Supplementary Information

Sensing a binding event through charge transport variations using an aromatic oligoamide capsule

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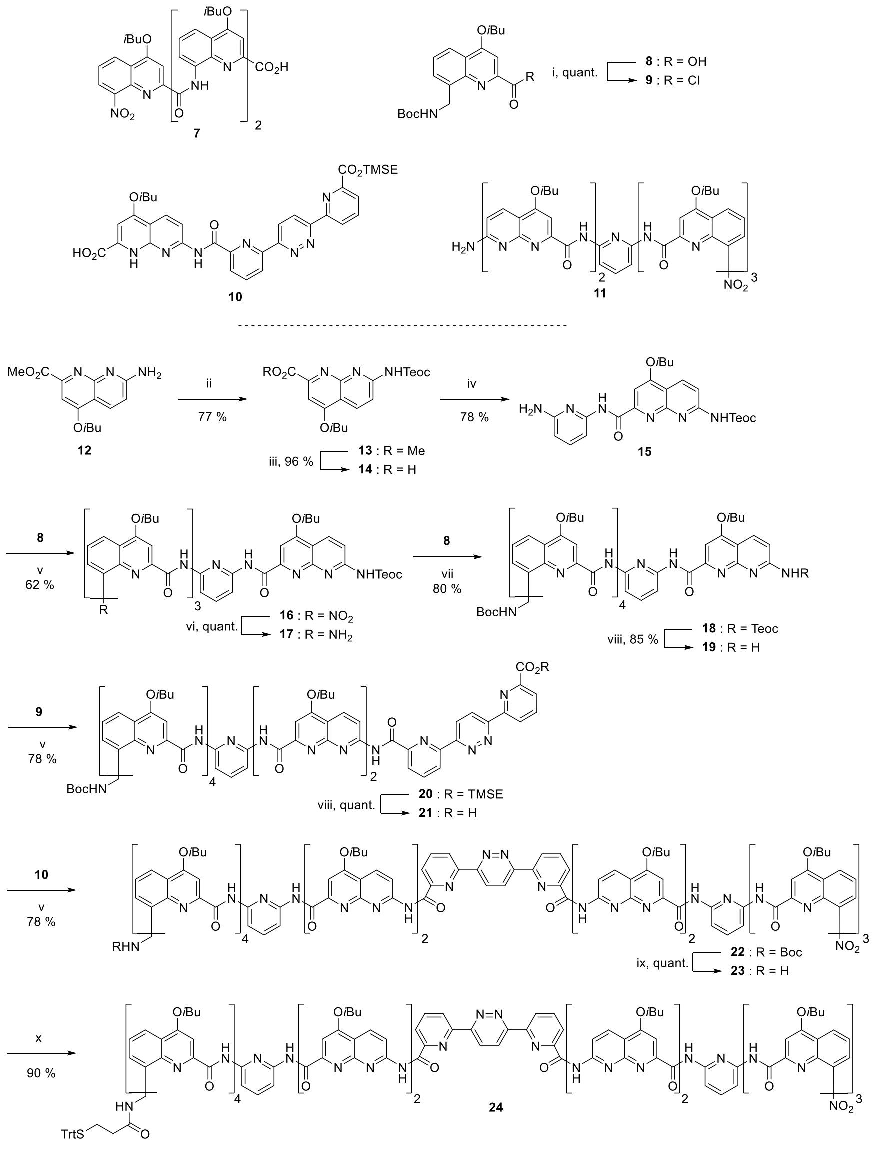
1. Protocols for chemical synthesis

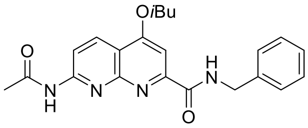
All reactions were carried out under a dry nitrogen atmosphere. Commercial reagents were purchased from Sigma-Aldrich, Alfa-Aesar or TCI and were used without further purification unless otherwise specified. Chloroform ($CHCl_3$) and diisopropylethylamine (DIEA) were distilled over calcium hydride (CaH_2) prior to use. Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel 60-F254 plates and observed under UV light. GPC purification was performed on an LC-9130G NEXT setup (Japan Analytical Industry Co., Ltd.) equipped with two preparative columns (Inner diameter of 20mm and length of 600mm): a JAIGEL 2.5H and a JAIGEL 3H, in conjugation with UV-600 NEXT UV detector and an FC-3310 fraction collector. Chloroform with 1% EtOH and 0.5% Et_3N was used as mobile phase, with a flow rate of 7.0 mL/min. ESI mass spectra were obtained from the Mass Spectrometry Laboratory at the European Institute of Chemistry and Biology (UMS 3033 - IECB), Pessac, France.

1.1 Synthesis of oligomer 23

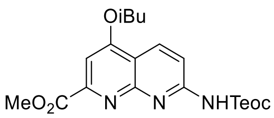


Scheme S1. i) $(COCl)_2$, $CHCl_3$, room temperature, 3 h. ii) TeocO-4-nitrophenyl, dioxane, reflux, 18 h. iii) LiI, THF/MeOH/H_2O, room temperature, 1 h. iv) 2,6-diaminopyridine, PyBOP, DIPEA, $CHCl_3$, 45 °C, 24 h. v) PyBOP, DIPEA, $CHCl_3$, 45 °C, 24 h. vi) 25 % Pd/C, NH_4CO_2H, cat. NH_4VO_3, EtOAc/MeOH/H_2O, 80 °C, 8 h. vii) DIPEA, $CHCl_3$, room temperature, 18 h. viii) TBAF, THF, room temperature, 4 – 18 h. ix) TFA, $CHCl_3$, r.t., 18 h. x) 3-(tritylthio)propionic acid, $CHCl_3$, 50 °C, 24 h.

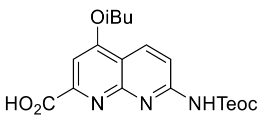
1.2 Experimental procedures



Model naphthyridine monomer (6). 1,8-Naphthyridine-2-carboxylic acid, 7-(acetylamino)-4-(2-methylpropoxy)-, methyl ester (0.946 mmol, 0.300g) was dissolved in a mixture of THF/MeOH/H2O (10 mL, 6:3:1, v/v). NaOH (2.84 mmol, 0.113g) was added to this mixture and the resulting slurry was vigorously stirred for 40 minutes at RT. The excess of KOH was subsequently quenched by the addition of 1M HCl. After evaporation of THF under reduced pressure, the aqueous phase was extracted by CH_2Cl_2. The organic layer was then washed with water, dried over $MgSO_4$ and evaporated to dryness. Acid AcHN-N(OiBu)-CO_2H was obtained as a white powder (75 %, 0.215 g) and was used without any further purification. Acid AcHN-N(OiBu)-CO_2H (0.714 mmol, 0.215 g) and HBTU (1.42 mmol, 0.541 g) were suspended in dry DMF (1mL). Then benzylamine (0.928 mmol, 101 µL) was added and the solution was stirred ar RT overnight. The solvents and excess reagent were removed under reduced pressure then the residue was purified by flash chromatography (SiO2) eluting with EtOAc:cyclohexane (20:80 vol/vol to 40 :60) and by precipitation from DCM/Et_2O to obtain **6** as a white solid (71%, 0.200 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.99 (s, 1H), 9.12 (t, 1H), 8.62 (d, 1H), 8.39(d, 1H), 7.58 (s, 1H), 7.45 – 7.25 (m, 5H), 4.58 (d, 2H), 4.15 (d, 2H), 2.28 – 2.17 (m, 1H), 1.08 (d, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 164.4, 163.5, 155.5, 154.9, 154.6, 139.7, 134.1, 128.9, 127.8, 127.4, 115.3, 113.7, 99.0, 75.4, 43.1, 28.1, 24.7, 19.3. HRMS (ES^+): *m/z* calcd for $C_{20}H_{30}N_3O_5Si$ $[M+H]^+$: 420.1949 found 420.1955. m/z calcd for $C_{22}H_{24}N_4O_3$ $[M+H]^+$: 393.1921 found 393.1932

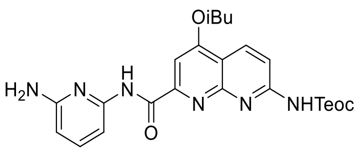


MeO_2C-N-NHTeoc (13). 2-(trimethylsilyl)-ethyl 4-nitrophenyl carbonate (6.3 g, 22.2 mmol) was added to a solution of **12**[1] (5 g, 18.5 mmol) in 80 mL of dioxane. The reaction was allowed to process under refluxing until complete. The solvent was removed under reduced pressure and the residue was purified by chromatography (SiO_2) eluting with EtOAc:cyclohexane (40:60 vol/vol) to give naphthyridine **13** as a white solid (77 %, 5.87 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, *J* = 9.1 Hz, 1H), 8.35 (d, *J* = 9.1 Hz, 1H), 7.64 (s, 1H), 7.53 (s, 1H), 4.40 – 4.27 (m, 2H), 4.05 (d, *J* = 6.5 Hz, 2H), 4.03 (s, 3H), 2.28 (ddt, *J* = 6.7 Hz, 1H), 1.18 – 1.04 (m, 8H), 0.08 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.22, 162.49, 154.59, 153.96, 152.43, 150.98, 132.94, 113.17, 112.99, 100.04, 74.74, 63.47, 52.12, 27.45, 26.24, 18.48, 16.93, -2.15. HRMS (ES^+): *m/z* calcd for $C_{20}H_{30}N_3O_5Si$ $[M+H]^+$: 420.1949 found 420.1955.



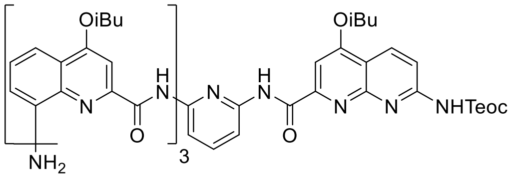
HO_2C-N-NHTeoc (14). LiOH (0.86 g, 36 mmol) was added to a solution of **13** (5 g, 12 mmol) in 60 mL of THF/MeOH/H_2O (8:1:1). The resulting slurry was stirred for 1 hours at room temperature and the reaction was monitored by TLC. The reaction was then quenched by a 5 % aqueous citric acid solution, and solvents were removed by evaporation. The residue was dissolved in dichloromethane and washed with distilled water and then with brine. Organic layer was dried over $MgSO_4$ and filtered. Solvent was evaporated to dryness and the residue was dried under vacuum to give naphthyridine acid **14** as a white solid (96 %, 4.64 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, *J* = 9.1 Hz, 1H), 8.44 (d, *J*

= 9.1 Hz, 1H), 7.78 (b, 1H), 7.64 (s, 1H), 4.42 – 4.29 (m, 2H), 4.10 (d, *J* = 6.6 Hz, 2H), 2.30 (dt, *J* = 13.3, 6.6 Hz, 1H), 1.18 – 1.04 (m, 8H), 0.09 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.16, 163.40, 156.72, 153.62, 152.12, 151.30, 133.92, 114.63, 113.14, 100.85, 76.61, 64.42, 28.03, 19.06, 17.54, -1.51. HRMS (ES^+): *m/z* calcd for $C_{19}H_{28}N_3O_5Si$ $[M+H]^+$: 406.1793 found 406.1805.

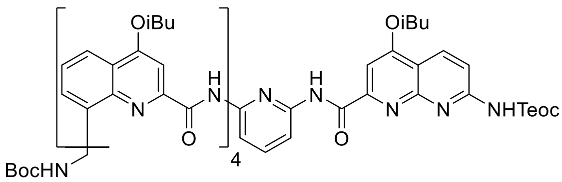


H_2N-PN-NHTeoc (15). Acid **14** (0.8 mmol, 325 mg) and 2,6-diaminopyridine (7.44 mmol, 812 mg) were dissolved in dry chloroform (20 mL). DIPEA (3.21 mmol, 0.56 mL) and PyBOP (3.21 mmol, 1.67 g) were added at room temperature and the reaction mixture was heated at 45 °C for 24 hours. The solvent was evaporated and the residue was dissolved in CH_2Cl_2, washed with a citric acid solution (5 % aq), water (3 times), dried over $MgSO_4$, filtered and then concentrated. The residue was purified by precipitation from minimum amount of MeOH to obtain dimer amine **15** as a white solid (78 %, 310 mg). ^1H NMR (300 MHz, $CDCl_3$) δ 10.43 (s, 1H), 8.60 (d, *J* = 9.1 Hz, 1H), 8.37 (d, *J* = 9.1 Hz, 1H), 7.81 (s, 1H), 7.77 – 7.71 (m, 1H), 7.52 (t, *J* = 7.9 Hz, 1H), 6.30 (dd, *J* = 8.0, 0.7 Hz, 1H), 4.41 – 4.29 (m, 4H), 4.10 (d, *J* = 6.6 Hz, 3H), 2.29 (dt, *J* = 13.3, 6.7 Hz, 1H), 1.18 – 1.05 (m, 8H), 0.08 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.01, 162.25, 157.62, 155.21, 154.60, 153.70, 153.64, 149.54, 139.92, 134.27, 114.12, 113.97, 104.66, 103.32, 98.76, 75.72, 64.46, 28.20, 19.27, 17.56, -1.44. HRMS (ES^+): *m/z* calcd for $C_{24}H_{33}N_6O_4Si$ $[M+H]^+$: 497.2327 found 497.2340.

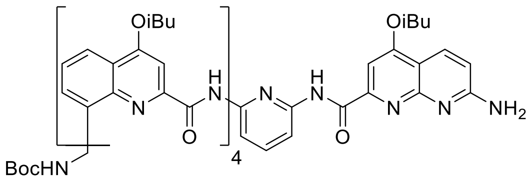
O_2N-Q_3PN-NHTeoc (16). Trimer acid **7**[2] (0.5 mmol, 390 mg) and dimer **10** (0.5 mmol, 250 mg) were dissolved in dry chloroform (5 mL). DIPEA (2.01 mmol, 0.35 mL) and PyBOP (2.01 mmol, 1.05 g) were added at room temperature and the reaction mixture was heated at 45 °C for 24 hours. The solvent was removed under reduced pressure and the residue was purified by chromatography (SiO_2) eluting with EtOAc:cyclohexane (30:70 vol/vol) to obtain pentamer **16** as a yellow solid (62 %, 368 mg). ^1H NMR (300 MHz, $CDCl_3$) δ 12.03 (s, 1H), 11.85 (s, 1H), 9.82 (s, 1H), 9.62 (s, 1H), 9.21 (dd, *J* = 7.7, 1.3 Hz, 1H), 8.73 (d, *J* = 9.1 Hz, 1H), 8.57 (td, *J* = 7.8, 1.4 Hz, 2H), 8.47 (d, *J* = 9.1 Hz, 1H), 8.17 – 8.04 (m, 2H), 7.99 (s, 1H), 7.87 – 7.72 (m, 3H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.59 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.49 – 7.37 (m, 1H), 7.32 (s, 1H), 7.08 (s, 1H), 6.90 (dd, *J* = 8.4, 1.3 Hz, 1H), 6.46 (t, *J* = 8.0 Hz, 1H), 4.41 (t, *J* = 8.6 Hz, 2H), 4.25 (d, *J* = 6.5 Hz, 2H), 4.11 (d, *J* = 6.6 Hz, 4H), 4.00 (d, *J* = 6.5 Hz, 2H), 2.54 – 2.27 (m, 3H), 2.17 (dt, *J* = 13.5, 6.8 Hz, 1H), 1.39 – 1.12 (m, 20H), 1.08 (d, *J* = 6.6 Hz, 6H), 0.14 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.87, 163.38, 163.21, 162.99, 162.32, 161.35, 160.86, 154.38, 154.31, 154.12, 153.76, 153.20, 150.78, 149.55, 148.56, 147.65, 145.09, 139.76, 139.23, 139.06, 138.87, 134.93, 134.39, 134.16, 128.19, 128.01, 126.27, 125.90, 124.35, 123.51, 122.26, 122.18, 119.24, 117.50, 116.35, 115.30, 114.14, 113.22, 110.38, 108.56, 99.77, 99.58, 98.64, 97.71, 75.83, 75.62, 75.44, 75.32, 64.54, 28.25, 28.19, 28.06, 26.95, 19.38, 19.32, 19.31, 19.17, 17.85, -1.06, -1.40, -1.74. HRMS (ES^+): *m/z* calcd for $C_{66}H_{73}N_{12}O_{12}Si$ $[M+H]^+$: 1253.5235 found 1253.5268.



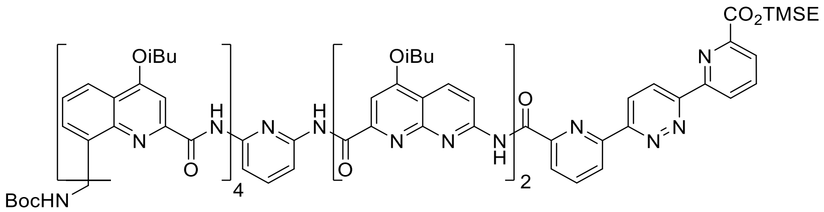
H_2N-Q_3PN-NHTeoc (17). To a solution of **16** (0.2 mmol, 250 mg) in EtOAc (2.4 mL) and MeOH (0.8 mL), 25 % Pd/C (62 mg) and NH_4VO_3 (31 mg) were added at room temperature. An aqueous solution of ammonium formate (750 mg in 0.8 mL of water) was added and the reaction mixture was stirred at 80 °C for 8 hours. After cooling down, the solution was filtered over celite. The filtrate was concentrated, and the residue was solubilized in CH_2Cl_2 and washed with water. The organic layer was dried over $MgSO_4$ and volatiles were removed under reduced pressure to yield pentamer **17** as a yellow solid (99 %, 0.244 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.17 (s, 1H), 12.07 (s, 1H), 9.77 (s, 1H), 9.49 (s, 1H), 9.06 (d, *J* = 6.7 Hz, 1H), 8.69 (d, *J* = 9.1 Hz, 1H), 8.55 (dd, *J* = 7.7, 1.3 Hz, 1H), 8.44 (d, *J* = 9.1 Hz, 1H), 8.11 – 7.99 (m, 2H), 7.88 – 7.63 (m, 6H), 7.49 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.16 (s, 1H), 7.07 – 6.93 (m, 2H), 6.79 (dd, *J* = 8.4, 1.3 Hz, 1H), 6.57 (t, *J* = 8.0 Hz, 1H), 5.90 (dd, *J* = 7.5, 1.3 Hz, 1H), 4.44 – 4.31 (m, 2H), 4.22 (d, *J* = 6.6 Hz, 2H), 4.08 – 3.86 (m, 8H), 2.36 (dq, *J* = 13.2, 6.5 Hz, 3H), 2.06 (dt, *J* = 13.4, 6.7 Hz, 1H), 1.29 – 1.07 (m, 20H), 1.01 (d, *J* = 6.7 Hz, 6H), 0.11 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.82, 163.19, 163.01, 162.78, 162.67, 161.84, 161.80, 160.14, 154.26, 154.16, 153.66, 153.20, 150.21, 148.95, 148.64, 148.38, 148.17, 143.35, 139.32, 138.48, 138.29, 136.26, 134.42, 134.32, 134.06, 127.27, 127.00, 126.63, 122.60, 121.94, 121.77, 117.10, 116.61, 115.79, 114.39, 114.08, 113.17, 109.53, 109.39, 108.63, 99.44, 98.54, 98.18, 97.92, 75.81, 75.36, 75.19, 74.81, 64.55, 28.28, 28.20, 28.14, 28.00, 19.45, 19.33, 19.32, 19.14, 17.97, -1.39. HRMS (ES$^+$): *m/z* calcd for $C_{66}H_{75}N_{12}O_{10}Si$ $[M+H]^+$: 1223.5493 found 1223.5531.



BocHN-Q^mQ_3PN-NHTeoc (18). Acid **8**[3] (0.156 mmol, 58 mg) was suspended in anhydrous $CHCl_3$ (3 mL). 1- chloro-N,N,2-trimethylpropenylamine (0.04 mL, 0.312 mmol) was added and the reaction was allowed to stir at room temperature for 3 h. The solvent and excess reagent were removed under vacuum and the residue was dried under vacuum for at least 1 h to yield acid chloride **9** as a white solid. To a solution of amine **16** (0.13 mmol, 160 mg) and distilled DIPEA (0.26 mmol, 0.05 mL) in dry $CHCl_3$ (1 mL) was added dropwise at 0 °C a solution of the freshly prepared acid chloride **9** in dry $CHCl_3$ (1 mL). The reaction was allowed to proceed at room temperature overnight. The solvents were removed under reduced pressure and the residue was purified by precipitation from minimum amount of MeOH to obtain hexamer **18** as a yellow solid (80 %, 173 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.20 (s, 1H), 11.69 (s, 1H), 11.48 (s, 1H), 9.74 (s, 1H), 9.53 (s, 1H), 8.72 – 8.56 (m, 3H), 8.39 (d, *J* = 9.0 Hz, 1H), 8.22 – 8.04 (m, 4H), 7.97 (d, *J* = 8.3 Hz, 1H), 7.88 – 7.62 (m, 4H), 7.45 (s, 1H), 7.39 – 7.26 (m, 5H), 7.14 (t, *J* = 7.7 Hz, 1H), 6.96 (s, 1H), 6.89 (s, 1H), 6.78 – 6.57 (m, 3H), 4.31 (dd, *J* = 17.5, 8.6 Hz, 4H), 4.22 – 4.05 (m, 5H), 3.99 (t, *J* = 6.3 Hz, 2H), 3.88 – 3.79 (m, 2H), 3.65 (t, *J* = 8.4 Hz, 1H), 3.49 (d, *J* = 4.9 Hz, 1H), 2.55 – 2.30 (m, 4H), 2.06 (dt, *J* = 12.9, 6.2 Hz, 1H), 1.26 (m, 21H), 1.09 (d, *J* = 8.9 Hz, 18H), 0.09 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.93, 163.70, 163.27, 162.92, 162.23, 162.02, 161.79, 161.08, 160.44, 155.46, 154.28, 153.58, 153.16, 150.85, 150.76, 149.62, 149.34, 148.66, 147.71, 144.88, 140.08, 138.20, 138.04, 137.92, 136.48, 134.28, 134.24, 133.74, 133.57, 127.55, 127.19, 127.03, 126.92, 125.89, 122.61, 122.33, 122.27, 121.74, 121.27, 118.19, 117.24, 116.75, 116.36, 116.27, 114.86, 114.12, 113.16, 110.05, 108.75, 99.13, 99.00, 98.76, 98.62, 98.15, 78.85, 75.90, 75.52, 75.41, 75.35, 64.56, 50.79, 40.27, 28.37, 28.35, 28.31, 28.23, 28.07, 19.51, 19.41, 19.35, 19.04, 17.91, 1.11, -1.40. HRMS (ES$^+$): *m/z* calcd for $C_{86}H_{99}N_{14}O_{14}Si$ $[M+H]^+$: 1579.7229 found 1579.7295.

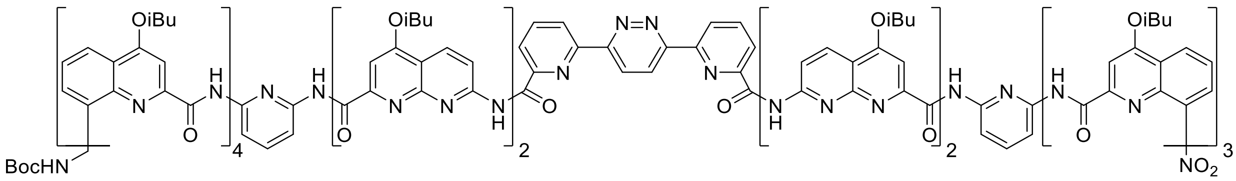


BocHN-Q^{m}Q$_3$PN-NH$_2$ (19). To a solution of hexamer **18** (0.108 mmol, 170 mg) in dry THF (1 mL) under nitrogen was added a solution 1 M of tetrabutylammonium fluoride in THF (1.0 mmol, 1 mL). The resulting mixture was stirred at room temperature for 4 hours. Volatiles were removed under reduced pressure to give a solid which was dissolved in EtOAc and washed distilled water (3 times) and then with brine. The organic layer was dried over $MgSO_4$, filtered, evaporated under reduce pressure and the residue was purified by precipitation from minimum amount of MeOH to give hexamer amine **19** as yellow solid (85 %, 135 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.19 (s, 1H), 11.69 (s, 1H), 11.44 (s, 1H), 8.59 (s, 2H), 8.13 (dt, *J* = 13.0, 6.9 Hz, 5H), 7.80 (dt, *J* = 16.1, 7.9 Hz, 2H), 7.71 – 7.56 (m, 2H), 6.99 (s, 1H), 6.62 (dd, *J* = 15.5, 6.8 Hz, 4H), 5.12 (s, 1H), 4.17 (s, 2H), 4.14 – 3.95 (m, 5H), 3.78 (s, 1H), 2.39 (ddq, *J* = 32.3, 13.3, 6.6 Hz, 4H), 1.98 (dt, *J* = 14.3, 6.0 Hz, 1H), 1.27 (m, 21H), 1.19 (d, *J* = 6.7 Hz, 6H), 1.10 (s, 9H), 1.01 (dd, *J* = 12.2, 6.5 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.78, 163.51, 163.29, 163.05, 162.75, 162.41, 162.00, 161.76, 160.60, 160.38, 160.08, 155.46, 155.32, 151.14, 150.86, 150.41, 149.71, 149.10, 148.83, 147.72, 144.64, 140.33, 138.15, 137.99, 137.74, 136.19, 133.77, 133.67, 133.57, 131.82, 127.25, 126.99, 126.40, 125.68, 122.34, 122.19, 121.73, 120.98, 118.21, 116.84, 116.49, 116.25, 116.20, 115.35, 112.20, 110.24, 109.53, 108.62, 99.00, 98.69, 98.30, 96.57, 78.65, 75.43, 75.19, 74.72, 40.14, 29.72, 28.31, 28.28, 28.25, 28.15, 28.12, 27.80, 19.46, 19.40, 19.24, 19.11, 18.54. HRMS (ES$^+$): *m/z* calcd for $C_{80}H_{87}N_{14}O_{12}$ [M+H]$^+$: 1435.6622 found 1535.6682.

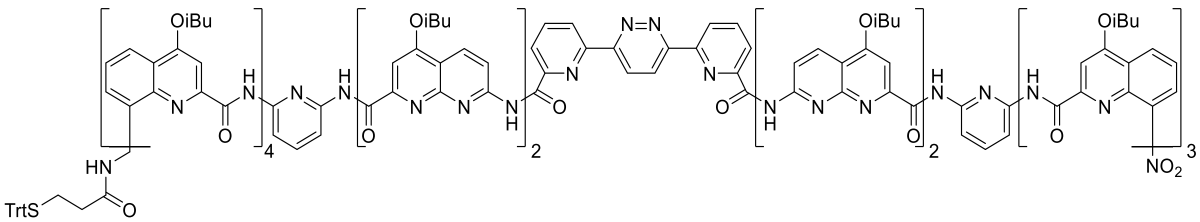


BocHN-Q^{m}Q$_3$PN$_2$PyrPyzPyr-CO$_2$TMSE (20). Hexamer amine **19** (0.081 mmol, 120 mg) and acid **10**[4] (0.081 mmol, 54 mg) were dissolved in dry chloroform (2 mL). DIPEA (0.32 mmol, 0.06 mL) and PyBOP (0.32 mmol, 169 mg) were added at room temperature and the reaction mixture was heated at 50 °C for 24 hours. The solvent was removed under reduced pressure and the residue was purified by recycling GPC to obtain oligomer **20** as a yellow solid (78 %, 132 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.96 (s, 1H), 11.48 (s, 1H), 11.13 (s, 1H), 10.78 (s, 1H), 10.55 (s, 1H), 10.27 (s, 1H), 9.08 (s, 1H), 9.01 – 8.64 (m, 6H), 8.56 – 8.42 (m, 2H), 8.42 – 8.25 (m, 2H), 8.22 – 8.07 (m, 2H), 8.04 – 7.75 (m, 9H), 7.69 (t, *J* = 8.0 Hz, 1H), 7.21 (dd, *J* = 8.0, 3.5 Hz, 3H), 7.01 – 6.78 (m, 7H), 6.73 (s, 1H), 6.53 (d, *J* = 6.9 Hz, 1H), 4.40 – 3.79 (m, 14H), 3.70 – 3.55 (m, 2H), 3.20 – 3.08 (m, 1H), 3.08 – 2.89 (m, 3H), 2.57 – 2.26 (m, 6H), 1.38 – 1.08 (m, 25H), 1.04 (s, 9H), 0.94 – 0.67 (m, 6H), 0.57 (d, *J* = 6.7 Hz, 3H), -0.33 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.66, 164.43, 164.01, 163.58, 163.36, 162.81, 162.77, 162.59, 162.17, 161.78, 161.44, 161.27, 161.15, 159.27, 156.77, 155.51, 155.37, 154.94, 154.76, 154.48, 153.96, 153.74, 152.50, 152.42, 152.27, 150.94, 150.26, 149.88, 149.38, 148.65, 148.35, 147.91, 147.13, 144.66, 140.16, 138.17, 137.75, 137.30, 136.37, 134.66, 134.43, 134.19, 133.64, 133.46, 127.29, 127.12, 126.92, 126.48, 125.99, 125.82, 125.60, 125.07, 123.85, 123.69, 122.18, 122.10, 121.09, 117.97, 117.26, 116.37, 116.18, 115.83, 115.27, 114.95, 114.55, 109.43, 108.33, 100.36, 98.85, 98.56, 98.36, 78.74, 76.04, 75.61, 75.27, 75.11, 74.89, 63.77, 53.56, 45.92, 40.17, 29.84, 28.39, 28.31, 28.22, 28.12, 27.98, 19.68, 19.61, 19.54, 19.43, 19.37, 18.67, 17.40, 8.96, 1.16, -1.84. HRMS (ES$^+$): *m/z* calcd for $C_{114}H_{120}N_{21}O_{17}Si$ [M+H]$^+$: 2082.8935 found 2082.9019.

BocHN-Q^m^Q$_3$PN$_2$PyrPyzPyr-CO$_2$H (21). To a solution of oligomer **20** (0.05 mmol, 100 mg) in dry THF (0.5 mL) under nitrogen was added a solution 1 M of tetrabutylammonium fluoride in THF (0.5 mmol, 0.5 mL). The resulting mixture was stirred at room temperature for 16 hours. Volatiles were removed under reduced pressure to give a solid which was dissolved in EtOAc and washed with a 5 % aqueous citric acid solution, distilled water (3 times), and then with brine. The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to yield product **21** which was used without any further purification. HRMS (ES$^+$): *m/z* calcd for $C_{109}H_{108}N_{21}O_{17}$ [M+H]$^+$: 1982.8227 found 1982.8309.



BocHN-Q^m^Q$_3$PN$_2$PyrPyzPyrN$_2$PQ$_3$-NO$_2$ (22). Previous oligomer acid **21** (0.038 mmol, 76 mg) and hexamer amine **10**[5] (0.38 mmol, 52 mg) were dissolved in dry chloroform (1 mL). DIPEA (0.15 mmol, 0.03 mL) and PyBOP (0.15 mmol, 80 mg) were added at room temperature and the reaction mixture was heated at 50 °C for 24 hours. The solvent was removed under reduced pressure and the residue was purified by recycling GPC to obtain oligomer **22** as a yellow solid (78 %, 99 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.62 (s, 1H), 11.43 (s, 1H), 11.23 (s, 1H), 10.96 (s, 1H), 10.51 (s, 1H), 10.43 (s, 1H), 10.37 (s, 1H), 10.00 (s, 1H), 9.86 (s, 1H), 9.85 (s, 1H), 9.64 (s, 1H), 8.90 – 8.77 (m, 2H), 8.73 – 8.49 (m, 5H), 8.42 (d, *J* = 7.3 Hz, 1H), 8.32 – 7.99 (m, 9H), 7.88 (ddd, *J* = 11.3, 7.4, 4.3 Hz, 4H), 7.71 (dd, *J* = 12.2, 8.3 Hz, 3H), 7.62 – 7.27 (m, 7H), 7.24 – 7.10 (m, 5H), 7.10 – 7.01 (m, 4H), 6.81 – 6.49 (m, 9H), 6.48 – 6.24 (m, 4H), 6.09 (s, 1H), 5.94 (t, *J* = 8.0 Hz, 1H), 5.80 (t, *J* = 7.9 Hz, 1H), 4.07 (d, *J* = 7.3 Hz, 6H), 3.93 (dq, *J* = 14.3, 6.4 Hz, 6H), 3.74 (ddd, *J* = 21.7, 13.6, 7.7 Hz, 7H), 3.24 (s, 1H), 2.96 – 2.71 (m, 2H), 2.60 – 2.35 (m, 8H), 2.35 – 2.14 (m, 5H), 1.38 – 1.21 (m, 38H), 1.21 – 0.96 (m, 19H), 0.92 (s, 9H), 0.71 (d, *J* = 6.6 Hz, 3H), 0.52 (dd, *J* = 13.0, 6.6 Hz, 6H), 0.41 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.70, 163.60, 163.08, 163.03, 162.88, 162.68, 162.57, 162.37, 162.27, 162.12, 161.99, 161.94, 161.42, 161.21, 160.82, 160.61, 160.52, 160.48, 159.49, 159.05, 155.16, 154.78, 154.51, 154.47, 154.12, 153.75, 153.65, 153.59, 153.47, 153.01, 152.82, 151.79, 151.65, 151.29, 151.15, 150.80, 150.74, 150.58, 150.50, 149.94, 149.64, 149.00, 148.89, 148.13, 147.98, 147.87, 147.61, 146.72, 146.38, 144.44, 144.26, 139.45, 139.27, 138.66, 138.45, 137.81, 137.73, 137.49, 137.38, 137.33, 136.93, 136.09, 134.46, 134.10, 134.00, 133.82, 133.66, 133.52, 133.40, 133.36, 127.77, 127.04, 126.58, 125.97, 125.72, 125.38, 125.04, 124.38, 124.13, 123.92, 123.59, 123.22, 123.09, 122.11, 121.96, 121.76, 121.56, 121.50, 121.43, 120.67, 117.79, 117.09, 116.25, 115.99, 115.78, 115.63, 115.45, 114.55, 114.46, 114.33, 114.20, 113.97, 113.52, 113.40, 109.14, 108.94, 107.52, 107.15, 100.82, 99.64, 98.82, 98.35, 98.27, 97.52, 96.69, 96.55, 96.47, 78.37, 75.75, 75.58, 75.17, 75.08, 74.96, 74.84, 74.22, 39.80, 29.70, 28.37, 28.33, 28.27, 28.21, 28.15, 28.12, 28.04, 28.00, 27.87, 27.57, 27.48, 19.53, 19.46, 19.42, 19.36, 19.28, 19.23, 19.23, 19.14, 19.07, 18.55, 18.38, 1.06. HRMS (ES$^+$): *m/z* calcd for $C_{182}H_{180}N_{36}O_{28}$ [M+2H]$^{2+}$: 1658.6879 found 1658.7002.



H_2N-Q^{m}Q$_3$PN$_2$PyrPyzPyrN$_2$PQ$_3$-NO_2 (23). Trifluoroacetic acid (0.4 mL) was added dropwise to a solution of **22** (0.028 mmol, 95 mg) in 1 mL of chloroform under nitrogen at room temperature. The resulting mixture was stirred at room temperature for 18 hours. Volatiles were removed under reduced pressure to give a solid which was dissolved in dichloromethane and washed with a saturated aqueous solution of $NaHCO_3$, distilled water and then with brine. The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to yield product **23** which was used without any further purification.

TrtS(CH_2)$_2$COHN-Q^{m}Q$_3$PN$_2$PyrPyzPyrN$_2$PQ$_3$-NO_2 (24). Previous oligomer acid **23** (0.028 mmol, 90 mg) and 3-(tritylthio)propionic acid (0.084 mmol, 30 mg) were dissolved in dry chloroform (1 mL). DIPEA (0.084 mmol, 0.015 mL) and PyBOP (0.084 mmol, 45 mg) were added at room temperature and the reaction mixture was heated at 50 °C for 24 hours. The solvent was removed under reduced pressure and the residue was purified by recycling GPC to obtain oligomer **24** as a yellow solid (90 %, 91 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.62 (s, 1H), 11.42 (s, 1H), 11.20 (s, 1H), 10.96 (s, 1H), 10.49 (s, 1H), 10.43 (s, 1H), 10.37 (s, 1H), 10.00 (s, 1H), 9.84 (s, 2H), 9.61 (s, 1H), 8.90 – 8.75 (m, 2H), 8.72 – 8.49 (m, 5H), 8.42 (dd, *J* = 7.8, 1.3 Hz, 1H), 8.32 – 8.06 (m, 8H), 8.00 (d, *J* = 6.9 Hz, 1H), 7.95 – 7.78 (m, 4H), 7.76 – 7.64 (m, 3H), 7.63 – 7.27 (m, 7H), 7.24 – 7.01 (m, 15H), 7.01 – 6.90 (m, 7H), 6.78 (s, 1H), 6.75 – 6.59 (m, 6H), 6.53 (t, *J* = 3.9 Hz, 2H), 6.44 (dd, *J* = 8.2, 1.3 Hz, 1H), 6.39 (s, 1H), 6.35 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.19 (d, *J* = 6.8 Hz, 1H), 6.09 (s, 1H), 5.85 (dt, *J* = 29.2, 7.9 Hz, 2H), 4.11 (dt, *J* = 15.4, 7.5 Hz, 6H), 3.97 (dt, *J* = 14.8, 7.1 Hz, 5H), 3.91 – 3.64 (m, 8H), 3.54 (t, *J* = 6.3 Hz, 1H), 3.17 (dd, *J* = 16.0, 5.9 Hz, 1H), 2.77 (t, *J* = 8.8 Hz, 1H), 2.57 – 2.36 (m, 7H), 2.35 – 2.15 (m, 4H), 2.06 – 1.78 (m, 3H), 1.38 – 1.20 (m, 44H), 1.14 (ddd, *J* = 10.7, 8.9, 6.7 Hz, 13H), 1.02 (t, *J* = 7.1 Hz, 6H), 0.66 (d, *J* = 6.6 Hz, 3H), 0.55 (d, *J* = 6.6 Hz, 3H), 0.48 (d, *J* = 6.7 Hz, 3H), 0.41 (d, *J* = 6.7 Hz, 3H), 0.07 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.02, 163.72, 163.63, 163.11, 163.04, 162.94, 162.66, 162.62, 162.52, 162.38, 162.29, 162.15, 162.00, 161.44, 161.22, 161.09, 160.82, 160.52, 160.44, 159.45, 159.02, 154.76, 154.47, 154.11, 153.82, 153.66, 153.53, 153.50, 153.03, 152.87, 151.82, 151.67, 151.26, 151.13, 150.82, 150.72, 150.56, 150.37, 149.92, 149.86, 149.01, 148.91, 148.17, 148.00, 147.85, 147.57, 146.70, 146.39, 144.50, 144.45, 144.08, 139.49, 139.28, 138.67, 138.44, 137.81, 137.67, 137.42, 136.90, 135.06, 134.44, 134.25, 134.09, 133.86, 133.68, 133.61, 133.51, 133.32, 133.24, 130.94, 129.32, 128.85, 127.79, 127.66, 127.05, 126.60, 126.39, 125.99, 125.76, 125.58, 125.34, 125.06, 124.41, 124.14, 123.94, 123.63, 123.48, 123.28, 123.10, 122.14, 121.92, 121.78, 121.63, 121.52, 121.45, 120.63, 117.83, 117.12, 116.39, 116.04, 115.99, 115.78, 115.49, 115.29, 114.52, 114.38, 114.18, 113.99, 113.52, 113.41, 109.19, 109.00, 107.53, 107.14, 100.87, 99.82, 98.83, 98.32, 97.52, 96.69, 96.55, 96.48, 75.76, 75.64, 75.58, 75.20, 75.11, 75.00, 74.82, 74.27, 66.36, 45.77, 38.64, 36.47, 34.71, 29.72, 28.40, 28.35, 28.29, 28.22, 28.16, 28.05, 27.85, 27.56, 27.50, 26.92, 19.55, 19.49, 19.43, 19.38, 19.30, 19.25, 19.19, 19.15, 19.08, 18.56, 18.40, 14.17, 8.61, 1.06. HRMS (ES$^+$): *m/z* calcd for $C_{199}H_{190}N_{36}O_{27}S$ $[M+2H]^{2+}$: 1773.7156 found 1773.7285.

2. Materials and Methods for NMR, ellipsometry, PM-IRRAS, C-AFM

Nuclear Magnetic Resonance NMR spectra were recorded on 4 different NMR spectrometers: (1) an Avance II NMR spectrometer (Bruker Biospin) with a vertical 7.05T narrow-bore/ultrashield magnet operating at 300 MHz for ^{1}H observation, 282 MHz for ^{19}F observation and 75 MHz for ^{13}C observation by means of a 5-mm direct BBO H/X probe with Z gradient capabilities; (2) an Avance 400 NMR spectrometer (Bruker Biospin) with a vertical 9.4T narrow-bore/ultrashield magnet operating at 400 MHz for ^{1}H observation by means of a 5-mm direct QNP ^{1}H/^{13}C/^{31}P/^{19}F probe with gradient capabilities; (3) an Avance III NMR spectrometer (Bruker Biospin) with a vertical 16.45T narrow-bore/ultrashield magnet operating at 700 MHz for ^{1}H observation by means of a 5-mm TXI ^{1}H/^{13}C/^{15}N probe with Z gradient capabilities. (4) an Avance III NMR spectrometer (Bruker Biospin) with a Standard Bore Cryo Probe operating at 800 MHz for ^{1}H observation by means of a 5-mm TCI ^{1}H/^{13}C/^{15}N probe with Z gradient capabilities. Chemical shifts are reported in parts per million (ppm, δ) with tetramethylsilane as an internal standard. ^{1}H NMR splitting patterns with observed first-order coupling are designated as singlet (s), doublet (d), triplet (t), or quartet (q). Coupling constants (J) are reported in hertz. Data processing was performed with Topspin 3.5 software. Samples were not degassed. $CDCl_3$ from Aldrich was used after filtration through an alumina pad.

NMR titrations. Titrations were performed in an NMR tube at 298.2 ± 0.1 K by adding aliquots of the stock solution of the guest by means of a Hamilton syringe to 0.500 mL solution of the capsule. After homogenization and equilibration NMR spectra were recorded. When free and bound receptor could be observed simultaneously (slow exchange), binding constants (K_a) were obtained by integration of signals. Values were obtained from several spectra and the results averaged. In the case where fast exchange was found, the data was fit using the HypNMR software.[6]

Monolayer preparation. All glassware employed for monolayer preparation was cleaned with hot piranha, (conc. H_2SO_4-H_2O_2 3:1, **warning**: piranha should be handled with caution; it reacts strongly in contact with organic compounds). Preparation of monolayers by *in situ* trityl deprotection were carried out as reported with some modifications.[7] Briefly, the corresponding trityl-protected derivative **23** was dissolved in an excess of trifluoroacetic acid (TFA) (1-3 mg in 80 µL TFA) to give a deep-yellow solution, and triethylsilane (5-10 µL) was added until the solution became faintly yellow. Then the solution was incubated for 30 min. The solution was evaporated under reduced pressure and dried in the vaccum line for 2h. The residue (sequence **2**) was dissolved in degassed EtOH-$CHCl_3$ 1:1 to a concentration of 1 mM. Gold substrates (300 nm Au on mica, Georg Albert PVD – Beschichtungen, Germany) were immersed in the solution and sealed after backfilling with Ar. The substrates were incubated 72 h at room temperature. Afterwards, the substrates were rinsed with $CHCl_3$ and dried with a stream of dry Ar.

Substrates for PM-IRRAS analysis were prepared by carrying out the same deprotection protocol and diluting the derivative to 0.1 mM solutions. Prior to immersion, gold substrate squares of ca 2.5 cm sides (200 nm Au on glass, Ssens, Netherlands) were cleaned in piranha solution (see warning above), thoroughly rinsed with milliQ water and immersed in EtOH for 20 min. After incubation (72 h at rt), the samples were rinsed with $CHCl_3$ and dried with a stream of dry Ar.

Ellipsometry. Ellipsometry measurements were carried out in a EP3 null-ellipsometer (Nanofilm, Germany) and analyzed with the software (EP4Model 1.0.1) provided with the instrument. The instrument was used in total internal reflection mode and both the intensity and the phase changes of the reflected light were monitored and converted into the ellipsometric angles Ψ and Δ. A wavelength range from 370 to 720 nm was scanned at a constant angle of incidence of 70 ºC. Film thickness was determined by fitting the ellipsometric angles to a built-up model of gold-organic-air. The optical parameters of the gold layer were obtained experimentally by measuring a bare gold substrate. The organic layer was modeled using a Cauchy model assuming a refractive index of 1.4. Results are expressed as the average and standard deviation of three independent monolayer preparations.

IR measurements. Infrared spectra of capsule **1** in absence and in presence of **5** were recorded with a ThermoNicolet Nexus 670 FTIR spectrometer at a resolution of 4 cm^{-1}, by coadding 50 scans. Samples were held in a 250 µm path length cell with BaF_2 windows. Concentration of capsule **1** was fixed at 2mM in $CDCl_3$ solution. Spectrum of **1**⊃**5** was measured in a 1:5 molar ratio. All infrared spectra were shown with solvent absorption subtracted out.

PM-IRRAS. PM-IRRAS spectra of capsule **2** in absence and in presence of **5** were recorded using a ThermoNicolet Nexus 670 FTIR spectrometer at a resolution of 4 cm^{-1} by co-adding several blocks of 1500 scans (30 min acquisition time). Generally, eight blocks (4 h acquisition time) were necessary to obtain PM-IRRAS spectra of SAMs with good signal-to-noise ratios. Experiments were performed at an incidence angle of 75º by using an external homemade goniometer reflection attachment and adding a ZnSe photoelastic modulator (PEM, Hinds Instruments, type III) after the polarizer[8,9] PM-IRRAS spectra are presented in terms of the IRRAS unit (i.e. 1-[Rp(d)/Rp(0)], where Rp(d) and Rp(0) stand for the p-polarized reflectance of the film/substrate and bare substrate systems, respectively) by using a calibration procedure.[9,10]

Conducting AFM. I-V curves were collected in air with a Dimension Icon AFM (Bruker) in PeakForce TUNA mode using PFTUNA tips (Bruker, platinum/iridium tip, nominal parameters: radius, 25 nm; spring constant, 0.4 N/m,). Substrates were grounded with a metal wire in contact with the gold surface. The tip spring constant was calibrated in order to calculate the applied force. Junctions were established at gentle tip pressures by defining 9 points distributed in a ca 2500 nm^2 area using the instrument's “point-and-shoot” feature. Forward and reverse currents were measured by triplicate in each point. Data was collected from several different areas on the sample and at different tip pressures. The same tip was employed to measure different monolayers to avoid differences arising from variable tip diameter. Comparative experiments were repeated with different tips.

Crystallography. The X-ray diffraction measurement was carried out at the ESRF on the tunable beamline FIP BM30A at a wavelength of 0.72 Å suitable for atomic resolution data collection considering the sample to detector distances accessible. The XDS package[11] was used to index and integrate data. The structure was solved with Shelxd[12] and refined by full-matrix least-squares method on F^2 with Shelxl-2016[11]. The Olex2 suite[13] was used for model building, only non-H atoms were refined with anisotropic displacement parameters. 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, CH2, NH). For the tetrafluorosuccinic acid ligands the H atoms for the carboxylic acid groups were positioned at the most probable site considering the observed C-O bond lengths. This was performed on only one of the two independent molecules of the asymmetric unit. In the second molecule, atomic displacement parameters were too high for accurate positioning of the protons. DFIX, AFIX, RIGU and EADP restraints and constraints were apply to model geometry of the molecules and thermal motion parameters mainly for isobutoxy side chains. Due to the large disorder solvent content the SQUEEZE[14] procedure was used to flattened the electron density map. A number of A-level and B-level alerts inherent to the data and refinement procedures of foldamers were detected using IUCR’s checkcif algorithm. The A-Alerts listed below do not reflect errors 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:

SHFSU01_ALERT_2_A The absolute value of parameter shift to su ratio > 0.20 Absolute value of the parameter shift to su ratio given 3.557 Additional refinement cycles may be required.THETM01_ALERT_3_A The value of sine(theta_max)/wavelength is less than 0.550 Calculated sin(theta_max)/wavelength = 0.4762PLAT080_ALERT_2_A Maximum Shift/Error .... 3.56 Why ?

Group 2 alerts is connected with decision made during refinement :

PLAT213_ALERT_2_A Atom N233 has ADP max/min Ratio ..... 5.4 prolat

PLAT213_ALERT_2_A Atom C77 has ADP max/min Ratio ..... 7.1 prolat

PLAT213_ALERT_2_A Atom C371 has ADP max/min Ratio ..... 6.2 prolat

PLAT213_ALERT_2_A Atom C460 has ADP max/min Ratio ..... 5.5 prolat

PLAT213_ALERT_2_A Atom C207 has ADP max/min Ratio ..... 5.2 prolat

PLAT213_ALERT_2_A Atom C250 has ADP max/min Ratio ..... 14.0 oblate

PLAT213_ALERT_2_A Atom C417 has ADP max/min Ratio ..... 8.1 oblate

PLAT242_ALERT_2_A Low 'MainMol' Ueq as Compared to Neighbors of C434 Check

PLAT413_ALERT_2_A Short Inter XH3 .. XHn H11C ..H46K . 1.80 Ang.

1-x,1-y,-z = 3_665 Check PLAT934_ALERT_3_A Number of (Iobs-Icalc)/Sigma(W) > 10 Outliers .. 17 Check

3. Solution studies

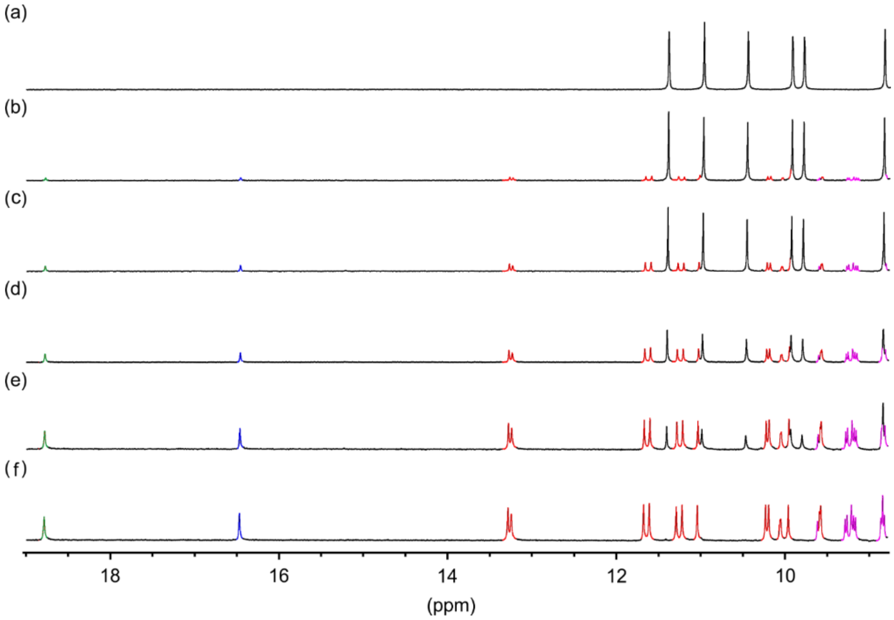


Fig. S1 Excerpts of the 400 MHz ^{1}H NMR spectra of capsule **1** at 1 mM in $CDCl_3$/MeCN-d3 (9:1 vol/vol) at 298 K in the presence of: (a) 0 equiv.; (b) 0.25 equiv.; (c) 0.5 equiv.; (d) 1.0 equiv.; (e) 1.5 equiv.; (f) 2.0 equiv. of tetrafluorosuccinic acid (**4**). Peaks in black correspond to amide proton resonances of the empty host: in red and pink are the amide proton and aromatic proton resonances of the complex, respectively; in green and blue are the proton resonances of the guest. K_a = 4450 M^{-1}.

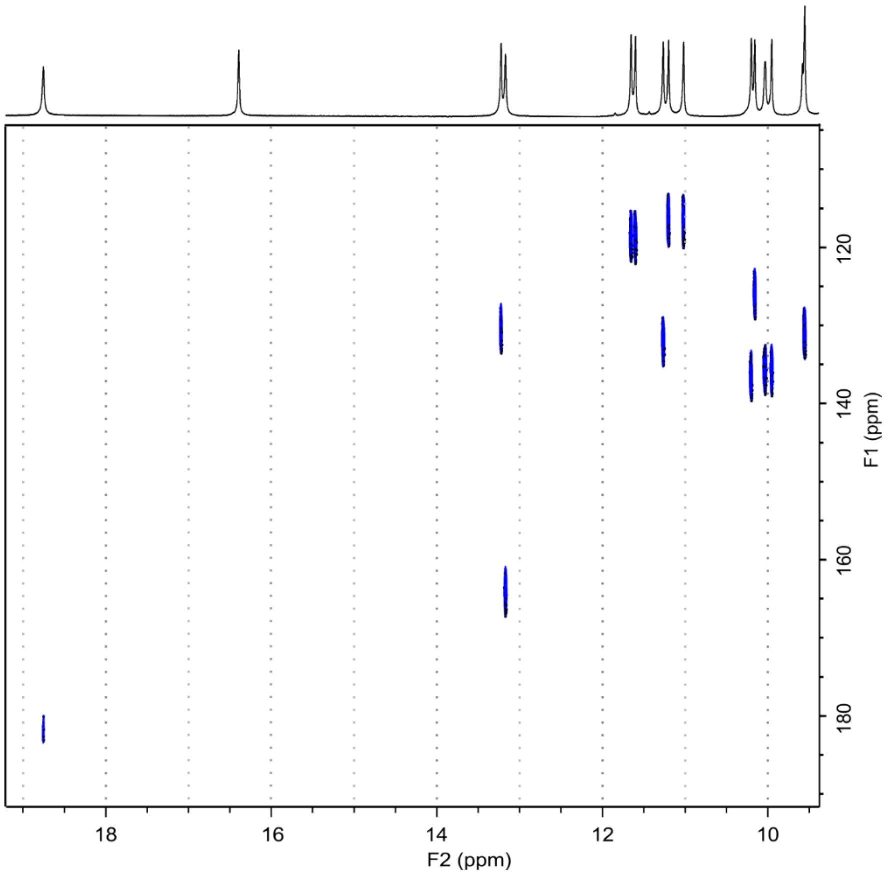


Fig. S2 (a) Part of the ^{1}H-^{15}N HSQC NMR spectrum (400 MHz) of capsule **1** at 6 mM in $CDCl_3$/MeCN-d3 (9:1 vol/vol) in the presence of 2.0 equiv. of tetrafluorosuccinic acid (**4**) at 298 K.

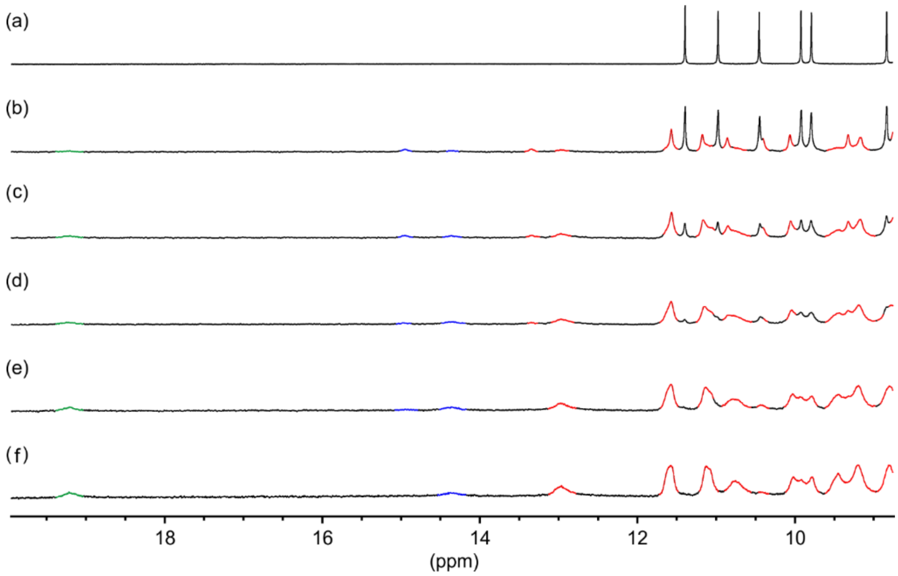


Fig. S3 Excerpts of the 400 MHz ^{1}H NMR spectra of capsule **1** at 1 mM in $CDCl_3$/MeCN-d_3 (9:1 vol/vol) at 298 K in the presence of: (a) 0 equiv.; (b) 1.0 equiv.; (c) 2.0 equiv.; (d) 3.0 equiv.; (e) 4.0 equiv.; (f) 5.0 equiv. of 2,2-difluorosuccinic acid (**5**). Resonances in black correspond to empty host amide protons: in red are the amide proton resonances of the complex; in green and blue are the proton resonances of the guest. K_a = 2100 M^{-1}.

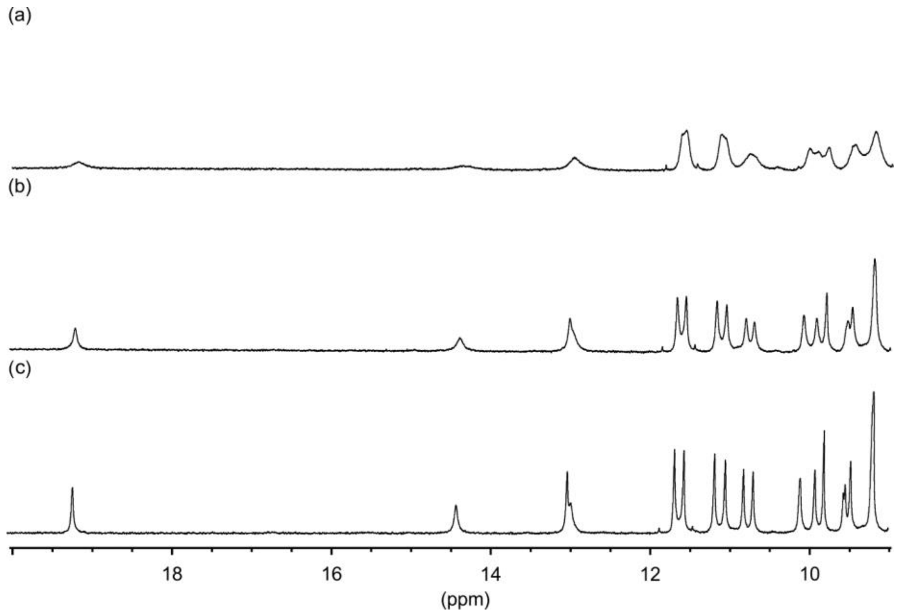


Fig. S4 Excerpts of the 400 MHz ^{1}H NMR spectra of capsule **1** at 2 mM in $CDCl_3$/MeCN-d3 (9:1 vol/vol) in the presence of 5.0 equiv. of 2,2-difluorosuccinic acid **5** at (a) 298 K; (b) 283 K and 273K.

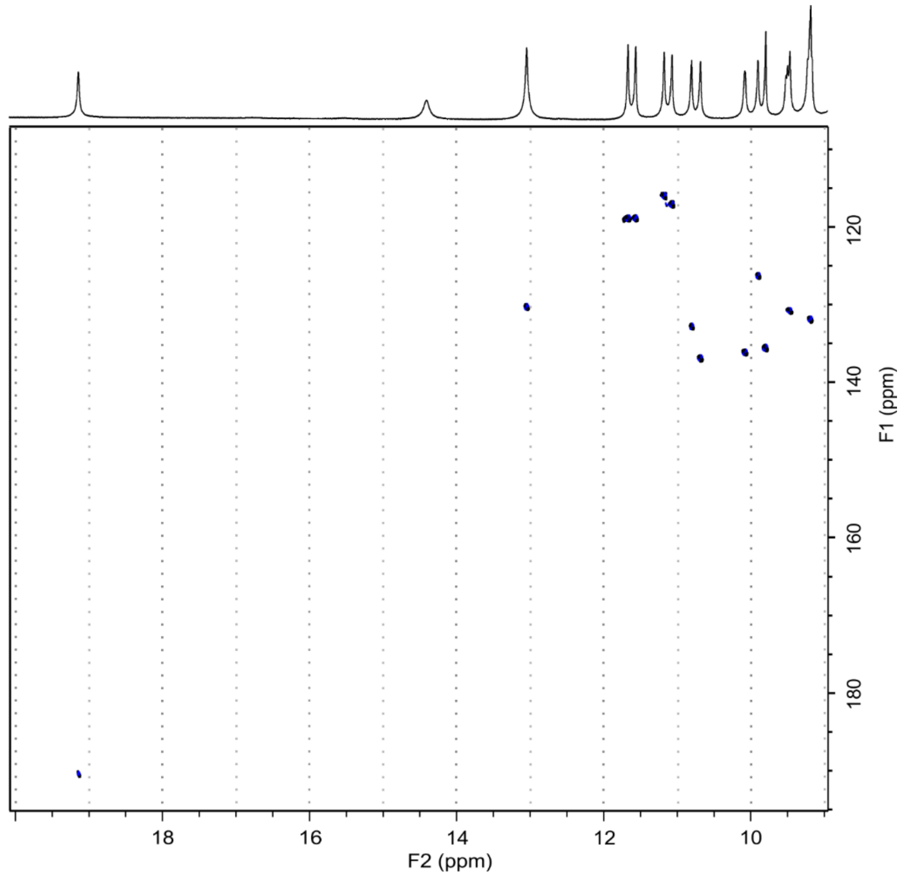


Fig. S5 (a) Part of the ^{1}H-^{15}N HSQC NMR spectrum (400 MHz) of capsule **1** at 6 mM in $CDCl_3$/MeCN-d3 (9:1 vol/vol) in the presence of 5.0 equiv. of 2,2-difluorosuccinic acid (**5**) at 273K.

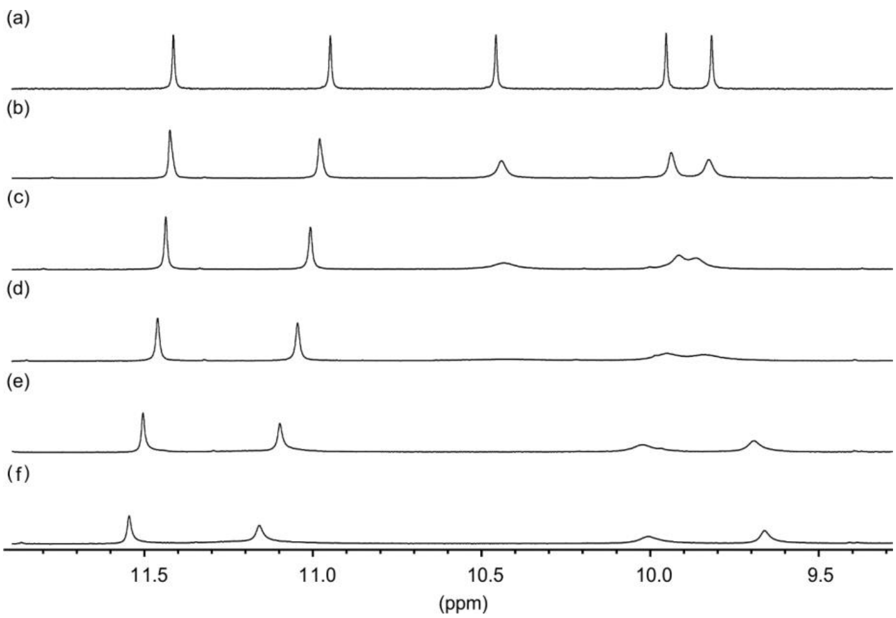


Fig. S6 Excerpts of the 400 MHz ^{1}H NMR spectra of capsule **1** at 2 mM in $CDCl_3$ at 298 K in the presence of: (a) 0 equiv.; (b) 1.0 equiv.; (c) 2.0 equiv.; (d) 4.0 equiv.; (e) 8.0 equiv.; (f) 20.0 equiv. of trifluoroacetic acid.

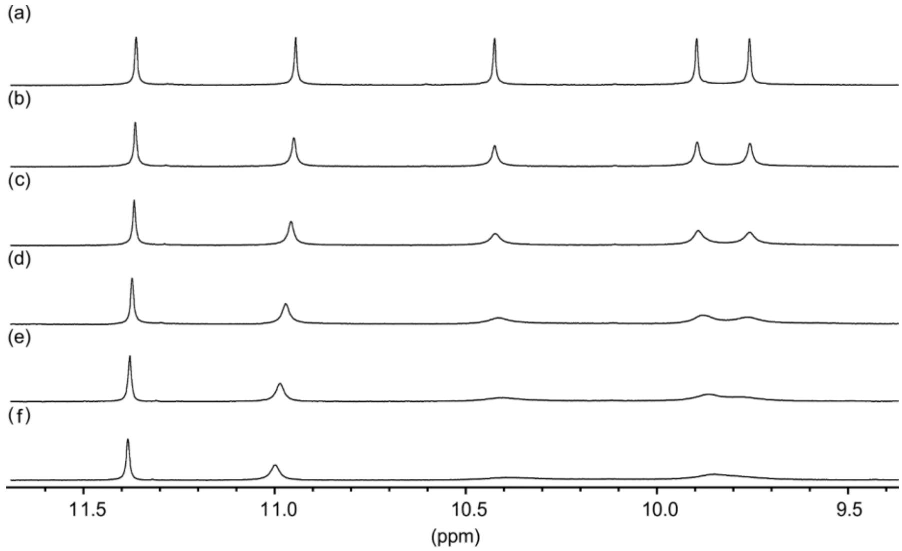


Fig. S7 Excerpts of the 400 MHz ^{1}H NMR spectra of capsule **1** at 2 mM in $CDCl_3$/MeCN-d3 (9:1 vol/vol) at 298 K in the presence of: (a) 0 equiv.; (b) 0.25 equiv.; (c) 0.5 equiv.; (d) 1.0 equiv.; (e) 1.5 equiv.; (f) 2.0 equiv. of hexadecafluorodecanedioic acid.

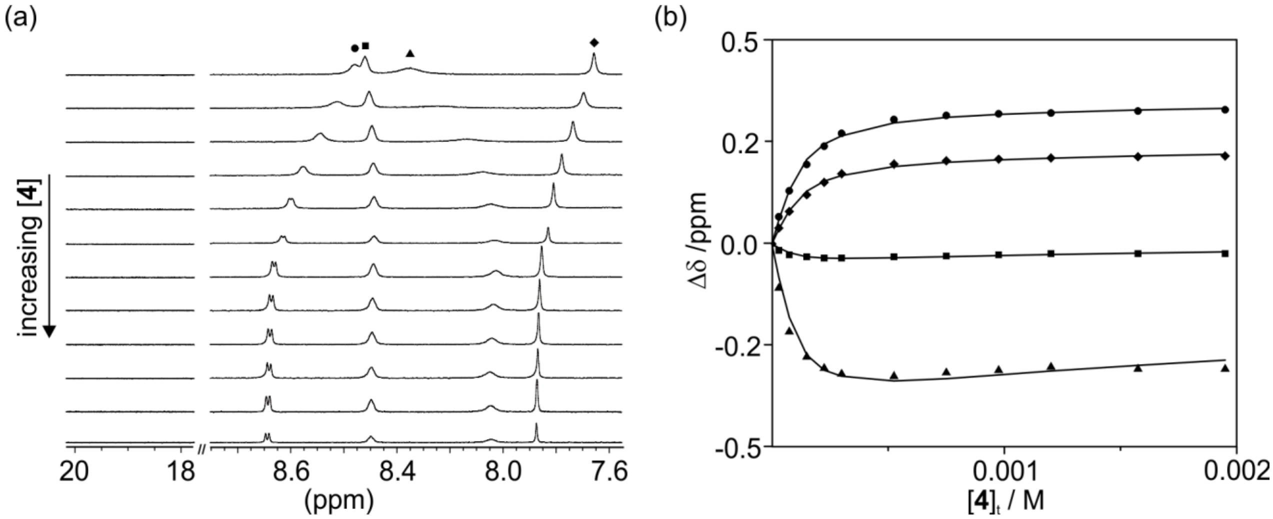


Fig. S8 Titration of **6** with **4** at 0.5 mM in $CDCl_3$/MeCN-d_3 (9:1 vol/vol) at 298 K: excerpts of the 700 MHz ^{1}H NMR spectra of **6** in the presence of increasing amounts of **4** (a) and corresponding fit of the data to a model containing 1:1 and 2:1 H:G complexes. K_a(1:1) = 2140 M^{-1}; K_a(2:1) = 14800 M^{-1}. The apparent positive cooperativity may be due to the likely dimerization of the acidic guest which was not considered in the model. K_a(2:1) may thus be overestimated. One can note that no resonance can be observed in the18-20 ppm region that would correspond to a naphthyridinium proton.

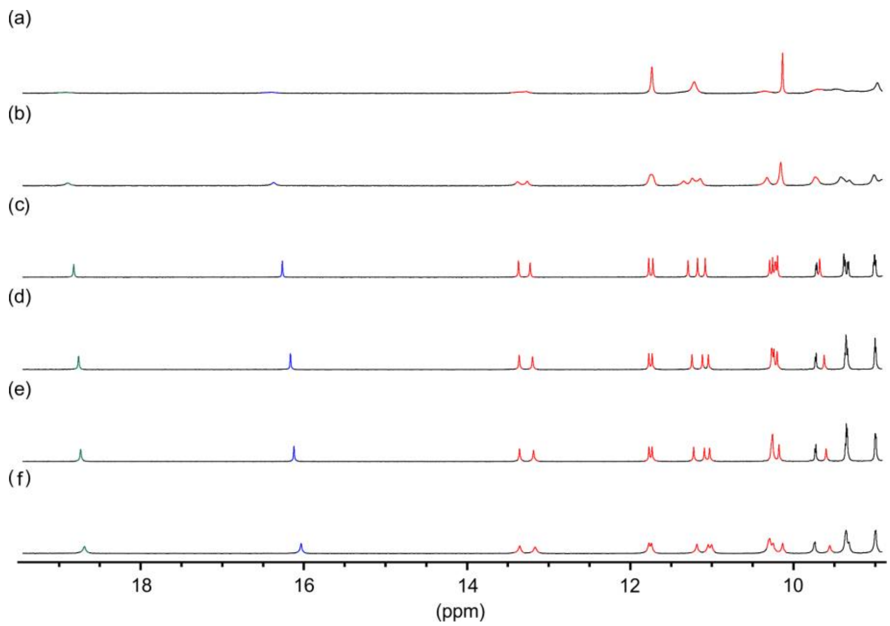


Fig. S9 Excerpts of the 400 MHz ^{1}H NMR spectra of capsule **1** at 2 mM in $C_2D_2Cl_4$/MeCN-d_3 (9:1 vol/vol) in the presence of 5.0 equiv. of tetrafluorosuccinic acid (**4**) at (a) 343 K; (b) 333 K; (c) 298K; (d) 273 K; (e) 263 K and (f) 243 K. Signals in green correspond to the proton resonance of the naphthyridinium proton; in blue to the proton resonance of monoprotonated guest **4**; and peaks in red and black to amide and aromatic proton resonances of the complex, respectively.

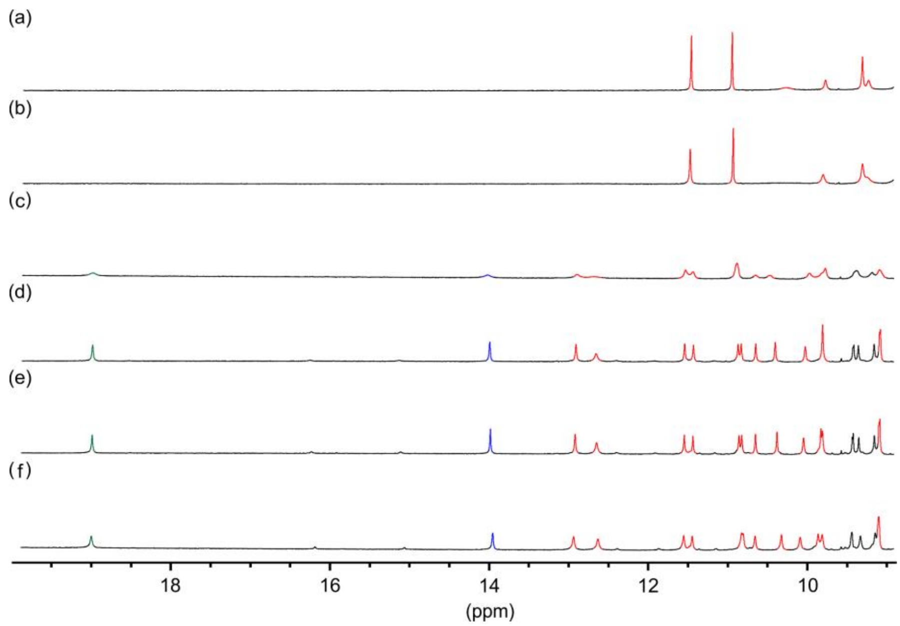


Fig. S10 Excerpts of the 400 MHz ^{1}H NMR spectra of capsule **1** at 2 mM in $C_2D_2Cl_4$/MeCN-d_3 (9:1 vol/vol) in the presence of 5.0 equiv. of 2,2-difluorosuccinic acid (**5**) at (a) 343 K; (b) 333 K; (c) 298K; (d) 273 K; (e) 263 K and (f) 243 K. Signals in green correspond to the proton resonance of the naphthyridinium proton; in blue to the proton resonance of monoprotonated guest **5**; and signals in red and black to amide and aromatic proton resonances of the complex, respectively.

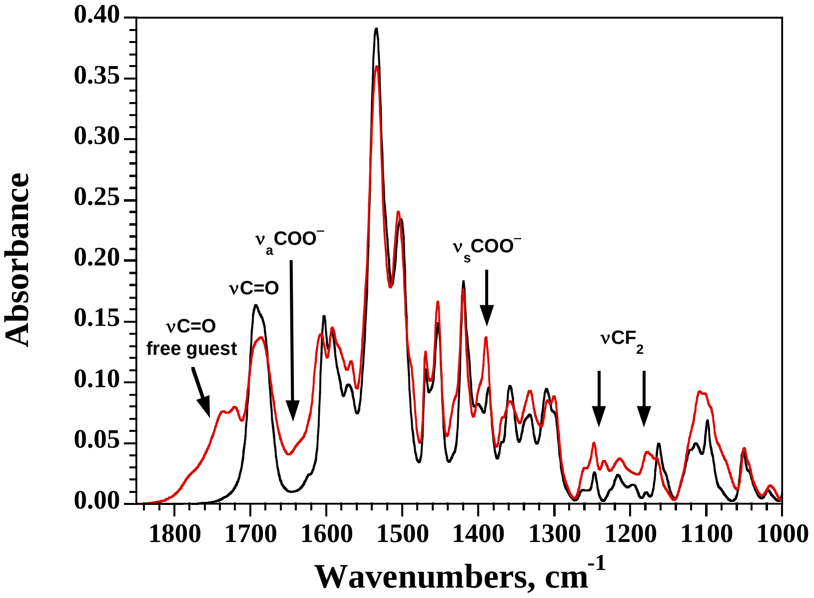


Fig. S11 IR spectra of capsule **1** at 2 mM in $CHCl_3$ in the absence (black spectrum) and the presence (red spectrum) of 5.0 equiv. of 2,2-difluorosuccinic acid (**5**) at 298K.

4. Surface Studies

4.1 Ellipsometry

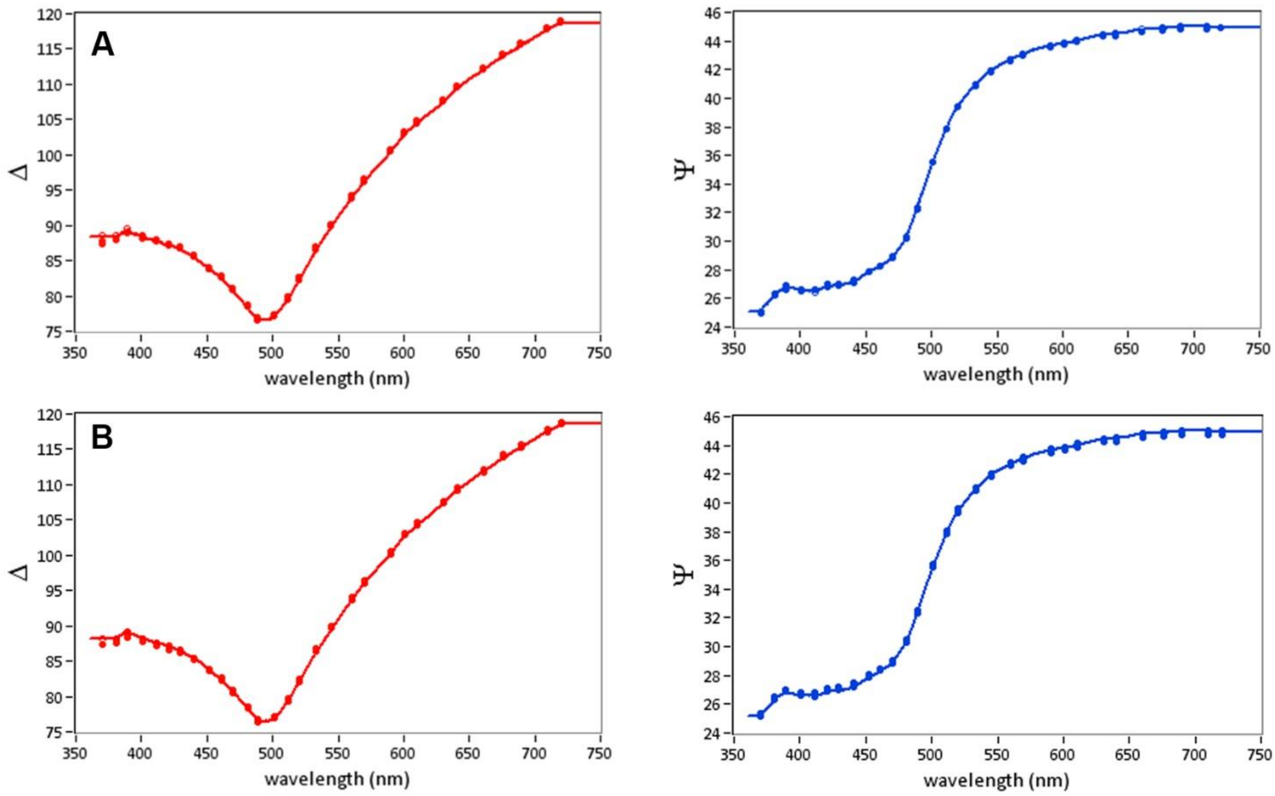


Fig. S12 Delta and Psi values for capsule **2** (A) and **2⊃5** (B) grafted to Au substrates over 370 – 720 nm and fit (solid lines) to thickness of 1.0 ± 0.1 nm for capsule 2 (A) and 1.1 ± 0.1 nm for **2⊃5** (B). For each graph, solid circles are overlay of three different data points collected at different locations on the substrate.

4.2 IR and PM-IRRAS measurements

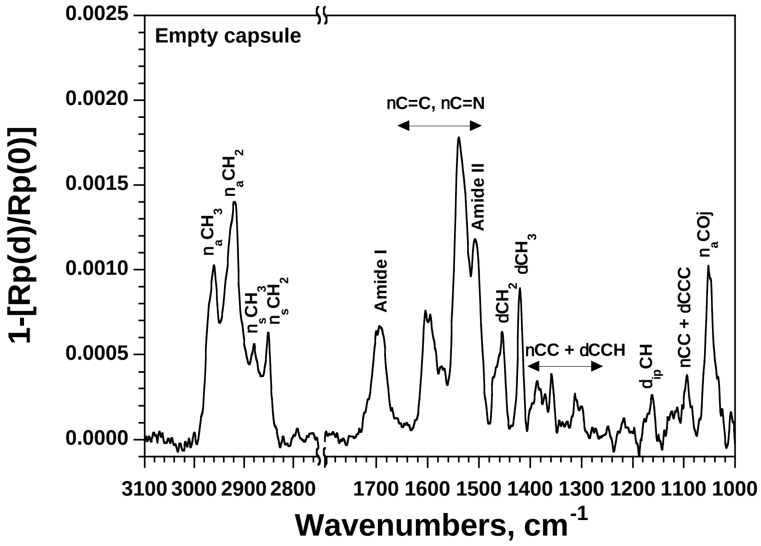


Fig. S13 PM-IRRAS spectra of a gold substrate grafted with **2** and assignment of the principal IR transitions.

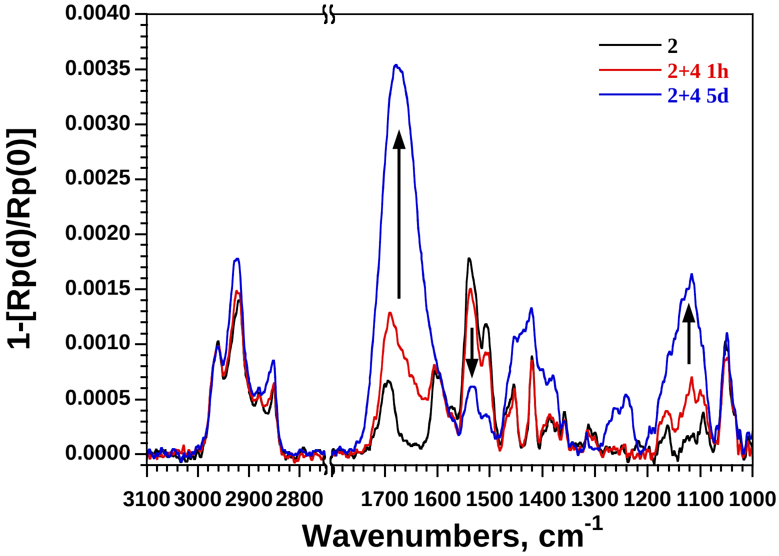


Fig. S14 PM-IRRAS spectra of a gold substrate grafted with **2** before (black curve) and after 1 hour (red curve) and 5 days (blue curve) incubation with tetrafluorosuccinic acid (**4**) at 1 mM in $CHCl_3$/MeCN (9:1) at 298K.

4.3 C-AFM measurements

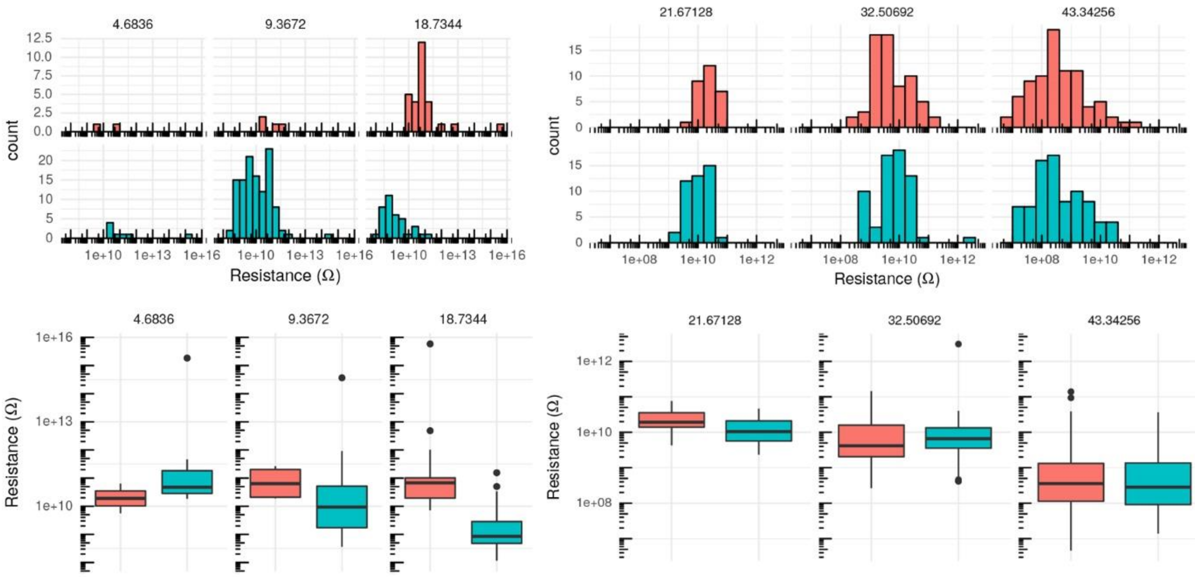


Fig. S15 Histograms (top) and boxplots (bottom) of the vertical resistance of monolayers of **2** (cyan) and **2⊃5** (red) obtained from the slope of the *I-V* curves measured using C-AFM at low bias at various applied tip force (shown above the datasets in nN). In the boxplots, the median resistance are represented by the solid lines whereas black dots represent experimental points which are at a distance higher than 1.5 times the interquartile range from the hinge.

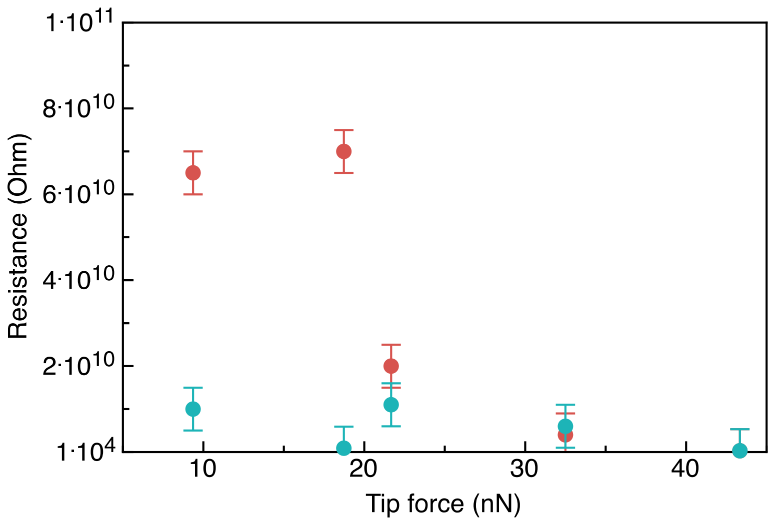


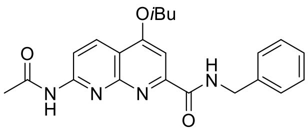
Fig. S16 Plot of the vertical resistance of monolayers of **2** (cyan) and **2⊃5** (red) vs. applied tip force.

5. Crystallographic data

Table S1. Crystal data and refinement details for the **1⊃4** complex (CCDC 2040639)

Empirical formula	$C_{334}H3_{09}Cl_6F_8N_{68}O_{60}$
Formula weight	6600.17
Temperature/K	100
Crystal system	monoclinic
Space group	P2(1)/n
a/Å	22.990(5)
b/Å	45.820(9)
c/Å	40.800(8)
α/°	90
β/°	90.92(3)
γ/°	90
Volume/Å3	42973(15)
Z	4
ρcalcg/cm3	1.020
μ/mm-1	0.114
F(000)	13772.0
Crystal size/mm3	0.1 × 0.1 × 0.1
Radiation	synchrotron ESRF FIP BM30A (λ = 0.7227)
2Θ range for data collection/°	2.03 to 20.129
Reflections collected	117148
Independent reflections	38600 [Rint = 0.0921, Rsigma = 0.0929]
Data/restraints/parameters	38600/561/4116
Goodness-of-fit on F2	1.524
Final R indexes [I>=2σ (I)]	R1 = 0.1398, wR2 = 0.3874
Final R indexes [all data]	R1 = 0.1869, wR2 = 0.4165
Largest diff. peak/hole / e Å-3	0.71/-0.56

6. ^{1}H NMR and ^{13}C NMR spectra of new synthetic compounds



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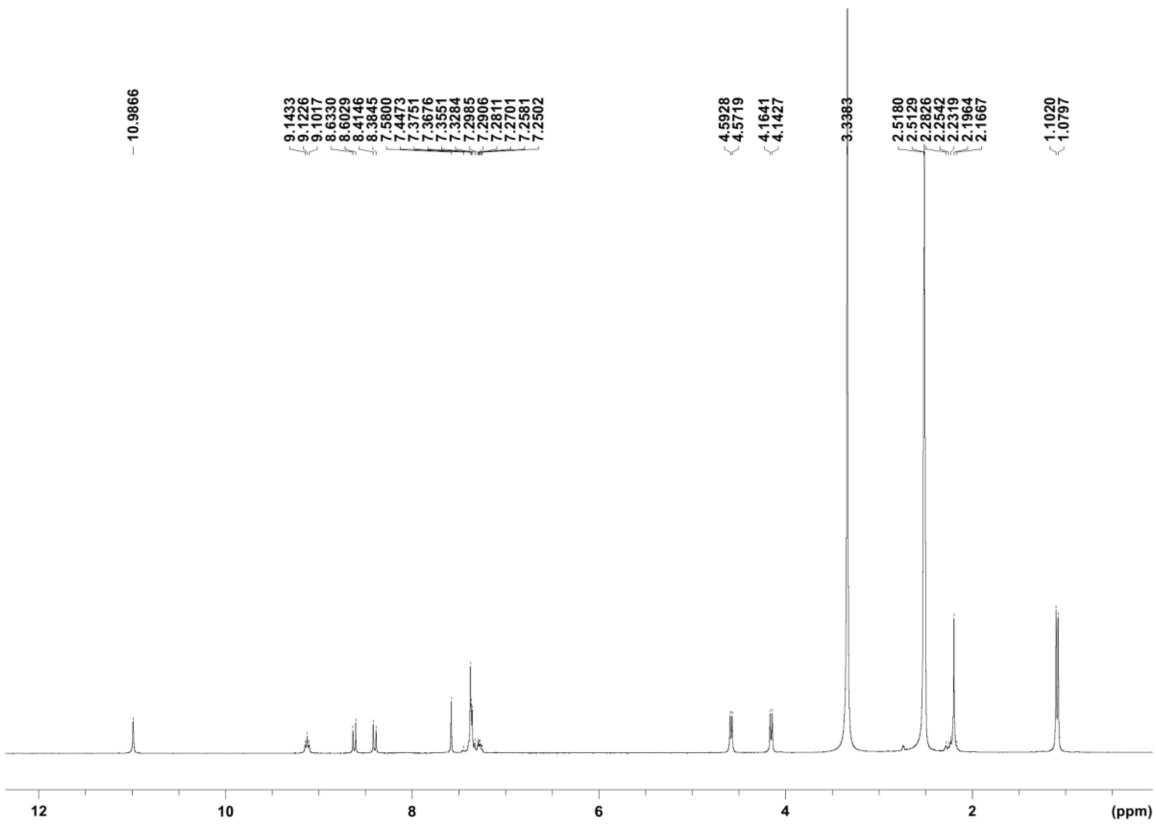
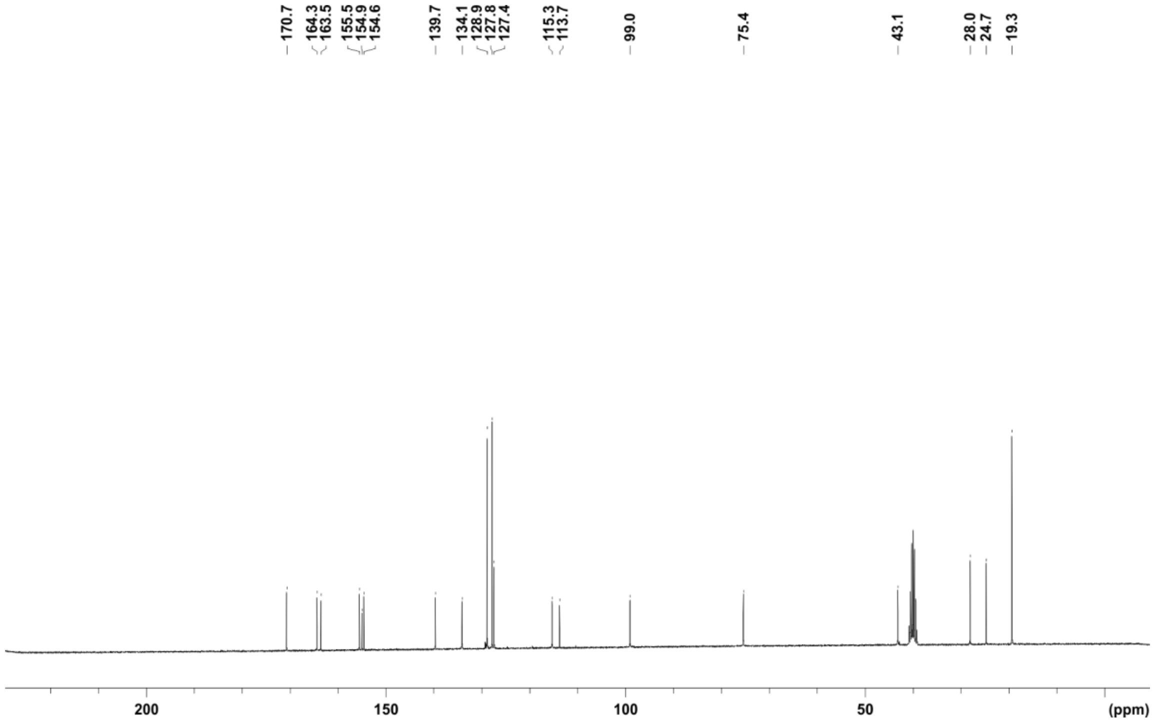
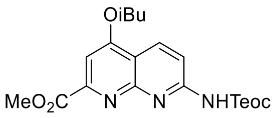
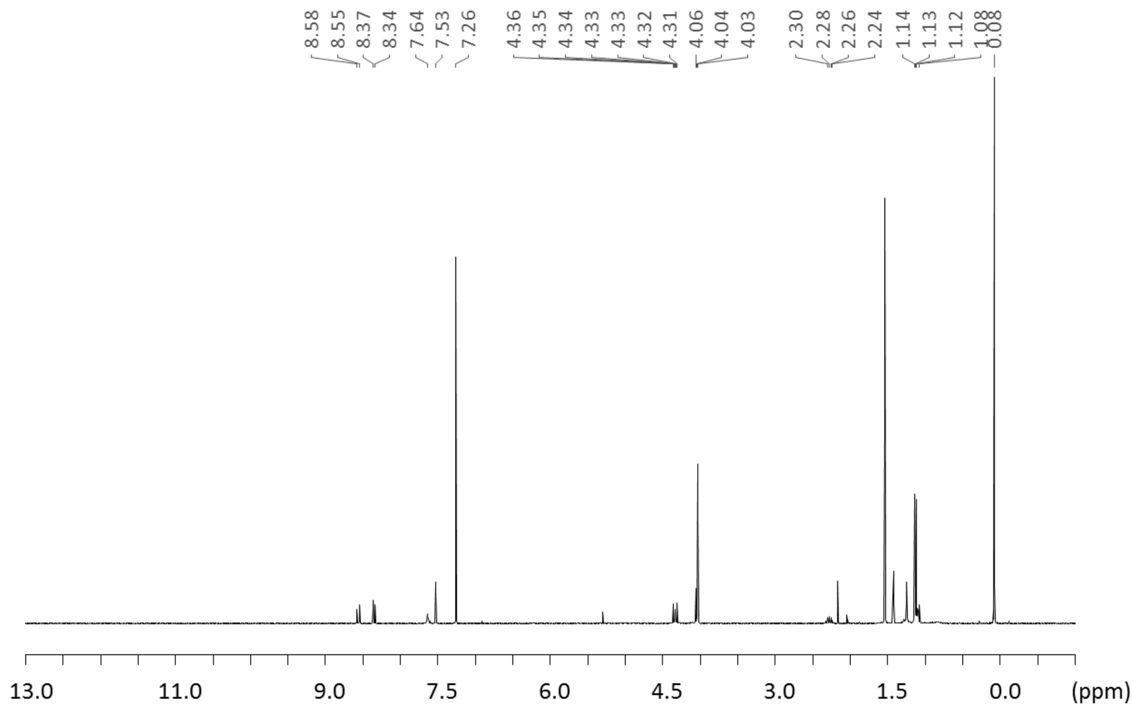
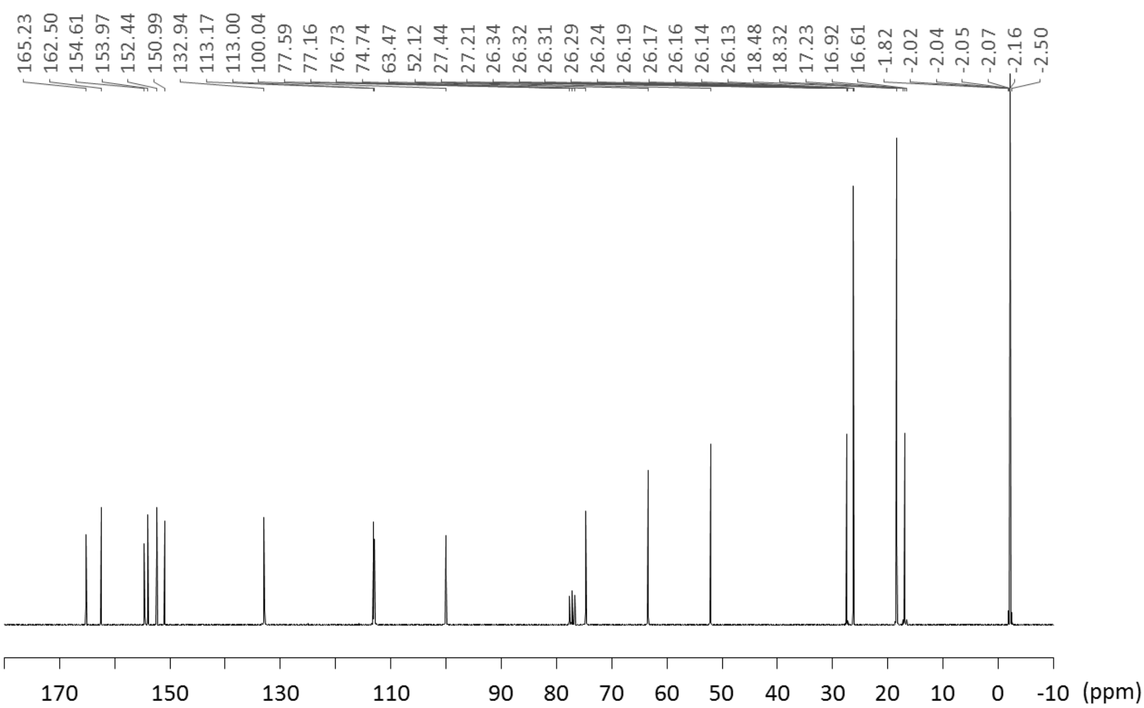


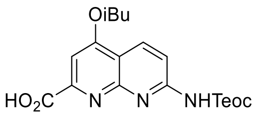




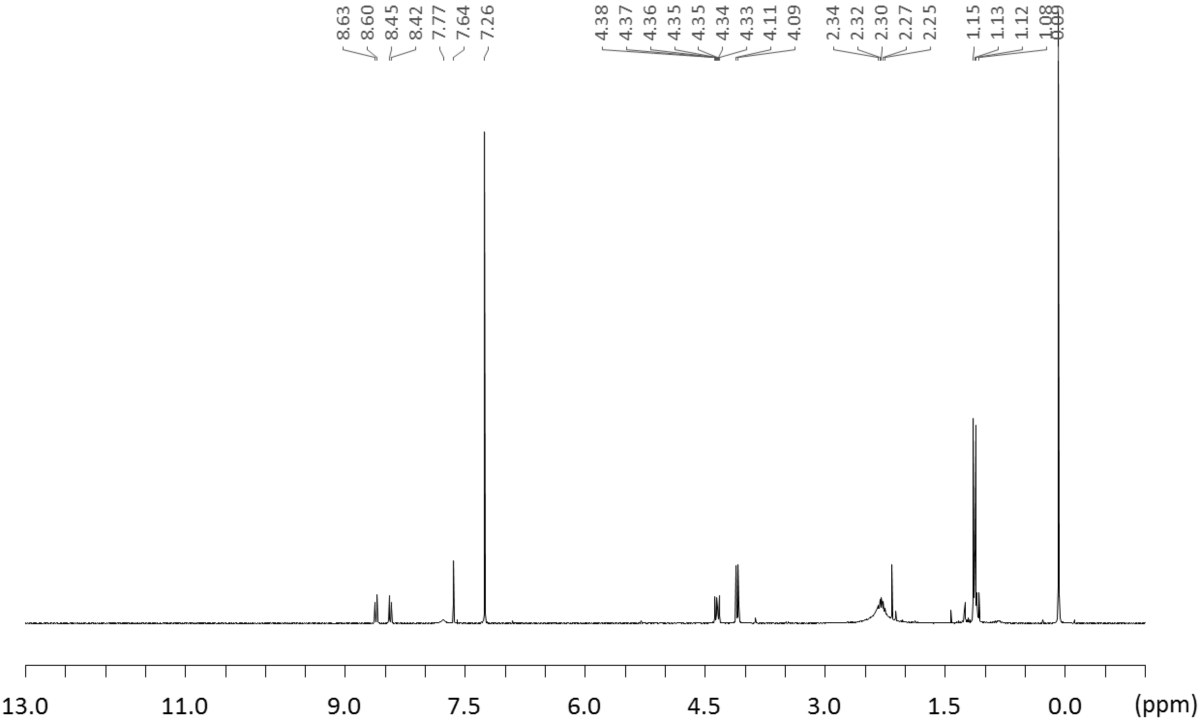
MeO$_2$C-N-NHTeoc **13**

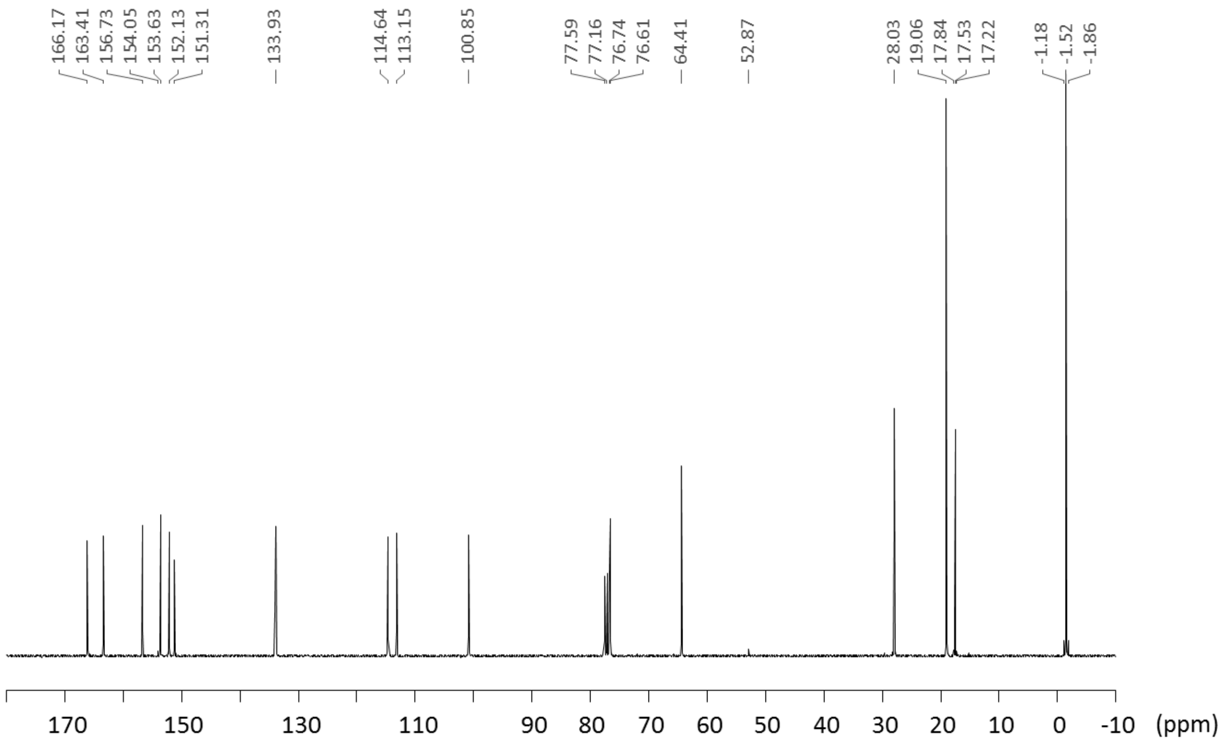


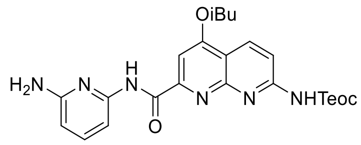




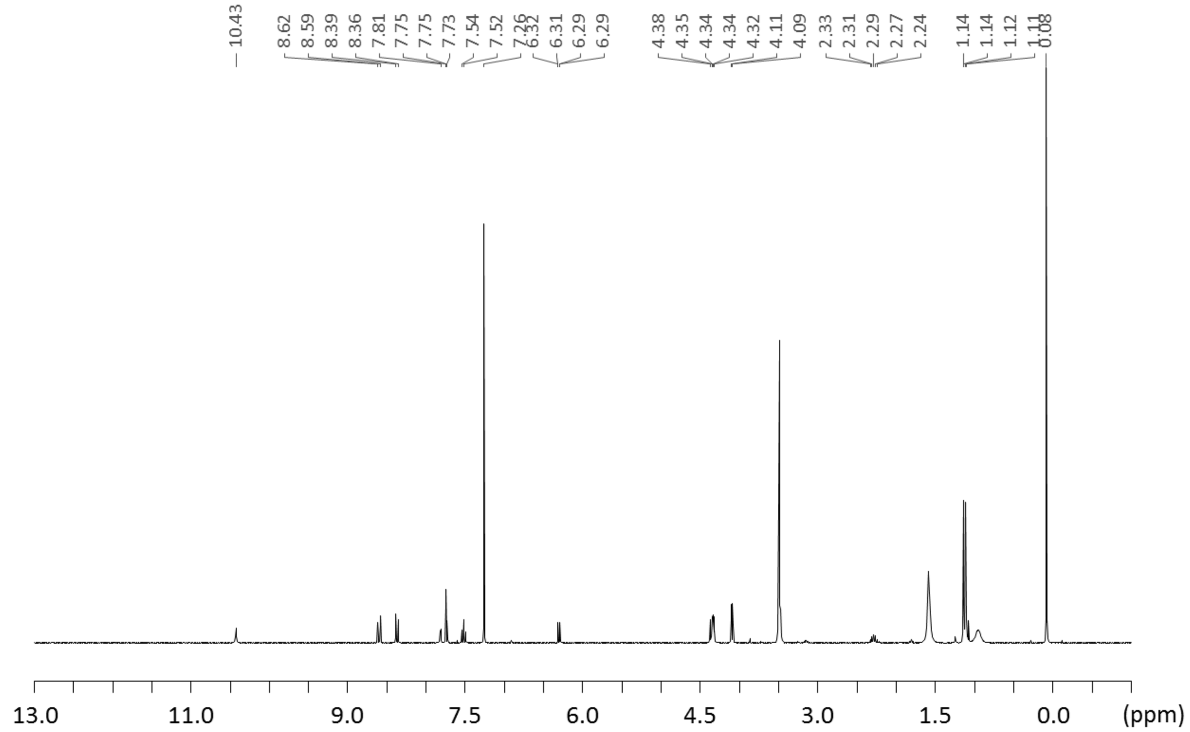
HO$_2$C-N-NHTeoc **14**

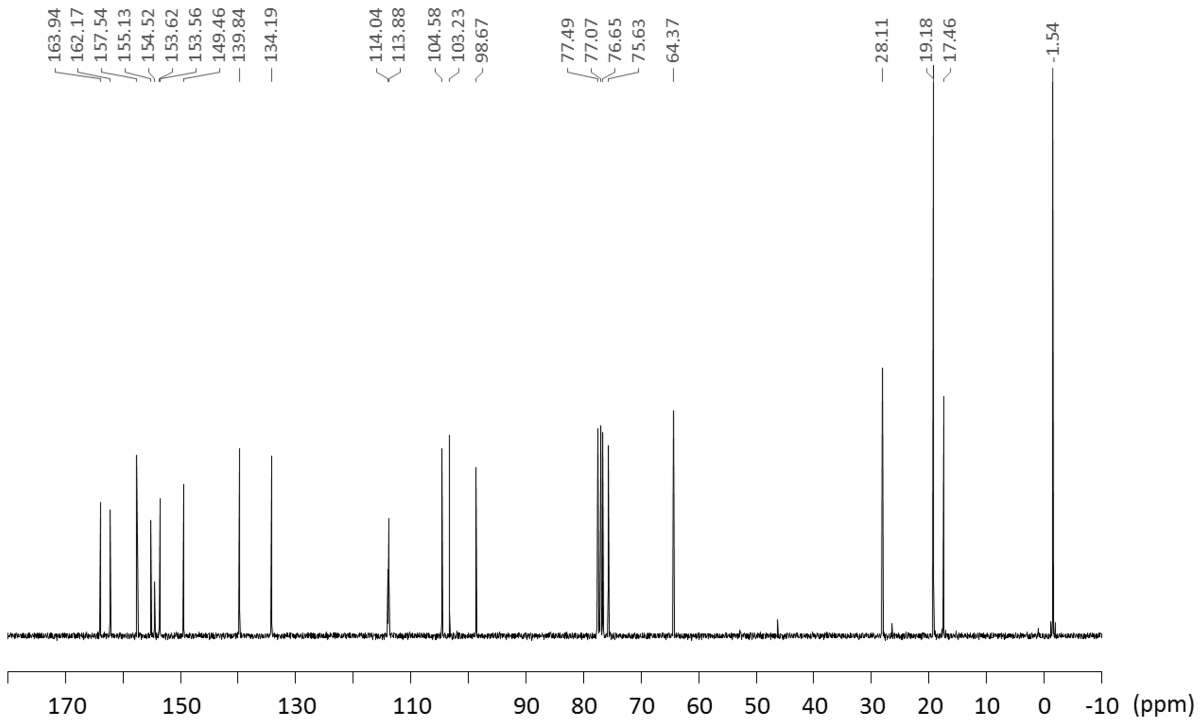


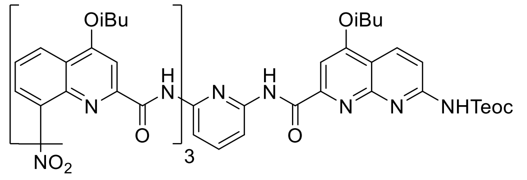




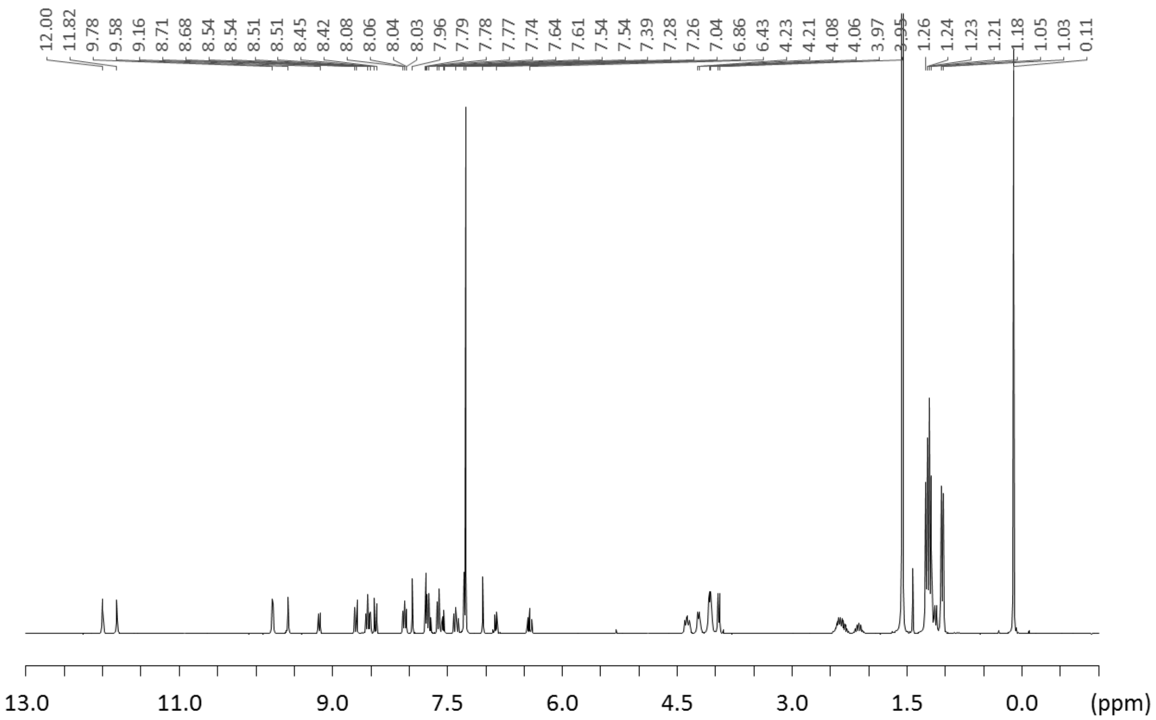
H$_2$N-PN-NHTeoc **15**

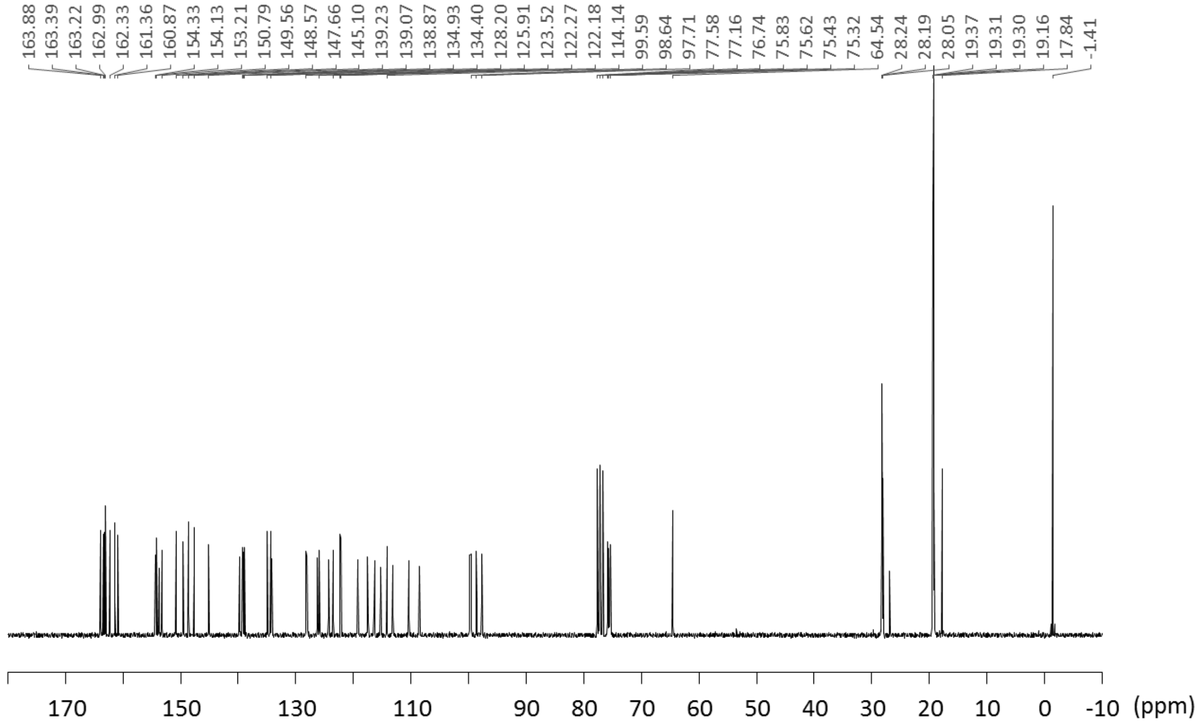


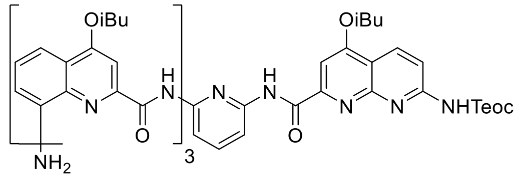




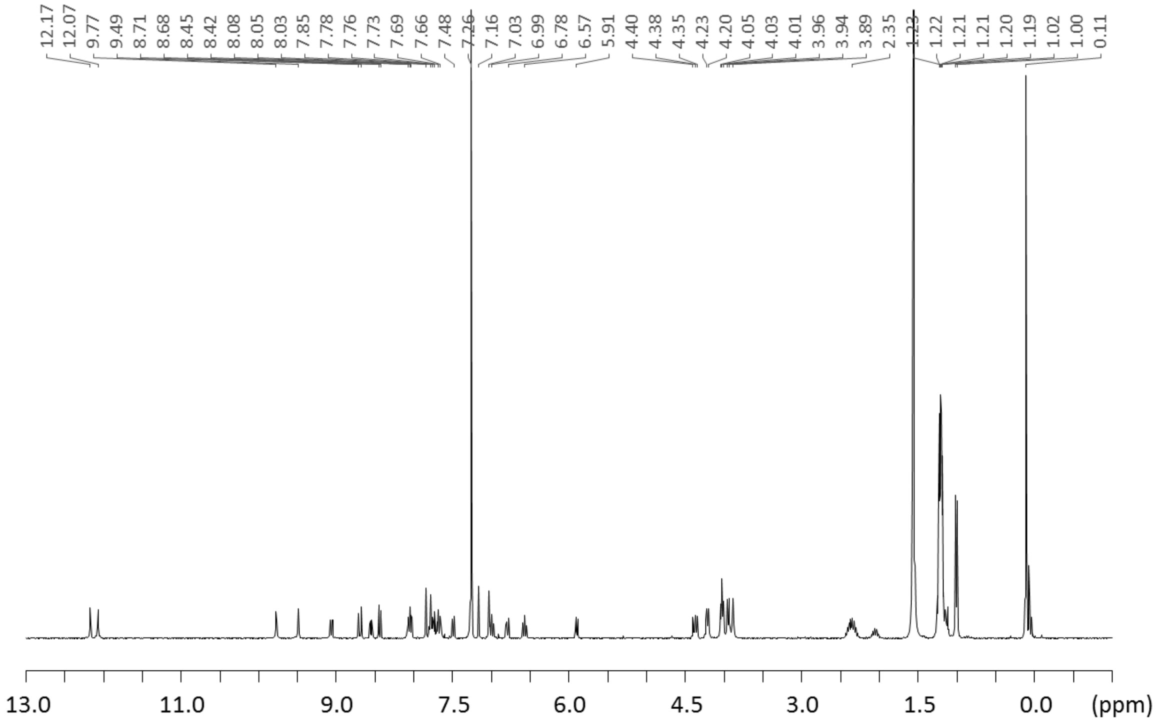
O_2N-Q_3PN-NHTeoc **16**

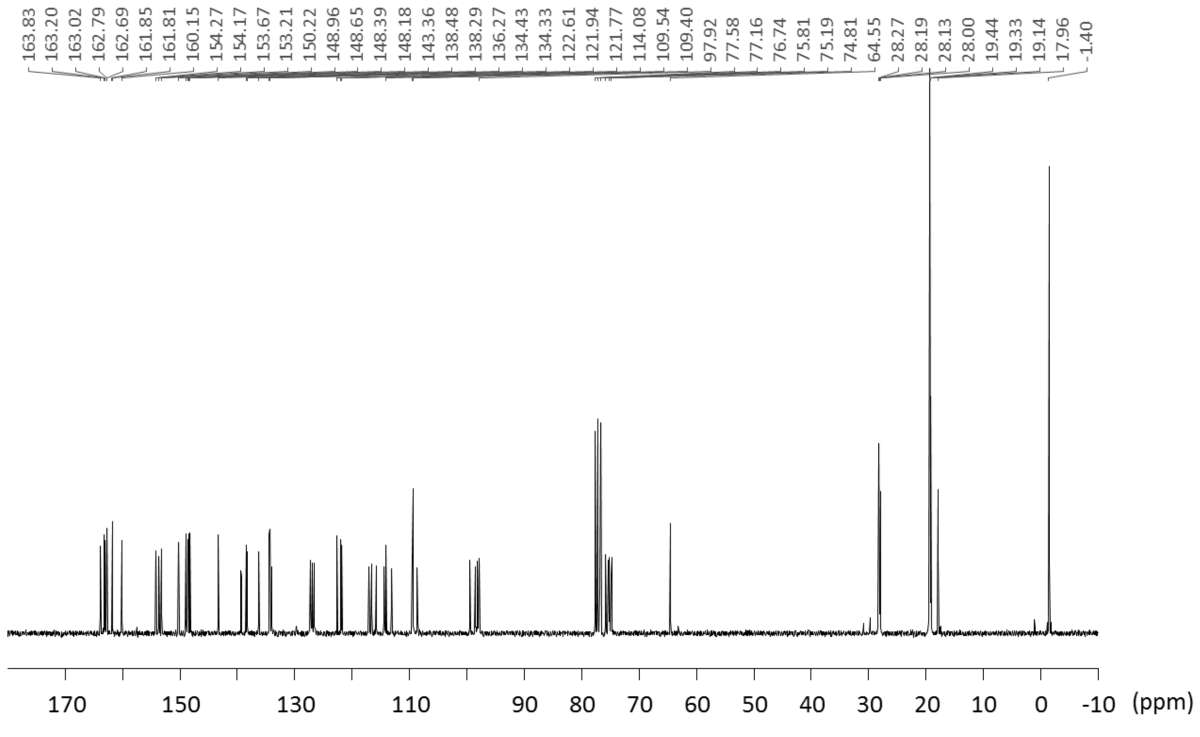


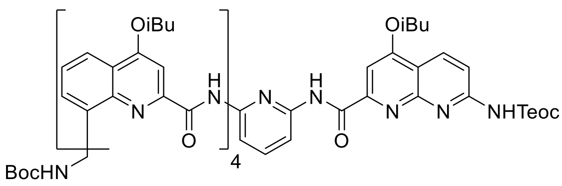




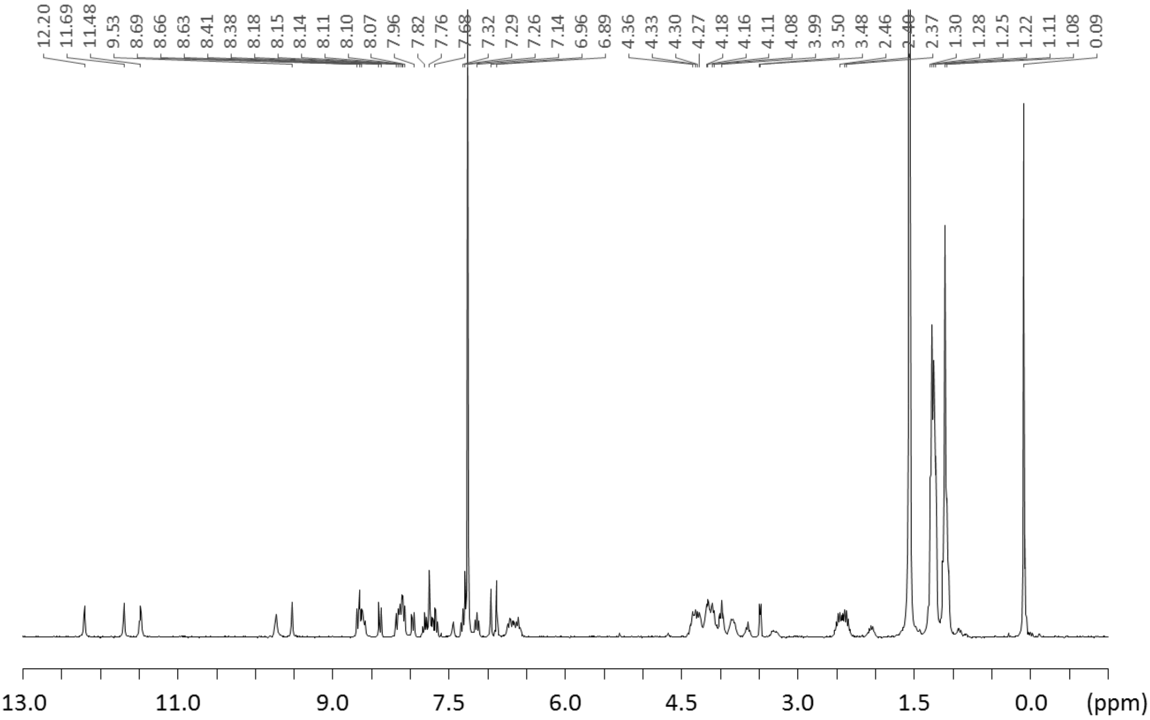
H$_2$N-Q$_3$PN-NHTeoc **17**

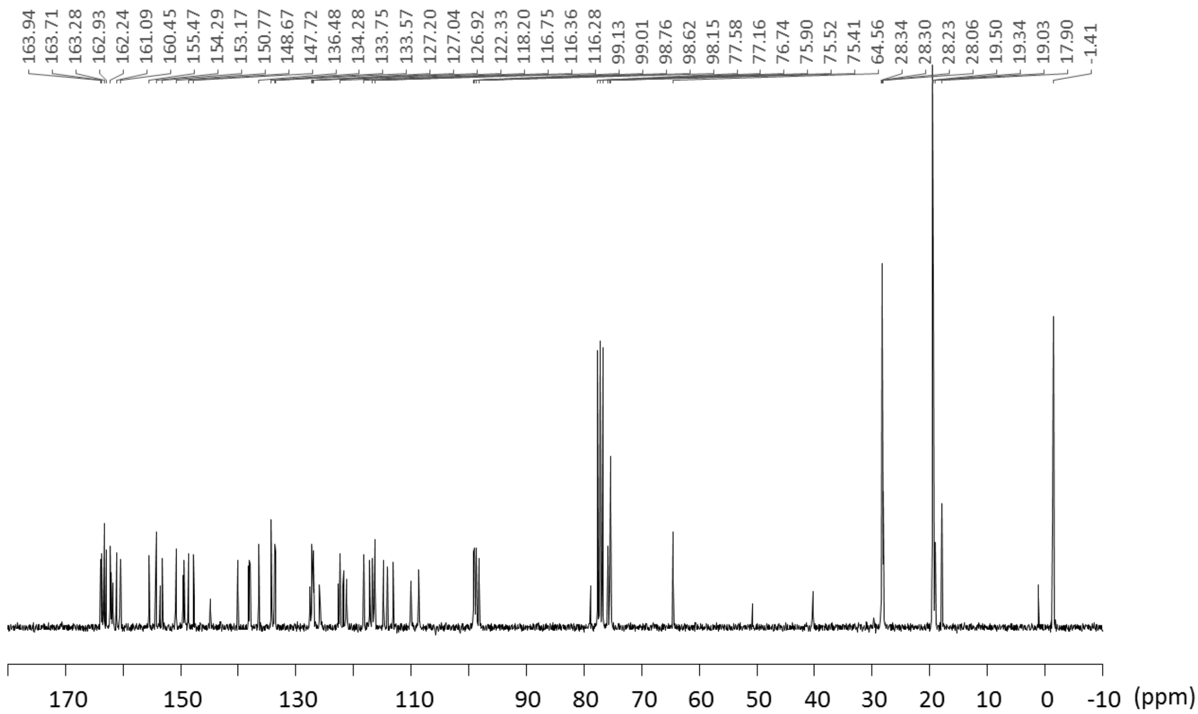


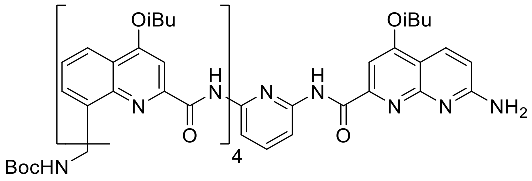




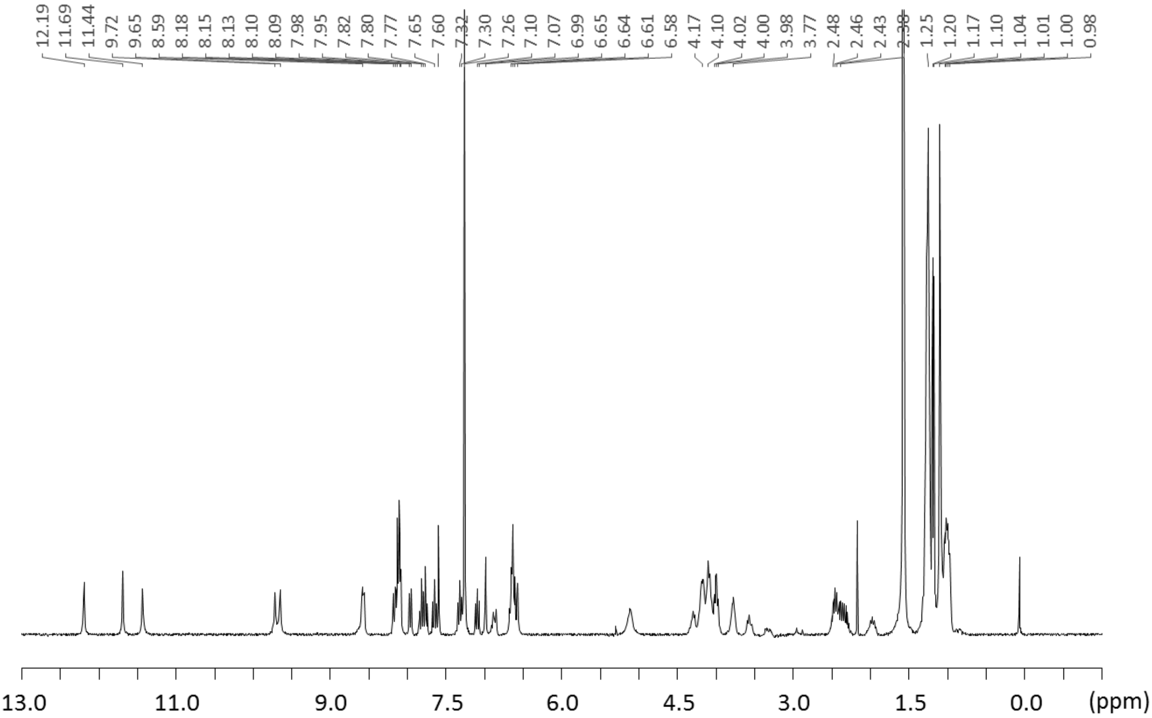
BocHN-Q^{m}Q$_3$PN-NHTeoc **18**

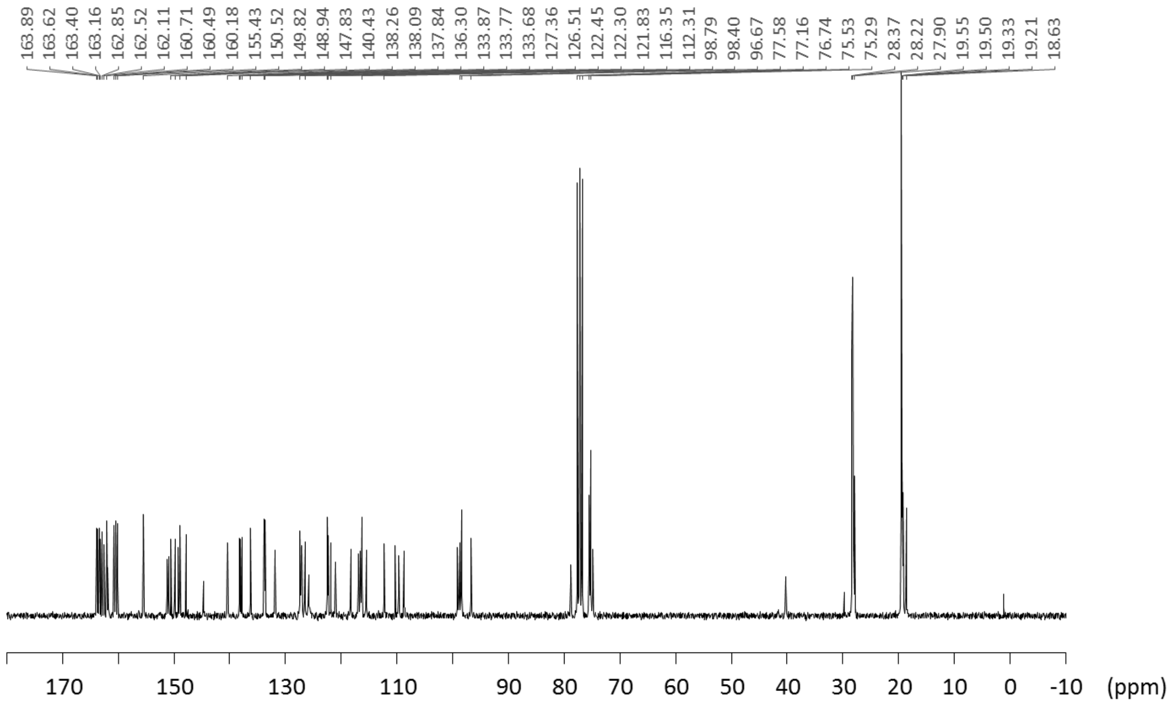


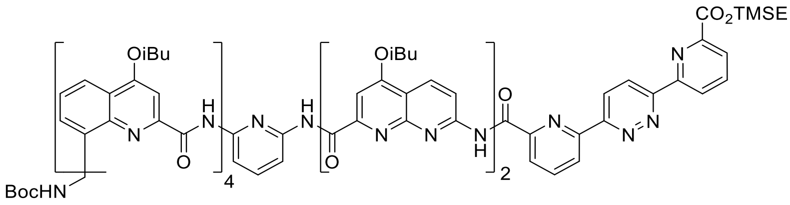




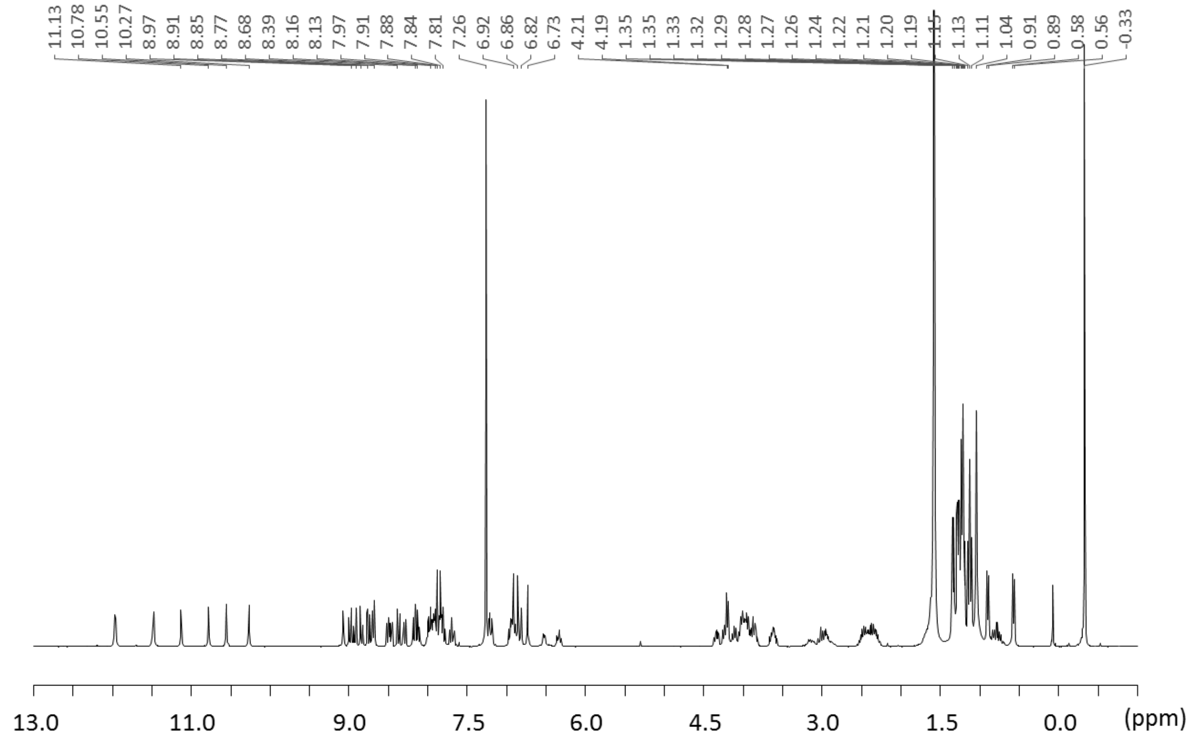
BocHN-$Q^{m}Q_3$PN-NH_2 **19**

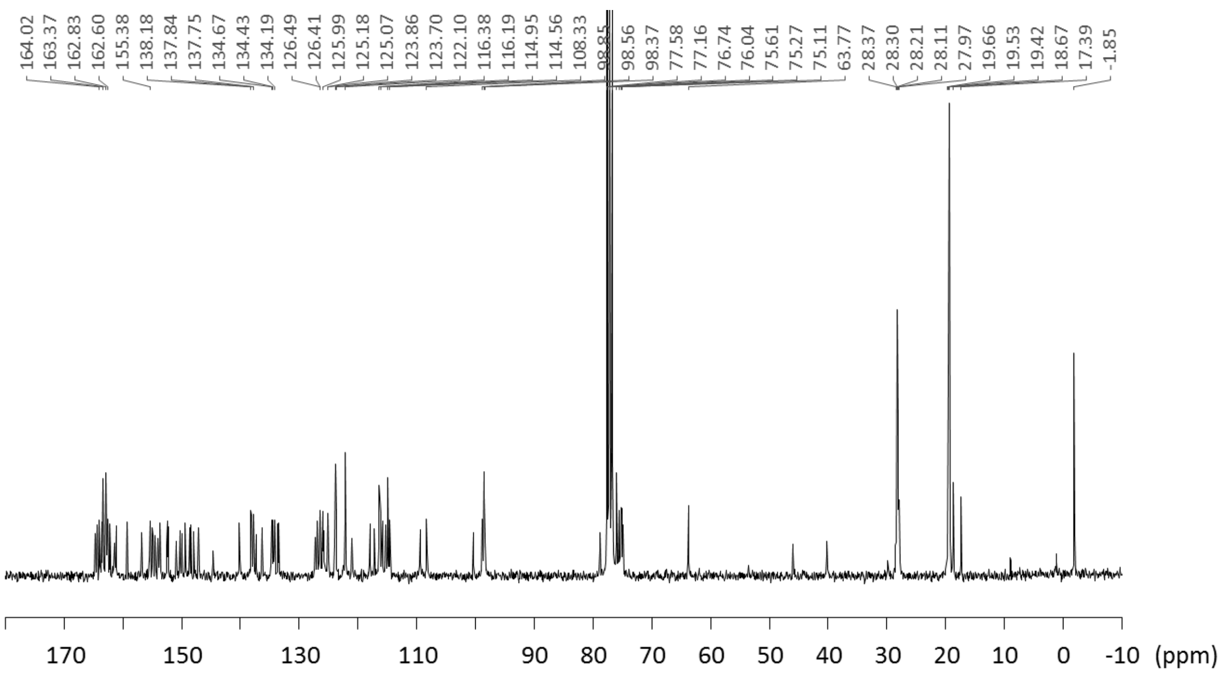


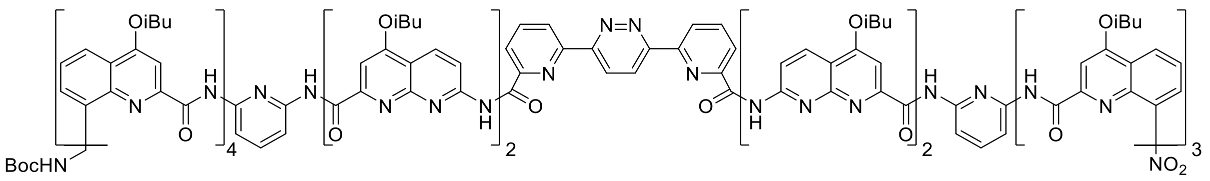




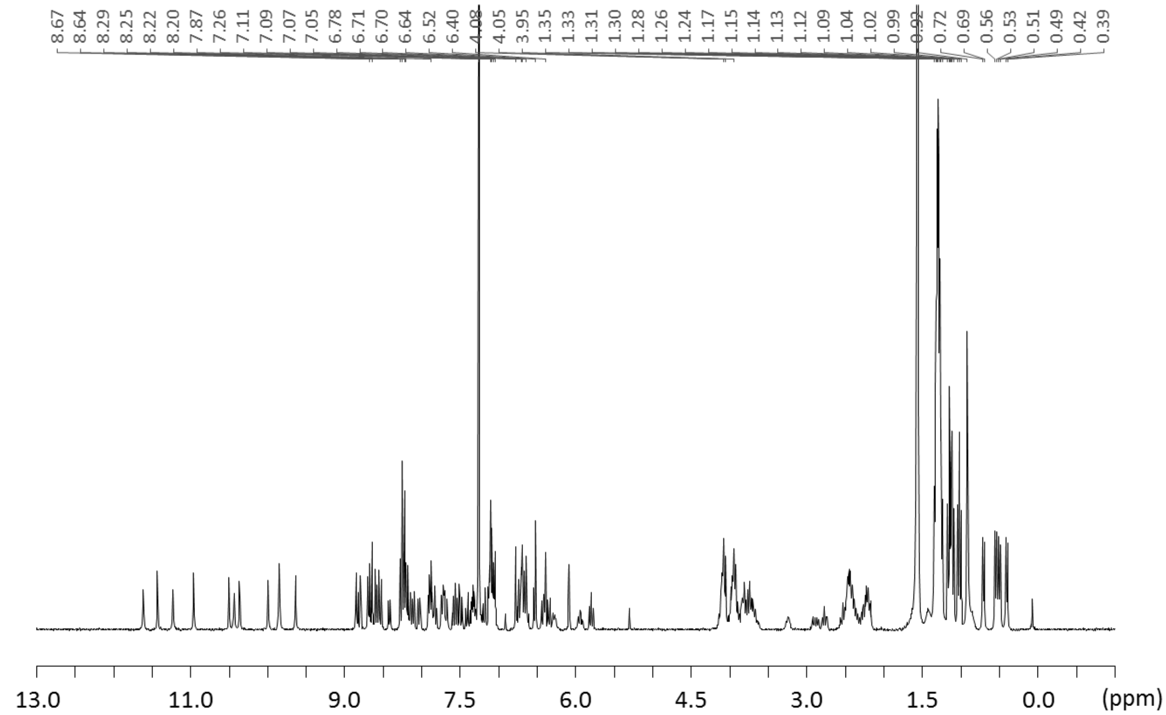
BocHN-Q^{m}Q$_3$PN$_2$PyrPyzPyr-CO$_2$TMSE **20**

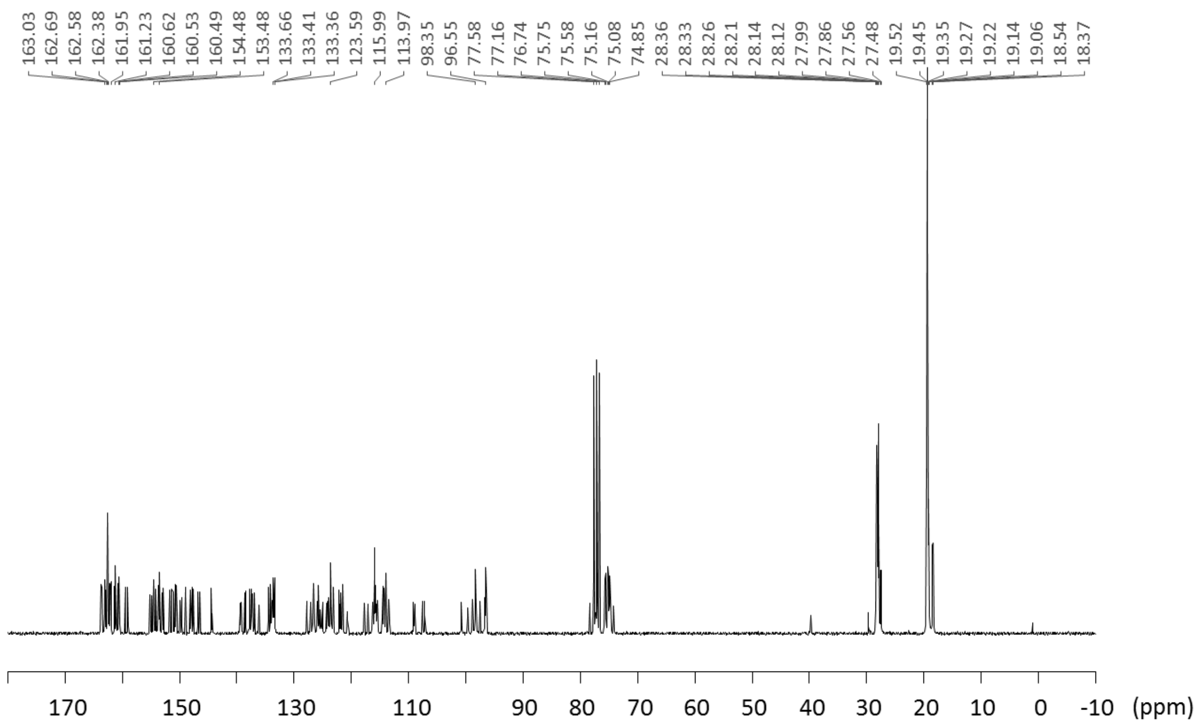


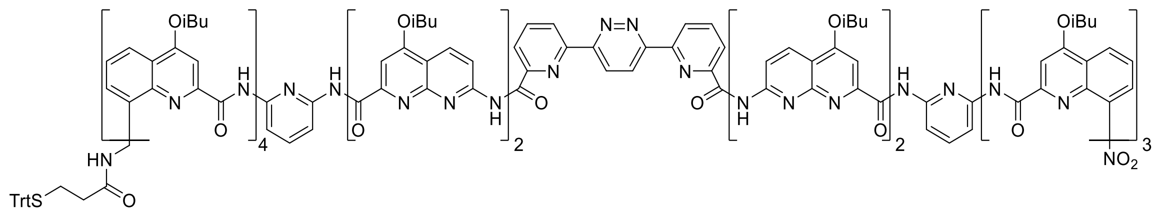




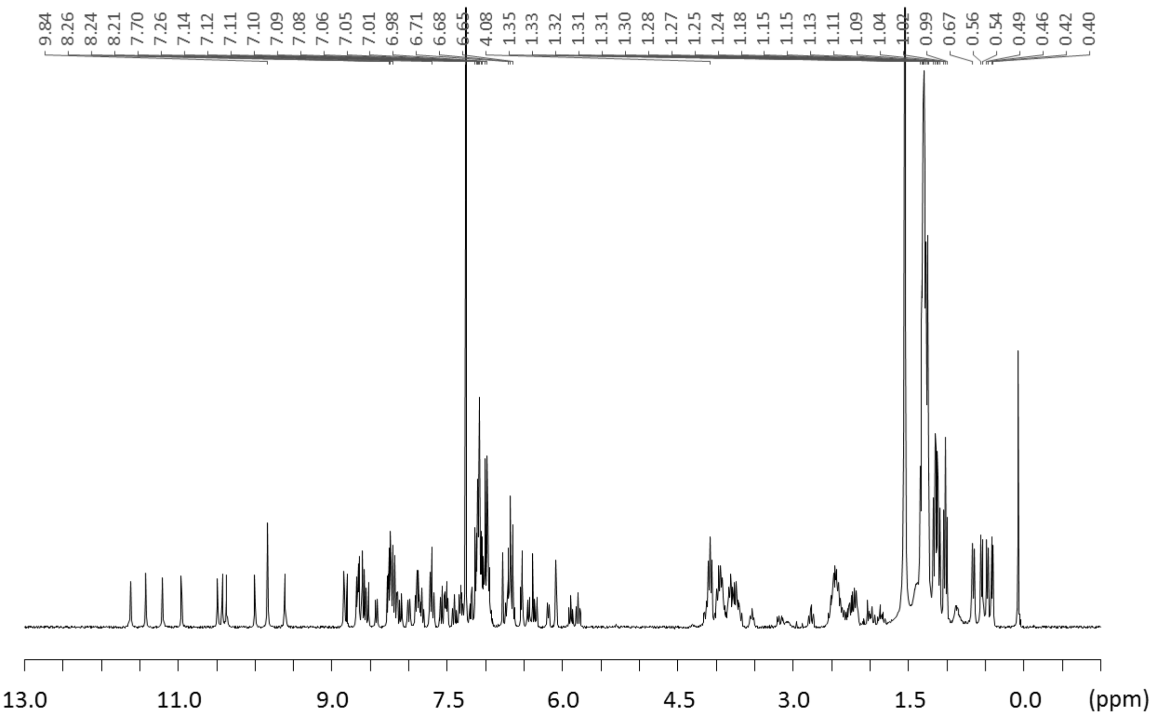
BocHN-$Q^mQ_3PN_2PyrPyzPyrN_2PQ_3$-$NO_2$ **22**

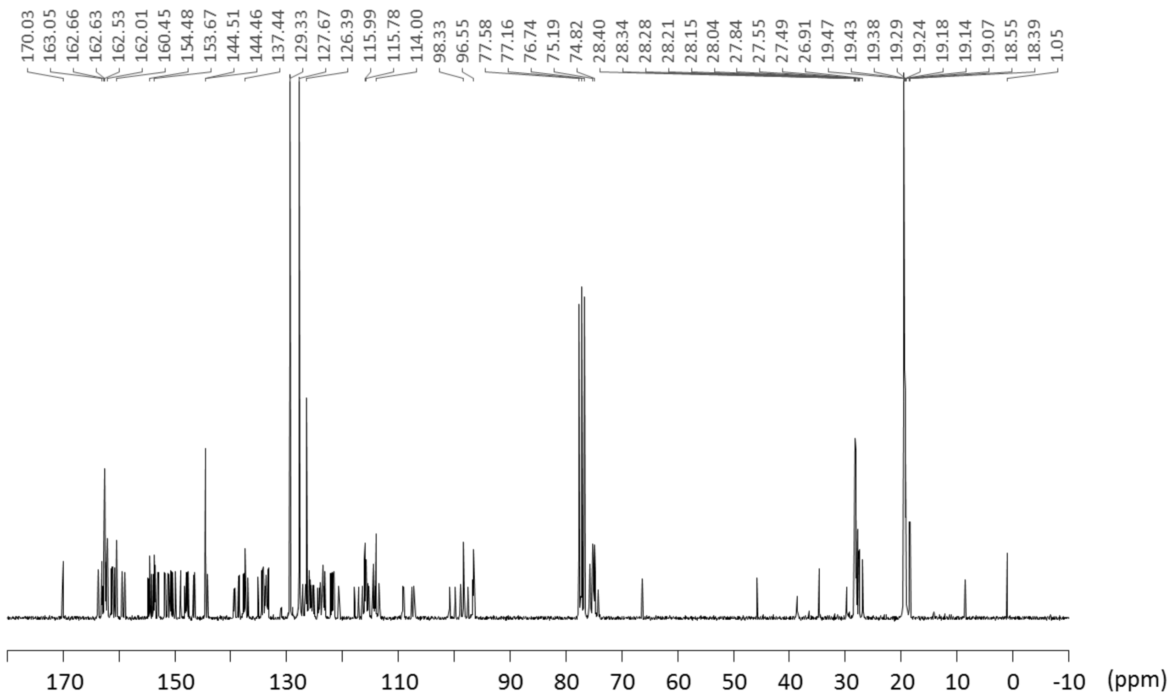






TrtS(CH$_2$)$_2$COHN-Q^{m}Q$_3$PN$_2$PyrPyzPyrN$_2$PQ$_3$-NO$_2$ **24**





7. References

1 Y. Ferrand, A. M. Kendhale, J. Garric, B. Kauffmann and I. Huc, *Angew. Chem. Int. Ed.* 2010, **49**, 1778.

2 T. Qi, T. Deschrijver and I. Huc, *Nat. Protoc.* 2013, **8**, 693.

3 X. Li, N. Markandeya, G. Jonusauskas, N. D. McClenaghan, V. Maurizot, S. A. Denisov and I. Huc, *J. Am. Chem. Soc.* 2016, **138**, 13568.

4 N. Chandramouli, Y. Ferrand, G. Lautrette, B. Kauffmann, C. D. Mackereth, M. Laguerre, D. Dubreui and I. Huc, *Nat. Chem.* 2015, **7**, 334.

5 Y. Ferrand, A. M. Kendhale, B. Kauffmann, A. Grélard, C. Marie, V. Blot, M. Pipelier, D. Dubreuil and I. Huc, *J. Am. Chem. Soc.* 2010, **132**, 7858.

6 a) C. Frassineti, S. Ghelli, P. Gans, A. Sabatini, M.S. Moruzzi and A. Vacca, *Anal. Biochem.* 1995, **231**, 374; b) C. Frassineti, L. Alderighi, P. Gans, A. Sabatini, A. Vacca ans S.Ghelli, *Anal. Bioanal. Chem.* 2003, **376**, 1041.

7 C. E. Inman, S. M. Reed and J. E. Hutchison, *Langmuir* 2004, **20**, 9144.

8 T. Buffeteau, B. Desbat and J. M. Turlet, *Appl. Spectrosc.* 1991, **45**, 380.

9 M. A. Ramin, G. Le Bourdon, N. Daugey, B. Bennetau, L. Vellutini and T. Buffeteau, *Langmuir* 2011, **27**, 6076.

10 T. Buffeteau, B. Desbat, D. Blaudez and J. M. Turlet, *Appl. Spectrosc.* 2000, **54**, 1646.

11 W. Kabsch, XDS. Acta Cryst. 2010 D66, 125.

12 O. V. Dolomanov, L. J .Bourhis, R. J . Gildea, J. A. K. Howard, H. Puschmann, *J. Appl. Cryst.* 2009, **42**, 339.

13 G. M. Sheldrick, *Acta Cryst.* 2015, A71, 3.

14 A. L. Spek, *J. Appl. Cryst.* 2003, **36**, 7.