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A Tripyrrolylmethane-Based Macrobicyclic Triazacryptand: X-ray Structure, Size-Selective Anion Binding, and Fluoride-Ion-Mediated Proton−Deuterium Exchange Studies

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Supporting Information

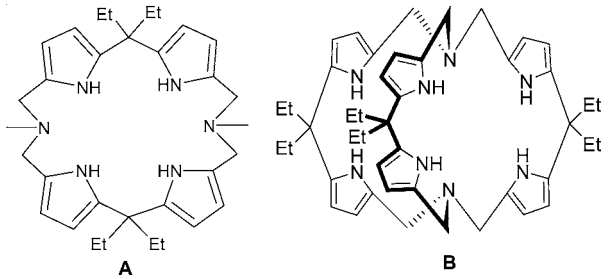
ABSTRACT: A new class of tripyrrolylmethane-based triazacryptand with bridgehead carbons and acyclic molecules were synthesized by the Mannich reaction of tripyrrolylmethane with primary or secondary amine hydrochloride and formaldehyde, respectively. The structure of the triazacryptand was determined by X-ray diffraction (XRD) method. The anion binding properties of both the bicyclic and acyclic receptors were studied by ^{1}H NMR titration method. The binding studies showed that both receptors exhibit very high affinity and bind strongly with the F^- ion in DMSO-d_6. However, the binding constant of azacryptand with F^- is much higher than that of the acyclic receptor. This is attributed to the preorganization of the azacryptand having a specific cavity size, and the strength and the number of hydrogen bonds formed by the F^- ion. This is supported by the crystal structures of F^-, Cl^-, and Br^- ion complexes of the bicyclic receptor and by DFT calculations. The X-ray structures showed that the azacryptand receptor forms an inclusion complex with only the F^- ion; other anions bind in the clefts of the macrobicycle, thus supporting a size-selective anion binding behavior. The high affinity and the selectivity of the macrobicycle as a neutral receptor of the F^- ion in the presence of other competitive anions in DMSO-d_6 were confirmed by ^{1}H NMR spectroscopy. Furthermore, the F^--ion-mediated hydrogen−deuterium exchanges were monitored by ^{19}F NMR spectroscopy, showing multiplets based on the formation of all possible deuterium-exchanged fluoride complexes in solution.

INTRODUCTION

Recognition of anions by synthetic hydrogen bonding receptors continues to be an active area of research.[1] Typically, the main objective of this research is to find a selectivity pattern of synthetic receptors for specific anions. The recognition, particularly, of the fluoride (F^-) ion has attracted attention, because of both its deleterious and beneficial effects[2] and its high enthalpy of hydration. Hence, a variety of cyclic,[3] bicyclic,[4] acyclic[5] and Lewis acid[6] synthetic receptor systems have been developed for fluoride recognition and/or sensing.[7] Among the hydrogen bonding receptors, macrobicycles are especially suitable receptors for the selective binding of specific anions, because of their tunable cavity size and shape (i.e., their preferential accommodation of only those guests which suit their respective cavity).[8] This has been demonstrated remarkably by Lehn and co-workers, using tris(2-aminoethyl)amine-based ammonium bicyclic receptors with different cavity sizes.[9] Most interestingly, Bowman-James and co-workers proved that the selectivity pattern can change with respect to the number of protonated amine groups; that is: it is pH-dependent.[10]

The first cryptand-like calixpyrrole containing pyrrole subunits with carbon bridgeheads was reported by Sessler and co-workers.[11] Kohnke and co-workers synthesized another cryptand-like hybrid calixpyrrole receptor with carbon bridgeheads and showed its selectivity toward the F^- ion.[12] Recently, we reported dipyrrolylmethane-based macrocycle (**A**)[13] and macrobicyclic azacryptand (**B**) with nitrogen bridgeheads, synthesized by Mannich reactions, which, as a neutral receptor, bind the F^- ion selectively in the presence of other competitive ions (see Chart 1).[14]

Chart 1. Macrocycles and Macrobicycles as Receptors for Anions Synthesized by the Mannich Reaction of Pyrrole Systems



This has inspired us to explore this strategy further in order to synthesize other bicyclic molecules for anion receptor studies. Herein, we report a new class of macrobicyclic triazacryptand and

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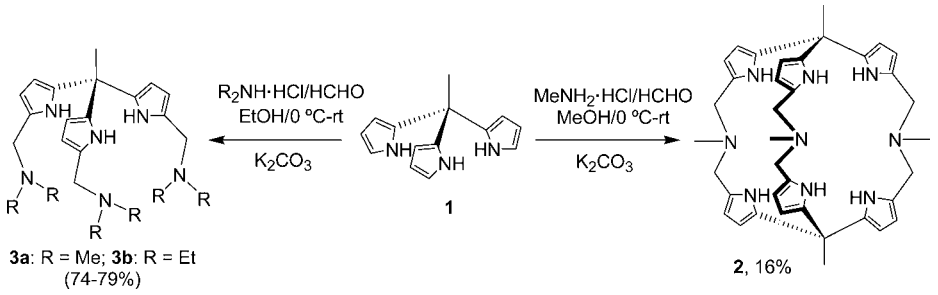
Scheme 1. Synthesis of the Macrobicyclic and Acyclic Molecules by the Mannich Reaction of the Tripyrrolylmethane System 1



acyclic molecules synthesized by the Mannich reaction of 1,1,1-(tripyrrolyl)ethane and their anion binding properties, as studied by both solution and solid-state methods supported by density functional theory (DFT) calculations. We also report the F^--ion-mediated proton/deuterium exchange studied by ^{19}F NMR spectroscopy.

RESULTS AND DISCUSSION

The Mannich reaction of a suitable tripyrrole system necessarily yields the desired bicyclic system, whereas use of the dipyrrolylmethane precursor with an ammonium salt gives the azacryptand **B** in Chart 1. This hypothesis was tested and reinforced using the tripyrrolylmethane precursor **1**. The reaction of **1** with a mixture of methylamine hydrochloride and formaldehyde, in a 1:1.5:3 molar ratio, gave 16% yield of the macrobicycle **2** after chromatographic separation, which is a new bicyclic hexahomotriazacryptand containing bridgehead C atoms. The corresponding reaction with the secondary amine hydrochloride yielded the acyclic molecule **3** in 74%−79% yield (see Scheme 1). Both compounds were characterized by spectroscopic methods. The structure of **2** was confirmed by X-ray structural analysis.

The most interesting features of the ^1H NMR spectrum of **2** in $CDCl_3$ at room temperature are the resonances due to the NH and CH_2 protons. The pyrrolic NH protons appear as one broad singlet at δ = 8.55 ppm and the methylene protons appear as a sharp singlet at δ = 3.41 ppm, suggesting that all these protons are equivalent, and the molecule probably possesses one rigid conformation only, *out*−*out* (*vide infra*), in solution which does not undergo interconversion between the three possible conformations: *in*−*in*, *in*−*out*, and *out*−*out*. Conversely, the azacryptand **B**[14] and other cryptands[15] show a broad resonance for the methylene protons at room temperature, because of their dynamic behavior in solution, and the cryptand-like calixpyrrole molecules[11,12] displayed two different NH resonances, because of their *in*−*in* and *in*−*out* conformations. In addition, the ^{13}C NMR spectrum of **2** in $CDCl_3$ shows only eight signals corresponding to the single isomer, being in the *out*−*out* conformation found in the solid state (*vide infra*), because of its highly symmetric nature.

The X-ray structure of **2**, along with selected bond lengths and angles and the refinement data, are given in Figure 1 and Table 1, respectively. The macrobicycle adopts an eclipsed conformation about the bridgehead C atoms with one water molecule residing inside the cavity, in addition to other lattice water molecules. The structure has one C_3 axis of symmetry passing through the bridgehead C atoms. The tripyrrolyl methyl groups are pointing outside the cavity, giving an *out*−*out* conformation to the molecule. This is in contrast to the *in*−*in*[11] and *in*−*out*[12] conformations observed for cryptand-like calixpyrrole molecules. All the

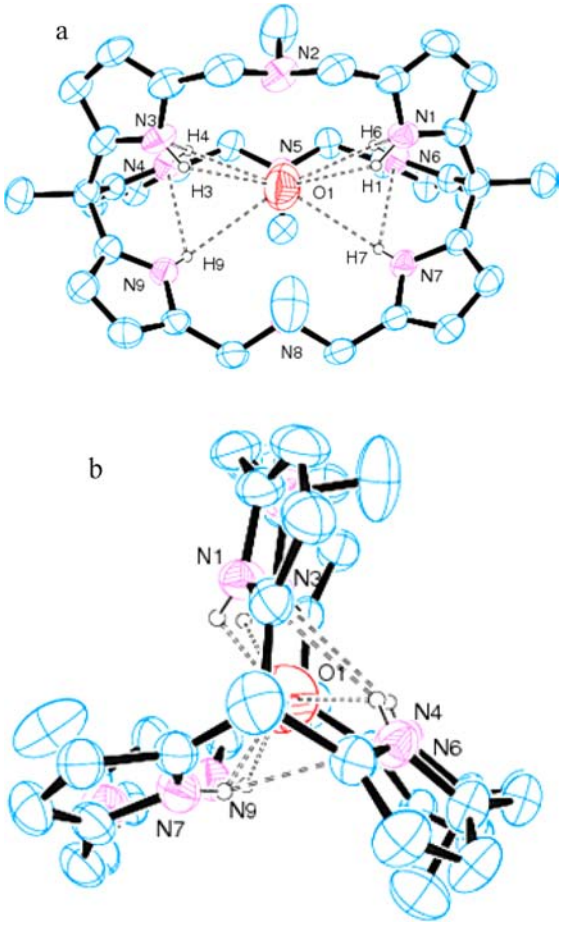


Figure 1. ORTEP diagram of **2**·4.9H_2O with 30% probability ellipsoids. (a) top view, and (b) view along the bridgehead carbon atoms showing the eclipsed conformation. Most H atoms and the water molecules are omitted for clarity. Selected bond lengths and angles: N1···O1, 3.208(4) Å; H1···O1, 2.51(3) Å; N1−H1···O1, 133(2)°; N9···O1, 3.312(4) Å; H9···O1, 2.71(2) Å; N9−H9···O1, 133(2)°; N6···N1, 3.215(4) Å; H6···N1, 2.61(3) Å; N6−H6···N1, 126(2)°.

pyrrolic NH groups are hydrogen-bonded to the O atom of the encapsulated water molecule. The distance between the two bridgehead carbons is 8.883 Å, indicating that it is a fairly elongated molecule.

Having synthesized a three-dimensional bicyclic molecule exhibiting a specific size, we attempted to explore its selective anion binding behavior using NMR titration methods. As observed for other pyrrole-based receptors, the NH resonance of **2** in DMSO-d_6 is shifted in the downfield region as aliquots of anions as their n-Bu_4N^+ salts were added. From these

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Table 1. Crystallographic Data for Compounds 2·4.9H_2O, [2·F^-][*n*-Bu_4N^+]·2H_2O (4), $[H_32]^{3+}[Cl^-]_3$·2.61H_2O (5), and $[H_32]^{3+}[Br^-]_3$·3H_2O (6)

	Value/Comment			
property	2·4.9H_2O	4	5	6
empirical formula	$C_{37}H_{54.8}N_9O_{4.9}$	$C_{53}H_{85}FN_{10}O_2$	$C_{37}H_{53.22}Cl_3N_9O_{2.61}$	$C_{37}H_{54}Br_3N_9O_3$
formula weight	704.10	913.31	772.22	912.62
wavelength	0.71073 Å	0.71073 Å	0.71073 Å	0.71073 Å
temperature (K)	298(2)°	298(2)°	298(2)°	298(2)°
crystal system	triclinic	monoclinic	monoclinic	monoclinic
color and shape	colorless, prism	colorless, prism	colorless, needle	colorless, plate
space group	$P\bar{1}$	$P2_1/n$	$P2_1/n$	$P2_1/n$
a	11.235(2) Å	13.2318(16) Å	10.863(2) Å	10.9136(17) Å
b	13.727(3) Å	17.875(2) Å	10.632(2) Å	10.8330(17) Å
c	17.366(4) Å	23.693(3) Å	35.653(7) Å	35.836(6) Å
α	68.096(7)°	90.0°	90.0°	90.0°
β	79.188(7)°	106.130(4)°	92.039(6)°	90.688(6)°
γ	66.159(7)°	90.0°	90.0°	90.0°
volume	2270.7(8) $Å^3$	5383.3(11) $Å^3$	4115.2(14) $Å^3$	4236.4(12) $Å^3$
Z	2	4	4	4
D_{calcd}	1.028 g cm^{-3}	1.127 g cm^{-3}	1.248 g cm^{-3}	1.431 g cm^{-3}
μ	0.070 mm^{-1}	0.072 mm^{-1}	0.268 mm^{-1}	2.902 mm^{-1}
F(000)	755	1992	1644	1872
crystal size	0.30 mm × 0.12 mm × 0.10 mm	0.27 mm × 0.19 mm × 0.19 mm	0.80 mm × 0.38 mm × 0.09 mm	0.32 mm × 0.30 mm × 0.10 mm
θ range	1.72°–25.37°	1.4°–26.34°	1.14°–25.30°	1.14°–25.73°
limiting indices	$-12 \le h \le 13$, $-15 \le k \le 16$, $-20 \le l \le 20$	$-16 \le h \le 16$, $-22 \le k \le 22$, $-29 \le l \le 29$	$-12 \le h \le 13$, $-12 \le k \le 12$, $-39 \le l \le 42$	$-13 \le h \le 13$, $-13 \le k \le 13$, $-43 \le l \le 43$
total/unique no. of reflns.	28062/8272	68804/10841	49155/7485	51538/7995
R_{int}	0.0522	0.1387	0.0866	0.1057
data/restr./params.	8272/1/460	10841/0/626	7485/0/478	7995/28/469
GOF (F^2)	0.909	1.000	1.056	0.928
*R*1, *wR*2	0.0627, 0.1650	0.0826, 0.1415	0.0624, 0.1388	0.0504, 0.1039
R indices (all data) *R*1, *wR*2	0.1326, 0.1896	0.2233, 0.1818	0.1100, 0.1553	0.1069, 0.1198
largest different peak and hole (e $Å^{-3}$)	0.547 and −0.157	0.212 and −0.177	0.242 and −0.252	0.454 and −0.399

complexation-induced shifts, the binding constants were calculated by fitting the data using the EQNMR program with a 1:1 (receptor:anion) model. The determined binding constants (K_a) for the halides and tetrahedral anions are given in Table 2,

Table 2. Binding Constants (K_a) Determined by ^{1}H NMR Titrations for 2 with Anions as their *n*-Bu_4N^+ Salts in DMSO-d_6 at 298 K

	F^-	Cl^-	Br^-	HSO_4^-	$H_2PO_4^-$
$\Delta\delta^a$	3.34[b]	1.22	0.32	0.40	0.43
K_a (M^{-1})	$>10^4$	69[c]	15[c]	30[c]	11[d]

[a] $\Delta\delta$ = the change in the chemical shift in ppm upon complexation obtained from EQNMR calculation. [b] Data obtained from experiment. [c] <30% error. [d] 55% error.

along with $\Delta\delta$. As can be seen from Table 2, the receptor binds strongly with the F^- ion with a very high affinity, compared to other anions. Interestingly, upon addition of the F^- ion to the receptor solution, ^{1}H spectra show two NH resonances: one for the free receptor as a singlet and the other for the complexed receptor as a doublet in the deshielded region with a coupling constant J(HF) = 34 Hz, which are observed up to the addition of 0.9 equiv of F^-, as shown in Figure 2 (also see Figure S26 in the Supporting Information). After the addition of 0.9 equiv of F^-, only the doublet appears. This indicates a slow complexation equilibrium on the NMR time scale and a strong interaction. Similar J(HF) coupling constants have been reported for fluoride complexes, because of strong interactions.[16] These observations indicate that the fluoride anion is encapsulated inside the cavity of the neutral receptor **2** and forms a 1:1 complex. Its binding constant was calculated to be $>10^4$ M^{-1} from the integrated intensity values of the NH resonances corresponding to the free form of the receptor and to the complex (see Figure S27 in the Supporting Information). In contrast to this, the binding constants for other larger anions are much lower, indicating weaker binding and, most likely, cleft bindings. It is also to be noted that, in the case of the sulfate ion titration experiment, the HSO_4^- ion was added. HSO_4^- can protonate the amine nitrogens to form a positively charged receptor, which would be expected to bind the sulfate dianion strongly via both electrostatic and hydrogen bonds to

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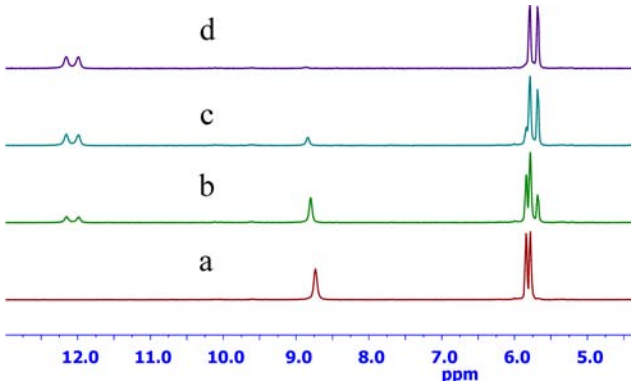

Figure 2. Partial ^{1}H NMR (200 MHz) spectra of **2** (0.0086 M) (spectrum a) and **2** upon the addition of 0.389 equiv of *n*-Bu_4NF (spectrum b), 0.778 equiv of *n*-Bu_4NF (spectrum c) and 0.973 equiv of *n*-Bu_4NF in DMSO-d_6 (spectrum d) at 298 K, showing the NH resonance splitting by the F^- ion and the slow complexation equilibrium.

give a high affinity constant. However, the observed lower values indicate that the cavity size is not voluminous enough for large-size anions, such as chloride, bromide, or sulfate ion to form an inclusion complex as the F^- ion does.

The consequence of F^- ion inclusion inside the cavity was observed by the pyrrolic NH resonance intensity, which decreased as aliquots of the F^- anion are added during the course of the titration experiment. After the addition of 2 equiv of F^- ions, the ^{1}H NMR spectra show the appearance of HF_2^- ions at δ = 16.12 ppm with J(HF) = 125 Hz. In addition, when the solution was heated in the presence of 6 equiv of F^- ions at 120 °C for ∼15 min the doublet due to the NH resonance has completely disappeared. This indicates that the F^- ions have mediated proton−deuterium exchange processes with the solvent DMSO-d_6, which has been reported previously for **B** in Chart 1 and amide-based anion receptors.[17] To validate the formation of intermediate fluoride inclusion complexes containing pyrrolic ND groups resulting from partial deuterium exchange, the progress of the H/D exchange was followed by proton-coupled ^{19}F NMR spectra. As shown in Figure 3, four multiplets have appeared upon the addition of 0.5 equiv of F^- to the solution of **2** in DMSO-d_6 with an immediate recording of the spectrum. These multiplets resulting from the coupling of fluoride with the pyrrolic protons are separated by ∼0.3 ppm and indicate the formation of different fluoride complexes of the receptor whose pyrrolic NH protons are partially replaced by deuterium. The multiplet at δ = −89.9 ppm can be assigned to the formation of the fluoride complex **4** represented as FH_6, and the other multiplets at δ = −90.3 ppm, δ = −90.6 ppm, δ = −90.9 ppm are assigned to the other fluoride complexes represented as FH_5D, FH_4D_2, and FH_3D_3, wherein one, two, and three pyrrolic NH protons are replaced with deuterium of the solvent, respectively. Upon the addition of 2 equiv of F^-, the multiplets due to the other H/D exchanged complexes FH_2D_4, FH_1D_5, and FD_6 are formed with an increased intensity at δ = −91.3 ppm, δ = −91.6 ppm, and δ = −91.9 ppm along with other multiplets, showing the continuously faster exchange rate in the presence of more F^- ions. When the solution was heated, the fully deuterium exchanged complex FD_6 is the only product formed, as shown by the ^{19}F and ^{1}H NMR spectra.

Fortunately, we were successful in crystallizing the fluoride complex of **2** from a dichloromethane solution of **2** containing a large excess of *n*-$Bu_4NF{\cdot}3H_2O$ by slow evaporation

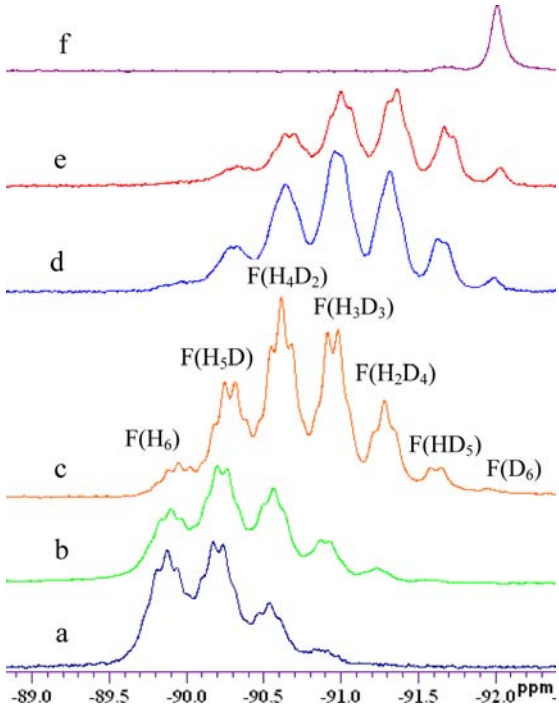

Figure 3. Partial proton coupled ^{19}F NMR (470.6 MHz) spectra of **2** (0.017 M) in DMSO-d_6 at 298 K in the presence of different molar ratios of F^-: (a) [**2**]:[*n*-Bu_4NF] = 1:0.5, (b) [**2**]:[*n*-Bu_4NF] = 1:1, (c) [**2**]:[*n*-Bu_4NF] = 1:2, (d) [**2**]:[*n*-Bu_4NF] = 1:3, (e) [**2**]:[*n*-Bu_4NF] = 1:4, and (f) recorded after heating the sample for spectrum (e) at 140 °C for 70 min. Spectrum (c) shows the peak assignment.

(Scheme 2). The structure of the fluoride complex **4** was unambiguously established by X-ray structural analysis. The molecular structure along with selected bond lengths and angles and the refinement data are given in Figure 4 and Table 1, respectively. The X-ray structure revealed the encapsulation of the F^- ion inside the cavity of the triazacryptand with two water molecules hydrogen bonded to the clefts. The countercation *n*-Bu_4N^+ is located outside which primarily interacts electrostatically and exhibits one CH···O(water)-type interaction. The inclusion of F^- ion inside the cavity causes changes in the conformation of the pyrrole rings, which are not fully eclipsed, in contrast to the eclipsed structure found for the free receptor **2**. Nonetheless, receptor adopts an eclipsed conformation about the bridgehead carbon−pyrrole β-carbon bonds. The F^- ion lies unsymmetrically inside the cavity; the distance of the F^- ion from the bridgehead C20 is 4.153 Å, while that from the other bridgehead C7 is 3.770 Å. The F^- ion is bound by four NH···F plus one OH···F hydrogen bonds; the remaining two pyrrolic NH groups are hydrogen-bonded to the water molecules. The donor−acceptor (N···F) bond distances range from 2.700(3) Å to 2.863(4) Å, which are slightly shorter than the distances [2.859(4)−2.914(4) Å] found in the structures of F^- ion complexes formed by the azacryptand **B**[14] as well as by the polyamide cryptand containing isophthalamide groups [2.9457(18)−3.1130(18) Å],[17a] but they fall in the range reported for the calix[4]pyrrole [2.790(2) Å[3a] and 2.732(6) Å[18]] and the polyamide cryptand containing 2,6-dicarboxamidopyridine groups [2.842(2)−2.887(2) Å][19] fluoride complexes. The distance between the two bridgehead carbons is 7.902 Å, which is shorter than that found in the structure of free macrobicycle **2**.

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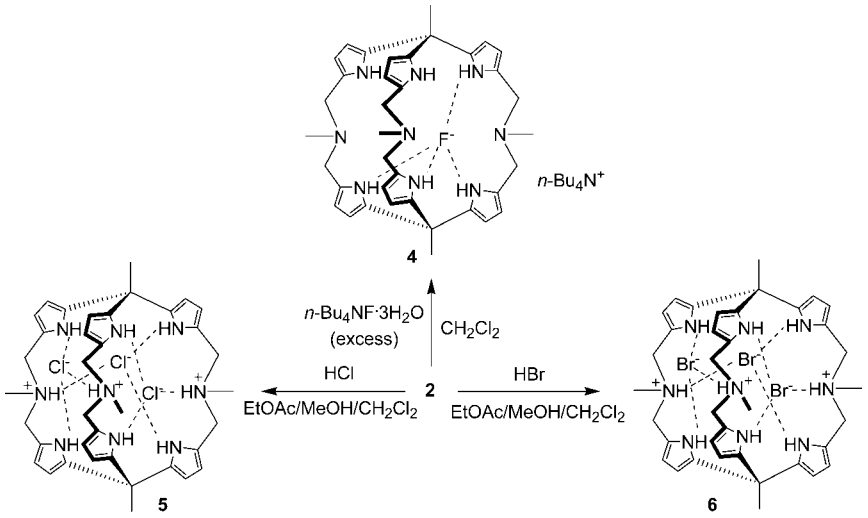
Scheme 2. Synthesis of F^-, Cl^-, and Br^- Ion Complexes of Receptor 2



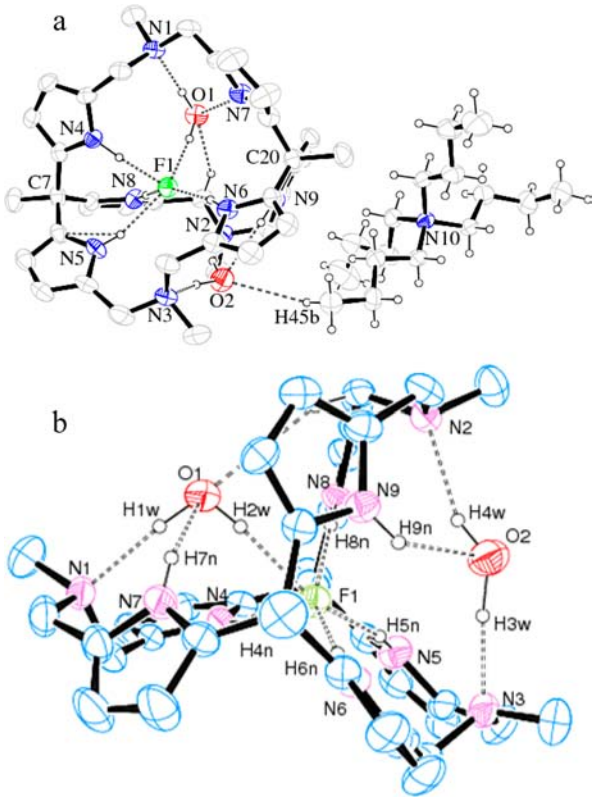


Figure 4. ORTEP diagram of $[2{\cdot}F^-][n\text{-}Bu_4N^+]{\cdot}2H_2O$ with 30% probability ellipsoids: (a) top view with n-Bu_4N^+ cation, and (b) view along the bridgehead C atoms without n-Bu_4N^+ cation showing the eclipsed conformation with F^- inside the cavity. Most H atoms are omitted for clarity. Selected bond lengths and angles: N4···F1, 2.715(4) Å; H4n···F1, 1.73(3) Å; N4–H4n···F1, 169(3)°; N5···F1, 2.869(4) Å; H5n···F1, 2.03(3) Å; N5–H5n···F1, 165(3)°; N6···F1, 2.745(4) Å; H6n···F1, 1.91(3) Å; N6–H6n···F1, 171(3)°; N8···F1, 2.709(4) Å; H8n···F1, 1.90(3) Å; N8–H8n···F1, 173(3)°; N7···O1, 2.914(4) Å; H7n···O1, 2.12(3) Å; N7–H7n···O1, 151(3)°; N9···O2, 3.005(5) Å; H9n···O2, 2.17(3) Å; N9–H9n···O2, 146(3)°.

In contrast to the reaction by which the fluoride complex **4** was formed, the corresponding reactions with n-Bu_4N^+ salts (Cl^- and Br^-) were not giving their encapsulated complexes. However, when **2** was treated with HCl or HBr in an aqueous EtOAc/MeOH/dichloromethane solvent mixture, the chloro complex **5** or the bromo complex **6** as a crystalline solid was readily obtained in 77% yield (see Scheme 2). These reactions indicate that receptor **2** is converted to its positively charged form by protonation upon which complexes are formed. This fuelled our curiosity and led us to investigate how Cl^- or Br^- ions are actually bound to the receptor.

Suitable single crystals of the hydrochloride and the hydrobromide complexes of **2** were obtained easily and directly from their syntheses, and their respective structures were determined by X-ray diffraction (XRD) studies. The molecular structures **5** and **6**, along with selected bond lengths and angles, are given in Figures 5 and 6, respectively. Their refinement data are given in Table 1. These X-ray structures revealed cleft binding motifs, not encapsulation, of three Cl^- or Br^- ions by the tripositively charged triazacryptand. In both structures, each halide ion is bound by two pyrrolic NH and one N^+H hydrogen bonds and receptor retained its eclipsed conformation. In the chloride complex **5**, the donor–acceptor (N···X) bond distances range from 3.034(3) Å to 3.279(4) Å and in the bromide complex **6**, they range from 3.163(4) Å to 3.404(4) Å; the latter was accompanied by CH···Br type hydrogen bonds. A very interesting difference between these two otherwise similar complexes is the distance between the bridgehead carbons: 8.530 Å in **5** and 8.370 Å in **6**. Even though, the amine N atoms are protonated to form the charged receptors, the Cl^- or Br^- ion is not encapsulated inside the cavity, emphasizing these anions are unable to enter into the cavity of the azacryptand, because of their size mismatches.

The ^{1}H NMR spectra of the chloro complexes **5** and bromo complexes **6** display an AB pattern for the methylene protons, which is in contrast to the fluoride complex **4** or the free receptor **2** showing only a singlet for these protons. For example, the methylene protons of **5** display an AB pattern at δ = 3.66 ppm as a doublet of a doublet, because of the coupling with the ammonium N^+H protons and at δ = 5.17 ppm as a doublet only; hence, its NMe groups appear as a doublet.

The high affinity of **2** for F^- over other anions was further confirmed by following the NH resonances in the ^{1}H NMR spectra (see Figure 7). The ^{1}H NMR spectrum of the mixture of anions such as Cl^-, Br^-, NO_3^-, HSO_4^-, and $H_2PO_4^-$ (1 equiv each) as their n-Bu_4N^+ salts in DMSO-d_6 gives a broad signal at δ = 9.53 ppm, which is close to the NH resonance

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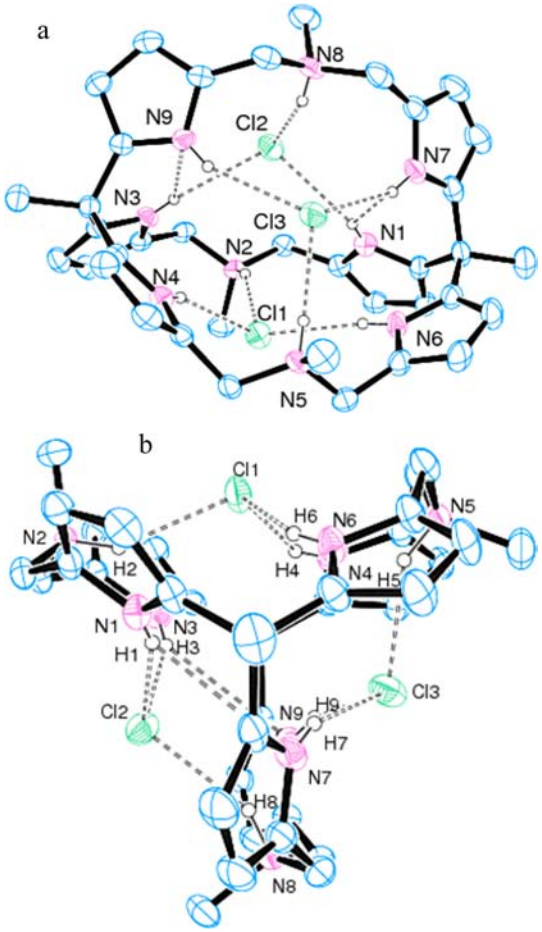

Figure 5. ORTEP diagram of $[H_32]^{3+}[Cl^-]_3 \cdot 2.61H_2O$ with 30% probability ellipsoids. (a) top view, and (b) view along the bridgehead carbon atoms showing the eclipsed conformation with the three Cl^- ions in the clefts. Most H atoms are omitted for clarity. Selected bond lengths and angles: N4···Cl1, 3.272(3) Å; H4···Cl1, 2.52(4) Å; N4–H4···Cl1, 154(3)°; N6···Cl1, 3.192(3) Å; H6···Cl1, 2.37(4) Å; N6–H6···Cl1, 158(3)°; N2···Cl1, 3.034(3) Å; H2···Cl1, 2.22(3) Å; N2–H2···Cl1, 148(3)°; N1···Cl2, 3.279(4) Å; H1···Cl2, 2.62(3) Å; N1–H1···Cl2, 154(4)°; N3···Cl2, 3.229(4) Å; H3···Cl2, 2.54(3) Å; N3–H3···Cl2, 156(3)°; N8···Cl2, 3.098(3) Å; H8···Cl2, 2.28(4) Å; N8–H8···Cl2, 153(3)°; N5···Cl3, 3.078(3) Å; H5···Cl3, 2.24(4) Å; N5–H5···Cl3, 147(3)°; N7···Cl3, 3.227(4) Å; H7···Cl3, 2.46(4) Å; N7–H7···Cl3, 157(3)°; N9···Cl3, 3.235(4) Å; H9···Cl3, 2.48(4) Å; N9–H9···Cl3, 157(3)°.

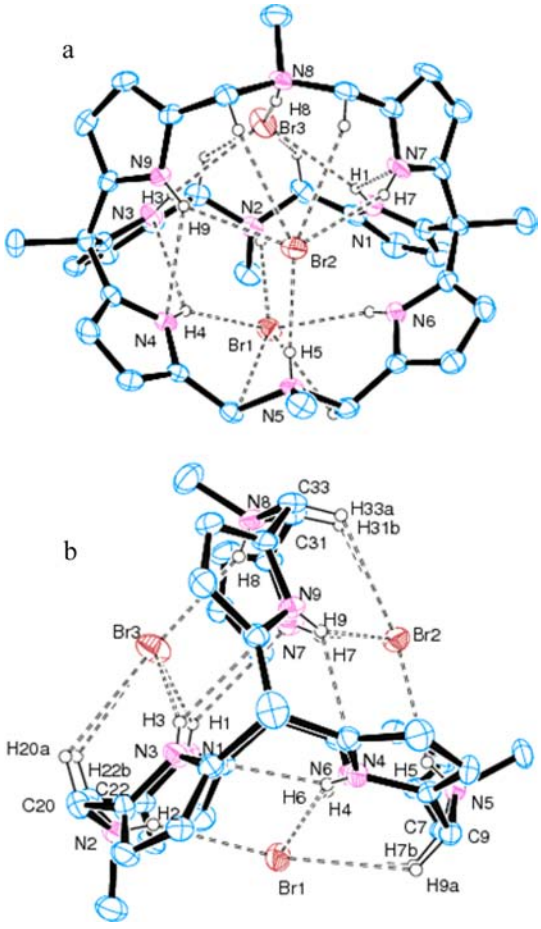

Figure 6. ORTEP diagram of $[H_32]^{3+}[Br^-]_3 \cdot 3H_2O$ with 30% probability ellipsoids. (a) top view, and (b) view along the bridgehead carbon atoms showing the eclipsed conformation with the three Br^- in the clefts. Most H atoms are omitted for clarity. Selected bond lengths and angles: N2···Br1, 3.228(4) Å; H2···Br1, 2.53(3) Å; N2–H2···Br1, 152(5)°; N4···Br1, 3.383(4) Å; H4···Br1, 2.70(3) Å; N4–H4···Br1, 151(5)°; N6···Br1, 3.379(4) Å; H6···Br1, 2.64(2) Å; N6–H6···Br1, 164(5)°; N5···Br2, 3.164(4) Å; H5···Br2, 2.48(3) Å; N5–H5···Br2, 148(5)°; N7···Br2, 3.331(4) Å; H7···Br2, 2.61(3) Å; N7–H7···Br2, 154(5)°; N9···Br2, 3.404(4) Å; H9···Br2, 2.67(5) Å; N9–H9···Br2, 148(4)°; N1···Br3, 3.361(4) Å; H1···Br3, 2.68(3) Å; N1–H1···Br3, 149(5)°; N3···Br3, 3.347(4) Å; H3···Br3, 2.64(3) Å; N3–H3···Br3, 156(5)°; N8···Br3, 3.188(4) Å; H8···Br3, 2.46(3) Å; N8–H8···Br3, 157(5)°.

displayed by the chloride complex formed during its titration experiment. When 1 equiv of F^- ions is added to this mixture, the NH resonance becomes a doublet at δ = 12.56 ppm, which is the same as observed for the fluoride complex **4** and confirms the selectivity of **2** toward F^-.

By an analogous manner of the anion binding with receptor **2**, the halide anion binding study with **3a** was carried out in DMSO-d_6. It is found that the binding constant of the F^- ion with **3a** is 1860 M^{-1}, while the binding constant for Cl^- or Br^- ion is too low to be measured, because their ^{1}H NMR spectra showed a negligible shift of the NH resonance upon the addition of Cl^- or Br^- ions. Although the order of anion binding remains the same as that observed for **2** (F^- > Cl^- > Br^-), the magnitude of the binding constant for **2** with F^- is much larger than that observed with **3a**. Given the flexibility, the presence of three tertiary amine groups, and the lesser number of anion binding groups (pyrrolic NH), the acyclic receptor **3a** is

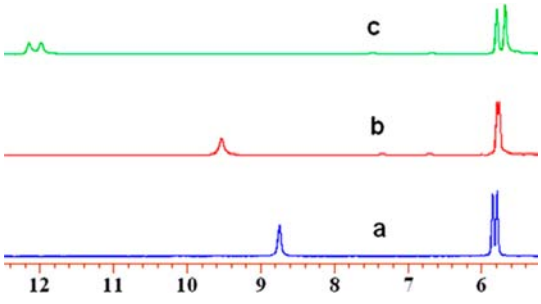

Figure 7. Partial ^{1}H NMR (200 MHz) spectra of (a) **2** (0.012 M), (b) **2** (0.012 M) in the presence of mixture of anions such as Cl^-, Br^-, NO_3^-, HSO_4^-, and $H_2PO_4^-$ (1 equiv each) as their *n*-Bu_4N^+ salts in DMSO-d_6 at 298 K; (c) spectrum obtained after adding 1 equiv of F^- ions to the solution, which gives the spectrum (b), showing a doublet, because of the coupling with the F^- ion for the NH protons and the predominant affinity of **2** toward F^- in the presence of other anions.

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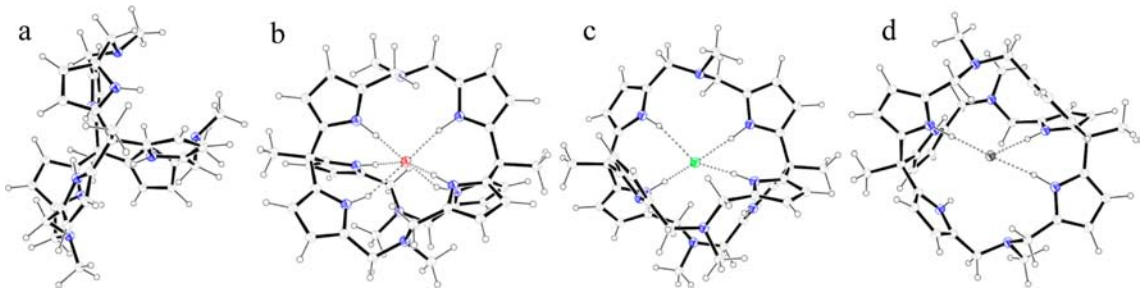

Figure 8. Density functional theory (DFT)-optimized geometries for (a) the free receptor **2**, and its neutral 1:1 halide anion complexes ((b) [**2**·F^-], (c) [**2**·Cl^-], and (d) [**2**·Br^-]).

expected to bind anions less strongly, compared to **2**. This points out that the preorganization of receptor **2**, by which the anion binding groups are in the right positions, is important, in addition to the specific cavity size of **2** and the inherent strength of the hydrogen bonds that are formed by the anions. If the hydrogen-bond strength is the only deciding factor for the selectivity of F^-, the acyclic receptor **3a** could have possessed a large K_a value for the F^- ion like **2** has, by forming a 2:1 (receptor:anion) complex as observed with the closely related receptor tripyrrolemethane ($HC(C_4H_4N)_3$),[20] because **3a** represents one-half of the macrobicycle **2**. Hence, it appears that, in addition to the favorable hydrogen-bonding ability of F^-, the preorganization of receptor, which is done here via the synthesis of a macrobicycle having a specific cavity size, is very important and plays a major role for the selective binding of F^- ion.

Density functional theory (DFT) calculations were performed to understand the observed selectivity of azacryptand **2** toward the F^- ion in solution. The energy-minimized structures of the 1:1 halide ion complexes and that of the free receptor are given in Figure 8. The binding energies for these complexes were calculated based on the equation

$$\mathrm{BE} = E_{\mathrm{complex}} - \left(E_{\mathrm{receptor}} + E_{\mathrm{anion}}\right)$$

where BE is the binding energy and E_{complex}, E_{receptor}, and E_{anion} are the energies of the corresponding complex, receptor, and anion, respectively. The calculated binding energies are −143.1, −77.3, and −52.5 kcal/mol for F^-, Cl^-, and Br^- ions, respectively. This decrease in energy can be rationalized by the electronegativity and the strength of the hydrogen bonds formed by these halide anions, which is $F^- > Cl^- > Br^-$.[20] In the optimized structure of the free receptor, the two NH groups of each wing are oriented in different directions and the structure is not fully eclipsed. Conversely, all NH groups are oriented toward the cavity and hydrogen-bonded in the structure of F^- complex. The number of NH···X (X = F, Cl, and Br) interactions decrease as the size of the halide ion increases. This indicates that cavity size is most suitable for the F^- ion, so that all NH groups interact and the stabilization energy is higher.

CONCLUSIONS

A new class of pyrrole-based macrobicyclic and acyclic receptors were synthesized by the Mannich reactions of the tripyrrolylmethane precursor and their anion binding properties were studied by NMR titration methods and X-ray structures. From both experimental and computational studies, it is shown that the very high affinity and selectivity of **2** as a neutral receptor toward F^- ion among the halide ions is predominantly determined by the strength and the number of hydrogen bonds that these ions form, which, in turn, is determined by the preorganization of the receptor. However, in the presence of oxoanions, this leads to the claim that the receptor chooses its guest based on both size and hydrogen-bond strength. Although oxoanions have multicenter hydrogen-bond acceptors, which can lead to better stability, compared to halide ions, receptor **2** does not show selectivity toward an oxoanion, because of their large size. Meanwhile, the larger-size halide ions bind only in the clefts of the protonated macrobicycle, thus supporting a size-selective anion binding behavior. The synthesis of other pyrrole-based macrobicycles and analysis of their respective anion binding properties are in progress.

EXPERIMENTAL SECTION

1,1,1-(Tripyrrolyl)ethane was prepared according to the literature procedure.[21] ^{1}H NMR (200 and 400 MHz), and ^{13}C NMR (50.3 and 100.6 MHz) spectra were recorded on Bruker ACF200 and AV400 spectrometers. ^{19}F NMR spectra were recorded on a 500 MHz spectrometer operating at 470.6 MHz for which 0.05% trifluorotoluene in $CDCl_3$ was used as an external reference resonating at −62.73 ppm. ^{1}H NMR chemical shifts are referenced with respect to the chemical shift of the residual protons present in the deuterated solvents. High-resolution mass spectra (ESI) were recorded using a LCT Orthogonal Acceleration TOF Electrospray Mass Spectrometer. FT-IR spectra were recorded using a Perkin−Elmer Spectrum Rx. Melting points were determined in open capillaries and were corrected using benzophenone as a reference.

Computational Methods. All the calculations were done with BP86 functional[22] and def2-SVP basis set,[23] using a TURBOMOLE program package.[24] The Resolution of Identity approximation[25] was used for speedup. Empirical dispersion correction[26] was employed to account for the noncovalent interaction.

Synthesis of Azacryptand (2). A solution of freshly prepared 1,1,1-(tripyrrolyl)ethane (3.12 g, 13.85 mmol) in methanol (150 mL) was added dropwise to a stirred mixture of methylamine hydrochloride (1.41 g, 20.88 mmol) and formaldehyde (39%, 3.19 mL, 41.54 mmol) at 0 °C. After stirring for 15 h (overnight) at room temperature, an aqueous solution of potassium carbonate (1.72 g, 12.44 mmol) was added and then stirred for another 3−4 h to give a solution with a colorless precipitate. The solvent was removed under vacuum, and the resultant residue was extracted with dichloromethane three times. The dichloromethane solution was dried over anhydrous Na_2SO_4 and filtered. The solvent was removed from the filtrate, and the resultant residue was loaded onto a column filled with silica gel (100−200 mesh). The column was eluted with a petroleum ether/ethyl acetate mixture (v/v 1:1) to give the first fraction. Removal of the solvent from the first fraction under vacuum afforded **2** as a colorless crystalline powder (0.80 g, 1.14 mmol, 16% with respect to 1,1,1-(tripyrrolyl)ethane). Suitable single crystals of **2** for the X-ray diffraction (XRD) study were obtained by slow evaporation of a solution of **2** in a petroleum ether/ethyl acetate/methanol mixture at room temperature. Melting point (mp) >200 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, ppm): δ = 1.99 (s, 9H,

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NMe), 2.09 (s, 6H, *meso* CMe), 3.41 (s, 12H, $CH_2N(Me)CH_2$), 5.94 (m, 6H, pyrrole β-CH), 6.00 (m, 6H, pyrrole β-CH), 8.55 (br s, 6H, NH). $^{13}C\{^1H\}$ NMR (50.3 MHz, $CDCl_3$, 25 °C, ppm): δ = 25.3 (CCH_3), 40.1 (*meso* C), 40.8 (NCH_3), 55.7 ($CH_2N(Me)CH_2$), 103.6 (pyrrole β-C), 109.4 (pyrrole β-C), 127.0 (pyrrole α-C), 138.0 (pyrrole α-C). FT-IR (KBr, cm^{-1}): ν = 3437 (vs), 3098 (w), 2975 (w), 2930 (w), 2834 (w), 1494 (w), 1455 (w), 1424 (m), 1371 (w), 1334 (w), 1284 (w), 1234 (w), 1202 (m), 1122 (m), 1037 (m), 1007 (m), 976 (m), 856 (w), 773 (vs), 671 (w). HRMS (+ESI): Calcd *m*/*z* for $[M+H^+]$ $C_{37}H_{46}N_9$: 616.3876, Found: 616.3878.

Synthesis of 3a. A solution of freshly prepared 1,1,1-(tripyrrolyl)-ethane (3.0 g, 13.31 mmol) in ethanol (200 mL) was added dropwise to a stirred mixture of dimethylamine hydrochloride (3.37 g, 41.32 mmol) and formaldehyde (39%, 3.17 mL, 41.21 mmol) at 0 °C. After stirring for 8−10 h at room temperature, an aqueous solution of potassium carbonate (2.90 g, 20.98 mmol) was added and then stirred for another 1 h to give a solution with a colorless precipitate. The solvent was removed under vacuum and the resultant residue was extracted with diethyl ether three times. The ether solution was dried over anhydrous Na_2SO_4 and filtered. The solvent was removed from the filtrate to give **3a** as a colorless gum-like solid (4.20 g, 10.59 mmol, 79%, with respect to 1,1,1-(tripyrrolyl)ethane). ^1H NMR (200 MHz, $CDCl_3$, 25 °C, ppm): δ = 1.96 (s, 3H, *meso* CMe), 2.15 (s, 18H, NMe), 3.32 (s, 6H, CH_2NMe_2), 5.84 (m, 3H, pyrrole β-CH), 5.90 (m, 3H, pyrrole β-CH), 8.46 (br s, 3H, NH). $^{13}C\{^1H\}$ NMR (50.3 MHz, $CDCl_3$, 25 °C, ppm): δ = 28.0 (CCH_3), 40.7 (*meso* C), 45.0 (NCH_3), 56.7 (CH_2NMe_2), 105.2 (pyrrole β-C), 107.5 (pyrrole β-C), 128.4 (pyrrole α-C), 137.0 (pyrrole α-C). FT-IR (KBr, cm^{-1}): ν = 3234 (s), 2976 (s), 2942 (s), 2859 (s), 2817 (s), 2775 (s), 1655 (w), 1585 (w), 1458 (m), 1357 (m), 1249 (w), 1202 (w), 1144 (w), 1097 (w), 1037 (m), 1013 (m), 988 (w), 846 (w), 773 (vs). HRMS (+ESI): Calcd *m*/*z* for $[M+H^+]$ $C_{23}H_{37}N_6$: 397.3080, Found: 397.3084.

Synthesis of 3b. It was synthesized as colorless gum-like solid by following the procedure for **3a**. This reaction involves 1.0 g (4.43 mmol) of 1,1,1-(tripyrrolyl)ethane, 1.51g, (13.78 mmol) of diethylamine hydrochloride, and 1.06 mL (39%, 13.78 mmol) of formaldehyde in 80 mL of ethanol. Yield: 74% (1.57 g, 3.29 mmol, with respect to 1,1,1-(tripyrrolyl)ethane). ^1H NMR (200 MHz, $CDCl_3$, 25 °C, ppm): δ = 0.97 (t, ^3J(H,H) = 7.0 Hz, 18H, CH_2-CH_3), 1.98 (s, 3H, *meso* CMe), 2.48 (q, ^3J(H,H) = 7.0 Hz, 12H, NCH_2Me), 3.47 (s, 6H, CH_2NEt_2), 5.84 (m, 3H, pyrrole β-CH), 5.90 (m, 3H, pyrrole β-CH), 8.85 (br s, 3H, NH). $^{13}C\{^1H\}$ NMR (50.3 MHz, $CDCl_3$, 25 °C, ppm): δ = 11.4 (NCH_2CH_3), 27.9 (CCH_3), 40.7 (*meso* C), 46.4 (NCH_2CH_3), 50.7 (CH_2NEt_2), 104.9 (pyrrole β-C), 107.1 (pyrrole β-C), 128.5 (pyrrole α-C), 136.8 (pyrrole α-C). FT-IR (KBr, cm^{-1}): ν = 3437 (s), 2970 (s), 2934 (m), 2817 (m), 1654 (w), 1585 (w), 1496 (w), 1459 (m), 1373 (m), 1285 (w), 1198 (m), 1119 (w), 1034 (m), 999 (w), 964 (w), 910 (w), 765 (vs), 519 (w). HRMS (+ESI): Calcd *m*/*z* for $[M+H^+]$ $C_{29}H_{49}N_6$: 481.4019, Found: 481.4015.

Synthesis of the Fluoride Inclusion Complex [2·F⁻][*n*-Bu₄N⁺]·2H₂O (4). To a dichloromethane solution (15 mL) of **2**·4.9H_2O (0.025 g, 0.036 mmol), an excess amount of *n*-$Bu_4NF·3H_2O$ (0.54 g, 1.73 mmol) was added. The solution was stirred for ∼15 min at room temperature. The solution then was allowed to evaporate slowly at room temperature. Colorless crystals suitable for XRD study were formed over a period of two weeks. The crystals were separated from the oily mother liquor and dried in air (∼0.020 g, 0.022 mmol, 62% yield). ^1H NMR (200 MHz, $CDCl_3$, 25 °C, ppm): δ = 0.98 (t, 12H, ^3J(H,H) = 6.7 Hz, CH_3 of the *n*-Bu group), 1.36 (m, 16H, $-CH_2CH_2-$ of the *n*-Bu group), 2.05 (s, 6H, CMe), 2.15 (s, 9H, NMe), 2.79 (t, 8H, ^3J(H,H) = 7.5 Hz, NCH_2 of the *n*-Bu group), 3.35 (s, 12H, $CH_2N(Me)CH_2$), 5.87 (s, 12H, pyrrole CH), 11.05 (very broad s, 6H, NH). HRMS (−ESI): Calcd *m*/*z* for $[M-n\text{-}Bu_4N^+]^-$ $C_{37}H_{45}N_9F$: 634.3782, Found: 634.3782.

Synthesis of the Chloride Complex $[H_32]^{3+}[Cl^-]_3$·2.61H_2O (5). A solution of HCl (12M, 13.85 μL, 0.166 mmol) in ethyl acetate/methanol (v/v 1:1) was layered on top of the solution of **2**·4.9H_2O (0.040 g, 0.057 mmol) in a ethyl acetate/methanol/dichloromethane (v/v 1: 1: 0.5) mixture. Colorless needle shaped crystals of **5** were formed over a period of two weeks. The crystals were separated by decanting the mother liquor and then dried in air (0.034 g, 0.044 mmol, 77% yield). Melting point (mp) >200 °C. ^1H NMR (200 MHz, $CDCl_3$, 25 °C, ppm): δ = 2.11 (s, 6H, *meso* CMe), 2.85 (d, 9H, ^3J(H,H) = 4.4 Hz, NMe), 3.66 (dd, 6H, *J*(H,H) = 12.6 and 8.8 Hz, $CH_2NH(Me)CH_2$), 5.17 (d, 6H, *J*(H,H) = 13.0 Hz, $CH_2NH(Me)$-CH_2), 5.98 (s, 6H, pyrrole β-CH), 6.19 (s, 6H, pyrrole β-CH), 9.63 (br s, 3H, ^+NH), 10.96 (br s, 6H, pyrrole NH). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C, ppm): δ = 27.7 (CCH_3), 40.5 (*meso* C), 40.6 (NCH_3), 55.4 ($CH_2N(Me)CH_2$), 104.3 (pyrrole β-C), 112.1 (pyrrole β-C), 119.4 (pyrrole α-C), 139.9 (pyrrole α-C).FT-IR (KBr, cm^{-1}): ν = 3233 (vs), 2991 (w), 2936 (w), 2679 (w), 1654 (w), 1624 (w), 1461 (m), 1443 (m), 1277 (m), 1207 (m), 1176 (m), 1109 (w), 1042 (m), 996 (w), 932 (w), 881 (m), 782 (vs), 692 (w). HRMS (+ESI): *m*/*z* for $[M-Cl^-]^+$ 688.3535, for $[M-2Cl^-+H^+]^{3+}$ 654.3765.

Synthesis of the Bromide Complex $[H_32]^{3+}[Br^-]_3$·3H_2O (6). A solution of HBr (46%, 36.41 μL, 0.207 mmol) in ethyl acetate/methanol (v/v 1:1) was layered on top of the solution of **2**·4.9H_2O (0.050 g, 0.07 mmol) in a ethyl acetate/methanol/dichloromethane (v/v 1:1:0.5) mixture. Colorless crystals of **6** were formed over a period of two weeks. The crystals were separated by decanting the mother liquor and then dried in air (0.05 g, 0.055 mmol, 77% yield). Melting point (mp) >200 °C. ^1H NMR (200 MHz, $CDCl_3$, 25 °C, ppm): δ = 2.07 (s, 6H, *meso* CMe), 2.91 (d, 9H, ^3J(H,H) = 4.8 Hz, NMe), 3.73 (dd, 6H, *J*(H,H) = 13.0 and 7.0 Hz, $CH_2NH(Me)CH_2$), 5.47 (d, 6H, *J*(H,H) = 13.0 Hz, $CH_2NH(Me)CH_2$), 6.00 (m, 6H, pyrrole β-CH), 6.21 (m, 6H, pyrrole β-CH), 9.10 (br s, 3H, ^+NH), 10.77 (br s, 6H, pyrrole NH). FT-IR (KBr, cm^{-1}): ν = 3240 (vs), 2989 (w), 2928 (w), 2791 (w), 2681 (w), 1654 (w), 1624 (w), 1461 (m), 1438 (m), 1364 (w), 1275 (m), 1205 (m), 1174 (m), 1108 (w), 1042 (m), 996 (w), 931 (w), 877 (m), 781 (vs), 690 (w). HRMS (+ESI): *m*/*z* for $[M-Br^-]^+$ 778.2291, for $[M-2Br^-+H^+]^{3+}$ 698.3007.

NMR Titrations. Using a 10 μL Hamilton Gastight syringe, all the titrations were carried out by adding an incremental amount of anions (F^-, Cl^-, Br^-, HSO_4^-, and $H_2PO_4^-$) (2 μL, 1 × 10^{-3} mmol, 0.195 equiv) as their *n*-tetrabutylammonium salts (0.5 M) in DMSO-d_6 to a NMR tube containing the receptor **2**·4.9H_2O (3.62 mg, 0.00514 mmol) in DMSO-d_6 (0.6 mL). After each addition, the spectrum was recorded and the NH resonance was monitored for calculating the association constants K_a by the EQNMR[27] and other methods.[28] By an analogous way, F^-, and Cl^- ions were titrated with the acyclic receptor **3a** (2.1 mg, 0.0053 mmol) in DMSO-d_6.

X-ray Crystallography. Single-crystal XRD data collections for these crystals were performed using a Bruker-APEX-II CCD diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71073 Å). The structures were solved by direct methods (SHELXS-97) and refined against all data by full-matrix least-squares methods on F^2 (SHELXL-97, WinGX version).[29] All non-hydrogen atoms were refined anisotropically. H atoms were refined isotropically on calculated positions using riding models unless bound to nitrogen or oxygen, which were generally located and refined without any geometric restraints. The unit cells of the structures **2**·4.9H_2O, **5**, and **6** contain 7, 10.44, and 12 lattice water molecules, respectively, which have been treated as a diffuse contribution to the overall scattering without specific atom positions by SQUEEZE/PLATON.[30] These routines necessarily contribute to the discrepancy between calculated and reported formulas in the CIF file (given in the Supporting Information).

In the structure of **2**, the water oxygen atom (O1) present inside the cavity of the macrobicycle **2** has full occupancy; the other two oxygen atoms (O2 and O3) present in the clefts have a 20% occupancy factor each, but could be clearly located. The number of water molecules per formula is 4.9 (3.5 from the lattice as *Z* = 2, 1 in the cavity of the structure, and 2 in the clefts with 20% occupancy each), (**2**·4.9H_2O). H atoms on water molecules were not refined. In the structure of **4**, the H atoms in water were located and refined isotropically with the thermal parameters equivalent to 1.2 times the thermal parameter value of the atom to which the H atoms are bonded. In the structure of **5**, the number of water molecules per formula is 2.61. In the structure of **6**, the number of water molecules per formula is 3. After locating them, the pyrrolic NH and ammonium hydrogen atoms,

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whose thermal parameters are dependent on their parent atoms, were refined with restraints (SADI) for the N−H distances to average these.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

X-ray crystallographic data of compounds **2**·4.9H_2O, [**2**·F^-][*n*-Bu_4N^+]·2H_2O (**4**), $[H_3\mathbf{2}]^{3+}[Cl^-]_3$·2.61$H_2O$ (**5**), and $[H_3\mathbf{2}]^{3+}[Br^-]_3$·3$H_2O$ (**6**) in CIF format. NMR spectra, IR spectra, details of binding constant calculations and DFT coordinates, and the total energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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