Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

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To cite this Article De Namor, Angela F. Danil , Aparicio-Aragon, Walther B. , Goitia, Maria Teresa and Casal, Alberto R.(2004) 'Cation Complexation by a Lower Rim Calix(4)arene Derivative: Structural, Electrochemical and Thermodynamic Studies', Supramolecular Chemistry, 16: 6, 423 — 433

To link to this Article: DOI: 10.1080/10610270410001721944

URL: http://dx.doi.org/10.1080/10610270410001721944

Supramolecular Chemistry, September 2004, Vol. 16 (6), pp. 423–433

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Cation Complexation by a Lower Rim Calix(4)arene Derivative: Structural, Electrochemical and Thermodynamic Studies

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Received (in Southampton, UK) 9 March 2004; Accepted 7 May 2004

The synthesis and characterization (^{1}H and ^{13}C NMR) of a partially substituted lower rim *p-tert*-butylcalix(4)arene, namely, 5,11,17,23-tetra-4-*tert*-butyl-25,27-bis(diethylphosphate amino)ethoxy-26,28-dihydroxycalix[4]arene (1), are reported. The solution thermodynamics of the ligand in a variety of solvents at 298.15 K was investigated through solubility (hence standard Gibbs energy of solution) measurements while the calorimetric technique was used to derive the standard solution enthalpy. These data were used to calculate the standard entropy of solution. An enthalpy–entropy compensation effect is shown and, as a result, slight variations are observed in the transfer Gibbs energies of this ligand from the reference to other solvents. ^{1}H NMR, conductance and calorimetric measurements were carried out to establish the degree of interaction of the ligand with univalent (Li^+, Na^+, K^+, Rb^+, Cs^+ and Ag^+) and bivalent (Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}, Pb^{2+}, Cd^{2+}, Hg^{2+}, Cu^{2+}, Zn^{2+}) cations in acetonitrile, methanol, *N*,*N*-dimethylformamide and propylene carbonate. No complexation was found between this ligand and univalent cations in these solvents. As far as the bivalent cations are concerned, interaction between 1 and these cations was found only in acetonitrile. The versatile behaviour of this ligand with bivalent cations in this solvent is reflected by the formation of complexes of different stoichiometry. Thus the interaction of 1 with alkaline-earth (Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}) and Pb^{2+} metal cations leads to the formation of 1:2 (cation:ligand) complexes. However, for other bivalent metal cations (Cu^{2+}, Zn^{2+}, Cd^{2+} and Hg^{2+}) the complex stoichiometry was found to be 1:1. The results are discussed in terms of the key role played by acetonitrile in processes involving calix[4]arene derivatives.

Keywords: Calixarenes; Thermodynamics; Metal cations

INTRODUCTION

The field of calixarene chemistry has developed in a relatively short period of time. As a result these ligands have received wide recognition in chemistry as assessed from the numerous papers [1] and books [2–6] published on these macrocycles. Lower and upper rim calixarene derivatives have shown interesting complexing properties with ionic and neutral species [7,8]. Lower rim derivatives of the cyclic tetramer have attracted particular interest because of the well-defined ‘cone’ conformation. This is mainly attributed to the different nature of the two cavities, which are the most significant feature of these macrocycles. In designing cation receptors, the nature of the donor atoms in the walls of the hydrophilic cavity is an important aspect to consider. However, in the lower rim calix[4]arene derivatives, the hydrophobic cavity has shown receptive properties for neutral species, which adds further complexity to the cation binding processes involving the hydrophilic cavity of these ligands relative to those characterized by the presence of a single hole (most crown ethers) or cavity (cryptands). Thus the solvent effect on the cation complexation process by calix[4]arene derivatives is quite unpredictable. This statement is corroborated by the versatile behaviour of acetonitrile in complexes formed between calix[4]arene ester and ketone derivatives [9–11] and bivalent cations in this solvent.

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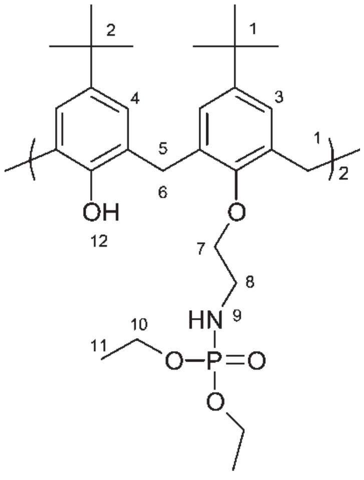
ISSN 1061-0278 print/ISSN 1029-0478 online © 2004 Taylor & Francis Ltd
DOI: 10.1080/10610270410001721944

In this paper we report the synthesis, ^{1}H and ^{13}C NMR and thermodynamic characterization of a partially substituted lower rim calix[4]arene derivative, namely, 5,11,17,23-tetra-4-*tert*-butyl-25, 27-bis(diethylphosphate amino)ethoxy-26,28-dihydroxycalix[4]arene **1**, and its interaction with univalent (Li$^+$, Na$^+$, K$^+$, Rb$^+$, Cs$^+$ and Ag$^+$) and bivalent (Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}, Pb^{2+}, Cd^{2+}, Hg^{2+}, Cu^{2+} and Zn^{2+}) metal cations. ^{1}H NMR, conductance and calorimetric measurements were carried out to establish the active sites of complexation of the macrocycle with the cation, determine the composition of the metal-cation complex and assess quantitatively the strength of complexation and therefore the selective behaviour of **1** for one cation relative to another.



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EXPERIMENTAL

p-tert-Butylcalix[4]arene, bromoacetonitrile, potassium carbonate and potassium hydrogen carbonate were purchased from Aldrich. Lithium aluminium tetrahydride, 18-crown-6 (18-C-6), diethyl chlorophosphate, tetra-*n*-butylammonium perchlorate (TBAP) and tetra-*n*-butylammonium bromide purchased from Fluka were used without further purification. Metal-cation (lithium, sodium, potassium, rubidium, silver, magnesium, calcium, strontium, barium, lead, cadmium, zinc, copper and mercury) perchlorates were purchased from Aldrich, and then dried over P_4O_{10} under vacuum for several days before use. Acetonitrile [12] (CH_3CN, HPLC grade, Hayman Ltd, high purity reagent), tetrahydrofuran (THF, Fisher reagent), methanol (MeOH, Fisher reagent, 99%), ethanol (EtOH, HPLC grade, Fisher), dichloromethane (CH_2Cl_2, Fisher), *N*,*N*-dimethylformamide (DMF, Fisher, AR), hexane (Hex, HPLC grade), 1-butanol (1-BuOH, Fisher), dimethylsulfoxide (DMSO, Fisher, AR) and propylene carbonate (PC, Fluka, >99% AR) were used without further purification.

Synthesis of 5,11,17,23-tetra-4-*tert*-butyl-25,27-di(nitrilomethoxy)-26,28-dihydroxycalix[4]arene (L_1) [13]

A solution of *p-tert*-butyl calix[4]arene (5.022 g, 7.738 mmol), 18-crown-6 (0.512 g, 1.937 mmol) and potassium carbonate (9.031 g, 34.35 mmol) was suspended in dry acetonitrile (150 mL). The mixture was then stirred for 1 h under a nitrogen atmosphere. This was followed by dropwise addition of bromoacetonitrile (7.035 g, 58.649 mmol). The reaction mixture was heated to 75°C and refluxed for 24 h with vigorous stirring. The course of the reaction was monitored by thin layer chromatography (TLC) using a hexane:ethyl acetate (8:2) mixture as the developing solvent system. After cooling, the solvent was removed under reduced pressure and a white solid was obtained. The solid was dissolved in dichloromethane, the mixture filtered, and then the dichloromethane was removed under reduced pressure. The residue was recrystallized from methanol. The mixture was left overnight at room temperature, and the crystals obtained were left in the piston drier at 90°C. The product was obtained in 75% yield. ^{1}H NMR (300 MHz, in $CDCl_3$); δ (ppm), J (Hz); 7.12 (s, 4H, Ar–**H**), 6.73 (s, 4H, Ar–**H**), 5.55 (s, 2H, Ar–**OH**), 4.23 (d, 4H, $J = 12.91$, –O–**CH_2**–CN), 4.79 (d, 4H, $J = 13.50$, Ar–**CH_2ax**–Ar), 3.45 (d, 4H, $J = 13.50$, Ar–**CH_2eq**–Ar), 1.34 (d, 18H, $J = 5.40$, –C–(C**H_3**)$_3$), 0.87 (d, 18H, $J = 8.70$, –C–(C**H_3**)$_3$).

Synthesis of 5,11,17,23-tetra-4-*tert*-butyl-25,27-di(aminoethoxy)-26,28- dihydroxycalix[4]arene (L_2)

A solution of L_1 (4.8 g, 6.60 mmol) in dry THF (150 mL) was added into a solution of $LiAlH_4$ (1.46 g, 38.48 mmol) in the same solvent (50 mL) under a nitrogen gas atmosphere and with continuous stirring. The temperature was kept at 0°C using an ice-bath and the reaction mixture was stirred for 6 h. The course of reaction was monitored by TLC using hexane:ethyl acetate (8:2) mixture as the developing solvent system. NaOH 20% solution (2 mL, 10 mmol) was added upon completion of the reaction, followed by distilled water (5 mL), until a white precipitate was produced. The mixture was filtered and the filtrate was evaporated under reduced pressure. The solid was recrystallized from ethanol; yield 70%. ^{1}H NMR (300 MHz, in $CDCl_3$); δ (ppm), J (Hz); 7.04 (s, 4H, Ar–**H**), 6.97 (s, 4H, Ar–**H**), 4.33 (d, 4H, $J = 12.91$, Ar–**CH_2ax**–Ar), 4.54 (t, 4H, $J = 4.65$, –O–**CH_2**–CH_2–), 3.37 (d, 4H, $J = 12.91$, Ar–**CH_2eq**–Ar), 3.31 (t, 4H, $J = 4.80$, –**CH_2**–NH_2), 1.17 (m, 36H, –C–(C**H_3**)$_3$).

Synthesis of 5,11,17,23-tetra-4-*tert*-butyl-25,27-bis(diethylphosphate amino)ethoxy-26, 28-bishydroxycalix[4]arene (1)

In a three-necked round-bottomed flask (250 mL) equipped with an ice-bath, L_2 (4.887 g, 6.65 mmol), potassium carbonate (1.369 g, 9.91 mmol) and potassium hydrogen carbonate (1.77 g, 17.73 mmol) were suspended in dry dichloromethane (100 mL). The mixture was left under continuous stirring for 30 min. This was followed by dropwise addition of diethyl chlorophosphate (1 mL, 7.94 mmol). The reaction mixture was left at room temperature for 48 h under vigorous stirring. The course of the reaction was monitored by TLC using hexane:ethyl acetate (8:2) mixture as the developing solvent system. The solvent was removed under reduced pressure and a white solid was obtained. The solid was recrystallized from acetonitrile. The mixture was left overnight at room temperature and the crystals obtained were left in a pistol drier at 60°C. The product was obtained in 70% yield, mp 179–180°C. Elemental analysis was carried out at the University of Surrey. Anal. Calcd.(%): C, 66.78; H, 8.41; N, 2.78. Found: C, 66.49; H, 8.62; N, 2.82. ^{1}H NMR (300 MHz), ($CDCl_3$); δ (ppm), J (Hz); 8.57 (s, 2H, Ar–**OH**), 7.03 (s, 8H, Ar–**H**), 5.20 (d, 2H, $J = 11.10$, –CH_2–N**H**–), 4.34 (d, 4H, $J = 13.20$, Ar–C$\mathbf{H_2}$**ax**–Ar), 4.13 (m, 12H, –O–C$\mathbf{H_2}$–CH_2, O–C$\mathbf{H_2}$–CH_3), 3.62 (m, 4H, –CH_2–C$\mathbf{H_2}$–NH), 3.37 (d, 4H, $J = 12.91$, Ar–C$\mathbf{H_2}$**eq**–Ar), 1.36 (m, 12H, O–CH_2–C$\mathbf{H_3}$), 1.21 (m, 36H, –C–(C$\mathbf{H_3}$)$_\mathbf{3}$). ^{13}C NMR (300 MHz) ($CDCl_3$) δ_C (ppm); 149.69, 148.87, 148.34, 142.86, 133.76, 127.96, 126.13, 125.65 (**Ar**), 77.16 (O**C**H_2CH_2NH), 62.56, 62.49 (O**C**H_2CH_3), 42.09 (OCH_2**C**H_2NH), 34.37, 33.98 (**C**(CH_3)$_3$), 32.33 (Ar**C**H_2Ar), 31.67, 31.28 (C(**C**H_3)$_3$) and 16.50, 16.40 (OCH_2**C**H_3).

Solubility Measurements

Saturated solutions of the ligand were prepared by adding an excess of **1** to the solvent. The mixtures were left in a thermostated bath at 298.15 K for several days until equilibrium was attained. Samples of the saturated solutions were withdrawn and placed in different porcelain crucibles that had been previously dried and accurately weighed. The solvent was carefully evaporated to constant weight. Blank experiments showed no impurities in the solvent. Analysis was performed at least by duplicate on the same equilibrium mixture. In CH_2Cl_2, $CHCl_3$ and DMSO, solvate formation was observed when **1** was exposed to a saturated atmosphere of the solvent.

^{1}H NMR Studies

^{1}H NMR measurements were recorded at 298 K using a Bruker AC-300E pulsed Fourier transform NMR spectrometer. Typical operating conditions for routine proton measurements involved 'pulse' or flip angle of 30°, spectral frequency (SF) of 300.135 MHz, delay time of 1.60 s, acquisition time (AQ) of 1.819 s, and line broadening of 0.55 Hz. Samples of the ligand ($\sim$0.5 mL, 6.0×10^{-3} mol dm^{-3}) were prepared in CD_3CN and placed in 5 mm NMR tubes using tetramethylsilane (TMS) as the internal reference. Stepwise addition of the metal cation salt dissolved in CD_3CN ($\sim 3.0 \times 10^{-2}$ mol dm^{-3}) was made until no further chemical shift changes were observed. Similar experiments were carried out in CD_3OD and d_6-DMF.

Conductance Measurements

For these measurements, the Wayne Kerr B642 Autobalance was used. For the determination of the constant of the conductivity cell, the method described previously [14] was used. The stoichiometry of the complexation process was assessed from conductance measurements. Thus fresh solutions of the metal-ion salt and the ligand in the appropriate solvent (CH_3CN, MeOH and PC) were prepared for each run. The cell was cleaned and dried and an accurately weighed solution of the metal-ion salt ($\sim$25 cm^3, 3.0×10^{-4} mol dm^{-3}) was added. The conductance was measured once thermal equilibrium was attained. This was followed by the addition of a solution of the ligand in the same solvent ($\sim$10 cm^3, 1.0×10^{-3} mol dm^{-3}). All measurements were taken at 298.15 K. Conductance measurements were also used to assess the range of concentrations at which the free and the complex salts are predominately in their ionic forms in solution.

Calorimetric Measurements

Calorimetric titrations were carried out to determine the stability constant (expressed as log K_s) and the enthalpy of complexation, $\Delta_c H$. For this purpose, the Tronac 450 calorimeter was used as an isoperibol titration calorimeter. The reproducibility of the apparatus was checked by chemical calibration using the protonation reaction of tris(hydroxymethyl)-aminomethane (THAM) with HCl 0.1 mol dm^{-3} in aqueous medium at 298.15 K. The enthalpy of protonation of THAM is well established [15]. Therefore, an aqueous solution of THAM was placed in the burette (previously calibrated) and incrementally titrated into the calorimetric vessel containing HCl (50 cm^3). The enthalpy value obtained of -47.63 ± 0.19 kJ mol^{-1} is in good agreement with that reported by Hill *et al.* (-47.49 kJ mol^{-1}) using the LKB calorimeter [15].

For complexes of moderate stability (log $K_s < 6$), direct calorimetric titrations were performed.

Thus a solution of the ligand ($50\,cm^3$, 6.0×10^{-4} to $1.5\times10^{-5}\,mol\,dm^{-3}$) in the reaction vessel was titrated with a solution of the metal-ion salt in the appropriate solvent (2.0×10^{-2} to $5.0\times10^{-2}\,mol\,dm^{-3}$). Corrections for the heat of dilution of the metal-ion salt were applied in all cases. Stability constant and enthalpy values for alkaline-earth metal cations and **1** in acetonitrile were derived from titration microcalorimetry. For this purpose, a four-channel heat conduction microcalorimeter (Thermometric 2277) was used. Electrical (static and dynamic) and chemical calibrations were carried out to check the reliability of the instrument [16]. For these measurements, a solution of the metal-ion salt (2.0×10^{-2} to $5.0\times10^{-2}\,mol\,dm^{-3}$) was prepared in acetonitrile, placed in the syringe and titrated into the vessel containing a solution of the ligand of interest ($2.8\,cm^3$, concentration range 9×10^{-4} to $1.7\times10^{-3}\,mol\,dm^{-3}$) prepared in the same solvent. About 18 injections were made at time intervals of 40 min. Corrections for the enthalpy of dilution of the titrant in the solvent were carried out in all cases. A computer program for TAM (Digitam 4.1 for Windows from Thermometric AB and select software AB Sweden) for 1:2 (metal cation:ligand) processes was used to calculate $\log K_s$ and $\Delta_c H$ values.

Determination of Enthalpies of Solution

Enthalpies of solution were measured with the Tronac 450 calorimeter. To check the reliability of the solution calorimeter, the standard enthalpy of solution of THAM in an aqueous solution of 0.1 M of HCl was determined. The value obtained ($\Delta_s H^o = -29.62 \pm 0.11\,kJ\,mol^{-1}$) is in good agreement with the one reported by Irving and Wadsö ($-29.71\,kJ\,mol^{-1}$) [17]. For the determination of the enthalpies of solution of **1** in different solvents, a procedure described elsewhere was used [18,19].

RESULTS AND DISCUSSION

Solution Thermodynamics of 1. Transfer Parameters

The results from the ^{1}H NMR studies involving this ligand show that **1** is in a 'cone' conformation in solution. This statement is corroborated by the two pairs of doublets at 3.37 and 4.34 ppm observed for the methylene bridge protons. This conformation was also found in the solid state. Indeed, the X-ray structure [20] provides indisputable evidence about the structure of the ligand and the presence of the phosphorus donor atoms in the pendant arms of **1** [20]. In order to proceed with solution studies of **1**, knowledge of the solubility of this ligand in various solvents is required. Thus solubility data for **1** in a variety of solvents at 298.15 K are reported in Table I. Also included in this table are the standard solution Gibbs energies, $\Delta_s G^o$, enthalpies, $\Delta_s H^o$ (derived from calorimetric measurements), and entropies, $\Delta_s S^o$, for this ligand in non-aqueous media.

Taking CH_3CN as the reference solvent, transfer thermodynamic parameters ($\Delta_t G^o$, $\Delta_t H^o$ and $\Delta_t S^o$) of **1** to other solvents were calculated. The data show that $\Delta_t G^o$ values from CH_3CN to dipolar aprotic (DMF and THF) and to protic (MeOH, EtOH, 1-BuOH) solvents are slightly negative (favourable transfer). This is not the case for hexane (inert solvent).

While the $\Delta_t G^o$ values of **1** from CH_3CN to other solvents do not differ significantly, large variations are observed in the transfer enthalpies and entropies of this ligand to other solvents. This is the result of an almost complete enthalpy–entropy compensation effect. Effects like these, where $\Delta_t G^o \cong 0\,kJ\,mol^{-1}$ and the enthalpy and the entropy are compensated, have been attributed by Grunwald and Steel [21] to solvent reorganization. Thus, the favourable transfer enthalpy, $\Delta_t H^o$, of **1** from CH_3CN to the protophilic dipolar aprotic solvents (DMF and THF) may be attributed to the acidic character of the ligand and its likely interaction with these solvents.

TABLE I Solubilities and derived standard Gibbs energies of solution, enthalpies and entropies of **1** in various solvents at 298.15 K. Transfer data from acetonitrile

Solvent	Solubility/ $mol\,dm^{-3}$	$\Delta_S G^o$/ $kJ\,mol^{-1}$	$\Delta_S H^o$/ $kJ\,mol^{-1}$	$\Delta_S S^o$/ $J\,K^{-1}\,mol^{-1}$	$\Delta_t G^o/kJ\,mol^{-1}$ ($CH_3CN \rightarrow s$)	$\Delta_t H^o/kJ\,mol^{-1}$ ($CH_3CN \rightarrow s$)	$\Delta_t S^o/J\,K^{-1}\,mol^{-1}$ ($CH_3CN \rightarrow s$)
CH_3CN	$(6.60 \pm 0.10)\times10^{-3}$	12.4 ± 0.2	26.9 ± 0.7	48	0	0	0
DMF	$(1.69 \pm 0.13)\times10^{-2}$	10.1 ± 0.2	21.5 ± 0.7	38	−2.3	−5.4	−10
THF	$(7.95 \pm 0.09)\times10^{-2}$	6.3 ± 0.2	24.4 ± 0.6	61	−6.1	−2.5	12
MeOH	$(5.01 \pm 0.08)\times10^{-2}$	7.4 ± 0.2	32.4 ± 0.6	151	−5.0	25.5	102
EtOH	$(4.23 \pm 0.05)\times10^{-2}$	7.8 ± 0.2	37.7 ± 0.8	100	−4.6	10.8	52
1-BuOH	$(4.10 \pm 0.10)\times10^{-2}$	7.9 ± 0.2	50.9 ± 0.2	144	−4.5	24.0	95
Hex	$(8.40 \pm 0.03)\times10^{-4}$	17.6 ± 0.3	83.0 ± 0.7	220	5.2	56.1	171
CH_2Cl_2	Very soluble	Solvate formation					
DMSO	Very soluble	Solvate formation					
$CHCl_3$	Very soluble	Solvate formation					

CH_3CN, acetonitrile; DMF, *N,N*-dimethylformamide; THF, tetrahydrofuran; MeOH, methanol; EtOH, ethanol; 1-BuOH, 1-butanol; Hex, hexane; CH_2Cl_2, dichloromethane; DMSO, dimethylsulfoxide; $CHCl_3$, chloroform.

TABLE II Chemical shift changes ($\Delta\delta$ ppm)* in the ^{1}H NMR spectra of **1** with alkaline-earth, heavy and transition metal cations in CD_3CN at 298 K

Proton	Free	Mg^{2+} (1:2)	Ca^{2+} (1:2)	Sr^{2+} (1:2)	Ba^{2+} (1:2)	Pb^{2+} (1:2)	Cd^{2+} (1:1)	Hg^{2+} (1:1)	Zn^{2+} (1:1)
1	1.16	0.01	0.00	0.01	0.01	0.01	0.01	0.00	0.01
2	1.21	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
3	7.21	0.03	0.02	0.02	0.01	0.03	0.02	0.02	0.03
4	7.26	0.03	0.03	0.00	0.00	0.02	0.02	0.02	0.03
5	3.45	0.05	0.05	0.04	0.04	0.04	0.05	0.04	0.05
6	4.31	−0.08	−0.09	−0.07	−0.08	−0.13	−0.12	−0.09	−0.14
7	4.08	0.07	0.07	0.07	0.06	0.10	0.09	0.06	0.11
8	3.52	0.06	0.04	0.02	0.04	0.06	0.04	0.06	0.05
9	5.19	0.11	0.10	−0.02	−0.19	0.09	0.03	overlap	0.14
10	4.08	0.07	0.07	0.07	0.06	0.10	0.08	0.05	0.10
11	1.29	0.03	0.04	0.03	0.05	0.06	0.05	0.05	0.07
12	8.55	−0.04	−0.06	−0.06	−0.09	−0.11	−0.11	−0.11	−0.14

*Chemical shift changes relative to the free ligand.

As far as the favourable transfer of **1** from CH_3CN to the alcohols is concerned, this process is entropically controlled as Δ_tH^o does not contribute favourably to the transfer of the ligand from a less (acetonitrile) to a more structured solvent (alcohol). Indeed, disruption of the solvent structure requires energy (endothermic process) and leads to an entropy increase. Having established the solution properties of **1**, we proceeded with the ^{1}H NMR studies with the aim of assessing the interaction of the ligand with metal cations.

^{1}H NMR Studies

No chemical shifts changes were observed in the ^{1}H NMR spectra by the addition of alkali-metal and silver cations to the solution of the ligand in CD_3CN, CD_3OD and d_6- DMF.

Results from ^{1}H NMR titrations of **1** with bivalent cations in CD_3CN, CD_3OD and d_6-DMF showed chemical shift changes only in CD_3CN and these are reported in Table II. As complexation proceeds in this solvent, the chemical shift changes for the *t*-butyl and the aromatic protons are not significant. Deshielding effects are observed for the equatorial protons (5), the methylene protons adjacent to the O (7 and 10), proton (8) and the proton (9) of the NH group indicating that the metal cations interact with the O and the N donor atoms. Shielding effects are observed for the axial (6) and the phenolic protons (12) for Cd^{2+}, Hg^{2+} and Zn^{2+} in CD_3CN. The differences between the chemical shifts of the methylene bridge (axial and equatorial) protons relative to that for the free ligand indicate that the complexes adopt a flattened 'cone' conformation [2–4]. An indication that the two pendant arms containing the donor atoms participate in the complexation process is reflected in the chemical shift changes observed for protons 5, 6, 7, 8, 10 and 11.

A similar situation is found for the alkaline-earth metal and lead(II) cations. However, the most striking feature of the ^{1}H NMR results for the bivalent cations in CD_3CN is that for the alkaline-earth and lead(II) metal cations and **1**, the most significant chemical shift changes for protons 5, 6, 9 and 10 occur at a metal-cation:ligand (M^{2+}/L) ratio of 0.5, while for the other bivalent metal cations changes are not observed until 1:1 (cation:ligand) stoichiometry is reached. This is illustrated in Fig. 1 where the results of ^{1}H NMR titrations of **1** with Ca^{2+} and Hg^{2+} are shown. In this figure, $\Delta\delta$ values (ppm) relative to the free ligand are plotted against the $M^{2+}/\mathbf{1}$ molar ratio. These findings suggest that in moving to the alkaline-earth and lead metal ion complexes, the stoichiometry appears to be altered from 1:1 to 1:2 (metal cation:ligand) ratio. As NMR does not always provide information regarding the correct stoichiometry of the complex, conductance and thermodynamic measurements were also undertaken.

Conductimetric Titrations

As far as the alkali-metal and silver cations are concerned, conductance data showed no indication of a change in slope at any given molar ratio in CH_3CN, MeOH or indeed PC. This is in accord with the ^{1}H NMR results obtained by the addition of the appropriate alkali-metal salt to the ligand in CD_3CN, CD_3OD and d_6-DMF. The same behaviour was observed with the bivalent cations in MeOH and PC. Indeed, conductance measurements showed no appreciable changes during the course of the titration. This is not the case in CH_3CN. In this solvent, the conductimetric titration curves show that for Cd^{2+}, Hg^{2+}, $Cu^{2+}$and Zn^{2+}, 1:1 complexes of moderate stability are formed. This is illustrated in Fig. 2 where molar conductances, Λ_m (S cm^2 mol^{-1}), resulting from the titration of Cu^{2+}, Cd^{2+}, and Hg^{2+} are plotted against the ligand:metal cation (L/M^{2+}) ratios respectively. For the alkaline-earth metal cations (Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}) and Pb^{2+}, changes in slope are observed at $L/M^{2+} = 1$ and 2,

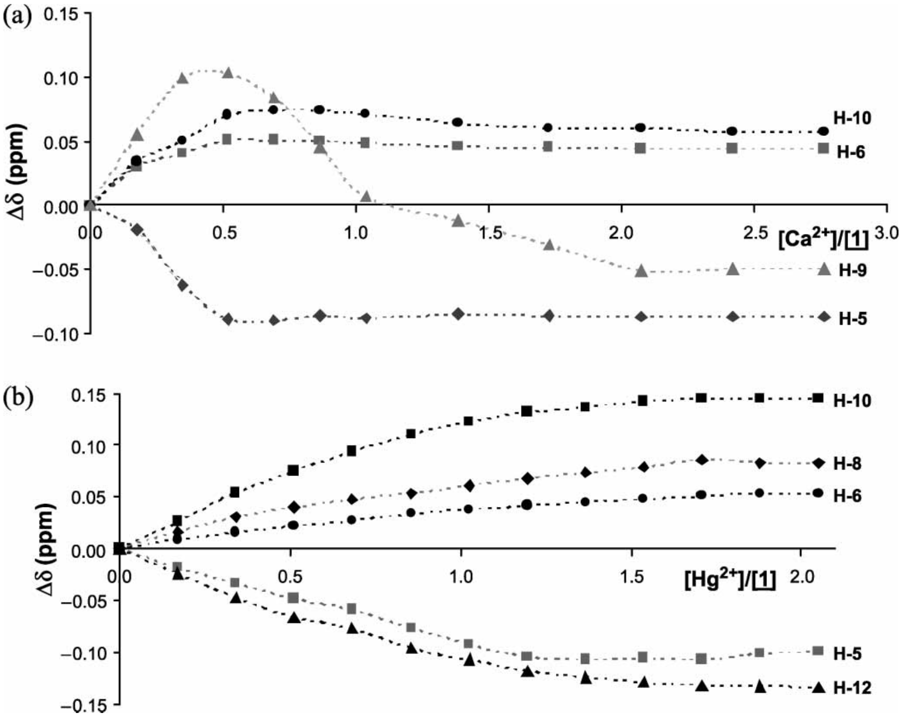

FIGURE 1 ^{1}H NMR titration curve for calcium (a) and mercury (b) cations (as perchlorates) with **1** in CD_3CN at 298 K.

showing the formation of 2:1 stoichiometry complexes. The processes taking place can be represented by the following equations:

$$M^{2+}(CH_3CN) + \mathbf{1}(CH_3CN) \rightarrow M^{2+}\mathbf{1}(CH_3CN) \quad (1)$$

$$M^{2+}\mathbf{1}(CH_3CN) + \mathbf{1}(CH_3CN) \rightarrow M^{2+}\mathbf{1}_2(CH_3CN) \quad (2)$$

An illustrative example is given in Fig. 3 where Λ_m values for the titration of Mg^{2+}, Ba^{2+} and Pb^{2+} with **1** are plotted against their corresponding L/M^{2+} ratios. The decreases in the Λ_m values upon complexation are merely attributed to the lower mobility of the cation in moving from M^{2+} to the $M^{2+}L$ and from the latter to $M^{2+}L_2$, given the increase in the size of the cation, while its overall charge is not altered. Having stated this, the data in Fig. 3 show that changes in Λ_m from $M^{2+}L$ to $M^{2+}L_2$ are not sharp. This is expected when large ions are involved. Therefore, we proceeded with calorimetric titrations to derive the thermodynamics of complexation of these systems. It may be argued that thermodynamics do not provide structural information. However, it is indisputable that any model proposed must fit the experimental thermodynamic

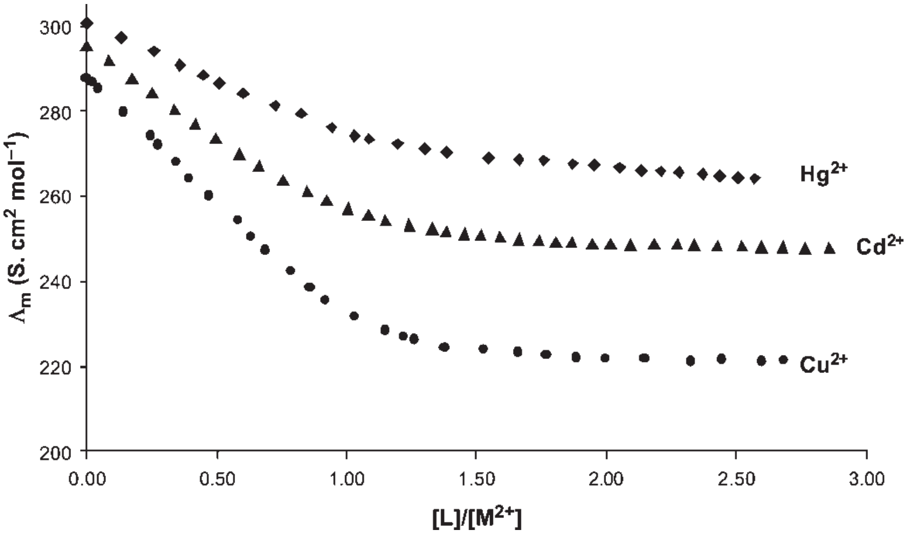

FIGURE 2 Conductimetric titration curves for copper, cadmium and mercury cations (as perchlorates) with **1** in acetonitrile at 298.15 K.

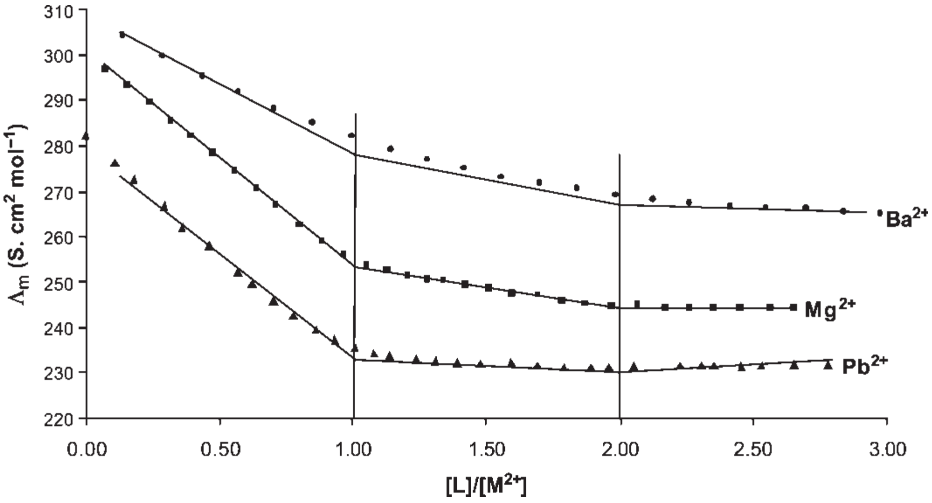

FIGURE 3 Conductimetric titration curves for magnesium, barium and lead cations (as perchlorates) with **1** in acetonitrile at 298.15 K.

data. Therefore, titration calorimetry provides a suitable tool to determine not only the thermodynamic parameters of complexation but also the composition of the metal-ion complex.

Thermodynamics of Complexation

The thermodynamics of complexation of **1** and bivalent cations in acetonitrile at 298.15 K is discussed separately according to the composition of the metal-ion complexes. Thus log K_s and derived standard Gibbs energies, $\Delta_c G^{\circ}$, enthalpies, $\Delta_c H^{\circ}$ and entropies, $\Delta_c S^{\circ}$, of complexation of 1:2 (metal cation:ligand) complexes are reported in Table III while corresponding data for 1:1 complexes are shown in Table IV. The different complex stoichiometries observed for the alkaline-earth and lead metal cations relative to other bivalent cations may be explained as follows.

There is considerable evidence from X-ray crystallographic studies [9,22,23] that in the solid state, fully functionalized calix[4]arene derivatives are able to form eight co-ordination complexes with alkali-metal cations. It is therefore reasonable to consider that alkaline-earth metal cations, because of their higher oxidation state relative to alkali-metal cations, are more likely to favour eight co-ordination with these ligands [24]. The same occurs with lead(II). As **1** is only partially substituted and therefore unable to offer eight hard donor atoms (as shown recently [9]) for complexation, these cations fulfil their requirement by interacting with two rather than with one ligand unit. X-ray crystallographic studies may assist in this interpretation regarding the structural arrangement of these complexes even though these are referred to the solid state. Attempts to isolate the complexes are in progress [9,21,25]. The experimental data obtained in this work fit into a 1:2 (metal cation:ligand) stoichiometry for alkaline-earth and lead metal cations. This is clearly demonstrated in the microcalorimetric data. Thus Fig. 4 shows a microcalorimetric curve for the titration of lead(II) against **1** that clearly indicates that the complex stoichiometry is 1:2 (M^{2+}:L). The error limits given refer to the fitting process. Treatment of data using a model for the formation of only 1:1 stoichiometry complexes failed, in fact the data do not fit such a model.

TABLE III Stability constants (log K_s) and derived standard Gibbs energies, enthalpies and entropies of **1** with alkaline-earth and lead metal cations in acetonitrile 298.15 K

	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}	Pb^{2+}
Log K_{s1}	5.14 ± 0.01	6.60 ± 0.01	5.45 ± 0.01	3.73 ± 0.01	4.99 ± 0.04
$\Delta_c G_1^o$/kJ mol^{-1}	−29.35 ± 0.06	−37.69 ± 0.06	−31.10 ± 0.06	−21.31 ± 0.06	−28.47 ± 0.2
$\Delta_c H_1^o$/kJ mol^{-1}	−21 ± 1	−19.5 ± 0.9	−7.1 ± 0.8	−15.5 ± 0.7	−15.8 ± 0.6
$\Delta_c S_1^o$/J K^{-1} mol^{-1}	29	61	80	20	42
Log K_{s2}	4.90 ± 0.01	4.62 ± 0.01	3.78 ± 0.01	2.42 ± 0.01	3.71 ± 0.06
$\Delta_c G_2^o$/kJ mol^{-1}	−27.96 ± 0.06	−26.36 ± 0.06	−21.56 ± 0.06	−13.81 ± 0.06	−21.3 ± 0.3
$\Delta_c H_2^o$/kJ mol^{-1}	−11.19 ± 0.03	−26.65 ± 0.06	−44.00 ± 0.05	−39.59 ± 0.08	−25 ± 2
$\Delta_c S_2^o$/J K^{-1} mol^{-1}	56	−1	−75	−86	−14
Log K_{s0}	10.04 ± 0.01	11.22 ± 0.01	8.73 ± 0.01	6.16 ± 0.01	8.70 ± 0.08
$\Delta_c G_0^o$/kJ mol^{-1}	−57.32 ± 0.06	−64.03 ± 0.06	−49.81 ± 0.06	−35.17 ± 0.06	−49.6 ± 0.4
$\Delta_c H_0^o$/kJ mol^{-1}	−32.0 ± 0.7	−46 ± 1	−51 ± 1	−55 ± 1	−41 ± 3
$\Delta_c S_0^o$/J K^{-1} mol^{-1}	85	60	−4	−67	29

TABLE IV Stability constants (log K_s) and derived standard Gibbs energies, enthalpies and entropies of **1** with copper, zinc, cadmium and mercury metal cations in acetonitrile at 298.15 K

Cation	log K_s	$\Delta_c G^o$/kJ mol^{-1}	$\Delta_c H^o$/kJ mol^{-1}	$\Delta_c S^o$/J K^{-1} mol^{-1}
Cu^{2+}	3.52 ± 0.01	−20.1 ± 0.06	−13.7 ± 0.8	21
Zn^{2+}	3.60 ± 0.01	−20.6 ± 0.06	−16.2 ± 0.6	15
Cd^{2+}	3.20 ± 0.03	−18.3 ± 0.17	−21.9 ± 0.7	−12
Hg^{2+}	3.07 ± 0.03	−17.5 ± 0.17	−5.9 ± 0.4	39

The pre-organization of the donor atoms in **1** is more favourable to stabilizing 1:1 complexes with other bivalent cations rather than with alkaline-earth and lead metal cations, or the former cations require either a lower co-ordination number or softer donor atoms for stabilization. Indeed, it is known that some of the heavy and transition metal cations often interact more strongly with a softer donor (such as nitrogen and sulfur) [26] than with oxygen.

As far as alkaline-earth and lead(II) metal cations are concerned, plots of log K_s (K_{s1}, K_{s2} and overall K_{s0}) against the ionic radius (Fig. 5) of the cation show the size-dominated behaviour often observed for alkaline-earth metal cations [24]. The highest stability observed for **1** is for Ca^{2+}. Thus, taking into account the overall stability constant ($K_{s0} = K_{s1} \times K_{s2}$), the selectivity of **1** for Ca^{2+} relative to other cations within the group, assessed from the selectivity factor $S = K_{s0}(Ca^{2+})/K_{s0}(M^{2+})$, is higher by factors of ~15, 3.31×10^2, 4.9×10^3 and 1.1×10^5 relative to Mg^{2+}, Pb^{2+}, Sr^{2+} and Ba^{2+} respectively.

The results in Table III show that the overall stability is in all cases enthalpy controlled to an extent that the maximum exothermicity (higher enthalpy stability) is found for the lowest solvated cation (Ba^{2+}). This is accompanied by the greatest entropy loss. Indeed, complexation entropies show the opposite pattern to the solvation entropies of these cations (increasingly more positive or less negative) from Mg^{2+} to Ba^{2+}. This is best illustrated by Fig. 6a, a plot of $\Delta_c H^o$ against $\Delta_h H^o$ of the cation [27]. The choice of $\Delta_h H^o$ rather than $\Delta_{solv} H^o$ is based on the few data available for the $\Delta_t H^o$ of these cations from H_2O to CH_3CN and the fact that the magnitude of the $\Delta_t H^o$ ($H_2O \rightarrow$ MeCN) values is small relative to their hydration enthalpies [9,26] and, therefore, the sequence in the $\Delta_h H^o$ is not altered. The same plot in terms of entropy is shown in Fig. 6b.

In summary, for alkaline-earth metal cations, the highest stability of **1** for Ca^{2+} and Mg^{2+} relative to other cations within the same group (Sr^{2+} and Ba^{2+}) is mainly attributed to the higher entropic contribution to the stability of the former relative to the latter cations for which the higher enthalpic stability is overcome by a considerable loss of entropy. On the other hand, for Pb^{2+} and **1**, the high stability is determined by the favourable enthalpy contribution.

As far as other bivalent metal cations are concerned, the results in Table IV show that there are no significant differences in the $\Delta_c G^o$ values for the different cations. There is a remarkable enthalpy–entropy compensation effect. This is shown in Fig. 7,

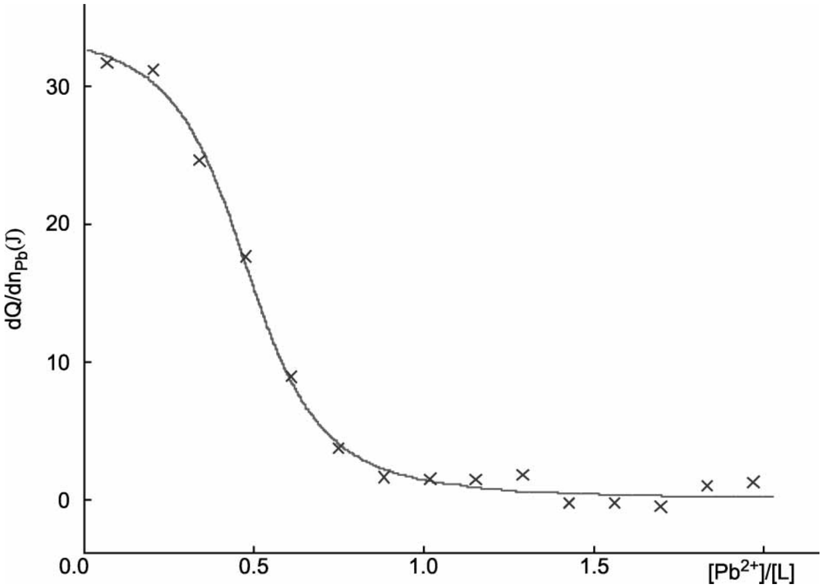

FIGURE 4 Microcalorimetric titration curve for lead(II) cation (as perchlorate) with **1** in acetonitrile at 298.15 K.

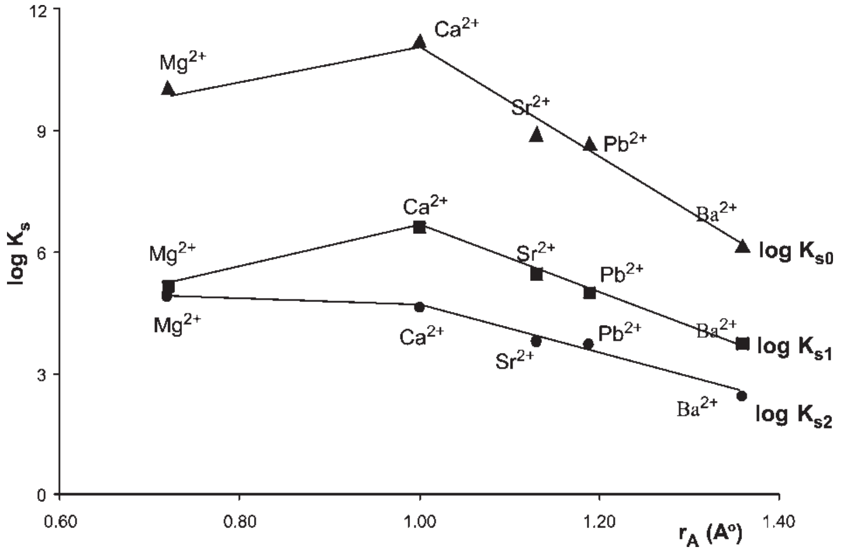

FIGURE 5 Plot of individual and overall log K_s values against the ionic radius of alkaline-earth and lead metal cations in acetonitrile at 298.15 K.

which is a plot of $\Delta_c H^o$ against $\Delta_c S^o$ for the various cations and this ligand in acetonitrile at 298.15 K.

In an attempt to analyse the effect of binding and cation desolvation on the enthalpies of complexation of **1** and these cations, the $\Delta_c H^o$ values are plotted against the hydration enthalpies, $\Delta_h H^o$, of these cations [9] (Fig. 8). Because of the additional factors, besides the electrostatic ones, that need to be considered when dealing with the first transition metal cations (highly polarizable), the latter

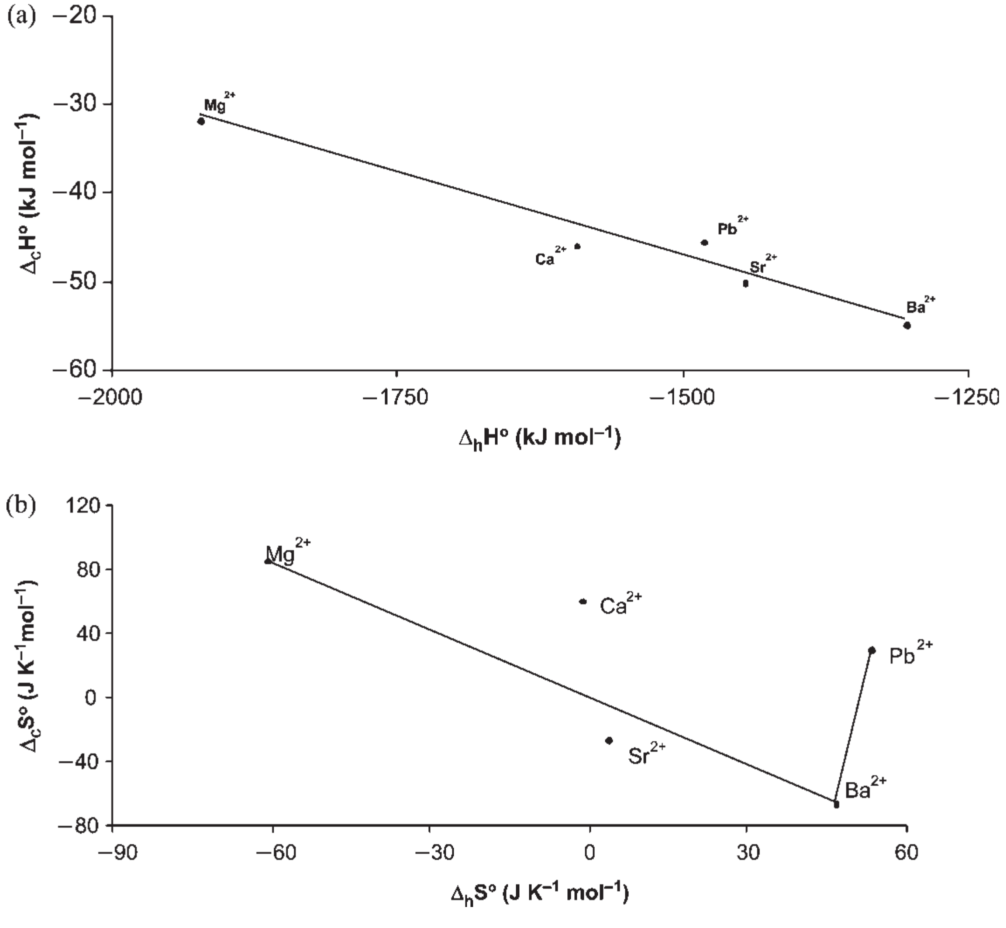

FIGURE 6 Plot of standard enthalpies and entropies of complexation against enthalpies and entropies of hydration of alkaline-earth metal cations at 298.15 K.

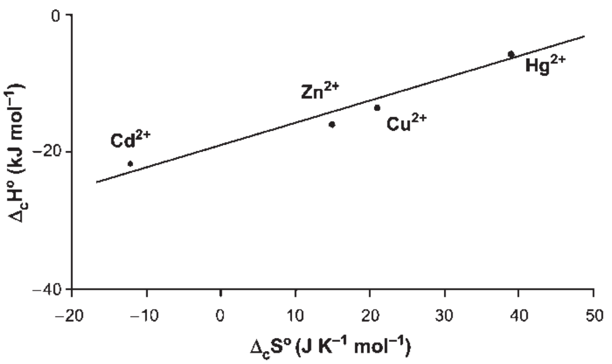

FIGURE 7 Plot of standard enthalpies of complexation against standard entropies of complexation for Cu^{2+}, Zn^{2+}, Cd^{2+} and Hg^{2+} metal cations in acetonitrile at 298.15 K.

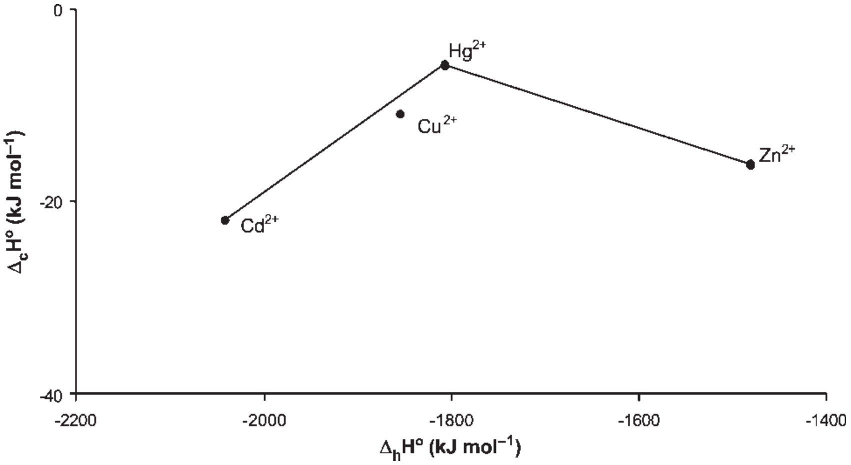

FIGURE 8 Plot of standard enthalpies of complexation against enthalpies of hydration of Cu^{2+}, Zn^{2+}, Cd^{2+} and Hg^{2+} metal cations at 298.15 K.

parameter rather than the ionic radii of the cations is selected [9,26]. Figure 8 shows that as the $\Delta_h H^o$ for the cation increases (becomes more negative), the stability of complex formation (in enthalpic terms) decreases. This may be attributed to the desolvation process (endothermic), which predominates over the binding process (exothermic), except for Zn^{2+}. For this cation, the energy associated with the binding process appears to predominate and an increase in enthalpic stability is observed for this cation and **1** in acetonitrile. Enthalpy values are compensated by entropy values and, as a result, the latter becomes more favourable on going from Cd^{2+} to Hg^{2+}. In fact, for the latter, the complexation process is entropically controlled.

CONCLUSION

From the above discussion we can conclude that among the solvents considered, complexation of **1** and bivalent cations occurs only in acetonitrile. This corroborates a previous statement [9] in that it is indeed the **1**–CH_3CN adduct rather than the free ligand that is interacting with these cations in this solvent. In fact the X-ray structure of the free ligand [28] shows that acetonitrile is found in the hydrophobic cavity of **1**. Although crystallographic data are referred to the solid state, this may also be the case in solution. Further work is required to investigate the different compositions observed in the formation of metal-ion complexes of **1** with alkaline-earth and lead (1:2 cation:ligand stoichiometry) relative to other heavy and transition metal cations (1:1 complexes). This is now in progress [25].

Acknowledgements

We thank the European Union (Contract ICA3-2000-30006) for financial support.

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