

Electronic Supplementary Information

Temperature-Induced Large Amplitude Conformational Change in the Complex of Oxatub[4]arene Revealed via Rotaxane Synthesis

Dong-Hao Li, Liu-Pan Yang, Hongxin Chai, Fei Jia, Hua Ke, and Wei Jiang*

Department of Chemistry, Southern University of Science and Technology,

Xueyuan Blvd 1088, Nanshan District, Shenzhen, 518055, P. R. China

**E-mail: jiangw@sustc.edu.cn*

Table of Contents

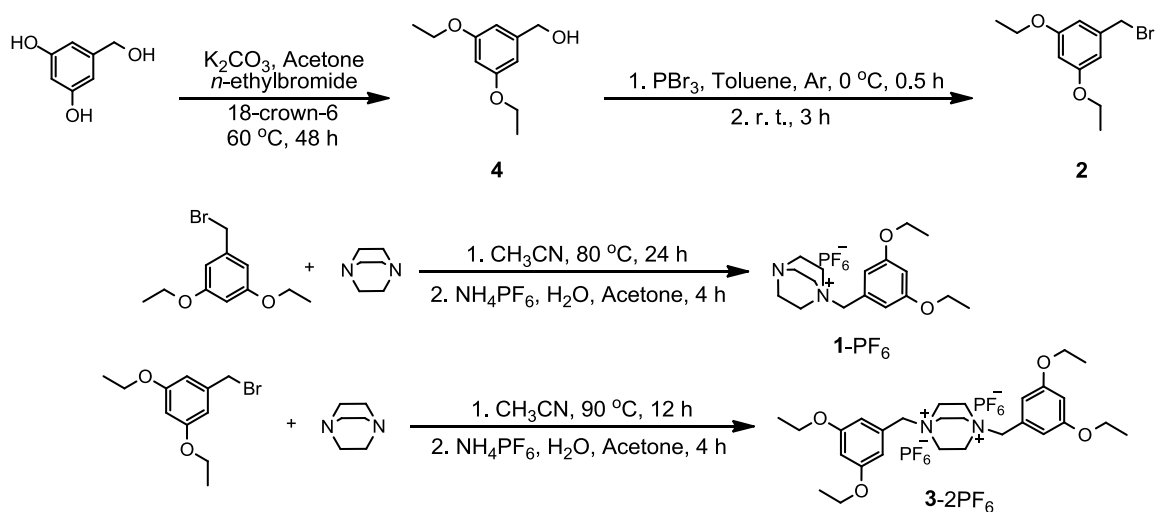
1. Experimental Section	S2
2. Characterization Data of 1⁺@TA4	S15
3. Characterization Data of Rotaxanes R-IV and R-III	S18
4. Rotaxane Synthesis at Different Temperatures	S22
5. Binding Constants of 1⁺@TA4 at Different Temperatures	S23
6. X-Ray Single Crystallography	S26
7. References	S27

1. Experimental Section

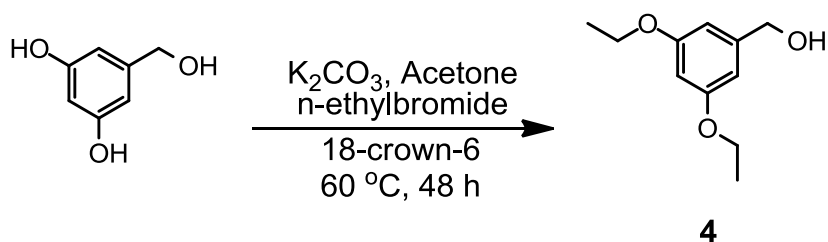
1.1 General. All the reagents involved in this research were commercially available and used without further purification unless otherwise noted. Solvents were either employed as purchased or dried prior to use by standard laboratory procedures. ^1H NMR, and ^1H - ^1H ROESY NMR spectra were recorded on Bruker Avance-400 or 600 spectrometers. All chemical shifts are reported in *ppm* with residual solvents as the internal standards. Electrospray-ionization time-of-flight high-resolution mass spectrometry (ESI-TOF-HRMS) experiments were conducted on an applied Q EXACTIVE mass spectrometry system. Molecular simulations were performed at the Semi-Empirical PM6 level of theory by using Spartan'14 (Wavefunction, Inc.). The synthesis of Oxatub[4]arene (**TA4**) has been reported.¹

1.2 Isothermal titration calorimetry, ITC. Titration experiments were carried out in 1,2-dichloroethane/ CH_3CN 1 : 1 (v/v) on a Nano ITC LV – 190 μL (Waters GmbH, TA Instruments, Eschborn, Germany). In a typical experiment, a 190 μL solution of **TA4** was placed in the sample cell at a concentration of 0.15 mM, and 50 μL of a solution of the hexafluorophosphate salt (1.0 mM in the same solvent) was in the injection syringe. The titrations consisted of 25 consecutive injections of 1.96 μL each with a 5 min interval between injections. Heats of dilution, measured by titration of the salt into the sample cell with blank solvent, were subtracted from each data set. All solutions were degassed prior to titration. The data were analysed using the instrumental internal software package and fitted with a 1:1 binding model. Errors are smaller than $\pm 10\%$.

1.3 Synthetic Procedures

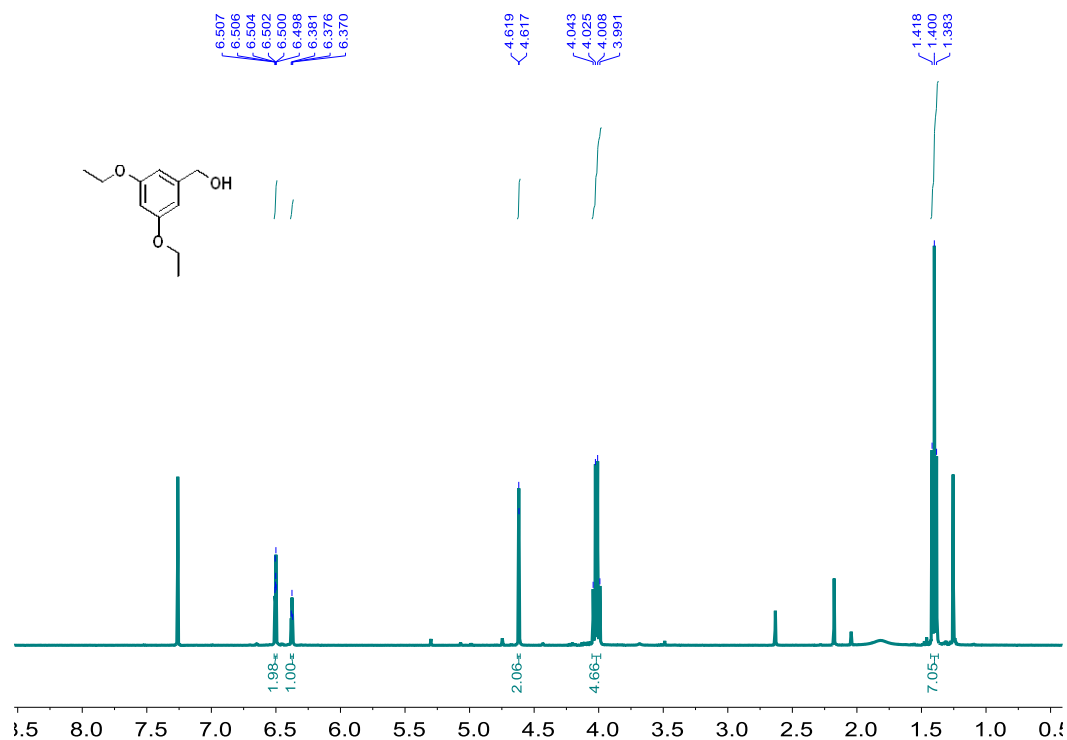


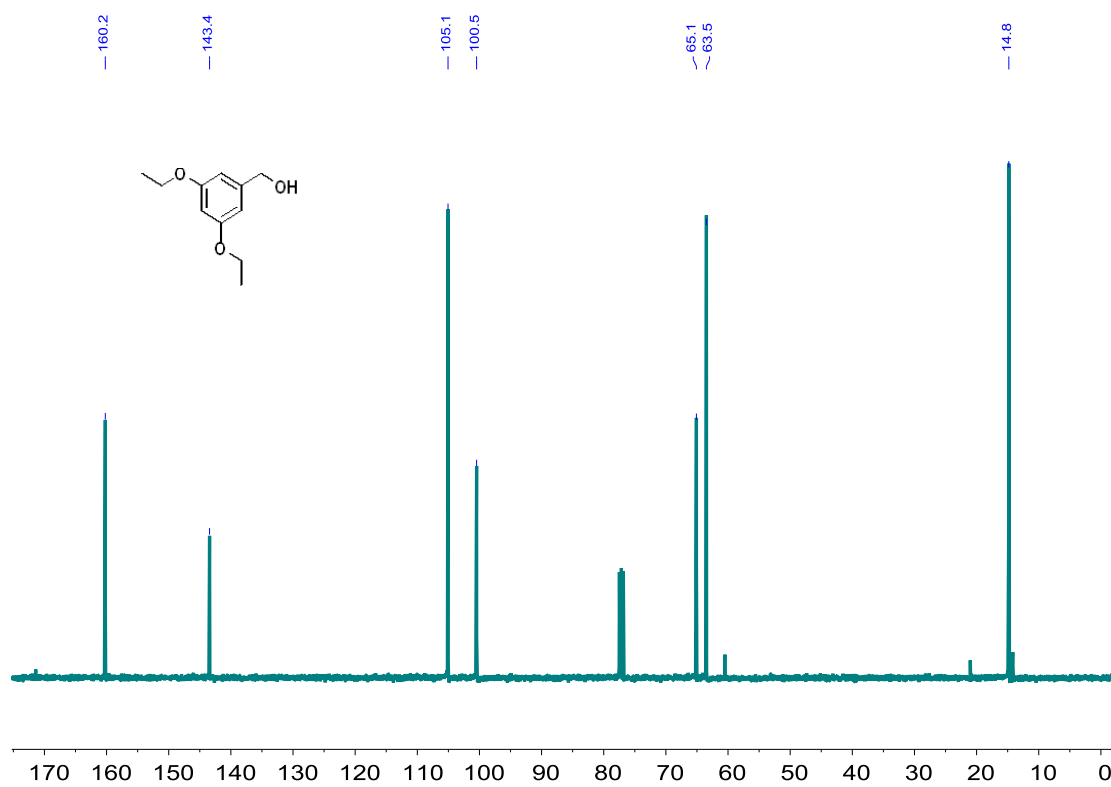
Compound 4²



The mixture of 5-(hydroxymethyl)benzene-1,3-diol (3.0 g, 21 mmol), *n*-ethylbromide (6.4 mL, 86 mmol) and 18-crown-6 (0.57 g, 2.1 mmol) in acetone (50 mL) was stirred for 48 h at 60 °C. After cooling to room temperature, the mixture was concentrated with rotary evaporator. Water (50 mL) was added to the mixture and then extracted with ethylacetate (60 mL \times 3). The organic phase was collected and then dried over anhydrous MgSO_4 . The solvent was removed under reduced pressure. The remaining residue was subject to column chromatography (SiO_2 , petroleum ether : ethylacetate = 2 : 1) to afford compound **4** (3.6 g, 86%) as a yellow solid.

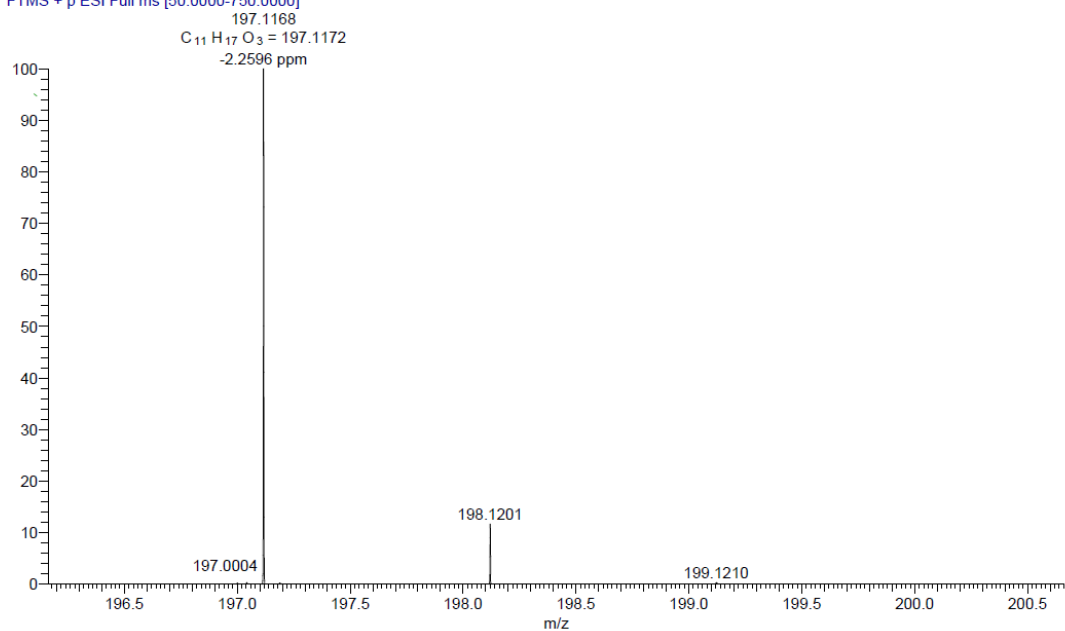
4. m.p. 37-39 °C; ^1H NMR (400 MHz, CDCl_3 , 298K): δ [ppm] = 6.51 (d, J = 2.0 Hz, 2H), 6.38 (t, J = 2.2 Hz, 1H), 4.62 (s, 1H), 4.02 (q, J = 7.0 Hz, 4H), 1.40 (t, J = 7.0 Hz, 6H); ^{13}C NMR (400 MHz, CDCl_3 , 298K): δ [ppm] = 160.2, 143.4, 105.1, 100.5, 65.1, 63.5, 14.8; ESI-MS: m/z calcd for $[\text{M}+\text{H}]^+ \text{C}_{11}\text{H}_{17}\text{O}_3^+$, 197.1172; found 197.1168 (error = -2.3 ppm).



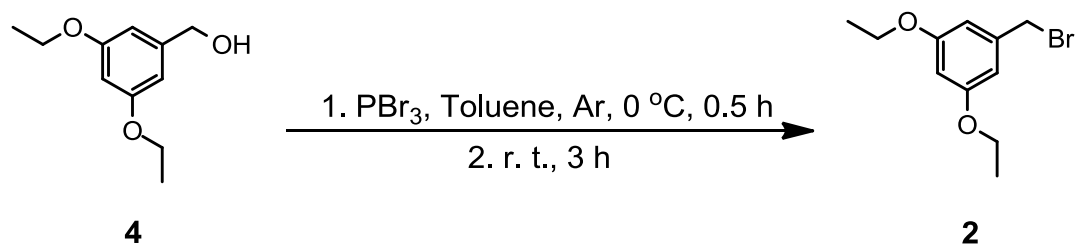


^{13}C NMR spectrum (400 MHz, CDCl_3 , 298 K) of compound 4

LDH-TF4-ROT-4_170329134345 #17 RT: 0.16 AV: 1 NL: 7.73E8
T: FTMS + p ESI Full ms [50.0000-750.0000]

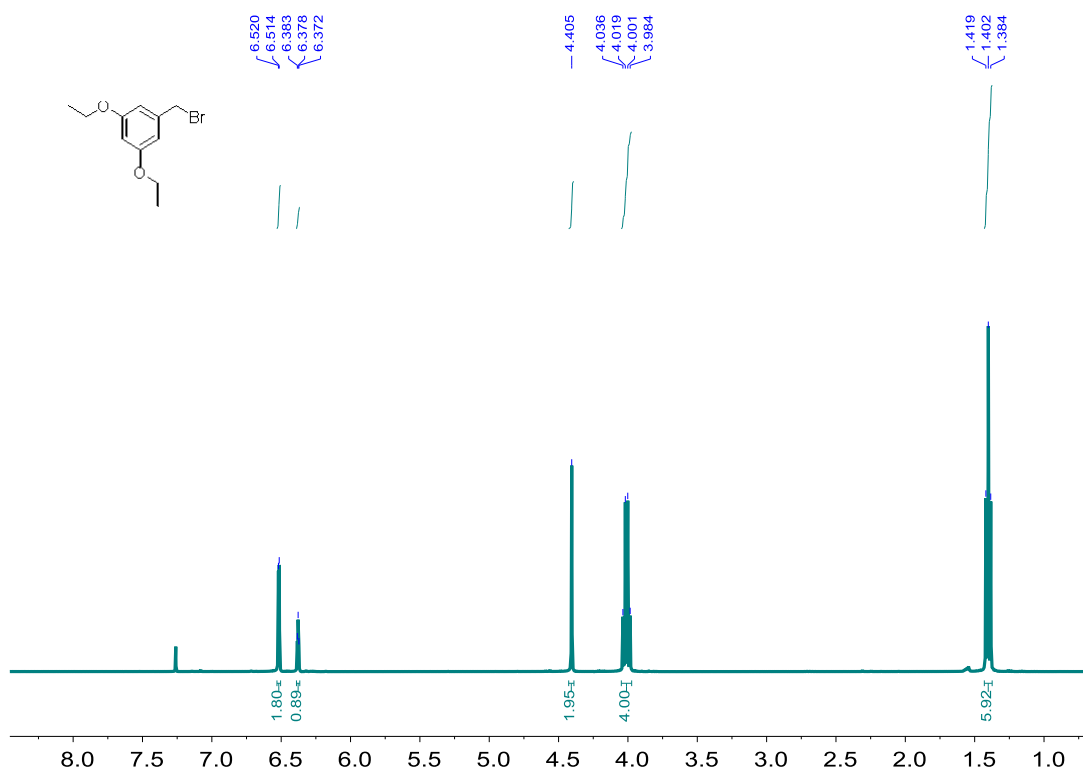


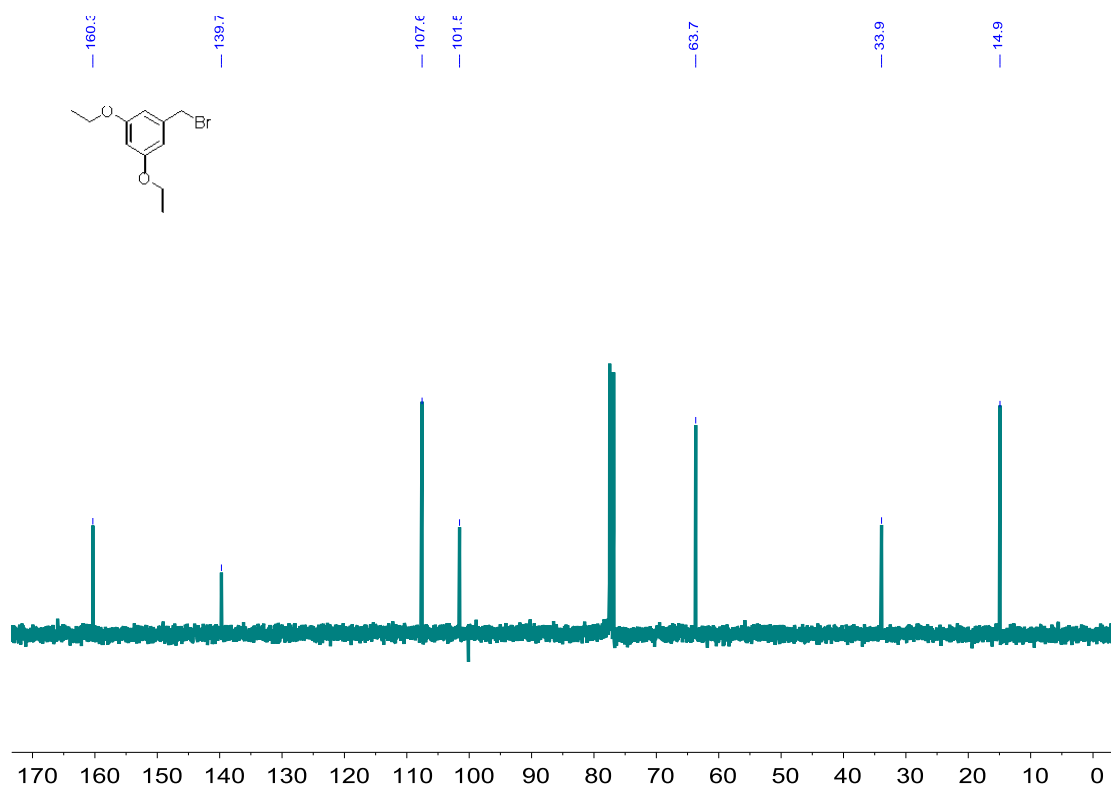
ESI-TOF mass spectrum of compound 4

Compound 2³

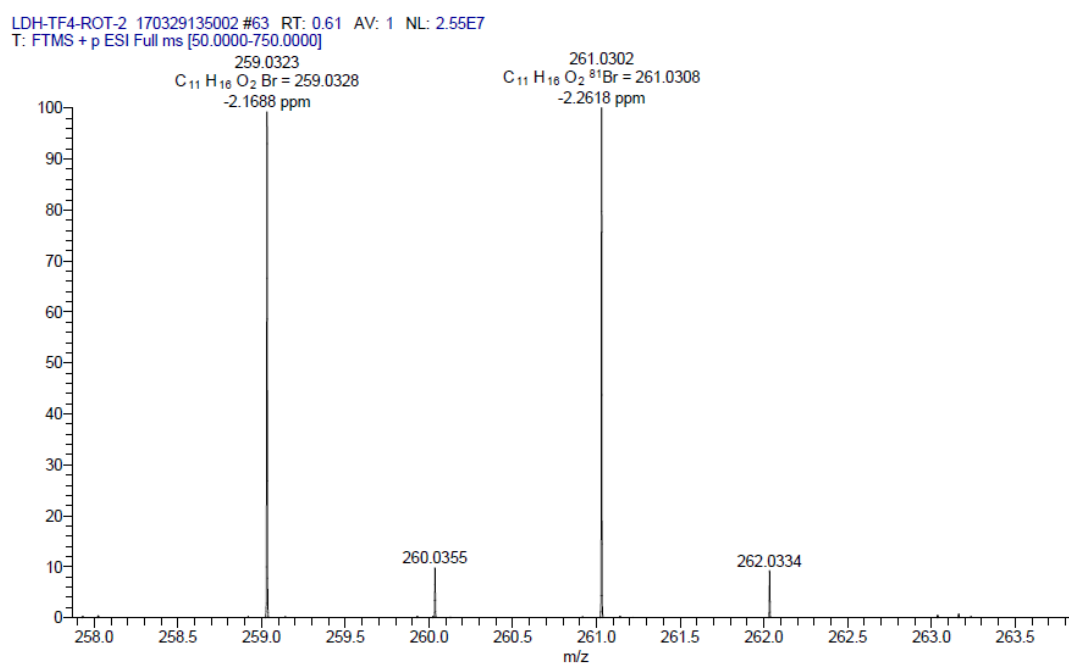
The compound **4** (3.6 g, 18 mmol) was dissolved in toluene (50 ml), the solution was cooled down by ice water bath. PBr₃ (0.43 ml, 28 mmol) was added to the solution. The mixture was stirred at room temperature for 3 h under argon. Ice water (20 ml) was added to the mixture to eliminate PBr₃, then the mixture was extracted by DCM (30 ml × 3). The solvent was removed under reduced pressure. The remaining residue was subject to column chromatography (SiO₂, petroleum ether : ethylacetate = 20 : 1) to afford compound **2** (2.8 g, 59%) as a white solid.

2. m.p. 102-103 °C; ¹H NMR (400 MHz, CDCl₃, 298K): δ [ppm] = 6.52 (d, *J* = 2.2 Hz, 2H), 6.38 (t, *J* = 2.2 Hz, 1H), 4.40 (s, 2H), 4.01 (q, *J* = 7.0 Hz, 4H), 1.40 (t, *J* = 7.0 Hz, 6H); ¹³C NMR (400 MHz, CDCl₃, 298K): δ [ppm] = 160.3, 139.7, 107.6, 101.6, 63.7, 33.9, 14.9; ESI-MS: *m/z* calcd for [M+H]⁺ C₁₁H₁₆BrO₂⁺, 259.0328; found 259.0323 (error = -2.2 ppm).



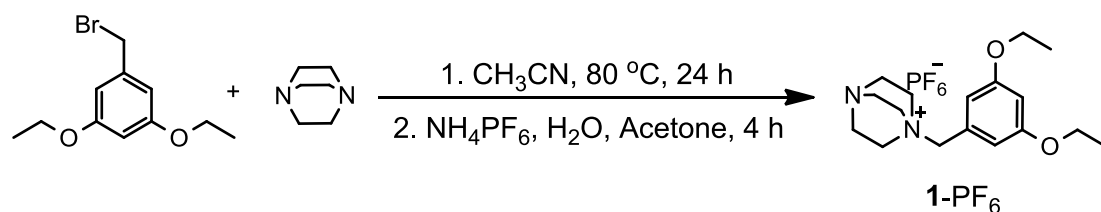


^{13}C NMR spectrum (400 MHz, CDCl_3 , 298 K) of compound 2



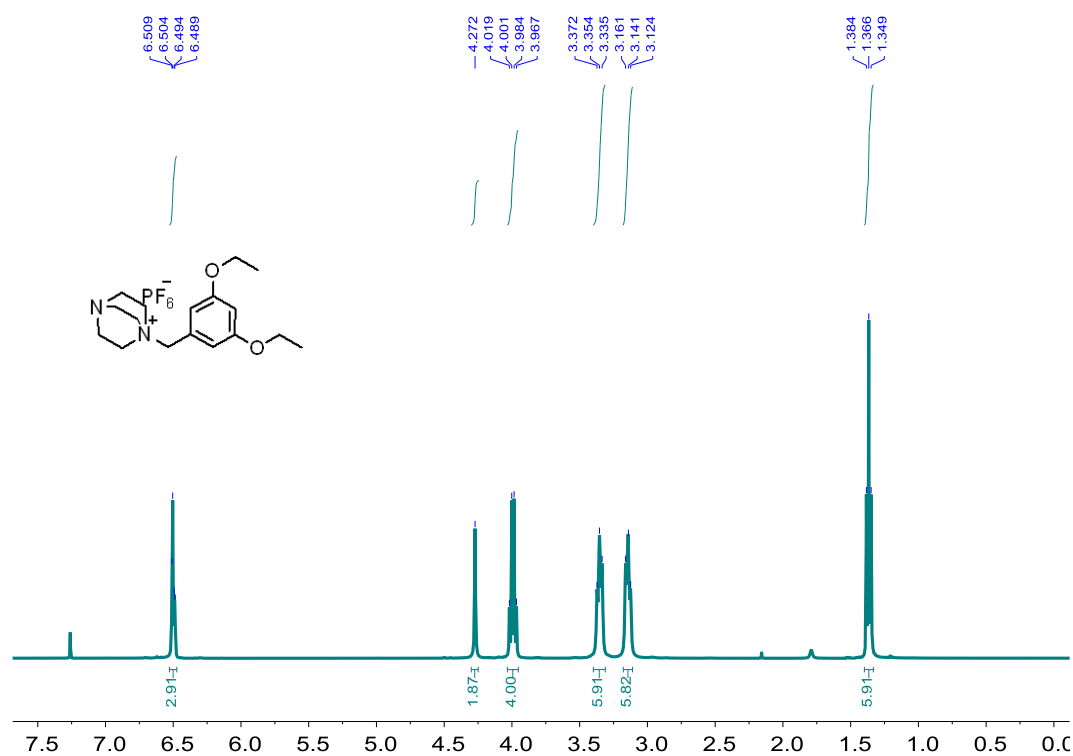
ESI-TOF mass spectrum of compound 2

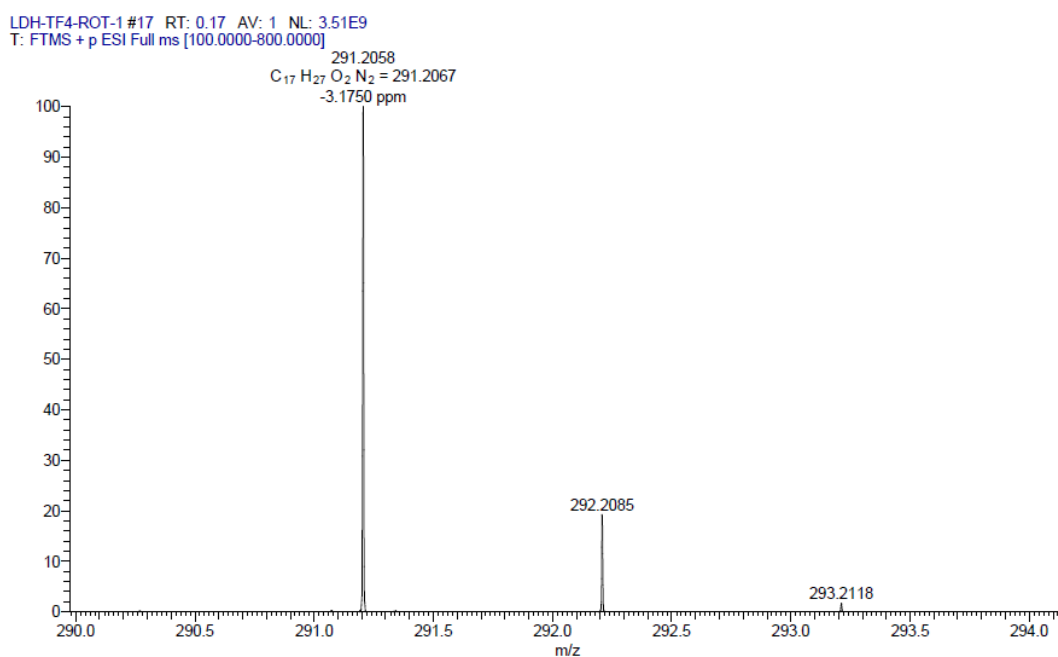
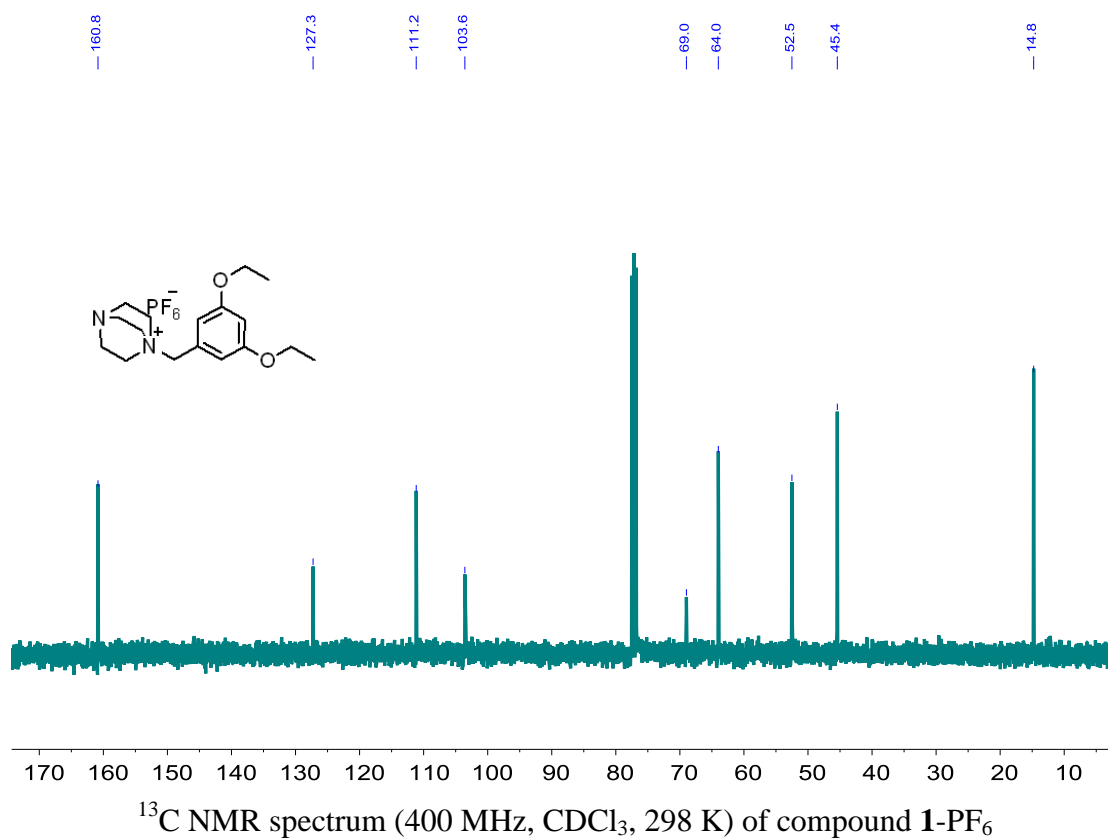
Compound 1-PF₆



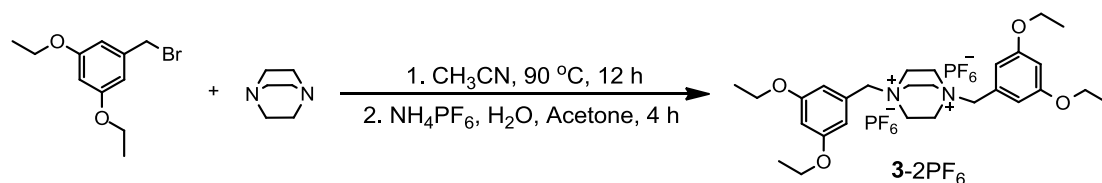
Compound **2** (3.0 g, 12 mmol) was dissolved in CH₃CN (10 mL) and dropwise added to the mixture of DABCO (4.0 g, 36 mmol) and CH₃CN (30 mL) stirred for 24 h at 80 °C. After cooling to room temperature, diethyl ether (30 mL) was added to the mixture to form precipitate, then the precipitate was filtered and washed with ether. The product was dried by vacuum. NH₄PF₆ (7.6 g, 48 mmol) was added into the solution of the white solid in water (20 ml) and acetone (10 mL). The mixture was stirred at room temperature for 4 h. The precipitate was formed, and filtered, and dried by vacuum to afford compound **1-PF₆** (3.5 g, 69%) as a white solid.

1-PF₆. m.p. 195-196 °C; ¹H NMR (400 MHz, CDCl₃, 298K): δ [ppm] = 6.50 (d, *J* = 2.0 Hz, 2H), 6.49 (t, *J* = 2.0 Hz, 2H), 4.27 (s, 2H), 3.93 (q, *J* = 7.0 Hz, 4H), 3.35 (t, *J* = 7.2 Hz, 6H), 3.14 (t, *J* = 7.2 Hz, 6H), 1.37 (t, *J* = 7.0 Hz, 6H); ¹³C NMR (400 MHz, CDCl₃, 298K): δ [ppm] = 160.8, 127.3, 111.2, 103.6, 69.0. 52.5, 45.4, 14.8; ESI-MS: *m/z* calcd for [M-PF₆]⁺ C₁₇H₂₇N₂O₂⁺, 291.2067; found 291.2058 (error = -3.2 ppm).



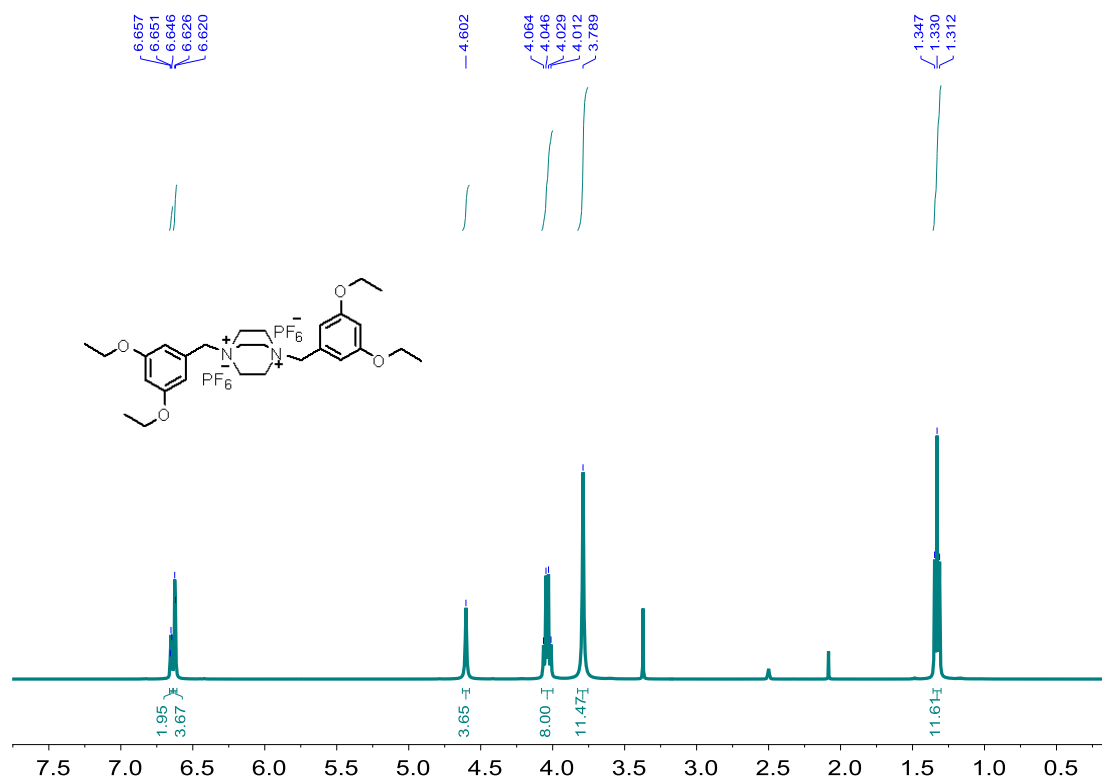


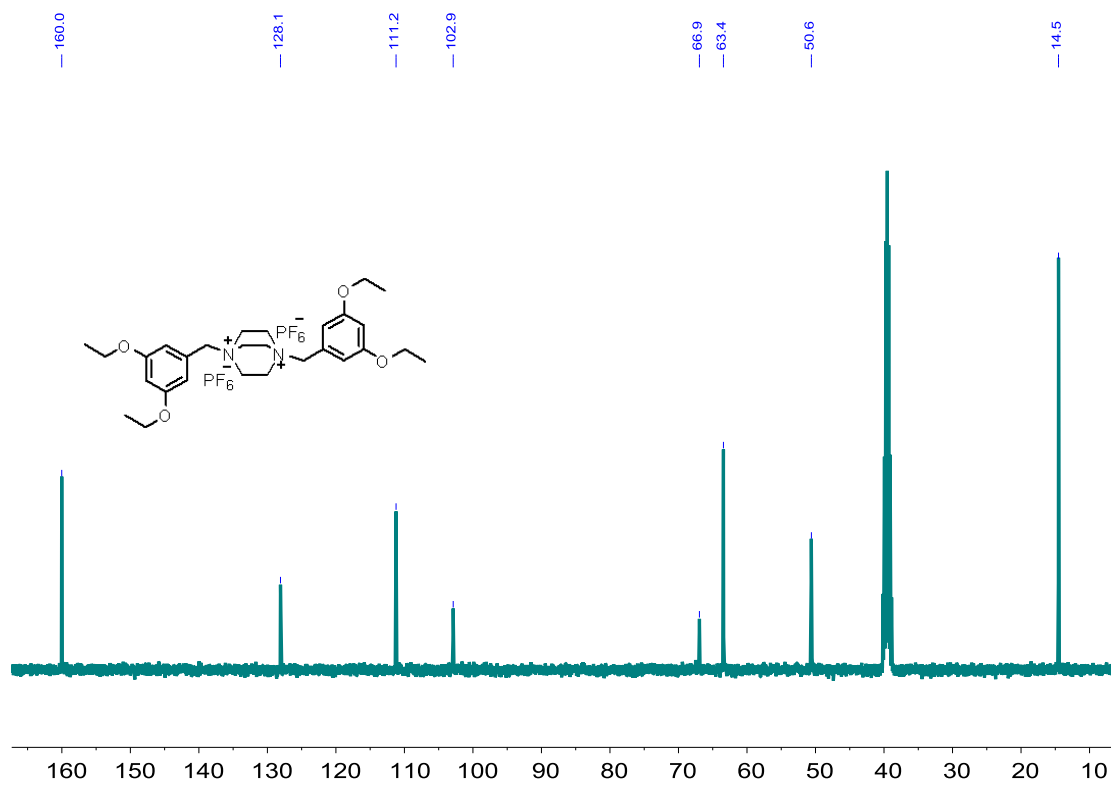
Compound 3-2PF₆



The mixture of Compound **2** (1.4 g, 5.4 mmol) and DABCO (0.12 g, 0.93 mmol) in acetonitrile (20 mL) was stirred for 48 h at 60 °C. After cooling to room temperature, diethyl ether (30 mL) was added to the mixture to form precipitate, then the precipitate was filtered and washed with ether. The product was dried by vacuum. NH₄PF₆ (0.58 g, 3.6 mmol) was added into the solution of the white solid in water (10 mL) and acetone (10 mL). The mixture was stirred at room temperature for 4 h. The precipitate was formed, and filtered, and dried by vacuum to afford compound **3-2PF₆** (0.63 g, 93%) as a white solid.

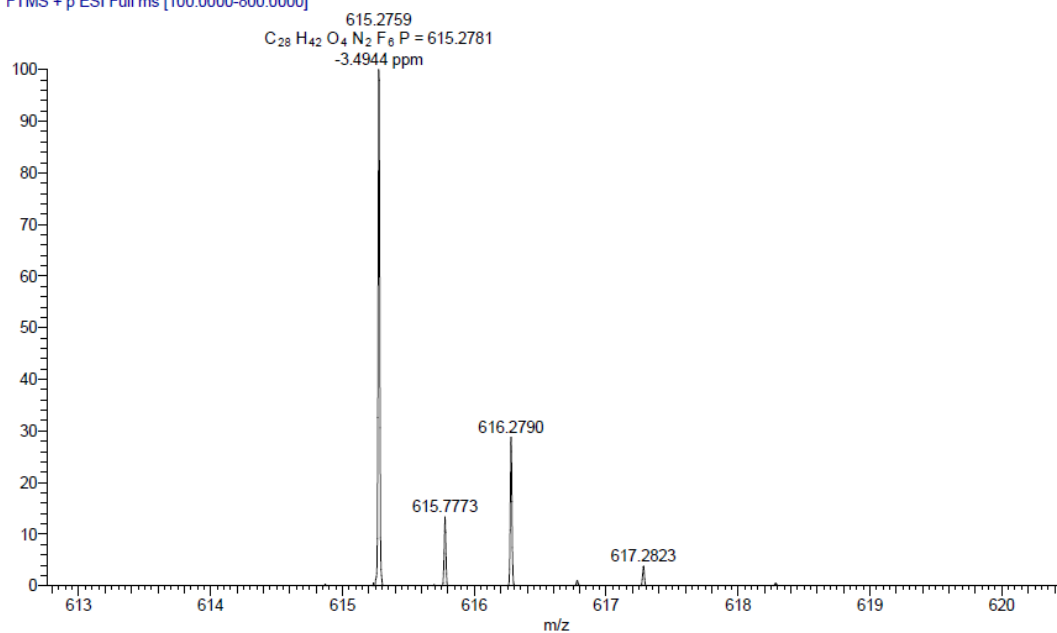
3-2PF₆, m.p. 281-282 °C; ¹H NMR (400 MHz, DMSO-*d*₆, 298K): δ [ppm] = 6.65 (t, *J* = 2.2 Hz, 2H), 6.62 (d, *J* = 2.2 Hz, 4H), 4.60 (s, 4H), 4.04 (q, *J* = 6.9 Hz, 8H), 3.79 (s, 12H), 1.33 (t, *J* = 7.0 Hz, 12H); ¹³C NMR (100 MHz, DMSO-*d*₆, 298K) δ [ppm] = 160.0, 128.1, 111.2, 102.9, 66.9, 63.4, 50.6, 14.5; ESI-MS: *m/z* calcd for [M-PF₆]⁺ C₂₈H₄₂F₆N₂O₄P⁺, 615.2781; found 615.2759 (error = -3.5 ppm).





¹³C NMR spectrum (100 MHz, DMSO-*d*₆, 298K) of compound **3-2PF₆**

LDH-TF4-ROT-3 170329131645 #15 RT: 0.14 AV: 1 NL: 1.32E9
T: FTMS + p ESI Full ms [100.0000-800.0000]

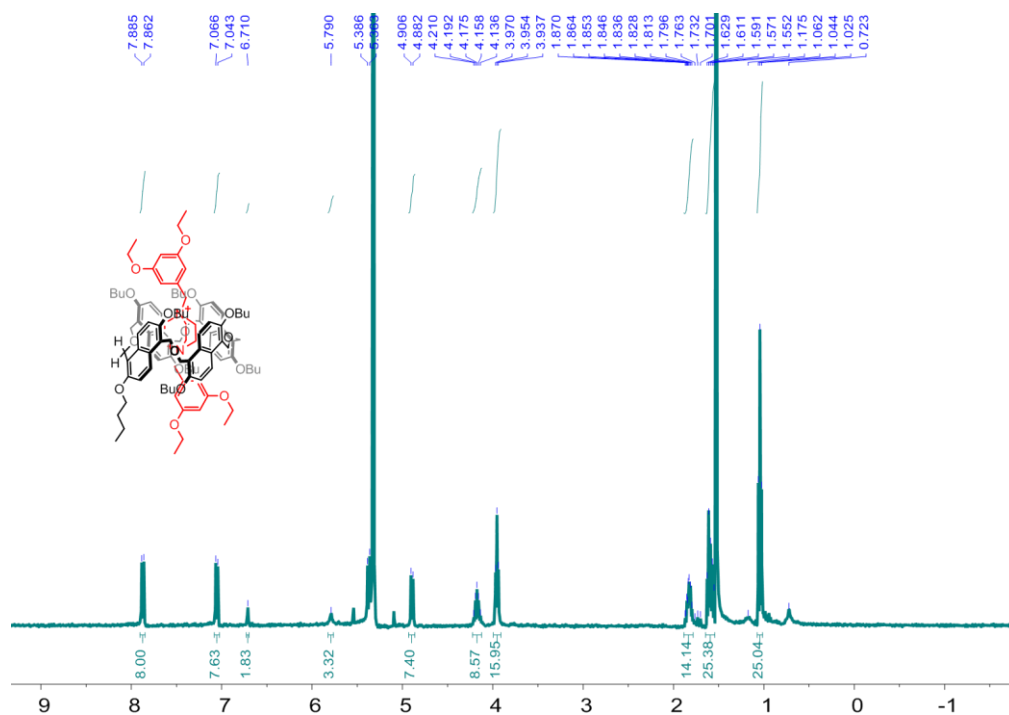


ESI-TOF mass spectrum of compound **3-2PF₆**

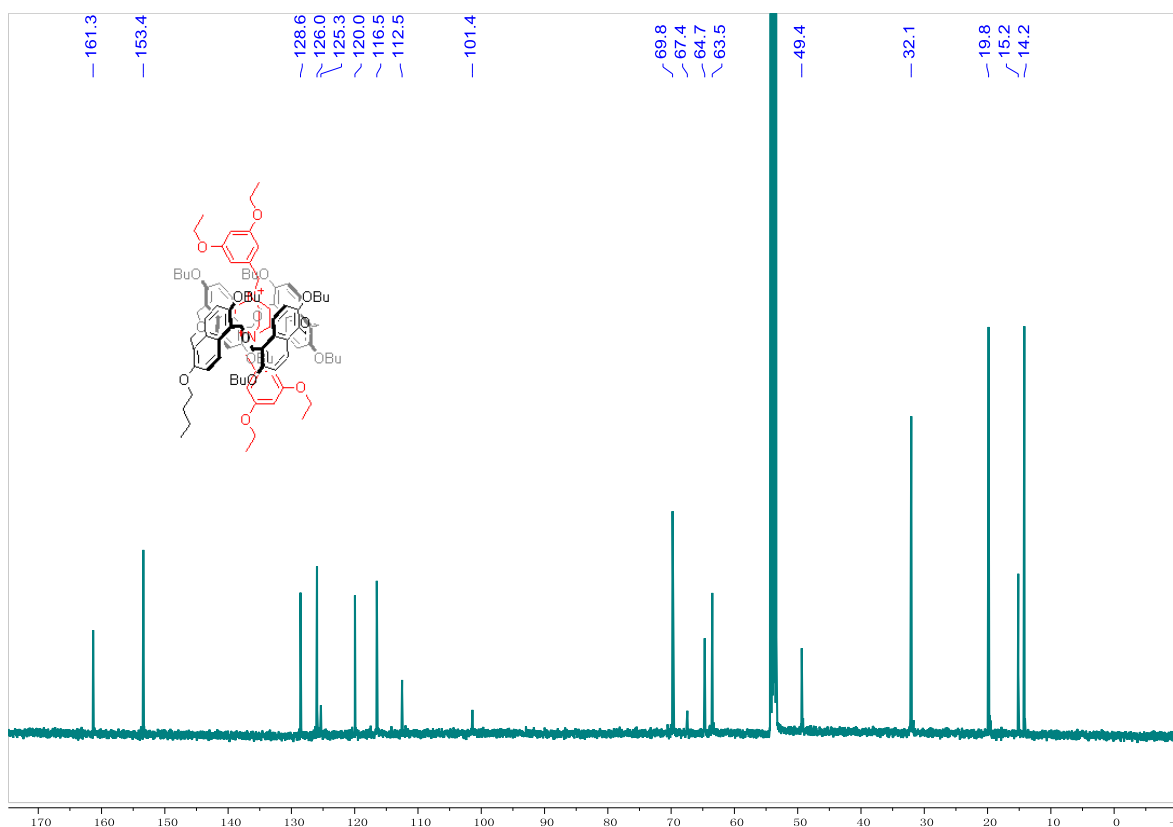
Rotaxane-IV

The mixture of **TA4** (50 mg, 40 μ mol) and Compound **1**-PF₆ (70 mg, 0.16 mmol) in 1,2-dichloroethane (20 mL) was stirred for 0.5 h at room temperature. Compound **2** (61.81 mg, 289 μ mol) and K₂CO₃ (54.94 mg, 398 μ mol) were added to the mixture and stirred for 72 h at room temperature. The solvent was removed and the remaining residue was subject to preparative thin-layer chromatography (Al₂O₃, petroleum ether : ethylacetate = 1 : 1) to afford a raw product. Then the raw product was dissolved in DCM (3 mL), *n*-hexane (30 mL) was added to the mixture to form precipitate, then the precipitate was filtered and washed with *n*-hexane. The filter cake was dried by vacuum to afford **R-IV** (30 mg, 37%) as a white solid.

R-IV. m.p. > 300 °C. ¹H NMR (400 MHz, CD₂Cl₂, 298 K): δ [ppm] = 7.87 (d, *J* = 9.4 Hz, 8H), 7.05 (d, *J* = 9.4 Hz, 8H), 6.71 (t, *J* = 1.6 Hz, 2H), 5.79 (br s, 4H), 5.37 (d, *J* = 9.4 Hz, 8H), 4.89 (d, *J* = 9.4 Hz, 8H), 4.22 – 4.12 (m, 8H), 3.95 (t, *J* = 6.4 Hz, 16H), 1.90 – 1.78 (m, 16H), 1.72 (d, *J* = 12.4 Hz, 4H), 1.59 (m, 28H), 1.17 (s, 6H), 1.04 (t, *J* = 7.4 Hz, 24H), 0.72 (s, 6H); ¹³C NMR (100 MHz, CD₂Cl₂, 298K) δ [ppm] = 161.3, 153.4, 128.6, 126.0, 125.3, 120.0, 116.5, 112.5, 101.4, 69.8, 67.4, 64.7, 63.5, 49.4, 32.1, 19.8, 15.2, 14.2. ESI-MS: *m/z* calcd for [M-2PF₆]²⁺ C₁₀₈H₁₄₆N₂O₁₆²⁺, 863.5331; found 863.5325 (error = -0.6 ppm); *m/z* calcd for [M-2PF₆-H]⁺ C₁₀₈H₁₄₅N₂O₁₆⁺, 1726.0589; found 1726.0504 (error = -4.9 ppm).



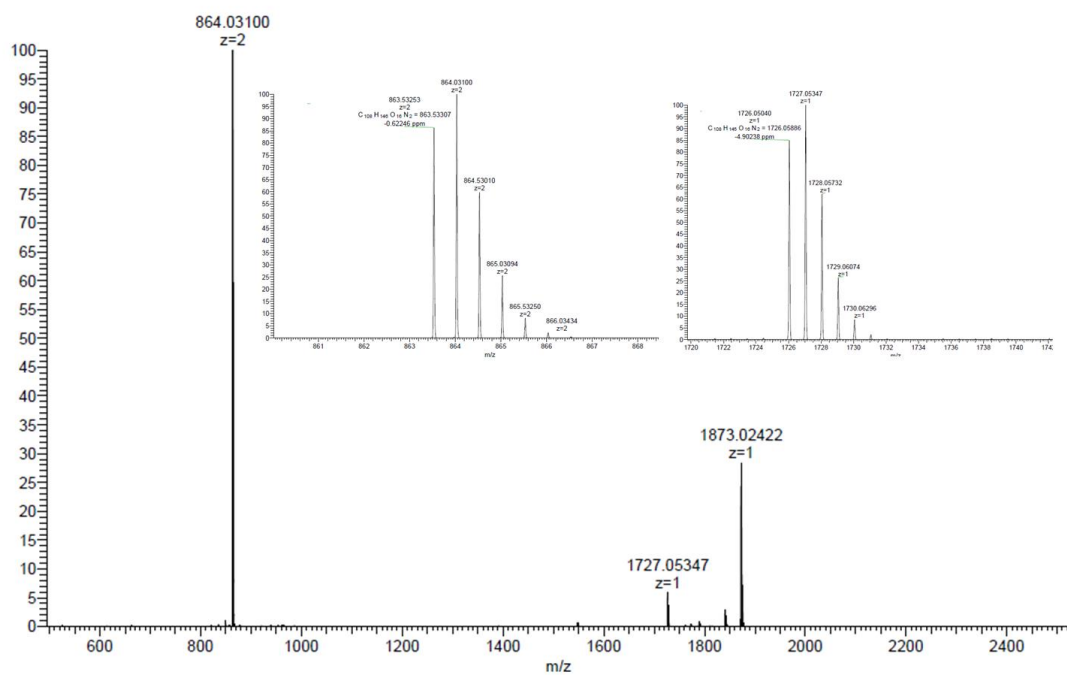
¹H NMR spectrum (400 MHz, CD₂Cl₂, 298 K) of **R-IV**



¹³C NMR spectrum (100 MHz, CD₂Cl₂, 298 K) of **R-IV**

Positive mode: Full scan(m/z=500-2500)

LDH-54-conf4-2 #7-9 RT: 0.07-0.09 AV: 2 NL: 1.03E10
T: FTMS + p ESI Full ms [500.00-2500.00]

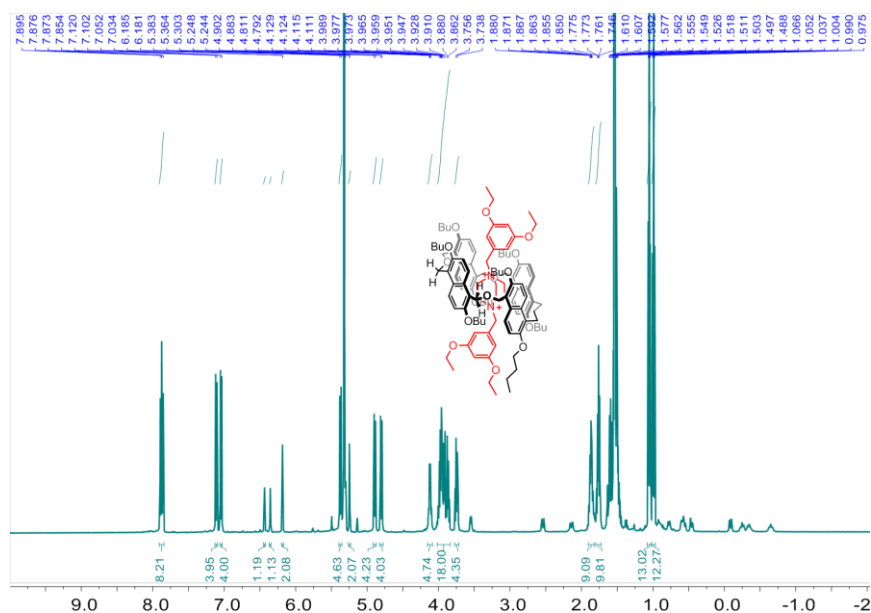


ESI-TOF mass spectrum of **R-IV**

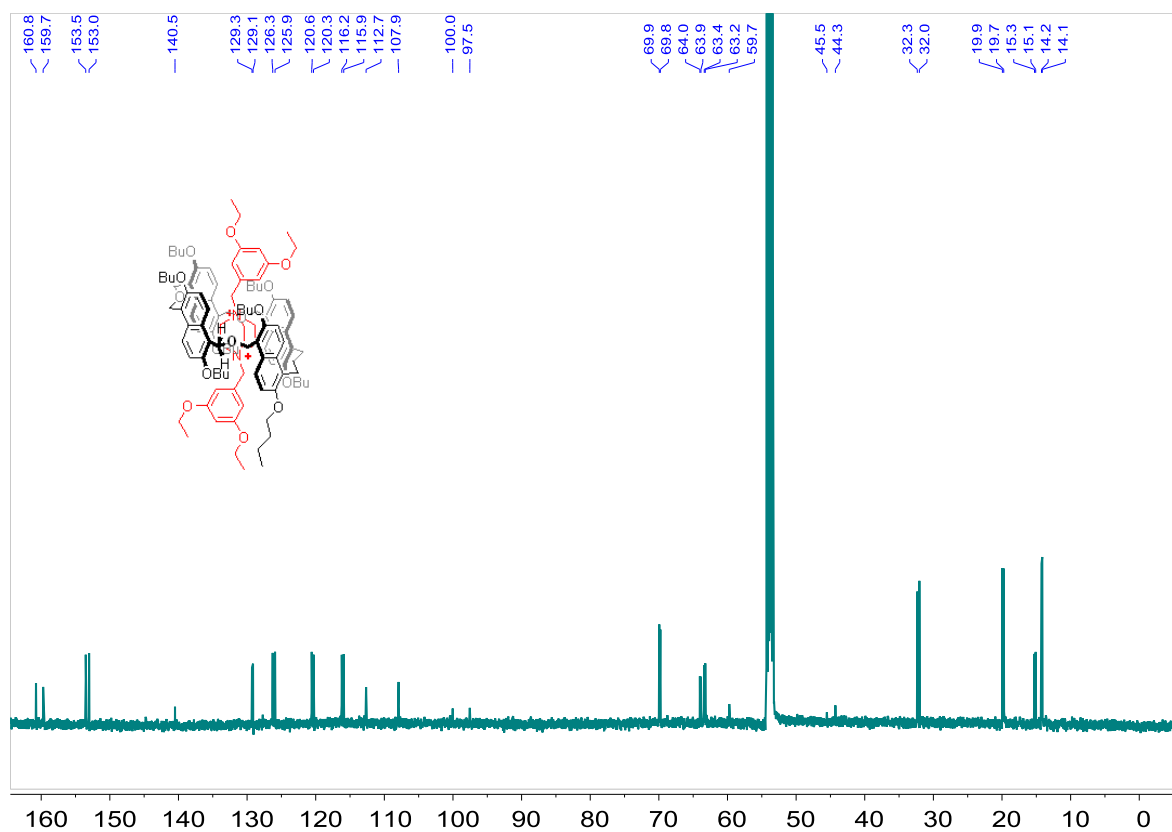
Rotaxane-III

The mixture of **TA4** (50 mg, 40 μ mol) and Compound **1**-PF₆ (70 mg, 0.16 mol) in 1,2-dichloroethane (20 mL) was stirred for 0.5 h at room temperature. Compound **2** (61.81 mg, 289 μ mol) and K₂CO₃ (54.94 mg, 398 μ mol) were added to the mixture and stirred for 72 h at 60 °C. The solvent was removed and the remaining residue was subject to preparative thin-layer chromatography (Al₂O₃, petroleum ether : ethylacetate = 1 : 2) to afford a raw product. Then the raw product was dissolved in DCM (3 mL). *n*-Hexane (30 mL) was added to the mixture to form precipitate which was filtered and washed with *n*-hexane. The filter cake was dried in vacuum to afford **R-III** (17 mg, 21%) as a white solid.

R-III. m.p. > 300 °C. ¹H NMR (400 MHz, CD₂Cl₂, 298K): δ [ppm] = 7.88 (d, *J* = 9.3 Hz, 4H), 7.87 (d, *J* = 9.3 Hz, 4H), 7.11 (d, *J* = 9.3 Hz, 4H), 7.04 (d, *J* = 9.3 Hz, 4H), 6.44 (t, *J* = 2.3 Hz, 1H), 6.36 (t, *J* = 2.2 Hz, 1H), 6.18 (d, *J* = 2.1 Hz, 2H), 5.37 (d, *J* = 9.5 Hz, 4H), 5.30 (d, *J* = 9.5 Hz, 4H), 5.25 (d, *J* = 2.2 Hz, 2H), 4.89 (d, *J* = 9.3 Hz, 4H), 4.80 (d, *J* = 9.3 Hz, 4H), 4.18 – 3.67 (m, 24H), 1.94 – 1.43 (m, 44H), 1.05 (t, *J* = 7.4 Hz, 12H), 0.99 (t, *J* = 7.4 Hz, 12H).; ¹³C NMR (100 MHz, CD₂Cl₂, 298K) δ [ppm] = 160.8, 159.7, 153.5, 153.0, 140.5, 129.3, 129.1, 126.3, 125.9, 120.6, 120.3, 116.2, 115.9, 112.7, 107.9, 100.0, 97.5, 69.9, 69.8, 64.0, 63.9, 63.4, 63.2, 59.7, 45.5, 44.3, 32.3, 32.0, 19.9, 19.7, 15.3, 15.1, 14.2, 14.1. ESI-MS: *m/z* calcd for [M-2PF₆]²⁺ C₁₀₈H₁₄₆N₂O₁₆²⁺, 863.5331, found 863.5319 (error = -1.4 ppm); *m/z* calcd for [M-2PF₆-H]⁺ C₁₀₈H₁₄₅N₂O₁₆⁺, 1726.0589; found 1726.0564 (error = -1.4 ppm).

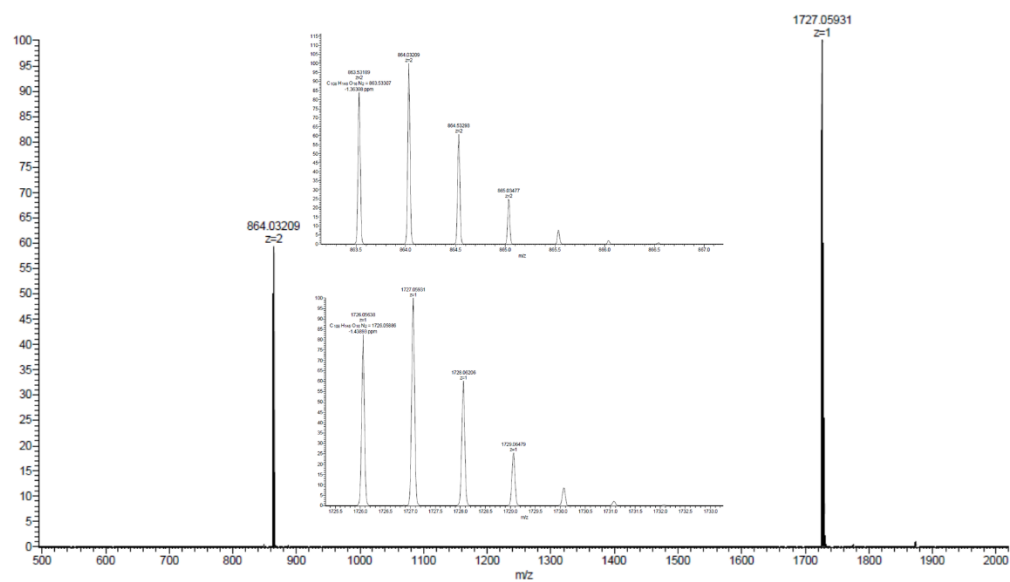


¹H NMR spectrum (500 MHz, CD₂Cl₂, 298 K) of **R-III**



¹³C NMR spectrum (100 MHz, CD₂Cl₂, 298 K) of **R-III**

YLP175-0723#19 RT: 0.08 AV: 1 SB: 82 0.31-0.68 NL: 2.16E9
T: FTMS + p ESI Full ms [500.00-2000.00]



ESI-TOF mass spectrum of **R-III**

2. Characterization Data of 1⁺@TA4

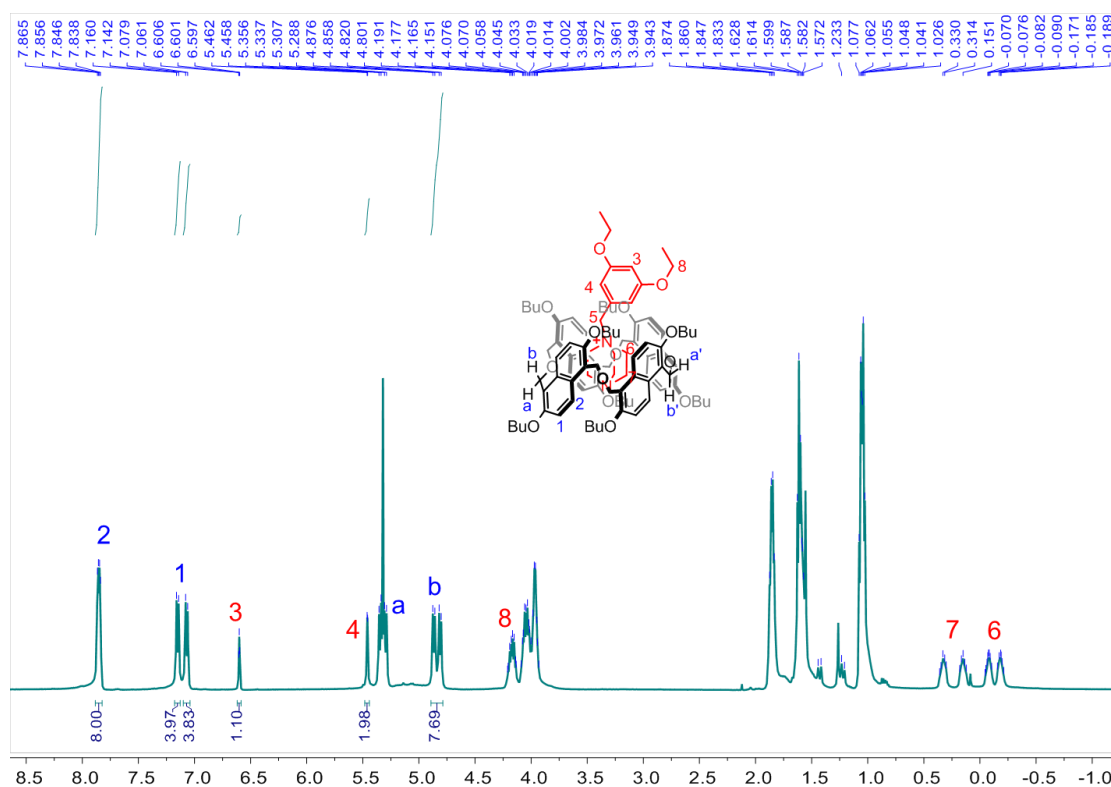


Fig. S1 ¹H NMR spectrum (500 MHz, CD₂Cl₂, 298 K) of 1⁺@TA4. The integrals show a 1:1 binding stoichiometry.

LDH-1-TA4 #21 RT: 0.13 AV: 1 NL: 3.65E8
T: FTMS + p ESI Full ms [200.0000-2000.0000]

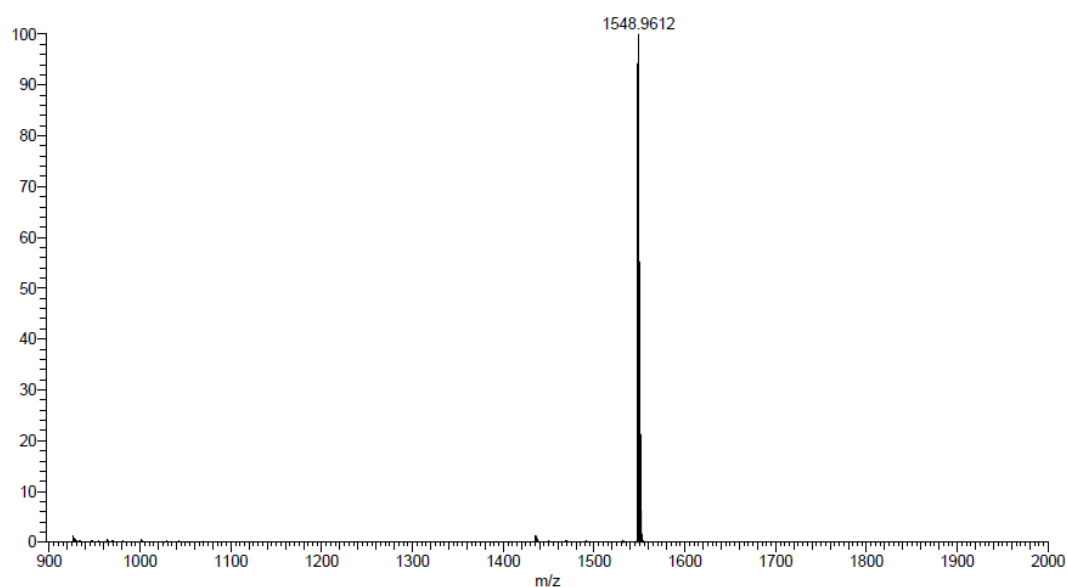


Fig. S2 ESI mass spectrum of 1⁺@TA4. The peak at m/z 1548 is assigned to the 1:1 complex 1⁺@TA4.

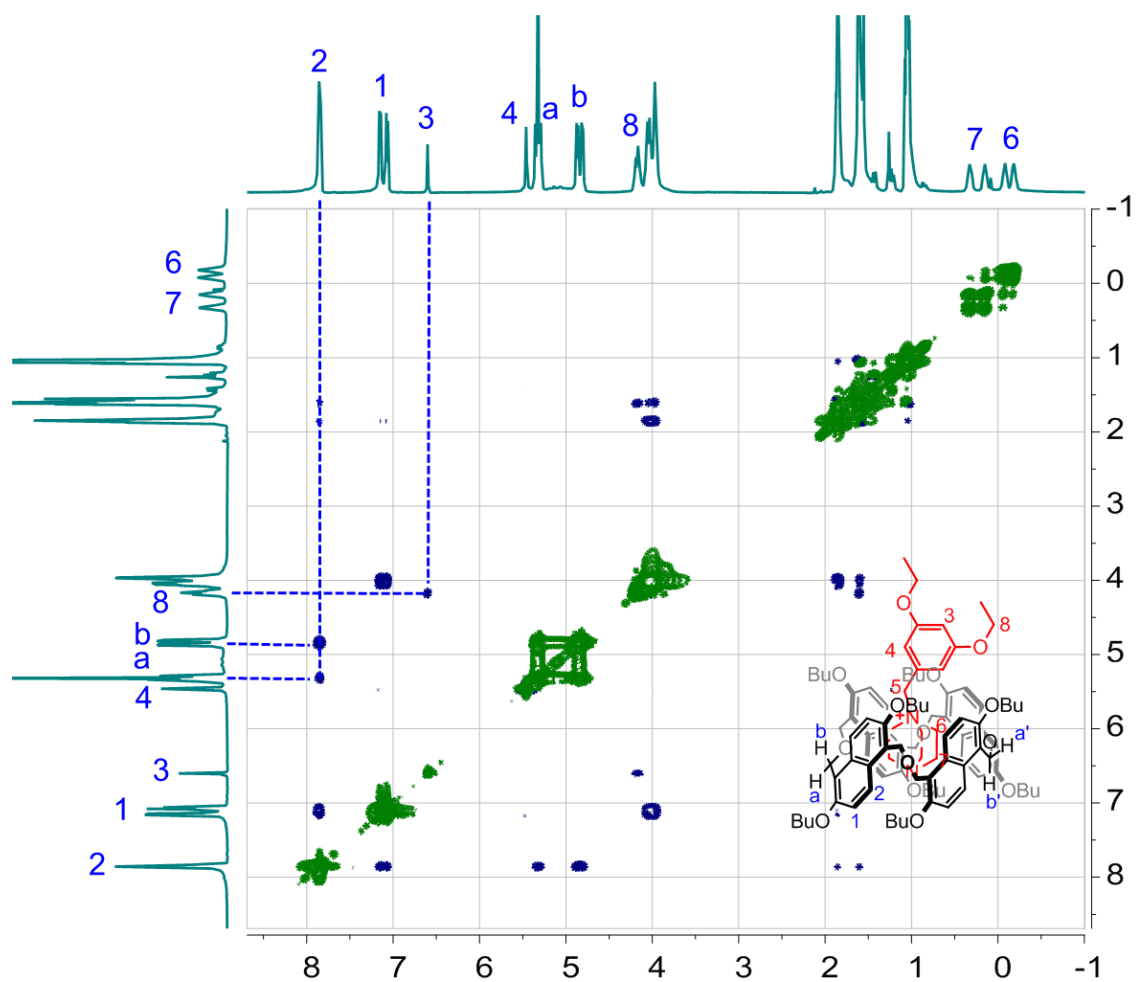


Fig. S3 ^1H , ^1H -ROESY NMR spectrum (500 MHz, CD_2Cl_2 , 298 K) of 1⁺@TA4

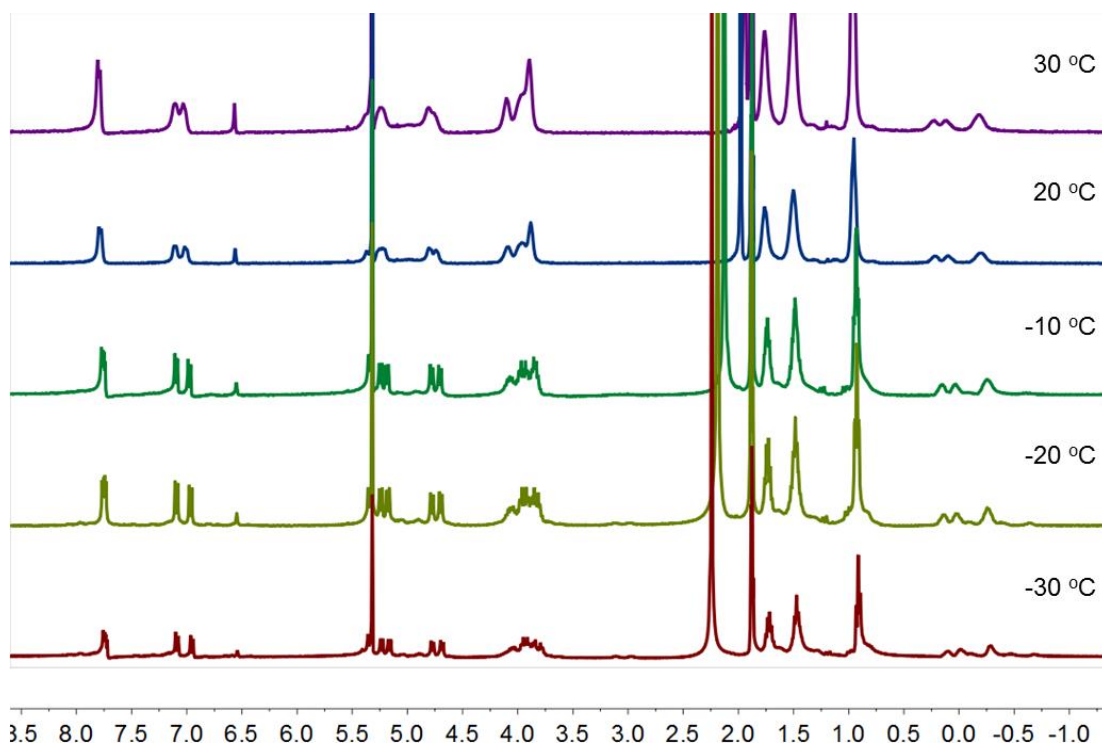


Fig. S4 Variable-temperature ^1H NMR spectra (400 MHz, $\text{CD}_2\text{Cl}_2:\text{CD}_3\text{DN}=1:1$) of **1⁺@TA4**. There is another conformer(s) exist, but the peaks became broadened with increasing temperature. Conformational assignment is not possible with NMR spectra.

3. Characterization Data of Rotaxanes R-IV and R-III

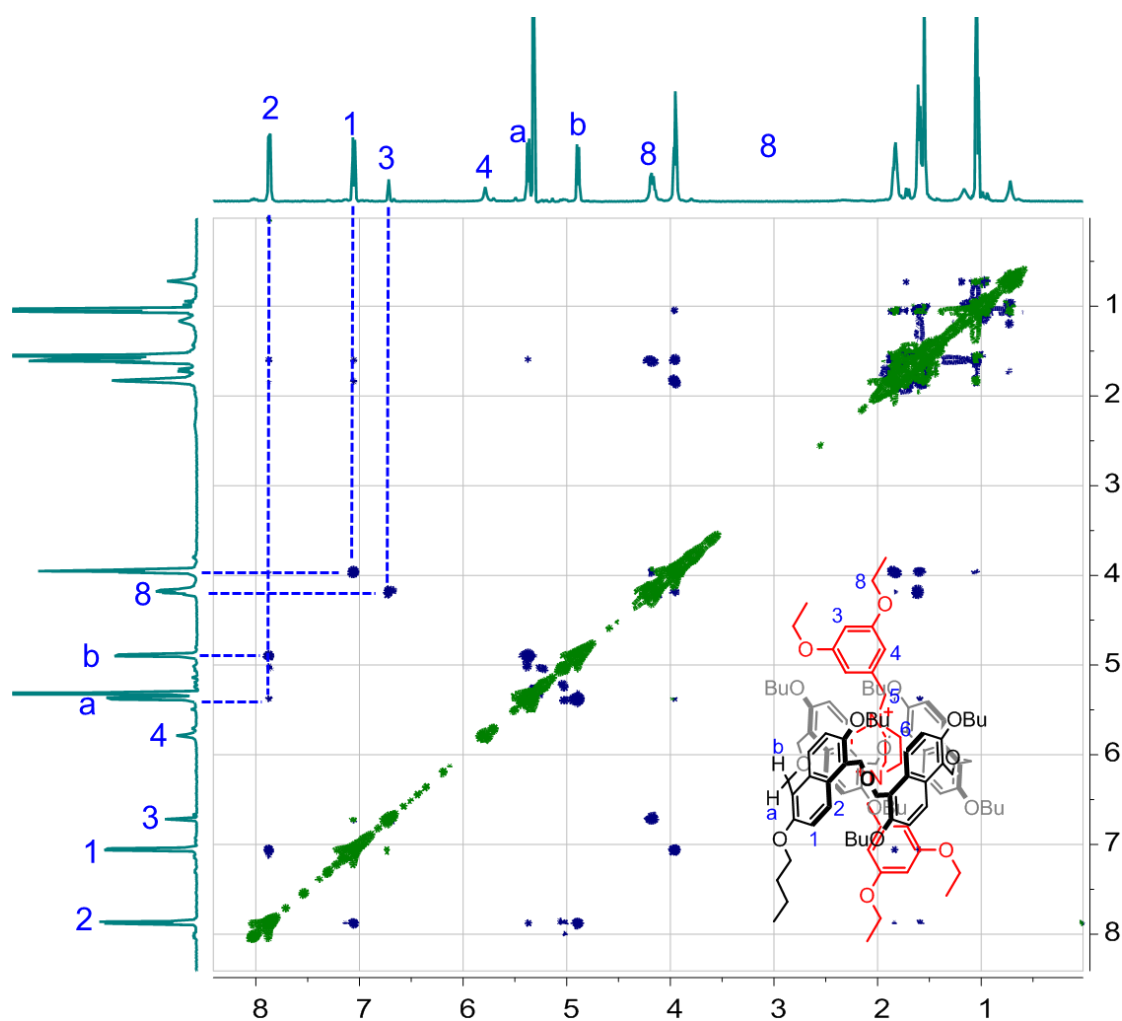


Fig. S5 $^1\text{H}, ^1\text{H}$ - ROESY NMR spectrum (500 MHz, CD_2Cl_2 , 298 K) of **R-IV**, an NOE effect was detected between proton 2 and both protons on the linker.

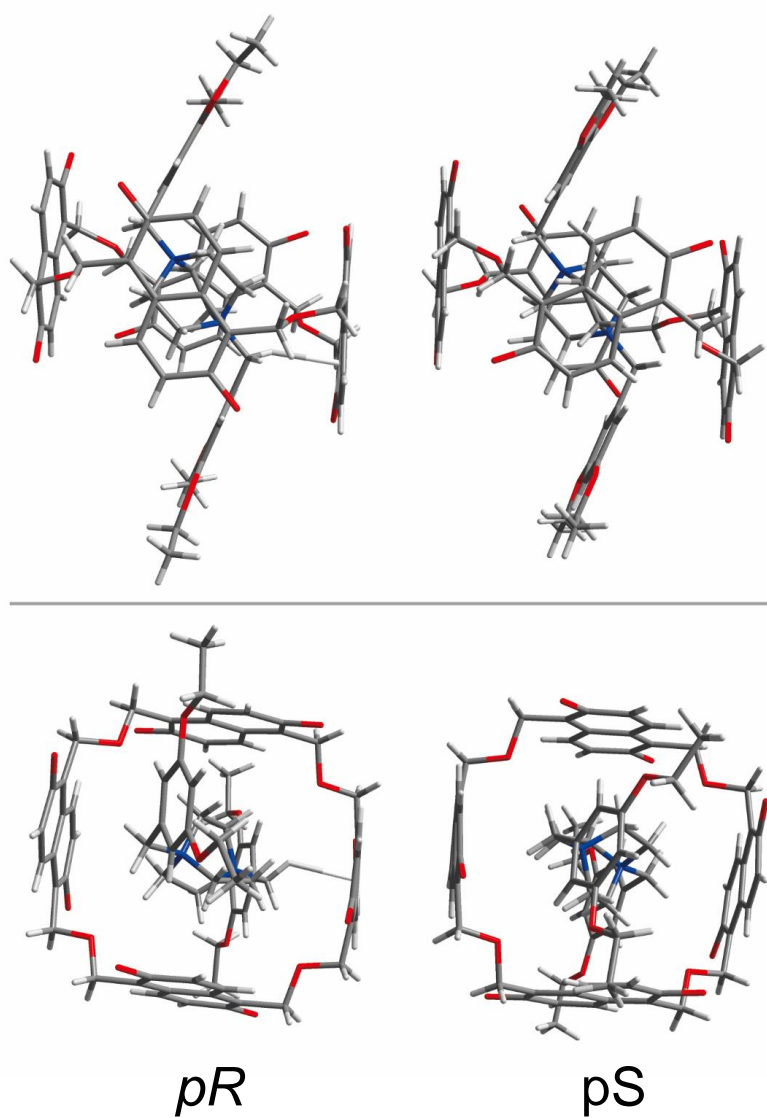


Fig. S6 The side view and top view of enantiomeric pair of **R-IV** in a same unit cell. Butyl groups are removed for viewing clarity. C deep gray, H light gray, O red, N blue.

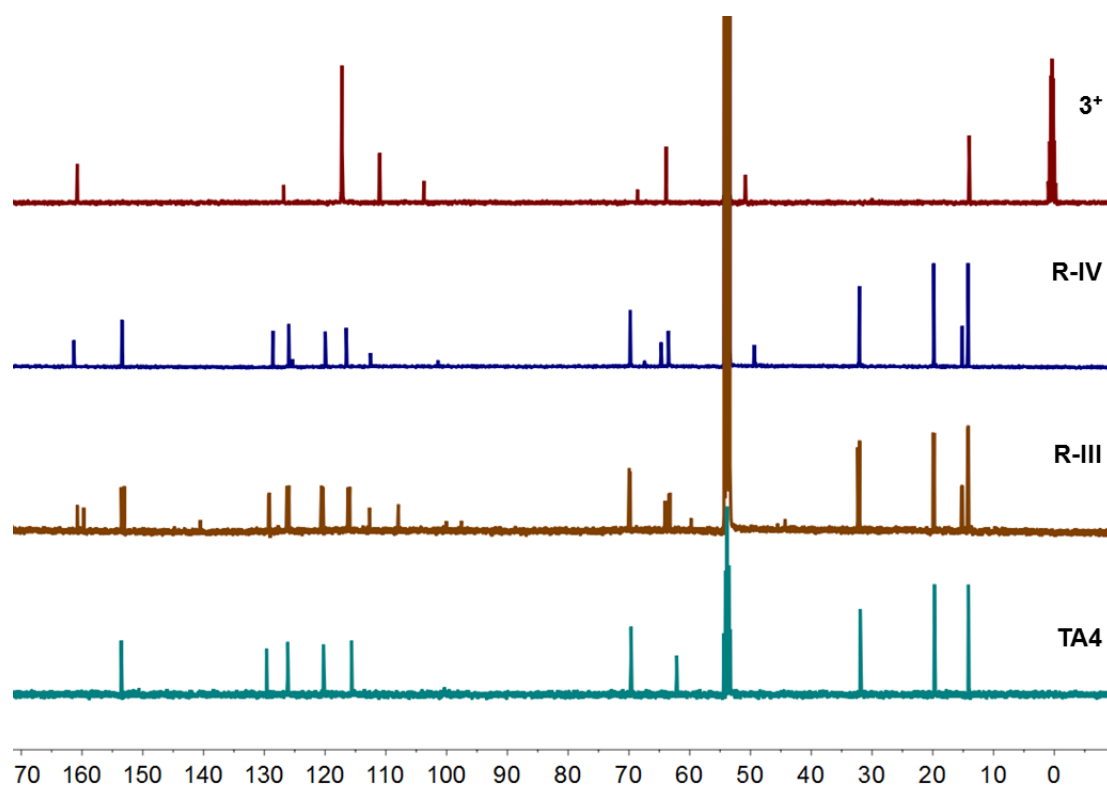


Fig. S7 ^{13}C NMR spectra (100 MHz, 6.0 mM, 25 $^{\circ}\text{C}$) of $\mathbf{3}^{2+}$ (CD_2Cl_2 insoluble) in CD_2Cl_2 : $\text{CD}_3\text{CN} = 1 : 10$ and **R-IV**, **R-III**, **TA4** in CD_2Cl_2 .

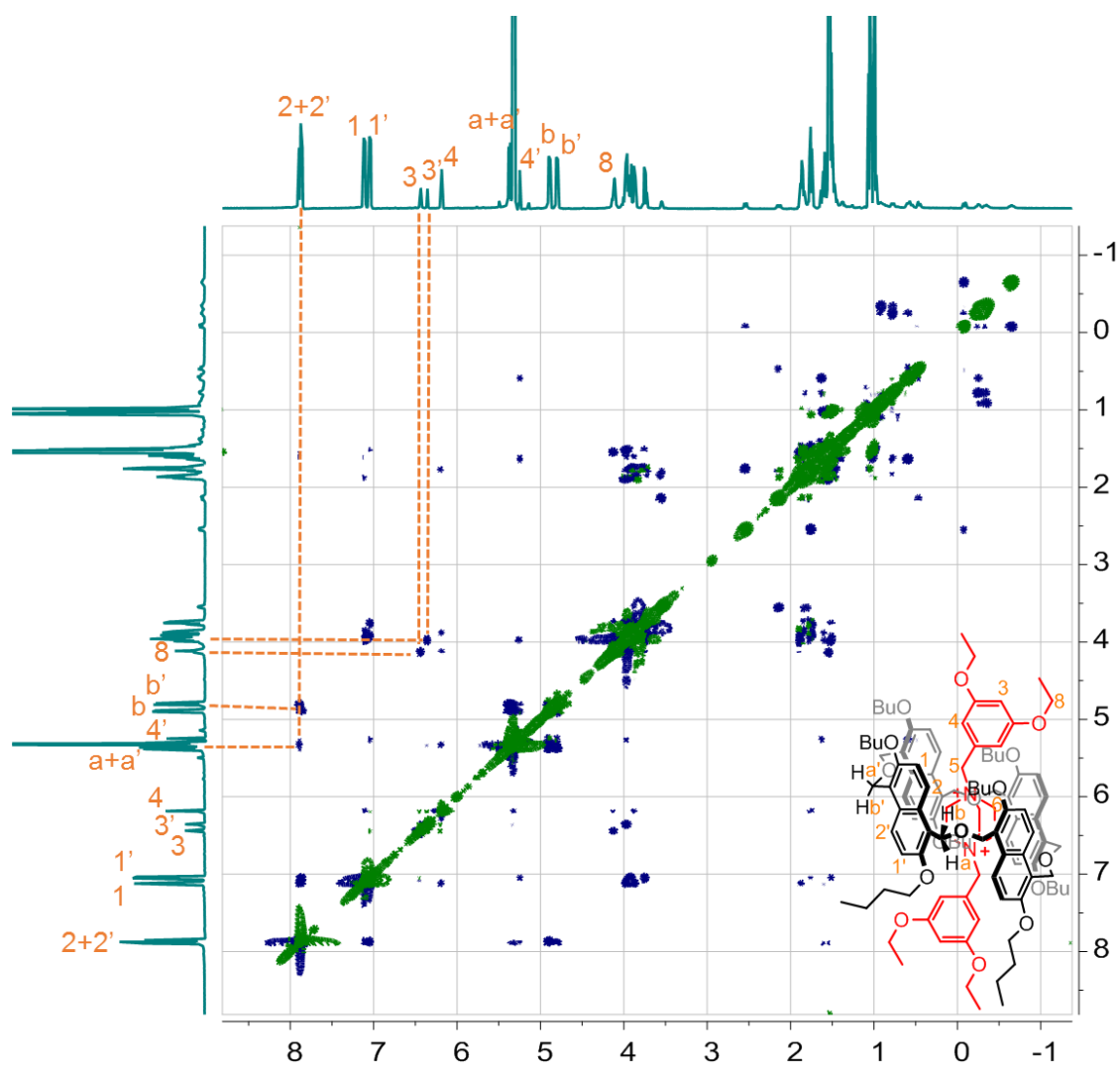


Fig. S8 Full ^1H , ^1H -ROESY NMR spectrum (500 MHz, CD_2Cl_2 , 298 K) of **R-III**. Protons 2 and 2' had NOE effect with protons a, a', b and b' on the linker.

4. Rotaxane Synthesis at Different Temperatures

The mixture of **TA4** (20 mg, 15.9 μmol) and Compound **1**-PF₆ (6.94 mg, 15.9 μmol) in 1,2-dichloroethane (5 mL) was stirred for 0.5 h at room temperature. Compound **2** (4.12 mg, 15.9 μmol) and K₂CO₃ (10.99 mg, 79.5 μmol) were added to the mixture and stirred for 72 h at different temperature. NH₄PF₆ (25.92 mg, 159 μmol) was added to the mixture and stirred for 2 h at room temperature. The solvent was removed and the remaining residue was directly subject to NMR experiment with methylene chloride-*d*₂ as solvent and pyrazine ($\delta = 8.6$ ppm) as internal standard. Conversions of **R-III** and **R-IV** and the overall conversion of the rotaxanes were determined by the integration of the peaks at $\delta = 7.0$ ppm and 7.8 ppm relative to the internal standard of pyrazine.

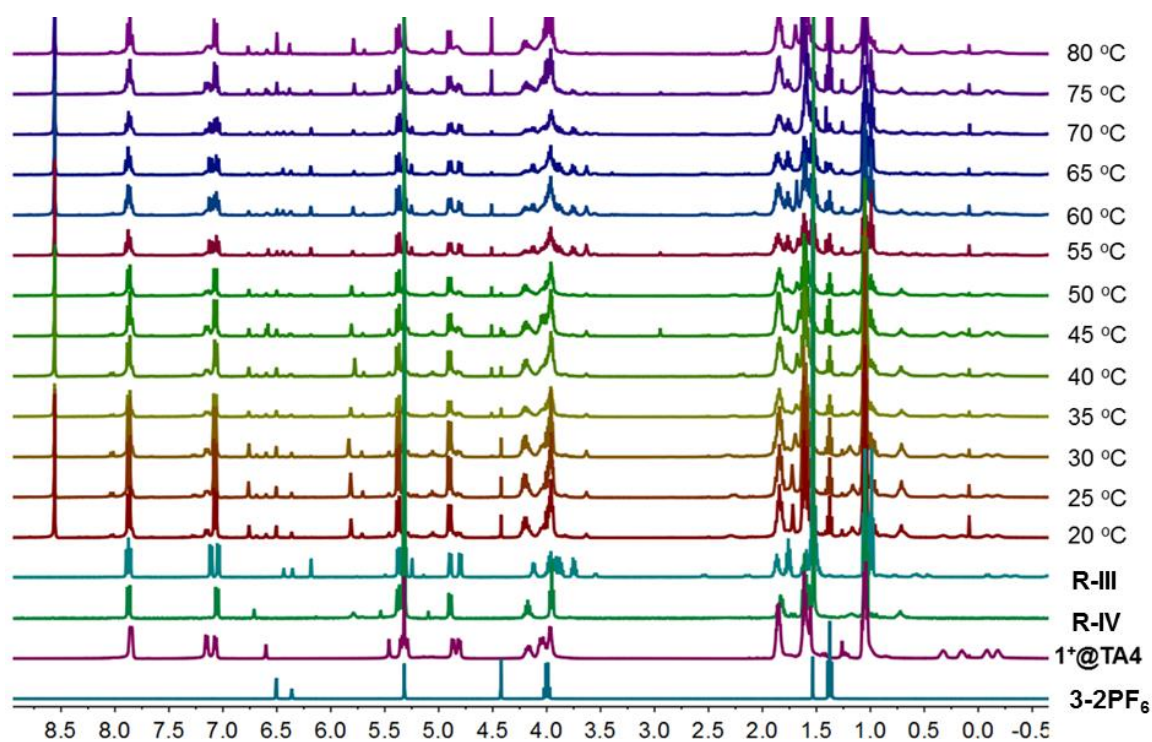


Fig. S9 ¹H NMR spectra of the crude products of the rotaxane syntheses at different temperatures.

5. Binding Constants of 1^+ @TA4 at Different Temperatures

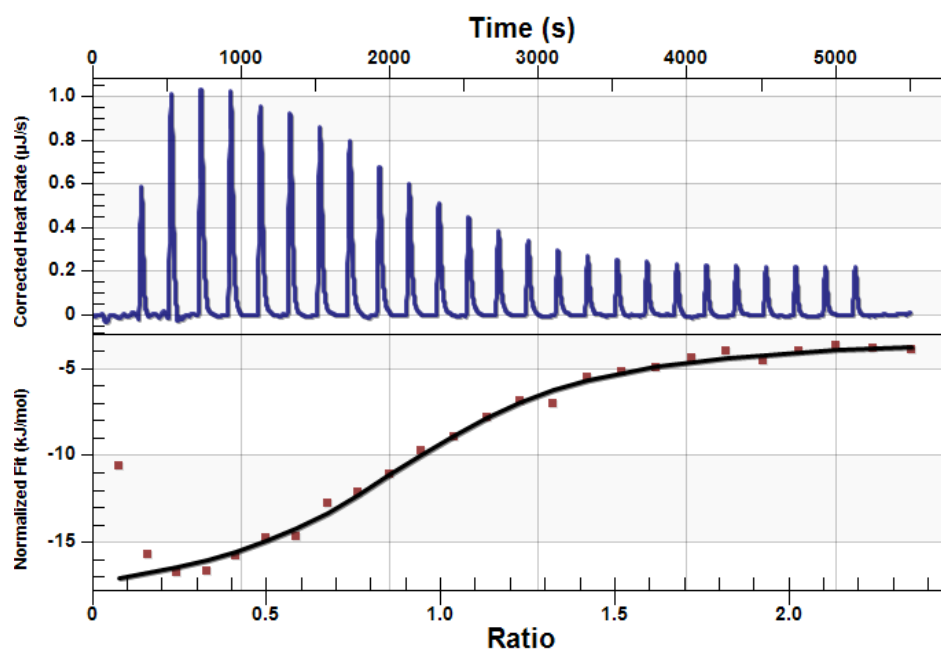


Fig. S10 Titration plot (heat flow versus time and heat versus guest/host ratio) obtained from ITC experiments of **TA4** with **1-PF₆** in the mixture of 1,2-dichloroethane and CH₃CN at different 5 °C.

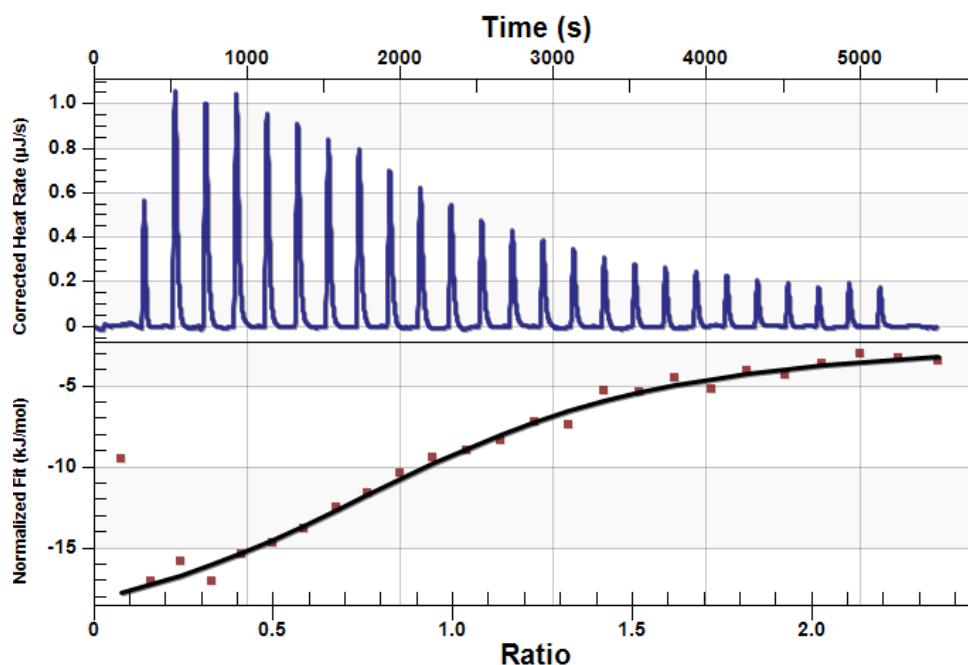


Fig. S11 Titration plot (heat flow versus time and heat versus guest/host ratio) obtained from ITC experiments of **TA4** with **1-PF₆** in the mixture of 1,2-dichloroethane and CH₃CN at different 15 °C.

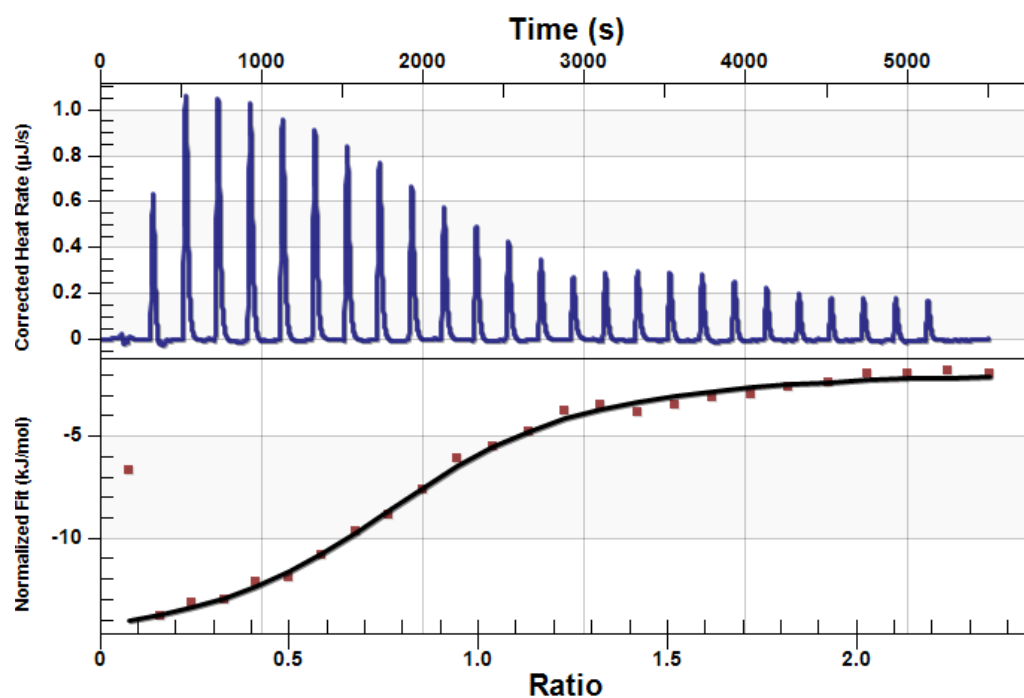


Fig. S12 Titration plot (heat flow versus time and heat versus guest/host ratio) obtained from ITC experiments of **TA4** with **1-PF₆** in the mixture of 1,2-dichloroethane and CH₃CN at different 25 °C.

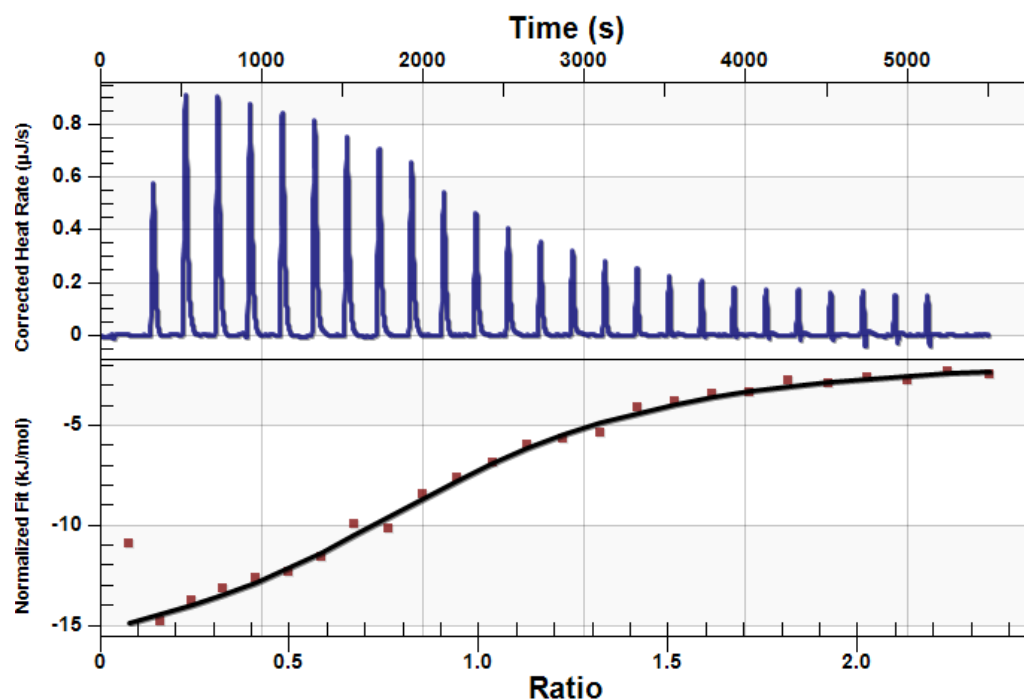


Fig. S13 Titration plot (heat flow versus time and heat versus guest/host ratio) obtained from ITC experiments of **TA4** with **1-PF₆** in the mixture of 1,2-dichloroethane and CH₃CN at different 35 °C.

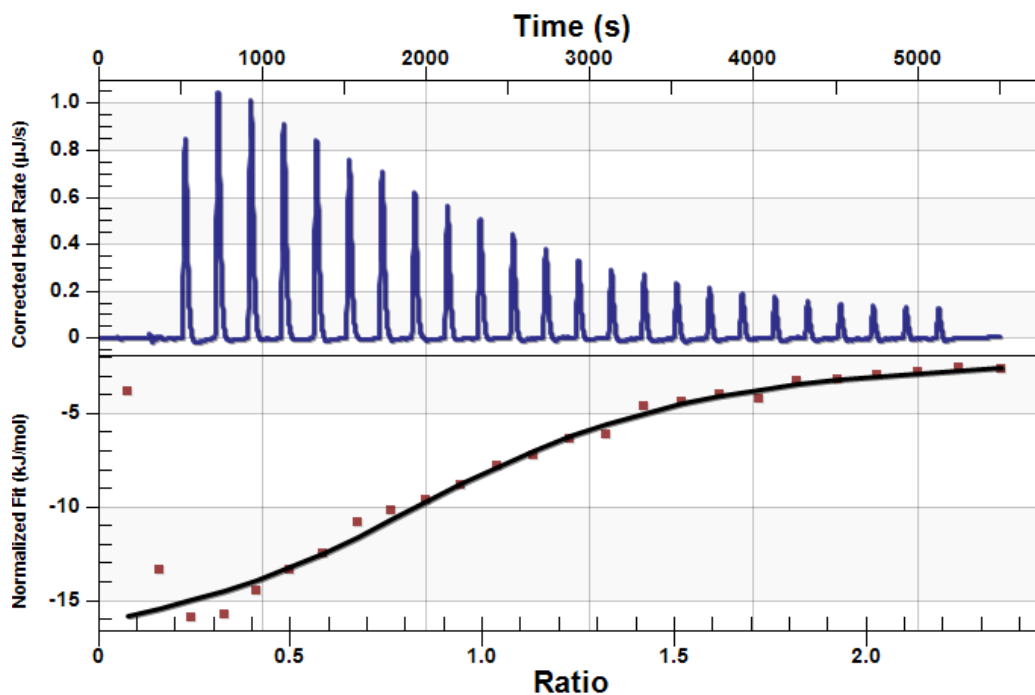


Fig. S14 Titration plot (heat flow versus time and heat versus guest/host ratio) obtained from ITC experiments of **TA4** with **1-PF₆** in the mixture of 1,2-dichloroethane and CH₃CN at different 45 °C.

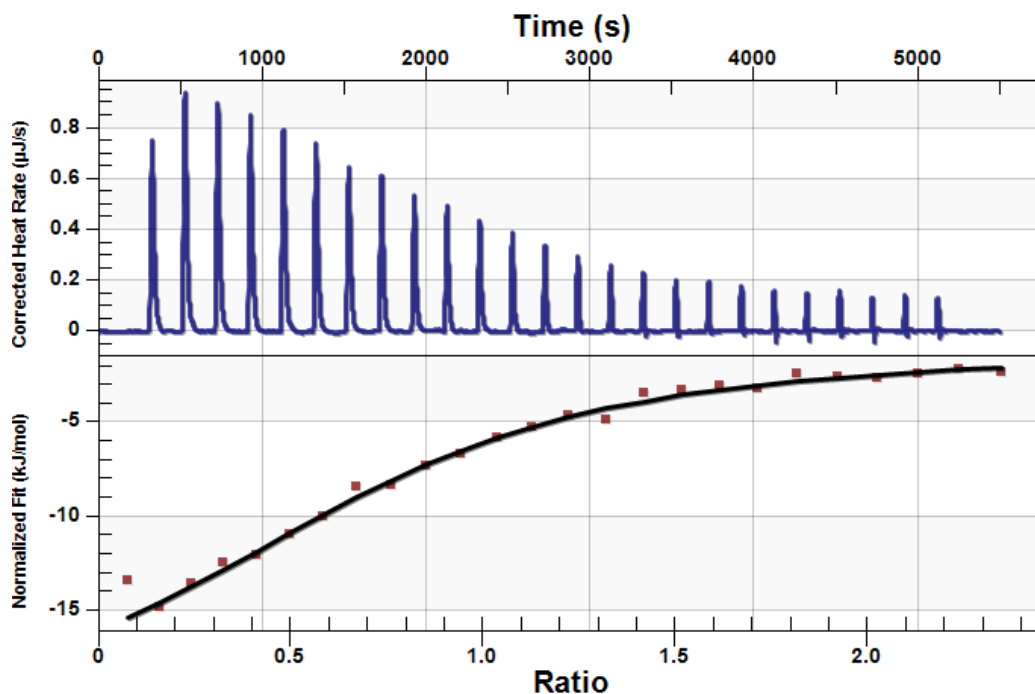


Fig. S15 Titration plot (heat flow versus time and heat versus guest/host ratio) obtained from ITC experiments of **TA4** with **1-PF₆** in the mixture of 1,2-dichloroethane and CH₃CN at different 55 °C.

6. X-Ray Single Crystallography

Crystal of **R-IV** was obtained via slow vaporization of **R-IV** in the solution of methylene chloride : methylcyclohexane = 1 : 1 at room temperature.

Crystal data for **R-IV** was collected on a Bruker APEX-II CCD with Cu K α radiation (λ = 1.369 Å) at 100 K. The structures were solved by the direct method and different Fourier syntheses. All calculations were performed by full-matrix least-squares methods on F^2 by using the SHELX-97 program,^{4,5} all non-hydrogen atoms were refined with anisotropic thermal parameters and the hydrogen atoms were fixed at calculated positions and refined by a riding mode.

Crystal Data for C₁₀₈H₁₅₀F₁₂N₂O₁₈P₂ (M = 2054.23 g/mol): monoclinic, space group P2₁/n, a = 17.6358(9) Å, b = 25.0174(12) Å, c = 26.0640(13) Å, β = 109.616(2)°, V = 10832.1(9) Å³, Z = 4, T = 100 K, μ (CuK α) = 1.084 mm⁻¹, D_{calc} = 1.260 g/cm³, 244296 reflections measured ($5.042^\circ \leq 2\theta \leq 134.254^\circ$), 18969 unique (R_{int} = 0.0620, R_{sigma} = 0.0315) which were used in all calculations. The final R_1 was 0.0598 ($I > 2\sigma(I)$) and wR_2 was 0.1847 (all data).

These crystal structures have been deposited in the Cambridge Crystallographic Data Centre (**R-IV**: CCDC-1898917). These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

7. References

- [1] F. Jia, Z. He, L.-P. Yang, Z.-S. Pan, M. Yi, R.-W. Jiang and W. Jiang, *Chem. Sci.*, 2015, **6**, 6731-6738.
- [2] C. Gao, Y. Jiang, C. Tan, X. Zu, H. Liu and D. Cao, *Bioorg. Med. Chem.*, 2008, **16**, 8670-8675.
- [3] C. Yu, X. Zhang, J. Zhang and Z. Shen, *Tetrahedron*, 2016, **72**, 4337-4345.
- [4] R. C. Clark and J. S. Reid, *Acta Cryst.*, 1995, **A51**, 887-897.
- [5] G. M. Sheldrick, *Acta Cryst.*, 2008, **A64**, 112-122.