Double-Cavity Calix[4]pyrrole Derivative with Enhanced Capacity for the Fluoride Anion

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A double-cavity calix[4]pyrrole derivative, *meso*-tetramethyl-tetra[*N*-(2-phenoxyethyl)-*N*′-phenylurea]calix-[4]pyrrole, **1**, with enhanced hosting ability for the fluoride anion has been designed and characterized. Its interaction with anions (fluoride, chloride, bromide, iodide, dihydrogen phosphate, hydrogen sulfate, perchlorate, nitrate, and trifluoromethane sulfonate) was qualitatively and quantitatively assessed through ^{1}H NMR, conductance, and calorimetric studies. The outcome of these investigations demonstrates that **1** interacts only with fluoride and dihydrogen phosphate anions in dipolar aprotic media. However, the composition of these complexes differs in that two units of fluoride are taken per unit of **1**, while a 1:1 anion/ligand complex is formed with the dihydrogen phosphate anion. Results from the ^{1}H NMR studies are striking in that these not only provide information about the active sites of the ligand−anion interaction but also allow the establishment of the sequence of events taking place during fluoride complexation. Thus, hydrogen-bond formation between the pyrrolic hydrogen and the fluoride anion is followed by the uptake of a second anion through the same type of interaction, but with the phenyl urea. It is also the latter group that is responsible for the interaction of **1** with the dihydrogen phosphate anion. Finally, this paper illustrates the importance of structural information for the interpretation of the thermodynamics associated with these systems.

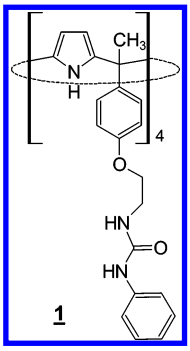
1. Introduction

The development of anion coordination has witnessed a great deal of interest in the past decade.[1,2] From both biological[3] and environmental[4] perspectives, it is very important to design ligands that have higher affinity toward a narrow range of anions to carry out specific tasks and to detect, selectively, the presence of nuisance anions in water. The interest in fluoride and phosphate chemistry is escalating as a result of the importance of their role. Phosphate anions play a fundamental role in biological systems to an extent that 70−75% of enzyme substrates and cofactors are anions that are very often phosphate residues, as in adenosine triphosphate and adenosine diphosphate.[5] On the other hand, although fluoride is currently used as a tool for dental caries control and prevention, it is now well-established that its uncontrolled use may cause odontogenesis disturbance and cytotoxicity on soft tissues.[6]

As a result of several factors, among which are the similar hydrophilicity and the hydration Gibbs energies, the design of selective receptors able to differentiate between fluoride and phosphate (dihydrogen phosphate) anions proved to be a challenging task to undertake.

In an attempt to enhance the capability of calixpyrrole toward anionic guests, a new calixpyrrole derivative, *meso*-tetramethyl-tetra[*N*-(2-phenoxyethyl)-*N*′-phenylurea]calix[4]pyrrole, **1**, with multiple binding sites distributed between two cavities for targeting anionic guests, was synthesized.

Structural and thermodynamic investigations involving **1** and its interaction with anions in solution are reported in this paper, including the following: (i) ^{1}H NMR studies in d_6-dimethylsulfoxide (DMSO) with the aim of investigating the presence of anion−ligand interactions and, if so, the active sites of the interaction of the macrocycle; (ii) conductometric studies to determine the complex composition in the appropriate solvent; and (iii) the thermodynamics of F^- and $H_2PO_4^-$ with **1** in *N*,*N*-dimethylformamide (DMF) at 298.15 K.



2. Experimental Section

A. Chemicals. *For ^{1}H NMR, Conductance, and Calorimetric Measurements.* Tetra-*n*-butylammonium fluoride trihydrate (99%, Fluka Chemical Co.), tetra-*n*-butylammonium chloride (97%, Fluka Chemical Co.), tetra-*n*-butylammonium bromide (99%, Aldrich Chemical Co.), and tetra-*n*-butylammonium iodide (99%, Aldrich Chemical Co.) were used. Tetra-*n*-butylammonium dihydrogen phosphate, hydrogen sulfate, nitrate, perchlorate, and trifluoromethane sulfonate (99%, Aldrich Chemical Co.) were dried over P_4O_{10} under vacuum for several days before use.

Meso-tetramethyl-tetra[*N*-(2-phenoxyethyl)-*N*′-phenylurea]-calix[4]pyrrole, **1**, was prepared at the Thermochemistry Laboratory, University of Surrey.

B. Synthesis of 1. A detailed approach for the preparation of **1** is given as supplementary data in Supporting Information.

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C. ^{1}H NMR Measurements. A Bruker AC-300E pulsed Fourier transform NMR spectrometer was used, and ^{1}H NMR measurements were recorded at 298 K. Typical operating conditions for the routine proton measurements involved a "pulse" or flip angle of 30°, spectral frequency of 300.135 MHz, delay time of 1.60 s, acquisition time of 1.819 s, and line broadening of 0.55 Hz.

A solution of the ligand under investigation was prepared in the appropriate deuterated solvent and then placed in a 5-mm NMR tube using tetramethylsilane as the internal reference.

The complexation behavior of the ligand **1** toward anions (fluoride, chloride, bromide, iodide, dihydrogen phosphate, hydrogen sulfate, perchlorate, nitrate, and trifluoromethane sulfonate as tetra-*n*-butylammonium salts) was studied by adding the anion salt (8.0×10^{-3} to 1.6×10^{-2} mol dm^{-3}) into the NMR tube containing the ligand dissolved in the same solvent (8.0×10^{-4} to 1.0×10^{-3} mol dm^{-3}). Stepwise additions of the anion salt were made, and the chemical shifts were recorded. Changes in the chemical shifts upon addition of the anion salt relative to the free ligand were calculated.

D. Conductance Measurements. *Conductometric Titrations of the Anions (as Tetrabutylammonium Counterion) with **1**.* For these measurements, a Wayne−Kerr model 7330 automatic LCR meter conductivity bridge at a frequency of 1 kHz was used. The conductance cell was a Russell-type glass-bodied electrode with a cell constant (determined using aqueous 0.10 mol dm^{-3} KCl solution) of 1.009 ± 0.001 cm^{-1}. For these experiments, the vessel was filled with the anion as the tetra(*n*-butylammonium) salt in the appropriate solvent (25 cm^3), and the conductance of the solution was measured. Then, a known volume of a solution of **1** in the same solvent was added stepwise into the vessel, and the conductance was measured after each addition. The temperature of the vessel was kept at 298.15 K using a thermostat.

E. Calorimetric Measurements. The thermodynamic parameters of the complexation of **1** with fluoride and dihydrogen phosphate anions [tetra(*n*-butylammonium) counterion] in DMF were determined by titration calorimetry. The four-channel heat-conduction calorimeter (Thermometric 2277) designed by Suurkuusk and Wadsö[7] was used. Electrical (static and dynamic) and chemical calibrations were carried out to check the reliability of the equipment.[8]

The reaction vessel was charged with a solution of the calix[4]pyrrole in DMF (2.8 cm^3). The anion [tetra(*n*-butylammonium) counterion] was injected incrementally using a 0.5-cm^3 gastight motor-driven Hamilton syringe. In each titration experiment, about 20 injections were made at time intervals of 30−45 min. For the calculations, 15 data points before the end point were considered. A correction for the enthalpy of dilution of the titrant in the solvent was carried out. A computer program for TAM (Digitam 4.1 for windows from Thermometric AB and Scitech Software AB, Sweden) was used to calculate log K_s and $\Delta_c H°$ values for the process under study.

3. Results and Discussion

A. ^{1}H NMR Titrations. The solvents that were selected are DMSO and DMF. The choice of these solvents was based on the following facts:

(i) d_6-DMSO is a commercially available solvent of low cost that was used to perform ^{1}H NMR measurements. Its properties are similar to those of DMF in that they are protophilic dipolar aprotic solvents.

(ii) There are no limitations in solubility of the ligand in these media.

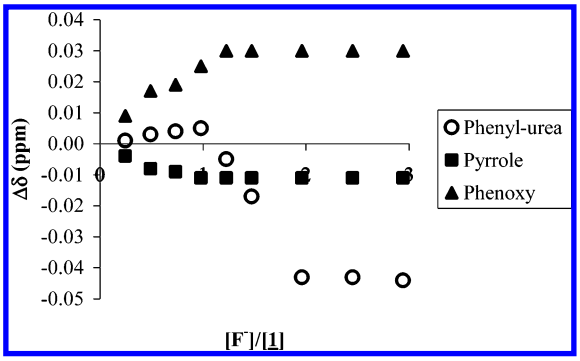

Figure 1. Chemical-shift changes, $\Delta\delta$ (ppm), against [F$^-$]/[**1**] at 298 K in the ^{1}H NMR titration of **1** with the fluoride anion salt in d_6-DMSO.

(iii) Anion salts are predominantly in their ionic forms. This is a requirement for rigorous thermodynamic studies.

Therefore, ^{1}H NMR titration was conducted in d_6-DMSO, and the chemical shifts of the protons of receptor **1** were recorded. Because the NH protons of the pyrrole and the urea groups could not be traced in the ^{1}H NMR spectrum in d_6-DMSO as a result of the broadness of the peak, the protons of the three aromatic moieties (the pyrrole, the phenoxy, and the phenyl urea) were monitored throughout the titration, and the differences in the chemical shifts between the free and the complex ligand were recorded. Significant chemical shifts were observed with F$^-$ and $H_2PO_4^-$, while no changes with respect to the ^{1}H NMR spectrum of the free ligand were found for the rest of the anions investigated (chloride, bromide, iodide, hydrogen sulfate, perchlorate, nitrate, and trifluoromethane sulfonate). Thus, Figure 1 illustrates the chemical-shift changes, $\Delta\delta$ (ppm), experienced by the phenyl urea, pyrrole, and the phenoxy protons with respect to the free ligand during the titration of **1** with the fluoride salt in d_6-DMSO at 298 K. These are plotted against the anion/ligand concentration ratios. The results are striking in that these not only provide information about the active sites of the ligand/anion interaction but also allow the establishment of the sequence of events taking place during the complexation process.

Indeed, the chemical-shift changes observed in the vicinity of the pyrrole and the phenoxy groups strongly suggest that the fluoride ions bind to the NH functionality via hydrogen-bond formation. However, the observation that (i) the chemical shift of the proton of these two moieties ceased to change once the 1:1 ratio was reached and (ii) the phenyl urea protons undergo significant chemical-shift changes from the 1:1 to the 2:1 concentration ratio provides a strong indication that the binding process involving **1** and the fluoride anions occurs in two stages. Thus, hydrogen-bond formation between the pyrrolic hydrogen (NH) and the anion is followed by the uptake of a second fluoride unit through the same type of interaction but with the phenyl urea protons. On the other hand, the chemical-shift changes of the phenyl urea group were predominant in the spectrum of **1** with $H_2PO_4^-$, where no changes were observed for the other two moieties (the pyrrole and the phenoxy) with this anion. Figure 2 shows that the phenyl urea protons undergo significant chemical-shift changes until the 1:1 concentration ratio is reached, suggesting that the process proceeds in a single stage with this anion.

In an attempt to corroborate further the ability of **1** to interact with anions and the composition of the complexes, we proceeded with conductometric studies, and these are now discussed.

B. Conductometric Titrations. The interaction of **1** with spherical (fluoride, chloride, bromide, and iodide) and non-

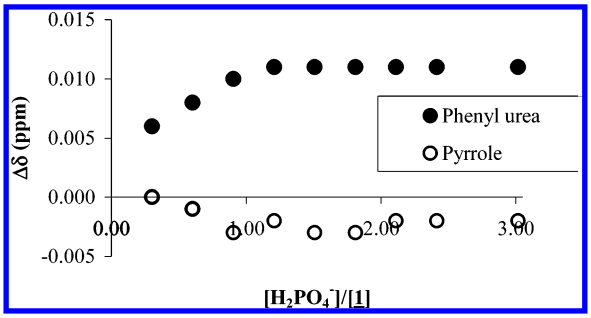

Figure 2. Chemical-shift changes, $\Delta\delta$ (ppm), against $[H_2PO_4^-]/[\mathbf{1}]$ at 298 K in the ^{1}H NMR titration of **1** with the dihydrogen phosphate anion salt in d_6-DMSO.

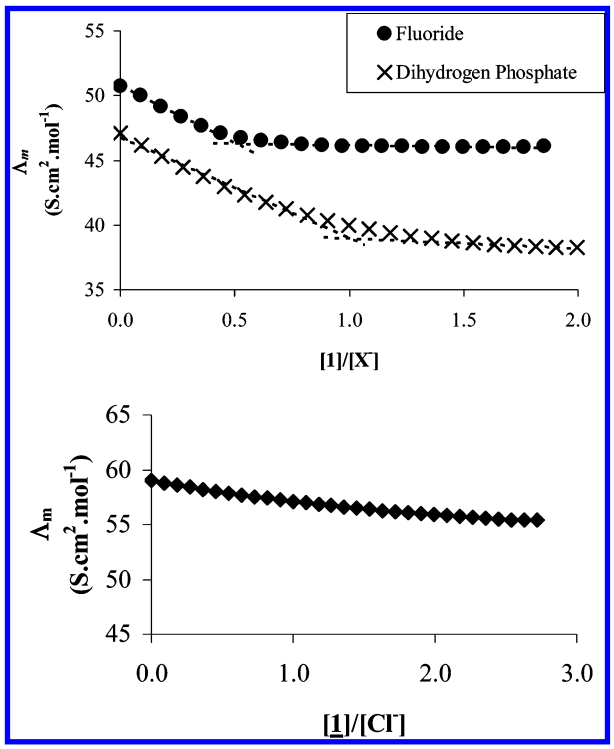

Figure 3. Conductometric curves for the titration of anions [tetra(*n*-butylammonium) counterion] with **1** in DMF at 298.15 K.

spherical (nitrate, perchlorate, hydrogen sulfate, and dihydrogen phosphate) anions was assessed through conductance measurements in DMF. Thus, the addition of **1** to tetra(*n*-butylammonium) salts containing fluoride and dihydrogen phosphate anions led to significant changes in the molar conductance, Λ_m. This statement is corroborated by the information given in Figure 3 where plots of Λ_m against the ligand/anion mole ratios for these anions are shown. As far as the fluoride anion is concerned, the well-defined change in curvature observed at a ligand/anion mole ratio of 0.5 indicates that two anions interact per unit of ligand. This is concomitant with the ^{1}H NMR investigations involving this anion and this ligand in a related solvent.

The conductometric curve (Figure 3) for the titration of $H_2PO_4^-$ with **1** in DMF shows a deflection at the 1:1 mole concentration ratio, suggesting that one anion is taken up per unit of receptor. In both cases, conductometric titration curves show a decrease in conductance upon addition of the ligand to the solution containing the anion salt in DMF. This is attributed to an increase in the size of the anion in moving from the free to the complex state, which results in a lower mobility and consequently a decrease in conductivity. No significant changes in the molar conductance values were observed for salts containing chloride, bromide, iodide, hydrogen sulfate, perchlorate, nitrate, and trifluoromethane sulfonate anions, indicating that either weak or no complexation takes place between these anions and this receptor (a representative example on the absence of interaction is shown for the chloride anion in Figure 3). In conclusion, the outcome of conductometric studies is concomitant with that of the ^{1}H NMR. Both investigations clearly reflect that the hosting capacity of this receptor is greater for the fluoride relative to the dihydrogen phosphate anion. In an attempt to gain quantitative information on the strength of anion−receptor interaction, we proceeded with the thermodynamic characterization of the binding process involving **1** and the relevant anions.

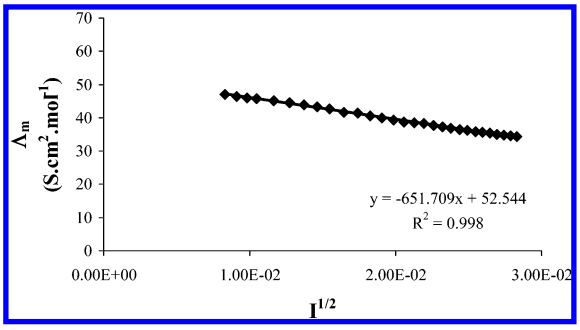

Figure 4. Molar conductances, S (cm^2 mol^{-1}), of F^- as a function of the square root of the ionic strength in DMSO at 298.15 K.

TABLE 1: Thermodynamics of the Complexation of 1 and the Anions in DMF at 298.15 K

anion	log K_s	$\Delta_cG°$ (kJ mol^{-1})	$\Delta_cH°$ (kJ mol^{-1})	$\Delta_cS°$ (J mol^{-1} K^{-1})
F^- (1:1)	4.3 ± 0.2	−24.6 ± 0.8	−21.1 ± 0.2	12
F^- (1:2)	2.8 ± 0.3	−15.7 ± 0.2	−6.4 ± 0.4	32
$H_2PO_4^-$ (1:1)	4.11± 0.03	−23.4 ± 0.2	−22.74 ± 0.02	3

C. Thermodynamics of Complexation. The first step in the thermodynamic characterization of the binding process is a clear definition and careful consideration of the process taking place in solution. Having determined the composition of the complex, the next step was to identify the speciation in solution. We have previously[9,10] shown that, in DMF and in DMSO (a representative example for the fluoride anion is shown in Figure 4), the free and complex salts exist predominantly in their ionic forms within the concentration range used for the determination of the thermodynamic parameters derived from titration calorimetry. Thus, the stability constants (expressed as log K_s), standard Gibbs energies, $\Delta_cG°$, enthalpies, $\Delta_cH°$, and entropies, $\Delta_cS°$, of complexation of fluoride and dihydrogen phosphate anions with **1** in DMF at 298.15 K are listed in Table 1.

In the case of fluoride, the data refer to the processes shown in eqs 1 and 2.

$$\mathbf{1}_{(DMF)} + F^-_{(DMF)} \xrightarrow{K_{s_1}} (\mathbf{1}{-}F)^-_{(DMF)} \quad (1)$$

$$(\mathbf{1}{-}F)^-_{(DMF)} + F^-_{(DMF)} \xrightarrow{K_{s_2}} (\mathbf{1}{-}F_2)^{2-}_{(DMF)} \quad (2)$$

For the dihydrogen phosphate, the data refer to the process described in eq 3.

$$\mathbf{1}_{(DMF)} + H_2PO^-_{4(DMF)} \xrightarrow{K_{s_1}} (\mathbf{1}{-}H_2PO_4)^-_{(DMF)} \quad (3)$$

As far as the fluoride anion is concerned, the thermodynamic data fit into a 1:2 ligand/anion model, while for dihydrogen phosphate, the data respond to a model involving a 1:1 process. Thus, calorimetric titration curves for these anions are shown

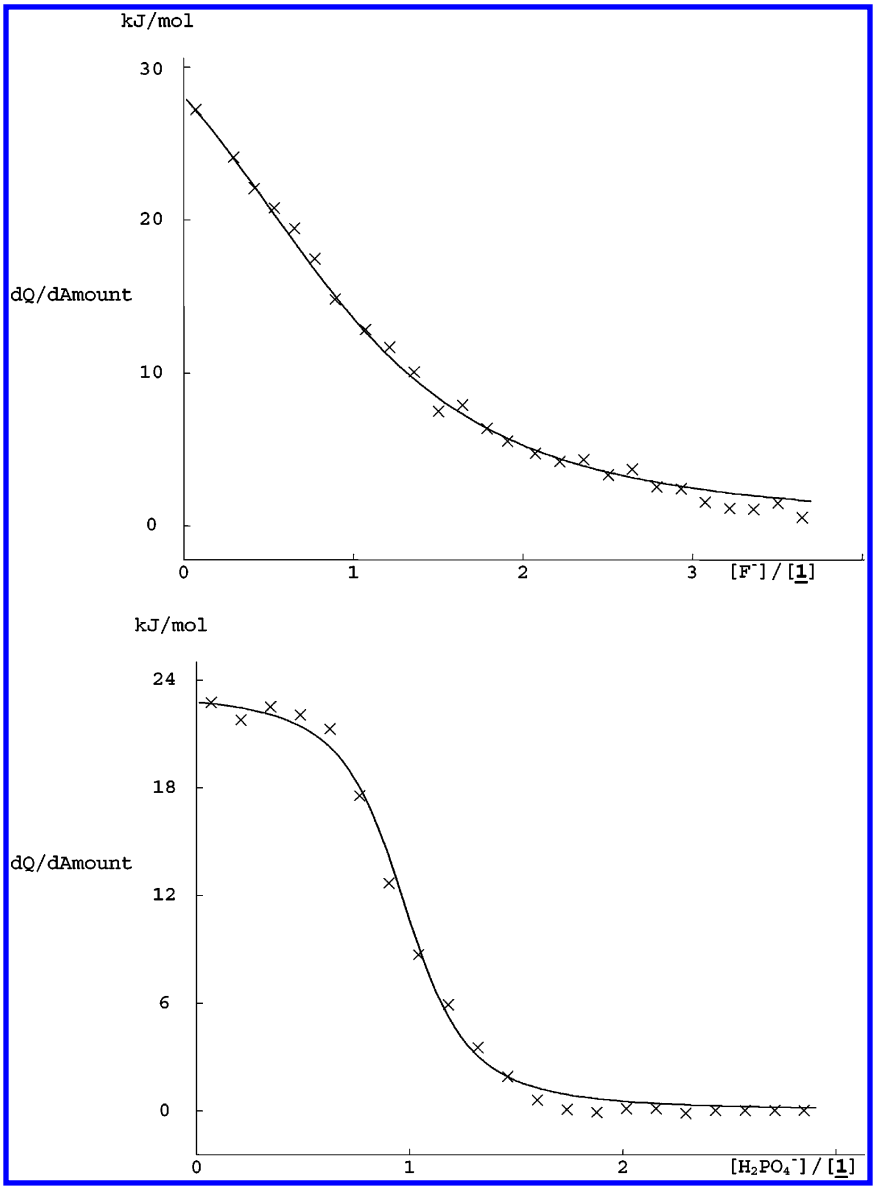

Figure 5. Plot of the enthalpy change vs [anion]/[ligand] for the calorimetric titration of **1** with F^- and $H_2PO_4^-$ [tetra(*n*-butylammonium) counterion] in DMF at 298.15 K.

in Figure 5. These findings are in accord with the results obtained from the conductance data and ^{1}H NMR studies. The thermodynamic parameters of the complexation of fluoride and **1** in this solvent reflect that both enthalpy and entropy contribute favorably to the Gibbs energy of the process. However, while the formation of the 1:1 complex is enthalpically controlled, it is indeed the entropic factor which contributes more favorably to the stability of the 1:2 ligand/anion complex. In an attempt to explain the thermodynamics involved in the complexation process, we recall the outcome of our ^{1}H NMR studies on this system, which unambiguously show that, while the first fluoride anion interacts with the pyrrolic hydrogen, the phenyl urea protons provide the site of interaction for the second anion. It is reasonable to assume that protophilic aprotic solvents such as DMSO and DMF are likely to interact with both the pyrrolic hydrogens and the phenyl urea protons. Evidence of the interaction between the pyrrolic protons and these solvents has been established in the solid state[11] and in solution.[11,12] However, steric effects in the former are likely to prevail when nonspherical anions or molecules (size and geometry) are involved, and, therefore, it is expected that the extent of hydrogen-bond formation between the phenyl urea protons and DMF is much greater than that for the pyrrolic protons. If so, more energy is to be required to remove the solvent in stage 2 (eq 2) than in stage 1 (eq 1) upon complexation with the anion. The thermodynamic implication of this statement is a decrease in enthalpic stability accompanied by an increase in entropy in moving from the 1:1 to the 1:2 complex. This explanation is concomitant with the thermodynamic parameters for the fluoride system shown in Table 1. This statement finds further support in the ^{1}H NMR results as follows. (i) The $H_2PO_4^-$ results clearly demonstrate that, unlike for the fluoride system in which this anion interacts with the pyrrolic protons, the active sites of the interaction of **1** with this anion are provided by the phenyl urea protons. (ii) The results for the other calixpyrrole derivatives in which the extended cavity involves ester and amide groups showed that there were no interactions between the pyrrole moiety and $H_2PO_4^-$ in deuterated DMSO.[13]

As far as the interaction of **1** and the $H_2PO_4^-$ anion is concerned, the complexation process is enthalpically controlled. However, it should be emphasized that, in this case, we are dealing with an anion that is able to enter multiple hydrogen-bond formations with the ligand through its oxygen atoms. In addition, the possibility of an interaction through the —C═O

groups of the phenyl urea groups and the OH moieties of the anion cannot be excluded. An inspection of the values shown in Table 1 may lead to the suggestion that the site of the interaction of this receptor with the fluoride anion for the formation of the 1:1 complex is the same as that for the dihydrogen phosphate given the similarities observed in the stability constants (hence, $\Delta_c G°$), the $\Delta_c H°$ values, and to an extent the $\Delta_c S°$ values for these two systems. However, this is indeed not the case, as reflected in the ^{1}H NMR studies.

The different stoichiometries of the ligand **1** complexes with fluoride and dihydrogen phosphate can be safely attributed to the size of the anions. The fluoride anion is the most electronegative of the halides and the smallest (1.33 Å);[5] thus, it is able to squeeze into the cavity and enter hydrogen-bond formation with the pyrrole moiety, as demonstrated by the ^{1}H NMR data. On the other hand, the dihydrogen phosphate anion (2.00 Å),[5] being larger than the fluoride, is not able to conquer the walls of the cavity, thus, limiting the interaction to the phenyl urea moiety.

We, therefore, conclude that, while it is indisputable that in the derivation of thermodynamics any model proposed must fit the experimental thermodynamic data, their interpretation requires structural information. Indeed, this paper illustrates with representative examples that conclusions based solely on thermodynamics can be misleading.

4. Conclusions

On the basis of the above discussion, the following conclusions are drawn.

(1) A double-cavity ligand showing enhanced hosting ability for the fluoride anion relative to dihydrogen phosphate has been, for the first time, synthesized and characterized. The ligand discriminates against other spherical (chloride, bromide, and iodide) and nonspherical (hydrogen sulfate, perchlorate, nitrate, and trrifluoromethane sulfonate) anions. This statement was corroborated by ^{1}H NMR and conductometric studies.

(2) Agreement between ^{1}H NMR, conductometric, and calorimetric investigations was found regarding the composition of the anion complexes in the medium under study. The active sites of complexation of the ligand were identified through ^{1}H NMR. As far as the fluoride−ligand complexation is concerned, the sequence of events taking place in the uptake of two fluoride ions by the ligand were also established by the ^{1}H NMR investigations.

(3) Structural information is required for the interpretation of the thermodynamics associated with these processes.

(4) Preliminary results show that this ligand has considerable scope in the design of ion-selective membranes for fluoride detection. This work is now in progress.[14]

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Supporting Information Available: A detailed description of the synthesis of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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