New Insights on Anion Recognition by Isomers of a Calix Pyrrole Derivative

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Two isomeric structures of *meso*-tetramethyltetrakis(3-hydroxyphenyl)calix[4]pyrrole, **4**-αα*ββ* and **4**-α*β*α*β*, have been isolated and characterized by ^{1}H NMR in different solvents (CD_3CN, CD_3OD, and DMSO-d_6) at 298 K. Standard Gibbs energies of solution derived from solubility data in various solvents were used to calculate the transfer Gibbs energy, $\Delta_t G°$, of these ligands using acetonitrile as the reference solvent. These results are consistent with the ^{1}H NMR studies in different media that show chemical shift changes observed in the resonances of the N**H** and the O**H** protons of these ligands. Solvate formation was observed when these isomers were exposed to saturated atmosphere of *N*,*N*-dimethylformamide, dimethyl sulfoxide and propylene carbonate. Anion interaction involving **4**-αα*ββ* and **4**-α*β*α*β* was investigated by ^{1}H NMR in CD_3CN while the complex composition was assessed through conductance measurements. Significant differences are observed in the affinity of these ligands for anions as well as in the composition of the fluoride complexes. Thus **4**-αα*ββ* shows selectivity for $H_2PO_4^-$ in acetonitrile while its isomer **4**-α*β*α*β* is selective for the fluoride anion. Again the complex composition is altered for the fluoride anion when complexed with **4**-αα*ββ* in acetonitrile (1:1 complex) relative to **4**-α*β*α*β* in the same solvent. The latter isomer shows an enhanced hosting ability for this anion. Thus two anions are taken up per unit of ligand. The thermodynamics of complexation of $H_2PO_4^-$ and these ligands in acetonitrile is discussed, and the results are compared with those involving calix[4]pyrrole and this anion in this solvent. It is shown that the isomers interact with two $H_2PO_4^-$ anions while one calix[4]pyrrole unit interacts with this anion. This paper demonstrates for the first time that the enthalpy parameter may be a suitable reporter of the number of hydrogen bonds formed when calix[4]pyrrole and its derivatives interact with the dihydrogen phosphate anion in acetonitrile. In moving from acetonitrile to *N*,*N*-dimethylformamide, **4**-αα*ββ* is unable to enter complexation with most anions, except fluoride, with which the formation of a 1:2 (ligand:anion) complex is demonstrated. The rather versatile behavior of these receptors for anions is explained on the basis of ^{1}H NMR evidence and solvation effects. These investigations highlight the importance of the medium effect on the stability of the complex and reflect the inherent nature of the solvent and its highly significant involvement in the complexation process.

Introduction

Key features of supramolecular chemistry[1−3] involve, first, recognition, where the macrocycle shows selectivity toward one substrate relative to another. Second, there is a chemical transformation in the nature of the guest upon complexation with the receptor, allowing the translocation of the guest to media it would not normally be able to pass through. It is this complex formation that is thought to be responsible for the transport of ionic species across lipophilic cell membranes. These requirements are fulfilled by calix[4]pyrroles,[4,6] which are a more recent addition to the assortment of macrocycles. Their basic ring structure resembles that of porphyrin. In the past, four pyrrole rings linked by methylene groups to form colorless compounds (that feature in the biosynthetic pathways to pyrrole pigments) were referred as porphyrinogens.[7] The term calix[4]pyrrole was later ascribed to these macrocycles and their derivatives because of their relation to calix[4]arene.[8] Calix[4]-pyrroles are known for their anion binding properties as these are able to enter hydrogen bond formation through the pyrrolic −NH− group. Starting with the calix[4]pyrrole, **1**, a detailed thermodynamic investigation was carried out involving this ligand and anions.[9] These studies demonstrated the selectivity of **1** for the fluoride anion among the halides in solution. Then **2**, a derivative of **1**, resembling the lower rim of the parent *p*-substituted calix[4]arene in shape and structure, was synthesized.[10] Investigations carried out on this ligand and the halide anions also revealed its selective behavior for these anions. More recently, a new double cavity calix[4]pyrrole derivative, **3**, was prepared and investigated by our group.[11] This receptor showed an enhanced capacity for the fluoride anion in solution. The effect of the introduced cavity on anion selectivity was highlighted.

In this paper we introduce two isomeric structures of *meso*-tetramethyltetrakis(3-hydroxyphenyl)calix[4]pyrrole denoted by **4**-αα*ββ* and **4**-α*β*α*β*, respectively, and their anion binding properties in acetonitrile. The medium effect is assessed through the complexation thermodynamics of **4**-αα*ββ* and anions in *N*,*N*-dimethyformamide.

Experimental

Chemicals Used. Pyrrole, 3-hydroxyacetophenone, and methanesulfonic acid were all purchased from Aldrich Chemical Co. Solvents used (acetonitrile, *N*,*N*-dimethylformamide, dichloromethane, methanol and diethyl ether) were HPLC grade from

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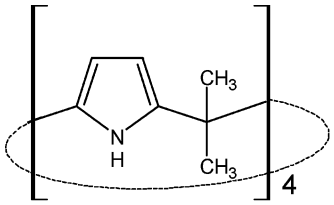
CHART 1



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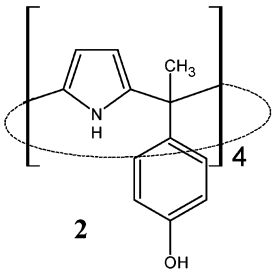

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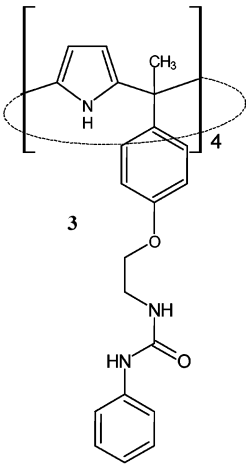

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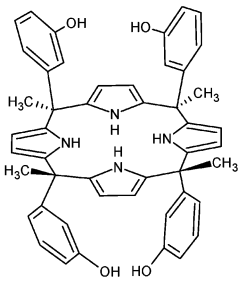
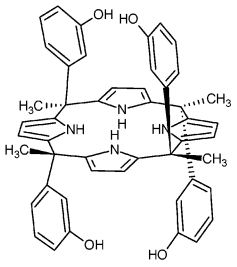


4- $\alpha\alpha\beta\beta$



4- $\alpha\beta\alpha\beta$

Fischer Chemical Co. For conductance and calorimetric measurements, acetonitrile and *N*,*N*-dimethylformamide were used as described elsewhere.[12] Tetra-*n*-butylammonium fluoride trihydrate (99%), chloride (97%) (both from Fluka Chemical Co.), and bromide (99%), iodide (99%), dihydrogen phosphate, hydrogen sulfate, nitrate, perchlorate, and trifluoromethane sulfonate (all 99% from Aldrich Chemical Co.) were dried over P_4O_{10} under vacuum for several days before use.

Synthesis of $\alpha\alpha\beta\beta$ and $\alpha\beta\alpha\beta$ Isomers of *meso*-Tetramethyltetrakis(3-hydroxyphenyl)calix[4]pyrrole. To a stirring solution of pyrrole (5 mL, 75 mmol) dissolved in methanol (100 mL) was added a solution of 3-hydroxyacetophenone (11 g, 80 mmol) in MeOH (100 mL). Methanesulfonic acid (1 mL) was then added, and the reaction mixture was left stirring overnight. Thin-layer chromatography (eluent dichloromethane:methanol, 95:5) indicated that all the starting materials reacted. The reaction mixture was added slowly to a separate flask of stirred distilled water (500 mL). The resulting orange precipitate was filtered, dissolved in diethyl ether and filtered gravitationally. The filtrate was evaporated in vacuo to give a beige solid, which was recrystallized from glacial acetic acid to give a solid that was further recrystallized from acetone to give a white compound, the $\alpha\alpha\beta\beta$ isomer (37% yield). ^{1}H NMR (acetone-d_6, 300 MHz, 298 K, ppm) characterization gave the following: 9.01 (s broad, 2H, N**H**); 8.78 (s broad, 2H, N**H**); 7.02 (t, 4H, Ar**H**); 8.04 (s broad, O**H**); 6.59 (d, 4H, Ar**H**); 6.52 (d, 4H, Ar**H**, $J = 7.8$ Hz); 6.61 (s, 4H, Ar**H**); 5.96 (d, 4H, Py**H**, $J = 2.4$ Hz); 5.70 (d, 4H, Py**H**, $J = 2.4$ Hz); 1.83 (s, 12H, C**H**$_3$). MS (FAB): m/z 741 [M^+]. Microanalysis was carried out at the University of Surrey. Calc: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.71; H, 6.01; N, 7.54.

The filtrate was then left overnight to recrystallize and the precipitated powder was further recrystallized from acetonitrile to give the $\alpha\beta\alpha\beta$ isomer in 34% yield. After drying under vacuum at 90 °C, the compound was characterized by ^{1}H NMR (acetone-d_6, 300 MHz, 298 K), which gave the following (in ppm): 8.79 (s broad, 2H, N**H**); 8.07 (s broad, 4H, O**H**); 7.05 (t, 4H, Ar**H**); 6.56 (d, 4H, Ar**H**, $J = 9.6$ Hz); 6.48 (d, 4H, Ar**H**, $J = 7.5$ Hz); 6.44 (s, 4H, Ar**H**); 6.02 (d, 8H, Py**H**, $J = 2.4$ Hz); 1.85 (s, 12H, C**H**$_3$). Microanalysis was carried out at the University of Surrey. Calc: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.75; H, 5.98; N, 7.55.

Solubility Measurements. Saturated solutions of the calix[4]pyrrole isomers were prepared by adding an excess amount of the solid to various organic solvents (acetonitrile, MeCN; ethanol, EtOH; and methanol, MeOH). The mixtures were left in a thermostated bath at 298.15 K for several days until equilibrium was reached. Aliquots of the saturated solutions were taken and analyzed gravimetrically in triplicate. Blank experiments were carried out. Solvate formation was checked by exposing the solid to a saturated atmosphere of the solvent for several days, following the procedure described in the literature.[13] The samples were weighed from time to time to check for any uptake of solvent. Solvate formation was observed in *N*,*N*-dimethylformamide, DMF; dimethyl sulfoxide, DMSO; and propylene carbonate, PC.

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

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

The complexation behavior of the ligands, **4**-$\alpha\alpha\beta\beta$ and **4**-$\alpha\beta\alpha\beta$ 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.

Conductometric Measurements. Conductometric titrations of the anions (as tetra-butylammonium counterion) with **4**-αα*ββ* and **4**-α*β*α*β* were carried out. 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 0.10 mol·dm^{-3} aqueous 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 solution of **4**-αα*ββ* and **4**-α*β*α*β* in the same solvent was added stepwise into the vessel and the conductance measured after each addition once equilibrium was reached. The temperature of the vessel was kept at 298.15 K using a thermostat.

Calorimetric Measurements. The thermodynamic parameters of complexation of **4**-αα*ββ* and **4**-α*β*α*β* with anions (tetra-*n*-butylammonium counterion) in acetonitrile and *N*,*N*-dimethylformamide were determined by titration calorimetry at 298.15 K. The four-channel heat conduction calorimeter (Thermometric 2277) designed by Suurkuusk and Wadsö[14] was used. Electrical (static and dynamic) and chemical calibrations were carried out to check the reliability of the equipment.[15]

The reaction vessel was charged with a solution of the calix-[4]pyrrole derivative in the appropriate solvent (2.8 cm^3). The anion (tetra-*n*-butylammonium counterion) solution 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. 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 Δ_cH values for the process under study.

Results and Discussion

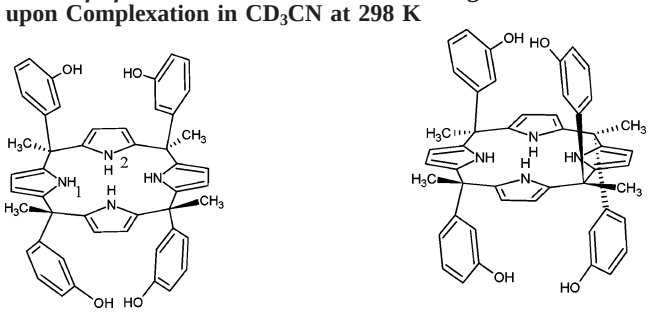
Solubilities and Derived Gibbs Energies of Solution and Transfer.[16,17] Solubility data for **4**-αα*ββ* and **4**-α*β*α*β* in various solvents at 298.15 K are reported in Table 1. These are the result of at least three analytical measurements carried out on the same saturated solution of the appropriate ligand. Thus the standard deviation of the data is also included in this table. In cases where no solvate formation was observed when the solid was exposed to a saturated atmosphere of the solvent, solubility data were used to calculate the standard Gibbs energies of solution, $\Delta_s G°$, referred to the standard state of 1 mol dm^{-3}. Taking acetonitrile as the reference solvent, the standard transfer Gibbs energies, $\Delta_t G°$ of these ligands from acetonitrile to the alcohols were calculated. $\Delta_s G°$ and $\Delta_t G°$ values are also included in Table 1. These results show that these ligands interact strongly with the alcohols relative to acetonitrile. These results are consistent with the ^{1}H NMR data carried out in CD_3CN, CD_3OD, and DMSO-d_6 at 298 K. Indeed, downfield shifts in the resonances of the N**H** protons were observed for both ligands in moving from CD_3CN to CD_3OD ($\Delta\delta$ values of 1.21 and 2.17 ppm for **4**-αα*ββ* and **4**-α*β*α*β* respectively) and to DMSO-d_6 ($\Delta\delta$ values of 1.50 and 2.55 ppm respectively). To a lesser extent, chemical shift changes were also observed for the O**H** protons and this is discussed later on. Having determined the solubility of these ligands, we proceeded with ^{1}H NMR studies in an attempt to assess the interaction of these ligands with anions.

TABLE 1: Solubilities and Derived Standard Gibbs Energies of Solution of 4-αα*ββ* and 4-α*β*α*β* in Nonaqueous Solvents at 298.15 K. Derived Standard Gibbs Energies of Transfer from Acetonitrile[a]

solvent	solubility/ mol dm^{-3}	$\Delta_s G°$/ kJ·mol^{-1}	$\Delta_t G°_{(MECN\rightarrow s)}$/ kJ·mol^{-1}
	4-αα*ββ*		
MeCN	(4.09 ± 0.05) × 10^{-3}	13.63 ± 0.03	0
MeOH	(8.67± 0.08) × 10^{-2}	10.51 ± 0.06	−3.12
EtOH	(1.44 ± 0.03) × 10^{-2}	6.06 ± 0.02	−7.57
DMF	solvate formation		
DMSO	solvate formation		
PC	solvate formation		
	4-α*β*α*β*		
MeCN	(4.05 ± 0.09) × 10^{-3}	13.66 ± 0.06	0
MeOH	(2.98± 0.04) × 10^{-2}	7.34 ± 0.03	−6.32
EtOH	(5.18 ± 0.03) × 10^{-2}	8.71 ± 0.04	−4.95
DMF	solvate formation		
DMSO	solvate formation		
PC	solvate formation		

[a] Abbreviations: acetonitrile, MeCN; methanol, MeOH; ethanol, EtOH; *N*,*N*-dimethylformamide, DMF; dimethyl sulfoxide, DMSO and propylene carbonate, PC.

TABLE 2: ^{1}H NMR Chemical Shifts ($\Delta\delta$/ppm) of 4-αα*ββ* and 4-α*β*α*β* and Their Chemical Shift Changes Observed upon Complexation in CD_3CN at 298 K



	4-αα*ββ*[a]			**4**-α*β*α*β*[b]	
anion	$H_{N(1)}$	$H_{N(2)}$	O*H*	H_N	O*H*
F^-	0.09	−0.31		5.48	0.22
Cl^-	0.08	−0.33	1.89	2.08	0.69
Br^-	0.12	−0.25	0.77	1.00	0.12
I^-	0.00	0.00	0.00	0.10	0.00
$H_2PO_4^-$	0.17	−0.28			0.12
HSO_4^-	0.14	−0.20			0.01

[a] $\Delta\delta$ values are the chemical shift changes relative to **4**-αα*ββ* (free ligand). δ Values for **4**-αα*ββ* are $H_{N(1)}$ = 7.90 ppm; $H_{N(2)}$ = 8.06 ppm and O**H** = 6.79 ppm. [b] $\Delta\delta$ values are the chemical shift changes relative to **4**-α*β*α*β* (free ligand). δ Values for **4**-α*β*α*β* are H_N = 6.92 ppm and O**H** = 7.96 ppm.

^{1}H NMR Measurements. The study of complexation of **4**-αα*ββ* with F^-, Cl^-, Br^-, I^-, $H_2PO_4^-$, and HSO_4^- (as tetra-*n*-butylammonium) salts in CD_3CN (Table 2) indicates that the **4**-αα*ββ* interacts with F^-, Cl^-, Br^-, and $H_2PO_4^-$. In qualitative terms, no significant selectivity trend is observed between these anions.

The most significant changes in the ^{1}H NMR spectrum were observed for the N**H** and O**H** protons. For this reason, these protons were monitored and the changes in their chemical shifts were recorded.

De-shielding of the $\mathbf{H}_{N1}$ proton indicates that the anions tend to interact with it. On the other hand, $\mathbf{H}_{N2}$ experiences a shielding effect upon complexation with these anions.

This is an unusual behavior for this proton. This behavior suggests that conformational changes of the pyrrole rings in the ligand are taking place upon complexation. This conformational change results in the orientation of the pyrrole proton

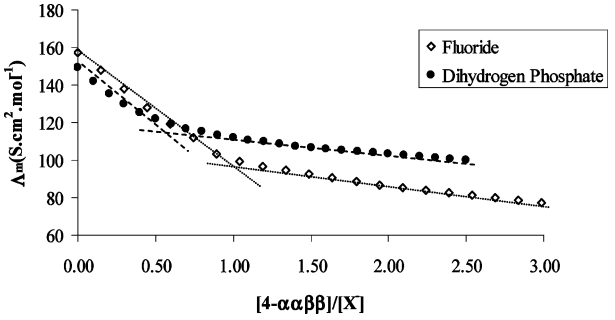


Figure 1. Conductometric curves for the titration of anions (tetra-*n*-butylammonium counterion) with **4**-α*α*β*β* in acetonitrile at 298.15 K.

(**H**$_{N2}$), thus shielding this proton from the external magnetic field. However, due to the broadness of the O**H** signal in the spectra with F^- and $H_2PO_4^-$ it was not possible to proceed with the evaluation of the $\Delta\delta$ values for this proton in the presence of these anions.

The other isomer of this ligand, **4**-α*β*α*β*, shows interaction with the fluoride anion as can be inferred from the $\Delta\delta$ values of the **H**$_N$ proton (Table 2). However, the broadness of the **H**$_N$ signals in the spectra involving F^-, $H_2PO_4^-$, and HSO_4^- prevented the calculation of the $\Delta\delta$ values for this proton with those anions in this solvent.

Therefore it can be concluded from the above discussion that both protons, NH and OH play significant roles in the complexation processes with anionic guests in solution, although the latter does not seem to interact strongly with $H_2PO_4^-$ when complexed with **4**-α*β*α*β* in acetonitrile.

Having established the site of interaction of this ligand and these anions, we proceeded with conductometric titrations in acetonitrile and *N*,*N*-dimethylformamide and these are now discussed.

Conductometric Titrations. The interaction of **4**-α*α*β*β* and **4**-α*β*α*β* with spherical (fluoride, chloride, bromide and iodide) and nonspherical (nitrate, perchlorate, hydrogen sulfate and dihydrogen phosphate) anions was assessed through conductance measurements in acetonitrile. Thus the addition of **4**-α*α*β*β* and **4**-α*β*α*β* 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 1 where plots of Λ_m against the ligand/anion mole ratios for these anions are shown. These findings demonstrate the ability of **4**-α*α*β*β* to complex with the fluoride anion in a 1:1 (ligand:anion) ratio relative to dihydrogen phosphate (1:2 ligand:anion) in acetonitrile at 298.15 K. In both cases, conductometric titration curves show a decrease in conductance upon addition of the ligand to the solution containing the anion salt in acetonitrile.

This can be attributed to the 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 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. On the other hand, receptor **4**-α*β*α*β* showed the ability to complex the fluoride anion and dihydrogen phosphate anions in 1:2 (ligand:anion) ratios.

This investigation clearly reflects that the hosting capacity of **4**-α*α*β*β* is greater for the dihydrogen phosphate relative to the fluoride anion.

To assess the medium effect on the complexation process, conductance measurements were carried out in *N*,*N*-dimethylformamide using **4**-α*α*β*β* as the ligand.

Plots of molar conductance, Λ_m, against the ratio of the concentration of the ligand and anion salt, derived from conductance values, show no changes in the gradient upon titrating the ligand with $H_2PO_4^-$, Cl^-, Br^-, and I^-, indicating that little or no complexation has occurred. In the case of the fluoride ion, however, a noticeable change in the gradient was observed with the largest changes in the curvature being at **4**-α*α*β*β*/F^- stoichiometry of 0.5 and 1, indicating, respectively, the formation of 1:2 and 1:1 ligand:anion complexes. On the basis of these results, it is concluded that the largest difference between the conductometric titrations of **4**-α*α*β*β* and anions in DMF relative to MeCN is that no interaction was observed between this ligand and $H_2PO_4^-$ in DMF, whereas in MeCN, **4**-α*α*β*β* formed a 1:2 ligand:anion complex with this anion. A similarity between these two solvents is that no significant changes in the molar conductances were seen in the conductometric titration involving the bromide and the iodide salts in MeCN or DMF, indicating that there is little or no complexation between this ligand and these anions in these solvents. As far as the fluoride anion and **4**-α*α*β*β* are concerned, conductometric data reflect a change in the composition of the complex in moving from MeCN (1:1) to *N*,*N*-dimethylformamide. In the latter solvent, two fluoride anions are taken up per unit of ligand. As a result of conductance studies, we proceeded with the thermodynamics of complexation of these ligands and anions in acetonitrile and *N*,*N*-dimethylformamide.

Thermodynamics of Complexation. Stability constants (expressed as log K_s) and derived standard Gibbs energies, $\Delta_c G°$, enthalpies, $\Delta_c H°$ and entropies, $\Delta_c S°$ of complexation of **4**-α*α*β*β* and **4**-α*β*α*β* with anions in acetonitrile and those for the fluoride anion and the former ligand in *N*,*N*-dimethylformamide at 298.15 K are listed in Table 3. These data are derived from log K_s and $\Delta_c H°$ values obtained from titration calorimetry. The standard deviation of the data is also included in Table 3.

The striking feature of the data is the selective behavior of the **4**-α*α*β*β* ligand for the dihydrogen phosphate anion in acetonitrile. Indeed, in this solvent the ligand is able to recognize selectively these anions with a higher capacity to uptake $H_2PO_4^-$ relative to fluoride and chloride anions. Thus the following trend of selectivity is observed for 1:1 complexes: $H_2PO_4^- > HP_2O_7^{3-} > F^- > Cl^- > I^-$.

It can be inferred that the orientation of the phenol group in **4**-α*α*β*β* turned the affinity of this isomer toward the tetrahedral dihydrogen phosphate (1:2 ligand:anion ratio) over the remaining spherical anions (1:1 ligand:anion ratio) (Figure 3) whereas the hydrogen pyrophosphate needs two units of ligand to complex at both sides of the trivalent anion. In acetonitrile, the complexation process involving **4**-α*α*β*β* and anions is enthalpy controlled and entropy destabilized.

A similar trend in terms of selectivity was observed for **4**-α*β*α*β* (Table 3) except that in this case the selectivity and the capacity of the ligand to interact with fluoride is enhanced. Thus the interaction of the ligand is greater with the fluoride than with the dihydrogen phosphate anion in acetonitrile. In addition, these results demonstrate that **4**-α*β*α*β* is able to take up two units of anion whereas **4**-α*α*β*β* forms only 1:1 complex in this solvent.

The difference between the two isomers is mainly structural, and therefore the variations observed in the binding properties can be related to the configuration of the ligands and the positions of the binding sites within each ligand. A proposed

TABLE 3: Thermodynamic Parameters of Complexation of 4-αα*ββ* and 4-α*β*α*β* with Anions in Dipolar Media at 298.15 K

anion	L:X[a]	log K_s	$\Delta_c G°$/ kJ·mol^{-1}	$\Delta_c H°$/ kJ·mol^{-1}	$\Delta_c S°$/ J·mol^{-1}·K^{-1}
			4-αα*ββ* (Acetonitrile)		
$H_2PO_4^-$	(1:1)	3.60 ± 0.02	−20.54 ± 0.04	−24.55 ± 0.06	−13
	(1:2)	2.50 ± 0.03	−14.43 ± 0.04	−22.63 ± 0.06	−28
	(overall)	6.1	−34.91	−47.2	−41
F^-	(1:1)	3.08 ± 0.02	−17.6 ± 0.1	−97.1 ± 0.8	−267
Cl^-	(1:1)	2.59 ± 0.04	−14.8 ± 0.2	−55.46 ± 0.04	−136
$HP_2O_7^{3-}$	(1:1)	3.26 ± 0.02	−18.6 ± 0.1	−38.5 ± 0.1	−67
	(2:1)	3.55 ± 0.02	−20.2 ± 0.1	−127.5 ± 0.2	−359
	(overall)	6.8	−38.8	−166	−426
			4-αα*ββ* (*N*,*N*-Dimethylformamide)		
F^-	(1:1)	3.4 ± 0.1	−19.2 ± 0.8	−13.6 ± 0.3	19
	(1:2)	3.2 ± 0.2	−18.2 ± 1.1	−7.6 ± 0.2	35
	(overall)	6.6	−37.4	−21.2	54
			4-α*β*α*β* (Acetonitrile)		
$H_2PO_4^-$	(1:1)	4.80 ± 0.02	−27.4 ± 0.3	−20.2 ± 0.1	25
	(1:2)	4.66 ± 0.10	−15.2 ± 0.5	−29.9 ± 0.6	−50
	(overall)	9.46	−42.6	−50.1	−25
F^-	(1:1)	5.00 ± 0.04	−28.5 ± 0.2	−31.4 ± 0.3	−10
	(1:2)	4.72 ± 0.01	−27.0 ± 0.1	−61.5 ± 0.3	−116
	(overall)	9.72	−55.5	−92.9	−126
Cl^-	(1:1)	2.36 ± 0.03	−13.5 ± 0.1	−86.3 ± 0.3	−244
$HP_2O_7^{3-}$	(1:1)	3.97 ± 0.03	−22.6 ± 0.5	−65.4 ± 0.1	−143
	(2:1)	3.25 ± 0.08	−18.6 ± 0.7	−83.2 ± 0.2	−217
	(overall)	7.22	−41.2	−148.6	−360

[a] L:X denotes the ligand to anion concentration ratio (complex composition).

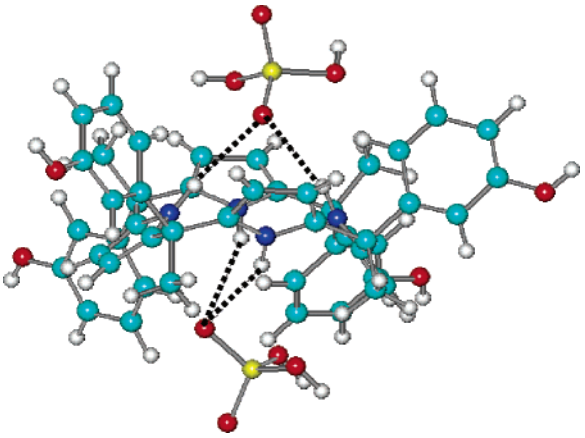


Figure 2. Molecular modeling of **4**-α*β*α*β*-$H_2PO_4^-$ (1:2) complex as determined by molecular simulation studies.

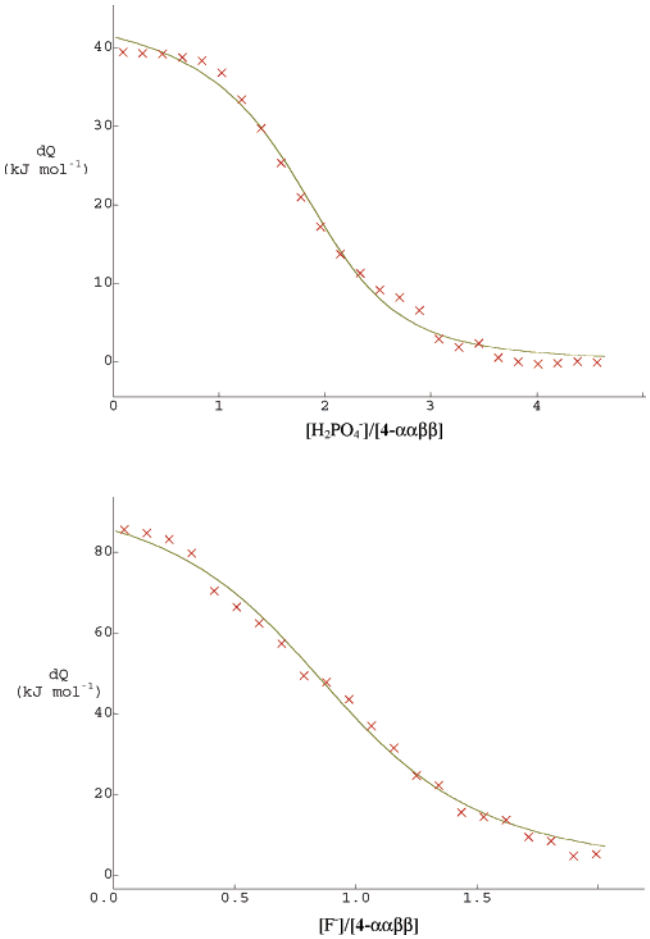


Figure 3. Plot of the enthalpy change vs [anion]/[ligand] concentration ratios for the calorimetric titration of **4**-αα*ββ* with $H_2PO_4^-$ and F^- (tetra-*n*-butylammonium counterion) in acetonitrile at 298.15 K.

explanation to this behavior can be inferred for the ^{1}H NMR data (Table 2) for the complexation of these ligands and anions in CD_3CN. The data presented in Table 2 show that for **4**-αα*ββ*, the signal for the OH protons is missing in the spectra related to the complexation of F^-, but it is clearly present in all the spectra of **4**-α*β*α*β*. It is possible that after anion complexation, the OH groups of **4**-αα*ββ* in CD_3CN are driven closely to each other as to stimulate the formation of intramolecular hydrogen bonding, which would cause a more pronounced deshielding effect on this proton resulting in its drift out the range of the spectra. Being involved in hydrogen bonding, the ability of OH protons to complex a second anion will decrease. This is not the case for **4**-α*β*α*β* as the ^{1}H NMR does not give evidence for an intramolecular hydrogen bond between the OH protons, hence rendering these protons free to host a second fluoride anion.

The results in Table 3 show that the **4**-α*β*α*β* isomer has a higher affinity for $H_2PO_4^-$ than the 4-αα*ββ* ligand. Given that the enthalpies associated with the complexation of these ligands and this anion in acetonitrile do not differ significantly, the higher stability observed for $H_2PO_4^-$ and **4**-α*β*α*β* in acetonitrile is attributed to the more favorable enthalpy found for this system relative to that involving **4**-αα*ββ* and this anion in this solvent. However, the higher stability of the 1:2 complex with **4**-α*β*α*β*

relative to its isomer is mainly due to the more favorable enthalpy of the former relative to the latter. Computer modeling studies show that the arrangement of minimum energy for these systems is that in which each $H_2PO_4^-$ (through its negatively charged oxygen) is hydrogen bonded to the NH functionalities of two pyrrole units of these ligands, as shown in Figure 2. It is highly striking to note that the overall enthalpy changes for these two ligands and $H_2PO_4^-$ in MeCN are quite close to the previously reported value[9] for the enthalpy of complexation of **1** and this anion in this solvent ($\Delta_c H° = -48.1$ kJ mol^{-1}). For this 1:1 complex, molecular modeling calculations suggest that the four NH groups in **1** participate in hydrogen bond formation with the negatively charged oxygen atom of the $H_2PO_4^-$ anion. Given that the $\Delta_c H°$ values for these two isomers and this anion in each individual step (formation of the 1:1 and the 1:2 complex) are approximately half of the enthalpy values for **1** and $H_2PO_4^-$, it follows that (i) there is an additive enthalpic contribution of NH···O$^-$ hydrogen bonds between these calix[4]pyrrole ligands and this anion in this solvent (ii) enthalpy data are suitable reporters of the number of hydrogen bonds that the ligands can form upon complexation with $H_2PO_4^-$. Further work is now in progress to investigate the applicability of these findings to other ligands containing NH functionalities and this anion.

Medium Effect.[8−10,18−20] In an attempt to explain the absence of interaction between **4**-αα*ββ* and most anions (except fluoride) in *N*,*N*-dimethylformamide, a close look at the thermodynamic parameters of transfer of the reactants and the product is required.

The transfer Gibbs energy of **4**-αα*ββ* from acetonitrile to *N*,*N*-dimethylformamide could not be calculated because this host as well as **4**-α*β*α*β* are highly solvated in the latter solvent relative to MeCN. In a previous paper[9] we have shown that the $\Delta_t G°(H_2PO_4^-)$(MeCN→DMF) $= -1.58$ kJ mol^{-1} (data based on the Ph_4AsPh_4B convention[21]), and therefore this anion is slightly better solvated in DMF relative to MeCN. It is quite clear then that the solvation of the complex is not strong enough to overcome that for the reactants, and therefore complexation of **4**-αα*ββ* and these anions is either very weak or nonexistent.

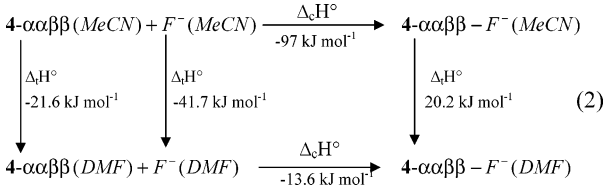
As far as the complexation of **4**-αα*ββ* and the fluoride anion is concerned, there are no data available on the $\Delta_t G°$ values for the fluoride anion, the free ligand and the complex from acetonitrile to *N*,*N*-dimethylformamide as to interpret it in terms of the standard Gibbs energies. Further evidence of the composition of the complex formed between **4**-αα*ββ* and fluoride anion in *N*,*N*-dimethylformamide was found from microcalorimetric studies that clearly reflect the formation of 2:1 (F$^-$:**4**-αα*ββ*) complex, thus corroborating the outcome of conductance studies.

As far as the contribution of enthalpy and entropy data to the Gibbs energies of complexation of **4**-αα*ββ* and the fluoride anion in DMF are concerned, this is explained as follows. Anion or ligand desolvation requires energy; therefore the enthalpic stability of the process decreases with a consequent increase in entropy (amount of disorder increases). Table 3 shows that the entropy changes for the two processes involving F$^-$ complexation with **4**-αα*ββ* in DMF are positive. It might be expected that because an addition reaction is occurring where two species are joining to form one, the decrease in the disorder of the system and thus a decrease of entropy on complexation would be dominant. However, the entropy parameter involves the entropy resulting from the release of solvent from the reactants on complexation. In this case the positive entropy values suggest that a large amount of desolvation is occurring which is also reflected in the lower enthalpy of complexation relative to the 1:1 process in acetonitrile.

Unable to analyze quantitatively the medium effect on the complexation of the fluoride anion and the **4**-αα*ββ* ligand in terms of Gibbs energies due to solvate formation of this ligand in DMF and the unavailability of data for the transfer Gibbs energies of the free and complex anion, the effect of the medium on complexation is analyzed in terms of enthalpy. Taking into account that the complexation enthalpy in two solvents (s_1 = MeCN; s_2 = DMF) is controlled by the difference in solvation of reactants and product in these solvents, the following relationship is used.

$$\Delta_c H°(\text{MeCN}) - \Delta_c H°(\text{DMF}) = \Delta_t H°(\textbf{4}\text{-}\alpha\alpha\beta\beta)(\text{MeCN}\rightarrow\text{DMF}) + \Delta_t H°(\text{F}^-)(\text{MeCN}\rightarrow\text{DMF}) - \Delta_t H°(\textbf{4}\text{-}\alpha\alpha\beta\beta\ \text{F}^-)(\text{MeCN}\rightarrow\text{DMF}) \quad (1)$$

This can be best illustrated in the following thermodynamic cycle (eq 2).



(2)

In eq 2, the upper and lower parts of the equation refer to the enthalpies of complexation of **4**-αα*ββ* with F$^-$ in acetonitrile and *N*,*N*-dimethylformamide, respectively. These data are given in Table 3. The enthalpy of transfer of **4**-αα*ββ* from MeCN to DMF was calculated from the standard enthalpies of solution, $\Delta_s H°$ of this ligand in acetonitrile ($\Delta_s H° = 28 \pm 1$ kJ mol^{-1}) and in *N*,*N*-dimethylformamide ($\Delta_s H° = 6.4 \pm 0.3$ kJ mol^{-1}). These were obtained by calorimetry. The value of $\Delta_t H°(\text{F}^-)$(MeCN→DMF) is that previously reported by us.[9] The $\Delta_t H°$ of the complex from MeCN to DMF was calculated through rearrangement of eq 1. Given that the interaction of the reactants (ligand and anion) are higher in DMF than in MeCN, it can be seen how the energy of desolvation of the reactants in DMF would reduce the enthalpy of complexation in this solvent and account for the gain in entropy observed in DMF relative to acetonitrile. In addition, the complexation enthalpy in acetonitrile is also favored by the higher interaction of the fluoride complex in this solvent relative to DMF as inferred from eq 2. In fact, the lower interaction of the 1:1 anionic complex of the **4**-αα*ββ* isomer with *N*,*N*-dimethylformamide relative to acetonitrile is a contributing factor for the enhanced capacity shown by this ligand for the fluoride anion in the former (2 fluoride ions per unit of host) relative to the latter solvent (1:1 complexation).

As far as pyrophosphate is concerned, this anion is essentially a symmetrical diphosphate ion with two negative charges (one in each oxygen) on one side and a monovalent charge on the other side. Thus the addition of the anion salt into the calorimeter vessel containing an excess amount of these ligands results in the simultaneous complexation of two units of the ligand per unit of pyrophosphate in a fashion similar to that previously shown for the calix[4]pyrrole and this anion in acetonitrile. Upon addition of an excess amount of the salt, the 2:1 complex seems to release one of the two ligand molecules that is already associated with the monovalent side of the anion to complex with the excess of free anion that has a free bivalent end. This is reflected in the enthalpy associated with the formation of the 2:1 complex of 4-αα*ββ* (3 times larger than that of the 1:1

complex) and in the consequent entropy drop observed. Molecular modeling calculations (using HyperChem Pro 6 Programm) suggest that the arrangement of lowest energy for this system is that in which each of the two negatively charged oxygens of $HP_2O_7^{3-}$ interacts with one pyrrole unit (through the −NH− groups) forming two −NH····O^- bonds while the monovalent charged oxygen of the $HP_2O_7^{3-}$ anion interacts with the NH functional groups of two pyrrole units. Thus four hydrogen bonds are involved in the formation of the 2:1 complex. The addition of an excess of the anion salt results in the departure of one unit of ligand from the 2:1 complex (energy is required) followed by the consequent interaction with the double negatively charged end of the anion. As a result, there is a decrease in enthalpic stability and an increase in entropy for the formation of the 1:1 relative to the 2:1 complex.

A similar interaction may take place with the 4-$\alpha\beta\alpha\beta$ ligand, although the enthalpy and entropy changes for the formation of the 1:1 and 2:1 complexes are not as dramatic as those for the 4-$\alpha\alpha\beta\beta$ ligand. However, the overall complex stability for these ligands and this anion in acetonitrile does not differ significantly.

Final Conclusions

(i) The two calix[4]pyrrole isomers, **4**-$\alpha\alpha\beta\beta$ and **4**-$\alpha\beta\alpha\beta$ can discriminate between anions in acetonitrile. Thus, whereas the **4**-$\alpha\alpha\beta\beta$ isomer is able to host two dihydrogen phosphate anions in acetonitrile relative to fluoride and other anions (1:1 complexes), **4**-$\alpha\beta\alpha\beta$ can still complex two dihydrogen phosphate as well as two fluoride anions relative to chloride.

(ii) Comparison between thermodynamic data for these isomers and the dihydrogen phosphate anion in acetonitrile with those involving calix[4]pyrrole and this anion in this solvent unambiguously demonstrate that the enthalpy parameter may be a suitable reporter of the number of hydrogen bonds formed between the NH functionalities of pyrrole units and the negatively charged oxygen atoms of the phosphate anion in solution. Further work in this area is required.

(iii) Investigations carried out with the **4**-$\alpha\alpha\beta\beta$ isomer and anions in *N*,*N*-dimethylformamide show no evidence of complex formation with dihydrogen phosphate and other spherical anions except fluoride, where the formation of a 1:2 ligand:anion complex (with an overall stability constant of 6.6) is demonstrated through conductometric and calorimetric measurements. This highlights the importance of the effect of the medium on the stability of a complex. Overall, the formation of complexes is less favorable in *N*,*N*-dimethylformamide than in acetonitrile. In terms of enthalpy, the 1:1 complexation process of fluoride with **4**-$\alpha\alpha\beta\beta$ isomer is more favorable in MeCN than in DMF by -83.5 kJ mol^{-1}. This is a reflection of the inherent nature of the solvent and its highly significant involvement in the complexation process.

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