Investigation of the Effects on Proton Relaxation Times upon Encapsulation in a Water-Soluble Synthetic Receptor

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Electronic Supplementary Information

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General Information

Cavitand **TCC** was synthesized and characterized according to literature procedures.[1] Deuterated NMR solvents were obtained from Cambridge Isotope Laboratories (Andover, MA), and used without further purification. All other materials were purchased from Sigma Aldrich (St. Louis, MO) or Fisher Scientific (Fairlawn, NJ), and were used as received. NMR spectra were recorded on a 11.7-T Bruker Avance III spectrometer (^{1}H resonance: 500.13 MHz). All NMR spectra were processed using TopSpin 4.0.

Sample Preparation

All samples containing a guest molecule bound to **TCC** were prepared in concentrations of 2 mM **TCC** and 3 mM guest in D_2O. Guest samples alone were prepared by dissolving the guest in the solvent of choice in the following concentrations: 70 mM **1-AdOH** in 1,1,2,2-tetrachloroethane-d_2 (TCE); 9 mM **1-AdOH** in D_2O; 42 mM **2-AdOH** in DMSO; 50 mM **2-AdOH** in TCE; 5 mM **2-AdOH** in D_2O; 7 mM **AdO** in D_2O; 70 mM **CyOH** in D_2O; 50 mM **CyO** in D_2O; 50 mM **THF** in D_2O. Samples were transferred to 5 mm NMR tubes from Norell.

Acquisition Methods

All T1 data were collected using a one-dimensional inversion recovery[2] (t1ir1d) experiment, Figure S-1, included with the TopSpin 4.0 software. The relaxation parameter (d7) was varied from 0 s to 3 s, depending on the time needed for signals to invert. Data were recorded using the following phase cycle: ph1=0 2; ph2=0 0 2 2 1 1 3 3.

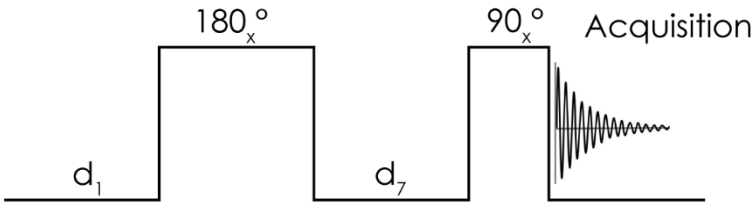


Figure S-1. Inversion recovery pulse sequence used to acquire T1 data.

All T2 data were collected using a one-dimensional Hahn spin echo experiment[3a,b] (cpmg1d; loop counter set to 1) included with the TopSpin 4.0 software, Figure S-2. The relaxation parameter (d20) was varied from 0 ms to 50 ms, depending on the time needed for signals to be sufficiently reduced. Data were recorded using the following phase cycle: ph1=0 0 2 2 1 1 3 3; ph2=1 3 1 3 0 2 0 2.

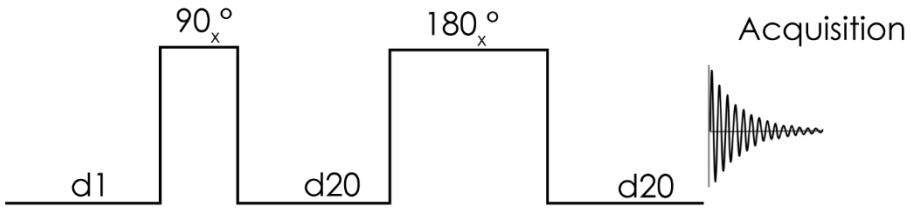


Figure S-2. Spin echo pulse sequence used to acquire T2 data.

All experiments were performed at room temperature (~25 °C) with 256 scans collected.

NMR Spectra

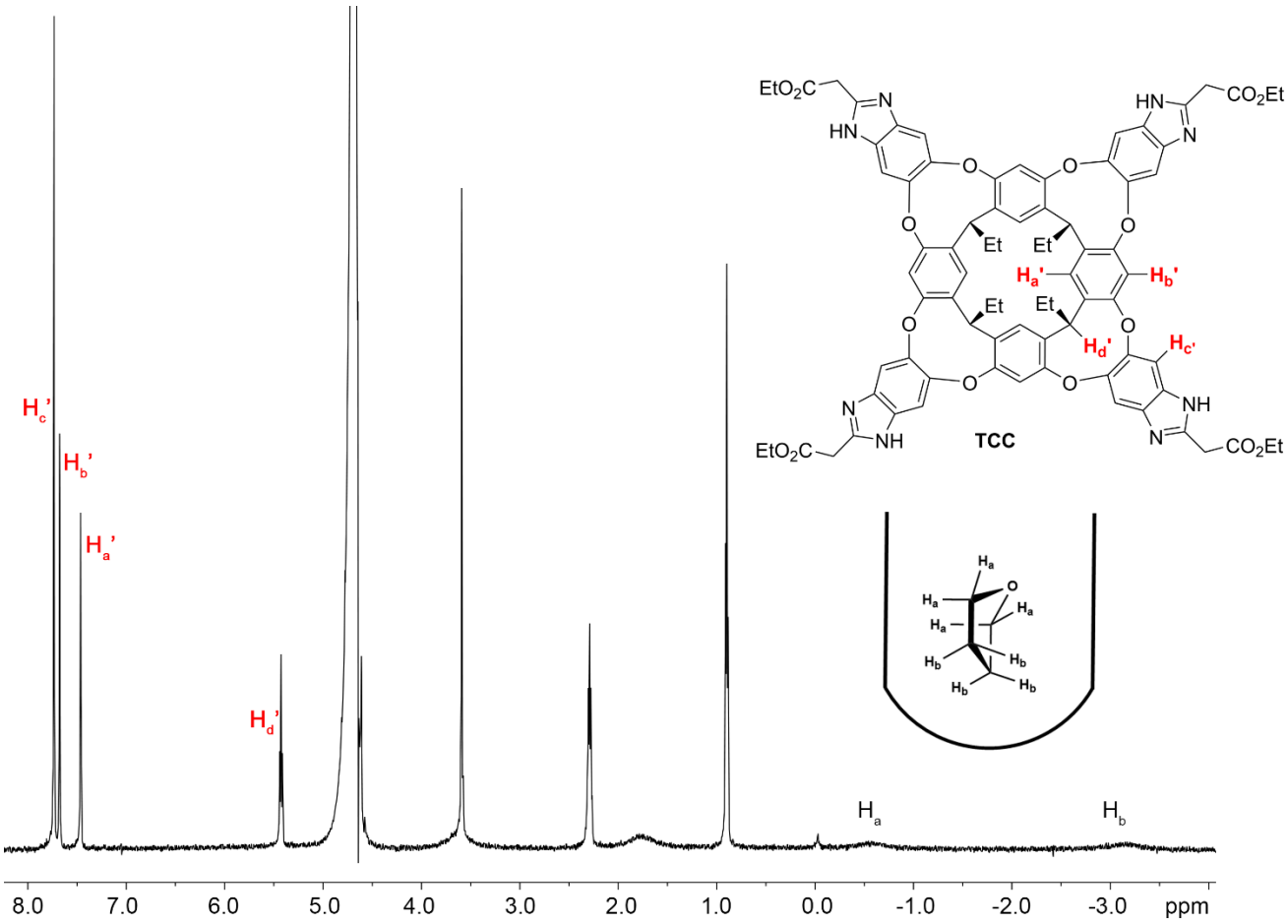


Figure S-3. Full ^{1}H NMR spectrum of **TCC•THF** (600 MHz, D_2O, 298K).

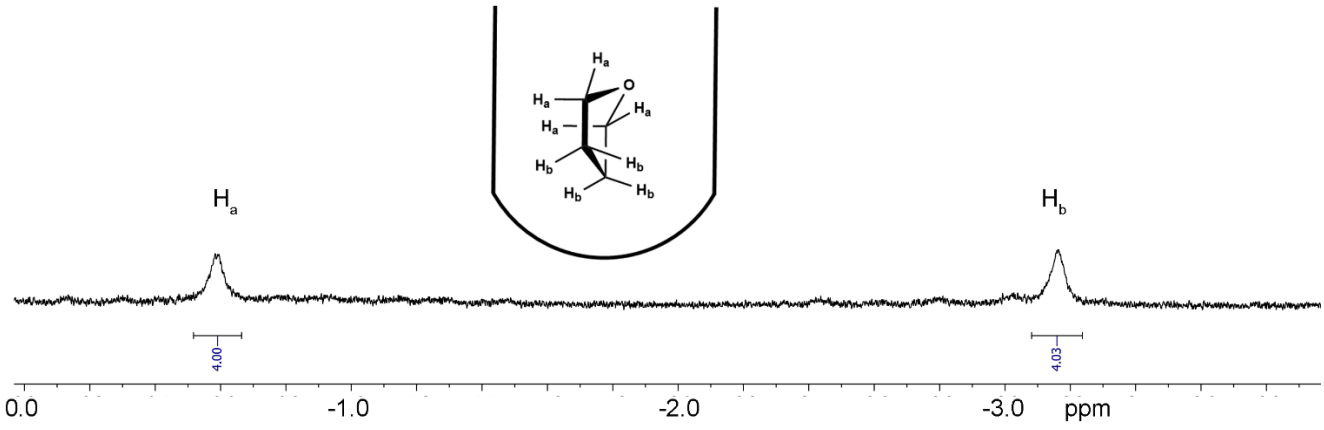


Figure S-4. Upfield region of the ^{1}H NMR spectrum of **TCC•THF** (500 MHz, D_2O, 298K).

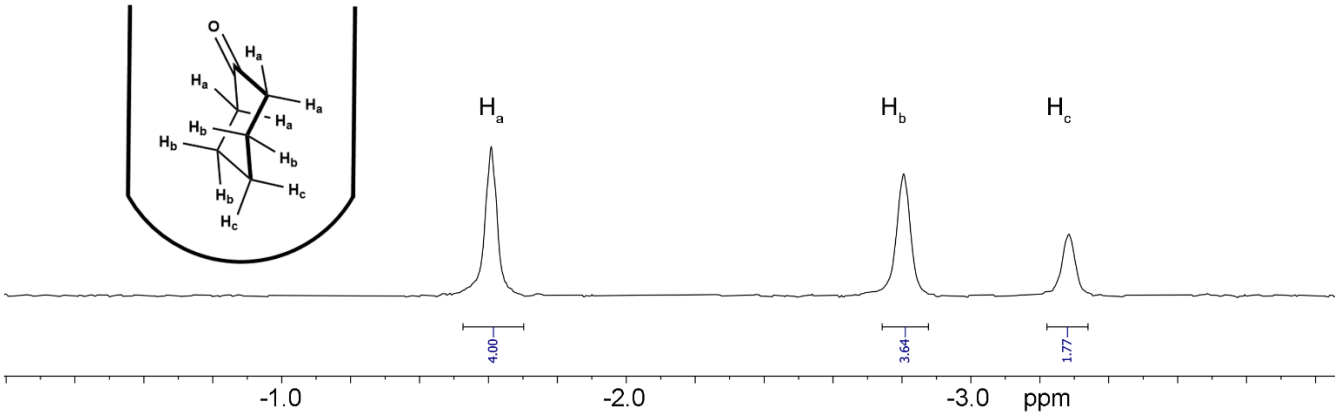


Figure S-5. Upfield region of the ^{1}H NMR spectrum of **TCC•CyO** (500 MHz, D_2O, 298K).

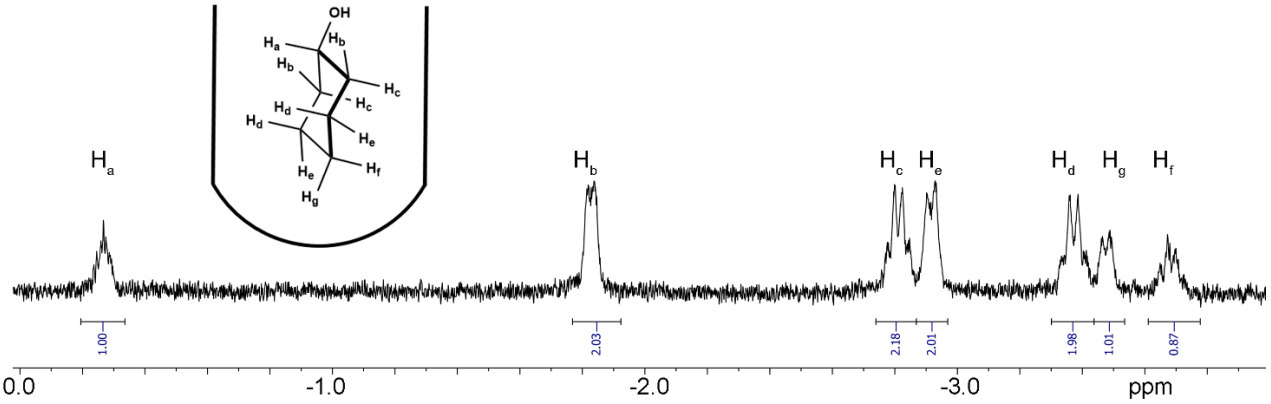


Figure S-6. Upfield region of the ^{1}H NMR spectrum of **TCC•CyOH** (500 MHz, D_2O, 298K).

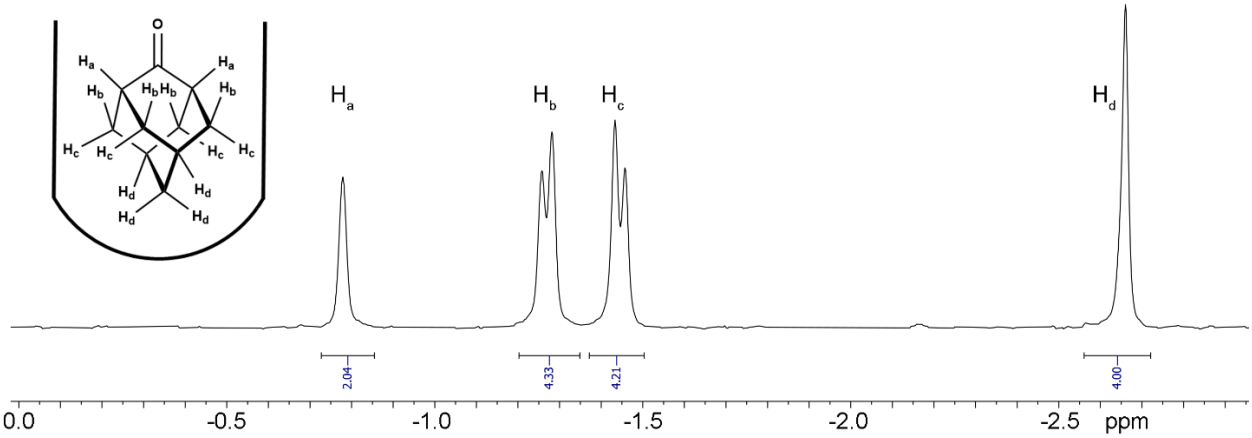


Figure S-7. Upfield region of the ^{1}H NMR spectrum of **TCC•AdO** (500 MHz, D_2O, 298K).

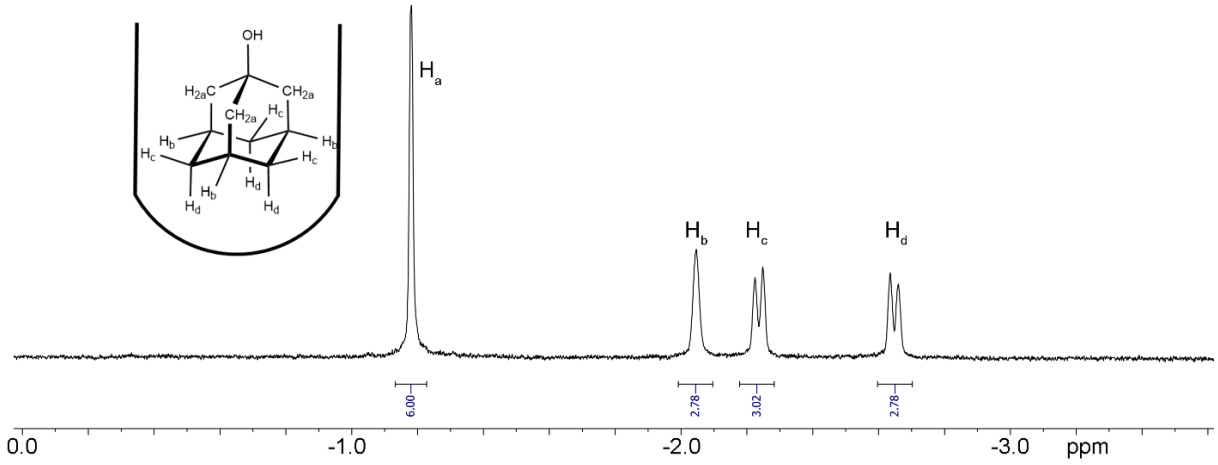


Figure S-8. Upfield region of the ^{1}H NMR spectrum of **TCC•1-AdOH** (500 MHz, D_2O, 298K).

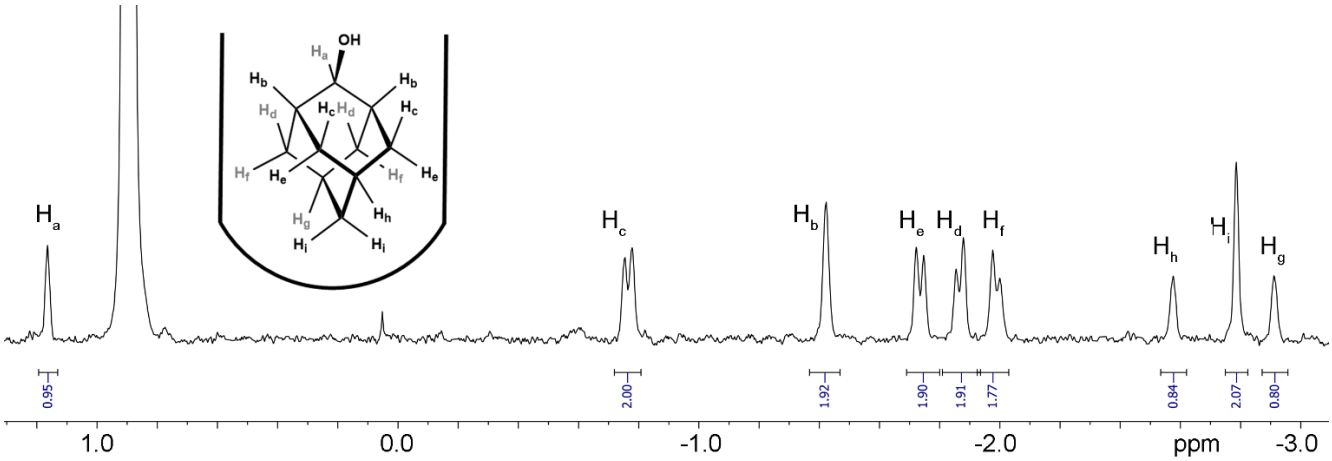


Figure S-9. Upfield region of the ^{1}H NMR spectrum of **TCC•2-AdOH** (500 MHz, D_2O, 298K).

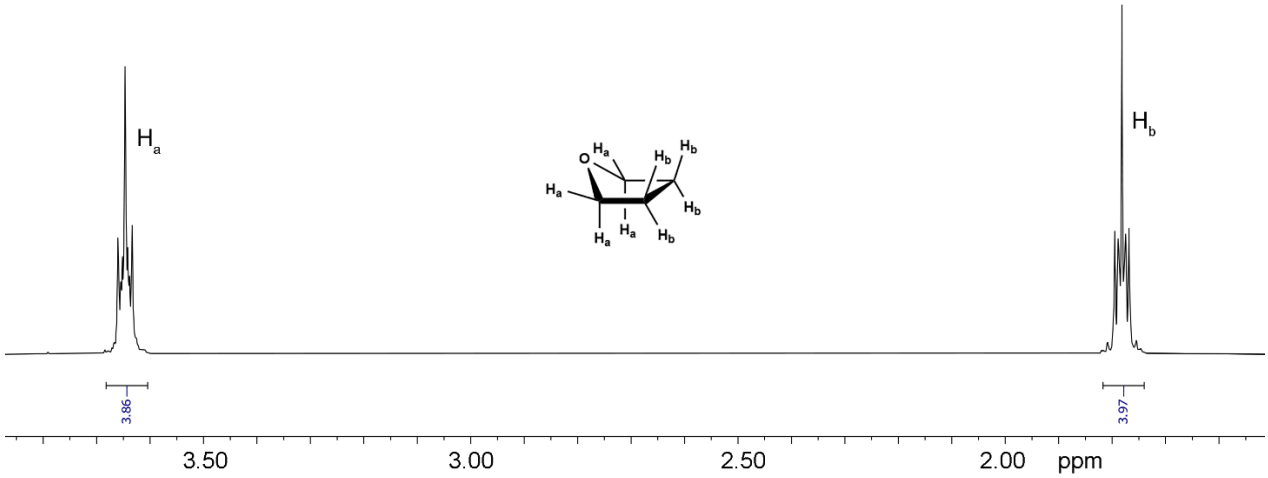


Figure S-10. ^{1}H NMR spectrum of **THF** (500 MHz, D_2O, 298K).

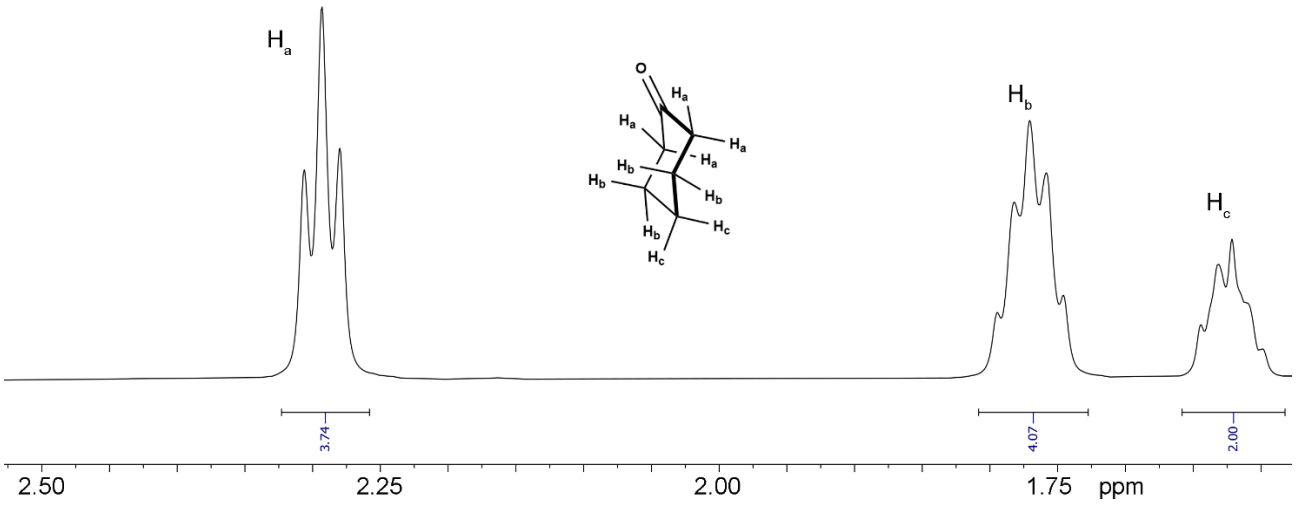


Figure S-11. ^{1}H NMR spectrum of **CyO** (500 MHz, D_2O, 298K).

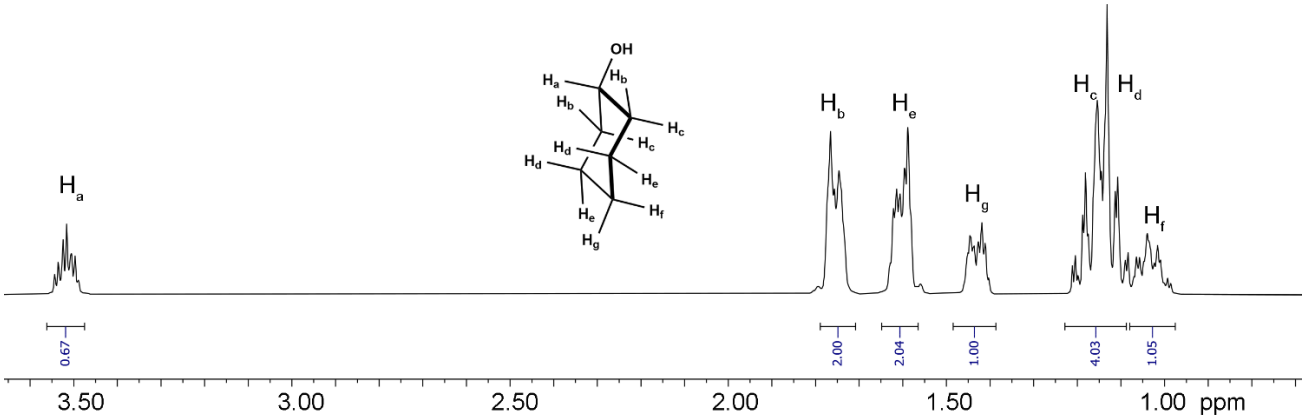


Figure S-12. ^{1}H NMR spectrum of **CyOH** (500 MHz, D_2O, 298K).

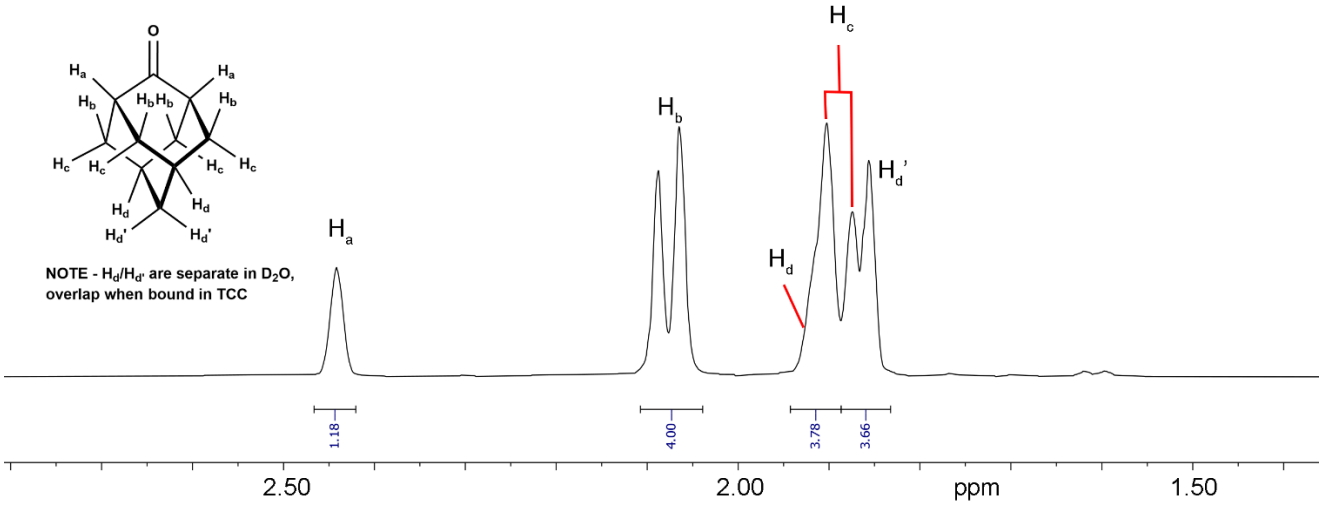


Figure S-13. ^{1}H NMR spectrum of **AdO** (500 MHz, D_2O, 298K).

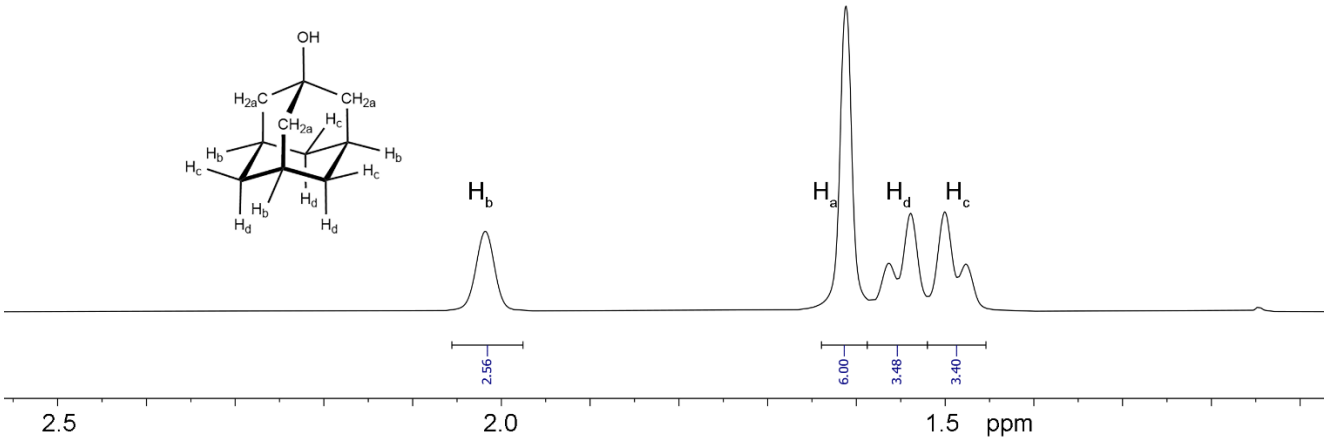


Figure S-14. ^{1}H NMR spectrum of **1-AdOH** (500 MHz, D_2O, 298K).

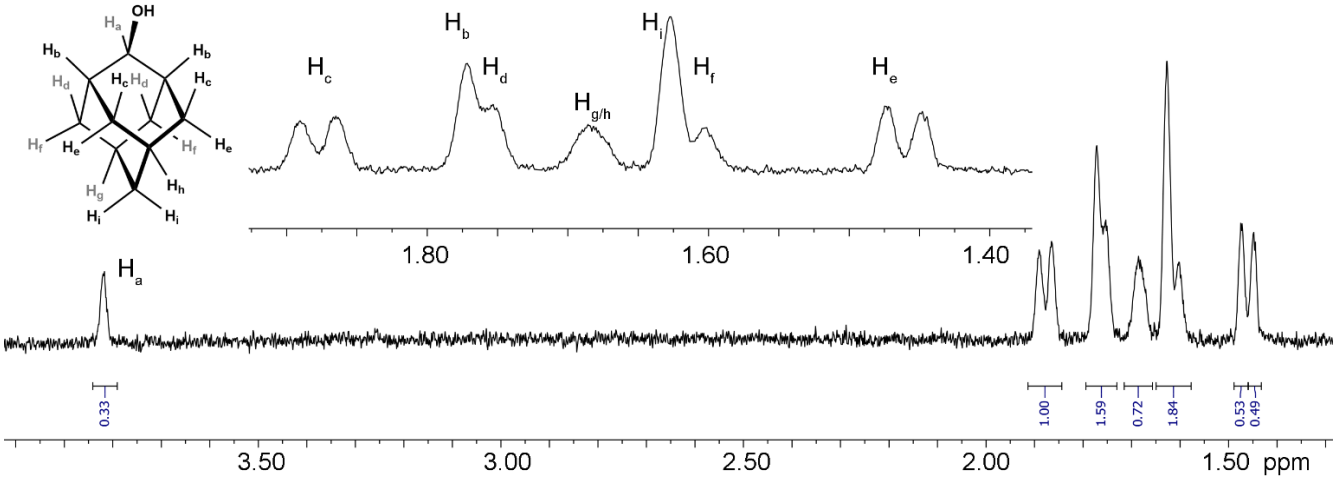


Figure S-15. ^{1}H NMR spectrum of **2-AdOH** (500 MHz, D_2O, 298K).

Relaxation Rate Data – Inversion Recovery (T1) Spectra for Guests and Host:Guest Complexes in D_2O

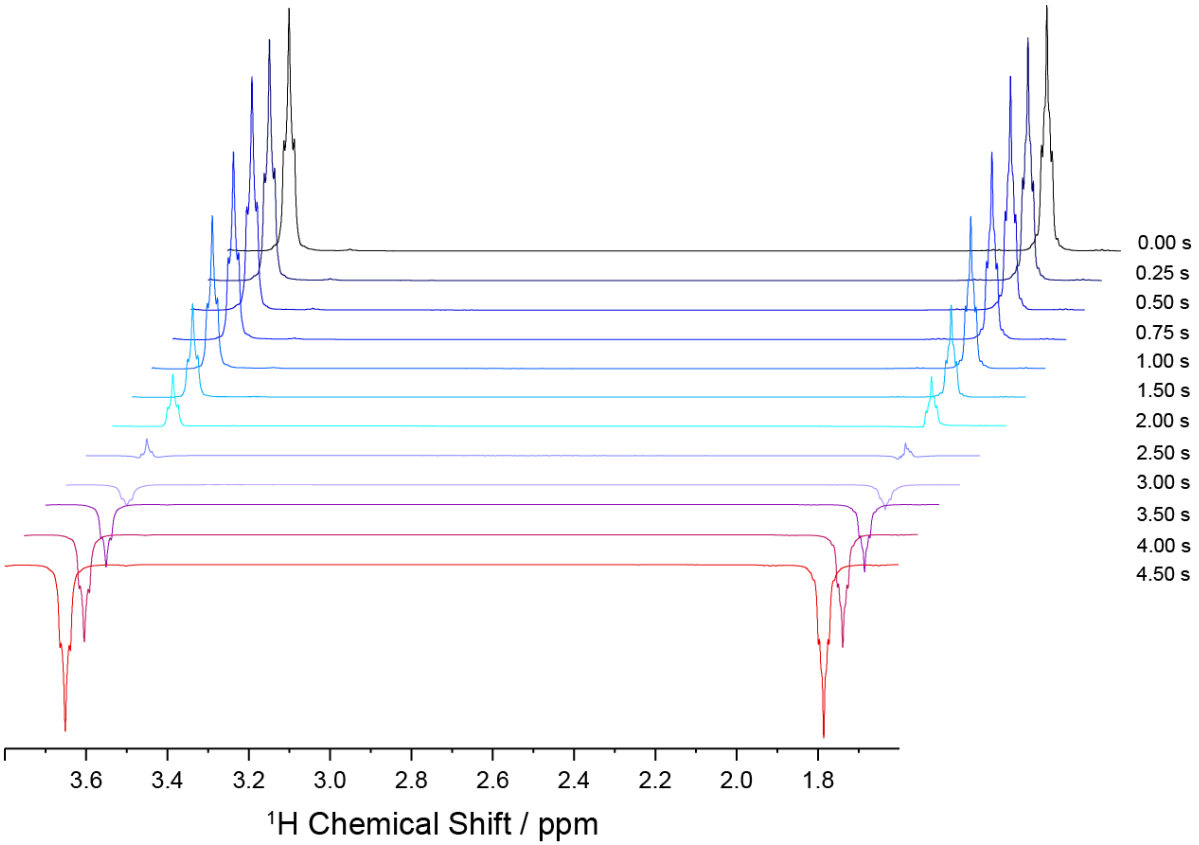


Figure S-16. Stacked NMR spectra for the inversion recovery experiments determining T1 for **THF** in D_2O, [**THF**] = 50 mM, D_2O, 500 MHz, 298 K.

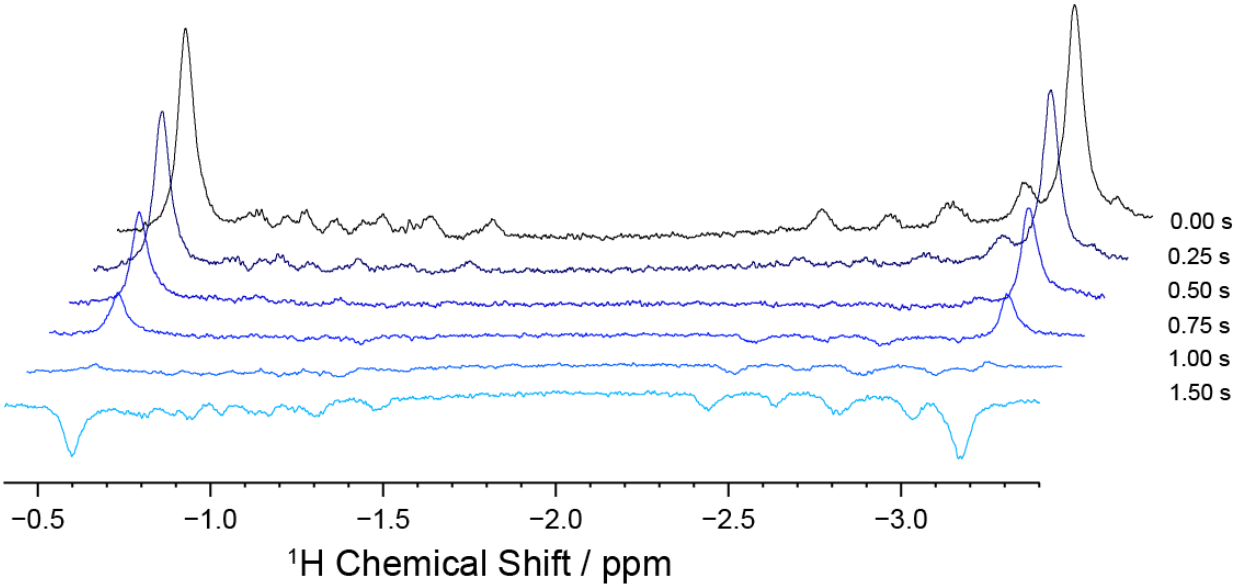


Figure S-17. Stacked NMR spectra for the inversion recovery experiments determining T1 for **THF** bound in **TCC** in D_2O, [**TCC**] = 2 mM, [**THF**] = 2 mM, D_2O, 500 MHz, 298 K.

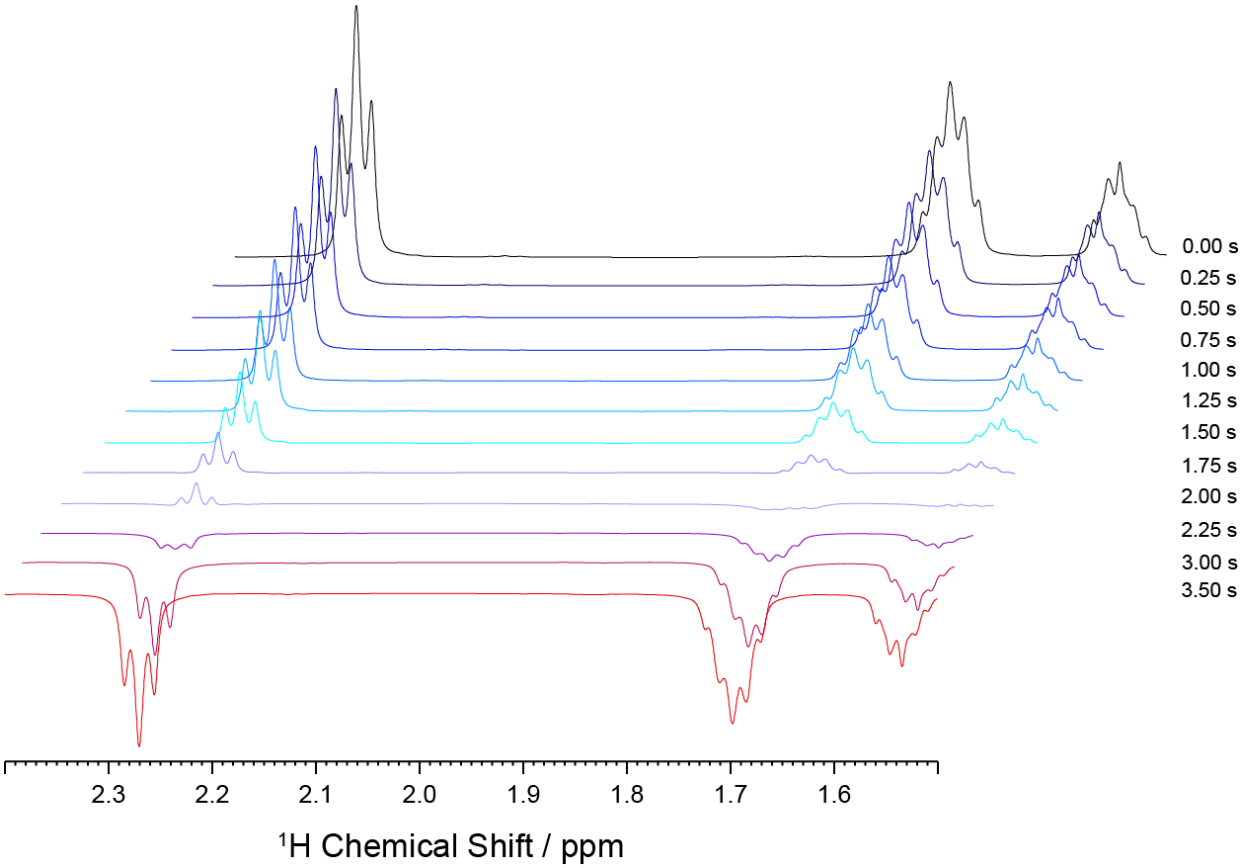


Figure S-18. Stacked NMR spectra for the inversion recovery experiments determining T1 for **CyO** in D_2O, [**CyO**] = 50 mM, D_2O, 500 MHz, 298 K.

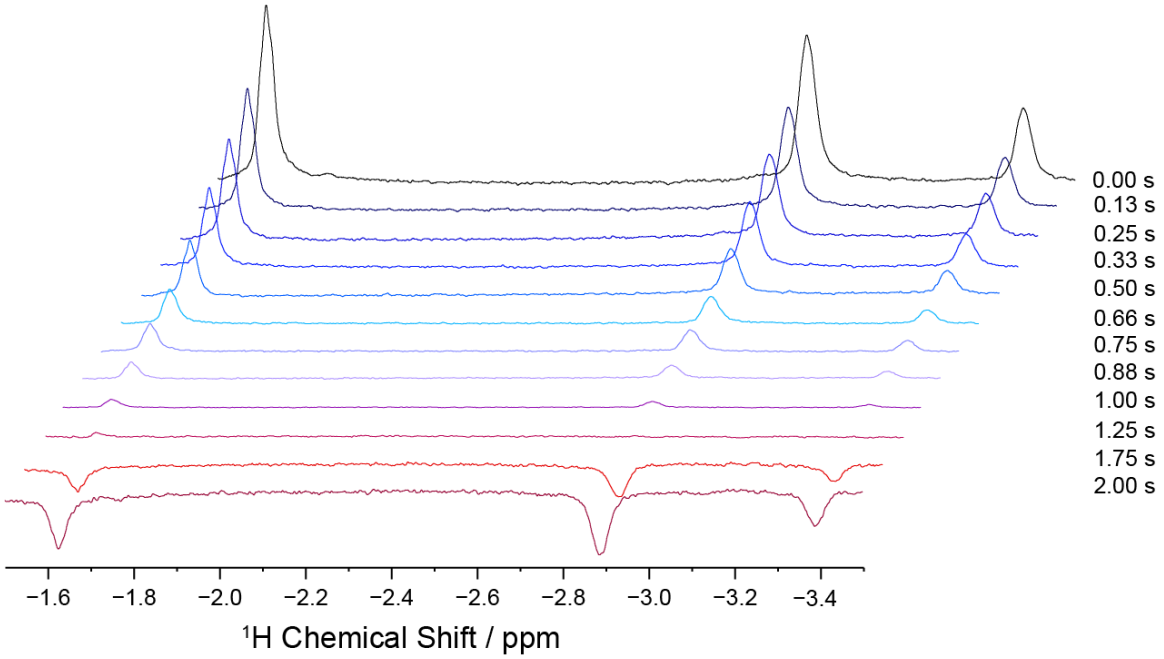


Figure S-19. Stacked NMR spectra for the inversion recovery experiments determining T1 for **CyO** bound in **TCC** in D_2O, [**TCC**] = 2 mM, [**CyO**] = 3 mM, D_2O, 500 MHz, 298 K.

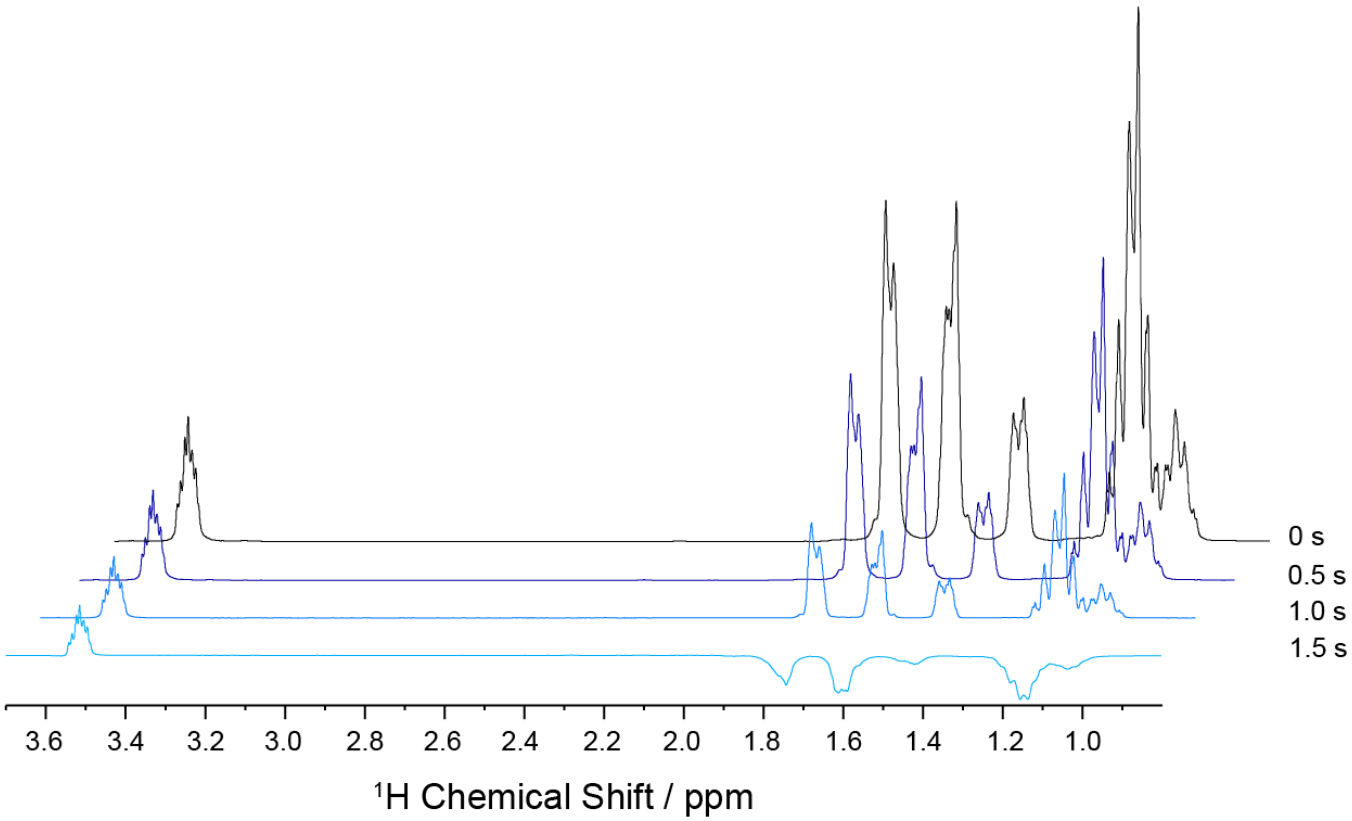


Figure S-20. Stacked NMR spectra for the inversion recovery experiments determining T1 for **CyOH** in D_2O, [**CyOH**] = 70 mM, D_2O, 500 MHz, 298 K.

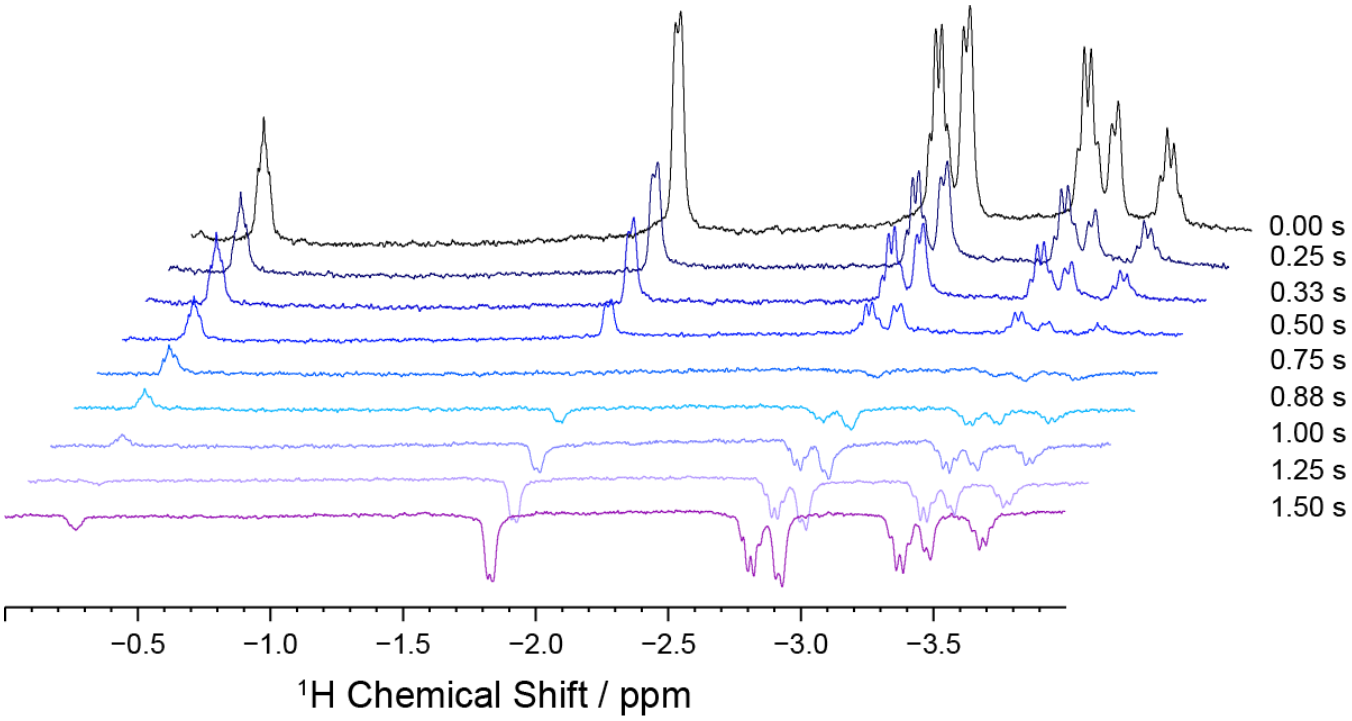


Figure S-21. Stacked NMR spectra for the inversion recovery experiments determining T1 for **CyOH** bound in **TCC** in D_2O, [**TCC**] = 2 mM, [**CyOH**] = 3 mM, D_2O, 500 MHz, 298 K.

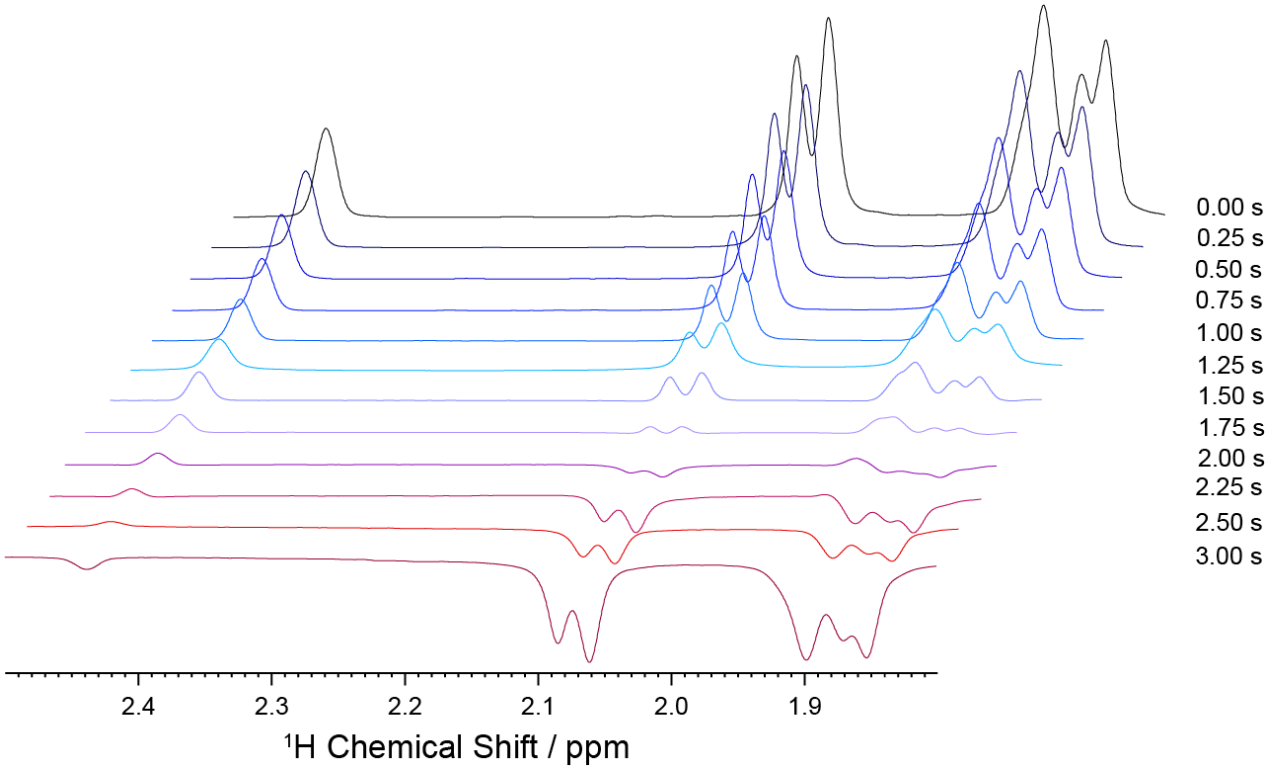


Figure S-22. Stacked NMR spectra for the inversion recovery experiments determining T1 for **AdO** in D_2O, [**AdO**] = 7 mM, D_2O, 500 MHz, 298 K.

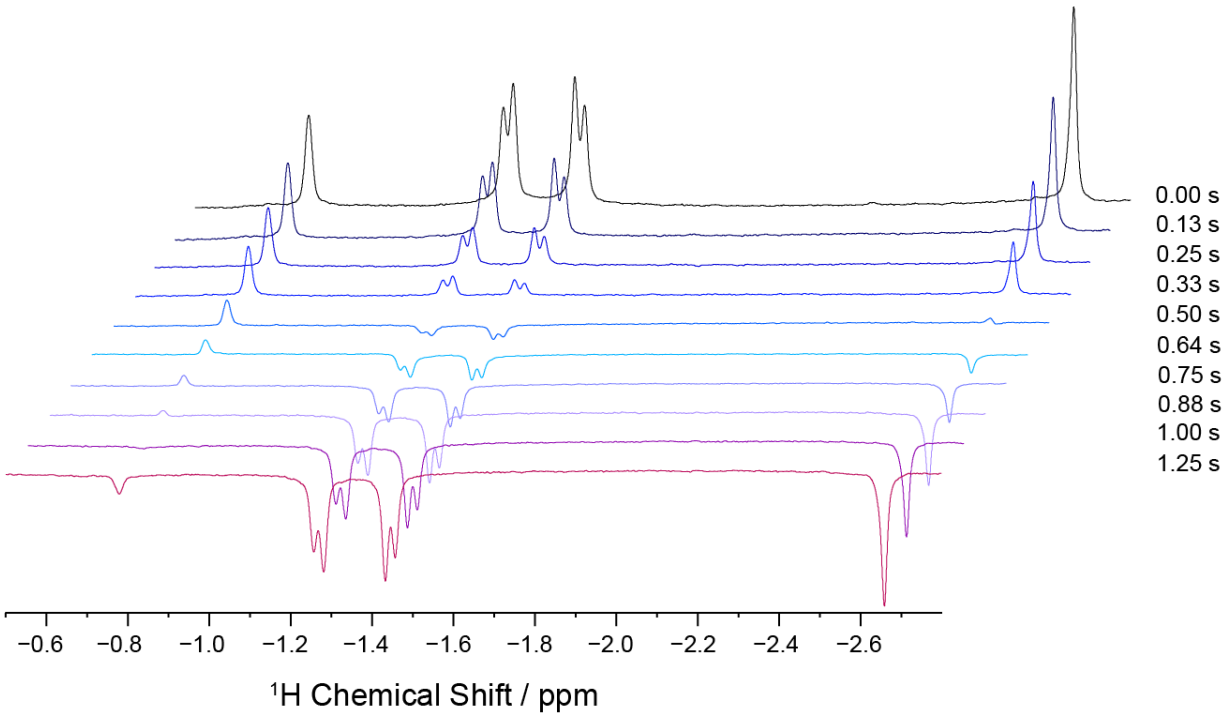


Figure S-23. Stacked NMR spectra for the inversion recovery experiments determining T1 for **AdO** bound in **TCC** in D_2O, [**TCC**] = 2 mM, [**AdO**] = 3 mM, D_2O, 500 MHz, 298 K.

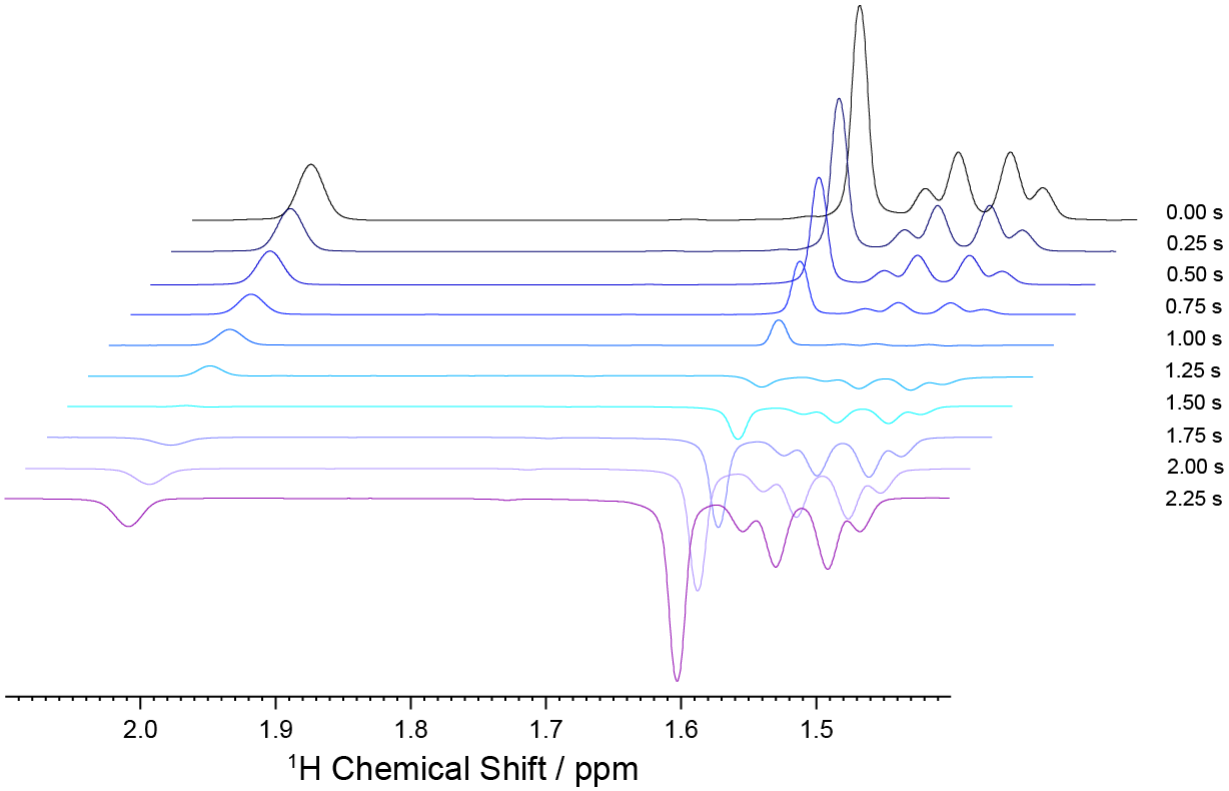


Figure S-24. Stacked NMR spectra for the inversion recovery experiments determining T1 for **1-AdOH** in D_2O, [**1-AdOH**] = 9 mM, D_2O, 500 MHz, 298 K.

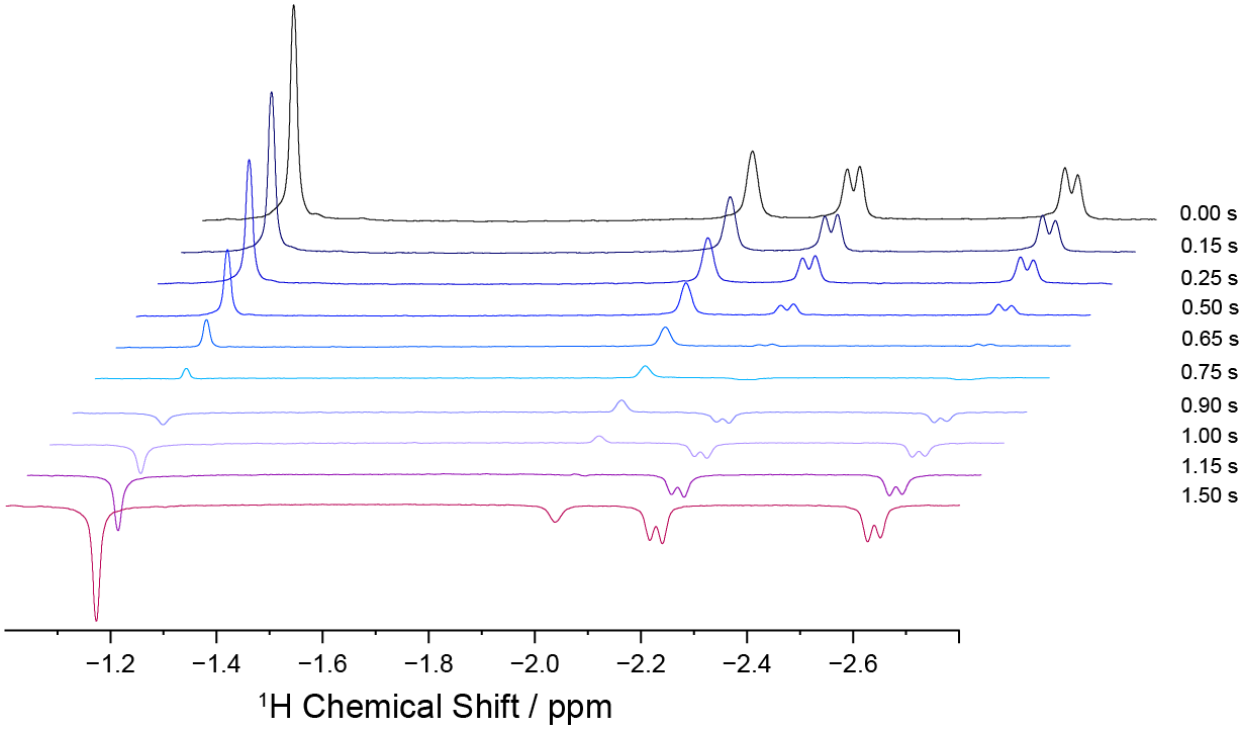


Figure S-25. Stacked NMR spectra for the inversion recovery experiments determining T1 for **1-AdOH** bound in **TCC** in D_2O, [**TCC**] = 2 mM, [**1-AdOH**] = 3 mM, D_2O, 500 MHz, 298 K.

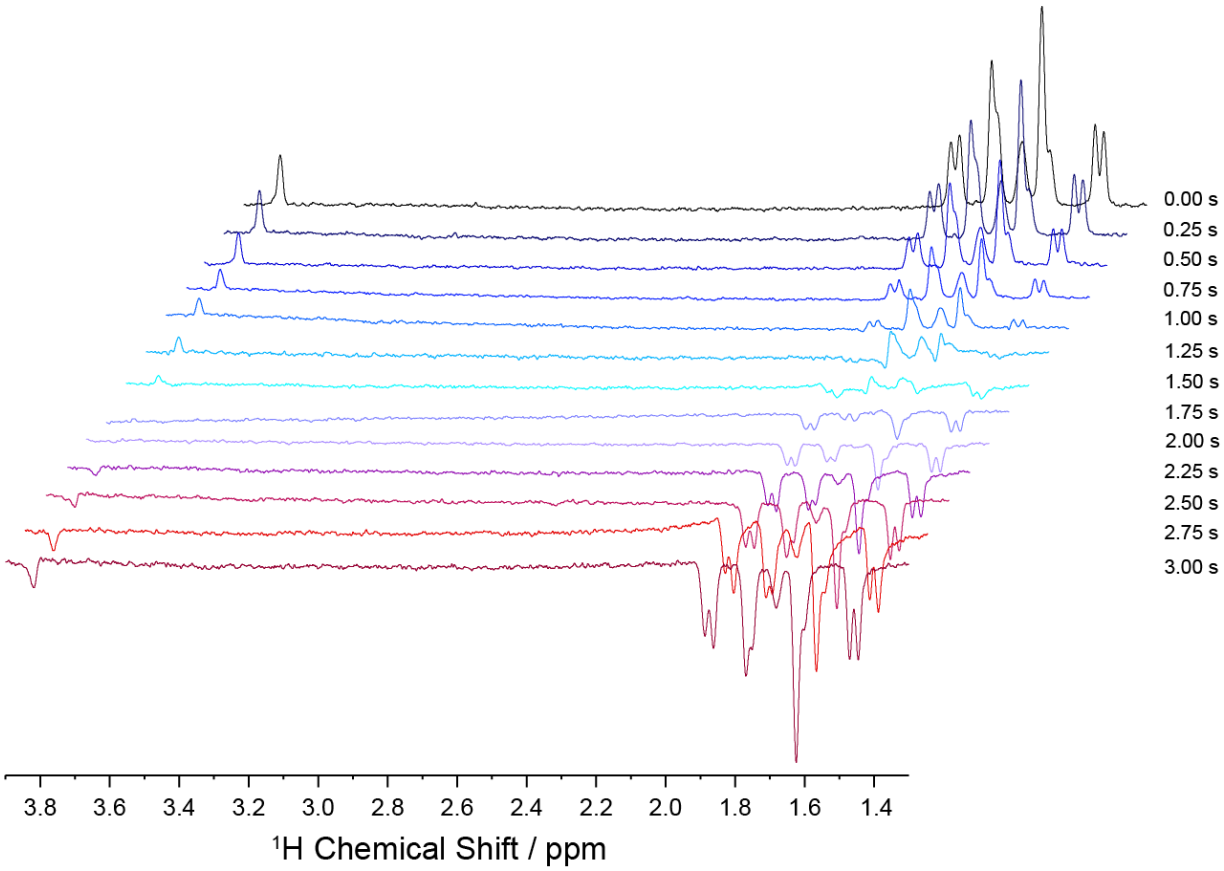


Figure S-26. Stacked NMR spectra for the inversion recovery experiments determining T1 for **2-AdOH** in D_2O, [**2-AdOH**] = 5 mM, D_2O, 500 MHz, 298 K.

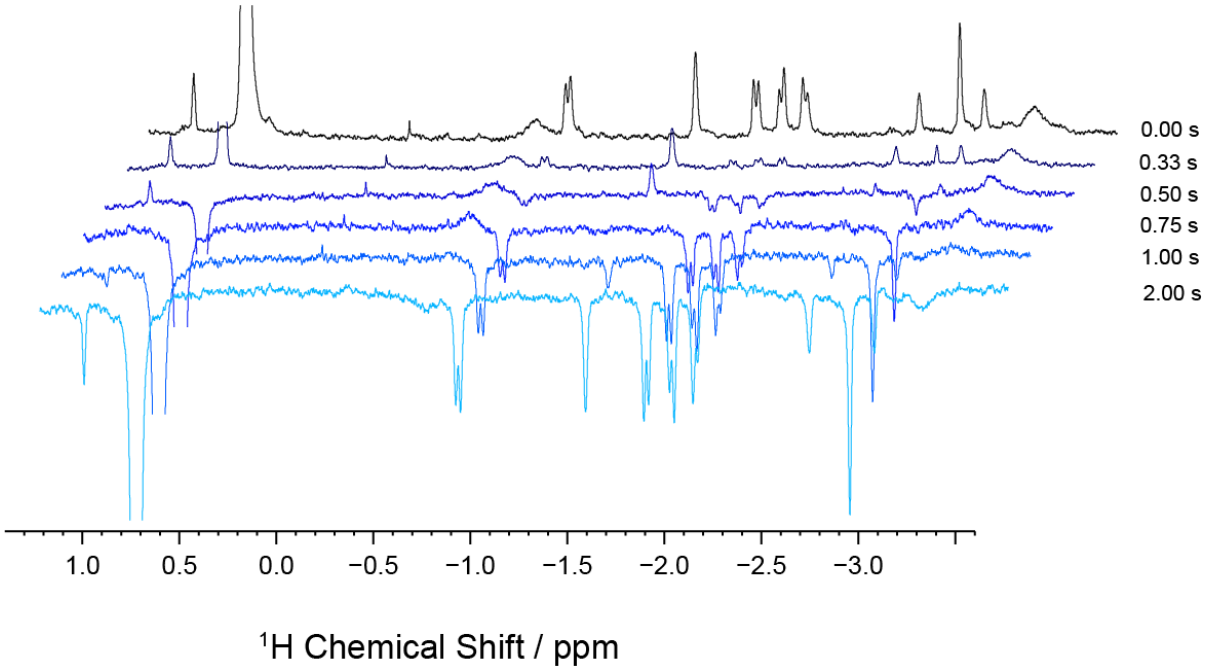


Figure S-27. Stacked NMR spectra for the inversion recovery experiments determining T1 for **2-AdOH** bound in **TCC** in D_2O, [**TCC**] = 2 mM, [**2-AdOH**] = 3 mM, D_2O, 500 MHz, 298 K.

Relaxation Rate Data – Spin Echo (T2) Spectra for Guests and Host:Guest Complexes in D_2O

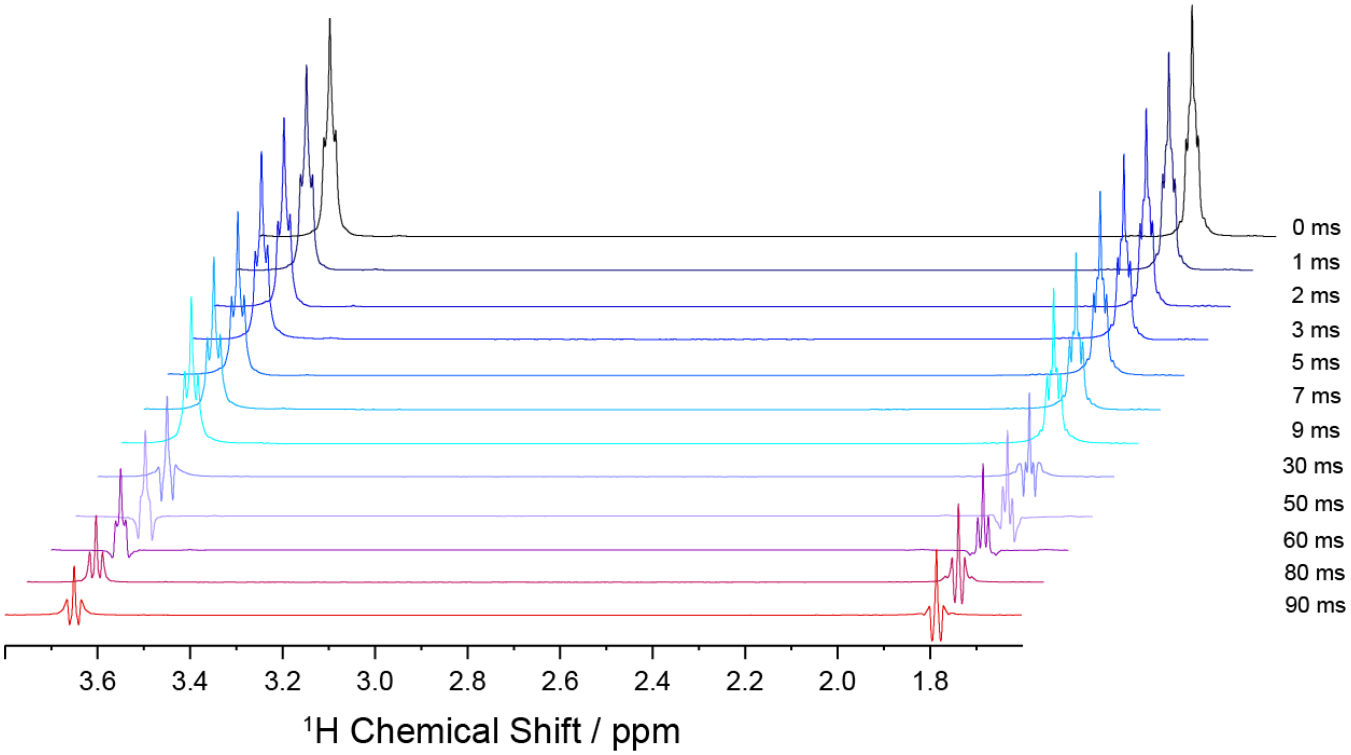


Figure S-28. Stacked NMR spectra for the CPMG-1D spin echo experiments determining T2 for **THF** in D_2O, [**THF**] = 50 mM, D_2O, 500 MHz, 298 K.

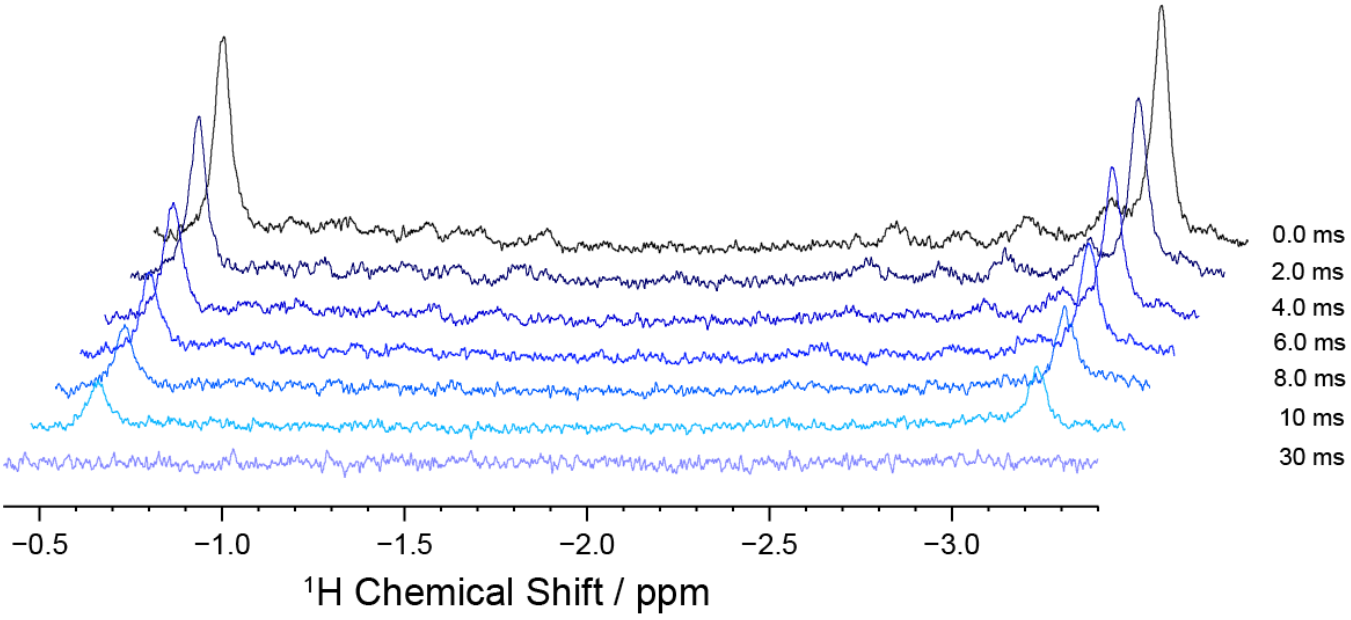


Figure S-29. Stacked NMR spectra for the CPMG-1D spin echo experiments determining T2 for **THF** bound in **TCC** in D_2O, [**TCC**] = 2 mM, [**THF**] = 2 mM, D_2O, 500 MHz, 298 K.

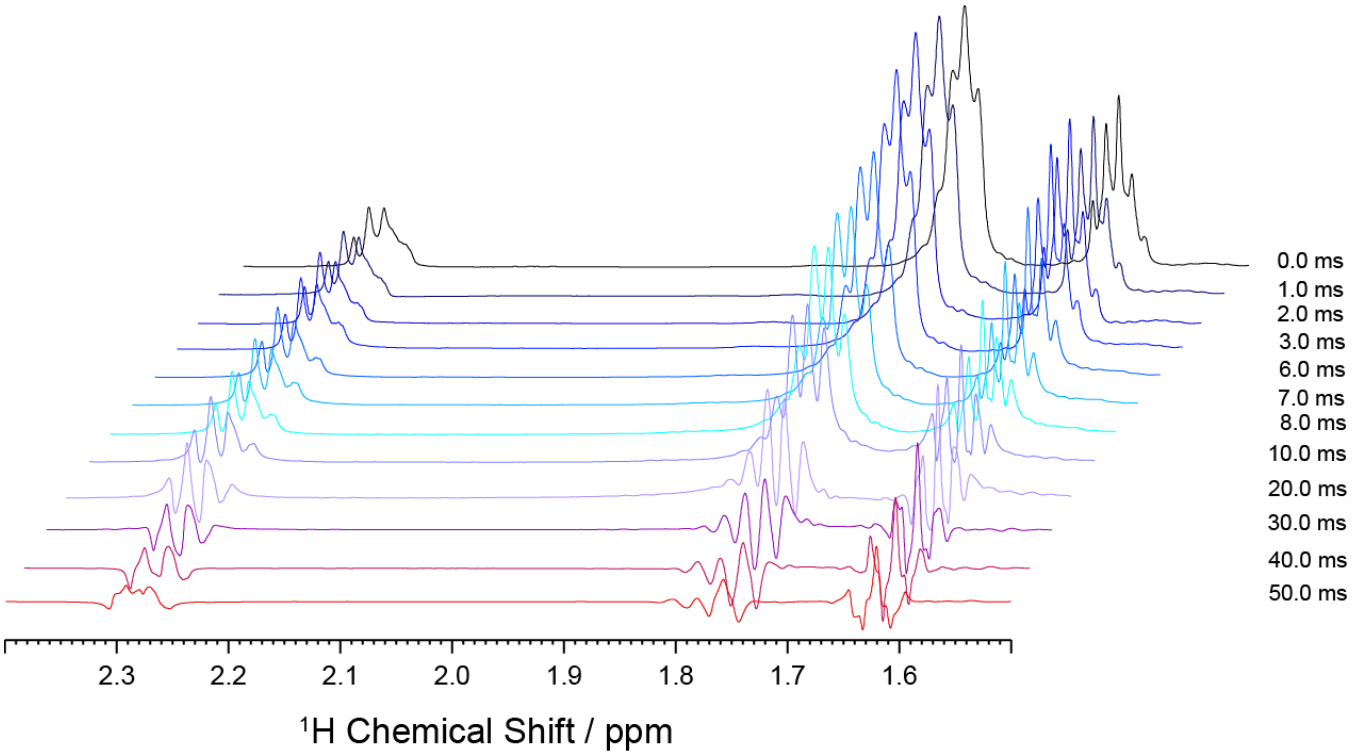


Figure S-30. Stacked NMR spectra for the CPMG-1D spin echo experiments determining T2 for **CyO** in D_2O, [**CyO**] = 50 mM, D_2O, 500 MHz, 298 K.

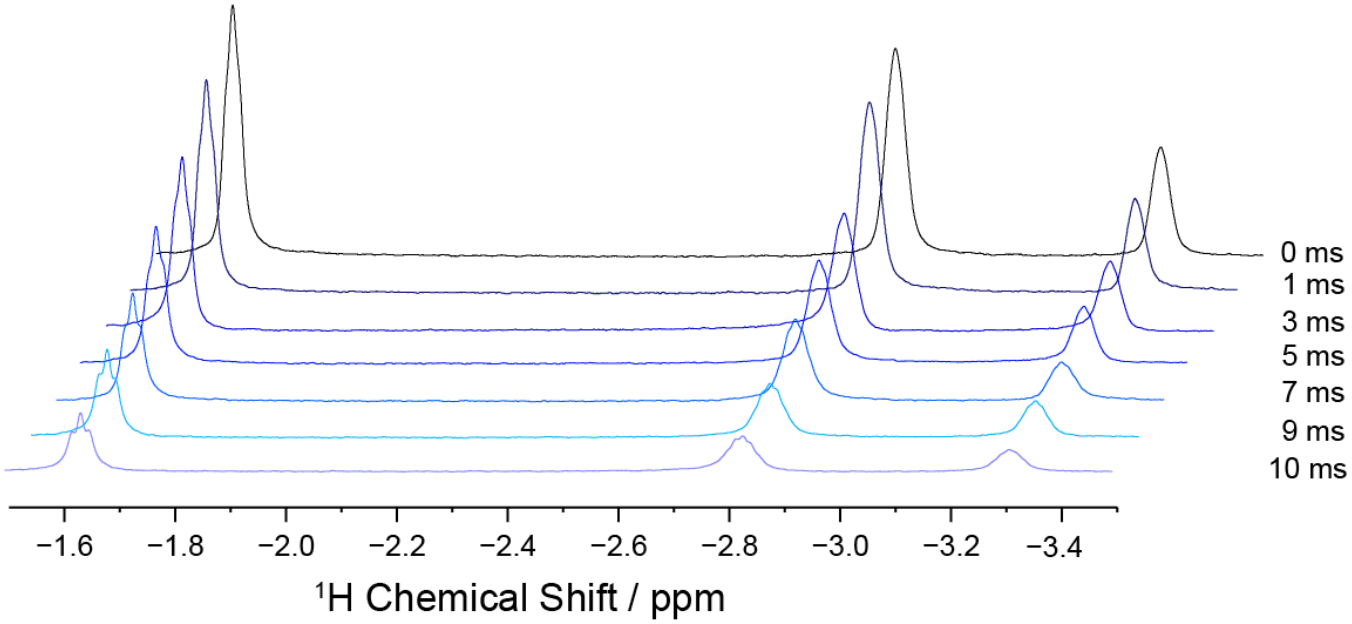


Figure S-31. Stacked NMR spectra for the CPMG-1D spin echo experiments determining T2 for **CyO** bound in **TCC** in D_2O, [**TCC**] = 2 mM, [**CyO**] = 3 mM, D_2O, 500 MHz, 298 K.

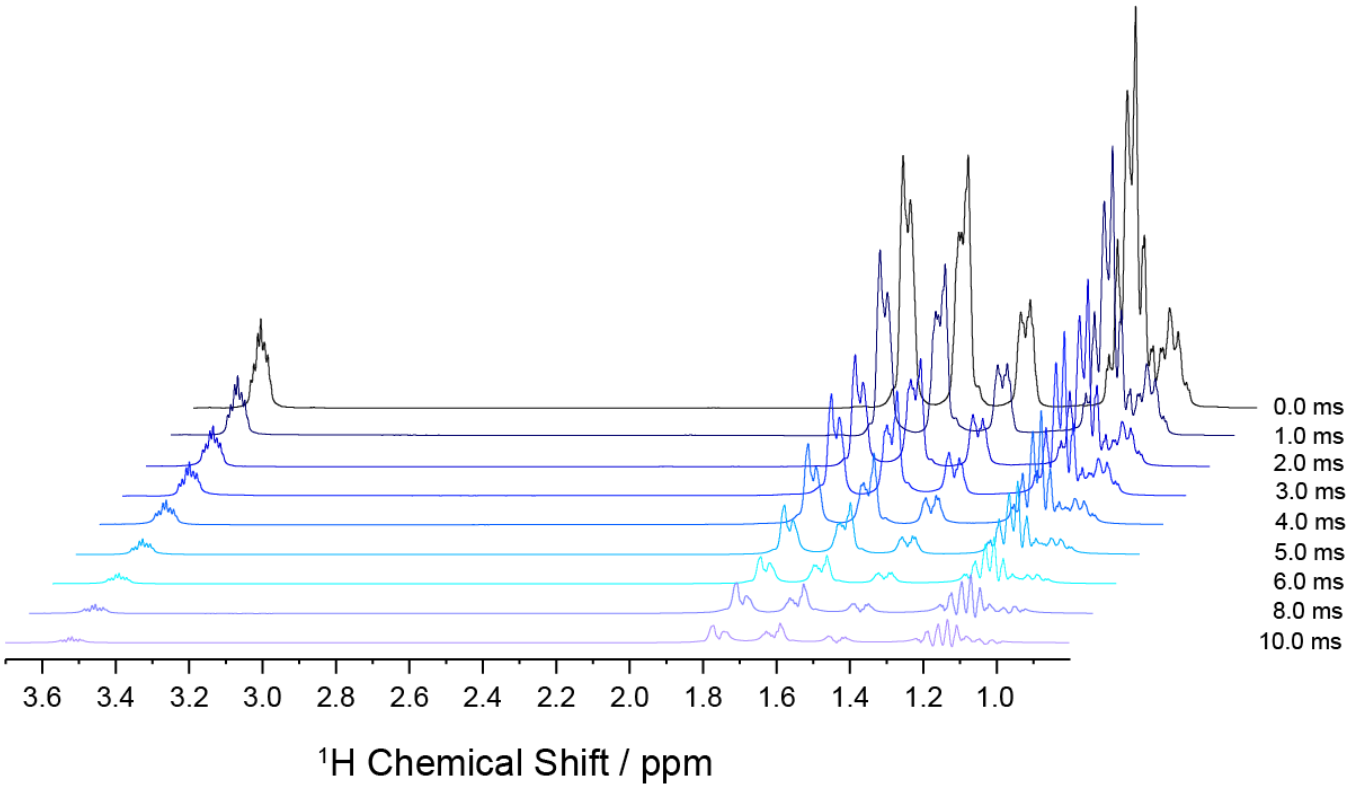


Figure S-32. Stacked NMR spectra for the CPMG-1D spin echo experiments determining T2 for **CyOH** in D_2O, [**CyOH**] = 70 mM, D_2O, 500 MHz, 298 K.

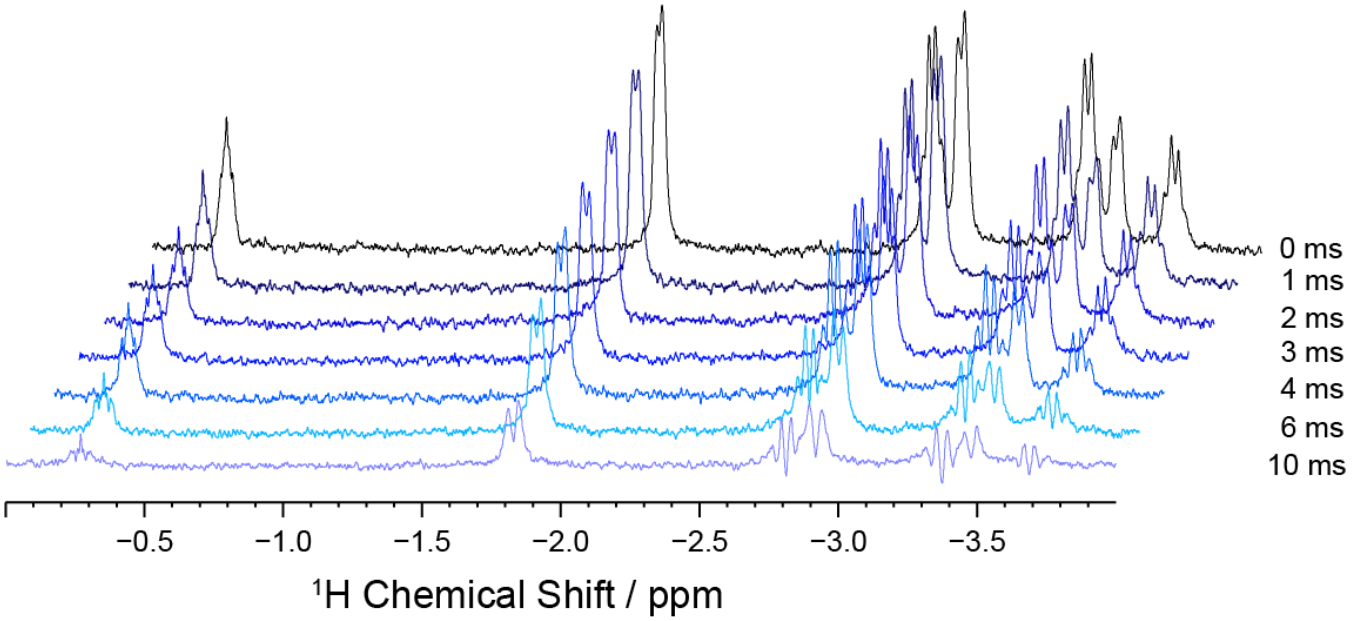


Figure S-33. Stacked NMR spectra for the CPMG-1D spin echo experiments determining T2 for **CyOH** bound in **TCC** in D_2O, [**TCC**] = 2 mM, [**CyOH**] = 3 mM, D_2O, 500 MHz, 298 K.

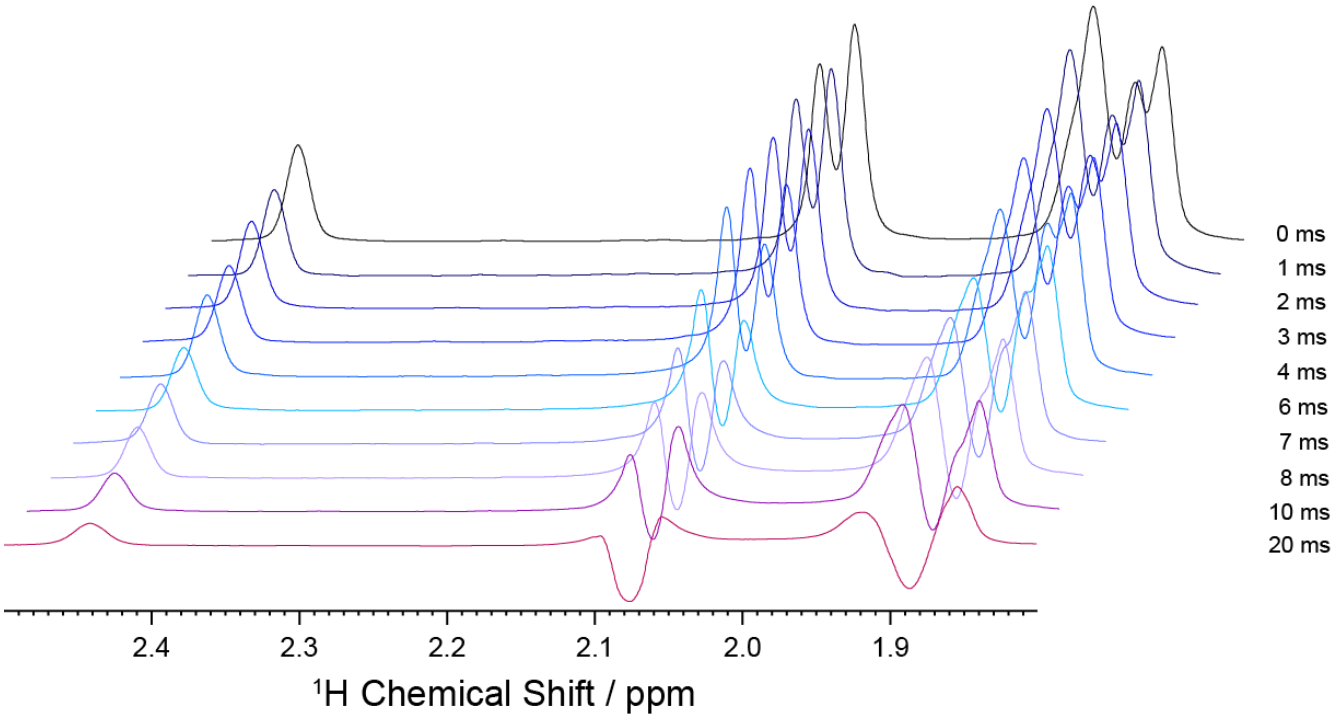


Figure S-34. Stacked NMR spectra for the CPMG-1D spin echo experiments determining T2 for **AdO** in D_2O, [**AdO**] = 7 mM, D_2O, 500 MHz, 298 K.

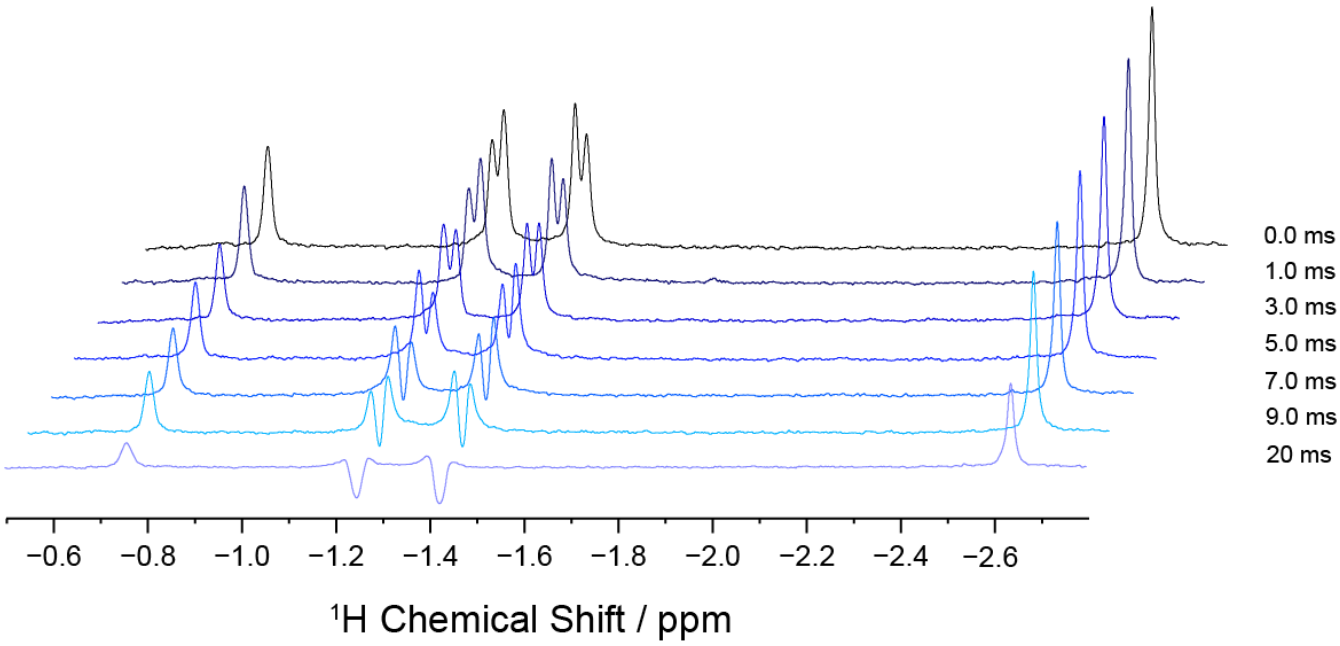


Figure S-35. Stacked NMR spectra for the CPMG-1D spin echo experiments determining T2 for **AdO** bound in **TCC** in D_2O, [**TCC**] = 2 mM, [**AdO**] = 3 mM, D_2O, 500 MHz, 298 K.

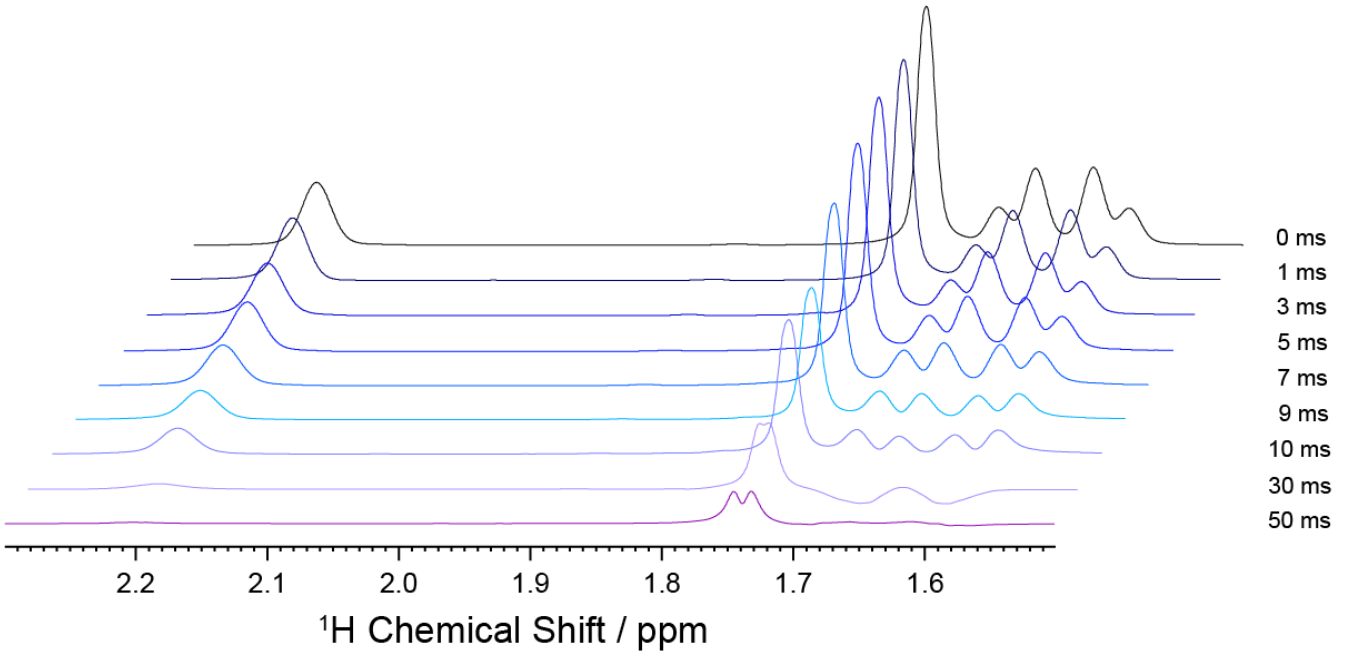


Figure S-36. Stacked NMR spectra for the CPMG-1D spin echo experiments determining T2 for **1-AdOH** in D_2O, [**1-AdOH**] = 9 mM, D_2O, 500 MHz, 298 K.

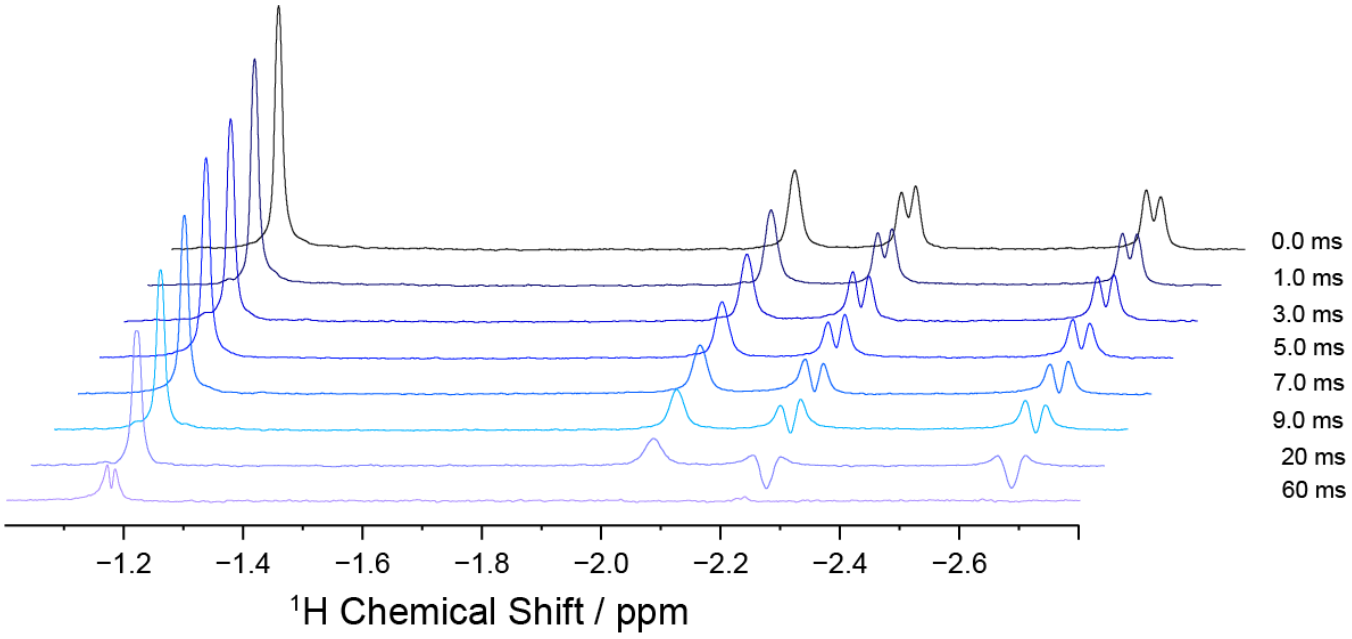


Figure S-37. Stacked NMR spectra for the CPMG-1D spin echo experiments determining T2 for **1-AdOH** bound in **TCC** in D_2O, [**TCC**] = 2 mM, [**1-AdOH**] = 3 mM, D_2O, 500 MHz, 298 K.

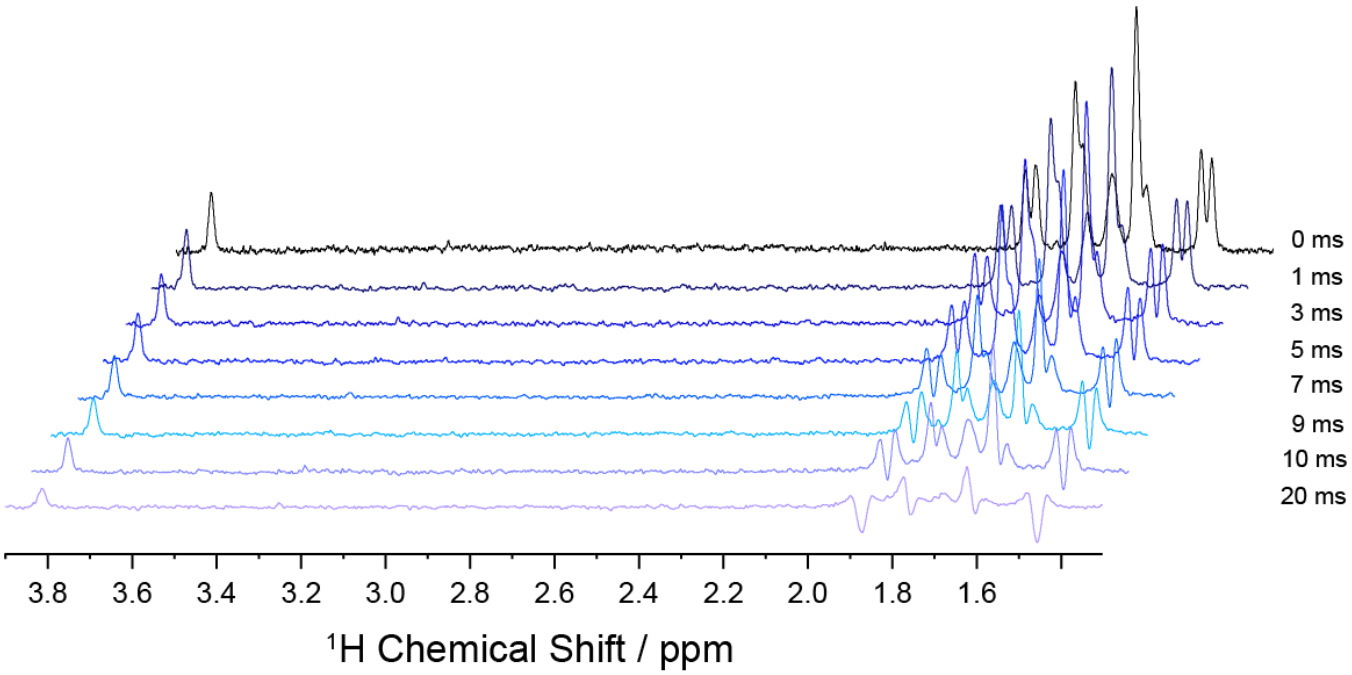


Figure S-38. Stacked NMR spectra for the CPMG-1D spin echo experiments determining T2 for **2-AdOH** in D_2O, [**2-AdOH**] = 5 mM, D_2O, 500 MHz, 298 K.

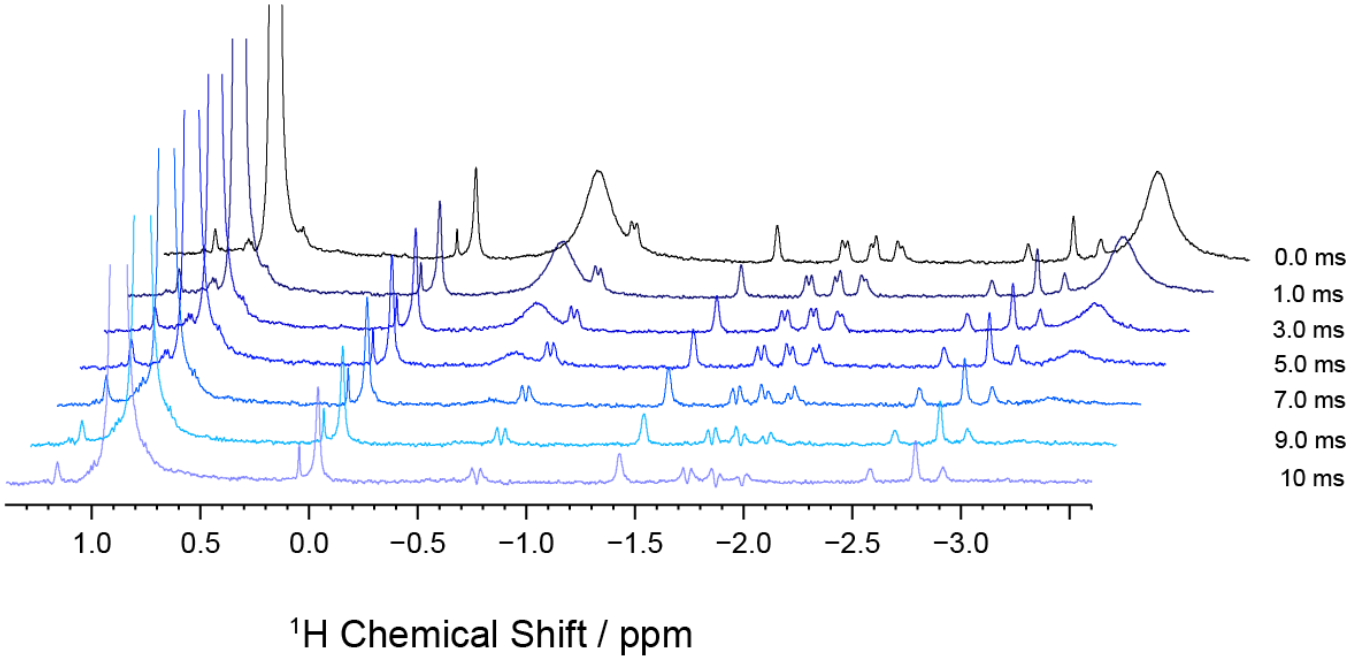


Figure S-39. Stacked NMR spectra for the CPMG-1D spin echo experiments determining T2 for **2-AdOH** bound in **TCC** in D_2O, [**TCC**] = 2 mM, [**2-AdOH**] = 3 mM, D_2O, 500 MHz, 298 K.

Control Experiments – T1 and T2 Spectra for Guests in non-D_2O solvents and of TCC

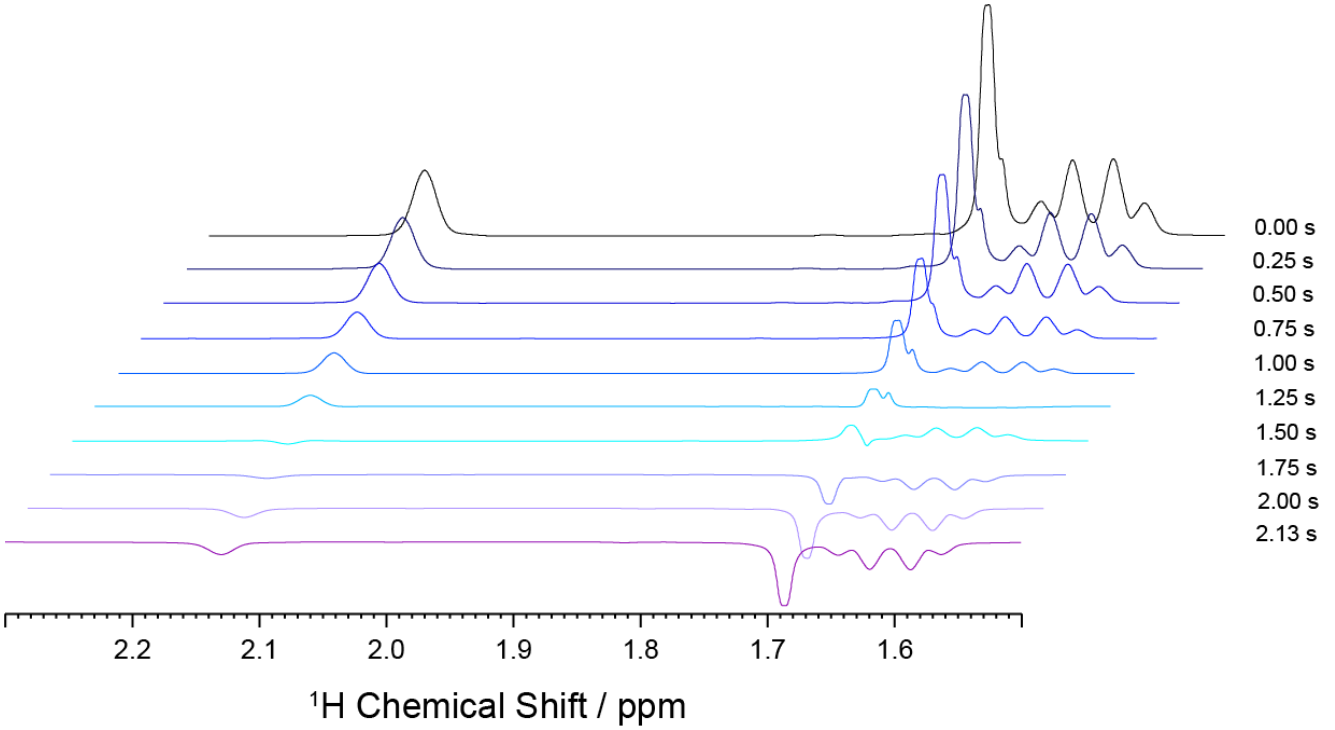


Figure S-40. Stacked NMR spectra for the inversion recovery experiments determining T1 for **1-AdOH** in TCE-d_2, [**1-AdOH**] = 70 mM, $C_2D_2Cl_4$, 500 MHz, 298 K.

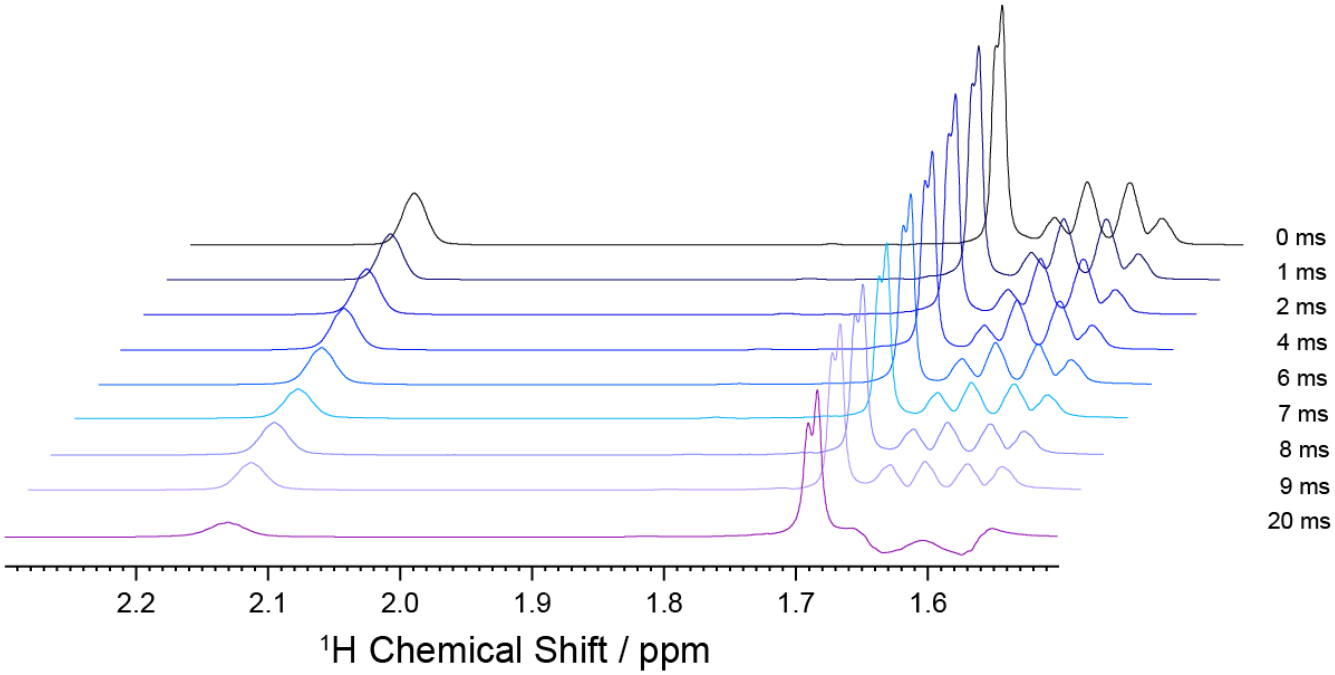


Figure S-41. Stacked NMR spectra for the CPMG-1D spin echo experiments determining T2 for **1-AdOH** in TCE-d_2, [**1-AdOH**] = 70 mM, $C_2D_2Cl_4$, 500 MHz, 298 K.

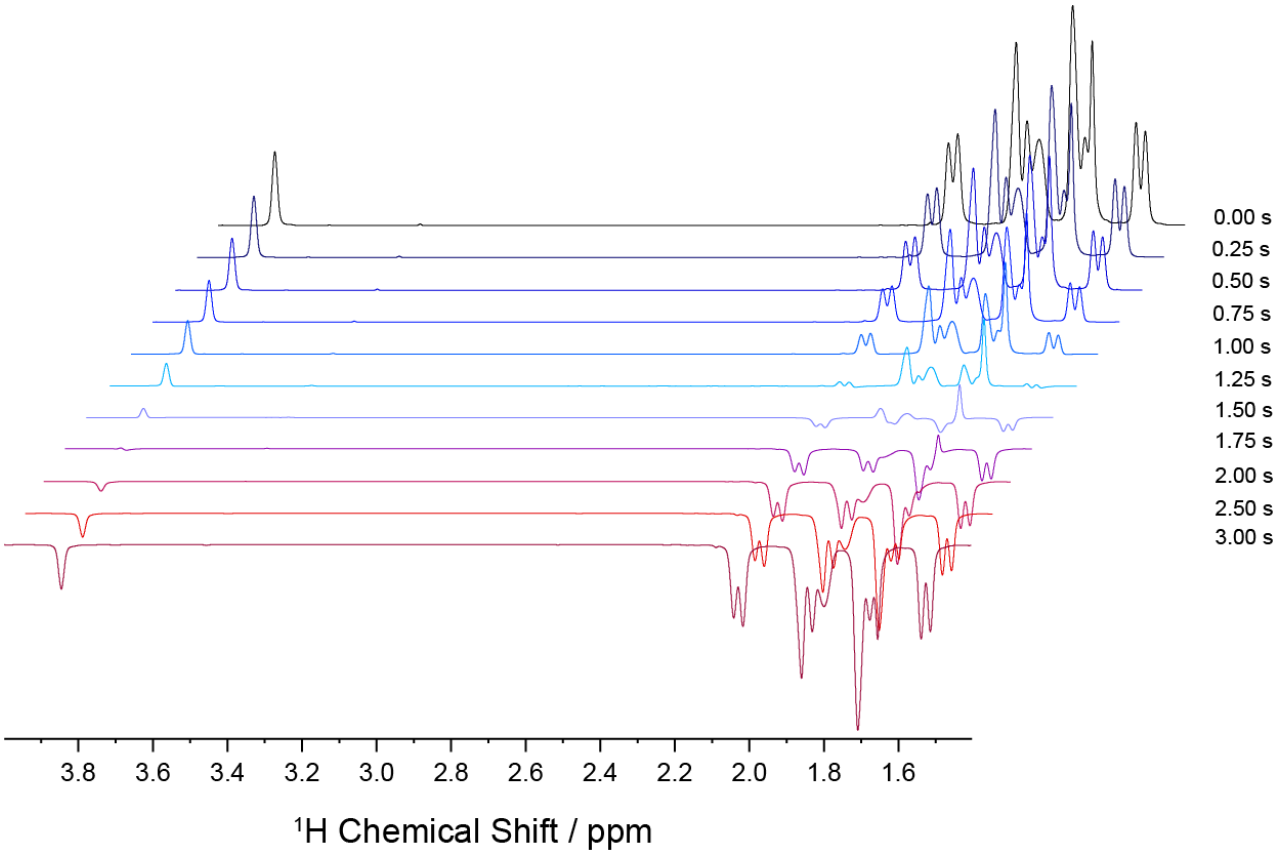


Figure S-42. Stacked NMR spectra for the inversion recovery experiments determining T1 for **2-AdOH** in TCE-d_2, [**2-AdOH**] = 50 mM, $C_2D_2Cl_4$, 500 MHz, 298 K.

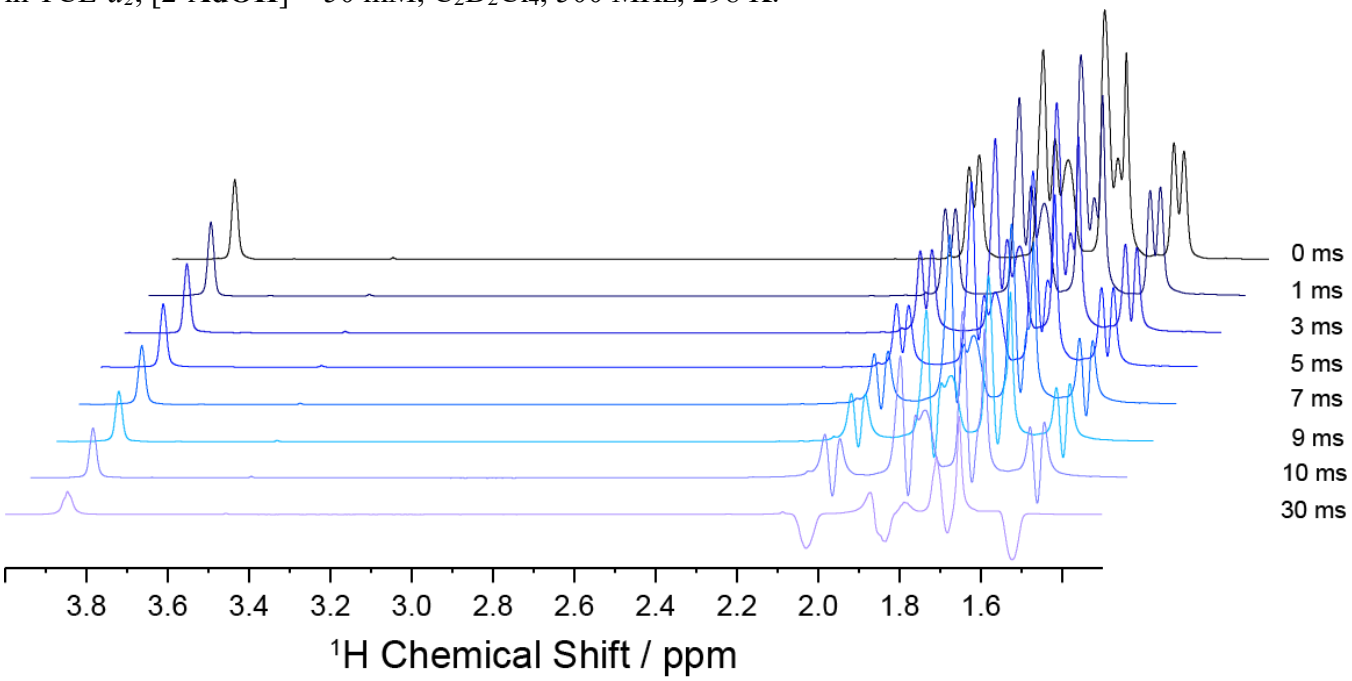


Figure S-43. Stacked NMR spectra for the CPMG-1D spin echo experiments determining T2 for **2-AdOH** in TCE-d_2, [**2-AdOH**] = 50 mM, $C_2D_2Cl_4$, 500 MHz, 298 K.

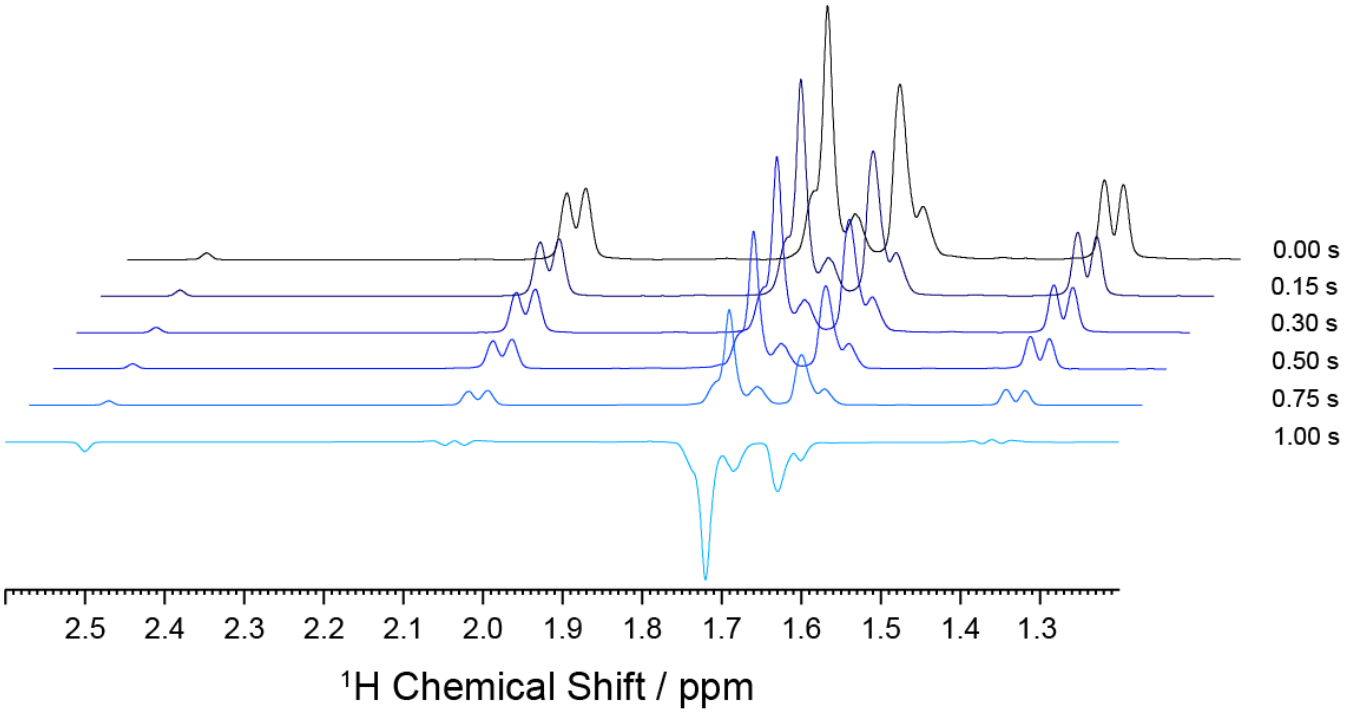


Figure S-44. Stacked NMR spectra for the inversion recovery experiments determining T1 for **2-AdOH** in DMSO-d_6, [**2-AdOH**] = 42 mM, DMSO-d_6, 500 MHz, 298 K.

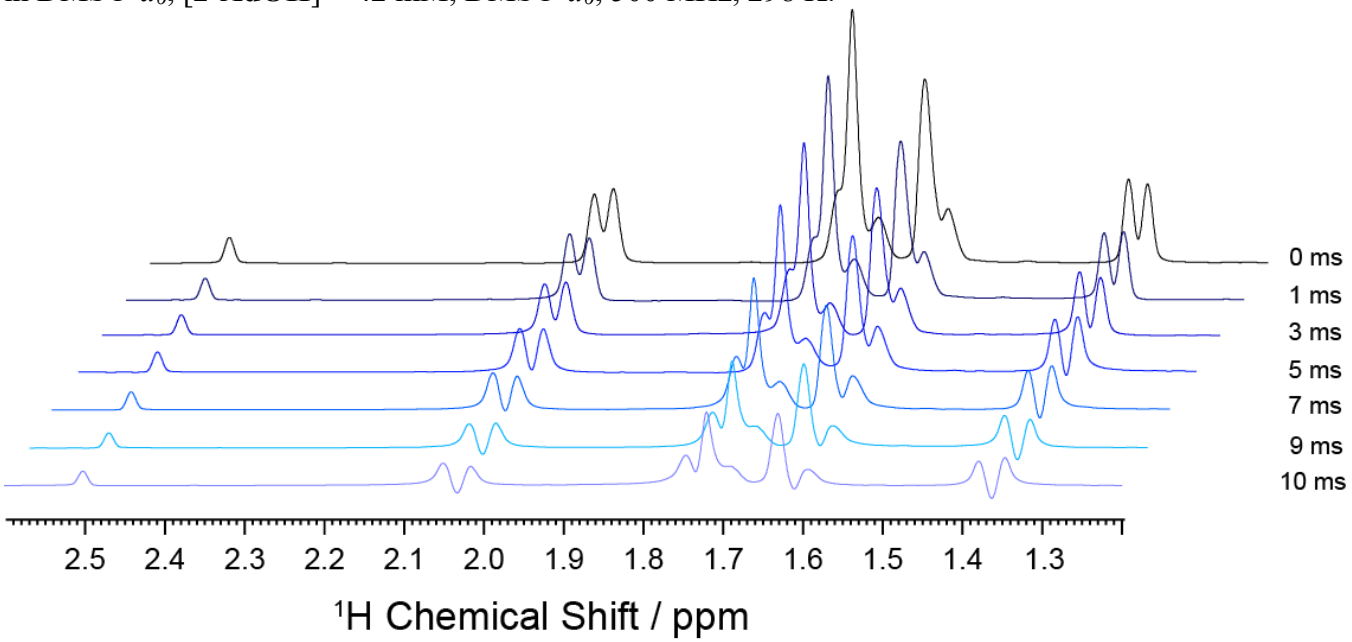


Figure S-45. Stacked NMR spectra for the CPMG-1D spin echo experiments determining T2 for **2-AdOH** in DMSO-d_6, [**2-AdOH**] = 42 mM, DMSO-d_6, 500 MHz, 298 K.

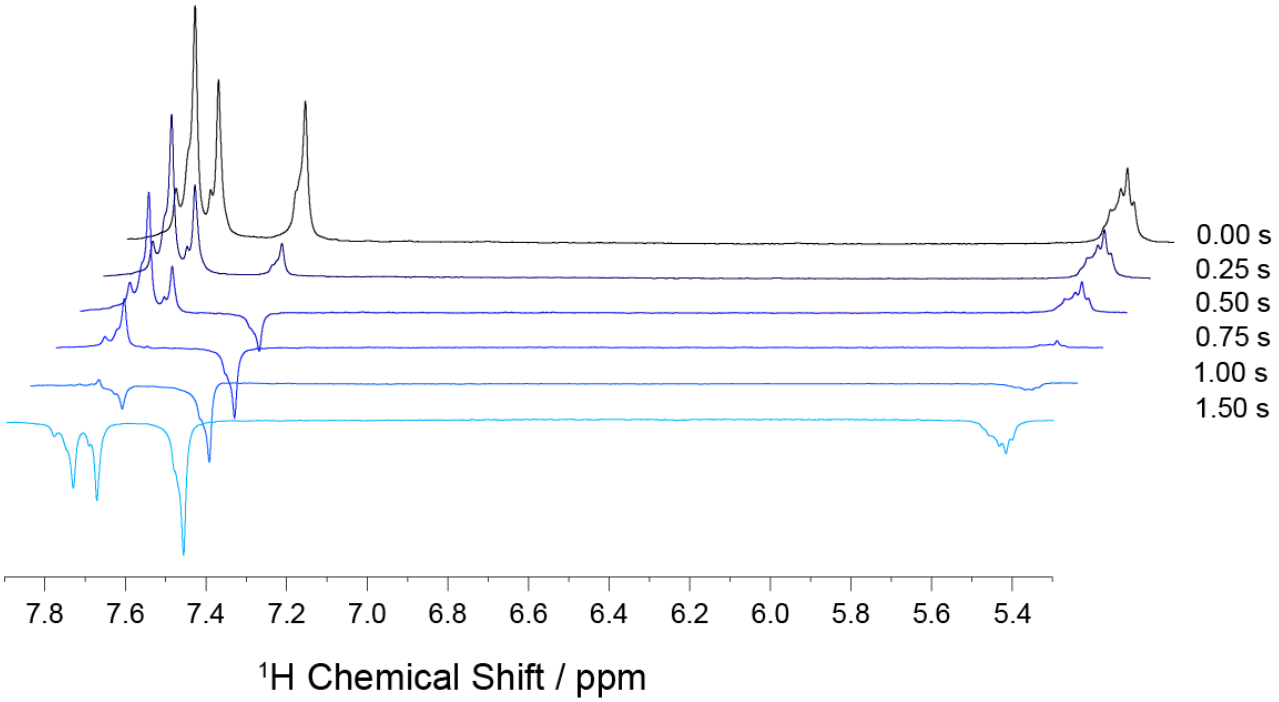


Figure S-46. Stacked NMR spectra for the inversion recovery experiments determining T1 for **TCC** with **THF** guest in D_2O, [**TCC**] = 2 mM, [**THF**] = 2 mM, D_2O, 500 MHz, 298 K.

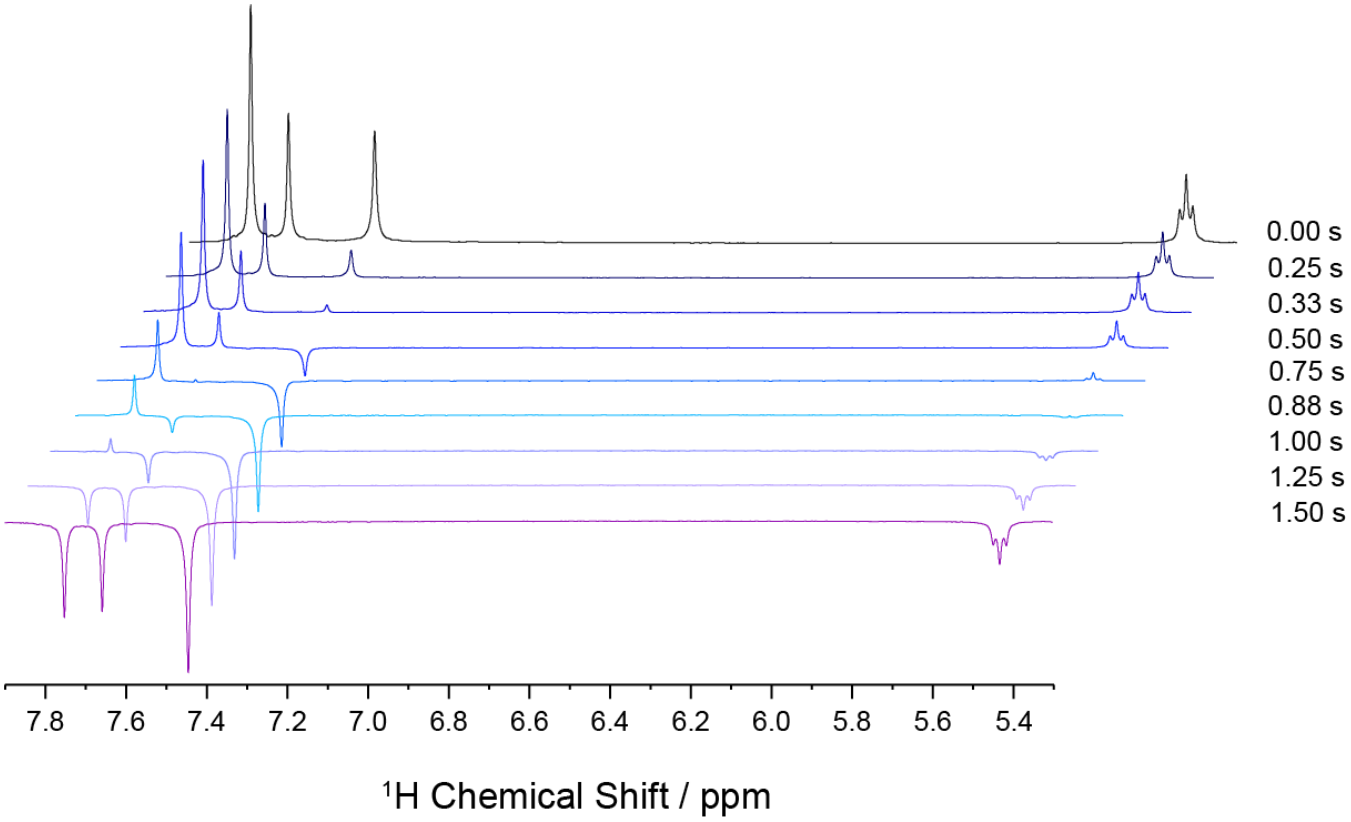


Figure S-47. Stacked NMR spectra for the inversion recovery experiments determining T1 for **TCC** with **CyOH** guest in D_2O, [**TCC**] = 2 mM, [**CyOH**] = 3 mM, D_2O, 500 MHz, 298 K.

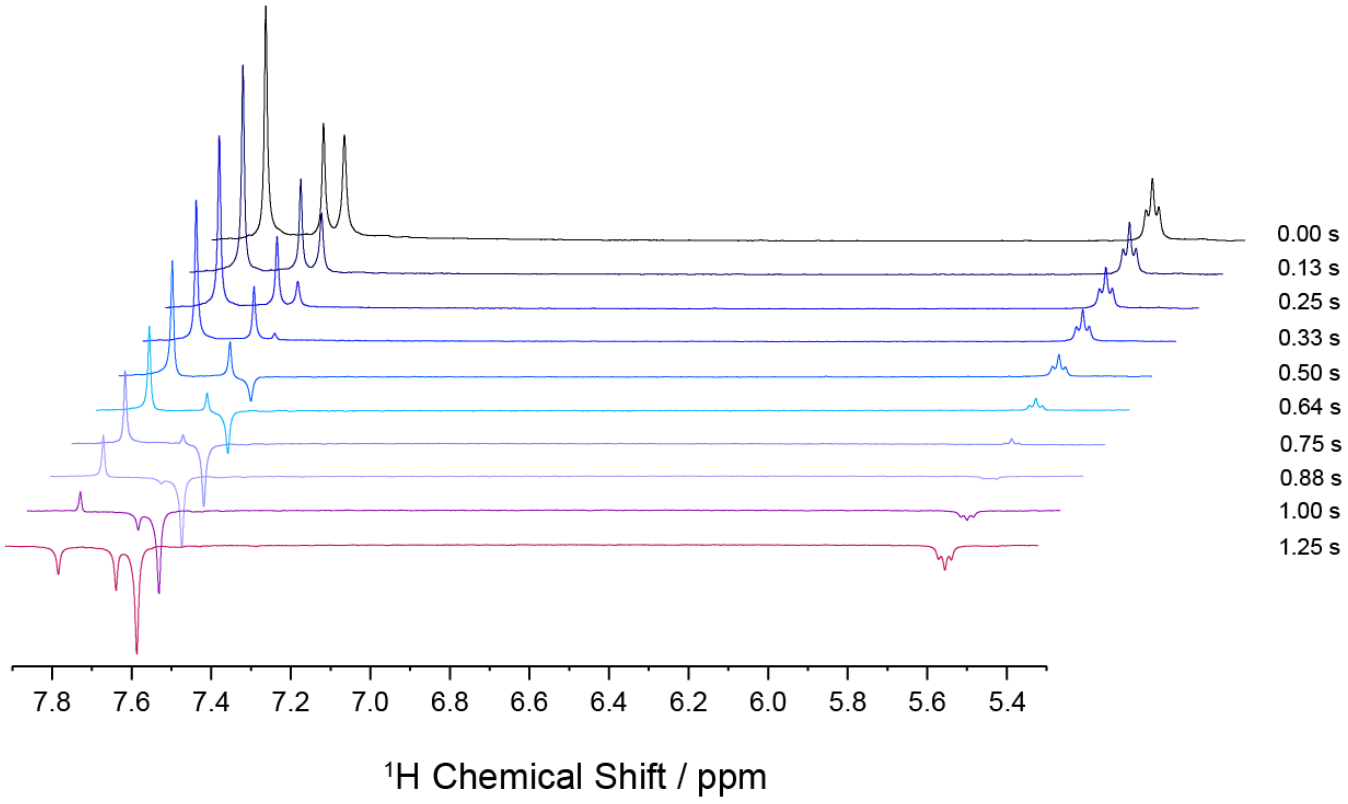


Figure S-48. Stacked NMR spectra for the inversion recovery experiments determining T1 for **TCC** with **AdO** guest in D_2O, [**TCC**] = 2 mM, [**AdO**] = 3 mM, D_2O, 500 MHz, 298 K.

Relaxation Data for 1-AdOH in Non-D_2O Data solvents

Table S-1. T1 and T2 relaxation times for **1-AdOH** free in 1,1,2,2-tetrachloroethane-d_2 (TCE). There is no bound data because **TCC** is insoluble in organic solvents.

Proton	T1 free in TCE (s)	T2 free in TCE (ms)
H_a	1.97 ± 0.07	38.7 ± 1.0
H_b	2.24 ± 0.11	18.1 ± 1.0
OH	2.27 ± 0.15	44.5 ± 1.2
H_c	1.74 ± 0.07	13.2 ± 0.5
H_d	1.71 ± 0.07	14.5 ± 0.5

Relaxation Data for 2-AdOH in Non-D_2O Data solvents

Table S-2. T1 and T2 relaxation times for **2-AdOH** free in 1,1,2,2-tetrachloroethane-d_2 (TCE). There is no bound data because **TCC** is insoluble in organic solvents.

Proton	T1 free in TCE (s)	T2 free in TCE (ms)
H_a	2.50 ± 0.17	28.9 ± 1.35
H_b	2.21 ± 0.23	33.9 ± 1.7
OH	2.86 ± 0.25	–
H_c	1.84 ± 0.08	14.2 ± 0.5
H_d	1.95 ± 0.08	17.2 ± 0.9
H_e	1.79 ± 0.08	16.4 ± 0.5
H_f	2.70 ± 0.10	55.7 ± 0.7
H_g	2.23 ± 0.23	24.4 ± 2.0
H_h	2.23 ± 0.23	24.4 ± 2.0
H_i	1.95 ± 0.09	26.0 ± 1.5

Table S-3. T1 and T2 relaxation times for **2-AdOH** free in DMSO. There is no bound data because **TCC** is insoluble in organic solvents.

Proton	T1 free in DMSO (s)	T2 free in DMSO (ms)
H_a	1.54 ± 0.37	48.5 ± 1.4
H_b	1.29 ± 0.19	27.6 ± 2.7
OH	1.45 ± 0.28	35.5 ± 3.5
H_c	1.46 ± 0.04	13.5 ± 0.6
H_d	1.48 ± 0.26	14.5 ± 0.8
H_e	1.46 ± 0.02	16.5 ± 1.0
H_f	1.46 ± 0.19	19.9 ± 2.6
H_g	1.48 ± 0.31	31.3 ± 1.3
H_h	1.48 ± 0.31	31.3 ± 1.3
H_i	1.47 ± 0.15	21.2 ± 1.1

Table S-4. T1 relaxation times for specific protons on the **TCC** wall (see Figure S-1 for assignment)

Cavitand Proton	Bound δ (ppm)	T1 Bound with CyOH (s)
H_c'	7.75	1.53 ± 0.05
H_b'	7.65	1.11 ± 0.02
H_a'	7.44	0.520 ± 0.011
H_d'	5.43	1.27 ± 0.06
Cavitand Proton	**Bound δ (ppm)**	**T1 Bound with AdO (s)**
H_c'	7.76	1.64 ± 0.06
H_b'	7.62	1.18 ± 0.02
H_a'	7.57	0.526 ± 0.013
H_d'	5.53	1.21 ± 0.06
Cavitand Proton	**Bound δ (ppm)**	**T1 Bound with THF (s)**
H_c'	7.73	1.51 ± 0.05
H_b'	7.67	1.10 ± 0.01
H_a'	7.46	0.524 ± 0.014
H_d'	5.42	1.26 ± 0.07

Data Fitting and Error Analysis

Data were fit in Mathematica to extract the T1 and T2 relaxation times. For each proton, a plot of intensity vs. relaxation delay time was prepared, and the resulting exponential plots were fit to the following equations[4] to determine T1 and T2, respectively:

$$M(t) = M_0 - 2M_0e^{-t/T1} \qquad \text{(Equation S1)}$$

$$M(t) = M_0e^{-t/T2} \qquad \text{(Equation S2)}$$

Error was determined by first calculating the residual for each peak in the fitting plot. The absolute values of the residual intensities were used to find the mean residual for each plot. The absolute value of the signal intensity for each plot was then calculated, and an overall percent error was found by dividing the residual mean by the signal intensity mean. This percentage was then multiplied by the relaxation time to give a final ± value for each time. An example of the analysis performed for each proton in each guest can be seen in Figures S-47 (T1 analysis) and S-48 (T2 analysis). This example comes from the analysis of proton a in **1-AdOH**.

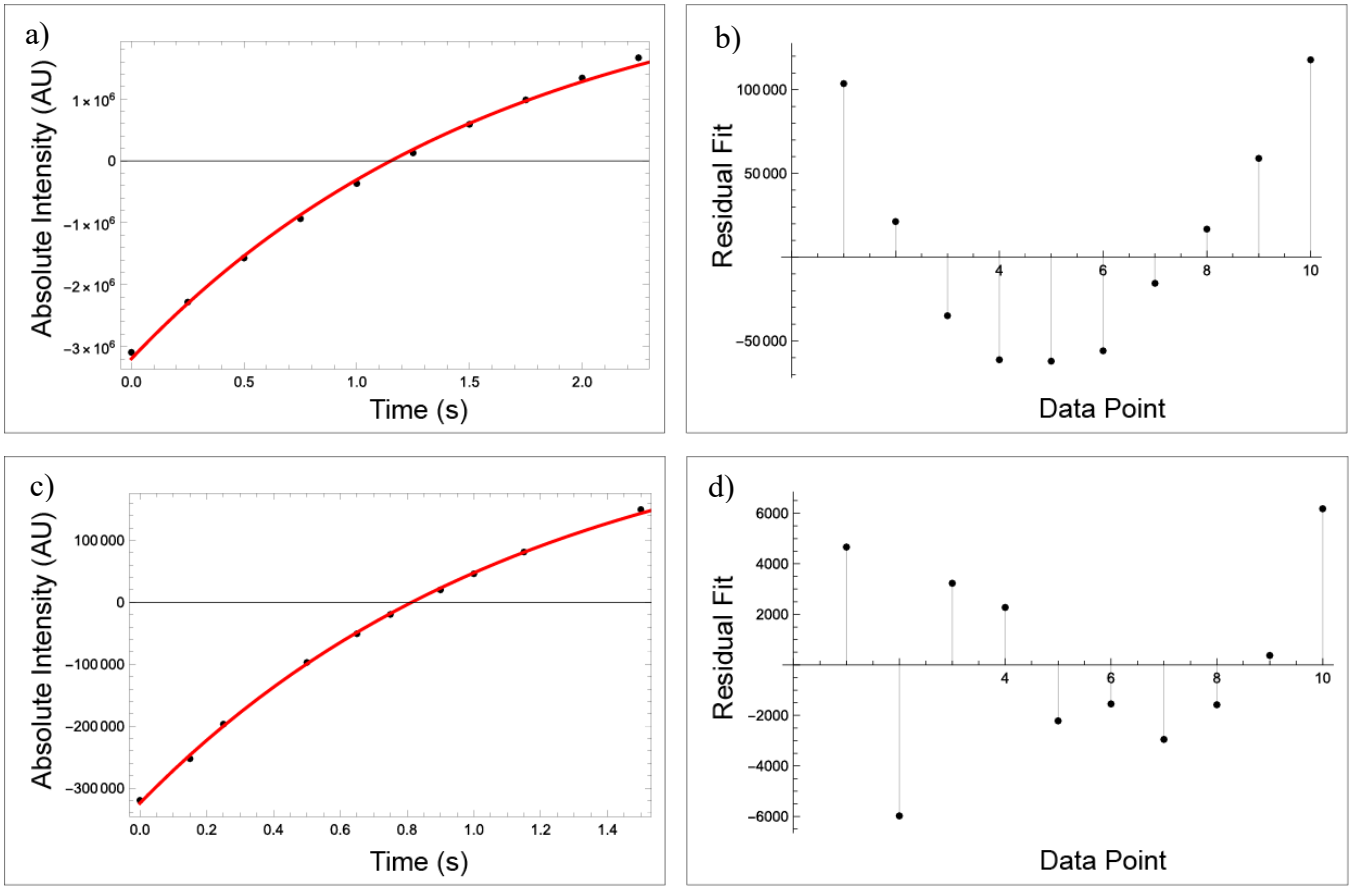


Figure S-49. Mathematica fits for the T1 data for proton a of **1-AdOH** in D_2O, free and bound. a) Intensity vs. time plot for the inversion recovery experiment for proton a while the guest is free. Black dots are the collected data while the solid red line is the fit of the model to the data; b) Residual plot for the intensity as a deviation from the model in a); c) Intensity vs. time plot for the inversion recovery experiment for proton a while the guest is bound in **TCC**. Black dots are the collected data while the solid red line is the fit of the model to the data; d) Residual plot for the intensity as a deviation from the model in c).

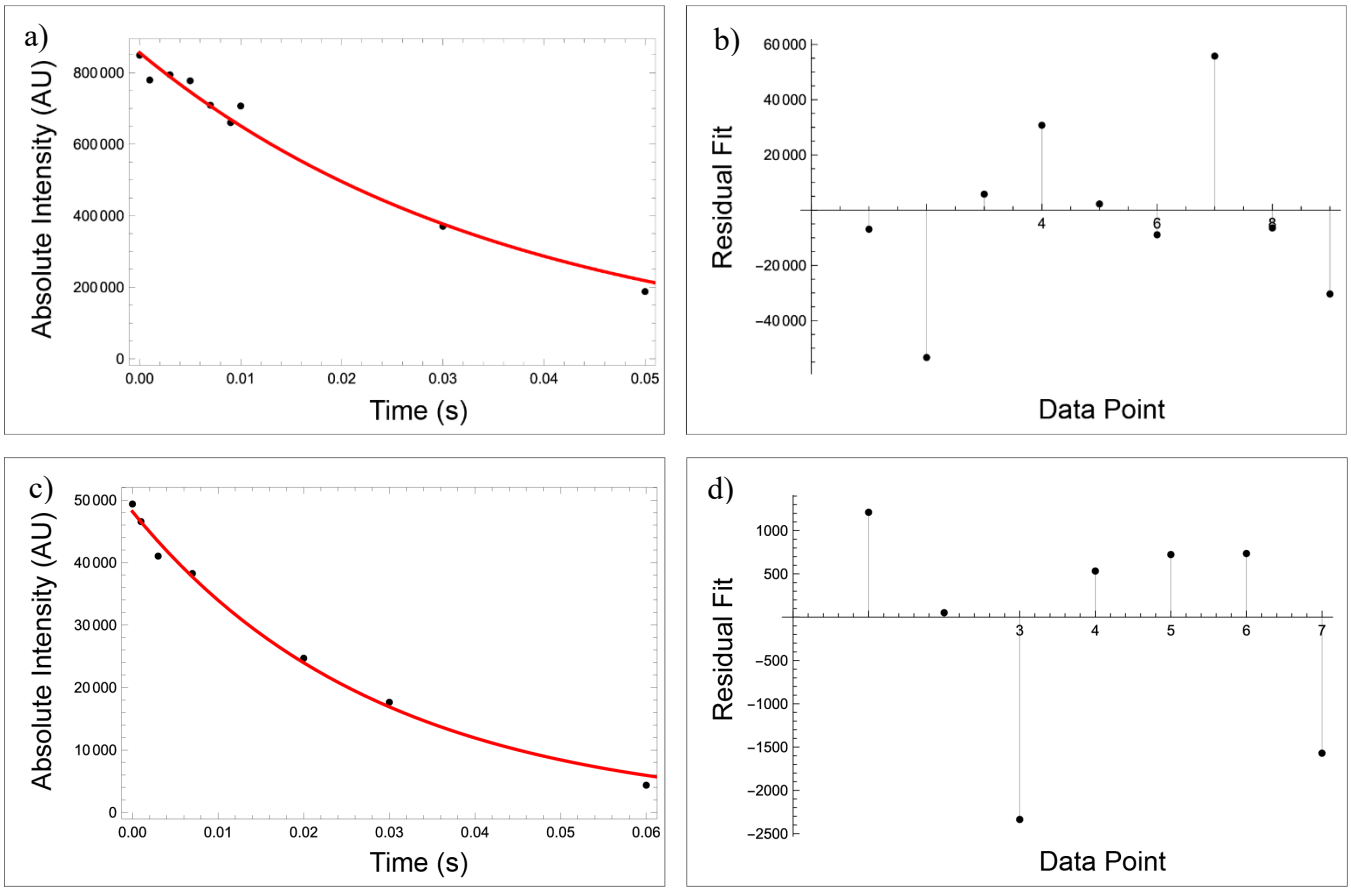
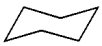
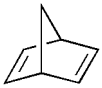
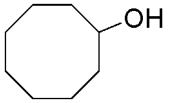
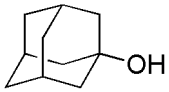
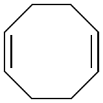


Figure S-50. Mathematica fits for the T2 data for proton a of **1-AdOH** in D_2O while free and bound. a) Intensity vs. time plot for the spin echo experiment for proton a while the guest is free. Black dots are the collected data while the solid red line is the fit of the model to the data; b) Residual plot for the intensity as a deviation from the model in a); c) Intensity vs. time plot for the spin echo experiment for proton a while the guest is bound in **TCC**. Black dots are the collected data while the solid red line is the fit of the model to the data; d) Residual plot for the intensity as a deviation from the model in c).

Guest Exchange Data[5]

Table S-5. Exchange rates of various guests (3 mM) between **1** (2 mM) and bulk solvent (D_2O) (reproduced from ref 5).

Guest	k (s^{-1})	$\Delta G^{\ddagger}_{in}$, kcal mol^{-1}
	14.6	16.0
	11.7	16.1
	9.8	16.2
	3.2	16.9
	1.8	17.2
	1.7	17.2

References

1. S. M. Biros, E. C. Ullrich, F. Hof, L. Trembleau and J. Rebek Jr., *J. Am. Chem. Soc.* 2004, **126**, 2870-2876.
2. E. D. Becker, J. A. Ferretti, R. K. Gupta, G. H. Weiss, *J. Magn. Reson*. 1980, **37**, 381-394.
3. *a*) E. L. Hahn, *Phys. Rev.*, 1950, **80**, 580-594.; *b*) S. Meiboom and D. Gill, *Rev. Sci. Instrum*., 1958, **29**, 688-691.
4. T. D. W. Claridge, *High-Resolution NMR Techniques in Organic Chemistry, 2nd Ed*., Elsevier, 2008.
5. R. J. Hooley, H. J. Van Anda, J. Rebek, Jr. *J. Am. Chem. Soc.*, 2007, **129**, 13464–13473.