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Macrocyclic arylopeptoids – a novel type of cyclic *N*-alkylated aromatic oligoamides forming nanotubular assemblies

Thomas Hjelmgaard,*[a,†] Olivier Roy,[b,c] Lionel Nauton,[b,c] Malika El-ghozzi,[b,c] Daniel Avignant,[b,c] Claude Didierjean,[d] Claude Taillefumier,[b,c] and Sophie Faure*[b,c]

[a] Department of Basic Sciences and Environment, University of Copenhagen, Thorvaldsensvej 40, 1871 Frederiksberg C, Denmark
[†] Current address: Rockwool International A/S, Group Research and Development, Hovedgaden 584, Entrance C, 2640 Hedehusene, Denmark
[b] CNRS, UMR6296, ICCF, BP 80026, 63171 Aubière, France
[c] Clermont Université, Université Blaise Pascal, Institut de Chimie de Clermont-Ferrand, BP 10448, 63000 Clermont-Ferrand, France
[d] CRM2, UMR 7036 CNRS-UL, Faculté des Sciences et Technologies, Université de Lorraine, BP 239, 54506 Vandoeuvre-lès-Nancy, France

Email: sophie.faure@univ-bpclermont.fr; thomas.hjelmgaard@rockwool.com.

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CH_2Cl_2 was distilled under N_2 from CaH_2 and stored over 4Å molecular sieves. CH_2Cl_2 and MeOH for column chromatography were distilled before use. DMF and DIPEA were dried over 4Å molecular sieves. All other solvents and chemicals obtained from commercial sources were used as received.

Melting points were determined on a on a Stuart SMP3 melting point apparatus and are uncorrected. NMR spectra were recorded on a 400 MHz Bruker AC 400 spectrometer. Chemical shifts are referenced to the residual solvent peak and *J* values are given in Hz. The following multiplicity abbreviations are used: (s) singlet, (d) doublet, (m) multiplet and (br) broad. Where applicable, assignments were based on COSY, HMBC, HSQC and *J*-mod-experiments. TLC was performed on Merck TLC aluminium sheets, silicagel 60, F_{254}. Progression of reactions was, when applicable, followed by HPLC and/or TLC. Visualizing of spots was effected with UV-light and/or ninhydrin in EtOH/AcOH. Flash chromatography was performed with Merck silica gel 60, 40-63 μm. HRMS were recorded on a Micromass Q-Tof Micro (3000V) apparatus.

HPLC analysis was performed on a Dionex instrument equipped with an Uptisphere® (ODB, 5 μm, 120 Å, 4.6×250 mm) and a Dionex UVD 340 detector (detection range = 210-400 nm) using as solvent A: water (0.1% TFA) and solvent B: MeCN in a proportion A/B 20:80 with a flow of 0.5 mL/min.

General experimental methods, *ortho*-arylopeptoids

CH_2Cl_2 (Sigma-Aldrich, Chromasolv® grade) and DMF (Sigma-Aldrich, puriss., anhydrous) used as solvents in reactions were dried over 4Å molecular sieves. DIPEA (Sigma-Aldrich, >99%), HATU (Sigma-Aldrich, >98%), TFA (Sigma-Aldrich, ReagentPlus®) and all other chemicals and solvents obtained from commercial sources were used as received.

Melting points were determined on a Mettler Toledo MP70 melting point system and are referenced to the melting points of benzophenone and benzoic acid. NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer. Chemical shifts are referenced to the residual solvent peak and *J* values are given in Hz. The following multiplicity abbreviations are used: (s) singlet, (d) doublet and (m) multiplet. Where applicable, assignments were based on COSY, HMBC, HSQC and *J*-mod-experiments. TLC was performed on Merck TLC aluminium sheets, silicagel 60, F_{254}. Progression of reactions was, when applicable, followed by HPLC and/or TLC. Visualizing of spots was effected with UV-light and/or ninhydrin in EtOH/AcOH. HRMS were recorded on a Micromass Q-Tof Micro (3000V) apparatus.

Analytical and preparative HPLC was performed on a Waters 2525 binary gradient module equipped with a Waters 2767 sample manager, a column fluidic organiser, a Gemini 110 column (C18, 5 μm, 110 Å, 4.6×100 mm) with flow = 1.0 mL/min for analytical HPLC or a Gemini 110 column (C18, 5 μm, 110 Å, 21.2×100 mm) with flow = 10.0 mL/min for preparative HPLC, and a UV fraction manager coupled with a Waters 2996 PDA detector; detection range = 210-400 nm; solvent A = MeOH/water/TFA 5:95:0.1 and solvent B = MeOH/water/TFA 95:5:0.1; Gradient for analytical HPLC (10 min runs): 50% B (0-2 min), 50→100% B (2-7 min), 100→50% B (7-9 min), 50% B (9-10 min); Gradient for preparative HPLC (20 min runs): 50% B (0-5 min), 50→100% B (5-15 min), 100→50% B (15-16 min), 50% B (16-20 min).

General experimental procedures

Method A; General procedure for macrocylization of *para*- and *meta*-arylopeptoid trimers

To a solution of the arylopeptoid trimer (0.080 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C was added TFA (0.5 mL) and the resulting mixture was stirred for 3 h at 0 °C. The solvents were then evaporated under reduced pressure and the residue was evaporated several times with CH_2Cl_2. The residue was dried *in vacuo*, yielding the crude termini deprotected arylopeptoid as a pale yellowish foam. To a solution of the crude arylopeptoid in CH_2Cl_2/DMF (4:1, 20 mL) at 0 °C under N_2 was added enough DIPEA (approx. 0.07 mL, 0.40 mmol) to turn the mixture slightly basic. HATU (35 mg, 0.092 mmol) was added and the resulting mixture was stirred for 3 d while allowing to warm slowly to rt. CH_2Cl_2 (20 mL) was added to the mixture. The organic layer was washed with satd. aq. $NaHCO_3$ (2×10 mL), satd. aq. NH_4Cl (2×10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated and dried *in vacuo*. Flash chromatography (CH_2Cl_2/MeOH 95:5) of the residue yielded the macrocycle.

Method B; General procedure for macrocylization of *ortho*-arylopeptoid trimers

To a solution of the arylopeptoid trimer (0.150 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C was added TFA (1.5 mL) and the resulting mixture was stirred for 3 h at 0 °C. The solvents were evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 (1.5 mL) at rt and TFA (1.5 mL) was added. The resulting mixture was stirred for 1 h at rt and the solvents were evaporated under reduced pressure. The residue was evaporated several times with CH_2Cl_2 and dried *in vacuo*, yielding the crude termini deprotected arylopeptoid as a pale yellowish foam. To a solution of the crude arylopeptoid in CH_2Cl_2/DMF (4:1, 30 mL) at 0 °C under N_2 was added enough DIPEA (approx. 0.13 mL, 0.75 mmol) to turn the mixture slightly basic. HATU (68.5 mg, 0.18 mmol) was added and the resulting was stirred for 3 d while allowing to warm slowly to rt. The solvents were evaporated under reduced pressure and the residue was taken up in EtOAc (20 mL). The organic layer was washed with satd. aq. $NaHCO_3$ (2×10 mL), satd. aq. NH_4Cl (2×10 mL) and brine (10 mL). The organic layer was concentrated under reduced pressure and the residue was evaporated a few times with EtOAc and dried *in vacuo*. Preparative HPLC of the residue yielded the macrocycles in >99% HPLC purity.

Experimental procedures and characterisation data of synthesised macrocyclic arylopeptoids

Cyclisation of *para*-arylopeptoid trimer *p*-1a (Et side chains)

Treatment of ***p*-1a** (45 mg, 0.080 mmol) by method A yielded cyclohexamer ***p*-3a** (22 mg, 57%). R_f (CH_2Cl_2/MeOH 90:10) = 0.56; mp = 146-148 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13-7.51 (24H, br m, 6×*o*-C_6H_4CON, 6×*m*-C_6H_4CON), 4.88-4.66 and 4.65-4.43 (12H, br m, 6×CONCH_2Ar), 3.65-3.40 and 3.38-3.14 (12H, br m, 6×CONCH_2CH$_3$), 1.30-1.05 (18H, br m, 6×CONCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8 (6C, 6×*C*ON), 139.2 and 138.8 (6C, 6×*ipso*-C_6H$_4$CON), 135.6 (6C, 6×*p*-C_6H$_4$CON), 128.1, 127.1 (24CH, 12×*m*-C_6H$_4$CON, 12×*o*-C_6H$_4$CON), 51.9 and 47.0 (6CH$_2$, br, 6×CON*C*H$_2$Ar), 43.4 and 40.1 (6CH$_2$, br, 6×CON*C*H$_2$CH$_3$), 13.9 and 12.3 (6CH$_3$, 6×CONCH$_2$*C*H$_3$); HRMS (TOF MS ES$^+$) calcd for $C_{60}H_{68}N_6O_6$ [M + 2H]$^{2+}$ *m*/*z* 484.2600, found 484.2596. HPLC: t_r = 8.43 min, purity = 90%.

Cyclisation of *para*-arylopeptoid trimer *p*-1b (*i*Pr side chains)

Treatment of ***p*-1b** (52 mg, 0.087 mmol) by method A yielded cyclohexamer ***p*-3b** as a colorless solid (28 mg, 61%). R_f (CH_2Cl_2/MeOH 95:5) = 0.61; mp = 238-240 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.27 (24H, br m, 6×*o*-C_6H_4CON, 6×*m*-C_6H_4CON), 4.71 (12H, br s, 6×CONCH_2Ar), 4.21 (6H, br s, 6×CONC*H*(CH$_3$)$_2$), 1.09 (36H, br s, 6×CONCH(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3 (6C, 6×*C*ON), 140.7 (6C, 6×*ipso*-C_6H$_4$CON), 135.4 (6C, 6×*p*-C_6H$_4$CON), 127.1, 126.8, 126.6, 126.5 (24CH, 12×*m*-C_6H$_4$CON, 12×*o*-C_6H$_4$CON), 50.9 (6CH, 6×CON*C*H(CH$_3$)$_2$), 43.2 (6CH$_2$, 6×CON*C*H$_2$Ar), 21.4 (12CH$_3$, 6×CONCH(*C*H$_3$)$_2$); HRMS (TOF MS ES$^+$) calcd for $C_{66}H_{80}N_6O_6$ [M + 2H]$^{2+}$ *m*/*z* 526.3070, found 526.3065. HPLC: t_r = 12.80 min, purity = 97%.

Cyclisation of *meta*-arylopeptoid trimer *m*-1a (Et side chains)

Treatment of ***m*-1a** (45 mg, 0.080 mmol) by method A yielded cyclotrimer ***m*-2a** (32 mg, 83%) as a colorless solid. R_f (CH_2Cl_2/MeOH 95:5) = 0.52; mp = 181-183 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51-7.00 (12H, m), 5.75-3.70 (6H, m, 3×CONCH_2Ar), 3.60-2.90 (6H, m, 3×CONCH_2CH$_3$), 1.30-0.80 (9H, m, 3×CONCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1 (3C$_q$, 3×*C*ON), 137.7, 137.4 (6C$_q$), 129.1, 128.8, 125.7, 124.8, 124.1, 123.6, 122.9, 122.4 (12CH), 47.1, 47.0, 46.1 (3CH$_2$, 3×CON*C*H$_2$Ar), 44.8 (CH$_2$, CON*C*H$_2$CH$_3$), 44.3 (CH$_2$, CON*C*H$_2$CH$_3$), 43.2 (CH$_2$, CON*C*H$_2$CH$_3$), 14.0, 13.9 (3CH$_3$, 3×CONCH$_2$*C*H$_3$); HRMS (TOF MS ES$^+$) calcd for $C_{30}H_{33}N_3O_3Na$ [M + Na]$^+$ *m*/*z* 506.2426, found 506.2420; HPLC: t_r = 7.58 min, purity = 96%.

Cyclisation of *meta*-arylopeptoid trimer *m*-1b (*i*Pr side chains)

Treatment of ***m*-1b** (48 mg, 0.080 mmol) by method A yielded cyclotrimer ***m*-2b** (37 mg, 88%) as a colorless solid. R_f (CH_2Cl_2/MeOH 95:5) = 0.41; mp = 152-154 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.12 (12H, m), 6.47 (1H, d, J = 16.0 Hz, CONC*H*HAr), 5.32 (1H, d, J = 16.0 Hz, CONC*H*HAr), 4.88 (1H, d, J = 15.2 Hz, CONC*H*HAr), 4.19 (1H, m, CONC*H*(CH_3)$_2$), 4.09 (1H, d, J = 15.2 Hz, CONCH*H*Ar), 4.10-3.90 (4H, m, 2×CONCH*H*Ar and 2×CONC*H*(CH_3)$_2$), 1.23 (3H, m, CONCH(C*H*$_3$)$_2$), 1.07 (9H, m, CONCH(C*H*$_3$)$_2$), 0.81 (6H, m, CONCH(C*H*$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 172.1 (3C$_q$, 3×*C*ON), 140.0 (2C$_q$), 139.2 (C$_q$), 138.5 (C$_q$), 137.7 (C$_q$), 137.1 (C$_q$), 129.0, 128.7, 127.9, 127.4, 125.4, 124.1, 123.8, 123.0, 122.8, 122.1 (12CH), 50.9, 50.8 (3CH, 3×CONC*H*(CH_3)$_2$), 43.7 (CH_2, CON*C*H$_2$Ar), 43.2 (CH_2, CON*C*H$_2$Ar), 42.1 (CH_2, CON*C*H$_2$Ar), 21.9 (CH_3, CONCH(*C*H$_3$)$_2$), 21.4 (3CH_3, 3×CONCH(*C*H$_3$)$_2$), 21.2 (CH_3, CONCH(*C*H$_3$)$_2$), 21.0 (CH_3, CONCH(*C*H$_3$)$_2$); HRMS (TOF MS ES$^+$) calcd for $C_{33}H_{39}N_3O_3Na$ [M + Na]$^+$ *m*/*z* 548.2889, found 548.2892; HPLC: t_r = 8.72 min, purity > 99%.

Cyclisation of *ortho*-arylopeptoid trimer *o*-1a (Et side chains)

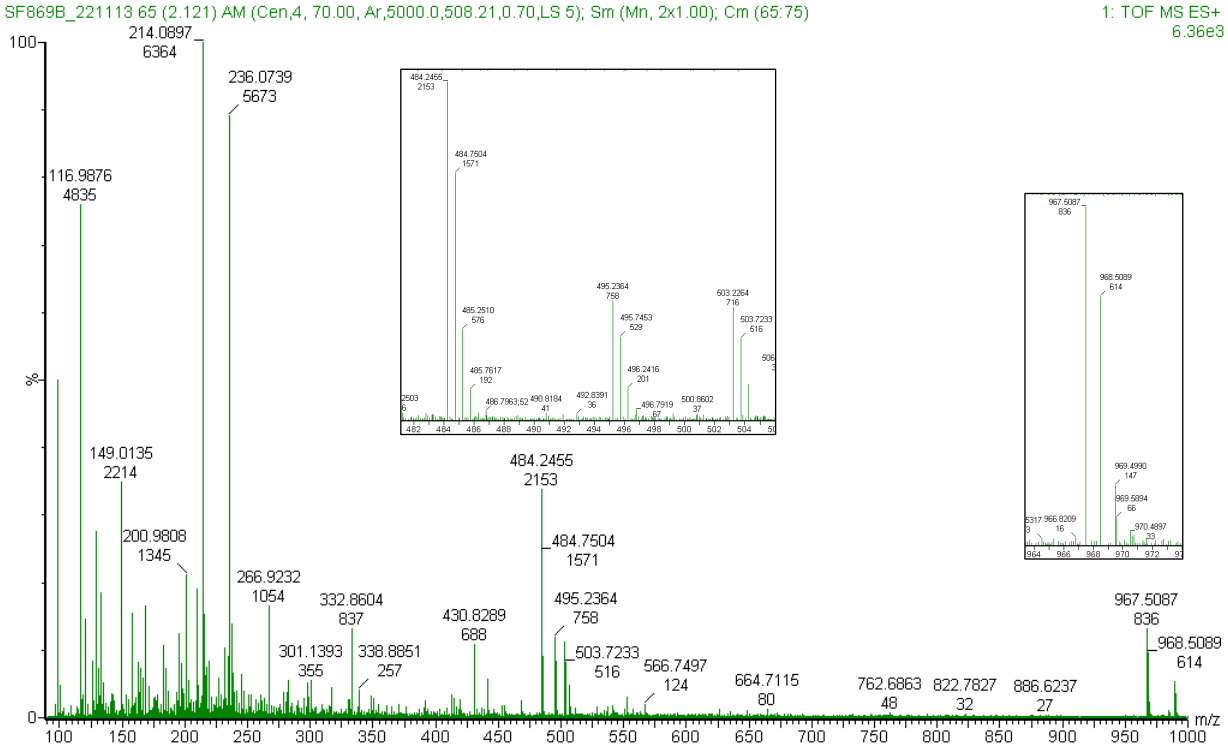
Treatment of ***o*-1a** (84 mg, 0.151 mmol) by method B yielded cyclotrimer ***o*-2a** (35 mg, 48%) as a colorless solid and cyclohexamer ***o*-3a** (33 mg, 45%) as a colorless solid. Data for cyclotrimer ***o*-2a**: R_f (CH_2Cl_2/MeOH 95:5) = 0.36; $t_{r,analytical}$ = 6.01 min; $t_{r,preparative}$ = 11.8 min; mp = 162-165 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80-6.88 (12H, m), 5.00-4.15 (6H, m, 3×CONC*H*$_2$Ar), 3.80-3.14 (4H, m, 2×CONC*H*$_2$CH$_3$), 2.44-2.14 and 1.85-1.60 (2×1H, 2×m, CONC*H*$_2$CH$_3$), 1.44-1.10 (6H, m, 2×CONCH$_2$C*H*$_3$), 0.82-0.61 (3H, m, CONCH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9, 170.8 (3C$_q$, 3×*C*ON), 135.1, 133.2 (6C$_q$), 133.7, 129.8, 129.5, 129.2, 128.5, 127.5, 127.3, 127.2, 126.1, 126.0 (12CH), 49.4 (3CH_2, 3×CON*C*H$_2$Ar), 45.9 (CH_2, CON*C*H$_2$CH$_3$), 43.8 (CH_2, CON*C*H$_2$CH$_3$), 41.6 (CH_2, CON*C*H$_2$CH$_3$), 14.2 (CH_3, CONCH$_2$*C*H$_3$), 13.2 (CH_3, CONCH$_2$*C*H$_3$), 12.5 (CH_3, CONCH$_2$*C*H$_3$); HRMS (TOF MS ES$^+$) calcd for $C_{30}H_{34}N_3O_3$ [M + H]$^+$ *m*/*z* 484.2600, found 484.2603. Data for cyclohexamer ***o*-3a**: R_f (CH_2Cl_2/MeOH 95:5) = 0.34; $t_{r,analytical}$ = 7.73 min; $t_{r,preparative}$ = 14.9 min; mp = 160-163 °C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81-6.77 (24H, m), 5.80-3.82 (12H, m, 6×CONC*H*$_2$Ar), 3.75-2.35 (12H, m, 6×CONC*H*$_2$CH$_3$), 1.44-0.40 (18H, m, 6×CONCH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8, 171.5, 170.8, 170.5 (6C$_q$, 6×*C*ON), 135.0, 133.9 (12C$_q$), 129.8, 129.6, 129.5, 127.7, 127.5, 127.3, 126.6, 126.4, 125.9, 125.5, 125.4 (24CH), 49.7, 48.9, 45.3, 45.0, 44.8, 40.1, 39.5 (12CH_2, 6×CON*C*H$_2$Ar and 6×CON*C*H$_2$CH$_3$), 14.0, 13.9, 13.9, 13.7, 13.5, 12.6, 12.4, 12.3 (6CH_3, 6×CONCH$_2$*C*H$_3$); HRMS (TOF MS ES$^+$) calcd for $C_{60}H_{66}N_6O_6Na$[M + Na]$^+$ *m*/*z* 989.4942, found 989.4956.

Cyclisation of *ortho*-arylopeptoid trimer *o*-1b (*i*Pr side chains)

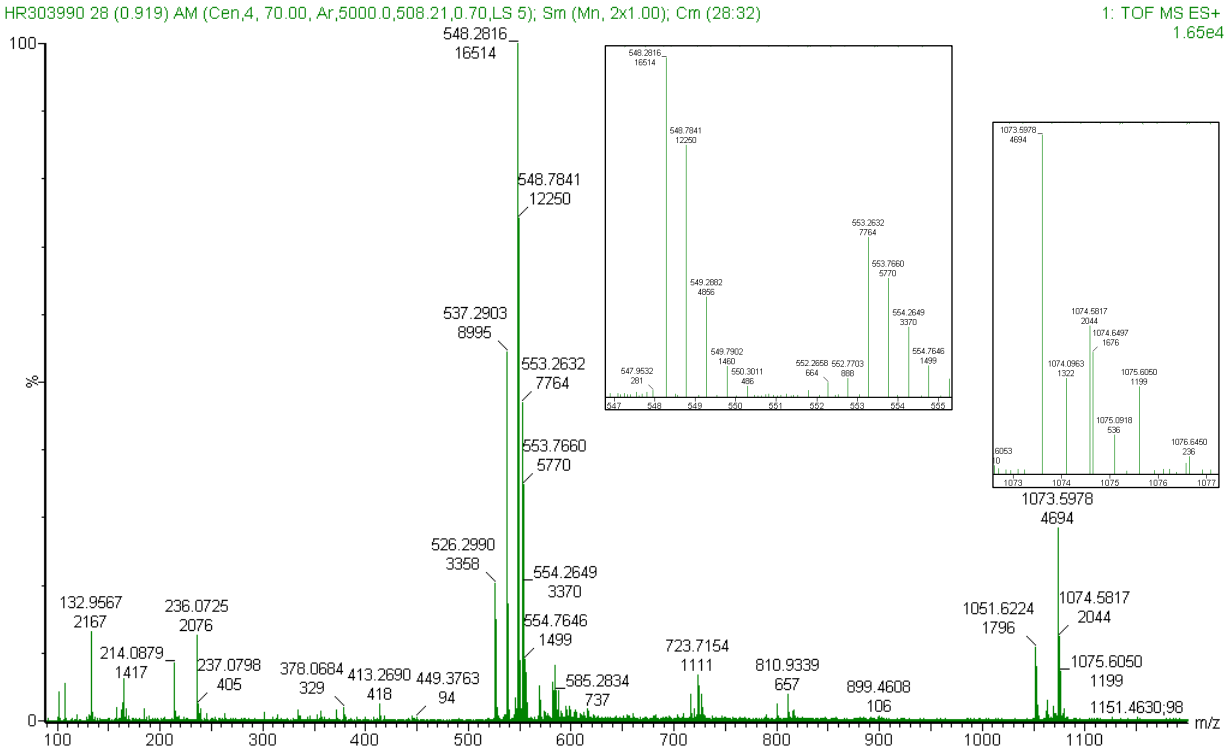
Treatment of ***o*-1b** (90 mg, 0.150 mmol) by method B yielded cyclotrimer ***o*-2b** (3 mg, 4%) and cyclohexamer ***o*-3b** (26 mg, 33%) as a colorless solid. Data for cyclotrimer ***o*-2b**: R_f (CH_2Cl_2/MeOH 95:5) = 0.39; $t_{r,analytical}$ = 7.74 min; $t_{r,preparative}$ = 15.1 min; Two isomers in 77:24 ratio were visible in ^{1}H NMR in $CDCl_3$ at rt. For the major isomer, separate signals for each of the two methyl groups on each isopropyl side chain were observed, presumably as a result of hindered rotation of the isopropyl side chains. For the minor isomer, in addition to separate signals for each of the methyl groups on each isopropyl side chain, the sets of signals for each side chain were splitted into two. Significant overlap of signals in the NMR spectrum hindered determination of the ratios of these splits so the contribution of each split has been set to 50% in the following (marked with an asterisk); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.10 (12H, m), 6.12 (0.76H, d, *J* = 15.1 Hz, CONC*H*HAr, major isomer), 5.71 (0.24H, d, *J* = 15.3 Hz, CONC*H*HAr, minor isomer), 5.60 (0.76H, d, *J* = 12.6 Hz, CONC*H*HAr, major isomer), 5.39 (0.24H, d, *J* = 13.7 Hz, CONC*H*HAr, minor isomer), 5.00-4.90 (0.24H + 0.12H*, m, CONC*H*HAr, minor isomer, 0.5×CONC*H*$(CH_3)_2$, minor isomer), 4.85 (0.76H, d, *J* = 16.0 Hz, CONC*H*HAr, major isomer), 4.29 (0.76H, d, *J* = 16.0 Hz, CONCH*H*Ar, major isomer), 4.16-4.08 (0.12H*, m, 0.5×CONC*H*$(CH_3)_2$, minor isomer), 4.11 (0.76H, d, *J* = 12.6 Hz, CONCH*H*Ar, major isomer), 4.06-3.83 (2.76H + 0.12H*, m, CONCH*H*Ar, major isomer, 2×CONCH*H*Ar, minor isomer, and 2×CONC*H*$(CH_3)_2$, major isomer, 0.5×CONC*H*$(CH_3)_2$, minor isomer), 3.79-3.73 (0.12H*, m, 0.5×CONC*H*$(CH_3)_2$, minor isomer), 3.69 (0.24H, d, *J* = 15.3 Hz, CONCH*H*Ar, minor isomer), 3.64-3.58 (0.12H*, m, 0.5×CONC*H*$(CH_3)_2$, minor isomer), 3.41-3.34 (0.12H*, m, 0.5×CONC*H*$(CH_3)_2$, minor isomer), 2.94-2.82 (0.76H, m, CONC*H*$(CH_3)_2$, major isomer), 1.74 (0.36H*, d, *J* = 6.4 Hz, 0.5×CONCH(C*H*$_3)_2$, minor isomer), 1.60-1.54 (0.36H*, 0.5×CONCH(C*H*$_3)_2$, minor isomer), 1.57 (2.28H, d, *J* = 6.7 Hz, CONCH(C*H*$_3)_2$, major isomer), 1.50 (0.36H*, d, *J* = 7.0 Hz, 0.5×CONCH(C*H*$_3)_2$, minor isomer), 1.45 (0.36H*, d, *J* = 6.6 Hz, 0.5×CONCH(C*H*$_3)_2$, minor isomer), 1.42-1.37 (0.36H*, 0.5×CONCH(C*H*$_3)_2$, minor isomer), 1.39 (2.28H, d, *J* = 6.9 Hz, CONCH(C*H*$_3)_2$, major isomer), 1.36 (2.28H, d, *J* = 7.0 Hz, CONCH(C*H*$_3)_2$, major isomer), 1.30 (2.28H, d, *J* = 6.6 Hz, CONCH(C*H*$_3)_2$, major isomer), 1.25 (2.28H, d, *J* = 6.6 Hz, CONCH(C*H*$_3)_2$, major isomer), 1.14-1.07 (0.72H*, m, 2×0.5×CONCH(C*H*$_3)_2$, minor isomer), 1.07-1.03 (0.72H*, m, 2×0.5×CONCH(C*H*$_3)_2$, minor isomer), 1.01 (0.36H*, d, *J* = 6.9 Hz, 0.5×CONCH(C*H*$_3)_2$, minor isomer), 0.66 (0.36H*, d, *J* = 7.1 Hz, 0.5×CONCH(C*H*$_3)_2$, minor isomer), 0.57-0.50 (0.36H*, 0.5×CONCH(C*H*$_3)_2$, minor isomer), 0.52 (2.28H, d, *J* = 6.8 Hz, CONCH(C*H*$_3)_2$, major isomer); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.2 (CH), 131.8 (CH), 128.9 (CH), 128.5 (CH), 128.3 (CH), 128.0 (CH), 127.5 (CH), 126.7 (CH), 126.2 (CH), 125.6 (CH), 125.3 (CH), 124.4 (CH), 52.5 (CH_2, CON*C*H_2Ar), 50.4 (2CH, 2×CONC*H*$(CH_3)_2$), 48.7 (CH, CONC*H*$(CH_3)_2$), 43.0 (CH_2, CON*C*H_2Ar), 42.7 (CH_2, CON*C*H_2Ar), 21.7 (CH_3, CONCH(*C*$H_3)_2$), 21.2 (CH_3, CONCH(*C*$H_3)_2$), 20.6 (CH_3, CONCH(*C*$H_3)_2$), 20.4 (CH_3, CONCH(*C*$H_3)_2$), 19.8 (CH_3, CONCH(*C*$H_3)_2$), 19.3 (CH_3, CONCH(*C*$H_3)_2$), the small amount of

product did not allow for satisfactory detection of the 12 quaternary backbone carbons; HRMS (TOF MS ES$^+$) calcd for $C_{33}H_{40}N_3O_3$ [M + H]$^+$ *m*/*z* 526.3070, found 526.3073. Data for cyclohexamer ***o*-3b**: R_f (CH_2Cl_2/MeOH 95:5) = 0.36; $t_{r,analytical}$ = 8.44 min; $t_{r,preparative}$ = 16.0 min; mp = 162-165 °C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51-7.40 (12H, m), 7.37-7.31 (12H, m), 5.08 (6H, d, *J* = 16.1 Hz, 6×CONC*H*HAr), 4.44 (6H, d, *J* = 16.1 Hz, 6×CONCH*H*Ar), 4.25-4.10 (6H, m, 6×CONC*H*$(CH_3)_2$), 1.31 (18H, d, *J* = 6.6 Hz, 6×CONCH(C*H*$_3$)CH_3), 1.05 (18H, d, *J* = 6.6 Hz, 6×CONCH(CH_3)C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9 (6C_q, 6×*C*ON), 135.7 (6C_q), 134.4 (6C_q), 129.4 (6CH), 126.8 (6CH), 126.0 (6CH), 125.2 (6CH), 51.5 (6CH, 6×CON*C*H$(CH_3)_2$), 40.9 (6CH_2, 6×CON*C*H$_2$Ar), 21.6 (6CH_3, 6×CONCH(*C*H$_3$)CH_3), 21.2 (6CH_3, 6×CONCH(CH_3)*C*H$_3$); HRMS (TOF MS ES$^+$) calcd for $C_{66}H_{80}N_6O_6$ [M + 2H]$^{2+}$ *m*/*z* 526.3070, found 526.3079.

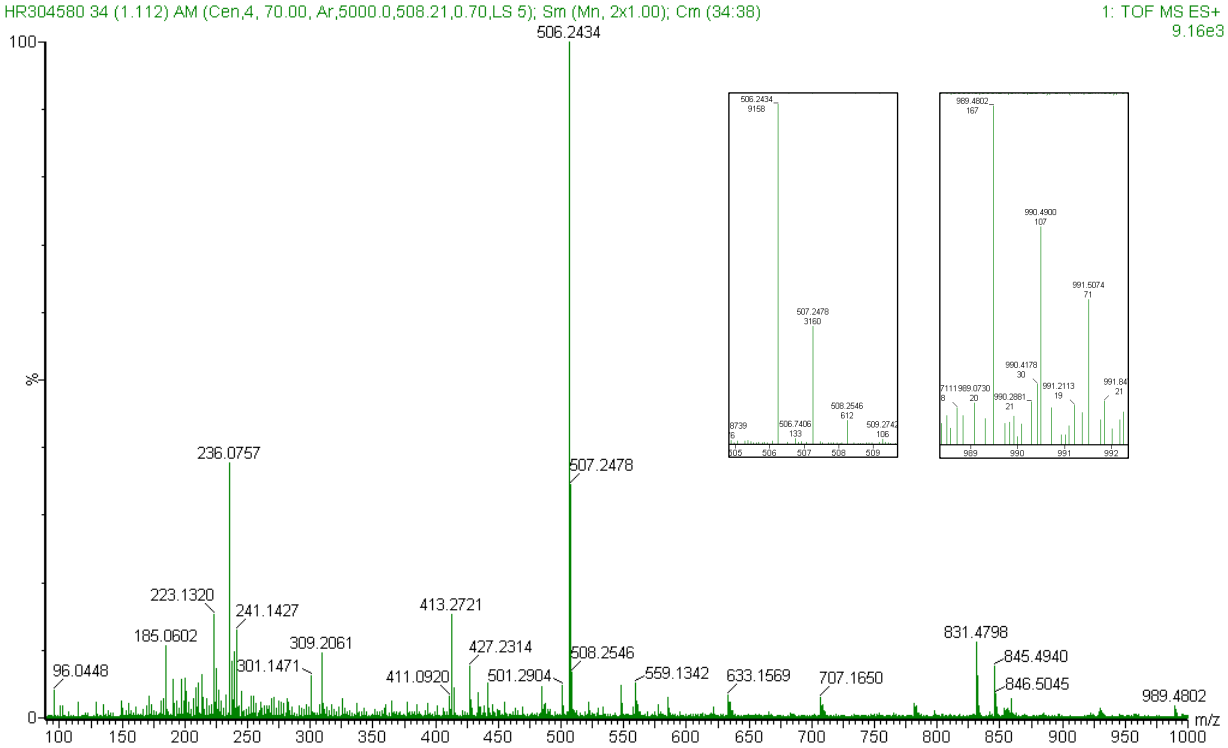
MS spectra of synthesised macrocyclic arylopeptoids



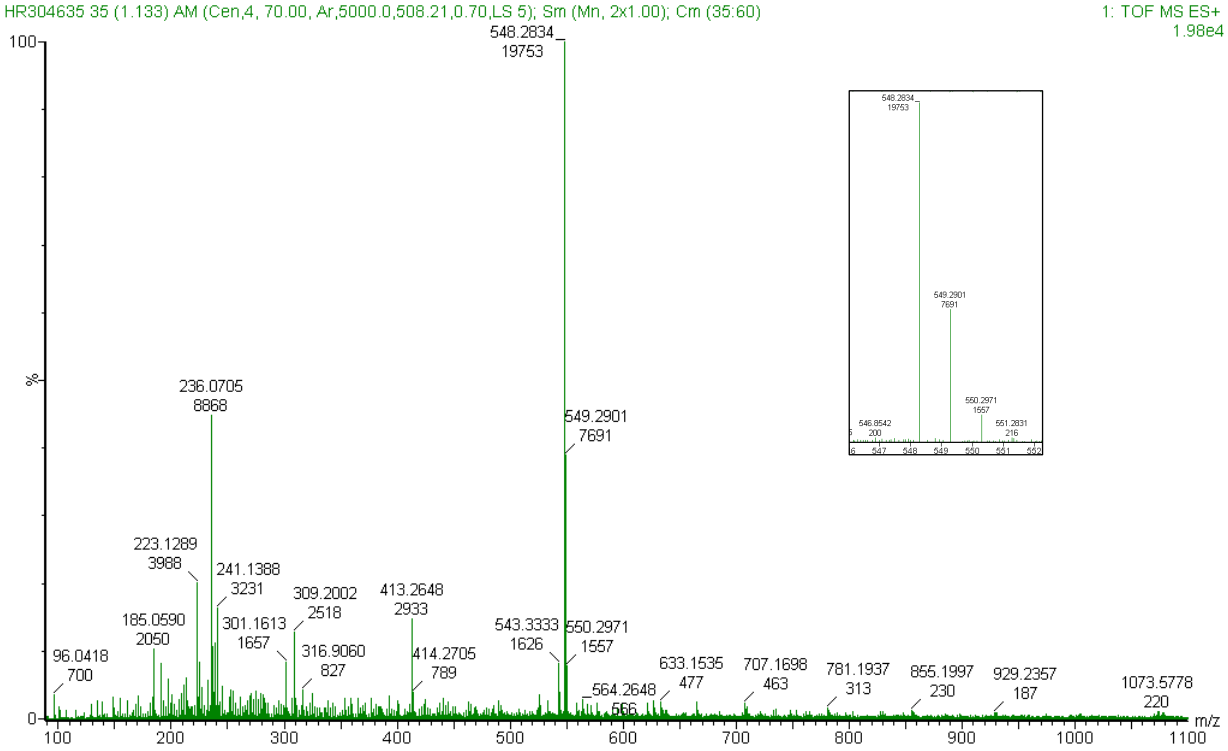
Mass spectra of cyclohexamer ***p*-3a**.



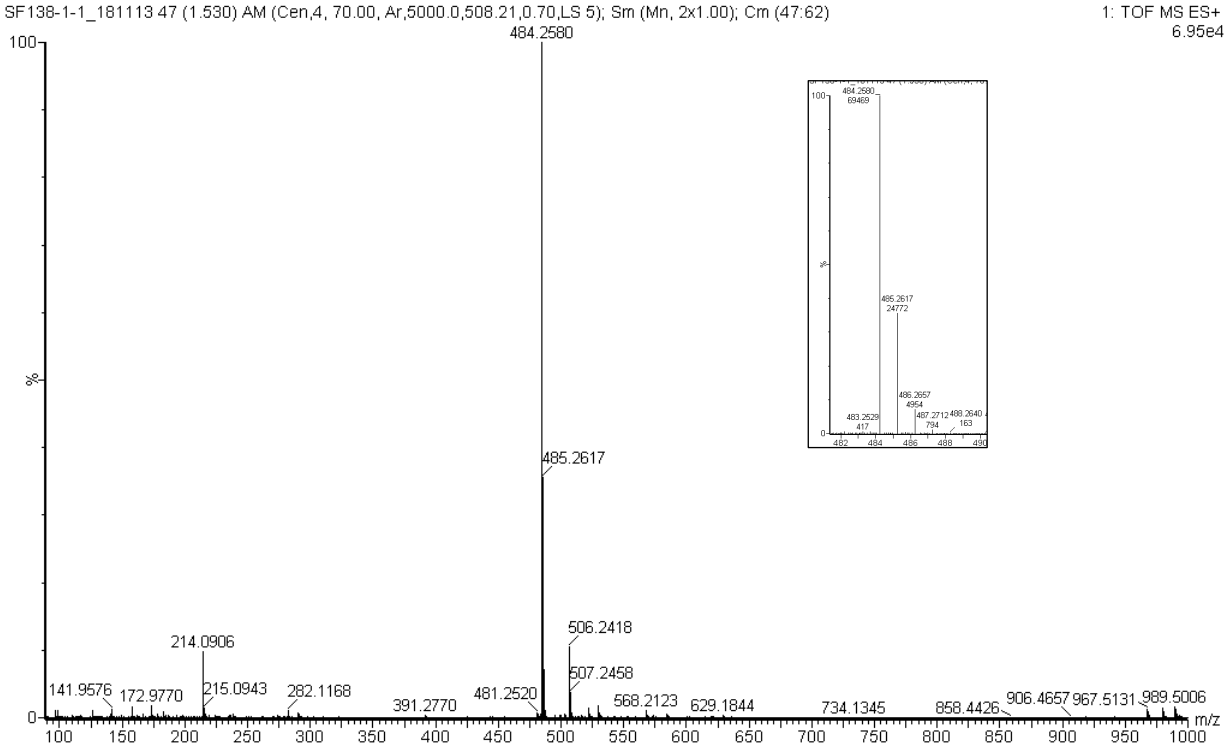
Mass spectra of cyclohexamer ***p*-3b**.



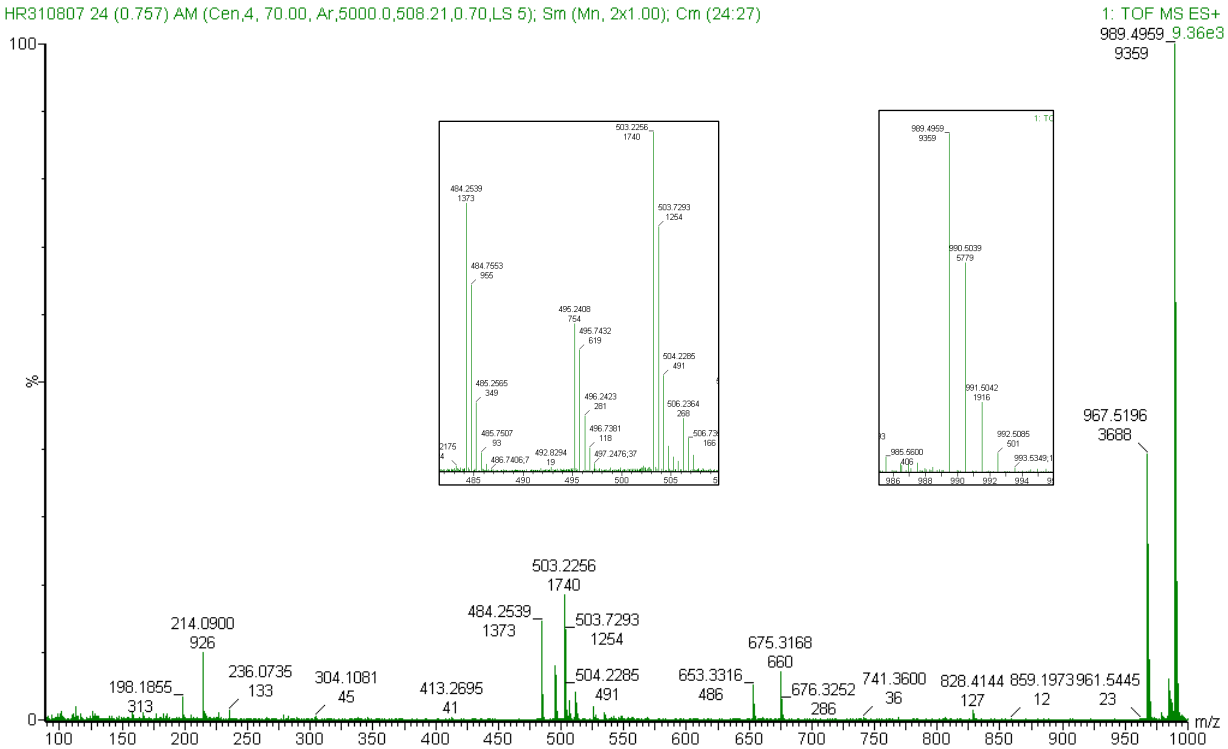
Mass spectra of cyclotrimer ***m*-2a**



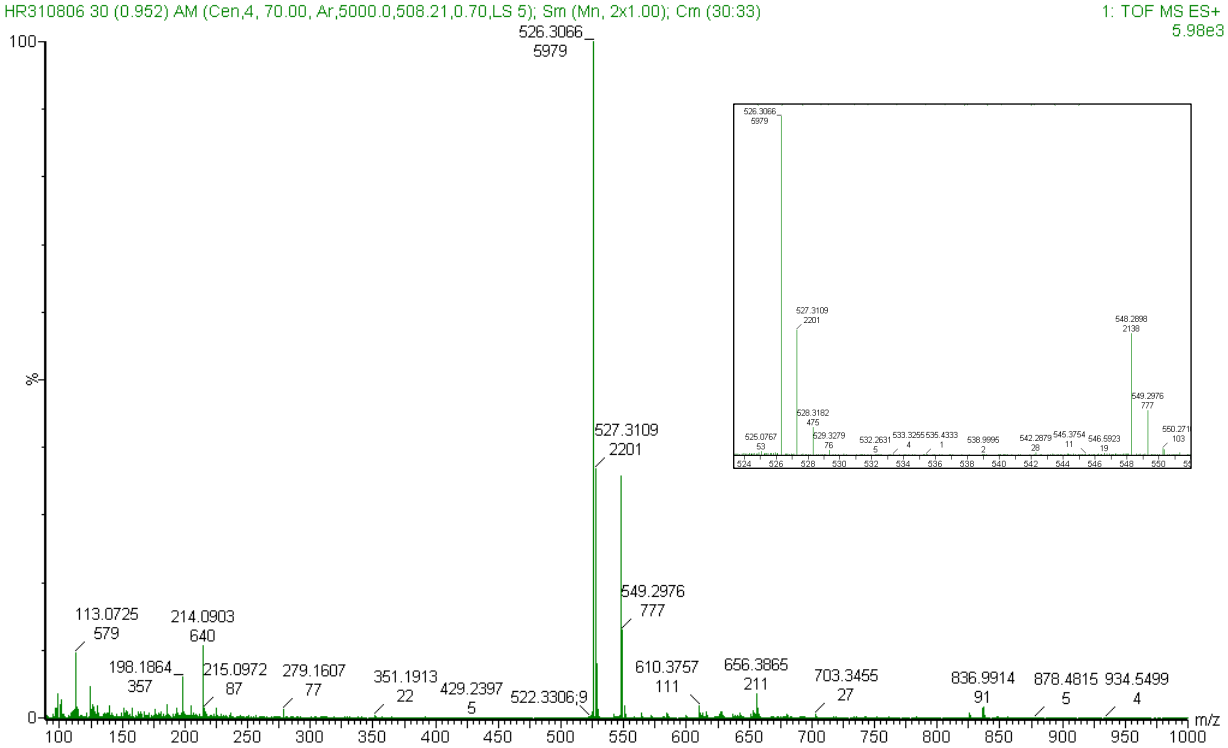
Mass spectra of cyclotrimer ***m*-2b**



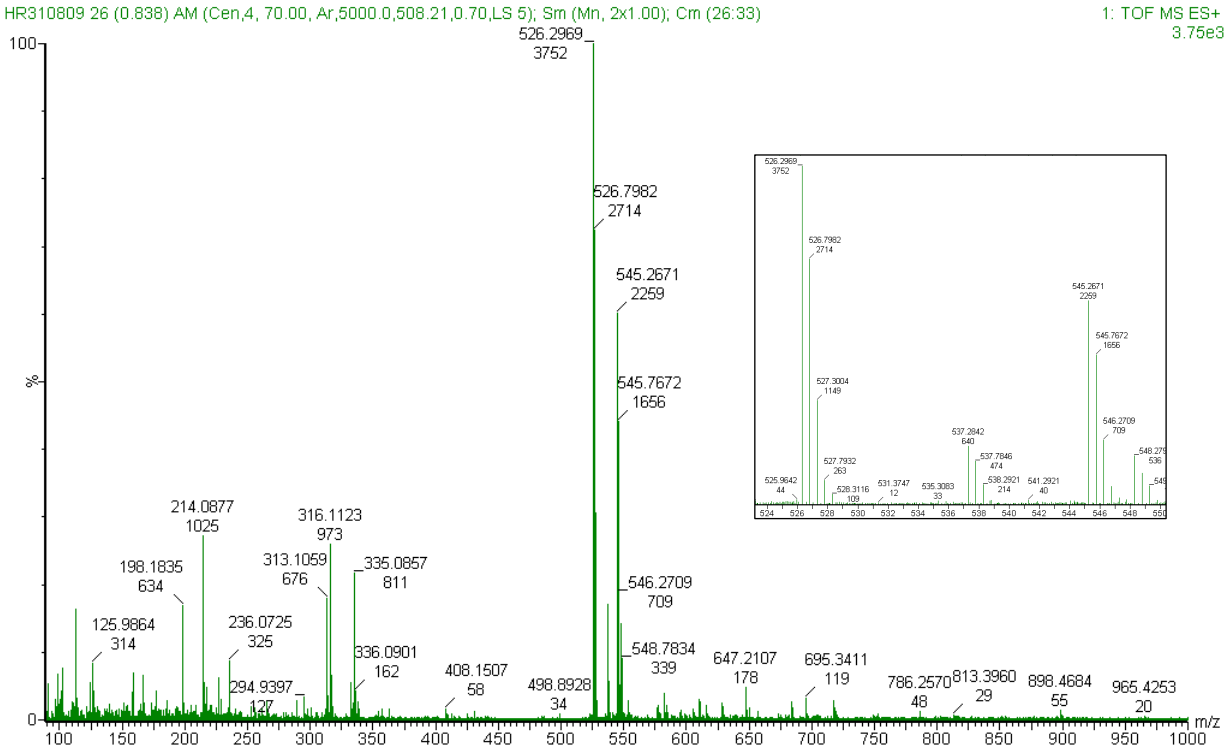
Mass spectra of cyclotrimer ***o*-2a**.



Mass spectra of cyclohexamer ***o*-3a**.

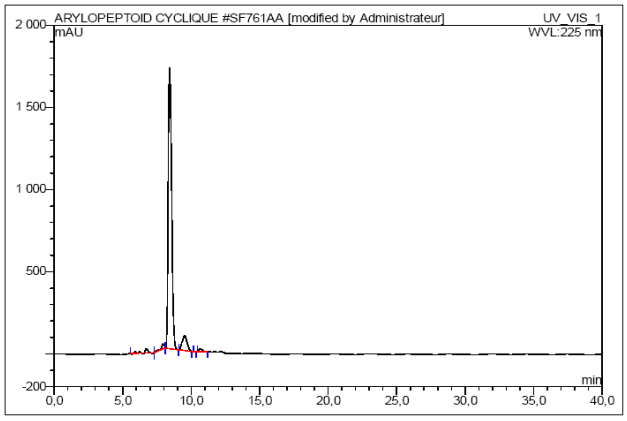


Mass spectra of cyclotrimer ***o*-2b**



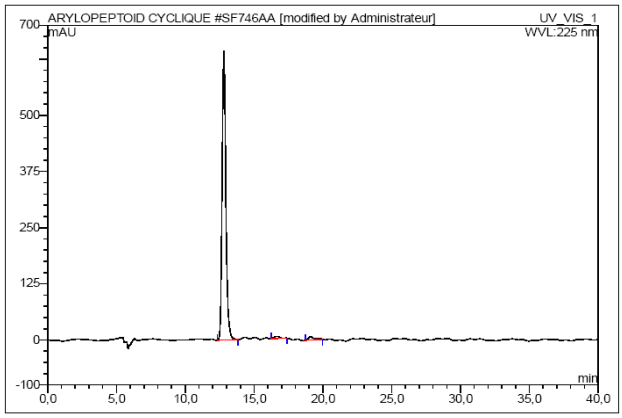
Mass spectra of cyclohexamer ***o*-3b**

HPLC profiles of synthesised macrocyclic arylopeptoids



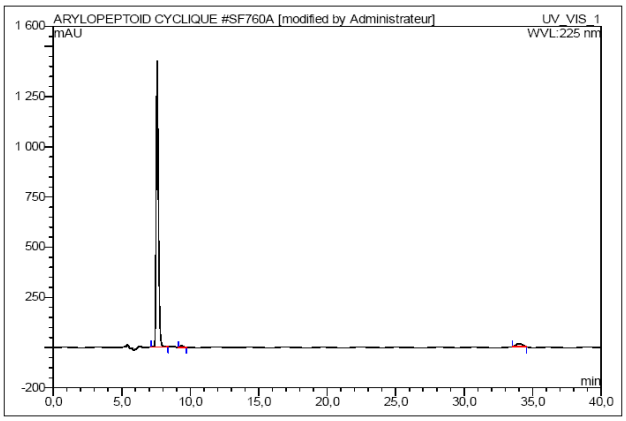
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	6,73	n.a.	25,753	6,600	1,19	n.a.	BMB*
2	7,96	n.a.	28,048	7,495	1,36	n.a.	BMB*
3	8,43	n.a.	1711,860	497,553	90,05	n.a.	BMB*
4	9,52	n.a.	90,025	37,425	6,77	n.a.	BMB*
5	10,22	n.a.	1,516	0,209	0,04	n.a.	BMB
6	10,67	n.a.	14,975	3,266	0,59	n.a.	BMB*
Total:			1872,177	552,546	100,00	0,000	

Cyclohexamer ***p*-3a** pure.



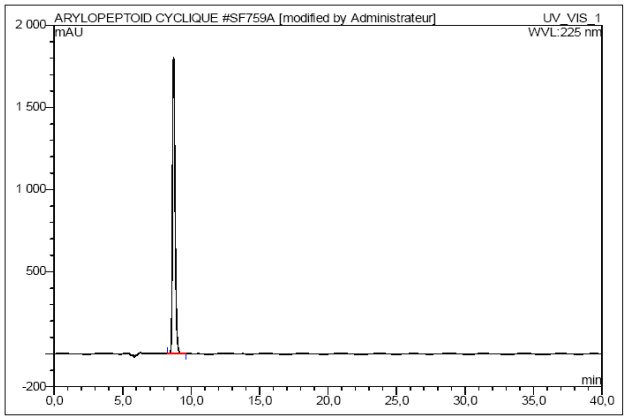
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12,80	n.a.	643,519	202,594	97,14	n.a.	BMB
2	16,66	n.a.	4,552	2,025	0,97	n.a.	BMB*
3	19,10	n.a.	7,175	3,945	1,89	n.a.	BMB*
Total:			655,245	208,564	100,00	0,000	

Cyclohexamer ***p*-3b** pure.



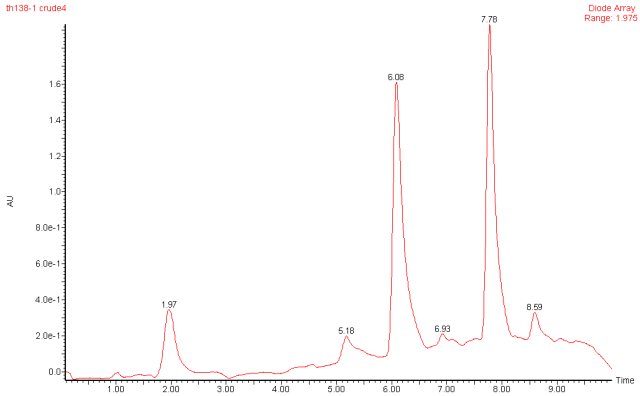
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7,58	n.a.	1425,564	274,950	96,31	n.a.	BMB*
2	9,38	n.a.	8,556	1,825	0,64	n.a.	BMB*
3	34,01	n.a.	15,964	8,717	3,05	n.a.	BMB*
Total:			1450,085	285,492	100,00	0,000	

Cyclotrimer ***m*-2a** pure.

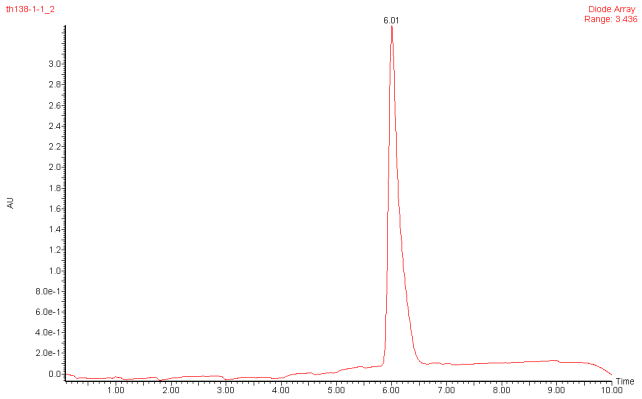


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	8,72	n.a.	1801,596	402,405	100,00	n.a.	BMB*
Total:			1801,596	402,405	100,00	0,000	

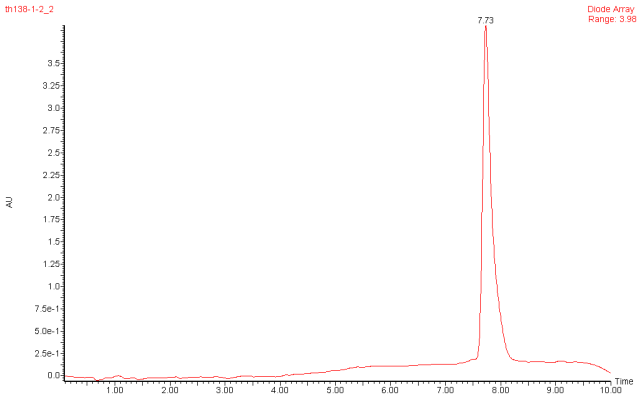
Cyclotrimer ***m*-2b** pure.



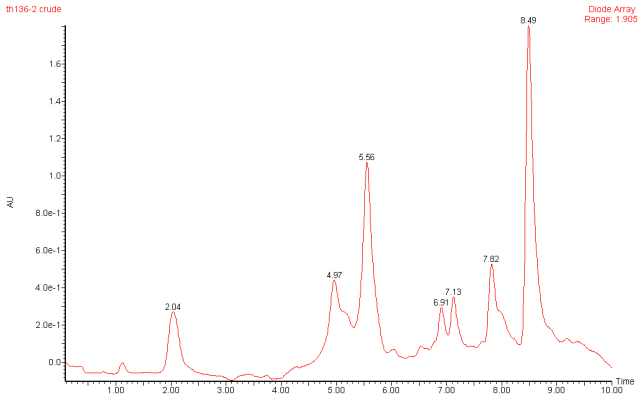
Crude reaction mixture from reaction of ***o*-1a**.



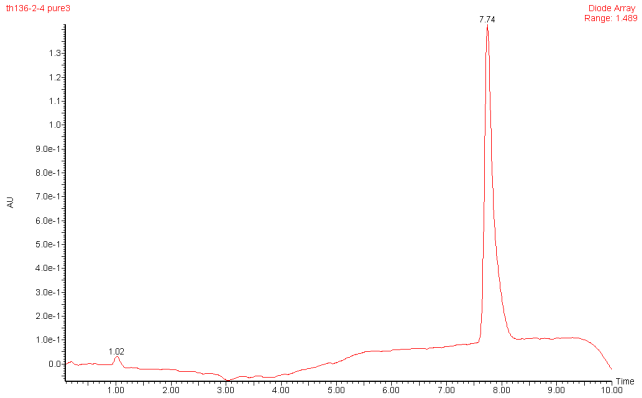
Cyclotrimer ***o*-2a** pure.



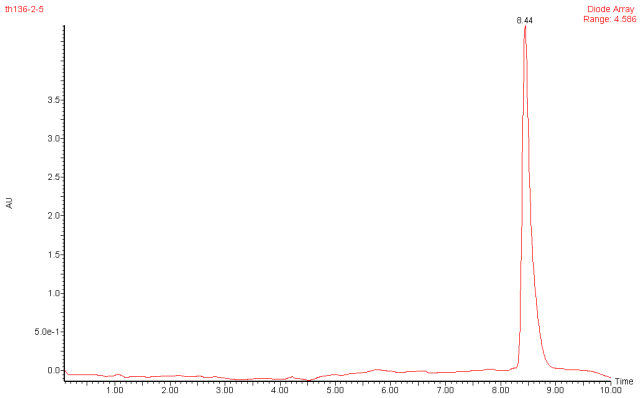
Cyclohexamer ***o*-3a** pure.



Crude reaction mixture from reaction of ***o*-1b**.

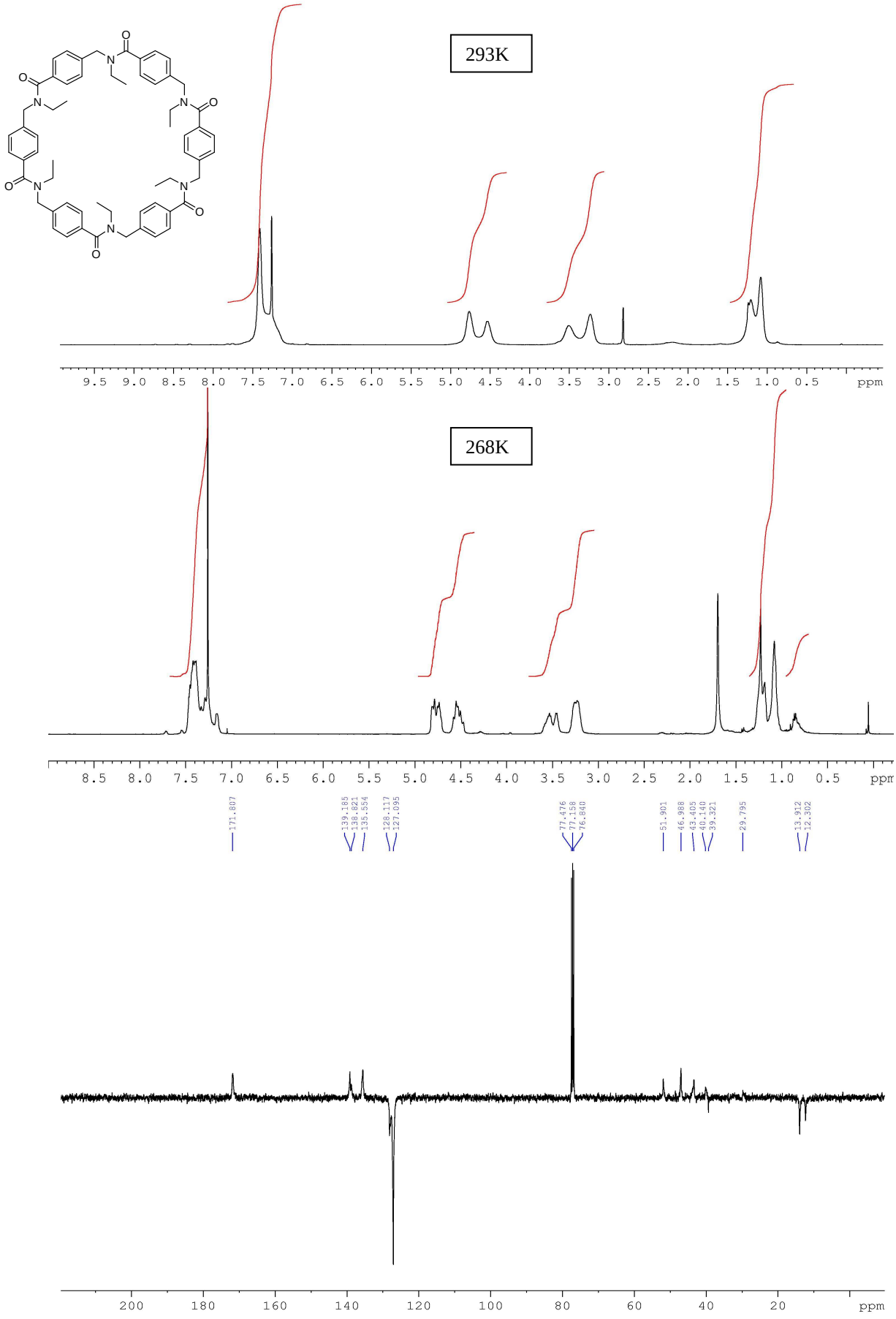


Cyclotrimer ***o*-2b** pure.

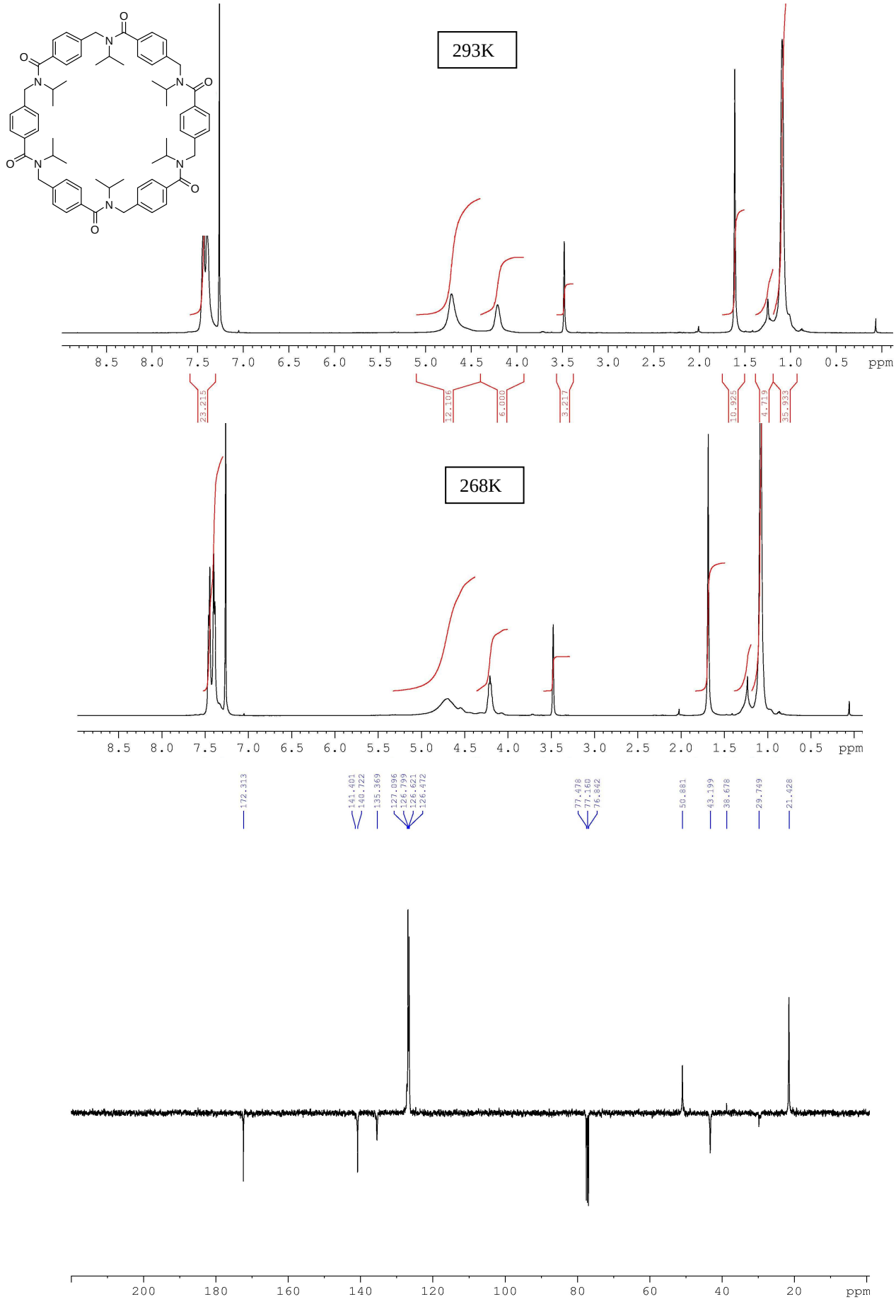


Cyclohexamer ***o*-3b** pure.

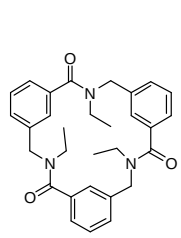
NMR spectra of *p*-3a ($CDCl_3$)

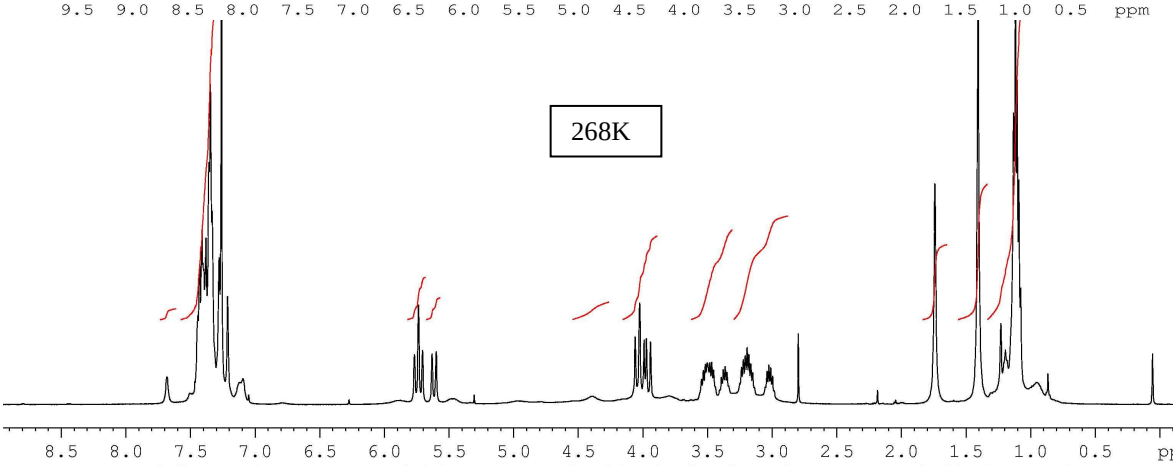


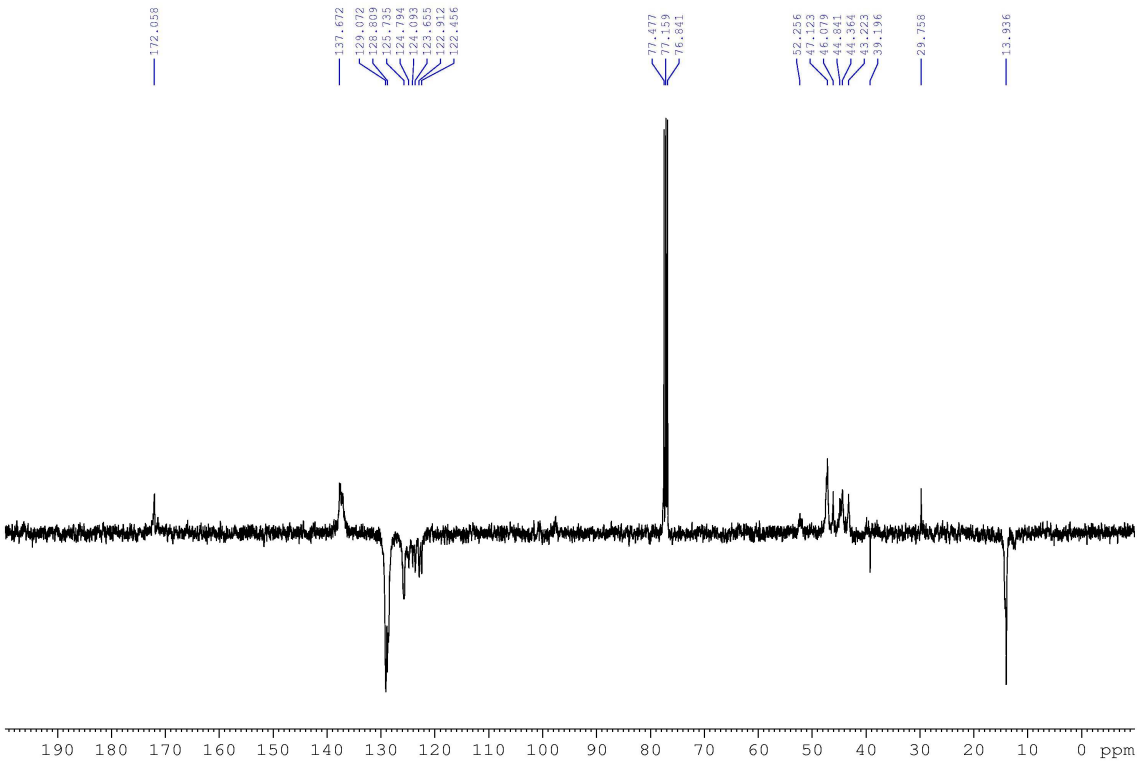
NMR spectra of *p*-3b ($CDCl_3$)



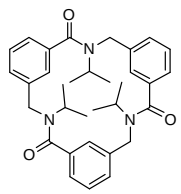
NMR spectra of *m*-2a ($CDCl_3$)

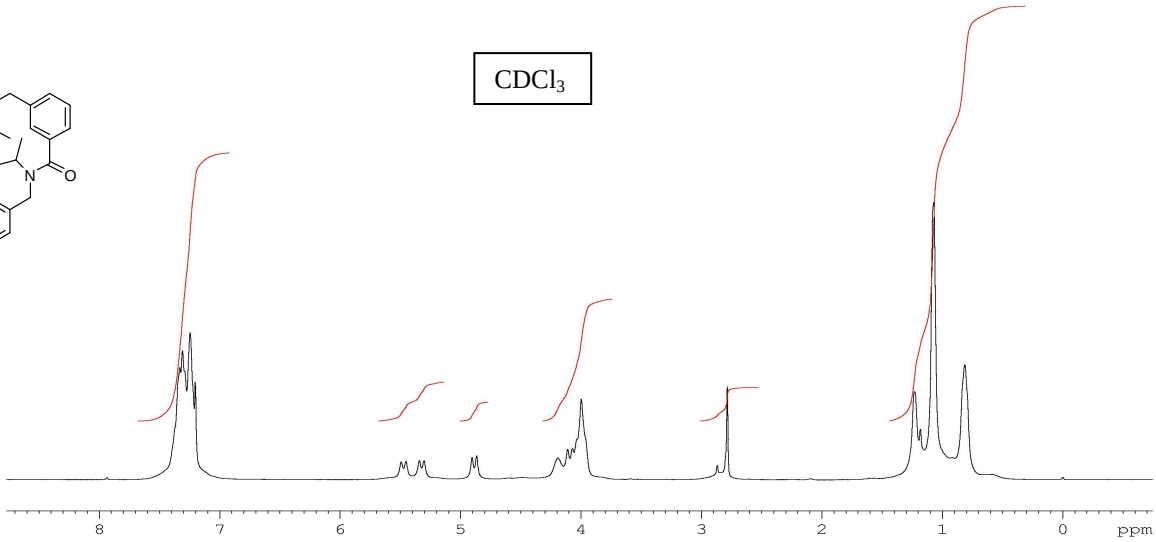


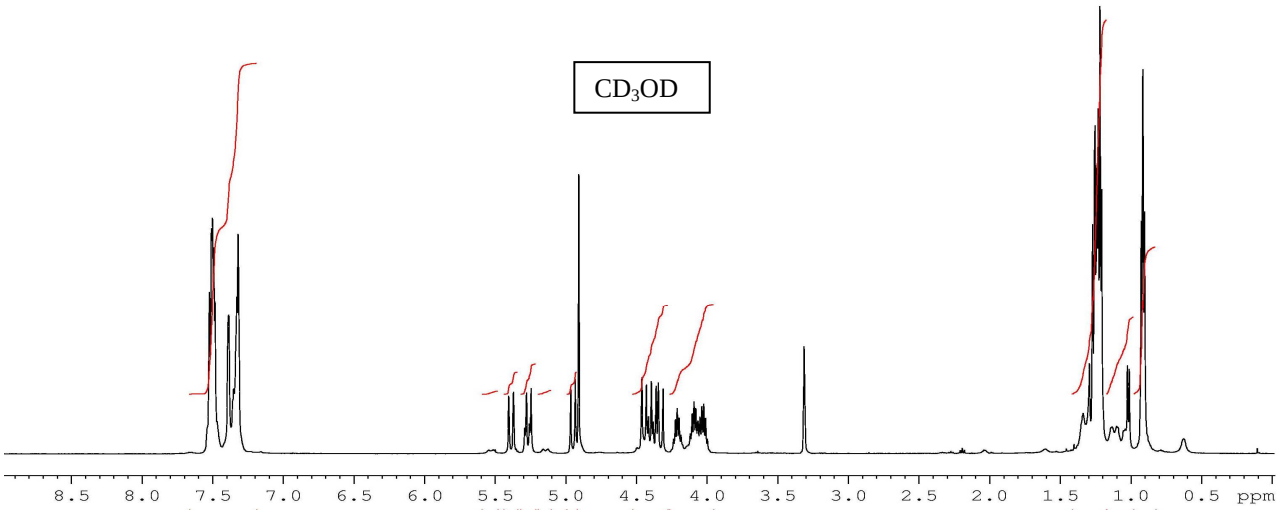


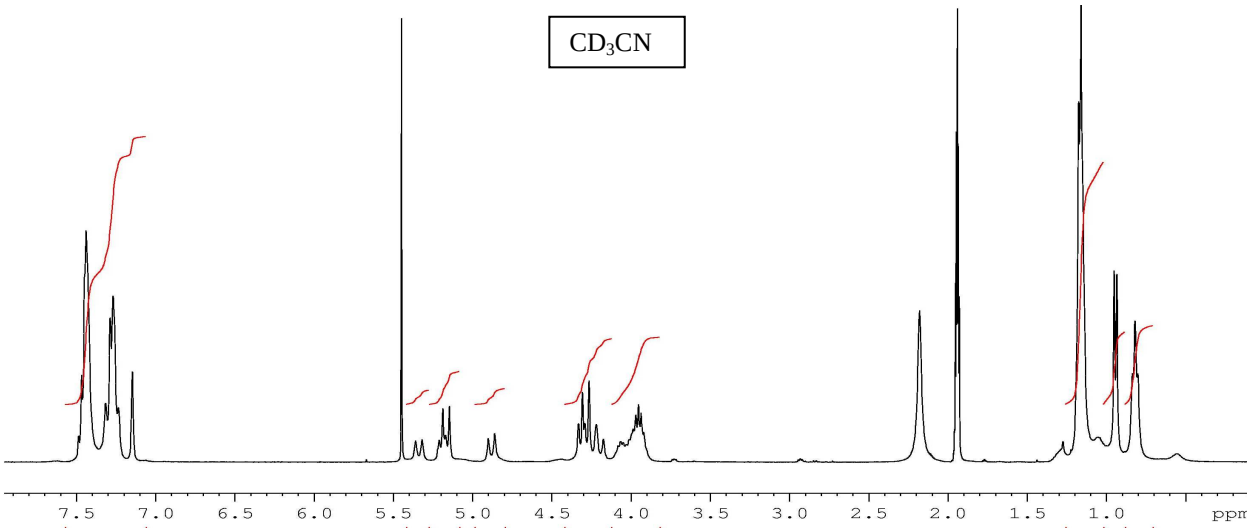


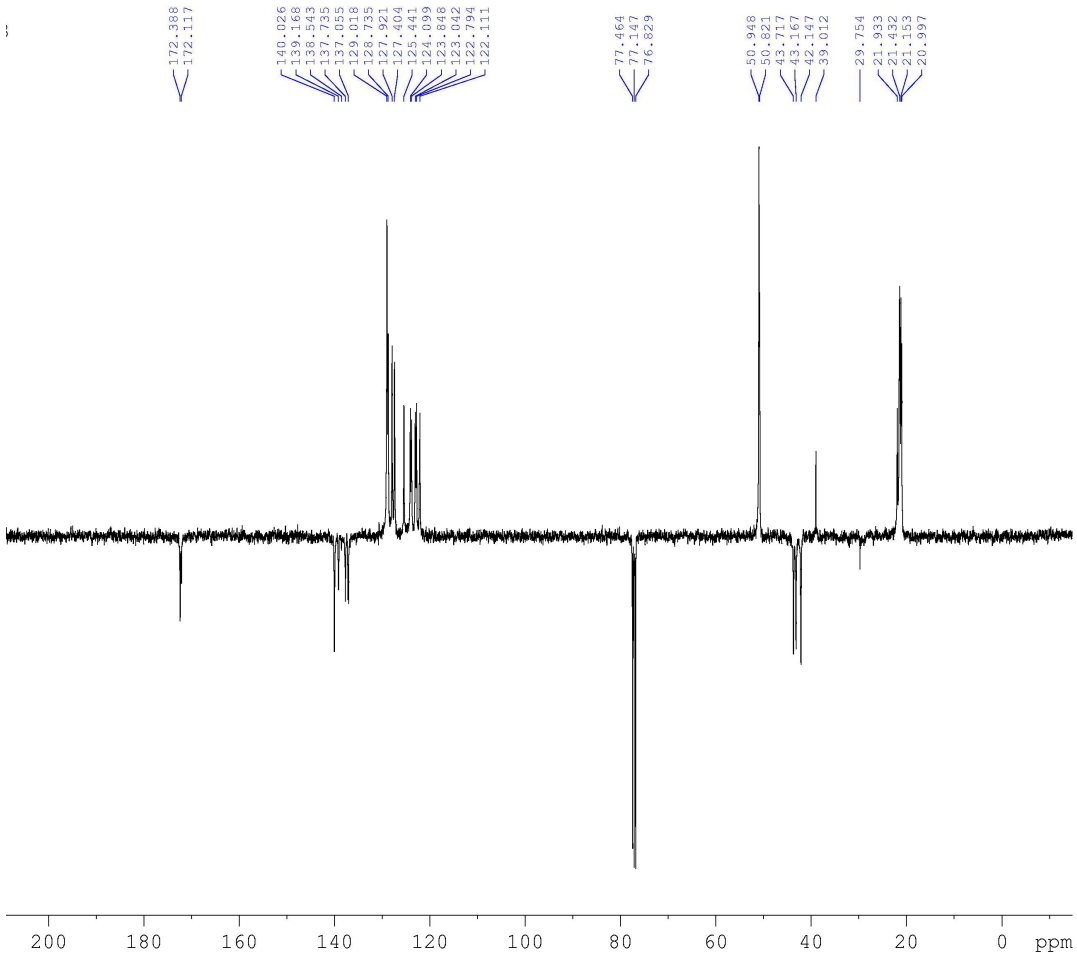
NMR spectra of *m*-2b







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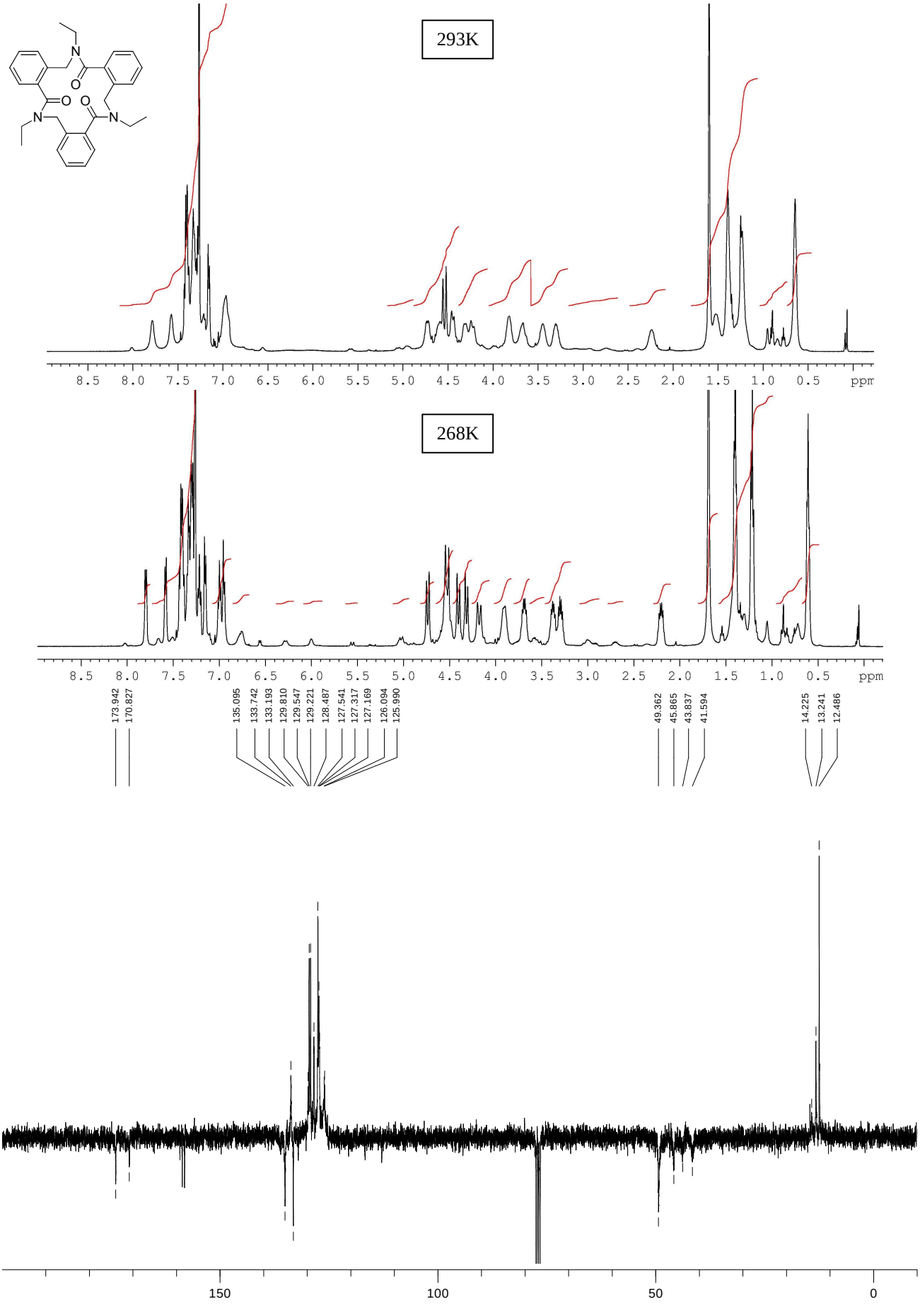
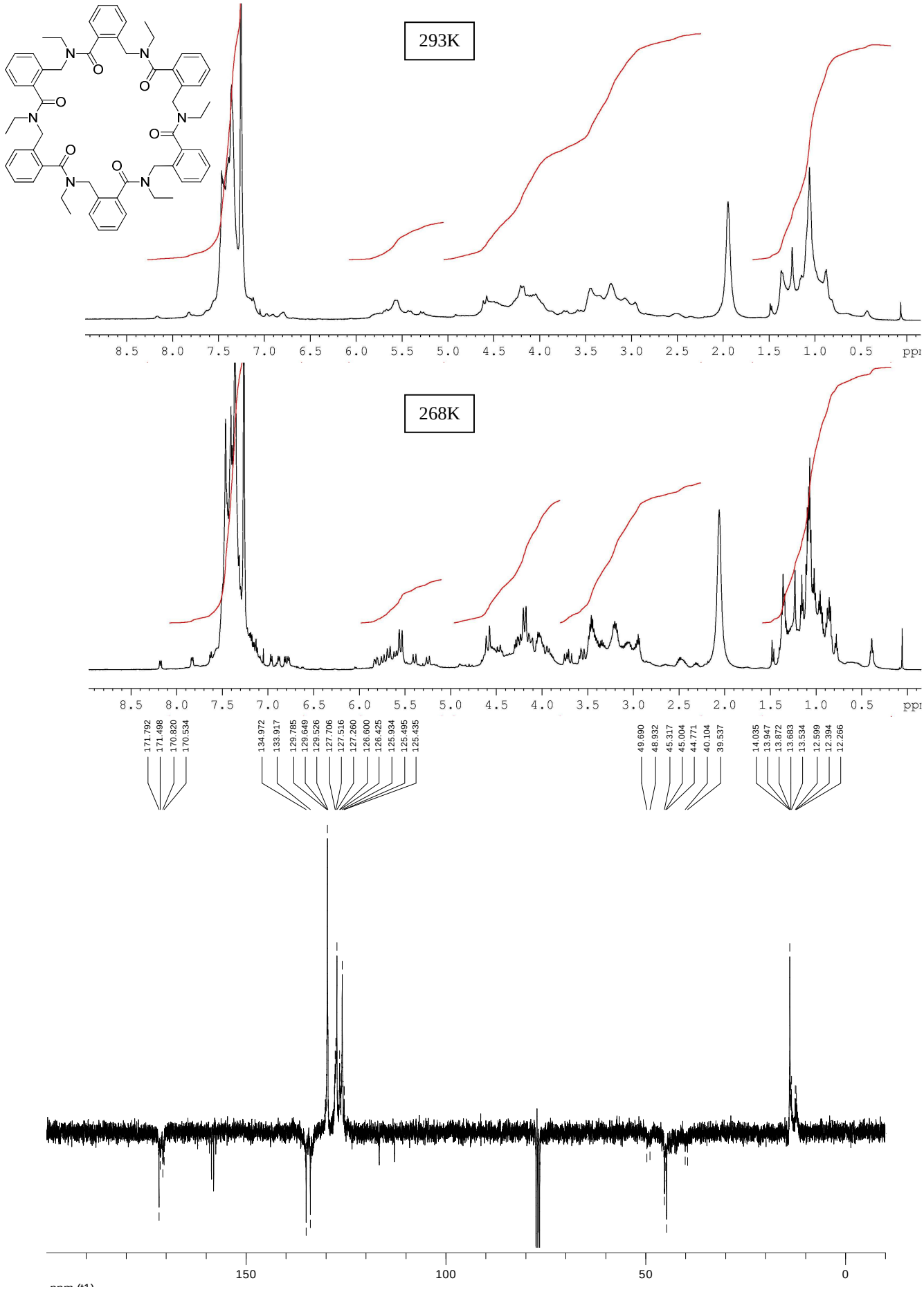
172.117
140.026
139.168
138.543
137.735
137.055
129.018
128.735
127.921
127.404
125.441
124.099
123.848
123.042
122.794
122.111
77.464
77.147
76.829
50.948
50.821
43.717
43.167
42.147
39.012
29.754
21.933
21.432
21.153
20.997
200
180
160
140
120
100
80
60
40
20
0
ppm

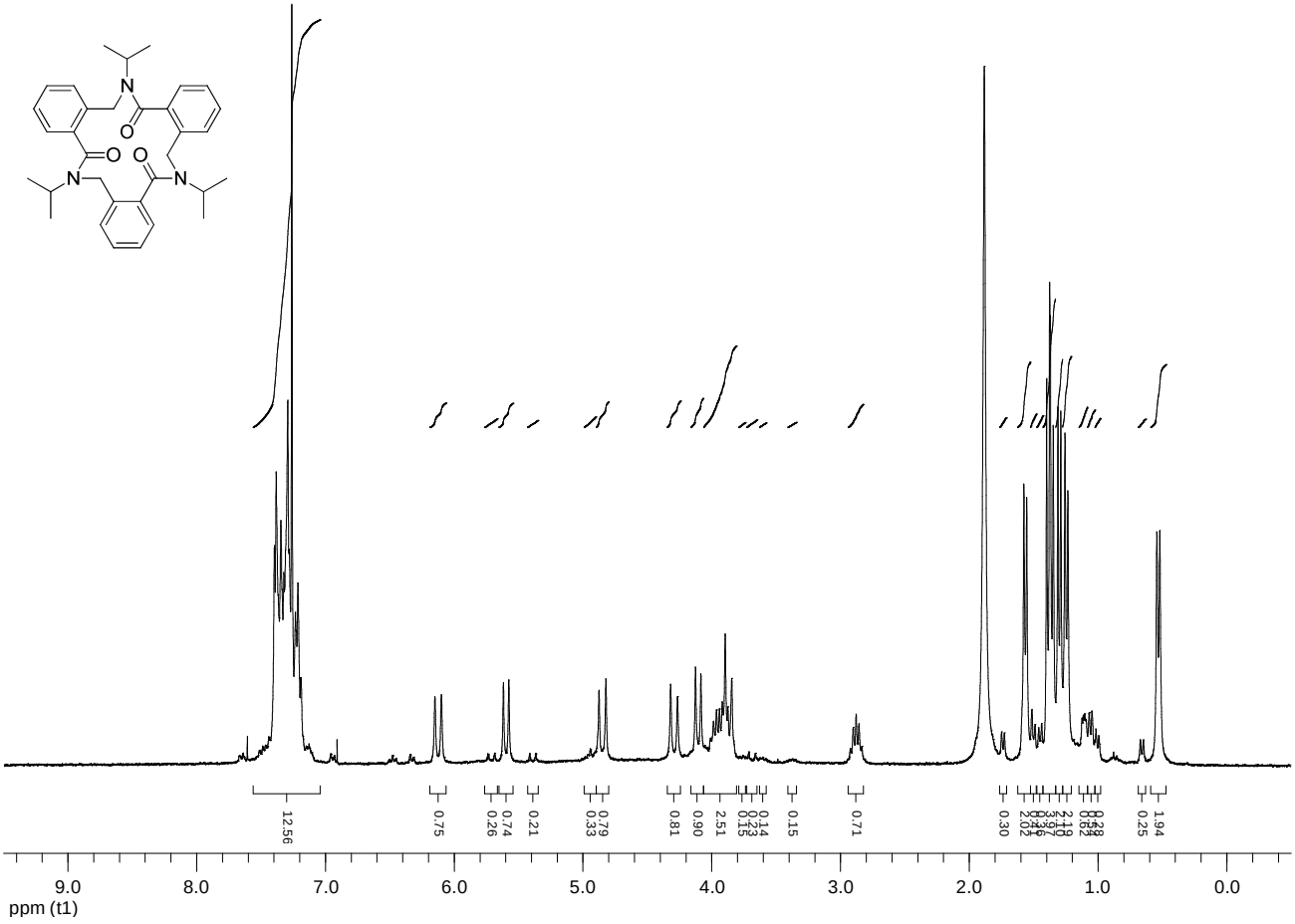
NMR spectra of *o*-2a ($CDCl_3$)

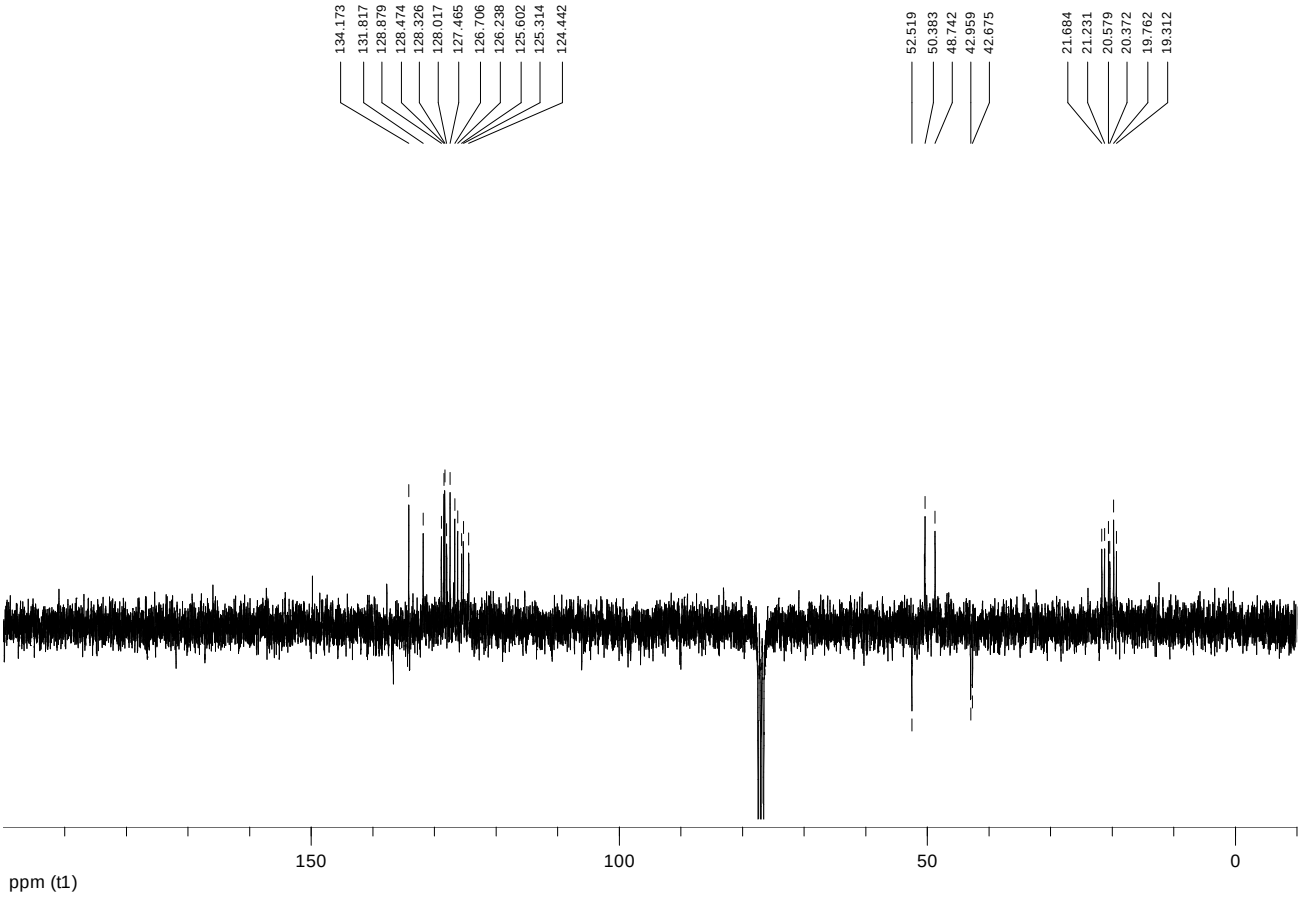


NMR spectra of *o*-3a ($CDCl_3$)

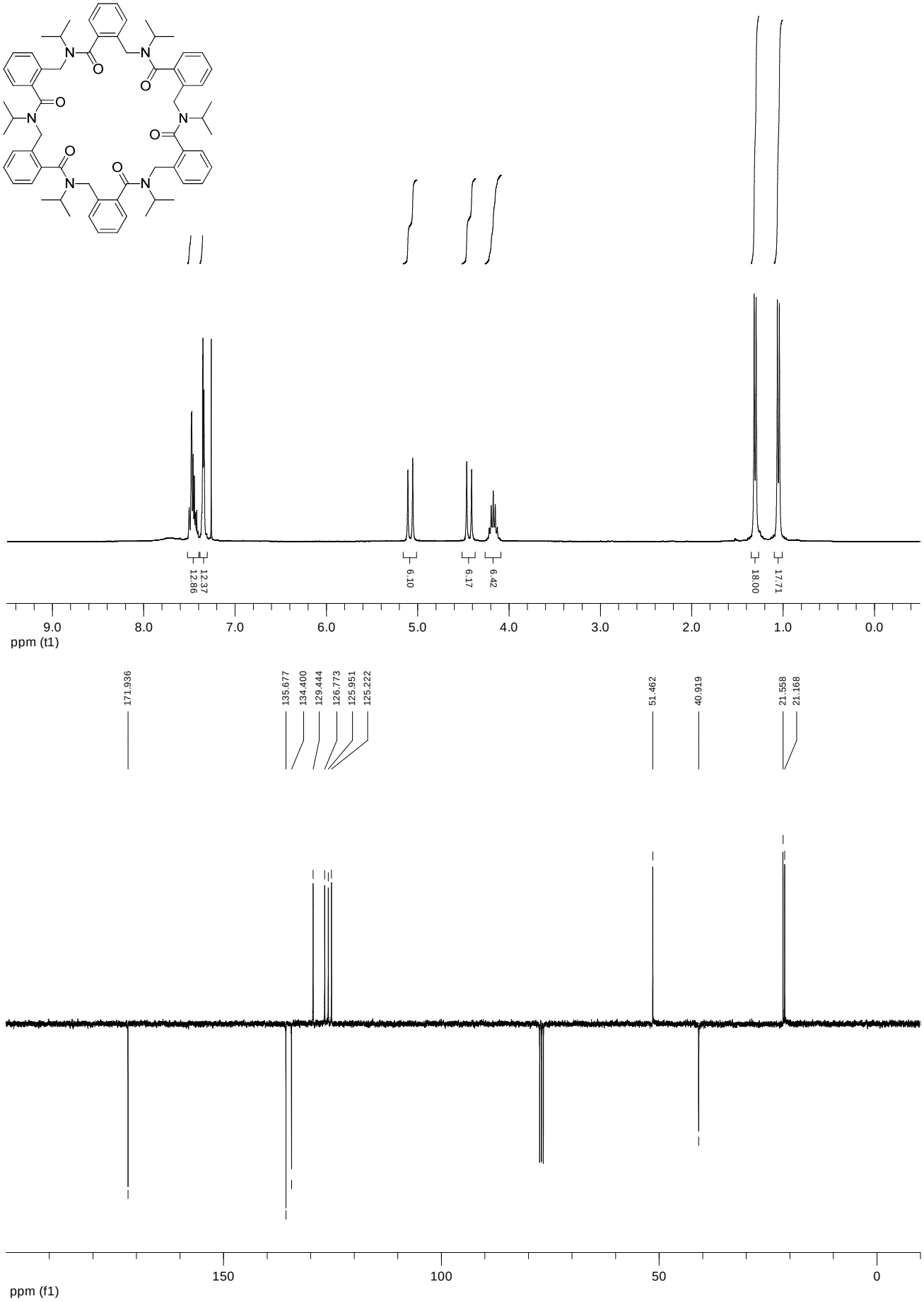


NMR spectra of *o*-2b ($CDCl_3$)





NMR spectra of *o*-3b ($CDCl_3$)



2D-NMR experiments of *o*-3b

2D NMR data were collected on a Bruker Avance 500 instrument operating at 500 MHz. NOESY acquisitions were performed at 293 K with the following parameters: spectral window = 5000 Hz in both dimensions; mixing time = 750 ms; number of transients = 32; number of increments = 256; number of points = 1024. Square cosine window functions were applied in both dimensions.

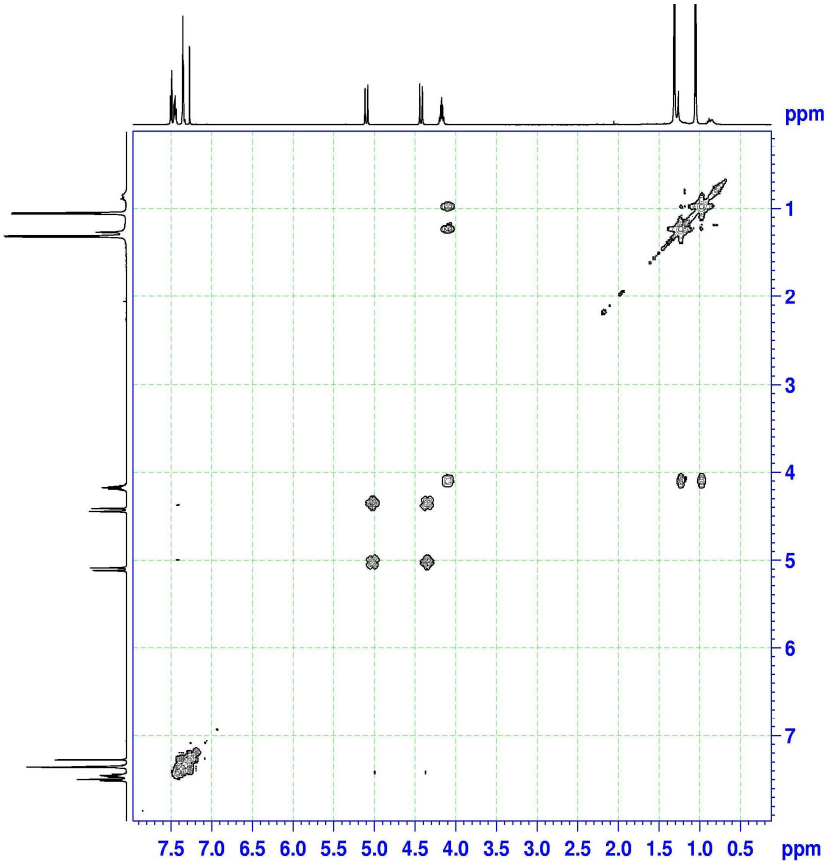


Figure S1. COSY experiment of ***o*-3b**

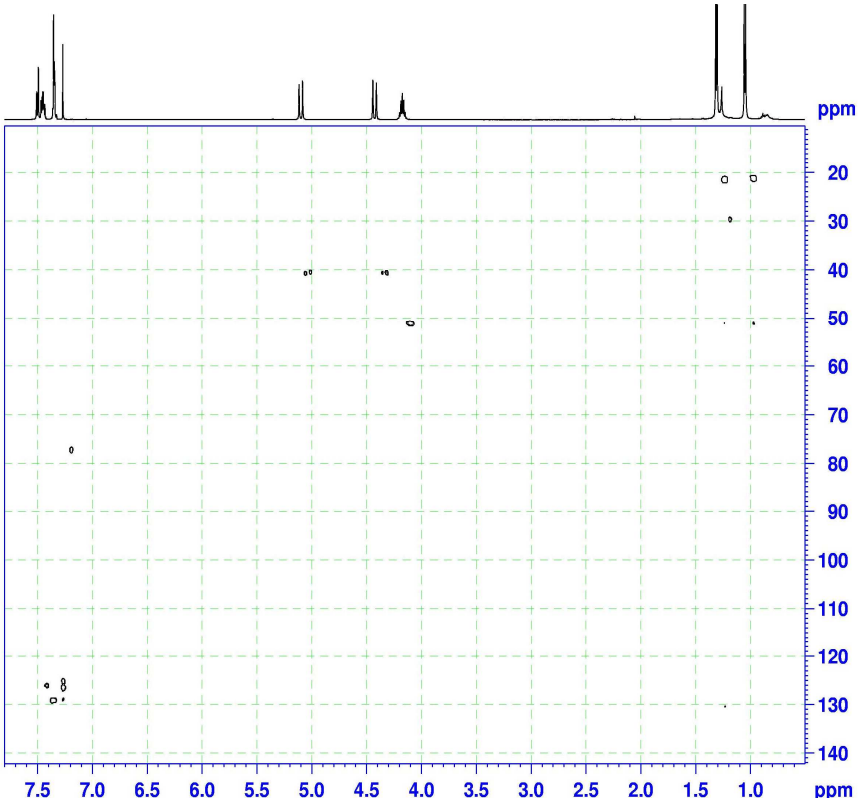


Figure S2. HSQC experiment of ***o*-3b**

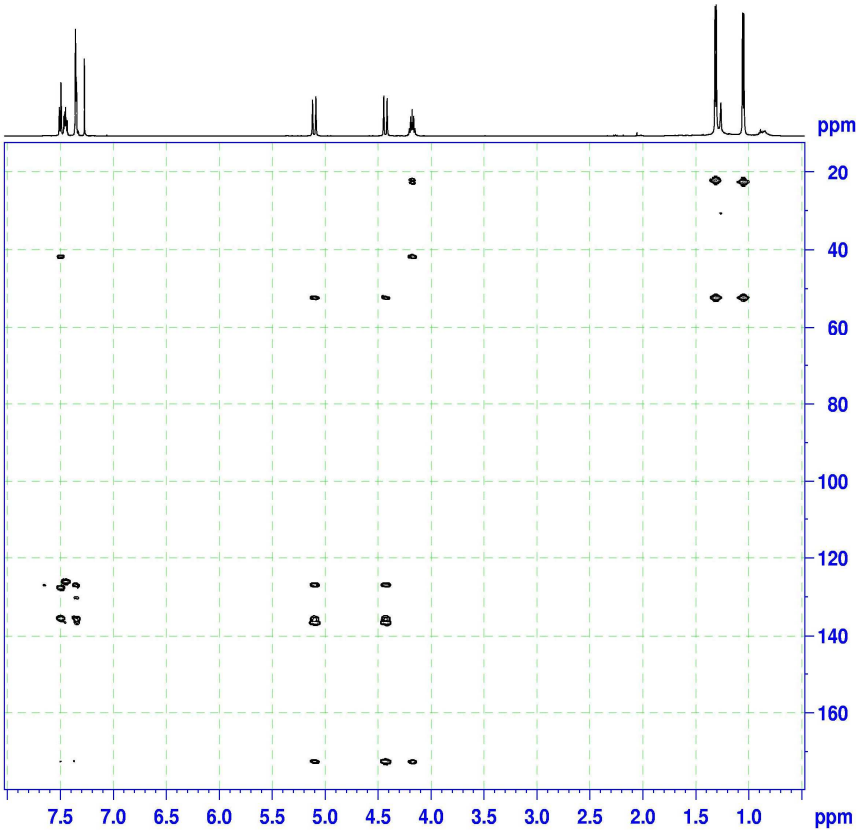


Figure S3. HMBC experiment of ***o*-3b**

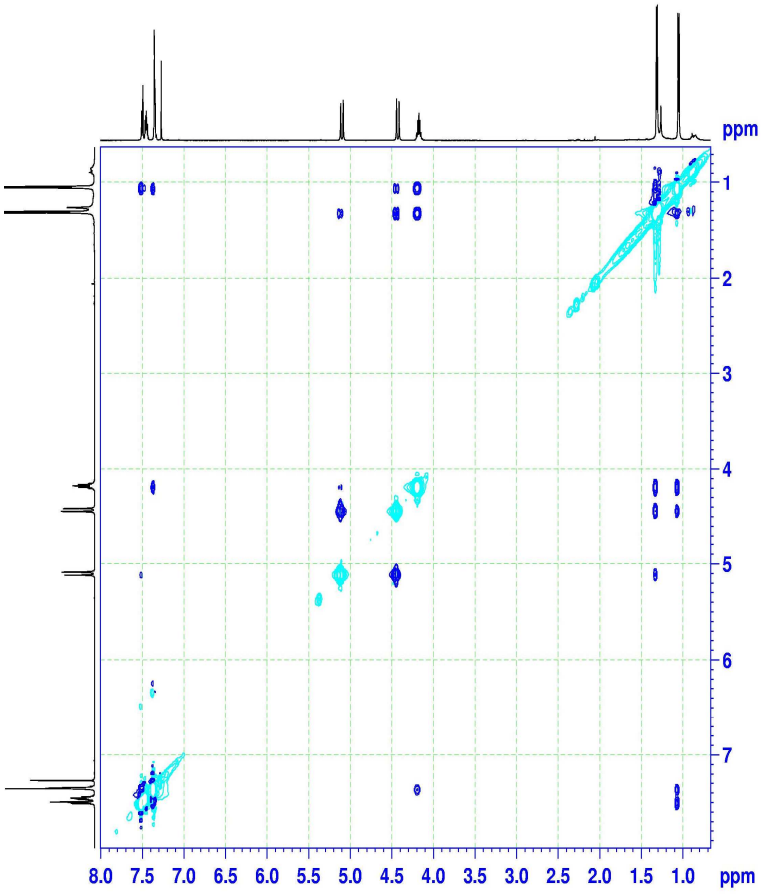


Figure S4. NOESY experiments on macrocycle ***o*-3b** (CD_3CN, 5 mM, 293K)

Crystallographic structures

Crystals of compound ***m*-2b** and ***o*-2a** have been obtained by slow evaporation of AcOEt and MeOH respectively. Crystals for compound ***o*-2a** exhibited weak diffracting power. Their X-ray data were collected at 296K with an APEX2 Bruker diffractometer equipped with a molybdenum microsource (λ = 0.71073 Å). Diffraction data were processed with the Bruker SAINT software package. The structure was solved by direct methods with SHELXS (Sheldrick G.M. *Acta Cryst.* **2008**, A64: 112) and the crystallographic refinements were conducted using CRYSTALS (Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. (2003). *J. Appl. Cryst.* **2003**, *36*, 1487). Electron density maps revealed the presence of disordered solvent around the cyclotrimer ***o*-2a**. Platon/Squeeze tool was used to take the scattering of a disordered solvent into account during the refinement (Spek A.L. *Acta Cryst.* **2009**, D65: 148-155).

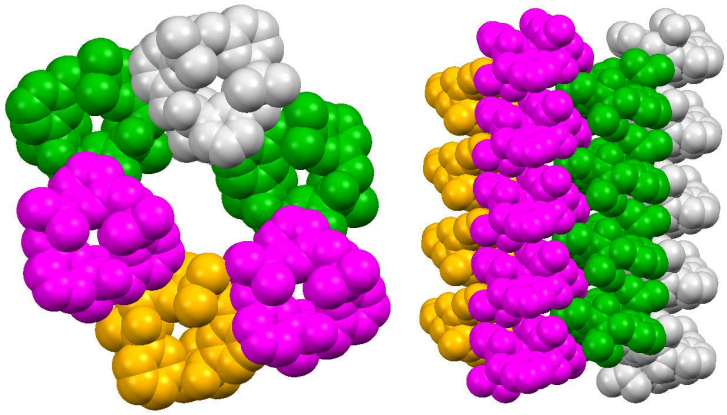


Figure S5. Top view and side view of the six parallel tube-like structures of macrocycle ***m*-2b**.

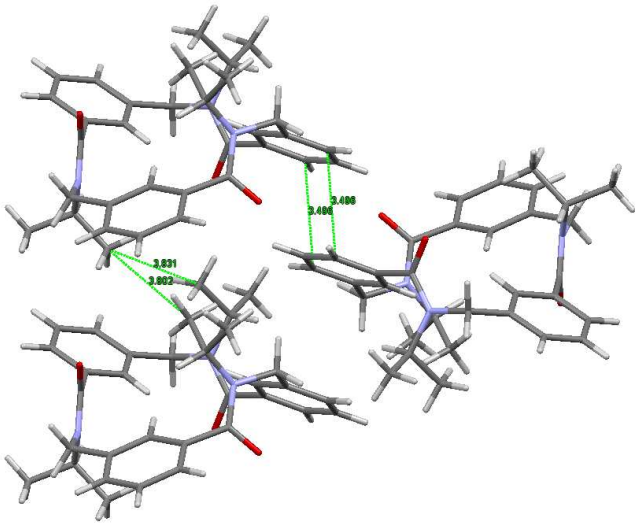


Figure S6. Weak interactions involved in the crystal packing of macrocycle ***m*-2b.**

Single crystals of compound ***o*-3b** have been obtained by slow evaporation of acetonitrile with a little amount of toluene. Crystals for compound ***o*-3b** exhibited weak diffracting power. Their X-ray data were collected at 100K with a D8 Venture Bruker diffractometer equipped with a molybdenum

microsource (λ = 0.71073 Å). Diffraction data were processed with the Bruker SAINT software package. The structure was solved by direct methods with SIR2004 (Burla M.C., Caliandro R., Camalli M., Carrozzini B., Cascarano G.L., De Caro L., Giacovazzo C., Polidori G. and Spagna R. *J. Appl. Cryst.* **2005**, 38: 381-388) and the crystallographic refinements were conducted using SHELXL-97 (Sheldrick G.M. *Acta Cryst.* **2008**, A64: 112-122). Electron density maps revealed the presence of ordered and disordered solvent around the cyclohexamer. Three acetonitrile molecules and one water molecule were added in the model. Platon/Squeeze tool was used to take the scattering of a disordered solvent into account during the refinement (Spek A.L. *Acta Cryst.* **2009**, D65: 148-155).

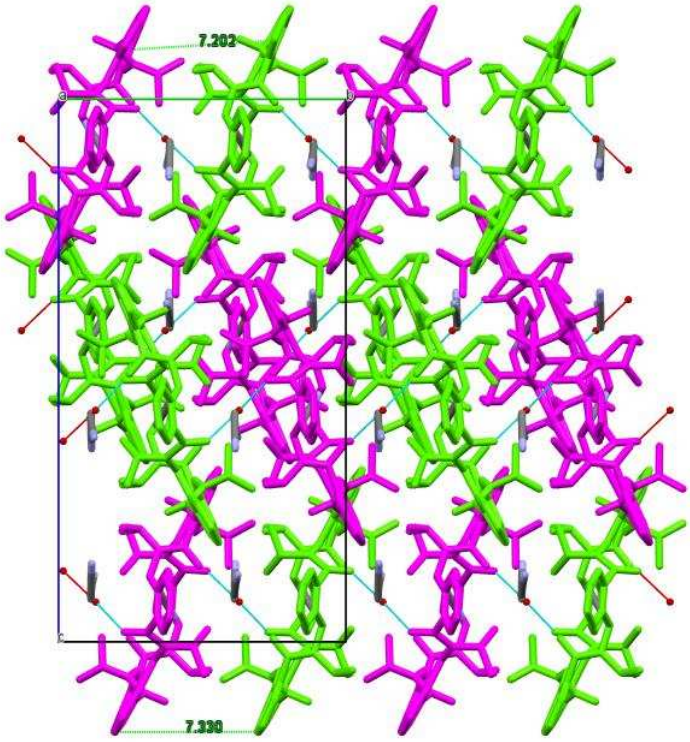


Figure S7. X-ray structure of macrocycle ***m*-2b**: crystal packing along a axis**.**

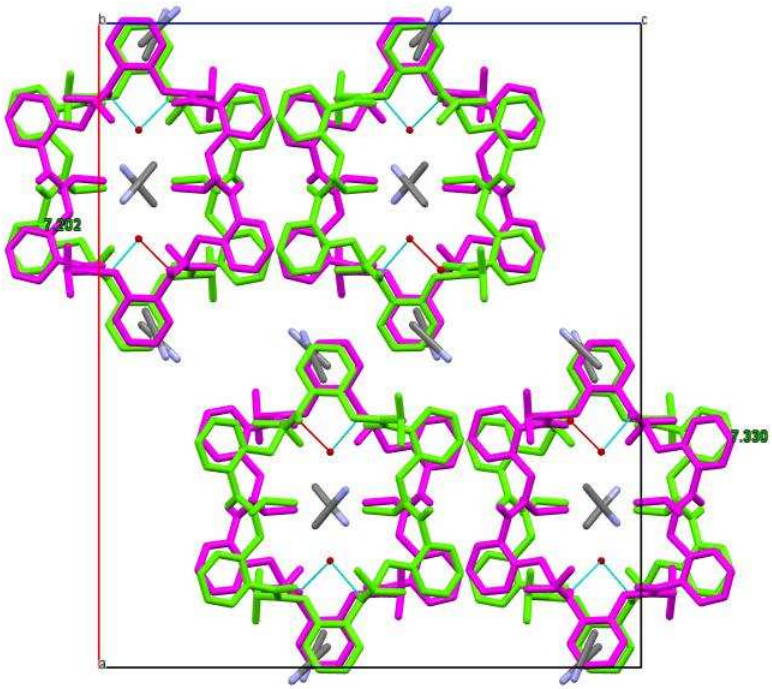


Figure S8. X-ray structure of macrocycle ***m*-2b**: crystal packing along b axis**.**

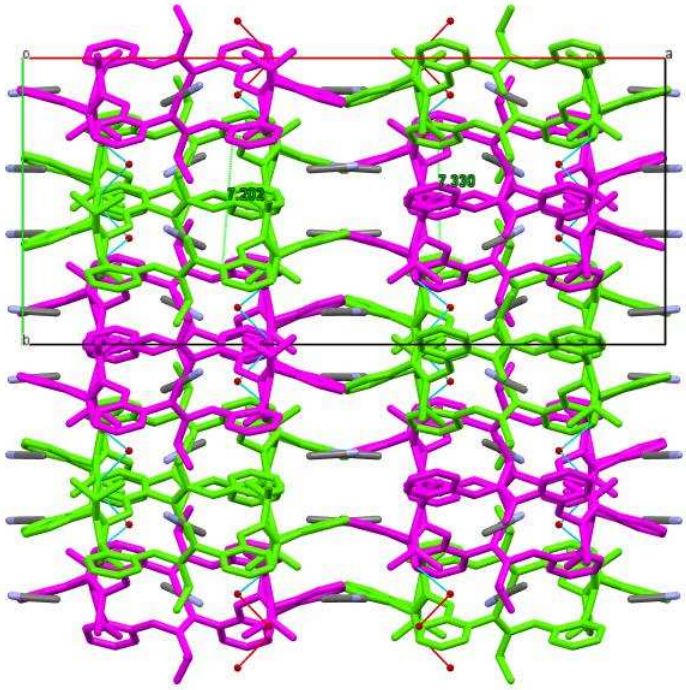


Figure S9. X-ray structure of macrocycle ***m*-2b**: crystal packing along c axis**.**

Molecular Modelling

Molecular Modelling on cycloarylopeptoid ***o*-2a**

Simulated annealing: Force Field: MMFF94, Charge MMFF94, Dielectric constant 1.0; 500 cycles with 2000 fs heating at 700°K following by cooling at 0°K using SYBYL-X 1.2 (Tripos International, St. Louis, MO, USA). All DFT computations were performed with B3LYP functional and 6-31G(d,p) bases set. The default criteria of Gaussian 09[i] for optimisation were used.

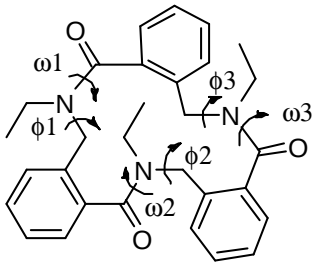


Figure S10. Structure of macrocyclic arylopeptoid ***o*-2a** with assignment of backbone torsion angles ω and ϕ.

Simulated annealing gave conformations for the four *cis/trans* states: *ccc*, *cct*, *ctt*, *ttt*. For each *cis/trans* state, we defined a subgroup according to a set of classifications: the ω angle was defined as either a *cis* (*c*) or *trans* (*t*) backbone amide, the ϕ angle was defined as either ($0<\phi<120$) and ($240<\phi<360$) or ($120<\phi<240$).

We found 12 subgroups and the geometries of the lowest energy conformation for each subgroup was optimized by QM calculations. Frequency calculations of the optimized structure yielded no imaginary frequencies, indicating a true stationary point on the potential energy surface. The resulting self-consistent field (SCF) energies were not corrected. Energies are listed in Table S1.

Table S1. Angles ϕ for each subgroup (as defined above) and their absolute and relative energies after optimisation by QM calculations.

	Absolute energy (hartree)	Relative energy (kcal/mol)	ϕ 1	ϕ 2	ϕ 3
ctt1	-1553.07845	0.00	-113.19	-71.00	69.56
ctt2	-1553.07753	0.58	133.11	69.31	64.95
ctt3	-1553.07607	1.50	100.11	-156.20	93.90
cct1	-1553.07582	1.65	157.70	128.94	-62.45
cct2	-1553.07556	1.82	-89.07	-103.92	-74.28
ttt1	-1553.07509	2.11	-136.32	-66.16	-158.65
cct3	-1553.07444	2.52	-68.10	115.84	150.43
ctt4	-1553.07418	2.68	146.39	132.01	44.36
ttt2	-1553.07212	3.97	148.96	-66.81	-65.57
ccc1	-1553.07124	4.53	-163.16	-61.41	102.82
ctt5	-1553.07019	5.18	143.47	157.88	130.82
cct4	-1553.06942	5.67	132.37	-168.43	134.96

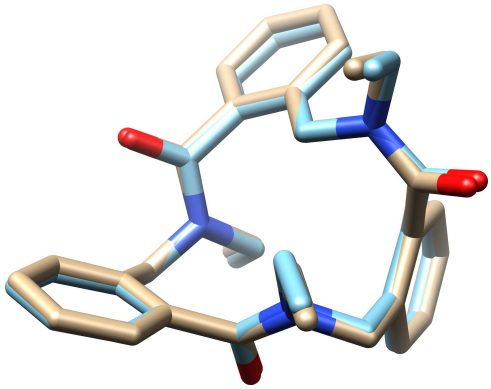


Figure S11. Superposition of X-ray structure of macrocyclic arylopeptoid ***o*-2a** (in blue) and *ctt*1 (in gold). RMDS of *ctt1* compared to the experimental crystal structure of ***o*-2a** using backbone: 0.097 Å using UCSF Chimera 1.6.2.[ii]

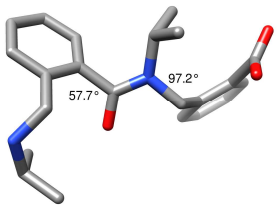
Molecular Modelling on cycloarylopeptoid ***o*-3b**

On the basis of NMR data collected on the macrocycle ***o*-3b** revealing a high degree of symmetry and *trans* conformation of tertiary amide bonds, we propose a model structure of the privileged conformation in solution using molecular modelling.

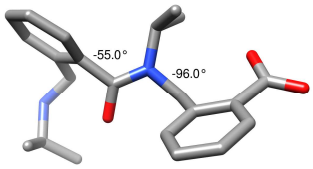
To this aim we first studied a dimeric model with *trans* conformation of amide bond. A random search using SYBYL-X 1.2[iii] was performed on 1000 cycles, each new conformation was minimized using tripos force field and Gasteiger Hückel charges with the following parameters: method; conjugated gradient, gradient value; 0.05, dielectric constant; 78.0, Energy cutoff; 3.0 kcal.mol^{-1}.

This random search revealed two families organized around the following two structures.

Both dimers were optimized[iv] by Gaussian g09 rev D and density functional theory[v] (B3LYP /6-31G(d,p))[vi] to give AB and BA conformations (Figure S12)



Conformation AB of the dimeric model



Conformation BA of the dimeric model

Figure S12. Optimized conformations of the dimeric model with backbone torsion angles (ω and ϕ) values.

This preliminary study on dimer shows that the sequence involved in the cyclohexamer can not contain AA or BB conformations. The cyclohexaarylopeptoid was thus constructed using alternating AB sequences. The obtained structure was optimized by Gaussian G09 rev D, using the density functional theory (B3LYP/6-31G(d,p)). The optimized structure revealed S6 symmetry (Figure S13).

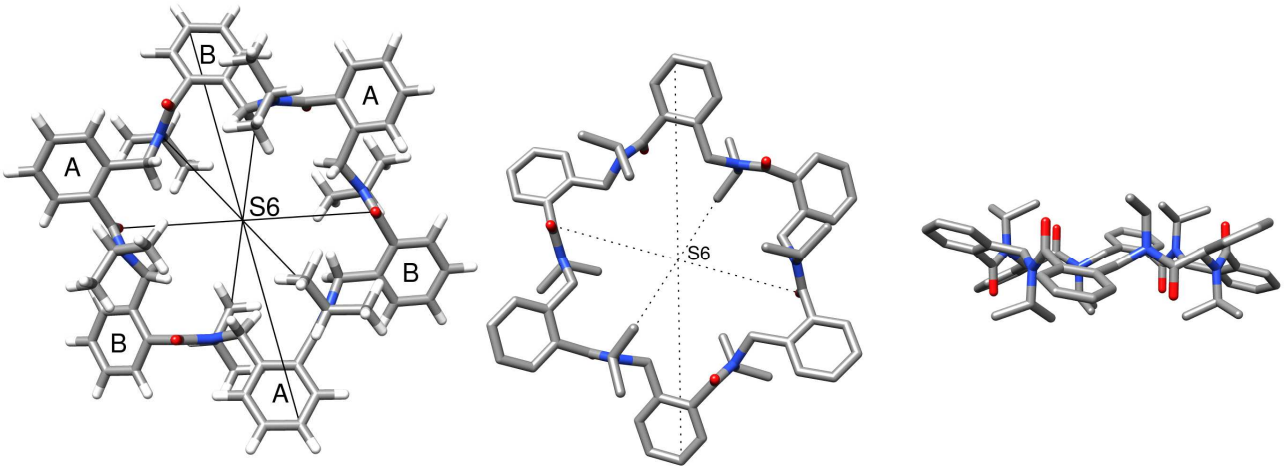


Figure S13. Predicted cyclohexamer conformation optimized by gaussian, with S6 symmetry group and alternating ABABAB sequence.

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[i] Gaussian 09, Revision D.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

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[iii] *SYBYL 7.3, Tripos International, 1699 South Hanley Rd., St. Louis, Missouri, 63144, USA*, s. d.

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[vi] a) S. H. Vosko, L. Wilk, and M. Nusair *Can. J. Phys.*, **58** (1980) 1200-11; b) C. Lee, W. Yang, and R. G. Parr *Phys. Rev. B*, **37** (1988) 785-89; c) G. A. Petersson, A. Bennett, T. G. Tensfeldt, M. A. Al-Laham, W. A. Shirley, and J. Mantzaris *J. Chem. Phys.*, **89** (1988) 2193-218.