CROATICA CHEMICA ACTA
CCACAA, ISSN 0011-1643, e-ISSN 1334-417X
Croat. Chem. Acta **86** (1) (2013) 1–19.
http://dx.doi.org/10.5562/cca2170

Feature Article

An Enchiridion of Supramolecular Thermodynamics: Calix[*N*]arene (*N*=4,5,6) Tertiary Amide Derivatives and their Ionic Recognition†

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RECEIVED SEPTEMBER 3, 2012; REVISED JANUARY 24, 2013; ACCEPTED FEBRUARY 15, 2013

Abstract. The importance of detailed thermodynamic studies in assessing the selective behaviour of macrocyclic receptors for one species relative to another in a given solvent and the medium effect on complexation processes involving ionic species are emphasised. Factors to be considered in the determination of thermodynamic parameters of complexation in non-aqueous solvents are highlighted. Particular reference is made to the need for considering the bulk of information available in the literature on the solution properties of electrolytes in non-aqueous medium in the selection of the solvent for ion complexation processes involving macrocycles.

A detailed thermodynamic study on the interaction of *p-tert*-butyl calix[*n*]arene (n = 4−6) tertiary amide derivatives with uni- and bivalent cations in protic (methanol) and dipolar aprotic (acetonitrile) media is reported. It is demonstrated that as the number of phenyl units in the macrocycle increases, the vital feature of the cyclic tetramer receptor for selective recognition of cations decreases significantly for the cyclic pentamer and almost disappears for the hexamer. Concluding remarks are included. (doi: 10.5562/cca2170)

Keywords: thermodynamics, supramolecular chemistry, calix[*n*]arenes, cation complexation

INTRODUCTION

Supramolecular Chemistry and Nanoscience/Nanotechnology have grown extensively in a relatively short period of time. These fields of research are closely related. In fact in the middle eighties the use of molecules as building blocks to construct nanoscale devices and machines emerged within the framework of Supramolecular Chemistry. The latter involves intermolecular interactions which result in larger structures while the molecular approach to Nanotechnology is concerned with the building up of devices within the nanoscale from atoms and molecules. It has been recently shown that calixarenes, products of the condensation reaction of *p*-substituted phenol and formaldehyde in alkaline medium and their derivatives are powerful tools for nano-technological developments.[1] Based on metal ion complexes, self assembled systems have been produced. Within this context it is relevant to emphasise the importance of thermodynamics in assessing the stability and selectivity of calixarenes for metal ions.[2–4] The synthetic and structural advances as well as the applications in the field of calixarene chemistry have been largely significant.[5–9] Although emphasis has been made about the selectivity issue,[10–12] few contributions are found in the literature reporting detailed thermodynamics on these systems in their interaction with neutral or ionic species. It is indeed from thermodynamics that a quantitative evaluation of the selective behaviour of a receptor for one species relative to another in a given solvent at a given temperature can be obtained from stability constant data for the systems involved. Unlike calix[*n*]arene esters[13–26] and to some extent calix[*n*]arene ketones,[27–29] no detailed thermodynamics have been reported on calix[*n*]arene tertiary amide derivatives and ionic species (by detailed thermodynamics the authors refer to processes in which the speciation in solution, the solution thermodynamics for reactants and product and the composition of the complex are investigated and the scope and limitations of the methodology used are considered in the determination of stability constants and enthalpies of complexation as discussed below). Recently a detailed study on the interactions of a lower rim calix[4]arene containing secondary amide

† This article belongs to the Special Issue devoted to the 85th anniversary of *Croatica Chemica Acta*.

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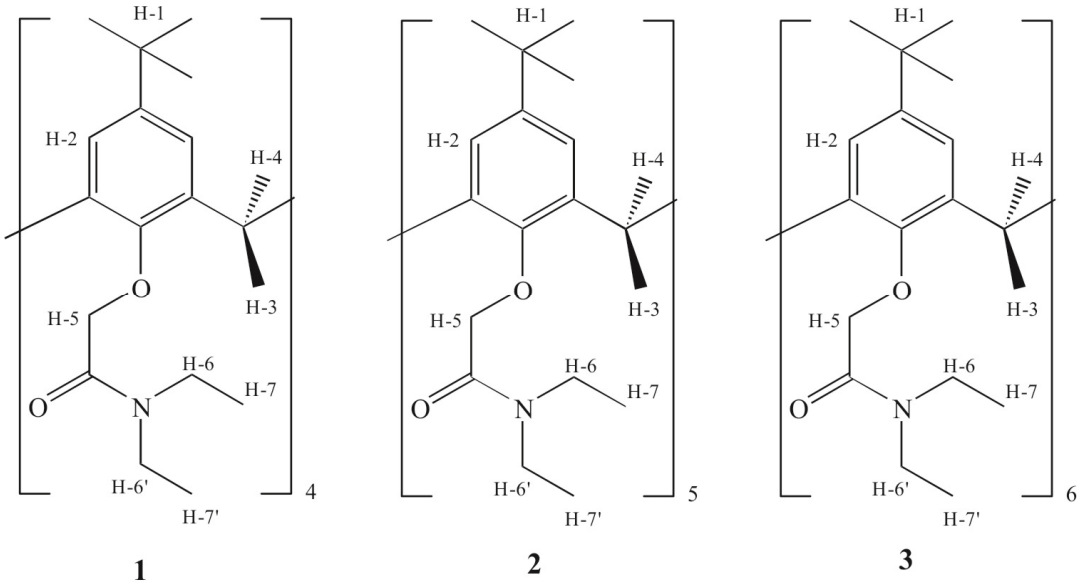


Figure 1. Structure of Receptors.

functionalities with alkali-metal cations involving thermodynamic, structural and computational studies has been reported.[30] Even though the receptor does not involve a tertiary amide it is worth mentioning this paper given that an integrated approach has been taken for complexation studies. This is encouraging in view of the fact that in most cases only qualitative data sets have been reported on calix[*n*]arene tertiary amide derivatives and metal cations. The main point of interest in this paper is to discuss the research so far carried out on *p-tert*-butyl calix[*n*]arene tertiary amide derivatives **L1, L2** and **L3 (**Figure 1) and ionic species in solution and to provide results on the basis of recent investigations aiming to assess the factors contributing to the thermodynamics of ion complexation processes in moving from the cyclic tetramer to the hexamer.

EXPERIMENTAL SECTION

Chemicals

p-tert-Butylphenol (98 %), *p*-formaldehyde (95 %), potassium-*tert*-butoxide (95 %), purchased from Aldrich were dried over P_4O_{10} under vacuum for several days before use. The *p-tert*-butyl-calix[4]arene, 18-crown-6, potassium carbonate (K_2CO_3) and 2-chloro-*N*,*N*-diethylacetamide were purchased from Aldrich and were used without further purification.

Metal cation salts as perchlorates, $LiClO_4.H_2O$, $NaClO_4.H_2O$, $KClO_4.H_2O$, $RbClO_4.H_2O$, $CsClO_4.H_2O$, $AgClO_4.H_2O$, $Mg(ClO_4)_2.2H_2O$, $Ca(ClO_4)_2.4H_2O$, $Sr(ClO_4)_2.2H_2O$, $Ba(ClO_4)_2.nH_2O$, $Ni(ClO_4)_2.6H_2O$, $Pb(ClO_4)_2.nH_2O$, $Cu(ClO_4)_2.6H_2O$, $Zn(ClO_4)_2.6H_2O$, $Cd(ClO_4)_2.H_2O$, $Hg(ClO_4)_2.H_2O$ and $(C_4H_9)_4NClO_4$ (Aldrich) were dried over P_4O_{10} under vacuum for several days before use. The absence of a water signal on the NMR spectra upon the addition of metal cation salts indicated the removal of water from these salts.

Acetonitrile, (HPLC grade, Fisher UK Scientific International) was placed over CaH_2, refluxed under a nitrogen atmosphere and the middle fraction collected for use in the experiments.[31] The water content determined by Karl Fisher titration was found to be less than 0.01 %.

Toluene, methanol, and dichloromethane (Fisher UK Scientific International) were purified as described in the literature.[32,33]

Solvents used for NMR measurements were deuterated acetonitrile, CD_3CN, chloroform, $CDCl_3$ and methanol, CD_3OD Cambridge Isotope Laboratories, Inc.

Synthesis of 5,11,17,23-*p-tert*-butyl-25,26,27,28-tetradiethylacetamide-calix[4]arene (L1)

p-tert-Butyl calix[4]arene (5 g), 18-crown-6 (0.53 g), potassium carbonate (10.66 g) and MeCN (250 ml) were mixed in a 500 ml three-necked-round bottom flask equipped with a condenser.[34] The mixture was stirred for one hour under a nitrogen atmosphere. Then 2-chloro-*N*,*N*-diethylacetamide (6.35 ml) was added and the temperature was increased to 80 °C for ten hours. The reaction time was followed by TLC using a DCM:MeOH (9:1) mixture. The product was rotary-evaporated to extract the solvent. Then DCM (100 ml) was added to the crude product and washed several times with a saturated solution of $NaHCO_3$ and hydrochloric acid (100 ml, 0.2 molar). The organic phase was extracted using a separatory funnel, and anhydrous magnesium sulphate (50 g), was added to remove any water residue left in DCM. The mixture was then fil-

tered gravitationally and rotary-evaporated until dry. The crude oil was dissolved in MeOH and refluxed. Small white crystals started to form upon cooling of the solvent. Further slow evaporation was required to give the resulting yield of 55−65 %. The product was dried at 80 °C under vacuum and stored in a desiccator containing calcium chloride.

^{1}H NMR ($CDCl_3$): δ/ppm 6.79(s, 2H, Ar-**H**), 5.22 (d, 1H, Ar-C**H$_2$**-AR), 5.047 (s, 2H, O-C**H$_2$**-CO), 3.35 (q, 4H, N-C**H$_2$**-CH_3), 3.21 (d, 1H, Ar-C**H$_2$**-AR), 1.156 (t, 6 H, CH_2-C**H$_3$**), 1.091 (s, 9**H**, 4-tert-but). Microanalysis was carried out at the University of Surrey, calcd. % C, 74.14; H, 9.15; N, 5.09; Found: % C, 74.02; H, 9.38; N, 5.00.

Synthesis of 5,11,17,23,29-penta-*tert*-butyl-31,32,33,34,35-pentadiethylacetamide calix[5]arene (L2)

The parent calix[5]arene was synthesised according to the procedure reported in the literature.[35,36]

p-*tert*-butyl calix[5]arene (1.00 g, 1.23 mmol), 18-crown-6 (0.1 g, 0.38 mmol), potassium carbonate (2.04 g, 14.79 mmol) and MeCN (200 ml) were mixed in a 500 ml three-necked-round bottom flask equipped with a condenser. The mixture was stirred for an hour under a nitrogen atmosphere. Then, 2-chloro-*N*,*N*-diethylacetamide (1.36 ml, 9.86 mmol) was added and the temperature was increased to 70 °C for two days. The reaction was followed by TLC using hexane: ethyl acetate (4:1) mixture as the developing solvent. The product was rota-evaporated to remove the solvent. DCM was added to the crude product and washed several times with a saturated solution of $NaHCO_3$ and hydrochloric acid (100 ml, 0.2 molar). The organic phase was extracted using a separatory funnel. Anhydrous magnesium sulphate (10 g) was added to remove any water residue left in DCM. The mixture was then gravitationally filtered and rotary-evaporated until dry. The crude oil was dissolved in methanol and refluxed. Small white crystals were formed upon cooling and after the slow evaporation of solvent. The yield obtained was 60−70 %. The product was dried at 80 °C under vacuum and stored in a desiccator containing calcium chloride.

^{1}H NMR ($CDCl_3$) δ/ppm: 6.79 (s, 2 **H**), 5.22 (d, 1 **H**), 5.047 (s, 2 **H**), 3.35 (q, 4 **H**), 3.21 (d, 1 **H**), 1.156 (t, 6 **H**), 1.091 (s, 9 **H**). Microanalysis was carried out at the University of Surrey, calcd. % C, 74.14; H, 9.15; N, 5.09; Found: % C, 74.02; H, 9.38; N, 5.00).

Solubility Measurements

Saturated solutions of **L1** and **L2** were prepared by the addition of an excess amount of the ligand into the solvents. The saturated solutions were left to reach equilibrium in a thermostatic bath at 298.15 K for several days. Aliquots of the solutions were taken and analysed gravimetrically in triplicate. Blank experiments were carried out in order to verify the absence of non-volatile impurities. Solvate formation was verified by exposing the solid to a saturated atmosphere of the appropriate solvent for several days.

^{1}H NMR Studies

^{1}H NMR measurements were recorded at 298 K using a Bruker AC-300E pulse Fourier transform NMR spectrometer. Typical operating conditions for routine proton measurements involved a "pulse" or flip angle of 30º, spectral frequency (SF) of 300 MHz, delay time of 1.60 s, acquisition of the ligand (≈0.5 ml, 6.0×10^{-3} mol dm^{-3}) in deuterated acetonitrile, CD_3CN, were placed in 5 mm NMR tubes using TMS (tetramethylsilane) as the internal reference.

Stepwise addition of the metal cation salt in CD_3CN (≈1.0×10^{-2} mol dm^{-3}) were made until no further chemical shift changes were observed. Similar experiments were carried out in deuterated methanol, CD_3OD.

Conductance Measurements

For these measurements, a Wayne Kerr B642 Autobalance Universal Bridge type B642 was used.

The conductivity cell constant was determined by the stepwise addition of an aqueous solution of KCl (0.1 mol dm^{-3}) to the cell containing deionised water.[37] The molar conductance for each addition was calculated using the Lind, Zwolenik and Fuoss equation.[38] From the molar conductances of KCl, the cell constant was calculated.

Conductometric titrations were carried out to determine the composition of the ligand/metal cation complex. Solutions of the ligand (≈$0.7-1 \times 10^{-3}$ mol dm^{-3}) and metal cation salts (≈1×10^{-4} mol dm^{-3}) were prepared in the corresponding solvent (MeCN and MeOH). The metal cation salt solution was added inside the cell and left to reach equilibrium (298.15 K). Thus the ligand solution was added stepwise into the metal salt solution and the molar conductance for each titration recorded. The procedure was repeated until the molar conductance of the solution showed no significant change.

Calorimetric Titrations

Calorimetric titrations (direct and competitive) were carried out in order to determine the stability constant (log Ks) and the enthalpy of complexation (ΔcH). An isoperibol calorimeter (Tronac 450) was used for this purpose. Calibration of the equipment was performed in order to ensure a good reliability of the data. For this, tris(hydroxymethyl)amino methane (THAM) was titrated into a solution of HCl (0.1 mol dm^{-3}) at 298.15 K.[39] The obtained value, −47.58 ± 0.08 kJ mol^{-1}, was compared with the ones reported in the literature[40](−47.47 kJ mol^{-1}) and found to be in good agreement.

For complexes with high stability constants (log K_s > 6), competitive calorimetric titrations were

performed. A solution of the metal cation (M_2^{q+}) salt was titrated into the vessel containing the ligand-metal ion (M_1L^{n+}) complex. The following process takes places:

$$M_1L^{n+}{}_{(s)} + M_2{}^{q+}{}_{(s)} \xrightarrow{K_{s(ov)}} M_2L^{q+}{}_{(s)} + M_1{}^{n+}{}_{(s)}$$

$$M_1{}^{n+}{}_{(\sigma)} + L_{(\sigma)} \xrightarrow{K_{s1}} M_1L^{n+}{}_{(\sigma)}$$

$$M_2{}^{q+}{}_{(s)} + L_{(s)} \xrightarrow{K_{s2}} M_2L^{q+}{}_{(\sigma)}$$

Stability constants and enthalpy of complexation were also determined by microcalorimetric titrations using a four channel heat conduction microcalorimeter (Thermal Activity Monitor 2277)[41] Electrical (static and dynamic) and chemical calibrations were carried out to check the reliability of the TAM 2277.[42,43] The calorimetric titrations were performed by adding a metal cation salt solution into the vessel containing the ligand solution. Corrections for the enthalpy of dilution of the titrant into the solvent were carried out in all cases. The data were recorded and processed using Digitam 4.1 for Windows from Thermometric AB and select software AB Sweden.

Potentiometric Titrations

These were also performed to determine the stability constant of the ligands with Na^+ and Ag^+ cations using sodium and silver selective electrodes respectively as previously described.[44]

RESULTS AND DISCUSSION

Thermodynamics of Complexation. Fundamental Concepts

Prior to the discussion of the research related to calixarene tertiary amide derivatives and their complexation with metal cations some fundamental concepts regarding the thermodynamics of ion complexation processes involving neutral ligands are first discussed.

Selection of the Solvent

The solvent plays a crucial role in the derivation of thermodynamic data for ion complexation processes. Many papers regarding the medium effect on the complexation process involving macrocycleshave been published by Danil de Namor and co-workers.[2,24–26,45–53] In selecting the solvent there are a number of issues which need to be carefully addressed such as i) The behaviour of electrolytes in non-aqueous solvents. There is a great deal of information in the literature addressing this issue.[54–58] Conductance studies have been carried out and successfully used to determine the ion-pair formation constants of electrolytes in different solvents.[59] The complexation process involving a cation M^{n+} and a receptor L in a solvent (s) to give the metal ion complex, ML^{n+} described in Eq. 1

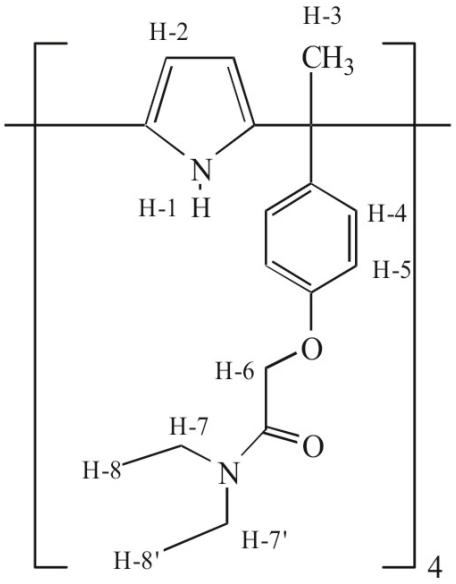


Figure 2. Structure of Receptors with two binding sites.

requires the free and the complex cations to be predominantly in their ionic form in solution. Quite clearly the counter-ion should not have any effect on the complexation process.

$$a\,M^{n+}(s) + b\,L(s) \xrightarrow{K_s} M_aL_b^{an+}(s) \qquad (1)$$

If this effect is observed,[60,61] other processes besides complexation are taking place in solution. As a result, the data should be referred to as 'apparent' data where ions and ion pairs are present in solution. To fulfil the fundamental issue of electroneutrality, a neutral receptor complexing either a cation or an anion must have a counter-ion, both may be present in solution as ions, ion-pairs or a mixture of both. This is dependent on the nature of the species involved but mainly on the permittivity of the medium and its solvating power. Such receptor cannot be regarded as an ion pair receptor. An ion pair receptor is that with the capability of complexing the cation and the anion by offering different active sites. A representative example for a calix[4]pyrrole amide derivative is shown in Figure 2 where the pyrrole NH proton interacts with the anion while the amide functionalities interact with the cation, ii) The behaviour of the ligand in solution. Hardly any attempts have been made to establish it. It is currently assumed that the monomer is predominant in solution iii) The composition of the complex needs to be established particularly when dealing with calixarene receptors where it is often found that the stoichiometry of the complex is altered by moving from one solvent to another.

Another important issue related to the solvent is its solvating power on the reactants and the products. As

far as processes involving 1:1 electrolytes are concerned, transfer Gibbs energies provide invaluable information regarding the differences in solvation of these electrolytes from one solvent to another.[62–66] Even more relevant are data for single-ion values.[67,68] Although these are based on an extra-thermodynamic convention it allows selecting the appropriate solvent to carry out the experimental work, particularly if the solvation properties of the receptor and the new electrolytes (metal-ion complex salt) are available from solubility measurements from which transfer Gibbs energies can be obtained. These data can be used to predict the relative strength of complexation in moving from one medium to another. Apart from the work reported by ourselves this approach has been hardly used in the general areas of calixarene and calixpyrrole chemistry. As previously stated[2] a great deal of experimental work assessing the counter-ion effect on cation extraction processes by calixarenes and derivatives could have been avoided by the use of single-ion transfer values, particularly in solvent systems such as water – dichloromethane for which these data are readily available.[69] Needless to mention comparative studies being made between complex stabilities and extraction data[70,71] without taking into account the various processes involved in the latter (phase transfer and ion-pair processes) relative to the former.[72]

Thermodynamics of Ion Complexation Processes: Methodology

Among the various techniques used to determine the complex stability; titration calorimetry offers advantages in that the stability constant (hence the Gibbs energy) and the enthalpy of complexation can be determined from a single titration. Therefore the entropy of complexation can be calculated from these data. Although this technique is concentration dependent and therefore has limitations when dealing with very strong complexes, these limitations can be overcome by carrying out competitive calorimetric titrations. The results can be checked by potentiometry which has been proved to be a suitable technique for the determination of highly stable complexes. This technique is based on the Nernst equation and therefore it is a function of the logarithmic scale of activity. Other techniques used are spectrometry, conductometry, NMR as well as calorimetry, all of them are concentration dependent and as such, their usefulness for obtaining accurate stability constant data depends on the magnitude of the stability constant.[50] Awareness on the scope and limitations of the techniques used is required in the determination of the stability constants of ion-macrocycle complexes. Having highlighted some important issues regarding the determination of thermodynamic parameters of complexation involving neutral ligands and ionic species, the next section addresses calixarene tertiary amide derivatives (**L1**, **L2** and **L3**) and their interaction with metal cations.

Calix[*n*]arene Tertiary Amide Derivatives. Solution Studies

The synthesis and characterisation of a number of calix[*n*]arene (n = 4,5,6,8) and their upper and lower rim derivatives including the ones containing amide functional groups in the narrow rim have been discussed in several books, reviews and papers.[5–9,73] The thermodynamics of complexation of calix[*n*]arene derivatives and metal cations in non-aqueous solvents have been investigated and reviewed in 1998.[2] As far as calix[4]arene amide derivatives are concerned until then only quantitative data for *p-tert*-butyl-tetraacetamide, **L1** and alkali-metal cations, Ag (I) and Ba (II) in methanol and Rb (I) Cs (I) and Ag (I) in acetonitrile have been reported.[74] From the information given for Ca(II) and Sr(II) in methanol (log $K_s \geq 9$), Li(I), Na(I) and K(I) (log $K_s \geq 8.5$) in acetonitrile at 298.15 K it can be concluded that high stability complexes are formed in these solvents. Since then, the only published data on receptor **L1** and cations is that involving lanthanides. Under the umbrella of thermodynamics, stability constants, enthalpies and entropies of complexation in methanol were reported.[61] Given that these data are dependent on the counter-ion, the data reported are considered as 'apparent' values where besides complexation other processes are taking place as previously discussed.[2] This is not surprising when dealing with 1:3 electrolytes which are much more likely to undergo ion-pair formation than 1:2 and 1:1 electrolytes even at low concentrations. As far as **L3** is concerned an interesting paper was published by Meier and Detellier[75] in which the complexation of this receptor with the caesium cation in mixed solvents was investigated. The results obtained show the formation of caesium complexes of different composition (Cs(I): **L3** = 1:1, 2:1, 3:1). X ray diffraction studies provided information regarding the active sites of complexation of this receptor with this cation for the 2:1 complex.

Considering that the solvation of the receptor plays a role in the complexation process but nothing is known regarding the solution thermodynamics of **L1, L2** and **L3** in different solvents, these studies were undertaken. Thus Table 1 reports the solubility of these receptors in various solvents. For systems in which the composition of the solid in equilibrium with the saturated solution is the same, the standard Gibbs energies of solution, $\Delta_s G^o$ in the various solvents at 298.15 K were calculated and the results are also included in Table 1. The role of solvation in complexation processes has been emphasized in several papers.[2,4,76,77] Therefore given that the $\Delta_s G^o$ values involves the contribution of solvation and crystal lattice Gibbs energies, the latter is eliminated by the calculation of the transfer Gibbs ener-

Table 1. Solubilities and standard Gibbs energy of solution of **L1** and **L2** in different solvents at 298.15 K. Standard Transfer Gibbs energy from acetonitrile to other solvent

Solvent[(a)]	Solubility / mol dm^{-3}		$\Delta_s G°$ / kJ mol^{-1}		$\Delta_t G°$ (MeCN) → s / kJ mol^{-1}	
	L1	**L2**	**L1**	**L2**	**L1**	**L2**
DMF	$(2.8 \pm 0.1) \times 10^{-2}$	----[(b)]	9.0 ± 0.2	----	−8.7	----
PC	$(3.8 \pm 0.1) \times 10^{-3}$	2.6×10^{-3}	13.8 ± 0.1	14.8	−3.5	1.1
n-Hex	----	4.3×10^{-4}	----	19.4	----	5.7
MeCN	$(8.1 \pm 0.3) \times 10^{-4}$	4.1×10^{-3}	17.9 ± 0.3	13.7	0	0
Tol	----	2.8×10^{-2}	----	9.1	----	−4.6
EtOH	$(4.1 \pm 0.2) \times 10^{-3}$	3.3×10^{-3}	13.9 ± 0.1	16.6	−4	2.9
MeOH	$(6.2 \pm 0.2) \times 10^{-3}$	2.7×10^{-3}	12.8 ± 0.1	14.8	−5	1.1

[(a)] Abbreviations for solvents: DMF, *N*,*N*-dimethylformamide; PC, propylene carbonate; *n*-Hex, Hexane; MeCN, acetonitrile; Tol, toluene; EtOH, ethanol; MeOH, Methanol.
[(b)] Solvate formation.

gies, $\Delta_t G°$ using acetonitrile as the reference solvent. Data are shown in Table 1. In general terms, higher solubilities in the alcohols are found for the calix[*n*]arene derivatives than for the parent compounds. This is mainly due to the strong hydrogen bond formation between the OH of the parent calix[*n*]arenes (intramolecular hydrogen bonding) while the calixarene amide derivatives may interact with the alcohols through hydrogen bond formation with the carbonyl or ethereal oxygens of the amide moiety (intermolecular hydrogen bonding). It is known that the amide group is more basic than the ketone or the ester. The basicity of the functional groups present in the pendant arms of the receptors is likely to have an impact on their solubility. A representative example of this statement is provided by solubility data and standard Gibbs energies of solution of calix[4]arene ester, ketone and amide derivatives given in Table 2. Thus the amide derivative has the highest solubility while the one with the lowest basicity (ketone) shows the lowest solubility in methanol.

Another aspect to emphasise is that related with the number of substituted phenol units in the macrocycle. In moving from **L1** to **L3** the solubility decreases in MeOH. These findings are likely to be related with the increase in the crystal lattice energy as the number of substituted phenol units increase. As expected this is reflected in the melting points of these receptors (**L1**= 196 ºC, **L2**= 241 ºC, **L3**= 254 ºC). The same pattern observed in MeOH is found in EtOH, although the changes in solubility are less pronounced in the latter solvent. Like for the parent cyclic pentamer in acetonitrile, a higher solubility is found for the calix[5]arene amide. Undoubtedly the different conformations adopted by these receptors in solution appear to play a role in the different solvation trends observed. However it should be emphasised that although the $\Delta_t G°$ values reflect the difference in solvation of a receptor in one solvent relative to another, they do not provide any direct information regarding the sites of ligand-solvent interactions. Having stated it from the availability of $\Delta_t G°$ values for the reactants (receptor and guest) and the product (complex) in two solvents, the ratio between the stability constants, $K_{s,}$ in two solvents , s_1 and s_2 (Eq. 2) can be calculated from the thermodynamic cycle (Eq. 3) introduced by us in 1977.[46]

$$S_{s_1}^{s_2} = \frac{K_s(s_1)}{K_s(s_2)} \tag{2}$$

$$\begin{aligned} \Delta_c G°(s_1) - \Delta_c G°(s_2) = \Delta_t G°[M^{n+}](s_1 \rightarrow s_2) + \\ + \Delta_t G°[L](s_1 \rightarrow s_2) - \Delta_t G°[ML^{n+}](s_1 \rightarrow s_2) \end{aligned} \tag{3}$$

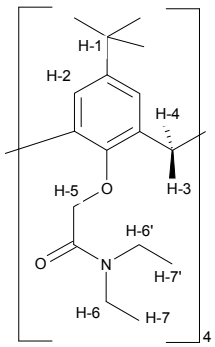
In fact this information leads to the assessment of the

Table 2. Solubilities and standard Gibbs energy of solution for calix[4]arene derivatives in methanol at 298.15 K

Ligand	Solubility / mol dm^{-3}	$\Delta_s G°$ / kJ mol^{-1}
Calix[4]arene ketone[2]	4.62×10^{-4}	19.04
Calix[4]arene ester[21]	3.65×10^{-3}	13.91
Calix[4]arene amide (L1)[(a)]	6.20×10^{-3}	12.80

[(a)] this work

Table 3. ^{1}H NMR data for **L1** and **L2** in various solvents at 298 K



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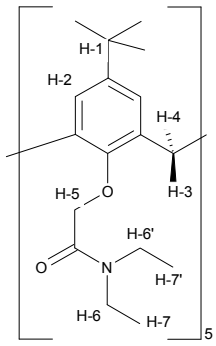


2

	$CDCl_3$[(a)]		CD_3CN[(a)]		CD_3OD[(a)]	
	L1	**L2**	**L1**	**L2**	**L1**	**L2**
H-1	1.09	1.02	1.19	1.14	1.09	1.03
H-2	6.79	6.90	7.13	7.14	6.82	6.95
H-3	5.22	4.99	5.26	5.05	4.96	4.85
H-4	3.21	3.32	3.24	3.27	3.18	3.31
H-5	5.05	4.75	5.01	4.85	4.96	4.73
H-6	3.35	3.40	3.38	3.38	3.38	3.42
H-7	1.16	1.11	1.1	1.18	1.18	1.14

[(a)] Deuterated solvents.

medium effect on the complexation process. This is an important aspect to consider.

From the information given in Table 1, solvents selected for these studies are now discussed. As far as **L1** is concerned, relative to methanol, acetonitrile is the poorest solvator for this ligand. In addition this solvent is also a poor cation solvator as assessed from the single-ion values for the transfer of cations from water to acetonitrile (data based on the Ph_4AsPh_4B convention).[63] Therefore from the point of view of the reactants, acetonitrile offers the most suitable complexation medium. Regarding **L2**, *n*-Hex is a poor solvator for this ligand. However this solvent together with toluene are not suitable for complexation for two reasons; i) the poor solubility of metal cation salts in these media ii) in the absence of solubility limitations, their unsuitability still remains due to the tendency of metal cations to undergo strong ion pair formation in these media. Therefore either methanol or propylene carbonate are the solvents to select for complexation studies. Given that i) most literature data on calix[4]arenes are in acetonitrile and ii) it was considered of interest to investigate the complexation behaviour of these systems in a protic and a dipolar aprotic solvent, these studies were carried out in acetonitrile and methanol so comparative studies on the ability of these receptors to interact with metal cations can be made.

^{1}H NMR of L1 and L2 in Various Solvents - The Medium Effect

^{1}H NMR data for **L1** and **L2** in three deuterated solvents, acetonitrile, CD_3CN, methanol, CD_3OD and chloroform, $CDCl_3$ (reference solvent) were obtained and are listed in Table 3. In all cases, the '*cone*' conformation is found. Thus the axial and equatorial hydrogens (H-3 and H-4) of the methylene bridge are non-equivalent and appear as a pair of doublets. However the conformational characteristic of the *'cone'* in calixarenes can be assessed from the difference between the chemical shifts of the axial and the equatorial protons ($\Delta\delta_{ax\text{-}eq}$).[7]

As far as **L1** is concerned these values are 2.01, 2.02 and 1.78 ppm in $CDCl_3$, CD_3CN and CD_3OD respectively. However for a system in a perfect *'cone'* conformation the $\Delta\delta_{ax\text{-}eq}$ value is generally around 0.90 ppm. These shift differences indicate the presence of a distorted '*cone*' conformation for **L1** in these solvents. Such distortion can be attributed to new effects on the methylene protons leading to a greater shielding of the equatorial protons (signal moves upfield) and a less shielding of the axial (signal moves downfield). The net result is an increase in the $\Delta\delta_{ax\text{-}eq}$. This distortion seems to be more pronounced in CD_3CN and $CDCl_3$ than in CD_3OD. Again the distortion of the *'cone'* is more pronounced in **L1** than in **L2**. For the latter, $\Delta\delta_{ax\text{-}eq}$ values are 1.67, 1.78 and 1.54 pm in $CDCl_3$, CD_3CN and

Table 4. ^{1}H NMR chemical shift changes of **L1** and **L2** upon complexation with monovalent metal cations in CD_3CN and CD_3OD at 298 K

Metal cation	**L1** (CD_3CN) $\Delta\delta$/ppm					**L2** (CD_3CN) $\Delta\delta$/ppm				
	H-2	H-3	H-4	H-5	H-6'	H-2	H-3	H-4	H-5	H-6'
Li^+	0.21	−0.66	0.17	−0.28	−0.17	0.18	−0.85	0.15	−0.28	−0.20
Na^+	0.23	−0.77	0.14	−0.45	−0.24	0.26	−0.78	0.17	−0.34	−0.23
K^+	0.25	−0.63	0.17	−0.38	−0.18	−0.06	−0.37	0.09	−0.16	−0.14
Rb^+	0.23	−0.63	0.14	−0.29	−0.18	−0.07	−0.41	0.11	−0.18	−0.13
Cs^+	0.24	−0.79	0.17	−0.42	−0.20	−0.02	−0.47	0.11	−0.21	−0.13
Ag^+	0.49	−0.34	0.28	−0.36	−0.18	0.20	−0.82	0.26	−0.10	−0.19
	L1 (CD_3OD) $\Delta\delta$/ppm					**L2** (CD_3OD) $\Delta\delta$/ppm				
	H-2	H-3	H-4	H-5	H-6'	H-2	H-3	H-4	H-5	H-6'
Li^+	0.41	−0.24	0.23	−0.13	−0.17	0.32	−0.44	overlap	−0.02	−0.11
Na^+	0.48	−0.40	0.24	−0.34	−0.21	0.38	−0.51	overlap	0.08	−0.13
K^+	0.49	−0.27	0.23	−0.28	−0.21	0.12	−0.60	overlap	0.04	−0.03
Rb^+	0.37	−0.18	0.15	−0.17	−0.19	0.12	−0.10	overlap	0.03	−0.05
Cs^+	0.03	−0.02	0.00	−0.01	−0.06	0.12	−0.21	overlap	0.01	−0.04
Ag^+	0.49	−0.34	0.28	−0.36	−0.18	---	---	---	---	---

CD_3OD respectively. However, the most remarkable feature of the data is the downfield chemical shift changes observed for the aromatic protons (**H-2**) (0.34 ppm for **L1** and 0.24 ppm for **L2**) in CD_3CN relative to $CDCl_3$. A similar behaviour has been previously found for other calix[4]arene derivatives.[2,14,15,22] This has been attributed to an interaction of the macrocycle through its hydrophobic cavity with the solvent. Given that this cavity is larger for the cyclic pentamer than for the tetramer, this interaction is expected to be greater for the latter relative to the former. As previously shown the presence of acetonitrile in the hydrophobic cavity of the ligand[22] has implications on the cation complexing ability of these macrocycles in this solvent relative to others.

Interaction of L1 and L2 with Metal Cations

^{1}H NMR studies of L1 and L2 with cations in CD_3CN and CD_3OD

This section will be discussed under the following headings

i) ^{1}H NMR studies of **L1** and **L2** with univalent cations in CD_3CN and CD_3OD at 298 K (Table 4)

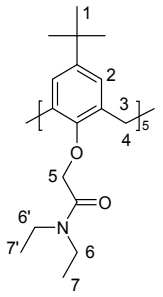
ii) ^{1}H NMR studies of **L1** and **L2** with bivalent cations in CD_3CN and CD_3OD at 298 K (Table 5)

i) Chemical shift changes ($\Delta\delta$, ppm) of **L1** with monovalent metal cations observed in CD_3CN relative to the free ligand show significant changes in the aromatic (H-2), the axial and the equatorial (H-3 and H-4), the methylene bridge (H-5) and the terminal protons (H-7). Thus strong shielding effects were observed for protons H-3, H-5 and H-7 possibly due to the inclusion of the metal cation inside the hydrophilic cavity forcing the pendant arms to move towards the inner region. However strong deshielding effects were observed in the aromatic and equatorial protons (H-2 and H-4 respectively) and this is attributed to the interaction of the metal cation with the lower rim (functionalised sites) and possibly a higher penetration of the solvent into the hydrophobic cavity of the complex ligand. Given that the conformational characteristics of the receptor can be assessed from $\Delta\delta_{ax\text{-}eq}$ values, these are now considered.

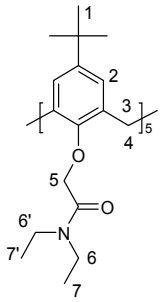
The degree of flattening of the *'cone'* reflected in the $\Delta\delta_{ax\text{-}eq}$ value of the metal cation complex, shows a decrease in the distortion of the *cone* relative to that of the free ligand. Thus the $\Delta\delta_{ax\text{-}eq}$ value (1.11 ppm) for the Na (I) complex is closer to that of a calix[4]arene in a perfect '*cone*' conformation ($\Delta\delta_{ax\text{-}eq}$ = 0.90 ppm). As for **L1** upon complexation with Li (I), K(I) , Rb (I), Cs(I) and Ag (I) metal cations, $\Delta\delta_{ax\text{-}eq}$ values (1.20, 1.22, 1.24, 1.51 and 1.40 ppm respectively) show a more distorted conformation than that for the Na (I) cation complex but lesser distortion as compared to that for the free ligand. As far as **L2** is concerned, different patterns were observed for Li (I), Na (I) and Ag (I) relative to the other monovalent metal cations in CD_3CN. This is observed in the deshielding of the aromatic protons (H-2) while the rest of the alkali-metal cations (K (I), Rb (I) and Cs (I)) appear to induce a slight shielding effect for

Table 5. ^{1}H NMR chemical shift changes of **L1** and **L2** upon complexation with monovalent metal cations in CD_3CN and CD_3OD at 298 K

				$\Delta\delta$/ppm				
^{1}H	Mg^{2+} complex	Ca^{2+}	Sr^{2+}	Ba^{2+}	Pb^{2+}	Zn^{2+}	Cd^{2+}	Hg^{2+}
H-1	0.04	0.05	0.05	0.08	0.07	0.06	0.06	0.07
H-2	0.24	0.35	0.36	0.36	0.37	0.29	0.29	0.33
H-3_{eq}	−1.23	−1.11	−1.05	−1.05	−1.01	−1.19	−1.19	−1.11
H-4_{ax}	overlap	0.34	−0.37	−0.29	0.38	0.26	0.26	0.33
H-5	overlap	−0.22	−0.24	−0.26	−0.12	−0.36	−0.36	overlap
H-6	overlap	overlap	0.11	0.18	0.14	0.15	0.15	overlap
H-6’	−0.13	overlap	−0.17	−0.18	−0.12	−0.11	−0.11	−0.12
H-7	overlap	overlap	---	overlap	overlap	overlap	overlap	overlap
H-7’	0.10	0.08	0.09	0.07	0.10	0.11	0.09	0.10
$\Delta\delta_{ax\text{-}eq}$	---	0.77	0.68	0.76	0.63	0.93	0.93	0.78



				$\Delta\delta$/ppm				
^{1}H	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}	Pb^{2+}	Zn^{2+}	Cd^{2+}	Hg^{2+}
H-1	−0.08	0.02	0.04	0.08	0.01	−0.02	0.01	0.01
H-2	−0.04	0.18	0.24	0.40	0.20	−0.04	0.17	0.20
H-3_{eq}	0.20	0.22	0.21	0.16	0.26	0.18	0.17	0.26
H-4_{ax}	−0.77	−0.65	−0.65	−0.85	−0.82	−0.82	−0.68	−0.82
H-5	−0.08	−0.09	−0.09	−0.29	−0.10	−0.12	−0.12	−0.10
H-6	0.05	0.05	0.04	0.04	0.07	0.05	0.05	0.07
H-6’	−0.12	−0.14	−0.16	−0.18	−0.17	−0.10	−0.11	−0.15
H-7	overlap	overlap	---	overlap	overlap	overlap	overlap	overlap
H-7’	0.01	0.01	0.01	0.28	0.08	0.07	0.01	0.08
$\Delta\delta_{ax\text{-}eq}$	0.80	0.90	0.91	0.76	0.70	0.81	0.93	0.70



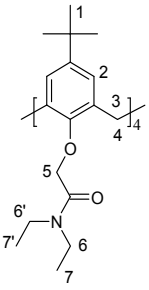
these protons. The values for the chemical shift changes for the axial and equatorial protons of Li (I), Na (I) and Ag (I) ($\Delta\delta_{ax\text{-}eq}$ = 0.78, 0.83, and 0.70 ppm) show that **L2** adopts a slightly flattened conformation close to a perfect *‘cone’*. However with larger metal cations (K (I), Rb (I) and Cs (I)), **L2** tends to adopt a more distorted conformation ($\Delta\delta_{ax\text{-}eq}$ = 1.32, 1.26 and 1.20 ppm).

As far as the complexation process involving **L1** and monovalent cations in CD_3OD is concerned, the $\Delta\delta_{ax\text{-}eq}$ values decrease in moving from the free ligand (1.78 ppm) to the cation complexes. Thus values of 1.31, 1.14, 1.28, 1.45 and 1.16 ppm are found for Li (I), Na (I), K (I), Rb (I) and Ag (I) respectively. The axial protons move upfield while the equatorial ones downfield. As a result, the $\Delta\delta_{ax\text{-}eq}$ values decrease relative to the free ligand and therefore the distortion of the ‘*cone*’ is reduced upon complexation. Similar ^{1}H NMR investigations were carried out with the same cations and **L2** in CD_3OD. These data are also shown in Table 4. Strong shielding effects of the axial protons are observed in the presence of the monovalent metal cations. The equatorial protons are overlapped and therefore the $\Delta\delta_{ax\text{-}eq}$ cannot be assessed.

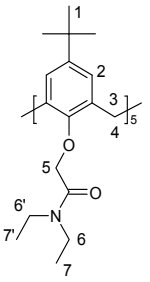
ii) Chemical shift changes of **L1** and **L2** upon complexation with bivalent cations in CD_3CN and CD_3OD at 298 K listed in Table 5 show that in the case of **L1** and bivalent cations in CD_3CN, chemical shift changes are more pronounced than those observed for monovalent ions in this solvent, particularly for protons 2 and 7’. As far as $\Delta\delta_{ax\text{-}eq}$ values are concerned, these are lower than 0.90 ppm suggesting that these complexes adopt a flattened *’cone*’ conformation in solution. A similar pattern is observed in CD_3OD (Table 6) where these values vary in the 0.50−0.80 ppm range. However The Ba (II) and Sr (II) complexes adopt a perfect ‘*cone*’ conformation in this solvent ($\Delta\delta_{ax\text{-}eq}$ = 0.90 ppm). This conformation is also observed for **L2** and Ca (II), Sr (II) and Cd (II) in CD_3CN. In addition, in this solvent a lineal relationship is shown between the chemical shift change of H-6’ and the ionic radius of the bivalent cation (Figure 3) suggesting a size effect on the chemical shift of this proton in acetonitrile. Unfortunately it was

Table 6. ^{1}H NMR chemical shift changes of **L1** and **L2** upon complexation with bivalent metal cations in CD_3OD at 298 K

				Δδ/ppm				
^{1}H	Mg^{2+} complex	Ca^{2+}	Sr^{2+}	Ba^{2+}	Pb^{2+}	Zn^{2+}	Cd^{2+}	Hg^{2+}
H-1	0.13	0.13	0.12	0.12	0.13	0.11	0.13	0.14
H-2	0.01	0.61	0.58	0.58	0.62	0.52	0.59	0.61
H-3_{eq}	Overlap	−0.73	−0.58	−0.58	−0.64	−0.73	−0.78	−0.72
H-4_{ax}	Overlap	0.47	0.40	0.40	0.49	Overlap	0.45	0.47
H-5	Overlap	Overlap	Overlap	−0.13	0.04	Overlap	Overlap	Overlap
H-6	Overlap	0.18	0.23	0.23	0.21	0.20	−0.07	−0.05
H-6’	Overlap	Overlap	−0.16	−0.17	0.15	0.14	−0.13	−0.11
H-7	Overlap	Overlap	overlap	Overlap	Overlap	0.12	0.13	0.16
H-7’	Overlap	Overlap	0.03	0.03	overlap	Overlap	Overlap	Overlap



				Δδ/ppm				
^{1}H	Mg^{2+} complex	Ca^{2+}	Sr^{2+}	Ba^{2+}	Pb^{2+}	Zn^{2+}	Cd^{2+}	Hg^{2+}
H-1	0.08	0.08	0.11	0.19	0.13	0.07	0.10	0.07
H-2	0.25	0.25	0.36	0.58	0.34	0.23	0.30	0.31
H-3_{eq}	Overlap	Overlap	Overlap	Overlap	Overlap	0.24	Overlap	Overlap
H-4_{ax}	−0.26	−0.26	−0.36	−0.52	−0.34	Overlap	−0.42	−0.38
H-5	0.26	0.26	0.15	0.30	0.29	Overlap	0.19	0.23
H-6	−0.05	−0.05	−0.07	−0.09	−0.03	−0.06	−0.05	−0.06
H-6’	0.12	0.12	0.16	0.11	0.15	0.08	0.05	0.12
H-7	0.07	0.07	0.05	0.05	0.09	0.08	0.07	0.08



not possible to calculate $\Delta\delta_{ax\text{-}eq}$ values for these cations in CD_3OD due to the interferences of the residual peaks for the solvent.

In summary from these NMR investigations involving uni- and bivalent cations it is relevant to emphasise the significant conformational differences observed in the $\Delta\delta_{ax\text{-}eq}$ values for Li (I) and Na (I) upon complexation with **L2** in CD_3CN relative to i) other univalent cations in this solvent and ii) the values for these cations and **L1** in the same solvent. The next section discusses the conductance behaviour of uni- and bivalent salts in acetonitrile and methanol upon addition of calix[*n*]arene amide derivatives in these solvents.

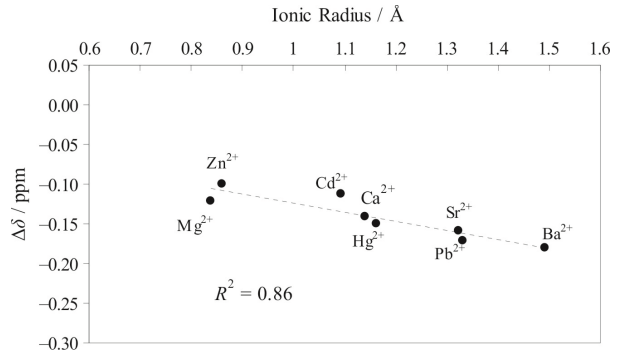


Figure 3. Chemical shift changes (ppm) of H-6’ for **L2** against of the ionic radii, (Å) of bivalent metal cations in CD_3CN at 298 K.

Conductance Studies of Calix[*n*]amides (*n* = 4, 5, 6) and Metal Cations

Conductometric Titrations

Conductometric titrations for metal cation salts in acetonitrile and methanol at 298.15 K were carried out by titrating the corresponding ligand (**L1, L2** or **L3**) onto the metal-ion salt. The molar conductance, Λ_m, for each addition was calculated and plotted against the ligand / metal cation (L / M^{n+}) concentration ratio (molar scale). Figure 4 shows representative data for **L1** and the sodium cation in acetonitrile and methanol respectively. In all cases the results show that:

i) As expected the Λ_m value for the free metal cation salt ($L/M^{n+} = 0$) would be slightly lower than the limiting molar conductance, Λ^o_m, of the corresponding salt as reported in the literature.[78]

ii) When ligand-metal cation interaction occurs, complexes of 1:1 stoichiometry are formed between **L1** and the relevant cations in these solvents.

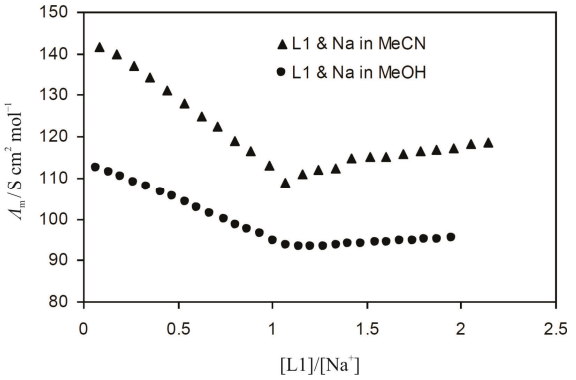


Figure 4. Conductometric curve for the titration of sodium (as perchlorate) and **L1** in acetonitrile and methanol at 298.15 K.

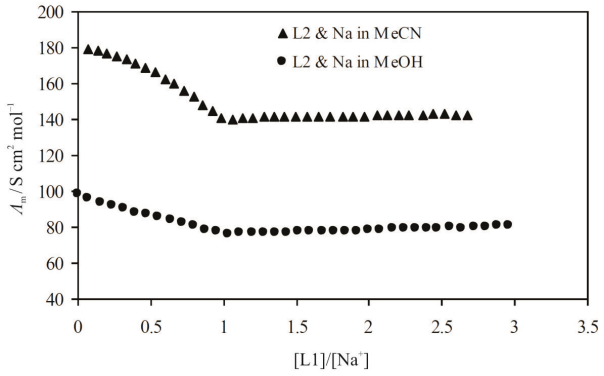


Figure 5. Conductometric curve for the titration of sodium (as perchlorate) and **L2** in acetonitrile and methanol at 298.15 K.

iii) From the intensity of the curvature of the conductometric titration curve it is observed that in acetonitrile relatively stable complexes are formed between **L1** with Na (I). Moderate changes in the curvature were found for K (I). The change of intensity in the curvature for the conductometric titrations of **L1** and Li (I) and Rb (I), showed the formation of weak complexes. A 1:1 complex was also found between this receptor and Ag (I) in acetonitrile. In most cases, Λ_m values decrease as the ligand is added to the metal-ion salt due to the reduction in the mobility of the complex relative to the free cation salt. In moving from acetonitrile to methanol the composition of the complexes remains the same but the stability decreases for Li (I) and Rb (I) while increases for Ag (I) showing the effect of cation solvation on the strength of complexation as previously discussed.[2,4]

Conductometric titration curves for **L1** and bivalent metal cations in MeCN showed the formation of 1:1 complexes with alkaline-earth , heavy metals (Pb(II), Cd(II), Hg(II), Cu (II)) as well as with Zn(II) and Ni(II) in both solvents.

As far as **L2** is concerned, Figure 5 shows representative titration curves for this ligand with the sodium cation in acetonitrile and methanol at 298.15 K. Complexes of moderate stability and 1:1 (ligand:metal cation) stoichiometry are found between **L2** and alkali-metal and silver cations in methanol. In the case of acetonitrile, complexes of 1:2 (ligand:metal cation) composition are found when this ligand interacts with lithium and sodium in this solvent. The titration curves for these cations and **L2** in MeCN showed a gradual decrease in conductance with a change in the curvature at the L:M^{n+} molar ratio of 0.5 indicating the formation of 1:2 complexes. Further addition of the ligand led to a further decrease in conductance and a clear break at the ligand:metal cation ratio of 1 was found reflecting that strong 1:1 complexes with these cations are formed. Completion of the reaction was shown by the small changes in conductance. The formation of 1:2 complexes between receptor **L2** and Li (I) and Na (I) in MeCN explain the differences found in the conformational changes reflected in the $\Delta\delta_{ax\text{-}eq}$ values for these systems relative to i) other cations and this receptor in this solvent and ii) the same cations and **L2** in MeOH**.** For other univalent cations (K (I), Rb (I), Cs (I), and Ag (I)) well defined break points were found revealing that 1:1 complexes of moderate stability are formed in acetonitrile. In MeOH only 1:1 complexes were found for univalent cations and **L2**. This is a typical example in which the medium effect plays a key role in the complexation process. Indeed acetonitrile is a poor cation solvator while methanol is a strong solvator[63] to the extent that the hosting capacity of the receptor is enhanced as to host two of the smallest cations per unit of receptor in acetonitrile while **L2** interacts with only one cation in methanol. The solvation of the functional groups in the pendant arms of the receptor capable of interacting with a protic solvent such as MeOH is likely to contribute to the lower hosting ability of this receptor for these cations in MeOH relative to MeCN. As far as bivalent cations and **L2** in MeCN and MeOH are concerned**,** complexes of 1:1 stoichiometry were found with all alkaline-earth metals and heavy metals tested (Hg (II), Pb (II), Cd (II)) and Zn (II)) although weaker complexes appear to be formed in MeOH relative to MeCN.

The solubility of **L3** in acetonitrile (Table 1) was found to be very low as to proceed with conductance studies in this solvent. Therefore conductance studies were performed in MeOH. No changes in conductance were observed for alkali-metal cations and this receptor in the alcohols. Only a slight break at the 1:1 ligand: metal cation ratio was found for Ag (I) and **L3** in MeOH indicating the formation of a very weak complex in this solvent. Among bivalent metal cations, 1:1 complexes of moderate stability are found for Ca (II), Sr (II), Ba (II), Cu (II), Cd (II), Hg (II) and Pb (II). However a 1:2 **L3**:Mg (II) complex is formed in MeOH as

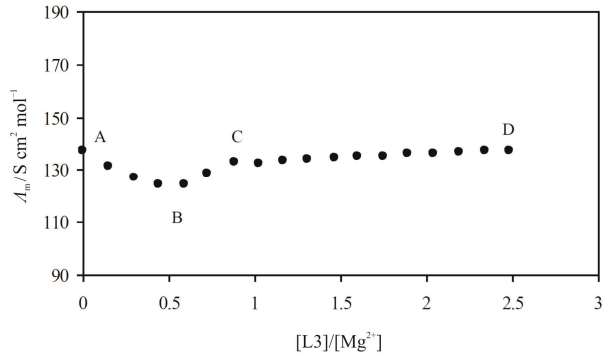


Figure 6. Conductometric curve for the titration of magnesium (as perchlorate) and **L3** in methanol at 298.15 K.

shown in the conductometric titration curve (Figure 6). Thus two breaks are observed. The first one occurs at a **L3**:Mg (II) ratio of 0.50 when an excess of the salt relative to the receptor is present in solution. Under these experimental conditions two metal cations are taken up by unit of receptor and a decrease in conductance is observed. Further addition of the receptor may result in the transport of one cation from the complex to the receptor. Consequently the conductance increases from B to C until the ligand: metal cation ratio reaches a value of 1 indicating the possible formation of a 1:1 $[Mg\mathbf{L3}]^{2+}$ complex. We have no experimental evidence as to suggest the mode by which **L3** can hold two cations. Quite clearly cations must be separated from each other to avoid electrostatic repulsion. It is known that several conformations can be found in solution for the amide derivative of the cyclic hexamer and the possibility of hosting two caesium cations per unit of receptor has been demonstrated earlier by Meier and Detellier[75] in solution and in the solid state.

The processes involved are shown in Eqs. 4 and 5

$$2Mg^{2+}(MeOH) + L3(MeOH) \rightarrow [Mg_2L3]^{4+}(MeOH) \quad (4)$$

$$[Mg_2L3]^{4+}(MeOH) + L3(MeOH) \rightarrow 2[MgL3]^{2+}(MeOH) \quad (5)$$

Having stated it, emphasis must be made about the fact that the break at the ligand:cation ratio of 1 does not necessarily imply the formation of a 1:1 complex. Indeed if the number of ligand units interacting equals that of the cation, a ligand:cation ratio of 1 will be obtained. The possibility of the process shown in Eq. 6 cannot be excluded

$$[Mg_2L3]^{4+}(MeOH) + L3(MeOH) \rightarrow [Mg_2L3_2]^{4+}(MeOH) \quad (6)$$

However this process (Eq. 6) seems unlikely to occur given that the size of the metal ion complex containing two ligands is much greater than that involving one ligand. Therefore the mobility of the former (Eq. 6) is expected to be lower than that for the latter (Eq. 5). Consequently the expected decrease in conductance for the process involving two receptors is not corroborated with the increase in conductance observed from B to C. No changes in conductance are observed from C to D.

Having (i) determined the composition of metal-ion complexes involving **L1** and **L2** in acetonitrile and methanol, and (ii) previous information regarding the concentration range at which these salts are predominantly in their ionic forms in these solvents, we proceeded with the thermodynamic characterisation of these systems and these are now discussed.

Thermodynamics of Complexation of L1, L2 and L3 with Metal Cations in Acetonitrile and Methanol

Although Tables 7 and 8 report thermodynamic data for calix[*n*]arenes (*n*=4,5,6) with uni- and bivalent metal cations in acetonitrile and methanol at 298.15 K the discussion will be carried out under the following headings:

i. Thermodynamics of complexation of **L1, L2** and **L3** with univalent metal cations in acetonitrile and methanol at 298.15 K.
ii. Thermodynamics of complexation of L1**, L2** and **L3** with bivalent metal cations in acetonitrile and methanol at 298.15 K.

i) The complexation of **L1** with univalent cations in MeCN shows the formation of very strong complexes in this solvent. Their high stability is enthalpically controlled and entropy destabilised except for Li (I) and Ag (I) which are entropically favoured. Data for **L1** and these cations in MeOH show large differences with literature values for Na (I) and K (I) in this solvent but good agreement between the two methods used by us (competitive titration calorimetry and potentiometry). Like in MeCN among the alkali-metal cations this receptor is selective for Na (I). However if the stability of the Ag (I) complex in MeOH is considered, this receptor is unable to distinguish between Ag (I) and Na (I) as reflected by the standard deviation of the data. No interaction between **L1** and Cs (I) was found in MeOH. In most cases the process is enthalpy controlled with unfavourable entropy except for Li (I) (enthalpy and entropy favoured). The medium effect on the complexation of **L1** with univalent cations can be assessed from the ratio between the stability constant for this receptor and a given cation in one solvent relative to another (Eq. 7).

$$S^{s_1}_{MeCN} = \frac{K_s(M^{n+})_{MeCN}}{K_s(M^{n+})_{s_1}} \quad (7)$$

Table 7. Thermodynamic Parameters of Complexation of **L1** and **L2** with monovalent metal cations in acetonitrile and methanol at 298.15 K

			MeCN					
	log K_s		$\frac{\Delta_c G°}{\text{kJ mol}^{-1}}$		$\frac{\Delta_c H°}{\text{kJ mol}^{-1}}$		$\frac{\Delta_c S°}{\text{J K}^{-1}\text{ mol}^{-1}}$	
Cation	**L1**	**L2**	**L1**	**L2**	**L1**	**L2**	**L1**	**L2**
Li^+	9.6[b]	4.8 (1:1)[a] 2.5 (1:2)[a]	−54.9	−27.4 −14.3	−51.7[b]	−76.4[a] −63.3[a]	11	−164 −164
Na^+	9.8[b]	5.6 (1:1)[a] 3.0 (1:2)[a]	−55.9	−32.0 −17.1	−67.6[b]	−39.2[a] −57.2[a]	−39	−24 −134
K^+	7.2[b]	5.9[a]	−41.1	−33.7	−52.8[b]	−37.8[a]	−39	−14
Rb^+	5.53[a]	5.8 [a]	−31.57	−33.1	−35.7[a]	−29.8[a]	−14	11
Cs^+	-	5.6[a]	-	−32.0	-	−21.1[a]	-	37
Ag^+	6.10[c]	4.5[a]	−34.82	−25.7	−28.7[a]	-	21[a]	-
			MeOH					
Cation	**L1**	**L2**	**L1**	**L2**	**L1**	**L2**	**L1**	**L2**
Li^+	4.1[a]	5.2[a]	−23.4	−29.7	−9.0[a]	−17.0[a]	48	43
Na^+	6.2[b]	5.1[a]	−35.4	−29.1	−46.5[b]	−31.0[a]	−37	−6
K^+	4.73[a]	5.4[a]	−27.0	−30.8	−33.8[a]	−57.9[a]	−23	−91
Rb^+	3.50[a]	5.8[a]	−20.0	−33.1	−22.4[a]	−69.3[a]	−8	−121
Cs^+	-	5.5[a]	-	−31.4	-	−55.7[a]	-	−82
Ag^+	6.60[c]	5.9[a]	−37.7	−33.7	−47[a],[b]	−41.5[a]	−31	−26

[a] Direct calorimetry. Standard deviations for log K_s values given with one decimal place are in the range ± 0.1−0.2. For log K_s values given with two decimal places, the standard deviations are ± 0.03−0.06. For $\Delta_c H°$ values are in the 0.1−0.5 kJ mol^{-1} range.

[b] Competitive titration calorimetry. Standard deviation in log K_s values is in the range ± 0.2−0.3. Standard deviation in the $\Delta_c H°$ values are in the ±. 0.5−0.7 kJ mol^{-1} range.

[c] Potentiometry.

Data presented in Table 9 shows that the selectivity of **L1** towards alkali metal cations in methanol relative to acetonitrile increases as the size of the metal cation increases. Data for the transfer Gibbs energy of metal cations from MeCN to MeOH show the level of solvation of these systems in one solvent relative to the other.[63]

A plot of the transfer Gibbs energy, $\Delta_t G°^{\text{MeOH}}_{\text{MeCN}}$ (data based on the Ph_4AsPh_4B convention), of alkali metal cations and silver cation from acetonitrile to methanol against the log ($S^{\text{MeOH}}_{\text{MeCN}}$) (Figure 7) shows a linear regression of the type:

$$\Delta_t G°(M^{n+})(\text{MeCN} \rightarrow \text{MeOH}) = a + b \log S^{\text{MeOH}}_{\text{MeCN}} \quad (8)$$

The positive values for the transfer Gibbs energies of Ag (I), Rb (I) and K (I) cations from acetonitrile to methanol ($\Delta_t G°^{MeOH}_{MeCN}$) show that these cations are more solvated in acetonitrile.[63] The negative values of $\Delta_t G°^{MeOH}_{MeCN}$ found for Li (I) and Na (I) reflect a better solvation of these cations in methanol relative to acetonitrile. The selectivity of **L1** towards metal cations in methanol relative to acetonitrile is strongly dependent on the solvation of the cations in these solvents. Therefore the selectivity of **L1** for univalent metal cations in methanol decreases as the solvation of these cations in the same solvent increases. This finding is concomitant with previous statements by Danil de Namor and co-workers[47] in that the most suitable complexation medium is that which is a poor solvator for the reactants and a good solvator for the product. This lineal relationship does not necessarily imply that the solvation of the receptor and the metal-ion complex do

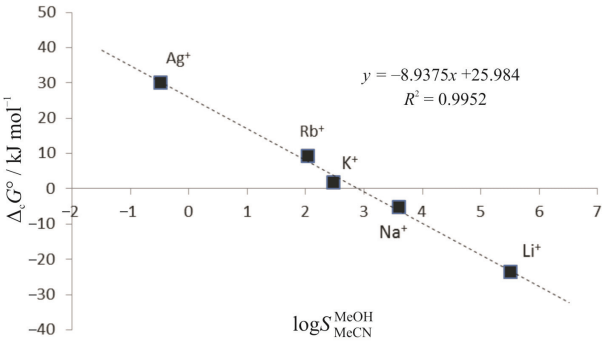


Figure 7. A plot of the transfer Gibbs energy of monovalent metal cations from MeCN to MeOH at 298.15 K (data based in the Ph_4AsPh_4B convention) against the selectivity of **L1** (logarithm scale), for these metal cations in MeOH relative to MeCN at 298.15 K.

Table 8. Thermodynamic Parameters of Complexation of **L1** and **L2** with bivalent metal cations in acetonitrile and methanol at 298.15 K

MeCN

	log K_s		$\Delta_c G°$ / kJ mol^{-1}		$\Delta_c H°$ / kJ mol^{-1}		$\Delta_c S°$ / J K^{-1} mol^{-1}	
	L1	**L2**	**L1**	**L2**	**L1**	**L2**	**L1**	**L2**
Mg^{2+}	9.9[b]	6.1[b]	−56.5	−34.8	−37.1[b]	−61.3[b]	65	−89
Ca^{2+}	14.5[b]	8.9[b]	−82.8	−50.8	−105.7[b]	−78.3[b]	−77	−92
Sr^{2+}	12.7[b]	10.1[b]	−72.5	−57.7	−78.3[b]	−85.6[b]	−19	−94
Ba^{2+}	10.4[b]	11.1[b]	−59.4	−63.4	−48.8[b]	−122.5[b]	36	−198
Pb^{2+}	11.0[b]	7.7[b]	−62.8	−44.0	−102.6[b]	−75.6[b]	−133	−106
Zn^{2+}	5.3[a]	4.4[a]	−30.3	−25.1	−37.8[a]	−105.9[a]	−25	−271
Cd^{2+}	11.5[b]	5.3[a]	−65.6	−30.3	−96.4[b]	−113.5[a]	−103	−279
Hg^{2+}	9.9[b]	5.8[a]	−56.5	−33.1	−90.3[b]	−122[a]	−113	−298
Cu^{2+}	5.30[a]	4.8[a]	−30.3	−27.4	−51.3[a]	−56.1[a]	−70	−96
Co^{2+}	5.50[a]	4.5[a]	−31.4	−25.7	−48.8[a]	−35.5[a]	−58	−33
Ni^{2+}	5.58[a]	5.5[a]	−31.9	−31.4	4.9[a]	−35.6[a]	123	−14

MeOH

	log K_s			$\Delta_c G°$ / kJ mol^{-1}			$\Delta_c H°$ / kJ mol^{-1}			$\Delta_c S°$ / J K^{-1} mol^{-1}		
	L1	**L2**	**L3**	**L1**	**L2**	**L3**	**L1**	**L2**	**L3**	**L1**	**L2**	**L3**
Mg^{2+}	3.4[a]	3.0[a]	--	−19.4	−17.2	---	−1.2[a]	34.8[a]	---	61	174	---
Ca^{2+}	11.3[b]	5.1[a]	4.11[a]	−65	−29.2	−23.6	−31[b]	−26.0[a]	25.5[a]	114	11	165
Sr^{2+}	9.1[b]	7.9[b]	5.20[a]	−51.9	−45.2	−29.7	−5.6[b]	−19.8[b]	18.3[a]	155	85	161
Ba^{2+}	6.1[b]	9.3[b]	4.20[a]	−35.4	−52.8	−24.2	0.5[b]	−17.8[b]	28.9[a]	120	117	178
Co^{2+}	5.70[a]		---	−32.5	−29.2	---	7.4[a]	−31.2[a]	---	133	−7	---
Cu^{2+}	4.30[a]	5.1[a]	4.10[a]	−24.5	−29.1	−23.2	13.2[a]	−42.4[a]	32.7[a]	126	−45	187
Cd^{2+}	6.44[b]	4.9[a]	5.70[a]	−36.7	−27.7	−32.5	−21.4[b]	−38.7[a]	11.7[a]	51	−37	148
Zn^{2+}	5.91[a]	5.0[a]		−33.7	−28.2		5.3[a]	−32.9[a]	---	131	−16	---
Hg^{2+}	4.6[a]	---	5.34[a]	−26.3	---	−30.5	−33.4[a]	----	13.9[a]	−24	---	149
Pb^{2+}	4.53[a]	4.9[a]	---	−25.9	−28	---	−23.5[a]	16.9[a]	---	8	151	---
Ni^{2+}	---	5.2[a]	---	---	−29.7	---	---	−35.6[a]	---	---	−20	---

[a] Direct calorimetry. Standard deviations for log K_s values given with one decimal place are in the range ± 0.1–0.2. For log K_s values given with two decimal places, the standard deviations are ± 0.03–0.06. For $\Delta_c H°$ values are in the 0.1–0.5 kJ mol^{-1} range.

[b] Competitive titration calorimetry. Standard deviation in log K_s values is in the range ± 0.2–0.3. Standard deviation in the $\Delta_c H°$ values are in the ± 0.2–0.9 kJ /mol range.

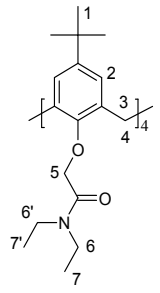
not contribute to the complexation but may compensate each other. A representative example is given by Eq. 9 expressed in the following thermodynamic cycle shown below where the higher solvation of the receptor in MeOH relative to MeCN is almost compensated by the higher solvation of the complex in MeCN than in MeOH.

$$\begin{array}{ccccc} Li^+(MeCN) & + & Ll(MeCN) & \xrightarrow{-55\ kJ\ mol^{-1}} & Li^+Ll(MeCN) \\ \downarrow -23.64\ kJ\ mol^{-1} & & \downarrow -5\ kJ\ mol^{-1} & & \downarrow 2.96\ kJ\ mol^{-1} \\ Li^+(MeOH) & + & Ll(MeOH) & \xrightarrow{-23\ kJ\ mol^{-1}} & Li^+Ll(MeOH) \end{array} \quad (9)$$

As for **L2**, complexation with univalent metal cations in acetonitrile at 298.15 K shows complex formation of 1:2 and 1:1 (ligand: metal cation) stoichiometries for Na (I) and Li (I) in this solvent. Thus **L2** shows a higher hosting capacity for these cations in MeCN than in MeOH. Computer modelling simulation was carried out

Table 9. Selectivity of **L1** for univalent metal cations in methanol relative to acetonitrile at 298.15 K

Metal cation	S^{MeOH}_{MeCn}
Li^+	3.2×10^5
Na^+	4.0×10^3
K^+	3.0×10^2
Rb^+	1.1×10^2
Ag^+	3.2×10^{-1}



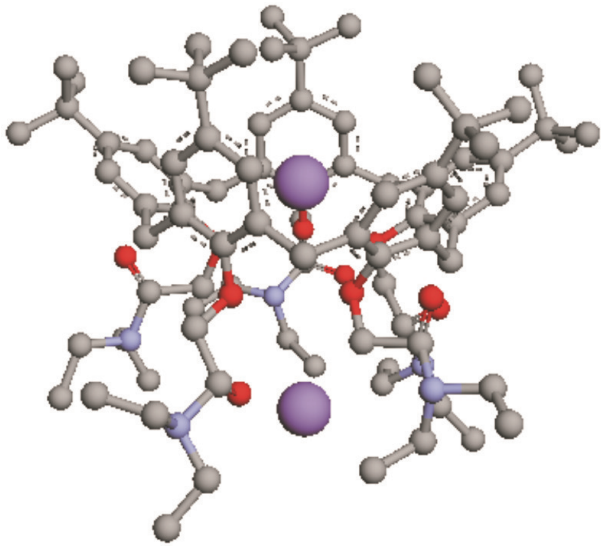


Figure 8. Molecular modelling of **L2**-2Na^+ (1:2) complex as determined by molecular simulation studies, the hydrogen atoms were removed to increase the clarity of the structure.

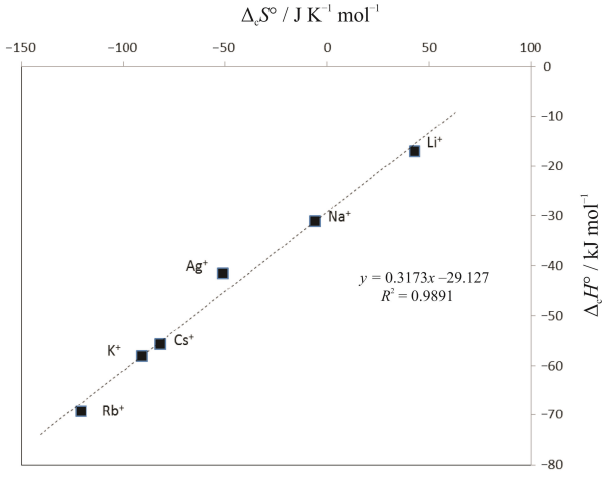


Figure 9. Plot for the enthalpies of complexation against the entropies of complexation of **L2** with univalent metal cations in methanol at 298.15 K.

using HyperChem 5.0, in vacuum conditions. These studies show that the arrangement of minimum energy for this system is that in which one Na (I) is held by 6 coordination sites provided by the oxygen donor atoms and the solvent molecule (MeCN), while the second Na (I) is coordinated to 5 oxygen donor atoms in the complex, as shown in Figure 8. A detailed investigation by X-ray diffraction studies on heavy metal cations (Cd (II) and Pb (II))[22] complexes with a calix[4]arene ester showed that the solvent is hosted in the hydrophobic cavity, thus, the solvent can provide a coordinating site for the cation through its nitrogen donor atom. Such is the case for the cadmium complex and this may be the case here.

Moderate stabilities were found for the other univalent metal cations (K (I), Rb (I), Cs (I) and Ag (I)) and **L2** in acetonitrile as shown in Table 7.

As for **L2** with alkali metal cations in methanol at 298.15 K, the highest stability constant was found for Rb^+ (log K_s = 5.8). However the standard deviation of the stability constant data (in logarithm terms) (± 0.2) shows the low discrimination of this ligand towards these metal cations. The similar standard Gibbs energy values for **L2** and alkali-metal cations give evidence of entropy-enthalpy compensation processes which Grunwald and Steel[79] attributed to solvent reorganisation. This is better depicted in the slope of 317.3 K calculated from a plot of enthalpies against entropies of complexation of **L2** with univalent metal cations in methanol which is not far from the temperature of 298.15 K (Figure 9). The complexation of **L2** with the lithium cation in methanol is enthalpically controlled and entropically favoured. As for the processes concerning **L2** and other univalent metal cations (Na (I), K (I), Rb (I) and Cs (I)), the processes were found to be enthalpically controlled and entropically unfavoured.

Complexation of **L2** with the Ag (I) cation in acetonitrile and methanol shows that like **L1** this ligand forms stronger complexes in the protic (MeOH) than in the dipolar aprotic solvent (MeCN). Thus the processes involving the complexation of both ligands with this cation in MeOH are enthalpically controlled and entropically unfavoured. In acetonitrile, the complexation process is enthalpically controlled and entropically favoured. The latter parameter reflects the strong cation desolvation upon complexation in this solvent. The lineal correlation between the transfer Gibbs energy, $\Delta_t G°^{\mathrm{MeOH}}_{\mathrm{MeCN}}$ (data based on the Ph_4AsPh_4B convention)[63], of alkali metal cations and silver cation from acetonitrile to methanol against the log($S^{\mathrm{MeOH}}_{\mathrm{MeCN}}$) found for **L1** is not followed for **L2** particularly for Ag (I) due to the higher solvation of the silver complex in MeCN relative to MeOH as shown in the thermodynamic cycle (Eq. 10).

$$\begin{array}{ccccc} Ag^+(MeCN) & + & L2(MeCN) & \xrightarrow{-25.5\ kJ\ mol^{-1}} & Ag^+L2(MeCN) \\ \downarrow 30.1\ kJ\ mol^{-1} & & \downarrow 1.10\ kJ\ mol^{-1} & & \downarrow 23.6\ kJ\ mol^{-1} \\ Ag^+(MeOH) & + & L2(MeOH) & \xrightarrow{-33\ kJ\ mol^{-1}} & Ag^+L2(MeOH) \end{array} \qquad (10)$$

ii) Data for bivalent cations and **L1** in MeCN (Table 8) show that this receptor forms very strong complexes with alkaline-earth and heavy metal (Hg (II), Pb (II) and Cd (II) cations in this solvent. Moderate stabilities are observed for Zn (II), Cu (II), Ni (II) and Co (II) complexes. For Mg (II) and Ba (II) these processes are enthalpically controlled and entropically favoured. For Ca (II), Sr (II), Pb (II), Zn (II), Cd (II), Hg (II), Cu (II) and Co (II) the processes are enthalpically stabilised and

entropically unfavoured. However for Ni (II) an inverted result is observed. The process is entropically controlled and enthalpically unfavoured. As far as MeOH is concerned, the only available stability constant value is that for Ba (II) and this differs from the value reported here derived from potentiometry and competitive titration calorimetry. Very strong complexes are found for Ca (II), Sr (II) and Ba (II) in this solvent. The highest stability constant in MeOH and MeCN is that for Ca (II). In MeOH, both parameters, enthalpy and entropy contribute favourably to the high stability observed for this system in this solvent with a slightly higher contribution from enthalpy. Data listed in Table 8 for Mg (II), Sr (II), Ba (II), Co (II), Cu (II) and Zn (II) show that these processes are entropically controlled and enthalpically unfavoured, except for Mg (II) and Sr (II) which are slightly enthalpically favoured. For Hg (II) and Pb (II) the processes are enthalpy controlled but for Hg (II) entropically unfavoured. For Cd (II) complexation is favoured by both, enthalpy and entropy. As far as **L2** and bivalent cations in MeCN are concerned the complex stability results from the enthalpy contribution given that the processes are entropically unfavoured to the extent that the maximum exothermicity is that for the Ba (II) cation and this receptor in this solvent. In MeOH, the enthalpy and entropy associated with the complexation of Mg (II) and **L2** is typical of systems involving a highly solvated cation for which the energy required for desolvation overcomes that of cation-receptor binding. As a result the process is endothermic and entropy controlled. For all other alkaline-earth metal cations the complex stability is enthalpy and entropy favoured. As far as transition and heavy metal cations are concerned the enthalpy controls the stability of these complexes while the entropy has a destabilising effect.

Given that **L3** is slightly soluble in MeCN, thermodynamic data shown in Table 8 are referred to MeOH. Among alkaline-earth metal cations, the stability of the complex decreases in moving from the cyclic tetramer to the cyclic hexamer for Ca (II) and Sr (II) to the extent that no complexation (or extremely weak was found for Mg (II). For Ba (II) the stability increases from **L1** to **L2** and decreases from **L2** to **L3.** In all cases the stability of complex formation is controlled by entropy given that these processes are endothermic. As expected different trends are observed for the complexation of alkaline-earth metal cations with **L1** relative to **L2**. This may be attributed to the increase in the size of the hydrophilic pseudo-cavity of **L2** and consequently on the number of donor atoms available for complexation. Thus among these cations **L1** is selective for Ca (II) in both solvents while **L2** shows the highest selectivity for Ba (II). In the following section the competition between cation desolvation (endothermic process) and cation-receptor binding (exothermic process) for systems involving bivalent cations in MeCN and MeOH is discussed.

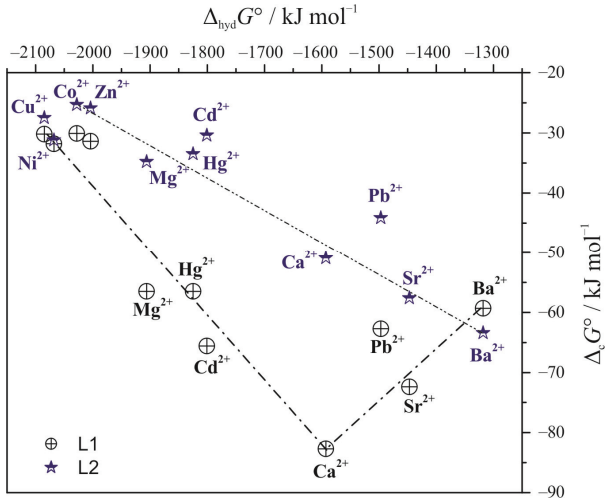


Figure 10. Plot of the standard Gibbs energies of hydration of the metal cations against the standard Gibbs energy of complexation of **L1** and **L2** with bivalent metal cations in acetonitrile at 298.15 K.

Contribution of Cation Solvation and Cation-receptor Binding to Complex Formation of L1, L2 and L3 with Bivalent Cations in Acetonitrile and Methanol

The information regarding transfer Gibbs energies of bivalent cations from one solvent to another is very limited. Therefore to assess the cation solvation upon complexation of bivalent cations and these receptors in these solvents attempts are made to establish whether or not a correlation is found between the thermodynamic parameters of complexation and corresponding data for the hydration of these ions.[80–83] Hydration rather than solvation is considered due to the limited amount of solvation data in these solvents. This is justified given that the trend observed in solvation is expected to be the same as that of hydration. In the complexation of macrocycles and metal cations in a given solvent, two main processes are taking place. These are cation desolvation and receptor binding. To obtain some information regarding which of these processes predominate, thermodynamic data of complexation are plotted against the standard Gibbs energies of hydration of the bivalent cations involved. This is shown in Figure10. The pattern observed is similar to that found for these systems in MeOH. This figure shows that the minimum Gibbs energy (higher stability constant) is that for Ca**L2** (II). It is clear that the extent of complexation increases from Ba (II) to Ca (II). However a drop in stability is observed from Ca (II) to Cu (II) as the standard hydration Gibbs energies of the ions increase. In conclusion the results show that from Ba (II) to Ca (II) the binding energy predominates over the energy required for cation desolvation. However from Ca (II) to Cu (II) the latter overcomes the former as cation solvation

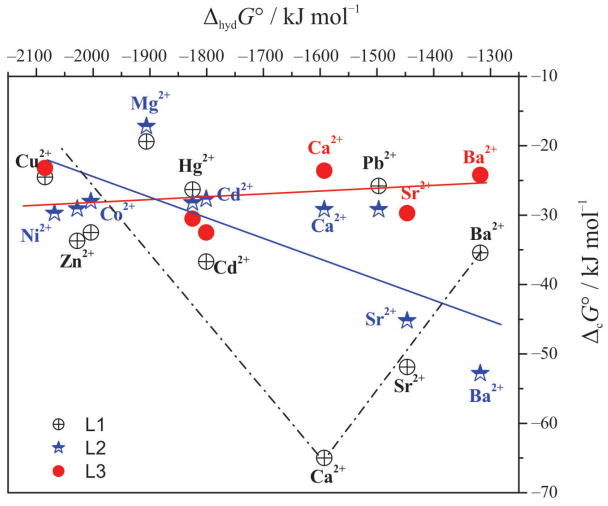


Figure 11. Plot of the standard Gibbs energies of hydration of the metal cations against the standard Gibbs energy of complexation of **L1**, **L2** and **L3** with bivalent metal cations in methanol at 298.15 K.

increases. In fact the same pattern applies in terms of enthalpy. This trend in Gibbs energies and enthalpies was also observed in MeOH, although binding energies are stronger in MeCN than in MeOH. The metal cations are more solvated in MeOH than in MeCN. The former solvent is a better cation solvator than MeCN. Therefore the energy required for cation desolvation upon complexation in MeOH is likely to be higher than in MeCN. This statement is corroborated by the endothermic character of the enthalpies associated with the complexation reactions involving **L1** and Ba (II), Co (II), Cu (II) and Zn (II) cations in MeOH.

The selectivity peak observed when complexation data involving **L1** were plotted against the cation hydration Gibbs energies is not observed for **L2** and these cations in MeCN or indeed in MeOH as shown in Figure 10. The same situation occurs with **L3** and metal cations in MeOH. This ligand shows poor discrimination for these metal cations as shown in Figure 11. It seems that the binding process is overcome strongly by cation desolvation, given that for all the systems investigated the distinctive feature of the data is that in all cases the complexation process is endothermic and entropy controlled. It is quite clear from these results that as the number of phenyl units in the structure of calix(*n*)arenes increases from $n = 4$ to $n = 6$, the flexibility of the ligand increases and therefore the receptors are unable to selectively recognise these metal cations in these solvents.

CONCLUDING REMARKS

The emphasis in this article lies on fundamental aspects of thermodynamics involving macrocyclic receptors and ionic guests and calls for the need of using an integrated approach, to ensure that the data reported are representative of the process taking place in solution so the concept of selectivity can be accurately addressed. The field of Supramolecular Chemistry requires a multidisciplinary approach within and outside Chemistry. Undoubtedly a great deal of experimental work and misleading statements could have been avoided if early work in the general area of Physical Chemistry and particularly on electrochemical and thermodynamic studies of electrolytes and neutral species would have been considered. Within this context emphasis should be made about the fact that the remarkable growth of interest in macrocyclic chemistry involving neutral receptors and their interaction with ionic species has resulted in an extensive broadening in the field of solution chemistry involving novel electrolytes and non-electrolytes and there is plenty of fascinating research waiting to be explored in this area.

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