Aza-macrocycles bearing lipophilic functions. Their synthesis and selective lithium complexation

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The synthesis of the novel macrobicyclic ligands 4[4,9]-dimethyl-4[1,4,7,9]-tetraaza-1(1,4)-benzena-4(1,7)-cyclododecanacyclohexaphane (L2) and 5-dodecyl-12,17-dimethyl-1,5,9,12,17-pentaazabicyclo[7.5.5]nonadecane (L3) is reported. The protonation constants of L2, together with those of the macrobicycles L4 and L5, have been potentiometrically determined both in water and in water–DMSO mixture (80:20, v/v, NaCl 0.15 mol dm^{-3}, 298.1 K). Coordination of Li^+ by these macrobicycles has been studied by means of ^{13}C and ^7Li NMR techniques. All ligands bind Li^+ in aqueous solution, while the other alkali metal ions are not complexed. Lithium complexation is achieved through the encapsulation of the metal ion into the cavity of the macrobicycle. The remarkable selectivity is due to the small dimension of the macrobicyclic cavity, in which only Li^+ can be lodged. The stability constants of the lithium complexes have been determined in water and in water–DMSO mixture (80:20, v/v, NaCl 0.15 mol dm^{-3}, 298.1 K) by means of potentiometric measurements.

The selective binding of alkali and alkaline earth cations by macrocyclic receptors has received much attention in the past few years.[1] These ligands may contain central hydrophilic cavities ringed with electronegative binding atoms and exterior frameworks exhibiting hydrophobic behaviour. The hydrophobic exteriors may allow them to solubilize metal ions in nonaqueous solvents or in membrane media, resulting in their potential use as models for carrier molecules in the study of active ion transport phenomena in biological systems.[2] Among alkali metals, there has been much interest in lithium and lithium ionophores,[3] due to their actual and potential application in medicine and technology.[4] Since polyethereal oxygens are hard bases that interact strongly with Li^+, several polyethereal macrocycles have been synthesized for lithium binding.[1-3,5-7] As a different approach Li^+ coordination can be obtained by using macropolycyclic polyamine receptors with small cavities where the metal ion can be encapsulated.[8,9]

Earlier, we have found that small aza-cages (Fig. 1), such as **L1**, can strongly coordinate Li^+ in aqueous solution; in the resulting complexes the metal ion is deeply embedded into the macrocyclic cavity, as shown by the crystal structure of the $[L1Li]^+$ cation[8] (Fig. 2).

Aiming to elucidate the coordination properties of Li^+ and to design better ionophores for it, we have now synthesized the two macrobicyclic ligands **L2** and **L3**. Both of them contain a three-dimensional cavity in which the metal ion can be encapsulated and hydrophobic moieties which may allow the resulting complexes to be solubilized in apolar solvents. In this paper we report on their synthesis, basicity and coordination properties towards Li^+. The protonation behaviour and Li^+ complexation by the two ligand **L4** and **L5**, which show structural features similar to **L2** and **L3**, have been also studied.

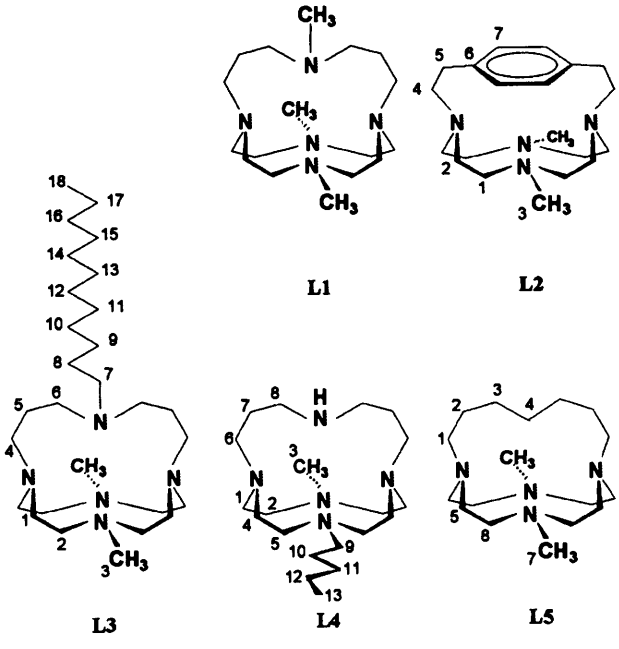


Fig. 1 Ligands with (non-systematic) numbering employed in ^{13}C NMR assignments

Results and discussion

Synthesis

Both **L2** and **L3** have been synthesized by using the macrocycle 1,7-dimethyl-1,4,7,10-tetraazacyclododecane **1**[10] as a precursor. The synthetic pathway for **L3** is depicted in Scheme 1. Reaction of dodecylamine with acrylonitrile gives the dinitrile **4**, which affords, after hydrolysis with gaseous HCl, the corresponding dicarboxylic acid **5** in almost quantitative yield. The critical cyclization step, reaction of **1** with acid chloride **6**, is carried out by using a high dilution procedure and affords, after purification by chromatography, the diamide **7** in rather good yield. Reduction of **7** to the polyamine **L3** is carried out with diborane.

L2 is obtained by using a similar procedure. Reaction of **1** with 1,4-phenylenediacetyl chloride **2** gives the diamide **3** analogous to **7**, which is reduced to the corresponding amine **L2**.

Synthesis of the lithium complexes is carried out by reaction of an excess of LiOH with the ligand in methanol at room

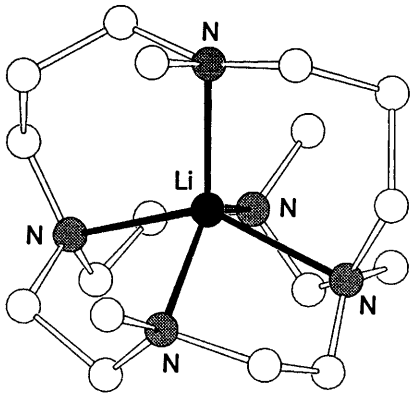
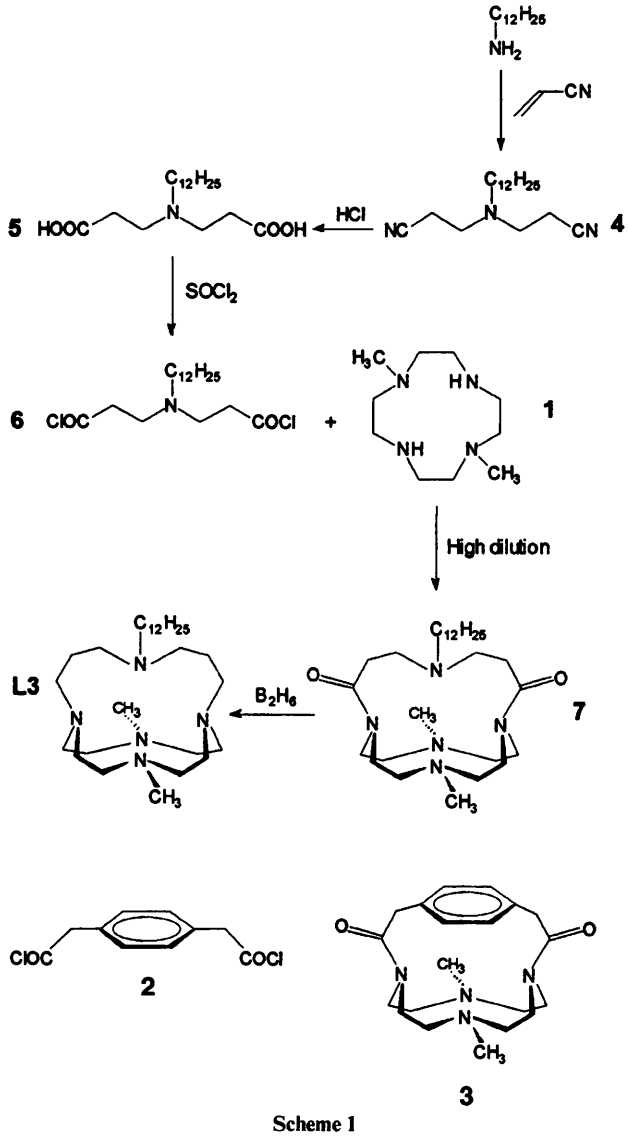


Fig. 2 ORTEP[17] drawing of the [LiL1]$^+$ cation



Scheme 1

temperature. After removal of the methanol and solubilization in aqueous alkaline solution, the complexes can be easily isolated from the reaction mixture by extraction with chloroform. It is to be noted that the Li^+ complexes of all the ligands under investigation can be readily extracted from aqueous solutions in $CHCl_3$ or CH_2Cl_2 and show a good solubility in these solvents (*ca.* 0.1 mol dm^{-3}). Particularly, the [LiL3]Cl complex is also soluble in benzene at room temperature (*ca.* 0.05 mol dm^{-3}).

Protonation

The protonation equilibria of **L1**, **L2**, **L4** and **L5** have been studied both in aqueous and in dimethyl sulfoxide (DMSO)–H_2O (80:20, v/v) solutions (0.15 mol dm^{-3} NaCl ionic medium) at 298.1 ± 0.1 K by means of potentiometric pH measurements and the results are reported in Table 1. The low solubility of **L3** in both media does not allow the determination of its basicity constants. Considering the proton transfer behaviour in aqueous solution, all ligands show similar features, exhibiting a high basicity in the first protonation step, and a moderate basicity in the second step. The third protonation process takes place at very low pH values and, in the case of **L5**, is undetectable in the pH range studied (2.5–11).

Table 1 Protonation constants (log *K*) of the ligands **L1**, **L2**, **L4** and **L5** potentiometrically determined in aqueous solution (0.15 mol dm^{-3} NaCl) and in DMSO–H_2O (v/v) at 298.1 K

	Aqueous solution			
Reaction	**L1**	**L2**	**L4**	**L5**
L + H = LH	11.83[a]	—[b]	11.22(2)[c]	12.0[d]
LH + H = LH_2	9.53	—	9.00(2)	7.86
LH_2 + H = LH_3	3.43	—	3.6(1)	
	DMSO–H_2O 80:20 (v/v)			
L + H = LH	15.0(1)	13.9(1)	15.4(1)	<13
LH + H = LH_2	4.1(1)	5.2(1)	4.2(1)	4.1
LH_2 + H = LH_3		1.7(1)		

[a] From ref. 8. [b] The low solubility of the product in aqueous solution does not allow the determination of the basicity constants. [c] Values in parentheses are the standard deviations on the last significant figure. [d] From ref. 13.

Indeed the value of the first protonation constant is unusually high for compounds having only tertiary amino groups, as in **L1** and **L5**, or just one secondary amine function, as in **L4**. Considering **L1** and **L5** there is a significant increase in proton affinity in the first protonation step with respect to the monocycle 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane (log K_1 = 9.7),[11] where only tertiary nitrogens are present. Both **L4** and **L5** are even more basic than the tetraazamacrocycle 1,7-dimethyl-1,4,7,10-tetraazacyclododecane (log K_1 = 10.7),[10] where secondary and tertiary nitrogen atoms are present. These features indicate that the hydrogen ion interacts very strongly with the nitrogen atoms to form the monoprotonated species, suggesting that in the $[HL]^+$ (L = **L1**, **L4** and **L5**) cation the acidic proton is bound inside the macrocyclic cavity, stabilized by a hydrogen bond network. This hypothesis is confirmed by the crystal structure of the $[HL1]^+$ cation,[8] which shows the acidic proton encapsulated into the cavity, giving rising to a hydrogen bond network which involves three nitrogen donors. Furthermore, the ^1H NMR spectra of both [HL4]Br and [HL5]ClO_4 in $CDCl_3$ exhibit a broad signal at 10.2 and 10.8 ppm, respectively, each integrating for one proton and attributable to one encapsulated, deshielded hydrogen-bonded N–H^+ proton. The signal disappears upon adding water, due to excessive linewidth, indicating a fast proton exchange on the NMR time scale.

In order to analyse solvation effects on the basicity of these ligands, their protonation constants (K_n)† have been determined in water–DMSO (80:20, v/v) mixed solvent (see Table 1). Furthermore, this solvent allows the constants for **L2** to be determined. It is to be noted that, for all ligands, the first basicity constant (K_1) in this medium is markedly higher than that found in aqueous solution, while the second one (K_2) is lower in water–DMSO mixture than in water. This effect can be attributed to the lower relative permittivity of the water–DMSO solution with respect to aqueous solution. Particularly, the increase of K_1 in water–DMSO is related to the lower solvation of the proton, which is more available to be bound to the amine groups of the ligand, while the decrease of K_2 is due to the

† $K_n = [LH_n^{n+}]/[LH_{(n-1)}^{(n-1)+}][H^+]$.

higher repulsion between positive charges experienced by the two N–H$^+$ groups in the medium with lower relative permittivity.

Lithium complexation

The coordination of alkali metal ions by the ligands **L2**, **L3**, **L4** and **L5** has been studied in aqueous solution by means of ^{1}H, ^{13}C and ^{7}Li NMR techniques. With ^{13}C and ^{1}H NMR spectroscopy as a diagnostic technique, no evidence is found for the complex formation with Na^+ or K^+. With Li^+, solid complexes were isolated and characterized. The Li^+ ion is readily coordinated by all the four ligands, and the equilibrium (1) has been

$$Li^+ + L \rightleftharpoons [LiL]^+ \qquad (1)$$

investigated by potentiometry and ^{1}H, ^{13}C and ^{7}Li NMR techniques.

Li^+ coordination is clearly shown by ^{13}C and ^{7}Li NMR spectra of solutions containing ligands **L2**–**L5** and Li^+ in alkaline aqueous solutions (0.2 mol dm^{-3} NMe_4OH). In the case of **L5**, the ^{7}Li NMR spectrum recorded on a solution containing an excess of Li^+ shows three sharp peaks, one for free lithium and two shifted by 2.12 and 2.57 ppm with respect to solvated lithium (Fig. 3). These latter are attributable to a complexed Li^+ ion, slowly exchanging with free Li^+ on the NMR time scale. The two peaks for complexed lithium are likely due to the presence in solution of two conformers for the [Li**L5**]$^+$ complex, herein denoted as **A** and **B**. Integration of the two ^{7}Li signals allows one to calculate the percentages of the two conformers (**A**: 66%, **B**: 34%).

Similar spectral features are found by recording spectra on aqueous solutions at high pH containing the preformed [Li**L5**]ClO_4 complex. Furthermore, ^{7}Li spectra of the [Li**L5**]ClO_4 complex in different solvents, such as MeOD or CD_3CN, show that the chemical shift of the complexed Li^+ is essentially independent of the solvent.

The independence of the ^{7}Li shift on the solvent and the slow exchange on the NMR time scale between free and complexed lithium indicate that the metal ion is encapsulated into the macrobicyclic cavity and thus isolated from the medium.

Further information can be obtained by comparing the ^{13}C NMR spectrum of the ligand with the spectrum of the [Li**L5**]$^+$ complex. The ^{13}C NMR spectrum of **L5** in D_2O at room temperature consists of seven signals [Fig. 4(*a*)], typical of a time-averaged C_{2v} symmetry of the ligand. On the other hand, the spectrum of the complex is composed of two subspectra, which can be attributed to the presence of the two conformers **A** and **B** [Fig. 4(*b*)], slowing interchanging on the NMR time scale. Although the signals of C-2, -3 and -4 cannot be confidently attributed, the subspectrum of the **A** conformer exhibits five signals for methylene carbons adjacent to the nitrogen donors (1A, 5A and 6A) and two sharp resonances at 39.3 and 39.8 ppm for the methyl groups (7A), each integrating to one carbon atom. This spectrum is typical of a C_s time-averaged symmetry for the complex **A**, with the lithium atom and the methylated nitrogens lying in the symmetry plane.

The subspectrum of the **B** conformer exhibits three resonances for the carbon atoms 1B, 5B and 6B and only one signal for the methyl groups at 41.6 ppm (7B), indicating a C_{2v} time-averaged symmetry.

Similar spectral features have been found for macrocycles **L2**, **L3** and **L4**. Considering **L2**, both ^{7}Li (Fig. 5) and ^{13}C NMR spectra (Fig. 6) of the [Li**L2**]$^+$ complex in D_2O solution at alkaline pH show the presence of two conformers in solution. The conformer **A** (20%, calculated from integration of the ^{7}Li spectrum) exhibits a C_s symmetry, with Li^+ and the N–CH_3 groups lying in the symmetry plane, while the **B** conformer (80%) shows a C_{2v} time-averaged symmetry [Fig. 6(*b*)].

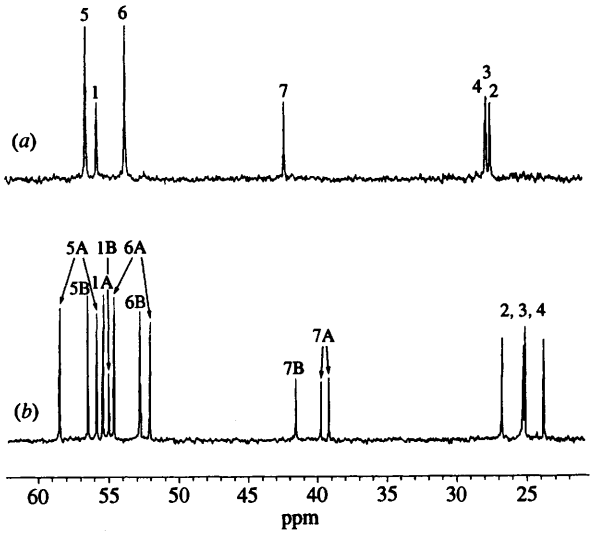


Fig. 4 ^{13}C NMR spectra of (*a*) and (*b*) [Li**L5**]$^+$ in D_2O solution at alkaline pH. Labels **A** and **B** refer to the two different conformers of the complex.

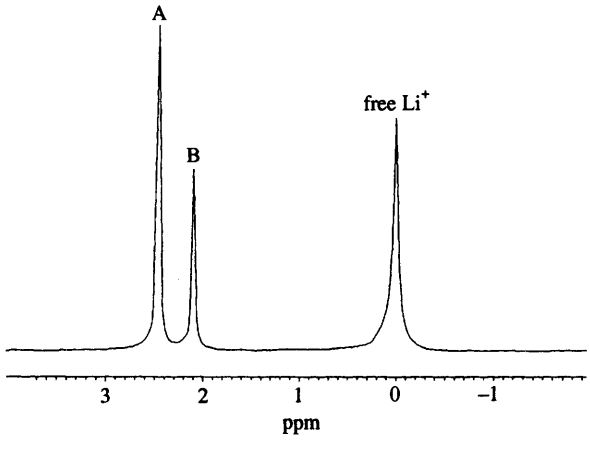


Fig. 3 ^{7}Li NMR spectrum of a D_2O solution containing **L5** in the presence of an excess of Li^+

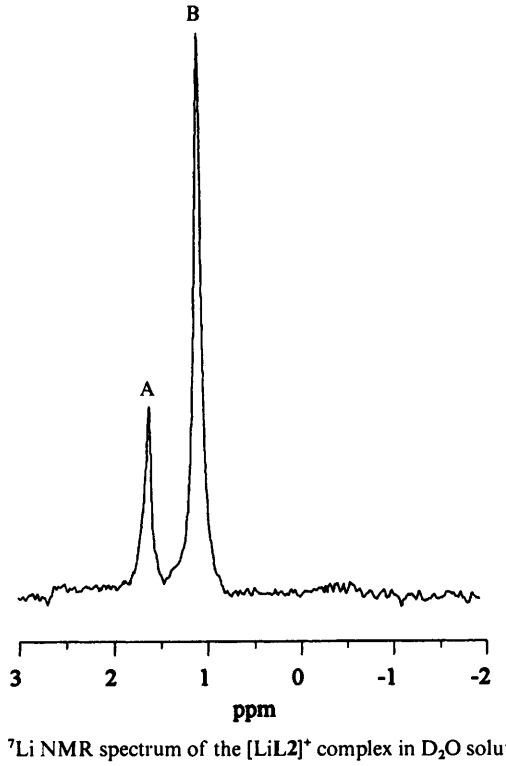


Fig. 5 ^{7}Li NMR spectrum of the [Li**L2**]$^+$ complex in D_2O solution

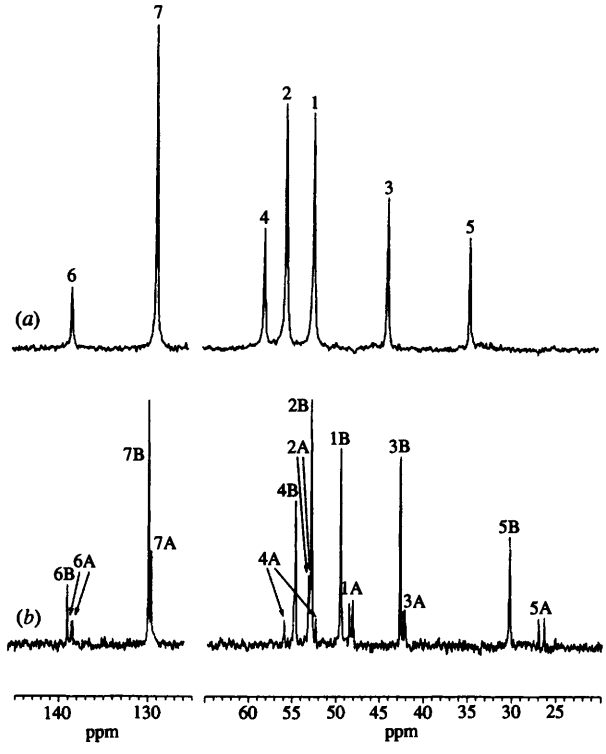


Fig. 6 ^{13}C NMR spectra of (*a*) **L2** and (*b*) $[LiL2]^+$ in D_2O solution at alkaline pH. Labels **A** and **B** refer to the two different conformers of the complex.

Table 2 ^7Li NMR chemical shifts (ppm) for the lithium complexes of the macrobicycles **L1–L5** in D_2O solution

L1	**L2**	**L3**	**L4**	**L5**
0.88[a,b]	1.25, 1.70[c]	0.97[b]	0.98, 1.02[c]	2.12, 2.57[c]

[a] From ref. 8. [b] For the $[LiL1]^+$ complexes only one peak is observed in ^7Li NMR spectra, due to the presence of only one conformer in solution. [c] Two peaks observed in ^7Li NMR spectra, due to the presence of two conformers in solution.

For all the ligands **L2–L5**, the ^7Li chemical shift of complexed Li^+ (Table 2) is independent of the solvent used. In the presence of an excess of Li^+ the spectra show sharp peaks, due to complexed and solvated Li^+ slowly exchanging on the NMR time scale. These results indicate that in the $[LiL]^+$ complexes (**L** = **L2**, **L3**, **L4** and **L5**) the metal ion is deeply embedded in the macrocyclic cavity.

It is noteworthy that these spectral features do not change even in the presence of Na^+ in large excess. In other words, lithium complexation is not influenced by the presence of Na^+ ion, even in high concentration, indicating that the ligands **L2–L5** are able to discriminate completely between Li^+ and Na^+. Such a selectivity is related to the small dimension of the macrobicyclic cavity, in which the larger Na^+ cannot be encapsulated.

The equilibrium (1) has also been studied by means of potentiometric pH measurements. In order to analyse the solvation effects on the process of Li^+ complexation, the stability constants of the $[LiL]^+$ complexes (see Table 3) have been determined both in aqueous and in DMSO–H_2O (80:20, v/v) solutions (0.15 mol dm^{-3} NaCl ionic medium, 298.1 ± 0.1 K). Due to the low solubility of **L3** in both media, the stability constant of its Li^+ complex cannot be determined.

All ligands show a good ability to encapsulate the Li^+ in aqueous solution. For **L1** and **L4** the equilibrium constants for reaction (1) are greater than 1000 (log K = 3.2 and 3.5, respectively), while a somewhat lower affinity for Li^+ is shown by **L5** (log K = 2.6).

Table 3 Stability constants (log K) of the Li^+ complexes with the ligands **L1**, **L2**, **L4** and **L5** potentiometrically determined in aqueous solution (0.15 mol dm^{-3} NaCl) and in DMSO–H_2O 80:20 (v/v) at 298.1 K

	Aqueous solution			
Reaction	**L1**	**L2**	**L4**	**L5**
$L + Li^+ = [LiL]^+$	3.2[a]	—[b]	3.5(1)[c]	2.6(1)
	DMSO–H_2O 80:20 (v/v)			
$L + Li^+ = [LiL]^+$	5.0(1)	3.6(1)	5.2(1)	—[b]

[a] From ref. 8. [b] The low solubility of the free amine does not allow the determination of the stability constant. [c] Values in parentheses are standard deviations on the last significant figure.

The stability constants of the lithium complexes are markedly higher in the less polar DMSO–H_2O (80:20, v/v) solvent, indicating that solvation effects strongly affect the process of Li^+ coordination. This result is in good accord with the insertion of the metal ion into the small hydrophobic cavity that requires removal of all the solvent molecules surrounding the free lithium ion. Such a process is more favoured in the solvent with lower polarity, in which the free metal ion is less solvated.

As for **L5** in water solution, in the DMSO–H_2O mixture **L2** forms a less stable complex than **L1** and **L4**. The crystal structure of $[LiL1]^+$ (Fig. 2) shows that the five nitrogen atoms are in the *endo* conformation and the metal ion is bound to all nitrogens.[8] A similar coordination environment can also be proposed for the Li^+ complex of **L4**, which includes five nitrogen donors within the macrocyclic framework. The lower stability of the **L2** and **L5** lithium complexes can be attributed to the presence of only four amine groups available for metal coordination. These results point out that, besides solvation effects, the number of nitrogen donors involved in the coordination also plays an important role in determining the stability of these complexes.

Conclusion

The molecular topology of the polyamines **L2–L5** is characterized by the presence of both three-dimensional cavities and hydrophobic moieties. All ligands form stable complexes with Li^+ in aqueous solution. Lithium complexation is achieved through the encapsulation of the metal ion into the cavity of these macrobicycles. All ligands examined do not coordinate other alkali metal ions. Such a remarkable selectivity is due to the small dimension of the macrobicyclic cavity, in which alkali metals larger than Li^+ cannot be encapsulated. Aliphatic chains as side arms (**L3** and **L4**) or aromatic moieties within the macrocyclic framework (**L2**) give lipophilic exteriors and allow the lithium complexes to be easily solubilized in nonaqueous solvents and extracted from aqueous solution. These features make these ligands promising Li^+ ionophores.

Experimental

Synthesis

Compounds **L4** and **L5** were synthesized as previously described.[12,13] The macrocycle **L3** was obtained following the synthetic procedure depicted in Scheme 1. Both **L2** and **L3** were prepared by using the macrocycle 1,7-dimethyl-1,4,7,10-tetraazacyclododecane **1**[10] as a precursor. Dodecylamine and 1,4-phenylenediacetic acid purchased from Aldrich Chemical Co.

1,4-Phenylenediacetyl chloride 2

1,4-Phenylenediacetic acid (2 g, 0.01 mol) was treated with thionyl chloride (24 g, 0.2 mol) at 50 °C for 20 h. The unchanged $SOCl_2$ was removed under reduced pressure, and the resulting yellowish solid was used without further purification.

$4^{4,9}$-Dimethyl-$4^{1,4,7,9}$-tetraaza-1(1,4)-benzena-4(1,7)-cyclododecanacyclohexaphane-3,5-dione 3

A sample of **1** (2 g, 0.01 mol) in 500 cm^3 of dry benzene and **2** (2 g, 0.01 mol) in 500 cm^3 of dry benzene containing triethylamine were added simultaneously to 500 cm^3 of dry benzene, with mechanical stirring over a period of 7 h at room temperature. The reaction mixture was filtered and evaporated to dryness to give a yellowish oil, which was dissolved in the minimum quantity of chloroform and chromatographed on neutral alumina (70–230 mesh, activity I), eluting with chloroform. The eluted fractions were collected and evaporated to dryness to obtain a colourless solid, yield 0.9 g (25%), mp 118–120 °C (Found: C, 66.6; H, 8.6; N 15.5. Calc. for $C_{20}H_{30}N_4O_2$: C, 67.01; H, 8.44; N, 15.63%).

$4^{4,9}$-Dimethyl-$4^{1,4,7,9}$-tetraaza-1(1,4)-benzena-4(2,7)-cyclododecanacyclohexaphane diperchlorate (L2·2HClO$_4$)

The reduction of **3** was carried out with diborane in dry tetrahydrofuran (THF). Diborane (0.01 mol) in dry THF (25 cm^3) was added dropwise under an inert atmosphere to a cooled solution (20 cm^3) of dry THF containing **3** (0.9 g, 2.5 mmol) over a period of 30 min. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature and was then refluxed for 6 h. The resulting solution was cooled to 0 °C, and water (10 cm^3) was added. The white solid obtained was dissolved in HCl–H_2O–MeOH (2:6:20 cm^3) and refluxed for 4 h. The resulting solution was evaporated to dryness and then the residue was dissolved in 15 cm^3 of water. The resulting solution was made strongly alkaline by addition of tetramethylammonium hydroxide. This solution was extracted by addition of tetramethylammonium hydroxide. This solution was extracted with chloroform (5 × 20 cm^3), and the combined extracts were dried over sodium sulfate. The solvent was removed under reduced pressure to give a colourless solid. The diperchlorate salt **L2**·2HClO$_4$ was obtained by the addition of a slight excess of $HClO_4$ to an ethanolic solution containing the free ligand. The white crystalline product was recrystallized from water, yield 0.7 g (85%) (Found: C, 45.2; H, 6.7; N, 10.4. Calc. for $C_{20}H_{36}Cl_2N_4O_8$: C, 45.20; H, 6.84; N, 10.56%); MS *m/z* (FAB): 331 ([M + H]$^+$); ^{13}C NMR: δ($CDCl_3$) 34.4 (C-5), 43.8 (C-3), 52.2 (C-1), 55.4 (C-2), 57.9 (C-4), 128.6 (C-7), 138.3 (C-6).

***N*-Dodecyl-2,2′-iminodipropionitrile 4**

A sample of dodecylamine (3.7 g, 0.02 mol) was treated with acrylonitrile (80 g, 1.5 mol) and glacial acetic acid (2.5 g, 0.042 mol). The resulting suspension was refluxed for 15 h and then evaporated to dryness and the residue was dissolved in chloroform (50 cm^3). The resulting solution was washed with aqueous NH_3 (0.1 mol dm^{-3}), then with water and dried over Na_2SO_4. The solution was chromatographed on neutral alumina (70–230 mesh, activity I), eluting with chloroform. The eluted fractions were collected and evaporated to dryness to obtain a colourless oil which was dissolved in ethanol (20 cm^3). By addition of water (100 cm^3) a white solid crystallized, yield 5.4 g (95%), mp 36–38 °C (Found: C, 74.3; H, 11.7; N, 14.4. Calc. for $C_{18}H_{33}N_3$: C, 74.17; H, 11.41; N, 14.42%).

***N*-Dodecyl-2,2′-iminodipropionic acid 5**

Gaseous HCl was bubbled through a refluxing solution of **4** (5.4 g, 0.019 mol) and water (2.5 g cm^3) in 1,2-dichloroethane (150 cm^3) for 15 h. The solution was then evaporated to dryness to give a yellowish solid which was dissolved in aqueous NaOH (0.1 mol dm^{-3}) (100 cm^3). Hydrochloric acid (0.1 mol dm^{-3}) was added dropwise until complete precipitation of a white solid, which was filtered off and recrystallized from acetone, yield 3.5 g (56%), mp 108–109 °C (Found: C, 65.5; H, 10.8; N, 4.2. Calc. for $C_{18}H_{35}NO_4$: C, 65.61; H, 10.71; N, 4.25%).

***N*-Dodecyl-2,2′-iminodipropionyl chloride 6**

A sample of **5** (3.3 g, 0.01 mol) was treated with thionyl chloride (24 g, 0.2 mol) at 30 °C for 20 h. The unchanged $SOCl_2$ was removed under reduced pressure, and the resulting yellowish solid was used without further purification.

5-Dodecyl-12,17-dimethyl-4,18-dioxo-1,5,9,12,17-pentaazabicyclo[7.5.5]nonadecane-2,7-dione 7

A sample of **1** (2 g, 0.01 mol) in 500 cm^3 of dry benzene and **6** (3.5 g, 0.01 mol) in 500 cm^3 of dry benzene containing triethylamine were added simultaneously to 500 cm^3 of dry benzene, with mechanical stirring over a period of 7 h at room temperature. The reaction mixture was filtered and evaporated to dryness to give a yellowish oil, which was dissolved in the minimum quantity of CH_2Cl_2 and chromatographed on neutral alumina (70–230 mesh, activity I), eluting with CH_2Cl_2. The eluted fractions were collected and evaporated to dryness to obtain a colourless oil, which was used without further purification, yield 1.5 g (30%) (Found: C, 68.9; H, 11.1; N, 14.1. Calc. for $C_{28}H_{55}N_5O_2$: C, 68.11; H, 11.23; N, 14.18%).

5-Dodecyl-12,17-dimethyl-1,5,9,12,17-pentaazabicyclo[7.5.5.]nonadecane trihydrochloride L3·3HCl

Diborane (0.012 mol) in dry THF (30 cm^3) was added dropwise under an inert atmosphere to a cooled solution (20 cm^3) of dry THF containing **3** (1.5 g, 3 mmol) over a period of 30 min. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature and was then refluxed for 6 h. The resulting solution was cooled to 0 °C, and water (5 cm^3) was added. The white solid obtained was dissolved in HCl–H_2O–MeOH (2:6:20 cm^3) and refluxed for 4 h. The resulting solution was evaporated to dryness and then the residue was dissolved in 100 cm^3 of water. The resulting suspension was filtered and the solution was made strongly alkaline by addition of sodium hydroxide. This solution was extracted with chloroform (5 × 20 cm^3), and the combined extracts were dried over sodium sulfate. The solvent was removed under reduced pressure to give a colourless oil, which was dissolved in ethanol. Addition of 70% $HClO_4$ gave the perchlorate salt as a waxy solid, which was recrystallized from water (1 dm^3). The white solid was then suspended in water (50 cm^3) and 0.1 mol dm^{-3} aqueous NaOH (50 cm^3) was added. The resulting suspension was stirred for 4 h and then extracted with $CHCl_3$ (50 × 20 cm^3). The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The trihydrochloride salt **L3**·3HCl·4H_2O was obtained by the addition of 37% HCl to an acetone solution containing the free amine. The product was recrystallized from methanol–acetone, yield 0.7 g (36%) (Found: C, 51.6; H, 10.9; N, 10.7. Calc. for $C_{28}H_{70}Cl_3N_5O_4$: C, 51.95; H, 10.90; N, 10.82%), MS *m/z* (FAB): 466 ([M + H]$^+$); ^{13}C NMR: δ($CDCl_3$)‡ 14.3 (C-18), 23.3, 23.7, 27.3, 29.7, 29.9, 30.0, 30.2, 30.8, 31, 32.5 (C-8–C-17 methylene groups of the dodecyl chain), 30.5 (C-5), 41.7 (C-3), 51.4 (C-2), 51.6 (C-6), 52.4 (C-4), 53.9 (C-1), 58.3 (C-7).

Preparation of the complexes

[LiL2]ClO$_4$ 8. A solution of LiOH (5 mg, 0.22 mmol) and $NaClO_4$·H_2O (70 mg, 0.5 mmol) in methanol (5 cm^3) was added to a solution of **L2** (14 mg, 0.04 mmol) in methanol (5 cm^3). The reaction mixture was stirred for 15 min and then evaporated to dryness. The white powder was dissolved in 0.1 mol dm^{-3} aqueous NaOH (5 cm^3) and the resulting solution was extracted with $CHCl_3$ (10 cm^3). The organic layer was separated and dried over Na_2SO_4. On addition of cyclohexane (20 cm^3) a white precipitate separated, yield 12 mg (69%) (Found: C, 54.6; H, 7.9; N, 12.7. Calc. for $C_{20}H_{34}LiClN_4O_4$: C, 54.98; H, 7.84; N, 12.82%), MS *m/z* (FAB): 338 ([Li**L2**]$^+$); ^{13}C NMR; δ($CDCl_3$):‡ A conformer: 26.5, 27.1 (C-5), 42.3, 42.4 (C-3), 48.3, 48.7 (C-1),

‡ The non-systematic numbering shown in Fig. 3 is used for the NMR assignments.

52.5, 56.1 (C-4), 53.2, 53.4, (C-2) 128.8 (C-7), 137.7, 137.8 (C-6); **B** conformer: 30.4 (C-5), 42.8 (C-3), 49.7 (C-1), 53.1 (C-2), 54.9 (C-4), 129.1 (C-7), 138.3 (C-6).

[LiL3]Cl 9. A solution of LiOH (10 mg, 0.44 mmol) in methanol (5 cm^3) was added to a solution of **L3**·3HCl (23 mg, 0.04 mmol) in methanol (10 cm^3). The reaction mixture was stirred for 6 h and then evaporated to dryness. The white product was dissolved in 0.1 mol dm^{-3} aqueous NaOH (5 cm^3) and the resulting suspension was extracted with $CHCl_3$ (10 cm^3). The organic layer was separated and dried over Na_2SO_4. The solution was concentrated and, on addition of light petroleum (20 cm^3), a white precipitate separated, yield 16 mg (76%) (Found: C, 66.0; H, 11.6; N, 13.6. Calc. for $C_{28}H_{59}LiClN_5$: C, 66.18; H, 11.70; N, 13.78%), MS *m/z* (FAB): 472 ([Li**L3**]$^+$); ^{13}C NMR: $\delta(CDCl_3)$‡ 14.3 (C-18), 23.3, 23.6, 27.3, 29.7, 29.5, 30.0, 30.2, 30.4, 30.7, 31.1 (C-8–C-17 methylene groups of the dodecyl chain), 31.5 (C-5), 43.1 (C-3), 49.6 (C-2), 52.4 (C-6), 53.0 (C-4), 54.8 (C-1), 58.7 (C-7).

[LiL4]ClO_4·H_2O 10. This compound was synthesized from **L4** (14 mg, 0.04 mmol) following the procedure reported for **8**, giving **10** as a white solid, yield 17 mg (86%) (Found: C, 50.1; H, 9.4; N, 14.5. Calc. for $C_{20}H_{45}LiClN_5O_5$: C, 50.28; H, 9.50; N, 14.67%); MS *m/z* (FAB): 360 ([Li**L4**]$^+$); ^{13}C NMR: $\delta(CDCl_3)$:‡ 13.3 (C-13), 2.22 (C-12), 27.1 (C-7), 27.3 (C-10), 29.4 (C-11), 40.1, 42.8 (C-3), 50.1, 50.8 (C -2), 51.0, 51.2 (C-5), 52.2, 52.3, 52.4, 52.5, 52.7, 53.2 (C-1, C-4, C-6), 54.2, 56.8 (C-8), 58.1, 58.5 (C-9).

[LiL5]ClO_4 11. This compound was synthesized from **L5** (12 mg, 0.04 mmol) following the procedure reported for **8**, giving **11** as a white solid, yield 13 mg (81%) (Found: C, 51.0; H, 9.0; N, 14.0. Calc. for $C_{17}H_{36}LiClN_4O_4$: C, 50.71; H, 9.02; N, 13.92%); MS *m/z* (FAB): 303 ([Li**L5**]$^+$); ^{13}C NMR: $\delta(CDCl_3)$‡ 23.9, 25.2, 25.3, 26.8 (C-2, C-3, C-4), 39.6, 39.8, 41.7 (C-7), 52.2, 52.9, 54.7 (C-6), 55.1, 55.5 (C-1), 55.9, 56.5, 58.6 (C-5).

NMR spectroscopy

200.0 MHz ^1H, 50.32 MHz ^{13}C and 77.78 MHz ^7Li NMR spectra were recorded in D_2O solution at 298 K on a Bruker AC-200 spectrometer. ^1H–^1H and ^1H–^{13}C 2D correlation experiments were performed to assign the signals. In ^1H NMR spectra peak positions are reported relative to HOD at 4.75 ppm. Dioxane was used as reference standard in ^{13}C NMR spectra (δ = 67.4 ppm). A 10^{-3} M solution of LiCl in D_2O was used as reference in ^7Li NMR spectra.

Potentiometric measurements

The protonation constants of the ligands and the stability constants of their lithium complexes were determined by pH-metric measurements (pH = $-\log[H^+]$) in aqueous and in DMSO–H_2O 80:20 (v/v) solutions at 298.1 K, by using the potentiometric equipment that has been already described.[14] In both cases 0.15 mol dm^{-3} NaCl was used as ionic medium. The reference electrode was an Ag/AgCl electrode in saturated KCl solution. The glass electrode was calibrated as a hydrogen concentration probe by titrating known amounts of HCl with CO_2-free NaOH solutions. The standard potential of the cell, E^0, and the ionic product of water were determined for both solvent systems (water and water–DMSO) by application of Gran's method.[15] At least three titration experiments were performed for each ligand. The computer program SUPERQUAD[16] was used to calculate the protonation constants and the stability constants from emf data.

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