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Loose-Fit Polyrotaxane Composed of γ-Cyclodextrin and Single Poly(Ethyelene Glycol) Chain: Making Room in γ-CD Cavity for Additional Inclusion Complexation

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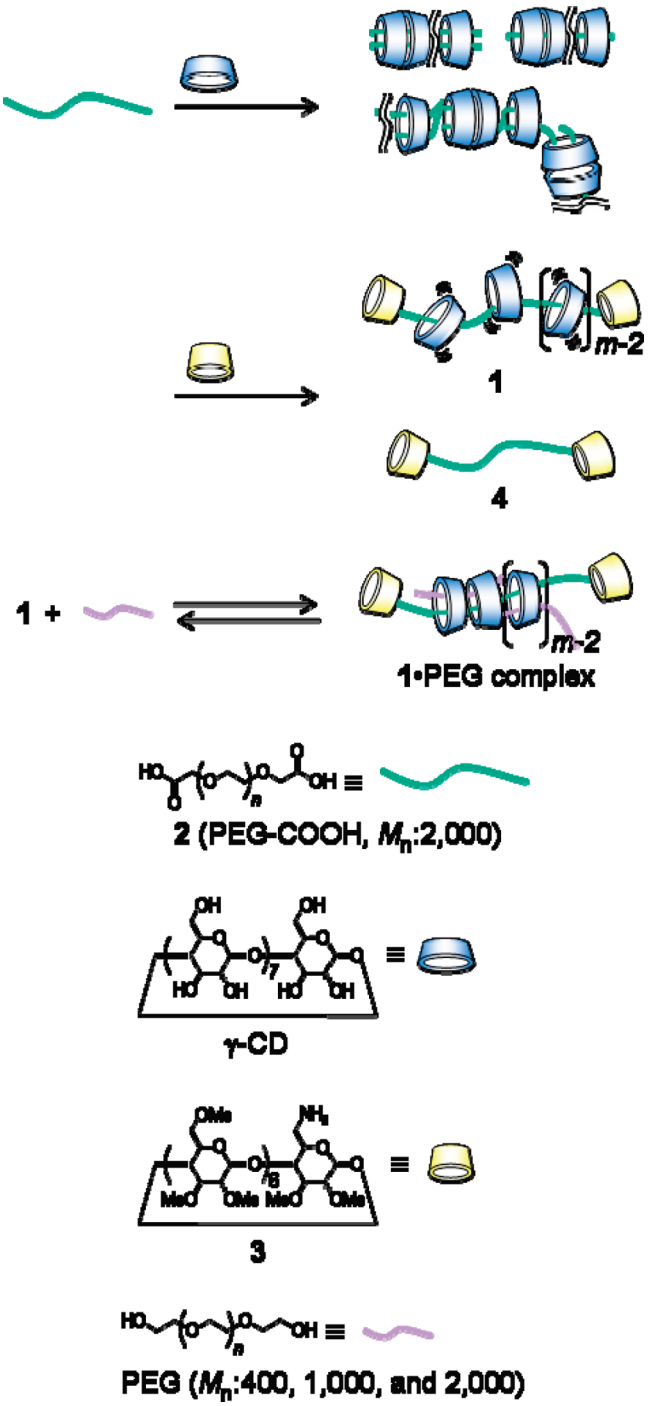
Cyclodextrin (CD)-based inclusion complexes have been paid much attention in the last decades for their potential as supermolecules,[1,2] in which CD molecules are assembled onto the linear polymeric guest molecules with a suitable size so as to fill the cavity.[3] It is worth mentioning that γ-CD has been reported to include two chains of linear polymeric guest such as poly(ethylene glycol) (PEG), although α-CD forms a single-stranded inclusion complex with such a polymeric chain.[4] Because it is easily imagined that a structure of single-stranded inclusion complexes is unambiguous, they are important precursors for the end-capping reaction at the terminals of polymeric chain with bulky molecules to give polyrotaxanes.[1,5] Also, the terminals of a polymeric chain in the inclusion complex of γ-CD would undergo an end-capping reaction, even with its ambiguous structures. We envisaged that a "loose" γ-CD-based polyrotaxane **1** containing only a single chain of PEG can be obtained if one of the included PEG chains is fortunately capped with a bulky molecule **3** during dissociation of the intermediary inclusion complex **2**·γ-CD (Scheme 1). In such a loose-bound relationship between the components, γ-CD would be endowed with additional inclusion of a guest polymer, as shown in Scheme 1. In this article, we report the preparation of a single-stranded polyrotaxane **1** composed of γ-CD and a single PEG chain as a novel class of molecular assemblies with "loose" structure thanks to mismatching in terms of the size-adequacy, which was characterized by ^{1}H NMR and MALDI-TOF mass spectroscopy. It was demonstrated that the cavity of γ-CD in **1** provided accommodation for PEG guests (M_n: 400, 1000, and 2000) to form an additional inclusion complex through ^{1}H NMR and XRD analyses.

An inclusion complex of γ-CD and PEG-COOH **2** (M_n: 2000) was prepared by mixing both components in water[4a,4b] as a precursor for the following end-capping reaction.[6] Monoaminated β-CD derivative **3**[7] was used as a bulky end-capping group to react with carboxylic terminals in the precursor complex. Single-stranded polyrotaxane **1** was isolated in 6% yield[8] and has the shortest retention time in GPC in the reaction mixture. No rotaxanated species was found other than **1**, even with the assumption of diverse inclusion complexes between γ-CD and **2**, as drawn in Scheme 1. Instead, most of the PEG component was found in **4** (PEG-[β-CD-$(OMe)_{20}$]$_2$), which was produced in over 90% yield through dissociation, followed by condensation at the terminals of **2**. GPC profiles for the polyrotaxane **1** and its components, β-CD-appended PEG **4** and γ-CD, are shown in Figure S1 in the Supporting Information.

The structure of **1** was first investigated by ^{1}H NMR spectroscopy in 1 wt % NaOD/D_2O. The spectrum was given as a simple integration of γ-CD and β-CD-appended PEG **4** and indicated that the components were present in a ratio of ca. 10:1 to construct the polyrotaxane **1** (Figure S2 in the Supporting Information).

The MALDI-TOF mass spectrum of **1** is shown in Figure 1a. An envelope of peaks is centered at ~16 600, ranging from 11 200 to 21 000, in which a repeating distribution is separated from the

Scheme 1. Preparation of the Single-Stranded Polyrotaxane 1 through the End-Capping Reaction of Intermediary Inclusion Complex 2·γ-CD with 3, and Additional Inclusion Complexation of 1 with a PEG Guest



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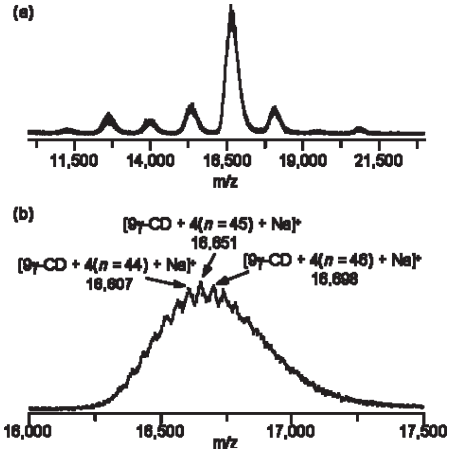

Figure 1. (a) MALDI-TOF mass spectrum of **1** and (b) its partial region around 16 600. Sinapinic acid was used as the matrix.

neighboring ones by 1297, corresponding to the molar mass of γ-CD. Detailed description of the MALDI-TOF mass spectrum is shown in Figure 1b. It was found that a repeating peak was separated from the neighboring peaks by 44, corresponding to the molar mass of an ethylene glycol (−CH_2CH_2O−) unit. The three peaks found at m/z values of 16 698, 16 651, and 16 607, for instance, can be ascribed to members (n = 46, 45, 44) of single-stranded polyrotaxane **1** possessing nine γ-CD molecules (16 695, 16 651, and 16 607 are theoretically calculated values for these structures, respectively). The similar repeating set was also found in the other distributions (m = 5−12). Averaging these members can satisfy the 10:1 ratio in the ^{1}H NMR spectrum even without considering any double-stranded species, which is in accordance with the fact that there exist no distribution overlaps at the same regions in Figure 1. The single-stranded structure of **1** with two terminals was further supported by a Job plot based on the complexation-induced chemical shifts in ^{1}H NMR spectroscopy upon complexation of **1** with adamantane carboxylic acid in 1 M $NaOD/D_2O$, which is known to be a suitable guest molecule for binding with β-CD.[9] The guest binding at the terminals of **1** was evidenced by a downfield shift of proton H^a in adamantane carboxylic acid. The 1:2 stoichiometry of the complex between **1** and adamantane carboxylic acid was confirmed by the plot exhibiting a peak at 0.67 (Figure 2).[10]

Considering the fact that the original γ-CD has a large enough cavity to include two molecules of PEG, the relation between γ-CD and the single PEG chain in **1** would be loose. Additional complexation of the single-stranded polyrotaxane **1** was examined with PEG chains (PEG_{400}, PEG_{1000}, and PEG_{2000}) as a macromolecular guest. In the presence of the PEG guest, the polyrotaxane **1** was first dissolved in water adjusted to a pH of 13 and then neutralized. During the dissolution−neutralization process, the inclusion complex **1**·PEG was formed as a white solid (Table S1 in the Supporting Information). The capturing of PEG into the solid was confirmed by the ^{1}H NMR spectrum showing the emphasized PEG signal. Powder X-ray diffraction analysis suggested the formation of inclusion complex of **1** with PEG_{2000} (Figure 3). A new peak at a 2θ of 7.5° was observed to indicate the emergence of a partially crystalline structure of γ-CD (Figure 3e), which is characteristic of γ-CD reported as the channel structure.[3e−3g,11] A similar peak is also observed in the diffractogram for the intermediary inclusion complex **2**·γ-CD (Figure 3c).[4b−4e,11] These diffractograms are different from that of γ-CD (Figure 3a) or PEG-COOH **2** (Figure 3b) itself. It is noted that washing of the complex **1**·PEG with an excess amount of water led to the disappearance of both the emphasized PEG signal in the ^{1}H NMR spectrum and the peak at 7.5° in the XRD

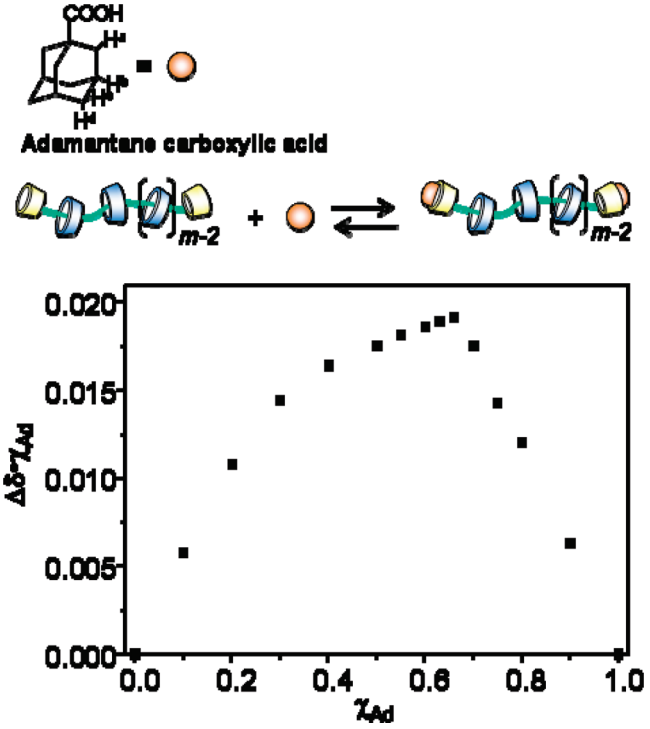

Figure 2. Job plot for the complexation of **1** with adamantane carboxylic acid (■ at proton H^a) in 1 M $NaOD/D_2O$ at 303 K. χ_{Ad} denotes the molar fraction of adamantane carboxylic acid.

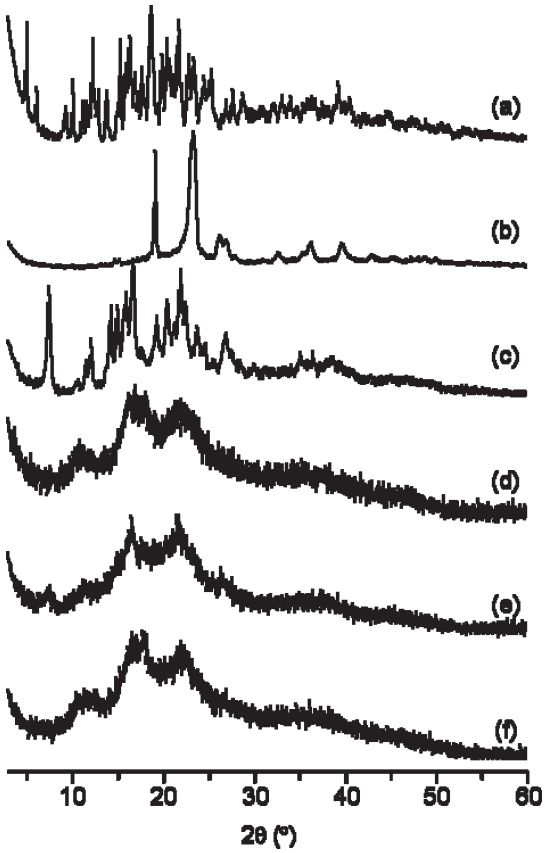

Figure 3. Powder X-ray diffractograms for (a) γ-CD, (b) **2**, (c) **2**·γ-CD, (d) **1**, (e) **1**·PEG_{2000}, and (f) **1**·PEG_{2000} after washing with excess water.

diffractogram to give the identical spectrum and pattern (Figure 3f) to those of **1** itself (Figure 3d). Similar results from

the other combinations (**1**·PEG_{400} and **1**·PEG_{1000}, Figure S3 in the Supporting Information) and a control experiment using α-CD-based polyrotaxane **5** are shown in Table S2 of the Supporting Information.

In conclusion, we have demonstrated the preparation of single-stranded "loose" polyrotaxane **1** composed of γ-CD and a single PEG chain. The MALDI-TOF mass spectrum revealed the single-stranded and doubly capped structure of **1** with repeating distributions of γ-CD and an ethylene glycol unit, which was further supported by a Job plot for the complexation at both terminals of **1** with adamantane carboxylic acid exhibiting the 1:2 stoichiometry. Complexation of **1** with additional PEG guests was demonstrated through the dissolution and neutralization process. In the complexes of **1**·PEG, a crystalline structure of γ-CD was found. We are now studying the complexation properties of a water-solubilized "loose" polyrotaxane with various guests in solution. Also, such a macromolecular inclusion complexation can exploit possible future applications for smart materials such as carriers of macromolecular drugs, gelators in reversible polymer networks, and so on.

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Supporting Information Available: Experimental details (materials, analyses, and synthetic procedures), gel permeation chromatograms, complexation of **1** with PEG guests, X-ray diffractograms, complexation of **5** with PEG_{2000}, ^{1}H NMR spectrum of **5**, and Job plot for the complexation of **5** with adamantane carboxylic acid. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) The precursor inclusion complex is composed of γ-CD and **2** in a ratio of ca. 9:1, which was calculated from the ^{1}H NMR spectrum measured in D_2O.

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(8) The yield of **1** was increased with reaction time up to 5 days. The single-stranded polyrotaxane **1** was not obtained at all by a similar condensation reaction in MeOH instead of water.

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(10) It was also confirmed by a similar plot that a single-stranded polyrotaxane **5**, in which 12 molecules of α-CD are threaded onto β-CD-appended PEG **4**, formed a 1:2 complex with adamantane carboxylic acid (Figure S6 in the Supporting Information). The ^{1}H NMR, and MALDI-TOF mass spectra of **5** are shown in Figure S4 and S5 in the Supporting Information.

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