

# A Partially Substituted Calix[4]resorcarene Receptor and Its Selective Recognition for Soft Metal Cations (Silver and Mercury)

Angela F. Danil de Namor\* and Jinane K. Chaaban

Thermochemistry Laboratory, Chemical Sciences, Faculty of Health and Medical Sciences, University of Surrey, Guildford, Surrey GU2 7XH, UK

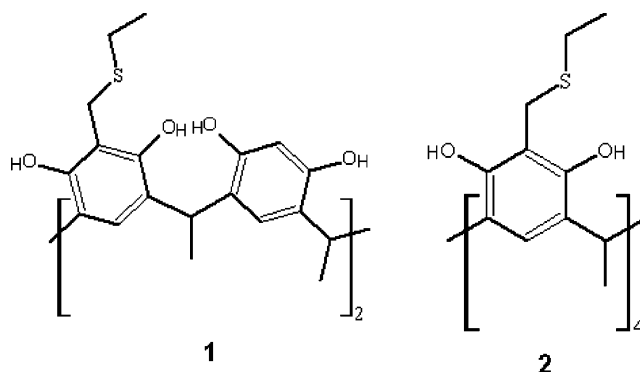
Received: September 7, 2007; In Final Form: November 10, 2007

A partially substituted calix[4]resorcarene receptor, namely, 5,17-ethylthiomethylated calix[4]resorcarene, **1**, has been synthesized and characterized by  $^1\text{H}$  NMR in  $\text{CD}_3\text{OD}$ ,  $\text{CDCl}_3$ , and  $\text{CD}_3\text{CN}$  and  $^{13}\text{C}$  NMR in  $\text{CD}_3\text{OD}$ , as well as by 2D NMR. Partition data in the methanol–hexane and acetonitrile–hexane solvent systems show that the monomeric species are predominant in these solvents. The solubility of **1** in various solvents was determined at 298.15 K. These data were used to calculate the standard solution Gibbs energy of **1** in these solvents. Taking hexane as the reference solvent, the standard transfer Gibbs energy of **1** to various solvents was calculated. Good agreement is found between the  $\Delta_{\text{t}}G^\circ$  values in the hexane–methanol and hexane–acetonitrile and the  $\Delta_{\text{p}}G^\circ$  values of this ligand in these solvent systems. The higher partition constant of **1** in the hexane–methanol relative to the hexane–acetonitrile solvent system contrasts with corresponding data for the fully functionalized receptor, **2**. This is explained in terms of the solvation differences of these receptors in these solvents as reflected in the  $\Delta_{\text{t}}G^\circ$  values. The cation complexing properties of this receptor were investigated through  $^1\text{H}$  NMR, conductance, calorimetric, and potentiometric methods. Among the metal cations (alkali, alkaline earth, heavy, and transition), **1** interacts only with  $\text{Ag}^+$  in methanol and  $\text{Hg}^{2+}$  in propylene carbonate, acetonitrile, methanol, and *N,N*-dimethylformamide. While **1** forms a 1:1 complex with  $\text{Ag}^+$  in methanol, the hosting ability of the receptor for the mercury cation is enhanced in methanol, acetonitrile, and *N,N*-diethylformamide. Thus,  $\text{Hg}^{2+}$  complexes of 1:2 (ligand:metal cation) stoichiometry are found in these solvents. In moving to propylene carbonate, the composition of the mercury complex is altered from 1:2 to 1:1. The results are compared with corresponding data for **2** and these metal cations in the appropriate solvents. The lack of stability observed for **2** and  $\text{Hg}^{2+}$  in acetonitrile resulting from the departure of pendant arms from the resorcarene backbone greatly contrasts with the high stability observed for **1** and this metal cation in the various solvents. Preliminary results on the extraction of silver picrate by this ligand in the water–dichloromethane solvent system are reported. Final conclusions are given.

## Introduction

Resorcarenes are products of the acid-catalyzed condensation reaction between resorcinol and an aliphatic or aromatic aldehyde.<sup>1–4</sup> The mechanism of formation of these compounds and the stereochemical properties have been discussed in the literature.<sup>5–8</sup> Functionalization of resorcarenes through the hydroxyl groups in the upper rim or the *ortho* position has led to the availability of a number of resorcarene based derivatives.<sup>9–19</sup> Recently,<sup>20</sup> we reported the synthesis of 5,11,17,23-ethylthiomethylated calix[4]resorcarene and its structural ( $^1\text{H}$  NMR and X-ray crystallography) and thermodynamic characterization. This receptor was able to form complexes of 1:1 (ligand:metal cation) composition with  $\text{Ag}^+$  and  $\text{Pb}^{2+}$  in acetonitrile and  $\text{Cu}^{2+}$  in methanol. The medium effect alters the composition of the silver complex to the extent that, in moving from acetonitrile to methanol, its stoichiometry changes from 1:1 to 1:2. Formation of metalates was found for  $\text{Cu}^{2+}$  and this ligand in acetonitrile. As far as mercury(II) is concerned, a multicharged complex of an undefined composition was found. This was attributed to the presence of highly charged smaller units (high mobility) resulting from the departure of pendant arms from the resorcarene backbone as demonstrated by X-ray crystallographic studies.

In this paper we report the synthesis of a partially functionalized resorcarene derivative, 5,17-ethylthiomethylated calix[4]resorcarene, **1**, and its structural and thermodynamic characterization in various solvents. Cation complexation processes were investigated by  $^1\text{H}$  NMR, conductometric, and calorimetric measurements. The results obtained with this receptor are compared with those previously reported<sup>20</sup> for the fully functionalized resorcarene, **2**.



## Experimental Section

**Chemicals.** For the synthetic work, ethanethiol (97%), resorcinol (98%, Aldrich Chemical Co.), and formaldehyde

(37%, Across Organics Chemical Co.) were used. For NMR measurements, deuterated acetonitrile ( $\text{CD}_3\text{CN}$ ), methanol ( $\text{CD}_3\text{-OD}$ ), chloroform ( $\text{CDCl}_3$ ), dimethyl sulfoxide ( $d_6\text{-DMSO}$ ), and tetramethylsilane (TMS) were all purchased from Aldrich Chemical Co. For the partition, solubility, conductometric, and calorimetric studies the solvent sources and purification were previously reported.<sup>20</sup> Tris[hydroxymethyl]aminomethane (99%, Aldrich Chemical Co.) and 18-crown-6 (18-C-6) (99%, Fisher Chemical Co.) were used for the standard reactions performed in the Tronac 450 and the TAM calorimeters.

For potentiometric measurements the tetra-*n*-butylammonium perchlorate (TBAP), electrochemical grade ( $\geq 99\%$ ), was obtained from Fluka Chemical Co. Cation salts used were lithium perchlorate (99%), sodium perchlorate monohydrate (98%), potassium perchlorate (99%), rubidium perchlorate (99%), cesium perchlorate (98%), magnesium perchlorate hexahydrate (99%), calcium perchlorate tetrahydrate (99%), strontium perchlorate hydrate, barium perchlorate trihydrate (99%), silver perchlorate (99.9%), lead perchlorate trihydrate, (98%), cadmium perchlorate hydrate, copper(II) perchlorate hexahydrate (98%), zinc perchlorate hexahydrate (98%), nickel perchlorate hexahydrate, and mercury(II) perchlorate hydrate (98%) from Aldrich Chemical Co. These were dried over phosphorus pentoxide under vacuum for several days before use.

**Synthesis of 5,17-Ethylthiomethylated Calix[4]resorcarene.** Into a three-necked round-bottom flask equipped with a condenser and a  $\text{CaCl}_2$  drying tube, calix[4]resorcarene (4 g, 7.3 mmol) was suspended in ethanoic acid (100 mL), and ethanethiol (2.2 mL, 29 mmol) was added. This was followed by the addition of formaldehyde (3.2 mL, 44 mmol) and ethanoic acid (40 mL). The reaction mixture was heated for a period of 12 h. The reaction was monitored by TLC using a chloroform: methanol (9:1) mixture as the developing solvent. After cooling, the solvent was removed under reduced pressure. The product was precipitated from the oily residue with acetonitrile and recrystallized from a mixture of acetonitrile and methanol (90:10). The crystals obtained were dried under vacuum at 50 °C over calcium chloride. The pure product was obtained in 40–45% yield.

**1** was characterized by  $^1\text{H}$  NMR (in various deuterated solvents) and  $^{13}\text{C}$  NMR in deuterated methanol and microanalysis.

$^1\text{H}$  NMR (300 MHz, in  $\text{CD}_3\text{OD}$ )  $\delta$  (ppm),  $J$  (Hz):  $\delta = 7.34$  (s, 1H, **H-2**), 7.23 (s, 1H, **H-4**), 6.31 (s, 1H, **H-3**), 4.53 (q, 2H,  $J = 7.2$ , **H-5**), 3.68 (s, 2H, **H-7**), 2.44 (q, 2H,  $J = 6.9$ , **H-8**), 1.72 (d, 6H,  $J = 7.2$ , **H-6**), 1.16 (t, 3H, **H-9**).

$^1\text{H}$  NMR (300 MHz, in  $\text{CDCl}_3$ )  $\delta$  (ppm),  $J$  (Hz):  $\delta = 8.86$  (s, 2H, **H-1**), 8.10 (s, 2H, **H-10**),  $\delta = 7.31$  (s, 1H, **H-2**), 7.22 (s, 1H, **H-4**), 6.27 (s, 1H, **H-3**), 4.54 (q, 1H,  $J = 7.2$ , **H-5**), 3.80 (s, 2H, **H-7**), 2.47 (q, 2H,  $J = 7.5$ , **H-8**), 1.72 (d, 6H,  $J = 7.2$ , **H-6**), 1.22 (t, 3H,  $J = 7.5$ , **H-9**).

$^1\text{H}$  NMR (300 MHz, in  $\text{CD}_3\text{CN}$ )  $\delta$  (ppm),  $J$  (Hz):  $\delta = 7.72$  (s, 2H, **H-1**), 7.46 (s, 2H, **H-10**), 7.38 (s, 1H, **H-2**), 7.29 (s, 1H, **H-4**), 6.34 (s, 1H, **H-3**), 4.45 (q, 1H,  $J = 7.2$ , **H-5**), 3.66 (s, 2H, **H-7**), 2.42 (q, 2H,  $J = 7.3$ , **H-8**), 1.72 (d, 6H,  $J = 7.5$ , **H-6**), 1.17 (t, 3H,  $J = 7.2$ , **H-9**).

$^{13}\text{C}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ )  $\delta_c$  (ppm):  $\delta = 151.59$  (**C\***—OH), 150.60 (**C**—OH), 126.60 (**C\***—OH—**C\***—bridge), 126.24 (COH—**C**—bridge), 125.68 (**C** meta), 121.22 (**C\*** meta), 115.01 (S—**C\***H<sub>2</sub>—**C\*** ortho), 102.55 (COH—CH ortho), 29.27 (CH bridge), 26.75 (S—CH<sub>2</sub>CH<sub>3</sub>), 26.38 (S—CH<sub>2</sub>—Ar), 20.41 (CH<sub>3</sub> bridge), 15.30 (S—CH<sub>2</sub>CH<sub>3</sub>). In addition, 2D NMR (HMQC and HMBC) in  $\text{CD}_3\text{OD}$  at 298 K was used to identify carbon and proton signals, mainly those corresponding to the aromatic

protons. Thus, from the  $^1\text{H}$ — $^{13}\text{C}$  HMQC spectrum, the protonated carbons were distinguished from the non-protonated ones. The latter were not visible in this spectrum. The HMBC experiment was used to provide further evidence concerning the identification of H-2, H-3 and H-4 and their corresponding carbons. Spectra are available on request.

Elemental analysis was carried out in duplicate at the University of Surrey. Experimental results are in good agreement with calculated ones: calculated %: C, 65.87; H, 6.40; found %: C, 65.52; H, 6.28.

**C\*** is the carbon corresponding to the resorcinol unit where the sulfur pendent arm is attached.

**Partition Experiments for the Determination of the Ligand Species in the Appropriate Solvent.** Partition experiments were carried out to investigate the speciation of the ligand in the solvents of interest. The procedure reported in the literature was used.<sup>21</sup> Thus, the solvents methanol/hexane and hexane/acetonitrile were mutually saturated before use. For the partition experiments, solutions containing different concentrations of **1** ( $1.0 \times 10^{-5}$ – $1.5 \times 10^{-3}$  mol dm<sup>-3</sup>) were prepared in methanol or acetonitrile saturated with hexane. Equal volumes of these solutions (10 cm<sup>3</sup>) and hexane (saturated with acetonitrile or methanol) were placed in separate tubes and shaken for 2 h. These were left in a thermostat bath at 298.15 K for several hours until equilibrium was achieved. Samples of both phases were taken, and the equilibrium concentration of the ligand in these solvents was determined by UV–vis spectrophotometry. Blank experiments in the absence of the receptor were carried out in all cases.

**Solubility Measurements.** The solubility of **1** in several organic solvents at 298.15 K was determined as described by Danil de Namor et al.<sup>22,23</sup> by preparing saturated solutions of these ligands in the appropriate solvents. These were placed in a thermostated bath at  $298.15 \pm 0.02$  K for several days to ensure that equilibrium was attained between the solid (sol) and its saturated solution (s).

Aliquots of the saturated solution were placed into preweighed porcelain crucibles. The solvent was evaporated carefully using a hot plate. The crucibles containing the solid left inside were kept in a desiccator over  $\text{CaCl}_2$ , and they were weighed until constant weight. Separate blank experiments were carried out to ensure the absence of any involatile materials in the pure solvent. All analyses were carried out in triplicate.

Solvate formation was checked by placing a small amount of the ligand on a watch glass over a saturated atmosphere of the appropriate solvent placed at the bottom of a closed desiccator.

**$^1\text{H}$  NMR Measurements.** A Bruker AC-300E pulse Fourier transform NMR spectrometer was used. Typical operating conditions for routine proton measurements involved pulse or flip angle of 30°, spectra width (SW) of 20.7 ppm, spectral frequency (SF) of 300.137 MHz, delay time of 1.60 s, acquisition time (AQ) of 1.819 s, and line broadening of 0.55 Hz.

For the Bruker DRX-500 pulse Fourier transform NMR spectrometer, the operating conditions involved were pulse or flip angle of 30°, spectra width (SW) of 15 ppm, spectral frequency (SF) of 500.150 MHz, delay time of 0.3 s, acquisition time (AQ) of 3.17 s, and line broadening of 0.3 Hz. Solutions of the samples of interest ( $9 \times 10^{-4}$ – $6 \times 10^{-3}$  mol dm<sup>-3</sup>) were prepared in the appropriate deuterated solvent. These were placed in 5 mm NMR tubes using TMS (tetramethylsilane) as the internal reference.

For complexation studies, metal-ion salts were added to solutions containing the ligand in the appropriate solvent.

Chemical shift changes relative to the ligand in the appropriate solvent were calculated.

**Carbon-13 NMR Measurements.** A Bruker DRX-500 pulse Fourier transform NMR spectrometer was used for the characterization. The operating conditions involved pulse or flip angle of 63°, spectra width (SW) of 298.9 ppm, spectral frequency (SF) of 125.78 MHz, delay time of 1.13 s, acquisition time (AQ) of 0.87 s, and line broadening of 3.0 Hz.

**Conductometric Titrations at 298.15 K.** For these measurements a Wayne-Kerr Autobalance Universal Bridge, type B642, was used. Conductometric titrations involving metal cation salts and **1** were carried out in different organic solvents at 298.15 K. To perform these measurements, the conductometric cell was filled with an accurate amount of the metal ion salt solution in the appropriate solvent (~25 mL). Then the electrodes were inserted into the cell. The solution was continuously stirred during the course of the titration. The closed system was placed in a thermostat bath at 298.15 K. After thermal equilibrium was achieved, accurate aliquots of the ligand ( $8 \times 10^{-4}$ – $1 \times 10^{-3}$  mol dm<sup>-3</sup>) were added to the conductometric cell containing the metal cation salt solution ( $5 \times 10^{-5}$ – $1 \times 10^{-4}$  mol dm<sup>-3</sup>) in the same solvent. The conductance was recorded after each addition once equilibrium was achieved. Thus, plots of molar conductances,  $\Lambda_m$ , against the ligand:cation ( $[L]/[M^{n+}]$ ) molar ratio were drawn.

**Calorimetric Titrations.** For these measurements, the Tronac 450 or the Thermal Activity Monitor (TAM 2277) calorimeters were used. For the former, the enthalpy of protonation of tris-(hydroxymethyl)aminomethane (THAM) in 0.1 mol dm<sup>-3</sup> hydrochloric acid (standard reaction) was determined<sup>24</sup> to check the accuracy and the reproducibility of the equipment. The standard chemical reaction for the TAM 2277 was that involving the complexation of 18-crown-6 with the barium cation in water at 298.15 K.<sup>25</sup>

In order to carry out calorimetric titrations with the Tronac 450, the calorimetric vessel was filled with the ligand solution (50 cm<sup>3</sup>,  $8 \times 10^{-4}$  mol dm<sup>-3</sup>) in the appropriate solvent. It was immersed into the thermostated bath until thermal equilibrium was reached. A solution of the metal ion salt in the same medium was added stepwise from the burette into the vessel. The temperature changes were monitored on a chart strip recorder. An electrical calibration was carried out after each experiment. These experiments were repeated at least three times for each titration involving **1** and different metal cations. Blank experiments were carried out in all cases to account for heat of dilution effects resulting from the addition of the metal cation salt solution to the solvent in the calorimetric vessel.

Microcalorimetric titrations using the 2277 Thermal Activity Monitor<sup>26,27</sup> were performed to double check the values of the stability constant and the heat of complexation of the results obtained with the Tronac calorimeter. In this experiment, the vessel was filled with a solution of the ligand in the appropriate solvent (8 cm<sup>3</sup>,  $8 \times 10^{-3}$ – $8 \times 10^{-4}$  mol dm<sup>-3</sup>). A solution of the ion salt (metal cations) in the same solvent (concentrations used were about 10 times higher than that of the ligand,  $8 \times 10^{-2}$ – $8 \times 10^{-3}$  mol dm<sup>-3</sup>) was injected from a 0.5 cm<sup>3</sup> gastight Hamilton syringe (24 injections; 0.0512 cm<sup>3</sup> for each run). This syringe was attached to a computer-operated syringe drive, at an average of 30 min intervals. Blank experiments were carried out in all cases. The experiments were carried out in duplicate.

**Potentiometric Titrations for the Determination of Stability Constants.** For the potentiometric titrations, a digital microprocessor pH-mV meter CAMLAB model HI 8417 was

**TABLE 1: Partition Constants of **1** in (a) Hexane–Methanol and (b) Hexane–Acetonitrile Solvent Systems at 298.15 K; Derived Partition Gibbs Energies**

$c_i^a$ /mol dm <sup>-3</sup>	$K_p$	$\Delta_p G^\circ$ /kJ mol <sup>-1</sup>
(a) Hexane–Methanol		
$2.27 \times 10^{-5}$	145.16	–12.34
$6.80 \times 10^{-5}$	145.05	–12.34
$9.06 \times 10^{-5}$	145.37	–12.34
$1.02 \times 10^{-4}$	145.19	–12.34
$1.13 \times 10^{-4}$	145.18	–12.34
$1.36 \times 10^{-4}$	145.16	–12.34
(b) Hexane–Acetonitrile		
$4.53 \times 10^{-5}$	18.89	–7.28
$5.67 \times 10^{-5}$	18.77	–7.27
$9.06 \times 10^{-5}$	18.59	–7.24
$1.02 \times 10^{-4}$	18.56	–7.24
$1.25 \times 10^{-4}$	18.51	–7.23
$1.59 \times 10^{-4}$	18.46	–7.23

<sup>a</sup>  $c_i$  is the initial concentration (mol dm<sup>-3</sup>) of the ligand in (a) methanol or (b) acetonitrile, both solvents saturated with hexane.

used. The electrochemical cell used was that developed by Cox et al.<sup>28</sup> (eq 1):



In this work, the stability constant of **1** with the silver cation salt solution in MeOH as solvent was determined at 298.15 K. Thus, the ligand solution ( $8.5 \times 10^{-4}$  mol dm<sup>-3</sup>) was prepared in a tetra-*n*-butylammonium perchlorate (TBAP) solution (0.05 mol dm<sup>-3</sup>) in the appropriate solvent. In this experiment, the indicator electrode was placed into a solution of silver perchlorate of known concentration ( $1.09 \times 10^{-3}$  mol dm<sup>-3</sup>) reaching thermal equilibrium; the solution was titrated with a solution of the ligand which was prepared in a solution of TBAP solution (0.05 mol dm<sup>-3</sup>) in the appropriate solvent. Potential readings were taken after each addition and were used for the calculation of the stability constant using the HYPERQUAD program.<sup>29</sup>

## Results and Discussion

The derivation of thermodynamic data for cation complexation processes requires information regarding the nature of the speciation in solution. Given that among the solvents selected for this study are acetonitrile (dipolar aprotic solvent) and methanol (protic solvent), partition experiments were carried out with the aim of assessing whether or not **1** is predominantly in its monomeric form in these solvents. Thus, partition data for **1** in the methanol–hexane and acetonitrile–hexane solvent systems at 298.15 K are reported in Table 1. These data were used to calculate the standard Gibbs energy of partition,  $\Delta_p G^\circ$ , for this ligand in these solvent systems. Given that  $K_p$  and consequently  $\Delta_p G^\circ$  values are not altered by changes in the ligand concentration, we conclude that monomeric species of **1** are predominant in these solvents. Comparison of  $K_p$  and  $\Delta_p G^\circ$  values for **1** relative to the fully substituted ligand (average  $K_p$  and  $\Delta_p G^\circ$  values in the methanol–hexane system are 12.72 and –6.31 kJ mol<sup>-1</sup> and in the acetonitrile–hexane are 80.86 and –10.89 kJ mol<sup>-1</sup>, respectively)<sup>30</sup> shows that for both ligands the partition process is favored. However, **1** is more favorably partitioned to methanol than **2** while the opposite is true for the hexane–acetonitrile solvent system. It follows that the partition of **2** from acetonitrile to methanol is not favored while the same process involving **1** is.

Before discussing these results, we proceed with solubility measurements for this ligand in various solvents including methanol, acetonitrile, and hexane. These are now discussed.



**TABLE 2: Solubilities, Standard Gibbs Energies of Solution ( $\Delta_s G^\circ$ ) of **1** in Various Solvents at 298.15 K, and Standard Transfer Gibbs Energies ( $\Delta_t G^\circ_{(\text{Hex} \rightarrow \text{s})}$ ) from Hexane to Various Solvents**

solvent <sup>a</sup>	solubility (mol dm <sup>-3</sup> )	$\Delta_s G^\circ$ (kJ mol <sup>-1</sup> )	$\Delta_t G^\circ_{(\text{Hex} \rightarrow \text{s})}$ (kJ mol <sup>-1</sup> )	$\Delta_p G^\circ$ (kJ mol <sup>-1</sup> )
Hex	$(3.13 \pm 0.01) \times 10^{-5}$	25.71	0	
MeCN	$(8.37 \pm 0.07) \times 10^{-4}$	17.56	-8.15	-7.25 <sup>b</sup>
MeOH	$(1.05 \pm 0.13) \times 10^{-2}$	11.29	-14.42	-12.34 <sup>b</sup>
EtOH	$(7.62 \pm 0.01) \times 10^{-2}$	6.38	-19.33	
1-BuOH	$(6.20 \pm 0.01) \times 10^{-2}$	6.89	-18.82	
1-PrOH	$(1.19 \pm 0.06) \times 10^{-2}$	10.98	-14.73	
PC	too soluble			
butanone	too soluble			
THF	too soluble			
DMF	too soluble			
DMSO	too soluble			
CDCl <sub>3</sub>	too soluble			

<sup>a</sup> Abbreviations used: acetonitrile, MeCN; methanol, MeOH; ethanol, EtOH; butanol, 1-BuOH; propan-1-ol, 1-PrOH; hexane, Hex; propylene carbonate, PC; tetrahydrofuran, THF; dichloromethane, DCM; *N,N*-dimethylformamide, DMF; dimethyl sulfoxide, DMSO; chloroform, CHCl<sub>3</sub>.

<sup>b</sup> Average value from data listed in Table 1.

**Solubility of **1**, Standard Gibbs Energies of Solution and Transfer.** Solubility data for **1** in various solvents at 298.15 K are reported in Table 2. These are the result of several analytical measurements carried out on the same saturated solution. The standard deviation of the data is also included in Table 2. Solvate formation was observed when **1** was exposed to saturated atmospheres of propylene carbonate, butanone, tetrahydrofuran, *N,N*-dimethylformamide, dimethyl sulfoxide, and chloroform. Therefore, the solution Gibbs energies of **1** in these solvents cannot be calculated. In fact, <sup>1</sup>H NMR data for **1** in CDCl<sub>3</sub> relative to CD<sub>3</sub>CN show a significant downfield shift ( $\Delta\delta = 1.14$  ppm) in the hydroxyl protons. Solvate formation was also observed for **2** in these solvents (except in propylene carbonate). Again, <sup>1</sup>H NMR data for **2** in CDCl<sub>3</sub> and *d*<sub>6</sub>-DMSO show downfield shifts of 0.41 and 1.14 ppm, respectively, in the hydroxyl protons in moving from CD<sub>3</sub>CN to these solvents.

In the absence of solvate formation, from solubility data the standard Gibbs energy of solution,  $\Delta_s G^\circ$ , was calculated, and these data are also included in Table 2. Taking hexane as the reference solvent, the standard transfer Gibbs energy of solution,  $\Delta_t G^\circ$ , for **1** to other solvents was obtained. Unlike in the partition process where the two solvents are mutually saturated, transfer data are referred to the process involving the solvents in their pure state. For systems in which the mutual solubility of the solvents involved is very low,  $\Delta_t G^\circ \approx \Delta_p G^\circ$ .<sup>30</sup> Table 2 shows that  $\Delta_t G^\circ$  and  $\Delta_p G^\circ$  values for **1** in the hexane–methanol and hexane–acetonitrile solvent systems follow this pattern. Indeed, good agreement is found between these two sets of data.

The  $\Delta_t G^\circ$  values (Table 2) show that methanol is a better solvator for **1** than acetonitrile. This explains the higher partition constant of **1** in the hexane–methanol relative to the hexane–acetonitrile solvent system. On the other hand, acetonitrile seems to be a better solvator for **2** [ $\Delta_t G^\circ$  (Hex  $\rightarrow$  MeCN) = -11.15 kJ mol<sup>-1</sup>] than methanol [ $\Delta_t G^\circ$  (Hex  $\rightarrow$  MeOH) = -8.71 kJ mol<sup>-1</sup>], which again is in accord with the higher partition constant of **2** in the hexane–acetonitrile relative to the hexane–methanol solvent system. The different behavior of these two ligands in these solvents was not quite obvious from the <sup>1</sup>H NMR data of **1** and **2** in CD<sub>3</sub>CN and CD<sub>3</sub>OD. Disappearance of the signal for the OH protons in CD<sub>3</sub>OD was observed in both cases. CD<sub>3</sub>OD is a protic solvent that is able to enter hydrogen bond formation with the OH protons. Fast exchange with the bulk CD<sub>3</sub>OD may also occur. In both cases, a deshielding effect of the OH protons will cause its signal to shift downfield and probably out of the range of the spectrum.

In summary among the solvents considered, the solvation trend for **1** is as follows:



**<sup>1</sup>H NMR Cation Complexation Studies.** <sup>1</sup>H NMR measurements consisting of the addition of an excess amount of the metal ion salt to a solution of the ligand in the approximate solvent were conducted. The aims were (i) to establish whether or not complex formation occurs, (ii) to identify whenever possible the active sites of interaction of the ligand with the cation, and (iii) to investigate the conformational changes that the ligand undergoes upon complexation.

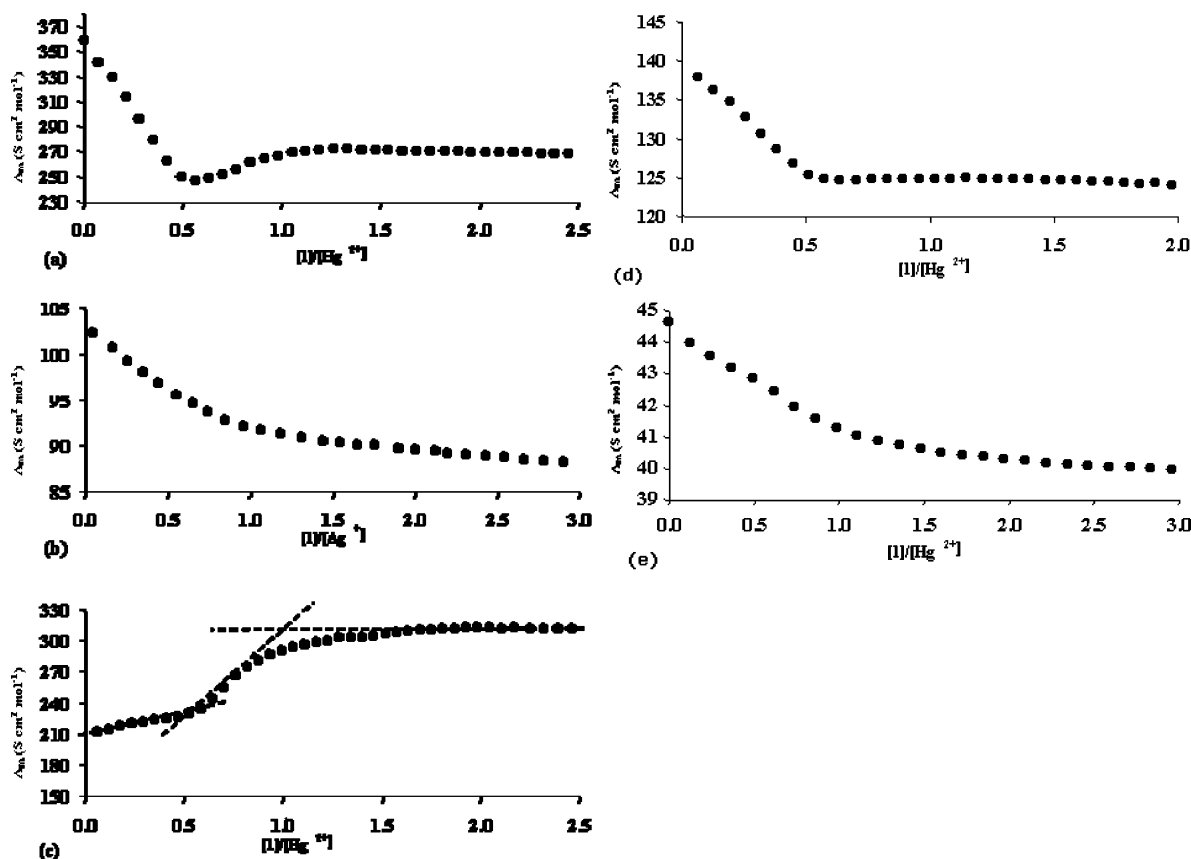
As far as CD<sub>3</sub>CN is concerned, the addition of alkali and alkaline-earth metal cations did not show any significant chemical shift changes in any of the protons. A similar behavior was observed in CD<sub>3</sub>OD.

The addition of heavy and Zn<sup>2+</sup> metal cations to **1** in CD<sub>3</sub>CN did not alter any of the proton chemical shifts of the ligand except for mercury(II) (Table 3). Distortion and new signals in the spectrum were observed upon addition of this cation salt to **1**. As a result, the protons of **1** could not be detected. This observation suggests that interaction of **1** and Hg<sup>2+</sup> may occur in acetonitrile. In CD<sub>3</sub>OD, significant chemical shift changes are observed for Ag<sup>+</sup> and Hg<sup>2+</sup> (Table 3). The most significant chemical shift changes were observed for H-7 and H-8 for Ag<sup>+</sup> and in H-7, H-8, and H-9 for Hg<sup>2+</sup> upon addition of the metal cation salt to **1**, which indicates that the sulfur donor atoms are the active sites of interaction. In addition, H-2 exhibits a significant downfield shift upon addition of Ag<sup>+</sup>. This may be due to the interaction of Ag<sup>+</sup> with the sulfur donor atom which will affect the aromatic protons of the resorcinol unit where the sulfur pendant arm is attached.

Cation–ligand interactions could also alter the conformation of the ligand resulting in chemical shift changes of the aromatic protons. The fact that these changes are also observed in H-2 but not in H-3 or H-4 strengthens the suggestion that the sites of interaction are mainly provided by the sulfur donor atoms. In an attempt to corroborate these findings and determine the composition of these complexes, conductometric measurements were performed in acetonitrile, methanol, dimethyl sulfoxide, *N,N*-dimethylformamide, and propylene carbonate. These are now described.

**Conductometric Titrations.** The range of solvents was extended in order to establish the medium effect on the composition of the complex since there is evidence in the literature of changes of complex stoichiometry resulting from altering the solvent.<sup>31</sup>





**Figure 1.** Conductometric curve for the titration of salts as perchlorates of (a)  $\text{Hg}^{2+}$  with **1** in acetonitrile at 298.15 K, (b)  $\text{Ag}^+$  and **1** in methanol, (c)  $\text{Hg}^{2+}$  and **1** in methanol, (d)  $\text{Hg}^{2+}$  and **1** in *N,N*-dimethylformamide, and (e)  $\text{Hg}^{2+}$  and **1** in propylene carbonate at 298.15 K.

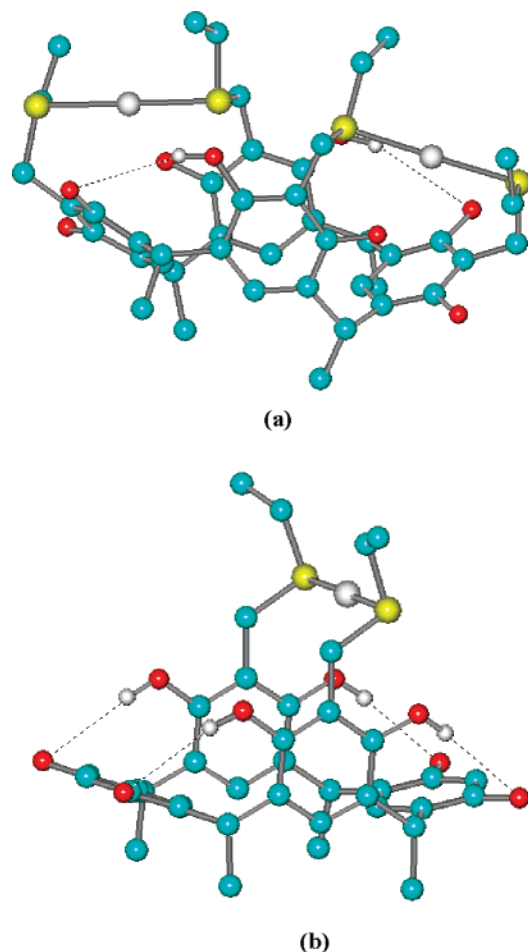
**TABLE 4: Thermodynamics of Complexation of 1 with Silver in Methanol and with Mercury(II) in Propylene Carbonate, Acetonitrile, Methanol, and *N,N*-Dimethylformamide at 298.15 K**

<b>1/M<sup>2+</sup></b>	ligand	log <i>K</i> <sub>s</sub>	Δ <sub>c</sub> <i>G</i> <sup>o</sup> ( <b>kJ mol<sup>-1</sup></b> )	Δ <sub>c</sub> <i>H</i> <sup>o</sup> (kJ mol <sup>-1</sup> )	Δ <sub>c</sub> <i>S</i> <sup>o</sup> ( <b>J K<sup>-1</sup> mol<sup>-1</sup></b> )
Methanol					
Ag <sup>+</sup> (1:1)	<b>1</b>	4.89 ± 0.03 <sup>a</sup>	−27.9 ± 0.2	−66.20 ± 0.07	−128
	<b>2</b>	9.53 ± 0.04 <sup>b</sup>	−54.4 ± 0.2	−32.40 ± 0.04 <sup>a</sup>	74
Propylene Carbonate					
Hg <sup>2+</sup> (1:1)	<b>1</b>	3.56 ± 0.07 <sup>a</sup>	−20.3 ± 0.4	−148.2 ± 0.5 <sup>a</sup>	−429
Acetonitrile					
Hg <sup>2+</sup> (1:1) (1:2) overall	<b>1</b>	11.51 ± 0.02 <sup>b</sup>	−65.7 ± 0.1		
		8.72 ± 0.06	−49.8 ± 0.3		
		20.24 ± 0.08	−115.5 ± 0.4		
Methanol					
Hg <sup>2+</sup> (1:1) (1:2) overall	<b>1</b>	13.91 ± 0.04 <sup>b</sup>	−79.4 ± 0.2		
		9.61 ± 0.04	−54.8 ± 0.2		
		23.52 ± 0.08	−134.2 ± 0.4		
<i>N,N</i> -Dimethylformamide					
Hg <sup>2+</sup> (1:1) (1:2) overall	<b>2</b>	10.49 ± 0.04 <sup>b</sup>	−59.9 ± 0.2		
		7.31 ± 0.03	−41.7 ± 0.1		
		17.80 ± 0.07	−101.6 ± 0.4		

<sup>a</sup> Titration calorimetry. <sup>b</sup> Potentiometry.

process leads to a breakage of two intramolecular hydrogen bonds, and therefore energy is required. The second  $\text{Ag}^+$  cation was found to be interacting with the two sulfur donor atoms of the remaining adjacent pendant arms (Figure 2b). As a result, the complexation of **2** and  $\text{Ag}^+$  is enthalpically less stable than that of **1**, and this cation in this solvent and it is entropically favored. This statement is further corroborated by the energy-minimized structure of **1** and  $\text{Ag}^+$  which suggests that no intramolecular hydrogen bonds are broken when the two sulfur atoms interact with this cation in this solvent (Figure 2). These findings are likely to have implications on the stability of the complex. The fact that for **2** the silver cation interacts with two

adjacent rather than with two alternate sulfur donor atoms as for **1** increases the cation-donor atom proximity and therefore the stability of the former relative to the latter ligand. As far as mercury is concerned, the only system for which  $\log K_s$ ,  $\Delta_c G^\circ$ ,  $\Delta_c H^\circ$ , and  $\Delta_c S^\circ$  values could be obtained is that in propylene carbonate where a 1:1 complex is formed. In other solvents such as acetonitrile, methanol, and *N,N*-dimethylformamide 1:2 (ligand:metal cation) complexes are formed. For these systems only stability constants and derived Gibbs energies of complexation are reported as determined by potentiometric titrations. Stability constants are too high to be measured calorimetrically. Indeed, the values are beyond the scope of this technique. It is

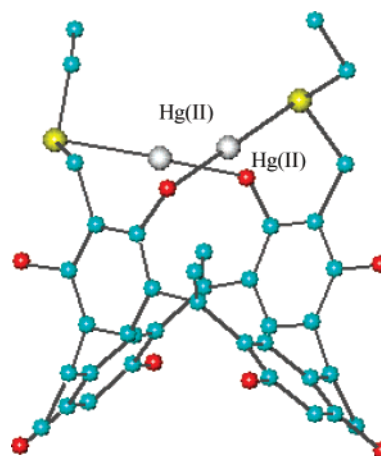


**Figure 2.** Equilibrium structures of (a)  $2\text{-Ag}^+$  and (b)  $1\text{-Ag}^+$  complex as determined by molecular simulations. Dotted line indicates hydrogen bond formation.

clear from these data that in propylene carbonate the hosting ability of **1** is reduced and this is a representative example of the role of the solvent on the complexation of resorcarene derivatives and metal cations.

Regarding the interaction of **1** with  $\text{Hg}^{2+}$ ,  $^1\text{H}$  NMR investigations reveal that mercury ions are interacting via the sulfur donor atoms. Molecular modeling (using Hyper-Chem Lite computer program) was carried out in order to find the preferred geometry of this system. The starting structure was that which corresponds to the free ligand (lowest energy). Energy minimization for various complex models was repeated several times to find the global minima. In fact, molecular modeling shows that the minimum energy for the  $\text{Hg}_2\text{L}^{4+}$  complex is that in which the first mercury ion interacts with **1** through the sulfur and hydroxyl oxygen donor atoms of a neighboring ring forming a linear mercury complex (Figure 3). In a similar fashion the second mercury cation satisfies its coordination number for linear complexation.

The contrasting behavior of **1** with mercury in these solvents relative to those involving **2** and this cation in acetonitrile<sup>20</sup> and methanol is striking. Indeed, for the latter ligand, the unusual jump in conductance observed in the titration of this ligand with mercury(II) after the formation of a multicharged complex of undefined composition was attributed to the presence of highly charged smaller units of high mobility. This was the result of the departure of pendant arms from the resorcarene backbone. This was in line with the outcome of X-ray diffraction studies of the isolated species. However, for the partially functionalized resorcarene, complexes of high stability are found between **1**



**Figure 3.** Modeling of the  $\text{Hg}_2\text{L}^{4+}$  complex as determined by molecular simulation studies. Hydrogen atoms and hydrogen bonding are not included in the structure of the complex for simplicity.

and this cation in these solvents. This may be attributed to the lower electrostatic repulsion resulting from the partial functionalization of the macrocycle and the higher stability conferred by the hydrogen bonding between the hydroxyl groups in **1** relative to **2**. The extraction properties of **1** for silver and mercury cations are now being investigated using the approach extensively discussed by Danil de Namor and co-workers<sup>31–34</sup> for cation extraction by calixarene derivatives. Preliminary experiments for silver picrate in the water–dichloromethane solvent system at 298.15 K in the absence and presence of **1** were carried out. Thus, distribution data in the absence of **1** were used to calculate the partition constant,  $K_p$  ( $1.44 \times 10^{-4}$ ), the distribution constant,  $K_d$  (62.98), and the ion-pair formation constant,  $K_a$  ( $4.37 \times 10^5$ ) for this salt in dichloromethane saturated with water. A  $K_d$  value of 62.14 was also obtained from distribution data in the presence of **1**. The extraction constant,  $K_{ex} = 2.10^8$  was also calculated. Further work is in progress to corroborate these data and to assess the ability of **1** to remove mercury from water. The anion effect on the extraction process is being investigated.

## Conclusions

From the above discussion it follows that:

(i) The partially substituted resorcarene derivative, **1**, having two sulfur donor atoms in its pendant arms is able to interact with the silver cation in methanol, forming a complex of 1:1 stoichiometry. However, its hosting capacity for mercury is enhanced to the extent that two mercury ions are taken up per unit of ligand in methanol, acetonitrile, and *N,N*-dimethylformamide. However, in propylene carbonate, the complex composition is altered and a 1:1 complex is formed.

(ii) Unlike for the fully substituted ligand, partial functionalization of the calix[4]resorcarene has led to the formation of highly stable complexes with mercury(II) in protic and dipolar aprotic media.

**Acknowledgment.** This work was funded by the European Commission. AFDdeN, Scientific Coordinator of Contracts ICA2-CT-2000-10052 and INCO-CT-2004-509159 thanks the Sponsor for the financial support provided to carry out this research. Thanks are also due to Drs. Ismael Abbas and Mohammed Shehab for their input in the molecular modelling and the calorimetric measurements.

## References and Notes

- (1) Thoden van Velzen, E. U.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1994**, *116*, 188.



- (2) Barrett, A. G. M.; Braddock, D. C.; Henschke, J. P.; Walker, E. R. *J. Chem. Soc., Perkin Trans.* **1999**, *1*, 873.
- (3) Roberts, B. A.; Cave, G. W. V.; Raston, C. L.; Scott, J. L. *Green Chem.* **2001**, *3*, 280.
- (4) Peterson, K. E.; Smith, R. C.; Mohan, R. S. *Tetrahedron Lett.* **2003**, *44*, 7723.
- (5) Weinelt, F.; Schneider, H. J. *J. Org. Chem.* **1991**, *56*, 5527.
- (6) Biali, S. E.; Böhmer, V.; Brenn, J.; Frings, M.; Thondorf, I.; Vogt, W.; Wöhnert, J. *J. Org. Chem.* **1997**, *62*, 8350.
- (7) Gutsche, C. D. Synthesis of Calixarenes and Thiacalixarenes. In *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, 2001.
- (8) Shivanyuk, A.; Paulus, E. F.; Böhmer, V.; Vogt, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1301.
- (9) Eisler, D.; Hong, W.; Jennings, M. C.; Puddephatt, R. J. *Organometallics* **2002**, *21*, 3955.
- (10) Moran, J. R.; Karbach, S.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 5826.
- (11) Cram, D. J.; Karbach, S.; Kim, H. E.; Knobler, C. B.; Maverick, E. F.; Ericson, J. L.; Helgeson, R. C. *J. Am. Chem. Soc.* **1988**, *110*, 2229.
- (12) Pietraszkiewicz, M.; Prus, P.; Pietraszkiewicz, O. *Tetrahedron* **2004**, *60*, 10747.
- (13) Manabe, O.; Asakura, K.; Nishi, T.; Shinkai, S. *Chem. Lett.* **1990**, 1219.
- (14) Schneider, U.; Schneider, H. *J. Chem. Ber.* **1994**, *127*, 2229.
- (15) Matsushita, Y.; Matsui, T. *Tetrahedron Lett.* **1993**, *34*, 7433.
- (16) Leigh, D. A.; Lannane, P.; Pritchard, R. G.; Jackson, G. *J. Chem. Soc., Chem. Commun.* **1994**, 389.
- (17) Yanagihara, R.; Tominaga, M.; Aoyama, Y. *J. Org. Chem.* **1994**, *59*, 6865.
- (18) Dueño, E. E.; Bisht, K. S. *J. Chem. Soc., Chem. Commun.* **2004**, 954.
- (19) Bryant, A.; Blanda, M. T.; Vincenti, M.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 2167.
- (20) Danil de Namor, A. F.; Chaaban, J. K.; Piro, O. E.; Castellano, E. *J. Phys. Chem. B* **2006**, *110*, 2442.
- (21) Findlay, A. *Practical Physical Chemistry*, 7th ed.; Longmans, Green and Co.: London, 1941.
- (22) Abraham, M. H.; Danil de Namor, A. F.; Schulz, R. A. *J. Chem. Soc., Faraday Trans. 1* **1980**, *76*, 869.
- (23) Danil de Namor, A. F.; Al Rawi, N.; Piro, O. E.; Castellano, E. E.; Gil, E. *J. Phys. Chem. B* **2002**, *106*, 779.
- (24) Eatough, D. J.; Christensen, J. J.; Izatt, R. M. *Experiments in Thermometric Titrimetry and Titration Calorimetry*; Brigham Young University Press: Provo, UT.
- (25) Briggner, L. E.; Wadsö, I. *J. Biochem. Biophys. Methods* **1991**, *22*, 101.
- (26) Suurkuusk, J.; Wadsö, I. *Chem. Scr.* **1982**, *20*, 155.
- (27) Nordmark, M. G.; Laynez, J.; Suurkuusk, J.; Wadsö, I. *J. Biochem. Biophys. Methods* **1984**, *10*, 187.
- (28) Cox, B. G.; Schneider, H. *Coordination and Transport Properties of Macrocyclic Compounds in Solution*; Elsevier: New York, 1992.
- (29) Gans, P.; Sabatini, A.; Vacca, A. *Talanta* **1996**, *43*, 1739.
- (30) Danil de Namor, A. F.; Hill, T.; Sigstad, E. *J. Chem. Soc., Faraday Trans. 1* **1983**, *79*, 2713.
- (31) Danil de Namor, A. F.; Goitia, M. T.; Casal, A. R.; Villanueva-Salas, J. *J. Phys. Chem. Chem. Phys.* **2001**, *3*, 5242.
- (32) Danil de Namor, A. F.; Sueros Velarde, F. J.; Casal, A. R.; Pugliese, A.; Goitia, M. T.; Montero, M.; Lopez Fraga, F. *J. Chem. Soc. Faraday Trans.* **1997**, *93*, 3955.
- (33) Danil de Namor, A. F.; Goitia, M. T.; Casal, A. R.; Sueros Velarde, F. J.; Barja Gonzalez, M. I.; Villanueva Salas, J. A.; Zapata Ormachea, M. L. *J. Phys. Chem. Chem. Phys.* **1999**, *85*, 2705.
- (34) Danil de Namor, A. F.; Pugliese, A.; Casal, A. R.; Llerena Barrios, M.; Aymonino, P. A.; Sueros Velarde, F. *J. Phys. Chem. Chem. Phys.* **2000**, *2*, 4355.