

Synthesis and Crystal Structure of a Small Bicyclic Tetraaza Proton Sponge, 1,4,7,10-Tetraazabicyclo[5.5.3]pentadecane Dibromide Perchlorate

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The bicyclic tetraamine 1,4,7,10-tetraazabicyclo[5.5.3]pentadecane (L1) has been synthesized by the reaction of the ditosylate of cyclen [1,7-bis(*p*-toluenesulfonyl)-1,4,7,10-tetraazacyclododecane] with the ditosylate of 1,3-propanediol followed by removal of the tosyl groups. The amine was isolated as the trihydrobromide, L1·3HBr, in an overall yield of 23% (based upon cyclen). The structure of L1·2HBr·HClO₄ has been solved by X-ray diffraction techniques at *T* = 120 K; *M_r* = 474.6, orthorhombic, *Pnma*, *a* = 17.583(4), *b* = 8.664(3), *c* = 11.707(3) Å, *Z* = 4, *D_x* = 1.77 g cm⁻³, MoKα = 0.71073 Å, μ = 46.7 cm⁻¹, *F*(000) = 960. *R*(*F*) = 0.0471 for 1815 reflections with *I* > 2σ(*I*) and *wR*(*F*²) = 0.0803 for all 2761 unique reflections. The H₃L1³⁺ cation exhibits a mirror plane, the secondary nitrogen atoms and a carbon atom lying in the plane. The distance between the tertiary nitrogen atoms is 2.567(4) Å, with one of the acidic hydrogen atoms situated midway between the two nitrogens. The distance between the two secondary nitrogen atoms is 5.194(7) Å, giving rise to a rather elongated conformation of the cyclen ring. The free base L1 behaves as a proton sponge, being a stronger base than hydroxide in water. The concentration protonation constants were determined by potentiometric measurements, which combined with ¹³C NMR studies gave p*K*₁ > 15, p*K*₂ = 7.242(8), p*K*₃ = 3.202(7) and p*K*₄ < -1. (1 M NaBr, 25 °C). The ¹³C NMR spectra of the mono- and triprotonated species correspond to a time-averaged C_{2v} symmetry in solution.

The synthesis of new macrocyclic and macrobicyclic polyamines is of current interest because they exhibit unusual basicity, redox behaviour and coordination chemistry.^{1–8} Structural modifications of the important macrocyclic ligands cyclam and cyclen involving ethylene or trimethylene bridging of the adjacent nitrogens have been reported^{9–13} (for ligand abbreviations see Appendix). Coordination compounds of these ligands with Ni(II) have been reported to exhibit very large ligand field strengths and to be unusually inert with respect to substitution. ‘Cross-bridging’ of cyclam or cyclen, i.e. bridging of non-adjacent nitrogens, leads to bicyclic tetraamines which may adopt conformations having all four nitrogen lone pairs pointing inside the cavity for complexation of metal ions. The bicyclic amine will have a relatively fixed geometry with respect to coordination, i.e. a short chain

(ethylene or trimethylene) will promote a (pseudo) tetrahedral coordination while a longer chain will favour a (distorted) square-planar coordination. It should be noted that cross-bridged cyclen derivatives with long chains like –CH₂–CH₂–X–CH₂–CH₂–, where X is a donor group such as O, NH or S, yield some very interesting pentadentate ligands which have been studied by Micheloni and co-workers.^{3,4,14,15} In the following, however, we use the term cross-bridging with reference only to those cases where the bridge does not contain any donor atoms.

Cross-bridging of cyclam to form a bicyclic tetraamine was reported for the first time by Weisman *et al.*,¹⁶ who synthesized the ethylene cross-bridged cyclam derivative, L5, shown in Fig. 1. The X-ray structure was reported for the diprotonated amine as a trifluoromethylsulfonate salt. The unusual basicity and alkali ion complexation of this interesting new type of macrobicycle was reported. The cage reacts as a proton sponge and forms stable com-

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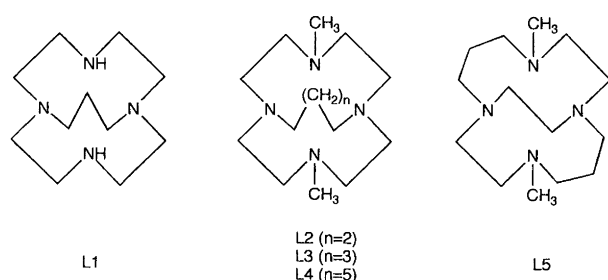


Fig. 1. Cross-bridged derivatives of cyclen and cyclam.

plexes with small cations such as lithium. Recently Micheloni and co-workers⁷ reported the synthesis and crystal structure of the cyclen analogue with a tetramethylene bridge (L2) shown in Fig. 1. This ligand exhibits properties similar to those reported for the cyclam derivative. Also penta- and heptamethylene cross-bridged compounds (L3 and L4) have been reported, and in both cases one effect of the longer bridges is the loss of proton sponge properties.^{18,19}

We present here a new and facile method for the synthesis of small bicyclic tetraamines with secondary amine groups at the non-bridgehead atoms. The method is illustrated by the reaction of cyclen (protected at two non-adjacent nitrogens by tosyl groups) with trimethylene bis(*p*-toluenesulfonate), which after removal of the tosyl groups gives the macrobicyclic cyclen derivative, L1, shown in Fig. 1.

Experimental

Materials. Cyclen·4HCl and trimethylene bis(*p*-toluenesulfonate) were synthesized by previously published methods.^{20,21} The method for the synthesis of cyclen·ts₂ given below is based upon a previous report.²² All other chemicals were of analytical grade.

Analyses. C, H, N and Cl analyses were made by Preben Hansen at the Microanalytical Laboratory at the H. C. Ørsted Institute, Copenhagen.

Table 1. ¹³C NMR chemical-shift data.

Compound	Solvent	δ (ppm)				
		C–N (sec)	C–N–ts	C–N(tert) ethylene	C–N(tert) trimethylene	C–C–C
Cyclen·4HCl	D ₂ O	44.9				
cyclen·ts ₂	CDCl ₃	48.9 ^a	49.1 ^a			
L1·ts ₂	CDCl ₃		49.1	59.2	54.6	31.2
L1·3HBr	D ₂ O ^b	46.4		52.1	54.5	18.3
L1·3HBr	Acid ^c	46.6		52.2	54.4	18.2
L1·3HBr	Base ^d	46.2		55.7	53.6	18.7

^aNo direct evidence for these assignments was obtained. ^bThe dominant species are 95% H₃L³⁺ and 5% H₂L²⁺. ^c1 M HCl. The same values were obtained for 0.2 M and 0.05 M HCl, respectively. All solutions with 5% D₂O. The dominant species is H₃L³⁺. ^d1 M NH₃/0.5 M NH₄Cl [pH 9.6 calculated from pK_a(NH₄⁺)=9.47 at unit ionic strength].³² The same values were obtained for 1 M NH₃, 0.3 M NaOH and 1.3 M NaOH, respectively. All solutions with 5% D₂O. The dominant species is HL¹⁺.

Mass spectra. Positive-ion FABMS were obtained on a Jeol AX505W mass spectrometer using glycerol or 3-nitrobenzyl alcohol as matrix.

NMR spectra. ¹H and ¹³C NMR spectra were measured at 5.87 T on a Bruker AC 250 NMR spectrometer equipped with a 5 mm probe. ¹H chemical shift values (δ) are referenced to internal dioxane [δ(dioxane)=3.75 ppm] for D₂O solutions. ¹³C chemical shift values (δ) are reported in ppm relative to internal TMS in CDCl₃ [δ(TMS)=0] and referenced to internal dioxane in D₂O or H₂O [δ(dioxane)=67.4 ppm]. ¹³C (dept) NMR spectra were used to distinguish CH₃ and CH₂ carbon atoms.

Potentiometric titrations. The concentration protonation constants *K_i*, were determined by regression analysis of the titration data from dissolution of L1·3HBr in an excess of HCl and titration with NaOH. *K_i*=[H_{*i*}L^{*i*+}]/([H_{*i-1*}L^{(*i-1*)+}][H⁺]); p*K_i*=log *K_i*.

Syntheses

1. *Cyclen*·ts₂, 1,7-bis(*p*-toluenesulfonyl)-1,4,7,10-tetraazacyclododecane. To a solution of cyclen·4HCl (15.6 g, 0.049 mol) in pyridine (47.5 ml) was added *p*-toluenesulfonyl chloride (18.7 g, 0.098 mol) during 45 min at 2–3 °C with constant stirring. The yellow mixture was left for 2 h at room temperature and, with cooling in an ice-bath, 5 M HCl (68.2 ml) was added within 15 min. The mixture was kept at 0 °C for 1 h and then the yellow precipitate was collected on a filter, washed several times with cold water and dried at 65 °C. Yield 19.2 g (82%). Analytical data: FABMS (*m/z*): 481 (*M*+H⁺, *M*=cyclen·ts₂). ¹³C NMR data are given in Table 1. The crude product contains about 5–10% tetratosylated cyclen as judged from the ¹³C NMR spectrum [δ(CH₂-Nts)=52.2 ppm for cyclen·ts₄].

2. *L1*·ts₂, 4,10-bis(*p*-toluenesulfonyl)-1,4,7,10-tetraazabicyclo[5.5.3]pentadecane. A solution of cyclen·ts₂ (4 g, 8.32 mmol), trimethylene bis(*p*-toluenesulfonate) (3.2 g, 8.32 mmol) and sodium carbonate (2 g, 19 mmol) in acetonitrile (200 ml) was refluxed for 6 days. The precipitate

was filtered off and washed three times with 96% ethanol (15 ml). The filtrates were added to the acetonitrile solution and the mixture was evaporated to dryness under reduced pressure using a rotary evaporator. This gave 5.0 g of a yellow powder of crude L1·ts₂. Analytical data: FABMS (*m/z*): 521 (*M* + H⁺, *M* = L1·ts₂). ¹³C NMR data are given in Table 1. On the basis of the ¹³C NMR spectrum, the product is estimated to contain about 10% cyclen tetratosylate.

3. *L1·3HBr*, 1,4,7,10-tetraazabicyclo[5.5.3]pentadecane trihydrobromide. The crude ditosylate (5.0 g) from preparation 2 was added to a mixture of 48% hydrobromic acid (40 ml) and glacial acetic acid (27 ml). The mixture was refluxed for 3 d and was then evaporated to dryness under reduced pressure using a rotary evaporator. The product was extracted three times with water (25 ml), and the combined extracts were evaporated to dryness under reduced pressure. This gave a viscous yellow oil which, after addition of acetone (50 ml), crystallized to a yellow, hygroscopic powder. The product was filtered off, washed several times with acetone and then dried at 80°C. Yield 3.1 g. The crude product was dissolved in hot water (4.4 ml, ca. 90°C), filtered, and then a saturated solution of sodium bromide (2.2 ml) was added while the solution was still hot. The mixture was cooled to 5°C and kept at that temperature for 2 h. Colourless crystals of the trihydrobromide crystallized. The crystals were filtered off, washed with 96% ethanol and dried in air. Yield 1.05 g (28% based upon cyclen·ts₂, 23% based upon cyclen). Analytical data: Calculated for C₁₁H₂₇N₄Br₃: C, 29.03; H, 5.98; N, 12.31; Br, 52.68. Found: C, 29.01; H, 6.02; N 12.23; Br, 53.05. FABMS *m/z*: 213 (*M* + H⁺, *M* = L1). ¹³C NMR data are given in Table 1, and ¹H NMR data are given under Results.

4. *L1·2HBr·HClO₄*, 1,4,7,10-tetraazabicyclo[5.5.3]pentadecane dibromide perchlorate. To a solution of L1·3HBr (90 mg) in water (2 ml, 90°C) was added a saturated aqueous solution of sodium perchlorate (0.4 ml, 25°C), and the mixture was placed at 5°C for 2 h. The needle-shaped colourless crystals were filtered off, washed with 96% ethanol and dried in air. The ¹³C NMR spectrum in D₂O of this sample was identical to that of the parent bromide salt.

X-ray techniques. Crystal and experimental data for the compound are listed in Table 2. The possible space groups were established from rotation and Weissenberg photographs using Cu radiation. Because the space group could be either *Pna*2₁ or *Pnma*, reflections of a quadrant of the limiting sphere (*h k l* and *h k \bar{l}*) were measured. The structure analysis has shown that the space group was *Pnma*, and thus the asymmetric unit of reflections is the octant with *h*, *k* and *l* positive. Since a loss of intensity of about 22% was observed, data collection using a new crystal was performed. The crystal was cooled to 120 K using the Crystream nitrogen gas cooler system.²³

The unit cell was derived from a least-squares fit of refined diffractometer setting angles for 25 reflections. Four standards were measured for intensity and orientation control after every 4 h. A loss of intensity of about 7.9% was observed. Therefore, a linear decay correction was applied. Afterwards, the intensities were corrected for Lorentz, polarization and absorption (Gaussian integration) effects.²⁴ The structure was solved by direct methods and refined by a full-matrix least-squares technique. The hydrogen atoms were all located from electron-density difference maps. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms attached to the nitrogen atoms were refined isotropically, whereas the other hydrogen atoms were refined with fixed isotropic thermal parameters, $U(\text{H}) = 1.2 \times U$ for attached carbon atom. The crystallographic computations were performed with SHELXS86²⁵ and SHELXL93.²⁶ The atomic scattering factors were taken from the literature.²⁷ The PLUTO program²⁸ was used for the illustrations and PLATON²⁹ for molecular geometry calculations.

The final positional parameters are listed in Table 3. Anisotropic thermal parameters, positional parameters for the hydrogen atoms, and a list of observed and calculated structure factors may be obtained from one of the authors (I. S.) on request.

Results

Syntheses and characterization. The synthesis of the macrobicyclic ligand L1 from cyclen is based upon the protection of two nonadjacent nitrogens by tosylation. The reaction of 1 mol of cyclen with 2 mol of tosyl chloride gave cyclen·ts₂ (82%) with only a minor amount of other tosylated products (mainly tetratosylate, 5–10%). The compound was identified by its FABMS (Experimental) and ¹³C NMR spectrum (Table 1). Reaction of cyclen·ts₂ with the ditosyl ester of 1,3-propanediol (acetonitrile, sodium carbonate) gave, as shown in Scheme 1, the tosylate of the cross-bridged product, which was identified by its FABMS and ¹³C NMR spectrum (Table 1). Finally, removal of the tosyl groups by reflux in a mixture of hydrobromic acid and acetic acid gave the macrobicyclic tetraamine, L1, as a trihydrobromide. The crude product contains cyclen (ca. 10%), which probably stems from the content of tetratosylated cyclen in the crude ditosylate. The pure trihydrobromide of L1 was obtained by a single recrystallization in a yield of 23% based upon cyclen. The compound was identified by elemental analysis, FABMS and by ¹H and ¹³C NMR spectra. The ¹³C NMR spectrum of L1·3HBr in D₂O exhibits four sharp signals (all CH₂). The assignments of the signals were made unambiguously on the basis of the relative intensities (4:4:2:1) and the chemical shift values (the resonance of aliphatic carbon atoms bound to N in tertiary amines are generally shifted significantly downfield relative to aliphatic carbon atoms bound to N in secondary amines), and are given in Table 1. The ¹H NMR spec-

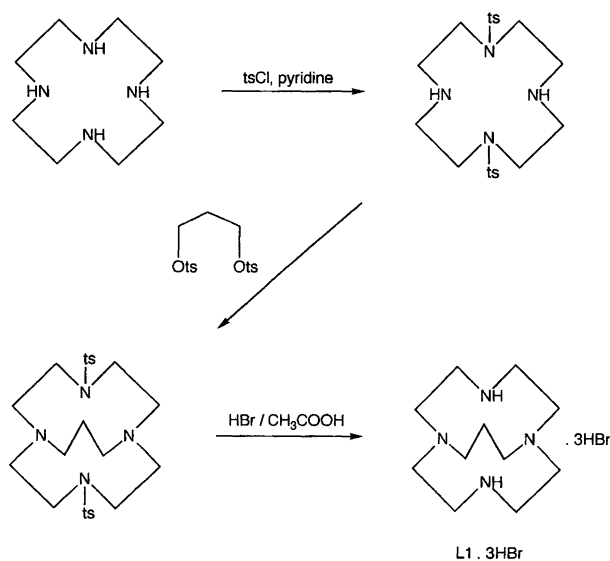
Table 2. Crystal and experimental data.

Formula	$C_{11}H_{27}N_4^{3+}, 2Br^-, ClO_4^-$
Formula weight	474.62
Crystal system	Orthorhombic
Space group	<i>Pnma</i> (No. 62)
Unit-cell dimensions/Å	$a=17.583(4)$ $b=8.664(3)$ $c=11.707(3)$
Unit-cell volume, $V/\text{Å}^3$	1783.4(9)
Formula units per unit cell, Z	4
$F(000)$	960
Calculated density, $D_x/\text{g cm}^{-3}$	1.77
Radiation	MoK α
Wavelength, $\lambda/\text{Å}$	0.71073
Linear absorption coefficient/ cm^{-1}	46.7
Temperature, T/K	120
Crystal description	Colourless
Crystal size/mm	0.30 × 0.075 × 0.05
Diffractometer:	Enraf-Nonius CAD-4F
Unit-cell determination	
No. of reflections used	25
θ -range/ $^\circ$	10.5–14.3
Intensity data collection:	
$\theta_{\text{max}}/^\circ$	30
Range of h	0–24
Range of k	0–12
Range of l	0–16
Scan mode	ω
Scan range, $\Delta\omega$	1.00 + 0.35 tan θ
Total number of unique reflections	2761
No. of independent reflections, [$I > 2\sigma(I)$]	1815
Corrections	Decay, Lorenz polarization and absorption
Transmission factors	0.4805–0.7637
Structure refinement:	
Minimization of	$\sum w(F_o ^2 - F_c ^2)^2$
Anisotropic thermal parameters	All non-hydrogen atoms
Isotropic thermal parameters	Hydrogen atoms
No. of refined parameters	161
Weighting scheme	$[\sigma^2(F_o^2) + (0.0258P)^2 + 0.26P]^{-1}$, $P = (F_o^2 + 2F_c^2)/3$
$R = \sum F_o - F_c / \sum F_o $	0.0471 (1815 reflections)
$wR^2 = [\sum w F_o^2 - F_c^2 ^2 / \sum w F_o^4]^{1/2}$	0.0803 (2761 reflections)
$S = [\sum w(F_o ^2 - F_c ^2)^2 / (N_{\text{obs}} - N_{\text{var}})]^{1/2}$	1.03
Final $(\Delta/\sigma)_{\text{max}}$	0.16
Final ΔQ_{min} and $\Delta Q_{\text{max}}/e \text{ Å}^{-3}$	–0.68 and 0.88

trum of $L1 \cdot 3HBr$ shows a quintet centred around 2.15 ppm (2 H, C–CH₂–C), a multiplet around 3.45 ppm [12 H, CH₂–N(tertiary)] and a multiplet around 3.78 ppm [8 H, CH₂–N(secondary)]. The 2D ¹H–¹³C correlation spectrum confirmed these assignments. It is noted that the ¹³C NMR spectrum corresponds to a time-averaged C_{2v} symmetry in solution. The change of the ¹³C NMR spectra as a function of pH is discussed below.

Crystal structure of $L1 \cdot 2HBr \cdot HClO_4$. Bond lengths and bond and torsion angles are listed in Table 4. The labelling of the atoms in the H_3L1^{3+} cation is shown in Fig. 2. The two bromide ions, the chloride ion and one of the oxygen atoms lie on the mirror plane. In the H_3L1^{3+} ion

the two secondary nitrogen atoms [N(1) and N(3)] and the middle carbon atom [C(6)] in the (CH₂)₃ bridge are positioned on the mirror plane. Two of the acidic hydrogen atoms are bound to the non-bridging nitrogen atoms [N(1) and N(3)], respectively. The third acidic hydrogen atom is localized on the mirror plane midway between N(2) and N(2'), the N···H···N hydrogen bonds being 1.308(14) Å. The least-squares refinement of the latter hydrogen atom led to a physically unreasonable thermal parameter, unless it was constrained to lie on the mirror plane. The N(2)–N(2') distance of 2.567(4) Å between the bridgehead nitrogen atoms is smaller than those found in $HL2^+$, H_3L2^{3+} , H_2L3^{2+} and H_2L4^{2+} (Table 5) and somewhat larger than the distance of 2.526(3) Å found



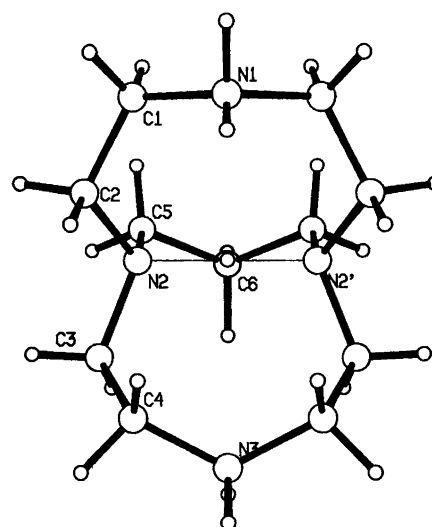
Scheme 1.

Table 3. Fractional atomic coordinates and equivalent isotropic thermal parameters (in Å²).

Atom	x	y	z	U_{eq}^a
N(1)	0.5154(3)	1/4	0.1941(4)	0.0167(16)
N(2)	0.35837(16)	0.1019(3)	0.2781(2)	0.0108(8)
N(3)	0.3252(3)	1/4	0.5336(4)	0.0130(12)
C(1)	0.4788(2)	0.0992(5)	0.1599(3)	0.0177(11)
C(2)	0.4303(2)	0.0202(4)	0.2489(3)	0.0151(11)
C(3)	0.3232(2)	0.0384(5)	0.3834(3)	0.0136(10)
C(4)	0.3579(2)	0.0993(4)	0.4931(3)	0.0136(9)
C(5)	0.3020(2)	0.1041(5)	0.1814(3)	0.0150(11)
C(6)	0.2543(3)	1/4	0.1899(5)	0.0160(17)
Cl	0.14004(8)	3/4	0.33820(10)	0.0173(4)
O(1)	0.14539(16)	0.6146(3)	0.2664(2)	0.0281(9)
O(2)	0.0685(2)	3/4	0.3977(3)	0.0273(12)
O(3)	0.2009(3)	3/4	0.4195(3)	0.0330(16)
Br(1)	0.05482(3)	1/4	0.03270(5)	0.0156(2)
Br(2)	0.14118(3)	1/4	0.50513(5)	0.0192(2)

$$^a U_{eq} = 1/3 \sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j.$$

in 1,6-diazabicyclo[4.4.4]tetradecane hydrochloride.³⁰ In the latter structure, in H_3L^{2+} and in H_2L^{3+} , the acidic hydrogen atoms are also positioned midway between the two nitrogen atoms. The conformation of the cyclen ring is rather elongated, the N(1)–N(3) distance being 5.194(7) Å between the non-bridging nitrogen atoms. A similar conformational feature is found in H_3L^{2+} . In the cyclen ring of the present structure the four C–N bond lengths average 1.495(6) Å and the two C–C bond lengths average 1.514(4) Å, which are in agreement with the values found in the $H_4cyclen^{4+}$ ring.³¹ The N(2)–C bond lengths in the cyclen ring are somewhat smaller than the N(1)–C(1) and N(3)–C(4) bond lengths. The C(1)–N(1)–C(1') and C(4)–N(3)–C(4') angles of 119.8(4) and 120.6(4)°, respectively, are somewhat larger than the C–N–C angles found in the other compounds previously mentioned. The crystal packing (Fig. 3) is influenced by hydrogen bonds. N(1) is bonded to the two bromine at-

Fig. 2. View of the H_3L^{3+} cation with atomic labelling. The thin lines are the N(2)···H···N(2') hydrogen bonds.

oms, the N(1)–H(1)···Br(1) [$1/2 + x, 1/2 - y, 1/2 - z$] bond and the N(1)–H(2)···Br(2) [$1/2 + x, 1/2 - y, 1/2 - z$] bond being 3.273(5) and 3.214(5) Å, respectively. Furthermore, N(3) is involved in hydrogen bonding, the N(3)–H(11)···Br(2) bond being 3.253(5) Å and the two N(3)–H(12)···O(1) [$1/2 - x, -1/2 + y, 1/2 + z$ and $1/2 - x, 1 - y, 1/2 + z$] bifurcated bonds both being 3.012(5) Å, since N(3) and H(12) are situated on the mirror plane.

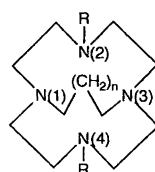
Concentration protonation constants of L1. The concentration protonation constants (K_i) of L1 were studied by potentiometric titration, which gave $pK_1 > 14$, $pK_2 = 7.242(8)$, $pK_3 = 3.202(7)$ and $pK_4 < 2$ (1 M NaBr, 25°C). In order to obtain a better estimate for the lower and upper limits, respectively, to pK_1 and pK_4 the ¹³C NMR spectrum of L1·3HBr was measured in basic and acidic solutions (Table 1). The spectrum of L1·3HBr (0.09 M) in 1.3 M NaOH (pH 14.2) is identical to that of pure HL^{1+} (measured at pH 9.6), and it is therefore estimated that $pK_1 > 15$. Likewise, the spectra of L1·3HBr (0.09 M) in 0.05, 0.2 and 1.0 M HCl, respectively, are identical or nearly identical to the spectrum of a 0.3 M solution of L1·3HBr in pure D₂O. (The latter solution contains approximately 95% H_3L^{3+} and 5% H_2L^{2+} .) It can therefore be concluded that protonation of H_3L^{3+} does not occur even in the most acidic solution studied, and it is estimated that $pK_4 < -1$.

It seems reasonable to assume that the sites of protonation found in the crystal are the same as those in solution. The first protonation is thus assumed to occur at the two tertiary nitrogen groups, and the following two protonations at the two secondary amine groups. $L1H^+$ is a very weak acid ($pK_1 > 15$), and its great stability is due to strong hydrogen bonds to the two tertiary nitrogen atoms. The protons bound to the secondary nitrogen atoms are not involved in intramolecular hydrogen bonds (pK_2 and pK_3), and their pK values are in the expected

Table 4. Bond lengths (in Å) and bond and torsion angles (in °).

N(1)–C(1)	1.510(5)	C(3)–C(4)	1.517(5)
N(2)–C(2)	1.489(4)	C(5)–C(6)	1.520(5)
N(2)–C(3)	1.485(4)	Cl–O(1)	1.446(3)
N(2)–C(5)	1.505(4)	Cl–O(2)	1.438(4)
N(3)–C(4)	1.503(4)	Cl–O(3)	1.432(5)
C(1)–C(2)	1.510(5)		
O(1)–Cl–O(2)	109.8(2)	C(2)–N(2)–C(5)	113.1(2)
O(1)–Cl–O(3)	109.7(2)	C(3)–N(2)–C(5)	110.8(3)
O(1)–Cl–O(1')	108.4(2)	C(4)–N(3)–C(4')	120.6(4)
O(2)–Cl–O(3)	109.4(2)	N(1)–C(1)–C(2)	116.7(3)
O(2)–Cl–O(1')	109.8(2)	N(2)–C(2)–C(1)	115.0(3)
O(3)–Cl–O(1')	109.7(2)	N(2)–C(3)–C(4)	114.0(3)
C(1)–N(1)–C(1')	119.8(4)	N(3)–C(4)–C(3)	114.5(3)
C(2)–N(2)–C(3)	111.6(3)	N(2)–C(5)–C(6)	108.9(3)
		C(5)–C(6)–C(5')	112.5(4)
C(1')–N(1)–C(1)–C(2)	–98.2(4)	C(3)–N(2)–C(5)–C(6)	84.1(4)
C(3)–N(2)–C(2)–C(1)	–166.7(3)	C(4')–N(3)–C(4)–C(3)	–88.4(5)
C(5)–N(2)–C(2)–C(1)	67.5(4)	N(1)–C(1)–C(2)–N(2)	68.2(4)
C(2)–N(2)–C(3)–C(4)	81.1(4)	N(2)–C(3)–C(4)–N(3)	85.2(4)
C(5)–N(2)–C(3)–C(4)	–151.9(3)	N(2)–C(5)–C(6)–C(5')	60.7(5)
C(2)–N(2)–C(5)–C(6)	–149.7(3)		

Table 5. Crystallographic data for 'cross-bridged' derivatives of cyclen.

R = H or CH₃

Cation	Distance/Å		Orientation of N ^a		Ref.
	N(1)–N(3)	N(2)–N(4)	N(1) and N(3)	N(2) and N(4)	
H ₃ L1 ³⁺	2.567(4)	5.194(7)	<i>endo</i>	<i>endo/exo</i> ^b	This work
HL2 ⁺	2.75(1)	4.42(1)	<i>endo</i>	<i>endo</i>	17
H ₃ L2 ³⁺	2.624(8)	5.531(7)	<i>endo</i>	<i>exo</i>	17
H ₂ L3 ²⁺	2.96(2) ^c	2.84(1) ^c	<i>endo</i>	<i>endo</i>	18 ^c
–	2.86(1) ^c	2.81(1) ^c	–	–	–
H ₂ L4 ²⁺	3.77(2)	4.45(2)	<i>endo</i>	<i>endo</i>	19

^aThe configurations *endo* and *exo*, respectively, of the compounds L2, L3 and L4 refer to the situation where the N–H⁺ bonds or the lone pairs of the tertiary nitrogen atoms are oriented toward the inside of the cavity or away from the cavity. In the case of L1 the same definition apply to the tertiary nitrogens atoms, while the secondary nitrogen atoms are assigned as *endo* if one N–H⁺ bond or one N lone-pair points to the inside. ^bOne nitrogen is *exo* and the other is on the borderline between *exo* and *endo*. ^cTwo conformations in the crystal. The very short N(2)–N(4) distance has been explained by the effect of a proton bound to N(2) and N(4) [the other proton being bound to the other pair of opposite nitrogen atoms, N(1) and N(3)].

region (cf. the corresponding values for cyclen², which are 9.7 and 1.7, respectively). The tetraprotonated species is a very strong acid ($pK_4 < -1$). This is in keeping with, e.g., the observation that cyclen² has $pK_4 < 1$, and in addition it is noted that protonation of H₃L1³⁺ requires that the hydrogen bond to one of the tertiary nitrogen

groups is broken, and this will add further stability to the triprotonated species relative to the tetraprotonated species.

The acid–base properties of L1 and L2 are similar (Table 6). Both amines act as proton sponges, i.e. they are monoprotinated at pH 14. In both cases the proton

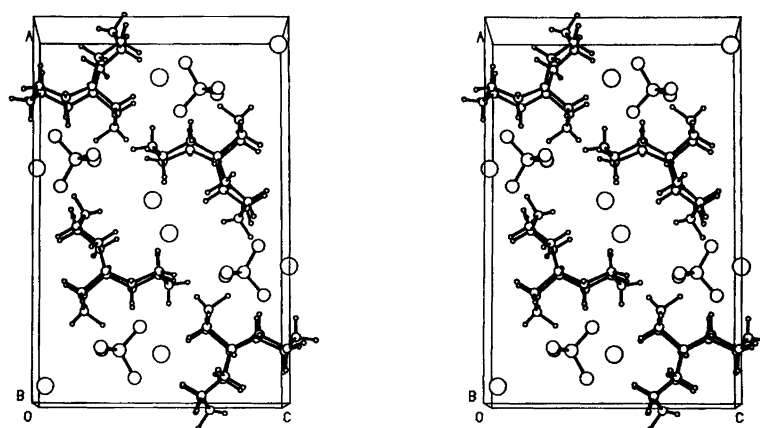


Fig. 3. Stereo view of the unit cell seen along the *b*-axis.

Table 6. Protonation constants^a of 'cross-bridged' derivatives of cyclam and cyclen (25 °C).

L	p <i>K</i> ₁	p <i>K</i> ₂	p <i>K</i> ₃	p <i>K</i> ₄	<i>I</i> / <i>M</i>	Ref.
L1	> 15	7.242(8)	3.202(7)	< -1	1.0	This work
L2	> 14	7.8(1)	< 2	—	0.15	17
L3	11.55(3)	6.94(3)	< 2	—	0.15	18
L4	12.00(6)	7.86 ^b	< 2	—	0.15	19
L5	> 13.5	10.8 ^b	—	—	D ₂ O ^c	16

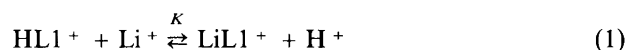
^a $K_i = [H_i L^{i+}] / ([H_{i-1} L^{(i-1)+}] [H^+])$; $pK_i = \log(K_i)$. Standard deviations in parentheses. ^b Standard deviation not reported. ^c Ionic strength not reported.

is stabilized by bonds to the two bridgehead nitrogen atoms. In the crystal structures these features are reflected by a very small distance between the two nitrogen atoms (Table 5). The species with longer bridges (L3 and L4) do not act as proton sponges ($pK_1 \approx 12$) and have both correspondingly longer N–N distances as shown in Table 5.

For all four cross-bridged cyclen derivatives, L1, L2, L3 and L4, the pK_2 values are in the region 7–8 as shown in Table 6. Since pK_2 in the case of L1 corresponds to protonation of a secondary amine, and in the case of the three other compounds to protonation of a tertiary amine a difference in pK values is to be expected. This is not the case, and other factors such as changes in conformations due to different substituents probably play an equally important role. The third protonation constant for L1 is significantly greater than those found for L2, L3 and L4, which at least qualitatively follows the difference in basicity (towards H^+) of dimethylamine and trimethylamine.

Reaction with metal ions. With the chemistry of the other cyclen cages in mind it was obvious to attempt coordination of Li^+ to L1, but no evidence for this reaction was obtained. The ¹³C NMR spectrum of a mixture of L1·3HBr (0.1 M) and LiCl (0.05 M) in 1 M NaOH (5% D₂O) heated to 100 °C for 1.5 h was identical to that of L1·3HBr in 1 M NaOH and no signals for a possible

lithium complex was observed. The concentration of the lithium complex is estimated to be less than 3% of C_{L1} . If it is assumed that equilibrium has been obtained under these conditions the upper limit value for the equilibrium constant defined in eqn. (1) is calculated as $K < 3 \times 10^{-15}$:



The small value of $K = \beta_1/K_1$ could be due to a very strong binding of the proton (K_1 large) or to a very weak binding of lithium (β_1 small). The formation constants of lithium complexes with some related cage ligands (pentaaza cages) are in the region $\beta_1 = 10^3$ – $10^5 M^{-1}$.^{14,15} If $\beta_1 > 10 M^{-1}$ is taken as a lower-limit estimate for the present system it follows that $K_1 > 3 \times 10^{15} M^{-1}$, which is in agreement with the NMR data. Preliminary experiments indicate that Cu^{2+} reacts with L1 to form a kinetically (as well as thermodynamically) very stable blue complex. This aspect is now being pursued.³³ Attempts to react L1 with Ni^{2+} and Co^{2+} have failed so far.

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Abbreviations

ts = *p*-toluenesulfonyl
 cyclen = 1,4,7,10-tetraazacyclododecane
 cyclen·ts₂ = 1,7-bis(*p*-toluenesulfonyl)-1,4,7,10-tetraazacyclododecane
 cyclam = 1,4,8,11-tetraazacyclotetradecane
 L1 = 1,4,7,10-tetraazabicyclo[5.5.3]pentadecane
 L1·ts₂ = 4,10-bis(*p*-toluenesulfonyl)-1,4,7,10-tetraazabicyclo[5.5.3]pentadecane
 L2 = 4,10-dimethyl-1,4,7,10-tetraazabicyclo[5.5.4]hexadecane
 L3 = 12,17-dimethyl-1,9,12,17-tetraazabicyclo[7.5.5]nonadecane

L4 = 4,10-dimethyl-1,4,7,10-tetraazabicyclo[5.5.5]heptadecane

L5 = 4,11-dimethyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane.

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