Supplementary Material (ESI) for Chemical Communications

Chemical Communications

Enhancing the Reactivity of 1,2,3-Triazoles in "Click" Macrocycles by Face-to-Face Dibenzylammonium Ion Binding

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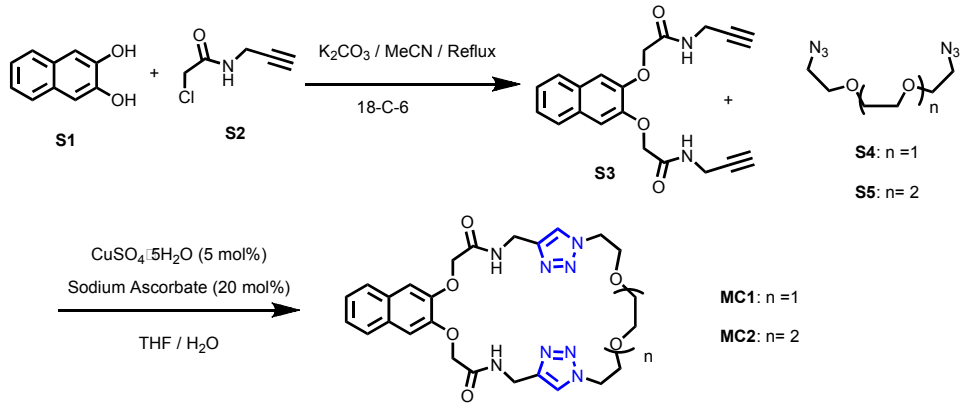
Electronic Supporting Information

Experimental Section

General Methods: Reagents were purchased from Aldrich or synthesized as described. Thin-layer chromatography (TLC) was carried out using aluminum sheets, precoated with silica gel 60F (Merck 5554). The plates were inspected by UV-light. Melting points were determined on an Electrothermal MEL-TEMP 3.0 apparatus and are uncorrected. Proton and carbon nuclear magnetic resonance spectra (^{1}H-NMR and ^{13}C-NMR) spectra were recorded on a Bruker Avance500 II or DRX500, using the deuterated solvent as lock and the residual solvent as internal standard. All chemical shifts are quoted using the δ scale, and all coupling constants (J) are expressed in Hertz (Hz). Electrospray mass spectra (ESI-MS) were measured on a Q-Tof Premier mass spectrometer from Micromass Technologies (now Waters Corporation). Matrix-assisted laser desorption ionization (MALDI) mass spectra were measured on 4800 MALDI TOF/TOF analyzer from Applied Biosystems.

Synthesis of Macrocycles MC1 and MC2



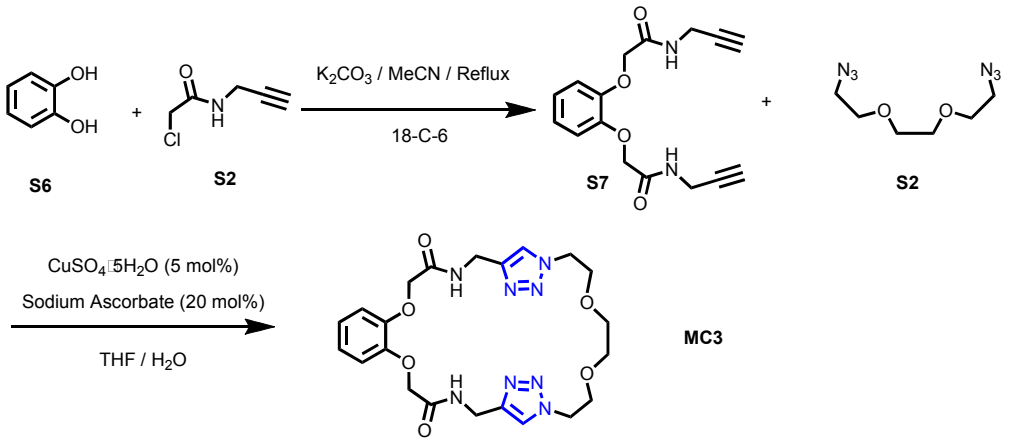
Preparation of S3: A mixture of 2,3-dihydroxynaphthalene (**S1**) (2.9 g, 18.1 mmol), chloride **S2** (5.0 g, 38.0 mmol), K_2CO_3 (6.3 g, 45.3 mmol), and 18-crown-6 (18-C-6) (0.33 g, 1.81 mmol) in MeCN (250 mL) was refluxed overnight under N_2. The

suspension was filtered and the filtrate was evaporated to give a residue that was recrystalized from Ethyl Acetate/Hexanes to give **S3** as white needle-like crystal (3.7 g, 58%). A second batch (2.3 g, 36%) was collected after concentration of the mother liquor. M.p. 181.0-181.5 °C; ^{1}H NMR ($CDCl_3$, 500 MHz, 298 K): δ = 7.71 (dd, J = 3.4 Hz, 6.2 Hz, 2 H), 7.42 (dd, J = 3.4 Hz, 6.2 Hz, 2 H), 7.20 (s, 2 H), 6.93 (br s, 2 H), 4.72 (s, 4 H), 4.19 (dd, J = 2.5 Hz, 5.5 Hz, 4 H), 2.29 (t, J = 2.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz, 298 K): δ = 167.7, 146.9, 129.6, 126.7, 125.5, 110.1, 79.0, 72.0, 68.5, 28.9; (FAB+): 357 (10%) $[M + Li]^+$; HRMS (FAB): $C_{20}H_{18}N_2O_4$ $[M + Li]^+$: calcd 357.1427, found 357.1429; elemental analysis calcd (%) for $C_{20}H_{18}N_2O_4$: C 68.56, H 5.18, N 8.00; found C 68.30, H 5.30, N 7.90.

Macrocycle MC1: A mixture of the diacetylene **S3** (0.10 g, 0.29 mmol) and diazide **S4** (57 mg, 0.29 mmol) was dissolved in THF/H_2O (15 mL/5 mL). $CuSO_4$•$5H_2O$ (3.6 mg, 14 μmol) and Sodium Ascorbate (11.3 mg, 58 μmol) were added under N_2 and the mixture was stirred at room temperature for 2 days. The resulting solution was concentrated and extracted with CH_2Cl_2. The combined organic solution was evaporated and subjected to column chromatography (SiO_2: EtOAc/MeOH 4:1) to give the product **MC1** as a white solid (104 mg, 66%). M.p. > 180 °C (dec.); ^{1}H NMR (CD_2Cl_2/CD_3CN, 500 MHz, 298 K): δ = 7.69–7.67 (m, 4 H), 7.49 (s, 2 H), 7.35 (dd, J = 9.2 Hz, 6.0 Hz, 2 H), 7.23 (s, 2 H), 4.64 (s, 4 H), 4.57, (d, J = 5.5 Hz, 4 H), 4.42 (t, J = 5.0 Hz, 4 H), 3.73 (t, J = 5.0 Hz, 4 H), 3.51 (s, 4 H); ^{13}C NMR (CD_2Cl_2/CD_3CN, 125 MHz, 298 K): δ = 167.4, 167.3, 147.4, 144.4, 144.4 129.0, 126.3, 124.4, 123.0, 69.2, 68.4, 67.7, 49.2, 33.8, 33.7; MS (FAB+): 557 (20%) $[M + Li]^+$; HRMS (FAB): $C_{26}H_{30}N_8O_6$ $[M + Li]^+$: calcd 557.2448, found 557.2441.

Macrocycle MC2: A mixture of the diacetylene **S3** (0.50 g, 1.4 mmol) and diazide **S5** (0.34 mg, 1.4 mmol) was dissolved in THF/H_2O (75 mL/25 mL). $CuSO_4$•$5H_2O$ (18 mg, 71 μmol) and Sodium Ascorbate (57 mg, 0.29 mmol) were added under N_2 and the mixture was stirred at room temperature for 2 days. The resulting solution was concentrated and extracted with CH_2Cl_2. The combined organic solution was evaporated and subjected to column chromatography (SiO_2: EtOAc/MeOH 4:1) to give the product **MC2** as a white solid (0.30 g, 35%). M.p. >140 °C (dec.); ^{1}H NMR (CD_2Cl_2/CD_3CN, 500 MHz, 298 K): δ = 7.69 (t, J = 3 Hz, 2 H), 7.59 (s, 2 H), 7.56 (br s, 2 H), 7.35 (dd, J = 6.0Hz, 3.0 Hz, 2 H), 7.23 (s, 2 H), 4.64 (s, 4 H), 4.45 (d, J = 5.5 Hz, 4 H), 4.42 (t, J = 5.0 Hz, 4 H), 3.79 (t, J = 5.0 Hz, 4 H), 3.52 (m, 4 H), 3.48 (m, 4 H); ^{13}C NMR (CD_2Cl_2/CD_3CN, 125 MHz, 298 K): δ = 169.4, 147.5, 144.5, 129.7, 126.3, 124.6, 123.5, 109.4, 70.0, 69.9, 68.8, 67.7, 50.0, 34.0; MS (FAB+): 595 (10%) $[M + H]^+$, 601 (35%) $[M + Li]^+$; HRMS (FAB): $C_{28}H_{34}N_8O_7$ $[M + Li]^+$: calcd 601.2710, found 601.2721.

Synthesis of the Macrocycle MC3



S7: A mixture of catechol (**S6**) (1.0 g, 9.1 mmol), chloride **S2** (2.5 g, 19.0 mmol), K_2CO_3 (3.1 g, 22.6 mmol), and 18-crown-6 (18-C-6) (0.17 g, 0.91 mmol) in MeCN (50 mL) was refluxed overnight under N_2. The suspension was filtered and the filtrate was evaporated to give a residue that was recrystallized from Ethyl Acetate/Hexanes to give **S7** as white crystal (1.4 g, 53%). A second batch (0.80 g, 29%) was collected after concentration of the mother liquor. ^{1}H NMR (CD_3OD, 500 MHz, 298 K): δ = 7.01 (t, J = 2.5 Hz, 4 H), 4.60 (s, 4 H), 4.08 (d, J = 2.5 Hz, 4 H), 2.62 (t, J = 2.5 Hz, 2 H); ^{13}C NMR (CD_3OD, 125 MHz, 298 K): δ = 169.6, 148.0, 122.6, 115.1, 79.0, 70.8, 68.4, 27.8; MS (FAB+): 301 (20%) $[M + H]^+$, 307 (40%) $[M + Li]^+$; HRMS (FAB): $C_{16}H_{16}N_2O_4$ $[M + H]^+$: calcd 301.1188, found 301.1182.

Macrocycle MC3: A mixture of the diacetylene **S3** (1.20 g, 4.0 mmol) and diazide **S4** (0.80 g, 4.0 mmol) was dissolved in THF/H_2O (210 mL/70 mL). $CuSO_4$•$5H_2O$ (50 mg, 0.20 mmol) and Sodium Ascorbate (0.40 mg, 2 mmol) were added under N_2 and the mixture was stirred at room temperature for 6 days. The resulting solution was concentrated and extracted with CH_2Cl_2. The combined organic solution was evaporated and subjected to column chromatography (SiO_2: EtOAc/MeOH 4:1) to give the product **MC3** as a white solid (0.67 g, 34%). ^{1}H NMR (CD_2Cl_2/CD_3CN, 500 MHz, 298 K): δ = 7.83 (br s, 2 H), 7.51 (s, 2 H), 7.01-6.93 (m, 4 H), 4.64 (d, J = 6.0 Hz, 4 H), 4.56 (s, 4 H), 4.49 (t, J = 5.0 Hz, 4 H), 3.80 (t, J = 5.0 Hz, 4 H), 3.58 (s, 4 H); ^{13}C NMR (CD_2Cl_2/CD_3CN, 125 MHz, 298 K): δ = 169.6, 148.0, 144.4, 123.4, 122.6, 115.2, 69.9, 68.8, 68.5, 50.0, 33.9; MS (FAB+): 501 (15%) $[M + H]^+$; HRMS (FAB): $C_{22}H_{28}N_8O_6$ $[M + H]^+$: calcd 501.2210, found 501.2213; elemental analysis calcd (%) for $C_{22}H_{28}N_8O_6$: C 52.79, H 5.64, N 22.39; found C 52.72, H 5.76, N 22.51.

The Attempted Stoppering Reaction Using "Click" Chemistry: A mixture of the macrocycle **MC3** (50 mg, 0.10 mmol), the azide-containing ammonium salt **5**•PF_6 (45 mg, 0.10 mmol), *t*-butylphenylacetylene (24 mg, 0.15 mmol), and diisopropylethylamine (2 mg, 15 μmol) was dissolved in CH_2Cl_2/MeCN (4:1, 2 mL). Under N_2 atmosphere, $CuPF_6$•4MeCN (4 mg, 10 μmol) was added and the mixture was stirred overnight at room temperature. The resulting solution was concentrated and subjected to column chromatography (SiO_2: CH_2Cl_2/MeOH 85:15) to give the cycloaddition product **6**-H•PF_6 as an off-white solid (58 mg, 92%) and the recovered starting material macrocycle **MC3** (47 mg, 95%).

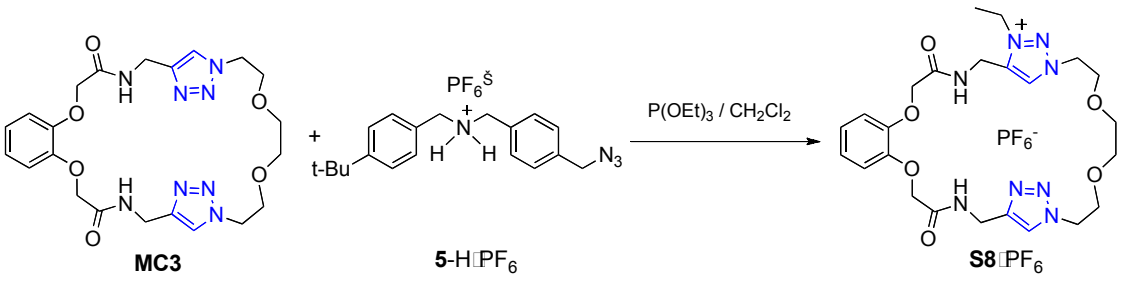
6-H•PF_6: M.p. > 171.0 °C (dec.); ^{1}H NMR ($CDCl_3$, 500 MHz, 298 K): δ = 7.70 (m, 3 H), 7.42 (d, J = 6.5 Hz, 2 H), 7.38 (d, J = 8.0 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 7.14 (d, J = 8.0 Hz, 2 H), 5.49 (s, 2 H), 3.91 (s, 2 H), 3.88 (s, 2 H), 1.32 (s, 9 H), 1.31 (s, 9 H); ^{13}C NMR (CD_3COCD_3, 125 MHz, 298 K): δ = 150.7, 150.3, 147.4, 138.1, 135.5, 134.7, 129.2, 128.5, 128.1, 125.6, 125.3, 125.2, 120.3, 54.8, 53.1, 52.1, 51.9, 34.3, 34.1, 30.7, 30.7; MS (FAB+): 467 $[M - PF_6]^+$.

Synthesis of the Triazolium 9•PF_6

A mixture of the macrocycle **MC1** (174 mg, 0.316 mmol) and the azide-containing ammonium salt **5**•PF_6 (120 mg, 0.264 mmol) was dissolved in CH_2Cl_2 (6 mL) under N_2 atmosphere and cooled down to 0 ˚C. Triethyl phosphite (0.11 mL, 0.633 mmol) was added dropwise through a syringe and the mixture was stirred overnight at room temperature. The resulting solution was concentrated and subjected to column

chromatography (SiO_2). The triazolium **9**•PF_6 was collected (86 mg, 45%) using an Ethyl Acetate/MeOH/NH_4PF_6 (50:50:1, v:v:w) mixture as the eluent.

9•PF_6: M.p. > 93.5 °C (dec.); ^{1}H NMR (CD_3COCD_3, 500 MHz, 298 K): δ = 8.58 (s, 1 H), 8.52 (t, J = 5.5 Hz, 1 H), 8.18 (t, J = 5.5 Hz, 1 H), 8.01 (s, 1 H), 7.81 (d, J = 3.0 Hz, 1 H), 7.80 (d, J = 3.0 Hz, 1 H), 7.51 (s, 1 H), 7.50 (s, 1 H), 7.43–7.40 (m, 2 H), 5.12 (d, J = 6.0 Hz, 2 H), 4.92–4.88 (m, 4 H), 4.83 (s, 2 H), 4.77 (s, 2 H), 4.60 (t, J = 5.5 Hz, 4 H), 3.95 (t, J = 5.0 Hz, 2 H), 3.91 (t, J = 5.0 Hz, 2 H), 3.59 (s, 4 H), 1.69 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (CD_3COCD_3, 125 MHz, 298 K): δ = 168.8, 167.4, 147.6, 147.5, 144.5, 141.8, 130.0, 129.8, 129.7, 126.6, 126.6, 124.9, 124.8, 122.7, 110.0, 109.7, 70.4, 69.7, 69.1, 68.4, 67.8, 67.5, 53.9, 50.2, 47.3, 33.9, 31.8, 13.4; MS (FAB+): 579 (40%) $[M - PF_6]^+$; HRMS (ESI+): $C_{28}H_{35}F_6N_8O_6P$ $[M - PF_6]^+$: calcd 579.2674, found 579.2680.



Synthesis of the MC3-Derivatized Triazolium S8•PF_6

A mixture of the macrocycle **MC3** (104 mg, 0.208 mmol) and the azide-containing ammonium salt **5**•PF_6 (94 mg, 0.208 mmol) was dissolved in CH_2Cl_2 (3 mL) under N_2 atmosphere and cooled down to 0 ˚C. Triethyl phosphite (71 μL, 0.42 mmol) was added dropwise through a syringe and the mixture was stirred overnight at room temperature. The resulting solution was concentrated and subjected to column chromatography (SiO_2).

The triazolium **S8**•PF_6 was collected (59 mg, 42%) using an Ethyl Acetate/MeOH/NH_4PF_6 (50:50:1, v:v:w) mixture as the eluent.

S8•PF_6: ^{1}H NMR (CD_3COCD_3, 500 MHz, 298 K): δ = 8.62 (br s, 1 H), 8.58 (s, 1 H), 8.16 (br s, 1 H), 8.00 (s, 1 H), 7.52 (m, 2 H), 7.12 (m, 1 H), 5.06 (d, J = 6.0 Hz, 2 H), 4.90 (m, 4 H), 4.68 (s, 2 H), 4.61 (m, 4 H), 4.57 (d, J = 5.5 Hz, 2 H), 3.98 (t, J = 5.0 Hz, 2 H), 3.92 (t, J = 5.0 Hz, 2 H), 3.62 (m, 4 H), 1.68 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (CD_3COCD_3, 125 MHz, 298 K): δ = 169.2, 168.0, 147.9, 147.9, 144.6, 141.6, 130.1, 122.9, 122.7, 115.4, 115.3, 70.3, 69.7, 69.0, 68.4, 67.5, 53.9, 50.1, 47.2, 34.0, 31.6, 30.6, 13.4; MS (FAB+): 529 (60%) $[M - PF_6]^+$.

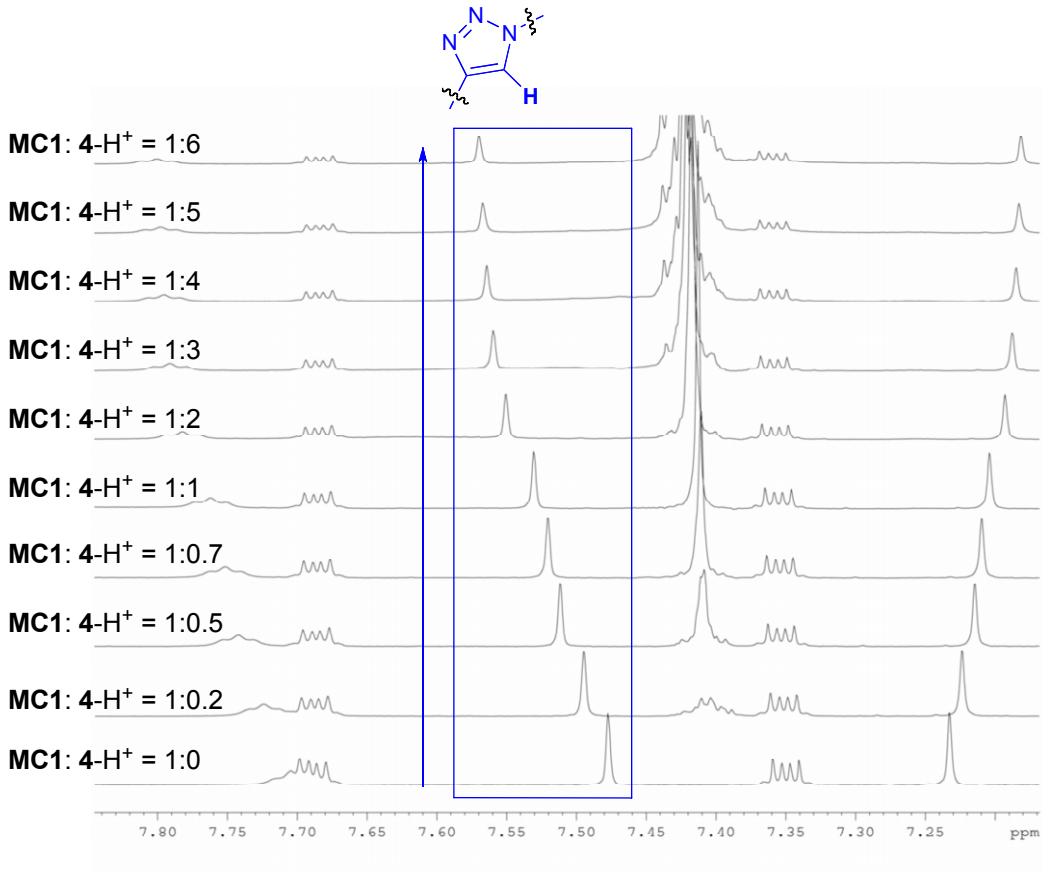
Measurements of Binding Constants Using ^{1}H NMR Spectroscopy

All ^{1}H NMR binding studies were carried out at 25 °C. Stock solutions of the macrocycles and the guests were prepared at 5.0 mM and 15.0 mM, respectively. Typically, an aliquot of the macrocycle's solution (0.60 mL) was transferred to an NMR tube, and aliquots of the guest solutions were added at different batches. ^{1}H NMR spectra were recorded upon each addition of the guest solution. The chemical shift changes of the triazole protons of the macrocycles (or the naphthyl singlet in the case of MC2) were conveniently followed and fitted into the WinEQNMR program[1] using a 1:1 binding isotherm to get the binding constants. The partial titration ^{1}H NMR spectra of each host-guest pairs were listed below, together with the fitting curve generated from the fitting program.

Reference:

1. For a discussion of its application in determining binding constant, see: M. J. Hayes, *J. Chem. Soc., Dalton Trans.*, **1993**, 311-312.

The ^{1}H NMR titration data of the pair of **MC1** and **4**-H^{+}

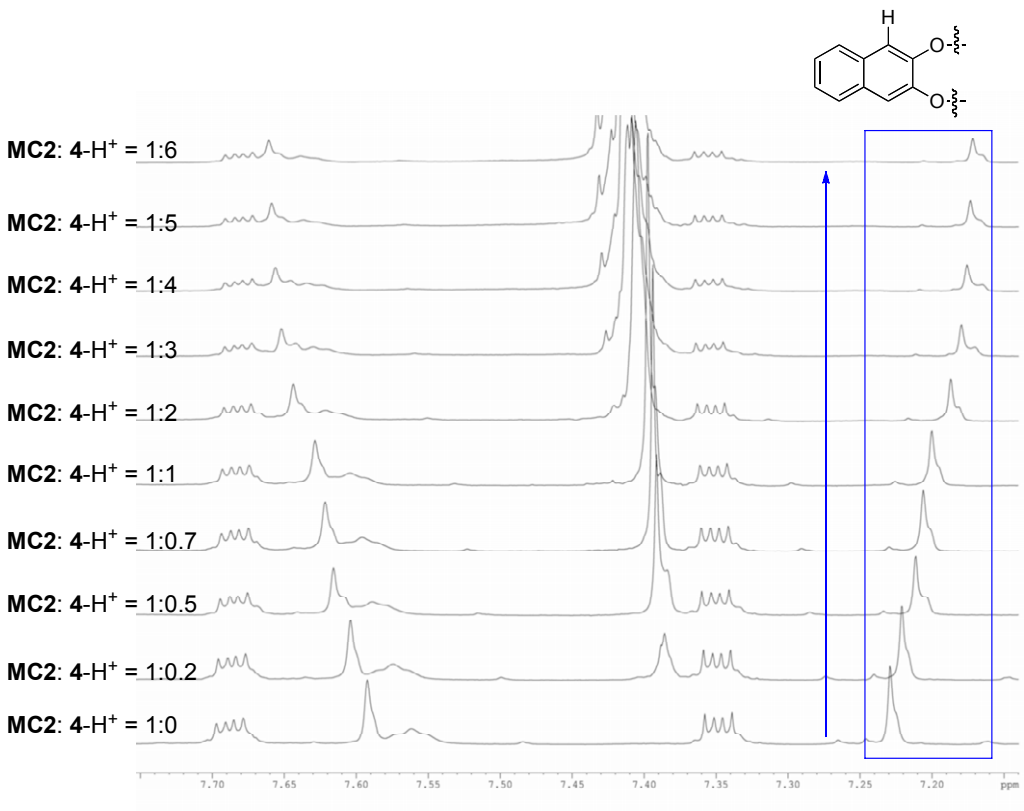


The fitting cure of the pair of **MC1** and **4**-H^{+}

δ / ppm

c_{guest} / mM

The ^{1}H NMR titration data of the pair of **MC2** and **4**-H^+

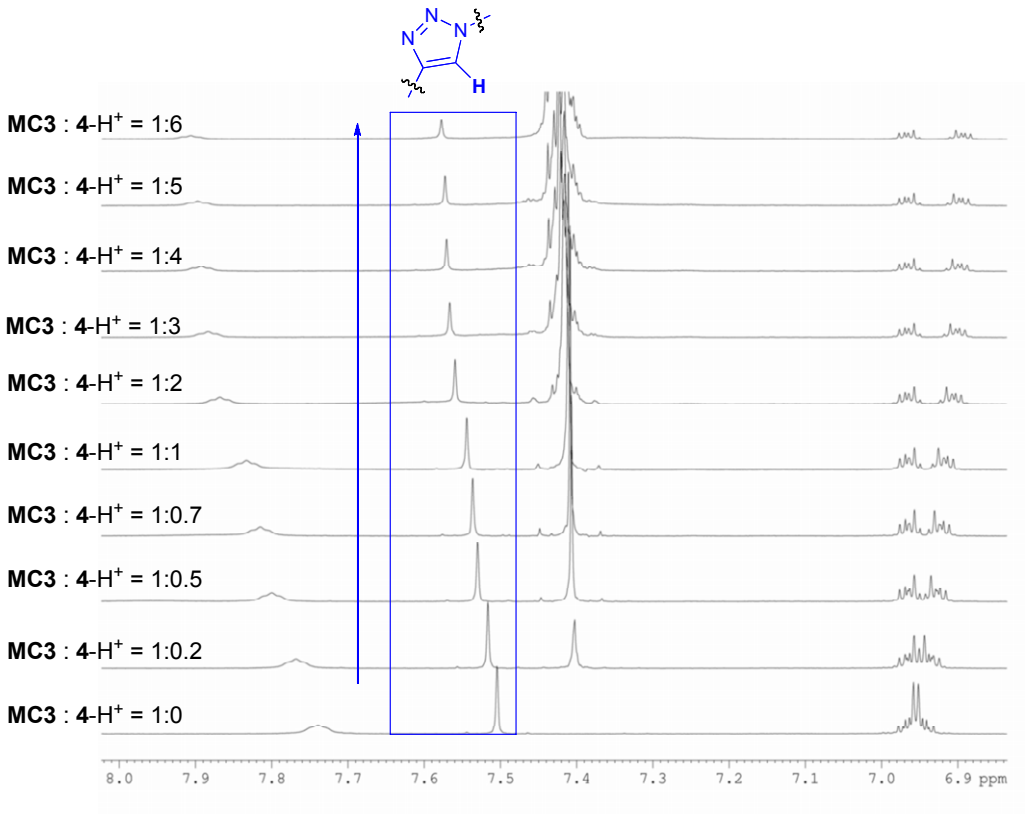


The fitting cure of the pair of **MC2** and **4**-H^+

δ / ppm

c_{guest} / mM

The ^{1}H NMR titration data of the pair of **MC3** and **4**-H^+

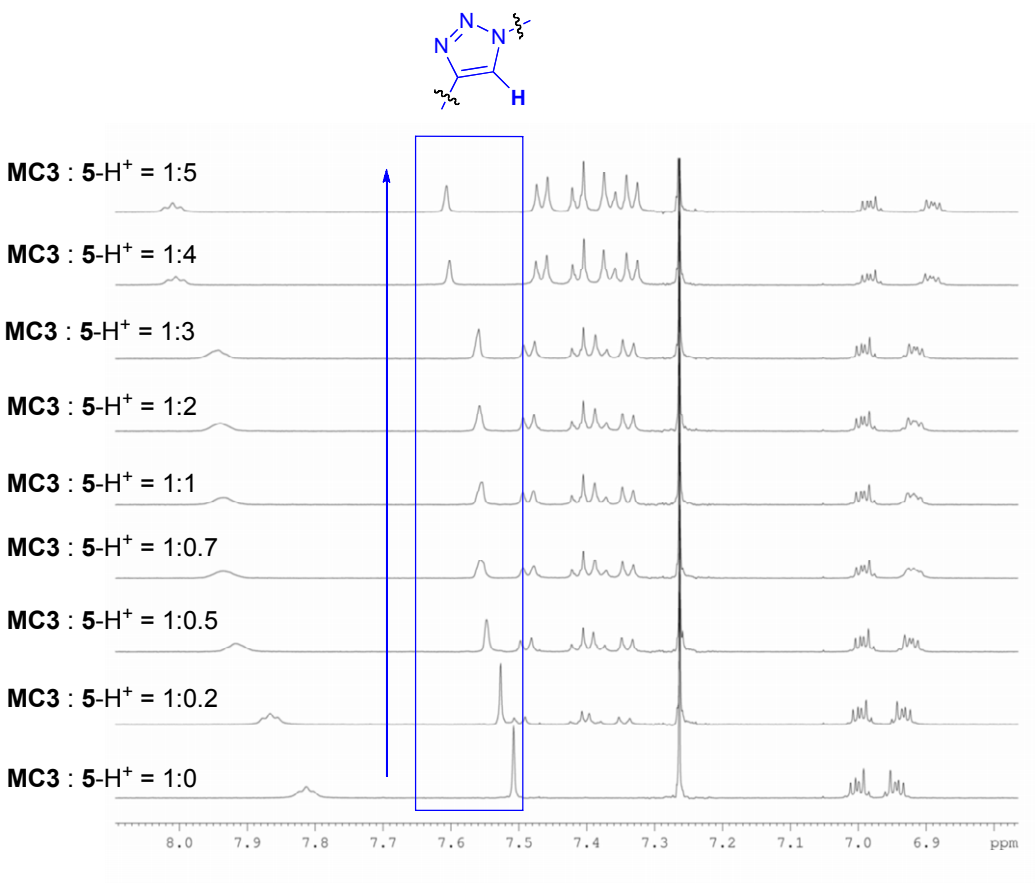


The fitting cure of the pair of **MC3** and **4**-H^+

δ / ppm

c_{guest} / mM

The ^{1}H NMR titration data of the pair of **MC3** and **5**-H$^+$

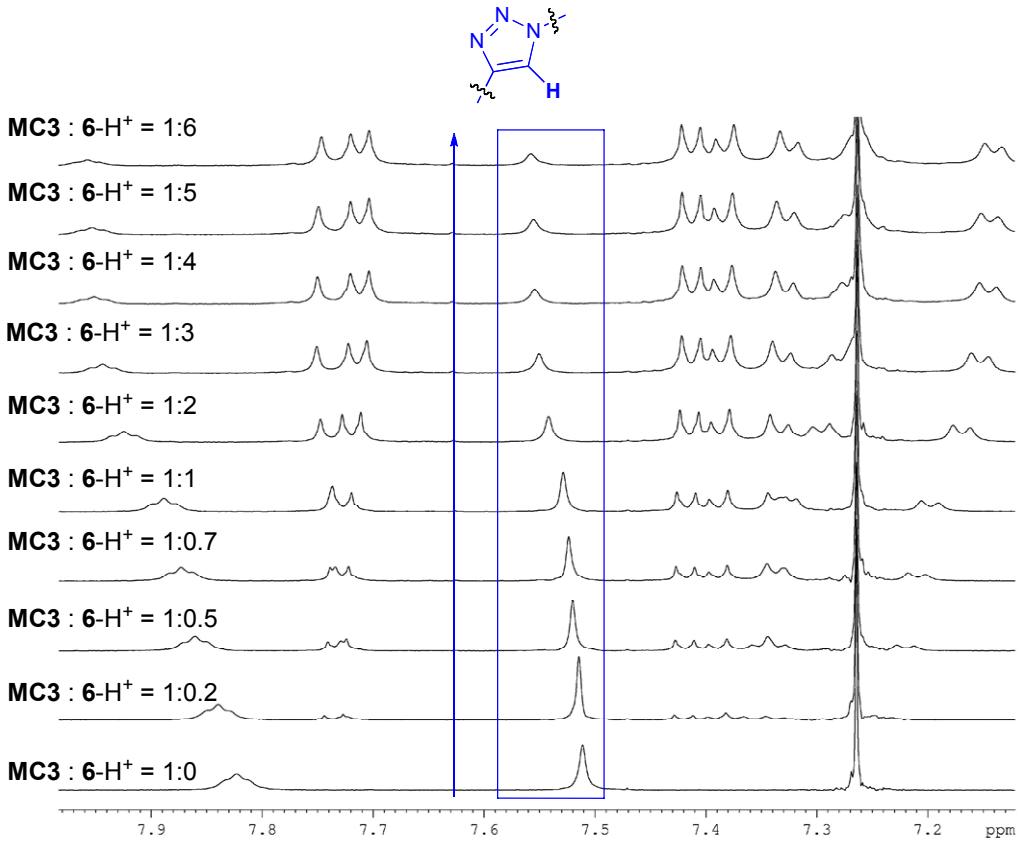


The fitting cure of the pair of **MC3** and **5**-H^+

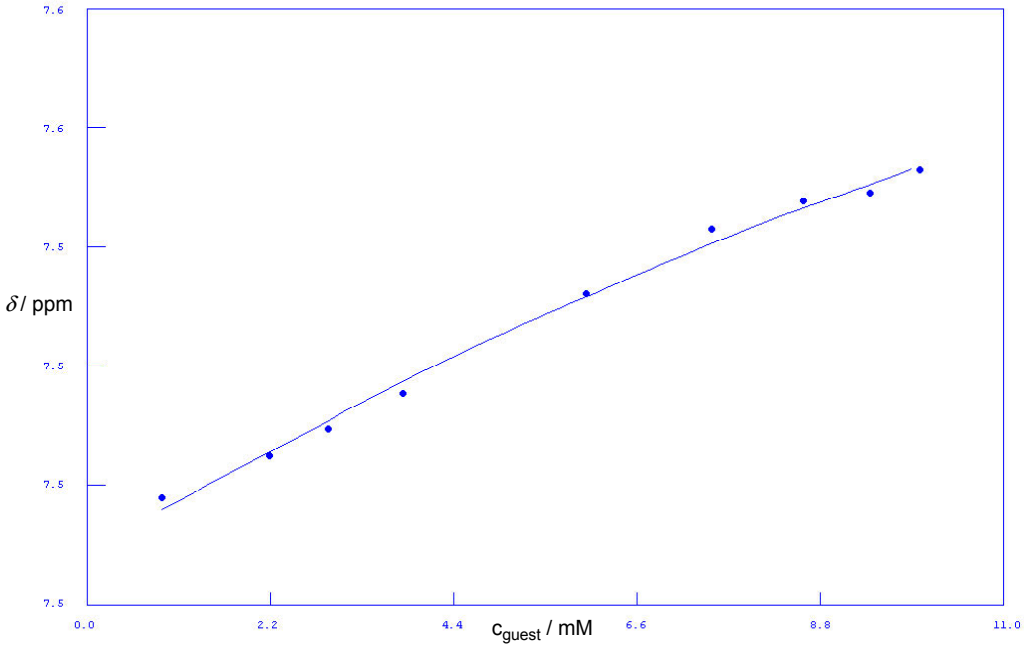
δ / ppm

c_{guest} / mM

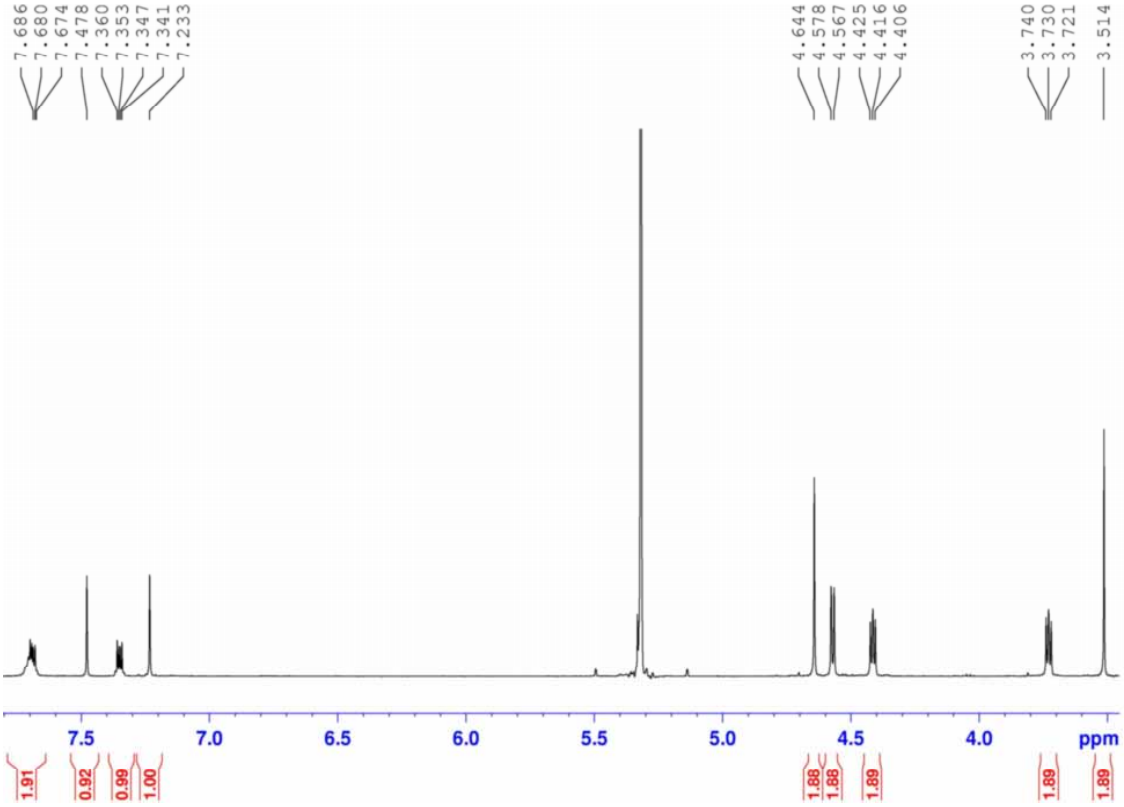
The ^{1}H NMR titration data of the pair of **MC3** and **6**-H^+



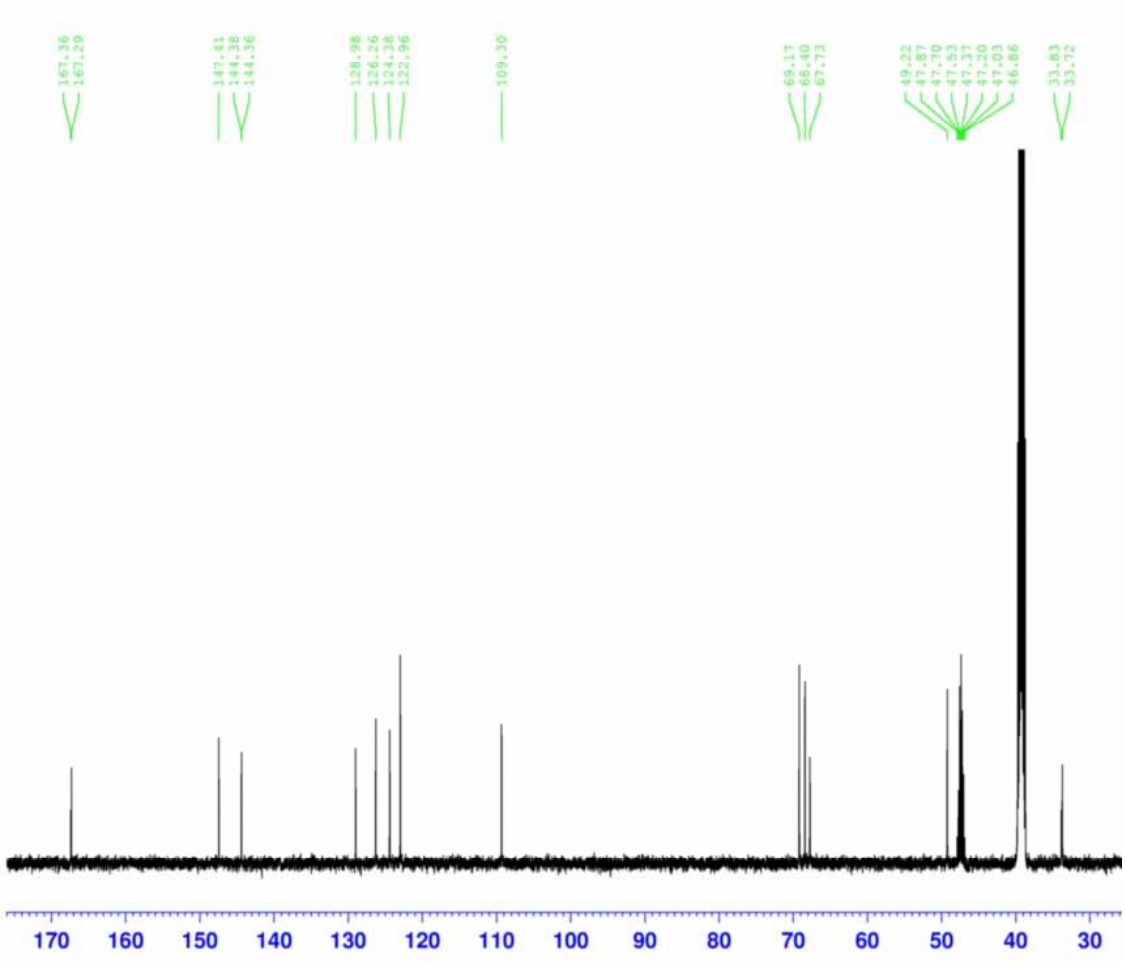
The fitting cure of the pair of **MC3** and **6**-H^+



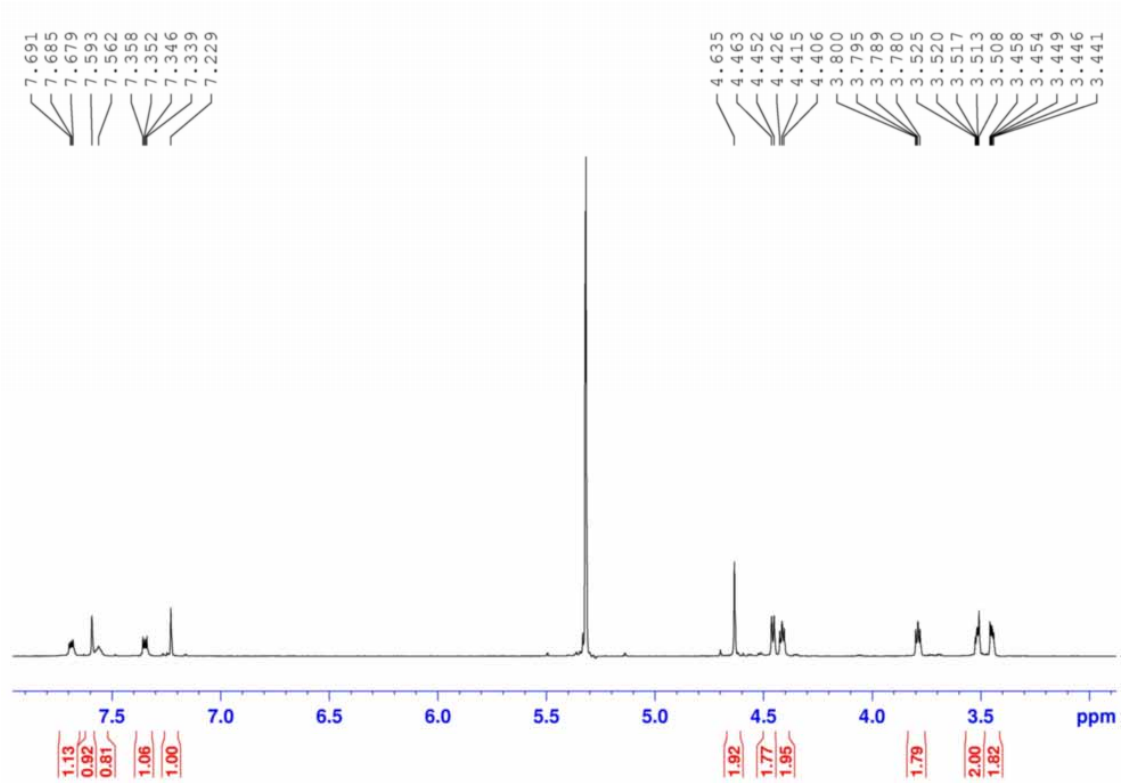
^{1}H NMR spectrum of **MC1**



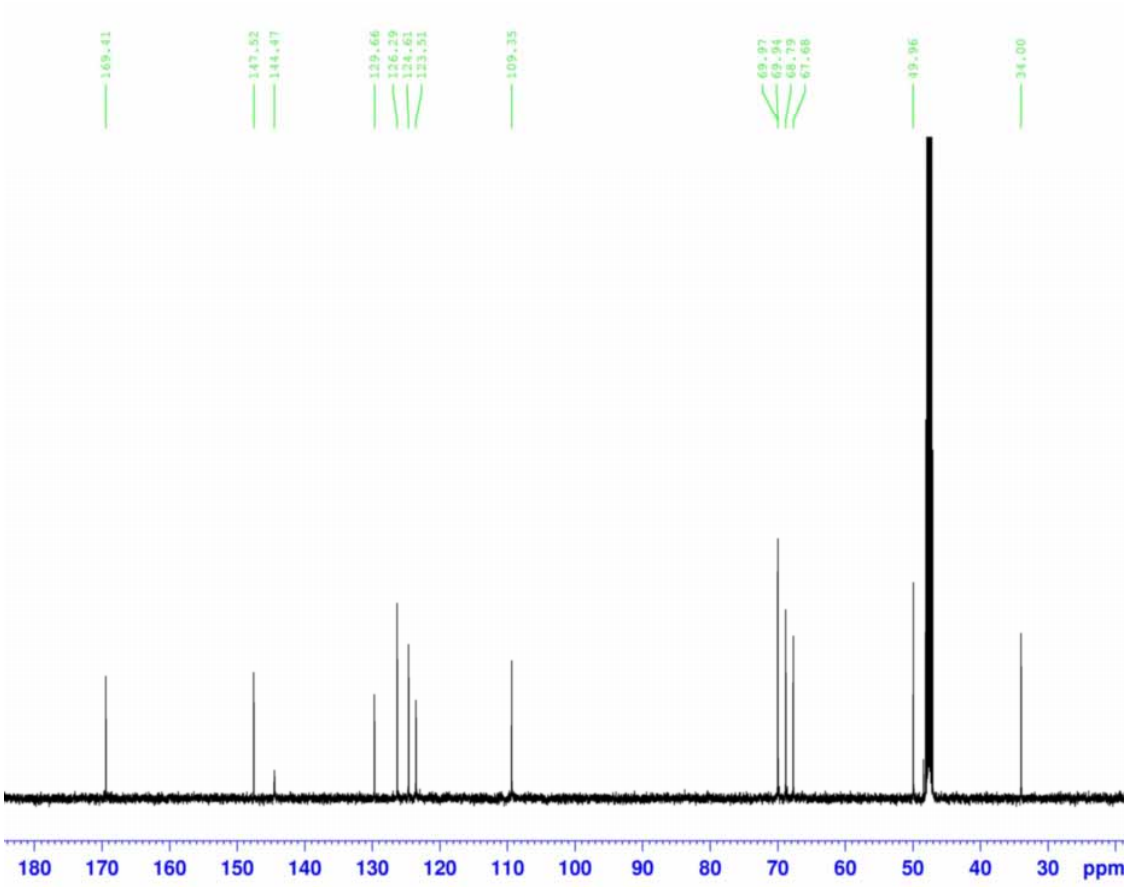
^{13}C NMR spectrum of **MC1**



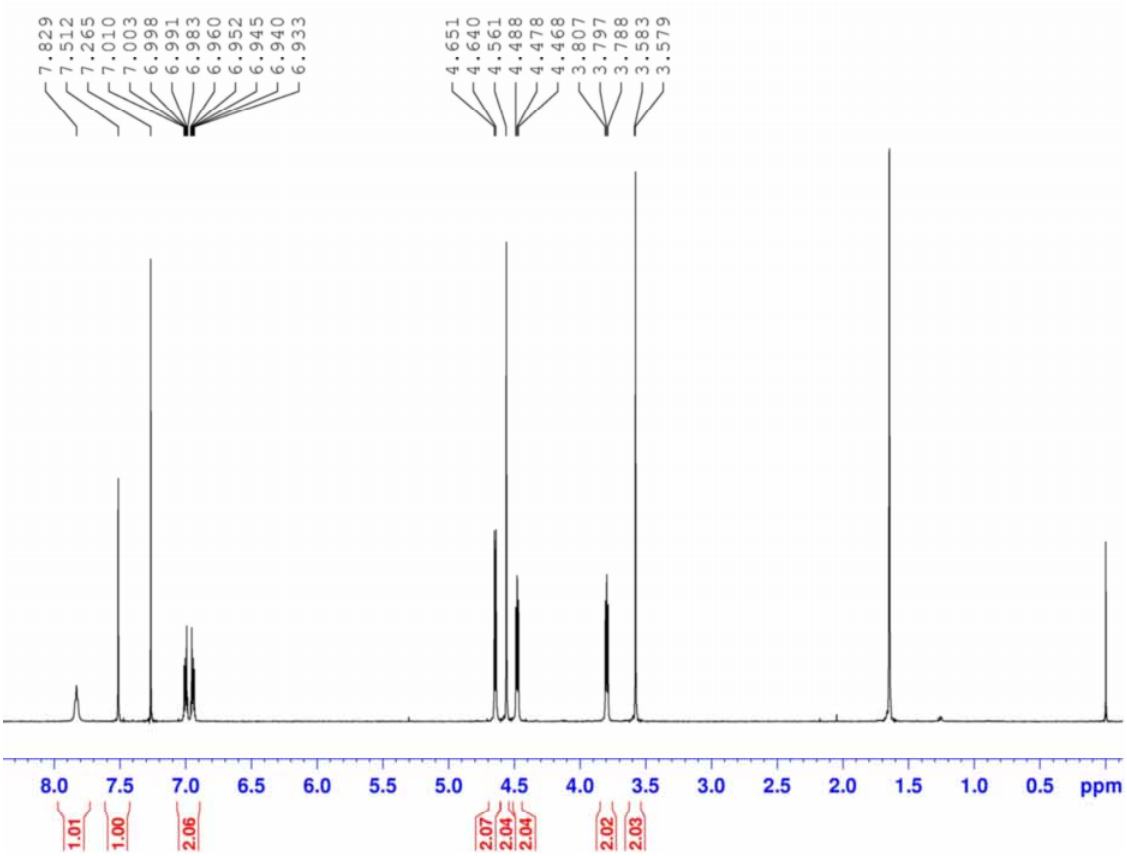
^{1}H NMR spectrum of **MC2**



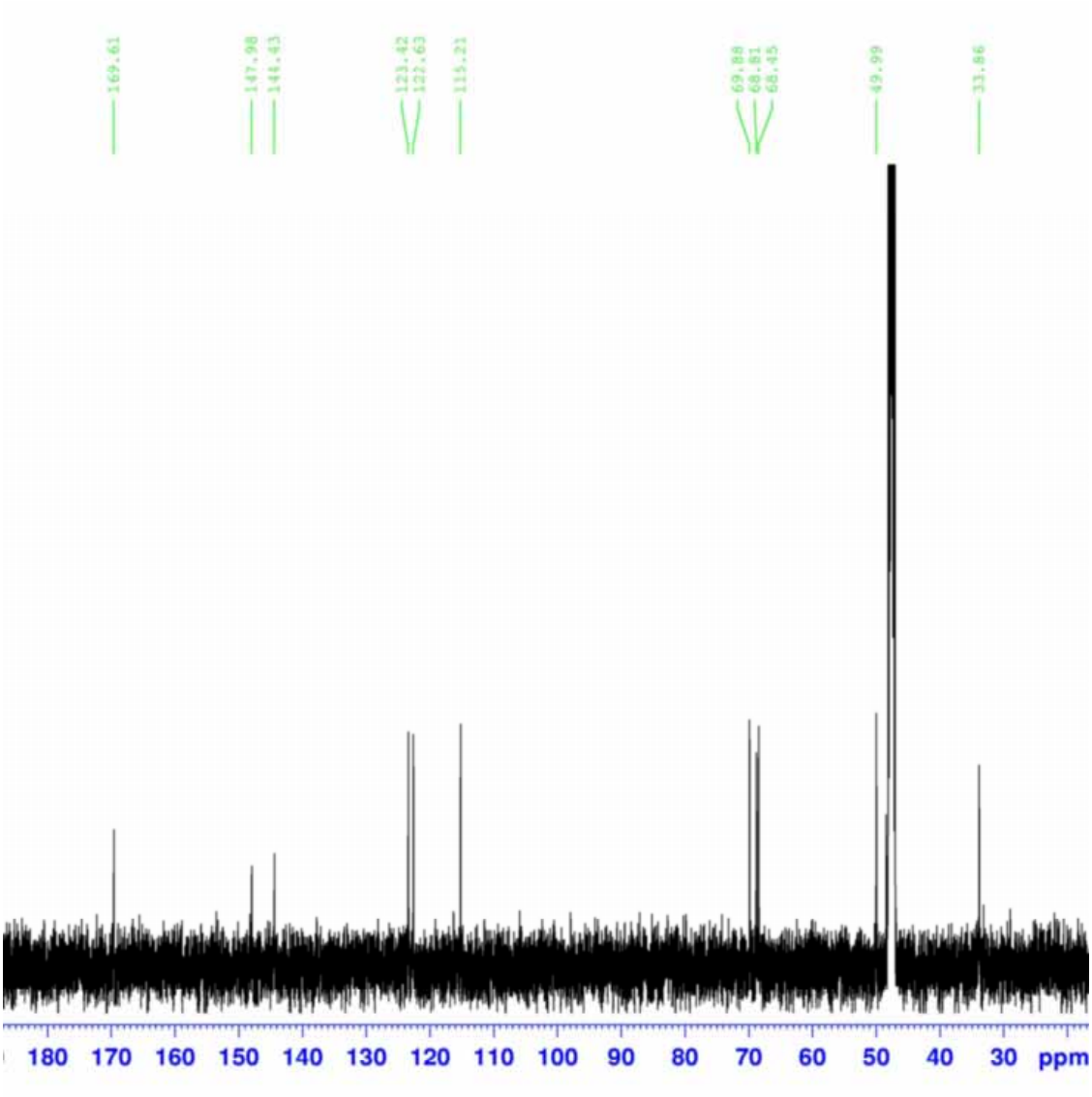
^{13}C NMR spectrum of **MC2**



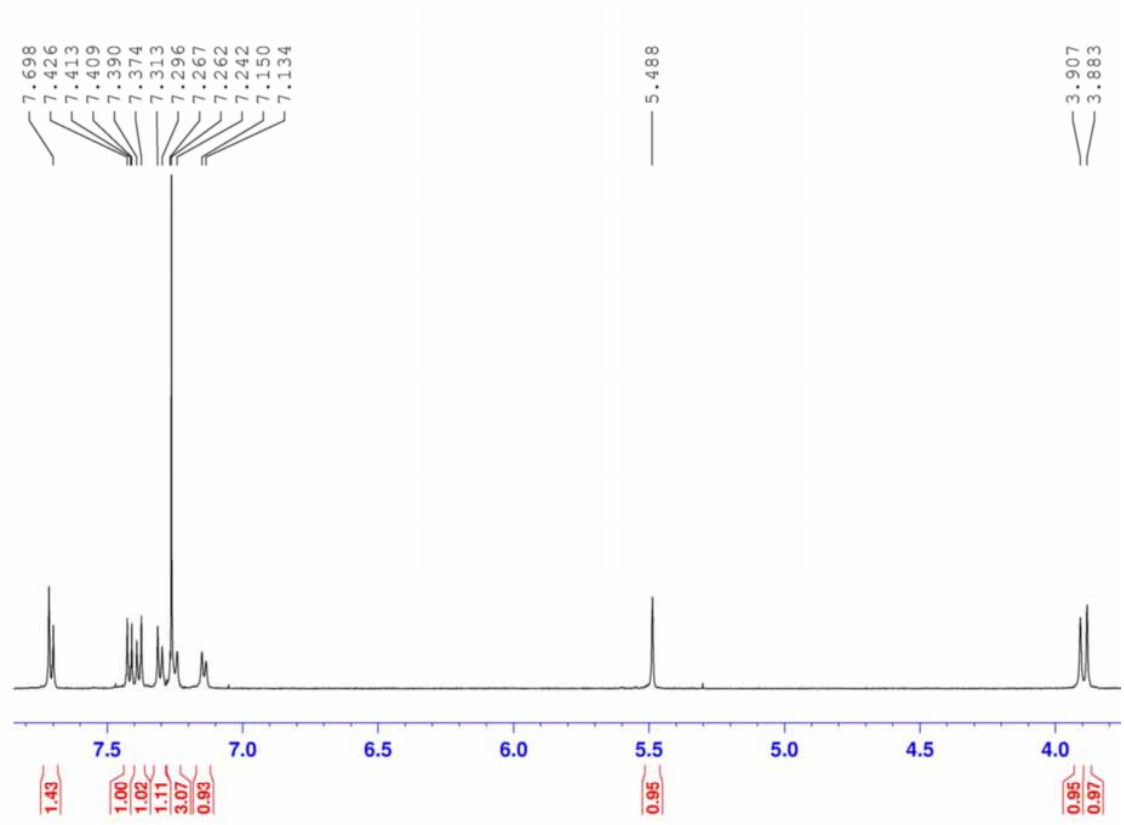
^{1}H NMR spectrum of **MC3**



^{13}C NMR spectrum of **MC3**

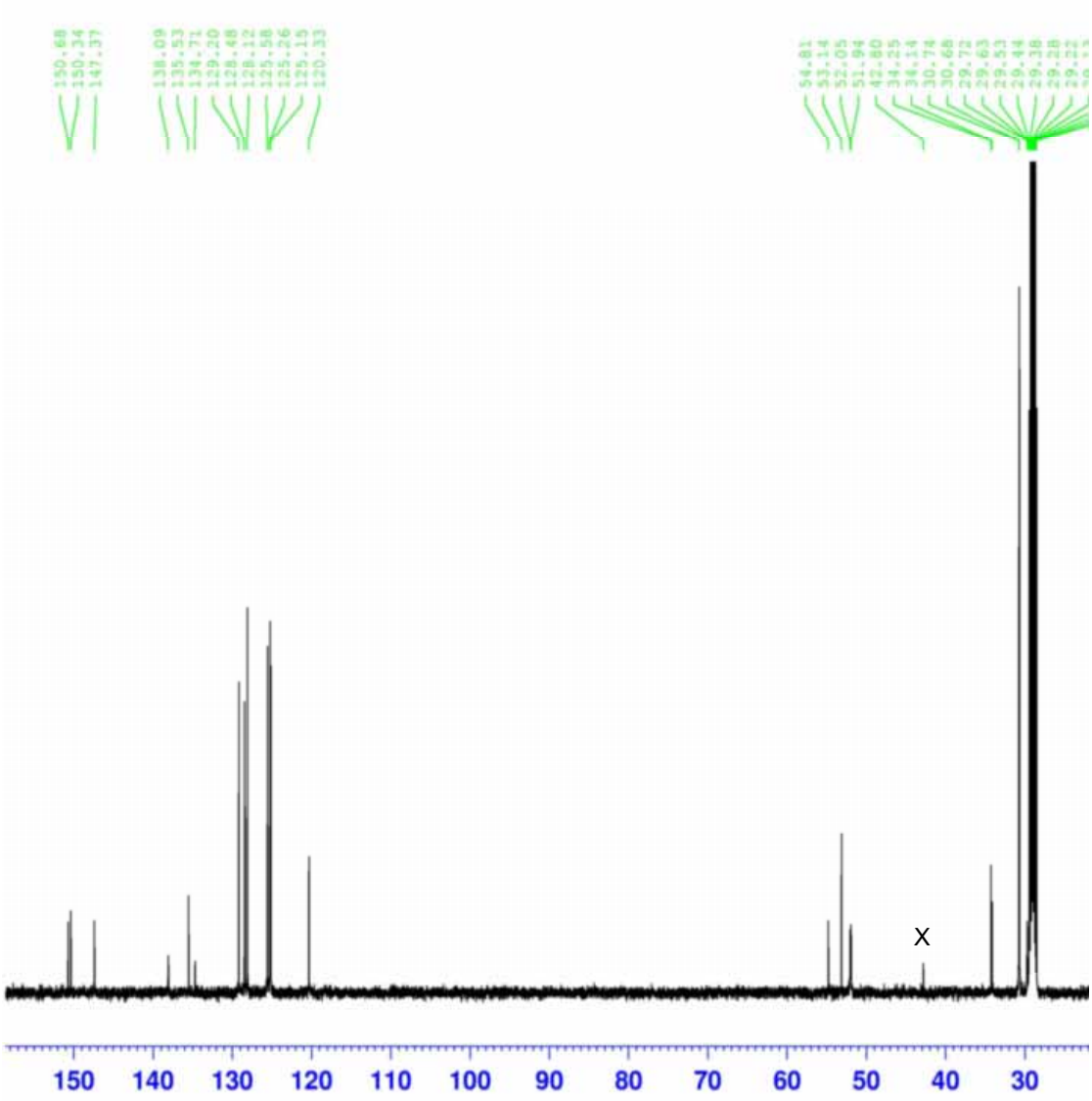


^{1}H NMR spectrum of **7**-H•PF_6

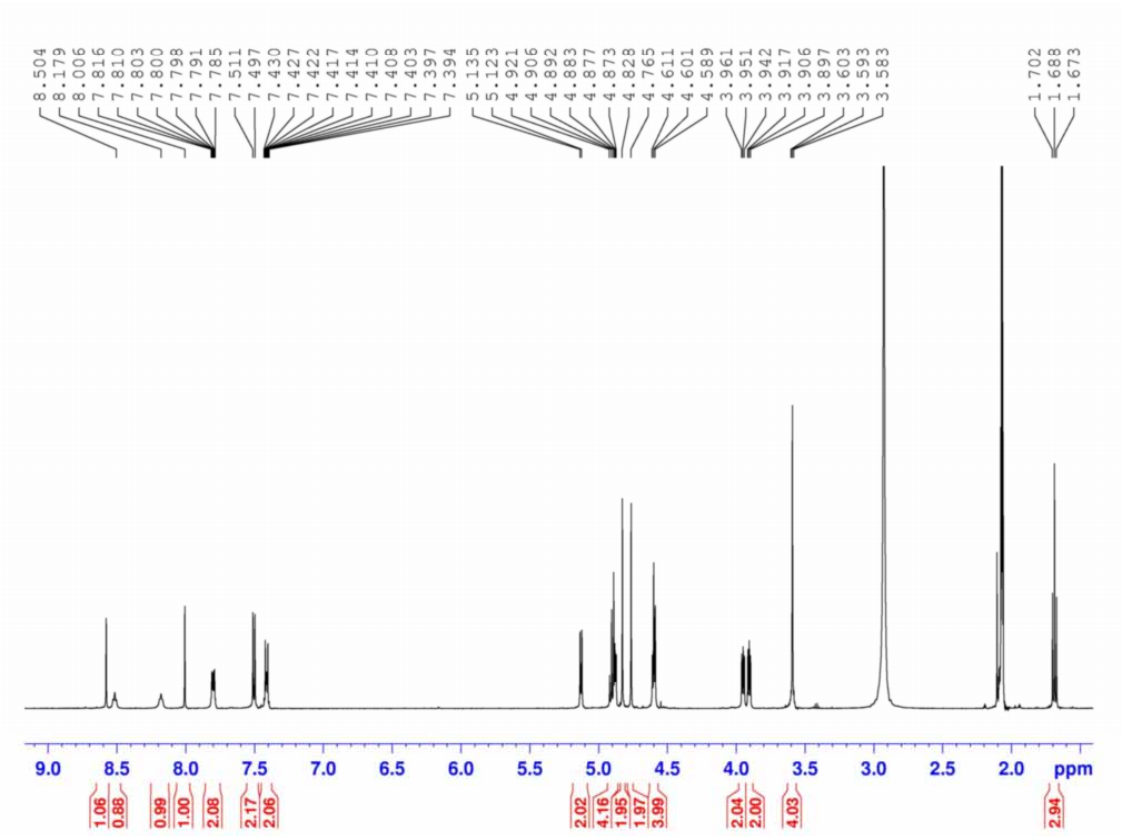


^{13}C NMR spectrum of **7**-H•PF_6

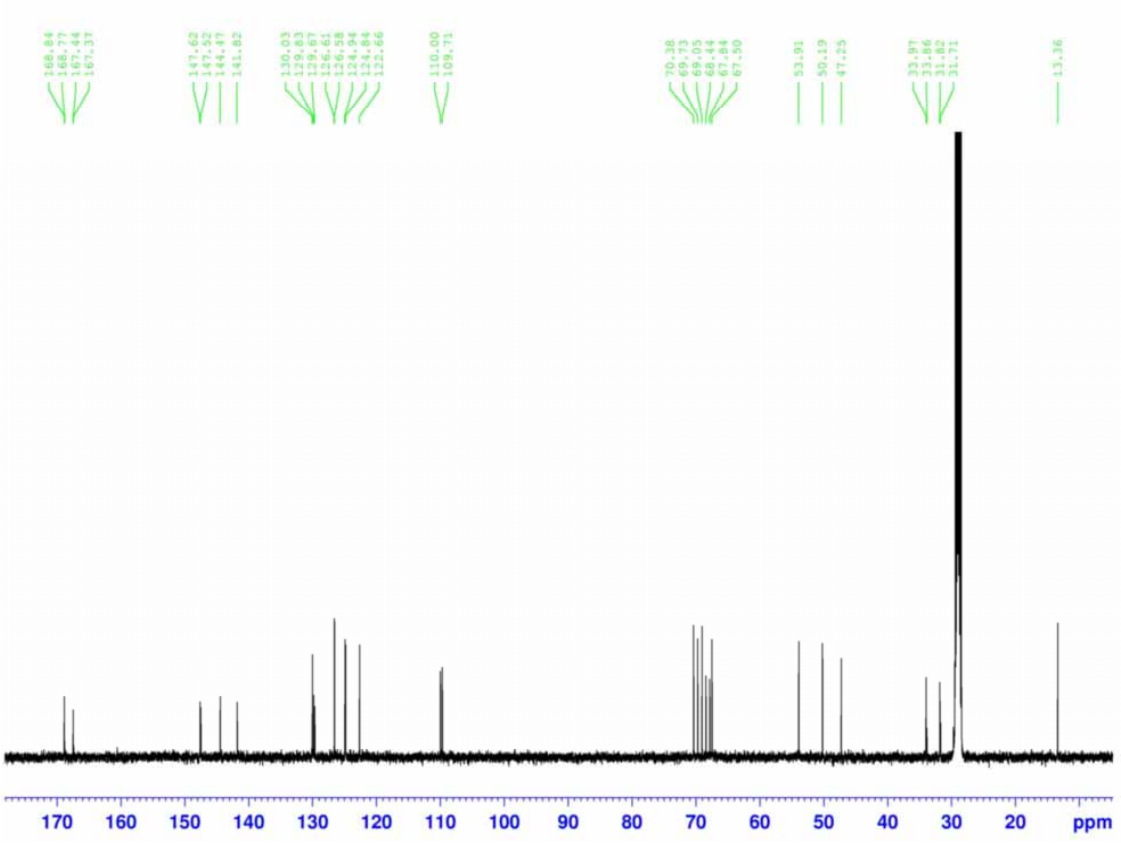
X: impurity



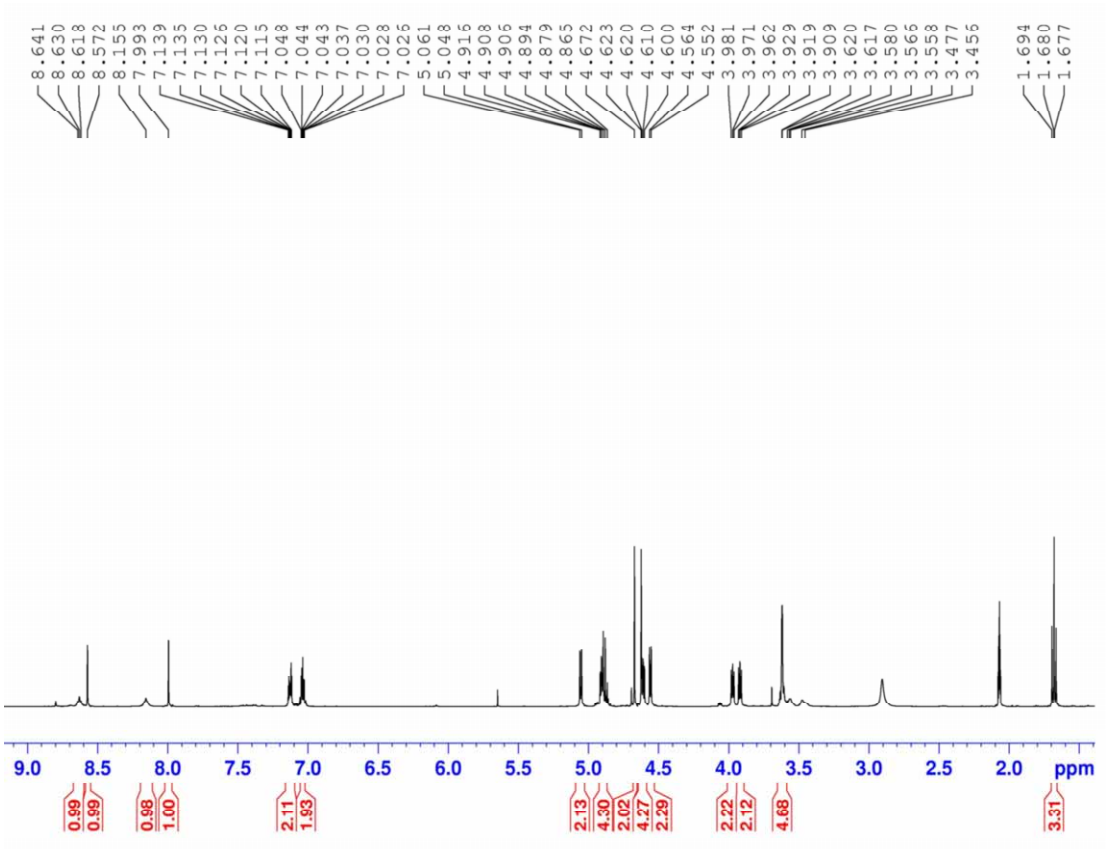
^{1}H NMR spectrum of **9**•PF_6



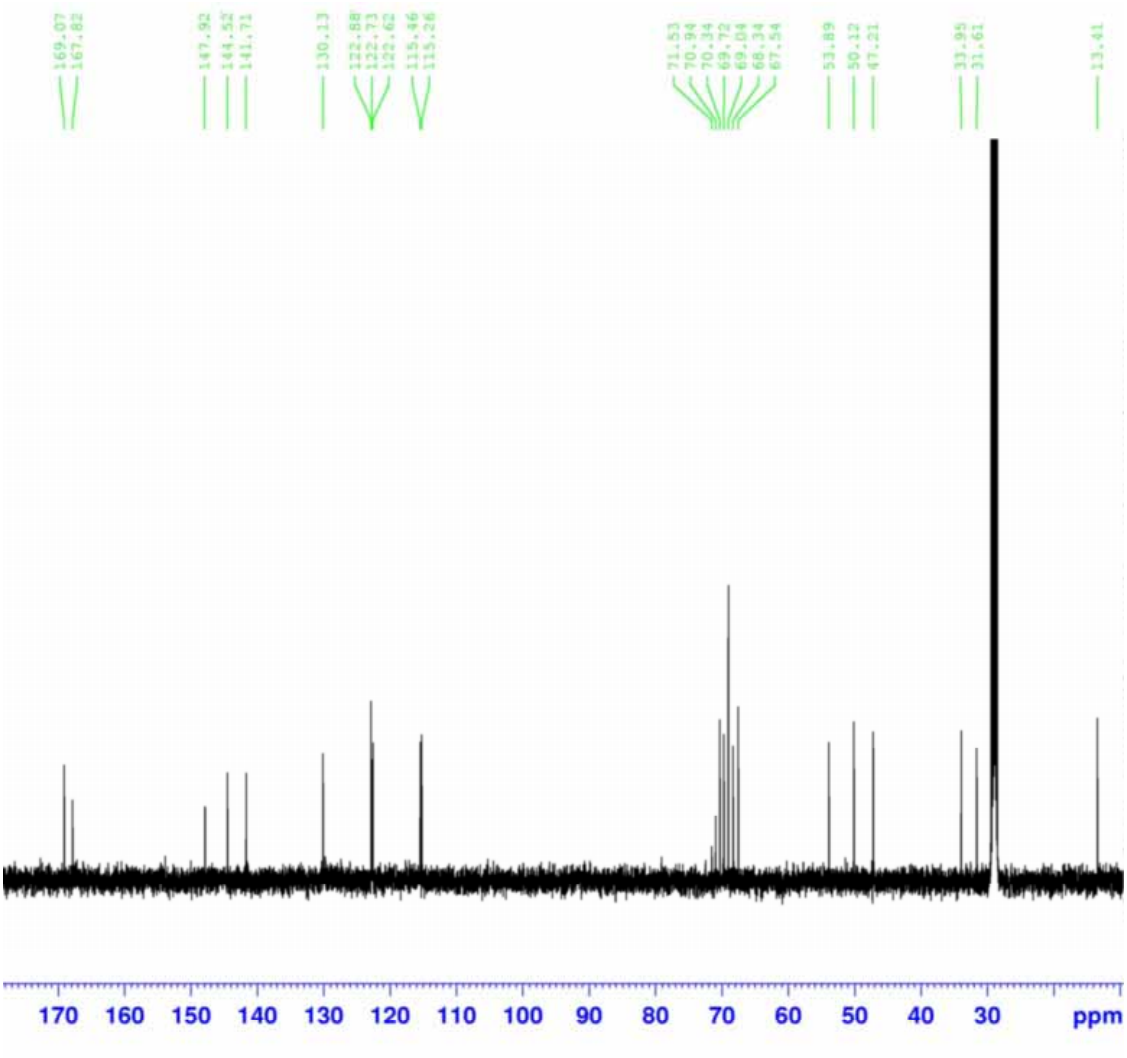
^{13}C NMR spectrum of **9**•PF_6



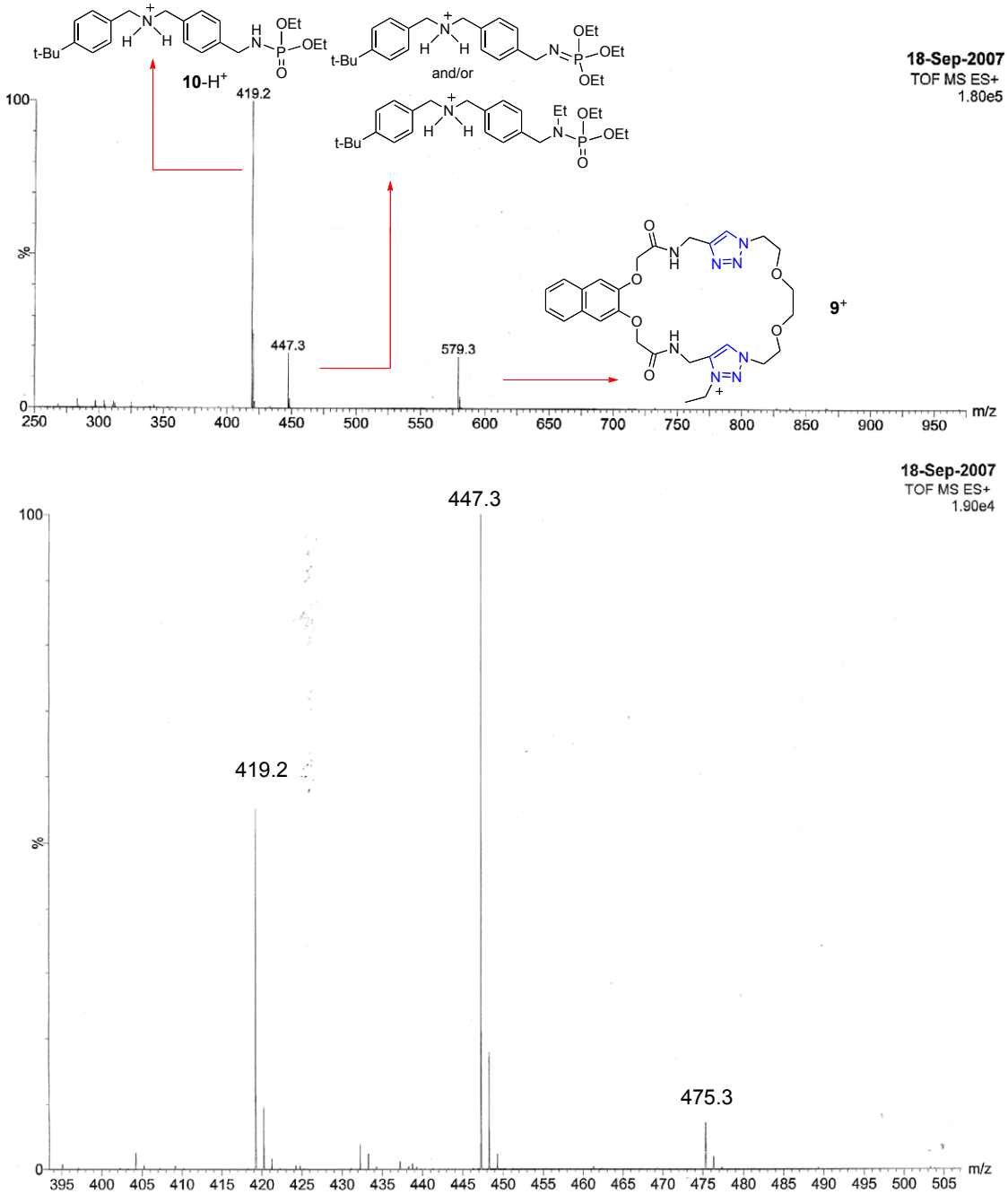
^{1}H NMR spectrum of **S8**•PF_6



^{13}C NMR spectrum of **S8**•PF_6

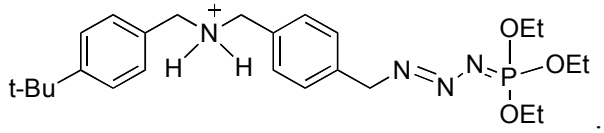


ESI-MS spectra of the Staudinger-Arbuzov reaction sequence with **MC1** (top) and without **MC1** (bottom).



ESI-MS spectrum of the reaction mixture contains (top spectrum, solvent MeOH) a prominent peak corresponding to **10**-H^+, together with the monoalkylated product $\mathbf{9}^+$. All the starting azide **5**-H^+ was consumed as indicated by the lack of signal at *m/z* 309. The *m/z* 447 peak might correspond to the intermediate phosphorimidate and/or a rearrangement product, *N*-ethyl phosphoramidate. The unreacted macrocycle **MC1** was not registered in this spectrum, which could be attributed to its much lower ionization

ability compared to the other ionic species. The bottom spectrum is the ESI-MS spectrum of the reaction mixture without **MC1**. The spectrum was taken under identical conditions as the top one. Two major peaks were observed at *m/z* 419 and 447, suggesting the presence of **10**-H^+ and similar other species as in the **MC1**-mediated reaction. The difference in the relative intensity between peaks 419 and 447 qualitatively indicated that the dealkylation process is more effective in the presence of **MC1**. In addition, the peak at *m/z* 475.3 in the bottom spectrum might correspond to the adduct



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