Synthesis of a Small Azacage which can Selectively encapsulate a Lithium Ion in Aqueous Solution

Andrea Bencini,[a] Antonio Bianchi,[a] Angela Borselli,[a] Mario Ciampolini,*[a] Mauro Micheloni,*[a] Nicoletta Nardi,[a] Paola Paoli,[a] Barbara Valtancoli,[a] Stefano Chimichi,[b] and Paolo Dapporto[c]

[a] *Department of Chemistry,*
[b] *Department of Organic Chemistry,*
[c] *Department of Energetics, University of Florence, Via Maragliano 75/77, I-50144-Florence, Italy*

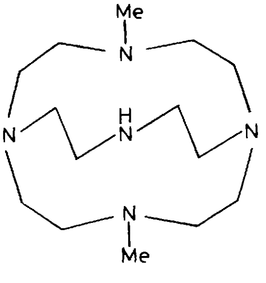
Synthesis of 4,10-dimethyl-1,4,7,10,15-penta-azabicyclo[5.5.5]heptadecane (**L**) which encapsulates a lithium ion in aqueous solution and the crystal structure of [LiL][ClO_4] are reported.

Small azacages are highly organized molecules showing unusual basicity and complexing properties.[1—3] The macrobicyclic cage 4,10-dimethyl-1,4,7,10,15-penta-azabicyclo-[5.5.5]heptadecane (**L**) is able to selectively encapusulate a lithium ion, forming a very stable Li^+ complex in aqueous solution ($\log K = 4.8 \pm 0.1$). A non-template procedure was used to synthesize the cage (**L**).

The synthesis involved the reaction of the tetra-azamacrocycle 1,7-dimethyl-1,4,7,10-tetra-azacyclododecane with *N*-tosyliminodiacetyl dichloride, followed by reduction and detosylation of the bicyclic diamide obtained.†

Refluxing (30 min) a methanolic solution of (**L**), $NaClO_4$, and a tenfold molar excess of LiOH, then evaporating to dryness, produced a white product which was extracted with $CHCl_3$, and slowly evaporated. To the solution, a small amount of cyclohexane was added, and colourless crystals of [LiL][ClO_4], suitable for *X*-ray analysis, were produced.

The equilibrium constant relative to the formation of this salt [equation (1)] was determined by a potentiometric, out-of-cell procedure.[4] Because (**L**) behaves as a base, the equilibrium in equation (1) is pH-dependent and the basicity constants of (**L**) were determined ($\log K_1 = 12.48$; $\log K_2 = 9.05$; $\log K_3 < 1$). The ^{13}C NMR spectrum of [LiL][ClO_4] in $CHCl_3$ solution consists of eight sharp signals at room temperature, two with methyl carbons unequivalent, giving rise to two signals. This spectrum is indicative of time-averaged C_s symmetry. The ^7Li spectrum of an aqueous solution containing a mixture of [LiL][ClO_4] and LiCl exhibits two sharp peaks, one for the complexed Li (δ +2.85 p.p.m.) and one for the free lithium, indicating a slow exchange between the two species on the NMR time scale. Furthermore, the chemical shift of the complexed lithium is essentially independent of the solvent, indicating a tight encapsulation of the metal ion and no co-ordinated solvent molecules.[5] The equilibrium constant of equation (1), $\log K = 4.8 \pm 0.1$, is as far as we know, the highest found for lithium azamacrocyclic complexes in aqueous solution. The crystal structure of the



(**L**)

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

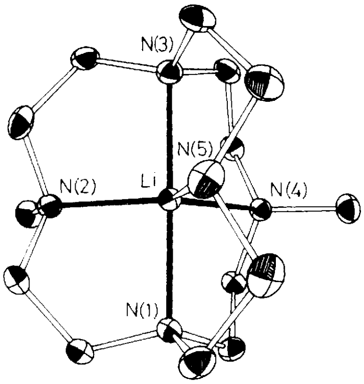

Figure 1. The ORTEP drawing of the cation [LiL]$^+$, showing the atom numbering scheme. Bond lengths: Li–N(1) 2.008(13), Li–N(2) 2.083(12), Li–N(3) 2.037(13), Li–N(4) 2.056(11), Li–N(5) 2.015(11) Å. Bond angles: N(1)–Li–N(3) 177.9(6), N(2)–Li–N(4) 120.7(5), N(2)–Li–N(5) 122.2(5), N(1)–Li–N(2) 90.0, N(1)–Li–N(4) 91.1(5), N(3)–Li–N(2) 90.5(5), N(3)–Li–N(5) 89.5(5), N(1)–Li–N(5) 88.5(5), N(4)–Li–N(5) 117.1(5), N(3)–Li–N(4) 90.5(5).

solid complex‡ confirms the ability of the cage (**L**) to 'swallow' lithium. Furthermore, lithium encapsulation is not influenced by the presence of a Na$^+$ ion, even in high concentrations, showing that (**L**) is able to fully discriminate between lithium and sodium ions. Potentiometric experiments carried out with differing amounts of Na$^+$ present and ^{23}Na NMR spectroscopic studies confirm this discrimination.

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

The *X*-ray crystal structure of the [LiL]$^+$ cation is shown in Figure 1, together with selected bond parameters. The Li atom is fitted inside the macrocyclic cavity, adopting a regular bipyramidal geometry. The Li–N distances are in the range 2.00—2.08 Å, much shorter than those found either in Li$^+$ (211) cryptate[6] (2.29 Å) or in other lithium–azamacrocyclic complexes[2,3] (2.11—2.45 Å), indicating that the cage (**L**) is well tailored to encapsulate the small Li$^+$ cation. The good match between the cation radius and the cavity hole produces a stable, strain-free complex.

In conclusion, different properties of the [LiL]$^+$ complex, such as high stability in aqueous solution, the highly deshielded ^{7}Li resonance, not influenced by the solvent, and the short Li–N bond distances in the solid complex, all indicate that the cage (**L**) is able to form selectively stable Li$^+$ complexes.

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‡ *Crystal data* for $C_{14}H_{31}ClLiN_5O_4$: colourless crystals, $M = 375.81$, monoclinic space group $P2_1/n$, $a = 15.046(11)$, $b = 8.893(4)$, $c = 15.305(8)$ Å, $\beta = 113.58(4)°$, $U = 1877(32)$ Å^3, $Z = 4$, $F(000) = 807.81$, $\mu = 1.79$ cm^{-1}, $D_c = 1.33$ g cm^{-3}, graphite monochromated Mo-K_α radiation ($\lambda = 0.7107$ Å). 3663 Reflections were collected on an Enraf-Nonius CAD4 automatic diffractometer in the range $5 \leqslant 2\theta \leqslant 50°$. 1385 Unique reflections with $I > 3\sigma(I)$ were used in the structure determination and refinement. The structure was solved by using direct methods and successive Fourier syntheses and refined to $R = 0.065$ and $R_w = 0.049$. Anisotropic thermal parameters were used for all the non hydrogen atoms. The hydrogen atoms linked to the carbon atoms were introduced in calculated positions. A delta-F map, calculated in the final stage of the refinement, showed unambiguously the presence of a hydrogen atom linked to N(5) atom. Thermal parameters of 0.05 were assigned to all the hydrogen atoms. 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.