A New Calix[4]pyrrole Derivative and Its Anion (Fluoride)/Cation (Mercury and Silver) Recognition

Angela F. Danil de Namor,*,† Ismail Abbas,† and Hassan H. Hammud‡

Laboratory of Thermochemistry, Chemistry Division, School of Biomedical and Molecular Sciences, University of Surrey, Guildford, Surrey GU2 7XH, United Kingdom, and Beirut Arab University, Faculty of Science, Beirut, Lebanon

A new calix[4]pyrrole-based macrocycle, *meso*-tetramethyl-tetrakis{4-[2-(ethylthio)ethoxy]phenyl}calix[4]-pyrrole, **7**, has been synthesized and fully characterized. Unlike other calixpyrrole derivatives that show selective interaction with anions, calixpyrrole **7** described in the present work forms stable complexes with both metal cations and anions. The thermodynamics of complexation of this ditopic calixpyrrole derivative with metal cations (Hg^{2+} and Ag^+) and the fluoride anion in nonaqueous solutions have been determined by titration calorimetry, and the host−guest composition has been investigated by using conductance measurements at 298.15 K. ^{1}H NMR studies provide clear evidence about the sites of complexation of **7** with the ionic species, which show that the NH groups are taking part in the complexation of this ligand with the fluoride anion while the sulfur donor atoms are responsible for the interaction with metal cations. Using the present data on **7** and structurally related analogues (**1**−**6**), the complexation behavior is discussed comparatively from the thermodynamic point of view. Possessing four sulfur-containing pendent arms, **7** displays an enhanced hosting ability for Hg^{2+} in acetonitrile. As compared with **1**, the calixpyrrole derivative, **7**, shows a unique interaction with fluoride among the anions investigated in acetonitrile and dimethyl sulfoxide. As far as the fluoride complex is concerned, the medium effect is assessed in terms of the thermodynamics of the transfer of reactants and product from acetonitrile (reference solvent) to dimethyl sulfoxide.

Introduction

Calixpyrroles are products of the condensation reaction between pyrrole and ketones in acidic medium.[1,2] The interest in these macrocycles is mainly attributed to the possibility offered by these ligands to interact with anions through hydrogen bond formation with the NH functionalities of the pyrrole units. We have previously[3] demonstrated that calix[4]pyrrole, **1**, interacts selectively with the halide ions in dipolar aprotic media (see Chart 1 for structures). The strength of complexation as assessed from thermodynamics is strongly dependent on the electronegativity of the anion.[4] Thus the stability constants were found to decrease down the group (from fluoride to iodide). We visualize the halide−calix[4]pyrrole complexation in these media as the transfer of the guest from a dipolar aprotic medium (acetonitrile) to a protic medium (the calix[4]pyrrole ligand). In fact, the results obtained mirror the sequence found in the single-ion transfer Gibbs energies (data based on the Ph_4AsPh_4B convention) of halides (from acetonitrile to a protic medium).[5] It was also shown that asymmetric anions such as dihydrogen phosphate and pyrophosphates are able to interact with calix[4]pyrrole and its derivatives. Replacement of one of the methyl groups by phenol in the calix[4]pyrrole's bridges led to the production of *meso*-tetramethyl-tetrakis(3-hydroxyphenyl)calix[4]pyrrole, **2**.[6] Polymerization of this derivative through the phenol rings resulted in a new material, capable of removing polluting anions from contaminated water.[4] More recently we reported[7] a double cavity calix[4]pyrrole derivative, namely, *meso*-tetramethyl-tetra[*N*-(2-phenoxyethyl)-*N*′-phenylurea]calix-

[4]pyrrole, **3**, with enhanced capacity to interact with anions. The thermodynamics of calix[1]thieno[3]pyrrole, **4**, and their interaction with ionic species have been recently reported.[8]

Lower rim calix[4]arenes containing soft donor atoms in their pendent arms, namely, 5,11,17,23-tetra-*tert*-butyl[25,27-bis(hydroxy)-26,28-bis(ethylthioethoxy)]calix[4]arene, **5**, and 5,11,17,23-tetra-*tert*-butyl[25,27-bis(ethylethanoate)oxy-26,28-bis(ethylthioethoxy)]calix[4]arene, **6**, have been shown to interact selectively with soft donor atoms such as mercury(II) and silver(I).[9,10] Mercury(II) is known for its toxicity.[11,12] A matter of great concern is its presence in water, which has serious implications in aquatic life where this is transformed into methyl mercury, which has a higher toxicity than the single ion. Thus, the consumption of mercury contaminated fish by humans leads to serious health problems. Therefore, the design of receptors able to remove mercury(II) from water is an area of great interest given that the attachment of these receptors to solid supports may provide the basis for the development of new technological approaches for addressing this issue. On the other hand, concern has been expressed about fluoride contamination and its effects on human health.[13] On the basis of the above statements, it would be useful to concentrate efforts in the design of a receptor able to interact with both ions.

In this paper we report the synthesis and characterization (structural and thermodynamic) of a calix[4]pyrrole derivative, namely, *meso*-tetramethyl-tetrakis{4-[2-(ethylthio)ethoxy]phenyl}-calix[4]pyrrole, **7**. The interesting features of this ligand are that (i) one of the methyl groups in the disubstituted methylene bridges has been replaced by 2-(ethylthioethoxy)-4-phenyl units. These units are analogous of the monomeric components of previously reported thiocalixarenes (**5** and **6**). They differ in

† University of Surrey.
‡ Beirut Arab University.

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CHART 1
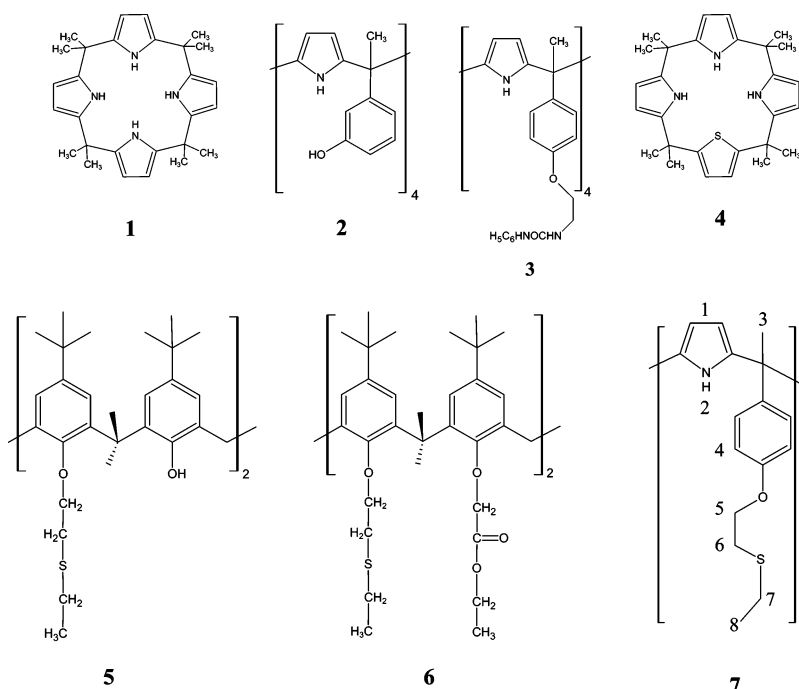
that the methylene bridges that link the monomeric components in **5** and **6** are nonexistent in this new derivative giving an enhanced flexibility to these groups. (ii) The pyrrole NH functionalities are free to interact with anions.

Given that this derivative has the potential to interact with anions and cations (through the donor atoms of the pendent arms of the disubstituted methylene bridges), its anion–cation complexation has been investigated through ^{1}H NMR, conductance, and calorimetric studies. The results are compared with previously reported calix[4]pyrrole and calix[4]arene derivatives. Final conclusions are given.

Experimental Section

a. Chemicals. 2-Chloroethyl ethyl sulfide (98%), pyrrole (99%), 4-hydroxyacetophenone, and methanesulfonic acid were all purchased from Aldrich Chemical Co. Hexane, ethanol, methanol, and acetone (HPLC grade, Fisher) were used without further purification. Acetonitrile (MeCN, Aldrich) and dimethyl sulfoxide (DMSO, Aldrich) were first refluxed in a nitrogen atmosphere with calcium hydride for several hours and then distilled.[14] Metal perchlorate hydrate (Aldrich) was dried over P_4O_{10} under vacuum for several days before use. The absence of a signal from residual water in the ^{1}H NMR spectra of **7** with the cations in acetonitrile (CD_3CN) and dimethyl sulfoxide (DMSO-d_6) provided indication that the salts used were anhydrous. Tetra-*n*-butylammonium halides (fluoride, chloride, bromide, and iodide), hydrogen sulfate, perchlorate, nitrate, and dihydrogen phosphate (Aldrich) were dried over P_4O_{10} under vacuum for several days before use. Deuterated acetonitrile (CD_3CN), methanol (CD_3OD), and dimethyl sulfoxide (DMSO-d_6) were purchased from Aldrich.

b. Synthesis of *meso*-Tetramethyl-tetrakis{4-[2-(ethylthio)-ethoxy]phenyl}calix[4]pyrrole (7). *meso*-Tetramethyl-tetrakis-(4-hydroxyphenyl)calix[4]pyrrole was prepared by a reported procedure.[15] A mixture of *meso*-tetramethyl-tetrakis-(4-hydroxyphenyl)calix[4]pyrrole (1.5 g, 2.02 mmol), K_2CO_3 (2.24 g), and 18-crown-6 (0.3 g) in MeCN (150 mL) was refluxed for 2 h, and 2-chloroethyl ethyl sulfide (1.9 mL) was

added gradually over a period of 5 min. The mixture was then refluxed for 12 h. The reaction was monitored by TLC using a dichloromethane/hexane/methanol (8:1.4:0.6) mixture as the developing solvent system. After cooling, the solvent was removed under reduced pressure. The solid afforded was dissolved in dichloromethane and extracted with a saturated solution of sodium bicarbonate and then with distilled water. The organic phase was separated and dried with magnesium sulfate and then filtered. The dichloromethane was removed by rotary evaporation, and the oily product obtained was recrystallized from methanol (60%). Microanalysis carried out for $C_{64}H_{76}N_4O_4S_4$. Calcd: C, 70.29; H, 7.00; N, 5.12%. Found: C, 70.02; H, 6.80; N, 4.98%. ^{1}H NMR, CD_3OD (298 K), δ (ppm): 9.06 (bs, 4H, N**H**), 6.88 (d, 8H, Ar**H**), 6.67 (d, 4H, Ar**H**), 5.75 (bs, 8H, pyrrole–**H**), 4.11 (t, 8H, **CH**_2–Ar), 2.87 (t, 8H, **CH**_2–S), 2.62 (q, 8H, **CH**_2–S), 1.87 (s, 12H, **CH**_3–bridge), 1.25 (t, 12H, **CH**_3–CH_2–S). FAB-MS (m/z): [M^+] calcd, 1093.577 ; found, 1093.500.

c. Solubility Measurements. To determine the solubility of *meso*-tetramethyl-tetrakis{4-[2-(ethylthio)ethoxy]phenyl}calix-[4]pyrrole, **7**, in the various solvents, saturated solutions of the macrocycle in the appropriate solvent were prepared. The mixtures were left in a thermostat at 298.15 K for 3 days until equilibrium was reached. Aliquots of the saturated solutions 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 **7** in the various solvents was checked by exposing the solid to a saturated atmosphere of the appropriate solvent for several days.[16]

d. ^{1}H NMR Measurements. ^{1}H NMR measurements were recorded at 298 K on 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. Solutions of **7** in the appropriate deuterated solvent (concentrations of $(1-5) \times 10^{-3}$ mol·dm^{-3}) were placed in

5 mm NMR tubes using TMS as the internal reference to measure the spectrum of the ligand. Then additions of cation and anion salt solutions in the same solvent (concentrations of $(1-2) \times 10^{-3}$ mol·dm^{-3}) were made. Changes in the chemical shifts upon the addition of the salt containing the appropriate ion relative to the free ligand were calculated.

e. Conductance Measurements. Conductance measurements at 298.15 K were carried out with a Wayne–Kerr autobalance universal bridge, type B642. The conductance cell was a Russell type glass bodied electrode with a cell constant (determined using 0.10 mol·dm^{-3} aqueous KCl solution) of 1.009 ± 0.001 cm^{-1}. A solution containing the cation or anion salt (concentration range from 4×10^{-5} to 6×10^{-3} mol·dm^{-3}) in the appropriate solvent was titrated with the ligand solution in the same solvent and the conductance measured after each addition once equilibrium was reached.

f. Titration Calorimetry. Stability constants (expressed as log K_s) and enthalpies of complexation of *meso*-tetramethyl-tetrakis{4-[2-(ethylthio)ethoxy]phenyl}calix[4]pyrrole with the appropriate cation or anion in different solvents were determined by calorimetry using a Tronac 450 titration calorimeter[17] or the 2277 thermal activity monitor (TAM).[18] As far as the former is concerned, the reliability of the equipment was tested by using the protonation reaction of THAM [tris(hydroxymethyl)aminomethane] with hydrochloric acid suggested by Wilson and Smith.[19] The value obtained ($\Delta_r H° = -47.5 \pm 0.6$ kJ·mol^{-1}) was in excellent agreement with that reported in the literature (-47.49 kJ·mol^{-1}).[20] For calorimetric determinations using the Tronac 450, a solution of the ligand in the appropriate solvent (1×10^{-3} to 6×10^{-3} mol·dm^{-3}) was titrated in a solution (50 mL) containing the cation or anion salt (concentration range, 5×10^{-3} to 2×10^{-2} mol·dm^{-3}) in the same solvent.

For measurements carried out with the TAM calorimeter, chemical calibration was carried out. For this purpose the log K_s values and the enthalpy of complexation, $\Delta_c H°$, of 18-crown-6 and Ba^{2+} in water at 298.15 K were determined.[21] For complexation studies involving **7** and the Hg^{2+} cation in MeCN, a solution of the ligand (1×10^{-3} to 6×10^{-3} mol·dm^{-3}) was placed in the vessel and the cation salt (concentration range, 2×10^{-2} to 5×10^{-2} mol·dm^{-3}) in the syringe. The mercury-(II) cation salt solution was injected incrementally using a 0.5 cm^3 gastight motor-driven Hamilton syringe. In each titration experiment, 24 injections were made at time intervals of 35 min. Corrections for the heat of dilution of the titrant in the solvent were made. A computer program for TAM (Digitam 4.1 for Windows from Thermometric AB and Scitech Software AB, Sweden) was used to calculate log K_s and the enthalpy of complexation ($\Delta_c H°$) for the process under investigation.

g. Standard Enthalpy of Solution. The enthalpies of solution, $\Delta_s H$ (kJ·mol^{-1}), of **7** at different concentrations (2×10^{-5} to 1×10^{-3} mol·dm^{-3}) in MeCN and DMSO at 298.15 K were determined calorimetrically using the Tronac 450 calorimeter. Thus, the empty glass ampules (at least six) filled with known quantities of the ligand were sealed. These were then placed on the holder at the end of the stirrer and immersed in the desired solvent in the reaction vessel. The system was then placed in a water bath until thermal equilibrium was attained. The ampule was broken by means of the plunger that goes through the stirrer rod, and the resulting temperature changes were recorded. After each experiment electric calibration was performed. The total heat recorded was the sum of the heat of solution and the heat of the ampule breaking. The latter was determined by breaking empty ampules in the same solvent under investigation and recording the heat change. The heat of

TABLE 1: Solubilities and Derived Standard Gibbs Energies of Solution of 7 in Nonaqueous Solvents at 298.15 K

solvent[a]	solubility (mol·dm^{-3})	$\Delta_s G°$ (kJ·mol^{-1})	$\Delta_t G°$ (kJ·mol^{-1})
MeOH	$(1.3 \pm 0.2) \times 10^{-3}$	16.51	0
PC	$(2.64 \pm 0.04) \times 10^{-2}$	9.01	-7.50
MeCN	solvate formation		
DMF	solvate formation		
DMSO	solvate formation		
CH$_2$Cl$_2$	solvate formation		
CHCl$_3$	solvate formation		

[a] Abbreviations: acetonitrile, MeCN; methanol, MeOH; ethanol, EtOH; *N,N*-dimethylformamide, DMF; dimethyl sulfoxide, DMSO; propylene carbonate, PC; dichloromethane, CH$_2$Cl$_2$; and chloroform, CHCl$_3$.

solution was calculated by subtracting the heat of the breaking of the empty ampule from the total heat recorded.

Results and Discussion

Solubilities and Derived Gibbs Energies of Solution. Table 1 reports the solubility on the molar scale of **7** in different solvents at 298.15 K for the process described in

$$\mathbf{7}(sol) \rightarrow \mathbf{7}(s) \tag{1}$$

These are the results of at least three analytical measurements carried out on the same saturated solution. Thus, the standard deviation of the data is also included in this table.

When the equilibrium between the solid (sol) and the solution (s) was reached and the solid phase was not altered by solvation, solubility data were used to calculate the standard Gibbs energy of solution, $\Delta_s G°$, referred to as the standard state of 1 mol·dm^{-3}. Solvate formation was observed when a solid sample of **7** was exposed to saturated atmospheres of acetonitrile (MeCN), *N,N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), chloroform (CHCl$_3$), and dichloromethane (CH$_2$Cl$_2$) (Table 1). Taking methanol as the reference solvent, the standard transfer Gibbs energies, $\Delta_t G°$, of this ligand from methanol to propylene carbonate was calculated. $\Delta_s G°$ and $\Delta_t G°$ values are also included in Table 1. It should be observed that the replacement of the methyl group in the disubstituted bridges of **1**, where solubility in PC[3] is 1.40×10^{-2} mol·dm^{-3}, by a bulkier moiety in **7** increases the polarizability of the latter as to enhance its solubility in the dipolar aprotic solvent (PC) and leads to solvation in another aprotic media. On the other hand, this bulky group in **7** may exert some steric hindrance on the functionalities of the pyrrole rings as to reduce the possibility of this ligand to interact with methanol through hydrogen-bond formation. As a result, the solubility of **7** in methanol is significantly reduced with respect to **1** (8.07×10^{-3} mol·dm^{-3}).[3] The variation observed in $\Delta_t G°$ value for this ligand from MeOH to PC is significant and would contribute favorably to the stability of complex formation in methanol relative to propylene carbonate, as far as **7** is concerned.

^{1}H NMR measurements were performed with the aim of investigating the complexing properties of **7** for cations and anions, and these are discussed in the next section.

^{1}H NMR Measurements. For these measurements three solvents were chosen, a protophobic (CD$_3$CN), a protophilic dipolar aprotic (DMSO-d_6), and a protic (CD$_3$OD) solvent. Chemical shift (δ, ppm) and chemical shift changes ($\Delta\delta$, ppm) relative to CD$_3$CN for **7** in CD$_3$OD and DMSO-d_6 are listed in Table 2. The ^{1}H NMR data for the free ligand in these solvents show significant downfield shifts in the NH protons ($\Delta\delta = 1.56$ ppm) in moving from CD$_3$CN to DMSO-d_6.

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TABLE 2: ^{1}H NMR Chemical Shifts (δ, ppm) and Differences in the Chemical Shifts ($\Delta\delta$, ppm) with Respect to CD$_3$OD for 7 in CD$_3$CN and DMSO-d_6 at 298 K

protons	CD$_3$CN δ (ppm)	CD$_3$OD δ (ppm)	CD$_3$OD $\Delta\delta$ (ppm)	DMSO-d_6 δ (ppm)	DMSO-d_6 $\Delta\delta$ (ppm)
1	6.01	5.75	−0.24	5.93	−0.08
2	7.87	9.07	1.20	9.43	1.56
3	1.83	1.87	0.04	1.71	−0.12
4	6.81	6.88	0.07	6.81	0.00
5	4.07	4.11	0.04	4.02	−0.05
6	2.87	2.85	−0.02	2.81	−0.06
7	2.62	2.62	0.00	2.59	−0.03
8	1.25	1.25	0.00	1.19	−0.06

Similarly, a marked deshielding effect is recorded for the same proton ($\Delta\delta = 1.20$ ppm) in moving from CD$_3$CN to CD$_3$OD. These are indicative that both CD$_3$OD and DMSO-d_6 are likely to interact with the ligand through hydrogen-bond formation between the NH protons and the hydroxyl groups in the former solvent while the basic oxygen atoms of DMSO-d_6 are taking part in the interaction with this ligand.

Table 3 reports the proton signals for the free ligand in CD$_3$CN and DMSO-d_6 as well as the chemical shift changes that protons (1−8) undergo after addition of the anion (as tetra-*n*-butylammonium) and cation (as perchlorates) salts to the ligand. As far as alkali, alkaline-earth, and transition metal cations are concerned, no significant chemical shift changes were observed upon the addition of these cation salts to the ligand in these solvents. Significant chemical shift changes were only observed by the addition of Ag$^+$ and Hg^{2+} (as perchlorates) to **7** in CD$_3$CN. For the Ag$^+$−**7** and Hg^{2+}−**7** complexes in CD$_3$-CN, significant deshielding effects are observed for H-5, H-6, and H-7 suggesting that complexation occurs through the sulfur atoms of the pendent arms.

On the other hand, proton NMR studies in CD$_3$CN and DMSO-d_6 at 298 K (Table 3) show that among the investigated anions (tetra-*n*-butylammonium as the counterion), only significant chemical shift changes in the pyrrolic(1) and aromatic-(4) protons are observed by the addition of F$^-$ to the ligand in these solvents. It was found that the addition of increasing amounts of Cl$^-$, Br$^-$, I$^-$, and H$_2$PO$_4^-$ anion salts to **7** in CD$_3$-CN and DMSO-d_6 caused no changes in the NMR spectra of this ligand in this solvent. However, the disappearance of the H_N signals in the spectrum involving the F$^-$ anion prevented the calculation of the $\Delta\delta$ values for this proton with this anion in these solvents. These findings provide a clear indication that
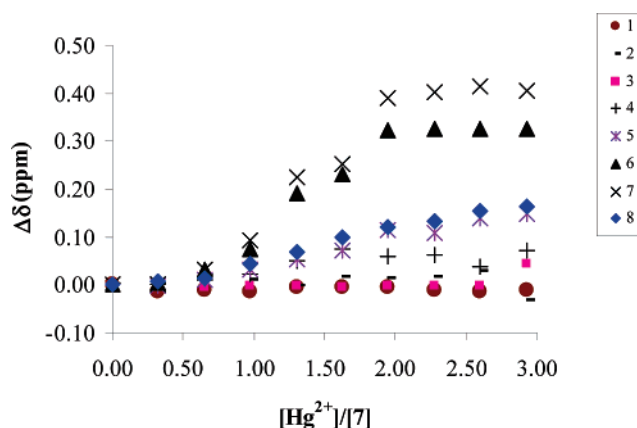
Figure 1. ^{1}H NMR titration of **7** with mercury(II) in CD$_3$CN at 298 K.

7 interacts with the F$^-$ anion via hydrogen-bond formation through the NH groups of the pyrrole units.

To further investigate the complexation of Hg^{2+} and **7** in solution, NMR titrations were conducted. Thus, **7** was titrated with mercury(II) perchlorate in CD$_3$CN (Figure 1). Considerable downfield shifts of H-6 and H-7 are observed and to a lesser extent for H-5 and H-8. The results show that the complexation is fast on the NMR time scale and furthermore suggests that the Hg(II) cation interacts with **7** through the sulfur atoms of the pendent arm. Inspection of Figure 1 gives preliminary knowledge about the stoichiometry of the complex, which appears to be 1:2 (**7**/Hg^{2+}) mole ratio. This fact is reflected in the shift observed in the resonance values of the methylene protons (6 and 7) bonded to the sulfur donor atoms. Conductometric titrations in acetonitrile and dimethyl sulfoxide were performed, and these are now discussed.

Conductometric Titrations. Conductometric titrations were carried out in MeCN and DMSO at 298.15 K. According to the ion−ligand strength, plots of molar conductance, Λ_m (S·cm^2·mol^{-1}), against the ligand/anion ratio showed two different patterns for complexes of moderate (broad break at the curvature so the composition of the complex was determined by extrapolating the lines at high and low ligand/anion mole ratios) and weak (slight or nonexisting changes in the slope) stability.

In a medium such as acetonitrile, a 1:1 complex of moderate stability was found for F$^-$ and **7** in this solvent while complexes

TABLE 3: Changes in the ^{1}H NMR Chemical Shifts for 7 and Cation and Anion Complexes in (a) CD$_3$CN and (b) DMSO-d_6 at 298 K

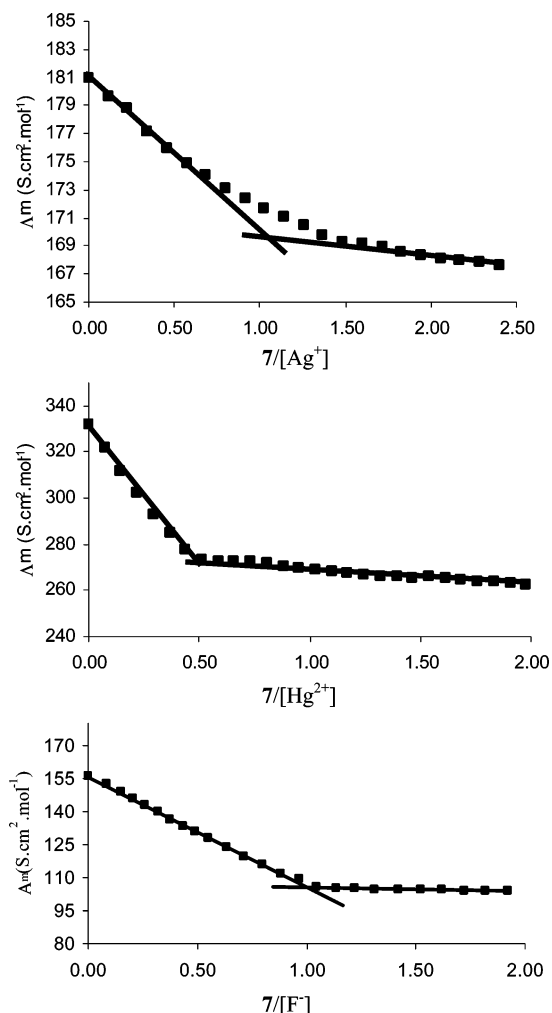|	$\Delta\delta$ (ppm) 1	2	3	4	5	6	7	8
				(a) In CD$_3$CN Solvent				
free ligand	6.01	7.87	1.83	6.81	4.06	2.87	2.62	1.25
				Metal Cations				
Ag$^+$	0.01	−0.01	0.00	0.00	0.08	0.25	0.23	0.09
Hg^{2+}	−0.01	−0.03	0.05	0.07	0.15	0.40	0.33	0.16
				Anion				
F$^-$	−0.11		−0.08	−0.12	−0.02	−0.04	−0.05	
				(b) In DMSO Solvent				
free ligand	5.93	9.43	1.71	6.81	4.02	2.81	2.59	1.19
				Metal Cations				
Ag$^+$	0.01	−0.01	0.00	0.00	0.01	0.03	0.03	0.03
Hg^{2+}	−0.01	0.01	−0.02	−0.01	0.05	0.04	−0.02	0.04
				Anion				
F$^-$	−0.11		−0.16	−0.24	−0.04	−0.01	−0.02	

Figure 2. Conductometric titration curve of silver(I), mercury(II) (as perchlorates), and fluoride (as tetra-*n*-butylammonium) with **7** in MeCN at 298.15 K.

of 1:1 and 1:2 (ligand/cation) ratios were observed for Ag$^+$ and Hg^{2+}, respectively, at 298.15 K.

We have previously demonstrated[9,22] through conductance and calorimetric measurements that the partially functionalized thiocalix[4]arene, **5**, with pendent arms analogous to **7**, forms a 1:1 complex with mercury(II) in acetonitrile. In fact, the X-ray structure of the mercury(II)−**5** complex shows that this cation interacts with the two sulfur donor atoms of **5** in a linear arrangement. Given the flexibility of the pendent arms in **7**, it seems reasonable to consider that each mercury(II) cation satisfies its linear arrangement by interacting with two sulfur atoms situated in adjacent positions.

The ability of **7**, having four sulfur donor atoms in its pendent arms, to host two Hg^{2+} cations suggests the linear interaction of each of the Hg^{2+} cations with two of the four available sulfur atoms. This assumption could be justified by (i) the ability of the calixarene derivative[9] having two of the same pendent arms in its lower rim to interact with only one Hg^{2+} cation in the same solvent and (ii) the crystal structure of mercury ethylmercaptide[23] Hg(S·C$_2$H$_5$)$_2$ showing a linear arrangement between Hg(II) and the ethylmercaptide groups. Representative examples of conductometric titration curves for the complexation of **1** with F$^-$, Ag$^+$, and Hg^{2+} ions in MeCN are shown in Figure 2. Since the electrolyte was placed in the vessel and then it was titrated with the ligand, the decrease in the conductance is attributed to the large size of the complexed anion as compared with that of the free anion. Very little changes in conductance

were recorded, and no slopes were observed for titrations involving alkali, alkaline-earth, transition metal cations, and anions (Cl$^-$, Br$^-$, I$^-$, and H$_2$PO$_4^-$) in this solvent. These findings were taken as indicative of the absence of interactions between this ligand and these cations and anions in this solvent.

In order to assess the medium effect on the complexation process, conductance measurements were carried out in dimethyl sulfoxide. Plots of molar conductance, Λ_m, against the ratio of the concentration of the ligand and anion salt (derived from conductance values) show no change in the gradient upon titrating the ligand with Cl$^-$, Br$^-$, I$^-$, and H$_2$PO$_4^-$ indicating that little or no complexation has occurred. However, a noticeable change in the slope of the conductometric titration curve was only observed for the fluoride anion with the largest change at 1:1 ligand/anion complex. No changes in the conductance were observed by the addition of the ligand to solutions containing alkali, alkaline-earth, and transition metal cations or indeed Ag$^+$ and Hg^{2+} cations. These findings corroborate the ^{1}H NMR investigations, which showed that the addition of these cation and anion salts to **7** in this deuterated solvent does not lead to changes in the chemical shifts of the ligand, suggesting either that very weak or that no complexation takes place between this ligand and these cations and anions.

On the basis of these results, it is concluded that the largest difference between the conductometric titrations of **7** and cations in DMSO relative to MeCN is that no interaction was observed between this ligand and Ag$^+$ and Hg^{2+} in DMSO, whereas in MeCN, **7** formed a 1:2 ligand/cation complex with Hg^{2+} and a 1:1 complex with Ag$^+$.

Having established the composition of the complexes, we proceeded with the thermodynamics of the complexation of these ligands and anions in acetonitrile and dimethyl sulfoxide.

Thermodynamics of Cations (Hg^{2+} and Ag$^+$) Complexation. Considering the composition of the metal−ion and metal−anion complexes in acetonitrile and dimethyl sulfoxide as discussed above and the concentration range at which the metal cations and anion salts are predominantly in their ionic forms in these solvent(s),[3,24] the complexation process between **7** and the metal cations, M^{n+} is represented by

$$M^{n+}(s) + \mathbf{7}(s) \rightarrow M^{n+}\mathbf{7}(s) \quad (2)$$
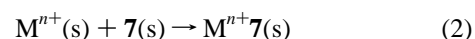
For Hg^{2+} in acetonitrile, a second process takes place as shown in

$$M^{n+}(s) + M^{n+}\mathbf{7}(s) \rightarrow M_2^{n+}\mathbf{7}(s) \quad (3)$$
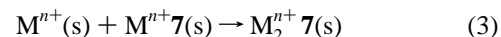
Similarly, thermodynamic data for the 1:1 complexation of anionic species X$^-$ and this ligand are referred to the process shown in eq 4.

$$X^-(s) + \mathbf{7}(s) \rightarrow \mathbf{7}X^-(s) \quad (4)$$
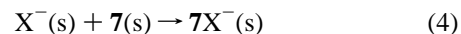
Thus Table 4 lists stability constants (expressed as log K_s), derived standard Gibbs energies, $\Delta_c G°$, enthalpies, $\Delta_c H°$, and entropies, $\Delta_c S°$, of the complexation of **7** with anions in MeCN and DMSO at 298.15 K.

As far as Hg(II) is concerned, the thermodynamic data for this system fit into a 1:2 ligand/cation model. Thus, the calorimetric curve for the titration of **7** and this cation in acetonitrile at 298.15 K is shown in Figure 3. This outcome is in accord with the results obtained from conductance measurements and ^{1}H NMR studies. The thermodynamic data reveal that in acetonitrile, the formation of the 1:1 and 1:2 complexes is enthalpically controlled. However, while the first process takes

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TABLE 4: Thermodynamic Parameters for the Complexation of the Cations with 5−7 in Acetonitrile and the Anions with 7 in Acetonitrile and Dimethyl Sulfoxide at 298.15 K

M^{n+}/L		$\log K_s$	$\Delta_c G^\circ$ (kJ·mol⁻¹)	$\Delta_c H^\circ$ (kJ·mol⁻¹)	$\Delta_c S^\circ$ (J·mol⁻¹·K⁻¹)
			In Acetonitrile Solvent		
			5[a]		
Hg²⁺	1:1	6.50 ± 0.03	−30.2 ± 0.2	−74 ± 1	−128
Ag⁺	1:1	3.20 ± 0.03	−18.3 ± 0.6	−20.6 ± 0.3	−8
			6[a]		
Hg²⁺	1:1	8.69	−49.6	−83	−112
Ag⁺	1:1	4.08	−24.03	−27.8	−13
			7[b]		
Hg²⁺	1:1	3.72 ± 0.02	−21.26 ± 0.01	−87.9 ± 0.7	−224
	2:1	1.85 ± 0.01	−10.53 ± 0.03	−7.3 ± 0.4	11
	overall	5.57 ± 0.03	−31.79 ± 0.04	−95.2 ± 0.3	−213
Ag⁺	1:1	3.2 ± 0.3	−18.1 ± 0.5	−54.9 ± 0.1	−124

L/X⁻		$\log K_s$	$\Delta_c G^\circ$ (kJ·mol⁻¹)	$\Delta_c H^\circ$ (kJ·mol⁻¹)	$\Delta_c S^\circ$ (J·mol⁻¹·K⁻¹)
			In Acetonitrile Solvent		
			7[b]		
F⁻	1:1	4.81 ± 0.06	−27.5 ± 0.3	−16.4 ± 0.3	37
			In Dimethyl Sulfoxide Solvent		
			7[b]		
F⁻	1:1	4.24 ± 0.09	−24.2 ± 0.5	−27.2 ± 0.3	−10

[a] Reference 9. [b] This work.
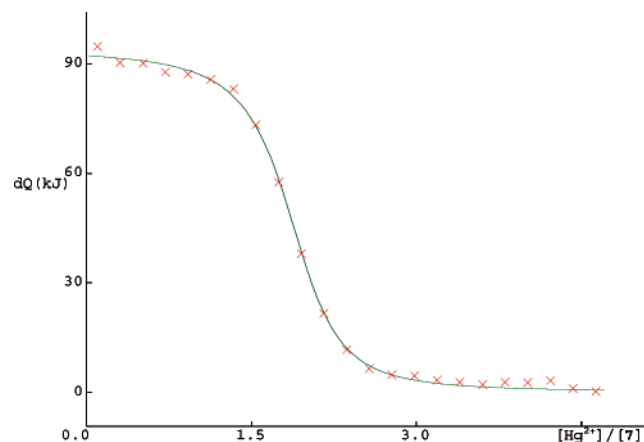
Figure 3. Enthalpy changes against Hg²⁺/**7** concentration ratios for the calorimetric titration of **7** with Hg²⁺ (as perchlorate) in acetonitrile at 298.15 K.

place with a loss in entropy, the formation of the 1:2 complex is entropically favored.

For comparison purposes in Table 4, thermodynamic data for the complexation of two calix[4]arene derivatives, **5** and **6**, and mercury(II) in acetonitrile at 298.15 K are included. An additive thermodynamic contribution of the pendent arms was demonstrated[9,10] for the complexation of these ligands (**5** and **6**) and this cation in acetonitrile. It was shown that **5** interacts with Hg(II) through a linear arrangement with the two sulfur donor atoms[9] of the pendent arms. As far as **7** is concerned, it is found that the 1:1 complexation of this ligand and Hg²⁺ in acetonitrile is enthalpically more favorable by 13.9 kJ·mol⁻¹ than that of **5** and this cation in this solvent.

The fact that the hosting capacity of **7** for mercury (1:2 ligand/ metal cation) is greater than that of **5** and this cation in MeCN leads us to suggest that in **7** each mercury interacts with the two sulfur atoms in adjacent pendent arms through a linear arrangement. However, the linear coordination for the 1:1 complex in **5** occurs through the two sulfur atoms in the pendent

TABLE 5: Selectivity Factor $S_{1/R}$ (R = 2, 3, 4, and 7) of Calix[4]pyrrole, 1, for the Fluoride Anion Relative to Another Receptor, R_2, in Acetonitrile (MeCN), *N,N*-Dimethylformamide (DMF), and Dimethyl Sulfoxide (DMSO) at 298 K

	$S_{1/R}$		
R_2	MeCN	DMF	DMSO
2-ααββ[a]	1349	2512	
2-αβαβ[a]	16		
3[b]		316	
4[c]	9	1230	282
7[d]	25		2

[a] References 6 and 3. [b] References 7 and 3. [c] References 8 and 3. [d] This work.

arms, which are known to be in alternate positions. This statement is based on the fact that the presence of four sulfur donor atoms in **7** would lead to an increase in the distance between them in order to minimize the electrostatic repulsion and enhance the stability of the molecule. On the other hand, the increase in the number of sulfur atoms and the higher flexibility of the pendent arms in **7** relative to **5** would lead to a greater capacity for Hg²⁺ cations in the former relative to the latter ligand.

As a result, a higher enthalpic stability and a greater loss of entropy will be observed for the Hg²⁺−**7** than for the Hg²⁺−**5** complex in this solvent. This statement is corroborated by the data shown in Table 4. However, the formation of the 2:1 (Hg²⁺/ **7**) complex would require a considerable rearrangement in the structure of the 1:1 complex as to allow the interaction of the second cation with the remaining sulfur atoms. Thus, a substantial drop in enthalpic stability and a sharp entropy increase are expected in moving from the 1:1 to the 1:2 complex. This interpretation is in accord with the data shown in Table 4.

Regarding the complexation of Ag⁺ and **7**, the process is enthalpically controlled but entropy destabilized. Again, a higher flexibility of the pendent arms in **7** relative to **5** and **6** is clearly shown in the greater loss of the entropy upon complexation of the former ligand and this cation with respect to the other two ligands. Undoubtedly the same stability observed for the formation of the Ag⁺−**7** and the Ag⁺−**5** complexes in aceto-nitrile is the result of a complete enthalpy−entropy compensation effect.

Thermodynamics of Anion Complexation. The thermodynamic data for the complexation of **7** and the fluoride anion in acetonitrile reflect that both enthalpy and entropy contribute favorably to the Gibbs energy of the process. On the other hand, the complexation process of the fluoride anion with **7** in dimethyl sulfoxide is enthalpically controlled. The higher stability of the complex formed between the fluoride anion and this ligand in acetonitrile relative to dimethyl sulfoxide is mainly attributed to the entropy change in the former relative to the latter given that the complexation process is enthalpically more favored in dimethyl sulfoxide.

The availability of stability constant data for calixpyrrole and its derivatives allows the calculation of the selectivity factor, $S_{1/R}$, which is calculated from the ratio of stability constants of calixpyrroles and the fluoride anion in a given solvent and temperature as shown in

$$S_{1/R} = \frac{K_s^\theta(\mathbf{1})}{K_s^\theta(R)} \qquad (5)$$

As can be inferred from an inspection of Table 5, the parent calix[4]pyrrole, **1**, is more selective for the fluoride anion than

TABLE 6: Enthalpies of Solution of 7 in Acetonitrile and Dimethyl Sulfoxide at 298.15 K

MeCN		DMSO	
c (mol·dm^{-3})	$\Delta_s H$ (kJ·mol^{-1})	c (mol·dm^{-3})	$\Delta_s H$ (kJ·mol^{-1})
1.68×10^{-4}	3.72	2.50×10^{-5}	8.96
2.65×10^{-4}	5.32	1.01×10^{-4}	7.77
2.56×10^{-4}	7.36	3.18×10^{-4}	3.44
3.60×10^{-4}	7.96	4.48×10^{-4}	4.31
6.66×10^{-4}	12.53	6.02×10^{-4}	2.64
8.78×10^{-4}	19.18	7.13×10^{-4}	1.24
		9.60×10^{-4}	0.32
$\Delta_s H° = -7.7 \pm 0.5$ kJ·mol^{-1}		$\Delta_s H° = 10.7 \pm 0.8$ kJ·mol^{-1}	

the other receptors (**2**, **3**, **4**, and **7**) in nonaqueous solvents at 298.15 K. Although the discrimination ability of calix[4]pyrrole, **1**, was not comparable, the anion binding properties of its derivatives (**2**–**4** and **7**) were tuned by the functionalization of this ligand. As such, the orientation of the phenol group in **2**-$\alpha\alpha\beta\beta$[6] turned the affinity of this ligand toward dihydrogen phosphate (1:2 ligand/anion ratio) over the spherical anions (1:1 ligand/anion ratio). On the other hand, the hosting ability of the double cavity calixpyrrole **3**[7] is greater for fluoride relative to the dihydrogen phosphate anion. Furthermore, the replacement of one pyrrole by a thiophene unit reduces the affinity of calixpyrrole **4** toward anions relative to the parent calix[4]pyrrole in the dipolar aprotic solvents. As far as calixpyrrole **7** is concerned, the replacement of one methyl group at the methylene bridge by a 4-[2-(ethylthio)ethoxy]phenyl pendent arm leads to a unique situation, which among the anions considered this receptor discriminates against all anions except fluoride in acetonitrile and dimethyl sulfoxide at 298.15 K. The absence of complexation between calixpyrrole **7** and other halide anions (chloride, bromide, and iodide) may be attributed to the bulkiness of the pendent arm, which might exercise some steric hindrance on the NH groups of the pyrrole rings and hence alter its binding ability.

The fact that the calixpyrrole derivative **7** is able to recognize soft metal cations (Hg^{2+} and Ag^{+}) as well as fluoride anion allows its inclusion in the list of ditopic receptors. However, it was not possible to investigate whether or not there is an additive thermodynamic contribution of any of these metal cations and the fluoride anion in acetonitrile due to the formation of metal–fluoride salts (as precipitates) during the titration process in this solvent. To assess the contribution of the reactants and the product to the complexation of **7** and the fluoride anion in these two solvents, we proceeded with the determination of the enthalpies of solution of the ligand from which transfer enthalpies can be calculated.
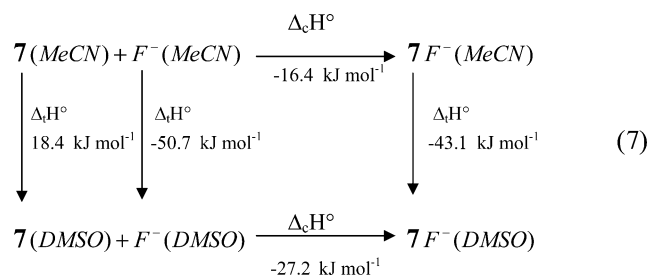
Enthalpies of Solution. The standard enthalpies of solution, $\Delta_s H°$, of **7** in MeCN and DMSO at 298.15 K are reported in Table 6. The standard deviation of the data is also included. These values were obtained from calorimetric measurements carried out at different molar concentrations (c, molar scale) of the ligand. Since $\Delta_s H$ values vary with changes in the ligand concentration, the standard enthalpy of solution, $\Delta_s H°$, value was calculated from the intercept at $c = 0$ of a plot of $\Delta_s H$ against the square root of the concentration, $c^{1/2}$. These data and those reported in the literature[3,8] for Bu$_4$NF in MeCN and DMSO at 298.15 K with complexation enthalpies reported in Table 4 are now used to assess the medium effect on the complexation process, and this is discussed in the next section.

The Medium Effect. The medium effect on the complexation process is controlled by the differences in the solvation of the

reactants and the product participating in the process in the two solvents, as shown in

$$\Delta_c P°(s_1) - \Delta_c P°(s_2) = \Delta_t P°(\mathbf{7})(s_1 \rightarrow s_2) +$$
$$\Delta_t P°(X^-)(s_1 \rightarrow s_2) - \Delta_t P°(\mathbf{7}X^-)(s_1 \rightarrow s_2) \quad (6)$$

This relationship reflects that for the reactants to favor complexation in s_1 relative to s_2, the reactants should be better solvated in the latter relative to the former solvent. The opposite is true for the anion complex. These differences are reflected in the thermodynamic parameters of transfer, $\Delta_t P°$ ($P = G$, H, S) of the ligand, the free anion (X$^-$), and the complex anion (**7**X$^-$) from a reference solvent (s_1) to another solvent (s_2). Unable to analyze quantitatively the medium effect on the complexation of the fluoride anion and **7** in terms of Gibbs energies, given that (i) the ligand undergoes solvation in MeCN and DMSO and (ii) there are no data available for the transfer Gibbs energies of the free and complex anion, the medium effect on complexation is analyzed in terms of enthalpy. Availability of the $\Delta_s H°$ values for **7** (see Table 6) and the fluoride anion from MeCN to DMSO[3,8] and the $\Delta_c H°$ values for this anion and **7** in these solvents (Table 4) allows the calculation of the $\Delta_t H°$ value for the **7**–fluoride complex from MeCN to DMSO through eq 6. By insertion of the appropriate quantities in the thermodynamic cycle (eq 7), it follows that the higher enthalpic

$$
\begin{array}{ccc}
 & \Delta_c H° & \\
\mathbf{7}(MeCN) + F^-(MeCN) & \xrightarrow{\text{-16.4 kJ mol}^{-1}} & \mathbf{7}F^-(MeCN) \\
\Big\downarrow \begin{smallmatrix}\Delta_t H° \\ 18.4 \text{ kJ mol}^{-1}\end{smallmatrix} \quad \Big\downarrow \begin{smallmatrix}\Delta_t H° \\ \text{-50.7 kJ mol}^{-1}\end{smallmatrix} & & \Big\downarrow \begin{smallmatrix}\Delta_t H° \\ \text{-43.1 kJ mol}^{-1}\end{smallmatrix} \quad (7)\\
\mathbf{7}(DMSO) + F^-(DMSO) & \xrightarrow[\text{-27.2 kJ mol}^{-1}]{\Delta_c H°} & \mathbf{7}F^-(DMSO) \\
\end{array}
$$

stability of the complexation process in DMSO relative to MeCN is attributed to the favorable contribution of the free and complexed ligand overcoming that for the free fluoride anion (unfavorable for complexation in DMSO).

Conclusions

From the above discussion the following conclusions are drawn: (1) In acetonitrile, **7** can be classified as a ditopic receptor given its ability to interact with soft metal cations (Hg^{2+} and Ag^{+}) and the fluoride anion as shown through the various approaches undertaken in this work. (2) The higher flexibility of this calixpyrrole relative to calixarene derivatives is clearly reflected in the thermodynamic data. (3) While the parent calix[4]pyrrole still remains the more suitable ligand to selectively recognize halide anions, **7** discriminates against all anions except fluoride in dipolar aprotic media (acetonitrile and dimethyl sulfoxide). This is an important aspect to consider in the selection of ligands for the removal of toxic ions from water. (4) The fact that this receptor does not interact with biologically essential ions seems to be promising in the search for decontaminating agents for the removal of mercury(II) and fluoride ions from nonaqueous solvents and to a much lesser extent from water, once grafted into solid supports. Research in this area is in progress.[25] Some encouraging results on calix[4]pyrrole containing polymers can be found in the literature.[4,25–27]

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