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Synthesis and Characterization of the New Macrocyclic Cage 5,12,17-Trimethyl-1,5,9,12,17-pentaazabicyclo[7.5.5]nonadecane (L), Which Can Selectively Encapsulate Lithium Ion. Thermodynamic Studies on Protonation and Complex Formation. Crystal Structures of the Salt [HL][Cl]·3H₂O and of the Lithium Complex [LiL][BPh₄]

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Synthesis and characterization of the new aza cage 5,12,17-trimethyl-1,5,9,12,17-pentaazabicyclo[7.5.5]nonadecane (L) are reported. The basicity behavior in aqueous solution has been investigated by potentiometric, microcalorimetric (25 °C, 0.15 mol dm⁻³ NaCl), and spectroscopic (^{13}C NMR) techniques. The cage L behaves as a fairly strong base (log K_1 = 11.83; $\Delta H°_1$ = −54.4 kJ mol⁻¹; $T\Delta S°_1$ = 13.1 kJ mol⁻¹) in the first protonation step, as a moderate base in the second step (log K_2 = 9.53; $\Delta H°_2$ = −42.7 kJ mol⁻¹; $T\Delta S°_2$ = 11.7 kJ mol⁻¹), and as a weak base in the last step (log K_3 = 3.43; $\Delta H°_3$ = −13.0 kJ mol⁻¹; $T\Delta S°_3$ = 6.6 kJ mol⁻¹). Enthalpic and entropic contributions are discussed in terms of molecular rigidity and translational entropy. The molecular structure of the monoprotonated salt [HL][Cl] has been determined by single-crystal X-ray analysis. The compound crystallizes in a triclinic unit cell (space group $P\bar{1}$) with lattice constants a = 9.192 (5) Å, b = 9.384 (8) Å, c = 15.648 (6) Å, α = 78.89 (5)°, β = 76.18 (4)°, and γ = 63.67 (5)°, with Z = 2. Least-squares refinement converged to R = 0.078 for 2445 observed reflections. The [HL]⁺ structure shows that the protonation occurs at the methylated apical nitrogen. Repulsions between methyl groups reduce the thermodynamic stability of monoprotonated species. A number of metal ions were tested for complex formation with L. The electronic spectra of the Cu(II) complex show the same features both in the solid state and in solution and are diagnostic of a distorted square-pyramidal structure. According to ^{13}C NMR spectroscopy there was no evidence of metal coordination with Na⁺ and K⁺, whereas encapsulation of the Zn(II) ion has been shown. The cage selectivity encapsulates Li⁺. The [LiL]⁺ complex formation equilibrium has been investigated by potentiometry, microcalorimetry, and ^{7}Li NMR techniques. The thermodynamic parameters $\Delta G°$ (−18.3 kJ mol⁻¹), $\Delta H°$ (−2.1 kJ mol⁻¹), and $\Delta S°$ (54.3 J mol K⁻¹) have been determined. The molecular structure of the complex [LiL][BPh₄] has been determined by single-crystal X-ray analysis. The compound crystallizes in a monoclinic unit cell (space group $C2/c$) with lattice constants a = 24.43 (1) Å, b = 20.04 (1) Å, c = 19.33 (2) Å, and β = 128.03 (6)°, with Z = 8. Least-squares refinement converged at R = 0.149 for 743 unique reflections. Li⁺ is completely enclosed in the cage cavity and adopts a five-coordinate geometry.

Introduction

Many new macrocyclic compounds have been synthesized in recent years in response to the ever increasing interest in the field of macrocyclic chemistry,[2] where theory and experiment merge in the design of chemical structures with desired properties. Our attention has been devoted to a series of small macrobicyclic cages of the general formula

$$X = NCH_3, \quad L$$
$$X = NH, \quad L1$$
$$X = O, \quad L2$$
$$X = S, \quad L3$$
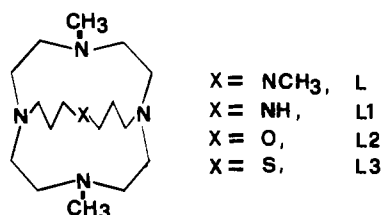
These cages are constructed from a twelve-membered tetraaza macrocycle (1) in which two trans nitrogen atoms are bridged by two propylene chains bound to the donor atom X (see structures L–L3). Molecular topology and size confer special proton-transfer and ligational properties to these small cages,[3] which contain cavities with convergently arranged binding sites. For example, only small cations, including protons, lithium, copper(II), etc., can be encapsulated with a high degree of selectivity. Two of these cages (L1 and L3) are "fast proton sponges",[4–6] which show an

extremely high basicity (higher than OH⁻ in aqueous solution) coupled with fast proton exchange. In the present paper, we report the synthesis, characterization, and ligation properties of the title compound, hereafter abbreviated as L.

Experimental Section

Synthesis of 5,12,17-Trimethyl-1,5,9,12,17-pentaazabicyclo[7.5.5]nonadecane (L). The macrocycle 1,7-dimethyl-1,4,7,10-tetraazacyclododecane (1) was prepared as previously described.[7]

N-Methylbis(3-hydroxypropyl)amine (3). To a solution of 50.0 g (0.37 mol) of bis(3-hydroxypropyl)amine (2) and 36.1 g (0.48 mol) of aqueous formaldehyde (40%) heated to 80 °C was added 23.2 g (0.50 mol) of formic acid (99%) over a period of 2 h. The reaction was continued for 1.5 h at 80 °C. After cooling, the excess formic acid was neutralized by adding 30.0 g (0.36 mol) of Na₂CO₃ dissolved in the minimum amount of water. The white precipitate was filtered out, the solution was concentrated under reduced pressure, and the residue was distilled under vacuum. The pure product 3 was collected as a colorless oil (71%), bp 203–206 °C (1 mmHg). Anal. Calcd for C₇H₁₇NO₂: C, 57.11; H, 11.64; N, 9.51. Found: C, 57.0; H, 11.8; N, 9.4.

O,O'-Bis(methylsulfonyl)-*N*-methylbis(3-hydroxypropyl)amine (4). To a stirred solution of 3 (3.0 g, 0.02 mol) and 3.0 g of triethylamine in anhydrous CH₂Cl₂ (200 cm³) at −10 °C was added dropwise a solution of methanesulfonyl chloride (6.7 g, 0.06 mol) in CH₂Cl₂ (50 cm³) over a period of 2 h. The reaction mixture was kept at −10 °C for 1 h and then stirred for 6 h at room temperature. The white precipitate was filtered out, washed with CH₂Cl₂, and dried under vacuum at 40 °C: yield 5.7 g of 4 (84%); mp 92–94 °C. Anal. Calcd for C₉H₂₂NS₂O₆Cl: C, 31.81; H, 6.52; N, 4.12. Found: C, 31.6; H, 6.7; N, 3.9.

5,12,17-Trimethyl-1,5,9,12,17-pentaazabicyclo[7.5.5]nonadecane Hydrochloride Dihydrate ([HL][Cl]·2H₂O). Finely powdered Na₂CO₃ (4.0 g, 0.038 mol) was added to a solution of compound 1 (2.0 g, 0.01 mol)

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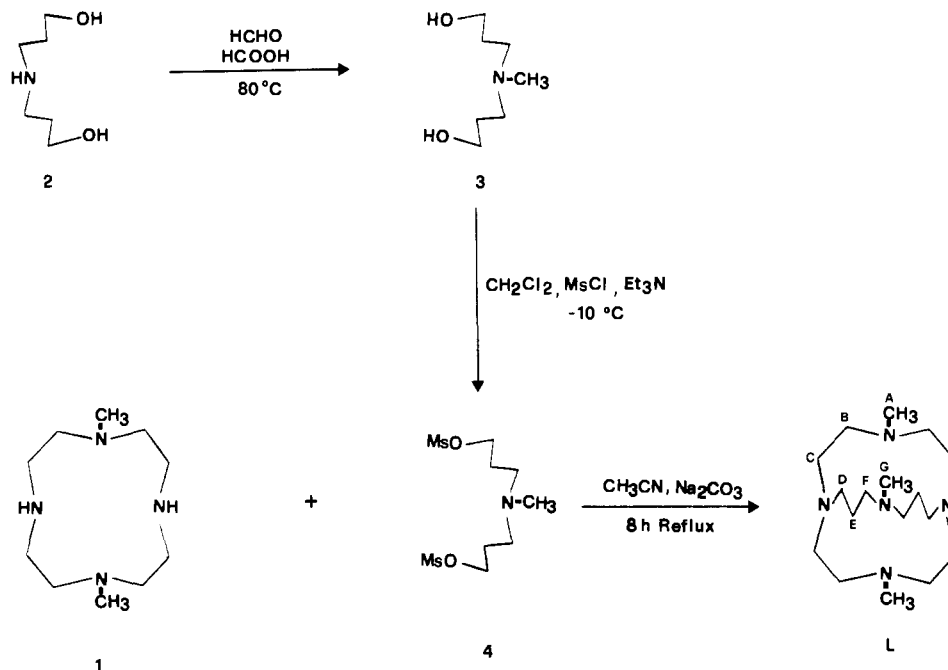
Figure 1. Reaction sequence for the synthesis of cage L.

Table I. ^{13}C NMR Chemical Shifts Data (ppm) for the Cage L and Lithium and Zinc(II) Complexes[a]

	A, A′	G	E	C, C′	B, B′	D	F
			Free L				
pH = 12.0	45.04	44.27	26.80	55.51	58.55	58.14	57.72
pH = 1.0	44.14	43.46	26.23	51.95/52.44	54.85/55.35	55.61	57.19
			[LiL]$^+$				
in D$_2$O	45.23/46.53	43.87	25.72	53.99/55.10	56.23/57.77	58.08	61.77
in CDCl$_3$	44.84/43.49	41.84	23.33	51.59/52.74	53.82/55.20	55.59	59.31
			[ZnL]$^{2+}$				
	47.06/47.08	46.80	24.41	55.34/55.88	56.43/59.70	61.98	64.32

[a] See Figure 1 for labeling. Tentative assignment for the methylene resonances (B, C, D, F).

in 100 cm³ of dry acetonitrile. The resulting suspension was heated to reflux, and a solution of **4** (3.6 g, 0.01 mol) in 60 cm³ of acetonitrile was added dropwise over a period of 8 h. The cooled suspension was filtered and then evaporated under reduced pressure to give a yellowish solid. The crude product was chromatographed on neutral alumina (70–230 mesh, activity I) with CHCl₃ as eluent to yield a white product, which was crystallized from a CHCl₃/cyclohexane mixture. Yield: 1.5 g (39%). Anal. Calcd for C₁₇H₄₂N₅O₂Cl: C, 53.17; H, 11.02; N, 18.23. Found: C, 53.3; H, 10.9; N, 18.1. For ¹³C NMR data, see Table I.

Preparation of [HL][Cl]·3H₂O. Well-formed crystals of [HL][Cl]·3H₂O, suitable for X-ray analysis, were obtained by slow evaporation of a solution of the dihydrate monochloride salt of L in benzene. When the solution was left standing, colorless crystals separated. To avoid disruption, one portion of the crystals was left in contact with the saturated benzene solution and subsequently used for X-ray analysis. Another portion was collected, washed with diethyl ether, and dried in a desiccator. Anal. Calcd for C₁₇H₄₄N₅O₃Cl: C, 50.79; H, 11.03; N, 17.42. Found: C, 50.5; H, 11.0; N, 17.2.

Preparation of Metal Complexes. [LiL][Cl]. A solution of LiOH (0.10 g, 4.2 mmol) and KOH (0.200 g, 3.56 mmol) in MeOH (40 cm³) was slowly added to a boiling solution of [HL]Cl·2H₂O (0.10 g, 0.26 mmol) in methanol (20 cm³). The mixture was refluxed for 30 min and evaporated to dryness with a rotary evaporator. The white product was extracted with CHCl₃ (10 cm³). On addition of 50 cm³ of cyclohexane, colorless crystals separated, which were washed with cyclohexane and dried in vacuo. Anal. Calcd for C₁₇H₃₉N₅OClLi: C, 54.90; H, 10.57; N, 18.83. Found: C, 54.5; H, 10.7; N, 18.5.

The [LiL][BPh₄] salt was obtained by refluxing (30 min) a methanolic solution of [HL][Cl], NaBPh₄, and a 20-fold molar excess of LiOH. On cooling, colorless crystals of [LiL][BPh₄], suitable for X-ray analysis, slowly separated.

[CuL][ClO₄]₂·H₂O. A solution of Cu[ClO₄]₂·6H₂O (0.048 g, 0.13 mmol) in MeOH (5 cm³) was added to a hot, neutralized solution of [HL][Cl]·2H₂O (0.05 g, 0.13 mmol) in MeOH (5 cm³). The resulting turquoise solution was acidified with HClO₄. On cooling, turquoise

crystals separated, which were filtered out and dried in a desiccator. (*Caution! Perchlorate salts of metal complexes can be explosive and must be handled with care. Compounds should not be heated as solids.*) Anal. Calcd for C₁₇H₃₉N₅O₉Cl₂Cu: C, 34.50; H, 6.64; N, 11.83. Found: C, 34.4; H, 6.7; N, 11.5.

[ZnL][ZnBr₄]. Equimolar acetonitrile solutions of free L and ZnBr₂ were mixed, and the resulting solution was refluxed for 1 h. A colorless solid separated, which was filtered and recrystallized from acetonitrile. Anal. Calcd for C₁₇H₃₅N₅Zn₂Br₄: C, 26.80; H, 4.89; N, 9.19. Found: C, 27.1; H, 5.0; N, 9.3.

Materials. All potentiometric and calorimetric measurements were carried out at constant ionic strength $I = 0.15$ mol dm⁻³. The ionic medium was prepared with NaCl (Merck Suprapur). Standardized CO₂-free solutions of NaOH, used in the potentiometric and calorimetric measurements, were prepared according to standard procedures.[8]

Protonation and Complex Formation Constant. The potentiometric titrations were carried out with a fully automatic apparatus, as described in ref 9. Three titration curves (210 data points) were used to determine the basicity constants of L. Due to the long time required for chemical equilibrium to be attained in the reaction between Li⁺ and the macrocyclic cage L, a batchwise potentiometric procedure was used to determine the stability constant of the complex [LiL]⁺. This procedure and its application to macrocyclic complexes have been described in ref 10. Ten aqueous solutions of the ionic medium (NaCl), containing different amounts of the complex [LiL][Cl] (concentration range 1–3 × 10⁻³ mol dm⁻³) and NaOH, were prepared in separate bottles. The solutions were maintained at 25 °C, and the magnitude of –log [H⁺] for each solution was measured periodically until a constant value was reached. The computer program SUPERQUAD[11] was used to process the potentiometric

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Table II. Crystallographic Data for [(C$_{17}$H$_{38}$N$_5$)Cl]·3H$_2$O

formula	C$_{17}$H$_{44}$ClN$_5$O$_3$	space gp	P$\bar{1}$
mol wt	402.02	D_{calcd}, g cm^{-3}	1.14
a, Å	9.192 (5)	radiation	Mo Kα (graphite
b, Å	9.384 (8)		monochromated)
c, Å	15.648 (6)	λ, Å	0.7107
α, deg	78.89 (5)	temp, °C	25
β, deg	76.18 (4)	μ, cm^{-1}	1.42
γ, deg	63.67 (5)	R^a	0.078
V, Å^3	1169 (1)	$R_w{}^b$	0.072
Z	2		

$^a R = \sum||F_o| - |F_c||/\sum|F_o|$. $^b R_w = [\sum w(|F_o| - |F_c|)^2/\sum w(F_o)]^{1/2}$.

Table III. Crystallographic Data for Li(C$_{17}$H$_{37}$N$_5$)]B(C$_6$H$_5$)$_4$

formula	C$_{41}$H$_{57}$BLiN$_5$	D_{calcd}, g cm^{-3}	1.14
mol wt	637.68	radiation	Mo Kα (graphite
a, Å	24.43 (1)		monochromated)
b, Å	20.04 (1)	λ, Å	0.7107
c, Å	19.32 (1)	temp, °C	25
β, deg	128.03 (6)	μ, cm^{-1}	0.34
V, Å^3	7454 (11)	R^a	0.149
Z	8	$R_w{}^b$	0.12
space gp	C2/c		

$^a R = \sum||F_o| - |F_c||/\sum|F_o|$. $^b R_w = [\sum w(|F_o| - |F_c|)^2/\sum w(F_o)^2]^{1/2}$.

data and calculate the basicity and stability constants.

Enthalpy of Protonation and Complex Formation. The enthalpies of protonation of L and the enthalpy of formation of [LiL]$^+$ were determined with a Thermometric AB thermal activity monitor (Model 2277) equipped with a perfusion/titration system and an Hamilton pump (Model Microlab M). The calorimetric system as well as the Hamilton pump were controlled by an IBM personal computer (Personal System 2 Model 30) and the computer program AUTOTAM.[12] The enthalpy of ionization of water was determined by adding a NaOH solution to a solution of HCl contained in the calorimetric vessel. The measured value, -13.55 (5) kcal mol^{-1}, is in agreement with literature values.[13]

Protonation Experiment. The calorimetric ampule was charged with 2 cm^3 of ligand (0.003 mol dm^{-3}). After equilibration (1 h), injections involving 20 μL of NaOH (0.02 mol dm^{-3}) as titrant were made by use of a 0.250-cm^3 gastight Hamilton syringe (Model 1750 LT) attached to a Microlab M system. Timing and sequence of injections were regulated by a microcomputer that was used for integration of the titration curves.[12] Under the reaction conditions and with employment of the determined stability constants, the amounts of each species present at equilibrium before and after each addition were calculated together with the corresponding enthalpies of reaction, by means of the KK88 computer program.[14]

Lithium Complex. In this case the ampule was charged with 2 cm^3 of ligand (0.25 mol dm^{-3}, pH > 12) and 20-μL injections of LiOH solution (0.25 mol dm^{-3}) were made. For each addition the reaction was considered complete when no further heat effect could be detected. Typically the reaction time was 50–55 min. Blank experiments, carried out to determine the enthalpy of dilution, demonstrated that this effect was negligible under the experimental conditions. Furthermore, to confirm the reaction time, the same reaction was monitored by a ^{7}Li NMR technique.

Spectroscopy. 300-MHz ^{1}H NMR spectra were recorded with a Varian VXR-300 spectrometer as D$_2$O solutions. The same instrument was used to record the ^{13}C spectra at an operating frequency of 75.43 MHz and the ^{7}Li spectra at a frequency of 116.59 MHz. The UV–vis spectra were recorded on a Perkin-Elmer Lambda 9 spectrophotometer.

X-ray Structure Analysis. Investigations on single crystals of [H-L][Cl]·3H$_2$O and [LiL][BPh$_4$] were carried out with an Enraf-Nonius CAD-4 X-ray diffractometer. A summary of the crystallographic data is reported in Tables II and III. Unit cell parameters were determined by least-squares refinement of diffractometer setting angles for 25 carefully centered reflections. Intensities were corrected for Lorentz and

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Table IV. Positional Parameters and Their Estimated Standard Deviations in Parentheses ($\times 10^4$) for [HL][Cl]·3H$_2$O

atom	x/a	y/b	z/c
Cl	9585 (2)	2553 (2)	5404 (1)
O1	5592 (4)	2607 (4)	3501 (3)
O2	2330 (6)	3837 (5)	4382 (3)
O3	8659 (5)	1117 (5)	4064 (3)
N1	2310 (5)	3770 (5)	8446 (3)
N2	5792 (5)	3309 (5)	8151 (3)
N3	6219 (5)	−57 (5)	7914 (3)
N4	2712 (5)	291 (5)	8446 (3)
N5	4116 (6)	2572 (5)	6630 (3)
C1	2988 (7)	4136 (7)	9086 (4)
C2	4483 (7)	4491 (7)	8698 (4)
C3	6999 (7)	3939 (7)	7701 (4)
C4	6580 (7)	1797 (6)	8672 (4)
C5	7414 (6)	374 (6)	8136 (4)
C6	5665 (7)	−1013 (6)	8667 (4)
C7	4132 (7)	−1218 (6)	8596 (4)
C8	1454 (7)	−69 (7)	8235 (4)
C9	2042 (7)	1264 (7)	9193 (4)
C10	1159 (7)	3045 (7)	8914 (4)
C11	1541 (7)	5156 (7)	7856 (4)
C12	1227 (7)	4808 (7)	7028 (4)
C131	2277 (10)	3188 (10)	6724 (5)
C141	4683 (10)	3845 (9)	6110 (5)
C151	4977 (11)	1084 (9)	6193 (5)
C16	6806 (8)	150 (7)	6267 (4)
C17	6934 (7)	−942 (7)	7121 (4)
C132	3080 (40)	4094 (36)	6445 (20)
C142	3461 (32)	1465 (29)	6214 (17)
C152	5831 (31)	2058 (31)	6240 (16)
H10	4383 (62)	2447 (59)	7384 (34)

polarization effects. During data collection, three reflections were monitored periodically as a check of the stability of the diffractometer and of the crystal. The structures were solved by direct methods and subsequently refined by a full-matrix least-squares technique. The function minimized was $\sum w(|F_o| - |F_c|)^2$, with $w = a/\sigma^2(F)$, where a is an adjustable parameter. All calculations were performed on a IBM personal computer, Model Personal System 2/80, with the SHELX-76 set of programs[15] that use the analytical approximation for the atomic scattering factors and anomalous dispersion corrections for all the atoms from ref 16. Tables IV and V list the final atomic coordinates for non-hydrogen atoms with estimated standard deviations. The molecular plots were produced by the program ORTEP.[17]

[HL][Cl]·3H$_2$O. Two positions were found for the carbon atoms linked to the nitrogen atom of the propylene bridge, which are in a disordered array. Population parameters of 0.75 and 0.25 have been assigned to the different positions on the basis of the result of the least-squares refinement. A ΔF map calculated in the final stage of the refinement showed unambiguously the presence of an hydrogen atom linked to the N-bridge atom. This hydrogen atom was refined. This ΔF map showed also some hydrogen atoms of the water molecules, which were introduced in the least-squares calculations in fixed positions with U of 0.08 Å^2 and a population parameter of 0.5 on account of an observed disordered array. The other hydrogen atoms of the macrobicycle were introduced in calculated positions with U of 0.06 Å^2; in the disordered fragment, only the hydrogens for the 0.75 population were introduced. Anisotropic temperature factors were used for the non-hydrogen atoms, except for the three carbon atoms having population parameters of 0.25.

[LiL][BPh$_4$]. The asymmetric unit contains two independent [LiL]$^+$ cations, which possess a 2-fold axis passing through the N-bridge and the Li$^+$ cation. Both cations are affected by disorder, as shown by the high values of the thermal parameters of the atoms of the ligand molecule and by the presence of the methyl carbons of the N-bridge, which obviously violate the 2-fold symmetry. On account of this disorder the refinement, where all the atoms were introduced with isotropic temperature factors, converged to an high value for the R factor. The phenyl groups of the [BPh$_4$]$^-$ anion were introduced in an idealized geometry and were refined as rigid groups. For the hydrogen atoms only those of the [BPh$_4$]$^-$ anion were introduced in calculated positions with U of 0.07 Å^2.

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Table V. Positional Parameters and Their Estimated Standard Deviations in Parentheses (×10⁴) for [LiL][BPh₄]

atom	x/a	y/b	z/c
Li1	0	1706 (54)	2500
N1	−998 (18)	2159 (18)	1096 (24)
N2	480 (24)	2071 (26)	1904 (30)
N3	0	640 (25)	2500
C31	−601 (34)	2320 (28)	733 (38)
C32	59 (34)	2558 (28)	1400 (42)
C33	1244 (25)	2283 (24)	2875 (34)
C34	1087 (24)	2620 (26)	3464 (33)
C35	−1692 (25)	1812 (22)	371 (31)
C36	647 (40)	429 (34)	3120 (50)
C37	209 (35)	492 (28)	1947 (38)
C38	890 (29)	791 (29)	2198 (35)
C39	599 (27)	1448 (31)	1649 (34)
Li2	5000	2053 (51)	2500
N4	3944 (21)	1604 (24)	1458 (32)
N5	5281 (32)	1723 (34)	1593 (38)
N6	5000	3180 (22)	2500
C40	4150 (31)	1179 (29)	919 (32)
C41	4749 (53)	1244 (44)	1151 (53)
C42	3320 (24)	2087 (21)	829 (30)
C43	3883 (30)	1218 (34)	1958 (51)
C44	4160 (38)	1317 (32)	2817 (52)
C45	4166 (40)	3309 (38)	1740 (51)
C46	5101 (33)	3242 (31)	1797 (39)
C47	5329 (39)	2947 (47)	1572 (55)
C48	5148 (41)	2363 (51)	1098 (53)
B	2705 (18)	9219 (19)	2720 (23)
C1	2109 (8)	9565 (11)	1869 (12)
C2	2286 (8)	10126 (11)	1620 (12)
C3	1774 (8)	10470 (11)	864 (12)
C4	1087 (8)	10252 (11)	355 (12)
C5	910 (8)	9691 (11)	604 (12)
C6	1422 (8)	9347 (11)	1361 (12)
C7	2631 (9)	8367 (15)	2674 (14)
C8	2982 (9)	8015 (15)	3454 (14)
C9	2949 (9)	7320 (15)	3446 (14)
C10	2565 (9)	6978 (15)	2656 (14)
C11	2214 (9)	7330 (15)	1876 (14)
C12	2247 (9)	8024 (15)	1884 (14)
C13	3524 (15)	9300 (9)	3003 (15)
C14	4096 (15)	9365 (9)	3877 (15)
C15	4764 (15)	9392 (9)	4118 (15)
C16	4860 (15)	9355 (9)	3484 (15)
C17	4288 (15)	9290 (9)	2610 (15)
C18	3620 (15)	9263 (9)	2369 (15)
C19	2685 (11)	9568 (14)	3472 (16)
C20	3050 (11)	10158 (14)	3866 (16)
C21	3018 (11)	10471 (14)	4479 (16)
C22	2620 (11)	10194 (14)	4697 (16)
C23	2255 (11)	9603 (14)	4304 (16)
C24	2287 (11)	9290 (14)	3691 (16)

Table VI. Thermodynamic Quantities of Stepwise Protonation of Cages in Aqueous Solution (25 °C, I = 0.15 (NaCl))

	cages (apical group)			
step	L^a (>N–CH₃)	L1^b (>NH)	L2^c (>0)	L3^d (>S)
	log k			
1	11.83 (1)^e	>14^f	>14	11.91
2	9.53	8.41	11.21	8.78
3	3.43			
	−$\Delta H°$/kJ mol^{-1}			
1	54.4			55.6
2	42.7			48.1
3	13.0			
	$T\Delta S°$/kJ mol^{-1}			
1	13.2			12.3
2	11.7			2.0
3	6.6			

^{a} This work. ^{b} From ref 4. ^{c} From ref 6. ^{d} From ref 18. ^{e} Values in parentheses are standard deviations on the last significant figure. ^{f} Kinetically active or fast proton sponges.

Results and Discussion

Protonation. The macrocycle L can take up a total of three protons both in the solid state and in aqueous solution. The thermodynamic parameters for protonation of L are reported in Table VI together with those for previously investigated cages of the series. All equilibria are rapidly established. The cage L exhibits high basicity in the first step of protonation (log k_1 = 11.83), a moderate basicity in the second step (log k_2 = 9.53), and a weak basicity in the last step (log k_3 = 3.43). Both $\Delta G°$ and $\Delta H°$ values for the first and second protonation reactions are unusually high for a compound having only tertiary nitrogen atoms.[19] Indeed, there is a significant increase in proton affinity for the first protonation step of tertiary nitrogens of the monocycle 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane (−$\Delta G°_1$ = 55.2 kJ mol^{-1}; see ref 19) and that of the cage L (−$\Delta G°_1$ = 67.5 kJ mol^{-1}; see Table VI). It appears that the proton-binding

characteristics of these compounds are strongly influenced by the molecular topology. Only in the third protonation step is there a sharp decrease in the basicity (see Table VI). This behavior is probably due to electrostatic repulsion between the positive charges located within the small, rigid molecular framework. Considering the enthalpy and entropy contributions to the stepwise protonation of L, the first step is characterized by a very favorable enthalpic term. In other words, the added hydrogen ion interacts very strongly with the nitrogen atoms to form the monoprotonated species HL$^+$. Even in the second protonation step the enthalpy change is very favorable. The entropy contribution is favorable in all steps. For the first and second steps of protonation, the two contributions are very similar ($\Delta S°_1$ = 43.9 and $\Delta S°_2$ = 39.2 J mol^{-1} K^{-1}; see Table VI), and only for the last step of protonation is the entropy contribution less positive ($\Delta S°_3$ = 22.1 J mol^{-1} K^{-1}; see Table VI). This trend is quite different from that found for monocyclic aza macrocycles, where the addition of the first and second proton are characterized by very different entropic contributions.[19] This can be explained by assuming that the stepwise addition of two protons to the already rigid molecule L to form HL$^+$ and H₂L^{2+} would not markedly enhance the molecular rigidity. Thus, the main contribution to the stepwise entropy change is that due to the release of water molecules from the hydrated proton that is being bound to nitrogens inside the cage cavity. The crystal structure of the monoprotonated species [HL]$^+$, discussed in the next section, indicates that the proton is well inside the cage cavity, supporting the hypothesis concerning the importance of the translational contribution. Also, in the last step of protonation the entropy change is still positive. In spite of the close proximity of three positive charges in the molecular framework, the stiffening effect seems to be rather limited.

In spite of the structural similarity of L1 and L, these two cages behave very differently in the first step of protonation. L1 behaves as a "fast proton sponge";[3-6] i.e., it has a very high basicity for the first protonation step, which is not measurable in aqueous solution, coupled with fast proton transfer. With the aim of rationalizing this marked difference in the first basicity step of L and L1, we have carried out an X-ray analysis of the [HL][Cl] salt and now compare the present results with that for [HL1][Br].[5]

Crystal Structure of [HL][Cl]·3H₂O. The structure of the compound consists of discrete [HL]$^+$ cations, chloride anions, and water molecules. Figure 2 shows an ORTEP[17] drawing of the cation with the atom labeling. Table VII provides selected bond lengths and angles as well as some significant nonbonding distances for the cation [HL]$^+$. The macrocycle is protonated at the methylated N-bridge atom N5 and displays an overall conformation similar to that of the related cage L1.[5] The four basal nitrogens are in the endo conformation with the ethylenic carbon atoms below the basal plane. The repulsions between the methyl group C141 attached to the apical nitrogen atom N5 and the methyl group C3 on N2 force the N5–H10 bond to point almost perpendicularly

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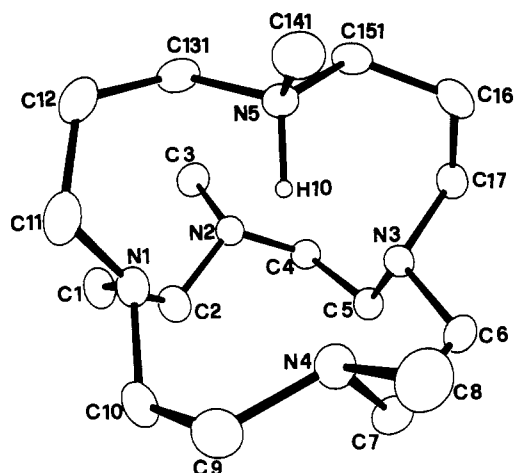
Figure 2. ORTEP drawing of the [HL]⁺ cation, showing the numbering scheme adopted. With the only exception of H10, the hydrogen atoms have been omitted for clarity.

Table VII. Distances (Å) and Angles (deg) for $C_{17}H_{44}ClN_5O_3$ with Estimated Standard Deviation in Parentheses

Distances			
N1–C1	1.46 (1)	N5–C152	1.44 (3)
N1–C10	1.481 (9)	N1–H10	2.26 (4)
N1–C11	1.442 (7)	N2–H10	2.41 (7)
N2–C2	1.449 (7)	N3–H10	2.34 (4)
N2–C3	1.457 (9)	N4–H10	3.07 (6)
N2–C4	1.459 (6)	N5–H10	1.23 (6)
N3–C5	1.456 (9)	C1–C2	1.52 (1)
N3–C6	1.470 (7)	C4–C5	1.513 (8)
N3–C17	1.479 (7)	C6–C7	1.54 (1)
N4–C7	1.464 (6)	C9–C10	1.525 (8)
N4–C8	1.46 (1)	C11–C12	1.51 (1)
N4–C9	1.465 (8)	C12–C131	1.49 (1)
N5–C131	1.50 (1)	C12–C132	1.63 (3)
N5–C141	1.53 (1)	C151–C16	1.53 (1)
N5–C151	1.475 (9)	C16–C17	1.513 (8)
N5–C132	1.34 (3)	C16–C152	1.61 (3)
N5–C142	1.69 (4)		

Angles			
C10–N1–C11	111.9 (6)	C131–N5–H10	106 (3)
C1–N1–C11	111.9 (5)	C131–N5–C151	111.3 (6)
C1–N1–C10	109.9 (5)	C131–N5–C141	109.9 (6)
C3–N2–C4	110.3 (5)	N1–C1–C2	114.7 (5)
C2–N2–C4	111.7 (4)	N2–C2–C1	115.0 (5)
C2–N2–C3	108.7 (5)	N2–C4–C5	113.5 (5)
C6–N3–C17	110.6 (5)	N3–C5–C4	111.7 (6)
C5–N3–C17	110.5 (5)	N3–C6–C7	115.1 (5)
C5–N3–C6	110.3 (5)	N4–C7–C6	113.9 (5)
C8–N4–C9	111.0 (5)	N4–C9–C10	112.8 (5)
C7–N4–C9	113.5 (5)	N1–C10–C9	112.8 (6)
C7–N4–C8	108.3 (5)	N1–C11–C12	115.1 (5)
C152–N5–H10	93 (3)	C11–C12–C132	102 (1)
C142–N5–H10	129 (3)	C11–C12–C131	117.2 (6)
C142–N5–C152	105 (1)	N5–C131–C12	118.2 (8)
C132–N5–H10	107 (3)	N5–C151–C16	115.0 (6)
C132–N5–C152	119 (2)	C151–C16–C17	108.4 (6)
C132–N5–C142	105 (2)	C17–C16–C152	123 (1)
C151–N5–H10	115 (2)	N3–C17–C16	112.8 (5)
C141–N5–H10	105 (3)	N5–C132–C12	119 (2)
C141–N5–C151	110.2 (5)	N5–C152–C16	113 (2)

toward the basal plane; the angle formed between the line through the N5–H10 bond and the average plane through N1, N2, N3, and N4 is 82°. As a consequence of this imposed conformation, the mean value of the hydrogen bond H10⋯N distances (2.54 Å) is significantly longer than that found for the H⋯N distances (2.36 Å) of the monoprotonated pentaazabicycle L1.[5] This suggests that the lower thermodynamic stability of the monoprotonated species [HL]⁺ with respect to the analogue [HL1]⁺ is attributable to a weaker hydrogen bond network, which stabilizes the former species. In other words, the basicity of L is weakened, thus allowing the full removal of the proton at pH > 12 and facilitating
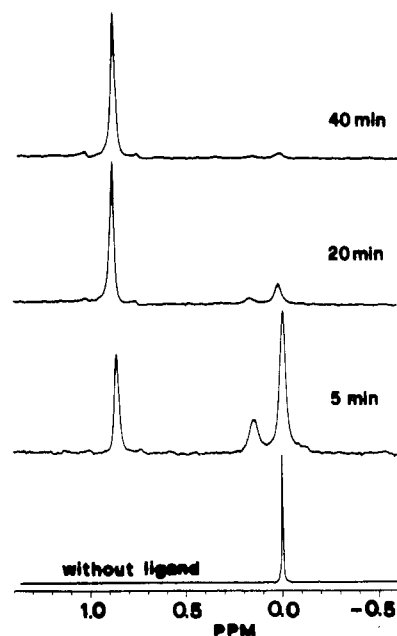

Figure 3. ⁷Li NMR spectra, taken at different times, after mixing solutions of LiOH (0.05 mol dm⁻³) and L (0.5 mol dm⁻³).

the insertion of small cations into the cage cavity. Preliminary results on this structure have been reported in ref 20.

Metal Complexes. One specific characteristic of these macrocyclic cages is the selective encapsulation of metal ions. Several metal ions including Li⁺, Na⁺, K⁺, Al³⁺, Ni²⁺, Cu²⁺, and Zn²⁺ were tested for complex formation with L. With ¹³C NMR spectroscopy as a diagnostic technique, no evidence is found for the complex formation with Na⁺, K⁺, or Al³⁺. With Ni²⁺ no complex was formed, even after prolonged heating at reflux of a reaction mixture of either nickel perchlorate or nickel chloride and the free amine L. With the other metal ions, solid complexes were isolated and characterized (see Experimental Section). The Li⁺ ion is readily encapsulated by L, and the equilibrium (1) was

$$\text{Li}^+(\text{aq}) + \text{L}(\text{aq}) = [\text{LiL}]^+(\text{aq}) \qquad (1)$$

investigated by potentiometry, microcalorimetry, and ¹³C and ⁷Li NMR techniques. The Li⁺ encapsulation is clearly shown by the ¹³C and ⁷Li NMR spectra of the complex. The ¹³C NMR spectrum of a solution containing the preformed [LiL][Cl] salt in strongly alkaline aqueous solution (0.2 mol dm⁻³ KOH) consists of ten sharp signals at room temperature (Table I) independent of the solvent, in contrast with the six very broad resonances observed for the ligand alone, at the same pH (Table I). The spectrum of the complex shows three resonances for the propylenic carbon atoms and four different signals for the eight methylene basal carbons, whereas the methyl carbons give rise to three signals, each integrating to one carbon atom. This spectrum is typical of a time-averaged C_s symmetry for the complex, with the lithium atom and the nitrogens of the N–CH₃ groups lying in the symmetry plane. The ⁷Li spectrum of the complex, recorded at a high pH, shows a sharp signal at +0.884 ppm shifted with respect to the solvated Li⁺ ion. This difference between the chemical shift of complexed and solvated Li⁺ even in such a highly solvating solvent as water is similar to shifts found previously for other cryptands[21] and shows that the resulting complex is very stable. With an excess of Li⁺, only two sharp signals are present (Figure 3), one for the complexed and one for the free lithium, indicating a slow exchange between the two species on the NMR time scale. ⁷Li NMR spectra were also measured at different temperatures.

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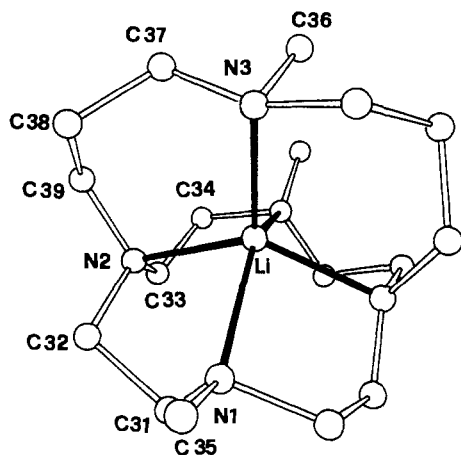
Figure 4. ORTEP drawing of one of the [LiL]$^+$ cations in [LiL][BPh$_4$], showing the numbering scheme adopted. Thermal parameters U of 0.04 Å^2 were assigned to all atoms.

The ^{7}Li NMR technique was used to estimate the reaction time for the equilibrium (1) at high pH. Spectra taken at different times after mixing an excess of L (0.5 mol dm^{-3} in 0.2 mol dm^{-3} KOH) and Li$^+$ (0.05 mol dm^{-3}, LiOH) indicate that almost 100% of the complex is formed after 50 min (Figure 3). Independent confirmation of this approximate reaction time was provided by calorimetric measurements that were carried out to determine the enthalpy of reaction 1. After 50 min no further heat effect was detectable for the reaction mixture (see Experimental Section). The equilibrium constant of reaction 1 is greater than 1000 (log K = 3.2 ± 0.1), indicating a good ability of L to encapsulate the Li$^+$. It is noteworthy that the driving force for this reaction is the entropy (ΔS° = 54.2 ± 0.2 J mol^{-1} K^{-1}), the enthalpy of reaction being only very slightly favorable ($-\Delta H^\circ$ = 2.1 ± 0.1 kJ mol^{-1}). These results are very different from those found for macrobicyclic cages having mainly oxygen as donor atoms, where the formation of lithium complexes is much more exothermic than in our case and the enthalpic contribution to the overall reaction spontaneity is much more important than the entropic contribution.[22] In the [LiL]$^+$ complex, insertion of the metal ion into the small hydrophobic cavity requires removal of all the water molecules that surround the free lithium ion in aqueous solution, thus raising the translational entropy change. The low exothermicity of complex formation can be explained by taking into account that the heat of reaction 1 is made up by opposing factors: an endothermic effect due to the breaking of the lithium–water molecule bonds and an exothermic effect due to the formation of the lithium–nitrogen bonds. It is also remarkable that lithium complex formation is not influenced by the presence of Na$^+$ ion, even in high concentration, indicating that L is able to discriminate completely between Li$^+$ and Na$^+$.

Crystal Structure of [LiL][BPh$_4$]. The structure of the compound consists of discrete [LiL]$^+$ cations and [BPh$_4$]$^-$ anions. Figure 4 shows an ORTEP drawing of the cation with the atom labeling. Selected bond lengths and angles are reported in Table VIII. The Li$^+$ is completely enclosed in the macrobicycle and adopts a five-coordinated geometry, which is best described as a distorted square pyramid. The metal ion is located 0.85 Å above the least-squares plane that passes through the basal nitrogen atoms N1, N2, N1′, and N2′. The Li–N distances are all in the range 2.14–2.45 Å, which are comparable with those reported for noncage aza macrocycles.[23] The very good agreement between the solid-state features and the solution behavior of the [LiL]$^+$

Table VIII. Selected Distances (Å) and Angles (deg) for C$_{41}$H$_{57}$BLiN$_5$

Distances			
Li1–N3	2.14 (12)	C31–C32	1.39 (8)
Li1–N1	2.45 (5)	N1′–C34	1.36 (8)
Li1–N2	2.21 (8)	C33–C34	1.56 (10)
N3–C36	1.33 (7)	C37–C38	1.54 (11)
N3–C37	1.47 (10)	C38–C39	1.56 (8)
Li2–N6	2.26 (11)	N4–C40	1.64 (10)
Li2–N4	2.26 (6)	N4–C42	1.57 (6)
Li2–N5	2.34 (10)	N4–C43	1.31 (12)
N6–C45	1.64 (7)	N5–C41	1.40 (11)
N6–C46	1.53 (9)	N5–C48	1.51 (12)
N1–C31	1.54 (11)	C40–C41	1.25 (15)
N1–C35	1.55 (5)	N5′–C44	1.38 (8)
N2–C32	1.31 (7)	C43–C44	1.37 (13)
N2–C33	1.69 (5)	C46–C47	1.07 (15)
N2–C39	1.44 (9)	C47–C48	1.38 (14)

Angles			
N2–Li1–N2′	141 (2)	N1–C31–C32	110 (6)
N2–Li1–N1′	88 (2)	N2–C32–C31	111 (5)
N1–Li1–N1′	136 (1)	N2–C33–C34	108 (5)
N1–Li1–N2	78 (2)	N1′–C34–C33	111 (4)
N3–Li1–N2	109 (2)	N3–C37–C38	119 (4)
N3–Li1–N1	112 (1)	C37–C38–C39	99 (5)
C36–N3–C37	81 (5)	N2–C39–C38	127 (5)
N5–Li2–N5′	147 (2)	C42–N4–C43	116 (6)
N5–Li2–N4′	82 (2)	C40–N4–C43	112 (5)
N4–Li2–N4′	133 (2)	C40–N4–C42	111 (4)
N4–Li2–N5	85 (2)	C41–N5–C48	116 (6)
N6–Li2–N5	106 (2)	N4–C40–C41	118 (6)
N6–Li2–N4	113 (1)	N5–C41–C40	137 (8)
C45–N6–C46	89 (4)	N4–C43–C44	128 (7)
C31–N1–C35	109 (4)	N5′–C44–C43	126 (8)
C33–N2–C39	106 (4)	N6–C46–C47	136 (7)
C32–N2–C39	129 (5)	C46–C47–C48	135 (12)
C32–N2–C33	117 (5)	N5–C48–C47	116 (7)

complex, such as the averaged C_s symmetry and the high thermodynamic stability, strongly suggests that the complex exhibits essentially the same stereochemistry both in aqueous solution and in the solid state.

Cu(II) Complex. The electronic spectra of the [CuL]$^{2+}$ complex in aqueous solution (10 400 (ϵ = 120), 14 000 (ϵ = 376), 31 000 cm^{-1}) and in the solid state (10 100, 14 180, 31 300 cm^{-1}) are essentially the same and are diagnostic of a distorted square-pyramidal structure.[4,24] As already found with the related complexes [CuL1]$^{2+}$ and [CuL2]$^{2+}$, [CuL]$^{2+}$ is also very inert toward strong acid solutions: [CuL]$^{2+}$ in 1 mol dm^{-3} HCl for 30 days shows no detectable decomposition. The geometry of the Zn(II) complex can be investigated by its ^{13}C NMR spectrum, which consists of 10 sharp signals at room temperature and is independent of the solvent and of the nature of the anions. In particular, the methyl carbons give rise to three sharp signals (see Table I), each integrating for one carbon atom. This spectrum is indicative of time-averaged C_s symmetry for the [ZnL]$^{2+}$ species with the zinc atom and the nitrogen atom of the N–CH$_3$ groups lying in the symmetry plane. As already found[4] for the related complex [ZnL1]$^{2+}$, the Zn(II) complex of L is very inert toward strong acidic media. These findings suggest the encapsulation of the Zn(II) ion within the cage cavity.

Supplementary Material Available: Tables of complete bond lengths and angles and positional and thermal parameters (6 pages); a listing of observed and calculated structure factors (16 pages). Ordering information is given on any current masthead page.

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