Communication

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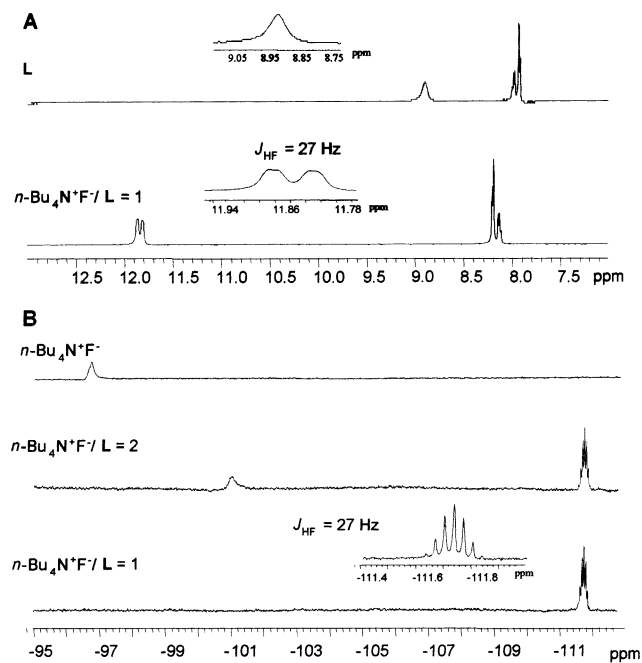
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New Polyamide Cryptand for Anion Binding

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Cryptands have figured prominently in receptor chemistry beginning with the first katapinand anion receptors of Park and Simmons,[1] through Lehn's ether-based cryptands for metal ions[2] and the aza cryptands for metal ions and anions.[3] The coordination chemistry of anions has also grown throughout this time frame,[4] including amide-based systems because of their amenability to functional applications such as ion-selective electrodes and separations. Reinhoudt reported one of the early examples of tren-based[5] amide anion receptors, while Crabtree has reported an acylic 2,5-diamide-substituted pyridine-based anion receptor.[6] Although multicyclic amides have been reported as anion hosts[7,8] and tren-based bicyclic amides have been used as iron-binding siderophore models,[9] a key dimension that has been missing in anion recognition has been tren-based amide cryptands. Herein is reported the tren-based polyamide cryptand, **L**, its binding with anions, structures of complexes with hydrochloric acid and fluoride, and an unusually informative ^{19}F solution spectrum showing ^{19}F coupling with all six amide protons.

L

The bicyclic aza cryptand **L** was synthesized in CH_2Cl_2 from the condensation of two equivalents of tris(2-aminoethyl)amine with three equivalents of 2,6-pyridinedicarbonyl dichloride in the presence of Et_3N as a base. **L** was isolated in 10% yield after column chromatography (neutral Al_2O_3, 5% CH_3OH in CH_2Cl_2).[10] Crystals suitable for X-ray diffraction were grown from the slow evaporation of a $CHCl_3/CH_3CN$ solution of **L** and revealed the hydrochloride complex. Crystals of the fluoride complex were grown from CH_3CN in the presence of excess $(n\text{-}Bu)_4NF$.

Although isolated as what was presumed to be the free base, the crystal structure of **L** revealed monoprotonated **L** and an encapsulated chloride, $[H\mathbf{L}(Cl)]\cdot H_2O\cdot CH_3CN$. The chloride is pseudo-six-coordinate (Figure 1A and B). Two of the hydrogen bonds are relatively long, Cl(1) to N(13) and N(28), (3.598(1) and 3.440(1) Å, respectively); two are within the normal range, Cl(1) to N(4) and N(19) (3.327(1) and 3.344(1) Å, respectively), while one is rather short, Cl(1) to N(1) at 3.200(1) Å. The latter hydrogen bond is to the protonated *endo* oriented bridgehead amine, and undoubtedly involves an additional electrostatic interaction. The distance between the two bridgehead amines (N(1)- - -N(16)) is 7.070 Å. Also, as seen in Figure 1B in the view down the bridgehead amines,

Figure 1. The crystal structures of the hydrochloric acid complex showing $[H\mathbf{L}(Cl)]$ (**A** and **B**) and the fluoride complex $[\mathbf{L}(F)]^-$ (**C** and **D**).

the chloride is not centered in the cavity but rather is placed to one side.

The crystal structure of the fluoride complex showed it to be $[\mathbf{L}(F)][(n\text{-}Bu)_4N]\cdot 0.895CH_3CN\cdot 0.105CH_2Cl_2$. The fluoride is centered in the cryptand cavity (Figure 1C and D), with hydrogen bonds to all six amide protons. The view down the pseudo-three-fold axis is quite striking, indicating a symmetric, but twisted, trigonal prism coordination pattern, with a twist angle averaging 36.6.° (Raymond found that related "catechol macrobicyclic ligands" used as siderophore models show trigonal twist angles ranging from 0° to 40°.[9]) Hydrogen bond distances are all about the same and range from 2.842(2) to 2.887(2) Å. The distance between bridgehead amines is 7.391 Å, slightly longer than that observed for the chloride complex.

The anion binding properties of **L** were investigated by ^1H NMR titration experiments[11] in DMSO-d_6 in the presence of various anions as their $n\text{-}Bu_4N^+$ salts: F^-, Cl^-, Br^-, HSO_4^-, $H_2PO_4^-$, CH_3COO^-, and NO_3^-. Association constants exceeded the $K \approx 10^5$ limit for NMR titrations in nonpolar solvents such as $CDCl_3$ and CH_3CN. Indeed, affinity of **L** for HCl is so great that it instantaneously scavenges the small amounts of HCl present in a $CDCl_3$ solution. This observation is also supported by the structure of the HCl salt obtained from recrystallization from a $CHCl_3/$

Figure 2. (**A**) ^{1}H NMR and (**B**) ^{19}F NMR spectra of **L** and **L** with n-BuN^{+}F^{-} in DMSO-d_6.

CH$_3$CN solution. Association constants for anions with **L** in DMSO-d_6 were obtained from titration curves using EQNMR.[12] The value of log K in dm^3/mol was the highest by far for F^{-} (>5.00,[13] slow exchange), followed by Cl^{-} (3.47), CH$_3$COO^{-} (3.38), and H$_2$PO$_4^{-}$ (3.30), with very weak binding observed for NO$_3^{-}$ (1.93), HSO$_4^{-}$ (1.83), and Br^{-} (1.60). All of the titration data gave the best fit for 1:1 stoichiometries of host to guest, in agreement with the Job plots indicating a maximum $\Delta\delta$ at $0.5 = $ [**L**]/([**L**] + [A^{-}]).

^{1}H and ^{19}F NMR spectra of **L** with F^{-} were especially informative (Figure 2, A and B, respectively). A new amide signal in the ^{1}H NMR spectrum at 11.85 ppm appears upon addition of F^{-} to **L** and is a doublet as a result of coupling with the fluoride ($J = 27$ Hz). Similar $^{1}H-^{19}F$ coupling has been seen in the proton NMR spectrum of a calixpyrrole fluoride receptor.[14] The ^{19}F spectrum in DMSO-d_6[15] revealed that encapsulation of the fluoride is almost certainly retained in solution. Not only is the fluoride signal shifted, as anticipated, from -96.7 to -111.7 ppm upon addition of **L**, but the new signal also appears as a septet. This observation is in keeping with interaction of the fluoride with six equivalent protons ($I = ^{1}/_2$) giving the $2nI + 1$ or septet pattern. Such a symmetrical pattern could only be achieved if the complex retains its symmetry in solution. The observation of both an internal and external F^{-} signal when greater than one equivalent of F^{-} is present, supports the presence of only one F^{-} in the cavity.

Binding for other anions varies over a fairly large range, with Cl^{-}, H$_2$PO$_4^{-}$, and AcO^{-} showing significant binding, although clearly not competing with that of F^{-}. The 100-fold increase each in affinity Br^{-} < Cl^{-} < F^{-} is probably related to both decreasing size and increasing hydrogen-bonding capability within the series. Large differences were observed when comparing ions of the same geometry, i.e., the two trigonal ions, CH$_3$COO^{-} $\gg$ NO$_3^{-}$, and the two tetrahedral ions H$_2$PO$_4^{-}$ $\gg$ HSO$_4^{-}$. This effect could most probably be explained by the fact that both NO$_3^{-}$ and HSO$_4^{-}$ have relatively weak hydrogen-bonding capabilities. Similar results have been reported by others.[16] Acetate may also bind inside the cavity, as seen by Anslyn for a more rigid, 1,3,5-triamidobenzene-capped receptor with pyridine spacers.[7]

In conclusion, the new tren-based amide cryptand displays high affinity for F^{-} and lesser affinities for Cl^{-}, CH$_3$COO^{-}, and H$_2$PO$_4^{-}$. The ^{19}F pattern indicates that the high symmetry observed in the solid state for the F^{-} complex is maintained in solution. The ability of the two bridgehead amines to attract protons adds to the chemical complexity of these ligands and its HCl scavenging capability. Tren-based amide cryptands thus represent a new class of ligands for anion binding, quite worthy of further study.

Supporting Information Available: Crystallographic data (CIF). Job plots, ^{1}H NMR spectra with Cl^{-} and F^{-}, plots of ^{1}H NMR titration curves with all anions (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.88 (s, 6H, NH), 7.97 (s, 3H, ArH), 7.93 (s, 6H, ArH), 3.37 (s, 12H, $-$CH$_2-$), 2.99 (s, 12H, $-$CH$_2-$); ^{13}C NMR (500 MHz, DMSO-d_6) δ 163.4 (C=O), 148.9, 139.5, and 124.1 (Ar), 54.5, and 38.5 ($-$CH$_2-$). FAB MS m/z 686.3 [MH]$^{+}$; Anal. Calcd for C$_{33}$H$_{39}$N$_{11}$O$_6$·6H$_2$O: C, 49.93; H, 6.48; N, 19.41. Found: C, 50.02; H, 6.58; N, 18.74.
(11) The titration was done by 20 measurements in DMSO-d_6 at room temperature on a Bruker AM500 spectrometer. Aliquots from a 20 mM stock solution of n-BuN^{+} salts were gradually added to a 2 mM solution of **L**. Standard deviations are less than 10% of the K value.
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(15) ^{19}F NMR spectra were recorded on a Bruker AM-500 spectrometer at 470.6 MHz, and the chemical shifts were recorded in ppm relative to that of aqueous NaF at -122.4 ppm in an external standard. 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 and [F^{-}] of 10 mM.
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