Sulfur-Containing Hetero-Calix[4]pyrroles as Mercury(II) Cation-Selective Receptors: Thermodynamic Aspects

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Two sulfur-containing hybrid calix[4]pyrrole derivatives (**III** and **IV**) have been synthesized and fully characterized. Several analytical techniques (^{1}H NMR, conductance measurements, UV−vis spectrophotometry, titration potentiometry, and titration calorimetry) have been used to assess the interaction between these hybrid calixpyrrole receptors and metal cations in acetonitrile and dimethylsulfoxide. The partition constants of calix-[4]pyrrole, **I**, **II**, and **IV** in the acetonitrile−hexane solvent system and the solubilities of the ligands in various solvents at 298.15 K were determined. ^{1}H NMR measurements reveal the sites of interaction of calixpyrrole ligands with metal cations in CD_3CN. Conductance and UV−vis spectrophotometric measurements were performed to establish the composition of mercury(II) calixpyrrole complexes in acetonitrile at 298.15 K. Titration calorimetry was used to quantitatively assess Hg(II)−calixpyrrole interactions. Thus the thermodynamics of complexation of calixpyrrole ligands with the mercury(II) cation in acetonitrile at 298.15 K are reported. Potentiometric titrations were also used to establish the stepwise stability constants for the complexation of calix[3]thieno[1]pyrrole with the Hg(II) cation in acetonitrile at 298.15 K. The results show that replacement of one or more pyrrole units by thiophene rings in calix[4]pyrrole has tuned significantly the discrimination ability of these ligands between anions and enables the produced hybrid calixpyrroles to bind selectively with Hg(II) in acetonitrile. No interaction was observed between these ligands and other metal cations in acetonitrile.

Introduction

Calix[4]pyrroles were first synthesized by Baeyer in 1886.[1] These are recognized for their selective interaction with anions.[2] We have reported in several papers detailed investigations on the complexation of these ligands with anions in dipolar aprotic media.[3−5] Thus, in a previous paper, the interaction of calix-[1]thieno[3]pyrrole, **I,** with halide and dihydrogen phosphate anions was discussed.[6] Although the majority of calix[4]pyrrole compounds have been investigated for anion complexation processes,[7−9] a few hybrid calix[4]pyrroles were reported as hosts for metal cations.[10,11] Indeed given that pyrrole- or thiophene-based macrocycles can recognize different guest ions, the proper design of host molecules containing these heterocycles may result in receptors with unique binding properties. The replacement of pyrrole in calixpyrroles by thiophene units can lead to efficient cation complexing agents. In recent years, extensive modifications in calix[4]pyrrole structures have been carried out.[12]

The production of highly selective cation receptors is an area of great interest for our group, particularly those that are able to enter selective interaction with heavy metal cations. The scope of supramolecular chemistry for the design of selective extracting agents opens the way for the development of new technological approaches for the removal of toxic metal cations from contaminated sources. Although we have previously reported sulfur-containing calix[4]arene derivatives[13,14] with complexing ability for heavy metal cations, the procedure used in the synthesis of calix[4]pyrroles is relatively simpler and less costly than those involved in the production of calix[4]arene derivatives. Consequently, the former offers a higher potential for the development of decontaminating agents for the removal of polluting ions than the latter.

Mercury has important industrial uses;[15] however its toxicity to human health and aquatic life is well-documented.[16,17] The control of mercury levels in water, soil, and air has generated much interest in the design of selective ligands for sequestering this toxic cation from the ecosystem.

In this paper we report:

(i) The synthesis and the characterization of four calix[4]-pyrrole receptors: calix[1]thieno[3]pyrrole, **I**; calix[2]thieno-[2]pyrrole, **II**; *N*,*N*-dimethyl-calix[2]thieno[2]pyrrole, **III**; and meso-tetramethyl-tetrakis-(thiophene) calix[4]pyrrole, **IV**. The interest in these ligands relies on the presence of sulfur, a soft donor atom, and as such, able to interact with a soft metal cation such as mercury. Thus, receptors **I** and **II** differ in the number of pyrrole units replaced by thiophene in the basic structure of calix[4]pyrrole. As far as **III** and **IV** are concerned, the former ligand differs from **II** in that the pyrrolic hydrogens were replaced by methyl groups while in **IV** the structure of calix-[4]pyrrole was modified by the replacement of methyl by thiophene units in the bridges.

(ii) All steps undertaken prior to proceeding with the thermodynamic characterization of the complexation process in acetonitrile to ensure that these data are referred to a well-defined process. In doing so, partition experiments were carried out to assess that in a dipolar aprotic solvent, such as acetonitrile, these receptors are as monomeric species in solution. The ^{1}H NMR approach was used to assess the presence of ligand−

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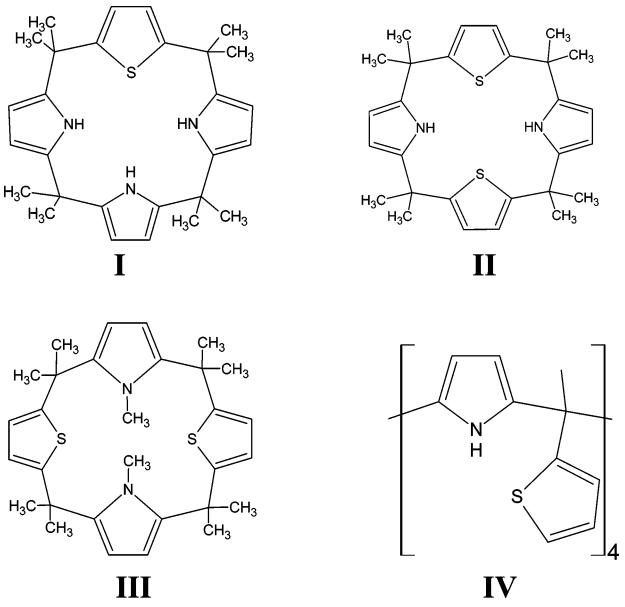

metal cation interactions in CD_3CN and whenever possible the active sites of complexation of these receptors with the Hg^{2+} cation. Conductance measurements were used for two purposes (1) to establish the complex composition through conductometric titrations in acetonitrile and (2) to determine the concentrations at which the metal ion salts are predominantly in their ionic forms in solution.

Experimental Section

Chemicals. Thiophene, 2-acetylthiophene, pyrrole, methanesulfonic acid, and *n*-butyllithium were obtained from Aldrich and used as purchased unless otherwise stated. Hexane, ethanol (EtOH), and acetone (HPLC grade, Fisher) were used without further purification. Mercury(II) perchlorate hydrate (98%, Aldrich) was dried over P_4O_{10} under vacuum for several days before use. Acetonitrile (Aldrich) was first refluxed in a nitrogen atmosphere with calcium hydride for several hours and then distilled.[18]

N,*N*-Dimethylformamide (DMF; HLPC grade, Aldrich) was dried using 4 Å molecular sieves (which had been dried in an oven at 300 °C for several hours).[18] The deuterated solvents, acetonitrile (CD_3CN), chloroform ($CDCl_3$), and dimethylsulfoxide (d_6-DMSO), were purchased from Aldrich.

Synthesis of Ligands. *Synthesis of Calix[1]thieno[3]pyrrole (**I**).* Ligand **I** was prepared by following a previously reported procedure.[6]

Anal. Calcd for $C_{28}H_{35}N_3S$: C, 75.46; H, 7.92; N, 9.43. Found: C, 75.62; H, 8.01; N, 9.63. FAB-MS: *m*/*z*, 446 [M^+]; found, 445.664.

^{1}H NMR, (CD_3CN) (298 K), δ (ppm): 7.84 (bs, H, N*H*), 7.41 (bs, 2H, N*H*), 6.65 (s, 2H, thiophene), 5.84−5.85 (d, 2H, pyrrole), 5.76−5.77 (d, 4H, pyrrole), 1.55 (s, 12H, CH_3), 1.50 (s, 12H, CH_3).

*Synthesis of Calix[2]thieno[2]pyrrole (**II**).* Ligand **II** was prepared by following a previously reported procedure.[19]

Anal. Calcd for $C_{28}H_{34}N_2S_2$: C, 72.68; H, 7.41; N, 6.05. Found: C, 72.51; H, 7.41; N, 6.18.

^{1}H NMR, (CD_3CN), δ (ppm): 7.70 (bs, 2H, N*H*), 6.68 (s, 4H, thiophene), 5.79 (d, 4H, pyrrole), 1.58 (s, 24H, CH_3).

*Synthesis of N,N-Dimethylcalix[2]thieno[2]pyrrole (**III**).* A tetrahydrofuran (50 mL) suspension of calix[2]thieno[2]pyrrole (1 mmol) and sodium hydride (4 mmol) was stirred under a nitrogen atmosphere at 50 °C for 1 h. It was then cooled down to room temperature. Then 18-crown-6 (4 mmol) was added, and the mixture was stirred for 30 min. Methyl iodide was then added (2 mmol), and the resulting solution was stirred for 4 h at room temperature. The mixture was poured into a saturated NH_4Cl aqueous solution and extracted with ether. The extract was washed with saturated $NaHCO_3$ and water, dried over anhydrous $MgSO_4$, and evaporated to dryness.

^{1}H NMR, (CD_3CN), δ (ppm): 6.65(s, 4H, thiophene), 5.99 (d, 4H, pyrrole), 2.88 (s, 6H, N−CH_3), 1.63 (s, 24H, CH_3).

*Synthesis of Meso-tetramethyl-tetrakis-(thiophene) Calix[4]-pyrrole (**IV**).* To a stirred mixture containing methanol (50 mL), pyrrole (2 mL, 0.028 mol), and 2-acetylthiophene (3 mL, 0.28 mol), methanesulfonic acid (1 mL) was added at room temperature under a nitrogen atmosphere. The precipitate obtained was filtered and washed with methanol (MeOH). It was then dissolved in acetone and reprecipitated by the addition of hexane. The white product obtained was collected, washed with hexane, and dried under vacuum over P_4O_{10}.

Anal. calcd for $C_{40}H_{36}N_4S_4$: C, 68.53; H, 5.18; N, 7.99. Found: C, 68.53; H, 5.18; N, 8.04.

^{1}H NMR, (CD_3CN), δ (ppm): 8.27 (bs, 4H, N*H*), 7.13 (s, 4H, thiophene), 6.76 (s, 4H, thiophene), 6.58 (s, 4H, thiophene), 5.64 (s, 8H, pyrrole), 1.47 (s, 12H, CH_3).

Partition Experiments. For the partition experiments carried out to investigate the speciation of the ligand in the solvents, we used the procedure reported in the literature.[20] Thus, the solvents, hexane and acetonitrile, were mutually saturated before use to avoid volume changes when mixed. For the partition experiments, solutions containing different concentrations of calixpyrrole ligands (from 1×10^{-5} to 1×10^{-3} mol dm^{-3}) were prepared in acetonitrile saturated with hexane. Equal volumes of these solutions (10 cm^3) and hexane (saturated with acetonitrile) were placed in separate tubes and shaken for 1 h. Then, these were left in a thermostated bath at 298.15 K for 12 h to ensure that equilibrium was achieved. Samples of both phases were taken, and the equilibrium concentrations of these ligands in these solvents were determined by UV−vis absorption spectrophotometry. Blank experiments in the absence of these receptors were carried out in all cases.

Solubility Measurements. To determine the solubility of these ligands in the various solvents, saturated solutions of calixpyrroles (**II** and **IV**) in the appropriate solvent were prepared. The mixtures were left in a thermostated bath 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 the calixpyrrole receptors in the various solvents was checked by exposing the solid to a saturated atmosphere of the appropriate solvent for several days.[21]

^{1}H NMR Measurements. ^{1}H NMR measurements were recorded at 298 K on a Brucker 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 1.6 s, acquisition time (AQ) of 1.81 s, and line broadening of 0.55 Hz. Solutions of **I**, **II**, **III**, and **IV** in the appropriate deuterated solvent ($1-5 \times 10^{-3}$ mol dm^{-3}) were placed in 5 mm NMR tubes using tetramethylsilane as the internal reference to measure the spectra of the ligands. Then additions of metal salt solutions in the same solvent ($1-2 \times 10^{-3}$ mol dm^{-3}) were made to obtain the ^{1}H NMR spectra of the metal complexes. Analyses of the interaction sites and the intensity of these

changes in the chemical shifts were carried out. Changes in the chemical shifts upon the addition of the cation salt relative to those of the free ligand were calculated.

Conductance Measurements. Conductance measurements at 298.15 K were carried out with a Wayne−Kerr autobalance universal bridge, type B642. The determination of the conductivity cell constant was performed as described elsewhere.[22] Fresh solutions of the metal ion salt and the ligands were prepared for each experimental run. For the titration experiments, the conductance cell was filled with the solution of the metal cation salt (concentration range from 4×10^{-5} to 6×10^{-3} mol dm^{-3}). After allowing the solution in the cell to attain thermal equilibrium, the ligand was added to the vessel in a stepwise titration, using a hypodermic syringe. Conductivity readings were recorded after each addition, and the molar conductance was calculated. A plot of molar conductance versus the ligand−metal ion concentration ratio was used to determine the stoichiometry of the complex.

Titration Calorimetry. Stability constants (expressed as log K_s) and enthalpies of complexation, $\Delta_c H$, of **I**−**IV** with the Hg^{2+} cation (perchlorate as the counterion) in acetonitrile were determined by calorimetry using a Tronac 450 titration calorimeter.[23] The reliability of the equipment was tested by using the protonation reaction of tris(hydroxymethyl)aminomethane (THAM) with hydrochloric acid suggested by Wilson and Smith.[24] 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}).[25] For calorimetric determinations using the Tronac 450, a solution of the ligand in the appropriate solvent (from 1×10^{-3} to 6×10^{-3} mol dm^{-3}) was titrated in a solution (50 mL) containing the mercury salt (concentration range from 5×10^{-3} to 2×10^{-2} mol dm^{-3}) in the same solvent.

Results and Discussion

Partition of Calixpyrrole Derivatives. Unlike protic solvents, dipolar aprotic solvents offer a suitable medium for dimerization. Therefore, this was investigated with the aim of identifying the speciation of these receptors in acetonitrile by evaluating the partition coefficients, K_p, of these ligands in this system over a wide range of concentrations (from 1×10^{-5} to 1×10^{-3} mol dm^{-3}). Therefore, partition data are referred to the process described in eq 1, taking acetonitrile (MeCN) as the reference solvent (s_1). In this equation, s_2 denotes hexane. In all cases, these solvents were mutually saturated (s_1 saturated with s_2 and vice versa)

$$\text{L } (s_1 \text{ saturated with } s_2) \overset{K_p}{\rightleftharpoons} \text{L } (s_2 \text{ saturated with } s_1) \quad (1)$$

The thermodynamic equilibrium (partition) constant, K_p, is defined by eq 2

$$K_p = \frac{[L]_{s_2}\gamma_{L(s_2)}}{[L]_{s_1}\gamma_{L(s_1)}} \quad (2)$$

In eq 2, $\gamma_{L(s_1)}$ and $\gamma_{L(s_2)}$ denote the activity coefficients of L in the two solvents. Since L is a nonelectrolyte and provided that low concentrations are used γ values are considered to be ~1. Thus, Table 1 reports the K_p values obtained at different concentrations of the ligand, c_i, in the acetonitrile−hexane solvent system. These data are used to calculate the standard partition Gibbs energy, $\Delta_p G°$, of these ligands, L, in this solvent system. The fact that no changes are observed in the $\Delta_p G°$ values by altering the concentrations of these ligands provides a clear indication that, within this concentration range, the monomeric species of these ligands predominate in solution. The obtained results show that the partition coefficients of calixpyrrole ligands follow the following sequence

TABLE 1: Partition Constants and Derived Partition Gibbs Energies of Calixpyrrole Derivatives in the Acetonitrile−Hexane Solvent System at 298.15 K

c^a (mol dm^{-3})	K_p	$\Delta_p G°$/kJ mol^{-1}
	calix[4]pyrrole	
1.02×10^{-4}	0.176	4.18
1.94×10^{-4}	0.178	4.15
3.96×10^{-4}	0.178	4.14
5.88×10^{-4}	0.177	4.16
7.60×10^{-4}	0.177	4.16
1.02×10^{-3}	0.177	4.16
average	0.177 ± 0.001	4.16 ± 0.01
	I	
9.82×10^{-5}	0.243	3.50
1.92×10^{-4}	0.242	3.52
3.75×10^{-4}	0.243	3.50
5.82×10^{-4}	0.239	3.55
7.52×10^{-4}	0.243	3.51
1.03×10^{-3}	0.243	3.50
average	0.242 ± 0.002	3.51 ± 0.02
	II	
2.01×10^{-4}	0.331	2.74
3.94×10^{-4}	0.330	2.75
5.98×10^{-4}	0.329	2.75
8.49×10^{-4}	0.331	2.74
9.64×10^{-4}	0.329	2.75
average	0.330 ± 0.001	2.75 ± 0.01
	III	
9.92×10^{-5}	0.482	1.81
1.96×10^{-4}	0.490	1.77
3.93×10^{-4}	0.493	1.75
5.94×10^{-4}	0.483	1.80
7.79×10^{-4}	0.482	1.81
1.02×10^{-3}	0.471	1.87
average	0.483 ± 0.008	1.79 ± 0.04

[a] c denotes the initial concentration of calixpyrrole ligands in acetonitrile.

$$\text{calix[4]pyrrole} > \textbf{I} > \textbf{II} > \textbf{III}$$

This is attributed to the decrease in the solubility of the hybrid calixpyrroles in nonaqueous solvents as the number of thiophene rings replacing the pyrrole rings in the parent calix[4]pyrrole increases.

Having determined the nature of the species in these solvents, we proceeded with the determination of the solubility of these ligands in different media at 298.15 K, as discussed below.

Solubilities and Derived Standard Gibbs Energies of Solution: Transfer Gibbs Energies from Acetonitrile. Solubility measurements were performed to ensure that calixpyrroles **II** and **IV** were soluble enough in the appropriate solvent to carry out the experimental work required for the derivation of:

(i) Thermodynamic data for the complexation process involving these ligands and various ions.

(ii) The enthalpy of solution of these ligands in the appropriate solvent. Solubility data for ligands **II** and **IV** in various solvents at 298.15 K are listed in Table 2. For comparison purposes the solubilities of calix[4]pyrrole and **I** previously reported[3,6] are also included in this table. These are the result of several analytical measurements carried out on the same equilibrium mixture. Solvate formation was observed when solid samples of receptor **II** were exposed to saturated atmospheres of chloroform and dichloromethane. Given that the calculation of the standard Gibbs energy of solution, $\Delta_s G°$, requires the same

TABLE 2: Solubility and Derived Gibbs Energies of Solution of Calix[4]pyrrole, I, II, and IV in Various Solvents at 298.15 K and Transfer Gibbs Energies from Acetonitrile (Reference Solvent)

solvent[a]	solubility (mol dm^{-3})	$\Delta_s G°$ (kJ mol^{-1})	$\Delta_t G°$ (MeCN → s)	
	calix[4]pyrrole[3]			
MeCN	$(1.39 \pm 0.05) \times 10^{-2}$	10.60	0.00	
MeOH	$(8.07 \pm 0.03) \times 10^{-3}$	11.95	1.35	
EtOH	$(6.27 \pm 0.08) \times 10^{-3}$	12.57	1.97	
DMF	$(1.36 \pm 0.04) \times 10^{-2}$	10.65	0.05	
PC	$(1.40 \pm 0.02) \times 10^{-2}$	10.58	−0.02	
hexane	$(2.36 \pm 0.07) \times 10^{-3}$	14.99	4.40	4.16[c]
	I[b]			
MeCN	$(9.38 \pm 0.05) \times 10^{-3}$	11.57	0.00	
MeOH	$(2.36 \pm 0.03) \times 10^{-3}$	15.01	3.43	
EtOH	$(3.32 \pm 0.03) \times 10^{-3}$	14.15	2.58	
$C_6H_5CH_3$	$(1.17 \pm 0.01) \times 10^{-2}$	11.02	−0.53	
DMF	$(1.85 \pm 0.04) \times 10^{-2}$	9.89	−1.68	
DMSO	$(1.06 \pm 0.04) \times 10^{-2}$	11.02	−0.55	
PC	$(3.34 \pm 0.06) \times 10^{-3}$	14.13	2.56	
C_6H_{14}	$(2.20 \pm 0.05) \times 10^{-3}$	15.17	3.60	3.51[c]
	II			
MeCN	$(6.67 \pm 0.05) \times 10^{-3}$	12.42	0.00	
MeOH	$(9.51 \pm 0.04) \times 10^{-4}$	17.25	4.83	
$C_6H_5CH_3$	$(8.34 \pm 0.01) \times 10^{-3}$	11.86	−0.56	
DMF	$(1.63 \pm 0.08) \times 10^{-2}$	10.20	−2.22	
C_6H_{14}	$(2.42 \pm 0.04) \times 10^{-3}$	14.93	2.51	2.75[c]
$CHCl_3$	very soluble			
CH_2Cl_2	very soluble			
	IV			
MeCN	$(1.73 \pm 0.23) \times 10^{-2}$	10.06	0.00	
MeOH	$(7.75 \pm 0.04) \times 10^{-4}$	17.75	7.49	
EtOH	$(5.65 \pm 0.08) \times 10^{-3}$	12.83	2.77	
DMF	$(5.10 \pm 0.03) \times 10^{-2}$	7.38	−2.68	
CH_2Cl_2	$(1.73 \pm 0.18) \times 10^{-1}$	4.35	−5.71	
DMSO	$(9.11 \pm 0.08) \times 10^{-2}$	5.94	−4.12	

[a] Abbreviations: MeCN, acetonitrile; MeOH, methanol; EtOH, ethanol; $C_6H_5CH_3$, toluene; DMF, *N*,*N*-dimethylformamide; $CHCl_3$, chloroform; CH_2Cl_2, dichloromethane; C_6H_{14}, hexane; DMSO, dimethylsulfoxide; PC, propylene carbonate. [b] Reference 6. [c] $\Delta_p G°$ values from Table 2.

composition of **II** in both phases, no further calculations were made for this ligand in these two solvents. In the absence of solvation, $\Delta_s G°$ values were calculated from $\Delta_s G° = -RT \ln s$, where s is the notation used to indicate the solubility of the ligand on the molar scale. These are listed in Table 2. These data are referred to the standard state of 1 mol dm^{-3}. As expected, the replacement of pyrrole by thiophene units (**I** and **II**) reduces the solubility of these ligands relative to calix[4]pyrrole particularly in protic media such as MeOH and EtOH. Thus, in moving from calix[4]pyrrole to **I** and **II**, there is an increase in the standard solution Gibbs energy of the process by ~3 and 5 kJ mol^{-1}, respectively, in MeOH. As the number of pyrrole units decreases, the solubility decreases. This may be partially attributed to a reduction in the number of hydrogen bonds that are likely to occur between the pyrrole units and the alcohols.

Since both the crystal lattice, $\Delta_{cl} G°$, and the solvation Gibbs energies, $\Delta_{solv} G°$, contribute to $\Delta_s G°$ values, the contribution of the former process is removed by the calculation of the standard transfer Gibbs energies, $\Delta_t G°$, of **II** and **IV** from a reference (s_1 = MeCN) to another solvent, s_2. These data reflect the difference in solvation of these receptors in s_2 relative to s_1 and are also included in Table 2. The variations observed in $\Delta_t G°$ values for **II** from MeCN to the various solvents are rather small ranging from 4.83 to −2.22 kJ mol^{-1} in transfers to methanol and DMF, respectively. Therefore the solvation of these ligands is unlikely to contribute significantly to the strength of complexation (or lack of it) of these macrocycles and ionic species as a result of the medium effect. The same conclusion applies to ligand **IV**. It is of interest to compare the $\Delta_t G°$ values referred to the process in which the pure solvents are involved with the $\Delta_p G°$ values for these ligands in the acetonitrile−hexane solvent system. The agreement found between the two sets of data for calix[4]pyrrole, calix[3]thieno[1]pyrrole, **I**; and calix[2]thieno[2]pyrrole, **II**, is typical of solvent systems of very low mutual solubility.[26,27]

TABLE 3: ^{1}H NMR Chemical Shifts (δ, ppm) and Chemical Shift Changes ($\Delta\delta$, ppm) (Relative to $CDCl_3$) of Calixpyrrole and its Derivatives in CD_3CN and d_6-DMSO at 298 K

	$CDCl_3$	CD_3CN		d_6-DMSO	
	δ (ppm)	δ (ppm)	$\Delta\delta$ (ppm)	δ (ppm)	$\Delta\delta$ (ppm)
		calix[4]pyrrole			
H_{NH}	7.05	7.49	0.35	9.27	2.22
$H_{pyrrole}$	5.90	5.79	−0.11	5.70	−0.20
H_{methyl}	1.51	1.48	−0.02	1.52	0.01
		I			
H_{NH}	7.00	7.42	0.41	8.58	1.57
H_{NH}	7.39	7.84	0.45	9.11	1.72
$H_{pyrrole}$	5.87	5.77	−0.10	5.73	−0.14
$H_{pyrrole}$	5.94	5.85	−0.10	5.70	−0.24
$H_{thiophene}$	6.64	6.65	0.01	6.69	0.04
H_{methyl}	1.53	1.50	−0.02	1.50	−0.02
H_{methyl}	1.60	1.55	−0.04	1.54	−0.06
		II			
H_{NH}	7.12	7.70	0.58	9.21	2.09
$H_{pyrrole}$	5.90	5.79	−0.11	5.69	−0.21
$H_{thiophene}$	6.71	6.68	−0.02	6.66	−0.05
H_{methyl}	1.65	1.58	−0.07	1.56	−0.08
		III			
$H_{N-methyl}$	2.79	2.87	0.08	2.72	−0.07
$H_{pyrrole}$	6.01	5.99	−0.02	5.75	−0.20
$H_{thiophene}$	6.65	6.65	0.00	6.60	−0.05
H_{methyl}	1.55	1.63	0.08	1.48	−0.07
		IV			
H_{NH}	7.45	8.28	0.83	9.87	2.42
$H_{pyrrole}$	5.90	5.64	−0.26	5.65	−0.25
$H_{thiophene}$	6.72	6.58	−0.14	6.90	0.18
H_{methyl}	1.53	1.47	−0.06	1.24	−0.29

To assess the sites of interactions of the receptors upon complexation with Hg(II), ^{1}H NMR measurements in CD_3CN were carried out at 298 K, and these are now discussed.

^{1}H NMR Measurements. The ^{1}H NMR spectra of sulfur-containing hybrid calixpyrrole ligands and alkali, alkaline-earth, heavy, and transition metal cations were measured in CD_3CN and d_6-DMSO at 298 K. The perchlorate anion was used as a counterion due to its lack of interaction with these macrocycles.[3]

The aim of this study was to obtain information regarding the interaction of calixpyrrole ligands with solvents and the sites of interaction of these ligands with metal cations. Chemical shift (δ, ppm) and chemical shift changes ($\Delta\delta$, ppm) relative to $CDCl_3$ for calix[4]pyrrole, **I**, and **II** in CD_3CN and d_6-DMSO are listed in Table 3. The ^{1}H NMR data for the free ligands in these solvents show significant downfield shifts in the NH protons in moving from $CDCl_3$ to CD_3CN and d_6-DMSO. However, a marked shielding effect is recorded for the pyrrolic protons in moving from $CDCl_3$ to CD_3CN and d_6-DMSO. As far as d_6-DMSO is concerned, this is a protophilic dipolar aprotic solvent and therefore able to interact with calixpyrroles through hydrogen bond formation between the pyrrolic protons and the basic oxygen of the solvent. The larger deshielding effect reported for the pyrrolic protons of free calixpyrrole ligands in

TABLE 4: Changes in the ^{1}H NMR Chemical Shifts ($\Delta\delta$ in ppm) for Calix[4]pyrrole, I−IV, and Their Hg(II) Complexes in CD_3CN at 298 K[a]

calix[4]pyrrole							
		H_{methyl}		$H_{pyrrole}$		H_{NH}	
free ligand		1.48		5.79		7.49	
Hg(II)		−0.07		−0.04		0.08	
I							
	H_{methyl}	H_{methyl}	$H_{pyrrole}$	$H_{pyrrole}$	$H_{thiophene}$	H_{NH}	H_{NH}
free ligand	1.51	1.55	5.77	5.85	6.65	7.42	7.84
Hg(II)	0.06	0.09	0.03	0.27	0.24	0.74	0.88
II							
	H_{methyl}		$H_{pyrrole}$		$H_{thiophene}$		H_{NH}
free ligand	1.58		5.79		6.68		7.70
Hg(II)	−0.02		0.15		0.33		0.98
III							
	H_{methyl}		$H_{pyrrole}$		$H_{thiophene}$		$H_{N-methyl}$
free ligand	1.63		5.99		6.65		2.88
Hg(II)	−0.05		0.35		0.33		−0.03
IV							
	H_{methyl}		$H_{pyrrole}$		$H_{thiophene}$		H_{NH}
free ligand	1.55		5.76		6.58		7.55
Hg(II)	0.01		0.20		0.47		

[a] No chemical shift changes were observed by adding other metal cation salts to these ligands in CD_3CN.

d_6-DMSO relative to CD_3CN (Table 3) explains the difference in the solvation of these receptors in the former solvent relative to the latter solvent (Table 2).

For comparison purposes, the parent calix[4]pyrrole was investigated for its interaction with the Hg(II) cation in CD_3CN at 298 K. The insignificant chemical shift changes found for the NH ($\Delta\delta = 0.08$ ppm) and pyrrolic protons ($\Delta\delta = -0.04$ ppm) suggest the absence of complexation between this ligand and the Hg(II) cation in acetonitrile (Table 4). This is also indicative of the incapability of the NH groups of the pyrrole units to bind with the Hg(II) cation in acetonitrile.

^{1}H NMR data for **I** and the mercury cation in deuterated acetonitrile at 298 K are also reported in Table 4. No chemical shift changes are observed for other cations and this ligand in this solvent. As far as mercury(II) is concerned, the downfield shift change in the thiophene protons upon complexation of **I** ($\Delta\delta = 0.24$ ppm) suggests that the interaction takes place through the sulfur donor atom of the thiophene ring. The significant chemical shift changes of the pyrrole protons ($\Delta\delta = 0.27$ ppm) may be attributed to the change in the conformation of **I** upon complexation. ^{1}H NMR studies carried out with **II** and the Hg(II) cation at 298 K are shown in Table 4. The same behavior as that observed for **I** was found upon complexation of **II** with the Hg^{2+} cation where significant chemical shift changes were observed for the thiophene ($\Delta\delta = 0.33$ ppm) and pyrrole ($\Delta\delta = 0.15$ ppm) protons. Inspection of the difference in the chemical shift values in Table 4 reveals that receptor **IV** interacts with Hg^{2+} through the sulfur donor atoms as the thiophene protons experience significant deshielding ($\Delta\delta = 0.47$ ppm) upon complexation.

In addition, the significant chemical shift changes recorded for the NH protons of **I** (0.74 ppm) and **II** (0.98 ppm) may be caused by changes in the conformation of these ligands upon complexation with the Hg(II) cation. This conclusion is based on:

(i) The absence of complexation between calix[4]pyrrole and Hg(II) cation in acetonitrile as indicated by the insignificant chemical shift changes of NH and pyrrolic protons upon the addition of an excess amount of Hg(II) to this ligand in this solvent at 298 K (Table 4).

(ii) The significant chemical shift changes of the thiophene protons upon complexation of the sulfur-containing calixpyrrole ligands with Hg(II) cation in acetonitrile, which was not the case when the medium effect was assessed (Table 3).

(iii) The increase in the chemical shift change of the pyrrolic protons of **III** (0.35 ppm) as compared with that of **II** (0.15 ppm) upon complexation with Hg(II) cation in acetonitrile, which is attributed to the $N-CH_3$ groups of the former ligand.

However, the resonance value for the NH group of **IV** is not reported due to the broadness of its peak. This observation also indicates that the Hg(II) cation is not interacting through the NH binding site; if it was, then the NH resonance is unlikely to be observed in the ^{1}H NMR spectrum.[28] To gain further information about the role of the NH functionalities of the pyrrole units in the complexation process, the interaction of **III** with metal cations was investigated. As can be inferred from Table 4, when the two NH groups in **II** are replaced by NCH_3 (**III**), significant chemical shift changes were observed for the pyrrolic and the thiophenic protons upon complexation of **III** with the Hg(II) cation. The large difference in the chemical shift changes of the pyrrolic protons between **II** and **III** is attributed to the N-methyl groups of the latter ligand. However, the chemical shift changes of the thiophenic protons of **III** ($\Delta\delta = 0.33$ ppm) are not affected by the presence of the NCH_3 groups in the ligand.

The complexation of these macrocycles with alkali, alkaline-earth, heavy, and transition metals in d_6-DMSO was also investigated. The insignificant chemical shift changes upon the addition of the metal ion salt to the ligand solution suggest the absence of interaction of these cations with these ligands in this solvent. Hence, the contribution of the hydrogen bonding between d_6-DMSO and the calixpyrrole ligands might explain the absence of interaction of these macrocycles with the metal cations in DMSO. In addition, metal cations are well solvated in DMSO as reflected in the transfer Gibbs energies from water to DMSO.[29,30]

Encouraged by the NMR results, conductance measurements were carried out to establish the composition of the Hg(II) complexes and to gain semiquantitative information regarding the strength of complexation of these ligands with Hg(II) in acetonitrile. The results are discussed in the following section.

Conductometric Titrations. Conductometric titrations in acetonitrile showed that among the metal cations investigated the complexation of mercury(II) with ligands **I**−**IV** in this solvent leads to a well-defined change in the curvature at the stoichiometry of the reaction, suggesting moderate stability of complex formation. However, the straight line obtained for the conductometric titration of calix[4]pyrrole with the Hg(II) cation suggests a weak or nonexistent complexation between this ligand and this cation in acetonitrile. Thus plots of molar conductance (Λ_m, S cm^2 mol^{-1}) versus the ligand/Hg^{2+} cation molar ratio in acetonitrile are shown in Figure 1. Since the electrolyte salt was placed in the conductance vessel, the decrease in conductivity on addition of the ligand is attributed to the large size of the complexed cation compared with that of the free cation. Therefore, the point of intersection corresponding to the stoichiometry of the reaction is obtained by extrapolating the slope of the curve at low and high ligand/Hg(II) cation ratios

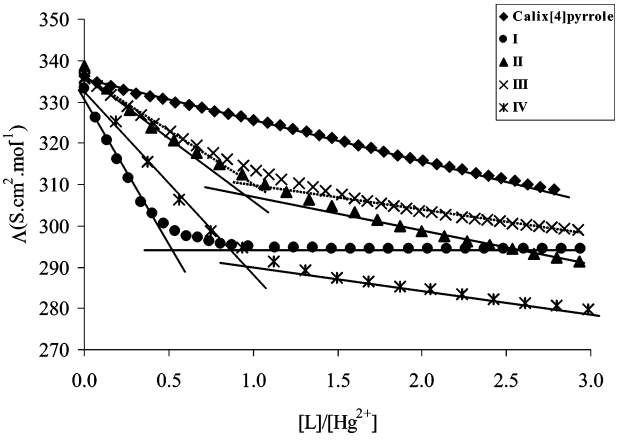

Figure 1. Conductometric titration curves of mercury(II) (as perchlorate) with **I**−**IV** in MeCN at 298.15 K.

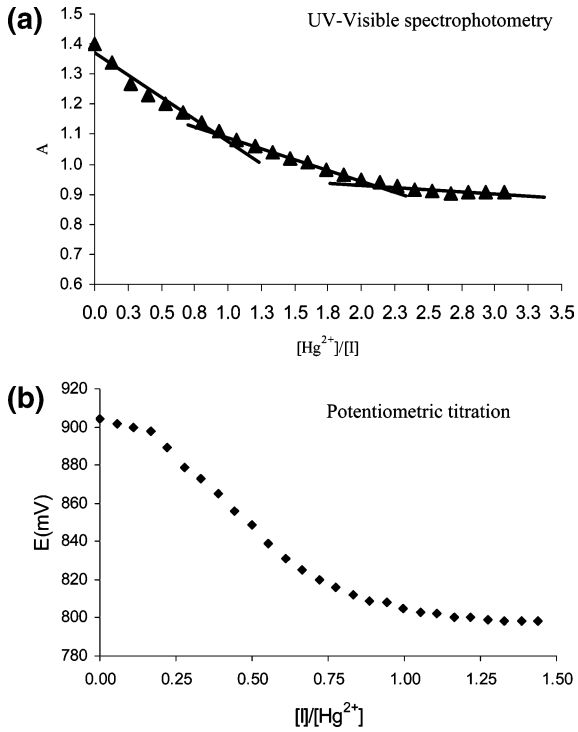

Figure 2. (a) Absorbance data (at 215 nm) vs mercury cation/**I** molar ratio in acetonitrile at 298 K. (b) Potential vs **I**/mercury cation molar ratio in acetonitrile at 298 K.

to give 1:1 (ligand/Hg^{2+}) complexes with **II**, **III** and **IV** and a 1:2 (ligand/Hg^{2+}) complex with **1**.

The 1:2 stoichiometry complex obtained by conductance measurements for the complexation of **I** (with only one sulfur donor atom) with the Hg(II) cation in acetonitrile was also corroborated by UV−vis spectrophotometric and potentiometric titrations. Thus, the absorbance data at 215 nm were plotted versus the Hg(II)/**I** molar ratios (Figure 2a). The points of intersection at 1:1 and 2:1 Hg(II)/**I** molar ratios suggest that two Hg(II) cations are taken up by one unit of ligand. The same complex composition was also derived from potentiometric titration as shown in Figure 2b where potential changes are plotted as a function of **I**/Hg^{2+} cation molar ratio. Therefore, the results from conductometric, UV spectrophotometric, and potentiometric titrations are in agreement regarding the composition of the complex.

^{1}H NMR data in d_6-DMSO suggested that the ligand may interact with this solvent (protophilic dipolar aprotic solvent) through hydrogen bond formation. Dimethylsulfoxide is known to be a good cation solvator.[31] We have previously shown that a good solvating medium for the reactants is not a suitable medium for complexation.[32] As a result, very weak or no complexation occurs between calixpyrrole ligands and Hg(II) in DMSO. No changes in conductance were observed when other metal cation salts were titrated with these ligands.

TABLE 5: Thermodynamic Parameters for the Complexation of Hg^{2+} (Perchlorate as the Counterion) and I−IV in Acetonitrile at 298.15 K

ligand	Hg^{2+}/L	log K_s	$\Delta_sG°$ (kJ mol^{-1})	$\Delta_sH°$ (kJ mol^{-1})	$\Delta_sS°$ (J mol^{-1} K^{-1})
I	1:1	6.9 ± 0.1^a	-39.1 ± 0.5	-70.5 ± 0.7^b	−105
	2:1	5.89 ± 0.07^a	-33.6 ± 0.4	0	112
II	1:1	4.00 ± 0.02^b	-22.6 ± 0.1	-37.8 ± 0.1^b	−51
III	1:1	3.85 ± 0.01^b	-21.9 ± 0.1	-17.6 ± 0.1^b	15
IV	1:1	2.96 ± 0.06^b	-16.9 ± 0.3	-71.6 ± 0.4^b	−184

[a] Potentiometry. [b] Calorimetry.

In the following section, the thermodynamics of complexation of **I**−**IV** with Hg(II) in acetonitrile at 298.15 K are discussed.

Thermodynamics of Complexation. Solution calorimetry has been used to obtain thermodynamic parameters that provide quantitative information about the strength of the complexation process. For strong complexes (log K_s > 6) stability constants were determined by potentiometry. The first step in the thermodynamic investigation of the complexation process is the formulation of an equation representative of the binding process taking place in solution. Having determined the composition of the host−guest complex and the speciation of the receptors in acetonitrile, the next step was to establish that the free and complex mercury electrolytes are predominantly ionic species in solution. We have previously shown that in acetonitrile[33] the free and complexed salts exist in their ionic forms within the concentration range used for the determination of the thermodynamic parameters derived from titration calorimetry.

For ligand−mercury ion complexation in acetonitrile at 298.15 K, the stability constant (expressed as log K_s), standard Gibbs energies, $\Delta_cG°$, enthalpies, $\Delta_cH°$, and entropies, $\Delta_cS°$, as determined by titration calorimetry are listed in Table 5.

Therefore, from the information gained from conductance and partition measurements, thermodynamic data for 1:1 complexes of calix[4]pyrrole (L = **II**, **III**, and **IV**) and Hg^{2+} are referred to the process shown in eq 3

$$Hg^{2+}\,(MeCN) + L\,(MeCN) \rightarrow Hg^{2+}L\,(MeCN) \qquad (3)$$

The complexation processes of these ligands with the Hg(II) cation in acetonitrile are enthalpically controlled while the processes are not entropically stabilized for ligands **II** and **IV**. However, the favorable entropy change for the complexation of the mercury cation with calixpyrrole **III** indicates that both the enthalpy and the entropy contribute to the stability of the complex.

Conductometric, spectrophotometric, and pontentiometric measurements reveal that **I** is able to host two mercury cations. However, the enthalpy change obtained by the calorimetric titrations upon complexation of **I** with Hg(II) in acetonitrile vanished after the formation of the 1:1 (**I**/Hg^{2+}) complex. This observation suggests that the second process (1:2 complex) in acetonitrile is entropically controlled, and therefore it was not possible to derive its stability constant by calorimetric titration. Consequently, the stability constant was obtained from potentiometric titrations. As far as the first process is concerned, the complexation of **I** with Hg(II) cation in acetonitrile is enthalpically controlled.

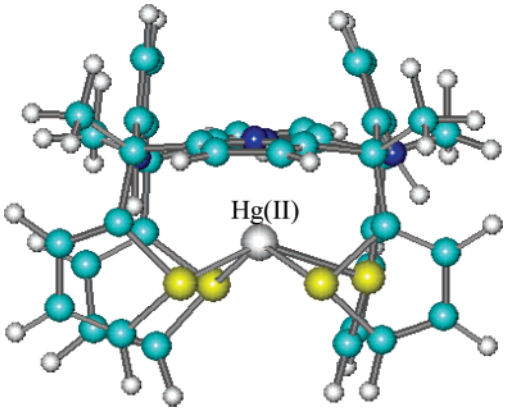

Figure 3. Molecular modeling of the **IV**−Hg^{2+} complex as determined by simulation studies.

Regarding the interaction of calixpyrrole, **I**, with Hg^{2+}, ^1H NMR investigations revealed that the mercury ions are interacting via the sulfur atoms. Molecular modeling (using the HyperChem Lite computer program) was carried out to find the preferred geometry of the lowest energy of this system. On the basis of the partition experiments, the possibility of **I** to be found in its dimeric form was excluded. As a result the geometry obtained for the lowest energy conformation of the free ligand was used as the starting structure. Energy minimization for various complex models was repeated several times to find the global minima. However, we can neither unambiguously distinguish between the favorable complex structures nor exclude the formation of any other models from the proposed ones. Therefore, attempts to obtain suitable crystals for X-ray measurements are in progress, but at this stage no explanation for this unusual complex composition can be offered.

It is interesting to compare the thermodynamic parameters for the complexation of the various calixpyrrole ligands with the Hg^{2+} cation in acetonitrile. As can be seen from Table 5, the lower stability constant obtained for the complexation of **IV** with the Hg(II) cation in acetonitrile suggests that complex formation of this ligand with this cation is not driven by equal participation of all sulfur donor atoms due to the possible electrostatic repulsion between these donor atoms in the thiophene units upon complexation. In fact, examination of the molecular modeling for the **IV**−Hg^{2+} system (Figure 3) reveals that calixpyrrole **IV** experiences large conformational changes upon complexation with Hg^{2+} due to the less symmetrical arrangement of the donor atoms in **IV,** leading to poor host preorganization, as reflected in the low stability constant (log $K_s = 2.96$) in this solvent.

Another striking thermodynamic feature is the variation of the standard enthalpies and entropies of complexation of calixpyrroles **II** and **III** with the Hg^{2+} cation, although the stabilities of both complexes are very similar as reflected in the log K_s values. Within this context, it is interesting to point out that the complexation stability of **II** with Hg^{2+} is totally enthalpy-driven, affording a negative $\Delta_c S°$ value (-51 J mol^{-1} K^{-1}). However, the similar complex stability value obtained for the complexation of **III** with the Hg(II) results from the favorable contributions of both the enthalpy and the entropy. The possibility of ligand **III**, containing N-methyl substituents, to lock the ring conformation and to undergo substantial conformational changes upon complexation cannot be excluded. This statement is corroborated by ^1H NMR studies that established that the pyrrolic protons of **III** undergo significant chemical shift changes upon complexation with the Hg(II) cation in acetonitrile (Table 4).

Conclusions

(1) Mercury(II) selective macrocycles resulting from the replacement of pyrrole by thiophene unit(s) in the parent calix[4]pyrrole have been successfully characterized. Partition experiments demonstrated that, within the ligand concentration range investigated, the monomeric species of these receptors are predominant in solution.

(2) Solubility data show that as the number of thiophene units increases the solubility decreases. This effect mostly observed in the alcohols is partially attributed to the reduction in the number of NH groups that are likely to enter hydrogen bonding with these solvents. Comparison between the partition (involving the mutually saturated solvents) and the transfer (involving the pure solvents) standard Gibbs energies of the calixpyrrole receptors in the hexane−acetonitrile solvent system indicates that the mutual solubility of these solvents is very low.

(3) ^1H NMR investigations in CD_3CN at 298 K show that receptors **I**−**IV** interact with the mercury(II) cation through the sulfur donor atoms of the thiophene rings. These ligands experienced substantial conformational changes upon complexation with Hg(II). This fact is corroborated by (i) the significant chemical shift changes in the NH and pyrrolic protons in moving from $CDCl_3$ (reference solvent) d_6-DMSO and (ii) the absence of interaction between the parent calix[4]pyrrole (four NH functional groups) and the mercury(II) cation in CD_3CN.

(4) Conductance measurements established that calixpyrrole **I** forms a 2:1 (Hg(II)/ligand) complex in acetonitrile at 298.15 K. This stoichiometry was also verified by potentiometric and UV−vis spectrophotometric studies. Unlike **I**, receptors **II**, **III**, and **IV** were found to interact with one Hg(II) cation per unit of ligand.

(5) The presence of the soft donor atoms has tuned the anion selectivity of calix[4]pyrrole. In fact, among the cations considered, its thiophene hybridized derivatives interact specifically rather than selectively with the Hg(II) cation in CD_3CN. The complexation processes of calixpyrrole derivatives (**I**, **II**, and **IV**) with the Hg(II) cation are enthalpically stable. However, the complexation process of the N-methyl-substituted calixpyrrole, **III**, with this cation in acetonitrile is both enthalpically and entropically controlled.

In the light of the above results we are currently investigating the capability of the polymeric material of calixpyrrole **IV** to remove the Hg(II) cation from aqueous solution. Physical and chemical parameters that might enhance the extraction process are to be examined in this study.[34]

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