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Note

A convenient method for the synthesis of macrocyclic dioxotetraamine ligands bearing pendent coordinating groups and the properties of their copper(II) complexes

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Abstract

A novel, simple approach to the synthesis of macrocyclic dioxotetraamine ligands bearing pendent coordinating groups is described. Reduction of 2*H*-1-benzopyran-3-carboxylic acid 2-oxo-ethyl ester or its derivatives with sodium borohydride and then aminolysing the products with triethylenetetraamine, without isolation of intermediates, leads to 12-(2′-hydroxyl)-benzyl-1,4,7,10-tetraazacyclotridecane-11,13-dione or the corresponding macrocyclic ligand. The ligands were characterized by elemental analysis, IR, ^{1}H NMR and MS. The ligands can be triprotonated including the phenolate. Five-coordinated $[Cu(H_{-2}L)]^-$ and four-coordinated $[Cu(H_{-1}L)]$ complexes were found to form in aqueous solution, i.e., the phenolic group can be coordinated to the copper(II) ion. Formation constants of the copper(II) complexes were determined by pH titration. These copper(II) complexes have axial symmetry according to their EPR spectra; the EPR parameters were obtained by computer fitting. Two redox processes appeared in the cyclic voltammogram in the range of −0.1 to −0.8 V (versus SCE); one is the oxidation of phenol hydroxyl and the other is the oxidation of a Cu(II) complex to a Cu(III) complex. Electron-withdrawing substituents increase the oxidation potential.

Keywords: Copper complexes; Macrocyclic ligand complexes; Amine complexes

1. Introduction

The structures and properties of macrocyclic dioxotetraamines are similar to those of a tripeptide. They are capable of coordinating to a divalent 3d cation with simultaneous extrusion of two hydrogen ions from the amido groups [1,2]. Transition metal(II) complexes of macrocyclic dioxotetraamines have shown some interesting properties and important biological functions such as models for metalloproteins and oxygen carriers [3–6]. Copper(II) complexes can be oxidized at moderately positive potentials to give authentic trivalent copper species that are stable in aqueous solution [7–9]. Such compounds can serve as models for some enzymes such as galactose oxidase [10] and may be used as effective oxidants and redox catalysts [11]. Unsubstituted macrocyclic dioxotetraamines of different ring size have been reported [12,13]. Nearly thirty ligands have been synthesized, but few of them contain pendent coordinating groups [3,14a]. The study of macrocyclic polyamines has been an active area of research with remarkable achievements [14b]. However, no convenient way of synthesizing this kind of ligand and no studies on the relationships between the structure and properties have been reported. Therefore the studies of macrocyclic dioxotetraamines are somewhat limited. According to Lehn's definition, the association of two or more chemical entities gives a supermolecular system [15]; complexes of macrocyclic dioxotetraamine may be taken as a supermolecule and have been reviewed by Santis et al. [16] and Lehn [17]. The introduction of substituents into a macrocycle may change its properties; it is now possible to tune the redox, electronic, kinetic and structural properties of metal ion complexes somewhat by the judicious choice of donor atoms on the pendent groups, and the number and type of substituents. The level of sophistication already reached in the syntheses of macrocycles with active substituents, ensures the application of these ligands and their complexes will expand in the coming years. Nevertheless,

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synthetic challenges still exist, notably in the areas of C-based pendent macrocycles and macrocycles with large numbers of intra- and extra-ring donors; these areas will provide interesting new chemistry for the future. The studies of new synthetic methods and the syntheses of dioxotetraamine macrocycles with pendent coordinating groups are of great theoretical importance as well as in terms of their prospective applications.

In this report, we describe a new synthetic route to 13-membered macrocyclic dioxotetraamine ligands bearing pendent coordinating groups through reduction of their coumarin derivatives with sodium borohydride followed by aminolysing of the products with triethylenetetraamine. Characterization of the ligands, the EPR spectra of their copper(II) complexes, the protonation and coordination properties and the electrochemical investigation of the oxidation behavior of the metal complexes have been studied. The relationships of electronic effects of the substituents in the ligands and the properties of their copper(II) complexes are also discussed.

2. Experimental

2.1. Synthesis of the ligands

2*H*-1-Benzopyran-3-carboxylic acid 2-oxo-ethyl ester (coumarin 3-carboxylic ester) and the other coumarin derivatives were prepared according to literature procedures [18–20]. 5-Bromo-2-hydroxyl and 3,5-dibromo-2-hydroxyl benzaldehyde used for the syntheses of the coumarin derivatives were prepared according to the methods of Lindemann et al. [21] and Clarke et al. [22]. Other reagents were commercial products used without further purification.

To 500 ml of an ethanol solution of the 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 the corresponding malonate ester [23], without isolation of intermediates. Triethylenetetraamine (0.1 mol) was added and the mixture was refluxed for 6 days. Most of the solvent was distilled off and the residue (about 50 ml) was isolated by silica gel chromatography. After elution with $CHCl_3$–MeOH (5:1) and evaporation of the solvent, the product 12-(2′-hydroxyl)-benzyl-1,4,7,10-tetraazacyclotridecane-11,13-dione, with or without substituent, was obtained in 10–13% yield.

2.2. Instruments

IR spectra were measured on a Nicolet 170 SXFT. Elemental analysis was determined on a Perkin-Elmer 240C instrument. Methanol solutions of the copper(II) complexes (mix 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 was recorded on a Bruker AM-500 spectrometer with d-DMSO as solvent. EI-MS spectra were measured on a ZAB-HS (VG Co., UK). The cyclic voltammograms were measured in aqueous solution at room temperature on a PARC model 273 electrochemical apparatus. The electrolyte was 0.4 mol dm^{-3} Na_2SO_4. A three-electrode system was employed: glassy carbon was used as working electrode, saturated calomel electrode (SCE) as a reference and Pt coil as counter electrode. The scan rate was 100 mV s^{-1} and the concentration of the complexes 2×10^{-3} mol dm^{-3} (1:1 ligand and copper(II) sulfate aqueous solution).

2.3. pH titration

The potentiometric equilibrium measurements of the ligands in the absence and presence of copper(II) ions were carried out with a Beckman pH meter model Φ71. The 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 from the pH of a standard acid. The temperature was maintained at 25 ± 0.1 °C. Each titration was performed in a solution of 50 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 was dissolved by adding HNO_3 and then titrated with 0.1 mol dm^{-3} NaOH. Redistilled (in quartzware equipment) water was used for 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 [24]. For each system at least two titrations were performed, each of them containing about 50 experimental points.

3. Results and discussion

3.1. Synthesis of C-functionalized macrocycles

Many functionalized macrocycles have been studied, but most of them are N-functionalized compounds. There are some studies on C-functionalized oxotetraamine macrocycles [25], but no convenient method for the synthesis of C-functionalized dioxotetraamine macrocycles was reported. Much progress has been made in the synthetic strategies and physical studies of macrocyclic complexes with pendent coordinating groups. Synthetic challenges, especially in C-functionalized macrocycles, still exist. Reviews on this topic have been reported recently [26].

A novel approach for the synthesis of the macrocyclic dioxotetraamines with pendent arms was carried out according to Scheme 1. The physical and spectral properties of the macrocyclic dioxotetraamines (L_1–L_4) thus obtained are summarized in Table 1.

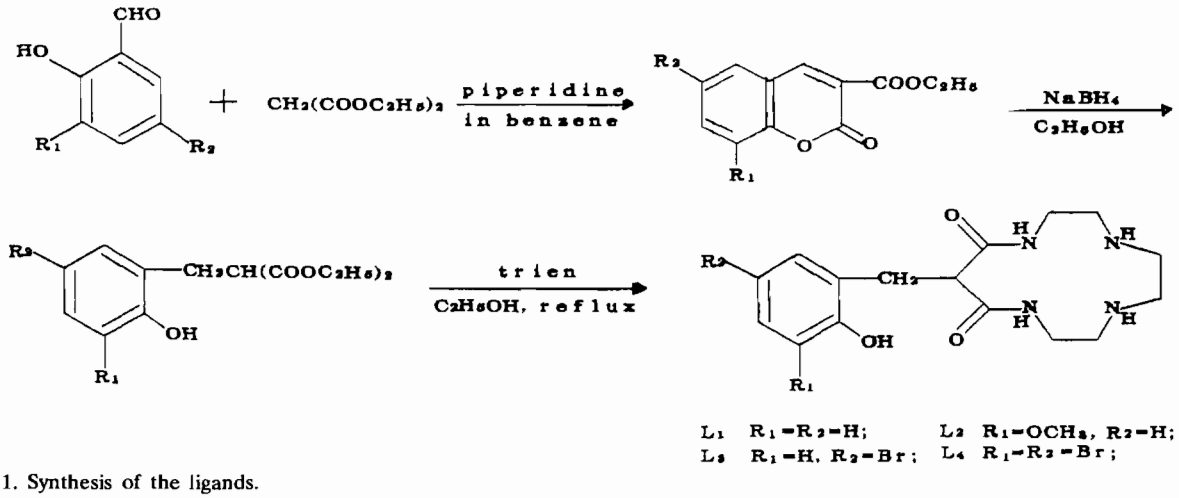
All the analytical and spectral data are in agreement with the theoretical requirement. The present preparation of cyclic dioxotetraamines has a significant advantage in that any desirable substituent can be introduced on the carbon atom of the macrocyclic skeleton. The C–C linkage does not alter the coordination properties of the macrocycles and thus all the advantages of cyclam remain intact [12,27,28]. Also the cyclized product is obtained predominantly under conventional conditions (concentration, solvent, temperature), and is more convenient than the high-dilution technique. The present approach is much simpler, the reflux time is much shorter than the three weeks for the synthesis of oxotetraamine macrocycles reported by Kimura [25], and coordinating groups can be easily introduced into the macrocycles via the C–C linkage. It is very difficult to do so in other synthetic routes. The present new method with its simplicity and versatility is widely applicable for the synthesis of novel metal chelating agents with various biomimetic functions.

3.2. Protonation and complexation

The acid–base behavior of the ligands in aqueous 0.1 mol dm^{-3} $NaNO_3$ at 25 °C was investigated through pH titration. In the pH range investigated (~3–11), the ligands can bind three protons, presumably two at the amine groups and one at the oxygen atom of the hydroxyl group (Scheme 2). The constants of the stepwise protonation equilibria have been determined and are listed in Table 2. For comparison, log K values of the stepwise protonation equilibra of similar macrocycles without pendent coordinating groups are also reported.

K_1 is the protonation constant of the phenolate. The values are nearly the same as in free phenol [29,30]. K_1 changes with the electronic effects of the substituents. It decreases with an increase in the electron-withdrawing effect. log K_1 is obviously larger than that of the similar phenol-containing 1,4,8,11-tetraazacyclotetradecane (log K=8.86) [31a]. This may be due to the difficulty the phenol ring has to orient vertically to achieve intramolecular hydrogen bonding with the nearest ring nitrogen atom because amido nitrogens cannot be protonated. The second protonation constants have the same tendency, but electronic effects of the substituents have little effect on the third protonation constant. The values of log K_2 are nearly the same as the protonation constants of the first amino group in 1,4,7,10-tetraazacyclotridecane-11,13-dione (8.78–9.05) [2,31b]. 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 1,4,7,10-tetraazacyclotridecane, as far as the first two amino N are concerned (log K_1=11.10, log K_2=10.10) [32]. In the case of 1,4,7,10-tetraazacyclotridecane, the formation of stable intramolecular hydrogen bonds between the ammonium and amino groups, *trans* to each other, has been hypothesized [33], an opportunity which is forbidden to the diamide macrocycle. The second amine protonation step of the dioxotetraamine involves a decrease of the log K value (3.8–5.5 log units) greater than that for 1,4,7,10-tetraazacyclotridecane (1.0 log units): this may be due to the fact that in triprotonated dioxotetraamine, the two ammonium ions are adjacent, whereas in the case of 1,4,7,10-tetraazacyclotridecane they should be *trans* to each other, which makes electrostatic repulsion less appreciable.

The incorporation of Cu(II) by the ligands in aqueous solution was studied to verify the species and to evaluate the complexation constant. The best fitting of the titration curve involves formation of the species

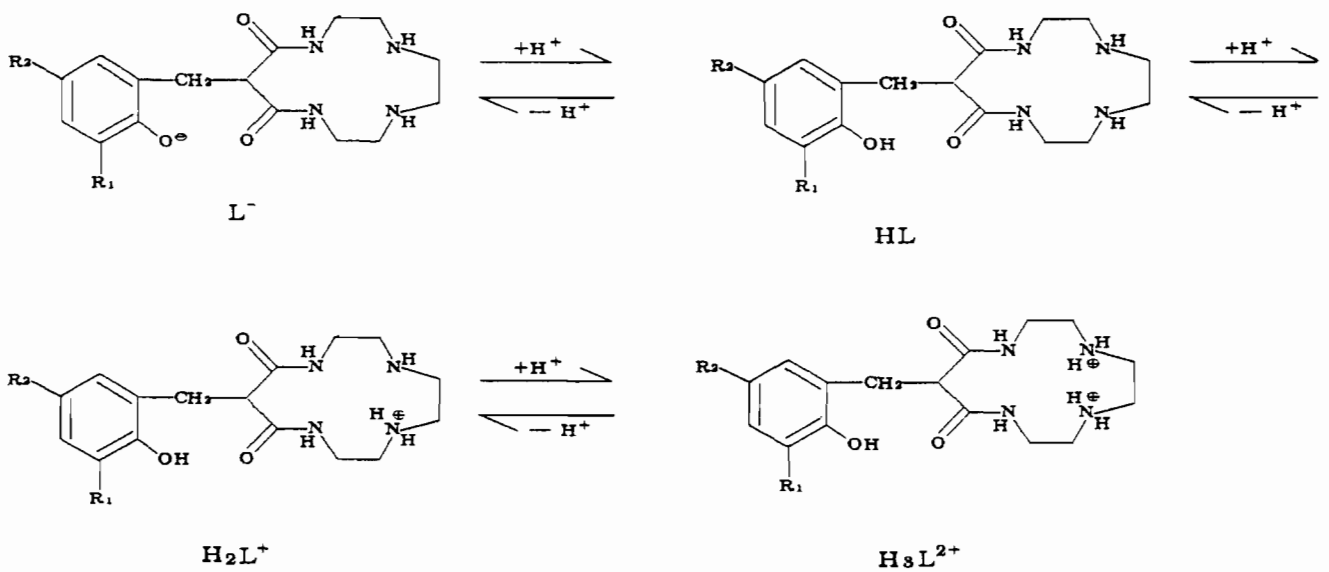


Scheme 1. Synthesis of the ligands.

Table 1
Physical and spectral properties of the macrocyclic dioxotetraamines

		L_1	L_2	L_3	L_4
Formula		$C_{10}H_{24}N_4O_3$	$C_{17}H_{26}N_4O_4$	$C_{18}H_{23}N_4O_3Br$	$C_{16}H_{22}N_4O_3Br_2$
State		colorless powder	colorless powder	colorless powder	colorless powder
Reaction time (days)		6	6	6	6
Melting point (°C)		218–219	234–236 dec. [a]	227–228 dec.	220 dec.
Elemental analysis (found)	C	56.59 (56.79)	58.27 (58.16)	48.13 (48.10)	40.19 (40.03)
	H	7.51 (7.15)	7.48 (7.70)	5.81 (5.86)	4.64 (4.78)
	N	16.78 (16.56)	15.99 (15.62)	14.03 (14.10)	11.72 (11.58)
IR (cm^{-1}) (KBr)	OH	3384	3382	3377	3344
	NH	3296, 1571	3270, 1563	3297, 1562	3391, 1547
	C–O	1244	1237, 1310	1242, 1321	1310, 1211
	C–N	1410, 1038	1410, 1041	1410, 1042	1410, 1051
	C=O	1680	1672	1673	1651
	Ar	3087, 745	3015, 714	3082, 878, 803	3043, 865
			2937, 1370 (CH_3)		693 (C-Br)
^1H NMR (500 MHz, d-DMSO) (ppm)		2.40 (4H, CH_2)	2.40 (4H, CH_2)	2.40 (4H, CH_2)	insoluble in DMSO
		2.50 (6H, CH_2)	2.50 (6H, CH_2)	2.50 (6H, CH_2)	
		2.68 (2H, Ar–CH_2)	2.70 (2H, Ar–CH_2)	2.68 (2H, Ar–CH_2)	
		2.90 (2H, CH_2)	2.90 (2H, CH_2)	2.90 (2H, CH_2)	
		3.50 (3H, NH, CH)	3.50 (3H, NH, CH)	3.50 (3H, NH, CH)	
		6.65, 6.73, 6.97 (4H, ArH)	6.61, 6.76 (3H, ArH)	6.71, 7.12 (3H, ArH)	
		7.86 (1H, OH)	7.88 (1H, OH)	7.89 (1H, OH)	
		9.35 (broad, CONH)	8.5 (broad, CONH)	9.7 (broad, CONH)	
			3.75 (3H, CH_3)		
Mass (*m/e*)		320 (M^+)	350 (M^+)	398, 400 (M^+) (1:1)	476, 478, 480 (M^+) (1:2:1)
		277 ($M^+ - CH_2CO$)	307 ($M^+ - CH_2CO$)	355, 357	433, 435, 437 (1:2:1)
		264	294	297, 299	420, 422, 424
		219	249	225, 227	375, 377, 379
		147	177	187	306
		107	107	118	278
		91	91	85	149
		73	73	73	73

[a] dec. denotes decomposition.



Scheme 2. Proposed arrangements of ligand protonation.

Table 2
Equilibrium constants for the stepwise protonation of the ligands [a] (aqueous 0.1 mol dm^{-3} $NaNO_3$ at 25 °C)

	L_1	L_2	L_3	L_4	L_5 [b]
log K_1	10.01(4)	10.26(4)	9.78(2)	9.39(3)	
log K_2	9.05(5)	9.05(4)	8.81(2)	7.31(4)	8.66
log K_3	3.66(5)	3.58(4)	3.68(3)	3.50(5)	3.04

[a] Uncertainties (standard deviations) in the last figure are given in parentheses.

[b] L_5 is 12-(4′-nitro)-benzyl-1,4,7,10-tetraazacyclotridecane-11,13-dione [36].

$[Cu(H_{-2}L)]^-$ and $[Cu(H_{-1}L)]$. The following reactions were found to take place:

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

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

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

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

In the complex $[Cu(H_{-2}L)]^-$, with two deprotonated amido groups coordinated to copper(II), the negative charges should not be considered to lie on the nitrogen atoms but to delocalize through a π mechanism into the entire NCO bond [34]. The complex $[Cu(H_{-2}L)]^-$ has a pyramidal geometry, with four ring nitrogens coordinated to copper(II) and phenolate at the apex coordinated to copper(II) as the fifth donor. In the complex $[Cu(H_{-1}L)]$, with one proton still attached, it should bind to the phenolic oxygen, that is, phenol does not coordinate to the copper(II) ion. The complex $[Cu(H_{-1}L)]$ has a square planar geometry (Scheme 3). Deprotonation of one amido group seems to be excluded [35]. Equilibrium constants are listed in Table 3.

From Fig. 1, it can be seen that all copper ions form the $[Cu(H_{-2}L)]^-$ complex at pH > 7. $[Cu(H_{-1}L)]$ has a maximum value (50%) at pH 5.3. It can also be seen from Table 3 that the stability constants increase with an increase in the basicity of the ligands. The formation constants of $[Cu(H_{-2}L)]^-$ increased by 3.5×10^4 with apical phenolate coordination. Plots of equilibrium constants of complexation versus protonation constants of the ligands showed that linear free energy relationships existed between them. Because of the steric hindrance of o-OCH_3, the stability of the complex $[Cu(H_{-2}L)]^-$ of L_2 was slightly decreased (Fig. 2). Steric hindrance does not exist in the complex $[Cu(H_{-1}L)]$ because the phenolic oxygen does not coordinate to copper(II), thus the relative coefficient of the latter is larger than that of the former.

$$\log K(1,1,-2) = -15.66 + 0.899 \log \beta_2 \qquad r = 0.996$$

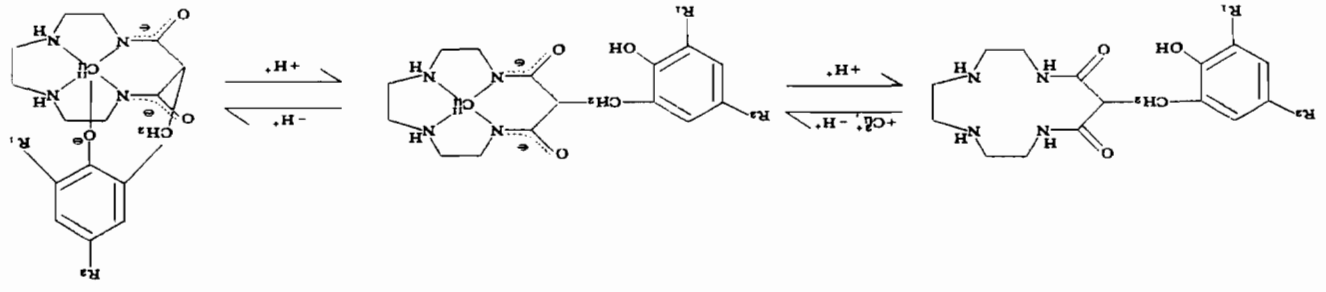
$$\log K(1,1,-1) = -10.94 + 0.944 \log \beta_2 \qquad r = 0.999$$

where $\beta_2 = K_1 \times K_2$.

3.3. EPR spectra

Fig. 3 presents the EPR spectra of the copper(II) complex of L_4 at room temperature and at 120 K (pH 7). 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 an isotropic spectrum is observed because of fast rotation of the complex. Similar EPR spectra were obtained for the other copper(II) complexes. The g and A parameters can be obtained by computer fitting using the revised QPOW program [37]. The experimental and computer fitted spectra are exactly the same (Fig. 3), indicating that the g and A parameters thus obtained are reliable. All the results are summarized in Table 4.

The g and A parameters are nearly the same at room temperature, that is the electronic effects of the axially coordinated phenolate have little affect on the EPR parameters of the copper(II) complexes. The g parameters of the complex containing phenol groups are larger than those of a similar complex without phenol groups (L_5). The coordination environment of the two kinds of complex is obviously different; the phenol hydroxyl group is coordinated to the copper(II) ion in the former. The difference between the $g_\perp$ and $g_\parallel$ parameters of the complexes at 120 K is small compared to α-amino acids copper(II) complexes [38]. According to the formulae [39] $g_\perp = g_e + 2\zeta\alpha^2/\Delta'_\perp$ and $g_\parallel = g_0 + 8\zeta\alpha^2/\Delta'_\parallel$, the ligand field is stronger (large Δ'), and the Cu–N bond has more covalence properties (small α) in the former. This may be the reason why 13-membered dioxotetraamines stabilize the Cu(III) state.



Scheme 3. Hypothesized coordinative arrangements of the complexes.

Table 3
Equilibria constants [a] for the complexation of copper(II) with macrocyclic dioxotetraamines (aqueous 0.1 mol dm^{-3} $NaNO_3$ at 25 °C)

Ligand	$Cu^{2+}+L^{-}=$ $[Cu(H_{-2}L)]^{-}+2H^{+}$ log $K(1,1,-2)$	$Cu^{2+}+L^{-}=$ $[Cu(H_{-1}L)]+H^{+}$ log $K(1,1,-1)$
L_1	1.58(5)	7.01(3)
L_2	1.56(7)	7.32(2)
L_3	1.07(8)	6.63(3)
L_4	−0.67(6)	4.83(2)
L_5	−2.96	

[a] Uncertainties (standard deviations) in the last figure are given in parentheses.

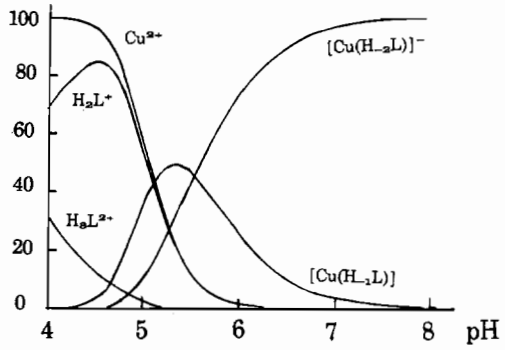


Fig. 1. Distribution diagram for the Cu^{2+}–L_3^{-} (1:1) system.

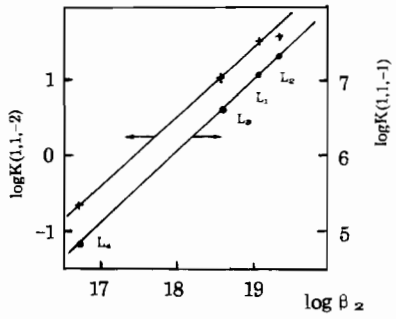


Fig. 2. Plots of log β_2 of the ligands vs. log $K(1,1,-1)$/log $K(1,1,-2)$ of their complexes; $\beta_2=K_1\times K_2$.

3.4. Cyclic voltammetry

One oxidation peak appeared in the range 0–0.15 V (versus SCE, E^1_{pa}) in the cyclic voltammogram of the free ligand (pH 5.5), indicating the oxidation of the phenol group. No much difference was found when the pH was increased to 8. On adding one equivalent of copper(II) sulfate to the solution (pH=5.5), the oxidation potential shifted slightly to positive, and an anodic peak appeared at 0.64 V (versus SCE). The oxidation peak of phenol hydroxyl at 0–0.15 V disappeared when the pH was increased to 7.0 and another anodic peak appeared at 0.47 V (Fig. 4). Thus, the copper(II) complex has two oxidation processes in the range −0.4–0.8 V (versus SCE) at pH 5.5–7.0. This means that the phenol hydroxyl group is coordinated

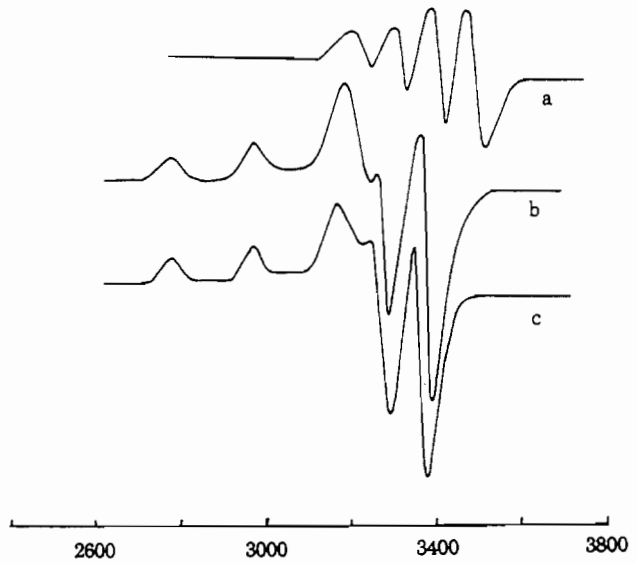


Fig. 3. X-band EPR spectra of the copper(II) complex of L_4: (a) at room temperature, (b) experimental spectra at 120 K, (c) computer-fitting spectra of 120 K.

Table 4
EPR parameters of copper(II) complex of macrocyclic dioxotetraamines

Ligand	Room temperature			120 K		
	g	A (G)	$A_\parallel$ (G)	$A_\perp$ [a] (G)	$g_\parallel$	$g_\perp$
L_1	2.097	91	197	38	2.180	2.044
L_2	2.105	89	195	36	2.182	2.046
L_3	2.102	90	200	35	2.186	2.046
L_4	2.100	90	197	37	2.178	2.047
L_5	2.086	90	203	34	2.165	2.046

[a] $A_\perp$ was calculated according to the formula $3A_{iso}=A_\parallel+2A_\perp$.

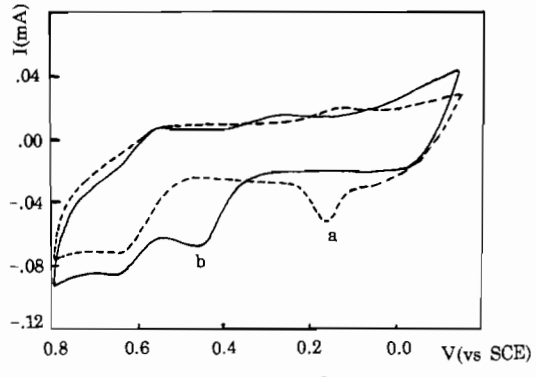


Fig. 4. Cyclic voltammogram of the Cu^{2+}–L_4 system. Scan rate 100 mV s^{-1}. (a) pH 5.5, (b) pH 7.0.

to the copper(II) ion, further supporting the results of EPR measurement and pH titration. The anodic peak E^2_{pa} and cathodic peak E^2_{pc} do not change with pH. The magnitudes of the anodic peak current i^2_{pa} and the cathodic peak current i^2_{pc} are of equal intensity (pH 7); this means that the redox processes are quasi-reversible. The half-wave potential can be calculated

Table 5
Parameters of cyclic voltammogram of macrocyclic dioxotetraamine copper(II) complexes (±0.005 V, vs. SCE)

	L_1		L_2		L_3		L_4		L_5
pH	5.5	7	5.5	7	5.5	7	5.5	7	7
E^1_{pa}	0.07	0.45	0.01	0.23	0.10	0.46	0.15	0.47	
E^2_{pa}	0.64	0.64	0.64	0.64	0.65	0.65	0.64	0.64	0.62
E^2_{pc}	0.52	0.52	0.50	0.50	0.53	0.53	0.55	0.55	0.55
$E^2_{1/2}$	0.58	0.58	0.57	0.57	0.59	0.59	0.60	0.60	0.59

according to $E_{1/2}=(E_{pc}+E_{pa})/2$. The magnitude of i^1_{pc} was too small to be determined accurately (pH 5.5–7), showing that this redox process is less reversible. Other copper(II) complexes have similar cyclic voltammograms. The parameters of the cyclic voltammograms of the macrocyclic copper(II) complexes are summarized in Table 5.

From Table 5, it can be seen that E^2_{pa}, E^2_{pc} and $E^2_{1/2}$ and the reversibility are similar to those of the copper(II) complex of the ligand L_5. The $E^2_{1/2}$ values are nearly the same as the $E(Cu^{III}/Cu^{II})$ potential of the 1,4,7,10-tetraazacyclotridecane-11,13-dione copper(II) complex [16,31b]. This redox process is therefore assigned to the oxidation of the copper(II) complexes to copper(III) complexes. E^1_{pa} obviously changed with the various substituents, but the substituents had little effect on the $E^2_{1/2}$ values. The oxidation of phenols is a complex area, various mechanistic courses may be followed and several different reactive intermediates can be formed [29]. There are no studies of the oxidation process of similar phenol containing macrocycles [25,31]. It is therefore very difficult to confirm the oxidation process of the phenol groups.

It can be seen from Table 5 that the half-wave potential of Cu(II)/Cu(III) increased with the increase of the electron-withdrawing effect of the substituents, that is an electron-withdrawing group R tends to increase the oxidation potential since electron-withdrawing substituents decrease the electron density on the phenolate and copper(II) ion. The lower the electron density, the more difficult it is to oxidize, i.e. electron-withdrawing substituents increase the E_{pa} and $E_{1/2}$ of the copper(II) complex.

It is very difficult to obtain crystals, even though pure solid complexes of dioxotetraamine macrocycles were obtained. So far, the crystal structure of the platinum(II) complex is the only one reported in the literature with this ligand [40]. We were unable to obtain crystals for these copper(II) complexes.

4. Conclusions

Various pendent phenol-substituted 13-membered macrocyclic dioxotetraamines have been synthesized. The simplicity and versatility of the new method are widely applicable for the synthesis of novel metal chelating agents with various biomimetic functions. When coordinated to the copper(II) ion, the ligands dissociated two hydrogen ions from the amido groups. The pendent phenols dissociate their protons upon interaction with copper(II), and the resulting phenolate oxygens come to the apical position to be a fifth donor. The degrce of phenol dissociation varies with pH, thus $[Cu(H_{-2}L)]^-$ and/or $[Cu(H_{-1}L)]$ formed in aqueous solution. The complexation constant for $[Cu(H_{-2}L)]^-$ (in phenolate form) is 3.5×10^4 times greater due to the apical phenolate coordination. Linear free energy relationships were found to exist between log β_2 of the ligands and log K of their complexes. The g parameters are also different from those of a similar ligand without phenol groups. Anodic peak potentials and half-wave potentials of the copper(II) complexes increased with the increase of electron-withdrawing effect of the substituents in the ligands.

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