Host–Guest Chemistry

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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 CD_3CN ($K_a = 200\ M^{-1}$).[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·PF_6 in CH_3CN under reduced pressure to afford a white solid, which we assumed to contain predominantly the [2]pseudorotaxane complex [**1**·**2**-H][PF_6] (Scheme 1). After dissolving portions of the solids in CD_3CN, we used ^{1}H NMR spectroscopy to monitor the ball-milling reaction of a 1:2 mixture of the [2]pseudorotaxane complex [**1**·**2**-H][PF_6] 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·PF_6 in 80 % yield.[11] The yield increased to 87 % when we increased the ratio of the macrocycle **1** and the dialdehyde thread **2**-H·PF_6 in the solid mixture to 1.2:1. The solution reaction of **1**, **2**-H·PF_6, and diamine **3** (50:50:100 mM) in CH_3CN did not proceed as efficiently as it did through ball-milling: traces of **2**-H·PF_6 remained detectable by TLC after 24 h. The use of ^{1}H NMR spectroscopy to monitor a slightly more dilute mixture (20:20:40 mM) in CD_3CN indicated that the reaction was complete after 24 h, and provided the [2]rotaxane **4**-H·PF_6 in 48 % yield.

When we mixed **1**, **2**-H·PF_6, and **3** as solids in a 1:1:2 ratio without first generating the solid [2]pseudorotaxane complex [**1**·**2**-H][PF_6], the same ball-milling conditions afforded a mixture of the [2]rotaxane **4**-H·PF_6 and the dumbbell-like salt **5**-H·PF_6 (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·PF_6 could occur during the grinding process, preforming the [2]pseudorotaxane [**1**·**2**-H][PF_6] 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·PF_6 in CD_3SOCD_3 and monitored its ^{1}H NMR spectra at 323 K over time. We detected no signals of the free components in the ^{1}H NMR spectrum recorded after 3 h, which suggests that

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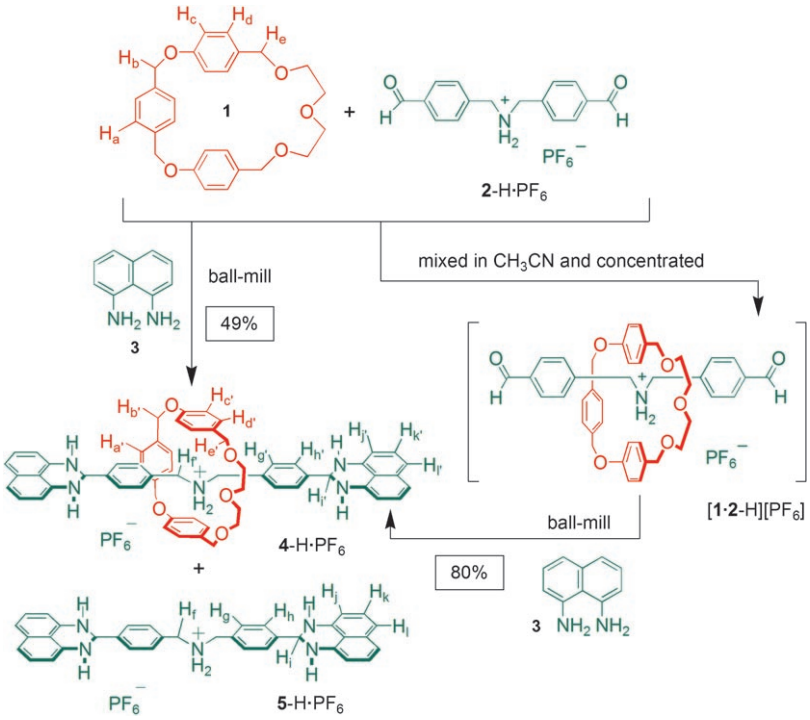


Scheme 1. Solid-state synthesis of the [2]rotaxane **4**-H·PF_6.

the terminal dihydropyrimidine groups are true stopper units for the macrocycle **1** and that the [2]rotaxane **4**-H·PF_6 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·PF_6, we turned our attention toward the syntheses of higher-order rotaxanes. We prepared the trisammonium salt **6**-H_3·3PF_6 (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**-H_3·3PF_6 (4:1) in CH_3CN contained mainly the [4]pseudorotaxane [**1**$_3$·**6**-H_3]-[3PF_6], which we subsequently ball-milled with the diamine **3** (4 equiv relative to **6**-H_3·3PF_6) under ambient conditions. ^{1}H NMR spectroscopic analysis suggested that the [4]rotaxane **7**-H_3·3PF_6 was the predominant product (Figure 3b) in the solid mixture after 1 h of ball-milling; **7**-H_3·3PF_6 was isolated in 65% yield after column chromatography.[15] The electrospray ionization (ESI) mass spectrum of **7**-H_3·3PF_6 revealed intense signals at *m*/*z* 1288.1 and 810.4, which correspond to [**7**-H_3·PF_6]$^{2+}$ and [**7**-H_3]$^{3+}$, 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**-H_3·3PF_6.

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**-H_3·3PF_6) with the solid obtained after concentrating a solution of dibenzo[24]crown-8 (DB24C8) and **6**-H_3·3PF_6 (4:1) in CH_3CN;[16] the corre-

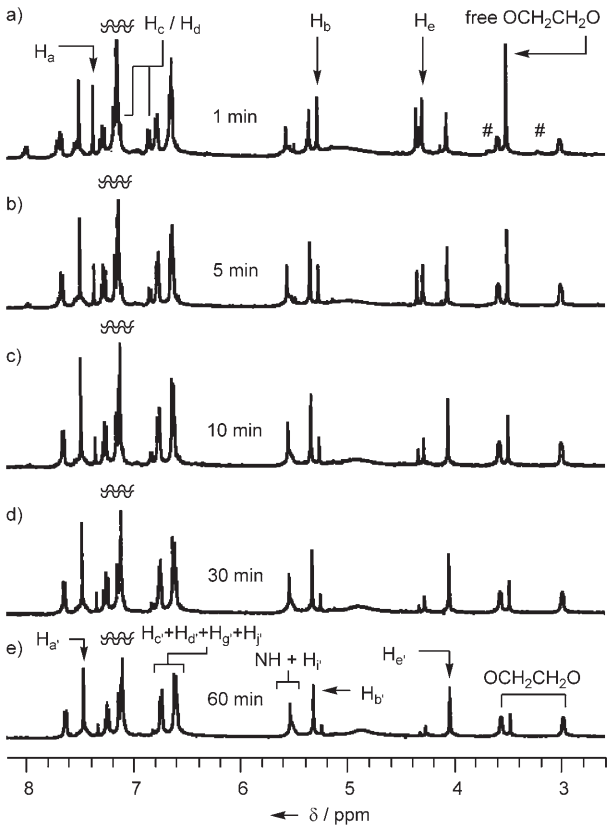


Figure 1. Partial ^{1}H NMR spectra (400 MHz, CD_3CN, 298 K) displaying the formation of the [2]rotaxane **4**-H·PF_6 from the pseudorotaxane [**1**·**2**-H][PF_6] after solid-state ball-milling for a) 1, b) 5, c) 10, d) 30, and e) 60 min. #: Signals from the pseudorotaxane [**1**·**2**-H][PF_6].

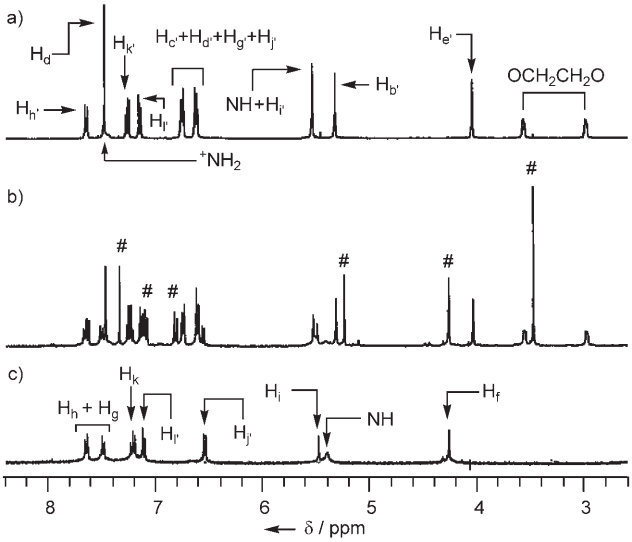
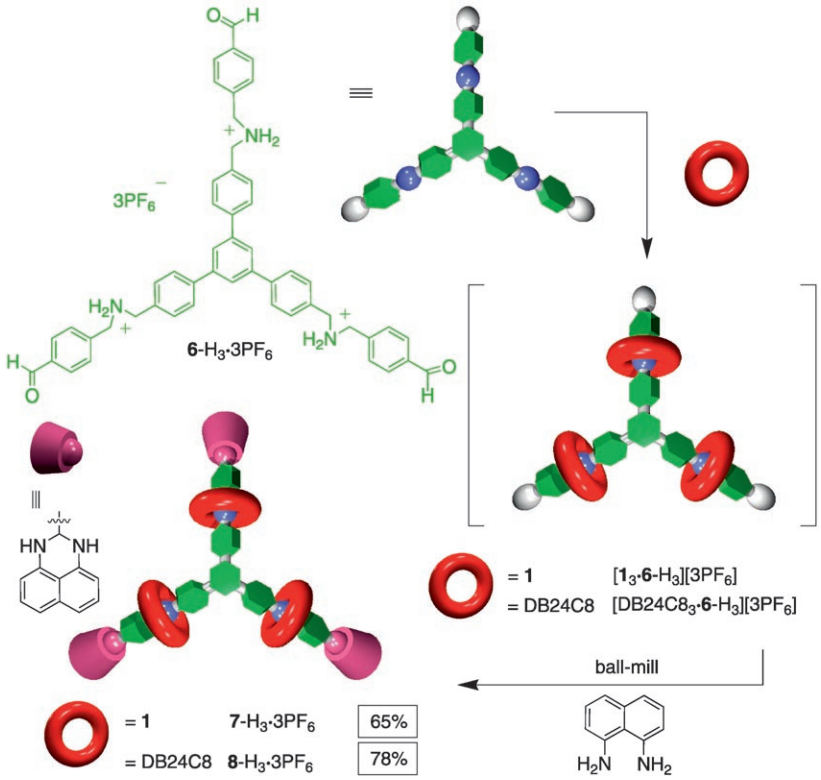


Figure 2. Partial ^{1}H NMR spectra (400 MHz, CD_3CN, 298 K) of a) the isolated [2]rotaxane **4**-H·PF_6, b) the solid mixture obtained from direct ball-milling of the solid mixture of **1**, **2**-H·PF_6, and **3** (1:1:2) for 1 h, and c) the dumbbell **5**-H·PF_6. #: Signals from the free macrocycle **1**.



Scheme 2. Solid-state syntheses of the [4]rotaxanes **7**- and **8**-H_3·3 PF_6.

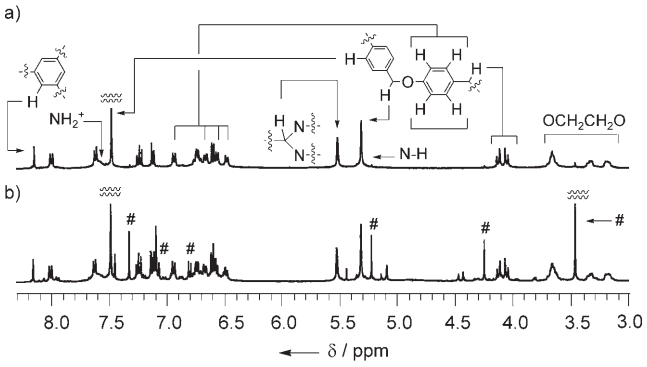


Figure 3. Partial ^{1}H NMR spectra (400 MHz, CD_3CN, 298 K) of a) the isolated [4]rotaxane **7**-H_3·3 PF_6 and b) the solid obtained after directly ball-milling a mixture of the putative [4]pseudorotaxane [**1**$_3$·**6**-H_3][3 PF_6] and the diamine **3** (**1**/**6**-H_3·3 PF_6/**3** = 4:1:4) for 1 h. #: Signals from the free macrocycle **1**.

sponding [4]rotaxane **8**-H_3·3 PF_6 was isolated in 78 % yield.[17] The ESI mass spectrum of **8**-H_3·3 PF_6 revealed intense peaks at *m*/*z* 2806.0, 1330.1, and 838.4, which correspond to [**8**-H_3·2 PF_6]$^+$, [**8**-H_3·PF_6]$^{2+}$, and [**8**-H_3]$^{3+}$, respectively. In contrast, the reaction between DB24C8, **6**-H_3·3 PF_6, and **3** (40:10:40 mM) in CD_3CN took 24 h to reach completion; ^{1}H NMR spectroscopy revealed that the yield of the [4]rotaxane **8**-H_3·3 PF_6 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·PF_6 (ball-milling of preformed pseudorotaxane): Macrocycle **1** (43 mg, 0.10 mmol) and dialdehyde **2**-H·PF_6 (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; MeOH/CH_2Cl_2, 2:98) to afford the [2]rotaxane **4**-H·PF_6 (88 mg, 80 %) and the dumbbell **5**-H·PF_6 (11 mg, 16 %). **4**-H·PF_6: m.p. > 270 °C (decomp); ^{1}H 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 (br s, 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 [**4**-H]$^+$ ($C_{62}H_{60}N_5O_5$): 954.4594; found: 954.4576. **5**-H·PF_6: m.p. > 220 °C (decomp); ^{1}H NMR (400 MHz, CD_3CN): δ = 4.26 (s, 4H), 5.37–5.42 (br s, 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 [**5**-H]$^+$ ($C_{36}H_{32}N_5$): 534.2658; found: 534.2681; calcd for [**5**+Na]$^+$ ($C_{36}H_{31}N_5Na$): 556.2472; found: 556.2420.

[2]Rotaxane **4**-H·PF_6 (direct ball-milling): The macrocycle **1** (43 mg, 0.10 mmol), the dialdehyde **2**-H·PF_6 (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; MeOH/CH_2Cl_2, 2:98) to afford the [2]rotaxane **4**-H·PF_6 (54 mg, 49 %) and the dumbbell **5**-H·PF_6 (30 mg, 44 %).

[4]Rotaxane **7**-H_3·3 PF_6: Macrocycle **1** (42 mg, 0.10 mmol) and the trialdehyde **6**-H_3·3 PF_6 (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; CH_3CN/CH_2Cl_2, 1:9) to afford the [4]rotaxane **7**-H_3·3 PF_6 as a light-brown solid (47 mg, 65 %). M.p. > 250 °C (decomp); ^{1}H 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 (br s, 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 [**7**-H_3·PF_6]$^{2+}$ ($C_{159}H_{156}N_9O_{15}PF_6$): 1288.0682; found: 1288.0699; calcd for [**7**-H_3]$^{3+}$ ($C_{159}H_{156}N_9O_{15}$): 810.3907; found: 810.3921.

[4]Rotaxane **8**-H_3·3PF_6: DB24C8 (45 mg, 0.10 mmol) and the trialdehyde **6**-H_3·3PF_6 (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; CH_3CN/CH_2Cl_2, 1:4) to afford the [4]rotaxane **8**-H_3·3PF_6 as a white solid (58 mg, 78%). M.p. >265°C (decomp); ^{1}H NMR (400 MHz, CD_3CN): δ = 3.50–3.62 (m, 24H), 3.62–3.82 (m, 24H), 3.98–4.10 (m, 24H), 4.69–4.82 (m, 12H), 5.26 (s, 6H), 5.36 (s, 3H), 6.54 (d, J = 8 Hz, 6H), 6.80 (s, 24H), 7.09 (d, J = 8 Hz, 6H), 7.19 (t, J = 8 Hz, 6H), 7.41 (s, 12H), 7.43 (d, J = 8 Hz, 6H), 7.47 (d, J = 8 Hz, 6H), 7.54 (s, 3H), 7.64 ppm (brs, 6H); ^{13}C NMR (100 Hz, CD_3CN): 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 $[\mathbf{8}\text{-}H_3\cdot PF_6]^{2+}$ ($C_{153}H_{168}N_9O_{24}PF_6$): 1330.0921, found: 1330.0910; calcd for $[\mathbf{8}\text{-}H_3]^{3+}$ ($C_{153}H_{168}N_9O_{24}$): 838.4067, found: 838.4075.

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[1] a) *Molecular Electronics: Science and Technology* (Eds.: A. Aviram, M. Ratner), New York Academy of Sciences, New York, **1998**; b) C. P. Collier, G. Mattersteig, E. W. Wong, Y. Luo, K. Beverly, J. Sampaio, F. M. Raymo, J. F. Stoddart, J. R. Heath, *Science* **2000**, *289*, 1172–1175; c) H. Yu, Y. Luo, K. Beverly, J. F. Stoddart, H.-R. Tseng, J. R. Heath, *Angew. Chem.* **2003**, *115*, 5884–5889; *Angew. Chem. Int. Ed.* **2003**, *42*, 5706–5711; d) J. W. Choi, A. H. Flood, D. W. Steuerman, S. Nygaard, A. B. Braunschweig, N. N. P. Moonen, B. W. Laursen, Y. Luo, E. DeIonno, A. J. Peters, J. O. Jeppesen, K. Xu, J. F. Stoddart, J. R. Heath, *Chem. Eur. J.* **2006**, *12*, 261–279; e) S. Saha, J. F. Stoddart, *Chem. Soc. Rev.* **2007**, *36*, 77–92.

[2] For recent examples, see a) A. B. Braunschweig, C. M. Ronconi, J.-Y. Han, F. Arico, S. J. Cantrill, J. F. Stoddart, S. I. Khan, A. J. P. White, D. J. Williams, *Eur. J. Org. Chem.* **2006**, 1857–1866; b) P. Mobian, J.-P. Collin, J.-P. Sauvage, *Tetrahedron Lett.* **2006**, *47*, 4907–4909; c) K.-W. Cheng, C.-C. Lai, P.-T. Chiang, S.-H. Chiu, *Chem. Commun.* **2006**, 2854–2856.

[3] The production of tight-binding ion pairs during the stoppering process is believed to lower the yields of several rotaxane syntheses; for examples, see a) S. J. Rowan, S. J. Cantrill, J. F. Stoddart, *Org. Lett.* **1999**, *1*, 129–132; b) Y.-L. Huang, W.-C. Hung, C.-C. Lai, Y.-H. Liu, S.-M. Peng, S.-H. Chiu, *Angew. Chem.* **2007**, *119*, 6749–6753; *Angew. Chem. Int. Ed.* **2007**, *46*, 6629–6633.

[4] a) K. Tanaka, F. Toda, *Chem. Rev.* **2000**, *100*, 1025–1074; b) *Solvent Free Organic Synthesis* (Ed.: K. Tanaka), Wiley-VCH, Weinheim, **2004**.

[5] The corresponding [2]rotaxane was synthesized in 85% yield from the film obtained after evaporating a solution of all three components. This elegant approach takes advantage of bringing the reactants together to generate the film, and thus may not be classified as a true solid/solid reaction. Directly grinding the three individual solids together gave the [2]rotaxane in only 11% yield; see A. Orita, J. Okano, Y. Tawa, L. Jiang, J. Otera, *Angew. Chem.* **2004**, *116*, 3810–3814; *Angew. Chem. Int. Ed.* **2004**, *43*, 3724–3728.

[6] a) N. Kihara, K. Hinoue, T. Takata, *Macromolecules* **2005**, *38*, 223–226; b) R. Liu, T. Maeda, N. Kihara, A. Harada, T. Takata, *J. Polym. Sci. Part A* **2007**, *45*, 1571–1574.

[7] a) J. Schmeyers, F. Toda, J. Boy, G. Kaupp, *J. Chem. Soc. Perkin Trans. 2* **1998**, 989–993; b) G. Kaupp, J. Schmeyers, M. R. Naimi-Jamal, H. Zoz, H. Ren, *Chem. Eng. Sci.* **2002**, *57*, 763–765.

[8] H. Yamamoto, K. Maruoka, *J. Am. Chem. Soc.* **1981**, *103*, 4186–4194.

[9] O. Maloshitskaya, J. Sinkkonen, V. V. Ovcharenko, K. N. Zelenin, K. Pihlaja, *Tetrahedron* **2004**, *60*, 6913–6921.

[10] a) P.-N. Cheng, P.-Y. Huang, W.-S. Li, S.-H. Ueng, W.-C. Hung, Y.-H. Liu, C.-C. Lai, S.-M. Peng, I. Chao, S.-H. Chiu, *J. Org. Chem.* **2006**, *71*, 2373–2375; b) C.-W. Chiu, C.-C. Lai, S.-H. Chiu, *J. Am. Chem. Soc.* **2007**, *129*, 3500–3501.

[11] When using the immediate solvent evaporation method (ISEM), that is, dissolving **1** (38 μmol), **2**-H·PF_6 (38 μmol), and **3** (76 μmol) in CH_3CN (0.5 mL) and then evaporating the solvent under reduced pressure, we found that the [2]rotaxane **4**-H·PF_6 was also generated in the resulting thin film. According to ^{1}H 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 ^{1}H NMR signals. These results show that the yield of **4**-H·PF_6 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].

[12] a) M. Asakawa, P. R. Ashton, R. Ballardini, V. Balzani, M. Belohradsky, M. T. Gandolfi, O. Kocian, L. Prodi, F. M. Raymo, J. F. Stoddart, M. Venturi, *J. Am. Chem. Soc.* **1997**, *119*, 302–310; b) P. R. Ashton, I. Baxter, M. C. T. Fyfe, F. M. Raymo, N. Spencer, J. F. Stoddart, A. J. P. White, D. J. Williams, *J. Am. Chem. Soc.* **1998**, *120*, 2297–2307; c) S.-H. Chiu, S. J. Rowan, S. J. Cantrill, P. T. Glink, R. L. Garrell, J. F. Stoddart, *Org. Lett.* **2000**, *2*, 3631–3634.

[13] We did not detect any signals for **4**-H·PF_6 in the ^{1}H NMR spectrum of a ball-milled equimolar mixture of the solid dumbbell **5**-H·PF_6 and the macrocycle **1**, which suggests that it was unlikely that this [2]rotaxane was generated through slippage.

[14] a) E. Weber, M. Hecker, E. Koepp, W. Orlia, M. Czugler, I. Csoregh, *J. Chem. Soc. Perkin Trans. 2* **1988**, 1251–1257; b) M. C. T. Fyfe, J. N. Lowe, J. F. Stoddart, D. J. Williams, *Org. Lett.* **2000**, *2*, 1221–1224; c) J. D. Badjic, C. M. Ronconi, J. F. Stoddart, V. Balzani, S. Silvi, A. Credi, *J. Am. Chem. Soc.* **2006**, *128*, 1489–1499.

[15] ^{1}H NMR spectroscopy indicated that direct ball-milling of a mixture of **1**, **6**-H_3·3PF_6, and **3** as solids in a 4:1:4 ratio—without prior generation of the putative solid [4]pseudorotaxane complex [**1**$_3$·**6**-H_3][3PF_6]—did not yield the [4]rotaxane **7**-H_3·3PF_6.

[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**-H_3·3PF_6 could also be generated by dissolving DB24C8 (50 μmol), **6**-H_3·3PF_6 (13 μmol), and **3** (50 μmol) in CH_3CN (1 mL) and then evaporating the solvent under reduced pressure. According to ^{1}H 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 (^{1}H 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.

