys.*, **31**, 1191 (1976).
(15) J. B. Mann, Los Alamos Scientific Laboratory Report No. LA-3690, 1967.
(16) (a) L. Noodleman, *J. Chem. Phys.*, **64**, 2343 (1976); (b) P. S. Bagus and B. I. Bennett, *Int. J. Quantum Chem.*, **9**, 143 (1975); (c) T. Ziegler, A. Rauk, and E. J. Bahrends, *Theor. Chim. Acta*, **43**, 261 (1977).
(17) S. Mitchell and G. A. Ozin, *J. Am. Chem. Soc.*, **100**, 6776 (1978).
(18) For recent reviews see (a) K. H. Johnson, *Annu. Rev. Phys. Chem.*, **26**, 39 (1975); (b) R. P. Messmer in "Modern Theoretical Chemistry", Vol. 8, G. A. Segal, Ed., Plenum Press, New York, 1977, p 215; (c) N. Rösch in "Electrons in Finite and Infinite Structures", P. Phariseau, Ed., Plenum Press, New York, 1977.
(19) For ESR spectra and other properties of the charge distribution, see D. A. Case and M. Karplus, *J. Am. Chem. Soc.*, **99**, 6182 (1977); *Chem. Phys. Lett.*, **39**, 33 (1976).
(20) For deformation densities see R. Salahub, A. E. Foti, and V. H. Smith, Jr., *J. Am. Chem. Soc.*, **99**, 8067 (1977).
(21) Recent examples of interpretation of spectra, structure, and reactivity from our own work include (a) ref 10 and 14; (b) J. G. Norman, Jr., H. J. Kolari, H. B. Gray, and W. C. Trogler, *Inorg. Chem.*, **16**, 987 (1977); (c) J. G. Norman, Jr., *Ibid.*, **16**, 1328 (1977); (d) J. G. Norman, Jr., and D. J. Gmur, *J. Am. Chem. Soc.*, **99**, 1446 (1977).
(22) D. R. Salahub, R. P. Messmer, and K. H. Johnson, *Mol. Phys.*, **31**, 529 (1976).
(23) M. Boring and J. W. Moskowitz, *Chem. Phys. Lett.*, **38**, 185 (1976).
(24) J. B. Danese, *J. Chem. Phys.*, **61**, 3071 (1974); *Chem. Phys. Lett.*, **45**, 150 (1977).
(25) L. L. Ames and R. F. Barrow, *Trans. Faraday Soc.*, **63**, 39 (1967).
(26) (a) P. Joyes and M. Leleyter, *J. Phys. B*, **6**, 150 (1973); (b) R. N. Dixon and I. L. Robertson, *Mol. Phys.*, **36**, 1099 (1978).
(27) A. B. Anderson, *J. Chem. Phys.*, **64**, 4046 (1976).
(28) The emission bands not accounted for in this way are thought to originate from concurrent molecular Ag_2^* radiative decay processes, the details of which will be reported in a future publication.
(29) S. Mitchell, D. F. McIntosh, and G. A. Ozin, in preparation.

Macrocyclic Ligand Complexation Kinetics. Solvent, Ring Size, and Macrocyclic Effects on the Formation and Dissociation Reactions of Copper(II)-Cyclic Polythiaether Complexes

Leonard L. Diaddario,[1a] L. Lawrence Zimmer,[1a] Thomas E. Jones,[1a] Lucia S. W. L. Sokol,[1a] Renato B. Cruz,[1a] Edmund L. Yee,[1a] L. A. Ochrymowycz,[1b] and D. B. Rorabacher*[1a]

Contribution from the Department of Chemistry, Wayne State University, Detroit, Michigan 48202, and the Department of Chemistry, University of Wisconsin at Eau Claire, Eau Claire, Wisconsin 54701.

Received July 26, 1977

Abstract: The kinetics of solvated Cu(II) reacting with a series of open-chain and macrocyclic polythiaethers have been studied in methanol-water mixtures at 25 °C using the stopped-flow and temperature-jump methods. From a determination of the dependence of the formation rate constant values on the solvent composition, it has been established that $Cu(H_2O)_6^{2+}$ represents the only reactive species of solvated Cu(II) over the range of 0-60% CH_3OH (by weight). Based on this observation, aqueous formation and dissociation rate constants have been generated for two open-chain tetrathiaethers, five cyclic tetrathiaethers, and one cyclic pentathiaether (i.e., Me_2- and Et_2-2,3,2-S_4; 12-, 13-, 14-, 15-, and 16-ane-S_4, and 15-ane-S_5). The 25 °C aqueous formation rate constants range from a low of $6.5 \times 10^3\ s^{-1}$ for the smallest macrocycle, 12-ane-S_4, to a high of $4.2 \times 10^6\ M^{-1}\ s^{-1}$ for the least sterically hindered open-chain ligand, Me_2-2,3,2-S_4, while the dissociation rate constant extremes are 2.6 and $4.5 \times 10^4\ s^{-1}$ for these same two ligand systems, respectively. Aqueous activation parameters have been obtainable for only one ligand system, 15-ane-S_4, for which the formation and dissociation values are $\Delta H_f^{\ddagger}$ (25 °C) = 6.1 kcal mol^{-1}, $\Delta S_f^{\ddagger} = -11$ eu, $\Delta H_d^{\ddagger} = 10$ kcal mol^{-1}, $\Delta S_d^{\ddagger} = -13$ eu. It is concluded that second-bond formation is the probable rate-determining step for all of the cyclic polythiaether complexes studied with the variable difficulty in achieving ring closure accounting for observed differences in the formation rate constants. The primary manifestations of the ring-size effect and the macrocyclic effect are associated with the final steps in the complexation process and, thus, tend to parallel the dissociation rate constants.

Introduction

During the last decade, macrocyclic ligands have attracted widespread attention due to two unique properties: (1) their ability to discriminate among closely related metal ions based on the relative fit of the ligand cavity size to the metal ion radius (*ring size effect*);[2-4] (2) the significant enhancement in complex stability constants which is generally exhibited by optimally fitting macrocyclic ligands relative to their open-chain analogues (*macrocyclic effect*).[2,3,5,6] Both the ring size and macrocyclic effects have been extensively examined from a thermodynamic standpoint[2,3,7-10] and the selectivity patterns are attributed to the combined effects of (1) metal ion solvation, (2) ligand solvation, and (3) ligand conformation,[7,11] the latter two effects being closely coupled. The combination of the foregoing properties is also manifested in the marked increase in membrane permeability exhibited toward selected metal ions when complexed by cyclic polyethers and related open-chain analogues.[12-14]

Largely as a result of the biological interest in the mechanism of metal ion transport, Eigen, Grell, Chock, and others have mounted a concerted effort to investigate the kinetics of alkali metal ions with cyclic polyether antibiotics and with related synthetic crown ethers.[11,15-17] Related studies on

0002-7863/79/1501-3511$01.00/0

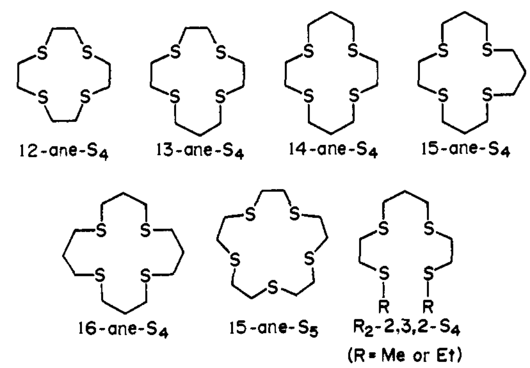


Figure 1. Ligands included in this work.

macrocyclic polyamine ligands reacting with transition-metal ions have been reported by Kaden[18] and by Kodama and Kimura.[9]

Owing to the weak solvation of the alkali metal ions, their rates of complex formation with the cyclic polyethers generally approach the diffusion limit.[15-17,19,20] Thus, the formation rate constants show little dependence on the nature of the reacting metal ion and the reaction mechanism cannot be analyzed in terms of a stepwise metal ion desolvation process.

On the other hand, the cyclic polyamine ligands used in other metal-ion studies are extensively protonated in the pH regions normally accessible to solvated metal ion species. As a result, only the rate constants for the reaction of mono- and diprotonated polyamine species are generally resolvable and these values invariably contain large electrostatic and conformational contributions arising from intramolecular hydrogen bonding. As we have noted earlier,[21] these contributions are difficult to evaluate quantitatively and have led to erroneous interpretations of both the ring size and macrocyclic effects.

In previous work we have managed to circumvent the latter difficulties by studying Cu(II)-polyamine reactions at very high pH (0.1-2.0 M NaOH), where $Cu(OH)_3^-$ and $Cu(OH)_4^{2-}$ represent the reactive metal ion species, using an open-chain ligand with only secondary donor atoms as a reference ligand.[21] However, the normal solvent-ligand exchange behavior of these hydroxymetal species has not been characterized and no comparable literature data are available for comparison. Thus, although a consistent set of relative rate constants was obtained, the specific reaction mechanism could not be analyzed in terms of stepwise metal desolvation.

All of the foregoing difficulties have now been circumvented in the current study in which we report extensive kinetic data on the reactions of solvated Cu(II) with a series of five macrocyclic polythiaether ligands and more limited data on a sixth macrocyclic and two related open-chain polythiaethers. These ligands are not only free of protonation and solvation effects but their Cu(II) complexes possess several other desirable properties which facilitate kinetic measurements including (1) strong absorption bands in the visible region ($\epsilon \approx 8000$ M^{-1} cm^{-1}) for spectral monitoring,[22] (2) formation and dissociation rate constants which are experimentally accessible,[23] and (3) the availability of an entire sequence of homologous cyclic and open-chain ligands.[24]

The reactions studied are of the general form

$$Cu^{2+} + L \underset{k_d}{\overset{k_f}{\rightleftharpoons}} CuL^{2+} \qquad (1)$$

where Cu^{2+} represents the solvated copper(II) ion and L represents the polythiaether ligand. Owing to the sparing solubility of the polythiaether ligands in aqueous solution, initial studies[23] were conducted in 80% methanol (by weight) using both the stopped-flow and temperature-jump methods. This work has now been extended to include the entire solvent range of 25-95% methanol, providing new insight into the role of solvation effects in influencing the reaction rates.

In the course of these studies it has been found that the rate constants for the *formation* of the Cu(II)-polythiaether reactions parallel the mole fraction of $Cu(H_2O)_6^{2+}$ over a wide range of solvent compositions. As a result, accurate estimates of the aqueous formation rate constants have been generated which permit a direct comparison of the polythiaether kinetic data to those for other aqueous Cu(II) systems. Moreover, for one polythiaether system (15-ane-S_4), activation parameters have been determined directly in aqueous solution which are contrasted to the corresponding solvent exchange parameters recently generated for $Cu(H_2O)_6^{2+}$.[25]

The specific ligands studied include six cyclic ligands (1,4,7,10-tetrathiacyclododecane (12-ane-S_4), 1,4,7,10-tetrathiacyclotridecane (13-ane-S_4), 1,4,8,11-tetrathiacyclotetradecane (14-ane-S_4), 1,4,8,12-tetrathiacyclopentadecane (15-ane-S_4), 1,5,9,13-tetrathiacyclohexadecane (16-ane-S_4), and 1,4,7,10,13-pentathiacyclopentadecane (15-ane-S_5)) and a related open-chain ligand (3,6,10,13-tetrathiapentadecane (Et_2-TTU or Et_2-2,3,2-S_4)). Preliminary aqueous kinetic data for a second open-chain ligand, 2,5,9,12-tetrathiatridecane (TTT or Me_2-2,3,2-S_4), are also included for comparison. All eight ligands are illustrated in Figure 1.

Experimental Section

Reagents. $Cu(ClO_4)_2$ was prepared by reacting suspended reagent grade $CuCO_3$ (Allied Chemical Co.) with reagent grade $HClO_4$ (73.6%, G. F. Smith Chemical Co.), partially evaporating, and recrystallizing twice from hot water. All polythiaethers were synthesized as previously described[24] and purified by column chromatography followed by sublimation, fractional distillation (where applicable), and/or recrystallization. Reagent grade absolute methanol (Matheson Coleman and Bell or Fisher Scientific) and distilled, deionized water were used for the preparation of all solvent mixtures.

Kinetic and Stability Constant Measurements. Stopped-flow kinetic measurements were made using a Durrum Model D-110 stopped-flow spectrophotometer equipped with glass and Kel-F tubing and fittings. Absorbance curves were recorded on a Tektronix 564B storage oscilloscope and the traces photographed with a Tektronix Model C-12 Polaroid camera equipped with a projected graticule to eliminate parallax errors. Relaxation measurements were made with a Joule-heating temperature-jump relaxation spectrometer manufactured by Messanlagen Studiengesellschaft, Goettingen, Germany, as previously described.[26,27] Independent stability constant measurements were carried out using a Beckman Acta V recording spectrophotometer.

All reactions were monitored at the wavelength maximum of the peak appearing in the vicinity of 400 nm ($\epsilon \sim 6000$-8000 M^{-1} cm^{-1}), representing the maximum absorbance of the respective Cu(II) complexes[22]—the uncomplexed Cu(II) ion and ligand being virtually transparent in this region. All kinetic and stability constant measurements were conducted at 25.0 ± 0.2 °C by thermostating the cell compartments of the instruments utilized. Ionic strength was controlled at 0.10 M using $HClO_4$.

Stock solutions of the various ligands were generally prepared by stirring samples of the solid ligand with the solvent for 2 h or more and filtering off the undissolved ligand using a fine glass frit. Aliquots of these saturated solutions were then used in the preparation of all subsequent experimental solutions which were generally in the concentration range of 5×10^{-6} to 10^{-4} M. Since the kinetic experiments were generally carried out under conditions where the Cu(II) was present in large excess, a knowledge of the specific ligand concentrations was unnecessary. For stability-constant measurements, the ligand concentrations were determined by potentiometric titrations with a standard Hg(II) solution using a Reilley mercury electrode as the indicating electrode.

Results

Stopped-Flow Kinetic Measurements. All of the Cu(II)-polythiaether complexes studied exhibit relatively small stability constants ($10 \leq K_{CuL} \leq 10^4$) so that the complexes are

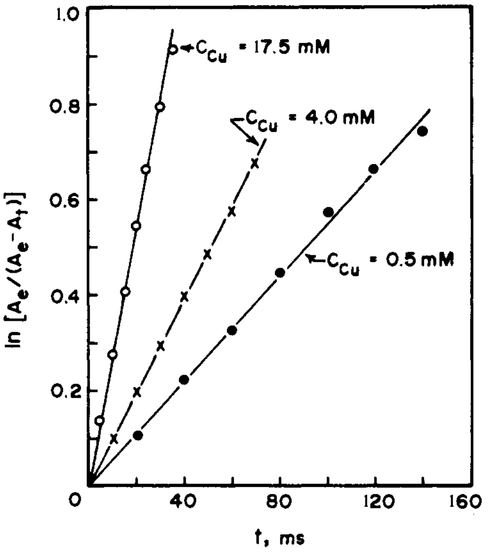


Figure 2. Typical stopped-flow data plotted in the form of eq 6 where the slope of each plot is equal to the respective value of k_{app}. Data shown are for the reaction of Cu(II) with 12-ane-S$_4$ in 80% CH$_3$OH at 25 °C, 0.10 M HClO$_4$.

incompletely formed at equilibrium. For those reactions accessible to stopped-flow measurements (involving 12-, 13-, 14-, 15-ane-S$_4$, and 15-ane-S$_5$), the observed reversible rate expression is of the form (charges omitted)

$$\frac{d[CuL]}{dt} = k_f[Cu][L] - k_d[CuL] \qquad (2)$$

In the presence of a large excess of Cu(II), the introduction of the mass balance relationships

$$C_{Cu} = [Cu] + [CuL] \qquad (3)$$

$$C_L = [L] + [CuL] \qquad (4)$$

followed by integration yields a linear equation

$$\ln\left(\frac{[CuL]_e}{[CuL]_e - [CuL]}\right) = k_{app}t \qquad (5)$$

which is conveniently plotted directly in terms of absorbance data

$$\ln\{A_e/(A_e - A_t)\} = k_{app}t \qquad (6)$$

In the foregoing equations, $[CuL]_e$ represents the equilibrium concentration of the copper complex; A_e and A_t represent the observed absorbance at equilibrium and at time t, respectively; and k_{app} is defined as

$$k_{app} = k_f[Cu] + k_d \qquad (7)$$

Typical plots of eq 6 and 7 are shown in Figures 2 and 3, respectively, for the Cu(II)-12-ane-S$_4$ system. As indicated by these illustrations, approximately 50–70 individual kinetic runs were used to determine each pair of k_f and k_d values in each solvent composition.

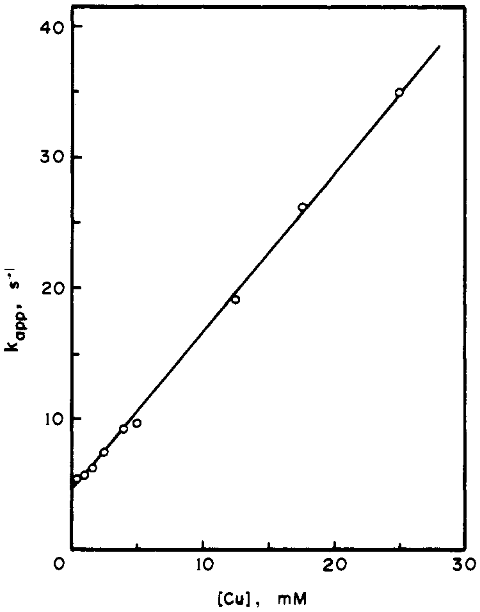


Figure 3. Typical plot of the collected kinetic data for a single reaction system in a single solvent composition according to eq 7 where the intercept is equal to the dissociation rate constant, k_d, and the slope yields the formation rate constant, k_f. Data shown are for the reaction of Cu(II) with 12-ane-S$_4$ in 80% CH$_3$OH at 25 °C, 0.10 M HClO$_4$. (The points plotted include the three values of k_{app} obtained form Figure 2.)

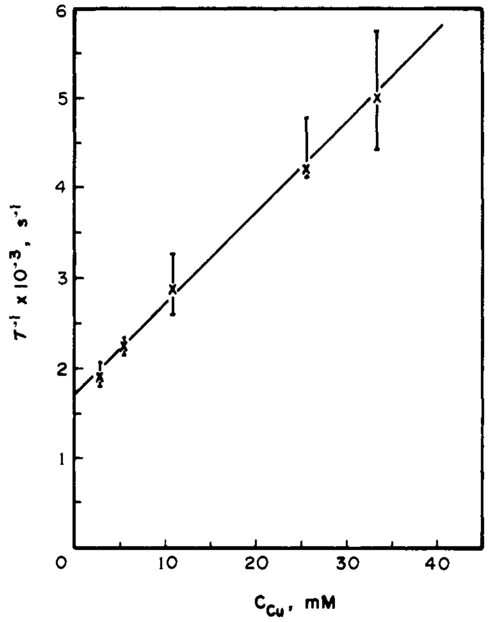


Figure 4. Typical temperature-jump relaxation data plotted in the form of eq 9 where the values of k_f and k_d are equal to the slope and intercept, respectively. The error bars define the range of reciprocal τ values obtained for a minimum of five replicate measurements at each Cu(II) concentration while x designates the median value for each data set. Data shown are for the Cu(II)-16-ane-S$_4$ system in 35% CH$_3$OH at 25 °C, 0.10 M HClO$_4$.

Temperature-Jump Relaxation Measurements. The kinetics of Cu(II) reacting with the largest cyclic ligand (16-ane-S$_4$) and the open-chain ligand (Et$_2$-2,3,2-S$_4$) were generally too fast to be studied successfully by the stopped-flow technique when reactant concentrations were increased to an observable range. For these systems, the temperature-jump relaxation method was applied. In agreement with eq 2, the relaxation equations for these systems were of the form[26,27]

$$\tau^{-1} = k_f([\overline{Cu}] + [\overline{L}]) + k_d \qquad (8)$$

where τ^{-1} represents the reciprocal relaxation time and $[\overline{Cu}]$ and $[\overline{L}]$ represent the equilibrium concentrations of uncomplexed Cu(II) and ligand, respectively. As with the stopped-flow studies, large excesses of Cu(II) were generally utilized so that eq 8 could be simplified to the form

$$\tau^{-1} = k_fC_{Cu} + k_d \qquad (9)$$

A typical plot of eq 9 is shown in Figure 4 for the Cu(II)-16-ane-S$_4$ system.

The resolved 25 °C k_f and k_d values for all reaction systems

Table I. Resolved Formation Rate Constants for Copper(II) Ion Reacting with Polythiaether Ligands as a Function of Methanol–Water Solvent Composition at 25 °C, 0.10 M ClO_4^- ($HClO_4$)

wt %	$[CH_3OH]/$		$10^{-4}k_f$, M^{-1} s^{-1}						
CH_3OH	$[H_2O]$	$\alpha_{6:0}$	12-ane-S_4	13-ane-S_4	14-ane-S_4	15-ane-S_4	16-ane-S_4	15-ane-S_5	Et_2-2,3,2-S_4
0	0	1.00				23.5 (9)			
25	0.187	1.42		5.6 (1)	9.3 (4)		15.8 (9)[a]	11.1 (6)[a] 29 (2)[a]	
30	0.241	1.54	0.408 (4)						
35	0.303	1.69		4.3 (1)	7.6 (1)		10.1 (4)	44 (2)	
40	0.375	1.88	0.379 (9), 0.375 (5)						
50	0.562	2.38	0.268 (3)	3.1 (1)	5.5 (4)		6.8 (5)	36 (3)	
60	0.843	3.22	0.183 (3), 0.232 (1)						
65	1.044	3.88		2.1 (1)	3.8 (2)		2.1 (3)[a]	21.5 (6)	
70	1.312	4.84	0.154 (4), 0.196 (2)						
80	2.249	8.91	0.122 (2)	1.38 (2)	2.6 (2)	4.3 (7)	2.9 (3)	14.6 (6)	25 (7)
90	5.061	27.8	0.0788 (7)	0.96 (6)	1.77 (4)		3.0 (3)[a]	7.9 (2)	
95	10.68	95.3	0.053 (1)	0.58 (2)	1.20 (2)		1.7 (1)	6.2 (1)	

[a] These values are apparently in error and were not utilized in subsequent evaluations of $k_{6:0}$ (see Figure 8).

Table II. Resolved Dissociation Rate Constants for Copper(II)-Polythiaether Complexes as a Function of Methanol–Water Solvent Composition at 25 °C, 0.10 M ClO_4^- ($HClO_4$)

wt %	$10^{-1}k_d$, s^{-1}						
CH_3OH	12-ane-S_4	13-ane-S_4	14-ane-S_4	15-ane-S_4	16-ane-S_4	15-ane-S_5	Et_2-2,3,2-S_4
0				9.5 (20)			
25		2.2 (2)	0.7 (1)		144 (6)[a]	10.3 (3) 8 (1)[a]	
30	0.29 (5)						
35		2.7 (1)	0.79 (7)		172 (8)	1.7 (6)	
40	0.3 (1), 0.34 (5)						
50	0.36 (3)	3.5 (2)	1.02 (6)		180 (10)	3 (2)	
60	0.45 (4), 0.41 (2)						
65		4.6 (1)	1.2 (1)		352 (7)[a]	5 (1)	
70	0.43 (4), 0.44 (2)						
80	0.44 (2)	5.1 (1)	0.86 (5)	20 (3)	322 (12)	15 (1)	2000 (100)
90	0.301 (8)	2.8 (1)	0.45 (4)		194 (7)[a]	10.3 (2)	
95	0.15 (2)	1.22 (3)	0.11 (2)		103 (3)	4.5 (1)	

[a] These values are apparently in error (see Table I).

in all methanol–water solvent compositions studied are shown in Tables I and II.

In the case of 15-ane-S_4, which is the most soluble of the polythiaether ligands studied, a sufficient amount of ligand could be dissolved in aqeuous Cu(II) solutions to permit the direct determination of aqueous kinetic parameters using the temperature-jump relaxation method. The values obtained in this manner at 25 °C are included in Tables I and II. Since the use of a single solvent system also eliminated potential complications arising from temperature-dependent solvation equilibria, the measurements on this system were extended to include a broader range of temperatures in order to yield the aqueous activation parameters. These values are listed in Table III along with corresponding values recently generated for the aqueous Cu(II)-NH_3 reaction.[25]

Stability Constant Measurements. For all systems, stability constant values may be calculated from the formation and dissociation rate constants listed in Tables I and II according to the relationship.

$$K_{CuL} = \frac{[CuL]}{[Cu][L]} = k_f/k_d \tag{10}$$

As an independent check on the internal consistency of the kinetic data, stability constant values were also obtained for several of the Cu(II)-polythiaether complexes in 80% methanol by means of equilibrium spectrophotometric measurements. Since all of the complexes are relatively weak, the method of McConnell and Davidson[28] was employed in which a series of solutions was prepared containing a constant concentration of ligand and varying amounts of Cu(II) in large excess. The resulting absorbance data were then plotted in the form[28]

$$\frac{bC_L}{A} = \frac{1}{\epsilon_{CuL}} + \frac{1}{\epsilon_{CuL}K_{CuL}C_{Cu}} \tag{11}$$

where b represents the path length of the spectrophotometric cell, A represents the measured absorbance, and ϵ_{CuL} is the molar absorptivity of the CuL complex at the wavelength chosen. When plotted in the form illustrated in Figure 5, K_{CuL} is obtained as the ratio of the intercept to the slope. As shown in Table IV, the K_{CuL} values obtained in this manner are in satisfactory agreement with the kinetically generated values. Stability constants determined in aqueous solution are also included in Table IV.

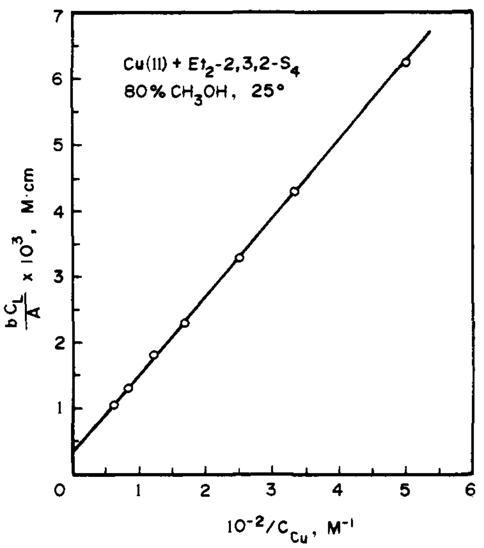


Figure 5. Graphical determination of the complex stability constant for the Cu(II)-Et$_2$-2,3,2-S$_4$ system in 80% CH$_3$OH at 25 °C, 0.10 M HClO$_4$. The data represent absorbance measurements obtained at 414 nm and are plotted according to eq 11 to yield K_{CuL} as the ratio of intercept/slope (b = 10.0 cm, c_L = 5.00 × 10^{-5} M).

Table III. Comparative Activation Parameters for Aquocopper(II) Ion Reacting with 15-ane-S$_4$ and with Ammonia in Aqueous Solution

	15-ane-S$_4$	NH$_3$[25]
$\Delta H_f^{\ddagger}$ (25 °C), kcal mol^{-1}	6.1 (±0.3)	4.5 (±0.4)
$\Delta S_f^{\ddagger}$, eu	−11	−3
$\Delta H_d^{\ddagger}$ (25 °C), kcal mol^{-1}	10 (±2)	9.5 (±0.5)
$\Delta S_d^{\ddagger}$, eu	−13	−5

Table IV. Comparative Stability Constant Values Obtained from Kinetic and Spectrophotometric Measurements for Copper(II)-Polythiaether Complexes in 80% Methanol and in Aqueous Solution at 25 °C, 0.10 M ClO$_4^-$ (HClO$_4$)

	80% CH$_3$OH		aqueous
ligand	log K_{CuL} (kinetic)	log K_{CuL} (spectro)	log K_{CuL} (spectro)
12-ane-S$_4$	2.44	2.51	3.39
13-ane-S$_4$	2.43		3.44
14-ane-S$_4$	3.48	3.48	4.34
15-ane-S$_4$	2.33		3.17[a]
16-ane-S$_4$	0.95	1.04	2.20
15-ane-S$_5$	2.99		4.18
Et$_2$-2,3,2-S$_4$	1.10	1.11, 1.43	2.18
Me$_2$-2,3,2-S$_4$		1.27	1.97

[a] The kinetically generated aqueous value is log K_{CuL} = 3.39.

Discussion

Solvent Effects on Formation Rate Constants. As documented in Table I, the solvent dependence of the formation rate constants has been adequately established for five of the Cu(II)-polythiaether reactions included in this work (viz., 12-, 13-, 14-, 16-ane-S$_4$, and 15-ane-S$_5$). All five systems show a consistent decrease in k_f values as the percentage of methanol increases (Figure 6). This consistency of behavior indicates that the effect of solvent upon the k_f values is independent of ligand structure. Thus, the *relative* differences in ligand reactivities may be analyzed from the data in any single solvent composition—such as our previously reported comparison in 80% methanol.[23]

Of paramount interest is the evaluation of k_f values applicable to aqueous solution since these values would then permit a direct comparison of the Cu(II)-polythiaether systems to existing aqueous data for other Cu(II) reactions. As illustrated in Figure 6, aqueous k_f values may be approximated by an empirical extrapolation of the k_f data to 0% CH$_3$OH. However, values generated in this manner may be inaccurate due to (1) the lack of experimental values over the extended solvent range of 0–25% CH$_3$OH and (2) the greater uncertainty of the data points in 25% CH$_3$OH (perhaps reflecting solubility problems) which largely influences any extrapolation procedure.

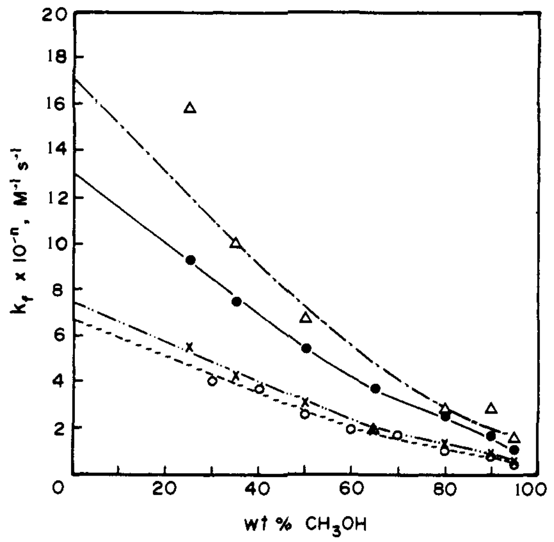


Figure 6. Plot of the resolved formation rate constants for the various Cu(II)-polythiaether systems as a function of solvent composition: ○, 12-ane-S$_4$ (n = 3); x, 13-ane-S$_4$ (n = 4); ●, 14-ane-S$_4$ (n = 4); △, 16-ane-S$_4$ (n = 4). The data for 15-ane-S$_5$ are coincident with the plot shown for 13-ane-S$_4$ being displaced by exactly one order of magnitude (n = 5) and are thus omitted for clarity (see Table I). The intercepts shown coincide with the aqueous values calculated subsequently by means of eq 18 (see Figure 7).

The availability of a more quantitative approach is suggested by our earlier studies on the kinetics of Ni(II) and Co(II) reacting with NH$_3$ in methanol-water mixtures.[26,29] In these studies we have shown that the observed k_f values in any methanol-water solvent composition can be equated to the sum of the kinetic contributions of all of the solvated metal ion species present, viz.,[26]

$$k_f = k_{6:0}\frac{[M_{6:0}]}{(\Sigma M)} + k_{5:1}\frac{[M_{5:1}]}{(\Sigma M)} + k_{4:2}\frac{[M_{4:2}]}{(\Sigma M)} + \ldots \quad (12)$$

where $M_{6:0}$, $M_{5:1}$, $M_{4:2}$, ..., represent $M(H_2O)_6^{2+}$, $M(H_2O)_5(CH_3OH)^{2+}$, $M(H_2O)_4(CH_3OH)_2^{2+}$, ..., respectively, and (ΣM) represents the total concentration of uncomplexed metal ion:

$$\begin{aligned}(\Sigma M) &= [M_{6:0}] + [M_{5:1}] + [M_{4:2}] + \ldots \\ &= C_M - [ML] \quad (13)\end{aligned}$$

In methanol-water mixtures (but *not* in ethanol-water mixtures)[30] the first two solvation equilibrium constants for Cu(II) (defined in molar concentration terms) are well behaved and have been evaluated spectrophotometrically at 25.0 °C, μ = 0.20 M, to yield[30,31]

$$Q_1 = \frac{[M_{5:1}][H_2O]}{[M_{6:0}][CH_3OH]} = 2.1 \quad (14)$$

$$Q_2 = \frac{[M_{4:2}][H_2O]}{[M_{5:1}][CH_3OH]} \approx 0.3 \quad (15)$$

(The more highly methanolated species of Cu(II) do not ap-

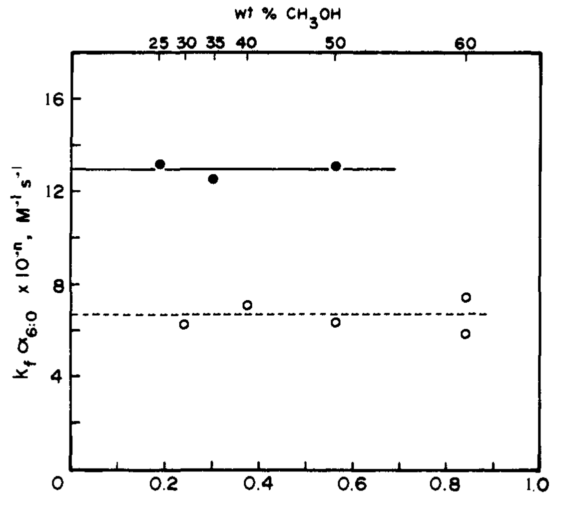


Figure 7. Resolution of aqueous k_f values (i.e., $k_{6:0}$) from experimental k_f data obtained in the solvent range of 25–60% methanol plotted in the form of eq 18: ○, 12-ane-S_4 (n = 3); ●, 14-ane-S_4 (n = 4). Increasingly positive deviations from the horizontal lines occur for k_f values as the methanol content exceeds 60% (see text and Figure 8).

pear to be present in significant concentrations within the solvent range of 0–95% CH_3OH.) These values then permit calculation of the reciprocal mole fraction of $M_{6:0}$ in any solvent composition, i.e.,

$$\alpha_{6:0} = \frac{(\Sigma M)}{[M_{6:0}]} = 1 + Q_1\left(\frac{[CH_3OH]}{[H_2O]}\right) + Q_1Q_2\left(\frac{[CH_3OH]}{[H_2O]}\right)^2 \qquad (16)$$

which, when substituted into eq 12, yields the following relationship upon rearrangement:

$$k_f\alpha_{6:0} = k_{6:0} + k_{5:1}Q_1\left(\frac{[CH_3OH]}{[H_2O]}\right) + k_{4:2}Q_1Q_2\left(\frac{[CH_3OH]}{[H_2O]}\right)^2 \qquad (17)$$

The applicability of eq 17 for describing the kinetic behavior of Cu(II) in methanol-water mixtures has been demonstrated in an independent study in this laboratory involving Cu(II) reacting with NH_3.[30] As with the corresponding Ni(II)-NH_3 system, the Cu(II)-NH_3 rate constants have been shown to fit the abbreviated linear equation

$$k_f\alpha_{6:0} = k_{6:0} + k_{5:1}Q_1([CH_3OH]/[H_2O]) \qquad (18)$$

over the solvent range of 0–90% CH_3OH. Moreover, the Cu(II)-NH_3 data yield a *zero slope* indicating that *$Cu(H_2O)_6{}^{2+}$ is the only kinetically significant species of solvated Cu(II)* over this entire solvent range.

As illustrated in Figure 7, for the 12- and 14-ane-S_4 systems, the linearity of eq 18 is maintained for the Cu(II)-polythiaether reactions over the solvent range of 0–60% methanol with a zero slope which permits an accurate evaluation of $k_{6:0}$. The resultant aqueous k_f values are listed in Table V.

In contrast to the Cu(II)-NH_3 system, the polythiaether reactions exhibit positive deviations in the rate-constant data above 60% methanol when plotting eq 18. Although this suggests that the $k_{4:2}$ term in eq 17 may be a contributing factor (as in the Co(II)-NH_3 system),[29] the data cannot be fitted by a simple quadratic expression such as eq 17.

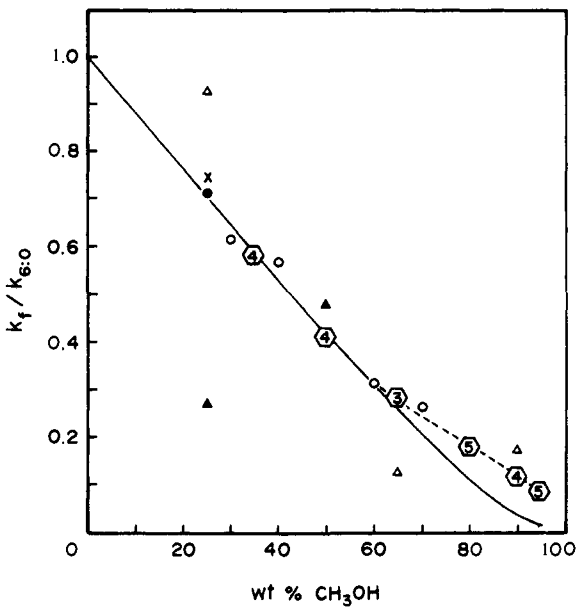


Figure 8. Composite plot of the normalized formation rate constants as a function of solvent composition showing (1) the close parallel between the experimental rate constants and the mole fraction of $Cu(H_2O)_6{}^{2+}$ (solid line) in the solvent region of 25–60% methanol and (2) the uniformity of deviations above 65% methanol (dashed line). The large hexagonal points represent three or more ligand systems which are virtually coincident, the number of coincident points being designated by the inserted numeral. Symbols for noncoincident points are identical with those used in Figure 6: ○, 12-ane-S_4; x, 13-ane-S_4; ●, 14-ane-S_4; △, 16-ane-S_4; ▲, 15-ane-S_5.

Table V. Calculated Formation ($k_{6:0}$) and Dissociation Rate Constants for Copper(II)–Polythiaether Complexes in Aqueous Solution at 25 °C, 0.10 M ClO_4^- ($HClO_4$)

ligand	$10^{-4}k_{6:0}$,[a] $M^{-1}s^{-1}$	80% $k_f/k_{6:0}$[a]	$10^{-1}k_d$ (H_2O), s^{-1}
12-ane-S_4	0.65[b]	0.19	0.26[c]
13-ane-S_4	7.4[b]	0.19	2.7[c]
14-ane-S_4	13[b]	0.20	1.1,[d] 0.6[c]
15-ane-S_4	23.5[d]	0.18	9.5,[d] 15.8[c]
16-ane-S_4	17[b]	0.17	106[c]
15-ane-S_5	75[b]	0.19	4.9[c]
Et_2-2,3,2-S_4	130[e]	(0.19)	860[c]
Me_2-2,3,2-S_4	420[f]		4500[c]
14-ane-S_3N	350[d]		
NH_3	15 000[g]		2100[g]

[a] $k_{6:0}$ represents the aqueous formation rate constant for $Cu(H_2O)_6{}^{2+}$ while 80% k_f represents the k_f value obtained in 80% methanol. [b] Calculated from graphical plots of eq 18 using k_f values experimentally determined in 25–60% CH_3OH (see text). [c] Calculated from $k_{6:0}$ values and aqueous K_{CuL} values (Table IV) using eq 10. [d] Experimental values determined directly in aqueous solution at 25 °C; for 14-ane-S_4 the aqueous k_d value was determined from flash photolysis experiments (M. Martin and D. B. Rorabacher, unpublished results). [e] Calculated from the k_f value determined in 80% CH_3OH (Table I) using the relationship in eq 19 (see text). [f] Estimated from an experimental k_f value of 1.1×10^5 $M^{-1}s^{-1}$ determined directly in aqueous solution at 5 °C assuming a normal Cu(II) E_a value of 5.6–6.7 kcal/mol. [g] Experimental values determined directly in aqueous solution at 25 °C (ref 25).

Whatever the source of the positive deviations in higher methanol compositions, the k_f trends are exceptionally uniform for all of the polythiaether systems. This fact is illustrated in Figure 8 where the normalized k_f values (i.e., $k_f/k_{6:0}$) for 12-, 13-, 14-, 16-ane-S_4, and 15-ane-S_5 are plotted against the solvent composition. In this figure, the solid curve represents the mole fraction of the $Cu_{6:0}$ species (i.e., $1/\alpha_{6:0}$), as calculated from eq 16, and the hexagonal symbols represent points where the data from three or more systems virtually coincide.

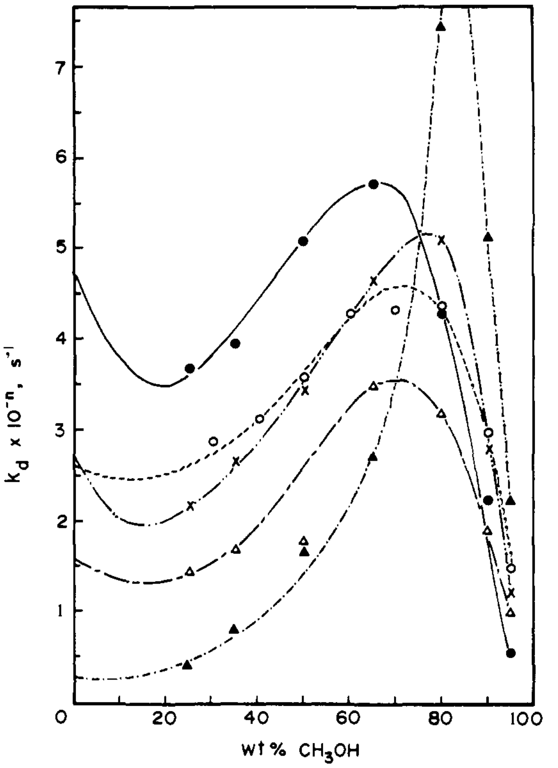


Figure 9. Plot of the resolved dissociation rate constant values for the various Cu(II)-polythiaether complexes as a function of solvent composition: ○, 12-ane-S_4 ($n = 0$); x, 13-ane-S_4 ($n = 1$); ●, 14-ane-S_4 ($n = 0.3$); △, 16-ane-S_4 ($n = 3$); ▲, 15-ane-S_5 ($n = 2.3$). The aqueous intercepts represented are those which have been calculated from the resolved aqueous formation rate constants and the experimental aqueous stability constants by means of eq 10 (see Table IV).

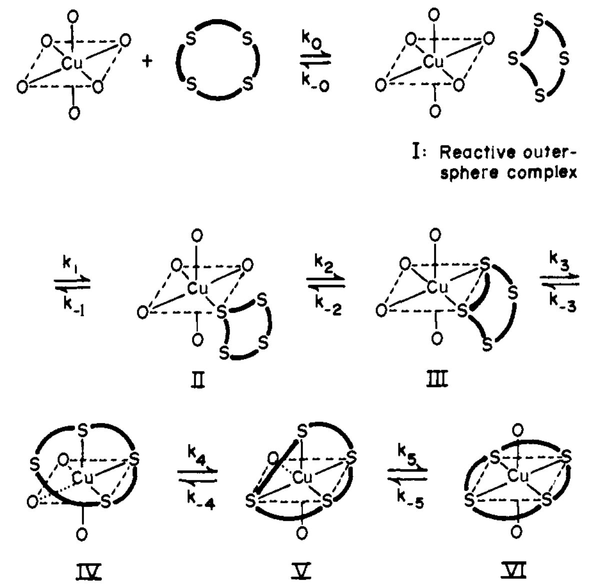


Figure 10. Proposed mechanism for the complex formation between $Cu(H_2O)_6^{2+}$ (where O designates a coordinated H_2O molecule) and a cyclic tetrathiaether. No attempt has been made to represent the changes in the original tetragonal (D_{4h}) symmetry which must accompany the substitution of sulfur donor atoms for water molecules in the inner coordination sphere. (The dotted coordinate bonds designated in intermediates IV and V represent solvent bonds which may be weakened by steric hindrance from the coordinated cyclic ligand.)[21]

Only the data points for 16-ane-S_4 and 15-ane-S_5 show any significant deviations from the normal trend, and these random deviations are wholly ascribed to the greater experimental error associated with these systems.

The uniform dependence of k_f values upon solvent composition is further emphasized in Table V, where the ratio of the k_f values in 80% CH_3OH (designated as 80% k_f to $k_{6:0}$), is shown to be constant within experimental error, i.e.

$$80\%\ k_f/k_{6:0} = 0.19 \qquad (19)$$

This observation is supported by the study on the Cu(II)-15-ane-S_4 system, in which the k_f value determined directly in aqueous solution is $k_{6:0} = 2.35 \times 10^5\ M^{-1}\ s^{-1}$, resulting in an experimentally determined ratio of 0.18 for 80% $k_f/k_{6:0}$ (see Tables I and V).

The constancy of the empirical relationship in eq 19 not only adds strong support to the accuracy of the $k_{6:0}$ values resolved by means of eq 18 but it also permits us to estimate the aqueous k_f value for the Cu(II) reaction with Et_2-2,3,2-S_4 for which only the 80% k_f value was experimentally determined. This value is included in Table V along with a (25 °C) $k_{6:0}$ value for the corresponding Me_2-2,3,2-S_4 reaction which was estimated on the basis of the value determined directly in aqueous solution at 5 °C.[32]

(Owing to the indirect means used in obtaining the aqueous rate constants for the two open-chain ligand systems, the values listed are presumed to be less accurate than the values obtained for the corresponding cyclic ligand systems. However, it is pertinent to note that, whereas two distinctly different approaches were utilized in estimating the aqueous k_f values for Me_2- and Et_2-2,3,2-S_4, the ratio of the resultant values is almost identical with the fourfold ratio previously found for *N,N'*-dimethyl- and *N,N'*-diethylethylenediamine reacting with aquonickel(II) ion,[33] indicating that the resolved rate constants largely reflect the differences in reactivity of terminal secondary donor atoms having methyl and ethyl substituents, respectively.)

Solvent Effects on Dissociation Rate Constants. The k_d values for the Cu(II) complexes of 12-, 13-, 14-, 16-ane-S_4, and 15-ane-S_5 also show qualitatively consistent trends when plotted as a function of the solvent composition as illustrated in Figure 9. Particularly noteworthy are the maxima in k_d values occurring for all systems in the vicinity of 65–80% methanol. Although maxima at similar solvent compositions have been observed previously for k_f values in Ni(II) and Co(II) systems[26,29,34] (representing a greater reactivity for the $M(H_2O)_5(CH_3OH)^{2+}$ species), this is the first known observation of such maxima for k_d values.

The k_d maxima do not coincide exactly for all of the Cu(II)-polythiaether systems, although the four cyclic tetrathiaethers exhibit relatively uniform behavior. The pentathiaether, 15-ane-S_5, exhibits a much larger relative maximum which is shifted to higher methanolic composition.

Once again, empirical extrapolations to aqueous conditions yield uncertain values and no mathematical relationship between k_d values and solvent composition has, as yet, been generated. However, using the aqueous stability constants determined directly for all eight complexes included in this work (Table IV) together with the calculated aqueous formation rate constants (Table V), we are enabled to calculate aqueous k_d values by means of eq 10. These values are included in Table V and are indicated as the intercepts to the experimental curves in Figure 9.

In view of the experimental errors in the stability-constant values, the accuracy of the aqueous k_d values may be no better than a factor of 2 in some cases. Thus the initial minima in k_d values at low methanol percentages, as indicated in Figure 9, may not be significant.

Reaction Mechanism. The stepwise mechanism for aquocopper(II) ion reacting with the cyclic tetrathiaethers should be similar to the mechanism previously proposed for the analogous cyclic tetramines.[21] As represented schematically in Figure 10, this mechanism involves the diffusion-controlled encounter of the two reactants to form an outer-sphere complex (I) followed by four successive intermediates (II, III, IV, V) involving the sequential bonding of the four sulfur donor atoms to the Cu(II) ion. Finally, an internal rearrangement is necessary to convert the complex to the final product (VI) in which all four sulfur donor atoms are in a planar array.[35]

Interestingly, crystal structure data are now available on a series of 14-ane-S_4 complexes in which the ligand has been shown to adopt essentially all of the configurations required for these intermediates, viz., (I) free ligand;[36] (II) a (bridged) singly bonded species;[37] (III) a (bridged) bidentate species;[38] (IV) a (polymeric) tridentate species;[39] (VI) a fully coordinated planar species.[40,41] Thus, each of the postulated intermediates appears to be structurally attainable with species V representing the only intermediate for which the structure of an analogous polythiaether compound is unavailable.

Although it is impossible to establish the position of the rate-determining step in this scheme on a purely a priori basis, the aqueous rate constants generated in this work may be compared to results obtained for other Cu(II) reactions[42] in order to establish a reasonable set of conclusions. For example, if first bond formation were the rate-determining step (i.e., $k_f = k_0 k_1 / k_{-0}$), the observed k_f values should approximate the rate constant for Cu(II) reacting with a neutral unidentate ligand such as NH_3 with corrections for statistical factors, steric effects, and ligand conformational effects.

The value of the Cu(II)-NH_3 formation rate constant, $k_{Cu}{}^{NH_3}$, in aqueous solution at 25°C has been evaluated as 2×10^8 M^{-1} s^{-1} in two independent studies.[25,43] Previous studies in this laboratory on ligand steric effects have revealed that substitution by a single alkyl group (ethyl or larger) on a nitrogen donor atom results in a fivefold decrease in the experimental k_f value[27] while substitution by a second alkyl group (ethyl or larger) results in a further decrease of 10-50-fold.

Assuming that steric effects for sulfur donor atoms are similar (or smaller[44]), an individual sulfur donor atom in an open-chain tetrathiaether such as Et_2-2,3,2-S_4 might be expected to bond with Cu(II) with a characteristic rate constant which is no more than 50-250-fold slower than that exhibited by NH_3. After correcting for a statistical factor of 4 for the number of donor atoms available, the minimum predicted rate constant for first-bond formation in the Cu(II)-Et_2-2,3,2-S_4 reaction is, in the absence of ligand conformational effects:

$$\begin{aligned} k_f \approx 4k_{Cu}{}^{NH_3}/(50\text{-}250) &= \frac{4(2 \times 10^8\ M^{-1}\ s^{-1})}{(50\text{-}250)} \\ &= (3\text{-}16) \times 10^6\ M^{-1}\ s^{-1} \qquad (20) \end{aligned}$$

It is to be noted that the evaluated aqueous k_f value for Cu(II) reacting with Et_2-2,3,2-S_4 is within a factor of 3 of the lower limit predicted above. This suggests that the rate-determining step for this reaction is at, or close to, the point of first-bond formation with the possibility that ligand conformational effects account for the slight difference between the experimental and predicted values.

In our previous evaluation of the k_f values for $Cu(OH)_3^-$ reacting with unprotonated open-chain and cyclic tetramines,[21] we concluded that the steric effects of secondary donor atoms were unaffected by ligand cyclization (based on the observation that the tetramine ligands corresponding to Et_2-2,3,2-S_4 and 14-ane-S_4 exhibited identical k_f values with $Cu(OH)_3^-$). Therefore, the 5-20-fold reduction in k_f values observed for 13-, 14-, 15-, and 16-ane-S_4 relative to Et_2-2,3,2-S_4 must be ascribed to ligand conformational effects manifested either (1) as a prior equilibrium preceding first bond formation (k_1) or (2) if the rate-determining step is beyond the point of first-bond formation, as a reflection of the relative difficulty of achieving ring closure.

The former explanation can be represented schematically as

$$M + \left\{ \begin{tikzcd} L_{(exo)} \arrow[r, "k_{f(exo)}"] \arrow[d, shift left] \arrow[d, phantom, "K_c"', shift right=3] & ML \\ L_{(endo)} \arrow[u, shift left] \arrow[r, "/" marking] & {} \end{tikzcd} \right. \qquad (21)$$

where

$$K_c = [L_{(endo)}]/[L_{(exo)}] \qquad (22)$$

In this scheme $L_{(exo)}$ and $L_{(endo)}$ represent different conformers of the cyclic ligands,[36] the latter designation representing all unreactive configurations. Previous investigators, examining the kinetic behavior of alkali metal ions reacting with cyclic polyether antibiotics,[15-17] have generally assumed that K_c is large (i.e., $L_{(endo)}$ is favored over $L_{(exo)}$) so that the observed formation rate constants are significantly diminished by the unfavorable conformational equilibria, viz.

$$k_f = k_{f(exo)}/(1 + K_c) \qquad (23)$$

(We have previously argued[21] that this conformational factor is of even greater importance in reactions involving the *protonated* cyclic polyamines where internal hydrogen bonding should greatly increase the mole fraction of unreactive conformers resulting in $K_c \gg 1$.)

In the case of the cyclic polythiaethers, however, it is not apparent that endo conformers should be favored. The only uncomplexed polythiaether for which a crystal structure has been determined, 14-ane-S_4, was isolated in an exo conformation.[36] Moreover, changes in solvent composition would be expected to alter the value of K_c significantly and the degree of change might well vary from ligand to ligand. It has already been noted, however, that the solvent dependency of the k_f values directly parallels the mole fraction of $[Cu(H_2O)_6{}^{2+}]$ over the solvent range of 25-60% methanol (Figures 7 and 8). Thus, it must be inferred that either (1) the reactive exo conformers are dominant (i.e., $K_c < 1$), or (2) the K_c values for all ligand systems are constant over this solvent range. The former explanation appears to be much more plausible and we conclude that ligand conformational equilibria probably do not influence the rate of first-bond formation in this solvent region to a significant extent.

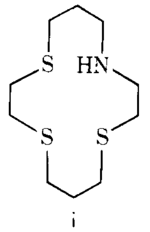
Thus, we are left with the conclusion that the k_f dependence on ligand ring size probably represents the relative difficulty of achieving chelate ring closure, indicating that the rate-determining step is beyond the point of first-bond formation. The most logical hypothesis is that the second-bond formation step is rate determining such that

$$k_f = \frac{k_0 k_1 k_2}{k_{-0} k_{-1}} = K_0 K_1 k_2 \qquad (24)$$

This hypothesis is consistent with our earlier conclusion that the tenfold difference observed in the rate constants of $Cu(OH)_4{}^{2-}$ reacting with the unprotonated tetramine analogues of Et_2-2,3,2-S_4 and 14-ane-S_4 were attributable to differences in the ease of chelate ring closure.[21] In reaching that conclusion the rate-determining step was presumed to be at the point of second-bond formation in the reaction of $Cu(OH)_4{}^{2-}$ with the cyclic tetramine ligands.

The suggestion that second-bond formation represents the rate-determining step in the cyclic polythiaether reactions with $Cu(H_2O)_6{}^{2+}$ is also consistent with the general observation that Cu(II)-S bonds are relatively weak. This is perhaps most evident from the fact that the k_d value for Cu(II)-Et_2-2,3,2-S_4 is approximately equal to k_d for Cu(II)-NH_3 (Table V) despite the fact that the former reaction involves the sequential breaking of four coordinate bonds. Thus it is probable that $k_1 \gg k_2$ as required for eq 24.

To test the foregoing hypothesis, we have recently conducted preliminary measurements on the reaction kinetics of $Cu(H_2O)_6^{2+}$ reacting with the monoazatrithiaether analogue of 14-ane-S_4, viz., 1,4,8-trithia-11-azacyclotetradecane (14-ane-S_3N) (i). Whenever the initial bond formed involves the nitrogen donor atom, the strength of the resultant Cu-N bond should be sufficient to reduce the value of k_{-1} to the point where $k_{-1} \ll k_2$[42] so that the first-bond formation should become the rate-determining step. Accordingly, the formation rate constant obtained for the *unprotonated* form of this ligand reacting with $Cu(H_2O)_6^{2+}$ in aqueous solution is 3.5×10^6 M^{-1} s^{-1} (25 °C, 0.10 M $NaClO_4$). Since only *one* nitrogen donor atom is available, this result is in excellent agreement with the rate-constant value predicted in eq 20 for such a reaction in which first-bond formation is the rate-determining step, i.e.


i

$$k_f = k_{Cu}{}^{NH_3}/(50\text{–}250) = (0.8\text{–}4) \times 10^6\ M^{-1}\ s^{-1} \quad (20a)$$

Having argued above that the rate-determining step is at the point of second-bond formation in the cyclic polythiaether reactions with Cu(II), it is significant to note that the aqueous activation enthalpy obtained for the formation of Cu(II)(15-ane-S_4) is only 1.5 kcal mol^{-1} larger than that for the corresponding reaction with NH_3. This implies that the Cu-H_2O bond undergoing rupture is step k_2 is still highly labile. By contrast, the activation entropy is significantly decreased, presumably reflecting the statistical unfavorability of closing the first chelate ring.

Implications of the Jahn-Teller Effect. The actual values of k_{-1} and k_2 cannot be estimated because of the complicating features introduced into Cu(II) chemistry by the presence of Jahn-Teller distortions. However, the solvent trends observed in this study reveal several mechanistically significant implications regarding the manifestation of the Jahn-Teller effect as it pertains to the substitutional lability of Cu(II). It is well recognized, for example, that the unusually high lability of the inner-sphere water molecules in $Cu(H_2O)_6^{2+}$ stems from the elongation of the axial bonds as a result of Jahn-Teller distortion. Moreover, all six waters appear to be equally labile due to the rapid inversion of the elongated axis. Both theoretical[45] and EPR[46] studies imply that the substitution of a unique donor atom into the inner-coordination sphere freezes out the dynamic aspects of the Jahn-Teller effect with the unique atom positioned on the unique axis. The unreactivity of $Cu_{5:1}$ relative to $Cu_{6:0}$ suggests that, when the unique atom is an alcoholic oxygen, the lability of all six coordinate bonds is lowered—presumably as a result of diminished tetragonal distortion (decreased axial elongation). Moreover, if the rate-determining step is at the point of second-bond formation, it is evident that the Cu(II)-alcoholic oxygen bond is the least labile bond since the $Cu_{5:1}$ species appears to retain its identity at the point of the rate-determining step.

In examining intermediate II in the reaction scheme for the tetrathiaethers (Figure 10), it is evident that this intermediate is analogous to the $Cu_{5:1}$ species and the coordinated sulfur donor atom must lie on the unique axis. If the lability of all inner-sphere donor atoms is similarly lowered in intermediate II, it is possible that $k_{-1} \ll k_1 \gg k_2$, implying an initial buildup of this intermediate. If such a buildup does occur, however, it must be rapidly achieved since no induction period is observed when monitoring the rate of formation of the final complex. Alternatively, it is conceivable that the Cu-S bond is significantly elongated in intermediate II such that k_{-1} may be exceptionally large, perhaps even comparable to or greater than k_1.

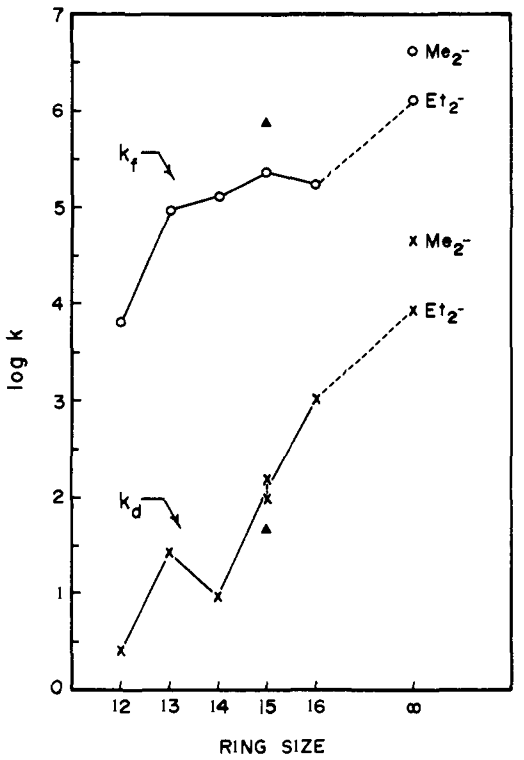


Figure 11. Ring-size effects for the tetrathiaether complexes of Cu(II) as manifested in the kinetic rate constants in aqueous solution at 25 °C, 0.10 M $HClO_4$. The open-chain tetrathiaethers with terminal methyl (Me_2-) and ethyl (Et_2-) groups are presumed to represent infinite ring size. The solid triangles represent the corresponding rate constant values for the pentathiaether, 15-ane-S_5.

Ring-Size Effects. Within the context of the foregoing discussion, ring-size effects upon the overall formation rate constant, as illustrated in Figure 11, are presumed to reflect primarily the relative ease of ring closure. The difference in k_f values for the 15-ane-S_4 vs. the 16-ane-S_4 complex may be satisfactorily explained by the greater ease of closing five-membered chelate rings relative to six-membered rings[47] while the still greater reactivity of the 15-ane-S_5 ligand may reflect not only the increase in the number of available five-membered rings but also the increased ring flexibility resulting from the introduction of another heteroatom. The fact that k_f values do not continue to increase as the number of potential five-membered chelate rings increases in the sequence 15-, 14-, 13-, 12-ane-S_4 presumably reflects the diminished ligand flexibility as the macrocycle diminishes in size. This factor becomes exceptionally apparent for 12-ane-S_4, where the ligand is too restricted to circumscribe the metal ion.[35]

The effects of constrained ligand flexibility are grossly evident in the k_d values (see Figure 11), where the increase in the dissociation rate constants amounts to about tenfold per unit change in ring size in the sequence 14-, 15-, 16-ane-S_4 with an additional 8-40-fold increase on going to the corresponding open-chain ligands (Et_2- and Me_2-2,3,2-S_4, respectively). The discontinuity in the k_d value for 13-ane-S_4 is presumed to reflect the fact that the Cu(II) ion is not coplanar with the donor atoms in this complex[35] and, thus, the fully complexed copper ion is already partly "out" of the ring. The further observation that k_d does not continue to increase for 12-ane-S_4, where Cu(II) is further out of the plane of the donor atoms,[35] is likely due to the overbalancing effect of the greater ligand rigidity extant with this small macrocycle as suggested by its anomalous k_f value.

The Nature of the Macrocyclic Effect. The foregoing considerations indicate that *the macrocyclic effect is kinetically manifested in the latter steps of the complexation process*, being associated with the process of completing the circumscription of the metal ion by the constrained cyclic ligand, i.e., steps k_3, k_4, and k_5, which occur after the point of the rate-determining step in the formation process. In view of the fact that the Cu–S bond lengths are constant (at 2.32 ± 0.02 Å) in both the open-chain and cyclic tetrathiaether complexes,[35,40] this conclusion is consistent with an assignment of the macrocyclic effect to entropic factors.

As exemplified by the relative stability constants for Cu(II)-14-ane-S_4 and Cu(II)-Et_2-2,3,2-S_4 in this work, the macrocyclic effect accounts for a stability increase of 100-fold in aqueous solution, becoming somewhat larger in more methanolic solvents. This is very close to the value obtained by Smith and Margerum with related Ni(II)-polythiaether complexes in nitromethane,[10] lending credibility to the contention that solvation effects do not play a *major role* in the macrocyclic effect for polythiaethers.

The trends in k_d values observed in Figure 9 do suggest that solvation effects are not entirely absent, however. Since the observed maxima in these k_d values roughly parallel the maxima in ligand solubility (as observed qualitatively), these trends suggest that the dissociation process is aided by the solvation of the partially dissociated ligands, thereby increasing the magnitude of the equilibrium constants preceding the rate-determining step (i.e., the ratios k_{-4}/k_4 and k_{-3}/k_3 are enhanced). Such effects should be greatly magnified in the case of the more highly soluble polyamines. This, then, provides a kinetic explanation for the solvation contribution to the macrocyclic effect, which was previously proposed by Hinz and Margerum[7] in thermodynamic terms, and accounts for the increased stability of macrocyclic ligand complexes despite the observed decrease in k_f values.

Acknowledgment. This work was supported by the National Institute of General Medical Sciences under Grants GM-12596 (to D.B.R.) and GM-20424 (to L.A.O. and D.B.R.).

References and Notes

(1) (a) Wayne State University; (b) University of Wisconsin—Eau Claire.

(2) (a) H. K. Frensdorff, *J. Am. Chem. Soc.*, **93**, 600 (1971); (b) C. J. Pedersen and H. K. Frensdorff, *Angew. Chem., Int. Ed. Engl.*, **11**, 16 (1972).

(3) (a) J. J. Christensen, J. O. Hill, and R. M. Izatt, *Science*, **174**, 459 (1971); (b) R. M. Izatt, D. J. Eatough, and J. J. Christensen, *Struct. Bonding* (*Berlin*), **16**, 161 (1973); (c) J. J. Christensen, D. J. Eatough, and R. M. Izatt, *Chem. Rev.*, **74**, 351 (1974).

(4) (a) D. H. Busch, K. Farmery, V. Goedken, V. Katovic, A. C. Melnyk, C. R. Sperate, and N. Tokel, *Adv. Chem. Ser.*, **No. 100**, 52 (1971); (b) L. Y. Martin, L. J. DeHayes, L. J. Zompa, and D. H. Busch, *J. Am. Chem. Soc.*, **96**, 4046 (1974); (c) D. D. Watkins, Jr., D. P. Riley, J. A. Stone, and D. H. Busch, *Inorg. Chem.*, **15**, 387 (1976); (d) Y. Hung, L. Y. Martin, S. C. S. C. Jackels, A. M. Tait, and D. H. Busch, *J. Am. Chem. Soc.*, **99**, 4029 (1977).

(5) D. K. Cabbiness and D. W. Margerum, *J. Am. Chem. Soc.*, **91**, 6540 (1969).

(6) This phenomenon is present to an even greater extent in macrobicyclic ligand complexes where it has been labeled the *Cryptate effect:* J. M. Lehn and J. P. Sauvage, *J. Am. Chem. Soc.*, **97**, 6700 (1975); J. M. Lehn, *Pure Appl. Chem.*, **49**, 857 (1977); *Acc. Chem. Res.*, **11**, 49 (1978).

(7) F. P. Hinz and D. W. Margerum, *J. Am. Chem. Soc.*, **96**, 4993 (1974); *Inorg. Chem.*, **13**, 2941 (1974).

(8) (a) L. Fabbrizzi, P. Paoletti, and A. B. P. Lever, *Inorg. Chem.*, **15**, 1502 (1976); (b) L. Fabbrizzi, *ibid.*, **16**, 2667 (1977); (c) A. Anichini, L. Fabbrizzi, P. Paoletti, and R. M. Clay, *Inorg. Chim. Acta Lett.*, **22**, L25 (1977); (d) *J. Chem. Soc., Dalton Trans.*, 577 (1978); (e) L. Fabbrizzi P. Paoletti, and R. M. Clay, *Inorg. Chem.*, **17**, 1042 (1978).

(9) (a) M. Kodama and E. Kimura, *J. Chem. Soc., Chem. Commun.*, 326, 891 (1975); (b) *J. Chem. Soc., Dalton Trans.*, 2341 (1976); (c) *ibid.*, 2269 (1977); (d) *ibid.*, 247 (1978).

(10) G. F. Smith and D. W. Margerum, *J. Chem. Soc., Chem. Commun.*, 807 (1975).

(11) P. B. Chock and E. O. Titus, *Prog. Inorg. Chem.*, **18**, 287 (1973).

(12) (a) B. C. Pressman, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **27**, 1283 (1968); (b) D. C. Tosteson, *ibid.*, **27**, 1269 (1968).

(13) (a) B. C. Pressman and D. H. Haynes in "The Molecular Basis of Membrane Function", D. C. Tosteson, Ed., Prentice-Hall, Englewood Cliffs, N.J., 1969, p 211 ff; (b) M. M. Shemyakin, V. K. Antonov, Ovchinnikov, and A. M. Shkrob, *ibid.*, p 173 ff.

(14) P. G. Hoffman and D. C. Tosteson, *J. Gen. Physiol.*, **58**, 438 (1971).

(15) (a) H. Diebler, M. Eigen, G. Ilgenfritz, G. Maass, and R. Winkler, *Pure Appl. Chem.*, **20**, 93 (1969); (b) M. Eigen in "Quantum Statistical Mechanics in the Natural Sciences", B. Kusunoglu, S. L. Mintz, and S. Widmayer, Eds., Plenum Press, New York, 1974, p 37; (c) P. B. Chock, F. Eggers, M. Eigen, and R. Winkler, *Biophys. Chem.*, **6**, 239 (1977).

(16) P. B. Chock, *Proc. Natl. Acad. Sci. U.S.A.*, **69**, 1939 (1972).

(17) (a) T. Funck, F. Eggers, and E. Grell, *Chimia*, 632, 637 (1972); (b) E. Grell, T. Funck, and F. Eggers, *Membranes*, **3**, 1 (1975); (c) E. Grell, I. Oberbaeumer, H. Ruf, and H. P. Zingsheim, *FEBS Symp.*, **42**, 147 (1977); (d) E. Grell and I. Oberbaeumer, *Mol. Biol. Biochem. Biophys.*, **24**, 371 (1977).

(18) (a) T. Kaden, *Helv. Chim. Acta*, **53**, 617 (1970); (b) A. P. Leugger, L. Hertli, and T. A. Kaden, *ibid.*, **61**, 2296 (1978).

(19) (a) E. Shchori, J. Jagur-Grodzinski, Z. Luz, and M. Shporer, *J. Am. Chem. Soc.*, **93**, 7133 (1971); (b) E. Shchori, J. Jagur-Grodzinski, and M. Shporer, *ibid.*, **95**, 3842 (1973); (c) M. Shporer and Z. Luz, *ibid.*, **97**, 665 (1975).

(20) E. Mei, A. I. Popov, and J. L. Dye, *J. Phys. Chem.*, **81**, 1677 (1977).

(21) C. T. Lin, D. B. Rorabacher, G. R. Cayley, and D. W. Margerum, *Inorg. Chem.*, **14**, 919 (1975).

(22) T. E. Jones, D. B. Rorabacher, and L. A. Ochrymowycz, *J. Am. Chem. Soc.*, **97**, 7485 (1975).

(23) T. E. Jones, L. L. Zimmer, L. L. Diaddario, D. B. Rorabacher, and L. A. Ochrymowycz, *J. Am. Chem. Soc.*, **97**, 7163 (1975).

(24) L. A. Ochrymowycz, C. P. Mak, and J. D. Michna, *J. Org. Chem.*, **39**, 2079 (1974).

(25) L. S. W. L. Sokol, T. D. Fink, and D. B. Rorabacher, *Inorg. Chem.*, submitted for publication.

(26) W. J. MacKellar and D. B. Rorabacher, *J. Am. Chem. Soc.*, **93**, 4379 (1971).

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

(28) H. McConnell and N. Davidson, *J. Am. Chem. Soc.*, **72**, 3164 (1950).

(29) L. G. Jambor, R. W. Taylor, and D. B. Rorabacher, *Inorg. Chem.*, submitted for publication.

(30) (a) L. G. Jambor, T. D. Fink, and D. B. Rorabacher, to be submitted for publication; (b) L. G. Jambor, Ph.D. Dissertation, Wayne State University, 1975; (c) T. D. Fink, Ph.D. Dissertation, Wayne State University, 1976.

(31) The symbols Q_1 and Q_2 are equivalent to the symbols K_1' and K_2', respectively, as used in ref 26.

(32) L. S. W. L. Sokol, M.S. Thesis, Wayne State University, 1977; the kinetics of the Cu(II)(Me_2-2,3,2-S_4) complex could not be resolved in aqueous solution at temperatures above 5 °C.

(33) (a) T. S. Turan and D. B. Rorabacher, *Inorg. Chem.*, **11**, 288 (1972); (b) T. S. Turan, *ibid.*, **13**, 1584 (1974).

(34) In addition to the k_f maxima observed for Ni(II) and Co(II) reacting with NH_3 (ref 26 and 29), maxima have also been observed for the reactions of Ni(II) with open-chain polyamines and poly(amino alcohols): F. R. Shu, W. J. MacKellar, and D. B. Rorabacher, unpublished results.

(35) Crystallographic structural determinations indicate that the four sulfur donor atoms lie in a single plane for each of the cyclic tetrathiaether complexes of Cu(II) included in this work. Whereas the Cu(II) ion is coplanar with the four sulfur donor atoms in the complexes with the larger macrocycles (14-, 15-, 16-ane-S_4), it is approximately 0.3 Å above this plane in the 13-ane-S_4 complex and approximately 0.5 Å above in the 12-ane-S_4 complex: V. Pett, E. R. Dockal, L. L. Diaddario, M. D. Glick, and D. B. Rorabacher, work in progress.

(36) R. E. DeSimone and M. D. Glick, *J. Am. Chem. Soc.*, **98**, 762 (1976).

(37) R. E. DeSimone and M. D. Glick, *J. Am. Chem. Soc.*, **97**, 942 (1975).

(38) N. W. Alcock, N. Herron, and P. Moore, *J. Chem. Soc., Chem. Commun.*, 886 (1976); cf. *J. Chem. Soc., Dalton Trans.*, 394 (1978).

(39) E. R. Dockal, L. L. Diaddario, M. D. Glick, and D. B. Rorabacher, *J. Am. Chem. Soc.*, **99**, 4530 (1977).

(40) M. D. Glick, D. P. Gavel, L. L. Diaddario, and D. B. Rorabacher, *Inorg. Chem.*, **15**, 1190 (1976).

(41) P. H. Davis, L. K. White, and R. L. Belford, *Inorg. Chem.*, **14**, 1753 (1975).

(42) D. B. Moss, C. T. Lin, and D. B. Rorabacher, *J. Am. Chem. Soc.*, **95**, 5179 (1973).

(43) H. Diebler and P. Rosen, *Ber. Bunsenges. Phys. Chem.*, **76**, 1031 (1972).

(44) Recent kinetic studies on monothiaethers reacting with Pd(II) suggest that steric effects may be slightly smaller in the case of alkyl substitution on sulfur donor atoms (although the latter reactions involve an associative mechanism and, thus, may not yield comparable results): T. E. Jones, J. R. Cole, and B. J. Nusser, *Inorg. Chem.*, **17**, 3680 (1978).

(45) I. B. Bersuker, *Coord. Chem. Rev.*, **14**, 357 (1975), and references cited therein.

(46) M. Noack, G. F. Kokoszka, and G. Gordon, *J. Chem. Phys.*, **54**, 1342 (1971).

(47) (a) A. Kowalak, K. Kustin, R. F. Pasternack, and S. Petrucci, *J. Am. Chem. Soc.*, **89**, 3126 (1967); (b) R. F. Pasternack and K. Kustin, *ibid.*, **90**, 2295 (1968).