

Thermodynamics of Copper(II) Complexation by Macrocyclic Tetrathioethers at 25 °C in Water–Methanol Mixtures and Acetonitrile: Correlations of Complexation Enthalpy and Ligand Conformational Preferences

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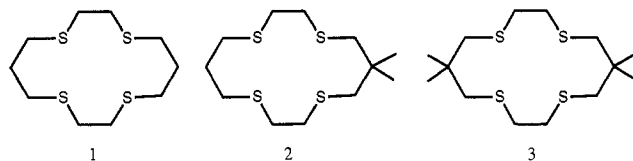
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The stability constants for the interaction of copper(II) ions with three 14-membered tetrathioethers (i.e., [14]aneS₄, Me₂[14]aneS₄, and Me₄[14]aneS₄) have been determined spectrophotometrically in water–methanol mixtures with various concentrations of ClO₄⁻ ion at 25 °C. The stability constant values, *K*₁, for Cu²⁺–L interaction increase from 2.48 for Cu([14]ane[S]₄)²⁺ to 3.04 for Cu(Me₂[14]aneS₄)²⁺ and 3.56 for Cu(Me₄[14]aneS₄)²⁺ in 80% methanol. The enthalpies of complex formation (ΔH_1) measured calorimetrically at 25 °C for Cu²⁺–L interaction in 0.1 M HClO₄ in 90% methanol were –0.87 kcal·mol⁻¹ for [14]aneS₄, –2.45 kcal·mol⁻¹ for Me₂[14]aneS₄ and –3.43 kcal·mol⁻¹ for Me₄[14]aneS₄. Corresponding ΔH_1 values (kcal·mol⁻¹) for acetonitrile ($\mu = 0.005$) were –9.02 for [14]aneS₄, –9.84 for Me₂[14]aneS₄, and –10.73 for Me₄[14]aneS₄. The perchlorate anion forms comparatively strong ternary complexes with Cu(II)–tetrathiomacrocyclic cations. The activity-corrected values for perchlorate association with these cations in 80% MeOH are as follows: log *K*₃ (25 °C) = 2.81 for Cu([14]aneS₄)²⁺, 3.03 for Cu(Me₂[14]aneS₄)²⁺, and 3.25 for Cu(Me₄[14]aneS₄)²⁺. The thermodynamic data, in conjunction with prior structural results, support our earlier hypothesis (Desper, J. M.; Gellman, S. H. *J. Am. Chem. Soc.* 1991, 113, 704) that the *gem*-dimethyl pairs reduce the conformational enthalpy cost required to organize the ligand for chelation.

Introduction

In the simplest rationalization of macrocycle–cation complexation in solution, the type and covalent juxtaposition of the macrocycle's ligating atoms are commonly discussed. More subtle effects on chelation can be exerted by peripheral substituents that affect the macrocycle's conformational preferences. Such effects have been explored for oxamacrocycles and azamacrocycles but have received little attention for thiomacrocycles.² Indeed, relatively few studies of polythioether–cation complexation in solution have been reported;^{3,4} most work in this area has focused instead on solid-state structure.⁵

Recently, the chelation properties of macrocyclic tetrathioethers 1–3 have been examined with Ni(ClO₄)₂ in CD₃NO₂⁶ and with



Cu(ClO₄)₂ in 4:1 H₂O–MeOH.⁷ For both transition metal ions, each additional *gem*-dimethyl pair leads to an incremental

improvement in binding affinity. On the basis of a comparison of crystallographic data for metal-free 1–3 with corresponding data for the Ni(II) and Cu(II) complexes, it was suggested that the *gem*-dimethyl-induced enhancement in affinity results at least in part from a diminished enthalpic cost associated with the adoption of a chelating conformation by the ligand.^{6,7} We now report the results of a more detailed investigation of the interactions between 1–3 and Cu(ClO₄)₂ in solution, involving both spectrophotometric and calorimetric methods.

Experimental Section

The copper perchlorate (Alfa) solutions were standardized by calorimetric titration using EDTA solutions. 1,4,8,11-Tetrathiocyclotetradecane ([14]aneS₄) (Aldrich) was recrystallized before use. The substituted macrocycles 6,6-dimethyl-1,4,8,11-tetrathiocyclotetradecane (Me₂[14]aneS₄) and 6,6,13,13-tetramethyl-1,4,8,11-tetrathiocyclotetradecane (Me₄[14]aneS₄) were synthesized and purified as described previously.^{6a,7} Acetonitrile (Baker, HPLC, water content 0.01%), methanol (Fisher, HPLC Grade, water content 0.05%), and mixtures of methanol and deionized distilled water were used as solvents. Perchloric acid (70%, Fisher, Reagent ACS grade), lithium chloride (Aldrich, Gold Label), and lithium nitrate (Baker, AR) were used. Perchloric acid solutions were standardized using tris(hydroxymethyl)aminomethane (THAM) as primary standard.

A Tronac Model 450 isoperibol calorimeter was used in this study. An electrical calibration was carried out for each solvent system. The accuracy of calibration was checked by reaction of THAM with HCl solution in water. Each experiment was repeated at least 5 times, and the results are reported as the average of all of these determinations. Comparatively high standard deviations are a result of (1) low solubility of ligands in 90% methanol, requiring use of dilute solutions, and (2) low heats of reaction. The use of 90% methanol as solvent was necessary because ligand solubility was too low for calorimetric measurements in 80% methanol.

Copper(II) perchlorate solutions (0.08–0.10 M) in 90% methanol were titrated into 2–4 mM ligand solutions in 0.10 M HClO₄ in 90% methanol. The ligand solutions in pure acetonitrile (0.03–0.04 M) were titrated into 1.5 mM Cu(ClO₄)₂ solutions in acetonitrile. The calorimetric procedure

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Table I. Conditional Stability Constants (K_4), ΔG_4 , ΔH_4 , and $T\Delta S_4$ Values for the Interaction of Copper(II) Ion with Several Tetrathiocyclotetradecanes in 90% Methanol ($\mu = 0.1$; HClO_4) and ΔH_4 Values in Acetonitrile ($\mu = 0.005$)

ligand	90% methanol				acetonitrile	
	$\log K_4^a$	$\log K_4^b$	$-\Delta H_4^a$ (kcal/mol)	$T\Delta S_4$ (kcal/mol)	$-\Delta G_4^a$ (kcal/mol)	$-\Delta H_4^a$ (kcal/mol)
[14]aneS ₄ (1)	3.64 ± 0.04	3.66 ± 0.03	0.87 ± 0.08	4.09 ± 0.09	4.96 ± 0.05	9.02 ± 0.07
Me ₂ [14]aneS ₄ (2)	4.52 ± 0.03	4.50 ± 0.06	2.45 ± 0.04	3.71 ± 0.06	6.16 ± 0.04	9.84 ± 0.08
Me ₄ [14]aneS ₄ (3)	5.12 ± 0.04	5.15 ± 0.07	3.43 ± 0.05 ^a	3.54 ± 0.07	6.97 ± 0.05	10.73 ± 0.08

^a Calorimetric. ^b Spectrophotometric.

and data reduction method used to determine the reaction enthalpies and stability constants have been described previously.⁸

Spectrophotometric measurements were carried out using a Perkin-Elmer 320 spectrophotometer. The stability constants were determined using a molar ratio approach⁹ with different ligand concentrations, a least-squares plot of the data, and an iteration procedure. Molar extinction coefficients in all cases were in the range $(8.4\text{--}8.7) \times 10^3 \text{ L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$. The Cu(II) concentrations were in the range 5×10^{-5} to 1×10^{-4} M. The λ_{max} was 390 nm for all perchlorate complexes studied.

Results

The stability constants for the interaction of copper(II) with a neutral ligand L can be written as

$$K_1 = [\text{CuL}^{2+}]/[\text{Cu}^{2+}][\text{L}] \quad (1)$$

The reaction of an anion with a macrocyclic complex can be described by both K_2 and K_3 :

$$K_2 = [\text{CuL}(\text{ClO}_4)^+]/[\text{Cu}^{2+}][\text{L}][\text{ClO}_4^-] \quad (2)$$

$$K_3 = [\text{CuL}(\text{ClO}_4)^+]/[\text{CuL}^{2+}][\text{ClO}_4^-] \quad (3)$$

The overall conditional constant of the reaction between copper(II) and the macrocyclic thioether L in the presence of anions can be written for a constant concentration of anion as

$$K_4 = ([\text{CuL}^{2+}] + [\text{CuL}(\text{ClO}_4)^+])/[\text{Cu}^{2+}][\text{L}] \quad (4)$$

The conditional stability constants (K_4) and corresponding enthalpies and entropies of complex formation are given in Table I. The stabilities of copper(II) complexes in acetonitrile are too high for determination by either the spectrophotometric or the calorimetric technique ($\log K_4 > 7$). Thus, only enthalpy changes are given for the reactions in acetonitrile solutions. Also, the only ClO_4^- present was that from $\text{Cu}(\text{ClO}_4)_2$.

The K_4 value is a function of anion concentration:

$$K_4 = K_1(1 + K_3[\text{ClO}_4^-]) \quad (5)$$

As K_4 is easy to determine using the calorimetric or the spectrophotometric technique, eq 5 allows the determination of both constants from the plot of K_4 vs anion concentration. The influence of ionic strength (μ) on the stability constants can be described as follows:

$$K_1 = ([\text{CuL}^{2+}]/[\text{Cu}^{2+}][\text{L}])(\gamma_{\text{CuL}}/\gamma_{\text{Cu}}\gamma_{\text{L}}) \quad (6)$$

$$K_3 = ([\text{CuL}(\text{ClO}_4)^+]/[\text{CuL}][\text{ClO}_4^-])(\gamma_{\text{CuLClO}_4}/\gamma_{\text{CuL}}\gamma_{\text{ClO}_4}) \quad (7)$$

Neglecting the difference of ionic radii of the ions with the same charge, one may define γ_n as the activity coefficient of a given

Table II. Conditional Stability Constants (K_4) for the Interaction of Copper(II) Ion with Several Tetrathiocyclotetradecanes in Water–Methanol (w/w 90%) Mixtures Together with Calculated K_1 and K_3 Values

ligand	$\log K_4$		$\log K_1$	$\log K_3^d$
	$[\text{ClO}_4^-] = 0.1^b$	$[\text{ClO}_4^-] = 0.0002^c$		
[14]aneS ₄ (1)	3.66 ± 0.03	2.46 ± 0.03	2.29 ± 0.04	3.47
Me ₂ [14]aneS ₄ (2)	4.50 ± 0.06	3.18 ± 0.03	3.01 ± 0.07	3.59
Me ₄ [14]aneS ₄ (3)	5.15 ± 0.07	3.72 ± 0.05	3.54 ± 0.07	3.71

^a Obtained from spectrophotometric data. ^b $\log \gamma_2 = -1.10$. ^c $\log \gamma_2 = -0.10$. ^d $K_3 = [\text{CuL}(\text{ClO}_4)^+]/[\text{CuL}][\text{ClO}_4^-]$, corrected using the $\log \gamma_2$ value.

ion with charge $\pm n$. In this case

$$K_1 = ([\text{CuL}^{2+}]/[\text{Cu}^{2+}][\text{L}])(\gamma_0)^{-1} \quad (8)$$

In the range of concentrations being used for stability constant calculations, $\mu \leq 0.025$, $\gamma_0 \approx 1$, and the K_1 value is practically independent of ionic strength. Only one activity coefficient term remains in the equation for K_3 :

$$K_3 = ([\text{CuL}(\text{ClO}_4)^+]/[\text{CuL}][\text{ClO}_4^-])(\gamma_2)^{-1} \quad (9)$$

For the determination of γ_n in aqueous solutions, the following empirical equation can be used:¹⁰

$$-\log \gamma_n = 0.5n^2\mu^{1/2}(1 + 1.6\mu^{1/2}) \quad (10)$$

It is known from the Debye–Hückel theory that the coefficient before μ depends on the dielectric constant D as $D^{-3/2}$ in a first term and as $D^{-1/2}$ in a second one. This allows us to rewrite eq 10 in the form

$$-\log \gamma_n = 0.5n^2(D_w/D_s)^{3/2}\mu^{1/2}/(1 + 1.6(D_w/D_s)^{1/2}\mu^{1/2}) \quad (11)$$

where D_w and D_s are the dielectric constants of water and solvent used, respectively. The values of γ_2 for 80% and 90% methanol calculated using this equation are given in Tables II and III.

The stability constants K_4 , K_1 , and K_3 are given in Tables II–IV. The comparatively small uncertainties of the constants confirm the accuracy of the model being used in this study. It can be seen in Table III that the $\log K_4$ values determined earlier⁷ are in good agreement with the values determined in the present study. A plot of $\log K_4$ vs methanol concentration is shown in Figure 1. The $\log K_4$ values plotted in Figure 1 are given in Table V.

Discussion

We previously proposed that the *gem*-dimethyl groups in the 6- and 13-positions of the 14-membered tetrathioether ring enhance Cu(II) affinity by reducing the enthalpic cost of chelation, a cost that arises because covalent bonds in the macrocyclic skeleton must be distorted from their inherent torsional preferences to allow tetracoordination.⁷ The data in Table I are consistent with this hypothesis. The increase in the conditional binding constant (K_4) across the series 1–3 is seen to be associated

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Table III. Conditional Stability Constants (K_4) for the Interaction of Copper(II) Ion with Several Tetrathiocyclotetradecanes in Water–Methanol (w/w 80%) Mixtures Together with Calculated K_3 and K_1 Values^a

[ClO ₄ ⁻]	-log γ_2	log K_4^b	log K_3^d	log K_3^e	log K_1
[14]aneS ₄					
0.0001	0.05	2.51 ± 0.02			2.48
0.0100	0.47	2.97 ± 0.01	2.32	2.79	
0.0150	0.51	3.07 ± 0.01	2.29	2.80	
0.0250	0.62	3.15 ± 0.02	2.17	2.79	
0.1	1.01	3.5 ^c	2.0	3.0	
Me ₂ [14]aneS ₄					
0.0001	0.05	3.09 ± 0.02			3.04
0.0010	0.15	3.31 ± 0.01	2.94	3.09	
0.0025	0.24	3.40 ± 0.02	2.72	2.96	
0.0045	0.31	3.51 ± 0.02	2.64	2.95	
0.0150	0.51	3.80 ± 0.02	2.50	3.01	
0.0250	0.62	3.97 ± 0.01	2.48	3.06	
0.10	1.01	4.2 ^c	2.1	3.1	
Me ₄ [14]aneS ₄					
0.0001	0.05	3.62 ± 0.06			3.56
0.0010	0.15	3.97 ± 0.01	3.19	3.34	
0.0025	0.24	4.11 ± 0.02	3.01	3.25	
0.0045	0.31	4.24 ± 0.01	2.93	3.24	
0.0150	0.51	4.50 ± 0.02	2.71	3.22	
0.0250	0.62	4.61 ± 0.04	2.61	3.23	
0.10	1.01	4.9 ^c	2.29	3.30	

^a The K_1 , K_3 , and K_4 values were determined from spectrophotometric data. ^b Each value is the average of four to eight experimental determinations. The uncertainties are given as standard deviations. ^c Reference 7. ^d $K_3 = [\text{CuL}(\text{ClO}_4)]/[\text{CuL}][\text{ClO}_4]$. ^e log K_3 corrected to $\mu = 0$ using the log γ_2 value.

Table IV. Stability Constants^a for the Interaction of Several Copper(II) Tetrathiocyclotetradecane Complexes with Several Anions in Water–Methanol (w/w 80%) Mixtures

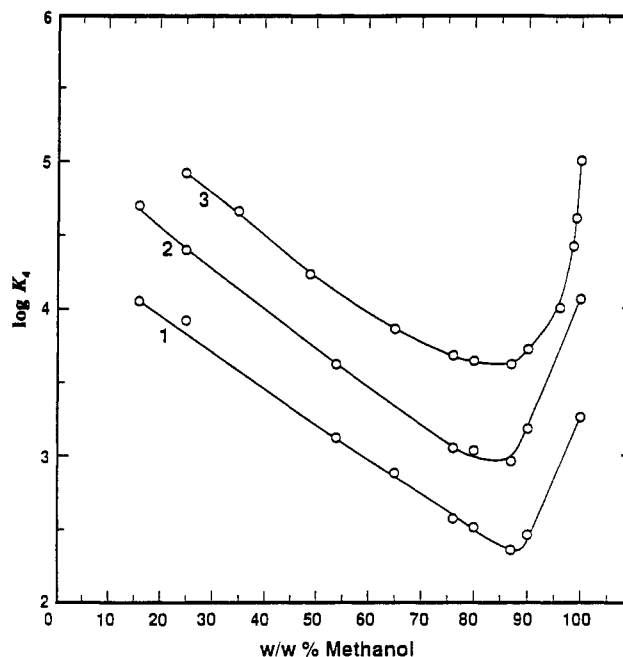
Cu(II) Complex	log K_3^b		
	ClO ₄ ⁻	NO ₃ ⁻	Cl ⁻
Cu[14]aneS ₄ ²⁺	2.81 ± 0.02		
CuMe ₂ [14]aneS ₄ ²⁺	3.03 ± 0.05		3.54 ± 0.05
CuMe ₄ [14]aneS ₄ ²⁺	3.25 ± 0.03	2.6 ± 0.1	3.4 ± 0.1

^a Values corrected to $\mu = 0$ using activity coefficients. ^b $K_3 = [\text{CuL}(\text{X})]/[\text{CuL}][\text{X}]$ (X = ClO₄⁻, NO₃⁻, or Cl⁻).

with a significant increase in the $-\Delta H_4$ term of complex formation. There is relatively little change in the entropy of complexation. Although the magnitude of ΔH_4 for all three macrocycles increases markedly on going from 90% methanol to acetonitrile, the differences in ΔH_4 from one macrocycle to another are similar in the two solvents. This similarity in the $\Delta\Delta H_4$ values suggests that solvation forces do not play a prominent role in determining relative Cu(II) affinities.

Perchlorate ion forms comparatively stable complexes with the three macrocycle–Cu(II) complexes (Table IV). The stabilities of these perchlorate complexes are similar to that observed for chloride ion and slightly higher than that for nitrate ion. As indicated in Table IV, the affinity of the macrocycle–Cu(II) complex for perchlorate ion increases slightly across the series 1–3. Since the differences among the thermodynamic parameters listed in Table I necessarily include effects arising from these differential perchlorate affinities, it is possible that the increasingly favorable enthalpy of complexation across the series 1–3 arises in part from the increasing perchlorate affinity across the series. We suspect that this contribution to the variation in net enthalpy of complexation among 1–3 is small, however, because the differences in log K_3 values among 1–3 are small (Table IV).

The stability of each perchlorate complex increases with increasing organic solvent content, e.g., for 1, log $K_3 = 1.38$ in water,^{4b} 2.81 in 80% methanol (Table IV), and 3.47 in 90% methanol (Table II). The structures of these perchlorate complexes in solution may be similar to the crystallographically

**Figure 1.** Plot of log K_4 for 1–3 vs methanol concentration (w/w %). $[\text{Cu}(\text{ClO}_4)_2] = 5.0 \times 10^{-5}$ with no additional electrolyte present; $T = 25$ °C.**Table V.** Conditional Stability Constants (K_4) for the Interaction at 25 °C of Copper(II) Ion with Several Tetrathiocyclotetradecanes in Water–Methanol Mixtures

% MeOH (w/w)	log K_4^a		
	1	2	3
0	4.05 ^b		
16	4.05	4.70	
25	3.92	4.40	4.92
35			4.66
49			4.23
54	3.12	3.62	
65	2.88	3.86	
76	2.57	3.05	3.68
80 ^c	2.51	3.09	3.62
87	2.36	2.95	3.62
90 ^d	2.46	3.18	3.72
96.2			4.00
98.7			4.42
99.3			4.61
100 ^e	3.26	4.06	5.00

^a Each value is the average of four to eight experimental determinations. The standard deviations were equal to or less than 0.05. $[\text{Cu}(\text{ClO}_4)_2] = 5.0 \times 10^{-5}$ M with no additional electrolyte present. ^b Reference 4b. The value of log $K_1 \sim$ log K_3 . ^c Data from Table II. ^d Data from Table III. ^e Water content 0.05%.

observed Cu(ClO₄)₂ complexes of 2 and 3 containing a *syn*-macrocycle conformation.⁷ In those crystal structures, the macrocycle is asymmetrically folded around the Cu(II) ion, leaving room for close approach of a single perchlorate to the metal center.

The conditional stability constants for Cu(II) complexation by 1 in water and 90% methanol are similar: the log K_4 values are 4.3^{4b} and 3.64 (Table I), respectively. The enthalpies and entropies of complexation, however, vary substantially between the two solvents. For water, $\Delta H_4 = -4.19$ kcal·mol⁻¹ and $\Delta S_4 = 5.7$ cal·deg⁻¹·mol⁻¹,^{4b} while for 90% methanol $\Delta H_4 = -0.87$ kcal·mol⁻¹ and $\Delta S_4 = 13.7$ cal·deg⁻¹·mol⁻¹. The explanation underlying these compensating changes in entropy and enthalpy is unclear.

The trend of log K_4 vs methanol concentration observed in Figure 1 for 1–3 is similar to that reported by Diaddario et al.¹¹ for dissociation rate constant values for a set of Cu(II)–polythioether complexes as a function of solvent composition (H₂O–

CH₃OH mixtures). In that study, the dissociation rate constants exhibited a maximum at about 80 wt % methanol. As indicated above, the log K_3 value increases with increasing methanol. Thus, the K_1 value must be decreasing by an even greater extent with increasing methanol than the trend shown in Figure 1.

Conclusion

Appropriately placed *gem*-dimethyl substituents on a 14-membered tetrathioether macrocycle lead to a predominantly enthalpic enhancement in Cu(II) affinity. The effects we have observed are similar in magnitude to ring size effects previously detected by Rorabacher et al. for Cu(II) chelation by macrocyclic tetrathioethers in water.^{4b} Thus, each additional *gem*-dimethyl pair leads to $\Delta\Delta H_4$ values in the range of -0.8 to -1.6

kcal·mol⁻¹ (Table I), while changing macrocycle size from 14 to 15 or 13 leads to a $\Delta\Delta H_4$ value of $+0.9$ or $+1.8$ kcal·mol⁻¹.^{4b} The enthalpic manifestation of the *gem*-dimethyl substituent effect is consistent with the hypothesis that the peripheral methyl groups decrease the torsional strain required for the 14-membered ring to adopt a chelating conformation.⁷

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Registry No. Methanol, 67-56-1; acetonitrile, 75-05-8; perchlorate, 14797-73-0.