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Cryptand ligands for selective lithium coordination

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Contents

Abstract

The binding properties, in aqueous solution, toward lithium ion of aza- and azaoxo-macrocycles with cage and cylindrical molecular topology are reviewed. The synthetic procedures and the acid–basic behavior are reported. Most of these compounds are able to selectively encapsulate the small lithium ion in aqueous solution. NMR spectroscopy, mainly ^{13}C and ^{7}Li, has been used to study the encapsulation equilibria. Few crystal structures of lithium complexes, indicating the lithium ion encapsulation have been reported.

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1. Introduction

There is at present a great interest in many chemical fields to design ligands for selective metal ions coordination, especially for ion size recognition, transport processes in biological systems, industrial and technological and other applications [1–18]. For this aim, macrocyclic compounds are a very attractive class of ligands and have received much attention recently. The development of new synthetic strategies has given the real possibility of merging theory and experiment in the design of chemical compounds with preordered properties.

Macrocyclic polyamines are versatile molecules that form well-defined complexes with a wide range of metal ions. The selectivity and stability of the metal complexes formed is due to many factors among which are, the number of nitrogen binding sites and their relative disposition, and the molecular framework with its preorganization binding sites. Among alkali metals, however, much interest has been dedicated to lithium and lithium ionophores. This growing interest in lithium is mainly derived from the actual and potential applications of Li^+ in science, medicine, and technology [19,20]. Lithium salts have been extensively, and successfully, used for the treatment of manic depression and other neurological and psychiatric disorders [19,21,22]. Lithium ions also exhibit antiviral activity against DNA type viruses [23]. However, the use of lithium salts as drugs is limited because of their side effects and toxicity. The mechanisms by which Li^+ is involved in biological systems are unknown. No natural molecules are known, and neither has any synthetic ionophore been prepared that would be selective enough to preferentially bind lithium ions in its physiological concentration. Furthermore, a facile lithium level determination in patients under treatment for manic depression through selective reactant would be very important. In fact, the elucidation of synthetic strategies and coordination properties of Li^+ should lead to both an improved understanding of its biological activity and to the design of better ligands to be used as ionophores.

2. Lithium properties

Although the alkali metals clearly show the effect of increasing size and mass on chemical and physical properties (i.e. melting points, lattice energies, heats of formation), lithium has some chemical behavior that parallels the chemistry of magnesium [24]. This results from the small size of the atom and ion and the large polarization power of the lithium ion, which leads to a greater tendency toward solvation as shown by its high hydration energy Table 1.

Lithium ion is usually tetrahedrally coordinated, whereas the heavier alkali ions have higher coordination numbers ($Na^+ = 6$ and $Cs^+ = 8$). The only time that more than four water molecules are contained in lithium hydrates is when additional hydration is contributed by the anion [24].

These particular properties have made the investigation of chelating reagents designed for lithium complexation very demanding, especially if complexation of

lithium ions is expected to occur in aqueous media. High selectivity of Li^+ over Na^+ could be anticipated only with ligands having small rigid cavities, which restrict complexation with Na^+ or other larger ions. To ensure strong interaction, which is a requisite for high sensitivity of the cromoionophore, the cavity should contain binding sites highly preorganized for Li^+ coordination.

Table 1
Cation diameters, radii, and hydration energy for hydrated cations

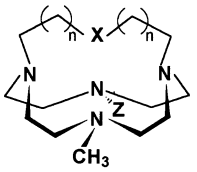
Cation	Diameter of ion (pm)	Radius of hydrated ion (pm)	Hydration energy (kJ mol^{-1})
Li^+	118[a]	340[b]	515[c]
Na^+	198[a]	276[b]	405[c]
K^+	274[a]	232[b]	321[c]

[a] Ref. [25].
[b] Ref. [26].
[c] Ref. [27].

3. Cryptands

The nature of donor atoms and the molecular topology are two of the most important parameters influencing the chemical properties of macrocyclic compounds. The aza-crown family, following the most studied crown-ether molecules, can be considered to be derived from the previous by replacing the oxygen donor atoms with softer nitrogen atoms. This has a relevant role in metal ion coordination. The presence of this kind of donor atom makes these compounds water soluble in a wide pH range and suitable to bind a wide variety of transition metal ions [28,29]. Since polyethereal oxygen atoms are hard bases that interact strongly with lithium ions, several polyethereal macrocycles have been synthesized as lithium binders [30–45]. A different approach to Li^+ coordination can be achieved by using macropolycyclic polyamine receptors having a small tridimensional cavity where the metal ion can be encapsulated.

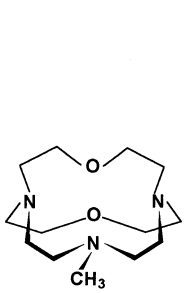
In this article, two classes of macrocyclic compounds, including some chromoionophoric ligands able to give a change of their optical properties with metal ion coordination, have been collected. These include small bicyclic cages formed by twelve-membered aza or oxa–aza macrocyclic units in which two *trans* nitrogen atoms are connected by a suitable bridge (Figs. 1, 5 and 6), and macrotricyclic ligands, with cylindrical topology, where two equal monocyclic units are connected through two appropriate bridges (Fig. 2) [46–51]. The chemistry of these compounds is very much influenced by three main characteristics: (i) size of the cavity; (ii) rigidity; and (iii) nature of the donor atoms. The size of the cavity is very small and only small ions can be encapsulated reaching a high degree of selectivity: most of these compounds are able to bind Li^+ strongly, but none shows an appreciable interaction with Na^+. Rigidity is the second important characteristic: the presence of short ethylenic chains on the twelve-member macrocyclic unit make this part of



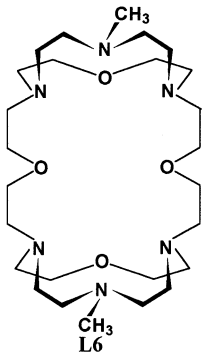
L1: X=C_6H_4, Z=CH_3, n=1
L2: X=N-$(CH_2)_{11}$-CH_3, Z=CH_3, n=2
L3: X=NH, Z=$(CH_2)_4$-CH_3, n=2
L4: X=N-CH_3, Z= CH_2-C_6H_5, n=1

Fig. 1. General drawing and abbreviations of the macrobicyclic cages. The apical group, the nitrogen substituent and the number of hydrocarbon atoms present in the bridging chains are given in parentheses.

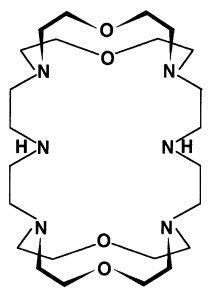
the molecule rather rigid. On the first class of compounds, the two methyl groups further contribute to the overall rigidity. Sometimes with the presence of the N or O donor atoms, extremely strong bases, stronger than OH^- in aqueous solution which have been termed: 'fast proton sponges' [52–55], were obtained.



L5



L6



L7

Fig. 2. Oxa–aza cages. Taken from Refs. [50,51].

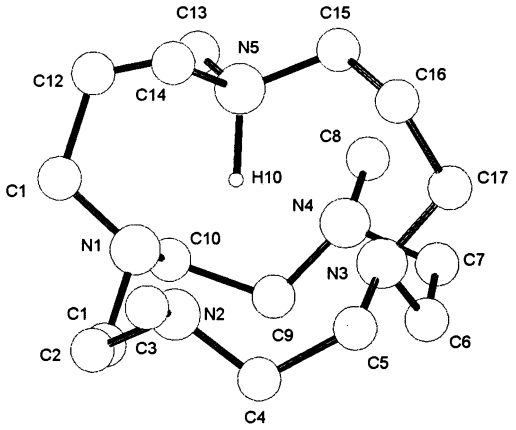


Fig. 3. Drawing of $[HL]^+$ cation of 5,12,17-trimethyl-1,5,9,12,17-pentaazabicyclo[7.5.5]nonadecane. Atomic coordinates taken from Ref. [60].

3.1. Synthetic procedure

All cages reported have been obtained by a non-template procedure. By reacting the twelve-member macrocyclic unit with the appropriate difunctionalized bridge it has been possible to obtain macrobicyclic and macrotricyclic ligands as reported in Scheme 1, derived by a $1+1$ or $2+2$ cyclization scheme, respectively.

The chromoionophoric ligands (Fig. 6) were synthesized essentially in two different ways: (i) attaching to a preformed cage periphery one chromophoric function sensible to the presence of the Li^+ into the cavity [53]; in this way the

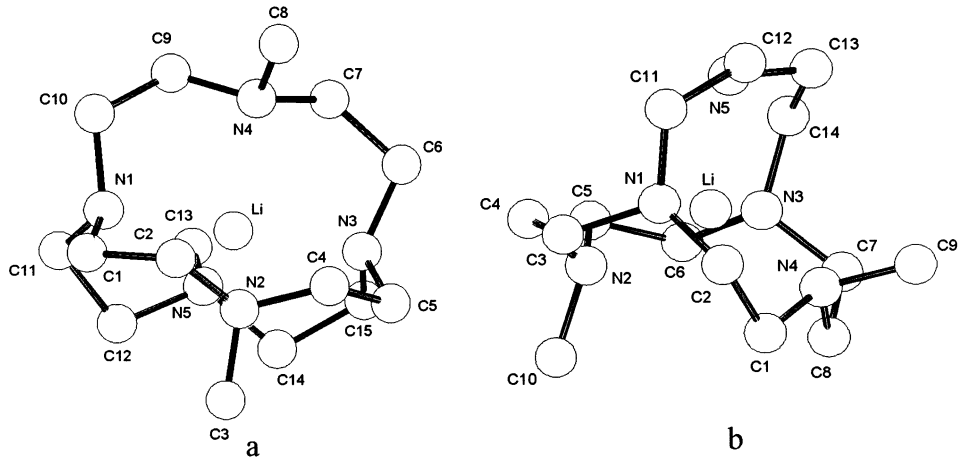
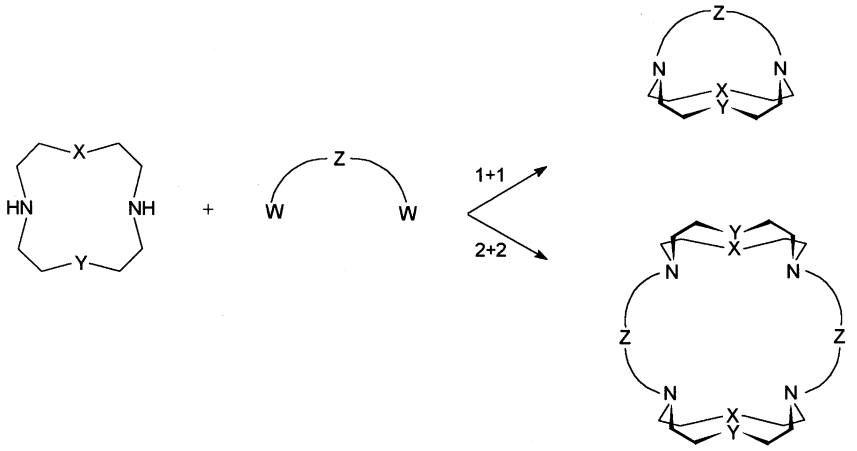


Fig. 4. Drawings of $[LiL]^+$ complexes, (a) L = 4,10,15-trimethyl-1,4,7,10,15-pentaazabicyclo[5.5.5]heptadecane, atomic coordinates taken from Ref. [69]. (b) L = 4,10-dimethyl-1,4,7,10,15-pentazabicyclo[5.5.5]heptadecane, atomic coordinates taken from Ref. [70].



Scheme 1. General reaction pathway for the synthesis of macrobicyclic and macrotricyclic cages.

overall molecular framework has not be altered because the binding characteristics are preserved; and (ii) introducing the chromogenic moiety in the skeleton of the macrocyclic system [56–58].

For **L1**–**L4** the precursor utilized is the twelve-member tetraazamacrocycle Me_2[12]aneN_4 synthesized by a well-established procedure [59]. In the cases reported here, using Me_2[12]aneN_4, only the $1+1$ cyclization products were observed. By substitution of one nitrogen with an oxygen atom, both the $1+1$ and $2+2$ addition products were indeed isolated (**L5** and **L6**, respectively) [50,51]. Moreover, only the oxa–aza macrotricyclic ligand **L7** was synthesized using a twelve-member macrocycle containing two oxygen atoms instead of two nitrogen atoms. Nevertheless, when the same N_2O_2 unit is used to synthesize the chromoionophores **L12**–**L15**, only the $1+1$ cyclization products were detected [56,58]. In conclusion, many factors concur in the cyclization reactions, they are influenced by reagents properties as the leaving groups, their stereochemistry, the reaction rate etc., and they must be analyzed step by step. Since all the syntheses were not-template, free, or at most, protonated macrocyclic cages were obtained.

3.2. Acid–basic behavior

All these cryptands are highly preorganized molecules and show unusual basicity and binding properties; moreover all of them have a tridimensional cavity in which the metal ion can be encapsulated and hydrophobic moieties which could make the complex soluble in apolar solvents. The acid–basic behavior is reported when possible in Table 2, as protonation constant values (log K), determined by potentiometric techniques in aqueous or in other solvent solution.

All these ligands exhibit high basicity in the first protonation step and the constant values for the first proton addition in aqueous solution are unusually high for compounds having only tertiary amino groups, as for example **L1** or **L4**, or just

Table 2
Potentiometrically determined protonation constants (log K) in aqueous solution and DMSO–H_2O 80:20 (v/v) at 25°C[a]

Reaction	Aqueous solution							
	L1	**L3**	**L4**	**L5**	**L6**	**L7**		**L10**
$H+L=HL$	–	11.22 (2)[a,b]	11.8 (1)[c]	11.46 (9)[d]	11.1 (1)[d]	10.09 (3)[e]	10.27 (3)[e]	–
$H+LH=LH_2$	–	9.00 (2)[b]	8.3 (1)[c]	5.40 (9)[d]	10.85 (9)[d]	9.27 (3)[e]	9.52 (3)[e]	–
$H+LH_2=LH_3$	–	3.6 (1)[b]	–	–	4.72 (9)[d]	6.54 (3)[e]	7.12 (3)[e]	–
$H+HL_3=HL_4$	–	–	–	–	2.76 (9)[d]	4.88 (3)[e]	4.62 (3)[e]	–
$H+HL_4=HL_5$	–	–	–	–	2.54 (9)[d]	3.75 (3)[e]	2.80 (3)[e]	–
$H+HL_5=HL_6$	–	–	–	–	–	3.07 (3)[e]	2.27 (3)[e]	–
	DMSO–H_2O							
$H+L=HL$	13.9 (1)[b]	15.4 (1)[b]	–	–	–	–	–	12.76(8)[f]
$H+LH=LH_2$	5.2 (1)[b]	4.2 (1)[b]	–	–	–	–	–	3.84(5)[f]
$H+LH_2=LH_3$	1.7 (1)[b]		–	–	–	–	–	–

[a] The last digit in parentheses is the standard deviation on the last significant figure. Measurements for **L7** were performed in two different ionic media: NaCl or $NaClO_4$ $I=0.15$ mol dm^{-3}. Measurements for **L1**–**L6** were performed in NaCl media: $I=0.15$ mol dm^{-3}. Measurements for **L10** were performed in DMSO–H_2O 50/50 (v/v) using Me_4NNO_3 as medium.
[b] Ref. [46].
[c] Ref. [47].
[d] Ref. [51].
[e] Ref. [50].
[f] Ref. [53].

one secondary amine function, as **L3** [46,47]. This behavior indicates that the hydrogen ion interacts very strongly with the nitrogen atoms stabilizing the monoprotonated species $[HL]^+$. In these $[HL]^+$ cations the acidic proton is probably enclosed inside the macrocyclic cavity, and is stabilized by a thick hydrogen bond network involving the nitrogen atoms. This situation is supported by crystal structures of similar compounds [60,61]. One example is reported in Fig. 3 for the monoprotonated species of the ligand 5,12,17-trimethyl-1,5,9,12,17-pentaazabicyclo[7.5.5]nonadecane; this structure just shows the acidic proton bound to the nitrogen atom N5 and further stabilized by hydrogen bonding involving the other four amine groups. It is also possible to observe that all five nitrogen atoms are in *endo* configuration to better interact with the proton.

Observing the second and third protonation constants values for the bicyclic ligands reported here, it is possible to note that there is a decrement heading for the second protonation constants from the first one while the third is not measurable. This behavior is justified in terms of electrostatic repulsion that is strongly present on the protonated molecules from the diprotonated species and due to a high density of positive charges close to each other.

This mainly affects the basicity constants of **L5** that act only as a diprotic base in the pH range investigated. It behaves as a strong base in the first protonation step but as weak base in the second one [51]. The sharp basicity decrease, six logarithmic units, again indicates a rather strong repulsion between the two positive charges forced by the molecular topology to stay close each other.

The different molecular topology and the increase of the amine nitrogen atoms, leads to a pentaprotic and hexaprotic base in the **L6** and **L7** compounds, respectively. The molecular topology with two identical subunits, separated by a rather long chain, has been used to explain such a protonation behavior [50,51]. It is very likely that the first two protons are lodged in the two monocyclic subunits, which are able to provide a similar chemical environment and feel each other very little. All compounds shown here do not behave as proton sponges, indicating that the peculiar hydrogen-bond arrangement, responsible for the very high basicity of some aza-cages, is less relevant in these cases [62–64]. The coordination of the lithium ion is in competition with the proton binding, so it is important not to have 'proton sponge' as receptors.

L8 **L9**

Fig. 5. 4,7,13,18-Tetraoxa-1,10-diazabicyclo[8.5.5]eicosane (**L8**) and 4,7,13-trioxa-1,10-diazabicyclo[8.5.5]eicosane (**L9**).

3.3. Lithium coordination

The coordination of alkali metal ions has been studied in aqueous solution by means of ^{1}H-, ^{13}C- and ^{7}Li-NMR spectra, potentiometric measurements and UV–Vis absorption techniques. On monitoring the lithium ion binding, its nuclear magnetic properties are very helpful. Lithium presents, magnetic number $I = 3/2$ and a natural abundance of 92.58% and usually the ^{7}Li-NMR spectra shows sharp peaks due to the nuclear lithium resonances. This feature connected to the molecular structure of such ligands allows one to identify the ion complexation. In fact, as in the addition of the first proton to the free amine, the stabilization of the Li^+ in the complex is aided by the inclusion of the ion inside the tridimensional cavity. This embedded situation blocks in solution on the NMR time scale, ion exchange from the complex species or from the free ions when present; in this case the resulting NMR spectra show both resonances, for the ion in the complexes and for the free solvated cation. Sometimes this behavior allows one to derive the formation constant of the complex [65].

The deep inclusion of the Li^+ ion makes it insensitive to the solvent, in this manner the chemical shift of the ion in the complex does not change when varying the medium.

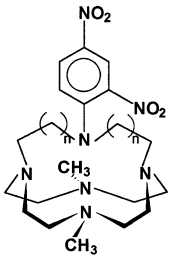
The lithium encapsulation inside the cavity, with subsequent ion isolation by the medium, is shown by crystal structures of analogous lithium complexes. Fig. 4 reports, for example, two $[LiL]^+$ cations with the related cages, 4,10,15-trimethyl-1,4,7,10,15-pentaazabicyclo[5.5.5]heptadecane (Fig. 4(a)) and 4,10-dimethyl-1,4,7,10,15-pentazabicyclo[5.5.5]heptadecane (Fig. 4(b)). In both examples, the lithium atom is enclosed inside the macrocyclic cavity; in the first one the ligand adopts a fairly regular bipyramidal geometry with the Li–N distances in the 2.01–2.08 Å range [69]. These distance values are similar to those found in the other complex, where the lithium ion is again wholly encapsulated by the ligand and lies at the center of a fairly regular trigonal–bipyramidal arrangement of the five nitrogen atoms.

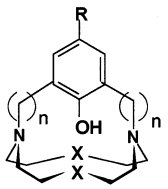
The ^{7}Li-NMR chemical shifts of the complexed species are collected in Tables 3 and 4; all the ligands reported here are lithium ion selective and they, except **L15**, do not or weakly interact with the other alkali ions. For the bicyclic cages, only the mononuclear complexed species were observed corresponding to the equilibrium (Eq. (1)):

$$Li^+ + L = [LiL]^+ \quad (1)$$

Indeed in the tricyclic ligands binuclear species were also achieved.

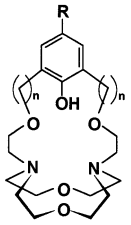
More than one complex species can be found in solution. For the **L2** ligand the ^{7}Li-NMR spectrum, recorded in alkaline aqueous solution and containing an excess of Li^+, showed three sharp peaks: at 0 ppm, ascribed to the free lithium, and two shifted by 1.25 and 1.70 ppm with respect to solvated lithium. The latter were attributed to the complexed Li^+ ion, slowly exchanging together and with free Li^+ on the NMR time scale [46]. The two peaks of the complexed lithium were attributed to the presence in solution of two conformers of the $[Li\mathbf{L2}]^+$ complex.





L10: n=1
L11: n=2

L12: X=O, R= N=N-Ph-NO_2, n=2
L13: X=O, R= N=N-Ph-NO_2, n=3



L14: R= N=N-Ph-NO_2, n=0
L15: R= N=N-Ph-NO_2, n=1

Fig. 6. General drawing and abbreviations of the chromoionophores cages. The number of hydrocarbon atoms present in the bridging chains are given in parentheses.

The solution containing the [Li**L4**][ClO_4] complex exhibits a sharp peak at 2.47 ppm, indicative of a highly deshielded cation and typical of lithium encapsulation [47]. Nevertheless **L5** exhibits the higher chemical shift value to confirm a stronger interaction of the oxygen atoms than the nitrogen [51].

Table 3
^{7}Li-NMR chemical shifts for the lithium complexes in solution

	L1[a]	**L2**[a]	**L3**[a]	**L4**[b]	**L5**[c]	**L6**[c]	**L7**[d]	**L10**[e]	**L11**[e]
δ (ppm)	1.25, 1.70[f]	0.97[f]	0.98, 1.02[f]	2.47[f]	3.91[f]	1.92, 1.85[g]	1.24[h]	3.52[g]	2.50[g]

[a] Ref. [46].
[b] Ref. [47].
[c] Ref. [51].
[d] Ref. [50].
[e] Ref. [57].
[f] D_2O solution.
[g] CD_3OD solution.
[h] CD_3OD solution and recorded at -40°C.

Again for those ligands the ^{7}Li chemical shift of complexed Li^{+} was independent of the solvent used, indicating that the metal ion is deeply embedded into the macrobicyclic cavity and thus isolated from the medium.

The ^{1}H- and ^{13}C-NMR spectra supported this conclusion. For example, the ^{1}H- and ^{13}C-NMR spectral features of the free amine in aqueous or methanolic solution, which change when the lithium complex is formed, were not found unchangeable even in the presence of a large excess of Na^{+} ion, for all the cages **L1**–**L7**, **L10** and **L11**. This evidence indicates that these species are able to completely discriminate between Li^{+} and Na^{+} ions [46,47,57].

The macrotricyclic ligands with cylindrical topology **L6** and **L7** showed the possibility to coordinate two lithium ions, one into each macrocyclic subunit [50,51]. To investigate the formation of these binuclear species in solution, ^{7}Li-NMR spectra with different LiCl ratios were recorded in CD_3OD solution at $-40°C$ for the ligand **L7**. The Li–**L7** system showed two main species, $[Li\mathbf{L7}]^{+}$ and $[Li_2\mathbf{L7}]^{2+}$ with the latter being the only one present at higher Li:**L7** ratio. In this case the lithium chemical shifts were solvent dependent indicating that the solvent has access to the lithium coordination sphere [50,51].

Solvent dependence was also found for the lithium complex of the cryptand **L9** (Fig. 5) which shows a variation of its ^{7}Li chemical shift over a 1.92 ppm range for the solvents studied, compared with a range of 2.61 ppm for solvated Li^{+} (Table 4).

This study suggests that direct interaction between Li^{+} in $[Li\mathbf{L9}]^{+}$ and the solvent occurs despite the inclusive structure observed for this cryptate in the solid state [66]; moreover the interaction with solvent can only occur if Li^{+} moves from the center of the cryptand cavity toward the 15-membered di-aza-trioxa ring, to produce an exclusive structure for the $[Li\mathbf{L9}]^{+}$ complex [48]. In a range of different solvents the ^{7}Li chemical shifts of $[Li\mathbf{L8}]^{+}$ are substantially independent of the nature of the solvent as shown in Table 4. Both **L8** and **L9** are able to coordinate the Na^{+} ion in some solvents indicating the loss of selectivity due to the increase of the cavity dimension [49].

Frequently, the low solubility of most of these complexes in aqueous solution does not permit one to determine their stability constants with potentiometric studies. When the potentiometric measurements are possible, they show the excellent ability of these topologies to encapsulate the Li^{+}. For **L3** and **L4** the equilibrium formation constants were found to be greater than 1000. The stability constants (Table 5) of the lithium complexes are markedly higher in the less polar solvent DMSO–H_2O (80:20; v/v), indicating that the solvation strongly affects the process of Li^{+} coordination. These results are in good accord with the insertion of the metal ion into the small hydrophobic cavity that requires the removal of all the solvent molecules surrounding the free lithium ion. Such a process is more favored in solvents with lower polarity, in which the free metal ion is less solvated [46].

Table 4
^{7}Li-NMR study of **L8** and **L9**[a]

Solvent	[L]/[Li^+]	[**L9**Li]$^+$ δ ppm	Li^+ (δ ppm)	Solvent	[L]/[Li^+]	[**L8**Li]$^+$ (δ ppm)	Li^+ (δ ppm)
CH_3CN	0.5	−2.15[b,c]	−0.26[b,c]	CH_3NO_2	1.0	0.41[d,e]	–
PC	0.8	−0.23[b,c]	−0.48[b,c]	PC	0.5	0.38[d,e]	0.52[d,e]
Acetone	0.8	−0.27[b,c]	1.02[b,c]	DMSO	0.8	0.39[d,e]	0.95[d,e]
Water	0.5	−0.216[b,c]	0.00[b,c]	Formamide	0.5	0.38[d,e]	−0.43[d,e]
DMF	0.5	−0.48[b,c]	0.19[b,c]	DMF	0.5	0.42[d,e]	−0.40[d,e]
Methanol	0.5	−0.35[b,c]	−0.75[b,c]				
Py	0.5	−1.01[b,c]	1.86[b,c]				

[a] Chemical shifts corrected for magnetic susceptibility using the expression: $\delta = \delta_{obs} - 4\pi/3(\chi_{ref} - \chi)$, where χ_{ref} and χ are the volume diamagnetic susceptibilities of the reference and sample solutions, respectively [67].

[b] Ref. [48].

[c] Chemical shift at 280 K and referenced to a 0.005 mol dm^{-3} solution of $LiClO_4$ in water as external reference.

[d] Ref. [49].

[e] Chemical shift at 303°C and referenced to an aqueous $LiClO_4$ solution at infinite dilution.

Table 5
Potentiometrically determined stability constants (log K) of the Li^+ complexes for the equilibrium $L + Li^+ = [LLi]^+$

Solvent	L1	L2	L3	L4	L8	L9
Aqueous solution	–	–	3.5[a,b]	3.0[b,c]	–	–
DMSO–H_2O	3.6[a]	–	5.2[a,d]	–	–	–
Methanol	–	–	–	–	8.0[e,f]	3.0[e,f]
Dimethylformamide	–	–	–	–	7.0[e,g]	1.8[e,f]

[a] Ref. [46].
[b] In aqueous solution, 0.15 mol dm^{-3} NaCl.
[c] Ref. [47].
[d] In DMSO–H_2O 80:20 (v/v) at 298.1 K.
[e] Ref. [48].
[f] Supporting electrolyte 0.05 mol dm^{-3} Et_4NClO_4.
[g] Ref. [68].

3.4. Chromoionophores

One of the chromophores most used is the phenolic fragment for its potential to contribute an oxygen donor atom to the metal binding; moreover the oxygen atom has a high directional effect in the coordination. The presence of the aromatic ring also gives a wide range of possible functionalizations, an indispensable requisite to obtain colored complexes. Only very few examples are present in the literature for phenol macrocycles based exclusively upon aza-crown ether derivatives, which are selective for alkali metal ions. Some are reported in Fig. 6.

Nevertheless appropriately functionalized full amine cages, such as **L10** and **L11**, could also be applied for a change in their optical properties up on lithium coordination. Both cages **L10** and **L11** were found able to selectively encapsulate Li^+ [57]. ^{7}Li-NMR spectra of the complexes are not influenced by the solvent used and the cages are selective toward Li^+. Both cages have optical absorption properties as expected for nitro derivatives: $\lambda_{max} = 347$ nm and 391 nm in methanol for **L10** and **L11**, respectively. In the lithium complexes the λ_{max} of the ligands do not change, but modifications in the absorption intensity are observable. A decrease in absorption intensity was detected, for example, for **L10** on lithium coordination, resulting in a value of $\varepsilon = 12700$ and 7000 for **L10** and [Li**L10**]$^+$, respectively [57].

Different behavior with phenolic cages where complexation also produces a change in the λ_{max} value, was observed (Table 6). A real bathochromic shift in the absorption maximum was found on lithium coordination, for ligand **L12** in 10% diethylene glycol monoethyl ether (DEGMEE) [56]. At pH 12 for chromoionophore **L12** there is a 133-nm bathochromic shift in the presence of Li^+[**L12**Li]$^+$. Interestingly chromogenic cryptand **L13** is inactive toward Li^+, Na^+ and K^+ in 10% DEGMEE, but exhibits a high preference for Li^+ in CH_2Cl_2–water extractions [56]. In this case a 153-nm shift in the absorption maximum to a longer wavelength is observable and a slightly higher molar absorptivity for the [**L13**Li]$^+$ form versus the **L13** form. The chromogenic cryptand **L14**, upon CH_2Cl_2 extraction

from water, exhibits a remarkable preference for lithium, resulting in a 134-nm bathochromic shift in the absorption maximum and in a considerably higher molar absorptivity for the complex form (Table 6). Ligand **L15** indeed does not seem to bind Li^+ or K^+ as only slight changes in both wavelength maximum and absorptivities are observed in the presence of these ions [58].

As in the previous ligands the increase of the tridimensional cavity leads to a partial or complete loss of selectivity toward the lithium ion.

4. Conclusions

The molecular topology of all ligands here reported is characterized by the presence of tridimensional cavities. The coordination skeleton, formed by all nitrogen amine atoms or mixed oxygen/nitrogen atoms, with the chromophoric moiety, sensitive to ion complexation, are other structural aspects related with these cages. In acid–basic behavior, this topology allows high basicity constants at least in the first protonation step. Owing to the electrostatic repulsion, the proximity of the amine functions does not permit one to obtaining the fully protonated specie in aqueous solution. For the small cages at most the triprotonated species is achieved.

Table 6
Spectral responses of chromogenic cryptands to lithium, sodium and potassium ions[a]

Compound	pH	Form[d]	$\lambda_{max,\ nm}$	ε (λ_{max})
L12	12.0	L	379[b]	13 300[b]
		LiL	512; 379[b]	8800; 12 600[b]
		NaL	379[b]	13 300[b]
		KL	379[b]	13 300[b]
L13	11.0	L	408[b]	12 400[b]
		LiL	561; 405[b]	14 670; 7590[b]
		NaL	407[b]	12 700[b]
		KL	408[b]	12 740[b]
L14	>12	L	409[c]	18 000[c]
		LiL	543[c]	32 000[c]
		NaL	408[c]	18 000[c]
		KL	410[c]	18 300[c]
L15	8	L	521[c]	12 200[c]
		LiL	518[c]	11 500[c]
		NaL	524[c]	15 600[c]
		KL	523[c]	12 700[c]

[a] Values in H_2O—DEGMEE (90+10, v/v) for compound **L12** and in CH_2Cl_2—H_2O for compound **L13**–**L15** at 25°C.
[b] Ref. [56].
[c] Ref. [58].
[d] L is the uncomplexed ligand; LiL, NaL and KL are the compound in the presence of large excess of lithium, sodium and potassium ions, respectively.

In lithium coordination, all the ligands form stable complexes with this ion. Only mononuclear lithium complexes were detected with the bicyclic ligands while binuclear complexes were also observed with the cylindrical topology ligands.

Except for **L15**, these receptors bind the lithium selectively over other alkali metal ions. The key for such selectivity could be ascribed to the dimensional cavity as well as the number of binding sites. In fact, when increasing the cavity dimension, the selectivity decreases and sometimes disappears. This also occurs with an increase in the number of donor atoms, as shown by the coordination behavior of **L15**. Chromogenic cryptands with remarkable selectivity for lithium over physiologically important cations have been designed just with the aim to monitor the lithium concentration in aqueous solutions. Some of the ligands collected here could really be improved in order to be used for the colorimetric determination of lithium as an alternative to ion-selective electrodes and atomic absorption spectrometry.

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