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A Conformationally Flexible, Urea-Based Tripodal Anion Receptor: Solid-State, Solution, and Theoretical Studies

David R. Turner,[†] Martin J. Paterson,[‡] and Jonathan W. Steed*,[†]

Department of Chemistry, University of Durham, South Road, Durham DH1 3LE, U.K., and Department of Chemistry, University of Århus, DK-8000 Århus C, Denmark

jon.steed@durham.ac.uk

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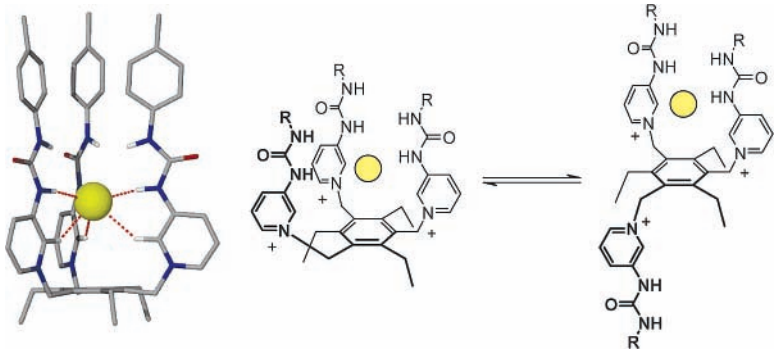

Tripodal tris(urea) cationic receptors **1** and **2** containing *p*-tolyl or octyl substituents, respectively, have been synthesized, and their association behavior with anionic guests has been studied via a variety of methods. The receptors are based around a hexasubstituted aryl core and contain both urea and pyridinium functionalities. For 1:1 complexes, anions reside within the central cavity of the host species, held by hydrogen bonds from both NH and CH donors. The following host−anion complexes have been characterized by X-ray crystallography: **1**−$(Br)_3$, **1**−$(PF_6)_3$·$2(CH_3)_2CO$, and **1**−$(NO_3)_{1.5}(PF_6)_{1.5}$. Each structure contains the receptor in a significantly different geometry, highlighting the anion-dependent conformational flexibility of **1**. Solution ^{1}H NMR spectroscopic titrations have shown the two host species to display significant affinity for both halides and hydrogen sulfate and strongly suggest the persistence of CH···X^- interactions despite the presence of "stronger" NH donor groups. Variable-temperature ^{1}H NMR studies on the more soluble octyl derivative **2** show that there is a distinct change in conformation associated with the formation of a 1:1 host/guest complex. Computations using density functional theory (with the B3LYP functional) have been employed to aid in understanding the geometry of the 1:1 host/chloride complexes of **1** and **2**. These experiments suggest that the lowest energy conformation for **1**−Cl is one in which the ureidopyridinium arms are orientated upward forming a cavity that is sealed by CH···π interactions, effectively forming a unimolecular capsule, whereas for **2** a less symmetrical "2-up, 1-down" geometry is favored.

Introduction

The binding of anionic guest species within synthetic receptors remains as challenging today as it was when the first host species were introduced some 40 years ago.[1−3] Further advances in host design can be aided by a detailed mechanistic understanding of the processes that occur during binding. Whereas the binding of guests within preorganized macrocyclic systems is relatively straightforward to understand, the binding processes of flexible podand receptors remain more elusive.[4]

The rapid rate of complexation and decomplexation within podand systems and the conformational changes that they are

* To whom correspondence should be addressed. Tel: +44 191 334 2085. Fax: +44 191 384 4737.
[†] University of Durham.
[‡] University of Århus.

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able to undergo upon binding can lead to potential uses as sensing devices when appropriate functional groups are appended.[5] Such receptors have a wide range of potential applications, in fields as diverse as environmental remediation and targeted drug delivery. Environmental sensors of hazardous or toxic species such as pertechnetate, a common radioactive pollutant,[6,7] and arsenate[8] are of particular interest. Physiologically, much attention has been aimed toward anions that display particular activity in relation to illness, such as the role of chloride transport in the treatment of cancers[9] and the manner in which dysfunctions of chloride channels arise from genetic disorders.[10] For example, steps toward synthetic mimics of prodigiosin, which helps maintain cell acidity, have been made using amide-based receptors.[11,12] Furthermore, from an economic viewpoint, swift and efficient removal of anions can be of great use in industrial processes.[13]

The nature of podand-type receptors necessitates that some form of "core" is present to which the functionalized arms are attached. The majority of examples in recent literature are dipodal or tripodal hosts which utilize substituted benzene cores,[14−23] tertiary amine centers,[24,25] or fused aromatic ring systems.[26,27] More complicated cores have also been employed, such as calixarenes[28] and the elegant tribenzyltrindane unit of Choi and co-workers.[29] Tripodal receptors in particular have been seen to act as highly effective anion-binding agents in examples by several groups. Anslyn and co-workers have engendered a significant catalog of receptors whose efficiency has been demonstrated through practical applications such as determining the aging of scotch by colorimetric assay,[18] following reaction kinetics,[20] and the detection of phosphate in saliva.[15] Kim et al. have developed a receptor that incorporates three imidazolium rings and binds to a central anion exclusively through $C-H^{+}\cdots X^{-}$ interactions.[21,22] A related benzoimidazolium-based receptor has also recently been reported by Duan, Meng, and co-workers.[23] These receptors both showed a selectivity for chloride and demonstrate that CH···X interactions, which have classically been termed "weak", have the potential to act in concert to provide a strong binding environment. Recently, the role of these "weak" interactions has been examined in detail by Hay and co-workers within benzene−anion systems and their derivatives.[30,31] The utilization of CH···X interactions has also been demonstrated within some simple "tweezer" receptors in which the backbone of the receptor participates in hydrogen bonding with the guest.[32,33]

We have previously investigated the anion-binding behavior of receptors bearing either electrochemical or fluorescent signaling units.[34−37] These receptors are centered around a hexasubstituted aryl core, with three functionalized arms and three ethyl arms to help force a binding ("3-up" or "cone") conformation.[38] The conformational flexibility of the receptors allows for a change in geometry to occur in order to bind guests within a central cavity above the plane of the aryl core, utilizing hydrogen bonds from the amine groups and the adjacent pyridyl CH, giving a total of six hydrogen bonds to the guest.[36] A logical step toward further improving the anion-binding ability of these tripodal receptors is to incorporate stronger, multiple hydrogen bond donors into the functionalized arms.[39] The urea moiety is known to be strong double hydrogen bond donor and, like the closely related amide group,[40−42] has been utilized effectively in a number of anion-binding systems.[40,42−51] In the case of urea,

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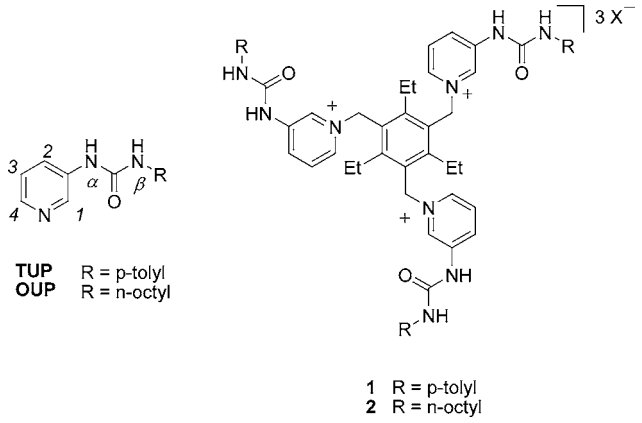
SCHEME 1. TUP and OUP Ligands (with Numbering Scheme Used for NMR Assignments) and the Tripodal Anion Receptors Incorporating These Ligands



both donor hydrogen atoms may face toward the guest, and the potential exists for the anion to be chelated to each arm in $R_1^2(6)$ motif.[52] Urea podands have been used as the basis for a number of coordination-complex receptors such as that reported by Gale, Loeb, and co-workers, in which a Pt(II)-based receptor adopts striking different geometries to bind to chloride and sulfate,[46] and those reported by Vilar and by ourselves.[52,53] Recent studies by Hay et al. have outlined theoretical approaches to the optimization of urea−anion interactions.[54,55] It has also recently been pointed out that urea is a better choice than the more acidic thiourea group, which has been observed to deprotonate much more readily in the presence of anions.[56] We now report two new receptor species, **1** and **2**, which utilize urea groups within the functional arms, significantly stronger hydrogen bond donors than the amine functionalities present within our previous examples. The binding ability and conformational flexibility of these new receptors are demonstrated through solid-state, solution, and computational studies.

Results and Discussion

Syntheses. The ligand 1-pyridin-3-yl-3-*p*-tolyl-urea (**TUP**, Scheme 1) has previously been reported by us as being readily obtainable from the reaction of 3-aminopyridine with *p*-tolyl isocyanate[57] and has been utilized within metal-based anion-binding tweezers and as part of metal-complex hosts for a novel water square studied by neutron diffraction.[52,57−59] A similar ligand has been reported recently in the context of coordination polymer assembly, and solid-state hydrogen-bonding patterns in related systems have been studied by Nangia et al.[60,61] The ligand 1-octyl-3-pyridin-3-ylurea (**OUP**) was prepared in an analogous manner to **TUP**, utilizing *n*-octyl isocyanate. The tripodal receptor species, **1** and **2**, were prepared by the reaction in dichloromethane of the appropriate ligand, **TUP** or **OUP**, respectively, with 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene. Counteranion metathesis were carried out to exchange bromide for the noncoordinating hexafluorophosphate anion by stirring solutions of the bromide salts in the presence of a large excess of TBA−PF_6 (TBA = tetrabutylammonium). Complete exchange was verified by bromide elemental analysis.

Crystallographic Studies. Three crystal structures of receptor **1** were obtained, containing different counteranions and displaying vastly different geometries of the host. Crystals were grown of the pure bromide and hexafluorophosphate salts (with enclathrated acetone), and a crystal was serendipitously obtained of a mixed hexafluorophosphate/nitrate structure.

Crystals with the composition **1**−3Br were obtained from a mixed MeOH/THF solution (∼50:50). The asymmetric unit contains two independent host−guest complexes that adopt similar geometries, Figure 1. The host adopts an alternating "up−down" conformation of the substituents around the central aryl core with the functionalized arms on the opposing face to the ethyl groups. Such an arrangement gives rise to a pseudocone geometry, forming a central cavity in which one of the bromide anions resides. Although this guest is centrally located, it only receives hydrogen bonds from one of the three urea groups. The other two urea "arms" face away from the cavity and interact with the remaining anions, one to each arm. The central anion also interacts with these other arms via CH···Br hydrogen bonds from the *ortho* protons of the pyridyl rings, as observed previously.[21−23,36] Interestingly, the upper NH of the central arm does not engage in an interaction with the central bromide anion, with the guest seemingly interacting preferentially with the three pyridyl CH groups. The persistence of CH···X interactions in the presence of potentially stronger NH donors has recently been highlighted by Gale and co-workers and by us.[36,62] In the case of the **1**−3Br structure, it is probable that the anion is drawn deeper into the cavity due to the positive charges of the pyridinium rings and the stability offered by three CH···X interactions over a single NH···X interaction. The interaction between the two independent molecules occurs through π-stacking between the arms and CH···Br^- interactions between the adjacent complexes, Figure 1c. This bromide-containing structure demonstrates the complementarity between the cavity of the host and the bromide anion and indicates that a strong 1:1 complex may be capable of forming in solution, although not necessarily in a C_3-symmetric conformation.

Crystals were also obtained of an acetone solvate of **1**−3PF_6. As with the bromide structure the three functional arms of the receptor are situated on one face of the core benzene-derived ring; however, there is no central cavity as the arms are folded inward over the aryl core, Figure 2, and mutually π-stack. One

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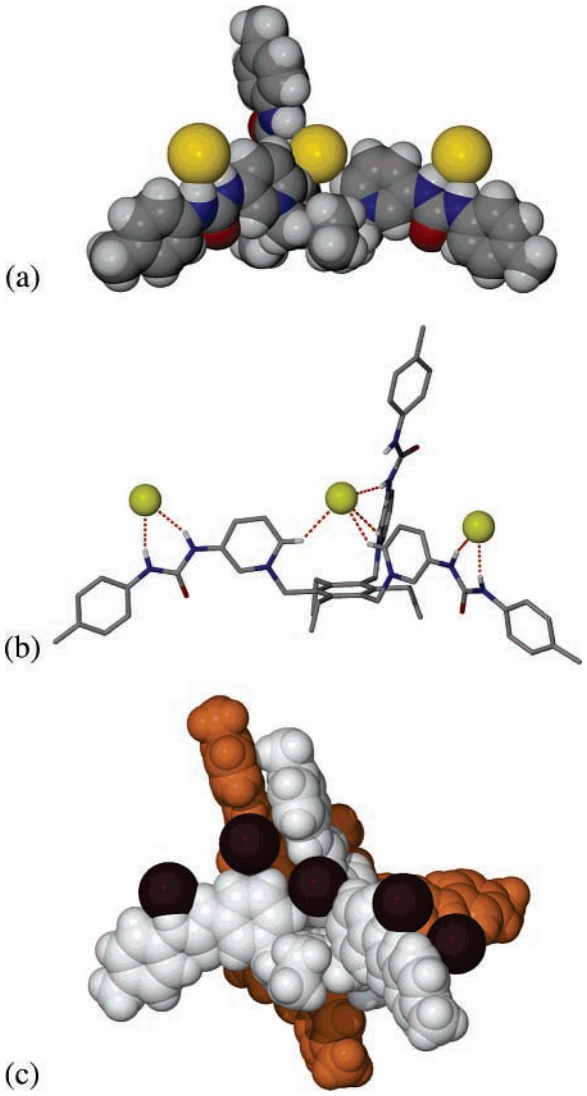

FIGURE 1. One independent host−guest complex from the crystal structure of **1**-3Br, showing (a) the close fit of a bromide anion within a central cavity, (b) the hydrogen bonding interactions to the anions, and (c) the packing between the two independent complexes, noting how the $(NH)_2\cdots X$ bound Br^- from the "back" complex also partakes in CH···Br interactions with the "front" complex.

of the ethyl groups is also facing "upwards" on the same face as the functionalized arms, so as to fill the space between two of the **TUP** arms. Only one of the PF_6^- ions binds to a urea group in an arrangement whereby one urea proton is acting as a bifurcated donor to the anion and the other is engaged in a more linear NH···F interaction, with an average N···F distance of 3.03 Å.[63] The remaining two PF_6^- anions are incorporated in the lattice engaging in numerous aryl and alkyl CH···F interactions, including to the enclathrated solvent (anion based on P1: 20 interactions between 2.34 and 3.19 Å, average of 2.82 Å; anion based on P2: 19 between 2.36 and 3.19 Å, average of 2.83 Å). The role of organic fluorine as a hydrogen bond acceptor remains a contested subject,[63−65] although there are increasing examples of fluoride containing compounds being utilized in crystal engineering.[66,67] The other two urea moieties in the structure are involved in NH···O hydrogen bonding to the two enclathrated acetone molecules, rather than with the remaining counteranions. The contrast in host geometry between this structure and that of the bromide salt is quite striking and clearly demonstrates the effect that different anions may have upon a conformationally flexible host species.

A third crystal structure was serendipitously obtained that contains a 1:1 mixture of nitrate and hexafluorophosphate anions. The geometry of the receptor is a somewhat unfolded version of the pure PF_6^- structure in order to accommodate hydrogen bonding between the nitrate anions and the urea moieties, Figure 3a. One nitrate anion within the asymmetric unit acts as a bridge to another arm of an adjacent host, meaning that all three arms are bound to nitrate anions in an $R_2^2(8)$ motif.[68] This arrangement leads to the formation of discrete dimers, connected by two nitrate anions, Figure 3b. Although the host is well ordered within the structure there is some disorder among the guest species, with a mixed nitrate/hexafluorophosphate position that could not be completely resolved, in addition to one complete nitrate anion and two-half occupancy PF_6^- anions per receptor. The structure also incorporates a partial occupancy water molecule; thus, the overall formulation for this crystal is **1**$-1.5(NO_3)1.5(PF_6)\cdot 0.5H_2O$.

Solution Behavior by ^{1}H NMR Spectroscopic Titration. The anion-binding behavior of the tripodal receptor species **1** and **2** in solution, as their hexafluorophosphate salts, has been studied through the use of ^{1}H NMR spectroscopic titration experiments. The signals have been assigned unambiguously by the use of NOE NMR spectra. As a control, dilution studies were carried out in the concentration range 1−100 mM and showed no evidence for self-association. Anion-binding titrations were carried out in the range 20−10 mM using both PF_6 and Br salts.

The relatively insoluble nature of some of the salts of **1**, particularly those of halides, necessitated that titrations using this host were carried out in DMSO-d_6 (a highly competitive solvent),[69] to avoid precipitation during the titration, whereas those of **2**, containing the long alkyl terminal groups, could be carried out in either acetone or acetonitrile. To assess the effect of counteranion competition, two initial titrations were carried out to compare the relative binding strengths of PF_6^- and Br^- by back-titrating TBA−Br into a solution of **1**$-3PF_6$ and comparing the results with a titration of TBA$-PF_6$ into a solution of **1**−3Br. As expected, the displacement of hexafluorophosphate by bromide occurs much more readily than the reverse process.[1] Data from the titration experiments were processed using the curve fitting program HypNMR.[70] The binding constants for the 1:1 complexes (K_{11}) for the complexes were 2800 and 12 M^{-1} for **1**$-3PF_6$ + TBA−Br and **1**−3Br + TBA$-PF_6$, respectively. The 1:1 binding constant for bromide is very high when compared to those for the previously studied amine-based receptors (500−3000 M^{-1} in acetonitrile, binding in DMSO is very weak), considering that the titration was

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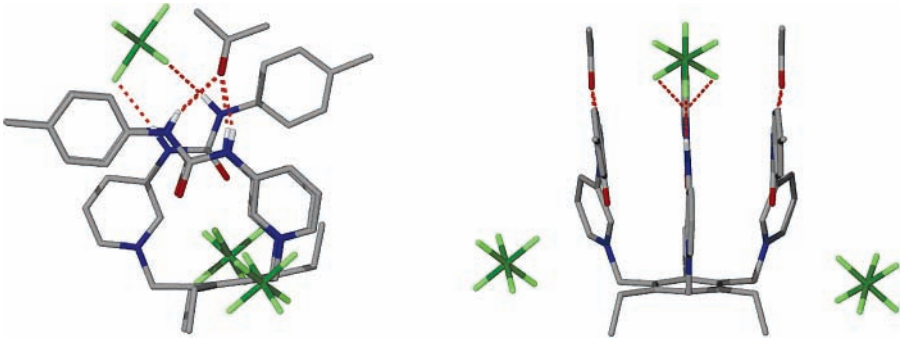

FIGURE 2. Two views of the X-ray crystal structure of **1**−3PF_6·2Me_2CO. Hydrogen atoms, other than those of the urea groups, are omitted for clarity.

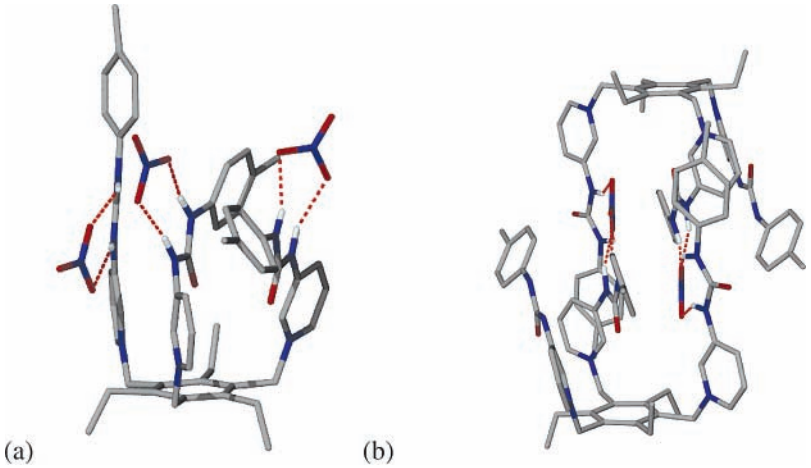

FIGURE 3. Geometry of the receptor **1** in the structure of **1**−$(NO_3)_{1.5}(PF_6)_{1.5}$·0.5H_2O (a) showing the binding to three nitrate anions, only two of which reside in the asymmetric unit and (b) the nitrate-bridged dimer.

TABLE 1. Binding Constants of Receptor 1−3PF_6 with Various Anions Obtained from ^{1}H NMR titrations in DMSO-d_6 with Anions Added as TBA Salts[a]

anion	log K_{11}	log K_{12}	log K_{13}
Cl^-	2.64	2.18	1.40
Br^-	3.46	2.99	1.21
I^-	1.61	0.60	1.05
NO_3^-	2.54	2.22	0.68
$CH_3CO_2^-$	3.21	3.70*	
HSO_4^-	1.93	1.60	1.56
$H_2PO_4^-$	3.70	3.68*	

[a] Values marked with an asterisk represent log($K_{12}K_{13}$) as individual binding constants for these two processes could not be ascertained. Titrations were carried out at 20 °C, and errors are less than 10%.

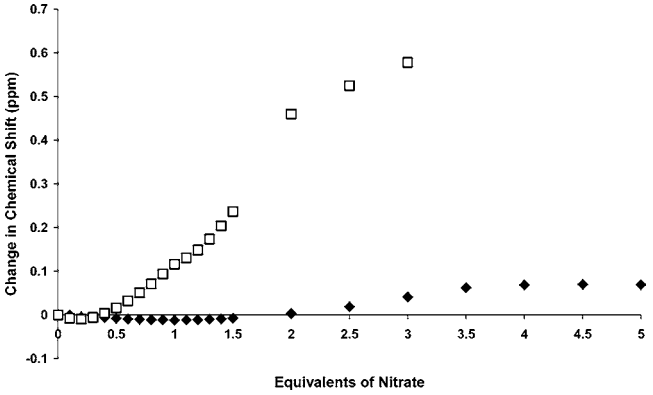

FIGURE 4. Comparison of the binding of nitrate by **1** in DMSO-d_6 (diamonds) and acetonitrile-d_3 (squares), following the H_1 proton signal (see Scheme 1 for numbering). Data are incomplete for the titration in acetonitrile due to precipitation.

conducted in a more polar solvent, and reflects the stronger hydrogen bond donor ability of the urea NH groups.[35,36]

Titrations were conducted using **1**−3PF_6 in DMSO-d_6 with a range of anions, Table 1. For $CF_3SO_3^-$ and ReO_4^-, very weak binding was observed. In general, the values of the binding constants obtained with **1** in DMSO-d_6 are reasonably modest, most likely due to the highly polar nature of the solvent. The extent to which the binding is suppressed by DMSO can be seen in Figure 4, showing a comparison between the binding of nitrate by **1** in DMSO and in acetonitrile.

An interesting trend is observed for the halide binding behavior of **1**. As expected, chloride produces the greatest changes in the chemical shift values of the urea NH protons during the titrations. This behavior is due to chloride having a greater charge density than bromide or iodide. However, the binding constants obtained from data analysis of the titrations show that bromide is bound more strongly, with K_{11} being an order of magnitude larger than that with chloride. It is thought that the bromide selectivity of **1** arises from the size difference between chloride and bromide (anionic radii of 1.81 and 1.96 Å, respectively).[71] The binding site in **1** potentially comprises a 6-fold array of hydrogen bonds donated by the urea groups,

(71) Cotton, F. A.; Wilkinson, G.; Murillo, C. A.; Bochman, M. *Advanced Inorganic Chemistry*, 6 ed.; John Wiley and Sons: New York, 1999.

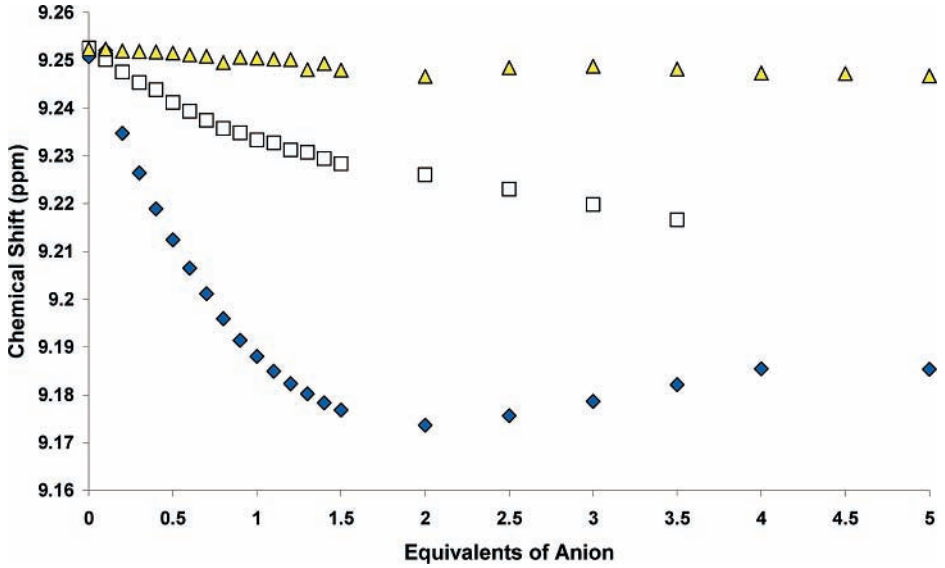

FIGURE 5. Chemical shift changes observed for H_1 during the titrations of **1** with halides in DMSO-d_6 (Cl^-, diamonds; Br^-, squares; I^- triangles). The curved shape of the plots, particularly noticeable for chloride, indicates binding for multiple anions.

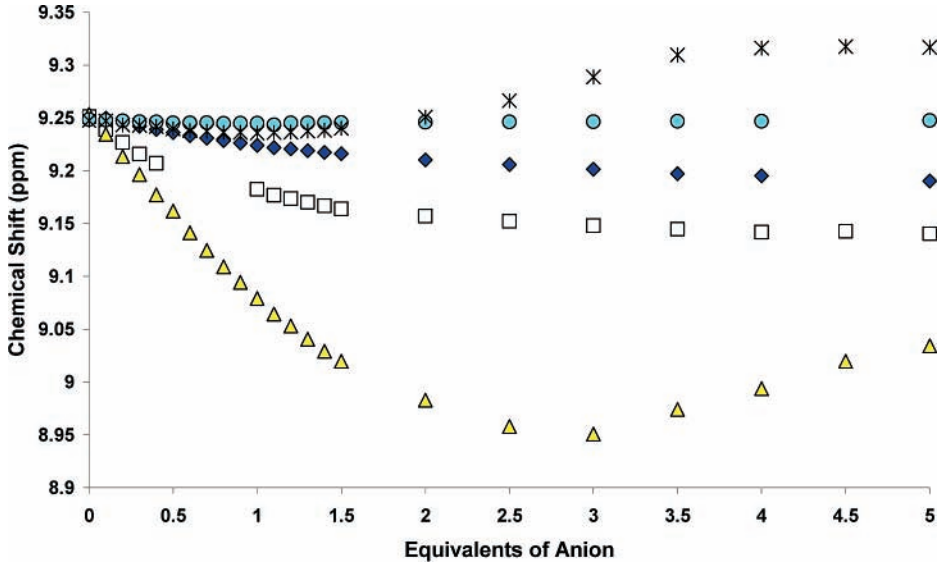

FIGURE 6. Titration plots of **1** with oxo-anions in DMSO-d_6, following the H_1 resonances: NO_3^-, diamonds; HSO_4^-, squares; $H_2PO_4^-$, triangles; ReO_4^-, circles; $CH_3CO_2^-$, crosses.

whereas the binding site within our previously studied systems (which show slightly more affinity toward chloride) is situated lower down in the receptor and utilizes pyridyl CH interactions in addition to those from the amine groups.[36] Due to the cavities adopting a cone-type geometry, it follows that species being preferentially bound higher up in the cone will benefit from a tighter encapsulation if they are larger, whereas smaller guests are more suited to binding deeper within the cavity. Iodide is apparently both too large and too weakly coordinating to display any significant binding with **1**. The slight changes in chemical shifts that are observed during the **1**−3PF_6/TBA−I titration are upfield ones, suggesting that the iodide guest is in fact bound less strongly than the displaced PF_6^- anion.

A significant feature observed during the titrations of **1** with halides is the behavior of the H_1 signal, the *o*-pyridyl proton adjacent to the urea group, Figure 5. There are at least two binding processes occurring during the chloride titration. The first equivalent of guest will give rise to a 1:1 complex, in which the halide guest resides within the central cavity. Subsequent addition of the anionic guest gives 1:2 and 1:3 complexes. The final complex is likely to be **1**-3Cl to balance the charge of the host (although further association cannot be ruled out) and may adopt a splayed geometry, possibly similar to that observed in the solid-state for **1**-3Br (vide supra). Such a geometry utilizes all of the strong hydrogen bond donors (the urea groups) to interact with all of the guests present. The value of K_{11} is, in all cases, higher than K_{12} and K_{13}, indicating that the initial binding event may be due to a chelation of the guest by the three arms, followed by situations in which each anion binds to separate arms.

Figure 6 shows the behavior of the signals corresponding to H_1 (H_4 is related) on titration with oxyanions. If it is assumed that the pyridyl rings of the functional arms are situated so that the plane of the ring is perpendicular to the plane of the aryl core, then one of the *ortho* protons (H_1 or H_4) must face toward the center of the cavity, i.e., directly above the aryl core. In a

TABLE 2. Binding Constants of Anions with 2 Determined by ^{1}H NMR Titrations in Acetonitrile-d_3[a]

anion	log K_{11}	log K_{12}	log K_{13}
Cl^-	3.85	1.96	2.93
Br^-	3.62	2.24	1.96
NO_3^-	3.46	2.66	1.89
$CH_3CO_2^-$	4.61	2.30	3.67
HSO_4^-	precipitation occurred during titration		

[a] Titrations were carried out at 20 °C, and errors are less than 10%.

1:1 complex with a cone conformation the H_1 proton should face the cavity interior, as only in this way can the urea groups converge. Chemical shift change ($\Delta\delta$) plots of the H_1 resonance as a function of added anion all show an initial decrease in the chemical shift value, although none as large as that observed for chloride. This change is attributed to be the result of a change in the geometry of the receptor in which the proton becomes directed toward the interior of the cavity. The behavior of the signal beyond 1 equiv depends on the anion. Acetate displays an increase in chemical shift very soon after this point, whereas dihydrogen phosphate does not produce an upward turn in the isotherm until the addition of ~3 equiv of the guest. The oxo anions are all of greatly differing geometry and symmetry, making direct comparisons difficult; however, it is likely that all are bound well to the urea groups due to the geometrical compatibility between donor and acceptor. This assertion is borne out by the fact that the largest host chemical shift changes observed during the titrations are for the urea NH protons. It is clear that geometrical changes are occurring as the host progresses from a pure hexafluorophosphate complex, past the 1:1 host−guest species toward the proposed final 1:3 complex, however, the suppressed binding in DMSO makes speculation about the possible geometries difficult.

Titrations of the more soluble octyl-substituted receptor **2** were carried out in acetonitrile. The change of solvent not only results in larger binding constants, Table 2, as expected due to decreased competition from the solvent, but also provides more detailed information about the conformation that the receptor adopts.

Titrations of **2** with chloride and bromide produce behavior similar to that observed for **1** in DMSO, i.e., increasing chemical shift for the H_α proton and sigmoidal behavior of the H_1 signal. The H_β signals in the chloride and bromide titrations of **1** in DMSO give uninflected plots; however, those from **2** in acetonitrile are more complex, see Figure S2 (Supporting Information). Inflection points occur in both of the curves after the addition of ~1 equiv of the guest. After this point, the rate of change in chemical shift ($\Delta\delta$) initially increases before the graphs trail off to a maximum. This behavior indicates that the "upper" NH protons of the urea do not play such an important role in the 1:1 complex as they do in the 1:2 and 1:3 species, suggestive of binding lower within the cavity, similar to the behavior of amine-based hosts we have previously reported.[36] It is interesting that hydrogen bonding to the pyridyl CH groups persists, despite the introduction of the urea donor. The titrations of **2** with chloride and bromide show clearly that there are three distinct processes when following the H_2 signals, Figure 7. It is believed that as a greater excess of the guest anion is added the 1:1 host−guest complex is disrupted and anions begin to bind individually to the arms, rather than in a chelating fashion. The inflection points in the curve occur at the points where 1 and 2 equiv of the guest are present.

For the H_1 resonance, sharp inflection points are observed for both bromide and chloride at ~1 equiv of the guest, Figure 8. It is believed that the initial decrease in chemical shift of the resonances is due to the proton facing into the cavity as a cone geometry is formed (i.e., positioned over the aryl core). With the addition of more than 1 equiv of the anion, the cone conformation is disturbed and a splayed geometry is adopted resulting in a downfield shift of the resonance. It is interesting that K_{13} is larger than K_{12} for both Cl^- and $CH_3CO_2^-$. While we do not have a definite explanation for this effect it could be rationalized by a relatively unfavorable conformational change upon binding the second equivalent of anion predisposing the host for binding the third.

Solution Behavior by Variable-Temperature NMR. Variable-temperature ^{1}H NMR spectra of **2**−3PF_6 were recorded in acetone-d_6, due to the low freezing point of this solvent. As the temperature is reduced, the urea and pyridyl signals display small changes in chemical shift and some broadening, although no peak splitting occurs. Variable-temperature ^{1}H NMR experiments were also conducted on samples of the receptor containing 0.7 and 1.0 equiv of NBu_4Cl. In the presence of 0.7 equiv of chloride receptor **2** displays very marked changes in its ^{1}H NMR spectrum as the temperature decreases. The signals corresponding to the urea and pyridyl signals all split into two at low temperature. These two sets of signals are attributed to the 1:1 species, **2**−Cl·2PF_6, and the free receptor, **2**−3PF_6. Splitting of the peaks is also observed for the 1:1 mixture, Figure 9, which is similar but much sharper than the 0.7 equiv spectra. The sharpness of the peaks is attributed to the stability of the 1:1 complex under these conditions, as suggested by the ^{1}H NMR spectroscopic titration data, reducing the fluxionality in the system.

Figure 10 shows a comparison between partial spectra at 180 K of **2**−3PF_6 by itself and when in the presence of 1 equiv of chloride. One set of signals from the chloride-containing sample corresponds well to those of the free receptor (**2**−3PF_6), while another distinct set of signals is also observed. This distinct set of signals, observed in both the experiments containing chloride, is therefore attributable to a conformer of the receptor that is binding to chloride. The peak integration suggests that the 1:1 complex may adopt a conformation in which only two of the arms bind to the anion with the resonances due to the third, free arm overlapping with the signals for the remaining uncomplexed receptor. This observation correlates with DFT studies (vide infra).

Computational Studies. The binding of chloride anion to **1** and **2** was studied in B3LYP calculations using an STO-3G basis set, augmented on the urea atoms by an additional SP shell and on the chloride by an extra S shell, four extra SP shells, and a D shell, as diffuse basis functions are crucial for describing the hydrogen bonding region (see the Supporting Information for a detailed description). Seven starting conformations for optimizations were identified by molecular mechanics calculations using either the Universal Force Field or the MMFF94 force field. These starting conformations used various combinations of the arms being "in" or "out" and "up" or "down" with respect to the central aryl core (see Scheme S1 in the Supporting Information).

Results for **1** show that the "3-up" (cone) conformation is the most stable, by 23.20 kcal mol^{-1}, Figure 11a. The "3-up" geometry has the three ***m*-TUP** arms arranged in a helical manner around the core and both the left and right-hand screws

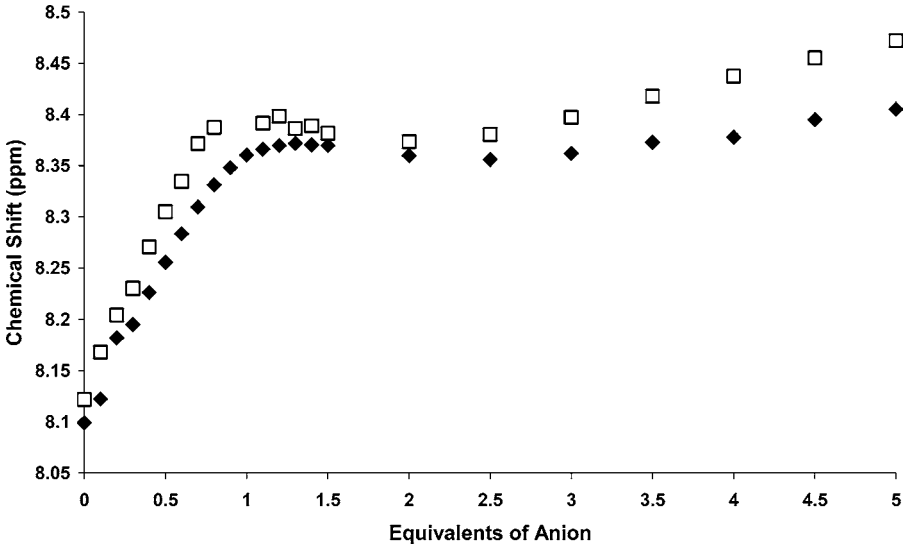

FIGURE 7. Plots of the H_2 proton during titrations of **2** in acetonitrile-d_3 with Br^- (diamonds) and Cl^- (squares). The shapes of the curves indicate that three distinct binding processes occur.

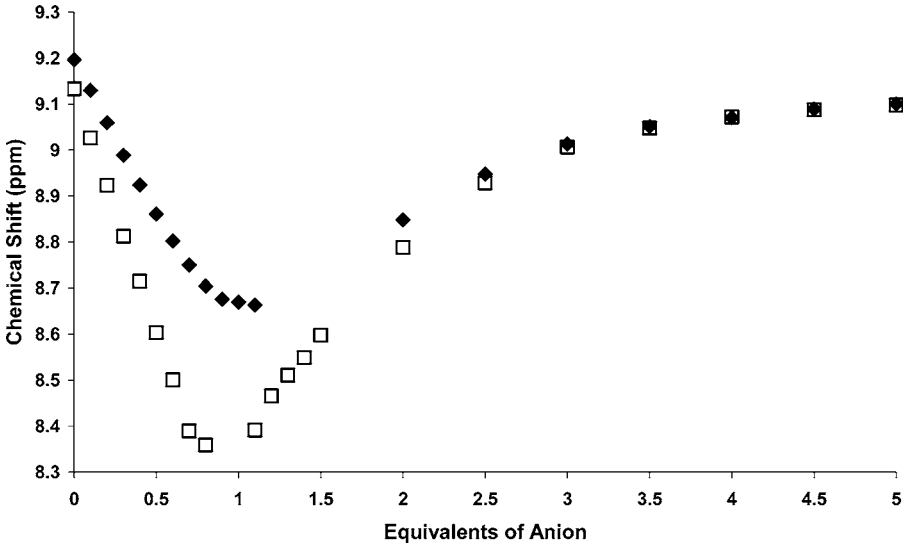

FIGURE 8. Plots of the H_1 proton in titrations of **2** in acetonitrile-d_3 with Br^- (diamonds) and Cl^- (squares). It is thought that the sharp inflection occurs as the receptor changes from a 1:1 cone conformation into a splayed geometry to accept further additions of the guest.

were found as local minima. The fact that these were minima was verified by means of an analytical frequency computation with only real frequencies observed, i.e., positive force constants. The geometry of the helices is C_3. It was found that there is a C_{3v} structure that presents a substantial barrier to the interconversion of the left and right-handed forms. The minimized structure shows the chloride anion residing low down within the central cavity. It is hydrogen bonded to the three urea protons closest to the pyridyl ring and to the three *o*-pyridyl protons (2.29 and 2.71 Å, respectively), not to the six urea protons as originally anticipated, but consistent with NMR spectroscopic titration data. The distance from the upper urea protons to the chloride guest is 3.29 Å. It is likely that the anion resides in this lower position due to the electrostatic attraction from the positively charged pyridinium groups. The stability of the "3-up" conformer compared to others may arise from the helical geometry that it adopts. This allows for edge-to-face π interactions between the tolyl rings at the top of the cavity, Figure 11a. These interactions apparently "seal" the receptor, effectively forming a unimolecular capsule, tied off in a manner akin to a purse string.[72]

The results of the DFT calculations on the octyl derivative **2** suggest, in contrast, that the "2-up" conformation is the more stable, Figure 11b. While the forces on the atoms for the "2-up" geometry converged to a minimum, the displacements did not fully converge due to the flatness of the potential energy surface. This issue is thought to arise from the conformationally flexible octyl ligands, leading to many conformations with energies very close to the global minimum. The same initial ligand conformation was used for both the "2-up" and "3-up" minimizations, therefore the final results, although not totally converging, retain a high degree of confidence. The stability of the "2-up" geometry compared to the "3-up" may be attributed

(72) Turner, D. R.; Pastor, A.; Alajarin, M.; Steed, J. W. In *Structure and Bonding*; Mingos, D. M. P., Ed.; Springer-Verlag: Heidelberg, 2004; Vol. 108, pp 97−168.

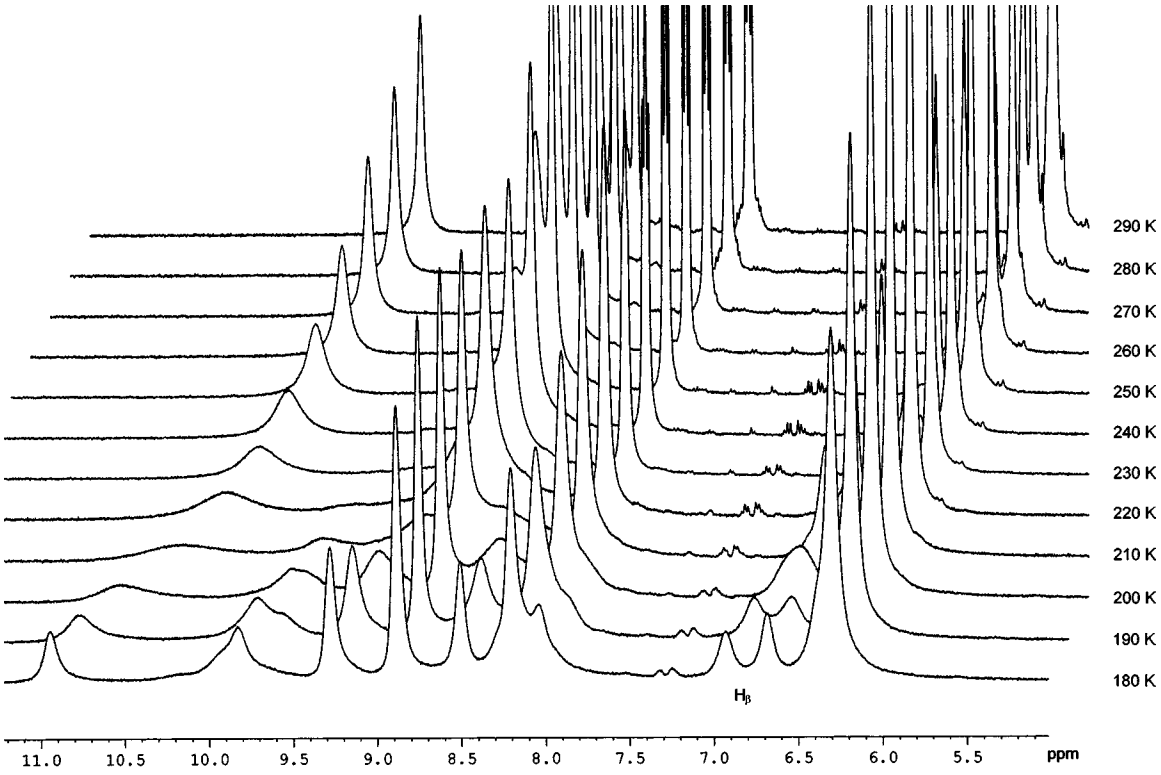

FIGURE 9. VT ^{1}H NMR spectra of **2**-3PF$_6$ in acetone-d_6 with 1.0 equiv of TBA-Cl. At low temperature there are twice as many peaks present as for the pure receptor.

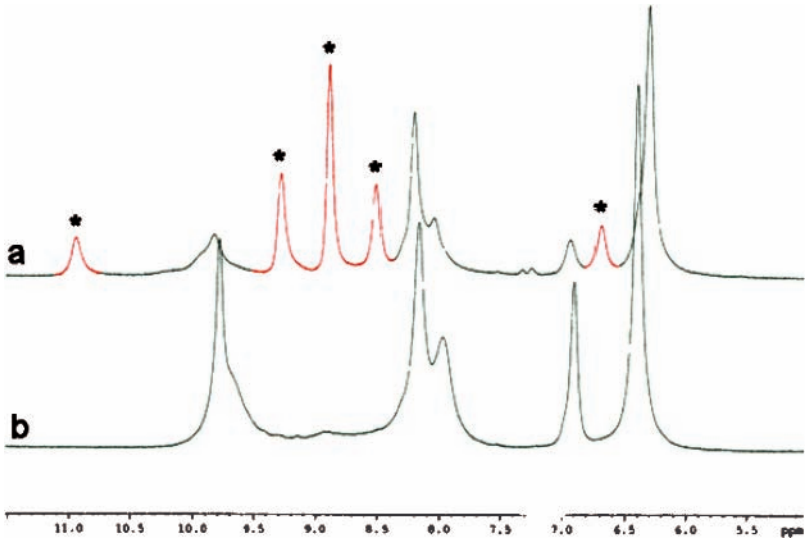

FIGURE 10. Comparison of the 180 K ^{1}H NMR spectra of **2**−3PF$_6$ with 1 equiv of chloride (a) and with no added anion (b). Peaks marked by asterisks correspond to the 1:1 chloride complex. It is thought that the **2**−Cl complex is unsymmetrical peaks corresponding to a nonbinding arm overlap with those of the free receptor.

to the steric repulsion between the octyl groups in the "3-up" geometry. It is an interesting point that the terminal groups of the ligands apparently play such an important role in determining the structure of the host/Cl$^-$ structure, overcoming the urea···Cl$^-$ interactions. The attractive forces between the tolyl groups are in sharp contrast to the steric repulsion between the octyl chains. This difference is hard to elucidate from ^{1}H NMR spectroscopic titration results, as it is likely that solvent effects, particularly for **1** which was titrated in DMSO, may overcome some of the host−guest interactions. The chloride anion within the "2-up" structure of **2** is chelated between the two arms that are on the same side of the core, without the additional CH···Cl$^-$ interactions that are seen in the "3-up" structure of **1**. The reason behind the chloride binding at the intended site within the "2-up" structure may be the manner in which the "3-up" structure of **1** is "sealed" at the upper end, squeezing the anion lower within the cavity. Indeed, the "2-up" structure of **1** obtained using MM also has the anion residing between the urea moieties with four NH···Cl$^-$ interactions.

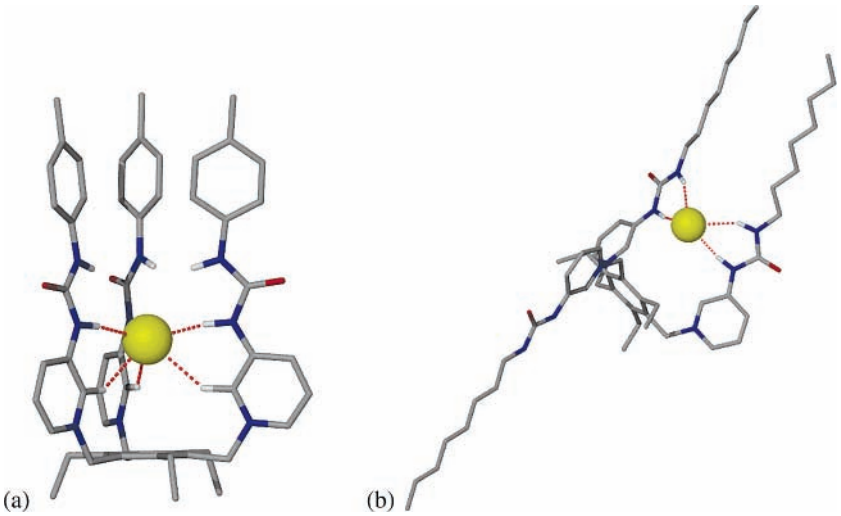

FIGURE 11. (a) DFT-minimized structure of the **1**−Cl complex showing the manner in which the anion is bound. (b) DFT-minimized structure of the 2-up, 1-down structure of **2**−Cl.

Conclusion

The readily prepared urea-containing tripodal receptors **1** and **2** have proven to be effective anion-binding hosts and represent an improvement upon existing amine-based systems. Crystal structures of **1** in the presence of different anion combinations have confirmed the flexibility of the receptor and the anion dependence of the receptor geometry. In solution the flexible nature of the receptors allows for a variety of simple, inorganic anions to be complexed. ^{1}H NMR spectroscopic titrations have demonstrated that multiple binding modes are observed with distinct 1:1 host−guest complexes observed. The existence of these 1:1 complexes has been confirmed through the use of low temperature ^{1}H NMR studies in which unique sets of resonances are located that correspond to the **2**−Cl complex. Theoretical studies using DFT have shown that the most likely conformation for the chloride complexes of **1** and **2** are different and suggests an unexpected dependence on the terminal group of the ligands.

Experimental Section

Syntheses. Syntheses were conducted under a standard atmosphere with no products displaying any signs of air or moisture sensitivity. The synthesis of the ligand **TUP** is similar to that of **OUP** and has been previously reported.[57] 1,3,5-Tri(bromomethyl)-2,4,6-triethylbenzene was prepared according to the literature method.[38]

1-Octyl-3-pyridin-3-ylurea (OUP). 3-Aminopyridine (0.30 g, 3.22 mmol) and *n*-octylisocyanate (0.50 g, 3.22 mmol) were dissolved in dichloromethane (50 mL) and refluxed for 24 h. The solution was cooled and the solvent removed under reduced pressure. The crude product was redissolved in methanol. Water was added until the solution just turned cloudy, and the mixture was then placed in a refrigerator at 4 °C overnight. The resulting precipitate was collected by filtration (0.65 g, 2.62 mmol, 81%). ^{1}H NMR (DMSO-d_6, 400 MHz, δ/ppm, J/Hz): 8.63 (1H, s, NH); 8.57 (1H, d, J = 2.8, ArH); 8.16 (1H, dd, J = 4.6, 1.4, ArH); 7.93 (1H, ddd, J = 7.2, 2.4, 1.6, ArH); 7.30 (1H, dd, J = 8.4, 4.4, ArH); 6.31 (1H, t, J = 5.4, NH); 3.13 (2H, q, J = 6.6, CH_2); 1.48 (2H, m, CH_2); 1.33 (10H, m, CH_2); 0.92 (3H, t, J = 6.4, CH_3). ^{13}C−{^{1}H} NMR (DMSO-d_6, 100 MHz, δ/ppm): 155.1, 141.93, 139.5, 137.21, 124.3, 123.4, 31.2, 30.0, 29.6, 28.7, 28.6, 26.3, 22.0, 13.9. EI-MS: m/z = 249 $[M]^+$. IR (ν/cm^{-1}): 1650 (s), 3300 (m), 3343 (m). Anal. Calcd for $C_{14}H_{23}N_3O$: C, 67.44; H, 9.30; N, 16.85. Found: C, 67.74; H, 10.18; N, 16.35.

1,3,5-Tris(TUP)-2,4,6-triethylbenzene Bromide (1−3Br). TUP (1.00 g, 4.41 mmol) and 1,3,5-tri(bromomethyl)-2,4,6-triethyl benzene (0.65 g, 1.47 mmol) were dissolved in methanol (50 mL) and the solution refluxed for 24 h. The solution was allowed to cool before THF was added until clouding was observed. The mixture was placed in a refrigerator for 5 days at 4 °C, during which time a pale beige solid formed. This solid was recovered by filtration to yield the pure bromide salt (1.22 g, 1.09 mmol, 74%). ^{1}H NMR (DMSO-d_6, 400 MHz, δ/ppm, J/Hz): 10.05 (3H, s, NH); 9.21 (6H, m, NH and ArH); 8.52 (3H, d, J = 5.6, ArH), 8.20 (3H, d, J = 8.4, ArH); 7.85 (3H, t, J = 7.2, ArH); 7.28 & 7.09 (12H, AA′BB′, d, J = 8.0, ArH); 6.07 (6H, s, CH_2); 2.72 (6H, b, CH_2); 2.26 (9H, s, CH_3); 0.88 (9H, b, CH_3). ^{13}C−{^{1}H} NMR (DMSO-d_6, 100 MHz, δ/ppm): 152.0, 150.2, 140.3, 136.3, 135.8, 132.6, 132.4, 132.1, 129.2, 128.1, 119.1, 57.4, 23.4, 20.3, 15.3. ES$^+$-MS: m/z = 1042 $[M - Br]^+$, 962 $[M - 2Br]^+$. IR (ν/cm^{-1}): 1717 (s), 3192 (w), 3264 (w). Anal. Calcd for $C_{54}H_{60}N_9O_3Br_3$: C, 57.75; H, 5.35; N, 11.23. Found: C, 56.57; H, 5.36; N, 11.49.

1,3,5-Tris(TUP)-2,4,6-triethylbenzene hexafluorophosphate (1−3PF$_6$). The bromide salt **1**−3Br (0.50 g, 0.45 mmol) was dissolved in methanol (50 mL) with 10 equiv of $NaPF_6$ (0.73 g, 4.52 mmol) and stirred at ambient temperature for 6 h. Water was added to precipitate out the desired PF_6 salt, which was recovered by filtration and dried under ambient conditions (0.34 g, 0.26 mmol, 57%). ^{1}H NMR (DMSO-d_6, 400 MHz, δ/ppm, J/Hz): 9.77 (3H, s, NH); 9.25 (3H, s, ArH); 9.07 (3H, s, NH); 8.45 (3H, d, J = 5.6, ArH); 8.09 (3H, d, J = 8.0, ArH); 7.79 (3H, t, J = 7.2, ArH); 7.25 & 7.08 (12H, AA′BB′, d, J = 8.0, ArH); 6.06 (6H, s, CH_2); 2.74 (6H, b, CH_2); 2.27 (9H, s, CH_3); 0.86 (9H, b, CH_3). ^{13}C-{^{1}H} NMR (DMSO-d_6, 100 MHz, δ/ppm): 152.0, 150.2, 140.4, 136.3, 135.7, 132.8, 132.5, 132.2, 129.2, 128.2, 127.9, 119.3, 57.37, 23.42, 20.34, 15.23. ES$^+$-MS: m/z = 1172 $[M - PF_6]^+$, 1026 $[M - 2(PF_6)]^+$, 440 $[M - 3(PF_6)]^{2+}$. IR (ν/cm^{-1}): 841 (m), 1719 (s), 3160 (w), 3388 (w). Anal. Calcd for $C_{54}H_{60}N_9O_3P_3F_{18}$: C, 49.20; H, 4.56; N, 9.57. Found: C, 49.27; H, 4.80; N, 9.79.

1,3,5-Tris(OUP)-2,4,6-triethylbenzene Bromide (2−3Br). OUP (0.4 g, 1.60 mmol) and 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene (0.24 g, 0.54 mmol) were dissolved in dichloromethane (50 mL), and the resulting solution was refluxed for 24 h. The solution was cooled and the solvent removed under reduced pressure. This yielded the bromide salt as a pale pink solid (0.51 g, 0.43 mmol, 79%). ^{1}H NMR (DMSO-d_6, 400 MHz, δ/ppm, J/Hz): 9.74 (3H, s, NH); 9.01 (3H, s, ArH); 8.26 (3H, d, J = 5.8, ArH); 8.10 (3H, d, J = 8.7, ArH); 7.75 (3H, dd, J = 8.5, 6.1); 6.60 (3H, t, J = 5.3, NH); 5.83 (6H, s, CH_2); 2.90 (6H, dd, J = 12.5, 6.44, CH_2); 2.32 (6H, b, CH_2); 1.10 (6H, b, CH_2); 1.06 (30H, m, CH_2); 0.67 (18H,

m, CH_3 & CH_3). ^{13}C-{^1H} NMR (DMSO-d_6, 100 MHz, δ/ppm): 154.2, 150.1, 144.8, 141.1, 135.7, 132.1, 131.8, 128.1, 57.3, 31.2, 30.0, 29.3, 28.7, 26.3, 23.4, 22.0, 15.3, 15.2, 13.9. EI^+-MS: m/z = 1189 $[M + H]^+$, 1108 $[M - Br]^+$, 514 $[M - 2Br]^{2+}$, 316 $[M - 3Br]^{3+}$. IR (ν/cm^{-1}): 1699 (s), 3196 (w), 3330 (w). Anal. Calcd for $C_{57}H_{90}N_9O_3Br_3$: C, 57.58; H, 7.58; N, 10.61. Found: C, 57.40; H, 7.71; N, 10.52.

1,3,5-Tris(OUP)-2,4,6-triethylbenzene Hexafluorophosphate (2−3PF$_6$). The bromide salt **2**-3Br (0.10 g, 0.08 mmol) was dissolved in methanol (50 mL) with an excess of $NaPF_6$ (0.43 g, 2.65 mmol). This solution was stirred at room temperature for 6 h. Water was added and a white precipitate formed. This solid was collected by filtration and washed with water (0.04 g, 0.03 mmol, 36%). ^1H NMR (DMSO-d_6, 400 MHz, δ/ppm, J/Hz): 9.53 (3H, s, ArH); 9.25 (3H, s, NH); 8.28 (3H, b, ArH); 8.14 (3H, d, J = 7.4, ArH); 7.87 (3H, b, ArH); 6.69 (3H, b, NH); 5.99 (6H, s, CH_2); 3.05 (6H, b, CH_2); 2.47 (6H, b, CH_2); 1.23 (30H, m, CH_2); 1.41 (6H, b, CH_2); 0.83 (18H, m, CH_3 & CH_3). $^{13}C-\{^1H\}$ NMR (DMSO-d_6, 100 MHz, δ/ppm): 154.1, 150.0, 141.1, 135.5, 132.4, 132.0, 128.2, 127.9, 57.3, 31.2, 29.3, 28.7, 28.6, 26.3, 23.4, 22.0, 15.1, 13.9. ES^+-MS: m/z = 1383 $[M]^+$, 1238 $[M - PF_6]^+$, 547 $[M - 2PF_6]^{2+}$, 316 $[M - 3Br]^{3+}$. IR (ν/cm^{-1}): 841 (s), 1681 (s), 3114 (w), 3388 (w). Anal. Calcd for $C_{57}H_{90}N_9O_3P_3F_{18}$: C, 49.46; H, 6.51; N, 9.11. Found: C, 49.50; H, 6.65; N, 9.02.

Crystallographic Details. Crystal data for **1**−3Br: $C_{54}H_{60}Br_3N_9O_3 \cdot 5.67MeOH$, M = 1304.51, 0.40 × 0.35 × 0.20 mm^3, triclinic, space group P-1 (No. 2), a = 14.3365(9) Å, b = 19.7335(19) Å, c = 26.4104(19) Å, α = 97.923(5)°, β = 90.040(4)°, γ = 106.804(5)°, V = 7077.9(10) Å^3, Z = 4, D_c = 1.224 g/cm^3, F_{000} = 2712, KappaCCD, Mo Kα radiation, λ = 0.71073 Å, T = 120(2) K, $2\theta_{max}$ = 46.0°, 21211 reflections collected, 17110 unique (R_{int} = 0.0983). Final GooF = 0.904, R1 = 0.1228, wR2 = 0.2976, R indices based on 5171 reflections with $I > 2\sigma(I)$ (refinement on F^2), 1156 parameters, 1059 restraints. Lp and absorption corrections applied, μ = 1.757 mm^{-1}. The structure was obtained from a very poor quality sample (best available) exhibiting very rapid loss of intensity with diffraction angle. The data set is therefore of low resolution but gives an overview of connectivity and packing. The model was refined with extensive FLAT and SADI restraints for the rigid portions of the molecule. One tolyl group based on C47B−C54B could not be located on the difference Fourier map and is apparently disordered. The disorder is correlated with that of Br6 which is split over (at least) two sites modeled as 50:50 Br6/Br6A. The tolyl group was placed in an idealized position and allowed to ride on the pivot atom. The structure also contains 2481.7 Å^3 of void space apparently filled by 5.67 molecules of methanol per formula unit (408 electrons/cell) which was modeled using the SQUEEZE procedure.[73] Nondisordered atoms were modeled anisotropically with ISOR restraints for all C, N, and O atoms. H atoms were placed in calculated positions and allowed to ride.

Crystal data for **1**−3PF$_6$·2$(CH_3)_2CO$: $C_{60}H_{72}F_{18}N_9O_5P_3$, M = 1434.18, colorless block, 0.20 × 0.20 × 0.10 mm^3, triclinic, space group P1 (No. 1), a = 11.8906(7) Å, b = 12.2442(8) Å, c = 13.4875(7) Å, α = 101.325(4)°, β = 96.590(4)°, γ = 117.117(3)°, V = 1666.17(17) Å^3, Z = 1, D_c = 1.429 g/cm^3, F_{000} = 742, $2\theta_{max}$ = 55.0°, 11511 reflections unique. Final GooF = 1.070, R1 = 0.0633, wR2 = 0.1342, R indices based on 9615 reflections with $I > 2\sigma(I)$ (refinement on F^2), 887 parameters, 3 restraints. Lp and absorption corrections applied, μ = 0.194 mm^{-1}. Absolute structure parameter = −0.04(10).[74]

Crystal data for **1**−$(NO_3)_{1.5}(PF_6)_{1.5} \cdot 0.5H_2O$: $C_{54}H_{61}F_9N_{10.50}O_8P_{1.50}$, M = 1202.59, colorless block, 0.50 × 0.30 × 0.20 mm^3, monoclinic, space group $C2/c$ (No. 15), a = 14.0745(2) Å, b = 26.5397(3) Å, c = 29.3483(4) Å, β = 96.0980(10)°, V = 10900.5(2) Å^3, Z = 8, D_c = 1.466 g/cm^3, F_{000} = 5008, Nonius KappaCCD, Mo Kα radiation, λ = 0.71073 Å, T = 120(2)K, $2\theta_{max}$ = 55.0°, 23169 reflections collected, 12062 unique (R_{int} = 0.0679). Final GooF = 1.031, R1 = 0.0849, wR2 = 0.2332, R indices based on 7415 reflections with $I > 2\sigma(I)$ (refinement on F^2), 785 parameters, 35 restraints. Lp and absorption corrections applied, μ = 0.162 mm^{-1}. The structure contains a mixed NO_3^-/PF_6^- site with the nitrogen and phosphorus positions being coincidental. The fluorine atoms of the PF_6^- anion could not be located on the Fourier difference map and the nitrate anion was refined with geometrical restraints.

NMR Titrations. Titrations were conducted by addition of small aliquots of a concentrated guest solution to a single NMR tube containing the host at 20 °C with a starting host concentration of 0.02 M. This was diluted to 0.01 M after the addition of five equivalents of the guest to ameliorate precipitation effects. Binding constants were analyzed using three or four independent resonances using the program HypNMR 2000.[70]

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Supporting Information Available: Scheme S1, Arms within a conical conformation of **1** or **2** (center) may rotate to (a) face away from the cavity or (b) move to the opposing side of the receptor (Page S2), Figure S1: Plots comparing the titrations of **1**-3PF$_6$ with TBA-Br (squares) and **1**-3Br with TBA-PF$_6$ (diamonds) in DMSO-d_6, following the H_α signal (page S2), Figure S2: Plots of the H_β proton chemical shift change in titration of **2** with Br^- (diamonds) and Cl^- (squares) in acetonitrile-d_3, showing a notable inflection point at around 1 equivalent of halide present (page S3),-computational Supporting Information (pages S4−S15), Crystallographic Details (page S16) and a detailed description of computational work (pages S17−S18). Crystallographic information files for all structures presented herein are also available (.cif). This material is available free of charge via the Internet at http://pubs.acs.org.

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