Selective Encapsulation of Lithium Ion by the New Azacage 5,12,17,Trimethyl-1,5,9,12,17-penta-azabicyclo[7.5.5]nonadecane (L). Thermodynamic Studies and Crystal Structures of the Lithium Complex [LiL][BPh_4] and of the Monoprotonated Salt [HL][Cl]·$(H_2O)_3$

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Multinuclear n.m.r. and thermodynamic studies in aqueous solution indicate that the cage-like azamacrobicycle 5,12,17-trimethyl-1,5,9,12,17-penta-azabicyclo[7.5.5]nonadecane (L) is able to selectively encapsulate the lithium ion, forming a stable 1 : 1 complex (log k = 3.1, $\Delta H^\circ = -2.1$ kJ mol^{-1}, $\Delta S^\circ = 52.3$ J mol^{-1} K^{-1}); the crystal structures of the complex [LiL][BPh_4] and of the monoprotonated salt [HL][Cl]·$3H_2O$ have been determined.

In recent years an ever growing interest has been shown in molecular recognition using macrocyclic compounds.[1] Our attention has been devoted to a small macrobicyclic cage 5,12,17-trimethyl-1,5,9,12-17-penta-azabicyclo[7.5.5]nonadecane (L), which belongs to a series of small cages previously studied.[2]

Molecular topology and size confer special proton-transfer and ligational properties to these cages, which contain cavities with convergently arranged binding sites.[2]

The cage (L) has been obtained by non-template synthesis involving the reaction of the tetra-azamacrocycle 1,7-dimethyl-1,4,7,10-tetra-azacyclododecane with bis(propyl-3-methanesulphonate)methylamine.[3]†

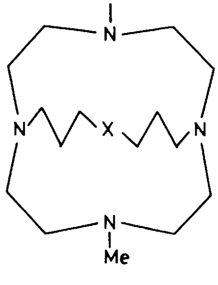
Well formed crystals of [HL][Cl]·$3H_2O$, suitable for X-ray analysis, were obtained by slow evaporation of a solution of the hydrate hydrochloride salt of (L) in benzene.

The [LiL][BPh_4] salt was obtained by refluxing (30 min) a methanolic solution of [HL][Cl], $NaBPh_4$ and a twentyfold molar excess of LiOH. On cooling, colourless crystals of [LiL][BPh_4], suitable for X-ray analysis, slowly separated.

The thermodynamic parameters ΔG°, ΔH° and $T\Delta S^\circ$ relative to the formation reaction (1) have been determined by potentiometry and microcalorimetry.[3] Because (L) behaves as a base, the equilibrium (1) is pH-dependent and the basicity constants of (L) have been first determined (log k_1 = 11.82; log k_2 = 9.53; log k_3 = 3.43)[3]

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

The ^{13}C n.m.r. spectrum of [LiL][Cl] in strong alkaline aqueous solution consists of ten sharp signals at room temperature. The methyl carbons give rise to three signals, each integrating for one carbon atom. This spectrum is typical of a time-averaged C_s symmetry for the complex, with the



L , X = N—Me

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† All reaction intermediates, as well as (L), exhibited satisfactory analytical and spectroscopic data.

lithium atom and the nitrogens of the >N–Me groups lying in the symmetry plane. The ^{7}Li spectrum of a solution containing both [LiL][Cl] and LiCl exhibits two sharp signals, one for the complexed Li (+0.884 p.p.m.) and one for the free lithium, indicating a slow exchange between the two species on the n.m.r. time scale. The ^{7}Li n.m.r. spectra taken at different times after mixing (L) and Li^+ ion in excess at $pH > 12$ indicate that almost 100% of complex is formed after 50 minutes. Indeed, calorimetric measurements confirm that within 50 minutes no more heat is evolved from the reaction mixture.[3] The equilibrium constant of reaction (1) [greater than 1000 ($\log k = 3.1 \pm 0.1$)] indicates a significant tendency of (L) to encapsulate the lithium ion. It is interesting to note that the driving force for this reaction is the entropy change ($\Delta S^\circ = 52.3 \pm 0.2$ J mol^{-1} K^{-1}), the enthalpy of reaction being only very slightly favourable ($-\Delta H^\circ = 2.1 \pm 0.1$ kJ mol^{-1}). For the $[LiL]^+$ complex the insertion of the metal ion into the small hydrophobic cavity causes the removal of all the water molecules which surround the free lithium ion in aqueous solution, thus raising the translational entropy. The low exothermicity of reaction (1) can be explained taking into account that the overall heat effect is made up of two, opposite, contributions: the endothermic effect due to the breaking of the lithium–water bonds and the exothermic effect due to the formation of the lithium–nitrogen bonds. It is also remarkable that the lithium encapsulation is not influenced by the presence of Na^+ ion, even in high concentrations, indicating that (L) is able to fully discriminate between lithium and sodium ions. Indeed only the proton can rapidly replace the lithium ion inside the cage cavity.

X-Ray analyses have shown the structural details of the Li^+ and H^+ inclusion compounds. The crystal structures of the cations $[LiL]^+$‡ and $[HL]^+$‡ are reported in Figures 1 and 2, respectively. The lithium ion is completely enclosed in the macrobicycle and adopts a five-co-ordinated geometry, which is best described as a distorted square pyramid. The metal ion is located above the least-squares plane passing through the basal nitrogen atoms N(1), N(2), N(1′) and N(2′) by 0.85 Å, the Li–N distances are all in the range 2.14—2.45 Å, well comparable with those reported for non-cage azamacrocycles.[4] The agreement between the solid state features and

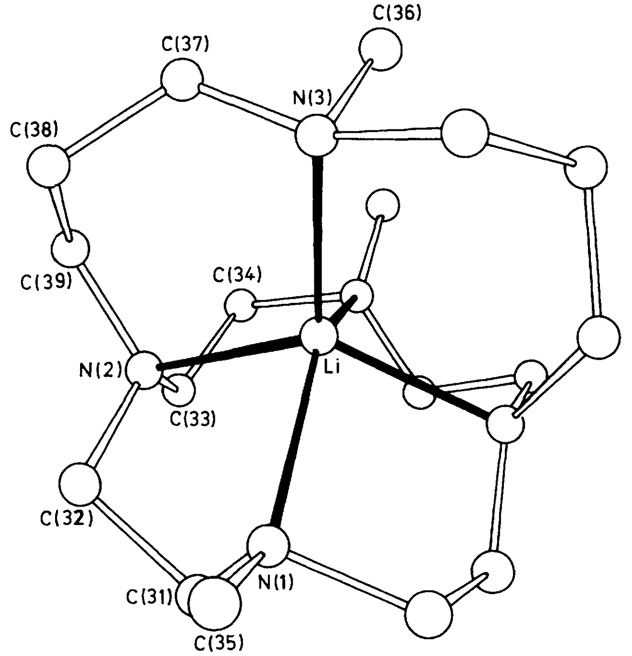

Figure 1. The crystal structure of one of two independent $[LiL]^+$ cations in $[LiL][BPh_4]$ showing the numbering scheme adopted. Thermal parameters U of 0.04 were assigned to all atoms. Selected bond lengths (Å): Li–N(1) 2.45(5), Li–N(2) 2.21(8), Li–N(3) 2.14(12). Selected bond angles (°): N(1)–Li–N(3) 112(1), N(1)–Li–N(2) 78(2), N(1)–Li–N(1′) 136(1), N(2)-Li-N(3) 109(2), N(2)–Li–N(2′) 141(2).

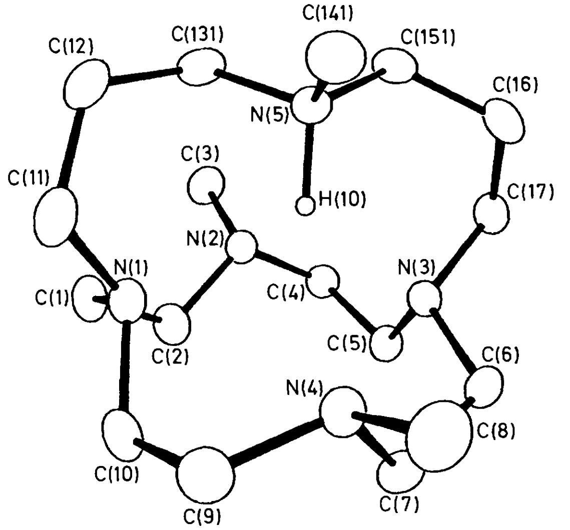

Figure 2. The crystal structure of the $[HL]^+$ cation in $[HL][Cl]\cdot 3H_2O$ showing the numbering scheme adopted. With the only exception of H(10) the hydrogen atoms have been omitted for clarity. Selected distances (Å): N(5)–H(10) 1.17, N(1) · · · H(10) 2.32, N(2) · · · H(10) 2.55, N(3) · · · H(10) 2.28, N(4) · · · H(10) 2.97.

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‡ *Crystal data* for $C_{41}H_{57}BLiN_5$: colourless crystals, $M = 637.68$, monoclinic, space group $C2/c$, $a = 24.43(1)$, $b = 20.04(1)$, $c = 19.33(2)$ Å, $\beta = 128.03(6)^\circ$, $V = 7454(11)$ Å^3, $Z = 8$, $F(000) = 2759.46$, $\mu = 0.34$ cm^{-1}, $D_c = 1.14$ g cm^{-3}, graphite monochromated Mo-K_α radiation ($\lambda = 0.7107$ Å). 3761 Reflections were collected on a Enraf-Nonius CAD4 automatic diffractometer in the range $5 < 2\theta < 40^\circ$. 743 Unique reflections with $I > 4.5\,\sigma(I)$ were used in structure solution and refinement. The structure was solved by direct methods and successive Fourier syntheses. Two independent $[LiL]^+$ cations possess a twofold axis passing through the N(3) atom and Li^+. Some degree of disorder was found in both cations as shown by the rather high thermal parameters of the carbon atoms and by the position of the methyl carbon of the N(3) atom which lies out of the twofold axis. One of the two molecules appears to be more disordered than the other; however the two cations have similar configurations, each with the lithium ion encapsulated into the macrobicyclic cavity. As a consequence of such disorder the full-matrix isotropic least-squares refinement, where the tetraphenyl borate anion was considered as a rigid group, gave $R = 0.149$ and $R_w = 0.121$. For $C_{17}H_{44}ClN_5O_3$: colourless crystals, $M = 402.02$, triclinic, space group $P\bar{1}$, $a = 9.192(5)$, $b = 9.384(8)$, $c = 15.648(6)$ Å, $\alpha = 78.89(5)$, $\beta = 76.18(4)$, $\gamma = 63.67(5)^\circ$, $V = 1169(1)$ Å^3, $Z = 2$, $F(000) = 443.90$, $\mu = 1.42$ cm^{-1}, $D_c = 1.14$ g/cm^3, graphite monochromated Mo-K_α radiation ($\lambda = 0.7107$ Å). 3185 Reflections were collected on an Enraf-Nonius CAD4 automatic diffractometer in the range $5 < 2\theta < 45^\circ$. 2445 Unique reflections having $I > 3\sigma(I)$ were used in structure solution and refinement. The structure was solved by direct methods and successive Fourier syntheses and refined to $R = 0.078$, $R_w = 0.072$. Two positions were found for the carbon atoms linked to the nitrogen atom of the 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 least-square refinement. A ΔF map calculated in the final stage of the refinement showed unambiguously the presence of an hydrogen atom linked to N(5) atom. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

the solution behaviour of the $[LiL]^+$ complex, such as the averaged C_s symmetry and the high thermodynamic stability, allows us to conclude that the complex exhibits essentially the same stereochemistry both in aqueous solution and in the solid state. In Figure 2 the structure of the cation $[HL]^+$ shows that the protonation occurs on the methylated apical nitrogen N(5) and that its overall conformation is similar to the one of the lithium complex. The repulsions between the methyl group C(14) attached to the apical nitrogen N(5) and the methyl group C(3) on N(3) force the N(5)–H(10) bond to point almost perpendicularly toward the basal plane. As a consequence of this imposed conformation the mean value of the hdyrogen bond H(10) $\cdots$ N distances (2.54 Å) is longer than that found (2.36 Å) in the related, non-methylated cage[2] (X = NH in the scheme, L1), reducing the stability of the monoprotonated species $[HL]^+$ with respect to $[HL1]^+$ ($\log k_1 > 14$, see ref. 2). In other words, the basicity of (L) is weakened thus allowing the full removal of the proton at pH > 12 and the insertion of the lithium ion.

In conclusion, the molecular topology of the small, fully methylated aza-cage (L) is well suited to allow the formation of a selective, stable lithium complex in aqueous solution. The solubility of the complex in both aqueous and non-aqueous solvents (chloroform, benzene *etc.*) stimulates attempts to synthesise more lipophilic derivatives of (L) in order to allow selective lithium transportation across synthetic membranes.

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