Electronic Supplementary Material (ESI) for Chemical Communications

Molecular Chirality and Chiral Capsule-type Dimer Formation of Cyclic Triamides via Hydrogen-Bonding Interactions

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Supporting Information **page**

1. Experimental

1.1. General

Melting points were determined by using a Yanako MP-J3 melting point apparatus and are uncorrected. Elemental analyses were carried out in the Microanalytical Laboratory, Faculty of Pharmaceutical Sciences, The University of Tokyo, and were within ±0.3% of the theoretical values. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-AL400 spectrometer or Bruker Avance 600 spectrometer, and chemical shifts are expressed in ppm relative to tetramethylsilane. Mass spectra were recorded on Bruker Daltonics microTOF-2focus spectrometer in the positive ion detection mode. CD spectra were recorded on a JASCO J-820. A specimen for measurement of the solid state spectrum was prepared as follows: 200 μg of **4a** was added to 110 mg of KBr (dried by heating before use), and the mixture was well-ground, and formed into the tablet with a radius of 5 mm.

1.2. Synthesis of cyclization precursors

Synthesis of monomethyl 5-aminoisophthalate

A solution of monomethyl 5-nitroisophthalate (1.998 g, 8.874 mmol) was hydrogenated with 10% Pd-C (0.203 g) in dry ethanol (60 ml) at room temperature under hydrogen atmosphere for 3 h. The reaction mixture was filtered over celite, and the filtrate was evaporated to afford monomethyl 5-aminoisophthalate (1.558 g, 7.990 mmol, 90%) as yellow powder. Mp 210-214°C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.90 (s, 1 H), 7.53 (s, 1 H), 7.51 (s, 1 H), 3.89 (s, 3 H); ^{13}C NMR (150 MHz, CD_3OD) δ 168.0, 166.9, 148.7, 131.7, 130.9, 119.4, 119.0, 118.9, 51.2; IR (KBr) : 1686, 1719 cm^{-1}.

Synthesis of monomethyl 5-(*n*-propylamino)isophthalate (6a)

n-Propyl iodide (1.5 ml) was added to a solution of monomethyl 5-aminoisophthalate (1.095 g, 5.613 mmol) in dry DMF (20 ml) under Ar atmosphere, and the mixture was stirred at 40°C for 3 days. The reaction mixture was evaporated, extracted with ethyl acetate. The organic layer was

washed with brine, dried over magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography *n*-hexane : ethyl acetate = 3 : 2) to afford **6a** (539 mg, 2.28 mmol, 41%) as yellow powder. Mp : 174-177°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1 H), 7.52 (s, 2 H), 3.93 (s, 3 H), 3.18 (t, *J* = 7.0 Hz, 2 H), 1.69 (sextet, *J* = 7.3 Hz, 2 H), 1.03 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (150 MHz, CD_3OD) δ 169.6, 168.5, 150.9, 133.0, 132.3, 119.2, 118.3, 117.8, 52.7, 46.4, 23.2, 11.9; IR (KBr) : 1687, 1714 cm^{-1}; HRMS (ESI), Calcd for $C_{12}H_{15}NNaO_4$ (MNa^+) 260.0893, Found 260.0892.

Synthesis of monomethyl 5-(*n*-pentylamino)isophthalate (6b)

n-Propyl iodide (4.0 ml) was added to a solution of monomethyl 5-aminoisophthalate (2.462 g, 12.63 mmol) in dry DMF (40 ml) under Ar atmosphere, and the mixture was stirred at 40°C for 4 days. The reaction mixture was evaporated, extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography *n*-hexane : ethyl acetate = 3 : 2) to afford **6b** (1.540 g, 5.811 mmol, 46%) as yellow powder. Mp : 139-141°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1 H), 7.49 (s, 2 H), 3.93 (s, 3 H), 3.19 (t, *J* = 6.8 Hz, 2 H), 1.66 (quintet, *J* = 7.3 Hz, 2 H), 1.44-1.34 (m, 4 H), 0.93 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.6, 166.9, 148.7, 131.6, 130.5, 119.9, 118.4, 118.0, 52.5, 44.1, 29.4, 29.1, 22.6, 14.2; IR (KBr) : 1705, 1716 cm^{-1}; HRMS (ESI), Calcd for $C_{14}H_{20}NO_4$ (MH^+) 266.1387, Found 266.1385.

1.3. Synthesis of cyclic triamides

Synthesis of 2a

A solution of **6a** (187 mg, 0.789 mmol) and Ph_3PCl_2 (1.168 g, 3.504 mmol, 4.4 eq) in 1,1,2,2-tetrachloroethane (20 ml) was heated at 120°C under Ar atmosphere for 9 h. The mixture was evaporated, and the residue was purified by silica gel column chromatography (*n*-hexane : ethyl acetate = 1 : 1) to afford **2a** (50 mg, 0.076 mmol, 29%) as colorless oil. ^{1}H NMR (400 MHz, CD_3OD) δ 7.73 (s, 6H), 7.42 (s, 3 H), 3.84 (s, 9 H), 3.85-3.71 (m, 6 H), 1.61 (sextet, *J* = 7.3 Hz,

6 H), 0.96 (t, J = 7.3 Hz, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.1, 164.8, 142.7, 139.5, 132.1, 131.1, 130.8, 127.8, 52.7, 51.7, 20.8, 11.3; IR (KBr) : 1657, 1731 cm^{-1}; HRMS (ESI), Calcd for $C_{36}H_{39}N_3NaO_9$ (MNa^+) 680.2579, Found 680.2579.

Synthesis of 2b

A solution of **6b** (585 mg, 2.21 mmol) and Ph_3PCl_2 (2.093 g, 6.281 mmol, 2.8 eq) in dry $CHCl_3$ (15 ml) was heated at 80°C under Ar atmosphere for 1 day. The mixture was evaporated, and the residue was purified by silica gel column chromatography (*n*-hexane : ethyl acetate = 3 : 2) to afford **2b** (425 mg, 0.573 mmol, 78%) as colorless oil. ^{1}H NMR (400 MHz, CD_3OD) δ 7.72 (s, 6 H), 7.41 (s, 3 H), 3.86 (s, 9 H), 3.91-3.73 (m, 6 H), 1.64-1.56 (br s, 6 H), 1.40-1.30 (br s, 12 H), 0.92 (t, J = 7.3 Hz, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.1, 164.9, 142.7, 139.5, 132.1, 131.1, 130.9, 127.9, 52.8, 50.4, 29.0, 27.2, 22.5, 14.1; IR (KBr) : 1655, 1732 cm^{-1}; HRMS (ESI), Calcd for $C_{42}H_{51}N_3NaO_9$ (MNa^+) 764.3518, Found 764.3521.

Synthesis of 3a

2 M sodium hydroxide (1 ml) was added to a solution of **2a** (46 mg, 0.070 mmol) in ethanol (3 ml), and the mixture was stirred at room temperature for 8 h. The reaction mixture was acidified by adding 2 M hydrochloric acid, evaporated, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated to afford **3a** (29 mg, 0.047 mmol, 66%) as colorless powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.26 (br s, 3 H), 7.76 (s, 3 H), 7.69 (s, 3 H), 7.10 (s, 3 H), 4.04-3.96 (m, 3 H), 3.59-3.51 (m, 3 H), 1.67-1.60 (m, 6 H), 0.99 (t, J = 7.3 Hz, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 168.7, 142.8, 139.4, 132.8, 131.7, 129.9, 129.1, 51.0, 21.0, 11.3; IR (KBr) : 1656, 1719 cm^{-1}; Anal. Calcd for $C_{33}H_{33}N_3O_9 \cdot 2H_2O \cdot 1/2MeOH$: C, 60.26 ; H, 5.89 ; N, 6.29. Found : C, 60.40 ; H, 5.68 ; N, 6.37; HRMS (ESI), Calcd for $C_{33}H_{34}N_3O_9$ (MH^+) 616.2296, Found 616.2290.

Synthesis of 3b

2 M sodium hydroxide (3 ml) was added to a solution of **2b** (336 mg, 0.453 mmol) in ethanol (5 ml), and the mixture was stirred at room temperature for 2 h. The reaction mixture was acidified by adding 2 M hydrochloric acid, evaporated, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated to afford **3b** (218 mg, 0.312 mmol, 69%) as colorless powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.32 (br s, 3 H), 7.76 (s, 3 H), 7.69 (s, 3 H), 7.10 (s, 3 H), 4.10-4.00 (m, 3 H), 3.61-3.50 (m, 3 H), 1.70-1.50 (br s, 6 H), 1.41-1.30 (br s, 12 H), 0.91 (t, J = 6.8 Hz, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 168.6, 142.8, 139.4, 132.8, 131.7, 129.9, 129.1, 49.5, 29.0, 27.4, 22.5, 14.1; IR (KBr) : 1718 cm^{-1}; Anal. Calcd for $C_{39}H_{45}N_3O_9 \cdot 3/2H_2O$: C, 64.45 ; H, 6.66 ; N, 5.78. Found : C, 64.75 ; H, 6.55 ; N, 5.85; HRMS (ESI), Calcd for $C_{39}H_{46}N_3O_9$ (MH^+) 700.3233, Found 700.3229.

Synthesis of 4a

7 M methanolic ammonia (5 ml) was added to a solution of **2a** (84 mg, 0.13 mmol), and the mixture was stirred at room temperature for 3 days. The reaction mixture was evaporated, and the residue was purified by silica gel column chromatography (CH_2Cl_2 : MeOH = 9 : 1) to afford **4a** (56 mg, 0.092 mmol, 72%) as colorless powder. Mp : 298-300°C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.59 (s, 6 H), 7.34 (s, 3 H), 3.84-3.75 (m, 3 H), 3.73-3.65 (m, 3 H), 1.57 (sextet, J = 7.3 Hz, 6 H), 0.94 (t, J = 7.3 Hz, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 168.0, 142.4, 139.1, 135.2, 130.0, 129.1, 125.4, 51.2, 20.3, 10.1; HRMS (ESI), Calcd for $C_{33}H_{36}N_6NaO_6$ (MNa^+) 635.2589, Found 635.2582.

Synthesis of 4b

7 M methanolic ammonia (7 ml) was added to a solution of **2b** (107 mg, 0.144 mmol), and the mixture was stirred at room temperature for 2 days. The reaction mixture was evaporated, and the residue was purified by silica gel column chromatography (CH_2Cl_2 : MeOH = 9 : 1) to afford **4b** (69 mg, 0.10 mmol, 69%) as colorless powder. Mp : 174-178°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44-8.30 (br s, 3 H), 7.56 (s, 6 H), 7.36-7.25 (br s, 3 H), 6.96 (s, 3 H), 3.99-3.78 (br s, 3 H),

3.74-3.53 (br s, 3 H), 1.69-1.46 (br s, 6 H), 1.38-1.20 (br s, 12 H), 0.94-0.77 (br s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.2, 169.0, 142.9, 139.3, 134.7, 130.5, 129.7, 126.1, 49.7, 29.0, 27.4, 22.5, 14.1; Anal. Calcd for $C_{39}H_{48}N_6O_6 \cdot H_2O$: C, 66.36 ; H, 7.00 ; N, 11.91. Found : C, 66.48 ; H, 6.80 ; N, 11.75; HRMS (ESI), Calcd for $C_{39}H_{48}N_6NaO_6$ (MNa^+) 719.3528, Found 719.3511.

Synthesis of 5a

40% methanolic methylammonia (1 ml) was added to a solution of **2a** (78 mg, 0.12 mmol), and the mixture was stirred at room temperature for 3 h. The reaction mixture was evaporated, and the residue was purified by silica gel column chromatography (CH_2Cl_2 : MeOH = 20 : 1) to afford **5a** (56 mg, 0.086 mmol, 72%) as colorless powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 3 H), 7.37 (s, 3 H), 7.06-7.01 (br s, 3 H), 6.93 (s, 3 H), 3.85-3.76 (m, 3 H), 3.64-3.55 (m, 3 H), 2.86 (d, J = 4.4 Hz, 9 H), 1.56 (sextet, J = 7.8 Hz, 6 H), 0.91 (t, J = 7.3 Hz, 9 H) ; HRMS (ESI), Calcd for $C_{36}H_{42}N_6NaO_6$ (MNa^+) 677.3058, Found 677.3043.

Synthesis of 5b

40% methanolic methylammonia (2 ml) was added to a solution of **2b** (116 mg, 0.156 mmol), and the mixture was stirred at room temperature for 10 h. The reaction mixture was evaporated, and the residue was purified by silica gel column chromatography (CH_2Cl_2 : MeOH = 19 : 1) to afford **5a** (69 mg, 0.093 mmol, 60%) as colorless powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 3 H), 7.32 (s, 3 H), 6.94 (s, 3 H), 6.81-6.76 (br s, 3 H), 3.89-3.81 (m, 3 H), 3.66-3.58 (m, 3 H), 2.90 (d, J = 4.9 Hz, 9 H), 1.62-1.51 (br s, 6 H), 1.35-1.20 (br s, 12 H), 0.87 (t, J = 6.8 Hz, 9 H) ; HRMS (ESI), Calcd for $C_{42}H_{54}N_6NaO_6$ (MNa^+) 761.3997, Found 761.3980.

2. Valuable temperature ^{1}H NMR

Figure S1. ^{1}H NMR of Compound **2a** in CD_3OD.

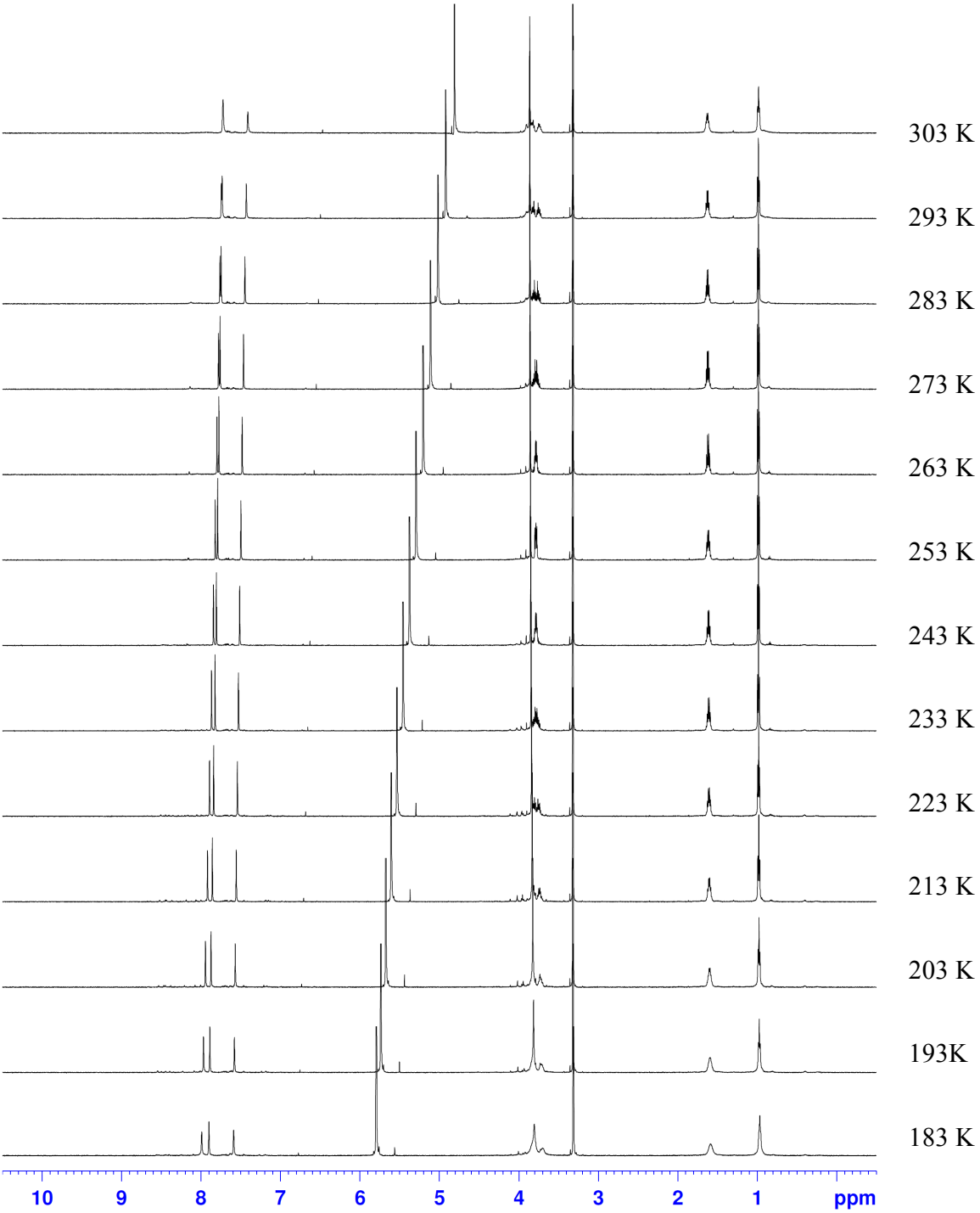


Figure S2. ^{1}H NMR of Compound **2a** in CD_2Cl_2.

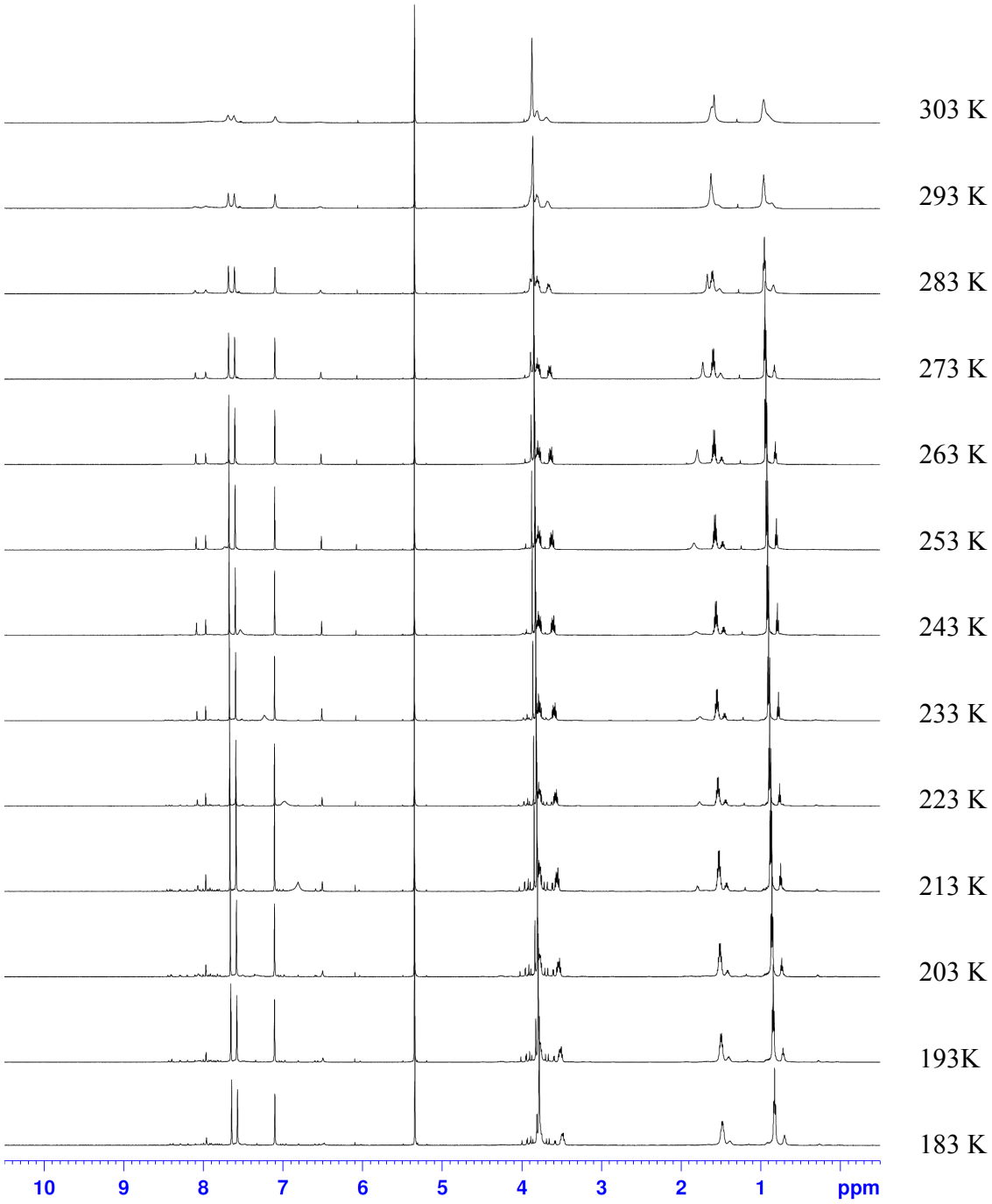


Figure S3. ^{1}H NMR of Compound **2b** in CD_3OD.

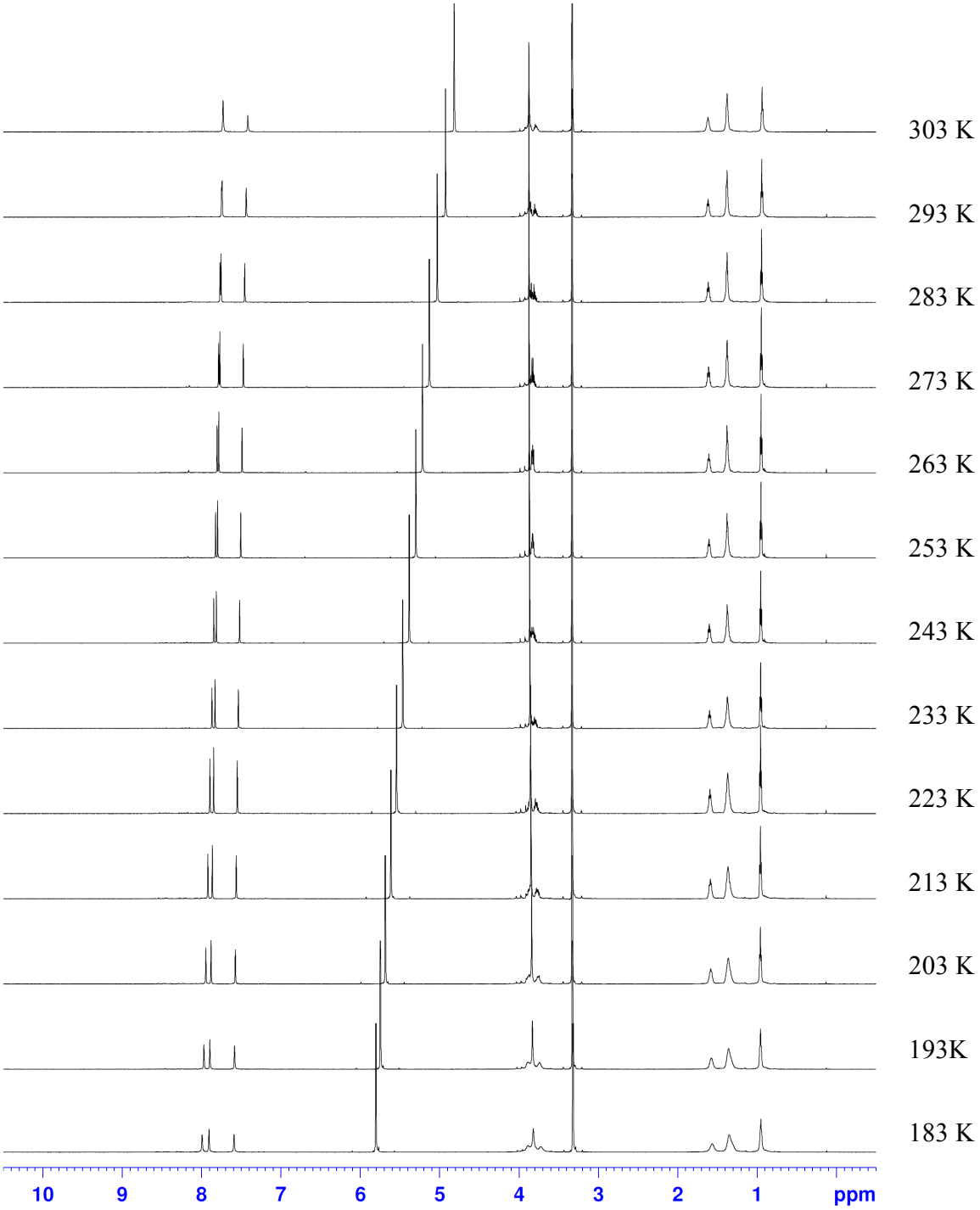


Figure S4. ^{1}H NMR of Compound **2b** in CD_2Cl_2.

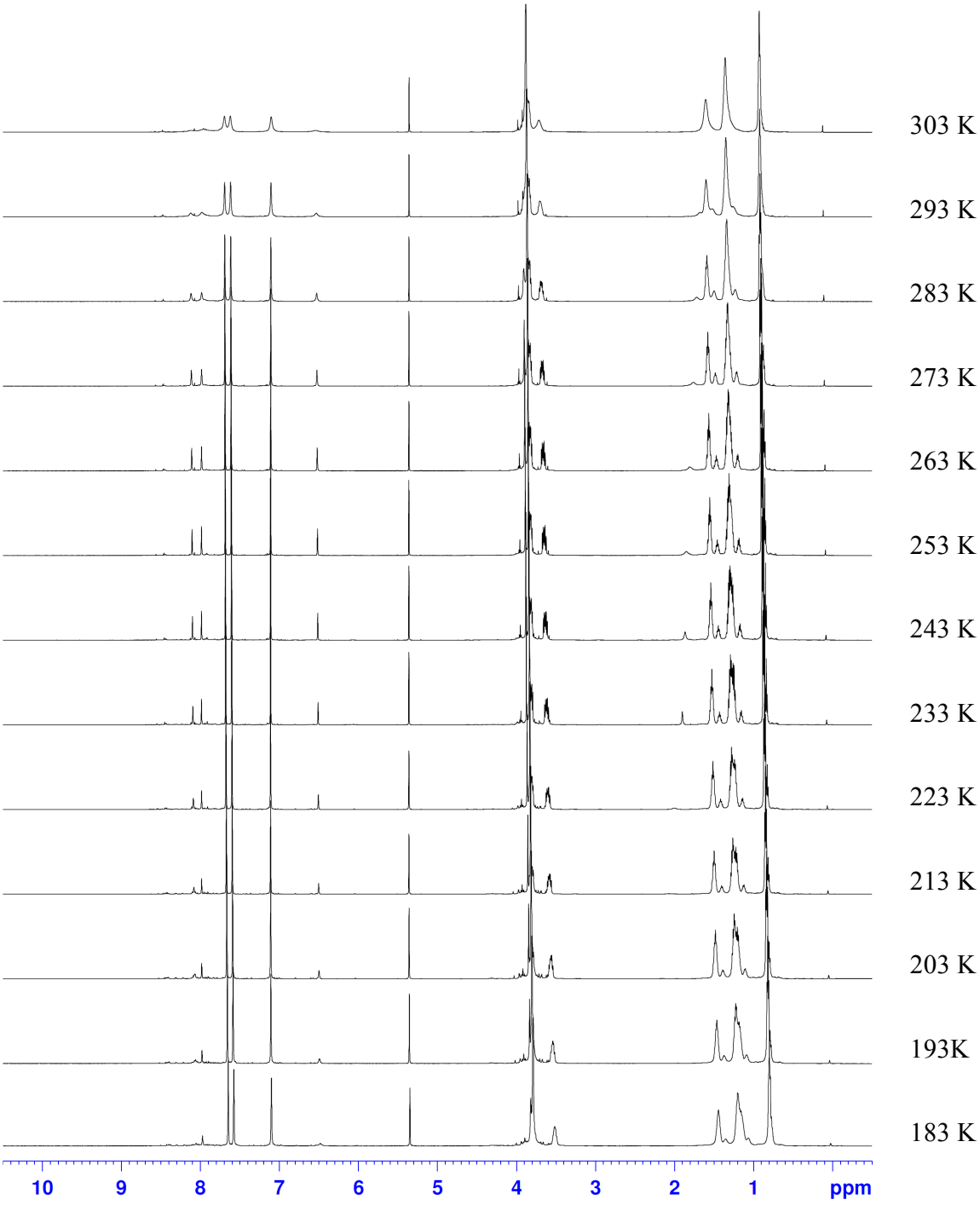


Figure S5. ^{1}H NMR of Compound **3a** in CD_3OD.

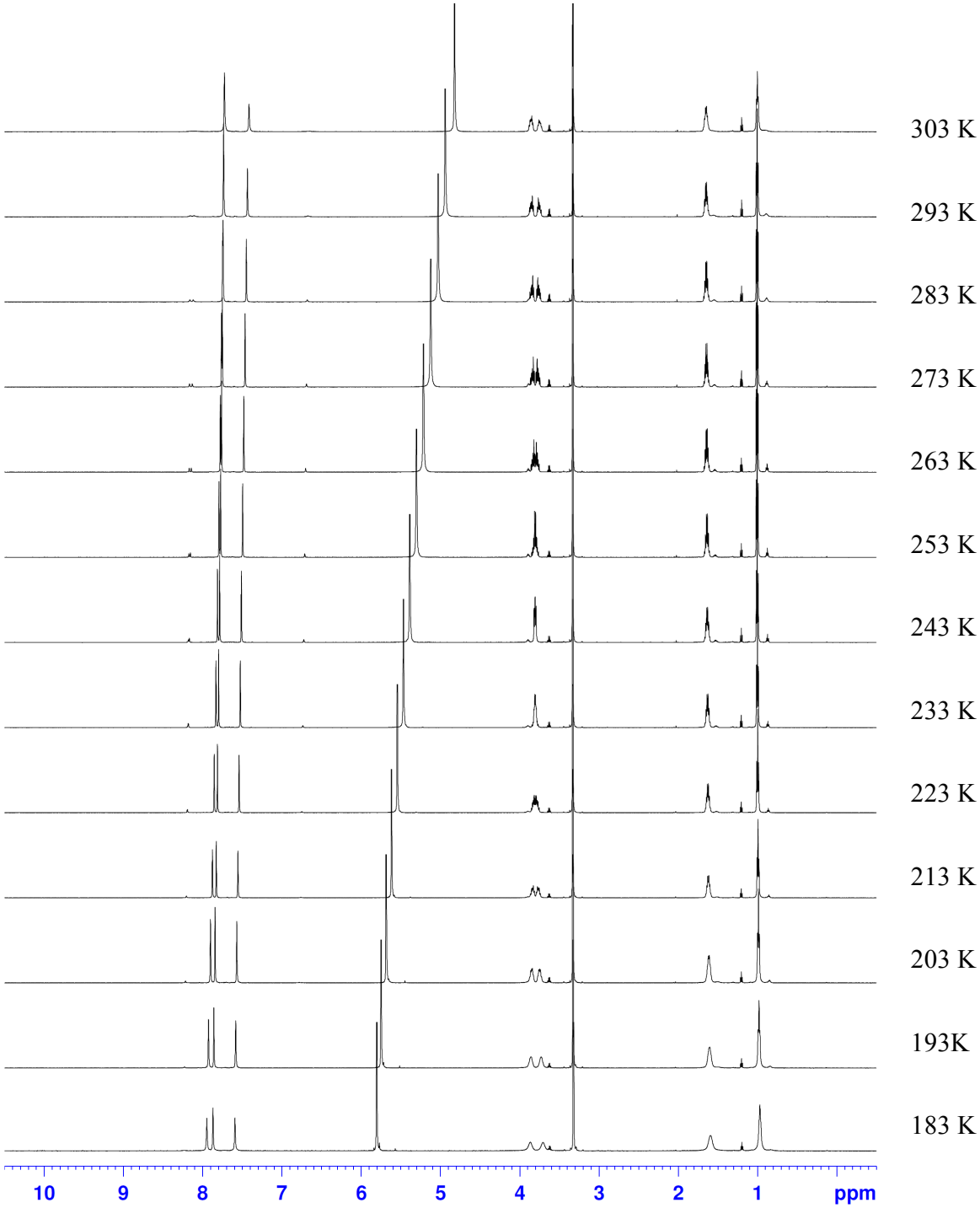


Figure S6. ^{1}H NMR of Compound **3a** in CD_2Cl_2.

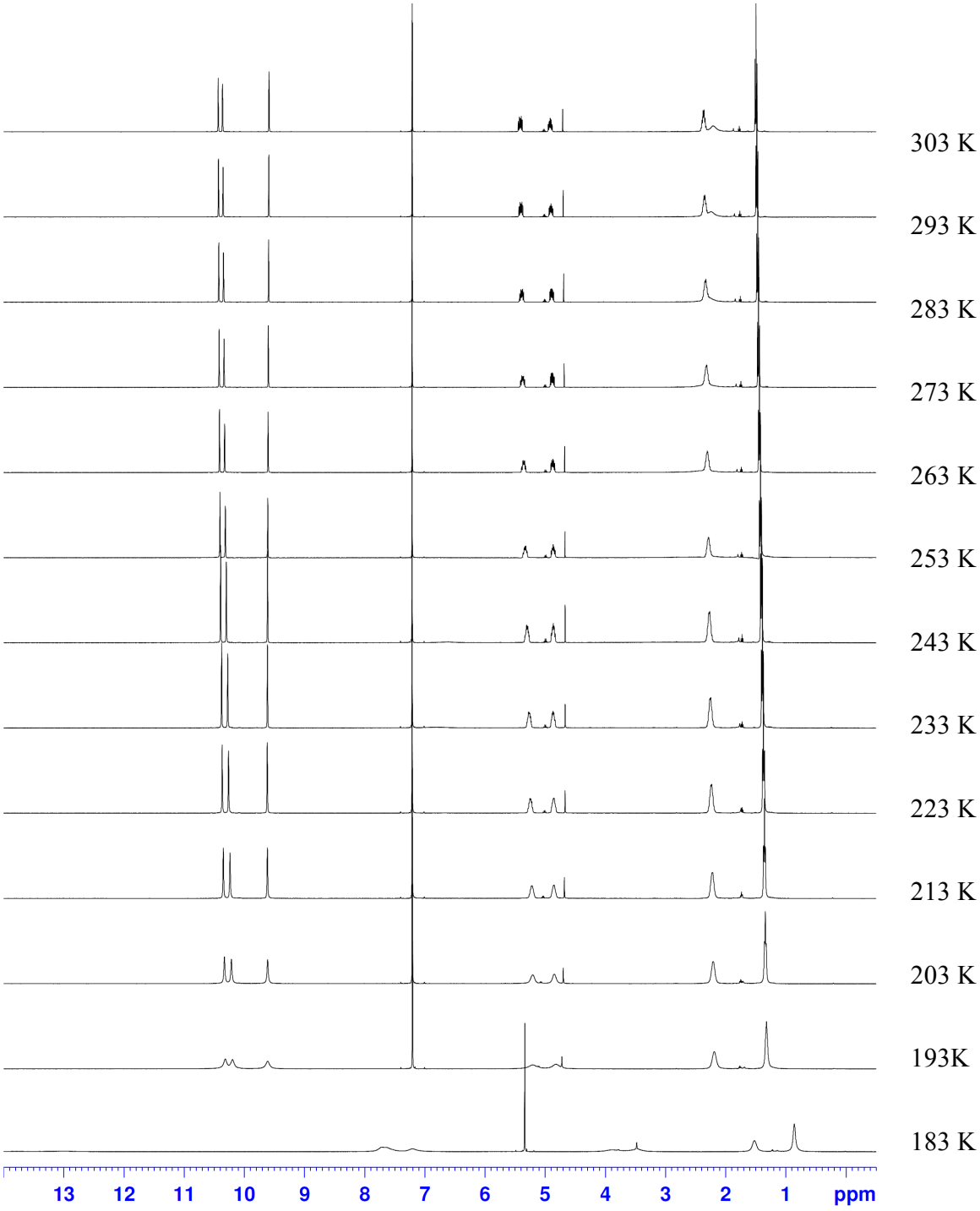


Figure S7. ^{1}H NMR of Compound **3b** in CD_3OD.

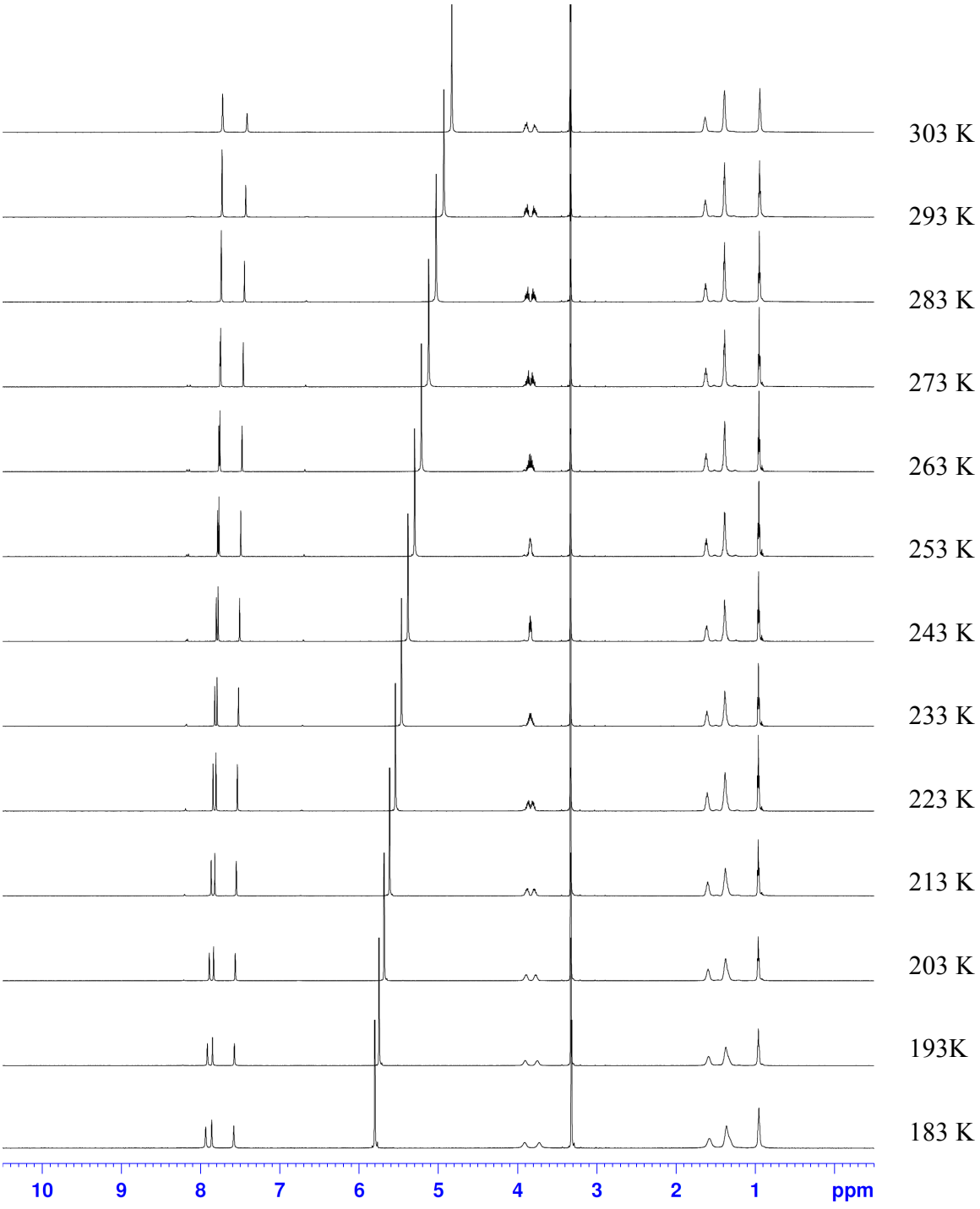


Figure S8. ^{1}H NMR of Compound **3b** in CD_2Cl_2.

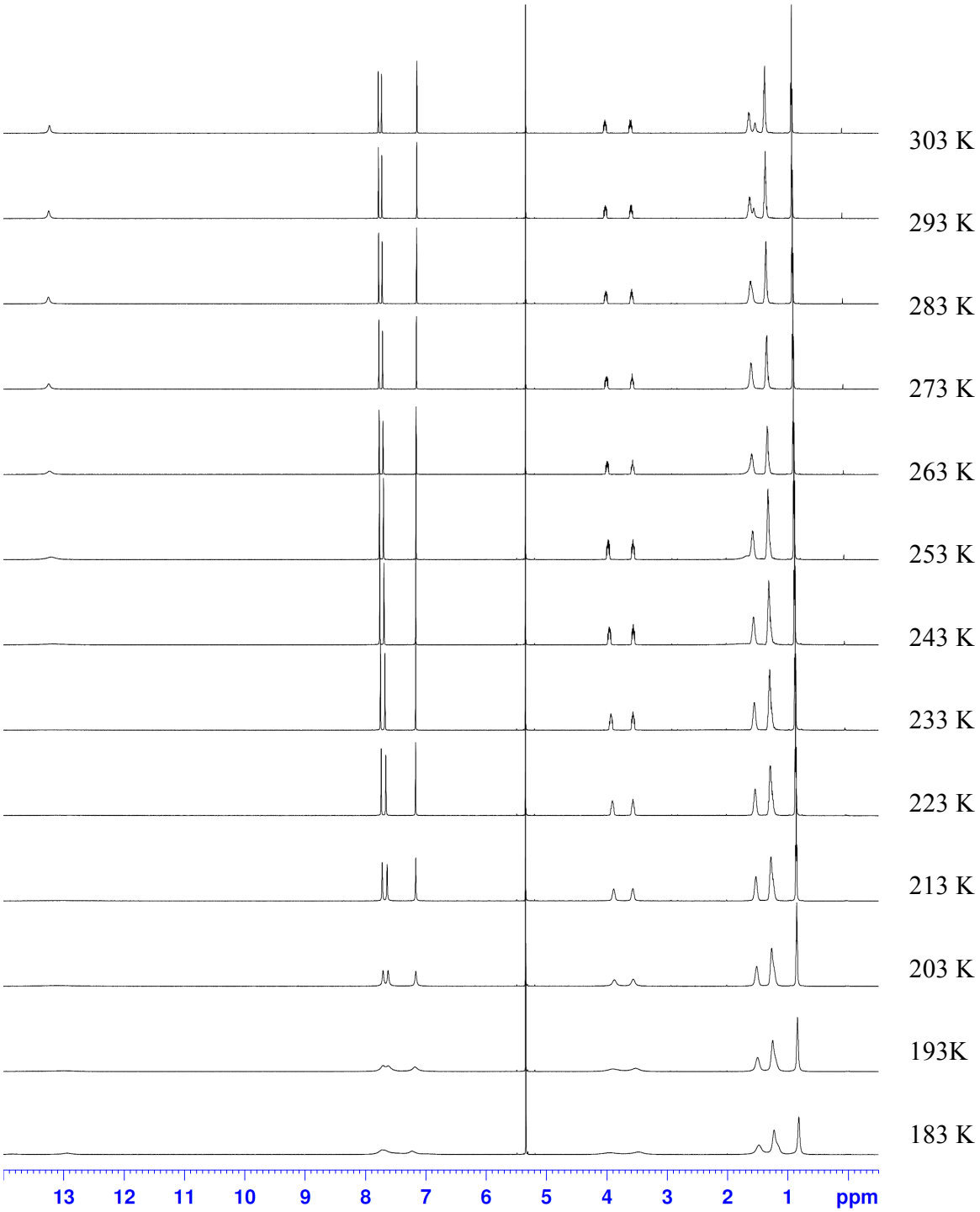


Figure S9. ^{1}H NMR of Compound **4a** in CD_3OD.

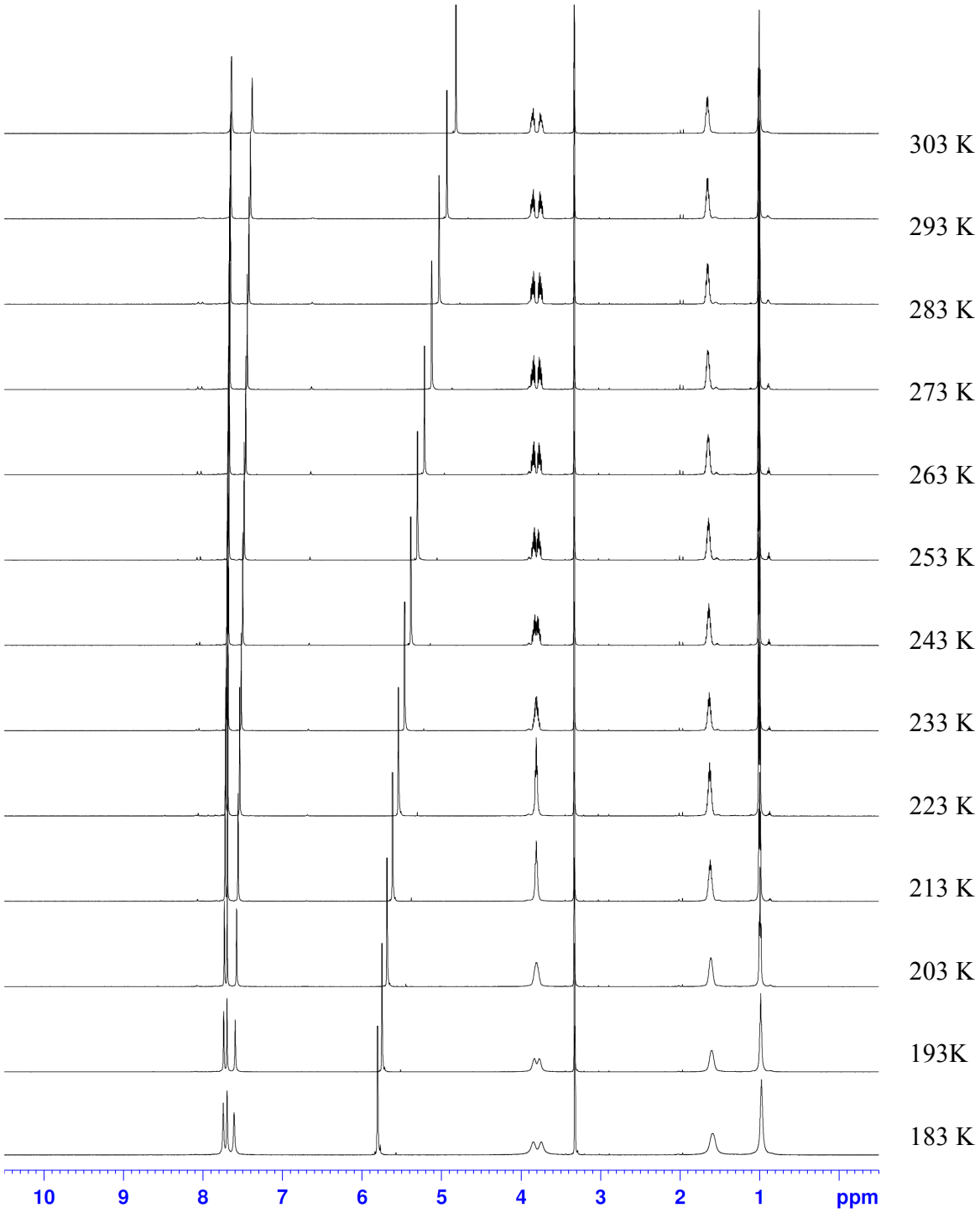


Figure S10. ^{1}H NMR of Compound **4b** in CD_3OD.

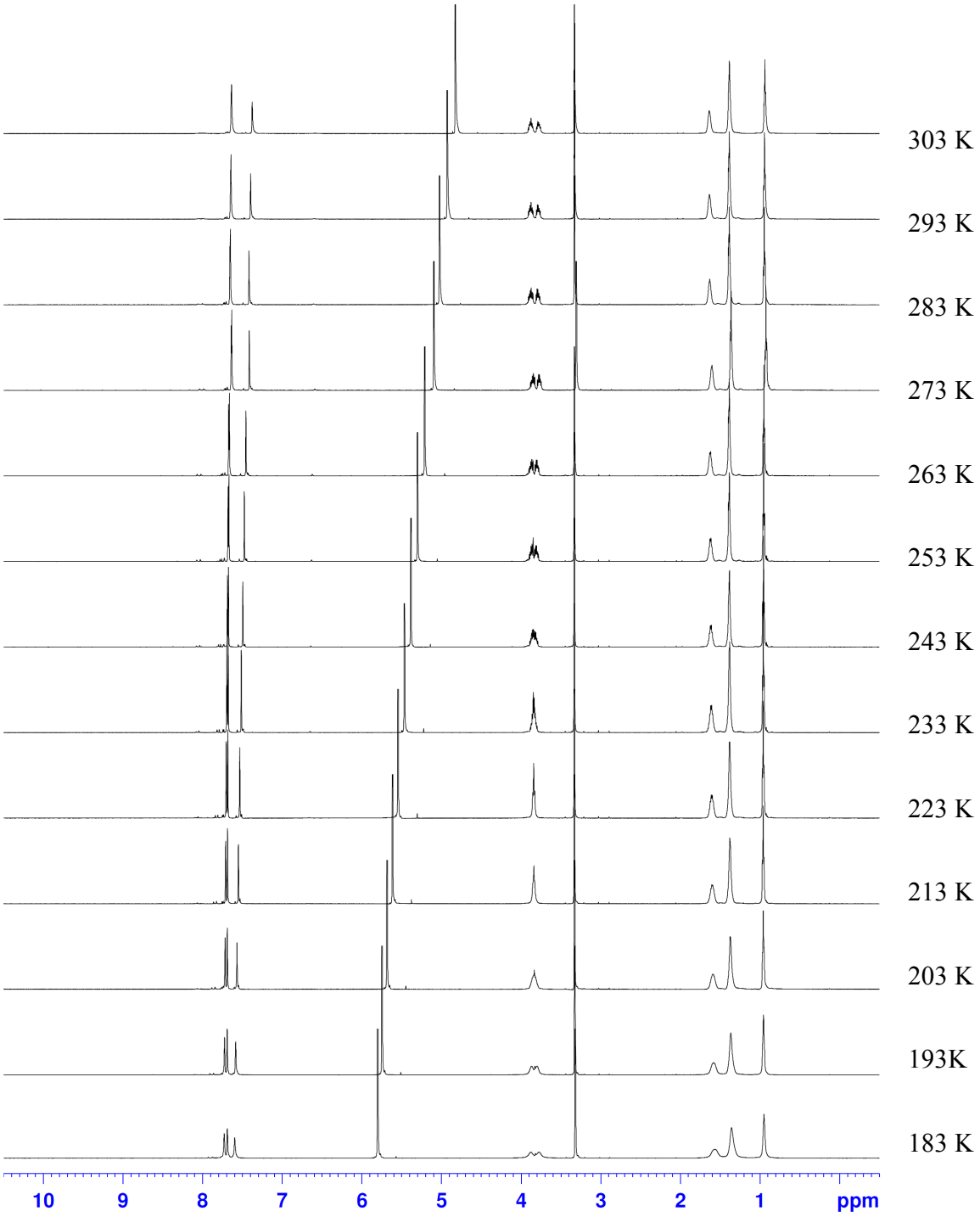


Figure S11. ^{1}H NMR of Compound **5a** in CD_3OD.

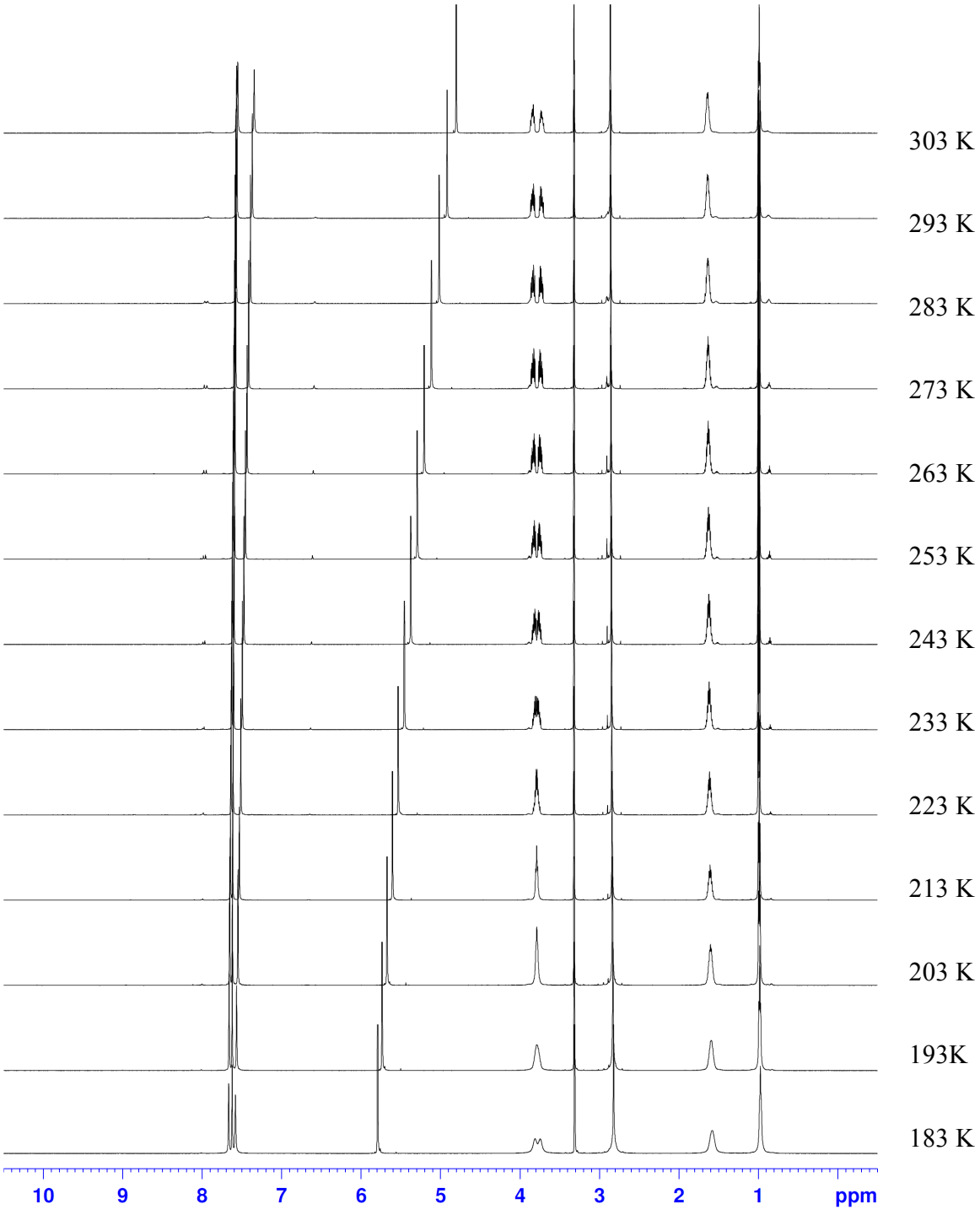


Figure S12. ^{1}H NMR of Compound **5a** in CD_2Cl_2.

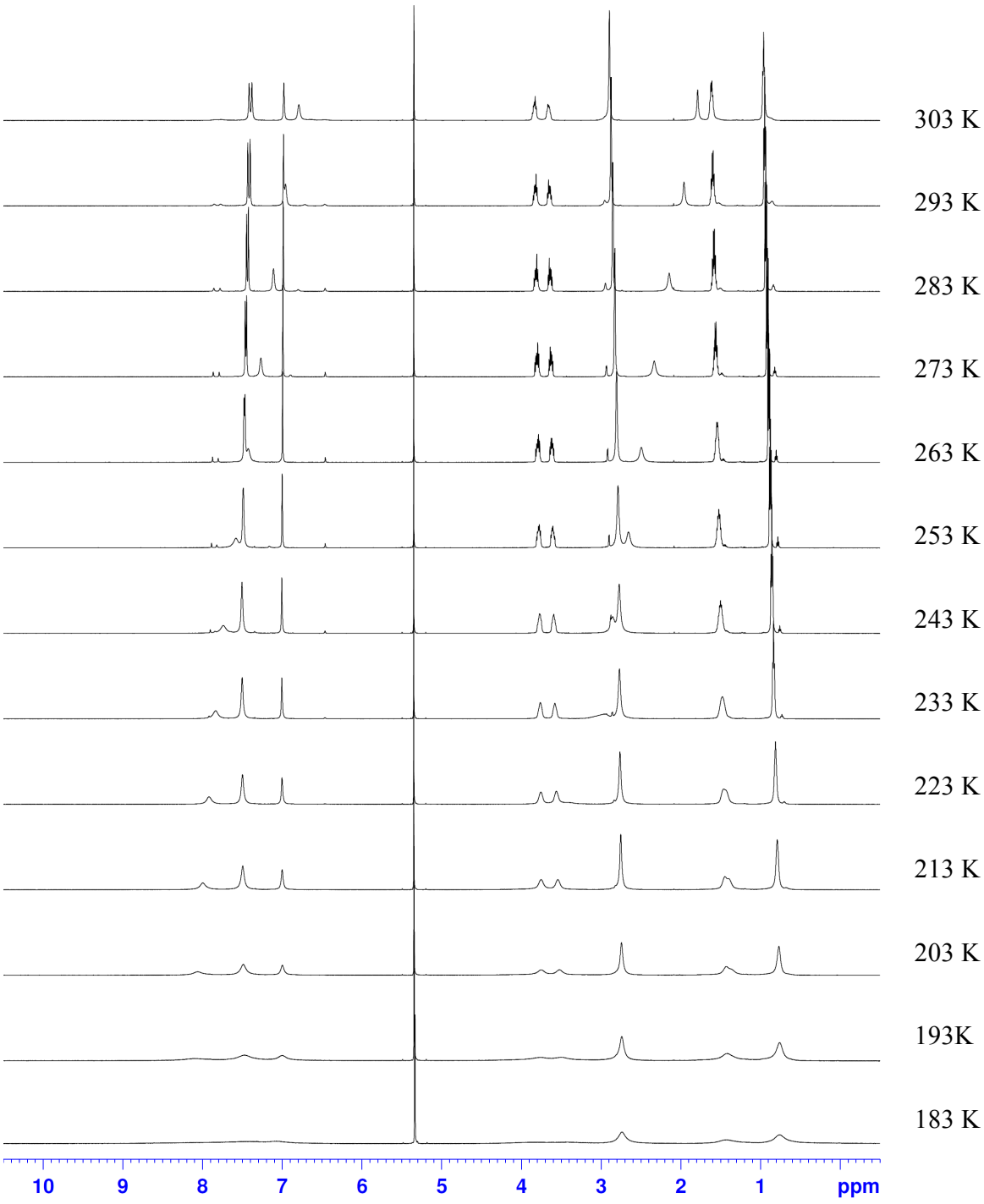


Figure S13. ^{1}H NMR of Compound **5b** in CD_3OD.

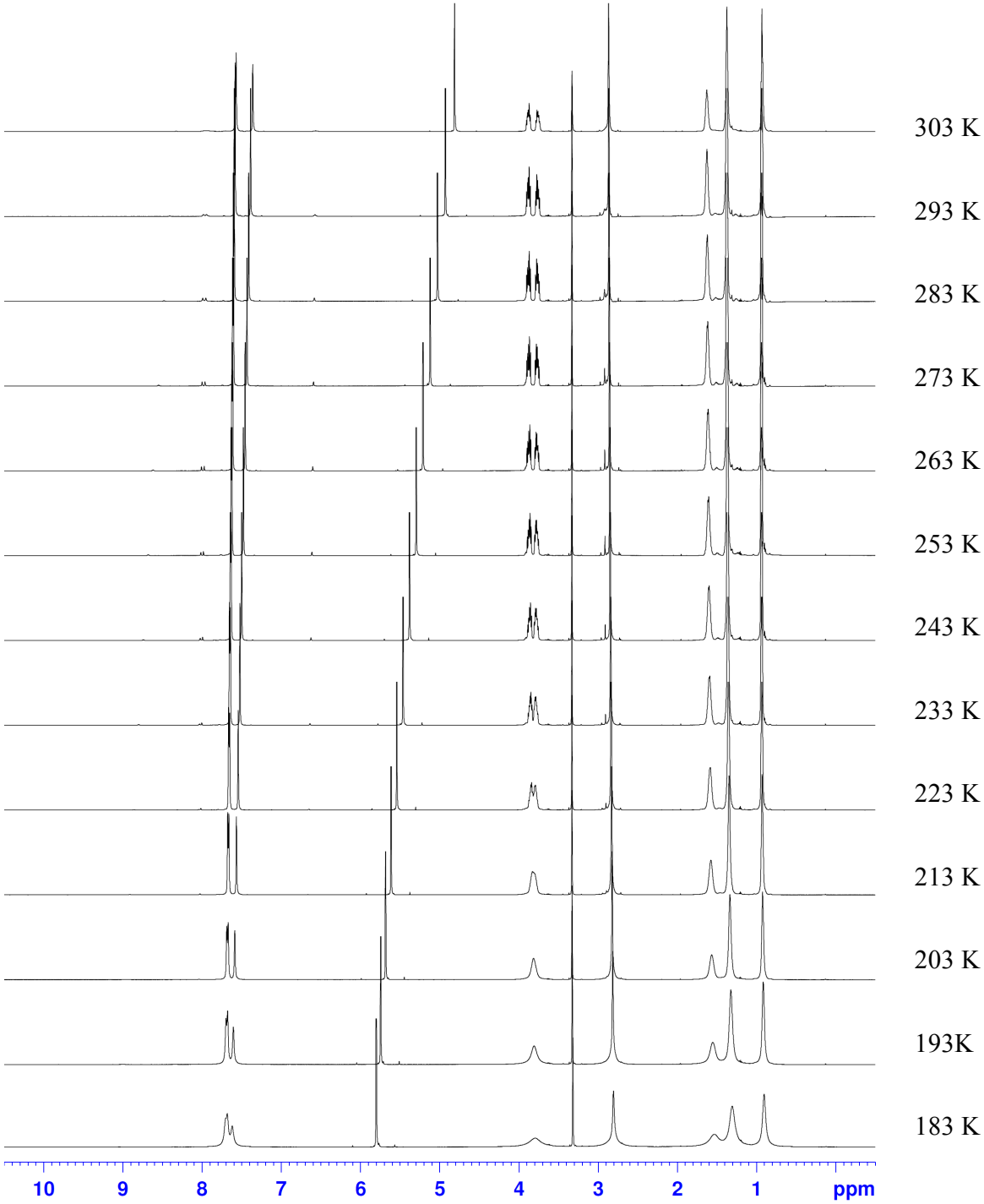
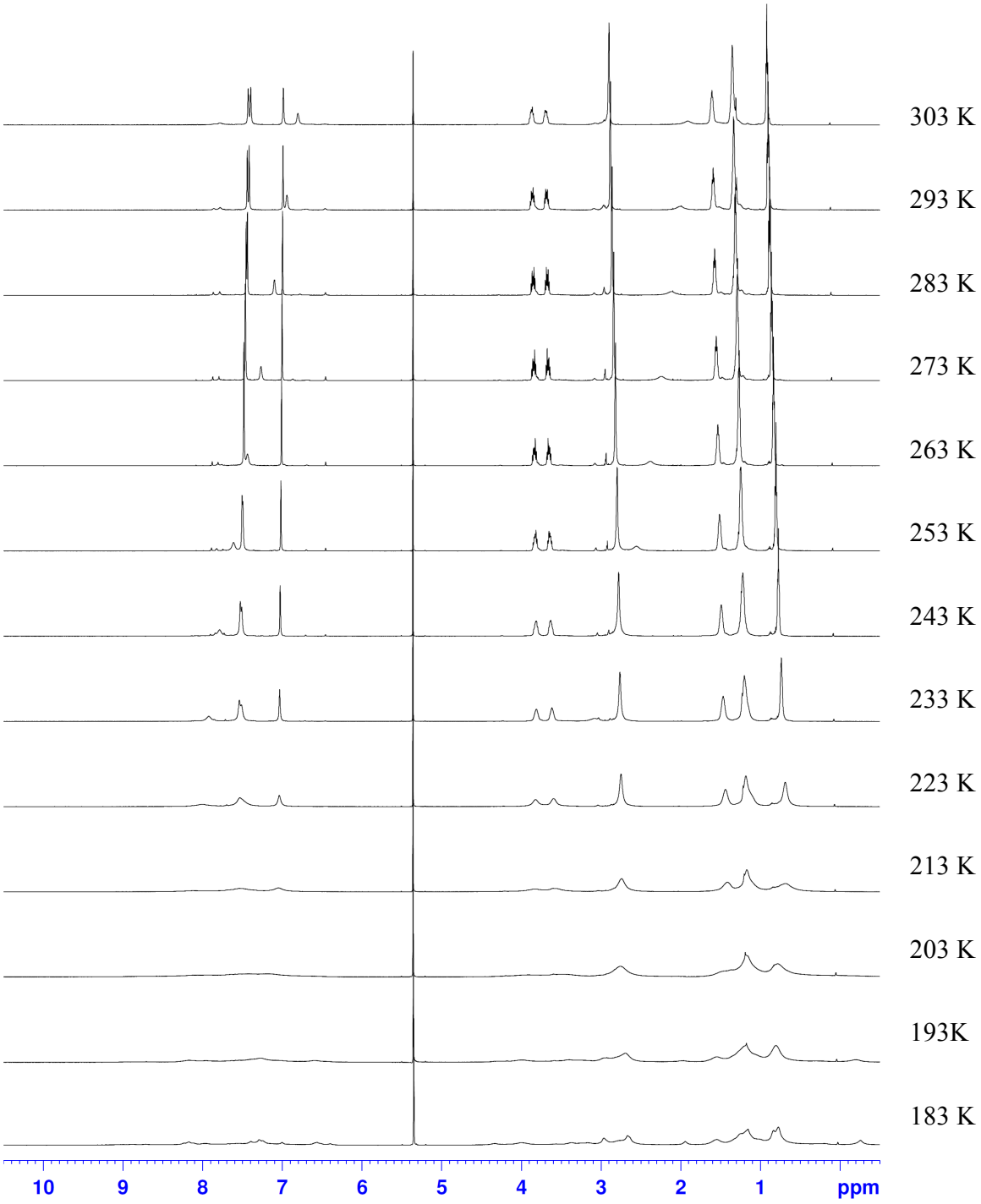


Figure S14. ^{1}H NMR of Compound **5b** in CD_2Cl_2.



3. X-ray Crystallographic Analysis

Measurement

Single crystal X-ray diffraction data of the crystals were collected on a CCD diffractometer with graphite monochromated MoKα (λ = 0.71073 Å) radiation. Data collections were carried out at low temperature using liquid nitrogen. The crystal structure was solved by direct methods SHELXS-97 and refined by full-matrix least-squares SHELXL-97.[1] All non-hydrogen atoms were refined anisotropically and hydrogen atoms were included as their calculated positions.

(1) A short history of SHELX. Sheldrick, G. M. *Acta Cryst.* **2008**, *A64*, 112–122.

Crystal data of 3a.

$C_{39}H_{45}N_3O_9 \cdot 1.5C_2N$, M = 756.83, hexagonal, $a = b$ = 16.5804(4), c = 19.1267(9) Å, V = 4553.7(3) Å^3, T = 120 K, space group $P6_3/m$, Z = 4, 22648 reflections measured, 3351 unique (R_{int} = 0.0243) reflections were used in all calculations. The final R_1 and wR_2 were 0.0797 and 0.2654 ($I > 2\sigma(I)$), 0.0932 and 0.2769 (all data). CCDC-808148. Acetonitrile molecules (N2, C14 and C15) were located in disordered two positions. The occupancies of the disordered atoms are refined. Hydrogen atoms of carboxyl groups were also located in disordered two positions. The positions of hydrogen atoms of an acetonitrile molecule were not calculated.

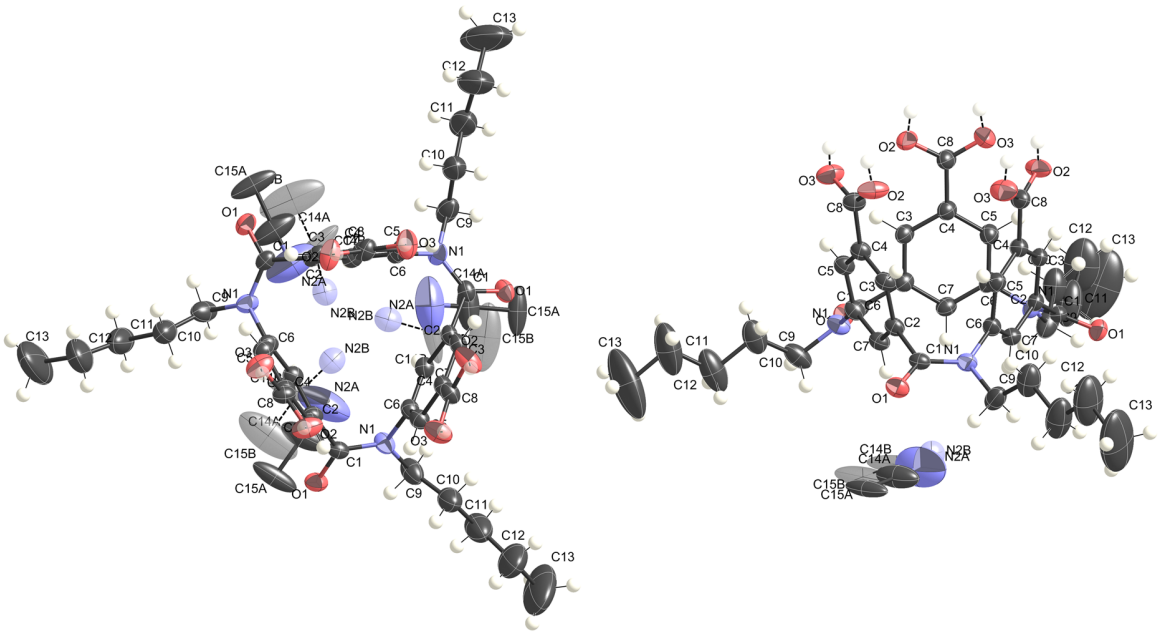


Figure S15. Thermal ellipsoid model of crystal **3a**. Top view (left) and side view (right). Expanded structures are indicated in the model. The ellipsoids of non-hydrogen atoms are drawn at the 50 % probability level while isotropic hydrogen atoms are represented by spheres of arbitrary size. The labels of hydrogen atoms are omitted for clarity. Disordered atoms are indicated and colored transparently.

Crystal data of 4a

$C_{33}H_{36}N_6O_6 \cdot 2CH_3CN \cdot 2H_2O$, M = 730.82, Tetragonal, $a = b$ = 15.344(15), c = 38.99(4) Å, V = 9180(16) Å^3, T = 253 K, space group $P4_32_12$ Z = 8, 45859 reflections measured, 9671 unique (R_{int} = 0.0421) reflections were used in all calculations. The final R_1 and wR_2 were 0.0864 and 0.2408 ($I > 2\sigma(I)$), 0.1355 and 0.2729 (all data). CCDC-859945. Two acetonitrile molecules are included in an asymmetric unit. One water molecule (O8) on a general position and two water molecules (O7 and O9) on the special positions are found. O7 and O9 have 0.5 occupancies respectively. Thus, total amount of two water molecules (1 + 0.5 +0.5) are included in an asymmetric unit. The positions of hydrogen atoms of the water molecules were not calculated. One propyl group (C28–C30) of the cyclic amide is located in disordered two positions. The occupancies of the disordered atoms are refined.

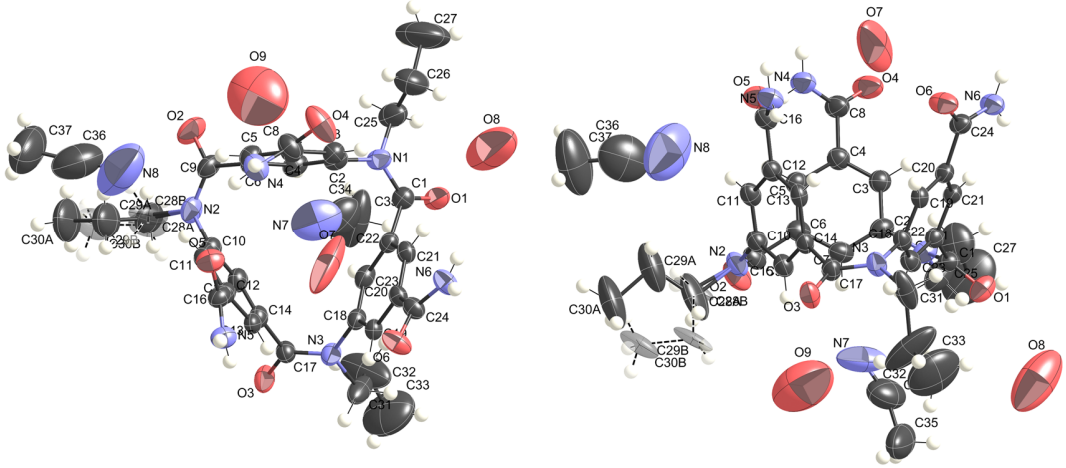


Figure S16. Thermal ellipsoid model of crystal **4a**. Top view (left) and side view (right). The ellipsoids of non-hydrogen atoms are drawn at the 30 % probability level while isotropic hydrogen atoms are represented by spheres of arbitrary size. The labels of hydrogen atoms are omitted for clarity. Disordered atoms are indicated and colored transparently.

Crystal data of 4b

$C_{39}H_{48}N_6O_6 \cdot CH_3OH \cdot 0.5H_2O$, M = 737.88, monoclinic, a = 15.2474(12), b = 29.608(2), c = 9.3379(7) Å, β = 103.0930(10)°, V = 4106.0(6) Å^3, T = 250 K, space group $P2_1/c$, Z = 4, 20265 reflections measured, 8364 unique (R_{int} = 0.0268) reflections were used in all calculations. The final R_1 and wR_2 were 0.0608 and 0.1817 ($I > 2\sigma(I)$), 0.0885 and 0.2043 (all data). CCDC-859944. One molecule of methanol and 0.5 molecule of water are included in an asymmetric unit. The positions of hydrogen atoms of the water molecule were not calculated.

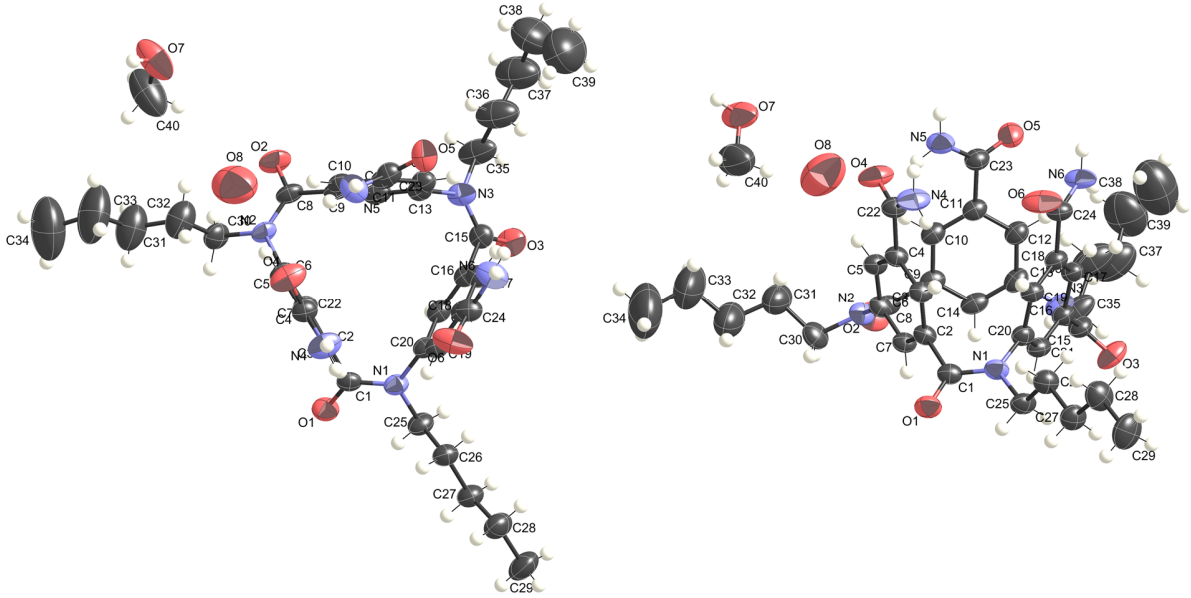


Figure S17. Thermal ellipsoid model of crystal **4b**. Top view (left) and side view (right). The ellipsoids of non-hydrogen atoms are drawn at the 50 % probability level while isotropic hydrogen atoms are represented by spheres of arbitrary size. The labels of hydrogen atoms are omitted for clarity.