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Snapshots of Fluoride Binding in an Aza Cryptand

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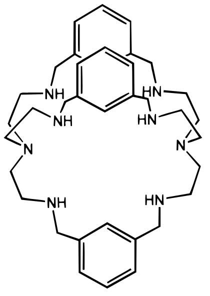
Thirty years after the first observation of halide encapsulation by katapinand receptors,[1,2] we have utilized ^{19}F NMR spectroscopy in conjunction with X-ray crystallography to provide snapshots of fluoride binding in an aza cryptand, **1**, over a range of pH values. The results provide definitive solution and solid-state evidence for the incorporation of fluoride in the cavity. This is, to our knowledge, the first study that integrates crystallographic findings with ^{19}F NMR data as a means of understanding the binding patterns of fluoride as a function of pH.



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Anion recognition and binding is an exciting and growing field in receptor chemistry.[3,4] Fluoride, being the smallest halide, has unique properties compared to its congeners as a result of its relative size and electronegativity. It is also an ion of prominence in health and environmental circles, for example, in the fluoridation of water[5,6] and in groundwater contamination emanating from certain industrial plants.[7] Hence, an understanding of the binding of fluoride to receptor species is of value for a variety of applications. While receptors for fluoride have been reported,[8−23] ^{19}F NMR has been sparingly used,[19−22] especially as a structural tool to probe solution structure over a range of pH values, for which no reports have appeared.

The ligand was synthesized according to published procedures.[24] At room temperature and 4 °C in water broad signals indicative of exchange processes on the NMR time scale were observed. Hence, a water−DMSO solution at -25 °C[25] was examined. At pH 2,[26,27] the major signal appears at -122 ppm with minor signals at -140 and -147 ppm (Figure 1). (The chemical shift for HF in the absence of macrocycle lies at -157 ppm, and a very small signal is seen in this region.) At this pH HF species should predominate, so we have tentatively assigned these signals as either HF ($pK_a(H_2O) = 3.15$, $pK_a(DMSO) = 15$[28]) or FHF^- interacting with highly protonated forms of the macrocycle. The disappearance of both signals above pH 4.5 supports the assignment as HF-derived species. From pH 3.5 to 4.5 a structural transition is clearly occurring with the appearance of two new broad resonances at -95 and -110 ppm, which sharpen and shift to -88 and -99 ppm by pH 5. These two signals are assigned to internally bound fluoride, based on similar assignments by other researchers,[19,22] but in different environments. As the pH is increased, the signal at -99 ppm broadens and shifts upfield until it disappears completely at pH 6.5. However, the signal at -89 ppm remains virtually unshifted and is the major signal as high as pH 7.5. The persistence of this signal is an extremely exciting finding, indicating that these aza cryptands are capable of significant *internal* binding even at neutral pH values. At pH 7, a signal begins to appear at -115 ppm while the signal at -89 ppm diminishes. The new resonance shifts and sharpens to a final signal at -117 ppm, which correlates well with that found for solvated fluoride in a water/DMSO mixture in the absence of macrocycle.

The crystal structure supports the ^{19}F solution studies, and the assignment of the internal fluoride. In fact, both a fluoride ion and a molecule of water inhabit the cavity in this solid-state snapshot (Figure 2).[29,30] This structural finding differs from that of a related receptor, bis-tren, in which a single fluoride resides on one side of the cavity.[8] The structure of the entire assembly was found to be more complex than anticipated and includes the

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(26) The pH of several samples was determined in H_2O using an Accumet 25 pH meter and Radiometer America micro pH electrode. Those samples were used to prepare analogous samples in mixed $DMSO/H_2O$ solution. The "apparent" pH of these solutions when remeasured was 0.6 unit higher and these are the pH values reported.

(27) ^{19}F NMR spectra were recorded on a Bruker AM-500 spectrometer at 470.6 MHz, and chemical shifts were recorded in ppm from neat Freon ($CFCl_3$). Data points (16 K) were taken for each spectrum over 256−1024 scans. The scan width was 41 666.7 Hz, and a line broadening of 20 Hz was used to improve the apparent signal-to-noise ratio. All spectra were recorded at -25 °C at 1:1 NaF−ligand (0.01 M in each) using 0.1 M KTs to maintain a constant ionic strength in $DMSO-H_2O$ (40:60 v/v) solution and adjusting pH with additions of TsOH or KOH. DMSO-d_6 (making up 10% of the solution) was used as internal reference.

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(29) Crystals suitable for X-ray analysis were obtained by dissolving the free base ligand in methanol (10 mL) and adding 48% HF until the solution reached a pH of 2. Most of the solvent was removed under reduced pressure, and isopropyl alcohol was added to precipitate a white solid. Recrystallization from aqueous ethanol gave colorless plates. Microanalytical data calcd for $\mathbf{1}\cdot1.5SiF_6^{2-}\cdot F^-\cdot 2FHF^-\cdot 7H_2O$: C 41.52, H 7.36, N 10.76. Found: C 41.85, H 7.47, N 10.77.

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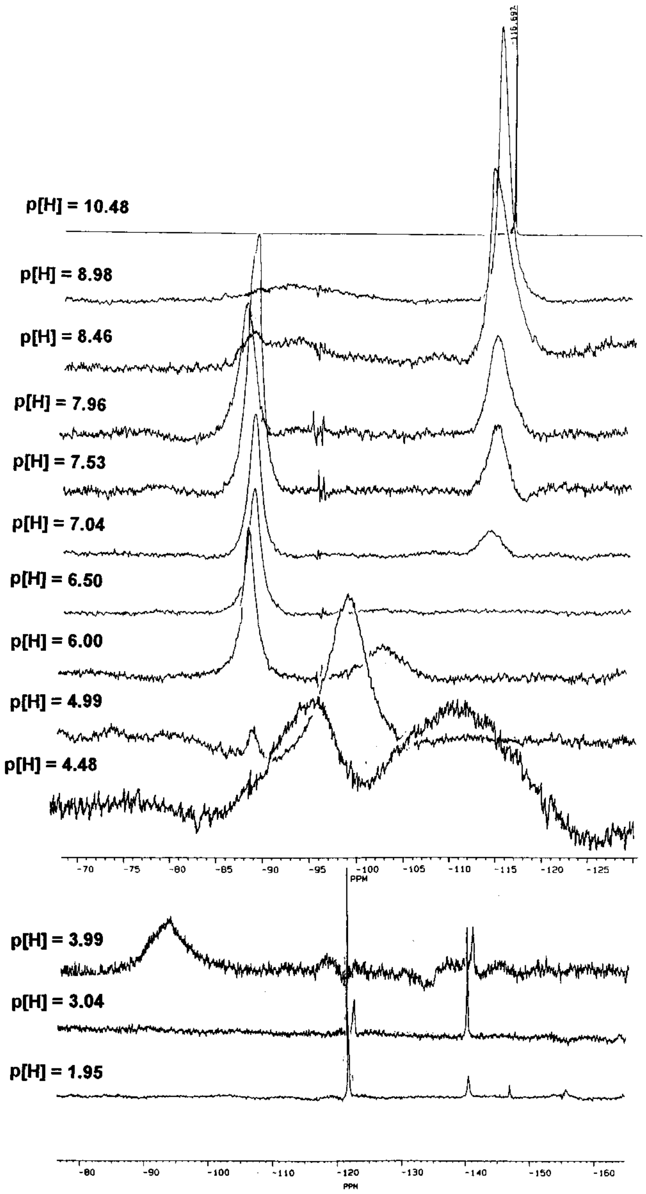

Figure 1. ^{19}F spectra as a function of pH using a 1:1 NaF:ligand ratio (0.01 M in each and 0.1 M in KTs) in a DMSO:H_2O (40:60 v/v) solution.

macrocycle with its inhabitants, 1.5 SiF_6^{2-} anions (one dianion sits on the crystallographically imposed inversion center), two bifluorides ($F-H\cdots F^-$), and six water molecules. An unanticipated occurrence of SiF_6^{2-} has been observed previously.[31] The encapsulated fluoride and water molecule were found to be shifted from the "central axis" between the two apical nitrogens of the macrocycle as seen in the view down the pseudo-3-fold axis (Figure 2B). The internal fluoride, F(1), exhibits pseudotetrahedral coordination via hydrogen bonds with three ammonium hydrogen atoms as well as with one hydrogen belonging to the internal water molecule. Although crystallographic evidence for the incorporation of two nitrates within this macrocycle has been obtained,[32] this is the first report of two different guests encapsulated within one of these simple Schiff base-derived receptors.

In conclusion, this study clearly shows the utility of combining ^{19}F NMR with crystallographic findings to obtain valuable information on recognition patterns over a range of pH values. It also confirms the ability of these cryptands to encapsulate anions over a significant pH range, in addition to providing solid-state evidence of the unusual occurrence of an anion and a neutral guest within a single bicyclic host. We are currently investigating the mechanisms of binding, selectivity aspects, and several different applications with respect to anion recognition in related systems.

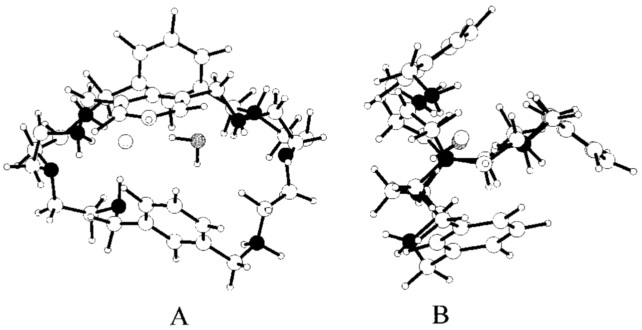

Figure 2. (A) Crystal view of **1** from the side, showing the fluoride and water molecule inside the cavity. (B) Crystal view of **1** as viewed down the "3-fold" axis.

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Supporting Information Available: An ORTEP diagram and additional ^{19}F data, including titration data for the tosylate salt of the macrocycle and fluoride from pH 2 to 11 at 0.5 pH intervals and over the same range for potassium tosylate and fluoride without the macrocycle (PDF). This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center, as supplementary publication No. CCDC-116337.

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(30) Crystal structure data for **1**$\cdot 1.5SiF_6^{2-}\cdot F^-\cdot 2FHF^-\cdot 7H_2O$ (empirical formula $C_{72}H_{152}N_{16}O_{14}F_{28}Si_3$ (two macrocycles); $M = 2046.3$, crystal dimensions (0.20 × 0.30 × 0.50 mm) $a = 14.243(3)$ Å, $b = 17.128(4)$ Å, $c = 11.384(3)$ Å, $\alpha = 98.68(2)°$, $\beta = 107.74(2)°$, $\gamma = 106.73(2)°$, $V = 2445(1)$ Å^3, $Z = 2$, $\rho_{calc} = 1.422$ g cm^{-3}, space group $P1$, No. 2), Cu Kα radiation ($\lambda = 1.54178$ Å), μ(Cu Kα) = 15.40 cm^{-1}, $F(000) = 1102$. Reflections were collected to a maximum 2θ value of 120.1° on a Rigaku AFC5R diffractometer by the $\theta-2\theta$ scan method. The 4232 independent reflections (of 7623 measured) for which $I > 3.0\ \sigma(I)$ were corrected for Lorentz and polarization effects. An empirical absorption correction was made (minimum and maximum transmission coefficients: 0.17, 0.22). The structure was solved by direct methods and refined by full-matrix least-squares techniques on F. Non-hydrogen atoms were refined anisotropically. In most cases for the macrocycle, and in all cases for the water and hydrogen fluoride molecules, hydrogen atoms were located from difference Fourier maps. Refinement converged to $R = 0.066$ and $R_w = 0.064$ (604 parameters). Minimum and maximum final electron density were -0.26 and 0.40 e$^-$ Å^{-3}. The weighting scheme was based on counting statistics and included a factor ($p = 0.010$) to downweight the intense reflections. All calculations were performed using the teXsan crystallographic software package of Molecular Structure Corporation. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center, as supplementary publication No. CCDC-116337. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, GB-Cambridge, CB21EZ (UK) (fax: 44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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