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Binding of secondary dialkylammonium salts by pyrido-21-crown-7

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ABSTRACT

Pyrido-21-crown-7 (**P21C7**) has been synthesized and shown to form [2]pseudorotaxanes spontaneously with secondary dialkylammonium ions. These complexes are stronger than their benzo-21-crown-7 counterparts and much stronger than their dibenzo-24-crown-8 counterparts. Based on this new **P21C7**/secondary dialkylammonium salt recognition motif, a [2]rotaxane terminated by phenyl groups as stoppers has been successfully constructed using the threading-followed-by-stoppering technique.

Secondary dialkylammonium salts have been widely used as guests of crown ethers and their derivatives in the construction of pseudorotaxane-, rotaxane-, and catenane-type threaded structures with many applications.[1,2] Recently, we reported that secondary dialkylammonium salts can thread through the cavity of benzo-21-crown-7 (**B21C7**) to form [2]pseudorotaxane- and [2]rotaxane-type threaded structures.[3] We found that **B21C7** can bind dialkylammonium salts more strongly than their traditional crown ether host dibenzo-24-crown-8 (**DB24C8**) and further demonstrated that **B21C7** is the smallest benzocrown ether, which is capable of forming threaded structures with secondary dialkylammonium salts. For the construction of more complicated mechanically interlocked threaded structures using the **B21C7**/secondary dialkylammonium salt recognition motif, it becomes worthwhile to functionalize **B21C7**. However, the use of mono- and difunctionalized *o*-phenylene crown ether hosts leads inevitably to complications as a result of the formation of stereoisomeric complexes when two or more hosts participate.[4]

In order to solve this symmetry-based problem that *o*-phenylene crown ethers have, one strategy employed by the Stoddart group is to replace one of the two catechol rings in **DB24C8** with a resorcinol ring to give benzo-*m*-phenylene-25-crown-8 (**BMP25C8**).[5] However, **BMP25C8** has much poorer binding of secondary dialkylammonium salts because it has forfeited one of the O–C–C–O repeating units from its constitution. Another strategy sought by the Stoddart group is to replace two –CH_2OCH_2– units of the 24-crown-8 cavity by 2,6-disubstituted pyridine rings to afford dipyrido-24-crown-8 (**DP24C8**).[4b] The strategy used by the Gibson group to solve the symmetry problem that *o*-phenylene crown ethers have is to introduce *m*-phenylene crown ethers.[6] By replacing both the catechol rings in **DB24C8** or dibenzo-30-crown-10 with resorcinol rings, they prepared bis-*m*-phenylene-26-crown-8 (**BMP26C8**), bis-*m*-phenylene-32-crown-10 (**BMP32C10**), and their derivatives.[6] Due to their symmetric nature, these substituted bis(*m*-phenylene) crown ethers can be easily prepared as pure compounds without tedious isomer separation, and they have simpler NMR spectra than those of their substituted bis(*o*-phenylene) analogues. However, **BMP26C8** and **BMP32C10** were shown not to complex effectively with secondary dialkylammonium salts.[6c]

Usually pyridine-containing crown ethers have stronger complexation to hydrogen-bonded guests than the analogous all-oxygen atom-containing crown ethers, since an aromatic nitrogen atom is a better hydrogen bond acceptor than either aliphatic or phenolic ether oxygen atoms.[4b,7] For example, the association constant (K_a) value, 1100 M^{-1}, of **DP24C8·DBA-Br** at 5 mM host and guest at 25 °C in acetonitrile was determined to be two times higher than the corresponding value, 352 M^{-1}, of **DB24C8·DBA-Br**.[4b] For another example, the binding of glycine to pyrido-18-crown-6 ($K_a = 1.6 \times 10^4\ M^{-1}$) was found to be four times stronger than that of 18-crown-6 ($K_a = 3.2 \times 10^3\ M^{-1}$) at 25 °C in methanol.[7] To solve the symmetry problem that functionalized *o*-phenylene crown ethers including benzo-21-crown-7 have, considering that the introduction of the pyridine nitrogen atom to the 21-crown-7 cavity will increase its binding to secondary dialkylammonium salts, and to further explore the 21-crown-7 cavity/secondary dialkylammonium salt recognition motif in the preparation of

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threaded structures, we prepared pyrido-21-crown-7 (**P21C7**),[8] which not only has the 21-crown-7 cavity but also can be functionalized at the C-4 position of its pyrido ring symmetrically,[4b] and used it in the preparation of [2]pseudorotaxane- and [2]rotaxane-type threaded structures.

The ability of **P21C7** to form [2]pseudorotaxanes with dialkylammonium salts **1**–**3** has been investigated by ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum (Fig. 1) of an equimolar solution of **P21C7** and dibutylammonium salt **1** in acetone-d_6 shows three sets of resonances for uncomplexed **P21C7**, uncomplexed **1**, and for the complex between **P21C7** and **1**, indicating the equilibrium between complexed and uncomplexed species is slow on the ^{1}H NMR time scale, allowing the determination of association constants to be made readily using the single-point method.[9] This implied the threading of **1** through the cavity of **P21C7** to form a pseudorotaxane. In the same way, complexations of **P21C7** with dialkylammonium salts **2** and **3** were also found to be slow-exchange systems, the same to **B21C7**-based complexes, **B21C7·1**, **B21C7·2** and **B21C7·3**,[3] and **DB24C8·4**,[2a] but in sharp contrast to **DB24C8·1**, **DB24C8·2**, **DB24C8·3**, and **DP24C8·4**, which are fast-exchange systems at room temperature.[2a,3,4b] From integrations of all peaks, the stoichiometries of all three complexation systems were determined to be 1:1. The K_a values[10] of **P21C7·1**, **P21C7·2**, and **P21C7·3** in acetone-d_6 are 1625 (±48) M^{-1}, 6396 (±224) M^{-1}, and 7479 (±299) M^{-1}, respectively. These values are higher than the corresponding K_a values,[3] 527 M^{-1}, 615 M^{-1}, and 1062 M^{-1}, of **B21C7**-based complexes **B21C7·1**, **B21C7·2**, and **B21C7·3** and much higher than the corresponding K_a values,[3] 135 M^{-1}, 155 M^{-1}, and 261 M^{-1}, of **DB24C8**-based complexes **DB24C8·1**, **DB24C8·2**, and **DB24C8·3** in acetone-d_6, indicating that **P21C7** is a more efficient host than **B21C7** and **DB24C8** for secondary dialkylammonium salts. The K_a increase from **P21C7·1** to **P21C7·2** to **P21C7·3** is a result of the acidity increase of *N*-methylene and ammonium hydrogens due to the increasing electron-withdrawing ability from propyl to phenyl to *p*-cyanophenyl substituents.

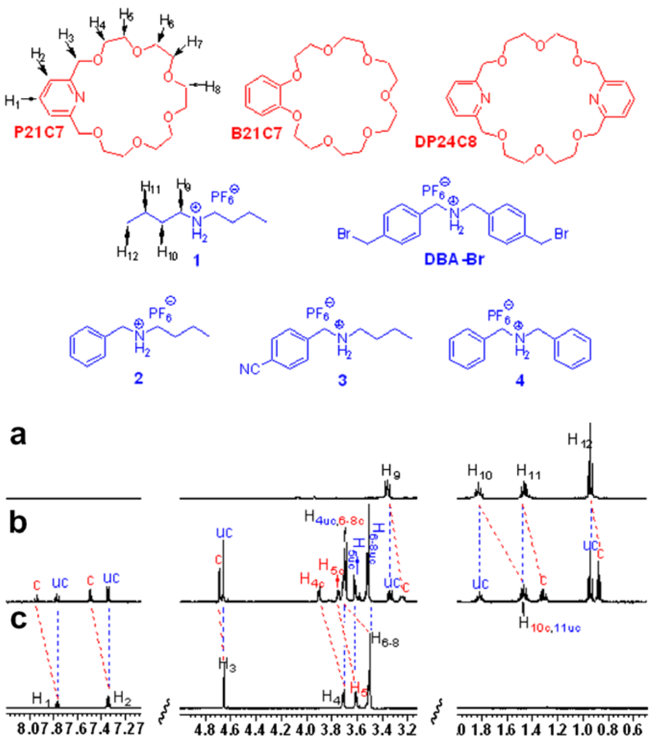
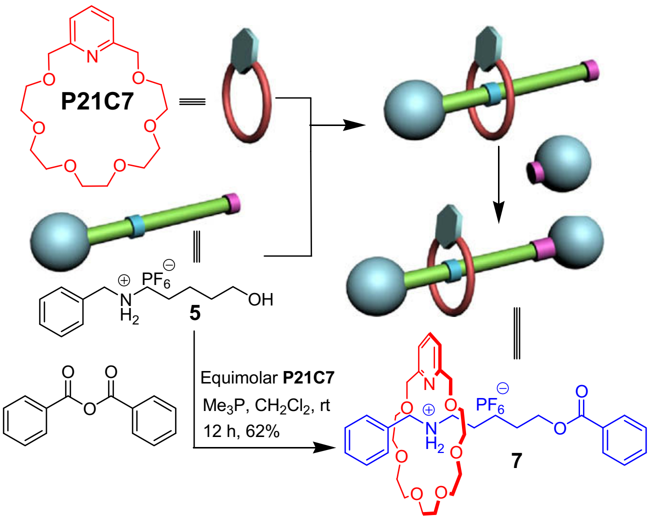


Figure 1. Partial ^{1}H NMR spectra (500 MHz, acetone-d_6, 22 °C) of 1.00 mM **1** (a), 1.00 mM **P21C7** and **1** (b), and 1.00 mM **P21C7** (c). Complexed and uncomplexed species are denoted by 'c' and 'uc', respectively.

Electrospray ionization mass spectra of equimolar acetone solutions of **P21C7** and each of **1–3** confirmed the 1:1 stoichiometries. A common mass fragment of $[\mathbf{M}-PF_6]^+$ was found: *m*/*z* 471.3 (64%) for **P21C7·1**, 505.3 (45%) for **P21C7·2**, and 530.3 (37%) for **P21C7·3**. The base peak is at *m*/*z* 342.1, corresponding to [**P21C7** + H]$^+$ for **P21C7·1**, while the base peaks are at *m*/*z* 364.1, corresponding to [**P21C7** + Na]$^+$ for both **P21C7·2** and **P21C7·3**.

We then prepared **P21C7**-containing [2]rotaxane using threading-followed-by-stoppering technique (Scheme 1).[11] Here, two phenyl groups were employed as the stoppers. Although **5** is quite soluble in MeOH, Me_2CO, CH_3CN, and Me_2SO, it is only slightly soluble in CH_2Cl_2, while **5** becomes soluble in this solvent after the addition of a molar equivalent of **P21C7**, indicating the formation of a stable complex **P21C7·5**. An equimolar dichloromethane solution of **P21C7** and **5** was treated with benzoic anhydride in the presence of trimethylphosphine as the catalyst[3,12] to yield the [2]rotaxane **7** in 62% yield (Scheme 1). Partial proton NMR spectra of the dumbbell-shaped component **6**, rotaxane **7** and **P21C7** in DMSO-d_6 are shown in Figure 2. The aromatic proton H_2 and ethyleneoxy proton H_3 of **P21C7** moved upfield and methylene protons H_d, H_h, and H_i on **6** moved downfield after the formation of rotaxane **7**. These chemical shift changes, which persisted even after excess triethylamine was added (Fig. S8), in DMSO proved that **7** is a rotaxane, since no complexation is expected in this highly polar solvent.[2a,3] The ESI mass spectrum of rotaxane **7** has a single peak at *m*/*z* 654.4 (100%) corresponding to $[\mathbf{7}-PF_6]^+$.

The solid-state structure (Fig. 3) is established by X-ray crystallography on a suitable single crystal grown by vapor diffusion of petroleum ether into an ethyl acetate solution of **7**.[13] It reveals the anticipated threading of the secondary dialkylammonium cation through the center of the **P21C7** macrocycle. Three *N*-methylene hydrogen atoms and two N-H hydrogen atoms are involved in seven hydrogen bonds (Fig. 3) comprising $N^+-H\cdots N$ (**A** in Fig 3), $C-H\cdots O\cdots$(**B**, **C** and **D** in Fig. 3) and $N^+-H\cdots O$ (**E**, **F**, and **G** in Fig. 3) with four oxygen atoms and the pyridine nitrogen atom of **P21C7**. In the crystal structure of a previously reported [2]rotaxane based on **B21C7** and the same dumbbell-shaped component **6**,[3] all four *N*-methylene hydrogens of the secondary dialkylammonium salt dumbbell-shaped component and all seven oxygen atoms of the 21-crown-7 cavity are involved in hydrogen bonding between the host and the guest in the solid state, while here one *N*-methylene hydrogen atom of the dumbbell-shaped component and two oxygen atoms of the 21-crown-7 cavity are not involved in hydrogen bonding between the host and the guest in the solid state



Scheme 1. Synthesis of [2]rotaxane **7**.

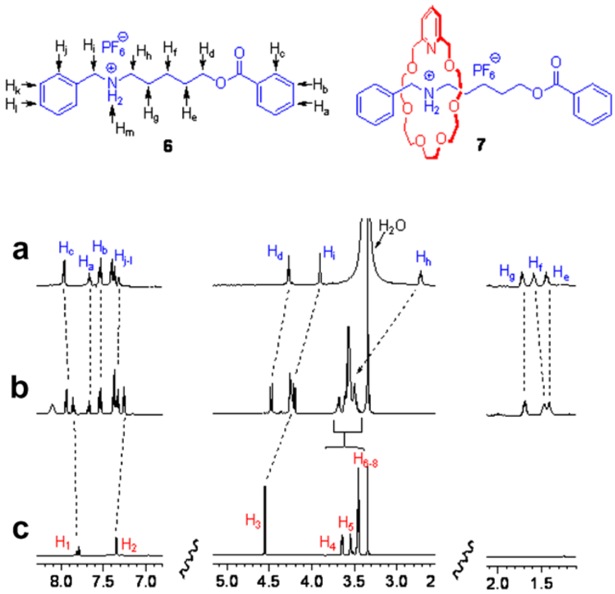


Figure 2. Partial ^{1}H NMR spectra (500 MHz, DMSO-d_6, 22 °C) of dumbbell-shaped component **6** (a), rotaxane **7** (b), and **P21C7** (c).

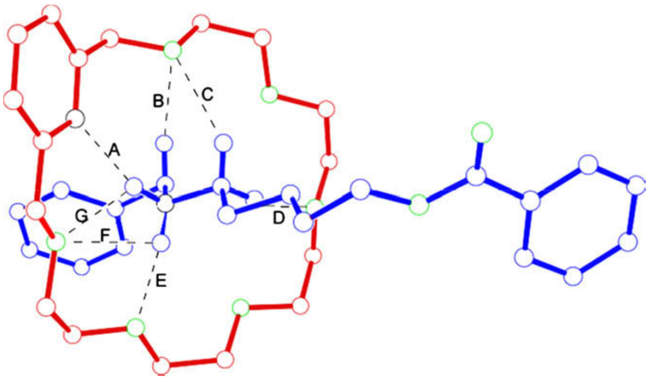


Figure 3. Crystal structure of the [2]rotaxane **7**. A PF_6 counterion, and hydrogens except the ones involved in hydrogen bonding have been omitted for clarity. **P21C7** is red, **6** is blue, hydrogens are magenta, oxygens are green, and nitrogen is black. Hydrogen-bond parameters: H···O distances (Å), C(N)–H···O(N) angles (°), C(N)···O(N) distances (Å) A, 2.18, 161, 3.04; B, 2.61, 140, 3.41; C, 2.51, 143, 3.33; D, 2.37, 161, 3.30; E, 2.00, 168, 2.89; F, 2.69, 95, 2.91; G, 2.30, 124, 2.91.

(Fig. 3), indicating that although both **P21C7** and **B21C7** are 21-membered rings, **P21C7** has a slightly bigger cavity than **B21C7**. This is in accordance with that the cavity of **DP24C8** is bigger than that of **DB24C8** so **DP24C8·4** is a fast-exchange system while **DB24C8·4** is a slow-exchange system at room temperature.[2a,3,4b]

In summary, here we have demonstrated that **P21C7** can bind widely used secondary dialkylammonium salt guests more strongly than **B21C7** and much more strongly than **DB24C8**. Therefore, **P21C7** is an attractive alternative for **DB24C8**, the traditionally used host for the secondary dialkylammonium salts. Furthermore, **P21C7**-based [2]pseudorotaxane- and [2]rotaxane-type threaded structures have been successfully prepared. Considering the high association constants of the complexes based on **P21C7** and secondary dialkylammonium salts (such as **1**–**3**) and the symmetric nature of the **P21C7** derivatives resulted from the substitution at the C-4 position of its pyrido ring,[4b] **P21C7** should be a versatile macrocyclic host for secondary dialkylammonium salts in the preparation of threaded structures. Currently, we are using the pyridine-21-crown-7/secondary dialkylammonium salt recognition motif in preparing other threaded structures, and the results will be reported in due course.

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Supplementary data

Synthetic procedures, characterizations, determination of association constants of **P21C7·1**, **P21C7·2**, and **P21C7·3**, and crystal data for rotaxane **7**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.110.

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7107 independent reflections, 478 parameters, 0 restraints, $F(000) = 1656$, $R_1 = 0.1130$, $wR_2 = 0.2795$ (all data), $R_1 = 0.0823$, $wR_2 = 0.2544$ [$I > 2\sigma(I)$], max. residual density $0.820\,\mathrm{e}\,\text{Å}^{-3}$, and GoF ($F^2$) = 1.126. Crystallographic data (excluding structure factors) for the structure in this Letter have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 687760. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: 144-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].