

Table II. Formation Constants, $\log K$, of Complexes of Ligands Based on the 18-aneN₂O₄ Ring^a

metal ion	substituent			
	-H ^b	-CH ₂ CH(CH ₃)OH ^c	-CH ₂ COO ^{-d}	-CH ₂ py ^e
Cu ²⁺	6.1	5.97		13.55
Ni ²⁺				8.80
Zn ²⁺	3.1	3.0	8.1	6.96
Cd ²⁺	5.25	7.64	11.9	10.96
Ca ²⁺	1.74 ^c	3.59	7.7	3.63
Sr ²⁺	2.6	4.05		4.87
Ba ²⁺	2.97	4.65		4.99
La ³⁺	~3.0 ^f	3.24	11.7	3.53
Pb ²⁺	6.8	8.57	13.5	11.67

^aThe donor groups indicated are attached to the two nitrogens of the ring of 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane. ^bTaken from ref 2. ^cFrom ref 9b. ^dFrom Hancock, R. D.; Shaikjee, M. S., to be submitted for publication. ^eThis work. ^fHancock, R. D.; Hearn, A., unpublished work.

$\Delta \log K$ vs. r^+ relationship is the same for DME-18-aneN₂O₄/(HSEtNH₂)₂ as for (py)₂-18-aneN₂O₄/(AMP)₂, then we can read off that $\Delta \log K$ for Pb²⁺ will be 5.9 log units, and adding this to the $\log \beta_2$ for (mercaptoethyl)amine to predict $\log K_1$ equals 26.1 for DME-18-aneN₂O₄. Similarly, $\log K_1$ for Cd²⁺ and Zn²⁺ can be predicted to be 22.9 and 16.3, respectively, with DME-18-aneN₂O₄, suggesting that this might indeed be a sufficiently powerful ligand for our purposes. In addition, the selectivity for Pb²⁺ and Cd²⁺ over Zn²⁺ should be very high, while $\log K_1$ with the Ca²⁺ ion is predicted to be only about 7.0, so that selectivity over Ca²⁺ will also be very high. We are at present synthesizing DME-18-aneN₂O₄ so that we can study its complexing properties and suitability for treating metal-poisoning problems.

An interesting feature of the complexing properties of (py)₂-18-ane-N₂O₄ is that (Table II) it binds very hard metal ions like Ca²⁺, Sr²⁺, and Ba²⁺, which are not normally considered to have much affinity for nitrogen donors, more strongly than does DHP-18-ane-N₂O₄. The poor affinity of these metal ions for nitrogen donor ligands arises from the fact that in the usual standard state the nitrogen donor ligand is competing with 55.5 M water. By comparison of (py)₂-18-aneN₂O₄ with DHP-18-aneN₂O₄, the pyridyl groups of the former ligand are placed on an equal footing with the hydroxypropyl groups of the latter, and it is seen that the pyridyl groups (Table II) are for all metal ions better donors than are the alcoholic groups. This fact suggests that recently reported¹⁶ cryptand ligands that have all pyridyl donor groups will display what may at first sight seem surprisingly high affinity for the alkaline-earth-metal ions. Indeed, the isolation of (py)₂-18-aneN₂O₄ as a sodium complex¹⁰ from solution, rather than as the free ligand, suggests that a surprisingly good affinity of pyridyl groups for alkali-metal ions will also be found.

Acknowledgment. We thank the Council Research Grants Committee of the University of the Witwatersrand, as well as the Foundation for Research Development, for generous financial support for this work. We thank Dr. M. Gulumian of the National Centre for Occupational Health for her support for and continuing interest in this work.

Registry No. (py)₂-18-aneN₂O₄, 103837-13-4; Cu, 7440-50-8; Ni, 7440-02-0; Zn, 7440-66-6; Cd, 7440-43-9; Ca, 7440-70-2; La, 7439-91-0; Sr, 7440-24-6; Pb, 7439-92-1; Ba, 7440-39-3.

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Synthesis and Metal Complexes of Macrocyclic Triamines Bearing a Phenol Pendant

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Received April 4, 1986

A novel, one-pot annelation method that "recycles" coumarin with the linear triamine 1,7-diamino-4-azaheptane has been applied to the synthesis of a phenol-pendant 12-membered macrocyclic triamine ([12]ane-N₃, **7**). The simplicity and versatility of this annelation method will be useful in the synthesis of a variety of macrocyclic spermidine alkaloid analogues. With Cu^{II}, Ni^{II}, and Zn^{II} the pendant phenol becomes phenolate at acidic pH to serve as the fourth donor. The resulting 1:1 metal complexes are more stable than the corresponding phenol-less [12]ane-N₃ complexes.

Introduction

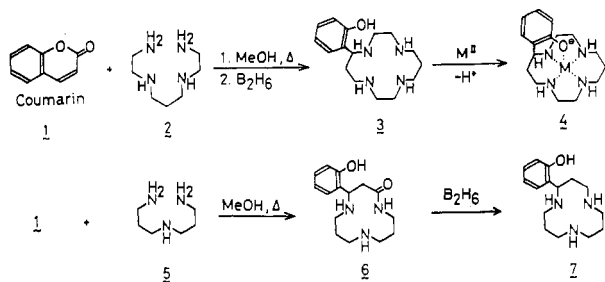
Cyclization of saturated triamine ligands has remarkable thermodynamic and kinetic effects on complex formation. Although metal complexes of macrocyclic triamines have been studied extensively,¹⁻⁹ they are limited to unsubstituted triamines with various ring sizes. These macrocyclic triamines coordinate

with transition-metal ions only facially for three-coordinated 1:1 complexes with the remaining coordination sites unoccupied (or solvated) in solutions or for six-coordinated 2:1 complexes.⁶⁻⁹ The triamine ligands that possess a potential fourth donor covalently attached to the macrocyclic rings might greatly affect the structure and properties of the complexes.

Recently,¹⁰ we have discovered a novel annelation method for the synthesis of a new phenol-appended tetraamine macrocycle (**3**) starting from coumarin (**1**) and a linear tetraamine such as **2** and described some of their unique complexes properties. The pendant phenol readily interacts with encapsulated metal ions below in a N₄ macrocycle, which causes dissociation of its proton for an apical coordination (see **4**) to enhance the stability or drastically modify the structure of the complexes. An X-ray crystal structure of Ni^{II} complex **4** has proved the most appro-

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privately designed phenol side arm for an axial donor.¹¹ Now we have successfully extended our synthetic method to obtain a new macrocyclic triamine ligand, phenol-pendant [12]ane-N₃ (7). Indeed, this phenol in general has strong interactions with Cu^{II}, Ni^{II}, Zn^{II}, and Co^{II}, as supported by perturbed UV spectra of the phenol. As a result, their 1:1 complexes are more stabilized with respect to the phenolate-less [12]ane-N₃ complexes. The phenolate interactions with metal ions in the macrocyclic triamines are generally stronger than those in the macrocyclic tetraamines.

Experimental Section

General Methods. All chemicals were of analytical reagent grade and were used without further purification. Melting points were determined by using a Yanaco micro melting point apparatus and were uncorrected. The IR spectra were recorded on a Shimadzu IR-408; UV-visible spectra, on a Shimadzu double-beam spectrophotometer UV 200S at 25.0 ± 0.1 °C using matched quartz cells of 1-cm path length; ¹H-NMR spectra, on a Hitachi R-40 high-resolution NMR spectrometer (90 MHz). Splitting patterns are indicated as follows: s, singlet, d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. ESR spectra were obtained at 77 K by using a JES-FE1X spectrometer operating at 9300 MHz and equipped with a dual cavity. A small sample of Mn^{II} was placed in the reference cavity. Two spectra were recorded for each sample, wherein the field was swept alternatively in opposite directions, and the average *g* values were calculated by the approximation method of Knenbühl.¹² The *g*_{||} values are accurate to ±0.05, and *g*_⊥ values to ±0.01. For TLC analysis throughout this work, Merck precoated TLC plates (silica gel 60 F₂₅₄) were used.

4-(2-Hydroxyphenyl)-1,5,9-triazacyclododecan-2-one (6). Equimolar amount of coumarin (1) (14.6 g, 0.1 mol) and 1,7-diamino-4-azaheptane (5) (13.1 g, 0.1 mol) in 1 L of dry methanol were refluxed for 2 weeks. After near complete evaporation of the solvent on a rotary evaporator, acetonitrile was added to crystallize the residue. Recrystallization from methanol-acetonitrile yielded 6 (mp 134 °C) as colorless crystals in 10% yield (2.8 g, 10 mmol). TLC: *R*_f 0.37 (CH₂Cl₂/MeOH/28% NH₃aq = 2:2:0.6). ¹H NMR (CD₃OD): δ 1.5–1.9 (4 H, br, N–C–CH₂–C–N), 2.2–3.1 (8 H, m, N–CH₂, N–COCH, CO–N–CH), 3.2–3.3 (1 H, m, CO–N–CH), 3.6–4.2 (2 H, q, N–COCH, Ar–CH), 6.4–7.1 (4 H, m, PhH). IR (KBr): 3250, 2900, 1640 cm⁻¹. Anal. Calcd for C₁₅H₂₃N₃O₂: C, 64.96; H, 8.36; N, 15.15. Found: C, 65.46; H, 8.58; N, 15.44.

2-(2-Hydroxyphenyl)-1,5,9-triazacyclododecan-2-one (7). Reduction of the monooxo precursor 6 (1.5 g, 5.4 mmol) with freshly distilled B₂H₆ in tetrahydrofuran (THF) yielded 7 (0.82 g, 2.2 mmol) as its trihydrochloride salt (mp 173 °C dec) in 40% yield, after recrystallization from 36% aqueous HCl–MeOH. TLC: *R*_f 0.82 (CH₂Cl₂/MeOH/28% NH₃aq = 2:2:0.6). ¹H NMR (CDCl₃): δ 1.5–1.9 (4 H, br, N–C–CH₂–C–N), 2.3–3.2 (6 H, br, N–CH₂), 3.7–4.0 (1 H, g, Ar–CH), 5.9 (4 H, br, NH, PhOH), 6.5–7.0 (4 H, m, PhH). IR (KBr): 3250, 2900 cm⁻¹. Anal. Calcd for C₁₅H₂₅N₃O·3HCl·1.5H₂O: C, 45.06; H, 7.82; N, 10.51. Found: C, 45.05; H, 7.54; N, 10.28.

4-Phenyl-1,5,9-triazacycloundecan-2-one (9). Equimolar amounts of cinnamic acid methyl ester (8) (68 mmol) and 1,7-diamino-4-azaheptane (5) (68 mmol) in dry methanol (700 mL) were refluxed for 2 weeks. The same workup as above yielded 9 (mp 138 °C) as colorless crystals in 18% yield (3.5 g, 12 mmol). TLC: *R*_f 0.30 (CH₂Cl₂/MeOH/28% NH₃aq = 2:2:0.6). ¹H NMR (CDCl₃): δ 1.4–1.8 (4 H, m, N–C–CH₂–C–N), 1.9 (2 H, br, NH), 2.4–3.1 (8 H, m, N–CH₂, N–CO–CH₂), 3.3–3.7 (2 H, m, CO–N–CH₂), 3.8–4.1 (1 H, t, Ph–CH), 7.1–7.5 (5 H, m, PhH), 9.0–9.3 (1 H, br, CO–NH). IR (KBr): 3250, 2800, 1620 cm⁻¹. The side product 10 was obtained as the monohydrochloride (mp 323 °C dec) in 5% yield based on the triamine 5 after addition of an aqueous 2 M HCl solution to the evaporated mother liquid. TLC: *R*_f 0.61 (CH₂Cl₂/MeOH/28% NH₃aq = 2:2:1). ¹H NMR (CDCl₃): δ 1.5–2.0 (5 H, m,

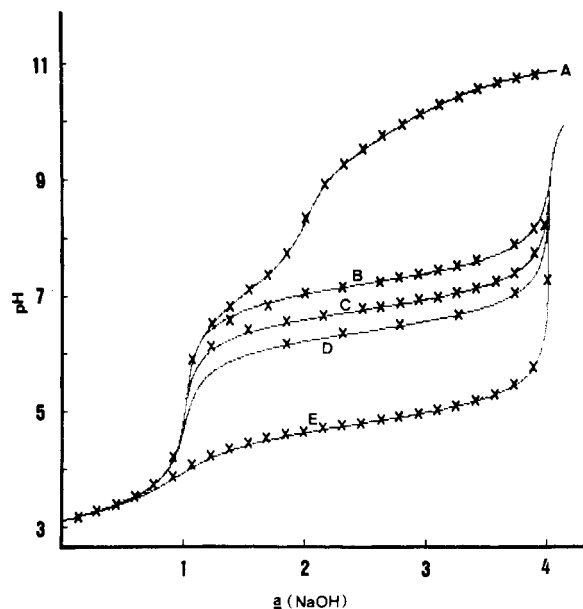


Figure 1. Calculated titration curves with experimental values (in dots) for (A) 1.00×10^{-3} M 7·3HCl alone, and for 1.00×10^{-3} M 7·3HCl in the presence of 1.00×10^{-3} M (B) Co^{II}, (C) Zn^{II}, (D) Ni^{II}, and (E) Cu^{II}, respectively.

N–C–CH₂–C–N), 2.5–2.8 (4 H, t, N–CH₂), 3.3–3.6 (4 H, g, CO–N–CH₂), 6.3–6.4 (2 H, d, CO–CH), 6.9–7.4 (12 H, m, PhH, CO–NH), 7.4–7.6 (2 H, d, Ph–CH). IR (KBr): 3350, 2950, 1650 cm⁻¹.

Potentiometric Titrations. Aqueous solutions (50 mL) of L-3HCl (*L* = 7, 1.00×10^{-3} M) with and without equimolar metal ion were titrated with carbonate-free 0.100 M NaOH aqueous solution. The pH values were read with an Orion 811 digitizer pH meter. The temperature was maintained at 25.00 ± 0.05 °C, and the ionic strength was adjusted to 0.10 M with NaClO₄. $-\log [H^+]$ values were estimated with a correction of -0.08 pH unit to the pH meter readings.¹³ All solutions were carefully protected from air by a stream of humidified argon. The electrode system was calibrated with pH 7.00 and 4.01 buffer solutions and checked by the duplicate theoretical titration curves of 4.00×10^{-3} M HClO₄ with 0.100 M NaOH solution at 25 °C and *I* = 0.10 M (NaClO₄) in the high and low pH regions. Because of the very high *pK*₁ value of macrocyclic polyamines aided further by phenolate anion, an alternative procedure was employed for ligand 7 that essentially compared the amine titration with a second blank titration. First, the pH–*a* data from the potentiometric titration of the amine salt with standard base were recorded in the interval from *a* = 3 to *a* = 4 (this corresponds to the reaction L [zwitter ion form] + OH⁻ → H₁L⁻ + H₂O). A second blank solution that contained sodium and perchlorate ion concentrations identical with the ligand solution at *a* = 3 was also titrated with the same standard base. Plots of pH vs. volume were made, and from the two curves differences in volume at various increments of pH were determined. This volume difference corresponds exactly to the amount of L titrated. The *pK*₁ of phenol-pendant [12]ane-N₃ was determined from 10 points taken from three separate titration pairs with solutions ranging in ligand concentrations from 1.00×10^{-3} to 5.00×10^{-3} M.

Equilibrium was not rapidly attained during any part of the titration of the Ni–7 system. Consequently, each titration point was obtained from a separately prepared solution to which had been added the desired quantity of NaOH. The solution was then stored under argon for over 1 week at room temperature (~25 °C) and thermostated for 1 h prior to the pH measurement.

Electrochemical Measurements. Dc polarography was performed with a Yanaco Polarographic Analyzer P-1100 system at 25.00 ± 0.05 °C and *I* = 1.5 M (Na₂SO₄). A three-electrode system was employed: Yanagimoto P10-RE rotary glassy-carbon-disk electrode as the working electrode, as Pt wire as the counter electrode, and a saturated calomel reference electrode (SCE) at 25 °C. The scan range was 0–1.2 V vs. SCE, and the scan speed was 10 mV s⁻¹.

Results

Determination of Protonation Constants for 7. The experimental acid–base titration equilibrium in the absence of metal ions is

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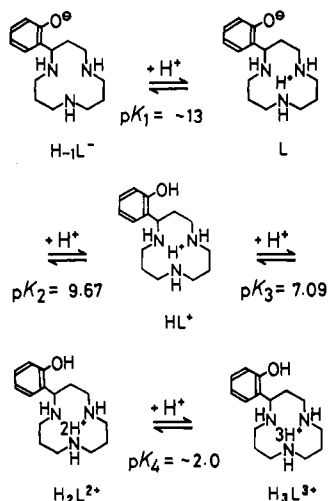
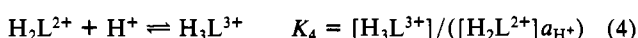
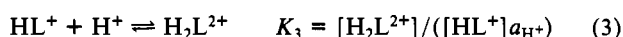
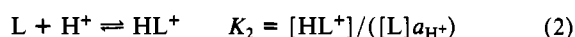
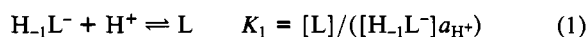


Figure 2. Scheme of the protonation equilibria of 7.

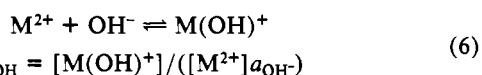
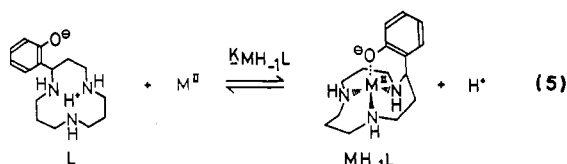
shown in dots on line A of Figure 1. The titration data were analyzed for equilibria 1–4, where $H_{-1}L^{-}$ denotes the phenol-



proton-dissociated ligand 7.

The log values of calculated mixed protonation constants K_1 , K_2 , K_3 , and K_4 are 13 , 9.67 ± 0.03 , 7.09 ± 0.02 , and 2.0 , respectively. The theoretical titration curve derived from the obtained $K_1 - K_4$ values is shown as line A of Figure 1. The pK_a value of 9.67 is assigned to the protonation of the phenolate, confirmed by the UV absorption spectral measurement on the bases of $\lambda_{max} = 273$ nm ($\epsilon = 2000$) for the phenol form and $\lambda_{max} = 292$ nm ($\epsilon = 3400$) for the phenolate form. The ligand structures with successive protonations are illustrated in Figure 2.

Determination of Cu^{II} , Ni^{II} , Zn^{II} , and Co^{II} Complexation Constants, $K_{MH_{-1}L}$. The titration data of 7 in the presence of each metal ion (see dots on lines B–E in Figure 1) were treated by the Schwarzenbach method¹⁴ for the 1:1 complexation (eq 5). The



metal hydrolysis (eq 6) was taken into account, where K_{OH} values are 4.6×10^6 for Cu^{II} , 1.2×10^3 for Ni^{II} , 1.1×10^5 for Zn^{II} ,¹¹ and 9.1×10^3 for Co^{II} .¹⁵

The obtained 1:1 complexation constants ($\log K_{MH_{-1}L}$) at 25 °C and $I = 0.1$ M ($NaClO_4$) are summarized in Table I, along with values of $\log K_{ML}$ ($H_{-1}L + M \rightleftharpoons MH_{-1}L$; calculated for comparison with those of M^{II} —the phenolate-less [12]ane- N_3 complexes). The theoretical titration curves based on the determined complexation constants are drawn in lines B–E of Figure 1.

Discussion

Ligand Synthesis. The treatment of coumarin (1) with 1,5-diamino-3-azapentane (dien) in refluxing MeOH gave a com-

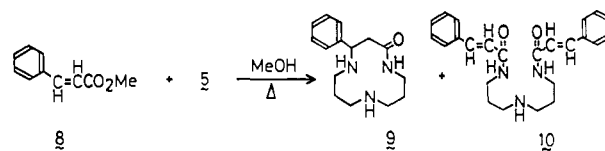
Table I. Metal(II)–Ligand 1:1 Complexation Constants ($\log K_{MH_{-1}L}$) and Calculated $\log K_{ML}$ Values at 25 °C and $I = 0.1$ M ($NaClO_4$)

metal	$\log K_{MH_{-1}L}^a$	$\log K_{ML}^b$	$\log K'_{ML}^c$
Co^{II}	-1.65 ± 0.03	11.4	
Zn^{II}	-0.42 ± 0.03	12.6	8.8
Ni^{II}	0.98 ± 0.05	14.0	10.9
Cu^{II}	5.38 ± 0.03	18.4	12.6

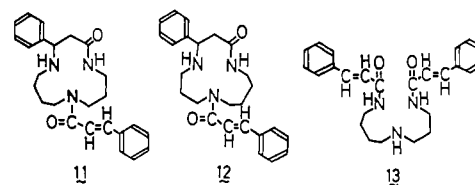
^a $K_{MH_{-1}L} = [MH_{-1}L]a_{H^{+}}/[L][M]$. ^b $K_{ML} (M^{-1}) = [MH_{-1}L]/[H_{-1}L][M]$. Calculation based on $K_{MH_{-1}L}$ values and approximate pK_a value of 13. ^c $K'_{ML} = [ML]/[L][M]$ in ref 4.

licated products mixture and failed to yield an anticipated 10-membered macrocyclic triamine. However, the treatment with homologous 5 afforded 6 as a sole reaction product (identified by TLC). Triamines with longer methylene chains (e.g. 1,8-diamino-4-azaoctane, “spermidine”) failed to yield the homologous cyclic products. Hence, 5 among the tested triamines should be of the most suitable chain length for the annelation that involves the reactions of the two terminal amines for the initial Michael addition followed by the lactamization. The reduction of the lactam function is successful only with diborane in THF, leading to desired triamine 7, isolated as a trihydrochloride salt.

In this annelation reaction coumarin (1) can be replaced by methyl cinnamate 8. Refluxing 8 and triamine 5 in MeOH for



2 weeks yielded a phenyl-pendent macrocycle (9) in 18% yield, along with a noncyclic diamidation product (10) in 5% yield. The reaction was neat, and only the two products were detected on TLC. The latter product was separated chromatographically and purified as a monohydrochloride salt. Our annelation methods can be used with cinnamate derivatives having various substituents on the benzene ring. It is very interesting to point out that cyclic 9 is a homologue of macrocyclic spermidine alkaloids celacinnine (11)¹⁶ and dihydroperiphylline (12)¹⁷ and that linear 10 is similar to maytenine (13).¹⁸ Some of these spermidine alkaloids were



reported to possess biological activities.¹⁹ Hence, 9 and 10 or their derivatives with substituted phenyls would be of interest from a biological point of view, too.

Binding of 7 with Metals. In aqueous solutions, Cu^{II} , Ni^{II} , Zn^{II} , and Co^{II} all interact with 7 (as $L \cdot 3H^{+}$) to release four protons simultaneously below neutral pH (see smooth buffer regions till $a = 4$ in Figure 1), which indicates the simultaneous N_3 and phenolate coordinations. This is in contrast to the complexation of 3 involving N_4 with the phenol coordinations in a stepwise fashion. A molecular model can build an ideal tetrahedral geometry with the N_3 and additional phenolate binding. The titration data all fit the 1:1 $MH_{-1}L$ formation. The 1:1 complex stabilities $K_{MH_{-1}L}$ follow the normal (Irving–Williams) order $Cu^{II} > Ni^{II} > Zn^{II} > Co^{II}$. The same stability order was reported for K'_{ML} ($= [ML]/[M][L]$) values of Cu^{II-} , Ni^{II-} , and Zn^{II-} [12]ane- N_3

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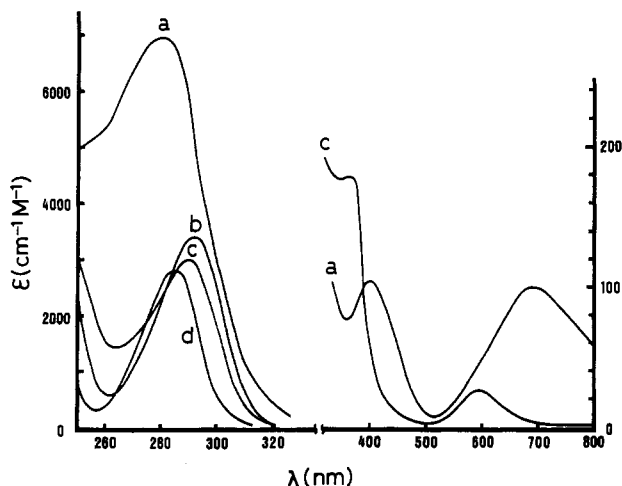
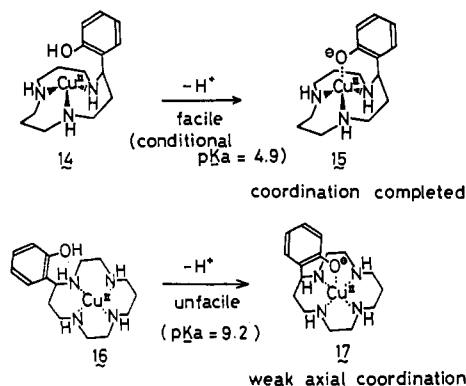


Figure 3. UV absorption spectra [λ_{\max} , nm (ϵ)] of (a) $\text{Cu}^{\text{II}}\text{H}_{-1}\text{L}$ [279 (7000), 392 (120), 690 (110)], (b) H_{-1}L^- [292 (3400)], (c) $\text{Ni}^{\text{II}}\text{H}_{-1}\text{L}$ [290 (3000), 363 (180), 590 (25)], and (d) $\text{Zn}^{\text{II}}\text{H}_{-1}\text{L}$ [285 (2800)] for $\text{L} = 7$ at 25 °C and $I = 0.1$ (NaClO_4).

complexes.⁴ However, the calculated stability constants K_{ML} ($=[\text{MH}_{-1}\text{L}]/[\text{H}_{-1}\text{L}][\text{M}]$) for the phenolate-pod macrocycle **7** are greater for each metal complex; see Table I. The 1:1 $\text{M}^{\text{II}}\text{-}[12]\text{ane-N}_3$ complexes tend to have an additional external hydroxyl ligand to satisfy the requirement for four-coordination.⁴

The UV and visible absorption spectra of these complexes are shown in Figure 3. The d-d transition spectra are reported for $\text{Cu}^{\text{II}}\text{-}[12]\text{ane-N}_3$ (689 nm, $\epsilon = 138$)⁸ and $\text{Ni}^{\text{II}}\text{-}[12]\text{ane-N}_3$ (612 nm, $\epsilon = 14$).⁵ The analogy in the ligand field spectrum of $\text{Cu}^{\text{II}}\text{-}[12]\text{ane-N}_3$ with or without phenolate is noteworthy. These visible spectra of $\text{Cu}^{\text{II}}\text{-macrocyclic N}_3$ are typical for Cu^{II} in a pseudotetragonal ligand field and not for pseudotetrahedral or trigonal symmetry. This result suggests that the coordination geometry of **7** about Cu^{II} may be viewed as a part of pseudooctahedron. The ESR spectrum of $\text{Cu}^{\text{II}}\text{-7}$ ($g_{\perp} = 2.06$, $g_{\parallel} = 2.24$, $A_{\parallel} = 165$ g at pH 11 and 77 K) is also similar to that of $\text{Cu}^{\text{II}}\text{-}[12]\text{ane-N}_3$ ($g_{\perp} = 2.05$, $g_{\parallel} = 2.24$, $A_{\parallel} = 169$ G).^{8,20} Other interesting spectral features are the phenolate $\pi\text{-}\pi^*$ UV bands at $\lambda_{\max} = 280\text{--}290$ nm characteristic to each metal complex, which is discussed in the following paragraph.

Phenol-Phenolate Equilibrium. The tetraprotonated (uncomplexed) ligand **7** shows four successive deprotonation constants (see Figure 2). The $\text{p}K_2$ value of 9.67 for the phenol attached to the monoprotonated triamine is almost comparable to the value for phenol itself, which indicates minor interaction of the phenol group with the monoprotonated cyclic triamine. By contrast, the phenol attached to diprotonated tetraamine, $[14]\text{ane-N}_4$ (cyclam), has a lower $\text{p}K_a$ value of 8.86 under the strong influence of the dipositive charge.¹⁰ However, when it comes to the dipositive $[12]\text{ane-N}_3$ with divalent transition-metal ions (in particular Cu^{II}), the dissociation of the phenol becomes very facile (see **15**). In the presence of equimolar metal ion (1 mM), the pH values for $[\text{phenolate form}]/[\text{phenol form}] = 1$ are 4.8, 6.4, 6.8, and 7.3, as calculated from $\log K_{\text{MH}_{-1}\text{L}}$ and $\log K_{1-4}$, for Cu^{II} , Ni^{II} , Zn^{II} , and Co^{II} , respectively. On the other hand, dissociation of the phenol on $\text{Cu}^{\text{II}}\text{-}[14]\text{ane-N}_4$ (see **17**) is not so enhanced (its $\text{p}K_a$ value is 9.2, potentiometrically determined²¹). Undoubtedly, the



difference is in the fourth vs. fifth axial donor coordination. In the $\text{Cu}^{\text{II}}\text{-tetraamine}$ system **16**, the axial interaction will be weaker due to the Jahn-Teller effect. In fact, one can identify both phenol form **16** and phenolate form **17** at different pH.²¹ On the other hand, the phenolate donor in **15** would saturate the $\text{Cu}^{\text{II}}\text{-N}_3$ coordination, and hence the strong interaction is expected. The stability enhancement ($\Delta \log K_{\text{ML}}$) of 5.8 (with N_3 system; see Table I) with respect to 1.5 (with the N_4 system)²¹ well illustrates the greater contribution to the phenolate coordination to the stability of macrocyclic N_3 systems.

The strong interaction of the phenolate with Cu^{II} in N_3 (**15**) is also manifested in considerable stabilization of the phenolate against oxidation ($E_{1/2} \sim +0.85$ V vs. SCE), while the phenolate in N_4 (**17**) is not particularly stabilized ($E_{1/2} \sim +0.5$ V) with respect to the uncoordinated ligand phenolate at pH 11 ($E_{1/2} \sim +0.5$ V). With loosely bound high-spin N^{II} complexes, the extent of the phenol deprotonation is not so sensitive (as with Cu^{II}) with the N_3 and N_4 macrocycles ($\text{p}K_a$ of 6.4 [conditional constant] vs. 6.3).

The UV absorption band ($\pi\text{-}\pi^*$) due to the phenolate ($\lambda_{\max} = 292$ nm, $\epsilon = 3400$) is appreciably shifted in wavelength and intensity in **15** upon coordination to Cu^{II} (see spectrum a, Figure 3), which suggests strong perturbation. In **17** a broad absorption band occurs at ~ 290 nm ($\epsilon = 7000$). On the other hand, with Ni^{II} (see spectrum c) and Zn^{II} (spectrum d) the bands are less deviated from that of the uncomplexed phenolate anion. This indicates ionic nature of the phenolate- Ni^{II} and -Zn^{II} bondings. In the N_4 system, the corresponding bands are at 293 nm ($\epsilon = 3700$) and 288 nm ($\epsilon = 2600$), respectively.²¹ With Co^{II} the phenolate absorption occurs broadly at ~ 280 nm.

Conclusion

Phenol-pendant 12-membered macrocyclic triamine $[12]\text{ane-N}_3$ (**7**) is synthesized from coumarin and 1,7-diamino-4-azaheptane. The simplicity of the present annelation method will be useful for the synthesis of a series of macrocyclic spermidine alkaloid analogues. The pendant phenol readily dissociates its proton upon interaction with metal ions Cu^{II} , Ni^{II} , Zn^{II} , and Co^{II} and becomes a strong fourth donor, which are concluded from potentiometric analysis. The 1:1 complexation constants are higher than those with phenol-less $[12]\text{ane-N}_3$. The $\text{Cu}^{\text{II}}\text{-coordinated}$ phenolate is stabilized against oxidation.

Registry No. 1, 91-64-5; 5, 56-18-8; 6, 104197-24-2; 7, 104197-25-3; 8, 103-26-4; 9, 104197-26-4; 10, 104197-27-5; $\text{Zn}^{\text{II}}\text{H}_{-1}\text{L}$, 104197-30-0; $\text{Ni}^{\text{II}}\text{H}_{-1}\text{L}$, 104197-31-1; $\text{Cu}^{\text{II}}\text{H}_{-1}\text{L}$, 104197-32-2; $\text{Co}^{\text{II}}\text{H}_{-1}\text{L}$, 104197-29-7.

(20) Isolation of crystalline $\text{Cu}^{\text{II}}\text{-7}$ complex has been unsuccessful.

(21) Kodama, M.; Kimura, E., unpublished data.