

# Highly efficient synthesis of [3]- and [5]-rotaxanes consisting of crown ether and a *sec*-ammonium salt

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[3]- and [5]-rotaxanes consisting of crown ether and ammonium salts were synthesized in high yields by a tributylphosphine-catalyzed end-capping method which provides a simple and practical means of obtaining higher-order rotaxanes.

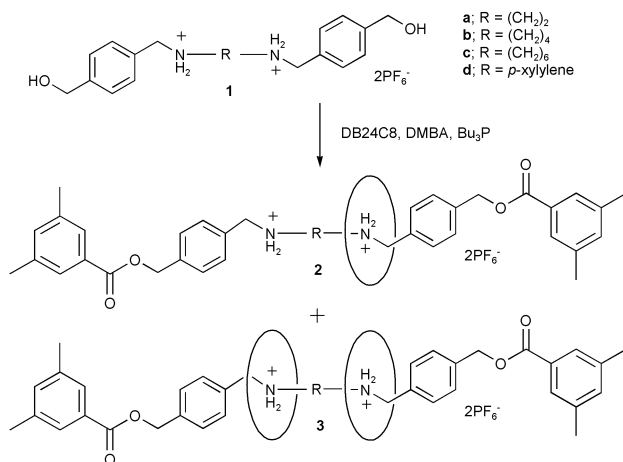
While the synthesis of [2]rotaxanes has been well established by a variety of approaches such as metal template, CT interaction and hydrogen bonding,<sup>1</sup> the synthesis of [3]- and higher-order rotaxanes still remains a challenging task.<sup>2</sup> So far, only very few [5]- and higher-order rotaxanes have been prepared.<sup>3</sup> Higher-order rotaxanes are necessary substances to construct molecular devices with complex functionality.<sup>4</sup> Our previous report described the protocol of high yielding synthesis of [2]rotaxanes by the threading of secondary ammonium salts into crown ethers followed by acylative end-capping.<sup>5</sup> Rotaxanes consisting of a crown ether and an ammonium salt seem quite promising because of their potential applicability based on their ease in structural modification.<sup>6</sup> Herein, we report the high yielding synthesis of [3]- and [5]-rotaxanes. This [5]rotaxane is the first that has no steric barrier to suppress the shuttling of the wheel on the axle.<sup>3a</sup>

The synthesis of [3]rotaxanes was achieved as shown in Scheme 1. Primary diamines were converted to bisammonium salt **1** via condensation with methyl 4-formylbenzoate, followed by LiAlH<sub>4</sub> reduction and protonation. The synthesis of the rotaxanes was carried out in CH<sub>2</sub>Cl<sub>2</sub>–CH<sub>3</sub>CN mixed solvent since the pseudorotaxane derived from the bisammonium salts was insoluble in less polar solvents. Although the axles (**1a–d**) were insoluble in CH<sub>2</sub>Cl<sub>2</sub>–CH<sub>3</sub>CN (1 : 1) at room temperature, **1b** and **1c** were dissolved upon the addition of DB24C8 via the formation of pseudorotaxane. Thus, a solution of **1** and DB24C8 was treated with 3 equiv. of 3,5-dimethylbenzoic anhydride (DMBA) and 20 mol% of tributylphosphine to end-cap the terminal hydroxy groups.<sup>5</sup> Both [2]rotaxane **2** and [3]rotaxane **3** formed were isolated by preparative HPLC. The preparation of **2** and **3** using various axle bisammonium salts is summarized in

Table 1. [3]Rotaxane **3c** was isolated in 64% yield while [2]rotaxane **2c** was also obtained in 30% yield.<sup>7</sup> As the length of the spacer (R) decreased, the yield of rotaxanes decreased. The first complexation seemed to inhibit the second complexation in the case of a shorter spacer.<sup>8</sup> When an ethylene spacer was used (**1a**), only a small percentage of [2]rotaxane was obtained. The solubility of **1a** in organic solvents was too low to form the pseudorotaxane. Based on the above results, the reaction condition was optimised for the preparation of [3]rotaxane **3c**: **3c** was obtained in 85% yield when the reaction was carried out using six equivalents of DB24C8 in CH<sub>2</sub>Cl<sub>2</sub>–CH<sub>3</sub>CN (2 : 1).

The structures of the [3]rotaxanes were confirmed by both FAB-MS and <sup>1</sup>H NMR spectra. In the <sup>1</sup>H NMR spectra, signals characteristic of rotaxane structures were observed: the benzylic protons attached to the ammonium group shifted to downfield by intramolecular CH...O hydrogen bonding with crown ether oxygens, and appeared as multiplet signals like other similar systems.<sup>9</sup> Further, the methylene protons of DB24C8 appeared as complex multiplet signals since each face of crown ether is diastereotopic. Finally, the rotaxane structure was fully confirmed by X-ray crystallographic analysis. Crystals of **3c** for analysis were obtained by recrystallization from CHCl<sub>3</sub>–EtOH. Fig. 1 shows the crystal structure of **3c**.<sup>10</sup> Both crown ethers were placed at each ammonium moiety to keep the hydrogen bonding interaction between the ammonium salt and crown ether components.

The successful synthesis of [3]rotaxane prompted us to investigate the synthesis of a [5]rotaxane. Tetrakisammonium salt **6**, in which the ammonium moieties were connected to each other by a hexamethylene spacer, was designed and synthesized starting from mono-protected hexamethylenediamine **4** as shown in Scheme 2. In the presence of 12 equiv. of DB24C8, **6** was dissolved in CH<sub>2</sub>Cl<sub>2</sub>–CH<sub>3</sub>CN (4 : 1) to form the corresponding pseudorotaxane. End-capping of the pseudorotaxane with DMBA was successfully achieved in the presence of tributylphosphine as catalyst. Purification by preparative HPLC generated the desired [5]rotaxane **7** in 72% yield.<sup>7</sup> The formation of lower-order rotaxane was not confirmed. The extremely high yield of **7** was attributed to both the high association constant between **6** and DB24C8, and the high catalytic activity of tributylphosphine in the acylation. The [5]rotaxane structure of **7** was confirmed by FAB-MS and NMR

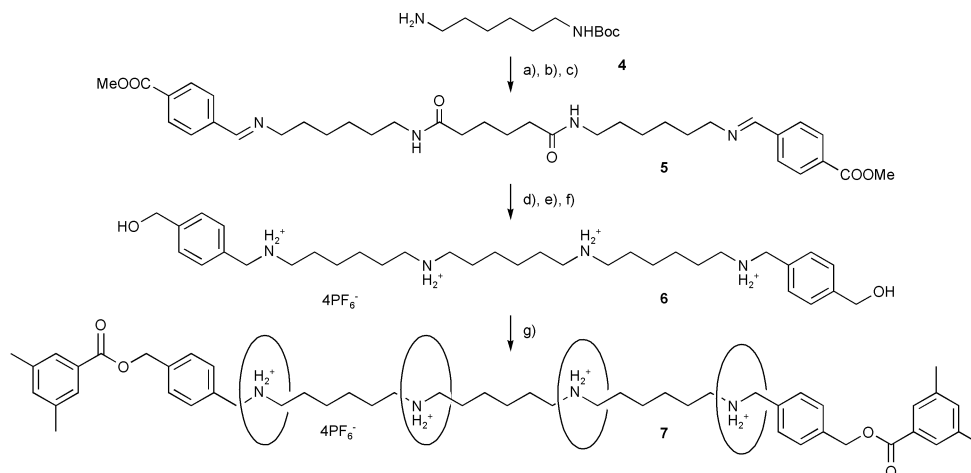


Scheme 1

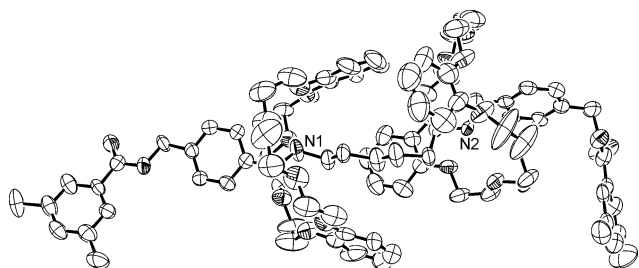
Table 1 Effect of spacer on the formation of [2]- and [3]-rotaxanes<sup>a</sup>

Ammonium salt	R	Yield (%)	
		[2]rotaxane <b>2</b>	[3]rotaxane <b>3</b>
<b>1a</b>	(CH <sub>2</sub> ) <sub>2</sub> <sup>b</sup>	< 6 <sup>c</sup>	0
<b>1b</b>	(CH <sub>2</sub> ) <sub>4</sub>	23	51
<b>1c</b>	(CH <sub>2</sub> ) <sub>6</sub>	30	64
<b>1d</b>	–CH <sub>2</sub> –C <sub>6</sub> H <sub>4</sub> –CH <sub>2</sub> –	36	64

<sup>a</sup> All reactions were carried out in CH<sub>2</sub>Cl<sub>2</sub>–CH<sub>3</sub>CN (1 : 1, 0.1 M<sup>–1</sup>) at room temperature using DMBA in the presence of 2.2 equivalents of DB24C8 and 20 mol% of Bu<sub>3</sub>P. <sup>b</sup> Carrying out in heterogeneous because of low solubility. <sup>c</sup> Determined by <sup>1</sup>H NMR.



**Scheme 2** Reagents and conditions: (a) adipoyl chloride,  $\text{CHCl}_3$ , rt, 89%, (b) trifluoroacetic acid, rt, (c) methyl 4-formylbenzoate,  $\text{CHCl}_3$ , reflux, 69% in two steps, (d)  $\text{LiAlH}_4$ , THF, reflux, (e) HCl, (f)  $\text{NH}_4\text{PF}_6$ , 60% in three steps, (g) 12 equivalents of DB24C8, DMBA, 20 mol% of  $\text{Bu}_3\text{P}$ ,  $\text{CH}_2\text{Cl}_2$ – $\text{CH}_3\text{CN}$  (4 : 1), rt, 24 h, 72%.



**Fig. 1** ORTEP drawing of [3]rotaxane **3c**. Hydrogens, counter anions ( $\text{PF}_6^-$ ) and solvents ( $\text{CHCl}_3$  and  $\text{EtOH}$ ) are omitted for clarity.

spectra. **7** could also be simply isolated by precipitation into MeOH in 58% yield. The simple and easy work-up is an important feature of this method.

In summary, we have demonstrated the practical and high-yielding synthesis of [3]- and [5]-rotaxanes consisting of crown ether and oligoammonium salt. The method described here can be applied to the synthesis of higher rotaxanes without significant decrease in yield. The rotaxanes thus obtained can be modified by neutralization of the ammonium group by acylation,<sup>6</sup> leading to the formation of neutral rotaxanes and it is currently under active investigation.

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- 3c**: mp 174–175 °C; IR (KBr) 3164, 1713, 1505, 1253, 1213, 840  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  7.62 (s, 4H), 7.46 (d,  $J$  8.4 Hz, 4H), 7.32 (s, 2H), 7.06 (br s, 4H), 6.96–6.93 (m, 8H), 6.89–6.85 (m, 8H), 5.29 (s, 4H), 4.56 (t,  $J$  5.6 Hz, 4H), 4.19–4.15 (m, 8H), 4.07–4.03 (m, 8H), 3.81–3.71 (m, 16H), 3.59–3.55 (m, 8H), 3.42–3.37 (m, 8H), 2.83 (br s, 4H), 2.35 (s, 12H), 1.07 (br s, 4H), 0.43 (br s, 4H); FAB-MS (matrix;  $m$ -NBA):  $m/z$  1664 [ $M - \text{PF}_6$ ] $^+$ . Anal. Calc. for  $\text{C}_{88}\text{H}_{114}\text{F}_{12}\text{N}_2\text{O}_{20}\text{P}_2 \cdot \text{CHCl}_3$ : C 55.41, H 6.01, N 1.45. Found: C 55.39, H 5.95, N 1.47%. **7**: mp 219–222 °C; IR (KBr) 3448, 1718, 1593, 1506, 1254, 1124, 841;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  7.65 (s, 4H), 7.40 (d,  $J$  8.0 Hz, 4H), 7.29 (s, 2H), 7.27 (d,  $J$  8.0 Hz, 4H), 7.06 (br s, 4H), 6.91–6.86 (m, 32H), 6.60 (br s, 4H), 5.21 (s, 4H), 4.57 (t,  $J$  6.7 Hz, 4H), 4.12–4.03 (m, 32H), 3.81–3.77 (m, 32H), 3.65 (s, 16H), 3.62–3.58 (m, 16H), 3.12–3.04 (m, 12H), 2.36 (s, 12H), 1.17 (br s, 12H), 0.79 (br s, 4H), 0.68 (br s, 8H); FAB-MS (matrix;  $m$ -NBA):  $m/z$  3050 [ $M - \text{PF}_6$ ] $^+$ ; Anal. Calc. for  $\text{C}_{148}\text{H}_{206}\text{F}_{24}\text{N}_4\text{O}_{36}\text{P}_4 \cdot \text{H}_2\text{O}$ : C 55.29, H 6.52, N 1.74. Found: C 55.05, H 6.59, N 1.68%.
- $K_a$  values of this system could not be determined by NMR experiments because the complexes could not be distinguished from each other.
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- Crystal data for [3]rotaxane **3c**:  $\text{C}_{90}\text{H}_{118}\text{F}_{12}\text{N}_2\text{O}_{20.50}\text{P}_2\text{Cl}_3$ ,  $M = 1952.21$ , monoclinic, space group  $C2/c$ ,  $a = 41.6032(9)$ ,  $b = 16.1461(3)$ ,  $c = 32.8652(7)$  Å,  $Z = 8$ ,  $V = 19740.3(6)$  Å $^3$ ,  $D_c = 1.314$   $\text{cm}^{-3}$ ,  $\mu(\text{Mo-K}\alpha) = 0.214$  Å, 76981 reflections were measured, 16980 were unique,  $R1 = 0.097$  and  $wR2 = 0.288$  for 16950 reflection with  $F > 3\sigma(F)$ . The structure was solved and refined on  $F$  squared using TEXSAN programs. CCDC 191668. See <http://www.rsc.org/suppdata/cc/b2/b207872d/> for crystallographic data in CIF or other electronic format.