5906 *Inorg. Chem.* **1999,** *38,* 5906−5909

Notes

Unusually High Selectivity of Polythiaethers for Copper(II) over Nickel(II)

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Received June 22, 1999

Introduction

In aqueous solution, thiaether sulfur donor atoms appear to be selective for metal ions in the so-called "copper triangle", specifically Pd(II), Pt(II), Cu(II), Cu(I), Ag(I), Au(I), and Hg(II).[2,3] In determining the stability constants for a large number of Cu(II)− and Cu(I)−polythiaether and −aminopolythiaether complexes in water and methanol−water mixtures,[4−10] we have noted that ligands containing predominantly thiaether sulfur donor atoms do not form observable complexes with any other divalent first-row transition metal ions.[11] Thus, the specific level of selectivity of polythiaethers for copper has never been established.

Complex formation of tetrathiaethers with Ni(II) has been observed in solvents of low complexing ability. Smith and Margerum[12] reported that a simple macrocyclic tetrathiaether complex, $Ni^{II}([14]aneS_4)$ ($[14]aneS_4$ = 1,4,8,11-tetrathiacyclotetradecane), was 180-fold more stable than its acyclic analogue, $Ni^{II}(Me_2\text{-}2,3,2\text{-}S_4)$ ($Me_2\text{-}2,3,2\text{-}S_4$ = 2,5,9,12-tetrathiatridecane) in nitromethane. Using the same solvent, Gellman and co-workers determined the *relative* stabilities of Ni(II) complexes formed with $[14]aneS_4$ and a few derivatives involving *gem*-dimethyl substitution at the 6 or 6,13 positions[13,14] as well as *cis*- or *trans*-cyclohexane replacing one of the ethylene bridges.[15] Neither group of workers established the absolute magnitude of the Ni(II) complex stability constants.

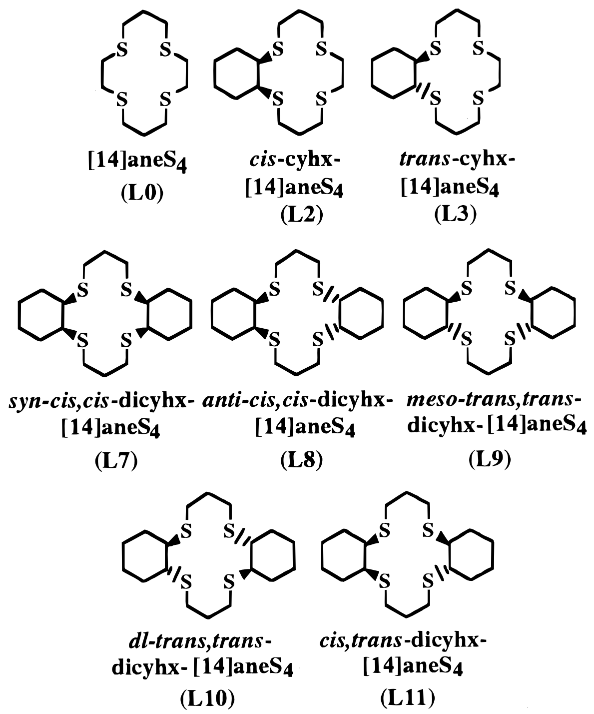

Figure 1. Ligands studied in this work.

Recently, we determined the stability constants of $Cu^{II}([14]aneS_4)$ and several of its derivatives in acetonitrile and noted that these values were 10^6 larger than in aqueous solution.[8] This suggested the feasibility of using the same solvent to obtain comparable stability constants for the corresponding Ni(II) complexes with the same eight macrocyclic ligands (Figure 1). The results, as reported in the current study, reveal that macrocyclic tetrathiaethers exhibit a greater degree of selectivity for Cu(II) over Ni(II) than any other known class of chelating agents.

Experimental Section

Reagents. The $Ni(ClO_4)_2$, $Cu(ClO_4)_2$, and $NaClO_4$ salts used for the current studies were prepared by the slow addition of $HClO_4$ to the metal carbonates. The products were first recrystallized from water, and the hydrated salts were then recrystallized from acetonitrile by evaporation to yield the acetonitrile salts. [**WARNING**! *Metal perchlorate salts are potentially explosive; isolated salts should never be dried and should not be subjected to shock! When recrystallizing from acetonitrile, metal perchlorate solutions should be allowed to evaporate at room temperature and only small quantities should be prepared at*

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10.1021/ic9907213 CCC: $18.00

a time with suitable protection!] The cyclohexanediyl derivatives of [14]aneS$_4$ were synthesized and purified as previously described.[8] Stock solutions of the Cu(II) and Ni(II) salts in acetonitrile were standardized by dilution with large amounts of water followed by titration with aqueous EDTA in ammonia buffer using murexide indicator. Acetonitrile solutions of the polythiaether ligands were standardized spectrophotometrically as the Cu(II) complexes using the molar absorptivity values previously determined.[8] HPLC grade acetonitrile was obtained from Fisher Scientific. The water content was previously found to be 0.017% (w/w) in a bottle of acetonitrile which had been opened 3 weeks earlier.[16] No attempt was made to dry the solvent further since the addition of water up to 3% was found to have no effect upon the stability constant results.

Instrumentation. Spectrophotometric measurements were made using a Cary Model 17D dual-beam spectrophotometer. The temperature was kept constant at 25.0 ± 0.2 °C using a circulating temperature bath, and the ionic strength was maintained at 0.15 M using NaClO$_4$.

Results and Discussion

UV−Visible Spectra. None of the ligands studied absorb in the visible or near-UV region. When dissolved in acetonitrile, Ni(ClO$_4$)$_2$ exhibits two weak absorbance peaks at 372 ($\epsilon = 8.1$) and 600 ($\epsilon = 5.4$) nm. Upon addition of excess [14]aneS$_4$ or one of its derivatives, two new peaks appear in the vicinity of 240 and 310 nm. The latter peak is presumed to represent a S → Ni charge transfer band with a molar absorptivity of approximately (3−20) × 10^3 M^{-1} cm^{-1}, depending upon the specific ligand used. This peak was used for all subsequent measurements.

Stability Constant Determinations. The conditional stability constants for the Ni(II) complexes are defined by the reaction

$$\mathrm{Ni^{2+}} + \mathrm{L} \rightleftharpoons \mathrm{Ni^{II}L'} \qquad K_{\mathrm{Ni^{II}L'}} \tag{1}$$

where the prime designation is intended to include any adducts formed with the perchlorate ion of the type Ni$^{\mathrm{II}}$L(ClO$_4$)$_x$ as previously found with the Cu(II) complexes in aqueous solution.[4,5,17] The possible existence of such adducts was not examined for the Ni(II) complexes but, if present, should be constant in all measurements since [ClO$_4^-$] was held at 0.15 M.

Since Ni(II)−polythiaether complexes are comparatively weak, the determination of their stability constants is facilitated by monitoring the concentration of the Ni$^{\mathrm{II}}$L species. The strong absorbance peak at 302−314 nm made it possible to apply the method of McConnell and Davidson[18] in a manner similar to that previously described for the corresponding Cu(II) complexes in aqueous solution.[4,5] The applicable relationship, as derived from mass balance expressions and Beer's law, may be written in the form

$$\frac{bC_{\mathrm{L}}}{A} = \frac{1}{\epsilon_{\mathrm{Ni^{II}L}}} + \frac{1}{\epsilon_{\mathrm{Ni^{II}L}} K_{\mathrm{Ni^{II}L'}} [\mathrm{Ni^{II}}]} \tag{2}$$

where b represents the path length of the spectrophotometric cell; C_{L} is the total concentration of ligand added; $\epsilon_{\mathrm{Ni^{II}L}}$ is the molar absorptivity of the Ni$^{\mathrm{II}}$L complex; A is the measured absorbance corrected for any contribution from uncomplexed Ni(II). In all cases, the value of [Ni$^{\mathrm{II}}$] was calculated iteratively by appropriate software as C_{Ni} − [Ni$^{\mathrm{II}}$L′].

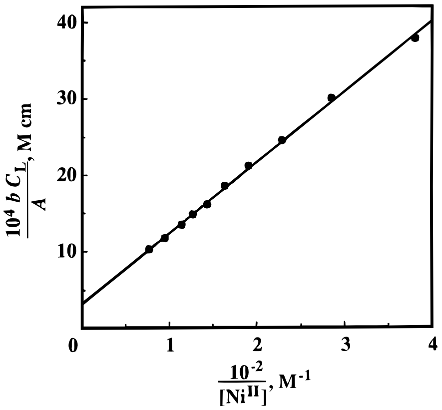

Figure 2. Plot of eq 2 for the stability constant determination of the Ni(II) complex with [14]aneS$_4$ at 25 °C, $\mu = 0.15$ M (NaClO$_4$). The molar absorptivity is equal to the reciprocal intercept while the stability constant is calculated as the intercept to slope ratio.

Table 1. Experimentally Determined Stability Constants and Major Absorbance Peaks for Nickel(II) Complexes Formed with [14]aneS$_4$ and Its Cyclohexanediyl Derivatives in Acetonitrile at 25 °C, μ = 0.15 M (NaClO$_4$)

complexed ligand	λ_{Max}, nm	$10^{-4}\epsilon_{\mathrm{Ni^{II}L}}$,[a] M^{-1} cm^{-1}	$10^{-4}K_{\mathrm{Ni^{II}L}}$,[a] M^{-1}
[14]aneS$_4$ (L0)	302	0.31 (2)	0.0036 (1)
cis-cyhx-[14]aneS$_4$ (L2)	310	1.26 (9)	0.075 (3)
trans-cyhx-[14]aneS$_4$ (L3)	306	1.98 (6)	0.20 (1)
syn-cis,cis-dicyhx-[14]aneS$_4$ (L7)	314	1.78 (5)	15.2 (4)
anti-cis,cis-dicyhx-[14]aneS$_4$ (L8)	310	1.46 (7)	3.5 (2)
meso-trans,trans-dicyhx-[14]aneS$_4$ (L9)	308	2.25 (6)	44 (3)
dl-trans,trans-dicyhx-[14]aneS$_4$ (L10)	308	1.05 (1)	29 (7)
cis,trans-dicyhx-[14]aneS$_4$ (L11)	310	0.981 (4)	9.2 (3)

[a] Values in parentheses are standard deviations relative to the last digit listed; thus, 0.31 (2) and 0.0036 (1) represent 0.31 ± 0.02 and 0.0036 ± 0.0001, respectively.

Figure 2 shows a typical plot of eq 2 for the Ni$^{\mathrm{II}}$([14]aneS$_4$) complex in acetonitrile. Optimal values of the slope and intercept and their standard deviations were determined by least-squares calculations. The molar absorptivity value was determined as the reciprocal intercept and the stability constant as the intercept/slope ratio. The stability constants for all eight Ni(II) complexes included in this work are given in Table 1 along with their standard deviations. This table also includes the specific wavelengths of the maximum absorbance peaks for the Ni$^{\mathrm{II}}$L complexes and the corresponding resolved molar absorptivity values.

Absolute Magnitude of the Ni(II)−Tetrathiaether Stability Constants. As listed in Table 1, the stability constants for the Ni(II) complexes formed with the eight macrocyclic tetrathiaether ligands range over 4 orders of magnitude—from 4 × 10 for Ni$^{\mathrm{II}}$([14]aneS$_4$) (L0) to 4 × 10^5 for Ni$^{\mathrm{II}}$(*meso-trans,trans*-dicyhx-[14]aneS$_4$) (L9). We have previously observed that the stability constants for the Cu(II) complexes formed with these same ligands are approximately 10^6 more stable in acetonitrile than in water.[8] If the same solvent effect applies to the Ni(II) complexes, Ni$^{\mathrm{II}}$([14]aneS$_4$) would be expected to have an aqueous stability constant of about 10^{-4} M^{-1}. Thus, it is not surprising that complex formation of the polythiaethers with Ni(II) has not been observed previously in aqueous media. However, for the strongest complex studied in the current work, Ni$^{\mathrm{II}}$(L9), we note that a 10^6-fold difference in stabilities between acetonitrile and water would suggest that the aqueous stability

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Table 2. Comparative Stability Constants for the Cu(II) and Ni(II) Complexes Formed with [14]aneS$_4$ and Its Cyclohexanediyl-Substituted Derivatives in Acetonitrile at 25 °C

coordinated ligand	log $K_{\mathrm{Cu^{II}L}}{}^{a}$	log $K_{\mathrm{Ni^{II}L}}{}^{b}$	Δ log $K_{\mathrm{M^{II}L}}$
[14]aneS$_4$ (L0)	10.8	1.6	9.2
cis-cyhx-[14]aneS$_4$ (L2)	12.2	2.9^{c}	9.3
trans-cyhx-[14]aneS$_4$ (L3)	12.2	3.3^{c}	8.9
syn-cis,cis-dicyhx-[14]aneS$_4$ (L7)	>14.8	5.2	>9.6
anti-cis,cis-dicyhx-[14]aneS$_4$ (L8)	11.9	4.5	7.4
meso-trans, trans-dicyhx-[14]aneS$_4$ (L9)	14.2	5.6	8.6
dl-trans, trans-dicyhx-[14]aneS$_4$ (L10)	−	5.5	−
cis,trans-dicyhx-[14]aneS$_4$ (L11)	13.3	4.9	8.4

^{a} $\mu = 0.10$ M (NaClO$_4$); ref 8. ^{b} $\mu = 0.15$ M (NaClO$_4$); this work. ^{c} Gellman and co-workers obtained Δ log $K_{\mathrm{Ni^{II}L}} = 2.0$ and 2.2−2.3 for Ni$^{\mathrm{II}}$(L2) and Ni$^{\mathrm{II}}$(L3), respectively, versus Ni$^{\mathrm{II}}$(L0) in nitromethane; ref 15.

Table 3. Comparative Stability Constants for Cu(II) and Ni(II) Complexes Involving Coordination to Four Donor Atoms in Aqueous Solution at 25 °C, $\mu = 0.1$ M (Except as Noted)

complex^{a}	log $K_{\mathrm{Cu^{II}L}}$	log $K_{\mathrm{Ni^{II}L}}$	Δ log $K_{\mathrm{M^{II}L}}$	ref
Amine Nitrogen Donor Atoms				
M$^{\mathrm{II}}$(NH$_3$)$_4$: β_4	12.9^{b}	8.1^{b}	4.8	20
M$^{\mathrm{II}}$(en)$_2$: β_2	20.1^{c}	14.1^{c}	6.0	21
	20.0^{d}	13.9^{d}	6.1	22
M$^{\mathrm{II}}$(trien)	20.1	14.1	6.0	23
	20.4^{e}	14.0^{e}	6.4	24
M$^{\mathrm{II}}$(2,3,2-tet)	23.9^{f}	16.4^{f}	7.5	25
M$^{\mathrm{II}}$(cyclam)	27.2^{g}	22.2	5.0	26, 27
Pyridyl Nitrogen Donor Atoms				
M$^{\mathrm{II}}$(bpy)$_2$: β_2	13.7	13.9	−0.2	28
M$^{\mathrm{II}}$(phen)$_2$: β_2	15.4	16.0	−0.6	28
	16.1^{e}	17.1^{e}	−1.0	29
Oxygen Donor Atoms				
M$^{\mathrm{II}}$(acac)$_2$: β_2	14.9^{h}	10.7^{h}	4.2	30
M$^{\mathrm{II}}$(oxal)$_2$: β_2	7.3	8.1^{i}	−0.8	31, 32
Combined Amine Nitrogen and Carboxvlate Oxygen Donor Atoms				
M$^{\mathrm{II}}$(gly)$_2$: β_2	15.1^{e}	10.6^{e}	4.5	33
M$^{\mathrm{II}}$(NTA)	12.7^{e}	11.3^{e}	1.4	34
M$^{\mathrm{II}}$(EDTA)^{j}	18.8^{e}	18.6^{e}	0.2	35
Combined Amine Nitrogen or Carboxylate Oxygen and Thiaether Sulfur Donor Atoms				
M$^{\mathrm{II}}$(DADTO)	11.3^{d,k}	7.9^{d,k}	3.4	36
M$^{\mathrm{II}}$(EDTDA)	5.3	4.3	1.0	37

^{a} en = ethylenediamine; trien = 1,4,7,10-tetraazadecane; 2,3,2-tet = 1,4,8,11-tetraazaundecane; cyclam = [14]aneN$_4$ = 1,4,8,11-tetraazacyclotetradecane; bpy = 2,2′-bipyridine; phen = 1,10-phenanthroline; acac = acetylacetonate; oxal = oxalate; gly = glycinate; NTA = nitrilotriacetate; EDTA = ethylenediamine-*N*,*N*,*N*′,*N*′-tetraacetate; DADTO = 1,8-diamino-3,6-dithiaoctane; EDTDA = (ethylenedithio)diacetate. ^{b} $\mu = 2$. ^{c} $\mu > 1$. ^{d} $\mu = 1$. ^{e} 20 °C. ^{f} $\mu = 0.5$. ^{g} $\mu = 0.2$. ^{h} μ = variable. ^{i} $\mu = 3$. ^{j} EDTA contains six donor atoms rather than four and is included for comparative purposes only. ^{k} 30 °C.

constant would be about 0.4. Such a $K_{\mathrm{Ni^{II}L}}$ value should result in an observable amount of complex formation in water in the presence of 1 M Ni(II). This experiment was tried and no complex formation was observed.

Stability Constant Trends. The data in Table 1 show that the substitution of cyclohexane groups on [14]aneS$_4$ results in a significant increase in the stability of the Ni(II) complexes. For L2 and L3, the enhancements in the Ni(II) complexes relative to Ni$^{\mathrm{II}}$(L0) are 20- and 50-fold, respectively. These values are comparable to the 25-fold enhancement observed earlier for the Cu(II) complexes with each of these two ligands relative to L0 in acetonitrile (Table 2).[8] Gellman et al.[15] observed that the stability enhancements for the Ni$^{\mathrm{II}}$(L2) and -(L3) complexes relative to Ni$^{\mathrm{II}}$(L0) in nitromethane were even greater at ≈100 and ≈150−200, respectively. In consideration of the rather approximate nature of the NMR data in Gellman's study, this level of agreement implies that similar trends exist in both solvents.

Selectivity of Tetrathiaethers for Cu(II) over Ni(II). The stability constant values listed in Table 2 for the Cu(II)−polythiaether complexes in acetonitrile were calculated from the formal potentials and the stability constants for the corresponding Cu$^{\mathrm{I}}$L complexes as determined by an indirect electrochemical method.[8] In view of the probable error inherent in the $K_{\mathrm{Cu^{II}L}}$ values obtained by this indirect approach, it is concluded that five of the seven ligands for which comparable stability constant data have been obtained for both Ni(II) and Cu(II) in acetonitrile (i.e., L0, L2, L3, L9, L11) exhibit an essentially constant selectivity ratio (represented as Δ log $K_{\mathrm{M^{II}L}}$ in Table 2) of approximately 10^9 in favor of the latter metal ion. Since, as noted above, we were unable to observe any complex formation for Ni$^{\mathrm{II}}$(L9) in aqueous solution, we conclude that the aqueous $K_{\mathrm{Ni^{II}L}}$ value is less than 0.1 for this complex. This implies that the aqueous selectivity of macrocyclic polythiaethers for Cu(II) over Ni(II) is also at least 10^9.

The stability constant ratios obtained for the complexes with L7 and L8 deviate from 10^9 by an amount which exceeds the anticipated experimental error. The crystal structures of uncomplexed L7 and its Cu(II) complex[19] indicate that the lone pairs on the four sulfur donor atoms have a predisposition to point in the same direction relative to the macrocyclic ring so that the d^9 Cu(II) ion sits above the donor atom plane in a square pyramidal complex. This coordination geometry is much less favorable for the d^8 Ni(II) ion, which prefers planar coordination, and we presume that it is this feature which accounts for the apparent enhancement in selectivity for Cu$^{\mathrm{II}}$(L7). The underlying basis for the reduced selectivity of L8 for Cu(II) relative to Ni(II) is less obvious, but is likely due to a related structural phenomenon.

Comparison to Other Chelating Agents. The 10^9 selectivity of the tetrathiaethers for Cu(II) relative to Ni(II) appears to belarger than for any other known class of ligands. Representative stability constants for these same two metal ions with a wide variety of representative ligands involving four donor atoms[20−37] are listed in Table 3. For the most part, the selectivity

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ratio for Cu(II) over Ni(II) maximizes at about 10^5-10^6 when four amine nitrogens are involved. Somewhat surprisingly, the acyclic 2,3,2-tet (i.e., 1,4,8,11-tetraazaundecane) ligand provides an additional $1^1/_2$ orders of magnitude in the selectivity ratio. The macrocyclic tetrathiaethers included in the current work are still an additional $1^1/_2$ orders of magnitude greater in their selectivity for Cu(II) over Ni(II) and are 3 or more orders of magnitude larger than the majority of chelating agents which favor complexation of Cu(II).

It is interesting to note that cyclam (i.e., [14]aneN_4), the tetramine equivalent of [14]aneS_4, is no more selective for Cu(II) than is ammonia. Ligands with oxygen donors generally exhibit even smaller selectivities for Cu(II) relative to Ni(II). When a fifth or sixth donor atom is added to the complex, the degree of selectivity also tends to decrease since Cu(II) does not effectively coordinate at axial sites due to Jahn−Teller distortion. Thus, the Cu(II) and Ni(II) complexes with EDTA are essentially equal in stability.[35]

Conclusion

The selectivity of the macrocyclic tetrathiaethers for Cu(II) relative to Ni(II) is approximately 10^9 in acetonitrile. Our inability to observe any formation of even the most stable $\mathrm{Ni^{II}}$−tetrathiaether complex in aqueous media implies that the aqueous selectivity of these ligands is also at least 10^9. Thus, the tetrathiaether ligands exhibit a markedly enhanced selectivity for Cu(II) over Ni(II) compared to all other common classes of quadridentate ligands. In combination with their apparent low toxicity,[38] the high level of selectivity of macrocyclic polythiaethers for Cu(II) suggests their potential use in copper chelation therapy.[11]

Acknowledgment. This work was supported by the National Science Foundation under Grant CHE-9528831.

IC9907213

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