Supporting Information

Cyclosporin A: Conformational Complexity and Chameleonicity

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NMR Data

NMR Acquisition + Processing

1H detected 1D and 2D NMR spectra were obtained using a Bruker 800 MHz AVANCE III HD spectrometer equipped with a 5.0 mm TCI cryoprobe and a z-gradient system. 1D proton spectra were recorded using a standard one-pulse sequence (30 degrees flip angle) with a relaxation delay of 1 s and an acquisition time of 2.94 s. 32 scans of 65536 points covering 11160.7 Hz were recorded. Data was zero-

filled to 65536 complex points and an exponential window function was applied with a line-broadening factor of 0.3 Hz prior to Fourier transformation.

All 2D experiments (except ROESY) for NMR assignment were recorded at a temperature of 298K with a relaxation delay of 1.0 s. For gradient COSY spectra,[1] a data matrix of 400 × 2048 points covering 11160.7 × 11160.7 Hz was recorded with 4 scans for each increment. Data was linear predicted to 1024 × 2048 points using 32 coefficients and zero filled to 2048 × 2048 points. A sine square bell-shaped window function was applied in F2 and F1 dimension, prior to magnitude mode type 2D Fourier transformation. For edited coherence order selective gradient HSQC spectra[2] using adiabatic inversion pulses on the carbon channel, a data matrix of 512 × 2048 points covering 33202.2 × 11160.7 Hz was recorded using 32 scans for each increment. Data was zero filled to 1024 × 2048 points prior to echo- anti echo type 2D Fourier transformation. A sine square bell-shaped window function shifted by $\pi/2$ in both dimensions was applied. For HMBC spectra,[3] a data matrix of 512 × 2048 points covering 44270.7 × 11160.7 Hz with 64 scans for each increment was recorded using a double low pass J-filter and F1 absorption mode. Data was zero-filled to 1024 × 2048 complex points and a sine bell shaped window function was applied in both F1 and F2. Data was converted to magnitude mode in F2 prior to analysis. ROESY[4] spectra was recorded with a relaxation delay of 1.5 s, a spin lock time of 300 ms and a data matrix of 512 × 2048 points covering 11160.7 × 11160.7 Hz. 16 scans were recorded for each increment. Data was zero filled to 1024 × 2048 points prior to States-TPPI type 2D Fourier transformation and a sine square bell-shaped window function

shifted by π/2 in both dimensions was applied. For MLEV-17 based TOCSY spectra,[5] a data matrix of 512 × 2048 points covering 9615.4 × 9602.5 Hz. 16 scans were recorded for each increment. Data was zero filled to 1024 × 2048 complex points prior to TPPI type 2D Fourier transformation. A sine square bell-shaped window function shifted by π/2 in both dimensions was applied. All spectra were referenced according to the internal solvent signal (^{1}H: $CDCl_3$ = 7.26 ppm and ^{13}C: $CDCl_3$ = 77.16 ppm).

Atom shift assignments

NMR spectra were matched to the structure of Cyclosporin A (CsA) in MestReNova primarily from HSQC, followed by inferential correlations from HMBC (especially through amide bonds), and COSY / TOCSY cross-peaks.

ROESY NOE's were acquired via oval 2D integration of peaks, measuring both cross-peaks separately, and calculating the average if both peaks appeared clean. Distances were calculated by normalizing each measured AUC to the AUC measured between both alpha protons on Sar[3] to their expected distance (1.797 Å).

$$Distance_{HEX,Å} = 1.797 \times (519.62/NOE_{AUC})^{1/6}$$

$$Distance_{CHX,Å} = 1.797 \times (854/NOE_{AUC})^{1/6}$$

$$Distance_{CDCl3,Å} = 1.797 \times (3774/NOE_{AUC})^{1/6}$$

Measured NOE's that were ambiguous or identified in a region of high background noise were not considered for identifying distance violations. Measured distances of 4.5 Å or higher were also not used. Diastereotopic protons and NMethyls were considered as centroids, noted as "?" in the atom ID.

Sampling Efficiency and Convergence Analysis of AMBER ff03

Detailed convergence analysis has been presented elsewhere.[6] Here, we briefly described how a convergence of the multicanonical energy distribution was obtained from a long trajectory (LT; i.e., 1.0×10^7 steps) and the first m steps of the simulation. Assuming the LT multicanonical energy distribution, lnP_{McMD}^{LT}, was converged (Figures S1a and b), a convergence of the first m steps in the LT would be calculated, as follows: $\Delta\ln P_{McMD}(m) = [\langle(\ln P_{McMD}^{m} - \ln P_{McMD}^{LT})^2\rangle_E]^{1/2}$. Similarly, the deviation of n × LT was calculated, as follows: $\Delta\ln P_{McMD}(n) = [\langle(\ln P_{McMD}^{n} - \ln P_{McMD}^{LT})^2\rangle_E]^{1/2}$. The energy average, $\langle \ldots \rangle_E$, was obtained from the energy ranges that are listed in Table S1.

Flat potential-energy distributions were obtained in each solvent, and the convergence, $\Delta\ln P_{\mathrm{McMD}}$, in the simulation steps was estimated (Figures S1a, b and S2). By setting the converged threshold at $\Delta\ln P_{\mathrm{McMD}}(\mathrm{m}) = 0.05$, most of the solvents converged at $\mathrm{m} \geq 5.0 \times 10^6$ steps (aggregating 2.88 μs). Figure S1b indicates that $\Delta\ln P_{\mathrm{McMD}}(\mathrm{n})$ was approximately converged to 0.05 within 256 independent LT runs (aggregating 5.12 μs). Based on these results, a common protocol was applied for all the solvents with

some margin (1.0×10^7 steps × 288 independent runs (aggregating 5.76 μs)). Thus, this simulation length was set as a standard protocol for the other AMBER:1xEHTs (x = 0, 2, and 4) force fields.

Neale, et al.[7] reported that an amide trans/cis isomerization was observed during high-temperature MD. Since the flat potential-energy region was set to correspond to the temperature between 280 and 1503 K, cis/trans isomerization was frequently observed mainly in N-methylated amino acids (Figure S1c). For those residues, the number of the isomeric changes between the trans/cis amide conformers, which occurred in one simulation (1.0×10^7 steps), was 4–15 on an average for the standard protocol trajectories. Therefore, the free-energy profiles and population along the dihedral angle, ω (the cis/trans amide isomer), could be precisely analyzed.

FEL analyses via the molecular shapes. The molecular shape is defined by the normalized principal moments of inertia and is represented by two-dimensional (2D) triangular graphs in which the left and right top corners are rod- and sphere-like, respectively, and the bottom is disk-like (Figures S4a–d). Although the relationship between the conformation and PC plane was already determined, the molecular-shape graphs were suitable for the rough comparison of the overall molecular shapes from the MD trajectories. Noteworthily, FEL exhibited the molecular-shape distribution of CsA rather than a single point under all the conditions.

With AMBER ff03, FELs evidently revealed that CsA adopted stable rod-like conformations in all the solvents (Figure S4a), and this corresponds to **1** (Figure 2b in the main text). FELs of the polar solvents exhibited a wider distribution in the molecular shape space, as well as along the PC plane, than those of the apolar solvents, indicating that CsA could adopt flexible conformations, i.e., the metastable conformations were widely distributed in the molecular shape space, except for the rod and sphere corners. With AMBER10:EHT, only the apolar solvents exhibited **1**. The distribution obtained in $CHCl_3$ with AMBER10:EHT was wider than those of AMBER ff03. Interestingly, another rod-like conformation (***E***) with only one or two IMHB(s), which has not been reported experimentally, appeared in the polar solvents and $CHCl_3$. With AMBER12:EHT, **1** was not observed in the molecular shape space. Moreover, ***E*** appeared in the polar solvents and $CHCl_3$. In all the solvents, the metastable conformation comprising rod-to-sphere shapes, which is the main characteristic of this force field, appeared. Conformation ***E*** was the most stable conformation in AMBER14:EHT. Although the overall distributions of all the solvents were similar, their detailed distributions were slightly different.

Surface areas. We have reported an excellent correlation between the cell permeability and SASA of CHX in cyclic hexapeptide diastereomers.[8] Thus, the smallest SASA conformation in the apolar solvents in ff03 could be the most permeable (Figure S5a). Generally, it is known that the polar surface area (PSA) of bRo5 compounds correlates with its permeability.[9] With ff03, the PSAs tended to be larger and smaller

in the polar and apolar solvents, respectively. Conversely, these tendencies were not observed in the AMBER1x:EHT force fields (Figure S5b).

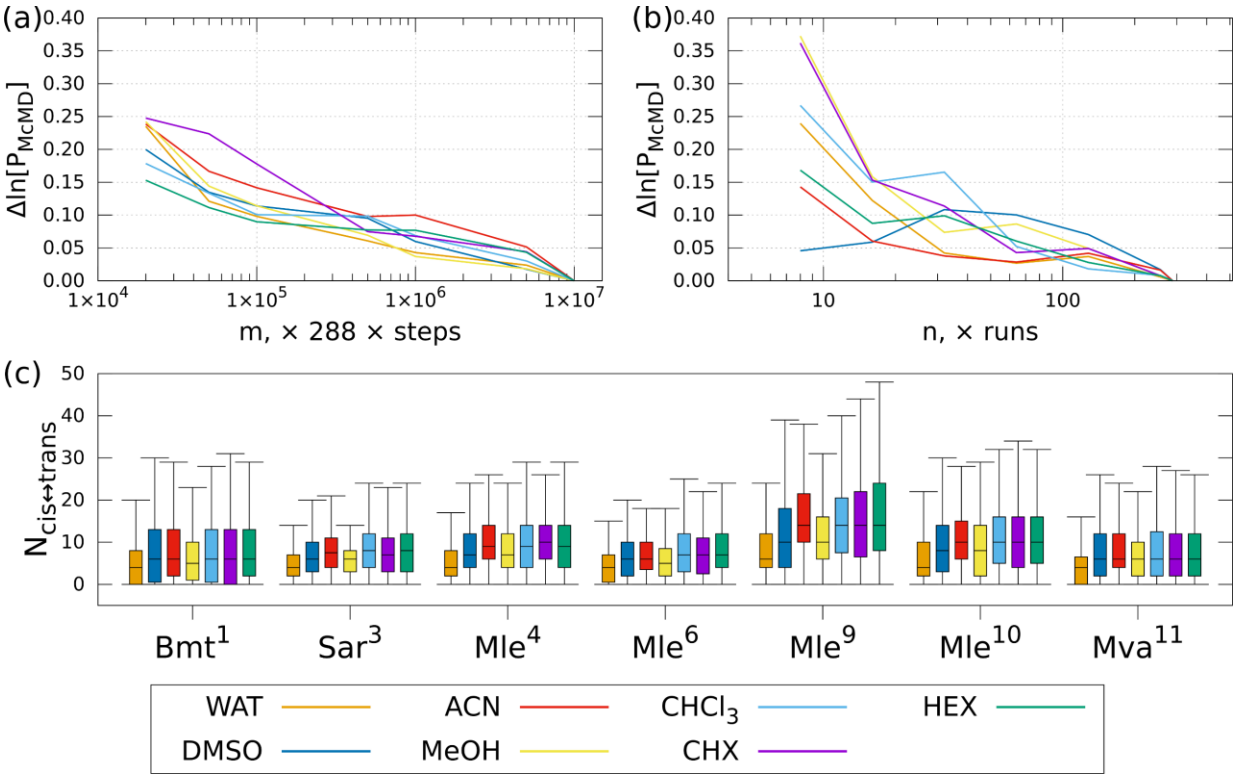

Figure S1. Dependencies of Δln P_{McMD} on the (a) first m steps and (b) n LTs in each solvent employing ff03. (c) Boxplot for the number of cis/trans isomeric changes in each N-methylated residue of LT trajectories with ff03. The color of each solvent is shown in the bottom box.

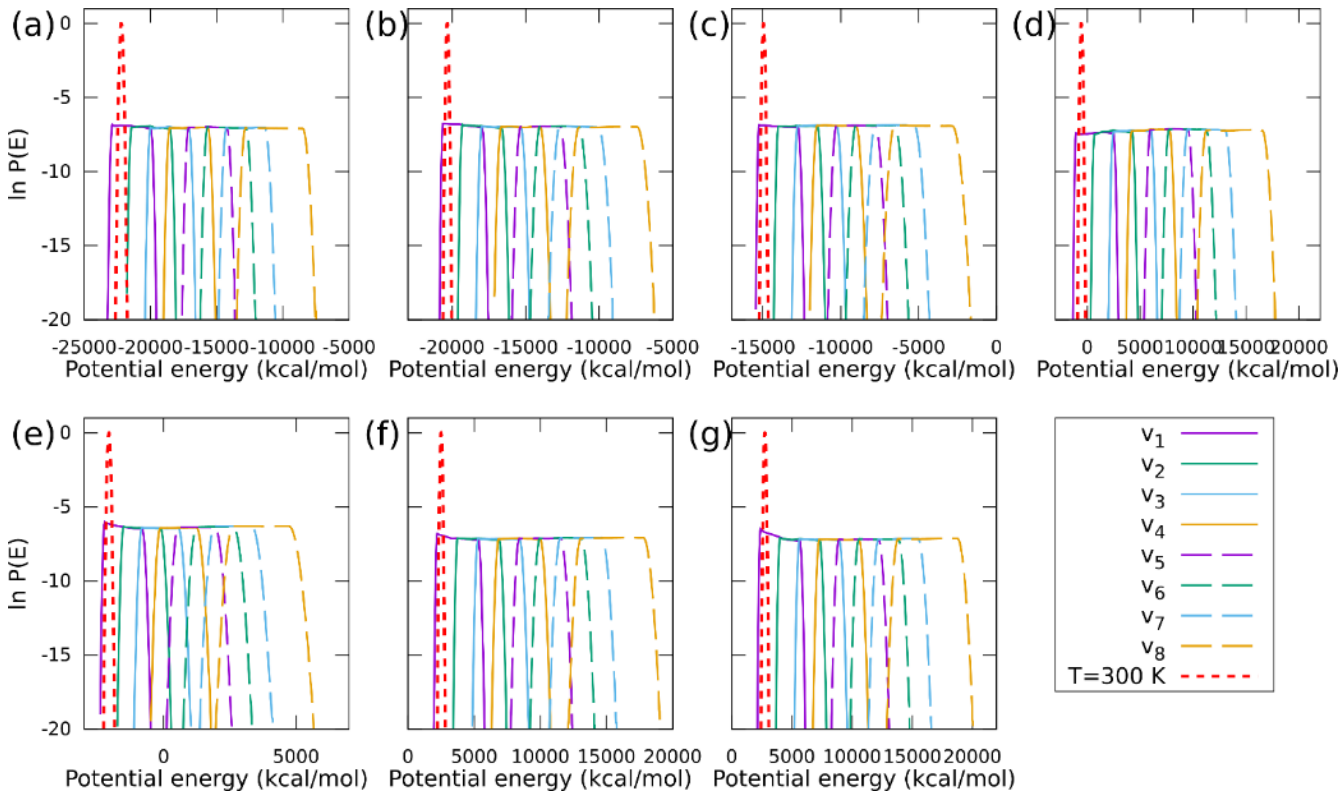

Figure S2. Flat potential energy distributions and a reweighted canonical distribution at T = 300 K for each solvent using ff03. (a) WAT, (b) DMSO, (c) ACN, (d) MeOH, (e) $CHCl_3$, (f) CHX, and (g) HEX.

Table S1. Zones for virtual states and real potential energy with ff03 in each solvent.

i	Virtual state range		WAT		DMSO		ACN		MeOH		$CHCl_3$		CHX		HEX	
			Real energy range		Real energy range		Real energy range		Real energy range		Real energy range		Real energy range		Real energy range	
	low	up	low	up	low	up	low	up	low	up	low	up	low	up	low	up
0	0.0	0.2	-22870.8	-19976.1	-20622.0	-17966.5	-15239.2	-12751.2	-1052.6	2464.1	-2224.9	-813.4	2201.0	5311.0	2392.3	5645.9
1	0.1	0.3	-21411.5	-18540.7	-19282.3	-16650.7	-13995.2	-11507.2	693.8	4210.5	-1507.2	-119.6	3756.0	6866.0	4019.1	7296.7
2	0.2	0.4	-19976.1	-17105.3	-17966.5	-15334.9	-12751.2	-10263.2	2464.1	5980.9	-813.4	550.2	5311.0	8421.1	5645.9	8923.4
3	0.3	0.5	-18540.7	-15669.9	-16650.7	-14019.1	-11507.2	-9019.1	4210.5	7727.3	-119.6	1244.0	6866.0	9976.1	7296.7	10574.2
4	0.4	0.6	-17105.3	-14234.5	-15334.9	-12679.4	-10263.2	-7775.1	5980.9	9497.6	550.2	1937.8	8421.1	11531.1	8923.4	12201.0
5	0.5	0.7	-15669.9	-12799.0	-14019.1	-11363.6	-9019.1	-6531.1	7727.3	11244.0	1244.0	2631.6	9976.1	13086.1	10574.2	13827.8
6	0.6	0.8	-14234.5	-11363.6	-12679.4	-10047.9	-7775.1	-5287.1	9497.6	13014.4	1937.8	3325.4	11531.1	14641.2	12201.0	15478.5
7	0.7	1.0	-12799.0	-8492.8	-11363.6	-7416.3	-6531.1	-2823.0	11244.0	16531.1	2631.6	4736.8	13086.1	17775.1	13827.8	18756.0

Unit of real energy range is kcal/mol.

Table S2. RMSD Between the C_α Atoms of the Conformations in Figure 2b.

Conformation	**1**	**2**	**3**	**4**	**5**	**6**	**7**	***A***	***B***	***C***	***D***	***E***
2	2.58											
3	2.82	0.55										
4	2.90	1.24	1.33									
5	1.66	2.40	2.47	2.51								
6	1.41	2.09	2.29	2.11	1.34							
7	3.08	3.27	3.61	2.99	3.00	2.74						
A	**0.70**	2.58	2.86	2.86	1.80	1.30	2.98					
B	2.66	0.95	**0.89**	1.37	2.39	2.08	3.69	2.66				
C	3.75	4.14	4.53	3.96	4.12	3.46	2.45	3.46	4.39			
D	2.57	2.25	2.32	1.97	2.15	2.11	2.60	2.77	2.58	3.99		
E	3.89	3.42	3.57	2.97	3.81	3.37	2.95	3.83	3.56	3.32	3.03	
F	3.53	3.82	4.03	3.48	3.12	3.28	2.42	3.60	4.10	3.53	2.97	3.06

Unit in angstrom (Å). The smaller RMSDs between experimentally and computationally derived structures (**1**–***A*** and **3**–***B***) are written in bold numbers.

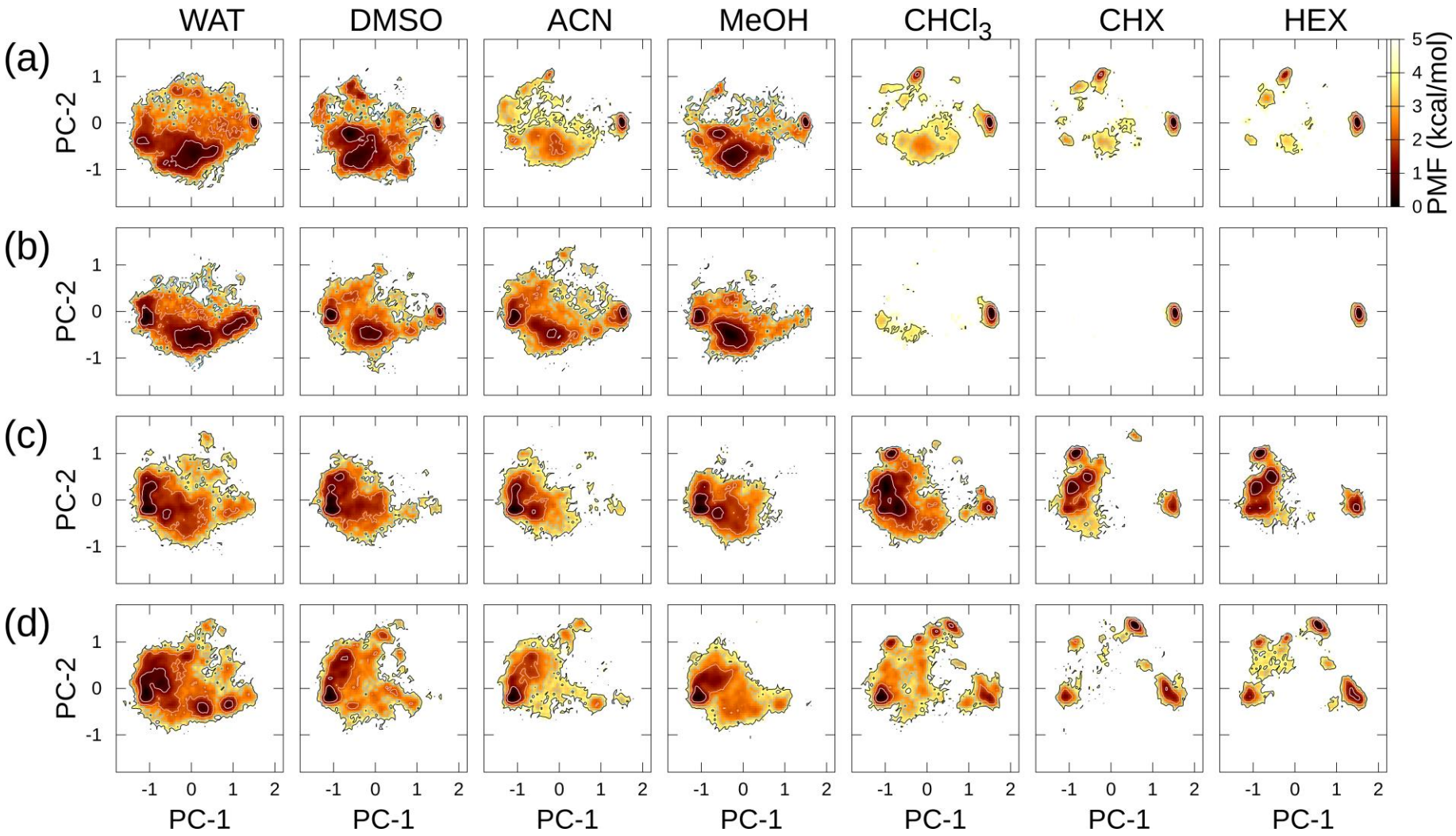

Figure S3. FELs along the PC-1 and PC-2 axes in each solvent at 300 K. (a) AMBER ff03, (b) AMBER10:EHT, (c) AMBER12:EHT, and (d) AMBER14:EHT. The contour lines of PMF = 1.0, 2.0, 3.0, and 4.0 kcal/mol are represented by the white, pink, sky-blue, and black lines, respectively. Figures S3a and b are identical to Figures 2a and 3 in the main text, respectively, and shown here for comparison with the other force fields.

TableS3. Positions of the representative conformation and its free energy value obtained from the FELs using ff03.

	WAT		DMSO		ACN		MeOH		$CHCl_3$		CHX		HEX	
ID	(PC-1,PC-2)	ΔF	(PC-1,PC-2)	ΔF	(PC-1,PC-2)	ΔF	(PC-1,PC-2)	ΔF	(PC-1,PC-2)	ΔF	(PC-1,PC-2)	ΔF	(PC-1,PC-2)	ΔF
1	(1.40,0.00)	1.00	(1.40,0.00)	0.71	(1.40,0.00)	0.00	(1.40,0.00)	0.75	(1.40,0.00)	0.00	(1.40,0.00)	0.00	(1.40,0.00)	0.00
2	(0.65,-1.10)	2.41	(0.65,-1.05)	1.35	(0.75,-1.10)	3.91	(0.70,-1.05)	3.25	(0.70,-1.05)	5.41	(0.70,-1.05)	np	(0.70,-1.05)	5.79
3	(0.65,-1.30)	3.87	(0.70,-1.35)	1.98	(0.70,-1.35)	np	(0.70,-1.35)	np	(0.70,-1.35)	np	(0.70,-1.35)	np	(0.70,-1.35)	np
4	(0.15,-1.15)	np	(0.05,-1.20)	np	(0.15,-1.20)	np	(0.05,-1.15)	np	(0.05,-1.15)	np	(0.10,-1.20)	np	(0.10,-1.20)	np
5	(0.95,-0.20)	2.22	(1.00,-0.25)	2.92	(0.95,-0.25)	3.62	(1.05,-0.30)	2.61	(1.05,-0.25)	4.36	(1.00,-0.25)	5.50	(0.95,-0.20)	5.63
6	(0.95,-0.35)	1.92	(0.95,-0.35)	2.41	(0.90,-0.40)	2.87	(0.85,-0.35)	2.82	(0.85,-0.40)	4.28	(0.95,-0.35)	5.43	(0.95,-0.35)	5.72
7	(-0.20,0.65)	2.64	(-0.15,0.65)	4.09	(-0.15,0.65)	4.34	(-0.15,0.65)	6.02	(-0.25,0.70)	3.98	(-0.25,0.75)	3.67	(-0.25,0.75)	4.53
A	(1.40,0.00)	1.00	(1.40,0.00)	0.71	(1.40,0.00)	0.00	(1.40,-0.05)	0.75	(1.40,0.00)	0.00	(1.40,0.00)	0.00	(1.40,-0.05)	0.00
B	(0.80,-1.25)	2.37	(0.75,-1.30)	1.21	(0.75,-1.25)	3.91	(0.80,-1.30)	3.25	(0.80,-1.30)	5.41	(0.80,-1.30)	np	(0.80,-1.30)	5.79
C	(-0.35,1.00)	2.90	(-0.25,1.10)	4.47	(-0.35,1.00)	1.73	(-0.30,1.00)	np	(-0.35,1.00)	0.81	(-0.35,1.00)	0.91	(-0.35,1.00)	1.14
D	(0.05,-0.60)	0.00	(0.05,-0.55)	0.00	(0.10,-0.65)	0.84	(0.05,-0.65)	0.00	(0.15,-0.55)	1.49	(0.10,-0.60)	2.64	(0.05,-0.60)	3.03
E	(-1.15,-0.05)	1.92	(-1.10,-0.10)	2.13	(-1.20,0.00)	2.52	(-1.10,-0.10)	2.83	(-1.20,0.00)	3.47	(-1.20,-0.10)	3.51	(-1.20,0.00)	3.85
F	(-0.75,0.85)	3.89	(-0.65,0.85)	1.90	(-0.65,0.85)	2.88	(-0.65,0.85)	3.47	(-0.70,0.85)	3.14	(-0.75,0.85)	2.93	(-0.65,0.85)	3.42

Unit in kcal/mol. np: no population or higher than 10.0 kcal/mol.

Table S4. Positions of the representative conformation and its free energy value obtained from the FELs using AMBER10:EHT.

	WAT		DMSO		ACN		MeOH		$CHCl_3$		CHX		HEX	
ID	(PC-1,PC-2)	ΔF	(PC-1,PC-2)	ΔF	(PC-1,PC-2)	ΔF	(PC-1,PC-2)	ΔF	(PC-1,PC-2)	ΔF	(PC-1,PC-2)	ΔF	(PC-1,PC-2)	ΔF
1	(1.40,0.00)	1.45	(1.45,0.00)	0.52	(1.45,0.00)	0.02	(1.40,0.00)	2.16	(1.45,0.00)	0.00	(1.45,0.00)	0.00	(1.45,0.00)	0.00
2	(0.70,-1.00)	2.76	(0.70,-1.05)	3.78	(0.70,-1.05)	3.54	(0.70,-1.05)	3.61	(0.70,-1.05)	np	(0.70,-1.05)	np	(0.70,-1.05)	np
3	(0.70,-1.35)	np	(0.70,-1.35)	6.56	(0.70,-1.35)	np	(0.70,-1.35)	np	(0.70,-1.35)	np	(0.70,-1.35)	np	(0.70,-1.35)	np
4	(0.10,-1.20)	np	(0.15,-1.20)	np	(0.10,-1.25)	np	(0.10,-1.20)	np	(0.10,-1.20)	np	(0.05,-1.20)	np	(0.05,-1.20)	np
5	(1.00,-0.30)	1.04	(1.05,-0.30)	2.61	(1.05,-0.20)	1.81	(1.00,-0.25)	2.49	(0.95,-0.30)	4.55	(1.05,-0.20)	6.38	(1.05,-0.20)	np
6	(0.95,-0.35)	0.68	(0.85,-0.45)	1.51	(0.85,-0.45)	1.30	(0.85,-0.40)	1.97	(0.85,-0.45)	3.82	(0.95,-0.35)	np	(0.90,-0.40)	np
7	(-0.25,0.65)	3.48	(-0.15,0.70)	2.49	(-0.25,0.65)	3.23	(-0.15,0.65)	3.72	(-0.25,0.75)	6.63	(-0.20,0.65)	np	(-0.20,0.75)	np
A	(1.45,-0.05)	1.46	(1.45,-0.05)	0.52	(1.45,-0.05)	0.06	(1.45,-0.05)	2.18	(1.45,-0.05)	0.02	(1.45,-0.05)	0.02	(1.45,-0.05)	0.04
B	(0.80,-1.30)	2.76	(0.80,-1.30)	3.77	(0.80,-1.30)	3.54	(0.80,-1.30)	3.61	(0.80,-1.30)	np	(0.80,-1.30)	np	(0.80,-1.30)	np
C	(-0.30,1.05)	4.69	(-0.30,1.05)	2.49	(-0.35,1.00)	2.12	(-0.35,1.05)	4.31	(-0.30,1.00)	4.23	(-0.25,1.10)	np	(-0.30,1.00)	5.61
D	(0.05,-0.60)	0.00	(0.05,-0.55)	0.32	(0.05,-0.55)	0.28	(0.05,-0.55)	0.00	(0.05,-0.60)	3.80	(0.15,-0.55)	5.44	(0.05,-0.60)	6.54
E	(-1.15,-0.10)	0.55	(-1.20,-0.10)	0.00	(-1.15,-0.10)	0.00	(-1.20,-0.10)	0.48	(-1.20,-0.10)	3.43	(-1.10,-0.10)	5.22	(-1.10,-0.10)	np
F	(-0.75,0.85)	np	(-0.65,0.85)	np	(-0.70,0.85)	2.76	(-0.75,0.90)	np	(-0.75,0.85)	5.61	(-0.75,0.95)	np	(-0.75,0.85)	np

Unit in kcal/mol. np: no population or higher than 10.0 kcal/mol.

Table S5. Positions of the representative conformation and its free energy value obtained from the FELs using AMBER12:EHT.

	WAT		DMSO		ACN		MeOH		$CHCl_3$		CHX		HEX	
ID	(PC-1,PC-2)	ΔF	(PC-1,PC-2)	ΔF	(PC-1,PC-2)	ΔF	(PC-1,PC-2)	ΔF	(PC-1,PC-2)	ΔF	(PC-1,PC-2)	ΔF	(PC-1,PC-2)	ΔF
1	(1.40,0.00)	2.05	(1.40,0.00)	2.89	(1.45,0.10)	2.74	(1.45,0.05)	np	(1.40,0.00)	0.45	(1.40,0.00)	0.00	(1.40,0.00)	0.00
2	(0.65,-1.00)	3.95	(0.65,-1.05)	np	(0.70,-1.05)	np	(0.70,-1.05)	np	(0.70,-1.05)	np	(0.70,-1.05)	np	(0.70,-1.05)	np
3	(0.70,-1.35)	4.24	(0.70,-1.35)	np	(0.70,-1.35)	np	(0.70,-1.35)	np	(0.70,-1.35)	np	(0.70,-1.35)	np	(0.70,-1.35)	np
4	(0.10,-1.15)	np	(0.15,-1.15)	np	(0.10,-1.20)	np	(0.10,-1.15)	np	(0.10,-1.20)	np	(0.10,-1.20)	np	(0.10,-1.20)	np
5	(1.00,-0.25)	1.53	(0.95,-0.30)	3.13	(1.05,-0.25)	3.47	(1.00,-0.20)	5.53	(1.05,-0.25)	2.35	(1.00,-0.20)	2.69	(1.05,-0.25)	2.77
6	(0.85,-0.35)	1.15	(0.85,-0.35)	2.16	(0.90,-0.40)	3.47	(0.90,-0.40)	3.55	(0.90,-0.35)	1.81	(0.90,-0.45)	np	(0.90,-0.40)	5.07
7	(-0.15,0.65)	2.01	(-0.25,0.75)	3.45	(-0.25,0.65)	4.37	(-0.25,0.65)	4.96	(-0.25,0.65)	2.26	(-0.25,0.75)	2.41	(-0.20,0.70)	3.54
A	(1.35,-0.05)	2.05	(1.35,0.00)	2.90	(1.35,-0.05)	2.74	(1.35,0.00)	np	(1.35,-0.05)	0.45	(1.40,0.00)	0.00	(1.40,0.00)	0.00
B	(0.80,-1.30)	3.73	(0.80,-1.30)	np	(0.80,-1.30)	np	(0.80,-1.30)	np	(0.80,-1.30)	np	(0.80,-1.30)	np	(0.80,-1.30)	np
C	(-0.35,1.05)	2.46	(-0.30,1.05)	4.03	(-0.30,1.10)	4.67	(-0.35,1.00)	4.93	(-0.25,1.00)	2.40	(-0.30,1.00)	1.60	(-0.30,1.05)	4.23
D	(0.10,-0.55)	0.52	(0.10,-0.55)	1.54	(0.15,-0.65)	1.73	(0.05,-0.60)	0.87	(0.10,-0.55)	0.68	(0.15,-0.60)	2.18	(0.05,-0.55)	3.07
E	(-1.20,0.00)	0.00	(-1.15,-0.10)	0.00	(-1.15,-0.10)	0.00	(-1.15,-0.05)	0.00	(-1.15,-0.10)	0.00	(-1.10,0.00)	0.27	(-1.10,-0.10)	0.69
F	(-0.65,0.85)	3.68	(-0.65,0.85)	3.18	(-0.65,0.85)	2.62	(-0.65,0.90)	3.43	(-0.75,0.95)	1.17	(-0.75,0.95)	0.75	(-0.75,0.95)	1.08

Unit in kcal/mol. np: no population or higher than 10.0 kcal/mol.

Table S6. Positions of the representative conformation and its free energy value obtained from the FELs using AMBER14:EHT.

	WAT		DMSO		ACN		MeOH		$CHCl_3$		CHX		HEX	
ID	(PC-1,PC-2)	ΔF	(PC-1,PC-2)	ΔF	(PC-1,PC-2)	ΔF	(PC-1,PC-2)	ΔF	(PC-1,PC-2)	ΔF	(PC-1,PC-2)	ΔF	(PC-1,PC-2)	ΔF
1	(1.40,0.05)	2.05	(1.45,0.05)	3.91	(1.50,0.00)	3.12	(1.45,0.05)	5.47	(1.50,0.00)	0.35	(1.50,0.10)	0.00	(1.45,0.00)	0.00
2	(0.70,-1.05)	4.00	(0.70,-1.05)	np	(0.70,-1.05)	np	(0.70,-1.05)	9.98	(0.70,-1.05)	6.09	(0.70,-1.05)	np	(0.70,-1.05)	np
3	(0.70,-1.35)	np	(0.70,-1.35)	np	(0.70,-1.35)	np	(0.70,-1.35)	np	(0.70,-1.35)	np	(0.70,-1.35)	np	(0.70,-1.35)	np
4	(0.10,-1.20)	np	(0.10,-1.20)	np	(0.05,-1.20)	np	(0.05,-1.15)	np	(0.10,-1.20)	np	(0.10,-1.20)	np	(0.10,-1.20)	np
5	(0.95,-0.30)	1.82	(0.95,-0.30)	3.02	(0.95,-0.30)	3.04	(0.95,-0.30)	2.41	(0.95,-0.30)	1.86	(1.00,-0.20)	2.31	(1.05,-0.20)	2.09
6	(0.85,-0.40)	0.42	(0.85,-0.35)	1.48	(0.85,-0.35)	1.43	(0.85,-0.45)	1.28	(0.90,-0.40)	1.34	(0.85,-0.40)	4.67	(0.85,-0.40)	2.45
7	(-0.25,0.65)	1.15	(-0.20,0.65)	1.48	(-0.20,0.65)	2.63	(-0.25,0.65)	3.63	(-0.20,0.70)	1.85	(-0.25,0.75)	2.87	(-0.20,0.65)	3.45
A	(1.40,-0.05)	2.05	(1.35,0.05)	3.91	(1.40,-0.05)	3.12	(1.45,-0.05)	5.47	(1.35,-0.05)	0.35	(1.35,-0.05)	0.02	(1.35,-0.05)	0.00
B	(0.80,-1.30)	4.00	(0.80,-1.30)	np	(0.80,-1.30)	np	(0.80,-1.30)	9.98	(0.80,-1.30)	6.09	(0.80,-1.30)	np	(0.80,-1.30)	np
C	(-0.25,1.00)	1.95	(-0.30,1.00)	1.41	(-0.30,1.05)	1.98	(-0.35,1.05)	4.26	(-0.30,1.05)	0.88	(-0.30,1.05)	2.18	(-0.30,1.05)	1.31
D	(0.15,-0.55)	1.33	(0.05,-0.55)	2.18	(0.15,-0.60)	3.23	(0.15,-0.55)	1.21	(0.05,-0.60)	3.09	(0.10,-0.60)	np	(0.05,-0.60)	np
E	(-1.20,-0.10)	0.00	(-1.20,-0.10)	0.00	(-1.20,-0.10)	0.00	(-1.15,-0.10)	0.00	(-1.20,-0.10)	0.00	(-1.20,-0.10)	0.99	(-1.15,-0.10)	0.96
F	(-0.70,0.90)	2.64	(-0.65,0.85)	1.56	(-0.75,0.85)	2.26	(-0.70,0.90)	2.62	(-0.75,0.95)	2.07	(-0.75,0.90)	3.02	(-0.75,0.85)	2.43

Unit in kcal/mol. np: no population or higher than 10.0 kcal/mol.

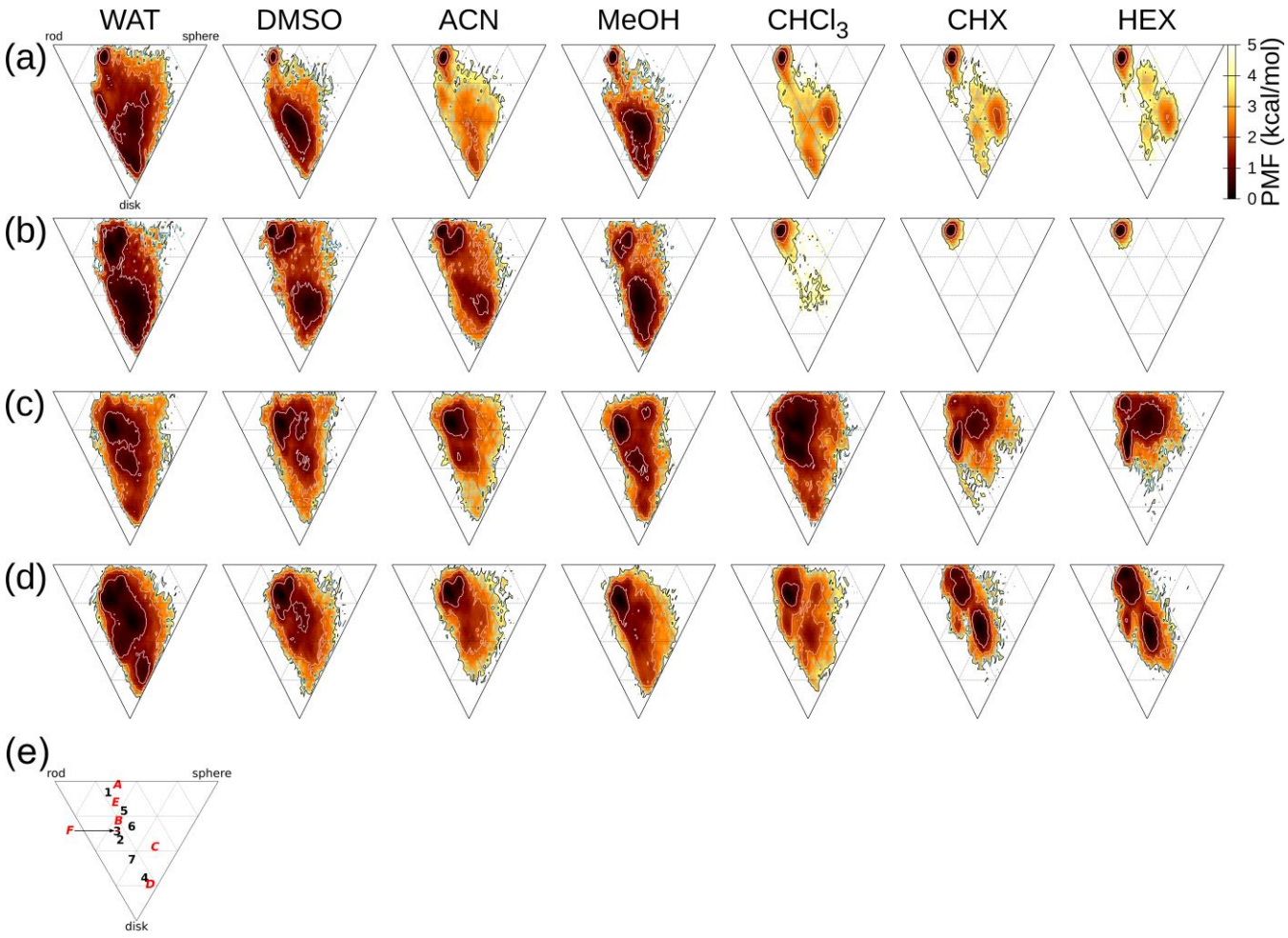

Figure S4. FELs of the molecular shape in each solvent and force field at T = 300 K. (a) AMBER ff03, (b) AMBER10:EHT, (c) AMBER12:EHT, and (d) AMBER14:EHT. The contour lines of PMF = 1.0, 2.0, 3.0, and 4.0 kcal/mol are represented by the white, pink, sky-blue, and black lines, respectively. (e) Relation between the position on the graph and the 3D conformation **1**-**7** and ***A***-***F*** in the main text (Figure 2b).

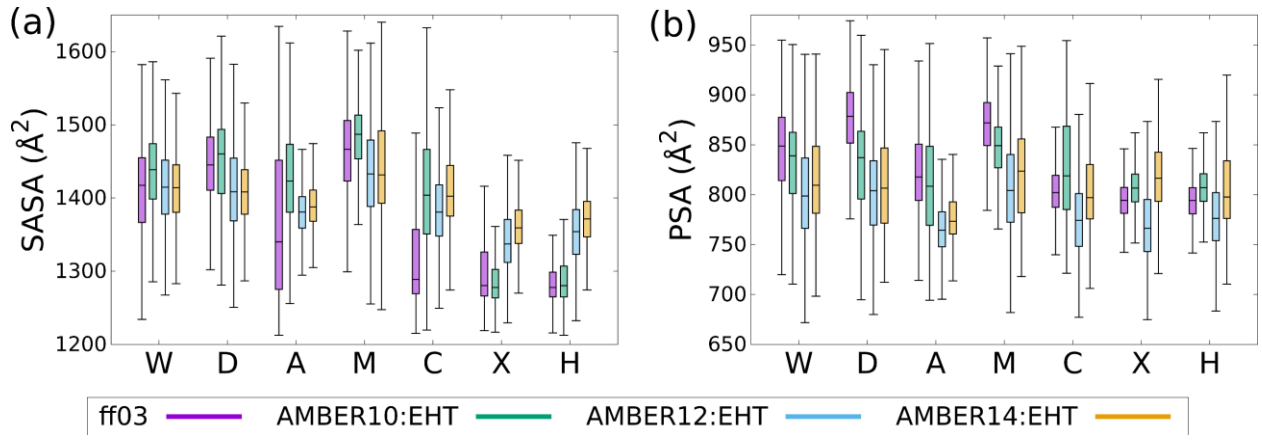

Figure S5. (a) Boxplots of SASA and (b) PSA in each solvent and force field obtained by an ensemble of 10,000 conformers at T = 300 K. W, D, A, M, C, X, and H represent WAT, DMSO, ACN, methanol, chloroform, CHX, and HEX, respectively.

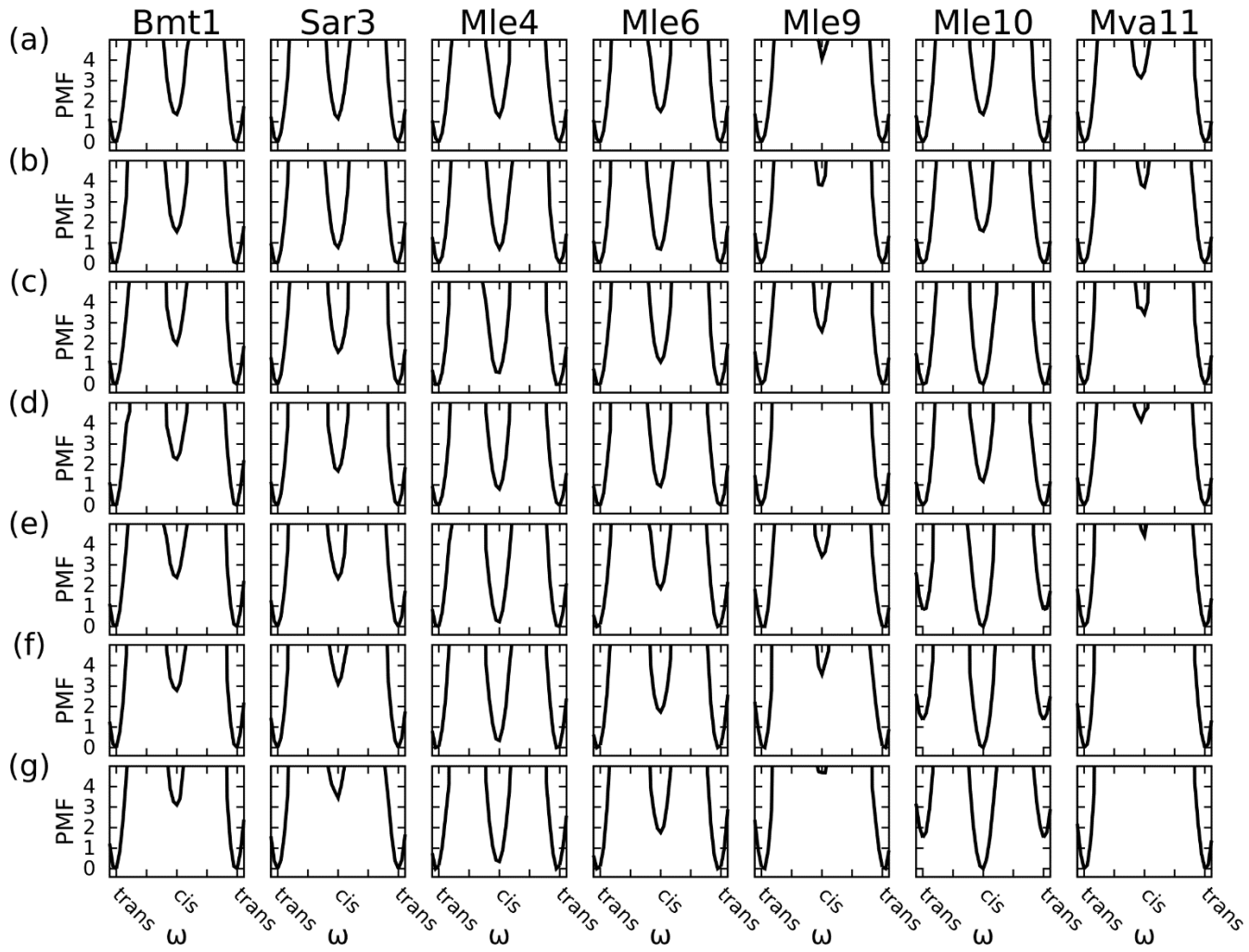

Figure S6. Free-energy profile along dihedral angle ω using ff03. (a) WAT, (b) DMSO, (c) ACN, (d) MeOH, (e) $CHCl_3$, (f) CHX, and (g) HEX. The unit for PMF is kcal/mol.

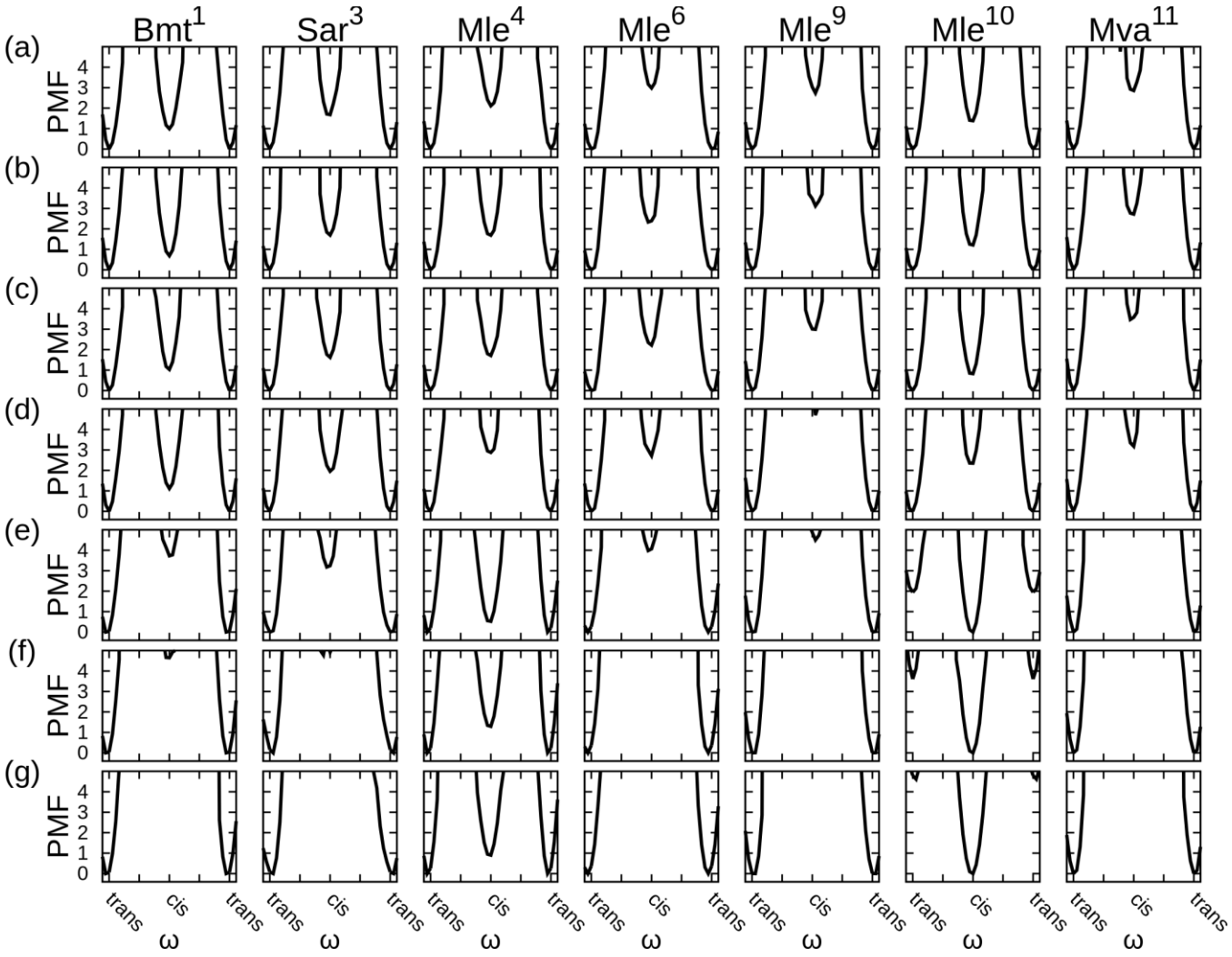

Figure S7. Free-energy profile along dihedral angle ω using AMBER10:EHT. (a) WAT, (b) DMSO, (c) ACN, (d) MeOH, (e) $CHCl_3$, (f) CHX, and (g) HEX. The unit for PMF is kcal/mol.

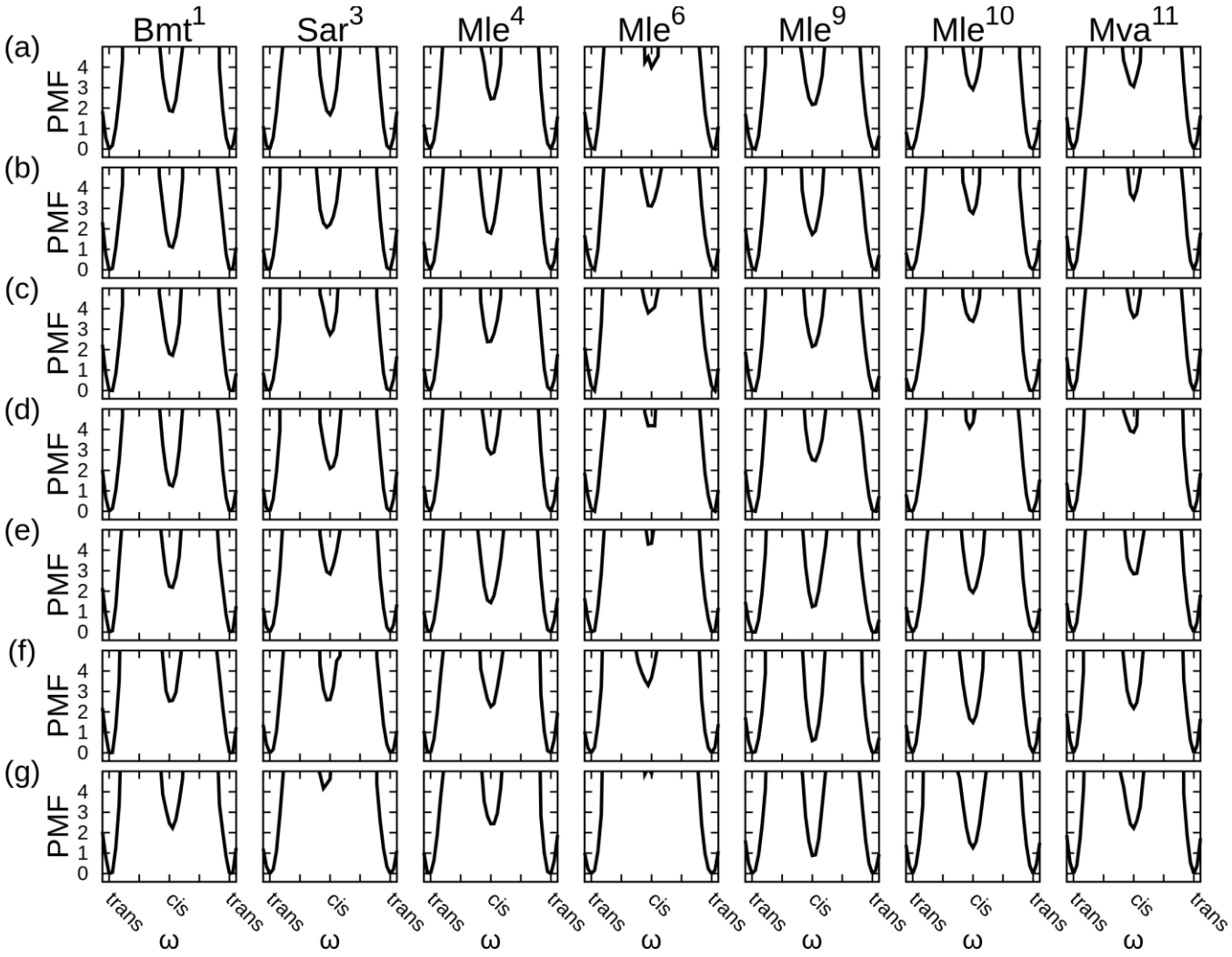

Figure S8. Free-energy profile along dihedral angle ω using AMBER12:EHT. (a) WAT, (b) DMSO, (c) ACN, (d) MeOH, (e) $CHCl_3$, (f) CHX, and (g) HEX. The unit for PMF is kcal/mol.

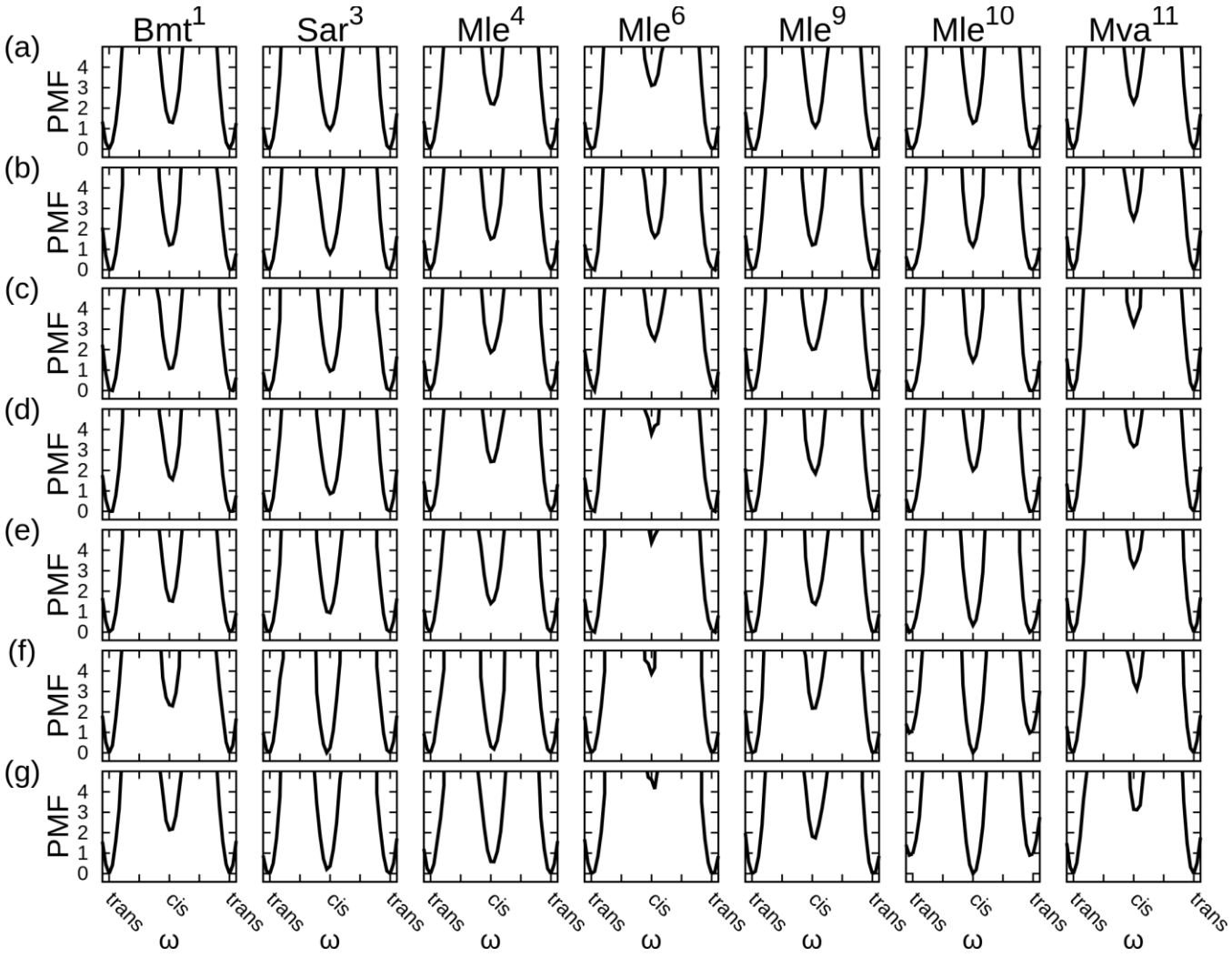

Figure S9. Free-energy profile along dihedral angle ω using AMBER14:EHT. (a) WAT, (b) DMSO, (c) ACN, (d) MeOH, (e) $CHCl_3$, (f) CHX, and (g) HEX. The unit for PMF is kcal/mol.

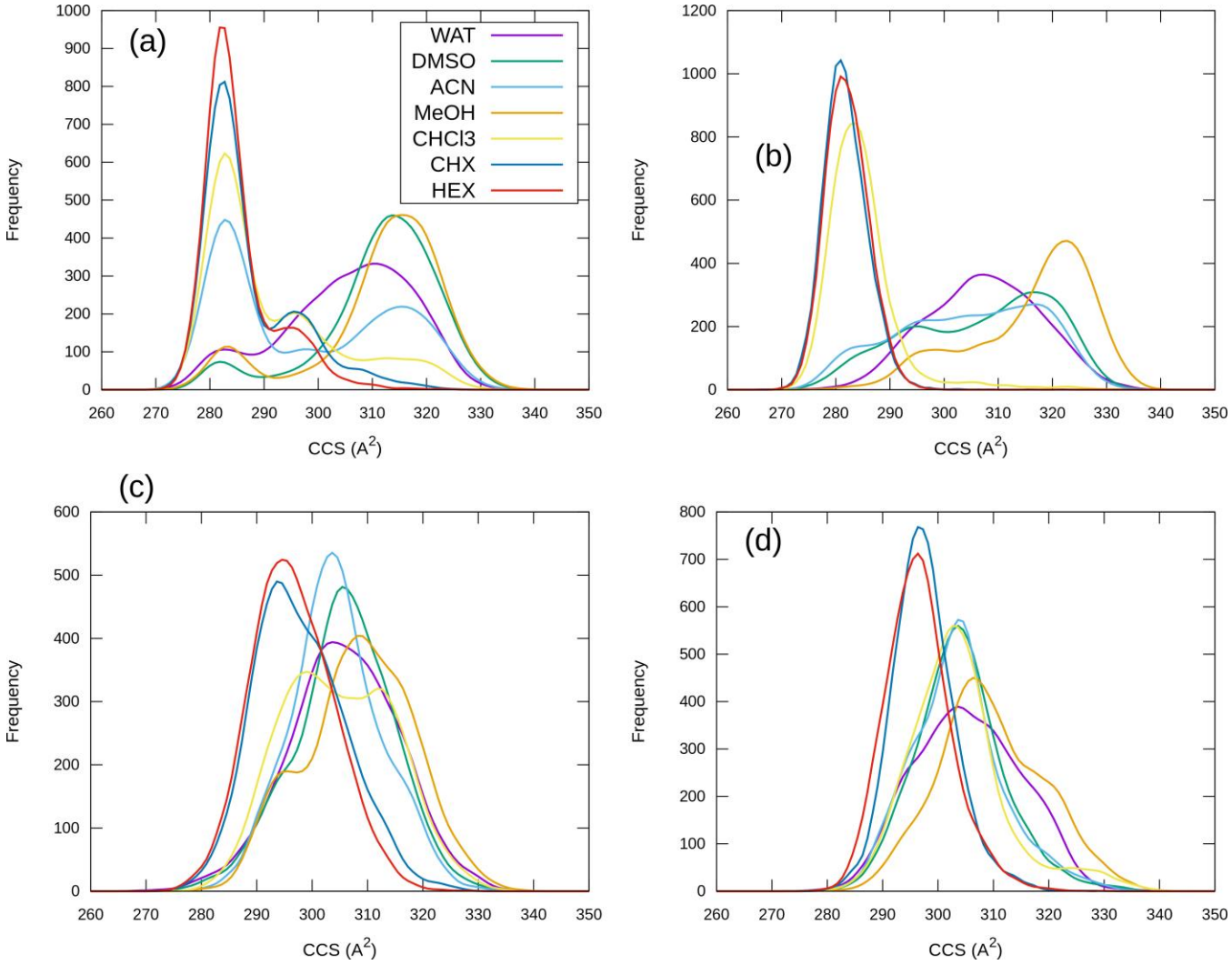

Figure S10. Distributions of CoSIMS[10] results of each solvent using (a) ff03, (b) AMBER10:EHT, (c) AMBER12:EHT, and (d) AMBER14:EHT.

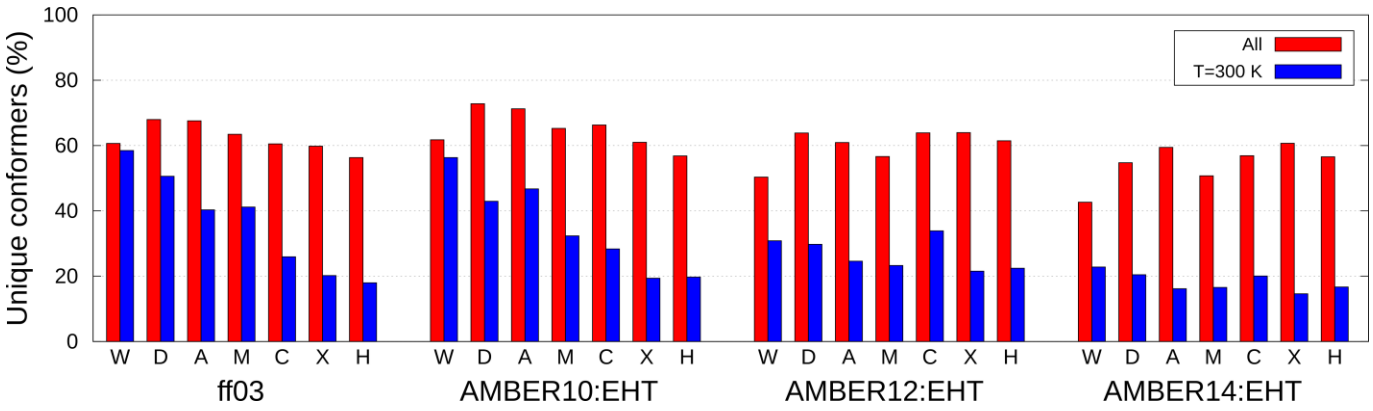

Figure S11. Coco-MD[6] like conformer counts. Unique conformer counts from aggregating all trajectories (2.88 million conformers) are plotted red bars, whereas, from the ensemble of T = 300 K (10,000 conformers) are plotted blue bars.

Table S7. Upper limit distance in $CDCl_3$.

Index	Atom1	Atom2	Distance(Å)	Type	f1(ppm)	f2(ppm)
1	:2@H	:5@HB	3.407	intercycle	2.41	7.94
2	:2@H	:5@H	3.118	intercycle	7.94	7.45
3	:3@HA12	:5@H	3.946	intercycle	4.72	7.45
4	:5@H	:1@HB	3.786	intercycle	7.46	3.79
5	:6@HA	:1@HA	2.669	intercycle	5.46	4.97
6	:6@HA	:1@HD22	3.070	intercycle	4.97	2.40
7	:6@HA	:1@HD1?	2.729	intercycle	4.97	0.70
8	:6@HG	:1@HD1?	3.045	intercycle	1.75	0.71
9	:7@H	:1@HA	2.975	intercycle	7.65	5.45
10	:8@H	:6@HB3	3.568	intercycle	7.15	2.05
11	:8@H	:6@HG	3.010	intercycle	7.15	1.75
12	:10@HA	:6@HB3	2.796	intercycle	5.06	2.07
13	:2@HA	:3@HA2?	2.128	sequential	5.02	3.38
14	:2@H	:1@HA	2.301	sequential	7.95	5.45
15	:2@H	:1@HB	2.845	sequential	7.94	3.79
16	:3@HA12	:4@HN?	2.101	sequential	3.09	4.71
17	:5@HA	:6@HN?	2.080	sequential	4.64	3.24
18	:5@H	:4@HA	2.899	sequential	7.46	5.32
19	:7@H	:6@HA	2.235	sequential	7.65	4.97
20	:7@H	:8@H	2.976	sequential	7.65	7.15
21	:8@HA	:9@HN?	2.166	sequential	3.10	4.82
22	:8@H	:7@HA	2.853	sequential	7.15	4.51
23	:9@HA	:10@HA	1.830	sequential	5.68	5.06
24	:9@HA	:10@HG	2.812	sequential	5.68	1.48
25	:11@HA	:1@HA2?	2.093	sequential	5.12	3.50
26	:1@HA	:1@HB	2.360	intraresidue	5.46	3.79
27	:1@HA	:1@HD22	2.825	intraresidue	5.46	2.39
28	:1@HA	:1@HD1?	2.668	intraresidue	5.46	0.70
29	:1@HA	:1@HA2?	3.363	intraresidue	5.46	3.50
30	:1@HB	:1@HD22	3.092	intraresidue	3.79	2.39
31	:1@HB	:1@HD1?	2.527	intraresidue	3.79	0.71

32	:1@HB	:1@HA2?	2.694	intraresidue	3.79	3.49
33	:1@HD22	:1@HD1?	3.463	intraresidue	0.70	2.39
34	:2@HA	:2@HB2	2.655	intraresidue	5.02	1.71
35	:2@HA	:2@H	3.043	intraresidue	7.95	5.01
36	:2@HB2	:2@H	3.717	intraresidue	7.95	1.71
37	:4@HA	:4@HB2	2.508	intraresidue	5.32	1.98
38	:4@HA	:4@HG	3.127	intraresidue	5.32	1.42
39	:5@HA	:5@HG2?	2.590	intraresidue	4.64	1.06
40	:5@HB	:5@HG2?	2.209	intraresidue	2.41	1.06
41	:5@HG2?	:5@H	3.211	intraresidue	7.46	1.07
42	:5@HA	:5@H	3.018	intraresidue	4.64	7.45
43	:5@H	:5@HB	2.643	intraresidue	2.41	7.46
44	:6@HA	:6@HB2	2.659	intraresidue	4.97	1.38
45	:6@HA	:6@HB3	2.909	intraresidue	4.97	2.04
46	:6@HA	:6@HG	2.878	intraresidue	4.97	1.75
47	:6@HB2	:6@HG	2.474	intraresidue	2.04	1.75
48	:6@HB3	:6@HN?	2.584	intraresidue	1.38	3.24
49	:6@HB2	:6@HN?	2.261	intraresidue	3.24	2.05
50	:6@HN?	:6@HG	3.085	intraresidue	1.75	3.24
51	:7@HA	:7@HB?	2.253	intraresidue	4.51	1.35
52	:7@H	:7@HA	3.025	intraresidue	7.65	4.51
53	:7@H	:7@HB?	2.843	intraresidue	7.65	1.34
54	:8@HA	:8@H	2.928	intraresidue	7.15	4.81
55	:9@HA	:9@HB2	3.078	intraresidue	5.68	2.11
56	:9@HA	:9@HG	2.796	intraresidue	1.31	5.68
57	:10@HA	:10@HG	2.827	intraresidue	5.06	1.49

Table S8. Upper limit distance in cyclohexane-d12.

Index	Atom1	Atom2	Distance(Å)	Type	f1(ppm)	f2(ppm)
1	:1@HA	:6@HD1?	3.119	intercycle	5.31	0.73
2	:1@HD23	:3@HA2?	3.744	intercycle	1.78	3.38
3	:1@HD23	:6@HB3	3.212	intercycle	1.78	1.14
4	:1@HZ	:6@HB2	3.473	intercycle	5.25	1.14
5	:2@H	:5@HB	3.671	intercycle	8.39	2.44
6	:2@H	:5@H	3.122	intercycle	8.39	7.17
7	:3@HA12	:5@H	3.671	intercycle	4.58	7.16
8	:6@HD1?	:11@HN?	2.921	intercycle	0.73	2.63
9	:6@HG	:10@HA	4.191	intercycle	5.10	1.94
10	:6@HG	:11@HN?	3.324	intercycle	1.93	2.64
11	:7@H	:1@HA	3.144	intercycle	7.81	5.31
12	:7@H	:11@HB	4.253	intercycle	7.81	2.19
13	:7@H	:11@HN?	3.246	intercycle	7.81	2.63
14	:8@HA	:11@HN?	3.591	intercycle	4.72	2.62
15	:8@H	:6@HG	3.223	intercycle	7.47	1.93
16	:9@HA	:11@HN?	3.278	intercycle	5.65	2.62
17	:10@HA	:6@HD1?	2.937	intercycle	5.10	0.73
18	:10@HG	:6@HD1?	2.965	intercycle	1.49	0.73
19	:11@HB	:7@HB?	2.463	intercycle	2.19	1.26
20	:11@HN?	:7@HB?	2.614	intercycle	2.62	1.26
21	:2@HA	:3@HA2?	2.196	sequential	4.94	3.38
22	:2@H	:1@HA	2.244	sequential	8.39	5.31
23	:2@H	:1@HB	3.410	sequential	8.39	3.92
24	:3@HA12	:4@HN?	2.179	sequential	4.58	3.05
25	:5@H	:4@HA	2.849	sequential	7.17	5.37
26	:5@H	:4@HN?	2.785	sequential	7.17	3.06
27	:7@H	:6@HA	2.207	sequential	7.81	5.20
28	:7@H	:6@HG	4.103	sequential	7.81	1.93
29	:7@H	:8@H	3.368	sequential	7.82	7.48
30	:8@H	:7@HA	2.645	sequential	7.48	4.35
31	:9@HA	:10@HA	1.945	sequential	5.66	5.09

32	:9@HA	:10@HG	2.991	sequential	5.67	1.49
33	:11@HA	:1@HA2?	2.118	sequential	5.00	3.47
34	:11@HN?	:10@HA	2.297	sequential	5.10	2.62
35	:1@HA	:1@HB	2.781	intraresidue	5.31	3.92
36	:1@HA	:1@HD22	3.312	intraresidue	5.30	1.80
37	:1@HA	:1@HA2?	3.299	intraresidue	5.31	3.47
38	:1@HB	:1@HD22	2.931	intraresidue	3.92	1.79
39	:1@HB	:1@HA2?	2.322	intraresidue	3.92	3.47
40	:1@HZ	:1@HD22	2.664	intraresidue	5.24	1.79
41	:1@CA2?	:1@HD22	3.702	intraresidue	1.79	3.47
42	:2@HB2	:2@H	3.770	intraresidue	1.66	8.39
43	:3@HA2?	:3@HA13	2.291	intraresidue	3.38	2.93
44	:4@HA	:4@HN?	3.347	intraresidue	5.37	3.05
45	:4@HN?	:4@HB2	2.304	intraresidue	3.05	1.53
46	:4@HN?	:4@HG	2.572	intraresidue	3.06	1.41
47	:5@HA	:5@HB	2.959	intraresidue	4.68	2.44
48	:5@HB	:5@HG1?	2.217	intraresidue	2.44	0.79
49	:5@H	:5@HB	2.661	intraresidue	7.17	2.45
50	:5@H	:5@HG2?	3.284	intraresidue	7.17	1.01
51	:6@HA	:6@HD1?	2.539	intraresidue	5.19	0.73
52	:6@HA	:6@HG	3.038	intraresidue	5.19	1.92
53	:7@HA	:7@HB?	2.284	intraresidue	4.35	1.26
54	:7@H	:7@HA	3.066	intraresidue	7.81	4.35
55	:7@H	:7@HB?	2.897	intraresidue	7.81	1.26
56	:8@HA	:8@H	3.000	intraresidue	7.48	4.72
57	:8@HB?	:8@H	2.868	intraresidue	7.48	1.17
58	:9@HA	:9@HG	3.236	intraresidue	5.66	1.32
59	:10@HA	:10@HG	2.996	intraresidue	5.10	1.49
60	:11@HA	:11@HG2?	2.595	intraresidue	0.91	4.99
61	:11@HN?	:11@HB	2.096	intraresidue	2.62	2.19

Table S9. Upper limit distance in n-hexane-d14.

Index	Atom1	Atom2	Distance(Å)	Type	f1(ppm)	f2(ppm)
1	:1@HB	:3@HA2?	3.522	intercycle	3.92	3.38
2	:1@HB	:6@HD1?	4.289	intercycle	3.92	0.78
3	:1@HD23	:3@HA2?	4.377	intercycle	1.79	3.38
4	:1@HD22	:6@HD1?	2.888	intercycle	1.80	0.78
5	:1@HZ	:6@HN?	4.403	intercycle	5.27	3.23
6	:1@HZ	:6@HD1?	3.729	intercycle	5.28	0.78
7	:2@H	:5@HB	3.285	intercycle	8.29	2.47
8	:2@H	:5@H	3.315	intercycle	8.30	7.19
9	:2@H	:6@HA	3.771	intercycle	8.30	5.20
10	:2@H	:7@H	4.103	intercycle	8.29	7.73
11	:3@HA12	:5@H	3.620	intercycle	4.61	7.19
12	:6@HA	:1@HD22	3.695	intercycle	5.19	1.80
13	:6@HA	:4@HA	4.488	intercycle	5.19	4.67
14	:6@HA	:11@HN?	3.709	intercycle	5.18	2.65
15	:6@HG	:10@HA	4.003	intercycle	1.91	5.10
16	:6@HG	:11@HN?	3.356	intercycle	1.91	2.65
17	:6@HN?	:1@HH?	3.637	intercycle	3.23	1.59
18	:7@HA	:5@HG1?	2.983	intercycle	4.38	0.83
19	:7@HA	:11@HN?	4.272	intercycle	4.37	2.65
20	:7@H	:1@HA	3.169	intercycle	7.74	5.37
21	:7@H	:11@HB	4.053	intercycle	7.75	2.20
22	:7@H	:11@HN?	2.928	intercycle	7.74	2.65
23	:8@HA	:11@HN?	3.362	intercycle	4.75	2.65
24	:8@H	:6@HB3	3.812	intercycle	7.42	2.10
25	:8@H	:6@HG	3.027	intercycle	7.42	1.91
26	:8@H	:11@HN?	3.579	intercycle	7.41	2.66
27	:9@HA	:11@HN?	3.223	intercycle	5.69	2.66
28	:9@HN?	:11@HN?	2.916	intercycle	3.20	2.65
29	:10@HA	:6@HD1?	2.853	intercycle	5.10	0.78
30	:11@HB	:7@HB?	2.698	intercycle	2.21	1.28
31	:1@CA2?	:11@HN?	3.827	sequential	3.48	2.65

32	:2@HA	:1@HA2?	3.844	sequential	4.98	3.49
33	:2@HA	:3@HA2?	2.168	sequential	4.98	3.39
34	:2@H	:1@HA	2.243	sequential	8.29	5.37
35	:2@H	:1@HB	3.182	sequential	8.29	3.92
36	:2@H	:3@HA2?	4.159	sequential	8.29	3.39
37	:3@HA13	:4@HA	4.329	sequential	2.94	5.39
38	:3@HA12	:4@HN?	2.164	sequential	4.61	3.06
39	:5@HA	:6@HN?	2.094	sequential	4.67	3.23
40	:5@HB	:4@HN?	3.896	sequential	2.48	3.06
41	:5@H	:4@HN?	2.703	sequential	7.19	3.06
42	:6@HN?	:5@HB	3.523	sequential	3.22	2.47
43	:7@HA	:6@HN?	4.036	sequential	4.37	3.23
44	:7@H	:6@HA	2.207	sequential	7.74	5.19
45	:7@H	:6@HG	3.701	sequential	7.74	1.91
46	:7@H	:8@H	3.558	sequential	7.75	7.42
47	:8@HA	:9@HN?	2.132	sequential	4.76	3.20
48	:8@H	:7@HA	2.637	sequential	7.42	4.37
49	:8@H	:7@HB?	4.299	sequential	7.41	1.29
50	:9@HA	:10@HA	1.880	sequential	5.69	5.10
51	:10@HA	:9@HN?	4.379	sequential	5.10	3.20
52	:10@HN?	:9@HA	4.110	sequential	2.61	5.70
53	:11@HA	:1@HA2?	2.083	sequential	5.04	3.49
54	:11@HN?	:10@HA	2.230	sequential	2.66	5.10
55	:1@HB	:1@HD22	3.065	intraresidue	3.92	1.81
56	:1@HB	:1@HD1?	2.406	intraresidue	3.92	0.87
57	:1@HB	:1@HG1	3.740	intraresidue	3.92	2.27
58	:1@HB	:1@HA2?	2.358	intraresidue	3.92	3.49
59	:1@HZ	:1@HD22	2.561	intraresidue	5.28	1.79
60	:1@HG1	:1@HD22	3.498	intraresidue	2.28	1.79
61	:1@HG1	:1@HA2?	4.247	intraresidue	2.27	3.48
62	:1@CA2?	:1@HD22	3.931	intraresidue	3.48	1.80
63	:3@HA2?	:3@HA12	3.713	intraresidue	4.60	3.39
64	:4@HN?	:4@HB2	3.957	intraresidue	2.07	3.06
65	:4@HN?	:4@HG	2.824	intraresidue	3.06	1.43

66	:5@H	:5@HB	2.527	intraresidue	7.19	2.48
67	:6@HA	:6@HB2	2.572	intraresidue	5.19	1.20
68	:6@HA	:6@HD1?	2.427	intraresidue	5.19	0.78
69	:6@HA	:6@HG	2.988	intraresidue	5.19	1.91
70	:6@HA	:6@HN?	3.351	intraresidue	5.19	3.23
71	:6@HN?	:6@HG	3.691	intraresidue	3.23	1.91
72	:7@H	:7@HA	3.123	intraresidue	7.74	4.38
73	:7@H	:7@HB?	2.526	intraresidue	7.75	1.28
74	:8@HB?	:8@H	2.593	intraresidue	1.18	7.42
75	:9@HA	:9@HG	3.259	intraresidue	5.70	1.34
76	:9@HA	:9@HN?	3.389	intraresidue	5.70	3.19
77	:9@HN?	:9@HG	2.842	intraresidue	3.20	1.34
78	:10@HN?	:10@HA	3.190	intraresidue	2.61	5.10
79	:11@HN?	:11@HB	2.218	intraresidue	2.66	2.20

Table S10. Amide NH Shift comparison

		HEX-d14		**CHX-d12**		**$CDCl_3$**	
Alias	**ID**	**ppm**	**J (Hz)**	**ppm**	**J (Hz)**	**ppm**	**J (Hz)**
Abu^{2}	:2@H	8.3	9.6	8.39	9.8	7.95	9.7
Ala^{7}	:7@H	7.75	7.1	7.81	7.1	7.67	7.5
Dal^{8}	:8@H	7.42	7.3	7.47	7.3	7.16	8.4
Val^{5}	:5@H	7.199	8.9	7.17	9.0	7.47	7.9

Table S11. RMSD of C_α between the top 10 lowest cNviol conformers obtained from the ff03 and AMBER10:EHT in $CHCl_3$.

		ff03										10EHT									
		S1	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**	**S9**	**S10**	**S1**	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**	**S9**	**S10**
ff03	**S1**	0.00																			
	S2	0.31	0.00																		
	S3	0.81	0.64	0.00																	
	S4	0.41	0.30	0.75	0.00																
	S5	0.37	0.39	0.73	0.51	0.00															
	S6	0.33	0.26	0.68	0.24	0.39	0.00														
	S7	0.51	0.34	0.64	0.33	0.48	0.34	0.00													
	S8	0.47	0.33	0.76	0.28	0.65	0.35	0.42	0.00												
	S9	0.43	0.33	0.76	0.35	0.45	0.37	0.27	0.37	0.00											
	S10	0.26	0.22	0.60	0.37	0.33	0.28	0.37	0.44	0.38	0.00										
10EHT	**S1**	0.84	0.71	0.82	0.58	0.95	0.70	0.68	0.60	0.79	0.75	0.00									
	S2	0.59	0.51	0.90	0.44	0.54	0.40	0.50	0.57	0.53	0.58	0.89	0.00								
	S3	0.51	0.40	0.73	0.24	0.50	0.29	0.33	0.42	0.42	0.42	0.56	0.47	0.00							
	S4	0.77	0.69	0.99	0.74	0.66	0.64	0.74	0.86	0.81	0.76	1.16	0.50	0.74	0.00						
	S5	0.67	0.58	0.81	0.55	0.81	0.60	0.62	0.54	0.68	0.60	0.42	0.87	0.51	1.07	0.00					
	S6	0.76	0.64	0.58	0.56	0.77	0.55	0.55	0.59	0.67	0.59	0.53	0.79	0.48	1.04	0.53	0.00				
	S7	0.89	0.75	0.62	0.69	0.80	0.67	0.64	0.74	0.74	0.71	0.68	0.85	0.56	1.09	0.70	0.29	0.00			
	S8	0.72	0.67	0.81	0.72	0.81	0.73	0.77	0.74	0.80	0.66	0.59	1.00	0.66	1.17	0.40	0.66	0.77	0.00		
	S9	0.68	0.59	0.81	0.54	0.75	0.58	0.63	0.56	0.67	0.61	0.49	0.81	0.46	1.04	0.31	0.55	0.61	0.45	0.00	
	S10	0.44	0.41	0.86	0.42	0.45	0.31	0.50	0.52	0.48	0.46	0.92	0.35	0.46	0.45	0.80	0.78	0.88	0.92	0.79	0.00

Unit in angstrom. The darkest red is set at 1.17.

Table S12. RMSD of C_α between the top 10 lowest cNviol conformers obtained from the ff03 and AMBER10:EHT in CHX.

		ff03										10EHT									
		S1	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**	**S9**	**S10**	**S1**	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**	**S9**	**S10**
ff03	**S1**	0.00																			
	S2	0.31	0.00																		
	S3	0.39	0.30	0.00																	
	S4	0.33	0.33	0.38	0.00																
	S5	0.40	0.32	0.38	0.52	0.00															
	S6	0.44	0.41	0.32	0.38	0.53	0.00														
	S7	0.37	0.30	0.25	0.40	0.42	0.31	0.00													
	S8	0.44	0.35	0.32	0.56	0.26	0.44	0.35	0.00												
	S9	0.42	0.47	0.41	0.57	0.32	0.55	0.47	0.39	0.00											
	S10	0.45	0.40	0.33	0.55	0.37	0.36	0.26	0.26	0.44	0.00										
10EHT	**S1**	0.35	0.37	0.34	0.28	0.53	0.28	0.28	0.50	0.49	0.42	0.00									
	S2	0.43	0.51	0.54	0.28	0.71	0.52	0.53	0.72	0.71	0.69	0.36	0.00								
	S3	0.48	0.52	0.39	0.54	0.52	0.37	0.33	0.42	0.48	0.29	0.37	0.62	0.00							
	S4	0.47	0.58	0.58	0.36	0.73	0.51	0.58	0.74	0.70	0.69	0.37	0.26	0.56	0.00						
	S5	0.37	0.32	0.37	0.48	0.31	0.51	0.37	0.35	0.35	0.37	0.41	0.60	0.42	0.60	0.00					
	S6	0.44	0.38	0.22	0.47	0.46	0.39	0.36	0.37	0.44	0.41	0.41	0.56	0.47	0.64	0.43	0.00				
	S7	0.40	0.41	0.37	0.39	0.49	0.37	0.32	0.49	0.49	0.36	0.26	0.49	0.31	0.43	0.36	0.46	0.00			
	S8	0.55	0.43	0.38	0.61	0.47	0.42	0.30	0.31	0.56	0.28	0.49	0.74	0.43	0.79	0.44	0.45	0.50	0.00		
	S9	0.48	0.46	0.41	0.56	0.48	0.37	0.32	0.35	0.56	0.33	0.47	0.70	0.41	0.73	0.51	0.51	0.51	0.25	0.00	
	S10	0.49	0.49	0.31	0.52	0.55	0.44	0.34	0.45	0.45	0.42	0.36	0.56	0.36	0.59	0.43	0.29	0.42	0.47	0.52	0.00

Unit in angstrom. The darkest red is set at 1.17.

Table S13. RMSD of C_α between the top 10 lowest cNviol conformers obtained from the ff03 and AMBER10:EHT in HEX.

		ff03										10EHT									
		S1	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**	**S9**	**S10**	**S1**	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**	**S9**	**S10**
ff03	**S1**	0.00																			
	S2	0.27	0.00																		
	S3	0.34	0.28	0.00																	
	S4	0.46	0.50	0.49	0.00																
	S5	0.53	0.48	0.46	0.31	0.00															
	S6	0.27	0.26	0.31	0.46	0.52	0.00														
	S7	0.67	0.63	0.60	0.59	0.41	0.67	0.00													
	S8	0.45	0.41	0.44	0.33	0.27	0.46	0.40	0.00												
	S9	0.45	0.33	0.31	0.49	0.51	0.35	0.67	0.42	0.00											
	S10	0.53	0.41	0.36	0.47	0.35	0.51	0.52	0.34	0.36	0.00										
10EHT	**S1**	0.39	0.41	0.43	0.32	0.32	0.41	0.50	0.36	0.52	0.49	0.00									
	S2	0.35	0.32	0.30	0.32	0.38	0.28	0.55	0.29	0.29	0.38	0.33	0.00								
	S3	0.46	0.49	0.50	0.34	0.29	0.51	0.43	0.38	0.60	0.48	0.22	0.42	0.00							
	S4	0.33	0.32	0.31	0.29	0.40	0.30	0.63	0.35	0.29	0.38	0.33	0.18	0.43	0.00						
	S5	0.54	0.47	0.40	0.36	0.41	0.48	0.60	0.37	0.33	0.33	0.45	0.29	0.48	0.28	0.00					
	S6	0.41	0.37	0.28	0.40	0.46	0.37	0.64	0.42	0.29	0.36	0.39	0.23	0.46	0.22	0.24	0.00				
	S7	0.24	0.25	0.28	0.40	0.46	0.23	0.59	0.35	0.32	0.41	0.37	0.25	0.43	0.27	0.40	0.30	0.00			
	S8	0.53	0.48	0.37	0.34	0.36	0.49	0.56	0.37	0.37	0.32	0.39	0.31	0.43	0.29	0.21	0.26	0.41	0.00		
	S9	0.27	0.36	0.51	0.53	0.60	0.39	0.76	0.51	0.57	0.62	0.50	0.46	0.56	0.44	0.65	0.56	0.38	0.68	0.00	
	S10	0.32	0.32	0.30	0.42	0.37	0.36	0.47	0.37	0.49	0.40	0.29	0.34	0.31	0.37	0.48	0.41	0.30	0.43	0.43	0.00

Unit in angstrom. The darkest red is set at 1.17.

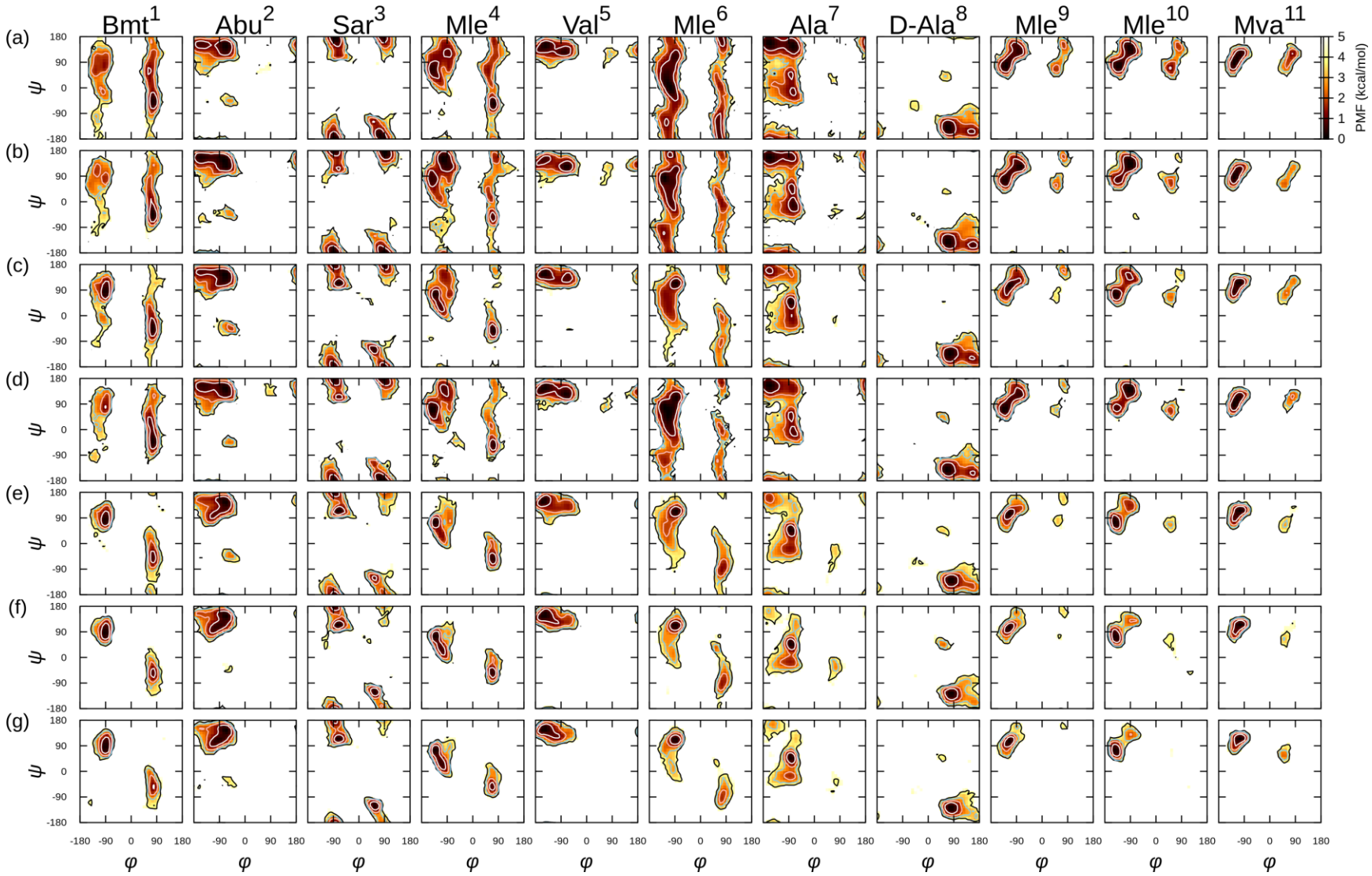

Figure S12. FELs of the backbone (ϕ,ψ) at T = 300 K using ff03 in (a) WAT, (b) DMSO, (c) ACN, (d) in MeOH, (e) $CHCl_3$, (f) CHX, and (g) HEX. The contour lines of the PMF = 1.0, 2.0, 3.0, and 4.0 kcal/mol are represented by the white, pink, sky-blue, and black lines, respectively.

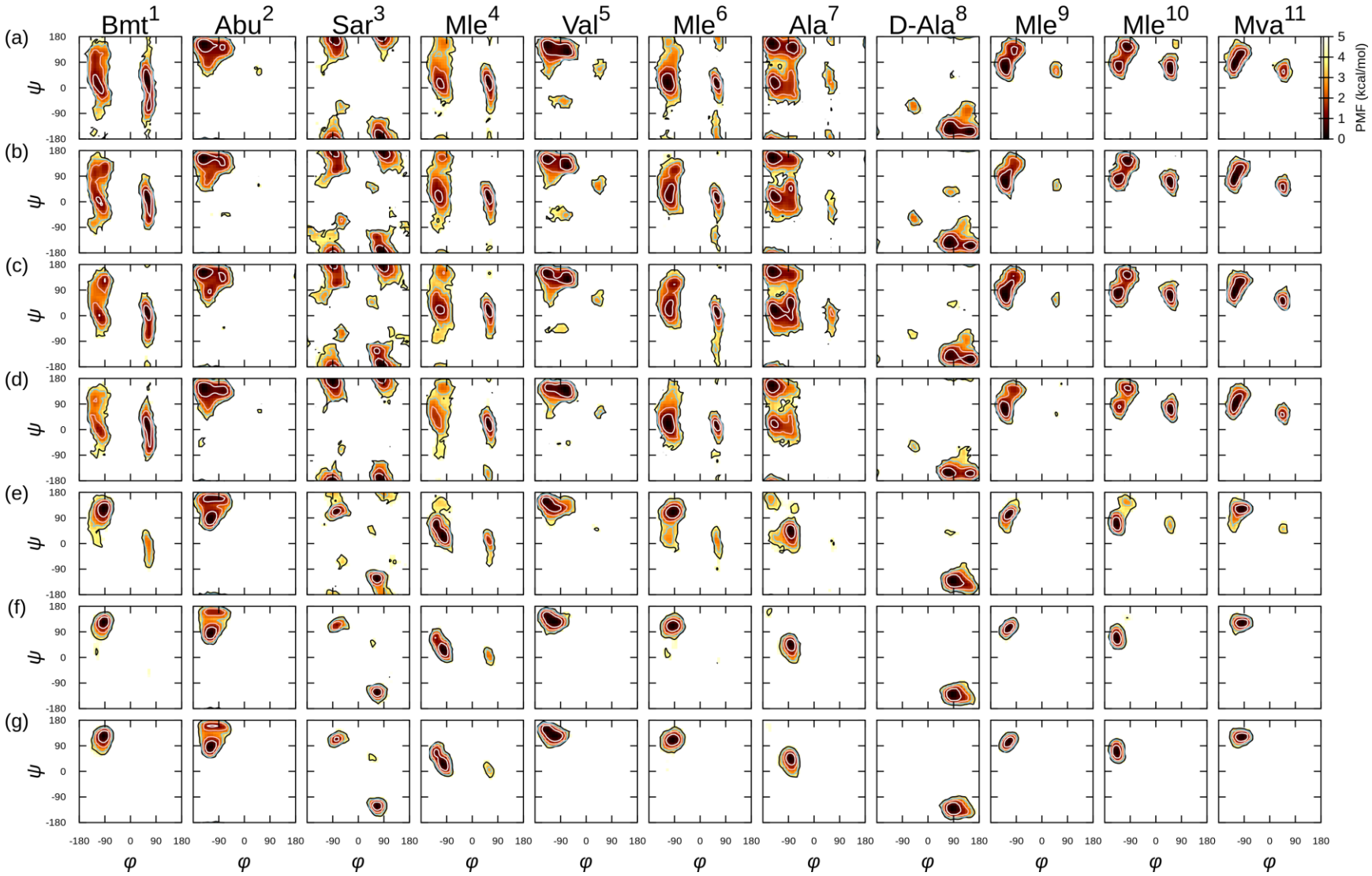

Figure S13. FELs of the backbone (ϕ,ψ) at T = 300 K using AMBER10:EHT in (a) WAT, (b) DMSO, (c) ACN, (d) in MeOH, (e) $CHCl_3$, (f) CHX, and (g) HEX. The contour lines of the PMF = 1.0, 2.0, 3.0, and 4.0 kcal/mol are represented by the white, pink, sky-blue, and black lines, respectively.

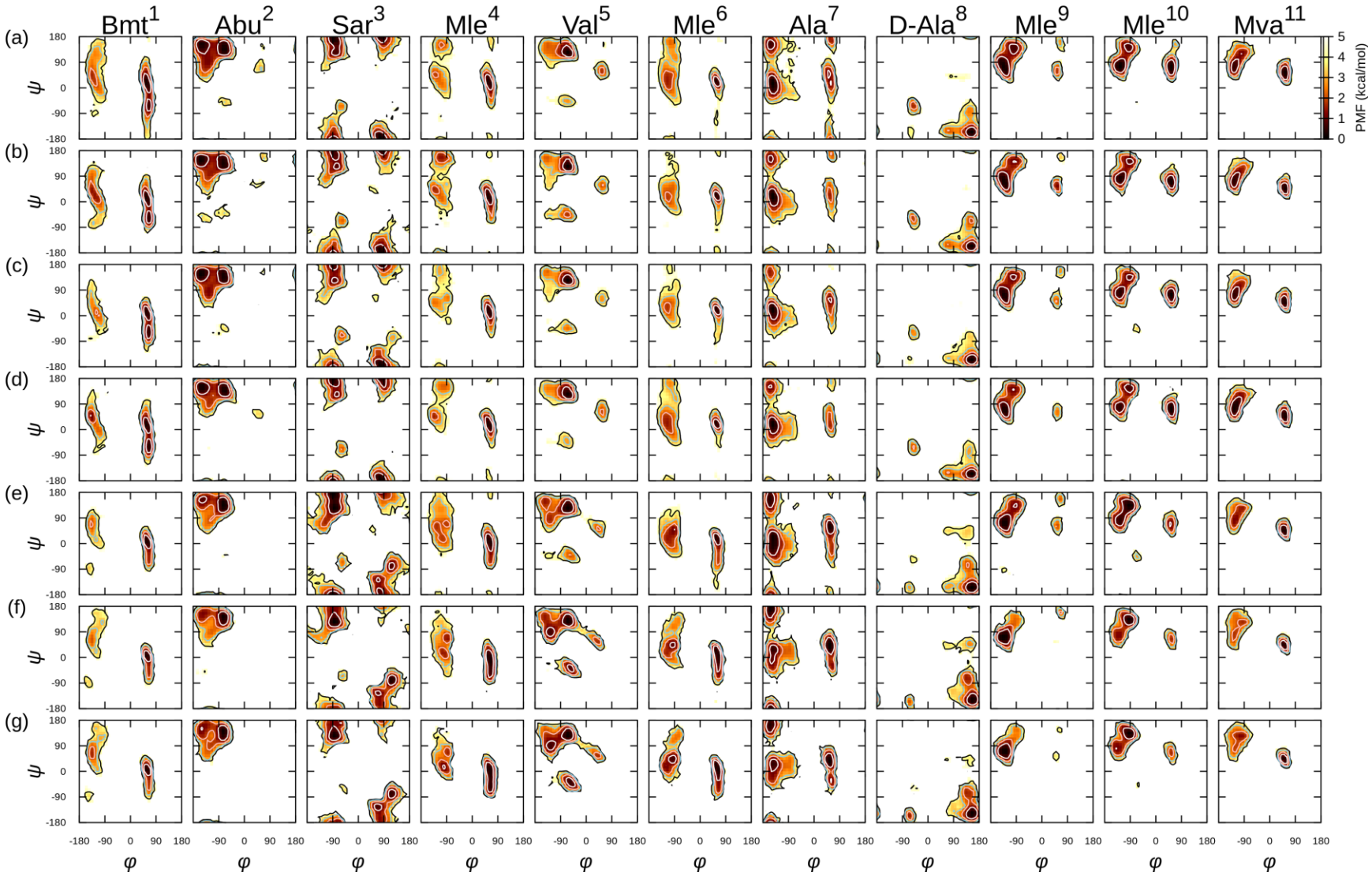

Figure S14. FELs of the backbone (ϕ,ψ) at T = 300 K using AMBER12:EHT in (a) WAT, (b) DMSO, (c) ACN, (d) in MeOH, (e) $CHCl_3$, (f) CHX, and (g) HEX. The contour lines of the PMF = 1.0, 2.0, 3.0, and 4.0 kcal/mol are represented by the white, pink, sky-blue, and black lines, respectively.

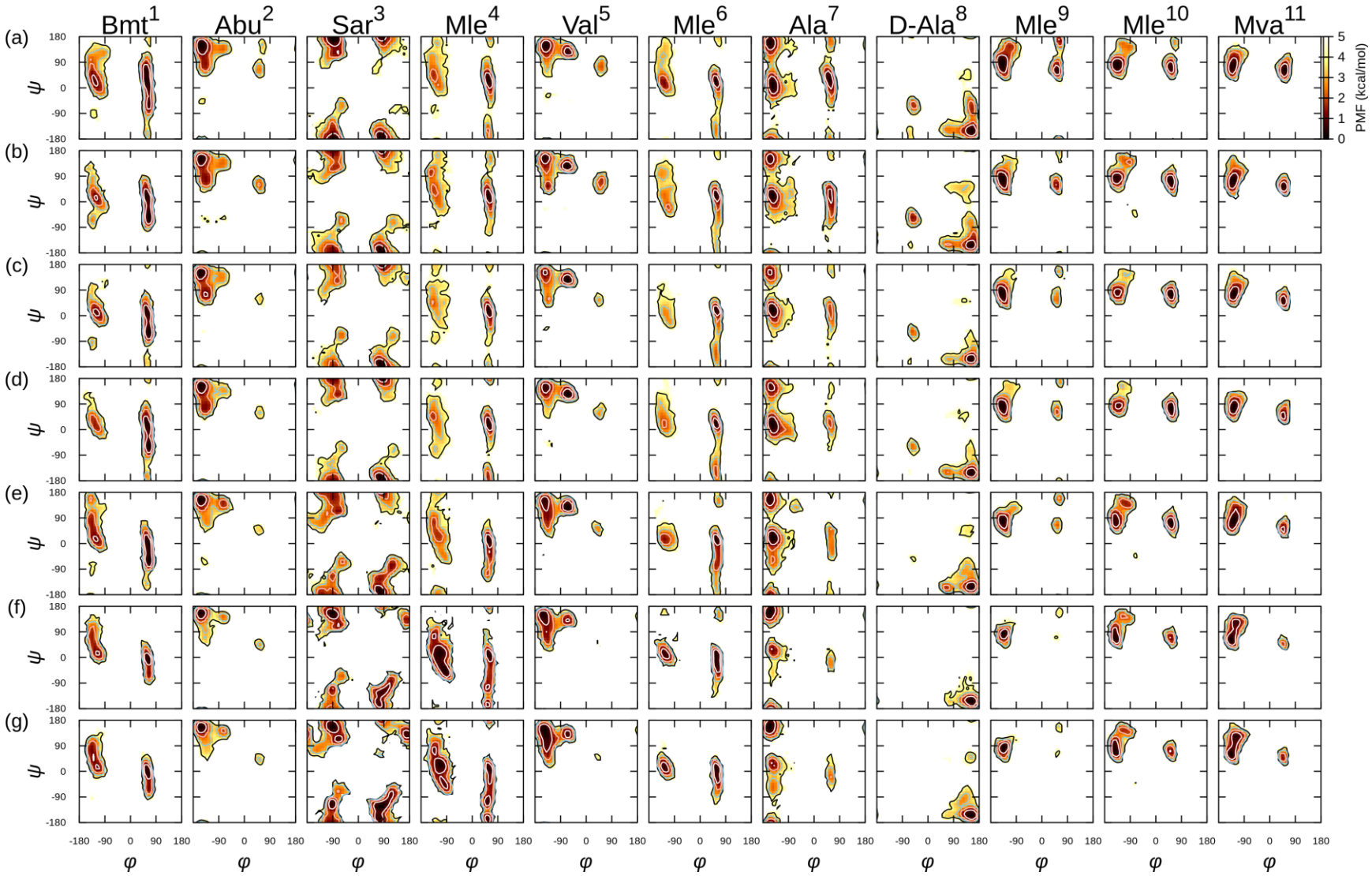

Figure S15. FELs of the backbone (ϕ,ψ) at T = 300 K using AMBER14:EHT in (a) WAT, (b) DMSO, (c) ACN, (d) in MeOH, (e) $CHCl_3$, (f) CHX, and (g) HEX. The contour lines of the PMF = 1.0, 2.0, 3.0, and 4.0 kcal/mol are represented by the white, pink, sky-blue, and black lines, respectively.

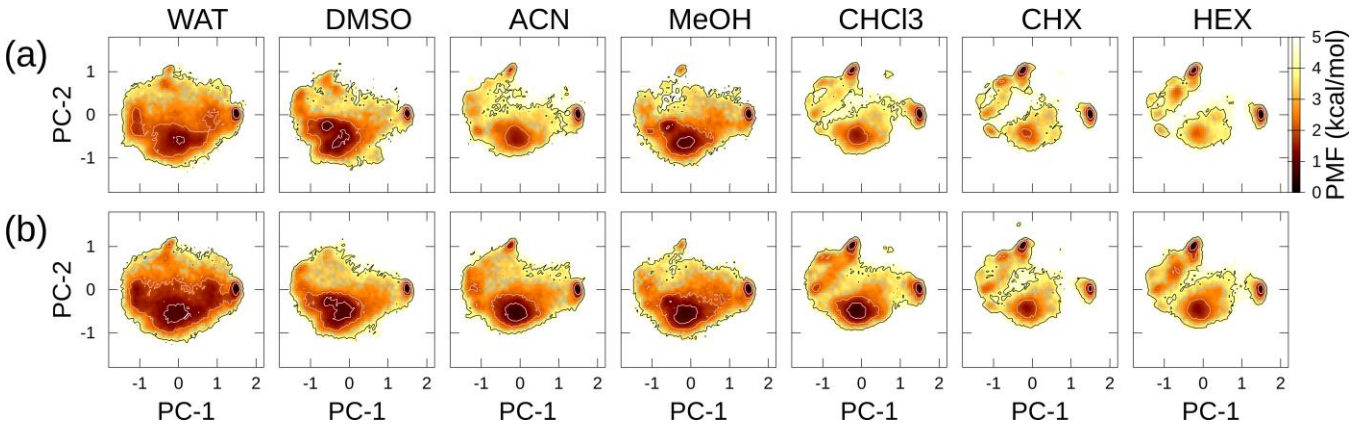

Figure S16. PCA of FELs along the PC-1 and PC-2 axes in each solvent using ff03. (a) at T = 400 K, and (b) T = 500 K. The contour lines of the PMF = 1.0, 2.0, 3.0, and 4.0 kcal/mol are represented by the white, pink, sky-blue, and black lines, respectively.

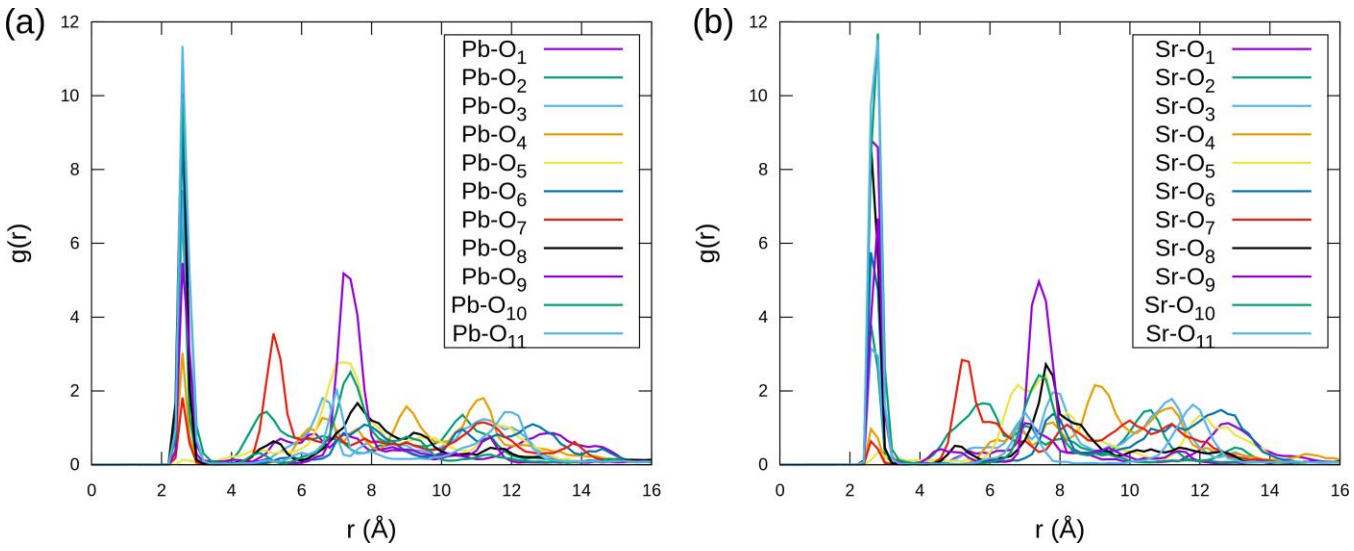

Figure S17. Radial distribution functions between metal ion and carbonyl oxygens. (a) Pb^{2+} and (b) Sr^{2+}.

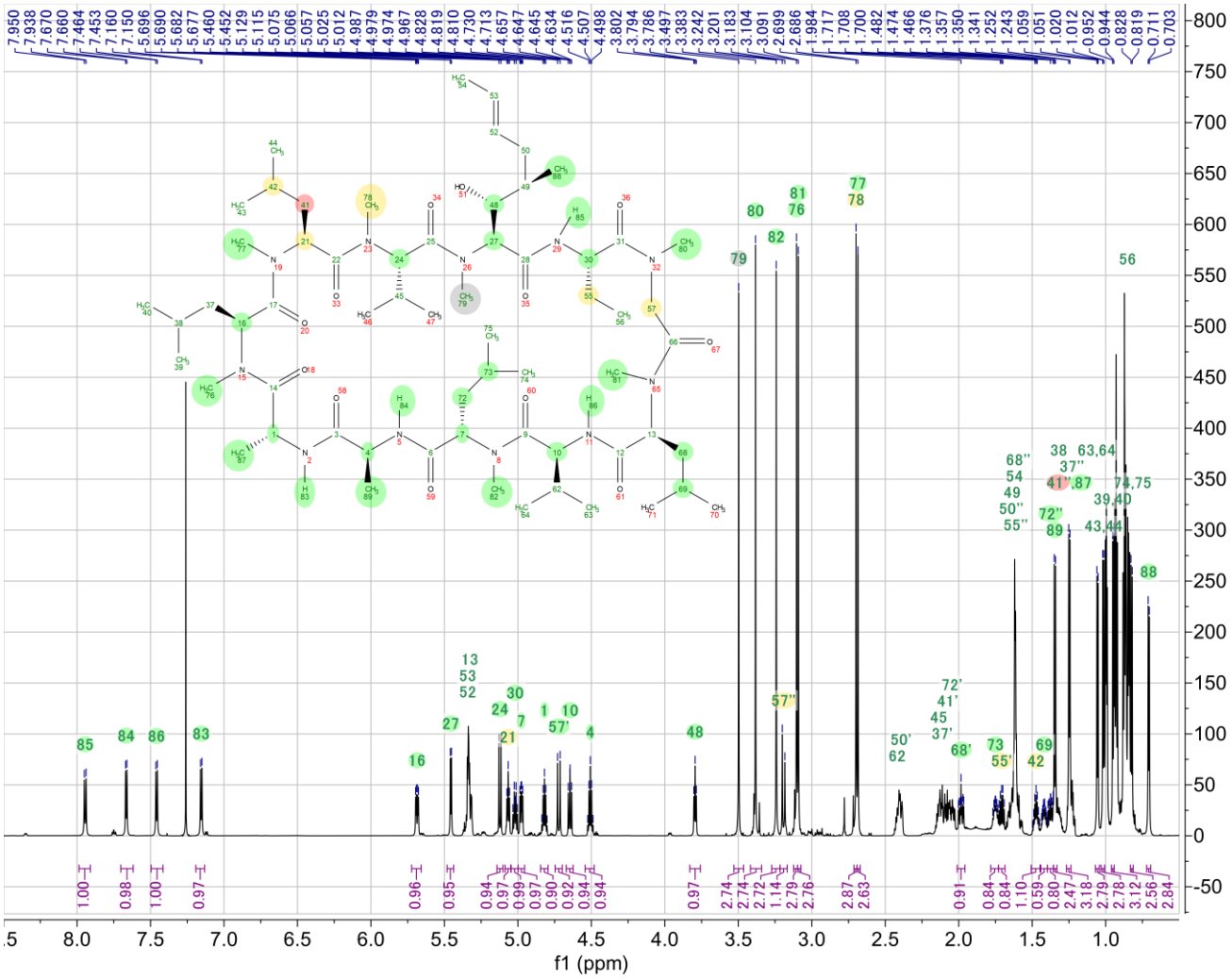

Figure S18. NMR Spectra of CsA in $CDCl_3$. ^1H NMR (800 MHz, $CDCl_3$) δ 7.94 (d, *J* = 9.7 Hz, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 5.69 (dd, *J* = 11.0, 4.4 Hz, 1H), 5.46 (d, *J* = 6.2 Hz, 1H), 5.12 (d, *J* = 10.9 Hz, 1H), 5.07 (t, *J* = 7.1 Hz, 1H), 5.02 (dt, *J* = 9.7, 7.4 Hz, 1H), 4.98 (dd, *J* = 9.9, 5.9 Hz, 1H), 4.82 (p, *J* = 7.0 Hz, 1H), 4.72 (d, *J* = 14.0 Hz, 1H), 4.65 (dd, *J* = 9.8, 8.3 Hz, 1H), 4.51 (p, *J* = 7.3 Hz, 1H), 3.79 (t, *J* = 6.7 Hz, 1H), 3.50 (s, 3H), 3.38 (s, 3H), 3.24 (s, 3H), 3.19 (d, *J* = 14.1 Hz, 1H), 3.10 (s, 3H), 3.09 (s, 3H), 2.70 (s, 3H), 2.69 (s, 3H), 2.45 – 2.35 (m, 2H), 2.17 – 2.02 (m, 4H), 1.98 (ddd, *J* = 14.6, 10.5, 4.0 Hz, 1H), 1.75 (dq, *J* = 8.6, 6.2 Hz, 1H), 1.71 (dt, *J* = 14.0, 7.1 Hz, 1H), 1.68 – 1.56 (m, 7H), 1.47 (hept, *J* = 6.5 Hz, 1H), 1.42 (ddp, *J* = 9.6, 6.7, 3.3 Hz, 1H), 1.37 (ddd, *J* = 13.5, 9.2, 6.1 Hz, 1H), 1.36 – 1.29 (m, 3H), 1.25 (d, *J* = 6.8 Hz, 3H), 1.06 (d, *J* = 6.5 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 3H), 1.00 (dd, *J* = 6.7, 4.5 Hz, 6H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 6H), 0.90 – 0.83 (m, 14H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.71 (d, *J* = 6.4 Hz, 3H).

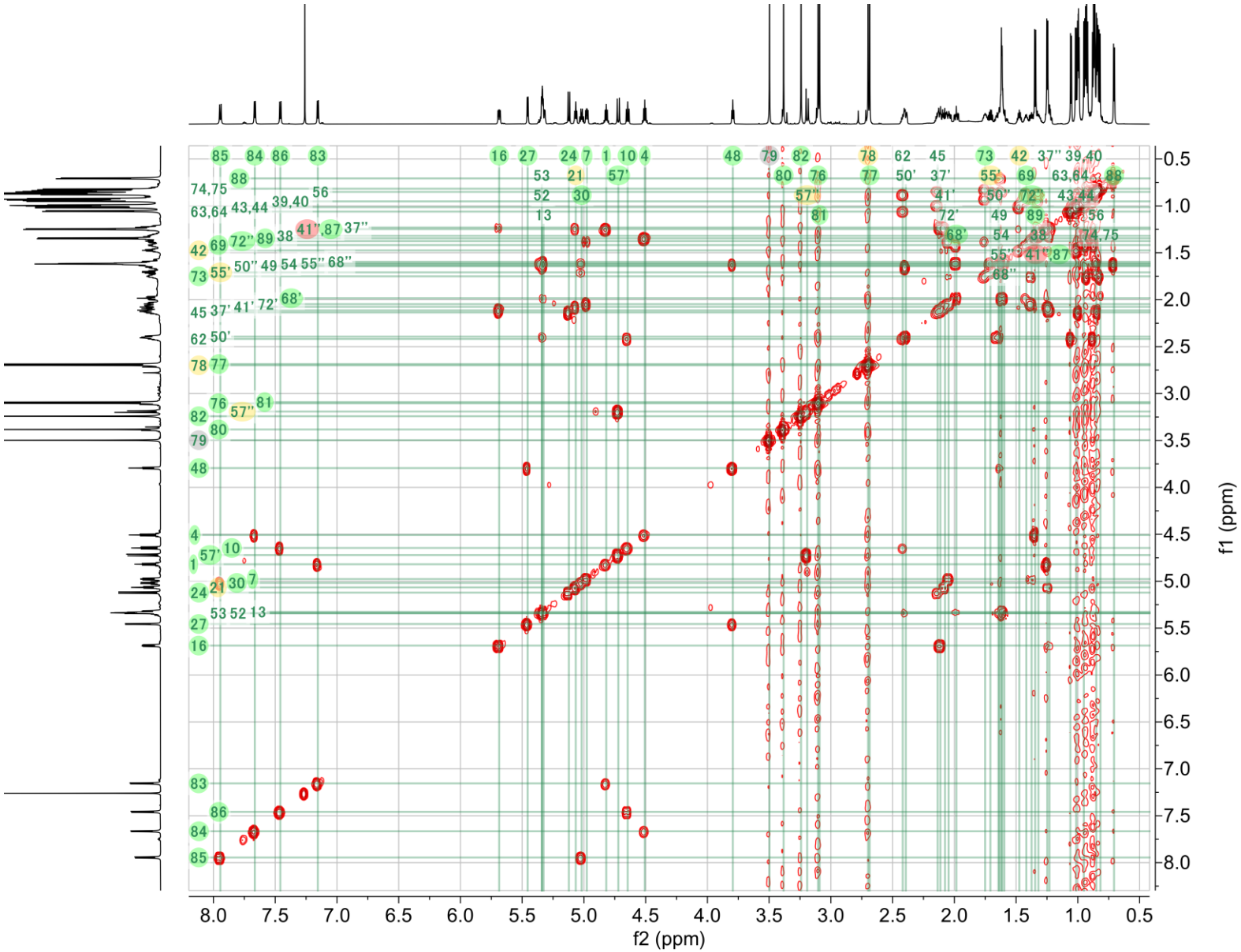

Figure S19. COSY Spectra of CsA in $CDCl_3$.

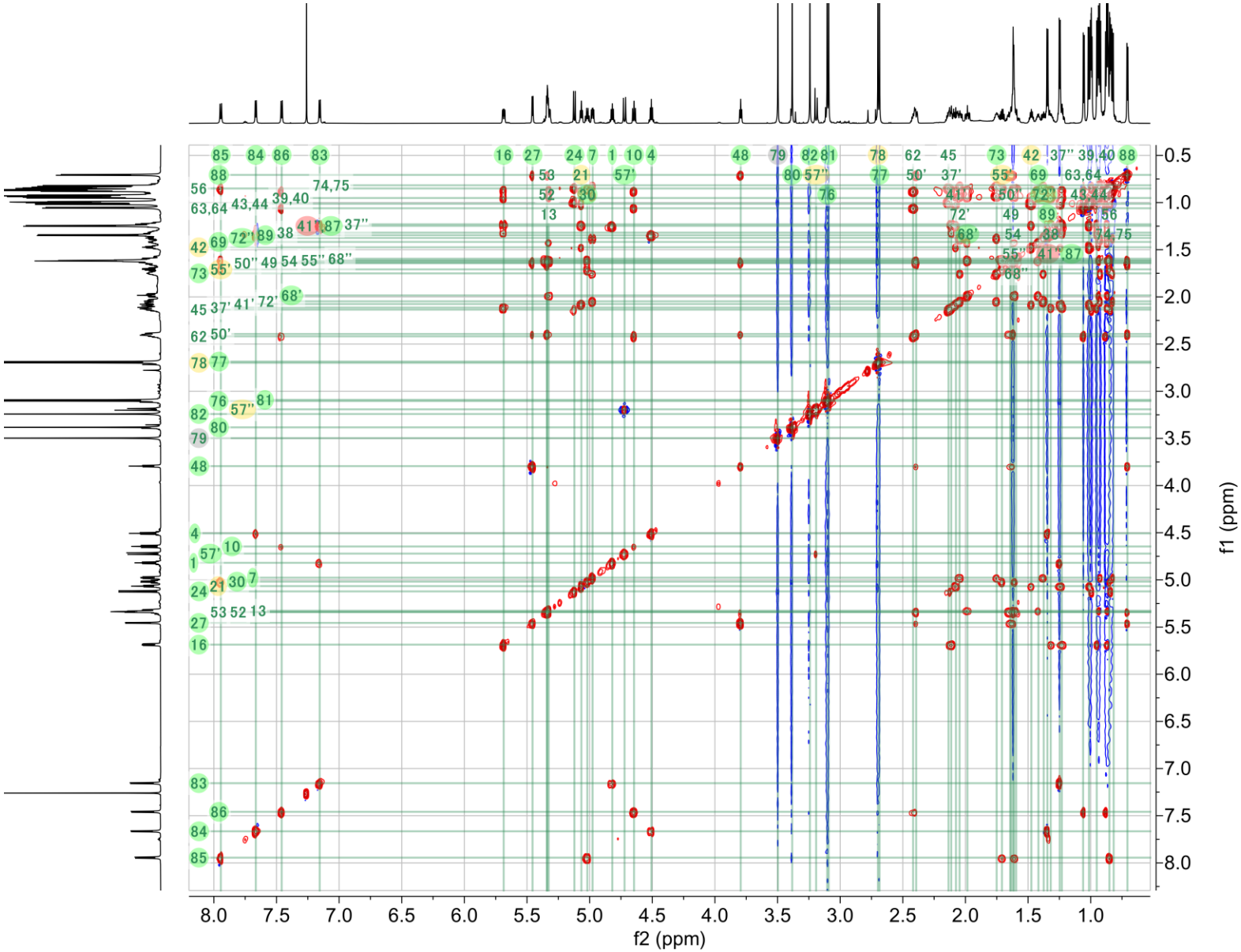

Figure S20. TOCSY Spectra of CsA in $CDCl_3$.

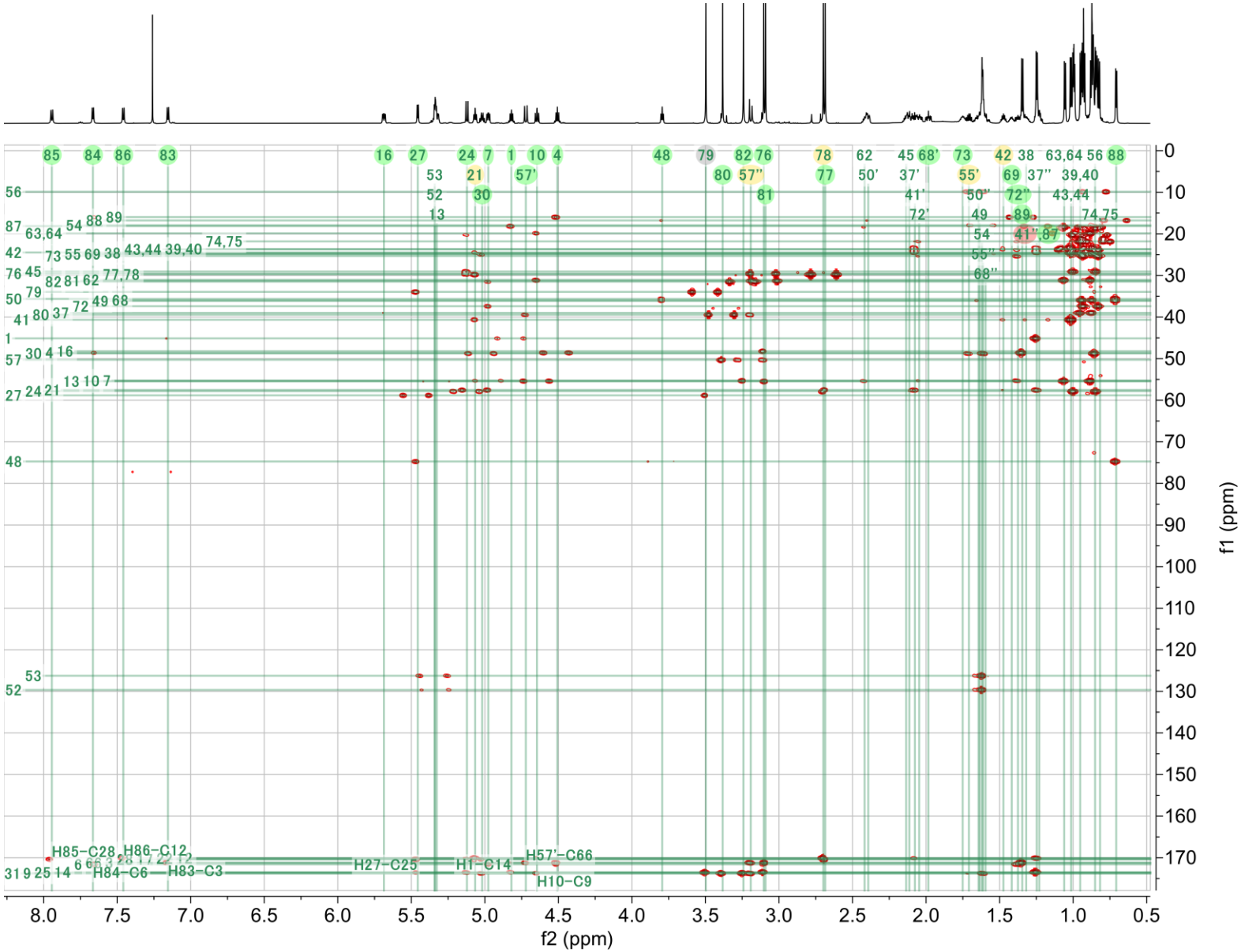

Figure S21. HMBC Spectra of CsA in $CDCl_3$.

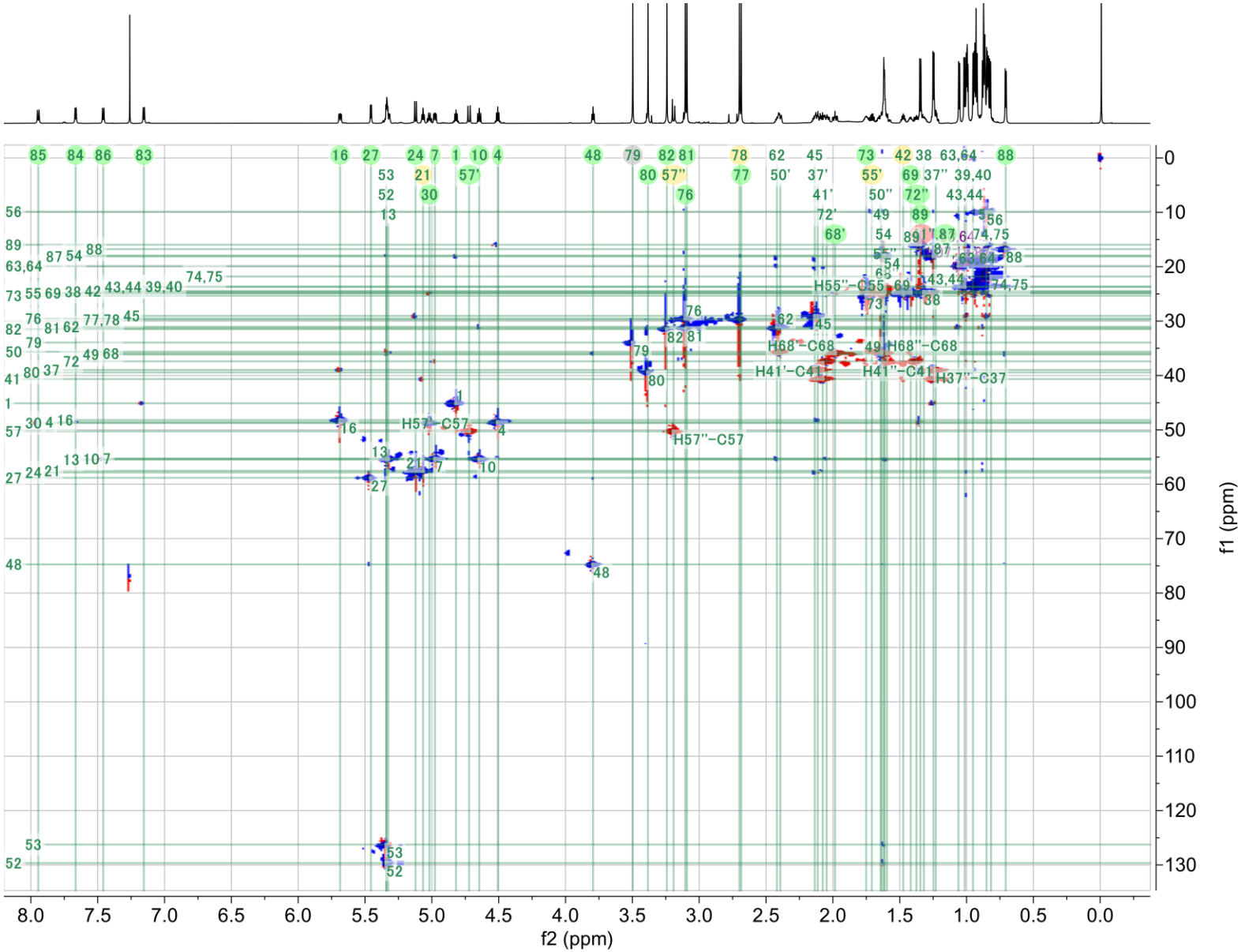

Figure S22. HSQC Spectra of CsA in $CDCl_3$.

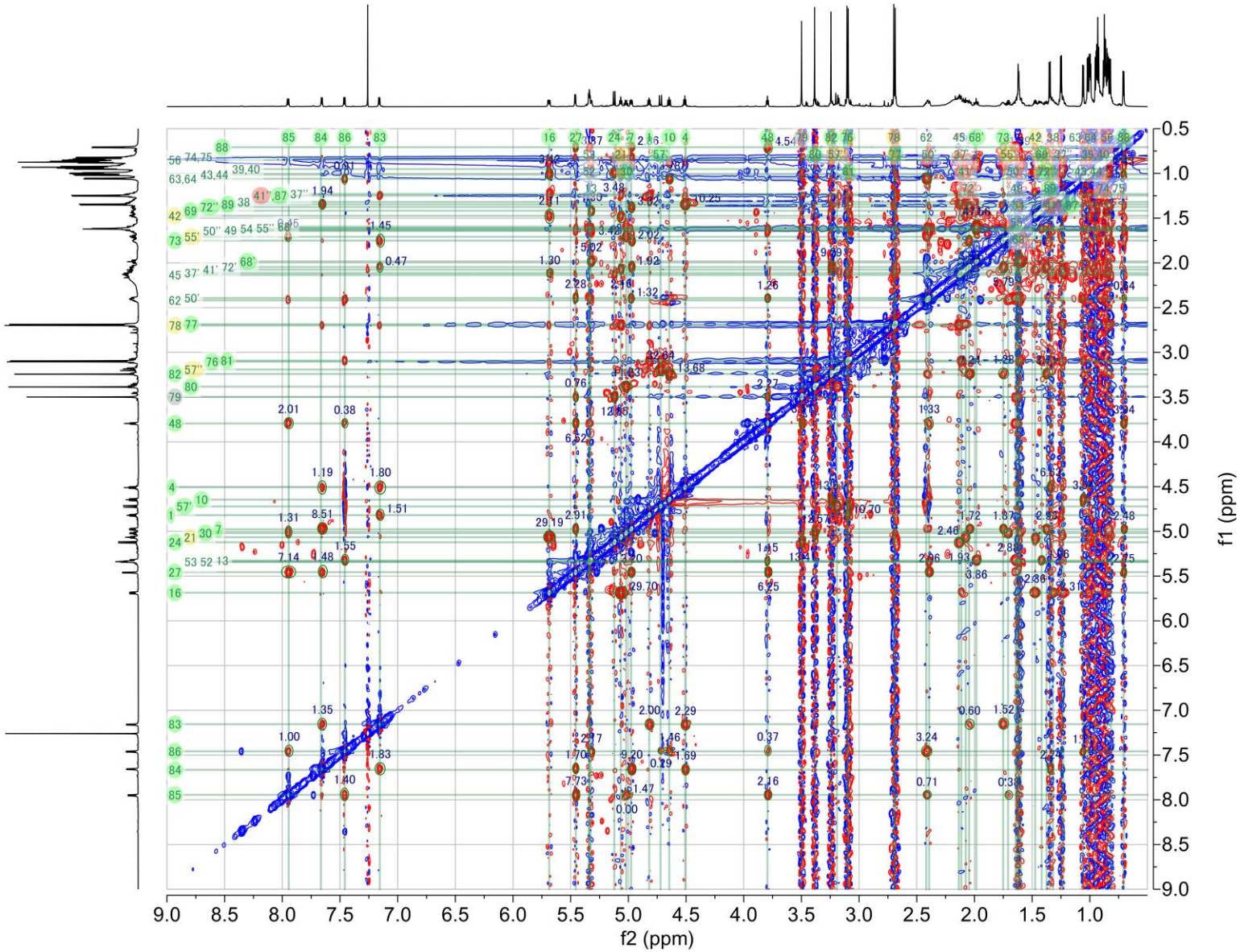

Figure S23. ROESY Spectra of CsA in $CDCl_3$.

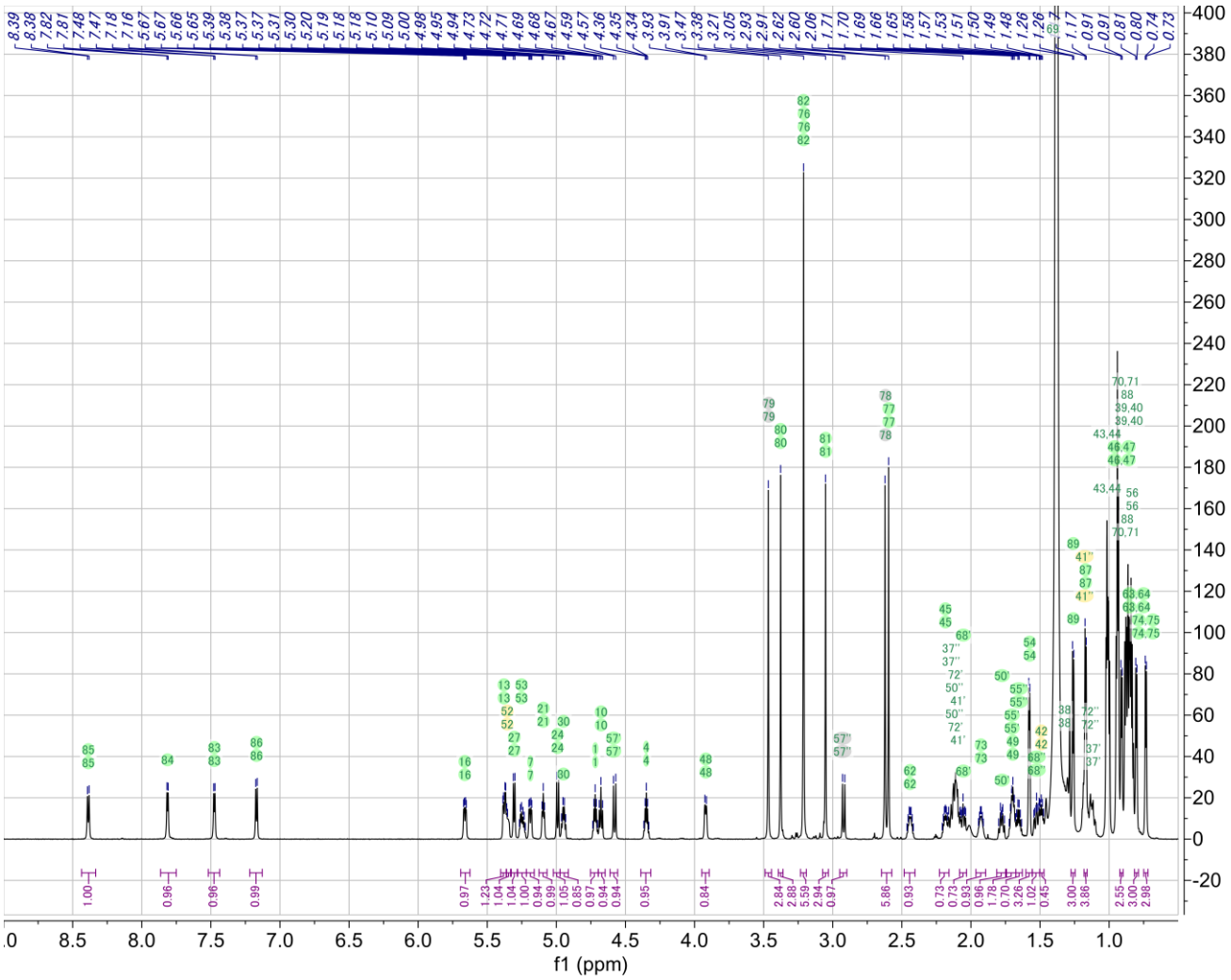

Figure S24. NMR Spectra of CSA in cyclohexane-d12 ^{1}H NMR (800 MHz, cyclohexane-d12) δ 8.39 (d, *J* = 9.8 Hz, 1H), 7.81 (d, *J* = 7.1 Hz, 1H), 7.47 (d, *J* = 7.3 Hz, 1H), 7.17 (d, *J* = 9.0 Hz, 1H), 5.66 (dd, *J* = 11.1, 4.4 Hz, 1H), 5.38 (dd, *J* = 11.9, 4.1 Hz, 1H), 5.35 (s, 1H), 5.31 (d, *J* = 9.2 Hz, 1H), 5.25 (dq, *J* = 13.4, 6.3 Hz, 1H), 5.19 (dd, *J* = 11.7, 4.5 Hz, 1H), 5.09 (t, *J* = 7.0 Hz, 1H), 4.99 (d, *J* = 11.2 Hz, 1H), 4.95 (q, *J* = 8.3 Hz, 1H), 4.72 (p, *J* = 6.9 Hz, 1H), 4.68 (t, *J* = 9.6 Hz, 1H), 4.58 (d, *J* = 13.3 Hz, 1H), 4.35 (p, *J* = 7.3 Hz, 1H), 3.92 (d, *J* = 9.0 Hz, 1H), 3.47 (s, 3H), 3.38 (s, 3H), 3.21 (s, 6H), 3.05 (s, 3H), 2.92 (d, *J* = 13.4 Hz, 1H), 2.61 (d, *J* = 20.7 Hz, 6H), 2.48 – 2.40 (m, 1H), 2.18 (tt, *J* = 13.2, 6.6 Hz, 1H), 2.06 (ddd, *J* = 14.7, 10.8, 4.0 Hz, 1H), 1.93 (dt, *J* = 11.6, 6.0 Hz, 1H), 1.78 (dt, *J* = 13.4, 9.7 Hz, 1H), 1.70 (h, *J* = 7.4 Hz, 2H), 1.65 (dt, *J* = 14.0, 7.1 Hz, 1H), 1.58 (d, *J* = 6.3 Hz, 3H), 1.52 (ddd, *J* = 15.1, 11.9, 3.4 Hz, 1H), 1.49 (q, *J* = 6.6 Hz, 0H), 1.26 (d, *J* = 7.2 Hz, 3H), 1.17 (d, *J* = 7.0 Hz, 4H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.73 (d, *J* = 6.5 Hz, 3H).

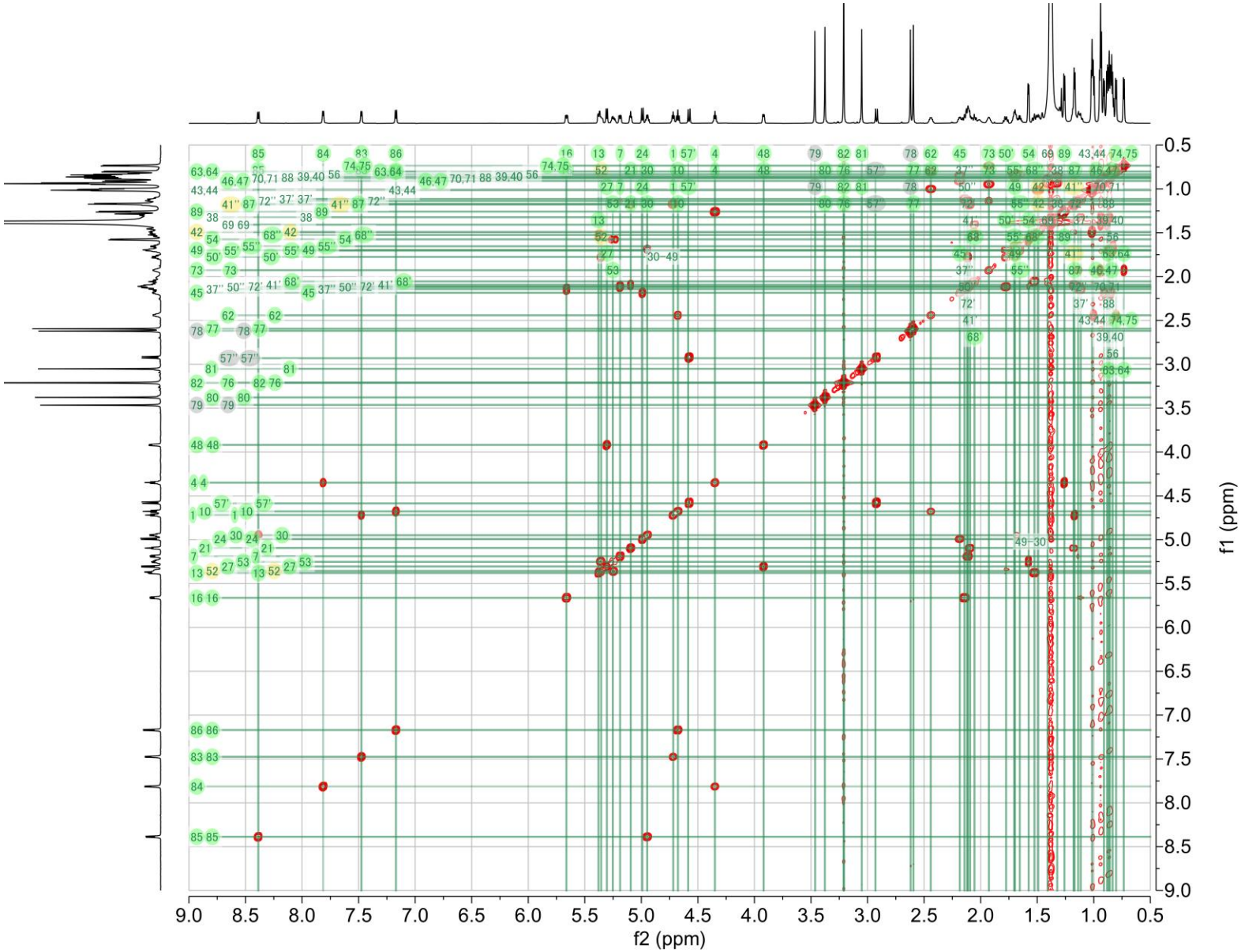

Figure S25. COSY Spectra of CSA in cyclohexane-d12.

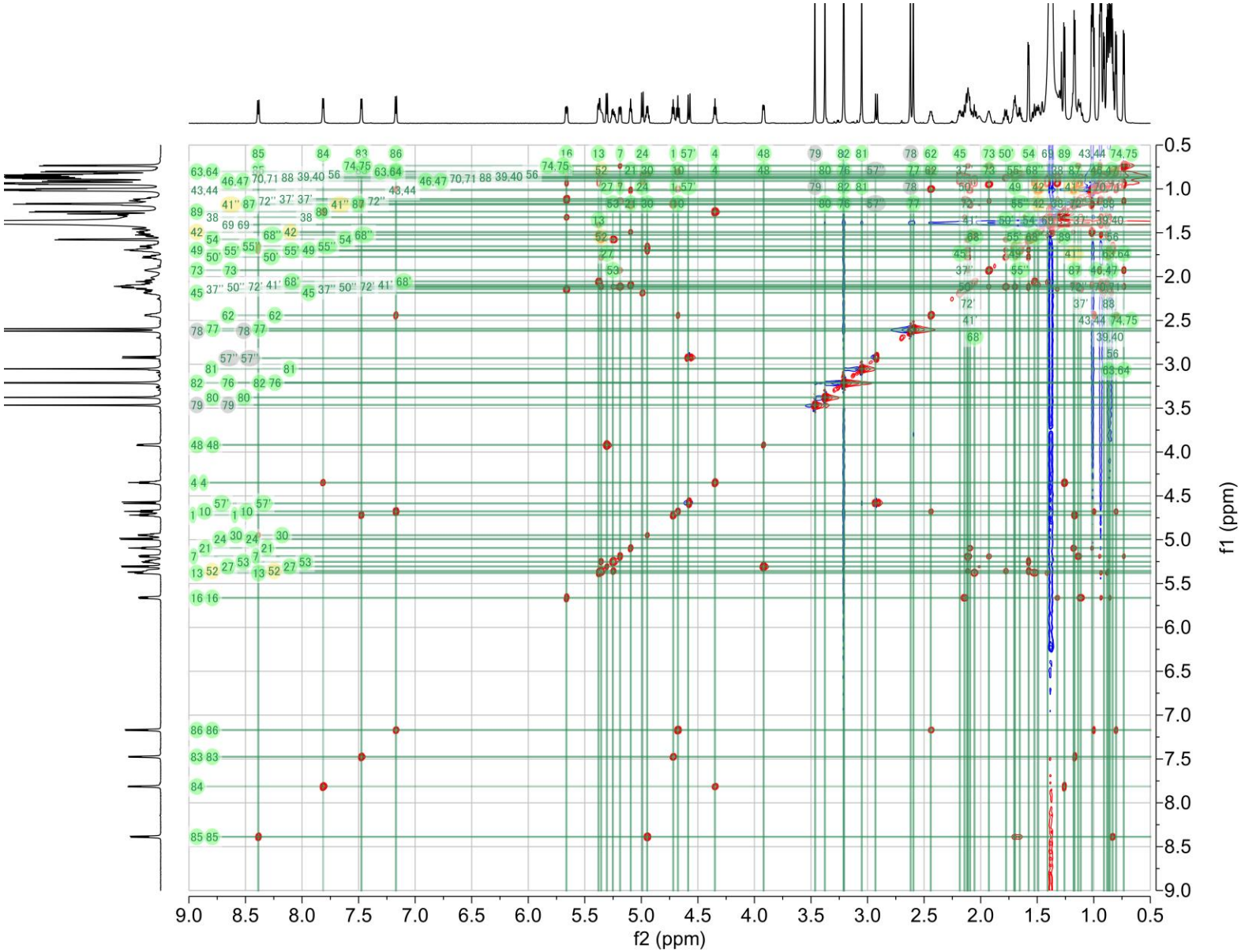

Figure S26. TOCSY Spectra of CSA in cyclohexane-d12.

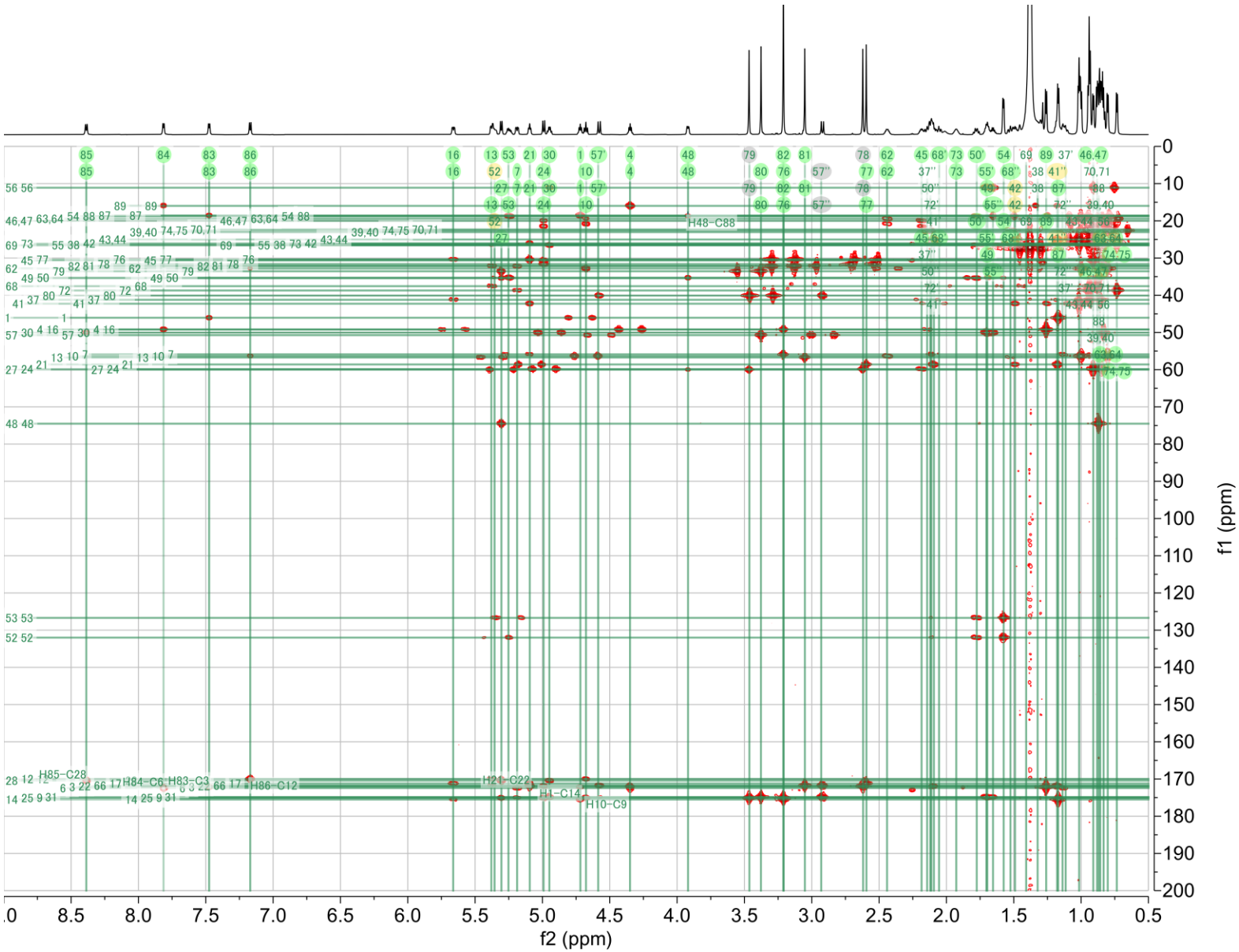

Figure S27. HMBC Spectra of CSA in cyclohexane-d12.

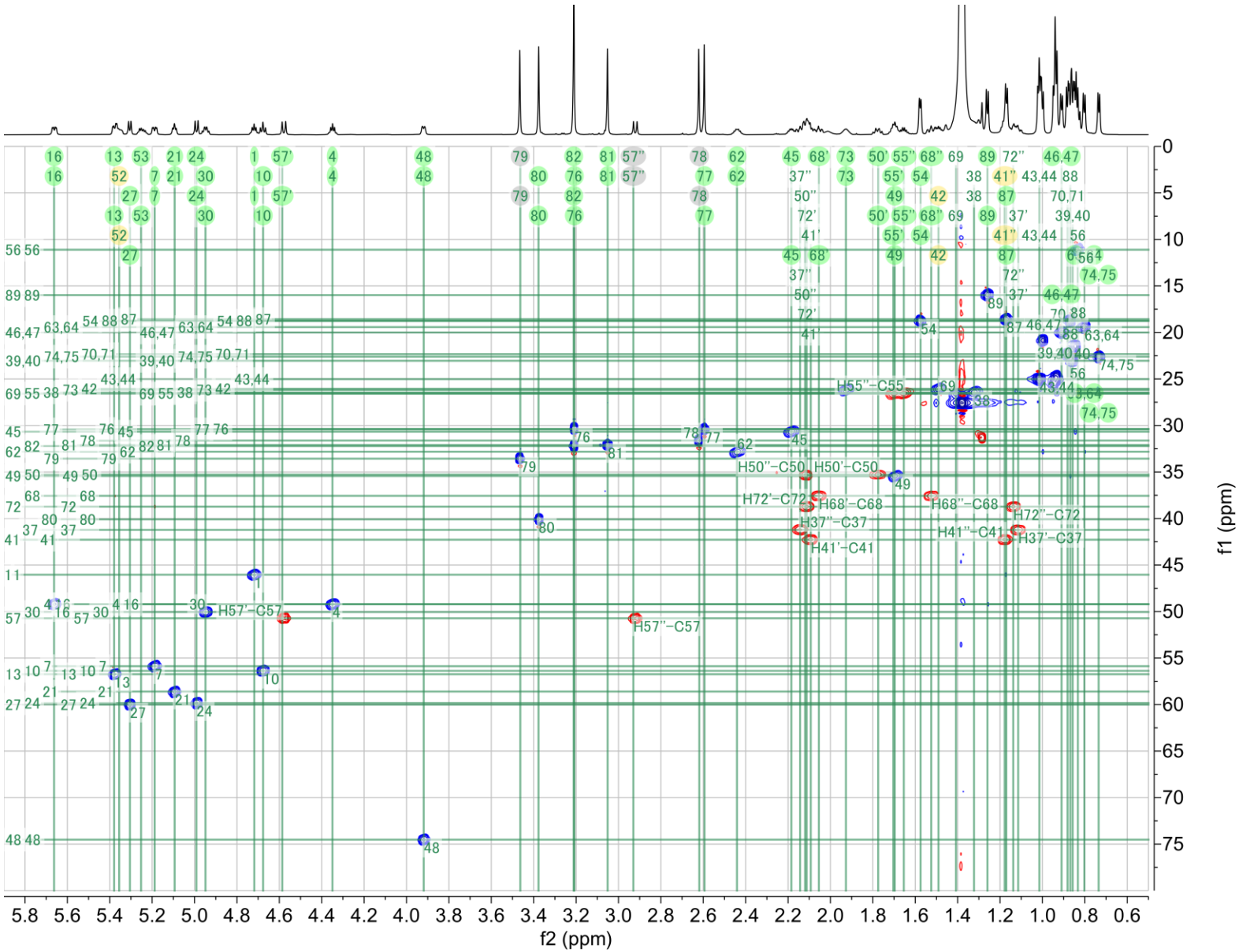

Figure S28. HSQC Spectra of CSA in cyclohexane-d12.

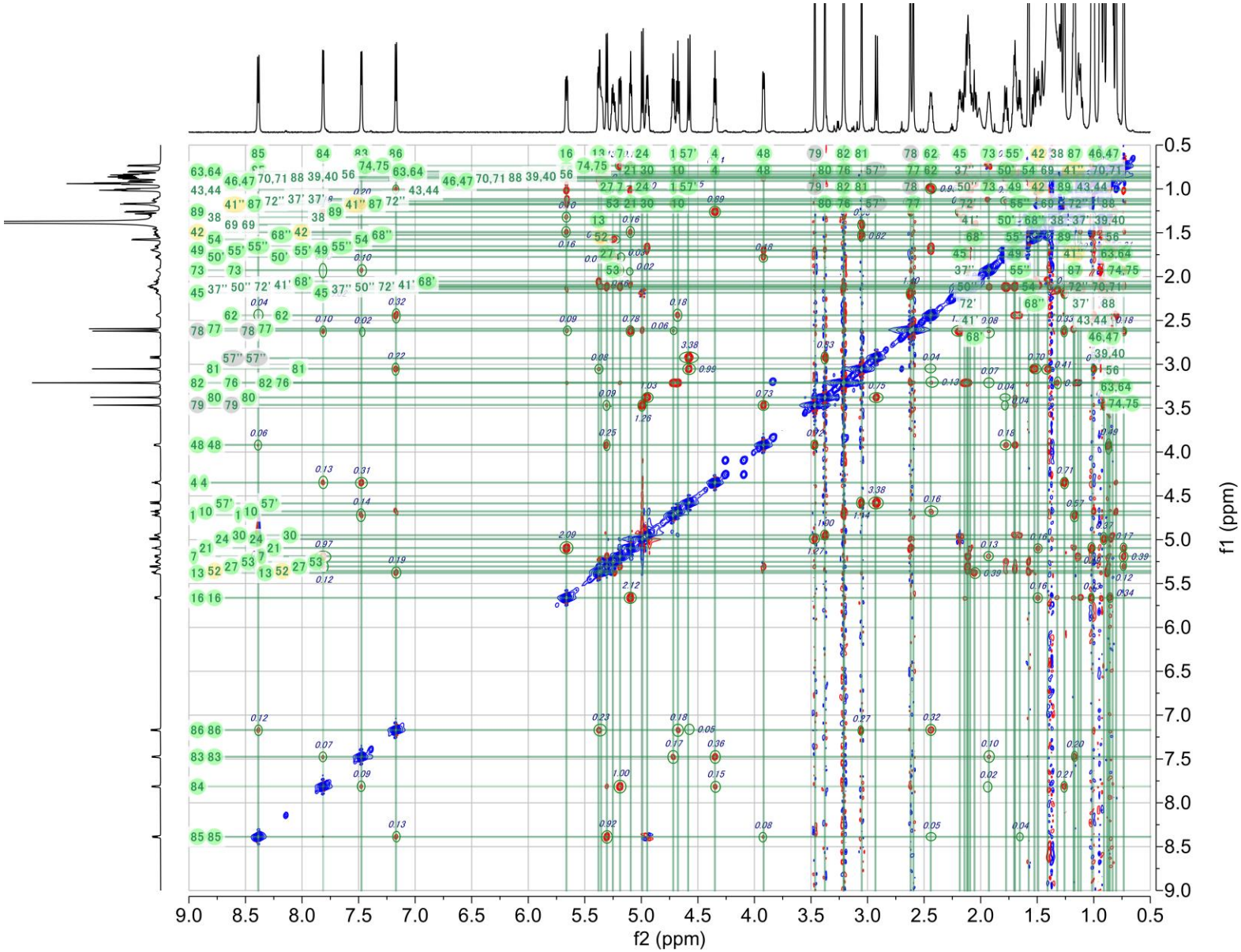

Figure S29. ROESY Spectra of CSA in cyclohexane-d12.

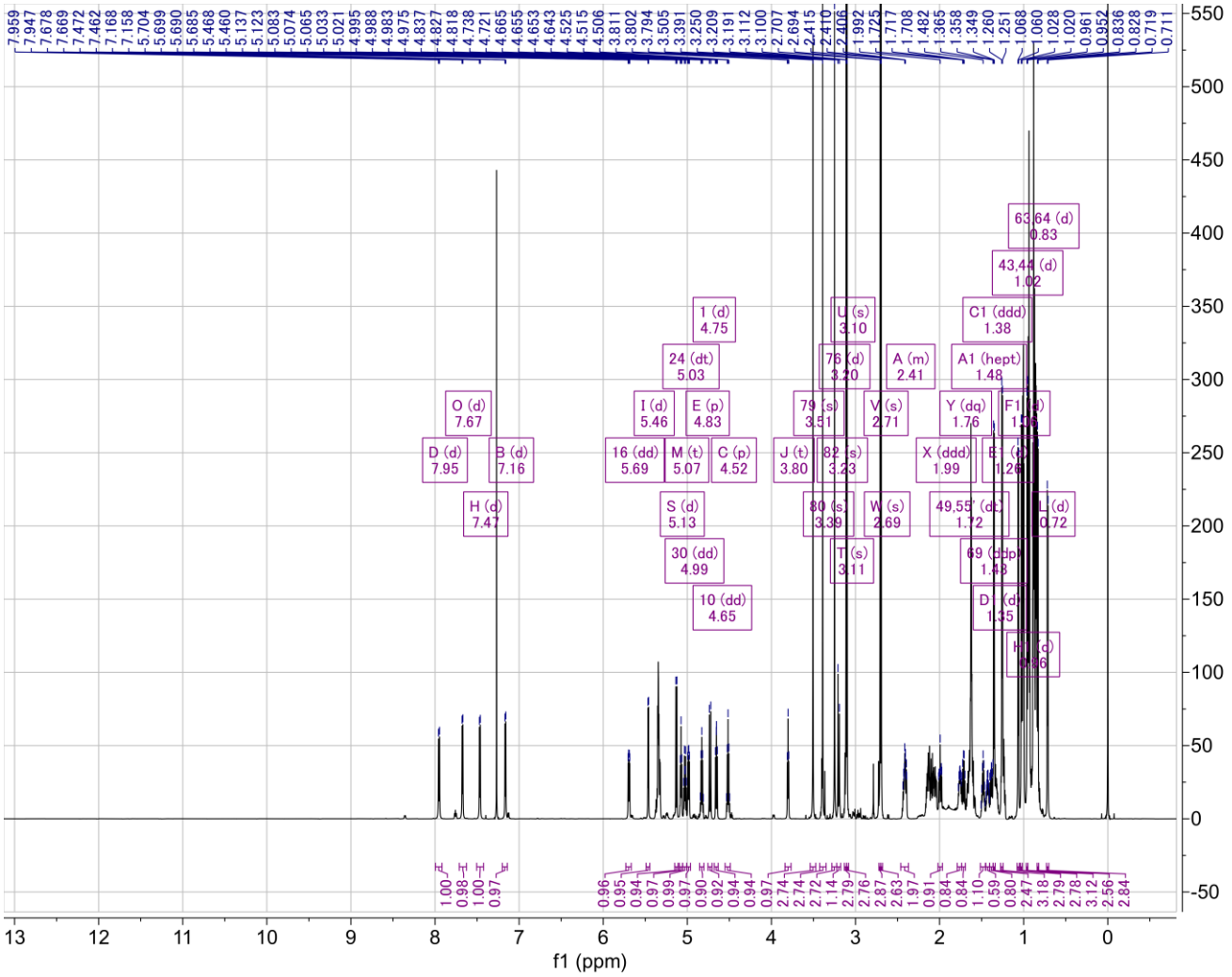

Figure S30. NMR Spectra of CsA in n-hexane-d14. ^{1}H NMR (800 MHz, $CDCl_3$) δ 8.30 (d, *J* = 9.6 Hz, 1H), 7.75 (d, *J* = 7.1 Hz, 1H), 7.42 (d, *J* = 7.3 Hz, 1H), 7.19 (d, *J* = 8.9 Hz, 1H), 5.70 (dd, *J* = 11.1, 4.4 Hz, 1H), 5.31 – 5.24 (m, 1H), 5.19 (dd, *J* = 11.2, 4.8 Hz, 1H), 5.10 (dd, *J* = 8.2, 5.8 Hz, 1H), 5.04 (d, *J* = 11.1 Hz, 1H), 4.99 (td, *J* = 9.0, 6.4 Hz, 1H), 4.75 (p, *J* = 7.0 Hz, 1H), 4.68 (t, *J* = 9.6 Hz, 1H), 4.61 (d, *J* = 13.4 Hz, 1H), 4.38 (p, *J* = 7.2 Hz, 1H), 3.92 (dd, *J* = 8.7, 3.7 Hz, 1H), 3.48 (s, 3H), 3.39 (s, 3H), 3.23 (s, 3H), 3.20 (s, 3H), 3.06 (s, 3H), 2.94 (d, *J* = 13.4 Hz, 1H), 2.66 (s, 3H), 2.62 (s, 3H), 2.47 (dp, *J* = 10.2, 6.7 Hz, 1H), 2.27 (s, 1H), 1.96 (s, 1H), 1.91 (ddtt, *J* = 12.5, 8.3, 5.8, 3.1 Hz, 1H), 1.83 (s, 0H), 1.80 (dt, *J* = 13.6, 9.4 Hz, 1H), 1.59 (d, *J* = 6.5 Hz, 4H), 1.53 (tq, *J* = 11.6, 4.1, 3.4 Hz, 2H), 1.48 (s, 1H), 1.43 (tdq, *J* = 9.6, 6.7, 3.3, 2.8 Hz, 1H), 1.28 (d, *J* = 7.3 Hz, 5H), 1.19 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 3H).

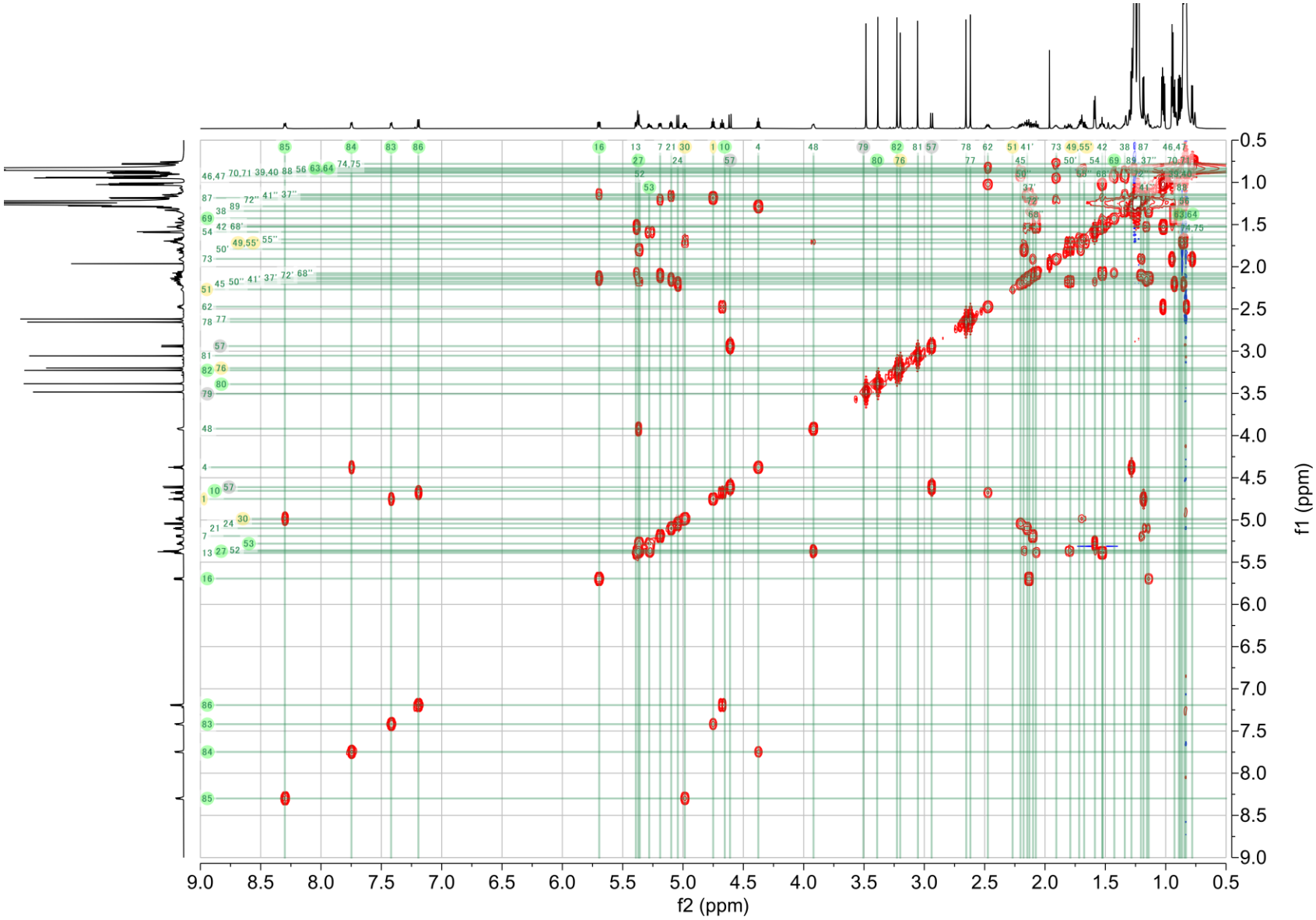

Figure S31. COSY Spectra of CsA in n-hexane-d14.

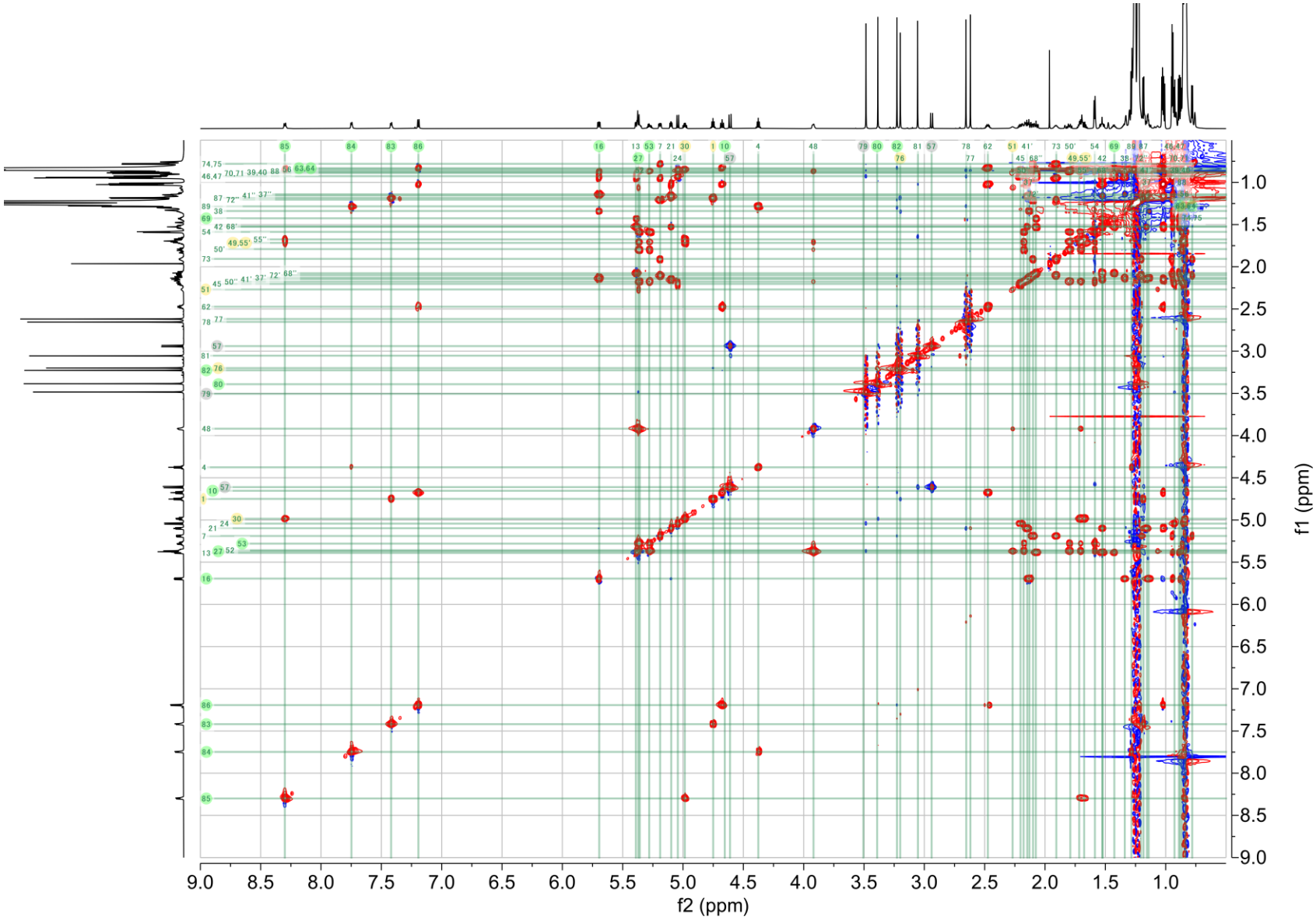

Figure S32. TOCSY Spectra of CsA in n-hexane-d14.

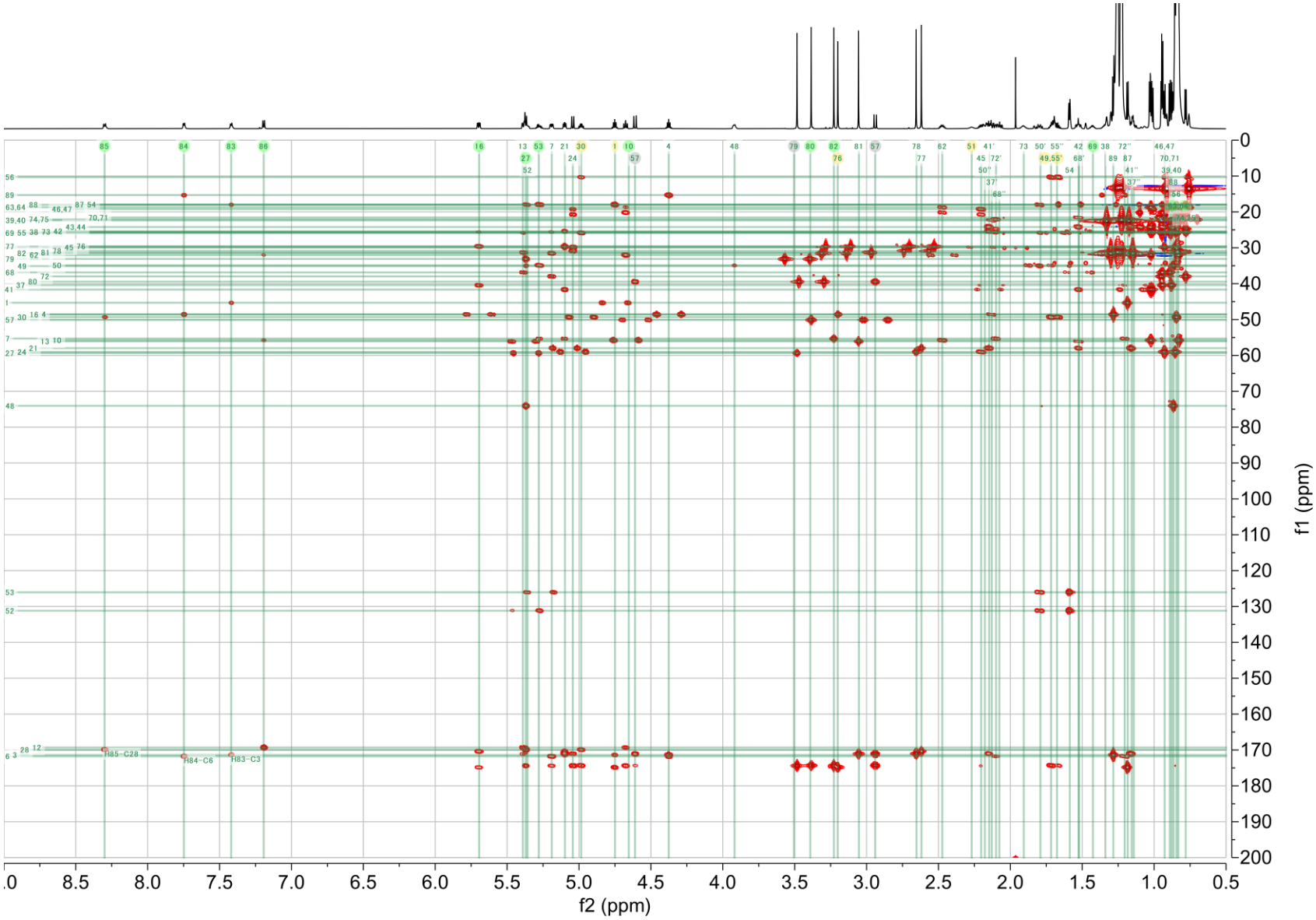

Figure S33. HMBC Spectra of CsA in n-hexane-d14.

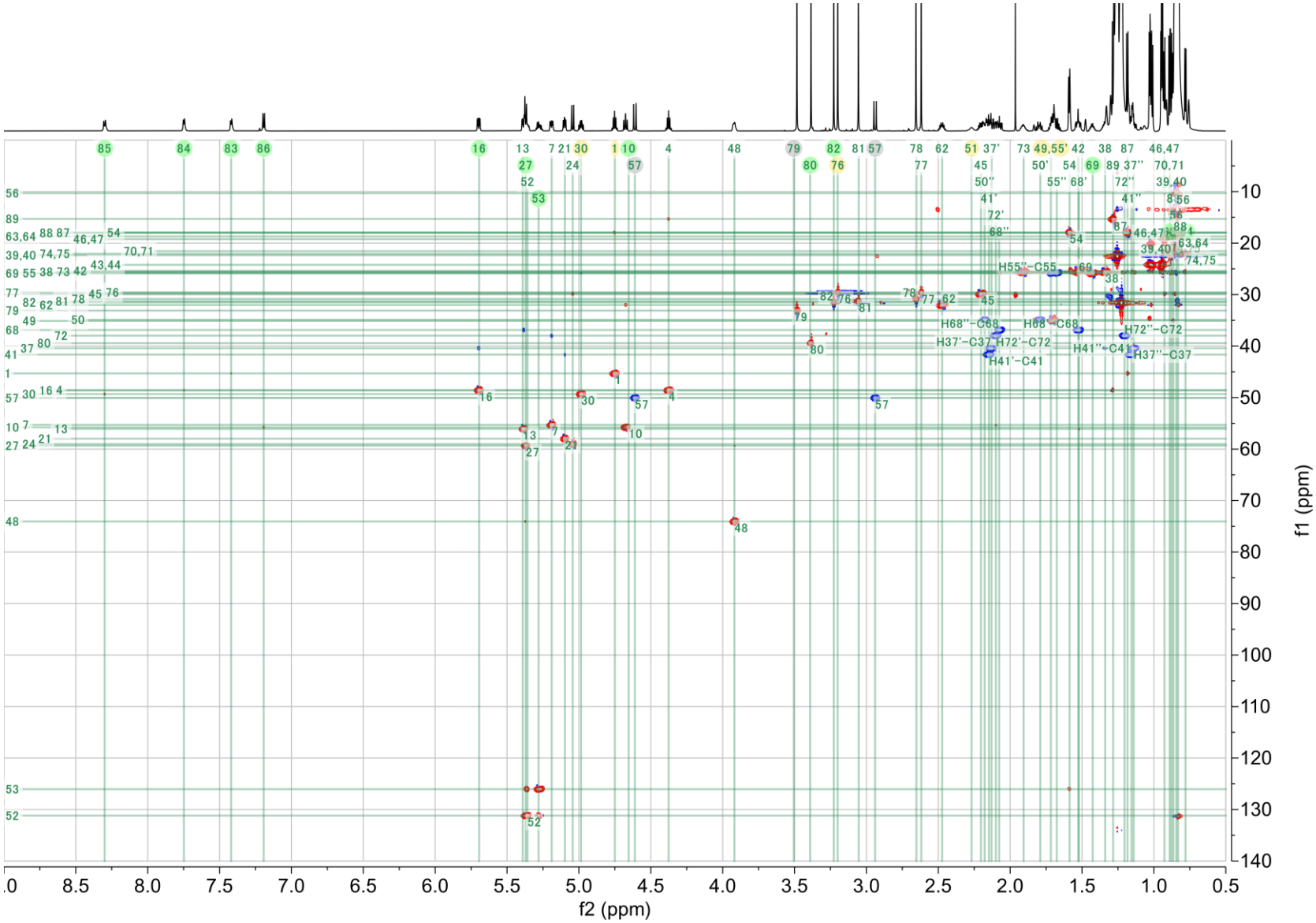

Figure S34. HSQC Spectra of CsA in n-hexane-d14.

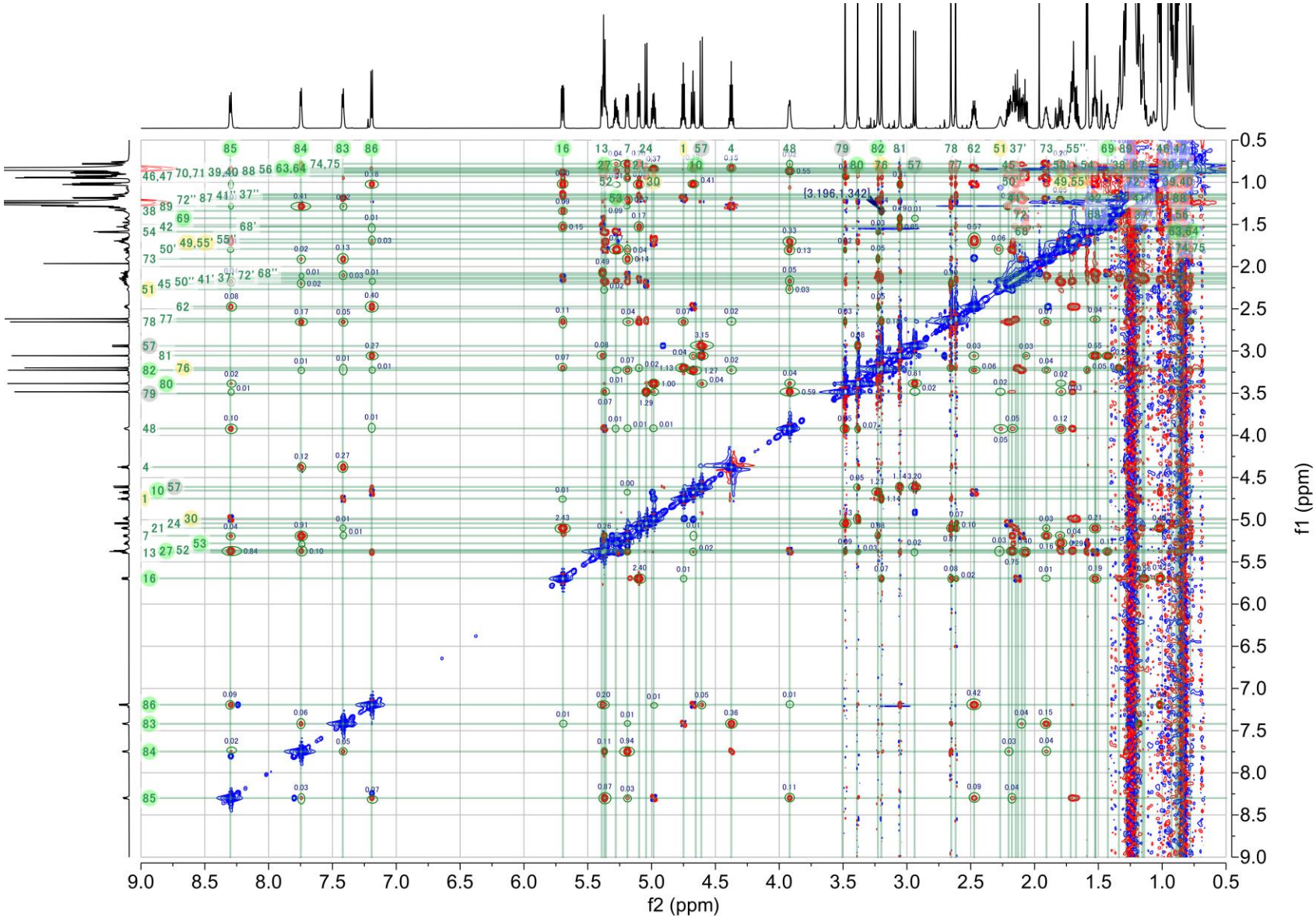

Figure S35. ROESY Spectra of CsA in n-hexane-d14.

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