A Calix(4)arene Pyridine Derivative and Its Monomeric Component: Structural and Thermodynamic Aspects of Their Complexation with Metal Cations

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The interaction of a calix(4)arene derivative, namely 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetra[2-(4-pyridyl)-methoxy]calix(4)arene, **1a**, and its monomeric component, *p-tert*-butylphenoxy-4-pyridine, **1b**, with metal cations has been investigated in acetonitrile and methanol. ^{1}H NMR measurements carried out in CD_3CN show the primary role played by the pyridyl nitrogens in their complexation with metal cations. Conductance measurements demonstrated that for all cations (except mercury) the composition of the metal ion complexes of **1a** is 1:1 (ligand:metal cation). However, **1a** hosts two mercury cations per unit of ligand. For the monomer **1b**, complexes of 2:1 (ligand:metal cation) stoichiometries are formed with the exception of Pb^{2+} (1:1 composition). The thermodynamics of complexation of these systems are reported in acetonitrile. Data in methanol are limited to stability constant values for mercury(II) and these ligands. This paper demonstrates for the first time that thermodynamic data for the complexation of the monomeric component of the ligand and metal cations contribute significantly to the interpretation of systems involving cation−calixarene interactions in solution.

Introduction

It has been widely demonstrated that calixarenes are excellent platforms for the design of receptor sites for binding ions and molecules.[1−4] Depending on the nature of the functional groups at the lower rim, calixarene derivatives show different and interesting complexing abilities.

Pyridinocalix[4]arenes have three structural isomers. The ability of these derivatives to interact with metal cations (hard or soft) appears to be largely dependent on the position of the nitrogen atoms of the pyridyl ring with respect to the ethereal oxygens,[5−8] although limited investigations have been carried out. The availability of one of these derivatives, namely, 5,-11,17,23-tetra-*tert*-butyl-25,26,27,28-tetra[2-(4-pyridyl)methoxy]-calix(4)arene referred to throughout the text as the 4-pyridinocalix-[4]arene (**1a**), led to the following work goals.

(i) The investigation of this derivative in its interaction with metal cations in nonaqueous media: For this purpose, ^{1}H NMR studies in CD_3CN were carried out with the aim of assessing the active sites of interaction of the macrocycle with these cations in this medium. These were followed by conductometric studies which were conducted for two purposes: (a) the determination of the composition of the metal−ion complex (conductometric titration) and (b) establishing the concentration range at which both the free and complex metal−ion salts are predominantly in their ionic forms in solution.

(ii) A quantitative assessment of the strength of the interaction of **1a** and metal cations in acetonitrile through the thermody-namic characterization of the complexation process: Depending on the magnitude of the stability constant, calorimetry and potentiometry were the techniques used to derive these data.

To explain the ^{1}H NMR and the thermodynamic data resulting from these studies, further investigations were carried out involving (a) complexation studies with *p-tert*-butylphenoxy 4-pyridine (**1b**; the monomeric component of **1a**) with metal cations in the same media and (b) molecular modeling with a HyperChem Lite computer program.

Experimental Section

Chemicals. Potassium iodide and carbonate, *p-tert*-butylphe-nol 99%, 4-picolyl chloride hydrochloride 97%, 18-crown-6, lead(II) perchlorate trihydrate 98%, cadmium(II) perchlorate hydrate, mercury(II) perchlorate 98%, zinc, copper, and nickel perchlorate salts as hexahydrates, deuterated acetonitrile (CD_3-CN), and methanol (CD_3OD) were purchased from Aldrich Chemical Co. All perchlorate salts were dried over P_4O_{10} under vacuum for several days before use.

Tris(hydroxymethyl)aminomethane, ultrapure grade 99.9% also purchased from Aldrich, was used without any further purification.

Acetonitrile, methanol, and dichloromethane (HPLC grade, Fisher UK Scientific International) were used. Acetonitrile was refluxed under a nitrogen atmosphere and distilled over calcium hydride.[9] The middle fraction of the distilled solvent was collected and the water content of the solvent was not higher than 0.02%. Tetra-*n*-butylammonium perchlorate, TBAP, Fluka, 99% electrochemical grade, was used without further purifica-tion.

Synthesis of 1a and 1b. The compound **1a** was synthesized and characterized as described elsewhere.[10] However, the

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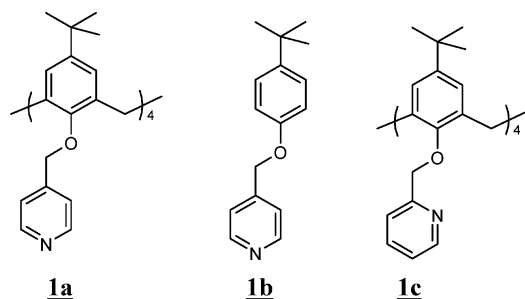§ University of Cadi Ayyad.

Figure 1. Structures of **1a**, **1b**, and **1c**.

monomer, **1b**, was prepared from 4-picolyl chloride hydrochloride (3.28 g, 20 mmol) and potassium carbonate (8.4 g, 60.8 mmol) in acetonitrile. The mixture was stirred under a nitrogen atmosphere for 30 min. Then potassium iodide (3.84 g, 23.1 mmol) was added and the mixture was heated under vigorous stirring at 70 °C for 1 h. A violet suspension was observed. After the solution was cooled, *p-tert*-butylphenol (2 g, 13.31 mmol), 18-crown-6 (0.1 g, 0.38 mmol), and potassium carbonate (3.4 g, 24.60 mmol) were added into the flask and the reaction was left for 12 h at 60 °C. The reaction was monitored by TLC, using an hexane:ethyl acetate (4:1) mixture as the developing solvent system. After the mixture was cooled, the solvent was removed under reduced pressure. The solid afforded was dissolved in dichloromethane and extracted with an aqueous solution of HCl (0.2 mol dm^3). The organic layer was collected and dried with MgSO$_4$, then filtered. The solvent was removed and a brown oil was obtained. Hexane (20 mL) was added to a round-bottomed flask containing the product until a precipitate appeared. This was filtered off and recrystallized from ethanol and acetone. White crystals were obtained (yield 78%). Microanalysis carried out for C$_{16}$H$_{19}$NO, calculated: C, 79.63, H, 7.94, N, 5.80. Found: C, 79.52, H, 7.80, N, 5.83.

^{1}H NMR (CDCl$_3$) (300 MHz), δ (ppm) 1.30 (s, 9H), 5.08 (s, 2H), 6.89 (d, 2H, $J = 9$ Hz), 7.32 (d, 2H, $J = 6$ Hz), 7.35 (d, 2H, $J = 9$ Hz), 8.62 (d, 2H, $J = 10$ Hz).

^{1}H NMR Measurements. ^{1}H NMR measurements were recorded at 298 K with 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°, a spectral frequency (SF) of 300.135 MHz, a delay time of 1.60 s, an acquisition time (AQ) of 1.819 s, and line broadening of 0.55 Hz.

Solutions of the samples under investigation were prepared in the appropriate deuterated solvent and then placed in 5 mm NMR tubes with TMS as the internal reference.

The complexation behavior of the ligands (**1a**, **1b**) toward cations was studied by adding the metal–ion salt (6.0 × 10^{-3} to 2.2 × 10^{-2} mol dm^{-3}) into the NMR tube containing a solution of the ligand dissolved in the same solvent (8.2 × 10^{-4} to 2.0 × 10^{-3} mol dm^{-3}). Stepwise additions of the metal–ion salt were made and chemical shifts were recorded. Changes in chemical shifts upon addition of the metal–ion salt relative to the free ligand were calculated.

Conductance Measurements. For these measurements, a Wayne Kerr Autobalance Universal Bridge, B642, was used. Conductometric titrations at 298.15 K for the determination of the cell constant and the composition of complexes formed were performed as described elsewhere.[11]

Potentiometric Measurements. Potentiometric measurements were carried out with a Metrohm 716 DMS Titrino automatic titrator containing a 728 stirrer module (Metrohm) equipped with a calomel (Hg/Hg$_2$Cl$_2$/KCl) reference double

junction electrode (Russell). Its internal electrolyte was filled with a saturated solution of LiCl in ethanol, while the external electrolyte was filled with a solution of TBAP (0.05 mol dm^{-3}) in acetonitrile or methanol. The concentration of the free mercury ion was measured with a mercury amalgam indicator electrode. Both electrodes were connected to a compact automatic titrator processor Metrohm 716 DMS Titrino. All titrations were performed at 298.15 ± 0.10 K in a water jacketed vessel. Before each measurement, the electrode was calibrated by incrementally titrating a solution of Hg(ClO$_4$)$_2$ (∼2.5 × 10^{-3} mol dm^{-3}) into the vessel containing a solution of TBAP in the appropriate solvent (20 cm^3, 0.05 mol dm^{-3}). Nernstian behavior was observed in all cases. The data were collected by a Hyperaccess System. This was followed by the titration of the ligand solutions (**1a** or **1b**, ∼1.5 × 10^{-3} mol dm^{-3} prepared in a 0.05 mol dm^{-3} TBAP solution) into the vessel containing the Hg^{2+} solution. The change in the potential was recorded and the Hyperquad program[12] was used to calculate the stability constant values derived from these measurements. All titrations were carried out in triplicate and an average stability constant value was calculated.

Calorimetric Titrations. Stability constants (log K_s) and enthalpies, $\Delta_c H°$, of complexation of **1a** and **1b** with metal cations in the appropriate solvent at 298.15 K were determined by calorimetric titrations with use of the Tronac 450 and the Thermometric 2277 activity monitor, TAM, calorimeters.
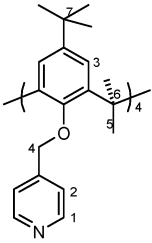
The Tronac 450 calorimeter was used as an isoperibol titration calorimeter.[13] The reproducibility of the apparatus was checked by determining the enthalpy of protonation of tris(hydroxymethyl)aminomethane (THAM) in water at 298.15 K. For this purpose, an aqueous solution of THAM (1.0 × 10^{-3} mol dm^{-3}) was titrated with hydrochloric acid (HCl, 0.1 mol dm^{-3}) at 298.15 K.[14] The value determined, −47.48 ± 0.08 kJ mol^{-1}, is in agreement with the one reported by Hill, Öjelund, and Wadsö[15] using an LKB reaction calorimeter.
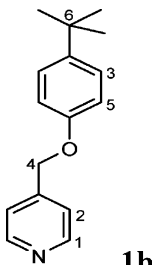
As far as complexation studies are concerned, for stability constant values lower than 10^6 (log K_s = 6), direct calorimetric titrations were performed. Thus a solution of **1a** (50 cm^3, 7.0 × 10^{-4} to 2.0 × 10^{-3} mol dm^{-3}) in acetonitrile was placed in the calorimetric vessel. The whole system was then immersed in a thermostated bath at 298.15 K and left to reach thermal equilibrium. Then the appropriate metal–ion salt (as perchlorate) (2.0–6.0 × 10^{-2} mol dm^{-3}) was prepared in the same solvent, placed in the buret, and titrated into the vessel containing the solution of **1a**.

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

For direct measurements performed with the four-channel heat conduction calorimeter (Thermometric, 2277 Thermal Activity Monitor, TAM) designed by Suurkuusk and Wadsö,[16] electrical (static and dynamic) and chemical calibrations were carried out to check the reliability of the equipment.[17] For complexation studies, the reaction vessel was charged with the ligand (**1b**, 6.0 × 10^{-4} to 1.5 × 10^{-3} mol dm^{-3}, 2.8 cm^3) in the appropriate solvent. The metal–ion salt (1.4 × 10^{-2} to 3.5 × 10^{-2} mol dm^{-3}) was injected incrementally, using a 0.5 cm^3 gastight motor driven Hamilton syringe. In each titration experiment, about 25 injections were made at time intervals of 30–45 min. For the calculations, 15 data points before the end point were considered. Corrections for the enthalpy of dilution of the titrant

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TABLE 1: Chemical Shift Changes ($\Delta\delta$ ppm) in the ^{1}H NMR Spectra of 1a[a] and 1b[b] with the Addition of Metal Cations in CD$_3$CN at 298 K

1a	H-1	H-2	H-3	H-4	H-5	H-6	H-7
Zn^{2+}	0.22	0.65	0.03	0.29	−0.17	0.12	0.03
Hg^{2+}	0.21	0.62	0.03	0.25	−0.17	0.12	0.04
Cd^{2+}	−0.15	0.18	0.05	−0.02	0.12	0.26	0.02
Pb^{2+}	0.15	0.50	0.03	0.21	−0.12	0.12	0.03
Ag^{2+}	0.01	0.28	0.07	0.03	0.23	0.27	0.04

1b	H-1	H-2	H-3	H-4	H-5	H-6	H-7
Zn^{2+}	0.22	0.65	0.03	0.29	−0.17	0.12	0.03
Hg^{2+}	0.21	0.62	0.03	0.25	−0.17	0.12	0.04
Cd^{2+}	−0.15	0.18	0.05	−0.02	0.12	0.26	0.02
Pb^{2+}	0.15	0.50	0.03	0.21	−0.12	0.12	0.03

[a] Chemical shift of the free ligand (ppm): H-1 = 8.43; H-2 = 7.20; H-3 = 7.18; H-4 = 4.81; H-5 = 4.14; H-6 = 3.0; H-7 = 1.16. [b] Chemical shift of the free ligand (ppm): H-1 = 8.56; H-2 = 7.38; H-3 = 6.92; H-4 = 5.12; H-5 = 7.29; H-6 = 1.28.

in the solvent were carried out in all cases. 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 ($\Delta_c H°$) for the process under study.

Results and Discussion

^{1}H NMR Studies. ^{1}H NMR measurements involving **1a** and **1b** and metal cations (Zn^{2+}, Hg^{2+}, Cd^{2+}, and Pb^{2+}) as perchlorates in CD$_3$CN and CD$_3$OD at 298 K were carried out. Due to the paramagnetic effect of Cu^{2+}, Co^{2+}, and Ni^{2+}, the ^{1}H NMR spectra of their complexes could not be investigated.

Chemical shift changes upon the addition of the corresponding salt to the appropriate ligand in CD$_3$CN are shown in Table 1. Chemical shifts for the free ligands are also included in this table. The pair of doublets observed for the bridging methylene protons (H-5 and H-6) in **1a** provides evidence that this ligand adopts a "*cone*" conformation in solution. It is also observed that the chemical shift separation of the proton signals of the methylene bridge in **1a** ($\Delta\delta$ 1.14 ppm) decreases to 0.85, 0.95, 0.98, and 1.00 ppm for Zn^{2+}, Hg^{2+}, Cd^{2+}, and Pb^{2+}, respectively, suggesting that the ligand adopts a more symmetrical "cone" conformation upon complexation.

The data in Table 1 show that the addition of Zn^{2+} to **1a** deshields most of the protons and the magnitude of the signal changes follows the sequence H-2 > H-4 > H-1 > H-6 > H-5. In fact the proton signal changes caused by Zn^{2+} follow the same order as those found for Hg^{2+} and Pb^{2+}. However, the actual values are quite close to those shown by Hg^{2+}. The

deshielding of H-2 (0.65, 0.62, and 0.50 ppm for Zn^{2+}, Hg^{2+}, and Pb^{2+}, respectively) is a result of a reduction of the electron density in the pyridine ring by donation of the nitrogen lone pair and by reduction of the ring current. The changes in the proton chemical shifts of **1a** produced by the addition of cadmium(II) are neither as large nor do these follow the same sequence as those produced by the addition of Zn^{2+}, Hg^{2+}, and Pb^{2+}. Both the H-5 (axial) and H-6 (equatorial) signals of **1a** became deshielded as a result of the interaction of **1a** with Cd^{2+}, while for the other cations, H-5 is shielded and H-6 deshielded. In the presence of Cd^{2+}, the H-1 signal becames shielded but the H-2 signal is deshielded. A ^{1}H NMR titration of **1a** with Cd^{2+} and Hg^{2+} in CD$_3$CN indicated that the initial deshielding produced by the donation of the nitrogen lone pair of electrons to Cd(II) and the resulting ring current reduction is not as large as that found for Hg(II) and this ligand and that the subsequent reduction in the paramagnetic shielding is felt by both the H-1 and H-2 signals which are deshielded. The ^{1}H NMR results indicate that although the pyridyl ring nitrogen is still the site of complexation for Cd^{2+} and Hg^{2+} these bind to **1a** differently. To determine the contribution of the calixarene framework to these results, the interaction of the monomer **1b** with these cations in CD$_3$CN was assessed by ^{1}H NMR. These results are also included in Table 1. From the results of this study it can be seen that (i) H-2 is more deshielded than H-1 indicating that the interaction of these cations with **1b** is similar to that of the pyridyl moiety in **1a**. (ii) Except for Zn^{2+}, the shift change in H-2 in **1b** is higher than that in **1a**, but in most cases, similar shift changes for H-1 are observed. This indicates that the paramagnetic shielding due to the lone pair is greater for this proton in **1b**. (iii) In all cases the nitrogen of the pyridyl ring in **1b** appears to provide the binding sites for these cations as observed for **1a**.

^{1}H NMR measurements carried out with **1a** and alkali and alkaline earth metal cations show no chemical shift changes by the addition of these cations to **1a** in CD$_3$CN and CD$_3$OD. It is therefore concluded that no interaction takes place between **1a** and these cations in these solvents. The same observation was found upon the addition of the alkali and alkaline earth metal cation salts to **1b**.

As far as **1a** and **1b** and metal cations in CD$_3$OD are concerned, no chemical shift changes were observed upon the addition Zn^{2+}, Cd^{2+}, and Pb^{2+} relative to the free ligand in CD$_3$-OD.

In an attempt to assess the composition of the metal−ion complexes in acetonitrile and to further check the interaction of these ligands and metal cations in methanol, conductance measurements were carried out and these are now discussed.

Conductometric Titrations. According to the strength of complexation between the ligand and the metal cation, plots of molar conductance (Λ_m, S cm^2 mol^{-1}) against ligand cation ratios **1a**/M^{n+}, **1b**/M^{n+} show three different patterns for strong (two straight lines with a sharp break at the reaction stoichiometry), moderate (broad break in the curvature so the composition of the complex is determined by extrapolating the lines prior to and after the end-point of the titration), and weak (slight or nonexisting changes in the slope) complexes.

Among the cations investigated, in acetonitrile (Zn^{2+}, Cd^{2+}, Cu^{2+}, Ni^{2+}, Pb^{2+}, Co^{2+}, Hg^{2+}, Ag$^+$), the complexation of Cd^{2+}, Cu^{2+}, Ni^{2+}, and Hg^{2+} with **1a** led to titration curves which are the result of a combination of two straight lines intersecting at the reaction stoichiometry of 1:1 for Cd^{2+}, Cu^{2+}, and Ni^{2+} and 1:2 for Hg^{2+}. These findings indicate the formation of highly stable complexes between **1a** and these cations in acetonitrile.

TABLE 2: Thermodynamic Parameters of Complexation of 1a and Metal Cations in Acetonitrile and Methanol at 298.15 K

Cation	log K_s	$\Delta_c G°$/kJmol^{-1}	$\Delta_c H°$/kJ mol^{-1}	$\Delta_c S°$/JK^{-1} mol^{-1}
		Acetonitrile		
Zn^{2+}	3.38 ± 0.03^a	-19.3 ± 0.1	-94.1 ± 0.4^a	-251
Cu^{2+}	4.95 ± 0.02^a	-28.2 ± 0.1	-101.7 ± 0.5^a	-246
Ni^{2+}	4.20 ± 0.02^a	-24.0 ± 0.1	-54.1 ± 0.1^a	-101
Co^{2+}	3.47 ± 0.04^a	-19.8 ± 0.2	-73.1 ± 0.6	-175
$Hg^{2+}(1)$	11.30 ± 0.03^b	-64.5 ± 0.2	-104.2 ± 0.4^a	-132
$Hg^{2+}(2)$	8.24 ± 0.05^b	-46.8 ± 0.3	-157.2 ± 0.5^a	-370
$Hg^{2+}(2+1)$	19.5 ± 0.1	-111.3 ± 0.6	-261.4 ± 0.9	-503
Cd^{2+}	5.36 ± 0.01^a	-30.59 ± 0.06	-53.9 ± 0.5^a	-78
Pb^{2+}	3.65 ± 0.03^a	-20.8 ± 0.2	-54.8 ± 0.4^a	-114
Ag^+	2.63 ± 0.04^a	-13.5 ± 0.2	-25.6 ± 0.1^a	-41
		Methanol		
$Hg^{2+}(2+1)$	17.1 ± 0.1^a	-97.7 ± 0.7	$-$	$-$

^{a} Calorimetric data, ^{b} Potentiometric data
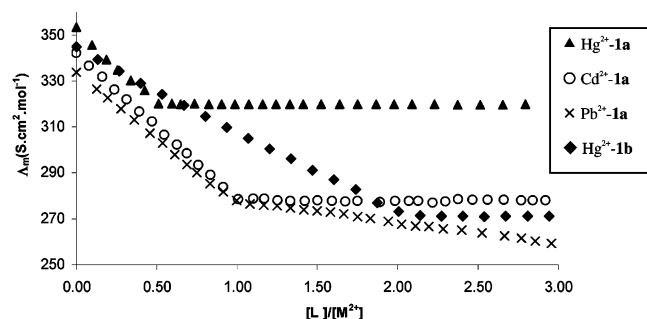
Figure 2. Conductometric titration curves for Cd^{2+}, Hg^{2+}, and Pb^{2+} with **1a** and **1b** in acetonitrile at 298.15 K.

Representative examples for the conductometric titrations of Hg^{2+} and Cd^{2+} and **1a** in acetonitrile at 298.15 K are shown in Figure 2.

Moderate complexation was observed for Zn^{2+}, Pb^{2+}, and Co^{2+} in acetonitrile as reflected in the broad curvature in the slope shown also in Figure 2 for the titration of Pb^{2+} with **1a** in acetonitrile. A weak complex is formed when **1a** interacts with the silver cation in acetonitrile. Thus slight changes were observed at the 1:1 complex stoichiometry.

As far as **1b** is concerned, conductometric titrations with these metal cations in acetonitrile show that except for Pb^{2+} (**1b**/Pb^{2+} =1) changes in the slope of the conductometric titration curves are observed at a ligand:metal cation ratio of 2, showing the formation of 2:1 complexes. This is illustrated in Figure 2 for the conductometric titration of Hg^{2+} and **1b** in acetonitrile at 298.15 K. In all cases, a decrease in the Λ_m values (lower mobility of the metal ion complex relative to that of the free cation salt) are observed until the complex stoichiometry is reached in acetonitrile. This was followed by very small or no variations in conductance upon increasing the ratio.

Conductometric titrations carried out in methanol show no changes in the slope when these metal cations (except Hg^{2+} and Ag^+) were titrated with **1a** in this solvent. Conductometric titration curves for **1a** and these cations (Hg^{2+}, Ag^+) are shown in Figure 3. As far as Hg^{2+} is concerned, the results show that the addition of **1a** to the mercury solution causes a significant decrease in conductivity and gives a sharp break point at the 1:2 (**1a**/Hg^{2+}) ratio, indicating that two mercury cations interact per unit of ligand. Further addition of the ligand does not produce any significant changes in conductivity.
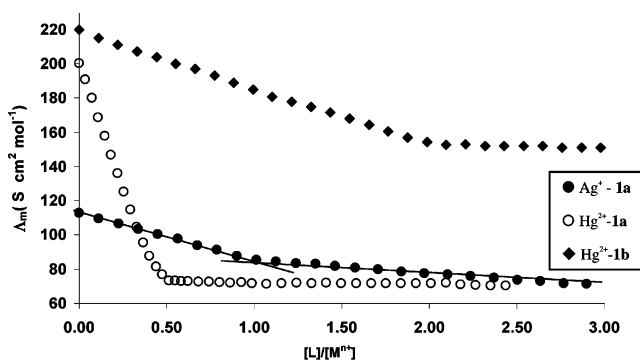
Figure 3. Conductometric titration curves for Hg^{2+} and Ag^+ with **1a** and Hg^{2+} with **1b** in methanol at 298.15 K.

Conductometric data for **1a** and Ag^+ in methanol produce a decrease in conductance as a result of complex formation. The break point observed at the 1:1 ligand:Ag^+ ratio provides information regarding the composition of the metal−ion complex. The relatively sharp break indicates that the interaction of **1a** and silver in methanol at 298.15 K is slightly stronger than that in acetonitrile. This is not surprising given the higher solvation of this cation in acetonitrile relative to methanol as assessed from the transfer of Gibbs energy of this cation from acetonitrile to methanol.[18] ($\Delta_t G° = 30.12$ kJ mol^{-1}, data based on Ph$_4$AsPh$_4$B) reported in the literature.[19]

The fact that no chemical shift changes were observed with the addition of these metal cations to **1a** in methanol may be attributed to the higher solvation of the ligand under the experimental conditions, particularly the interaction of the pyridine nitrogens with alcohols via hydrogen bond formation.[20]

However, in moving from acetonitrile to methanol, the ability of **1b** to interact with the metal cations under investigation is reduced to Hg^{2+}, which shows a strong 2:1 ligand:metal stoichiometry complex as illustrated in Figure 3.

No interaction was found between **1b** and Ag^+ in both solvents. These findings may be attributed to the high solvation of the silver cation in acetonitrile, while methanol is a good solvator (through hydrogen bond formation) for **1b**.

In the following section, the thermodynamics of complexation of **1a** and **1b** with metal cations in acetonitrile and mercury and these ligands in methanol at 298.15 K is discussed.

Thermodynamic Studies. Stability constants (expressed as log K_s), standard Gibbs energies, $\Delta_c G°$, enthalpies, $\Delta_c H°$, and entropies, $\Delta_c S°$, of complexation of **1a** and metal cations in acetonitrile at 298.15 K are listed in Table 2. Also included in this table is the stability constant for this ligand and Hg^{2+} in methanol. Titration calorimetry was the technique selected for systems with log K_s values lower than 6. Calorimetric titration curves are as informative as conductometric titration curves for the determination of the stoichiometry of the complexes. A representative example is shown in Figure 4 where the calorimetric titration of **1b** with Pb^{2+} (as perchlorate) in acetonitrile at 298.15 K is shown. Heat changes during the course of the titration as a function of the metal cation/ligand concentration ratio show that the composition of the complex formed between this cation and this ligand (1:1) is in agreement with that found from conductometric titrations.

For stronger complexes (log $K_s > 6$) stability constants were determined by potentiometry. The results show that for 1:1 complexes in acetonitrile, the highest stability is exhibited by the Cd^{2+}:**1a** complex. Thus the stability constant follows the sequence
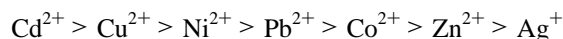
$$Cd^{2+} > Cu^{2+} > Ni^{2+} > Pb^{2+} > Co^{2+} > Zn^{2+} > Ag^+$$

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TABLE 3: Thermodynamic Parameters of 1b and Metal Cations in Acetonitrile and Methanol at 298.15 K

Cation	log K_s	$\Delta_c G°$/kJmol^{-1}	$\Delta_c H°$/kJ mol^{-1}	$\Delta_c S°$/JK^{-1} mol^{-1}
Acetonitrile				
Zn^{2+}(1)	3.87 ± 0.02[a]	-22.1 ± 0.1	-21.9 ± 0.1[a]	0.5
Zn^{2+}(2)	3.29 ± 0.01[a]	-18.79 ± 0.02	-58.0 ± 0.7[a]	-131
Zn^{2+}(1+2)	7.16 ± 0.02	-40.85 ± 0.09	-79.9 ± 0.8	-132
Cu^{2+}(1)	4.07 ± 0.01[a]	-23.24 ± 0.05	-62.3 ± 0.2[a]	-131
Cu^{2+}(2)	3.85 ± 0.01[a]	-21.97 ± 0.01	-152.8 ± 0.7[a]	-439
Cu^{2+} (1+2)	7.92 ± 0.01	-45.21 ± 0.04	-215.1 ± 0.9	-560
Ni^{2+}(1)	3.74 ± 0.01[a]	-21.34 ± 0.03	-44.7 ± 0.6[a]	-78
Ni^{2+}(2)	2.92 ± 0.01[a]	-16.66 ± 0.02	-104 ± 1[a]	-292
Ni^{2+}(2+1)	6.66 ± 0.02	-38.00 ± 0.05	-148.0 ± 0.1	-370
Co^{2+}(1)	3.66 ± 0.01[a]	-20.89 ± 0.08	-21.7 ± 0.1[a]	-3
Co^{2+}(2)	3.22 ± 0.01[a]	-18.39 ± 0.02	-64.6 ± 0.7[a]	-155
Co^{2+}(1+2)	6.88 ± 0.01	-39.28 ± 0.06	-86.3 ± 0.8	-158
Hg^{2+}(1)	6.26 ± 0.06[b]	-35.7 ± 0.3	-131 ± 1[b]	-320
Hg^{2+}(2)	6.36 ± 0.03[b]	-36.3 ± 0.2	-30.8 ± 0.1[b]	18
Hg^{2+}(1+2)	12.62 ± 0.03	-72.0 ± 0.2	-162.3 ± 0.3	-303
Pb^{2+}	3.92 ± 0.02[a]	-22.4 ± 0.1	-58.0 ± 0.5[a]	-119
Methanol				
Hg^{2+} (2+1)	9.22 ± 0.06[a]	-52.6 ± 0.3	-	-

[a] Calorimetric data, [b] Potentiometric data
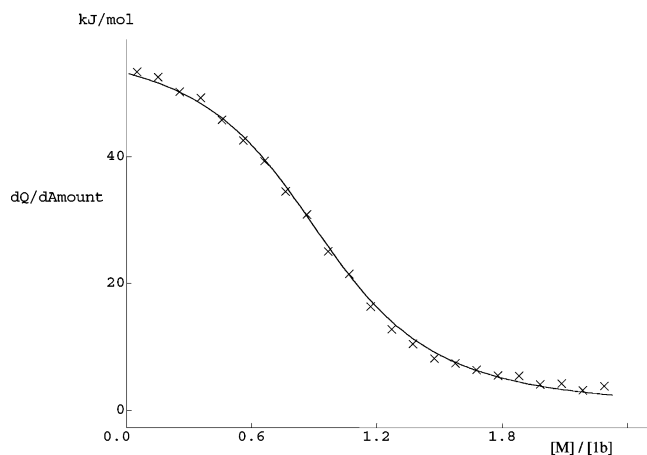
Figure 4. Plot of the enthalpy change vs [metal]/[ligand] concentration ratios for the calorimetric titration of **1b** with Pb^{2+} (as perchlorate) in acetonitrile at 298.15 K.

As far as enthalpies and entropies are concerned, data in Table 2 reflect that the complexation process is enthalpically controlled and takes place with a decrease (unfavorable) of entropy. For comparison purposes, thermodynamic studies of its monomeric component, **1b**, and these metal cations were undertaken. Thus log K_s, $\Delta_c G°$, $\Delta_c H°$, and $\Delta_c S°$ for **1b** and the corresponding cations in acetonitrile are listed in Table 3. In methanol, the log K_s value for Hg^{2+} and **1b** is also included in this table. Complexation data for Cd^{2+} and the monomer could not be obtained due to the difficulties encountered in establishing the composition of the complex.

In an attempt to interpret further the thermodynamics of these systems in the following section, Hg^{2+} and Ag$^+$ are discussed separately.

Mercury(II) Complexes of 1a and 1b in Acetonitrile and Methanol. We were unable to obtain suitable crystals of the mercury−**1a** complex for X-ray diffraction studies. As a result, molecular modeling with a HyperChem Lite computer program was carried out. Conductometric measurements reflect that **1a** is able to host two mercury cations. Thus two possible arrangements can be suggested: (i) First, each mercury ion interacts with two nitrogen atoms that are opposite to each other, "*trans*", giving rise to a structure in which one metal cation is
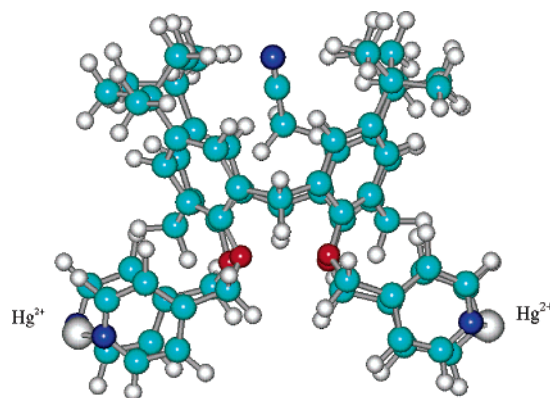

Figure 5. Molecular modeling of the mercury(II) complex with **1a**, using the HyperChem Lite computer program.

above the other in the hydrophilic region of the ligand. However, this structure is not symmetrical and as such is not corroborated by the ^{1}H NMR spectra which show the same pattern of splitting as the free ligand. (ii) Second, each mercury cation binds to two nitrogen atoms that are adjacent to each other, "*cis*". In this case, the metal ions in the complex are opposite to each other and the structure is symmetrical. After refinement, the results suggest that the "*cis*" conformation with a molecule of acetonitrile sitting in the hydrophobic cavity of the ligand is energetically more stable and probably that which exists in solution (Figure 5). X-ray structures of several calix(4)arene complexes with metal cations containing a molecule of acetonitrile in the hydrophobic cavity have been reported.[21]

Having stated this, the thermodynamic stabilities of this cation with **1a** and **1b** in methanol and acetonitrile are now considered. Indeed as far as methanol is concerned, for the process defined by eq 1

$$\mathbf{1a}_{(MeOH)} + 2Hg^{2+}{}_{(MeOH)} \rightarrow [Hg_2-\mathbf{1a}]^{4+}{}_{(MeOH)} \qquad (1)$$
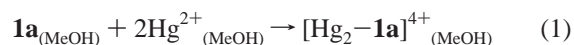
the overall stability constant, log K_1 + log K_2 = 17.11, while 2 units of monomer **1b** are required for one unit of Hg^{2+} (eq 2).

$$2(\mathbf{1b})_{(MeOH)} + Hg^{2+}{}_{(MeOH)} \rightarrow [Hg-(\mathbf{1b})_2]^{2+}{}_{(MeOH)} \qquad (2)$$
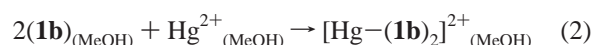
For this process, log K_1 + log K_2 = 9.22. This value is about half of the value obtained for **1a** and this cation (eq 1) in this solvent. Indeed the fact that two monomers are required to complex one mercury unit and one unit of calix(4)arene (formed by four monomers) hosts two mercury cations is a clear indication that the concept of additivity (previously discussed by us in complexation processes involving mercury(II) and other calix(4)arene derivatives)[22] is also applicable for this system in methanol. However this concept is not applicable, at least in quantitative terms, for the complexation process in acetonitrile. The complex stoichiometry of **1a** and **1b** with the mercury cation in this solvent is the same as that shown in methanol (eqs 1 and 2).

Complexation of 1a and 1b with the Silver Cation. X-ray crystallographic studies previously reported by us[10] have shown that the isomer of **1a**, 2-pyridinocalix(4)arene, **1c**, interacts with the silver cation through its ethereal oxygens and pyridyl nitrogens. Thus **1c** provides eight coordination sites to the silver cation. However, the crystal structure shows a higher affinity of Ag$^+$ for nitrogen than for oxygen (bond length Ag$^+$−N = 2.483 Å; Ag$^+$−O = 2.923 Å). The position of the pyridyl nitrogen in **1a** is far from that of the ethereal oxygen. Therefore

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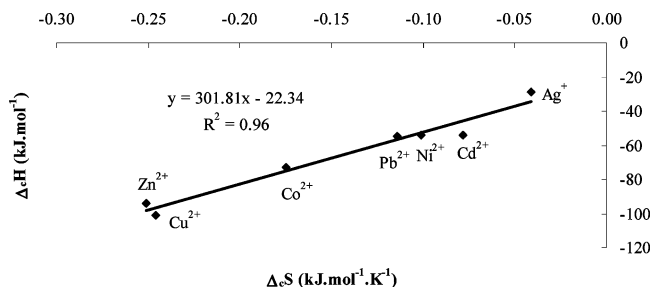
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Figure 6. Standard entropy vs standard enthalpy of complexation of metal cations with **1a** in acetonitrile at 298.15 K.
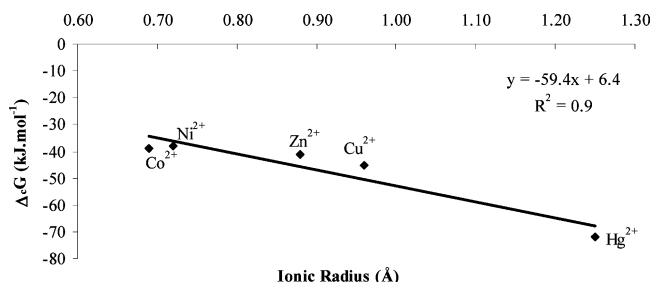

Figure 7. Linear relationship between Gibbs energy and ionic radius of the complexation of **1b** with metal cations in acetonitrile at 298.15 K.

based on the higher affinity of Ag^+ with the former donor atom, it is expected that the pyridyl nitrogens provide the sites of interaction for this cation in this solvent. This is corroborated by (i) the ^1H NMR data which show no chemical shift changes for the protons close to the ethereal oxygens (Table 1), (ii) the thermodynamic stability of **1a** with Ag^+ in acetonitrile (log K_s = 2.63), which is about half of the value obtained for this cation and **1c** in this solvent (log K_s = 5.00),[10] and (iii) the contrasting behavior observed in the entropy of these systems. Thus while there is a decrease in entropy (negative $\Delta_c S°$ value) upon complexation of **1a** and Ag^+, a significant increase in entropy is found for the process involving **1c** and this cation. This increase in entropy must be attributed to the higher desolvation of the cation upon complexation with **1c** (X-ray structure shows the cation encapsulated in the hydrophilic cavity and this is most likely to occur in solution). However, this is unlikely to be the case for **1a** and the silver cation. For this system, complexation may take place at the periphery of the ligand due to the position of the pyridyl nitrogens (outside the cavity) and therefore the cation may be quite exposed to the solvent.

*Interaction of **1a** and **1b** with Zn^{2+}, Cu^{2+}, Co^{2+}, Pb^{2+}, Ni^{2+}, and Cd^{2+}.* No dramatic differences are found in the thermodynamic stability of the complexes of **1a** and cations (except Hg^{2+}) as a result of an enthalpy−entropy compensation effect.[23] In fact the linear relationship observed in Figure 6 has a slope of 301.8 K, which is close to the experiment temperature of 298.15 K. This effect attributed by Grunwald and Steel[23] to solvent reorganization has been previously shown by other calix(4)-arene derivatives on their complexation with metal cations. However, the size of the cation appears to have a significant role in its interaction with **1b** in acetonitrile. This statement is corroborated by the linear relationship observed between the thermodynamic stability and the cation size (Figure 7). Thus stability is enhanced by an increase in the size of the cation. This finding demonstrates the selective behavior of the monomer for the least solvated cation as a result of the competition between the ligand and the solvent for the cation. Thus the highest solvated cations are more reluctant to interact with the ligand. The above observations may be attributed to the ability

of the monomer to orient itself freely around the ionic guest, an option that is not fully available to the macrocycle.

An interesting point to stress is that the thermodynamics of **1a** and **1b** with Pb^{2+} in acetonitrile is characterized by a similar set of quantitative data and the same complex composition (1:1 metal cation:ligand stoichiometry). For both ligands, their interaction with this cation led to significant chemical shift changes in the aromatic protons (H-2) of the pyridyl ring (Table 1). However, these are more pronounced for the monomer than the cyclic tetramer. We are now proceeding with investigations in different media to gain some insight on the interactions involved in these systems.

Conclusions

This paper demonstrates the following:

(i) In pyridinocalix(4)arenes, the position of the pyridyl nitrogens relative to the ethereal oxygens plays a primary role in the hosting abilities of these macrocycles for metal cations. Comparison between **1a** and **1c** (isomers) shows that while the latter is able to interact with alkali−metal cations,[7,10] this ability is lost for **1a** and these cations in acetonitrile. This is clearly demonstrated by the ^1H NMR studies discussed in this paper. As the distance between the pyridyl nitrogens and the ethereal oxygen increases (**1a**) the ligand is unable to provide the necessary coordination sites required to complex alkali−metal cations. To a lesser extent this is also the case for Ag^+. Indeed in moving from **1c** to **1a**, the interaction with this cation weakens considerably.

(ii) Further studies are required on the thermodynamics of complexation of the monomeric components of calix(4)arene derivatives and metal cations. This information is needed to (a) gain further insight on complexation processes involving calixarene derivatives and (b) proceed with a quantitative assessment on the contribution of donor atoms to the thermodynamic stability of complex formation involving these macrocycles.

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