Supporting Information for:

Deuterium Equilibrium Isotope Effects in a Supramolecular Receptor for Hydrosulfide

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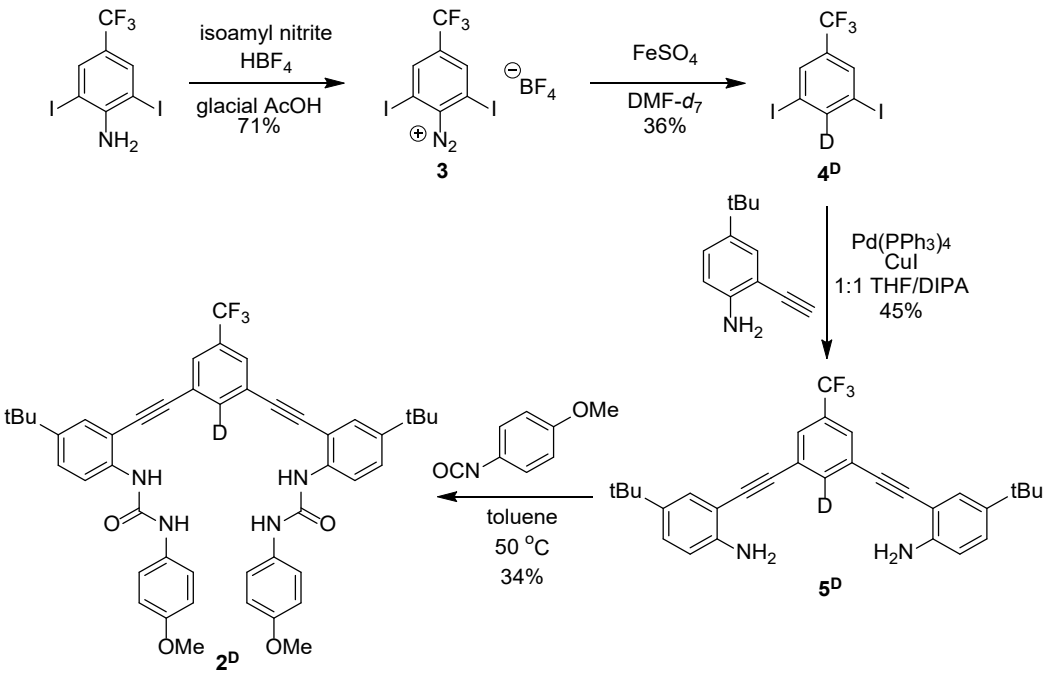
Synthesis.

General Methods. All reagents were purchased from commercial sources and used as received, unless otherwise noted. NMR spectra were acquired at room temperature on a Bruker Avance-III-HD 600 MHz (^{1}H 600 MHz, ^{13}C 151 MHz, ^{19}F 565 MHz, ^{2}H 76.75 MHz) spectrometer with a Prodigy multinuclear broadband BBO CryoProbe. ^{1}H and ^{13}C chemical shifts (δ) are reported in ppm relative to residual $CHCl_3$ (^{1}H: 7.26 ppm, ^{13}C: 77.16 ppm), CH_3CN (^{1}H: 1.94 ppm, ^{13}C: 118.26 ppm), or DMSO (^{1}H: 2.50 ppm, ^{13}C: 39.52 ppm) shifts. ^{19}F chemical shifts are referenced to $CFCl_3$ (δ = 0 ppm) as an external standard. ^{2}H chemical shifts are reported in ppm relative to residual $CDCl_3$ (7.26 ppm), CD_3CN (1.94), or DMSO-d_6 (2.50 ppm). High-resolution mass spectra (HRMS) were recorded on a Waters XEVO G2-SX mass spectrometer. Tetrabutylammonium hydrosulfide (TBASH),[1] 2,6-diiodo-4-trifluoromethylaniline,[2] 4-tertbutyl-2-((trimethylsilyl)ethynyl)aniline,[3] and host **2^H**[4] were synthesized according to previous reports. *Note*: Hydrogen sulfide and related salts are highly toxic and should be handled carefully to avoid exposure.



Scheme S1. Synthetic pathway to the selective deuteration of anion receptor **2^D**.

2,6-Diiodo-4-trifluoromethyldiazonium tetrafluoroborate (3). This preparation was adapted from previous reports.[5] A solution of 2,6-diiodo-4-trifluoromethylaniline[2] (0.25 g, 0.61 mmol), glacial AcOH (1.0 mL), and 48% HBF_4 (0.18 mL) was stirred at 25 °C. Isoamyl nitrite (0.14 mL) was combined with glacial AcOH (2.0 mL) and added dropwise over 5 min to produce a bright yellow solution. After stirring the reaction mixture at 25 °C for 15 min, diethyl ether (2.0 mL) was slowly added. The resulting liquid was placed in a -20 °C freezer for 16 h, and the solid product was isolated by vacuum filtration and washed with diethyl ether to afford **3** (0.25 g, 0.48 mmol, 71%) as a bright yellow solid. *Note*: Caution should be observed when working with isoamyl nitrite or isolating diazonium salts as a solid as these compounds are known to be shock sensitive and explosive.[6,7] ^{1}H NMR (600 MHz, CD_3CN) δ: 8.59 (s, 2H).

^{13}C NMR (151 MHz, CD_3CN) δ: 140.2 (q, *J* = 34.7), 139.7 (q, *J* = 3.0), 133.1, 121.4 (q, *J* = 274.8), 102.9. ^{19}F (565 MHz, CD_3CN) δ: 4.7, -151.8.

1,3-Diiodo-2-duetero-5-trifluoromethylbenzene (4^D)

This preparation was adapted from previous reports.[8] A solution of $FeSO_4$ (0.54 g, 2.0 mmol) and DMF-d_7 (10 mL) was allowed to stir for 15 min. A separate solution containing **2** (1.0 g, 2.0 mmol) dissolved in DMF-d_7 (4 mL) was added dropwise over 10 min to the stirring solution. The solution was allowed to stir for an additional 15 min before adding water to precipitate a solid. The precipitate was isolated by vacuum filtration and washed with water to afford **4^D** (0.28 g, 0.71 mmol, 36%) as a tan solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.91 (s, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 148.3 (t, *J* = 27.2), δ 133.7 (q, *J* = 33.7), δ 133.7 (q, *J* = 1.5), δ 121.9 (q, *J* = 273.8), δ 94.6. ^{19}F (565 MHz, $CDCl_3$) δ -63.0. ^{2}H (76.75 MHz, $CDCl_3$) δ 8.29. HRMS (TOF-MS-ASAP) $[M]^+$ calc'd for $C_7H_2DF_3I_2$ 398.8339, found 398.8317.

Deuterated dianiline intermediate (5^D)

This preparation was adapted from previous reports.[4] A suspension of 4-tertbutyl-2-((trimethylsilyl)ethynyl)aniline[3] (0.68 g, 2.4 mmol), K_2CO_3 (1.90 g, 13.8 mmol), MeOH (20 mL), and Et_2O (10 mL) was stirred at 25 °C for 3 h. The suspension was diluted with water and extracted with CH_2Cl_2 (15 mL, x3) and washed with brine (15 mL, x2). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to afford a dark brown oil. The oil was dissolved in THF (20 mL) and DIPA (20 mL) and purged with N_2 for 40 min. The solution was cannulated into an N_2-purged solution of **4^D** (0.36 g, 0.92 mmol), $Pd(PPh_3)_4$ (0.032 g, 0.046 mmol), CuI (0.0017 g, 0.0092 mmol), THF (20 mL), and i-$PrNH_2$ (20 mL). The solution was stirred for 18 h at 50 °C, cooled, and concentrated *in vacuo*. The resulting oil was dissolved in CH_2Cl_2 and filtered through a 3 cm silica plug, which was washed with additional CH_2Cl_2. The filtrate was concentrated *in vacuo* and the resulting brown oil was purified by column chromatography (5:1 hexanes/EtOAc) to afford **5^D** (0.20 g, 0.41 mmol, 45%) as a brown solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.71 (s, 2H), 7.40, (d, *J* = 2.0, 2H), 7.24 (dd, *J* = 8.4, 2H), 6.70 (d, *J* = 8.4, 2H), 4.19 (s, 4H), 1.30 (s, 18H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 145.8, 141.2, 136.7 (t, *J* = 25.7), 131.5 (q, *J* = 33.2), 129.0, 128.0, 127.4 (q, *J* = 3), 124.9, 124.6 (q, *J* = 273.3), 114.6, 106.6, 92.1, 89.1, 34.1, 31.5. ^{19}F (565 MHz, $CDCl_3$) -63.1. ^{2}H (76.75 MHz, $CDCl_3$) δ: 7.90. HRMS (TOF-MS-ASAP) $[M+H]^+$ calc'd for $C_{31}H_{31}DN_2F_3$ 490.2580, found 490.2549.

Deuterated arylethynyl bisurea host (2^D)

This preparation was adapted from previous reports.[4] All glassware was dried in a 110 °C oven overnight. A round bottom flask was charged with dry toluene (100 mL) and **5^D** (0.20 g, 0.41 mmol). 4-Methoxyphenyl isocyanate (0.16 mL, 1.2 mmol) was added dropwise, and the solution was stirred for 46 h at 50 °C. The reaction became cloudy upon completion, and the precipitate was collected by vacuum filtration to afford **2^D** (0.11 g, 0.14 mmol, 34%). ^{1}H NMR (600 MHz, 10% DMSO-d_6/CD_3CN) δ: 8.87 (s, 2H), 8.08 (d, *J* = 8.8, 2H), 7.99 (s, 2H), 7.96 (s, 2H), 7.56 (d, *J* = 2.2, 2H), 7.45 (dd, *J* = 8.8, 2H), 7.38 (d, *J* = 8.9, 4H), 6.84 (d, *J* = 8.9, 4H), 3.72 (s, 6H), 1.31 (s, 18H). ^{13}C NMR (151 MHz, 10% DMSO-d_6/CD_3CN) δ: 156.2, 153.9, 145.9, 139.5, 133.5, 131.8 (q, *J* = 32.2), 129.8, 128.7 (q, *J* = 3.6), 128.3, 125.4, 124.5 (q, *J* = 272.8), 121.8, 120.7, 114.9, 111.6, 93.2, 89.2, 55.9, 34.8, 31.4. ^{19}F (565 MHz, 10% DMSO-d_6/CD_3CN) δ: -63.2. ^{2}H (76.75 MHz, 10% DMSO-d_6/CD_3CN) δ: 8.28. HRMS (TOF-MS-ASAP) $[M+H]^+$ calc'd for $C_{47}H_{45}DN_4O_4F_3$ 788.3534, found 788.3543.

NMR Spectra.

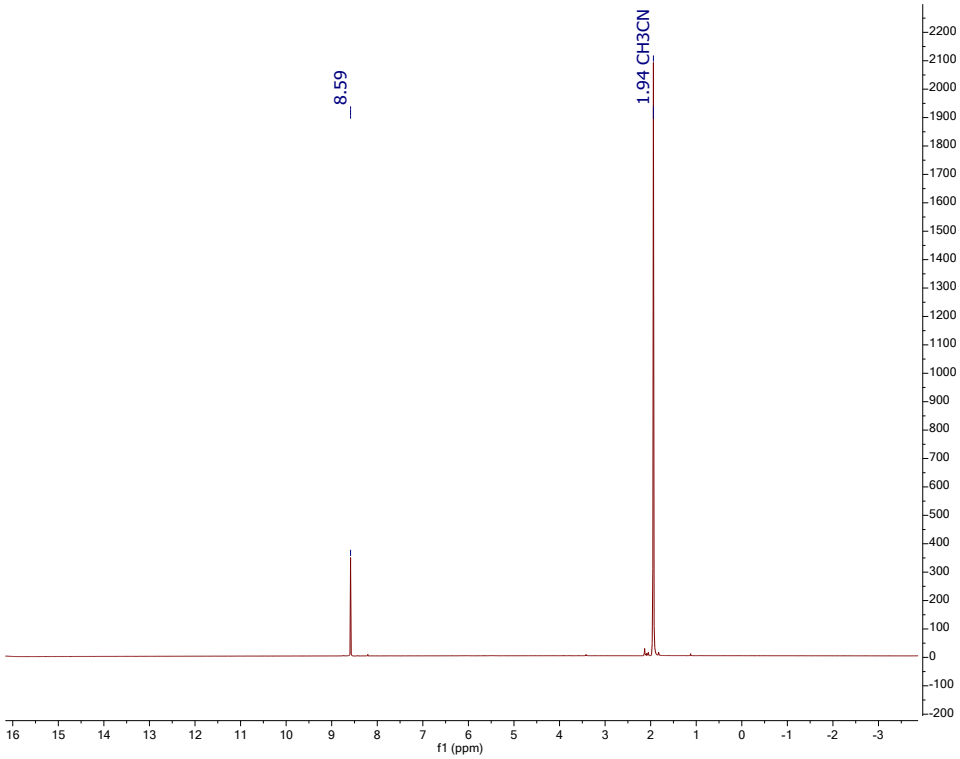


Figure S1. ^{1}H NMR spectrum of **3** in CD_3CN.

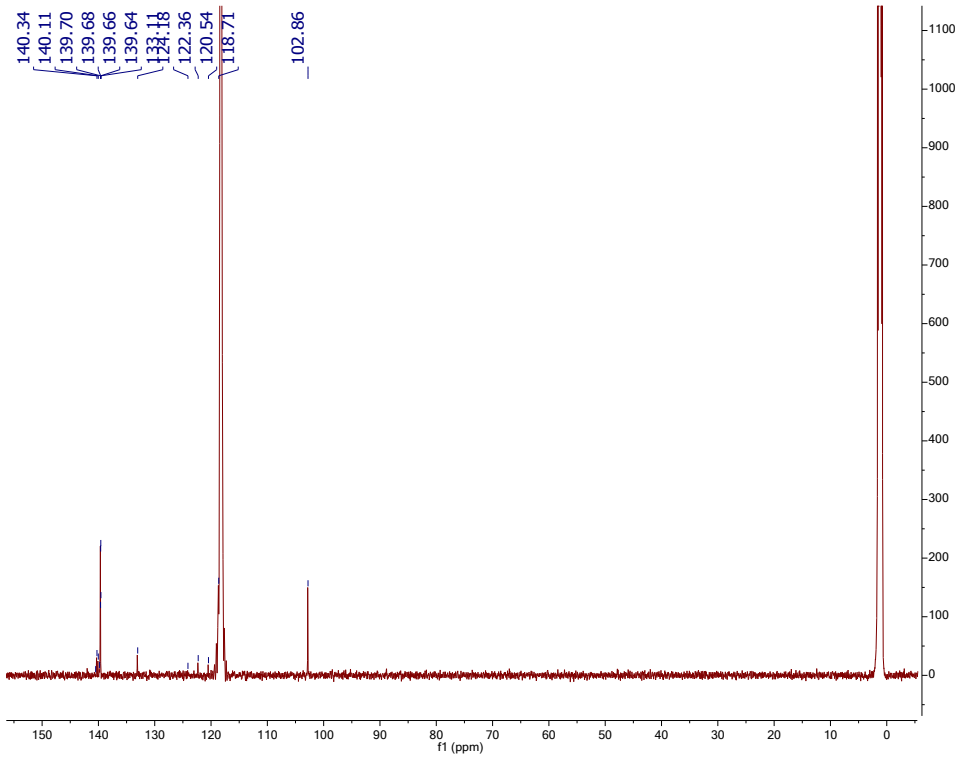


Figure S2. $^{13}C\{^{1}H\}$ NMR spectrum of **3** in CD_3CN.

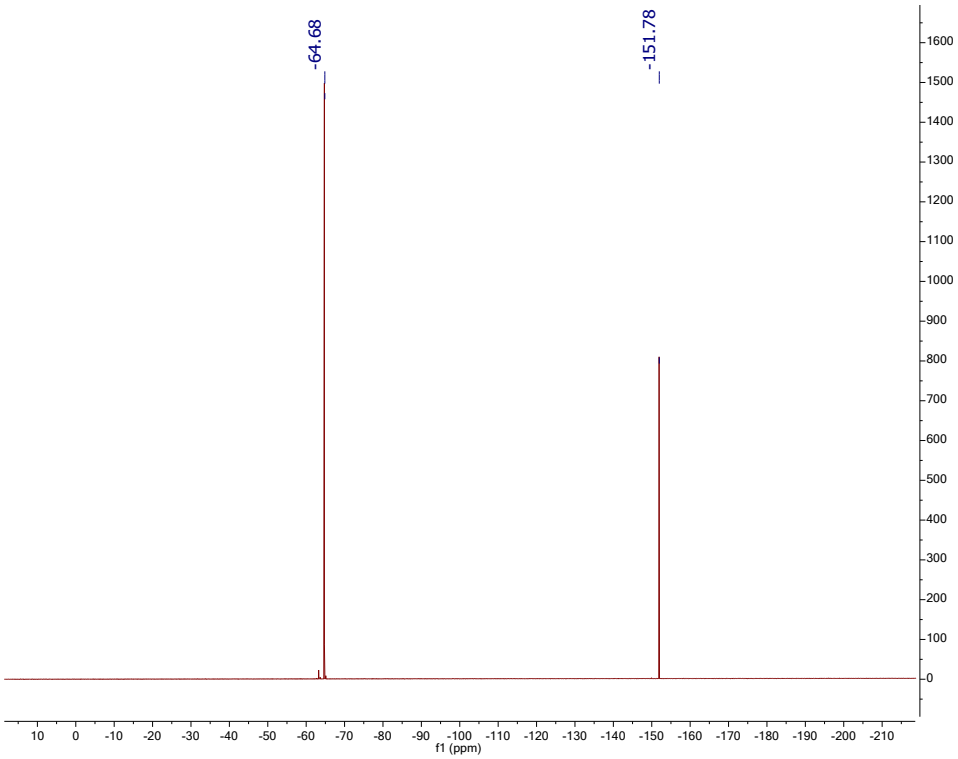


Figure S3. ^{19}F NMR spectrum of **3** in CD_3CN.

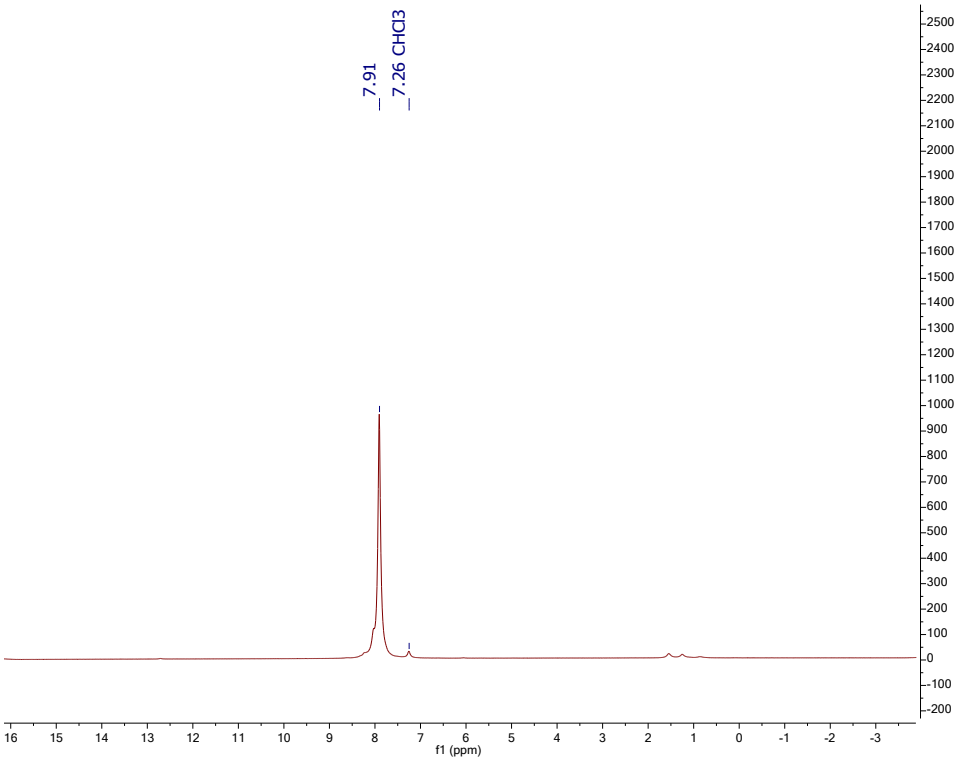


Figure S4. ^{1}H NMR spectrum of $\mathbf{4^D}$ in $CDCl_3$.

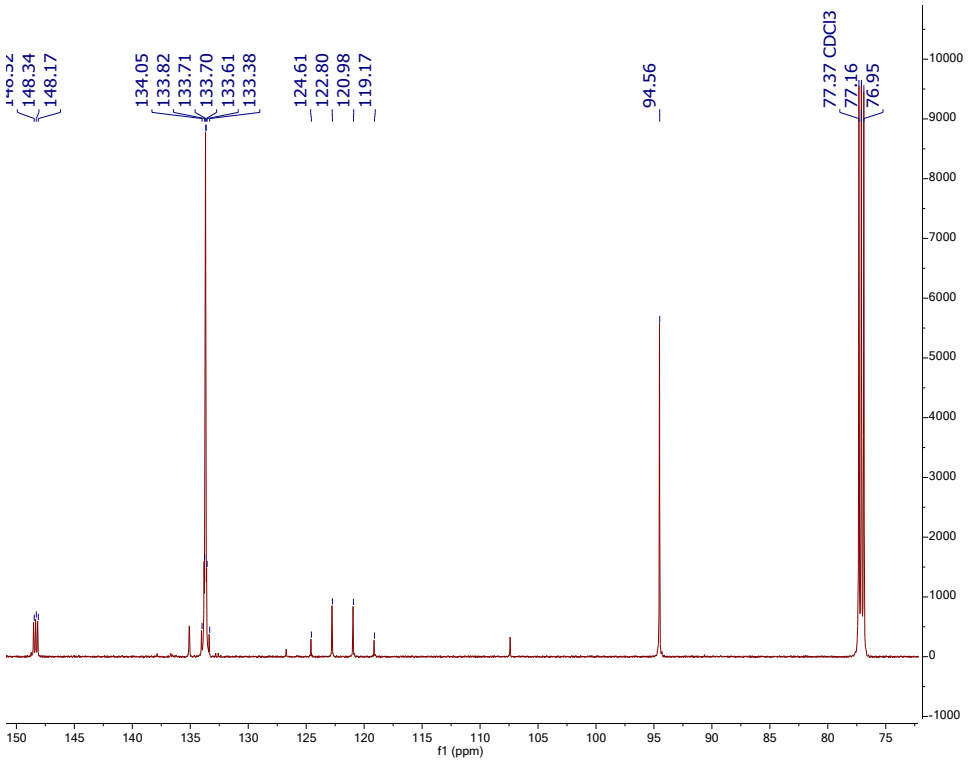


Figure S5. $^{13}C\{^{1}H\}$ NMR spectrum of **4^{D}** in $CDCl_3$.

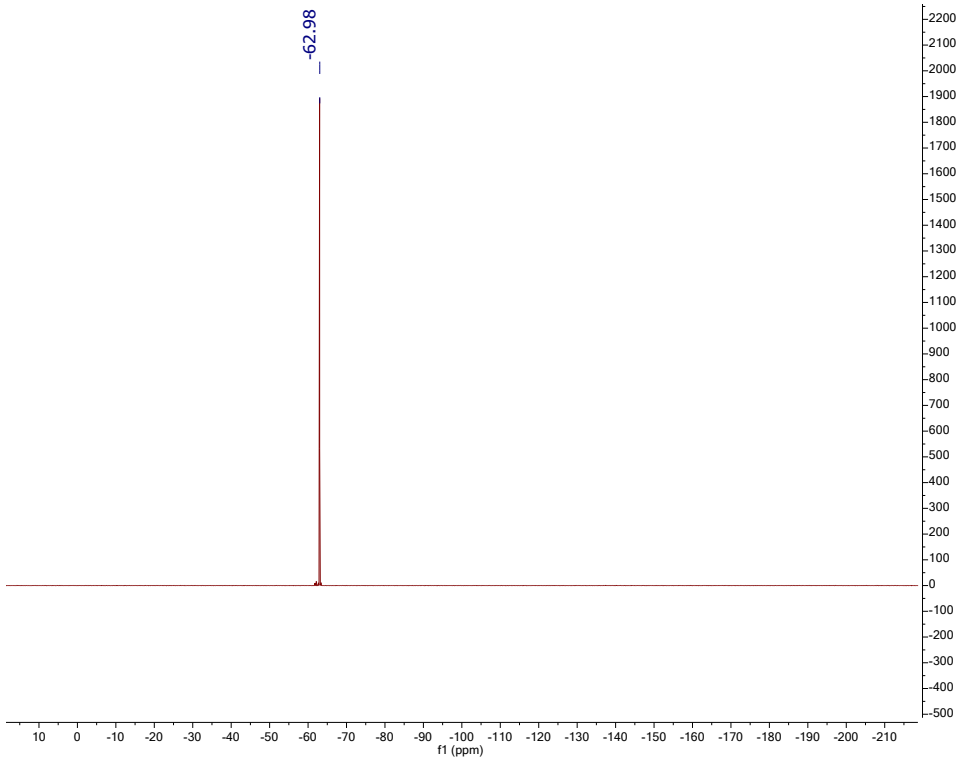


Figure S6. ^{19}F NMR spectrum of **4^{D}** in $CDCl_3$.

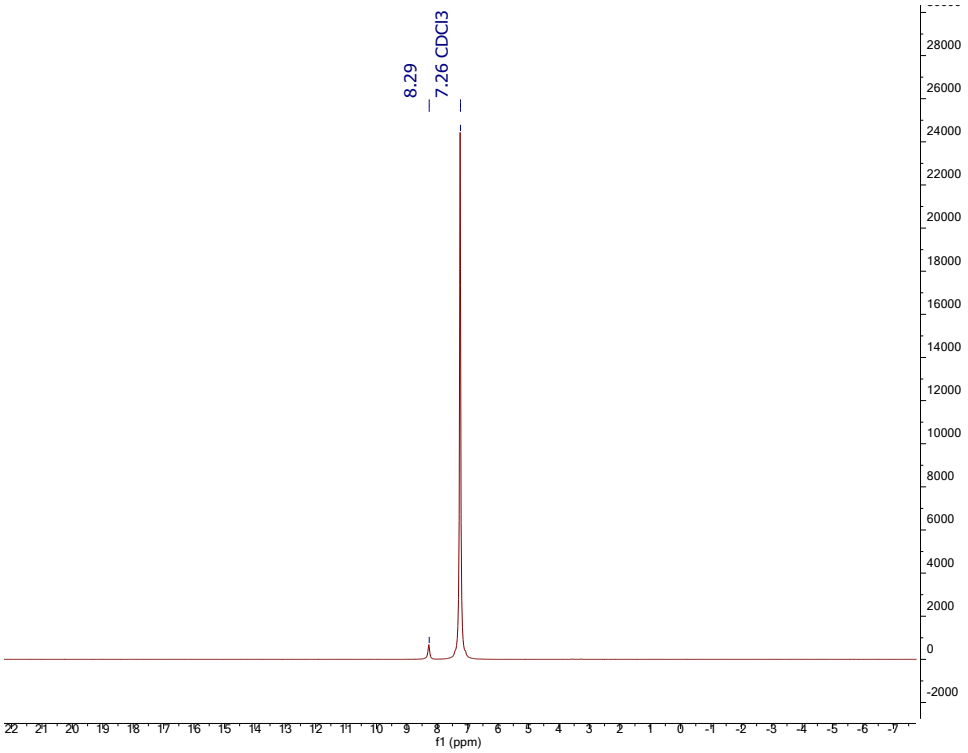


Figure S7. ^{2}H NMR spectrum of **4^{D}** in $CHCl_3$.

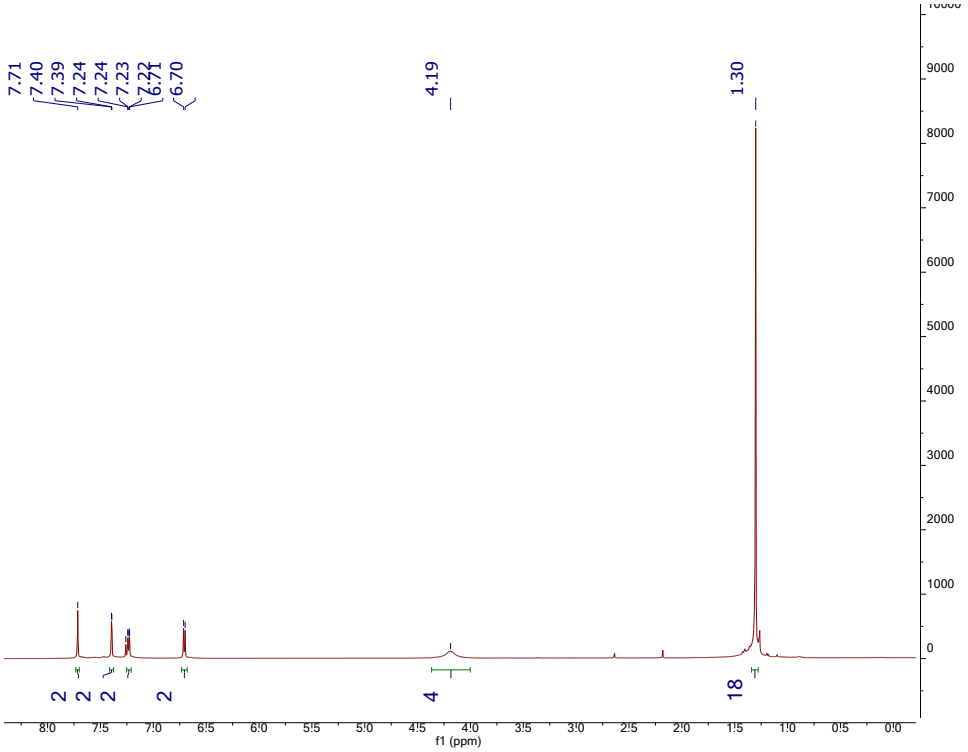


Figure S8. ^{1}H NMR spectrum of **5^{D}** in $CDCl_3$.

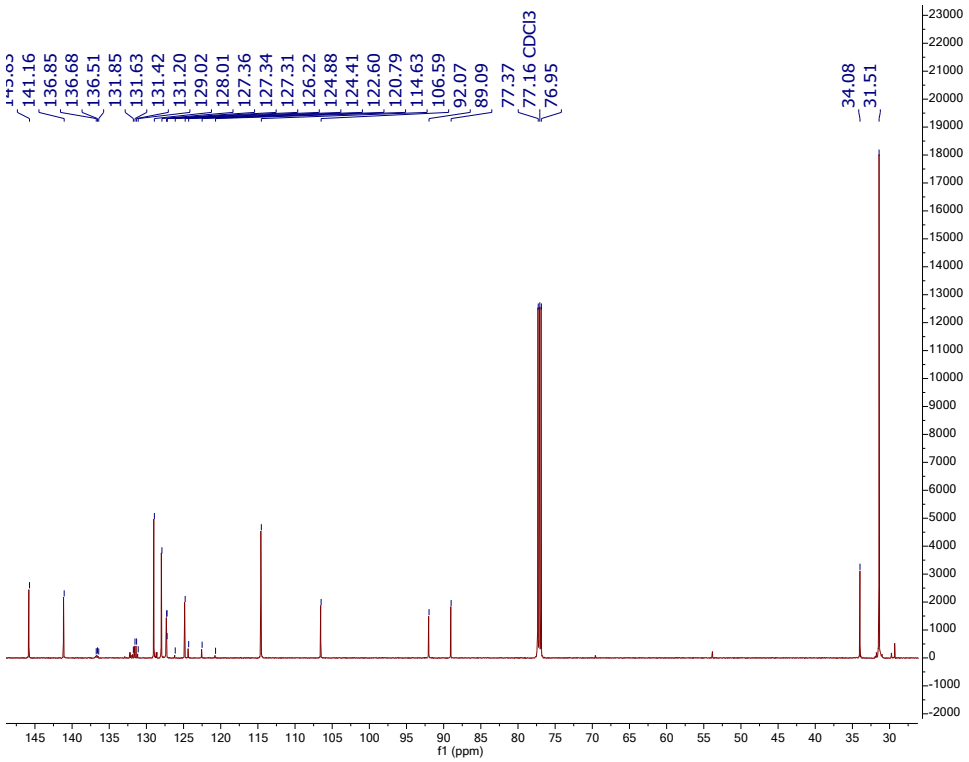


Figure S9. $^{13}C\{^{1}H\}$ NMR spectrum of **5^{D}** in $CDCl_3$.

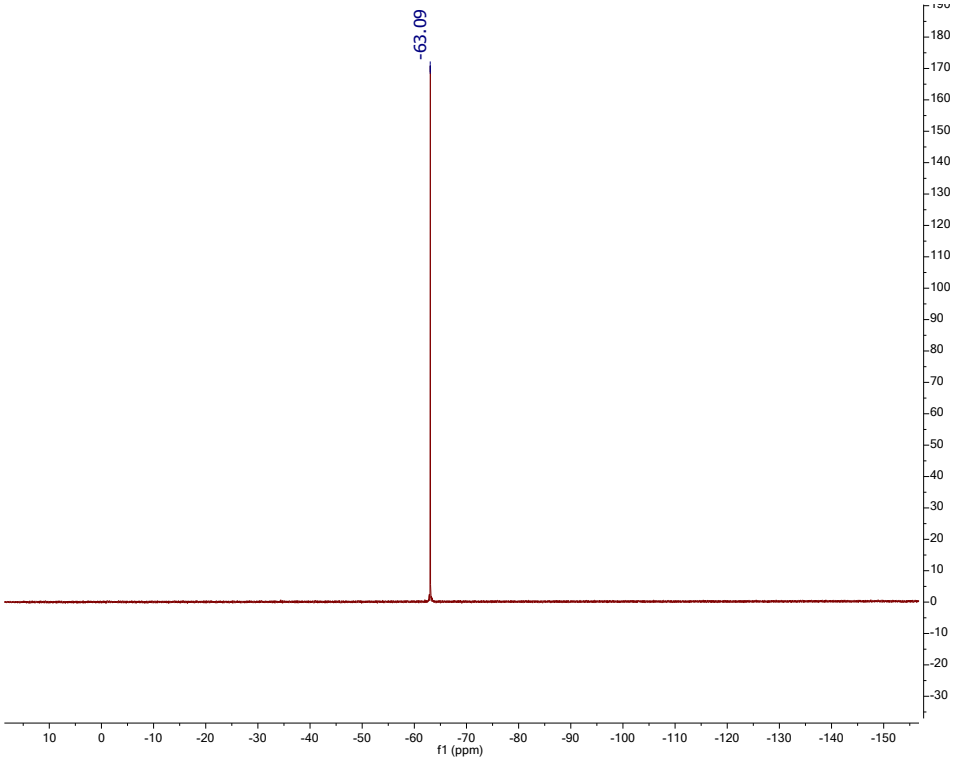


Figure S10. ^{19}F NMR spectrum of **5^{D}** in $CDCl_3$.

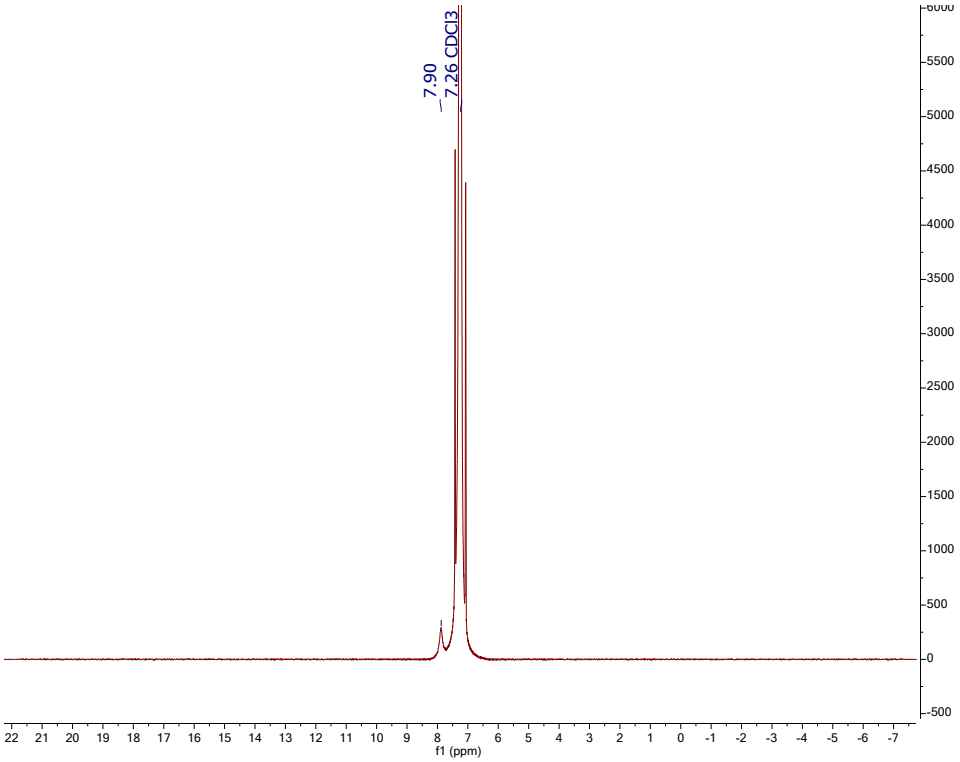


Figure S11. ^{2}H NMR spectrum of **5^{D}** in $CHCl_3$.

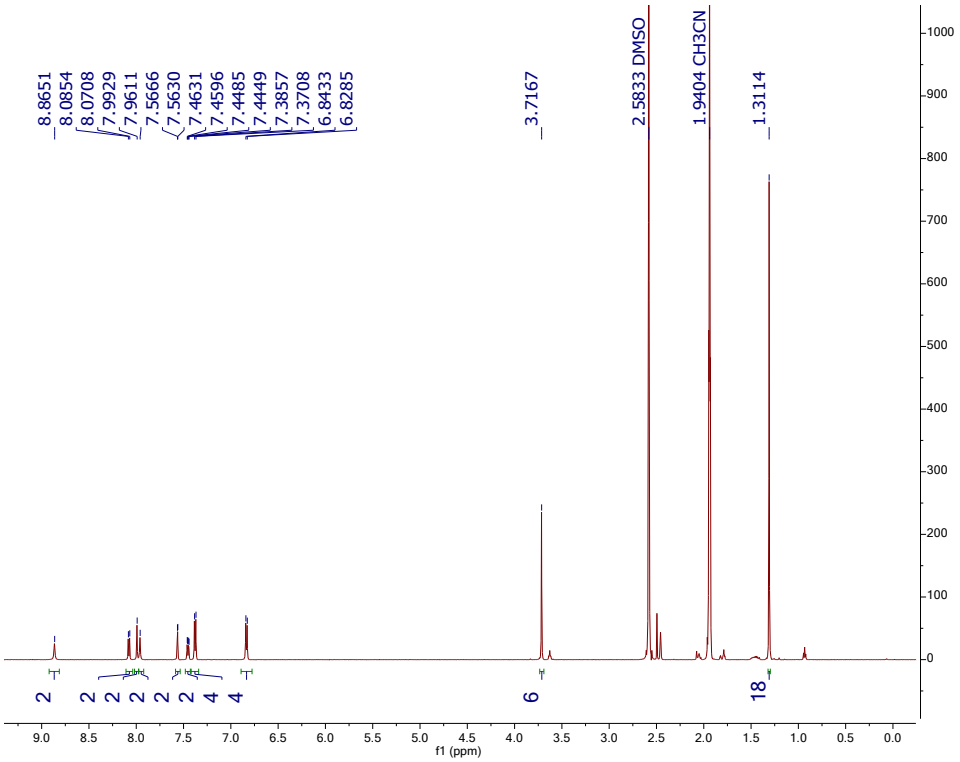


Figure S12. ^{1}H NMR spectrum of **2^{D}** in 10% DMSO-d_6/CD_3CN.

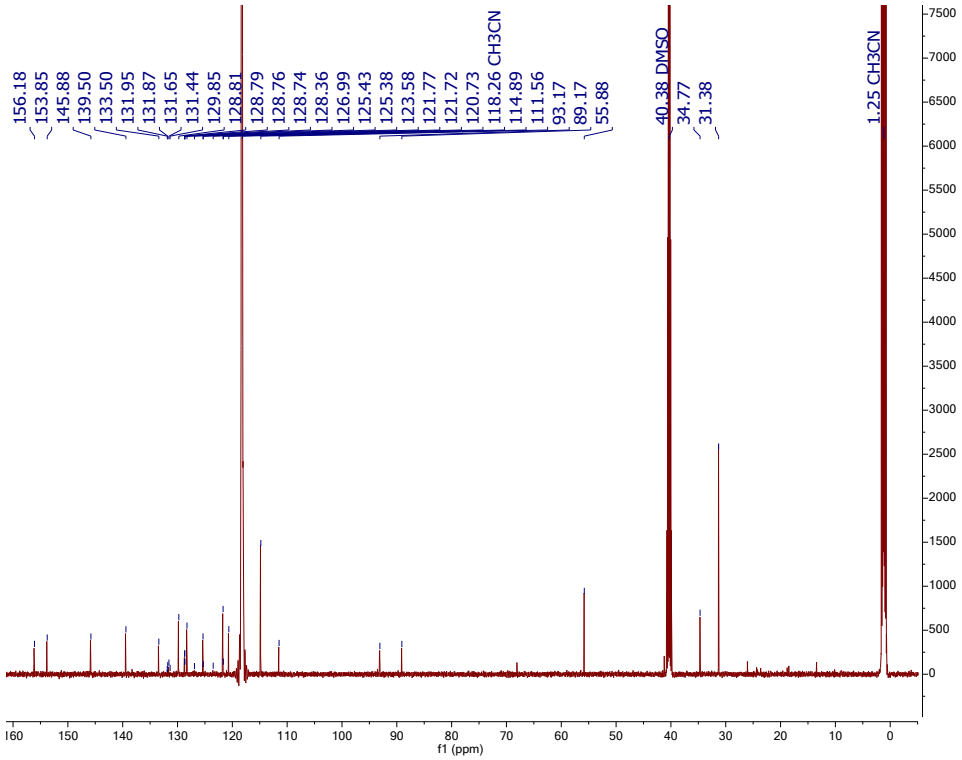


Figure S13. $^{13}C\{^{1}H\}$ NMR spectrum of **2^{D}** in 10% DMSO-d_6/CD_3CN.

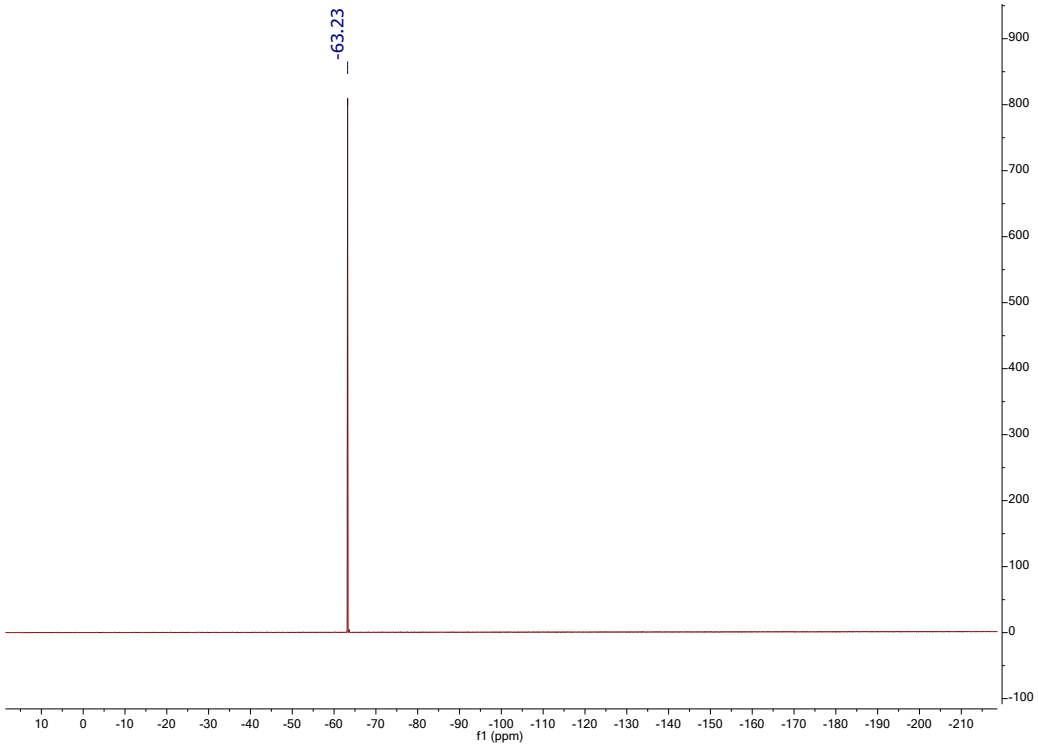


Figure S14. ^{19}F NMR spectrum of **2^{D}** in 10% DMSO-d_6/CD_3CN.

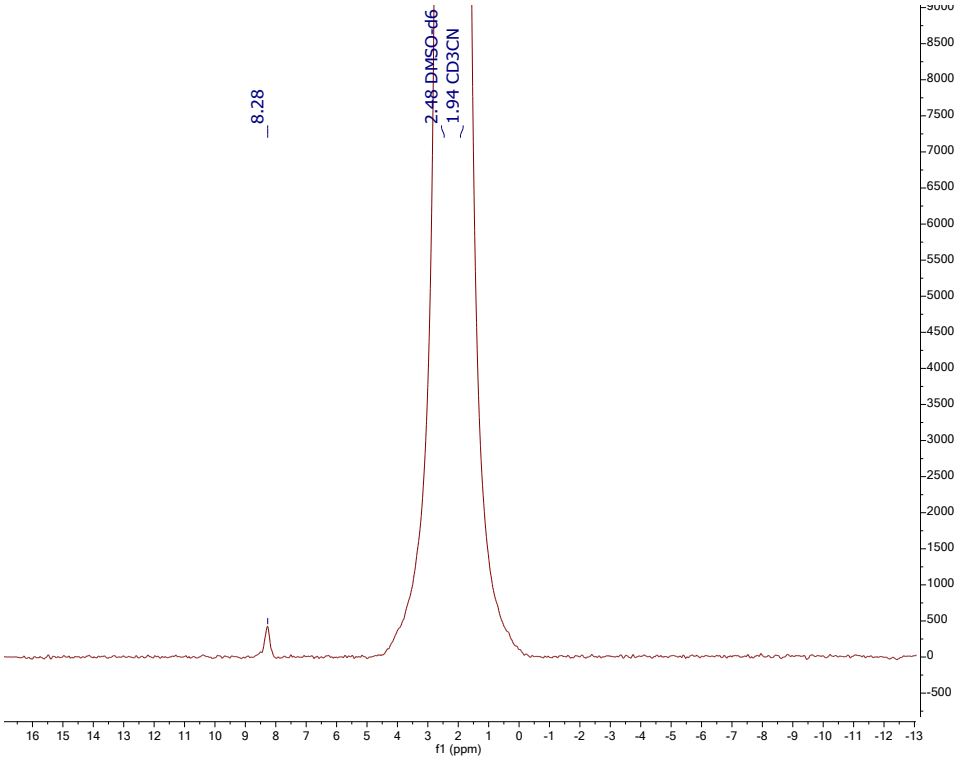


Figure S15. ^{2}H NMR spectrum of **2^{D}** in 10% DMSO/CH_3CN.

Competitive Titration of 2^H and 2^D.

General Methods. Samples were prepared under an inert atmosphere using an Innovative Atmospheres N_2-filled glovebox. CD_3CN and DMSO-d_6 were distilled from calcium hydride under reduced pressure, deoxygenated by purging with N_2 and stored over 4 Å molecular sieves in an inert atmosphere glove box. Tetrabutylammonium chloride (TBACl) and tetrabutylammonium bromide (TBABr) were recrystallized by layering an anhydrous THF solution under anhydrous Et_2O. Tetrabutylammonium hydrosulfide (TBASH) was synthesized according to previous reports.[1] *Note*: Hydrogen sulfide and related salts are highly toxic and should be handled carefully to avoid exposure.

General Procedure for NMR Titrations.

Method A.

A solution of $\mathbf{2^H}$ and $\mathbf{2^D}$ in 10% DMSO-d_6/CD_3CN (combined concentration between 5.71 and 13.46 mM) was prepared and 500 µL was added to a septum-sealed NMR tube. A stock solution of guest (TBASH, TBACl, or TBABr) was prepared in 10% DMSO-d_6/CD_3CN (54.69 – 223.09 mM). Aliquots of the guest solution were added to the NMR tube using Hamilton gas-tight syringes, and ^{13}C NMR spectra were recorded at 25°C after each addition of guest. The Δδ of the C^{ab}, C^1, and C^2 of $\mathbf{2^H}$ and $\mathbf{2^D}$ were used to follow the progress of the titration, and DEIE were determined using the Perrin method.[9]

Method B.

A solution of $\mathbf{2^H}$ and $\mathbf{2^D}$ in 10% DMSO-d_6/CD_3CN (combined concentration between 4.65 and 6.04 mM) was prepared and 500 µL aliquots were added to four J-young NMR tubes. A stock solution of TBASH was prepared in CD_3CN (47.18 – 81.29 mM). For each point in the titration, TBASH stock solution and DMSO-d_6 were added to a new solution of $\mathbf{2^H}$ and $\mathbf{2^D}$ inside an N_2-glovebox shortly before obtaining a ^{13}C NMR spectra. The Δδ of the C^{ab}, C^1, and C^2 of $\mathbf{2^H}$ and $\mathbf{2^D}$ were used to follow the progress of the titration, and DEIE were determined using the Perrin method.[9]

Competitive ^{13}C NMR Titration Representative Data.

Table S1. Representative competitive titration between $\mathbf{2^H}$ and $\mathbf{2^D}$ with Cl^- in 10% DMSO-d_6/CD_3CN at 25°C.

Entry	V_{Guest} (µL)	[$\mathbf{2^H}$] (mM)	[$\mathbf{2^D}$] (mM)	[Cl^-] (mM)	δ C^{ab} ($\mathbf{2^H}$) (ppm)	δ C^{ab} ($\mathbf{2^D}$) (ppm)	δ C^1 ($\mathbf{2^H}$) (ppm)	δ C^1 ($\mathbf{2^D}$) (ppm)	δ C^2 ($\mathbf{2^H}$) (ppm)	δ C^2 ($\mathbf{2^D}$) (ppm)
1	0	7.4	2.8	0	125.5158	125.4206	93.2006	93.1679	89.1431	89.1625
2	10	7.2	2.7	1.5	125.4586	125.3627	93.2448	93.2117	89.210	89.1440
3	50	6.5	2.5	8.0	125.2459	125.1484	93.4583	93.4213	89.0492	89.0715
4	60	5.8	2.2	14.4	125.1863	125.0894	93.5353	93.4970	89.0370	89.0597
5	200	4.3	1.3	28.4	125.1896	125.0942	93.5570	93.5180	89.0795	89.1019

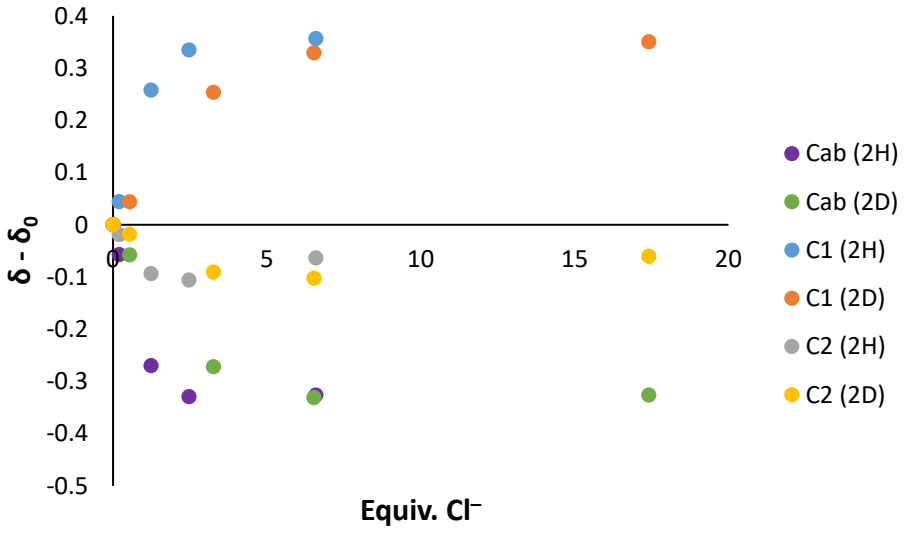


Figure S16. Binding isotherm for Cl^- binding with a mixture of $\mathbf{2^H}$ and $\mathbf{2^D}$ in 10% DMSO-d_6/CD_3CN at 25°C.

Table S2. Representative competitive titration between $\mathbf{2^H}$ and $\mathbf{2^D}$ with Br^- in 10% DMSO-d_6/CD_3CN at 25°C.

Entry	V_{Guest} (µL)	[$\mathbf{2^H}$] (mM)	[$\mathbf{2^D}$] (mM)	[Br^-] (mM)	δ C^{ab} ($\mathbf{2^H}$) (ppm)	δ C^{ab} ($\mathbf{2^D}$) (ppm)	δ C^1 ($\mathbf{2^H}$) (ppm)	δ C^1 ($\mathbf{2^D}$) (ppm)	δ C^2 ($\mathbf{2^H}$) (ppm)	δ C^2 ($\mathbf{2^D}$) (ppm)
1	0	9.4	4.1	0	125.5253	125.4301	93.2145	93.1818	89.1588	89.1780
2	5	9.3	4.0	1.1	125.4977	125.4008	93.2280	93.1959	89.1571	89.1772
3	10	9.1	3.9	3.2	125.4451	125.3496	93.2538	93.2223	89.1546	89.1743
4	60	8.1	3.5	14.1	125.2864	125.1897	93.3491	93.3152	89.1485	89.1692
5	200	5.8	2.5	37.5	125.1987	125.1029	93.4268	93.3909	89.1687	89.1896
6	500	3.5	1.5	62.6	125.1856	125.0898	93.4606	93.4253	89.2015	89.2217

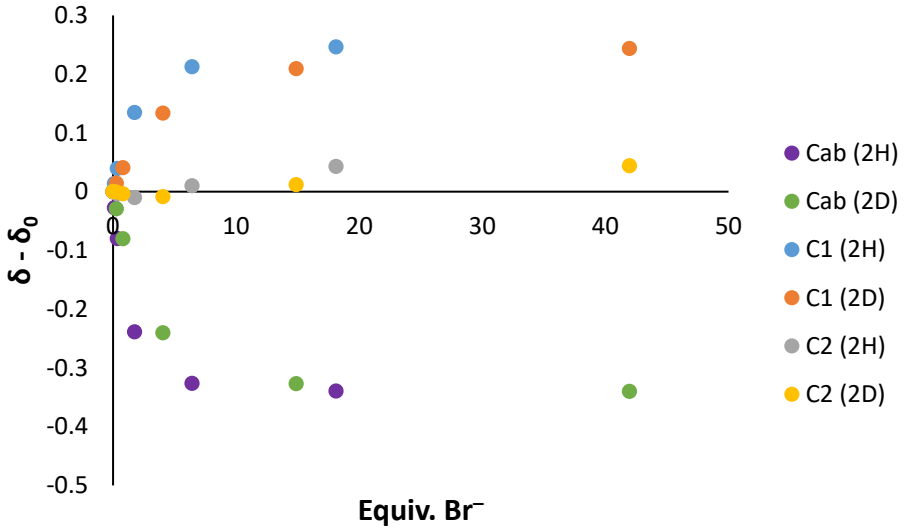


Figure S17. Binding isotherm for Br^- binding with a mixture of $\mathbf{2^H}$ and $\mathbf{2^D}$ in 10% DMSO-d_6/CD_3CN at 25°C.

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