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# $Na^+$ Ion Templated Threading of Oligo(ethylene glycol) Chains through BPX26C6 Allows Synthesis of [2]Rotaxanes under Solvent-Free Conditions

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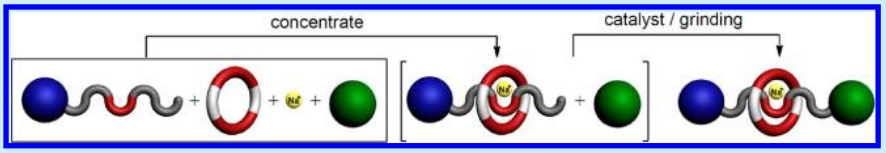
Supporting Information




**ABSTRACT:** Threading of di-, tri-, and tetra(ethylene glycol) through the macrocycle BPX26C6 in the presence of templating $Na^+$ ions was proven by the synthesis of the corresponding [2]rotaxanes under solvent-free conditions. Among them, a [2]rotaxane featuring both tetra(ethylene glycol) and carbamate stations behaves as a molecular switch that can be controlled reversibly through the application of the KTFPB/[2.2.2]cryptand reagent pair.

Ethylene glycol and its oligomers and polymers are applied widely in many fields, from industrial manufacturing to biological production.[1] In supramolecular chemistry, oligo(ethylene glycol) units have long been critical motifs within crown ethers, endowing them with the ability to complex various metal ions and to form pseudorotaxanes with various cationic guests, including dialkylammonium,[2] pyridinium,[3] and imidazonium ions.[4] Oligo(ethylene glycol) motifs also commonly appear in the molecular structures of typical crown ether–like macrocycles in interlocked molecular switches, not only for their ability to conveniently adjust the ring size but also to confer residual guest complexation properties. In contrast, although the threading of poly(ethylene glycol) chains through cyclodextrins has been applied to generate polypseudorotaxanes and polyrotaxanes in aqueous solution,[5] linear oligo(ethylene glycol)s are rarely applied as primary guest recognition units for synthetic hosts in the formation of interweaved and/or interlocked structures in common organic solvents.[6] Recently, we reported the self-assembly of a [2]catenane based on the orthogonal placement of two di(ethylene glycol) chains templated by the $Na^+$ ion.[7] We wished to test whether such a templating strategy could be applied to direct the threading of an oligo(ethylene glycol) chain through an oligo(ethylene glycol)-containing macrocycle, thereby facilitating the synthesis of corresponding rotaxanes (Figure 1). If relatively chemically inert, yet readily accessible and derivatized, oligo(ethylene glycol)s could become primary recognition units within rotaxanes, and it would also be possible to synthesize molecular switches having relatively simple and robust structures. Herein, we report the construction of [2]rotaxanes based on the threading of di-, tri-, and tetra(ethylene glycol) through bis-*para*-xylyl[26]crown-6 (BPX26C6),[8] templated by $Na^+$ ions, under solvent-free conditions; one such [2]rotaxane, featuring both tetra(ethylene glycol) and carbamate stations, behaves as a $K^+$-controllable molecular switch.

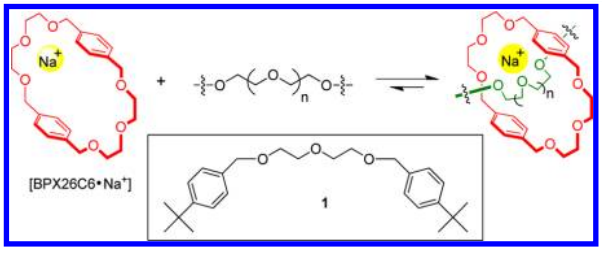



**Figure 1.** Chemical structure of **1** and the concept of threading oligo(ethylene glycol)s through the cavity of BPX26C6 with the assistance of templating $Na^+$ ions.

To investigate the possibility of assembling two oligo(ethylene glycol)-containing species, a linear guest and a macrocyclic host, linked by a $Na^+$ ion as the template, we synthesized the threadlike molecule **1** from di(ethylene glycol) and *p*-*tert*-butylbenzyl bromide (see the Supporting Information). The $^1H$ NMR spectrum of an equimolar mixture (10 mM) of BPX26C6, the threadlike species **1**, and sodium tetrakis(3,5-trifluoromethylphenyl)borate (NaTFPB) in $CDCl_3$ featured signals for the macrocyclic component that were almost identical to those of an equimolar mixture of BPX26C6 and NaTFPB (i.e., in the absence of **1**) under similar conditions; in addition, the shifts in the signals for the aromatic and ethylene glycol units of **1** in the presence of BPX26C6 and NaTFPB were minor relative to those of **1** alone in the same

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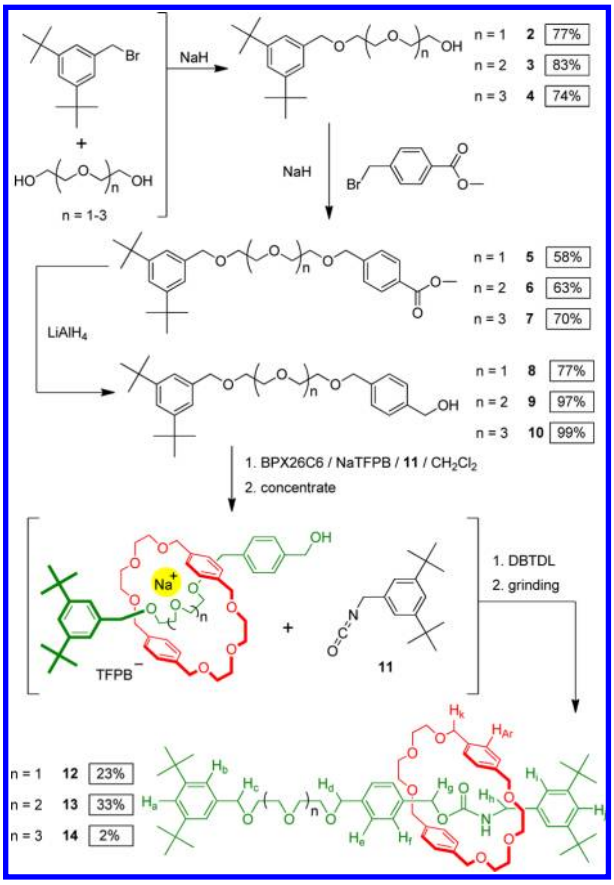
solvent. Nevertheless, the $^1$H NMR spectrum of an equimolar (10 mM) mixture of **1** and NaTFPB revealed significant upfield shifts for the signals of the aromatic and ethylene glycol units of **1**. Taken together, these features suggest that the $Na^+$ ions in the mixture of BPX26C6, **1**, and NaTFPB were complexed predominately with BPX26C6 rather than with **1** (not surprisingly, as would be expected for the macrocyclic effect)[9] and that the association of **1** with the BPX26C6·$Na^+$ complex was not particularly strong. Thus, to prove the existence of [2]pseudorotaxanes formed through $Na^+$ ion templated complexation of the oligo(ethylene glycol)-containing macrocycle and oligo(ethylene glycol)-containing threadlike molecules in solution, it was necessary to synthesize and isolate the corresponding [2]rotaxanes (Scheme 1). To do so, we

**Scheme 1. Synthesis of the [2]Rotaxanes 12−14**

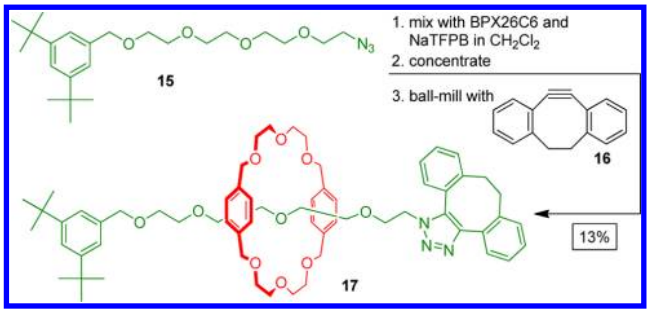



synthesized the threadlike molecules **8−10** in three steps from their corresponding oligo(ethylene glycol)s. The oligo(ethylene glycol)s were first alkylated with 3,5-di-*tert*-butylbenzyl bromide to give the alcohols **2−4**, which we subsequently alkylated with methyl 4-bromomethylbenzoate to afford the esters **5−7**. We obtained the alcohols **8−10** after $LiAlH_4$-mediated reduction of these esters.

Possibly because of weak association of the host and guest components, the $^1$H NMR spectra of the crude products obtained after adding the isocyanate **11** into an equimolar mixture of BPX26C6, a threadlike oligo(ethylene glycol) (**8**, **9**, or **10**), and NaTFPB in $CH_2Cl_2$ featured no obvious signals belonging to the [2]rotaxanes **12−14**; subsequent purification afforded no such [2]rotaxanes, instead yielding the corresponding dumbbell-shaped oligo(ethylene glycol)s and free BPX26C6 as major products. In a previous study, we demonstrated that the efficiency of synthesizing [2]rotaxanes from weakly interacting host/guest systems can be improved significantly under solvent-free conditions, where the concentration of the host/guest complexes can be increased significantly and their unfavorable dissociation, induced by reagents or side products, can be minimized;[10] therefore, we turned our attention to preparing the [2]rotaxanes **12−14** under solvent-free conditions. Because the isocyanate **11** is a liquid and relatively sensitive to moisture in the air, instead of coating the materials on a solid support to perform ball-milling, we concentrated a $CH_2Cl_2$ solution of a threadlike oligo(ethylene glycol) (**8**, **9**, or **10**), the macrocycle BPX26C6, NaTFPB, and the isocyanate **11** (1:2.5:2.5:5) to give a sticky liquid, which we presumed comprised the isocyanate stopper and the [2]pseudorotaxane [(BPX26C6·$Na^+$)⊃**8−10**].[11] After adding the neat catalyst di-*n*-butyltin dilaurate (DBTDL), we stirred/ground the neat liquid mixture using a strong magnet to manually control the motion of the magnetic stirrer inside the sealed flask. After the liquid mixture had solidified completely (typically less than 30 min), we ground the solid mixture for an additional 5 min. Subsequent chromatographic purification of the solid mixture gave the desired [2]rotaxane (**12**, **13**, or **14**; yield: 23, 33, or 2%, respectively).

To exclude the possibility of the [2]rotaxanes **12−14** having been synthesized from intermediates formed from the $Na^+$ ion templated association of the isocyanate **11** and BPX26C6, we wished to perform a stoppering reaction under similar solvent-free conditions but instead using a stoppering reagent lacking functional groups capable of strongly chelating $Na^+$ ions (unlike the C═O group in the isocyanate). Because the "click" reaction between an azide and a strained alkyne can proceed smoothly in the absence of a catalyst,[12] which itself might have disturbed our host/guest recognition, we selected such a reaction for our control experiment. Thus, we mixed the azide-terminated tri(ethylene glycol) derivative **15** with BPX26C6 and NaTFPB in $CH_2Cl_2$ and then concentrated the mixture to give a solid, which we ball-milled in the presence of the benzannulated cyclooctyne **16**[12b] (a solid) to afford the [2]rotaxane **17** in 13% yield after column chromatography (Scheme 2). This result

**Scheme 2. Synthesis of the [2]Rotaxane 16 through a Click Reaction under Solvent-Free Conditions**




supports our proposed mechanism for the formation of [2]pseudorotaxane structures through the recognition of linear oligo(ethylene glycol) chains by BPX26C6, stabilized by a templating $Na^+$ ion, in concentrated solutions or in the absence of solvent (Scheme 1). The absence of any detectable signals for the [2]rotaxanes **12−14** in the $^1$H NMR spectra of the crude products obtained when we repeated their syntheses under otherwise identical conditions, but in the absence of NaTFPB, suggested that the $Na^+$ ion template was crucial for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efficient threading of each oligo(ethylene glycol) unit through the cavity of BPX26C6.

The success in synthesizing the [2]rotaxanes **12**–**14** confirmed that the di-, tri-, and tetra(ethylene glycol) derivatives reside favorably within the cavity of BPX26C6 in the presence of templating $Na^+$ ions. The higher yield of the [2]rotaxane **13** relative to that of the [2]rotaxane **12** under similar conditions was presumably due to the tri(ethylene glycol) motif of the threadlike molecule **9** containing one more oxygen atom than the di(ethylene glycol) unit of the threadlike molecule **8**, thereby increasing its affinity to the templating $Na^+$ ion and stabilizing the corresponding [2]pseudorotaxane to a greater extent. Interestingly, however, extending the threadlike molecule by one more ethylene glycol unit, forming **10**, led to increased flexibility that disrupted the synthesis of the [2]rotaxane **14**. We suspect that the very low yield of the [2]rotaxane **14** also resulted from its tetra(ethylene glycol)-derived threadlike precursor having the ability to almost fulfill the coordination number of the $Na^+$ ion, thereby decreasing its need to cooperate with BPX26C6 in the binding of the template. This observation supports our original design and implies that similar strategies based on metal ion–templated threading might be inefficient when the host or guest can, by itself, largely fulfill the coordination number of the templating metal ion.

As displayed in Figure 2, the $^1$H NMR spectra of the [2]rotaxanes **12**–**14** are quite similar, except for the signals of

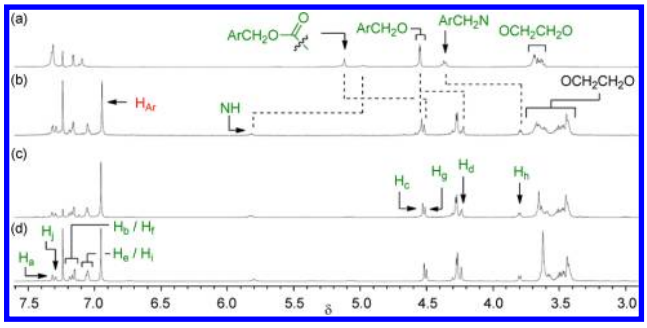


**Figure 2.** $^1$H NMR spectra (400 MHz, $CDCl_3$, 298 K) of (a) the free dumbbell-shaped component of the [2]rotaxane **12** and (b–d) the [2]rotaxanes (b) **12**, (c) **13**, and (d) **14**.

their oligo(ethylene glycol) units in the range $\delta$ 3.35–3.70. We used 2D COSY and NOESY experiments to identify most of the signals in the $^1$H NMR spectra of the [2]rotaxanes **12**–**14** in $CDCl_3$ at 298 K (Figure 2). Relative to the $^1$H NMR spectrum of its free dumbbell-shaped component, the spectrum of the [2]rotaxane **12** features significant upfield shifts of the two carbamate-adjacent benzylic protons ($H_g$, $H_h$), from $\delta$ 5.1 and 4.36 to $\delta$ 4.52 and 3.80, respectively, together with a downfield shift of the carbamate's NH proton, from $\delta$ 4.99 to 5.80, suggesting the encircling of the BPX26C6 component around the carbamate station and the existence of possible [N–H···O] hydrogen bonds between the components under these conditions. The presence of cross peaks for the signals of the aromatic protons ($H_{Ar}$) of BPX26C6 and the terminal benzylic protons ($H_h$) adjacent to the carbamate station in the 2D NOESY spectrum of the [2]rotaxane **12** in $CDCl_3$ at 298 K (see the Supporting Information) is consistent with the encircling of the macrocyclic component around the carbamate unit under these conditions. Because the C=O group in the carbamate unit can also combine with the BPX26C6 component to complex a $Na^+$ ion, the addition of NaTFPB into $CDCl_3$ solutions of the [2]rotaxanes **12**–**14** led to broadening of the signals to various degrees, suggesting shuttling of the BPX26C6 component (or its $Na^+$ ion complexed form) between the oligo(ethylene glycol) and carbamate stations. Possibly because of its larger size and lower charge density, the $K^+$ ion is a weaker template than the $Na^+$ ion when mediating the threading of urea or amide functionalities through BPX26C6;[13] we suspected, however, that its weaker interactions in the binding pocket generated from the C=O group of the carbamate station and the BPX26C6 component and its higher coordination number might result in its preference for the ethylene glycol station (i.e., higher number of oxygen atoms), thereby making the $K^+$ ion a suitable agent for switching the [2]rotaxanes between their two different states.

Because the $^1$H NMR spectra of the [2]rotaxane **14** (Figure 3a) and its free dumbbell-shaped component (Figure 3d) in

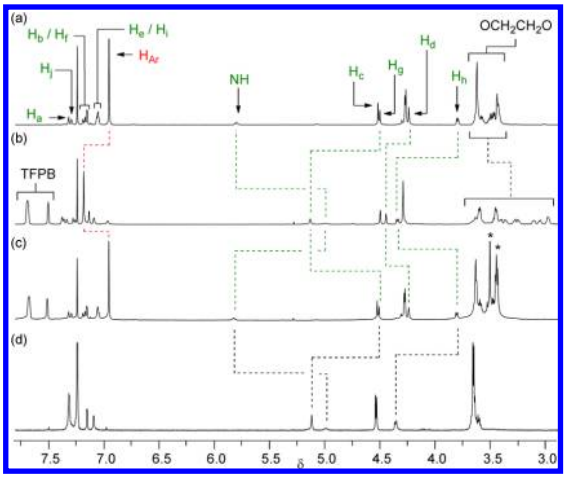


**Figure 3.** $^1$H NMR spectra (400 MHz, $CDCl_3$, 298 K) of (a) the [2]rotaxane **14** (10 mM); (b) the mixture obtained after adding KTFPB (1 equiv) to the solution in (a); (c) the mixture obtained after adding [2.2.2]cryptand (1 equiv) to the solution in (b); and (d) the free dumbbell-shaped component of the [2]rotaxane **14**. *Signals of [2.2.2]cryptand.

$CDCl_3$ were similar to those of the [2]rotaxane **12** (Figure 2b) and its free dumbbell-shaped component (Figure 2a), respectively, we suspect that the interlocked BPX26C6 component of **14** also encircled its carbamate station under these conditions. Figure 3b reveals that the addition of KTFPB (1 equiv) to the solution of the [2]rotaxane **14** in $CDCl_3$ migrated the relatively upfield and downfield signals of its benzylic ($H_g$, $H_h$) and carbamate NH protons, respectively, back to positions similar to those in the spectrum of the free dumbbell-shaped component of the [2]rotaxane **14** (Figure 3d), suggesting that the interlocked BPX26C6 component no longer resided around the carbamate station under these conditions.[14] In addition, the spreading and upfield shifts of the signals of the ethylene glycol protons and the downfield shift of the signals of the aromatic xylyl protons suggested that the BPX26C6 component had moved away from the carbamate station and most likely resided at the tetra(ethylene glycol) station to allow cooperative chelation of the $K^+$ ion. This concept was supported by the corresponding 2D NOESY spectra, in which cross signals appeared between the xylyl protons of the BPX26C6 component and the terminal benzylic


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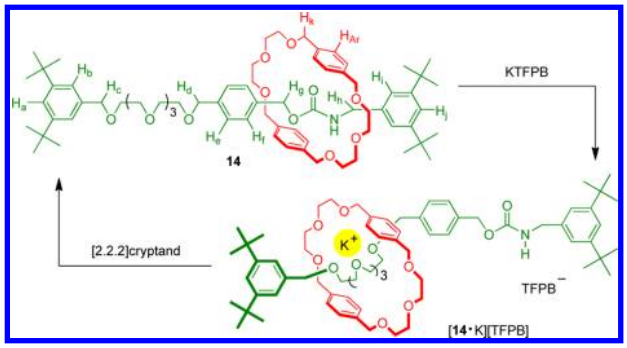
protons ($H_c$) adjacent to the tetra(ethylene glycol) station in the presence of $K^+$ ions. Thus, it appears that the addition of $K^+$ ions induced the migration of the interlocked BPX26C6 component from its original position, encircling the carbamate station, to a new position, encircling the tetra(ethylene glycol) station, generating the new translational structure $[\mathbf{14}\cdot K]^+$ (Scheme 3). Subsequent addition of [2,2,2]cryptand (1

**Scheme 3. [2]Rotaxane 14 Behaves as a $K^+$ Ion Controllable Molecular Switch**




equiv), a very strong binder of $K^+$ ions, to the solution provided a $^1$H NMR spectrum similar to that obtained in the absence of any additives, suggesting the regeneration of the original state of the [2]rotaxane **14** (Figure 3c). Thus, the [2]rotaxane **14** is a molecular switch that can be controlled reversibly through application of the KTFPB/[2.2.2]cryptand reagent pair.

We have demonstrated that relatively chemically inert and readily accessible oligo(ethylene glycol)s can function as primary recognition units for the assembly of [2]rotaxanes under solvent-free conditions. In addition, we have found that one such interlocked molecule, the [2]rotaxane **14**, behaves as a metal ion controllable molecular switch, where the addition and removal of $K^+$ ions results in the interlocked BPX26C6 component in the [2]rotaxane encircling the tetra(ethylene glycol) and carbamate stations, respectively, of the dumbbell component. We believe that this simple recognition system will have great potential for application in the development of robust interlocked structures and molecular switches exhibiting new functions.

## ■ ASSOCIATED CONTENT

### Supporting Information

Synthetic procedures and characterization data for the [2]-rotaxanes. This material is available free of charge via the Internet at http://pubs.acs.org

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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(11) No signals representing the [2]rotaxane were present in the $^1$H NMR spectrum of this mixture (see the Supporting Information). The reaction between an isocyanate and an alchohol proceeds extremely slowly at room temparature in the absence of a suitable catalyst; see: Furusho, Y.; Sasabe, H.; Natsui, D.; Murakawa, K.-i.; Takata, T.; Harada, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 179.

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(14) The $^1$H NMR spectrum of an equimolar mixture of KTFPB and the [2]rotaxane **12** or **13** in $CDCl_3$ featured broadening of the signals.