Acta Chemica Scandinavica, 1995: 49: 555–563
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ACTA
CHEMICA SCANDINAVICA
ISSN 0904–213X

An Inert Proton Coordinated Inside a Nearly Tetrahedral Tetraamine Cavity. Synthesis and X-Ray Crystal Structure of the Aquatrichlorozincate(II) Salt of the Inside Monoprotonated Amine 1,4,8,11-Tetraazatricyclo-[6.6.2.$2^{4,11}$]octadecane

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Springborg, J., Olsen, C. E. and Søtofte, I., 1995. An Inert Proton Coordinated Inside a Nearly Tetrahedral Tetraamine Cavity. Synthesis and X-Ray Crystal Structure of the Aquatrichlorozincate(II) Salt of the Inside Monoprotonated Amine 1,4,8,11-Tetraazatricyclo[6.6.2.$2^{4,11}$]octadecane. – Acta Chem. Scand. 49: 555–563 © Acta Chemica Scandinavica 1995.

The reaction of the bicyclic tetraamine L1·3HBr (L1 = 1,4,7,10-tetraazabicyclo[5.5.3]pentadecane) with the ditosylate of 1,3-propanediol affords the inside protonated form of the tricyclic amine 1,4,8,11-tetraaza tricyclo[6.6.2.$2^{4,11}$]octadecane (L). Monoprotonated L was isolated as a perchlorate, [HL]ClO_4 (57%). The tricyclic structure of HL^+ was established by ^1H and ^{13}C NMR spectroscopy, which shows that the cation in solution has a time-averaged D_{2d} symmetry. The crystal structure of the salt [HL][$Zn(H_2O)Cl_3$]·H_2O has been solved by X-ray diffraction at T = 120 K, M_r = 461.2, monoclinic, $P2_1$, a = 11.505(4), b = 8.186(4), c = 11.185(6) Å, β = 105.87(3)°, Z = 2, D_x = 1.52 g cm^{-3}, MoKα = 0.71073 Å, μ = 16.2 cm^{-1}, $F(000)$ = 484, $R(F)$ = 0.0448 for 2411 reflections with $I > 2\sigma(I)$ and $wR(F^2)$ = 0.1032 for all 3244 unique reflections. In the HL^+ cation the acidic hydrogen atom is situated between the two bridgehead nitrogen atoms N(2) and N(4), the N(2)···H and the N(4)···H distances being 1.38(9) and 1.35(9) Å, respectively. The distances from the hydrogen atom to the other two bridgehead nitrogen atoms N(1) and N(3) are 2.29(9) and 2.13(9) Å, respectively. The distance between N(2) and N(4) is 2.636(7) Å and that between N(1) and N(3) is 3.081(7) Å, giving rise to a slightly elongated conformation of the 12-membered tetraaza ring. HL^+ is aprotic in the pH range 0–14 and it is unusually inert with respect to exchange of the proton bound to the four nitrogen atoms. From ^1H NMR measurements it is estimated that the rate constant for the dissociation of the proton in 1 M NaOD must be less than 2×10^{-8} s^{-1} at 25 °C.

The study of new cyclic and bicyclic polyamines is of current interest since these classes of compounds exhibit very interesting properties such as unusual basicity, redox behaviour and coordination chemistry.[1–9] Derivatives of the important macrocyclic ligands cyclam and cyclen involving ethylene or tri-, tetra-, penta- and heptamethylene bridging of the non-adjacent nitrogens have been reported recently.[10–14] This leads to bicyclic tetraamines, which may adopt conformations having all four nitrogen lone pairs pointing inside the cavity for complexation of metal ions (Fig. 1). Some of these cages react as proton sponges and some form stable complexes with small cations such as lithium.[3,4,10,14] Less attention has been paid to the corresponding class of tricyclic tetraamines, whose smallest member is the classical compound urotropin or 'hexamethylenetetraamine' (Fig. 2). The crystal structure of hexamethylenetetraamine reported by Dickinson and

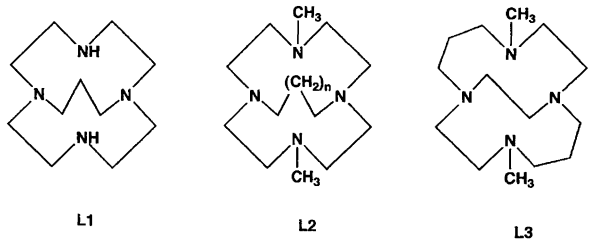

Fig. 1. Bicyclic tetraamines are strong bases ($pK_a > 14$) and very inert complexes with Li^+ or Cu^{2+} have been reported. L2 have been synthesized for n=2, 3 and 5.

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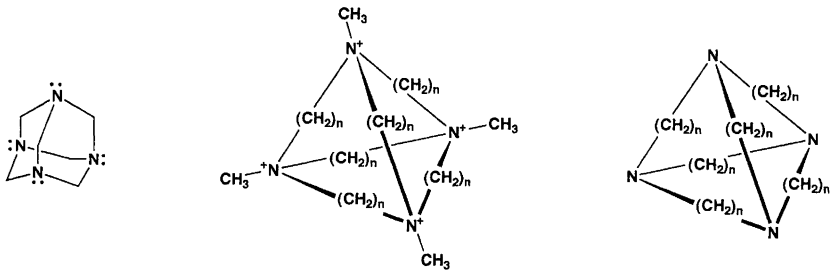


Fig. 2. Urotropin (hexamethylenetetraamine) and some higher members of the tricyclic tetraaza cages ($n=6$ or 7).

Raymond in 1923 was the first structure of an organic compound obtained by X-ray diffraction.[15] As shown in Fig. 2 the four lone pairs of the nitrogen bridgehead are oriented outside the cavity. Only few examples of larger tricyclic amines have been reported. Schmidtchen[16–21] has synthesized and studied large tricyclic tetraamines and their quaternary derivatives (Fig. 2). Related large tricyclic compounds with 1,3-xylenane bridges have been reported by Takemura *et al.*[22] The studies of these compounds have been focused on the ability of the quaternary derivatives (or the protonated forms) to form inclusion compounds with anions. The quaternary hexa- and heptamethylene derivatives (Fig. 2) form inclusion compounds with, e.g., halide anions, exhibit discrimination according to size, and react with biologically important compounds such as AMP, ATP and NAD.[20] They also catalyze bimolecular nucleophilic organic substitution reactions.[21] Finally, it should be noted that prior to these studies Graf and Lehn reported[23] related cages based upon 5-oxapentamethylene chains, as exemplified by the 'soccer ball' shown in Fig. 3. These compounds form coordination compounds with cations, neutral molecules and anions.[9,24–26] We present here a facile method for the synthesis of a small tricyclic tetraamine derived from the bicyclic tetraamine L1 shown in Fig. 1. This is, to our knowledge, the first example of a macrotricyclic compound containing only small chains ($n = 2$ or 3) with four donor atoms in an approximately tetrahedral arrangement.

Experimental

Abbreviations. L, 1,4,8,11-tetraazatricyclo[6.6.2.2^{4,11}]-octadecane; L1, 1,4,7,10-tetraazabicyclo[5.5.3]pentadecane; cyclen, 1,4,7,10-tetraazacyclododecane; cyclam, 1,4,8,11-tetraazacyclotetradecane.

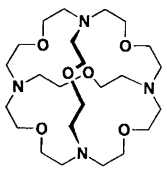


Fig. 3. 'Soccer-ball'.

Materials. The compounds L1·3HBr and trimethylene bis(*p*-toluenesulfonate) were obtained from methods given in the literature.[14,27] 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.

Mass spectra. Positive-ion FABMS were obtained on a Jeol AX505W mass spectrometer using a mixture of hydroxyethyl disulfide and dimethyl sulfoxide as matrix.

NMR spectra. ^{1}H and ^{13}C NMR spectra were measured at 5.87 T on a Bruker AC 250 NMR spectrometer equipped with a 5 mm probe. ^{1}H chemical-shift values (δ) are reported in ppm and are referenced to internal dioxane [δ(dioxane) = 3.75 ppm] for D_2O solutions. ^{13}C chemical-shift values (δ) are referenced to internal dioxane [δ(dioxane) = 67.40 ppm] for D_2O solutions. ^{13}C DEPT NMR spectra were used to assign CH_2 carbon atoms.

Potentiometric titrations. The pH measurements were made using Radiometer equipment as reported previously.[28]

X-Ray techniques. Crystal and experimental data for the compound are listed in Table 1. The possible space groups were established from rotation and Weissenberg photographs using Cu radiation. The crystal was cooled to 120 K, using a Crystream nitrogen gas cooler system.[29] The unit-cell parameters were 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. Only a quadrant of the limiting sphere ($h\ k\ l$ and $h\ k\ \bar{l}$) were measured, because the crystal suddenly disappeared during the data collection. Therefore, only 99 reflections with k negative were measured. Unfortunately it was not possible to get good single crystals, and since the present crystal was the most suitable of several, we decided to determine the structure with the data obtained for the present crystal. A loss of intensity of about 1.1% was observed. Therefore, a linear decay correction was applied. Afterwards the intensities were corrected for Lorentz, polarization and

Table 1. Crystal and experimental data.

Formula	$C_{14}H_{29}N_4^+$, $Zn(H_2O)Cl_3^-$, H_2O
Formula weight	461.20
Crystal system	Monoclinic
Space group	$P2_1$ (No. 4)
Unit-cell dimensions	
a/Å	11.505(4)
b/Å	8.186(4)
c/Å	11.185(6)
β/°	105.87(3)
Unit-cell volume, *V*/Å^3	1013.3(8)
Formula units per unit cell, *Z*	2
F(000)	484
Calculated density D_x/g cm^{-3}	1.52
Radiation	MoKα
Wavelength, λ/Å	0.71073
Linear absorption coefficient/cm^{-1}	16.2
Temperature, *T*/K	120
Crystal description	Colourless
Crystal size/mm	0.16×0.15×0.02
Diffractometer	Enraf-Nonius CAD-4F
Unit-cell determination	
No. of reflections used	25
θ-range/°	10.5–15.1
Intensity data collection	
θ_{max}/°	30
Range of *h*	0–16
Range of *k*	0–11
Range of *l*	−15–15
Scan mode	ω–2θ
Scan range, Δω	1.00+0.35 tan θ
Total number of unique reflections	3244
No. of independent reflections, [$I > 2\sigma(I)$]	2411
Corrections	Decay, Lorenz polarization and absorption
Transmission factors	0.7996–0.9639
Structure refinement	
Minimization of	$\Sigma w(\|F_o\|^2 - \|F_c\|^2)^2$
Anisotropic thermal parameters	All non-hydrogen atoms
Isotropic thermal parameters	Hydrogen atoms
No. of refined parameters	248
Weighting scheme	$[\sigma^2(F_o^2)+(0.0521P)^2]^{-1}$, $P=(F_o^2+2F_c^2)/3$
$R=\Sigma\|\|F_o\|-\|F_c\|\|/\Sigma\|F_o\|$	0.0448 (2411 reflections)
$wR2=[\Sigma w\|F_o^2\|-\|F_c^2\|^2/\Sigma wF_o^4]^{1/2}$	0.1032 (3244 reflections)
$S=[\Sigma w(\|F_o\|^2-\|F_c\|^2)^2/(N_{obs}-N_{var})]^{1/2}$	1.02
Final $(\Delta/\delta)_{max}$	0.10
Final $\Delta\varrho_{min}$ and $\Delta\varrho_{max}$/e Å^{-3}	−0.50 and 0.48

absorption (Gaussian integration) effects.[30] The structure was solved by the Patterson method with partial structure expansion and refined by a full-matrix least-squares technique. One of the bridging carbon atoms [C(10)] can flip between two almost equally populated positions. The hydrogen atoms attached to oxygen, nitrogen, to the carbon atoms in the cyclen ring and in the non-disordered $(CH_2)_3$ bridge could all be located from electron-density difference maps. The non-hydrogen atoms were refined anisotropically and the hydrogen atom attached to nitrogen was refined isotropically, whereas the hydrogen atoms attached to oxygen were refined with fixed isotropic thermal parameters $U(H) = 1.5U$ for attached oxygen atom. In order to reduce the number of parameters the hydrogen atoms attached to the carbon atoms (including atoms of the two disordered components) were all generated with fixed isotropic thermal parameters, $U(H) = 1.2U$ for attached carbon atom. The origin was fixed by use of least-squares restraints.[31] The Flack *x*-parameter is 0.02(2), indicating that this is the correct absolute structure.[32] The crystallographic computations were performed with SHELXS86[33] and SHELXL93.[34] The atomic scattering factors were taken from the literature.[35] The PLUTO program[36] was used for the illustrations and PLATON[37] for molecular geometry calculations. The final positional parameters are listed in Table 2. Anisotropic thermal parameters, positional parameters for the hydrogen atoms and a list of observed and calculated structure factors

Table 2. Fractional atomic coordinates and equivalent isotropic thermal parameters (in Å^2)

Atom	*x*	*y*	*z*	U_{eq} [a]
Zn	0.12502(6)	0.49966(6)	0.19428(5)	0.0236(2)
C1(1)	0.28286(12)	0.66697(17)	0.20342(12)	0.0263(4)
C1(2)	0.17229(12)	0.29616(17)	0.33547(12)	0.0277(4)
C1(3)	−0.04504(12)	0.63764(17)	0.19658(12)	0.0273(4)
O	0.0769(5)	0.4007(6)	0.0228(4)	0.0422(16)
O(W)	0.1278(4)	1.0073(7)	0.1292(4)	0.0434(14)
N(1)	0.5519(4)	0.0877(5)	0.3349(4)	0.0240(12)
N(2)	0.7811(4)	0.1254(6)	0.2855(4)	0.0228(12)
N(3)	0.6122(4)	0.3490(6)	0.1628(4)	0.0270(14)
N(4)	0.7126(4)	0.3539(5)	0.4178(4)	0.0187(11)
C(1)	0.6243(6)	−0.0540(7)	0.3301(6)	0.0309(16)
C(2)	0.7101(5)	−0.0272(6)	0.2485(6)	0.0284(17)
C(3)	0.8107(6)	0.2165(8)	0.1844(5)	0.0307(17)
C(4)	0.6993(6)	0.2956(8)	0.0987(5)	0.0354(19)
C(5)	0.6323(5)	0.5099(9)	0.2218(5)	0.0275(16)
C(6)	0.7224(5)	0.5060(8)	0.3486(4)	0.0248(14)
C(7)	0.6013(5)	0.3425(7)	0.4561(5)	0.0214(14)
C(8)	0.5605(5)	0.1635(7)	0.4532(5)	0.0264(17)
C(9)	0.4351(5)	0.0998(8)	0.2404(6)	0.0327(17)
C(10) [b]	0.4084(9)	0.2538(14)	0.1660(11)	0.029(3)
C(10′)	0.4334(10)	0.1588(15)	0.1184(11)	0.029(3)
C(11)	0.4856(6)	0.3165(9)	0.0946(6)	0.0429(19)
C(12)	0.8881(5)	0.0986(7)	0.3939(6)	0.0298(17)
C(13)	0.9237(5)	0.2545(7)	0.4709(5)	0.0290(16)
C(14)	0.8225(5)	0.3220(7)	0.5208(5)	0.0254(16)

[a] $U_{eq} = 1/3\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \boldsymbol{a}_i \cdot \boldsymbol{a}_j$. [b] The population factors for C(10) and C(10′) are 0.52(1) and 0.48(1), respectively.

may be obtained from one of the authors (I. S.) on request.

Synthesis. **Caution.** Mechanical handling and heating of amine perchlorates represents a potential danger. However, we have never experienced an explosion with the present compound.

[HL]ClO$_4$. A mixture of L1·3HBr (1.00 g, 2.2 mmol) and Na_2CO_3 (1.17 g, 11 mmol) in acetonitrile (280 ml) was added to molecular sieves (4.5 g, 4 Å, Merck) and refluxed for 24 h. Then trimethylene bis(*p*-toluenesulfonate) (0.929 g, 2.42 mmol) was added and the mixture was refluxed for 6 d under nitrogen. Evaporation of the filtered reaction mixture to dryness gave a white solid. The product was dissolved in water (12 ml), and a saturated solution of sodium perchlorate (6 ml) was added to the filtered solution. The precipitate was filtered off, washed thoroughly with water and dried in air. This gave 0.44 g (57%) of pure [HL]ClO$_4$. FABMS (*m/z*): 253 (HL$^+$). Analytical data: Calculated for $C_{14}H_{29}ClN_4O_4$: C, 47.65; H, 8.28; Cl, 10.1; N, 15.88. Found: C, 47.34; H, 8.40; Cl, 9.9; N, 15.80. NMR data are given in Table 3 and Fig. 4 (see also Results).

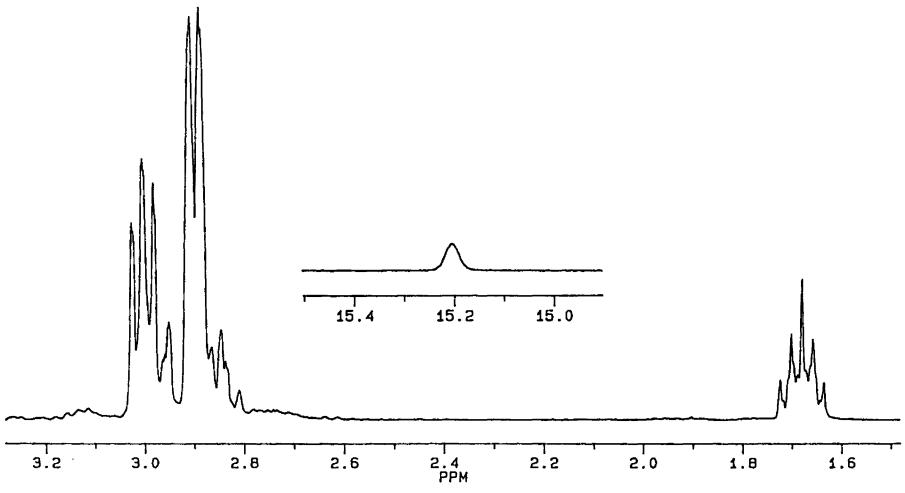


Fig. 4. ^{1}H NMR spectrum of HL$^+$ in D_2O.

Table 3. Selected ^{13}C and ^{1}H NMR chemical-shift data at 25 °C for $[HL]ClO_4$.[a]

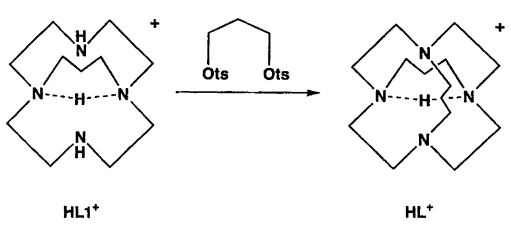
Solvent	δ(ppm) N–C $-(CH_2)_2-$	N–*C* $-(CH_2)_3-$	C–*C*–C $-(CH_2)_3-$	^{1}H H···N
1 M NaOD	55.93	53.34	24.61	15.20
1 M D_2O	55.93	53.33	24.60	15.17
0.1 M DCl	55.93	53.31	24.57	15.24

[a] For each solution identical values were obtained for solutions kept 1 h and 24 h, respectively, at 25 °C.

$[HL][Zn(H_2O)Cl_3]\cdot H_2O$. One volume of 4 M $Li_2[ZnCl_4]$ was added to an aqueous solution of the crude product of $[HL]ClO_4$ (ca. 0.1 g ml^{-1}) and the mixture was kept at room temperature for 24 h. Colourless plates of $[HL][Zn(H_2O)Cl_3]\cdot H_2O$ crystallized. The product was filtered off, washed twice with ice-cold water and dried in air. The crystals were identified by their ^{1}H and ^{13}C NMR spectra and by an X-ray crystal structure analysis (see below). Analytical data: Calculated for $C_{14}H_{33}Cl_3N_4O_2Zn$: C, 36.46; H, 7.21; N, 12.15. Found: C, 36.06; H, 6.85; N, 12.08.

Results

Synthesis and characterization. The macrotricyclic cage HL^+ has been made by the reaction of L1·3HBr with 10% excess of the ditosyl ester of 1,3-propanediol as shown in Scheme 1. HL^+ was obtained as a pure perchlorate salt (yield 57%). The compound was identified by elemental analysis and FABMS (see Experimental) and by its ^{1}H and ^{13}C NMR spectra. The ^{13}C NMR spectrum in D_2O exhibits three sharp signals (all CH_2) with the relative intensities (4:2:1) as expected. The chemical-shift values are all in the expected[14] regions (Table 3). The ^{1}H NMR spectrum shown in Fig. 4 has a quintet centred around 1.69 ppm (4 H, C–CH_2–C), a multiplet centred around 2.91 ppm [16 H, CH_2(ethylene)-N], a multiplet centred around 3.02 ppm [8 H, CH_2(trimethylene)-N], and a singlet at 15.2 ppm (1 H, HN^+). These assignments were supported by the 2D ^{1}H-^{13}C correlation spectrum. The singlet at 15.2 ppm integrates for one proton and is assigned to the proton in the center of the molecule coordinated to the nitrogen atoms. The δ-value is in the region reported for a series of inside protonated bicyclic diamines such as monoprotonated 1,6-diazabicyclo[4,4,4]dodecane (Fig. 7), which has δ = 17.4 ppm.[6,38] The ^{13}C NMR spectrum shows that the cation in solution has a time-averaged D_{2d} symmetry. The high symmetry (as opposed to the lack of symmetry found in the crystal) is explained by fast equilibria between different conformations of the ethylene and trimethylene chains, including different coordinations of the proton in the center. It seems likely that the unsymmetrical binding of the proton found in the crystal (see below) also persists in solution. From the X-ray data it is shown that the proton in the center is hydrogen-bonded to two nitrogen atoms with only weak interactions to the other two nitrogen atoms. It is found that the two short N–H distances are nearly equal, but it can not be established with certainty whether the hydrogen bond with the two short distances is of the single minimum or double minima type. The present case is related to the cases where one proton forms strong hydrogen bonds to two N donor atoms. In the latter cases it has been possible to distinguish between single-minimum and double-minima hydrogen bonds by $^{1}H/^{2}H/^{3}H$ NMR spectroscopy.[38] We are now investigating the prospect of this and other spectroscopic techniques to explore the present system.



Scheme 1.

The fact that the product is HL^+ prompts the question of whether the proton is incapsulated during or after the formation of the cage. In the latter case the free amine L1 should react with the ditosylate to form the free base L followed by reaction with a proton. A serious argument against this proposal is the expected low concentration of the free amine L1 ($HL1^+$ has $pK_a > 15$ in H_2O).[14] Furthermore, it is not known whether L reacts fast or slowly with H^+ to form the inside protonated product HL^+, but the same arguments as presented below to explain the observed inertness of HL^+ with respect to dissociation suggest that L, likewise is reluctant to form the inside protonated form of HL^+. Therefore it seems more likely that it is $HL1^+$ which is the reactive species and that the cage is formed in its inside protonated form as suggested in Scheme 1. We note that the conformation of $HL1^+$ as found in the crystal structure[14] is strongly influenced by the coordination of H^+ to the two tertiary nitrogen atoms and is close to being optimal for nucleophilic attack on the two secondary nitrogen groups leading to the formation of L. It is also noted that the proton bound to the two bridgehead nitrogen atoms prevents these groups from reacting with the tosylate to give quaternary side-products. This suggests that the present reaction may be described as proton assisted, i.e. the proton acts as an internal template similar to the more common metal-assisted and template organic reactions.[1-9]

Crystal structure. Bond lengths and bond and torsion angles are listed in Table 4. The labelling of the atoms in the HL^+ cation is shown in Fig. 5. The compound consists of HL^+ and $Zn(H_2O)Cl^-_3$ ions and one water molecule. In the HL^+ cation the acidic hydrogen atom is situated between the two bridgehead nitrogen atoms N(2)

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

Zn–Cl(1)	2.254(2)	N(4)–C(6)	1.487(7)
Zn–Cl(2)	2.2572(19)	N(4)–C(7)	1.460(8)
Zn–Cl(3)	2.265(2)	N(4)–C(14)	1.482(7)
Zn–O	2.015(5)	C(1)–C(2)	1.532(9)
N(1)–C(1)	1.438(8)	C(3)–C(4)	1.519(9)
N(1)–C(8)	1.440(7)	C(5)–C(6)	1.511(7)
N(1)–C(9)	1.468(8)	C(7)–C(8)	1.536(8)
N(2)–C(2)	1.488(7)	C(9)–C(10)	1.495(13)
N(2)–C(3)	1.470(8)	C(9)–C(10′)	1.443(14)
N(2)–C(12)	1.489(8)	C(10)–C(11)	1.442(13)
N(3)–C(4)	1.450(8)	C(12)–C(13)	1.531(8)
N(3)–C(5)	1.463(9)	C(13)–C(14)	1.526(8)
N(3)–C(11)	1.472(8)	C(10′)–C(11)	1.478(14)
Cl(1)–Zn–Cl(2)	112.31(6)	N(1)–C(1)–C(2)	112.4(5)
Cl(1)–Zn–Cl(3)	112.59(6)	N(2)–C(2)–C(1)	110.4(5)
Cl(1)–Zn–O	107.19(17)	N(2)–C(3)–C(4)	111.6(5)
Cl(2)–Zn–Cl(3)	113.80(6)	N(3)–C(4)–C(3)	113.2(5)
Cl(2)–Zn–O	108.67(15)	N(3)–C(5)–C(6)	112.8(5)
Cl(3)–Zn–O	101.41(17)	N(4)–C(6)–C(5)	112.1(5)
C(1)–N(1)–C(8)	119.1(5)	N(4)–C(7)–C(8)	110.0(5)
C(1)–N(1)–C(9)	116.9(5)	N(1)–C(8)–C(7)	112.0(4)
C(8)–N(1)–C(9)	116.9(5)	N(1)–C(9)–C(10)	117.8(6)
C(2)–N(2)–C(3)	115.9(4)	N(1)–C(9)–C(10′)	118.5(7)
C(2)–N(2)–C(12)	111.8(4)	C(9)–C(10)–C(11)	123.0(8)
C(3)–N(2)–C(12)	112.8(5)	N(3)–C(11)–C(10)	116.7(7)
C(4)–N(3)–C(5)	116.7(5)	N(3)–C(11)–C(10′)	117.2(7)
C(4)–N(3)–C(11)	114.1(5)	N(2)–C(12)–C(13)	111.7(5)
C(5)–N(3)–C(11)	114.1(5)	C(12)–C(13)–C(14)	113.2(5)
C(6)–N(4)–C(7)	113.8(4)	N(4)–C(14)–C(13)	110.7(4)
C(6)–N(4)–C(14)	112.5(4)	C(9)–C(10′)–C(11)	124.2(9)
C(7)–N(4)–C(14)	113.0(4)		
C(8)–N(1)–C(1)–C(2)	−120.2(6)	C(4)–N(3)–C(11)–C(10)	137.0(7)
C(9)–N(1)–C(1)–C(2)	90.1(6)	C(5)–N(3)–C(11)–C(10)	−85.2(8)
C(1)–N(1)–C(8)–C(7)	120.5(5)	C(7)–N(4)–C(6)–C(5)	−68.8(6)
C(9)–N(1)–C(8)–C(7)	−89.7(6)	C(14)–N(4)–C(6)–C(5)	161.1(5)
C(1)–N(1)–C(9)–C(10)	−127.6(7)	C(6)–N(4)–C(7)–C(8)	146.4(4)
C(8)–N(1)–C(9)–C(10)	82.0(8)	C(14)–N(4)–C(7)–C(8)	−83.7(5)
C(3)–N(2)–C(2)–C(1)	−146.2(5)	C(6)–N(4)–C(14)–C(13)	−76.9(5)
C(12)–N(2)–C(2)–C(1)	82.6(6)	C(7)–N(4)–C(14)–C(13)	152.6(5)
C(2)–N(2)–C(3)–C(4)	70.2(6)	N(1)–C(1)–C(2)–N(2)	51.4(7)
C(12)–N(2)–C(3)–C(4)	−159.1(5)	N(2)–C(3)–C(4)–N(3)	33.8(7)
C(2)–N(2)–C(12)–C(13)	−151.9(5)	N(3)–C(5)–C(6)–N(4)	−36.1(6)
C(3)–N(2)–C(12)–C(13)	75.4(6)	N(4)–C(7)–C(8)–N(1)	−53.0(6)
C(5)–N(3)–C(4)–C(3)	84.4(6)	N(1)–C(9)–C(10)–C(11)	56.3(12)
C(11)–N(3)–C(4)–C(3)	−139.0(6)	C(9)–C(10)–C(11)–N(3)	−57.3(12)
C(4)–N(3)–C(5)–C(6)	−82.6(6)	N(2)–C(12)–C(13)–C(14)	58.6(6)
C(11)–N(3)–C(5)–C(6)	140.8(5)	C(12)–C(13)–C(14)–N(4)	−56.9(6)

and N(4), the N(2)···H and the N(4)···H distances being 1.38(9) and 1.35(9) Å, respectively. The distances from the hydrogen atom to the other two bridgehead nitrogen atoms N(1) and N(3) are 2.29(9) and 2.13(9) Å, respectively. The N(2)···N(4) distance of 2.636(7) Å is slightly larger than the distance of 2.567(4) Å found in $L1{\cdot}2HBr{\cdot}HClO_4$,[14] whereas the N(1)···N(3) distance of 3.081(7) Å is larger than found in other similar compounds.[11,12] In the 12-membered tetraaza ring of the present structure the eight N–C bond lengths average 1.463(7) Å and the four C–C bond lengths 1.523(6) Å, which for the N–C bond is somewhat smaller than the value of 1.495(6) Å and for the C–C bond is slightly larger than the value of 1.514(4) Å found in $L1 \cdot 2HBr \cdot HClO_4$.[14] The N(1)–C bonds in the cyclen ring are somewhat shorter than the other N–C bonds and the C(1)–N(1)–C(8) angle is larger than the other C–N–C angles in the ring. In the $(CH_2)_3$ bridge between N(1) and N(3) the middle carbon atom is disordered, i.e. it can flip between the two almost equally populated positions C(10) and C(10′). In the $Zn(H_2O)Cl_3^-$ anion the bond lengths and angles are in agreement with values

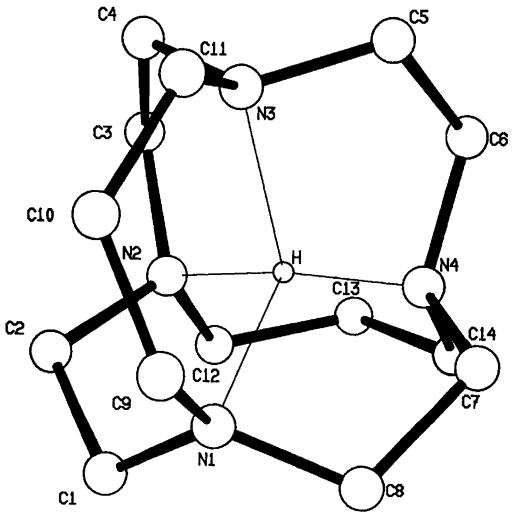


Fig. 5. View of the HL^+ cation with atomic labelling. The thin lines are the N···H···N 'hydrogen bonds'.

found in similar compounds. The crystal packing is shown in Fig. 6. The water molecule is hydrogen-bonded to Cl(1) and Cl(2), the O–H···Cl(1) [$\bar{x}$, $^1/_2+y$, $\bar{z}$] and the O–H···Cl(2) [$\bar{x}$, $1^1/_2+y$, $\bar{z}$] being 3.290(6) and 3.245(6) Å, respectively.

Inertness of HL^+. Potentiometric measurements of solutions of $[HL]ClO_4$ in HCl or NaOH showed that HL^+ is aprotic in the pH region 2–12. This result was confirmed by measuring the ^1H and ^{13}C NMR spectra of $[HL]ClO_4$ in acidic, neutral and basic solution. Identical spectra were obtained for solutions of $[HL]ClO_4$ in 0.1 M HCl, D_2O and 1 M NaOH (Table 3), respectively, and thus it is concluded that HL^+ does not undergo acid–base processes in the pH region 1–14 (within the timescale of days, see below). Furthermore, the ^1H NMR measurements showed that HL^+ is unusually inert with respect to exchange of the proton bound to the nitrogen atoms. As mentioned above, this proton can be observed as a singlet at $\delta = 15.2$ ppm. The ^1H NMR and ^{13}C spectra of a solution of $[HL]ClO_4$ in D_2O and 0.1 M DCl did not change within 24 h at 25 °C, and the intensity of the singlet at $\delta = 15.2$ ppm remained unchanged (within the estimated error, ca. 5%). The same results were obtained for a solution in 1 M NaOD, in which case it was shown that even after two months no measurable decrease in the intensity had taken place. Therefore it can be concluded that the rate constant for dissociation of the proton must be less than 2×10^{-8} s^{-1} (1 M NaOD, 25 °C). The inertness of HL^+ with respect to proton exchange is easily understood considering that the proton is totally encapsulated in a very rigid, but relatively strainless, cage. Any movement in the direction of dissociation of the proton will at some point go through a very strained transition state. This extreme inertness places the HL^+ cation as one of the most inert protonated amines reported. Among the few other examples with similar inert protons is the inside protonated bicyclic diamine 1,6-diazabicyclo[4.4.4]tetradecane studied by Alder *et al.*[38–41] for which the proton can not be inserted into or removed from the cavity by normal proton-transfer reactions (Fig. 7). Another example is 1,7-diaza-4,10,15-trioxabicyclo[5.5.5]heptadecane ([1.1.1] cryptand) studied by Lehn and co-workers[42–44] (Fig. 8). Protonation of this amine is very sluggish, and removal of the proton from the cavity can not be accomplished by normal proton-transfer reactions.

The free amine L is probably a strong base, but because of the inertness with respect to proton exchange it has not been possible to obtain an estimate for the base strength. In this context it is relevant that on the basis of strain energy changes it has been estimated[5] that the inside monoprotonated [4.4.4] diamine (Fig. 7) has $pK_a = 25$. NMR data for strong acidic solutions of HL^+ indicate small but significant changes in the chemical-shift values compared to those given in Table 3. At present it is not clear if these changes are due to medium effects or to formations of further protonated species such as e.g. H_2L^{2+}. This aspect is now being pursued.

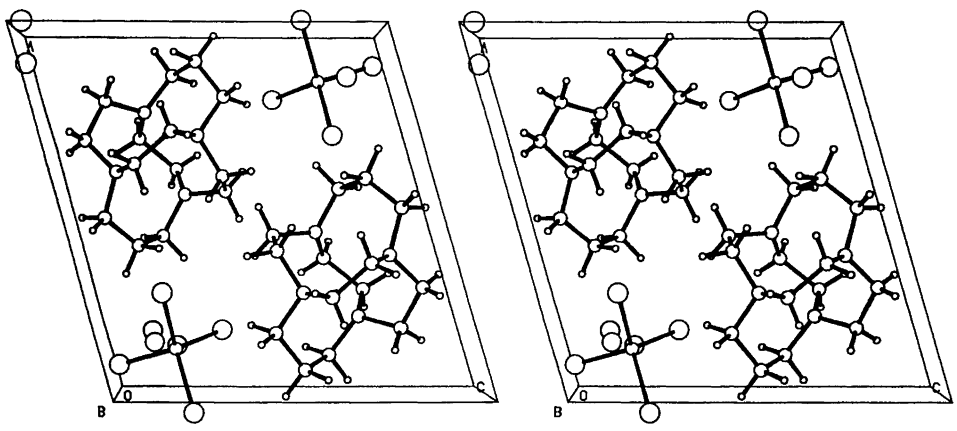


Fig. 6. Stereoview of the unit cell along the *b*-axis.

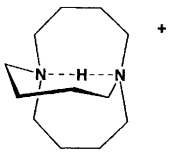


Fig. 7. The inside monoprotonated form of 1,6-diazabicyclo[4.4.4]tetradecane. The proton is bound symmetrically to the two nitrogen atoms and can not be removed by normal proton-transfer reactions.

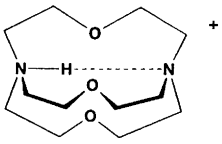


Fig. 8. The inside monoprotonated form of 1,7-diaza-4,10,15-trioxabicyclo[5.5.5]heptadecane ([1.1.1] cryptand). The proton is bound unsymmetrically to the two nitrogen atoms and can not be removed by normal proton-transfer reactions.

Concluding remarks

Several failed attempts to synthesize small tetraaza cages initially prompted us to suspect that the last step was made 'impossible' for steric reasons. In addition to steric properties, the acid–base properties of the bicyclic precursor could also be prohibitive for the final ring closure. For example, if the protonation of L1 had occurred at the two secondary amine groups (and not at the two tertiary groups as is the case) clearly the reactivity for electrophilic substitution would have been reduced considerably. The present study shows that small tricyclic tetraaza cages can be made by traditional organic synthetic methods. Our ultimate goal with this project is to synthesize small tetraaza cages in order to study their coordination compounds with Lewis acids. This goal has only been fulfilled partially, since L is too small to accommodate space for encapsulation of most other Lewis acids apart from H^+ with the possible exception of e.g. Be^{2+}. We are now trying to synthesize analogues with larger cavities, and a promising candidate is the tetraamine with six trimethylene chains. Models of this cage show that there is a relatively strain-free conformation, with all four lone pairs of the nitrogen donor atoms pointing inside the cavity and with a distance from the center to each nitrogen atom of ca. 2.0 Å, which is the ideal distance for complexation with many transition-metal ions. While the present cage, as mentioned, probably has little to offer in terms of coordination chemistry with metal ions, it will undoubtedly have interesting properties in its own right as already indicated by the present results. The related bicyclodiazaalkanes (as exemplified by the [4.4.4] diamine in Fig. 7) have shown a rich chemistry which, in addition to protonation reactions, includes unusual redox chemistry (N–N bond formation) and increased bridgehead reactivity (C–N bond formation and cleavage).[5,6] It is expected that L and its analogues will exhibit the same kind of reactions, and we intend to examine these aspects further. Finally, attempts to synthesize the analogue to L with six ethylene bridges are in progress, but have so far failed. This cage offers the intriguing question as to whether the inside protonated form will be unsymmetrical or symmetrical with four identical H–N hydrogen bonds.

Acknowledgements. Financial support from the Danish Research Council is acknowledged. We also thank Paulette Olsen and Saima Naeem for technical assistance.

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Received October 31, 1994.