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Fluoride: Solution- and Solid-State Structural Binding Probe

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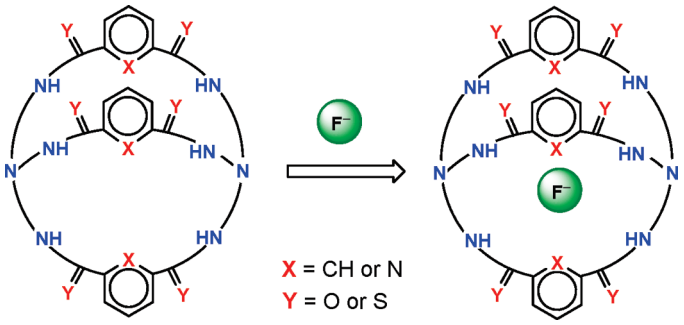

Solid-state and solution studies were performed to determine if F^- is encapsulated by anion hosts in both media. X-ray crystal structure determinations were compared with both ^1H and ^{19}F solution NMR data. Three hosts were studied: (1) two polyamide hosts, one with isophthaloyl spacers and the other with pyridine spacers, and (2) a polythioamide host with pyridine spacers. Binding studies showed that the pyridine-containing amide cryptand shows the highest affinity ($K_a > 10^5$ in DMSO-d_6), with the other hosts at least a factor of 10 lower. All of the cryptands appear to encapsulate F^- in solution, where a deuterium-exchange reaction with DMSO-d_6 can be monitored by ^{19}F NMR. Four crystal structures are reported and compared: two for the pyridine-containing free base hosts and two for encapsulated F^- complexes of the two amide-based cryptands.

Introduction

The binding of anions with supramolecular hosts is a fascinating and growing field.[1,2] Researchers have relied on a variety of methods to investigate structural interactions and binding propensities. X-ray crystallography has historically been the method of choice for definitive structural answers because it gives an atomic-level view of host/guest interactions, albeit in the solid state. A variety of titration techniques have been used to determine anion-binding constants in solution. Information concerning selectivity issues and structure in solution are important to most analytical applications and can only be answered with other techniques. ^{19}F NMR can be used as a very effective probe for examining the interaction of the highly electronegative F^- ion with hosts in solution. Comparisons of solution- and solid-state structures can therefore be made.

Encapsulation of targeted anions represents perhaps the most desirable structural host/guest interaction. This is especially true for macrocyclic hosts and it ultimately can lead to size and shape selectivity. Because of their spherical shape, halides ideally lend themselves to encapsulation in cryptand[3−5]

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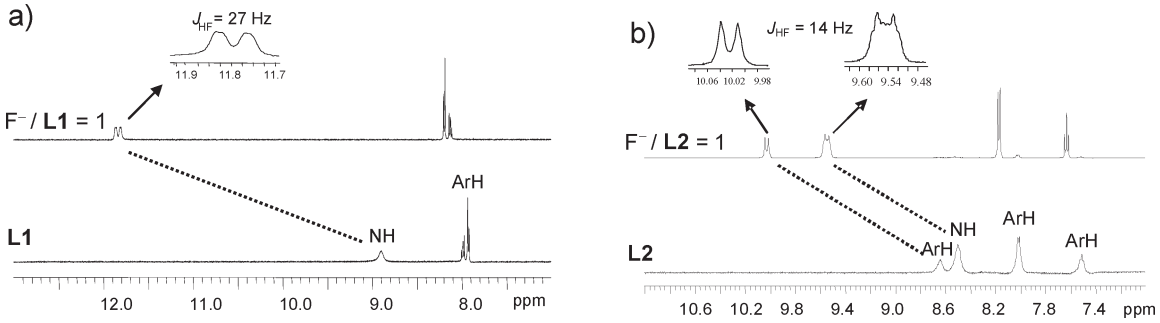
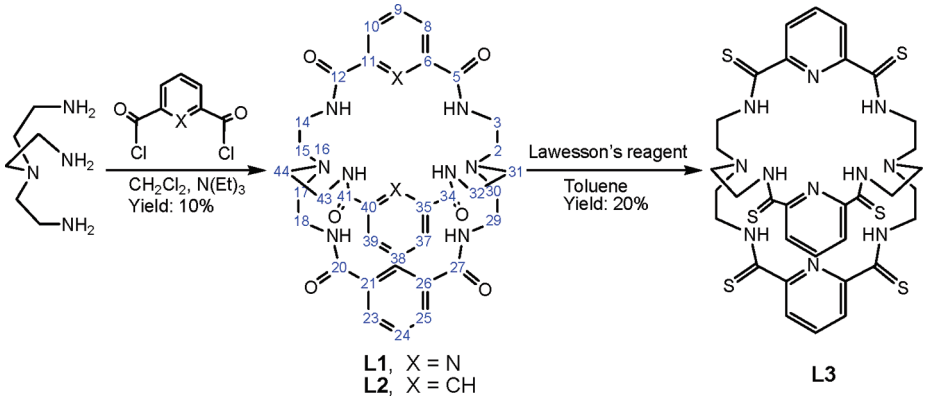


FIGURE 1. ^{1}H NMR spectra of (a) **L1** and (b) **L2** with n-$Bu_4N^+F^-$ in DMSO-d_6.

SCHEME 1. Synthesis of L1−L3 Showing the General Numbering Scheme for Carbon Atoms Used in the Crystallographic Labeling



and macropolycyclic hosts.[6] This is what occurs for the two F^- complexes reported herein. Solution-binding studies are reported for F^- ion with one thioamido- and two amido-cryptands along with crystal structures for two free bases and F^- complexes with two of the hosts. The results emphasize the benefit of utilizing both multinuclear NMR solution studies and X-ray crystallography to elucidate solution and solid-state structural proclivities of anion complexes.

Results and Discussion

Synthesis. The synthetic procedures for the cryptands are straightforward. With the exception of the thioamide, they consist of a one-step condensation reaction as reported previously.[7] High-dilution techniques are used, and although the yields are relatively low, the simple one-step synthetic pathway to the amido-cryptands compensates for this. Two equivalents of tris(2-aminoethyl)amine and 3 equiv of the respective 2,6-pyridine or isophthaloyl dicarbonyl dichloride, both in large amounts of CH_2Cl_2, are added to a solution of an equal amount of CH_2Cl_2 in the presence of Et_3N as a base (Scheme 1).[7] The pyridine thioamide cryptand can be readily obtained by treating the amido-cryptand with Lawesson's reagent,[8,9] but the isophthaloyl thioamide analogue cannot.

^{1}H NMR Studies. The ^{1}H NMR spectra of F^- with the cryptands **L1−L3** in DMSO-d_6 indicate proton coupling with the internally held $I = 1/2F^-$. A new doublet amide NH signal at 11.85 ppm appears upon addition of F^- to **L1** (J_{HF} = 27 Hz) (Figure 1a), and a similar pattern is observed for the thioamide cryptand **L3**. Both the amide and isophthaloyl H atoms in **L2** couple with F^- (J_{HF} = 14 Hz) (Figure 1b). Similar coupling of pyrrole NH with bound F^- has also been observed by Sessler and Gale.[10,11]

^{19}F NMR Studies. The F^- signal shifts upfield from free F^- at −96.7 to bound F^- at −111.7 ppm upon addition of **L1** to a solution of F^- in DMSO-d_6. The new signal appears as a septet (J_{HF} = 27 Hz) due to coupling of F^- with the six equivalent amide H atoms (no. of multiplets = $2nI + 1$, where I = nuclear spin and n = number of atoms) (Figure 2a,b). These findings provide further confirmation that F^- is present as an inclusion complex in solution. A similar upfield shift is observed with the thioamide **L3**. However, in addition to the septet (J_{HF} = 25 Hz), the spectrum consists of a series of multiplets (Figure 2d), which are the result of deuterium exchange as described below.

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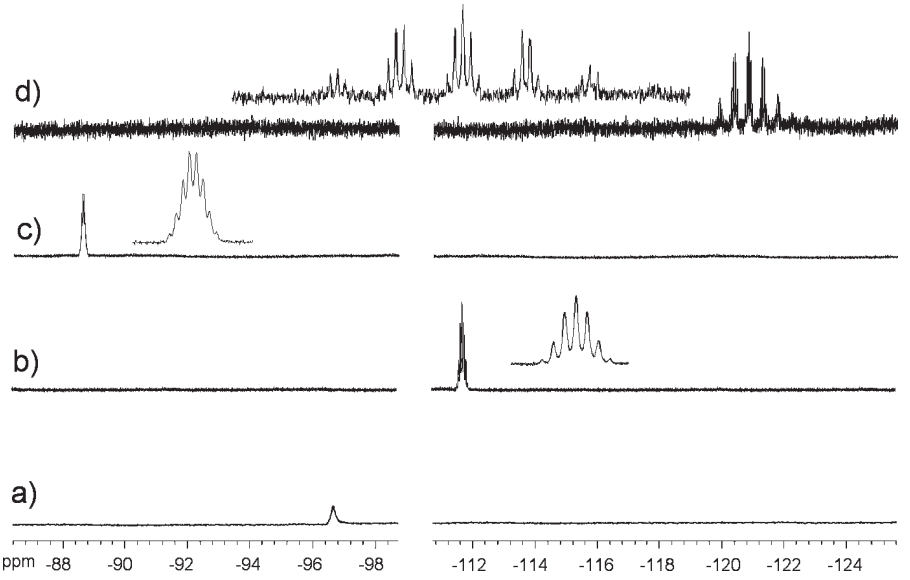
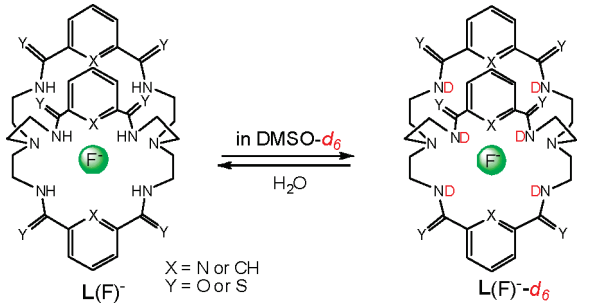


FIGURE 2. ^{19}F NMR spectra at 23 °C in DMSO-d_6 of (a) n-$Bu_4N^+F^-$ without receptors and upon addition of 1 equiv of (b) **L1**, (c) **L2**, and (d) **L3**.

SCHEME 2. Schematic Representation of Deuterium Exchange



The F^- undergoes a downfield shift for the isophthaloyl-containing cryptand **L2** and displays a higher order multiplet pattern (J_{HF} = 14 Hz) (Figure 2c). This multiplet was subsequently determined to be an unresolved dectet that resulted from F^- coupling with the six amide and three phenyl H atoms. The upfield chemical shifts of the F^- signal with **L1** and **L3** can probably be attributed to the presence of the lone pair of electrons on the pyridine N atoms, which tends to shield the F^-; the downfield shift observed for **L2** is most likely the result of the ring current of aromatic ring. Similar H-bonding coupling of bound F^- in ^{19}F NMR has previously been observed with pyrrole NH protons in calix[4]pyrrole−fluoride complexes.[11]

Deuterium Exchange. Over time, the ^{19}F spectra of **L1** and **L2** both displayed a series of multiplets similar to that seen immediately in the spectrum of the thioamido cryptand **L3**. This solution phenomenon has been attributed to D exchange between the amide or thioamide H atoms and the methyl D atoms of the DMSO-d_6 (Scheme 2). The series appears slightly upfield of the highest order multiplet, with each signal evenly separated by 0.46, 0.31, and 0.44 ppm for the three hosts **L1**, **L2**, and **L3**, respectively (Figure 3).

A complete series of D exchange signals from septet (coupling with six N*H* atoms) through singlet (six N*D* atoms) was obtained for **L1** when it was first heated and then allowed to stand at room temperature for several days

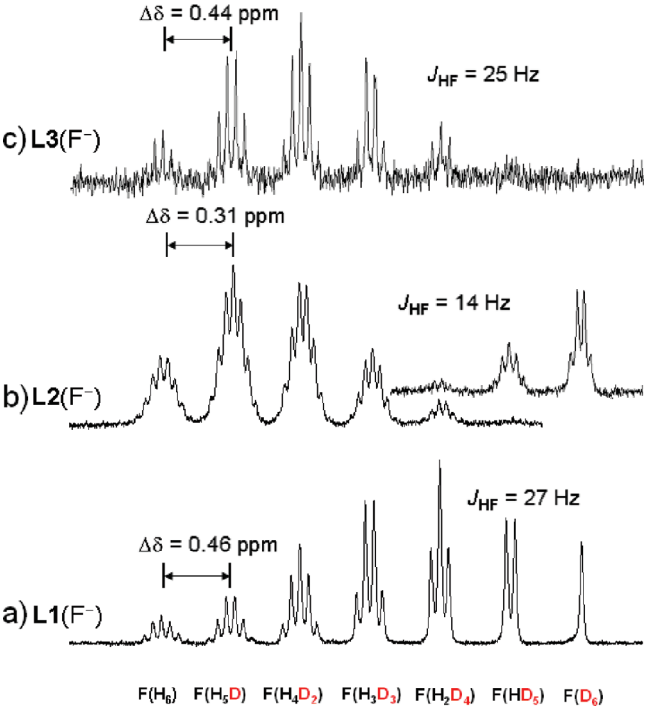


FIGURE 3. ^{19}F NMR spectra at 23 °C in DMSO-d_6 of n-$Bu_4N^+F^-$ with various ratios of receptors: (a) 0.5:1 **L1**/F^-; (b) 1:1 **L2**/F^- and 0.5:1 **L2**:F^- (inset); (c) 1:1 **L3**/F^- .

(Figure 3a). However, for **L2** the series ends in a quartet due to coupling of the F^- with the remaining nonexchangeable phenyl H atoms. The series reverts to the original single multiplet upon addition of H_2O. ^{19}F NMR spectroscopy provides a unique tool for probing the nature of the H bonds between amide H atoms and F^-. This technique can give direct evidence of D exchange from the DMSO-d_6 solvent to the amide H atoms. In fact, the highly basic F^- is known to extract protons from weak acids, including DMSO.[12]

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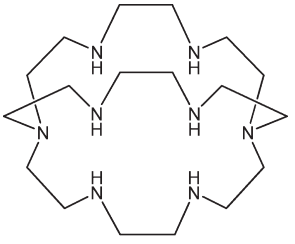
Fluoride Binding Studies. All three hosts display high affinity for F^-, as anticipated by the strong H-bonding tendency of this ion. **L1**, **L2**, and **L3** all showed slow exchange in DMSO-d_6 upon addition of up to 1 equiv of $[n\text{-}Bu_4N^+][F^-]$ at room temperature. Calculations using EQNMR[13] indicate very high binding for **L1** at the limits of NMR detectability ($K = 8.1 \times 10^5$) and binding slightly more than a factor of 10 lower for **L2** ($K = 3.3 \times 10^4$) and **L3** ($K = 3.2 \times 10^4$). In general, for simple amido-based monocycles, the pyridine analogue displays significantly higher binding than the isophthaloyl derivative, so the superior binding of **L1** is as anticipated. We and others have attributed this to the preorganization effect of the pyridine N atom on the nearby amide H atoms.[14,15]

The lessened affinity for **L3** for F^-, however, is not easily explained. In the monocycles, the thioamides show heightened binding for anions as we communicated earlier.[9] Indeed, the rationale for exploring thioamides was for their enhanced H-bonding capability that we predicted would result in higher anion affinities.[16] The crystal structures of the two free bases, described below, do not shed light on the situation, since both the amido- and thioamido- cryptand are structurally very similar and almost superimposable. The only real experimental difference between the two hosts, then, is in the ^{19}F NMR, and involves the exchange process. As seen in Figure 2d, the thioamide **L3** undergoes amide H atom exchange when immediately placed in solution, while the exchange process for the corollary amides **L1** and **L2** is slower, occurring over days. It is possible that the enhanced acidity of the thioamide group works against binding, since in a dissociative mechanism for D exchange the host would bear a negative or repelling charge to an incoming F^- during any given instance in the rapid exchange process.



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A number of other selective hosts for F^- have been reported.[10,11,17−23] One of the most interesting is the tiny octaazacryptand, **1**, which shows highly selective binding for F^- over a wide pH range in water (binding constant (K) of 4.0×10^3 M^{-1} at neutral pH).[17] The unusually high affinity was attributed to the small size of the cryptand, which was predicted to be too small to encapsulate larger anions.[18] This host was later shown by us to also encapsulate Cl^- at low pHs[19] and by Ghosh to selectively encapsulate Cl^- in a 500-fold excess of Br^-.[20] Other F^- selective host systems have included acyclic,[21,22] monocyclic,[23] and bicyclic hosts[24,25] in various organic or mixed organic/aqueous solvent systems. Gale has recently studied an acyclic cleft-containing host that contains both indole and amide H-bond donors that have a high selectivity for F^- ($>10^4$ M^{-1}) over Cl^- (<10 M^{-1}) in a DMSO-d_6/0.5% H_2O solution.[21] Sessler and co-workers have published several cyclic polypyrrole receptors showing high selectivities for F^-. They found that the diprotonated sapphyrin binds F^- quite efficiently with binding constants (K) of 2.8×10^5 M^{-1} calculated from optical titration studies in MeOH.[10] The intriguing and highly analogous cryptand formed from nine pyrroles showed strong binding in CD_2Cl_2 with a wide range of anions having different host−guest stoichiometries: NO_3^-, L/A = 1:2; F^-, L/A = 1:1; and Cl^-, L/A = 2:1.[22] Unfortunately, binding constants for these systems were determined in different solvents, making comparisons of binding affinities difficult.[10,24] Nonetheless, while **L1**−**L3** display high affinity for F^- as noted above ($K \sim 10^4$−10^5 in DMSO), considering that high binding is also observed for both acyclic and monocyclic hosts, one can infer that increased dimensionality, while ideal for encapsulation, is not always necessary for tight binding.

Crystal Structures of Free Bases. Crystal structures for solvated free bases of **L1** and **L3** were determined. Both the heptahydrate of **L1** and the CH_3CN adduct of **L3** showed similar binding of solvent on one side of the host. All six amide H atoms are pointed inside the cavity for both **L1** and **L3** (Figure 4a−d). As noted earlier, this has been attributed by us and others to a preorganization effect of the pyridine lone electron pair forming a semicircular internal H-bonded network with the two contiguous amide groups.[14,15] The macrocycles adopt an overall "flattened" conformation with two of the three arms pointing in the same direction with nearly superimposed stacking of their pyridine rings. $N_{py}\cdots N_{py}$ distances are 3.799 Å for **L1** and 3.885 Å for **L3**. The major difference is a slight offset of the pyridine rings in **L3** relative to **L1**. Quite similar bridgehead amine N···N distances of 5.857 and 5.687 Å are observed for **L1** and **L3**, respectively. The similarity of conformations for **L1** and **L3** can be seen in the superposition (with a rms separation of 0.80 Å) of their 50 non-H atoms (Figure 5). The asymmetric

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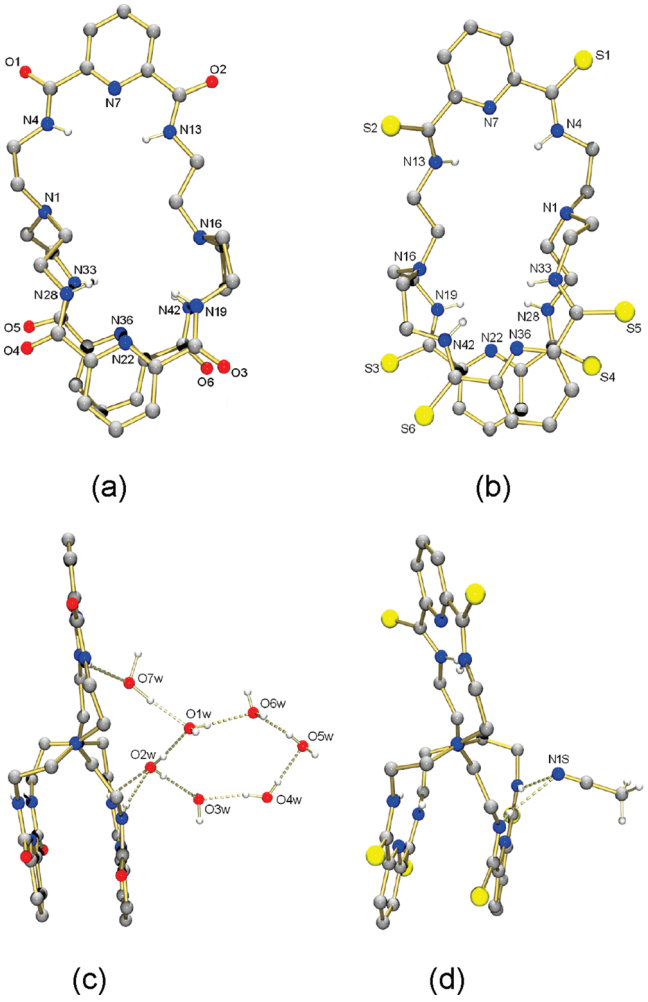

FIGURE 4. Perspective views of **L1**·7H_2O (a and c) and **L3**·CH_3CN (b and d): (a) and (b) perpendicular to the bridgehead amine axis; (c) and (d) down the bridgehead axis. Solvent molecules were omitted in (a) and (b) for clarity.

unit of crystalline-hydrated free base **L1** contains seven H_2O molecules that all lie outside the macrocyclic cavity. As previously reported, six of these H_2O molecules form a hexagonal ring between the cryptands that is similar to that of the hexagonal form of ice (Figure 4c); the seventh H_2O molecule bridges from the hexagonal array to the host.[26] In addition to having similar solid-state molecular conformations, the crystal structures of the solvated cryptands are also alike. The CH_3CN N(1s) atom, in solvated **L3** (Figure 4d) adopts a H-bonded position relative to the macrocycle that is similar to that of the O(2w) atom in solvated **L1** (Figure 4c) [$NH_{am}\cdots N_{CH3CN}$ distances of 3.157(3) and 3.169(4) Å compared to $NH_{am}\cdots O(2w)$ distances of 2.979(2) and 3.261(2)].

Crystal Structures of the F^- Complexes. The F^- complex of **L1** crystallized as the solvated tetra-*n*-butylammonium salt, with the neutral host containing one encapsulated F^- ion. Disordered partial-occupancy CH_3CN and CH_2Cl_2 solvent molecules occupy a common volume of the unit cell outside

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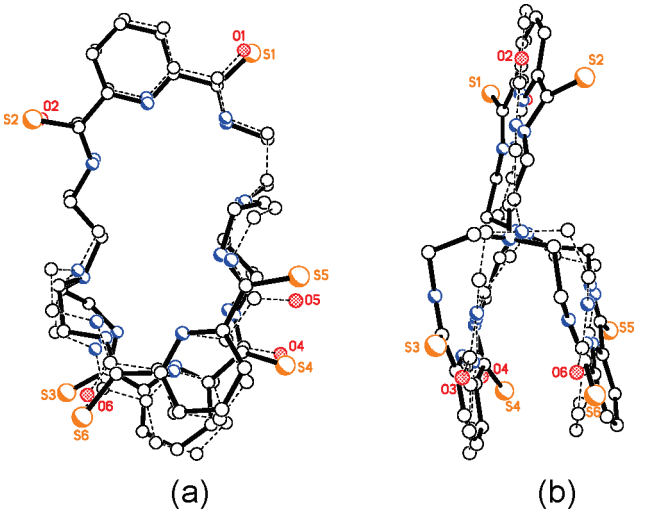

FIGURE 5. Two perspective views (a and b) of 50 non-H atoms for **L1** (broken line) superimposed on those for **L3** (solid line).

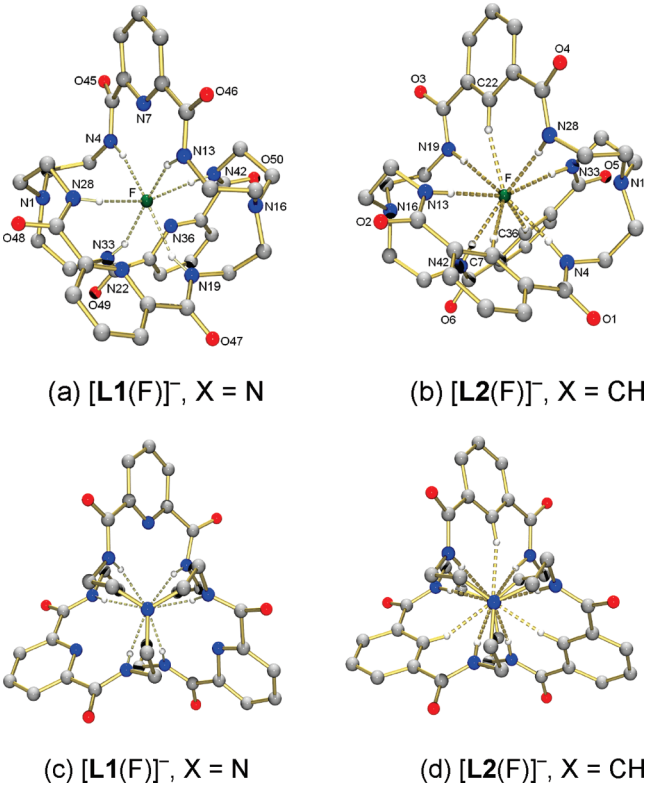

FIGURE 6. Perspective views of $[\mathbf{L1}(F)]^-$ and $[\mathbf{L2}(F)]^-$, respectively: (a and b) perpendicular to the bridgehead amine axis and (c and d) down the bridgehead N···N vector. The *n*-Bu_4N^+ ions and solvent molecules of crystallization were omitted for clarity.

the macrocycle cavity. Unlike the conformation observed for **L1** in **L1**·7H_2O, the three macrocycle chains emanating from the bridgehead amines in this $[\mathbf{L1}(F)]$ complex form a pinwheel-like structure with pseudo-C_3 symmetry and a bridgehead N···N separation of 7.391 Å. All six amide NH hydrogen atoms surround the F^- ion in a distorted trigonal prismatic geometry, with a trigonal twist angle (calculated using the positions of the six amide nitrogen atoms) of 23.4°. N···F distances range from 2.822(2) to 2.889(2) Å (Figure 6a). These

amide H-bonding distances are longer than most N−H···F^- interactions because the cryptand structure has constrained six NH groups to be within hydrogen-bonding distance of the singly charged fluoride. The *n*-Bu_4N^+ counterion and the disordered solvent do not interact with the cryptand.

The F^- complex of the isophthaloyl host **L2** also crystallized as the tetra-*n*-butylammonium salt [*n*Bu_4N][**L2**(F)] with the neutral host containing one encapsulated F^- ion. The macrocycle conformations in [**L1**(F)] and [**L2**(F)] are very similar. In fact, their 50 non-H atoms superimpose with an rms deviation of 0.42 Å. However, the bridgehead N···N separation of 7.876 Å is 0.485 Å longer in **L2** than in **L1**. This longer bridgehead N···N separation is presumably the result of steric repulsion induced by the internally oriented isophthaloyl H atoms in **L2** which replace the pyridine lone pairs in **L1**. These three isophthaloyl H atoms and the six amide H atoms are essentially equidistant (2.11 to 2.24 Å) from the encapsulated F^- anion. This close interaction obviously also exists in solution where coupling between the F^- and the amide H atoms as well as the isophthaloyl H atoms was observed in the ^{19}F NMR spectra. The nine H atoms surrounding the encapsulated F^- in [**L2**(F)]$^-$ describe a distorted tricapped trigonal prism with the amide H atoms representing the trigonal prism as in [**L1**(F)]$^-$ and the isophthaloyl H atoms as the "caps". The trigonal prism has a 25.2° trigonal twist from idealized trigonal prismatic geometry.

Conclusions

Bicyclic cryptand hosts with differing H-bond donor functional groups (amide vs thioamide) and spacers (pyridine vs isophthaloyl) have been synthesized by simple one- or two-step procedures. The similar cryptand frameworks have allowed for an evaluation of anion-binding propensities and structural influences. The effect of preorganization has also been assessed by comparing **L1** hosts containing pyridine (prone to preorganize adjacent amides) and **L2** hosts containing isophthaloyl (no preorganization of adjacent amides) spacers. Binding studies indicated that the preorganized pyridine host **L1** showed superiority in F^- binding.

The encapsulation of the F^- in **L1** and **L2** was confirmed by crystal structures as well as solution ^{19}F NMR studies. Coupling between the F^- and the amide H atoms as well as the isophthaloyl H atoms in **L2** was observed. The strong H-bonding interactions between amides and the bound F^- facilitated an interesting deuterium exchange of amide NHs in solution. The crystal structures of the two solvated free bases, the amide and thioamide, were virtually superimposable. Both showed a stacking of two of the pyridine arms, indicating a preference for this interaction and the resulting conformation. In the two F^- complexes the crystal structures showed that macrocycles were pulled in to surround the strongly bound F^- ion.

These studies emphasize the utility of F^- ion as a probe for both solid-state and solution studies of anion binding. They also settle the question of whether the anion remains encapsulated in solution and reveal some unanticipated chemistry, the D exchange reaction. Finally, these findings add to the growing information base and understanding of the aptitude of amide- and thioamide-based cryptands as hosts for anions.

Experimental Section

Reagents. The reagents were obtained from commercial suppliers and used as received without further purification unless otherwise indicated.

L1. A three-neck, round-bottom flask equipped with two dropping funnels was filled with dry CH_2Cl_2 (500 mL) under Ar. The funnels were charged with 2,6-pyridinedicarbonyl dichloride (2.76 g, 13.53 mmol) in CH_2Cl_2 (300 mL) and tris-(2-aminoethyl)amine (1.32 mL, 9.02 mmol) and triethylamine (3.77 mL, 27.06 mmol) in CH_2Cl_2 (300 mL). The reagents were added simultaneously at equal rates over a period of 1 h, and the reaction mixture was stirred for an additional 24 h. The solvent was evaporated, and the residue was redissolved in 300 mL of CH_2Cl_2. The organic phase was washed with saturated $NaHCO_3$ solution (200 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by alumina column chromatography, eluting with 2% of CH_3OH in CH_2Cl_2 to give the amide cryptand **L1** (10%) as a white powder: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.88 (br s, 6H), 7.97 (s, 3H), 7.93 (s, 6H), 3.37 (s, 12H), 2.99 (s, 12H); ^{13}C NMR (500 MHz, DMSO-d_6) δ 163.4 (C=O), 148.9, 139.5, 124.1, 54.5, 38.5; FAB MS *m*/*z* 686.3 $[MH]^+$. Anal. Calcd for $C_{33}H_{39}N_{11}O_6\cdot 6H_2O$: C, 49.93; H, 6.48; N, 19.41. Found: C, 50.02; H, 6.58; N, 18.74.

L2. A three-neck, round-bottom flask equipped with two dropping funnels was filled with dry CH_2Cl_2 (500 mL) under Ar. The funnels were charged with isophthaloyl dichloride (2.0 g, 9.86 mmol) in CH_2Cl_2 (300 mL), and tris(2-aminoethyl)amine (0.98 mL, 6.56 mmol) and triethylamine (2.74 mL, 19.68 mmol) in CH_2Cl_2 (300 mL). The reaction carried out as above for **L1**, except it was not washed with $NaHCO_3$. The crude product was purified by alumina (basic) column chromatography, eluting with 2% CH_3OH in CH_2Cl_2 to give the isophthaloyl amide cryptand **L2** (15%) as a white powder: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.50 (s, 6H), 8.64 (s, 3H), 8.02 (d, J(H,H) = 7.0 Hz, 6H), 7.52 (t, J(H,H) = 7.0 Hz, 3H), 3.21 (s, 12H), 2.62 (s, 12H); ^{13}C NMR (500 MHz, DMSO-d_6) δ 165.6 (C=O), 133.7, 130.3, 128.2, 125.1, 57.8, and 38.5; FAB MS *m*/*z* 683.5 $[MH]^+$. Anal. Calcd for $C_{36}H_{42}N_8O_6\cdot H_2O$: C, 61.70; H, 6.33; N, 15.99. Found: C, 61.50; H, 6.32; N, 15.75.

L3. Lawesson's reagent[27] was added to the solution of the receptor **L1** in toluene (100 mL), and the mixture was refluxed for 2 d. A color change from yellow to orange was observed. The solvent was evaporated, and the crude product was purified by alumina (neutral) column chromatography, eluting with 1% of CH_3OH in CH_2Cl_2 to give the thioamide cryptand **L3** (15%) as a yellow powder: ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.63 (s, 6H), 8.41 (d, J(H,H) = 7.4 Hz, 6H), 7.95 (t, J(H,H) = 7.4 Hz, 3H), 3.81 (s, 12H), 3.26 (s, 8H); ^{13}C NMR (500 MHz, DMSO-d_6) δ 188.3 (C=S), 148.6, 139.4, 126.2, 49.5, and 42.8; FAB MS *m*/*z* 782 $[MH]^+$. Anal. Calcd for $C_{33}H_{39}N_{11}S_6\cdot 2H_2O$: C, 48.44; H, 5.30; N, 18.83; S, 23.52. Found: C, 48.01; H, 4.65; N, 17.77; S, 23.22.

NMR. Slow exchange was observed in the titrations of **L1**, **L2**, and **L3** with F^- ion. For ^{19}F NMR spectra, the aqueous NaF signal (δ = −122.4) was used as an external standard. All spectra were recorded at 23 °C and [F^-] of 10 mM. Temperature studies were performed with three different samples in different host/F^- ratios (0.5:1, 1:1, and 2:1) to obtain a complete series of deuterium-exchange signals. ^{19}F NMR spectra in temperature studies were recorded after the samples were heated in DMSO-d_6 at 150 °C for 1 h followed by cooling to 23 °C.

X-ray Crystallography. Crystals of the free ligands, **L1**·7(H_2O) and **L3**·CH_3CN, suitable for X-ray diffraction were grown by the slow evaporation of CH_3CN and MeOH/CH_3CN

(27) Scheibye, S.; Pedersen, B. S.; Lawesson, S. -O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229–238.

solutions, respectively. Crystals of [*n*-Bu_4N][**L1**(F)]·0.895(CH_3CN)·0.105(CH_2Cl_2) were obtained by the slow evaporation of CH_3CN in the presence of excess *n*-Bu_4NF. Crystals of [*n*-Bu_4N][**L2**(F)] were obtained by the slow evaporation of a $CHCl_3/CH_3CO_2C_2H_5$ solution in the presence of excess *n*-Bu_4NF.

Single-domain specimens for each of these four compounds were used to perform solid-state structure determinations. Detailed information about the structure refinements including tables of data collection information and H-bonding distances and angles is given in the Supporting Information.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of **L1**, **L2**, and **L3** in DMSO-d_6, ^1H NMR spectra of **L1**, **L2**, and **L3** with *n*-$Bu_4N^+F^-$ in DMSO-d_6, detailed ^{19}F NMR spectra of temperature studies with F^- complexes, mass spectra of **L1** and $[\mathbf{L1}(F)]^-$-d_6, ^2H NMR spectrum of $[\mathbf{L1}(F)]^-$-d_6, and detailed information about the X-ray crystallography. This material is available free of charge via the Internet at http://pubs.acs.org.