J. Phys. Chem. A **2006,** *110,* 9575−9584

Cation/Anion Recognition by A Partially Substituted Lower Rim Calix[4]arene Hydroxyamide, A Ditopic Receptor

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Received: April 6, 2006; In Final Form: June 7, 2006

The complexation ability of a partially substituted lower rim calix[4]arene hydroxyamide derivative, 25,27-bis[*N*-(2-hydroxy-1,1-bishydroxymethylethyl)amino- carbonylmethoxy]calix[4]arene-26,28-diol, **1**, for cations and anions was investigated through ^{1}H NMR, conductometry, spectrophotometry, and calorimetry in dipolar aprotic media. ^{1}H NMR studies of **1** in the deuterated solvents (acetonitrile, methanol, and dimethylsulfoxide) reflect ligand−solvent interactions in methanol and dimethylsulfoxide. As far as the cations are concerned, a selectivity peak is found when standard Gibbs energies of complexation of **1** with cations (alkaline-earth, zinc, and lead) are plotted against corresponding data for cation hydration. This finding reflects the key role played by the desolvation and binding processes in the overall complexation of this receptor and these cations in acetonitrile. This is also interpreted in terms of enthalpy and entropy data. Factors such as, the nature and the arrangement of donor atoms in the hydrophilic cavity of the ligand on cation complexation process, are discussed. This paper also addresses anion complexation processes. It is found that **1** interacts through hydrogen bond formation with fluoride, dihydrogen phosphate, and pyrophosphate in acetonitrile and *N*,*N*-dimethylformamide. The thermodynamics associated with these processes is fully discussed taking into account literature data involving calix[4]pyrroles and these anions in these solvents. Previous work regarding the water solubility of these ligands is discussed. It is concluded that **1** behaves as a ditopic ligand in dipolar aprotic media.

Introduction

The structures of calixarenes were proposed about 60 years ago.[1] However, research in this area remained dormant until Gutsche and co-workers[2] published the one pot synthesis of these macrocycles and their purification. It was indeed this outstanding contribution which has led to the development of the area of calixarene chemistry. These macrocycles are best known for their cation complexation properties[3,4] and to a lesser extent for their ability to interact with neutral species.[5] However, the relatively easy lower and upper functionalization of these macrocycles has motivated the introduction of pendent arms containing moieties capable of interacting with anions through hydrogen bond formation.[6] This interesting development has undoubtedly enhanced the scope of these macrocycles. Thirteen years ago, Dietrich[7] visualized the potential use of the amide functional group in anion complexation processes on the basis of the work published by Kimura and Beer.[8] Calixarenes provide an excellent platform for the introduction of these functional groups as shown in the literature.[9] Smukste and Smihrud[10] reported the synthesis of lower rim calix[4]arene derivatives containing hydroxyamides in their pendant arms. These compounds were obtained by the condensation of calix[4]arenes with unprotected hydroxyamines and were reported to be water soluble. However, the ability of these ligands to solubilize in water was tested in buffer solution at pH = 6.8. Given the nature of the moieties found in the pendant arms of these ligands, we decided to investigate the cation and anion binding properties of 25,27-bis[*N*-(2-hydroxy-1,1-bishydroxymethylethyl)-aminocarbonylmethoxy]calix[4]arene-26,28-diol (**1**) (Chart 1). In this paper, we report ^{1}H NMR, conductometric, and thermodynamic studies on the complexation of **1** with cations and anions in acetonitrile. The medium effect on anion complexation processes is discussed from studies carried out in *N*,*N*-dimethylformamide.

Experimental Section

Chemicals. *P*-*tert*-Butylcalix[4]arene, 95%, aluminum chloride, 99%, ethylbromo-acetate, 98%, barium chloride, 99.99%, and ethoxymethoxy carbonyl-1-2-dihydroquinoline, EEDQ, 99%, were purchased from Aldrich Chemical Co. and used without further purification. Tris(hydroxymethyl)aminomethane (THAM), 99.9%, was purchased from Aldrich and was recrystallized from a water/methanol (50:50) mixture. The crystals were washed with methanol and dried at room temperature for 24 h and then these were stored in a vacuum desiccator for 3 days. Phenol, 99%, 18-crown-6, ≥99%, and phosphorus pentoxide, 99%, were used as purchased from Fisher Chemical Company.

Tetra-*n*-butylammonium fluoride trihydrate (99%) and chloride (97%) were purchased from Fluka Chemical Co.; tetra-*n*-butylammonium bromide, iodide, dihydrogen phosphate, perchlorate, nitrate, hydrogen sulfate, and hydrogen pyrophosphate (99%) were purchased from Aldrich Chemical Co. These were dried over P_4O_{10} under vacuum for several days before use.

The deuterated solvents acetonitrile (CD_3CN), methanol (CD_3OD), dimethyl sulfoxide (d_6-DMSO), and all metal cation perchlorate salts (lithium, 99%, sodium monohydrate, 98%, potassium, 99%, rubidium, 99%, cesium, 98%, magnesium

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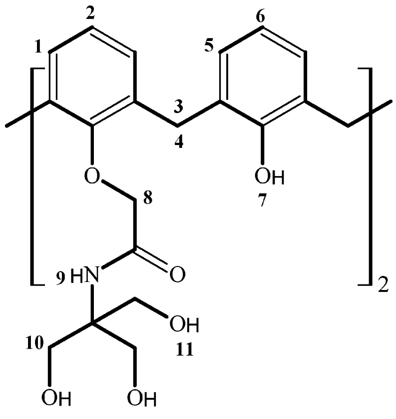
10.1021/jp062154s CCC: $33.50

CHART 1



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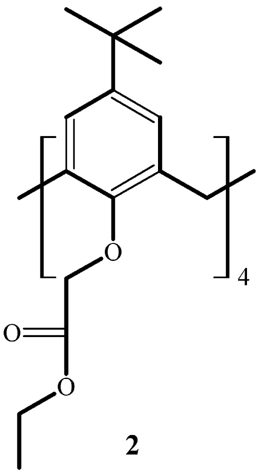

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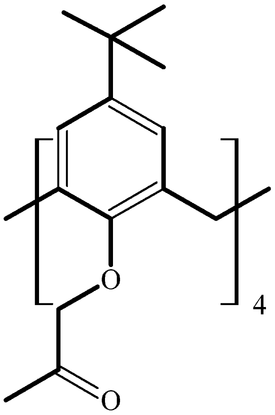

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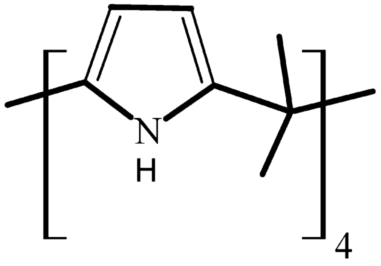

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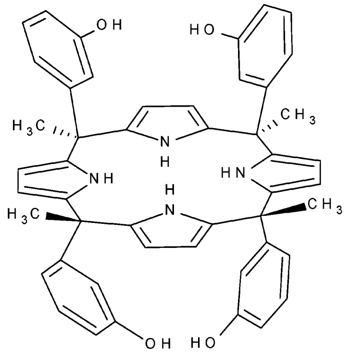

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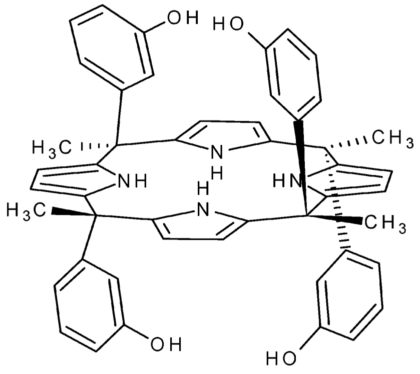

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hexahydrate, 99%, calcium tetrahydrate, 99%, strontium hydrate, barium trihydrate, 99%, silver, 99.9%, lead trihydrate, 98%, cadmium hydrate, copper hexahydrate, 98%, zinc hexahydrate, 98%, nickel hexahydrate, and mercury hydrate, 98%) were purchased from Aldrich. The salts were dried over phosphorus pentoxide (P_4O_{10}) under vacuum for several days before use. The absence of a signal from the residual water in the ^1H NMR spectra of **1** with the cations in CD_3CN provided indication that the salts used were anhydrous.

Potassium chloride (99%, Fisher) was recrystallized from deionized water and dried at 120 °C for 3 days before its use for conductometric measurements.

Methanol, MeOH (HPLC grade, Fisher), tetrahydrofuran, THF (Aldrich), chloroform, $CHCl_3$ (Aldrich), propylene carbonate, PC (Aldrich), dichloromethane, DCM (HPLC grade, Aldrich), dimethylsulfoxide, DMSO (Fisher), butan-1-ol, BuOH (99%, Fisher), and diethyl ether, DEE (HPLC grade, Fisher) were used without further purification,

Pyridine (99.99%, Fisher) was refluxed[11] over sodium hydroxide pellets in a round-bottomed flask fitted with a reflux condenser protected by a drying tube containing calcium chloride. Then the mixture was distilled with careful exclusion of moisture. The middle fraction of the distilled pyridine was used immediately.

N,N-dimethylformamide,[12] DMF (HPLC grade, Fisher), was dried over 3 Å molecular sieves (which have been previously dried at 300 °C overnight for 72 h) and subsequently distilled under reduced pressure. The middle fraction of the distilled solvent was used.

Toluene (Fisher) was kept under a sodium wire for several days and then it was fitted with a reflux condenser over calcium hydride. The mixture was distilled (under argon atmosphere) using benzophenone as an indicator and the distilled toluene was used immediately. Acetonitrile, MeCN (HPLC, Hayman), was distilled as described elsewhere.[13]

Synthesis of 25,27-Bis[*N*-(2-hydroxy-1,1-bishydroxymethylethyl)aminocarbonylmethoxy]-calix[4]arene-26,28-diol (1). This ligand was prepared according to the procedure described by Smukste and Smihrud[10] except that it was further purified by dissolving the remaining material in an ethanol/dichloromethane (90:10) mixture and left overnight. The crystals obtained were dried at 80 °C under vacuum. The yield was 90%. Compound **1** was characterized by ^{1}H NMR in CD_3CN, CD_3OD, and d_6-DMSO and by ^{13}C NMR in d_6-DMSO and microanalysis. The results are as follows: ^{1}H NMR (300 MHz, CD_3CN) δ (ppm) J (Hz): $\delta = 8.38$ (s, 1H, **H-9**), 7.65 (s, 1H, **H-7)**, 7.18, 6.99 (d, 4H, **H-1**, **H-5**), 6.83, 6.74 (t, 2H, $J = 7.6$, **H-2**, **H-6**), 3.84 (t, 3H, $J = 5.4$, **H-11**), 4.54 (s, 2H, **H-8**), 4.28 (d, 1H, $J = 14.7$, **H-4**), 3.76 (d, 6H, $J = 5.70$, **H-10**), 3.50 (d, 1H, $J = 13.5$, **H-3**). ^{1}H NMR (500 MHz, CD_3OD) δ (ppm), J (Hz): $\delta = 7.16$, 6.93 (d, 2H, **H-5**, **H-1**), 6.78, 6.73 (t, 2H, $J = 7.5$, **H-6**, **H-2**), 4.59 (s, 2H, **H-8**), 4.36 (d, 1H, $J = 13.46$, **H-4**), 3.92 (s, 6H, **H-10**), 3.49 (d, 1H, $J = 1.54$, **H-3**). ^{1}H NMR (500 MHz, d_6-DMSO), δ (ppm), J (Hz): $\delta = 8.13$ (s, 1H, **H-9**), 7.98 (s, 1H, **H-7)**, 7.19, 7.04 (d, 4H, $J = 7.6$, **H-1**, **H-5**), 6.82, 6.66 (t, 2H, $J = 7.5$, **H-2**, **H-6**), 4.78 (t, 3H, $J = 5.7$, **H-11**), 4.55 (s, 2H, **H-8**), 4.35 (d, 1H, $J = 13.1$, **H-4**), 3.73 (d, 6H, $J = 5.7$, **H-10**), 3.48 (d, 1H, $J = 13.2$, **H-3**). ^{13}C NMR (500 MHz, d_6-DMSO): $\delta = 169.68$ (**CO**), 153.8, 153.28, 134.2, 130.07, 129.58, 128.40, 126.37, 120.15 (aromatic carbons), 75.58 (O**C**H2CO), 63.63 (NH-**C**-CH2), 61.23 (C-**C**H2−OH), 31.79 (**C** bridge).

Microanalysis carried out at the University of Surrey for $C_{40}H_{46}N_2O_{12}$ gave anal. calcd: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.30; H, 6.25; N, 3.71.

Solubility Measurements. To determine the solubility of **1** in acetonitrile (MeCN), saturated solutions were prepared by adding an excess amount of **1** to the solvent. The mixtures were left in a thermostated bath at 298.15 K for several days to ensure that equilibrium between the solid and its saturated solution was achieved. Aliquots of the saturated solution were taken from the same equilibrium mixture and analyzed gravimetrically in triplicate. Blank experiments were carried out to ensure the absence of any nonvolatile material in the pure solvent. The possibility of solvate formation of **1** in MeCN, DMF, and DMSO was checked by the De Ligny method[14] which consists of exposing the solid placed in a desiccator to a saturated atmosphere of the appropriate solvent.

^{1}H NMR Measurements. ^{1}H NMR measurements were recorded at 298 K using a Bruker AC-300 E pulsed Fourier Transform NMR spectrometer. Typical operating conditions for routine proton measurements involved a “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 or a Bruker DRX-500 pulse Fourier Transform NMR spectrometer. The operating conditions involved a pulse or flip angle of 30°, spectra width (SW) of 15 ppm, SF of 500.150 MHz, delay time of 0.3 s, AQ of 3.17 s, and line broadening of 0.3 Hz. A solution of **1** (0.5 mL), in the appropriate solvent (CD_3CN, CD_3OD, and d_6-DMSO) was placed in 5 mm NMR tubes. ^{1}H NMR chemical shifts were referenced to TMS (0.00 ppm) when the medium was either CD_3CN or CD_3OD. For measurements in d_6-DMSO, ^{1}H NMR and ^{13}C NMR chemical shifts were referenced to 2.54 and 40.45 ppm, respectively.

^{1}H NMR Studies on the Interaction of 1 with Metal Cations. The complexation behavior of **1** toward metal cations and anions at 298 K was studied using the ^{1}H NMR technique (Bruker AC-300 E pulsed Fourier Transform NMR spectrometer), by adding the metal-ion (or anion) salt in excess (5×10^{-3} to 6×10^{-2} mol·dm^{-3}) into the NMR tube containing the ligand (8×10^{-4} to 6×10^{-3} mol·dm^{-3}) dissolved in the appropriate solvent. Changes in the chemical shifts upon the addition of cation or anion salts were measured using the spectrum of the free ligand as reference.

Conductance Measurements. Conductance measurements at 298.15 K were carried out using a Wayne-Kerr model 7330 automatic LCR meter conductivity bridge at a frequency of 1 kHz. The conductance cell was a Russell-type glass-bodied electrode with a cell constant of 0.99 ± 0.01 cm^{-1}.

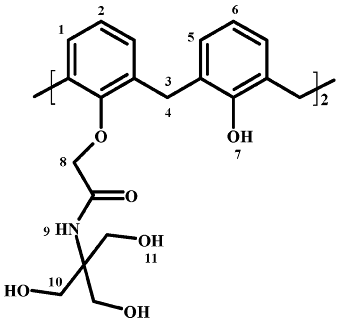
Conductometric titrations were carried out. Thus, a solution of the metal cation or the anion salt (concentration range from 8×10^{-5} to 1×10^{-4} mol·dm^{-3} depending on the salt used) was placed in the conductometric cell in the appropriate solvent (25 cm^3) and titrated with a solution of the ligand (concentration range from 8×10^{-4} to 2×10^{-3} mol·dm^{-3}) in the same solvent. The conductance was measured after each addition.

Titration Calorimetry. Stability constants, log K_s, and enthalpies, Δ_cH, of complexation of **1** with the appropriate metal cation or anion at 298.15 K were determined by direct calorimetric titration using the Tronac 450[15] as an isoperibol titration calorimeter or the 2277 Thermal Activity Monitor (TAM).[16] As far as the former is concerned, 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 an aqueous solution of hydrochloric acid (HCl, 0.1 mol·cm^{-3}) at 298.15 K.[17] The value obtained (−47.7 ± 0.8 kJ·mol^{-1}) was in excellent agreement with that reported by Wilson and Smith[18] (−47.49 kJ·mol^{-1}) at 298.15 K. As far as complexation studies are concerned, a solution of **1** (8×10^{-4} to 3×10^{-3} mol·dm^{-3} concentration range) in the appropriate solvent was placed in the vessel (50 cm^3) and the metal cation or the anion salt (4×10^{-3} to 2×10^{-2} mol·dm^{-3} concentration range) in the same solvent was placed in the syringe. The latter was added from a 2 cm^3 buret connected by a silicone tube to the reaction vessel once thermal equilibrium was achieved. These experiments were repeated four times for each metal cation. Blank experiments were carried out in all cases to account for dilution effects resulting from the addition of the salt to the solvent placed in the calorimetric vessel.

For measurements carried out with the TAM calorimeter, a chemical calibration using 18-crown-6 and Ba^{2+} in water at 298.15 K was performed as described elsewhere.[19] The reaction vessel was charged with 2.8 cm^3 of **1** in the appropriate solvent. The anion salt was injected incrementally using a 0.5 cm^3 gastight motor-driven Hamilton syringe. In each titration experiment, approximately 20 additions were injected at time intervals of 30−45 min. Corrections for the enthalpy of dilution of the titrant in the solvent were performed. A computer program for TAM (Digitam 4.1 for Windows from Thermometric AB and Scitech Software AB, Sweden) was used to calculate the stability constant (log K_s) and the enthalpy of complexation (Δ_cH) for the process under investigation.

UV Measurements. UV titration experiments in acetonitrile were carried out with a CECIL 8000 series spectrophotometer at 298 K with the aim of checking the stability constant[20] derived from calorimetric titrations of **1** with some metal cations. These titrations were accomplished through a stepwise addition of the cation salt in acetonitrile (~1×10^{-3} mol·dm^{-3}) to a solution of **1** (2.99×10^{-4} mol·dm^{-3}) in the same solvent. This was

TABLE 1: ^{1}H NMR Data for 1 in Several Deuterated Solvents at 298 K



	δ (ppm)		
	CD_3CN	CD_3OD	d_6-DMSO
1	7.18	6.93	7.19
5	6.99	7.16	7.04
2	6.83	6.73	6.82
6	6.74	6.78	6.66
3	3.5	7.49	3.48
4	4.28	4.36	4.35
7	7.65	3.49	7.98
8	4.54	4.59	4.55
9	8.38		8.13
10	3.76	3.92	3.73
11	3.84		4.78

followed by a 15 min interval (in which the reaction cell was left under continuous stirring to ensure mixing) after which readings were taken. The data were collected and processed using the Hyperquad program[21]for the calculation of the stability constant (log K_s) of the appropriate cation (II) complex.

Results and Discussion

^{1}H NMR Measurements of 1 in Different Solvents. ^{1}H NMR data for the free ligand in CD_3CN, CD_3OD, and d_6-DMSO at 298 K are shown in Table 1. The data reveal that this macrocycle adopts a "cone" conformation in these solvents. This statement is based on the differences observed in the chemical shifts of the axial and equatorial protons of the methylene bridge, $\Delta\delta_{ax-eq}$. Thus, values of 0.78, 0.87, and 0.88 ppm were calculated from the ^{1}H NMR data in CD_3CN, CD_3OD, and d_6-DMSO, respectively. These values are well within those assigned by Gutsche[2] ($\Delta\delta_{ax-eq} = 0.90 \pm 0.20$ ppm) for a calix[4]arene in a perfect "cone" conformation. These findings strongly suggest that extensive hydrogen bond formation between the functional groups in the pendant arms is likely to take place and this must play a key role in the stabilization of the macrocycle in an almost perfect "cone" conformation in these solvents. This is in accord with molecular modeling studies carried out by Smukste and Smihrud[10] on this ligand. These studies suggested the formation of an assortment of hydrogen bonds between adjacent pendant arms as well as within the same pendant arm. Computer modeling studies, particularly referred to the system in "vacuo", are not necessarily representative of the process in solution but often provide relevant clues regarding intramolecular interactions. A more convincing argument is that found in the literature[22] which demonstrates that calixarene derivatives with pendant arms able to form hydrogen bonds are found in an almost perfect "cone" conformation, otherwise these derivatives show a "flattened" cone conformation in solution.[22,23] Careful analysis of the ^{1}H NMR spectra of **1** in the various solvents (Table 1) shows the medium effect. Thus, significant downfield shifts are observed for H-7 (phenolic proton) ($\Delta\delta = 0.33$ ppm) and H-11 ($\Delta\delta = 0.94$ ppm) in moving from acetonitrile (protophobic aprotic solvent) to dimethyl sulfoxide (protophilic aprotic solvent) while upfield changes are found for H-9. These changes seem to indicate that d_6-DMSO interacts with this ligand through hydrogen bond formation. Downfield shifts are also observed in moving from CD_3CN to CD_3OD (protic solvent) in H-5 and H-10 which again indicate that this solvent is also able to enter hydrogen bond formation with the ligand. As far as ^{1}H NMR data in CD_3CN and d_6-DMSO are concerned, these findings are in accord with the solubility of this ligand in acetonitrile and in protophilic dipolar aprotic solvents such as dimethyl sulfoxide in that **1** undergoes solvate formation (too soluble) in the latter solvents while the solubility of **1** in acetonitrile is $(8.31 \pm 0.06) \times 10^{-4}$ mol·dm^{-3} at 298.15 K. Having characterized this ligand in these solvents, we proceeded with ^{1}H NMR studies aiming to assess the interaction of this ligand with ionic species (cations and anions) in CD_3CN. In an attempt to investigate the medium effect on anion complexation, ^{1}H NMR studies were also carried out in d_6-DMSO.

TABLE 2: ^{1}H NMR Chemical Shifts (δ) and Chemical Shift Changes ($\Delta\delta$) of the Ligand Protons of 1 Prior to and after the Addition of Alkaline-earth and Some Transition and Heavy Metal Cations in CD_3CN at 298 K

CD_3CN	δ (ppm)	$\Delta\delta$ (ppm)					
(protons)	free ligand	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}	Pb^{2+}	Zn^{2+}
1 }	7.18	0.00	0.00	0.01	0.00	dist.	0.00
5 }	6.99	0.11	−0.03	0.01	−0.02		0.01
2 }	6.83	0.06	0.01	0.01	0.01		0.03
6 }	6.74	−0.03	−0.01	−0.01	0.01		0.00
3	3.50	0.06	−0.02	−0.03	−0.03		−0.01
4	4.28	−0.07	−0.06	−0.03	−0.04		−0.03
7	7.65	0.23	−0.06	−0.06	−0.06		−0.06
8	4.54	0.17	0.10	0.07	0.03		0.09
9	8.38	−0.24	−0.13	−0.11	−0.09		−0.27
10	3.76	0.05	−0.04	−0.03	0.01		0.04
11	3.84	1.57	0.60	0.34	0.11		0.91

^{1}H NMR Complexation Studies of 1 with Cations in CD_3CN. For cation complexation processes, perchlorate salts were used given that this counterion does not interact with this ligand as shown later on. As far as alkali-metal cations are concerned, no significant chemical shift changes were observed by the addition of perchlorate salts to **1** in CD_3CN. This is not the case for alkaline-earth and some transition and heavy metal cation salts. Thus, Table 2 reports the chemical shift changes observed for these metal cations in CD_3CN at 298 K.

As far as alkaline-earth metal cations are concerned, significant changes in chemical shifts were clearly observed in H-7, H-8, H-9, and H-11 upon the addition of Mg^{2+} to **1**. This behavior was similar to that observed upon addition of an excess amount of Sr^{2+} to **1** in acetonitrile. Thus, upon addition of this metal cation salt, H-8 and H-11 exhibited downfield chemical shift changes relative to the free ligand. Significant chemical shift changes were also observed for H-8, H-9, and H-11 when a solution of the Ca^{2+} salt was added to the ligand. Only a downfield shift of H-11 was found by addition of Ba^{2+} in this solvent. No significant chemical shift changes were observed for other protons. These findings suggest that the carbonyl, the ethereal, and the hydroxyl oxygens of the pendent arms may take part in the complexation process. The hydroxyl groups are able to rotate easily as to interact with alkaline-earth metal cations. In fact, it should be noted that the greatest chemical shift changes are those for H-11 to an extent that this becomes smaller as the size of the cation increases (from Mg $^{2+}$ to Ba^{2+}). This pattern is the same as that observed for H-8 and metal cations in this solvent. No significant chemical shift changes

TABLE 3: ^{1}H NMR Chemical Shifts (δ) and Chemical Shift Changes ($\Delta\delta$) of the Ligand Protons of 1 by the Addition of Anions in CD_3CN and d_6-DMSO at 298 K

	δ	$\Delta\delta$ (ppm)							
(protons)	Free L4	$H_2PO_4^-$	HSO_4^-	NO_3^-	ClO_4^-	F^-	Cl^-	Br^-	I^-
				CD_3CN					
1	7.18	−0.06	−0.01	0.00	0.00	dist.[a]	−0.02	−0.01	0.00
5	6.99	−0.04	−0.02	−0.01	0.01		−0.03	−0.02	−0.01
2	6.83	−0.07	0.00	0.00	0.01		−0.03	−0.02	0.00
6	6.74	−0.07	−0.01	−0.01	0.00		−0.03	−0.02	0.00
3	3.5	−0.10	−0.02	−0.01	0.00		−0.04	−0.03	0.00
4	4.28	0.15	0.04	0.01	0.00		0.09	0.07	0.03
7	7.65		0.07	−0.01	0.00		0.07	0.04	0.01
8	4.54	0.16	0.05	0.00	0.00		0.06	0.07	0.02
9	8.38	0.27	0.07	−0.02	0.00		0.00	−0.02	−0.01
10	3.76	−0.07	0.00	0.00	0.01		−0.05	−0.04	0.00
11	3.84			0.12	0.00		1.02		0.10
				d_6-DMSO					
1	7.19	−0.02	0.00	0.00	0.00	br.[b]	0.00	0.00	0.00
5	7.04	−0.03	−0.01	0.00	−0.01		−0.01	−0.01	−0.01
2	6.82	−0.04	0.00	0.00	0.00		−0.01	0.00	0.00
6	6.66	−0.04	0.00	−0.01	−0.01		0.00	0.00	−0.02
3	3.48	−0.05	−0.01	0.00	−0.01		−0.01	−0.01	−0.01
4	4.35	0.05	−0.01	0.00	0.00		0.00	0.00	0.00
7	7.98		−0.01	−0.01	−0.01		−0.01	−0.02	−0.01
8	4.55	0.03	−0.01	−0.01	−0.01		−0.01	−0.01	−0.01
9	8.13	Br.	−0.01	0.00	−0.01		−0.01	−0.01	−0.01
10	3.73	−0.03	0.00	0.00	0.00		0.01	0.00	0.00
11	4.78	0.03	0.01	0.01	0.00		0.02	0.01	0.00

[a] Dist.: distorted (^{1}H NMR peaks are undetectable within the NMR scale). [b] Br.: broad (the maximum of the ^{1}H NMR signals cannot be assigned properly).

are observed in the aromatic protons. This could suggest that no conformational changes occur upon complexation of this ligand with these cations in this solvent.

As far as other metal cations are concerned, the addition of Pb^{2+} to **1** led to a distortion in the signals to an extent that these could not be detected. The addition of Zn^{2+} to this ligand shows significant chemical shift changes for H-8, H-9, and H-11. These findings suggest that complexation is taking place between **1** and the zinc metal cation. It could be concluded that the active sites of interaction are the hydroxyl and carbonyl groups of the pendent arms in the lower rim of **1**.

^{1}H NMR Complexation Studies of 1 and Anions in CD_3CN and d_6-DMSO. Chemical shift changes in the ligand protons are in CD_3CN and d_6-DMSO reported in Table 3. The addition of fluoride (tetra-*n*-butylammonium as counterion) to **1** led to distortion of the signals of all protons. To a lesser extent, this was also the case for $H_2PO_4^-$ where the proton signals for H-7 and H-11 could not be assigned due to the slow exchange in the NMR time scale during the complexation process. Downfield shifts are observed for H-4, H-8, and H-9. This is not surprising due to the possibilities offered by this anion to interact with the ligand through hydrogen bond formation. Interaction in the lower rim may lead to the upfield signal observed for H-3 and H-6 as a result of the aperture of the upper rim.

The addition of chloride to **1** led to a significant downfield chemical shift change for H-11, but other protons remained essentially unchanged. No interaction was observed by the addition of bromide, iodide, hydrogen sulfate, or perchlorate to this ligand in this solvent. Therefore, from ^{1}H NMR studies, we conclude, that among the anions investigated in CD_3CN, **1** interacts with F^- and $H_2PO_4^-$.

^{1}H NMR data in d_6-DMSO are also included in Table 3. Smaller chemical shift changes are observed in this solvent relative to CD_3CN which may be in part attributed to the higher ligand−solvent interaction in d_6-DMSO relative to CD_3CN as discussed above. Like in CD_3CN, all protons' signals are distorted by the addition of fluoride to the ligand while $H_2PO_4^-$ leads to a significant downfield shift in the NH proton. The remaining protons appear to be practically unchanged. Insignificant chemical shift changes are observed by the addition of Cl^-, Br^-, I^-, HSO_4^-, and NO_3^- to **1** in d_6-DMSO. In an attempt to corroborate further the outcome of ^{1}H NMR studies and to establish the composition of the complexes, conductometric titrations were carried out and these are now discussed.

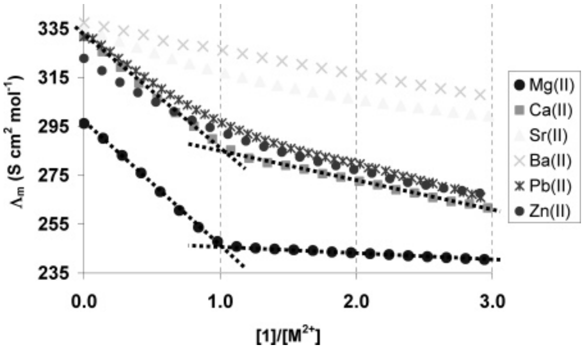


Figure 1. Conductometric curves for the titration of Mg^{2+}, Ca^{2+}, Sr^{2+}, and Ba^{2+} (perchlorate as counterion) with **1** in MeCN at 298.15 K.

Conductometric Titrations of Metal Cation Salts and 1 in Acetonitrile at 298.15 K. Plots of molar conductance, Λ_m, against the ligand/metal cation concentration ratio **1**/M^{n+} for the alkali-metal cations led to straight lines without any changes observed by increasing the 1/M^{n+} ratio. These findings are in agreement with the ^{1}H NMR data which show insignificant chemical shift changes by the addition of these metal cations to **1** in CD_3CN. As far as the alkaline-earth metal cations are concerned (Figure 1), a sharp break in the conductometric titration curve is observed for Mg^{2+} at the ligand/metal cation concentration ratio of 1 indicating that one metal cation interacts with one unit of ligand. However, in moving from Mg^{2+} along the alkaline-earth metal cation series, the sharpness of the break

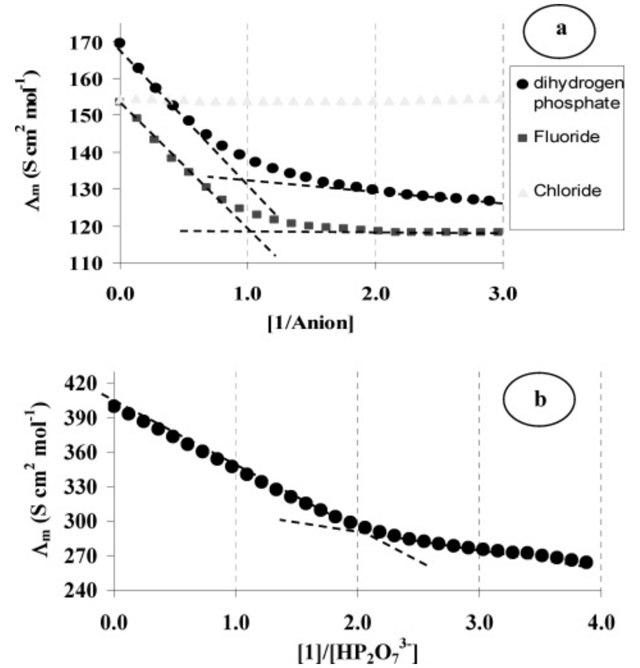


Figure 2. Conductometric curves for the titration of (a) dihydrogen phosphate, fluoride, and chloride and (b) hydrogen pyrophosphate anions (tetra-*n*-butylammonium as the counterion) with **1** in MeCN at 298.15 K.

decreases and therefore extrapolation of the linear portions of the conductometric titration curves was required to identify the composition of the complex in this solvent as shown in Figure 1. These results provide a strong indication that there is a definite size effect which suggests that the strength of complexation follows the sequence

$$\mathrm{Mg}^{2+} > \mathrm{Ca}^{2+} > \mathrm{Sr}^{2+} > \mathrm{Ba}^{2+}$$

This is in accord with the chemical shift changes observed for this ligand and these cations in CD_3CN. However, the complex composition is not altered. In all cases, Λ_m values at a **1**/M^{n+} = 0 are within those expected for the molar conductances of alkaline-earth perchlorates at 298.15 K in acetonitrile.[24] In all cases, Λ_m values decrease as the titration proceeds due to the formation of 1/M^{n+} complexes whose sizes are expected to be larger than those for the free cation, the M^{2+} cation salt. Once the 1:1 (**1**/M^{2+}) ratio is reached, Λ_m values remain constant or slightly decreases depending on the magnitude of the stability constant. As far as transition and heavy metal cations are concerned, breaks in the conductometric titration curves were found only for Zn^{2+} and Pb^{2+}. The small changes in the curvature of the titration curves found for these cations and this ligand in acetonitrile suggest that relatively weak complexes are formed. No changes in the curvature of the titration curve were found for Cd^{2+}, Ag^{+}, Hg^{2+}, Co^{2+}, and Ni^{2+} as emerged from ^{1}H NMR investigations in this solvent.

Conductometric Titrations of Anions with 1 in Dipolar Aprotic Media. Conductometric titrations of halide, dihydrogen phosphate, hydrogen pyrophosphate, hydrogen sulfate, nitrate, and perchlorate (tetra-*n*-butylammonium as counterion) and **1** in acetonitrile and dimethylsuphoxide at 298.15 K were carried out. The choice of Bu_4N^+ as the counterion was based on the lack of interaction of this cation with this ligand as assessed from ^{1}H NMR. Plots of molar conductances vs the ligand/X$^-$ concentration ratio for fluoride, dihydrogen phosphate, and hydrogen pyrophosphate are shown in Figure 2. The sharpest break in the curvature of the titration curve was found for fluoride and the mildest one for pyrophosphate with dihydrogen phosphate between these two. However, the composition of the complex was found to be 1:1 for fluoride and dihydrogen phosphate while two ligands are required to complex hydrogen pyrophosphate. Complexes with 2:1 stoichiometry were also found for this anion in its complexation with calix[4]pyrrole derivatives as previously discussed by Danil de Namor and Shehab.[25] Straight lines were obtained in the conductometric titration curves of chloride, bromide, iodide, hydrogen sulfate, nitrate, and perchlorate salts indicating that no interaction occurs between **1** and these anions in this solvent.

Conductometric titrations of anions with **1** in dimethylsulfoxide led to continuous straight lines without any apparent break in curvature. These findings led to the conclusion that very weak or no complexation takes place between these anions and **1** in this solvent. This was also the case when the medium was propylene carbonate. However, conductometric titration curves of anions with **1** in *N*-*N*-dimethylformamide follow a pattern similar to that found in acetonitrile.

From conductance studies we can conclude the following:

(i) Ligand **1** complexes with alkaline-earth metal cations, lead, and zinc cations in acetonitrile forming 1:1 complexes in this solvent. The results so far suggest that there is a size effect in moving from Mg^{2+} to Ba^{2+} which needs to be corroborated quantitatively from stability constant data.

(ii) This calix[4]arene derivative interacts with fluoride, dihydrogen phosphate anions giving 1:1 (ligand/anion) complexes while two units of ligand are required to complex one unit of the hydrogen pyrophosphate anion in acetonitrile and *N*-*N*-dimethylformamide. Very weak or no complexation occurs in dimethylsulfoxide and propylene carbonate.

Having established the composition of these complexes, we proceeded with the thermodynamics of complexation of these systems and these are now discussed.

Thermodynamics of Cation Complexation. Titration calorimetry (macro and micro) was the technique selected for the determination of the stability constant (expressed as log K_s) and the enthalpy of complexation. In doing so, the concentrations of metal cation salts used in the experimental work are within the range in which these salts are predominantly as ionic species in solution.[24] Therefore, log K_s values are referred to the process described in eq 1

$$\mathrm{M}^{2+}(\mathrm{MeCN}) + \mathbf{1}(\mathrm{MeCN}) \rightarrow \mathrm{M}^{2+}\mathbf{1}(\mathrm{MeCN}) \qquad (1)$$

where the standard state for reactants and products is 1 mol·dm^{-3}.

Using the relationship

$$\Delta_c G^\circ = -RT \ln K_s \qquad (2)$$

standard Gibbs energies of complexation were calculated. Thus, the combination of $\Delta_c G^\circ$ and $\Delta_c H^\circ$ leads to the calculation of $\Delta_c S^\circ$ values. These data are reported in Table 4. Stability constants measured by UV spectrophotometry are also included in this table. As previously stated,[26] cation desolvation and ligand binding energy play a predominant role in the stability of complex formation of macrocycles and metal cations. It is the balance between these two processes which undoubtedly contributes to the stability of the process. Given (i) the lack of data for the solvation Gibbs energies, $\Delta_{solv}G^\circ$, of these cations in acetonitrile and (ii) that the trend observed in the solvation is the same as that observed in the hydration Gibbs energies for these cations, complexation Gibbs energies for these cations

TABLE 4: Thermodynamic Parameters of the Complexation of 1 and Metal Cations (perchlorate as counterion) in MeCN at 298.15 K

1 (MeCN)	log K_s	$\Delta_cG°$ (kJ·mol^{-1})	$\Delta_cH°$ (kJ·mol^{-1})	$\Delta_cS°$ (J·mol^{-1}·K^{-1})
Mg^{2+}	$5.68^a \pm 0.01$	-32.39 ± 0.02	$-17.7^a \pm 0.2$	49
Zn^{2+}	$5.16^a \pm 0.04$ $4.98^b \pm 0.09$	-29.4 ± 0.2	$-19.2^a \pm 0.6$	34
Ca^{2+}	$4.12^a \pm 0.02$ $3.9^b \pm 0.3$	-23.5 ± 0.1	$-37.6^a \pm 0.6$	−47
Sr^{2+}	$3.95^a \pm 0.13$ $3.77^b \pm 0.1$	-22.6 ± 0.7	$-24.4^a \pm 0.3$	−6
Pb^{2+}	3.50 ± 0.04	-20.0 ± 0.2	$-30.8^a \pm 0.1$	−36
Ba^{2+}	$3.48^a \pm 0.06$ $3.1^b \pm 0.2$	-19.9 ± 0.3	$-14^a \pm 1$	19

[a] Macrocalorimetry data. [b] UV spectrophotometric data.

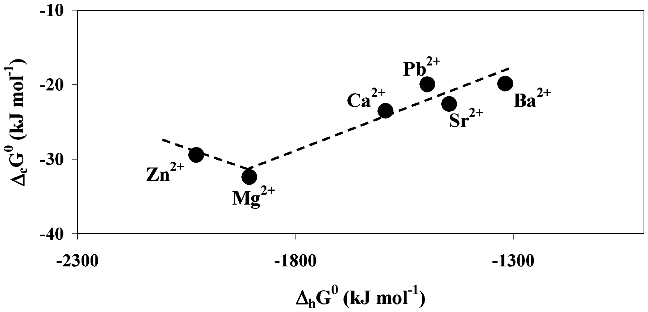


Figure 3. $\Delta_cG°$ values for **1** against $\Delta_hG°$ of bivalent metal cations in acetonitrile.

and **1** are plotted against the $\Delta_hH°$ values.[26] This is shown in Figure 3. The trend observed is one which demonstrates that as far as Ba^{2+}, Sr^{2+}, Pb^{2+}, Ca^{2+}, and Mg^{2+} are concerned, the absolute binding energy overcomes the increased energy required for the desolvation process. As a result, maximum stability is reached for Mg^{2+} after which the binding energy is not enough to overcome that required for desolvation and therefore a decrease in the complex stability is observed for Zn^{2+} which is the cation with the highest hydration Gibbs energy. Cations such as Ni^{2+} and Cu^{2+} whose $\Delta_hG°$ values are greater than those for Zn^{2+} are not complexed by this ligand.

To analyze the thermodynamic origin of the selectivity peak observed in terms of Gibbs energies, we proceeded to analyze the effect of cation desolvation and ligand binding in terms of enthalpies. Thus, plots of complexation enthalpies vs their corresponding, $\Delta_hH°$ values, respectively, for these cations are shown in Figure 4. In fact, the maximum enthalpic stability (more negative $\Delta_cH°$) is found for Ca^{2+} and **1** in acetonitrile. Thus, the selectivity peak observed in terms of $\Delta_cG°$ is enthalpic in origin except for Mg^{2+}. It is indeed the entropy term (favorable) which contributes to the higher complex stability observed for this cation and this ligand in this solvent.

At this stage, it is important to emphasize that the nature of the donor atoms as well as their arrangement in their lower rim of the macrocycle are important factors to consider. Indeed, soft metal cations such as Cd^{2+}, Hg^{2+}, and Ag^+ with lower hydration (or solvation) Gibbs energies than Mg^{2+} (hard metal cation) are unable to enter complexation with this ligand in this solvent. We have previously[27] demonstrated that fully substituted lower rim calixarenes containing oxygen donor atoms such as calix[4]arene esters, **2**, and ketones, **3**, interact with these cations in this solvent. This observation leads to the suggestion that a reduction of the number of donor atoms or indeed a lower basicity as well as the arrangement of donor atoms in the lower rim may be responsible for the lack of complexation of **1** with soft metal cations as well as for the decrease in stability observed for this ligand relative to **2** and **3** (see Chart 1).

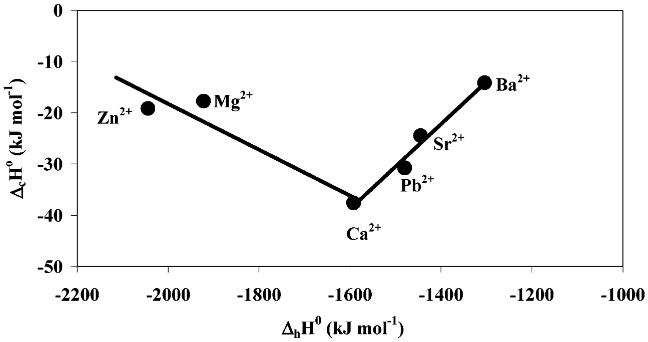


Figure 4. $\Delta_cH°$ values for **1** against $\Delta_hH°$ of bivalent metal cations in acetonitrile.

The unavailability of thermodynamic data for partially substituted calix[4]arene amide derivatives in acetonitrile does not allow for assessment of the effect of the hydroxyl groups on the interaction of **1** with alkaline-earth metal cations. The participation of the OH functional groups in the binding process which are absent in calix[4]arene amides may alter significantly the selectivity pattern of these ligands for these cations relative to **1.**

Thermodynamics of Anion Complexation: The Medium Effect. Thermodynamic data for the complexation of **1** with anions (fluoride, dihydrogen phosphate, and hydrogen pyrophosphate) in acetonitrile and *N*-*N*-dimethylformamide at 298.15 K are reported in Table 5. The standard deviation of the data is also shown in this table. For fluoride and dihydrogen phosphate, the reported values are referred to the process described in eq 3

$$\mathbf{1}(s) + X^-(s) \rightarrow \mathbf{1}X^-(s) \tag{3}$$

In eq 3, X^-, $\mathbf{1}X^-$, and s denote the free and complex anion and the solvent, respectively. As far as the hydrogen pyrophosphate anion is concerned, the data for the 2:1 (ligand/anion) complex corresponds to the process shown in eq 4. Thus, the

$$\mathbf{1}X^-(s) + \mathbf{1}(s) \rightarrow \mathbf{1}_2X^-(s) \tag{4}$$

overall thermodynamic data for this anion listed in Table 5 results from the combination of eqs 3 and 4 which led to the formulation of eq 5

$$2\mathbf{1}(s) + X^-(s) \rightarrow \mathbf{1}_2X^-(s) \tag{5}$$

A striking feature of these data is that while for the fluoride anion, the process is entropically controlled, this is not the case for the complexation of $H_2PO_4^-$ and $HP_2O_7^{3-}$ with **1**, in both solvents. Indeed, for the latter anions, the stability of the process is due to the enthalpic contribution given that there is a considerable loss of entropy upon complexation with these anions. As far as the fluoride anion is concerned, the $\Delta_tG°$ value for this anion from acetonitrile to *N*-*N*-dimethylformamide could not be obtained because both salts undergo solvate formation when exposed to saturated atmospheres of these solvents. On the other hand, the ligand undergoes solvation when exposed to an atmosphere of DMF. This is not the case in acetonitrile. Therefore, the ligand is much more solvated in DMF than

TABLE 5: Thermodynamic Parameters of the Complexation of 1 and Anions in MeCN and DMF at 2981.15 K

anion (L:M) (MeCN)	log K_s	$\Delta_c G°$ ($kJ \cdot mol^{-1}$)	$\Delta_c H°$ ($kJ \cdot mol^{-1}$)	$\Delta_c S°$ ($J \cdot mol^{-1} \cdot K^{-1}$)
		Acetonitrile		
F^-	$5.69^a \pm 0.03$	-32.4 ± 0.2	$-14.4^a \pm 0.3$	61
$H_2PO_4^-$	$3.84^a \pm 0.06$	-21.9 ± 0.3	$-46.3^a \pm 0.1$	−82
$HP_2O_7^{3-}$				
(1:1)	5.10 ± 0.08	-29.1 ± 0.5	-59.3 ± 0.2	−101
(2:1)	3.51 ± 0.08	-20.1 ± 0.5	-57.3 ± 0.2	−125
Overall	8.6^b	−49.1	-116.6^b	−226
		N,*N*-Dimethylformamide		
F^-	$4.30^a \pm 0.05$	-24.5 ± 0.3	$-12.1^a \pm 0.7$	42
$H_2PO_4^-$	$4.06^a \pm 0.02$	-23.15 ± 0.09	$-26.4^a \pm 0.2$	−11
$HP_2O_7^{3-}$				
(1:1)	4.91 ± 0.09	-28.0 ± 0.5	-40.75 ± 0.03	−43
(2:1)	3.82 ± 0.08	-21.8 ± 0.5	-35.72 ± 0.06	−47
Overall	8.7^b	−50	-76.47^b	−89

[a] Macrocalorimetric data. [b] Microcalorimetric data.

MeCN. On the basis of these statements and taking into account eq 6, it follows that

$$\Delta_c G°_{(MeCN)} - \Delta_c G°_{(DMF)} = \Delta_t G°(F^-)_{(MeCN \rightarrow DMF)} + \Delta_t G°(\mathbf{1})_{(MeCN \rightarrow DMF)} - \Delta_t G°(\mathbf{1}F^-)_{(MeCN \rightarrow DMF)} \quad (6)$$

the higher stability (more favorable $\Delta_c G°$) in acetonitrile relative to DMF must be attributed to the contribution of both the higher solvation of the ligand in DMF and that of the anionic complex in MeCN.

Analysis of eq 6 for $H_2PO_4^-$ shows that the $\Delta_t G°(H_2PO_4^-) = -1.58$ $kJ \cdot mol^{-1}$. This value reflects that there are not dramatic differences in the solvation of this anion in these solvents. On the other hand, as discussed above, **1** is much better solvated in DMF than in MeCN. Therefore, the similar stability observed for this anion in these solvents appears to indicate that the anion complex must be better solvated in DMF than in MeCN to the extent that the favorable solvation of the product in DMF balances that of the reactants leading to complexes of similar stability.

We have previously shown[28] that the complexation enthalpy is a suitable reporter of the number of hydrogen bonds involved in the complexation of this anion and calix[4]pyrroles when the medium is acetonitrile. Thus, the interaction of **4** with this anion takes place between the negatively charged oxygen atom of the $H_2PO_4^-$ anion and the NH functional group of the four pyrrole units of this ligand. However, **5** and **6** are able to form 1:2 complexes with this anion. Thus, in the first step, the active sites of the macrocycle are provided by the NH of only two pyrrole units, while the remaining two in **4** host the second anion. For each of these systems (**4**, **5**, and **6** with $H_2PO_4^-$), the overall enthalpies of complexation (see Table 6) are −48.1, −47.2, and −50.1 $kJ \cdot mol^{-1}$, respectively, in acetonitrile. However, for **4** and **5**, these values are reduced to approximately half for each individual process involved in the formation of 1:2 complexes. These findings led to the suggestion that the $\Delta_c H°$ values for these systems in acetonitrile reflect the number of hydrogen bonds involved in the interaction of calix[4]pyrroles and this anion in this solvent.

Unlike **4**, **5**, and **6** (see Chart 1), the calixarene derivative **1** has only two NH functionalities but a number of potential neighboring sites able to enter hydrogen bond formation.

Molecular modeling calculations suggest that the complex of lowest energy (maximum stability) is that in which four hydrogen bonds are formed involving (i) the negatively charged oxygen of the anion with two NH of the amide functional groups, (ii) one OH of the anion with an OH of the ligand, and (iii) an intermolecular hydrogen bond between the carbonyl oxygen and an OH group of the ligand as shown in Figure 5. Given that the overall enthalpies for the formation of 1:1 and 1:2 complexes between these ligands and $H_2PO_4^-$ in acetonitrile do not differ significantly, the different stabilities observed for these complexes are due to the entropic contribution which differs significantly in moving from one ligand to another. In fact, the trend in entropy follows the sequence

$$\mathbf{6} > \mathbf{5} > \mathbf{4} > \mathbf{1}$$

It is expected that the formation of 1:2 complexes (three components to give one) will lead to a greater entropy loss than that involving 1:1 complexes (two components to give one). However, the reverse trend is observed which may be attributed to solvation and conformational changes taking place upon complexation of **5** and **6** with this anion in this solvent. In moving from acetonitrile to *N*-*N*-dimethylformamide, the stability of **1** and $H_2PO_4^-$ is slightly higher in the latter relative to the former solvent. This is attributed to the entropy gain in DMF relative to MeCN.

As far as $HP_2O_7^{3-}$ is concerned, this anion is characterized by a double negative charge on one end and a single one on the other end (which can oscillate between two oxygen atoms). The interaction of this ligand with this anion in both solvents occurs in an analogous manner to that observed with calix[4]pyrrole and its derivatives in that two ligands interact with one $HP_2O_7^{3-}$ unit to form a 2:1 (ligand/anion) complex. It is expected that the double negatively charged end of the anion interacts with **1** to form the 1:1 complex. Thus, in both solvents, the stability is greater than that observed for the 1:1 complex involving hydrogen phosphate, as a result of higher enthalpic and entropic contributions than those observed for this ligand and $H_2PO_4^-$ in this solvent. Molecular modeling calculations suggest that the two negatively charged oxygen atoms of the anion interact with the two NH functionalities of the ligand for the formation of the 1:1 complex. For the 2:1 complex, the ligand interacts in a similar way to that found for $H_2PO_4^-$, except that intramolecular bond formation between the carbonyl and OH group is not observed. Although the formation of the 2:1 complex between **1** and $HP_2O_7^{3-}$ is enthalpically more favorable than that for the 1:1 complexation process, the entropy loss is such that the complex stability decreases significantly. It is interesting to note that the overall stability of **1** and $HP_2O_7^{3-}$ in acetonitrile is about the same as that previously reported for **4** and this anion in this solvent. However, for **1**, the process is enthalpically less stable but entropically more favorable than that involving **4** and $HP_2O_7^{3-}$ in this solvent. In moving from

TABLE 6: Thermodynamic Parameters of Complexation of 1, 4, 5, and 6 with Fluoride, Dihydrogen Phosphate, and Hydrogen Pyrophosphate in Acetonitrile and 1, 4, and 5 with Fluoride and 1 and 4 with Dihydrogen Phosphate and Hydrogen Pyrophosphate in *N*,*N*-Dimethylformamide

ligand	anion (L:X)	log K_s	$\Delta_cG°$ (kJ·mol^{-1})	$\Delta_cH°$ (kJ·mol^{-1})	$\Delta_cS°$ (J·mol^{-1}·K^{-1})
(a) Acetonitrile					
F^-					
1	1:1	5.69 ± 0.03	−32.4 ± 0.2	−14.4 ± 0.3	61
4	1:1	6.21 ± 0.03	−35.4 ± 0.2	−43.5 ± 0.3	−27
5	1:1	3.08 ± 0.02	−17.6 ± 0.1	−97.1 ± 0.8	−267
6	1:1	5.00 ± 0.04	−28.5 ± 0.2	−31.4 ± 0.3	−10
	1:2	4.72 ± 0.01	−27.0 ± 0.1	−61.5 ± 0.3	−116
	overall	9.72	−55.5	−92.9	−126
$H_2PO_4^-$					
1	1:1	3.84 ± 0.06	−21.9 ± 0.3	−46.3 ± 0.1	−82
4	1:1	5.00 ± 0.08	−28.5 ± 0.5	−48.1 ± 0.1	−66
5	1:1	3.60 ± 0.02	−20.54 ± 0.04	−24.55 ± 0.06	−13
	1:2	2.50 ± 0.03	−14.43 ± 0.04	−22.63 ± 0.06	−28
	overall	6.1	−34.91	−47.2	−41
6	1:1	4.80 ± 0.02	−27.4 ± 0.3	−20.2 ± 0.1	25
	1:2	2.7 ± 0.1	−15.2 ± 0.5	−29.9 ± 0.6	−50
	overall	9.46	−42.6	−50.1	−25
$HP_2O_7^{3-}$					
1	1:1	5.10 ± 0.08	−29.1 ± 0.5	−59.3 ± 0.2	−72
	2:1	3.51 ± 0.08	−20.1 ± 0.5	−57.3 ± 0.2	−125
	overall	8.61	−49.1	−116.6	−226
4	1:1	4.17 ± 0.02	−23.8 ± 0.1	−89.5 ± 0.1	−220
	2:1	4.44 ± 0.02	−25.3 ± 0.1	−184.2 ± 0.2	−533
	overall	8.61	−49.1	−273.7	−753
5	1:1	3.26 ± 0.02	−18.6 ± 0.1	−38.5 ± 0.1	−67
	2:1	3.55 ± 0.02	−20.2 ± 0.1	−127.5 ± 0.2	−359
	overall	6.8	−38.8	−166	−426
6	1:1	3.97 ± 0.03	−22.6 ± 0.5	−65.4 ± 0.1	−143
	2:1	3.25 ± 0.08	−18.6 ± 0.7	−83.2 ± 0.2	−217
	overall	7.22	−41.2	−148.6	−360
(b) *N*,*N*-Dimethylformamide					
F^-					
1	1:1	4.30 ± 0.05	−24.5 ± 0.3	−12.1 ± 0.7	42
4	1:1	6.8 ± 0.3	−39.0 ± 0.5	−26.2 ± 0.5	43
5	1:1	3.4 ± 0.1	−19.2 ± 0.8	−13.6 ± 0.3	19
	1:2	3.2 ± 0.2	−18.2 ± 1.1	−7.6 ± 0.2	35
	overall	6.6	−37.4	−21.2	54
$H_2PO_4^-$					
1	1:1	4.06 ± 0.02	−23.15 ± 0.09	−26.4 ± 0.2	−11
5	1:1	4.80 ± 0.1	−27.4 ± 0.6	−18.8 ± 0.3	29
$HP_2O_7^{3-}$					
1	1:1	4.91 ± 0.09	−28.0 ± 0.5	−40.75 ± 0.03	−43
	2:1	3.82 ± 0.08	−21.8 ± 0.5	−35.72 ± 0.06	−47
	overall	8.7	−50	−76.47	−89
4	1:1	4.08 ± 0.02	−23.3 ± 0.1	−22.95 ± 0.03	+1
	2:1	5.04 ± 0.07	−28.8 ± 0.4	−39.91 ± 0.07	−37
	overall	9.12	−52.1	−62.86	−36

acetonitrile to DMF, the overall stability of the 2:1 complex (log $K_{ov} = 9.12$) is very close to that found in acetonitrile (log $K_{ov} = 8.61$) while the stability of complex formation for the individual processes (1:1 and 2:1 ligand/anion) differs significantly. Therefore, there is an entropy−enthalpy compensation effect in these solvents responsible for the similar overall stability observed for this anion and **1** in this solvent. This is also applicable to the system involving **4** and this anion in these solvents.

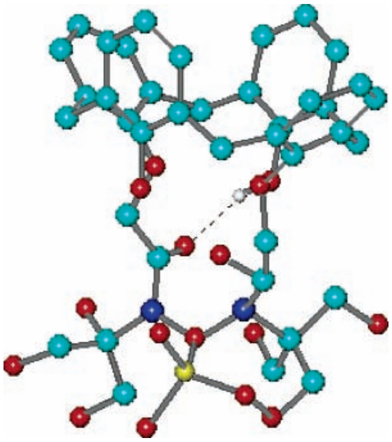


Figure 5. Equilibrium structure of the **1**−$H_2PO_4^-$ complex as determined by molecular simulation.

Hydroxyamide Calix[4]arene Derivatives and Water Solubility. The solubility of this ligand in water (in a phosphate buffer) of 1.8 × 10^{-5} mol·dm^{-3} reported in the literature[10] could not be corroborated by solubility measurements carried out by us in the absence of buffer (pure water) at 298.15 K. In fact, the water solubility of this ligand was undetectable by either UV spectrometry, ^{1}H NMR, or gravimetry. Although no interaction was observed between **1** and anions in solvents such as dimethylsulfoxide and propylene carbonate, this paper unambiguously shows through ^{1}H NMR, conductance, and thermodynamic investigations that this receptor is able to recognize dihydrogen phosphate in acetonitrile and *N*,*N*-dimethylformamide. We therefore consider that the water solubility claimed for these ligands is the result of measurements carried out in the presence of buffer solutions pH = 6.8 (at this pH, [$H_2PO_4^-$]

$\cong$ [HPO_4^{2-}]) and this is due to the interaction of **1** with these species and it is not an inherent property of the ligand.

Final Conclusions

From the above discussion the following conclusions are drawn:

(i) ^{1}H NMR studies suggest that this receptor is able to interact with cations through the carbonyl, the phenolic, and the hydroxyl oxygens of the pendant arms and with anions (fluoride, dihydrogen phosphate, and pyrophosphate) through hydrogen bond formation involving the NH moieties. These findings are corroborated by conductance measurements which also provide information regarding the composition of the complexes in acetonitrile. The strength of interaction was determined through thermodynamic investigations involving the relevant ionic species and **1** in acetonitrile.

As far as cations are concerned, a selectivity peak is found in terms of Gibbs energies. This selectivity peak reveals the contribution of both, the binding and the desolvation energies in the overall process of complexation. However, the fact that soft cations such as Cd^{2+}, Hg^{2+}, and Ag^{+} with lower solvation energies than Mg^{2+} are unable to interact with this receptor provides a strong indication that the nature of the donor atoms in the pendant arms of calixarenes, as well as their arrangements in the lower rim, are important factors to consider in the selection of pendant arms to be attached to calixarenes.

(ii) The inclusion of this ligand in the list of water soluble calix[4]arene derivatives is misleading, and therefore, the solubility in water of other ligands in this series needs to be revised.

(iii) The fact that this investigation demonstrates that different moieties in the pendent arms serve as active sites for complexation with cations and anions leads to the conclusion that **1** may be classified as a ditropic receptor.

Acknowledgment. The authors thank the European Commission for the financial support provided under Contract INCO-CT-2004-509159.

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