Supporting Information

Molecular interactions in remdesivir-cyclodextrin systems

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NMR measurements were carried out on a 600 and a 400 MHz Varian DDR NMR spectrometer (Agilent Technologies, Palo Alto, CA, USA), equipped with a 5 mm inverse-detection probehead and a gradient module at 298 K. Standard pulse sequences and processing routines available in VnmrJ 3.2C/Chempack 5.1 and MestreNova 14.2.0 were used.

1H NMR spectra for the Job's plot and the titration were recorded with 16 scans with a spectral window of 5.1 kHz and a 2 s relaxation delay. The complete resonance assignment of remdesivir were established from 1D ^{1}H (16 scans, 2 s relaxation delay, 6 kHz spectral window) and ^{13}C (30000 scans, 1 s relaxation delay, 33.8 kHz spectral width), 2D^{1}H-^{1}H gCOSY (4 scans were collected on 1024·512 data points, 1 s relaxation delay), NOESY (8 scans were collected on 1024·512 data points with a mixing time of 300 ms), ^{1}H–^{13}C gHSQCAD (4 scans, 1 s relaxation delay, $^{1}J_{CH}$ = 140 Hz, spectral width of F1 = 6 kHz, F2 = 27.1 kHz) and HMBC (4 scans, 1 s relaxation delay, $^{3}J_{CH}$ = 8 Hz, spectral width of F1 = 6 kHz, F2 = 32.5 kHz) experiments, both in DMSO-*d*$_6$ (ref. δ = 2.50) and D_2O, pH = 2.0 (ref. methyl singlet δ = 3.31 ppm of internal CH_3OH). Complete resonance assignments of cyclodextrins were established from 1D ^{1}H (64 scans, 1 s relaxation delay, 2.4 kHz spectral window) and 2D-2D ^{1}H-^{1}H gCOSY (4 scans were collected on 1024·512 data points, 1 s relaxation delay), ^{1}H–^{13}C gHSQCAD (4 scans, 1 s relaxation delay, $^{1}J_{CH}$ = 140 Hz, spectral width of F1 = 2.4 kHz, F2 = 12 kHz) and HMBC (8 scans, 1 s relaxation delay, $^{3}J_{CH}$ = 8 Hz, spectral width of F1 = 2.4 kHz, F2 = 19 kHz) experiments. To explore spatial proximity of the host-guest complexes 2D ROESY spectra were acquired with spectral width of 5.4 kHz collecting 16 and 32 scans on 1258·512 data points, applying mixing times of 300 and 400 ms.

Table 1. Complete ^{1}H NMR resonances assignment for remdesivir (in DMSO-d_6 and in D_2O at pH 2.0, 600 MHz).

No.	**^{1}H**	
	DMSO-d_6	**D_2O pH 2.0**
	(ref. DMSO δ_H= 2.50 ppm)	**(ref. MeOH δ_H = 3.31 ppm)**
1	6.82 (d, *J* = 4.5 Hz, 1H)	7.00 (d, *J* = 4.9 Hz, 1H)
2	6.88 (d, *J* = 4.5 Hz, 1H)	7.23 (d, *J* = 4.9 Hz, 1H)
3	4.63 (m, 1H)	4.87 (m, 1H)
4	3.94 (m, 1H)	4.42 (m, 1H)
5	4.23 (m, 1H)	4.52 (m, 1H)
6	4.08 (m, 1H)	4.24 (m 1H)
6’	4.25 (m, 1H)	4.38 (m, 1H)
7-8	7.34 (m, 2H)	6.88 (d, *J* = 8.0 Hz, 2H)
9-10	7.18 (m, 2H)	7.28 (t, *J* =7.8 Hz, 2H)
11	7.16 (m, 1H)	7.18 (t, *J* =7.5 Hz, 2H)
12	3.81 (m, 1H)	3.69 (m, 1H)
13	1.20 (d, *J* = 7.1 Hz, 3H)	1.26 (d, *J* = 7.4, 3H)
14	3.86 (dd, *J* = 10.9 Hz, 5.7 Hz, 1H)	3.94 (dd, *J* = 10.8 Hz, 5.7 Hz, 1H)
14’	3.95 (dd, *J* = 10.9 Hz, 5.7 Hz, 1H)	4.01 (dd, *J* = 10.8 Hz, 5.7 Hz, 1H)
15	1.41 (m, 1H)	1.45 (m, 4H)
16-17	1.24 (m, 4H)	1.25 (m, 4H)
18-19	0.79 (t, *J* = 7.4 Hz, 6H)	0.80 (t, *J* = 7.5 Hz, 6H)
20	7.92 (s, 1H)	7.95 (s, 1H)

Table 2. Complete ^{1}H NMR resonance assignment for cyclodextrins (D_2O at pH 2.0, ref. MeOH δ_H = 3.31 ppm, 400 MHz).

No.	βCD	γCD	per-6-SBE-βCD	Sugammadex
1	5.03 (d, *J* = 3.7 Hz, 1H)	5.07 (d, *J* = 3.9 Hz, 1H)	5.01 (d, *J* = 3.7 Hz, 1H)	5.12 (d, *J* = 3.8 Hz, 1H)
2	3.61 (dd, *J* = 9.9, 3.6 Hz, 1H)	3.61 (dd, *J* = 9.8, 3.8 Hz, 1H)	3.60 (m, 1H)	3.63 (dd, *J* = 9.9, 3.7 Hz, 1H)
3	3.93 (t, *J* = 9.5 Hz, 1H)	3.90 (t, *J* = 9.6 Hz, 1H)	3.91 (m, 1H)	3.88 (t, *J* = 9.5 Hz, 1H)
4	3.55 (t, *J* = 9.3 Hz, 1H)	3.55 (t, *J* = 9.4 Hz, 1H)	3.62 (m, 1H)	3.52 (t, *J* = 9.3 Hz, 1H)
5	3.82 (m, 1H)	3.82 (m, 1H)	3.90 (m, 1H)	3.97 (t, *J* = 9.1 Hz, 1H)
6	3.84 (m, 2H)	3.83 (m, 2H)	3.71 (m, 1H)	3.23 (m, 1H)
6’			3.80 (m, 1H)	2.91 (m, 1H)
7	-	-	3.60 (m, 1H)	2.89 (t, *J* = 7.2 Hz, 2H)
7’	-	-	3.52 (m, 1H)	
8	-	-	1.69 (m, 2H)	2.70 (t, *J* = 7.2 Hz, 2H)
8’	-	-		
9	-	-	1.76 (m, 2H)	-
9’	-	-		-
10	-	-	2.90 (m, 2H)	-
10’	-	-		-

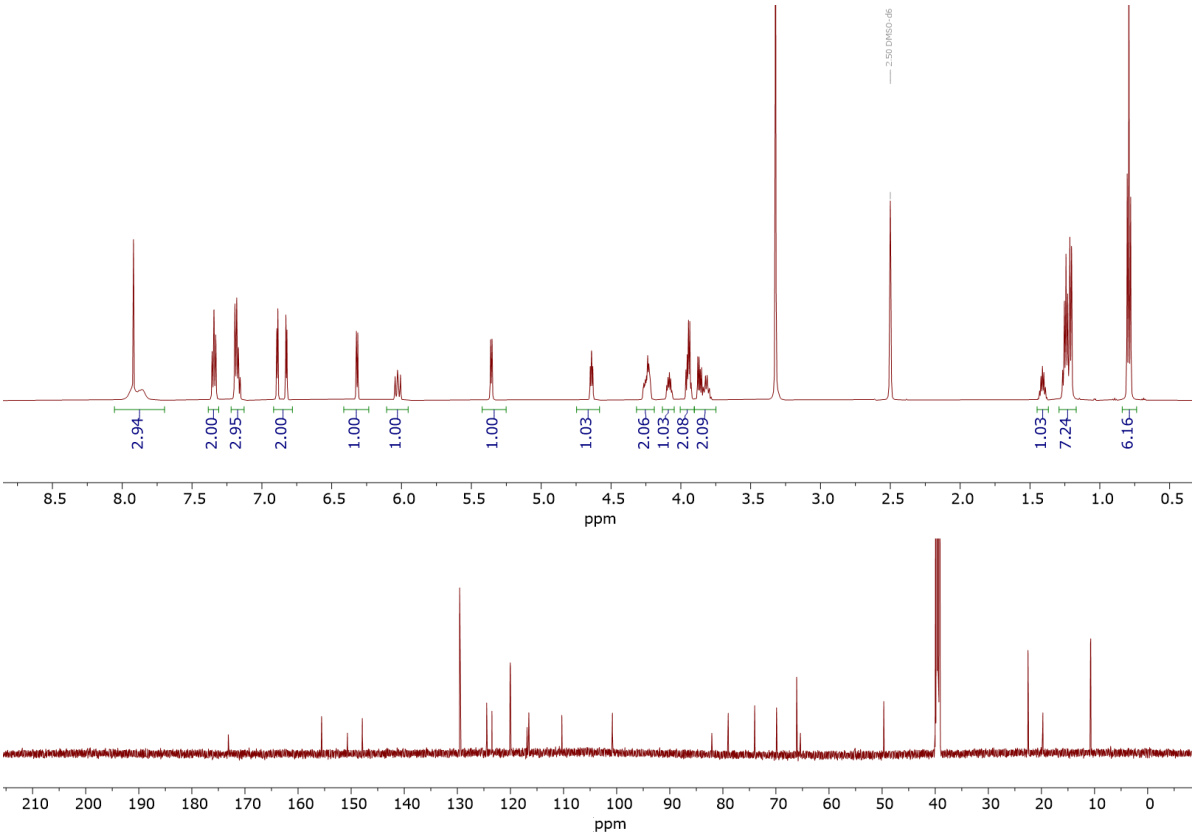

Figure S1. ^{1}H and ^{13}C NMR spectra of remdesivir (DMSO-d_6, 600 MHz).

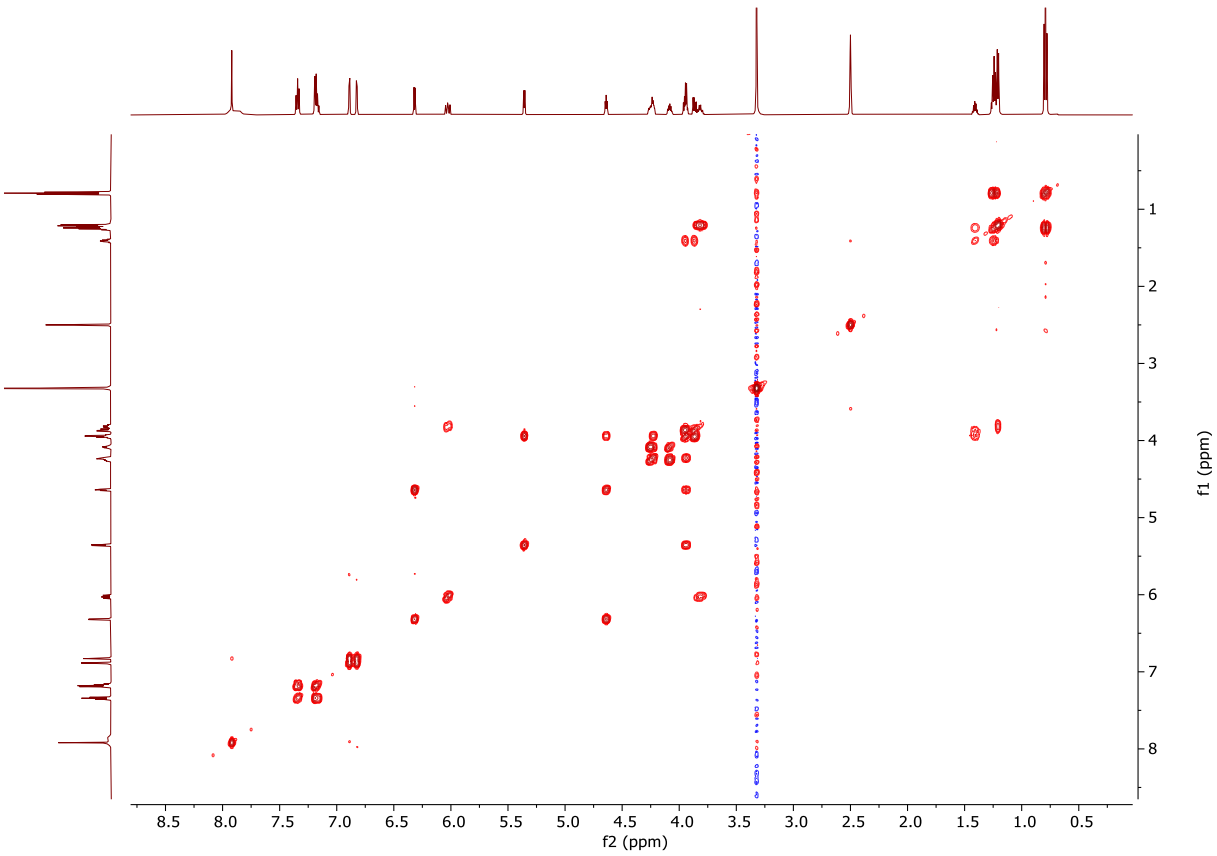

Figure S2. COSY spectrum of remdesivir (DMSO-d_6, 600 MHz).

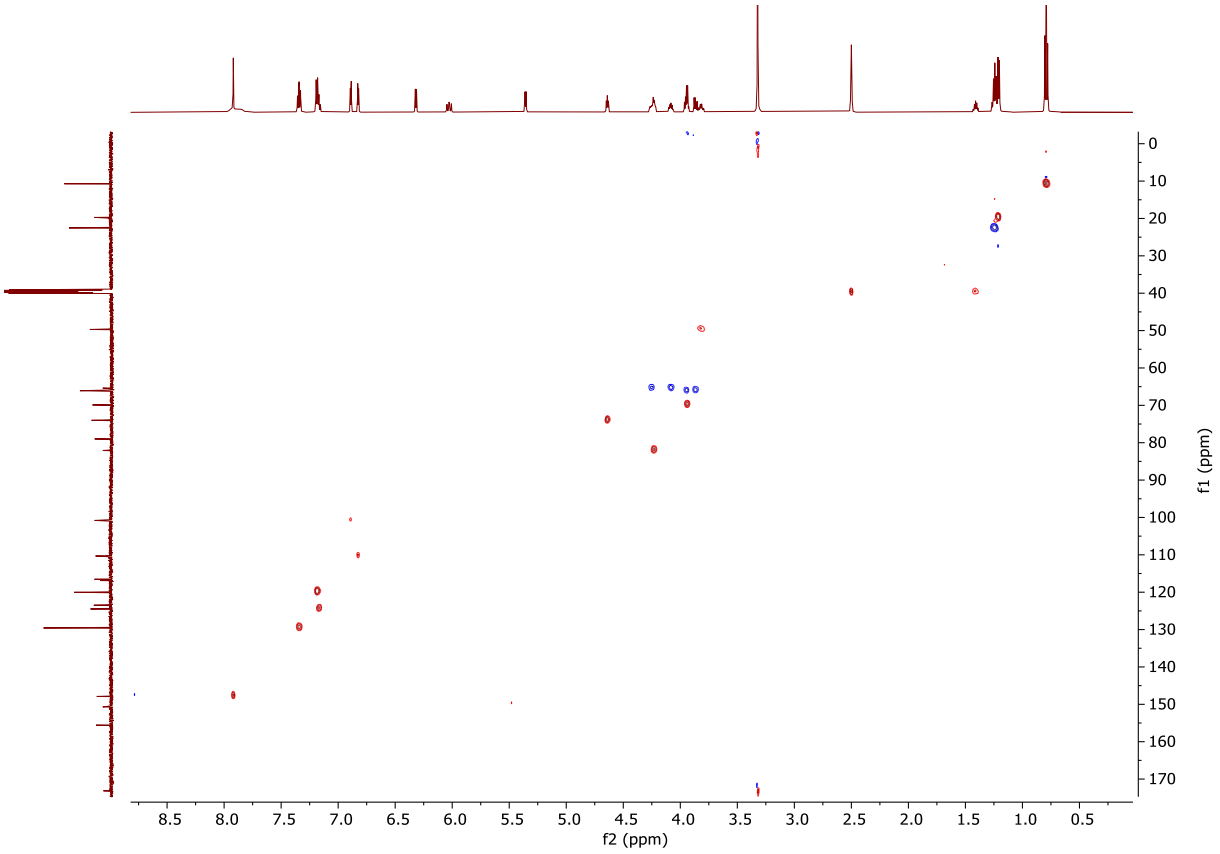

Figure S3. DEPT-edited HSQC spectrum of remdesivir (DMSO-d_6, 600 MHz).

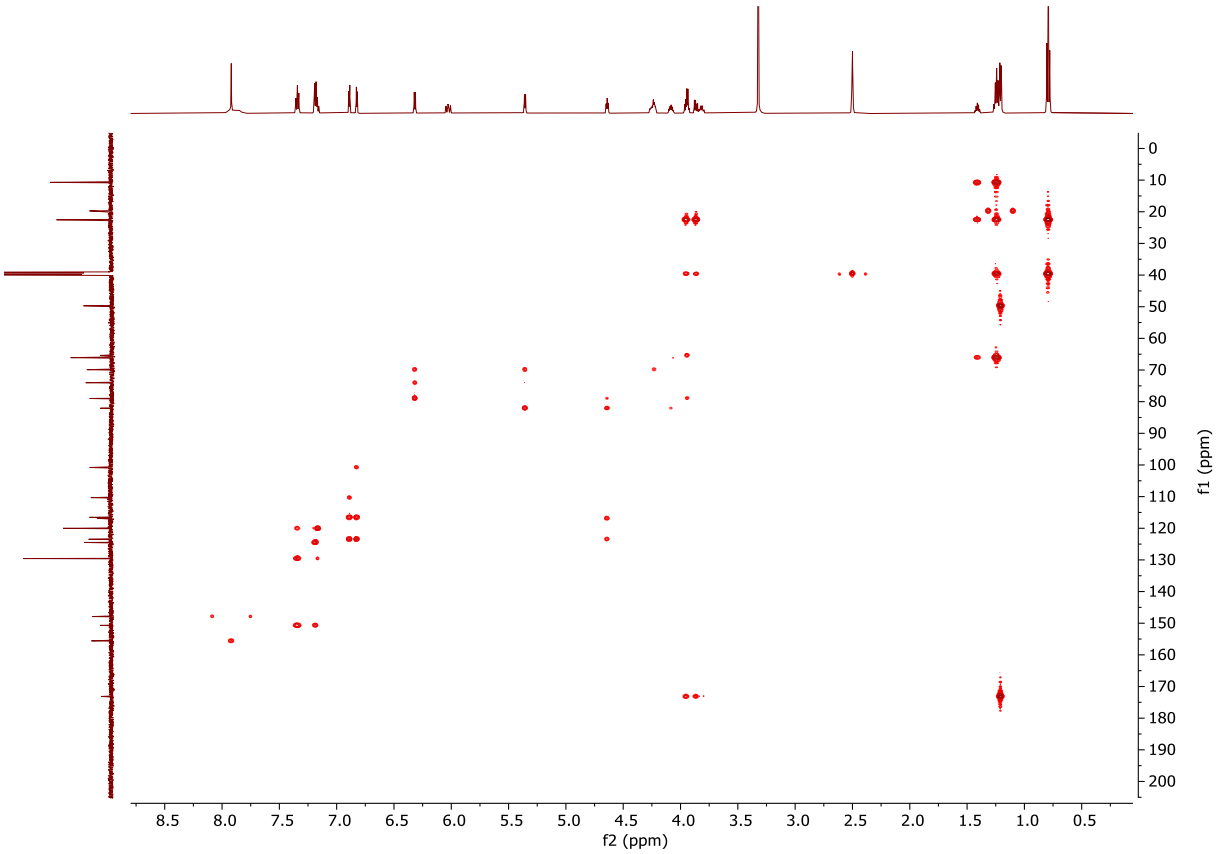

Figure S4. HMBC spectrum of remdesivir (DMSO-d_6, 600 MHz).

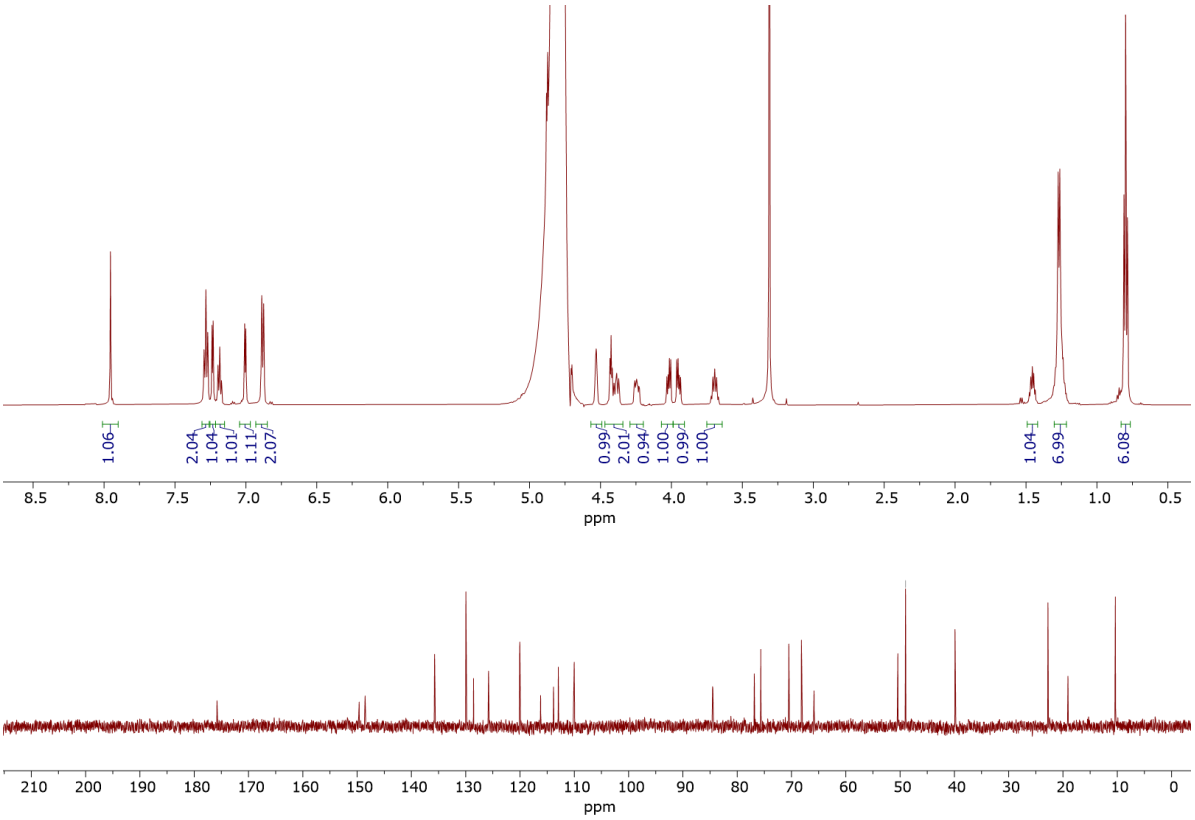

Figure S5. ^{1}H and ^{13}C NMR spectra of remdesivir (D_2O, pH 2.0, 600 MHz).

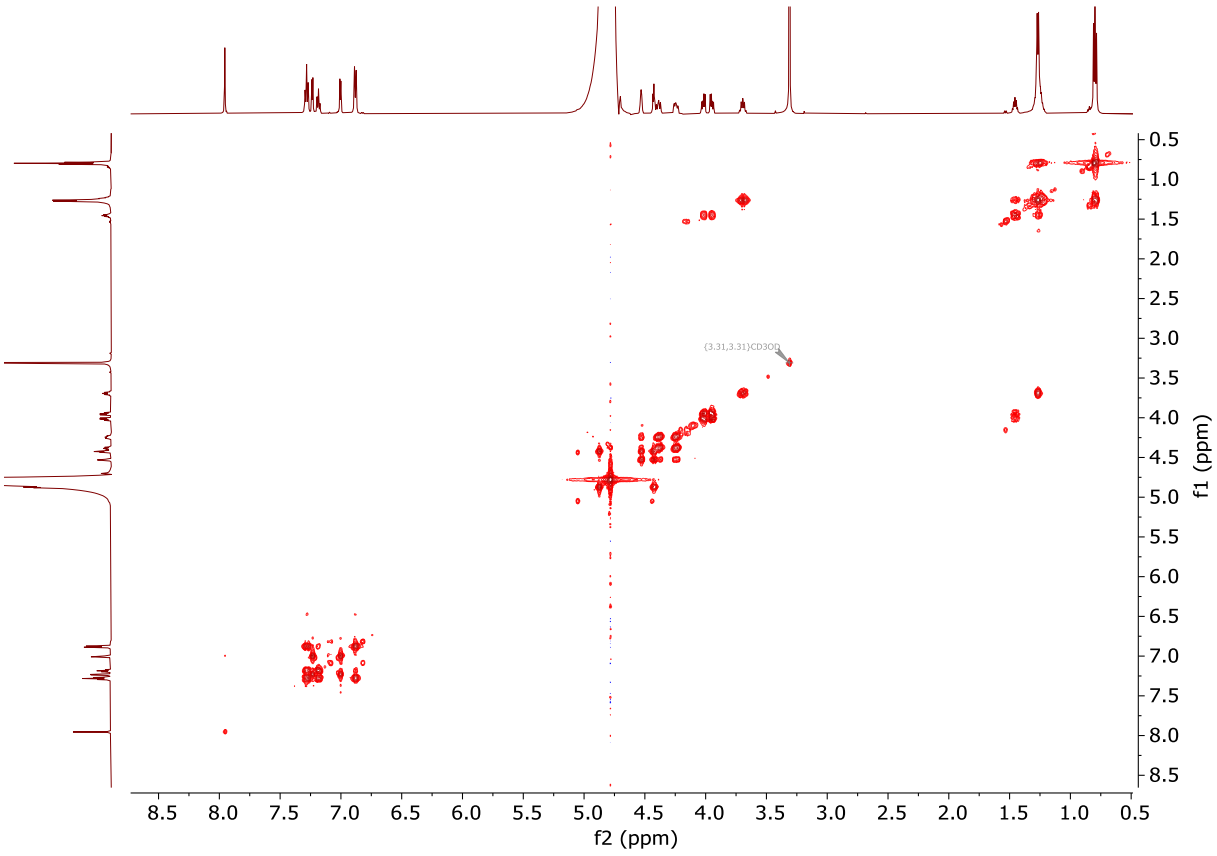

Figure S6. COSY spectrum of remdesivir (D_2O, pH 2.0, 600 MHz).

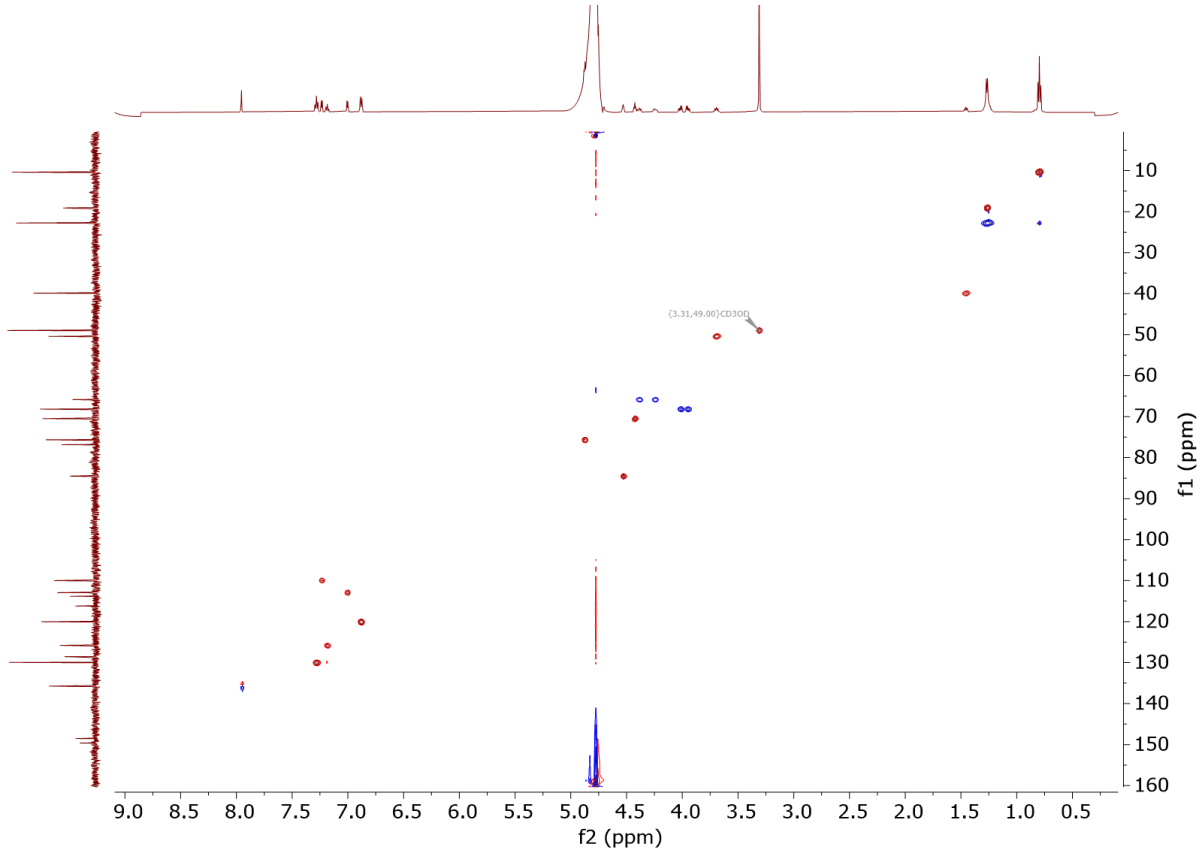

Figure S7. DEPT-edited HSQC spectrum of remdesivir (D_2O, pH 2.0, 600 MHz).

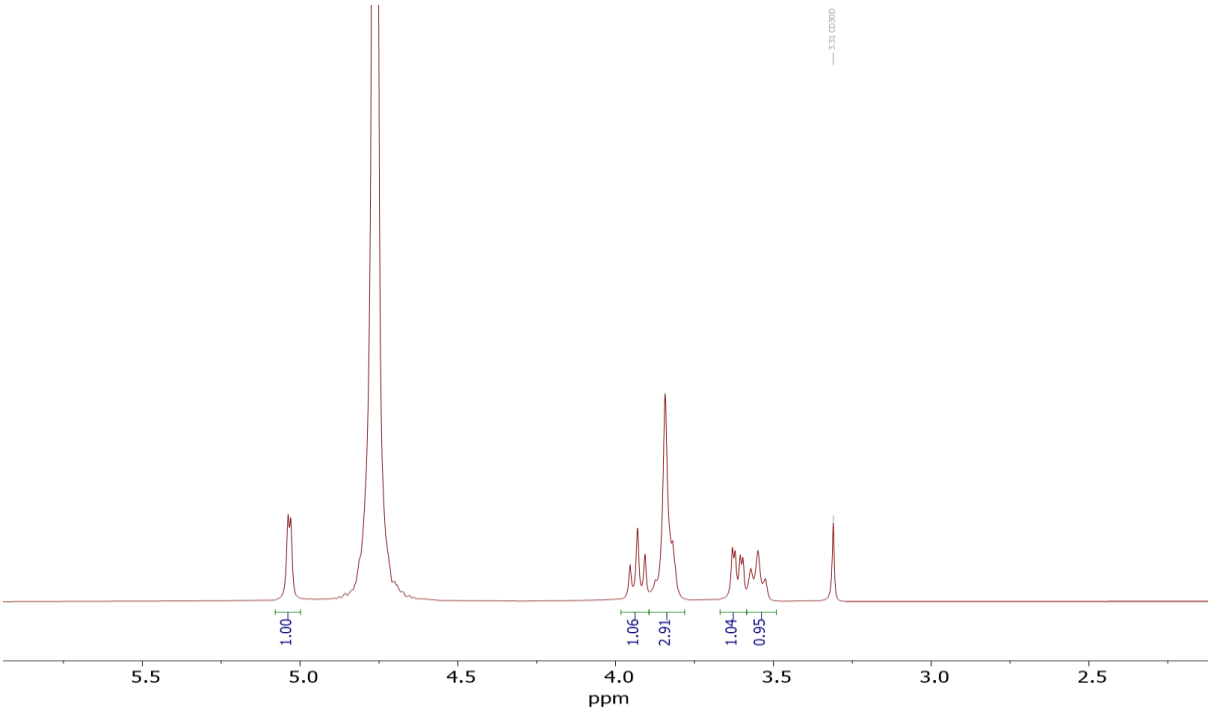

Figure S8. ^1H NMR spectrum of βCD (D_2O, pH 2.0, 400 MHz).

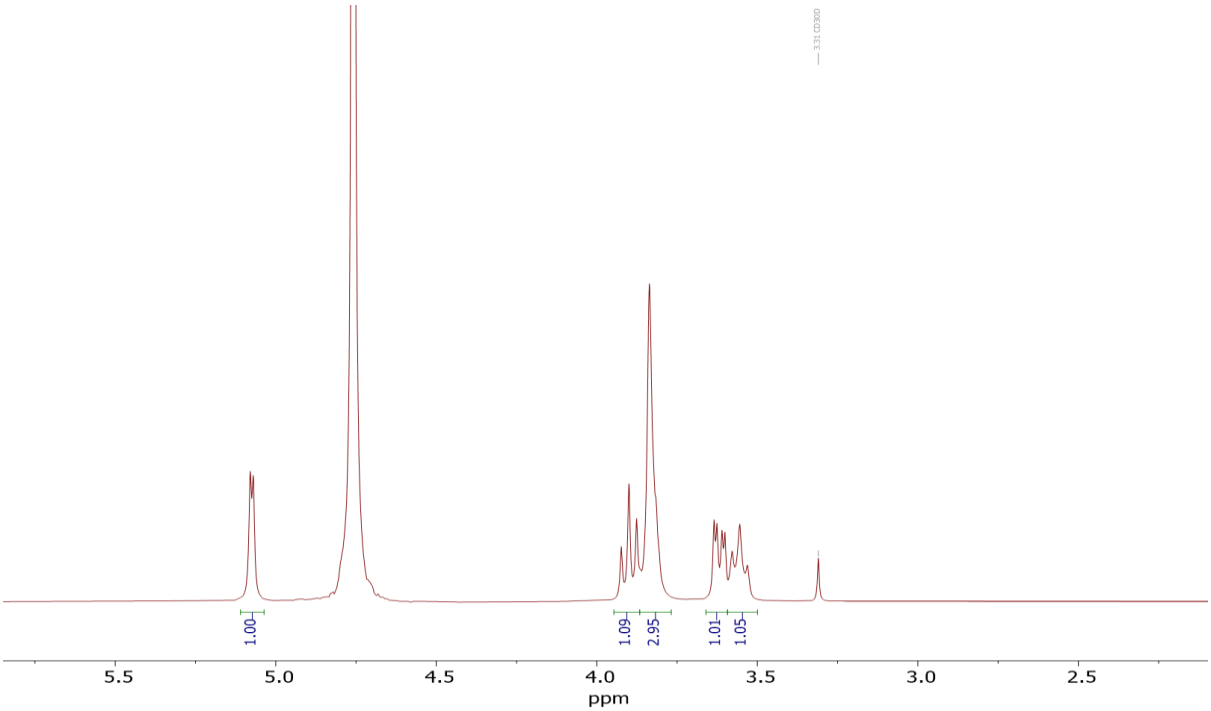

Figure S9. ^{1}H NMR spectrum pf γCD (D_2O, pH 2.0, 400 MHz).

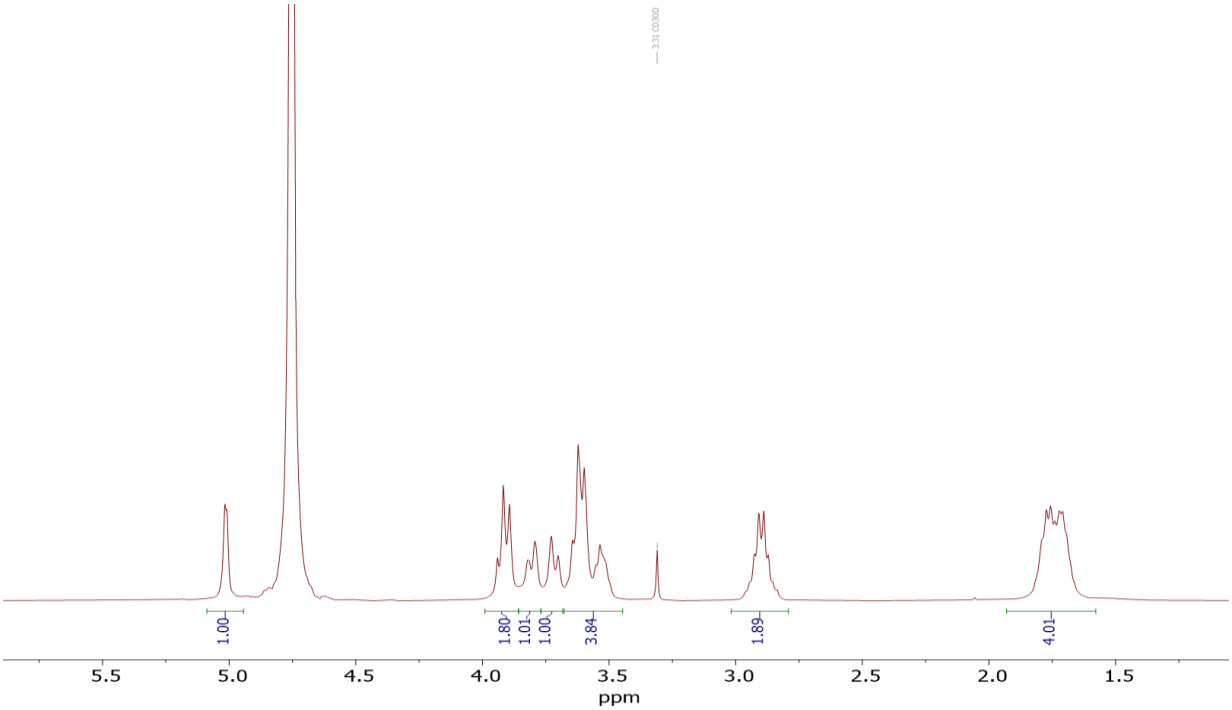

Figure S10. ^{1}H NMR spectrum of per-6-SBEβCD (D_2O, pH 2.0, 400 MHz,).

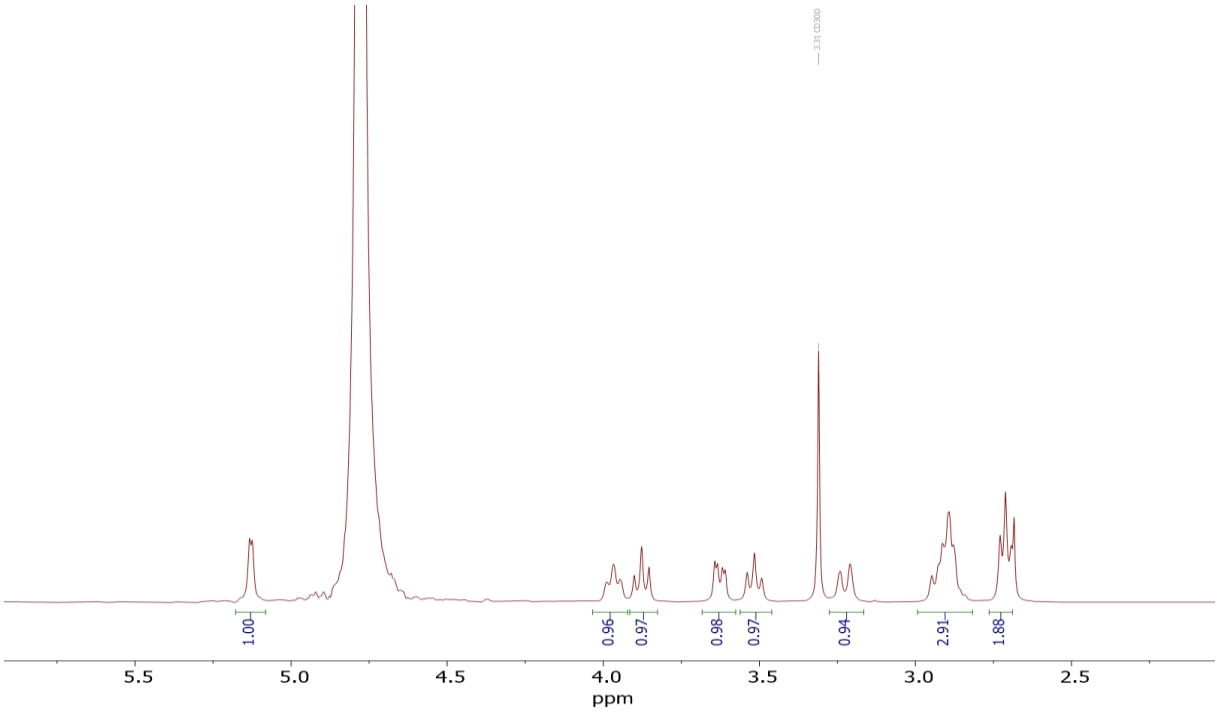

Figure S11. ^{1}H NMR spectrum of sugammadex (D_2O, pH 2.0, 400 MHz).

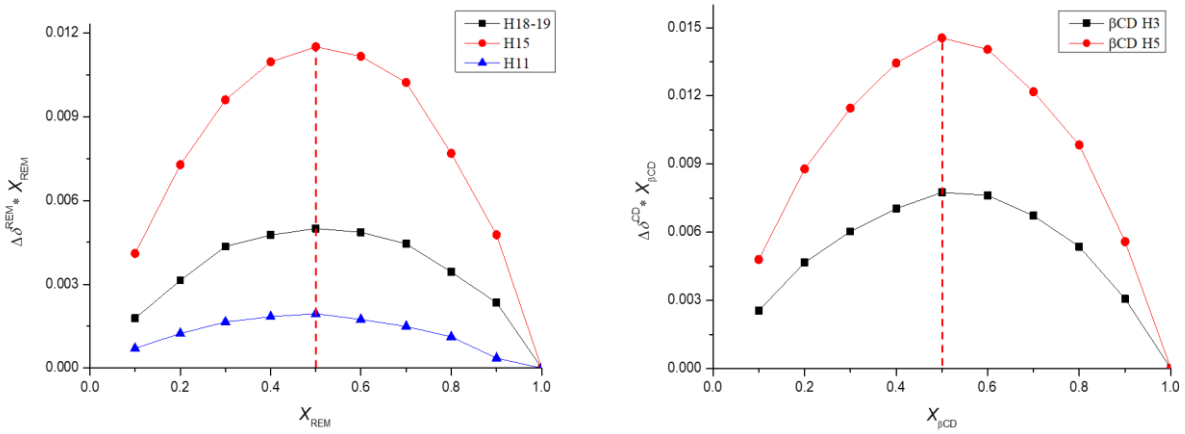

Figure S12. Job's plot for the selected ^{1}H resonances of REM (left) and βCD (right) both showing maximum at 0.5, that suggest 1:1 molar ratio for the complex in aqueous solution at pH 2.0.

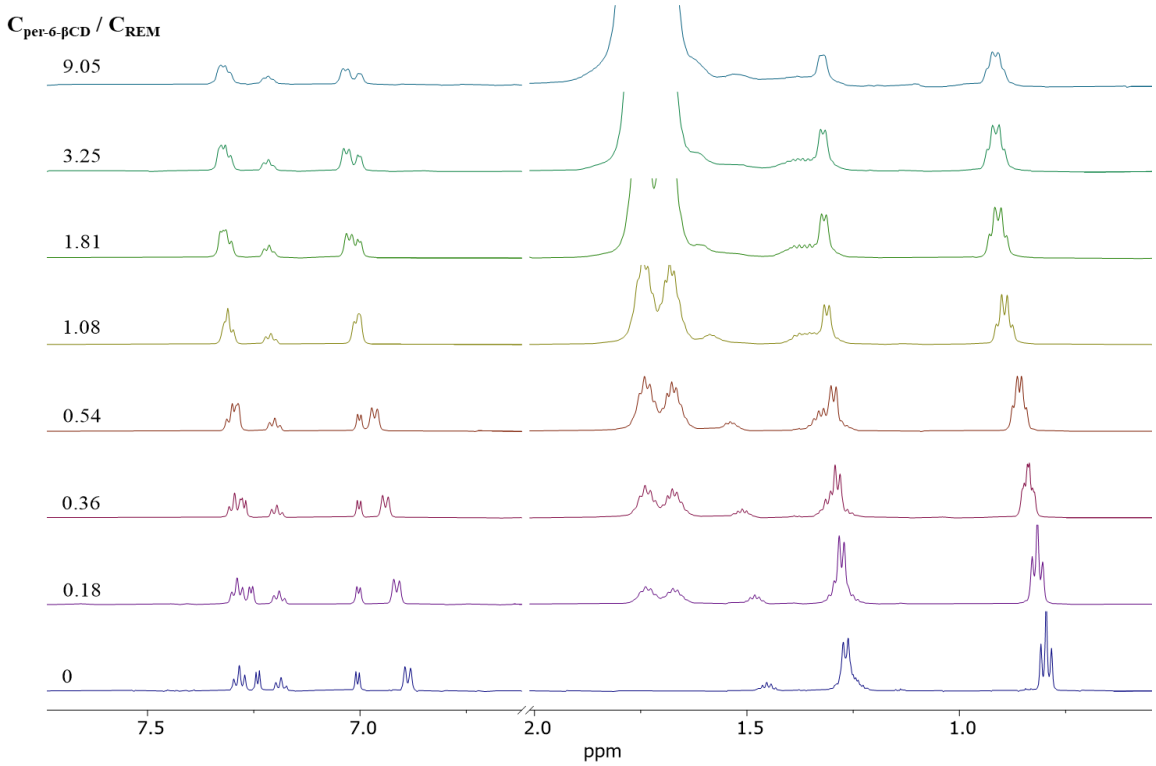

Figure S13. Representative ^{1}H NMR chemical shift changes of REM upon titration with per-6-SBEβCD.

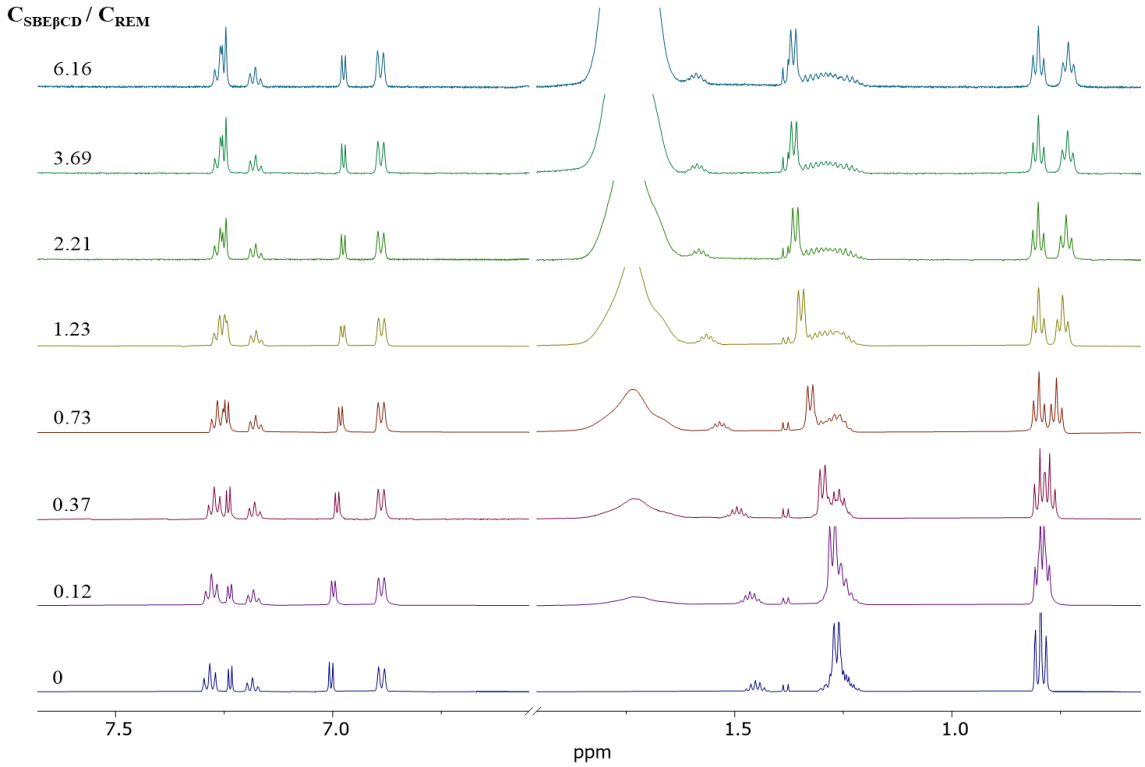

Figure S14. Representative ^{1}H NMR chemical shift changes of REM upon titration with SBEβCD.

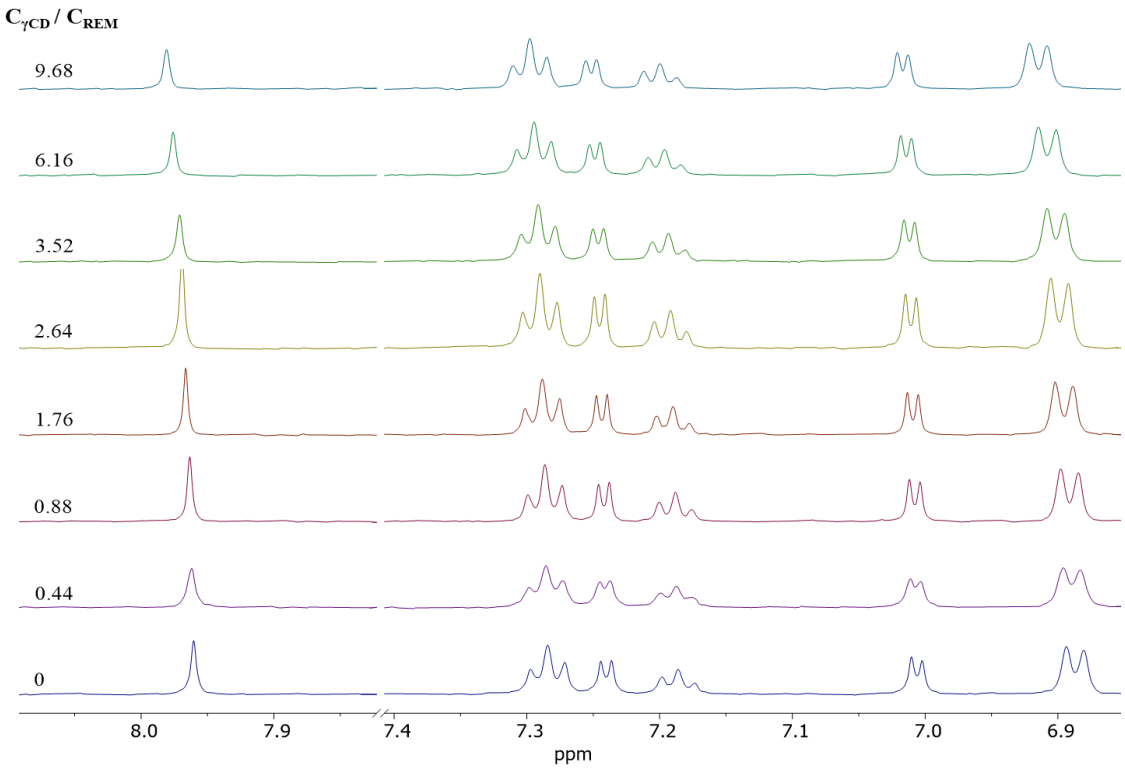

Figure S15. Representative ^{1}H NMR chemical shift changes of REM upon titration with γCD.

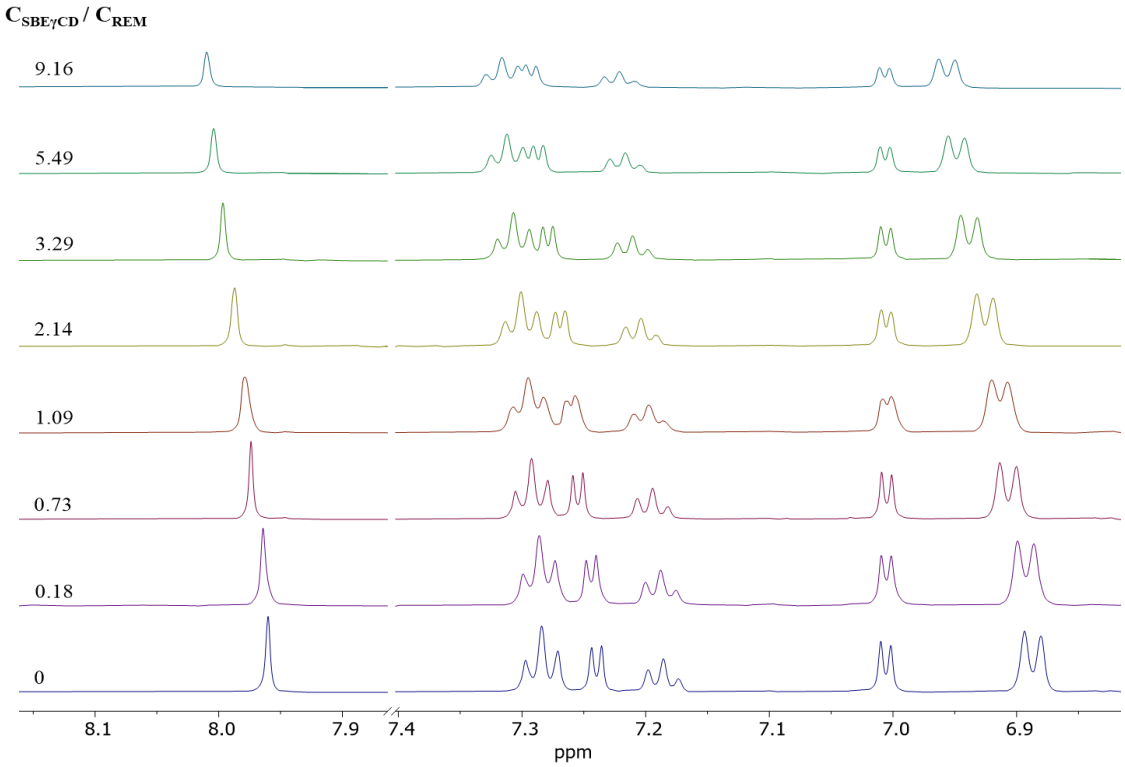

Figure S16. Representative ^{1}H NMR chemical shift changes of REM upon titration with SBEγCD.

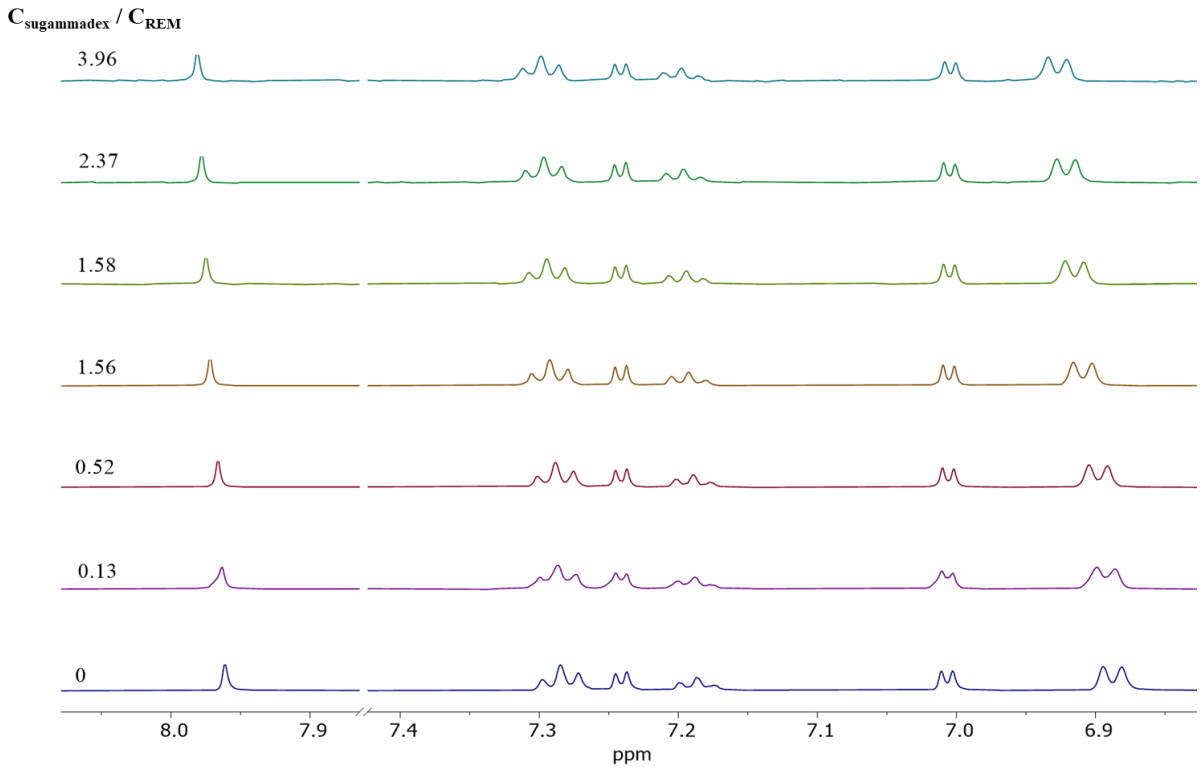

Figure S17. Representative ^{1}H NMR chemical shift changes of REM upon titration with sugammadex.

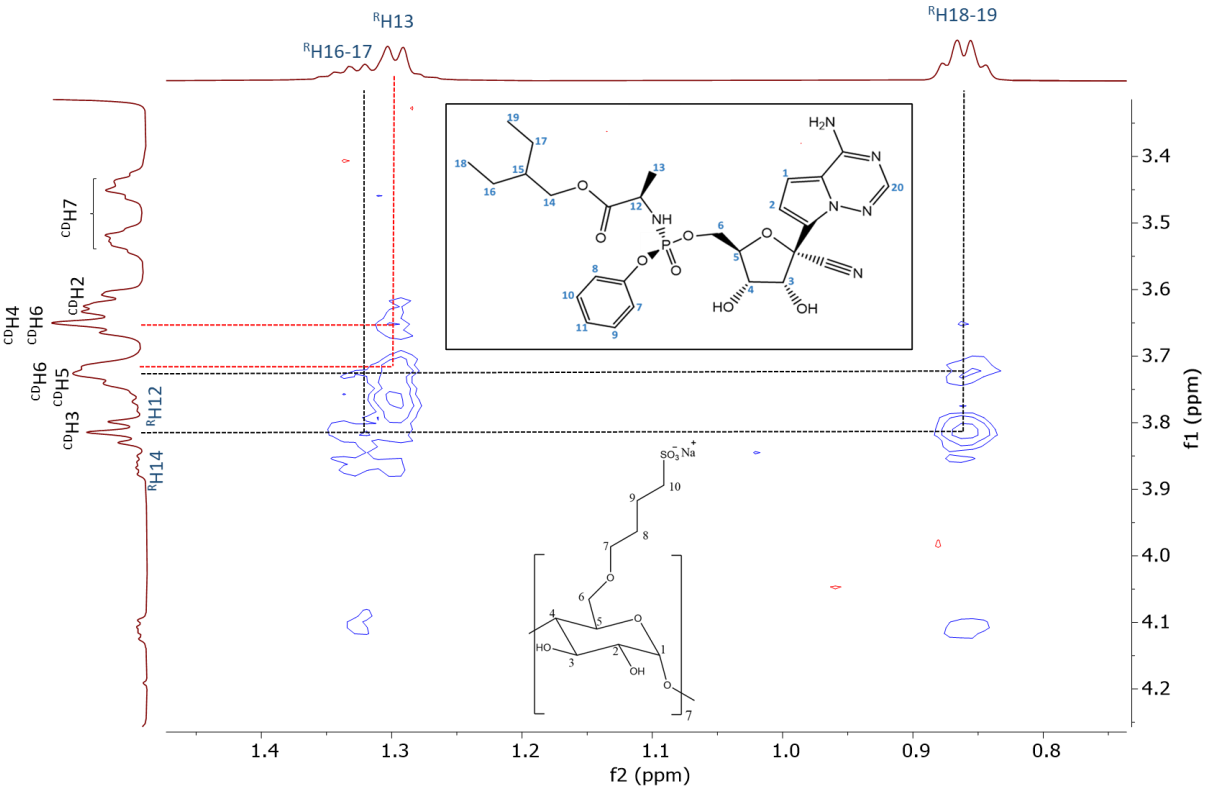

Figure S18. 2D ROESY spectrum of the 1:1 REM:per-6-SBEβCD molar ratio sample.

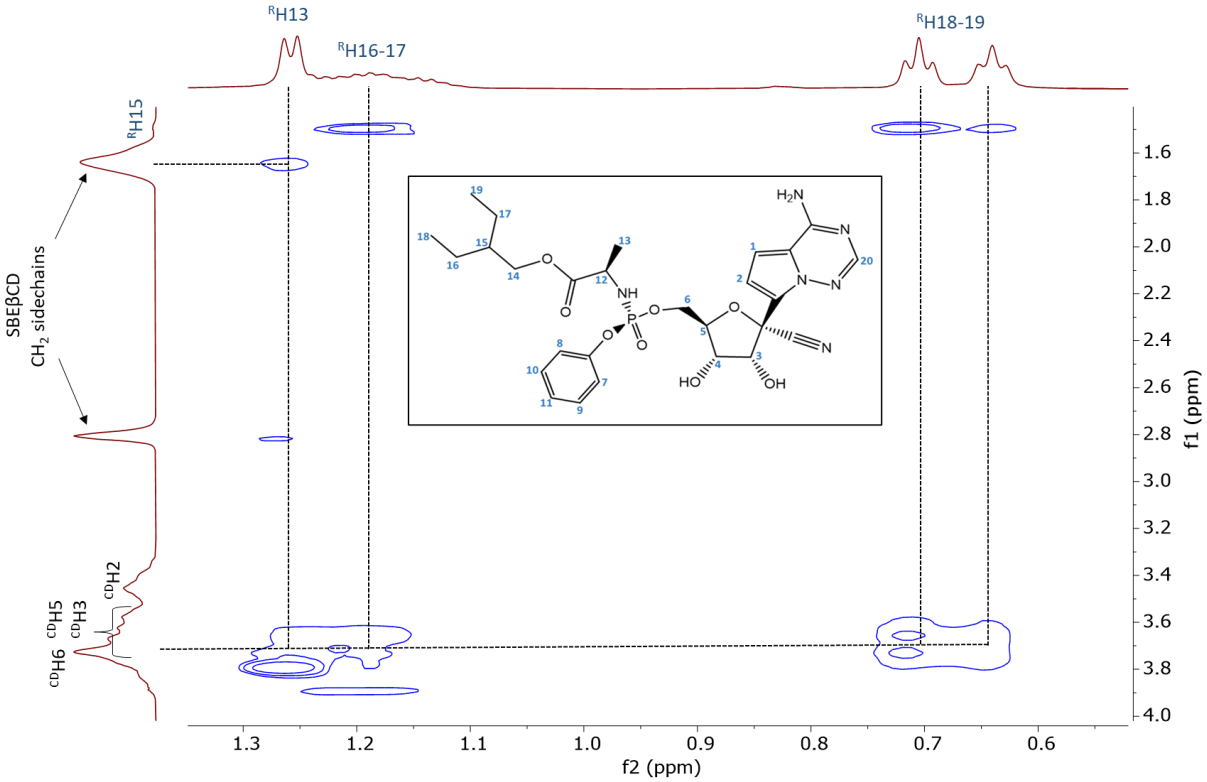

Figure S19. Partial 2D ROESY spectrum of the 1:3 REM:SBEβCD molar ratio sample.

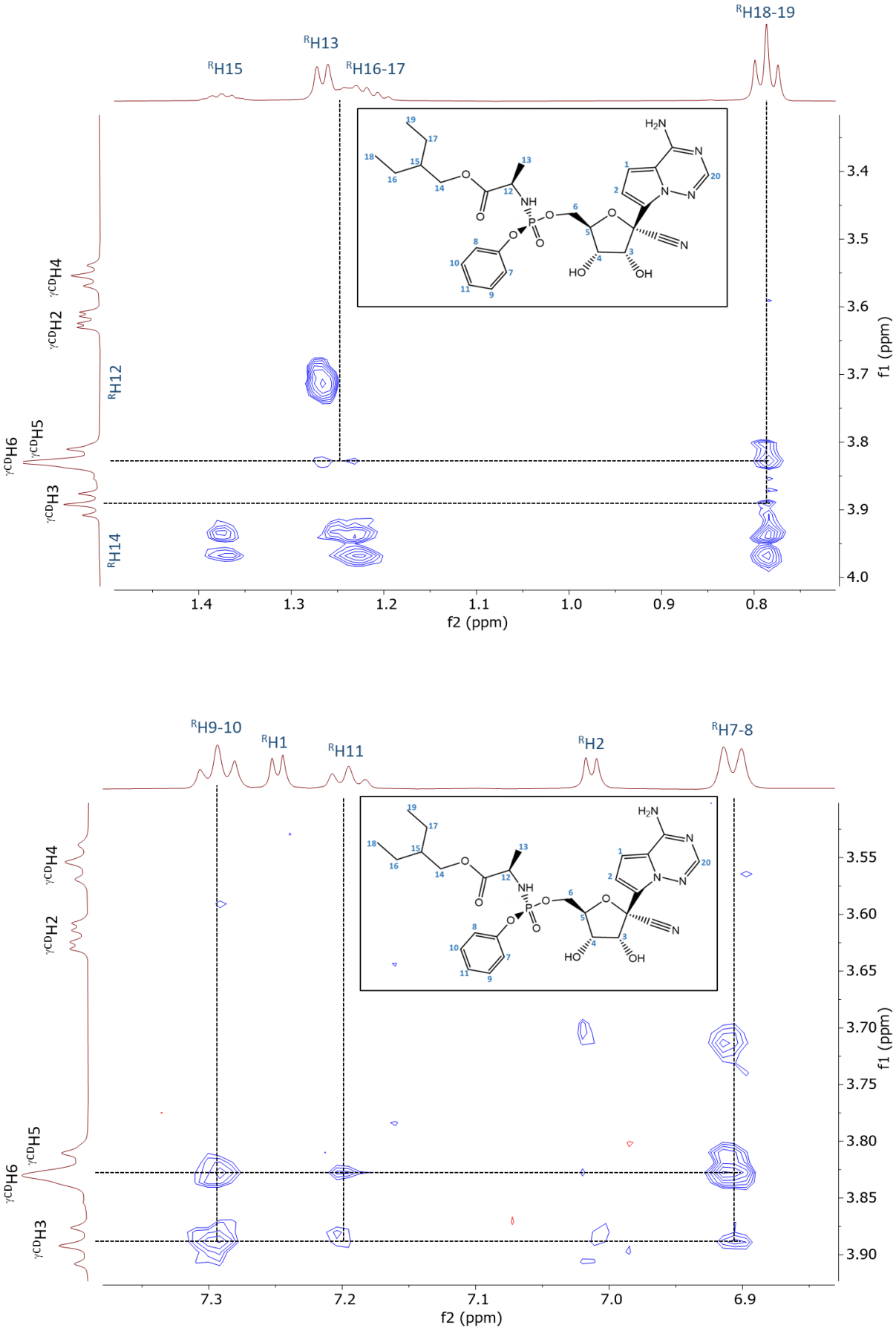

Figure S20. Partial 2D ROESY spectra of the 1:3 REM:γCD molar ratio sample.

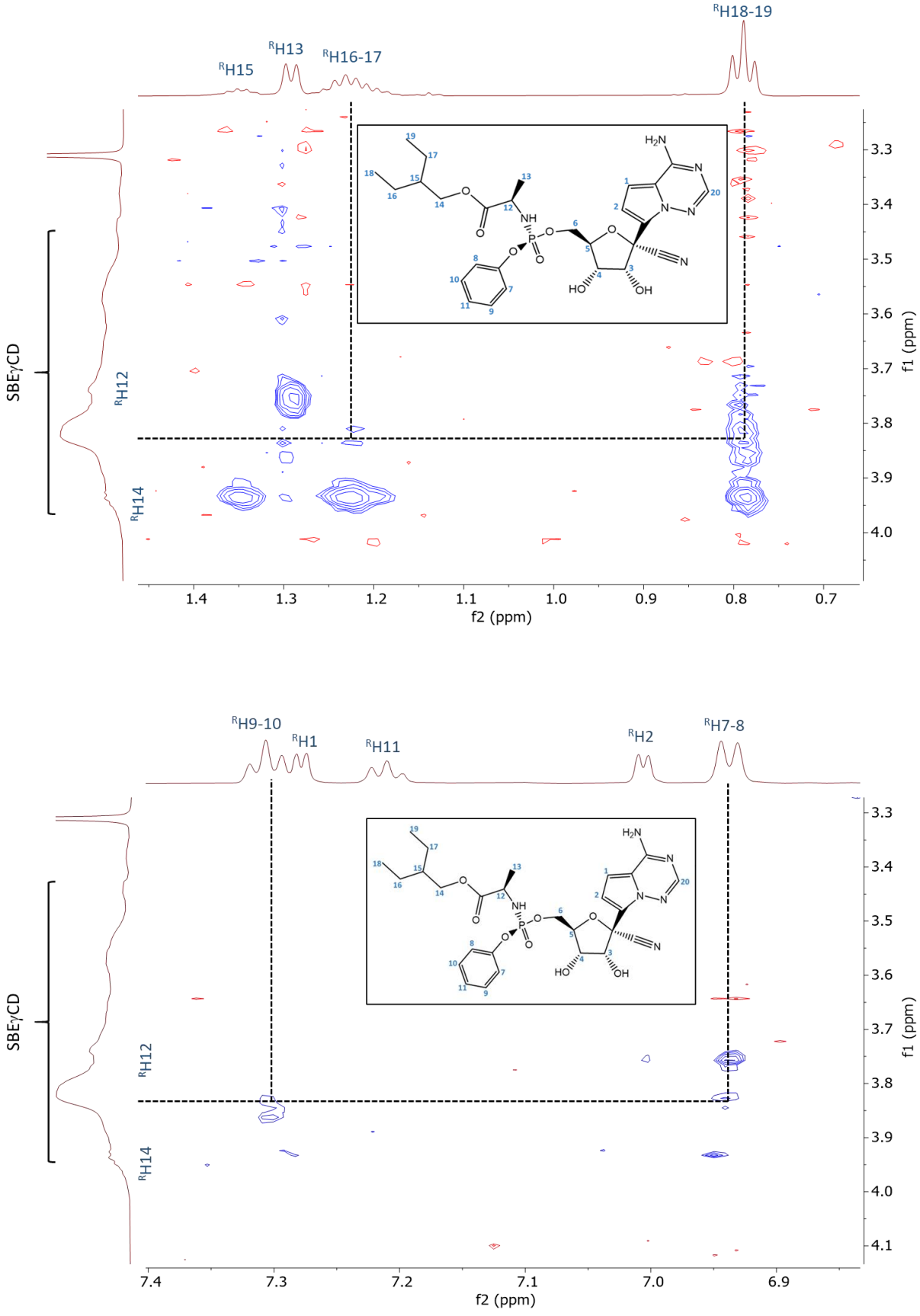

Figure S21. Partial 2D ROESY spectra of the 1:3 REM:SBEγCD molar ratio sample.

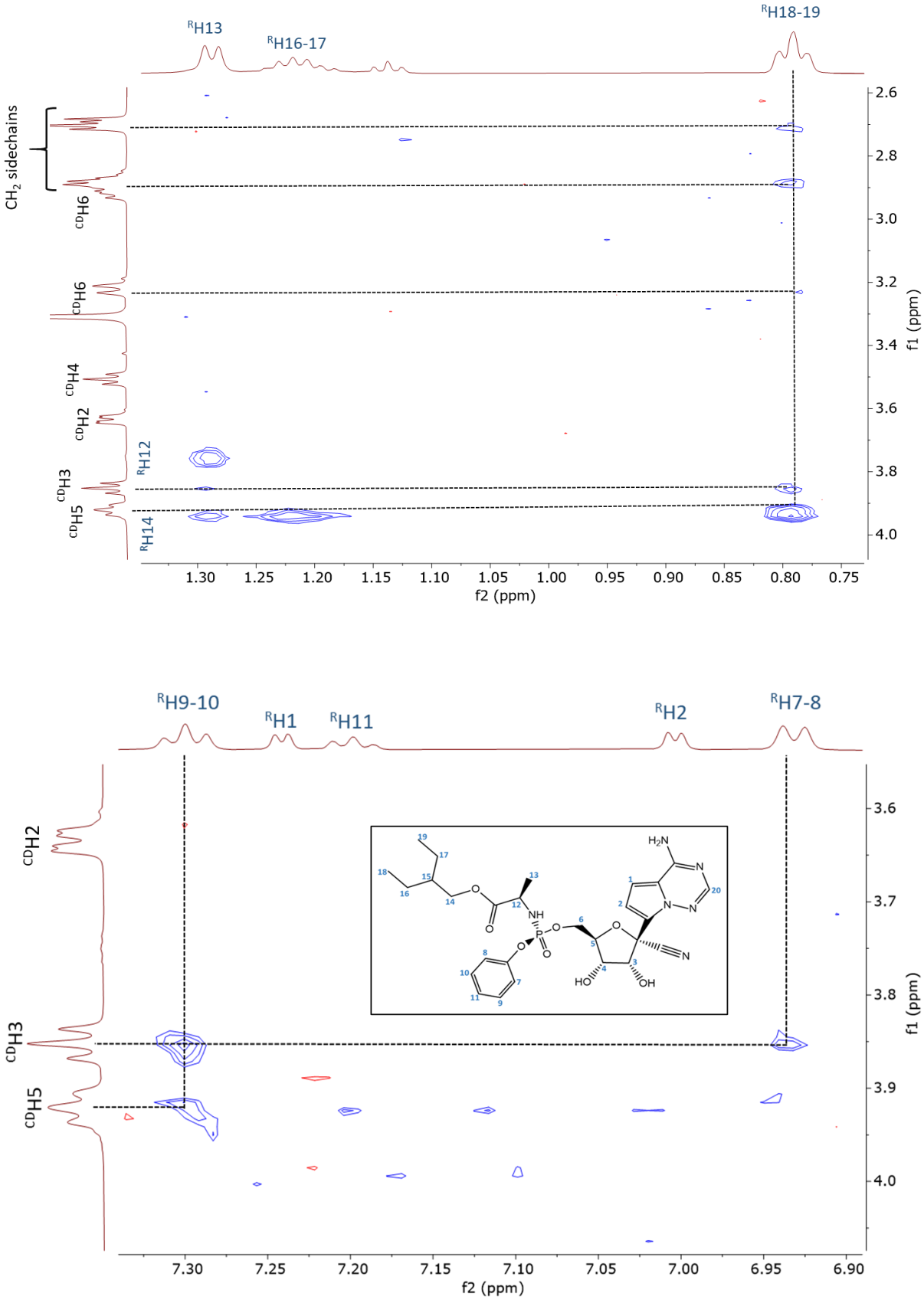

Figure S22. Partial 2D ROESY spectra of the 1:2 REM:sugammadex molar ratio sample.