

Reversing a Rotaxane Recognition Motif: Threading Oligoethylene Glycol Derivatives through a Dicationic Cyclophane

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Although rotaxanes¹ can now be obtained efficiently using template-directed² protocols that rely upon supramolecular assistance to covalent synthesis,³ there are still a limited number of recognition motifs that can be exploited for the preparation of these interlocked molecular compounds⁴ which hold out so much promise⁵ for the fabrication of actuators, amplifiers, motors, sensors, and switches⁶ at the nanoscale level. Here, we report our recent success in reversing an already well-established⁷ recognition motif—namely, one in which NH_2^+ centers in the rod sections of the dumbbell components of the rotaxanes are encircled by macrocyclic polyether components.

Certain rodlike components, containing appropriately spaced NH_2^+ centers, are known⁸ to form 1:1 complexes, both in solution and in the solid state with bisparaphenylene[34]crown-10 (BPP34C10). In addition, we have recently reported⁹ that BPP34C10 can encircle a dicationic cyclophane in which two dibenzylammonium ions (DBA^+) are joined through the para positions on their phenyl rings by $-\text{CH}_2\text{CH}_2-$ units. In the course of this research, we have discovered that a slightly larger dicationic cyclophane, where the two cross- DBA^+ links are $-\text{CH}_2\text{OCH}_2-$ units, can be threaded by molecules that contain oligoethylene glycol chains, resulting in the formation of 1:1 complexes of the [2]pseudorotaxane type. In essence, the original recognition motif (Figure 1) has been turned simultaneously outside-in and inside-out, a fact that has been proved beyond any doubt by the stoppering of both ends of the rod component in the [2]pseudorotaxane to give a stable [2]rotaxane.

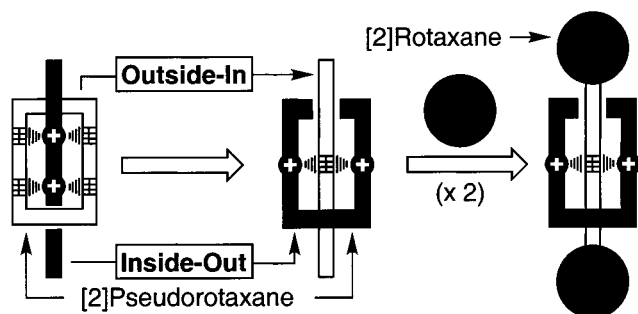
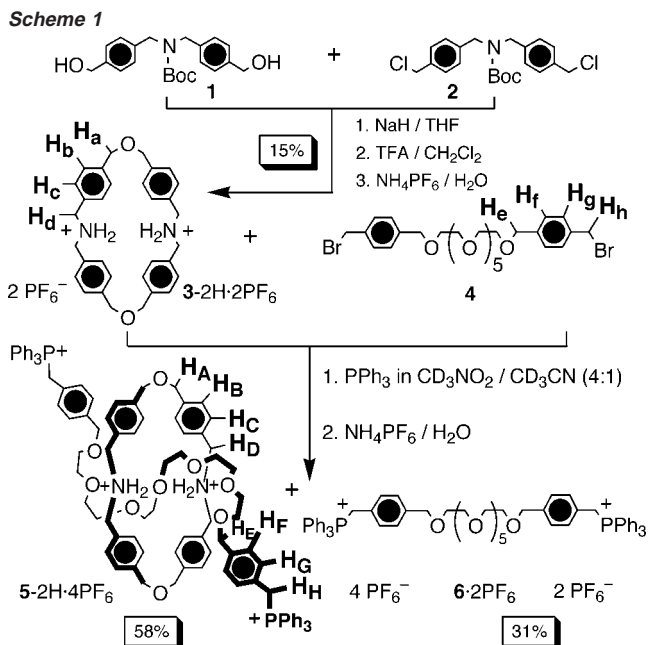


Figure 1. Reversal of a recognition motif at the [2]pseudorotaxane level and the subsequent trapping of it as a [2]rotaxane.

When the diol **1**¹⁰ was reacted (Scheme 1) with the dichloride **2**¹¹ at high dilution in THF under basic conditions (NaH) and the product was subjected to Boc-deprotection (TFA/ CH_2Cl_2), followed by counterion exchange ($\text{NH}_4\text{PF}_6/\text{H}_2\text{O}$), the dicationic cyclophane **3-2H·2PF₆** was isolated in a yield of 15% overall. An inspection of space-filling molecular models suggested that a hexaethylene glycol chain provides an appropriate number of acceptor oxygen atoms to allow it to form the maximum number of hydrogen bonds with donor hydrogen atoms on each of the two NH_2^+ centers in



3-2H⁺. Accordingly, the dibromide **4** was prepared by reacting (NaH/DMF) hexaethylene glycol with a 5-fold excess of 1,4-bis-(bromomethyl)benzene. When **3-2H·2PF₆** and **4** were mixed in equimolar (10 mM) amounts in CD_3NO_2 , dramatic shifts were observed (Figure 2b) in the ¹H NMR spectrum recorded at 298 K for the signals associated with the CH_2N^+ and CH_2O groups, as compared with those recorded for the relevant groups in the free cyclophane **3-2H·2PF₆** (Figure 2a) and in the free dibromide **4** (Figure 2c). Not only is the signal for the CH_2N^+ protons (**H_d**)

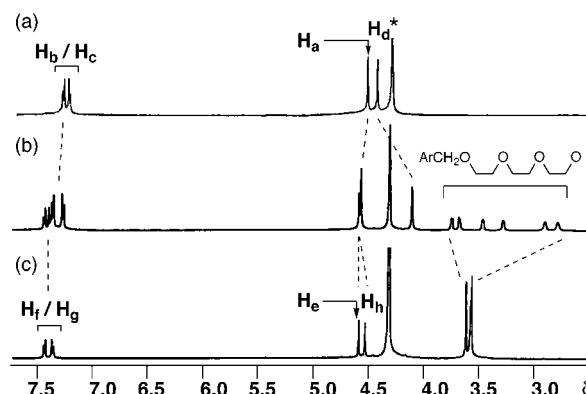


Figure 2. ¹H NMR spectra (500 MHz/ $\text{CD}_3\text{NO}_2/10$ mM/298 K) of (a) cyclophane **3-2H·2PF₆**, (b) a mixture of cyclophane **3-2H·2PF₆** and thread **4**, and (c) thread **4**.

shifted upfield by 0.34 ppm, but the “tight” multiplet (δ 3.50–3.65) for the six constitutionally heterotopic pairs of OCH_2 protons within the three different $-\text{OCH}_2\text{CH}_2\text{O}-$ units of **4** is dispersed out over a wide chemical shift range (δ 2.70–3.80), revealing all six signals well-resolved from each other. The chemical shifts of the signals for both the CH_2N^+ and CH_2O protons are highly temperature dependent. Raising the temperature decreases complexation, while lowering it increases complexation. When ^1H NMR titration experiments were carried out at 298 K in CD_3NO_2 with the three most high field CH_2O proton signals as probes, an average binding constant of $2900 \pm 750 \text{ M}^{-1}$ was obtained.¹¹ To establish the existence of the [2]pseudorotaxane $3\text{-}2\text{H}^+\text{D}$ in solution, an excess of PPh_3 was added to a solution ($\text{MeNO}_2/\text{MeCN}$, 4:1) of $3\text{-}2\text{H}\cdot 2\text{PF}_6$ (150 mM) and **4** (50 mM), according to a literature procedure.¹² Following counterion exchange ($\text{NH}_4\text{PF}_6/\text{H}_2\text{O}$) and column chromatography ($\text{SiO}_2:\text{MeCN}/\text{CH}_2\text{Cl}_2$, 3:7) the [2]rotaxane¹³ $5\text{-}2\text{H}\cdot 4\text{PF}_6$ was isolated, along with the dumbbell compound $6\cdot 2\text{PF}_6$ in 58 and 31% yields, respectively. The ^1H NMR spectra of $5\text{-}2\text{H}\cdot 4\text{PF}_6$ and $6\cdot 2\text{PF}_6$ in CD_3NO_2 (10 mM) at 298 K are shown in Figures 3c and 3a, respectively. The spectrum of the [2]rotaxane $5\text{-}2\text{H}\cdot 4\text{PF}_6$ is very different from that recorded (see Supporting Information) after mixing the cyclophane $3\text{-}2\text{H}\cdot 2\text{PF}_6$ and the dumbbell compound $6\cdot 2\text{PF}_6$ together under the same conditions (10 mM in CD_3NO_2 at 298 K). Also, an equimolar (10 mM each) mixture of $5\text{-}2\text{H}\cdot 4\text{PF}_6$ and $6\cdot 2\text{PF}_6$ in CD_3NO_2 at 298 K resulted in an ^1H NMR spectrum (Figure 3b) that corresponds to the superimposition of the two spectra (a and c in Figure 3) for the two separate components. These experiments establish (1) the constitutional authenticity and integrity of the [2]rotaxane and (2) the lack of any interchange with its dumbbell and cyclophane components in solution, i.e., the triphenylphosphonium groups are stable stoppers which could presumably be exchanged for numerous other groups with use of Wittig chemistry.¹⁴

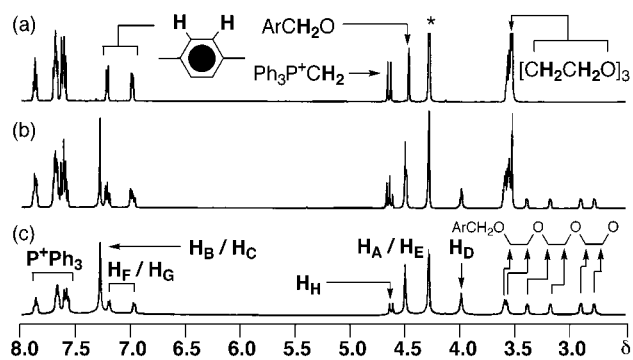


Figure 3. ^1H NMR spectra (500 MHz/ $\text{CD}_3\text{NO}_2/10 \text{ mM}/298 \text{ K}$) of (a) dumbbell $6\cdot 2\text{PF}_6$, (b) a mixture of dumbbell $6\cdot 2\text{PF}_6$ and [2]rotaxane $5\text{-}2\text{H}\cdot 4\text{PF}_6$, and (c) [2]rotaxane $5\text{-}2\text{H}\cdot 4\text{PF}_6$.

Our demonstration of the feasibility of reversing the already much-studied⁷ recognition motif between the NH_2^+ centers in secondary dialkylammonium ions and the oxygen atoms in crown ethers means that we are now once again in a position to design, synthesize, and characterize a wide range of interlocked molecular compounds and polymers, including those incorporating the omnipresent poly(ethylene glycol)s (PEGs) as their threadlike components. Given the rapidly growing importance¹⁵ of PEG

conjugates with biologically active molecules, the ability to adorn them with positively charged beads is an attractive proposition.

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Supporting Information Available: Experimental details for the synthesis of all new compounds and ^1H NMR, ^{13}C NMR, and mass spectra (ESMS and FAB) of the [2]rotaxane $5\text{-}2\text{H}\cdot 4\text{PF}_6$ (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (13) Data for [2]rotaxane $5\text{-}2\text{H}\cdot 4\text{PF}_6$: ^1H NMR (CD_3NO_2 , 500 MHz): δ 2.78–2.84 (m, 4H), 2.91–2.98 (m, 4H), 3.16–3.23 (m, 4H), 3.36–3.42 (m, 4H), 3.55–3.65 (m, 8H), 4.00 (s, 8H), 4.45–4.60 (m, 12H), 4.65 (d, $J = 14.4 \text{ Hz}$, 4H), 6.97 (dd, $J = 2 \text{ Hz}$, 8 Hz, 4H), 7.20 (d, $J = 8 \text{ Hz}$, 4H), 7.29 (s, 16H), 7.55–7.65 (m, 12H), 7.65–7.73 (m, 12H), 7.87 (t, $J = 7.5 \text{ Hz}$, 6H); ^{13}C NMR (CD_3NO_2 , 125 MHz): δ 31.4 ($J_{\text{P-C}} = 48.9 \text{ Hz}$), 53.2, 70.7, 71.2, 71.3, 71.7, 71.8, 72.0, 73.5, 118.7 ($J_{\text{P-C}} = 85.8 \text{ Hz}$), 128.0 ($J_{\text{P-C}} = 8.4 \text{ Hz}$), 129.2, 130.0 ($J_{\text{P-C}} = 3.1 \text{ Hz}$), 130.7, 131.5 ($J_{\text{P-C}} = 12.5 \text{ Hz}$), 132.5 ($J_{\text{P-C}} = 5.4 \text{ Hz}$), 135.5 ($J_{\text{P-C}} = 9.6 \text{ Hz}$), 136.8 ($J_{\text{P-C}} = 2.9 \text{ Hz}$), 140.6 ($J_{\text{P-C}} = 4.0 \text{ Hz}$), 141.2 (one signal is “missing”, presumably because of two overlapping signals); MS (FAB) m/z 1783 [$\text{M} - \text{H} - 2\text{PF}_6$] $^+$ and 1637 [$\text{M} - 2\text{H} - 3\text{PF}_6$] $^+$; MS (ESMS) $m/z = 892$ [$\text{M} - 2\text{PF}_6$] $^{2+}$, 820 [$\text{M} - \text{H} - 3\text{PF}_6$] $^{2+}$, 746 [$\text{M} - 2\text{H} - 4\text{PF}_6$] $^{2+}$.
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