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pH Dependence of Polypseudorotaxane Formation between Cationic Linear Polyethylenimine and Cyclodextrins

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ABSTRACT: A series of linear polyethylenimines (LPEIs) with various molecular weights were synthesized and used for pH-dependent polypseudorotaxane formation with α- or γ-cyclodextrins (α-, γ-CDs). The polypseudorotaxane formation was significantly dependent on the pH of the aqueous media. The maximum yield of the recovered polypseudorotaxane precipitates was observed at pH 11.0, whereas no complexation was observed in the pH range below 8.0 due to the protonation of secondary amine groups in LPEI backbones. This suggests that the ionization of the secondary amine groups leads to dethreading of CD molecules because PEI chains with cationic nature disfavor the hydrophobic cavities of CDs. The solid-state ^{13}C CP/MAS NMR and X-ray diffraction measurements verified the successful formation of crystalline polypseudorotaxanes through the inclusion complexation. In addition, ^{1}H NMR analysis showed that LPEI formed a 2:1 inclusion complex with α-CD ([EI]:[α-CD] = 2:1) and a 4:1 complex with γ-CD ([EI]:[γ-CD] = 4:1) as reported in the poly(ethylene glycol)-based polypseudorotaxane system. Such unique pH-controllable polypseudorotaxane formation may be useful in designing many building blocks for stimuli-responsive polyrotaxanes.

Introduction

It has been found that cyclodextrins (CDs) are threaded onto many kinds of water-soluble linear polymers to produce polypseudorotaxanes or polyrotaxanes since 1990s. Most of the research in the initial stage was focused on finding host−guest pairs between various polymers and CDs, which underwent polypseudorotaxane formation in aqueous phases through specific selectivity.[1] To date, a majority of the literature has been focused on the ionic polymers formed from the linear polymers with nonionic nature such as poly(ethylene glycol) (PEG), poly(propylene glycol) (PPG), and their block copolymers.[1,2] On the other hand, there was limited research involving the threading of CDs onto polyelectrolytes.[3−6] For example, Wenz et al. have reported on the preparation of polypseudorotaxanes based on α-CD and polycation guests such as poly(iminooligomethylene) at acidic pH conditions.[3] They demonstrated that the inclusion process largely depended on the degree of protonation of the amino groups along the polymer chain. In the following papers, they reported on the kinetics and temperature-dependent threading of the CDs onto the polymer chain.[4] Although the ionic polymers have attracted growing interest as a polymeric guest, most reports were concerned with the threading process of CDs and the formation of complexes in water-soluble states at a fixed pH. Since the hydrophilicity or the hydrophobicity in ionic polymers can be readily modulated depending on the pH, it is expected that the variance in pH may result in a unique polypseudorotaxane formation, which has been impossible with nonionic polymers. In an attempt to develop such a pH-dependent complexation system, our group obtained a unique polypseudorotaxane between cationic poly(ϵ-lysine) and α-CD under various environmental conditions.[6] The polypseudorotaxane formation was significantly affected by the pH or the ionic strength in aqueous media, and stable crystalline precipitates could be obtained through the complexation between deprotonated poly(ϵ-lysine) and α-CD at the range of pH 8.5−11.5. On the basis of this study, we assumed that any other cationic polymers could be included in the CD cavity to form crystalline precipitates in a specific pH range. So far, for the design of function-specific supramolecular structures, synthetic polymers have shown many advantages as basic components, including the feasibility of various chemical modifications as well as the molecular weight control of polymers. Therefore, it is needed to find useful synthetic ionic polymers for pH-sensitive polypseudorotaxanes rather than naturally synthesized ionic polymers such as poly(ϵ-lysine).

In this work, we synthesized linear polyethylenimines (LPEIs) with various molecular weights to form polypseudorotaxanes with CDs in aqueous media. Although LPEI transforms between double-stranded helices due to the crystal structure, it could form a fully extended state by the dehydration and the absorption of water.[7] In addition, since LPEI has secondary amine groups (pK_a 8.9) ionizable below a specific pH like poly(ϵ-lysine), stable polypseudorotaxanes with CDs could be obtained under specific solution conditions.[8b] In the meantime, it is well-known that PEG forms a 2:1 inclusion complex

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with α-CD ([EG]:[α-CD] = 2:1) and a 4:1 inclusion complex with γ-CD ([EG]:[γ-CD] = 4:1).[1a] Because LPEI is a structural analogue to PEG with an N−H moiety in place of the oxygen atom, we hypothesized that LPEI would form double-stranded polypseudorotaxanes with γ-CDs. In this paper, a significant pH-dependent complexation of LPEI with α- or γ-CDs and the unique characteristics of the resulted polypseudorotaxanes are presented.

Experimental Section

Materials. 2-Methyl-2-oxazoline was purchased from Aldrich Co. and distilled over calcium hydride. Poly(2-ethyl-2-oxazoline) was supplied by Aldrich Co. and used without further purification. Methyl tosylate, α-CD, and γ-CD were purchased was purchased from Wako Pure Chemical Co. (Tokyo, Japan) and vacuum-distilled prior to use. Organic solvents were purified by usual distillation methods. The other synthetic reagents were used as received without further purification.

Synthesis of Linear Polyethylenimine. A series of LPEIs with various molecular weights were prepared according to previously reported methods.[9] As a representative example, LPEI with M_w 3200 was synthesized as follows. Under argon, 2-methyl-2-oxazoline (25 g), methyl tosylate (0.74 g), and dry acetonitrile (100 mL) were placed in 300 mL of dry flask, and the mixture was kept at 70 °C under gentle stirring. After 48 h, the solvent was removed under reduced pressure, and the residue was dissolved in a mixture of distilled water (250 mL) and concentrated hydrochloric acid (400 mL). The mixture was refluxed for 48 h. Sodium hydroxide was added to the mixture at 0 °C until the solution became slightly basic. The resulting precipitates were collected by filtration and washed with water until the filtrate became neutral. The residue was dried in vacuo at 60 °C for 48 h to give the polymer quantitatively. The hydrolysis ratio was higher than 98% by ^{1}H NMR analysis. From the method, low molecular weight LPEIs (M_w 2200 and 3200) could be obtained. To prepare high molecular weight LPEI (M_w 22 000 and 87 000), poly(2-ethyl-2-oxazoline) was used and the same procedure for the low molecular weight LPEI was applied.

^{1}H NMR (CDCl$_3$): δ (ppm) = 2.70 (s, $-CH_2CH_2NH-$) and 1.57 (s, $-CH_2CH_2NH-$). FT-IR (KBr): 3262 (ν_{N-H}), 2843 (ν_{C-H}), 1552 (δ_{N-H}), 1478 (δ_{C-H}), and 1127 (ν_{C-N}).

Preparation of Polypseudorotaxane. The synthesized LPEIs were used to prepare polypseudorotaxanes with α- or γ-CD. LPEI (0.2 g, 4.6 mmol in monomer unit) was dissolved in 5 mL of phosphate buffered solution (0.1 M, pH 5.5) at 60 °C, and the solution was slowly added to the predetermined amounts of CD solutions (25 mL). After initial stirring for 10 min, the pH of the mixtures was adjusted from 3.0 to 13.0 with adding HCl or NaOH solution, followed by stirring for another 60 min at 60 °C. With cooling the solutions to room temperature, they became turbid and formed hydrogels.[8b] The formed hydrogels were slowly heated again by gel-melting temperature with continuous stirring. With gradually decreasing the solution temperature to 20 °C, the transparent mixtures turned to turbid solutions. Repeated heating and cooling processes induced further inclusion and precipitates in the end, which were collected by centrifugation and then washed with distilled water to remove the free LPEIs and uncomplexed CDs. The resulting products were dried in vacuo at 60 °C to give the polypseudorotaxanes.

Characterization. The chemical composition and the molecular weight of the resulting polymers were confirmed by ^{1}H NMR using a 400 MHz FT-NMR spectrometer (GSX-400, JEOL, Japan). The stoichiometry and the number-average molecular weight of the polypseudorotaxanes were also determined by the peak integration of ^{1}H NMR spectra using a 750 MHz FT-NMR spectrometer (Varian, Palo Alto, CA) in D$_2$O containing 0.1 M DCl. To evaluate the chemical composition of the polypseudorotaxane, FT-IR spectra were recorded on a VALOR-III FT-IR spectrometer (Jasco, Tokyo, Japan) in the range between 4000 and 400 cm^{-1}, with a resolution of 2 cm^{-1} and 64 scans. The solid-state ^{13}C CP/MAS NMR spectra were recorded at 100.4 MHz on a JNM-GSX 400 NMR spectrometer with a sample spinning rate of 6 kHz at 19 °C. CP spectra were acquired with a 5 ms contact time, a 10 s repetition time, and 18 000 accumulations. The crystallinity changes in the polypseudorotaxanes formation were confirmed by X-ray diffraction measurements, performed with powder diffractometry (RINT2000, Rigaku, Japan) and also image-plate photography using graphite-monochromatized Cu Kα radiation (λ = 1.542 Å).

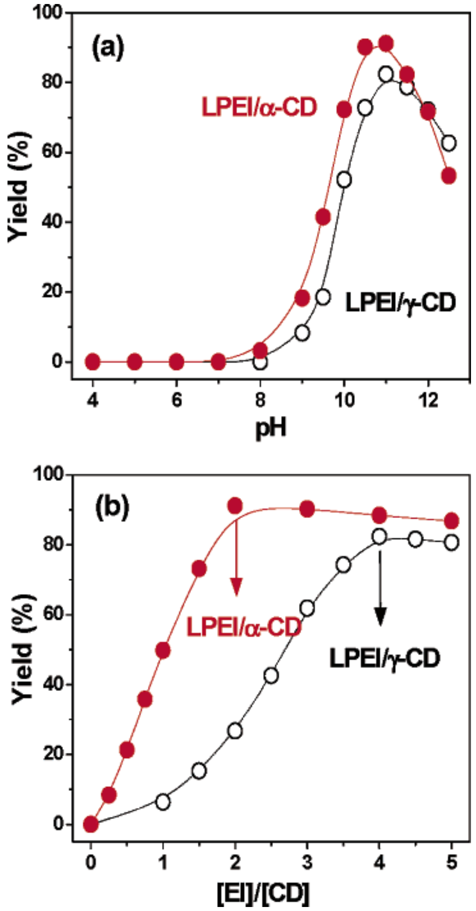

Figure 1. Changes in the yields of LPEI (M_w 3200)/α-CD and LPEI (M_w 3200)/γ-CD polypseudorotaxanes as a function of pH (a) and the continuous variation plot for the polypseudorotaxane formation between [EI] and [CD] at pH 11.0 (b).

Results and Discussion

pH Dependence for Polypseudorotaxane Formation. For stable polypseudorotaxanes, LPEIs and CDs in the solutions were mixed at 60 °C to decrease the energy barrier of cationic charge for polypseudorotaxane formation.[8−11] The pH of the mixtures was changed from 3 to 13 by using appropriate buffer solutions with the addition of HCl or NaOH. As shown in Figure 1a, a striking change in the yield of LEPI (M_w 3200)/α-CD was observed around pH 9.0. The yield exhibited the maximum at pH 11.0, and no complex formation was observed in the pH range below 8.0. The polypseudorotaxanes of LPEI (M_w 3200) with γ-CDs showed a very similar tendency to that of the α-CD system with a pH variation. It can be considered that this pH-dependent polypseudorotaxane formation is closely related to the protonation of secondary amine groups of LPEI. Since the pK_a of LPEI is known to be 8.9 in phosphate buffered solution (0.5 M NaCl),[12] the

Table 1. Preparation of the Polypseudorotaxanes Based on Cationic LPEI with α- or γ-CDs at pH 11.0

	α-CD		γ-CD	
M_w of LPEI[a]	N_s[b]	yield (%)	N_s[b]	yield (%)
2 200	2.1	89.1	4.5	83.5
3 200	2.1	91.2	4.8	82.4
22 000	2.4	79.8	5.6	81.7
87 000	2.9	76.5	7.4	70.2

[a] The weight-average molecular weight of LPEI was estimated by ^{1}H NMR and GPC (eluent: 1% formic acid). [b]The threading ratio of PEI repeating units per CD ([EI]/[CD]) was determined by the peak integration of ^{1}H NMR spectra.

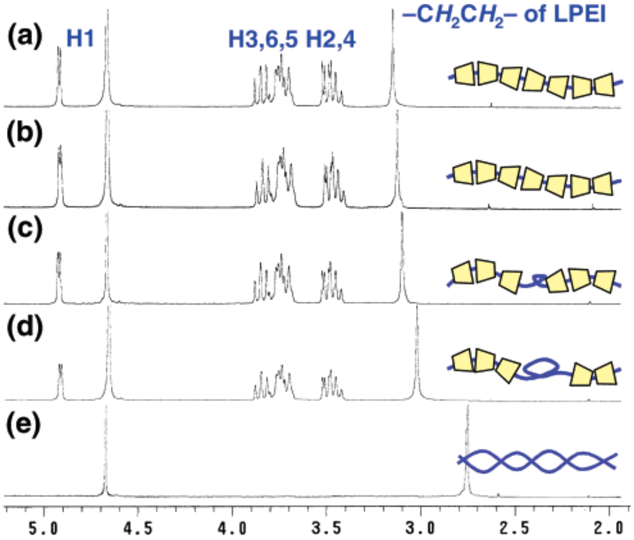

Figure 2. ^{1}H NMR spectra for α-CD polypseudorotaxanes in D_2O containing 0.1 M DCl: LPEI (M_w 2200)/α-CD (a), LPEI (M_w 3200)/α-CD (b), LPEI (M_w 22 000)/α-CD (c), LPEI (M_w 87 000)/α-CD (d), and LPEI (M_w 3200) (e).

protonation degree of the amino groups in LPEI increases with decreasing pH below 8.9. In this study, the polypseudorotaxane formation was carried out in 0.1 M PBS, which gives almost similar salt conditions. The low yields below pH 8 in Figure 1 suggest that the salt did not affect the complex formation, but the protonation of the secondary amines is a dominant role for dethreading of CDs onto LPEI chain. This result is in accord with the previous report that the dissociation of CDs resulted in a decrease of the yield at the low-pH conditions because the hydrophobic cavities of CDs are energetically disfavorable to the protonated amino groups.[13]

Stoichiometry. To verify the stoichiometry of the polypseudorotaxane formation between LPEI and α- or γ-CDs, the polypseudorotaxanes were prepared with various feed ratios at pH 11.0. The structural compositions of the prepared polypseudorotaxanes were calculated from ^{1}H NMR characterization. As shown in Figure 1b, the yield of polypseudorotaxanes using LPEI (M_w 3200) exhibited the maximum corresponding to the molar feed ratio of two and four EI units per α- and γ-CDs, respectively. Table 1 shows the stoichiometry of LPEI repeating units per CD ([EI]/[CD]) for all the synthesized LPEIs with α- or γ-CDs at pH 11.0. The stoichiometry of the polypseudorotaxanes between low molecular weight LPEIs (M_w 2200 and 3200) and α-CDs was found to be about 2.1 (Figure 2a,b). It is the same result as previously reported PEG-based polypseudorotaxanes because the length of the LPEI repeating unit is almost the same to that of PEG (3.3 Å).[1b] In the case of LPEI (M_w 2200)/γ-CD polypseudorotaxanes (Figure 3a), the stoichiometry was about 4.5. This result suggests that γ-CDs include double-stranded PEI chains in the cavity because the cavity of γ-CD (diameter 8.5 Å) is twice as large as that of α-CD (diameter 4.5 Å).[1a] As shown in Figures 2 and 3, the stoichiometry gradually increased with the molecular weights of LPEI because the long chain property of the polymeric guest resulted in crystalline precipitates with incomplete threading of CDs onto the polymer chain.[8b]

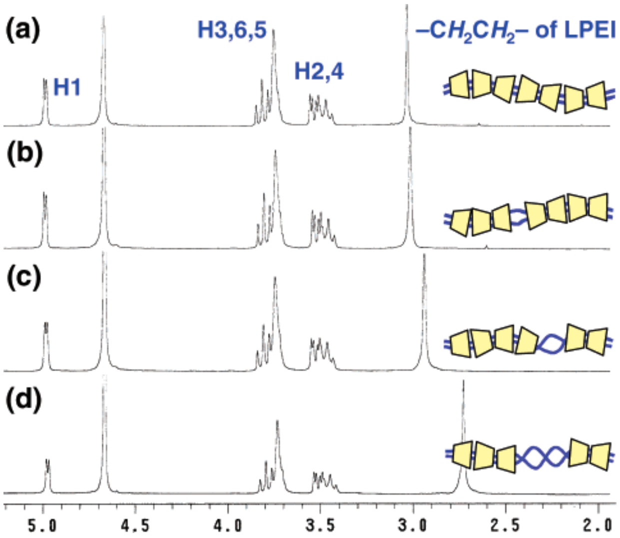

Figure 3. ^{1}H NMR spectra for γ-CD polypseudorotaxanes in D_2O containing 0.1 M DCl: LPEI (M_w 2200)/γ-CD (a), LPEI (M_w 3200)/γ-CD (b), LPEI (M_w 22 000)/γ-CD (c), and LPEI (M_w 87 000)/γ-CD (d).

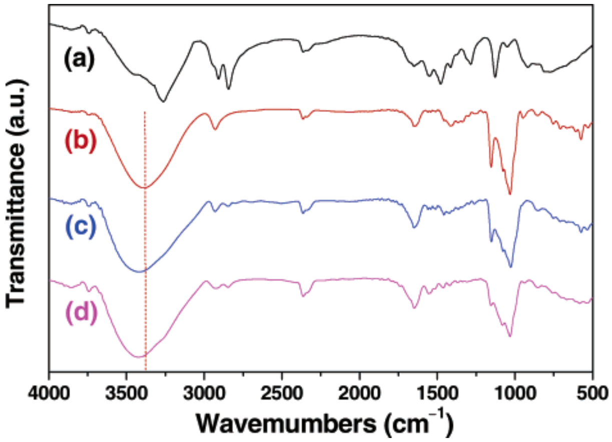

Figure 4. FT-IR spectra of LPEI (M_w 3200) (a), α-CD (b), LPEI (M_w 3200)/α-CD (c), and LPEI (M_w 3200)/γ-CD (d).

FT-IR Spectroscopy. Figure 4 shows the FT-IR spectra of LPEI (M_w 3200), α-CD, and the polypseudorotaxanes of LPEI (M_w 3200) with α- or γ-CDs. The extremely broad bands between 4000 and 3000 cm^{-1} are normally assigned to the O−H stretching modes for CD and the N−H stretching modes for LPEI, respectively. As shown in Figure 4a, the sharp peak at 3262 cm^{-1} in LPEI originates in the crystalline phase of LPEI, while the shoulder around 3370 cm^{-1} originates in an amorphous phase of LPEI that appears to have weaker hydrogen-bonding interactions.[14] In Figure 4c, a broad peak observed at 3420 cm^{-1} seems to be shifted from 3389 cm^{-1} for pure α-CD and 3370 cm^{-1} for LPEI spectra. This shift is likely due to hydrogen bonds of the O−H groups of CDs with the included polymeric chain.[15]

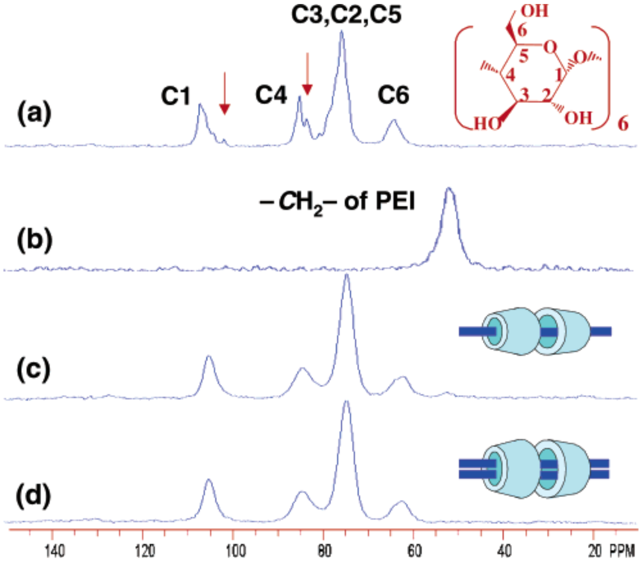

Figure 5. Solid-state ^{13}C CP/MAS NMR spectra of α-CD (a), LPEI (M_w 3200) (b), LPEI (M_w 3200)/α-CD (c), and LPEI (M_w 3200)/γ-CD (d).

The bands observed in the 3000−2500 cm^{-1} region for α-CD (Figure 4a) and for LPEI (M_w 3200)/α-CD complex (Figure 4c) are slightly different. LPEI has several strong bands due to the C−H stretching mode at 2908 and 2843 cm^{-1}, while α-CD has a band around 2940 cm^{-1}. A broad shoulder around 2876 cm^{-1}, as well as the shifted C−H stretching mode of α-CD at 2945 cm^{-1} appeared in the spectra of LPEI/α-CD polypseudorotaxane (Figure 4c), seems to be attributed to the included LPEI segments in their polypseudorotaxanes.

In the region from 1500 to 1100 cm^{-1}, LPEI shows several types of modes—CN stretching at 1140 cm^{-1}, CH$_2$ twisting around 1284 cm^{-1}, and NH bending parallel to the chain axis and NH bending mixed with CH$_2$ scissors from 1470 to 1490 cm^{-1}.[14] On the other hand, these bands disappeared in the spectrum of LPEI/α-CD complex. There are some stretching modes of the glucosidic group (C−O−C, at 1189 cm^{-1}) coupled with C−C (1092 cm^{-1}) and C−O (1042 cm^{-1}) stretching modes, which are very similar to the α-CD spectrum.[16]

There are no significant differences in the spectra of the polypseudorotaxanes between LPEI/α-CD and LPEI/γ-CD (Figure 4d). The center for O−H stretching modes shifted to higher frequency, and new bands appeared at 2857 cm^{-1} with a shoulder at 2930 cm^{-1} for LPEI (M_w 3200)/γ-CD polypseudorotaxanes, which are different from γ-CD. These characteristic bands suggest that the cationic LPEI chains are included inside the channels of γ-CDs.

Solid-State ^{13}C CP/MAS NMR Spectroscopy. The polypseudorotaxane formation was also confirmed by solid-state ^{13}C CP/MAS NMR spectroscopy. As shown in Figure 5b, the broad ethylene peaks of LPEI (M_w 3200) indicate that each methylene of PEI is difficult to move and locates in a different environment.[1c] On the other hand, the spectrum of α-CD itself shows strong splitting for all C$_{1-6}$ resonances, indicating that α-CD molecules are in a rigid, less symmetric cyclic conformation.[17,18] The C$_4$ and C$_6$ of CDs are also broadened at higher magnetic fields because they are difficult to move due to the hydrogen bonds between CDs and/or LPEI chain. Although CDs assume less symmetrical conformation in the crystal when it does not include a guest in the cavity, the complexed CDs adopt symmetrical cyclic conformations, and each glucose unit of CDs in the complexes is in a similar environment.[19] This result indicates that CDs in both PEI/α-CD and PEI/γ-CD polypseudorotaxanes have adopted more symmetric cyclic conformations. In addition, the peak characteristic of the glycoside linkages for α-CD at 98 and 80 ppm disappeared in the spectra of the LPEI (M_w 3200)/α-CD polypseudorotaxane. Figure 5d shows that γ-CDs include double-stranded PEI chains in the cavity, which is coincident with the result of ^{1}H NMR study. These results indicate that both LPEI/α-CD and LPEI/γ-CD form stable channel-structured polypseudorotaxanes.

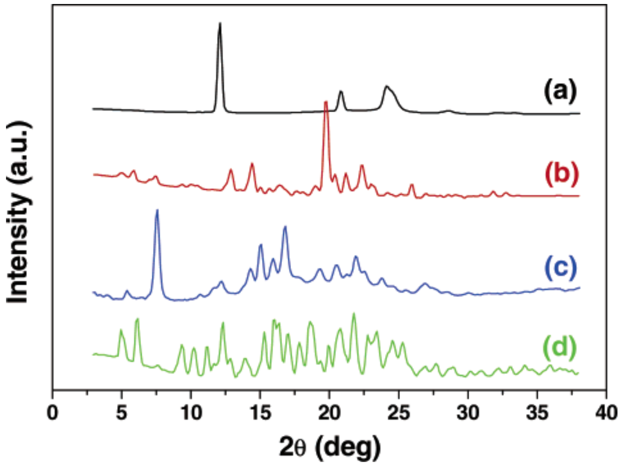

Figure 6. X-ray diffraction patterns for LPEI (M_w 87 000) (a), LPEI (M_w 87 000)/α-CD (b), LPEI (M_w 87 000)/γ-CD (c), and γ-CD (d).

Powder X-ray Diffraction Measurements. Figure 6 shows wide-angle X-ray diffraction patterns of the guest polymer LPEI (M_w 87 000), LPEI (M_w 3200)/α-CD, LPEI (M_w 87 000)/γ-CD polypseudorotaxanes, and the host γ-CD. LPEI is remarkably hygroscopic and can exist in multiple crystalline phases depending on the amount of water absorbed.[7] LPEI obtained from 2-oxazoline is highly crystalline owing to its linear structure and exhibits three major peaks at $2\theta = 11.8°$, 20.5°, and 23.8°, which are characteristics to the pseudohexagonal arrangement of the double-stranded helical chains in the anhydrate state (Figure 6a).[20]

Both LPEI/α-CD and LPEI/γ-CD polypseudorotaxanes show a quite different pattern from that of the host CDs or the guest polymers. The profile of LPEI (M_w 3200)/α-CD (Figure 6b) is very similar to the pattern reported for PEG/α-CD polypseudorotaxanes,[1,21] where the strong peak at $2\theta = 20.0°$ ($d = 4.44$ Å) has been assigned to 210 reflection of the hexagonal form with the lateral unit-cell dimension $a = 13.6$ Å. The axial dimension $c = 16$ Å corresponding to 001 spacing ($2\theta = 5.5°$) indicates that two α-CD units are included in the repeating distance, suggesting the head-to-head dimer stacking of α-CD molecules along the polymer chain axis.

The pattern of LPEI (M_w 87 000)/γ-CD shown in Figure 6c is a characteristic of the channel structure of γ-CD-containing polypseudorotaxanes.[22] The reflections indicate a tetragonal unit cell with dimensions $a = 23.7$ Å and $c = 23.1$ Å, and the characteristic peak at $2\theta = 7.5°$ can be assigned to the overlapping 200 and 002 reflections. The distance between the adjacent polypseudorotaxane chains is $a/\sqrt{2} = 16.8$ Å. The unit-cell dimensions are nearly equal to those of the polypseudorotaxanes composed of low molecular weight com-

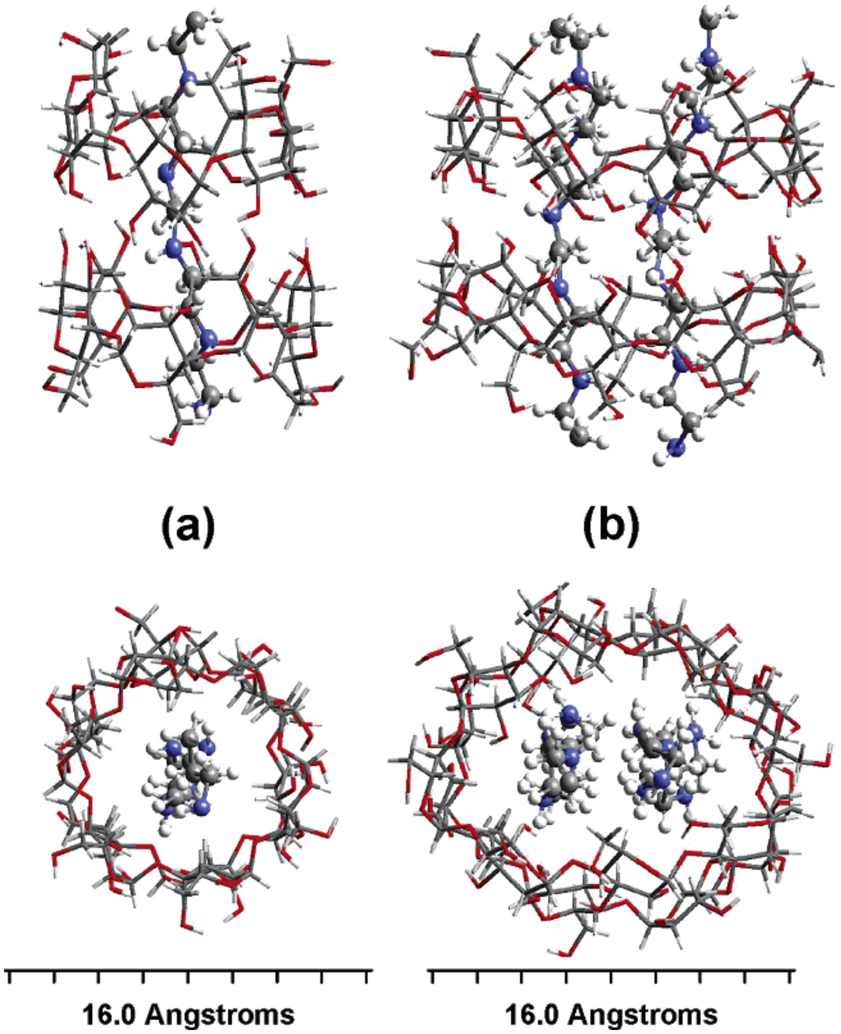

Figure 7. Graphical representation of the computer-generated trajectories for the polypseudorotaxanes of LPEI/α-CD (a) and LPEI/γ-CD (b). The MD simulation performed for 10 ps at 300 K on the polypseudorotaxanes. For clarity, LPEI is shown in a ball-and-stick representation, CDs are shown in stick representation, and water molecules have been omitted.

pounds and γ-CDs.[23] Therefore, the γ-CD arrangements in the crystal structures are considered to be isomorphous, suggesting the trimer stacking of γ-CD molecules in which three γ-CD units are engaged in the *c* interval in a fashion of head-to-head, tail-to-tail, and head-to-tail sequences. In this case, to observe this phenomenon more clearly, we adapted the longest main-chain containing polypseudorotaxane, LPEI (M_w 87 000)/γ-CD system. On the other hand, some γ-CD complexes showed quite different diffraction patterns. The peaks of poly(dimethylsiloxane)s/γ-CD complexes were attributed to the hexagonal packing with $a = 17$ Å.[24] Takeo et al. reported that the crystal structure of a γ-CD complex changed by dehydration from the tetragonal to the hexagonal one.[25] Although the latter packing is fairly denser than the former, the tetragonal structure prevailed in our samples, which means that CDs are included onto the LEPI chains but do not cover the entire length in the polypseudorotaxanes.

Molecular Dynamic Simulations. The molecular dynamics (MD) simulation was carried out with Cerius[2] software (version 4.2, Accelrys, San Diego, CA).[26] Two series of energy terms, valence (bond, angle, torsion, and inversion) and nonbond (hydrogen bond, van der Waals, and Coulomb), were selected in a Dreiding force field (number volume temperature (NVT) dynamic method, temperature = 300 K, time = 1−96 ps). The trajectories of the insertion angles and rotation of the LPEI inside the α- and γ-CDs give detailed information on the dynamics of the polypseudorotaxanes. As shown in Figure 7, the MD simulations for the polypseudorotaxanes show that the LPEI chains are well included in two close α-CDs and γ-CDs, respectively. The conformation of LPEI and the interchain hydrogen bonding between neighboring CDs are well observed. Both LPEI/α-CDs and LPEI/γ-CDs form stable crystalline-structured polypseudorotaxanes. In the case of LPEI/γ-CDs, when the polymeric guests are intramolecularly stacked, the size of the whole hydrophobic moiety becomes large enough to fill almost all the space inside of the γ-CD cavity resulting in a high degree of size/shape complementarity and thus is potentially able to form a stable host−guest complex.[27] These results agree well with the results of X-ray diffraction measurements.

Conclusions

The polypseudorotaxane formation between LPEIs and α- or γ-CDs was significantly dependent on pH, and the crystalline polypseudorotaxanes were formed at pH > 8.0. It was found that LPEI forms a 2:1 inclusion complex with α-CD and a 4:1 inclusion complex with γ-CD like PEG. To our best knowledge, it is the first observation that the cationic polymer can form crystalline polypseudorotaxanes with γ-CD as well as α-CD via pH variation. From the results of X-ray diffraction and solid-state ^{13}C CP/MAS NMR spectroscopic methods, LPEI confined to the CD channels lost its original crystalline properties but formed a channel-type crystalline structure with CDs due to the long chain nature of LPEI. Molecular dynamic simulations well confirmed this structure of polypseudorotaxanes.

On the basis of the supramolecular association and dissociation at a limited pH range, this stimuli-responsive polypseudorotaxanes can be promising for constructing pH-triggered supramolecular architectures in the field of drug delivery and tissue engineering. In addition, the double-stranded inclusion phenomenon of the polycation inside hosts opens a new possibility of artificial gene delivery carrier that inspires a double helix of DNA. The microscopic measurement to support the geometry of the polypseudorotaxane formation between LPEI and γ-CD is now in progress.

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