Supporting Information

A Cyclochiral Conformational Motif Constructed Using a Robust Hydrogen Bonding Network

Kenji Mishiro*, Takumi Furuta*, Takahiro Sasamori, Kazuhiro Hayashi, Norihiro Tokitoh, Shiroh Futaki, and Takeo Kawabata

Institute for Chemical Research, Kyoto University Uji Kyoto 611-0011

*mishiro@fos.kuicr.kyoto-u.ac.jp

*furuta@fos.kuicr.kyoto-u.ac.jp

General

Melting points were measured using a Yanagimoto micro point apparatus.

NMR spectra were obtained with a JEOL ECX-400 PKT spectrometer, chemical shift being given in ppm units (^{1}H NMR in $CDCl_3$: tetramethylsilane as internal standards, indicating 0, ^{1}H NMR in DMSO-d_6: residual DMSO as internal standards, indicating 2.49, ^{1}H NMR in *o*-dichlorobenzene-d_4: residual *o*-dichlorobenzene as internal standards, indicating 6.94, ^{13}C NMR in $CDCl_3$: $CDCl_3$ as internal standards, indicating 77.0) and spin-spin coupling constants being given in Hz units.

IR spectra were recorded with a JASCO FT-IR 4200 spectrometer.

The mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded with a JEOL JMS-DX 300 mass spectrometer and a JEOL-DX 700 mass spectrometer.

Elemental analysis was performed with a Yanagimoto CHN CORDER MT-5. The analysis results obtained were within 0.3 % of the theoretical values. The weight of samples was determined using a METTLERTOLEDO UMx2 ulta micro balance.

Specific rotation was measured with Horiba SEPA-200 automatic digital polarimeter. UV/Vis absorption spectra were recorded with a JASCO V-550 UV/Vis spectrophotometer. CD spectra were recorded with JASCO J-720 W spectropolarimeter.

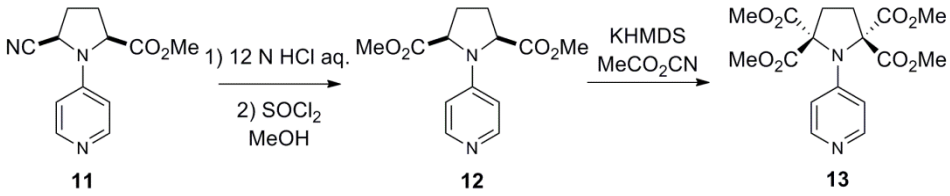
Silica gel column chromatography was carried out by using Silica gel 60 N (spherical, neutral, 63 ~ 210 μm, Kanto Chemical Co., Inc.) or Ultra Pure Silica Gel (230-400mesh, SILYCYCLE).

TLC analysis and preparative TLC (PTLC) were performed on commercial glass plates bearing a 0.25 mm layer and 0.5 mm layer of Merck Kiesel–gel 60 F_{254}, respectively. Analytical HPLC was run with a JASCO PU-2089 Plus instrument, equipped with a Daicel CHIRALCEL ODH or CHIRALPAK ID (4.6 mm × 250 mm) and a JASCO UV-2075 Plus UV/Vis detector.

Anhydrous THF was purchased from Kanto Kagaku and pre-treated with activated MS4Å more than 1 day. Anhydrous toluene was purchased from Wako and distilled from calcium hydride, and distilled toluene was kept over MS4Å. HMDS was purchased from Acros and distilled from calcium hydride, and distilled HMDS was kept over MS4Å.

All other chemical reagents were commercially purchased and used without further purification.

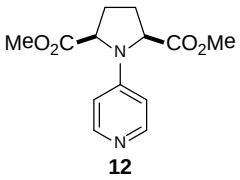
Preparation of 13



Scheme S1. Synthetic route from **11** to **13**

11 (100 mg, 0.43 mmol)[1] was dissolved in 12N aqueous HCl (2.0 mL) and stirred under reflux. After 5 h, the mixture was concentrated *in vacuo*. The residue was dissolved into MeOH (2.0 mL) and stirred at 0 °C. To the stirred mixture, $SOCl_2$ (0.13 mL, 1.73 mmol) was added at 0 °C. After stirred for 10 min, the mixture was heated and stirred under reflux. After stirred for 2 h under reflux, the mixture was cooled to rt and concentrated *in vacuo*. The residue was neutralized with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The Organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give **12** (108 mg, 95%) as a colorless solid.

***cis*-dimethyl 1-(pyridin-4-yl)pyrrolidine-2,5-dicarboxylate (12)**

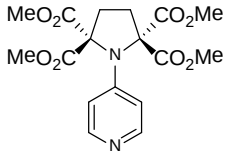


Colorless solid. m.p. 86-88 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 6.4 Hz, 2H), 6.43 (d, J = 6.4 Hz, 2H), 4.42-4.34 (m, 2H), 3.78 (s, 6H), 2.42-2.28 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.34 (2C), 150.85, 149.86 (2C), 107.71 (2C), 61.34 (2C), 52.53 (2C), 29.22 (2C). IR (KBr) 3482, 3465, 3088, 3023, 2994, 2960, 2870, 1747, 1596, 1544, 1510, 1440, 1389, 1360, 1324, 1278, 1204, 1176, 1105, 1082, 1054, 1022, 987, 964 cm^{-1}. MS m/z (rel intensity) 287 ($M+Na^+$, 33), 265 ($M+H^+$, 100), 205 (26). HRMS Calcd for $C_{13}H_{17}N_2O_4$ ($M+H^+$): 265.1188, found, 265.1187.

30% KH dispersed in mineral oil (500 mg, ca. 3.7 mmol) was poured into 100 mL two necked flask and washed with dry hexane (10 mL × 2) under Ar atmosphere. Remaining hexane was removed *in vacuo* to give white powder of KH and the powder was suspended in anhydrous THF (20 mL). To the stirred suspension, HMDS (0.85 mL, 4.0 mmol) was added dropwise at rt. Then the mixture was heated and stirred under reflux. After H_2 gas generation stoped, the mixture was cooled to − 78 °C. To the stirred mixture, a solution of **12** (323 mg, 1.22 mmol) in THF (10 mL) was added dropwise. After stirring for 30 min, methyl cyanoformate (0.29 mL, 3.66 mmol) was added to the mixture at − 78 °C. After 1 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was neutralized with saturated

aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was separated and washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified with SiO_2 column (AcOEt : MeOH = 80 : 1) to give **13** as a colorless solid (351 mg, 76%).

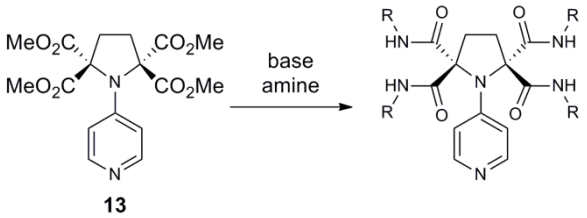
tetramethyl 1-(pyridin-4-yl)pyrrolidine-2,2,5,5-tetracarboxylate (13)



13

Colorless solid. m.p. 105-108 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 5.0 Hz, 2H), 6.45 (d, *J* = 5.0 Hz, 2H), 3.75 (s, 12H), 2.64 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.01 (4C), 149.14, 149.02 (2C), 110.29 (2C), 75.16 (2C), 53.27 (4C), 36.00 (2C). IR (KBr) 3453, 3015, 2959, 1745, 1592, 1550, 1510, 1460, 1432, 1352, 1267, 1196, 1172, 1153, 1108, 1062, 1016, 993 cm^{-1}. MS m/z (rel intensity) 403 ($M+Na^+$, 12), 381 ($M+H^+$, 100), 321 (27). HRMS Calcd for $C_{17}H_{21}N_2O_8$ ($M+H^+$): 381.1298, found, 381.1303. Anal Calcd for $C_{17}H_{20}N_2O_8$: C, 53.68; H, 5.30; N, 7.37. Found: C, 53.71; H, 5.45; N, 7.39.

Preparation of 1 - 10

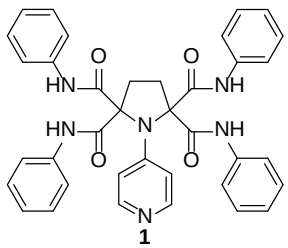


13

Scheme S2. General synthesis of **1-10**

1-10 were synthesized by condensation of **13** and corresponding amine. Aniline, *p*-bromoaniline, *p*-methoxyaniline, 1-naphthylamine, benzylamine, *n*-hexylamine, *tert*-butylamine, 4-heptylamine, (*R*)-1-(1-naphthylethyl)-amine were commercially purchased. Dicyclohexylmethylamine was synthesized according to a literature procedure. [2]

N2,N'2,N5,N'5-tetraphenyl-1-(pyridin-4-yl)pyrrolidine-2,2,5,5-tetracarboxamide (1)

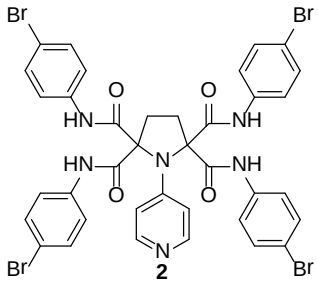


1

60% NaH dispersed in mineral oil (32 mg ca. 0.79 mmol) was added into 10 mL two necked flask and washed with dry hexane (2.0 mL × 2) under Ar atmosphere. Remaining hexane was removed *in vacuo* to give white powder of NaH and the powder was suspended in anhydrous THF (1.0 mL). To the stirred suspension, aniline (79 μL, 0.87 mmol) was added dropwise at rt. Then the mixture was heated to 50 °C. After 1 h, the mixture was cooled to 0 °C. To the stirred mixture, **13** (30 mg, 0.079 mmol) was added at 0 °C and the mixture was gradually warmed to rt. After 4 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was separated and washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified with SiO_2 column (AcOEt : hexane = 1 : 2) to give **1** as a colorless solid (31 mg, 63%).

Colorless solid. m.p. 282-283 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.17 (s, 2H), 11.95 (s, 2H), 8.28 (d, *J* = 5.6 Hz, 2H), 7.79-7.66 (m, 8H), 7.46-7.33 (m, 8H), 7.25-7.16 (m, 4H), 6.41 (d, *J* = 5.6 Hz, 2H), 2.95-2.75 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.14 (2C), 168.38 (2C), 150.26 (2C), 147.63, 137.16 (2C), 136.87 (2C), 129.18 (4C), 129.00 (4C), 125.51 (2C), 125.45 (2C), 120.88 (4C), 120.54 (4C), 109.76(2C), 74.44 (2C), 38.20 (2C). IR (KBr) 3293, 3127, 3034, 1679, 1645, 1594, 1532, 1499, 1444, 1348, 1238, 1220 cm^{-1}. MS m/z (rel intensity) 647 ($M+Na^+$, 7), 625 ($M+H^+$, 53), 504 (10), 154 (100). HRMS Calcd for $C_{37}H_{33}N_6O_4$ ($M+H^+$): 625.2563, found, 625.2565.

N2,N'2,N5,N'5-tetrakis(4-bromophenyl)-1-(pyridin-4-yl)pyrrolidine-2,2,5,5-tetracarboxamide (2)

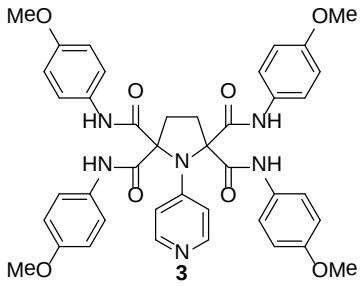


2

60% NaH dispersed in mineral oil (75 mg ca. 0.39 mmol) was added into 10 mL two necked flask and washed with dry hexane (2.0 mL × 2) under Ar atmosphere. Remaining hexane was removed *in vacuo* to give white powder of NaH and the powder was suspended in anhydrous THF (1.0 mL). To the stirred suspension, *p*-bromoaniline (75 mg, 0.43 mmol) was added at rt. Then the mixture was heated to 50 °C. After 1 h, the mixture was cooled to 0 °C. To the stirred mixture, **13** (30 mg, 0.079 mmol) was added at 0 °C and the mixture was gradually warmed to rt. After 1 h, the mixture was heated to 50 °C. After 3 h stirring, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was separated and washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified with SiO_2 column (AcOEt : hexane = 1 : 3) to give **2** as a colorless solid (18 mg, 24%).

Colorless solid. m.p. > 300 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.05 (s, 2H), 11.85 (s, 2H), 8.22 (d, *J* = 6.4 Hz, 2H), 7.59-7.35 (m, 16H), 6.26 (d, *J* = 6.4 Hz, 2H), 2.87-2.64 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.06 (2C), 168.47 (2C), 150.38 (2C), 147.35, 136.06 (2C), 135.66 (2C), 132.27 (4C), 132.07 (4C), 122.29 (4C), 122.17 (4C), 118.56 (2C), 118.51 (2C), 109.56 (2C), 74.35 (2C), 38.18 (2C). IR (KBr) 3175, 3035, 1682, 1650, 1587, 1536, 1486, 1395, 1335, 1229, 1072, 1008 cm^{-1}. MS m/z (rel intensity) 941 ($M+H^+$, 8), 742 (2), 154 (100). HRMS Calcd for $C_{37}H_{29}Br_4N_6O_4$ ($M+H^+$): 940.8948, found, 940.8946.

N2,N'2,N5,N'5-tetrakis(4-methoxyphenyl)-1-(pyridin-4-yl)pyrrolidine-2,2,5,5-tetracarboxamide (3)

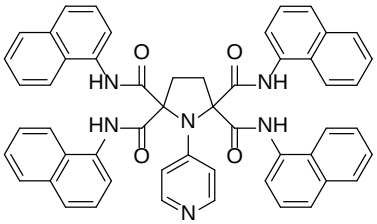


3

60% NaH dispersed in mineral oil (25 mg ca. 0.63 mmol) was added into 10 mL two necked flask and washed with dry hexane (2.0 mL × 2) under Ar atmosphere. Remaining hexane was removed *in vacuo* to give white powder of NaH and the powder was suspended in anhydrous THF (1.0 mL). To the stirred suspension, *p*-anisidine (78 mg, 0.63 mmol) was added dropwise at rt. Then the mixture was heated to 50 °C. After 1 h, the mixture was cooled to 0 °C. To the stirred mixture, **13** (20 mg, 0.053 mmol) was added at 0 °C and the mixture was gradually warmed to rt. After 3 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was separated and washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified with SiO_2 column (AcOEt : hexane = 1 : 2) to give **3** as a colorless solid (28 mg, 71%).

Colorless solid. m.p. 254-256 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.05 (s, 2H), 11.80 (s, 2H), 8.20 (d, *J* = 6.4 Hz, 2H), 7.60-7.46 (m, 8H), 6.89-6.76 (m, 8H), 6.33 (d, *J* = 6.4 Hz, 2H), 3.74 (s, 6H), 3.72 (s, 6H), 2.82-2.65 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.72 (2C), 168.07 (2C), 157.09 (2C), 157.03 (2C), 150.12 (2C), 147.85, 130.40 (2C), 130.14 (2C), 122.37 (4C), 122.01 (4C), 114.25 (4C), 114.10 (4C), 109.77 (2C), 74.25 (2C), 55.50 (2C), 55.47 (2C), 38.11 (2C). IR (KBr) 3189, 3039, 1679, 1646, 1593, 1550, 1510, 1462, 1415, 1341, 1303, 1242, 1174, 1033 cm^{-1}. MS m/z (rel intensity) 767 ($M+Na^+$, 3), 745 ($M+H^+$, 23), 594 (5), 154 (100). HRMS Calcd for $C_{41}H_{41}N_6O_4$ ($M+H^+$): 745.2986, found, 745.2996.

N2,N'2,N5,N'5-tetra(naphthalen-1-yl)-1-(pyridin-4-yl)pyrrolidine-2,2,5,5-tetracarboxamide (4)

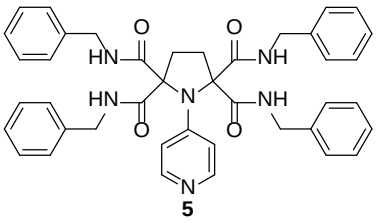


4

60% NaH dispersed in mineral oil (21 mg ca. 0.53 mmol) was added into 10 mL two necked flask and washed with dry hexane (2.0 mL × 2) under Ar atmosphere. Remaining hexane was removed *in vacuo* to give white powder of NaH and the powder was suspended in anhydrous THF (1.0 mL). To the stirred suspension, 1-naphthylamine (83 mg, 0.58 mmol) was added at rt. Then the mixture was heated to 50 °C. After 1 h, the mixture was cooled to 0 °C. To the stirred mixture, **13** (20 mg, 0.053 mmol) was added at 0 °C and the mixture was gradually warmed to rt. After 5 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was separated and washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified with SiO_2 column (AcOEt : hexane = 1 : 2) to give **4** as a brown solid (11 mg, 25%).

Brown solid. m.p. 168-170 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.55 (s, 2H), 12.48 (s, 2H), 8.40 (d, *J* = 6.4 Hz, 2H), 8.12 (d, *J* = 8.3 Hz, 2H), 8.06 (d, *J* = 7.3 Hz, 2H), 7.88-7.20 (m, 24H), 6.75 (d, *J* = 6.4 Hz, 2H), 3.35-3.05 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.16 (2C), 169.37 (2C), 150.51 (2C), 148.05, 134.26 (2C), 133.94 (2C), 131.99 (2C), 131.65 (2C), 128.83 (2C), 128.68 (2C), 128.32 (2C), 127.50 (2C), 126.88 (2C), 126.48 (2C), 126.27 (2C), 126.21 (4C), 125.87 (2C), 125.56 (2C), 125.24 (2C), 123.15 (2C), 122.16 (2C), 120.80 (2C), 118.83 (2C), 110.19 (2C), 74.80 (2C), 38.99 (2C). IR (KBr) 3158, 3054, 2979, 1681, 1649, 1630, 1594, 1543, 1502, 1395, 1339, 1285, 1208, 1015 cm^{-1}. MS m/z (rel intensity) 825 ($M+H^+$, 11), 154 (100). HRMS Calcd for $C_{53}H_{41}N_6O_4$ ($M+H^+$): 825.3189, found, 825.3191.

N2,N'2,N5,N'5-tetrabenzyl-1-(pyridin-4-yl)pyrrolidine-2,2,5,5-tetracarboxamide (5)



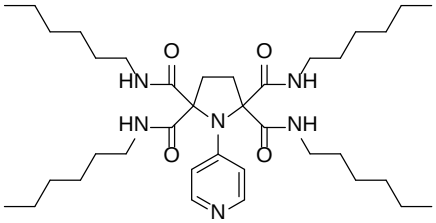
5

To a stirred solution of benzylamine (0.23 mL, 2.1 mmol) in anhydrous THF (2.0 mL), was added 1.45 M *n*-butyllithium in hexane (1.45 mL, 2.1 mmol) at – 78 °C. After stirring for 30 min, **13** (80 mg, 0.21 mmol) was added and the mixture was kept stirring at – 78 °C. After 4 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted

with AcOEt. The organic layer was separated and washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified with SiO_2 column (AcOEt : hexane = 1 : 2) to give **5** as a colorless solid (26 mg, 18%).

Colorless solid. m.p. 153-155 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.84 (t, J = 5.7 Hz, 2H), 10.15 (t, J = 5.7 Hz, 2H), 8.02 (d, J = 6.4 Hz, 2H), 7.32-7.02 (m, 20H), 5.96 (d, J = 6.4 Hz, 2H), 4.40 (d, J = 6.0 Hz, 4H), 4.36 (A part of ABX, J_{AB} = 14.7 Hz, J_{AX} = 6.7 Hz, 2H), 4.24 (B part of ABX, J_{AB} = 14.7 Hz, J_{BX} = 4.8 Hz, 2H), 2.46-2.25 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.45 (2C), 170.57 (2C), 149.49 (2C), 147.66, 137.76 (2C), 137.63 (2C), 128.73 (4C), 128.43 (4C), 127.70 (4C), 127.61 (6C), 127.23 (2C), 109.87 (2C), 73.54 (2C), 43.99 (2C), 43.77 (2C), 37.58 (2C). IR (KBr) 3213, 3033, 1672, 1644, 1599, 1538, 1502, 1453, 1349, 1220, 1176 cm^{-1}. MS m/z (rel intensity) 703 (M+Na$^+$, 12), 681 (M+H$^+$, 72), 546 (22), 413 (15), 154 (100). HRMS Calcd for $C_{41}H_{41}N_6O_4$ (M+H$^+$): 681.3189, found, 618.3195.

N2,N'2,N5,N'5-tetrahexyl-1-(pyridin-4-yl)pyrrolidine-2,2,5,5-tetracarboxamide (6)

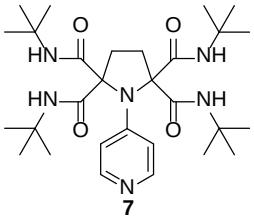


6

To a stirred solution of *n*-hexylamine (115 μL, 0.87 mmol) in anhydrous THF (3.0 mL), was added 1.6 M *n*-butyllithium in hexane (0.49 mL, 0.79 mmol) at – 78 °C. After stirring for 30 min, **13** (30 mg, 0.079 mmol) was added and the mixture was kept stirring at – 78 °C. After 5.5 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was separated and washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified with SiO_2 column (AcOEt : hexane = 1 : 2) to give **6** as a colorless oil (37 mg, 71%).

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.29 (t, J = 5.0 Hz, 2H), 9.82 (t, J = 5.5 Hz, 2H), 8.13 (d, J = 6.4 Hz, 2H), 6.02 (d, J = 6.4 Hz, 2H), 3.36-2.98 (m, 8H), 2.52-2.23 (m, 4H), 1.58-1.02 (m, 32H), 0.83 (t, J = 6.6 Hz, 6H), 0.77 (t, J = 6.9 Hz, 6H) . ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.22 (2C), 170.39 (2C), 149.32 (2C), 148.09, 109.67 (2C), 73.53 (2C), 40.10 (2C), 40.01 (2C), 37.51 (2C), 31.38 (2C), 31.30 (2C), 29.12 (2C), 28.69 (2C), 26.61 (2C), 26.54 (2C), 22.52 (2C), 22.50 (2C), 14.00 (2C), 13.96 (2C). IR (KBr) 3215, 3051, 2956, 2929, 2858, 1674, 1644, 1598, 1550, 1506, 1463, 1349, 1225, 1177 cm^{-1}. MS m/z (rel intensity) 674 (M+Na$^+$, 26), 658 (M+H$^+$, 100), 528 (32), 399 (5). HRMS Calcd for $C_{37}H_{65}N_6O_4$ (M+H$^+$): 657.5067, found, 657.5068.

N2,N'2,N5,N'5-tetra-tert-butyl-1-(pyridin-4-yl)pyrrolidine-2,2,5,5-tetracarboxamide (7)

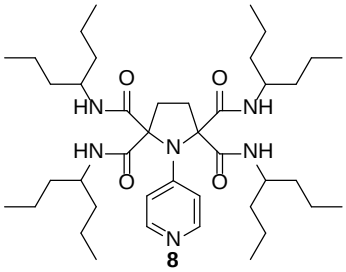


7

To a stirred solution of *tert*-butylamine (0.13 mL, 1.26 mmol) in anhydrous THF (2.0 mL), was added 1.5 M *n*-butyllithium in hexane (0.70 mL, 1.05 mmol) at – 78 °C. After 30 min, **13** (40 mg, 0.105 mmol) was added and the mixture was kept stirring at – 78 °C. After 7 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was separated and washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified with SiO_2 column (AcOEt : hexane = 1 : 2) to give **7** as a colorless solid (45 mg, 79%).

Colorless solid. m.p. 213-215 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.70 (s, 2H), 9.65 (s, 2H), 8.14 (d, *J* = 6.4 Hz, 2H), 6.03 (d, *J* = 6.4 Hz, 2H), 2.45-2.15 (m, 4H), 1.29 (s, 18H), 1.22 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.79 (2C), 168.96 (2C), 148.86 (2C), 148.79, 109.88 (2C), 73.97 (2C), 51.81 (2C), 51.50 (2C), 37.67 (2C), 28.35 (6C), 28.09 (6C). IR (KBr) 3213, 3048, 2970, 1677, 1643, 1599, 1544, 1501, 1455, 1393, 1363, 1347, 1226, 1176, 1072, 991 cm^{-1}. MS m/z (rel intensity) 567 ($M+Na^+$, 4), 545 ($M+H^+$, 100), 445 (12), 345 (3). HRMS Calcd for $C_{29}H_{49}N_6O_4$ ($M+H^+$): 545.3815, found, 545.3827.

N2,N'2,N5,N'5-tetra(heptan-4-yl)-1-(pyridin-4-yl)pyrrolidine-2,2,5,5-tetracarboxamide (8)



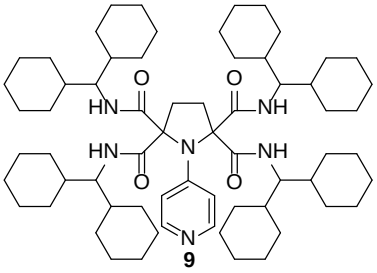
8

To a stirred solution of 4-heptylamine (87 μL, 0.58 mmol) in anhydrous THF (1.0 mL), was added 1.45 M *n*-butyllithium in hexane (0.36 mL, 0.53 mmol) at – 78 °C. After 30 min, **13** (20 mg, 0.053 mmol) was added and the mixture was kept stirring at – 78 °C. After 1.5 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was separated and washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified with SiO_2 column (AcOEt : hexane = 1 : 3) to give **8** as a colorless solid (32 mg, 86%)

Colorless solid. m.p. 109-111 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (d, *J* = 8.3 Hz, 2H), 9.62 (d, *J* = 8.7 Hz, 2H) 8.17 (d, *J* = 6.4 Hz, 2H), 6.13 (d, *J* = 6.4 Hz, 2H), 4.05-3.79 (m, 4H), 2.64-2.30 (m, 4H),

1.60-1.08 (m, 32H), 0.95 (t, *J* = 7.3 Hz, 6H), 0.90 (t, *J* = 6.9 Hz, 6H), 0.86 (t, *J* = 7.3 Hz, 6H), 0.80 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.90 (2C), 169.75 (2C), 148.90 (2C), 148.09, 110.15 (2C), 73.66 (2C), 49.99 (2C), 49.33 (2C), 37.77 (2C), 37.52 (2C), 37.15 (2C), 36.73 (2C), 36.39 (2C), 19.65 (2C), 19.27 (2C), 19.16 (2C), 19.04 (2C), 14.01 (2C), 13.96 (2C), 13.94 (2C), 13.71 (2C). IR (KBr) 3194, 3041, 2959, 2931, 2871, 1674, 1643, 1599, 1545, 1504, 1461, 1352, 1225, 1180, 1151 cm^{-1}. MS m/z (rel intensity) 735 (M+Na$^+$, 6), 713 (M+H$^+$, 100), 570 (25), 429 (6). HRMS Calcd for $C_{41}H_{73}N_6O_4$ (M+H$^+$): 713.5693, found, 713.5693.

N2,N'2,N5,N'5-tetrakis(dicyclohexylmethyl)-1-(pyridin-4-yl)pyrrolidine-2,2,5,5-tetracarboxamide (9)

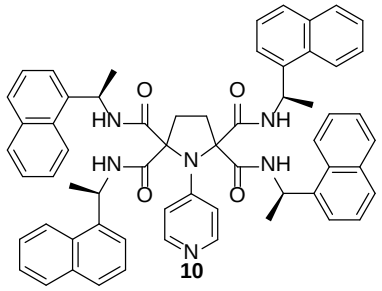


9

To a stirred solution of dicyclohexylmethylamine (520 mg, 2.7 mmol) in anhydrous THF (5.0 mL), was added 1.46 M *n*-butyllithium in hexane (1.73 mL, 2.5 mmol) at – 78 °C. After 30 min, **13** (97 mg, 0.25 mmol) was added and the mixture was kept stirring at – 78 °C. After 3 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was separated and washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified with SiO_2 column (AcOEt : hexane = 1 : 9) to give **9** as a colorless solid (152 mg, 58 %).

Colorless solid. m.p. 298-300 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (d, *J* = 9.6 Hz, 2H), 9.76 (d, *J* = 9.6 Hz, 2H), 8.12 (d, *J* = 6.4 Hz, 2H), 6.32 (d, *J* = 6.4 Hz, 2H), 3.74-3.52 (m, 4H), 2.68-2.40 (m, 4H), 1.94-0.65 (m, 86H), 0.55-0.36 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.89 (2C), 169.33 (2C), 148.44 (2C), 147.39, 111.75 (2C), 73.97 (2C), 59.43 (2C), 58.61 (2C), 39.20 (2C), 38.52 (2C), 38.30 (2C), 38.00 (2C), 37.84 (2C), 31.04 (2C), 30.79 (2C), 30.63 (2C), 30.37 (2C), 28.25 (2C), 27.83 (2C), 26.50 (4C), 26.45 (4C), 26.39 (2C), 26.34 (2C), 26.29 (8C), 26.18 (4C), 26.02 (2C), 25.80 (2C). IR (KBr) 3206, 3034, 2928, 2852, 1673, 1639, 1600, 1540, 1449, 1349, 1220 cm^{-1}. MS m/z (rel intensity) 1034 (M+H$^+$, 23), 950 (5), 810 (5), 589 (2), 55 (100). HRMS Calcd for $C_{65}H_{105}N_6O_4$ (M+H$^+$): 1033.8197, found, 1033.8196.

N2,N'2,N5,N'5-tetrakis((*R*)-1-(naphthalen-1-yl)ethyl)-1-(pyridin-4-yl)pyrrolidine-2,2,5,5-tetracarboxamide (10)



10

To a stirred solution of (*R*)-1-(1-naphthylethyl)-amine (248mg, 1.5 mmol) in anhydrous THF (5.0 mL), was added 1.64 M *n*-butyllithium in hexane (0.8 mL, 1.3 mmol) at – 78 °C. After 30 min, **13** (50 mg, 0.13 mmol) was added and the mixture was kept stirring at – 78 °C. After 2.5 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was separated and washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified with SiO_2 column (AcOEt : hexane = 1 : 1) to give **10** as a colorless solid (42.1 mg, 34%).

Colorless solid. m.p. 110-118 °C. $[\alpha]_D^{19}$ = 36 (c 0.10, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.96-10.84 (m, 2H), 10.26-10.13 (m, 2H), 8.42 (d, *J* = 6.4 Hz, 1.46H), 8.03-6.91 (m, 28.54H), 6.32 (d, *J* = 6.4 Hz, 1.46H), 5.90-5.72 (m, 4H), 5.43 (d, *J* = 6.4 Hz, 0.54H), 2.81-2.58 (m, 1.08H), 2.14-1.85 (m, 2.92H), 1.70 (d, *J* = 6.9 Hz, 4.38H), 1.69 (d, *J* = 6.9 Hz, 1.62H), 1.57 (d, *J* = 6.9 Hz, 1.62H), 1.47 (d, *J* = 6.9 Hz, 4.38H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.32, 169.88, 169.55, 169.12, 149.63, 148.57, 148.43, 146.82, 138.46, 138.12, 137.90, 133.89, 133.55, 130.84, 130.47, 130.31, 128.85, 128.81, 128.76, 128.34, 128.16, 127.67, 127.53, 126.39, 126.25, 126.10, 125.86, 125.72, 125.67, 125.37, 125.32, 125.25, 125.17, 123.13, 122.90, 122.85, 122.82, 122.76, 122.39, 122.29, 109.87, 109.82, 73.59, 73.46, 45.62, 45.54, 45.47, 45.44, 37.95, 37.13, 21.35, 21.28, 21.00, 20.92. IR (KBr) 3199, 3039, 2973, 2928, 2871, 1669, 1639, 1597, 1525, 1449, 1376, 1345, 1222, 1176, 1120, 1084, 1057, 1033, 993 cm^{-1}. MS m/z (rel intensity) 937 ($M+H^+$, 22), 155 (100). HRMS Calcd for $C_{61}H_{57}N_6O_4$ ($M+H^+$): 937.4441, found, 937.4436.

Preparation of 10-HCl

10 (2.8 mg, 3.0 μmol) was dissolved in MeOH and 12 N aqueous HCl (0.05 mL) was added to the solution. After stirring for 10 min at rt, the mixture was concentrated *in vacuo*. The residue was dissolved in $CDCl_3$ (0.6 mL) and the ratio of **10a-HCl** and **10b-HCl** in $CDCl_3$ at 20 °C was detected by ^{1}H NMR.

10-HCl salt ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.43 (d, *J* = 8.3 Hz, 0.64H), 10.25 (d, *J* = 8.3 Hz, 1.36H), 10.04 (d, *J* = 8.3 Hz, 1.36H), 9.98 (d, *J* = 8.3 Hz, 0.64H), 8.33 (br s, 0.64H), 7.92-6.88 (m, 26.64H), 6.70-6.56 (m, 1.36H), 6.42 (br s, 0.64H), 6.00 (br s, 1.36H), 5.80-5.56 (m, 4H), 4.93 (br s, 1.36H),

2.81-2.48 (m, 2.72H), 2.15-1.75 (m, 1.28H), 1.67 (d, *J* = 6.9 Hz, 4.08H), 1.62 (d, *J* = 6.9 Hz, 1.92H), 1.53 (d, *J* = 6.9 Hz, 4.08H), 1.40 (d, *J* = 6.9 Hz, 1.92H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.95, 167.59, 167.21, 154.90, 152.46, 139.83, 137.68, 137.52, 137.46, 137.26, 137.23, 133.91, 133.89, 133.56, 133.53, 130.61, 130.43, 130.35, 130.16, 129.29, 129.22, 129.00, 128.98, 128.82, 128.46, 128.03, 126.46, 126.42, 126.28, 126.19, 125.82, 125.73, 125.69, 125.50, 125.35, 125.20, 125.10, 125.05, 122.99, 122.73, 122.53, 122.43, 122.36, 122.03, 110.65, 110.06, 74.71, 74.59, 46.15, 46.07, 45.57, 45.52, 37.66, 37.21, 21.22, 20.81, 20.04.

1. Synthesized according to our previous report.

Kawabata, T.; Muramatsu, W.; Nishio, T.; Shibata, T.; Uruno, Y.; Schedel, H.

J. Am. Chem. Soc. **2007**, *129*, 12890–12895.

2. Synthesized according to the literature procedure.

Bowles, P.; Clayden, J.; Helliwell, M.; McCarthy, C.; Tomkinson, M.; Westlund, N.

J. Chem. Soc., Perkin Trans. 1, **1997**, 2607–2616.

X-ray Crystallographic Analysis of 1.

The intensity data were collected on a Rigaku/MSC Mercury CCD diffractometer with graphite monochromated MoKα radiation (λ = 0.71070 Å). Single crystals of **1** suitable for X-ray analysis were obtained by slow recrystallization at room temperature. The structure was solved by a direct method (SIR-2004)* and refined by full-matrix least-squares procedures on F2 for all reflections (SHELXL-97).** All hydrogen atoms were refined isotropically, while all other atoms were refined anisotropically. Crystal data: $C_{37}H_{32}N_6O_4$, M = 624.69, T = 173(2) K, monoclinic, *C*2/c (no.15), 0.30 × 0.05 × 0.05 mm^3, a = 15.959(7) Å, b = 13.032(5) Å, c = 15.286(6) Å, V = 3147(2) $Å^3$, Z = 4, D_{calc} = 1.319 gcm^{-3}, μ = 0.088 mm^{-1}, 2θmax = 51.00, 10902 measured reflections, 2932 independent reflections (Rint = 0.0544), 222 refined parameters, GOF = 1.058, R_1 = 0.0581 and wR_2 = 0.1263 [$I > 2\sigma(I)$], R_1 = 0.0901 and wR_2 = 0.1444 [for all data], largest diff. peak and hole 0.179 and –0.226 e.$Å^{-3}$. These data has been depositied with the Cambridge Crystallographic Data Center as CCDC 948984.

X-ray Crystallographic Analysis of 10.

The intensity data were collected on a Rigaku/MSC Mercury CCD diffractometer with graphite monochromated MoKα radiation (λ = 0.71069 Å). Single crystals of **10** suitable for X-ray analysis were obtained by slow recrystallization at room temperature. The structure was solved by a direct method (SIR-2004)* and refined by full-matrix least-squares procedures on F2 for all reflections (SHELXL-97).** All hydrogen atoms were refined isotropically, while all other atoms were refined anisotropically. Crystal data: $C_{61}H_{56}N_6O_4$, M = 937.12, T = 173 (2) K, orthorhombic, $P2_12_12_1$ (no.19), a = 9.0103 (2) Å, b = 14.1379 (2) Å, c = 39.4878 (9) Å, V = 5030.22 (18) $Å^3$, Z = 4, D_{calc} = 1.237 gcm^{-3}, μ = 0.078 mm^{-1}, 2θmax = 50.98, 36180 measured reflections, 9345 independent reflections (Rint = 0.0996), 644 refined parameters, GOF = 1.012, R_1 = 0.0539 and wR_2 = 0.0922 [$I > 2\sigma(I)$], R_1 = 0.1307 and wR_2 = 0.1154 [for all data], largest diff. peak and hole 0.166 and –0.198 e.$Å^{-3}$. These data has been depositied with the Cambridge Crystallographic Data Center as CCDC 948985.

Reference:

* (SIR-2004)

Burla, M. C.; Caliandro, R.; Camalli, M.; Carrozzini, B.; Cascarano, G. L.; Caro, L. D.; Giacovazzo, C.; Polidori, G.; Spagna, R. *J. Appl. Cryst.* **2005**, *38*, 381.

** (SHELX-97)

(a) Sheldrick, G. M. *Acta Crystallogr. Sect. A* **1990**, *46*, 467. (b) Sheldrick, G..

SHELX-97 Program for Crystal Structure Solution and the Refinement of

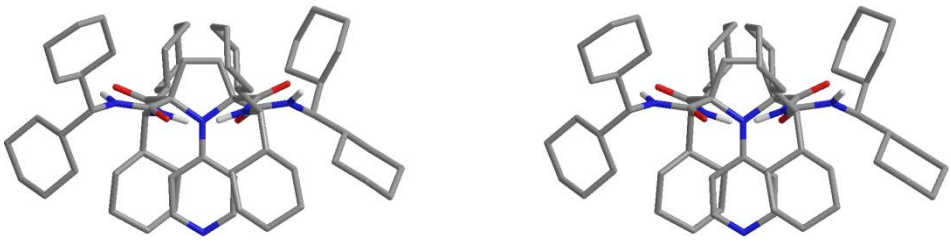
Crystal Structures, Institüt für Anorganische Chemie der Universität

Göttingen, Tammanstrasse 4, D-3400 Göttingen, Germany, 1997.

Conformational Search of 9

An energy-minimized conformer was generated by a molecular modeling search with OPLS2005 force field with the GB/SA solvation model for chloroform using MacroModel V 9.0 (20,000 steps MCMM). Stereoview of the conformer was shown below.

(a)



(b)

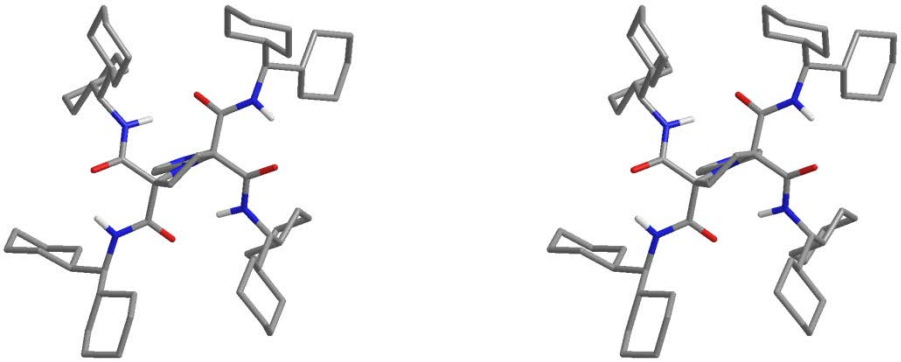


Figure S1. Energy-minimized structures of **9** (a) Side View (b) Top view

HPLC analysis of 1

A solution of **1** in CH_2Cl_2 (75 mM, 20 μL) was submitted to chiral HPLC separation (Daicel, CHIRALPAK ID, 4.6 mm × 250 mm) eluent: hexane/CH_2Cl_2/Et_2NH = 60/40/0.1, flow rate: 1.0 mL/min, temperature: 0 °C; first eluting enantiomer t_R =28.7 min; second eluting enantiomer t_R = 33.2 min.

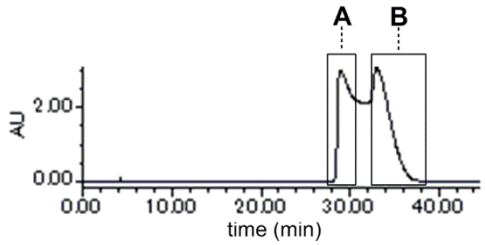


Figure S2. HPLC Chromatogram of **1**

CD analysis of 1

Fraction A and B separated by HPLC were collected separately in 30 mL flask being cooled with dry ice/acetone bath. CD spectra of the fractionated solutions were readily measured at 0 °C.

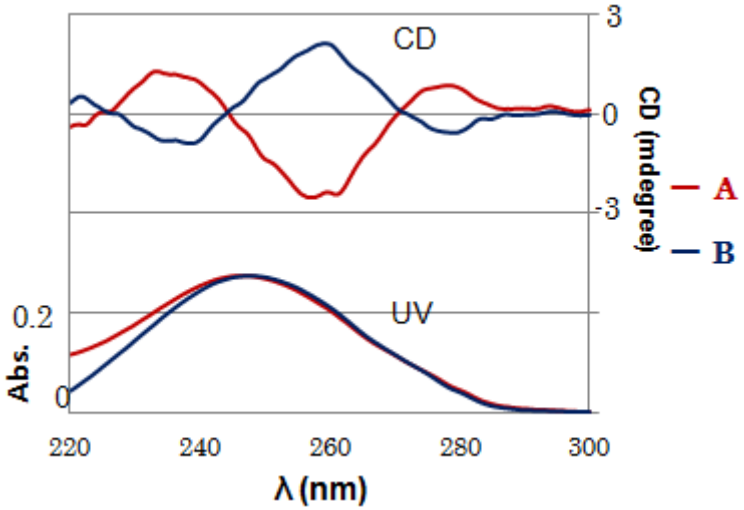


Figure S3. CD and UV spectra of **1** at 0 °C (hexane/CH_2Cl_2/Et_2NH = 60/40/0.1)

Time dependent CD analysis

Time dependent CD spectra of **1** were recorded at 0 °C. The rate constant k for inversion was determined by plotting $\ln(CD_0/CD_t)$ versus time using CD intensity at 258 nm. The half-life of racemization and the racemization barrier were calculated by linear regression analysis according to the below equations.

(1) $\ln(CD_0/CD_t) = 2kt$

(2) $t_{1/2} = \frac{\ln 2}{2k}$

(3) $\Delta G^{\ddagger} = -RT\ln\frac{hk}{k_B T}$

R = gas constant
T = Temperature
h = Plank's constant
k_B = Boltzmann constant
t = time

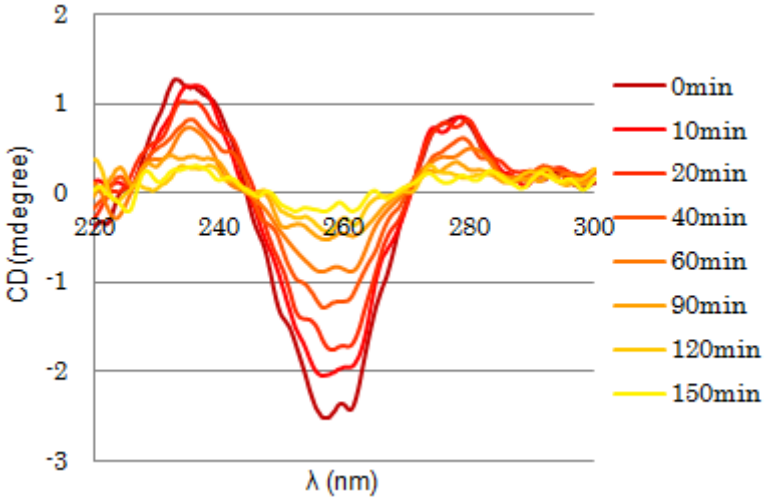
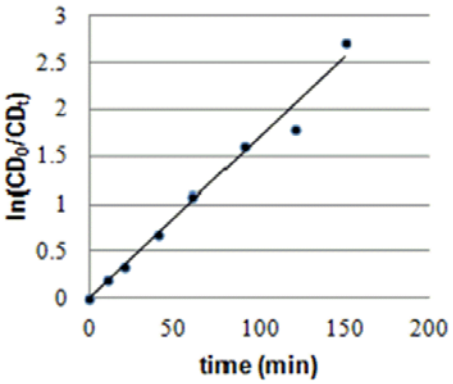


Figure S4. Time dependent CD spectra of **A** at 0 °C (hexane/CH_2Cl_2/Et_2NH = 60/40/0.1)

Table S1. Time dependent CD of **A** at 258 nm (0°C)

time (min)	CD_{258nm} (mdegree)
0	– 2.47802
10	– 2.02299
20	– 1.75777
40	– 1.24752
60	– 0.83434
90	– 0.4979
120	– 0.41437
150	– 0.1652



slope = 2k = 1.7×10^{-2} min^{-1} (*R* = 0.992)
$t_{1/2}$ = 40 min, $\Delta G^{\ddagger}$ = 20.7 kcal/mol (0 °C)

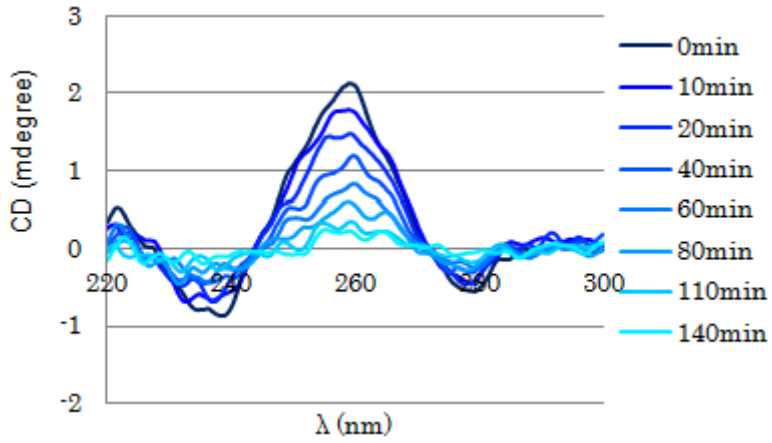
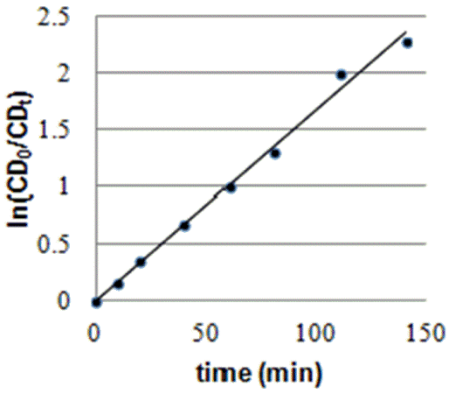


Figure S5. Time dependent CD spectra of **B** at 0 °C (hexane/CH_2Cl_2/Et_2NH = 60/40/0.1)

Table S2. Time dependent CD of **B** at 258 nm (0°C)

time (min)	CD_{258nm} (mdegree)
0	2.068776
10	1.771806
20	1.447776
40	1.054456
60	0.755309
80	0.564612
110	0.279244
140	0.211907



slope = 2k = 1.7×10^{-2} min^{-1} (R = 0.997)

$t_{1/2}$ = 40 min, $\Delta G^{\ddagger}$ = 20.7 kcal/mol (0 °C)

HPLC analysis of 9

A solution of **9** in CH_2Cl_2 was submitted to chiral HPLC separation (Daicel, CHIRALPAK ID, 4.6 mm × 250 mm) eluent: hexane/CH_2Cl_2/Et_2NH = 75/25/0.1, flow rate: 1.0 mL/min, temperature: 0 °C; first eluting enantiomer t_R =12.7 min; second eluting enantiomer t_R = 16.2 min.

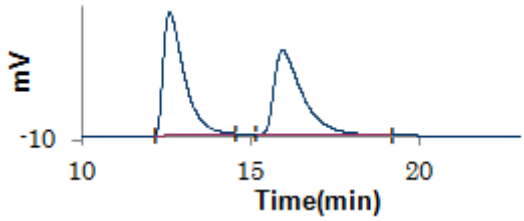


Figure S6. HPLC Chromatogram of **9**

Semipreparative scale separation of 9

A solution of racemic **9** in CH_2Cl_2 (40 mM, 50 μL) was submitted to preparative chiral HPLC separation (Daicel CHIRALPAK ID: 250 mm x 10 mm) eluent: hexane/CH_2Cl_2/Et_2NH = 75/25/0.1, UV: 254 nm, flow rate: 5.0 mL/min, temperature: 0 °C; first eluting enantiomer $[\alpha]_D^{19}$ – 42 (99% ee, c 0.1, hexane); second eluting enantiomer $[\alpha]_D^{19}$ + 40 (97% ee, c 0.1, hexane). Fractionated solution was concentrated *in vacuo* at 0 °C to give a colorless solid of **(-)-9** and **(+)-9**. These solids were kept in freezer at – 20 °C without racemization.

Racemization barrier analysis of 9 in *o*-dichlorobenzene by HPLC

The rate constant k for inversion at each temperature was determined by plotting $\ln(ee_0/ee_t)$ versus time according to the equation $[\ln(ee_0/ee_t) = 2kt]$. Hence, from the Eyring equation, the activation parameters were determined by plotting ln(k/T) versus 1/T wherein

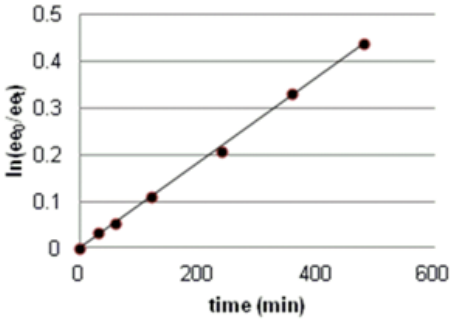
(1) $\Delta H^{\ddagger} = -R \times slope$

(2) $\Delta S^{\ddagger} = R \times [intercept + \ln (h/k_B)]$

R = gas constant
h = Plank's constant
k_B = Boltzmann constant

Table S3. Time dependent ee of **9** in *o*-dichlorobenzene (20 °C)

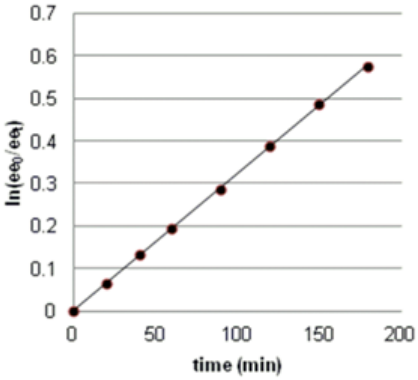
time (min)	ee
0	96
30	93
60	91
120	86
240	78
360	69
480	62



slope = 2k = 9.1x10^{-4} min^{-1} (R > 0.999)

Table S4. Time dependent ee of **9** in *o*-dichlorobenzene (30 °C)

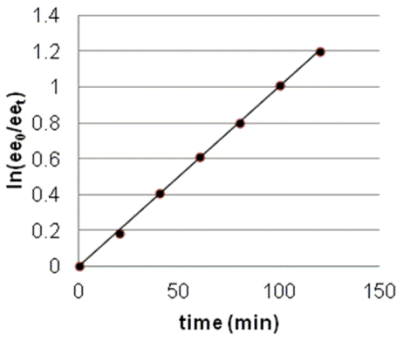
time (min)	ee
0	96
20	90
40	84
60	79
90	72
120	65
150	59
180	54



slope = 2k = 3.2x10^{-3} min^{-1} (R > 0.999)

Table S5. Time dependent ee of **9** in *o*-dichlorobenzene (40 °C)

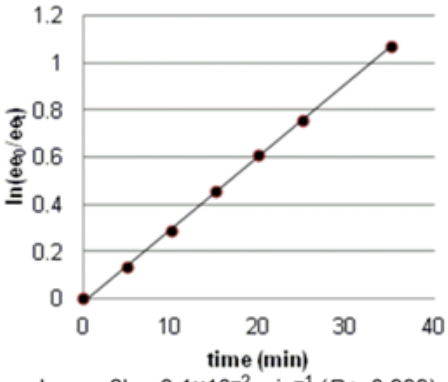
time (min)	ee
0	96
20	80
40	64
60	52
80	43
100	35
120	29



slope = 2k = 1.0×10^{-2} min^{-1} ($R > 0.999$)

Table S6. Time dependent ee of **9** in *o*-dichlorobenzene (50 °C)

time (min)	ee
0	96
5	84
10	72
15	61
20	52
25	45
35	33



slope = 2k = 3.1×10^{-2} min^{-1} ($R > 0.999$)

Table S7. Eyring plot of the racemization of **9** in *o*-dichlorobenzene

T (K)	k (s^{-1})
293	7.56×10^{-6}
303	2.68×10^{-5}
313	8.40×10^{-5}
323	2.57×10^{-4}

$\Delta H^{\ddagger}$ = 21.4 kcal/mol
$\Delta S^{\ddagger}$ = – 8.8 cal/mol·K
$\Delta G^{\ddagger}$ = 23.8 kcal/mol (0 °C)

Racemization barrier analysis of 9 in hexane and CH_2Cl_2 by HPLC

The rate constant k for inversion was determined by plotting $\ln(ee_0/ee_t)$ versus time. The half-life of racemization and the racemization barrier were calculated by linear regression analysis according to the below equations.

(1) $\ln(ee_0/ee_t) = 2kt$

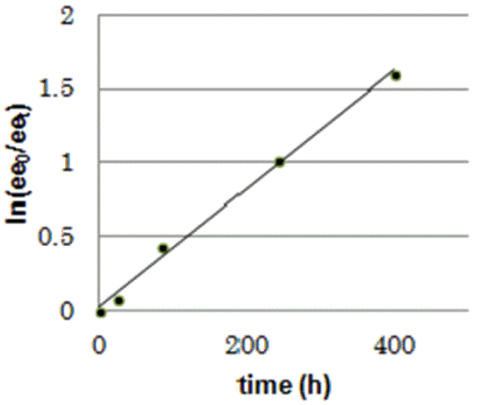
(2) $t_{1/2} = \frac{\ln 2}{2k}$

(3) $\Delta G^{\ddagger} = -RT\ln\frac{hk}{k_B T}$

R = gas constant
T = Temperature
h = Plank's constant
k_B = Boltzmann constant
t = time

Table S8. Time dependent ee of **9** in hexane (20 °C)

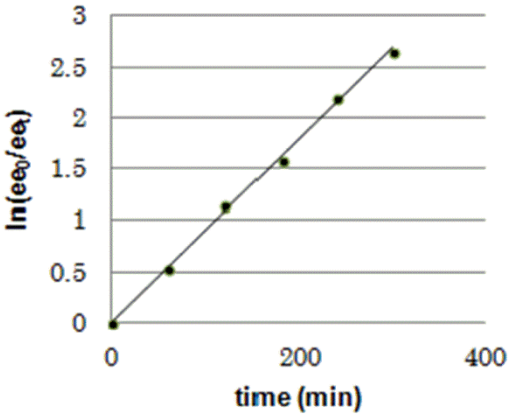
time (h)	ee
0	99
24	91
84	64
240	36
398	20



slope = $2k = 4.0\times10^{-3}$ h^{-1} (R = 0.998)
$t_{1/2}$ = 173 h, $\Delta G^{\ddagger}$ = 25.5 kcal/mol (20 °C)

Table S9. Time dependent ee of **9** in CH_2Cl_2 (20 °C)

time (min)	ee
0	98
60	58
120	31
180	20
240	11
300	7



slope = $2k = 8.9\times10^{-3}$ min^{-1} (R = 0.999)
$t_{1/2}$ = 78 min, $\Delta G^{\ddagger}$ = 22.7 kcal/mol (20 °C)

HPLC analysis of 10 at 0 °C and 18 °C

A solution of **10** in CH_2Cl_2 was submitted to chiral HPLC separation (Daicel, CHIRALPAK ID, 4.6 mm × 250 mm) eluent: hexane/CH_2Cl_2/Et_2NH = 70/30/0.1, flow rate: 1.0 mL/min, temperature: 0 °C; first eluting conformer t_R =4.3 min; second eluting conformer t_R = 6.7 min.

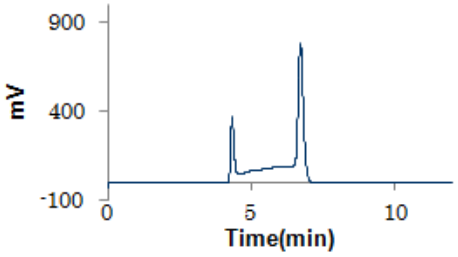


Figure S7. HPLC Chromatogram of **10** (0 °C)

A solution of **10** in CH_2Cl_2 was submitted to chiral HPLC separation (Daicel, CHIRALPAK ID, 4.6 mm × 250 mm) eluent: hexane/CH_2Cl_2/Et_2NH = 70/30/0.1, flow rate: 1.0 mL/min, temperature: 18 °C; first eluting conformer t_R =4.2 min; second eluting conformer t_R = 5.9 min.

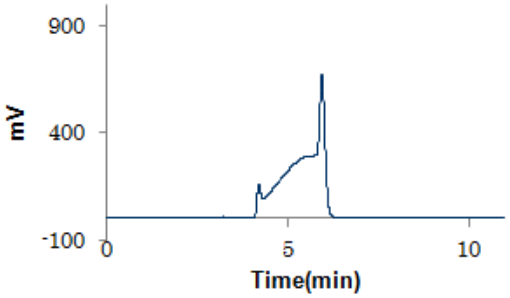


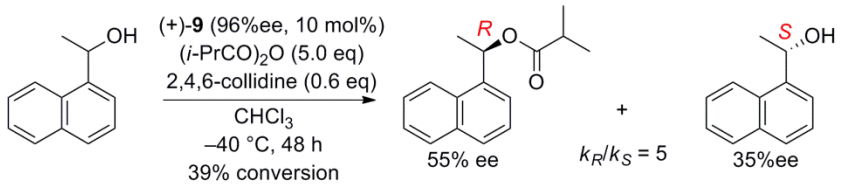
Figure S8. HPLC Chromatogram of **10** (18 °C)

Experiment of Scheme 1

To a stirred solution of 1-(1-naphthyl)ethylalcohol (3.3 mg, 19 μmol), 2,4,6-collidine (1.5 μL, 12 μmol) and **(-)-9** (98% ee, 2.0 mg, 1.9 μmol) in $CHCl_3$ (40 μL), was added isobutyric anhydride (16 μL, 97 μmol) at – 40 °C. After 48 h, the mixture was diluted with hexane (1.0 mL) and 20 μL of the mixture was submitted to chiral HPLC analysis to detect ee of **(-)-9** [98%ee, no racemization of **(-)-9** occurred].The reaction mixture was quenched with 40% $MeNH_2$/MeOH (0.10 mL) and concentrated *in vacuo*. The residue was purified by preparative TLC (AcOEt : hexane = 4 : 1) to obtain isobutyrate of the alcohol (59% ee, *S* major) and remaining alcohol (36% ee, *R* major). Ee of the isobutyrate was detected by chral HPLC. (Daicel, CHIRALCEL ODH, 250 mm × 4.6 mm), eluent hexane/IPA = 98/2, UV 254 nm, flow rate 1.0 mL/min. *R*-isomer, t_R 5.4 min and *S*-isomer, t_R 7.3 min. Absolute structure of the isobutyrate was identified by comparison with an authentic sample of *R* isomer prepared using (*R*) 1-(1-naphthyl)ethylalcohol purchased from Aldrich. Ee of the recovered alcohol was detected after isobutyration with excess amount of $(i\text{-PrCO})_2O$, triethylamine and DMAP in $CHCl_3$.

Acylative kinetic resolution of a racemic secondary alcohol in the presence of (+)-9

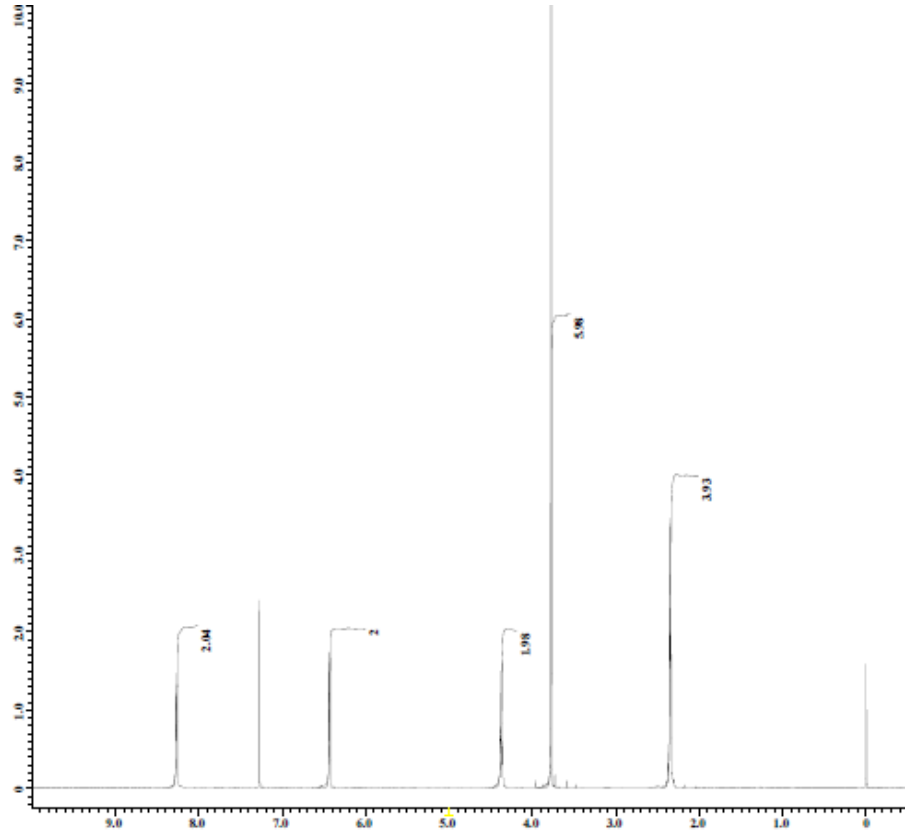
The acylative kinetic resolution was also taken place in the presence of **(+)-9** (96%ee, 10 mol%) under the same condition with Scheme 1 to give 55% ee (*R* major) of isobutyrate and 35% ee (*S* major) of recovered alcohol ($k_R/k_S = s = 5$).

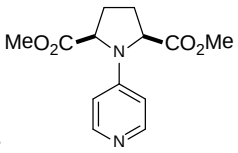


Scheme S3. Acylative kinetic resolution in the presence of **(+)-9**

NMR Spectra

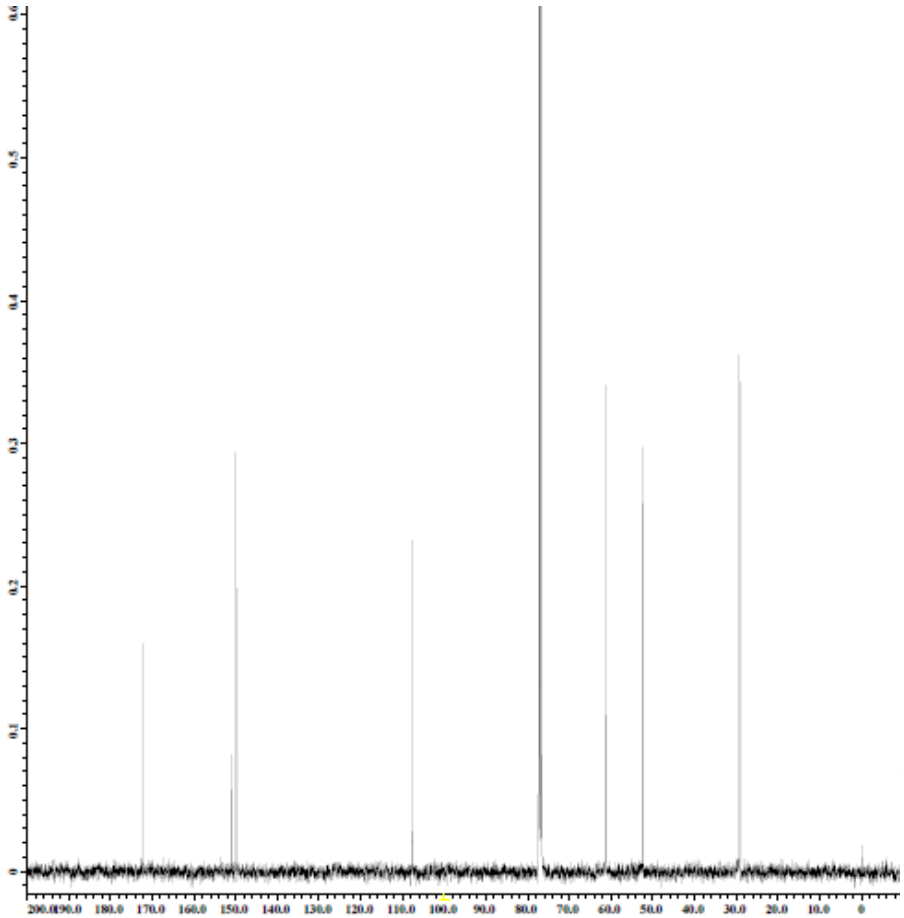
^{1}H NMR spectrum of **12** ($CDCl_3$)

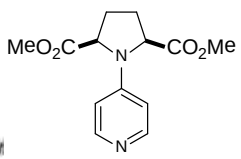




12

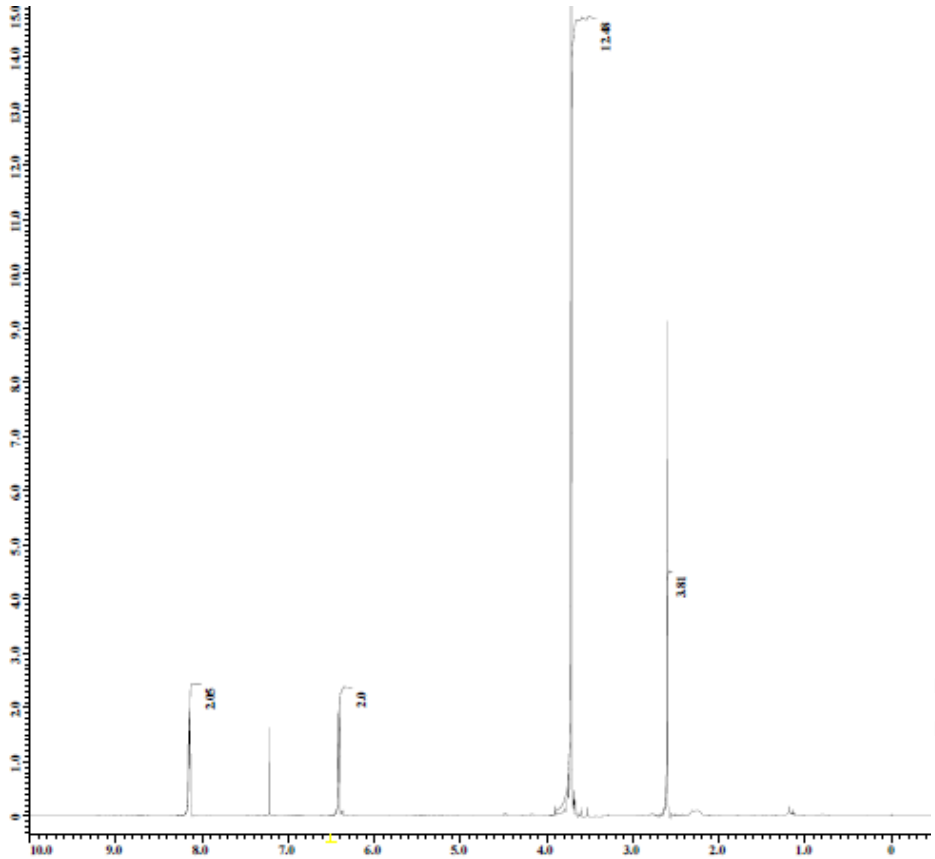
^{13}C NMR spectrum of **12** ($CDCl_3$)

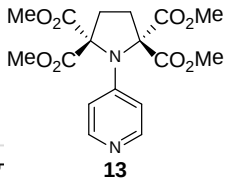




12

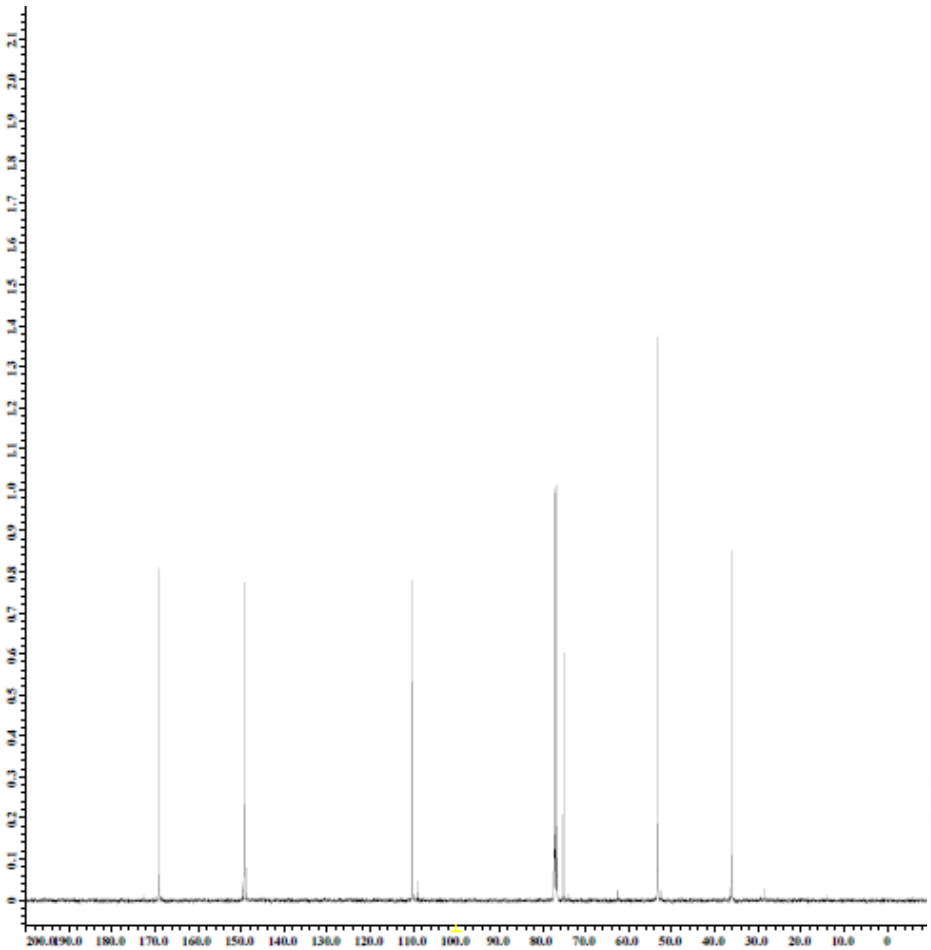
^{1}H NMR spectrum of **13** ($CDCl_3$)

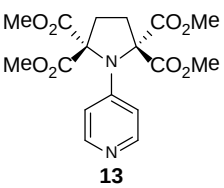




13

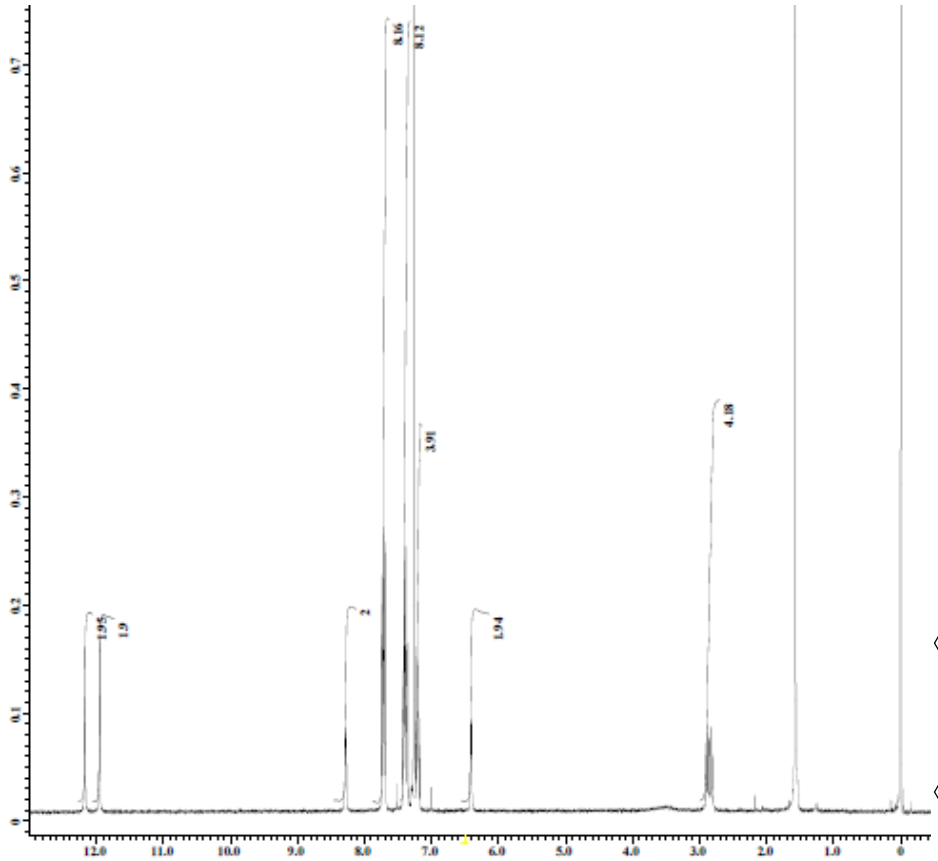
^{13}C NMR spectrum of **13** ($CDCl_3$)

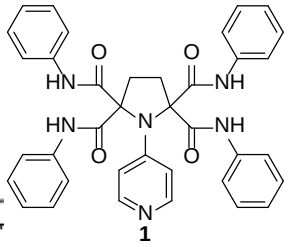




13

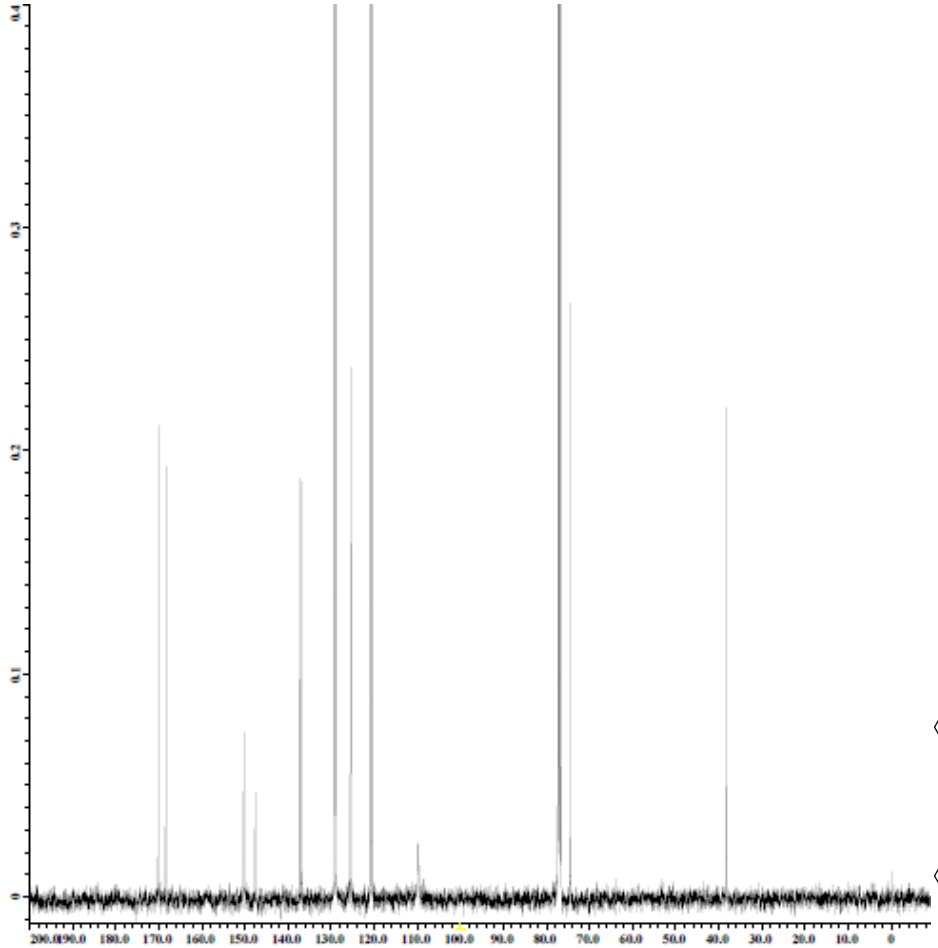
^{1}H NMR spectrum of **1** ($CDCl_3$)

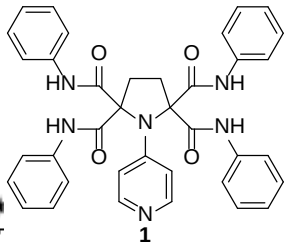




1

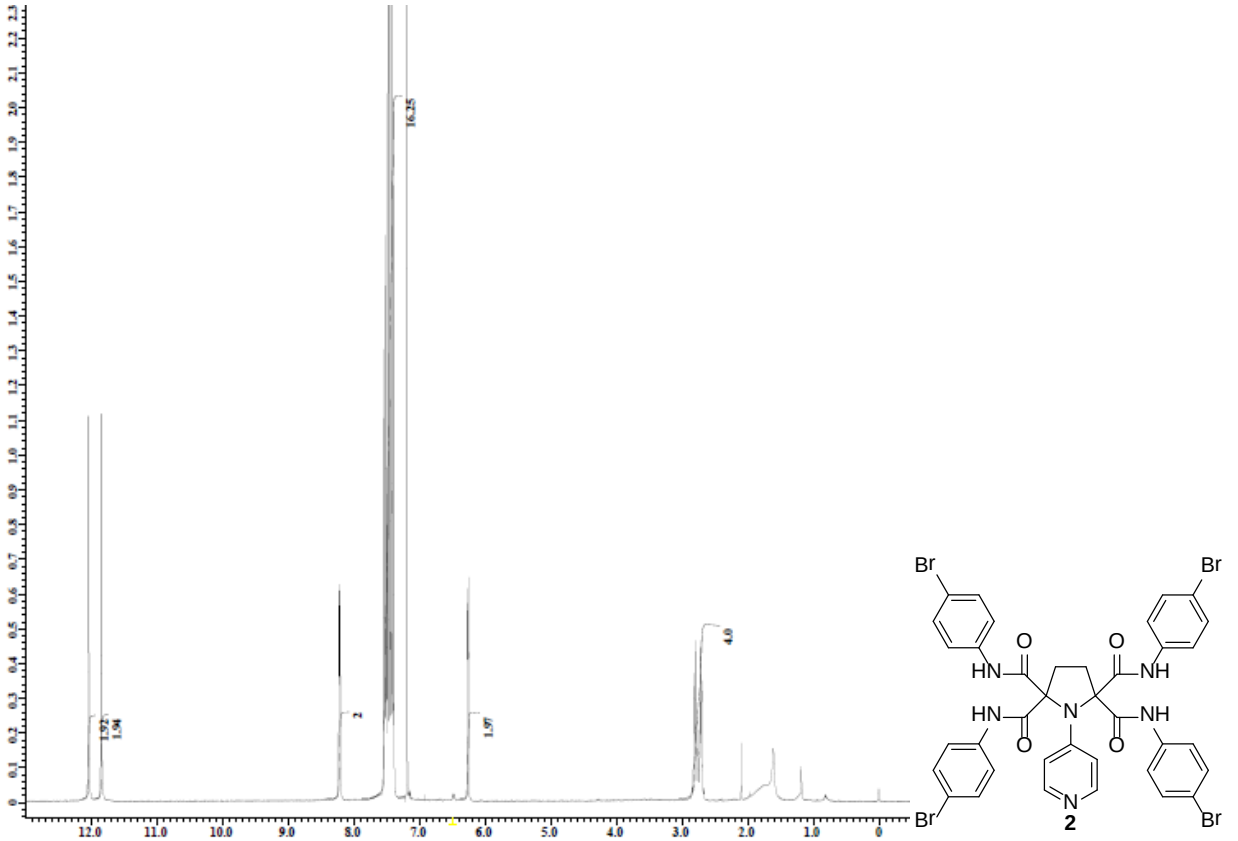
^{13}C NMR spectrum of **1** ($CDCl_3$)



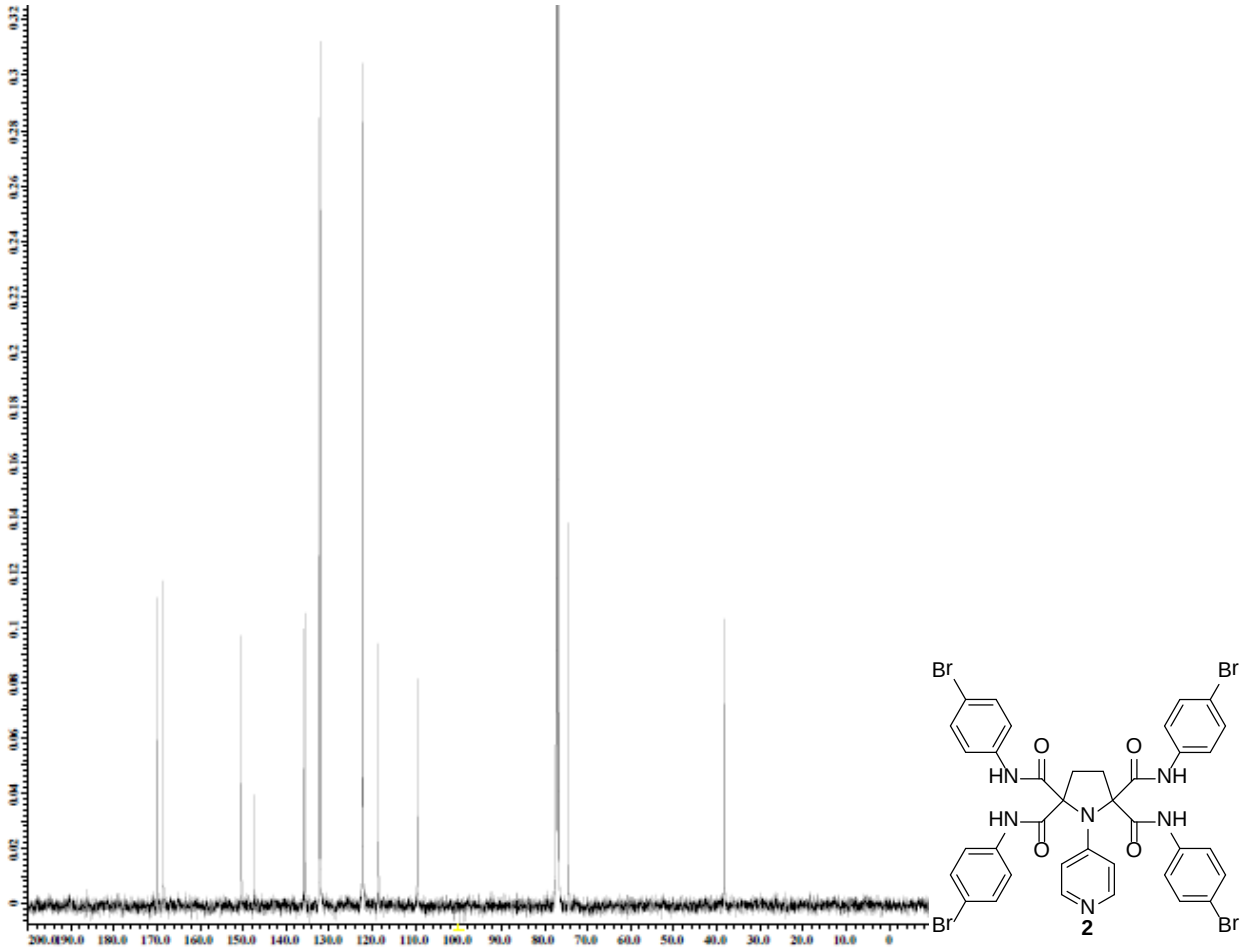


1

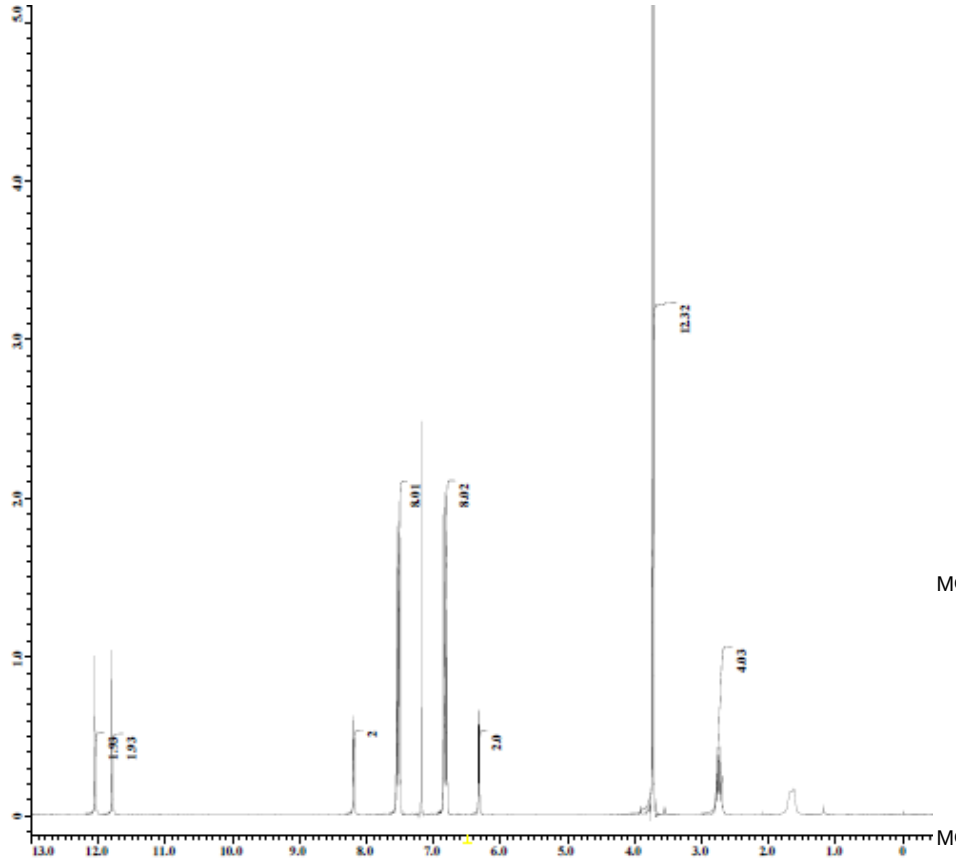
^{1}H NMR spectrum of **2** ($CDCl_3$)

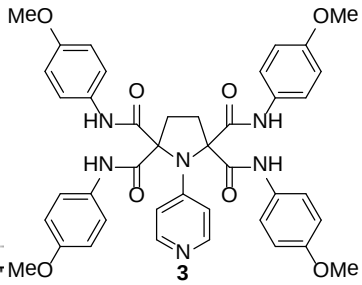


^{13}C NMR spectrum of **2** ($CDCl_3$)

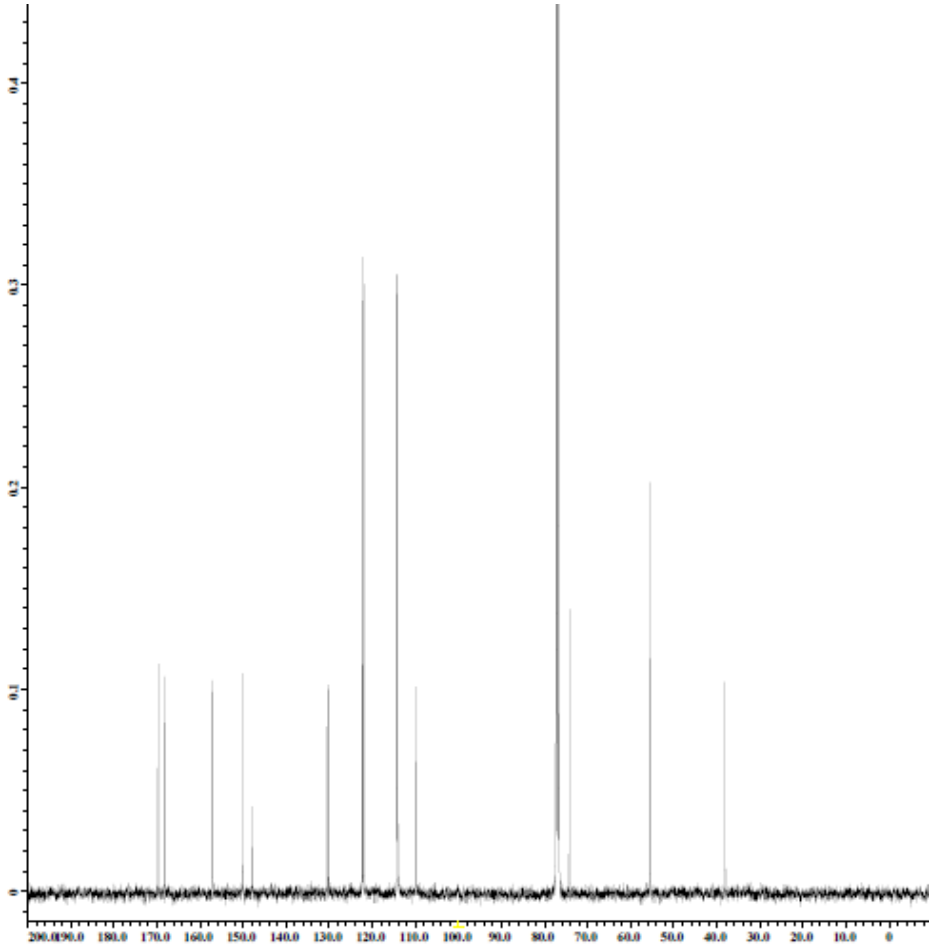


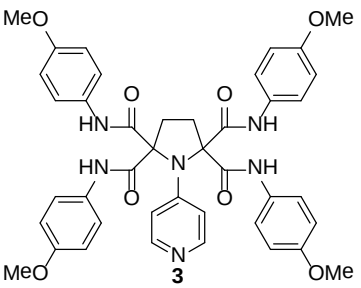
^{1}H NMR spectrum of **3** ($CDCl_3$)



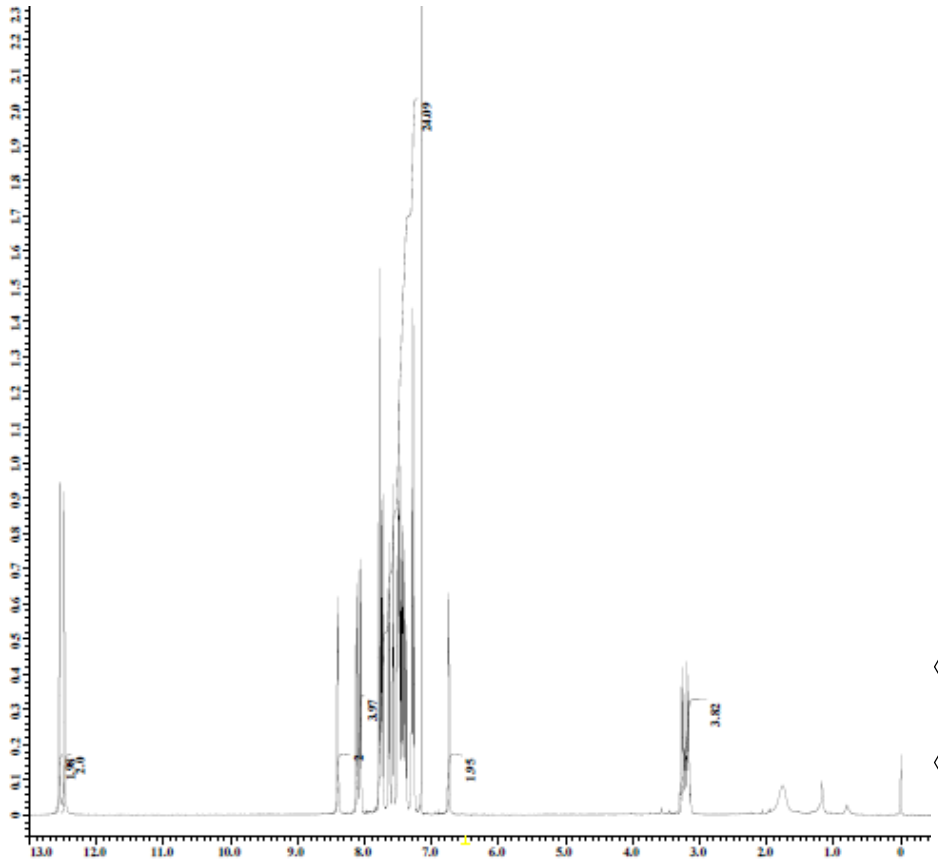


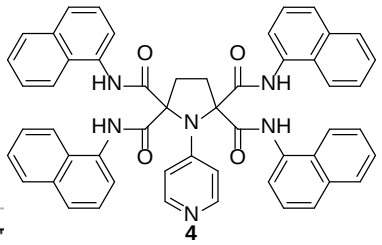
^{13}C NMR spectrum of **3** ($CDCl_3$)



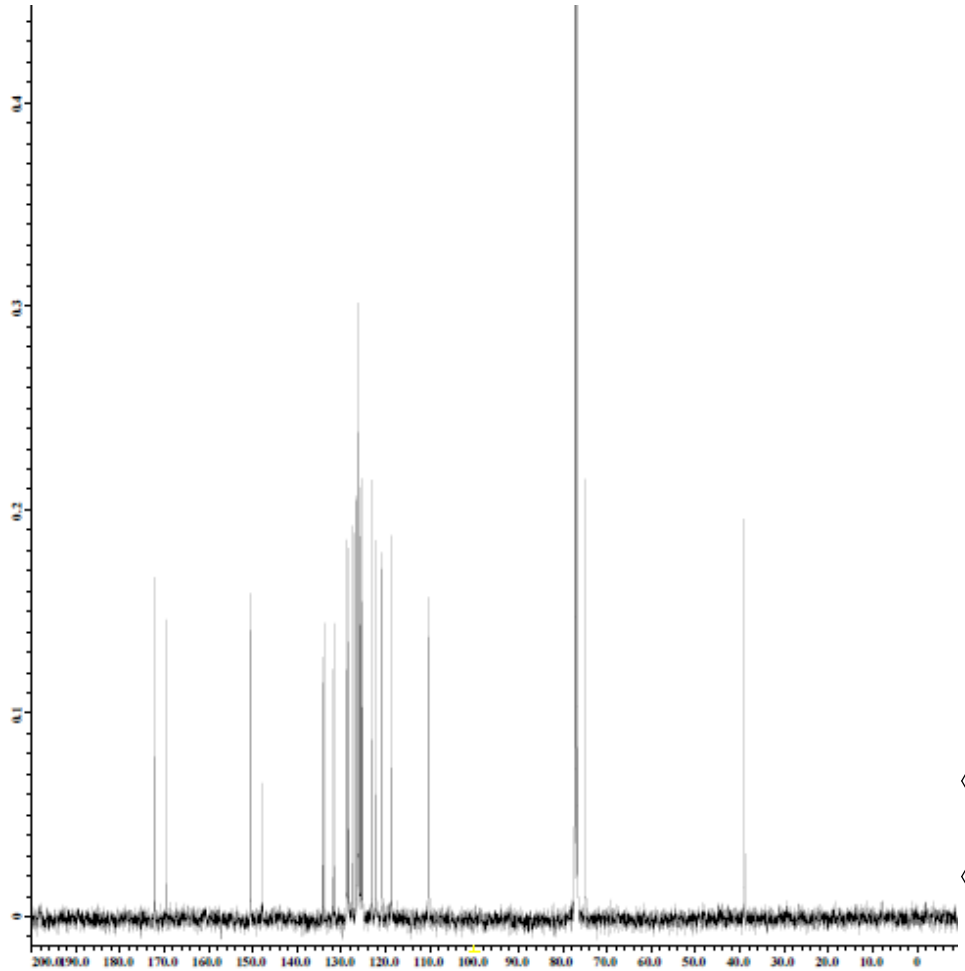


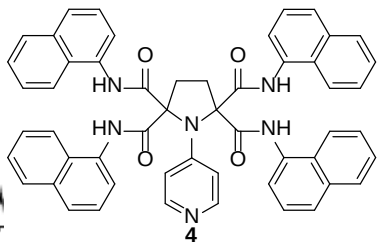
^{1}H NMR spectrum of **4** ($CDCl_3$)



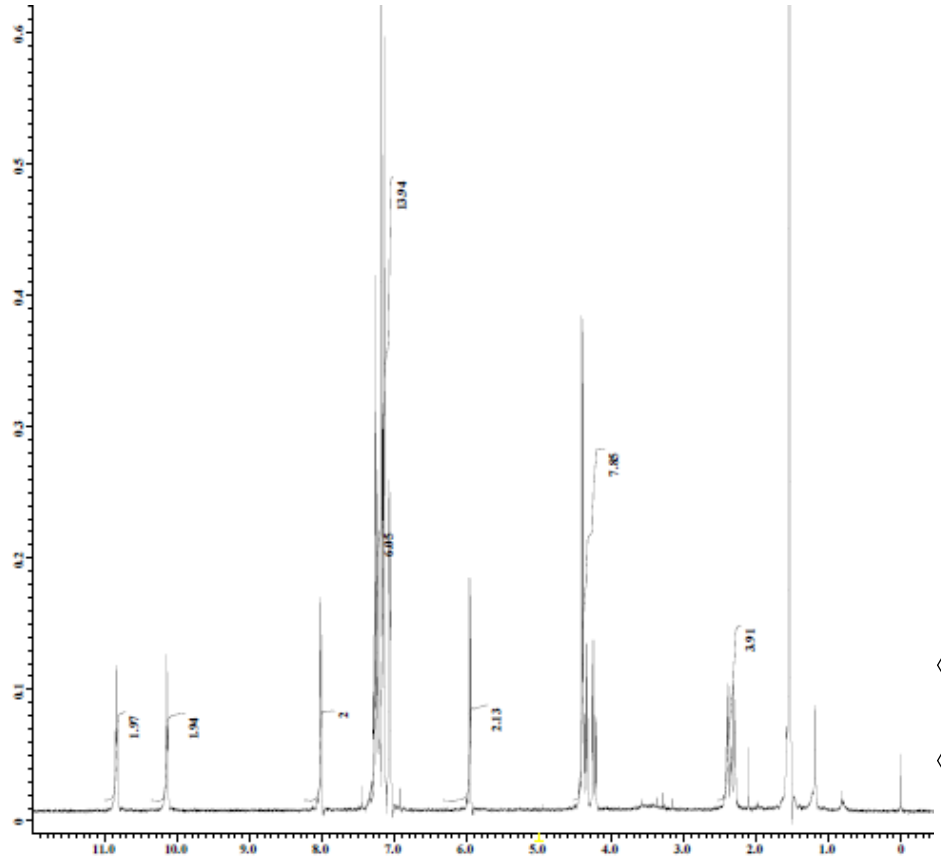


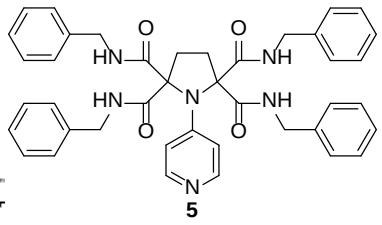
^{13}C NMR spectrum of **4** ($CDCl_3$)





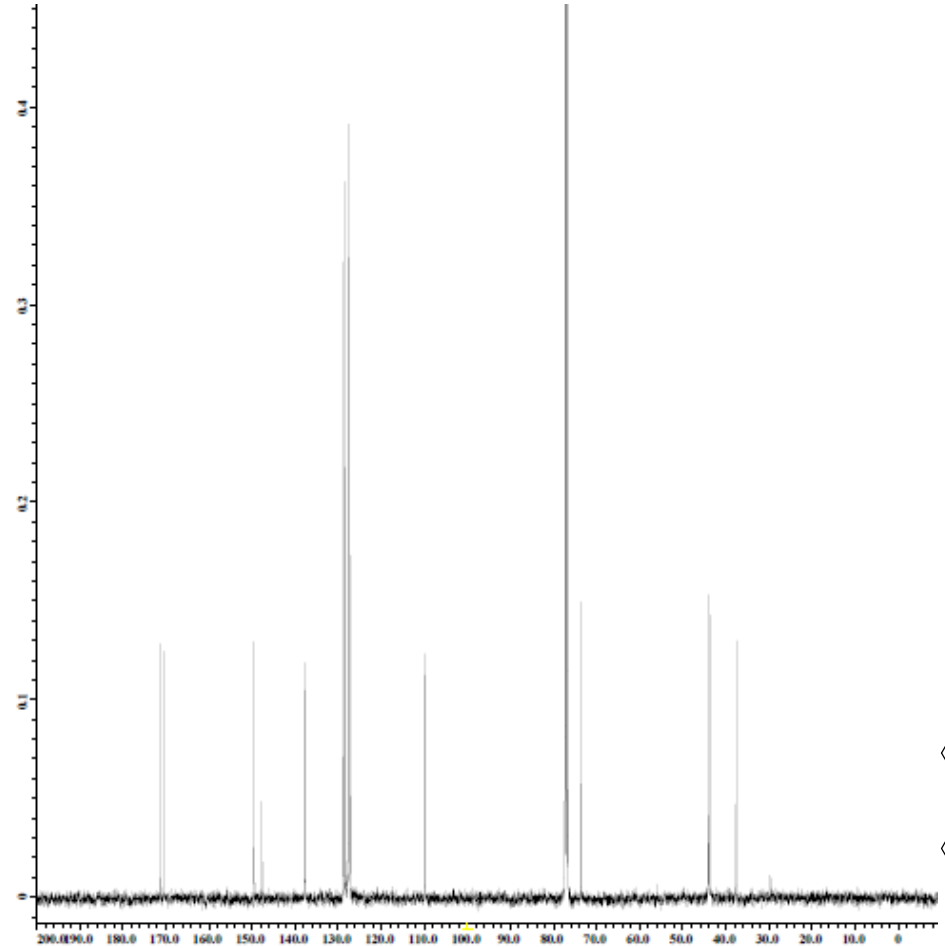
^{1}H NMR spectrum of **5** ($CDCl_3$)

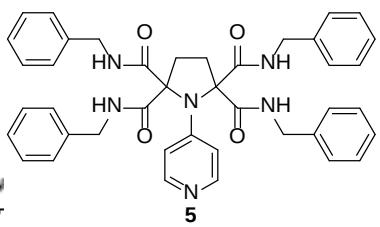




5

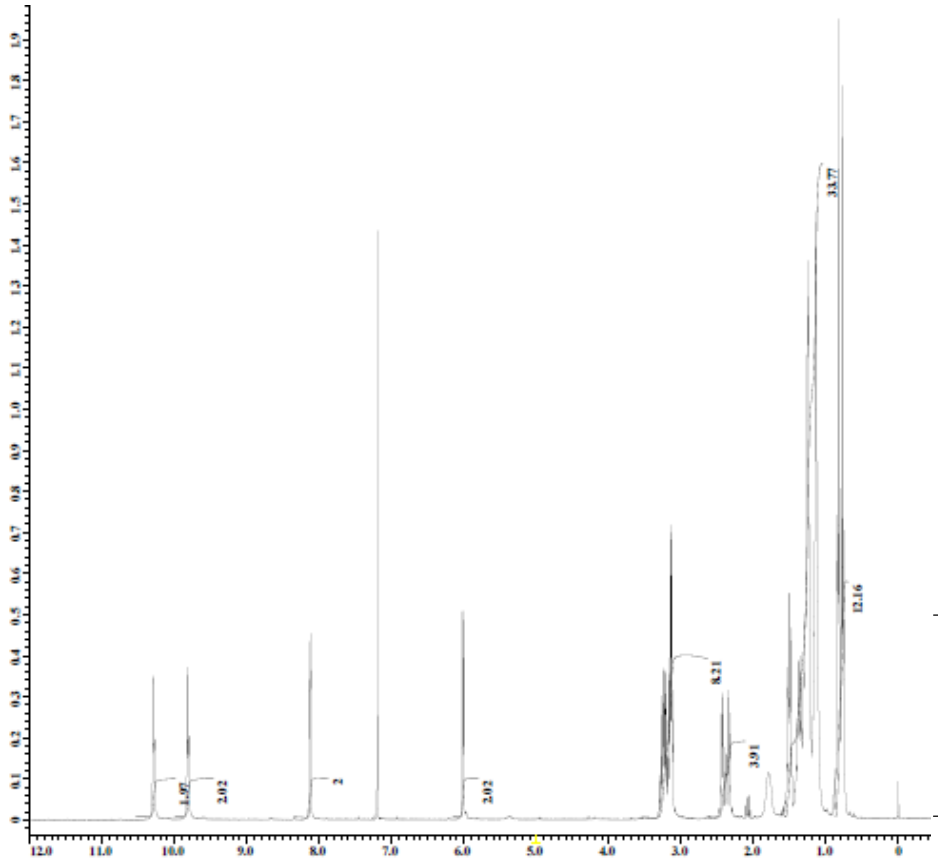
^{13}C NMR spectrum of **5** ($CDCl_3$)

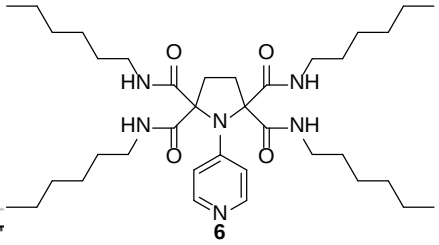




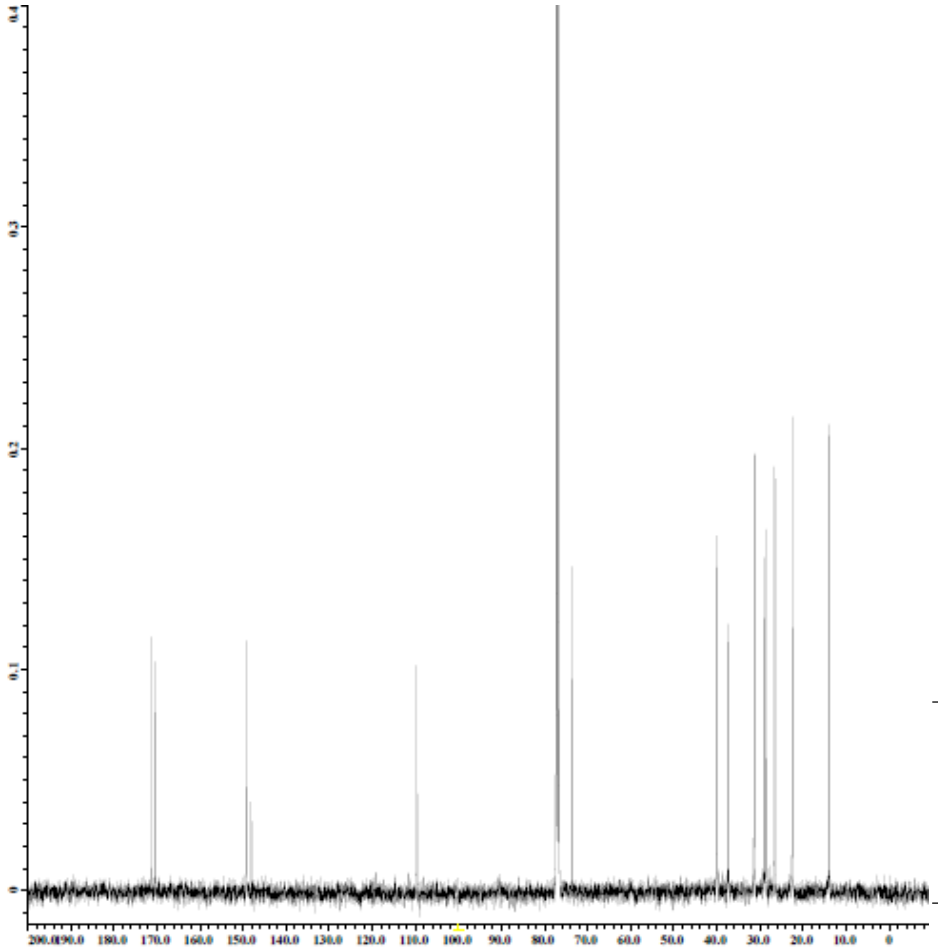
5

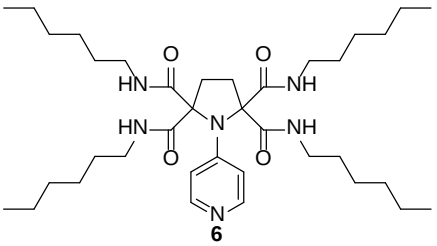
^{1}H NMR spectrum of **6** ($CDCl_3$)



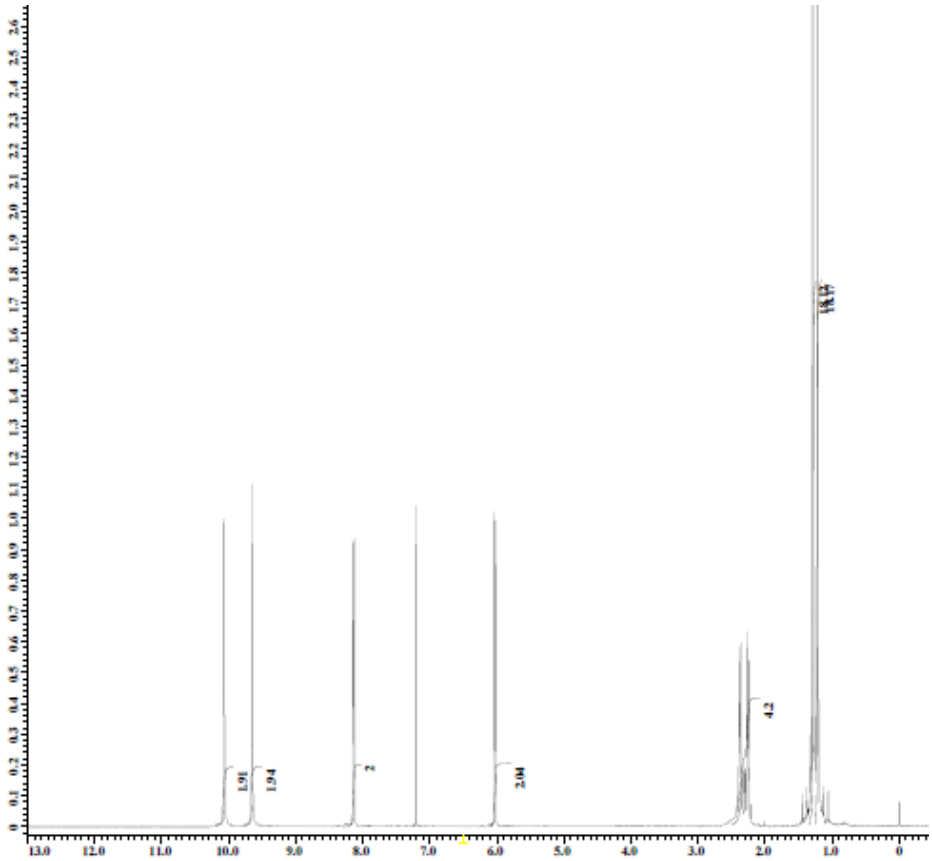


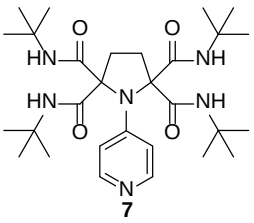
^{13}C NMR spectrum of **6** ($CDCl_3$)





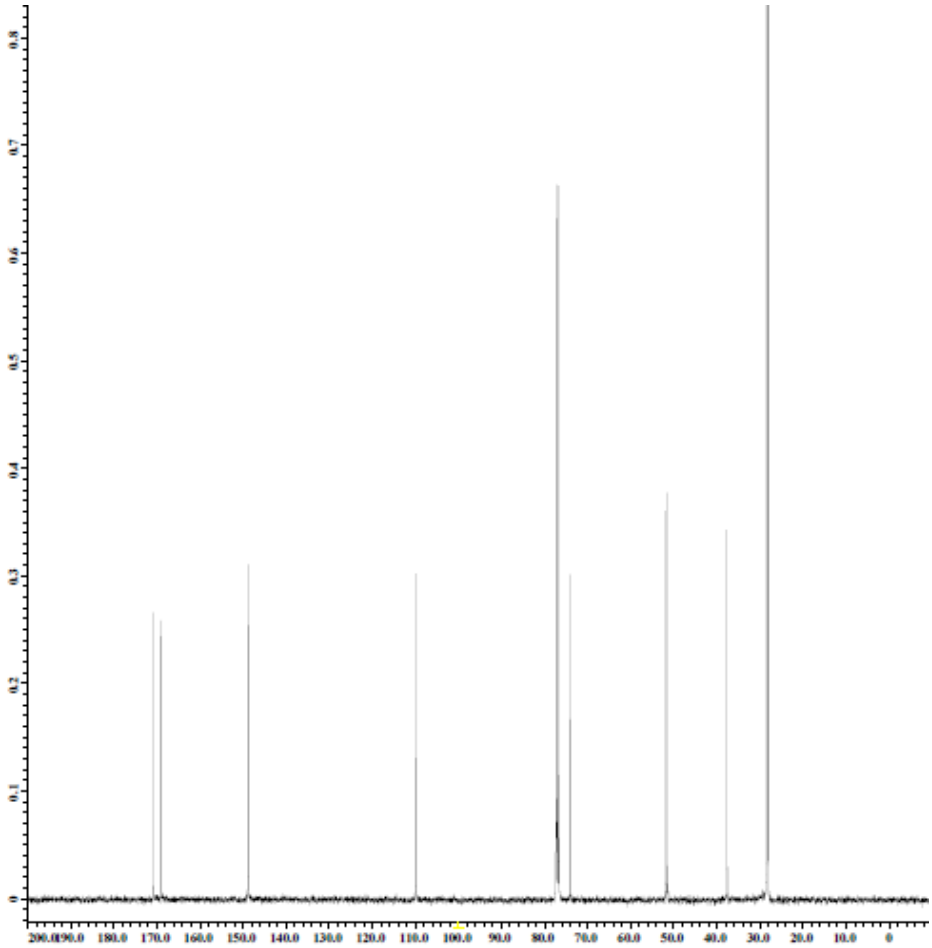
^{1}H NMR spectrum of **7** ($CDCl_3$)

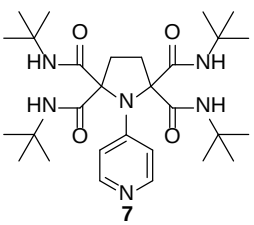




7

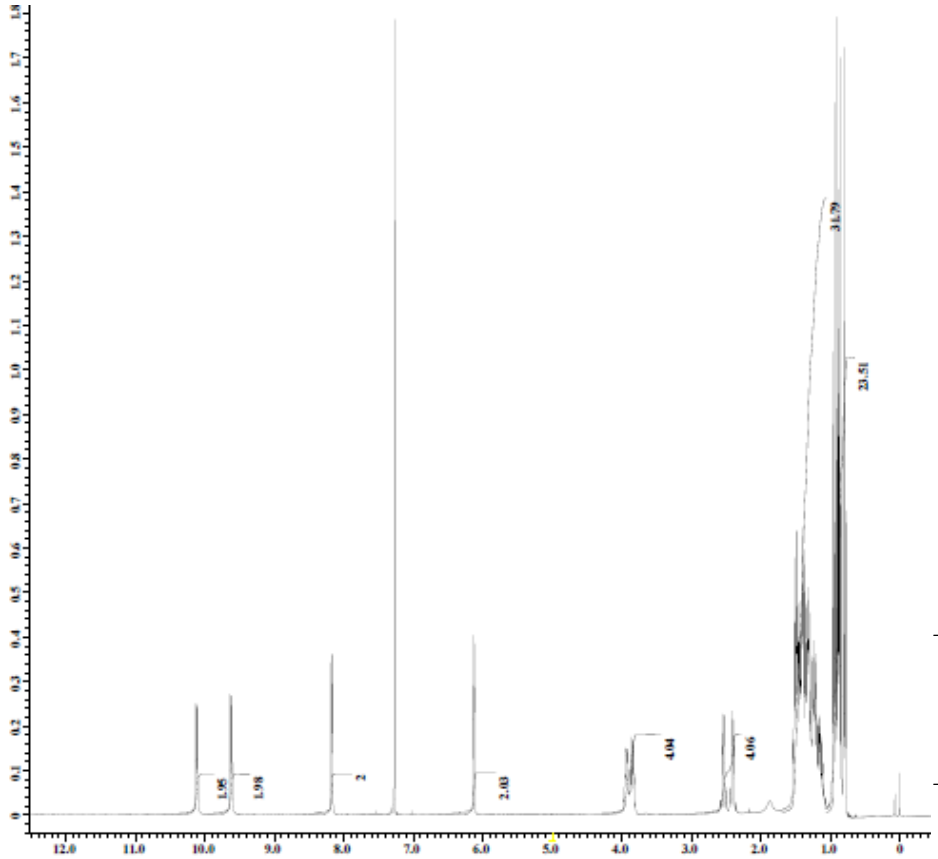
^{13}C NMR spectrum of **7** ($CDCl_3$)

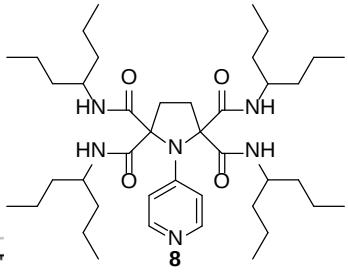




7

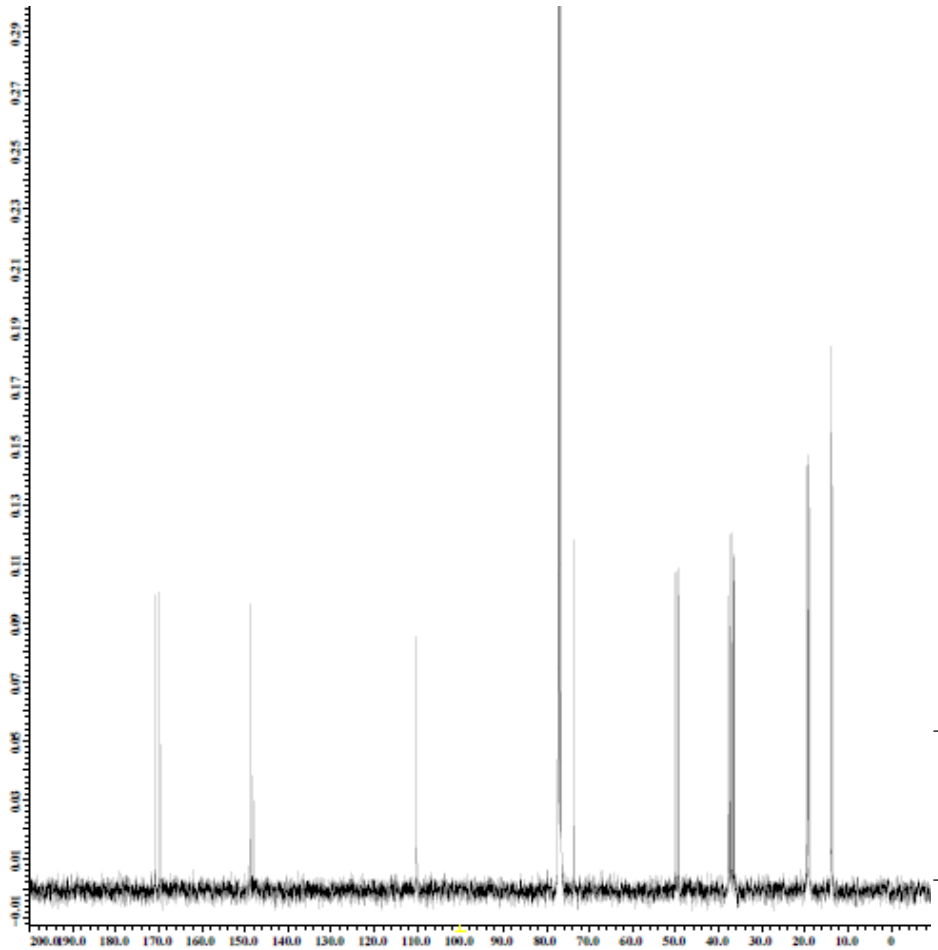
^{1}H NMR spectrum of **8** ($CDCl_3$)

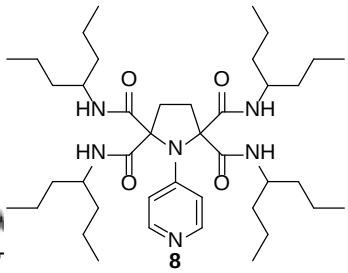




8

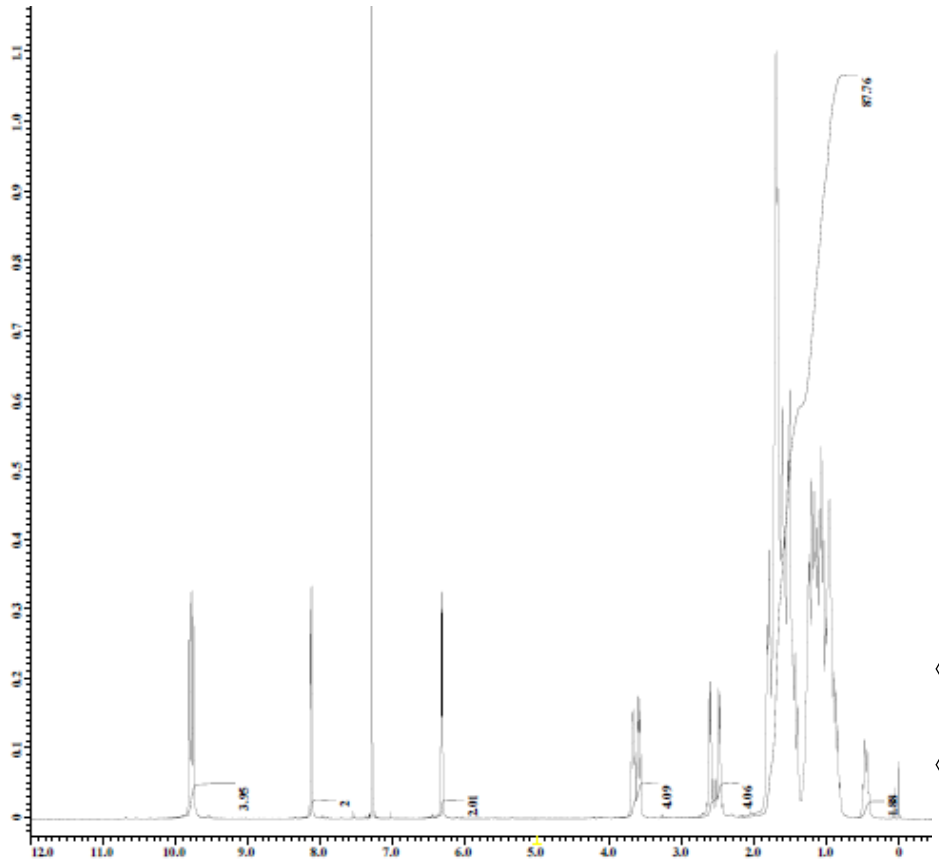
^{13}C NMR spectrum of **8** ($CDCl_3$)

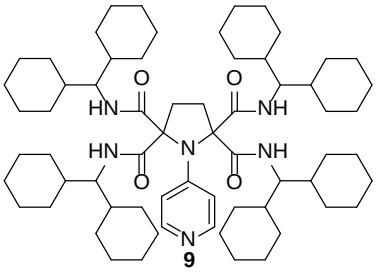




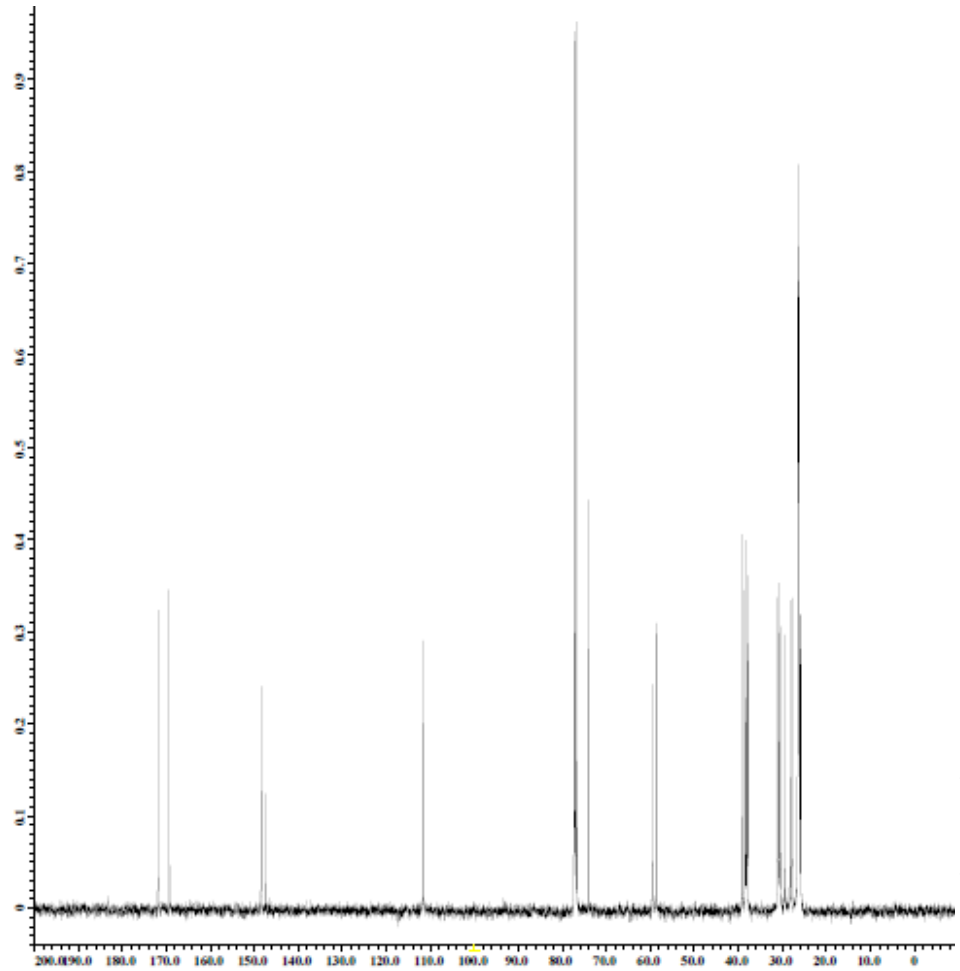
8

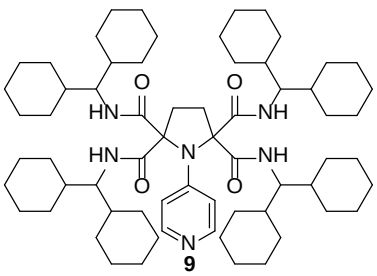
^{1}H NMR spectrum of **9** ($CDCl_3$)



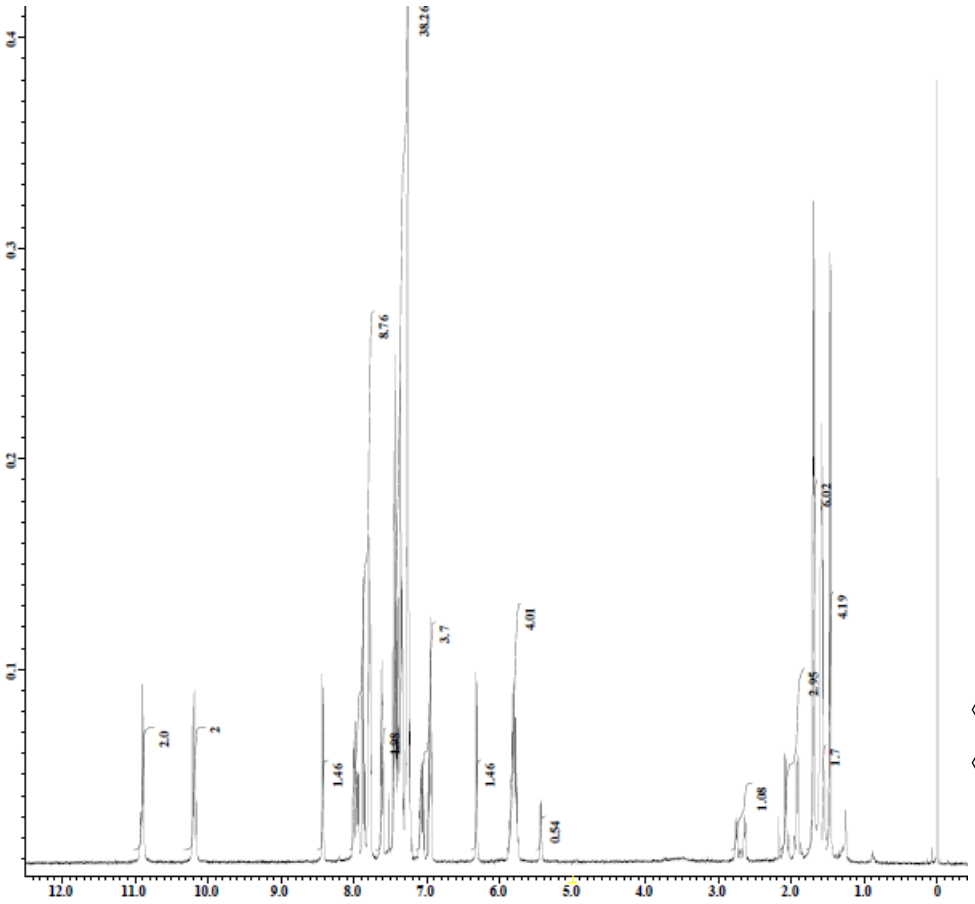


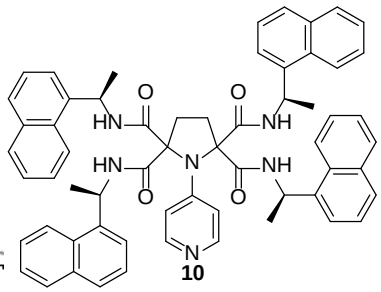
^{13}C NMR spectrum of **9** ($CDCl_3$)



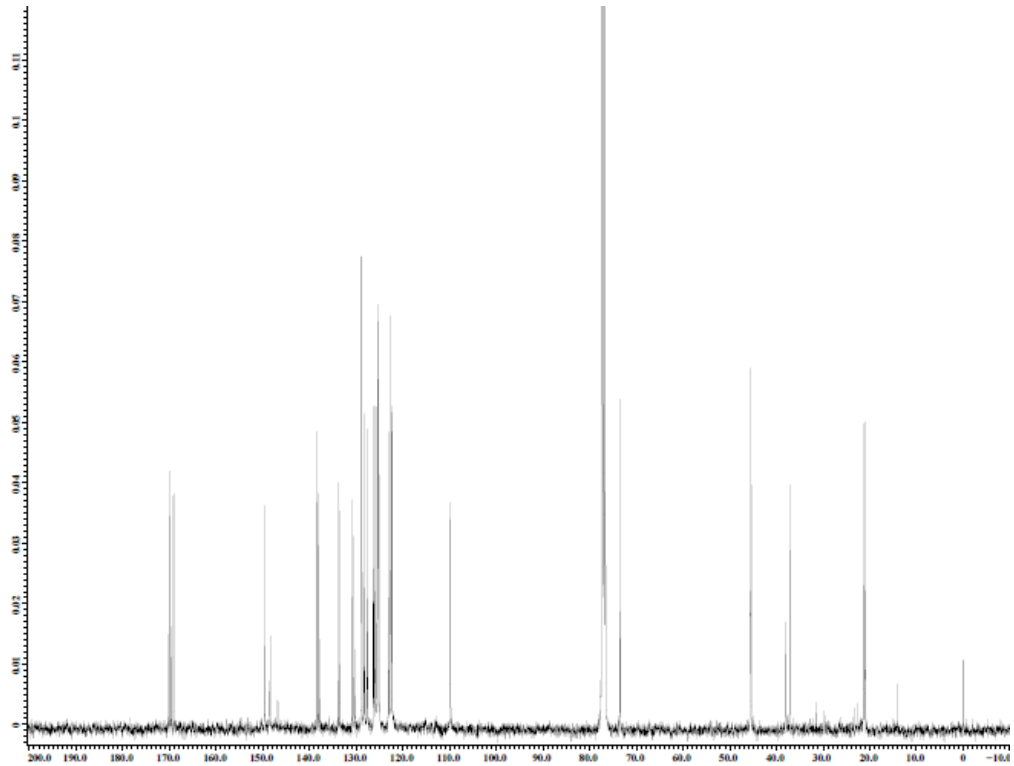


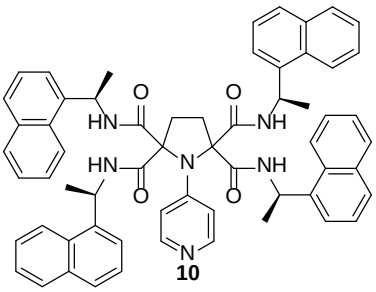
^{1}H NMR spectrum of **10** ($CDCl_3$)



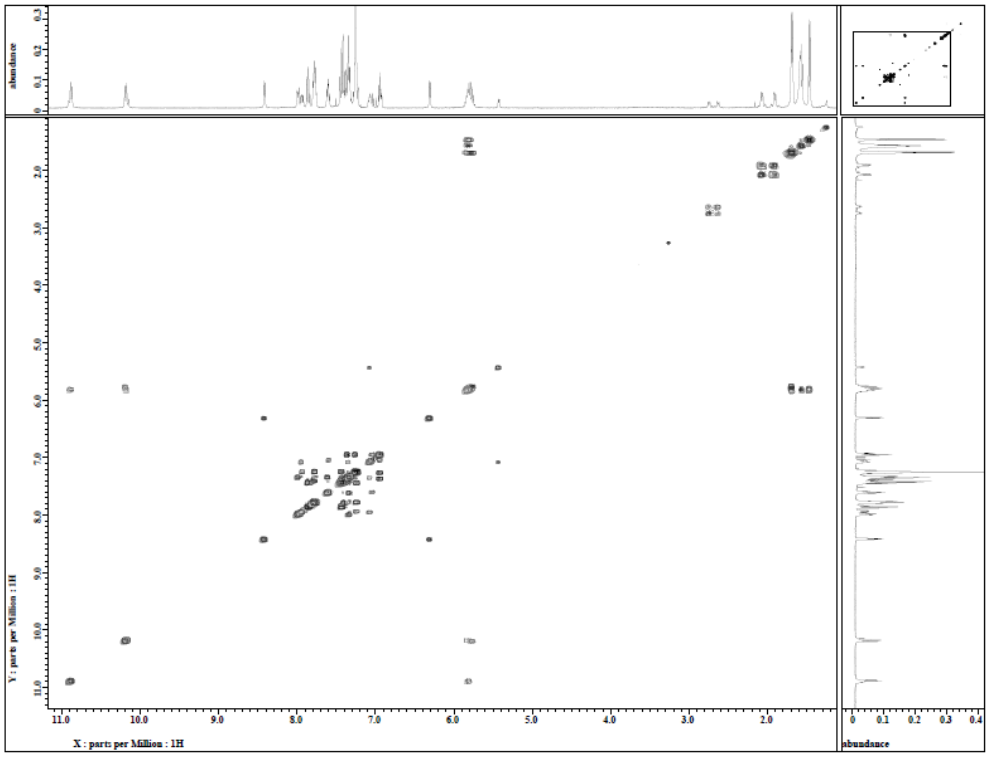


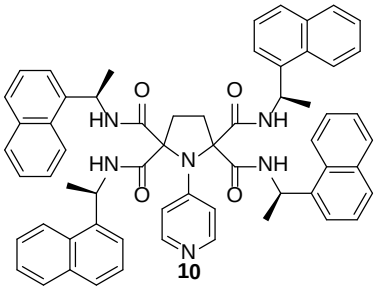
^{13}C NMR spectrum of **10** ($CDCl_3$)





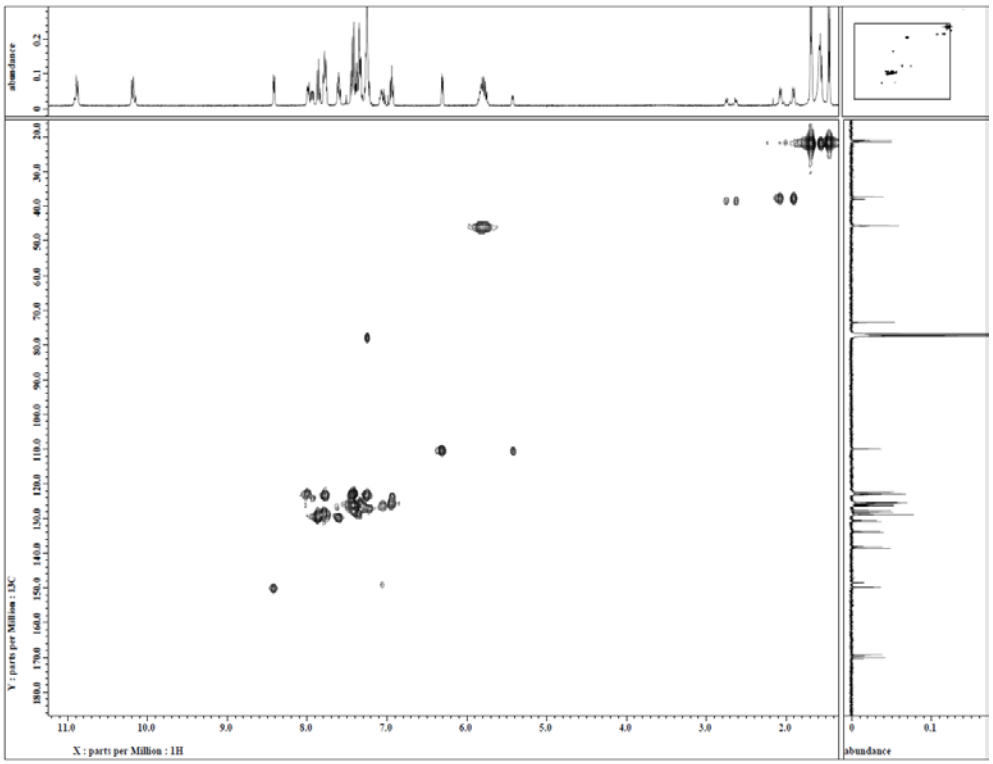
^{1}H-^{1}H COSY NMR spectrum of **10** ($CDCl_3$)

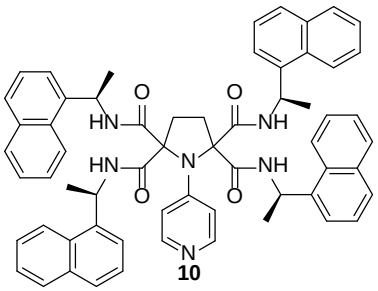




10

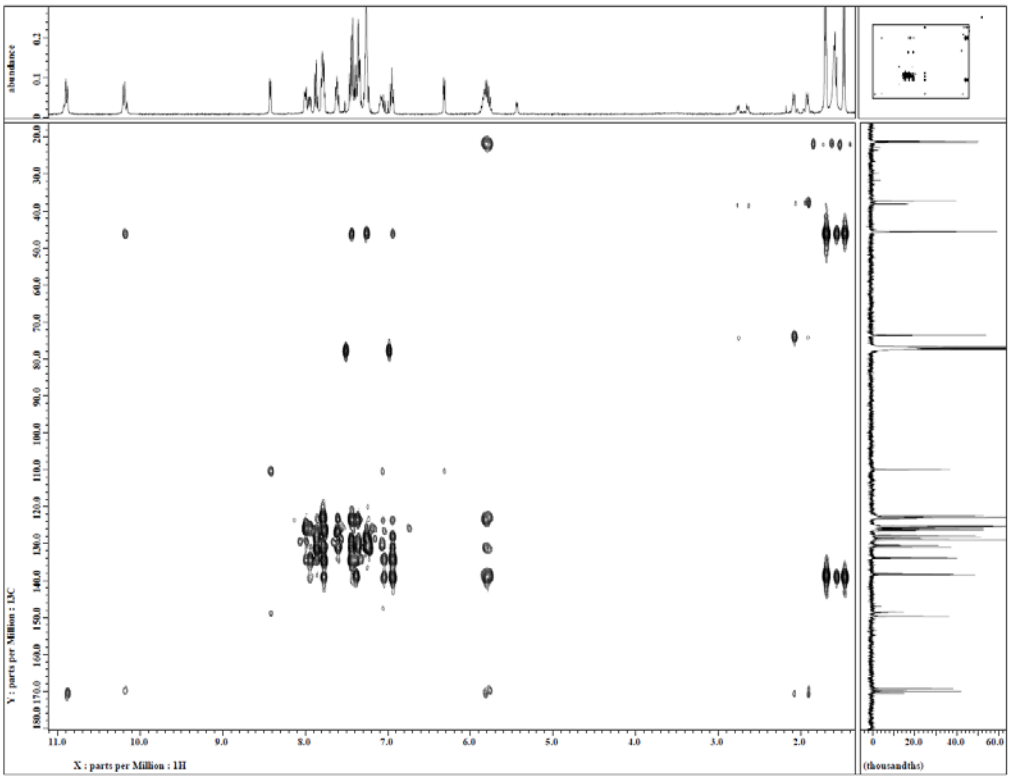
^{1}H-^{13}C HMQC NMR spectrum of **10** ($CDCl_3$)

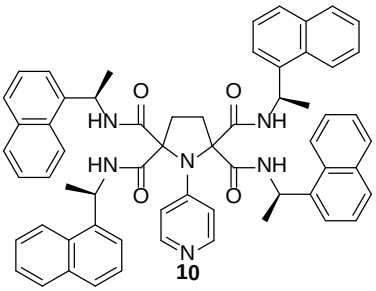




10

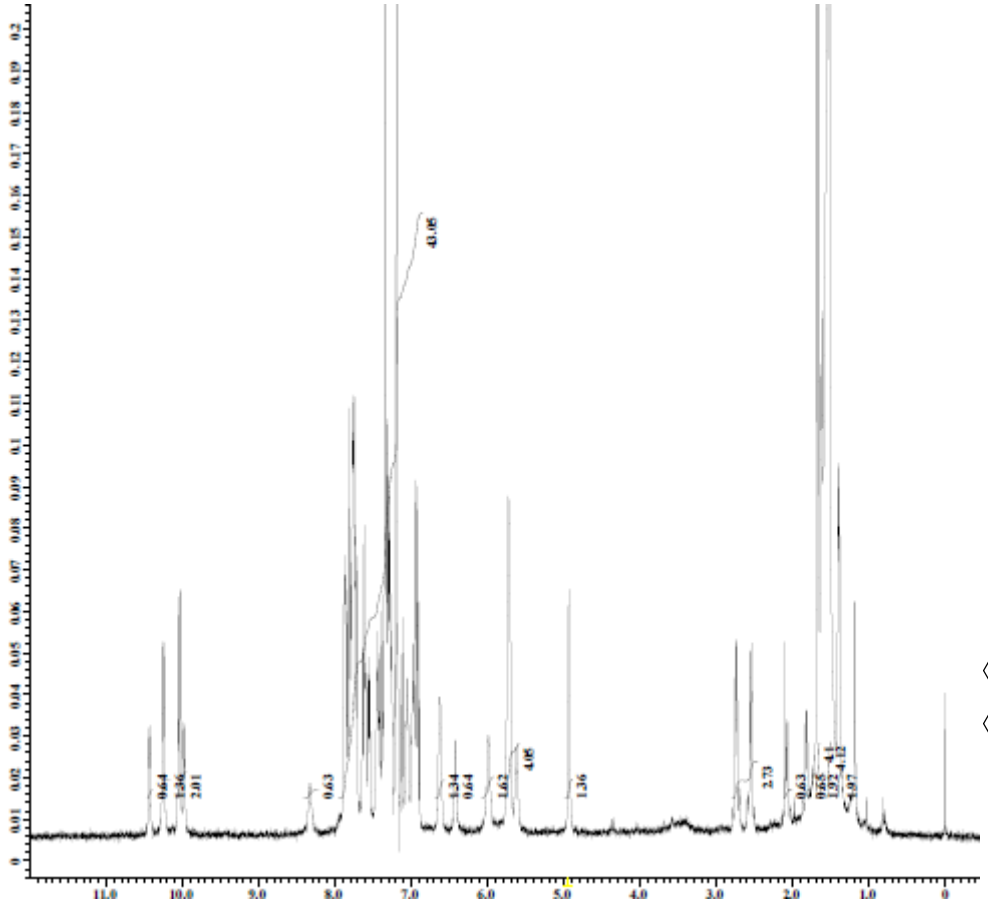
^{1}H-^{13}C HMBC NMR spectrum of **10** ($CDCl_3$)

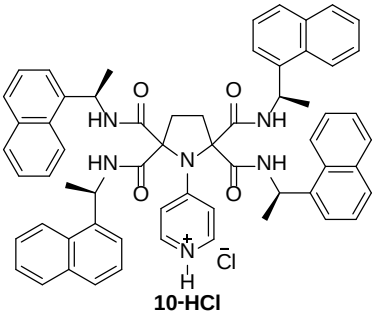




10

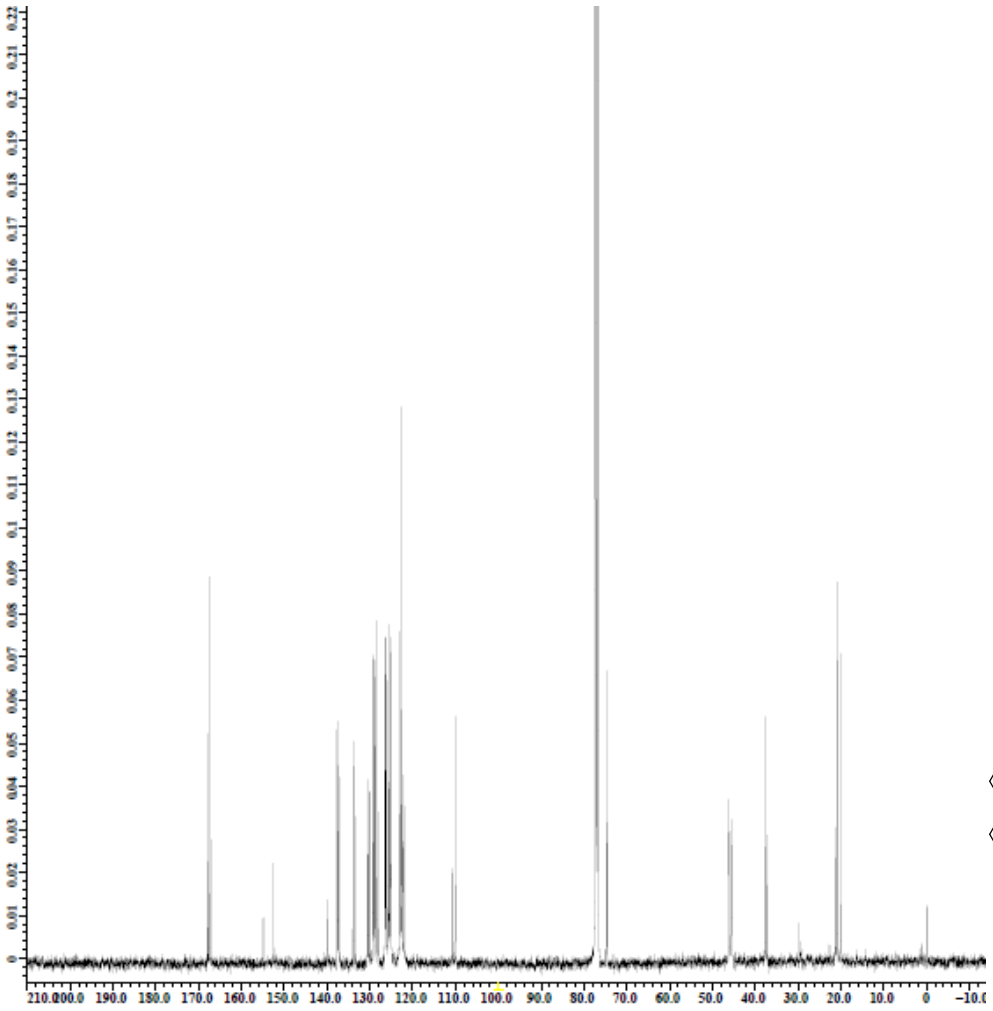
^{1}H NMR spectrum of **10-HCl** ($CDCl_3$)

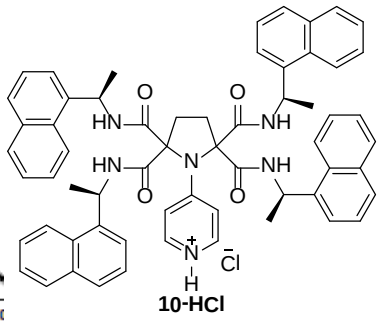




10-HCl

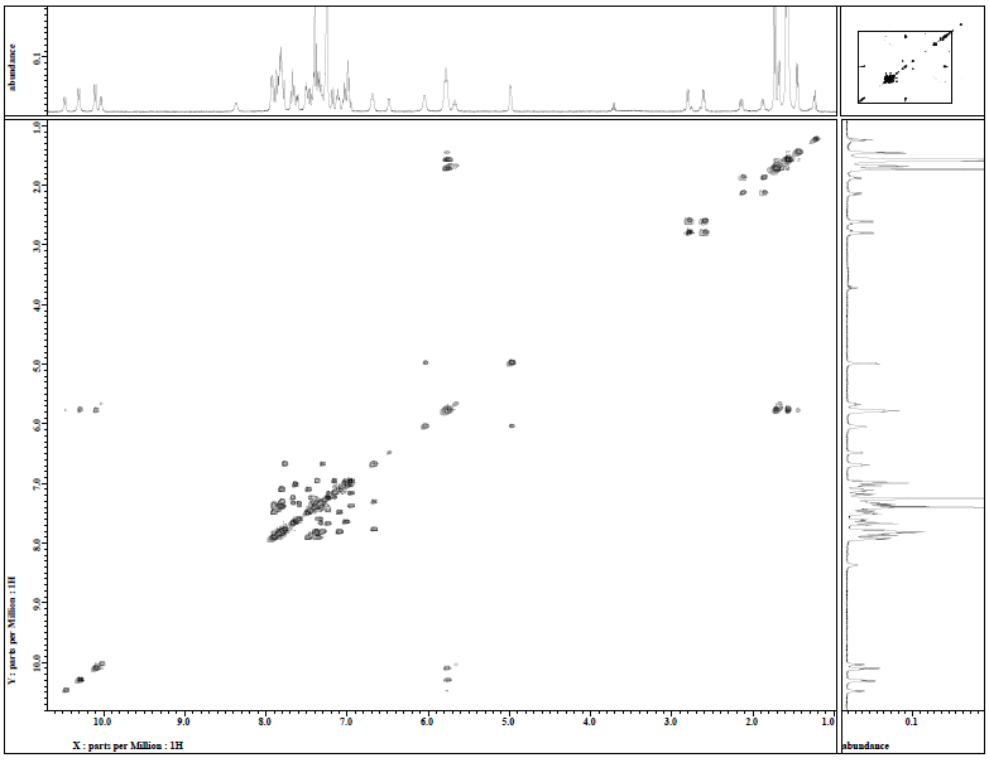
^{13}C NMR spectrum of **10-HCl** ($CDCl_3$)

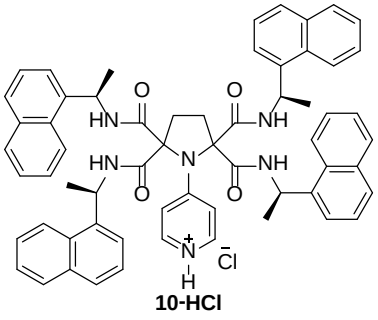




10-HCl

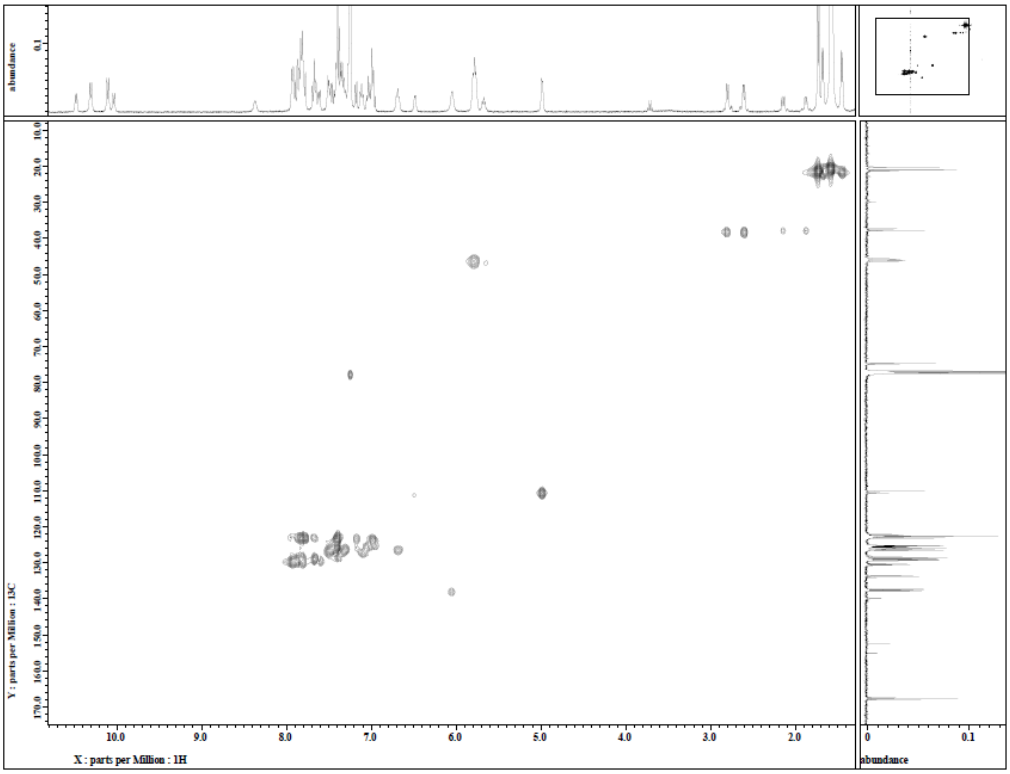
^{1}H-^{1}H COSY NMR spectrum of **10-HCl** ($CDCl_3$)

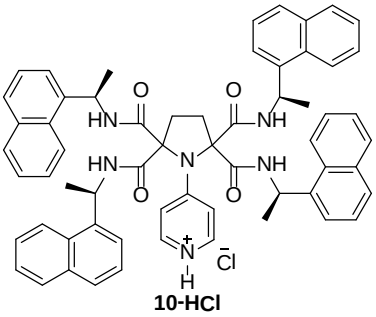




10-HCl

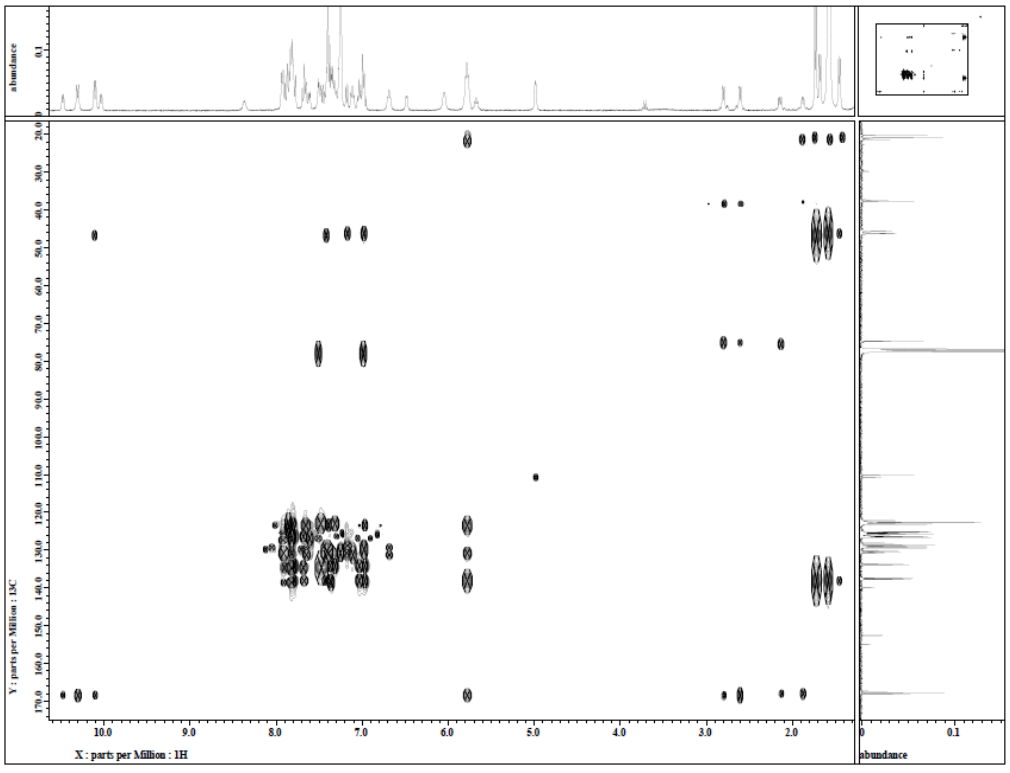
^{1}H-^{13}C HMQC NMR spectrum of **10-HCl** ($CDCl_3$)

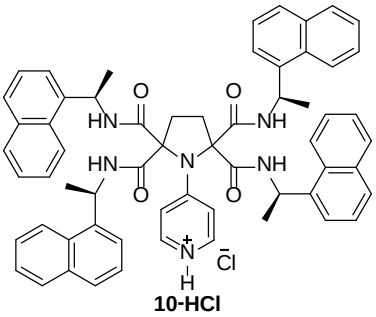




10-HCl

^{1}H-^{13}C HMBC NMR spectrum of **10-HCl** ($CDCl_3$)





10-HCl

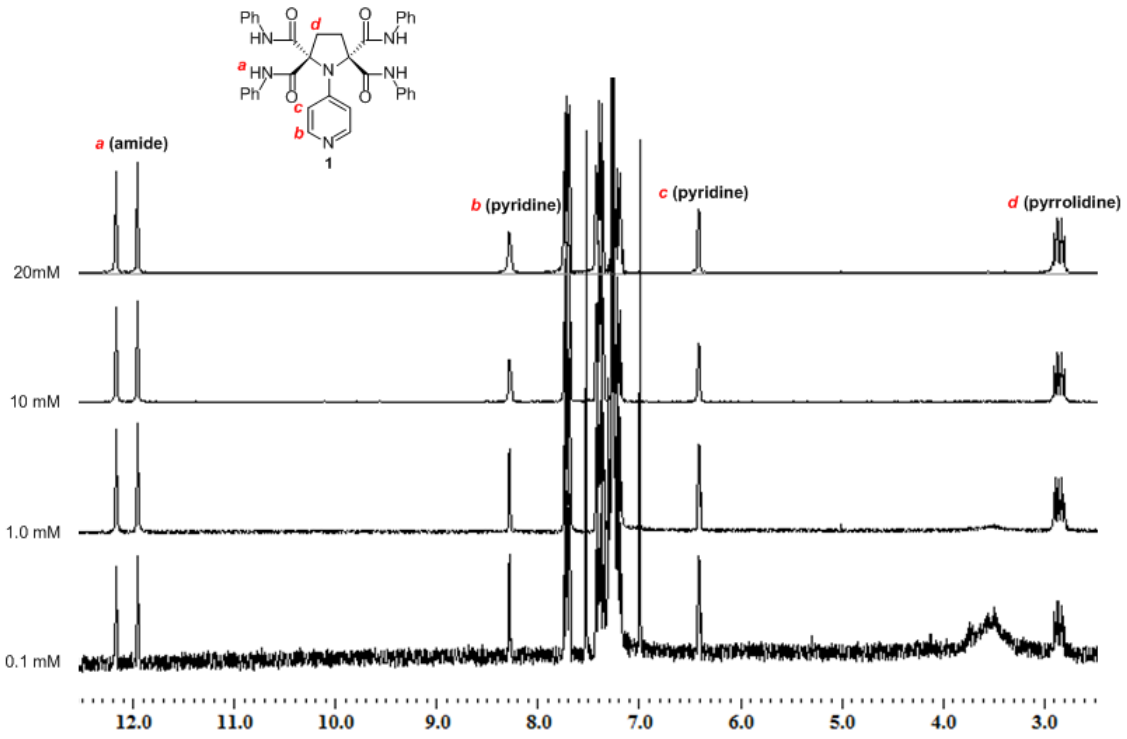


Figure S9. ^{1}NMR spectra of **1** with different concentrations (20 °C, $CDCl_3$)

VT NMR Experiment

Racemization barrier analysis of **1**-**8** in *o*-dichlorobenzene-d_4 and DMSO-d_6 were conducted by full line shape analysis of VT NMR spectra. VT NMR spectra were recorded at 400 MHz on a JEOL ECX-400 PKT spectrometer. Natural line widths for each spectrum were determined using pyridine C(2)-H signals as spectator signals. The chemical shifts of the amide protons at close to coalescence were determined from a plot of $\nu_A - \nu_B$ (in Hz) vs T at temperatures well below coalescence. Simulated spectra for the amide protons were generated using WINDNMR-Pro and compared with the acquired spectra using difference spectra. From these simulations, the rate constant k for inversion could be determined as a function of temperature. Hence, from the Eyring equation, the activation parameters could be determined by plotting ln(k/T) versus 1/T wherein

(1) $\Delta H^{\ddagger} = -R \times \text{slope}$

(2) $\Delta S^{\ddagger} = R \times [\text{intercept} + \ln (h/k_B)]$

$\left\langle \begin{array}{l} R = \text{gas constant} \\ h = \text{Plank's constant} \\ k_B = \text{Boltzmann constant} \end{array} \right\rangle$

Racemization barrier analysis of **1** (*o*-dichlorobenzene-d_4)

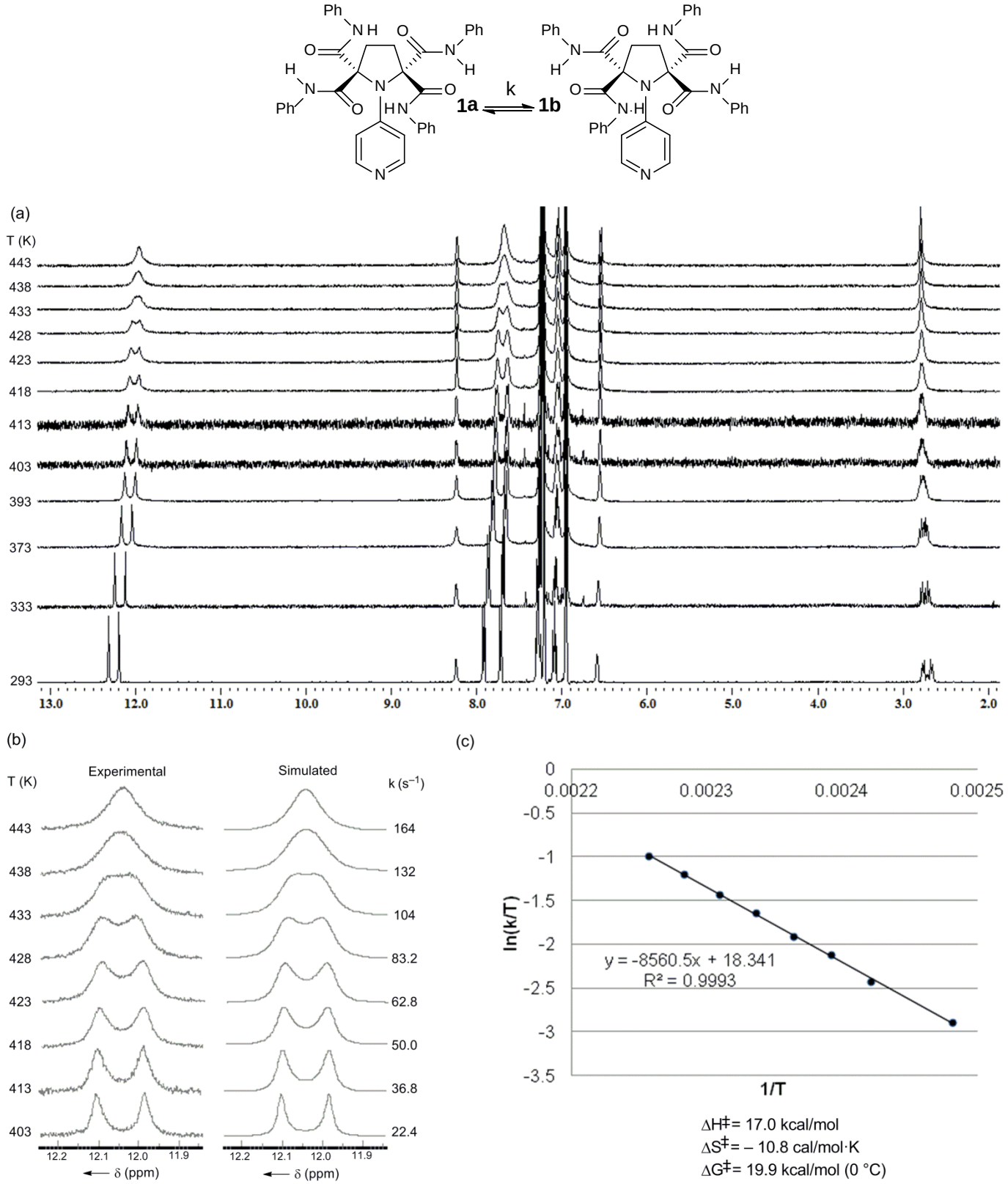


Figure S10. (a) VT NMR spectra of **1**. (b) Full line shape analysis of amide protons of **1**. (c) Eyring plot

Racemization barrier analysis of **2** (*o*-dichlorobenzene-d_4)

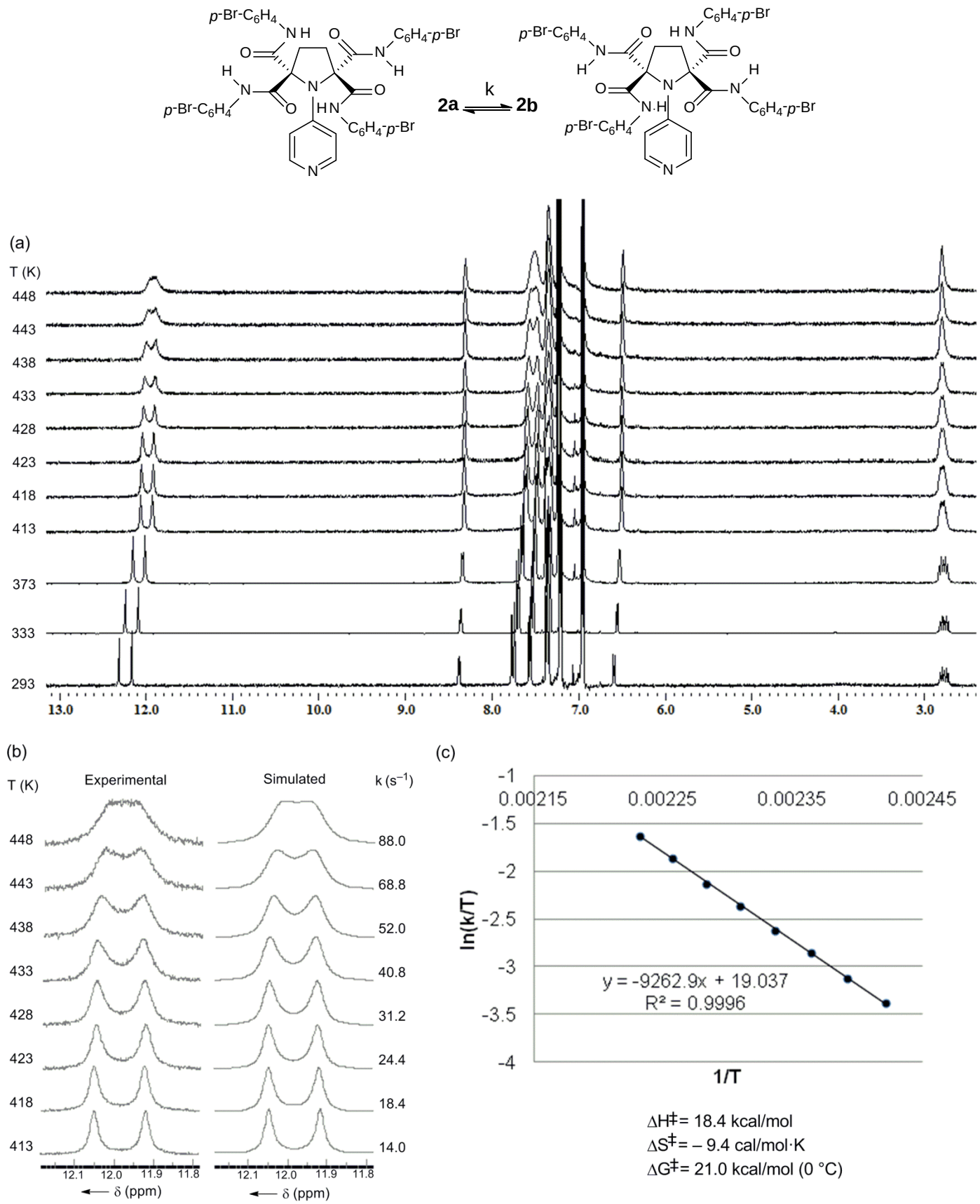


Figure S11. (a) VT NMR spectra of **2**. (b) Full line shape analysis of amide protons of **2**. (c) Eyring plot

Racemization barrier analysis of **3** (*o*-dichlorobenzene-d_4)

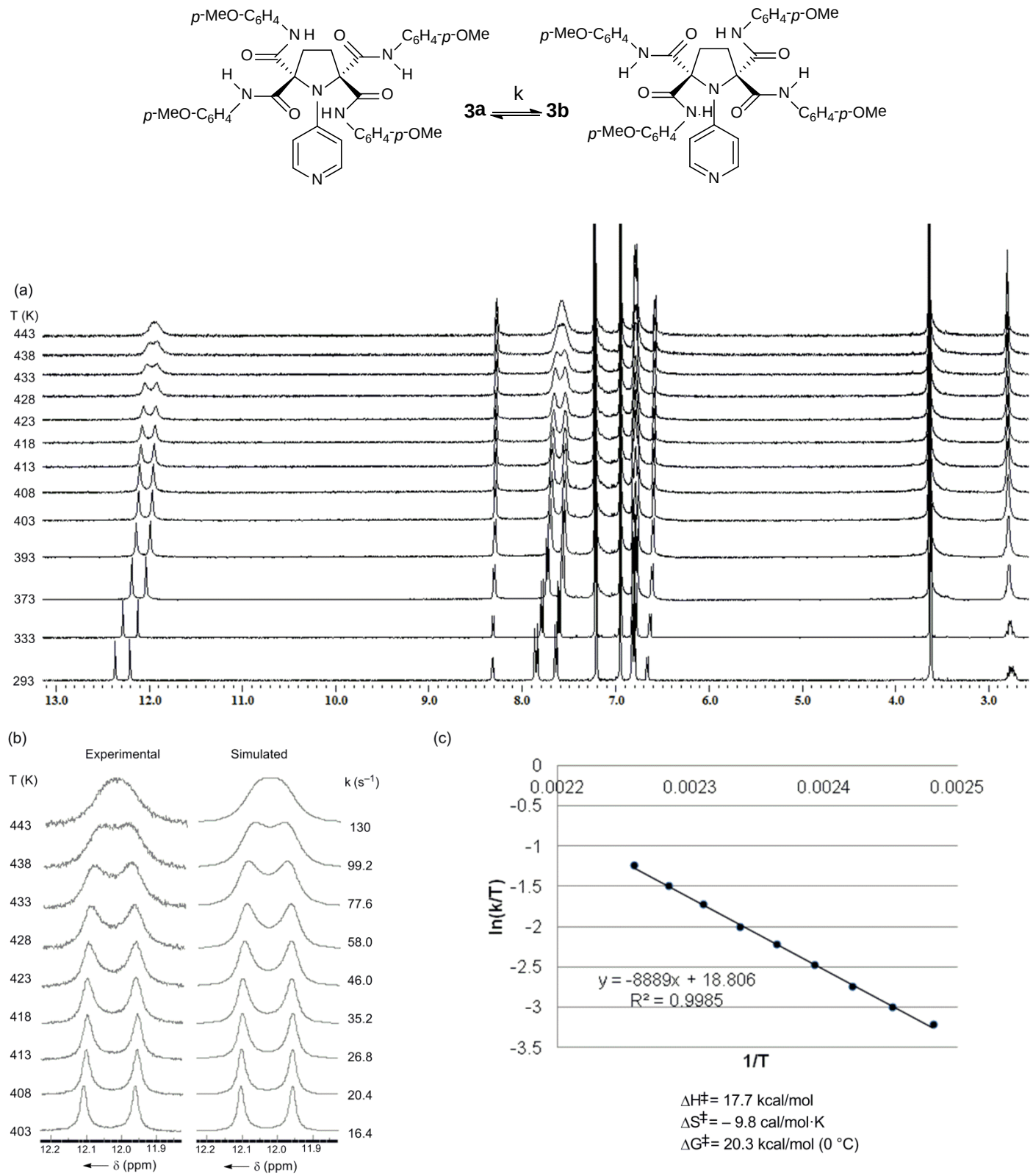


Figure S12. (a) VT NMR spectra of **3**. (b) Full line shape analysis of amide protons of **3**. (c) Eyring plot

Racemization barrier analysis of **4** (*o*-dichlorobenzene-d_4)

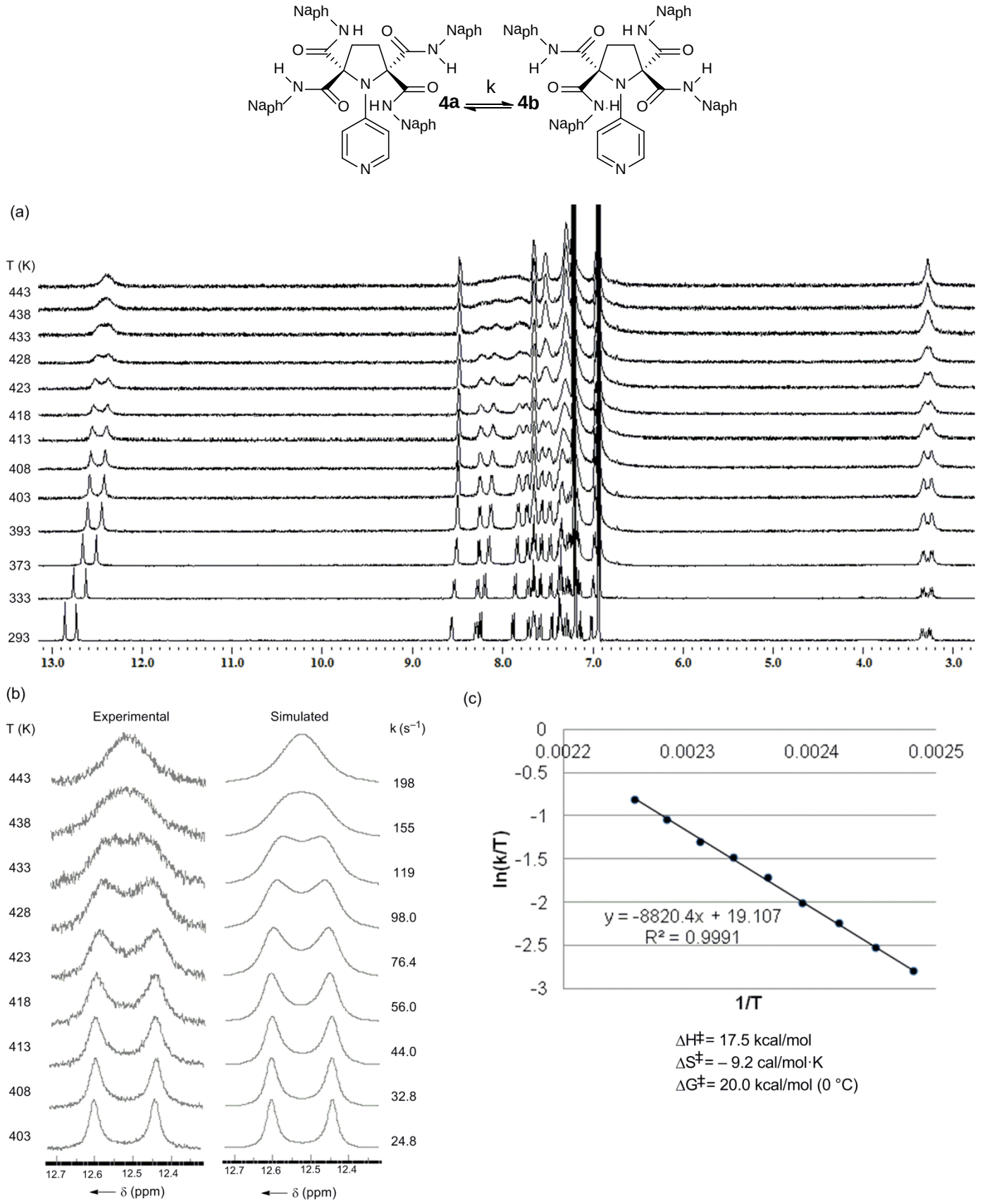


Figure S13. (a) VT NMR spectra of **4**. (b) Full line shape analysis of amide protons of **4**. (c) Eyring plot

Racemization barrier analysis of **5** (*o*-dichlorobenzene-d_4)

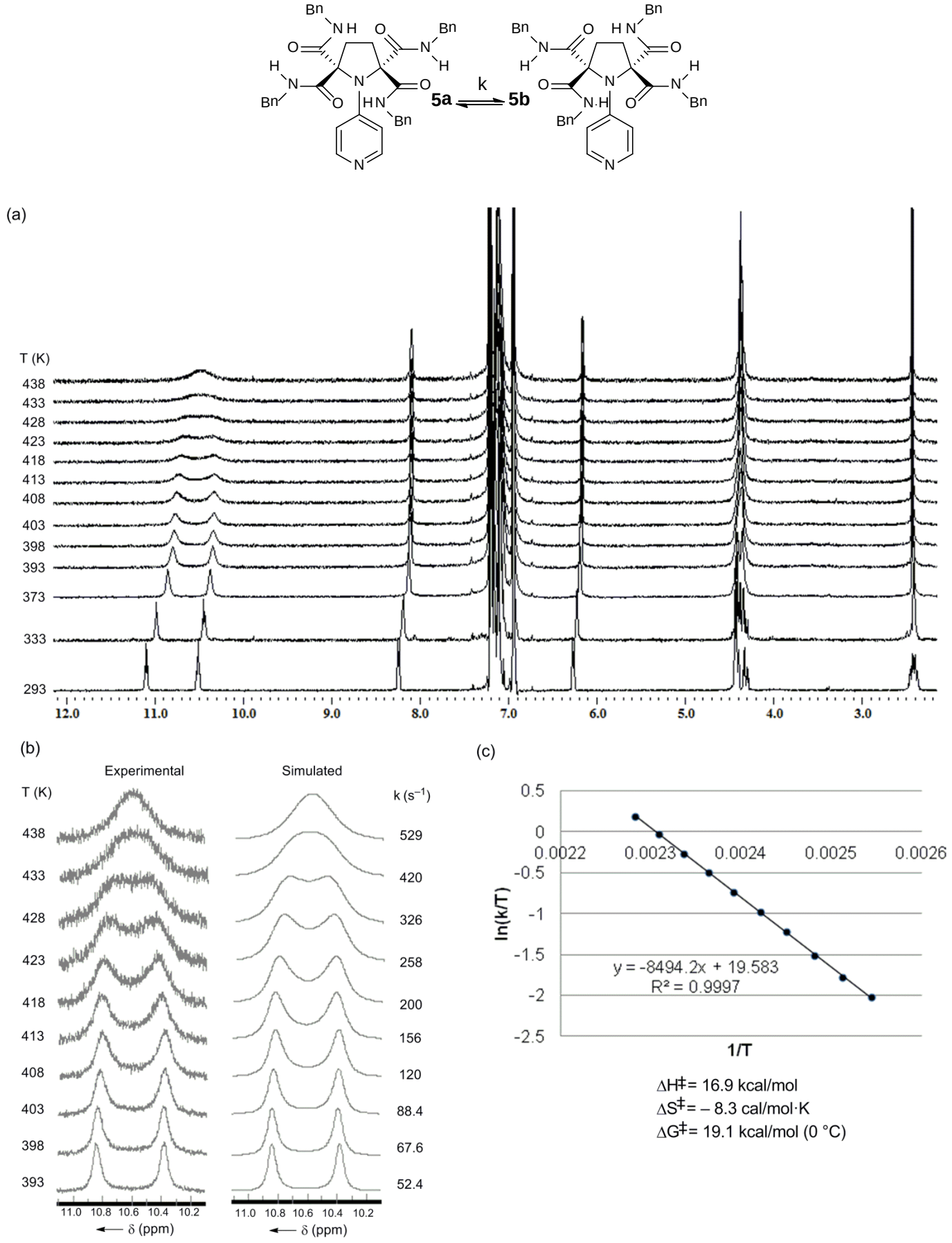


Figure S14. (a) VT NMR spectra of **5**. (b) Full line shape analysis of amide protons of **5**. (c) Eyring plot

Racemization barrier analysis of **6** (*o*-dichlorobenzene-d_4)

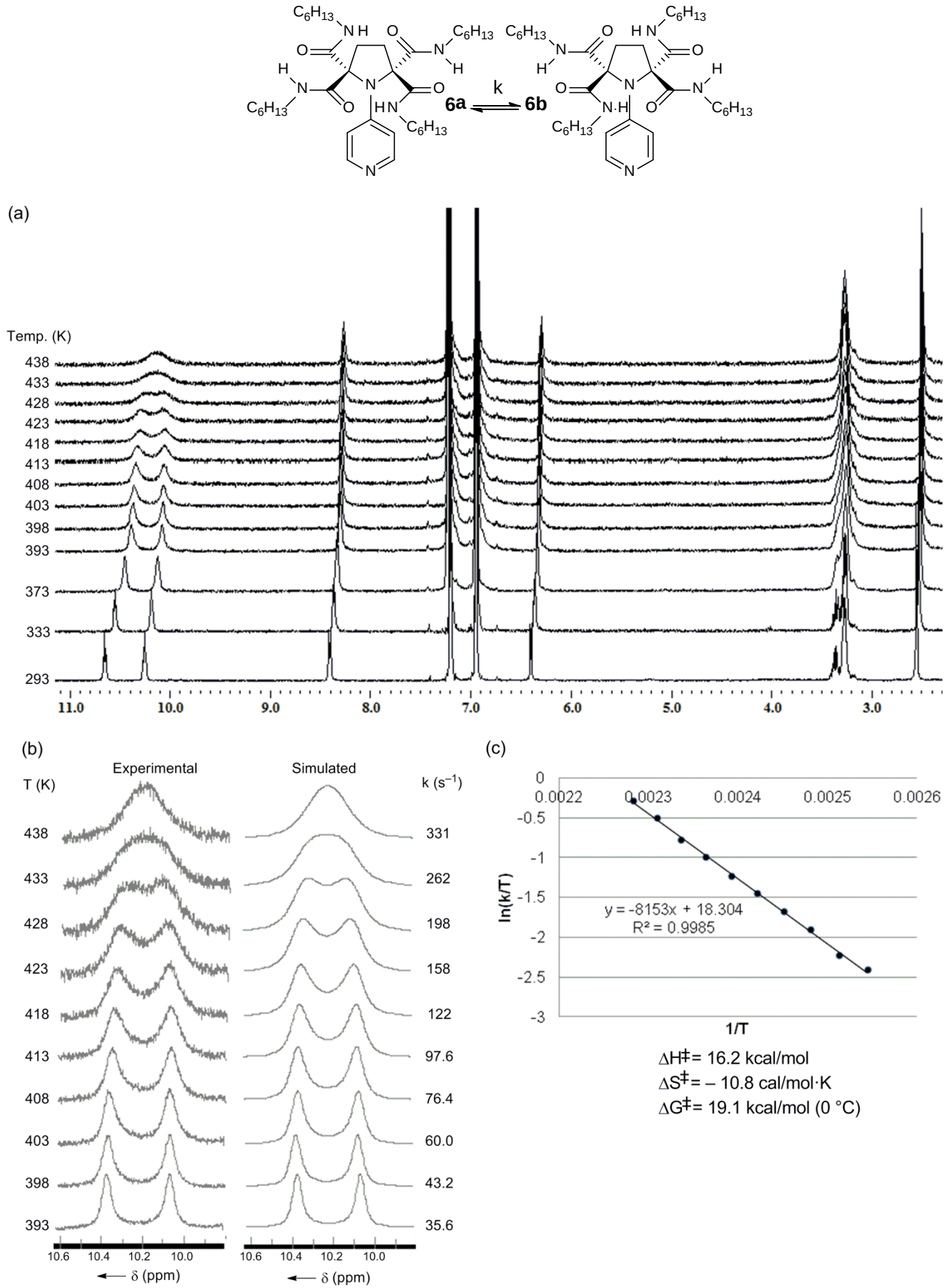


Figure S15. (a) VT NMR spectra of **6**. (b) Full line shape analysis of amide protons of **6**. (c) Eyring plot

Racemization barrier analysis of **7** (*o*-dichlorobenzene-d_4)

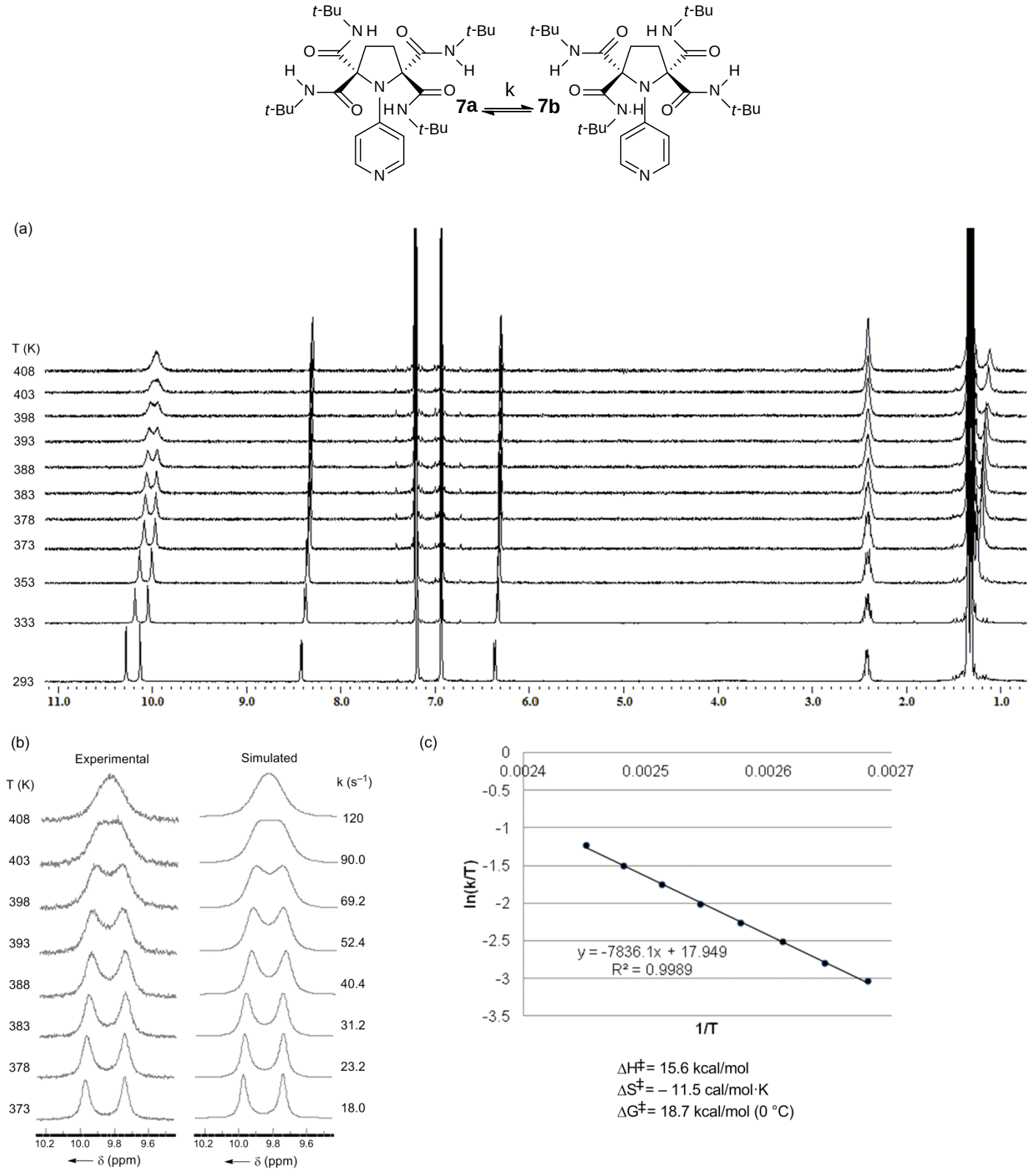


Figure S16. (a) VT NMR spectra of **7**. (b) Full line shape analysis of amide protons of **7**. (c) Eyring plot

Racemization barrier analysis of **8** (*o*-dichlorobenzene-d_4)

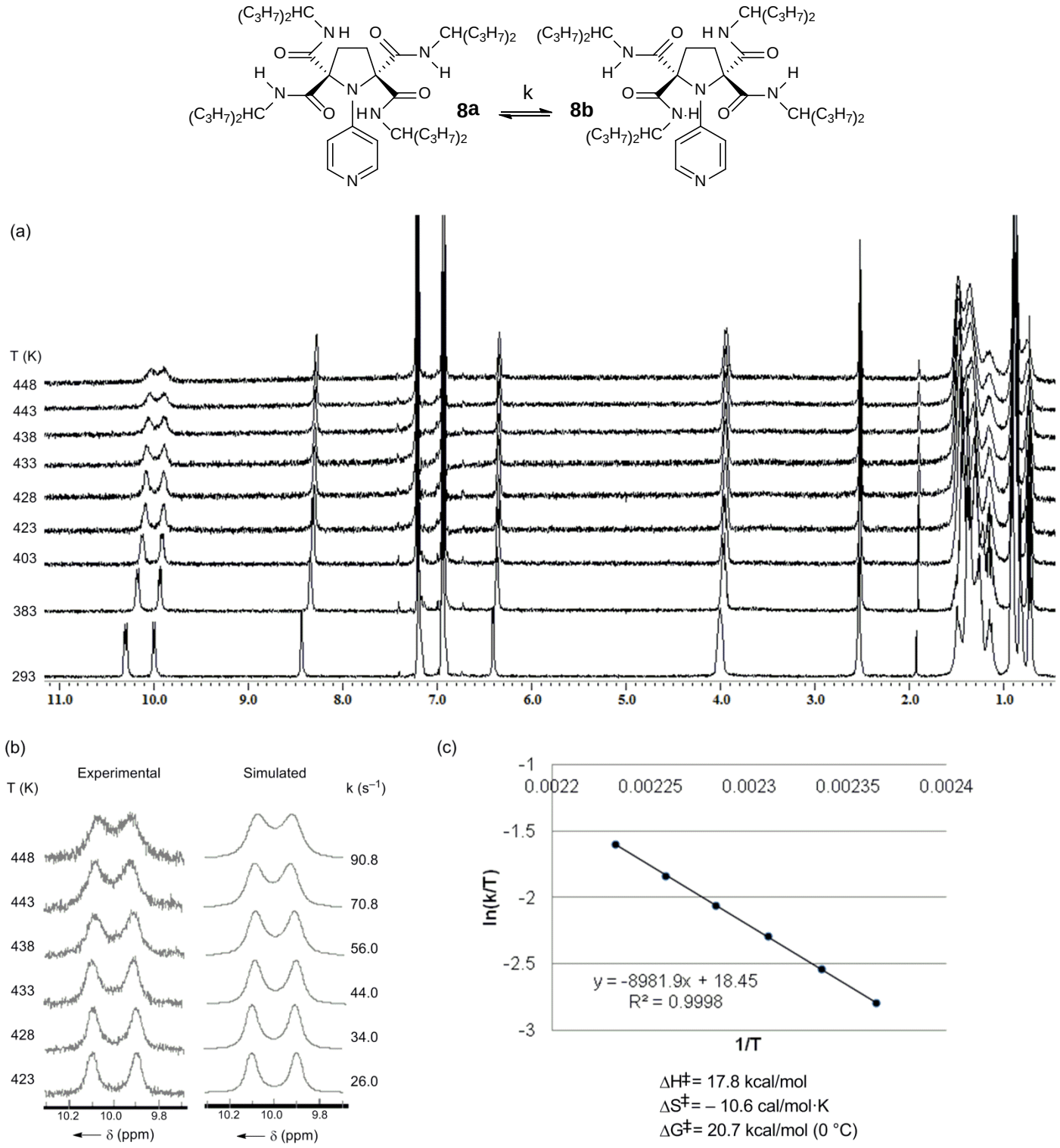


Figure S17. (a) VT NMR spectra of **8**. (b) Full line shape analysis of amide protons of **8**. (c) Eyring plot

Racemization barrier analysis of **7** (DMSO-d_6)

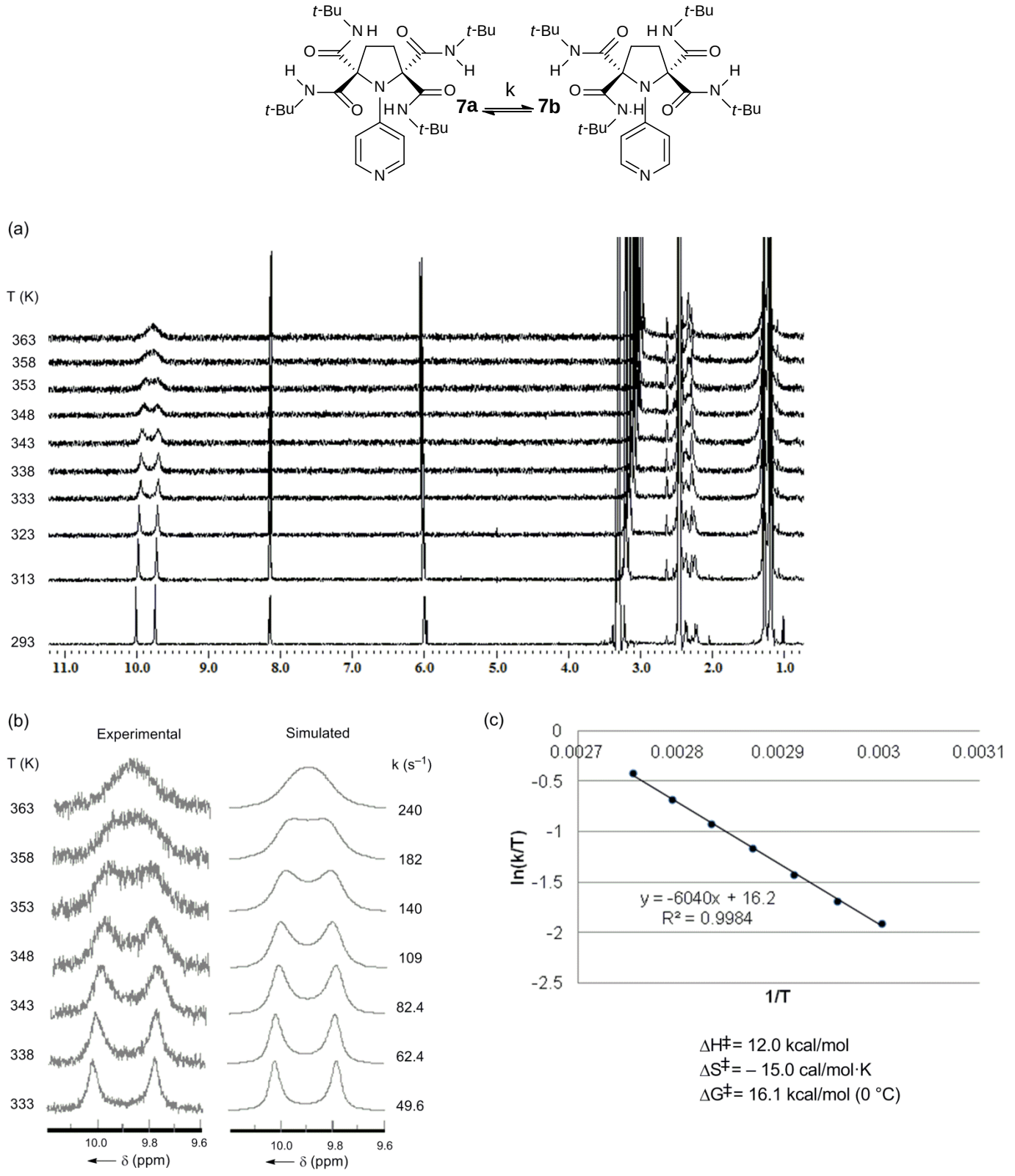


Figure S18. (a) VT NMR spectra of **7**. (b) Full line shape analysis of amide protons of **7**. (c) Eyring plot

Racemization barrier analysis of **8** (DMSO-d_6)

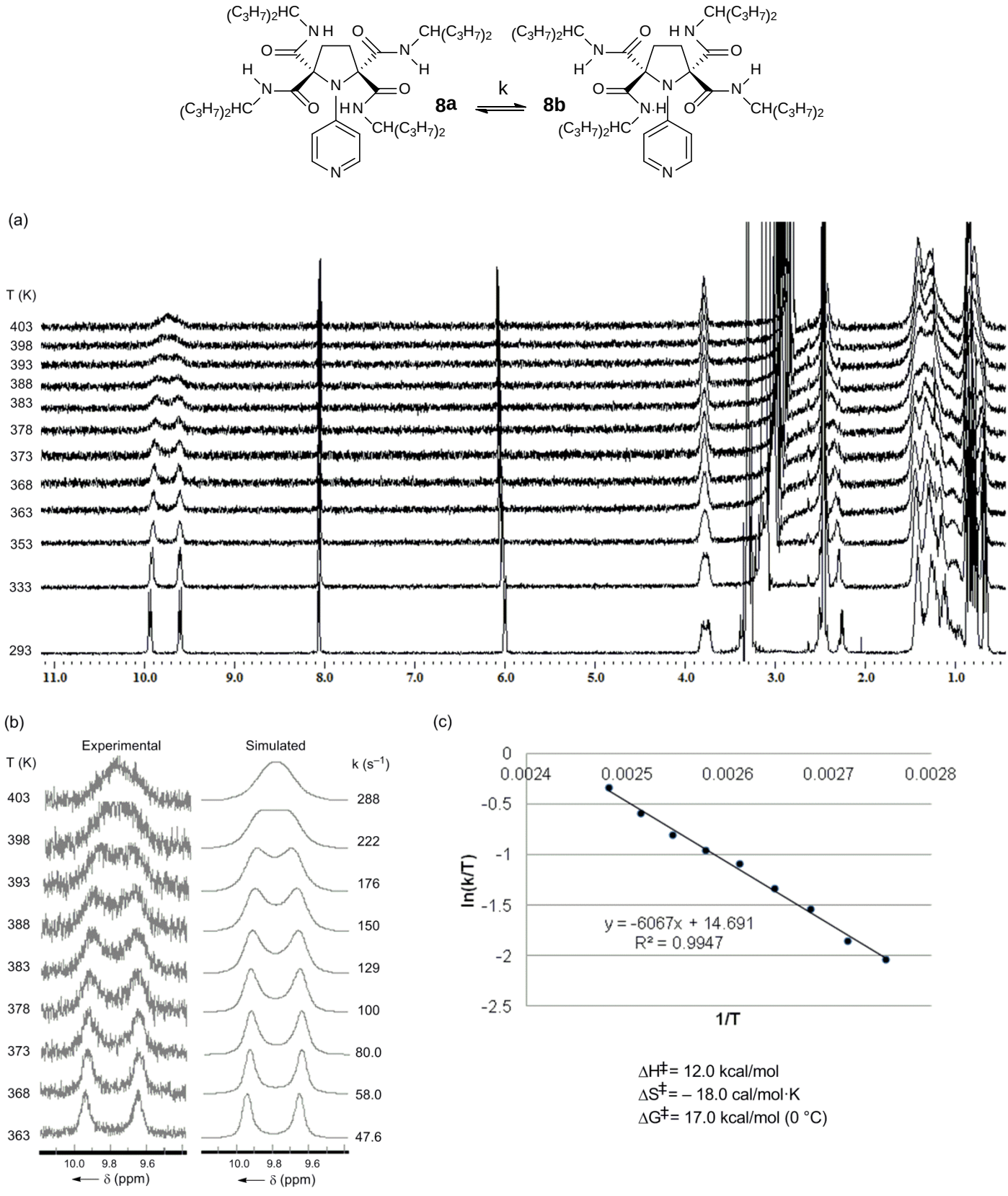


Figure S19. (a) VT NMR spectra of **8**. (b) Full line shape analysis of amide protons of **8**. (c) Eyring plot