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Molecular Switch Based on Very Weak Association between BPX26C6 and Two Recognition Units

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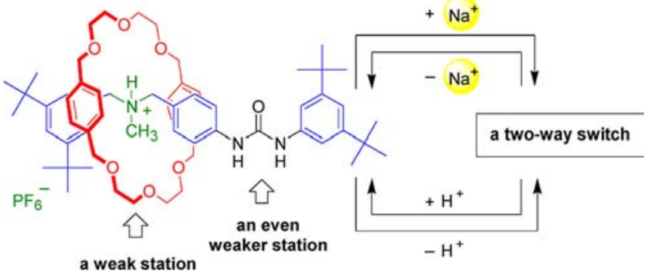
ABSTRACT



A [2]rotaxane has been constructed through metal ion-templated pseudorotaxane formation from a weakly interacting host (bis-*p*-xylyl[26]crown-6)/guest (diphenylurea derivative) complex and post-assembly modification to form another weakly interacting tertiary ammonium ion recognition site for the host. The combination of this pair of weakly interacting components allowed bifunctional (pH, Na^+ ions) switching of the crown ether unit, highlighting the potential applicability of weakly associated components within molecular switches.

Rotaxane-type molecular switches are prototypical molecular machines that find applications in such fields as sensing,[1] organogelation,[2] materials delivery,[3] and molecular memory.[4] To ensure clean and clear switching, it is necessary to balance the stabilization energies of the complexes formed between the interlocked macrocyclic unit and its various recognition sites in the dumbbell-shaped unit of the rotaxane, both before and after application of a stimulus.[5] For simplicity, rotaxane-type molecular switches generally comprise one macrocyclic unit and one dumbbell-shaped moiety featuring two recognition units, with a reasonable difference in the two association constants in the ground state.[5] The relative difficulty of deprotonating a simple rotaxane based on recognition of dibenzo[24]crown-8 (DB24C8) and the dibenzylammonium (DBA) ion, unless another weaker binding station (e.g., bipyridinium ion) is present in the dumbbell-shaped component, highlights the importance of selecting an

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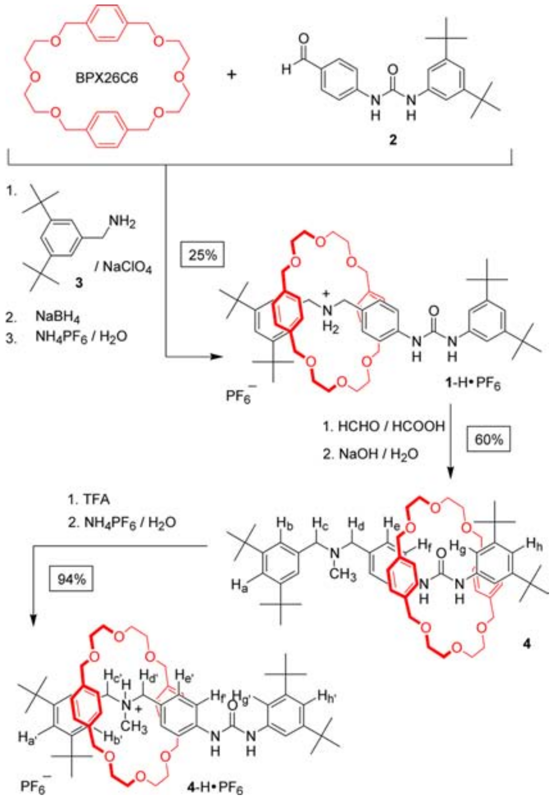
appropriate second station when designing a molecular switch.[6] The search for new threading guests for macrocycles with reasonable affinity in solution is never straightforward, thereby limiting the development of new molecular switches. Theoretically, weakly binding guest units would serve as perfectly acceptable primary recognition sites in molecular switches if an even weaker recognition unit for the macrocycle were present in the dumbbell-shaped component. Using this concept, many guest units that do not, when isolated, exhibit particularly high binding affinities for macrocycles have the potential to act as primary or secondary recognition sites in interlocked molecular switches, potentially increasing the number of recognition units available for the construction of new molecular switches. Two questions arise: (i) How do we assemble rotaxanes efficiently from weakly associated host/guest components? (ii) How do we choose which combinations of recognition units are appropriate for constructing molecular switches? Herein, we report a new molecular switch constructed using the concept of weak recognition. We constructed this [2]rotaxane first by using a metal ion to template the formation of a pseudorotaxane from bis-*p*-xylyl[26]crown-6 (BPX26C6)[7] and a diphenylurea derivative and then modifying the pseudorotaxane post-assembly to form another weakly interacting tertiary ammonium ion recognition site for the crown ether component, the migration of which between the tertiary ammonium center and the diphenylurea station we could control using in situ base/acid treatment or metal ion addition/removal.

Scheme 1. Synthesis of the Molecular Switch **4**-H$\cdot$PF$_6$



To facilitate the synthesis of the [2]rotaxane, we sought a host/guest system that associates with the requirement of a template because the binding strength would be weakened significantly simply by removing the template after interlocking the components. Previously, we reported that a diphenylurea unit can thread through the macrocycle BPX26C6 in the presence of a templating Na$^+$ ion;[8] we suspected that the ethylene glycol units of BPX26C6 would interact weakly with the NH units of the diphenylurea station in the resulting rotaxane after removal of the template. For the stoppering reaction, we chose reductive amination[9] because of the potential to covalently modify the resulting secondary amine to form a tertiary ammonium center that would interact significantly weaker with the crown ether component.[10] Thus, after removal of the Na$^+$ ion that facilitated the synthesis, we expected the tertiary ammonium center and the diphenylurea unit to serve as suitable stations for the translocation of the BPX26C6 component.

We isolated the [2]rotaxane **1**-H$\cdot$PF$_6$ in 25% yield after (i) mixing BPX26C6, the aldehyde **2**, the amine **3**, and NaClO$_4$ in CH$_2$Cl$_2$, (ii) reducing the resulting imine, and (iii) acidification (Scheme 1). Two triplets (at δ 2.75–2.90) for the methylene protons adjacent to the NH$_2^+$ center appeared in the ^{1}H NMR spectrum of **1**-H$\cdot$PF$_6$ (Figure 1a); strong cross-signals for these protons to the aromatic and ethylene glycol protons of BPX26C6 appeared in the 2D NOESY spectrum, suggesting that the macrocyclic unit resided about the NH$_2^+$ center in the ground state of this [2]rotaxane. The very weak interaction between BPX26C6 and the diphenylurea station, relative to that between the macrocyclic unit and the DBA$^+$ station, was confirmed by our inability to transfer the macrocyclic component to the diphenylurea station upon the addition of Et$_3$N in CDCl$_3$, even when we added more than 50 equiv of the base.

We methylated the DBA$^+$ center of the [2]rotaxane **1**-H$\cdot$PF$_6$ through treatment with formaldehyde and formic acid,[10b] providing the [2]rotaxane **4** after washing the resulting solution with aqueous NaOH and purifying the residue through column chromatography; acidification and anion exchange gave the [2]rotaxane **4**-H$\cdot$PF$_6$. We recorded 2D COSY and NOESY spectra to identify the signals of the protons of the two methylated [2]rotaxanes (see the Supporting Information) and the positions of their interlocked BPX26C6 components. The observation of

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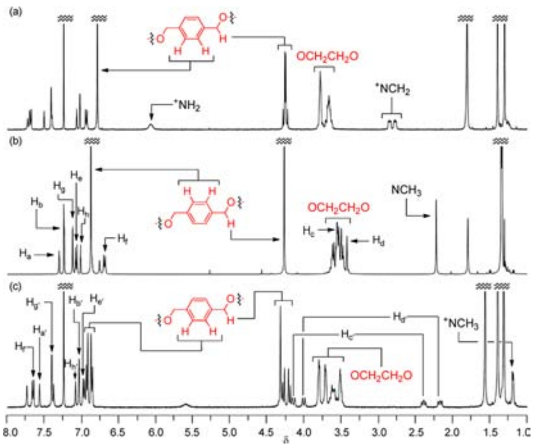
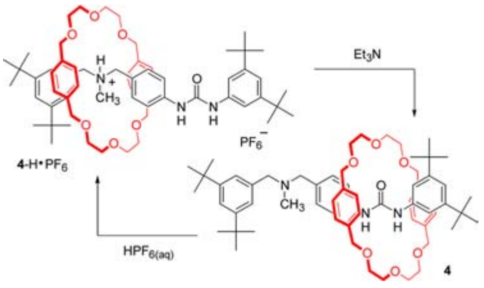


Figure 1. ^{1}H NMR spectra (400 MHz, CDCl$_3$, 298 K) of the [2]rotaxanes (a) **1**-H·PF$_6$, (b) **4**, and (c) **4**-H·PF$_6$.

cross-peaks between the signals of the ethylene glycol protons of the BPX26C6 unit and only the protons adjacent to the diphenylurea station (H$_f$, H$_g$) in **4** (Figure 1b) and only the protons associated with the tertiary ammonium ion center (H$_{b'}$, H$_{c'}$, H$_{d'}$, H$_{e'}$) in **4**-H·PF$_6$ (Figure 1c) suggested that the macrocyclic component encircled the urea station in the former [2]rotaxane and the tertiary ammonium ion station in the latter. Thus, the binding affinity of the BPX26C6 unit toward the tertiary amine station in the [2]rotaxane **4** is significantly weaker than it is toward the diphenylurea station, implying that the [2]rotaxane **4**-H·PF$_6$ is a molecular switch that can be operated through in situ base/acid control (Scheme 2).[11]

Scheme 2



Addition of 12 equiv of Et$_3$N to a CDCl$_3$ solution of the [2]rotaxane **4**-H·PF$_6$ resulted in a spectrum (Figure 2b) similar to that of the [2]rotaxane **4**; i.e., disappearance of the complicated splitting pattern of the methylene protons adjacent to the ammonium center (H$_{c'}$, H$_{d'}$) and of the benzylic protons of the BPX26C6 unit (caused by the local asymmetry of the tertiary ammonium ion center), together with a downfield shift of the signals of the aromatic protons closest to the ammonium center (H$_{b'}$, H$_{e'}$) and an upfield shift of the aromatic protons near the urea station (H$_{f'}$, H$_{g'}$). These signals suggest the successful deprotonation of the tertiary ammonium ion and subsequent migration of the BPX26C6 unit from the tertiary amine center to the urea station. Introducing 12 equiv of HPF$_6$ to this solution resulted in a spectrum similar to that of the [2]rotaxane **4**-H·PF$_6$ in the absence of any additive, indicating that, under these conditions, the macrocyclic component had returned to encircle the protonated tertiary amine center. Because *N*,*N*-bis(4-*tert*-butylbenzyl)-*N*-methylammonium hexafluorophosphate[12] and bis(4-(hexyloxy)-phenyl)urea[13] both exhibited very weak binding affinities toward BPX26C6 in their equimolar mixtures in CDCl$_3$ (10 mM), the [2]rotaxane **4**-H·PF$_6$ acts as an unique acid/base-controllable molecular switch in solution, which features two very weakly associating recognition units.

If we assume that the selectivities for the interlocked BPX26C6 components in the [2]rotaxanes **1**-H·PF$_6$ and **4** for encircling their corresponding diphenylurea stations are 0 and 100%, respectively, we then can estimate the preference for the macrocyclic unit residing about the tertiary ammonium ion center over the diphenylurea station in the [2]rotaxane **4**-H·PF$_6$ simply by considering the chemical shifts of its urea-adjacent aromatic protons as molar fraction averages of those same signals in the [2]rotaxanes **1**-H·PF$_6$ and **4**. Using the aromatic protons H$_{f'}$ and H$_{g'}$ as references, we calculated that in CDCl$_3$ the interlocked BPX26C6 unit residues predominately about the tertiary ammonium ion center, rather than the diphenylurea station, in the [2]rotaxane **4**-H·PF$_6$ with a 97:3 distribution ratio, providing a difference in free energy of 2.1 kcal mol^{-1} between the two translational isomers.[14]

Next, after proving that the [2]rotaxane **4**-H·PF$_6$ behaves as a base/acid-controllable molecular switch, we were interested in finding other stimuli to reverse the stabilization energy preference of the BPX26C6 unit toward the two stations so that the operation of the switch **4**-H·PF$_6$ could also be achieved without significantly weakening the binding affinity of the macrocyclic component to the tertiary ammonium ion center. Previously, we had demonstrated that a [2]rotaxane comprising a BPX26C6 unit and a dumbbell-shaped component featuring a diphenylurea unit could be synthesized by taking advantage of the templating effects of metal ions.[8] We suspected that the same collaboration among recognition components would provide sufficiently strong interactions to attract the macrocycle away from the $^+$N(CH$_3$)H center and toward the urea station. If so, the addition and removal of metal ions would drive the transfer of the BPX26C6 unit between the diphenylurea and tertiary ammonium stations, allowing the [2]rotaxane **4**-H·PF$_6$ to function as a molecular switch that is controlled through host/guest–collaborated metal ion complexation (Scheme 3).

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(11) An acid/base-controllable molecular switch based on a tertiary ammonium ion and DB24C8 has been reported; see ref 10b.

(12) The association constant (K_a) of this tertiary ammonium salt to BPX26C6 in CDCl$_3$ was determined by ^{1}H NMR titration experiments to be 11 ± 2 M^{-1}. See the Supporting Information for the titration curve.

(13) Huang, Y.-L.; Hung, W.-C.; Lai, C.-C.; Liu, Y.-H.; Peng, S.-M.; Chiu, S.-H. *Angew. Chem., Int. Ed.* **2007**, *46*, 6629–6633.

(14) The association constant (K_a) of the diphenylurea station to BPX26C6 in CDCl$_3$ was, thus, estimated to be ca. 0.3 M^{-1}.

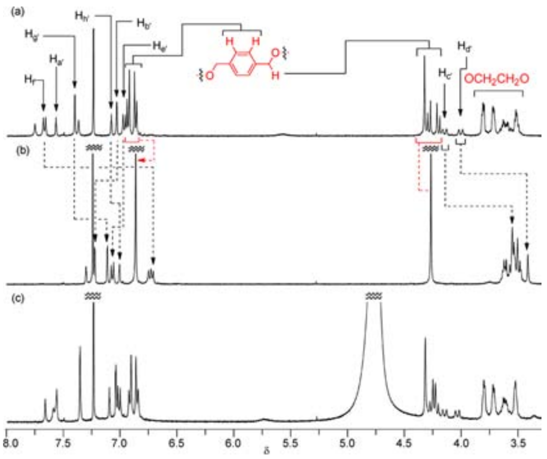
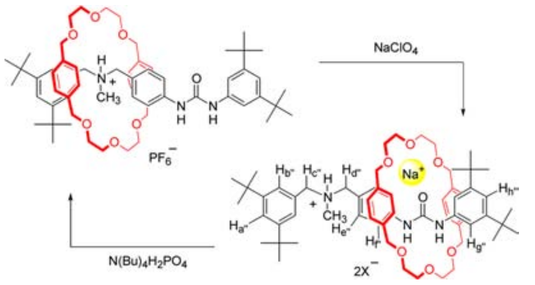


Figure 2. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of (a) the [2]rotaxane **4**-H$\cdot PF_6$ (3 mM); (b) the mixture obtained after adding Et_3N (12 equiv) to the solution in (a); and (c) the mixture obtained after adding HPF_6 (12 equiv) to the solution in (b).

Scheme 3



Gradual addition of $NaClO_4$ to a $CDCl_3$ solution of the [2]rotaxane **4**-H$\cdot PF_6$ at room temperature resulted in a decrease in the intensity of its signals in the ^{1}H NMR spectrum (Figure 3) together with a new set of signals of increasing intensity, suggesting that the rate of exchange between the two species was slow under these conditions. The growing signal at δ 2.76 in the ^{1}H NMR spectra, associated with the methyl protons of the tertiary ammonium ion center, is positioned very close to that of the same protons of the corresponding isolated dumbbell-shaped salt component of the [2]rotaxane **4**-H$\cdot PF_6$; together with the upfield and downfield shifts of the aromatic protons close to the diphenylurea ($H_{f''}$, $H_{g''}$) and $^+N(CH_3)H$ ($H_{b''}$, $H_{e''}$) centers, respectively, in the ^{1}H NMR spectra, these signals suggest that the BPX26C6 component resided about the diphenylurea station under these conditions.

The addition of 2 equiv of tetrabutylammonium phosphate ($NBu_4H_2PO_4$) to a solution of **4**-H$\cdot PF_6$ and $NaClO_4$ removed the Na^+ ions, which had presumably coordinated in the pocket formed by the C=O group of the urea station and the ethylene glycol chains of the BPX26C6 unit, forming the less soluble NaH_2PO_4[15] and resulting in a ^{1}H NMR spectrum similar to that of the original [2]rotaxane **4**-H$\cdot PF_6$.[16] In other words, removing the Na^+ ion from the [2]rotaxane shifted the macrocyclic component back to encircle the tertiary ammonium center. Thus, the [2]rotaxane **4**-H$\cdot PF_6$ behaves as a molecular switch that can be operated also by the addition and removal of Na^+ ions.

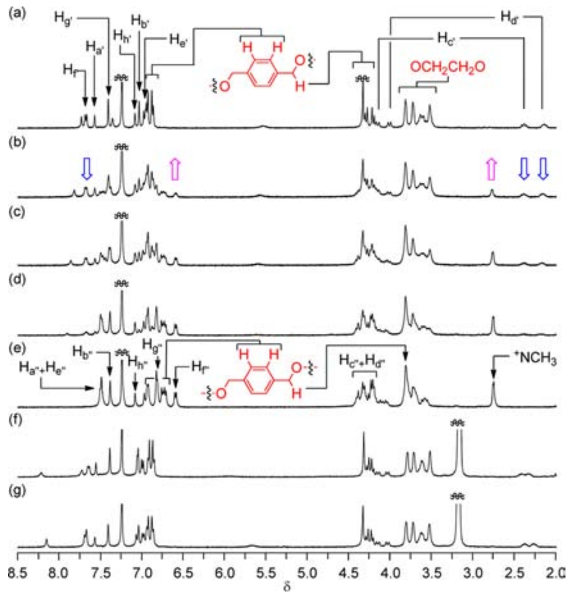


Figure 3. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of (a) the [2]rotaxane **4**-H$\cdot PF_6$ (3 mM); (b–e) the mixtures obtained after adding (b) 0.5, (c) 1.0, (d) 1.5, and (e) 2.0 equiv of $NaClO_4$ to the solution in (a); (f) the mixture obtained after adding $NBu_4H_2PO_4$ (2 equiv) to the solution in (e); and (g) a mixture of **4**-H$\cdot PF_6$ (3 mM) and NBu_4ClO_4 (6 mM).

Our demonstration of the use of two very weakly interacting stations to construct a bifunctional (pH and Na^+ ion) molecular switch highlights the potential importance of weakly associated components within molecular switches. This approach offers the possibility of incorporating some of the many weakly associated species, which we might have overlooked previously, as useful components for the construction of molecular switches exhibiting versatile functions when suitably integrated into interlocked molecules.

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Supporting Information Available. 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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[15] The precipitation of NaH_2PO_4 from $CDCl_3$ had been reported; see: Oh, J. M.; Cho, E. J.; Ryu, B. J.; Lee, Y. J.; Nam, K. C. *Bull. Korean Chem. Soc.* **2003**, *24*, 1538–1540.

[16] The ^{1}H NMR spectrum of a solution of NBu_4ClO_4 (6 mM) and **4**-H$\cdot PF_6$ (3 mM) in $CDCl_3$ (Figure 3g) indicated that the presence of this salt may be responsible for the slight differences in the signal found in Figure 3a,f.

The authors declare no competing financial interest.