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Fluoride-Facilitated Deuterium Exchange from DMSO-d_6 to Polyamide-Based Cryptands

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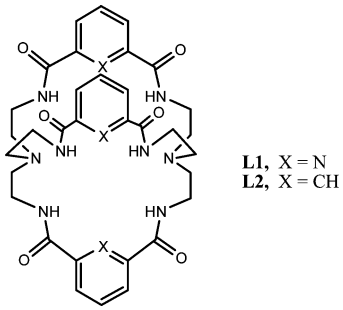
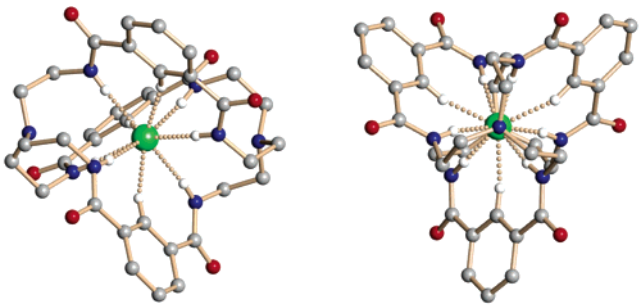
Fluorine-19 NMR spectroscopy can be a valuable tool in evaluating the structural aspects of solution chemistry.[1] We have found it particularly useful in identifying the solution binding modes of fluoride in anion receptors.[2,3] For example, in a recent communication, we reported the crystal structure and binding of fluoride ion in DMSO with a hexaamido-based cryptand, **L1**.[3] The definitive septet pattern observed for the fluoride indicated coupling of the fluoride nucleus $I = {}^1/_2$ with the six NH protons, and confirmed that fluoride encapsulation persists even in solution.[3] The isolation and crystallographic characterization of a related amido cryptand with a *m*-xylyl spacer, **L2**, added another dimension to the study because of the presence of three additional hydrogen bond contacts between the fluoride and the phenyl hydrogens. During further investigations of **L1** and **L2** over a period of time, a series of multiplets appeared in the ^{19}F spectra, indicative of chemical changes. Herein is reported the solution chemistry responsible for the dynamic process over time: deuterium exchange with the NMR solvent.

The study of fluoride binding with synthetic receptors can be complicated by the fact that in very dry aprotic solvents, fluorides, and particularly tetraalkylammonium fluorides, are strong enough bases to extract protons from weak acids, including solvents such as DMSO. This chemistry is well established and has been utilized for a wide variety of organic syntheses involving fluoride.[4] Using weakly acidic anion receptors (hexaamido cryptands, **L1** and **L2**) in conjunction with the weakly acidic solvent DMSO-d_6, we now can fully document the elegant chemistry involved in a multiple deuterium exchange process. The findings indisputably indicate that deuteriums from the DMSO-d_6 used in the NMR experiments replace multiple amide hydrogens in **L1** and **L2** over time.



L1, X = N
L2, X = CH

L1 was synthesized by reacting three equivalents of 2,6-pyridinedicarbonyl dichloride with two equivalents of tris(2-aminoethyl)amine in the presence of Et_3N as base as previously reported.[3] **L2** was synthesized in a similar manner by substituting isophthaloyl dichloride for the pyridine spacer. Crystals of the fluoride complex suitable for X-ray diffraction were grown from the slow evaporation of a $CHCl_3/CH_3CO_2C_2H_5$ solution of **L2** in the presence of excess [(*n*-Bu)$_4$N][F].



A **B**

Figure 1. Perspective views of [**L2**(F)]$^-$. (A) Side view. (B) End view down the pseudo-three-fold axis. The *n*-Bu_4N^+ counterion and the partial solvents of crystallization are not shown for clarity.

The structure of the fluoride complex [**L2**(F)][(*n*-Bu)$_4$N]·0.5$CHCl_3$·0.5$C_4H_8O_2$ is quite similar to that of **L1** with respect to the positioning of the fluoride ion in the center of the cavity.[3] An unusual feature of the structure of **L2**, however, is that very short distances are observed to all three *m*-xylyl CHs pointing in the cavity in addition to the anticipated hydrogen bonds to the six amide protons (Figure 1). The coordination geometry resulting from the three added CH···F protons is most clearly seen in the view down the pseudo-three-fold axis (Figure 1B). The six amide hydrogens plus the three phenyl hydrogens form an almost perfect tricapped trigonal prism hydrogen bond coordination geometry. The amide hydrogens make up the vertexes of the trigonal prism, but are twisted 35° from the pure eclipsed geometry. It is relatively rare that such strong hydrogen bonds are seen between aryl protons and a hydrogen bond acceptor. Normally, when they do occur, they are found in carbons adjacent to an electron-withdrawing group.[5] The C−H···F bonds average 3.05 Å and range from 3.042(2) to 3.076(2) Å, while the NH···F bonds also average 3.05 Å and range from 2.9457(18) to 3.1130(18) Å.

The septet observed in the ^{19}F NMR spectrum of a freshly made solution of **L1** with F^- is shifted upfield from the signal of the free fluoride at −96.7 ppm.[3] An even higher-order multiplet is observed in the ^{19}F spectrum of [**L2**(F)]$^-$ in DMSO-d_6; however, it is shifted downfield at −88.6 ppm. This downfield shift is anticipated due to the deshielding provided by the ring currents of the in-plane aromatic rings. The upfield shift seen for **L1** is probably due to the proximity of the lone electron pairs on the relatively close pyridine nitrogens (average F- - -N_{py} = 3.12 Å).[3]

Upon observing additional multiplet patterns arising for both **L1** and **L2** over time, we decided to examine the influence of increased temperature and different ligand:F ratios on the process. At room temperature only the septet, sextet, and quintet are observed for 1:1 ratios of ligand:F over several weeks. By decreasing the ligand concentration to **L1**:F = 0.5:1 and increasing the temperature to 150 °C, only a singlet at −115 ppm is observed. After this solution

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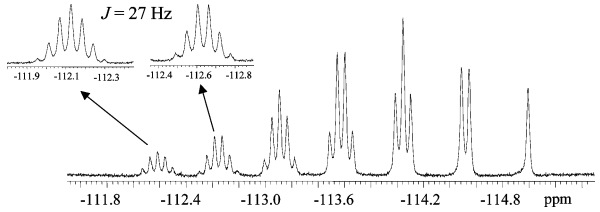

Figure 2. ^{19}F NMR spectrum of **L1**:(n-Bu)$_4$N$^+$F$^-$ = 0.5:1 after heating at 150 °C for 1 h in DMSO-d_6 followed by storage at 25 °C for 10 d.

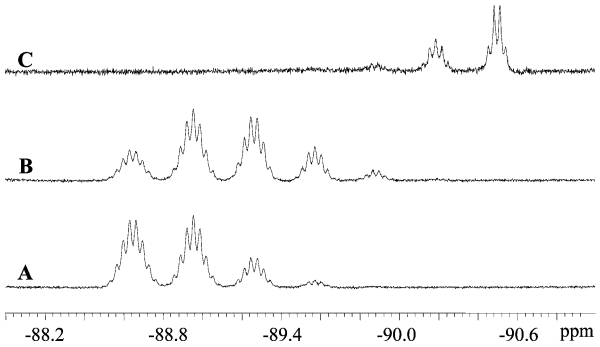

Figure 3. ^{19}F NMR spectra of **L2** recorded at 25 °C after adding (n-Bu)$_4$N$^+$F$^-$ in different ratios: (A) **L2**:F$^-$ = 2:1, (B) **L2**:F$^-$ = 1:1, and (C) **L2**:F$^-$ = 0.5:1 and heating for 1 h at 150 °C in DMSO-d_6.

is stored for 10 d, a series of multiplets ranging from singlet to septet is observed (Figure 2). Coupling within each multiplet is 27 Hz, and the distance between multiplets is 0.46 ppm. In **L2**, evenly spaced (0.31 ppm) multiplets are also observed (internal coupling = 14 Hz), culminating in a quartet rather than a singlet (Figure 3).

The patterns observed for both **L1** and **L2** are indicative of successive replacement of each of the amide hydrogens with deuteriums. In **L1** the sequence culminates in a singlet, indicative of no proton coupling with fluoride. In **L2** the quartet is consistent with fluoride coupling with the three nonexchangeable hydrogens in the *m*-xylyl spacer. No exchange or decomposition of DMSO was observed in the absence of fluoride at 150 °C. In both cases, the addition of H_2O reverses the reaction, and over time the series of multiplets is replaced with the original multiplet of the nondeuterated amides. There is no indication of FH in the ^{19}F NMR spectra (signal anticipated at −143.1 ppm) which is commonly seen in these types of exchange reactions.[6]

The solution ^{19}F spectra of [**L2**(F)]$^-$ are additionally noteworthy in that they indicate that the strong CH···F hydrogen bonding is maintained even in solution. This is also corroborated in the ^{1}H NMR, which shows the dual coupling of the internal fluoride by the appearance of doublets for both the CH and NH resonances (10.02 and 9.55 ppm, respectively, J = 14 Hz).

Other experimental methods were employed to confirm deuterium transfer. In the ^{2}H NMR, a deuterium signal was seen at 11.9 ppm, approximately where anticipated for a deuterated amide. DMSO-d_6 and D_2O signals were also seen at 2.50 and 3.35 ppm, respectively. Fast atom bombardment spectrometry was also used to examine **L1** in both the nondeuterated and deuterated forms. In a protio 2-nitrobenzyl alcohol (*m*-NBA) matrix the totally deuterated [**L1**(F)-d_6]$^-$ yielded a spectrum with a shifted isotopic cluster populated to the M + 6 ion (Figure 4). Such a pattern demonstrates incorporation of up to six deuteriums and most probably results from back-exchange of the amide deuteriums with protons in the matrix.

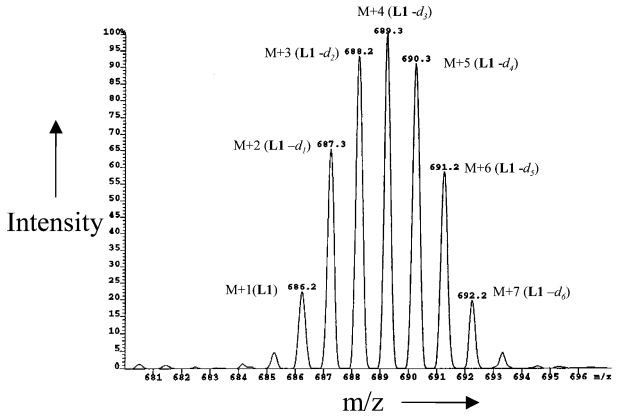

Figure 4. FAB mass spectrum of deuterated [**L1**(F)-d_6][(n-Bu)$_4$N].

The solution encapsulation of fluoride along with the high fluoride affinities (log $K \geq$ 5.0 for **L1** and 4.5 for **L2**) makes it possible to follow this exchange by ^{19}F NMR spectroscopy. Some exchange may also occur in monocyclic corollaries, but the binding of fluoride (log $K \approx 2-3$) is considerably lower, and the ^{19}F NMR spectra are less revealing.

In conclusion, fluoride-assisted deuterium exchange between DMSO-d_6 and the tren-based amide cryptands **L1** and **L2** has been clearly documented using ^{19}F NMR spectroscopy. The solution chemistry is probably aided by the sequestration of the internal fluoride ion. Furthermore, the relatively rare event of strong hydrogen bonding between a phenyl hydrogen and the encapsulated fluoride has been verified both in the solid state and in solution. Last, the crystal structure of [**L2**(F)]$^-$ indicates the almost perfect tricapped trigonal prism structure observed in nine-coordinate transition metal complexes, thus increasing the number of structural corollaries between transition metal and anion complexes.

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Supporting Information Available: Crystallographic data in CIF format. Synthetic details and additional ^{1}H, ^{2}H, and ^{19}F NMR spectra and mass spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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