Five Additional Macrocycles that Allow the Na+ Ion–Templated Threading of Guest Units Featuring a Single Urea or Amide Functionality

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ARTICLE

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Five analogues of the macrocycle BPX26C6 are also capable of recognizing single urea and/or amide functionalities in the presence of templating Na^+ ions. We have unambiguously confirmed the formation of such [2]pseudorotaxane complexes in solution through syntheses of corresponding [2]rotaxanes.

Introduction

Because the threading of a guest through the cavity of a macrocyclic host generally requires precise structural complementarity of their recognition units to maximize noncovalent interactions between the components, the molecular structures of strong recognition pairs are generally quite specific; indeed, the number of recognition systems that are frequently used remains limited.[1] Pseudorotaxanes—systems characterized by a macrocyclic host encircling a threaded guest—are precursors for the synthesis of rotaxanes, which have become valuable materials in academic research related to sensing,[2] gelation,[3] molecular/material transportation,[4] and molecular electronic devices;[5] as a result, much effort continues to be focused on the development of new types of threaded host/guest systems. Because the molecular structures of useful (macro)molecules for various applications can be quite specific, we are interested in developing new and generally applicable molecular recognition systems for host molecules to recognize simple and common functionalities in their guests. Amides and ureas are functional groups found in many natural and artificial (macro)molecules (e.g., nylon, polyurea, peptides); if guests containing one such functionality could thread through macrocyclic hosts, it would be possible to introduce interlocked components into such (macro)molecules with very little modification of their original structures. The resulting interlocked or interwoven (macro)molecules would possibly maintain their original valuable properties while gaining additional functions arising from their interlocked components (e.g., controllable switching[6] or structure preservation[7]).

Recently, we realized such a molecular recognition system by using a Na^+ ion to template the threading of guest molecules featuring a single urea or amide functionality through the cavity of the macrocycle bis-*para*-xylyl[26]crown-6 (BPX26C6)[8] (Figure 1).[9] The molecular structure of BPX26C6 features two di(ethylene glycol) and xylene motifs, making symmetrical mono-substitution difficult and potentially complicating spectroscopic characterization of its derivatives. Therefore, we wished to examine the structural flexibility of the host in these Na^+ ion–templated recognition systems. If we could replace one of the di(ethylene glycol) units in the host structure with other linking groups or functional analogues then the greater structural flexibility of these recognition systems would presumably increase their potential for application in various fields (Figure 1). Herein, we report the syntheses of five analogues of the macrocycle BPX26C6 and their ability to form [2]pseudorotaxanes, under the influence of a templating Na^+ ion, with guest species containing a single urea and/or amide unit; we unambiguously confirmed this behavior in solution through syntheses of corresponding [2]rotaxanes.

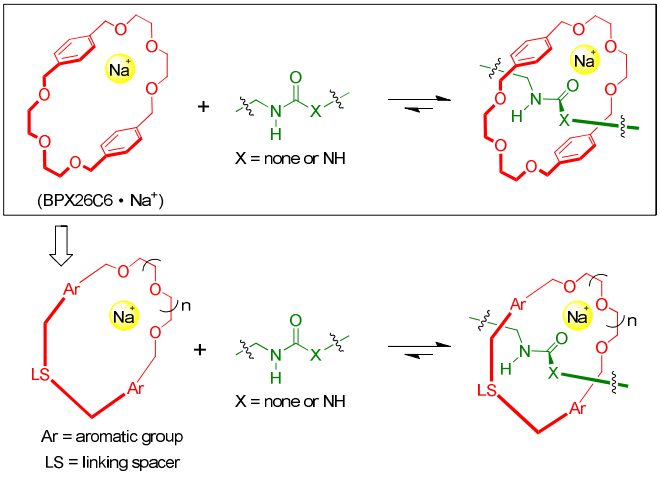


Figure 1. Structural representation of the concept of threading non-conjugated urea or amide moieties through the cavity of BPX26C6 and its macrocyclic analogues with the assistance of a templating Na^+ ion.

Results and Discussion

Synthesis of the Macrocycles

In a previous study, we found that the formation of a pseudorotaxane

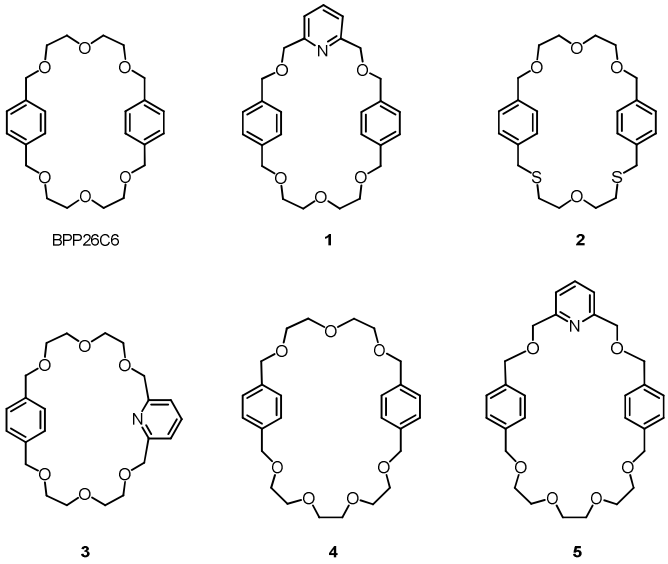
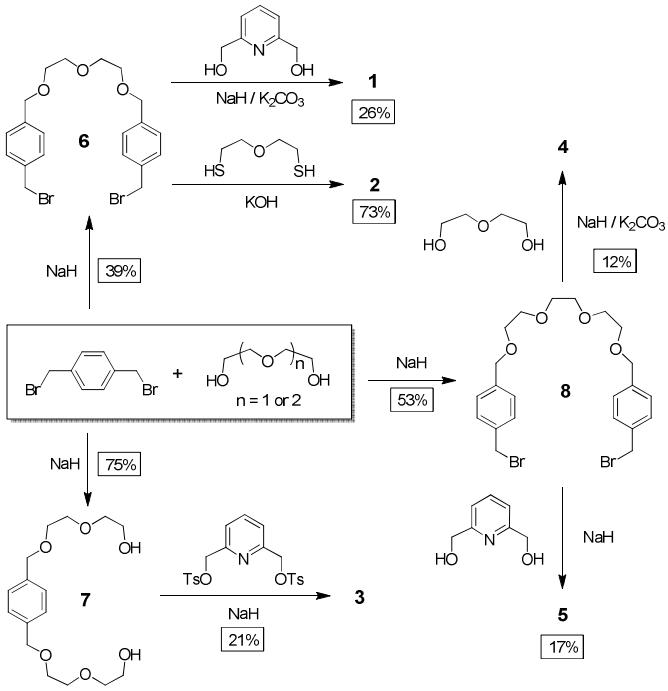


Figure 2. Macrocycles tested for the recognition of guest species featuring a single urea or amide functionality.

between BPX26C6 and a urea/amide guest in a less-polar solvent involves chelation of a Na^+ ion simultaneously to one of the di(ethylene glycol) chains in BPX26C6 and to the C=O group of the urea/amide guest, in addition to possible [N–H···O] hydrogen bonding between the NH proton of the amide/urea unit and the other di(ethylene glycol) chain of the host (Figure 1).[9] We suspected that such guest recognition would also occur if one or both of the di(ethylene glycol) loops in BPX26C6 were replaced by structurally similar moieties, such as 2,6-dihydroxymethylpyridine or tri(ethylene glycol) units. Accordingly, we synthesized the macrocycles **1**–**5** (Figure 2).



Scheme 1. Syntheses of the macrocycles **1**–**5**.

The reaction of an excess of dibromo-*p*-xylene with di(ethylene glycol) under basic conditions gave the dibromide **6**, which underwent macrocyclization with 2,6-pyridinedimethanol and bis(2-mercaptoethyl) ether to afford the macrocycles **1** and **2**, respectively (Scheme 1). In contrast, the reaction of an excess of di(ethylene glycol) with dibromo-*p*-xylene under basic conditions allowed isolation of the diol **7**, which we reacted with 2,6-pyridinedimethanol ditosylate[10] to give the macrocycle **3**. Using one tri(ethylene glycol) unit to bridge two dibromo-*p*-xylene moieties, we obtained the dibromide **8**, which we then reacted with di(ethylene glycol) and 2,6-pyridinedimethanol to afford the macrocycles **4** and **5**, respectively.

[2]Pseudorotaxane Formation

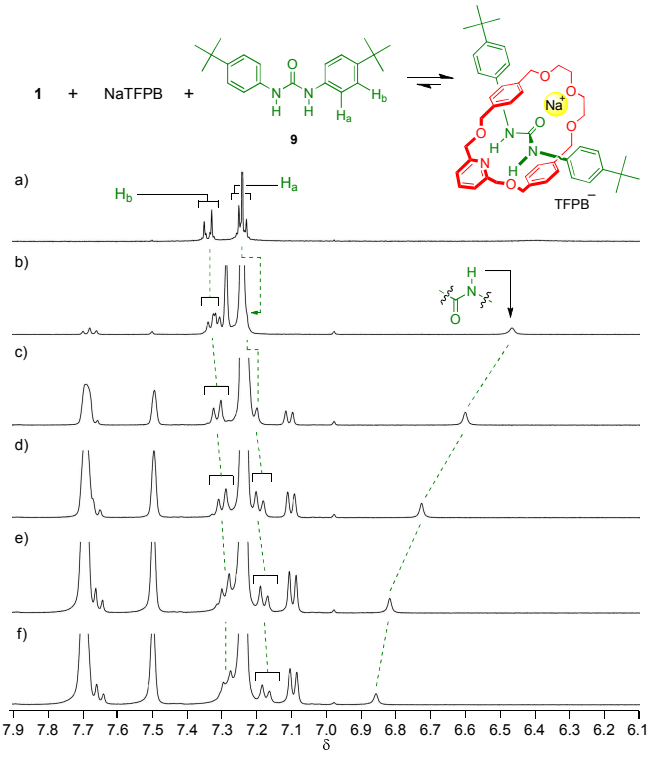


Figure 3. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of a) the threadlike urea **9**, b) an equimolar mixture of **1** and **9** (5 mM), and c–f) mixtures of **1**, **9**, and NaTFPB at concentrations of c) 5/5/5, d) 5/10/10, e) 5/15/15, and f) 5/20/20 mM.

We used the threadlike molecule **9**,[9] in which a urea unit is conjugated to two aromatic rings, to test whether these macrocycles could be employed to form [2]pseudorotaxane-like complexes under the influence of a templating Na^+ ion. Figure 3 presents the ^{1}H NMR spectrum of an equimolar (5 mM) mixture of the macrocycle **1** and the threadlike urea **9** in $CDCl_3$; it reveals significant shifts in the signals of the guest species after we added sodium tetrakis(3,5-trifluoromethylphenyl)borate (NaTFPB)[11] (5 mM)—a salt that experiences weak ion pairing in this solvent—to this solution. This observation suggested the importance of the Na^+ ion for its ability to template the efficient threading of **9** through the cavity of **1**. Upon gradually increasing the concentrations of the macrocycle **1** and NaTFPB from an initial equimolar mixture of the host, guest, and template (each 5 mM) to 20 mM, the signal of the NH protons and those of the aromatic protons H_a and H_b shifted downfield and upfield, respectively (Figures 3b–f). The shifts of these signals in the ^{1}H NMR spectra are consistent with the macrocycle **1** encircling

the urea unit, with the formation of [N–H···O] hydrogen bonds between the NH units of the urea moiety and the oxygen or nitrogen atoms of the 2,6-pyridinedimethanol motif leading to the downfield shift of the signal of the NH units. At the same time, the shielding of protons H_a and H_b by the *p*-xylene motifs of the macrocycle led to upfield shifts of their signals in the ^{1}H NMR spectra.

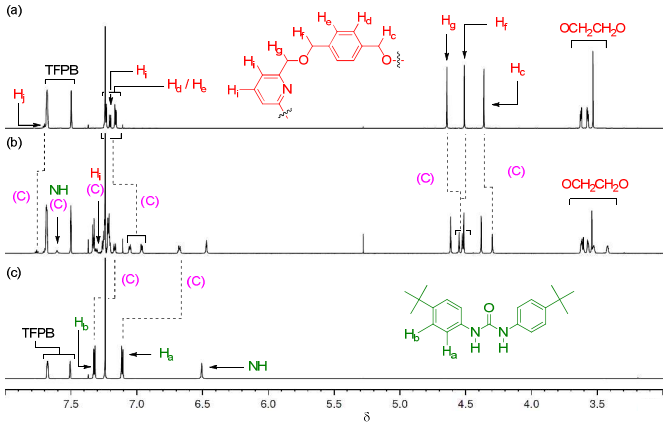
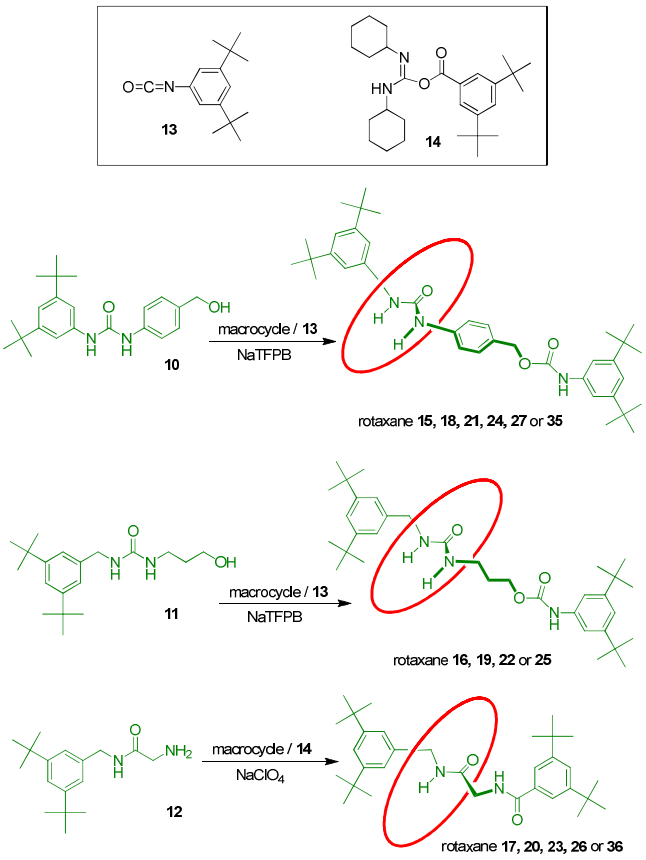


Figure 4. Partial ^{1}H NMR spectra (800 MHz, $CDCl_3$, 298 K) of a) an equimolar (5 mM) mixture of NaTFPB and the macrocycle **5**, b) an equimolar (5 mM) mixture of NaTFPB, **5**, and the threadlike urea **9**, and c) an equimolar (5 mM) mixture of NaTFPB and **9**. The descriptor (C) refers to the "complexed" state of the components.

We performed similar ^{1}H NMR titration experiments for equimolar (5 mM) mixtures of NaTFPB, the macrocycle **2** or **3**, and the threadlike urea **9** in $CDCl_3$; again, the templating effect of the Na^+ ion led to similar trends in the migration of the signal of the NH units of the urea moiety upon adding excess amounts of the macrocycle and NaTFPB, supporting the formation of Na^+ ion–containing [2]pseudorotaxanes in both cases (see Supporting Information). In contrast to the situations for the macrocycles **1**–**3**, where the rates of complexation and decomplexation to the threadlike urea **9** were both rapid on the ^{1}H NMR spectroscopic timescale at 400 MHz and 298 K, the complexation of the macrocycles **4** and **5** to the same guest occurred with slow exchange under similar conditions. Figure 4 reveals that the ^{1}H NMR spectra of an equimolar (5 mM) mixture of the macrocycle **5**, NaTFPB, and the threadlike urea **9** in $CDCl_3$ displayed an additional set of signals, which we assign to the Na^+ ion–templated [2]pseudorotaxane formed from the host **5** and the guest **9**, based on the significant upfield shifts of their aromatic protons (H_a, H_b, H_d, and H_e; determined from 2D COSY and NOESY spectra). Assuming infinite binding affinity between the macrocycle **5** and a Na^+ ion in $CDCl_3$, we determined (based on the single-point method)[12] the association constant (K_a) for the interaction between the Na^+ ion–complexed BPX26C6 and the threadlike urea **9** to be approximately 140 M^{-1}. The rates of complexation/decomplexation of the [2]pseudorotaxanes formed in solution from the guest **9** and the hosts **1**–**5** appear to be affected by more than the apparent cavity size of the macrocycle and the steric bulk of the terminal group of the threadlike urea; such behavior is consistent with the prior observation of the rates of threading/dethreading of a dibenzylammonium ion through the cavity of the "smaller" macrocycle dipyrido[24]crown-8 being faster than those through its "larger" analogue dibenzo[24]crown-8 in $CDCl_3$.[13] Nevertheless, although the spectroscopic evidence supported the formation of threaded complexes, we wished to synthesize corresponding [2]rotaxanes to prove unambiguously that [2]pseudorotaxanes did indeed form from these recognition components in solution.

[2]Rotaxane Syntheses

We synthesized the threadlike species **10**–**12** with anticipation that the formation of their [2]pseudorotaxanes in solution would lead to corresponding [2]rotaxanes after stoppering reactions (Scheme 2). For the threadlike urea derivatives **10** and **11**, we used the isocyanate **13** as the stoppering agent for the syntheses of the corresponding [2]rotaxanes. To demonstrate that the recognition of amide functionalities by the macrocycles **1**–**5** could be applied directly to the syntheses of interlocked or interwoven structures featuring pure peptide chains, without introducing any additional functionality (e.g., carbamate units, if isocyanate **13** was used) into the structure of the peptide thread, we employed a common peptide coupling reaction to attach the stoppering agent **14** to the threadlike amide **12**. Because sodium perchlorate



Scheme 2. Syntheses of [2]rotaxanes featuring various macrocyclic components.

($NaClO_4$) provided yields comparable with those obtained when using NaTFPB as the template, but with less-tedious purification, when synthesizing [2]rotaxanes from the amide **12** and BPX26C6, here we selected $NaClO_4$ as the templating salt for the assembly of amide-based [2]rotaxanes incorporating the macrocycles **1**–**5**. Thus, we mixed each of these macrocycles with NaTFPB or $NaClO_4$ and a threadlike guest (**10**, **11**, or **12**) in CH_2Cl_2 (250 mM:250 mM:100 mM) and then added a stoppering agent (**13** or **14**, 105 mM) to test whether we could isolate a corresponding [2]rotaxane after chromatographic purification (Table 1).[14] Notably, when we repeated the [2]rotaxane syntheses of the conjugated urea **10** and the non-conjugated amide **12** in the absence of NaTFPB, but under otherwise identical conditions, we observed no signals for the

corresponding interlocked molecules in the ^{1}H NMR spectra of the crude products (see Supporting Information). This result confirms the importance of the Na^+ ion template for efficient threading of the urea and amide units through the cavities of these macrocycles.

Our successful syntheses of the [2]rotaxanes **18**–**20** suggested that a Na^+ ion is also capable of templating the threading of a single conjugated or non-conjugated urea or amide functionality through the cavity of the macrocycle **1**. The comparable yields of the [2]rotaxanes synthesized using either BPX26C6 or **1** suggest that a 2,6-dihydroxymethylpyridine motif is a suitable replacement for a di(ethylene glycol) loop in the macrocycle in this system.[15] The presence of the pyridyl unit in macrocycle **1** provides the option of symmetrical functionalization at its 4-position, increasing the synthetic feasibility of using such intertwined or interlocked structures as vectors for chemically or biologically potent species. The ^{1}H NMR spectra of the purified [2]rotaxane **18** displayed no signal belonging to the TFPB counter anion of the templating Na^+ cation (Figure 5b); we suspect that the template was lost during the aqueous extraction and chromatography processes (i.e., the complexation of the templating Na^+ ion to the binding pocket in the [2]rotaxanes was not particularly strong under these conditions).

Table 1. [2]Rotaxanes synthesized from various macrocycles, threadlike components, and stoppering agents[a]

rotaxane	macrocycle interlocked	thread used	stoppering reagent used	yield (%)
15[b]	BPX26C6	**10**	**13**	40
16[b]	BPX26C6	**11**	**13**	8
17[b]	BPX26C6	**12**	**14**	28
18	**1**	**10**	**13**	38
19	**1**	**11**	**13**	10
20	**1**	**12**	**14**	24
21	**2**	**10**	**13**	9
22	**2**	**11**	**13**	–[c]
23	**2**	**12**	**14**	–[c]
24	**3**	**10**	**13**	8
25	**3**	**11**	**13**	–[c]
26	**3**	**12**	**14**	11
27	**4**	**10**	**13**	–[d]
31	**4**	**30**	**29**	13
34	**4**	**33**	**29**	10
35	**5**	**10**	**13**	43
36	**5**	**12**	**14**	11

[a] Reaction performed by mixing a macrocycle, NaTFPB, a threadlike component, and a stopping agent (250 mM/250 mM/100 mM/105 mM) in CH_2Cl_2. [b] See reference 9. [c] Corresponding [2]rotaxane was not obtained under these conditions. [d] The 3,5-di-*tert*-butylbenzyl terminus is not sufficiently sterically bulky to prevent dissociation of the macrocycle **4**.

Because guest complexation was not affected significantly after changing the central oxygen atom of one of the di(ethylene glycol) loops of BPX26C6 to the nitrogen atom of a pyridyl unit, we wished to test the hosting ability of the macrocycle **2**, in which we replaced the two terminal oxygen atoms of a di(ethylene glycol) loop with sulfur atoms. Although we expected weaker noncovalent

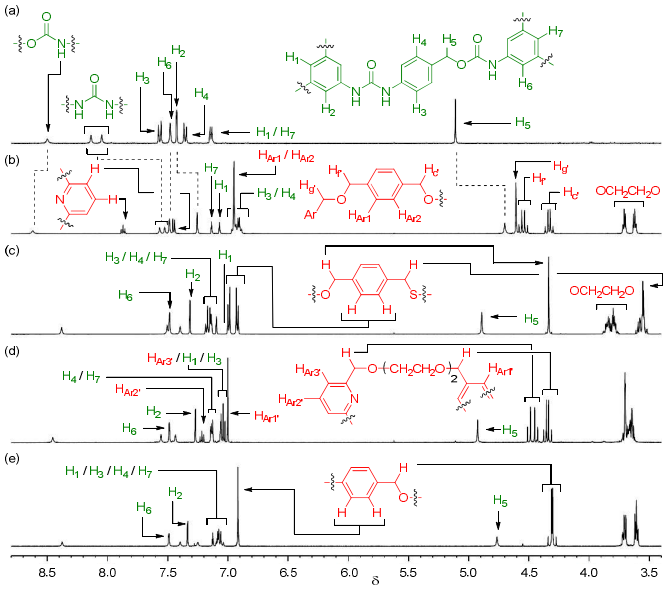


Figure 5. Partial ^{1}H NMR spectra (400 MHz, CD_3COCD_3, 298 K) of a) the dumbbell-shaped component of the [2]rotaxane **18** and b–e) the [2]rotaxanes b) **18**, c) **21**, d) **24**, and e) **15**.

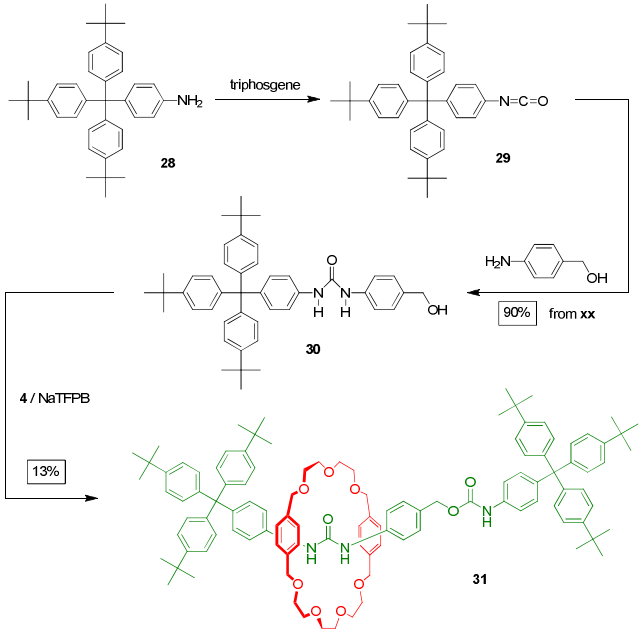
interactions between these sulfur atoms and the templating Na^+ ion and the NH proton(s) of the guests, we did obtain the urea-containing [2]rotaxane **21** in 9% yield. Thus, the recognition of a urea-containing threadlike molecule does not require the macrocycle to feature two di(ethylene glycol) moieties—a certain degree of structural flexibility through the incorporation of sulfur atoms is tolerated in the modification of the second di(ethylene glycol) loop. Nevertheless, the relatively low yield of the [2]rotaxane **21** and our inability to synthesize the [2]rotaxanes **22** and **23** from the threadlike guests **11** and **12** (featuring non-conjugated urea and amide groups, respectively) under similar conditions suggest limited utility of the macrocycle **2** in such host/guest systems.

We obtained the macrocycle **3** by replacing one of the *p*-xylyl groups of BPX26C6 with a 2,6-lutidinyl unit. When stoppering a mixture of this macrocycle and the threadlike conjugated urea **10**, we obtained the [2]rotaxane **24**, but in a disappointing isolated yield of only 8%. When we tested the threadlike non-conjugated urea **11** for its ability to serve as the guest unit under similar synthetic conditions, we did not observe any signals for the [2]rotaxane **25** in the ^{1}H NMR spectra of the crude product or of any of the fractions after chromatographic purification. We suspect that the low efficiencies of Na^+ ion templation in the assembly of the macrocycle **3** with these urea derivatives resulted from the relatively small ring (25 atoms; cf. 26 atoms for BPX26C6) and unfavorable conformation of the macrocycle, thereby weakening the ion–dipole interactions, [N–H···O] hydrogen bonds, and/or π-stacking interactions between the macrocycle **3** and the Na^+ ion template and/or the urea-containing guests. The same structural constraints presumably also affected the formation of the [2]pseudorotaxane from the macrocycle **3**, a Na^+ ion, and the non-conjugated amide **12**; although we isolated the corresponding [2]rotaxane **26**, its yield was low (11%) relative to those of the [2]rotaxanes **17** and **20**. Nevertheless, we confirmed that the macrocycle **3** has the ability to recognize non-conjugated amide functionalities when assisted by templating Na^+ ions.

To avoid overlap of the aromatic signals with the signal of the residual $CHCl_3$ in the NMR solvent and to increase the solubility of their dumbbell-shaped guest components, in Figure 5 we compare

the ^{1}H NMR spectra of the [2]rotaxanes **17**, **21**, **24**, and **15** in CD_3COCD_3, rather than in $CDCl_3$. Although this more polar solvent may weaken the potential hydrogen bonding interactions between the interlocked macrocyclic components and the urea and carbamate units in the dumbbell-shaped components, we observed upfield shifts in the signals of the terminal aromatic protons (H_2) adjacent to the urea stations, but nearly unchanged ones for protons H_6 next to the carbamate units of the dumbbell-shaped guests when interlocked with the macrocycles **1**–**3** or BPX26C6 in these four [2]rotaxanes; thus, these macrocycles still prefer, although possibly not too strongly, to reside on the urea station rather than the carbamate center in CD_3COCD_3 at room temperature.[16] We also observed significant upfield shifts in the signals for the benzylic (H_5) and aromatic (H_3, H_4) protons of the linking groups between the urea and carbamate stations in the ^{1}H NMR spectra of all four [2]rotaxanes, implying that the interlocked macrocyclic components did not reside at the urea and carbamate stations for very long under these conditions, possibly because CD_3COCD_3, a hydrogen-bond-competitive solvent, forced the macrocyclic components to interact with the aromatic linking groups instead. Among these four [2]rotaxanes, the ^{1}H NMR spectrum of **18** displayed the greatest upfield shifts of protons H_{3-5}, possibly because of extra shielding provided by the pyridyl group of its macrocyclic component or because its structural rigidity preorganized the macrocyclic component for enhanced aromatic stacking.

The macrocycle **4** is an analog of BPX26C6 in which one of the di(ethylene glycol) units has been replaced by a tri(ethylene glycol) loop. Although we expected the Na^+ ion–templated threading of urea and amide guests through this macrocycle to be feasible (because of its high structural similarity to BPX26C6), we experienced trouble with the purification of the [2]rotaxanes generated from the reactions of **4**, NaTFPB, the threadlike guests **10**–**12**, and the stoppering units **13** and **14**, presumably because of dissociation of the macrocyclic component **4** from the [2]rotaxanes. Indeed, we observed (^{1}H NMR spectroscopy) the free macrocycle **4** and the dumbbell-shaped component as the major species in a $CDCl_3$ solution of the chromatographically isolated "[2]rotaxane" **27** that had been left at room temperature for 16 h (Figure 6), confirming that a 3,5-di-*tert*-butylphenyl unit is not a true stopper for the macrocycle **4**.[17] Therefore, we synthesized the threadlike urea derivative **30**—from the reaction of 4-aminobenzyl alcohol with the trityl-derived isocyanate **29** transformed from the amine **28**[18]—and mixed it with the macrocycle **4**, NaTFPB, and the isocyanate **29** in CH_2Cl_2 (100 mM:250 mM:250 mM:105 mM) to afford the desired conjugated urea–based [2]rotaxane **31** in 13% yield (Scheme 3).



Scheme 3. Syntheses of [2]rotaxanes **31** featuring trityl stoppering groups to interlock the macrocycle **4**.

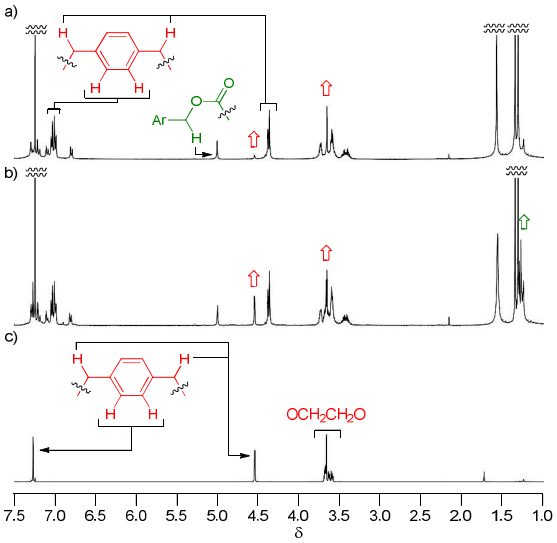
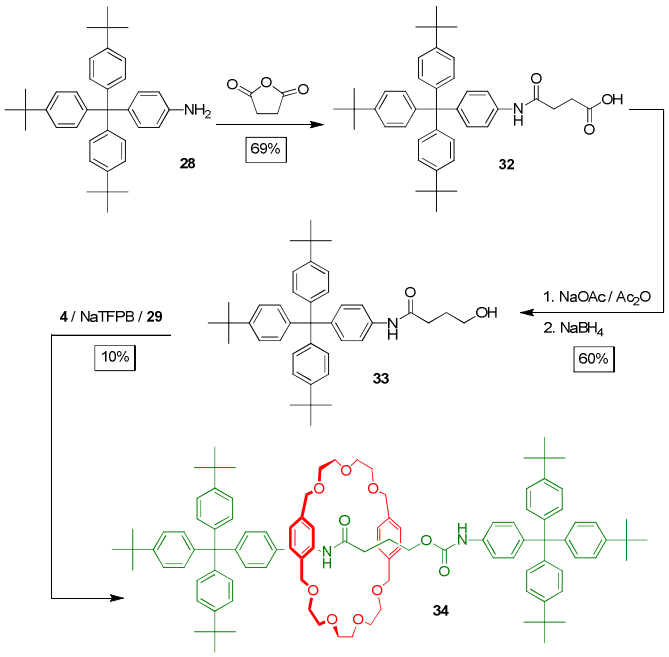


Figure 6. a, b) Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) revealing the dissociation of the macrocycle **4** from the solution of the [2]rotaxane **27** after a) 0 and b) 16 h. c) Corresponding spectrum of the macrocycle **4**.

Reacting succinic anhydride with the amine **28** gave the



Scheme 4. Synthesis of the [2]rotaxane **34** featuring trityl stoppering groups to interlock the macrocycle **4**.

carboxylic acid **32**, which we then transformed into the corresponding succinimide (Scheme 4). Subsequent $NaBH_4$-mediated reduction afforded the trityl-terminated conjugated amide **33**, which we tested for its ability to recognize the macrocycle **4** in the presence of a Na^+ ion. Indeed, we isolated the corresponding [2]rotaxane **34** in 10% yield. The lower yields for the syntheses of the [2]rotaxanes **31** and **34**, relative to those for the BPX26C6-containing [2]rotaxanes **15** and **17**, suggested that the macrocycle **4** is more flexible and less preorganized for this Na^+ ion–templated self-assembly process, even though it contains an additional oxygen atom—relative to BPX26C6—for interaction with the metal template or NH groups of the threadlike urea **30** or amide **33**.

The macrocyclic component interlocked in the [2]rotaxane **35** is the macrocycle **5**, which features the di(ethylene glycol) motif of macrocycle **4** replaced by a 2,6-bis(hydroxymethyl)pyridine unit. It appears that the ring size of **5** is smaller than that of **4**, because the 3,5-di-*tert*-butylphenyl group was a true stopper for the macrocycle **5**, allowing us to isolate the [2]rotaxane **35** in 43% yield after column chromatography. The comparable yields for the [2]rotaxanes **35** and **15** suggest that the structural rigidity of the 2,6-bis(hydroxymethyl)pyridine unit and the extra oxygen atom in the tri(ethylene glycol) loop of the macrocycle **5** overcame the negative structural effects of its increased size, relative to that of BPX26C6, when recognizing the conjugated urea guest. The macrocycle **5** can also form [2]pseudorotaxanes with threadlike non-conjugated amide derivatives in the presence of templating Na^+ ions; we synthesized such a [2]rotaxane, **36**, from a mixture of **5**, NaTFPB, the threadlike non-conjugated amide derivative **12**, and the stoppering agent **14**.

Conclusions

We have demonstrated that the macrocycles **1**–**5**, all of which are analogues of BPX26C6, are also capable of recognizing single urea and/or amide functionalities in the presence of templating Na^+ ions, forming [2]pseudorotaxanes. Our ability to isolate corresponding [2]rotaxanes not only confirmed the formation of the [2]pseudorotaxanes in solution but also indicated that metal ion–templated recognition is not unique to BPX26C6—indeed, it is a more general property shared with several macrocyclic analogues and derivatives. Thus, we believe that this highly flexible molecular recognition system might be useful for introducing interlocked structures into various potent molecules or (bio)polymers featuring one or more urea or amide functionalities; we are currently investigating new avenues of research in this direction.

Experimental

General: All glassware, stirrer bars, syringes, and needles were either oven- or flame-dried prior to use. All reagents, unless otherwise indicated, were obtained from commercial sources. Anhydrous CH_2Cl_2 and MeCN were obtained by distillation from CaH_2 under N_2. Reactions were conducted under N_2 or Ar atmospheres. Thin layer chromatography (TLC) was performed on Merck 0.25 mm silica gel (Merck Art. 5715). Column chromatography was performed using Kieselgel 60 (Merck, 70–230 mesh). Melting points were determined using a Fargo MP-2D melting point apparatus. For NMR spectroscopy, the deuterated solvent was used as the lock, while either the solvent's residual protons or TMS was employed as the internal standard. Chemical shifts are reported in parts per million (ppm). Multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad).

Dibromide 6: NaH (2.10 g, 52.3 mmol) was added to a solution of di(ethylene glycol) (2.22 g, 20.9 mmol) in THF (200 mL) and then the mixture was stirred at room temperature for 30 min. Dibromo-*p*-xylene (22.1 g, 83.7 mmol) was added to the mixture, which was then heated under reflux for 16 h. The solvent was evaporated under reduced pressure and the residue purified (SiO_2; EtOAc/hexanes, 1:5) to afford a colorless oil (3.84 g, 39%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.60–3.65 (m, 4H), 3.65–3.70 (m, 4H), 4.47 (s, 4H), 4.54 (s, 4H), 7.29 (d, *J* = 8 Hz, 4H), 7.34 (d, *J* = 8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.3, 69.6, 70.7, 72.7, 128.0, 129.1, 137.0, 138.7; HRMS (ESI) *m*/*z* $[M + H]^+$: $C_{20}H_{25}Br_2O_3$, calcd. 471.0170, found 471.0197.

Macrocycle 1: A solution of the dibromide **6** (4.28 g, 9.05 mmol) and 2,6-pyridinedimethanol (1.26 g, 9.05 mmol) in DMF (200 mL) was added to a suspension of NaH (2.17 g, 54.3 mmol) and K_2CO_3 (7.49 g, 54.3 mmol) in DMF (700 mL) and then the mixture was stirred at room temperature for 7 days. The solvent was evaporated under reduced pressure and the residue partitioned between CH_2Cl_2 (2 × 250 mL) and water (250 mL). The combined organic phases were dried ($MgSO_4$) and concentrated; the residue was purified (SiO_2; EtOAc/hexanes, 4:6) to afford a white solid (1.04 g, 26%). M.p. 78–79 °C; ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 3.60–3.66 (m, 8H), 4.51 (s, 4H), 4.54 (s, 4H), 4.61 (s, 4H), 7.31 (s, 8H), 7.39 (d, *J* = 7.6 Hz, 2H), 7.80 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 70.3, 71.4, 71.9, 72.5, 73.1, 122.1, 128.2, 128.9, 137.9, 138.3, 139.2, 158.6; HRMS (ESI) *m*/*z* $[M + H]^+$: $C_{27}H_{32}NO_5$, calcd. 450.2280, found 450.2273.

Macrocycle 2: A solution of the dibromide **6** (3.24 g, 6.87 mmol) and bis(2-mercaptoethyl) ether (950 mg, 6.87 mmol) in toluene (1 L) was added to a solution of KOH (1.38 g, 24.6 mmol) in EtOH (2.1 L) and then the mixture was stirred at room temperature for 5 days. The solvent was evaporated under reduced pressure and the residue partitioned between CH_2Cl_2 (2 × 250 mL) and water (250 mL). The combined organic phases were dried ($MgSO_4$) and concentrated; the residue was purified (SiO_2; EtOAc/hexanes, 1:2) to afford a white solid (2.26 g, 73%). M.p. 66–67 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.52 (t, *J* = 6.4 Hz, 4H), 3.54 (t, *J* = 6.4 Hz, 4H), 3.64–3.71 (m, 8H), 3.76 (s, 4H), 4.56 (s, 4H), 7.25 (d, *J* = 7 Hz, 4H), 7.28 (d, *J* = 7 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.0, 36.1, 69.5, 70.8, 70.8, 72.7, 127.6, 129.0, 137.2, 137.4; HRMS (ESI) *m*/*z* $[M + H]^+$: $C_{24}H_{33}O_4S_2$, calcd. 449.1820, found 449.1858

Diol 7: NaH (910 mg, 22.7 mmol) was added to a solution of di(ethylene glycol) (4.83 g, 45.5 mmol) in THF (20 mL) and then the mixture was stirred at room temperature for 30 min. Dibromo-*p*-xylene (2.00 g, 7.58 mmol) was added to the mixture, which was then heated under reflux for 16 h. The solvent was evaporated under reduced pressure and the residue partitioned between CH_2Cl_2 (2 × 50 mL) and water (50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated; the residue was purified (SiO_2; MeOH/CH_2Cl_2, 1:9) to afford a colorless oil (1.78 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.52–3.62 (m, 8H), 3.62–3.72 (m, 8H), 4.53 (s, 4H), 7.30 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 61.7, 69.4, 70.4, 72.4, 73.0, 127.9, 137.5; HRMS (ESI) *m*/*z* $[M + H]^+$: $C_{16}H_{27}O_6$, calcd. 315.1808, found 315.1832.

Macrocycle 3: A solution of the diol **7** (7.92 g, 25.2 mmol) and 2,6-pyridinedimethanol ditosylate (11.3 g, 25.2 mmol) in THF (200 mL) was added to a suspension of NaH (5.04 g, 126 mmol) in THF (800 mL) and then the mixture was heated under reflux for 3 days. The solvent was evaporated under reduced pressure and the residue partitioned between CH_2Cl_2 (2 × 500 mL) and water (500 mL). The

combined organic phases were dried ($MgSO_4$) and concentrated; the residue was purified (SiO_2; MeOH/EtOAc/hexanes, 2:49:49) to afford a colorless oil (2.20 g, 21%). ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 3.62–3.70 (m, 12H), 3.72–3.77 (m, 4H), 4.52 (s, 4H), 4.67 (s, 4H), 7.26 (s, 4H), 7.37–7.41 (m, 3H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 70.5, 71.1, 71.6, 71.9, 73.3, 74.7, 120.0, 128.3, 137.9, 138.9, 159.4; HRMS (ESI) *m/z* $[M + H]^+$: $C_{23}H_{32}NO_6$, calcd. 418.2230, found 418.2269.

Dibromide 8: NaH (8.00 g, 200 mmol) was added to a solution of tri(ethylene glycol) (12.0 g, 80.0 mmol) in THF (800 mL) and then the mixture was stirred at room temperature for 30 min. Dibromo-*p*-xylene (84.5 g, 320 mmol) was added to the mixture, which was then heated under reflux for 16 h. The solvent was evaporated under reduced pressure and the residue purified (SiO_2; EtOAc/hexanes, 3:7) to afford a colorless oil (21.8 g, 53%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.59–3.70 (m, 12H), 4.45 (s, 4H), 4.52 (s, 4H), 7.29 (d, *J* = 8 Hz, 8H), 7.33 (d, *J* = 8 Hz, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.2, 69.4, 70.4, 70.5, 72.5, 127.8, 128.9, 136.8, 138.5; HRMS (ESI) *m/z* $[M + H]^+$: $C_{22}H_{29}Br_2O_4$, calcd. 515.0433, found 515.0468.

Macrocycle 4: A solution of the dibromide **8** (4.67 g, 9.05 mmol) and di(ethylene glycol) (960 mg, 9.05 mmol) in DMF (200 mL) was added to a suspension of NaH (1.81 g, 45.2 mmol) and K_2CO_3 (6.24 g, 45.2 mmol) in DMF (800 mL) and then the mixture was stirred at room temperature for 7 days. The solvent was evaporated under reduced pressure and the residue partitioned between CH_2Cl_2 (2 × 250 mL) and water (250 mL). The combined organic phases were dried ($MgSO_4$) and concentrated; the residue was purified (SiO_2; EtOAc/hexanes, 4:6) to afford a colorless oil (500 mg, 12%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.58–3.69 (m, 20H), 4.54 (s, 4H), 4.54 (s, 4H), 7.27 (s, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 69.3, 70.6, 70.7, 70.7, 72.7, 72.8, 127.5, 127.5, 137.4, 137.6 (one signal was missing, possibly because of signal overlap); HRMS (ESI) *m/z* $[M + Na]^+$: $C_{26}H_{36}O_7Na$, calcd. 483.2359, found 483.2344.

Macrocycle 5: A solution of the dibromide **8** (5.22 g, 10.1 mmol) and 2,6-pyridinedimethanol (1.41 g, 10.1 mmol) in THF (200 mL) was added to a suspension of NaH (2.02 g, 50.6 mmol) in THF (800 mL) and then the mixture was heated under reflux for 3 days. The solvent was evaporated under reduced pressure and the residue partitioned between CH_2Cl_2 (2 × 500 mL) and water (500 mL). The combined organic phases were dried ($MgSO_4$) and concentrated; the residue was purified (SiO_2; MeOH/EtOAc/hexanes, 2:49:49) to afford a white solid (850 mg, 17%). M.p. 96–97 °C; ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 3.54–3.64 (m, 12H), 4.51 (s, 4H), 4.51 (s, 4H), 4.63 (s, 4H), 7.29 (d, *J* = 8 Hz, 4H), 7.30 (d, *J* = 8 Hz, 4H), 7.39 (d, *J* = 7.6 Hz, 2H), 7.78 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 70.5, 71.5, 71.6, 72.4, 72.8, 73.3, 121.8, 128.4, 128.9, 138.0, 138.5, 139.3, 158.8; HRMS (ESI) *m/z* $[M + H]^+$: $C_{29}H_{36}NO_6$, calcd. 494.2543, found 494.2492; $[M + Na]^+$: $C_{29}H_{35}NO_6Na$, calcd. 516.2362, found 516.2306.

Isocyanate 29: A solution of triphosgene (88.0 mg, 0.298 mmol) in toluene (140 mL) was added to a solution of the amine **28** (300 mg, 0.596 mmol) and Et_3N (0.414 mL, 2.98 mmol) in toluene (20 mL) at 0 °C and then the mixture was warmed to room temperature and stirred for 16 h. After filtration, the filtrate was concentrated under reduced pressure to afford a yellow solid (284 mg, 90%), which was used directly without further purification.

Urea 30: A solution of the isocyanate **29** [transformed from 264 mg (0.524 mmol) of the amine **28** in THF (3 mL)] was added to a solution of 4-aminobenzyl alcohol (61.0 mg, 0.496 mmol) in THF (3 mL) and then the mixture was stirred at room temperature for 16 h. The solvent was evaporated under reduced pressure and then the residue was purified (SiO_2; MeOH/CH_2Cl_2, 2:98) to afford a white solid (276 mg, 90%). M.p. 246–247 °C; ^{1}H NMR (400 MHz, CD_3SOCD_3): δ = 1.25 (s, 27H), 4.41 (d, *J* = 5.6 Hz, 2H), 5.06 (t, *J* = 5.6 Hz, 1H), 7.04 (d, *J* = 8.8 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 6H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.25–7.34 (m, 8H), 7.37 (d, *J* = 8.4 Hz, 2H), 8.63 (s, 1H), 8.64 (s, 1H); ^{13}C NMR (100 MHz, CD_3SOCD_3): δ = 31.2, 34.1, 62.7, 62.8, 117.5, 117.9, 124.4, 127.2, 130.0, 130.7, 135.9, 137.3, 138.4, 140.3, 144.0, 147.8, 152.6; HRMS (ESI) *m/z* $[M + H]^+$: $C_{45}H_{53}N_2O_2$, calcd. 653.4107, found 653.4133.

Carboxylic Acid 32: A solution of the amine **28** (544 mg, 1.08 mmol) in toluene (1.5 mL) was added slowly to a solution of succinic anhydride (108 mg, 1.08 mmol) in toluene (50 mL) and then the mixture was stirred at room temperature for 3 h. The solution was then partitioned between EtOAc (50 mL) and 10% $HCl_{(aq)}$ (50 mL); the organic phase was dried and concentrated to afford a white solid (449 mg, 69%). M.p. > 330 °C; ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 1.30 (s, 27H), 2.66 (s, 4H), 7.10–7.20 (m, 8H), 7.32 (d, *J* = 8.8 Hz, 6H), 7.55 (d, *J* = 8.8 Hz, 2H), 9.22 (s, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 31.7, 32.2, 35.0, 64.2, 119.0, 125.2, 131.5, 132.1, 138.3, 143.0 145.2, 149.3, 170.9, 174.1 (one signal was missing, possibly because of signal overlap); HRMS (ESI) *m/z* $[M - H]^-$: $C_{41}H_{48}NO_3$, calcd. 602.3634, found 602.3671.

Amide 33: A mixture of the carboxylic acid **32** (150 mg, 0.248 mmol) and NaOAc (10.2 mg, 0.124 mmol) in dry Ac_2O (5 mL) was heated at 75 °C with stirring for 5 h. After cooling to room temperature, the solvent was evaporated under reduced pressure and the residue partitioned between water (20 mL) and CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with $NH_4Cl_{(aq)}$ (50 mL), dried ($MgSO_4$), and concentrated. The crude succinimide was dissolved in isopropyl alcohol (2 mL) and THF (2 mL); $NaBH_4$ (47.3 mg, 1.25 mmol) was added at 0 °C and then the mixture was stirred at room temperature for 16 h. After partitioning between water (20 mL) and CH_2Cl_2 (2 × 20 mL), the combined organic phases were dried ($MgSO_4$) and concentrated; the residue was purified (SiO_2; EtOAc/hexanes, 1:1) to afford a white solid (87.6 mg, 60%). M.p. 293–294 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (s, 27H), 1.95 (quint, *J* = 6 Hz, 2H), 2.50 (t, *J* = 6.4 Hz, 2H), 3.73 (t, *J* = 5.6 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 6H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 6H), 7.34 (d, *J* = 8 Hz, 2H), 7.44 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.9, 31.4, 34.3, 34.8, 62.3, 63.3, 118.6, 124.1, 130.7, 131.8, 135.3, 143.6, 143.8, 148.4, 171.5; HRMS (ESI) *m/z* $[M + H]^+$: $C_{41}H_{52}NO_2$, calcd. 590.3998, found 590.3968.

[2]Rotaxane 18: A solution of the urea derivative **10** (421 mg, 1.19 mmol), the macrocycle **1** (1.33 g, 2.97 mmol), and NaTFPB (2.63 g, 2.97 mmol) in CH_2Cl_2 (5 mL) was added to a solution of the isocyanate **13** [transformed from 1.23 g (5.94 mmol) of 3,5-di-*tert*-butylaniline] and di-*n*-butyltintin dilaurate (220 μL, 0.356 mmol) in CH_2Cl_2 (5 mL) and then the mixture was stirred at room temperature for 16 h. The solvent was evaporated under reduced pressure and then the residue was purified (SiO_2; EtOAc/hexanes, 3:7) to afford a white solid (465 mg, 38%). M.p. 111–112 °C; ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 1.32 (s, 18H), 1.34 (s, 18H), 3.59–3.65 (m, 4H), 3.65–3.72 (m, 4H), 4.30 (d, *J* = 12 Hz, 2H), 4.36 (d, *J* = 12 Hz, 2H), 4.50 (d, *J* = 12 Hz, 2H), 4.58 (d, *J* = 12 Hz, 2H), 4.60 (s, 4H), 4.67 (s, 2H), 6.85–7.00 (m, 12H), 7.08 (t, *J* = 1.6 Hz, 1H), 7.14 (t, *J* = 1.6 Hz, 1H), 7.28 (d, *J* =1.6 Hz, 2H), 7.44 (d, *J* = 7.6 Hz, 2H), 7.49 (d, *J*= 1.2 Hz, 2H), 7.57 (s, 1H), 7.60 (s, 1H), 7.85 (t, *J* = 7.6 Hz, 1H), 8.64 (s, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 31.9, 32.0, 35.5, 35.6, 66.5, 69.6, 71.4, 72.3, 73.3, 73.5, 113.7, 114.0, 116.1, 117.1, 119.1, 121.2, 128.7, 128.9, 128.9, 130.7, 137.6, 138.4, 138.5, 140.1, 140.3, 140.8, 151.5, 151.9, 152.3, 154.3, 159.0; HRMS (ESI) *m/z* $[M + H]^+$: $C_{64}H_{83}N_4O_8$, calcd. 1035.6211, found 1035.6189.

[2]Rotaxane 19: A solution of the urea derivative **11** (163 mg, 0.509 mmol), the macrocycle **1** (572 mg, 1.27 mmol), and NaTFPB (1.13 g, 1.27 mmol) in CH_2Cl_2 (2.5 mL) was added to a solution of the isocyanate **13** [transformed from 523 mg (2.54 mmol) of 3,5-di-*tert*-butylaniline] and di-*n*-butyltintin dilaurate (94.5 μL, 0.152 mmol) in CH_2Cl_2 (2.5 mL) and then the mixture was stirred at room temperature for 16 h. The solvent was evaporated under reduced pressure and then the residue was purified (SiO_2; MeOH/EtOAc/hexanes, 2:49:49) to afford a colorless oil (51 mg, 10%). ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 0.80 (t, *J* = 6.4 Hz, 2H), 1.31 (s, 18H), 1.31 (s, 18H), 2.30–2.32 (m, 2H), 3.27 (t, *J* = 6 Hz, 2H), 3.56–3.65 (m, 8H), 4.12 (d, *J* = 5.6 Hz, 2H), 4.35 (s, 4H), 4.49 (s, 4H), 4.55 (s, 4H), 4.82 (t, *J* = 5.2 Hz, 1H), 5.47 (t, *J* = 5.2 Hz, 1H), 7.11 (t, *J* = 1.6 Hz, 1H), 7.11–7.20 (m, 10H), 7.34–7.40 (m, 5H), 7.77 (t, *J* = 7.6 Hz, 1H), 8.49 (s, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 31.9, 32.0, 35.5, 35.6, 37.6, 45.3, 63.7, 70.1, 71.4, 72.2, 73.4, 73.8, 113.5, 116.8, 121.3, 121.6, 123.3, 129.6, 129.7, 138.0, 138.4, 138.6, 140.3, 141.1, 151.4, 151.9, 154.2, 158.5, 158.6 (one signal was missing, possibly because of signal overlap); HRMS (ESI) *m*/*z* [M + H]$^+$: $C_{61}H_{85}N_4O_8$, calcd. 1001.6367, found 1001.6393.

[2]Rotaxane 20: A solution of 3,5-di-*tert*-butylbenzoic acid (235 mg, 1.00 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (207 mg, 1.00 mmol) in CH_2Cl_2 (2 mL) was stirred at 0 °C for 2 h and then added to a solution of the amide **12** (110 mg, 0.398 mmol), the macrocycle **1** (450 mg, 1.00 mmol), and $NaClO_4$ (122 mg, 1.00 mmol) in CH_2Cl_2 (2 mL). The solution was stirred at room temperature for 16 h before the solvent was evaporated under reduced pressure and the residue purified (SiO_2; MeOH/EtOAc/hexanes, 2:49:49) to afford a white solid (91.3 mg, 24%). M.p. 127–128 °C; ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 1.30 (s, 18H), 1.34 (s, 18H), 3.10 (d, *J* = 5.2 Hz, 2H), 3.43–3.60 (m, 8H), 3.84 (d, *J* = 5.2 Hz, 2H), 4.28–4.38 (m, 8H), 4.52 (d, *J* = 12 Hz, 2H), 4.59 (d, *J* = 12 Hz, 2H), 7.08–7.17 (m, 11H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.35 (s, 1H), 7.37 (t, *J* = 2 Hz, 1H), 7.47 (s, 1H), 7.58 (s, 3H), 7.74 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 31.9, 32.0, 35.4, 35.6, 43.4, 44.5, 69.9, 71.2, 71.9, 73.0, 73.8, 121.0, 121.8, 122.9, 124.2, 125.4, 129.4, 129.6, 136.4, 137.9, 138.0, 138.3, 139.3, 151.0, 151.1, 158.5, 167.9, 168.5; HRMS (ESI) *m*/*z* [M + H]$^+$: $C_{59}H_{80}N_3O_7$, calcd. 942.5996, found 942.6056; [M + Na]$^+$: $C_{59}H_{79}N_3O_7Na$, calcd. 964.5816, found 964.5868.

[2]Rotaxane 21: A solution of the urea derivative **10** (94.7 mg, 0.267 mmol), the macrocycle **2** (300 mg, 0.669 mmol), and NaTFPB (593 mg, 0.669 mmol) in CH_2Cl_2 (1 mL) was added to a solution of the isocyanate **13** [transformed from 275 mg (1.33 mmol) of 3,5-di-*tert*-butylaniline] and di-*n*-butyltin dilaurate (49.7 μL, 0.080 mmol) in CH_2Cl_2 (1 mL) and then the mixture was stirred at room temperature for 16 h. The solvent was evaporated under reduced pressure and then the residue was purified (SiO_2; EtOAc/hexanes, 1:3) to afford a white solid (24.7 mg, 9%). M.p. 95–96 °C; ^{1}H NMR (400 MHz, CD_3CN): δ = 1.30 (s, 18H), 1.35 (s, 18H), 2.44–2.58 (m, 4H), 3.45–3.56 (m, 8H), 3.67–3.80 (m, 8H), 4.30 (s, 4H), 4.91 (s, 2H), 6.90 (d, *J* = 8 Hz, 4H), 6.94 (d, *J* = 8 Hz, 4H), 7.03 (d, *J* = 8.4 Hz, 2H), 7.05–7.18 (m, 4H), 7.22 (d, *J* =1.6 Hz, 3H), 7.30–7.33 (m, 3H), 7.70 (s, 1H); ^{13}C NMR (100 MHz, CD_3CN): δ = 30.1, 31.7, 31.8, 35.5, 35.6, 36.0, 67.0, 69.9, 70.4, 71.6, 73.8, 113.8, 114.0, 116.5, 118.8, 128.7, 129.2, 129.3, 130.2, 136.6, 138.6, 139.2, 140.5, 140.6, 151.7, 152.0, 152.1, 154.3 (one signal was missing, possibly because of signal overlap); HRMS (ESI) *m*/*z* [M + H]$^+$: $C_{61}H_{84}N_3O_7S_2$, calcd. 1034.5751, found 1034.5788.

[2]Rotaxane 24: A solution of the urea derivative **10** (187 mg, 0.528 mmol), the macrocycle **3** (550 mg, 1.32 mmol), and NaTFPB (1.17 g, 1.32 mmol) in CH_2Cl_2 (2.5 mL) was added to a solution of the isocyanate **13** [transformed from 541 mg (2.64 mmol) of 3,5-di-*tert*-butylaniline] and di-*n*-butyltin dilaurate (98.0 μL, 0.158 mmol) in CH_2Cl_2 (2.5 mL) and then the mixture was stirred at room temperature for 16 h. The solvent was evaporated under reduced pressure and then the residue was purified (SiO_2; MeOH/EtOAc/hexanes, 2:49:49) to afford a white solid (40.0 mg, 8%). M.p. 92–93 °C; ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 1.32 (s, 18H), 1.36 (s, 18H), 3.61–3.75 (m, 16H), 4.31 (d, *J* = 12 Hz, 2H), 4.36 (d, *J* = 12 Hz, 2H), 4.44 (d, *J* = 12.4 Hz, 2H), 4.49 (d, *J* = 12.4 Hz, 2H), 4.92 (s, 2H), 7.00–7.10 (m, 9H), 7.11–7.15 (m, 3H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 1.2 Hz, 2H), 7.44 (s, 1H), 7.48 (s, 2H), 7.56 (s, 1H), 8.47 (s, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 31.9, 32.0, 35.5, 66.9, 69.2, 70.3, 71.1, 71.2, 73.7, 74.7, 113.8, 115.9, 117.2, 118.8, 121.3, 128.9, 129.4, 130.1, 137.3, 138.1, 139.9, 141.0, 141.0, 151.4, 151.9, 152.4, 154.5, 158.1 (two signals were missing, possibly because of signal overlap); HRMS (ESI) *m*/*z* [M + H]$^+$: $C_{60}H_{83}N_4O_9$, calcd. 1003.6160, found 1003.6122.

[2]Rotaxane 26: A solution of 3,5-di-*tert*-butylbenzoic acid (262 mg, 1.12 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (231 mg, 1.12 mmol) in CH_2Cl_2 (2.25 mL) was stirred at 0 °C for 2 h and then added to a solution of the amide **12** (124 mg, 0.449 mmol), the macrocycle **3** (468 mg, 1.12 mmol), and $NaClO_4$ (137 mg, 1.12 mmol) in CH_2Cl_2 (2.25 mL). After stirring the mixture at room temperature for 16 h, the solvent was evaporated under reduced pressure and then the residue was purified (SiO_2; MeOH/EtOAc/hexanes, 2:49:49) to afford a white solid (44.9 mg, 11%). M.p. 165–166 °C; ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 1.24 (s, 18H), 1.33 (s, 18H), 3.35–3.71 (m, 18H), 4.07 (d, *J* = 12 Hz, 2H), 4.13 (d, *J* = 6 Hz, 2H), 4.28–4.41 (m, 6H), 6.93 (d, *J*= 7.6 Hz, 2H), 7.00 (s, 4H), 7.08 (d, *J* = 1.6 Hz, 2H), 7.30–7.36 (m, 2H), 7.47 (s, 3H), 7.58 (t, *J* = 5.6 Hz, 1H), 8.40 (t, *J* = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 31.9, 32.0, 35.3, 35.6, 44.0, 44.5, 69.4, 70.6, 71.1, 71.1, 73.6, 73.8, 120.9, 121.7, 123.2, 124.2, 125.0, 129.3, 134.9, 137.3, 138.2, 140.3, 150.1, 151.1, 158.2, 167.0, 170.2; HRMS (ESI) *m*/*z* [M + H]$^+$: $C_{55}H_{80}N_3O_8$, calcd. for 910.5945, found 910.5978; [M + Na]$^+$: $C_{55}H_{79}N_3O_8Na$, calcd. 932.5765, found 932.5791.

[2]Rotaxane 31: A solution of the urea derivative **30** (250 mg, 0.383 mmol), the macrocycle **4** (536 mg, 1.15 mmol), and NaTFPB (1.02 g, 1.15 mmol) in CH_2Cl_2 (1.95 mL) was added to a solution of the isocyanate **29** [transformed from 964 mg (1.91 mmol) of the amine **28**] and di-*n*-butyltin dilaurate (71.2 μL, 0.115 mmol) in CH_2Cl_2 (1.95 mL) and then the mixture was stirred at room temperature for 16 h. The solvent was evaporated under reduced pressure and then the residue was purified (SiO_2; EtOAc/hexanes, 4:6) to afford a colorless oil (82.0 mg, 13%). ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 1.30 (s, 27H), 1.32 (s, 27H), 3.40–3.45 (m, 4H), 3.54–3.58 (m, 8H), 3.61 (s, 4H), 3.66–3.70 (m, 4H), 4.32–4.37 (m, 8H), 5.00 (s, 2H), 6.94–7.02 (m, 10H), 7.08 (d, *J* = 8.8 Hz, 2H), 7.13–7.20 (m, 14H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.30–7.37 (m, 14H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.54 (s, 1H), 7.70 (s, 1H), 8.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.4, 31.4, 34.3, 34.3, 63.2, 66.8, 68.8, 69.3, 70.6, 70.7, 70.9, 73.2, 117.1, 118.1, 124.0, 124.0, 127.7, 127.8, 127.9, 128.6, 128.8, 130.7, 130.8, 131.3, 131.8, 135.8, 136.7, 136.8, 137.2, 139.6, 140.5, 142.2, 143.9, 144.2, 148.2, 148.3, 151.4, 153.6 (two signals were missing, possibly because of signal overlap); HRMS (ESI) *m*/*z* [M + Na]$^+$: $C_{109}H_{131}N_3O_{10}Na$, calcd. 1664.9732, found 1665.0294.

[2]Rotaxane 34: A solution of the amide **33** (80.2 mg, 0.136 mmol), the macrocycle **4** (156 mg, 0.334 mmol), and NaTFPB (300 mg, 0.334 mmol) in CH_2Cl_2 (0.5 mL) was added to a solution of the isocyanate **29** [transformed from 341.6 mg (0.678 mmol) of the amine **28**] and di-*n*-butyltintin dilaurate (25.3 μL, 0.041 mmol) in CH_2Cl_2 (0.5 mL) and then the mixture was stirred at room

temperature for 16 h. The solvent was evaporated under reduced pressure and then the residue was purified (SiO_2; EtOAc/hexanes, 4:6) to afford a white solid (21.0 mg, 10%). M.p. 252–253 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80–0.90 (m, 2H), 1.29 (s, 54H), 1.53–1.65 (overlapping with the signal for water, 2H), 3.39–3.70 (m, 22H), 4.33–4.41 (m, 8H), 7.05–7.15 (m, 24H), 7.20–7.27 (m, 14H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.86 (s, 1H), 8.33 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.9, 29.7, 31.4, 32.8, 34.3, 63.2, 63.3, 69.2, 69.5, 70.6, 70.6, 70.8, 73.2, 73.3, 116.8, 117.9, 124.0, 128.3, 130.8, 131.6, 131.6, 136.7, 136.8, 137.1, 137.1, 141.2, 142.0, 144.1, 144.1, 148.3, 148.3, 153.7, 171.3 (five signals were missing, possibly because of signal overlap); HRMS (ESI) *m/z* [M + Na]$^+$: $C_{105}H_{130}N_2O_{10}Na$, calcd. 1601.9623, found 1602.0217.

[2]Rotaxane 35: A solution of the urea derivative **10** (56.7 mg, 0.160 mmol), the macrocycle **5** (197 mg, 0.400 mmol), and NaTFPB (355 mg, 0.400 mmol) in CH_2Cl_2 (0.8 mL) was added to a solution of the isocyanate **13** [transformed from 164 mg (0.800 mmol) of 3,5-di-*tert*-butylaniline] and di-*n*-butyltin dilaurate (30.3 μL, 0.048 mmol) in CH_2Cl_2 (0.8 mL) and then the mixture was stirred at room temperature for 16 h. The solvent was evaporated under reduced pressure and then the residue was purified (SiO_2; EtOAc/hexanes, 4:6) to afford a colorless oil (74.5 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 18H), 1.33 (s, 18H), 3.35–3.50 (m, 4H), 3.61–3.70 (m, 8H), 4.38 (s, 4H), 4.49–4.60 (m, 8H), 4.91 (s, 2H), 6.73 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 7.00–7.10 (m, 9H), 7.12 (d, *J* = 1.6 Hz, 1H), 7.18 (d, *J* = 1.6 Hz, 2H), 7.30 (s, 2H), 7.40 (d, *J* =7.6 Hz, 2H), 7.46 (s, 1H), 7.57 (s, 1H), 7.63 (s, 1H), 7.76 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 31.4, 31.5, 34.8, 34.8, 66.5, 69.0, 70.6, 70.9, 71.8, 73.0, 112.9, 113.2, 116.0, 117.1, 118.1, 120.6, 127.7, 128.2, 128.3, 128.4, 136.0, 137.4, 137.7, 137.7, 139.1, 139.2, 151.0, 151.5, 151.7, 153.7, 157.6 (one signal was missing, possibly because of signal overlap); HRMS (ESI) *m/z* [M + H]$^+$: $C_{66}H_{87}N_4O_9$, calcd. 1079.6473, found 1079.7648.

[2]Rotaxane 36: A solution of 3,5-di-*tert*-butylbenzoic acid (216 mg, 0.922 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (190 mg, 0.922 mmol) in CH_2Cl_2 (1.75 mL) was stirred at 0 °C for 2 h and then added to a solution of the amide **12** (102 mg, 0.369 mmol), the macrocycle **5** (455 mg, 0.922 mmol), and $NaClO_4$ (113 mg, 0.922 mmol) in CH_2Cl_2 (1.75 mL). After stirring the mixture at room temperature for 16 h, the solvent was evaporated under reduced pressure and then the residue was purified (SiO_2; MeOH/EtOAc/hexanes, 4:48:48) to afford a colorless oil (40.0 mg, 11%). ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 1.25 (s, 18H), 1.32 (s, 18H), 3.30–3.52 (m, 14H), 3.85 (d, *J* = 5.6 Hz, 2H), 4.39 (s, 4H), 4.45 (s, 4H), 4.59 (s, 4H), 6.99 (d, *J* = 1.6 Hz, 2H), 7.20 (d, *J* = 8Hz, 4H), 7.26 (m, 5H), 7.31 (t, *J* = 1.6 Hz, 1H), 7.37 (d, *J* = 7.6 Hz, 2H), 7.60–7.62 (m, 2H) 7.66 (d, *J* = 1.6 Hz, 2H), 7.75 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 31.9, 32.0, 35.4, 35.6, 43.9, 44.1, 70.4, 71.4, 71.5, 72.3, 72.8, 73.8, 121.1, 121.8, 122.9, 124.0, 125.9, 129.1, 129.3, 135.5, 138.0, 138.2, 138.6, 139.7, 151.1, 151.3, 158.9, 167.8, 169.2; HRMS (ESI) *m/z* [M + H]$^+$: $C_{61}H_{84}N_3O_8$, calcd. for 986.6258, found 986.6211; [M + Na]$^+$: $C_{61}H_{83}N_3O_8Na$, calcd. 1008.6078, found 1008.6021.

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1 (a) D. B. Amabilino and J. F. Stoddart, *Chem. Rev.*, 1995, **95**, 2725; (b) *Molecular Catenanes, Rotaxanes and Knots*; J.-P. Sauvage and C. Dietrich-Buchecker, Eds.; VCH-Wiley: Weinheim, **1999**; (c) E. R. Kay and D. A. Leigh, *Top. Curr. Chem.*, 2005, **262**, 133; (d) B. Champin, P. Mobian and J.-P. Sauvage, *Chem. Soc. Rev.*, 2007, **36**, 358; (e) J. E. Beves, B. A. Blight, C. J. Campbell, D. A. Leigh and R. T. McBurney, *Angew. Chem. Int. Ed.*, 2011, **50**, 9260.

2 (a) P. H. Kwan, M. J. MacLachlan and T. M. Swager, *J. Am. Chem. Soc.*, 2004, **126**, 8638; (b) N.-C. Chen, P.-Y. Huang, C.-C. Lai, Y.-H. Liu, Y. Wang, S.-M. Peng and S.-H. Chiu, *Chem. Commun.*, 2007, 4122; (c) O. Hayashida and M. Uchiyama, *Org. Biomol. Chem.*, 2008, **6**, 3166; (d) J. J. Gassensmith, S. Matthys, J.-J. Lee, A. Wojcik, P. V. Kamat and B. D. Smith, *Chem. Eur. J.*, 2010, **16**, 2916; (e) M. J. Chmielewski, J. J. Davis and P. D. Beer, *Org. Biomol. Chem.*, 2009, **7**, 415; (f) N. H. Evans, C. J. Serpell and P. D. Beer, *Chem. Commun.*, 2011, **47**, 8775.

3 (a) Y.-L. Zhao, I. Aprahamian, A. Trabolsi, N. Erina and J. F. Stoddart, *J. Am. Chem. Soc.*, 2008, **130**, 6348; (b) S.-Y. Hsueh, C.-T. Kuo, T.-W. Lu, C.-C. Lai, Y.-H. Liu, H.-F. Hsu, S.-M. Peng, C.-h. Chen and S.-H. Chiu, *Angew. Chem. Int. Ed.*, 2010, **49**, 9170; (c) Y. Kohsaka, K. Nakazono, Y. Koyama, S. Asai and T. Takata, *Angew. Chem. Int. Ed.*, 2011, **50**, 4872.

4 (a) J. W. Lee and K. Kim, *Top. Curr. Chem.*, 2003, **228**, 111; (b) X. Wang, X. Bao, M. McFarland-Mancini, I. Isaacsohn, A. F. Drew and D. B. Smithrud, *J. Am. Chem. Soc.*, 2007, **129**, 7284; (c) A. Fernandes, A. Viterisi, F. Coutrot, S. Potok, D. A. Leigh, V. Aucagne and S. Papot, *Angew. Chem. Int. Ed.*, 2009, **48**, 6443; (d) M. W. Ambrogio, T. A. Pecorelli, K. Patel, N. M. Khashab, A. Trabolsi, H. A. Khatib, Y. Y. Botros, J. I. Zink and J. F. Stoddart, *Org. Lett.*, 2010, **12**, 3304; (e) J. M. Baumes, J. J. Gassensmith, J. Giblin, J.-J. Lee, A. G. White, W. J. Culligan, W. M. Leevy, M. Kuno and B. D. Smith, *Nature Chem.*, 2010, **2**, 1025; (f) J. Berná, D. A. Leigh, M. Lubomska, S. M. Mendoza, E. M. Pérez, P. Rudolf, G. Teobaldi and F. Zerbetto, *Nat. Mater.*, 2005, **4**, 704.

5 (a) C. P. Collier, E. W. Wong, M. Belohradský, F. M. Raymo, J. F. Stoddart, P. J. Kuekes, R. S. Williams and J. R. Heath, *Science*, 1999, **285**, 391; (b) J. E. Green, J. W. Choi, A. Boukai, Y. Bunimovich, E. Johnston-Halperin, E. DeIonno, Y. Luo, B. A. Sheriff, K. Xu, Y. S. Shin, H.-R. Tseng, J. F. Stoddart and J. R. Heath, *Nature*, 2007, **445**, 414.

6 (a) B. L. Feringa, W. R. Browne, Eds. *Molecular Switches*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2011. For a recent review, see: (b) J. Berba, S. M. Goldup, A.-L. Lee, D. A. Leigh, M. D. Symes, G. Teobaldi and F. Zerbeto, *Angew. Chem. Int. Ed.*, 2008, **47**, 4392; (c) A. Coskun, M. Banaszak, R. D. Astumian, J. F. Stoddart and B. A. Grzybowski, *Chem. Soc. Rev.*, 2012, **41**, 19.

7 (a) E. Arunkumar, C. C. Forbes, B. C. Noll and B. D. Smith, *J. Am. Chem. Soc.*, 2005, **127**, 3288; (b) S.-Y. Hsueh, C.-C. Lai, Y.-H. Liu, S.-M. Peng and S.-H. Chiu, *Org. Lett.*, 2007, **9**, 4523; (c) A. Fernandes, A. Viterisi, F. Coutrot, S. Potok, D. A. Leigh, V. Aucagne and S. Papot, *Angew. Chem. Int. Ed.*, 2009, **48**, 6443.

8 (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 and S.-H. Chiu, *J. Org. Chem.*, 2006, **71**, 2373; (b) Y.-C. You, M.-C. Tzeng, C.-C. Lai and S.-H. Chiu, *Org. Lett.*, 2012, **14**, 1046.

9 Y.-H. Lin, C.-C. Lai, Y.-H. Liu, S.-M. Peng and S.-H. Chiu, *Angew. Chem. Int. Ed.*, 2013, **52**, 10231.

10 B. Cabezon, J. Cao, F. M. Raymo, J. F. Stoddart, A. J. P. White and D. J. Williams, *Chem. Eur. J.*, 2000, **6**, 2262.

11 The very weak ion-pairing tendency of the TFPB anion in less-polar solvents enhances the binding of its countercations as both threading

guests and templates; see: (a) C. Gaeta, F. Troisi and P. Neri, *Org. Lett.*, 2010, **12**, 2092; (b) N.-C. Chen, C.-J. Chuang, L.-Y. Wang, C.-C. Lai and S.-H. Chiu, *Chem. Eur. J.*, 2012, **18**, 1896; (c) L.-Y. Wang, J.-L. Ko, C.-C. Lai, Y.-H. Liu, S.-M. Peng and S.-H. Chiu, *Chem. Eur. J.*, 2013, **19**, 8850. For a discussion of ion-pairing behavior in the complexation of crown ethers and dialkylammonium ions in solvents having low dielectric constants, see (d) J. W. Jones and H. W. Gibson, *J. Am. Chem. Soc.*, 2003, **125**, 7001; (e) H. W. Gibson, J. W. Jones, L. N. Zakharov, A. L. Rheingold and C. Slebodnick, *Chem. Eur. J.*, 2011, **17**, 3192.

12 For a description of the single-point method, see: (a) P. R. Ashton, E. J. T. Chrystal, P. T. Glink, S. Menzer, C. Schiavo, N. Spencer, J. F. Stoddart, P. A. Tasker, A. J. P. White and D. J. Williams, *Chem. Eur. J.*, 1996, **2**, 709; (b) P. R. Ashton, M. C. T. Fyfe, S. K. Hickingbottom, J. F. Stoddart, A. J. P. White and D. J. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1998, 2117.

13 T. Chang, A. M. Heiss, S. J. Cantrill, M. C. T. Fyfe, A. R. Pease, S. J. Rowan, J. F. Stoddart, A. J. P. White and D. J. Williams, *Org. Lett.*, 2000, **2**, 2947.

14 We employed a catalytic amount of di-*n*-butyltintin dilaurate in the reactions of isocyanates with alcohols. Such reactions generally proceed extremely slowly at room temperature in the absence of a suitable catalyst; see: Y. Furusho, H. Sasabe, D. Natsui, K.-i Murakawa, T. Takata and T. Harada, *Bull. Chem. Soc. Jpn.*, 2004, **77**, 179.

15 Macrocycles featuring 2,6-pyridinedimethanol units can be used to synthesize rotaxanes through metal ion-templated "click" or Diels–Alder reactions; see: (a) V. Aucagne, K. D. Haenni, D. A. Leigh, P. J. Lusby and D. B. Walker, *J. Am. Chem. Soc.* 2006, **128**, 2186; (b) J. D. Crowley, K. D. Hanni, D. A. Leigh and A. M. Z. Slawin, *J. Am. Chem. Soc.* 2010, **132**, 5309.

16 A [2]rotaxane-type of molecular switch based on BPX26C6 and a diphenylurea recognition site had been constructed; see: T.-W. Lu, C.-F. Chang, C.-C. Lai and S.-H. Chiu, *Org. Lett.*, 2013, **15**, 5742.

17 The potential energy for the passage of the terminus of a threadlike guest through a macrocycle is related in a complex manner to the structures of the host/guest components and the noncovalent interactions between them in the transition state. For further discussions, see: (a) S.-H. Chiu, S. J. Rowan, S. J. Cantrill, P. T. Glink, R. L. Garrell and J. F. Stoddart, *Org. Lett.*, 2000, **2**, 3631; (b) Y. Tachibana, N. Kihara, Y. Furusho and T. Takata, *Org. Lett.*, 2004, **6**, 4507; (c) T. Matsumura, F. Ishiwari, Y. Koyama and T. Takata, *Org. Lett.*, 2010, **12**, 3828; (d) L.-Y. Wang, J.-L. Ko, C.-C. Lai, Y.-H. Liu, S.-M. Peng and S.-H. Chiu, *Chem. Eur. J.*, 2013, **19**, 8850.

18 (a) H. W. Gibson, S.-H. Lee, P. T. Engen, P. Lecavalier, J. Sze, Y. X. Shen and M. Bheda, *J. Org. Chem.*, 1993, **58**, 3748; (b) S. Altobello, K. Nikitin, J. K. Stolarczyk, E. Lestini and D. Fitzmaurice, *Chem. Eur. J.*, 2008, **14**, 1107.

