Solvent Control on the Selective, Nonselective, and Absent Response of a Partially Substituted Lower Rim Calix(4)arene Derivative for Soft Metal Cations (Mercury(II) and Silver(I)). Structural and Thermodynamic Studies

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The solvent control on the ability of a partially substituted lower rim calix(4)arene derivative 5,11,17,23,-tetra-*tert*-butyl[25,27-bis(hydroxy)-26,28-bis(ethylthioethoxy)]-calix(4)arene, **1** to host soft metal cations (Hg(II) and Ag(I)) is demonstrated through ^{1}H NMR, electrochemical (conductance measurements), and thermodynamic characterization of the complexation process in a wide variety of solvents. Solvent−ligand interactions were assessed from ^{1}H NMR measurements involving **1** and various solvents in $CDCl_3$. Thus, the formation of a 1:1 **1**−CH_3CN adduct is reported. As far as metal cations are concerned, depending on the medium their complexation with **1** was only observed for Hg(II) and Ag(I). Thus, in acetonitrile, **1** is more selective for Hg(II) relative to Ag(I) by a factor of 2.2×10^3. In methanol the selectivity is reversed to an extent that the affinity of **1** for Ag(I) is 1.4×10^3 higher than that for Hg(II). However, **1** is unable to recognize selectively these cations in *N*,*N*-dimethylformamide while in propylene carbonate the ability of **1** to interact with these cations is lost. An outstanding feature of thermodynamics emerges when an assessment is made of the ligand effect on the complexation of these cations and analogues calix(4)arene derivatives. Thus, in acetonitrile the thermodynamics of cation complexation by the hydrophilic cavity of a calix(4)arene containing mixed pendant groups is built up from thermodynamic data for the same process involving derivatives with common functionalities at the narrow rim. This is a unique example of the additive contribution of pendant arms in the field of thermodynamics of calixarene chemistry.

Introduction

The removal of heavy metal cations from contaminated sources is an area of priority concern.[1,2] A great deal of effort has been focused on the design of selective macrocyclic extracting agents for the removal of these species from water and soil.[3] Particular attention is paid to mercury and its speciations due to the toxicological impact of these species on human health.[4] Sulfur containing calix(4)arene derivatives are efficient extracting agents in phase transfer processes involving soft metal cations. This aspect of calixarene chemistry has been addressed by Roundhill and Shan.[5] These authors have emphasized the role of thermodynamics (selectivity) and fast kinetics in the selection of extracting agents for phase transfer processes involving metal cations. Much of the interest generated in calixarenes stem from the selective and versatile behavior of these ligands in their interaction with neutral and ionic species.[6−9] Calix(4)arene derivatives have unique properties in that, through molecular inclusion of the solvent in the hydrophobic cavity, the hosting ability of the hydrophilic cavity for metal cations may be significantly altered relative to that of the free ligand.[10] Thus, the extent of solvent-ligand interactions is an important aspect to consider in (i) the design and synthesis of these receptors, (ii) the selection of the complexation media, and (iii) the choice of the solvent for phase transfer processes. This statement is corroborated by recent work[11,12] which demonstrated that the medium effect on the complexation of calix(4)-arene derivatives and metal cations may lead to the formation of strikingly selective and stable complexes in one medium while a complete lack of complexation may be observed in another medium. In addition, changes in the complex composition have been also observed in moving from one solvent to another.[13] Despite the synthetic and structural developments in the field of calixarene chemistry, investigations on the capacity of these macrocycles to respond to the presence of ionic and neutral species in different media are very limited. This is an important factor in selectivity, a fundamental concept in molecular recognition,[14] one of the main features of supramolecular chemistry.[15]

This paper reports structural and thermodynamic studies of a partially substituted derivative, 5,11,17,23,tetra-*tert*-butyl[25,27-bis(hydroxy)-26,28-bis(ethylthioethoxy)]-calix(4)arene, **1**, and its neutral (^{1}H NMR) and cation complexes (^{1}H NMR, conductometric, electrochemical and thermodynamic investigations), in various media. Solvents selected are those in which at low salt concentrations, ions rather than ion pairs predominate in solution.

Selectivity changes exhibited by **1** for soft metal cations (Ag^+ and Hg^{2+}) as a result of the medium effect are demonstrated. The thermodynamics of cation complexation involving analogous calix(4)arene derivatives in acetonitrile is used to build up a model in which the additive contribution of pendant arms is demonstrated.

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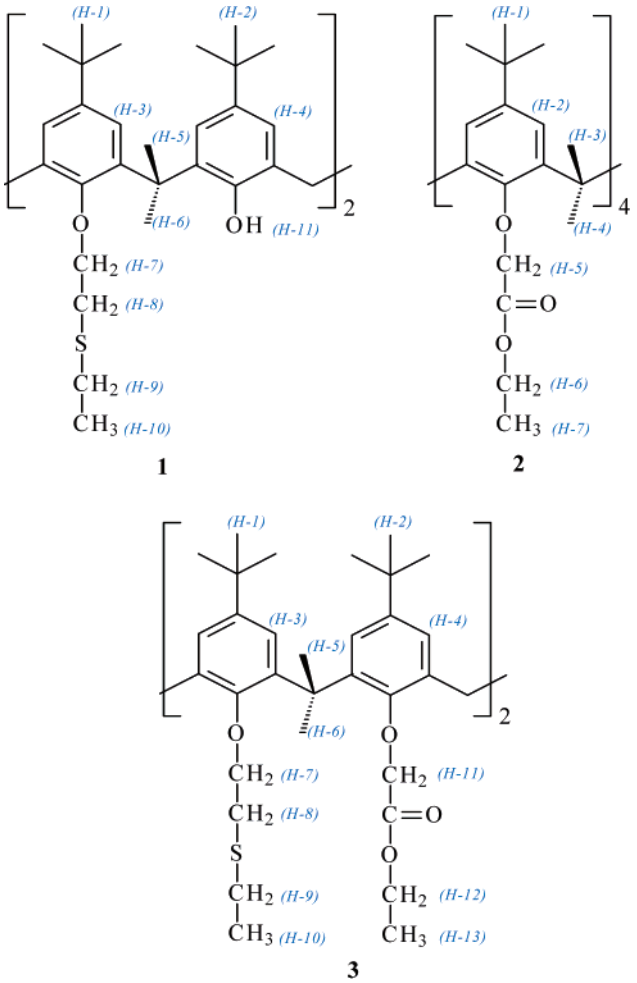

Figure 1. Structures of ligands **1**, **2**, and **3**.

Experimental Section

Synthesis and Characterization of Ligand 1. Ligand **1** (Figure 1) was synthesized and characterized as reported elsewhere.[12]

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_4O_{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.[16]

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.[17]

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

Deuterated chloroform, $CDCl_3$, dichloromethane, CD_2Cl_2, acetonitrile, CD_3CN, methanol, CD_3OD, *N*,*N*-dimethylformamide, C_3D_7NO, and tetramethylsilane, TMS, were purchased from Aldrich.

^{1}H NMR Measurements. ^{1}H NMR measurements in $CDCl_3$, CD_3CN, CD_3OD, and C_3D_7NO 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.

The complexation behavior of **1** toward metal cations and neutral species at 298 K was studied using the ^{1}H NMR technique, by adding the metal-ion salt or the neutral species (2.0×10^{-3} to 3.5×10^{-3} mol dm^{-3}) into the NMR tube containing the ligand dissolved in the appropriate solvent (9.0×10^{-4} to 1.0×10^{-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 titrant 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.[11]

Isolation of the Mercury(II) and Silver(I) Complexes of 1 from Acetonitrile and Methanol, Respectively. Stoichiometric quantities of the mercury(II) perchlorate salt and **1** dissolved in acetonitrile were mixed and refluxed, and then the solutions were left at room temperature until crystals were formed. For the silver(I) complex, the metal salt was added in a 1:3 stoichiometry (**1**:Ag^+) and the solution was refluxed. Upon cooling at room-temperature crystals formed quickly.

Calorimetric Titrations. Determination of the Thermodynamic Parameters of Complexation. For direct calorimetric titrations, Tonac 450 and the Thermal Activity Monitor (TAM) calorimeters were used. As far as the former is concerned, this was operated as an isoperibol titration calorimeter.[18] 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) with hydrochloric acid (HCl, 0.1 mol dm^{-3}) at 298.15 K.[19] The value determined -47.50 ± 0.08 kJ. mol^{-1} is in agreement with the one reported by Hill, Öjelund, and Wadsö[20] using an LKB reaction calorimeter.

A solution of the perchlorate salt of selected metal ions [$(2.0-5.0) \times 10^{-2}$ mol dm^{-3}] was prepared in the solvent of interest, placed in the buret. The whole system was then immersed in a thermostated water bath at 298.15 K and allowed to reach thermal equilibrium. Then the metal-ion salt solution in the buret was titrated into the vessel containing a solution of **1** (50 cm^3, 6.0×10^{-4} to 1.0×10^{-3} mol dm^{-3}), prepared in the same solvent.

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

TABLE 1: ^{1}H NMR Chemical Shifts (δ, ppm) and Difference in the Chemical Shifts ($\Delta\delta$, ppm) with Respect to $CDCl_3$, for 1 in $CDCl_3$, $CDCl_2$, CD_3CN, CD_3OD, and C_3D_7NO at 298 K

protons	$CDCl_3$	CD_2Cl_2		CD_3CN		CD_3OD		C_3D_7NO	
1	δ/ppm	δ/ppm	$\Delta\delta$/ppm	δ/ppm	$\Delta\delta$/ppm	δ/ppm	$\Delta\delta$/ppm	δ/ppm	$\Delta\delta$/ppm
H-1,2	0.93, 1.30	1.12, 1.22	0.19, −0.08	1.15, 1.20	0.22, 0.10	1.07, 1.23	0.14, −0.07	1.04, 1.27	0.11, −0.03
H-3,4	7.06, 6.75	7.02, 7.03	−0.04, 0.28	7.22, 7.16	0.16, 0.41	7.12, 7.05	0.06, 0.30	7.30, 7.23	0.24, 0.48
H-5(eq)	3.32	3.35	0.03	3.40	0.08	3.38	0.06	3.55	0.23
H-6(ax)	4.31	4.32	0.01	4.30	0.01	4.36	0.04	4.38	0.07
H-7	4.12	4.14	0.02	4.15	0.03	4.15	0.03	4.19	0.07
H-8	3.10	3.19	0.09	3.21	0.11	3.20	0.10	3.27	0.17
H-9	2.71	2.71	0.00	2.71	0.00	2.75	0.04	2.79	0.08
H-10	1.33	1.33	0.00	1.32	−0.01	1.36	0.03	1.34	0.01
H-11	7.00	out of range	−	8.11	1.11	out of range	−	8.40	1.40

that no ion-pair formation occurred within the working concentration range. All measurements were conducted in triplicate.

For direct calorimetric titrations, the four-channel heat conduction microcalorimeter (Thermometric, 2277 thermal activity monitor, TAM) designed by Suurkuusk and Wadsö[21] was used. Electrical (static) and chemical calibrations were carried out to check the reliability of the equipment.[22]

The reaction vessel was charged with 2.8 cm^3 of the ligand (6.0×10^{-4} to 1.0×10^{-3} mol dm^{-3}) in the appropriate solvent. The metal-ion salt (1.4×10^{-2} to 3.0×10^{-2} mol dm^{-3}) was injected incrementally using an automated 0.25 cm^3 gastight motor driven Lund syringe. In each titration experiment, about 20 injections were made at time intervals of 40−50 min. Corrections for the heat 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 the $\Delta_c H°$ 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 (as perchlorate) in the solvents investigated by the direct method. The electrochemical cell and the methodology implemented were detailed elsewhere.[12] Stability constant calculations were performed using the HYPERQUAD program.[23]

Results and Discussion

^{1}H NMR Measurements for the Free Ligand. Conformational Tuning. The effect of the solvent on the ligand's conformation was studied by ^{1}H NMR.

Chemical shifts (δ ppm) and chemical shift changes ($\Delta\delta$ ppm) relative to $CDCl_3$ for **1** in CD_2Cl_2, CD_3CN, CD_3OD, and C_3D_7NO at 298 K are listed in Table 1.

The conformation in which the ligand stands in is depicted according to the difference in the chemical shifts between the axial and equatorial protons, $\Delta\delta_{ax-eq}$.[24] A value of $\Delta\delta_{ax-eq} = 0.9 \pm 0.2$ ppm is expected for a ligand in a perfect "cone" conformation while a $\Delta\delta_{ax-eq} = 0.5 \pm 0.1$ ppm is for a flattened "cone" conformation.[24] As far as **1** is concerned, the $\Delta\delta_{ax-eq}$ values (Table 1) in $CDCl_3$, CD_2Cl_2, CD_3CN, CD_3OD, and C_3D_7NO are 0.99, 0.97, 0.90, 0.98, and 0.83 ppm, respectively. These findings indicate that, in the solvents investigated, **1** adopts a perfect "cone" conformation.

However, a marked deshielding effect is recorded for the aromatic protons, $\Delta\delta$ H-3,4 = 0.16, 0.41 ppm respectively and for those of the *p-tert*-butyl groups, $\Delta\delta$ H-1,2 = 0.22, 0.10 ppm, respectively in CD_3CN relative to $CDCl_3$. In addition, in CD_3OD and CD_2Cl_2 one of the aromatic protons shows a significant deshielding effect while no significant changes are observed for other protons.

On the other hand, in C_3D_7NO, the protons of both aromatic rings show a relatively higher deshielding effect, $\Delta\delta$ H-3,4 = 0.24, 0.48 ppm, compared to the ones observed in CD_3CN, CD_2Cl_2, and CD_3OD successively (Table 1). This effect relative to $CDCl_3$ is found to be linearly correlated with the $\Delta\delta_{ax-eq}$ values suggesting that the more deshielded the protons of the aromatic rings are, as a result of the medium, the more flattened is the conformation adopted by the hydrophobic cavity of the ligand.

TABLE 2: Difference in the Chemical Shifts ($\Delta\delta$, ppm), for the Protons of 1 upon Titration with Acetonitrile (MeCN) in $CDCl_3$ at 298 K[a]

	$\Delta\delta^b$			H−(MeCN)	
[MeCN]/[**1**]	H-1,2	H-3,4	H-11	δ	$\Delta\delta^c$
0.2	0.00, 0.03	0.00, 0.03	0.08	0.35	−1.75
0.5	0.01, 0.03	0.00, 0.05	0.16	0.44	−1.66
1.0	0.02, 0.06	0.01, 0.09	0.28	0.62	−1.48
1.2	0.03, 0.07	0.07, 0.10	0.33	0.70	−1.40
1.7	0.03, 0.08	0.01, 0.12	0.42	0.84	−1.26
2.2	0.04, 0.10	0.01, 0.14	0.48	0.95	−1.15
3.0	0.05, 0.11	0.01, 0.16	0.55	1.10	−1.00
4.0	0.05, 0.12	0.02, 0.18	0.62	1.21	−0.89

[a] H-5, -6, -7, -8, -9, and -10 showed no significant chemical shifts ($\Delta\delta$ = 0.01−0.04 ppm). [b] Relative to the free ligand, **1** (see Table 1). [c] Relative to the chemical shifts for acetonitrile in $CDCl_3$ at 298 K, δ = 2.10 ppm.

However, the prominent values in C_3D_7NO relative to CD_3CN are more likely to be due to the interaction of C_3D_7NO with ligand sites other than those found in the vicinity of its hydrophobic cavity. A possible explanation for this observation is that unlike other solvents, C_3D_7NO is a protophilic dipolar aprotic solvent. As such its basic oxygens may interact with the phenolic protons of the ligand.

As far as CD_3CN is concerned, interaction between the hydrophobic cavity and this solvent is suggested. This statement is based on earlier findings reported for the tetraester calix(4)arene derivative **2**[11] and for the diester diethyl sulfoxy calix(4)arene derivative **3**.[12]

Therefore, in an attempt to gain further insight on the interaction of **1** with the solvent molecules, ^{1}H NMR titrations were performed in $CDCl_3$ at 298 K and these are now discussed.

^{1}H NMR Titration Experiments. Hosting Ability of the Hydrophobic Cavity for Neutral Species. ^{1}H NMR titrations of **1** with acetonitrile and methanol were carried out in $CDCl_3$ (as a reference solvent) at 298 K.

Chemical shifts (δ ppm) and the chemical shift changes ($\Delta\delta$ ppm) for the resonance line of acetonitrile and methanol in $CDCl_3$ as a function of the stoichiometric ratio are given in Tables 2 and 3, respectively.

As far as the data in Table 2 are concerned, significant chemical shift changes for one of the aromatic (H-3,4), *p-tert*-butyl (H-1,2) and the hydroxyl (H-11) protons of **1** are found. A striking observation is that related to the appearance of the

TABLE 3: Difference in the Chemical Shifts ($\Delta\delta$, ppm), for the Protons of 1 upon Titration with Methanol (MeOH) in $CDCl_3$ at 298 K[a]

	H-11	H(CH_3)−(MeOH)	
[MeOH]/[**1**]	$\Delta\delta$[b]	δ	$\Delta\delta$[c]
0.25	0.07	3.20	−0.29
0.50	0.08	3.21	−0.28
0.75	0.09	3.22	−0.27
1.00	0.10	3.23	−0.26
1.25	0.11	3.25	−0.24
1.75	0.12	3.27	−0.22
2.25	0.14	3.28	−0.21
3.00	0.15	3.31	−0.18

[a] H-1 to H-10 showed no significant chemical shifts ($\Delta\delta = \pm 0.01$ ppm). [b] Relative to the free ligand, **1** (see Table 1). [c] Relative to the chemical shifts for the methyl group of methanol in $CDCl_3$ at 298 K, $\delta = 3.49$ ppm.

acetonitrile signal at an upfield shift of 0.62 ppm (Figure 2), which corresponds to a MeCN/**1** stoichiometry of **1** relative to its ordinary position in $CDCl_3$ ($\delta = 2.10$ ppm). The shielding effect ($\Delta\delta = -1.75$ ppm) that the protons of acetonitrile are undergoing in this solvent provides clear evidence that a molecule of this solvent is sitting deep within the vicinity of the hydrophobic cavity of **1**. Hence its protons are being shielded by the induced ring effect.

No other significant chemical shifts are observed for other protons throughout the course of the titration.

The outcome of the ^{1}H NMR titration of **1** with methanol in $CDCl_3$ is shown in Table 3. This table shows that H-11 is deshielded while shielding of the protons of the methyl group of the alcohol occurs. However, significant chemical shift changes are observed neither for the aromatic protons of the hydrophobic cavity nor for those of the hydrophilic cavity (Figure 2). On the other hand, titration of **1** with *N*,*N*-dimethylformamide in $CDCl_3$ (Figure 2) shows no changes in any of their protons, suggesting lack of interaction between this solvent and the hydrophobic cavity of **1**.

These findings encouraged us to gain further insight into solvent-ligand interactions. Given that modification of the hydrophilic cavity will affect the degree of aperture of the hydrophobic nest and as a result its interaction with the solvent ligands containing similar pendant arms, ligands **2**[11] and **3**[12] were selected.

Thus, ^{1}H NMR titrations with these ligands and acetonitrile in $CDCl_3$ at 298 K were performed.

The shielding effect for the protons of acetonitrile in $CDCl_3$, was the most interesting aspect of this investigation. No changes for the difference in the chemical shifts recorded were observed by increasing the mole ratio ($\Delta\delta = -0.1$ and -0.12 ppm with **2** and **3** respectively). It is found that the shielding of the acetonitrile protons ($\Delta\delta = -1.48$, -0.1, and -0.12 ppm) with **1**, **2** and **3** in $CDCl_3$ respectively, are again correlated with $\Delta\delta_{ax-eq}$ as well as with the deshielding effect observed for the Ar−H of the free ligands in CD_3CN at 298 K. Thus, as the hydrophobic cavity of the free ligand becomes flatter in CD_3CN, more pronounced is the shielding effect for acetonitrile's protons by the ligand in $CDCl_3$. Hence the solvent is deeply wrapped within the aromatic cavity. This is corroborated by the increase in (i) the deshielding effect for the Ar−H protons of **1** in CD_3CN and (ii) the shielding effect shown by the protons of acetonitrile.Having discussed ligand−solvent interactions from ^{1}H NMR studies, we proceeded with complexation studies of **1** and metal cations in different media.

The Medium Effect on the Complexation of 1 and Metal Cations. To assess (i) the medium effect on the interaction of **1** and metal cations, (ii) the active sites of **1** participating in the cation complexation process, and (iii) conformational changes that the ligand undergoes upon cation complexation, ^{1}H NMR titrations were carried out in CD_3CN, CD_3OD, and C_3D_7NO at 298 K.

In all the ^{1}H NMR titrations performed, no evidence of water molecules observed in the spectra. This indicates that water (if at all present) does not act as a ligand or interfere in the complexation process between this ligand and the metal cations investigated. A representative example is given in Figure 3, for the titration of **1** with Ag^+ in CD_3OD at 298 K.

As far as alkali, alkaline-earth and transition metal cations are concerned, no chemical shift changes were observed upon addition of these cation salts to the ligand in these solvents.

^{1}H NMR chemical shift changes were only observed by the addition of Ag^+ and Hg^{2+} (as perchlorates) to **1** in CD_3CN, CD_3OD, and C_3D_7NO. ^{1}H NMR data listed in Tables 4 and 5 respectively show that the complex composition is 1:1 (M^{n+}:1) in these solvents. For the Ag^+-**1** complex in CD_3CN, CD_3OD and C_3D_7NO, significant deshielding effects are observed for H-8, 9, 10 in the following sequence, C_3D_7NO > CD_3OD > CD_3CN. These findings unambiguously demonstrate that cation−ligand interaction occurs through the sulfur atoms of the pendant arms. Similar conclusions were drawn for the Ag^+-**3** complex, where only the sulfur atoms provide the sites of interaction with this cation.[12] Alkali and alkaline-earth metal cations are hard cations and these are expected to interact with hard donor atoms such as oxygen. Although oxygen atoms are present at the lower rim of **1** their number are not enough to satisfy the co-coordinating demands of these cations.

Soft metal cations such as Hg^{2+} and Ag^+ are known to interact with soft donor atoms such as sulfur. However, the fact that **1** does not interact with other soft metal cations is a strong indication that the pre-organization of the binding sites together with the coordinating requirements of the cation play a significant role in the complexation process.

On the other hand, the $\Delta\delta_{ax-eq}$ values for the Ag^+ complexes in CD_3CN, CD_3OD and C_3D_7NO (0.84, 0.75, and 0.65 respectively) suggest that the hydrophobic cavity of **1** undertakes a significant adjustment in the latter relative to the former solvent. This is accompanied by the considerable shielding effect of H-11, which appears to reposition itself more within the core of the aromatic rings area resulting upon complexation. A similar interpretation applies to the Hg^{2+}-**1** complex in the same solvents. Unlike for the Ag^+-**1** complex, the deshielding effect observed for Hg^{2+}-**1** in the various solvents follows the sequence $CD_3CN \approx C_3D_7NO$ > CD_3OD. In addition for this complex, the flattening degree of the cone tends to increase successively when moving from CD_3CN and CD_3OD to C_3D_7NO.

Unlike for the Ag^+-**1** complex in CD_3CN, significant chemical shift changes are observed in the aromatic (H-3,4) and one of the *p-tert*-butyl group protons (H-1,2), of the Hg^{2+}-**1** complex in this solvent. These findings strongly suggest that in the latter complex the solvent is likely to be hosted in the hydrophobic cavity of the ligand. On the other hand, X-ray structures for the complexes Hg^{2+}-**1** (Figure 4a[25]) and Ag^+-**1** (Figure 4b), does not corroborate with the observation made in solution. As far as Hg^{2+}-**1** complex is concerned, the Hg^{2+} binds with the two sulfur moieties of the pendant arms as suggested from ^{1}H NMR analysis, however, no acetonitrile molecule was found in the hydrophobic cavity. The Ag^+-**1** complex has formed after treating the ligand solution with an excess of Ag^+ which resulted in the formation of a supramolecular structure. The following section discusses conductance studies carried out for these

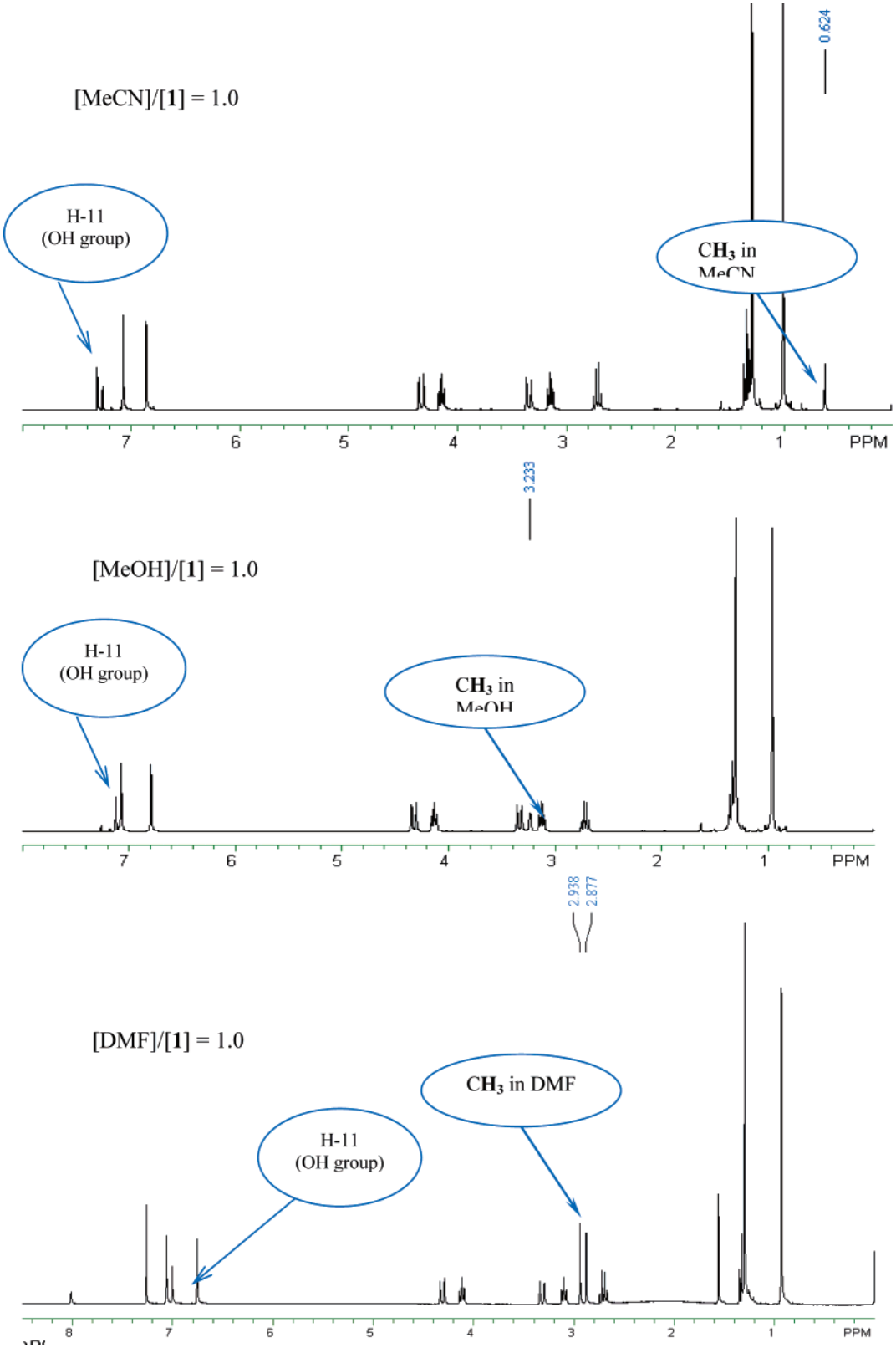

Figure 2. ^{1}H NMR spectra for **1** and MeCN, MeOH and DMF in $CDCl_3$ at 298 K.

systems in three dipolar aprotic (MeCN, DMF, and PC) and two protic (MeOH and EtOH) solvents.

Conductometric Titrations. The main aim of conductance studies was to (i) establish the composition of the metal-ion complexes in solution and (ii) determine the concentration range in which ions are the predominant species in solution. This concentration range is to be used in all physicochemical measurements performed and discussed later on in this paper.[11]

Thus, plots of molar conductance, Λ_m (S cm^2 mol^{-1}) against the ligand: cation ratio (**1**/M^{n+}) are illustrative of complexes of different strengths. (1) For strong complexes, two straight lines with a sharp break at the reaction stoichiometry are found, (2) complexes of moderate stability are characterized by a continuous variation in the molar conductance resulting in a broad break in the curve, so the composition of the complex was determined by extrapolating the data at low and high ligand/metal cation

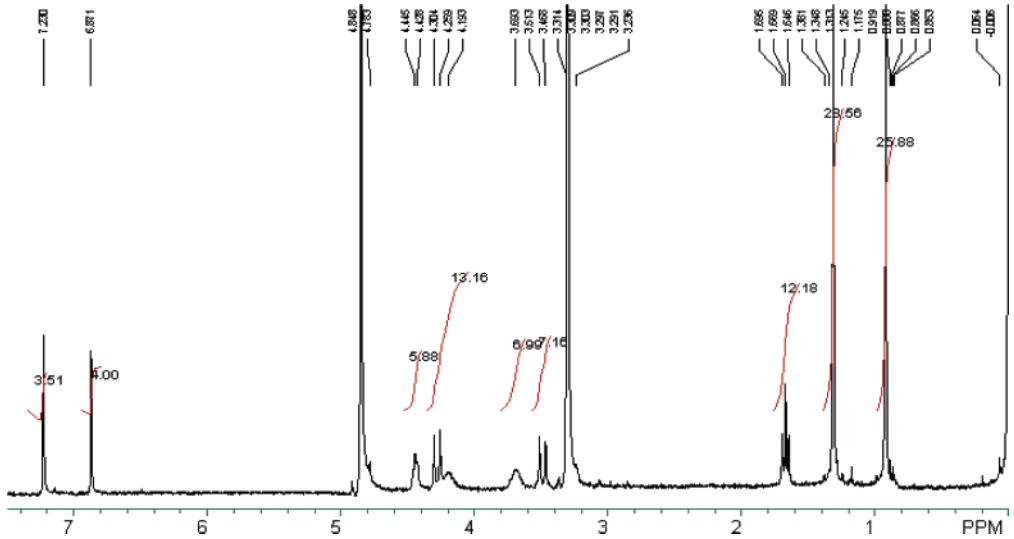

Figure 3. ^{1}H NMR spectrum from the titration of **1** with Ag^+ in CD_3OD, showing the absence of water molecules (which appears normally in the region of 2 ppm), at 298 K.

TABLE 4: Chemical Shift Changes ($\Delta\delta$, ppm)[a] in the ^{1}H NMR Spectrum of 1 with Ag^+ as Perchlorate in CD_3CN, CD_3OD, and C_3D_7NO at 298 K

protons Ag^+-**1**	$\Delta\delta$/ppm		
	CD_3CN	CD_3OD	C_3D_7NO
H-1,2	−0.02, 0.00	0.04, 0.04	−0.02, 0.01
H-3,4	0.02, 0.01	0.10, 0.09	0.02, 0.08
H-5(eq)	0.02	0.13	0.11
H-6(ax)	−0.05	−0.10	−0.07
H-7	0.03	0.15	0.19
H-8	0.10	0.28	0.36
H-9	0.11	0.26	0.39
H-10	0.05	0.12	0.17
H-11	−0.07		−0.25

[a] See Table 2 for the chemical shifts (δ ppm) of the free ligand in the corresponding solvent at 298 K.

TABLE 5: Chemical Shift Changes ($\Delta\delta$, ppm)[a] in the ^{1}H NMR Spectrum of 1 with Hg^{2+} as Perchlorate in CD_3CN, CD_3OD, and C_3D_7NO at 298 K

protons $Hg^{2+}-$**1**	$\Delta\delta$/ppm		
	CD_3CN	CD_3OD	C_3D_7NO
H-1,2	0.21, −0.08	−0.11, 0.06	−0.01, 0.01
H-3,4	0.14, 0.47	−0.13, 0.07	0.01, 0.07
H-5(eq)	0.12	0.08	0.08
H-6(ax)	−0.04	−0.06	−0.02
H-7	0.12	0.2	0.21
H-8	0.33	0.11	0.71
H-9	0.39	overlapped	0.69
H-10	0.13	0.21	0.21
H-11			−0.45

[a] See Table 2 for the chemical shifts (δ, ppm) of the free ligand in the corresponding solvent at 298 K.

ratio, and (3) a slight or nonexisting change in the slope of the curve denotes weak complexation.

Some illustrative examples are now given which strongly reflect the medium effect on the complexation process. Thus, in acetonitrile, the conductometric titration curve for Ag^+ and **1** (Figure 5a) has shown the formation of a relatively weak complex. On the other hand, the conductometric titration curve for Hg^{2+} and **1** suggested the formation of a strong complex in this solvent. The opposite trend is found in methanol where the capacity of the ligand to interact with Ag^+ (Figure 5b) is greater (stronger complex) than that for Hg^{2+} (Figure 5c) (weaker complex). In *N*,*N*-dimethylformamide, moderate complexation takes place between this ligand and these cations (an illustrative example is shown in Figure 5d, for Hg^{2+} and **1**).

The increase in size in moving from the free to the complex cation is reflected in the decrease observed in the Λ_m values upon addition of the ligand to the metal cation in these solvents.

In all cases, complexes of 1:1 (ligand:metal cation) stoichiometry are formed as shown by the extrapolation at low and high ligand to metal cation ratio.

Nonexisting changes in the conductance were recorded for alkali metal, alkaline-earth metal, transition metal, Pb^{2+}, and Cd^{2+} cations in all solvents investigated. These findings corroborate the ^{1}H NMR investigations in which addition of these cation salts to **1** in the relevant deuterated solvent showed no changes in the chemical shifts of the ligand, suggesting that either very weak or no complexation takes place between this ligand and these cations. Another illustrative example of the medium effect on the complexation of **1** with metal cations is that in propylene carbonate where cation recognition by **1** is totally lost. No complexation was observed with any of the cations considered including Ag^+ and Hg^{2+}.

At this stage it is appropriate to emphasize the ligand effect on the complexation process. Within this context, cation complexation data of **1** are compared with corresponding data involving an analogous ligand, **3**.

Markedly, the removal of the two-ester pendant arms in **3** to yield the partially substituted ligand, **1**, with two thioethyl arms, eliminated the ability of the latter to complex cations other than Ag^+ and Hg^{2+} in MeCN, MeOH, EtOH, and DMF.

Having established the composition of the metal ion complexes of Ag^+ and Hg^{2+} in these solvents, the concentration range at which ions are predominantly in solution was investigated through conductance measurements carried out at different concentrations of the metal-ion salt. This is particularly relevant when metal(II) salts are involved due to the higher tendency of bivalent cations relative to univalent ones to interact with the counterion particularly in nonaqueous media.[11,12] The observed linear relationship provides an indication that within this concentration range, ions are predominantly in solution.

However, the role of thermodynamics in assessing quantitatively the selective behavior of **1** for Hg^{2+} and Ag^+ in different media cannot be underestimated. Thus, the following section concerns the medium effect on the thermodynamics of complexation of **1** and soft metal cations in the various solvents.

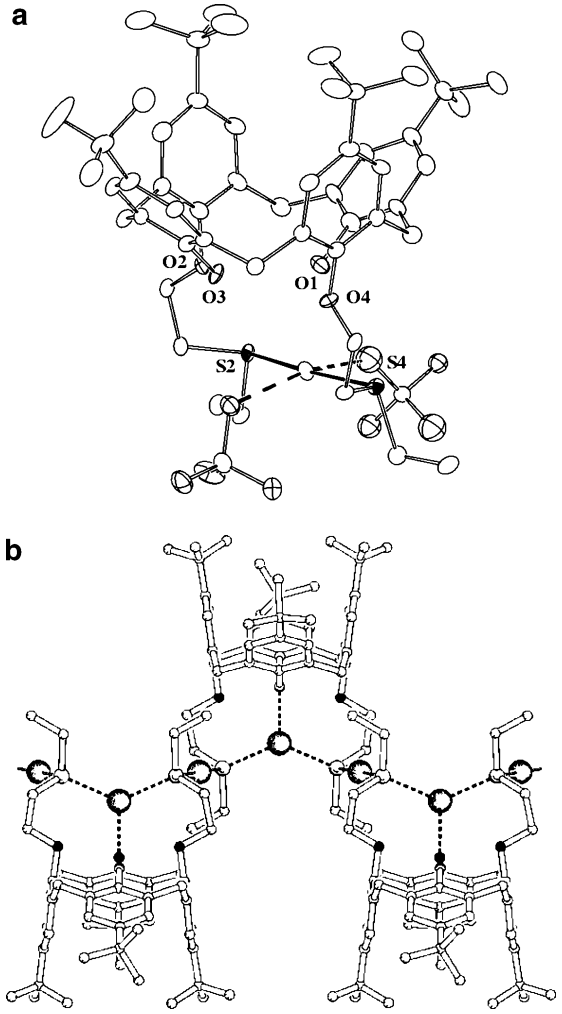

Figure 4. (a) Side view of the mercury(II) complex with **1** in the Hg(**1**)$(ClO_4)_2$·2MeCN crystal. Only one of the two positions exhibited by the rotationally disordered perchlorate ion is included in the plot. For clarity, only a few representative atomic labels are shown. Mercury−sulfur bonds are emphasized by full lines and Hg···O(perch) and O−H···O(pend) contacts by dashed lines. (b) Supramolecular structure of the Ag_2**1**$(ClO_4)_2$ complex in the solid as viewed along the local mirror plane. Ag(I) ions are indicated by large, shadowed disks, sulfur atoms by open circles of intermediate size and oxygen atoms by small dark disks. Dashed lines indicate silver-ligand bonds. For clarity, the perchlorate ions and the H atoms are not included in the plot.

Thermodynamics of Complexation. Medium Effect. Having determined the composition of the metal-ion complexes in the various solvents and the concentration range at which the metal ion salts are predominantly in their ionic forms in these solvents, the complexation of **1** with metal cations, M^{n+} is represented by eq 1.

$$M^{n+}(s) + L(s) \rightarrow M^{n+}L(s) \qquad (1)$$

Stability constants (expressed as log K_s), standard Gibbs energies, $\Delta_c G°$, enthalpies, $\Delta_c H°$, and entropies, $\Delta_c S°$ of complexation of **1** with Ag^+ and Hg^{2+} in MeCN, MeOH, EtOH, and DMF at 298.15 K are listed in Table 6. It should be noted that the accuracy of the calorimetric data has been carefully checked through the calculation of the enthalpies of coordination, (referred to the process in which the reactants and the product are in the solid state). The relevance of these data has been extensively discussed by us in previous papers.[8,9] Thus, the average values for the enthalpies of coordination of these systems (-50.2 ± 0.5 and -53.9 ± 0.5 kJ mol^{-1} for Ag(**1**)ClO_4 and Hg(**1**)$(ClO_4)_2$ respectively derived from complexation and solution enthalpies of reactants and product in the various solvents) unambiguously demonstrate the validity of the data reported in this paper. Detailed information is given elsewhere.[25]

Inspection of stability constant data (Table 6) reflects the striking effect of the medium on the complexation process. Thus, in DMF, although complexes of moderate stability are formed, the ability of the ligand to selectively recognize these cations is very poor while in MeOH, selective recognition for Ag^+ relative to Hg^{2+} is shown by the selectivity factor ($S = K_{sAg^+}/K_{sHg^{2+}}$). This unambiguously demonstrates that **1** is more selective for the former relative to the latter cation by a factor of 1.4×10^3. On moving from methanol to ethanol, S drops significantly ($S = 8$). However, in acetonitrile, the selectivity of **1** for these cations follows the opposite trend to that observed in methanol. In fact **1** is more selective for Hg^{2+} by a factor of 2.2×10^3 relative to Ag^+. These findings provide a textbook example of the medium effect on the complexation process involving calixarene derivatives and soft metal cations.

Ligand Effect. Another outstanding feature of thermodynamics emerges when the ligand effect on the complexation of these cations in these solvents is considered. In doing so thermodynamic data for **1** are compared with corresponding data for the tetraethyl ester derivative, **2** and its analogue, **3**. It should be noted that **3** has mixed pendant arms, half are those found in **2**, while the other half are common to **1** (see Figure 1). As far as the complexation of Hg^{2+} and these ligands in acetonitrile is concerned, an additive cooperative effect of the ester and the thioethyl pendant arms of **2** and **1** respectively (through the O in **2** and sulfur donor atoms in **1**) to the complexation of **3** and this cation in this solvent is amazingly demonstrated through thermodynamics. Indeed the data fit into a model in which the hydrophilic cavity of **3** is built from the contribution of two of the four-ester pendant arms of **2** and two thioethyl arms of **1** as detailed in Table 7. This table shows the thermodynamic parameters of complexation ($\Delta_c G°$, $\Delta_c H°$, and $T\Delta_c S°$) for these ligands and Hg^{2+} in acetonitrile (second column in Table 7). Then data for **2** and **1** are split into four and two respectively to calculate the impact of each arm (third column in Table 7). The sum of the contributions of two ester and two thioethyl pendant arms from **2** and **1** yields $\Delta_c G°$, $\Delta_c H°$, and $T\Delta_c S°$ values for the complexation of **3** and Hg^{2+} in acetonitrile (last column in Table 7). For this system ,excellent agreement is found between the data obtained directly (column 2, Table 7) and indirectly (last column in Table 7). This unique example in which the energetics of cation complexation by the hydrophilic cavity of a calixarene containing mixed pendant arms at the lower rim can be built up from the same process involving derivatives with common functionalities at the narrow rim is unambiguouly demonstrated. We believe that the concept of additivity is also applied to Ag^+ and **3** in acetonitrile. For this system, the difficulty in assessing it quantitatively is that the interaction of **2** and Ag^+ in this solvent is very weak ($\log K_s \approx 1$), therefore it is not possible to accurately determine this value by implementing the techniques available (titration calorimetry, potentiometry, and UV spectrophotometry). From the above discussion, it follows that in the complexation of these two cations and **3** in acetonitrile, although the strongest interaction occurs with the pendant arms containing sulfur donor atoms, the ester pendant arms are also participating in the binding process.

The lack or very weak response found for **2** and these metal cations in solvents other than acetonitrile is reflected in the relatively small differences observed in the stability constants

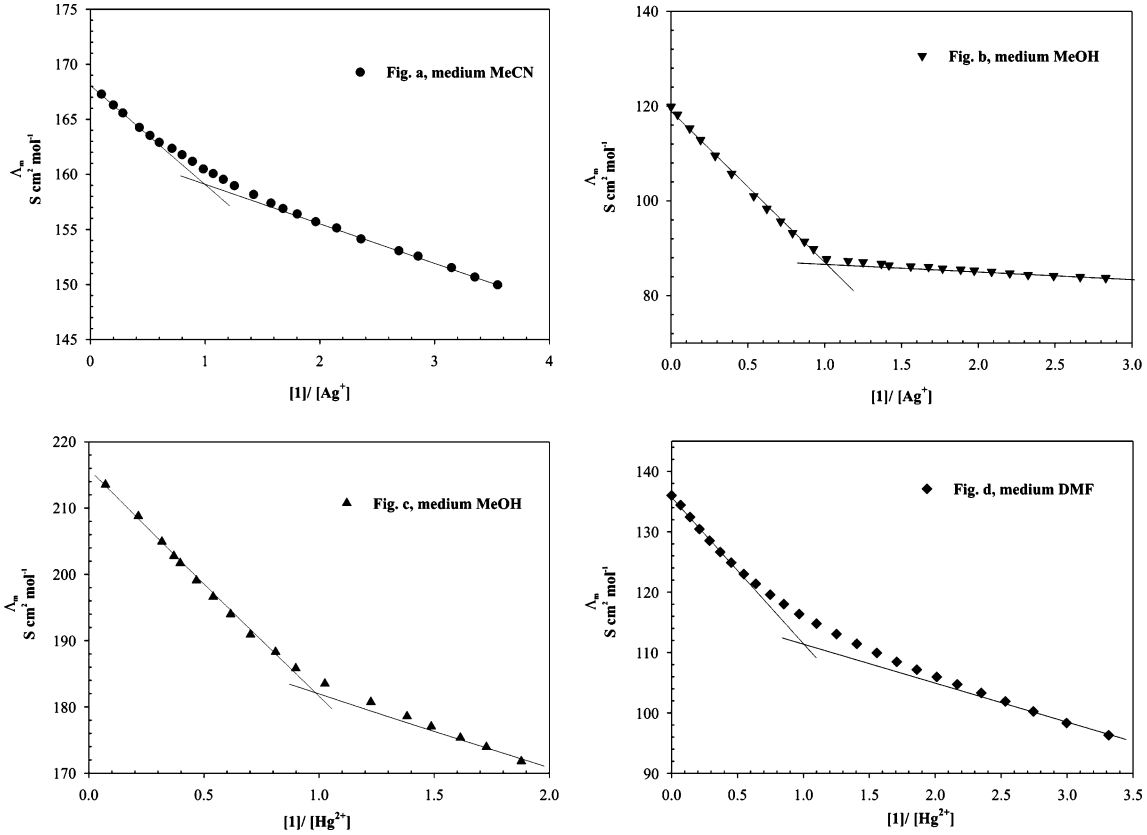

Figure 5. (a) Conductometric titration curve of Ag^+ (as perchlorate) with **1** in acetonitrile at 298.15 K. (b) Conductometric titration curve of Ag^+ (as perchlorate) with **1** in methanol at 298.15 K. (c) Conductometric titration curve of Hg^{2+} (as perchlorate) with **1** in methanol at 298.15 K. (d) Conductometric titration curve of Hg^{2+} (as perchlorate) with **1** in *N*,*N*-dimethylformamide at 298.15 K.

TABLE 6: Thermodynamic Parameters of Complexation of 1, 2, and 3 with Mercury(II) and Silver(I) (as Perchlorates) in Acetonitrile, Methanol, Ethanol, and *N*,*N*-Dimethylformamide at 298.15 K

complex	log K_s	$\Delta_cG°$/kJ mol^{-1}	$\Delta_cH°$/kJ mol^{-1}	$\Delta_cS°$/J K^{-1} mol^{-1}
		Acetonitrile		
Hg^{2+}−**1**	6.50 ± 0.03[b]	−30.2 ± 0.2	−74 ± 1[a]	−128
Hg^{2+}−**3**	8.69[d]	−49.6	−83[a,d]	−112
Hg^{2+}−**2**	3.69[a]	−21.01	−21.1[a]	−0.3
Ag^+−**1**	3.20 ± 0.03[a]	−18.3 ± 0.6	−20.6 ± 0.3[a]	−8
	3.1 ± 0.1[c]			
Ag^+−**3**	4.08[a]	−24.03	−27.8[a]	−13
		Methanol		
Hg^{2+}−**1**	4.12 ± 0.03[a]	−23.5 ± 0.2	−19.7 ± 0.4[a]	13
Hg^{2+}−**3**	3.66[a]	−20.9	−72[a]	−170
Ag^+−**1**	7.26 ± 0.03[a]	−41.4 ± 0.1	−45.7 ± 0.4[a]	−14
Ag^+−**3**	7.71[c]	−44	−71.4[a]	−92
		Ethanol		
Hg^{2+}−**1**	5.33 ± 0.02[a]	−30.4 ± 0.1	−22.17 ± 0.55[a]	28
Ag^+−**1**	6.26 ± 0.02[c]	−35.73 ± 0.1	−39.77 ± 0.57[a]	−14
Ag^+−**3**	6.87 ± 0.02[c]	−39.21 ± 0.21	−63.68 ± 0.84[a]	−82
		N,N-Dimethylformamide		
Hg^{2+}−**1**	4.83 ± 0.03[a]	−27.85 ± 0.31	−22.34 ± 0.10	18
Hg^{2+}−**3**	5.07[a]	−29	−38[a]	−31
Ag^+−**1**	4.24 ± 0.02[a]	−24.2 ± 0.2	−38.4 ± 0.08[a]	−48
	4.20 ± 0.03[c]			
Ag^+−**3**	4.65[c]	−26.5	−48[a]	−71

[a] Values determined using "direct macrocalorimetric titration". [b] Using "microcalorimetric titration". [c] Using "potentiometirc titration" methods. [d] Using competitive macrocalorimetric titration.

(hence $\Delta_cG°$) for **1** and **3** and the appropriate cation in these solvents. In summary, the ligand effect on the stability of complex formation is relatively small in the alcohols and *N*,*N*-dimethylformamide. However, this is not reflected in the $\Delta_cH°$ and $\Delta_cS°$ which for a given system in a given solvent these parameters are greatly compensated. This enthalpy−entropy compensation effect is observed for both cations in *N*,*N*-dimethylformamide. As a result, in this solvent, both ligands are unable to recognize selectively these cations.

Final Conclusions

Previous work carried out by us demonstrated the low affinity of the calixarene ester derivative, **2**, for mercury(II) relative to

TABLE 7: Thermodynamic Parameters of Complexation, Pendant Arms, and Additive Contributions for Mercury(II) Complexes with 1, 2, and 3 in Acetonitrile at 298.15 K

complex	$\Delta_c H°$/kJ mol^{-1}	pendant arm contribn/kJ mol^{-1}	additive contribn/kJ mol^{-1}
Hg^{2+}−**2**	−21.1[a]	−5.3	
Hg^{2+}−**1**	−74	−37	
Hg^{2+}−**3**	−83 ± 1[b]		−84.6[a]
	−83 ± 2		

complex	$T\Delta_c S°$/kJ mol^{-1}	pendant arm contribn/kJ mol^{-1}	additive contribn/kJ mol^{-1}
Hg^{2+}−**2**	−0.1[a]	0	
Hg^{2+}−**1**	−36.8	−18.4	
Hg^{2+}−**3**	−33.2[b]	-	−36.8[b]

complex	$\Delta_c G°$/kJ mol^{-1}	pendant arm contribn/kJ mol^{-1}	additive contribn/kJ mol^{-1}
Hg^{2+}−**2**	−21.1[a]		
Hg^{2+}−**1**	−37.2	−5.3	
Hg^{2+}−**3**	−49.6	−18.6	−47.8[b]

[a] Sum of two ester + two thioethyl pendant arms (kJ mol^{-1}) = (2 × (−5.30) + 2 × (−18.4)) = −84.6 kJ mol^{-1}. [b] (−5.3 × 2) + (−18.6 × 2) = −47.8 kJ mol^{-1} and (0 × 2) + (−18.4 × 2) = −36.8 kJ mol^{-1}.

other bivalent cations in acetonitrile.[11] Partial replacement of two ester pendant arms in **2** by thioethyl substituents, **3**, has enhanced dramatically the affinity of this ligand for Hg^{2+} relative to other cations.[12] However, the removal of ester containing pendant arms from **3** has led to a receptor, **1**, whose selectivity for soft metal cations or lack of it, is entirely dependent on the medium. Having stated it, the behavior of acetonitrile in complexation processes is unique:

(i) Ligand−solvent binding induces a conformational change that turns this macrocycle selective to Hg^{2+} relative to Ag^{+} making it functional as mercury extracting agent in phase transfer processes. This finding resembles the induced fit model for enzyme−substrate binding.[14]

(ii) It leads to adducts exquisitely organized to the extent that the complexation thermodynamic data for these cations fit into a model in which the hydrophilic cavity of **3** is built up from the contribution of analogous receptors (**1** and **2**) containing common pendant arms.

Thus, the additive energetic contribution shown in this paper should be investigated for other calixarene−cation systems.

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