Unique Inclusion Complex Formation between Skeleton-Modified Cyclodextrin and Polymers

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Cyclodextrins (CDs) are a class of cyclic oligosaccharides consisting of several α-(1,4)-linked D-glucopyranose units. Each CD molecule possesses a hydrophobic cavity into which organic molecules of the appropriate size and shape can be incorporated in aqueous media. The inclusion ability of CDs has been studied extensively and has been applied to many fields including food science, cosmetics, and pharmaceutical industries.[1−6] CDs can form inclusion complexes with polymers as well as low-molecular-weight compounds. The inclusion complexes of CDs with polymers, called pseudopolyrotaxanes, have been actively studied as a supramolecular architecture. For example, Harada et al. reported that α-CD forms a crystalline inclusion complex with poly(ethylene glycol).[7−10] This inclusion complex has been applied as a building block for topological gels[11] and a carrier for drug delivery.[12] The complexation of chemically modified CDs, such as methylated CD[13] and triacetylated CD,[14] with polymeric guests has also been reported.[15−21] However, the types of CD derivatives reported in those studies have been limited to the ones prepared by modification of the hydroxyl groups on the upper and/or lower rims of the CDs. Inclusion complex formation between skeleton-modified CDs,[22−25] such as aromatic-spacer-inserted CDs,[24] and polymeric guests has not been reported thus far. Recently, we reported the facile synthesis of skeleton-modified CD derivatives bearing a β-(1,4)-glucosidic bond from permethylated α- and β-CDs.[25] These CD derivatives showed different inclusion selectivity toward *m*- and *p*-nitrobenzoates from their parent permethylated CDs. Since the skeleton-modified CDs have very different cavity shapes from conventional CD derivatives, they are expected to show a unique inclusion ability toward polymeric guests and to form new inclusion complexes with the polymeric guests.

In this communication, we report the unique complex formation behavior of a skeleton-modified CD derivative, in which one α-(1,4) glucosidic bond from a permethylated α-CD is replaced by a β-(1,4) glucosidic bond, with various polymeric guests including polytetrahydrofuran (PTHF, $M_w = 1000$), poly(ϵ-caprolactone) (PCL, $M_w = 1250$), poly(propylene glycol) (PPG, $M_w = 2000$), and poly(acrylic acid) (PAA, $M_w = 1800$).

The synthesis of skeleton-modified CD derivative bearing a β-(1,4)-glucosidic bond was carried out according to the previously reported method.[25] An aqueous solution (1.0 mL) of skeleton-modified CD **1** (36.7 mg, 3.0×10^{-5} mol) or permethylated α-CD **2** (36.7 mg, 3.0×10^{-5} mol) as a control was agitated with the polymeric guests by ultrasonication for 1 h at 65 °C. The formed precipitate was collected by centrifugal separation and washed with hot *n*-hexane and then with distilled water at 65 °C twice and at 25 °C once to remove any uncomplexed polymeric guests and CD derivatives. After lyophilization, the obtained solids were analyzed by X-ray diffraction (XRD) and ^{1}H NMR (Table 1). When host **1** was mixed with the guest polymer at room temperature without ultrasonication, no precipitation was observed. It is generally accepted that complex formation between permethylated CDs and a guest polymer proceeds in three steps:[11,13] First, the polymer is included into the CD cavity by ultrasonication to generate hydrophilic complexes. Second, the threaded CD molecules are partially stacked along the polymer axis upon heating, and finally the intermolecular hydrophobic interactions between the CDs in the complexes cause the precipitation of the inclusion complex. In the case of host **1**, the precipitation may occur via a mechanism similar to the conventional methylated CDs (Figure 1).

When PTHF was used as a guest, the precipitate was formed in both cases of **1** and **2**. Here, the amount of **2**−PTHF precipitated was greater than that of **1**−PTHF. This result may show that **2** can more effectively form a complex with PTHF as compared to **1**. XRD analysis is an effective method for evaluating the formation of inclusion complexes between CD derivatives and polymeric guests.[13] The XRD patterns of the precipitates of **1**−PTHF and **2**−PTHF were clearly different from those of the corresponding free hosts (Figure 2), suggesting that these precipitates correspond to the inclusion complexes between the hosts and PTHF. The characteristic peaks (2θ = 7.41°, 12.8°, and 19.7°) of the α-CD−PEG complex[26] were also observed in the **1**−PTHF (2θ = 7.82°, 13.1°, and 19.1°) and **2**−PTHF precipitates (2θ = 7.76°, 12.5°, and 19.9°). These results suggest that these inclusion complexes adopt a columnar structure similar to that of the α-CD−PEG complex.

^{1}H NMR measurements of the precipitates were carried out in DMSO-d_6 to determine the host−guest stoichiometries. The stoichiometry (**1**:tetramethylene oxide unit) estimated from the integration ratio of the anomeric protons of host **1** to the β-methylene protons of PTHF was 1:3.5 (Figure 3). On the other hand, in the case of host **2**−PTHF, the stoichiometry was estimated to be 1:1.5 (**2**:tetramethylene oxide unit). These results show that the cavity size of **2** is more appropriately fitted to the cross-sectional size of PTHF as compared to **1**. These findings are consistent with the above-mentioned results in that a larger amount of precipitate was formed in **2**−PTHF than in the case of **1**−PTHF.

Hosts **1** and **2** also formed the precipitates when mixed with PCL. The XRD patterns of these precipitates indicated that the **1**−PCL and **2**−PCL complexes were formed with a columnar structure. The host−guest stoichiometries in the complexes were in ratios of 1:4.5 (**1**:CL unit) and 1:1 (**2**:CL unit), respectively. These results suggest that the capability of the skeleton-modified α-CD **1** to form an inclusion complex with a linear polymer is lower than that of the normal permethylated α-CD **2**.

Next, the formation of inclusion complexes of hosts **1** and **2** with guest polymers containing a methyl substituent (PPG) or a carboxyl substituent (PAA) on the chain was examined. Host **2** formed a precipitate with PPG but did not form a precipitate with PAA. This observation may indicate that the threading of **2** onto the PAA chain was hindered due to a geometric mismatch between PAA and the cavity of **2**. On the other hand, the skeleton-modified α-CD **1** formed precipitates with PAA as well as with PPG. In the XRD patterns of the **1**−PAA precipitate, different peaks from those of **1** and PAA alone were observed. This result suggests that a complex was formed between **1** and

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Table 1. Precipitate Formation between CD Derivatives (Hosts) and Guest Polymers

	host mg (mol)	guest	M_w	mg (mol)	precipitation[a]	yield[b] (mg)	composition[c] CD:guest unit
1	36.7 (3.0×10^{-5})	PTHF	1000	2.10 (2.1×10^{-6})	○	5.8 (0.9)	1:3.5
		PCL	1250	3.38 (2.7×10^{-6})	○	9.9 (2.9)	1:4.5
		PPG	2000	3.40 (1.7×10^{-6})	○	8.8 (0.8)	1:2.0
		PAA	1800	4.32 (2.4×10^{-6})	○	4.3 (1.0)	1:5.0
2	36.7 (3.0×10^{-5})	PTHF	1000	2.10 (2.1×10^{-6})	○	25.7 (1.9)	1:1.5
		PCL	1250	3.38 (2.7×10^{-6})	○	26.3 (2.2)	1:1.0
		PPG	2000	3.40 (1.7×10^{-6})	○	4.7 (1.0)	1:5.6
		PAA	1800	4.32 (2.4×10^{-6})	×		

[a] After washed with *n*-hexane and distilled water. [b] The weight of guest polymer in the precipitate is shown in parentheses. [c] Estimated from ^{1}H NMR spectra.

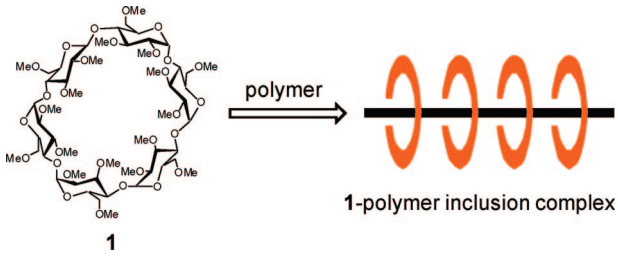

Figure 1. Schematic illustration of inclusion complex formation between skeleton-modified CD derivative **1** and a polymer.

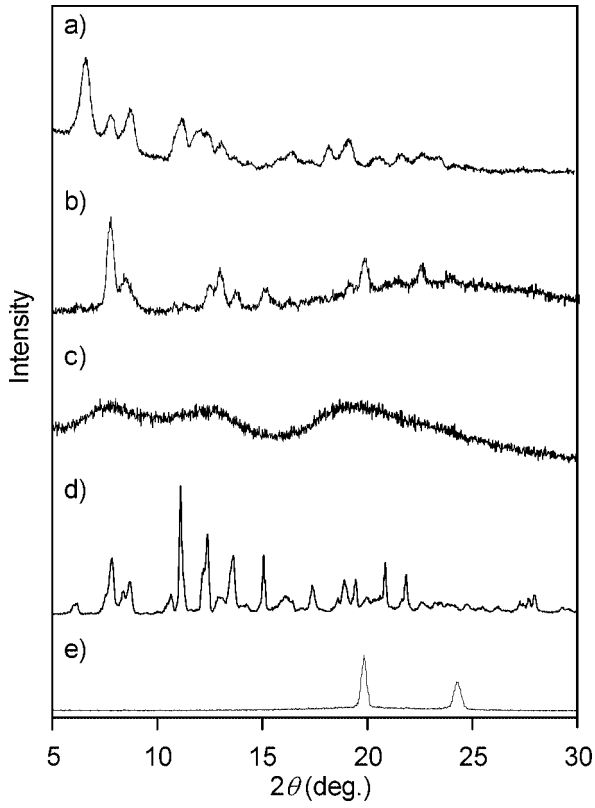

Figure 2. XRD patterns of (a) **1**−PTHF precipitate, (b) **2**−PTHF precipitate, (c) **1**, (d) **2**, and (e) PTHF.

PAA and that this complex has a columnar structure (2θ = 7.88°, 12.4°, and 19.2°) (Figure 4). Figure 5 shows the FT-IR spectra of the **1**−PAA complex, **1**, and PAA.

The C═O stretching vibration band at 1698 cm^{-1} in the FT-IR spectrum of PAA was shifted to 1732 cm^{-1} upon the complex formation with **1**. This shift can be attributed to the cleavage of intra- or intermolecular hydrogen bonds between the carboxyl groups of PAA by the threading of **1** onto the PAA chain, strongly supporting the formation of an inclusion complex

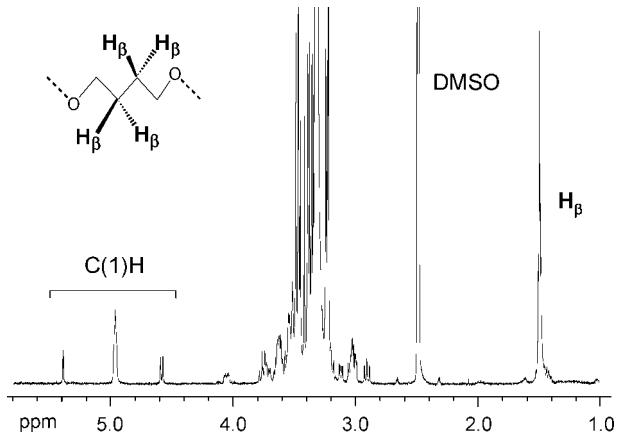

Figure 3. ^{1}H NMR spectrum of the **1**−PTHF precipitate in DMSO-d_6 at 25 °C.

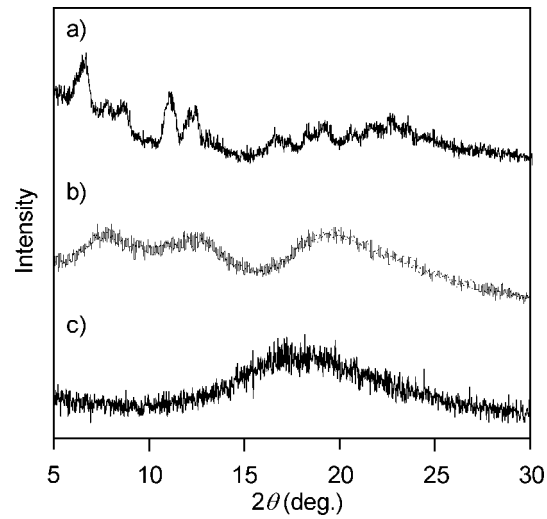

Figure 4. XRD patterns of (a) **1**−PAA precipitate, (b) **1**, and (c) PAA.

between **1** and PAA. The host−guest stoichiometry estimated from the ^{1}H NMR spectrum was in a ratio of 1:5 (**1**:AA unit) (Figure 6). On the other hand, in a pH 10 solution, **1** did not form a precipitate with PAA. This phenomenon can be explained by considering that the threading of **1** onto the PAA chain did not occur due to the conversion of the carboxyl (−COOH) groups of PAA into the more hydrophilic carboxylate ($-COO^-$) groups. Thus, the **1**−PAA complex may function as a novel, pH-responsive pseudopolyrotaxane.

Hosts **1** and **2** also formed precipitates when mixed with PPG. The XRD measurements of these precipitates indicated that the **1**−PPG and **2**−PPG complexes were formed with a columnar structure. The stoichiometries of these complexes were in ratios

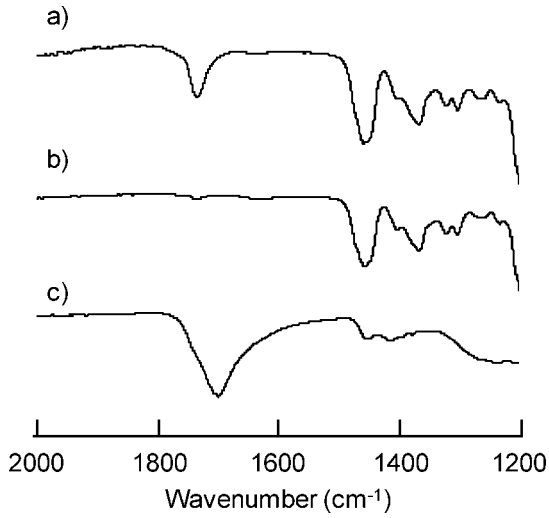

Figure 5. FT-IR spectra of (a) **1**−PAA precipitate, (b) **1**, and (c) PAA.

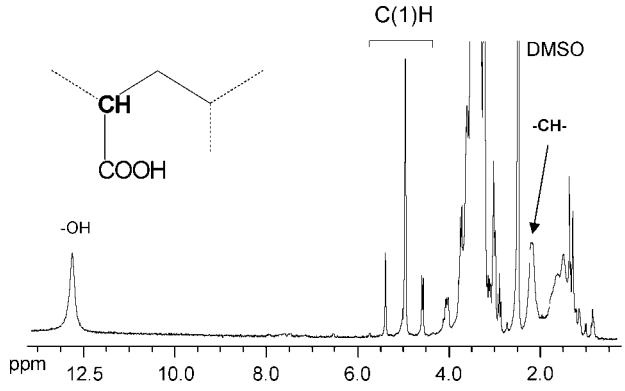

Figure 6. ^{1}H NMR spectrum of the **1**−PAA precipitate in DMSO-d_6 at 25 °C.

of 1:2 (**1**:PG unit) and 1:5.6 (**2**:PG unit), respectively. Thus, the **1**−PPG complex appears to be a stoichiometric inclusion compound, similarly to the cases of **2**−PTHF and **2**−PCL complexes. Interestingly, the amount of precipitate from **1**−PPG was greater than that of **2**−PPG. This result indicates that skeleton-modified CD **1**, which bears an ellipsoid cavity, is more effective for inclusion complex formation with polymer guests with substituents on their main chain, as compared to the conventional CD derivatives.

In conclusion, we demonstrated that the skeleton-modified CD derivative, which bears a β-(1,4) glucosidic bond, formed an inclusion complex with not only conventional polymeric guests such as PTHF, PCL, and PPG but also with PAA to generate novel pseudopolyrotaxanes. This is the first example of a CD−PAA inclusion complex. The skeleton-modified CD derivative was found to effectively form inclusion complexes with polymeric guests with substituents on the main chain rather than with the linear polymer. The inclusion complex between PAA and the skeleton-modified CD may be used as a pH-responsive supramolecular architecture in the fields of drug delivery and tissue engineering.

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Supporting Information Available: XRD patterns, ^{1}H NMR spectra, and chemical shifts of the inclusion complex. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Wenz, G. *Angew. Chem., Int. Ed.* **1994**, *106*, 851.
(2) Connors, K. A. *Chem. Rev.* **1997**, *97*, 1325.
(3) Rekharsky, M. V.; Inoue, Y. *Chem. Rev.* **1998**, *98*, 1875.
(4) Breslow, R.; Dong, S. D. *Chem. Rev.* **1998**, *98*, 1997.
(5) Rizzarelli, E.; Vecchio, G. *Coord. Chem. Rev.* **1999**, *188*, 343.
(6) Chen, W. H.; Hayashi, S.; Tahara, T.; Nogami, Y.; Koga, T.; Yamaguchi, M.; Fujita, K. *Chem. Pharm. Bull.* **1999**, *47*, 588.
(7) Harada, A.; Kamachi, M. *Macromolecules* **1990**, *23*, 2821.
(8) Harada, A.; Li, J.; Kamachi, M. *Nature (London)* **1992**, *356*, 325.
(9) Harada, A.; Li, J.; Kamachi, M. *Macromolecules* **1993**, *26*, 5698.
(10) Harada, A.; Li, J.; Kamachi, M.; Kitagawa, Y.; Katsube, Y. *Carbohydr. Res.* **1998**, *305*, 127.
(11) Kidowaki, M.; Zhao, C.; Kataoka, T.; Ito, K. *Chem. Commun.* **2006**, 4102.
(12) Ooya, T.; Yui, N. *J. Controlled Release* **2002**, *80*, 219.
(13) Okada, M.; Kamachi, M.; Harada, A. *J. Phys. Chem. B* **1999**, *103*, 2607.
(14) Born, M.; Ritter, H. *Macromol. Rapid Commun.* **1996**, *17*, 197.
(15) Casu, B.; Reggiani, M.; Sanders, G. R. *Carbohydr. Res.* **1979**, *76*, 59.
(16) Yagi, T.; Aoshima, R.; Kuwahara, M.; Shibata, H. *J. Inclusion Phenom.* **1993**, *16*, 231.
(17) Holzgrabe, U.; Mallwitz, H.; Branch, S. K.; Terry, M.; Jefferies, T. M.; Wiese, M. *Chirality* **1997**, *9*, 211.
(18) Müller, B. W.; Brauns, U. *Int. J. Pharm.* **1985**, *26*, 77.
(19) Yoshida, A.; Yamamoto, M.; Irie, T.; Hirayama, F.; Uekama, K. *Chem. Pharm. Bull.* **1989**, *37*, 1059.
(20) Folkman, J.; Weisz, P. B.; Joullie, M.; Li, W. W.; Ewing, W. R. *Science* **1989**, *243*, 1490.
(21) Okada, Y.; Tachibana, M.; Koizumi, K. *Chem. Pharm. Bull.* **1990**, *38*, 2047.
(22) Morales, J. C.; Zurita, D.; Penadés, S. *J. Org. Chem.* **1998**, *63*, 9212.
(23) Hoffmann, B.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **2002**, *85*, 265.
(24) Kida, T.; Michinobu, T.; Zhang, W.; Nakatsuji, Y.; Ikeda, I. *Chem. Commun.* **2002**, 1596.
(25) Kikuzawa, A.; Kida, T.; Nakatsuji, Y.; Akashi, M. *J. Org. Chem.* **2005**, *70*, 1253.
(26) Topchieva, I. N.; Tonelli, A. E.; Panova, I. G.; Matuchina, E. V.; Kalashnikov, F. A.; Gerasimov, V. I.; Rusa, C. C.; Rusa, M.; Hunt, M. A. *Langmuir* **2004**, *20*, 9036.

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