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Structural Role of Guest Molecules in Rapid and Sensitive Supramolecular Assembling System Based on β-Cyclodextrin-Conjugated Poly(ϵ-lysine)

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ABSTRACT: Supramolecular assembling systems governed by intermolecular cooperative host−guest complexation and ionic interactions were investigated based on β-cyclodextrin-conjugated poly(ϵ-lysine) as a supramolecular host and several hydrophobic guest moieties. The geometric conformations for the inclusion complexation were characterized by 2D-ROESY NMR, and the pH- and thermoreversible properties were investigated by UV−vis measurements. In addition, systematic kinetics and thermodynamics of the supramolecular formation were studied by stopped-flow spectrophotometry and isothermal titration calorimetry, respectively. The trajectories of the binding site, the penetration depth of the guest moiety inside the β-cyclodextrin, ionic function groups, and other geometrical features gave detailed information on the rapidly stimuli-responsive supramolecular assembly formation.

Introduction

Cyclodextrins (CDs) and chemically modified CDs recognize a variety of organic and inorganic molecules in aqueous solution.[1,2] The molecular recognition phenomena by various CD derivatives have been a subject of special attention in the past decade as suitable models for enzyme−substrate binding process and receptor−drug interactions.[3,4] Precise and favorable geometric arrangements between host and guest molecules play an important role in designing new functional systems.[1−4]

In those studies positively cooperative self-assembly approaches offer the possibility of generating larger and more complex supramolecular structures.[5] Encapsulation of guest molecules during the self-assembly process is also an interesting possibility, especially coupled with pH-controlled reversible pseudorotaxane formation, suggesting several types of applications.[6] In these pseudorotaxanes the rates of formation and dissociation strongly depend on the molecular structure of the guest molecules.[7] Nishikawa et al. supported this hypothesis in the complexes between amino acids and β-CDs. The stability of the complexes was mainly governed by the hydrophobicity of the guest molecules, which control the dissociation rate of the complexes.[8] Yoshida et al. reported on those kinetic studies using stopped-flow methods: the molecular recognitions by β-CDs are considerably dependent on the steric and electronic properties such as size, shape, charge, and hydrophobicity of the substituent in guest molecules.[9]

On the basis of these studies, the supramolecular formation of β-CD-conjugated poly(ϵ-lysine) (β-CDPL) with 3-(trimethylsilyl)propionic acid (TPA) was evaluated in our previous papers.[10] This system showed temperature-induced phase transition owing to the reversible inclusion complexation and dissociation; in addition, it underwent pH-induced phase transitions via intermolecular ionic interactions. The induction time of the β-CDPL/TPA system was found to be very short (within 100 ms), resulting from cooperative intermolecular interactions of inclusion complexation and ionic interactions. However, despite their apparent simplicity, the structural factors of the guest molecules to modulate the cooperative intermolecular interactions are not yet elucidated.

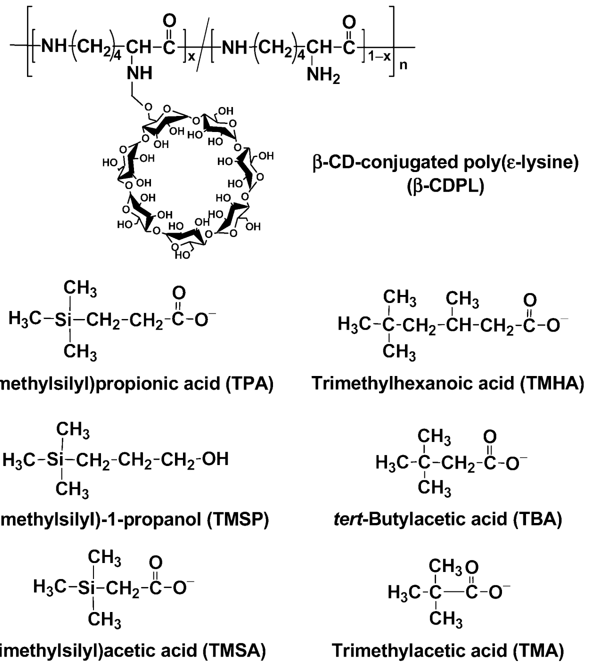

Figure 1. Chemical structures of β-CD-conjugated poly (ϵ-lysine) (β-CDPL) and various TPA analogues.

Here we describe the conformational geometry of the guest molecules, the systematic thermodynamics, and the kinetics in the supramolecular formation between β-CDPL and various TPA analogues (Figure 1). In this system the relative charges are important to stabilize the supramolecular assemblies through cooperative electrostatic attractions.[11,12] To confirm the contribution of ionic interactions to the supramolecular formation, 3-(trimethylsilyl)-1-propanol (TMSP) was selected as a guest due to the nonionic group in its terminal. The effects of the guest length and the penetration depth on the inclusion complexation were evaluated by using

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relatively short alkyl-chain-containing guest moieties such as 3-(trimethylsilyl)acetic acid (TMSA), *tert*-butylacetic acid (TBA), and trimethylacetic acid (TMA). Additionally, compared to the bulky hydrophobic group of TPA composed of trimethylsilyl group, some *tert*-butyl-group-containing small molecules such as trimethylhexanoic acid (TMHA), TBA, and TMA were introduced as guest moieties in β-CDPL solutions.

Experimental Section

Synthesis of β-CDPL. The detailed synthetic method for β-CDPL was introduced in previous reports.[10] Briefly, PL (0.27 mmol) was allowed to react with a predetermined amount of mono-6-aldehyde-β-CD in 0.2 M acetate buffer (pH 4.4) at 25 °C. After being stirred for 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. The representative chemical structure is depicted in Figure 1.

^{1}H NMR (D$_2$O, β-CDPL): δ 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), 1.78–1.00 (3m, β, δ, and γ protons, PL).

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

Chemical Composition. The chemical composition of β-CDPL was confirmed by ^{1}H NMR using a 300 MHz FT-NMR spectrometer (Varian, Palo Alto, CA) and FT-IR spectra with a VALOR–III FT-IR spectrometer (Jasco, Tokyo, Japan). To verify the geometric arrangements of inclusion complexation in detail, 2D-ROESY NMR measurements were carried out in terms of observing dipolar interactions (nuclear Overhauser effects) using a 750 MHz FT-NMR (Varian, Palo Alto, CA).[13]

Isothermal Titration Calorimeter (ITC). The ITC experiments were carried out using an Omega isothermal titration calorimeter (MicroCal, Inc., Northampton). The reaction cell and injection syringe were filled with guest (1.0×10^{-4} M) and β-CDPL aqueous solutions (3.0×10^{-3} M), respectively. This arrangement minimized the contributions from the heat of dilution of the guest. Twenty portions, 7.5 μL each, of the β-CDPL solution were injected to the guest solution with intervals of 3 min, and the heat generation was recorded. Heat of dilution was also observed to correct the observed binding heats. The obtained calorimetric data were processed by Origin for ITC (ver. 5.0, MicroCal, Inc.).

UV–Vis and Stopped–Flow Spectrometries. Complexation-induced aggregations or clouding behaviors of the mixture solutions between β-CDPL and various TPA analogues 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). The excitation wavelength was fixed at 500 nm, and the spectral band passes were 1.5 nm. A temperature ramp of 2 °C/min was used.

The kinetics of the supramolecular assembly formation was studied using a stopped-flow spectrophotometer (RA-2100HS, Otsuka Electronics, Osaka, Japan). Stoichiometric reactions were performed with a pH variation (pH 3–12) of CDPL solutions and equivalent molar ratio of guest solutions. The concentrations presented were the final concentration after mixing. The reaction was followed up in terms of changes of absorbance with time at $\lambda_{\max} = 500$ nm using a conventional UV–vis spectrophotometer (RA-2530, Otsuka Electronics). The kinetic measurements were performed at 10 °C with the stopped-flow compartment thermostated by an external water bath (RML-6, Otsuka Electronics). pH measurements were carried out with a digital pH meter (HM-30V, TOA Electronics, Kobe, Japan) equipped with a glass electrode.

Results and Discussion

Conformational Geometry. To verify the conformational geometry of the inclusion sites, 2D-ROESY NMR measurements were carried out in terms of observing dipolar interactions (nuclear Overhauser effects).[13] In this study we divided the guest samples into two groups in terms of the size of the hydrophobic inclusion site, trimethylsilyl-group-containing moieties (TPA, TMSP, and TMSA), and *tert*-butyl-group-containing guests (TMHA, TBA, and TMA).

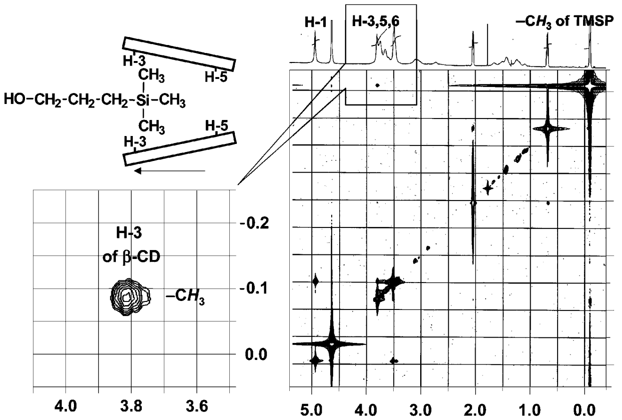

Figure 2. Partial contour plots of the 2D-ROESY NMR spectrum, and a proposed structure of TMSP/β-CDPL inclusion complex in D$_2$O.

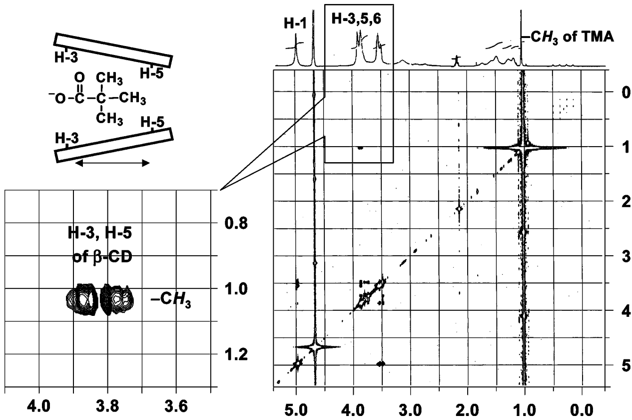

Figure 3. Partial contour plots of the 2D-ROESY NMR spectrum, and a proposed structure of TMA/β-CDPL inclusion complex in D$_2$O.

In our previous paper[10a] the partial contour plots of the TPA/β-CDPL complex spectra showed that the signals of H-3 protons of β-CD were correlated with the resonance of methyl protons of TPA with a stoichiometry of 1:1. In the case of the TMSP/β-CDPL system, strong NOE cross-peaks are observed between H-3 of β-CD and the methyl groups of TMSP, while no NOEs are found between H-5 of β-CD and any protons of TMSP (Figure 2). The same phenomenon is observed in all the systems of β-CDPL with the trimethylsilyl-group-containing moieties. This result indicates that the H-3 protons of β-CD are the most prone to be affected by the inclusion process and the inclusion complexation occurs preferably from the secondary (larger) ring side of β-CD.[14] On the other hand, in the cases of *tert*-butyl groups, stronger NOEs are observed with H-5 of β-CD in addition to the cross-peaks with H-3 (Figure 3). From the ROESY spectra, stronger host–guest NOE peaks are observed for the complexes of TMA with β-CD, indicating deeper penetration of TMA than TMSP. It can be assumed that the bulky trimethylsilyl group of the guest moiety acted as a stopper to prevent deep penetration in the complex formation with β-CD because the bond length of Si–C

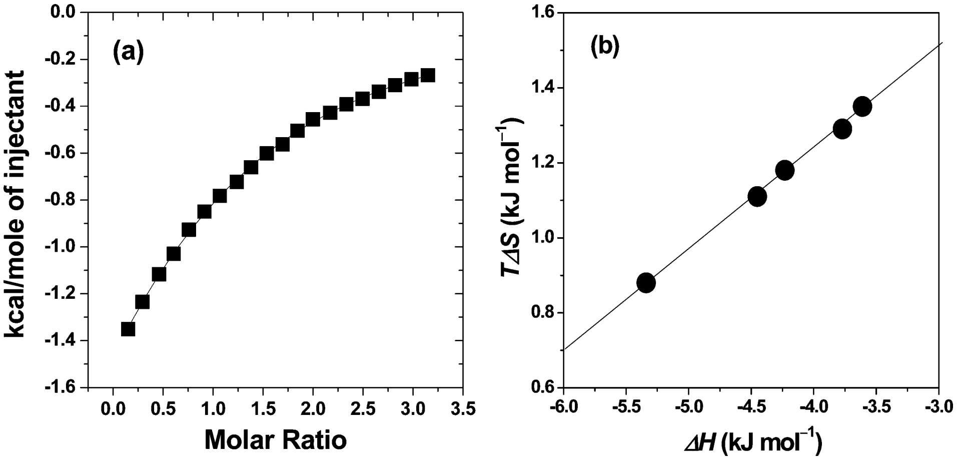

Figure 4. Microcalorimetric titration of TPA by β-CDPL (a), and enthalpy−entropy compensation plots for the complexes of β-CDPL with various guest moieties (b). The concentrations of the guest moieties and β-CDPL were 1.0×10^{-4} and 3.0×10^{-3} M, respectively.

Table 1. Binding Constants and Thermodynamic Parameters for the 1:1 Complexes between Hydrophobic Guest Moieties and β-CDPL Solutions at 283 K in 0.1 M Phosphate Buffer

guest moiety	ΔG, kJ mol^{-1}	ΔH,[a] kJ mol^{-1}	$T\Delta S$, kJ mol^{-1}	K_S,[a] 10^{-3} M^{-1}
TPA	−5.06	−3.77	1.29	6.41
TMSP	−4.96	−3.61	1.35	6.27
TMHA	−6.22	−5.34	0.88	8.39
TBA	−5.56	−4.45	1.11	7.57
TMA	−5.41	−4.23	1.18	7.03

[a] The binding enthalpy ΔH and the binding constant K_s were obtained as fitting parameters using Origin software (ver. 5.0).

(1.87 Å) is longer than that of C−C (1.42 Å) as well as the atomic radius of silicon (1.17 Å) is larger than that of carbon (0.77 Å). It is concluded that the trimethylsilyl group interacts mainly with the H-3 proton of the secondary ring side of β-CD, while the *tert*-butyl group penetrates more deeply to interact with both H-3 and H-5 protons of β-CD.

Thermodynamics. Of central importance for understanding and evaluation the phenomena of molecular interaction (host−guest complexation) is to know the binding constants and, even more important, the thermodynamic parameters, enthalpy and chain combination with structural data on the supermolecule formation.[15] The thermodynamics of the inclusion complexation were analyzed by isothermal titration calorimetry (ITC) at 10 °C. Taking into account the originally included or interacting water molecules, Inoue et al.[19a] reported the 1:1 complexation reaction of a guest (G) with a CD host (CD) as follows

$$G\cdot gH_2O + CD\cdot hH_2O \leftrightarrow G\cdot CD\cdot(g + h - i)H_2O + iH_2O \quad (1)$$

where g represents the number of water molecules interacting with the free guest, h the number of tightly bound hydration water molecules inside the free CD cavity, and i the net displacement of water upon complexation.

The binding constant (K_S) for the 1:1 complexation of the conjugated β-CD with a guest molecule is expressed by

$$K_s = \frac{[G:CDPL]}{[CDPL] \times [G]} \quad (2)$$

where [CDPL] is the concentration of β-CD in the β-CDPL, [G] is the concentration of the guest molecules, and [G:CDPL] is the concentration of the inclusion complex. For ionic guest molecules the counterions are omitted in the figures because they do not take part in the complexation process. In addition, ITC reports host−guest interactions solely in terms of reversible binding processes because the solution concentrations are very low (1.0×10^{-4} M for the guests, 3.0×10^{-3} M for β-CDPL). Here we used the simplest binding model, which for individual guest molecules bind to discrete binding sites in a noncooperative fashion. Notably, a diminution in the enthalpy of binding is accompanied by a compensating increase in the entropic term, a trend previously reported.[16] The enthalpy change (ΔH) and binding constant (K_S) were evaluated by the nonlinear regression fitting of the binding isotherm. The Gibbs free energy change (ΔG) and the entropy change (ΔS) were obtained from the following equation

$$\Delta G = -RT \ln K_s = \Delta H - T\Delta S \quad (3)$$

Table 1 summarizes the thermodynamic parameters of β-CDPL with each guest complex. All the guest molecules showed negative and positive values of ΔH and $T\Delta S$, respectively. On the whole, according to the theory of enthalpy−entropy compensation, the gain in the enthalpy on the formation of inclusion complex is achieved with the loss in entropy.[17] The small value of ΔS is primarily due to the restricted rotation of the host and guest in the complex formed. The negative enthalpy change in these guest moieties reveals the presence of hydrophobic interactions in the cavity of β-CDPL and the head part of the guest.

On the basis of Table 1, the validity of the compensatory enthalpy−entropy relationship was also examined for β-CDPL complexation and shown to afford a good to an excellent linear plot for TPA analogues (Figure 4b). The gradually increasing tendency of the slope and intercept in this plot as the guest size and length increase are consistent with well-established structural features and dynamics of β-CDPL.

Compared with the trimethylsilyl group of TPA (Figure 4a), the *tert*-butyl groups of TMHA, TBA, and TMA significantly increased the negative value of ΔH. This indicates that the complex stability is enhanced through the simultaneous contributions of enthalpic gain, arising from the strong electrostatic interactions and newly formed van der Waals contacts, and less positive reaction entropy (entropic loss) from the restricted freedom.[18,19] In addition, the methyl-branched aliphatic chain located on the inside of the β-CD cavity (TMHA/β-CDPL) led to more increased changes in enthalpic and entropic values. It results from an additional increase of van der Waals interactions between the introduced methyl group and the walls of the cavity, leading to an enthalpic gain and compensating for the accompanying entropic loss.[20]

The contribution of decreasing alkyl chain length to complex stability was evaluated by Hansch's hydrophobic constant π parameter.[21] As shown in Table 1, the ΔG and ΔH values are less negative when decreasing the length of alkyl chains of the guests. Because the alkyl chains with a maximum of five carbon atoms can be accommodated in the CD cavity (depth 7.9 Å),[22] the TMA molecule may be inserted into the β-CD cavity entirely. This shows that inclusion of the carboxyl group into the β-CD cavity leads to tightly bound solvation. This results in a decrease of ΔH as well as ΔS because the release of bound water molecules from the β-CD cavity and rearrangement of nearby water molecules appear to play a decisive role in determining the overall complexation thermodynamics.[23] In the case of TMSP/β-CDPL, the ΔG and ΔH values are very similar to those of the TPA system because the hydroxyl group and carboxylate moiety remain in bulk water after inclusion complexation. This result indicates that the charged carboxyl group located in bulk water is prevented from direct interaction with the CD.[19a]

From the results we conclude that the trimethylsilyl group is sterically unfavorable to complexation; therefore, they cannot be completely accommodated within the CD cavity, which results in higher ΔH values than with *tert*-butyl-moiety-containing guests because van der Waals interactions are highly dependent not only on the size but also on the shape of the guest molecule.[19a] In the case of the TMSA/β-CDPL system, we could not obtain any stable thermodynamic data due to the relatively low critical temperature.

Stimuli-Responsive Properties. To investigate how the exposed carboxyl group of the guests out of the β-CD cavity affects supramolecular formation with β-CDPL, various TPA analogues with different lengths and penetration depths to the CD cavity were mixed with β-CDPL solution, and the stimuli sensitivity was observed by UV−vis spectrometry at each optimal pH and temperature. Before the measurements we confirmed the contribution of ionic interactions to supramolecular formation using TMSP, which has a nonionic group at its terminus. As reported in our previous paper, TPA forms a supramolecular assembly at pH 6.0 with β-CDPL, represented as critical phase transitions with a small change of pH and/or temperature.[10a] In the case of the TMSP/β-CDPL system, there was no change of transmittance in pH and/or temperature variations, although the possibility of inclusion complexation was confirmed by 2D-ROESY NMR spectra. These results indicate that the transmittance changes are induced by the attractive ionic interactions between the cationic group of the main chain and the anionic end group of the guest moiety inserted into the conjugated β-CD cavity.

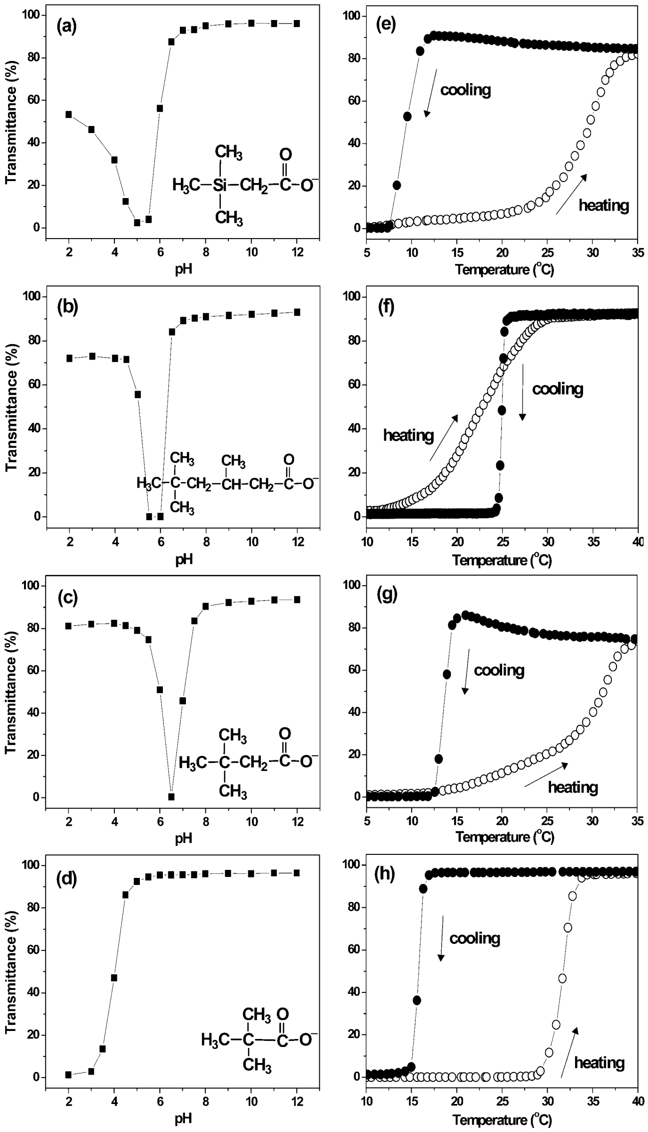

Figure 5. Guest and host (DS 44.3%) mixtures in 0.1 M phosphate buffer (1:1 inclusion, 5 wt %); the pH-responsive transmittance change of TMSA/β-CDPL at 5 °C (a), TMHA/β-CDPL at 10 °C (b), TBA/β-CDPL at 10 °C (c), and TMA/β-CDPL at 10 °C (d), and the thermal hysteresis of TMSA/β-CDPL pH 5.0 (e), TMHA/β-CDPL at pH 6.0 (f), TBA/β-CDPL at pH 6.5 (g), and TMA/β-CDPL at pH 3.0 (h).

The effect of alkyl chain length on supramolecular assembly formation was confirmed using TMSA since it has a lack of methylene compared to TPA (Figure 1). From the UV−vis spectra of TMSA/β-CDPL (Figure 5a), a sharp pH-dependent transmittance change was observed at a range of pH from 5.0 to 5.5, which was similar to that of the TPA/β-CDPL system. However, the thermosensitive behavior was found to be unstable with a pronounced hysteresis. It might be correlated with the compensation effect between the host−guest interactions and cooperative ionic interactions. Although TMSA and β-CDPL form an inclusion complex, the chain length of TMSA is similar to the cavity of β-CD (8 Å); therefore, the anionic end group of the guest could

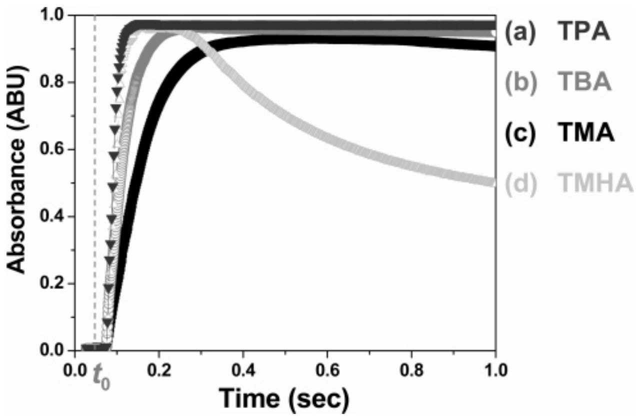

Figure 6. Typical time course of absorbance changes observed at 500 nm after mixing of [β-CDPL] (4.7×10^{-4} M) and [guest] (7.3×10^{-3} M) solutions (stoichiometry 1:1): TPA/β-CDPL at pH 6.0 (a), TMHA/β-CDPL at pH 6.0 (b), TBA/β-CDPL at pH 6.5 (c), and TMA/β-CDPL at pH 3.0 (d). The samples were prepared in 0.1 M phosphate buffer at 10 °C. The mixing time and dead time were 100 and 60 ms, respectively, and t_0 is the starting point of the measurement.

not be exposed easily to the exterior of the β-CD cavity.[19b] As a result, thermal complexation between TMSA and β-CDPL showed larger hysteresis with instability than that of TPA/β-CDPL systems.

From the results of molecular modeling we found that the penetration depth of the guest moiety into the CD cavity is important to determine exposure of the terminal carboxyl group of the guest (data not shown). To investigate the effect on supramolecular formation, some *tert*-butyl-group-containing compounds (TMHA, TBA, and TMA) were introduced to β-CDPL solutions at each appropriate pH and temperature. As shown in Figure 5b, the TMHA/β-CDPL system shows very similar transition behaviors to the TPA/β-CDPL system with both pH and temperature change. Even though TMHA penetrates more deeply than TPA into the β-CD cavity, the carboxyl group of TMHA can be exposed to the outside of the β-CD cavity and interact with the primary amine group of the main chain due to the relatively long alkyl chain.

On the other hand, a sharp gelation at pH 6.0−6.5 was observed in the TBA/β-CDPL system, but they had very unstable thermal properties with a large hysteresis (Figure 5c,g). It might result from the length of TBA, which is short enough to be penetrated into the β-CD cavity. Therefore, the carboxyl group of TBA might be entirely covered by the β-CD cavity, which results in a distorted hysteresis like the TMSA/β-CDPL system. In the case of TMA/β-CDPL, they did not show pH-dependent phase transition but thermosensitive property (Figure 5d,h). Since TMA is relatively short compared to the depth of the β-CD cavity, the carboxyl group is sterically hindered by the β-CD inclusion and intermolecular ionic interactions could not occur. The sharp phase separation observed at low pH was due to protonation of the carboxyl group, which increased the affinity between TMA and the β-CD cavity.[19a] This means that simple host−guest complexation and dissociation are the major interactions of the sharp gel−sol transition with temperature in the TMA/β-CDPL system.

Kinetics by Stopped−Flow Spectrophotometry. Stoichiometric reactions were performed between β-CD-PL and an equivalent molar ratio of the guest solutions at each optimum pH.[25] As shown in Figure 6, when the host−guest solutions are mixed together, the absorbance at 500 nm of the mixtures dramatically increased with various time scales. Previously we verified that fast aggregation in the TPA/β-CDPL system was induced by dual cooperative interactions, specific host−guest interaction and intermolecular ionic interaction, which acted simultaneously in the formation of a supramolecular assembly. These results suggest that β-CDPL and TPA moiety might form a supramolecular assembly through the following two-step mechanism, where the first step is a fast inclusion complexation process of a guest moiety into the secondary ring side of a β-CD (k_1) and the second step is a subsequent intermolecular ionic interaction between the formed inclusion complexes (k_2)

$$\mathrm{CDPL} + \mathrm{G} \overset{k_1}{\longleftrightarrow} [\mathrm{G{:}CDPL}]_1 \overset{k_2}{\longleftrightarrow} [\mathrm{G{:}CDPL}]_n \qquad (4)$$

In this study, we could observe a time-dependent absorbance change by varying the alkyl chain length of guest moieties in the mixtures. In the case of TPA/β-CDPL, k_1 and k_2 occurred simultaneously and the increased turbidity was maintained for a long time (Figure 6). The TMHA/β-CDPL system at pH 6.0 showed a very similar time course to that of TPA due to the structural similarity; however, the molecular recognition clearly occurred as a two-step process (Figure 6d): a rapid binding process of the trimethylsilyl group by a specific host−guest interaction followed by a subsequent intermolecular−structural transformation of the inclusion complexes to reach equilibrium conditions with stable final aggregation.[25a]

By introducing a shorter guest moiety than TPA in β-CDPL solution, a relatively slow gelation was observed. As shown in Figure 6b, the TBA/β-CDPL system takes ca. 0.15 s to reach the maximum gelation point at pH 6.5, while ca. 0.08 s is needed for the TPA/β-CDPL system (Figure 6a). In addition, the TMA/β-CDPL system shows the slowest absorbance change (ca. 0.41 s) in the group at pH 3 (Figure 6c). This might result from protonation of TMA being complexed into the β-CD cavity, which played a dominant role in leading to a hydrophobic aggregation, while multifaceted interactions participated in the aggregation phenomena simultaneously in the other systems. This result indicates that the dual interactions of inclusion complexation and ionic interactions act cooperatively to lead to fast supramolecular complexation in the TPA system. In the case of the TMSA/β-CDPL system, the absorbance change could not be observed due to the relatively low aggregation temperature.

Conclusions

The molecular recognition process is the result of several interactions (van der Waals, hydrogen bonding, hydrophobic interactions, etc.), which are dependent on the nature and structure of the groups present on each component of the complex.[26] In this point of view the guest molecules, TPA analogues, have a hydrophobic part to interact with the β-CD cavity and an anionic end group for the intermolecular ionic interactions with the amino group of PL. The contribution of the hydrophobic part to supramolecular aggregation was confirmed by 2D-ROESY NMR and calorimetric titration methods. The smaller radius and bond length of carbon compared to silicon led to a different conformation; the methyl groups in the *tert*-butyl groups were found to be closer to the smaller rim of β-CD (H-5), and the binding constants were larger than that of trimethylsilyl groups. The role of ionic interactions in the phase transitions of β-CDPL-based supramolecular assembly was confirmed by changing the end group of the guest moieties. The length and penetration depth of the guest molecules strongly affected the supramolecular aggregations with β-CDPL, which acted as a noncovalent cross-linker by intermolecular ionic interactions.

On the basis of specific host−guest interactions and cooperative intermolecular ionic interactions, such a supramolecular-complexed system will play an important role as a building block of multistimuli-responsive hydrogel systems. Further study along this line using supramolecular guests is now in progress.

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