

Preparation of Loose-fit Polyrotaxane Composed of β -Cyclodextrin and Poly(ethylene glycol) Derivatives through the Slipping–Expanding Protocol

Ryo Katoono,^{*1,2} Yuichiro Kobayashi,¹ and Nobuhiko Yui^{1,2}

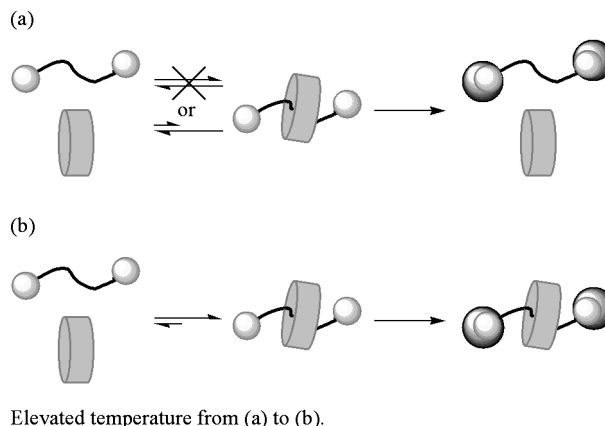
¹School of Materials Science, Japan Advanced Institute of Science and Technology, Nomi, Ishikawa 923-1292

²JST, CREST, Chiyoda-ku, Tokyo 102-0075

(Received May 31, 2010; CL-100511; E-mail: katoono@jaist.ac.jp)

At an elevated temperature, a methylated β -cyclodextrin (β -CD) derivative was self-assembled onto a poly(ethylene glycol) (PEG) chain attached to bulky end groups (*slipping*), and entrapped through a chemical modification at the end groups (*expanding*), leading to an interlocked species. The preparation of a loose-fit polyrotaxane composed of β -CD and PEG was demonstrated as the slipping–expanding protocol.

Polyrotaxanes have an interlocked structure in which a number of cyclic molecules are threaded on a linear polymeric chain capped with bulky end groups,¹ and have been attracting a lot of attention as a building block to construct nanoarchitectures and to design functional materials² since an unprecedented synthetic approach was discovered in 1992.^{3a} Harada et al. reported successful preparations of cyclodextrin (CD)-based polyrotaxanes by threading of a polymeric chain into the CD cavity, followed by endcapping with bulky molecules.³ The slipping approach is also available to construct rotaxanes, as reported by Stoddart and other scientists.^{4,5} We envisaged that an integration of the two above-mentioned approaches would provide a methodology for constructing polyrotaxanes with a variety of combinations of cyclic and linear components.⁶ One can imagine a dumbbell-shaped molecule that has no station for entrapping a ring. When a mismatched ring is selected, each of the components would prefer an uncomplexed state due to insufficient energy to overcome the barrier or small gain in enthalpy upon rotaxanation (Scheme 1a). In such a system, if the temperature is elevated, rotaxanated species would be formed through a thermodynamic stabilization in an entropy-driven manner, involving a change in the states of solvation. Enlargement of the end groups through a reaction at the elevated temperature would allow the intermediary complex to be interlocked species, as drawn in Scheme 1b. It would be of advantage in the construction of a loose-fit polyrotaxane⁷ with mismatching in terms of size-adequacy, for instance, a combination of β -CD and PEG. Here we report the preparation of a loose-fit polyrotaxane composed of β -CD and PEG derivatives through the slipping–expanding protocol, based on the

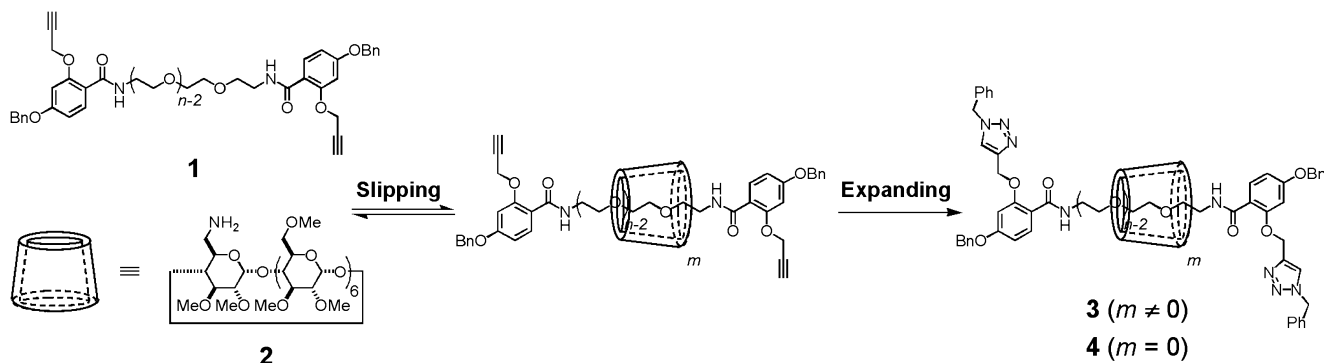


Scheme 1.

complexation between mismatched components, followed by enlargement of the end groups. Thus, we designed the dumbbell-shaped PEG derivative **1** with a 2-propynyl-appended benzoyl group at each end to entrap cyclic molecules by slipping on–off at an elevated temperature, and to lock in these molecules by enlargement of the ends through a 1,3-dipole addition reaction with an azide compound.⁸ Monoaminated permethylated β -CD derivative **2**⁹ was employed as a cyclic molecule with mismatch in size (Scheme 2).

The dumbbell-shaped **1** was prepared by a reaction of PEG ($M_n = 950$ – 1050) bis(2-aminoethyl) ether (PEGBA) and 4-benzyl-oxy-2-(2-propynyloxy)benzoyl chloride, which was obtained by a stepwise alkylation of methyl 2,4-dihydroxybenzoate, followed by hydrolysis, and treatment with thionyl chloride (Scheme S1).¹²

A preliminary test-mixing of **1** and unmodified β -CD in water at 25/60 °C for 3 weeks successfully gave a solid containing **1** and β -CD in a ratio of 1:10, although no precipitate was formed upon mixing PEGBA and β -CD under any conditions, as expected.^{3c} It seems that β -CD was self-assembled onto **1** with the help of intermolecular hydrogen bonding forming a precipitate.¹⁰



Scheme 2.

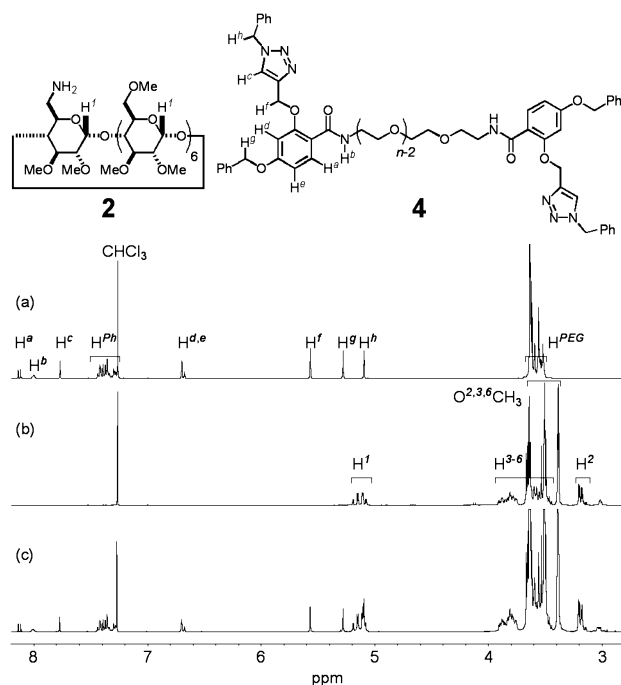


Figure 1. ^1H NMR spectra (400 MHz) of (a) dumbbell **4**, (b) ring **2**, and (c) polyrotaxane **3** (Entry 3), measured in CDCl_3 at room temperature.

Table 1. Conditions for slipping, the number (m) of **2** in **3**, determined by ^1H NMR, and yields of **3**^a

Entry	Temp/ $^{\circ}\text{C}$	Time/day	m	Yield of 3 /%
1	60	3	1.0	17
2	60	7	2.5	14
3	60	14	3.4	14
4	60	21	3.6	14
5	rt	14	—	<1
6	60	7	—	<1

^aConcentrations of **1** and **2** were constant ($[\mathbf{1}] = 6 \times 10^{-2} \text{ M}$ and $[\mathbf{2}] = 7 \times 10^{-1} \text{ M}$). Mixing at lower concentrations ($[\mathbf{1}] < 3 \times 10^{-2} \text{ M}$ and $[\mathbf{2}] < 4 \times 10^{-1} \text{ M}$) failed to give **3**. The yields of **3** were calculated based on **1** with an assumption that the repeating distribution of an ethylene glycol unit in **1** (averaged $n = 24$) was invariable. Conditions for the expanding reaction are as follows: BnN_3 (10 equiv), CuSO_4 (0.8 equiv), and (+)-ascorbic acid (2 equiv), for 3 h at the same temperature as in the slipping process (Entries 1–5) and rt (Entry 6).

Mixing of **1** and **2** in water at $25/60^{\circ}\text{C}$ led to no change in appearance due to high water-solubility of **2**,¹¹ thus the transparent solution was subjected to the expanding reaction in one pot after a period of slipping to give loose-fit polyrotaxanes **3** in 14–17% yield, which was successfully isolated in pure form by silica gel column chromatography and gel permeation chromatography due to the differences in R_f value (0.44 for **3**, 0.36 for **4**, and 0.09 for **2**, eluted with 10% $\text{MeOH}/\text{CH}_2\text{Cl}_2$ on SiO_2) and retention time (see experimental section and Figure S1).¹² The β -CD derivative **2** was found in association with a PEG component in the ^1H NMR spectrum of **3** exhibiting a simple integration of each component (Figure 1). The content of **2** in a series of **3** was increased with time for slipping (Table 1, Entries 1–4). Isolation of polyrotaxanes **3** can support the slipping and entrapping of **2** onto **1** in water at 60°C . It is noted that the slipping and expanding reaction at room temperature did not lead to a sufficient amount of rotaxane, but gave a dumbbell **4** in 88% yield

through a simple enlargement of the ends (Table 1, Entry 5). Also, an expanding reaction at room temperature failed to hold a ring even after maintaining the system at 60°C for 7 days (Table 1, Entry 6).

These results are interesting in terms of controlling the content of cyclic molecules in a CD-based polyrotaxane. In some cases, especially for polymeric chains with large molecular weights, self-assembly of cyclic molecules onto a long polymeric chain can lay down in the course of threading to give a partially covered pseudopolyrotaxane as a solid, which is not always arbitrarily controlled by mixing conditions such as ratios, concentrations, temperatures, and others.

In conclusion, we demonstrated a synthetic approach, the slipping–expanding protocol, for the construction of a loose-fit polyrotaxane, based on the complexation between mismatched components of β -CD and PEG derivatives, followed by enlargement of the ends of PEG through a chemical modification. The protocol, in principle, would be applied to a wide variety of polyrotaxane preparations. When the β -CD derivative is linked by a spacer, self-assembly of the linked derivative onto the dumbbell-shaped PEG at an elevated temperature would be also interesting in terms of designing a novel class of thermoresponsive materials, which is in progress and will be reported soon.

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- The ^1H NMR spectrum of **1** itself ($[\mathbf{1}] = 3.2 \times 10^{-2} \text{ M}$) measured in D_2O at room temperature showed broadened resonances, whose intensity was remarkably increased at 60°C , although the solution remained turbid in appearance at both temperatures due to the hydrophobic inhereance in **1**. No difference was found in the spectra of **2** itself ($[\mathbf{2}] = 3.5 \times 10^{-1} \text{ M}$) measured in D_2O at both temperatures, exhibiting sharpened resonances. Upon mixing of them in D_2O , significant downfield shifts were induced for the protons of terminal group in **1**, which were observed at both temperatures. The intensity of the resonances was unchanged in the two spectra measured at room temperature and 60°C , unlike in the case of **1** itself.
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