Synthesis of Novel Macrocyclic Polyamines with a Pendant Phenol Group and Properties and Structures of Their Copper(II) Complexes

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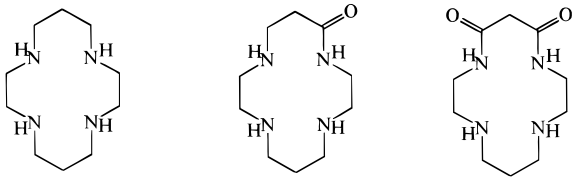
A series of new dioxocyclams with pendant phenol groups has been synthesized from coumarin 3-carboxylic ester and linear polyamines in refluxing methanol/ethanol. Corresponding saturated cyclam derivatives were obtained by B_2H_6·THF reduction. Reaction of a dioxocylam derivative with $Cu(ClO_4)_2$ in aqueous solution yields a singly deprotonated dioxotetraamine copper(II) complex, whose X-ray crystal structure has shown that the enolic tautomer of an amido group was coordinated to copper(II). X-ray crystal data for $[C_{17}H_{25}N_4O_3Cu]$-ClO_4·H_2O: monoclinic, space group $P2_1/a$, $a = 15.554(3)$ Å, $b = 8.478(2)$ Å, $c = 17.250(3)$ Å, $\beta = 111.4(1)°$, $V = 2117(1)$ Å^3, $Z = 4$, $D_c = 1.614$ mg/mm^3, $F(000) = 1068$, $R = 0.040$ and $R_w = 0.044$. When coordinated to copper(II), the amido group deprotonates with p$K_a = 4.3$. Potentiometric, electrochemical, and EPR spectral data of the complexes were studied. In the pH region 3−9, the substituent phenol does not coordinate to the copper(II) ion; however, substituents do have some effect on their Cu(II)/Cu(III) potential and complex stability. In this study, we show that, besides doubly deprotonated copper(II) complexes, singly deprotonated dioxotetraamine complexes also exist both in aqueous solution and in the solid state with considerable stability. The existence of the singly deprotonated dioxotetraamine copper(II) complex undoubtedly indicates that the complex deprotonates stepwise and not simutaneous. This is a new conceptual discovery. The results provide us critical evidence for a discussion of the detailed mechanism of complex formation and acid dissociation.

Introduction

Polyamine macrocycles possess cavities capable of providing a favorable environment for transition metal ions.[1] The strength of the ion binding is determined by ion size, macrocyclic cavity size, and ligand conformation.[2,3] Typically, the 14-membered tetraamine macrocycles cyclam, monooxocyclam, and dioxocyclam (Chart 1), like porphyrins and corrin, incorporate metal ions into their cavities and form a stable square planar complex with several configurations.[4,5] Macrocyclic oxopolyamines are unique metal chelators; their structure bears the dual features of macrocyclic polyamines and oligopeptides.[6−9] Because of their important biological functions and some unusual properties, oxopolyamines have been extensively studied, and structural feactures for biological significance are well recognized.[6−15] The two amido groups in macrocyclic dioxotetraamine are equivalent, when coordinated to a 3d metal ion, amido groups will be deprotonated simultaneously.[15] As for dioxotetraamine, the presence of a nondeprotonated or a singly deprotonated complex is unlikely;[15] therefore, complexes of this kind of ligand with nondeprotonated amido groups were generally not considered in previous studies.[6−15] Recently, in the study of formation constants and dissociation kinetics and mechanisms, Kaden and Hay predicted that singly deprotonated dioxocyclamcopper(II) complexes may exist in solution[16] and such singly deprotonated

Chart 1



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species are seen with other tripeptides[17] and diamides,[18] but there was no X-ray structure evidence until now.

Recently we have discovered a new and versatile synthetic method that leads to a novel class of macrocyclic dioxotetraamine with an aromatic pendant group attached at a ring carbon atom.[7] The synthesis uses coumarin 3-carboxylic ester and linear polyamines as starting materials. This method does not involve Michael addition, and the reacting time is much shorter than the method reported by Kimura.[19]

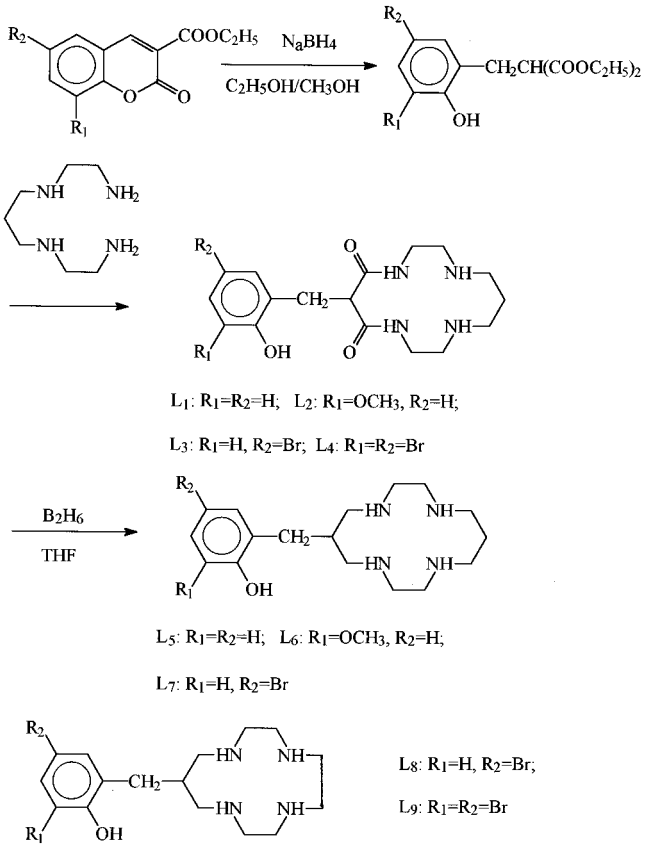
In the present study, we have applied our new method to the synthesis of a new series of macrocyclic dioxotetraamines and saturated polyamines with phenol as pendants and have observed the coordination properties and redox behavior of their copper(II) complexes. The unique feature of the new complex lies in that both amido(peptide) nitrogen atoms coordinated to copper(II) with one amido group deprotonated, the other amido hydrogen "migrated" to the amido oxygen to form a C-hydroxyl Schiff base (enolic tautomer) instead of deprotonation occurring. The enolic tautomer of amide was coordinated to the metal ion. This is a new conceptual discovery at least in the knowledge of macrocyclic dioxotetraamines.

Experimental Section

Materials. 2*H*-1-Benzopyran-3-carboxylic acid 2-oxoethyl ester (coumarin 3-carboxylic ester) and other coumarin derivatives were prepared as previously reported.[7] The B_2H_6·THF solution was synthesized as described by H. C. Brown.[20]

C-Functionalized Macrocyclic Dioxotetraamine. To 500 mL of an ethanol solution of coumarin derivative (0.1 mol) at room temperature was added slowly with stirring a sodium borohydride (0.1 mol) ethanol solution (200 mL). The mixture was reacted for 30 min to give corresponding malonate ester. To this solution, without isolation of the intermediates, was added $H_2N(CH_2)_2NH(CH_2)_3-NH(CH_2)_2NH_2$ (0.1 mol), and the mixture was refluxed for 6 days. Most of the solvent was distilled off, and the residue (about 50 mL) was allowed to stand overnight. The white products 6-(2′-hydroxyl)benzyl-1,4,8,11-tetraazacyclotridecane-5,7-dione, with or without substituent, was obtained in 15% yields. L_1: mp 232−234 °C dec. Anal. Calcd for $C_{17}H_{26}N_4O_3$ (L_1): C, 60.88; H, 7.65; N, 16.35. Found: C, 61.05; H, 7.84; N, 16.75. Infrared spectra (KBr pellet, cm^{-1}): 3371, 3311, 3217; 3059 w (Ar−H), 1664 s (ν(C═O)), 1275 (C−N). ^{1}H NMR (DMSO-*d*, ppm): 6.96 (2H), 6.74 (1H), 6.64 (1H), 3.42 (2H), 2.89 (2H), 2.68 (2H), 2.50 (6H), 2.43 (4H). MS (EI): 334 (M^+), 304, 290, 276, 233, 147, 113, 99, 70, 56. L_2: mp 224−226 °C dec. Anal. Calcd for $C_{18}H_{28}N_4O_4$·0.5H_2O (L_2): C, 57.85; H, 7.59; N, 14.45. Found: C, 57.88; H, 7.83; N, 15.00. Infrared spectra (KBr pellet, cm^{-1}): 3290, 3248; 3077 w (Ar−H), 1646 s (ν(C═O)), 1281 (C−O). ^{1}H NMR (DMSO-*d*, ppm): 6.77 (1H), 6.61 (2H), 3.75 (3H), 3.40 (3H), 3.35 (4H), 2.90 (2H), 2.80 (2H), 2.54 (6H), 1.51 (2H). MS (EI): 364 (M^+), 306, 263, 220, 177, 137, 113, 99, 70, 56. L_3: mp 216−218 °C dec. Anal. Calcd for $C_{17}H_{25}N_4O_3Br$·0.5H_2O (L3): C, 48.68; H, 5.64; N, 12.93. Found: C, 48.35; H, 5.96; N, 13.27. Infrared spectra (KBr pellet, cm^{-1}): 3329, 3219; 3060 w(Ar−H), 1658 s (ν(C═O)), 1270 (C−O). ^{1}H NMR (DMSO-*d*, ppm): 7.13 (2H), 6.71 (1H), 3.43 (6H), 2.83 (4H), 2.60 (6H), 1.51 (2H). MS (EI): 412 (M^+), 382, 356, 313, 270, 227, 198, 156, 127, 113, 99, 70, 56. L_4: mp 212−214 °C dec. Anal. Calcd for $C_{17}H_{24}N_4O_3Br_2$·H_2O (L_4): C, 40.34; H, 4.88; N, 10.58. Found: C, 39.99; H, 5.14; N, 10.98. Infrared spectra (KBr pellet, cm^{-1}): 3317, 3217; 3067 w(Ar−H), 1664 s (ν(C═O)), 1245 (C−O). No NMR data were available because of its low solubility. The syntheses of the ligands are summarized in Scheme 1.

Scheme 1. Synthesis of the Ligands



Saturated Polyamines. A 150 mL aliquot of anhydrous THF was added to 0.01 mol of macrocyclic dioxotetraamine in a 250 mL three-necked round-bottom flask at 0 °C, under nitrogen atomsphere, and then 50 mL of 1 M B_2H_6·THF solution was added. The reacting mixture was refluxed for 24 h and then cooled in an ice-water bath. Then 10 mL of H_2O was added to decompose unreacted B_2H_6. A 20 mL aliquot of 6 M HCl was added, all liquid was distilled off under reduced pressure, and the solid residue was dissolved in methanol, the methanol was distilled off to remove most of the H_3BO_3 (as its methyl ester), and the remaining solid was recrystallized in methanol−HCl (10%). Some white powder precipitated upon standing. Yield: 30%. Anal. Calcd for $C_{17}H_{30}N_4O$·3HCl·5H_2O (L_5·3HCl·5H_2O): C, 40.51; H, 8.69; N, 11.11. Found: C, 40.30; H, 8.35; N, 11.11. Infrared spectra (KBr pellet, cm^{-1}): 3625, 3360, 3232, 2300−3600 (br), 1291, 1081, 1451, 762. ^{1}H NMR (D_2O, ppm): 7.08 (2H), 6.60 (2H), 2.99 (12H), 2.80 (4H), 2.53 (2H), 2.24 (1H), 1.60 (2H). Anal. Calcd for $C_{18}H_{32}N_4O_2$·3HCl·5H_2O (L_6·3HCl·5H_2O): C, 40.49; H, 8.49; N, 10.49. Found: C, 40.28; H, 8.05; N, 10.13. Infrared spectra (KBr pellet, cm^{-1}): 3625, 3360, 2300−3600 (br), 1273, 1077, 1478, 762. ^{1}H NMR (D_2O, ppm): 6.86 (1H), 6.80 (1H), 6.70 (1H), 3.75 (2H), 3.32 (2H), 3.28 (2H), 3.13 (3H), 2.94 (6H), 2.76 (2H), 2.54 (2H), 2.05 (2H), 1.78 (1H). Anal. Calcd for $C_{17}H_{29}N_4OBr$·3HCl·5H_2O (L_7·3HCl·5H_2O): C, 38.67; H, 6.87; N, 10.61. Found: C, 38.42; H, 6.62; N, 10.55. Infrared spectra (KBr pellet, cm^{-1}): 3442, 2300−3600 (br), 1268, 1060, 1485, 778. ^{1}H NMR (D_2O, ppm): 7.20 (2H), 6.69 (1H), 3.00 (12H), 2.80 (4H), 2.49 (2H), 2.21 (1H), 1.60 (2H). Anal. Calcd for $C_{16}H_{27}N_4OBr$·3HCl·5H_2O (L_8·3HCl·5H_2O): C, 34.68; H, 7.28; N, 10.11. Found: C, 34.72; H, 6.96; N, 10.13. Infrared spectra (KBr pellet, cm^{-1}): 3400, 2300−3600 (br), 1267, 1059, 1462. Anal. Calcd for $C_{16}H_{26}N_4OBr_2$·3HCl·H_2O (L_9·3HCl·H_2O): C, 33.27; H, 5.15; N, 9.54. Found: C, 33.22; H, 5.41; N, 9.69. Infrared spectra (KBr pellet, cm^{-1}): 3457, 3302, 3190, 2300−3600 (br), 1245, 1097, 1451, 762. ^{1}H NMR (D_2O, ppm): 7.57 (1H), 7.24 (1H), 2.98 (10H), 2.83 (6H), 2.58 (3H), 2.24 (1H). All these reduced ligands have no ν(C═O) absorption at 1640−1670 cm^{-1} in the IR spectra.

Preparation of the Complexes. In the preparation of copper(II) complex, ligand L_1 (335 mg, 1 mmol) was dissolved in 20 mL of an aqueous solution of $Cu(ClO_4)_2$ (1 mmol). The solution was filtered,

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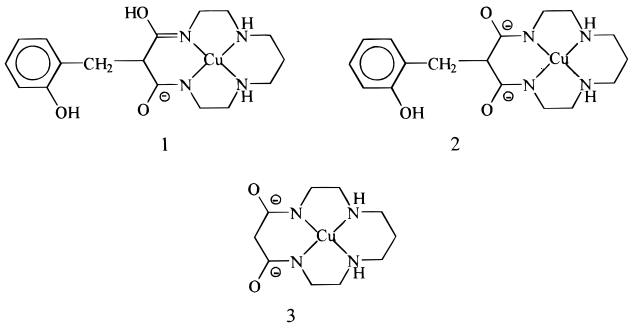
Chart 2. Structures of Complexes **1**, **2**, and **3**



and the filtrate was allowed to stand at room temperature for several days during which red crystals of $[C_{17}H_{25}N_4O_3Cu]\cdot ClO_4\cdot H_2O$ (**1**) suitable for X-ray structure analysis were obtained in 80% yield. Anal. Calcd for $[C_{17}H_{25}N_4O_3Cu]\cdot ClO_4\cdot H_2O$: C, 39.69; H, 5.29; N, 10.89. Found: C, 39.65; H, 4.86; N, 10.57. Infrared spectra (KBr pellet): 3558, 3509, 3264, 3232; 3025 w (Ar-H), 2400−2700 m (enolic tautomer), 1683 s (ν(C═N)), 1597 s (ν(C═O)), 1107 s (ClO_4), 995, 762, 626s cm^{-1}. EPR (110 K, methanol): $A_{\|} = 210$ G, $g_{\|} = 2.168$, $g_{\perp} = 2.048$. Electronic spectra in H_2O: 495 (77), 275 (700), 225 nm (1600). Reflectance spectra: 490, 293, and 238 nm.

When ligand L_1 reacted with $Cu(ClO_4)_2$ under neutral condition (adjusted by NaOH solution to pH = 7−8), a doubly deprotonated pink complex $C_{17}H_{24}N_4O_3Cu\cdot 2H_2O$ (**2**) was obtained in 60% yield. Calcd for $C_{17}H_{24}N_4O_3Cu\cdot 2H_2O$: C, 47.37; H, 6.55; N, 13.0. Found: C, 47.04; H, 5.77; N, 12.62. Infrared spectra (KBr pellet): 3357 (br, H_2O), 3188, 3127 (OH, NH), 3042 (Ar—H), 1596 s (ν(C═O)), 1486, 1384, 1252, 1075, 937, 760. EPR (110 K, methanol): $A_{\|} = 211$ G, $g_{\|} = 2.168$, $g_{\perp} = 2.035$. Electronic spectra in H_2O: 505 (115), 275 (500), 225 nm (1200). Reflectance spectra: 517, 290, and 238 nm.

For comparison, dioxocyclam reacted with $Cu(ClO_4)_2$ under the same conditions as in the preparation of complex **1** (i.e. without adjusting pH of the solution) to give a purple complex, $C_{10}H_{18}N_4O_2Cu\cdot 4.5H_2O$ (**3**), in 60% yield. Anal. Calcd for $C_{10}H_{18}N_4O_2Cu\cdot 4.5H_2O$: C, 30.19; H, 7.60; N, 14.08. Found: C, 30.36; H, 7.11; N, 14.03. Infrared spectra (KBr pellet): 3371 (br, H_2O), 3138 (NH), 1604 (C═O), 1547, 1399, 1265, 1078, 935, 717 cm^{-1}. EPR (110 K, methanol): $A_{\|} = 215$ G, $g_{\|} = 2.172$, $g_{\perp} = 2.038$. Electronic spectra in H_2O: 515 (158), 240 (900) nm. Reflectance spectra: 517, 290, and 238 nm. The proposed structures of complexes **1**−**3** are shown in Chart 2.

Caution! Perchlorate salts of metal complexes with organic ligands are potentially explosive. Only small amounts of material should be prepared, and these should be handled with caution. The complex described in this report has, so far, been found to be safe when used in small quantities.

Instruments. IR spectra were measured on a Nicolet 170 SXFT. Elemental analysis was determined on P-E 240C instrument. Methanol solutions of copper(II) complexes (mixed 1:1 ligand and copper(II) nitrate methanol solution) had their pH adjusted with NaOH. Methanol solutions at 120 K and at room temperature were used for measurement of EPR spectra on a Bruker ER-200-D-SRC10 spectrometer. NMR spectra were recorded on a Bruker AM-500 spectrometer with DMSO-*d* or D_2O as solvents. EI−MS spectra were measured on a ZAB-HS (VG Company, UK). The cyclic voltammograms were measured in aqueous solution at room temperature on PARC Model 273 electrochemical apparatus. The electrolyte was 0.5 mol·dm^{-3} Na_2SO_4. A three electrode system was employed. Glassy carbon was used as a working electrode and a saturated calomel electrode (SCE) as reference and Pt coil as counter electrode. The scan rate was 100 mV/s. Concentration of complexes was 2×10^{-3} mol·dm^{-3} (1:1 ligand and copper(II) sulfate aqueous solution).

pH Titration. The potentiometric equilibrium measurements of the ligands in the absence and in the presence of copper(II) ions were carried out with a Beckman pH meter Model Φ71. Electrode response was standardized with buffer solutions at pH 4.003, 6.864, 9.182, and 12.460. The hydrogen ion activity coefficient was calculated through the pH value of standard acid. The temperature was maintained at 25 ± 0.1 °C. Each titration was performed in a solution of 20 mL adjusted to 0.1 ionic strength with $NaNO_3$. Typical concentrations of experimental solutions were 1×10^{-3} mol·dm^{-3} in ligand with molar concentrations of metal ion equivalent to that of the ligand. The free ligand (base) was dissolved in an adequate amount of dilute HNO_3 and then titrated with 0.1 mol·dm^{-3} NaOH. Redistilled water (in quartzware equipment) was used for preparing all the solutions. $NaNO_3$ and $Cu(NO_3)_2$ were recrystallized before use. The data were processed on a computer using the TIT program.[21] For each system at least two titrations were performed, each titration contained about 50 experimental points.

X-ray Diffraction Measurements. X-ray examination and data collection procedures were performed at room temperature on an Enraf-Nonius CAD4 diffractomer. Data for the red crystal having approximate dimensions of 0.2 × 0.3 × 0.3 mm were collected at 299 K using the $\omega-2\theta$ scan mode (θ range 2.0−23.0). Unit-cell parameters were determined from the positions of 25 carefully centered reflections in the range $8.21 < \theta < 12.17°$. A total of 2976 unique reflections were measured, of which 1982 with $I > 3\sigma(I)$ were used in the structure determination. All data were corrected for empirical absorption correction. The structure was solved by direct methods by using SDP-PLUS. Full-matrix least-squares refinement was carried out by minimizing the function $\sum w(|F_o| - |F_c|)^2$. Cu and four N atoms were located on an *E*-map. Remaining atoms were located on subsequent difference maps. The positions of all non-hydrogen atoms were refined with anisotropic displacement factors. Except two water hydrogens that cannot be located on the *E*-map, all other H-atom positions were refined, but their isotropic thermal parameters were held fixed. The convergence of the last stage of full-matrix least-squares refinement reached $R = 0.040$ and $R_w = 0.044$. The highest peak in the final difference Fourier map had a height of 0.34 e/Å^3. The maximum negative peak in the final difference electron density synthesis was −0.52 e/Å^3. Crystal data for $[C_{17}H_{25}N_4O_3Cu]\cdot ClO_4\cdot H_2O$ (**1**): monoclinic, space group $P2_1/a$, $a = 15.554(3)$ Å, $b = 8.478(2)$ Å, $c = 17.250(3)$ Å, $\beta = 111.4(1)°$, $V = 2117(1)$ Å^3, $Z = 4$, $D_c = 1.614$ mg/mm^3, $F(000) = 1068$.

Results and Discussion

Synthesis of the Ligands. The functionalization of macrocycles allows us to modify or introduce new properties into a ligand: it can make the ligand more selective toward a metal ion, it can increase or decrease the thermodynamic stability and the kinetic inertness, it can change the solubility and extractability into an organic phase, and it can covalently attach the macrocycle to a polymeric support or to a protein.[1,22] Functionalization can be achieved using either a carbon or a nitrogen atom of the ring as an attaching point. The carbon-substituted derivatives have the advantage of not influencing the nature of the heteroatomic donor group and are ideal substituents. The present preparation of cyclic dioxotetraamine has a significant advantage in that any desirable substituent can be introduced on the carbon atom of the macrocyclic skeleton. The size of the macrocycle can be changed easily by judicious choice of the linear tetraamine. Also, for synthesis of 14-membered macrocyclic dioxotetraamine, the products can precipitate out from solution without using silica gel chromatography and are easier to obtain than in the synthesis of 13-membered analogs.[7]

The procedure for synthesis of the saturated polyamine is somewhat different from the previously reported method.[19,24] Adding excess strong base cannot extract the free ligand because of the presence of a phenolic group. By adding excess $HClO_4$, we cannot obtain pure solid ligand because of the large solubility (ligand $HClO_4$ salt) and phenolic oxidation. Here we just added

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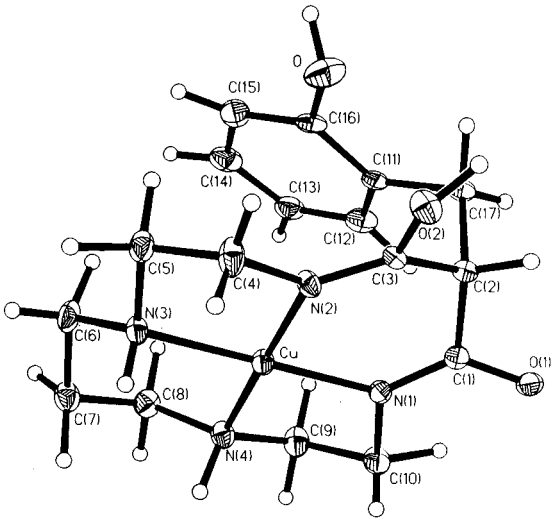


Figure 1. Structural representation of complex cation $[Cu(C_{17}H_{25}N_4O_3)]^+$.

Table 1. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Coefficients ($Å^2 \times 10^3$) of $[Cu(C_{17}H_{25}N_4O_3)]\cdot ClO_4\cdot H_2O$ ($U(eq) = (1/3)\sum_i\sum_j U_{ij}a_i^*a_j^*a_ia_j$)

atoms	*x*	*y*	*z*	*U*(eq)
Cu	7103(1)	1657(1)	7387(1)	26(1)
Cl	5440(1)	3068(3)	4255(1)	54(1)
O	9721(3)	3620(6)	9024(3)	54(1)
O(1)	6603(3)	1060(5)	9549(3)	30(1)
O(2)	7853(3)	5574(5)	8886(3)	35(1)
O(11)	6081(3)	3921(7)	4935(3)	71(1)
O(12)	4958(4)	1975(8)	4569(4)	90(1)
O(13)	4807(4)	4128(7)	3696(4)	92(1)
O(14)	5908(5)	2261(8)	3814(5)	109(1)
N(1)	6728(3)	968(6)	8277(3)	27(1)
N(2)	7549(3)	3677(5)	7908(3)	26(1)
N(3)	7482(3)	2437(6)	6466(3)	28(1)
N(4)	6655(3)	−460(6)	6885(3)	29(1)
C(1)	6919(4)	1560(7)	9009(3)	25(1)
C(2)	7610(4)	2941(6)	9287(3)	24(1)
C(3)	7650(4)	4089(7)	8645(4)	24(1)
C(4)	7708(5)	4785(7)	7314(4)	41(1)
C(5)	8088(5)	3828(7)	6773(4)	38(1)
C(6)	7864(5)	1269(7)	6036(4)	39(1)
C(7)	7233(5)	−142(8)	5734(4)	39(1)
C(8)	7186(5)	−1199(7)	6420(4)	39(1)
C(9)	6587(4)	−1470(7)	7557(4)	37(1)
C(10)	6181(4)	−495(7)	8072(4)	37(1)
C(11)	9013(4)	1300(7)	9262(4)	29(1)
C(12)	8874(4)	−317(8)	9161(4)	38(1)
C(13)	9258(4)	−1164(8)	8685(5)	46(1)
C(14)	9788(5)	−438(8)	8305(4)	46(1)
C(15)	9944(4)	1179(8)	8411(4)	44(1)
C(16)	9567(4)	2029(7)	8899(4)	32(1)
C(17)	8597(4)	2235(7)	9782(4)	31(1)
O(15)	5368(4)	2496(7)	6387(4)	73(1)

excess HCl and methanol; after all of the H_3BO_3 was sublimed as its esters, pure solid polyamine(as its HCl salt) was obtained.

Description of the Crystal Structure. A perspective view of the complex compound $[C_{17}H_{25}N_4O_3Cu]\cdot ClO_4\cdot H_2O$ is shown in Figure 1. Positional parameters and their estimated standard deviations are reported in Table 1. Selected bond distances and bond angles are listed in Table 2.

The cation of complex **1** is characterized by an essentially square planar coordination geometry around the metal center, formed by two secondary amino nitrogens and two peptide nitrogens (Figure 1). The oxygen of phenol is not coordinated to the metal ion. The Cu(II)−N(amido) bond distance is much shorter than the Cu(II)−N(secondary amine) bond distance, indicating comparatively strong coordination. We can see from the structure of complex **1** that hydrogen atoms are not attached

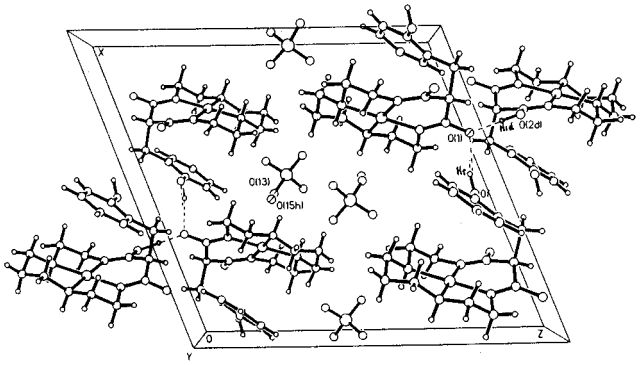


Figure 2. Packing diagram of the complex compound $[Cu(C_{17}H_{25}N_4O_3)]\cdot ClO_4\cdot H_2O$.

to either amido nitrogen, however, there is one hydrogen H(1) bound to carbonyl oxygen O(2). This indicates that only one amido hydrogen deprotonated and the other hydrogen "migrated" to the carbonyl oxygen. In the complex with two deprotonated amido groups, the two Cu−N(amido) bond distances are nearly the same.[17,25] In complex **1**, the Cu−N(1) distance is obviously shorter than Cu−N(2) bond distance. This is because the hydrogen bound to N(1) has been deprotonated, leaving a negative charge delocalized on N(1)−C(1)−O(1), which increases the coordination ability of N(1). The hydrogen bound to N(2) is "transferred" to the carbonyl oxygen O(2), while no such effect exists for N(2)−C(3)−O(2). Because of the hydrogen migration, the double bond formed between N(2)−C(3) has a shorter bond distance than that of C(1)−N(1) or similar compounds.[17,26] In complex **1**, the IR spectrum at 2400−2700 cm^{-1} indicates that it has an enolic tautomer structure,[27] which strongly supports the "migration" of the amido hydrogen to the carbonyl oxygen and is in agreement with the X-ray crystal structure. Such IR features do not exist for complex **2** and **3**. The protonation constant of phenol is log $K = -9.9$,[29] while the pH value of crystal **1** in aqueous solution is 4.3; therefore, deprotonation of the phenol group should not occur. Also, since there is an anion in complex **1**, phenolic OH deprotonation is improbable.

Figure 2 is a packing diagram of the complex. The distance O(1)−H1d is 1.427 Å, O(1)−H1d−O(2) is 176.3°, the O(1)−H_f distance is 1.862 Å, and the O(1)−H_f−O_f angle is 166.1°. These data show that intermolecular hydrogen bonds are formed between O(1) and O(2) and between O(1) and O_f as shown in the unit cell. It is this migrated amido hydrogen atom that helps to form the C(3)−O(2)−H···O(1)′ that binds together the two molecules and stabilizes the crystal structure (Figure 2).

Protonation and Complexation. The acid−base behavior of the ligands in aqueous 0.1 mol·dm^{-3} $NaNO_3$ at 25 °C has been investigated through pH titration. Figure 3 shows the titration curves of L_1 and its copper(II) complex. Figure 4 represents the titration curves of L_9 and its complex. In the pH range investigated (ca. 3−11), the dioxotetraamines can bind three protons, presumably two at the amine groups and one at the oxygen atom of one of the amide carbonyls. The stepwise protonation equilibria constants have been determined and are shown in Table 3.

(25) Zhu, S. R.; Luo, Q. H.; Shen, M. C.; Huang, L. R. *Acta Crystallogr.* **1992**, *C48*, 1926.
(26) Siegfried, L.; Neuburger, M.; Zehnder, M.; Kaden, Th. A. *J. Chem. Soc., Chem. Commun.* **1994**, 951.
(27) Newman, G. A.; Pauwels, P. J. S. *Tetrahedron* **1969**, *25*, 4605.
(28) Barton, S. D.; Ollis, W. D. *Comprehensive Organic chemistry*, Pergamon: Oxford, England, 1979; Vol. 1, pp 709, 739.
(29) Yao, Y. B.; Xie, T.; Gao, Y. M. *Handbook of physical chemistry*; Science and Technology Press: Shanghai, China, 1985; p 789.

Table 2. Selected Bond Lengths (Å) and Angles (deg)

Cu−N(1)	1.921(6)	Cu−N(2)	1.941(4)	Cu−N(3)	1.999(6)
Cu−N(4)	2.004(5)	O(1)−C(1)	1.273(8)	O(2)−C(3)	1.327(7)
N(1)−C(1)	1.289(8)	N(2)−C(3)	1.273(8)	O−C(16)	1.373(8)
C(11)−C(17)	1.508(10)	C(2)−C(17)	1.577(8)	C(1)−C(2)	1.543(8)
C(2)−C(3)	1.492(9)	O−H	0.899(24)	N(3)−H(3)	0.938(19)
N(4)−H(4)	0.945(20)	O(2)−H(1)	1.125(25)		
N(1)−Cu−N(2)	93.5(2)	N(1)−Cu−N(4)	85.1(2)	N(2)−Cu−N(3)	85.2(2)
N(3)−Cu−N(4)	96.3(2)	O(1)−C(1)−N(1)	125.1(5)	O(2)−C(3)−N(2)	120.1(5)
O(1)−C(1)−C(2)	115.9(5)	N(1)−C(1)−C(2)	119.0(6)	O(2)−C(3)−C(2)	117.1(5)
N(2)−C(3)−C(2)	122.7(5)	C(2)−C(17)−C(11)	114.9(5)	C(1)−C(2)−C(17)	108.1(4)
C(3)−C(2)−C(17)	110.7(5)	C(16)−O−H	107.2(10)	C(3)−O(2)−H(1)	113.8(8)
Cu−N(3)−H(3)	100.4(17)	Cu−N(4)−H(4)	105.0(9)		

Table 3. Protonation Constants of the Macrocyclic Dioxotetraamines (Aqueous 0.1 mol·dm^{-3} $NaNO_3$ at 25 ± 0.1 °C)[a]

ligands	log β_1	log β_2	log β_3	log K_1	log K_2	log K_3	log K_4
L_1	10.08 ± 0.03	19.56 ± 0.03	25.39 ± 0.03				
L_2	10.30 ± 0.03	19.81 ± 0.04	25.51 ± 0.04				
L_3	9.75 ± 0.03	18.73 ± 0.03	24.47 ± 0.07				
L_4	9.55 ± 0.02	18.47 ± 0.03	24.33 ± 0.05				
L_7	11.27 ± 0.04	21.46 ± 0.05	28.26 ± 0.07	11.27	10.13	6.86	<3
L_9	11.64 ± 0.05	22.00 ± 0.07	30.30 ± 0.09	11.64	10.36	8.30	<3
L′[b]	10.01	19.06	22.72	10.01	9.05	3.66	
13-dioxo[c]	9.05	12.87			9.05	3.82	
dioxocyclam	9.67 ± 0.02	15.57 ± 0.04			9.67	5.90	
13aneN$_4$[d]				11.10	10.10	1.7	
14aneN$_4$[e]				11.50	10.30	1.6	

[a] $\beta_n = [H_nL)]/[H^+]^n[L^-]$, $K_n = [H_nL]/[H^+][H_{n-1}L]$. [b] L′ is 12-(4′-hydroxyl)-benzyl-1,4,7,10-tetraazacyclotridecane-11,13-dione.[7] [c] 13-dioxo is 1,4,7,10-tetraazacyclotridecane-11,13-dione.[7] [d] 13aneN$_4$ is 1,4,7,10-tetraazacyclotridecane.[15] [e] 14aneN$_4$ is 1,4,8,11-tetraazacyclotrtradecane.[15]

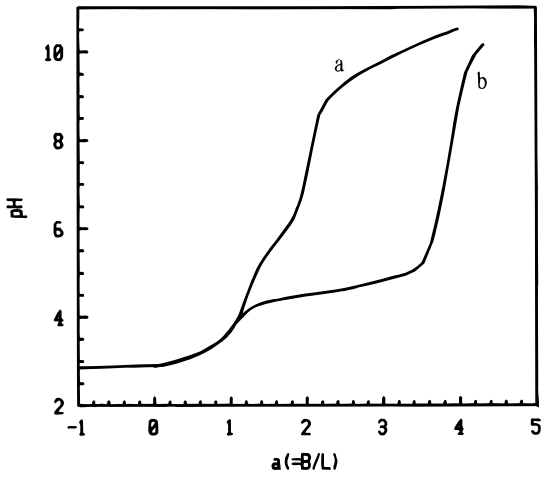


Figure 3. Titration curves of ligand L_1 and its copper(II) complex: (a) 1.00 × 10^{-3} mol·dm^{-3} L_1·2HNO_3; (b) 1.00 × 10^{-3} mol·dm^{-3} L_1·2HNO_3 + 1.00 × 10^{-3} mol·dm^{-3} $Cu(NO_3)_2$.

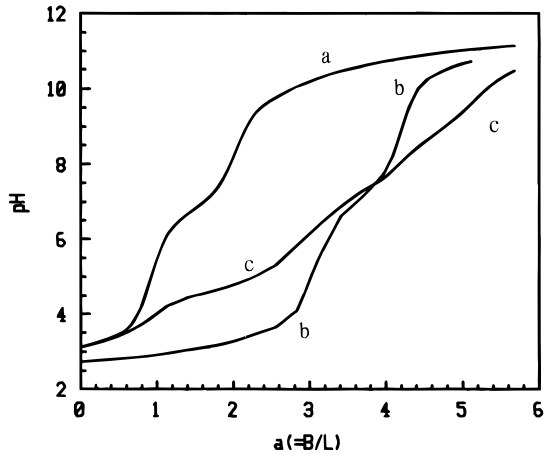


Figure 4. Titration curves of ligand L_9 and its complex: (a) 1.00 × 10^{-3} mol·dm^{-3} L_9·3HCl; (b) 1.00 × 10^{-3} mol·dm^{-3} L9.3HCl + 1.00 × 10^{-3} mol·dm^{-3} $Cu(NO_3)_2$; (c) 1.00 × 10^{-3} mol·dm^{-3} L_9·3HCl + 1.00 × 10^{-3} mol·dm^{-3} $Zn(NO_3)_2$.

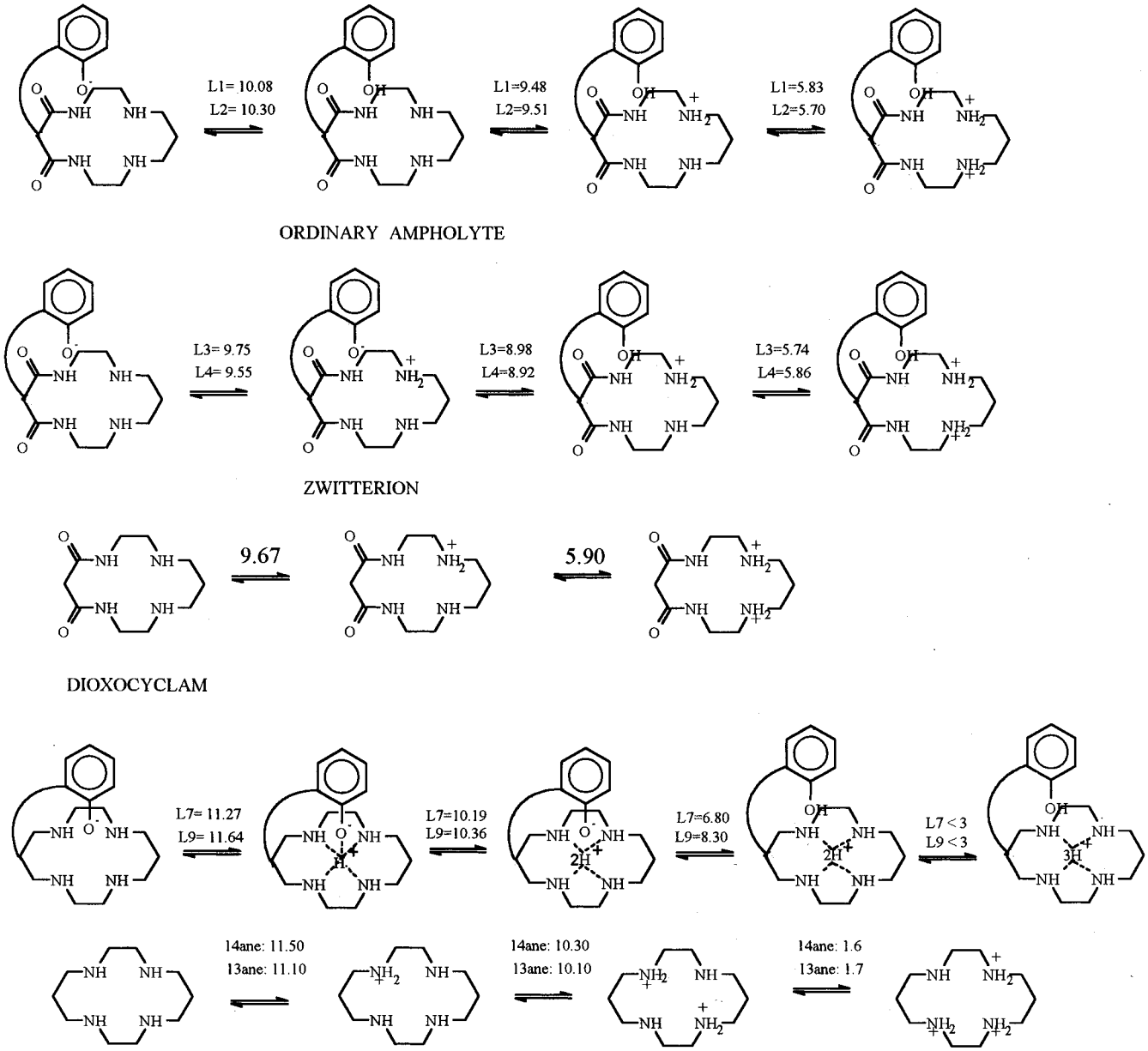
For comparison, log K values of the stepwise protonation equilibra of similar 13-membered macrocycles, 12-(4′-hydroxyl)benzyl-1,4,7,10-tetraazacyclotridecane--11,13-dione (L′),[7] 1,4,7,-10-tetraazacyclotridecane-11,13-dione (13-dioxo), and 1,4,7,10-tetraazacyclotridecane (13aneN$_4$),[15] are also reported.

For macrocyclic dioxotetraamine, K_1 is the protonation constant of the phenolate for L_1 and L_2. The values are nearly the same as in free phenol.[28,29] For L_3 and L_4, K_2 is assigned to be the protonation constant for the phenolate. The protonation constants of phenolates change with the electronic effects of the substituents. They decreased with an increase of electron-withdrawing substituents to the ring. Such an experimental design allows us to analyze the present protonation constants based on careful comparisons of the expected substitutent effects from the array of compounds studied (as shown in Scheme 2). The log K values for the first secondary-amine protonation are nearly the same as or less than the protonation constants of the first amino group in 1,4,8,11-tetraazacyclotridecane-12,14-dione. As shown in Scheme 2, species L_3 and L_4 probably form zwitterions near pH 9.4, whereas species L_1 and L_2 probably form ordinary ampholytes near that pH. The bromine substitutents appear to shift the phenolic pK_a by over one log unit. The value of log K_3 is much smaller than log K_2; this may be due to the accumulation of positive charges in the ring. It should be noted that these ligands are much weaker bases than the fully saturated analogue 1,4,8,11-tetraazacyclotridecane, as far as the first two amino N atoms are concerned. In the case of 1,4,8,-11-tetraazacyclotridecane, formation of stable intramolecular hydrogen bonds between ammonium and amino groups, trans to each other, has been hypothesized.[30] It is impossible to form a trans intramolecular hydrogen bond in the diamide macrocycle.

When a macrocyclic dioxotetraamine was reduced to a macrocyclic polyamine, its protonation constants increased

(30) Micheloni, M.; Peoletti, P.; Vacca, A. *J. Chem. Soc., Perkin Trans. 2* **1978**, 945.

Scheme 2. Proposed Arrangements of Macrocyclic Polyamines and the log K Values of the Stepwise Protonation



considerably. K_1 and K_2 values of the C-functionalized polyamines are nearly the same as those of the protonation constants of the two amino groups in 13aneN$_4$ and 14aneN$_4$;[15] thus the first and second protonation constants are attributed to the protonation of the C-functionalized saturated polyamines (Scheme 2). For these two ligands, the first and second protonation constants are slightly larger than those for the corresponding macrocyclic dioxotetraamines. This indicates that there is some interaction between the phenolate oxygen and the proton bound to the secondary amine as shown in Scheme 2. The proposed hydrogen-bonding interaction, by which the proton bound to the macrocycle is stabilized, has thus increased the protonation constants for the secondary amines. Because the phenolate oxygen interacted with the proton of the macrocycle, the protonation of the phenolate oxygen would consume some energy to overcome the H-bond breakage of phenolate oxygen; therefore, its protonation constant decreased considerably. In the present case, the phenolic pK_as in L_7 and L_9 are as low as 6.80 and 8.30.

The incorporation of Cu(II) by the ligands in aqueous solution was studied to identify the species formed and to evaluate the complexation constants of these compounds. We can see through pH titration curves that the complex deprotonates two protons from free neutral ligands (HL) at pH 6. The best fitting of the titration curve involves formation of the species [Cu(H$_{-1}$L)] and [CuL]$^+$, the following reactions were found to take place:

$$Cu^{2+} + L^- = [Cu(H_{-1}L)] + H^+ \quad (1)$$

$$K(11\bar{1}) = [H^+][Cu(H_{-1}L)]/[Cu^{2+}][L^-]$$

$$Cu^{2+} + L^- = [CuL]^+ \quad (2)$$

$$K(110) = [CuL^+]/[Cu^{2+}][L^-]$$

Here figures in parentheses indicate the stoichiometric number of metal, ligand (L^-), and hydrogen ions in the formation reactions, respectively. Namely, (11$\bar{1}$) and (110) denote complexes [Cu(H$_{-1}$L)] and [CuL]$^+$, respectively. In the present terminology, HL is phenolate-protonated ligand, L^- is phenolate-deprotonated free ligand, and $H_{-1}L^{2-}$ is amido-deprotonated ligand. $H_{-1}L^{2-}$ can exists only in complexes.

The positively charged complex CuL$^+$ (110) has been characterized by X-ray crystal structure analysis. Further

Table 4. Equilibrium Constants for the Complexation of Copper(II) with Macrocyclic Dioxotetraamines (Aqueous 0.1 mol·dm^{-3} $NaNO_3$ at 25 ± 0.1 °C)

	L_1	L_2	L_3	L_4	dioxocyclam
log $K(110)^a$	14.10 ± 0.02	14.41 ± 0.03	13.52 ± 0.03	13.32 ± 0.04	4.81 ± 0.07 ($11\bar{1}$)
log $K(11\bar{1})^b$	9.80 ± 0.03	10.17 ± 0.03	9.33 ± 0.02	9.00 ± 0.04	0.53 ± 0.02 ($11\bar{2}$)

^{a} $K(110) = [CuL^+]/[Cu^{2+}][L^-]$. ^{b} $K(11\bar{1}) = [H^+][Cu(H_{-1}L)]/[Cu^{2+}][L^-]$.

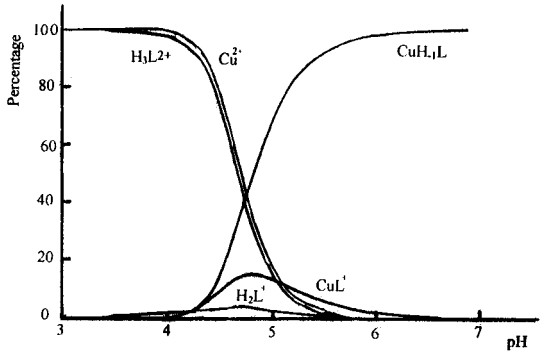


Figure 5. Distribution diagram for the Cu(II)−L_1 system.

deprotonation of CuL^+ gives a neutral complex $CuH_{-1}L$ ($11\bar{1}$). As for all macrocyclic dioxotetraamine copper(II) complexes, the two amido groups deprotonated when coordinated to copper(II) ion at pH 6; that is the phenol group does not dissociate its proton (coordinated to metal ion) in the complex, corresponding to one amido hydrogen "migrated" to phenolate oxygen. As shown in Figure 3, at the ratio total base (B)/total ligand (L) = 4 or higher, the pH of the solution increased quickly to 10; this indicates that no strong interaction exists between the phenol group and copper(II) ion, which further confirms the fact that phenol does not coordinate to copper(II) ion. This, in our opinion, is due to the fact that the generally strong in-plane ligand field produced by the 14-membered macrocyclic dioxotetraamine causes strong tetragonal distortion and weakens the interaction with an intramolecular axial donor.

The equilibrium constants of reactions 1 and 2 are listed in Table 4. From Table 4 we can see that positively charged $[CuL]^+$ does exist and has considerable stability. Figure 5 shows that $[CuL]^+$ has a maximum value (16% of the total metal ion) at pH 4.8. For dioxocyclam complex, the positively charged complex has a maximum value about 20%; this indicates that the amido hydrogens were dissociated stepwise but not simultaneously, and this is quite different from the conclusion of Kimura[15] and supports the suggestion of Kaden and Hay.[16]

It is seen from Table 4 that the stability constants of the two complexes increased with the increase of the basicity of ligands. In fact, in reactions 1 and 2, the negatively charged ligand (phenolate) was protonated after coordination, this means that reactions 1 and 2 include the phenolate protonation. If phenolate protonation was subtracted, the following reactions were obtained:

$$Cu^{2+} + L' = [Cu(H_{-2}L')] + 2H^+ \qquad (1')$$

$$K(11\bar{2}) = [H^+]^2[Cu(H_{-2}L')]/[Cu^{2+}][L']$$

$$Cu^{2+} + L' = [CuH_{-1}L']^+ + H^+ \qquad (2')$$

$$K(11\bar{1}) = [CuH_{-1}L^+][H^+]/[Cu^{2+}][L']$$

Here L′(=HL) is neutral free (phenolic protonated) ligand. $11\bar{2}$ and $11\bar{1}$ in parentheses indicate that the complex deprotonates two protons and one proton from the amido groups, respectively.

The equilibrium constants (log K) of (1′) and (2′) for L_1 are −0.28 and 4.02, respectively. The log $K(11\bar{2})$ value is larger than that of the dioxocyclam−copper(II) complex. This means that even though the phenolate does not coordinate to copper(II) ion, it increases the stability of its copper(II) complex.

From careful analysis of the stability constants, we have Scheme 3. From this scheme, the following three conclusions are particularly appealing. (1) The binding constants of the free neutral ligands with copper(II) ions (with concomitant deprotonation) range from 4.02 to 4.81. (2) The difference between log $K(110)$ and log$K(11\bar{1})$, that is the pK_a of the keto−OH (enolic tautomer), is rather constant (4.2−4.3) for all the compounds in Table 4. This means that the coordinated enolic structure of the amido group is a middle−strong acid, suggesting that the deprotonation constant of amido hydrogen increased considerably when the group was coordinated to the copper(II) ion. There should be another pK_a around 9−10 in the compounds corresponding to the ionization of the phenolic group, which is not likely coordinated to the cupric ion, as the X-ray structure clearly suggests. (3) The logs of the formation constants of the doubly-deprotonated cupric complexes range from −0.3 to +0.3 (Scheme 3), these values are larger than that of dioxocyclam complex and indicate that substituents stablize their cupric complexes. Electronic spectra (in water) of cupric complexes of doubly-deprotonated L_1−L_4 show d−d transition absorbance in the range of 490−505 nm, while dioxocyclam−copper(II) complex absorbs at 515 nm. Substituents also decrease the absorption coefficients of their complex. All these observations clearly indicate that substituents increase the ligand field strength. It may be the reason why substituents stablize their cupric complex. The crystal structure of the complex shows that the phenol molecule is located above the copper(II) ion. Such stacking interaction may increase the stability of these complexes.

The stability of saturated polyamine copper(II) complexes is rather large. All of the ligands can coordinate to copper(II) at pH < 4, and the complex formation process is slow (about 30 min to reach equilibrium). For this reason, it is difficult to determine their stability constants by the pH titration method.

Protonation constants of dioxotetraamines and stability constants of their copper(II) complexes vary with temperature. By plotting ln K vs $1/T$, the values of ΔH, ΔS, and ΔG of the protonation reaction can be obtained. Table 5 shows the results for L_1.

The protonation process is an exothermic reaction. The enthalpy of formation (ΔH) for the phenolate is the largest among the three protonation processes. While the second protonation process (the first protonation of the macrocyclic amine) has the largest ΔS value. This means that when the macrocyclic amine protonates, solvent entropy increased considerably due to the H-bonding formation in the macrocyclic cavity. Because of the great solvation entropy of the first amine protonation, the third protonation entropy decreased. Exactly in the same way, the ΔH, ΔS and ΔG of coordination reactions 1 and 2 were determined. $\Delta H = -1.74 \times 10^4$ J/mol and $\Delta S =$ 135 J/mol·K for reaction 1, and $\Delta H = -2.40 \times 10^4$ J/mol and $\Delta S = 194$ J/K·mol for reaction 2. These data show that the coordination processes 1 and 2 are exothermic reactions. In

Scheme 3. Hypothesized Coordinative Arrangements of the Complexes

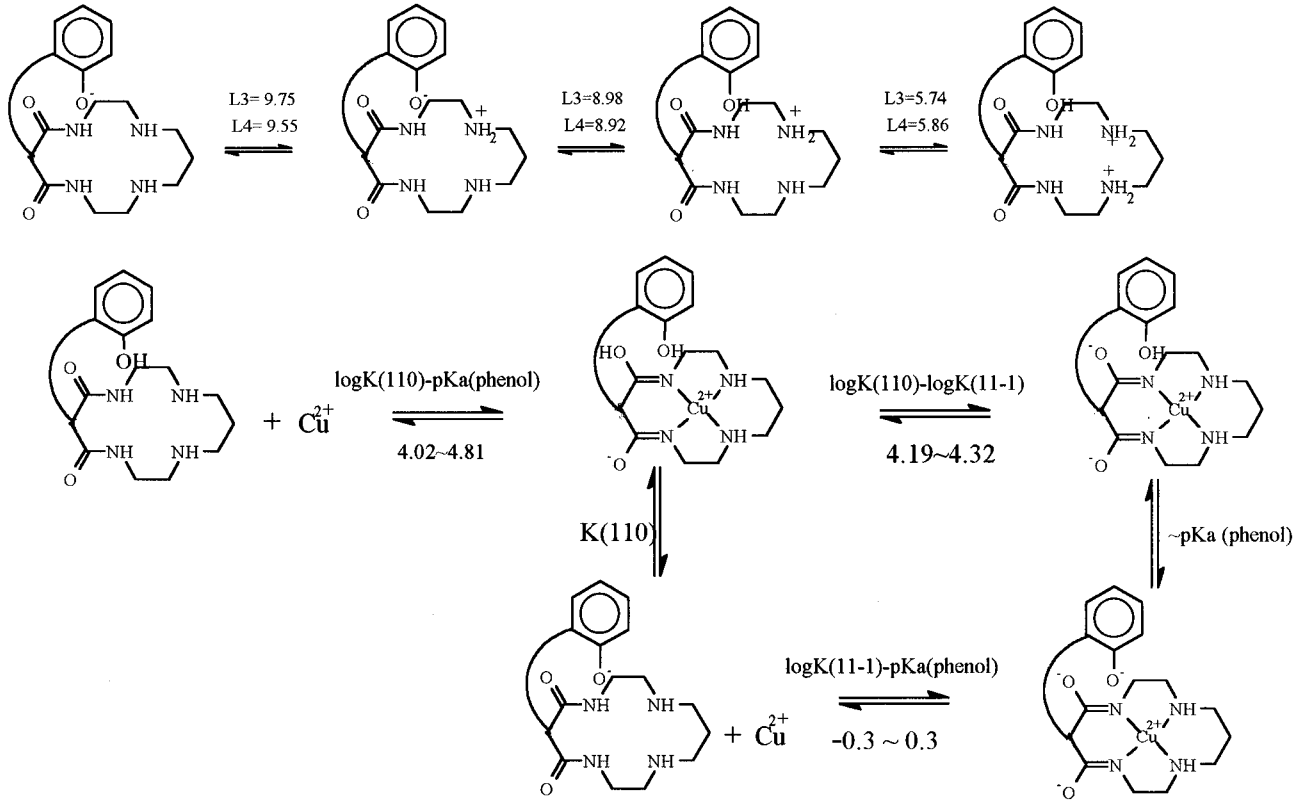


Table 5. Protonation Constants of L_1 at Different Temperatures and Thermodynamic Parameters ΔH (kJ/mol), ΔS (J/K·mol), and ΔG (kJ/mol) (I = 0.1 mol·dm^{-3} KNO_3)

	15 °C	25 °C	35 °C	45 °C	55 °C	$-\Delta H$	ΔS	$-\Delta G$	corr coef r
log K_1	10.21	10.08	9.89	9.76	9.58	28.4	97.2	57.4	0.996
log K_2	9.68	9.49	9.43	9.33	9.25	18.5	121	54.6	0.984
log K_3	5.94	5.83	5.64	5.54	5.48	22.0	37.4	33.1	0.989

fact, in reactions 1 and 2, the negatively charged ligand (phenolate) was protonated after coordination; this means that reactions 1 and 2 include the phenolate protonation. If the phenolate protonation is excluded, the enthalpy and entropy changes of reaction 1′ are $\Delta H = 1.1 \times 10^4$ J/mol and $\Delta S =$ 37.8 J/mol·K. while for reaction 2′, $\Delta H = 4.4 \times 10^3$ J/mol and $\Delta S = 96.8$ J/K·mol. This demonstrates that reactions 1′ and 2′ are endothermic because of the deprotonation of amido groups. This result is in agreement with our previous report.[13] Reaction 3 has $\Delta H = 6.6 \times 10^3$ J/mol and $\Delta S = -59$ J/mol·K. This value further confirms that the deprotonation of the amido group is an endothermic process.

We have determined through correlation analysis of the equilibrium constants of complexation and the protonation constants of ligands that

$$\log K(110) = 1.504 \log \beta_1 - 1.081 \quad r = 0.996$$

$$\log K(11\bar{1}) = 1.334 \log \beta_1 - 3.604 \quad r = 0.991$$

This shows that the linear free energy relationships also exist in the present macrocyclic dioxotetraamine−copper(II) complex system.

EPR Spectra. Figure 6 presents EPR spectra for the copper(II) complex of L_1 at room temperature and at 120 K. It can be seen that the complex has an axially symmetric spectrum at 120 K, with three lines clearly visible in the parallel region. While at room temperature, only one isotropic spectrum is observed. Similar EPR spectra can be seen for the other copper(II) complexes as shown by the g and A parameters that are listed in Table 6.

Table 6. EPR Parameters of Macrocyclic Dioxotetraamine−Copper(II) Complexes in Neutral Methanol Solution

	room temp		110 K			
ligand	g	A (G)	$A_\perp$ (G)	$A_\parallel$ (G)	$g_\parallel$	$g_\perp$
L_1	2.099	99	43	211	2.168	2.035
L_2	2.098	99	43	211	2.167	2.035
L_3	2.099	99	43	211	2.169	2.035
dioxocyclam	2.102	95	37	215	2.172	2.038
L′ [a]	2.097	91	38	197	2.180	2.044
L_5	2.109	90				
L_6	2.111	90				
L_8	2.109	90				
L_9	2.097	90				

[a] L′ is 12-(4′-hydroxyl)-benzyl-1,4,7,10-tetraazacyclotridecane-11,13-dione.[7]

The g and A parameters are nearly the same for the three C-substituted 14-membered dioxotetraamine copper(II) complexes. The compounds have a square-planar configuration with $g_\parallel/A_\parallel$ (cm^{-1} unit) values of about 100. Although the EPR parameters of the dioxotetraamine complexes do not change much, the EPR parameters of the corresponding polyamine complex change appreciably. The 110 K EPR spectra of saturated polyamines are rather complicated, indicating that the coordination environment of this complex is quite different from that of dioxotetraamine−copper(II) complexes. Further studies to explain these discrepancies are in progress.

Table 7. M(II)/M(III) Half-Wave Potentials[a] of Some Complexes in Neutral Aqueous Solution at 25 °C $I = 0.5$ mol·dm^{-3} Na_2SO_4

	L_1	L_2	L_3	L_4	L′	dioxo cyclam	L_8	L_5	L7	L6
$E_{1/2}^{Cu}$	0.64	0.62	0.66	0.68	0.58	0.64	1.00	1.00		
$E_{1/2}^{Ni}$	0.72	0.72	0.73	0.73	0.81		0.64	0.46	0.46	0.45

[a] $E_{1/2} = (E_{pa} + E_{pc})/2$ vs SCE value.

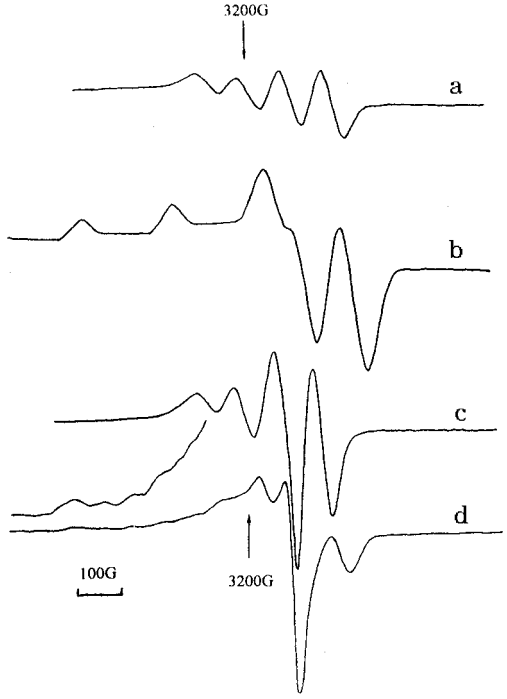


Figure 6. X-Band EPR spectra of copper(II) complexes in neutral methanol solution: (a) L_1 complex at room temperature; (b) L_1 complex at 110 K; (c) L_5 complex at room temperature; (d) L_5 complex at 110 K.

Cyclic Voltammetry. One oxidation peak appeared in the range of 0−0.15 V (vs SCE) in the cyclic voltammogram of the free ligand (pH 5.5) as reported previously.[7] For all the copper(II) complexes, Cu(II)/Cu(III) redox processes are quasi-reversible. The half-wave potential can be calculated according to $E_{1/2} = (E_{pc} + E_{pa})/2$. The Cu(II)/Cu(III) half-wave potentials for L_1, L_2, L_3, and L_4 copper(II) complexes are summarized in Table 7.

The half-wave potentials of Cu(II)/Cu(III) of dioxocyclam derivatives increased with the addition of electron-withdrawing substituents; i.e., an electron-withdrawing group R tends to increase the oxidation potential. Using the dioxocyclam complexes for comparison, phenol substitution increases Cu(II)/Cu(III) potentials and decreases Ni(II)/Ni(III) potentials. The d^8 metal ions (Ni^{2+} and Cu^{3+}) tend to form square-planar complexes, and the substituents have little influence on such metal ions. Both Ni^{3+} and Cu^{2+} tend to form distorted octahedral complexes. In our opinion, this indicates that substituents stabilize the Cu^{2+} and Ni^{3+} oxidation levels, indicating that substituents increase the Cu(II)/Cu(III) and decrease the Ni(II)/Ni(III) potentials. These phenomena demonstrate that the phenol substituents interact with a central copper(II) or copper(III) ion in solution. The crystal structure of the complex shows that the phenol molecule covers the copper(II) ion. Such an interaction may influence the potential and stability of their complexes.

Conclusion. Various substituted phenol-pendant 14-membered macrocyclic dioxotetraamines and corresponding saturated polyamines have been synthesized. When coordinated to copper(II) ion, the ligands dissociated two hydrogen ions from amido groups stepwise instead of demonstrating a concomitant double deprotonation as reported previously.[15] We find that the enolic structure of the amido moiety is coordinated to the metal ion. Because the amido group coordinates to the metal ion, the amido hydrogen (enolic structure) dissociates easily with a $pK_a = 4.2-4.3$. Anodic peak potentials and half-wave potentials of the copper(II) complexes increased with the increase of electron-withdrawing effect of the substituents on the ligands. We conclude that the coordination environments of saturated polyamine complexes are different from those of the dioxotetraamine complexes.

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Supporting Information Available: Tables of crystallographic experimental details, atomic parameters, bond lengths, bond angles, anisotropic thermal parameters, hydrogen atom parameters, and intermolecular hydrogen bonds (8 pages). Ordering information is given on any current masthead page.

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