Electronic Supporting Information

De novo approach and facile synthesis of water-soluble interlocked and non-interlocked organic cages

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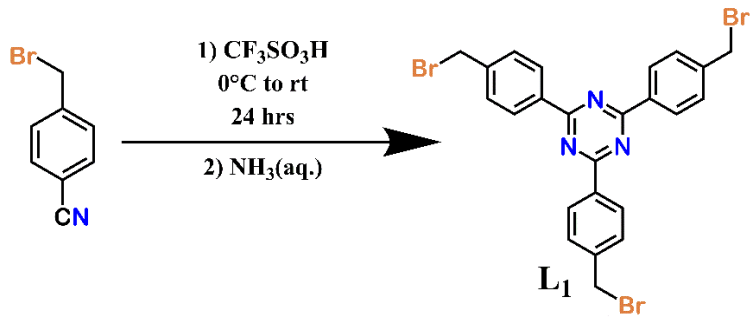
Contents:

1.1 Materials and methods:

General chemicals and the solvents were purchased from commercially available suppliers and were used without further purification. All the reactions were carried out under nitrogen atmosphere. The NMR spectra of the newly prepared materials were recorded on BRUKER 400 MHz and 500 MHz spectrometers. The chemical shifts (δ) in the ^{1}H NMR spectra were reported in ppm relative to the tetramethylsilane, which was used as an internal standard (δ = 0.00 ppm) or the resonance of the proton resulting from partial deuteriation of the NMR solvents: D_2O (δ = 4.79 ppm), $CDCl_3$ (δ = 7.26 ppm), CD_3CN (δ = 1.94 ppm) and DMSO-d_6 (δ = 2.50 ppm). ^{13}C NMR spectra were recorded using the same instruments at 100 MHz, 125 MHz and all the chemical shifts (δ) were reported in ppm relative to external $CDCl_3$ at 77.8-77.2 ppm, CD_3CN at 1.32, 118.26 ppm and DMSO-d_6 at 39.52 ppm. Electrospray ionization mass spectra were recorded using Agilent 6538 Ultra-High Definition (UHD) Accurate Mass Q-TOF spectrometer along with the use of standard spectroscopic grade solvents.

1.2 Synthesis

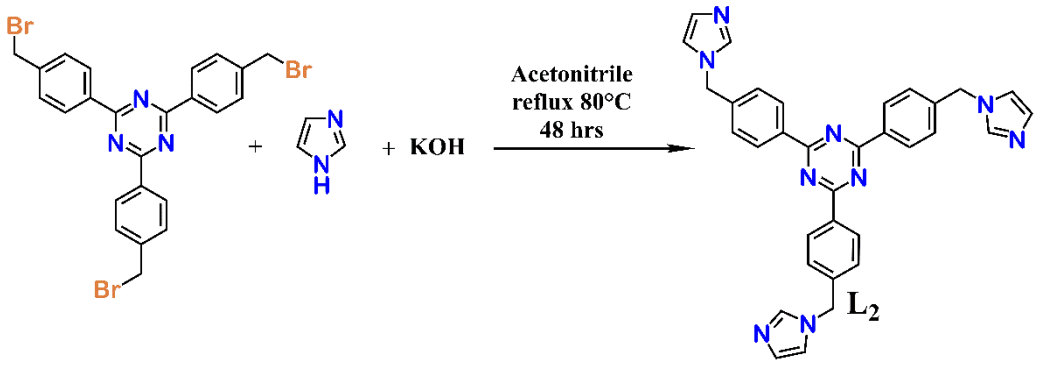
Synthesis of L_1: To a 250 mL round-bottom flask kept in an ice bath, CF_3SO_3H (triflic acid) (15.3 mmol) was added. The solution was stirred for 10 minutes, after that solid 4-(bromomethyl)benzonitrile (5.1 mmol) was added. The mixture was stirred at room temperature for 24 h and then poured into 100 mL of crushed ice. The mixture was then neutralised with aq. NH_3. The white solid powder which precipitated out was then filtered to obtain the ligand **L_1**. Yield: 89%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.72 (d, 6H), 7.60 (d, 6H), 4.59 ppm (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.15, 142.30, 136.09, 129.49, 129.4, 32.73 ppm. HRMS (ESI): $C_{24}H_{18}Br_3N_3$, $[M + Na]^+$ = 609.81 (calc.) found: 609.80.



Scheme S1: Synthetic route for the preparation of the ligand **L_1**.

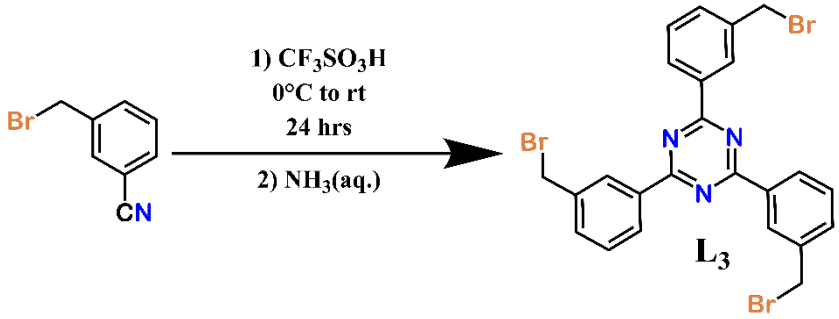
Synthesis of L_2: Imidazole (10.2 mmol) and KOH (20.4 mmol) were taken in a 100 mL round-bottom flask with 25 mL acetonitrile. The mixture was stirred for 2 h, after which ligand **L_1**

(1.7 mmol) was added. The mixture was then put for reflux at 80 °C for 48 h. The solvent was then evaporated and the remaining solid was washed thoroughly with water. This yielded the ligand **L2** as a white solid. Yield: 91%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.72 (d, 6H), 7.61 (s, 3H), 7.33 (d, 6H), 7.13 (s, 3H), 6.95 (s, 3H), 5.25 ppm (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.19, 140.85, 137.72, 137.42, 136.03, 129.68, 127.39, 119.43, 50.58 ppm. HRMS (ESI): $C_{33}H_{27}N_9$, $[M + H]^+$ = 550.24 (calc.) found: 550.24; $[M + Na]^+$ = 572.24 (calc.) found: 572.25.



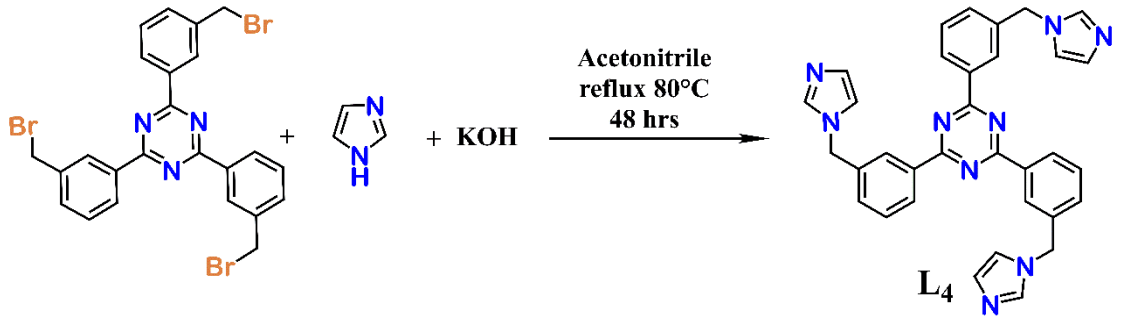
Scheme S2: Synthetic route for the preparation of the ligand **L2**.

Synthesis of L3: To a 250 mL round-bottom flask kept in an ice bath, CF_3SO_3H (triflic acid) (15.3 mmol) was added. The solution was stirred for 10 minutes, after that solid 3-(bromomethyl)benzonitrile (5.1 mmol) was added. The mixture was stirred at room temperature for 24 hours and then poured into 100 mL of crushed ice. The mixture was then neutralised with aq. NH_3. The white solid powder which precipitated out was then filtered to obtain the ligand **L3.** Yield: 910 mg (1.55 mmol, 91%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.76 (s, 3H), 8.73 (d, 3H), 7.69 (d, 3H), 7.61 (dd, 3H), 4.69 ppm (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.28,138.47, 136.59, 133.56, 133.3, 129.4, 129.19, 33.16 ppm. HRMS (ESI): $C_{24}H_{18}Br_3N_3$, $[M + Na]^+$ = 609.81 (calc.) found: 609.89.



Scheme S3: Synthesis of the ligand **L3**.

Synthesis of L_4: Imidazole (10.2 mmol) and KOH (20.4 mmol) was taken in a 100 mL round-bottom flask with 25 mL acetonitrile. The mixture was stirred for 2 h, after which ligand **L_3** (1.7 mmol) was added. The mixture was then put for reflux at 80 ^{o}C for 48 h. The solvent was then evaporated and the remaining solid was washed thoroughly with water. This yielded the ligand **L_4** as a white solid. Yield: 855 mg (1.55 mmol, 91%). ^{1}H NMR ($CDCl_3$, 125 MHz): δ = 8.68 (d, 3H), 8.47 (s, 3H), 7.69 (s, 3H), 7.61 (dd, 3H), 7.4 (d, 3H), 7.15 (s, 3H), 7.01 (s, 3H), 5.32 ppm (s, 3H). ^{13}C NMR ($CDCl_3$, 500 MHz): δ = 171.21, 137.78, 137.47, 136.99, 136.61, 131.38, 129.96, 128.9, 127.74, 119.50, 50.67 ppm. HRMS (ESI): $C_{33}H_{27}N_9$, $[M + H]^{+}$= 550.24 (calc.) found: 550.26 $[M + Na]^{+}$= 572.24 (calc.) found: 572.25.



Scheme S4: Synthesis of the ligand **L_4**.

Synthesis of 1: **L_1** (0.047 mmol) was dissolved in 100 mL of 4:1 (v/v) mixture of $CHCl_3$ and CH_3CN in a 250 mL two-neck round-bottom flask. **L_2** (0.047 mmol) and TBAI (Tetra-butylammonium iodide) (0.142 mmol) were also dissolved in 100 mL of 4:1 (v/v) mixture of $CHCl_3$ and CH_3CN and added dropwise to the previous solution slowly over a period of 6-8 h. The resulting mixture was refluxed for 4 days. After completion, the precipitate was collected. It was then dissolved in hot water discarding the undissolved part, then by evaporating the solvent the product (cage **1**) was isolated as white powder. Yield: (0.006 mmol, 26%). ^{1}H NMR (D_2O, 400 MHz): δ = 9.0 (s), 8.24 (s, 6H), 8.14 (s, 6H), 7.63 (d, 12H), 7.43 (d, 12H), 7.26 (d, 12H), 6.01 (d, 12H), 5.64 (d, 12H), 5.51 ppm (d, 12H).

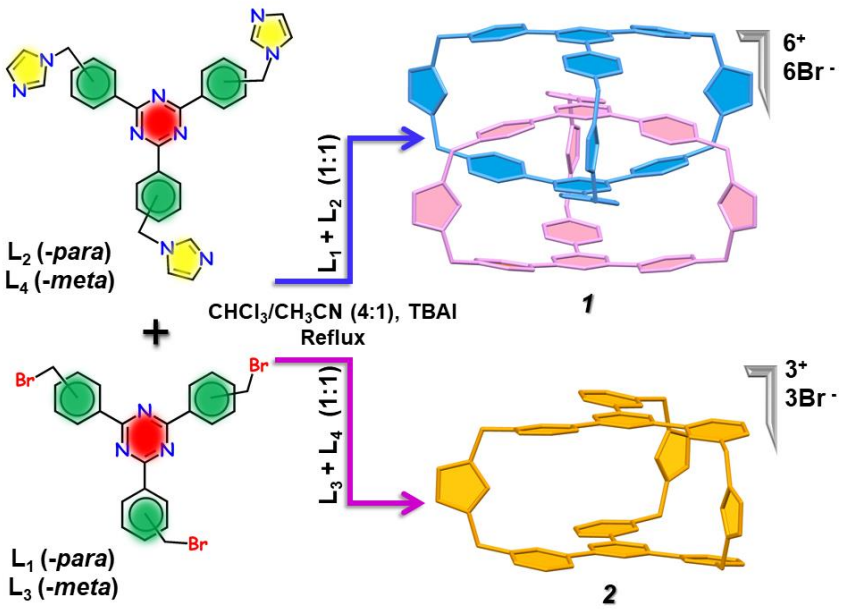
Synthesis of 1(PF_6): **1** (0.006 mmol) was dissolved in minimum quantity of hot H_2O and 12 equivalents of KPF_6 (0.072 mmol) were added to it. The mixture was stirred over-night and the resultant precipitate was collected via centrifugation to yield **1(PF_6)**. Yield: (0.0054 mmol, 94%). ^{1}H NMR (CD_3CN, 500 MHz): δ = 8.4(s, 6H), 8.08 (s, 6H), 8.01 (s, 6H), 7.68 (bs, 12H), 7.41 (bs, 12H), 7.25 (bs, 12H), 6.03 (bs, 12H), 5.58 (s, 12H), 5.47 ppm (s, 12H). ^{13}C NMR (CD_3CN, 125 MHz): δ = 170.56, 168.47, 139.84, 139.41, 136.25, 134.5, 133.97, 130.92, 130.55, 129.44, 128.6, 124.47, 124.11, 54.36, 54.07 ppm. HRMS (ESI): $C_{114}H_{90}N_{24}$ $[M(PF_6)_3]^{3+}$ = 743. 5568 (calc.) found: 743. 5462.

Synthesis of 2: **L_3** (0.047 mmol) was dissolved in 100 mL of 4:1 mixture of $CHCl_3$ and CH_3CN in a 250 mL two-neck round-bottom flask. **L_4** (0.047 mmol) and TBAI (0.142 mmol) were also dissolved in 100 mL of 4:1 mixture of $CHCl_3$ and CH_3CN and added dropwise to the previous

solution slowly over a period of 6-8 hours. The resultant total solution was refluxed for 4 days. After completion, the resultant precipitate was collected via centrifugation. This yielded the free cage (**2**). Yield: (0.018 mmol, 39%). ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 10.18 (s), 8.19 (s, 3H), 7.72 (s, 3H), 7.69 (d, 3H), 7.32(d, 3H), 7.09(dd, 3H), 5.76 ppm (dd, 6H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 169.71, 138.61, 136.76, 135.44, 131.57, 129.54, 127.36, 124.69, 124.48, 52.10 ppm.

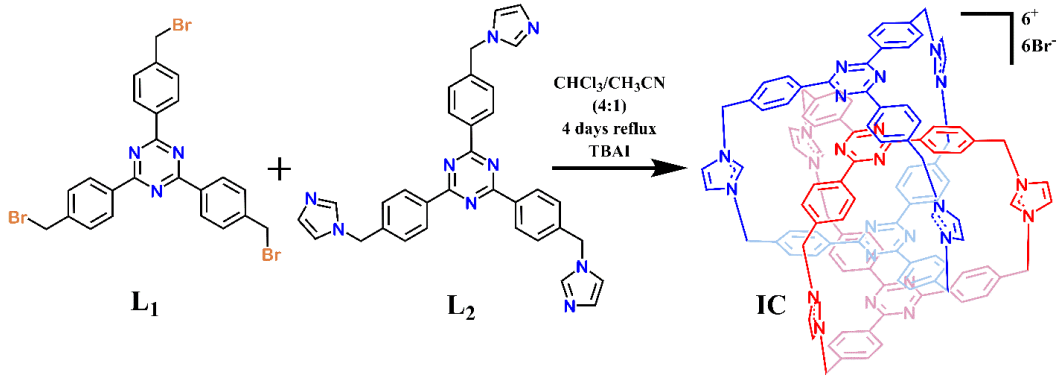
Synthesis of 2(PF$_6$): **2** (0.006 mmol) was dissolved in minimum quantity of hot H_2O and 6 equivalents of KPF_6 (0.036 mmol) was added to it. The mixture was stirred over-night and the resultant precipitate was collected via centrifugation to yield **2**(PF_6). Yield: (0.0057 mmol, 95%). ^{1}H NMR (CD_3CN, 400 MHz): δ = 9.34 (s), 7.83 (d, 6H), 7.68 (d, 3H), 7.46 (d, 3H), 7.16 (dd, 3H), 5.68 (s, 6H). HRMS (ESI): $C_{57}H_{45}N_{12}$ $[M']^{3+}$ = 299.1279 (calc.) found: 299.1279.

Optimization methods: All the theoretical calculations were performed using Gaussian 09 package.[1] **1** and **2** were optimized using hybrid B3LYP functional with a basis set 6-31G (for C, H and N).[2] No symmetry constraints were used during the optimization procedure.



Scheme S5: General scheme for the synthesis of interlocked cage **1** and non-interlocked cage **2**.

1.3 Synthesis and characterization of 1



Scheme S6: Schematic presentation of the synthesis of **1**.

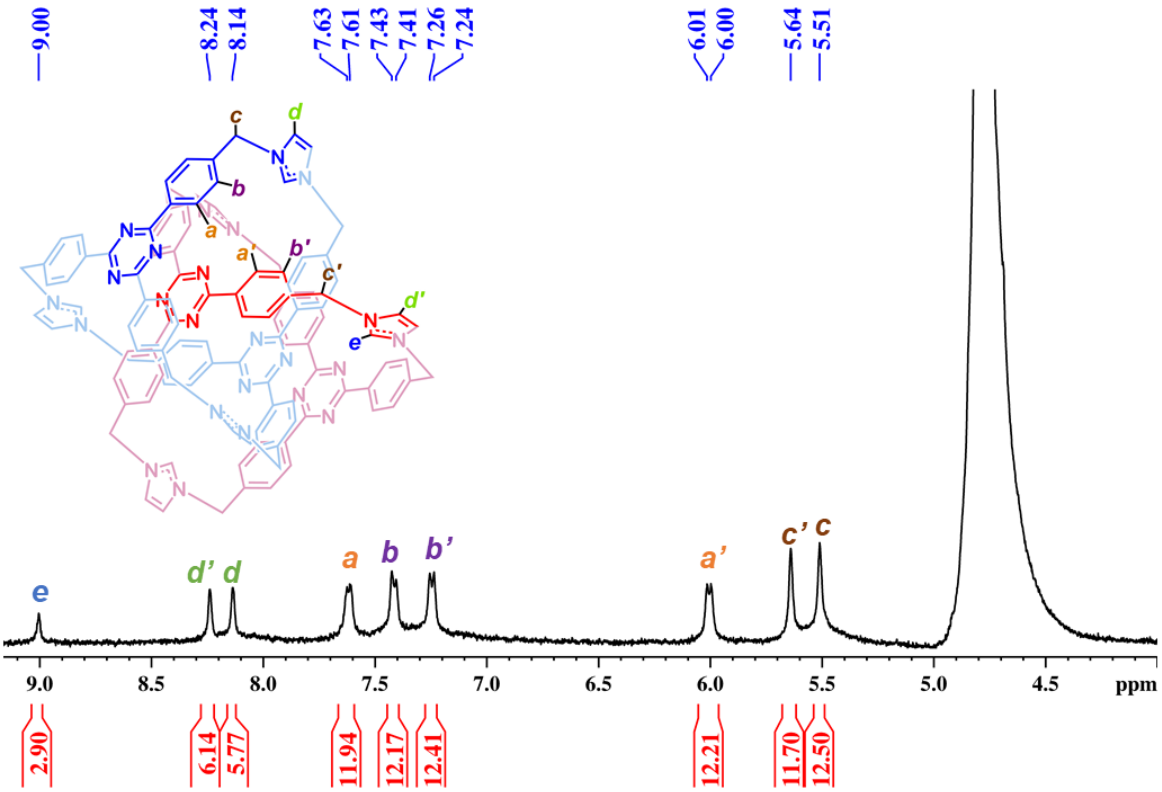


Fig. S1: ^{1}H NMR spectrum of **1** (D_2O, 298 K).

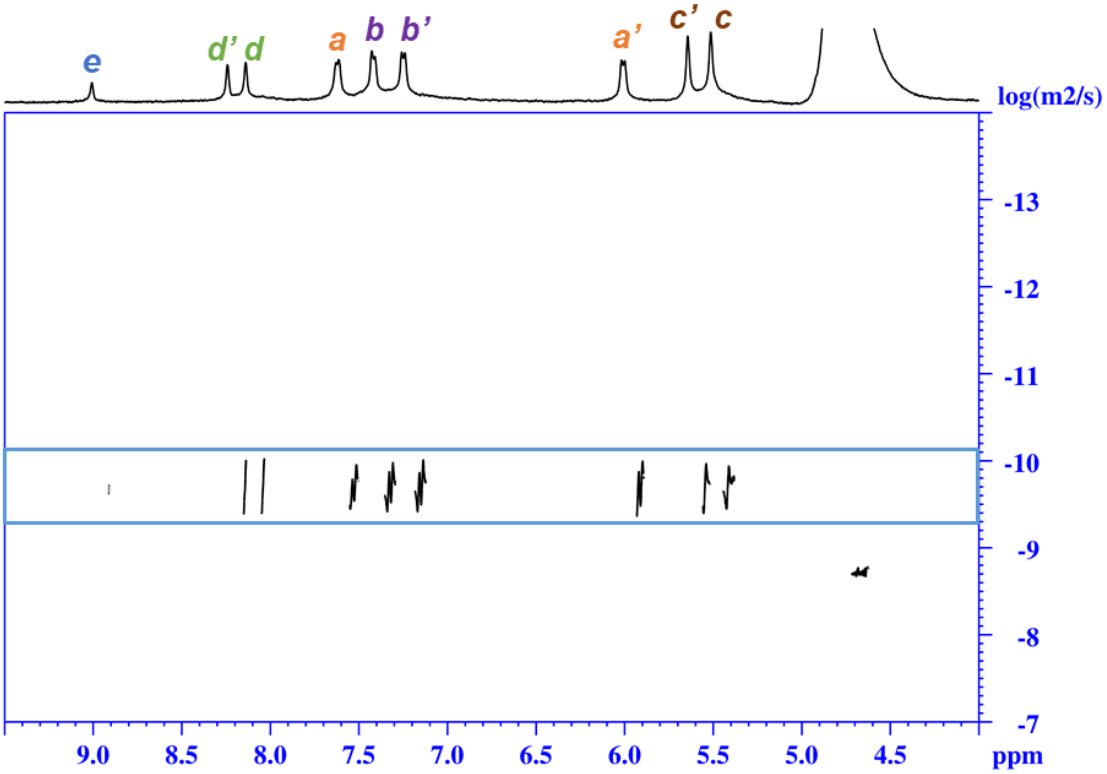


Fig. S2: ^{1}H DOSY NMR spectrum of **1** (D_2O, 298 K).

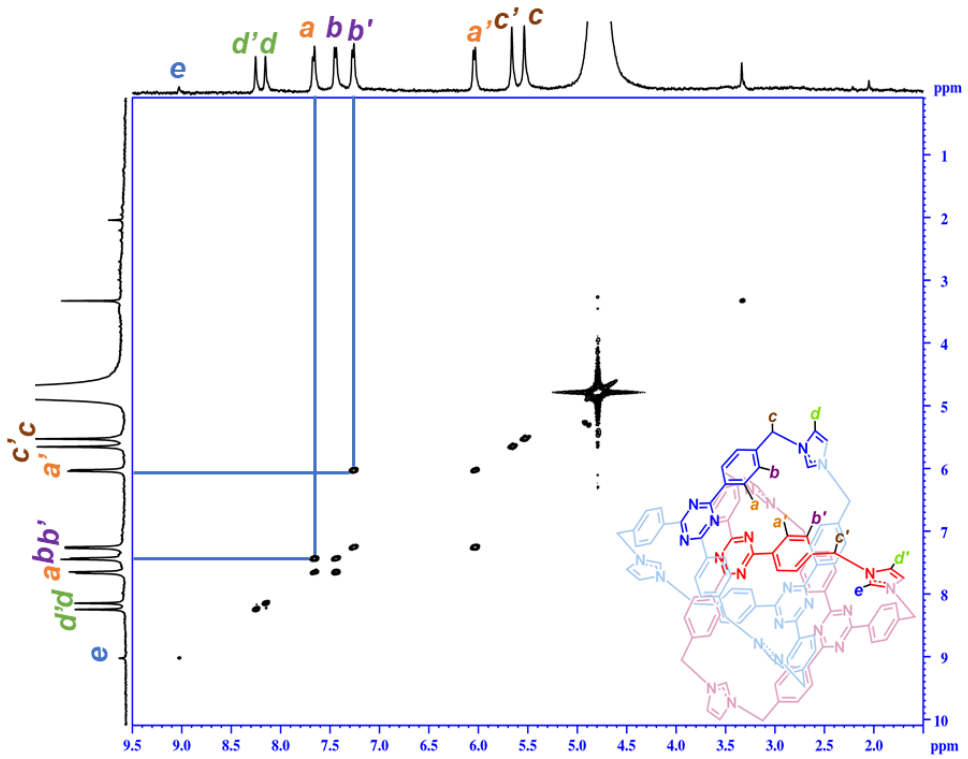


Fig. S3: ^{1}H-^{1}H COSY NMR spectrum of **1** (D_2O, 298 K). The rectangular positions show the interaction between neighbouring protons.

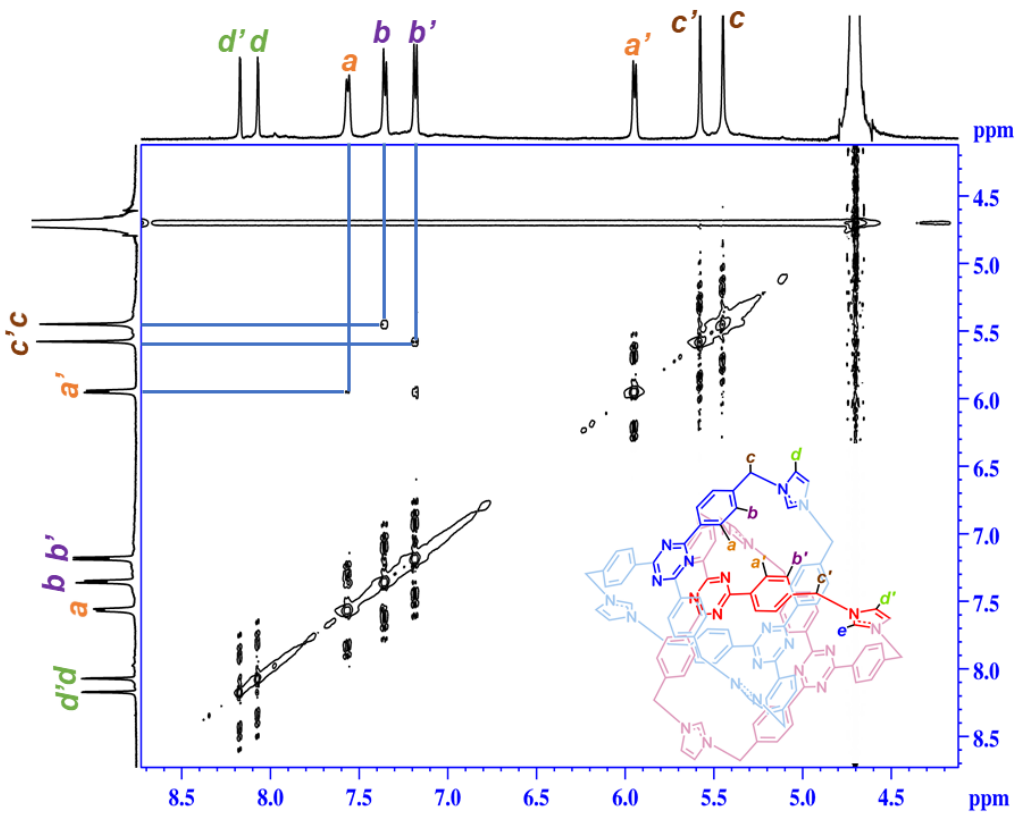


Fig. S4: ^{1}H-^{1}H NOESY NMR spectrum of **1** (D_2O, 298 K). The rectangular positions show the interactions between the protons.

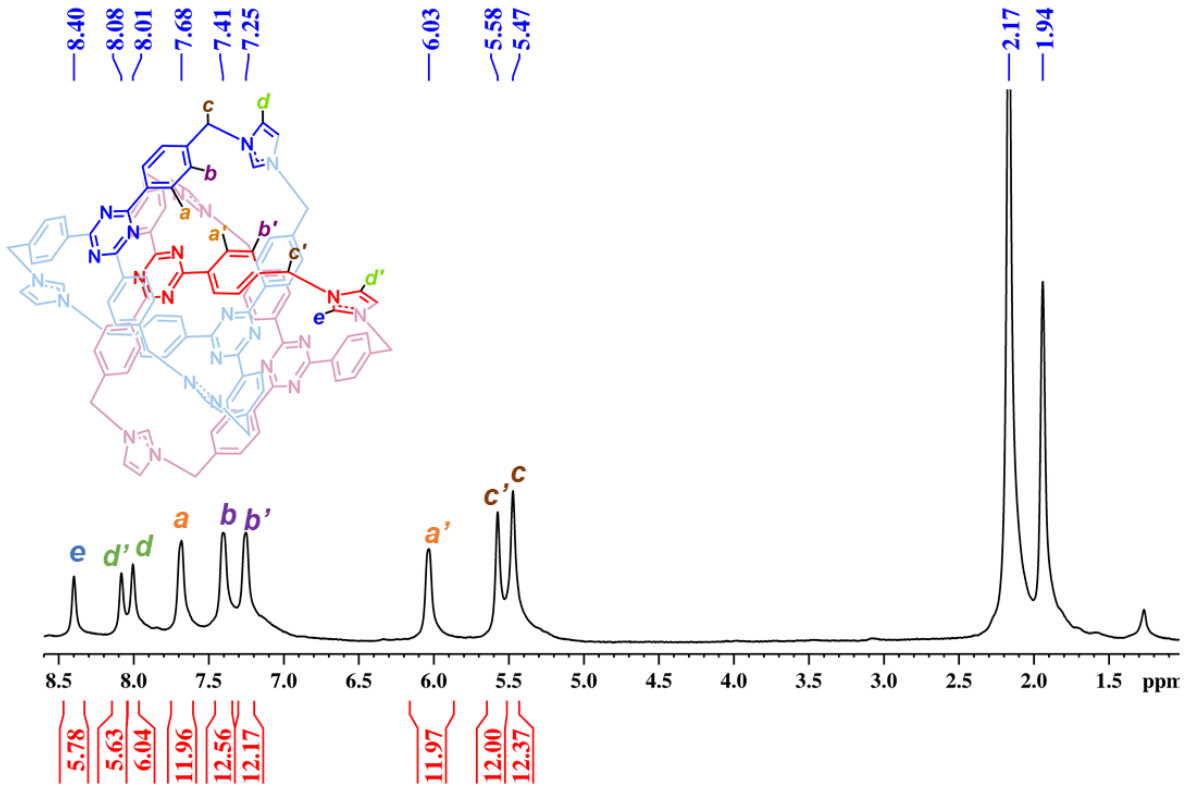


Fig. S5: ^{1}H NMR spectrum of **1(PF$_6$)** (CD_3CN, 298 K).

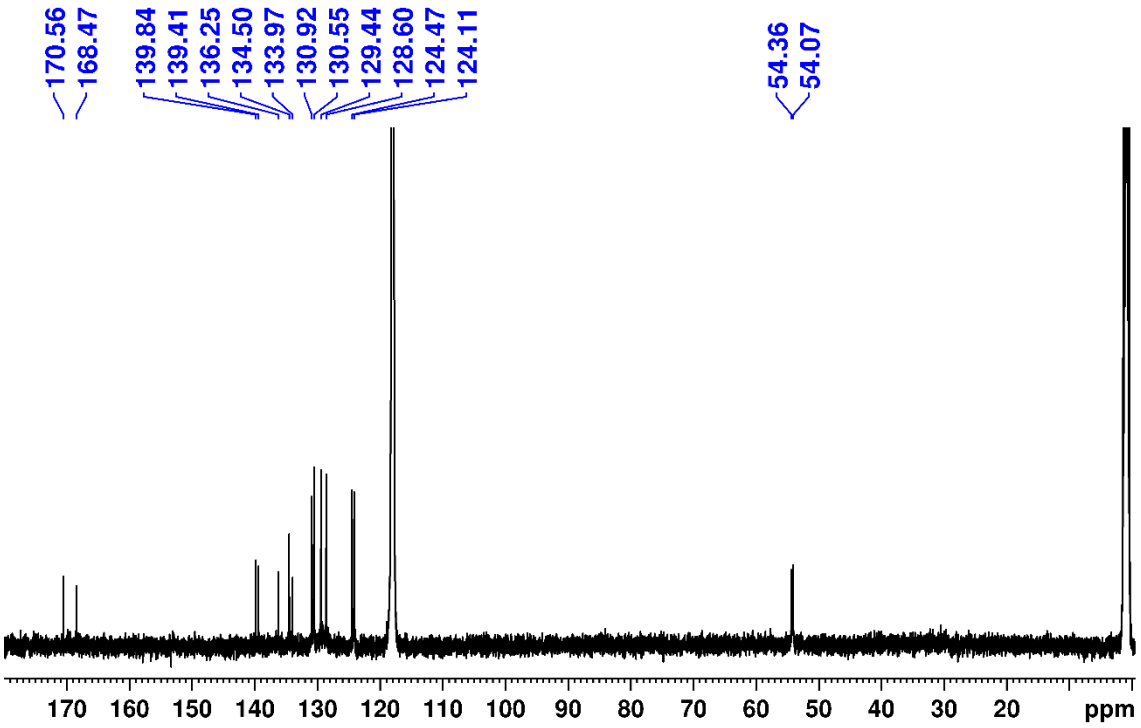


Fig. S6: ^{13}C NMR spectrum of **1(PF$_6$)** (CD_3CN, 298 K).

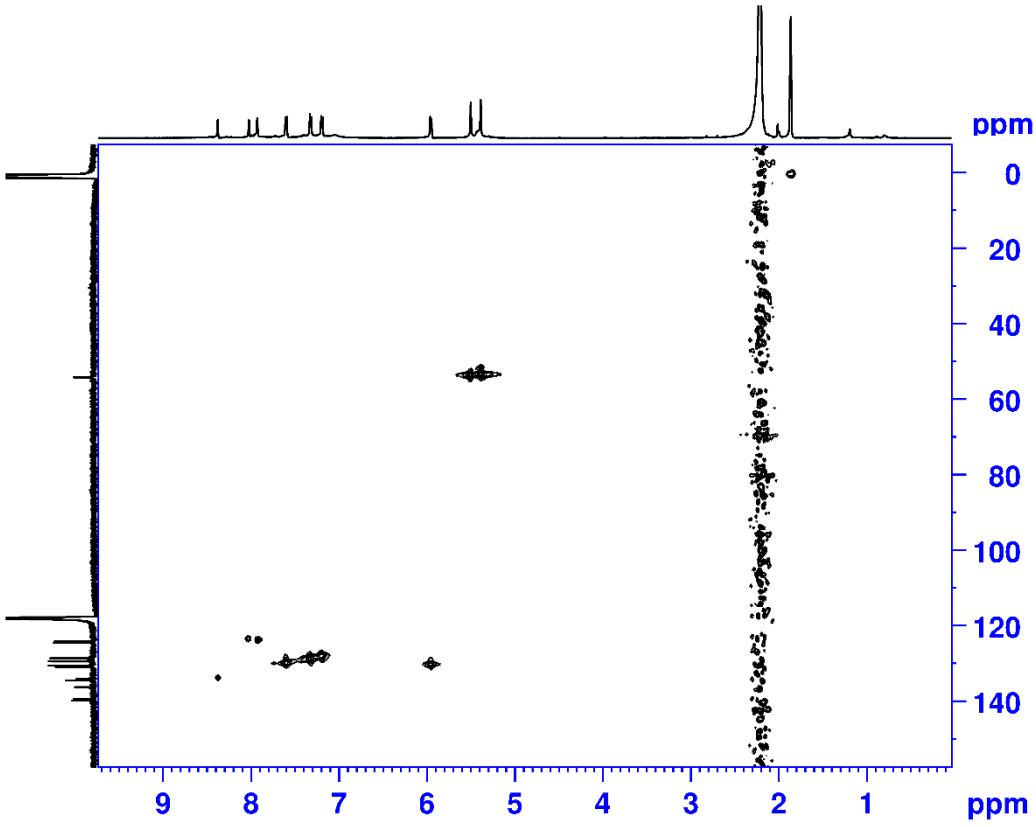


Fig. S7: ^{13}C-^{1}H HMQC NMR spectrum of **1(PF$_6$)** (CD_3CN, 298 K).

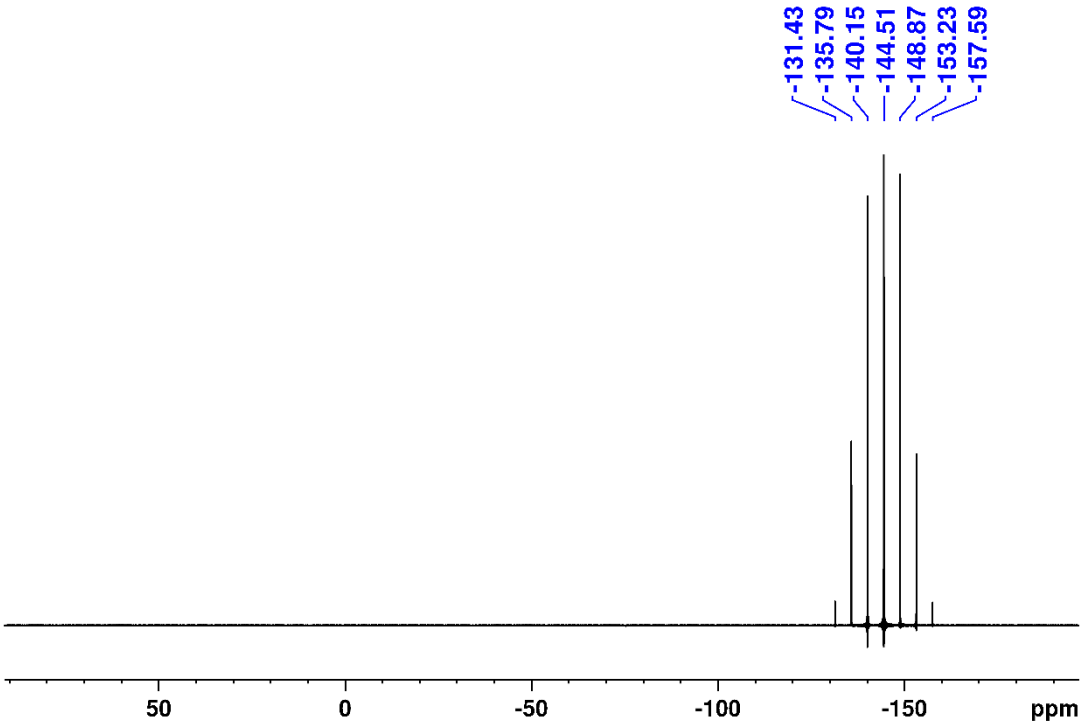


Fig. S8: ^{31}P NMR spectrum of **1(PF$_6$)** (CD_3CN, 298 K).

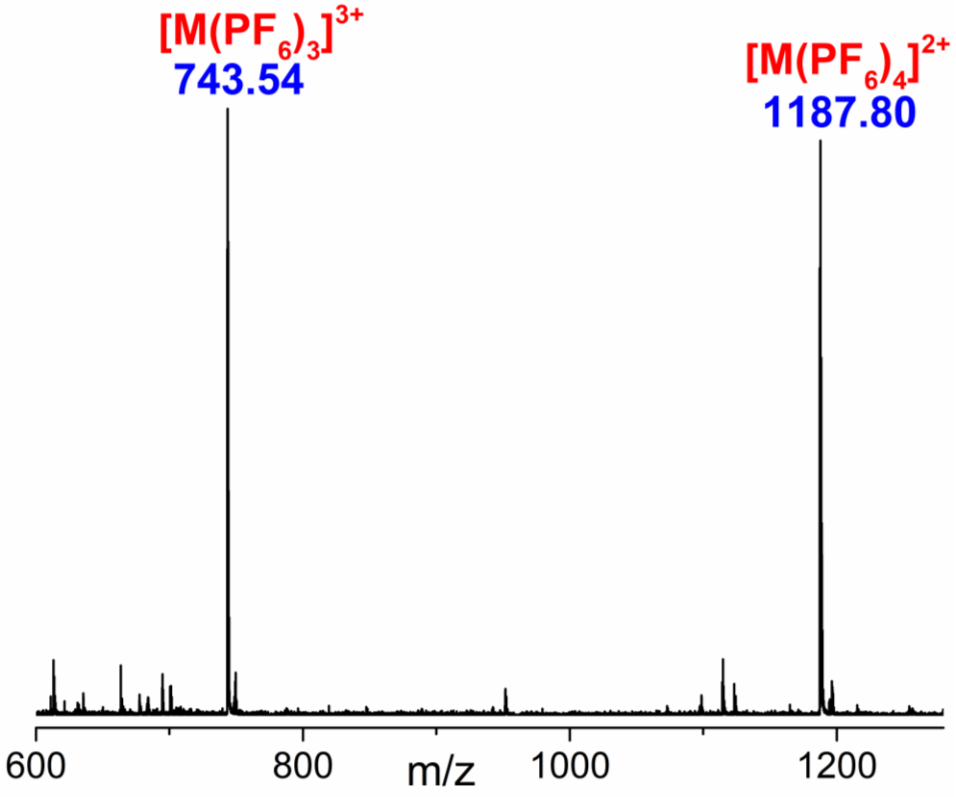


Fig. S9: Electrospray ionization mass spectrum of **1**.

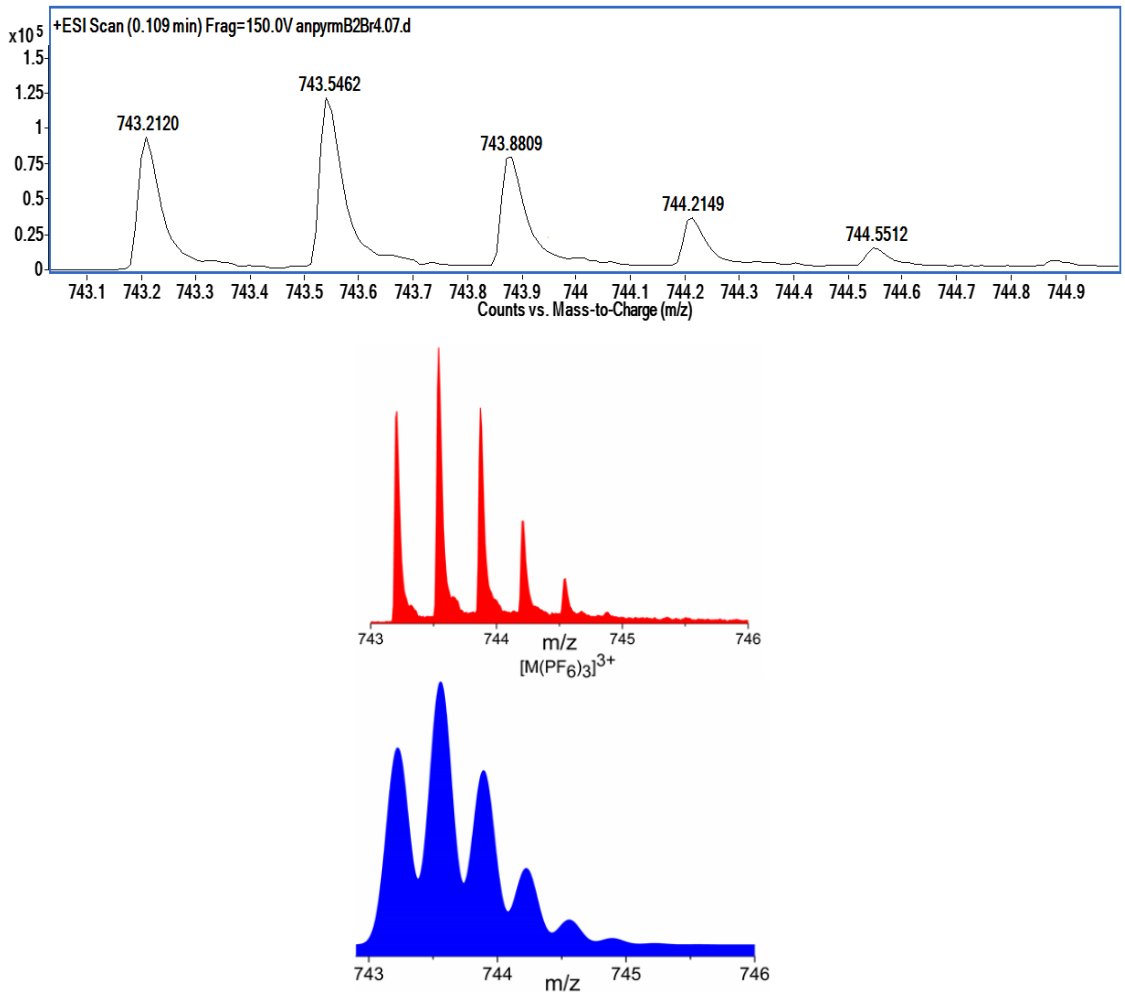
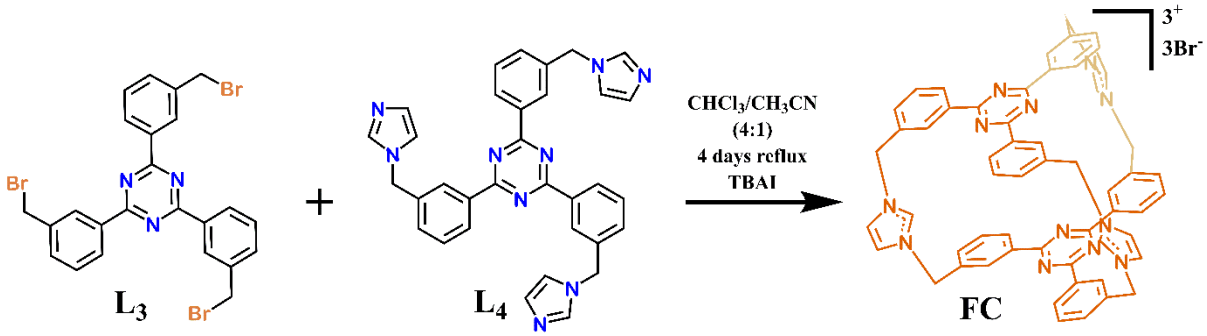


Fig. S10: Isotopic distribution patterns of **1** experimental (red), theoretical (blue) of the **$[M(PF_6)_3]^{3+}$** fragments.

1.4 Synthesis and characterization of 2



Scheme S7: Schematic presentation of the synthesis of **2**.

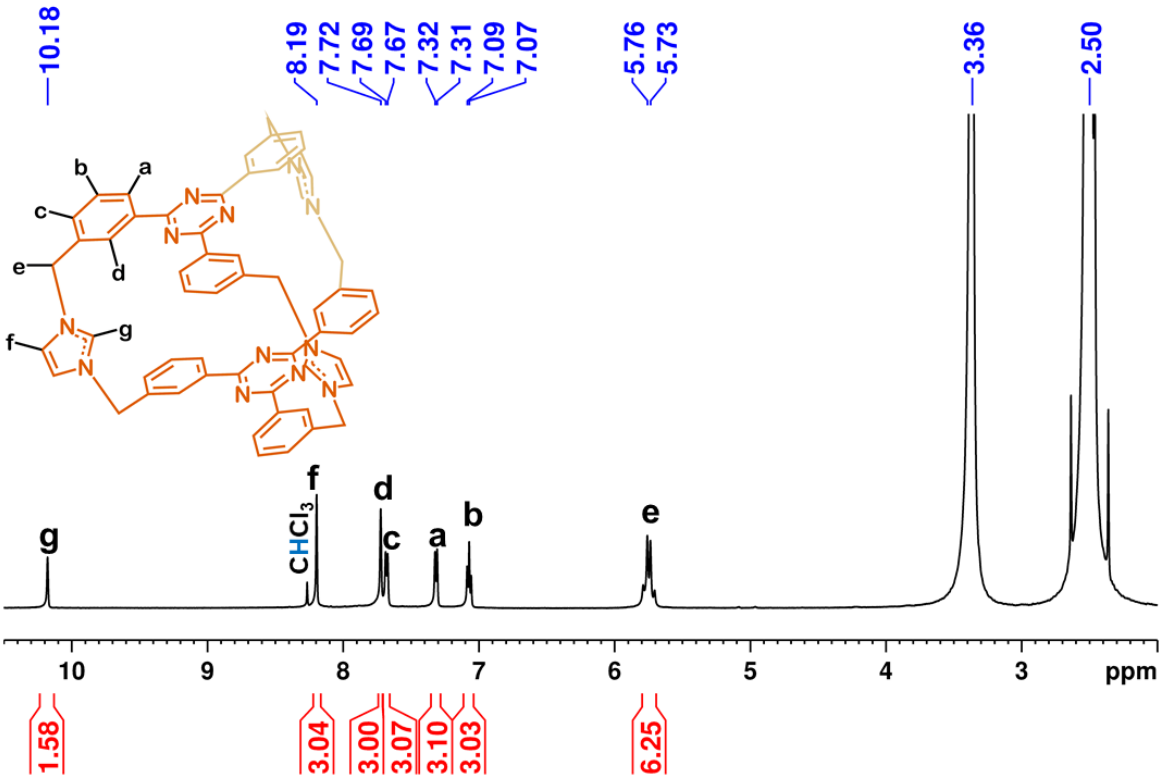


Fig. S11: ^{1}H NMR spectrum of **2(Br)** (DMSO-d_6, 298 K).

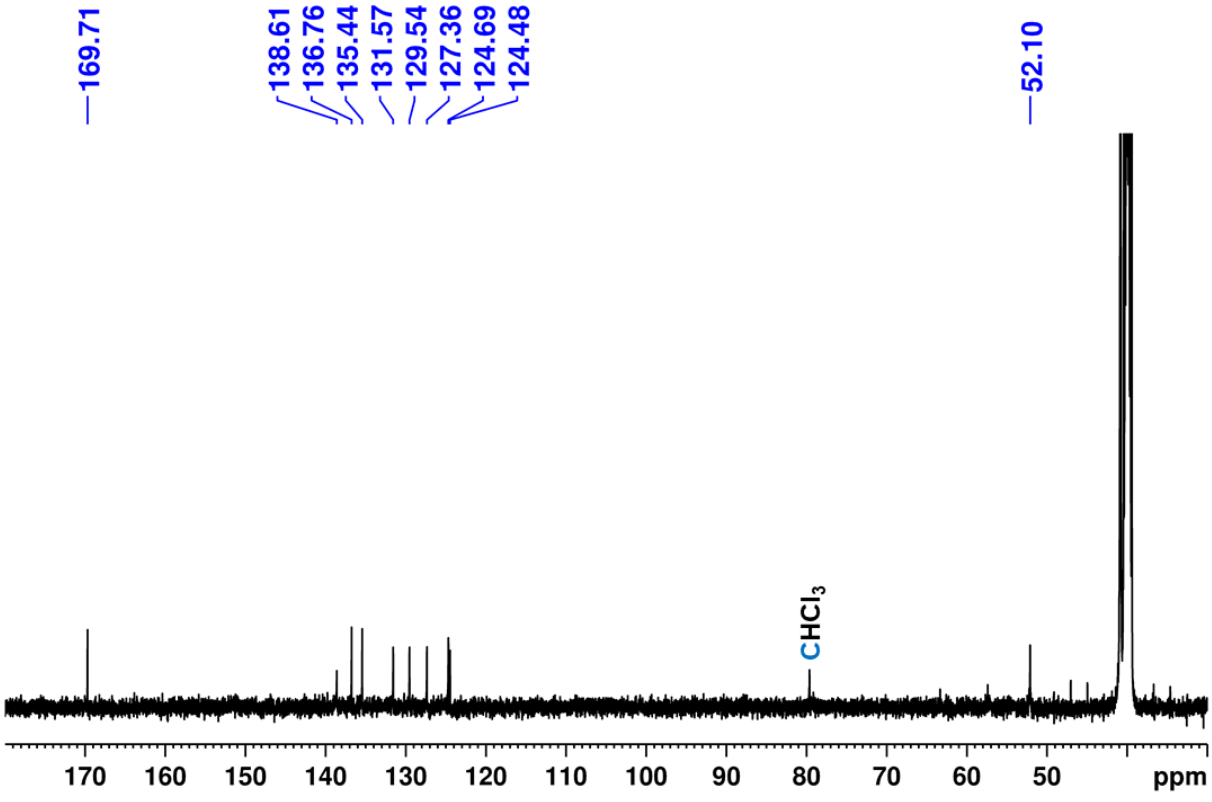


Fig. S12: ^{13}C NMR spectrum of **2(Br)** (DMSO-d_6, 298 K).

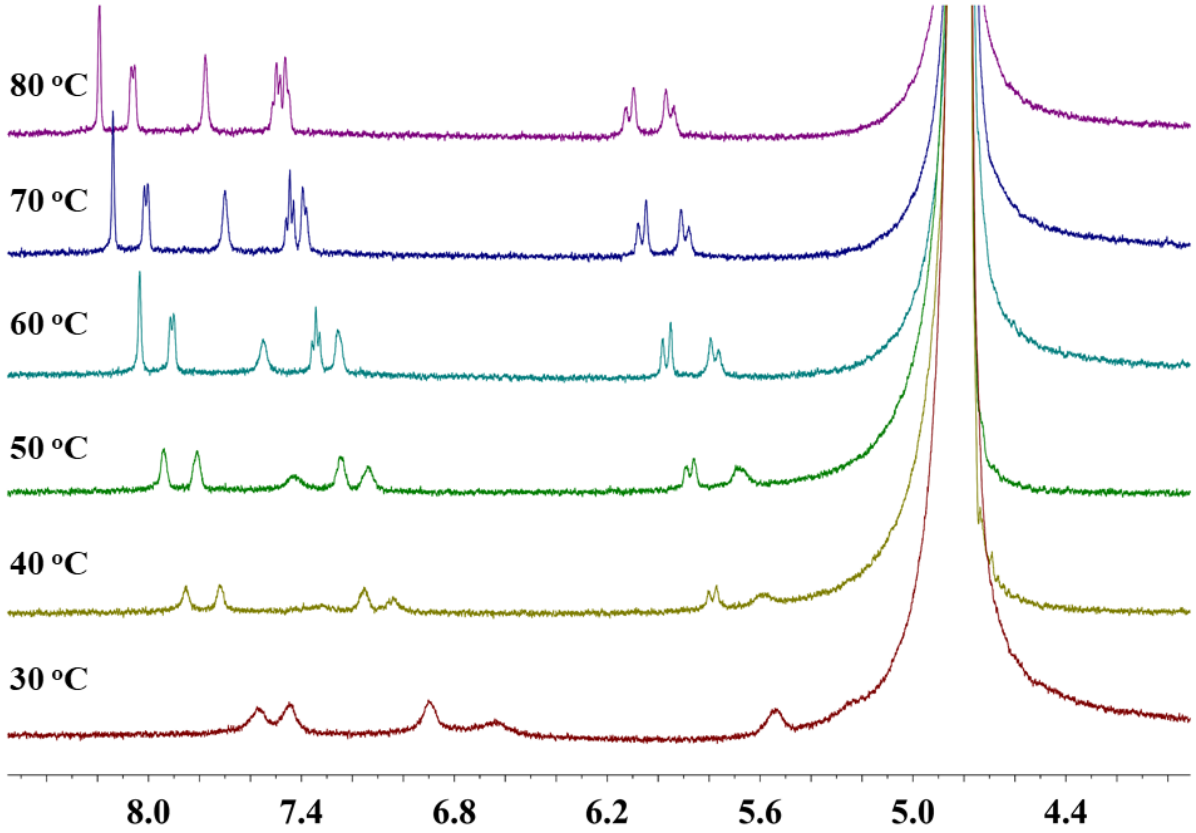


Fig. S13: ^{1}H VT-NMR spectrum of **2(Br)** (D_2O).

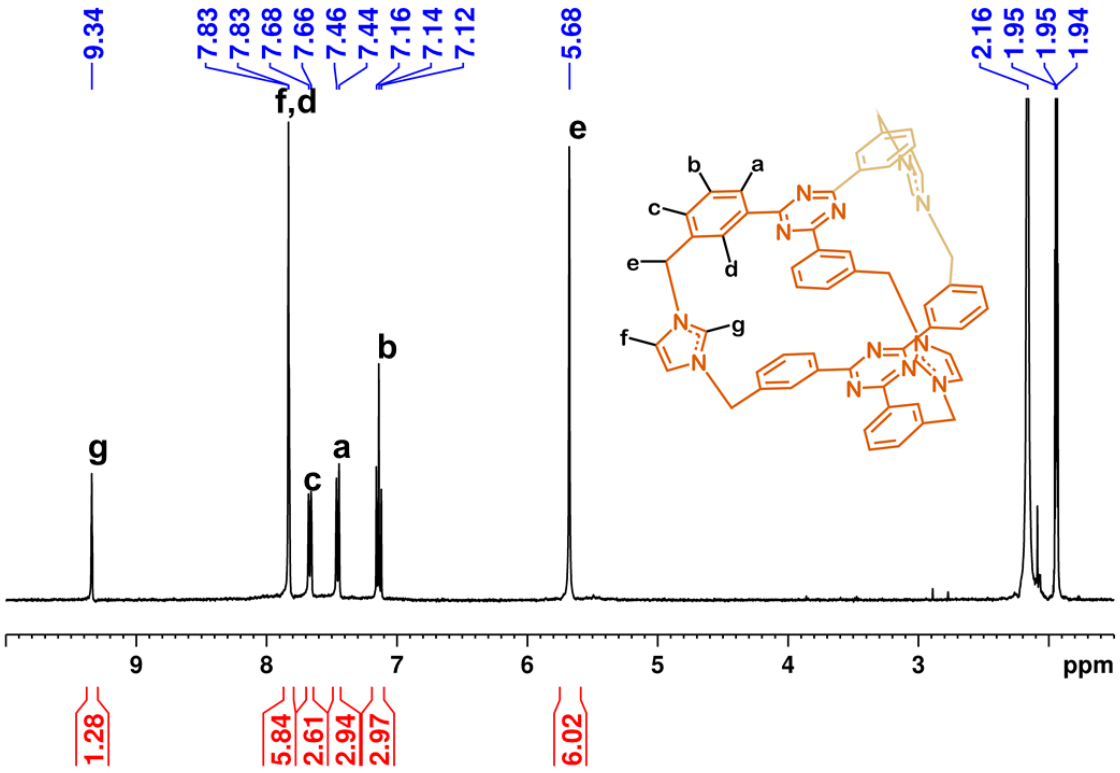


Fig. S14: ^{1}H NMR spectrum of **2(PF$_6$)** (CD_3CN, 298 K).

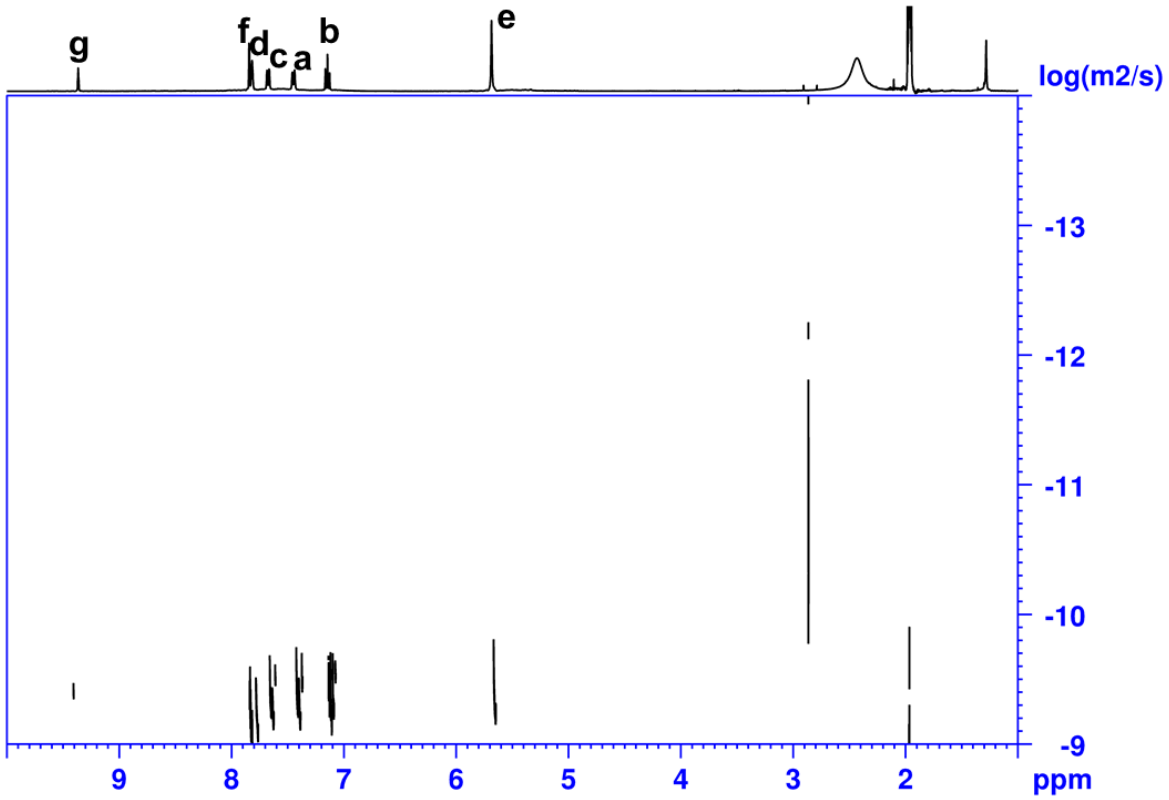


Fig. S15: ^{1}H DOSY NMR spectrum of **2(PF$_6$)** (CD_3CN, 298 K).

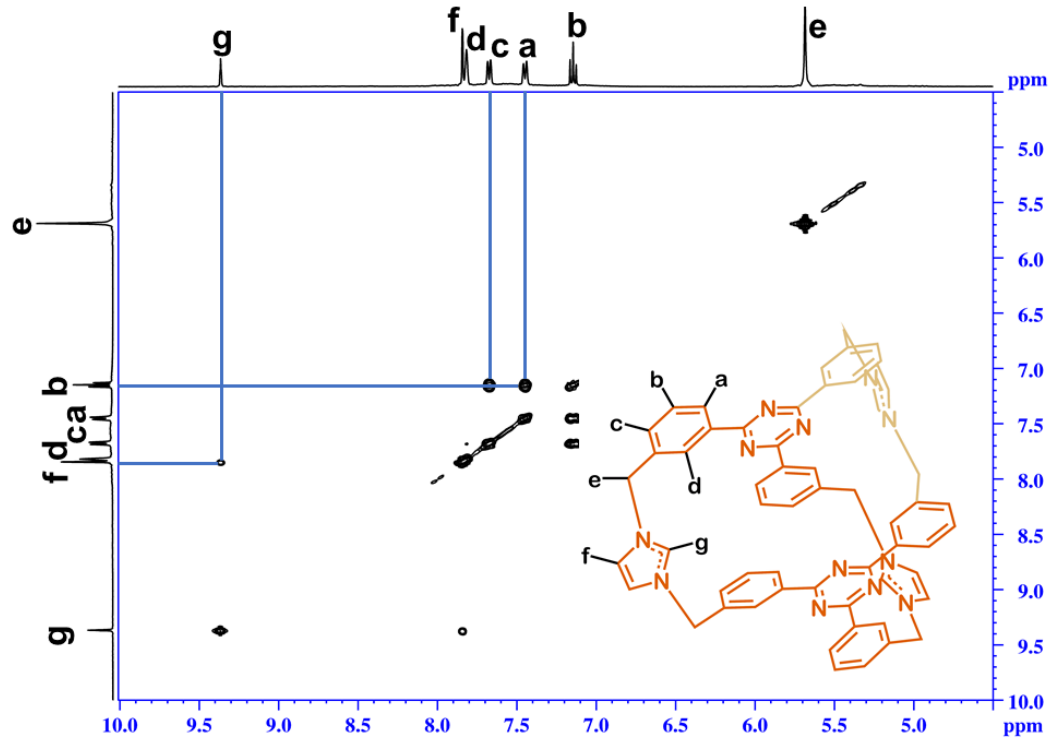


Fig. S16: ^{1}H-^{1}H COSY NMR spectrum of **2** (CD_3CN, 298 K). The rectangular positions show the interaction between neighbouring protons.

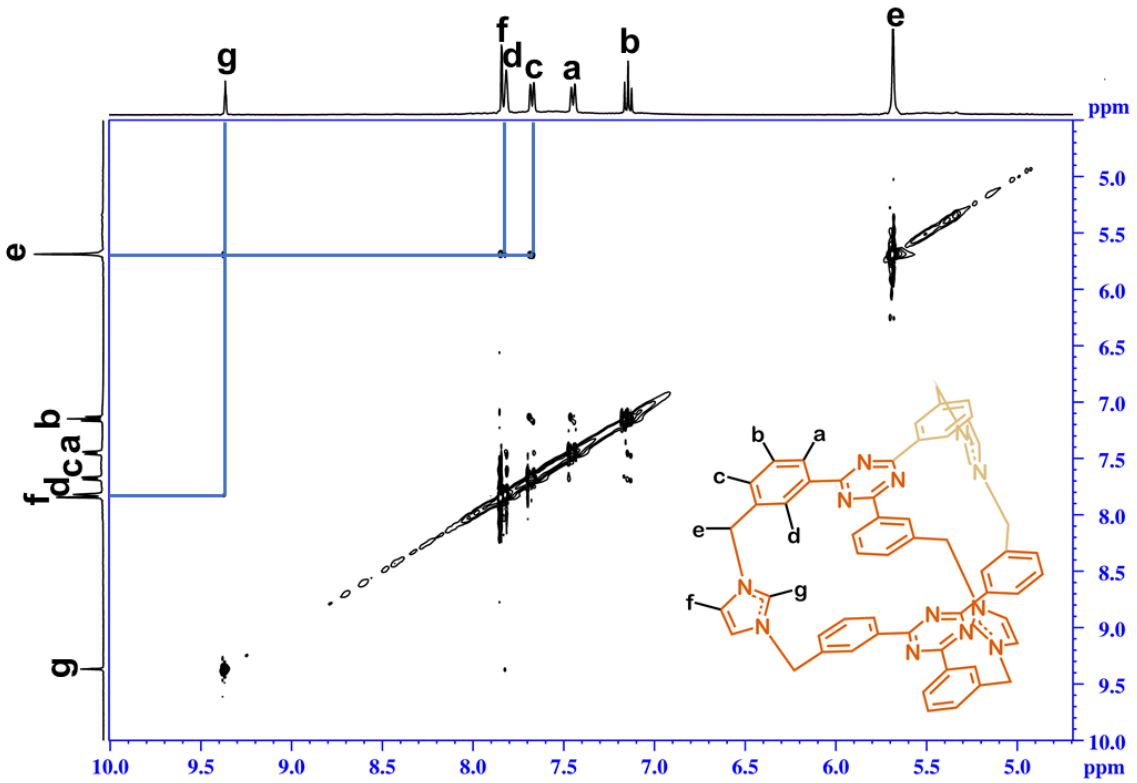


Fig. S17: ^{1}H-^{1}H NOESY NMR spectrum of **2** (CD_3CN, 298 K). The rectangular positions show the interaction between protons.

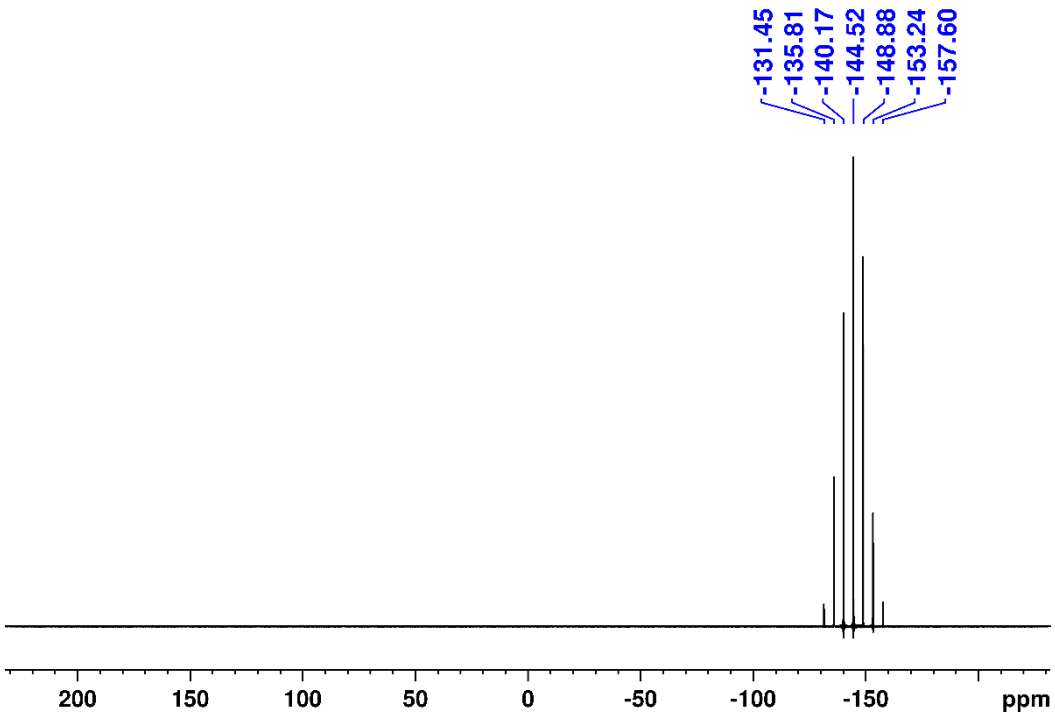


Fig. S18: ^{31}P NMR spectrum of **2(PF$_6$)** (CD_3CN, 298 K).

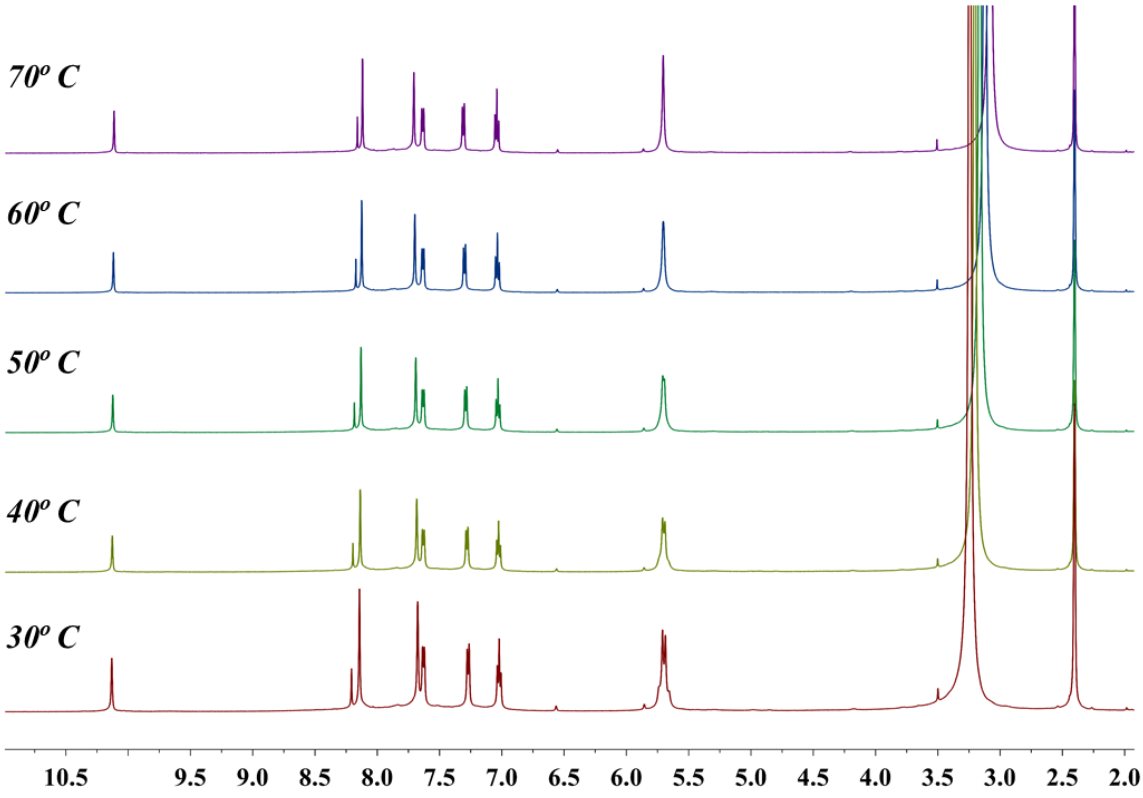


Fig. S19: ^{1}H VT-NMR spectrum of **2(Br)** (DMSO-d^{6}).

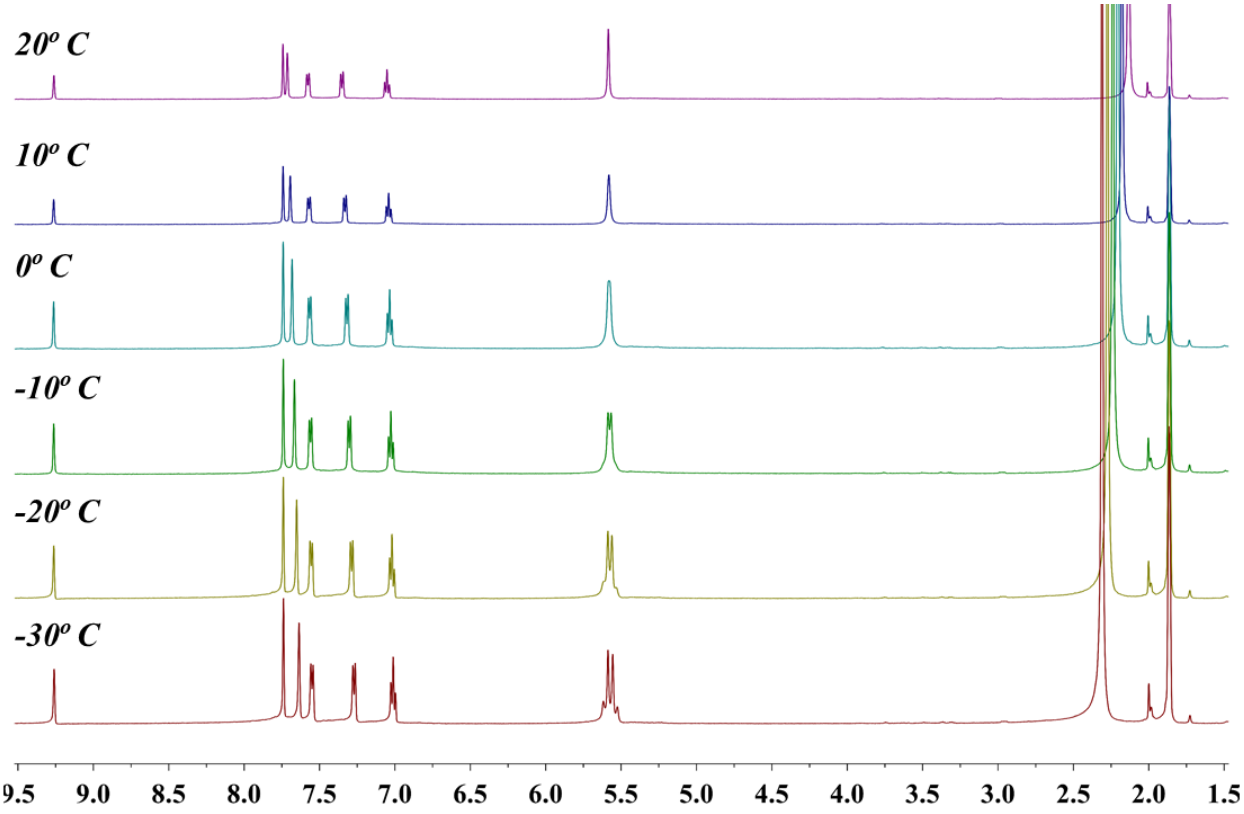


Fig. S20: ^{1}H VT-NMR spectrum of **2(PF$_6$)** (CD_3CN).

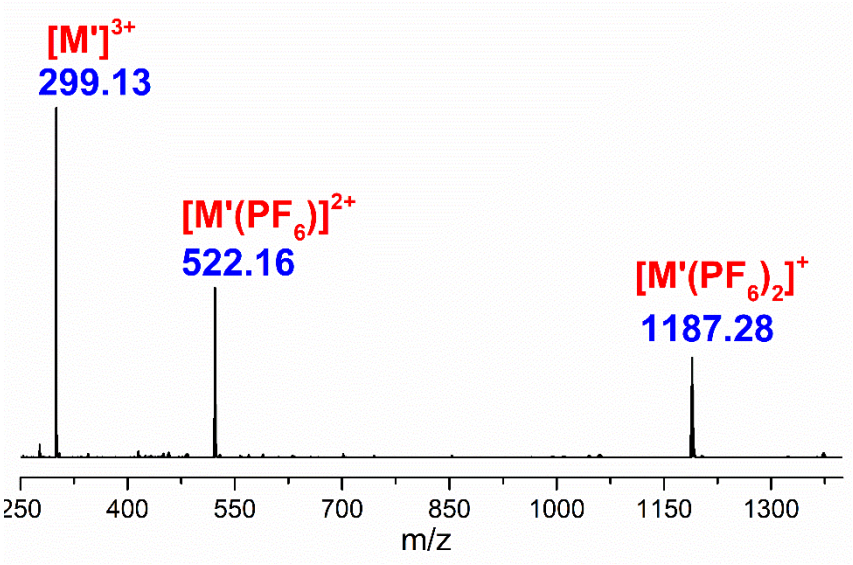


Fig. S21: Electrospray ionization mass spectrum of **2**.

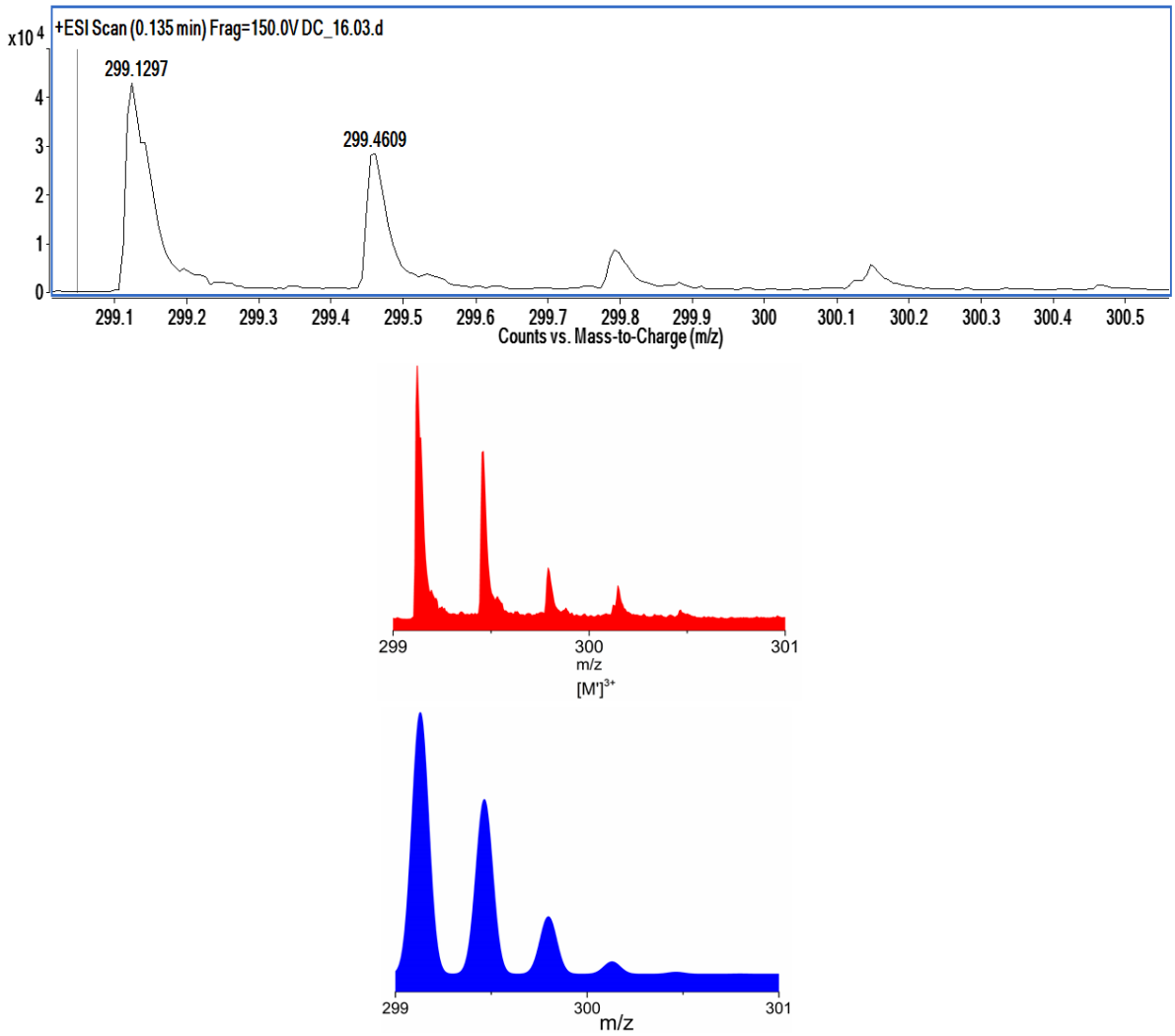


Fig. S22: Isotopic distribution patterns of **2** experimental (red) theoretical (blue) of the **[M']**$^{3+}$ fragment.

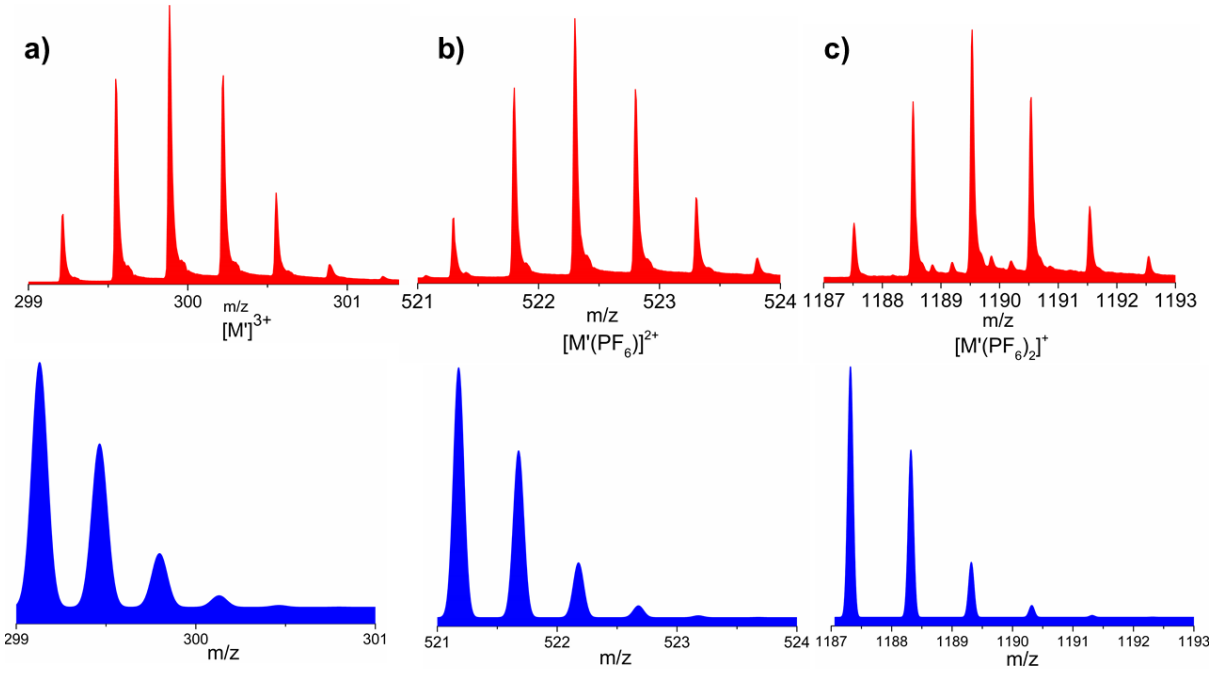


Fig. S23: Isotopic distribution patterns of 2 (recorded in CD_3CN): a) experimental (red) theoretical (blue) of the **[M']**$^{3+}$ fragment, b) **[M'(PF$_6$)]**$^{2+}$, c) **[M'(PF$_6$)$_2$]**$^{+}$ fragments.

2. Optimized structures of 1 and 2.

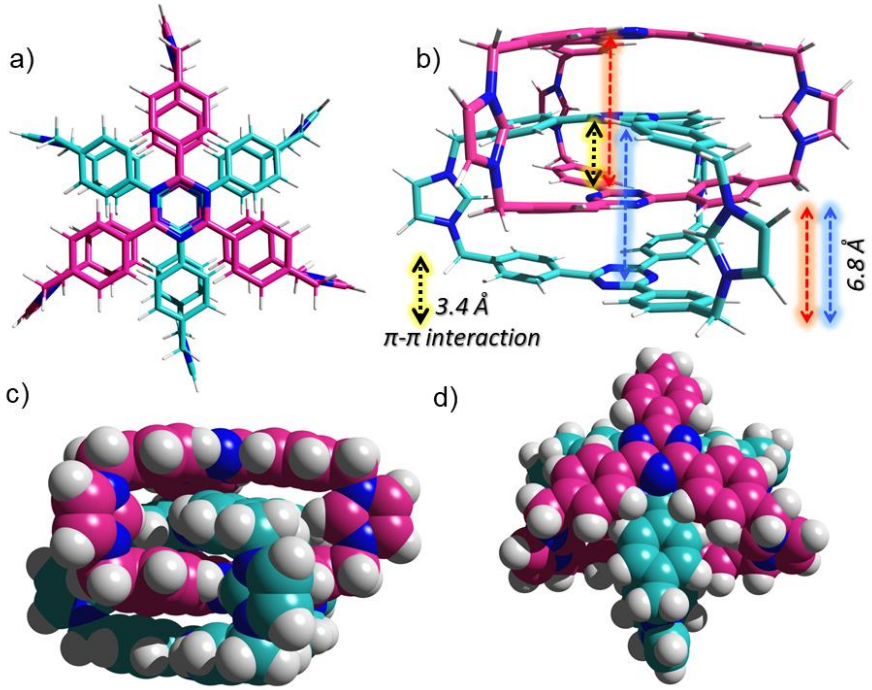


Fig. S24: Optimised structure of **1** (B3LYP/6-31G level): a) top view of **1**, b) side view of **1** (showing panel distances), c) side view of **1**(space filled model with H atoms). d) top view of **1** (space filled model with H atoms). [Pink, Cyan atoms denote C atoms; white atoms denote H atoms; Deep-Blue atoms denote N atoms].

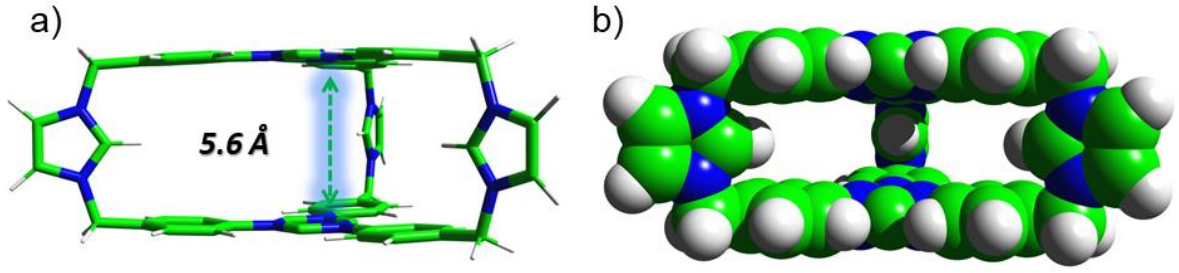


Fig. S25: Optimised structure of **hypothetical free cage** (B3LYP/6-31G level): a) Side view (showing panel distances), b) Side view (space filled model with H atoms). [Green, white, blue atoms denote C, H and N respectively].

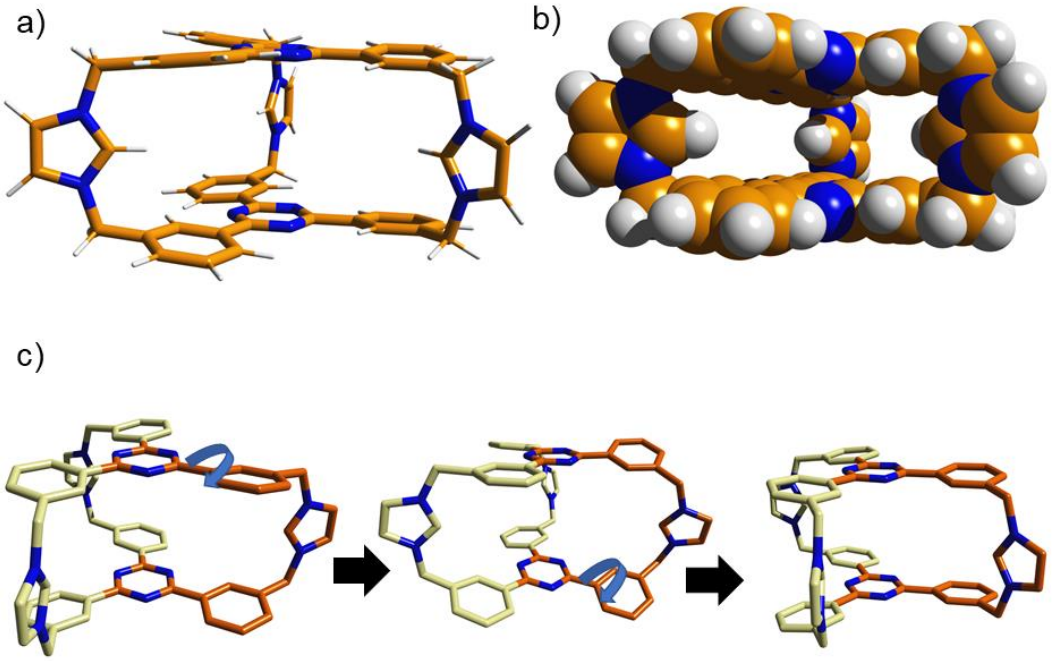


Fig. S26: Optimised structure of **2** (B3LYP/6-31G level): a) side view of **2**, b) side view of **2** (space filled model with H atoms). c) some of the different conformers of **2** accessible via simple bond rotation. [Orange, Yellow atoms denote C atoms; White atoms denote H atoms; Blue atoms denote N atoms]

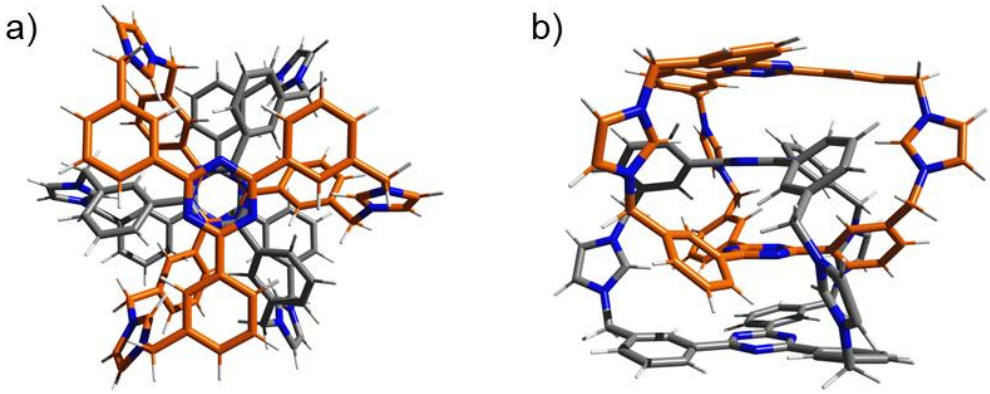


Fig. S27: Optimised structure of **hypothetical interlocked cage** (B3LYP/6-31G level): a) top View, b) side view [Orange, Grey atoms denote C atoms; White atoms denote H atoms; Deep-Blue atoms denote N atoms]

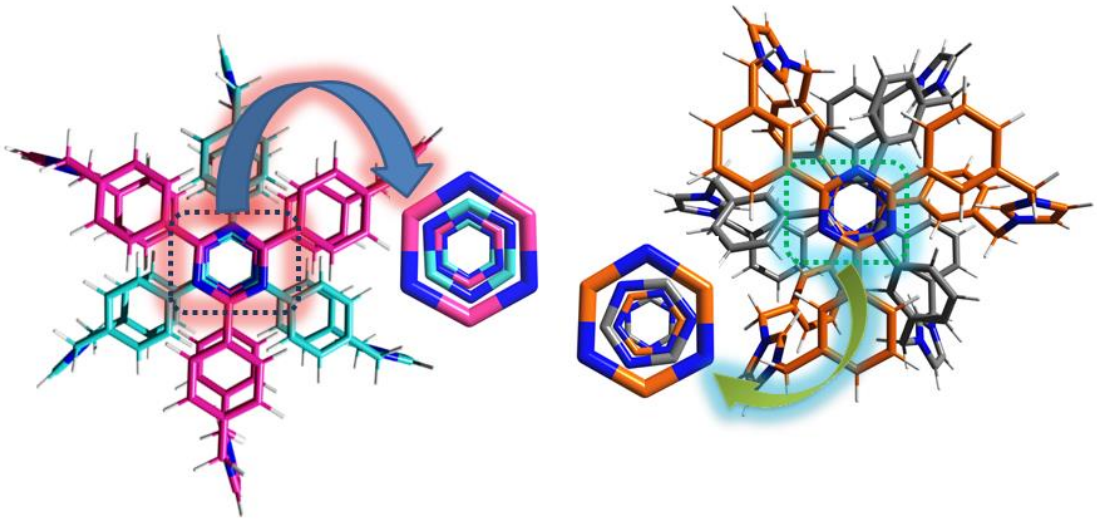


Fig. S28: Top view of **1** vs hypothetical cage(meta) showing absence of any proper π- π stacking in the meta analogue. [Cyan, Pink, Orange, Grey atoms denote C atoms; White atoms denote H atoms; Deep-Blue atoms denote N atoms]

3. NMR spectra of the building blocks:

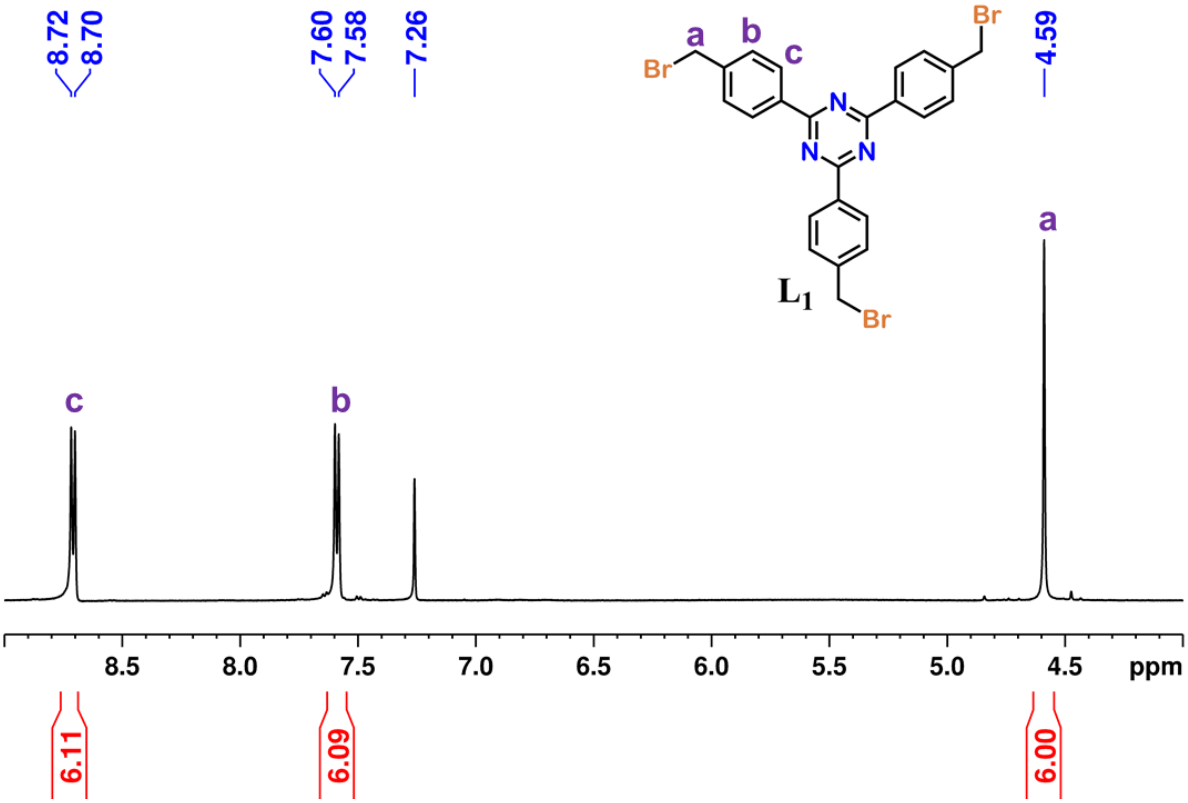


Fig. S29: ^{1}H NMR spectrum of compound **L1** ($CDCl_3$, 298 K).

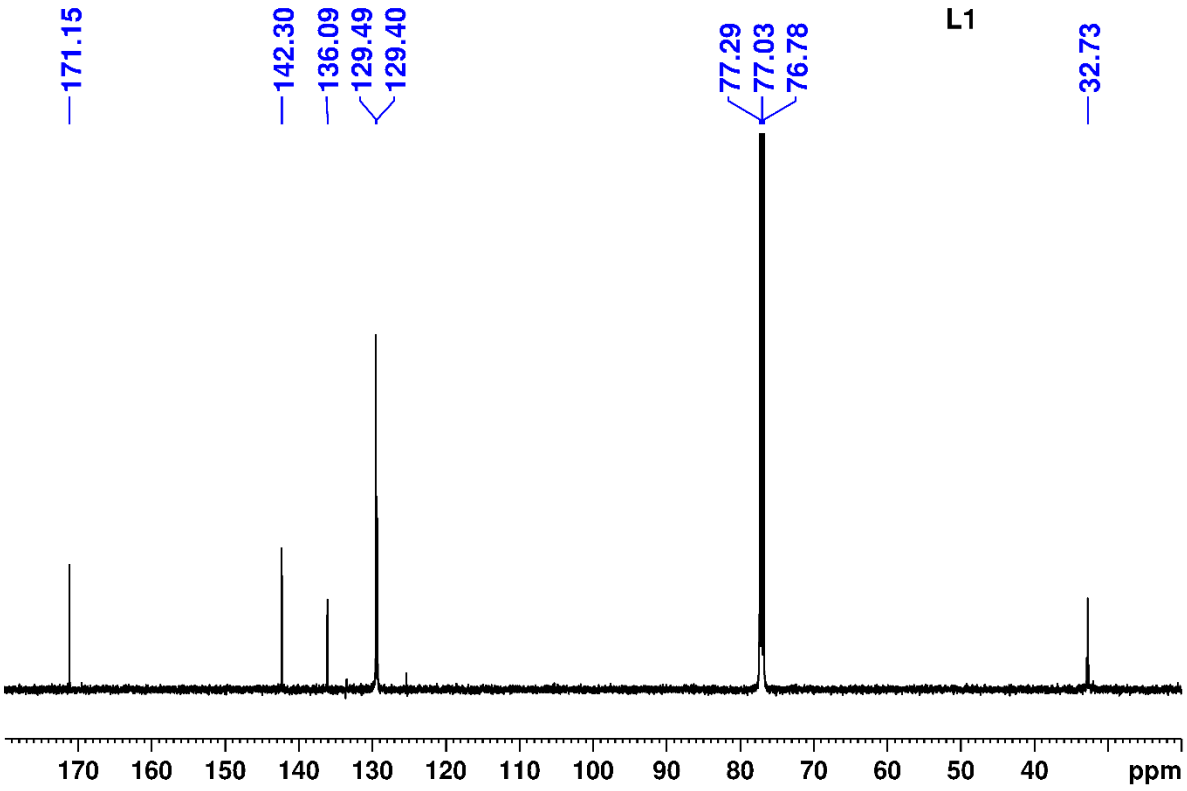


Fig. S30: ^{13}C NMR spectrum of compound **L1** ($CDCl_3$, 298 K).

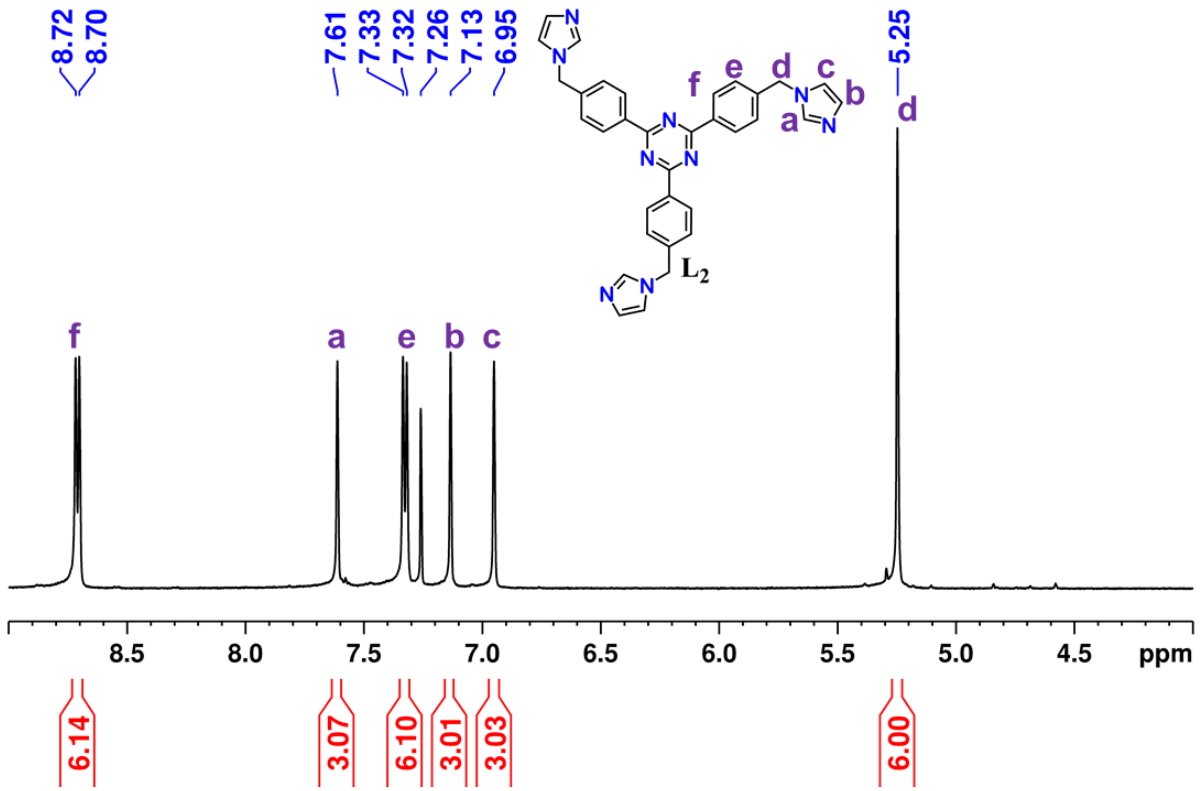


Fig. S31: ^{1}H NMR spectrum of compound **L2** ($CDCl_3$, 298 K).

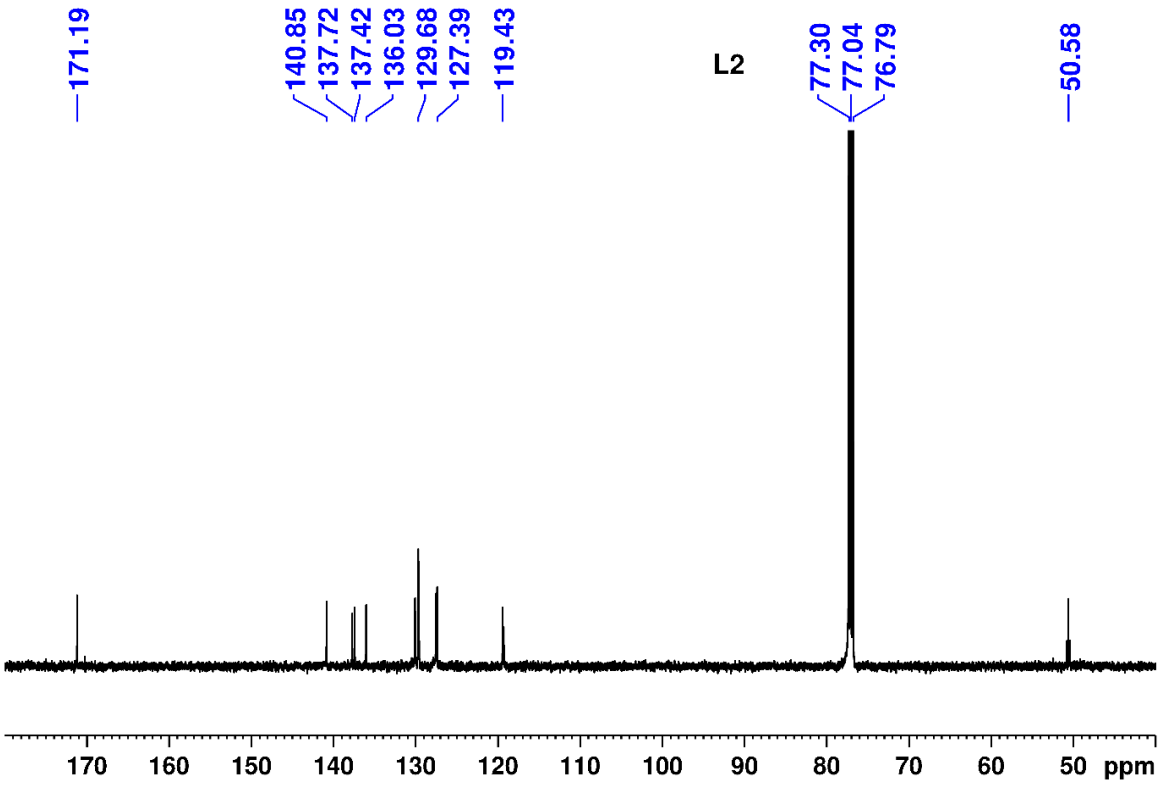


Fig. S32: ^{13}C NMR spectrum of compound **L2** ($CDCl_3$, 298 K).

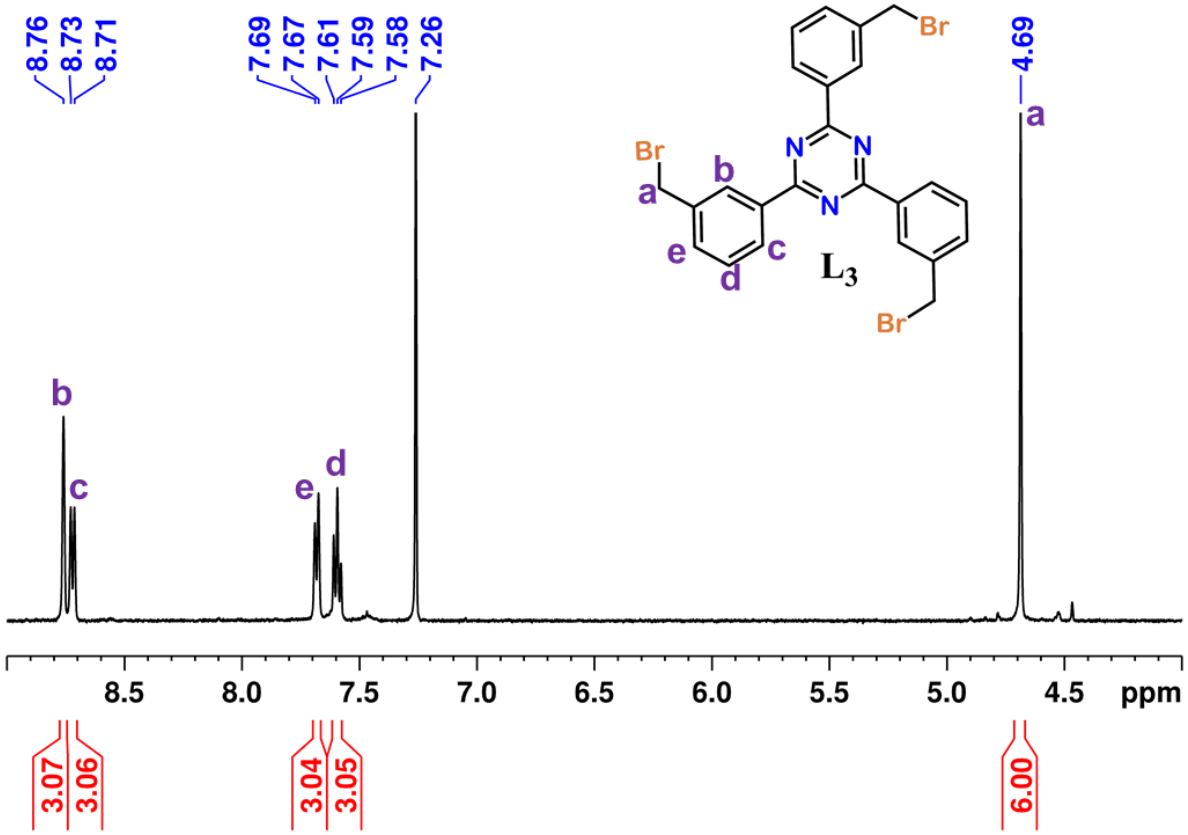


Fig. S33: ^{1}H NMR spectrum of compound **L3** ($CDCl_3$, 298 K).

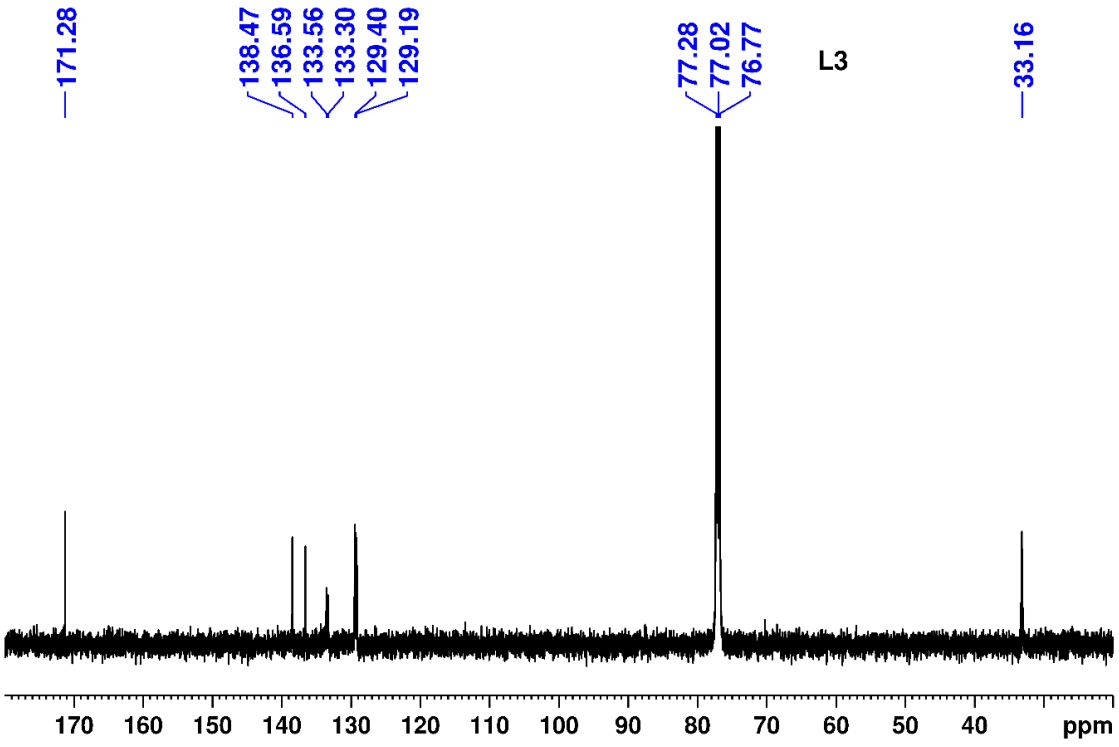


Fig. S34: ^{13}C NMR spectrum of compound **L3** ($CDCl_3$, 298 K).

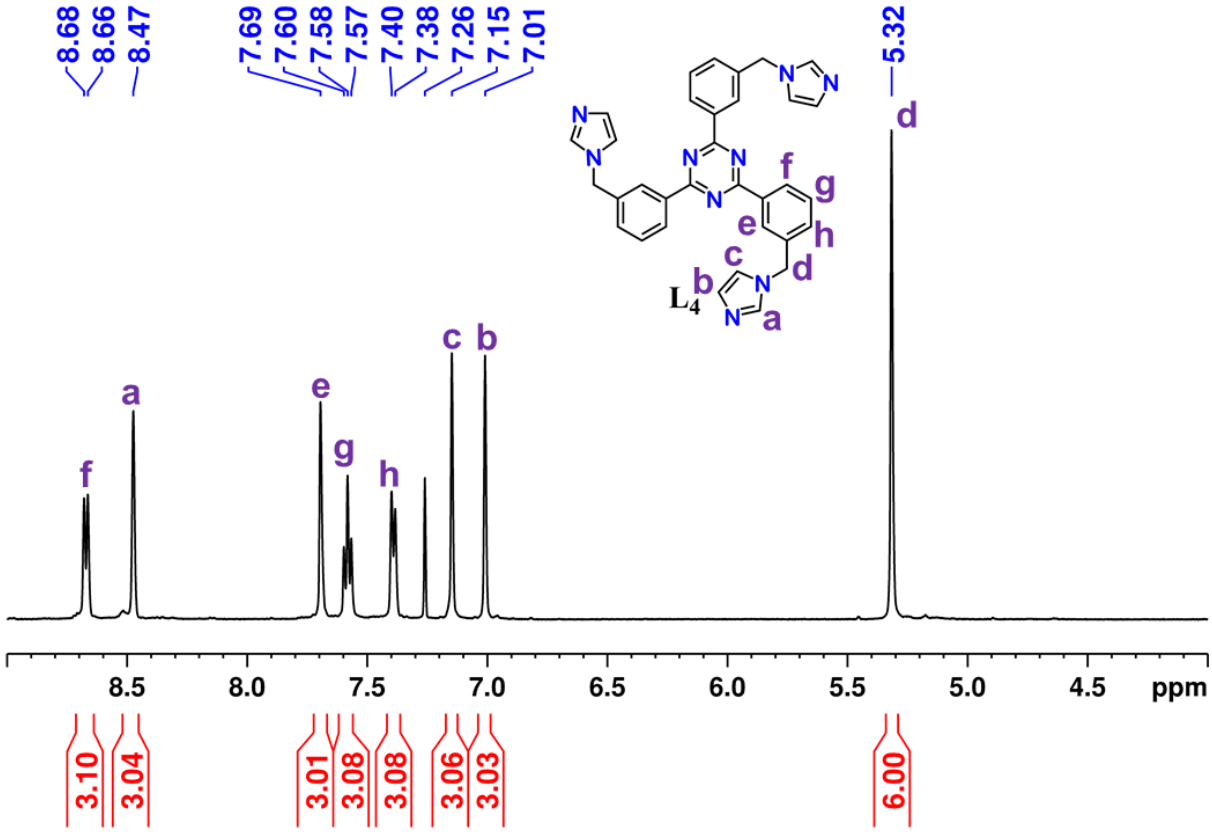


Fig. S35: ^{1}H NMR spectrum of compound **L4** ($CDCl_3$, 298 K).

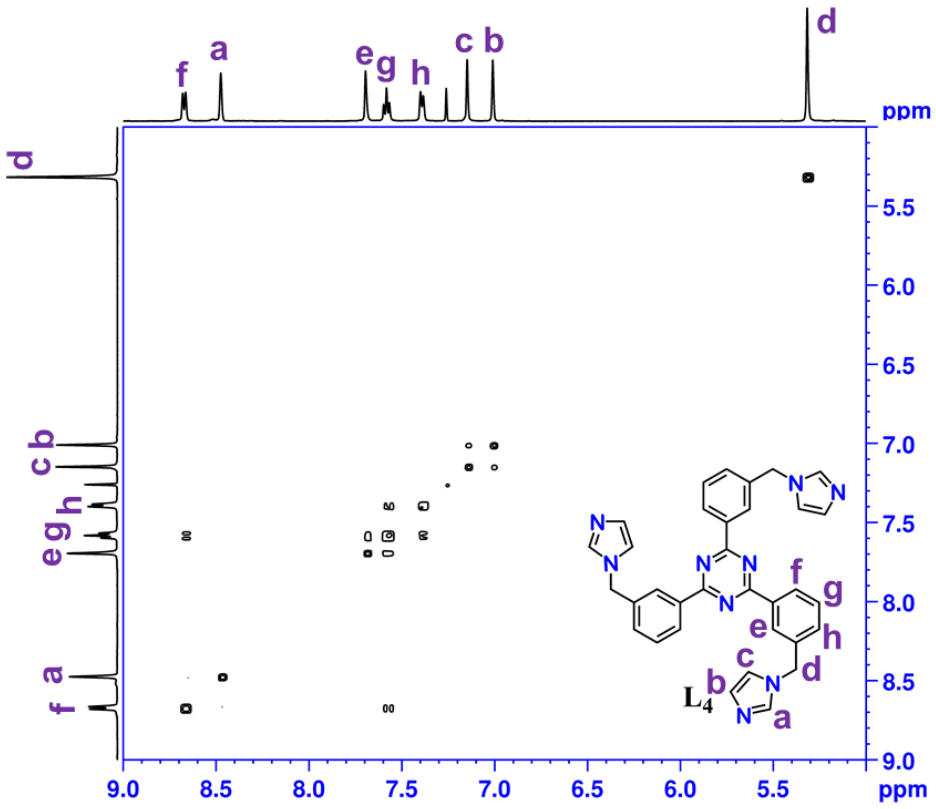


Fig. S36: ^{1}H-^{1}H COSY NMR spectrum of compound **L4** ($CDCl_3$, 298 K).

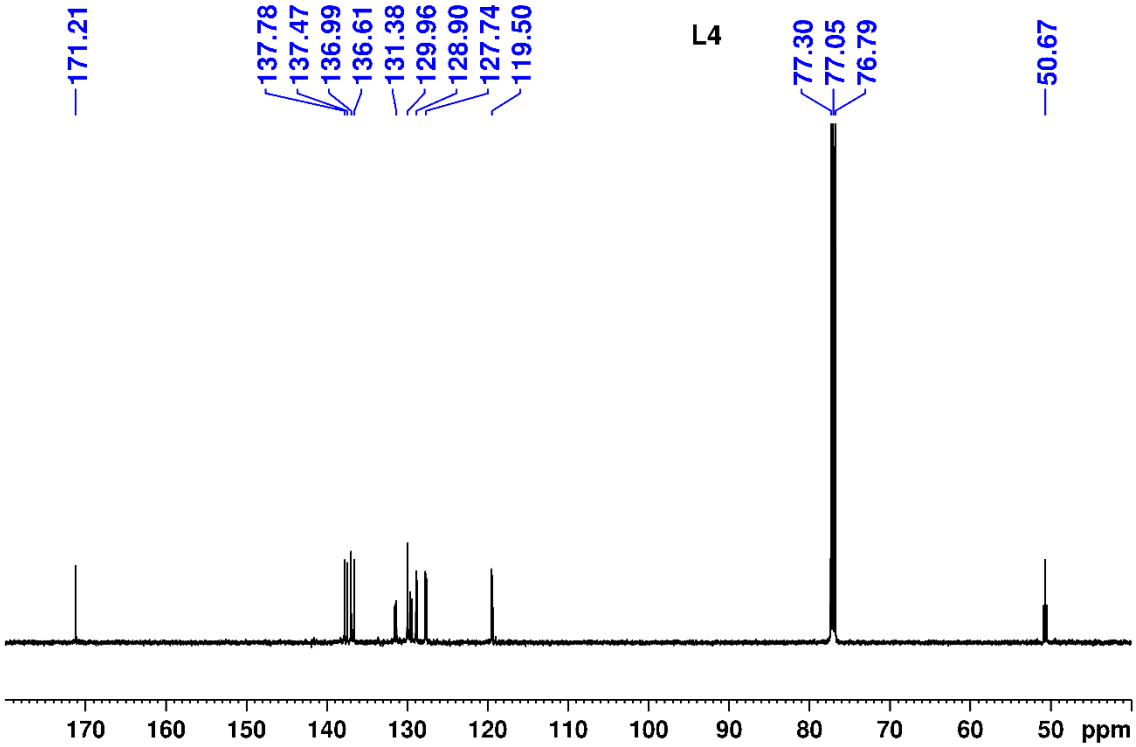


Fig. S37: ^{13}C NMR spectrum of compound **L4** ($CDCl_3$, 298 K).

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2 (a) A. D. Becke, *Phys. Rev. A*, 1988, **38**, 3098; (b) C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B*, 1988, **37**, 785-789.