

Efficient Solvent-Free Syntheses of [2]- and [4]Rotaxanes**

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Rotaxanes have potential applicability as molecular actuators and switches within mesoscale molecular electronic devices.^[1] Among the protocols devised for preparing rotaxanes, threading followed by stoppering^[2] has attracted the most attention. Nevertheless, synthesizing rotaxanes in high yields by this approach can be challenging because several factors affect the formation of the precursor pseudorotaxanes in solution—for example, low association constants for the interactions between the thread- and beadlike components, the use of competing solvents and/or elevated temperatures, and the formation of interfering by-products during the stoppering process.^[3] Although solvent-free conditions^[4] would, in theory, minimize the degree of dissociation of the pseudorotaxane complexes during the stoppering reaction and allow high-order rotaxanes to be generated more efficiently, a new challenge arises in choosing a suitable stoppering reaction that can be performed by grinding a well-mixed solid phase. To the best of our knowledge, only two types of rotaxanes have been synthesized through solid-to-solid grinding: one through the reaction of a mixture of bis-*p*-phenylene[34]crown-10, a benzyl bromide derivative incorporating a bipyridinium recognition site, and a pyridine-containing stopper,^[5] and the other through ball-milling of polypseudorotaxane complexes—comprising α -cyclodextrin and poly(tetrahydrofuran) components—with isocyanate stoppers.^[6] Both of these cases gave low-to-moderate yields of their desired products (< 45 %), thus suggesting that these reactions are not suitable for the efficient syntheses of higher-order rotaxanes. Herein, we report a new solid-state ball-milling reaction that produces both [2]- and [4]rotaxanes efficiently and in high yield.

The formation of imines through the dehydration of aldehydes and primary amines can be achieved in high yield by solid-state ball-milling.^[7] As imines are in general easily hydrolyzed, we were not inclined to use this condensation reaction to construct higher-order rotaxanes. Instead, we

turned our attention toward the formation of hexahydropyrimidines by condensing carbonyl compounds with 1,3-diamines.^[8] We chose 1,8-diaminonaphthalene (**3**) as a suitable diamine for the reaction with a threadlike moiety terminated with a formyl group because of its steric bulk and the stability of the resulting dihydropyrimidine stopper units.^[9]

Previously, we reported that the oxygen-deficient macrocycle **1** forms a complex with a dibenzylammonium (DBA) ion in CD₃CN ($K_a = 200 \text{ M}^{-1}$).^[10] Thus, as the first step toward preparing a [2]rotaxane under solvent-free conditions from such components, we concentrated an equimolar mixture of the macrocycle **1** and the dialdehyde **2-H-PF₆** in CH₃CN under reduced pressure to afford a white solid, which we assumed to contain predominantly the [2]pseudorotaxane complex [**1-2-H**][PF₆] (Scheme 1). After dissolving portions of the solids in CD₃CN, we used ¹H NMR spectroscopy to monitor the ball-milling reaction of a 1:2 mixture of the [2]pseudorotaxane complex [**1-2-H**][PF₆] and 1,8-diaminonaphthalene at ambient temperature. A new set of signals appeared with increasing intensity over time (Figure 1). After 1 h, these signals were predominant (Figure 1e), so we subjected the mixture to column chromatography and isolated the [2]rotaxane **4-H-PF₆** in 80 % yield.^[11] The yield increased to 87 % when we increased the ratio of the macrocycle **1** and the dialdehyde thread **2-H-PF₆** in the solid mixture to 1.2:1. The solution reaction of **1**, **2-H-PF₆**, and diamine **3** (50:50:100 mM) in CH₃CN did not proceed as efficiently as it did through ball-milling: traces of **2-H-PF₆** remained detectable by TLC after 24 h. The use of ¹H NMR spectroscopy to monitor a slightly more dilute mixture (20:20:40 mM) in CD₃CN indicated that the reaction was complete after 24 h, and provided the [2]rotaxane **4-H-PF₆** in 48 % yield.

When we mixed **1**, **2-H-PF₆**, and **3** as solids in a 1:1:2 ratio without first generating the solid [2]pseudorotaxane complex [**1-2-H**][PF₆], the same ball-milling conditions afforded a mixture of the [2]rotaxane **4-H-PF₆** and the dumbbell-like salt **5-H-PF₆** (Figure 2b) in yields of 49 and 44 %, respectively. To the best of our knowledge, this process is by far the most efficient synthesis of a rotaxane by direct grinding of the macrocyclic, threadlike, and stoppering components as independent solids.^[5] Although this result indicates that the threading of the macrocycle **1** around the threadlike dialdehyde **2-H-PF₆** could occur during the grinding process, preforming the [2]pseudorotaxane [**1-2-H**][PF₆] as a solid substantially increased the yield of the reaction.

To prove that this solid-state rotaxane synthesis occurred through threading followed by stoppering, rather than by slippage,^[12] we dissolved the [2]rotaxane **4-H-PF₆** in CD₃SOCD₃ and monitored its ¹H NMR spectra at 323 K over time. We detected no signals of the free components in the ¹H NMR spectrum recorded after 3 h, which suggests that

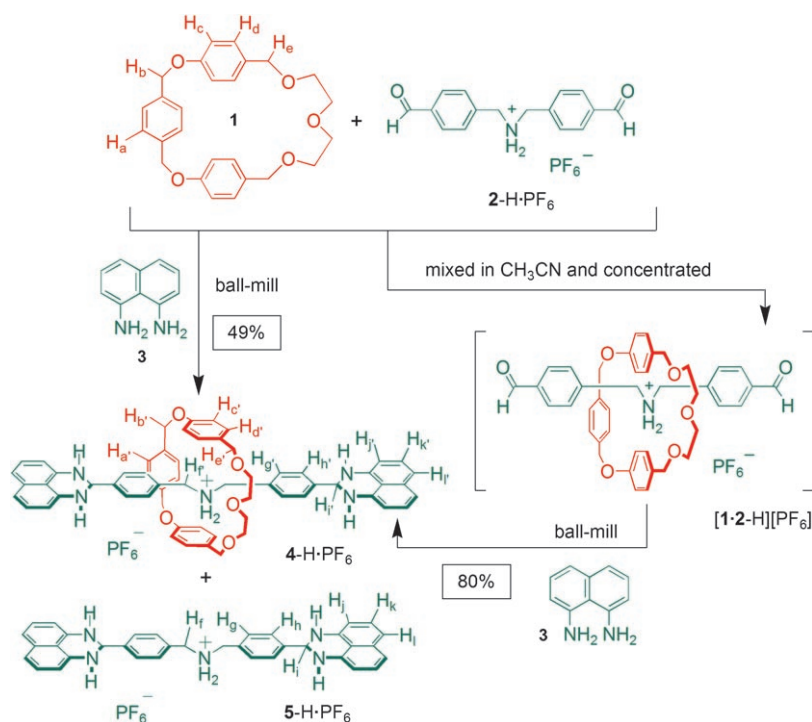
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Scheme 1. Solid-state synthesis of the [2]rotaxane 4-H·PF₆.

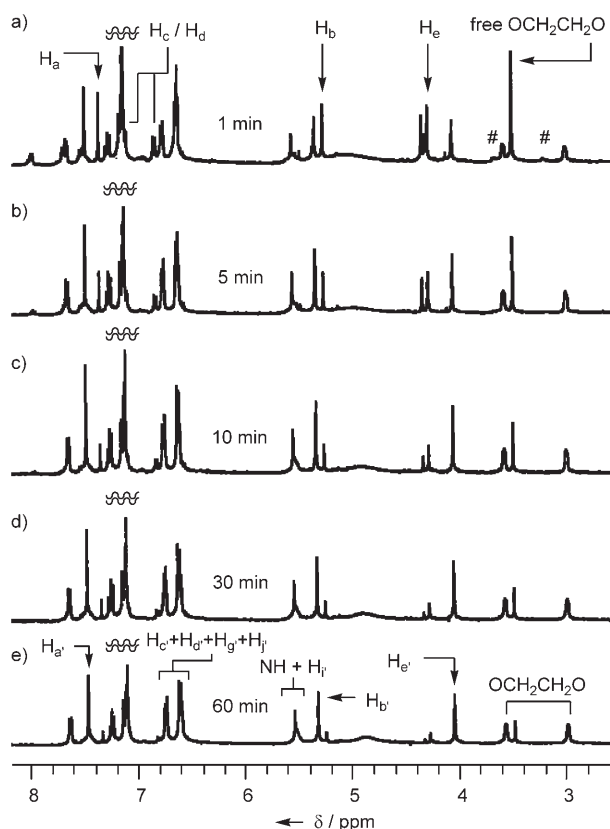


Figure 1. Partial ¹H NMR spectra (400 MHz, CD₃CN, 298 K) displaying the formation of the [2]rotaxane 4-H·PF₆ from the pseudorotaxane [1·2-H][PF₆] after solid-state ball-milling for a) 1, b) 5, c) 10, d) 30, and e) 60 min. #: Signals from the pseudorotaxane [1·2-H][PF₆].

the terminal dihydropyrimidine groups are true stopper units for the macrocycle **1** and that the [2]rotaxane 4-H·PF₆ was not the product of a slippage synthesis.^[13]

As solid-state ball-milling was such an efficient method of synthesizing the [2]rotaxane 4-H·PF₆, we turned our attention toward the syntheses of higher-order rotaxanes. We prepared the trisammonium salt 6-H₃·3 PF₆ (Scheme 2) from 1,3,5-tris(*p*-formylphenyl)-benzene^[14] as a suitable guest species (see the Supporting Information).

We assumed that the solid obtained after concentrating a solution of the macrocycle **1** and 6-H₃·3 PF₆ (4:1) in CH₃CN contained mainly the [4]pseudorotaxane [1₃·6-H₃][3 PF₆], which we subsequently ball-milled with the diamine **3** (4 equiv relative to 6-H₃·3 PF₆) under ambient conditions. ¹H NMR spectroscopic analysis suggested that the [4]rotaxane 7-H₃·3 PF₆ was the predominant product (Figure 3b) in the solid mixture after 1 h of ball-milling; 7-H₃·3 PF₆ was isolated in 65% yield after column chromatography.^[15]

The electrospray ionization (ESI) mass spectrum of 7-H₃·3 PF₆ revealed intense signals at *m/z* 1288.1 and 810.4, which correspond to [7-H₃·PF₆]²⁺ and [7-H₃]³⁺, respectively. The good matches between the observed and calculated isotope patterns (see the Supporting Information) for these ions support the successful synthesis of the [4]rotaxane 7-H₃·3 PF₆.

To prove the generality of this approach, we applied the same ball-milling process to the solid obtained after mixing the diamine **3** (4 equiv relative to 6-H₃·3 PF₆) with the solid obtained after concentrating a solution of dibenzo[24]crown-8 (DB24C8) and 6-H₃·3 PF₆ (4:1) in CH₃CN;^[16] the corre-

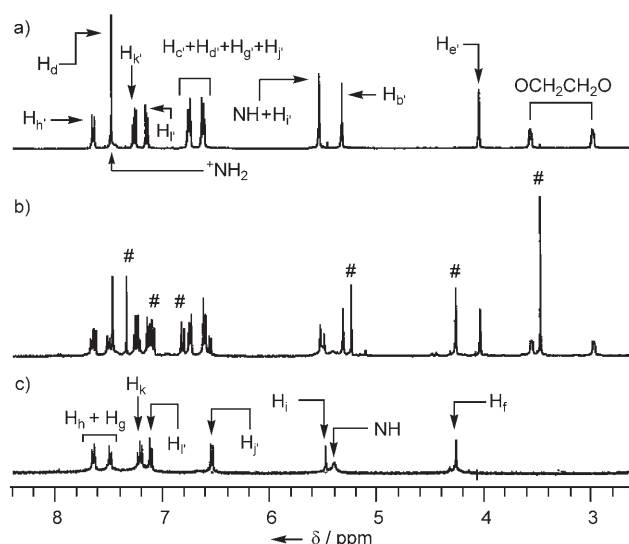
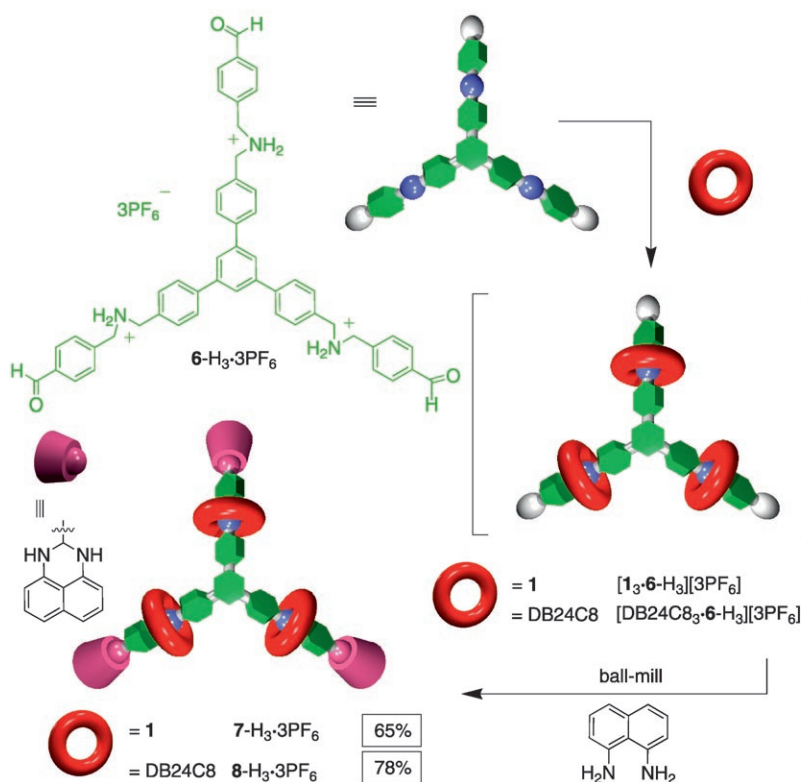


Figure 2. Partial ¹H NMR spectra (400 MHz, CD₃CN, 298 K) of a) the isolated [2]rotaxane 4-H·PF₆, b) the solid mixture obtained from direct ball-milling of the solid mixture of **1**, 2-H·PF₆, and **3** (1:1:2) for 1 h, and c) the dumbbell 5-H·PF₆. #: Signals from the free macrocycle **1**.



Scheme 2. Solid-state syntheses of the [4]rotaxanes **7-** and **8-H₃·3PF₆**.

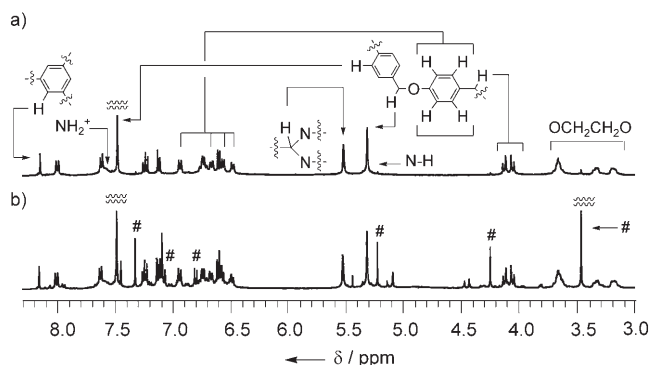


Figure 3. Partial ^1H NMR spectra (400 MHz, CD_3CN , 298 K) of a) the isolated [4]rotaxane **7-H₃·3PF₆** and b) the solid obtained after directly ball-milling a mixture of the putative [4]pseudorotaxane $[\text{13}\cdot\text{6-H}_3][\text{3PF}_6]$ and the diamine **3** ($[\text{1/6-H}_3\cdot\text{3PF}_6/\text{3}] = 4:1:4$) for 1 h. #: Signals from the free macrocycle **1**.

sponding [4]rotaxane **8-H₃·3PF₆** was isolated in 78% yield.^[17] The ESI mass spectrum of **8-H₃·3PF₆** revealed intense peaks at m/z 2806.0, 1330.1, and 838.4, which correspond to $[\text{8-H}_3\cdot 2\text{PF}_6]^+$, $[\text{8-H}_3\cdot \text{PF}_6]^{2+}$, and $[\text{8-H}_3]^{3+}$, respectively. In contrast, the reaction between DB24C8, **6-H₃·3PF₆**, and **3** (40:10:40 mm) in CD_3CN took 24 h to reach completion; ^1H NMR spectroscopy revealed that the yield of the [4]rotaxane **8-H₃·3PF₆** was 39%.

The solid-state condensations occurring in ball-milled mixtures of 1,8-diaminonaphthalene and benzaldehyde derivatives are convenient, waste-free (water is the only by-product), and efficient reactions for preparing interlocked

molecules such as [2]- and [4]rotaxanes. We believe that this approach will also be useful for constructing other complicated interlocked molecules, several of which are currently under investigation in our laboratory.

Experimental Section

General methods for the ball-milling process: The ball-milling was performed using a Retsch MM 200 swing-mill containing two 5 mL stainless-steel cells and two stainless-steel balls (diameter: 7 mm). The mill was operated at a frequency of 22.5 Hz at room temperature.

[2]Rotaxane **4-H·PF₆** (ball-milling of preformed pseudorotaxane): Macrocycle **1** (43 mg, 0.10 mmol) and dialdehyde **2-H·PF₆** (40 mg, 0.10 mmol) were dissolved in CH_3CN (0.5 mL). The solvent was evaporated under reduced pressure to afford a white solid, which was mixed with 1,8-diaminonaphthalene (**3**; 33 mg, 0.21 mmol) and ball-milled at room temperature for 1 h. The resulting solid was purified by chromatography (SiO_2 ; $\text{MeOH}/\text{CH}_2\text{Cl}_2$, 2:98) to afford the [2]rotaxane **4-H·PF₆** (88 mg, 80%) and the dumbbell **5-H·PF₆** (11 mg, 16%). **4-H·PF₆**: m.p. > 270°C (decomp); ^1H NMR (400 MHz, CD_3CN): δ = 2.00–2.25 (m, 4H), 2.95–2.98 (m, 4H), 3.54–3.56 (m, 4H), 4.03 (s, 4H), 5.30 (s, 4H), 5.51 (s, 6H), 6.58–6.61 (m, 8H), 6.71–6.75 (m, 8H), 7.12 (d, J = 8 Hz, 4H), 7.23 (t, J = 8 Hz, 4H), 7.46 (s, 4H), 7.40–7.45 (brs, 2H), 7.62 ppm (d, J = 8 Hz, 4H); ^{13}C NMR (100 Hz, CD_3CN): δ = 51.3, 67.5, 68.4, 69.8, 71.4, 74.5, 106.2, 114.1, 116.9, 117.6, 128.0, 128.4, 128.7, 129.2, 131.8, 132.0, 135.8, 138.3, 143.3, 143.4, 158.2 ppm (one signal is missing, possibly because of signal overlap); HRMS (FAB): m/z calcd for $[\text{4-H}]^+$ ($\text{C}_{62}\text{H}_{60}\text{N}_5\text{O}_5$): 954.4594; found: 954.4576. **5-H·PF₆**: m.p. > 220°C (decomp); ^1H NMR (400 MHz, CD_3CN): δ = 4.26 (s, 4H), 5.37–5.42 (brs, 4H), 5.48 (s, 2H), 6.54 (d, J = 7 Hz, 4H), 7.11 (d, J = 7 Hz, 4H), 7.21 (t, J = 7 Hz, 4H), 7.49 (d, J = 8 Hz, 4H), 7.65 ppm (d, J = 8 Hz, 4H); ^{13}C NMR (100 Hz, CD_3CN): δ = 52.2, 67.5, 106.2, 113.9, 117.6, 127.9, 129.1, 131.1, 131.6, 135.6, 143.1, 144.0 ppm; HRMS (FAB): m/z calcd for $[\text{5-H}]^+$ ($\text{C}_{36}\text{H}_{32}\text{N}_5$): 534.2658; found: 534.2681; calcd for $[\text{5+Na}]^+$ ($\text{C}_{36}\text{H}_{31}\text{N}_5\text{Na}$): 556.2472; found: 556.2420.

[2]Rotaxane **4-H·PF₆** (direct ball-milling): The macrocycle **1** (43 mg, 0.10 mmol), the dialdehyde **2-H·PF₆** (40 mg, 0.10 mmol), and 1,8-diaminonaphthalene (**3**; 33 mg, 0.21 mmol) were mixed and then ball-milled at room temperature for 1 h. The crude product was purified by chromatography (SiO_2 ; $\text{MeOH}/\text{CH}_2\text{Cl}_2$, 2:98) to afford the [2]rotaxane **4-H·PF₆** (54 mg, 49%) and the dumbbell **5-H·PF₆** (30 mg, 44%).

[4]Rotaxane **7-H₃·3PF₆**: Macrocycle **1** (42 mg, 0.10 mmol) and the trialdehyde **6-H₃·3PF₆** (30 mg, 25 μmol) were dissolved in CH_3CN (0.5 mL). The solvent was then evaporated under reduced pressure to afford a white solid, which was mixed with 1,8-diaminonaphthalene (**3**; 16 mg, 0.10 mmol) and ball-milled at room temperature for 1 h. The crude product was purified by chromatography (SiO_2 ; $\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$, 1:9) to afford the [4]rotaxane **7-H₃·3PF₆** as a light-brown solid (47 mg, 65%). M.p. > 250°C (decomp); ^1H NMR (400 MHz, CD_3NO_2): δ = 1.80–1.90 (m, 6H), 2.63–2.75 (m, 6H), 3.28–3.45 (m, 12H), 3.76 (s, 12H), 4.09 (d, J = 9 Hz, 6H), 4.24 (d, J = 9 Hz, 6H), 5.26 (s, 6H), 5.36 (s, 12H), 5.57 (s, 3H), 6.42 (dd, J = 8, 2 Hz, 6H), 6.54 (d, J = 8 Hz, 6H), 6.61 (d, J = 8 Hz, 6H), 6.67 (dd, J = 8, 2 Hz, 6H), 6.86 (dd, J = 8, 2 Hz, 6H), 6.93 (dd, J = 8, 2 Hz, 6H), 7.14–7.18 (m, 12H), 7.24–7.26 (m, 6H), 7.54 (s, 12H), 7.67 (d, J = 8 Hz, 6H), 7.70–7.80 (brs, 6H), 8.08 (d, J = 8 Hz, 6H), 8.23 ppm (s, 3H); ^{13}C NMR (100 Hz, CD_3NO_2): δ = 49.7, 50.9, 67.3, 67.6, 69.6, 70.8, 73.9, 105.8, 113.5, 115.2, 116.7, 117.2, 125.5, 127.2, 127.5, 127.8, 128.7, 130.1, 131.4, 131.6, 131.8, 131.9, 135.1, 137.8, 141.6, 142.0, 142.5, 157.5, 157.6 ppm; HRMS (ESI): m/z calcd for $[\text{7-H}_3\cdot \text{PF}_6]^{2+}$ ($\text{C}_{159}\text{H}_{156}\text{N}_9\text{O}_{15}\text{PF}_6$): 1288.0682; found: 1288.0699; calcd for $[\text{7-H}_3]^{3+}$ ($\text{C}_{159}\text{H}_{156}\text{N}_9\text{O}_{15}$): 810.3907; found: 810.3921.

[4] Rotaxane **8**-H₃-3PF₆: DB24C8 (45 mg, 0.10 mmol) and the trialdehyde **6**-H₃-3PF₆ (30 mg, 25 μ mol) were dissolved in CH₃CN (0.5 mL). The solvent was then evaporated under reduced pressure to afford a white solid, which was mixed with 1,8-diaminonaphthalene (**3**; 16 mg, 0.10 mmol) and ball-milled at room temperature for 1 h. The crude product was purified by chromatography (SiO₂; CH₃CN/CH₂Cl₂, 1:4) to afford the [4]rotaxane **8**-H₃-3PF₆ as a white solid (58 mg, 78%). M.p. >265 °C (decomp); ¹H NMR (400 MHz, CD₃CN): δ = 3.50–3.62 (m, 24 H), 3.62–3.82 (m, 24 H), 3.98–4.10 (m, 24 H), 4.69–4.82 (m, 12 H), 5.26 (s, 6 H), 5.36 (s, 3 H), 6.54 (d, J = 8 Hz, 6 H), 6.80 (s, 24 H), 7.09 (d, J = 8 Hz, 6 H), 7.19 (t, J = 8 Hz, 6 H), 7.41 (s, 12 H), 7.43 (d, J = 8 Hz, 6 H), 7.47 (d, J = 8 Hz, 6 H), 7.54 (s, 3 H), 7.64 ppm (brs, 6 H); ¹³C NMR (100 MHz, CD₃CN): δ = 48.6, 48.7, 62.8, 64.4, 66.6, 67.1, 101.6, 108.8, 109.5, 113.0, 117.5, 121.4, 123.4, 123.5, 124.1, 126.0, 126.3, 128.0, 128.7, 131.1, 137.1, 137.6, 138.6, 138.9, 143.8 ppm; HRMS (ESI): m/z calcd for [8-H₃-PF₆]²⁺ (C₁₅₃H₁₆₈N₉O₂₄PF₆): 1330.0921, found: 1330.0910; calcd for [8-H₃]³⁺ (C₁₅₃H₁₆₈N₉O₂₄): 838.4067, found: 838.4075.

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- [11] When using the immediate solvent evaporation method (ISEM), that is, dissolving **1** (38 μ mol), **2**-H-PF₆ (38 μ mol), and **3** (76 μ mol) in CH₃CN (0.5 mL) and then evaporating the solvent under reduced pressure, we found that the [2]rotaxane **4**-H-PF₆ was also generated in the resulting thin film. According to ¹H NMR spectroscopy, the reaction was finished after 5 h with a maximum yield of 64%, as determined from integration of the signals of the interlocked and free macrocycles (see the Supporting Information). By using the ball-milling approach, the same mixture gave a yield of 87% after 1 h of grinding, as determined by integration of the ¹H NMR signals. These results show that the yield of **4**-H-PF₆ from the ball-milling reaction was higher. For details of the ISEM approach, see A. Orita, G. Uehara, K. Miwa, J. Otera, *Chem. Commun.* **2006**, 4729–4731 and Ref. [5].
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- [15] ¹H NMR spectroscopy indicated that direct ball-milling of a mixture of **1**, **6**-H₃-3PF₆, and **3** as solids in a 4:1:4 ratio—without prior generation of the putative solid [4]pseudorotaxane complex [**1**₃-**6**-H₃][3PF₆]⁺—did not yield the [4]rotaxane **7**-H₃-3PF₆.
- [16] For a discussion of the self-assembly of DB24C8 and DBA⁺, see a) M. C. T. Fyfe, J. F. Stoddart, *Adv. Supramol. Chem.* **1999**, *5*, 1–53; for a discussion of the complexity that can arise from ion pairing in this recognition system, see b) W. J. Jones, H. W. Gibson, *J. Am. Chem. Soc.* **2003**, *125*, 7001–7004.
- [17] The [4]rotaxane **8**-H₃-3PF₆ could also be generated by dissolving DB24C8 (50 μ mol), **6**-H₃-3PF₆ (13 μ mol), and **3** (50 μ mol) in CH₃CN (1 mL) and then evaporating the solvent under reduced pressure. According to ¹H NMR spectroscopy, this ISEM reaction required 5 h to reach completion; the yield was 52% based on integration of signals of the aromatic protons of the interlocked and free DB24C8 moieties (see the Supporting Information). By using the ball-milling approach, the corresponding reaction afforded the [4]rotaxane in 82% yield (¹H NMR spectroscopy) after 1 h. The yields of the isolated [4]rotaxanes from the ISEM and ball-milled approaches were 50 and 78%, respectively; thus, the latter approach was superior.