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ORIGINAL ARTICLE

Synthesis of the macrotricyclic ligands 8,18 dioxa-1,5,11,15-tetraaza-[13.5.2.2^{5,11}]-eicosane (L1) and 7,16 dioxa-1,4,10,13-tetraaza-[11.5.3.3^{4,10}]-octadecane (L2). Crystal structures of the copper(II) complexes, [Cu(L1)](ClO$_4$)$_2$ and [Cu(L2)](ClO$_4$)$_2$·CH$_3$NO$_2$

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Abstract Two isomeric polymacrocyclic ligands, L1 and L2 have been synthesized and the corresponding copper(II) complexes prepared. Reaction of the macrobicycle 15-oxa-1,5,8,12-tetraazabicyclo[10.5.2]nonadecane (L3) with diglycolyl chloride in base, yielded a diamide and following reduction, led to formation of the tricyclic ligand L1. A single crystal X-ray study of the blue, [Cu(L1)](ClO$_4$)$_2$, (C2/c monoclinic, a = 33.518(4), b = 16.3778(18), c = 13.7391(19) Å, β = 90.56(3)°, V = 7541.8 (16) Å^3, Z = 12, R (F_0) = 0.065, R_w = 0.066) reveals the presence of two independent [Cu(L1)]$^{2+}$ cations displaying either five- or six- coordinate geometry. In the former distorted square pyramid, only one of the ether oxygens of the ligand is bound to the copper center, Cu–N_1 = 2.083(7), Cu–N_2 = 2.076(9), Cu–O_1 = 2.276(11) Å and the Cu–O bond is at the longer end of axial distances of this type. However, the six-coordinate species is considerably more distorted, with in equivalence in both the metal-nitrogen and -oxygen bonds, Cu–N_1 = 2.082(7), Cu–N_2 = 2.096(7), Cu–N_3 = 2.103(7), Cu–N_4 = 2.068(7), Cu–O_1 = 2.597(7), Cu–O_2 = 2.427(7) Å, N(1)–Cu–O(1) = 71.0(2), N(3)–Cu–O(1) = 71.6(2), O(1)–Cu–O(2) = 64.6(2). The ligand L2 has been synthesized by reaction of the ten-membered macrocycle 1-oxa-4,8-diaza decane, (10-N_2O) in dichloromethane with two moles of chloroacetyl chloride. The bis-pendant-armed product was further reacted with another mole of 10-N_2O to yield a tricyclic diamide. The crystal structure of the intermediate diamide (Pnam, no.62 orthorhombic, a = 13.712(9), b = 9.111(5), c = 15.110(7) Å, V = 1887.6 Å^3, Z = 8, R = 0.103, R_w = 0.103) has been determined. Subsequent reduction led to the formation of L2. The ligand is readily protonated to give a diammonium cation, [H_2L2]$^{2+}$. A single

Two new isomeric macrotricyclic ligands (L1) and (L2) have been prepared. L1 was prepared by reaction of the corresponding tetraazamacrobicycle with diglycolyl chloride in base, followed by reduction. Whereas, L2 was prepared by coupling of [10]aneN_2O with chloroacetyl chloride in two steps followed by reduction. Crystals of the copper(II) complex of L1 showed the presence of two species within the unit cell: a) a five-coordinate ion with one of the [10]aneN_2O units uncoordinated, and b) the distorted six-coordinate Cu(II) ion shown. The isomeric ion, [Cu(L2)]$^{2+}$, based on bridging across the 1,11 and 4,8-N donors of the cyclam ring, shows only the five-coordinate form.

It is a pleasure to recognize the contributions to macrocyclic chemistry made by friend and colleague Len Lindoy.

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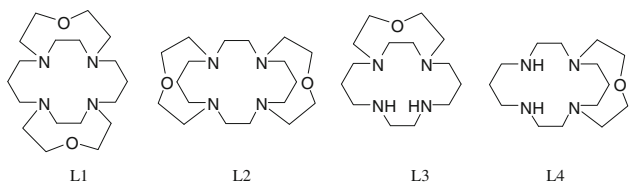
crystal structure of the $[Cu(L2)](ClO_4)_2{\cdot}CH_3NO_2$ complex ($P2_1/c$, monoclinic a = 9.731(3), b = 16.065(5), c = 18.076(6) Å, $\beta = 91.627(7)°$, V = 2824.5 (15) $Å^3$, Z = 4, $R_1 = 0.090$, $wR_2 = 0.215$) indicates considerable asymmetry in the cyclam plane ($Cu–N_1 = 2.099(11)$, $Cu–N_2 = 2.061(10)$, $Cu–N_3 = 2.065(10)$, $Cu–N_4 = 2.111(11)$, $Cu-O_{12} = 2.410(7)$ Å) with one of the ether oxygens is coordinated to the metal, while the other is unbound. The ligand adopts a syn-configuration with both the attached macrocyclic units on the same side of the cyclam ring. Spectroscopic studies are reported.

Keywords Macrotricyclic · Encapsulated metal ion · Crystal structures of Cu(II) complexes

Introduction

The coordination chemistry of the tetraazamacrocycle, cyclam, (1,4,8,11-tetraazacyclotetradecane and its derivatives continues to provide a rich source of interesting metal ion complexes of differing molecular structure [1–7] in part, owing to the variety of conformational isomers [4, 6] produced. First row transition metal ions in particular, have been shown to form complexes of considerable thermodynamic and kinetic stability. Previous studies in this laboratory [8–15] have reported the syntheses of macrobicyclic pentacoordinate ligands 15-X-1,4,8,11-tetraazabicyclo[10.5.2]nonadecane (L3) (Scheme 1) in which a 9-membered cyclononane ring ([9]aneN_2X where X = NH, O, S) is "fused" to an ethylene segment of the 14-membered tetraaza-cyclam ring. Each of the (L3) cations adopts the *trans*-I conformation in the solid state for both Ni(II) and Cu(II) complexes. More recently, the isomeric 10-membered pendant ligands have been prepared [11–13] where *trans*-III geometries have been identified. There are relatively few examples of selectively 1,4 or 1,8 or 4,8-N, N′-di-functionalized cyclam ligands that have been prepared [14–17], owing, in part, to the competitive formation of other substituted species in the preparations. Examples of N_4O_2 donor complexes have been proposed in the stabilization of radioisotopes for medical applications [18, 19]. Tetra-aza-macrotricyclic ligands have also been shown recently to exhibit inclusion of hydrogen ions and other small ionic species [20, 21] and may play a role as outer-sphere redox agents.

In this paper, we present a further extension of our macrobicyclic approach, by the attachment of an additional ring to yield macrotricyclic ligands. An interesting result of this work is to examine the geometries of the complexes formed.



Scheme 1

Experimental

Synthesis

The ligand 15-oxa-1,5,8,12-tetraazabicyclo[10.5.2]nonadecane (L3) was synthesized as described previously [10]. Diglycolyl chloride (95%), chloroacetyl chloride (98%), dichloromethane, BH_3.THF (1 M in THF), K_2CO_3 and $Cu(ClO_4)_2{\cdot}6H_2O$ were purchased from Aldrich Chemical Co., and used without any further purification. Sephadex CM C-25 was purchased from Aldrich Chemical Co. $Na_2S{\cdot}9H_2O$ was purchased from BDH. Triethylamine from BDH was dried over molecular sieves before use. Benzene (Caledon) and dichloromethane (Aldrich) were fractionally distilled from CaH_2 and stored under nitrogen before use.

Caution! Transition-metal perchlorates are known to be hazardous and must be treated with care, especially in the presence of organic solvents.

8,18-Dioxa-1,5,11,15-tetraazatricyclo [13.5.2.$2^{5,11}$]tetracosane (L1)

To a vigorously stirred benzene (2500 cm^3) in a 10 L flask, solutions of a mixture of L3, (0.976 g, 3.609 mmol) and triethylamine (1.51 cm^3, 10.827 mmol) in benzene (50 cm^3) and diglycolyl chloride (0.45 cm^3, 3.609 mmol) in dry benzene (50 cm^3) were added simultaneously and slowly from a motor-driven syringe over a period of 10 h. An atmosphere of dry nitrogen was maintained. The mixture was stirred for an additional 2 days and then filtered to remove triethylammonium chloride. Removal of solvent under vacuum yielded a colorless oil (~1.1 g) containing several products. The crude tricyclic diamide mixture was refluxed in BH_3.THF (110 cm^3, 1 M in THF) for 24 h under an atmosphere of nitrogen. Water (5 cm^3) was added dropwise carefully to the cooled solution in order to destroy the excess BH_3. Following removal of solvents the white solid residue was refluxed in HCl (6 M, 60 cm^3) for 4 h. After the solution had been cooled and basified to pH 14 with KOH pellets, it was extracted with chloroform using a continuous extraction apparatus. The organic layer was dried over K_2CO_3, filtered, and taken to dryness to yield a colorless oil (0.431 g) containing a mixture of

ligands. The pure free ligand, L1 were isolated via separation of its copper(II) complex as described below.

The mixture of ligands was dissolved in deionized H_2O (50 cm^3) and an excess of copper(II) perchlorate hexahydrate (1.50 g, 4.048 mmol) was added with stirring. The solution turned to a blue/purple color immediately but was heated to 80 °C for 1 h to ensure completion of the complex formation. Upon cooling, the solution was filtered and then passed down a Sephadex CM C-25 cation exchange resin column using 0.1 M and 0.2 M $NaClO_4$ as the eluent. With 0.1 M $NaClO_4$, three bands were obtained. The first two were blue/purple and the third, most intense, was deep blue in color. Further slow elution with 0.2 M $NaClO_4$ yielded additional purple bands.

Isolation of pure [Cu(L1)]$(ClO_4)_2$

This complex was isolated and characterized from this third band. A small portion of the solution was concentrated to approximately 10 cm^3 and $NaClO_4 \cdot H_2O$ (0.300 g, 2.134 mmol) was added. Solution was allowed to stand for 2 weeks whereupon X-ray quality deep blue crystals were obtained. Calc. (found) for $[Cu(C_{18}H_{36}N_4O_2)](ClO_4)_2$.% C, 35.33 (35.90); H, 6.09(6.03); N, 9.16(9.31). MS (LSIMS): 502.1 ($[Cu(L1)](ClO_4)^+$), 403.2 ($[Cu(L1)]^+$).

The major portion of the third blue band was concentrated to approximately 50 cm^3 and an aqueous solution of $Na_2S \cdot 9H_2O$ (0.25 g, 1.041 mmol) was added. The complex solution turned colorless immediately. After refluxing for 1 h to ensure the removal of Cu(II), the CuS formed was filtered off. The aqueous solution was basified to pH 14 with NaOH pellets and extracted with chloroform (5 × 30 cm^3). The combined organic extracts were dried with K_2CO_3, filtered and the solvent was removed under reduced pressure to yield a colorless oil. Yield: 0.172 g (14%) ^{13}C NMR ($CDCl_3$): 73.8 (4C, –$\underline{C}H_2$–O–); 57.2, 56.1, 55.7 (4C each, –$\underline{C}H_2$–N–); 28.0 (2C, –$\underline{C}H_2$–). ^{1}H ($CDCl_3$): 4.0–3.2 (8H, 2 broad overlapping singlets,–C$\underline{H}_2$–O–); 3.1–2.3 (24H, m,–C$\underline{H}_2$–N–); 1.48 ppm (4H, quintet, –C$\underline{H}_2$–). MS (methane CI): m/e 341 (M + 1), 369 (M + 29).

5,8-Bis(2-ethoxyethanol)-17-oxa-1,5,8,12-tetraazabicyclo-[10.5.2]nonadecane (L7)

The first blue/purple band was concentrated and the complex was decomposed with $Na_2S \cdot 9H_2O$ to removed the copper(II) ion as described above. A small amount of this product was confirmed to be the bis-armed intermediate formed through incomplete cyclisation.

Yield: 0.078 g (5%). ^{13}C NMR ($CDCl_3$): δ75.2, 72.4, 69.4 (2C each, –$\underline{C}H_2$–O–); 61.9 (2C, –$\underline{C}H_2$–OH); 57.6, 57.2, 56.7, 54.7, 52.9, 51.7 (2C each, –$\underline{C}H_2$–N–); 25.8 (2C, –$\underline{C}H_2$–). ^{1}H ($CDCl_3$): δ 4.7–3.4 (16H, m, –C$\underline{H}_2$–O–); 3.0-2.3 (24H, m, –C$\underline{H}_2$–N–); 1.47 (4H, broad singlet, –C$\underline{H}_2$–). MS (CI): m/e 447 (M + 1), 475 (M + 29), 487 (M + 41).

4,8-bis(chloroacetyl)-1-oxa-4,8-diazadecane, L5

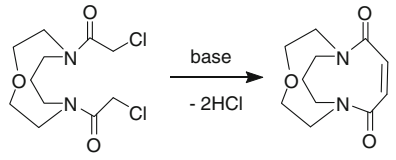
The macrocycle 1-oxa-4,8-diazadecane ([10]aneN_2O) (2 g, 14 mmol) was dissolved under nitrogen in 450 mL of dichloromethane and 50 mL of water in a 2 L 3-necked flask, and cooled to 0 °C. With rapid stirring, chloroacetyl chloride (10 mL, 62 mmol) in 250 mL dichloromethane and potassium carbonate (18 g, 65 mmol) in 250 mL water were added simultaneously drop-wise over a period of 2 h. After this addition was completed, the reaction mixture was allowed to warm to room temperature, and stirred for a further period of 2 h. The aqueous layer was removed, and the organic layer was washed with water (2 × 200 mL). The combined organic layer was dried with anhydrous sodium sulphate, and the solvent was removed under reduced pressure. The residue was recrystallized from hot methanol. Yield = 2 g (82%). ^{1}H NMR ($CDCl_3$): 2.20, 2.31 (m, 2H, C$\underline{H}_2$–C), 3.50, 3.58 (m, 2 + 2H, C$\underline{H}_2$–N), 3.68, 3.75 (m, 2H, C$\underline{H}_2$–Cl), 4.12 (m, 2H, C$\underline{H}_2$–O). ^{13}C NMR ($CDCl_3$): 27.9, 28.6 ($\underline{C}H_2$–C), 40.8, 41.0, 41.3, 41.4 ($\underline{C}H_2$–O), 46.2, 46.7, 46.8 48.3, 49.36, 49.40, 49.9, 50.1 (C$\underline{H}_2$–N), 68.0, 69.5, 70.0, 70.3 ($\underline{C}H_2$–Cl), 166.7, 167.1, 167.2 ($\underline{C}$=O). MS (CI): m/z 298 (M + 1), 326 (M + 29), 338 (M + 41).

7,16-dioxa-1,4,10,13-tetraazatricyclo [11.5.3.3^{4,10}]octadecane 3,11-dione (L6)

Into a 4-necked round bottom flask, fitted with a condenser, a nitrogen inlet, and a high-speed overhead stirrer, was placed 4 L of dry acetonitrile and sodium carbonate (10 g, 94 mmol). The ligand [10]aneN_2O (1.6 g, 11.4 mmol) and 4,8-bis(chloroacetyl)-1-oxa-4,8-diazadecane (3.4 g, 11.4 mmol) (L5), each in 200 mL dry acetonitrile, were added simultaneously and dropwise over a period of 48 h. The reaction mixture was then heated for a further 12 h period. After filtration of the white precipitate, the solvent was removed under reduced pressure to yield a residue that was recrystallized from a minimum amount of hot acetonitrile, to give a white crystalline solid. Yield = 2.6 g (62%). An X-ray quality single crystal was obtained and the structure of this diamide was determined.

^{1}H NMR ($CDCl_3$): 1.46, 2.10 (m, C$\underline{H}_2$–C), 2,52, 2.89, 3.27 (m, C$\underline{H}_2$–N), 3.76, 4.08 (m, C$\underline{H}_2$–O). ^{13}C NMR ($CDCl_3$): 23.2, 27.5 (C$\underline{H}_2$–C), 45.4, 46.1, 56.3, 61.9, 62.1 (C$\underline{H}_2$–N), 72.0, 73.4 ($\underline{C}H_2$–O), 170.5 ($\underline{C}$=O). MS (CI): m/z 368 (M+), 369 (M + 1), 397 (M + 29), 409 (M + 41).

In a separate experiment, when the reaction was carried out in dimethylacetamide with Cs_2CO_3 as base, L6 was also the major product but appreciable amounts of an enedione (L8) were also isolated presumably through elimination of two moles of HCl and ring closure via a carbine intermediate.



L5 L8

7,16-dioxa-1,4,10,13-tetraazatricyclo[11.5.3.3^{4,10}]octadecane (L2)

The bis-amide L6 (0.3 g) was dried under vacuum for 24 h. BH_3.THF (1 M) (15 mL) was added under nitrogen at 0 °C. The solution was then refluxed under nitrogen for 24 h. After cooling in an ice bath, the excess borane was destroyed by the slow addition of water. Upon removal of the solvent, 25 mL of 6 M aqueous HCl was added. The slurry was refluxed for 3 h, during which time the solid dissolved. The solution was basified by the addition of potassium hydroxide (pH 14), and extracted with 5 × 20 mL dichloromethane. The organic layers were combined, dried with anhydrous sodium sulfate, filtered and taken to dryness. The resulting pale yellow oil was used without further purification. Yield was quantitative.

^{1}H NMR ($CDCl_3$): 1.16, 1.45 (m, 4H, C$\underline{H}_2$–C), 2.14, 2.30 (24H, C$\underline{H}_2$–N), 3.26, 3.38 (m, 8H, C$\underline{H}_2$–O); ^{13}C NMR ($CDCl_3$): 28.1 ($\underline{C}H_2$–C), 53.2 (CH$_2$–$\underline{C}$H$_2$–CH$_2$–N), 53.4 (N–$\underline{C}$H$_2$–CH$_2$–N), 54.5 (O–$\underline{C}$H$_2$–CH$_2$–N), 65.7 ($\underline{C}H_2$–O). MS (CI): m/z 341 (M + 1), 369 (M + 29).

$[H_2(L2)](ClO_4)_2$

The free tricyclic ligand, (L2) was dissolved in water and 1 mL 0.1 M $HClO_4$ was added. The white crystals, which began to precipitate immediately, were filtered and recrystallized from minimum amount of hot water.

^{1}H NMR) (D_2O): 1.82, 2.30 (m, 1 + 1H, CH_2–C), 2.60, 2.84, 3.1 (m, 8H, CH_2–N), 3.58 (m, 6H, CH_2–N and CH_2–O), 4.18 (m, 2H, CH_2–O); ^{1}H NMR (CD_3CN): 1.89, 2.35 (m, 1 + 1H, CH_2–C), 2.58, 2.73, 2.92, 3.17 (m, 8H, CH_2–N), 3.60 (m, 6H, CH_2–N and CH_2–O), 4.15 (m, 2H, CH_2–O), 8.82 (br, NH); ^{13}C NMR (D_2O): 19.0 (CH_2–C), 50.1 (C–C–CH_2–N), 53.1 (O–C–CH_2–N, N–C–CH_2–N), 66.3 (CH_2–O); ^{13}C NMR (CD_3CN): 20.0 (CH_2–C), 51.3 (C–C–CH_2–N), 53.8 (O–C–CH_2–N, N–C–CH_2–N), 66.7 (CH_2–O). MS(FAB): m/z 341.2 (LH^+), 441.2 ($[LH_2(ClO_4)]^+$).

$[Cu(L2)](ClO_4)_2$

The tricyclic ligand (L2) (0.16 g, 4.8 mmol) was dissolved in 20 mL methanol, to which was added $Cu(ClO_4)_2.6H_2O$ (0.178 g, 4.8 mmol) in 5 mL methanol. Initially a green precipitate was observed, but after 30 min of refluxing, a royal blue solution formed, which was refluxed for a further 30 min. The solution was gravity filtered, and taken to dryness. The residue was dissolved in water again and purified by Sephadex CM-C25 column chromatography with 0.1 M sodium perchlorate as eluent. The salt was further purified by slow evaporation of the aqueous sodium perchlorate solution to give royal blue crystals. These crystals were further crystallized by diffusing diethyl ether into an acetonitrile solution. Yield = 0.265 g (92%).

MS (FAB): m/z 341.2 (LH^+), 403.2 ($[Cu^{II}(L2–H^+))]^+$ and $[Cu^{I}(L2)]^+$), 502.1 ($[Cu^{II}(L2)(ClO_4^-)]^+$) MS (ES): m/z 171.1 ($[H_2L2]^{2+}$), 201.6 ($[CuL]^{2+}$), 341.3 $(HL2)^+$, 403.2 ($[Cu^{II}(L2\text{-}H)^-]^+$), 502.2 ($[Cu^{II}(L)(ClO_4^-)]^+$).

Calc. (found) for $Cu(L2)(ClO_4)_2{\cdot}CH_3CN$ % C 36.60 (36.45) H 6.06(5.95) N 10.11(9.41)%.

$[Cu(L2)](ZnCl_3H_2O)_2$

To $[Cu(L2)](ClO_4)_2$ (300 mg) was added 3 M HCl (2 mL) and 1 g of $ZnCl_2$, and the mixture was heated to 80 °C for 1.5 h. Slow evaporation of the solution resulted in formation of a viscous oil. Isopropanol was allowed to diffuse into the solution resulting in blue plates, of X-ray quality, being formed over several days.

MS (ES): m/z 171.1 ($[LH]^{2+}$), 201.6 ($[CuL]^{2+}$); MS (FAB): m/e 170.8 ($ZnCl_3^-$). Calc.(found) for Cu(L)$(ZnCl_3H_2O)_2.(CH_3CH_2CH_2OH)$ % C 28.79(28.65) H 5.45(5.27) N 6.89(7.03.)

Crystallography

Crystal structure determinations L6, $[Cu(L1)](ClO_4)_2$ and $[Cu(L2)(ClO_4)_2{\cdot}CH_3NO_2$ were carried out as follows:

7,16-dioxa-1,4,10,13-tetraazatricyclo[11.5.3.3$^{4.10}$]octadecane 3,11-dione (L6)

A thin white crystal of dimension 0.50 × 0.84 × 0.08 mm, grown from an aqueous acetonitrile solution was used. The crystal was mounted on a glass Lindemann tube and following Weissenberg and precession photography was mounted in a Nonius CAD4 diffractometer. The cell

was refined using 21 centered reflections over the range $\theta = 15$–$42°$. Of the 1284 reflections measured, 630 were used. No decomposition of the crystal was observed during the data acquisition. For the molecule L6 absorption corrections were made [22] and the structure solved by direct methods [23]. The refinement converged with a maximum shift/esd of 0.01 and a maximum peak of 0.45 eÅ^{-3}.

$[Cu(L1)](ClO_4)_2$

A crystal of dimensions 0.10 × 0.20 × 0.30 mm was mounted in a glass Lindemann tube and optically centred in an Enraf–Nonius CAD-4 diffractometer employing graphite-monochromated Mo-K_α radiation. The structure of $[Cu(L1)](ClO_4)_2$ was solved using the PC version of NRCVAX [24–26] implemented on 80486 processor based IBM compatible computer. The unit cell was refined by using 24 reflections in the 2θ range 30–42°. The diffraction data were collected using the $\theta/2\theta$ scan mode. A total of 5809 reflections were collected. Of the 5554 unique reflections observed, 3550 reflections with $I_{net} > 2.50\sigma(I_{net})$ were included in the final least squares refinement for 109 atoms and 528 parameters. Absorption corrections were made and all non-hydrogen atoms were refined anisotropically. Minimum and maximum transmission factors were estimated to be 0.876 and 0.981, respectively.

$[Cu(L2)](ClO_4)_2$

Data for $[Cu(L2)](ClO_4)_2.CH_3NO_2$ were collected on a Smart 1000 CCD area detector diffractometer with graphite-monochromated Mo-K (= 0.71073 Å) radiation and the cell parameters were determined from a non-linear least squares fit of the data. The structure was solved, after an adsorption correction by the SADABS method [27], by direct methods by use of the SHELX 97 (Sheldrick, 1990) program [28]. In all cases, non-hydrogen atoms were treated anisotropically and hydrogen atoms were treated using the riding model and placed in calculated positions.

Mass spectroscopic data were obtained using LSIMS technique on a Kratos Concept instrument for complexes and intermediates. Mass spectra of the organic ligands were measured on a Finnegan GC 330 mass spectrograph using standard chemical ionisation techniques. Bruker WM-250 and AC-300 n.m.r. spectrometers were used to record the ^1H and ^{13}C n.m.r. spectra. UV–visible spectra were measured on a Varian dual beam Cary 5 UV–Vis-NIR spectrophotometer. Elemental analyses were performed by Canadian Microanalytical Services, Vancouver, BC, Canada.

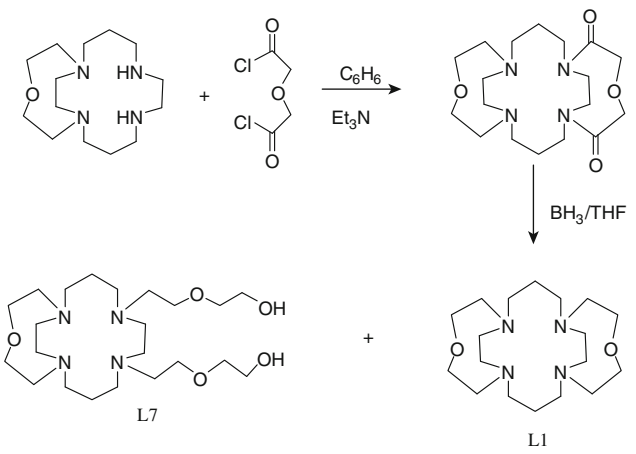
Results

Synthesis

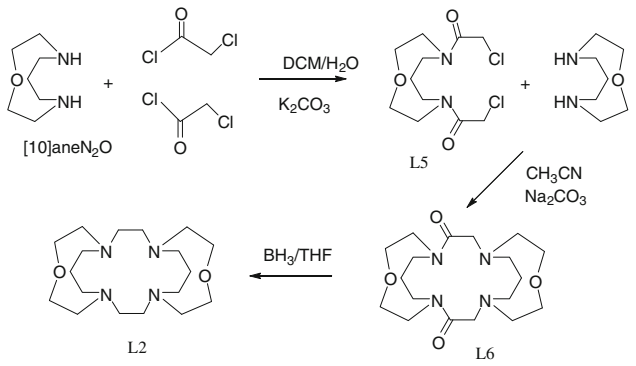
The synthesis of ligand L1 is illustrated in Scheme 2. Under high dilution conditions and with vigorous stirring, the bicyclic ligand was reacted with diglycolyl chloride in the presence of triethylamine at room temperature in dry benzene. The mass spectrum of the reduced crude material showed evidence for L1 but also other products. Therefore, it was decided to complex the crude ligand with Cu(II) and purify it on a Sephadex CM C-25 cation exchange column as the Cu(II) complex. Numerous bands were observed on the column, the most intense being the third which was blue in colour. After removal of Cu(II) by reaction with Na_2S, the free ligand L1 was obtained in a moderate yield. Attempts were made to analyze other bands in a similar manner. The first was determined to be 5,8-bis(2-ethoxyethanol)-15-oxa-1,5,8,12-tetraazabicyclo[10.5.2]nonadecane (L7) arising from the reaction of the diglycolyl chloride with each of the secondary nitrogen atoms of the bicycle. The third band appeared uniform in color upon initial elution. However, upon purification crystals of $[Cu(L1)](ClO_4)_2$ did not appear homogeneous and showed the presence of two types of crystals. Structure determination of one of these crystals confirmed the presence of both an ordered 6-coordinate cation and a disordered 5-coordinate cation. The Ni(II) complex of L1 also formed quite readily. However, elemental analysis was consistent with the presence of the counter anion, $[Ni(ClO_4)_4]^{2-}$.

7,16-dioxa-1,4,10,13-tetraazatricyclo[11.5.3.3^{4,10}]octadecane (L2).

The overall synthetic approach is outlined in Scheme 3 and involves the fusion of [10]aneN_2O to the bis-pendant



Scheme 2 Synthesis of L1



Scheme 3 Synthesis of L2

armed 4,8-bis(chloroacetyl)-1-oxa-4,8-diazadecane, L5. High dilution conditions in acetonitrile were required to produce the tricyclic bis-amide L6 in approximately 60% yield. Reduction of the amide with excess diborane in THF produced an yellow oil of the tricyclic ligand in essentially quantitative yields. This synthesis does not preclude the formation of either the *syn* or the *anti*-isomers. ^{13}C NMR studies of L6 show the presence of both five major and five minor peaks (ascribed to a second isomer). Mass spectra of both L5 and L2 show the presence of only one molecular weight product, suggesting that the two products are isomers.

Molecular structure

Experimental parameters, atom co-ordinates, thermal parameters and full listing of bond lengths and angles for all the following structures are available as Supplementary information.

7,16-dioxa-1,4,10,13-tetraazatricyclo[11.5.3.3$^{4.10}$]octadecane 3,11-dione (L6)

The structure was solved in the orthorhombic space group Pnam (No. 62) with atoms O1, O2, C4 and C10 occupying special positions. The ether oxygens are in a *trans* disposition and the amides are in a *cis* orientation, both with respect to the cyclam ring (see Fig. 1). Bond lengths are as anticipated in this type of macrocycle with both the shorter C5–N1 [1.345(15)] and C5–O3 [1.256(14)] Å bonds. Likewise, the bond angles O3–C5–N1, 120.9(1.3), C6–C5–O3, 120.2(1.3) and C6–C5–N1, 119.0(1.3)° are as anticipated for an amide. There are relatively few structures of this type.

$[Cu(L1)](ClO_4)_2$

Two independent cations (Fig. 2) were observed and disorder was observed in the oxygen atoms of one of the two cations and in two of the perchlorates. All hydrogen atoms were placed in calculated positions ($D_{C\text{-}H} = 1.08$ Å) and were given isotropic thermal parameters based upon the atom to which they are bonded. However, eight hydrogen atoms of the disordered cation were not included (C107 and C108). The refinement converged with a maximum shift to estimated standard deviation (e.s.d.) of 0.000 in the final cycle, and a maximum peak of 0.560 e Å^{-3} at an $R(F_0)$ value of 0.065 ($R_w = 0.066$). The structure was also solved and refined in the noncentrosymmetric space group Cc. A similar R-value was obtained but the problem of disorder was not resolved. In the case of ligand L1 both 5- and 6-coordinate structures are observed. The latter exhibits considerable distortion, although the *cis*-conformation is maintained despite differences in the Cu–N and both Cu–O distances. For the less well-defined 5-coordinate isomer, the bond lengths are more similar but the Cu–O bond lengths are shorter. This is reasonable considering that in the 5-coordinate cation, the non-coordination ether oxygen is pointing away from the cyclam plane and thereby removing any ambiguity in the coordination geometry at the copper center. Whereas in the 6-coordinate cation both ether oxygens are pointing inwardly towards the centre of the cyclam plane and complete for coordination to the copper centre and thereby to a longer Cu–O distance observed in this cation.

$Cu(L2)](ClO_4)_2$

The quality of the data, while lacking accuracy, is considered sufficiently good to permit inspection of the geometry of the metal ion. In this case there was evidence for a single isomer with a *syn* form of the macrotricycle with only one of the oxygen donors bonded to the metal center (Fig. 3). However, in this instance the Cu–N bonds of the cyclam core show variations from Cu(1)–N(2) = 2.061(10) to Cu(1)–N(4) = 2.111(11) with Cu(1)–O(12) = 2.410(7) Å.

It is of interest that for the Cu(II) complexes investigated in this study the Cu–O axial and Cu–N equatorial distances are well within the statistical average as indicated in the Cambridge Structural Data base. (See Supplementary data).

Solution studies

Electronic spectroscopy

The observed absorptions for the 5- and 6-coordinate $(CuL1)^{2+}$ species are typical of copper(II) complexes with amine donor atoms Table 1. Although the charge transfer peaks are fairly close, there is a difference in the visible region

Table 1 UV–Vis data (H_2O): [λ max (nm, ε (M^{-1} cm^{-1})] $[M(L)]2^+$

Complex Ion	Data
6-coord. $[Cu(L1)]^{2+}$	602(100), 316(3413)
5-coord. $[Cu(L1)]^{2+}$	570(61), 308(3269)
$[Cu(L2)]^{2+}$	615(162), 314(4930)
$[Cu(9\text{-aneN}_2O)_2]^{2+}$	546, 740, 265(4620)
$[Cu([10]aneN_2O)_2]^{2+}$	581(50)
$[Cu(L3)]^{2+}$	522(102)

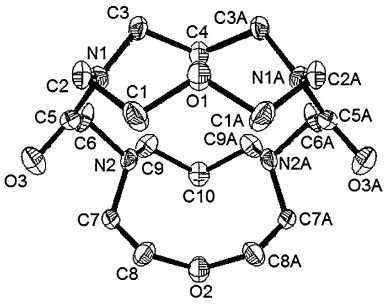


Fig. 1 Structure of L6

suggesting possible solvation changes. The maxima for the d–d transitions 6- coordinate $Cu(L1)^{2+}$ (602 nm) and 5-coordinate ion (570 nm) are lower in energy and closer to that of the $[Cu([10]aneN_2O)_2]^{2+}$ (581 nm) [29] than the predominantly 5-coordinate species of $Cu(L3)^{2+}$ and $Cu(L4)^{2+}$, respectively (522 and 520 nm) [9, 12] probably due to the increase in axial coordination for an octahedral rather than a five-coordinate complex, which is known to decrease the energy of d–d transitions in copper complexes [29, 30].

NMR studies

Two isomers, *syn*- and *anti*-, of ligand L1 are possible. High field ^{13}C NMR studies of the tricyclic amide ligand

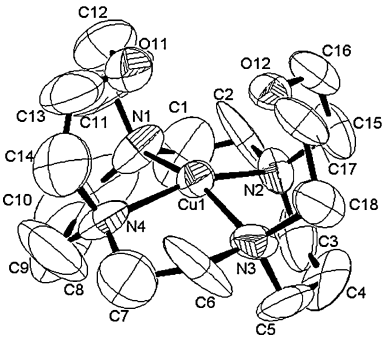


Fig. 3 Structure of $[CuL2]^{2+}$ Ion

L6 show the presence of five major peaks together with a second (minor) set of five peaks which are ascribed to a second isomer. The ratios of the major to minor isomer identified were not consistent, and varied erratically in preparations. Inter-conversion of the two isomers after formation of the tricycle seems extremely unlikely, since isomerisation would require nitrogen inversion, a process highly restricted by the interlinking carbon chains. The two isomers have been tentatively assigned, based on the shielding of the carbon atom adjacent to the ether atom. Isomer A, the major product, is assigned as the *syn* isomer since the carbon atoms adjacent to the ether oxygen would be more shielded by close presence to the oxygen atom in the second ring. This results in the ^{13}C resonance being shifted to a lower frequency in the *syn*- than in the *anti*-isomer, as observed in the spectra (Table 2).

Protonation of L2

The basicity of ligand L2 results in the free amine being readily protonated in aqueous solution. The pK_a of $[HL2]^+$ is expected to be >11, based on similar bridged molecules [29, 32, 33]. Addition of a 0.1 M perchloric acid solution to the free amine gave the diammonium salt, $[H_2L2](ClO_4)_2$, which crystallised readily from aqueous solution. The

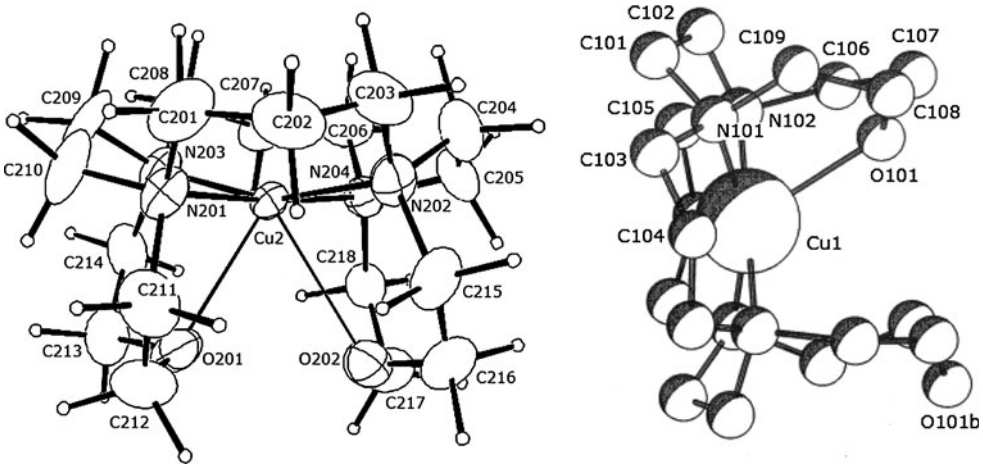


Fig. 2 Structure of Six- and Five- Coordinate $Cu(L1)]^{2+}$ Ions

Table 2 ^{13}C Chemical shifts (ppm) for isomers of L6

Isomer	C–CH_2–C	CH_2–N	CH_2–O
A (major)	28.1	53.2, 53.4, 54.5	65.7
B (minor)	27.2	56.8, 57.3, 58.3	73.3

Table 3 ^{13}C NMR data obtained for the $[H_2(L2)]$ $(ClO_4)_2$

Carbon type	(D_2O)/ppm	(CD_3CN)/ppm
C–CH_2–C	19.0	20.0
C–C–CH_2–N	50.1	51.3
N–CH_2–C–N and O–C–CH_2–N	53.1	53.8, 54.0
O–CH_2–C–N	66.3	66.7

assignment of the ^{13}C NMR resonances obtained is tabulated in Table 3. Similar spectra were obtained for the compound in CD_3CN and D_2O, with only slight shifts in peak positions. The two peaks observed in the ^{13}C NMR spectrum at approximately 54 ppm in CD_3CN were not resolved in aqueous media. The presence of only five resonances in the ^{13}C spectra in CD_3CN suggests that the symmetry of the tricycle is maintained when protonated. Two possibilities which could account for this are: (a) each proton is bonded symmetrically between two nitrogen atoms, or (b) the protons within the cavity are undergoing rapid exchange on the NMR timescale, so that an averaged signal is observed. The broad resonance at 8.8 ppm observed in the ^1H NMR spectrum of $[H_2(L2)](ClO_4)_2$ in acetonitrile is attributed to the NH^+ proton, consistent with that for other protonated amines [31, 32] and integrates to approximately to two protons. The absence of the broad NH^+ resonance in D_2O suggests that the protons are associated with ligand exchange with the bulk D_2O solvent, also rapid on the NMR timescale. In acetonitrile, this exchange is slower owing to the small quantities of water present in solution. The addition of water to the acetonitrile solution results in the disappearance of this resonance. Very basic NaOH solutions (pH $\sim$ 14), are required to remove the protons from the cavity, placing the pK_a of L2 at approximately 13. Protonation has also been identified crystallographically in the $[H_4L3]^{4+}$ ion [10] where all secondary and tertiary *N*-donors are involved, in the $[H_2(cyclam)]^{2+}$ ion [34] and in the macrotricycle containing an N_4S_2 donor set. [20, 35, 36] Clearly, these polymacrocyclic ligand systems are extremely strong bases, to the extent that is exceedingly difficult to remove the protons in many instances.

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