Thermodynamics of Host−Guest Interactions in Lower Rim Functionalized Calix[4]arenes and Metal Cations: The Medium Effect

Angela F. Danil de Namor,*,† Samir Chahine,† Eduardo E. Castellano,‡ and Oscar E. Piro§

Laboratory of Thermochemistry, Chemistry Division, School of Biomedical and Molecular Sciences, University of Surrey, Guildford, Surrey GU2 7XH, United Kingdom, Instituto de Física de São Carlos, Universidade de São Paulo, C. P. 369, 13560 São Carlos (SP), Brazil, and Departamento de Física, Facultad de Ciencias Exactas, Universidad Nacional de La Plata and Instituto IFLP (CONICET-UNLP), C.C. 67, 1900 La Plata, Argentina

A new calix[4]arene derivative containing mixed pendant arms in its lower rim, 5,11,17,23-tetra-*tert*-butyl-[25,27-bis(ethylethanoate)oxy-26,28-bis(ethylthioethoxy)]-calix[4]arene, **1**, has been synthesized and characterized by ^{1}H and ^{13}C NMR. ^{1}H NMR data carried out in CDCl$_3$, CD$_3$CN, CD$_3$OD, and C$_3$D$_7$NO suggest that as far as acetonitrile is concerned, the hydrophobic cavity is likely to embrace a solvent molecule. It is shown that the hosting capacity of **1** toward metal cations is greater in acetonitrile than in *N,N*-dimethylformamide and in methanol. Thus, in the former solvent, complexation with various cations (Li$^+$, Na$^+$, Ag$^+$, Ca^{2+}, Cu^{2+}, Hg^{2+}, and Pb^{2+}) occurs while in the latter media, **1** interacts only with Ag$^+$ and Hg^{2+}. This statement is corroborated by ^{1}H NMR, conductance, calorimetric and potentiometric measurements. It is concluded that through molecular inclusion of acetonitrile in the hydrophobic cavity of **1**, the hydrophilic cavity of the resulting adduct becomes more receptive to host metal cations than that of the free ligand. In propylene carbonate, the results show that the ligand loses its ability to interact with metal cations. Thus in acetonitrile, selective recognition of **1** for Hg^{2+} is demonstrated to an extent that the selectivity for this cation is greater by factors of 1.8×10^3, 1.9×10^3, 6.9×10^3, 1.8×10^4, 4.1×10^4 and 4.5×10^4, relative to Pb^{2+}, Na$^+$, Li$^+$, Cu^{2+}, Ag$^+$, and Ca^{2+}, respectively. This statement is supported by the thermodynamic characterization of the complexation process involving these systems in acetonitrile, *N,N*-dimethylformamide and in methanol. Thus, the medium effect on the binding process is carefully assessed. The results show that replacement of two ester groups in two alternate pendant arms of the tetraester calix[4]arene derivative by thioethyl moieties has altered significantly the binding capacity and the selective behavior of the latter relative to the former. Final conclusions are given.

Introduction

The historical developments leading to the synthesis of calixarenes are well documented.[1−5] Although the reaction of phenol and formaldehyde dates back to 1872,[6] it was the work of Gutsche,[7] a century later that led to the revival of these interesting macrocycles. Since then the field of calixarene chemistry has grown extensively. This is mainly attributed to the versatile behavior of these macrocycles, the ease of upper and lower rim functionalization and their wide range of applications.

Although the procedures used to synthesize these macrocycles are established, the design of calixarene-based receptors able to interact selectively with a given guest is a challenging area of research. We have recently shown[8] the role of the solvent in complexation processes involving calix[4]arene ester and ketone derivatives and bivalent metal cations in that, among the solvents investigated, interaction was only observed in acetonitrile. Thus, the versatile behavior of acetonitrile in the coordination chemistry of these ligands with toxic metal cations, namely lead

and cadmium was shown in the X-ray structures of these metal-ion complexes.[8] Particularly striking is the structure of the tetraester calix(4)arene complex with cadmium(II) and acetonitrile with the participation of the solvent molecule (sitting in the hydrophobic cavity of the ligand) interacting directly with the cation through its nitrogen donor atom. Thus, the coordination number around the cation was found to be nine. However, when moving from the ester to the ketone derivative the interaction of Cd^{2+} with the N atoms of acetonitrile predominates over that involving one of the carbonyl oxygen donor atoms of the ligand, which is excluded from participating in the coordination process. As a result the coordination number of Cd^{2+} is altered from 9 (calixarene ester) to 8 (calixarene ketone). In an attempt to gain further insight into the binding properties of calix(4)arene derivatives toward uni- and bivalent cations and particularly to enhance their selectivity for heavy metal cations, mainly Hg^{2+} (an environmentally unfriendly cation), while lowering their interaction with alkali and alkaline-earth metal cations (biologically important ions), we set up to:

(i) synthesize a new ligand containing alternate ester and thioethyl functional groups in the pendant arms.

(ii) investigate the thermodynamics of complexation of this ligand and metal cations in various solvents.

Thus, this paper reports the synthesis of **1** and its structural characterization by ^{1}H NMR and ^{13}CNMR. The effect of the

---

* Corresponding author. E-mail: a.danil-de-namor@surrey.ac.uk.
† University of Surrey.
‡ Universidade de São Paulo.
§ Universidad Nacional de La Plata and Instituto IFLP (CONICET−UNLP).

Thermodynamics of Host−Guest Interactions

J. Phys. Chem. B, Vol. 108, No. 31, 2004 **11385**

solvent on the free ligand is assessed by carrying out ^{1}H NMR measurements in various solvents (CDCl$_3$, CD$_3$CN, CD$_3$OD, and C$_3$D$_7$NO). Qualitative (^{1}H NMR), semiquantitative (conductance measurements) and quantitative (titration calorimetry macro and micro) assessments on the binding properties of **1** for metal cations led to establish the sites of interaction of the ligand with the metal cation, the composition of the complex formed and the strength of ligand−cation interaction in different media. Thus, the selective behavior of **1** for a given metal cation relative to another is discussed.

Experimental Section

Preparation, ^{1}H and ^{13}C NMR Characterization of 5,11,17,23-Tetra-*tert*-butyl[25,27-bis(ethylethanoate)oxy-26,28-bis(ethylthioethoxy)]-calix[4]arene, 1. 1 was prepared from 5,11,17,23-tetra-*tert*-butyl[25, 27-bis(hydroxy)-26, 28-bis(ethyl-thioethoxy)]-calix[4]arene (4.00 g, 4.85 mmol) and sodium hydride, 95% pure (1.20 g, 0.5 mmol) in tetrahydrofurane. The mixture was stirred under a nitrogen atmosphere for 30 min. Ethyl bromoacetate (3.5 cm^3) was added gradually over a period of 15 min. The mixture was refluxed at 65 °C for 12 h. The reaction was monitored by TLC using hexane:ethyl acetate (4:1) mixture as the developing solvent system. After cooling, the solvent was removed under reduced pressure. The solid afforded was dissolved in dichloromethane, extracted with a saturated solution of sodium bicarbonate and then, with distilled water. The organic phase was separated and dried with magnesium sulfate, then filtered. The dichloromethane was removed by rotary evaporation and the oily product obtained was recrystallized from hot ethanol.

1 was obtained in 60−65% yield; melting point 174−176 °C. ^{1}H NMR (300 MHz) (CDCl$_3$) δ_H 6.58, 6.38 (s, Ar**H**), 4.53 (d, J = 4.2 Hz, ArCH$_{eq}$**H$_{ax}$**), 4.52 (s, OC**H$_2$**COO), 4.28 (q, J = 2.4 Hz, COOC**H$_2$**CH$_3$), 4.16 (t, J = 2.7 Hz, OC**H$_2$**S), 3.22 (t, J = 2.2 Hz, OCH$_2$C**H$_2$**S), 3.18 (d, J = 4.2 Hz, ArC**H$_{eq}$**H$_{ax}$), 2.65 (q, J = 2.4 Hz, SC**H$_2$**CH$_3$), 1.32 (t, J = 2.4 Hz, COOCH$_2$C**H$_3$**), 1.29 (t, J = 2.4 Hz, SCH$_2$C**H$_3$**), and 1.23, 0.91 ppm (s, C(C**H$_3$**)$_3$). ^{13}C NMR (300 MHz) (CDCl$_3$) δ_C 169.86 (OCH2**C**OO), 153.89, 152.46, 145.31, 145.17,134.94. 132.49, 125.63, 125.21 (**Ar**), 74.12 (O**C**H$_2$CH$_2$S), 72.23 (OCH$_2$**C**H$_2$S), 60.97 (O**C**H$_2$COO), 34.20, 33.89 (**C**(CH$_3$)$_3$, 31.80, 31.55 (C(**C**H$_3$)$_3$), 31.38 (COO**C**H$_2$CH$_3$), 31.19 (Ar**C**H$_2$Ar), 26.36 (S**C**H$_2$CH$_3$), 15.47 (COOCH$_2$**C**H$_3$), 14.54 (SCH$_2$**C**H$_3$). Elemental analysis, calculated % C, 72.25, H, 8.49; found % C, 72.35, H, 8.47.

Chemicals. Lithium perchlorate 99.5%, sodium perchlorate monohydrate 98%, potassium perchlorate 99%, rubidium perchlorate 99.9%, magnesium (II) perchlorate hexahydrate 99%, calcium (II) perchlorate hexahydrate 99%, strontium (II) perchlorate hydrate, barium (II) perchlorate hydrate, lead (II) perchlorate trihydrate 98%, zinc (II) perchlorate hexahydrate, cadmium (II) perchlorate hydrate, mercury (II) perchlorate 98%, cobalt (II) perchlorate hexahydrate, nickel (II) perchlorate hexahydrate, copper (II) perchlorate hexahydrate, and silver perchlorate 99%, were all purchased from Aldrich Chemical Co. These were dried over P$_4$O$_{10}$ under vacuum for several days before use.

Tris(hydroxymethyl)aminomethane, (THAM), ultrapure grade 99.9% from Aldrich and tetra-*n*-butylammonium perchlorate, (TBAP), electrochemical grade (≥99%) from Fluka Chemical Company were used without any further purification.

Acetonitrile, MeCN, (Aldrich; HPLC-grade) was purified by refluxing the solvent in a nitrogen atmosphere and distilled over calcium hydride. The middle fraction of the distilled solvent was used.[9]

N,N-Dimethylformamide, DMF, (Fisher; HPLC-grade) was dried over 3 Å molecular sieves (which have been dried in an oven at 300 °C overnight) for 72 h followed by distillation under reduced pressure.[10]

Methanol, MeOH, (Fission; HPLC-grade) and propylene carbonate anhydrous 99.7%, PC, (Aldrich) were used without further purification.

Deuterated chloroform, CDCl$_3$; acetonitrile, CD$_3$CN; methanol, CD$_3$OD; *N,N*-dimethylformamide, C$_3$D$_7$NO and tetramethylsilane TMS, were purchased from Aldrich.

^{1}H and ^{13}C NMR Measurements of 1. ^{1}H NMR measurements in CDCl$_3$, CD$_3$CN, CD$_3$OD, and C$_3$D$_7$NO 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.

For ^{13}C NMR measurements, SF of 75.469; SW of 301.15 MHz; pulse width of 350; delay time of 0.279 s; AQ of 0.721 s; and line broadening of 0.55 Hz were used with TMS as internal reference.

^{1}H NMR Measurements. Complexation Studies. The complexation behavior of **1** toward metal cations at 298 K was studied using the ^{1}H NMR technique, by adding the metal-ion salt (2.5×10^{-3} to 5.0×10^{-3} mol dm^{-3}) into the NMR tube containing the ligand dissolved in the appropriate solvent (1.0×10^{-3} to 2.0×10^{-3} mol dm^{-3}). Stepwise additions of the metal-ion salt were made and chemical shifts were recorded. Changes in chemical shifts upon addition of the metal-ion salt relative to the free ligand were calculated.

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

Conductometric titrations at 298.15 K for the determination of the cell constant and the composition of complexes formed were performed as described elsewhere.[8]

Calorimetric Titrations. For macrocalorimetric titrations (direct and competitive), the Tronac 450 calorimeter was used as an isoperibol titration calorimeter.[11] It is equipped with a 2 cm^3 buret connected by a silicone tube to the reaction vessel. The reproducibility of the apparatus was checked by carrying out the standard reaction of protonation of an aqueous solution of tris(hydroxymethyl)aminomethane (THAM) in hydrochloric acid (HCl, 0.1 mol dm^{-3}) at 298.15 K.[12] The value determined -47.48 ± 0.08 kJ. mol^{-1} is in agreement with the one reported by Hill, Öjelund, and Wadsö[13] using an LKB reaction calorimeter.

For stability constant values lower than 10^6 (log K_s = 6), direct calorimetric titrations were performed. A solution of the metal-ion perchlorate salt of selected metal ions (2.0−5.0×10^{-2} mol dm^{-3}) was prepared in acetonitrile, placed in the buret, and titrated into the vessel containing a solution of **1**, (50 cm^3, 6.0×10^{-4} − 1.5×10^{-3} mol dm^{-3}) prepared in the same solvent.

For log K_s values higher than 6, competitive calorimetric titrations were performed. A solution of the metal-ion salt (2.0−5.0×10^{-2} mol dm^{-3}) was prepared in acetonitrile, placed in the buret and titrated into the vessel containing a solution of **1** complexed with a metal cation, (M^{n+}), (50 cm^3, **1**, 6.0×10^{-4} to 1.5×10^{-3} mol dm^{-3}; $n_{M^{n+}} = 3 n_1$; where $n_{M^{n+}}$, and n_1 are the number of moles of the metal cation salt in the vessel and **1**, respectively), prepared in the same solvent. The stability constant of the complex in the vessel was lower than that

TABLE 1: ^{1}H NMR Chemical Shifts (δ ppm) and Difference in the Chemical Shifts ($\Delta\delta$ ppm) with Respect to CDCl$_3$, for Ligand 1 in CDCl$_3$, CD$_3$CN, CD$_3$OD, and C$_3$D$_7$NO at 298 K

protons 1	CDCl$_3$ δ ppm	CD$_3$CN δ ppm	$\Delta\delta$ ppm	CD$_3$OD δ ppm	$\Delta\delta$ ppm	C$_3$D$_7$NO δ ppm	$\Delta\delta$ ppm
H-1, 2	1.23, 0.91	1.22, 1.05	−0.01, 0.14	1.27, 0.91	0.04, 0.00	1.25, 0.94	0.02, 0.03
H-3, 4	6.58, 6.98	6.96, 7.18	0.38, 0.20	6.61, 7.08	0.03, 0.10	7.16, 6.71	0.42, −0.27
H-5 (eq.)	3.18	3.27	0.09	3.17	−0.01	3.25	0.07
H-6 (ax.)	4.53	4.51	−0.02	4.53	0.00	4.54	0.01
H-7	4.16	4.08	−0.08	4.15	−0.01	4.16	0.00
H-8	3.22	3.23	0.01	3.25	0.03	3.27	0.05
H-9	2.65	2.64	−0.01	2.69	0.04	Ov^a	
H-10	1.29	1.27	−0.02	1.36	0.07	1.30	0.01
H-11	4.52	4.55	0.03	4.47	−0.05	4.58	0.06
H-12	4.28	4.19	−0.09	4.30	0.02	4.23	−0.05
H-13	1.32	1.28	−0.04	1.29	−0.03	1.28	−0.04

^{a} Ov: Overlapped.

expected between **1** and the metal cation under investigation placed in the buret hence enabling the latter to compete and replace the metal cation of the complex salt in the vessel.

The whole system was then immersed in a thermostated water bath at 298.15 K and allowed to reach thermal equilibrium.

Furthermore the titration was carried out in recorded time intervals. A chart recorder was used to monitor the reaction taking place in the vessel. Corrections for the heat of dilution were also made by titrating the solution in the buret into the vessel with the free solvent of interest. An electrical calibration was carried out after each titration experiment.

Thermodynamic parameters for a single system were determined at different concentrations of the metal-ion salt, to ensure that no ion-pair formation occurred within the working concentration range. All measurements were conducted in triplicate.

For microcalorimetric titrations (direct), the four-channel heat conduction microcalorimeter (Thermometric, 2277 Thermal Activity Monitor, TAM) designed by Suurkuusk and Wadsö[14] was used. Electrical (static and dynamic) and chemical calibrations were carried out to check the reliability of the equipment.[15]

The reaction vessel was charged with 2.8 cm^3 of the ligand (6.0×10^{-4} to 1.5×10^{-3} mol dm^{-3}) in the appropriate solvent. The metal-ion salt (1.4×10^{-2} to 3.5×10^{-2} mol dm^{-3}) was injected incrementally using a 0.5 cm^3 gastight motor driven Hamilton syringe. In each titration experiment, about 20 injections were made at time intervals of 30−45 min. Corrections for the enthalpy of dilution of the titrant in the solvent were carried out in all cases. A computer progamme for TAM (Digitam 4.1 for Windows from Thermometric AB and Scitech Software AB, Sweden) was used to calculate the log K_s and $\Delta_c H°$ values for the process under study.

Potentiometric Titrations. Determination of the Stability Constant. The potentiometric titration technique was used to determine the stability constant for the complexation of **1** with the silver cation by the direct method and with Na$^+$ and Li$^+$ as perchlorates by the competitive method in acetonitrile at 298.15 K. The electrochemical cell used was that developed by Schneider et al.[16,17] A schematic representation is given in eq 1

$$Ag/Ag^+, X \text{ M}// 0.05 \text{ M } (Bu^t_4NClO_4)// 0.01 \text{ M}, Ag^+/Ag \quad (1)$$
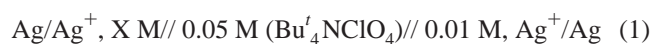
The indicator and the reference silver electrode rods were immersed each in separate jacket-thermostated glass vessels. The reference silver electrode was immersed in a solution of silver perchlorate in acetonitrile (2.5×10^{-3} mol dm^{-3}) and the indicator electrode in a solution of TBAP, where the titration was performed and the activity of the free silver was measured. Constant ionic strength was maintained by using TBAP (0.05

mol.dm^{-3}) in all solutions, including the filling solution of the salt bridge between the two glass vessels.

A digital micro-processor pH/mV-meter CAMLAB model HI 8417, was used to measure the potential changes during the course of the titration. The volume of the titrant was added by a micropipet.

A solution of silver perchlorate in acetonitrile was incrementally added into the titration vessel containing TBAP in the same solvent. The performance of the electrode showed a Nernstian behavior.

Subsequently, a solution of **1** prepared in acetonitrile was titrated to an excess of the silver cation in the vessel of the indicator electrode, until the formation of a stable silver-**1** complex. Potential changes were recorded and used to calculate the stability constant of the Ag$^+$-**1** complex. A second titration was performed in which a solution of the cation (Na$^+$ or Li$^+$) salt was added to the same vessel containing the Ag$^+$-**1** complex. A competitive reaction took place between Ag$^+$ and the other metal cation over **1**, resulting in the formation of the Na$^+$ or Li$^+$ complex with **1**. This competitive titration was accompanied by a change in the potential, which was recorded and used for the calculation of the stability constant of the Na$^+$ or the Li$^+$-**1** complex. All stability constant calculations were performed using the HYPERQUAD program.[18]

Results and Discussion.

^{1}H NMR Measurements. Effect of the Solvent. Calix[4]-arene are more likely to enter specific interactions with the solvent than any other macrocycle due to the ability of a hydrophobic cavity to host neutral species. Therefore, the effect of the solvent on the free ligand **1** was assessed through ^{1}H NMR measurements in CDCl$_3$, CD$_3$CN, CD$_3$OD and C$_3$D$_7$NO at 298 K.

Thus Table 1 lists the chemical shifts (δ ppm) and their changes ($\Delta\delta$ ppm) in CD$_3$CN, CD$_3$OD and C$_3$D$_7$NO relative to CDCl$_3$ (reference solvent).

It is well established[19] that the difference in the chemical shifts $\Delta\delta_{ax-eq} = \delta_{ax} - \delta_{eq}$ (axial, ax. and equatorial, eq.) between the bridging methylene protons provides (i) information regarding the conformation of the ligand in a given solvent and (ii) an indication of the flattening degree of the "cone". Thus $\Delta\delta_{ax-eq} = 0.9 \pm 0.2$ ppm is expected for a ligand in a perfect "cone" conformation while a $\Delta\delta_{ax-eq}$ value of 0.5 ± 0.1 corresponds to a flattened ligand in a "cone" conformation. The $\Delta\delta_{ax-eq}$ values (Table 1) in CDCl$_3$, CD$_3$CN, CD$_3$OD, and C$_3$D$_7$NO are 1.35, 1.24, 1.36, and 1.30 ppm. The fact that these values are greater than 0.9 ppm indicates that the macrocycle adopts a distorted "cone" conformation.

Thermodynamics of Host−Guest Interactions

J. Phys. Chem. B, Vol. 108, No. 31, 2004 **11387**
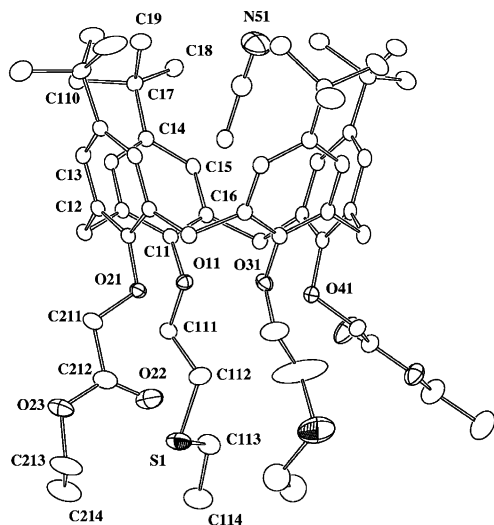
Figure 1. View of the molecular complex of **1** with acetonitrile (**1·**MeCN). For clarity, only one monomer with a carbonyl-containing pendant arm and one sulfur-bearing pendant group has been completely labeled to show the numbering scheme.

However, a significant deshielding effect is observed for the aromatic protons (H-3, 4) of **1** in CD_3CN relative to other solvents. In fact, the ^1H NMR spectrum of **1** in C_3D_7NO shows that one of the aromatic protons is deshielded while a shielding effect is observed for the other. As far as **1** in CD_3CN is concerned, a similar effect was found for the tetraester calix-(4)arene derivative and this was attributed to the interaction of acetonitrile with the hydrophobic cavity of the ligand.[20] In fact, based on the observations from ^1H NMR studies in these solvents, we isolated **1** from *N,N*-dimethylformamide and from acetonitrile and X-ray diffraction studies were performed on both crystals.[21] Thus recrystallization from acetonitrile lead to the formation of the **1** CH_3CN adduct with the solvent sitting in the hydrophobic cavity of the ligand (see Figure 1). Recrystallization of **1** from *N,N*-dimethylformamide led to the formation of the free ligand (see Figure 2). In the following section ^1H NMR complexation studies of **1** and metal cations in various solvents are discussed.

^1H NMR Complexation Studies with Univalent and Bivalent Cations in Different Media. In an attempt to assess whether complexation takes place between **1** and metal cations in these solvents and if so to identify the active sites of interaction of the ligand, ^1H NMR titrations of **1** and metal cations in CD_3CN, CD_3OD and C_3D_7NO at 298 K were carried out.

Chemical shift changes ($\Delta\delta = \delta_1 - \delta_2$, where δ_1 and δ_2 denotes the chemical shifts of the complex and the free ligand, respectively) upon the addition of the metal-ion salt to **1** in the appropriate solvent (CD_3CN, CD_3OD, and C_3D_7NO) are shown in Tables 2−4.

As far as acetonitrile is concerned (Table 2), the results show that the uptake of the metal cation by **1** in this solvent has led to conformational changes of this ligand. This is best illustrated by the difference in the chemical shifts of the bridging methylene protons ($\Delta\delta_{ax-eq} = \delta_{ax} - \delta_{eq}$). In all cases, the axial protons are deshielded while the equatorial ones are shielded, this leads to a decrease in the $\Delta\delta_{ax-eq}$ values.

In fact, we visualize calixarene derivatives as "glove stretchers". Therefore, in a flattened conformation the size of the hydrophobic cavity increases while that of the hydrophilic cavity decreases. The reverse is true for $\Delta\delta_{ax-eq}$ values greater than 0.90 ppm. As demonstrated below, these observations appear
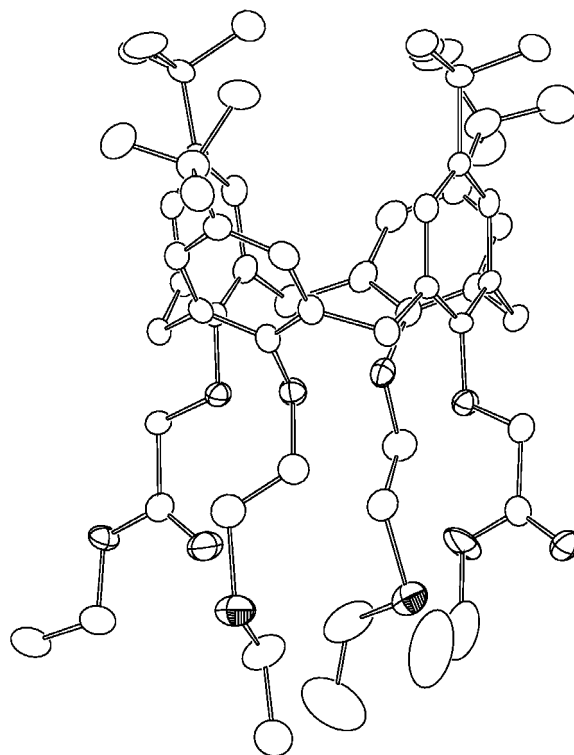
Figure 2. Side view of one representative 5,11,17,23-tetra-*tert*-butyl-[25,27-bis(ethyl ethanoate)oxy-26,28-bis(ethylthioethoxy)-calix[4]arene, **1** in the solid, showing the non-H atomic displacement ellipsoids at the 30% probability level. Crossed and hatched ellipsoids denote oxygen and sulfur atoms, respectively. For clarity, the hydrogen atoms are not included in the plot.

to have significant implications on the uptake or rejection of ionic and neutral species by these receptors. On the basis of these statements, it follows that the ligand adopts an undistorted 'cone' conformation when complexed with Li^+, Na^+, Ag^+, and Hg^{2+} cations (with $\Delta\delta_{ax-eq}$ values of 0.80, 0.81, 1.11, and 1.07 ppm respectively) relative to the free ligand.

However, flattened "cone" conformations are observed for the complexation of **1** with Pb^{2+} and Ca^{2+} cations in acetonitrile as assessed from the $\Delta\delta_{ax-eq}$ values of 0.45 and 0.46 ppm, respectively.

Another aspect to consider is the remarkable chemical shift changes shown by the aromatic protons (H-3 and H-4) and to a much lesser extent by the *p-tert*-butyl protons (H-1 and H-2) of metal-ion complexes in CD_3CN. Each of the following three pairs of complexes (Li^+-**1**, Na^+-**1**), (Ca^{2+}-**1**, Pb^{2+}-**1**) and (Hg^{2+}-**1**, Ag^+-**1**) show similar chemical shifts for H-3 and H-4. This is an indication that the conformation of the hydrophobic cavity is similar for each pair of these complexes. This is in accord with the early observation regarding the similar chemical shift differences between equatorial and axial protons for these pairs.

The similarity in the conformation adopted by these pairs of metal cations by the hydrophilic cavity forces the arms participating in the binding process to move closer to embrace the cation. On the other hand, the remaining arms (not taking part in the complexation process) are expected to repel each other due to electrostatic effects. As a consequence, the aromatic rings of the nonparticipating arms will stand parallel to each other while the ones involved in the binding process will become more flattened relative to the free ligand. This is observed in the case of the lithium and sodium complexes where these two alkali-metal cations (hard metal cations) are attracted by the carbonyl and ethereal atoms (hard donor atoms), whereas the

TABLE 2: Chemical Shift Changes (Δδ ppm)[a] in the ¹H NMR Spectrum of 1 with Metal Cations in CD₃CN at 298 K

1/ M^{n+}	H-1, 2	H-3, 4	H-5 (eq.)	H-6 (ax.)	H-7	H-8	H-9	H-10	H-11	H-12	H-13
Li^+	−0.01, 0.15	0.21, 0.4	0.24	−0.19	0.11	−0.47	−0.1	−0.01	0.21	0.33	0.15
Na^+	0, 0.16	0.23, 0.43	0.25	−0.17	0	−0.41	−0.07	0	0.06	0.27	0.12
K^+	0, 0.03	0.04, 0.06	0.05	−0.01	0	−0.05	0	0.01	−0.03	0.04	0.01
Ca^{2+}	−0.01, 0.14	0.35, 0.54	0.49	−0.29	0.24	−0.36	0.01	0.04	0.47	0.43	0.18
Hg^{2+}	Ov	0.09, −0.22	0	−0.16	Ov.	0.57	0.44	Ov.	−0.09	0.08	0.13
Ag^+	0.07, −0.13	0.07, −0.22	−0.02	−0.14	0.12	0.37	0.18	0.09	−0.13	0.03	−0.03
Pb^{2+}	0, 0.18	0.32, 0.56	0.41	−0.36	0.11	0.25	0.6	0.17	0.36	0.33	0.23

[a] Relative to the free ligand. Chemical shifts for **1**, (ppm); H-1, 2 = 1.22, 1.05; H-3, 4 = 6.96, 7.17; H-5 (eq.) = 3.27; H-6 (ax.) = 4.51; H-7 = 4.08; H-8 = 3.23; H-9 = 2.64; H-10 = 1.27; H-11 = 4.55; H-12 = 4.12; H-13 = 1.28 ppm.

TABLE 3: Chemical Shift Changes (Δδ Ppm)[a] in the ¹H NMR Spectrum of 1 with Metal Cations in CD₃OD at 298 K

1/ M^{n+}	H-1, 2	H-3, 4	H-5 (eq.)	H-6 (ax.)	H-7	H-8	H-9	H-10	H-11	H-12	H-13
Ag^+	0.08, −0.08	0.15, −0.1	0.05	−0.19	0.28	0.6	0.29	0.07	−0.09	0.03	0.02
Hg^{2+}	0.07, −0.06	0.16, −0.06	0.09	−0.24	Ov.	Ov.	Ov.	0.16	−0.01	0.06	0.03

[a] Relative to the free ligand. Chemical shifts for **1**, (ppm); H-1, 2 = 1.27, 0.91; H-3, 4 = 7.08, 6.61; H-5 (eq.) = 3.15; H-6 (ax.) = 4.53; H-7 = 4.15; H − 8 = 3.25; H − 9 = 2.69; H-10 = 1.36; H-11 = 4.47; H-12 = 4.30; H-13 = 1.29 ppm.

TABLE 4: Chemical Shift Changes (Δδ Ppm)[a] in the ¹H NMR Spectrum of 1 with Metal Cations in C₃D₇NO at 298 K

1/M^{n+}	H-1, 2	H-3, 4	H-5 (eq.)	H-6 (ax.)	H-7	H-8	H-9	H-10	H-11	H-12	H-13
Ag^+	0.1, −0.1	0.17, −0.13	0.04	−0.11	0.22	0.53	0.34	0.11	−0.09	0.03	0.00
Hg^{2+}	0.1, −0.09	0.20, −0.11	0.07	−0.14	0.46	0.38	Ov.	0.23	−0.04	0.03	0.02

[a] Relative to the free ligand, **1**. Chemical shifts for **1**, (ppm); H-1, 2 = 1.25, 0.94; H-3, 4 = 7.16, 6.71; H-5 (eq.) = 3.25; H-6 (ax.) = 4.54; H-7 = 4.16; H − 8 = 3.27; H − 9 = overlapped; H-10 = 1.30; H-11 = 4.58; H-12 = 4.23; H-13 = 1.28 ppm.

shielding effect observed in the protons adjacent to the sulfur atoms strongly suggest that the sulfur containing arms are not participating in the binding process. Again the (Ca^{2+}-**1**) complex also shows a pronounced deshielding effect in the protons of the ester arms (H-11, -12, -13), while this effect is less pronounced for H-7 and almost negligible for H-9 and 10. However, the shielding effect that H-8 undergoes upon complexation with Ca^{2+} suggests that the interaction with this cation takes place through the carbonyl and ethereal oxygen atoms while the sulfur arms are not likely to participate in the process. It should be noted that the most marked deshielding effect is observed for the protons adjacent to both; carbonyl and sulfur atoms (H-7, -8, -9, -10, -11, -12, -13) in the Pb^{2+}-**1** complex, indicating that in CD₃CN the ligand uses both donor atoms, *S* and *O* (carbonyl and ethereal) upon complexation with this cation.

¹H NMR data for the Ag^+-**1** complex show that the protons of the sulfur containing arms (H-7, -8, -9, -10) are deshielded while those for the ester arms (H-11 and H-13) are shielded. These observations together with the insignificant change found for H-12 suggests that the silver cation is likely to interact only with the sulfur atoms of the ligand. On the other hand, Hg^{2+} appears to interact with the sulfur atoms and to a lesser extent with the oxygen donor atoms. Unlike the ester derivative in CD₃CN, no significant chemical shift changes were observed for Mg^{2+}, Sr^{2+}, Ba^{2+}, and Cd^{2+} and **1** in this solvent, despite the fact that the latter is a soft metal cation and therefore it is expected to interact with a soft donor atom such as sulfur. This finding reveals the effect of the conformation (comparing conformation of **1** to that of ester derivative) on the selective behavior of the ligand for metal cations, and this is discussed later. Unlike acetonitrile, ¹H NMR data shown in Tables 3 and 4, carried out in CD₃OD and C₃D₇NO respectively, reveal that in these solvents this ligand only complexes with Ag^+ and Hg^{2+} cations (as perchlorates). This is mainly attributed to the presence of sulfur containing pendant arms. This statement is corroborated by (i) the lack of complexation observed for the tetraester[8] and silver and bivalent cations in any solvent except

acetonitrile and (ii) the chemical shift changes observed for the protons of the sulfur containing arms upon interaction with these cations.

Having established the sites of complexation of the ligand with metal cations, conductometric titrations were performed with the aim of establishing the composition of the metal-ion complexes.

Conductometric Titrations. The derivation of accurate thermodynamic data requires knowledge of the process-taking place when **1** interacts with a metal cation in a given solvent in order to formulate an equation representative of the process. Thus conductometric titrations were carried out in acetonitrile, methanol, *N,N*-dimethylformamide and propylene carbonate at 298.15 K. The aim was to establish the composition of the metal-ion complex in the appropriate solvent. According to the ion-ligand strength, plots of molar conductance, Λ_m against the ligand: cation ratio (**1**/M^{n+}) showed three different patterns for strong (two straight lines with a sharp break at the reaction stoichiometry), moderate (broad break in the curvature so the composition of the complex was determined by extrapolating the lines prior and after the end point of the titration) and weak (slight or nonexisting changes in the slope) complexes.

As far as acetonitrile is concerned, among the cations investigated, strong complexes of 1:1 stoichiometry were found for Li^+, Na^+, Pb^{2+}, and Hg^{2+}. A representative example is shown in Figure 3, for the conductometric titration of Hg^{2+} with **1** in acetonitrile at 298.15 K. The decrease in conductance observed by the addition of the ligand to the metal cation in this solvent is due to the size effect in moving from the free to the complex (larger) cation.

Moderate complexation was observed for Ca^{2+} and Ag^+ in acetonitrile as reflected in the broad curvature in the slope of the curve shown in Figure 4, where a plot of Λ_m values against the **1**:Ag^+ ratio is given as a representative example.

Very little changes in molar conductance were recorded and no slope were observed for K^+, Mg^{2+}, Sr^{2+}, Ba^{2+}, Zn^{2+}, Cd^{2+}, Ni^{2+}, and Co^{2+} in acetonitrile at 298.15 K. These observations provide a strong indication that very weak or no complexation occurs with these metal cations and **1** in acetonitrile.

Thermodynamics of Host−Guest Interactions

J. Phys. Chem. B, Vol. 108, No. 31, 2004 **11389**
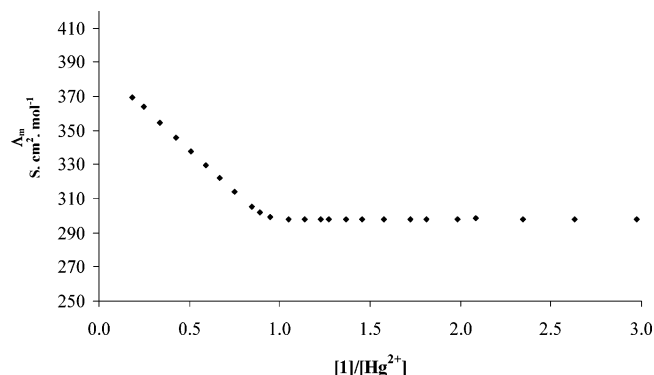
Figure 3. Conductometric titration curve of Hg^{2+} (as perchlorate) with **1** in acetonitrile at 298.15 K.
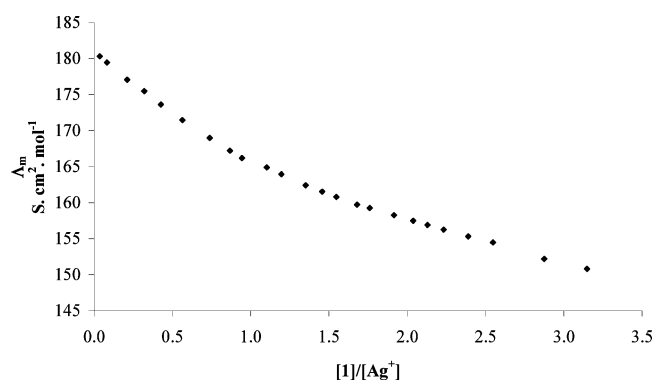

Figure 4. Conductometric titration curve of Ag^+ (as perchlorate) with **1** in acetonitrile at 298.15 K.

As far as methanol and *N,N*-dimethylformamide are concerned, complexation was observed with Ag^+ and Hg^{2+} in these solvents. No changes in the slope of the conductometric titration curves were noted for other cations (Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}, Zn^{2+}, Cd^{2+}, Cu^{2+}, Ni^{2+}, and Co^{2+}) in these solvents.

When the medium was propylene carbonate, no changes were observed in the slope of the plot of Λ_m against **1**:M^{n+} ratio by the addition of the metal cation salts (Li^+, Na^+, K^+, Rb^+, Cs^+, Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}, Pb^{2+}, Hg^{2+}, Zn^{2+}, Cd^{2+}, Cu^{2+}, Ag^+, Ni^{2+}, Co^{2+}) in this solvent.

Both ^{1}H NMR and conductance measurements provided enough evidence about the scope of the ligand to complex metal cations in one solvent relative to another. The most striking feature of these data is that the hosting ability of **1** for metal cations appears to be controlled by the media. Indeed while in acetonitrile, **1** is able to interact with various cations (Li^+, Na^+, Ca^{2+}, Pb^{2+}, Hg^{2+}, Ag^+, and Cu^{2+}), its hosting ability in methanol and *N,N*-dimethylformamide is reduced to two metal cations (Ag^+ and Hg^{2+}). However, in moving from these two solvents to propylene carbonate, the ability of **1** to interact with metal cations is entirely lost. As discussed in the previous section the X-ray structures (referred to the solid state) provide an indisputable evidence that (i) as a result of recrystallization, two different compounds have been obtained and (ii) the presence of acetonitrile in the hydrophobic cavity exert an allosteric effect on the hydrophilic cavity to an extent that an enlargement of the latter relative to that of the free ligand occurs. These results together with the chemical shift changes observed for the aromatic protons in CD_3CN relative to other solvents suggest that in solution the **1**.CH_3CN adduct is also formed. As a result, the hosting ability of the latter relative to the free ligand for metal cations in solution is enhanced as to embrace cations other than Ag^+ and Hg^{2+} (as observed in MeOH and DMF).

At this stage, it is relevant to compare these results with those previously reported[8] for cation complexation processes involving ethyl *p-tert*-butylcalix[4]arene tetraethanoate, **2** and bivalent cations in acetonitrile. Clearly, on one hand the replacement of ester functional groups in two alternate pendent arms by thioethyl moieties **1** (sulfur are soft donor atoms) to interact with hard metal cations (Sr^{2+}, K^+, Rb^+, Cs^+, and Ba^{2+}). On the other hand, it is expected that the capability of **1** (sulfur is a soft donor atom) reduces the ability of the latter to interact with soft metal cations is enhanced. In fact, this is the case for Ag^+ (no interaction was found between **2** and Ag^+) and Hg^{2+}. However, the most notable aspect of these comparative studies is that a soft metal cation such as Cd^{2+} interacts with **2** but not with **1** in acetonitrile.[8]
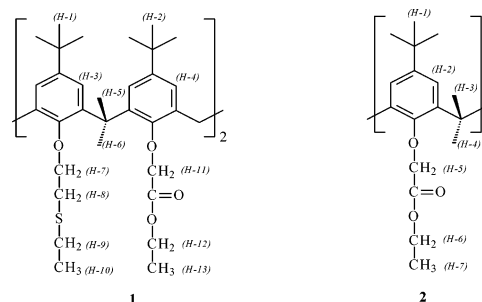

In an attempt to explain the lack of complexation of **1** with Cd^{2+} in acetonitrile relative to **2** and this cation in the same solvent, ^{1}H NMR data in CD_3CN for these two ligands are considered.

The difference in the chemical shifts between the axial and equatorial protons of **1** ($\Delta\delta_{ax-eq} = 1.26$ ppm; see Table 1) in CD_3CN is smaller than that of **2** ($\Delta\delta_{ax-eq} = 1.55$ ppm),[8] thus indicating that the former ligand displays a less distorted "cone" conformation than the latter. Therefore, the aromatic rings in **2** are expected to stand up in a more symmetrical fashion than in **1**. This observation may be attributed to the higher electrostatic repulsion between the pendant arms of the calix[4]arene ester due to the higher dipolar moment (1.72 D)[22] of the four carbonyl groups in the hydrophilic cavity.

Replacement of the two-ester groups in **2** by thioethyl moieties **1**, is expected to reduce electrostatic repulsion between the pendant arms. As a result, the hydrophilic cavity of **2** is likely to be more open (larger size) than that of **1**, and therefore, **2** is pre-organized to interact with Cd^{2+} while **1** is not.

On the basis of the semiquantitative information provided by conductance studies we proceeded with the determination of the thermodynamic parameters of complexation and these are discussed in the following section.

Thermodynamics of Complexation. It will be seen from the discussion in the previous sections that metal-ion complexes of 1:1 (metal cation: ligand) stoichiometry are found in the solvents investigated. However, besides defining the complex composition, which is required to formulate an equation representative of the complexation process, it is imperative to identify the speciations in solution particularly when nonaqueous solvents are involved. A particular feature of multicharged cations is their tendency to interact with the anion in solution through the formation of ion-pairs. Such occurrence should be either minimized as much as possible or indeed corrections should be applied to account for these effects in the determination of reliable thermodynamic data. To assess the concentration range at which metal(II) cation salts are predominantly in their ionic forms, conductance measurements at different ionic strengths, I, were carried out. A representative example is given
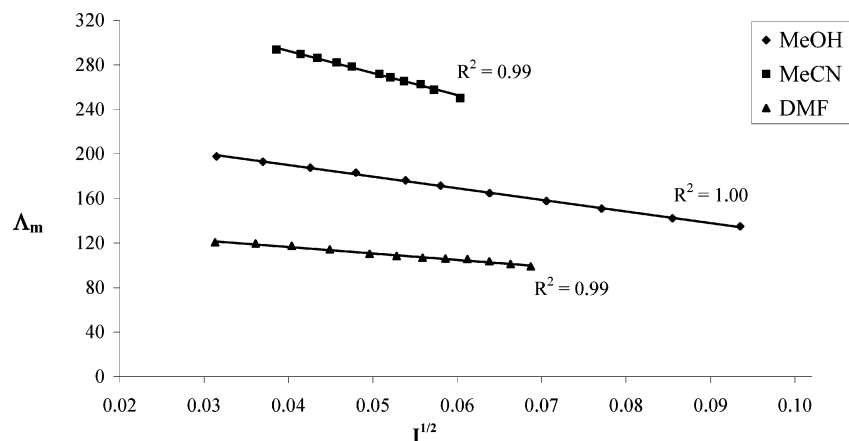
Figure 5. Plot of the Λ_m vs. $I^{1/2}$ for Hg(ClO$_4$)$_2$ solution in acetonitrile, methanol and *N,N*-dimethylformamide, at 298.15 K.

in Figure 5, where Λ_m values for Hg(ClO$_4$)$_2$ in acetonitrile, methanol and *N,N*-dimethylformamide at 298.15 K are plotted against the square root of the ionic strength, $I^{1/2}$. The straight lines obtained are indicative that ions are predominantly in solution and therefore physicochemical measurements were performed within these concentration ranges. The same behavior was found in the conductance behavior of metal-ion complex salts. On these bases, the thermodynamic data are referred to the process described as

$$M^{n+} (s) + \mathbf{1} (s) \rightarrow M^{n+}\mathbf{1} (s) \qquad (2)$$
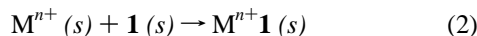
Stability constants (expressed as log K_s) of **1** with various metal cations (Li$^+$, Na$^+$, K$^+$, Ag$^+$ Ca^{2+}, Pb^{2+}, Hg^{2+}, and Cu^{2+}) in acetonitrile were measured by titration calorimetry (macro and micro) as well as by competitive potentiometry using silver electrodes. Enthalpy data were derived from calorimetry (macro and micro). Table 5 reports log K_s and derived standard Gibbs energies, $\Delta_c G°$, enthalpies, $\Delta_c H°$ and entropies, $\Delta_c S°$ of complexation of **1** and metal cations in acetonitrile, methanol and *N,N*-dimethylformamide at 298.15 K. These results will be discussed in terms of the solvent and the ligand effects.

Solvent Effect. A quick inspection of the data reveals the crucial role played by the solvent in complexation processes involving calixarene derivatives and metal cations. The most remarkable feature of the data in acetonitrile is the selective behavior of **1** for Hg^{2+} relative to other metal cations in this solvent. In quantitative terms, the selectivity factor ($S = [K_{s(Hg^{2+})}]/[K_{s(M^{n+})}]$) indicates that **1** is more selective for Hg^{2+} relative to Pb^{2+}, Na$^+$, Li$^+$, Cu^{2+}, Ag$^+$ and Ca^{2+} by a factor of 1.8×10^3, 1.9×10^3, 6.9×10^3, 1.8×10^4, 4.1×10^4 and 4.5×10^4, respectively. However, in methanol and in *N,N*-dimethylformamide, **1** discriminates against all hard and moderate cations while still recognizing the soft ones (Ag$^+$ and Hg^{2+}). Particularly striking is the reverse trend in complex stability observed for these two cations and **1** in these solvents. Thus for mercury(II) and **1**, the medium effect on the strength of complexation follows the sequence

$$MeCN > DMF > MeOH$$

For silver, the trend observed is

$$MeOH > DMF > MeCN$$

These changes in stability and therefore selectivity with solvent variation can be quantitatively assessed by taking the stability constant ratio for each cation in one solvent relative to another ($S = [K_{s(S1)}/K_{s(S2)}]$).

Thus, Hg^{2+} and **1** is more stable in MeCN (s$_1$) than in DMF (s$_2$) and MeOH (s$_2$) by factors of 4.2×10^3 and 1.1×10^5, respectively. The same analysis carried out for Ag$^+$ shows that the stability of this cation and **1** is greater in MeOH (s$_1$) than in DMF (s$_2$) and MeCN (s$_2$). This contrasting behavior is being analyzed in terms of the solution properties of the reactants (metal cation and ligand) and the product (metal ion complex) in these media.[23]

As far as enthalpies and entropies are concerned, the data listed in Table 5 show that the processes are enthalpy controlled. Indeed, in all cases, there is a loss of entropy (except for Ca^{2+} and **1** in MeCN) upon complexation of **1** and metal cations in the various solvents. However it seems appropriate to stress that the higher stability of Ag$^+$ relative to Hg^{2+} and **1** in MeOH is entirely attributed to the more favorable entropy (less negative) of the former cation and this ligand relative to the latter. Indeed inspection of Table 5 shows that the $\Delta_c H°$ values for these cations and **1** in methanol are very close, indicating that the enthalpy contribution to complex stability (hence, $\Delta_c G°$) is about the same.

Ligand Effect. An assessment on the stability of complex formation with ligand structure can be made by considering the thermodynamics of cation complexation of a closely related ligand, **2**.[8] Thus log K_s, $\Delta_c G°$, $\Delta_c H°$, and $\Delta_c S°$ values in acetonitrile at 298.15 K are also included in Table 5. As shown above (see ^{1}H NMR Section), replacement of two ester functional groups in **2** by thioethyl moieties, **1** has altered substantially the affinity of the former relative to the latter for metal cations. Besides the discriminating behavior of **1** between the small (Li$^+$ and Na$^+$) and the larger (K$^+$ and Rb$^+$, no complexation takes place) alkali-metal cations, there is a considerable decrease in complex stability for the former cations in acetonitrile when moving from **2** to **1**.

Thus log K_s values of **1** with Li$^+$ and Na$^+$ are lower by 1.3 and 2.4 log units respectively relative to **2** and these cations.[31] These result from a decrease in enthalpic stability ($\sim$16 and 13 kJ·mol^{-1} for the Li$^+$-**1** and Na$^+$-**1** relative to Li$^+$-**2** and Na$^+$-**2** complexes). Although the entropic term is more favorable for Li$^+$-**1** relative to Li$^+$-**2**, this is not enough to overcome the more favorable enthalpy of the latter relative to the former. For the sodium cation, the higher stability of this cation with **2** relative to **1** is due to the enthalpic contribution since for both, Na$^+$-**1** and Na$^+$-**2**, the $\Delta_c S°$ values are approximately the same. A similar behavior is found for **1** and alkaline-earth metal cations in acetonitrile. Unlike **2**, which recognize selectively these cations, **1** interacts only with Ca^{2+} in this solvent. However, the lower stability of this cation with **1** relative to **2** is attributed

Thermodynamics of Host−Guest Interactions

J. Phys. Chem. B, Vol. 108, No. 31, 2004 **11391**

TABLE 5: Thermodynamic Parameters of Complexation of 1 and Related Ligand 2 and Metal Cations in Various Solvents at 298.15 K

| ligand	cation	log K_s	$\Delta_c G°$/kJ·mol^{-1}	$\Delta_c H°$/kJ·mol^{-1}	$\Delta_c S°$/J.K^{-1}·mol^{-1}
		acetonitrile			
1	Li$^+$	4.87 ± 0.05[a]; 4.82 ± 0.30[a]	−27.7 ± 0.3[a]	−33.9 ± 0.9[a]	−21[a]
2	Li$^+$	6.2[b]	−35.4[b]	−48.8[b]	−45[b]
1	Na$^+$	5.42 ± 0.01[a]; 5.41 ± 0.01[a]	−30.90 ± 0.11[a]	−56.0 ± 0.5[a]	−84[a]
2	Na$^+$	7.8[b]	−44[b]	−69[b]	−83[b]
1	K$^+$	no complexation[a]			
2	K$^+$	4.04[b]	−23.06[b]	−45.8[b]	−76[b]
1	Rb$^+$	no complexation[a]			
2	Rb$^+$	2.05[b]	−11.70[b]	−23[b]	−39[b]
1	Ag$^+$	4.21 ± 0.07[a]; 3.95 ± 0. 05[a]	−24.03 ± 0.41[a]	−27.8 ± 0.4[a]	−13[a]
2	Ag$^+$	no complexation[b]			
1	Ca^{2+}	4.04 ± 0.04[a]	−23.7 ± 0.2[a]	−19.8 ± 0.2[a]	13[a]
2	Ca^{2+}	8.15[c]	−46.23[c]	−53.8[c]	−25[c]
1	Sr^{2+}	no complexation[a]			
2	Sr^{2+}	5.35[c]	−30.48[c]	−37.6[c]	−24[c]
1	Ba^{2+}	no complexation[a]			
2	Ba^{2+}	4.34[c]	−24.80[c]	−29.6[c]	−16[c]
1	Cd^{2+}	no complexation[a]			
2	Cd^{2+}	4.08[c]	−23.29[c]	−22.4[c]	3[c]
1	Pb^{2+}	5.44 ± 0.04[a]	−31.0 ± 0.1[a]	−46 ± 2[a]	−52[a]
2	Pb^{2+}	7.39[c]	−42.18[c]	−59.7[c]	−59[c]
1	Hg^{2+}	8.69 ± 0.05[a]	−49.6 ± 1.2[a]	−83 ± 2[a]; −83 ± 1[a]	−112[a]
2	Hg^{2+}	3.69[c]	−21.01[c]	−21.1[c]	−0.3[c]
1	Cu^{2+}	4.30 ± 0.02[a]	−25.5 ± 0.3[a]	−71.3 ± 0.8[a]	−154[a]
2	Cu^{2+}	no complexation[c]			
		methanol			
1	Ag$^+$	7.71 ± 0.05[a]	−44.0 ± 0.2[a]	−71.4 ± 0.8[a]	−92[a]
2	Ag$^+$	no complexation			
1	Hg^{2+}	3.66 ± 0.03[a]	−20.9 ± 0.2[a]	−72 ±1[a]	−170[a]
2	Hg^{2+}	no complexation[c]			
		N,N-dimethylformamide			
1	Ag$^+$	4.65 ± 0.03[a]	−26.5 ± 0.2[a]	−48 ± 1[a]	−71[a]
2	Ag$^+$	no complexation[c]			
1	Hg^{2+}	5.07 ± 0.03[a]	−29.0 ± 0.2[a]	−38 ±1[a]	−31[a]
2	Hg^{2+}	no complexation[c]			

[a] This work. [b] Ref 24. [c] Ref 8.

to the considerable loss in enthalpic stability ($\sim$35 kJ·mol^{-1}) for the former relative to the latter ligand, which overcomes the gain in entropy found in this solvent. The decrease in stability observed for these cations and **1** in acetonitrile is concomitant with the outcome of ^{1}H NMR investigations in CD$_3$CN, which strongly suggest that the sulfur donor atoms are unlikely to participate in the complexation process involving Li$^+$, Na$^+$, and Ca^{2+} and **1** in this solvent. This is concomitant with the recently isolated crystals of Na·**1**·ClO$_4$ complex from acetonitrile. Indeed X-ray diffraction studies have shown that in the solid state, only the pendant arms containing ester groups interact with the sodium cation and a molecule of acetonitrile is found in the hydrophobic cavity (see Figure 6).

As far as the heavy metal cations are concerned, ^{1}H NMR data pertinent to the Pb^{2+}-**1** complex suggest that the coordination between this cation and **1** is likely to involve oxygen as well as sulfur donor atoms in CD$_3$CN. Therefore, it follows that the decrease in stability of Pb^{2+} and **1** relative to **2** may be due to the lower affinity of the sulfur (**1**) relative to the oxygen donor atoms (**2**) for this cation in this solvent. Therefore, it is concluded that the decrease in stability of **1** and Pb^{2+} relative to **2** and this cation in acetonitrile is mainly attributed to the loss in enthalpic stability of the former relative to the latter.

Quite remarkable is the gain in complex stability for Hg^{2+} in moving from **2** to **1** in acetonitrile. Thus, the log K_s value for this cation and **1** in this solvent increases by 5 log units
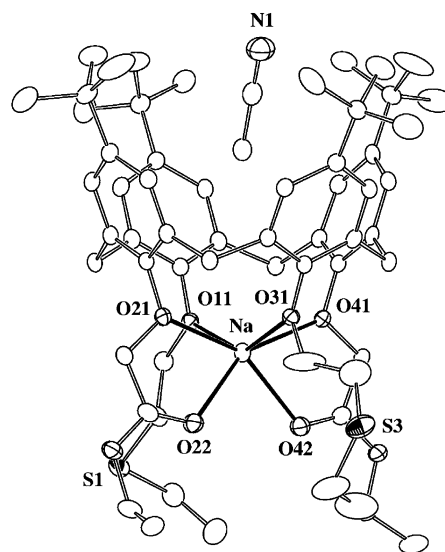
Figure 6. Molecular drawing of the sodium and acetonitrile complex with **1**. Ligand−metal bonds are indicated by full lines.

relative to **2**. This enhancement in stability is controlled by the enthalpy term, which is about 62 kJ.mol^{-1} greater (more negative) than that for Hg^{2+}-**2** complex in acetonitrile. It is indeed this higher stability (in enthalpic terms) which overcome the greater loss in entropy found in the complexation of Hg^{2+}

11392 *J. Phys. Chem. B, Vol. 108, No. 31, 2004*

Danil de Namor et al.

with **1** with respect to the same cation and **2** in acetonitrile. While no complexation is found between **2** and Cu^{2+} in acetonitrile, **1** is able to interact with this cation in this solvent and the binding process is enthalpy driven.

Conclusions

From the above discussion, the following is concluded:

(i) ^{1}H NMR studies in CD_3CN suggest the formation of the **1.**MeCN adduct in solution as found in the solid state. These findings lead to the conclusion that in acetonitrile, cation complexation proceeds via the adduct while in *N,N*-dimethylformamide and most likely in methanol, the free ligand is involved in the complexation process. Indeed the involvement of acetonitrile in the hydrophobic cavity of the ligand exerts an "*allosteric effect*" by which the hydrophilic cavity in the adduct is more receptive to host cations than that for the free ligand. This is corroborated by (i) the differences observed in the axial and equatorial protons of the methylene bridge which provide indication that the hydrophilic cavity is more open in the adduct than in the free ligand and (ii) the wider range of cations interacting with the **1.**MeCN adduct (Li^+, Na^+, Ca^{2+}, Pb^{2+}, Cu^{2+}, Hg^{2+}, and Ag^+) relative to the free ligand (only Hg^{2+} and Ag^+) in *N,N*-dimethylformamide and methanol. In all cases, 1:1 complexes are formed as assessed from conductance and calorimetric measurements.

(ii) The replacement of ester functional groups, **2**, in two alternate pendant arms by thioethyl moieties, **1**, reduces the aperture of the hydrophilic cavity (as shown by ^{1}H NMR) to an extent that in acetonitrile the adduct is able to discriminate between the smaller (Li^+, Na^+, and Ca^{2+}) and the larger (K^+, Rb^+, Sr^{2+}, and Ba^{2+}) alkali and alkaline-earth metal cations. This statement is corroborated by ^{1}H NMR, conductance and thermochemical investigations, which show no complexation with the latter cations. On the other hand, the presence of soft donor atoms in the hydrophilic cavity reduces the interaction of **1·**MeCN adduct with the hard cations (Li^+, Na^+, and Ca^{2+}) (see thermodynamic data). ^{1}H NMR data in CD_3CN indicate that no coordination occurs between these metal cations and the sulfur donor atoms of the ligand. In addition the X-ray crystallographic study on the complex of **1** with $NaClO_4$ and acetonitrile demonstrates that in the solid state, cation coordination occurs through the four ethereal and two carbonyl oxygen atoms with no participation of sulphur donor atoms. However, the presence of sulfur donor atoms in the structure of the new ligand enhances substantially the stability of complex formation with soft donor atoms such as mercury(II). Unlike for the tetraethyl ester derivative, **2**, Ag^+ and Cu^{2+} are able to form 1:1 complexes with **1·**MeCN. In moving from acetonitrile to methanol and *N,N*-dimethylformamide, the free ligand is only

able to interact with Ag^+ and Hg^{2+}. However in propylene carbonate the ability of the ligand to host metal cations is entirely lost.

References and Notes

(1) Gutsche, C. D.; *Calixarenes. Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; Royal Society of Chemistry, 1989.

(2) *Calixarenes. A Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer V., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1991.

(3) *Calixarenes 50th Anniversary, Commemorative Volume*; Vicens, J., Asfari, Z., Harrowfield, J. M., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1994.

(4) Gutsche, C. D., *Calixarenes Revisited. Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry, 1988.

(5) *Calixarenes 2001*; Asfari, Z., Böhmer V., Harrowfield, I. M., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2001.

(6) Baeyer, A. *Chem. Ber.* **1872**, *5*, 25, 280, 1094.

(7) Gutsche, C. D.; Muthukrishnan, R. *J. Org. Chem.* **1978**, *43*, 4905.

(8) Danil de Namor, A. F.; Chahine, S.; Kowalska, D.; Castellano, E. E.; Piro, E. O. *J. Am. Chem. Soc.* **2002**, *124*, 12 824.

(9) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon Press Ltd.: Oxford, UK, 1980.

(10) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Textbook of Practical Organic Chemistry*, 5th ed.; Longman Group UK Limited, 1989.

(11) Christensen, J. J.; Izatt, R. M.; Hansen, L. D. *The Rev. Sci. Instr.* **1965**, *36*, 779.

(12) Eatough, D. J.; Christensen, J. J.; Izatt, R. M. *Experiments in Thermometric Titrimetry and Titration Calorimetry*; Brigham Young University Press: Provo, Utah, USA, 1974.

(13) Hill, J. O.; Öjelund, G.; Wadsö, I. *J. Chem. Thermodyn.* **1969**, *1*, 111.

(14) Suurkuusk, J.; Wadsö, I. *Chim. Script.* **1982**, *20*, 155.

(15) *LKB 2277 Thermal Activity Monitor, Instruction Manual*; LKB Produkter AB: Bromma Sweden, 1985.

(16) Gutknecht, J.: Schneider, H.; Stroka, J. *J. Inorg. Chem.* **1978**, *17*, 3326.

(17) Cox, B. G.; Schneider, H.; Stroka, J. *J. Am. Chem. Soc.* **1978**, *100*, 4746.

(18) Gans, P.; Sabatini, A.; Vacca, A. *Talanta* **1996**, *43*, 1739.

(19) Gutsche, C. D. *Aldrichim. Acta.* **1995**, *28*, 3.

(20) Danil de Namor, A. F.; Cabaleiro, M. C.; Vuano, B. M.; Salomon, M.; Pieroni, O. I.; Pacheco Tanaka, D. A.; Ng, C. Y.; Llosa Tanco, M. A.; Rodriguez, N. M.; Cardenas Garcia, J. D.; and Casal, A. R. *Pure Appl. Chem.* **1994**, *66*, 435.

(21) Danil de Namor, A. F.; Chahine, S.; Castellano, E. E.; Piro, E. O., unpublished work.

(22) McMurry, J. *Organic Chemistry*, 5th ed.; Brooks/Cole: Pacific Grove, California, 2000.

(23) Danil de Namor, A. F.; Chahine, S., work in progress.

(24) Danil de Namor, A. F.; Gil, E.; Llosa Tanco, M. A.; Pacheco Tanaka, D. A.; Pulcha Salazar, L. E.; Schulz, R. A.; Wang, J. *J. Phys. Chem.* **1995**, *99*, 16776.