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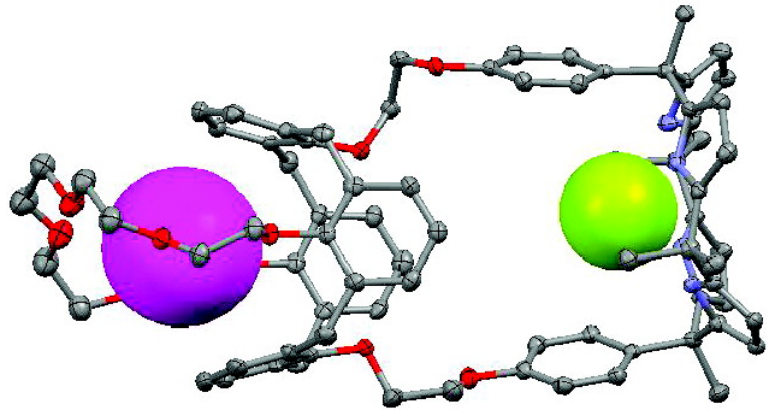

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Crown-6-calix[4]arene-Capped Calix[4]pyrrole: An Ion-Pair Receptor for Solvent-Separated CsF Ions

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Abstract: An ion-pair receptor, **1**, containing both cation- and anion-recognizing sites, has been synthesized and characterized. Single-crystal X-ray diffraction structural studies and ^{1}H NMR spectroscopic analyses confirmed that **1** forms stable 1:1 complexes with CsF in solution and in the solid state in spite of the large separation enforced between the receptor-bound anion and cation. In 9:1 $CDCl_3/CD_3OD$, binding of fluoride anion within the calix[4]pyrrole core of **1** was not observed in the absence of a cobound cesium cation; however, it was seen in this solvent mixture under conditions where a Cs^+ cation was bound to the crown ether-strapped calix[4]arene subunit.

Introduction

Over the past several decades, a large number of macrocyclic compounds have been synthesized and studied as potential cation receptors.[1] In addition, as the importance of anions in biology, the environment, and medicine has become increasingly well-recognized, attention has been focused on the design and construction of anion receptors.[2] However, in spite of their potential utility in such areas as salt solubilization, ion extraction, and through-membrane transport, relatively little effort has been devoted to the synthesis and study of so-called ion-pair receptors, which are species that can complex both an anion and a cation concurrently and with specificity.[3−6] While a number of host systems that contain both anion and cation binding sites are known, enhanced binding of an ion pair, where binding of the cation enhances binding of the anion or vice versa, is generally seen only in systems wherein the two ion-binding sites are held in close proximity.[7] Consequently, in most cases it is so-called contact ion pairs rather than solvent- or spatially separated ion pairs that are bound, thereby avoiding the presumably unfavorable separation of two oppositely charged ions.[5,6,8] In fact, we are aware of only two closely related examples of structurally characterized, spatially separated ion-pair complexes.[6a−c] However, in neither case was strong ion-pair binding observed in solution.[9] Therefore, we sought to explore whether it would be possible to produce a receptor that could bind a specific cation−anion pair with high affinity in the form of a solvent-separated ion pair. We were particularly interested in a system

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(7) While a number of systems were prepared early on that contained both anion-and cation-binding subunits constrained at remote sites within the same molecular framework, few of these displayed cooperative anion *plus* cation binding in solution or coupled anion *and* cation complexation in the solid state. Thus, they are not considered to be bona fide ion-pair receptors. For reviews of these systems, see: (a) Kirkovits, G. J.; Shriver, J. A.; Gale, P. A.; Sessler, J. L. *J. Inclusion Phenom. Macrocyclic Chem.* **2001**, *41*, 69–75. (b) Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 191–221.
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(9) Binding constants for the complexation of ion pairs were not actually recorded, perhaps because of a combination of poor solubility and slow binding kinetics. However, modest increases in the anion-binding affinities were observed in the presence of cations.[6a−c]

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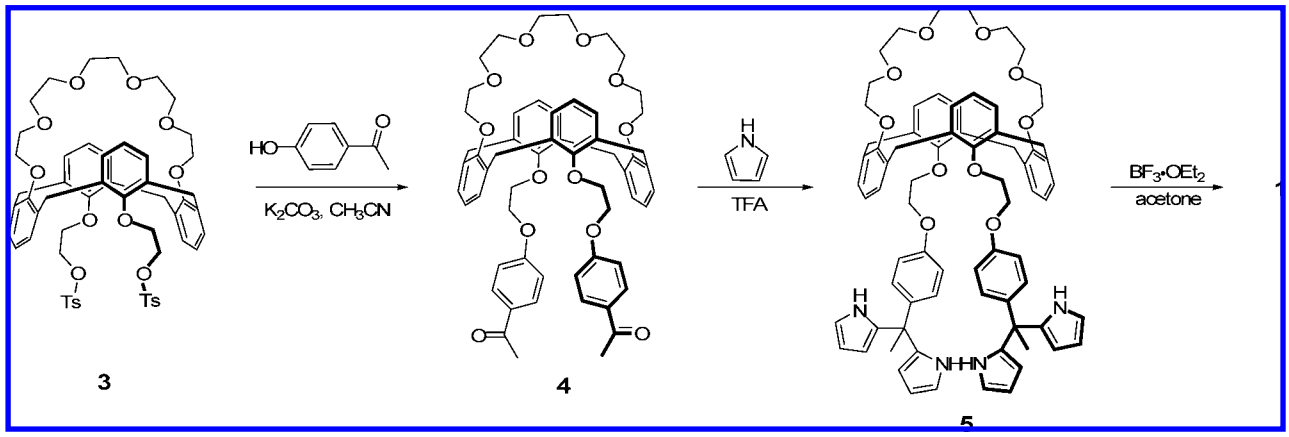
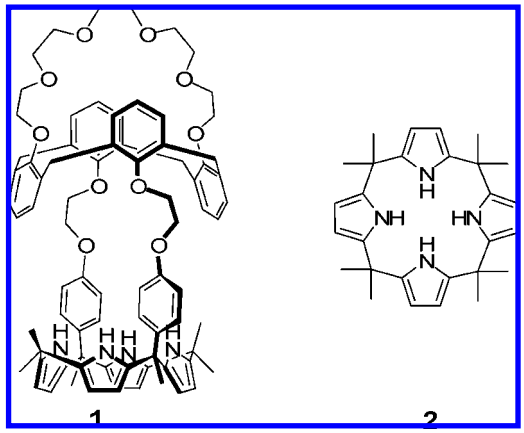
Scheme 1. Synthesis of Compound **1**



that could be used to stabilize ion pairs involving the cesium cation because of its importance in solvent separations targeted for use in radioactive-waste purification.[10] With such considerations in mind, we have prepared the crown-6-calix[4]arene-capped calix[4]pyrrole **1** and show here that it (1) forms a solvent-separated ion-pair complex with CsF in the solid state and (2) binds its constituent ions (Cs^+ and F^-) in a highly cooperative fashion in organic solvents (e.g., 9:1 $CDCl_3$/CD_3OD).



The ion-pair receptor **1** was designed to bring together both an anion-binding core and a cation-recognizing subunit in such a way that a large separation between the constituent ions of a bound ion pair would be enforced. Calix[4]pyrrole (**2**)[11] and calix[4]arene crown-6[12] were chosen as the anion- and cation-binding species, respectively. Previous work had established that these receptor systems could be used individually to effect the binding of fluoride anion and cesium cation, respectively, at least in organic media. Accordingly, CsF was selected as the target salt for possible ion-pair complexation.

Results and Discussion

The synthesis of receptor **1** is shown in Scheme 1. First, the calix[4]arene crown-6 ditosylate **3**[13] was reacted with 4′-hydroxyacetophenone in acetonitrile in the presence of excess K_2CO_3 at reflux; this afforded diketone **4** in quantitative yield. Subsequent condensation of the latter species with pyrrole in the presence of excess trifluoroacetic acid at 65 °C then gave the dipyrromethane **5** in 46% yield. This key precursor was then condensed with acetone in the presence of a catalytic amount of $BF_3 \cdot OEt_2$ to give **1** in 18% yield.[14]

Initial evidence that **1** can act as a receptor for CsF in the form of a solvent-separated ion pair came from single-crystal X-ray diffraction analysis. Suitable crystals were obtained by allowing a chloroform/methanol solution of receptor **1** to undergo slow evaporation in the presence of excess cesium fluoride. The resulting structure revealed that **1** forms a 1:1 complex with cesium fluoride, **1**·CsF (Figure 1). The Cs^+ ion in **1**·CsF is included in the calix[4]arene crown ether ring with $Cs^+ \cdots O$ distances of 3.08−3.36 Å, while distances of 3.43−3.63 Å characterize the presumed π−cation interactions involving the Cs^+ ion and the aromatic carbon atoms at the meta and para positions with respect to the phenoxy groups. On the other hand, the bound F^- anion is hydrogen-bound to the NH groups of the calix[4]pyrrole subunit (with $N \cdots F^-$ distances in the range 2.74−2.78 Å) as well as to a molecule of methanol. The presence of this hydrogen-bound methanol molecule serves to ensure that there is no direct interaction between the cobound, spatially separated Cs^+ and F^- ions in the solid-state complex **1**·CsF. This absence of interaction is likely reinforced by the large gap between the calix[4]pyrrole anion-binding subunit and the crown-strapped calix[4]arene cation-recognition site. In fact,

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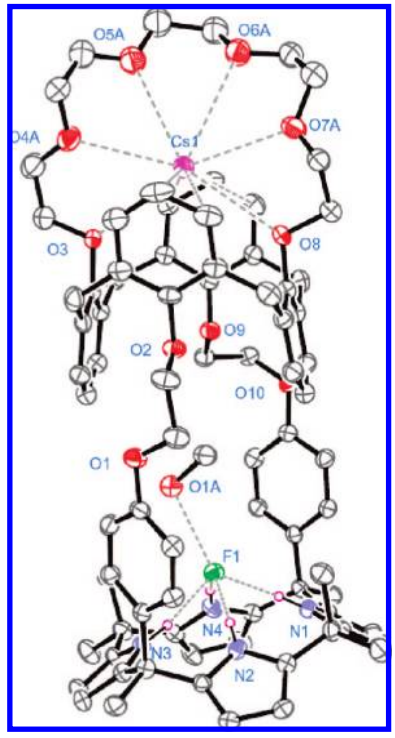

Figure 1. View of the **1**·CsF complex showing a partial atom-labeling scheme. Displacement ellipsoids are scaled to the 30% probability level. Most of the hydrogen atoms have been removed for clarity. Atoms in the ether linkage are disordered, and the higher-occupancy atoms are shown.

the separation of 10.92 Å between the Cs^+ and F^- ions seen in the solid-state structure of **1**·CsF is much longer than the $Cs^+ \cdots F^-$ distance seen in the solid-state structure of the CsF complex of *meso*-octamethylcalix[4]pyrrole **2**.[15,16] This latter species, although capable of functioning as an ion-pair receptor under certain biphasic extraction conditions,[10a] contains no independent cation-recognition site. On the basis of these findings, we suggest that at least in the solid state, the formation of the strong complex **1**·CsF containing individual, solvent-separated ions is energetically favorable relative to other possible scenarios, such as complexation of a contact ion pair.

The ability of **1** to bind halide anion salts in solution was probed via ^{1}H NMR spectroscopy, initially using $CDCl_3$ as the solvent. In contrast to what was seen in the case of other calix[4]pyrrole derivatives, including the various other strapped calix[4]pyrroles prepared to date, in this solvent system only the addition of soluble fluoride anion salts (e.g., tetrabutylammonium fluoride, TBAF) served to engender spectroscopic changes consistent with anion binding (i.e., no other TBA halide anion salts had an effect on the ^{1}H NMR spectrum; see Figures S1 and S2 in the Supporting Information). This apparent selectivity is thought to reflect a combination of a less accessible anion-binding site and a more rigid calix[4]pyrrole core enforced by the rather inflexible phenoxy spacers.

The changes observed in the ^{1}H NMR spectrum when **1** was subjected to titration with TBAF in $CDCl_3$ are shown in Figure S1 in the Supporting Information. The anion-free form of **1** displays a broad singlet at $\delta = 6.74$ ppm for the NH protons and two triplets, at $\delta = 6.04$ and 5.95 ppm, for the β-pyrrolic protons. Addition of 0.4 and 0.8 equiv of TBAF gave rise to two sets of distinguishable resonances for all of the proton signals. These peaks were ascribed to the anion-free and fluoride-bound forms of **1** and were consistent with the anion-binding/decomplexation equilibrium being slow on the ^{1}H NMR time scale. Such slow exchange kinetics is consistent with strong anion binding, a conclusion further supported by the observation of significant changes in the β-pyrrolic and especially the pyrrolic NH proton signals. The singlet associated with the NH proton resonance seen in free **1** was shifted to lower field by roughly 6 ppm (final $\delta \approx 12.7$ ppm) upon the addition of fluoride anion. The signal also was split into a doublet ($J = 44.0$ Hz), a finding that is ascribable to coupling between the bound fluoride anion and the NH protons.[17]

Very different behavior was seen when analogous ^{1}H NMR spectroscopic analyses were carried out in 10% (v/v) CD_3OD in $CDCl_3$. Under these conditions, no evidence of fluoride anion binding was seen (even after two days) when **1** was treated with 5 equiv of TBAF (Figure 2b).[18] This lack of appreciable interaction is attributed to the stronger solvation of the fluoride ion by this more polar medium (Figure 3).

In contrast to what was seen with TBAF, the addition of 5 equiv of cesium perchlorate induced remarkable changes in the signals for both the aromatic protons of the calix[4]arene core and the aliphatic protons of the crown-6 ring (Figure 2c). Particularly noteworthy is the considerable downfield shift of the H_d proton on the inverted phenoxy group, as would be expected if the oxygen atom of this moiety were involved in cesium cation complexation. This stands in contrast to the β-pyrrolic and the meso aromatic proton signals associated with the calix[4]pyrrole subunit, for which little appreciable change was seen. Taken together, these findings are consistent with the expectation that the addition of $CsClO_4$ leads to the formation of a cation-bound complex wherein the cesium cation is encapsulated in the calix[4]arene crown-6 ring and the perchlorate anion is bound either weakly or not at all by the calix[4]pyrrole core (Figures 2c and 3 and Figure S4c in the Supporting Information).

In analogy to what was seen with $CsClO_4$, the addition of 5 equiv of CsF to receptor **1** in 10% CD_3OD in $CDCl_3$ led to downfield shifts in the proton signals of both the calix[4]arene and the crown-6 ring (see Figure 2d and Figure S4d in the Supporting Information); this is what would be expected if the Cs^+ cation were being bound well in this case also.[12] However, in contrast to what was seen with TBAF, the use of CsF led to significant upfield changes in the signals of both the β-pyrrolic and meso aromatic protons of the calix[4]pyrrole moiety (Figures 2d and 3). Such observations are fully consistent with binding of the fluoride anion in the calix[4]pyrrole cavity of receptor **1**, thus indicating that **1** binds both Cs^+ and F^- ions as an ion-pair complex **1**·CsF in a manner analogous to what

(15) In the CsF complex of **2**, the F^- ion is symmetrically bound to the four NH groups of the calix[4]pyrrole via four hydrogen bonds at a $N \cdots F^-$ distance of 2.79 Å, whereas the Cs^+ ion is symmetrically encapsulated within the cone-like cavity of the calix[4]pyrrole via $\pi-$cation interactions with a distance of 3.39 Å between the Cs^+ ion and the centroids of the pyrrole rings. The F^- ion interacts with both the Cs^+ ion in the same complex and the one in an adjacent complex with separation distances of 3.69 Å and 2.77 Å, respectively.

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(18) In this solvent system, the pyrrolic NH proton signal originally seen at $\delta = 6.74$ ppm in $CDCl_3$ either shifts to lower field as the result of interactions with the CD_3OD solvent or disappears as a consequence of D/H exchange (Figures 2 and 3 and Figure S3 in the Supporting Information).

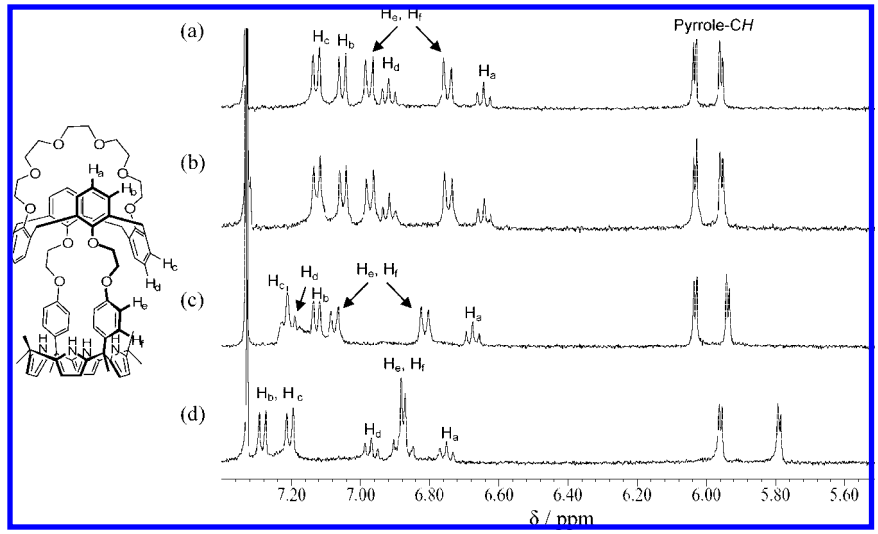

Figure 2. Partial ^{1}H NMR spectra of (a) **1** only, (b) **1** with 5 equiv of TBAF, (c) **1** with 5 equiv of $CsClO_4$, and (d) **1** with 5 equiv of CsF in 10% (v/v) CD_3OD in $CDCl_3$.

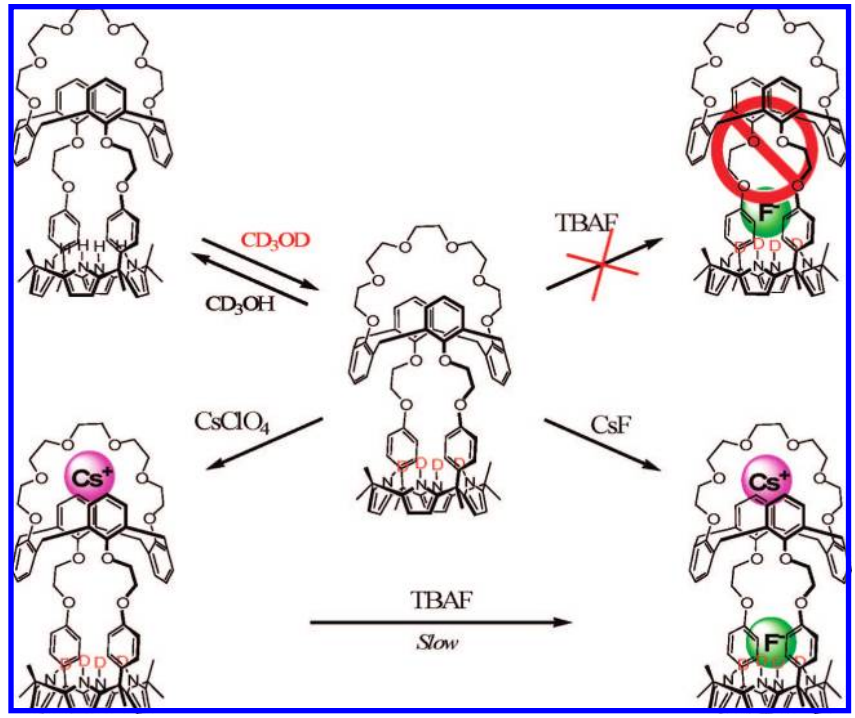

Figure 3. Proposed binding interactions involving **1** and various Cs^+ and F^- salts in 10% (v/v) CD_3OD in $CDCl_3$.

is seen in the solid sate. It is thus concluded that the binding of the cesium cation to the crown ether ring plays a very critical role in inducing binding of the fluoride anion to the calix[4]pyrrole portion of receptor **1**, which is otherwise not observed in the absence of Cs^+ in this solvent system. None of the other cations tested (specifically, Li^+, Na^+, and K^+) were found to produce such an effect.

Further support for the above conclusion came from the finding that addition of TBAF to a preformed cesium complex (i.e., **1**·Cs^+ formed via eq 1) gave rise to the formation of a cobound CsF complex analogous to that produced from CsF alone, albeit at a rate that is slow on the NMR time scale (Figure S6 in the Supporting Information). Presumably, this reflects the slow kinetics associated with counteranion exchange (eq 2). In any event, it is noteworthy that a diffraction-grade single crystal grown in the presence of both $CsClO_4$ and TBAF yielded exactly the same structure (that shown in Figure 1) as a datum crystal grown in the presence of CsF only.

$$CsClO_4 + \mathbf{1} \rightarrow [\mathbf{1}\cdot Cs]ClO_4 \quad (1)$$

$$[\mathbf{1}\cdot Cs]ClO_4 + TBAF \rightarrow \mathbf{1}\cdot CsF + TBAClO_4 \quad (2)$$

Isothermal titration calorimetry (ITC) was utilized to quantify the affinity of compound **1** for Cs^+ and F^- in a solvent mixture analogous to that used for the latter ^{1}H NMR spectroscopic studies (i.e., 10% MeOH in $CHCl_3$). The resulting titration of CsF [0.08 mM] with **1** [1.1 mM] was highly exothermic ($\Delta H = -16.2$ kcal/mol). The data could be fit well to a 1:1 binding profile, yielding a binding energy of $\Delta G = -7.6$ kcal/mol and a binding constant of $K_a = 3.8 \times 10^5$ M^{-1} while revealing a

Table 1. ITC Titration Data for **1**, **1**·F^-, and **1**·Cs^+ Measured at 298 K[a]

host	solvent	guest[b]	ΔH (kcal/mol)	$T\Delta S$ (kcal/mol)	ΔG (kcal/mol)	K_a (M^{-1})
1	CH_3CN	CsTPB	−6.7	1.3	−8.1	8.0×10^5
1·F^-	CH_3CN	CsTPB	−6.0	2.3	−8.3	1.2×10^6
1	CH_3CN	TBAF	−6.2	0.8	−7.0	1.3×10^5
1·Cs^+	CH_3CN	TBAF	−7.2	−0.4	−6.8	1.1×10^5
1	$CH_3OH/CHCl_3$[c]	CsF	−16.2	−8.6	−7.6	3.8×10^5

[a] Errors estimated to be less than 15%. [b] CsTPB is cesium tetraphenylborate; TBAF is tetrabutylammonium fluoride. [c] 10% (v/v).

strong opposing entropy ($T\Delta S = -8.6$ kcal/mol) (Table 1). However, when the concentrations of both **1** and CsF were increased, a second event in the early stages of the titration became prevalent. While further study is in order, it is possible that this latter finding reflects changes in overall solvation for which simple receptor-free control experiments did not account.

Efforts to analyze the individual ion-binding events using ITC were also made. In this case, titrations using TBAF and cesium tetraphenylborate (CsTPB) were carried out, albeit in acetonitrile because of solubility considerations.[19] First, CsTPB was titrated into **1**; this resulted in a K_a value of 8.0×10^5 M^{-1}. Next, CsTPB was titrated into a 3:1 TBAF/**1** mixture; this gave rise first to a set of exothermic signals, which were followed by a series of endothermic traces toward the end of the titration. Fitting to a 1:1 profile proved to be clean and yielded a K_a value of 1.2×10^6 M^{-1}, a small increase in the affinity compared with what was observed in the absence of fluoride.

In a separate experiment, the interaction of TBAF with **1** was studied; this yielded a K_a of 1.3×10^5 M^{-1}. TBAF was then titrated into a 2:1 CsTPB/**1** mixture, and the resulting isotherm again showed an initial exothermic interaction followed by endothermic signals toward the end of the titration. However, as above, this data could be fit well to a 1:1 binding isotherm, yielding a K_a value of 1.1×10^6 M^{-1}. Thus, in acetonitrile it appears that the binding of each individual ion is virtually independent of that for the other ion and that the affinity of **1** for cesium is about an order of magnitude greater than that for fluoride. Such behavior stands in marked contrast to what was seen in 9:1 $CDCl_3/CD_3OD$ (see above) and leads to the conclusion that the binding behavior of **1**, like that of simple calix[4]pyrrole **2**,[11a,e] is subject to a strong solvent dependence. This is perhaps not surprising, given the interplay of the relatively complicated and contradictory effects involved (e.g., receptor, salt, and individual-ion solvation; ion pairing; and receptor−cation, receptor−anion, and receptor−ion-pair interactions). However, the key point is that in all of the solvents tested to date, including acetonitrile, concurrent binding of both an anion (F^-) and a cation (Cs^+) can be effected using receptor **1**.

(19) CsTPB is not appreciably soluble in either chloroform or 10% methanol in chloroform.

Conclusions

An ion-pair receptor **1** containing both cation- and anion-recognition sites has been synthesized. The X-ray crystal structure and ^1H NMR spectroscopic analysis provide support for the conclusion that **1** forms a stable 1:1 complex with CsF in spite of the large separation enforced between the anion and the cation. In more competitive media, such as 10% methanol in chloroform, little evidence of fluoride anion binding was observed in the absence of a cobound cesium cation, on the basis of which it is suggested that binding of this cation to the crown ether-strapped calix[4]arene makes possible the complexation of a fluoride anion within the calix[4]pyrrole core of **1**.

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Supporting Information Available: Synthetic details, NMR spectroscopic data, ITC analyses, X-ray structural data for **1**·CsF, and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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