Synthesis, Crystal Structure and Ligational Properties of a New Macrotricyclic Ligand†

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The synthesis and characterization of the new macrotricycle 10,22,28,32-tetraoxa-1,4,7,13,16,18-hexaazatricyclo[17.5.5.5^{7,13}]tetratriacontane L is reported. Its basicity in aqueous solution has been investigated by potentiometric and spectroscopic (^{1}H, ^{13}C NMR) techniques. The basicity constants have been determined (25 °C, I = 0.15 mol dm^{-3}) in two ionic media. Macrotricycle L behaves as a hexaprotic base: log K_1 = 10.27(3), log K_2 = 9.52(3), log K_3 = 7.12(3), log K_4 = 4.62(3), log K_5 = 2.80(3), log K_6 = 2.27(3) in $NaClO_4$ and log K_1 = 10.09(3), log K_2 = 9.27(3), log K_3 = 6.54(3), log K_4 = 4.88(3), log K_5 = 3.75(3), log K_6 = 3.07(3) in NaCl. The constants relative to the equilibrium $Cl^- + H_nL^{n+} \rightleftharpoons H_nLCl^{(n-1)+}$ have been measured: n = 5, log K = 2.48(3); n = 6, log K = 3.59(3). The crystal structure of L has been determined by single-crystal X-ray analysis. The compound crystallizes in a triclinic unit cell (space group $P\bar{1}$, $Z = 2$) with lattice constants a = 8.984(5), b = 12.122(2), c = 14.667(3) Å, α = 109.52(2), β = 105.47(3), γ = 95.24(3)°. Least-squares refinement converged at R = 0.088 (R' = 0.075) for 3198 unique reflections with $I > 4\sigma(I)$. The structure shows that the molecule has a skewed cylindrical shape, the bases being formed by the two N_2O_2 macrocycles with the $N(CH_2CH_2)_2$ chains constituting the walls. The cylindrane L binds two Li^+ ions and the resulting complex has been studied by ^{7}Li NMR spectroscopy. Copper(II) and cadmium(II) complexes with L have been investigated in aqueous solution and their stability constants determined by potentiometric techniques. For both metals the following species have been found: $[ML]^{2+}$, $[MLH]^{3+}$, $[ML(OH)]^+$ and $[ML(OH)_2]$.

The study of synthetic macrocyclic compounds is a very important area of chemistry.[1] So far our own research interest has been devoted to both mono- and bi-cyclic azamacrocycles.[2–9] Now we are extending our study to another molecular topology, having synthesized the new macrotricyclic ligand 10,22,28,32-tetraoxa-1,4,7,13,16,18-hexaazatricyclo[17.5.5.5^{7,13}]tetratriacontane (L). In this cylindrane, two oxoaza monocyclic units are arranged at a defined distance through two bridging units each containing a secondary nitrogen atom.

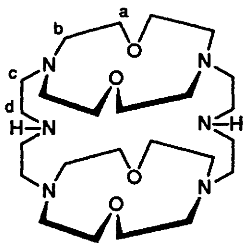

Fig. 1 Ligand L with atom labelling used in NMR assignments

Experimental

Synthesis of the Macrotricyclic Ligand (L).—The macrotricycle L (Fig. 1) was obtained following the synthetic pathway depicted in Scheme 1. The macrocycle 1,7-dioxo-4,10-diazacyclododecane **1** was obtained as reported in ref. 10 and the *N*-tosyliminodiacetyl dichloride **2** was obtained as reported in ref. 9.

Tricyclic tetraamide **3**. A solution of **1** (3.48 g, 0.02 mol) and NEt_3 (5.5 cm^3) in dry benzene (500 cm^3) and a solution of **2** (6.5 g, 0.02 mol) in dry benzene (500 cm^3) were added simultaneously by means of a two-channel peristaltic pump, to 1 dm^3 of dry benzene in a 3 dm^3 four-necked flask, equipped with a mechanical stirrer and condenser over a period of 7 h. The reaction mixture was then evaporated to dryness under reduced pressure. The yellowish crude product obtained was dissolved in concentrated NaOH and the resulting solution was extracted with chloroform (3 × 70 cm^3). The combined extracts were dried (Na_2SO_4) and then evaporated under reduced pressure.

The solid yellowish product was chromatographed over an Al_2O_3 (basic, 7-230 mesh, activity II-III) column with chloroform. The eluted solution was evaporated to dryness under reduced pressure. The white product obtained was recrystallized from 1,2-dichloroethane, and dried (60 °C) under vacuum (1.5 g, 18%), ν_{max}(Nujol): 1635w (C=O) cm^{-1} (Found: C, 53.0; H, 6.5; N, 9.7. Calc. for $C_{38}H_{54}N_6O_{12}S_2$: C, 53.65; H, 6.40; N, 9.85%).

4,16-*Ditosyl*-10,22,28,32-*tetraoxa*-1,4,7,13,16,18-*hexaazatricyclo*[17.5.5.5^{7,13}]*tetratriacontane* (L′). The reduction of tetraamide **3** was carried out with diborane in dry tetrahydrofuran (thf). Compound **3** (3.2 g, 7.5 mmol) was placed in a round-bottom, three-necked flask and dry thf (40 cm^3) was added. The resulting suspension was cooled at 0 °C and diborane (1 mol) also in dry thf (100 cm^3) was added dropwise under an inert atmosphere over a period of 30 min. The cooling bath was removed and the reaction mixture was kept to room temperature for 0.5 h before being refluxed for 6 h. The solution was then cooled to 0 °C, and the excess of diborane was destroyed with water (3 cm^3). The white solid obtained was dissolved in HCl–H_2O–MeOH (6:9, 30 cm^3) and refluxed for

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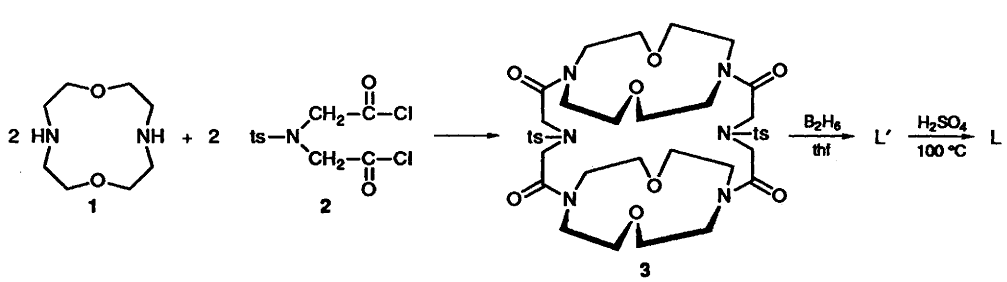
† *Supplementary data available:* see Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1992, Issue 1, pp. xx–xxv.



Scheme 1 Reaction pathway for the synthesis of the tricyclic compound L; ts = p-$MeC_6H_4SO_2$

Table 1 Crystal data and intensity collection parameters for L·H_2O

Formula	$C_{24}H_{52}N_6O_5$
M	504.7
Space group	$P\bar{1}$
a/Å	8.984(5)
b/Å	12.122(2)
c/Å	14.667(3)
α/°	109.52(2)
β/°	105.47(3)
γ/°	95.24(3)
U/Å^3	1422(1)
Z	2
D_c/g cm^{-3}	1.18
F(000)	556
μ(Mo-Kα) cm^{-1}	0.78
T	Ambient
Scan rate/° min^{-1}	5.49
Scan mode	θ–2θ
Scan width/°	0.70 + 0.35 tanθ
2θ range/°	5–50
No. of reflections collected	5212
Unique obs. reflections [$I > 4.0\sigma(I)$]	3198
Refined parameters	325
R^a	0.088
R'^b	0.075

[a] $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [b] $R' = [\Sigma w(|F_o| - |F_c|)^2/\Sigma wF_o^2]^{\frac{1}{2}}$.

5 h. The reaction mixture was evaporated to dryness under reduced pressure. The residue was treated with a strong alkaline solution (3.5 g, 10 cm^3) and extracted with $CHCl_3$ (4 × 50 cm^3). The combined extracts were dried over Na_2SO_4 and then evaporated to dryness under reduced pressure. The residue was treated with methanol (50 cm^3) and the white solid obtained was filtered off and dried (50 °C) under vacuum. Yield (2.0 g, 66.7%), m.p. 178–180 °C (Found: C, 57.4; H, 7.7; N, 10.5. Calc. for $C_{38}H_{62}N_6O_8S_2$: C, 57.40; H, 7.85; N, 10.55%).

10,22,28,32-*Tetraoxa*-1,4,7,13,16,18-*hexaazatricyclo*-[17.5.5.5^{7,13}]*tetratriacontane* (L). A 2 g (5 mmol) sample of the tosyl derivative L′ was dissolved in concentrated H_2SO_4 (4 cm^3, 96%), and the solution was heated to 100 °C for 48 h. The reaction mixture was then ice-cooled and added dropwise to cold diethyl ether (100 cm^3). The crude sulfate of L which precipitated was washed with cold diethyl ether and dried in vacuum. This product was dissolved in water (10 cm^3) and an NaOH solution (2 g, 4 cm^3) added. The resulting solution was extracted with $CHCl_3$ (5 × 50 cm^3), and the combined extracts were dried over Na_2SO_4 and then evaporated to dryness under reduced pressure, affording a sticky oil. On treatment with hexane a white solid was obtained, which was filtered off, washed with hexane and dried (0.86 g, 71.7%) (Found: C, 56.9; H, 10.5; N, 16.5. Calc. for $C_{24}H_{50}N_6O_4{\cdot}H_2O$: C, 57.10; H, 10.40; N, 16.65%).

[Li_2L][BPh_4]$_2$·H_2O. The solid binuclear lithium complex was obtained by treating L (0.2 g, 0.4 mmol) and LiOH (0.07 g, 2.8 mmol) dissolved in methanol (80 cm^3) with $NaBPh_4$ (0.28 g, 0.8 mmol). The resulting suspension was concentrated to 30 cm^3 and left to cool at room temperature. The white solid formed was filtered off, washed with methanol and dried (Found: C, 74.9; H, 8.0; N, 7.1. Calc. for $C_{72}H_{92}B_2Li_2N_6O_5$: C, 74.75; H, 7.95; N, 7.25%).

Reagents.—Sodium chloride (Merck Suprapur) was used as an ionic medium. Standardized CO_2-free solutions of NaOH were prepared as reported in ref. 11.

Potentiometric Measurements.—The potentiometric titrations were carried out in 0.15 mol dm^{-3} NaCl or 0.15 mol dm^{-3} $NaClO_4$ solutions at 298.15 K, by using the equipment (potentiometer, cell, burette, stirrer, microcomputer, *etc.*) described in ref. 12. The acquisition of the e.m.f. data was performed with the computer program PASAT.[12] The reference electrode was an Ag–AgCl electrode in saturated KCl solution. The glass electrode was calibrated as a hydrogen concentration probe by titration of known amounts of HCl with CO_2-free NaOH solutions and determining the equivalent point by Gran's method,[13] which gives the standard potential, E° and K_w. The computer program SUPERQUAD[14] was used to process the potentiometric data and calculate both protonation and stability constants. Stock solutions of $CuCl_2$ and $Cd(NO_3)_2$ were prepared in double-distilled water, and their concentrations determined gravimetrically by standard methods.

Spectroscopy.—A 200 MHz Bruker AC-200 instrument was used to record the ^{13}C NMR spectra at an operating frequency of 50.33 MHz and ^7Li NMR spectra at 77.78 MHz.

Preparation of L·H_2O.—Crystals of L·H_2O suitable for X-ray analysis were obtained by evaporating a hexane solution containing L at room temperature.

X-Ray Structure Analysis.—Crystal data and other crystallographic details are reported in Table 1. A colourless crystal of approximate dimensions 0.3 × 0.2 × 0.1 mm was mounted on an Enraf-Nonius CAD4 automatic diffractometer and used for data collection at room temperature with graphite-monochromated Mo-Kα radiation. Cell constants were determined by least-squares fitting of 25 accurately centred reflections. The intensities of three standard reflections were monitored periodically during data collection to check the stability of the crystal and of the diffractometer; no loss of intensity was observed. Intensity data were corrected for Lorentz and polarization effects. The positions of the non-hydrogen atoms were located by the direct method of SIR 88[15] and successively refined by the full-matrix least-squares technique. Two positions were found for the O(4) oxygen atom [O(4), O(4′)], which were refined with an occupancy factor of 0.5 each. The hydrogen atoms of the carbon atoms bound to the disordered oxygen atom [C(18) and C(19)] were not included in the calculation, while all the others were introduced in calculated position with an overall thermal parameter U of 0.05 Å^2 and their positions were varied on the basis of the shift of the linked carbon atoms. All the other atoms were treated anisotropically. A ΔF map carried out in the final refinement stage showed the presence of an oxygen atom of a water molecule. Refinement, performed by full-matrix least-squares techniques, gave

Table 2 Atomic coordinates ($\times 10^4$) of L, with estimated standard deviations (e.s.d.s) in parentheses

Atom	*X*/*a*	*Y*/*b*	*Z*/*c*
N(1)	−2154(4)	1976(3)	3969(3)
C(1)	−1104(4)	2305(4)	5021(3)
C(2)	619(5)	2486(4)	5103(4)
O(1)	1048(4)	3461(3)	4835(2)
C(3)	2598(5)	3583(5)	4771(4)
C(4)	2652(5)	4162(4)	4021(4)
N(2)	1778(4)	3356(3)	2987(3)
C(5)	823(5)	3899(4)	2362(4)
C(6)	−703(5)	4034(4)	2595(4)
O(2)	−1615(4)	2870(11)	2292(2)
C(7)	−2944(5)	2870(4)	2649(4)
C(8)	−2531(5)	3039(4)	3767(3)
C(9)	−3609(5)	1148(4)	3729(3)
C(10)	−3370(5)	−1(4)	3898(3)
N(3)	−4834(4)	−920(3)	3293(3)
C(11)	−4977(6)	−1842(4)	3722(4)
C(12)	−6403(6)	−2813(4)	3025(4)
N(4)	−6224(5)	−3415(4)	2043(3)
C(13)	−5348(7)	−4381(4)	2000(4)
C(14)	−4141(6)	−4328(4)	1461(4)
O(3)	−2915(5)	−3365(4)	2110(3)
C(15)	−1879(7)	−3152(5)	1573(5)
C(16)	−2431(6)	−2642(5)	783(4)
N(5)	−2974(4)	−1543(4)	1147(3)
C(17)	−4192(7)	−1347(5)	369(4)
C(18)	−5813(8)	−1664(9)	303(6)
O(4)	−6260(7)	−2686(6)	409(5)
O(4′)	−6280(11)	−1626(11)	978(7)
C(19)	−7676(7)	−2625(6)	801(5)
C(20)	−7532(7)	−3624(6)	1152(4)
C(21)	−1731(6)	−500(4)	1797(4)
C(22)	−638(5)	−80(4)	1306(3)
N(6)	587(4)	907(3)	2104(3)
C(23)	1624(6)	1431(4)	1666(4)
C(24)	2675(5)	2566(4)	2485(4)
O(5)	7767(4)	149(3)	6513(3)

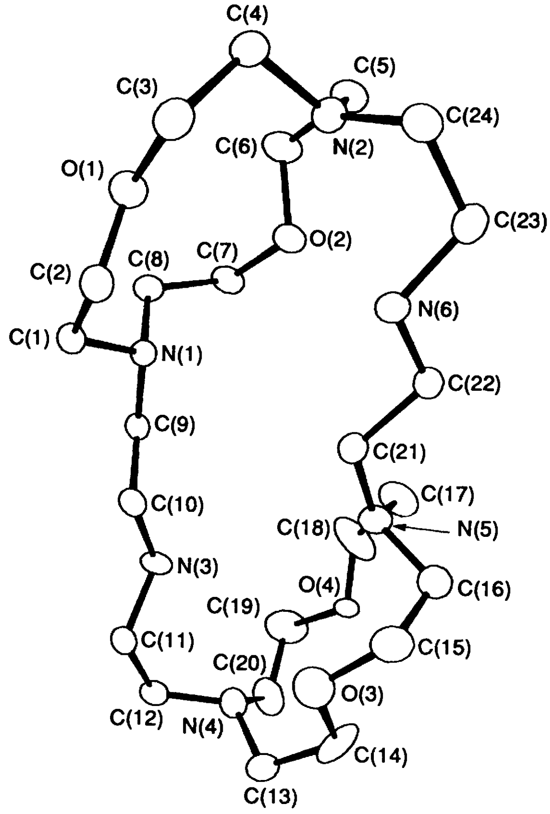


Fig. 2 ORTEP drawing of L, showing the numbering scheme adopted. For clarity only one position for the O(4) atom is shown

convergence factors $R = 0.088$ and $R' = 0.075$. All calculations, carried out on an IBM PS/2 model 80 computer, were performed with the SHELX 76 [16] set of programs which use the analytical approximation for the atomic scattering factors and anomalous dispersion corrections for all the atoms taken from ref. 17. The molecular plot was produced by the ORTEP [18] program. Table 2 shows the final atomic coordinates with estimated standard deviations.

Additional material available from the Cambridge Crystallographic Data Centre comprises H-atom coordinates and thermal parameters.

Results and Discussion

Crystal Structure of $L{\cdot}H_2O$.—The ORTEP drawing of L is shown in Fig. 2 and bond distances and angles not involving the hydrogen atoms are given in Table 3. The structure consists of molecules of L and water molecules of crystallization. Each ligand molecule interacts with two water molecules, as indicated by the short contacts involving the oxygen atom of the water molecule O(5) and the secondary nitrogen atoms N(3) and N(6): N(3) ··· O(5) ($\bar{x} + 1, \bar{y}, \bar{z} + 1$) 2.901(6) and N(6) ··· O(5) ($\bar{x}, \bar{y}, \bar{z} + 1$) 2.928(6) Å. Both these distances fall into the expected range for either N–H ··· O or O–H ··· N hydrogen bonds. Unfortunately the data quality did not allow us to locate the positions of the hydrogen atoms of the water molecule or the hydrogens of the secondary nitrogen atoms to enable an accurate description of these interactions to be made. The molecule has a cylindrical shape, the bases being formed by the N_2O_2 macrocycles, with the $N(CH_2CH_2)_2$ chains constituting the walls. The donor atoms of the N_2O_2 macrocyclic subunits deviate significantly from the mean-square planes, with lower deviations occurring for N(4), O(3), N(5) and O(4′) [max. deviation 0.08(1) Å]. In both macrocyclic subunits the oxygen and nitrogen atoms are located in opposite sides of each plane. The mean plane through N(1), O(1), N(2) and O(2) forms dihedral angles of 36.3(1) and 47.1(1)° with those defined by N(4), O(3), N(5), O(4) and N(4), O(3), N(5), O(4′) respectively. The four bridgehead nitrogen atoms point inside the molecular cavity, as well as the oxygen atoms O(2), O(3) and O(4′), while O(1) and O(4) are oriented away from the molecular cavity.

The nitrogen atoms of each diethylenetriamine chain, which displays a *trans-gauche* conformation for the N–C–C–N dihedral angles, are closely arranged along two mean-squares lines which are parallel to each other to within 7.9(1)°. The angles between these mean lines and the macrocyclic subunits N_2O_2 range from 36.2(1) to 44.2(1)° so that the overall shape of the molecule is that of a skewed cylinder. The molecular void has approximate dimensions of 6.5 × 4 × 3.5 Å as estimated from the distances between the donor atoms.

Protonation.—In Table 4 two sets of basicity constants of L, measured in two different ionic media [$NaClO_4$ or NaCl], are reported. The basicity behaviour of L is discussed by using the first set of basicity constants, obtained in the non-interacting perchlorate ionic medium. The second set (see Table 4), obtained in chloride ionic medium has been employed to determine the chloride anion interaction (see following paragraph) with protonated species of L, and in metal-complex formation equilibria. For L there are six protonation sites: four tertiary and two secondary nitrogens. Indeed, L behaves as a hexaprotic base in aqueous solution and, in the first protonation step, shows moderately strong basicity ($\log K_1 = 10.27$). The basicity is only slightly reduced in the second protonation step, with $\log K_2 = 9.52$. These values are rather high and two questions can be raised: which atom is protonated first? and how much does the molecular topology influence the protonation behaviour? In

Table 3 Bond distances (Å) and angles (°) of L, with e.s.d.s

N(1)–C(1)	1.475(5)	N(1)–C(8)	1.465(7)
N(1)–C(9)	1.455(6)	C(1)–C(2)	1.509(7)
C(2)–O(1)	1.417(7)	O(1)–C(3)	1.418(6)
C(3)–C(4)	1.497(9)	C(4)–N(2)	1.451(5)
N(2)–C(5)	1.448(7)	N(2)–C(24)	1.449(7)
C(5)–C(6)	1.509(8)	C(6)–C(2)	1.427(6)
O(2)–C(7)	1.426(7)	C(7)–C(8)	1.518(8)
C(9)–C(10)	1.519(7)	C(10)–N(3)	1.486(5)
N(3)–C(11)	1.466(8)	C(11)–C(12)	1.514(6)
C(12)–N(4)	1.441(7)	N(4)–C(13)	1.463(8)
N(4)–C(20)	1.435(7)	C(13)–C(14)	1.512(10)
C(14)–O(3)	1.395(6)	O(3)–C(15)	1.427(9)
C(15)–C(16)	1.483(10)	C(16)–N(5)	1.442(7)
N(5)–C(17)	1.455(7)	N(5)–C(21)	1.457(5)
C(17)–C(18)	1.441(10)	C(18)–O(4)	1.339(14)
C(18)–O(4′)	1.163(15)	O(4)–C(19)	1.528(11)
O(4′)–C(19)	1.565(13)	C(18)–C(20)	1.468(12)
C(21)–C(22)	1.508(8)	C(22)–N(6)	1.466(5)
N(6)–C(23)	1.473(8)	C(23)–C(24)	1.510(6)
C(8)–N(1)–C(9)	109.3(4)	C(1)–N(1)–C(9)	113.4(4)
C(1)–N(1)–C(8)	111.0(4)	N(1)–C(1)–C(2)	112.7(4)
C(1)–C(2)–O(1)	111.0(4)	C(2)–O(1)–C(3)	113.6(4)
O(1)–C(3)–C(4)	108.4(4)	C(3)–C(4)–N(2)	111.2(4)
C(4)–N(2)–C(24)	114.4(4)	C(4)–N(2)–C(5)	115.0(4)
C(5)–N(2)–C(24)	114.6(4)	N(2)–C(5)–C(6)	111.0(4)
C(5)–C(6)–O(2)	108.2(4)	C(6)–O(2)–C(7)	113.5(4)
O(2)–C(7)–C(8)	113.8(4)	N(1)–C(8)–C(7)	113.6(4)
N(1)–C(9)–C(10)	114.3(4)	C(9)–C(10)–N(3)	108.6(4)
C(10)–N(3)–C(11)	111.6(4)	N(3)–C(11)–C(12)	109.4(4)
C(11)–C(12)–N(4)	111.3(5)	C(12)–N(4)–C(20)	117.9(5)
C(12)–N(4)–C(13)	114.3(4)	C(13)–N(4)–C(20)	115.9(5)
N(4)–C(13)–C(14)	111.6(5)	C(13)–C(14)–O(3)	107.7(5)
C(14)–O(3)–C(15)	109.7(5)	O(3)–C(15)–C(16)	118.7(6)
C(15)–C(16)–N(5)	113.7(5)	C(16)–N(5)–C(21)	114.9(5)
C(16)–N(5)–C(17)	114.1(4)	C(17)–N(5)–C(21)	114.6(5)
N(5)–C(17)–C(18)	118.4(6)	C(17)–C(18)–O(4′)	126.2(8)
C(17)–C(18)–O(4)	117.7(7)	C(18)–O(4)–C(19)	110.5(7)
C(18)–O(4′)–C(19)	118.9(9)	O(4′)–C(19)–C(20)	125.4(7)
O(4)–C(19)–C(20)	97.1(6)	N(4)–C(20)–C(19)	116.0(5)
N(5)–C(21)–C(22)	117.0(4)	C(21)–C(22)–N(6)	108.0(4)
C(22)–N(6)–C(23)	111.0(4)	N(6)–C(23)–C(24)	108.7(4)
N(2)–C(24)–C(23)	111.7(5)		

order to answer these questions and obtain more structural information on this macrotricycle in solution we recorded its ^1H and ^{13}C NMR spectra over a wide pH range. The ^{13}C NMR spectrum of L in aqueous solution at high pH exhibits four sharp signals at room temperature assigned as follows: δ_C = 69.3 (C^a), 56.5 (C^c), 54.6 (C^b) and 47.9 (C^d), indicating a D_{2h} symmetry mediated on the NMR time-scale. The ^1H and ^{13}C NMR chemical shifts as a function of pH are illustrated in Fig. 3. The overall pH range investigated can be divided into different regions, according to the different number of protons bound. In the highest pH region (pH > 12.5) the compound L can be considered to be essentially unprotonated. On lowering the pH the monoprotonated species $[HL]^+$ becomes prevalent (pH, 9.5–10.5). In this region the largest change in the chemical shifts is that of carbon c (see Fig. 1), which shows a marked upfield shift due to the so-called 'β effect',[19] a fact indicating that the secondary nitrogens are involved in the first protonation step. Furthermore, the most influenced protons are those bound to carbon d, which are closest to the protonated nitrogen atom and experience the largest downfield shift [Fig. 3(*a*)]. The addition of another proton also influences significantly carbon c which experiences a further upfield shift, thus indicating that the second proton is bound by the other secondary nitrogen atom. The large downfield shift of the resonance of the proton bound to carbon d in the pH region of 8.5–10 is also in agreement with this. The involvement of the two secondary nitrogen atoms in the first two protonation steps explains well the high values of the first two protonation constants of L since, as is well known, secondary nitrogens are, in aqueous solution, more basic than tertiary nitrogens.[20]

As the degree of protonation of L increases a decrease in basicity is expected and log K_3 = 7.12. The analysis of the ^1H

Table 4 Logarithms of the basicity and formation constants of L in aqueous solution at 25 °C. The last digit in parentheses is the standard deviation on the last significant figure. For basicity constants, measurements were in two different ionic media: $NaClO_4$ or NaCl, *I* = 0.15 mol dm^{-3}.

	log *K*	
Reaction	$NaClO_4$	NaCl
$H^+ + L \rightleftharpoons HL^+$	10.27(3)	10.09(3)
$H^+ + HL^+ \rightleftharpoons H_2L^{2+}$	9.52(3)	9.27(3)
$H^+ + H_2L^{2+} \rightleftharpoons H_3L^{3+}$	7.12(3)	6.54(3)
$H^+ + H_3L^{3+} \rightleftharpoons H_4L^{4+}$	4.62(3)	4.88(3)
$H^+ + H_4L^{4+} \rightleftharpoons H_5L^{5+}$	2.80(3)	3.75(3)
$H^+ + H_5L^{5+} \rightleftharpoons H_6L^{6+}$	2.27(3)	3.07(3)
$6H^+ + L \rightleftharpoons H_6L^{6+}$	36.60	37.60
$Cl^- + H_5L^{5+} \rightleftharpoons H_5LCl^{4+}$	2.48(3)	
$Cl^- + H_6L^{6+} \rightleftharpoons H_6LCl^{5+}$	3.59(3)	
$Cu^{2+} + L \rightleftharpoons CuL^{2+}$ *		18.9(1)
$Cu^{2+} + L + H^+ \rightleftharpoons [CuLH]^{3+}$		22.1(1)
$Cu^{2+} + L + H_2O \rightleftharpoons [CuL(OH)]^+ + H^+$		14.8(1)
$Cu^{2+} + L + 2H_2O \rightleftharpoons [CuL(OH)_2] + 2H^+$		9.7(1)
$[CuL]^{2+} + H^+ \rightleftharpoons [CuLH]^{3+}$		3.2
$Cd^{2+} + L \rightleftharpoons [CdL]^{2+}$ *		12.3(1)
$Cd^{2+} + L + H^+ \rightleftharpoons [CdLH]^{3+}$		20.1(1)
$Cd^{2+} + L + H_2O \rightleftharpoons [CdL(OH)]^+ + H^+$		2.0(1)
$Cd^{2+} + L + 2H_2O \rightleftharpoons [CdL(OH)_2] + 2H^+$		−9.2(1)
$[CdL]^{2+} + H^+ \rightleftharpoons [CdLH]^{3+}$		7.8

* Precipitation of the $[ML][ClO_4]_2$ species prevented the study of the equilibria in perchlorate medium.

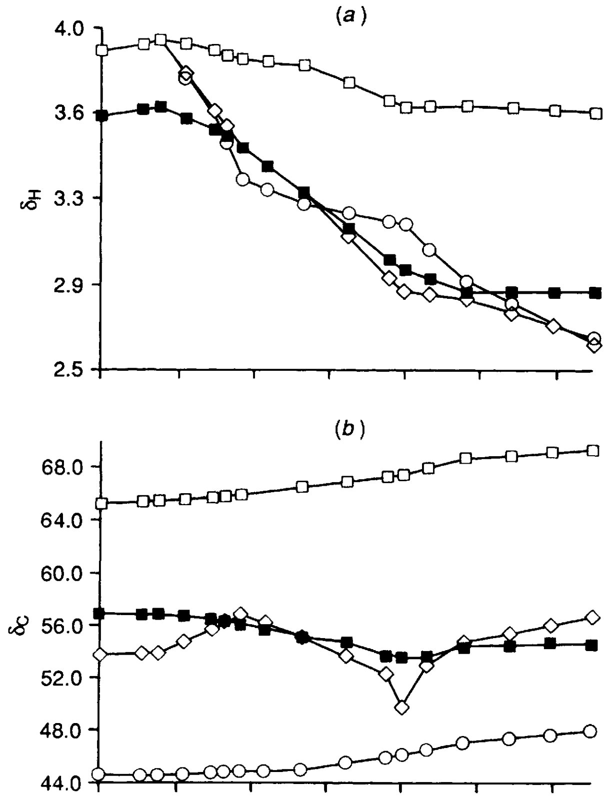


Fig. 3 ^1H (top) and ^{13}C NMR (bottom) chemical shift variation as a function of pH for L; a (□), b (■), c (◇) and d (○)

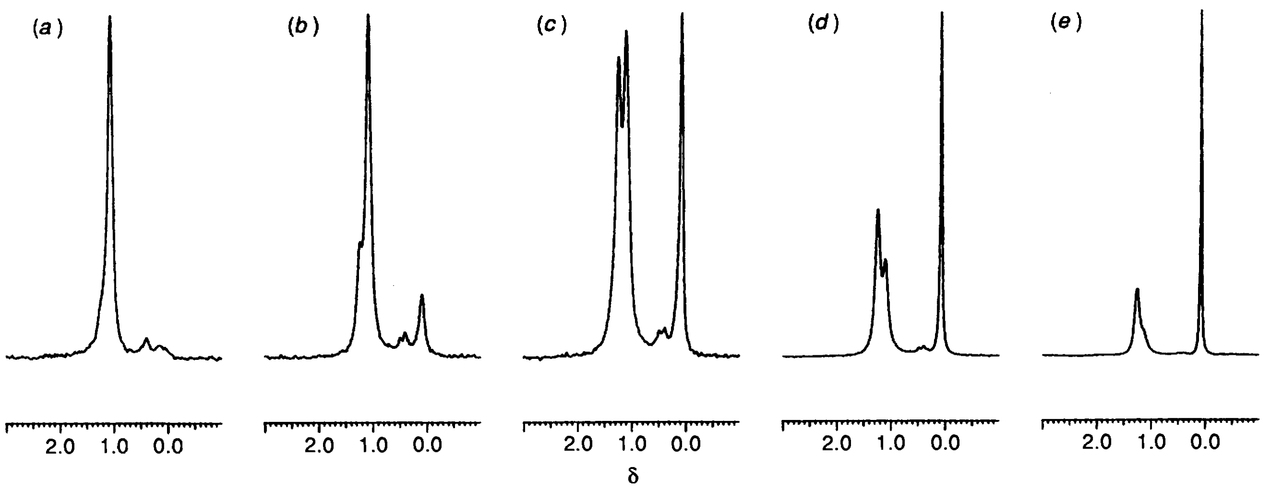


Fig. 4 ^{7}Li NMR spectra in MeOD, recorded at −40 °C with different Li:L ratios (*a*) 0.5:1; (*b*) 1:1; (*c*) 1.5:1; (*d*) 2:1; and (*e*) 3:1

and ^{13}C chemical shifts trends around pH 6, where the species H_3L^{3+} represents *ca.* 90% of total L, indicates that two protons are bound in the two N_2O_2 subunits and the third proton is shared by the two secondary nitrogens. In fact, the upfield shift of carbons a and d, coupled with the downfield shift of carbon c is indicative that the protonation involves mainly the tertiary nitrogens. In the fourth protonation step (log K_4 = 4.62) the repulsion between the four positive charges imposes the proton distribution on the four tertiary nitrogen atoms. The steep downfield shift experienced by protons on carbons b and c in the pH region of 4–7.5 (Fig. 4) and the upfield shift of carbon d further suggests the above proton distribution in the tetracharged H_4L^{4+} species. Finally in the last two protonation steps (log K_5 = 2.80, log K_6 = 2.27) the remaining two secondary nitrogen atoms are protonated.

Anion Co-ordination.—Co-ordination of anions by highly charged macrocyclic species is a well documented phenomenon.[2,21] In some cases, together with equilibrium studies, the species formed have been characterized by X-ray analysis.[22] In this case a strong interaction between the Cl^- anion and the highly protonated and charged species H_5L^{5+} and H_6L^{6+} has been detected, the equilibrium constants being *ca.* 300 and *ca.* 3900 respectively (see Table 4). The electrostatic nature of this interaction is demonstrated by the fact that log *K* increases with the charge on the macrocycle and becomes measurable only with the most protonated species. It is also interesting to compare the stepwise protonation constants obtained in two different ionic media (see Table 4). In the first three protonation steps L is less basic in the NaCl ionic medium than in $NaClO_4$. In the fourth step, when the overall positive charge becomes +4 and the interaction with Cl^- significant, the basicity of L in NaCl becomes greater than in $NaClO_4$. This trend continues in the last two protonation steps with L becoming considerably more basic in NaCl than in $NaClO_4$. It is expected that the formation of the adduct with Cl^-, which involves a partial charge neutralization, stabilizes the protonated species of L.

Metal Complexes.—In order to investigate the co-ordination ability of cylindrane L toward metal ions we studied three different metal ions: Li^+, Cu^{2+} and Cd^{2+}.

Lithium was chosen since it is the smallest among the alkali-metal cations and thus the best candidate to form binuclear complexes with macrocycles having many donor atoms. Indeed a binuclear complex with stoichiometry $[Li_2L][BPh_4]_2$ has been isolated in the solid state (see Experimental section). The ^{7}Li NMR spectrum of the preformed solid complex in acetonitrile solution exhibits only one sharp peak at δ 2.04. To investigate the formation of the binuclear species in solution, ^{7}Li NMR spectra with different LiCl:L ratios have been recorded in MeOD solution at −40 °C. The spectra have been gathered in Fig. 4. At low Li:L (1:2) ratio a sharp peak at δ 1.1 dominates the spectrum which also shows a weak peak due to free lithium ion [see Fig. 4(*a*)]. The peak at δ 1.1 can be attributed to a mononuclear complex. As the Li:L ratio increases a second peak at δ 1.24, attributable to a binuclear species, appears. As the intensity of the latter peak increases that of the mononuclear species decreases, indicating an equilibrium between the two species. Finally at a high Li:L ratio (3:1) only the peak at δ 1.24 is present. In conclusion for the Li–L system two main species, $[LiL]^+$ and $[Li_2L]^{2+}$ are present in solution, with the latter being the only one present at high Li:L ratio. Other general considerations can be made: (*i*) peaks in all ^{7}Li NMR spectra are rather sharp and well resolved indicating a slow exchange between species on the NMR time-scale under the experimental conditions used; (*ii*) lithium chemical shifts are solvent dependent indicating that the solvent has access to the lithium co-ordination sphere.

The complexation of Cu^{II} was studied owing to its ability to adapt itself to different stereochemical arrangements of donor atoms. Under the experimental conditions used, and in spite of many donor atoms available, only mononuclear species are formed (see Table 4). This is a rather surprising behaviour since macrotricycles with similar molecular topology have been successfully employed in the formation of binuclear complexes with copper(II).[23] The high stability of the $[CuL]^{2+}$ complex (log *K* = 18.9) and its low (log *K* = 3.2) protonation constant, when compared with the first basicity constant of L (log *K* = 10.09), to form the $[CuLH]^{3+}$ species, indicate that all six nitrogen atoms are involved in co-ordination to Cu^{2+}. This fact presumably hinders the formation of polynuclear species.

For the bulky Cd^{II} ion only mononuclear species are expected and indeed are the only ones observed (Table 4), and are of the same type as those found for the Cu^{II}–L system.

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