Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

Large-Amplitude Conformational Changes in Self-Assembled Multi-Stranded Aromatic Sheets

*Joan Atcher, Pedro Mateus, Brice Kauffmann, Frédéric Rosu, Victor Maurizot, and Ivan Huc**

anie_202014670_sm_miscellaneous_information.pdf
anie_202014670_sm_movie_S1.mp4
anie_202014670_sm_movie_S2.mp4
anie_202014670_sm_movie_S3.mp4

TABLE OF CONTENTS

1. ABBREVIATIONS

AcOEt: ethylacetate.

CCS: collisional cross sections.

DCM: dichloromethane.

DIAD: diisopropyl azodicarboxylate.

DIPEA: *N*,*N*-diisopropylethylamine.

DMF: *N*,*N*-dimethylformamide.

ESI: electrospray ionization.

Ghosez's reagent: 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine.

GPC: gel permeation chromatography.

HRMS: high-resolution mass spectrometry.

IM-MS: ion mobility-mass spectrometry.

NMR: nuclear magnetic resonance.

Piv: pivaloyl (2,2-dimethylpropanoyl).

PPh_3: triphenylphosphine.

PyBOP: benzotriazol-1-yl-oxy-tripyrrolidinophosphonium hexafluorophosphate.

TFA: trifluoroacetic acid.

THF: tetrahydrofuran.

TLC: thin layer chromatography.

VT: variable temperature.

2. GENERAL METHODS

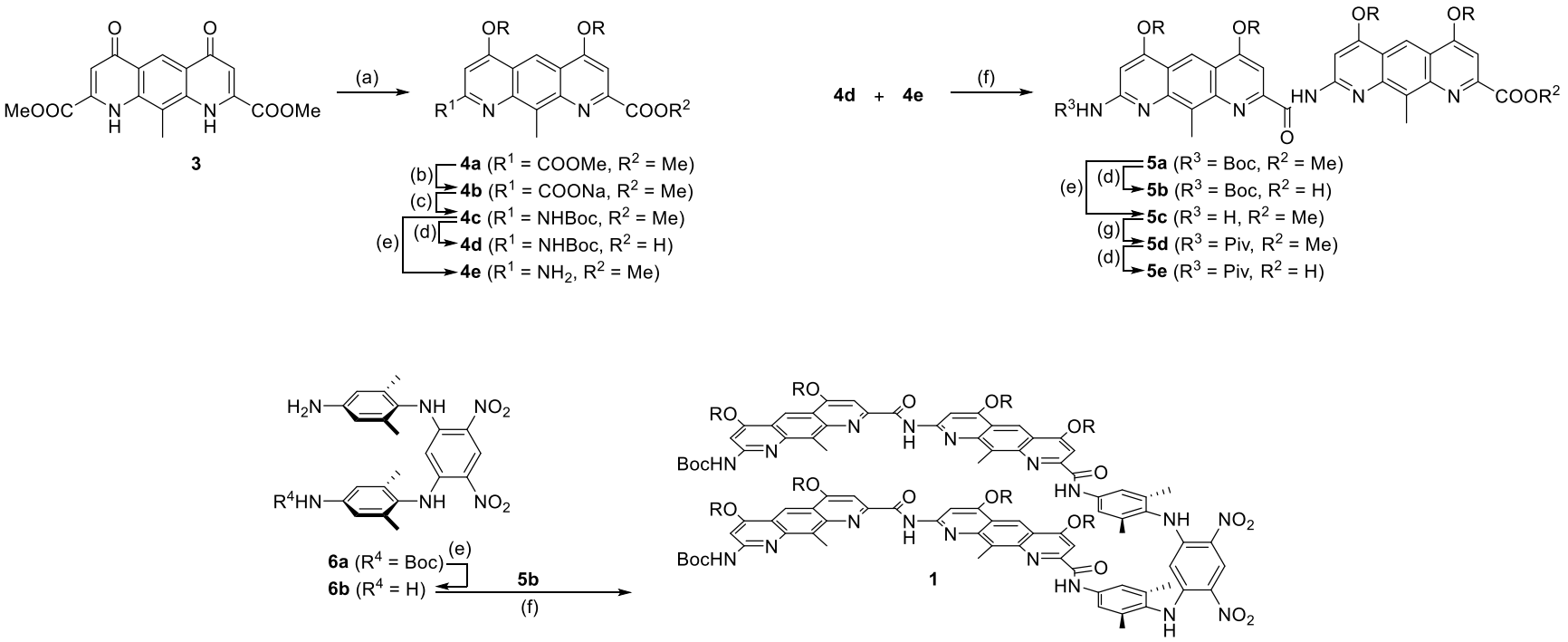
NMR spectroscopic experiments were carried out on five different instruments. NMR instruments at the IECB technology platform: **(1)** Avance II 300 MHz Bruker BioSpin (300 MHz for ^{1}H observation) equipped with a BBO H/X probe; **(2)** DPX-400 Bruker BioSpin (400 MHz for ^{1}H observation) equipped with a QNP $^{1}H/^{13}C/^{31}P/^{19}F$ probe; **(3)** Avance III 700 MHz Bruker BioSpin (700 MHz for ^{1}H observation) equipped with a TXI $^{1}H/^{13}C/^{15}N$ probe. NMR instruments at the analytical division at the Faculty for Chemistry and Pharmacy in LMU: **(4)** Avance III HD 400 MHz Bruker BioSpin (400 MHz for ^{1}H observation) equipped with a broadband probe; **(5)** Avance III HD 500 MHz Bruker BioSpin (500 MHz for ^{1}H observation) equipped with a CryoProbe™ Prodigy broadband probe. Chemical shifts (δ) are reported in parts per million (ppm) relative to trimethylsilane (TMS), and coupling constants (*J*) are reported in Hertz (Hz). ^{1}H NMR splitting patterns are designated as singlet (s), broad singlet (brs), doublet (d), triplet (t), septet (sep), multiplet (m) and broad multiplet (brm). Samples were not degassed.

Preparative recycling GPC purifications were performed on a LC-91XXII NEXT series instrument equipped with polymer-based JAIGEL-HR 20 x 600 mm columns (Japan Analytical Industry Co., Ltd.) at a flow rate of 7.5 $mL \cdot min^{-1}$ with a mobile phase composed of 1% EtOH (vol/vol) and 0.5% Et_3N (vol/vol) in HPLC grade chloroform. Monitoring by UV detection was carried out at 254 nm, 280 nm, 300 nm and 360 nm. Collected fractions were washed twice with saturated aqueous NH_4Cl to remove the Et_3N.

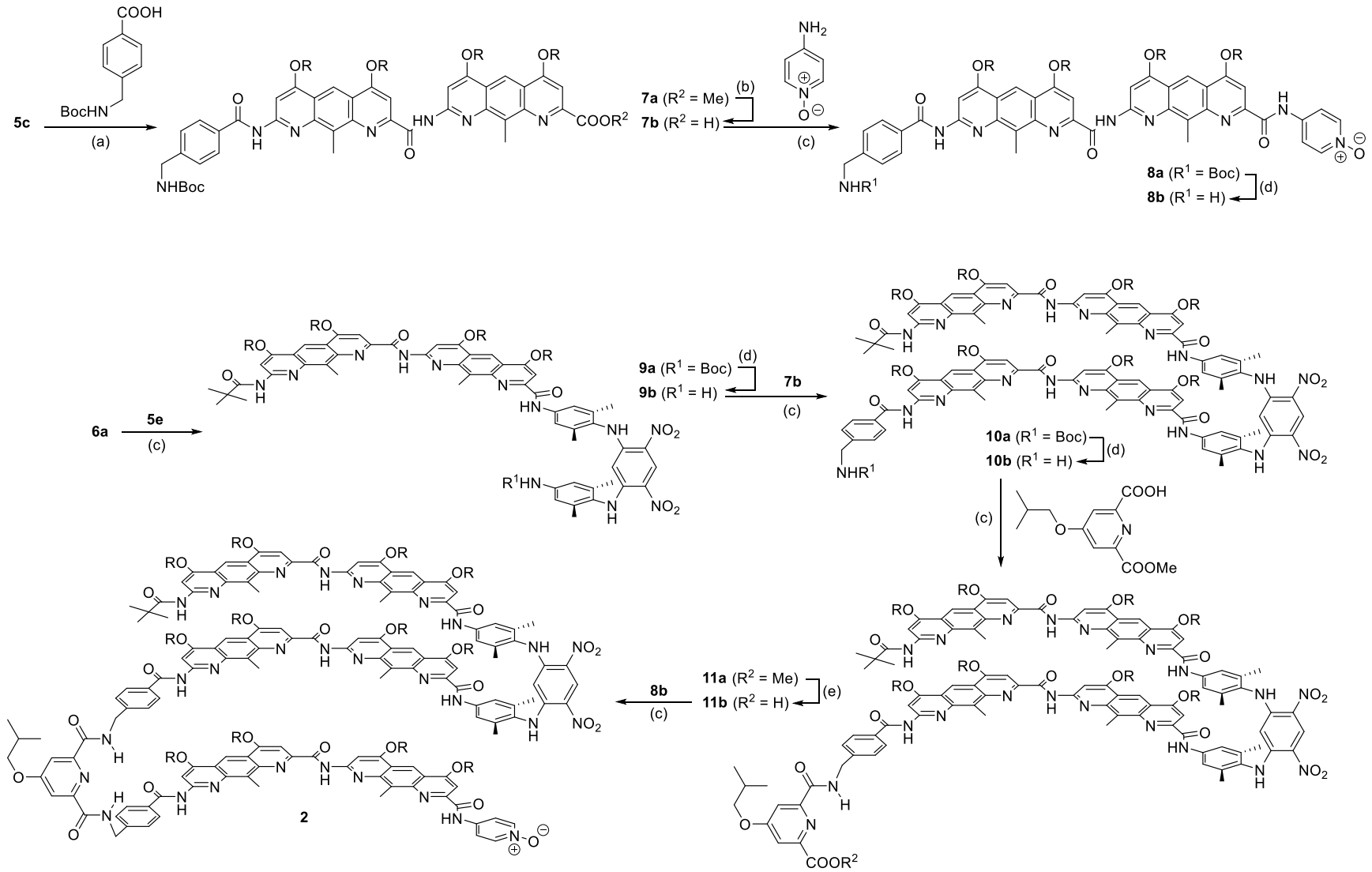
HRMS (ESI+) experiments were performed using a **(1)** Thermo Fisher Scientific Exactive Orbitrap instrument, HESI-II electrospray source operated in positive ion mode (IECB Mass Spectrometry facility); and **(2)** Bruker micrOTOF II instrument operating in positive ion mode.

3. SYNTHETIC PROTOCOLS

3.1. Synthetic schemes



Scheme S1. Synthetic pathway for the synthesis of monomer **4**, dimer **5** and compound **1** (R = $OCH_2CH(CH_2CH_3)_2$). Reagents and conditions: (a) 2-ethyl-1-butanol, PPh_3, DIAD, dry THF; (b) NaOH, MeOH/THF; (c) i. oxalyl chloride, dry DCM, ii. trimethylsilyl azide, dry DCM, iii. *tert*-butanol; (d) $LiOH \cdot H_2O$, $MeOH/H_2O$/THF; (e) TFA/DCM; (f) PyBOP, dry DIPEA, dry $CHCl_3$; (g) pivaloyl chloride, dry DIPEA, dry $CHCl_3$.



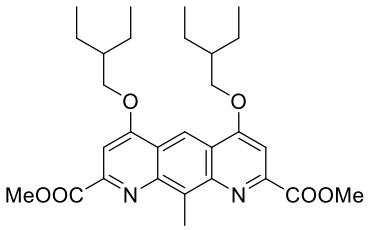
Scheme S2. Synthetic pathway for the synthesis of compound **2** (R = $OCH_2CH(CH_2CH_3)_2$). Reagents and conditions: (a) i. Ghosez's reagent, dry DCM, ii. dry DIPEA, dry $CHCl_3$; (b) $LiOH{\cdot}H_2O$, $MeOH/H_2O/THF$; (c) PyBOP, dry DIPEA, dry $CHCl_3$; (d) TFA/DCM; (e) LiI, dry pyridine.

3.2. Materials and methods for chemical synthesis

Commercial reagents were purchased from Sigma-Aldrich, TCI Chemicals or Alfa-Aesar and were used without further purification. DCM and THF were dried over alumina columns (MBRAUN SPS-800 solvent purification system) whereas chloroform and diisopropylethylamine were distilled over CaH_2 prior to use. Reactions were monitored by TLC on Merck silica gel 60 F_{254} plates and observed under UV light. Column chromatography purifications were carried out on Merck GEDURAN Si60 (40-63 µm).

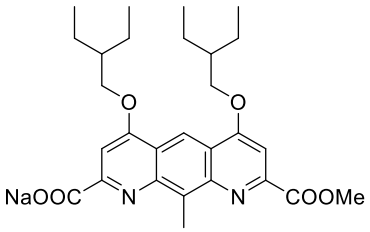
Compound **3**[1] and the turn unit based on 4,6-dinitro-1,3-phenylenediamine, *i.e.* compounds **6a-b**,[2] were synthesized as previously reported. Also 4-isobutoxy-6-(methoxycarbonyl)picolinic acid (CAS: 1236183-22-4)[3] and 4-aminopyridine 1-oxide (CAS: 3535-75-9)[4] were prepared as previously described.

3.3. Synthesis of monomeric compounds **4a-e**



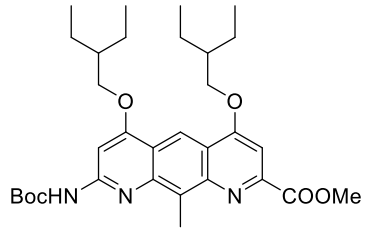
Chemical Formula: $C_{29}H_{38}N_2O_6$

Synthesis of compound **4a**: Compound **3** (30.0 g, 87.6 mmol), 2-ethyl-1-butanol (27.0 mL, 219 mmol) and triphenylphosphine (57.5 g, 219 mmol) were suspended in dry THF (375 mL), under inert atmosphere of N_2. The slurry was cooled down to 0 °C in an ice-bath and DIAD (43.0 mL, 219 mmol) was added dropwise under stirring. The resulting mixture was stirred at 0 °C for 30 minutes and then at room temperature for 48 hours, after which volatiles were removed *in vacuo*. The crude product was purified by precipitation from DCM/MeOH (1:1, v/v, slow evaporation of DCM), to give 37.1 g (83% yield) of compound **4a** as a bright yellow solid. HRMS (ESI+) calcd. for $C_{29}H_{39}N_2O_6$ $[M+H]^+$ (m/z): 511.2803, found: 511.2807. ^{1}H NMR (300 MHz, CDCl3, 298 K) δ 9.10 (s, 1H, CH_{Ar}), 7.52 (s, 2H, CH_{Ar}), 4.27 (d, J = 5.4 Hz, 4H, OCH_2), 4.10 (s, 6H, $COOCH_3$), 3.50 (s, 3H, $ArCH_3$), 1.90 (sep, J = 6.1 Hz, 2H, $C\underline{H}(CH_2CH_3)_2$), 1.78 – 1.53 (m, 8H, $CH(C\underline{H}_2CH_3)_2$), 1.04 (t, J = 7.5 Hz, 12H, $CH(CH_2C\underline{H}_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ 166.5, 163.5, 149.8, 145.8, 139.1, 121.6, 113.5, 98.7, 71.1, 53.3, 41.1, 23.8, 13.1, 11.5.



Chemical Formula: $C_{28}H_{35}N_2NaO_6$

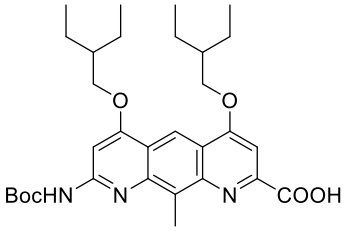
Synthesis of compound **4b**: A solution of NaOH (910 mg, 22.8 mmol) in MeOH (15 mL) was slowly added to a solution of compound **4a** in 650 mL of THF/MeOH (3:1, vol:vol). The reaction mixture was stirred at room temperature for 24 h, during which time the product precipitated from solution. The white/yellow solid was filtered off, washed with cold MeOH (200 mL) and Et_2O (100 mL), and dried under reduced pressure, obtaining 7.03 g (69% yield) of compound **4b** as pale white/yellow solid. HRMS (ESI+) calcd. for $C_{28}H_{37}N_2O_6$ $[M+H]^+$ (m/z): 497.2646, found: 497.2645. ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ 9.15 (s, 1H, CH_{Ar}), 7.61 (s, 1H, CH_{Ar}), 7.54 (s, 1H, CH_{Ar}), 4.31 (d, *J* = 5.4 Hz, 2H, OCH_2), 4.28 (d, *J* = 5.4 Hz, 2H, OCH_2), 4.11 (s, 3H, $COOCH_3$), 3.43 (s, 3H, $ArCH_3$), 1.99 – 1.84 (m, 2H, $C\underline{H}(CH_2CH_3)_2$), 1.77 – 1.41 (m, 8H, $CH(C\underline{H}_2CH_3)_2$), 1.09 – 0.99 (2 x t, 12H, $CH(CH_2C\underline{H}_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 165.1, 164.4, 163.5, 150.4, 148.1, 145.7, 143.3, 137.1, 121.7, 121.3, 114.2, 99.1, 96.5, 71.8, 71.4, 53.3, 41.1, 41.0, 23.8, 23.7, 12.7, 11.5, 11.4.



Chemical Formula: $C_{32}H_{45}N_3O_6$

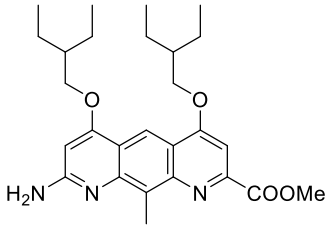
Synthesis of compound **4c**: Oxalyl chloride (7.75 mL, 90.4 mmol) was added dropwise to a slurry of compound **4b** (6.01 g, 11.6 mmol) in 30 mL of dry DCM, under inert atmosphere of N_2. After 4 hours stirring at room temperature, volatiles were removed *in vacuo* (4 hours under high vacuum). The resulting yellow/orange solid was redissolved in 30 mL of dry DCM and then trimethylsilyl azide (5.18 mL, 39.4 mmol) was added slowly, under inert atmosphere of N_2. After stirring at room temperature for 20 hours, volatiles were removed under reduced pressure. Then, 30 mL of anhydrous *tert*-butanol were added and the resulting yellow slurry was refluxed for 12 hours. Solvent was removed under reduced pressure. The crude product was dissolved in DCM and filtered through Celite®. After removal of solvents, the product was purified by precipitation from DCM/MeOH (2:1, vol:vol, slow evaporation of DCM) and by flash chromatography (SiO_2) using AcOEt/cyclohexane as eluent (from 5% to 20% AcOEt), to give 4.71 g (72% yield) of compound **4c** as a yellow solid. HRMS (ESI+) calcd. for $C_{32}H_{46}N_3O_6$ $[M+H]^+$ (m/z): 568.3381, found: 568.3377. ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ 8.96 (s, 1H, CH_{Ar}), 7.68 (s, 1H, CH_{Ar}), 7.57 (brs, 1H, NH), 7.44 (s, 1H, CH_{Ar}), 4.30 – 4.18 (2 x d, 4H, OCH_2), 4.08 (s, 3H, $COOCH_3$), 3.22 (s, 3H, $ArCH_3$), 1.97 – 1.78 (m, 2H, $C\underline{H}(CH_2CH_3)_2$), 1.75 – 1.48 (m, 17H, 8 x $CH(C\underline{H}_2CH_3)_2$, 9 x $OC(CH_3)_3$), 1.09 – 0.96 (2 x t, 12H, $CH(CH_2C\underline{H}_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 163.7, 163.5, 152.9, 152.6, 149.2, 146.0, 145.1, 133.5,

119.8, 118.9, 113.3, 97.5, 91.7, 81.1, 70.8, 70.5, 53.0, 41.1, 41.1, 28.2, 23.8, 23.8, 12.4, 11.5, 11.4.



Chemical Formula: $C_{31}H_{43}N_3O_6$

Synthesis of compound **4d**: A solution of $LiOH \cdot H_2O$ (222 mg, 5.28 mmol) in H_2O (1 mL) was added dropwise to a solution of compound **4c** (1.00 g, 1.76 mmol) in 9 mL of THF/MeOH (8:1, vol:vol). The reaction mixture was stirred at room temperature for 4 hours, after which complete conversion of the starting material was observed by TLC. Then 15 mL of 5% aqueous citric acid were added to neutralize the excess of base. The mixture was diluted with $CHCl_3$, washed with 5% aqueous citric acid and saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure, obtaining 966 mg (99% yield) of compound **4d** as a yellow solid. HRMS (ESI+) calcd. for $C_{31}H_{44}N_3O_6$ $[M+H]^+$ (m/z): 554.3225, found: 554.3226. ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ 9.01 (s, 1H, CH_{Ar}), 7.74 (s, 1H, CH_{Ar}), 7.61 (brs, 1H, NH), 7.56 (s, 1H, CH_{Ar}), 4.30 (d, *J* = 5.4 Hz, 2H, OCH_2), 4.25 (d, *J* = 5.1 Hz, 2H, OCH_2), 3.13 (s, 3H, $ArCH_3$), 1.99 – 1.78 (m, 2H, $C\underline{H}(CH_2CH_3)_2$), 1.73 – 1.54 (m, 17H, 8 x $CH(C\underline{H}_2CH_3)_2$, 9 x $OC(CH_3)_3$), 1.09 – 0.97 (2 x t, 12H, $CH(CH_2C\underline{H}_3)_2$). ^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ 166.3, 164.2, 164.0, 153.8, 152.5, 148.7, 145.9, 142.8, 130.7, 120.5, 118.9, 114.8, 95.9, 92.3, 81.8, 72.0, 71.0, 41.3, 41.1, 28.4, 23.9, 23.8, 12.1, 11.6, 11.5.

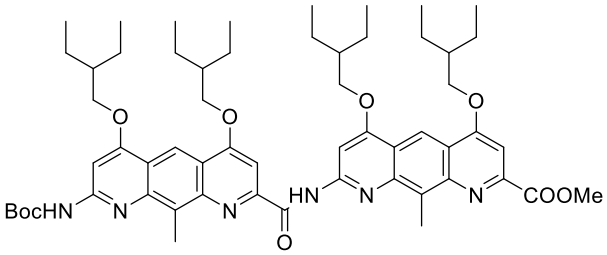


Chemical Formula: $C_{27}H_{37}N_3O_4$

Synthesis of compound **4e**: TFA (4 mL) was added to a solution of compound **4c** (1.00 g, 1.76 mmol) in DCM (4 mL). The mixture was stirred at room temperature for 3 hours, after which complete conversion of the starting material was observed by TLC. Volatiles were removed *in vacuo* and then the residue was dissolved in $CHCl_3$, washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure, obtaining 828 mg (quant. yield) of compound **4e** as a yellow solid. HRMS (ESI+) calcd. for $C_{27}H_{38}N_3O_4$ $[M+H]^+$ (m/z): 468.2857, found: 468.2858. ^{1}H NMR (300 MHz, CDCl3, 298 K) δ 8.86 (s, 1H, CH_{Ar}), 7.41 (s, 1H, CH_{Ar}), 6.09 (s, 1H, CH_{Ar}), 4.89 (brs, 2H, NH_2), 4.22 (d, *J* = 5.3 Hz, 2H, OCH_2), 4.14 – 4.03 (m, 5H, 2 x OCH_2, 3 x $COOCH_3$), 3.20 (s, 3H, $ArCH_3$), 1.94 – 1.78 (m, *J* = 6.1 Hz, 2H, $C\underline{H}(CH_2CH_3)_2$), 1.73 – 1.50 (m, 8H, $CH(C\underline{H}_2CH_3)_2$), 1.08 – 0.97 (2 x t, 12H, $CH(CH_2C\underline{H}_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 163.8, 163.4, 158.3, 149.3,

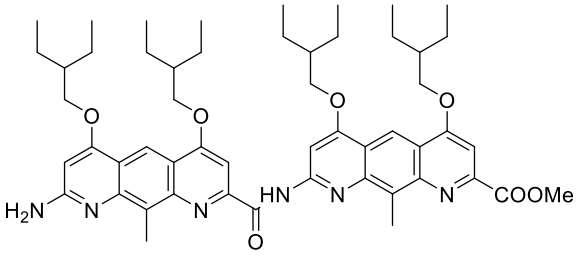
146.9, 145.7, 130.6, 119.0, 118.0, 113.5, 97.6, 90.6, 70.8, 70.5, 53.2, 41.2, 41.1, 23.9, 12.6, 11.5, 11.5.

3.4. Synthesis of dimeric compounds **5a-e**



Chemical Formula: $C_{58}H_{78}N_6O_9$

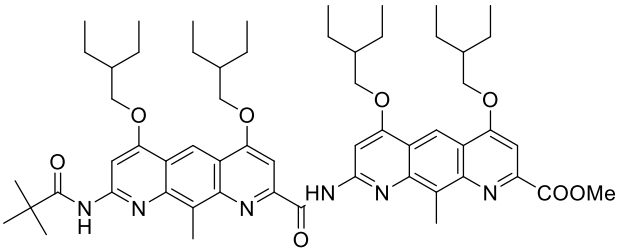
Synthesis of compound **5a**: Dry DIPEA (1.20 mL, 6.87 mmol, freshly distilled over CaH_2) was added to a solution of amine **4e** (803 mg, 1.72 mmol), carboxylic acid **4d** (979 mg, 1.77 mmol) and PyBOP (2.68 g, 5.15 mmol) in dry $CHCl_3$ (15 mL, freshly distilled over CaH_2) under inert atmosphere of N_2. After 26 hours stirring at room temperature, volatiles were removed *in vacuo*. Then the residue was dissolved in DCM, washed with 5% aqueous citric acid, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by precipitation from DCM/MeOH (first slow evaporation of DCM, then 2 hours at 4 °C to force precipitation), to give 1.45 g (84% yield) of compound **5a** as a yellow solid. HRMS (ESI+) calcd. for $C_{58}H_{79}N_6O_9$ $[M+H]^+$ (m/z): 1003.5903, found: 1003.5838. ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ 11.18 (s, 1H, NH), 9.03 (s, 1H, CH_{Ar}), 9.00 (s, 1H, CH_{Ar}), 8.24 (s, 1H, CH_{Ar}), 7.72 (s, 1H, CH_{Ar}), 7.69 (s, 1H, CH_{Ar}), 7.63 (s, 1H, NH), 7.47 (s, 1H, CH_{Ar}), 4.36 – 4.22 (4 x d, 8H, OCH_2), 4.11 (s, 3H, $COOCH_3$), 3.41 (s, 3H, $ArCH_3$), 3.35 (s, 3H, $ArCH_3$), 1.99 – 1.82 (m, 4H, $CH(CH_2CH_3)_2$), 1.76 – 1.52 (m, 25H, 16 x $CH(CH_2CH_3)_2$, 9 x $OC(CH_3)_3$), 1.11 – 0.98 (4 x t, 24H, $CH(CH_2CH_3)_2$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 164.6, 164.2, 164.1, 164.0, 163.9, 153.1, 152.7, 152.2, 150.6, 149.5, 146.3, 145.5, 145.3, 134.7, 133.0, 120.5, 120.1, 119.5, 119.3, 113.8, 113.6, 97.9, 95.2, 93.3, 91.9, 81.5, 71.3, 71.0, 71.0, 70.8, 53.3, 41.3, 41.2, 41.2, 28.5, 24.0, 23.9, 23.9, 12.8, 12.6, 11.6, 11.6, 11.6, 11.5.



Chemical Formula: $C_{53}H_{70}N_6O_7$

Synthesis of compound **5c**: TFA (6 mL) was added to a solution of compound **5a** (634 mg, 0.632 mmol) in DCM (6 mL). The mixture was stirred at room temperature for 2 hours, after which complete conversion of the starting material was observed by TLC. Volatiles were

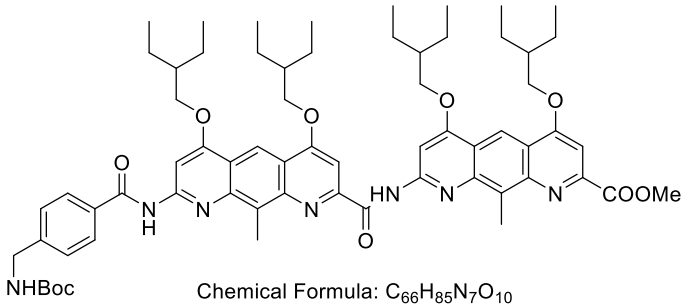
removed *in vacuo* and then the residue was dissolved in DCM, washed twice with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure, obtaining 556 mg (97% yield) of compound **5c** as a yellow solid. HRMS (ESI+) calcd. for $C_{53}H_{71}N_6O_7$ $[M+H]^+$ (m/z): 903.5379, found: 903.5356. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ 11.21 (s, 1H, NH), 9.03 (s, 1H, CH_{Ar}), 8.90 (s, 1H, CH_{Ar}), 8.25 (s, 1H, CH_{Ar}), 7.66 (s, 1H, CH_{Ar}), 7.47 (s, 1H, CH_{Ar}), 6.11 (s, 1H, CH_{Ar}), 4.98 (brs, 2H, NH_2), 4.32 (d, *J* = 5.3 Hz, 2H, OCH_2), 4.29 (d, *J* = 5.6 Hz, 2H, OCH_2), 4.26 (d, *J* = 5.5 Hz, 2H, OCH_2), 4.14 – 4.08 (m, 5H, 2 x OCH_2, 3 x $COOCH_3$), 3.40 (s, 3H, $ArCH_3$), 3.32 (s, 3H, $ArCH_3$), 1.97 – 1.83 (m, 4H, $C\underline{H}(CH_2CH_3)_2$), 1.76 – 1.53 (m, 16H, $CH(C\underline{H}_2CH_3)_2$), 1.10 – 0.99 (4 x t, 24H, $CH(CH_2C\underline{H}_3)_2$). ^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ 166.9, 164.6, 164.4, 164.1, 163.9, 163.4, 158.3, 152.3, 150.4, 149.5, 146.3, 145.9, 145.5, 134.8, 130.5, 120.6, 119.6, 119.2, 118.1, 113.6, 113.6, 97.9, 94.9, 93.4, 90.6, 71.1, 71.0, 71.0, 70.6, 53.3, 41.3, 41.2, 41.2, 41.2, 23.9, 23.9, 23.9, 12.8, 12.6, 11.6, 11.6, 11.5, 11.5.



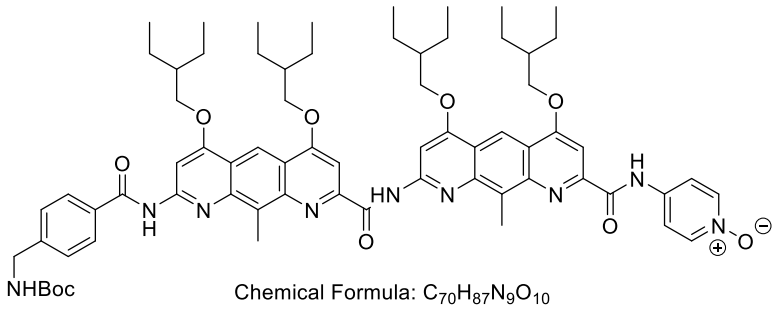
Chemical Formula: $C_{58}H_{78}N_6O_8$

Synthesis of compound **5d**: Pivaloyl chloride (184 µL, 1.49 mmol) was added dropwise to a solution of amine **5c** (675 mg, 0.747 mmol) and dry DIPEA (1.30 mL, 7.47 mmol, freshly distilled over CaH_2) in dry $CHCl_3$ (20 mL, freshly distilled over CaH_2), under inert atmosphere of N_2. After 2 hours stirring at room temperature, volatiles were removed *in vacuo*. Then the residue was dissolved in $CHCl_3$, washed with 5% aqueous citric acid, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by precipitation from DCM/MeOH (slow evaporation of DCM), to give 611 mg (83% yield) of compound **5d** as a yellow solid. HRMS (ESI+) calcd. for $C_{58}H_{79}N_6O_8$ $[M+H]^+$ (m/z): 987.5954, found: 987.6087. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ 11.21 (s, 1H, NH), 9.04 (s, 1H, CH_{Ar}), 9.03 (s, 1H, CH_{Ar}), 8.41 (brs, 1H, NH), 8.25 (s, 1H, CH_{Ar}), 8.04 (s, 1H, CH_{Ar}), 7.71 (s, 1H, CH_{Ar}), 7.48 (s, 1H, CH_{Ar}), 4.33 (d, *J* = 5.3 Hz, 2H, OCH_2), 4.31 (d, *J* = 5.6 Hz, 2H, OCH_2), 4.29 – 4.24 (2 x d, 4H, OCH_2), 4.11 (s, 3H, $COOCH_3$), 3.41 (s, 3H, $ArCH_3$), 3.40 (s, 3H, $ArCH_3$), 1.97 – 1.84 (m, 4H, $C\underline{H}(CH_2CH_3)_2$), 1.76 – 1.59 (m, 16H, $CH(C\underline{H}_2CH_3)_2$), 1.44 (s, 9H, Piv), 1.09 – 1.00 (4 x t, 24H, $CH(CH_2C\underline{H}_3)_2$). ^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ 178.2, 166.9, 164.6, 164.2, 164.1, 163.9, 153.1, 152.2, 150.7, 149.5, 146.3, 145.5, 145.2, 134.7, 133.4, 120.6, 120.5, 119.6, 114.0, 113.6, 97.9, 95.3, 93.3, 71.3, 71.0, 53.3, 41.3, 41.3, 41.2, 41.2, 40.4, 27.7, 23.9, 23.9, 12.8, 12.7, 11.6, 11.6, 11.5.

3.5. Synthesis of dimer derivatives **7a-b** and **8a-b**



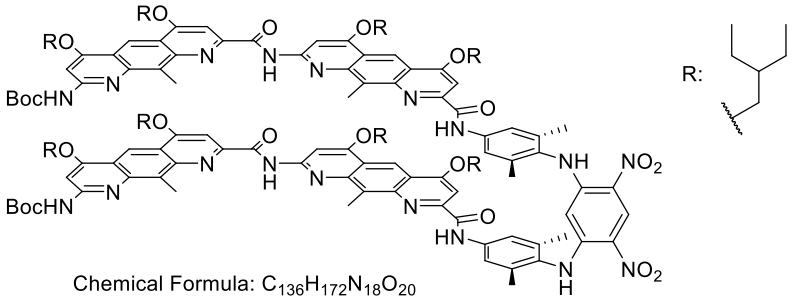
Synthesis of compound **7a**: Ghosez's reagent (371 µL, 2.81 mmol) was added dropwise to a suspension of the commercially available 4-(Boc-aminomethyl)benzoic acid (353 mg, 1.40 mmol, CAS: 33233-67-9) in dry DCM (6 mL) under inert atmosphere of N_2. After 3 hours stirring at room temperature, volatiles were removed *in vacuo* (4 hours drying in the high vacuum pump to ensure complete removal of the excess of Ghosez's reagent). The resulting acid chloride was redissolved in dry $CHCl_3$ (15 mL, freshly distilled over CaH_2) and added dropwise to a solution of amine **5c** (634 mg, 0.702 mmol) and dry DIPEA (978 µL, 5.62 mmol) in dry $CHCl_3$ (20 mL, freshly distilled over CaH_2) under inert atmosphere of N_2. After 12 hours stirring at room temperature, volatiles were removed *in vacuo*. Then the residue was dissolved in DCM, washed with 5% aqueous citric acid and saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2) using acetone/DCM as eluent (from 10% to 20% acetone) to give 622 mg (83% yield) of compound **7a** as a yellow solid. HRMS (ESI+) calcd. for $C_{66}H_{86}N_7O_{10}$ $[M+H]^+$ (m/z): 1136.6431, found: 1136.6546. ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ 11.15 (s, 1H, NH), 9.02 (2 x s, 2H, CH_{Ar}), 8.88 (brs, 1H, NH), 8.22 (s, 1H, CH_{Ar}), 8.17 – 7.92 (brm, 3H, CH_{Ar}), 7.72 (s, 1H, CH_{Ar}), 7.54 – 7.37 (m, 3H, CH_{Ar}), 4.97 (brs, 1H, NH), 4.43 (d, J = 6.2 Hz, 2H, NHC<u>H</u>$_2$), 4.38 – 4.20 (4 x d, 8H, OCH_2), 4.11 (s, 3H, $COOCH_3$), 3.41 (2 x s, 6H, $ArCH_3$), 2.02 – 1.84 (m, 4H, C<u>H</u>$(CH_2CH_3)_2$), 1.81 – 1.60 (m, 16H, $CH(C\underline{H}_2CH_3)_2$), 1.50 (s, 9H, $OC(CH_3)_3$), 1.14 – 0.96 (4 x t, 24H, $CH(CH_2C\underline{H}_3)_2$). ^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ 166.8, 164.6, 164.1, 163.8, 156.1, 156.0, 152.1, 149.5, 146.3, 145.4, 134.8, 130.6, 128.1, 127.8, 120.5, 119.6, 113.6, 97.9, 95.7, 93.2, 80.0, 71.4, 71.1, 53.3, 44.5, 41.3, 41.2, 41.2, 28.6, 23.9, 23.9, 12.7, 11.6, 11.6, 11.6, 11.5.



Synthesis of compound **8a**: $LiOH{\cdot}H_2O$ (91.0 mg, 2.17 mmol) was added to a solution of methyl ester **7a** (821 mg, 0.723 mmol) in 20 mL of THF/MeOH/H_2O (8:1:1, vol:vol:vol). The mixture was stirred at room temperature for 3.5 hours, after which complete conversion of the starting material was observed by TLC. The mixture was diluted with $CHCl_3$, washed with 5% aqueous

citric acid and saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure, to obtain crude carboxylic acid **7b** as a yellow solid. HRMS (ESI+) calcd. for $C_{65}H_{84}N_7O_{10}$ $[M+H]^+$ (m/z): 1122.6274, found: 1122.6360. Then 4-aminopyridine 1-oxide (CAS: 3535-75-9, 382 mg, 3.47 mmol)), PyBOP (1.88 g, 3.61 mmol), dry $CHCl_3$ (15 mL, freshly distilled over CaH_2), dry DMF (10 mL) and finally dry DIPEA (140 µL, 0.802 mmol, freshly distilled over CaH_2) were added to the same flask under inert atmosphere of N_2. After 24 hours stirring at 30 °C, volatiles were removed *in vacuo*. The residue was dissolved in $CHCl_3$, washed with 5% aqueous citric acid (careful mixing to prevent emulsion formation), saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by precipitation from DCM/MeOH (slow evaporation of DCM) and by GPC, to give 419 mg (48% yield) of compound **8a** as a yellow solid. HRMS (ESI+) calcd. for $C_{70}H_{88}N_9O_{10}$ $[M+H]^+$ (m/z): 1214.6649, found: 1214.6721. ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ 10.83 (s, 1H, NH), 10.65 (s, 1H, NH), 9.10 – 8.46 (brm, 3H, 2 x CH_{Ar}, 1 x NH), 8.29 – 7.86 (brm, 6H, CH_{Ar}), 7.73 (d, *J* = 6.8 Hz, 2H, CH_{Ar}), 7.59 (s, 1H, CH_{Ar}), 7.51 – 7.21 (brm, 3H, CH_{Ar}), 6.54 – 5.71 (brm, 1H, NH), 4.42 (d, *J* = 5.4 Hz, 2H, NHC$\underline{H}_2$), 4.37 – 4.29 (2 x d, 4H, OCH_2), 4.27 (d, *J* = 5.2 Hz, 2H, OCH_2), 4.16 (brs, 2H, OCH_2), 3.37 (s, 3H, $ArCH_3$), 3.24 (brs, 3H, $ArCH_3$), 2.05 – 1.85 (m, 4H, C$\underline{H}(CH_2CH_3)_2$), 1.80 – 1.60 (m, 16H, CH(C$\underline{H}_2CH_3)_2$), 1.54 (s, 9H, $OC(CH_3)_3$), 1.18 – 1.00 (4 x t, 24H, $CH(CH_2C\underline{H}_3)_2$). ^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ 164.2, 164.0, 163.6, 163.1, 162.7, 156.8, 151.8, 149.4, 145.3, 144.4, 139.4, 136.6, 132.7, 127.9, 127.6, 119.9, 119.1, 118.8, 115.7, 113.3, 94.9, 94.2, 93.4, 92.9, 79.6, 71.7, 71.5, 71.1, 44.5, 41.4, 41.1, 40.9, 28.7, 23.8, 23.8, 23.7, 23.6, 12.6, 11.6, 11.5, 11.5, 11.4.

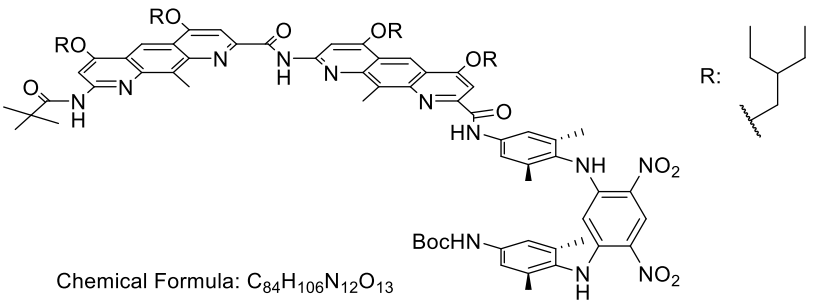
3.6. Synthesis of compound **1**



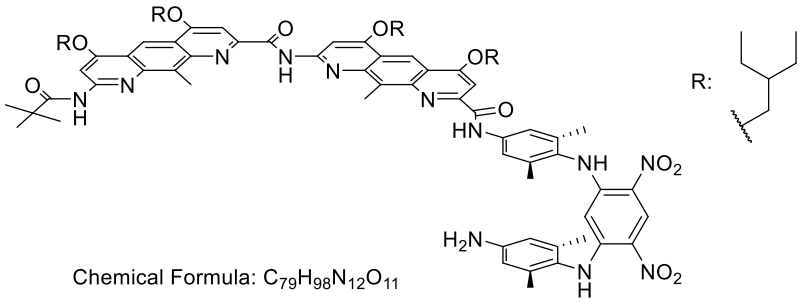
Synthesis of compound **1**: $LiOH \cdot H_2O$ (21.2 mg, 505 µmol) was added to a solution of methyl ester **5a** (169 mg, 168 µmol) in 11 mL of THF/MeOH/H_2O (20:1:1, vol:vol:vol). The mixture was stirred at room temperature for 2 hours, after which complete conversion of the starting material was observed by TLC. The mixture was diluted with $CHCl_3$, washed with 5% aqueous citric acid and saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure, to obtain crude carboxylic acid **5b** as a yellow solid. HRMS (ESI+) calcd. for $C_{57}H_{77}N_6O_9$ $[M+H]^+$ (m/z): 989.5747, found: 989.5660. Then diamine **6b** (35 mg, 80 µmol), PyBOP (125 mg, 0.241 mmol), dry $CHCl_3$ (7 mL, freshly distilled over CaH_2) and finally dry DIPEA (140 µL, 0.802 mmol, freshly distilled over CaH_2) were added to the same flask under inert atmosphere of N_2. After 17 hours stirring at 45 °C, volatiles were removed *in vacuo*. The residue was dissolved in $CHCl_3$, washed with 5% aqueous citric acid, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2) using AcOEt/cyclohexane as eluent (from 10% to 17% AcOEt) to give 154 mg (81% yield) of compound **1** as a yellow solid. HRMS (ESI+) calcd. for $C_{136}H_{173}N_{18}O_{20}$ $[M+H]^+$ (m/z): 2378.3068, found: 2378.3094. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 10.49 (s, 2H, NH), 10.48 (s, 2H, NH), 9.36 (s, 1H, CH_{Ar}), 9.02 (s, 2H, NH), 8.52 (s, 2H, CH_{Ar}), 8.45 (s, 2H, CH_{Ar}), 7.96 (s, 2H, CH_{Ar}), 7.33 (brs, 2H, NH), 7.31 (s, 2H, CH_{Ar}), 7.17 (s, 2H, CH_{Ar}), 7.08 (s, 2H, CH_{Ar}), 4.83 (s, 1H, CH_{Ar}), 4.42 – 4.21 (m, 8H, OCH_2), 4.16 – 3.97 (m, 8H, OCH_2), 3.27 (s, 6H, $ArCH_3$), 3.23 (s, 6H, $ArCH_3$), 2.14 (s, 12H, $ArCH_3$), 2.08 – 1.96 (m, 4H, C<u>H</u>$(CH_2CH_3)_2$), 1.96 – 1.85 (m, 4H, C<u>H</u>$(CH_2CH_3)_2$), 1.82 – 1.56 (m, 50H, 32 x CH(C<u>H</u>$_2CH_3)_2$, 18 x $OC(CH_3)_3$), 1.17 – 1.01 (4 x t, 48H, CH(CH_2C<u>H</u>$_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 163.9, 163.7, 163.5, 163.1, 162.8, 162.4, 152.3, 152.3, 151.5, 150.5, 149.6, 148.4, 144.9, 144.6, 144.2, 138.1, 137.4, 132.7, 132.3, 130.1, 129.3, 125.0, 119.7, 119.4, 118.7, 118.6, 113.1, 112.9, 94.8, 94.6, 94.3, 92.5, 91.4, 81.3, 71.5, 71.4, 71.3, 71.0, 41.4, 41.2, 41.0, 28.5, 23.7, 23.7, 23.6, 18.1, 12.6, 12.2, 11.6, 11.5.

Note: Due to internal dynamics of compound **1** at 298 K, the four CH_{Ar} of the two 2,6-dimethylbenzene-1,4-diamine rings show very broad NMR signals that are difficult to distinguish from the baseline. For that reason, in the spectra described above, the signals of this aromatic system are not mentioned. See VT-NMR experiments for compound **1** in section 5.3.

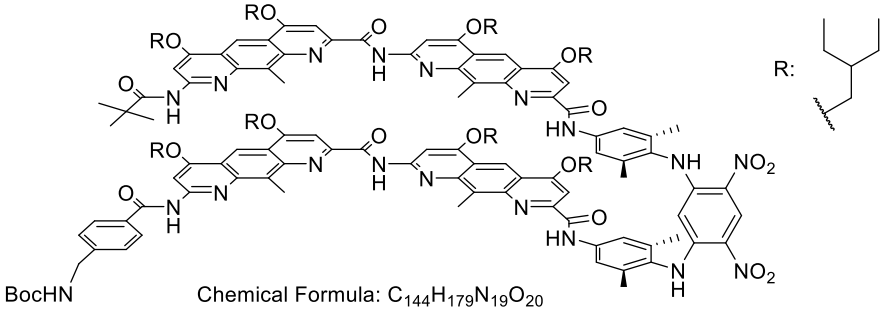
3.7. Synthesis of compound **2**



Synthesis of compound **9a**: $LiOH \cdot H_2O$ (73.9 mg, 1.76 mmol) was added to a solution of methyl ester **5d** (579 mg, 0.587 mmol) in 10 mL of THF/MeOH/H_2O (8:1:1, vol:vol:vol). The mixture was stirred at room temperature for 2.5 hours, after which complete conversion of the starting material was observed by TLC. The mixture was diluted with $CHCl_3$, washed with 5% aqueous citric acid and saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure, to obtain crude carboxylic acid **5e** as a yellow solid. HRMS (ESI+) calcd. for $C_{57}H_{77}N_6O_8$ $[M+H]^+$ (m/z): 973.5797, found: 973.5907. Then amine **6a** (378 mg, 0.704 mmol), PyBOP (916 mg, 1.76 mmol), dry $CHCl_3$ (15 mL, freshly distilled over CaH_2) and finally dry DIPEA (818 µL, 4.69 mmol, freshly distilled over CaH_2) were added to the same flask under inert atmosphere of N_2. After 24 hours stirring at room temperature, volatiles were removed *in vacuo*. Then the residue was dissolved in $CHCl_3$, washed with 5% aqueous citric acid, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2) using acetone/DCM as eluent (from 15% to 20% acetone) to give 738 mg (84% yield) of compound **9a** as a yellow solid. HRMS (ESI+) calcd. for $C_{84}H_{107}N_{12}O_{13}$ $[M+H]^+$ (m/z): 1491.8075, found: 1491.8180. ^1H NMR (300 MHz, $CDCl_3$, 298 K) δ 11.25 (s, 1H, NH), 10.42 (s, 1H, NH), 9.36 (s, 1H, CH_{Ar}), 9.16 (s, 1H, NH), 9.13 (s, 1H, NH), 9.08 (s, 1H, CH_{Ar}), 9.05 (s, 1H, CH_{Ar}), 8.38 (brs, 1H, NH), 8.26 (s, 1H, CH_{Ar}), 8.05 (s, 1H, CH_{Ar}), 7.74 (s, 1H, CH_{Ar}), 7.72 (s, 1H, CH_{Ar}), 7.48 (s, 2H, CH_{Ar}), 7.05 (s, 2H, CH_{Ar}), 6.67 (s, 1H, NH), 4.93 (s, 1H, CH_{Ar}), 4.40 – 4.29 (3 x d, 6H, OCH_2), 4.27 (d, J = 5.3 Hz, 2H, OCH_2), 3.43 (s, 3H, $ArCH_3$), 3.41 (s, 3H, $ArCH_3$), 2.11 (s, 6H, $ArCH_3$), 2.02 (s, 6H, $ArCH_3$), 2.00 – 1.84 (m, 4H, $C\underline{H}(CH_2CH_3)_2$), 1.79 – 1.59 (m, 16H, $CH(C\underline{H}_2CH_3)_2$), 1.45 (s, 9H, $C(CH_3)_3$), 1.15 (s, 9H, Piv), 1.12 – 0.99 (4 x t, 24H, $CH(CH_2C\underline{H}_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ 178.0, 164.6, 164.1, 164.0, 163.9, 162.9, 153.1, 152.9, 152.3, 151.0, 150.5, 148.4, 148.2, 145.4, 145.2, 145.0, 138.1, 137.0, 136.9, 136.6, 133.1, 133.0, 130.5, 129.5, 129.2, 125.0, 120.4, 120.3, 119.8, 119.5, 119.4, 118.9, 114.0, 113.9, 95.4, 95.3, 94.0, 93.4, 93.1, 80.2, 71.3, 71.2, 71.1, 41.3, 41.2, 40.3, 28.0, 27.7, 23.9, 18.1, 18.1, 12.7, 12.6, 11.6, 11.5.

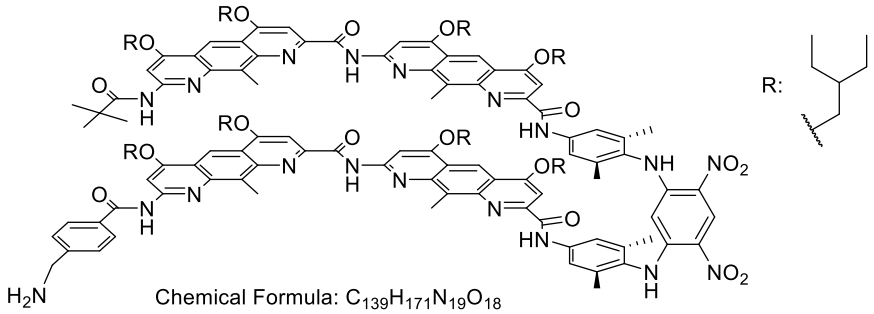


Synthesis of compound **9b**: TFA (5 mL) was added to a solution of compound **9a** (705 mg, 0.473 mmol) in DCM (5 mL). The mixture was stirred at room temperature for 2 hours, after which complete conversion of the starting material was observed by TLC. Volatiles were removed *in vacuo* and then the residue was dissolved in DCM, washed twice with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure, obtaining 645 mg (98% yield) of compound **9b** as a yellow solid. HRMS (ESI+) calcd. for $C_{79}H_{99}N_{12}O_{11}$ $[M+H]^+$ (m/z): 1391.7551, found: 1391.7614. ^1H NMR (300 MHz, $CDCl_3$, 298 K) δ 11.23 (s, 1H, NH), 10.46 (s, 1H, NH), 9.34 (s, 1H, CH_{Ar}), 9.16 – 8.94 (4 x s, 4H, 2 x NH, 2 x CH_{Ar}), 8.39 (brs, 1H, NH), 8.24 (s, 1H, CH_{Ar}), 8.05 (s, 1H, CH_{Ar}), 7.71 (s, 1H, CH_{Ar}), 7.70 (s, 1H, CH_{Ar}), 7.52 (s, 2H, CH_{Ar}), 6.29 (s, 2H, CH_{Ar}), 4.89 (s, 1H, CH_{Ar}), 4.40 – 4.30 (3 x d, 6H, OCH_2), 4.27 (d, J = 5.3 Hz, 2H, OCH_2), 3.55 (brs, 2H, NH_2), 3.45 (s, 3H, $ArCH_3$), 3.41 (s, 3H, $ArCH_3$), 2.10 (s, 6H, $ArCH_3$), 2.04 – 1.83 (m, 10H, 4 x C<u>H</u>$(CH_2CH_3)_3$, 6 x $ArCH_3$), 1.81 – 1.58 (m, 16H, $CH(C\underline{H}_2CH_3)_3$), 1.44 (s, 9H, Piv), 1.14 – 0.98 (4 x t, 24H, $CH(CH_2C\underline{H}_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ 178.0, 164.7, 164.6, 164.1, 164.0, 163.8, 162.7, 153.1, 152.3, 151.1, 150.5, 149.1, 148.2, 146.4, 145.4, 145.2, 145.0, 137.2, 137.0, 136.8, 133.0, 132.7, 130.6, 129.4, 125.2, 125.0, 124.9, 120.4, 120.3, 119.5, 119.4, 119.3, 114.9, 114.0, 95.3, 94.3, 93.4, 93.1, 71.4, 71.4, 71.2, 41.3, 41.2, 40.3, 27.7, 23.9, 18.1, 17.9, 12.7, 12.6, 11.6, 11.5.

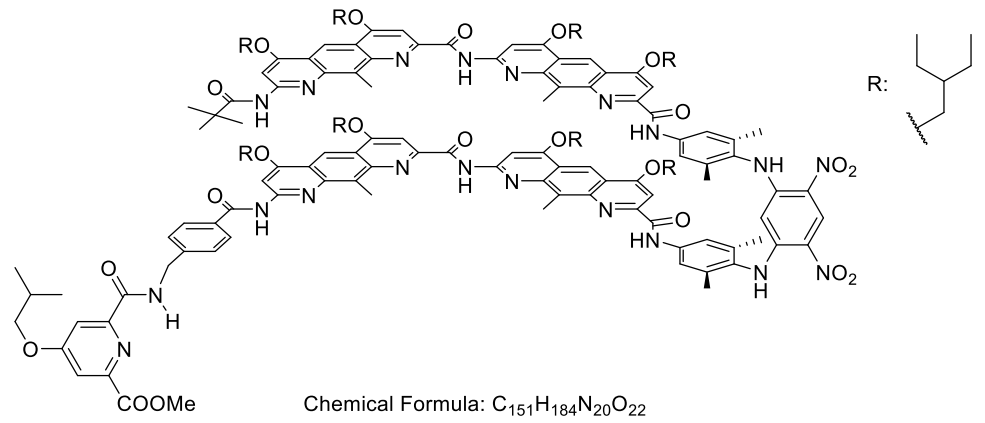


Synthesis of compound **10a**: Dry DIPEA (621 µL, 3.56 mmol, freshly distilled over CaH_2) was added to a solution of amine **9b** (620 mg, 0.445 mmol), carboxylic acid **7b** (550 mg, 0.490 mmol; obtained as described in the synthetic protocol of **8a**) and PyBOP (1.16 g, 2.23 mmol) in dry $CHCl_3$ (50 mL, freshly distilled over CaH_2) under inert atmosphere of N_2. After 72 hours stirring at room temperature, volatiles were removed *in vacuo*. Then the residue was dissolved in $CHCl_3$, washed with 5% aqueous citric acid, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2) using AcOEt/cyclohexane with 0.2% triethylamine as eluent (from 15% to 25% AcOEt) to give 934 mg (84% yield) of compound

10a as a yellow solid. HRMS (ESI+) calcd. for $C_{144}H_{180}N_{19}O_{20}$ $[M+H]^+$ (m/z): 2495.3647, found: 2495.3699. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ 10.45 (s, 1H, NH), 10.39 (s, 1H, NH), 10.34 (s, 1H, NH), 10.26 (s, 1H, NH), 9.30 (s, 1H, CH_{Ar}), 8.96 (s, 1H, NH), 8.95 (s, 1H, NH), 8.71 – 7.06 [brm, 21H, 19 x CH_{Ar}, 2 x NH; sharp peaks included in this broad multiplet: 7.81 (s, 1H, CH_{Ar}), 7.45 (s, 1H, CH_{Ar})], 6.67 (brs, 1H, CH_{Ar}), 4.93 (brs, 1H, NH), 4.78 (s, 1H, CH_{Ar}), 4.48 – 3.75 (brm, 18H, 16 x OCH_2, 2 x $NHC\underline{H}_2$), 3.45 – 3.13 (3 x s, 9H, $ArCH_3$), 2.99 (brs, 3H, $ArCH_3$), 2.08 (s, 6H, $ArCH_3$), 2.06 (s, 6H, $ArCH_3$), 2.01 – 1.91 (m, 4H, $C\underline{H}(CH_2CH_3)_2$), 1.90 – 1.77 (m, 4H, $C\underline{H}(CH_2CH_3)_2$), 1.75 – 1.50 (m, 32H, $CH(C\underline{H}_2CH_3)_2$), 1.45 (s, 9H, $C(CH_3)_3$), 1.12 (s, 9H, Piv), 1.10 – 0.95 (8 x t, 48H, $CH(CH_2C\underline{H}_3)_2$). ^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ 177.7, 164.1, 163.9, 163.7, 163.5, 163.4, 163.1, 163.0, 162.3, 162.3, 162.2, 156.1, 152.7, 151.5, 151.1, 150.6, 150.3, 149.4, 148.4, 148.2, 145.0, 144.9, 144.6, 144.4, 144.2, 138.1, 138.0, 137.2, 133.0, 132.3, 132.1, 130.1, 129.9, 129.3, 127.7, 125.0, 125.0, 119.9, 119.6, 118.9, 118.6, 118.5, 113.2, 112.8, 94.7, 93.8, 93.2, 92.3, 80.0, 71.6, 71.3, 71.3, 71.2, 44.5, 41.3, 41.3, 41.2, 41.2, 41.1, 41.0, 40.8, 40.0, 29.8, 28.6, 27.4, 23.7, 23.6, 23.6, 23.5, 23.4, 18.0, 12.6, 12.4, 12.3, 11.6, 11.5, 11.5, 11.4.

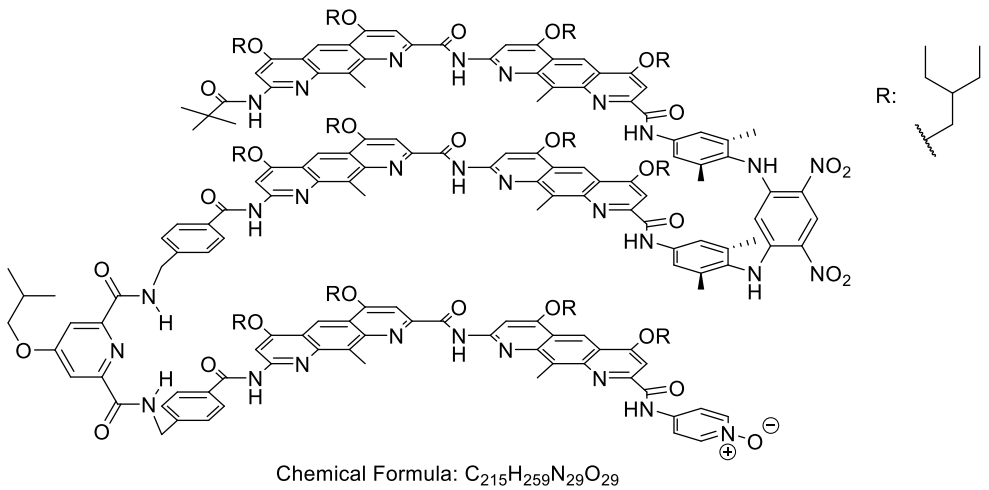


Synthesis of compound **10b**: TFA (3.5 mL) was added to a solution of compound **10a** (931 mg, 0.373 mmol) in DCM (3.5 mL). The mixture was stirred at room temperature for 3 hours, after which complete conversion of the starting material was observed by TLC. Volatiles were removed *in vacuo* and then the residue was dissolved in DCM, washed twice with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure, obtaining 829 mg (93% yield) of amine **10b** as a yellow solid. HRMS (ESI+) calcd. for $C_{139}H_{172}N_{19}O_{18}$ $[M+H]^+$ (m/z): 2395.3122, found: 2395.3302. ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ 10.52 (s, 1H, NH), 10.46 (s, 1H, NH), 10.41 (s, 1H, NH), 10.33 (s, 1H, NH), 9.36 (s, 1H, CH_{Ar}), 9.03 (s, 1H, NH), 9.02 (s, 1H, NH), 8.75 – 7.18 [brm, 21H, 19 x CH_{Ar}, 2 x NH; sharp peaks included in this broad multiplet: 7.88 (s, 1H, CH_{Ar}), 7.52 (s, 1H, CH_{Ar})], 6.73 (brs, 1H, CH_{Ar}), 4.85 (s, 1H, CH_{Ar}), 4.46 – 3.83 (brm, 18H, 16 x OCH_2, 2 x $NHC\underline{H}_2$), 3.50 – 3.21 (3 x s, 9H, $ArCH_3$), 3.05 (brs, 3H, $ArCH_3$), 2.14 (s, 6H, $ArCH_3$), 2.13 (s, 6H, $ArCH_3$), 2.10 – 1.85 (m, 8H, $C\underline{H}(CH_2CH_3)_2$), 1.81 – 1.54 (m, 32H, $CH(C\underline{H}_2CH_3)_2$), 1.20 (s, 9H, Piv), 1.18 – 1.00 (8 x t, 48H, $CH(CH_2C\underline{H}_3)_2$). ^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ 177.5, 164.2, 163.9, 163.7, 163.6, 163.4, 163.2, 163.0, 162.4, 162.4, 162.3, 152.7, 151.5, 151.2, 150.7, 150.4, 149.4, 148.4, 148.2, 145.0, 144.9, 144.8, 144.7, 144.4, 144.3, 144.2, 138.1, 138.1, 137.3, 133.0, 132.3, 132.1, 130.1, 129.9, 129.3, 127.6, 125.0, 125.0, 119.9, 119.7, 118.9, 118.6, 118.5, 113.2, 112.9, 112.9, 95.3, 94.7, 93.8, 93.2, 92.4, 71.6, 71.4, 71.3, 71.2, 46.3, 41.4, 41.3, 41.2, 41.2, 41.1, 41.1, 40.9, 40.0, 29.8, 27.4, 23.7, 23.6, 23.6, 23.5, 23.4, 18.0, 12.6, 12.4, 12.3, 11.6, 11.5, 11.5, 11.5, 11.4, 11.4.



Chemical Formula: $C_{151}H_{184}N_{20}O_{22}$

Synthesis of compound **11a**: Dry DIPEA (686 µL, 3.94 mmol, freshly distilled over CaH_2) was added to a solution of amine **10b** (786 mg, 0.328 mmol), 4-isobutoxy-6-(methoxycarbonyl)picolinic acid (CAS: 1236183-22-4, 208 mg, 0.820 mmol) and PyBOP (1.28 g, 2.46 mmol) in dry $CHCl_3$ (25 mL, freshly distilled over CaH_2) under inert atmosphere of N_2. After 72 hours stirring at room temperature, volatiles were removed *in vacuo*. Then the residue was dissolved in $CHCl_3$, washed with 5% aqueous citric acid, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2) using AcOEt/cyclohexane as eluent (from 30% to 40% AcOEt) to give 730 mg (85% yield) of compound **11a** as a yellow solid. HRMS (ESI+) calcd. for $C_{151}H_{185}N_{20}O_{22}$ $[M+H]^+$ (m/z): 2630.3967, found: 2630.4014. ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ 10.52 (s, 1H, NH), 10.47 (s, 1H, NH), 10.38 (s, 1H, NH), 10.34 (s, 1H, NH), 9.37 (s, 1H, CH_{Ar}), 9.04 (s, 1H, NH), 9.03 (s, 1H, NH), 8.77 – 7.13 [brm, 24H, 21 x CH_{Ar}, 3 x NH; sharp peaks included in this broad multiplet: 7.96 (d, *J* = 2.5 Hz, 1H, CH_{Ar}), 7.89 (s, 1H, CH_{Ar}), 7.76 (d, *J* = 2.5 Hz, 1H, CH_{Ar}), 7.51 (s, 1H, CH_{Ar})], 6.74 (brs, 1H, CH_{Ar}), 4.86 (s, 1H, CH_{Ar}), 4.83 (d, *J* = 6.5 Hz, 2H, $NHC\underline{H}_2$), 4.47 – 3.81 [brm, 21H, 18 x OCH_2, 3 x $COOCH_3$; sharp peaks included in this broad multiplet: 4.00 (s, 3H, $COOCH_3$), 3.94 (d, *J* = 6.5 Hz, 2H, $OC\underline{H}_2CH(CH_3)_2$)], 3.52 – 3.21 (3 x s, 9H, $ArCH_3$), 3.06 (brs, 3H, $ArCH_3$), 2.25 – 1.50 (m, 53H, 12 x $ArCH_3$, 8 x $C\underline{H}(CH_2CH_3)_2$, 1 x $C\underline{H}(CH_3)_2$, 32 x $CH(C\underline{H}_2CH_3)_2$), 1.21 – 0.99 (m, 63H, 9 x Piv, 48 x $CH(CH_2C\underline{H}_3)_2$, 6 x $CH(C\underline{H}_3)_2$). ^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ 177.7, 167.8, 165.2, 164.2, 164.0, 163.9, 163.7, 163.6, 163.4, 163.2, 163.1, 162.4, 162.4, 162.3, 152.7, 151.9, 151.5, 151.2, 150.7, 150.4, 149.5, 148.4, 148.2, 145.0, 144.9, 144.7, 144.4, 144.3, 144.3, 138.1, 138.1, 137.3, 133.0, 132.3, 132.1, 130.1, 130.0, 129.3, 128.2, 125.1, 125.0, 119.9, 119.7, 118.9, 118.7, 118.6, 118.5, 115.0, 113.2, 112.9, 112.9, 111.2, 95.2, 94.7, 93.9, 93.2, 92.4, 75.4, 71.6, 71.3, 71.3, 71.2, 53.1, 43.3, 41.4, 41.3, 41.2, 41.2, 41.1, 41.1, 40.9, 39.9, 29.8, 28.2, 27.3, 23.7, 23.7, 23.6, 23.5, 23.4, 19.2, 18.1, 12.6, 12.4, 12.3, 11.6, 11.5, 11.5, 11.5, 11.5, 11.4, 11.4.



Chemical Formula: $C_{215}H_{259}N_{29}O_{29}$

Synthesis of compound **2**: TFA (3 mL) was added to a solution of compound **8a** (96 mg, 79 µmol) in DCM (3 mL). After 4 hours stirring at room temperature, volatiles were removed *in vacuo* and then the residue was dissolved in $CHCl_3$, washed with saturated aqueous $NaHCO_3$ (careful mixing to prevent emulsion formation), dried over $MgSO_4$ and concentrated under reduced pressure, obtaining 91 mg (quant. yield) of amine **8b** as a yellow solid. HRMS (ESI+) calcd. for $C_{65}H_{80}N_9O_8$ $[M+H]^+$ (m/z): 1114.6124, found: 1114.6188. Separately, LiI (94 mg, 0.70 mmol) was added to a slurry of methyl ester **11a** (185 mg, 70.3 µmol) in dry pyridine (10 mL, degassed by freeze-thaw). The suspension was protected from light and heated to reflux temperature under inert atmosphere of N_2, observing the complete solubilization of the starting material. After stirring at reflux temperature for 8 hours, volatiles were removed *in vacuo*. Then the residue was dissolved in $CHCl_3$, washed three times with 0.1 M aqueous HCl, two time with 10% aqueous $Na_2S_2O_3$ and one more time with 0.1 M aqueous HCl, dried over $MgSO_4$ and concentrated under reduced pressure. In the same flask, the crude carboxylic acid **11b,** together with PyBOP (183 mg, 0.352 mmol) and the crude amine **8b** (86 mg, 77 µmol), were dissolved in dry $CHCl_3$ (30 mL, freshly distilled over CaH_2) under inert atmosphere of N_2. Then dry DIPEA (98 µL, 0.562 mmol, freshly distilled over CaH_2) was added. After 32 hours stirring at 35 °C, volatiles were removed *in vacuo*. Then the residue was dissolved in $CHCl_3$, washed with 5% aqueous citric acid, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by precipitation from DCM/MeOH (slow evaporation of DCM) and by GPC, to give 84 mg (32% yield over the two steps) of compound **2** as a yellow solid. HRMS (ESI+) calcd. for $C_{430}H_{522}N_{58}O_{58}$ $[2M+4H]^{4+}$ (m/z): 1856.4915, found: 1856.4932.

Note: see NMR characterization of this compound in section 5.3.

4. NMR SPECTRA

4.1. Intermediates

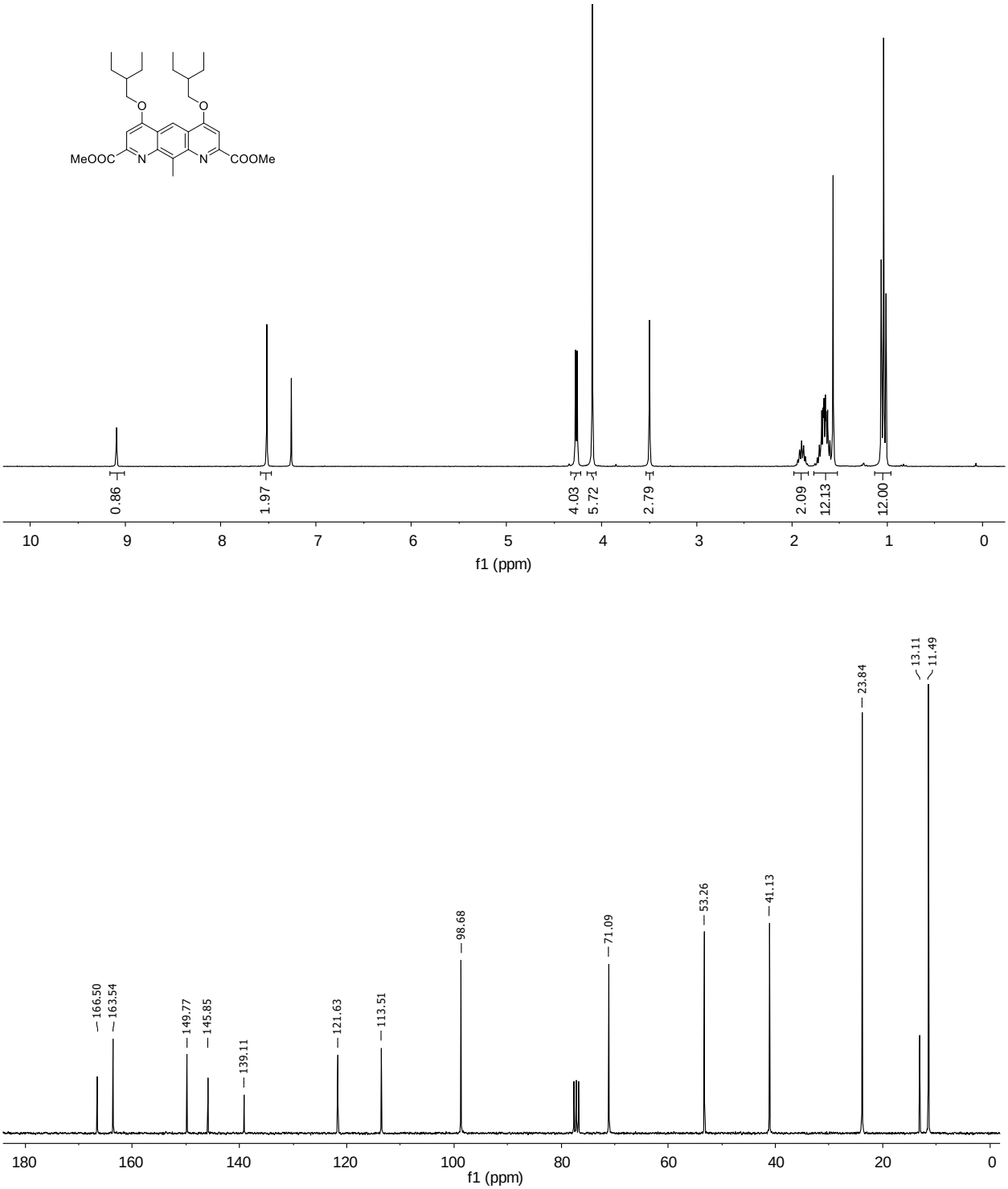


Figure S1. ^{1}H (300 MHz, $CDCl_3$, 298 K) and ^{13}C (75 MHz, $CDCl_3$, 298 K) NMR spectra of compound **4a**.

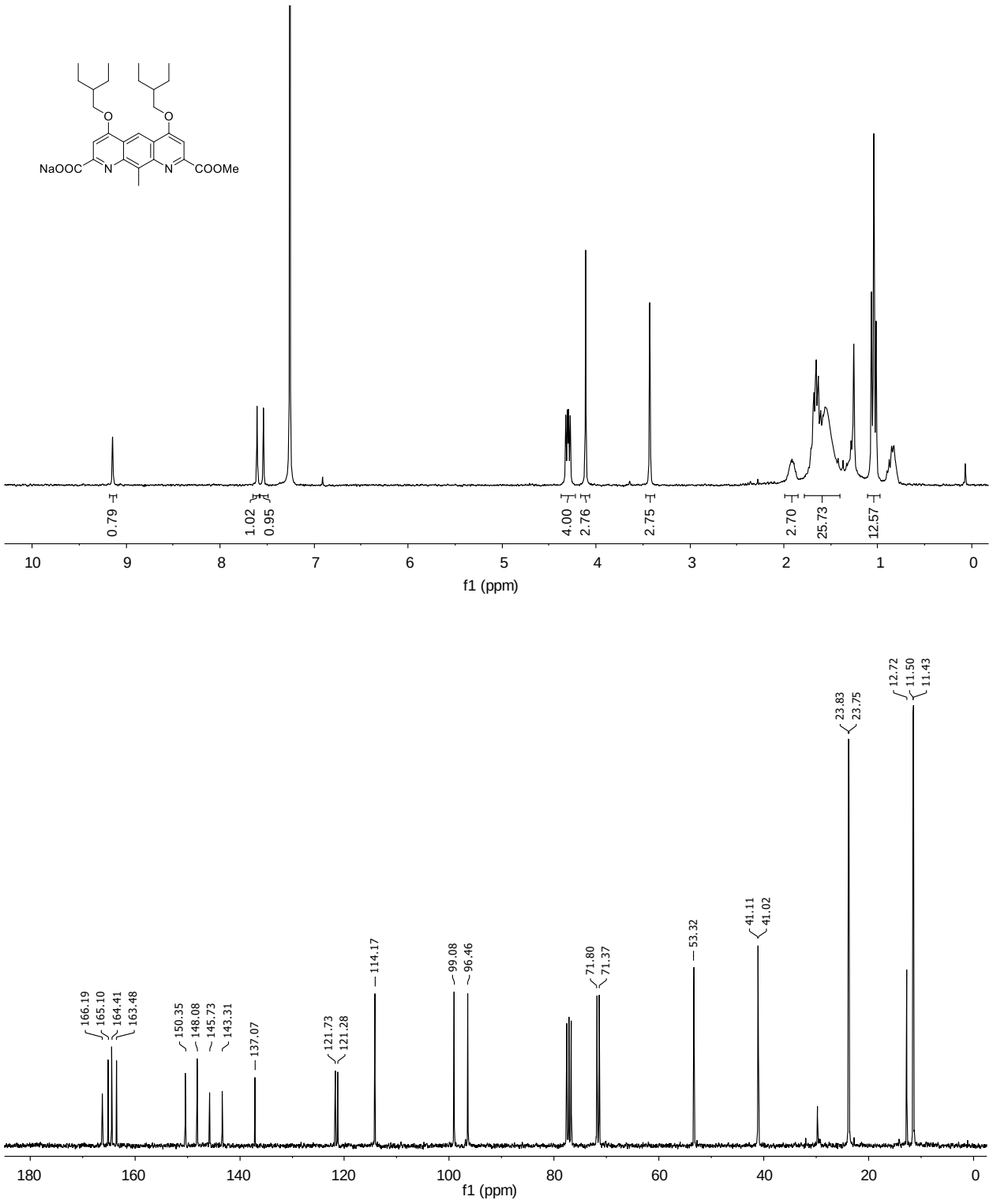


Figure S2. ^{1}H (300 MHz, $CDCl_3$, 298 K) and ^{13}C (75 MHz, $CDCl_3$, 298 K) NMR spectra of compound **4b**.

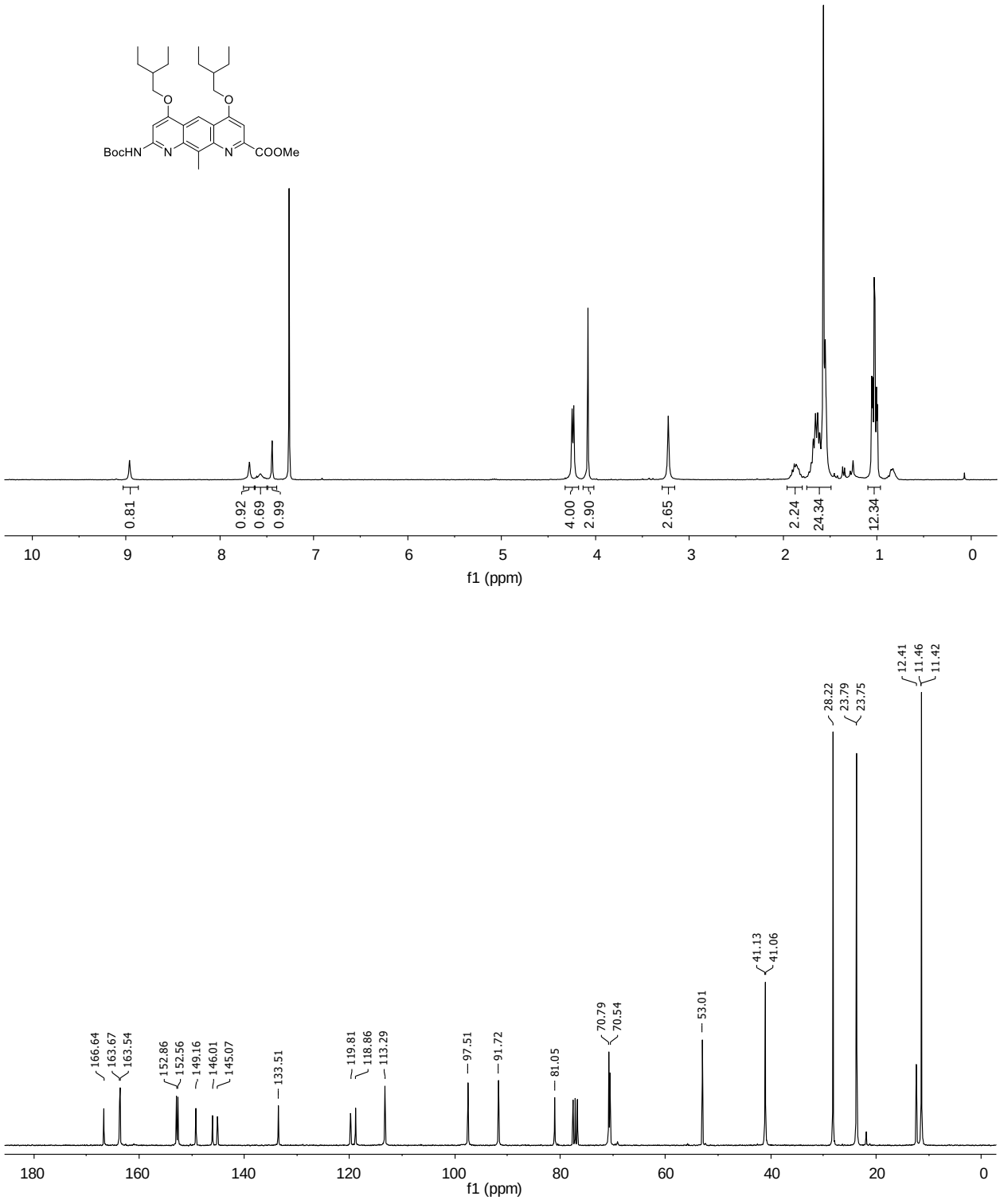


Figure S3. ^{1}H (300 MHz, $CDCl_3$, 298 K) and ^{13}C (75 MHz, $CDCl_3$, 298 K) NMR spectra of compound **4c**.

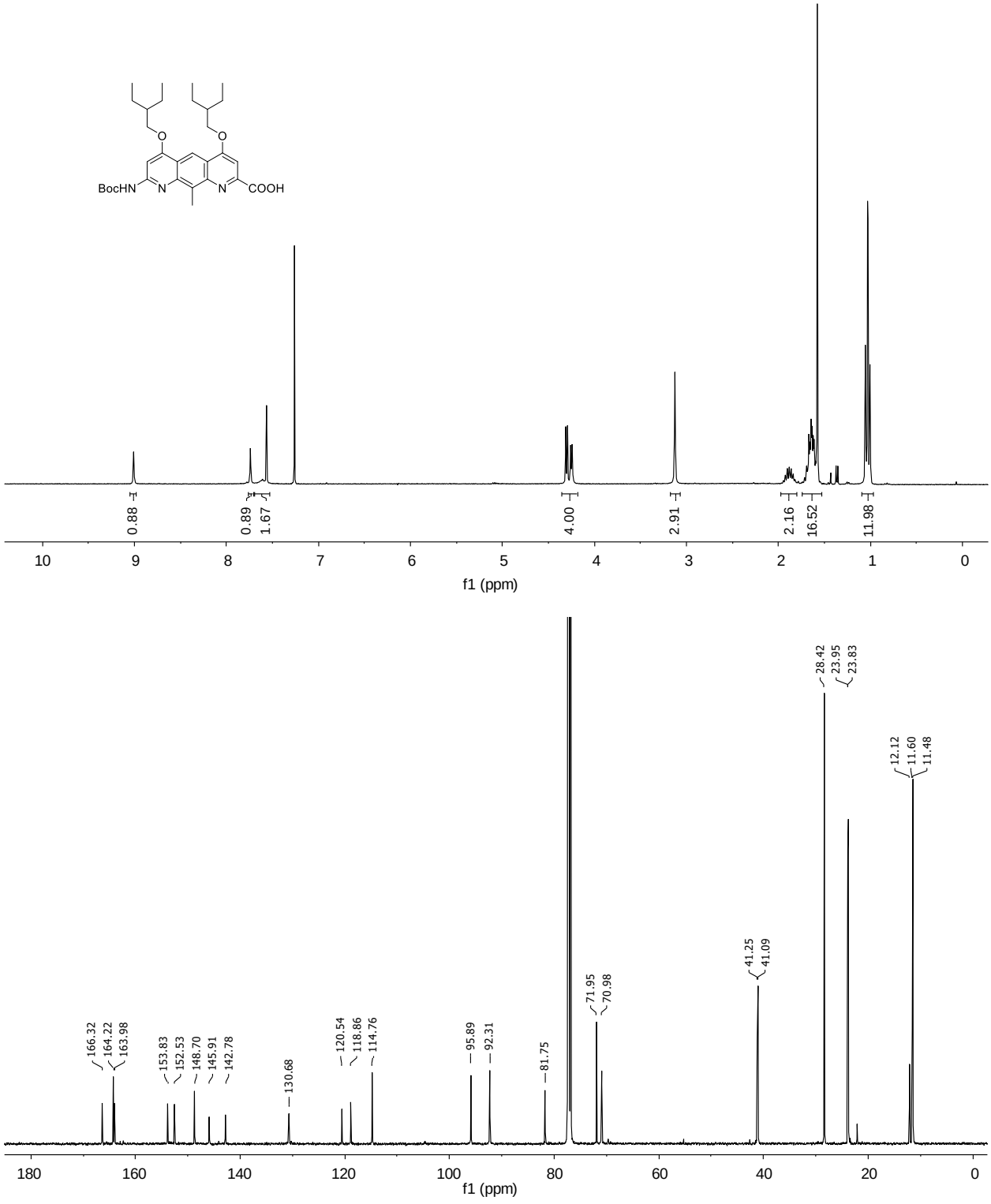


Figure S4. ^{1}H (300 MHz, $CDCl_3$, 298 K) and ^{13}C (126 MHz, $CDCl_3$, 298 K) NMR spectra of compound **4d**.

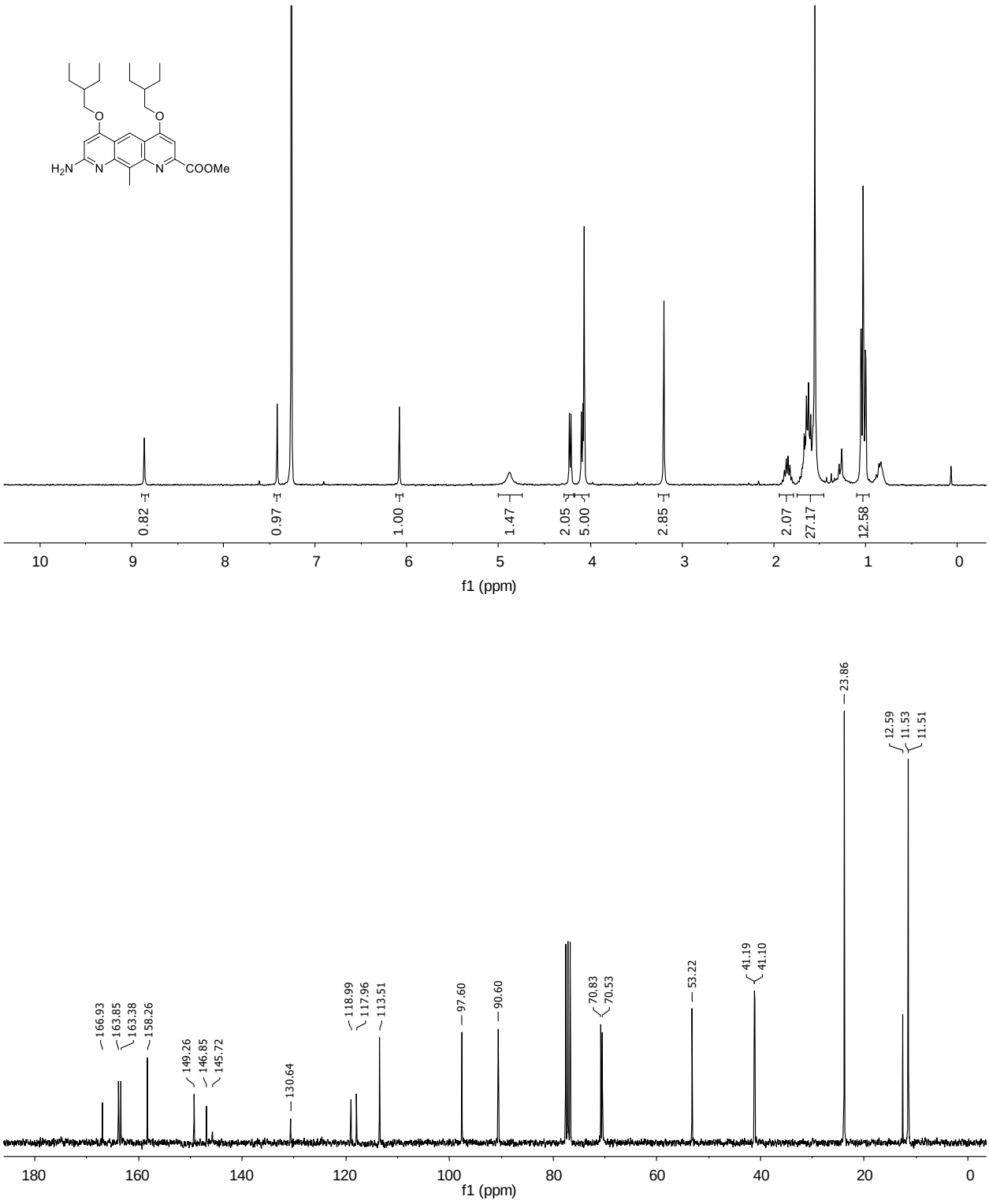


Figure S5. ^{1}H (300 MHz, $CDCl_3$, 298 K) and ^{13}C (75 MHz, $CDCl_3$, 298 K) NMR spectra of compound **4e**.

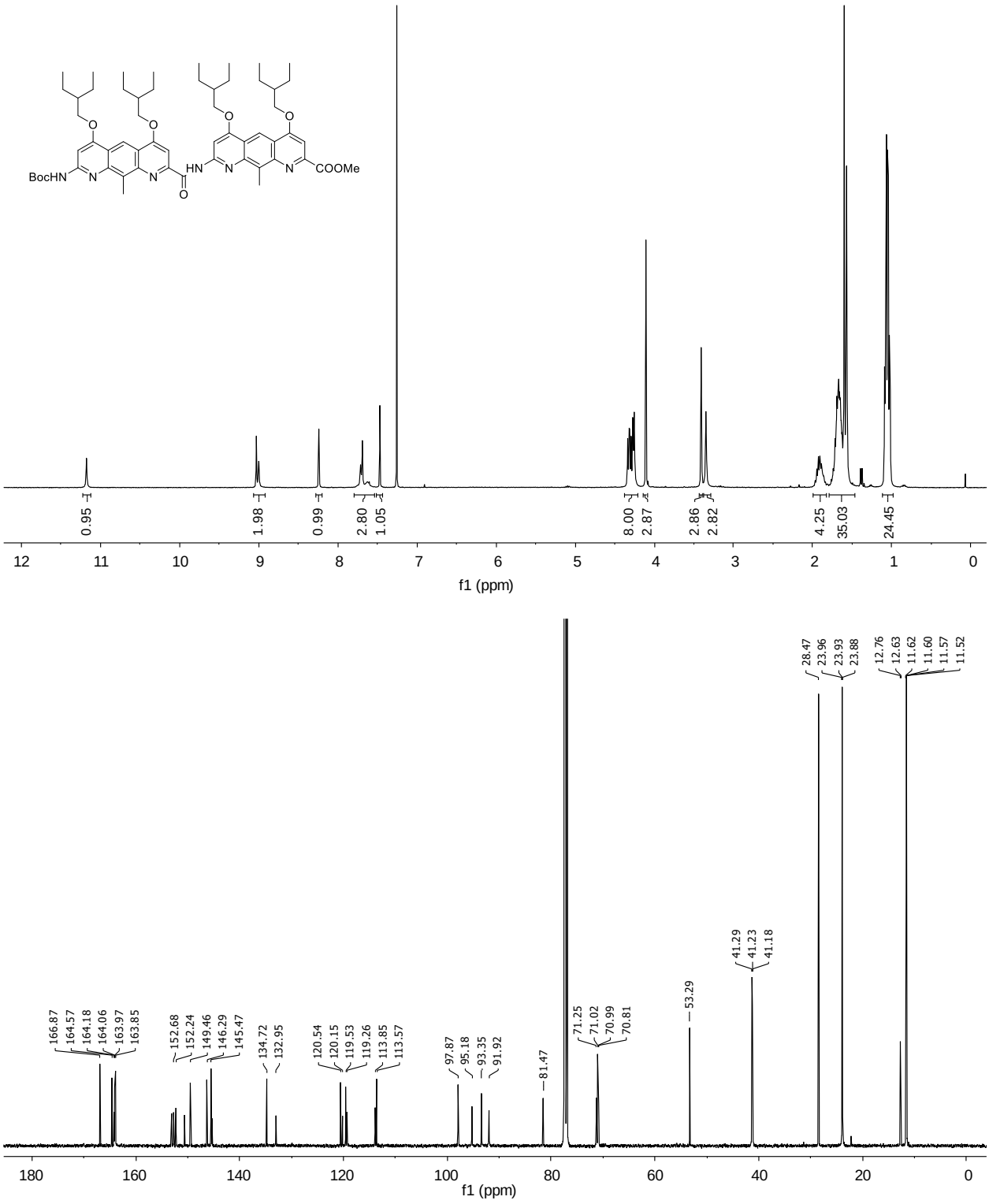


Figure S6. ^{1}H (300 MHz, $CDCl_3$, 298 K) and ^{13}C (126 MHz, $CDCl_3$, 298 K) NMR spectra of compound **5a**.

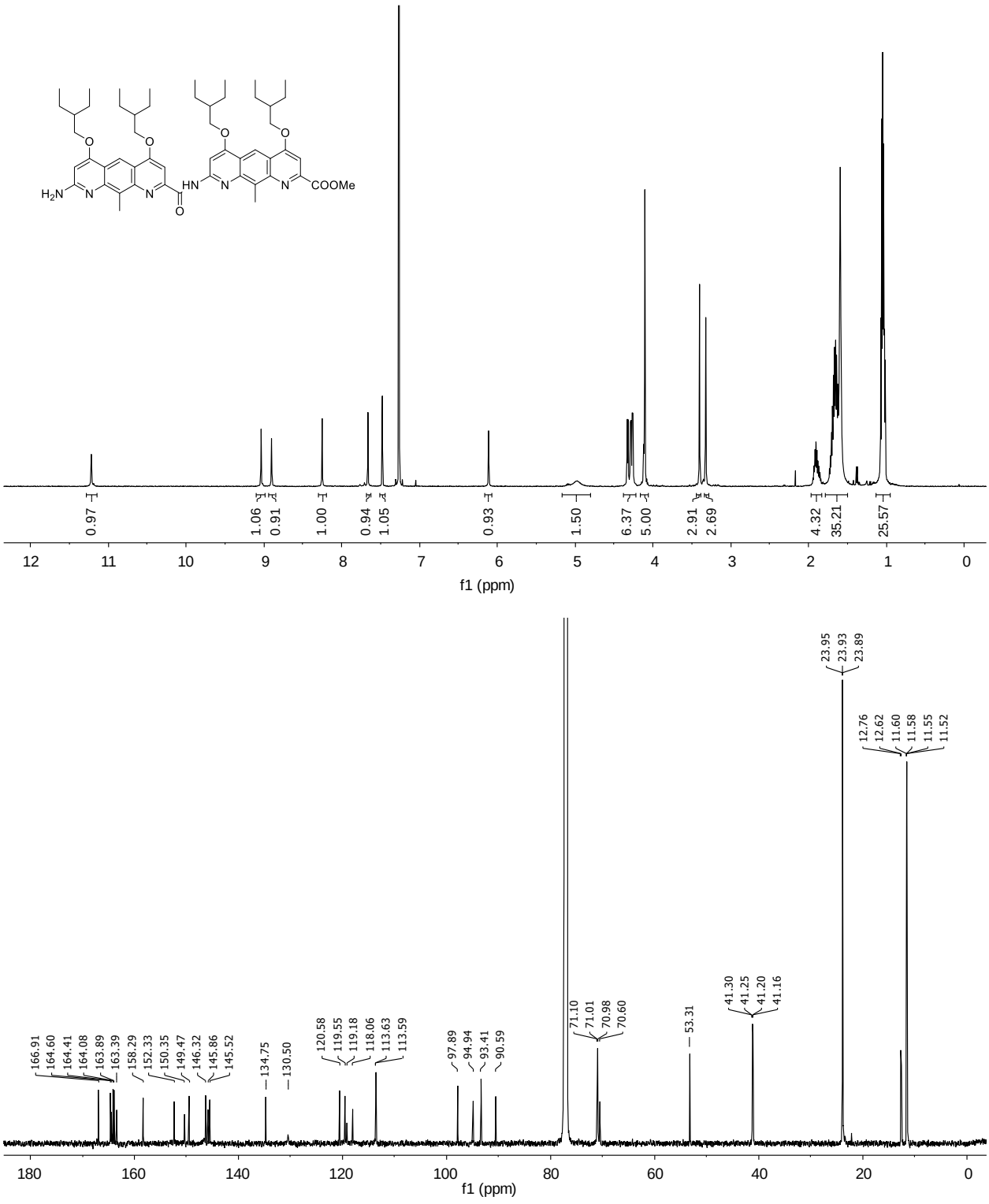


Figure S7. ^{1}H (500 MHz, $CDCl_3$, 298 K) and ^{13}C (126 MHz, $CDCl_3$, 298 K) NMR spectra of compound **5c**.

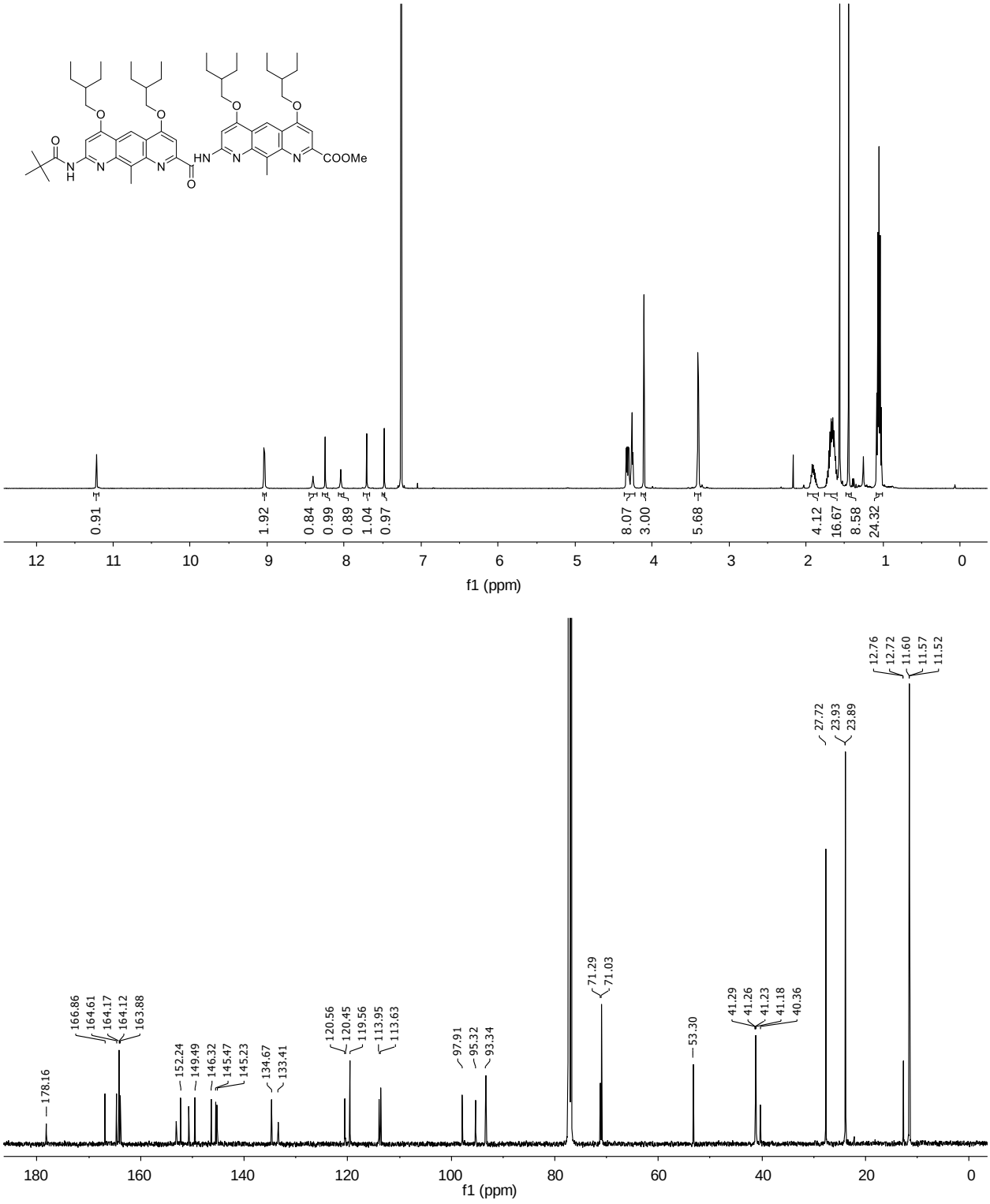


Figure S8. ^{1}H (500 MHz, $CDCl_3$, 298 K) and ^{13}C (126 MHz, $CDCl_3$, 298 K) NMR spectra of compound **5d**.

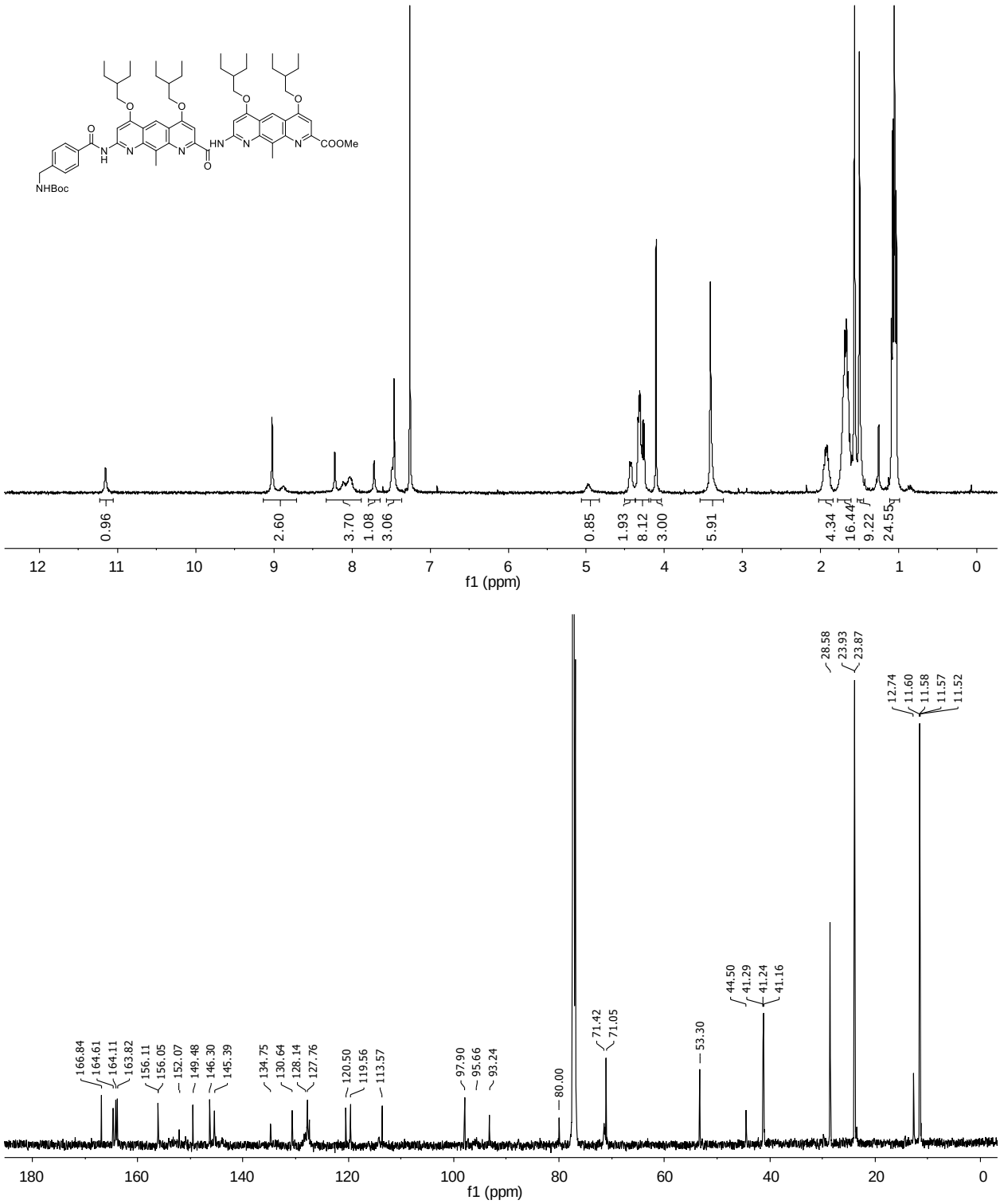


Figure S9. ^{1}H (300 MHz, $CDCl_3$, 298 K) and ^{13}C (126 MHz, $CDCl_3$, 298 K) NMR spectra of compound **7a**.

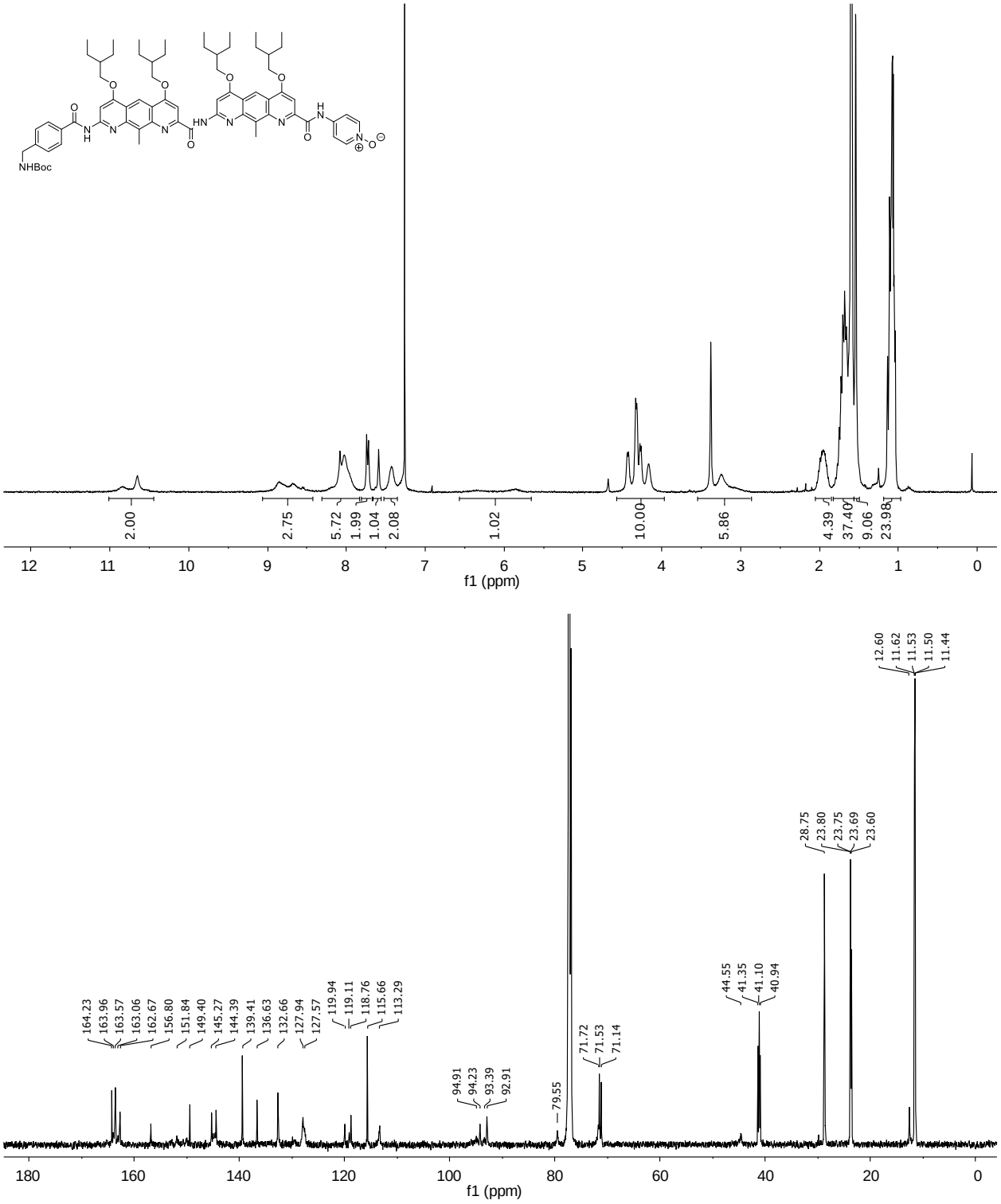


Figure S10. ^{1}H (300 MHz, $CDCl_3$, 298 K) and ^{13}C (126 MHz, $CDCl_3$, 298 K) NMR spectra of compound **8a**.

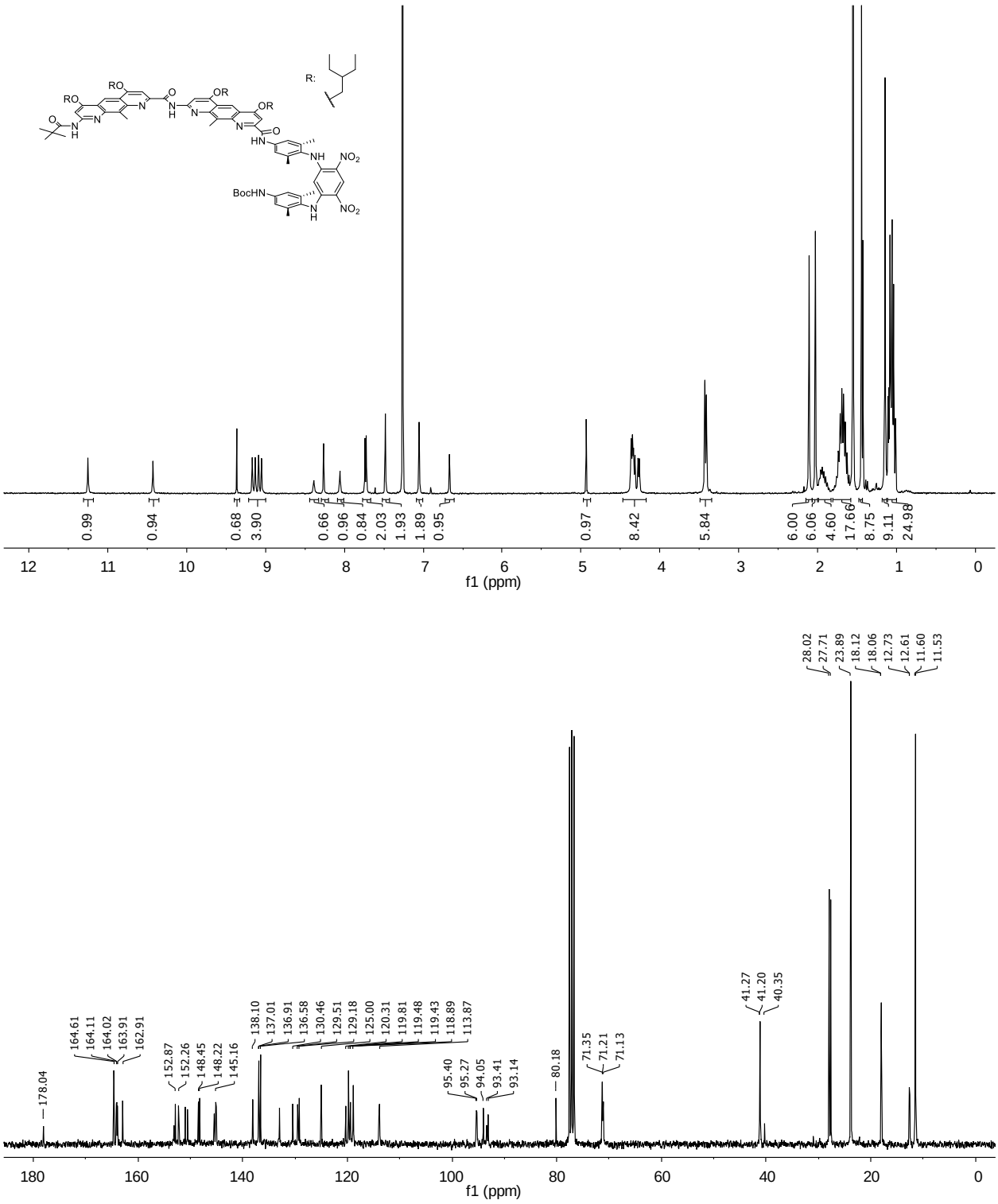


Figure S11. ^{1}H (300 MHz, $CDCl_3$, 298 K) and ^{13}C (75 MHz, $CDCl_3$, 298 K) NMR spectra of compound **9a**.

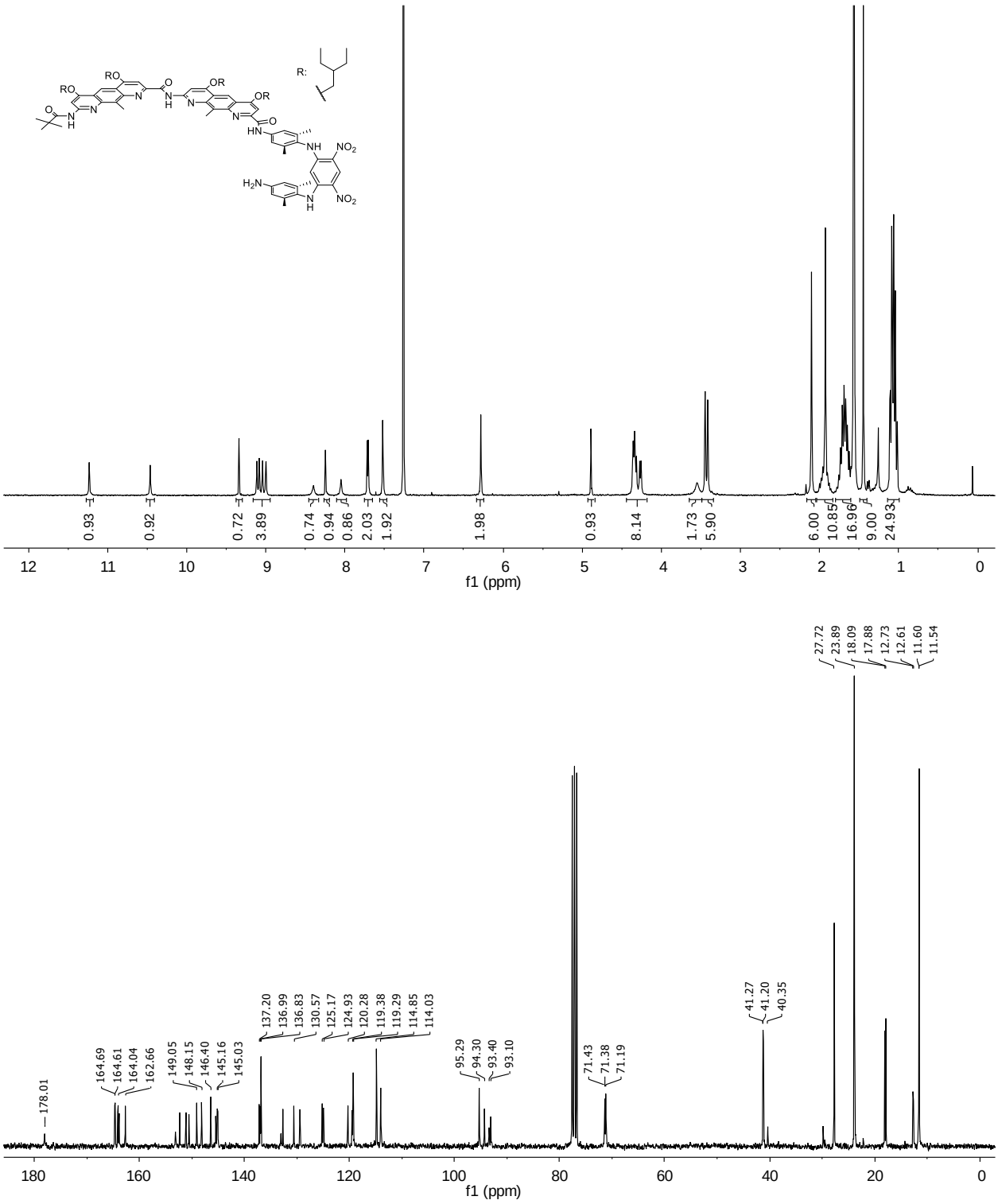


Figure S12. ^{1}H (300 MHz, $CDCl_3$, 298 K) and ^{13}C (75 MHz, $CDCl_3$, 298 K) NMR spectra of compound **9b**.

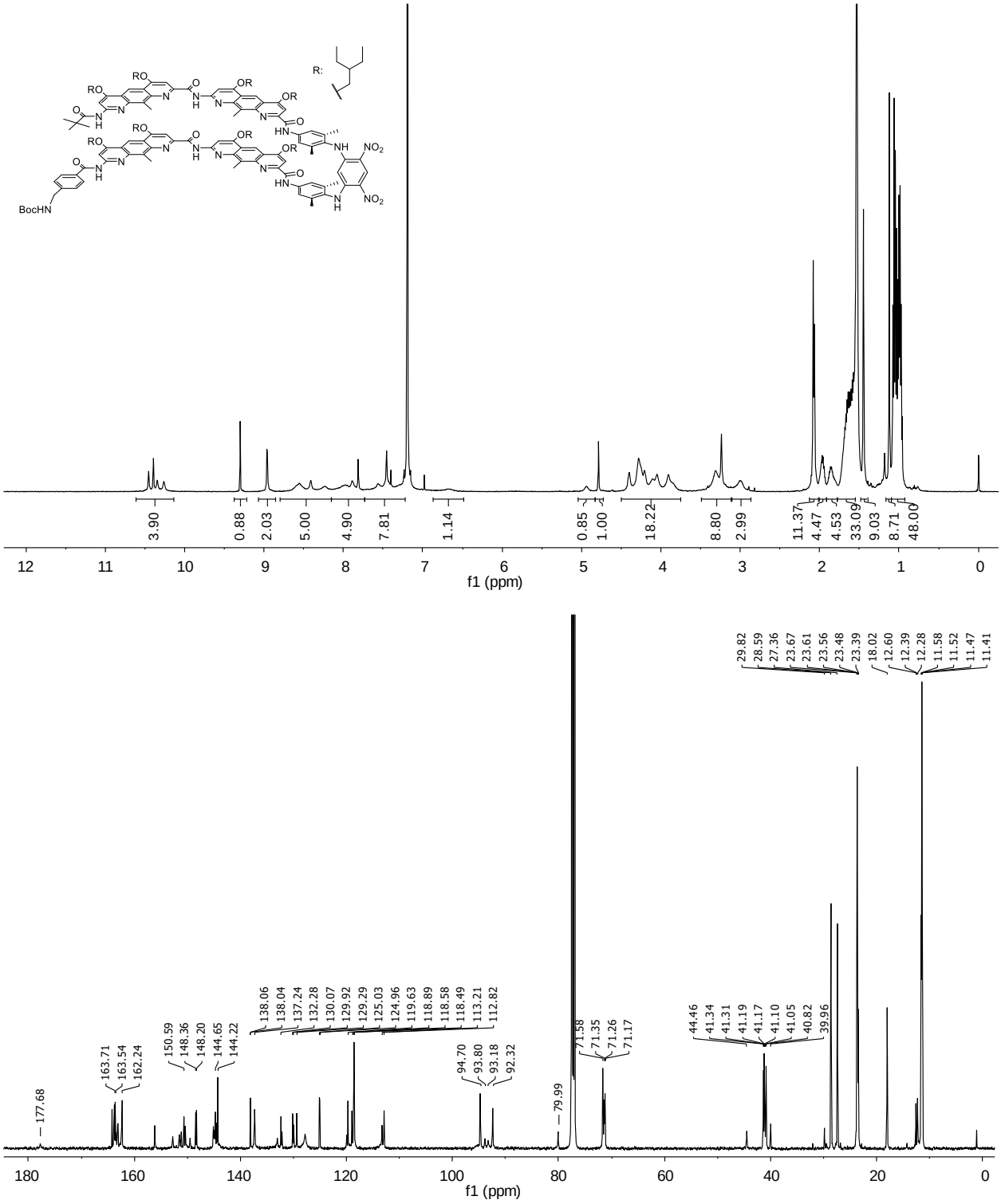


Figure S13. ^{1}H (500 MHz, $CDCl_3$, 298 K) and ^{13}C (126 MHz, $CDCl_3$, 298 K) NMR spectra of compound **10a**.

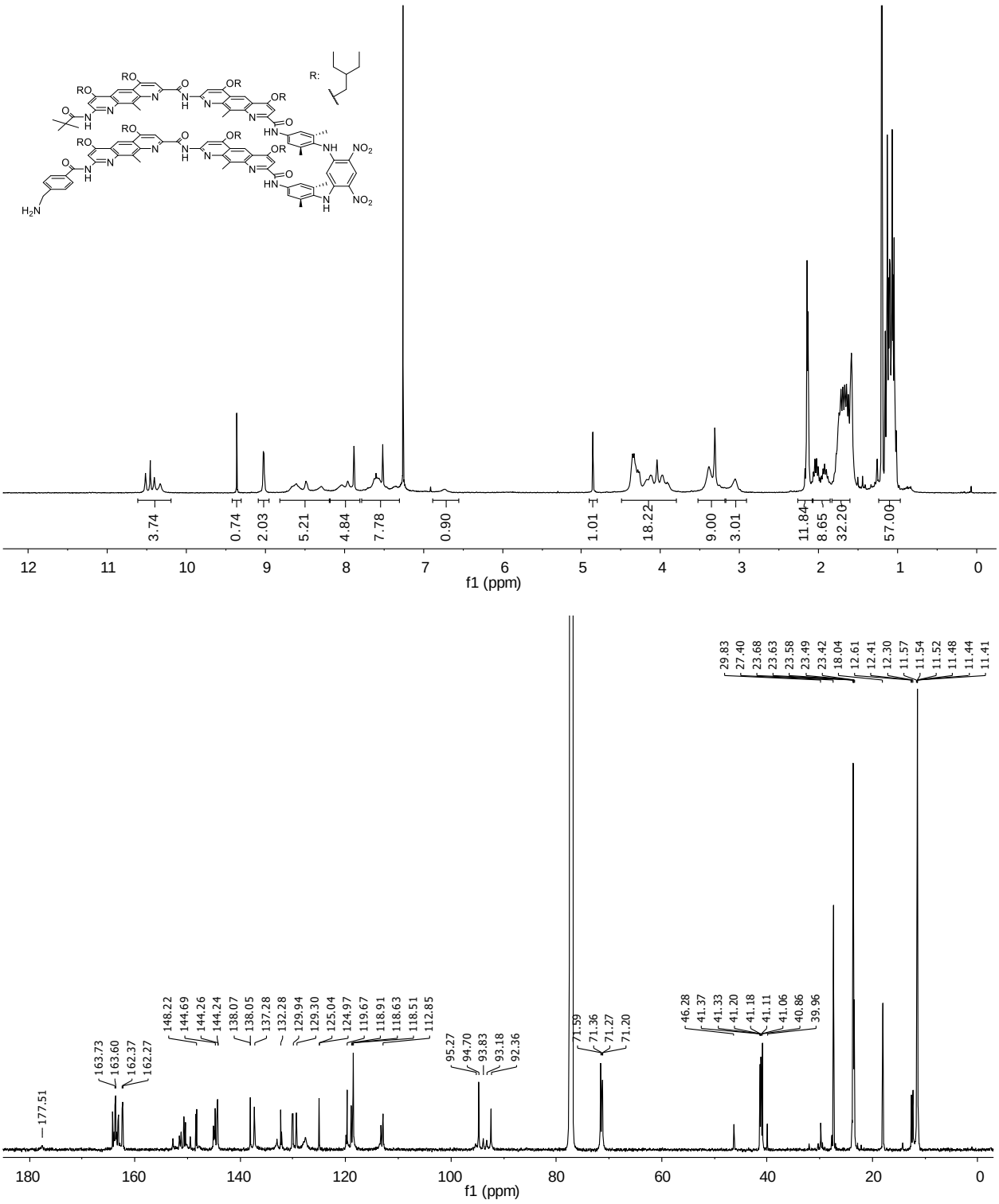


Figure S14. ^{1}H (300 MHz, $CDCl_3$, 298 K) and ^{13}C (126 MHz, $CDCl_3$, 298 K) NMR spectra of compound **10b**.

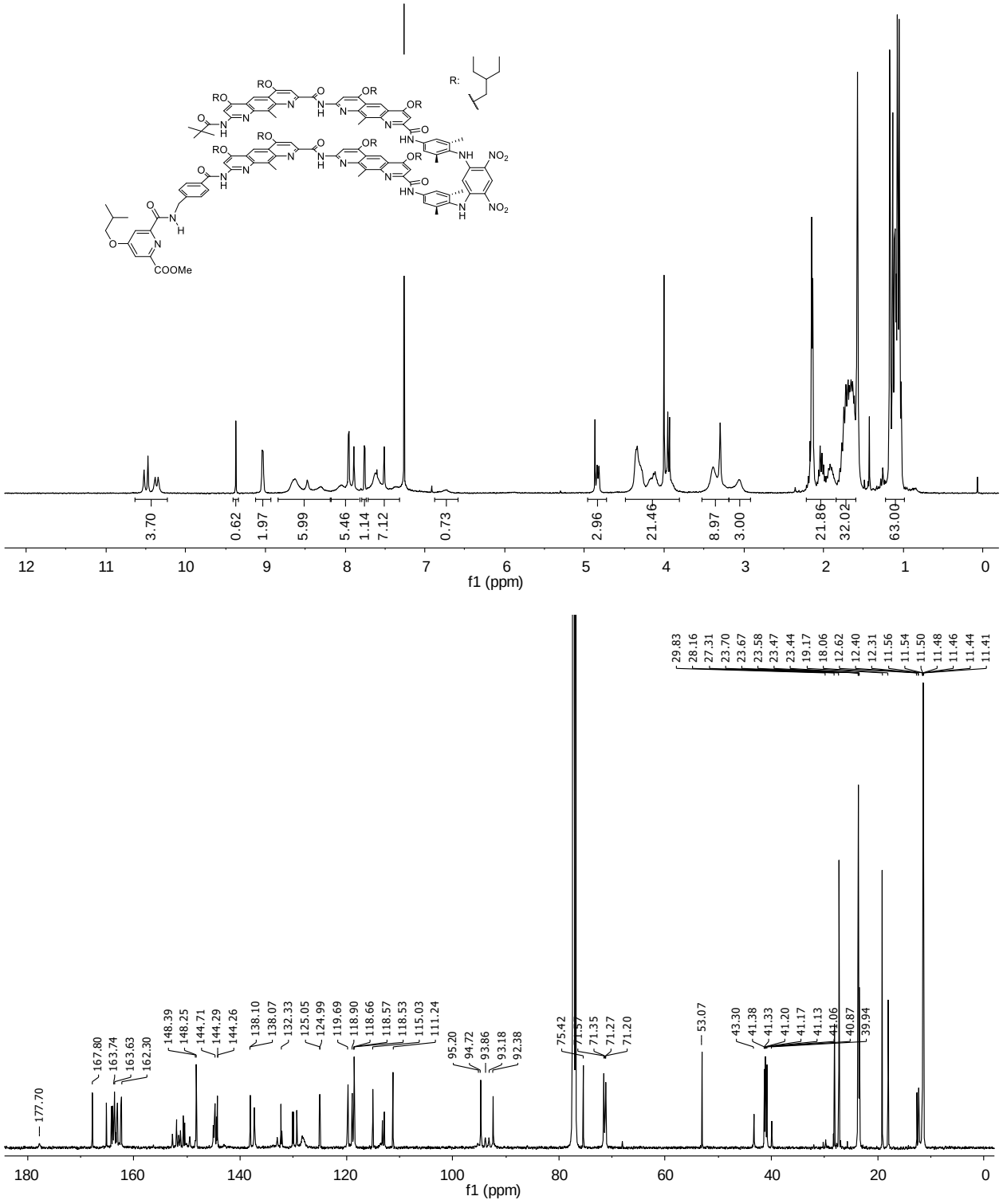


Figure S15. ^{1}H (300 MHz, $CDCl_3$, 298 K) and ^{13}C (126 MHz, $CDCl_3$, 298 K) NMR spectra of compound **11a**.

4.2. Compound **1**

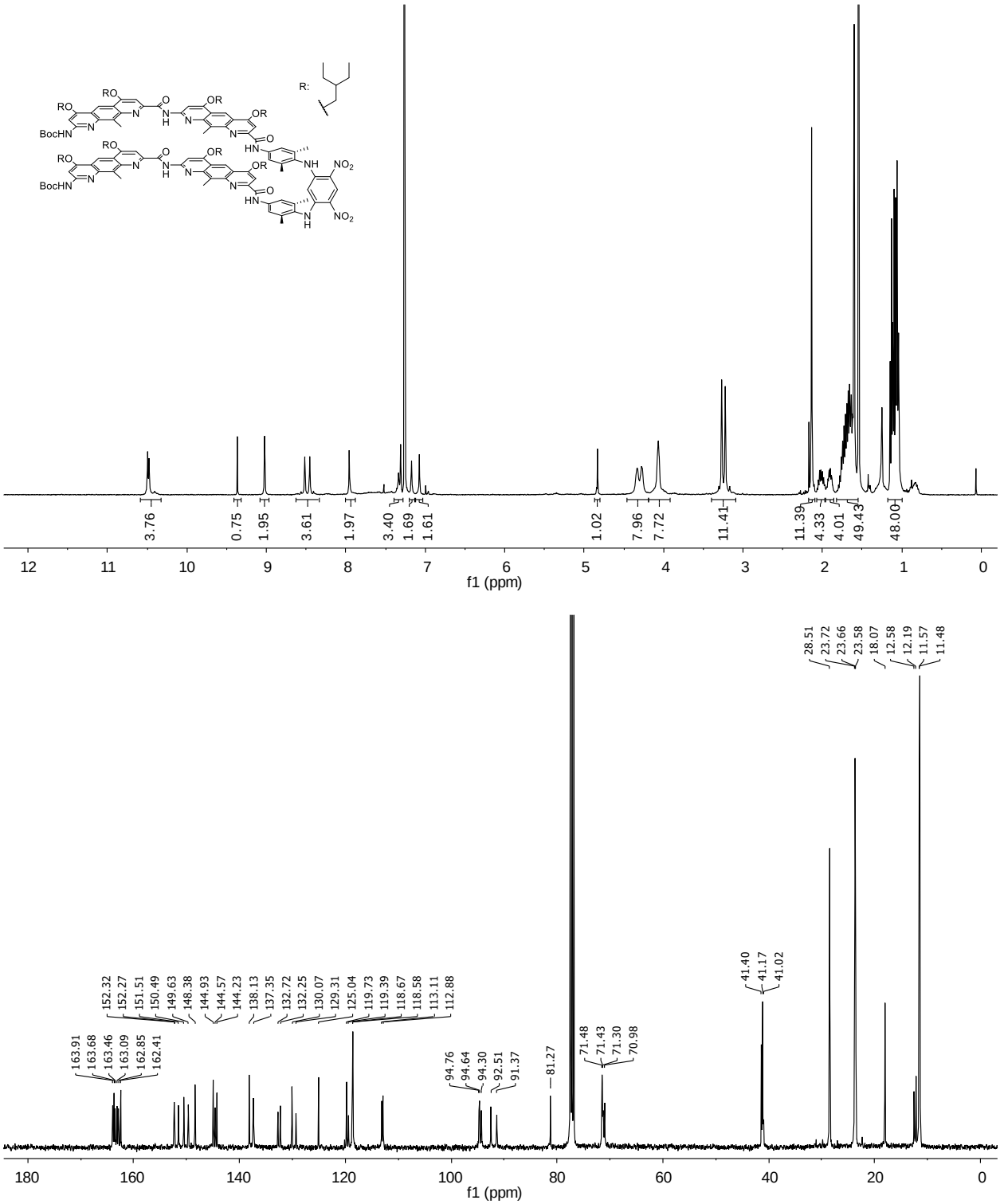


Figure S16. ^{1}H (400 MHz, $CDCl_3$, 298 K) and ^{13}C (101 MHz, $CDCl_3$, 298 K) NMR spectra of compound **1**.

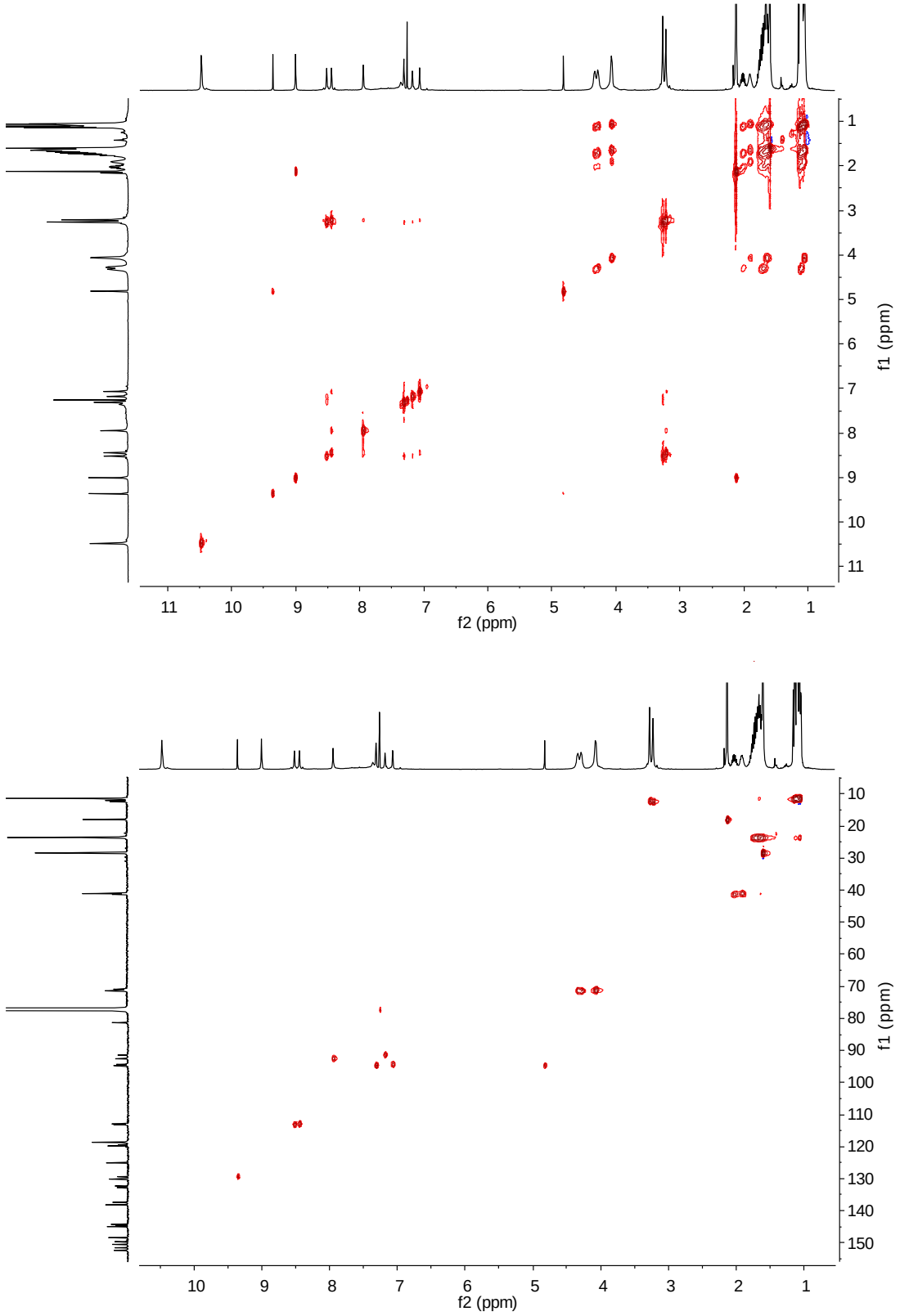


Figure S17. ^{1}H-^{1}H gTOCSY (400 MHz, $CDCl_3$, 298 K) and ^{1}H-^{13}C gHSQC (400 MHz, $CDCl_3$, 298 K) NMR spectra of compound **1**.

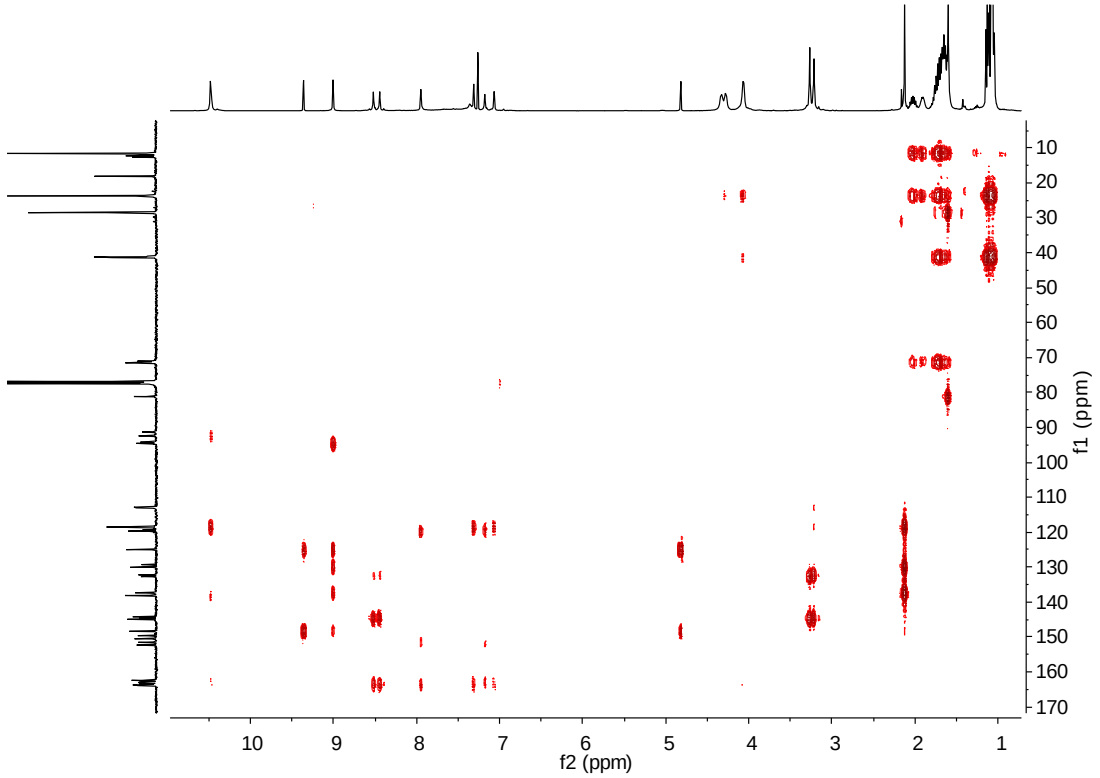


Figure S18. ^{1}H-^{13}C gHMBC (400 MHz, $CDCl_3$, 298 K) NMR spectrum of compound **1**.

5. NMR STUDIES

5.1. Color code for the assignment

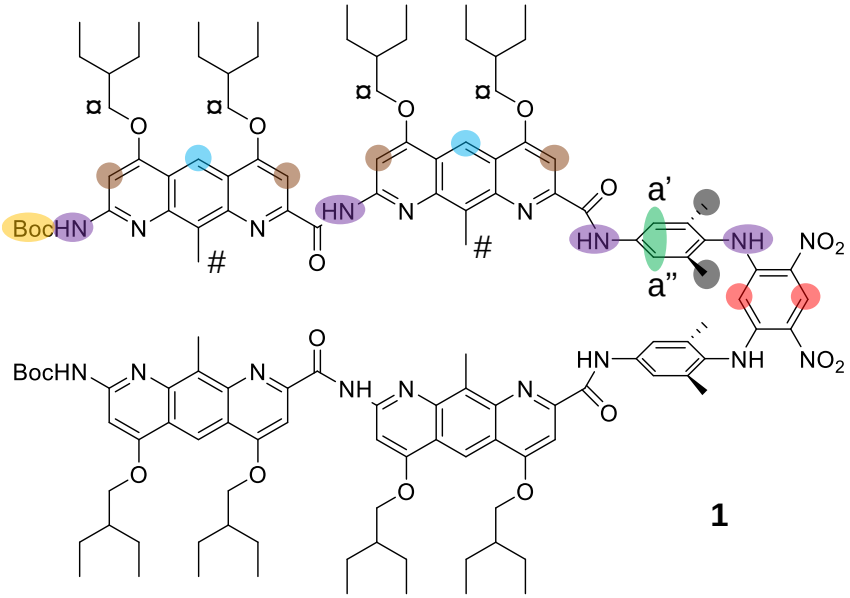


Figure S19. Chemical structure with the color code for the NMR assignment of compound **1**.

5.2. Dilution experiments

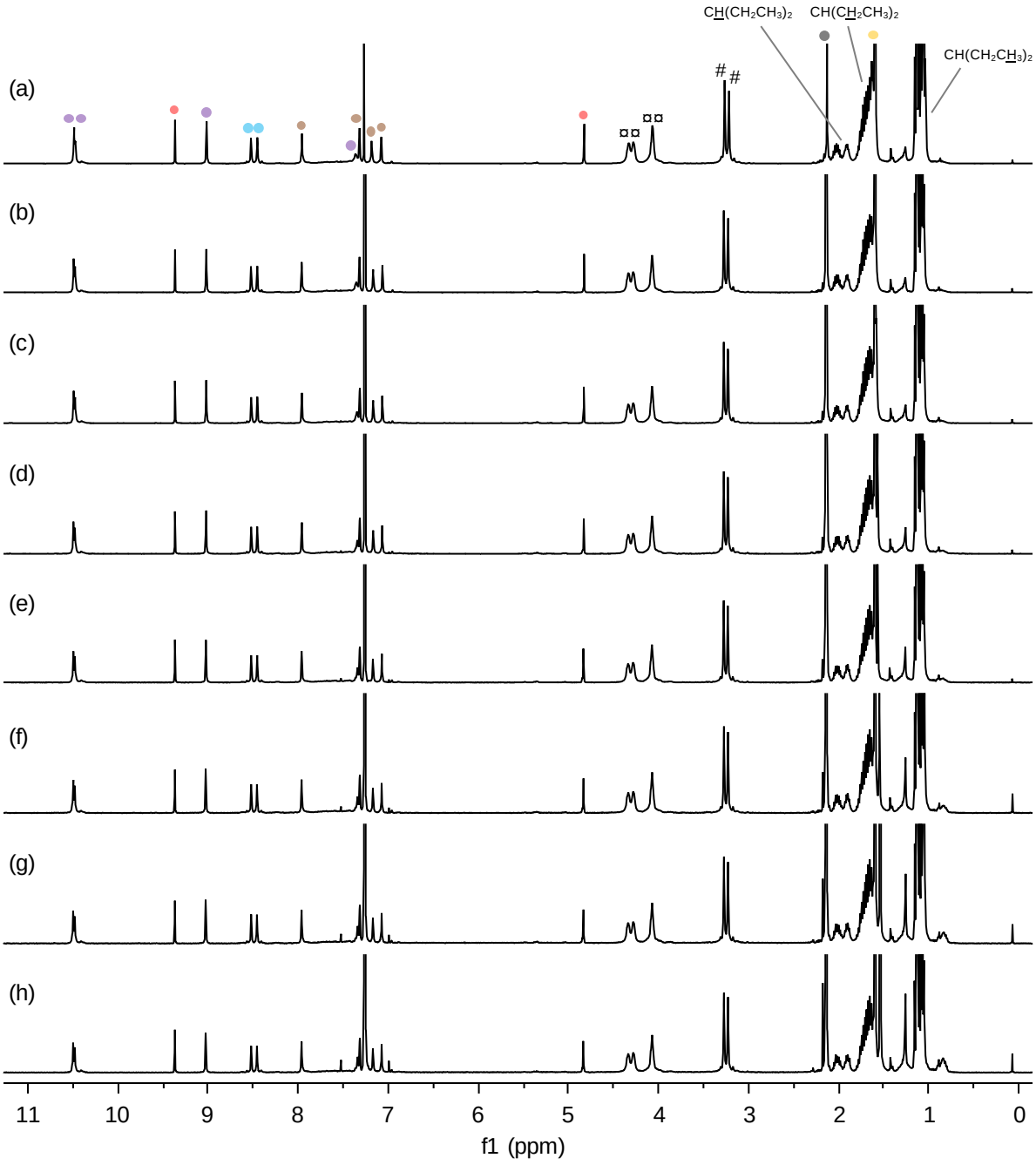


Figure S20. ^{1}H (400 MHz, $CDCl_3$, 298 K) spectra of compound **1** at different concentrations: (a) 8.40 mM; (b) 6.00 mM; (c) 4.67 mM; (d) 3.23 mM; (e) 2.21 mM; (f) 1.23 mM; (g) 0.74 mM; (h) 0.50 mM.

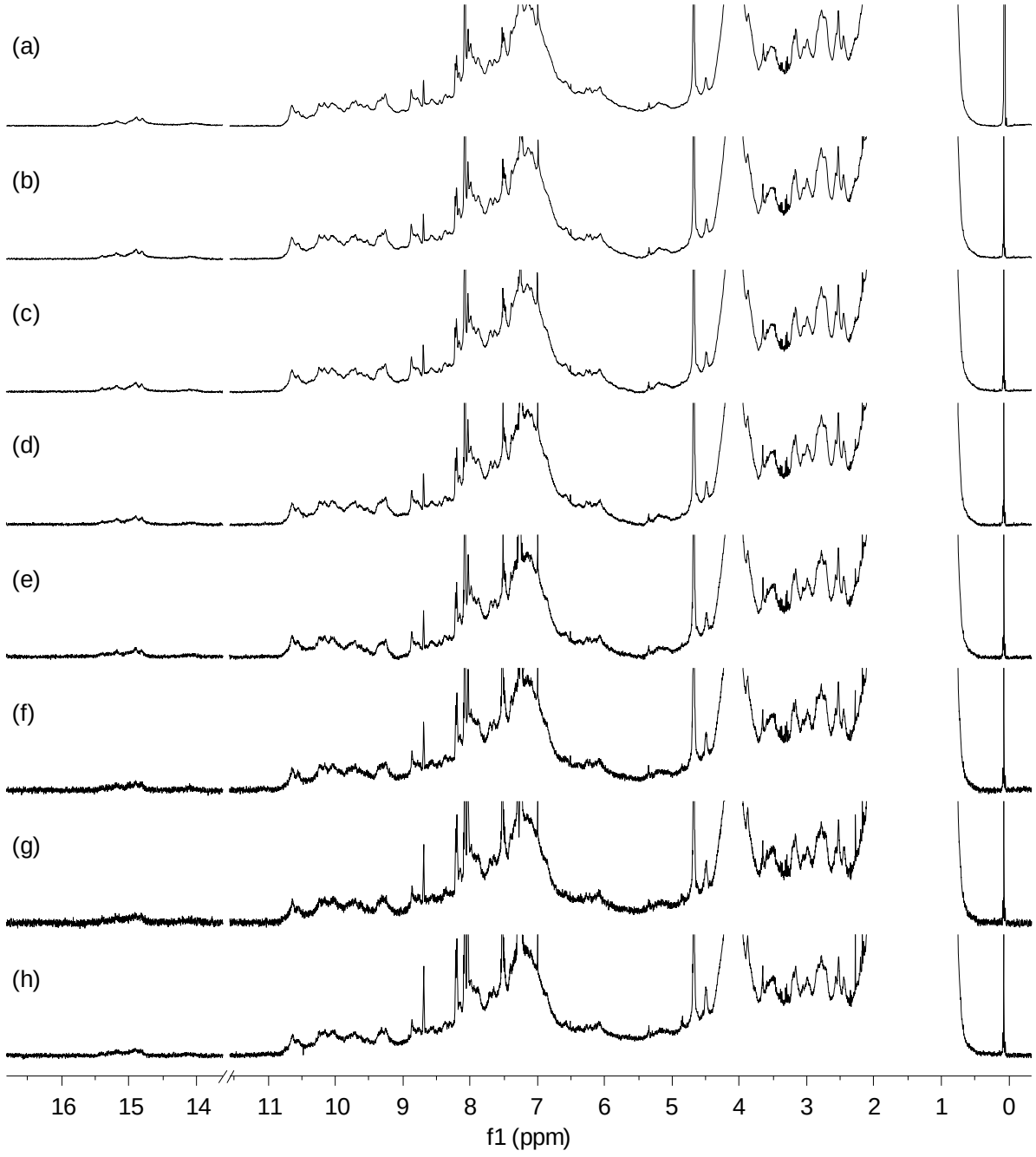


Figure S21. ^{1}H (400 MHz, $CDCl_3$, 298 K) spectra of compound **2** at different concentrations: (a) 8.28 mM; (b) 5.91 mM; (c) 4.60 mM; (d) 3.18 mM; (e) 2.18 mM; (f) 1.21 mM; (g) 0.84 mM; (h) 0.54 mM.

5.3. VT experiments in different solvents

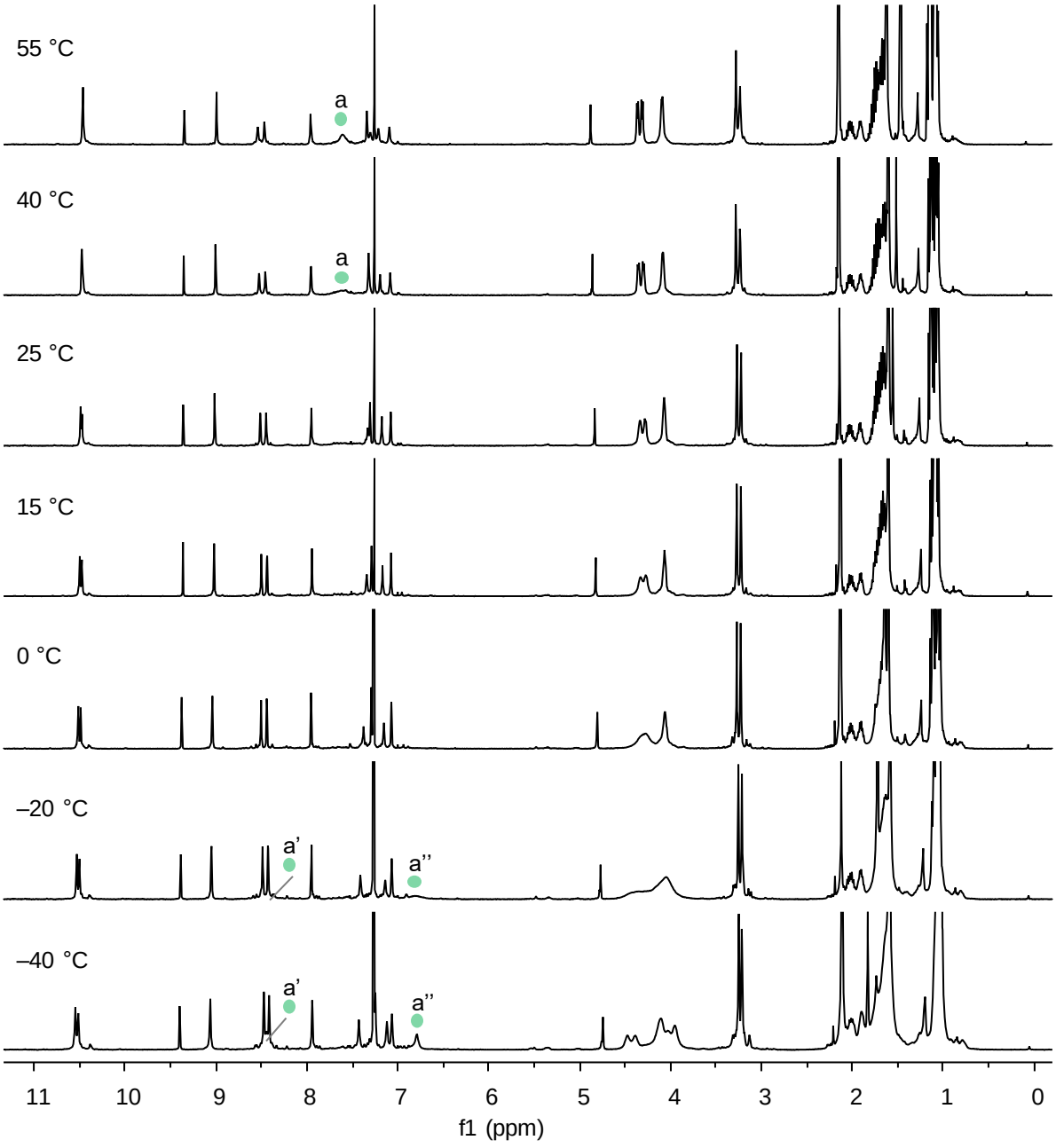


Figure S22. ^{1}H (400 MHz, $CDCl_3$) spectra of compound **1** (2.21 mM) at different temperatures.

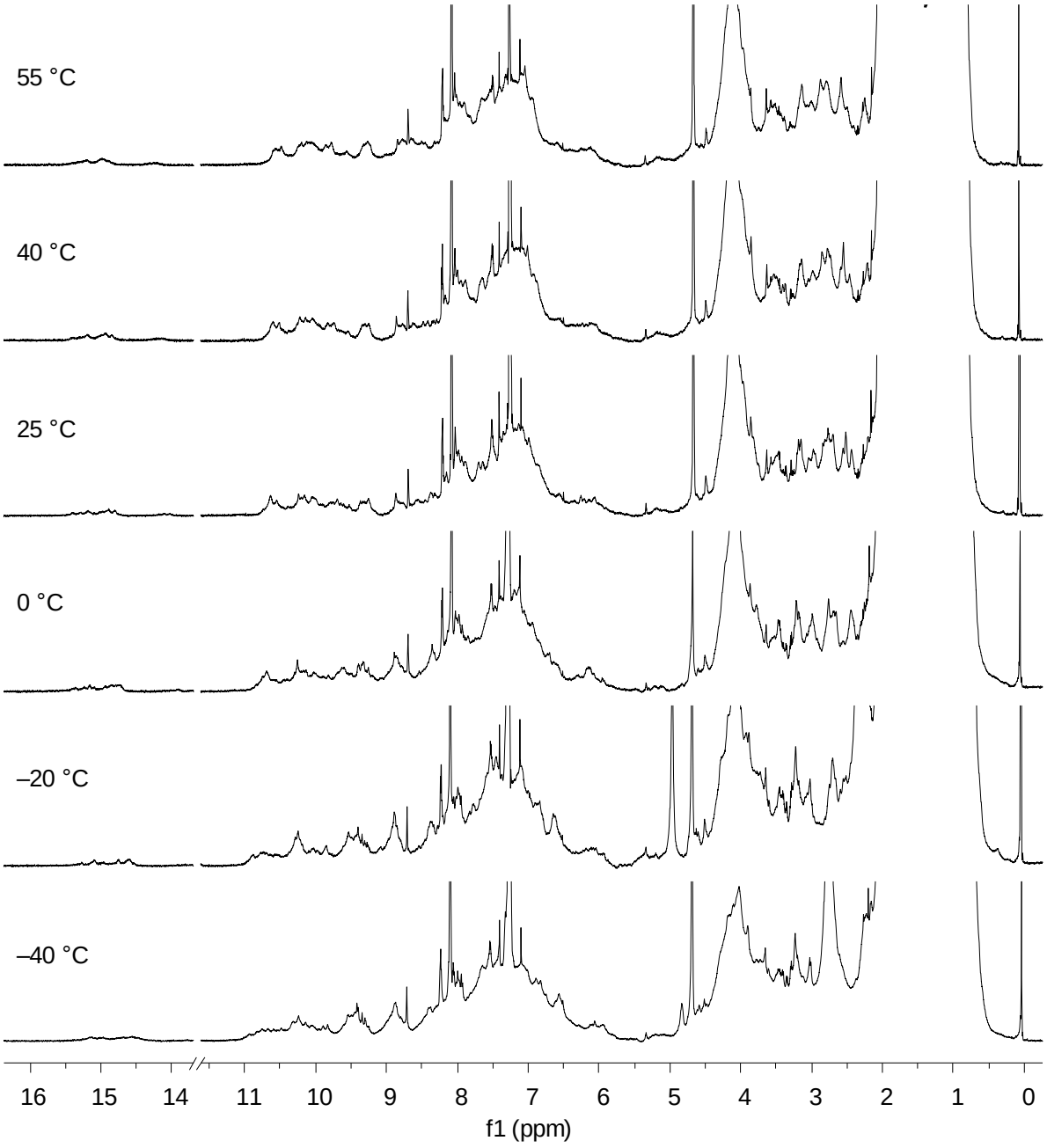


Figure S23. ^{1}H (700 MHz, $CDCl_3$) spectra of compound **2** (2.18 mM) at different temperatures.

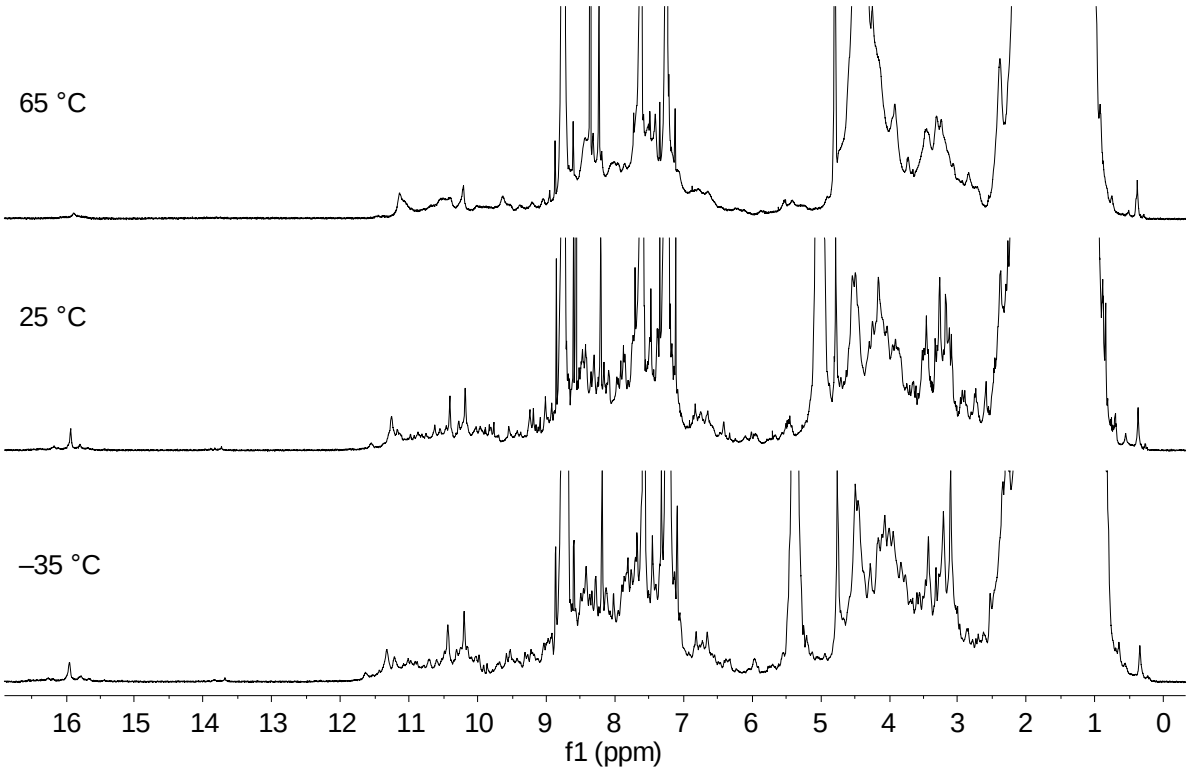


Figure S24. ^{1}H (700 MHz, pyridine-d_5) spectra of compound **2** (2.20 mM) at different temperatures.

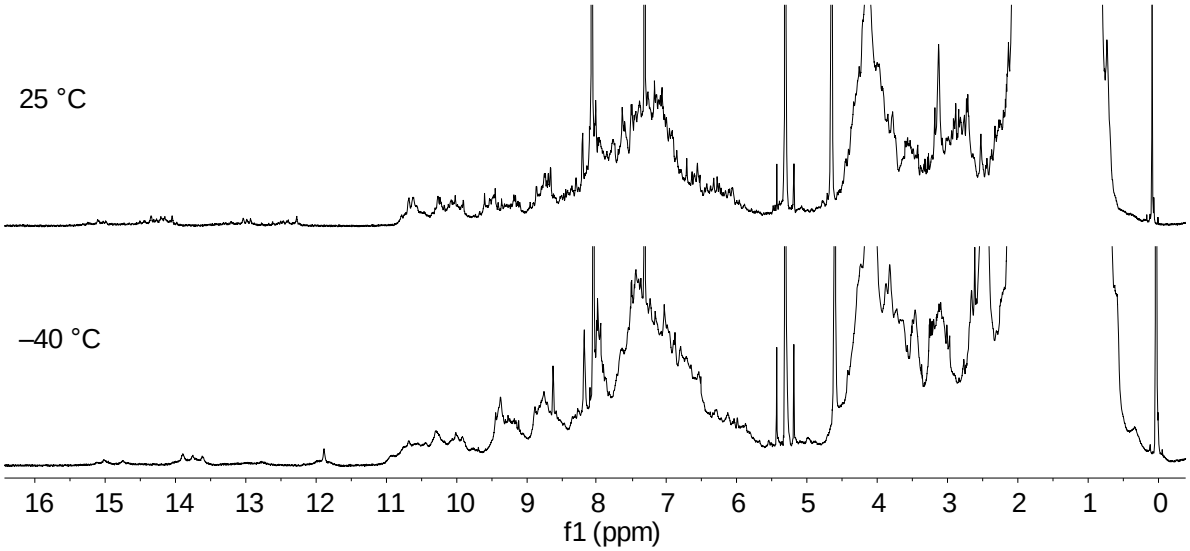


Figure S25. ^{1}H (700 MHz, CD_2Cl_2) spectra of compound **2** (2.20 mM) at different temperatures.

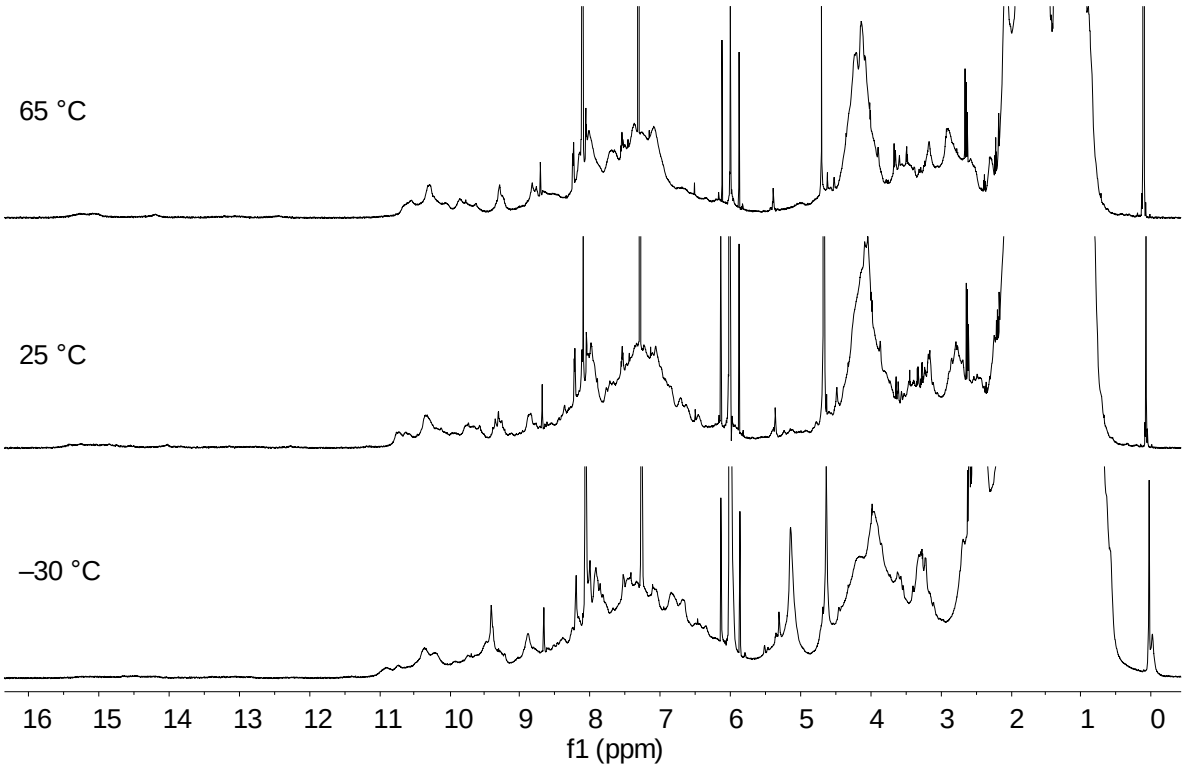


Figure S26. ^{1}H (700 MHz, 1,1,2,2-tetrachloroethane-d_2) spectra of compound **2** (2.20 mM) at different temperatures.

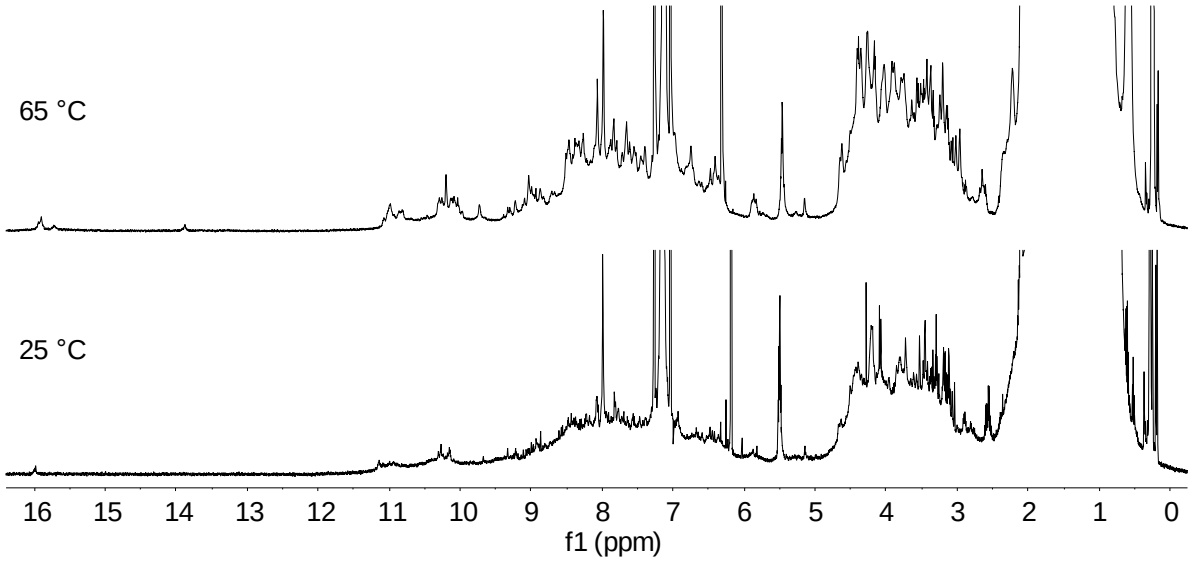


Figure S27. ^{1}H (700 MHz, benzene-d_6) spectra of compound **2** (saturated sample) at different temperatures.

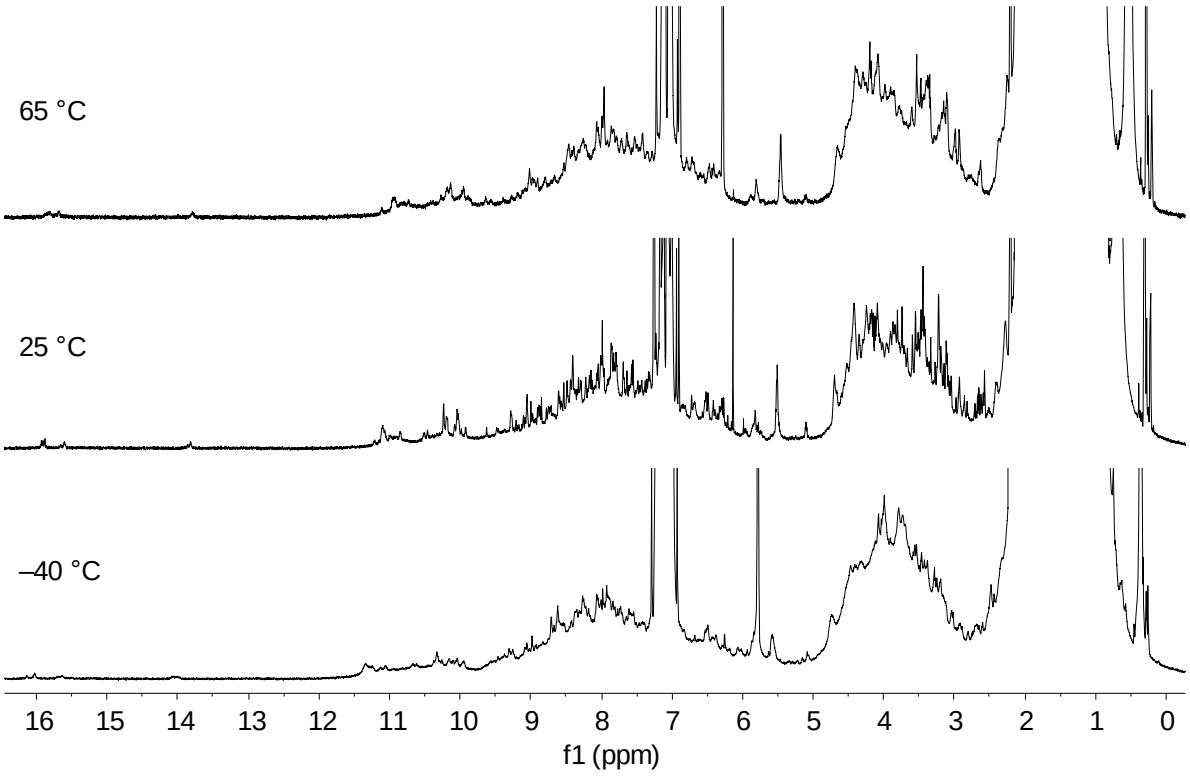


Figure S28. ^{1}H (700 MHz, toluene-d_8) spectra of compound **2** (saturated sample) at different temperatures.

6. MOLECULAR MODELING

Energy minimizations and stochastic dynamic simulations were carried out using MacroModel (Schrödinger Release 2019-1: MacroModel, Schrödinger, LLC, New York, NY, 2019) with Maestro interface (Schrödinger Release 2019-1: Maestro, Schrödinger, LLC, New York, NY, 2019).

First of all, the two crystal structures obtained for dimer **2**$_2$ were energy minimized with the OPLS3e force-field as implemented in the software, using the Steepest Descent (SD, gradient) minimization method with 500 maximum iterations, no solvent (constant dielectric, 1.0), the extended cutoff option and without any constrain. The obtained energy minimized structures, one for each crystal structure, served as the starting point for the stochastic dynamic simulations. These were performed using the OPLS3s force-field as implemented in the software, 500 steps of Truncated Newton Conjugate Gradient (TNCG, gradient), no solvent (constant dielectric, 1.0), the extended cutoff option and without any constrain. The simulations were performed for 10 ns at different temperatures (200, 300, 400, 500, 600, 700, 800 and 900 K), with different time step values (1.5 fs for T = 200-400 K and 1.0 fs for T = 500-900 K), and 1 ps as equilibration time. Structures were sampled every 10 ps and several distances were monitored during the simulation (see Figure S29).

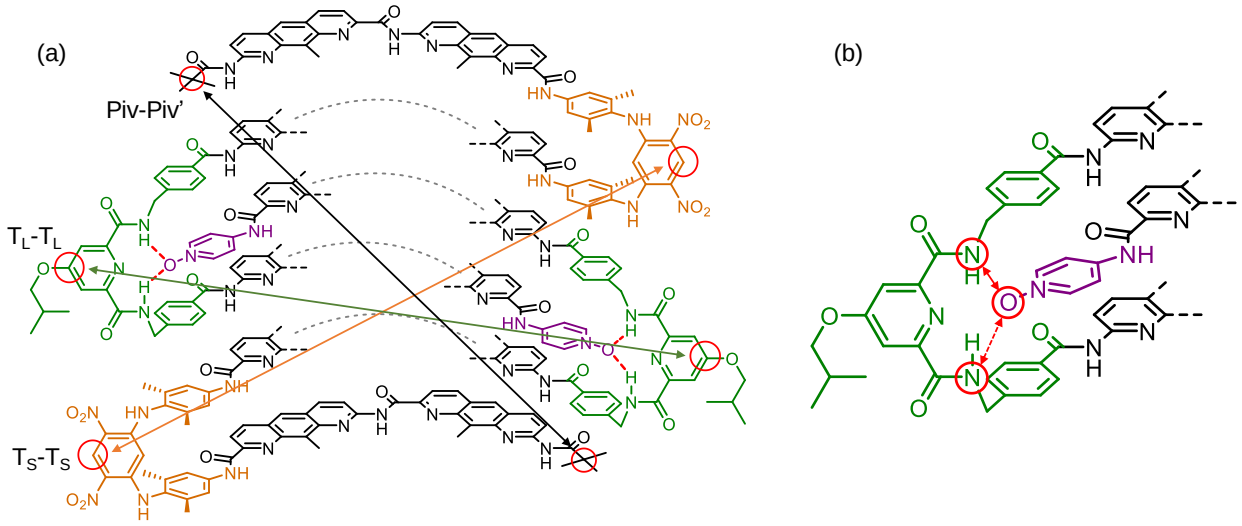


Figure S29. Representation of the distances monitored during the stochastic dynamic simulations carried out with **2**$_2$: (a) distance between the two pivaloyl terminating groups (black arrow), the two **T**$_S$ (orange arrow) and the two **T**$_L$ (green arrow); (b) distances between the heteroatoms involved in the H-bonds established by the *N*-oxide groups (solid and dashed red arrows). The red circles indicate the atoms used to measure the distances. The side-chains and the four inner aromatic layers of the assembly are omitted for clarity.

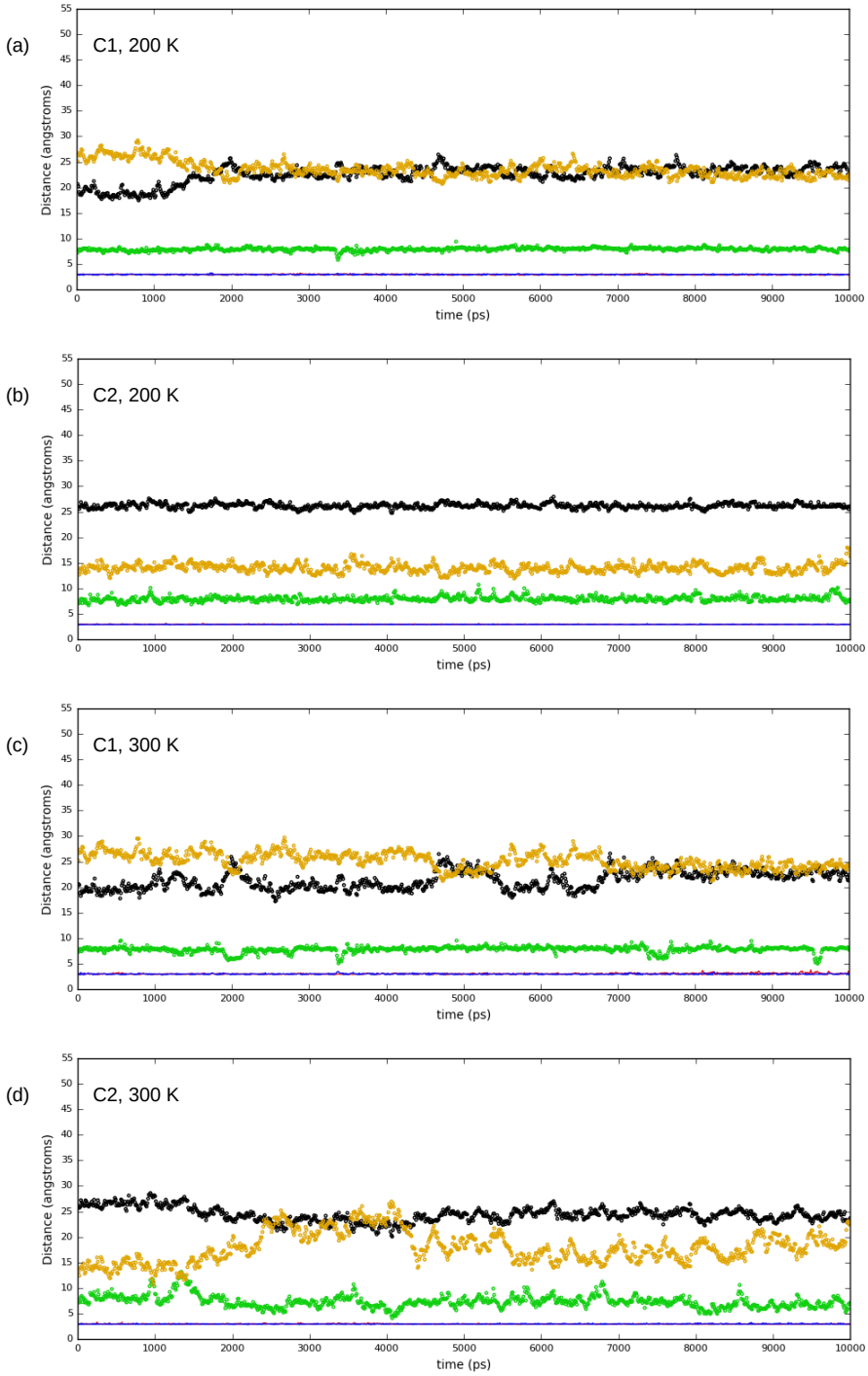


Figure S30. Results obtained from the 10 ns stochastic dynamic simulations carried out with dimer **2**$_2$ using crystal structures C1 (a,c) and C2 (b,d) as initial point, at T = 200 K (a,b) and T = 300 K (c,d). The graphics represent the distance between the two pivaloyl groups (black hollow circles), the two **T**$_S$s (orange hollow circles) and the two **T**$_L$ (green hollow circles). The distance between the heteroatoms involved in the four potential H-bonds (two for each *N*-oxide) is also represented (solid and dashed red lines for the H-bonds of one *N*-oxide; solid and dashed blue lines for the H-bonds of the other *N*-oxide). See in Figure S29 the atoms used to measure the distances. C1 ↔ C2 transitions do not occur at 200-300 K.

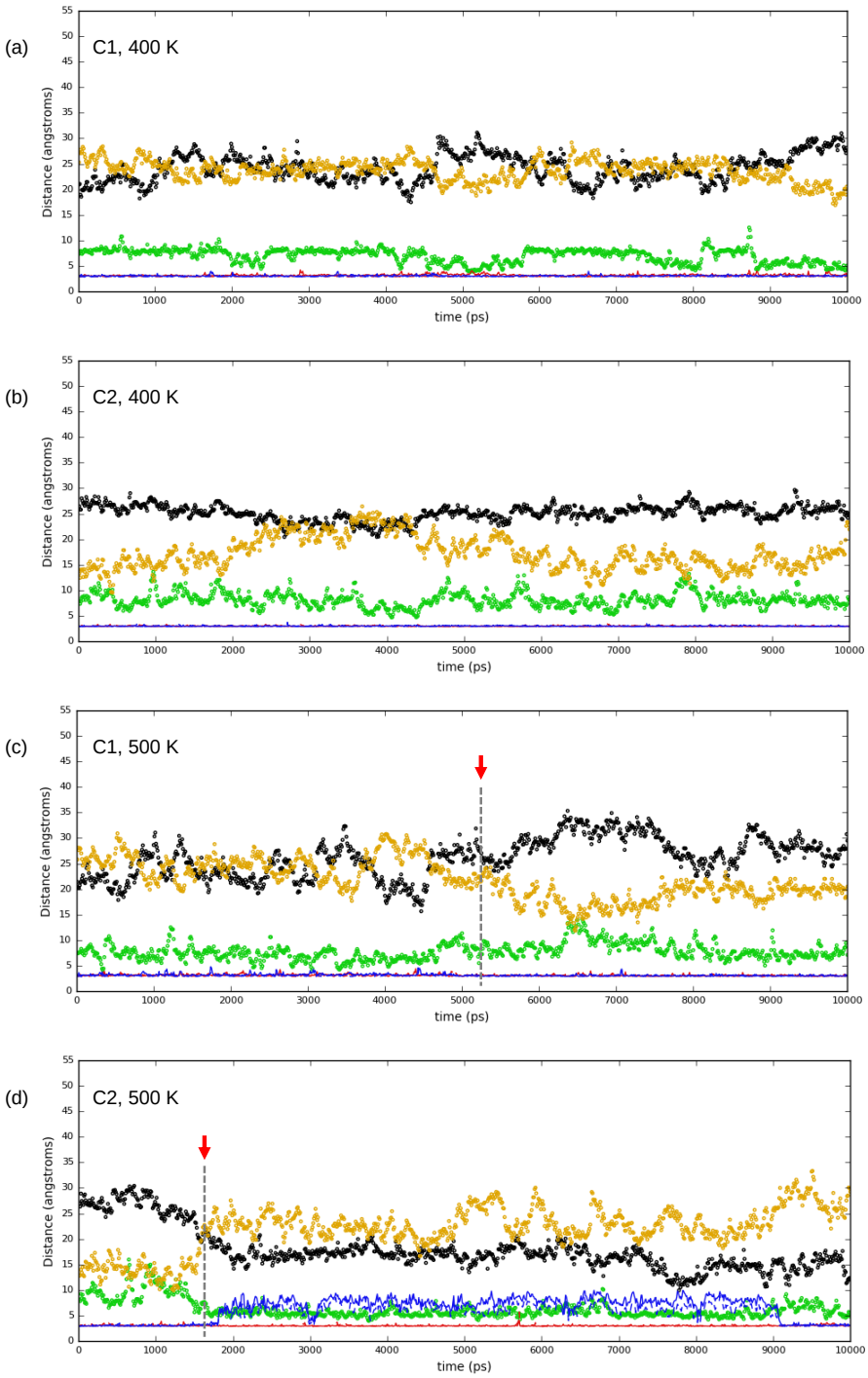


Figure S31. Results obtained from the 10 ns stochastic dynamic simulations carried out with dimer $\mathbf{2}_2$ using crystal structures C1 (a,c) and C2 (b,d) as initial point, at T = 400 K (a,b) and T = 500 K (c,d). The graphics represent the distance between the two pivaloyl groups (black hollow circles), the two $\mathbf{T}_S$ (orange hollow circles) and the two $\mathbf{T}_L$ (green hollow circles). The distance between the heteroatoms involved in the four potential H-bonds (two for each *N*-oxide) is also represented (solid and dashed red lines for the H-bonds of one *N*-oxide; solid and dashed blue lines for the H-bonds of the other *N*-oxide). See in Figure S29 the atoms used to measure the distances. C1 ↔ C2 transitions, indicated with a red arrow and a gray dashed vertical line, occur at 500 K but not at 400 K.

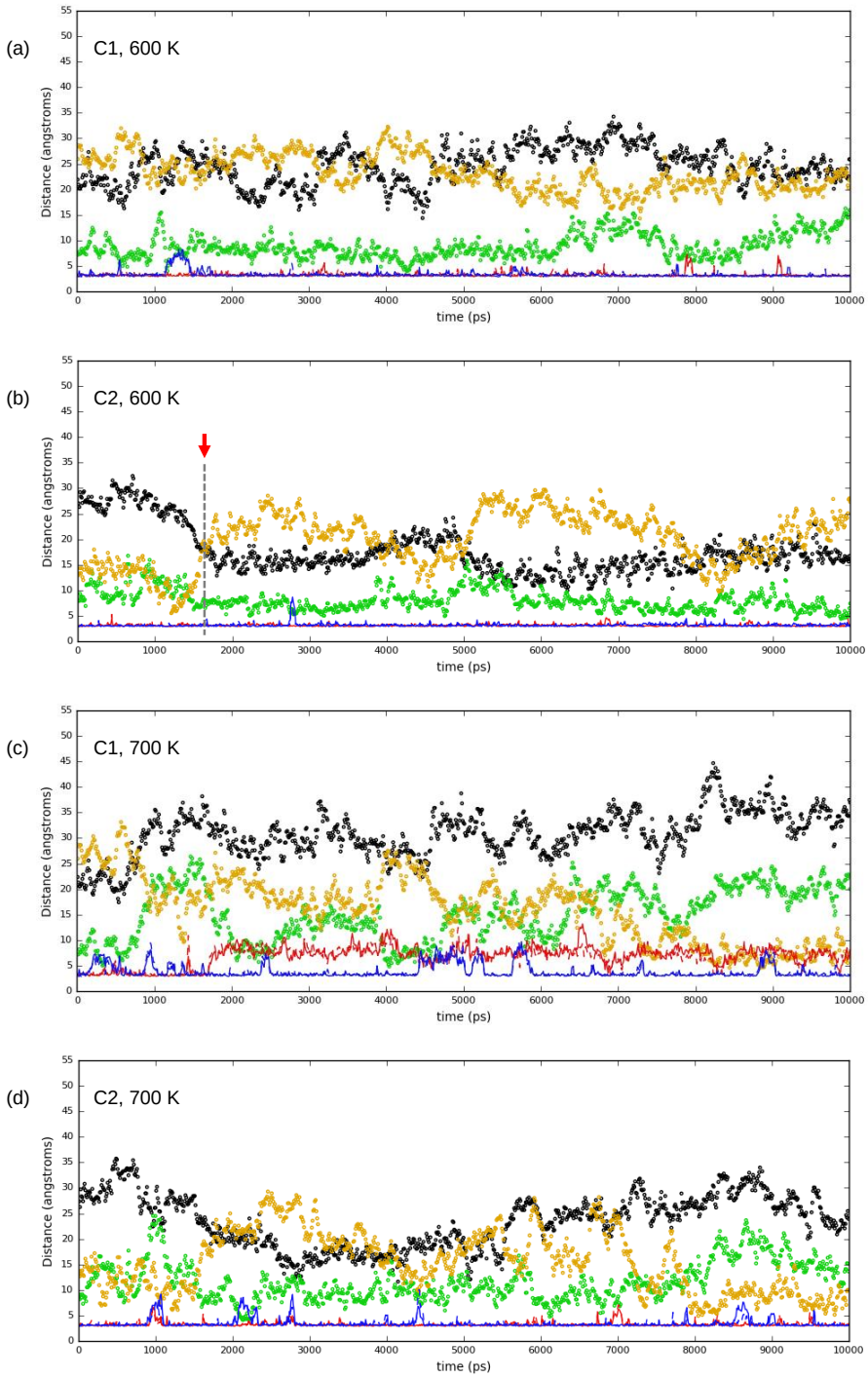


Figure S32. Results obtained from the 10 ns stochastic dynamic simulations carried out with dimer $\mathbf{2_2}$ using crystal structures C1 (a,c) and C2 (b,d) as initial point, at T = 600 K (a,b) and T = 700 K (c,d). The graphics represent the distance between the two pivaloyl groups (black hollow circles), the two $\mathbf{T_S}$ (orange hollow circles) and the two $\mathbf{T_L}$ (green hollow circles). The distance between the heteroatoms involved in the four potential H-bonds (two for each *N*-oxide) is also represented (solid and dashed red lines for the H-bonds of one *N*-oxide; solid and dashed blue lines for the H-bonds of the other *N*-oxide). See in Figure S29 the atoms used to measure the distances. C1 ↔ C2 transitions are indicated only in (b) with a red arrow and a gray dashed vertical line.

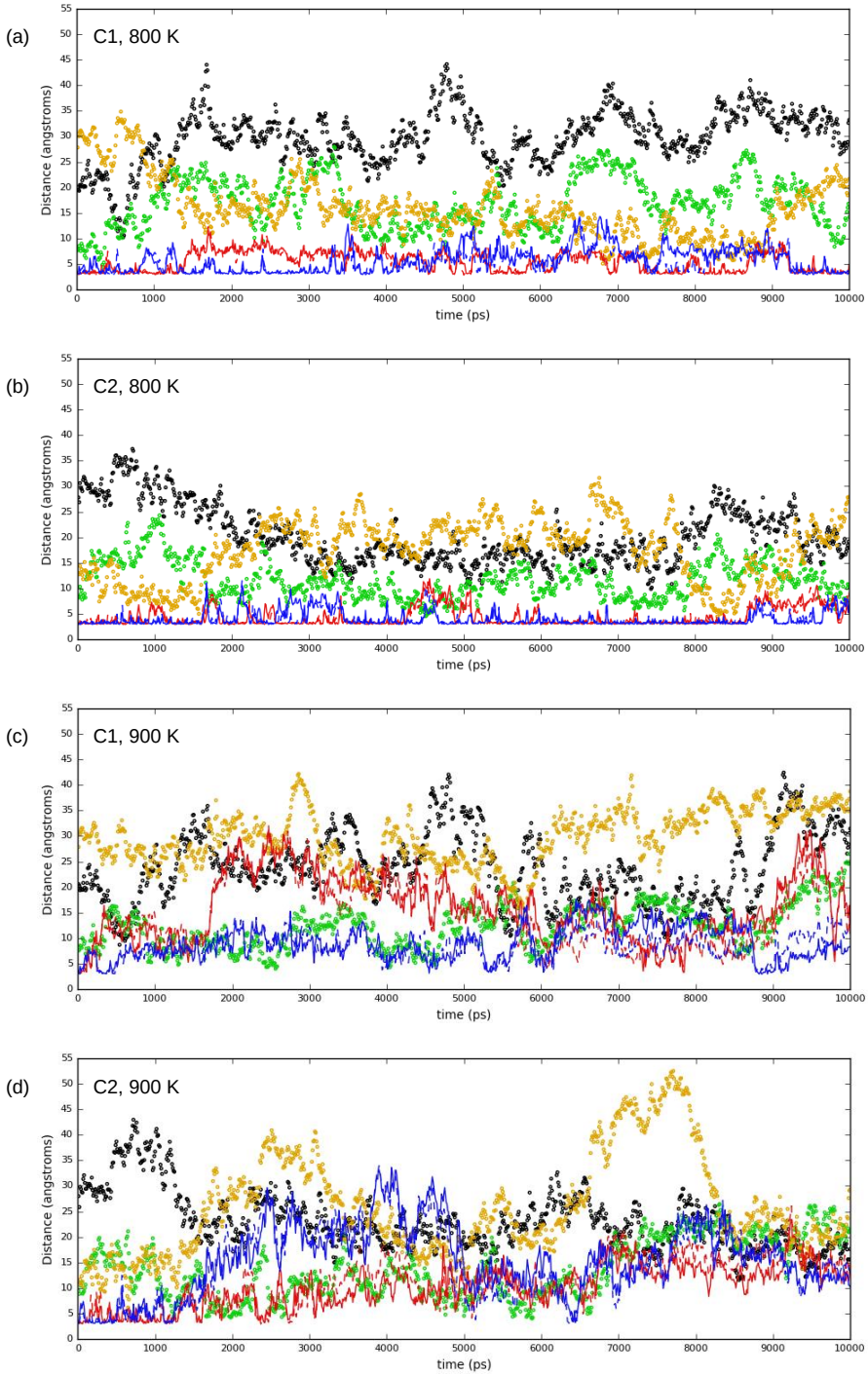


Figure S33. Results obtained from the 10 ns stochastic dynamic simulations carried out with dimer $\mathbf{2_2}$ using crystal structures C1 (a,c) and C2 (b,d) as initial point, at T = 800 K (a,b) and T = 900 K (c,d). The graphics represent the distance between the two pivaloyl groups (black hollow circles), the two $\mathbf{T_S}$ (orange hollow circles) and the two $\mathbf{T_L}$ (green hollow circles). The distance between the heteroatoms involved in the four potential H-bonds (two for each *N*-oxide) is also represented (solid and dashed red lines for the H-bonds of one *N*-oxide; solid and dashed blue lines for the H-bonds of the other *N*-oxide). See in Figure S29 the atoms used to measure the distances. C1 ↔ C2 transitions are not indicated.

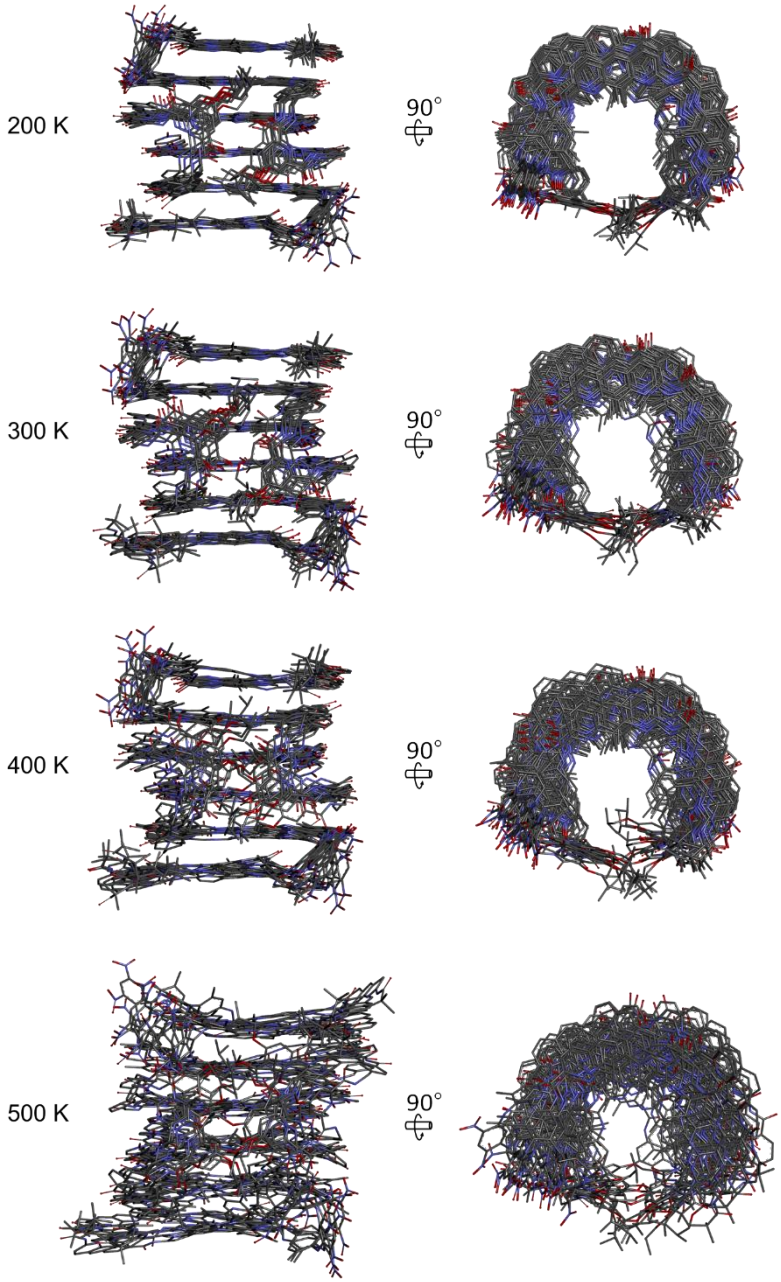


Figure S34. Selected snapshots (10 for each temperature, sampled every 1 ns) from the stochastic dynamic simulations carried out for $\mathbf{2}_2$, starting from the crystal structure C1, at 200-500 K. The side-chains of **A** ($OCH_2CH(CH_2CH_3)_2$) are omitted for clarity.

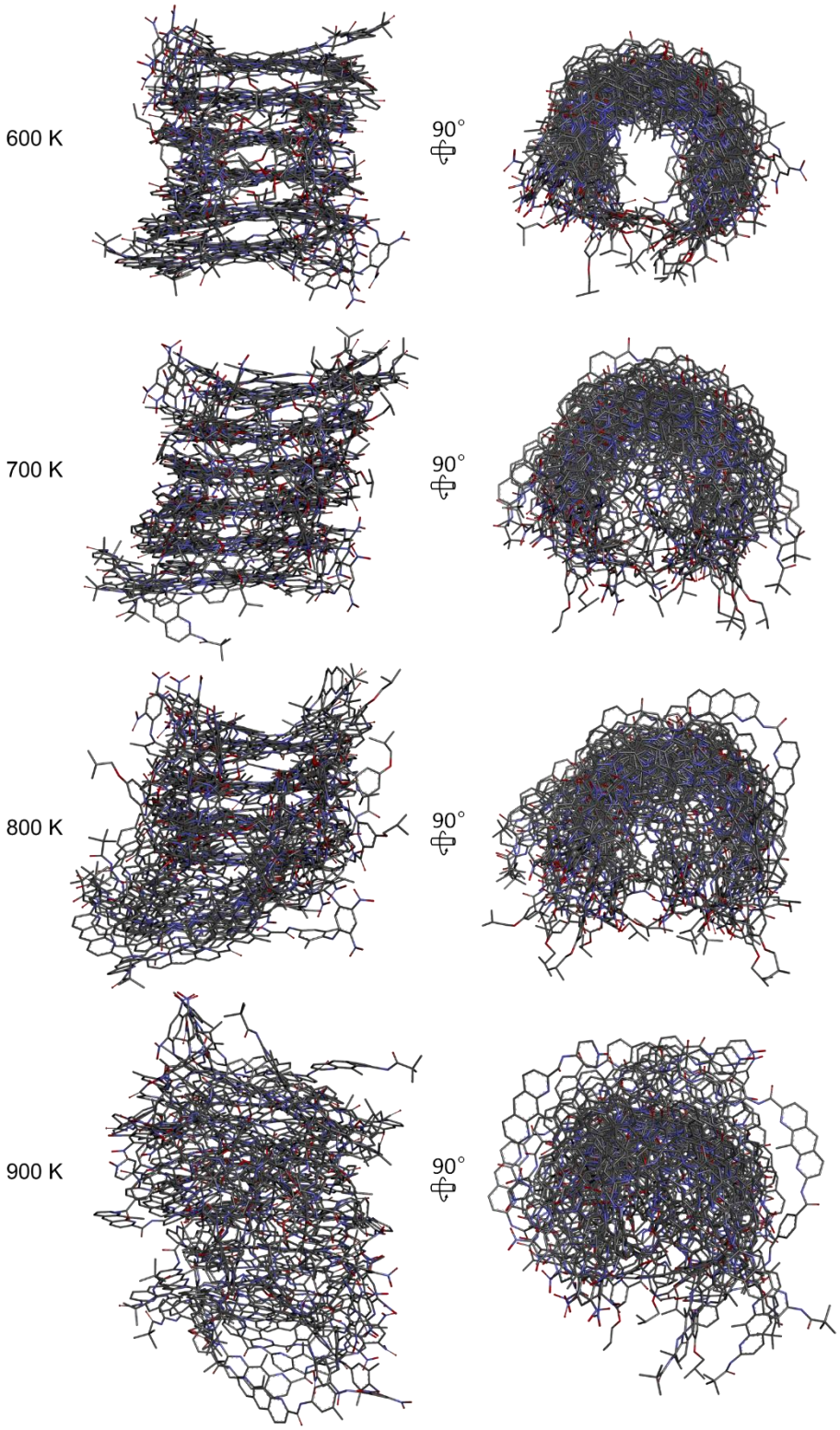


Figure S35. Selected snapshots (10 for each temperature, sampled every 1 ns) from the stochastic dynamic simulations carried out for $\mathbf{2}_2$, starting from the crystal structure C1, at 600-900 K. The side-chains of **A** ($OCH_2CH(CH_2CH_3)_2$) are omitted for clarity.

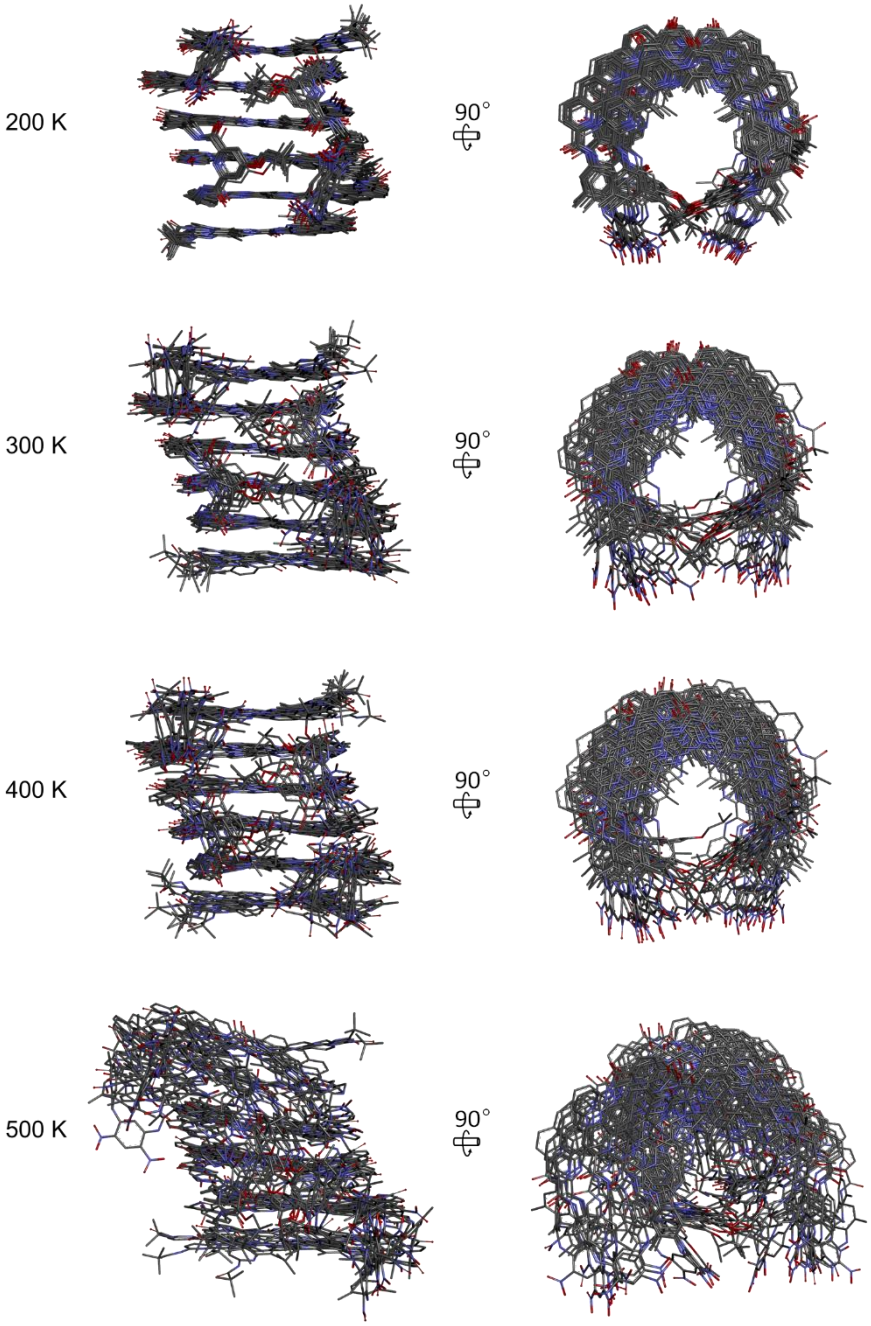


Figure S36. Selected snapshots (10 for each temperature, sampled every 1 ns) from the stochastic dynamic simulations carried out for $\mathbf{2}_2$, starting from the crystal structure C2, at 200-500 K. The side-chains of **A** ($OCH_2CH(CH_2CH_3)_2$) are omitted for clarity.

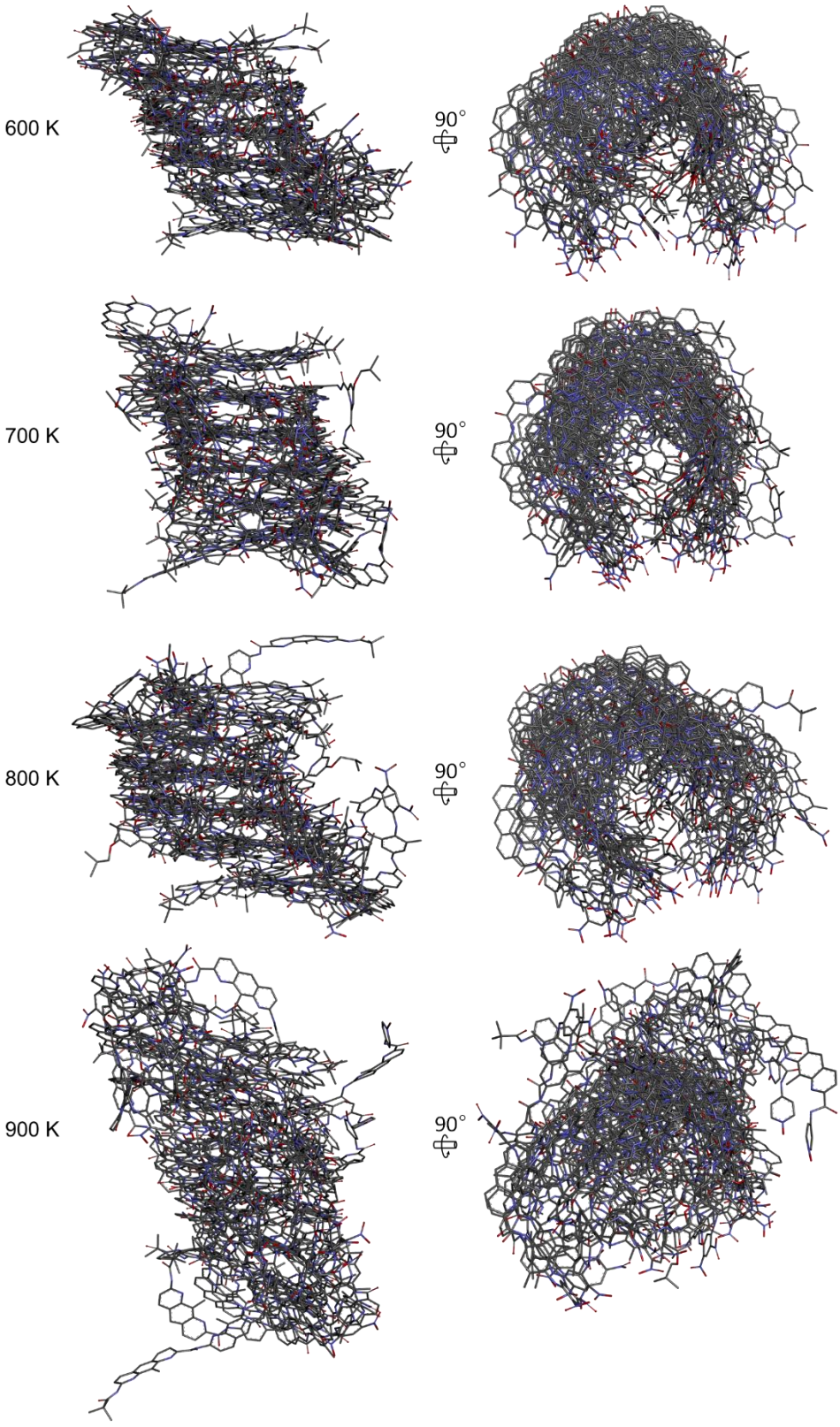


Figure S37. Selected snapshots (10 for each temperature, sampled every 1 ns) from the stochastic dynamic simulations carried out for $\mathbf{2}_2$, starting from the crystal structure C2, at 600-900 K. The side-chains of **A** ($OCH_2CH(CH_2CH_3)_2$) are omitted for clarity.

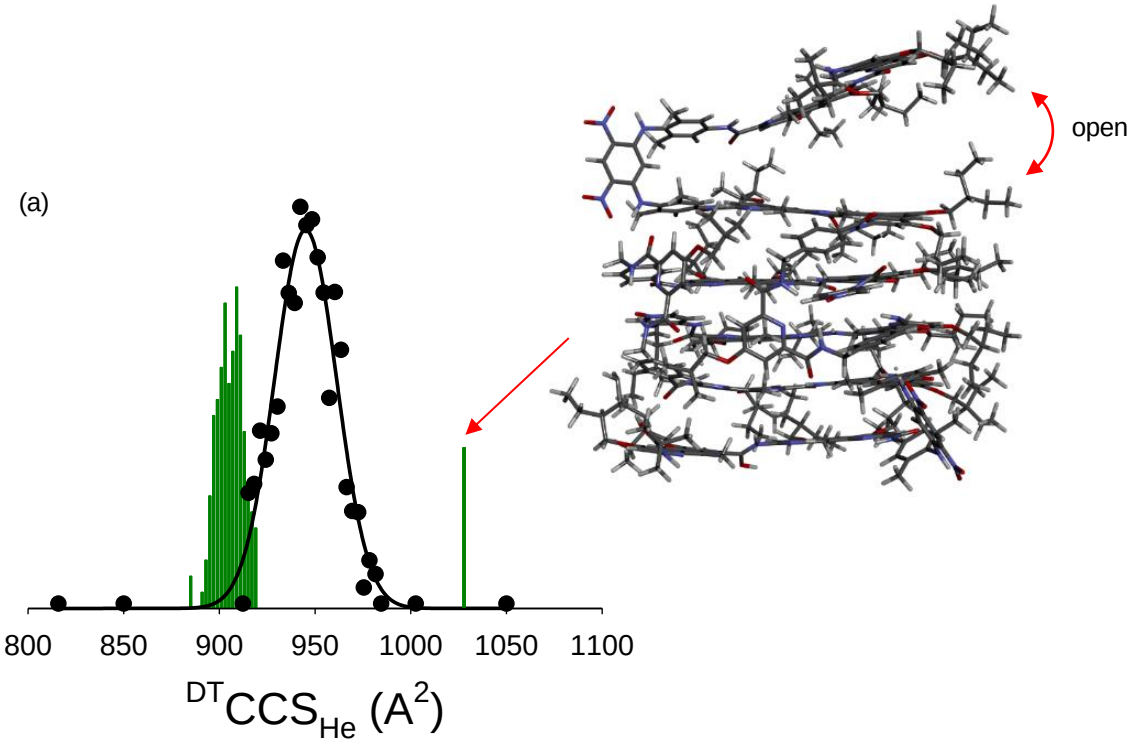
7. IM-MS STUDIES

IM-MS experiments were performed on an Agilent 6560 DTIMS-Q-TOF (Agilent Technologies, Santa-Clara, CA) instrument with the dual-ESI source operated in positive ion mode. The injection flow rate was 190 µL/h. All spectra were acquired in soft conditions (JASMS, 2018, 29, 2189). The drift tube was operated in Helium at a pressure of 3.89 Torr. Step-field experiments (5 voltages for each sample) were performed to determine the CCS.

Molecular modeling and calculation of the theoretical collisional cross sections $^{TM}CCS_{He}$ were performed for the two crystal structures obtained for **2_2** (C1 and C2). The side chains that were not resolved in the crystal structures were constructed and protons added. Additional protons were added to reach the experimental charge state (+3).

Geometry optimizations and molecular dynamics simulations were performed using Gaussian 16 rev. B.01 software. The structures $[C1+3H]^{3+}$ and $[C2+3H]^{3+}$ were optimized using a semi-empirical quantum method with the PM7 Hamiltonian.

Born-Oppenheimer molecular dynamics simulation was performed (using gradient only) with a time step of 0.2 fs at a temperature of 296 K. A 1000 fs trajectory was produced and structures were extracted every 10 fs to calculate the theoretical collisional cross section $^{TM}CCS_{He}$ with the mobcal code using trajectory model.



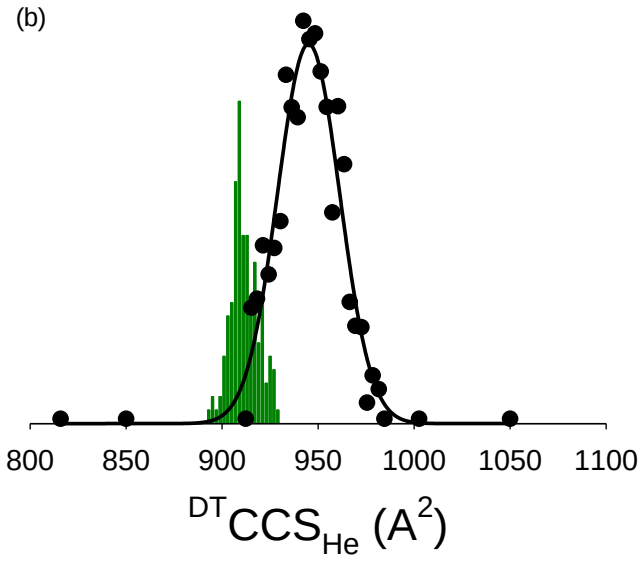


Figure S38. Comparison between the experimental collisional cross section (black dots) obtained for $\mathbf{2_2}^{3+}$, and the theoretical collisional cross sections (green histograms) calculated for the snapshots sampled during the molecular dynamics simulations performed for (a) $[C1+3H]^{3+}$ and (b) $[C2+3H]^{3+}$. The histograms are constructed with 18 bins. The theoretical CCS was also determined for a partially unfolded (manual opening) structure. The calculated value falls outside the experimental distribution.

8. CRYSTALLOGRAPHIC DATA

8.1. X-ray crystallography

Single crystal X-ray diffraction data for the molecules **1** and **2** (C1) were collected on a RigakuFRX rotating anode (2.97 kW) diffractometer at the IECB x-ray facility (CNRS UMS 3033 – INSERM US001, Université de Bordeaux) with a microfocus beam at the CuKα wavelength focused by high flux Osmic Varimax mirrors. The x-ray source is equipped with a Dectris Pilatus 200K detector and an AFC11 partial chi goniometer allowing omega scans. The crystals were mounted on cryoloops and flashfrozen under a nitrogen gas stream at 130 K. Data were processed with the CrysAlis PRO[5] software. The data for compound **2** (C2) were collected at ESRF (Tunable Beamline FIP BM30A, λ = 0.810Å) on a flashfrozen crystal at 100K and processed with the XDS package[6]. All structures were solved with the ShelXD[7] structure solution program using the WEED algorithm with random omit maps after real space refinement to reduce "model bias" or "over-emphasis" from strong contributors. The Olex2 suite[8] was used for model building and structure refinement with the ShelXL[9] package running Least Squares minimization.

All non-H atoms were refined anisotropically for molecule **1**. Only non-H atoms of the backbone were refined with anisotropic displacement parameters for molecule **2** (C1 and C2). For backbone atoms of all molecules and observable side chains of molecule **1** H-atoms were positioned geometrically and constrained depending on their environment. Those H-atoms were refined in the riding-model approximation, with Uiso(H)=1.2Ueq (CH, CH_2, NH). For molecules **2** (C1 and C2), only observable side chains carbon atoms were modelized and restrained with isotropic displacement parameters. DFIX, AFIX, SADI and RIGU restraints were apply to model geometry and thermal motion parameters in both large structures. Due to the large disorder solvent content in all three structures, the SQUEEZE[10] procedure was used to flattened electron density map by calculating the solvent contribution to the structure factors by back-Fourier transformation of the electron density found in the solvent-accessible region of a phase-optimized difference electron-density map.

The refinement of crystal structures of **2** (C1 and C2) faced problems commonly observed with large foldamers, i.e. large volume fractions of disordered solvent molecules, radiation damage, and high thermal motion for long side chains leading to weak diffraction intensities, incompleteness of the data, moderate or low resolution. Thus, it is not surprising that a number of A-level and B-level alerts were detected using IUCR's checkcif algorithm. Some are listed below and have been divided into two groups:

Group 1 alerts illustrate weak quality of the data and refinement statistics if compared to that expected for small molecule structures from highly diffracting crystals:

PLAT031_ALERT_4_A Refined Extinction Parameter Within Range

THETM01_ALERT_3_A The value of sine(theta_max)/wavelength is less Calculated sin(theta_max)/wavelength = 0.4554

LAT084_ALERT_3_A High wR2 Value (i.e. > 0.25)…

Group 2 alerts is connected with decision made during refinement and explained below:

PLAT080_ALERT_2_A Maximum Shift/Error

PLAT241_ALERT_2_A High ’MainMol’ Ueq as Compared to Neighbors of

PLAT242_ALERT_2_A Low ’MainMol’ Ueq as Compared to Neighbors of

PLAT415_ALERT_2_A Short Inter D-H..H-X

PLAT430_ALERT_2_A Short Inter D...A Contact…

8.2. Table 1: Crystal data and structure refinement for molecule **1** (CCDC 2040478)

Empirical formula	$C_{136}H_{171}Cl_3N_{18}O_{20}$
Formula weight	2484.25
Temperature/K	130
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	20.717(3)
b/Å	26.200(4)
c/Å	29.241(4)
α/°	90
β/°	91.334(4)
γ/°	90
Volume/Å^3	15867(4)
Z	4
ρ_{calc}g/cm^3	1.040
μ/mm^{-1}	1.015
F(000)	5296.0
Crystal size/mm^3	0.2 × 0.2 × 0.2
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	4.266 to 108.478
Index ranges	$-21 \leq h \leq 19$, $-26 \leq k \leq 25$, $-30 \leq l \leq 30$
Reflections collected	82939
Independent reflections	18881 [R_{int} = 0.0682, R_{sigma} = 0.0554]
Data/restraints/parameters	18881/1309/1624
Goodness-of-fit on F^2	1.291
Final R indexes [I>=2σ (I)]	R_1 = 0.1153, wR_2 = 0.3380
Final R indexes [all data]	R_1 = 0.1502, wR_2 = 0.3634
Largest diff. peak/hole / e Å^{-3}	1.09/-0.71

8.3. Table 2: Crystal data and structure refinement for molecule **2** (C1) (CCDC 2040479)

Empirical formula	$C_{397}H_{186}N_{58}O_{58}$
Formula weight	6696.03
Temperature/K	130
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	26.4710(8)
b/Å	44.7123(13)
c/Å	42.0854(12)
α/°	90
β/°	97.402(3)
γ/°	90
Volume/Å^3	49396(3)
Z	4
ρ_{calc}g/cm^3	0.900
μ/mm^{-1}	0.514
F(000)	13752.0
Crystal size/mm^3	0.1 × 0.1 × 0.1
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	3.738 to 89.2
Index ranges	$-23 \leq h \leq 23$, $-40 \leq k \leq 40$, $-37 \leq l \leq 37$
Reflections collected	292423
Independent reflections	38520 [R_{int} = 0.1779, R_{sigma} = 0.0784]
Data/restraints/parameters	38520/59730/4055
Goodness-of-fit on F^2	1.701
Final R indexes [I>=2σ (I)]	R_1 = 0.2071, wR_2 = 0.5093
Final R indexes [all data]	R_1 = 0.3086, wR_2 = 0.5784
Largest diff. peak/hole / e Å^{-3}	1.58/-0.34

8.4. Table 3: Crystal data and structure refinement for molecule **2** (C2). (CCDC 2040480)

Empirical formula	$C_{370}H_{185}N_{58}O_{57}$
Formula weight	6354.75
Temperature/K	100
Crystal system	monoclinic
Space group	Cc
a/Å	32.576(7)
b/Å	41.119(8)
c/Å	42.547(9)
α/°	90
β/°	111.33(3)
γ/°	90
Volume/Å^3	53086(21)
Z	4
ρ_{calc}g/cm^3	0.795
μ/mm^{-1}	0.076
F(000)	13068.0
Crystal size/mm^3	0.1 × 0.1 × 0.1
Radiation	Synchrotron FIP BM30A (λ = 0.810)
2Θ range for data collection/°	2.544 to 45.12
Index ranges	$-30 \leq h \leq 30$, $-38 \leq k \leq 38$, $-40 \leq l \leq 40$
Reflections collected	167716
Independent reflections	46075 [R_{int} = 0.0689, R_{sigma} = 0.0605]
Data/restraints/parameters	46075/60313/3913
Goodness-of-fit on F^2	1.546
Final R indexes [I>=2σ (I)]	R_1 = 0.1665, wR_2 = 0.3855
Final R indexes [all data]	R_1 = 0.2385, wR_2 = 0.4543
Largest diff. peak/hole / e Å^{-3}	0.51/-0.42
Flack parameter	-0.08(19)

9. REFERENCES

[1] F. F. Molock and D. W. Boykin, *J. Heterocycl. Chem.* **1983**, 20, 681.

[2] (a) L. Sebaoun, V. Maurizot, T. Granier, B. Kauffmann and I. Huc, *J. Am. Chem. Soc.* **2014**, *136*, 2168; (b) A. Lamouroux, L. Sebaoun, B. Wicher, B. Kauffmann, Y. Ferrand, V. Maurizot and I. Huc, *J. Am. Chem. Soc.* **2017**, *139*, 14668.

[3] B. Baptiste, J. Zhu, D. Haldar, B. Kauffmann, J.-M. Léger and I. Huc, *Chem. Asian. J.*, **2010**, 5, 1364.

[4] (a) E.S. Hand and W. W. Paudler, *J. Heterocycl. Chem.* **1983**, 12, 1063; (b) A. S. Kurbatova, Yu. V. Kurbatov and V. K. Yu, *Chem. Heterocycl. Com.* **1983**, 19, 203.

[5] Rigaku Oxford Diffraction, **2015**.CrysAlis PRO. RigakuOxford Diffraction, Yarnton, England.

[6] Kabsch, W. XDS. Acta Cryst. D66, 125-132, **2010**.

[7] G. M. Sheldrick, Acta Cryst., **2015**, A71, 3-8.

[8] O.V. Dolomanov, L. J .Bourhis, R.J . Gildea, J.A.K. Howard, H. Puschmann, J. Appl. Cryst., **2009**, 42, 339-341.

[9] G. M. Sheldrick, Acta Cryst., **2015**, C71, 3-8.

[10] A. L. Spek, J. Appl. Cryst., **2003**, 36, 7.

10. SUPLEMENTARY MOVIES

Movie S1: structure of C1 at 300K

Movie S2: structure of C2 at 300K

Movie S3: transition from C1 to C2 at 500K

These movies will be made available on the Wyley-VCH Website and/or on Prof. Huc's webpage (currently: https://huc.cup.uni-muenchen.de/)