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An exclusive fluoride receptor: fluoride-induced proton transfer to a quinoline-based thiourea

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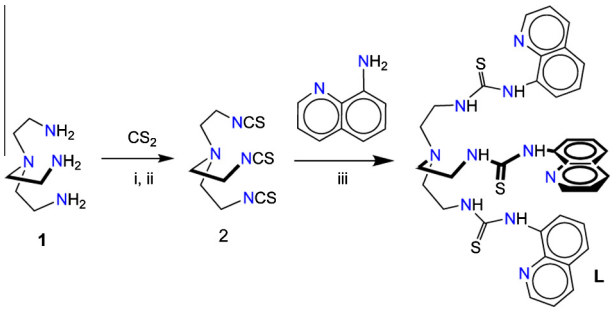
ABSTRACT

A new quinoline-based tripodal thiourea has been synthesized, which exclusively binds fluoride anion in DMSO, showing no affinity for other anions including chloride, bromide, iodide, perchlorate, nitrate, and hydrogen sulfate. As investigated by ^{1}H NMR, the receptor forms both 1:1 and 1:2 complexes yielding binding constants of 2.32(3) (in log β_1) and 4.39(4) (in log β_2), respectively. The quinoline groups are protonated by fluoride-induced proton transfer from the solution to the host molecule. The 1:2 binding is due to the interactions of one fluoride with NH binding sites of urea sites and another fluoride with secondary $^+$NH binding sites within the tripodal pocket. The formation of both 1:1 and 1:2 complexes has been confirmed by theoretical calculations based on density functional theory (DFT).

The development of selective fluoride receptors has attracted significant attention because of the key roles played by fluoride anions in environmental, biological, and health-related processes.[1] The human consumption of fluoride over a prolonged period of time increases the risk of several health related problems including dental fluorosis, reproductive defects, and gastrointestinal infections.[2] However, the fluoride anion is distinct from other halides, showing strong basicity and high hydration energy due to the considerably high bond strength (569 kJ mol^{-1}) of its conjugated acid (HF).[3] Therefore, fluorides, particularly hygroscopic tetraalkylammonium fluorides, can extract protons from weakly acidic aprotic solvents like DMSO and CH_3CN.[3,4] In addition, the binding of fluoride anion can be hampered with highly acidic receptors including ureas and thioureas due to the potential ability of the fluoride to deprotonate NH groups in aprotic solvents.[5] Such deprotonations often can lead to an intense color change (red) that is due to the formation of the highly stable $[HF_2]^-$ species, and not related to host–guest complexation.[5] In order to design effective fluoride receptors, it is important to have NH groups serve as the primary recognition units that should interact with fluoride without deprotonation.

While there are several classes of anion receptors containing neutral NH groups including ureas, thioureas, amides, pyrroles, imidazoles, and indoles,[6–11] exclusive fluoride receptors that selectively recognize fluorides over others anions are indeed rare.[6] In most cases, such receptors bind other anions also, thereby hampering the selectivity for fluoride. Herein we report a new quinoline based tripodal *tris*-thiourea receptor **L** that exclusively binds fluoride over other halides via NH interactions in DMSO. Furthermore, we demonstrate that quinoline groups can be protonated due to the fluoride-induced proton transfer from the solvent to the host molecule, providing secondary binding sites for fluoride anions.

L was synthesized in a two-step reaction as shown in Scheme 1. Tripodal amine (tren) **1** was reacted with carbon disulfide under



Scheme 1. Synthetic pathway to the tripodal thiourea **L**: (i) *N*,*N*′-dicyclohexylcarbodiimide; (ii) dry THF; (iii) CH_2Cl_2.

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nitrogen atmosphere at cold temperature to yield the tren-based isothiocyanate **2**. The final product **L** was synthesized from the reaction of **2** and 8-aminoquinoline at low temperature.

Solution binding studies of **L** for anions were performed with ^{1}H NMR titrations using $[n\text{-}Bu_4N]^+A^-$ (A^- = F^-, Cl^-, Br^-, I^-, ClO_4^-, NO_3^-, and HSO_4^-) in DMSO-d_6. At first, the anion binding ability of **L** was screened by the addition of an excess amount of the respective anion (five equivalents) to the host solution. As shown in Figure 1, the free **L** shows two peaks for two NH groups (NH1 = 10.21 ppm and NH2 = 8.84 ppm) that remain almost unchanged in the presence of Cl^-, Br^-, I^-, ClO_4^-, NO_3^-, and HSO_4^-, which could be the effect of the attached electron-donating groups reducing the NH acidity of thiourea groups. In contrast, both NH resonances shift significantly after the addition of fluoride anion: the NH1 proton shifts downfield ($\Delta\delta$NH1 = 1.13 ppm) and the NH2 proton shifts upfield ($\Delta\delta$NH2 = 1.27 ppm). In addition, all other aromatic protons are observed to shift upfield in the presence of fluoride. These results indicate that the ligand interacts exclusively with fluoride among other anions via hydrogen bonding interactions. Interestingly, a new sharp peak appears at 11.18 ppm, which could be the result of the formation of quinoline NH^+—a potential secondary binding site formed from the interactions of basic quinoline N groups and HF. The appearance of NH^+ at 11–12 ppm is well documented for the related organic salts (e.g. pyridinium chlorides).[12] Presumably, the very hygroscopic TBAF abstracts protons in DMSO solution from the crystalline salt (TBAF·$3H_2O$)/moisture rather than from the thiourea groups. In general, the removal of NH protons causes the disappearance of NH peaks, which has not been observed in the present case. It is assumed that the quinoline moieties act as electron-donating groups, making the N–H bonds strong enough for the interactions with the fluoride without deprotonation. The change in the chemical shift of NH resonances of **L**, as recorded with an increasing amount of TBAF at room temperature (Fig. 2), gave the best fit for a 1:2 (host/guest) binding model (Fig. 3),[13] yielding the binding constants, $\log\beta_1 = 2.32(3)$, and $\log\beta_2 = 4.39(4)$. The binding stoichiometry was confirmed by a Job's plot analysis (Fig. S11). The 1:2 binding could be due to the interactions of one fluoride with NH binding sites and another fluoride with secondary $^+$NH binding sites within the tripodal pocket, as verified by DFT calculations (discussed later).

UV–vis studies were further performed to evaluate the binding ability of **L** for anions in DMSO. The free receptor displayed an absorption band (λ_{max}) at 335 nm in the absence of an anion. With the exception for fluoride, the receptor did not show any change in its absorption patterns for other anions in DMSO (Fig. 4). This observation is fully consistent with the ^{1}H NMR data showing no interactions for Cl^-, Br^-, I^-, ClO_4^-, NO_3^-, and HSO_4^-. The addition of

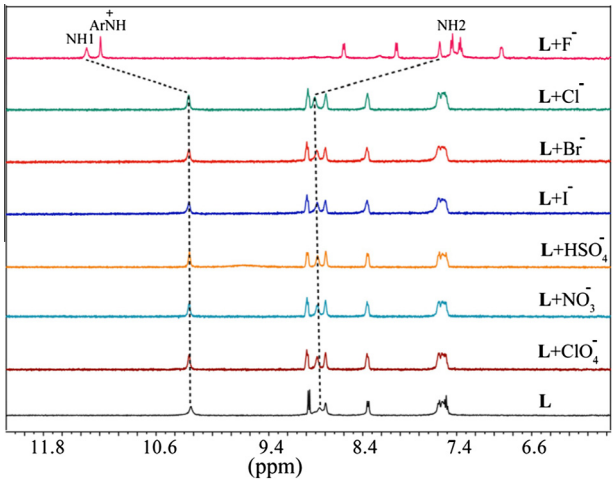

Figure 1. Partial ^{1}H NMR spectra of **L** (2 mM) in the presence of 5 equiv of different anions in DMSO-d_6 (*NH1* = CSN*H*Ar, N*H2* = CH_2N*H*CS).

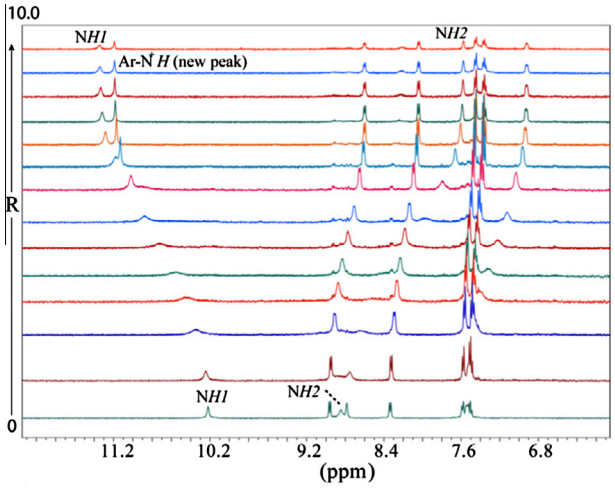

Figure 2. ^{1}H NMR spectra of **L** (2 mM) with an increasing amount of TBAF (R = $[TBAF]_0/[\mathbf{L}]_0$) in DMSO-d_6.

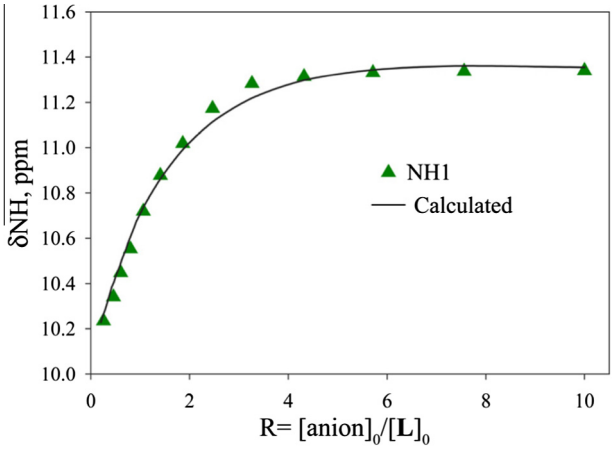

Figure 3. ^{1}H NMR titration plots of **L** (2 mM) with an increasing amount of TBAF (R = $[TBAF]_0/[\mathbf{L}]_0$) in DMSO-d_6.

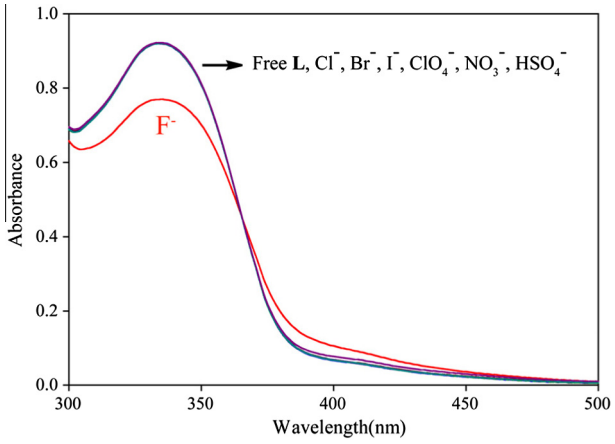

Figure 4. Changes in absorption spectra of **L** (5×10^{-5} M) in the presence of 10 equiv of different anions in DMSO.