Electronic Supplementary Information

Receptor Conformational Change Induces Fluoride Binding

Despite Water Competition

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1. General Procedures and Instrumentation

All experiments were carried out in a dry argon atmosphere. 4 Å molecular sieves were activated *in vacuo* at 180 °C for several days. Dry tetrahydrofuran (THF), diethyl ether, and dichloromethane (DCM) were purchased from Sigma-Aldrich and were stored over 4Å molecular sieves. was purchased from Aldrich. Trimethyl borate, 2.5 M solution of *n*-butyllithium in hexanes, N,N-dimethylbenzylamine, trifluoroacetic acid, and all deuteriated solvents (DMSO- d_6 , D_2O , CDCl₃ and CF₃CO₂D) were purchased from Sigma-Aldrich. DMSO- d_6 and CDCl₃ were stored over activated 4 Å molecular sieves. Trimethyl borate was redistilled before use.

¹H, ¹³C, and ¹⁹F spectra were recorded on a 400 MHz Varian Spectrometer (at 400, 100 MHz, and 376 MHz respectively) or 600 MHz Varian Spectrometer (at 600 MHz, 150 MHz, and 564 MHz, respectively). ¹¹B NMR spectra were recorded on a Bruker AC250 250 MHz Spectrometer at 80 MHz using quartz NMR tubes. All NMR spectra were recorded at 25 °C unless otherwise noted and were referenced to TMS or residual solvent signals. All numbers referring to NMR data obtained are in parts per million (ppm). High-resolution mass spectra were carried out at the EPSRC mass spectrometry centre in Swansea on a LTQ Orbitrap XL instrument. pH/pD measurements were performed using a Hanna HI 208 pH meter.

2. Synthesis of Tripodal Receptor [1](CF₃CO₂)₃

Synthetic steps:



Tris(amine)borane 3 was prepared using a slightly modified protocol derived from the procedure described by Yoshimoto et al (Ref 1).

A 2.5 M hexanes solution of *n*-BuLi (19.2 mL, 48 mmol) was added to a dry diethyl ether (60 mL) solution of *N*,*N*-dimethylbenzylamine (7.5 mL, 50 mmol) under argon at 0 °C. The cooling bath was removed and the reaction mixture was stirred for 48h at room temperature. The resulting heterogeneous mixture (the organolithium intermediate forms a white suspension in ether) was cooled to 0 °C and trimethyl borate (2 mL, 17 mmol) was added dropwise and reacted for 16 h at room temperature. The reaction mixture was quenched with 1.5 mL of water and the solvents were removed in *vacuo*. The resulting solid was solubilised in dichloromethane (160 mL), and washed with water (2x 15 mL). The organic layer was dried over magnesium sulfate, filtered and evaporated to give a white solid, which was sonicated in petroleum ether and filtrated to give 4.51 g (61%) of white product.

¹H NMR (600 MHz, CDCl₃) δ (ppm) 2.10 (broad s, 18H, N(CH₃)₂ × 3), 3.27 (broad s, 6H, (CH₂) × 3), 6.9-7.5 (broad m, 12H, C₆H₄ × 3), 14.6 (broad s, 2H, H₂O).

Tripodal receptor [1](CF₃CO₂)₃ was obtained by treatment of compound **3** (0.5 g, 1.16 mmol) with 3 equivalents (266 μ L) of trifluoroacetic acid in 5 mL of DCM at 0 °C. After stirring for 10 minutes at this temperature, the ice-bath was removed and the solvent evaporated in *vacuo* (rotary evaporator then high vacuum pump for 16 hours) to yield 832 mg (98%) of white solid.

¹H NMR (600 MHz, D₂O) δ (ppm) 2.4 (broad s, 18H), 3.9 (broad s, 6H), 7.22-7.45 (broad m, 12H). ¹³C NMR (100 MHz, D₂O) δ (ppm) 41.7 (broad s), 62.1 (broad s), 116.0 (q), 126.7 (s), 128.7 (s), 132.3 (broad s), 135.0 (broad s), 155.6 (broad s), 162.6 (q). ¹¹B NMR (80 MHz, D₂O) δ (ppm) 3.6 (broad s). HRMS-EI (m/z): $[M-2]^+$ calcd for C₂₇H₃₇BN₃, 414.3076; found, 414.3075.

3. Titration with NaOH

A 25 mM solution of receptor [1](CF₃CO₂)₃ (283 mg in 15 mL water) was prepared and titrated using a 0.2 M NaOH solution. The results are summarised in the Table below:

Volume NaOH 0.2 M	0	0.36	0.75	0.85	0.95	1.15	1.35	1.45	1.56	1.65
added (mL)										
Observed pH	1.10	1.18	1.24	1.28	1.33	1.46	1.59	1.68	1.79	2.03
Volume NaOH 0.2 M added (mL)	1.77	1.85	1.90	1.95	2.00	2.20	2.40	2.60	2.70	2.90
Observed pH	2.57	5.36	6.55	6.73	6.79	6.90	7.00	7.11	7.17	7.32
Volume NaOH 0.2 M	3.15	3.35	3.50	3.60	3.70	-	-	-	-	-
added (mL)										
Observed pH	7.53	7.84	8.25	8.70	9.11	-	-	-	-	-

The receptor started to precipitate at pH 9.



For comparison, note that the pK_a values for protonated 2,2'diaminodiethylamine are 3.58, 8.86, and 9.65 (Ref 2)

4. ¹H NMR Binding Studies of [1](CF₃CO₂)₃ with Various Anions Stock solution of receptor [1](CF₃CO₂)₃ (4 mM in D₂O at pD 2.4)

A stock solution was prepared by dissolving receptor [1](CF₃CO₂)₃ [MW=755.48 g.mol⁻¹] (15.1 mg, 0.02 mmol) in D₂O using a volumetric flask to give a 4 mM solution. The pH of the solution was adjusted to 2.0 ± 0.1 with CF₃CO₂D (less than 20 µL was necessary). pD \approx pH read + 0.44 = 2.4 ± 0.1 (Ref 3).



Figure S1. ¹H NMR spectrum (600 MHz, D₂O) of [1](CF₃CO₂)₃ (4 mM).

Stock solution of potassium chloride (80 mM in D_2O at pD 2.4 ± 0.1)

A stock solution was prepared by dissolving potassium chloride (29.8 mg, 0.4 mmol) in 5 mL D₂O using a volumetric flask to give a 80 mM solution. The pH of the solution was adjusted to 2 (pD = 2.4 ± 0.1) with CF₃CO₂D.



Figure S2. ¹H NMR spectrum (600 MHz, D_2O) of [1](CF₃CO₂)₃ (3.6 mM) in the presence of KCl (7.3 mM) after 20 h at 25 °C.

Stock solution of potassium bromide (80 mM in D_2O at pD 2.4 ± 0.1)

A stock solution was prepared by dissolving potassium bromide (47.6 mg, 0.4 mmol) in 5 mL D₂O using a volumetric flask to give a 80 mM solution. The pH of the solution was adjusted to 2 (pD = 2.4 ± 0.1) with CF₃CO₂D.



Figure S3. ¹H NMR spectrum (600 MHz, D₂O) of $[1](CF_3CO_2)_3$ (3.6 mM) in the presence of KBr (7.3 mM) at pD = 2.4 ± 0.1 after 5 h.

Stock solution of sodium cyanide (80 mM in D_2O at pD 2.4 ± 0.1)

A stock solution was prepared by dissolving sodium cyanide (19.6 mg, 0.4 mmol) in 5 mL D₂O using a volumetric flask to give a 80 mM solution. The pH of the solution was carefully adjusted to 2 (pD = 2.4 ± 0.1) with CF₃CO₂D in a fume hood.



Figure S4. ¹H NMR spectrum (600 MHz, D₂O) of $[1](CF_3CO_2)_3$ (3.5 mM) in the presence of NaCN (10.5 mM) at pD = 2.4 ± 0.1 after 5 h.



Figure S5. ¹H NMR spectrum (600 MHz, D_2O) of [1](CF₃CO₂)₃ (approx. 3.4 mM) in the presence of NaCN (approx. 10.2 mM) after 2 h at 25 °C and pD 5.5 (adjusted using a 0.05 M NaOD solution in D_2O). The arrows indicate the presence of a new species.

Stock solution of sodium nitrate (80 mM in D_2O at pD 2.4 ± 0.1)

A stock solution was prepared by dissolving sodium nitrate (34.0 mg, 0.4 mmol) in 5 mL D₂O using a volumetric flask to give a 80 mM solution. The pH of the solution was adjusted to 2 (pD = 2.4 ± 0.1) with CF₃CO₂D.



Figure S6. ¹H NMR spectrum (600 MHz, D₂O) of $[1](CF_3CO_2)_3$ (3.6 mM) in the presence of NaNO₃ (7.3 mM) at pD 2.4 ± 0.1 after 1 h.

Stock solution of potassium fluoride (80 mM in D_2O at pD 2.4 ± 0.1)

A stock solution was prepared by dissolving potassium fluoride (23.2 mg, 0.4 mmol) in 5 mL D₂O using a volumetric flask to give a 80 mM solution. The pH of the solution was adjusted to 2 (pD = 2.4 ± 0.1) with CF₃CO₂D.



Figure S7. ¹H NMR spectrum (600 MHz, D₂O) of $[1](CF_3CO_2)_3$ (3.6 mM) in the presence of KF (7.3 mM) at pD 2.4 ± 0.1 after 30 minutes.

5. ¹³C, ¹¹B, and ¹⁹F NMR Spectra





Figure S8. ¹³C NMR spectrum (100 MHz, D₂O) of [1](CF₃CO₂)₃ at $pD = 2.4 \pm 0.1$.



Figure S9. ¹³C NMR spectrum (150 MHz, D₂O) of $[1](CF_3CO_2)_3$ (20 mM) in the presence of KF (40 mM) at pD = 2.4 ± 0.1 .

5.2¹¹B NMR spectra of tris(amine)borane 3 and



tris(ammonium)borane [1](CF₃CO₂H)₃

Figure S10. ¹¹B NMR spectrum (80 MHz, CDCl₃) of tris(amine)borane 3.



Figure S11. ¹¹B NMR spectrum (80 MHz, D_2O) of tris(ammonium)borane [1](CF₃CO₂)₃.

5.3 ¹¹B NMR spectra borane-fluoride complex [1-F]²⁺



Figure S12. ¹¹B NMR spectrum (80 MHz, DMSO-d6/D₂O : 84/16) of [1](CF₃CO₂)₃

(10 mM) in the presence of KF (20 mM).



Figure S13. ¹¹B NMR spectrum (80 MHz, D₂O) of $[1](CF_3CO_2)_3$ (10 mM) in the presence of KF (20 mM) at pD = 2.4 ± 0.1 .

5.4 ¹⁹F NMR reference spectra of KHF₂ and KF in acidic D₂O



Figure S14. ¹⁹F NMR spectrum (564 MHz, D₂O) of KHF₂ (50 mM), TFA as reference.

(Chemical shift for HF_2^- is comparable to that previously determined, Ref 4).



Figure S15. ¹⁹F NMR spectrum (564 MHz, D_2O) of KF (20 mM) at pD 2.4 ± 0.1 in D_2O , TFA as reference.

5.5 ¹⁹F NMR spectra of boron-fluoride complex [1-F]²⁺ in D₂O and



DMSO-d6/D₂O solutions



The fluorine signal of the complex is not clearly detected in D_2O , presumably due to chemical exchange. However, a clear signal is observed in DMSOd6/H₂O as shown below.



Figure S17. ¹⁹F NMR spectrum (564 MHz, DMSO-d6/D₂O : 86/14) of [1](CF₃CO₂)₃

(20 mM) in the presence of KF (20 mM) at pD=2.4 \pm 0.1, TFA as reference.



6. High Resolution Mass Spectrometry Analysis of [1](CF₃CO₂)₃

7. Determination of the Binding Constant for [1.F]²⁺

The binding constant was determined in the mixture H_2O/D_2O (80/20) at 3.6 mM of receptor (pH 2.5) in the presence of 1 equivalent of potassium fluoride.

 1^{3+} + F⁻ \rightarrow (1-F)²⁺

The binding constant is expressed as:

$$k_{\text{binding}} = \frac{[(1-F)^{2+}]}{[1^{3+}][F^{-}]}$$
 (Eq. 1)

The ratio $\frac{[(1-F)^{2^+}]}{[1^{3^+}]}$ can be determined from the ¹H NMR spectrum of the mixture by integration of protons of the complex and free receptor.

The concentration of free fluoride [F⁻] is calculated the following way:

The total fluoride concentration $[F_{Total}]$ is distributed between the species F⁻, HF and HF₂⁻, which are involved in the following equilibria:

HF \longrightarrow H⁺ + F⁻ with $K_a = [H^+][F^-]/[HF]$ (Eq. 2)

 $F^- + HF \longrightarrow HF_2^-$ with $K_f = [HF_2^-][HF]/[F^-]$ (Eq. 3)

The total fluoride concentration is: $[F_{Total}] = [F^-] + [HF] + 2[HF_2^-]$

Using (Eq. 1) and (Eq.2) we obtain:

 $[F_{Total}] = [F^{-}] + [H^{+}][F^{-}]/K_{a} + 2 K_{f} [H^{+}][F^{-}]^{2}/K_{a}$

Or
$$[F_{\text{Total}}] - [F^-] = [H^+][F^-](1 + 2 K_f [F^-])/K_a$$

Since the maximum value of [F⁻] is 4×10^{-3} M and $K_f \approx 4.0$ (Ref 5):

2
$$K_{\rm f}$$
 [F⁻] < 0.032 << 1 and [F_{Total}] - [F⁻] \approx [H⁺][F⁻]/ $K_{\rm a}$
Or [F-] \approx [F_{Total}]/(1+ [H⁺]/ $K_{\rm a}$)

Using this expression in (Eq. 1), we obtain:

$$K_{\text{binding}} \approx \frac{[(1-F)^{2+}]}{[1^{3+}]} \times \frac{(1+[H^+])/K_a)}{[F_{\text{Total}}]}$$

With $[H^+] = 10^{-pH}$ and $K_a \approx 7.07 \times 10^{-4}$ M (Ref 5)

We found:

$$\frac{[(\mathbf{1}-\mathbf{F})^{2^+}]}{[1^{3^+}]} = 2.5 \pm 0.5$$

Therefore,
$$K_{\text{binding}} \approx 2.5 \text{ x} \frac{(1 + 10^{-2.5} / 7 \times 10^{-4})}{3.6 \times 10^{-3}}$$

 $K_{\text{binding}} = 3.8 \times 10^3 \pm 1.9 \times 10^3 \text{ M}^{-1}$

8. ¹H NMR of the complex $[1-F]^{2+}$ at Various pH in H₂O/D₂O : 80/20

An equimolar solution of $[1](CF_3CO_2)_3$ (3.6 mM) and KF (3.6 mM) was prepared and the pH was adjusted using a sodium hydroxide solution. The spectrum (600 MHz) were taken after 2 h at 25 °C. No solvent suppression techniques were used.



Figure S18. ¹H NMR spectrum (600 MHz, D_2O) of [1](CF₃CO₂)₃ (3.6 mM) in the presence of KF (3.6 mM) at pH 2.5, 4.5 and 6.5.

9. Computer Modeling

Modeling of the tris(ammonium)boraryl fluoride complex was perform using Maestro MacroModel v9.9, Schrödinger, Inc., New York, NY, 2012. The calculations were carried out using the OPLS-AA force field and the GB/SA continuum solvent model for water. The structures were submitted to a conformational search using Monte Carlo Multiple Minimum (MCMM). Each conformation was minimized for up to 800 steps using the conjugate gradient method. The 3D coordinates of the two most stable symmetrical conformations 1 and 2 are presented below:

Conformation 1

Conformation 2



Potential Energy: -887.331 KJ/mol



Potential Energy: -786.779 KJ/mol

Note that the OPLS-AA force field may not be able to recognize well CH...F hydrogenbonding interactions. Therefore **conformation 2** of the complex may be more stable than predicted by this force field.

X, Y, Z Coordinates

Conformation 1

C -2.7372 5.7529 -	C -0.4636 0.6892	C -6.2792 1.8905
0.8499	0.0777	3.2525
C -1.4950 6.1642 -	C -1.5912 0.6078	N -1.2482 0.4682 -
0.3413	2.2265	2.2660
C -3.1998 4.4313 -	C 0.5871 -0.0846	C -1.2698 1.0672 -
0.6549	0.6219	3.6178
C -0.7124 5.2539	C -0.3120 1.1606 -	C -1.0480 -0.9991 -
0.3832	1.3625	2.3224
C -1.1666 3.9373	C 0.5476 -0.5162	N -4.9417 -0.6079 -
0.5771	1.9572	0.4904
C -2.3985 3.4799	C -0.5422 -0.1590	C -4.4503 -1.8024 -
0.0426	2.7640	1.2103
B -2.8670 1.9200	C -4.4445 3.0245	C -6.3816 -0.3695 -
0.3072	2.1307	0.7473
C -4.5821 4.0871 -	C -5.5080 3.0439	N -4.5071 3.1793 -
1.1935	3.0505	2.3521
C -1.6004 1.0249	C -4.8951 0.6936	C -5.8351 2.6622 -
0.8707	1.6216	2.7466
C -4.1275 1.8691	C -5.9655 0.7193	C -3.7771 3.7479 -
1.3710	2.5449	3.5096
F -3.2873 1.3760 -	C -4.5905 -0.6340	H -3.3429 6.4702 -
0.8999	0.9406	1.3869

Н -1.1519 7.1785 -	Н -6.5519 -0.1711	H -5.0032 -2.6942 -
0.4925	2.7265	0.9130
Н 0.2372 5.5643	H -3.5324 -0.8603	Н -3.3976 -1.9833 -
0.7967	1.0572	1.0011
Н -0.5374 3.2776	H -5.1224 -1.4487	H -6.5788 -0.3106 -
1.1558	1.4340	1.8177
Н -5.1695 3.6270 -	H -7.0973 1.8986	H -6.9900 -1.1773 -
0.4013	3.9596	0.3394
H -5.1215 4.9936 -	H -2.1413 0.6693 -	Н -6.7254 0.5632 -
1.4721	1.8124	0.3011
H -2.4004 0.8723	H -2.0902 0.6606 -	H -3.9663 2.4065 -
2.8907	4.2097	1.9593
Н 1.4439 -0.3456	H -1.3978 2.1469 -	Н -6.3737 2.2637 -
0.0158	3.5684	1.8888
Н 0.7114 1.0102 -	H -0.3380 0.8698 -	H -6.4487 3.4508 -
1.7093	4.1488	3.1836
H -0.4827 2.2344 -	H -1.7948 -1.4669 -	H -5.7379 1.8620 -
1.4062	2.9640	3.4807
Н 1.3582 -1.1043	Н -0.0635 -1.2437 -	H -3.7084 3.0206 -
2.3651	2.7224	4.3187
H -0.5744 -0.4684	H -1.1302 -1.4592 -	H -4.2863 4.6311 -
3.7995	1.3382	3.8968
H -3.8688 3.9315	H -4.4047 0.2013 -	H -2.7606 4.0392 -
2.0220	0.8081	3.2467
H -5.7270 3.9463	H -4.5600 -1.6788 -	
3.6044	2.2879	

Conformation 2

C -2.3873 5.3707 -	C -0.7910 0.1995 -	C -6.6470 2.1235
1.9039	0.4212	2.2707
C -1.2287 5.8010 -	C -1.8106 0.5622	N 0.7526 0.8356 -
1.2349	1.7621	2.2970
C -2.9945 4.1325 -	C 0.1187 -0.7027	C 0.9671 0.7687 -
1.5844	0.1808	3.7594
C -0.6638 4.9927 -	C -0.6383 0.4851 -	C 1.2055 2.1266 -
0.2366	1.9181	1.7298
C -1.2405 3.7455	C 0.0765 -0.9567	N -5.2805 -1.7123
0.0625	1.5624	0.8639
C -2.3895 3.2770 -	C -0.8809 -0.3087	C -5.4356 -2.9586
0.6185	2.3577	0.0818
B -2.9660 1.7822 -	C -4.5199 2.9951	C -4.2577 -1.8492
0.2671	1.4808	1.9262
C -4.2970 3.7627 -	C -5.6757 3.1362	N -5.3050 4.8501 -
2.3001	2.2693	2.2569
C -1.8075 0.8107	C -5.2622 0.7955	C -6.4028 4.6327 -
0.3687	0.7400	3.2247
C -4.3023 1.8472	C -6.4392 0.9609	C -5.8152 5.1206 -
0.6818	1.5089	0.8931
F -3.3506 1.2146 -	C -5.0681 -0.5286 -	H -2.8121 6.0132 -
1.4573	0.0047	2.6623

Н -0.7810 6.7546 -	H -7.1953 0.1887	H -4.5246 -3.1923 -
1.4794	1.5322	0.4705
Н 0.2196 5.3217	H -5.7658 -0.5417 -	H -6.2530 -2.8717 -
0.2930	0.8428	0.6345
Н -0.7777 3.1376	H -4.0721 -0.6370 -	H -4.4820 -2.6965
0.8264	0.4247	2.5745
H -4.0479 3.5157 -	H -7.5447 2.2328	H -3.2669 -2.0056
3.3329	2.8638	1.4982
H -4.7798 2.8865 -	Н 1.3372 0.1218 -	H -4.2188 -0.9613
1.8766	1.8918	2.5573
H -2.5452 1.0378	Н 2.0112 0.9588 -	H -4.8246 5.6840 -
2.3959	4.0091	2.5557
Н 0.8707 -1.2045 -	Н 0.7136 -0.2184 -	H -6.0151 4.5262 -
0.4118	4.1471	4.2383
H -1.2609 1.3076 -	Н 0.3547 1.5052 -	H -6.9687 3.7326 -
2.2588	4.2809	2.9821
H -0.9674 -0.4028 -	Н 2.2477 2.3187 -	Н -7.0932 5.4765 -
2.4591	1.9851	3.2268
Н 0.7847 -1.6388	Н 0.6069 2.9540 -	H -6.5093 5.9613 -
2.0127	2.1124	0.8977
H -0.9123 -0.4874	Н 1.1338 2.1298 -	H -6.3398 4.2528 -
3.4236	0.6422	0.4918
H -3.7945 3.7958	H -6.1608 -1.5586	H -5.0055 5.3743 -
1.4883	1.3295	0.2089
H -5.8206 4.0281	H -5.6620 -3.8024	
2.8630	0.7341	

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