Efficient synthesis of a hetero[4]rotaxane by a "threading-stoppering-followed-by-clipping" approach†

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A "threading-stoppering-followed-by-clipping" approach was used for the synthesis of a hetero[4]rotaxane, in which one cucurbit[6]uril (CB[6]) and two hetero crown ether macrocycles are threaded onto one dumbbell-shaped molecule. The process involves three steps: (1) threading of a CB[6] macrocycle onto a thread containing two dialkylammonium sites to form a CB[6]-based pseudo[2]rotaxane; (2) stoppering of the as-formed pseudo[2]rotaxane by imine condensation reaction followed by reduction/protonation to afford a CB[6]-based [2]rotaxane with two new dialkylammonium sites; and (3) selective clipping of two hetero crown ether macrocycles onto the newly-formed ammonium sites and subsequent reduction of the imine bonds in each crown ether to afford the final hetero[4]rotaxane in good yield. The whole process was followed by NMR spectroscopy and the structure of the hetero[4]rotaxane was confirmed by NMR spectroscopy, elemental analysis and mass spectrometry.

Introduction

Since the earliest synthesis of rotaxanes was reported in 1967,[1] there have been a large number of rotaxane molecules prepared by diversified strategies such as threading-followed-by-stoppering,[2] slipping,[3] and clipping[4] due to their potential applications in molecular electronic devices,[5] nanoactuators,[6] macroscopic liquid transport,[7] mesoporous silica-mounted nanovalves[8] and controlled drug release.[9] Therefore rotaxanes have been of steadily increasing attention in recent decades.[10] Recently, some new synthetic strategies were reported for the synthesis of mechanically interlocked rotaxanes. For example, Leigh *et al.* described an efficient approach to prepare rotaxanes in which a transition metal ion in the cavity of a macrocycle can template and catalyze the formation of rotaxanes.[11] They also reported the synthesis of a series of homogeneous rotaxanes by iterative addition of multiple rings onto a single binding site.[12] In addition, other methods such as threading-followed-by-shrinking,[13] threading-followed-by-swelling[14] and others[15] have been used to synthesize rotaxanes. Until today, most of the above methods were limited to the synthesis of homorotaxanes which are composed of same macrocycles and binding sites.[16] In contrast, heterorotaxanes possess a structural character in which the macrocycles and the binding sites on the dumbbell-like thread have different chemical composition, and they could exhibit multifunctional character owing to the existence of different components.[17] Thus, heterorotaxanes could be a complementary structure of the normal homogeneous rotaxanes. The synthesis of heterorotaxanes is more challenging due to their structural complexity, that is, different components must be selectively located at specific binding sites, and this requires a careful design of templates and appropriate self-sorting binding process.[18] Although the general synthetic methods such as "threading", "stoppering" and "clipping" for the homogenous rotaxanes can be applied to the synthesis of heterorotaxanes, it is still not an easy task to assemble multiple components into a well-defined complex. It becomes even more challenging when two or more very similar binding sites are involved in the self-sorting binding process. Due to the synthetic challenges, only few examples of heterorotaxanes have been reported. For example, Schalley *et al.* described the synthesis a hetero[3]rotaxane by self-sorting threading of different crown ethers onto a thread with different dialkylammonium binding sites followed by stoppering.[17] Anderson *et al.* reported a hetero[3]rotaxane with two different π-systems clasped in a γ-cyclodextrin macrocycle.[19] Li *et al.* also reported the synthesis of hetero[3]rotaxanes with two different macrocycles by a "clipping" approach.[20] Recently, pseudo-heterorotaxanes based on self-assorting threading of cucurbit[6]uril and cucurbit[7]uril were also reported.[21] However, the difficulties of synthesis and separation still restricted the development of heterorotaxanes. Herein we report an efficient synthesis of a hetero[4]rotaxane in which two different macrocycles are selectively encircled onto two different but similar binding sites by a new "threading-stoppering-followed-by-clipping" approach.

Results and discussion

Design of synthetic strategy

As mentioned above, the synthesis of a hetero[n]rotaxane requires multiple templates and self-sorting binding. Herein, in our target hetero[4]rotaxane molecule, a dumbbell-shaped thread containing two types of dialkylammonium binding sites is selectively encircled by two hetero crown ether macrocycles and one cucurbit[6]uril (CB[6]) ring as depicted in Scheme 1. Such a design is based on two facts: (1) the CB[6] has high affinity with the alkylammonium salts to form pseudorotaxanes,[22] and our recent work showed

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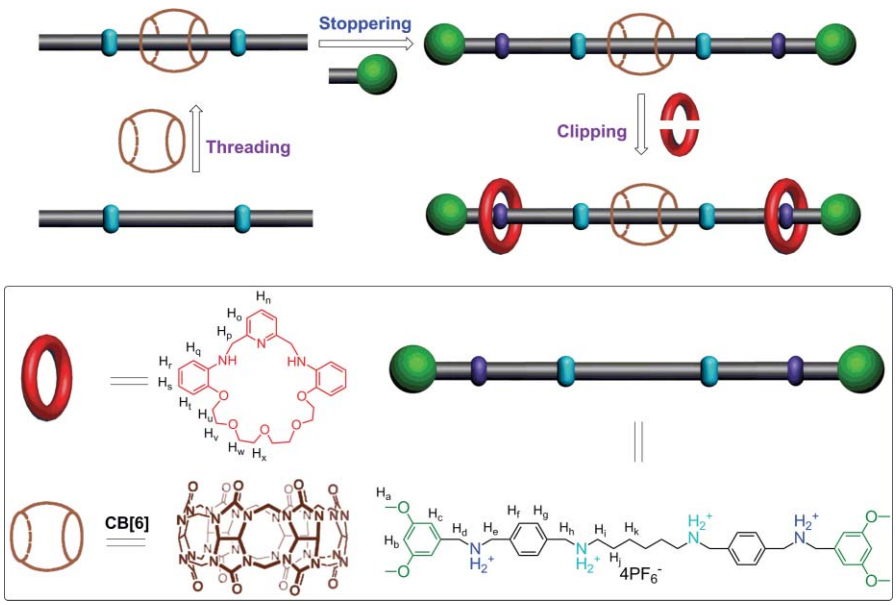
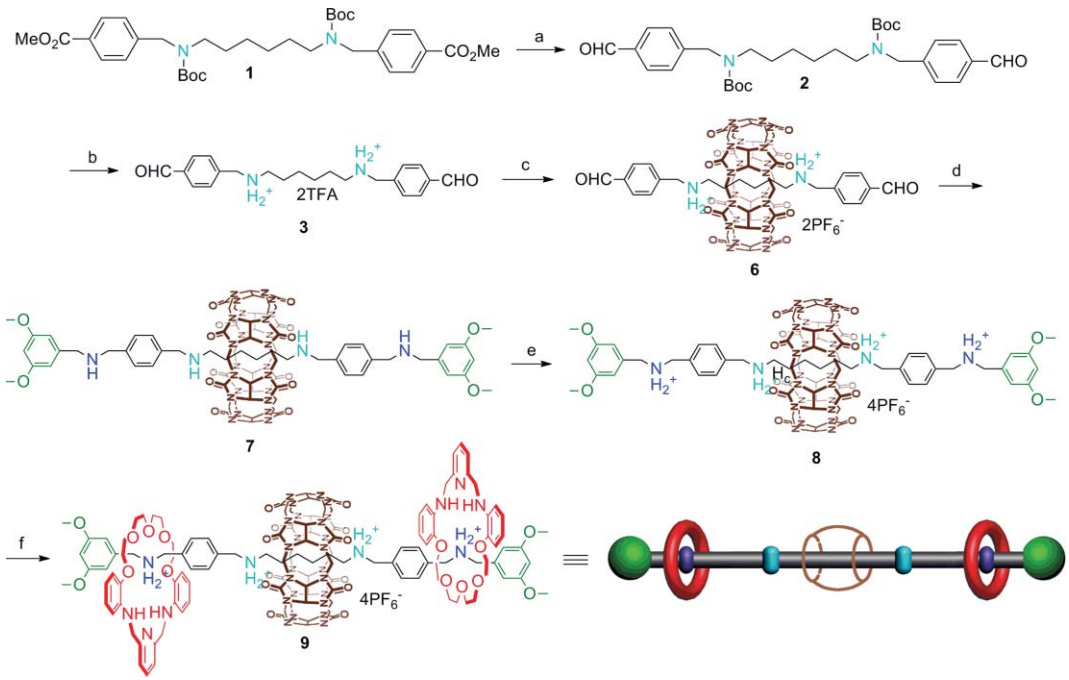


Scheme 1 The schematic representation of the "threading-stoppering-followed-by-clipping" approach for the synthesis of a hetero[4]rotaxane.



Scheme 2 Regents and conditions: (a) (i) $LiAlH_4$, THF; (ii) PCC, DCM, 33%; (b) TFA, DCM, quantitative; (c) (i) CB[6], H_2O, reflux; (ii) NH_4PF_6 (aq), 87%; (d) (i) 3,5-dimethoxybenzylamine, toluene; (ii) $NaBH_4$, THF–MeOH, 96%; (e) (i) TFA, DCM, (ii) NH_4PF_6 (aq), 85%; (f) (i) 2,6-pyridinedicarboxaldehyde, tetraethyleneglycol bis(2-aminophenyl)ether, CH_3CN; (ii) BH_3·THF, 94%.

that pure CB-based pseudo[n]rotaxanes (n = 2, 3, 4, 5) could be separated from their acid aqueous solutions by a simple threading-followed-by-precipitation method;[23] (2) a series of homogeneous [n]rotaxanes have been prepared by clipping of the subunits of a wheel-like component onto the dibenzylammonium sites on a dumbbell-like thread molecule.[4] In the first step, a CB[6] ring is threaded onto a thread containing two dialkylammonium sites together with two terminal functional groups. This is followed by stoppering reactions by attaching two bulky stoppers to form a [2]rotaxane. In this stage, it is necessary to ensure that no dethreading of CB[6] takes place and two new binding sites (herein, dibenzylammonium) should also be generated by functional group transformation. Finally, a clipping reaction will be conducted to form two new macrocycles surrounding the newly generated dialkylammonium sites.

Synthesis and characterizations of the hetero[4]rotaxane 9

Scheme 2 outlines the detailed synthetic route of a key intermediate ammonium salt **3** containing two terminal aldehyde groups. The

starting material **1** was first synthesized according to literature.[24] The symmetrical diester **1** with two Boc-protected dialkyl diamines was reduced by $LiAlH_4$ in dry THF and the obtained alcohol was subsequently oxidized in dry DCM by pyridinium chlorochromate (PCC) to give the dialdehyde **2** in 33% yields for two steps. Removal of the Boc groups and simultaneous protonation of **2** by treatment with trifluoroacetic acid (TFA) in DCM afforded the ammonium salt **3** in a quantitative yield. The key intermediate compound **3** was then submitted for a threading process with CB[6] to form a pseudo[2]rotaxane and we found that the choice of solvent was very important in such a threading process. Threading of CB[6] onto **3** was conducted in different solvents and followed by ^{1}H NMR spectroscopy. It was found that there was no effective threading in CF_3CO_2D/D_2O (1 : 1, v/v), a good solvent system to dissolve both compounds (see Figure S1 ESI†). Such weak binding is due to the high affinity of CB[6] with the protons in solvent.[22] In the 0.2 M NaCl in D_2O, when one equivalent CB[6] was added, the resonances for the aldehyde protons and aromatic protons of **3** were split into two sets of peaks, with one set showing an upfield shift whereas the second set displaying almost no shift (Figure S2 ESI†), indicating that one of the benzaldehyde units was encircled by CB[6] to form a pseudo[2]rotaxane **4**. Addition of excessive CB[6] led to a dynamic mixture of pseudo[2]rotaxane and pseudo[3]rotaxane **5** (Scheme 3), but it was clear that no CB[6] ring was threaded onto the central hexyl chain because there is no obvious shift of the resonances for the hexyl after threading. This also suggests that one portal of the CB[6] binds with the dialkyl ammonium site while the second portal strong binds with Na^+ in water.[22] When the threading was performed in pure water under reflux for 24 h under nitrogen atmosphere, the CB[6] was successfully threaded onto the central hexyl chain (Scheme 3) to form a pseudo[2]rotaxane **6** due to the strong binding between the two dialkyl ammonium sites and CB[6].[22] After cooling, the excessive insoluble CB[6] was removed by filtration and the filtrate was treated with saturated NH_4PF_6 solution to give the **6** as white precipitate in nearly quantitative yield after this counter-ion exchange process.[23] The resonances of central methylene protons were shifted upfield to $\delta = 0.45$–0.70 ppm due to the shielding effect of CB[6] on the hexyl chain. In addition, the resonance at 5.76 ppm correlated to the *endo*-H of the methylene bridges in the CB[6] was split into multiple peaks due to the binding of ammonium site with CB[6]. Electrospray ionization mass spectrometry (ESI-MS) further confirmed the formation of a pseudo[2]rotaxane **6** (see ESI†).

Scheme 3 The schematic representation of the threading process of CB[6] with compound **3** in different solvents.

Subsequently, condensation of the as-formed pseudo-[2]rotaxane **6** with 3,5-dimethoxybenzylamine gave the respective imine [2]rotaxane in a high yield, which was reduced by $NaBH_4$ to give the kinetically stable amine [2]rotaxane **7** in 98% yield. During the reduction, the ammonium sites close to the CB[6] ring were also neutralized and re-protonation of the free amine with excess of TFA and subsequent counter-ion exchange with NH_4PF_6 afforded the [2]rotaxane **8** in 85% yield for two steps. Most importantly, the CB[6] did not slip out from the thread during the condensation and reduction processes and two new dibenzylammonium sites were generated which are ready for the subsequent clipping reaction. The structure of the [2]rotaxane **8** was confirmed by both NMR (Fig. 1A) and ESI mass spectrometry (see ESI†). The clipping reaction to form a dynamic hetero[4]rotaxane was then conducted in CD_3CN by mixing the [2]rotaxane **8** together with two equivalents each of tetra(ethylene glycol) bis(2-aminophenyl)ether and 2,6-pyridinedicarboxaldehyde,[4] and the reaction was followed by ^{1}H NMR spectroscopy. Upon clipping reaction, the resonances of the stopper units (-CH_3 and -Ph) protons were shifted upfield, indicating that the clipping reaction took place at the dibenzylammonium sites. A characteristic resonance peak at 8.72 ppm assigned to imine protons was observed (Fig. 1B). The as-formed rotaxane was not separated due to the dynamic character of the imine bond and it was submitted to subsequent reduction by BH_3·THF to afford the kinetically stable hetero[4]rotaxane **9** in 94% yield for two steps after repeated washing the solid by chloroform and methanol. Compared with the dynamic hetero[4]rotaxane, the resonance for the ammonium protons (-NH_2^+-) close to the stopper also showed an upfield shift.[4] Moreover, the two sets of resonance peaks of stopper units (-Ph) displayed crossed upfield and downfield shift. Through the 2D NOESY NMR experiment, we identified some obvious signals for the correlations between macrocycle components (CB[6] and crown ether) and the dumbbell-shaped component in the hetero[4]rotaxane **9**. For example, the benzene rings of the dumbbell-shaped component were strongly shielded by the hetero crown ether components and obvious correlations were observed between the crown ethers and the central benzene ring (H_f, H_e) and the neighboring–CH_2-NH_2^+-CH_2- (H_d, H_e) sites. Similarly, correlation of the resonaces for CB[6] with the central hexyl unit was observed (see Figure S4–S6 ESI†). The structures of the final hetero[4]rotaxane **9** was also confirmed by ESI mass spectrometry and elemental analysis. Three peaks at m/z = 657.02 for $[M+H_2O\text{-}4PF_6^-]^{4+}$, 875.81 for $[M+H_2O\text{-}3PF_6^-\text{-}HPF_6]^{3+}$ and 924.40 for $[M+H_2O\text{-}3PF_6^-]^{3+}$ with

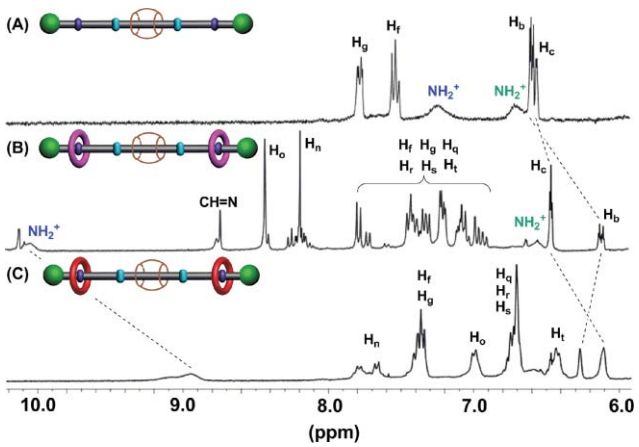


Fig. 1 Partial ^{1}H NMR spectra (300 MHz, CD_3CN, 298 K) of **8** (A); clipping reaction mixture (dynamic rotaxane) (B) and **9** (C) (the protons are labelled in Scheme 1).

well resolved isotope distribution were observed for **9** in CH_3CN (see Supporting Information).[25] The obtained heterorotaxane is also kinetically stable and no obvious change of their NMR spectra recorded in DMSO-d_6 at different temperatures was observed (Figure S3 ESI†).

Conclusions

In conclusion, a "threading-stoppering-followed-by-clipping" approach was used for the efficient synthesis of a hetero[4]rotaxane **9**. Compound **9** represents as a new member of heterorotaxane family which are usually not easy to synthesize. In principle, this method can also be used for the synthesis of more complicated and higher order heterorotaxanes if the threading, stoppering and clipping processes do not interfere with each other. In particular, we are interested in the synthesis of functional heterorotaxanes in which different components with specific functionalities are introduced in one mechanically interlocked structure by a similar synthetic strategy in the future.

Experimental

Materials and methods

All reagents and starting materials were obtained from commercial suppliers and used without further purification. Column chromatography was performed on silica gel 60 (Merck 40–60 nm, 230–400 mesh). Deuterated solvents (Cambridge Isotope Laboratories) for NMR spectroscopic analyses were used as received. All NMR spectra were recorded on Bruker AMX500 at 500 MHz and Bruker ACF300 at 300 MHz spectrometers. All chemical shifts are quoted in ppm, relative to tetramethylsilane, using the residual solvent peak as a reference standard. The 2D NOESY spectra of **9** were recorded on Bruker AMX500 at 500 MHz over a spectral width of 5122 Hz with a mixing time 500 ms and a relaxation time of 2.5 s. Melting points were determined on a Buchi Melting point B-450 apparatus and were uncorrected. Elemental analyses (C, H, N) were performed on a Vario EL Elementar (Elementar Analyzensysteme, Hanau, Germany). Mass spectra were recorded on a Finnigan MAT LCQ with ESI ionization and Bruker Autoflex MALDI-TOF instrument using 1,8,9-trihydroxyanthracene as a matrix.

Synthesis of the dialdehyde 2 and ammonium 3. A suspension of $LiAlH_4$ (0.15 g, 4.0 mmol) in anhydrous THF (20 mL) was slowly added *via* a dropping funnel to a solution of compound **1** (0.61 g, 1.0 mmol) in anhydrous THF (10 mL) at 0 °C, and the resulting suspension was stirred under nitrogen atmosphere for 24 h. The reaction mixture was subsequently quenched by slowly adding the ground powder of $Na_2SO_4{\cdot}10H_2O$ and Celite (1 : 1, w/w). After stirring for 30 min, the mixture was filtered and the excess of solvent in the filtrate was removed under vacuum to give the diol. The solution of the obtained diol in dry DCM (10 mL) was added dropwise to a suspension of pyridinium chlorochromate (PCC) (0.65 g, 3.0 mmol) in dry DCM (30 mL) at 0 °C. The mixture was allowed to warm up to room temperature and stirred for overnight under nitrogen atmosphere. The reaction was quenched by adding 1 M NaOH (10 mL) and the organic phase was washed with H_2O (200 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed under vacuum and the residue was purified by column chromatography (silica gel, EtOAc–hexane = 1/3 to 1/1, v/v) to give the title product **2** as a yellow oil in 33% yield. Compound **2** is unstable and thus it was used immediately for next deprotection step of. To a solution of **2** (0.11 g, 0.2 mmol) in dry DCM (20 mL), trifluoroacetic acid (0.3 mL, 4.0 mmol) was added and the mixture was stirred for 15 h at room temperature under nitrogen atmosphere. The solvent was removed under vacuum to give the **3**. Compound **2**: ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm = 9.99 (s, 2H, CHO), 7.83 (d, J = 8.1 Hz, 4H, Ar), 7.36 (br, 4H, Ar), 4.47 (br, 4H, CH_2), 3.16 (br, 4H, CH_2), 1.40–1.53 (m, 22H, Boc and CH_2), 1.23–1.25 (m, 4H, CH_2). Compound **3**, m.p. 187.5 °C (decomp.): ^{1}H NMR (300 MHz, CF_3CO_2D/D_2O = 1 : 1, v/v): δ ppm = 9.93 (br, 2H, CHO), 8.00 (br, 4H, Ar), 7.66 (br, 4H, Ar), 4.27–4.45 (m, 4H, CH_2), 3.03–3.19 (m, 4H, CH_2), 1.77 (br, 4H, CH_2), 1.38 (br, 4H, CH_2). ^{13}C NMR (75 MHz, CF_3CO_2D/D_2O): δ ppm = 199.20, 135.35, 134.74, 134.69, 134.34, 54.79, 51.20, 29.22, 27.47. ESI MS: m/z = 375.21 ([M–2 CF_3COOH + Na^+]), calculated exact mass: 375.20. Anal. Calcd for $C_{22}H_{30}F_{12}N_2O_2P_2$: C, 41.00; H, 4.69; N, 4.35. Found: C, 40.87; H, 4.82; N, 4.20.

Synthesis of pseudo[2]rotaxane 6. To a solution of the **3** in H_2O, cucurbit[6]uril (0.24 g, 0.24 mmol) was added and the mixture was refluxed for 24 h under nitrogen atmosphere. After cooling, the mixture was filtered and the filtrate was treated with saturated NH_4PF_6 (2 mL, aq) to yield a white precipitate. The solid was collected by filtration, washed with water and dried under vacuum to give the title compound **6** in 87% yield. Compound **6**, m.p. 218.4 °C (decomp.): ^{1}H NMR (300 MHz, CD_3CN): δ ppm = 10.06 (s, 2H, CHO), 7.91–8.01 (m, 8H, Ar), 5.76 (m, 12H, CB), 5.36 (br, 12H, CB), 4.44 (br, 4H, CH_2), 4.16 (m, 12H, CB), 2.93 (br, 4H, CH_2), 0.40–0.64 (br, 8H, CH_2). ESI MS: m/z = 684.24 ([M + H_2O - 2PF_6^-]), calculated exact mass: 684.27. Anal. Calcd for $C_{58}H_{68}F_{12}N_{26}O_{15}P_2$: C, 41.98; H, 4.13; N, 21.95. Found: C, 41.82; H, 4.32; N, 21.87.

Synthesis of [2]rotaxane 7. A mixture of **6** (328 mg, 0.2 mmol) and 3,5-dimethoxybenzylamine (67 mg, 0.4 mmol) in dry MeCN (10 mL) and $CHCl_3$ (10 mL) was stirred for 2 h at room temperature. The solvents were removed under vacuum, and toluene (10 mL) was added. The mixture was stirred at room temperature for 2 h and the toluene was removed at 60 °C on a rotary evaporator. Additional toluene was added and removed again. Such process was repeated for 3 times, so that the trace amount of water was removed from the reaction system and the imine was obtained in quantitative yield. To a solution of imine (387 mg, 0.20 mmol) in dry THF (15 mL) and MeOH (15 mL), $NaBH_4$ (151 mg, 4.0 mmol) was added in small portion. After stirring for 24 h at room temperature, the solvents were removed under vacuum, and the residue was collected by filtration and washed with water and $CHCl_3$, and dried under vacuum to give the title product **7** in 98% yield. Compound imine: ^{1}H NMR (300 MHz, CD_3CN): δ ppm = 8.49 (s, 2H, CH=N), 7.77–7.98 (m, 8H, Ar), 6.53 (br, 4H, Ar), 6.4 (br, 2H, Ar), 5.76 (m, 12H, CB), 5.35 (br, 12H, CB), 4.72 (s, 4H, CH_2), 4.36 (br, 4H, CH_2), 4.16 (m, 12H, CB), 3.76 (br, 12H, CH_3), 2.92 (br, 4H, CH_2), 0.38–0.62 (br, 8H, CH_2). Compound **7**, m.p. > 300.0 °C: ^{1}H NMR (300 MHz, DMSO): δ ppm = 7.61–7.66 (m, 4H, Ar), 7.41–7.44 (m, 4H, Ar), 6.53 (br, 4H, Ar), 6.35 (br, 2H, Ar), 5.61 (m, 12H, CB), 5.49 (br, 12H, CB), 4.37 (m, 12H, CB), 4.28 (br, 4H, CH_2), 3.73 (br, 12H, CH_3), 3.72 (br, 4H, CH_2), 3.64 (br, 4H, CH_2), 2.81

(br, 4H, CH_2), 0.34–0.85 (br, 8H, CH_2). ESI MS: m/z = 835.35 ([M + H_2O + $2H^+$]), 556.23 ([M + H_2O + $3H^+$]); calculated exact mass: 835.38, 556.58. MALDI-TOF MS: m/z = 1688.681 ([M + H_2O + H^+]). Anal. Calcd for $C_{76}H_{92}F_{12}N_{28}O_{17}$: C, 54.67; H, 5.55; N, 23.49. Found: C, 54.80; H, 5.41; N, 23.33.

Synthesis of [2]rotaxane 8. To a suspension of **7** (330 mg, 0.2 mmol) in dry DCM (20 mL), TFA (0.6 mL, 8.0 mmol) was added at room temperature. After stirring for overnight under nitrogen atmosphere, the solvent was removed under vacuum. The residue was dissolved in MeOH (1 mL), and then saturated NH_4PF_6 (2 mL, aq) was added to yield a white precipitate. After filtering, washing with H_2O and dry under vacuum, the title compound **8** was obtained in 85% yield. compound **8**, m.p. 241.0 °C: ^{1}H NMR (300 MHz, CD_3NO_2): δ ppm = 7.92 (m, 4H, Ar), 7.63 (m, 4H, Ar), 6.64 (br, 4H, Ar), 6.57 (br, 2H, Ar), 5.86 (m, 12H, CB), 5.47 (br, 12H, CB), 4.53 (br, 4H, CH_2), 4.52 (br, 4H, CH_2), 4.40 (br, 4H, CH_2), 4.30 (m, 12H, CB), 3.79 (br, 12H, CH_3), 3.00 (br, 4H, CH_2), 0.49–0.85 (br, 8H, CH_2). ESI MS: m/z = 835.34 ([M + H_2O - $2HPF_6$ - $2PF_6^-$]), 556.23 ([M + H_2O - HPF_6 - $3PF_6^-$]), calculated exact mass: 835.37, 556.58. Anal. Calcd for $C_{76}H_{96}F_{24}N_{28}O_{17}P_4$: C, 40.50; H, 4.29; N, 17.40. Found: C, 40.35; H, 4.42; N, 17.27.

Synthesis of hetero[4]rotaxane 9. A mixture of **8** (89 mg, 0.04 mmol), 2,6-pyridinedicarboxaldehyde (11 mg, 0.08 mmol) and tetraethyleneglycol bis(2-aminophenyl)ether (30 mg, 0.08 mmol) were stirred for 2 h in dry CH_3NO_2 under nitrogen atmosphere. Then BH_3·THF solution (0.3 mL) was added and the mixture was further stirred overnight. The solvents were removed under vacuum to yield a white precipitate. After washing with DCM and MeOH, the title product **9** was obtained in 94% yield. Compound **9**, m.p. 235.2 °C: ^{1}H NMR (500 MHz, CD_3CN): δ ppm = 8.95 (br, 2H, NH_2^+), 7.65–7.80 (br, 2H, Py), 7.34–7.38 (br, 8H, Ar), 6.99 (br, 4H, Ar), 6.71 (br, 12H, Ar), 6.43–6.47 (br, 4H, Ar), 6.27 (br, 2H, Ar), 6.11 (br, 4H, Ar), 5.70 (m, 12H, CB), 5.34 (br, 12H, CB), 4.53 (br, 20H, CH_2), 4.14 (m, 12H, CB), 3.73–4.10 (br, 32H, CH_2), 3.41 (br, 12H, CH_3), 2.80 (br, 4H, CH_2), 0.33–0.56 (br, 8H, CH_2). ESI MS: m/z = 924.41 ([M + H_2O - $3PF_6^-$]); 875.82([M + H_2O - HPF_6 - $3PF_6^-$]); 657.02 ([M + H_2O - $4PF_6^-$]), calculated exact mass: 925.39, 876.74, 657.81. Anal. Calcd for $C_{130}H_{162}F_{24}N_{34}O_{27}P_4$: C, 48.60; H, 5.08; N, 14.82. Found: C, 48.51; H, 4.99; N, 15.01.

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