Chemistry–A European Journal

Supporting Information

Controlling Swing Rates in Macrocyclic Molecular Mortise Hinges

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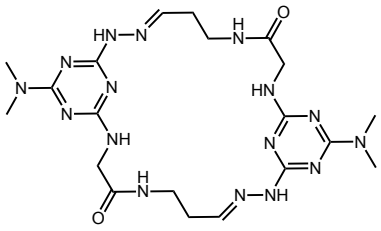
SECTION I

Chart S1. Compounds described in the supporting material



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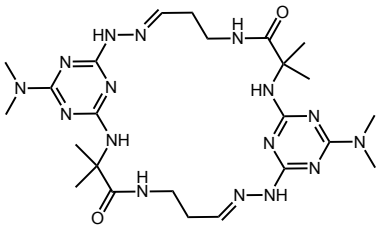

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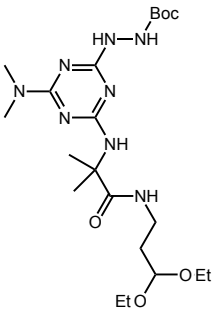

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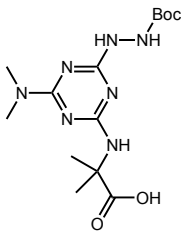

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SECTION II – General Experimental Details

General Chemistry and synthesis. Flash chromatography experiments were carried out on silica gel with a porosity of 60Å, particle size 50–63 m, surface area 500 – 600 m^2/g, a bulk density of 0.4 g/mL and a pH range of 6.5 -– 7.5. Dichloromethane/methanol was used as the eluent for chromatographic purification. Thin-layer chromatography experiments were carried out in sealed chambers and visualized with UV or submersion in ninhydrin (1.5g ninhydrin in 100mL of n-butanol and 3.0mL acetic acid) followed by heating. Excess solvents were removed via rotary evaporation on a Buchi Rotavapor RII with a Welch Self-Cleaning Dry Vacuum System. All workup and purification procedures were carried out with reagent-grade solvents under ambient atmosphere.

NMR Spectroscopy. All 1D ^1H NMR and $^{13}C\{^1H\}$ NMR spectra occurring at room temperature and higher were recorded on a 400 MHz Bruker Avance spectrometer at Texas Christian University. Chemical shifts were referenced to the corresponding solvent resonances (e.g. DMSO-d_6, d = 2.52 ppm). Deuterated NMR solvents were used as purchased from either a bottle or ampule. Low temperature spectra were acquired on a 500 MHz Varian NMR spectrometer at the University of North Texas in Denton. All structural assignments were made utilizing information from COSY and HSQC experiments. Variable temperature experiments were performed by first adjusting the temperature with sample inserted and allowing the tube to equilibrate for five minutes after the desired temperature was reached.

Calculations of Tc. T_c was calculated by plotting chemical shifts as a function of temperature. Three lines were fit for each resonance. Two were defined by the positions of the last two resonances prior to coalescence. A third was extrapolated back from coalesced resonances. The intersection point was used as the T_c whenever possible. Alternatively, the temperatures of the last decoalesced resonances and first coalesced resonances were averaged.

Estimation of error in Tc. The errors reported in $\Delta G^‡$ derive from uncertainty in estimates of T_c and δ. A 5 K range (± 2.5 K) and d ±0.05 ppm were used to recalculate $\Delta G^‡$. These values rarely exceeded 0.1 kcal/mol. These ranges appear in the supporting information.

Crystallography Methods. Single colourless plate-shaped crystals of **1** and **2** were grown via slow evaporation of methanol and DMSO-d_6, respectively. Once a suitable crystal was selected and mounted, diffraction data was collected. For **1**, data was collected at Texas Christian University at 100 K on a Bruker D8Quest Diffractometer. Diffraction data for **2** was collected at Texas A&M University at 110K on a Bruker Photon 3 kappa microsource diffractometer. Data collection, frame integration, and data reduction were carried out using APEX2 software.[S1] Initial structure determinate and refinements were performed using XT structure solution program and refined by full matric least squares minimization using XL.[S2,S3] All non-hydrogen atoms were refined anistropically while hydrogen atom positions were calculated geometrically and refined using the riding model.

S1. O.V. Dolomanov and L.J. Bourhis and R.J. Gildea and J.A.K. Howard and H. Puschmann, Olex2: A complete structure solution, refinement and analysis program, *J. Appl. Cryst.*, **2009**, *42*, 339-341.

S2. Sheldrick, G.M., Crystal structure refinement with ShelXL, *Acta Cryst.*, **2015**, *C71*, 3-8.

S3. Sheldrick, G.M., ShelXT-Integrated space-group and crystal-structure determination, *Acta Cryst.*, **2015**, *A71,* 3-8.

SECTION III – Crystallographic Details

Figure S0. Atom labels for **2** (tcu2022_21_26_ajm2) with contour levels set to 50%. CCDC: 2242912.

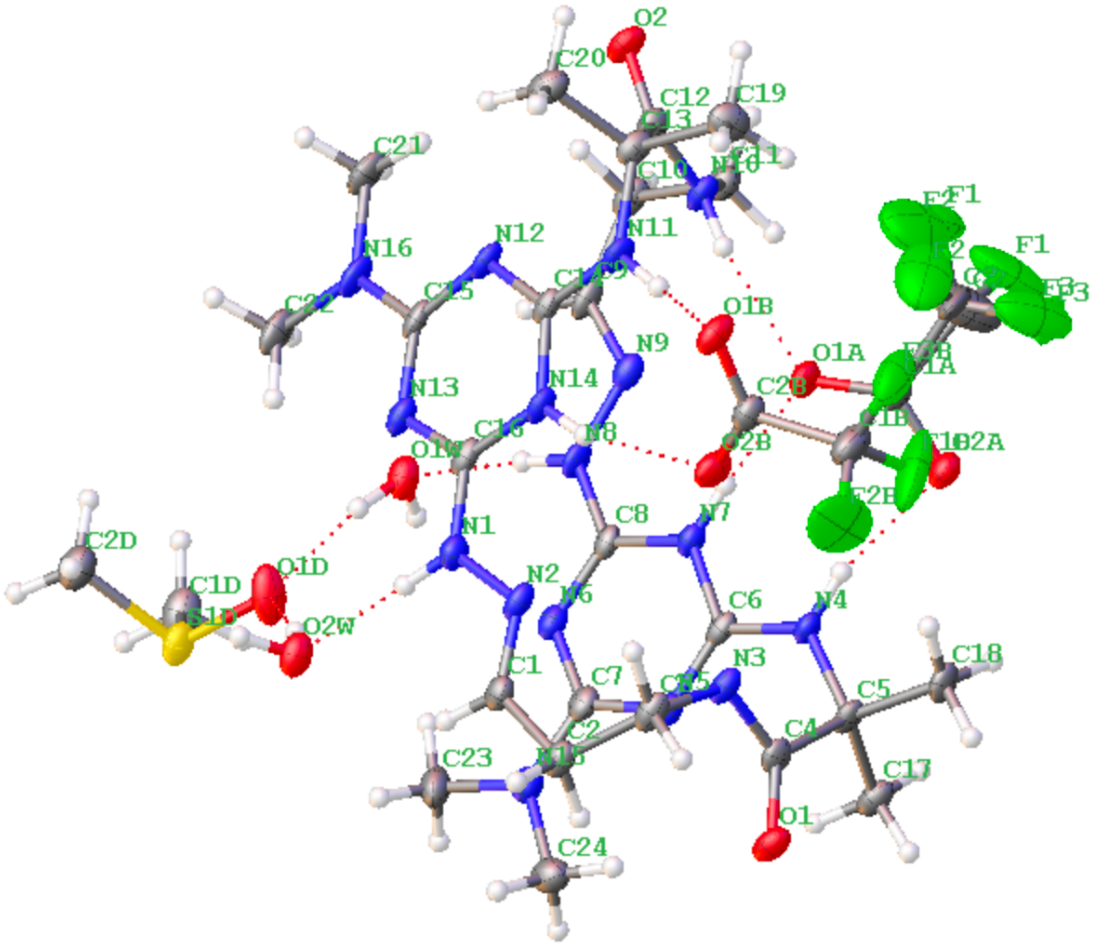


Table S1. Crystal data and structure refinement for **2** (tcu2022_21_26_ajm2).

Compound	**tcu2022_21_26_AJM2**
Formula	$C_{30}H_{51}F_6N_{16}O_9S$
$D_{calc.}$/ g cm^{-3}	1.435
μ/mm^{-1}	1.512
Formula Weight	925.92
Colour	colourless
Shape	plate-shaped
Size/mm^3	0.23×0.11×0.01
T/K	110.00(10)
Crystal System	triclinic
Space Group	P-1
a/Å	13.2085(4)
b/Å	13.6846(3)
c/Å	13.7479(4)
α/°	86.475(2)
β/°	63.402(3)
γ/°	75.024(2)
V/Å^3	2142.29(11)
Z	2
Z'	1
Wavelength/Å	1.54184
Radiation type	Cu K_α
Θ_{min}/°	3.350
Θ_{max}/°	65.088
Measured Refl's.	7295
Indep't Refl's	7295
Refl's I≥2 σ(I)	6661
R_{int}	.
Parameters	613
Restraints	54
Largest Peak	1.039
Deepest Hole	-0.507
GooF	0.821
wR_2 (all data)	0.2331
wR_2	0.2295
R_1 (all data)	0.0847
R_1	0.0813

Table S2A. Bond Lengths for **2** (tcu2022_21_26_AJM2).

Atom	Atom	Length/√Ö	Atom	Atom	Length/√Ö
S1D	O1D	1.511(3)	N10	C12	1.330(5)
S1D	C1D	1.776(5)	N11	C13	1.471(5)
S1D	C2D	1.777(4)	N11	C14	1.333(5)
O1A	C1A	1.243(5)	N12	C14	1.322(5)
O2A	C1A	1.251(5)	N12	C15	1.352(5)
C1A	C2_1	1.537(8)	N13	C15	1.351(5)
C1A	C2_2	1.50(2)	N13	C16	1.328(5)
F1B	C1B	1.314(6)	N14	C14	1.373(5)
F2B	C1B	1.327(6)	N14	C16	1.355(5)
F3B	C1B	1.308(5)	N15	C7	1.329(5)
O1B	C2B	1.245(5)	N15	C23	1.466(5)
O2B	C2B	1.231(5)	N15	C24	1.458(5)
C1B	C2B	1.551(6)	N16	C15	1.343(5)
O1	C4	1.226(5)	N16	C21	1.459(6)
O2	C12	1.236(5)	N16	C22	1.456(6)
N1	N2	1.396(4)	C1	C2	1.492(5)
N1	C16	1.330(5)	C2	C3	1.524(6)
N2	C1	1.268(5)	C4	C5	1.545(5)
N3	C3	1.457(5)	C5	C17	1.523(5)
N3	C4	1.344(5)	C5	C18	1.532(5)
N4	C5	1.476(4)	C9	C10	1.483(6)
N4	C6	1.339(5)	C10	C11	1.527(6)
N5	C6	1.310(5)	C12	C13	1.545(5)
N5	C7	1.359(5)	C13	C19	1.535(6)
N6	C7	1.349(5)	C13	C20	1.525(5)
N6	C8	1.314(5)	C2_1	F1_1	1.314(8)
N7	C6	1.379(5)	C2_1	F2_1	1.363(9)
N7	C8	1.364(5)	C2_1	F3_1	1.298(7)
N8	N9	1.384(5)	C2_2	F1_2	1.314(9)
N8	C8	1.333(5)	C2_2	F2_2	1.362(10)
N9	C9	1.275(5)	C2_2	F3_2	1.297(8)
N10	C11	1.451(5)			

Table S2B. Bond Angles for **2** (tcu2022_21_26_AJM2).

Atom	Atom	Atom	Angle	Atom	Atom	Atom	Angle
O1D	S1D	C1D	105.7(2)	C17	C5	C4	111.1(3)
O1D	S1D	C2D	105.1(2)	C17	C5	C18	108.4(3)
C2D	S1D	C1D	98.6(2)	C18	C5	C4	108.2(3)
O1A	C1A	O2A	128.7(4)	N4	C6	N7	116.8(3)
O1A	C1A	C2_1	115.2(4)	N5	C6	N4	120.5(3)
O1A	C1A	C2_2	120.9(10)	N5	C6	N7	122.7(3)
O2A	C1A	C2_1	116.0(4)	N6	C7	N5	124.7(4)
O2A	C1A	C2_2	109.8(10)	N15	C7	N5	117.4(3)
F1B	C1B	F2B	106.6(5)	N15	C7	N6	117.9(3)
F1B	C1B	C2B	112.3(4)	N6	C8	N7	122.9(3)
F2B	C1B	C2B	109.3(4)	N6	C8	N8	117.5(3)
F3B	C1B	F1B	107.6(4)	N8	C8	N7	119.6(3)
F3B	C1B	F2B	106.2(4)	N9	C9	C10	123.3(4)
F3B	C1B	C2B	114.4(4)	C9	C10	C11	115.5(3)
O1B	C2B	C1B	115.1(3)	N10	C11	C10	112.2(3)
O2B	C2B	O1B	129.3(4)	O2	C12	N10	123.8(3)
O2B	C2B	C1B	115.6(3)	O2	C12	C13	120.2(3)
C16	N1	N2	120.6(3)	N10	C12	C13	116.0(3)
C1	N2	N1	113.6(3)	N11	C13	C12	110.3(3)
C4	N3	C3	121.4(3)	N11	C13	C19	106.0(3)
C6	N4	C5	123.0(3)	N11	C13	C20	111.6(3)
C6	N5	C7	116.1(3)	C19	C13	C12	108.3(3)
C8	N6	C7	116.3(3)	C20	C13	C12	111.5(3)
C8	N7	C6	116.9(3)	C20	C13	C19	109.0(3)
C8	N8	N9	121.6(3)	N11	C14	N14	117.2(3)
C9	N9	N8	114.1(3)	N12	C14	N11	120.1(3)
C12	N10	C11	122.2(3)	N12	C14	N14	122.7(3)
C14	N11	C13	123.7(3)	N13	C15	N12	125.9(3)
C14	N12	C15	115.5(3)	N16	C15	N12	117.1(4)
C16	N13	C15	115.2(3)	N16	C15	N13	117.0(4)
C16	N14	C14	117.3(3)	N1	C16	N14	120.1(3)
C7	N15	C23	121.9(4)	N13	C16	N1	116.6(4)
C7	N15	C24	122.7(3)	N13	C16	N14	123.2(4)
C24	N15	C23	115.4(3)	F1_1	C2_1	C1A	112.7(6)
C15	N16	C21	121.9(4)	F1_1	C2_1	F2_1	103.0(6)
C15	N16	C22	122.0(4)	F2_1	C2_1	C1A	109.9(6)
C22	N16	C21	116.1(3)	F3_1	C2_1	C1A	113.9(5)

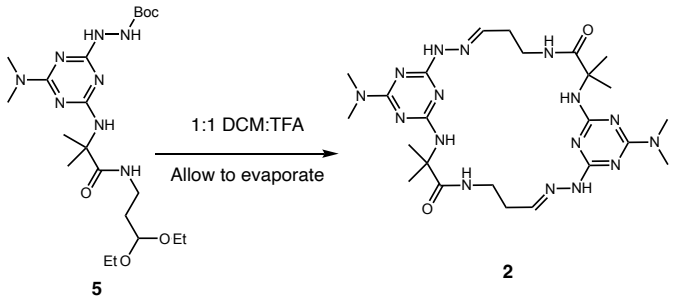
Table S2B continued. Bond Angles for **2** (tcu2022_21_26_AJM2).

N2	C1	C2	122.2(4)	F3_1	C2_1	F1_1	111.6(7)
C1	C2	C3	115.7(3)	F3_1	C2_1	F2_1	104.8(6)
N3	C3	C2	112.5(3)	F1_2	C2_2	C1A	115.2(16)
O1	C4	N3	123.6(3)	F1_2	C2_2	F2_2	104(2)
O1	C4	C5	120.8(3)	F2_2	C2_2	C1A	110.3(18)
N3	C4	C5	115.4(3)	F3_2	C2_2	C1A	119(2)
N4	C5	C4	110.5(3)	F3_2	C2_2	F1_2	106.9(19)
N4	C5	C17	112.5(3)	F3_2	C2_2	F2_2	100(2)
N4	C5	C18	105.9(3)				

SECTION IV – Experimental Details

Macrocyclization to yield 2

The macrocycle was obtained by the procedure illustrated and described below.



Acetal **5** (0.075 g) was dissolved in 1 mL of DCM in a 3 mL vial equipped with a mini stir bar. Trifluoroacetic acid (1 mL) was added over 1 minute via pipette. Evaporation occurred over the course of 5 days. The dried residue was then analyzed by NMR. The reaction can be described as quantitative as an off white solid.

^{1}H NMR (DMSO-D_6, 400 MHz): δ 12.10 (s, 1H), 11.72 (s, 1H), 8.89 (s, 1H), 7.84(t, J = 5.8 Hz, 1H), 7.38 (s, 1H), 3.47 (s, 1H), 3.22 (s, 1H), 3.13 (s, 3H), 3.08 (s, 3H), 2.70 (s, 1H), 2.39 (s, 1H), 1.48 (s, 6H). ^{13}C{^{1}H} NMR (DMSO-D_6, 100 MHz): δ 172.2, 161.3, 153.2, 152.6, 151.9, 57.6, 37.0, 36.9, 34.7, 30.9, 27.5, 22.8.

^{1}H NMR (CD_3CN, 400 MHz): δ 10.08 (s, 1H), 7.95 (s, 1H), 7.73 (s, 1H), 7.42 (t, J = 2.7 Hz, 1H), 4.08 (m, 1H), 3.23 (s, 1H), 3.15 (s, 3H), 3.11 (s, 3H), 2.77 (s, 1H), 2.57 (s, 1H), 1.72 (s, 3H), 1.61 (s, 3H). ^{13}C{^{1}H} NMR (CD_3CN, 100 MHz): δ 175.2, 161.7, 153.5, 152.9, 148.9, 57.9, 36.7, 36.3, 34.5, 31.2, 27.1, 21.3.

^{1}H NMR (CD_3OD, 400 MHz): δ 7.32 (t, J = 2.7 Hz, 1H), 3.64 (s, 1H), 3.52 (s, 1H), 3.22 (2, 3H), 3.17 (s, 3H), 2.86 (s, 1H), 2.49 (s, 1H), 1.64 (s, 6H). ^{13}C{^{1}H} NMR (CD_3OD, 100 MHz): δ 174.7, 161.6, 153.3, 152.8, 149.8, 57.6, 36.1, 35.8, 34.4, 30.7, 26.7, 21.2.

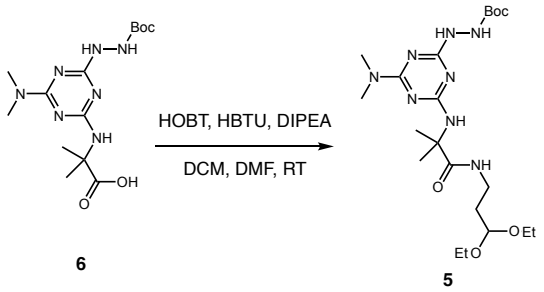
^{1}H NMR (D_2O, 400 MHz): δ 7.29 (t, J = 2.7 Hz, 1H), 3.46 (m, 2H), 3.08 (s, 3H), 3.03 (s, 3H), 2.72 (m, 1H), 2.42 (d, J = 20 Hz, 1H), 1.54 (s, 3H), 1.48 (s, 3H). ^{13}C{^{1}H} NMR (D_2O, 100 MHz): δ 175.9, 161.0, 152.6, 151.9, 151.0, 57.5, 36.5, 36.3, 34.5, 30.4, 27.2, 21.1.

^{1}H NMR (Pyridine-D_5, 400 MHz): δ 12.94 (s, 1H), 10.41 (s, 1H), 3.94 (s, 1H), 3.69 (s, 1H), 3.06 (s, 4H), 2.77 (s, 3H), 2.28 (d, J = 18 Hz, 1H), 1.88 (s, 6H). ^{13}C{^{1}H} NMR (Pyridine-D_5, 100 MHz): δ 173.8, 161.2, 155.8, 155.3, 149.0, 58.0, 36.3, 35.7, 34.8, 31.3, 27.4, 23.0.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{24}H_{40}N_{16}O_2$ 585.3593; Found 585.3591.

Synthesis of 5

Intermediate **5** was prepared as illustrated and described below.



6 **5**

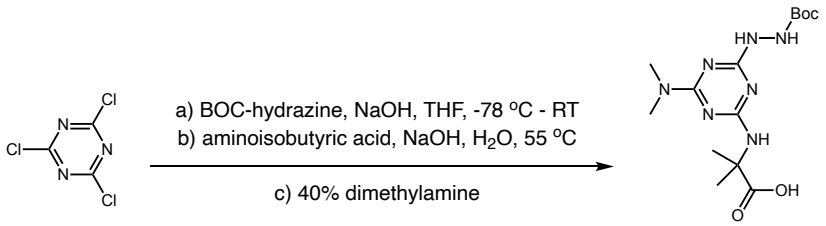
4 (0.231 g, 0.65 mmol) was dissolved in 4 mL DCM and 2.5 mL DMF for solubility purposes. The following reagants were all added as either a powder or neat liquid to the reaction flask: diisopropyl ethylamine (0.209 g, 1.625 mmol), HOBT (0.105 g, 0.78 mmol), HBTU (0.296 g, 0.78 mmol), and 3,3-diethoxypropyl-1-amine (0.115 g, 0.78 mmol). The reaction was allowed to stir overnight at room temperature before drying with an airstream. The resulting oil was diluted with 30 mL ethyl acetate and washed 3 times with H_2O and once with brine before drying of magnesium sulfate. Column chromatography in 5% MeOH in DCM afforded 0.085 g pure product (27.4 %) as a white powder.

^{1}H NMR (CD_3OD, 400 MHz): δ 7.66 (s, 1H), 4.46 (s, 1H), 3.61 (m, 2H), 3.45 (m, 2H), 3.24 (q, J = 6.3 Hz, 2H), 3.07 (s, 6H), 1.74 (q, J = 6.3 Hz, 2H), 1.51 – 1.49 (m, 15H), 1.18 (t, J = 7.2 Hz, 6H). ^{13}C{^{1}H} NMR (CD_3OD, 100 MHz): δ 176.8, 173.9, 167.4, 165.5, 101.5, 80.0, 61.3, 56.3, 35.2, 34.9, 29.3, 27.3, 24.8, 23.8, 19.4, 14.3.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{21}H_{40}N_8O_5$ 485.3194; Found 485.3194.

Synthesis of 6

6 was prepared in one-pot by sequential addition to cyanuric chloride as illustrated and described below.



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To a 100 mL round bottom flask, 1.0 g of cyanuric chloride (5.4 mmol) and 15 mL of THF were combined. The resulting solution was allowed to cool to -78 °C using an acetone/dry ice bath. At this time, 0.713 g (5.4 mmol) of BOC-hydrazine was dissolved in 5 mL of THF. The BOC-hydrazine solution was added to an addition funnel and allowed to drop into the reaction flask at a rate of one drop per second. Next, 5.4 mL of 1 M NaOH was added to the addition funnel and allowed to drop in at a rate of five drops per second. At this time, the dry ice bath was removed and the solution was allowed to slowly warm to room temperature. After 45 minutes, all BOC-hydrazine was consumed and a UV spot which stained bright yellow under ninhydrin appeared at an $R_f = 0.9$.

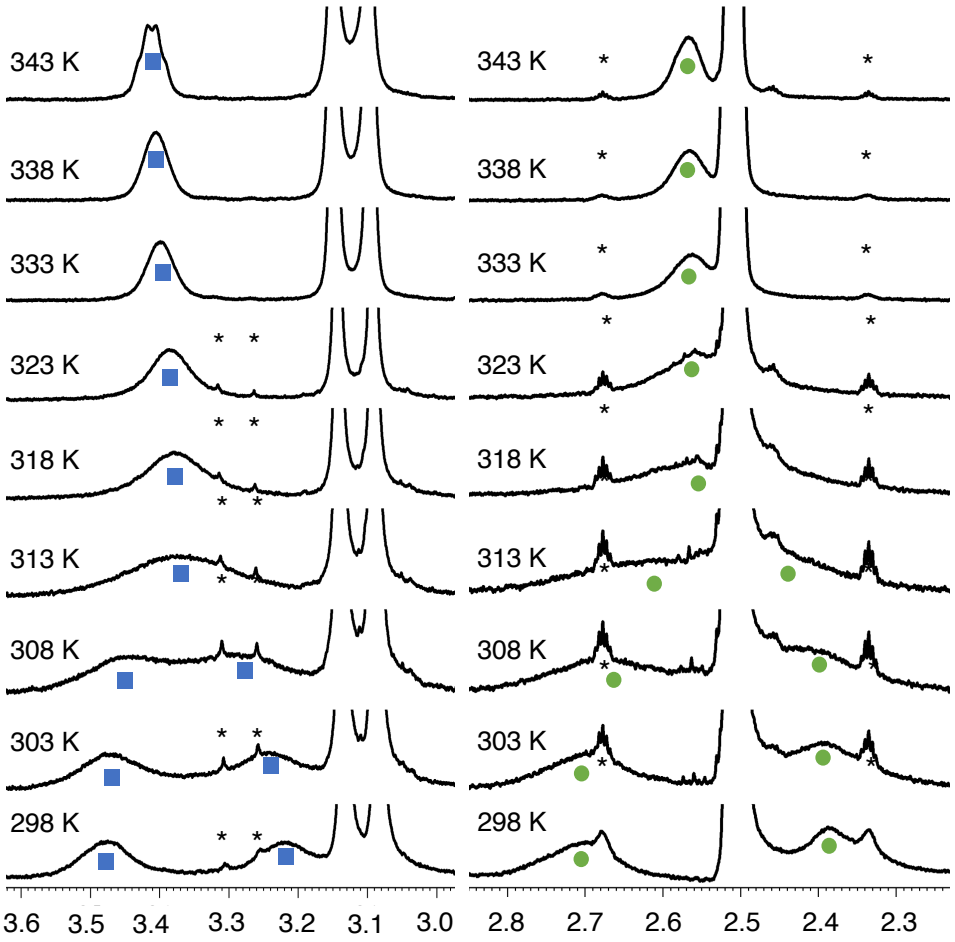
At this time, a solution of aminoisobutyric acid was prepared by dissolving 1.115 g acid (10.8 mmol) in 5 mL of water and 16.2 mL (16.2 mmol) of 1 M NaOH. The pH of the reaction flask was measured to be pH 11 and 1 M HCl was used to bring the pH to pH 8. The reaction flask was heated to 55 °C overnight before TLC showed full conversion to a new UV spot (yellow by ninhydrin) at $R_f = 0.2$.

Next, a 40% aqueous solution of dimethylamine (1.83 g, 16.2 mmol) was dropped in over one minute through a water condenser. The reaction was allowed to react for 3 hours before adding an additional 0.9 g of the 40% aqueous solution of dimethylamine (8.1 mmol) to ensure no dimethylamine boiled off. After an additional hour of reaction time, TLC showed consumption of the low R_f UV spot and a new spot appeared at $R_f = 0.4$ (yellow by ninhydrin). The reaction was acidified to pH 5 before extracting four times with ethyl acetate. Column chromatography was performed on the crude material in 5% MeOH in DCM. The resulting pure product was a white powder (0.246 g, 12.8%).

^{1}H NMR (CD_3OD, 400 MHz): δ 3.11 (s, 6H), 1.64 (s, 6H), 1.49 (s, 9H). $^{13}C\{^1H\}$ NMR (CD_3OD, 100 MHz): δ 181.3, 166.8, 164.8, 157.4, 80.2, 57.0, 48.4, 35.1, 27.7, 24.2.
HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{14}H_{25}N_7O_4$ 356.2041; Found 356.2037.

SECTION V – Determination of Coalescence Temperature

Figure S1. Variable Temperature 400MHz ^{1}H NMR Spectra of 2 in DMSO-d_6 and T_c plots. Resonances are indicated with blue squares (C1 & C2) and green circles (B1 & B2). Plots reveal coalescence temperature, T_c. The shaded triangles corresponds to errors associated with temperature (±2.5 K).



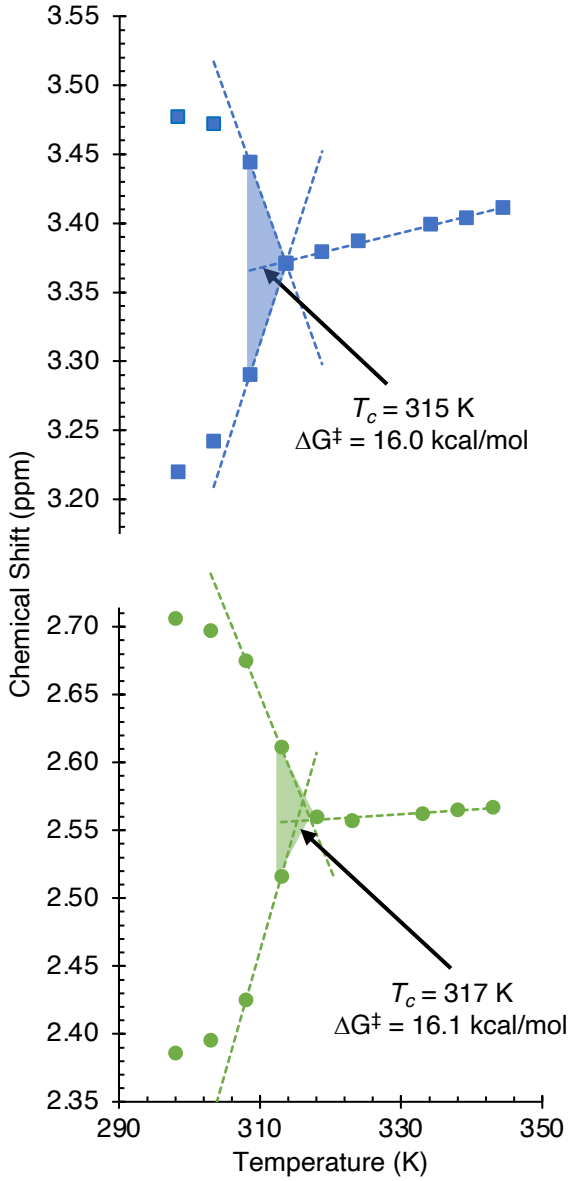


Figure S2. Variable Temperature 400MHz ^{1}H NMR Spectra of 2 in CD_3OD and T_c plots. Resonances are indicated with blue squares (C1 & C2), green circles (B1 & B2), and red triangles (B-Me). Plots reveal coalescence temperature, T_c. The shaded triangles corresponds to errors associated with temperature (±2.5 K).

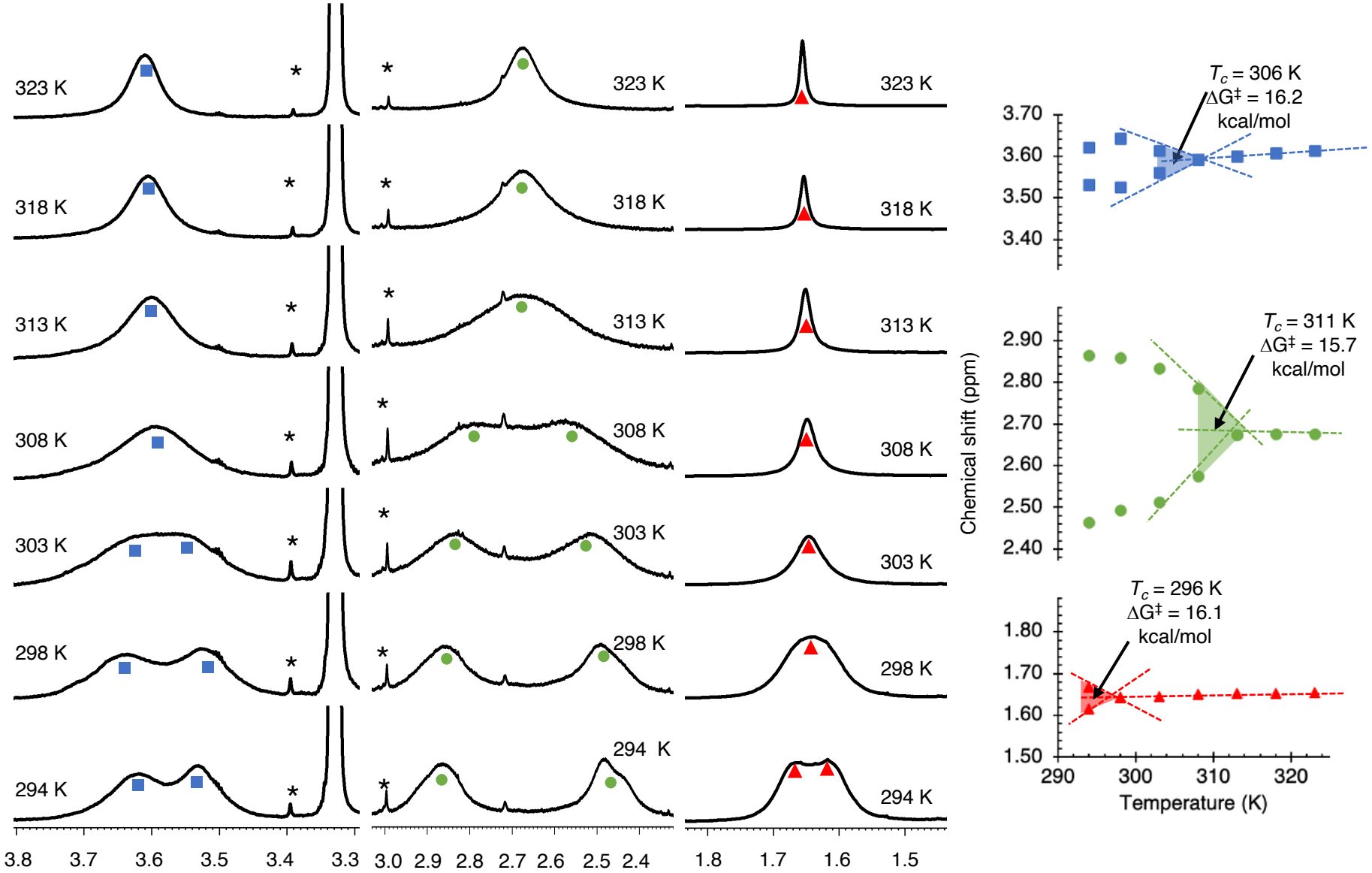


Figure S3. Variable Temperature 400MHz ^{1}H NMR Spectra of 2 in CD_3CN and T_c plots.
Resonances are indicated with blue squares (C1 & C2), green circles (B1 & B2), and red triangles (B-Me). Plots reveal coalescence temperature, T_c. The shaded triangles corresponds to errors associated with temperature (±2.5 K).

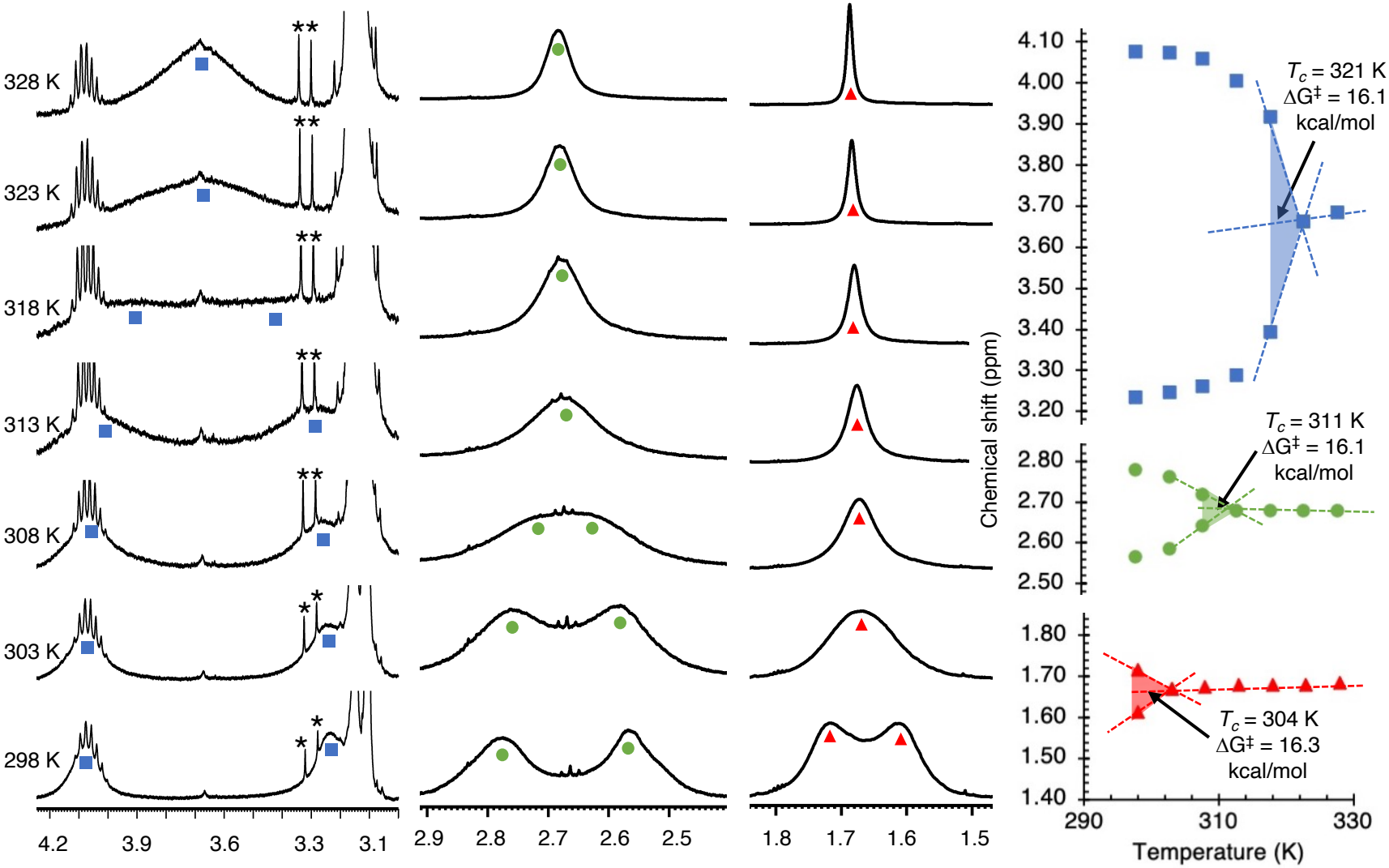


Figure S4. Variable Temperature 400MHz ^{1}H NMR Spectra of 2 in D_2O and T_c plots. Resonances are indicated with blue squares (C1 & C2), green circles (B1 & B2), and red triangles (B-Me). Plots reveal coalescence temperature, T_c. The shaded triangles corresponds to errors associated with temperature (±2.5 K).

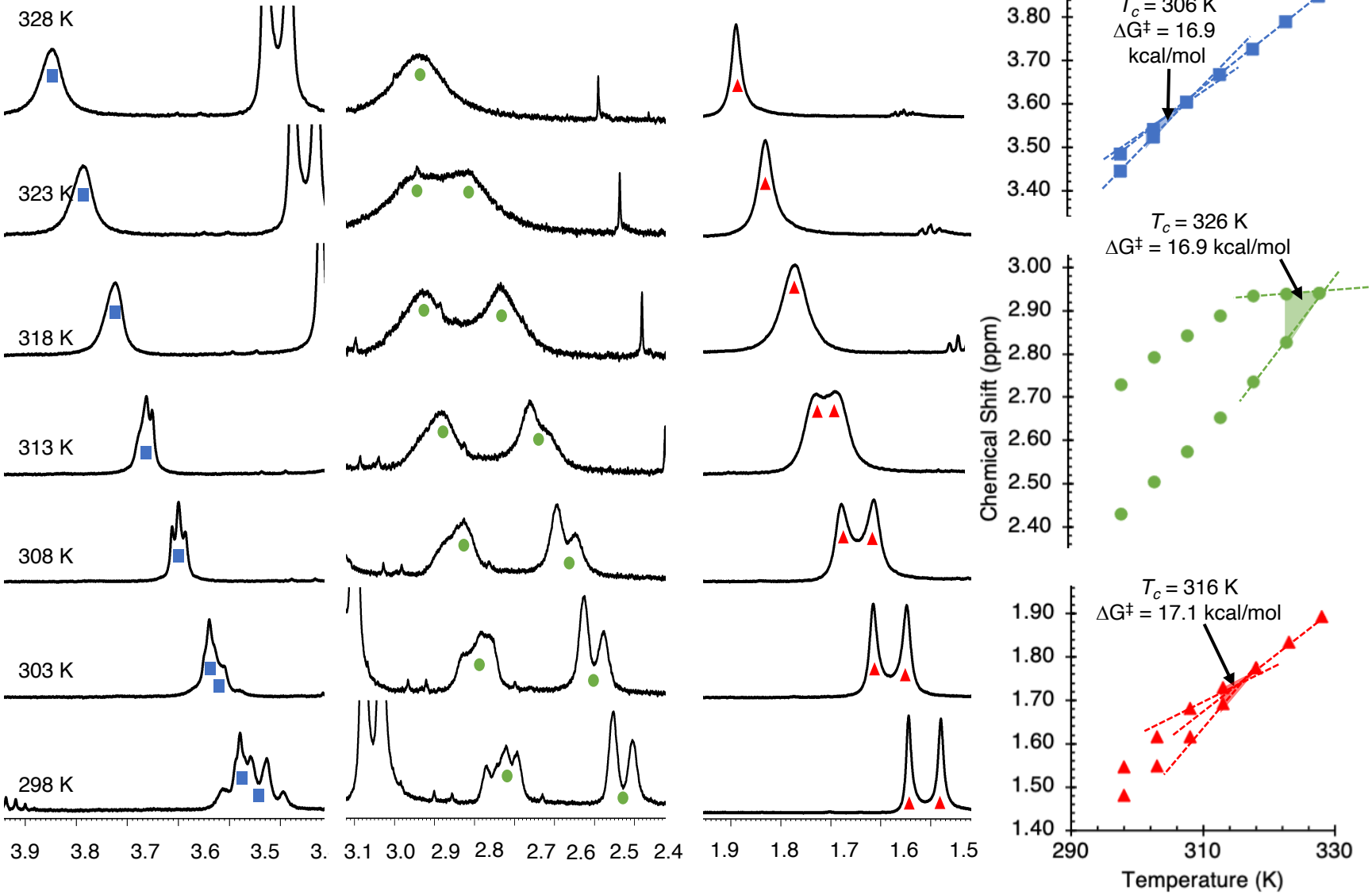
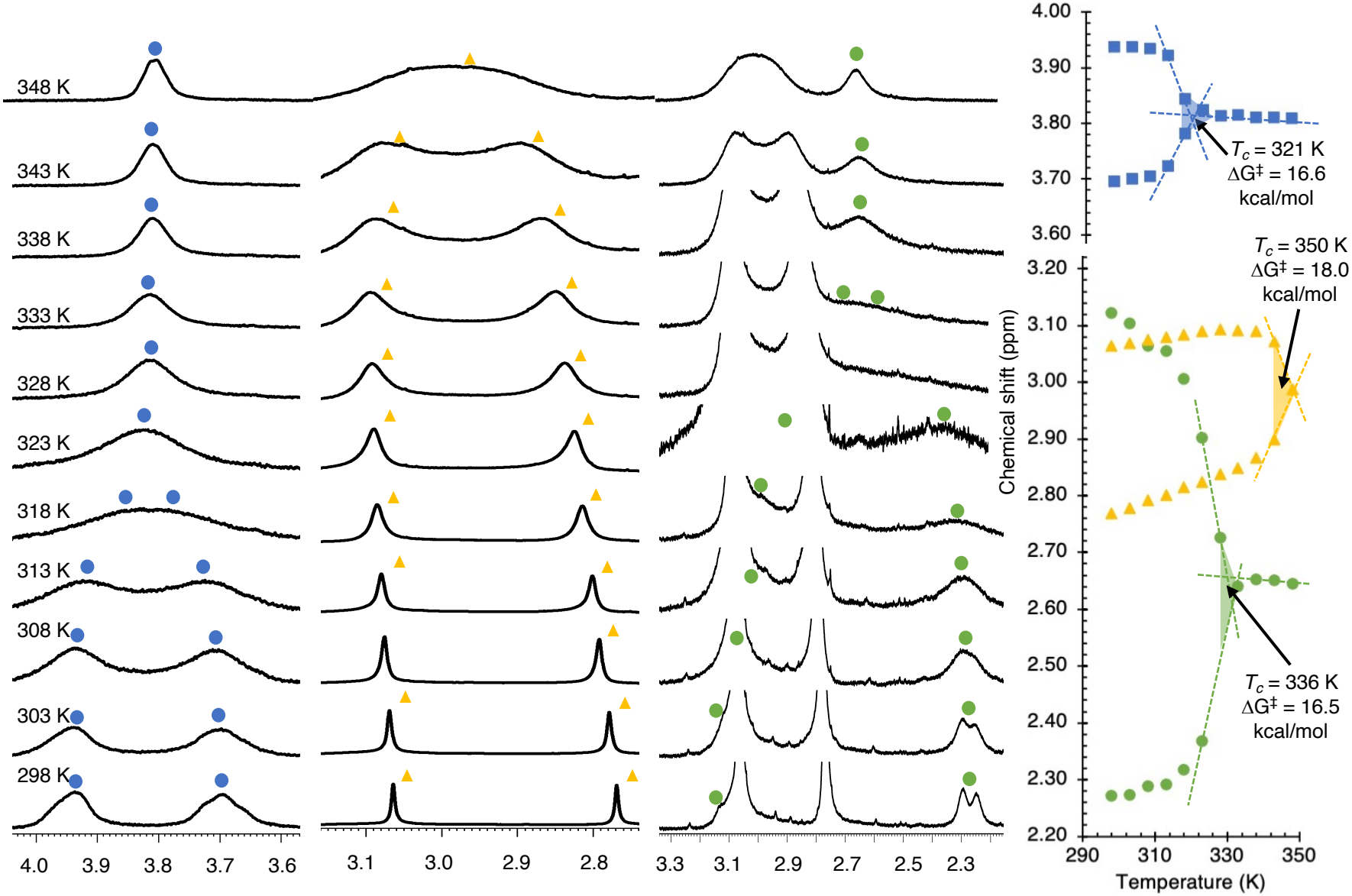


Figure S5. Variable Temperature 400MHz ^{1}H NMR Spectra of 2 in *Pyridine-d$_5$*. and Tc plots. Resonances are indicated with blue squares (C1 & C2), green circles (B1 & B2), and yellow triangles (M1 & M2). Plots reveal coalescence temperature, T_c. The shaded triangles corresponds to errors associated with temperature (±2.5 K).



SECTION VI – Spectra

Figure S6. The 400 MHz ^{1}H NMR spectrum of 2 in DMSO-D_6 at 25 °C.

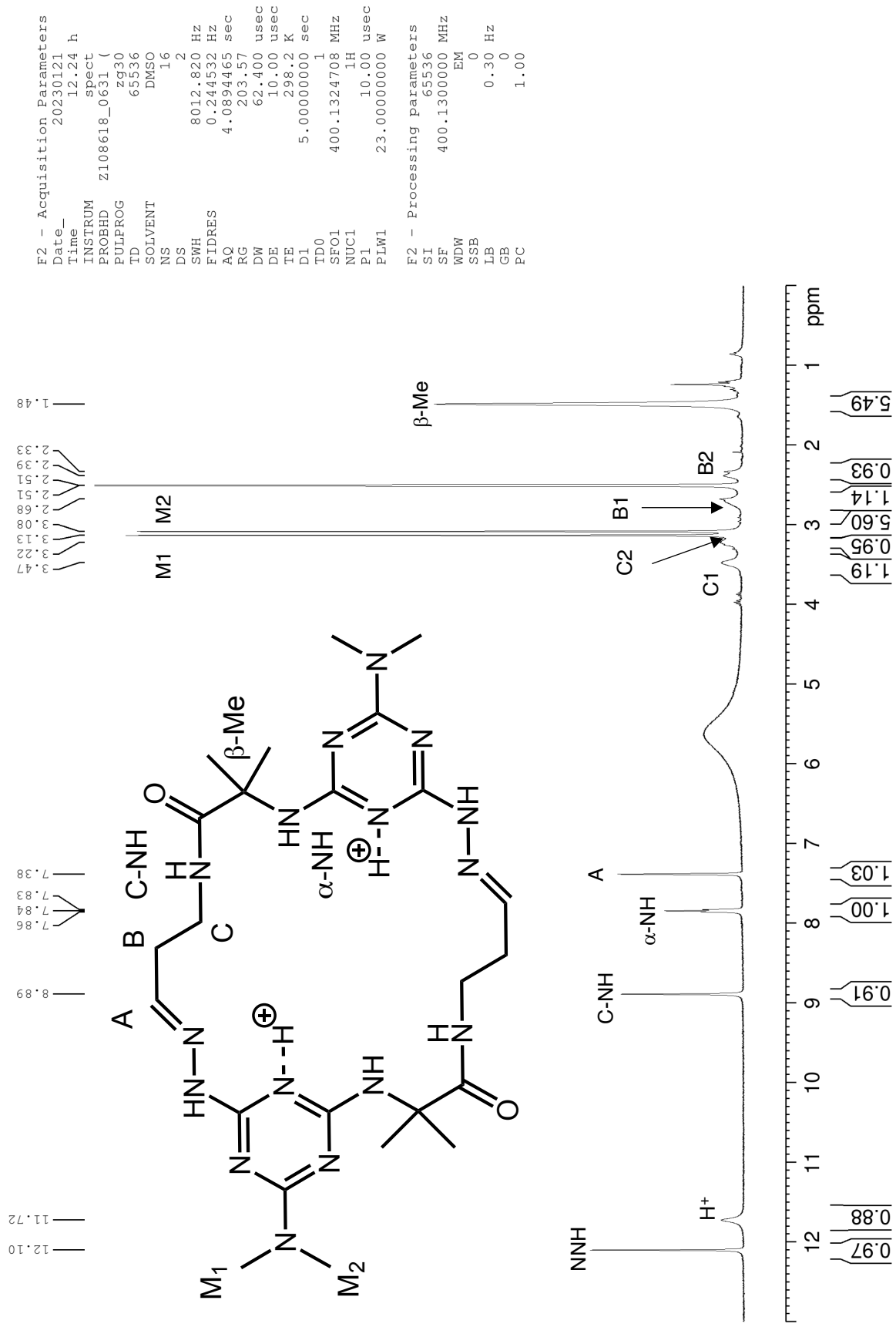


Figure S7. The 400 MHz ^{1}H NMR spectrum of 2 in CD_3CN at 25 ºC.

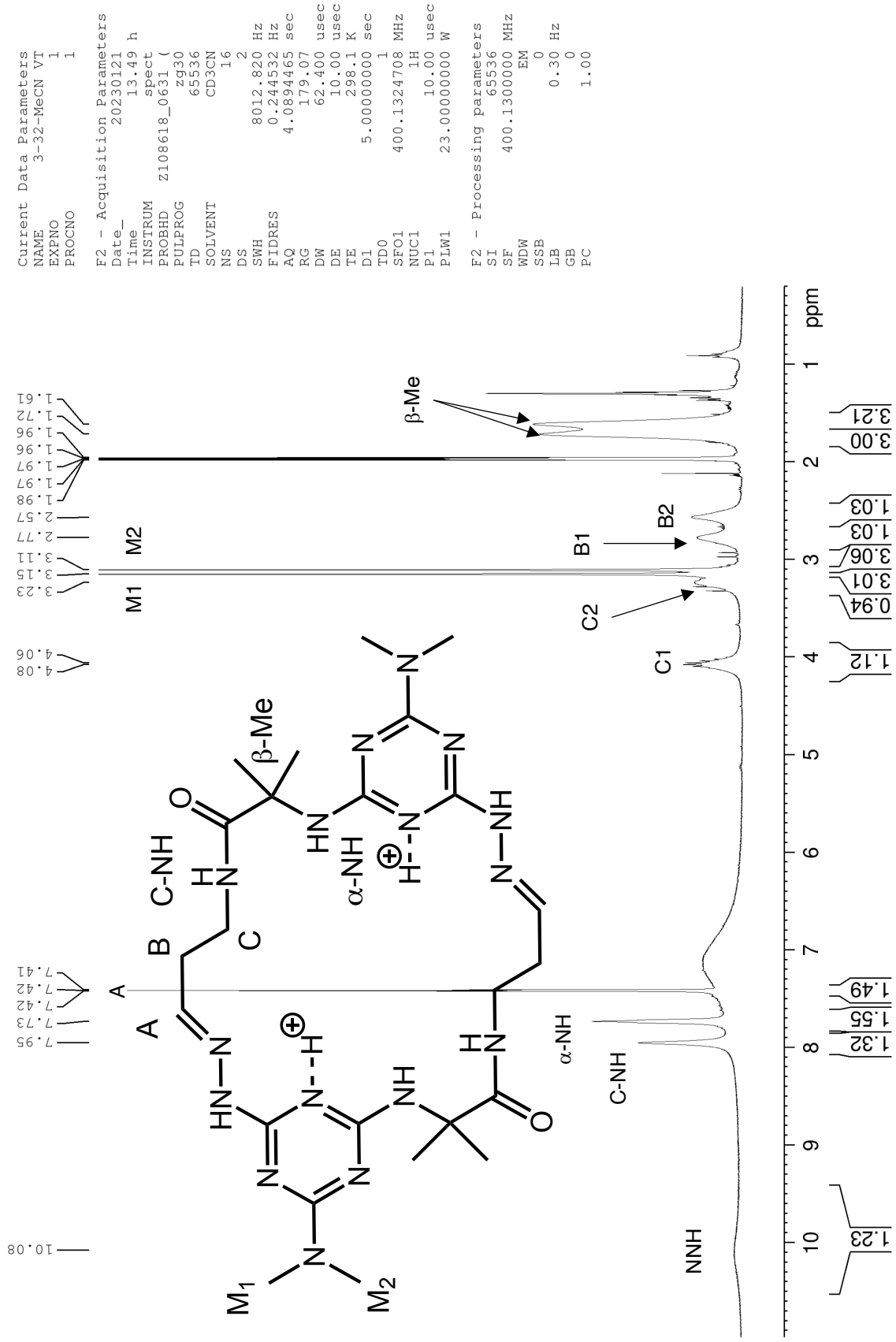


Figure S8. The 400 MHz ^{1}H NMR spectrum of 2 in CD_3OD at 25 °C.

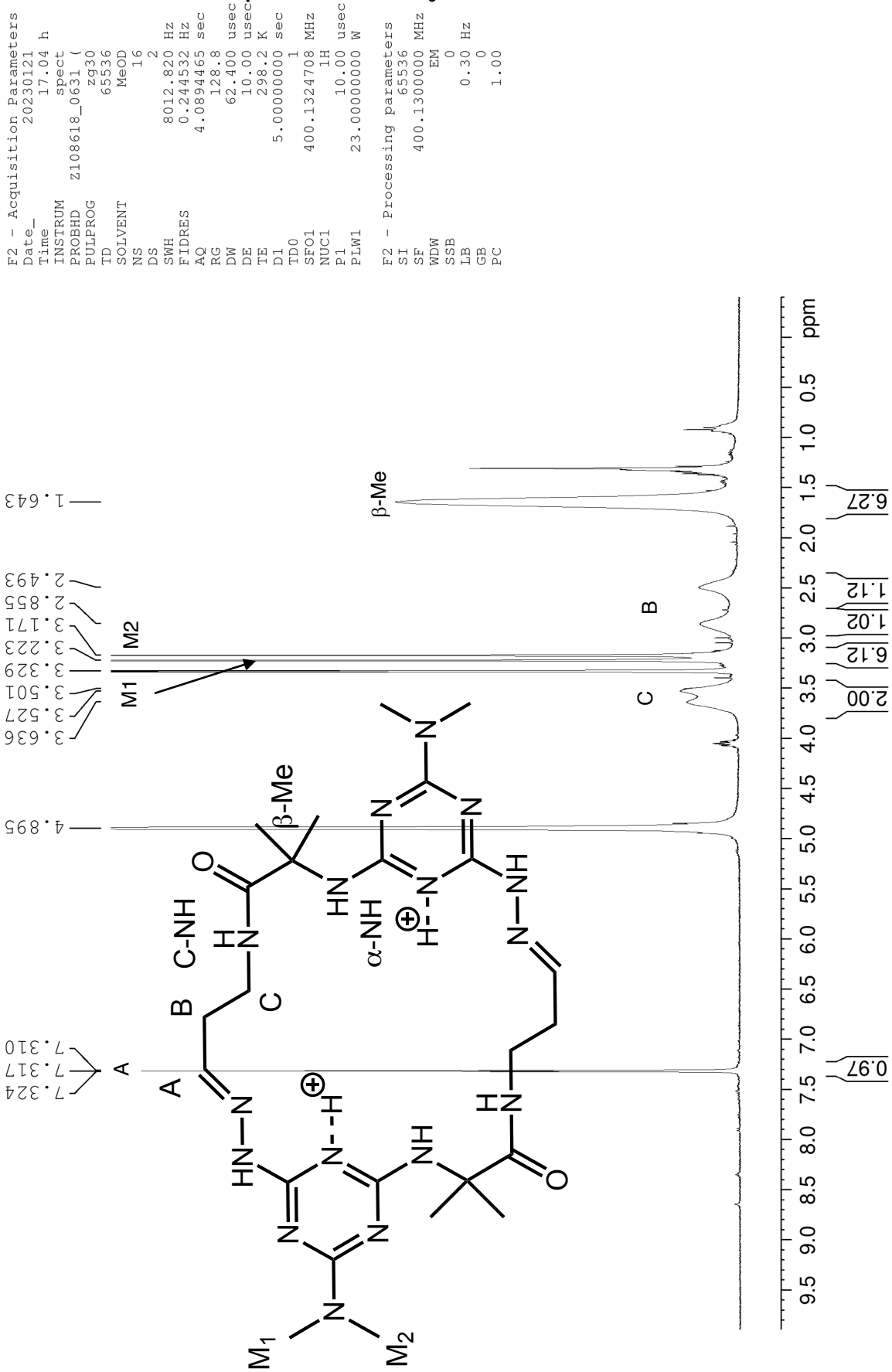


Figure S9. The 400 MHz ^{1}H NMR spectrum of **2** in D_2O at 25 ºC.

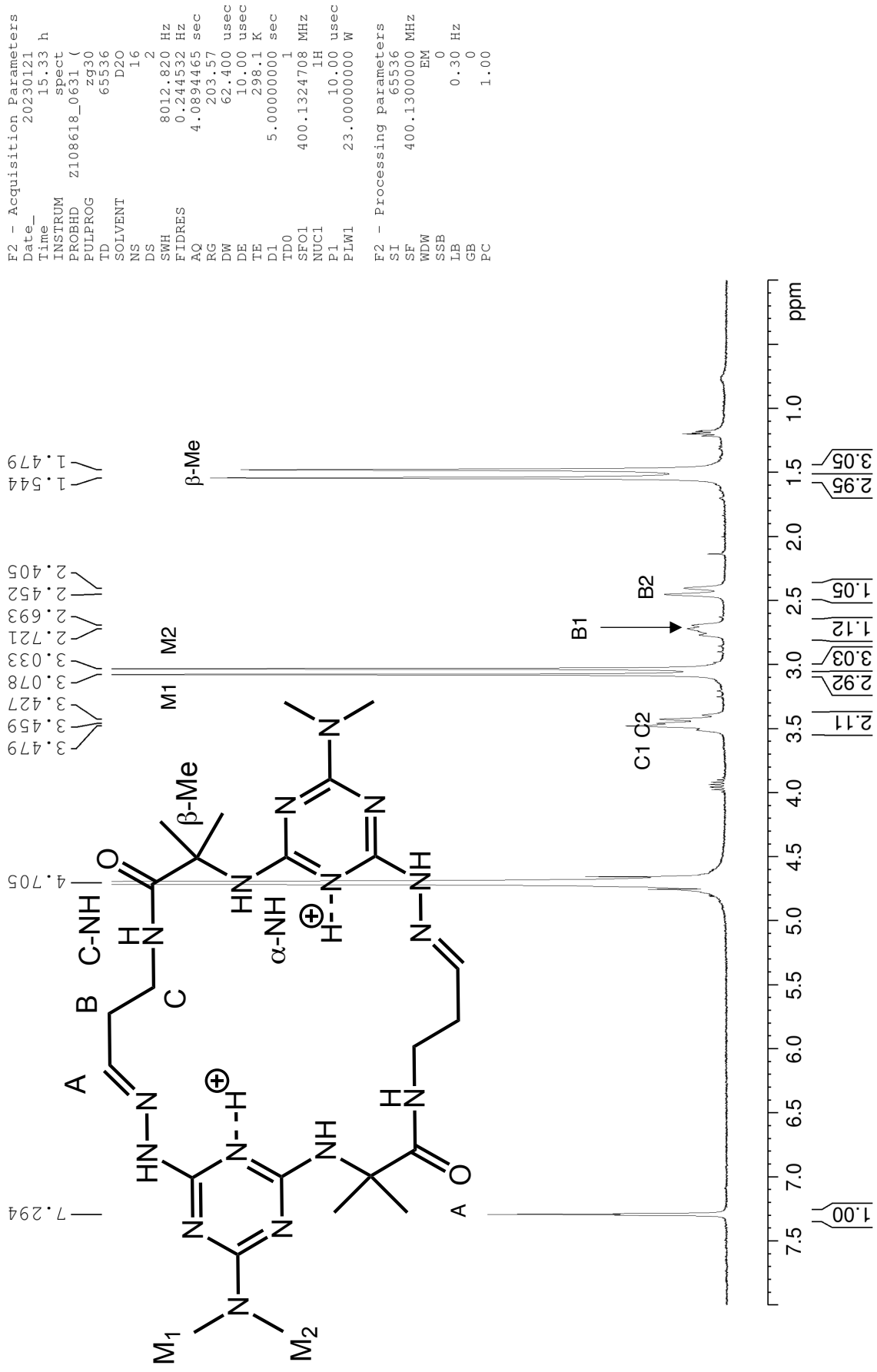


Figure S10. The 400 MHz ^{1}H NMR spectrum of 2 in pyridine-d_5 at 25 °C.

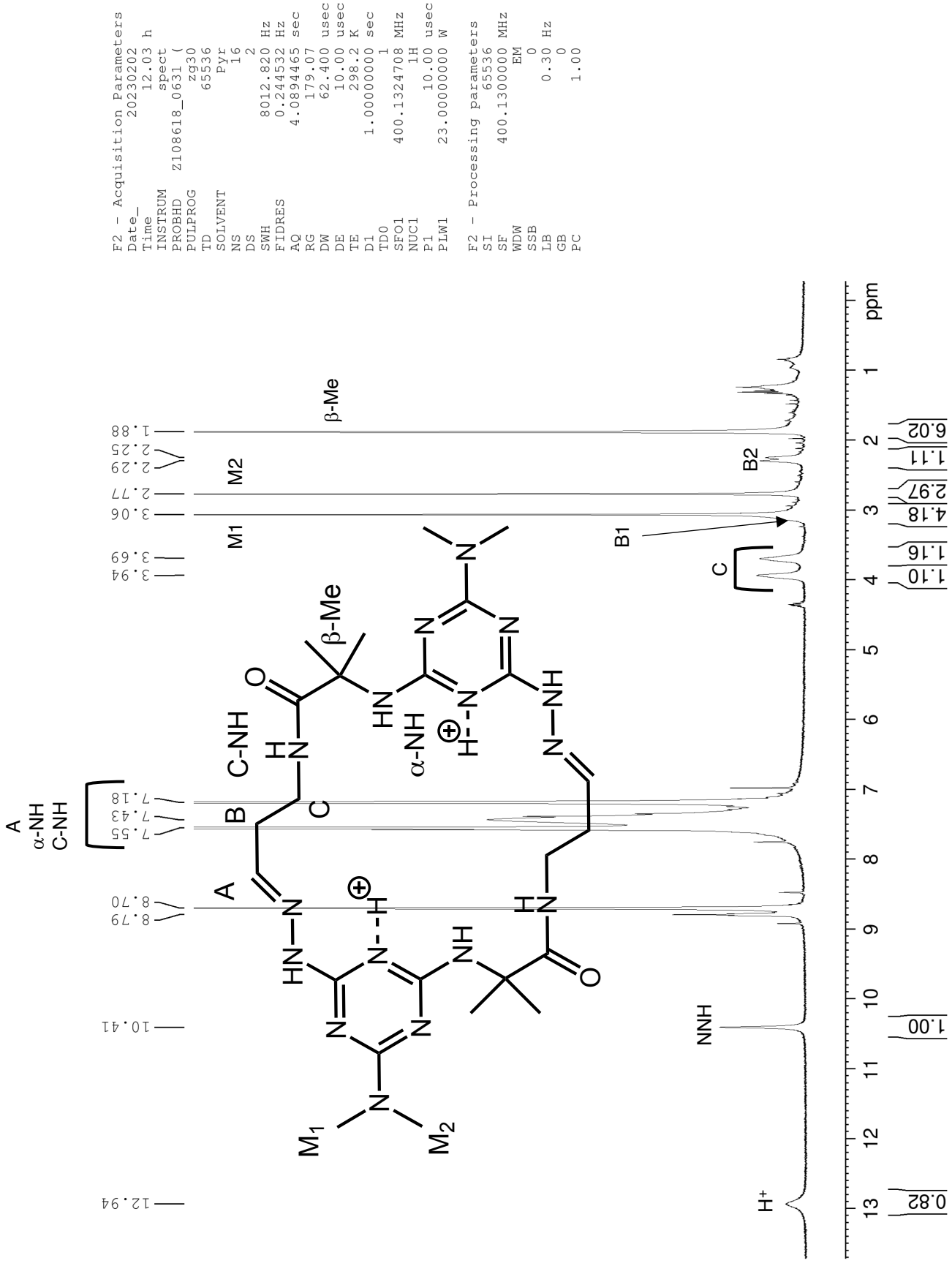


Figure S11. The 400 MHz variable temperature NMR of 2 in DMSO-d_6.

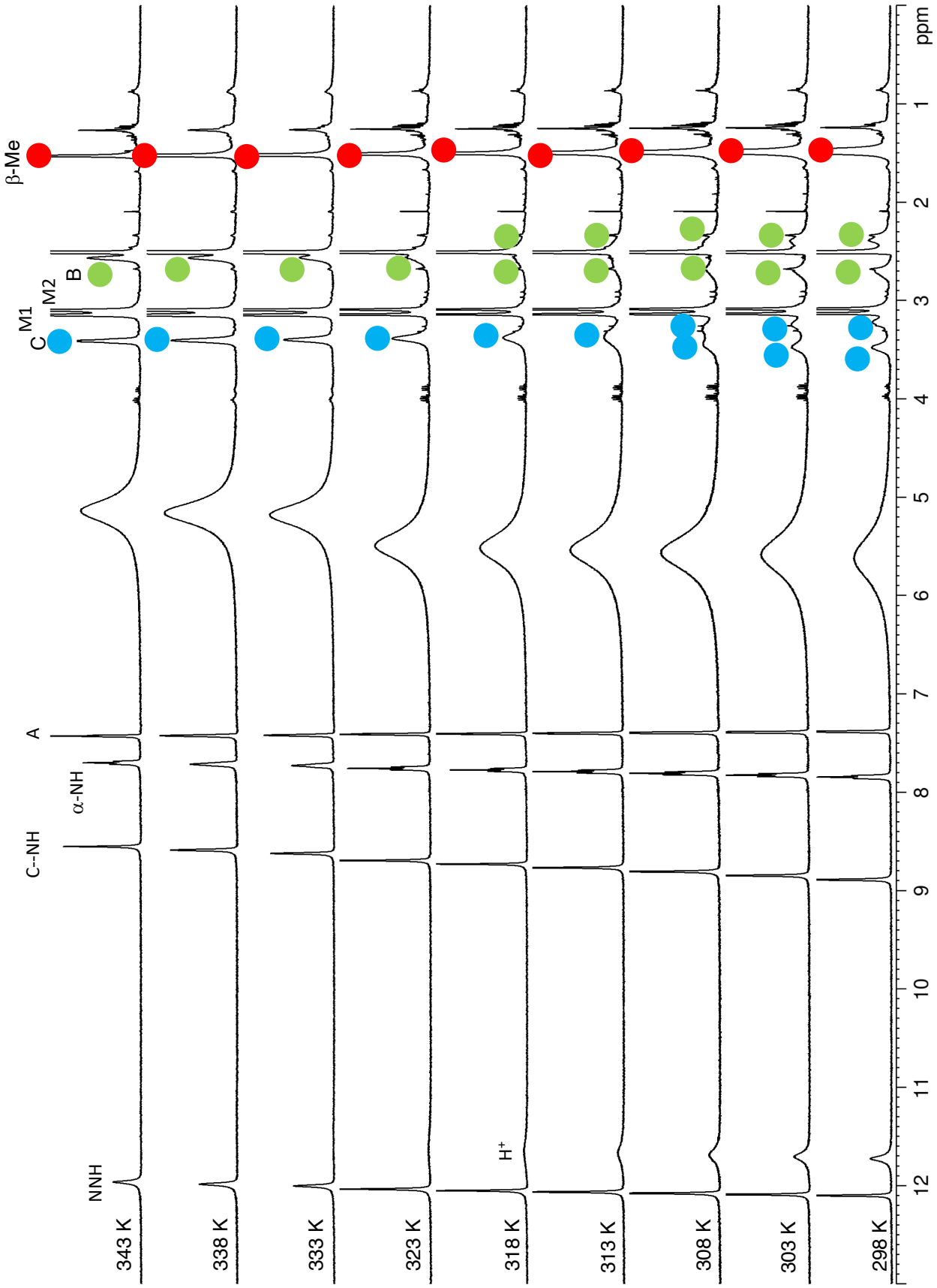


Figure S12. The 400 MHz variable temperature NMR of 2 in CD_3CN.

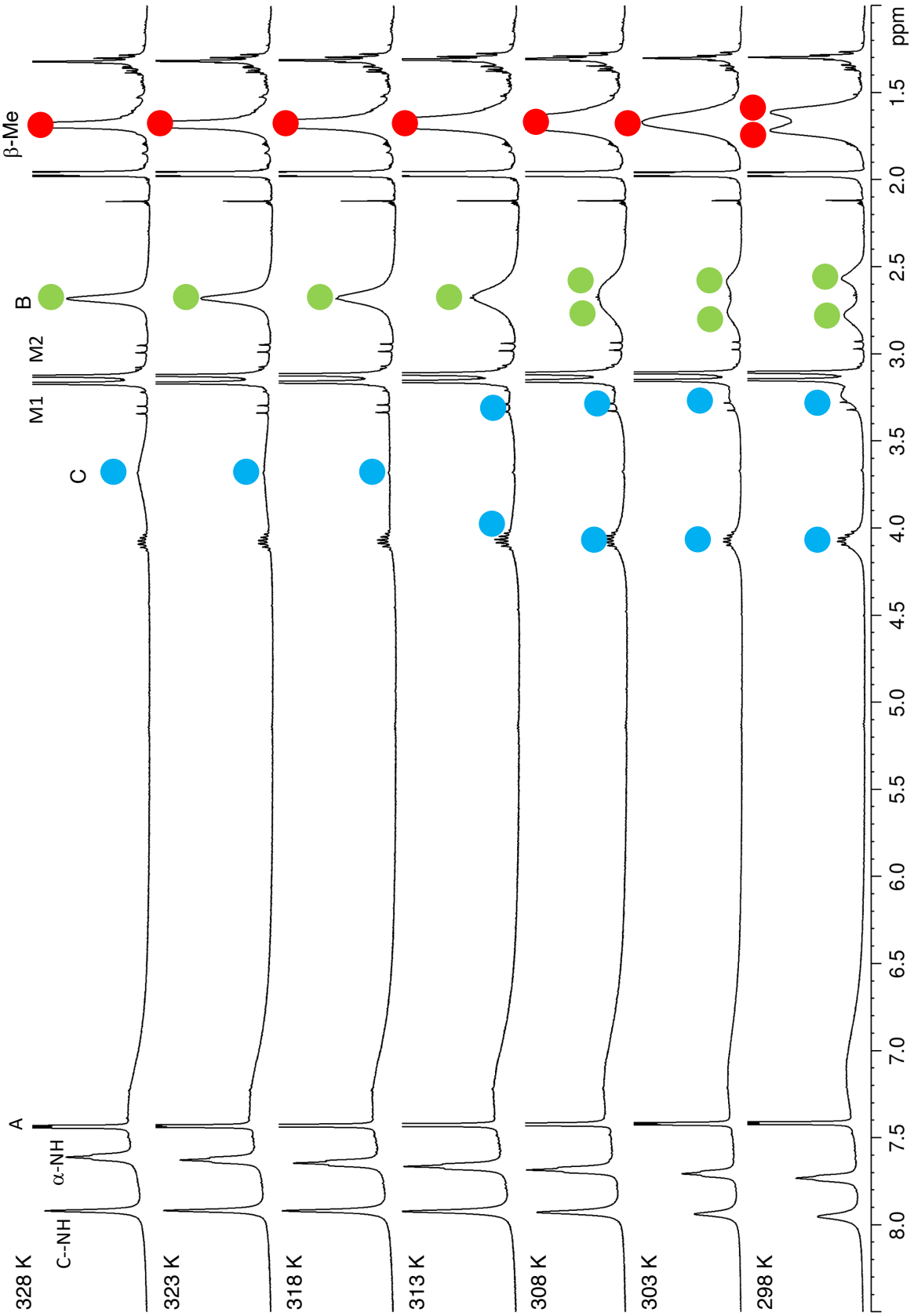


Figure S13. The 400 MHz variable temperature NMR of 2 in CD_3OD.

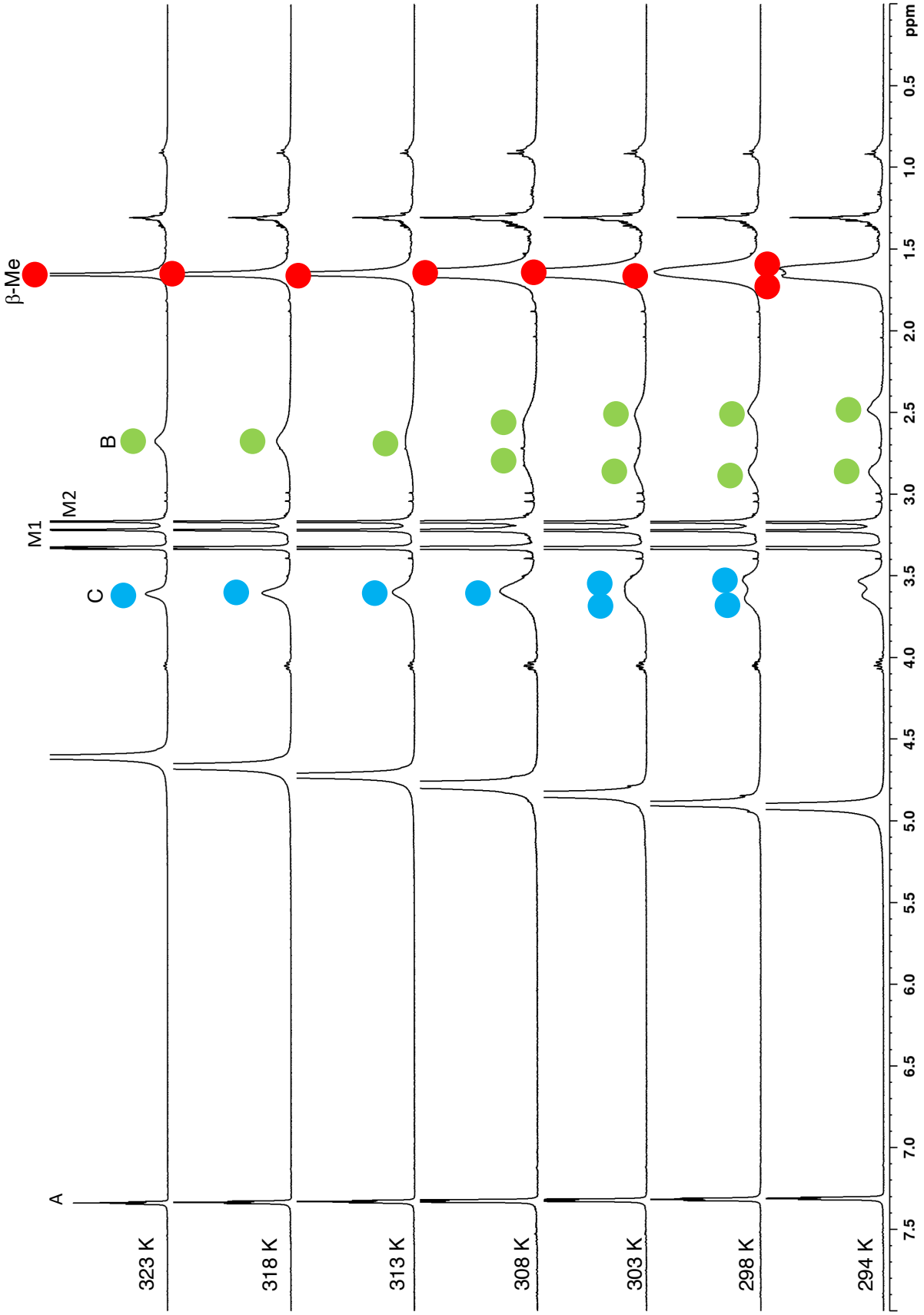


Figure S14. The 400 MHz variable temperature NMR of 2 in D_2O.

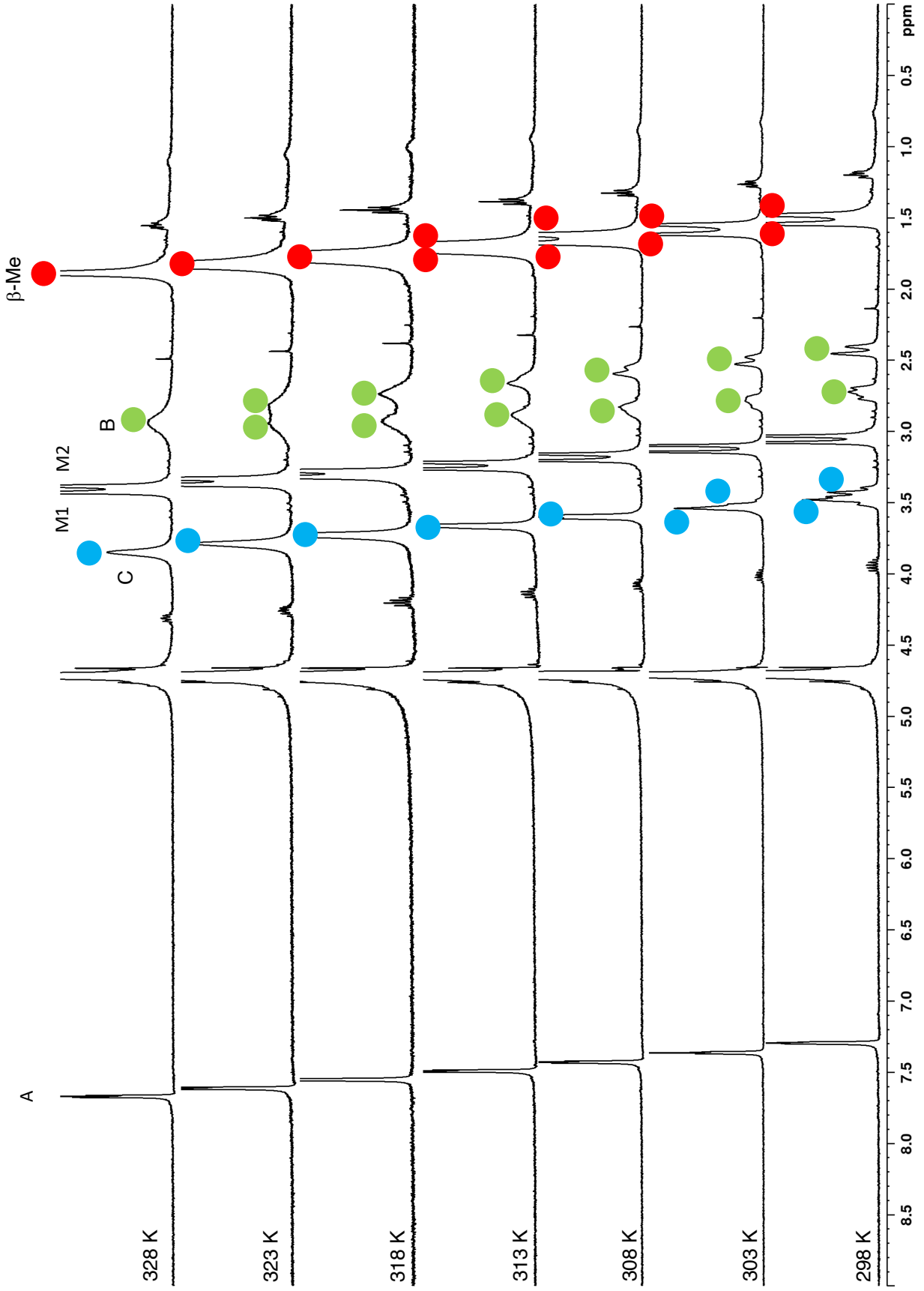


Figure S15. The 400 MHz variable temperature NMR of 2 in pyridine-d_5.

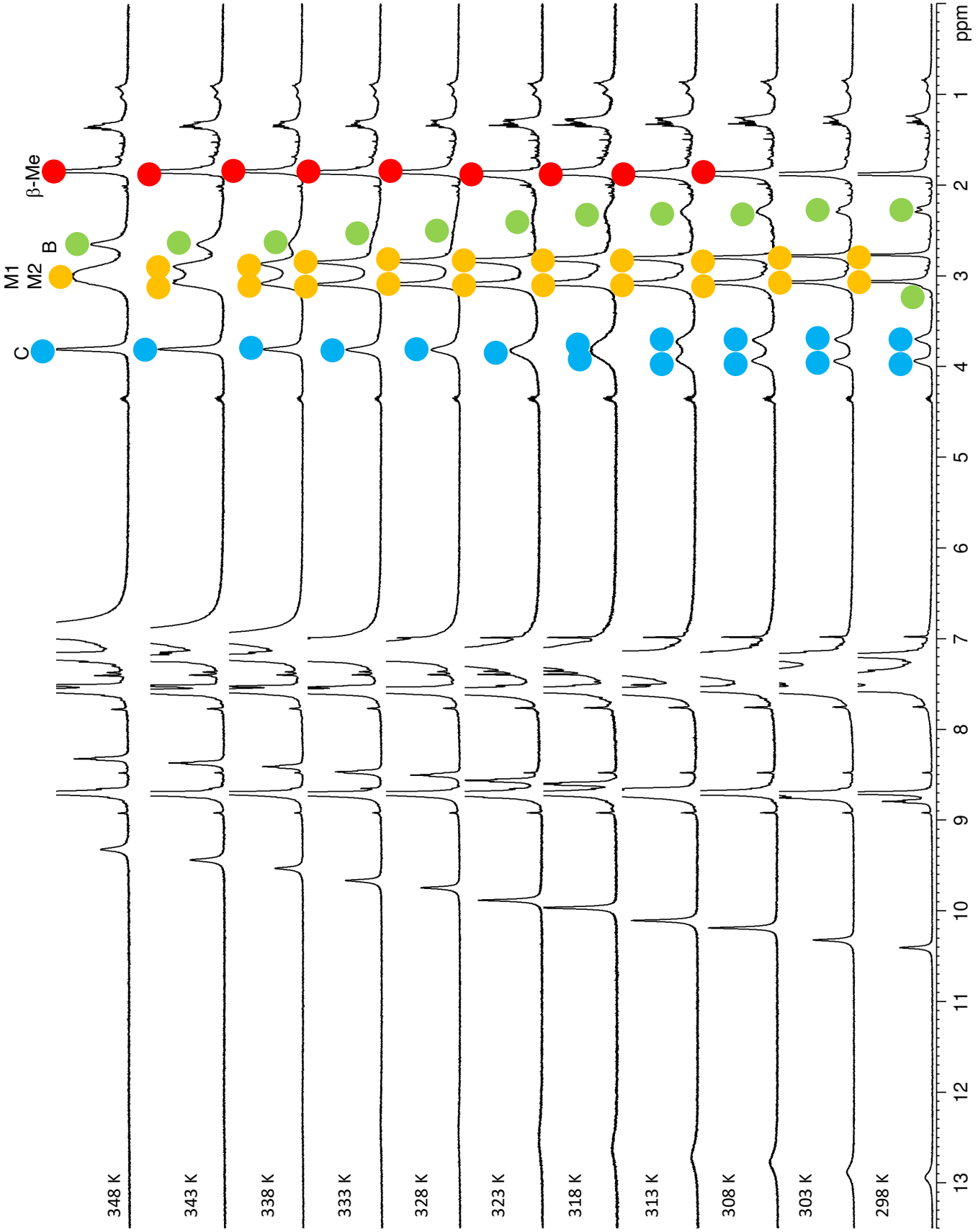


Figure S16. The 500 MHz variable temperature NMR of 2 in CD_3CN.

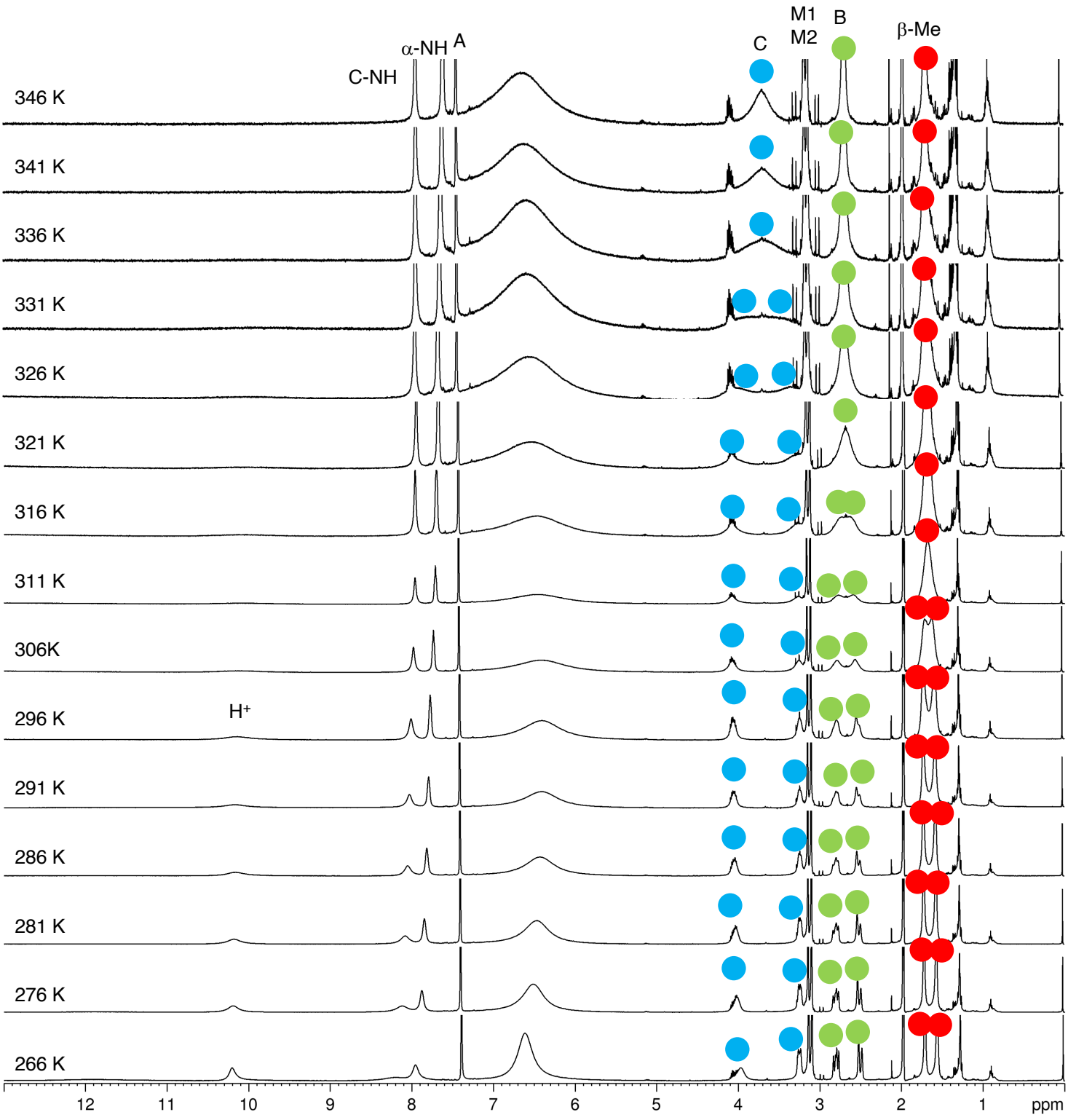


Figure S17. The 500 MHz variable temperature NMR of 2 in CD_3OD.

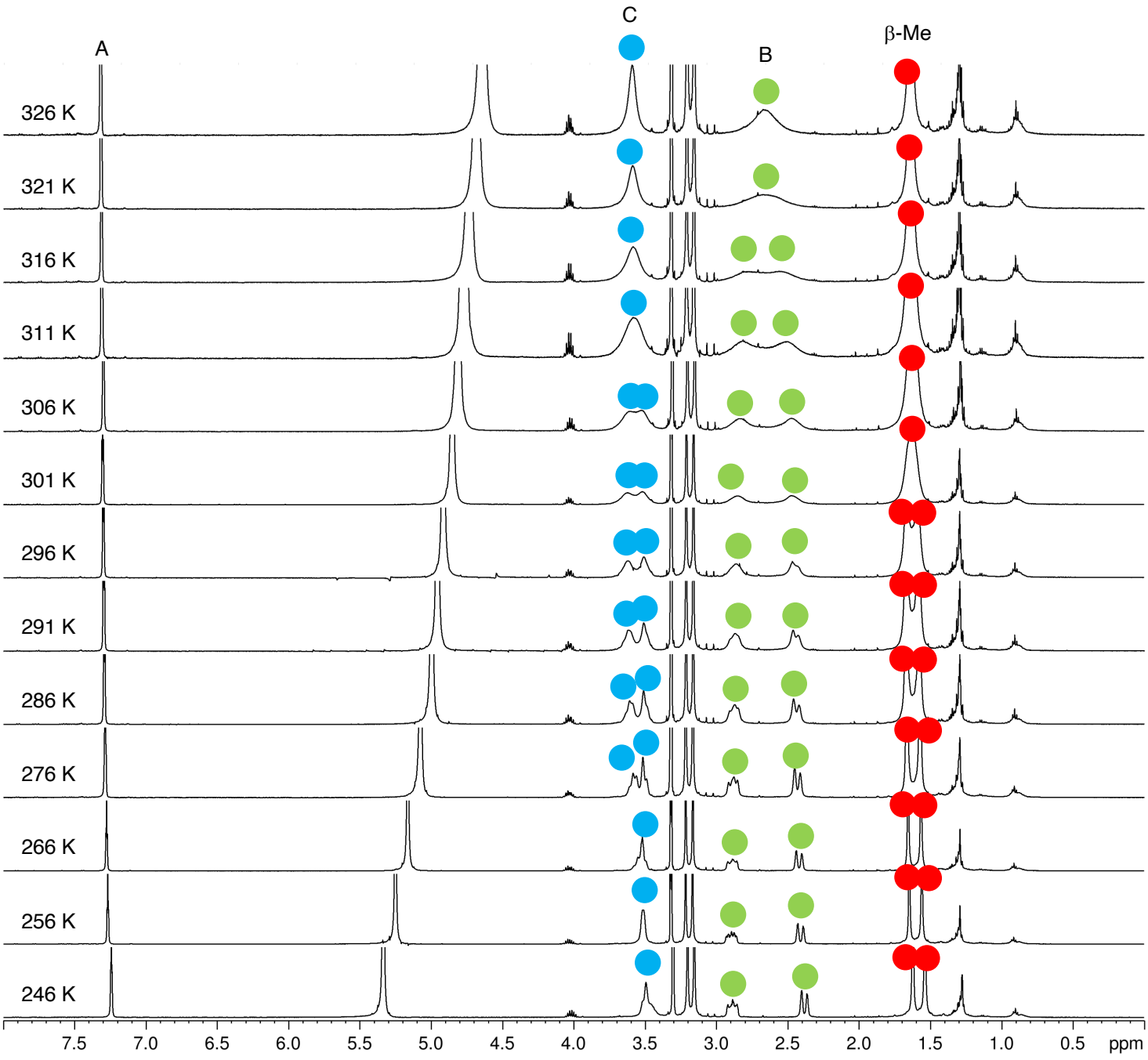


Figure S18. The 500 MHz variable temperature NMR of 2 in pyridine-d_5.

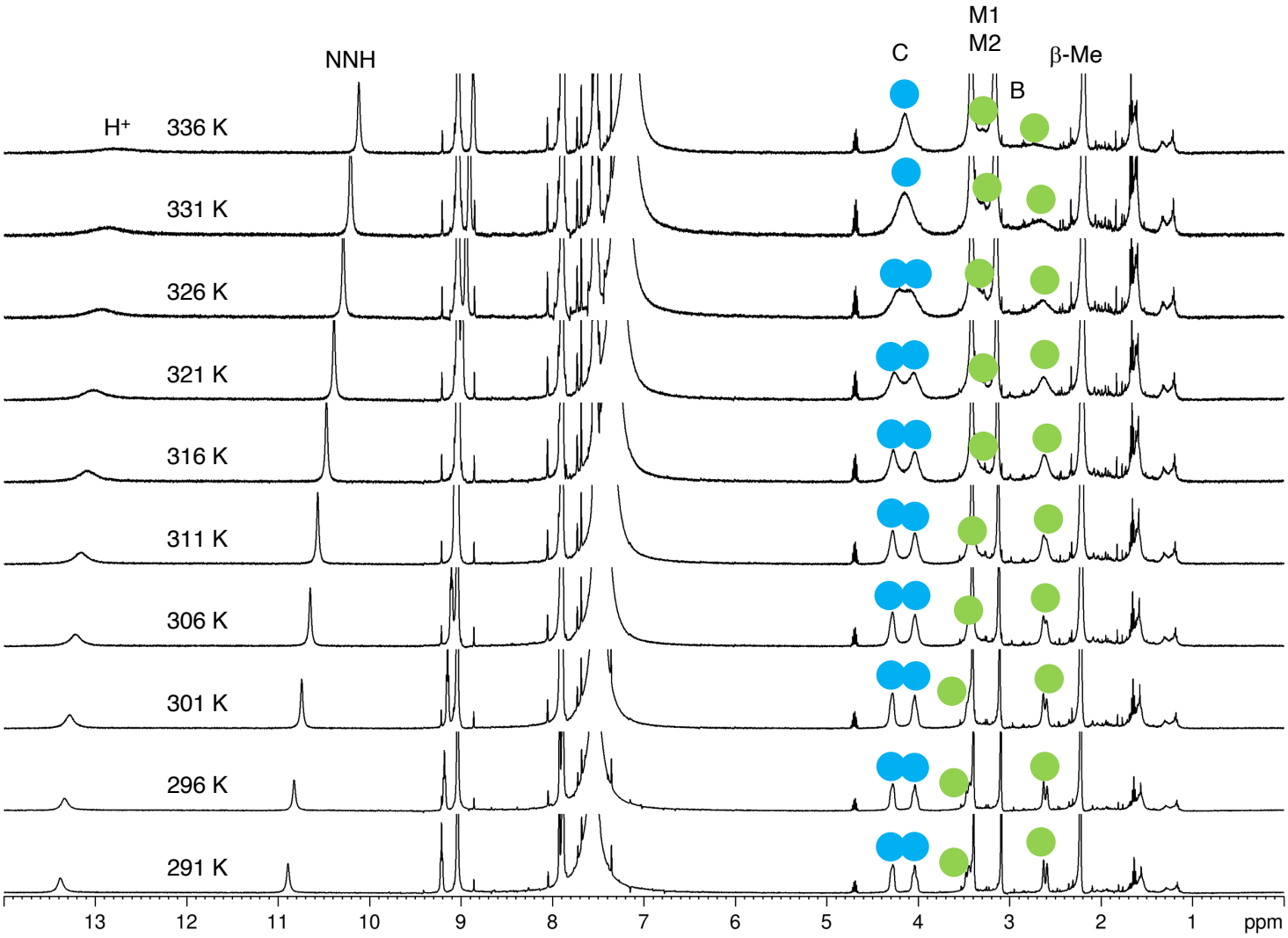


Figure S19. The 400 MHz ^{13}C NMR spectrum of 2 in DMSO-d_6 at 25 ºC.

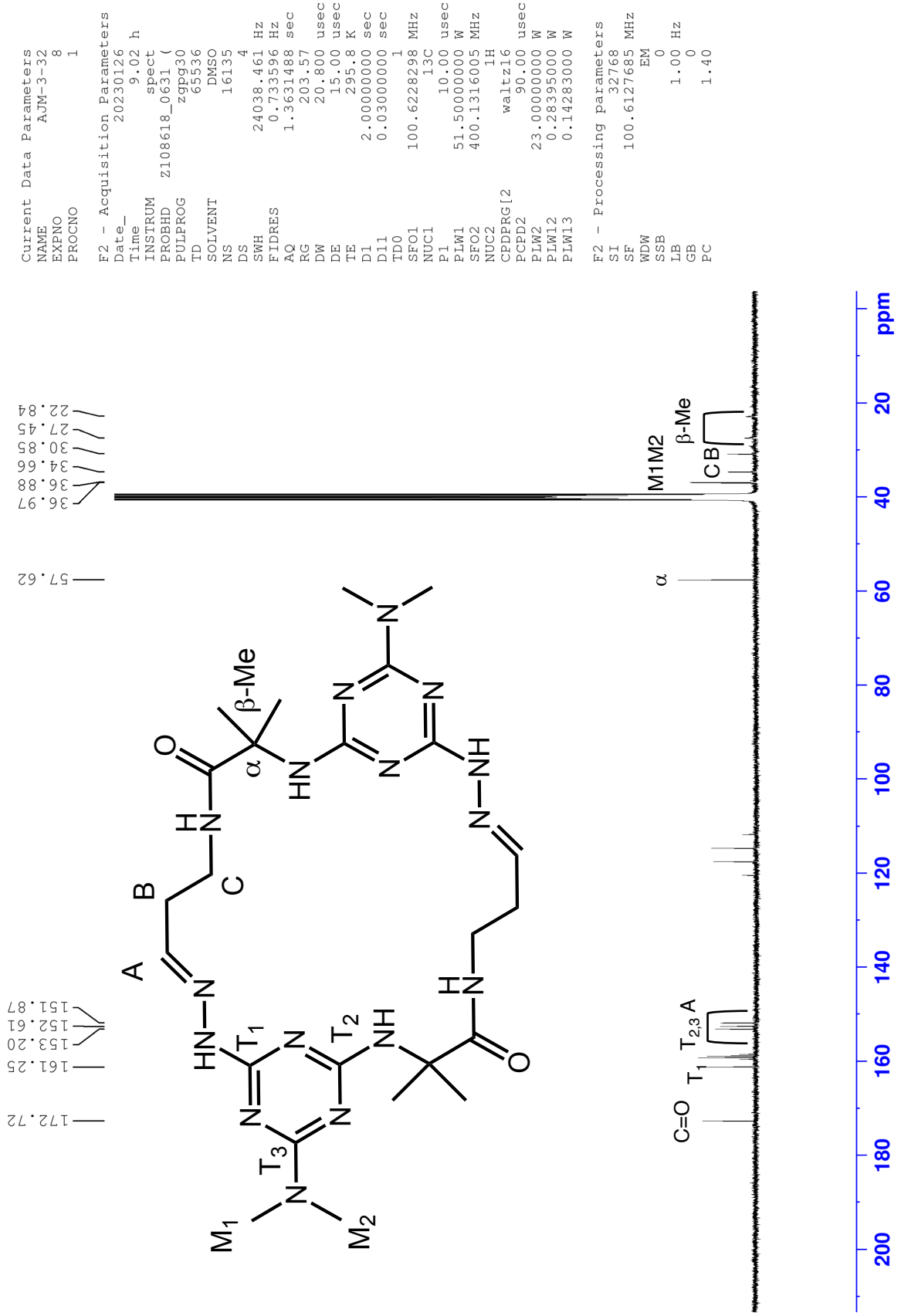


Figure S20. The 400 MHz ^{13}C NMR spectrum of 2 in CD_3CN at 25 ºC.

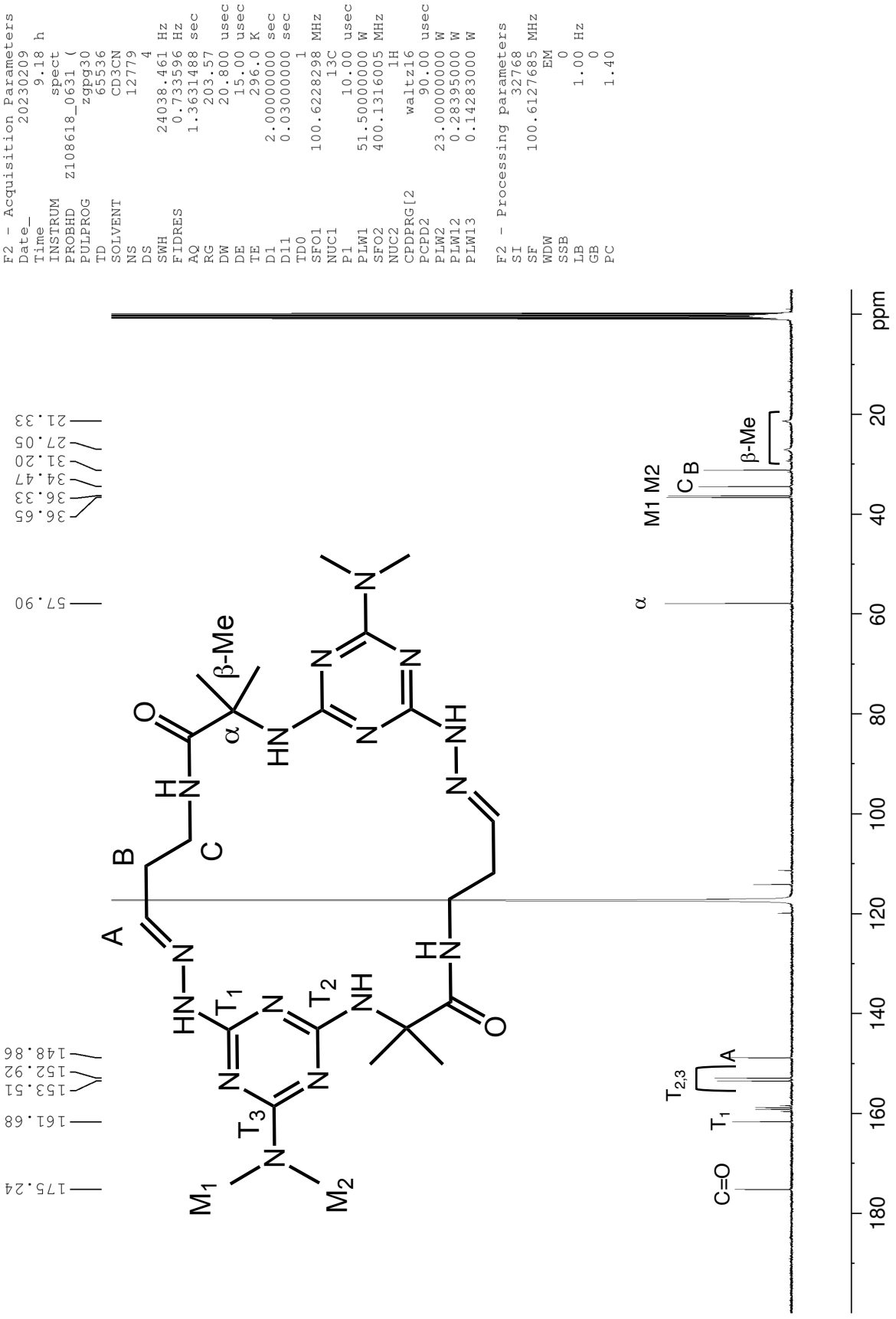


Figure S21. The 400 MHz ^{13}C NMR spectrum of 2 in CD_3OD at 25 ºC.

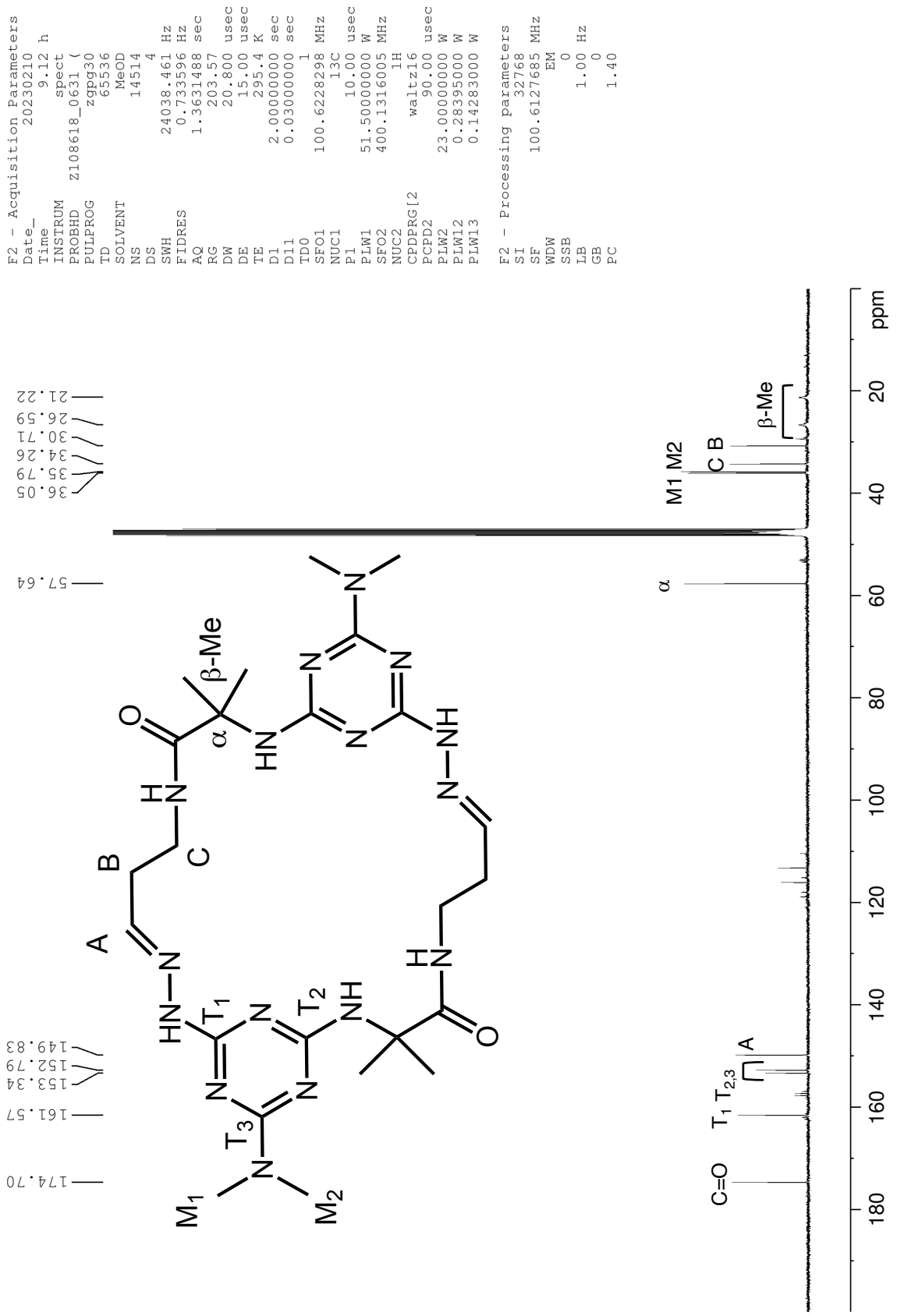


Figure S22. The 400 MHz ^{1}H NMR spectrum of 2 in D_2O at 25 °C.

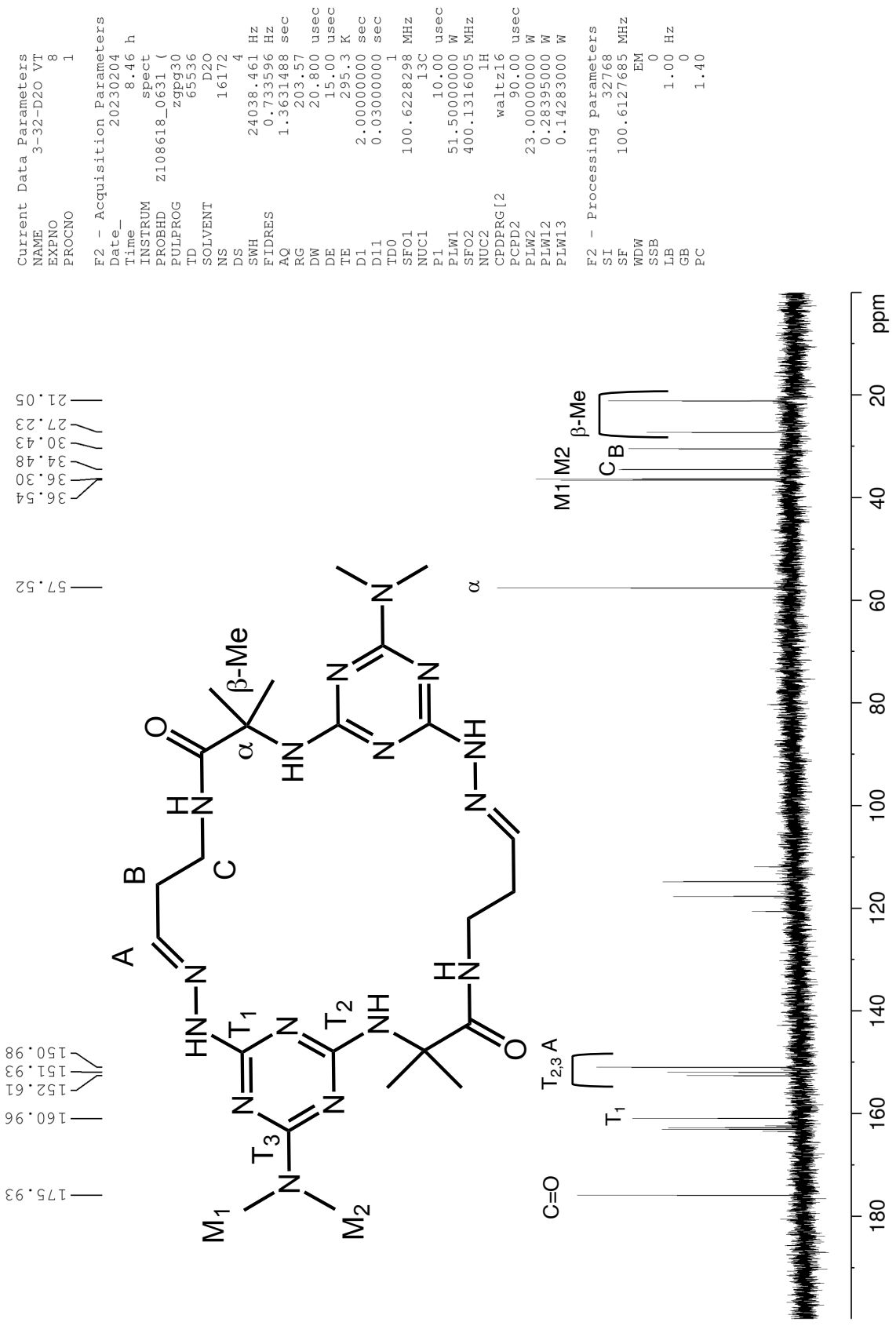


Figure S23. The 400 MHz ^{1}H NMR spectrum of 2 in pyridine-d_5 at 25 ºC.

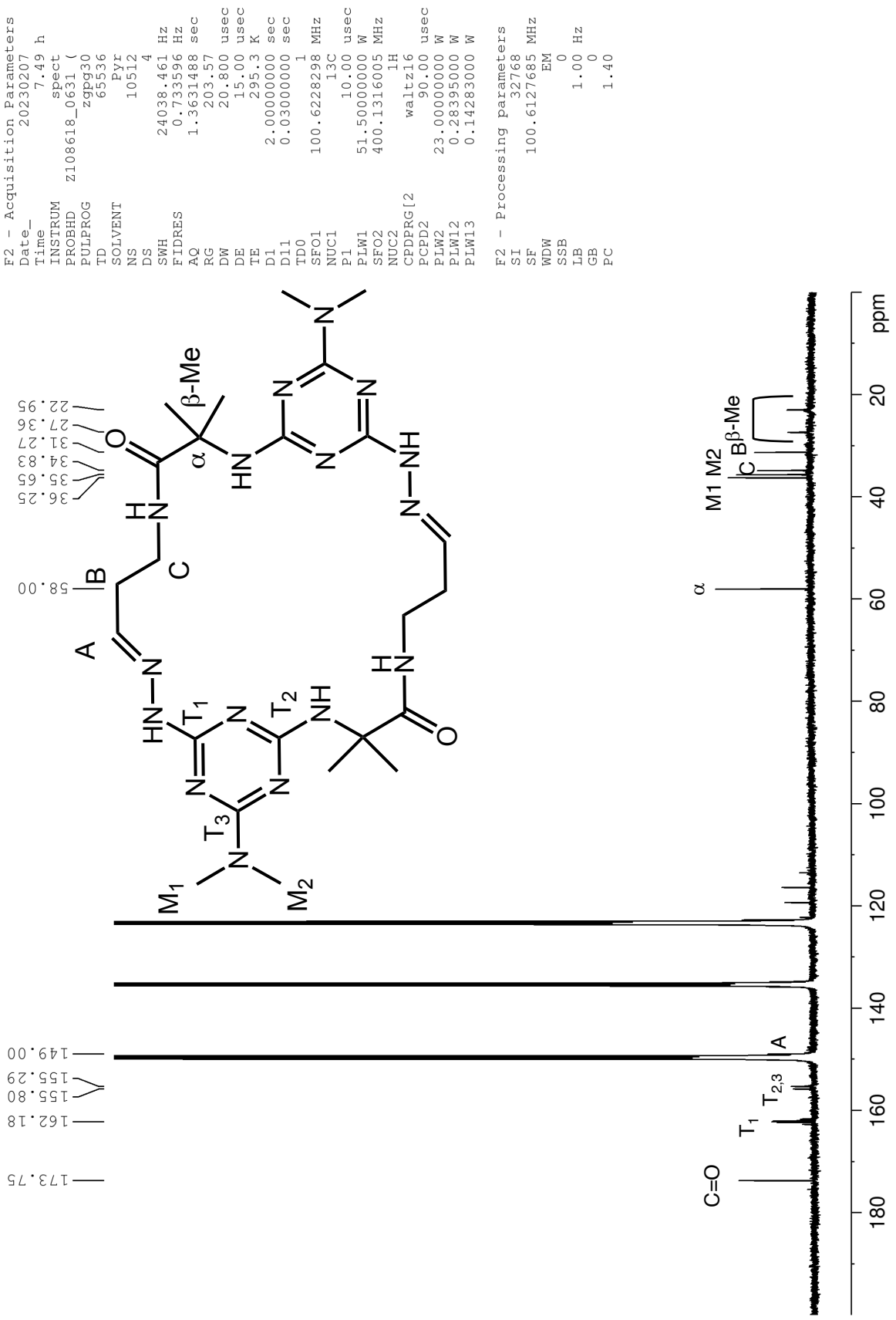
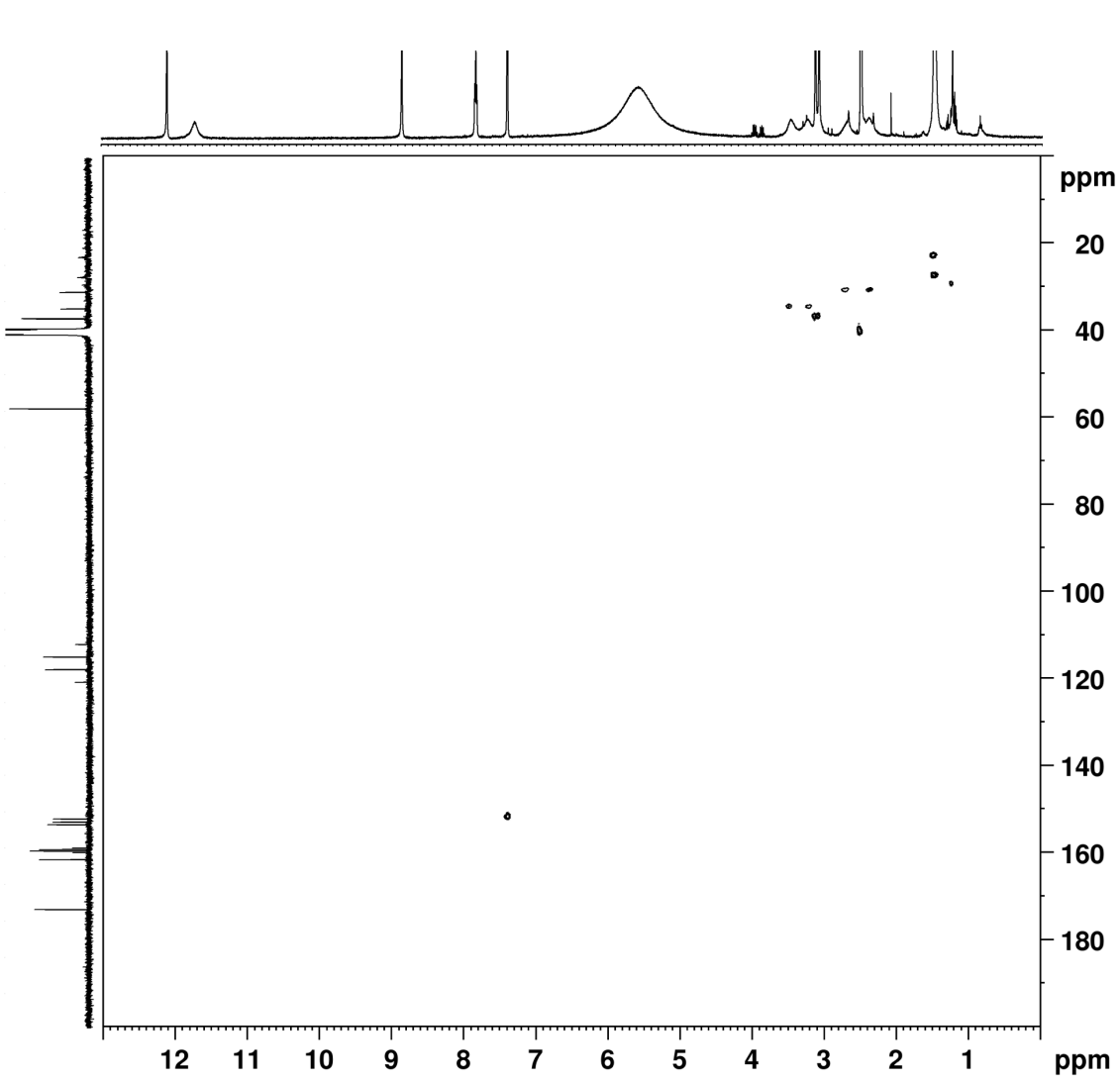


Figure S24. The 400 MHz HSQC NMR spectrum of 2 in DMSO-d_6.

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SOLVENT             DMSO
NS                     8
DS                    32
SWH             5040.323 Hz
FIDRES          9.844380 Hz
AQ              0.1015808 sec
RG                203.57
DW                99.200 use
DE                10.00 use
TE                294.1 K
CNST2         145.0000000
CNST17         -0.5000000
D0            0.00000300 sec
D1            1.50000000 sec
D4            0.00172414 sec
D11           0.03000000 sec
D16           0.00020000 sec
D21           0.00360000 sec
D24           0.00089000 sec
IN0           0.00002900 sec
TDav                   1
SFO1          400.1326646 MHz
NUC1                  1H
P1                 10.00 use
P2                 20.00 use
P28              1000.00 use
PLW1         23.00000000 W
SFO2         100.6225887 MHz
NUC2                 13C
CPDPRG[2 bi_p5m4sp_4sp.2
P3                 10.00 use
P14               500.00 use
P24              2000.00 use
P31              2119.00 use
P63              1500.00 use
PLW0                   0 W
PLW2         51.50000000 W
PLW12         0.80469000 W
SPNAM[3] Crp60,0.5,20.1
SPOAL3               0.500
SPOFFS3                0 Hz
SPW3          7.86859989 W
SPNAM[7]    Crp60comp.4
SPOAL7               0.500
SPOFFS7                0 Hz
SPW7          7.86859989 W
SPNAM[14 Crp32,1.5,20.2
SPOAL14              0.500
SPOFFS14               0 Hz
SPW14         3.35730004 W
SPNAM[18  Crp60_xfilt.2
SPOAL18              0.500
SPOFFS18               0 Hz
SPW18         1.51580000 W
SPNAM[31 Crp32,1.5,20.2
SPOAL31              0.500
SPOFFS31               0 Hz
SPW31         0.83932000 W
GPNAM[1]     SMSQ10.100
GPZ1                80.00 %
GPNAM[2]     SMSQ10.100
GPZ2                20.10 %
GPNAM[3]     SMSQ10.100
GPZ3                11.00 %
GPNAM[4]     SMSQ10.100
GPZ4                -5.00 %
P16              1000.00 use
P19               600.00 use

F1 - Acquisition parameters
TD                   256
SFO1          100.6226 MHz
FIDRES       134.698273 Hz
SW               171.347 ppm
FnMODE    Echo-Antiecho

F2 - Processing parameters
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SF           400.1300000 MHz
WDW                 QSINE
SSB                     2
LB                      0 Hz
GB                      0
PC                   1.40

F1 - Processing parameters
SI                  1024
MC2        echo-antiecho
SF           100.6127685 MHz
WDW                 QSINE
SSB                     2
LB                      0 Hz
GB                      0
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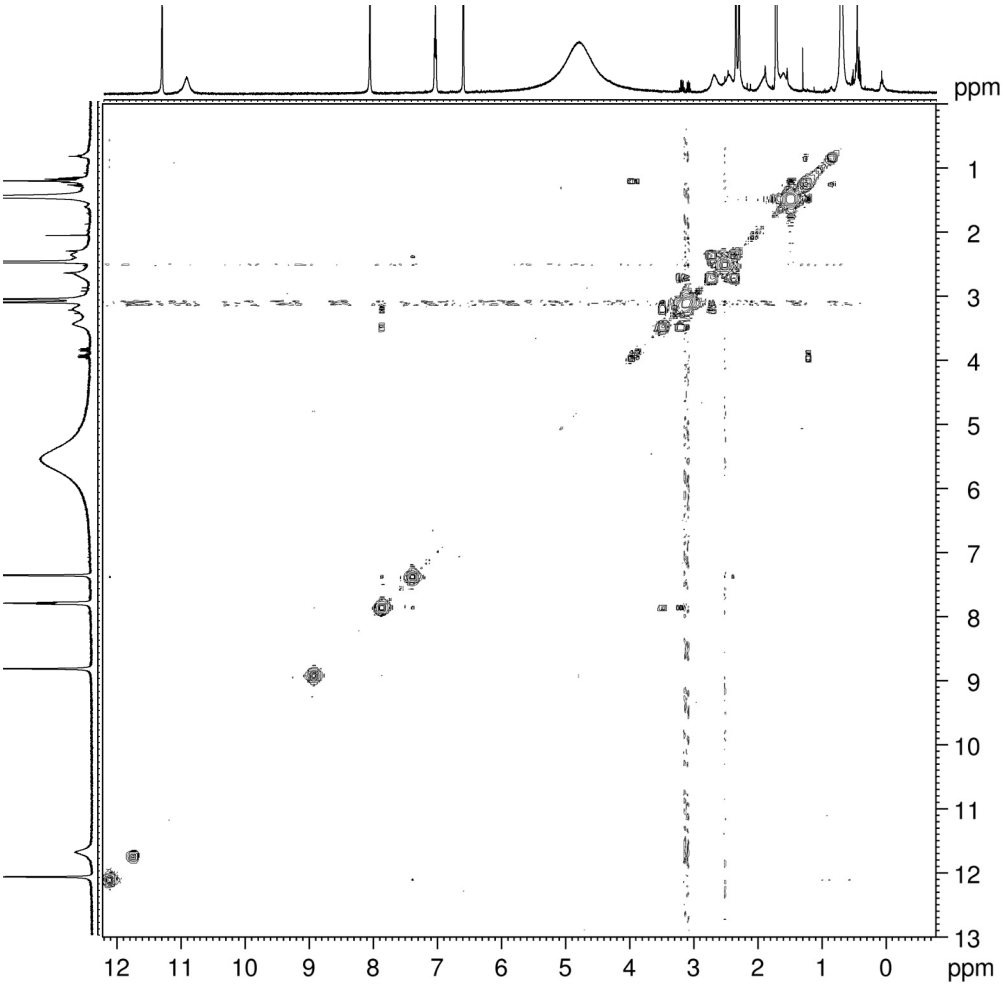
Figure S25. The 400 MHz COSY NMR spectrum of 2 in DMSO-d_6.

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PROCNO                       1

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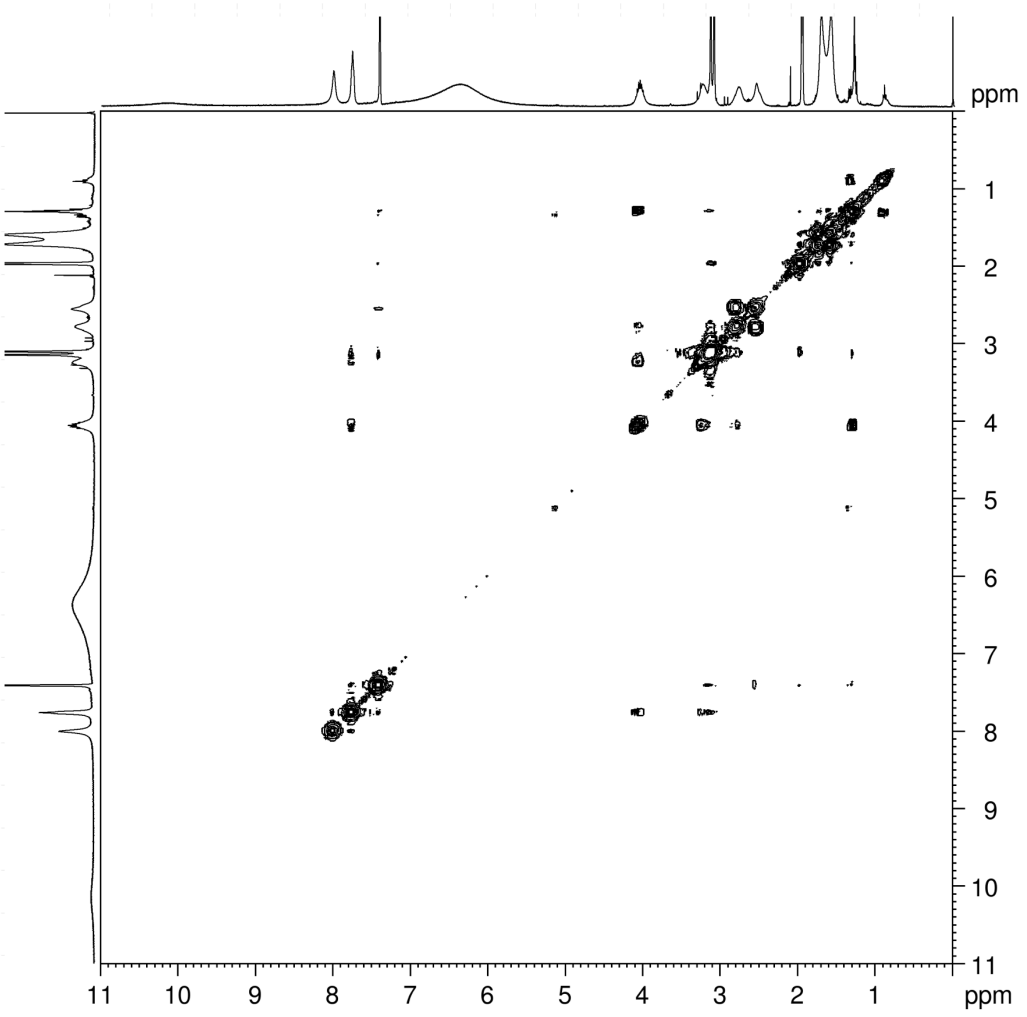
PULPROG               cosyqf45
TD                       2048
SOLVENT                  DMSO
NS                          8
DS                         16
SWH                  5030.181 Hz
FIDRES               4.912286 Hz
AQ                  0.2035712 sec
RG                       128.8
DW                      99.400 usec
DE                      10.00 usec
TE                      294.0 K
D0                 0.00000300 sec
D1                 2.00000000 sec
IN0                0.00019880 sec
TDav                        1
SFO1               400.1326457 MHz
NUC1                       1H
P1                      10.00 usec
PLW1              23.00000000 W

F1 - Acquisition parameters
TD                        128
SFO1                 400.1326 MHz
FIDRES              78.596581 Hz
SW                     12.571 ppm
FnMODE                    QF

F2 - Processing parameters
SI                        1024
SF                400.1300000 MHz
WDW                       SINE
SSB                          0
LB                           0 Hz
GB                           0
PC                        1.40

F1 - Processing parameters
SI                        1024
MC2                         QF
SF                400.1300000 MHz
WDW                       SINE
SSB                          0
LB                           0 Hz
GB                           0
```

Figure S26. The 400 MHz COSY NMR spectrum of 2 in CD_3CN.

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Date_            20230208
Time                20.27 h
INSTRUM              spect
PROBHD    Z108618_0631 (
PULPROG          cosyqf45
TD                   2048
SOLVENT             CD3CN
NS                      8
DS                     16
SWH              4213.483 Hz
FIDRES           4.114729 Hz
AQ               0.2430293 sec
RG                 203.57
DW                118.667 usec
DE                  10.00 usec
TE                  294.9 K
D0             0.00000300 sec
D1             2.00000000 sec
IN0            0.00023740 sec
TDav                    1
SFO1         400.1323107 MHz
NUC1                   1H
P1                  10.00 usec
PLW1         23.00000000 W

F1 - Acquisition parameters
TD                    128
SFO1             400.1323 MHz
FIDRES          65.817184 Hz
SW                 10.527 ppm
FnMODE                 QF

F2 - Processing parameters
SI                    1024
SF           400.1300000 MHz
WDW                   SINE
SSB                      0
LB                       0 Hz
GB                       0
PC                    1.40

F1 - Processing parameters
SI                    1024
MC2                     QF
SF           400.1300000 MHz
WDW                   SINE
SSB                      0
LB                       0 Hz
GB                       0
```
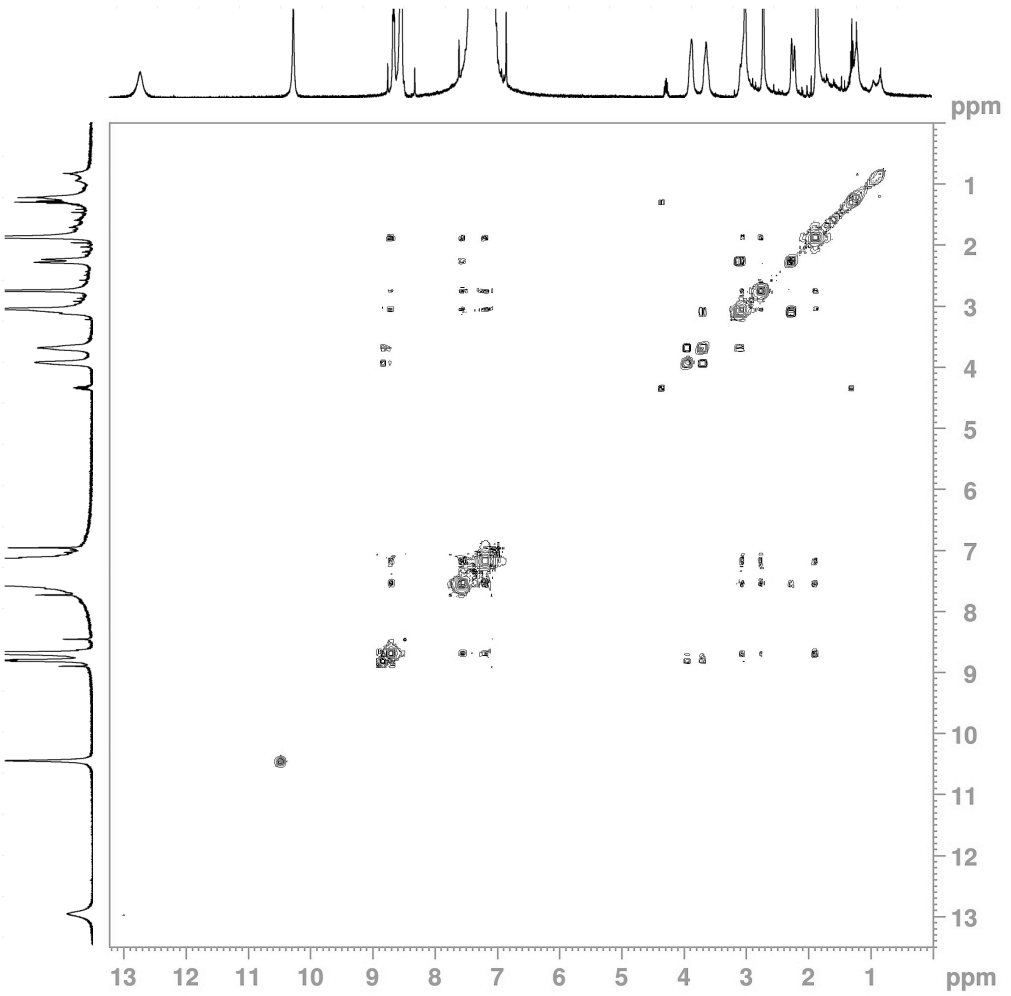

Figure S27. The 400 MHz COSY NMR spectrum of 2 in pyridine-d_5

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EXPNO                  2
PROCNO                 1

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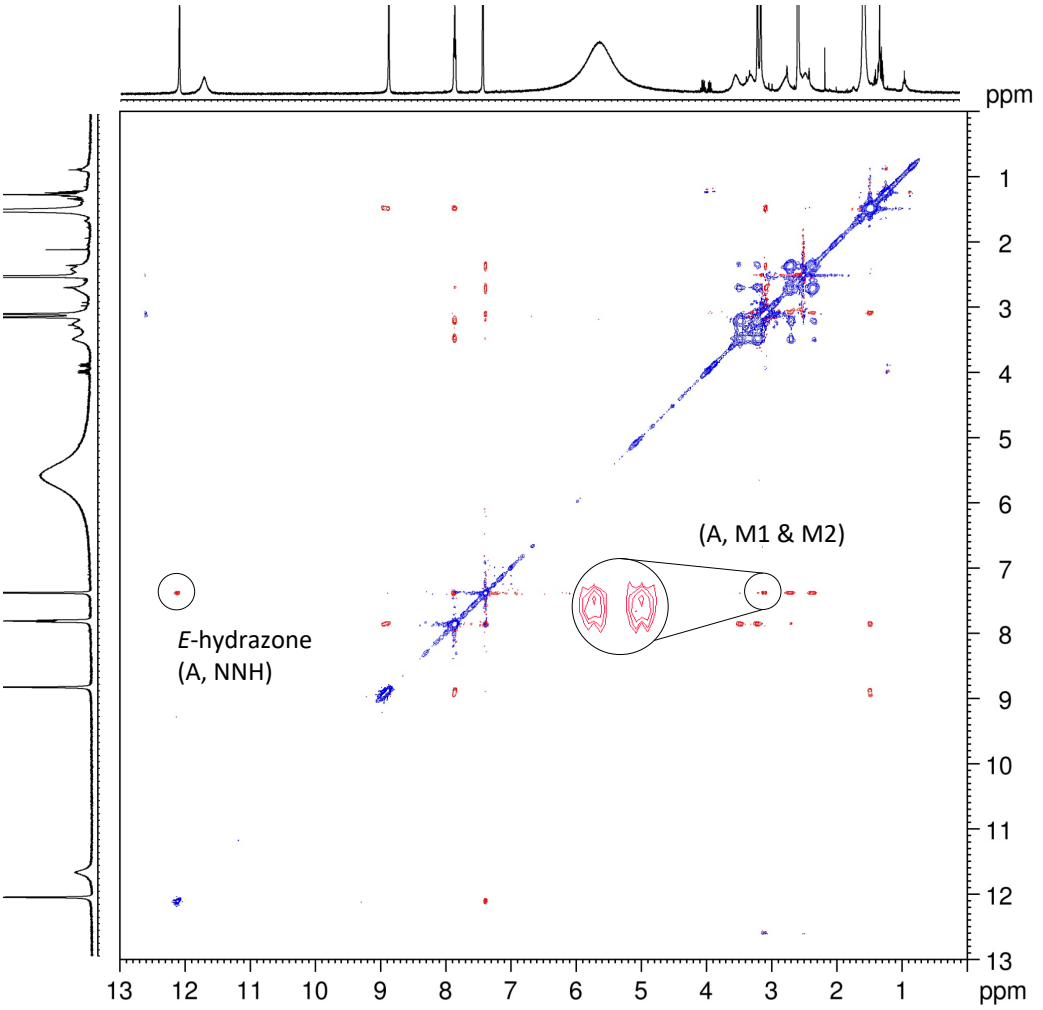
PULPROG         cosygf45
TD                 2048
SOLVENT             Pyr
NS                    8
DS                   16
SWH             5434.783 Hz
FIDRES          5.307405 Hz
AQ              0.1884160 sec
RG                203.57
DW                92.000 usec
DE                10.00 usec
TE                295.2 K
D0             0.00000300 sec
D1             2.00000000 sec
IN0            0.00018400 sec
TDav                   1
SFO1         400.1328036 MHz
NUC1                  1H
P1                 10.00 usec
PLW1         23.00000000 W

F1 - Acquisition parameters
TD                   128
SFO1            400.1328 MHz
FIDRES          84.918480 Hz
SW                13.582 ppm
FnMODE                QF

F2 - Processing parameters
SI                  1024
SF           400.1300000 MHz
WDW                 SINE
SSB                    0
LB                     0 Hz
GB                     0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2                   QF
SF           400.1300000 MHz
WDW                 SINE
SSB                    0
LB                     0 Hz
GB                     0
```

Figure S28. The **400 MHz rOesy NMR spectrum of 2 in DMSO-*d*$_6$.**

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Current Data Parameters
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EXPNO                       12
PROCNO                       1

F2 - Acquisition Parameters
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Time                      7.53 h
INSTRUM                   spect
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PULPROG          roesyphpr.2
TD                        2048
SOLVENT                   DMSO
NS                           8
DS                          16
SWH                  4901.961 Hz
FIDRES               4.787071 Hz
AQ                   0.2088960 sec
RG                        66.4
DW                     102.000 usec
DE                      10.00 usec
TE                      295.1 K
D0                0.00009163 sec
D1                2.00000000 sec
D11               0.03000000 sec
D12               0.00002000 sec
D13               0.00000400 sec
IN0               0.00020400 sec
L4                         370
P15                200000.00 usec
TDav                         1
SFO1              400.1325972 MHz
NUC1                       1H
P1                      10.00 usec
P25                    270.00 usec
PLW1              23.00000000 W
PLW9               0.00009200 W
PLW27              0.12620001 W

F1 - Acquisition parameters
TD                         256
SFO1                400.1326 MHz
FIDRES             38.296570 Hz
SW                     12.251 ppm
FnMODE          States-TPPI

F2 - Processing parameters
SI                        2048
SF                400.1300000 MHz
WDW                     QSINE
SSB                         2
LB                          0 Hz
GB                          0
PC                       1.00

F1 - Processing parameters
SI                        1024
MC2             States-TPPI
SF                400.1300000 MHz
WDW                     QSINE
SSB                         2
LB                          0 Hz
GB                          0
```

Figure S29. Mass spectrum of 2.

Formula Predictor Report - Eric_2022_FI_LCMS_2142023_4.lcd

Data File: D:\SCAAC\Ben\Data\02142023\Eric_2022_FI_LCMS_2142023_4.lcd

Elmt	Val.	Min	Max
H	1	0	300
C	4	0	24
N	3	0	16

Elmt	Val.	Min	Max
O	2	0	2

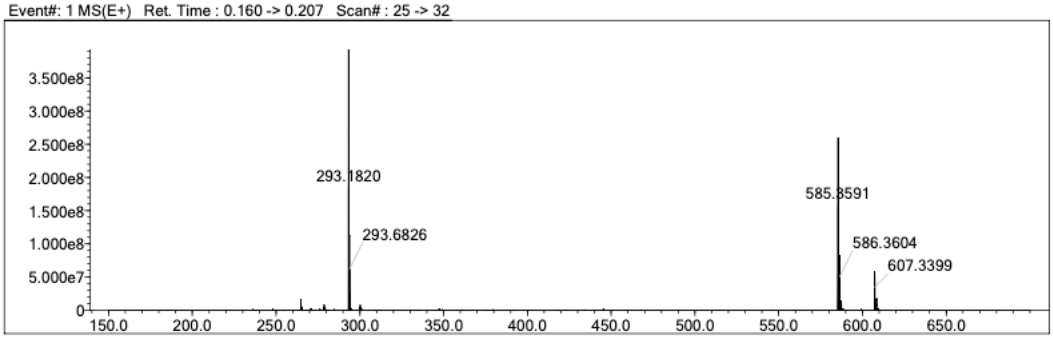
Use Adduct
H

Error Margin (ppm): 10
HC Ratio: unlimited
Max Isotopes: all
MSn Iso RI (%): 75.00

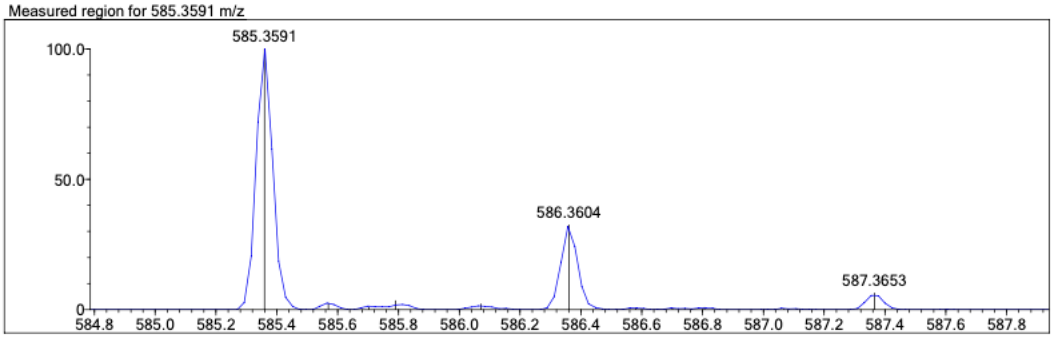
DBE Range: -2.0 - 1000.0
Apply N Rule: yes
Isotope RI (%): 1.00
MSn Logic Mode: AND

Electron Ions: both
Use MSn Info: no
Isotope Res: 10000
Max Results: 500

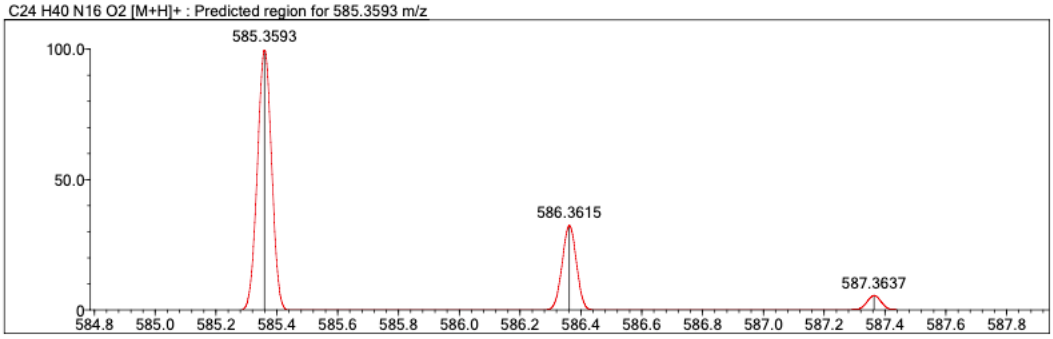
Event#: 1 MS(E+) Ret. Time : 0.160 -> 0.207 Scan# : 25 -> 32



Measured region for 585.3591 m/z



C24 H40 N16 O2 [M+H]+ : Predicted region for 585.3593 m/z



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	100.00	C24 H40 N16 O2	[M+H]+	585.3591	585.3593	-0.2	-0.34	100.00	13.0

Figure S30. The 400 MHz ^{1}H NMR spectrum of 5 in CD_3OD.

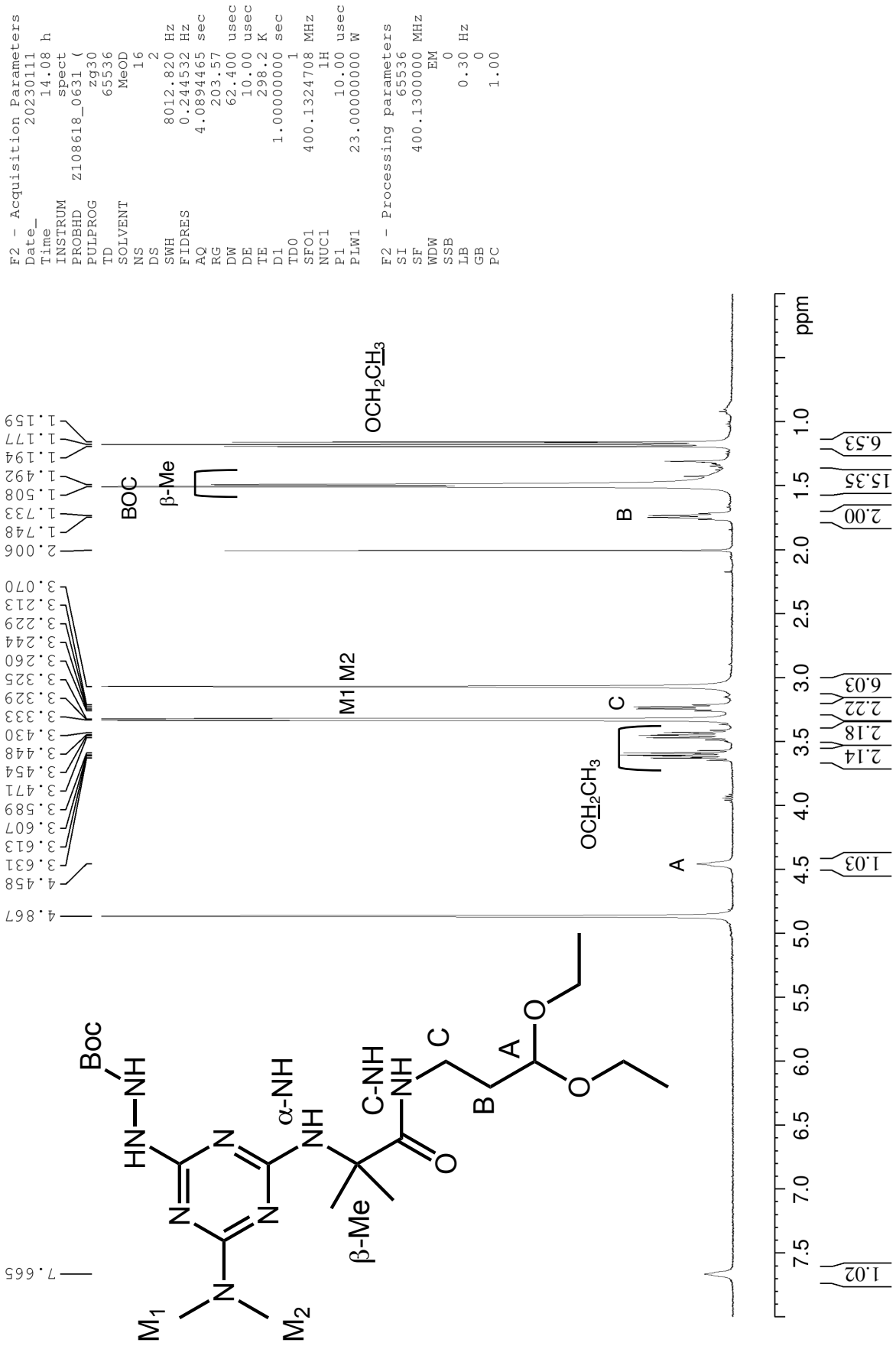


Figure S31. The 400 MHz ^{13}C NMR spectrum of 5 in CD_3OD.

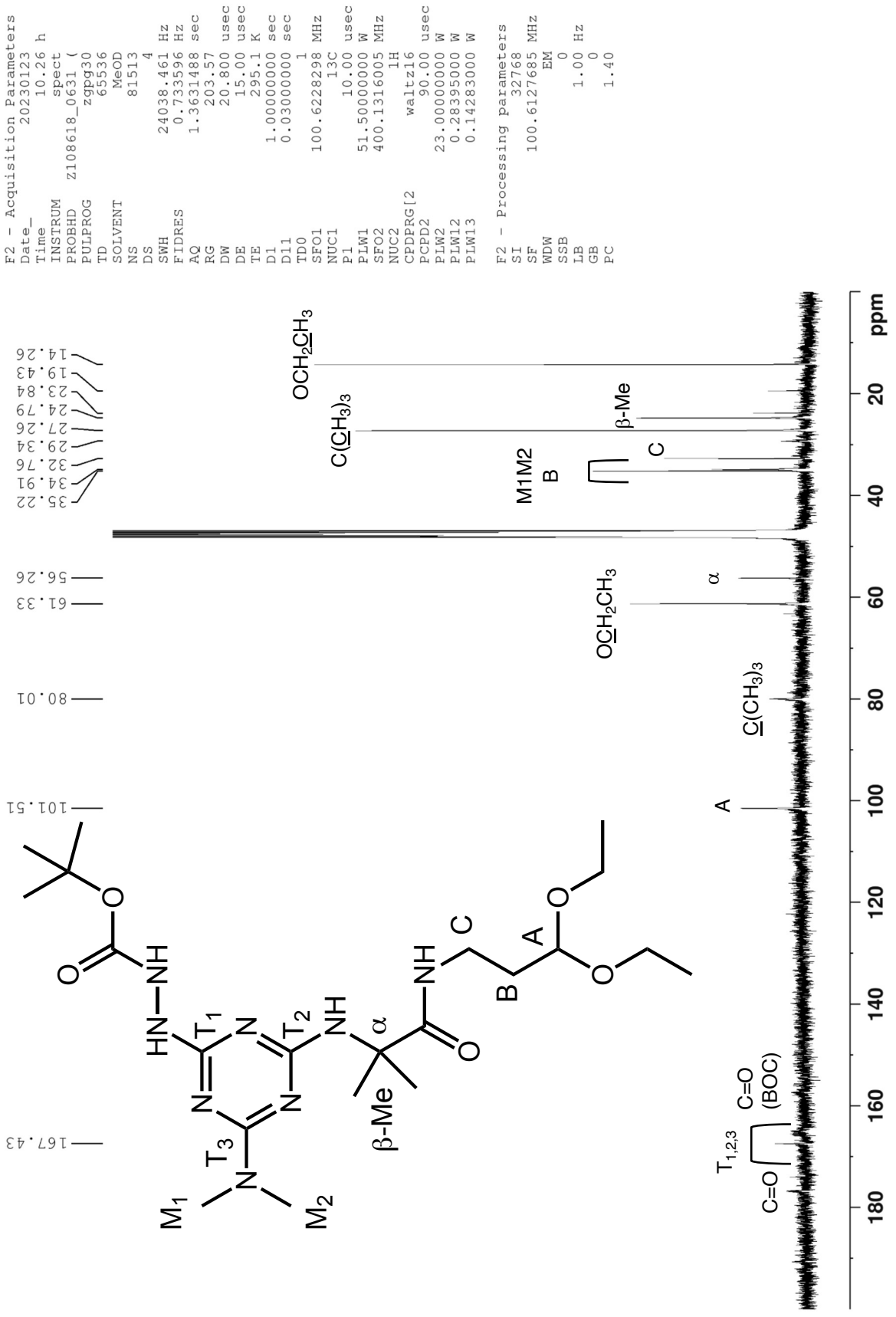


Figure S32. Mass spectrum of 5.

Formula Predictor Report - Eric_2021_FI_LCMS_2142023_3.lcd

Data File: D:\SCAAC\Ben\Data\02142023\Eric_2021_FI_LCMS_2142023_3.lcd

Elmt	Val.	Min	Max
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C	4	0	150
N	3	0	12

Elmt	Val.	Min	Max
O	2	0	12

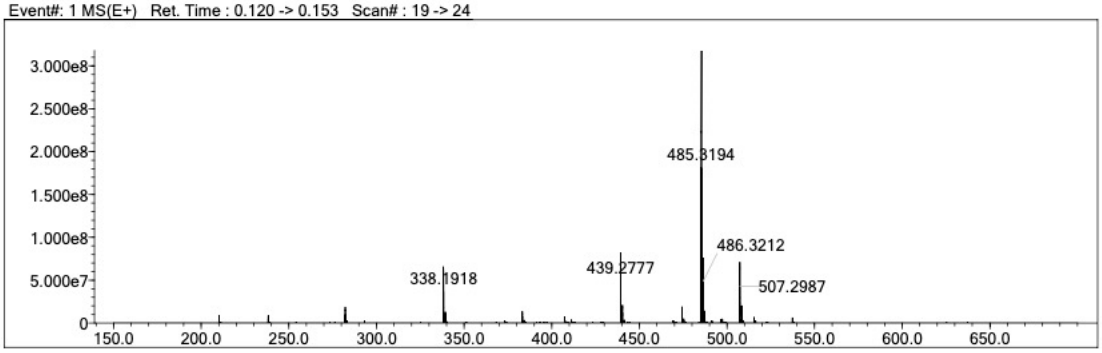
Use Adduct
H

Error Margin (ppm): 10
HC Ratio: unlimited
Max Isotopes: all
MSn Iso RI (%): 75.00

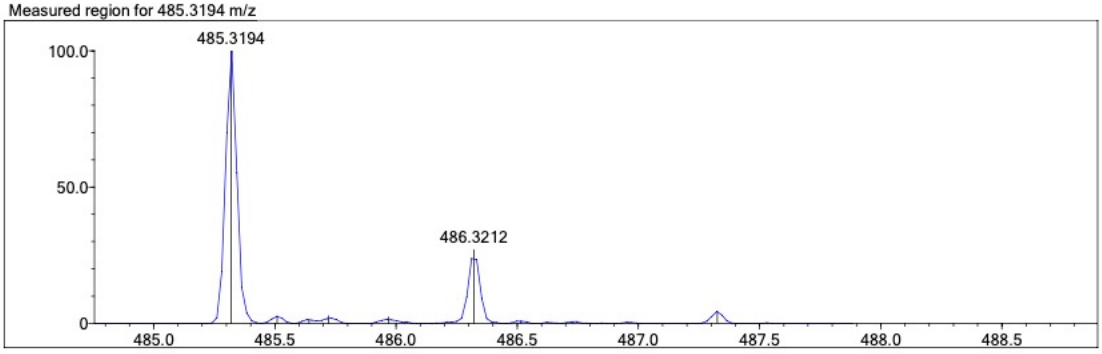
DBE Range: -2.0 - 1000.0
Apply N Rule: yes
Isotope RI (%): 1.00
MSn Logic Mode: AND

Electron Ions: both
Use MSn Info: no
Isotope Res: 10000
Max Results: 500

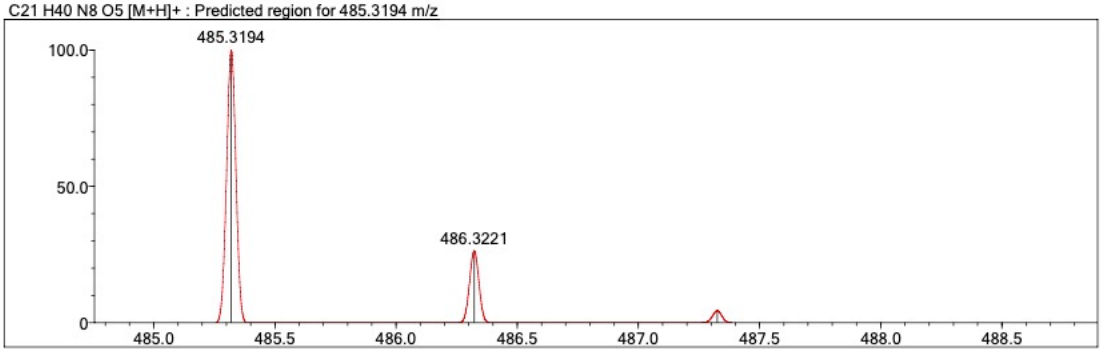
Event#: 1 MS(E+) Ret. Time : 0.120 -> 0.153 Scan# : 19 -> 24



Measured region for 485.3194 m/z



C21 H40 N8 O5 [M+H]+ : Predicted region for 485.3194 m/z



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	98.36	C21 H40 N8 O5	[M+H]+	485.3194	485.3194	-0.0	0.00	98.36	6.0

Figure S33. The 400 MHz ^{1}H NMR spectrum of 6 in CD_3OD.

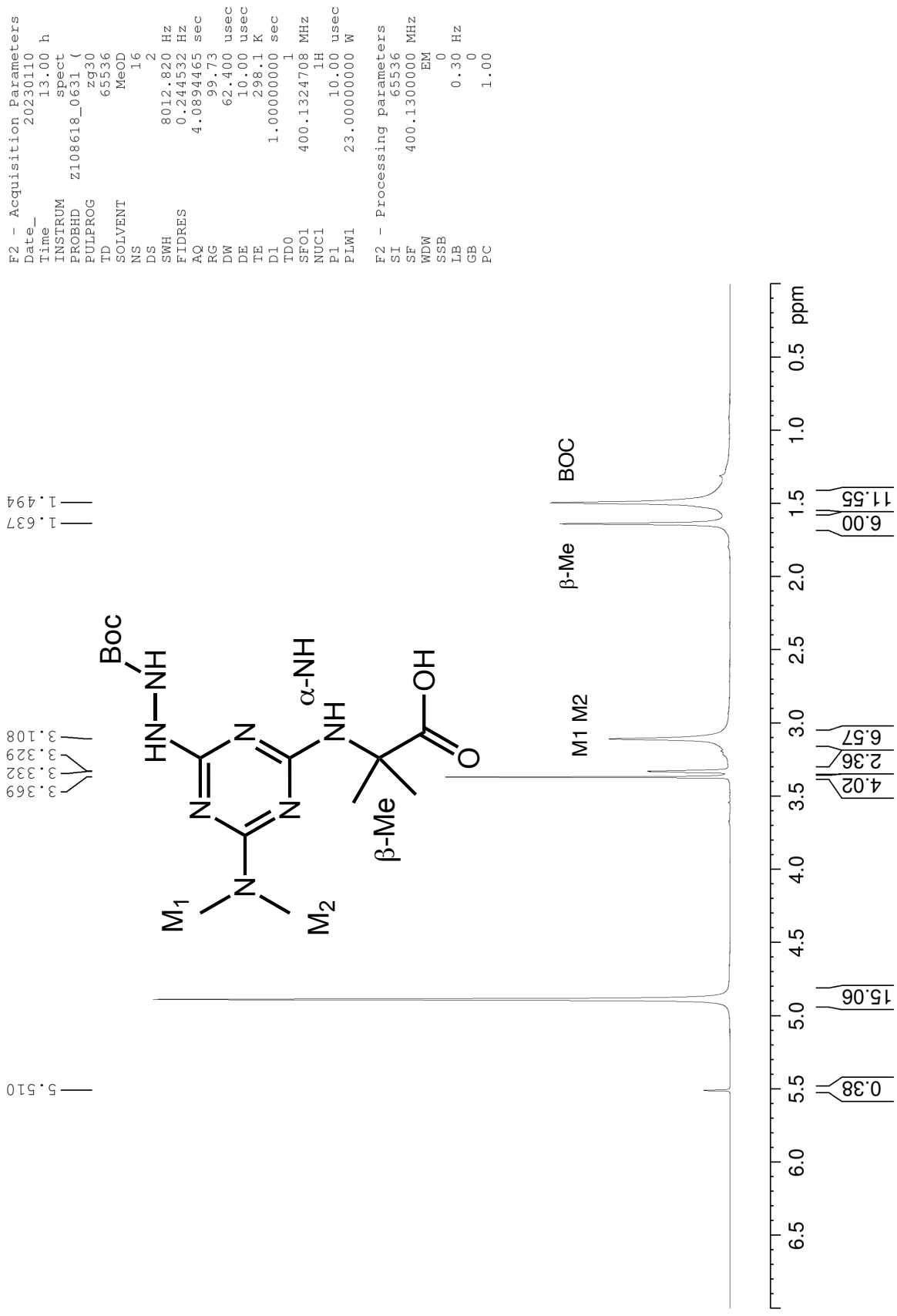


Figure S34. The 400 MHz ^{13}C NMR spectrum of 6 in CD_3OD.

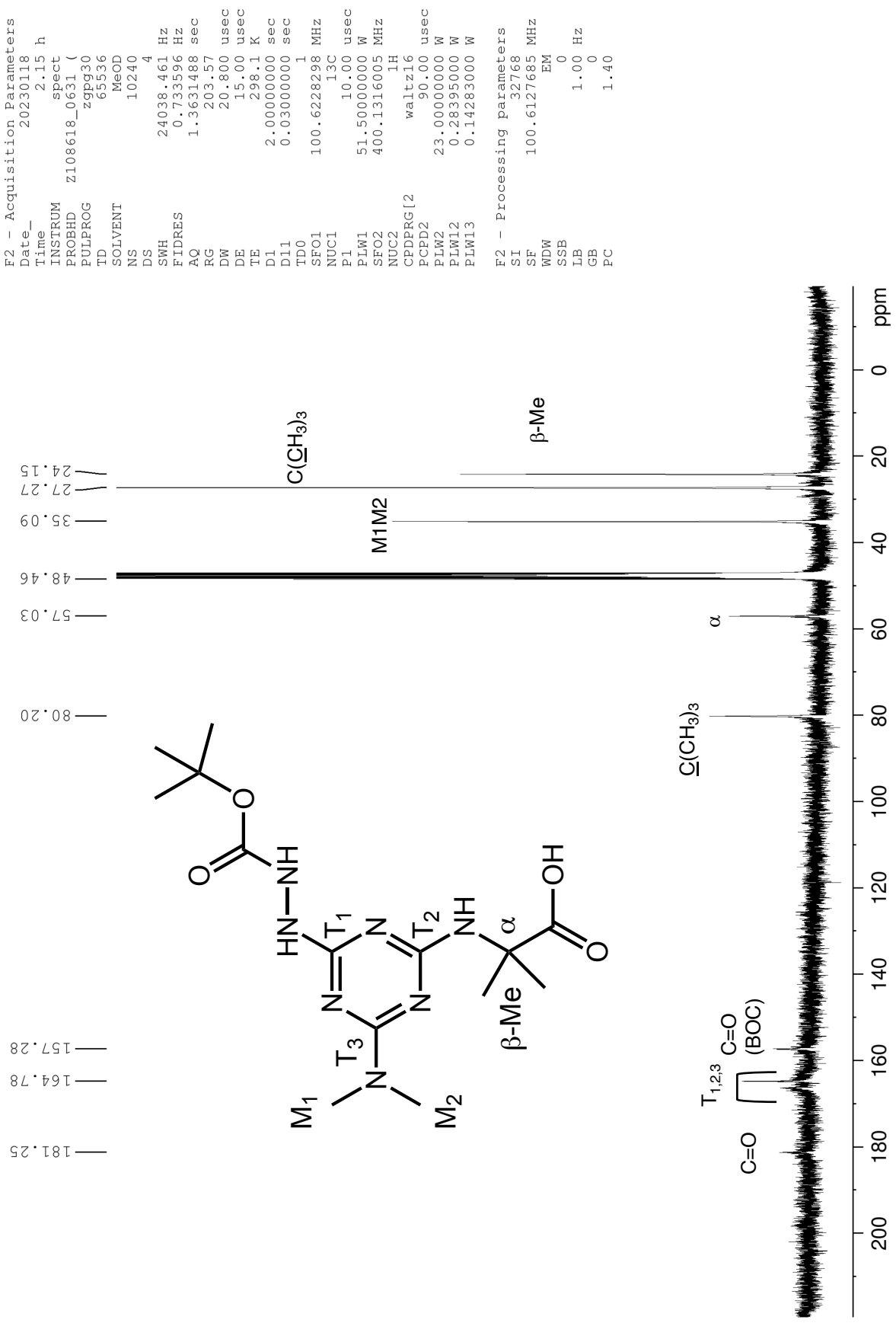


Figure S35. Mass spectrum of 6.

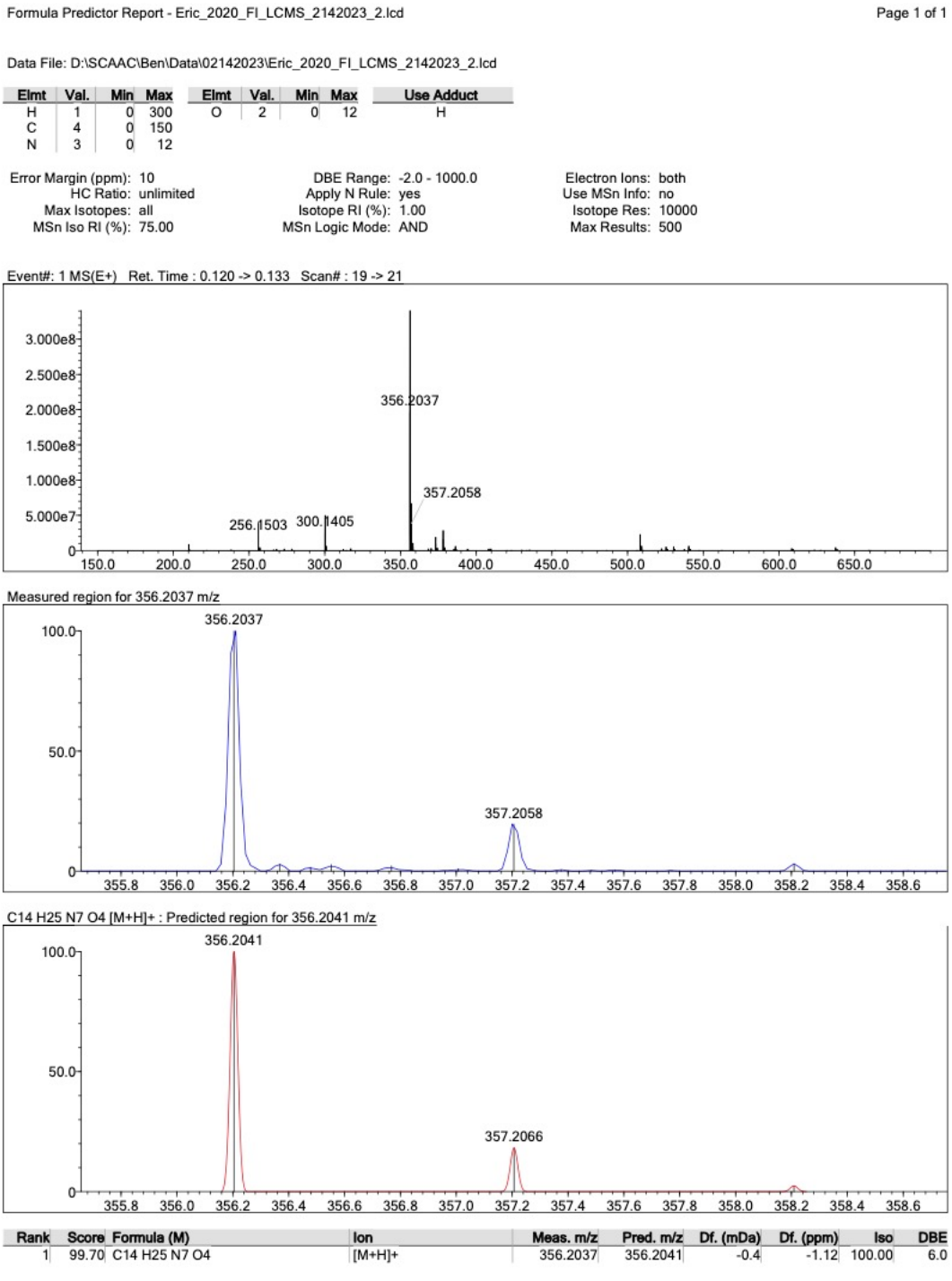
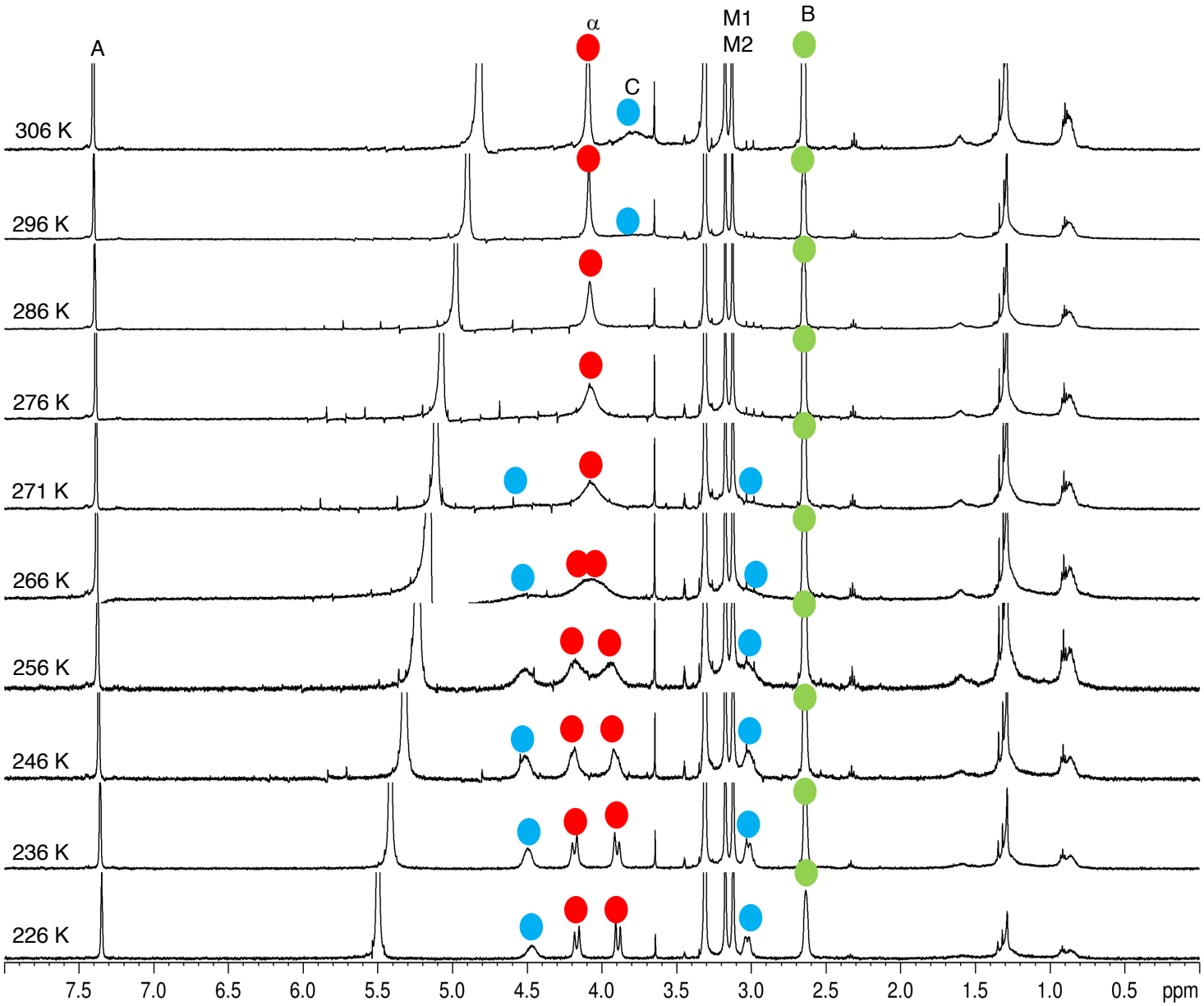


Figure S36. The 500 MHz variable temperature NMR of 1 in CD_3OD.



VII. Tables of Numerical Data and Analysis

Table S3. Numerical data and analysis for 2 in DMSO-d_6 at 400 MHz. Cells colored correspond to calculations based on liberal error margin including ±2.5 K and ±0.05 ppm.

DMSO-d_6	MHz	T_c (K)	n1 (ppm)	n2 (ppm)	Δ (ppm)	k(r) sec^{-1}	ΔG‡ (kJ/mol)	ΔG‡ (kcal/mol)	Error (kcal/mol)
C measured	400	310.5	3.477	3.220	0.257	228	66.9	16.0	
C error high	400	313.0	3.477	3.220	0.257	228	67.4	16.1	0.1
C measured	400	308.0	3.477	3.220	0.257	228	66.3	15.9	0.1
δ error high	400	310.5	-	-	0.307	273	66.4	15.9	0.1
δ error low	400	310.5	-	-	0.207	184	67.4	16.1	0.1
B measured	400	315.5	2.706	2.386	0.32	284	67.4	16.1	
B error high	400	318.0	2.706	2.386	0.32	284	68.0	16.2	0.1
B error low	400	313.0	2.706	2.386	0.32	284	66.9	16.0	0.1
δ error high	400	315.5	-	-	0.42	195	68.4	16.3	0.2
δ error low	400	315.5	-	-	0.22	373	66.7	15.9	0.2

Average: 16.1 kcal/mol ±0.1

Table S4. Raw Chemical Shift Data for 2 in DMSO-d_6 at 400 MHz. The coalescence temperature is indicated in color. An arrow indicates that the shifts are coalesced at the temperature indicated so only one shift is reported.

T (°C)	C_a (ppm)	C_e (ppm)	B_a (ppm)	B_e (ppm)	Me1 (ppm)	Me2 (ppm)
298	3.477	3.220	2.706	2.386	1.486	←
303	3.472	3.242	2.697	2.395	1.49	←
308	3.444	3.290	2.675	2.425	1.493	←
313	3.371	3.371	2.611	2.516	1.496	←
318	3.379	←	2.56	2.56	1.502	←
323	3.387	←	2.557	←	1.51	←
333	3.399	←	2.562	←		
338	3.404	←	2.565	←		
343	3.411	←	2.567	←		

Table S5. Numerical data and analysis for 2 in CD_3OD at 400 MHz. Cells colored correspond to calculations based on liberal error margin including ±2.5 K and ±0.05 ppm. The low δ error determination for the geminal methyls were not included in the average ΔG‡ nor the error determination.

CD_3OD	MHz	T_c (K)	n1 (ppm)	n2 (ppm)	Δ (ppm)	k(r) sec^{-1}	ΔG‡ (kJ/mol)	ΔG‡ (kcal/mol)	Error (kcal/mol)
C measured	400	305.5	3.643	3.525	0.118	105	67.7	16.2	-
C error high	400	308.0	3.477	3.220	0.118	105	68.3	16.3	0.1
C measured	400	308.0	3.477	3.220	0.118	105	67.2	16.1	0.1
δ error high	400	305.5	-	-	0.168	149	66.8	16.0	0.2
δ error low	400	305.5	-	-	0.068	60	69.1	16.5	0.3
B measured	400	310.5	2.865	2.463	0.402	324	66.0	15.8	
B error high	400	313.0	2.865	2.463	0.402	324	66.5	15.9	0.1
B error low	400	308.0	2.865	2.463	0.402	324	65.4	15.6	0.2
δ error high	400	310.5	-	-	0.452	369	65.6	15.7	0.1
δ error low	400	310.5	-	-	0.352	280	66.3	15.9	0.1
Me measured	400	296	1.668	1.616	0.052	46	67.6	16.1	
Me error high	400	298	1.668	1.616	0.052	46	68.0	16.3	0.2
Me error low	400	293	1.668	1.616	0.052	46	66.9	16.0	0.1
δ error high	400	296	-	-	0.102	91	65.9	15.8	0.3
δ error low	400	296	-	-	0.002	2	75.6	18.1	2.0

Average: 16.0 kcal/mol ±0.2

Table S6. Raw Chemical Shift Data for 2 in CD_3OD at 400 MHz. The coalescence temperature is indicated in color. An arrow indicates that the shifts are coalesced at the temperature indicated so only one shift is reported.

T (°C)	C_a (ppm)	C_e (ppm)	B_a (ppm)	B_e (ppm)	Me1 (ppm)	Me2 (ppm)
294	3.622	3.532	2.865	2.463	1.668	1.616
298	3.643	3.525	2.858	2.493	1.6422	←
303	3.613	3.561	2.834	2.512	1.645	←
308	3.593	3.593	2.784	2.575	1.651	←
313	3.600	3.600	2.673	2.673	1.652	←
318	3.608	←	2.676	←	1.652	←
323	3.614	←	2.676	←	1.655	←

Table S7. Numerical data and analysis for 2 in CD_3CN at 400 MHz. Cells colored correspond to calculations based on liberal error margin including ±2.5 K and ±0.05 ppm.

CD_3CN	MHz	T_c (K)	n1 (ppm)	n2 (ppm)	Δ (ppm)	k(r) sec^{-1}	ΔG‡ (kJ/mol)	ΔG‡ (kcal/mol)	Error (kcal/mol)
C measured	400	320.5	4.076	3.236	0.840	746	66.0	15.8	-
C error high	400	323.0	3.477	3.220	0.840	746	66.5	15.9	0.1
C measured	400	318.0	3.477	3.220	0.840	746	65.4	15.6	0.2
δ error high	400	320.5	-	-	0.890	791	65.8	15.7	0.1
δ error low	400	320.5	-	-	0.068	702	66.1	15.8	0.0
B measured	400	310.5	2.781	2.567	0.214	190	67.3	16.1	
B error high	400	313.0	2.781	2.567	0.214	190	66.8	16.0	0.1
B error low	400	308.0	2.781	2.567	0.214	190	67.9	16.2	0.1
δ error high	400	310.5	-	-	0.264	235	66.8	16.0	0.1
δ error low	400	310.5	-	-	0.164	146	68.0	16.3	0.2
Me measured	400	305.5	1.719	1.616	0.103	92	68.1	16.3	
Me error high	400	308.0	1.719	1.616	0.103	92	68.7	16.4	0.1
Me error low	400	305.0	1.719	1.616	0.103	92	67.5	16.1	0.2
δ error high	400	310.5	-	-	0.153	136	67.1	16.0	0.3
δ error low	400	310.5	-	-	0.053	47	69.8	16.7	0.4

Average: 16.1 kcal/mol ±0.2

Table S8. Raw Chemical Shift Data for 2 in CD_3CN at 400 MHz. The coalescence temperature is indicated in color. An arrow indicates that the shifts are coalesced at the temperature indicated so only one shift is reported.

T (°C)	C_a (ppm)	C_e (ppm)	B_a (ppm)	B_e (ppm)	Me1 (ppm)	Me2 (ppm)
298	4.076	3.236	2.781	2.567	1.719	1.616
303	4.075	3.248	2.762	2.587	1.672	1.672
308	4.060	3.263	2.718	2.644	1.675	←
313	4.005	3.290	2.680	2.680	1.680	←
318	3.918	3.395	2.680	←	1.680	←
323	3.664	3.664	2.680	←	1.680	←
328	3.685	←	2.680	←	1.687	←

Table S9. Numerical data and analysis for 2 in D_2O at 400 MHz. Cells colored correspond to calculations based on liberal error margin including ±2.5 K and ±0.05 ppm.

D_2O	MHz	T_c (K)	n1 (ppm)	n2 (ppm)	Δ (ppm)	k(r) sec^{-1}	ΔG‡ (kJ/mol)	ΔG‡ (kcal/mol)	Error (kcal/mol)
C measured	400	305.5	3.481	3.443	0.038	34	70.6	16.9	-
C error high	400	308.0	3.481	3.443	0.038	34	71.2	17.0	0.1
C measured	400	303.0	3.481	3.443	0.038	34	70.0	16.7	0.2
δ error high	400	305.5	-	-	0.088	78	68.4	16.4	0.5
δ error low	400	305.5	-	-	0.008	7	71.2	17.0	0.1
B measured	400	325.5	2.728	2.428	0.300	267	69.8	16.7	
B error high	400	328.0	2.728	2.428	0.300	267	70.4	16.8	0.1
B error low	400	323.0	2.728	2.428	0.300	267	69.3	16.6	0.1
δ error high	400	325.5	-	-	0.350	311	69.8	16.6	0.1
δ error low	400	325.5	-	-	0.250	222	69.4	16.8	0.1
Me measured	400	315.5	1.545	1.480	0.065	58	71.6	17.1	
Me error high	400	318.0	1.545	1.480	0.065	58	72.2	17.2	0.1
Me error low	400	323.0	1.545	1.480	0.065	58	71.0	17.0	0.1
δ error high	400	315.5	-	-	0.115	102	70.1	16.8	0.3
δ error low	400	315.5	-	-	0.015	13	75.4	18.0	0.9

Average: 16.9 kcal/mol ±0.2

Table S10. Raw Chemical Shift Data for 2 in D_2O at 400 MHz. The coalescence temperature is indicated in color. An arrow indicates that the shifts are coalesced at the temperature indicated so only one shift is reported.

T (°C)	C_a (ppm)	C_e (ppm)	B_a (ppm)	B_e (ppm)	Me1 (ppm)	Me2 (ppm)
298	3.481	3.443	2.728	2.428	1.545	1.480
303	3.539	3.522	2.791	2.502	1.615	1.548
308	3.602	3.602	2.841	2.572	1.68	1.616
313	3.665	←	2.886	2.65	1.729	1.692
318	3.725	←	2.933	2.735	1.775	1.775
323	3.788	←	2.937	2.826	1.833	←
328	3.848	←	2.939	2.939	1.892	←

Table S11. Numerical data and analysis for 2 in pyridine-d_5 at 400 MHz. Cells colored correspond to calculations based on liberal error margin including ±2.5 K and ±0.05 ppm.

pyridine-d_5	MHz	T_c (K)	n1 (ppm)	n2 (ppm)	Δ (ppm)	k(r) sec^{-1}	ΔG‡ (kJ/mol)	ΔG‡ (kcal/mol)	Error (kcal/mol)
C measured	400	320.5	3.937	3.696	0.241	214	69.3	16.6	-
C error high	400	323.0	3.937	3.696	0.241	214	69.8	16.7	0.1
C measured	400	318.0	3.937	3.696	0.241	214	68.7	16.4	0.2
δ error high	400	320.5	-	-	0.291	259	68.8	16.4	0.2
δ error low	400	320.5	-	-	0.191	170	69.9	16.7	0.1
B measured	400	335.5	3.122	2.272	0.850	755	69.1	16.5	
B error high	400	338.0	3.122	2.272	0.850	755	69.7	16.7	0.2
B error low	400	333.0	3.122	2.272	0.850	755	68.6	16.4	0.1
δ error high	400	335.5	-	-	0.900	800	69.0	16.5	0.0
δ error low	400	335.5	-	-	0.800	711	69.3	16.6	0.1
DMA measured	400	350	3.064	2.77	0.294	261	75.3	18.0	
DMA error high	400	352.5	3.064	2.77	0.294	261	75.9	18.1	0.1
DMA error low	400	347.5	3.064	2.77	0.294	261	74.8	17.9	0.1
δ error high	400	350.0	-	-	0.344	306	74.9	17.9	0.1
δ error low	400	350.0	-	-	0.244	217	75.9	18.1	0.1

Average: 16.6 kcal/mol ±0.1

Table S12. Raw Chemical Shift Data for 2 in pyridine-d_5 at 400 MHz. The coalescence temperature is indicated in color. An arrow indicates that the shifts are coalesced at the temperature indicated so only one shift is reported.

T (°C)	C_a (ppm)	C_e (ppm)	B_a (ppm)	B_e (ppm)	Me1 (ppm)	Me2 (ppm)	Aux2 (ppm)	Aux2 (ppm)
298	3.937	3.696	3.122	2.272	1.881	←	3.064	2.77
303	3.937	3.700	3.105	2.275	1.878	←	3.069	2.779
308	3.935	3.705	3.064	2.289	1.873	←	3.076	2.793
313	3.922	3.723	3.056	2.292	1.869	←	3.08	2.801
318	3.844	3.782	3.006	2.319	1.864	←	3.085	2.815
323	3.824	3.824	2.902	2.369	1.862	←	3.090	2.825
328	3.813	3.813	2.727	2.727	1.856	←	3.093	2.838
333	3.815	←	2.641	←	1.853	←	3.092	2.849
338	3.81	←	2.654	←	1.850	←	3.090	2.867
343	3.81	←	2.652	←	1.847	←	3.072	2.900
348	3.809	←	2.646	←	1.844	←	2.988	2.988

Table S13. Numerical data and analysis for 2 in CD_3OD at 500 MHz. Cells colored correspond to calculations based on liberal error margin including ±2.5 K and ±0.05 ppm.

CD_3OD	MHz	T_c (K)	n1 (ppm)	n2 (ppm)	Δ (ppm)	k(r) sec^{-1}	ΔG‡ (kJ/mol)	ΔG‡ (kcal/mol)	Error (kcal/mol)
C measured	500	308.5	3.625	3.516	0.109	121	68.1	16.3	-
C error high	500	313.0	3.625	3.516	0.109	121	69.1	16.5	0.2
C measured	500	305.0	3.625	3.516	0.109	121	67.3	16.1	0.2
δ error high	500	305.5	-	-	0.159	177	67.1	16.0	0.3
δ error low	500	305.5	-	-	0.059	66	69.6	16.6	0.3
B measured	500	321.0	2.886	2.384	0.502	558	66.8	16.0	
B error high	500	323.5	2.886	2.384	0.502	558	67.4	16.1	0.1
B error low	500	318.5	2.886	2.384	0.502	558	66.3	15.8	0.2
δ error high	500	321.0	-	-	0.552	613	66.6	15.9	0.1
δ error low	500	321.0	-	-	0.452	502	67.1	16.0	0.0
Me measured	500	303.5	1.671	1.576	0.095	106	67.2	16.1	
Me error high	500	305.0	1.671	1.576	0.095	106	67.6	16.2	0.1
Me error low	500	301.0	1.671	1.576	0.095	106	66.7	15.9	0.2
δ error high	500	303.5	-	-	0.145	162	66.2	15.8	0.3
δ error low	500	303.5	-	-	0.045	51	69.1	16.5	0.4

Average: 16.1 kcal/mol ±0.2

Table S14. Numerical data and analysis for 2 in CD_3CN at 500 MHz. Cells colored correspond to calculations based on liberal error margin including ±2.5 K and ±0.05 ppm.

CD_3CN	MHz	T_c (K)	n1 (ppm)	n2 (ppm)	Δ (ppm)	k(r) sec^{-1}	ΔG‡ (kJ/mol)	ΔG‡ (kcal/mol)	Error (kcal/mol)
C measured	500	333.5	4.074	3.275	0.799	887	68.3	16.3	-
C error high	500	336.0	4.074	3.275	0.799	887	68.8	16.4	0.1
C measured	500	331.0	4.074	3.275	0.799	887	67.7	16.2	0.1
δ error high	500	333.5	-	-	0.849	943	68.1	16.3	0.0
δ error low	500	333.5	-	-	0.749	832	68.4	16.4	0.1
B measured	500	318.5	2.804	2.506	0.298	558	67.7	16.2	
B error high	500	321.0	2.804	2.506	0.298	558	68.2	16.3	0.1
B error low	500	316.0	2.804	2.506	0.298	558	67.1	16.0	0.2
δ error high	500	318.5	-	-	0.348	613	67.3	16.1	0.1
δ error low	500	318.5	-	-	0.248	502	68.2	16.3	0.1
Me measured	500	308.5	1.71	1.559	0.151	168	67.2	16.1	
Me error high	500	311.0	1.71	1.559	0.151	168	67.8	16.2	0.1
Me error low	500	306.0	1.71	1.559	0.151	168	66.7	15.9	0.2
δ error high	500	308.5	-	-	0.201	223	66.5	15.9	0.2
δ error low	500	308.5	-	-	0.101	112	68.2	16.3	0.2

Average: 16.2 kcal/mol ±0.1

Table S15. Numerical data and analysis for 2 in pyridine-d_5 at 500 MHz. Cells colored correspond to calculations based on liberal error margin including ±2.5 K and ±0.05 ppm.

pyridine-d_5	MHz	T_c (K)	n1 (ppm)	n2 (ppm)	Δ (ppm)	k(r) sec^{-1}	ΔG‡ (kJ/mol)	ΔG‡ (kcal/mol)	Error (kcal/mol)
C measured	500	328.5	4.285	4.036	0.249	277	70.4	16.8	-
C error high	500	331.0	4.285	4.036	0.249	277	70.9	17.0	0.2
C measured	500	326.0	4.285	4.036	0.249	277	69.8	16.7	0.1
δ error high	500	328.5	-	-	0.299	332	69.9	16.7	0.1
δ error low	500	328.5	-	-	0.199	221	71.0	17.0	0.2
B measured	500	341.0	3.446	2.61	0.836	929	69.7	16.7	
B error high	500	343.5	3.446	2.61	0.836	929	70.3	16.8	0.1
B error low	500	338.5	3.446	2.61	0.836	929	69.2	16.5	0.2
δ error high	500	341.0	-	-	0.886	984	69.6	16.6	0.1
δ error low	500	341.0	-	-	0.786	873	69.9	16.7	0.2

Average: 16.8 kcal/mol ±0.2

Table S16. Numerical data and analysis for 1 in CD_3OD at 500 MHz. Cells colored correspond to calculations based on liberal error margin including ±2.5 K and ±0.05 ppm.

CD_3OD	MHz	T_c (K)	n1 (ppm)	n2 (ppm)	Δ (ppm)	k(r) sec^{-1}	$\Delta G^{\ddagger}$ (kJ/mol)	$\Delta G^{\ddagger}$ (kcal/mol)	Error (kcal/mol)
C measured	500	280.5	4.516	3.036	1.480	1644	55.6	13.3	-
C error high	500	283.0	4.516	3.036	1.480	1644	56.1	13.4	0.1
C measured	500	278.0	4.516	3.036	1.480	1644	55.1	13.2	0.1
d error high	500	280.5	-	-	1.530	1699	55.5	13.3	0.0
d error low	500	280.5	-	-	1.430	1588	55.7	13.3	0.0
α measured	500	267.5	4.185	3.900	0.285	317	56.6	13.5	
α error high	500	270.0	4.185	3.900	0.285	317	57.1	13.6	0.1
α error low	500	265.0	4.185	3.900	0.285	317	56.0	13.4	0.1
δ error high	500	267.5	-	-	0.335	372	56.2	13.4	0.1
δ error low	500	267.5	-	-	0.235	261	57.0	13.6	0.1

Average: 13.4 kcal/mol ±0.1