Control of Rapid Phase Transition Induced by Supramolecular Complexation of β-Cyclodextrin-Conjugated Poly(ε-lysine) with a Specific Guest

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ABSTRACT: β-Cyclodextrin-conjugated poly(ε-lysine) (β-CDPL) was synthesized and used as a polymeric host for inclusion complexation with 3-trimethylsilylpropionic acid (TPA). The specific host−guest interaction was analyzed by electrospray ionization mass and X-ray diffraction spectroscopies. In this system, TPA included into the hydrophobic cyclodextrin cavity acted as a physical cross-linker by cooperative hydrophobic and ionic interactions, which gave an important role in viscosity or transmittance changes near physiological conditions. The pronounced effect of pH on the change of viscosity was supported by rheological data. On the other hand, reversible phase transitions of the supramolecular assembling system occurred very rapidly in response to minute changes of temperature, which was verified by UV−vis measurements. The delicate control of critical aggregation temperature was accomplished by changing the degree of substitution as well as varying molar feed ratio or solution concentrations across their upper critical solution temperature. This rapid and elaborate supramolecular assembling system is promising as smart materials and can find a broad range of applications.

Introduction

Cyclodextrins (CDs), composed of six, seven, or eight D-glucopyranose units, possess truncated cone-shaped hydrophobic cavities, at the narrow side are the primary and at the wide side the secondary hydroxyl groups. No hydroxyl groups are inside the cavity, so that this region of the molecule is hydrophobic and can include various hydrophobic guest molecules, such as organic, inorganic, and biological molecules to form stable host−guest inclusion complexes.[1] The inclusion complexation of these host−guest systems occurs through various interactions, such as hydrogen bonding, van der Waals, electrostatic, or hydrophobic interactions. Although the magnitude of bond energy is not so large compared to a covalent bond, physical interaction plays a key role in many chemical and biological systems. In this sense, CDs have been extensively studied as supramolecular receptors.[2]

Recently, to improve the molecular binding abilities of the native CDs, a great deal of effort has been concentrated on the design and synthesis of novel CD derivatives. A wide variety of native and chemically modified CDs have been employed in the studies of their molecular recognition behaviors with various guest molecules.[3,4] On the basis of these studies, we recently designed a new biocompatible and biodegradable polymeric host by chemical conjugation of CDs into poly(ε-lysine) main-chain (CDPL), which was used to construct unique supramolecular-structured assembly with 3-trimethylsilylpropionic acid (TPA).[5,6] Structurally, TPA has two specific characteristic parts, hydrophobic and ionic groups at both ends, which play a dominant role in inducing dual complexation phenomena: host−guest interaction and cooperative ionic interaction with supramolecular cationic CDPL. In the β-CDPL/TPA system, the induction time of supramolecular aggregates observed by a stopped flow spectrophotometer was found to be very short (within 100 ms), which resulted from the inclusion complexation between the polymeric hosts and specific guest molecules. At the same time, they are likely to associate each other because of the cooperative intermolecular interactions between the inclusion complexes. On the basis of this dual complex interactions, this supramolecular assembly showed rapid responses with a small change of pH or temperature (Figure 1).[6]

In this study, we focused on investigating the specific interactions affecting the supramolecular assembly system and controlling the critical aggregation point with small changes of temperature in aqueous media. The degree of substitution (DS) of CDs per PL monomer unit, molar feed ratio, and solution concentrations were changed to evaluate how the critical aggregation temperature in the β-CDPL/TPA system could be affected. Furthermore, the effect of pH on the viscosity change in the mixture solution of β-CDPL and specific anionic guest molecules was investigated by rheological measurements. The obtained results suggest that changing the compositions and solution concentrations of β-CDPL systems could modulate the critical response rapidly and reversibly with a small change of pH or temperature.

Results and Discussion

Preparation of Inclusion Complexes. The synthetic results of β-CDPL are presented in Table 1. DS and molecular weight of copolymers were determined by the peak integration in ^{1}H NMR spectra.

In our previous report,[6] the inclusion complexation of β-CDPL with TPA was confirmed by 2D-NMR spectroscopy. However, the stoichiometry was not checked. To investigate the stoichiometry of α- or β-CD with TPA, electrospray ionization (ESI) spectroscopy coupled on external source Fourier transform ion cyclotron resonance mass spectrometry (FTMS) was used. As shown

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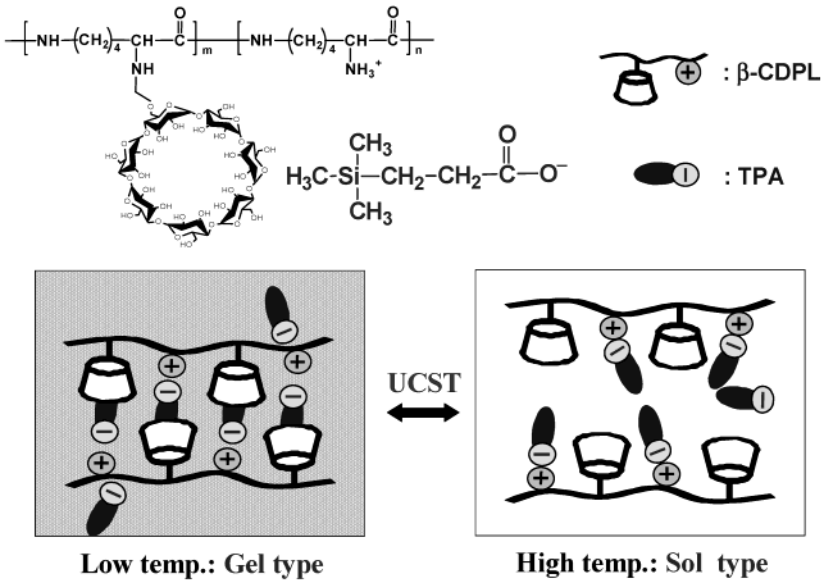

Figure 1. Schematic illustration of the interactions between cationic *β*-CDPL and anionic TPA molecules, controlling phase transition: association of supramolecular assembly at low-temperature induced by cooperative intermolecular interaction, leading to viscosity increase (a) and dissociation at high temperature (b).

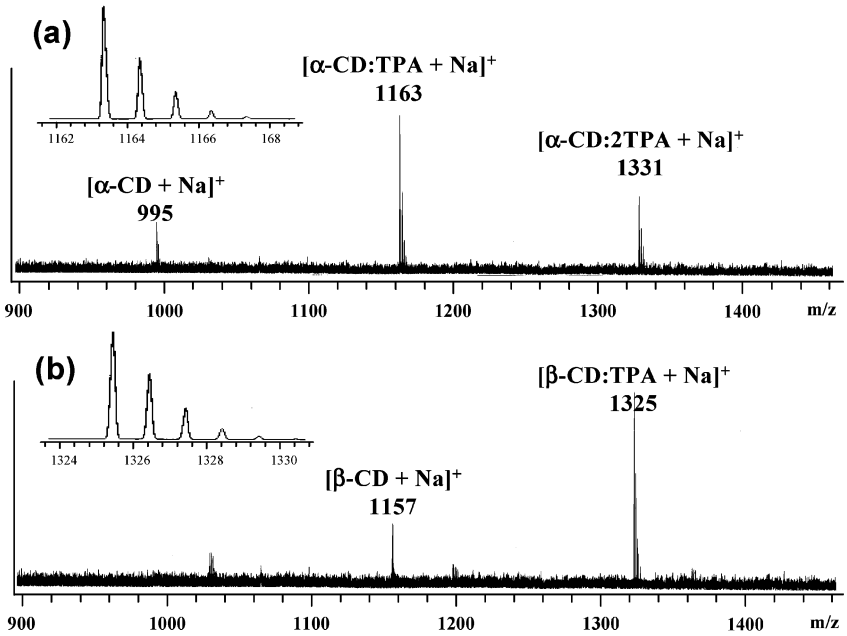

Figure 2. ESI-MS spectra of inclusion complexes of α-CD/TPA (a) and *β*-CD/TPA (b).

Table 1. Synthetic Results Derived from *β*-CDPLs[a]

code	feed ratio (ald-CD:Lys)	DS (%)	CD/CDPL (wt %)	M_n (g/mol)	yield (%)
CDPL-1	1.0:1	36.6	76.1	17 100	62.5
CDPL-2	1.5:1	42.4	78.7	19 200	58.0
CDPL-3	2.0:1	48.6	81.0	21 500	64.2

[a] The degree of *β*-CD substitution per PL monomer unit (DS) and the number-average molecular weight of *β*-CDPLs (M_n) were determined by the peak integration of ^{1}H NMR spectra.

in Figure 2, in the case of α-CD/TPA solution, both $[\alpha\text{-CD:TPA+Na}]^+$ and $[\alpha\text{-CD:2TPA+Na}]^+$ were observed at *m*/*z* 1163 and *m*/*z* 1331, respectively, which indicates that α-CD and TPA form complexes with stoichiometry 1:1 and 1:2. The desired complex $[\beta\text{-CD:TPA+Na}]^+$ was observed at *m*/*z* 1325 in large abundance, which means that *β*-CD and TPA form an inclusion complex with stoichiometry 1:1. The sodium cationized α-CD (*m*/*z* 995) and *β*-CD (*m*/*z* 1157) are also observed because CDs coordinated to various cations including NH_4^+, Na^+, or K^+ under these conditions.[7]

Powder X-ray Diffraction Measurements. To characterize the change of crystalline structure after inclusion complexation, we measured the X-ray diffraction patterns of the freeze-dried *β*-CDPL/TPA inclusion complex as well as host and guest molecules. TPA contained several peaks corresponding to the crystalline form (Figure 3b) while *β*-CDPL was mainly amorphous with a poor crystalline part (data not shown). In the case of a physical mixture of *β*-CDPL/TPA (Figure 3c), it showed very similar crystalline peaks to those of TPA. In contrast, the diffraction spectrum of the *β*-CDPL/TPA inclusion complex (Figure 3d) exhibited an entirely halo pattern, especially in the range of 5−10° in which crystalline diffraction peaks of TPA disappeared, and, in addition, some reflections mainly including a broad

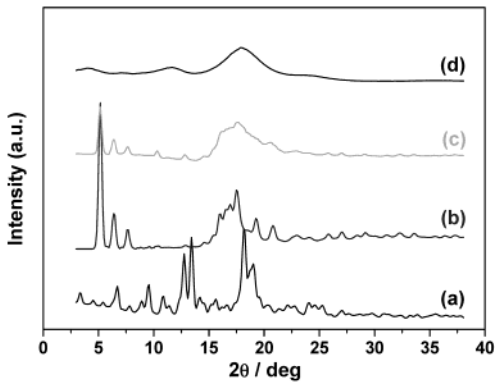

Figure 3. Powder X-ray diffraction patterns of β-CD (a), TPA (b), a physical mixture of β-CDPL/TPA (c), and an inclusion complex of β-CDPL/TPA with stoichiometry 1:1 (d).

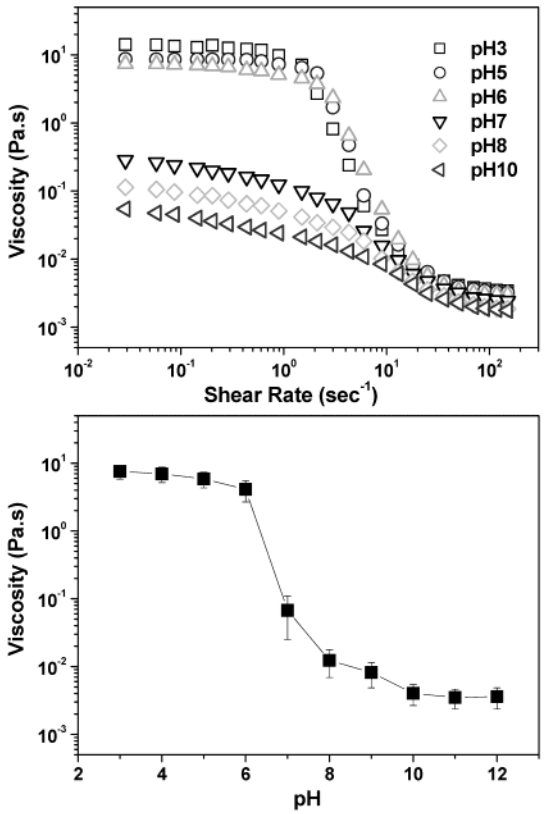

Figure 4. Viscosity changes in 1:1 mixture solutions of β-CDPL-3 with TPA (10 wt %) at 20 °C: effect of increasing pH on the dependence of mixture viscosity on shear rate (top) and change of zero-shear viscosity as a function of pH (bottom).

one at $2\theta = 17.9°$. This diffuse halo resulted from the amorphous state of β-CDPL indicates that TPA molecules are included into CD cavities entirely.

Rheological Measurements. The effect of pH on the viscosity change in β-CDPL/TPA mixture solutions was studied by rheological measurements at high concentration (10 wt %). From pH 3 to pH 12, there was no significant change in the transmittance in the β-CD/TPA system or the control β-CDPL solution (data not shown). As shown in Figure 4, all the systems showed nearly independent viscosity changes with the shear rate (Newtonian behavior) at low shear rates (less than 1 s^{-1}), while they were shear thinning at high shear rates. This shear thinning is attributed to ruptures of host−guest interactions due to mechanical forces.[8] The high viscosity was observed in acid conditions and more shear thinning in the β-CDPL/TPA solutions at lower pH. Upon increasing pH over 6, a dramatic decrease in the solution viscosity was observed; furthermore, the pronounced shear thinning observed at low pH was diminished, and the solutions became Newtonian-like over a wide range of shear rates. The onset of the shear thinning also shifted to higher shear rates with increasing pH.

Iliopoulos et al. reported that most gels based on physical association are indeed shear sensitive.[9] TPA molecules bound electrostatically to the β-CDPL main chain, while at the same time they tend to associate each other because of cooperative intermolecular interactions. In doing so, they create cross-links between the copolymer chains, resulting in the formation of a network that tends to increase the viscosity of the system. In addition to the rheological effects shown in Figure 4, evidence for the intermolecular interactions between the copolymer chains via the TPAs included in the CD cavities has also been provided from ESI-MS and X-ray diffraction spectroscopies (Figures 2 and 3, respectively). From these results, it is confirmed that the enhancement of the solution viscosity results from the strong interactions occurring in the mixture solutions between cationic β-CDPL and oppositely charged guest molecules, which is stabilized by both electrostatic attractions and cooperative hydrophobic effects.[10] In this case, the ionizable α-amino groups of PL and carboxylic groups of TPA played an important role for controlling the intermolecular aggregations in response to a change of pH in aqueous media.

Effects of Molar Feed Ratio. Thermoreversible phase transitions based on supramolecular assembly between β-CDPL and TPA solutions were observed by UV−vis measurements. These solutions showed rapid phase transitions in response to small temperature changes across their upper critical solution temperature (UCST).[6] On a decrease in temperature from 50 to 0 °C at pH 6, all the systems underwent a sudden phase transition with the temperature change of 1−2 °C. To investigate the effect of guest concentrations on the change of critical temperature in the mixture, UV absorbance and transparent changes were investigated with increasing molar feed ratios of TPA. There was no significant intensity change at low concentration region of TPA, but above a certain critical point (0.6 mol of TPA for 1 wt % β-CDPL solution) the intensity increased significantly (data not shown). On the basis of this test, we further investigated the change of the critical aggregation point with increasing stoichiometry as a function of temperature (Figure 5). As increasing TPA molar ratio from 1:1 to 1:5 in a β-CDPL solution (1 wt %), the critical temperature decreased gradually from 32.7 °C (1:1) to 10.5 °C (1:5) under cooling processes. Over the stoichiometry of 1:10, the mixture solutions showed a post-aggregation phenomenon like a polyelectrolyte−surfactant system. Goddard reported that the interactions in mixtures of polyelectrolytes with oppositely charged surfactants generally result in an associative phase separation and can be characterized by three distinct regions with increasing surfactant concentration:[11] (a) a clear one-phase region where the polymer is in excess; (b) a precipitation region, at which the surfactant-to-polymer ratio is close or equal to charge neutralization; (c) a clear post-precipitation region, where redissolution of the complex can take place (charge reversal of the complex caused by an

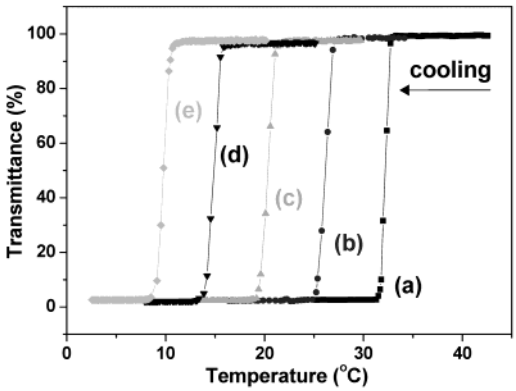

Figure 5. Transmittance changes of *β*-CDPL solution with increasing TPA molar ratio in 0.1 M phosphate buffer at pH 6; stoichiometry of [CD] and [TPA] is 1:1 (a), 1:2 (b), 1:3 (c), 1:4 (d), and 1:5 (e). The amount of TPA was estimated on the basis of the equilibrium amount of *β*-CD on CDPL-3 (DS 48.6%).

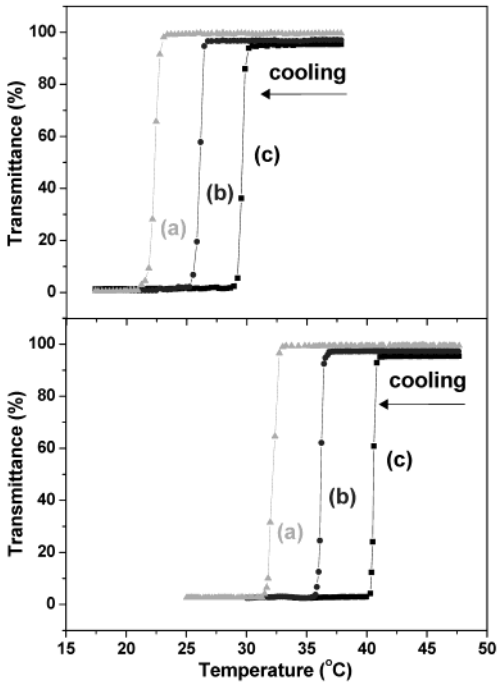

Figure 6. Transmittance changes in 1:1 mixture solutions of *β*-CDPL with TPA as a function of temperature in 0.1 M phosphate buffer at pH 6; inclusion complexes of CDPL-1/TPA (top) and CDPL-3/TPA (bottom) with concentrations of 1 (a), 3 (b), and 5 wt % (c).

excess of surfactant). In the last region, the viscosity of the mixed system usually decreases. From this report, the result of Figure 5 suggests that the excess amount of anions in TPA increase the water solubility of the complex, resulting in decreasing the critical temperature. In addition, the physical cross-link density increased upon the addition of TPA to the system, but a further increase of the TPA concentration (beyond a stoichiometry of 1:10) does not lead to a higher solution viscosity but rather to a precipitation.

Effects of DS and Solution Concentrations. Figure 6 shows the concentrations and DS dependence of the critical phase transitions with a 1:1 inclusion complex solution. It is obvious that the critical aggregation temperature increases with the concentration of the mixture solutions, although the temperature region was different from DS. In the case of the CDPL-3/TPA

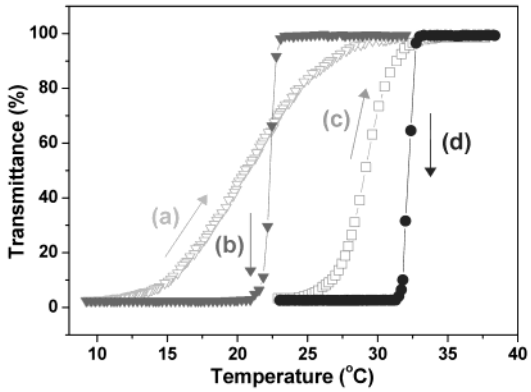

Figure 7. Transmittance changes in 1:1 mixture solutions of *β*-CDPL/TPA solutions as a function of temperature in 0.1 M phosphate buffer at pH 6 (1 wt %; the amount of TPA was estimated on the basis of the equilibrium amount of *β*-CD on *β*-CDPL); the heating curves for the complexes with CDPL-1 (DS 36.6%) and CDPL-3 (DS 48.6%) are designated (a) and (c), respectively. The cooling curves are similarly labeled as (b) and (d).

complex, the critical points were found to be 32.7, 36.5, and 40.8 °C, corresponding to the concentrations 1, 3, and 5 wt % solutions, respectively. A similar tendency was observed in the CDPL-1/TPA inclusion complex, but the critical points were lower than those of the CDPL-3 series. When the concentration of the mixture solution was below 0.5 wt %, it was not observed any phase transition, the point of which indicates the critical aggregation concentration of the 1:1 mixture solution. Amiel and Sebille interpreted this kind of point as an increase in the percentage of intermolecular over intramolecular host−guest links.[12]

The different critical points between CDPL-1 and CDPL-3 series suggest that the critical aggregation temperature could be tailored by varying the DS of CDs up to 50%. Deratani et al. synthesized poly(1-vinylimidazole)-supported *β*-CD conjugates and studied their solution behaviors with adding salts.[13] They reported that the cooperativity depended on the distance between neighboring CD molecules in the polymer structure. The attachment of CD moieties onto a macromolecular chain can improve the complexing ability by providing a high local concentration of binding sites. They form more stable inclusion complexes with large substrates due to a cooperation effect in binding between the adjacent units in the polymeric host. In our case, as shown in Figure 6, the critical point increased from 22.7 to 32.7 °C with increasing the DS from 33.6% (CDPL-1) to 48.6% (CDPL-3) in 1 wt % mixture solutions. The other concentrations of the mixture solution also showed very regular and delicate changes of critical aggregation temperatures with changing DS. A high proportion of the CD units in the medium are available for complexation with an additional guest without disrupting the aggregates.[14]

Thermoreversibility of *β*-CDPL/TPA Systems. Hysteresis was observed between heating and cooling transitions when temperature went up and down at 1 °C/min. As shown in Figure 7, a pronounced hysteresis was found, which indicates the interactions between *β*-CDPL chains and oppositely charged guest moieties.[6] The precipitation under cooling process was correlated well with the onset of thermal hysteresis in the association transition. The complexation between CDPL-3 and TPA showed more cooperative interactions and smaller

hysteresis than that of CDPL-1/TPA mixture solutions. When the heating rate was reduced, the temperature of the association-to-dissociation transition remained stationary.[15] In addition, thermal hysteresis was also reduced with increasing the solution concentrations as well as increasing stoichiometry to 1:5 (data not shown). Griffith et al. reported that a thermal hysteresis of the bis-PNA/DNA complex system is observed between heating and cooling curves because the rate of association to form complexes is faster than the rate of dissociation process.[16] In their bis-PNA/DNA complex system, melting data showed more cooperative melting, higher melting temperature, and smaller hysteresis than observed for the single PNA. In the case of the CDPL-3/TPA system, the forces on aggregate formation are identical due to the same number of host and guest molecules (48.6% DS; 1:1 stoichiometry), leading to electroequivalent condition; therefore, there is a reduced thermal hysteresis as repeating heating and cooling processes.

Conclusions

In the present study, we showed that the UCST could be tailored with varying DS of CDs to the β-CDPL main chain as well as changing the concentrations of guest moieties or mixture solutions based on the supramolecular assembly. The transition temperatures showed very delicate and minute changes near physiological conditions. Furthermore, we also examined the viscosity enhancement and gel formation occurring upon the addition of anionic guest TPA to the cationic β-CDPL. A pronounced effect of pH and the added TPA on the change of viscosity and on the zero-shear viscosity was observed. The result of rheological measurements indicates that the TPA included into hydrophobic CD cavities by specific host−guest interactions acted as a physical cross-linker by cooperative hydrophobic and ionic interaction, which gave a more important increase of viscosity at low pH. Upon increasing pH over 6.0, the cooperative intermolecular interactions were weakened, and thus the relaxation time of the mixture solution decreased significantly. In addition, the shear rate value where the transition from Newtonian to shear thinning behavior occurred was decreased as well as the onset point was shifted to the upfield. This rapid and delicate supramolecular assembling system is promising as smart materials and can find a broad range of applications, because its functionality is variable or switchable in response to many kinds of stimuli simultaneously. Such supramolecular assembling system is of importance not only in basic studies such as a model for molecular recognitions and enzyme−substrate interactions of biological systems but also for practical applications such as drug delivery systems, separation operations in biotechnology, processing of agricultural products, sensors, and actuators.[17] Kinetics and thermodynamic study on detailed complexation mechanism are in progress.

Experimental Section

Materials. β-CD was purchased from Wako (Tokyo, Japan) and purified by recrystallization in distilled water, followed by drying in vacuo at 60 °C. Poly(ϵ-lysine) ($M_w = 4090$, $M_w/M_n = 1.14$) was kindly supplied by Chisso Co. Ltd. (Tokyo, Japan). TPA and sodium cyanoborohydride were purchased from Aldrich (Milwaukee, WI). Dimethyl sulfoxide (DMSO, Wako) was dried over CaH_2 and distilled. The other synthetic reagents were used as received without further purification.

Inclusion Complexation of β-CDPL with TPA. The inclusion complexation of β-CDPL with TPA was achieved by simply adding TPA aqueous solution into β-CDPL aqueous solution with various molar feed ratios. β-CDPL was prepared by a coupling reaction between monoaldehyde activated β-CD and PL according to a previously reported method.[6] Briefly, β-CDPL was prepared by a coupling reaction between aldehyde-β-CD and PL. PL (0.27 mmol) was allowed to react with a predetermined amount of aldehyde-β-CDs in 0.2 M acetate buffer (pH 4.4) at 25 °C because the formation of Schiff's base is accelerated at the lower pH region.[18] After stirring 1 h, 2 equiv of sodium cyanoborohydride was added to the resulting solutions. The mixture was stirred for 72 h and then neutralized with 2 M sodium hydrate, followed by dialysis against water and freeze-drying. The chemical composition of β-CDPL was confirmed by ^{1}H NMR and FT-IR spectrometries.

^{1}H NMR (D_2O): $\delta = 4.96$ (s, 7 H, H-1, CD), 4.00−3.35 (2m, CD protons), 3.35−2.9 (3m, α and ϵ protons, PL), and 1.78−1.00 (3m, β, δ, and γ protons, PL).

FT-IR (KBr): 3413 (s, OH), 2929 (s, C−H), 1637 (s, C═O), 1559 (m, N−H), 1458 (m, C−H), and 1200−800 cm^{-1} (m, C−C and C−O).

Characterization. The chemical composition of β-CDPL was confirmed by ^{1}H NMR and FT-IR measurements using a 750 MHz FT-NMR spectrometer (Varian, Palo Alto, CA) and FT-IR spectra with a VALOR-III FT-IR spectrometer (Jasco, Tokyo, Japan), respectively. The complexes of α- or β-CD with TPA were prepared as references, and the stoichiometry of their inclusion complexes was confirmed by ESI spectroscopy with a BioAPEXII 70e (Bruker Daltonics, Billerica, MA) triple-quadrupole mass spectrometer equipped with an electrospray ion source (Analytica of Branford, Inc.). Ions were produced from the solution of 1×10^{-6} M CD and a 10-fold excess of TPA. The source temperature was set at 150 °C, and the mass range was limited to m/z 1200. The samples were dissolved in a 50:50 (v/v) mixture of methanol/water and injected at a flow rate of 15 μL/h into the ESI source of the mass spectrometer. The crystallinity change in complex formation of β-CDPL with TPA was confirmed by X-ray diffraction measurements, performed with a powder diffractometer (RINT2000, Rigaku, Japan) and two-dimensional image-plate photography using graphite-monochromatized Cu Kα radiation ($\lambda = 1.542$ Å). Physical mixture was made of grinding β-CDPL and TPA with a 1:1 molar ratio.

The viscosity change in the β-CDPL/TPA mixture solution with various pHs was measured by a rheometer Rheosol-G3000 (UBM, Kyoto, Japan) with a stainless steel cone-and-plate geometry system (cone angle 1.996°, diameter 40 mm). Measurements were taken at 20 °C, and the cone-to-plate distance was 40 μm. Complexation-induced aggregations or clouding behaviors of the mixture solutions between β-CDPL and TPA were measured by observing light transmittance using a UV−vis spectrophotometer (V-550, Jasco, Tokyo, Japan). The observation cell was thermostated by a temperature controller (ETC-505T, Jasco, Tokyo, Japan). The excitation wavelength was fixed at 500 nm, and the spectral bandpasses were 1.5 nm. A temperature ramp of 1 °C/min was used.

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