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Effect of Host–Guest Interactions on the Cloud Points of Neutral Thermosensitive Homopolymers: Poly(*N*-n-propylmethacrylamide) and Polymers with Similar Structures

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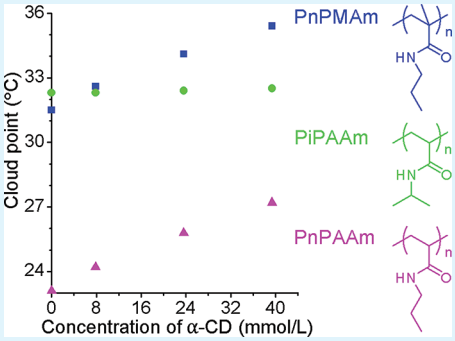
Supporting Information

ABSTRACT: We investigated effect of cyclodextrins (CDs) on the cloud point of several thermosensitive polymers that are not ionizable. α-CD increased the cloud point of the poly(*N*-n-propylmethacrylamide) (PnPMAm) aqueous solution; by contrast, β-CD or γ-CD did not affect the cloud point of the PnPMAm solution. The cloud point of the PnPMAm solution increased gradually with an increase in the concentration of α-CD. Furthermore, we compared the effect of the CDs on the cloud points of four polymers with similar structures. As for poly(*N*-isopropylacrylamide) (PiPAAm), neither α-CD nor β-CD affected its cloud point. On the basis of the effect of the differently sized CDs on the cloud point of five polymers and the corresponding NOESY NMR data, we inferred that steric hindrance by the main chain of PiPAAm might be responsible for the bulky CD being unable to form a complex with the short isopropyl group.



KEYWORDS: *stimuli-responsive polymers, cyclodextrin, inclusion complex*

1. INTRODUCTION

Thermosensitive polymers can undergo significant property changes in a controlled fashion by a temperature stimulus.[1−5] Thermosensitive polymers have potential in a variety of applications, such as the stationary phase in chromatography, separation of biomacromolecules, surface modification, drug delivery, and drug release.[6−8] The application in a given area may require a thermosensitive polymer with a specific cloud point and, therefore, tuning the cloud point of the thermosensitive polymers is an important research subject. Random copolymerization with another hydrophilic or hydrophobic monomer is a common method used to tune the cloud point of a thermosensitive polymer. Takei and co-workers reported that the introduction of the relatively hydrophilic acrylamide increased the cloud point of poly(*N*-isopropylacrylamide) (PiPAAm); by contrast, the introduction of the hydrophobic *N*-butylacrylamide lowered the cloud point.[9] In addition, the temperature response of a polymer is often affected by salts,[10,11] solvents,[12,13] surfactants,[14,15] pH,[16,17] oxidation.[18]

A cyclodextrin (CD), a cyclic oligosaccharide, has the shape of a hollow truncated cone. In water, it is able to form inclusion complexes with many different (organic, inorganic, neutral, and ionic) molecules.[19−25] Host–guest systems containing CD has been used in photocontrolled molecular devices[19] and switch of surface wettability.[26] A CD is a good host not only for small molecules but also for polymers.[27−31] Extensive studies have been made on inclusion complexes of various PEO with CDs.[32−35] Kim and co-workers reported controlled release of guest molecules from mesoporous silica particles on the basis of pH-responsive polyethyleneimine/CD polypseudorotaxane.[36] There are some reports about the complexation between CDs and copolymer side groups.[37−39] Recently, host–guest interactions have been used to control the cloud point of thermosensitive homopolymers. Ritter and co-workers synthesized poly(*N*-(3-(dimethylamino)propyl)-methacrylamide).[40] The polymer solution shows thermosensitive properties only at pH 14. After randomly methylated β-cyclodextrin (RM-β-CD) was added to the polymer solution, the cloud point of the solution increased. We have previously reported that the addition of RM- β-CD or β-CD increases the cloud point of a poly(2-(dimethylamino)ethyl methacrylate) (PDMAEMA) solution at pH 9.18.[41] On the basis of an inclusion complexation equilibrium, we deduced an equation that describes the relationship between the cloud point and the concentration of RM- β-CD. However, because the tertiary amino groups of PDMAEMA can be protonated, the pH can affect the cloud point of PDMAEMA significantly. To avoid the influence of pH, we need to carry out related experiments in basic buffer solutions, and thus the system becomes more complicated to study.

In this article, we studied effect of CDs on the cloud point of thermosensitive polymers that are not ionizable (Scheme 1). First, we added different CDs in poly(*N*-n-propylmethacrylamide) (PnPMAm) solutions. β-CD or γ-CD did not affect the cloud point of the PnPMAm solution; by contrast, α-CD

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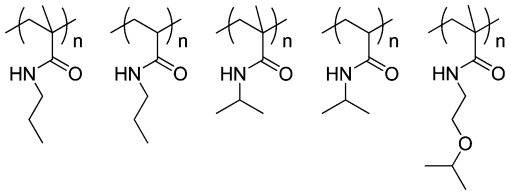
Scheme 1. Chemical Structures of Five Polymers



increased the cloud point of the PnPMAm solution. Second, β-CD had roughly no effect on the cloud point of PiPAAm[40,42] whereas α-CD increased the cloud point of PnPMAm. These phenomena inspired us to compare the influence of CDs on the cloud points of four polymers with similar structures (Scheme 1): PnPMAm, poly(*N*-n-propylacrylamide) (PnPAAm), poly(*N*-isopropylmethacrylamide) (PiPMAm), and PiPAAm.

2. EXPERIMENTAL SECTION

2.1. Materials. α-CD, RM-β-CD, and azobisisobutyronitrile (AIBN) were purchased from Aldrich. γ-CD was obtained from J&K chemical. β-CD, n-propylamine, and isopropylamine were purchased from Sinopharm Chemical Reagent Company. 2-Isopropoxyethylamine was purchased from Tokyo Chemical Industry. Methacryloyl chloride and acryloyl chloride were purified by vacuum distillation. All other chemicals were analytical reagents and were used without further purification.

2.2. Synthesis of Polymers. A dichloromethane solution of methacryloyl chloride was added dropwise to n-propylamine in a dichloromethane suspension of sodium carbonate at 5 °C. The mixture was then stirred at room temperature for 12 h. The crude product was purified by column chromatography using petroleum ether/ethyl acetate (1:1) mixture as an eluent. The structure of *N*-n-propylmathacrylamide was confirmed by NMR. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.73 (1H, −NH−), 5.69, 5.30 (2H, $\underline{CH_2}$=C(CH_3)−), 3.25 (2H, −NH−$\underline{CH_2}$−), 1.96 (3H, CH_2=C($\underline{CH_3}$)−), 1.56 (2H, −$\underline{CH_2}$−CH_3), 0.92 (3H, −CH_2−$\underline{CH_3}$) ppm. PnPMAm was synthesized in freshly distilled methanol with AIBN as a free radical initiator. A mixture of monomer, initiator and solvent was degassed by three freeze−pump−thaw cycles. Polymerization was carried out at 60 °C for 24 h. The polymer was purified by precipitation from methanol into petroleum ether/diethyl ether (1:1) mixture three times. The obtained polymer was dried in vacuum at 90 °C (white powder). The structure of PnPMAm was confirmed by NMR. ^{1}H NMR (500 MHz, D_2O): δ 7.62 (1H, −NH−), 2.99 (2H, −NH−$\underline{CH_2}$−), 1.68 (2H, −CH_2−, main-chain), 1.42 (2H, −$\underline{CH_2}$−CH_3), 1.03 (3H, −C($\underline{CH_3}$)−, main-chain), 0.83 (3H, −CH_2−$\underline{CH_3}$) ppm. PnPAAm, PiPAAm, PiPMAm, and poly(*N*-(2-isopropoxyethyl)methacrylamide) (PiPEMAm) were synthesized in the same manner. The number-average molecular weights of PnPMAm, PiPMAm, PnPAAm, PiPAAm, and PiPEMAm were 2.66×10^4, 2.73×10^4, 2.3×10^4, 5.68×10^4, and 6.34×10^3, respectively.

2.3. Instrumentation. The average molecular weight of PnPMAm was measured with gel permeation chromatography (Waters 410, refractive index detector, polystyrene calibration) using DMF as a mobile phase. The average molecular weight of PiPAAm, PnPAAm, PiPMAm, and PiPEMAm was measured with gel permeation chromatography (Prominence HPLC LC-20A Shimadzu, refractive index detector, polystyrene calibration) using THF as the mobile phase. Transmittance−temperature curves were obtained by measuring the transmittance at 500 nm using a UV−vis spectrometer (UV-2450, Shimadzu) with a thermostatic accessory. A temperature program (0.5 °C/min) was run using a PID temperature controller (708p, Xiamen Yudian) mounted on a thermostatic bath (THD-1006, Ningbo Tianheng). All NMR spectra were recorded on a Bruker Avance-500 NMR spectrometry (500 MHz) in D_2O at 298 K. HDO (4.70 ppm) was used as an internal reference for the NMR spectrum of PnPMAm.

3. RESULTS AND DISCUSSION

3.1. Effect of the Cyclodextrins on the Cloud Point of PnPMAm Solution. First, we recorded a transmittance−temperature curve for a 1.0 g/L PnPMAm solution (molar concentration of the repeat unit is 7.87 mmol/L) during heating (Figure 1a). The cloud point of the PnPMAm solution

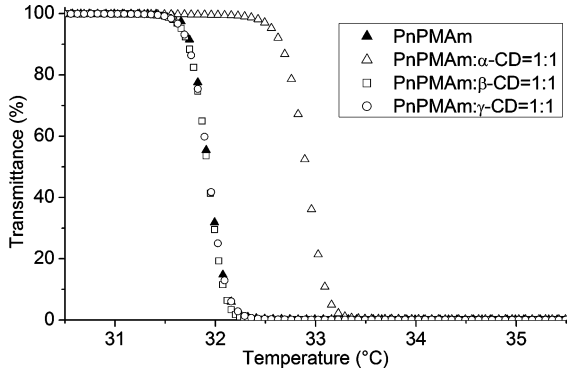


Figure 1. Transmittance−temperature curves obtained at a heating rate of 0.5 °C/min: (a) 7.87 mmol/L PnPMAm (▲); (b) 7.87 mmol/L PnPMAm and 7.87 mmol/L α-CD (Δ); (c) 7.87 mmol/L PnPMAm and 7.87 mmol/L β-CD (□); (d) 7.87 mmol/L PnPMAm and 7.87 mmol/L γ-CD (○).

was found to be 31.6 °C. The method for determining the cloud point has been described in the Supporting Information of our previous work.[41] We then studied the influence of different CDs on the cloud point of the PnPMAm solution while maintaining the molar ratio of the polymer repeat unit to CD at 1:1. As shown in Figure 1, the addition of β-CD or γ-CD has almost no effect on the cloud point of the PnPMAm solution. In contrast, the addition of α-CD increased the cloud point of the PnPMAm solution. These phenomena imply that the polymer side group and the hydrophobic cavity of α-CD match in size and inclusion complexes were formed in solution. However, the hydrophobic cavity of β-CD and γ-CD may be too large to form an inclusion complex with a polymer side group.

3.2. Inclusion Complexation between α-CD and PnPMAm. Inclusion complexation between α-CD and PnPMAm was studied by a two-dimensional nuclear Overhauser effect spectroscopy (2D NOESY) NMR experiment. As shown in Figure 2, there are correlation signals between the inner protons (H3, H5) of α-CD and the protons (Ha, Hb) of the n-propyl group of PnPMAm. These data indicate the formation of an inclusion complex between α-CD and polymer side groups.

The stoichiometry of the inclusion complex of PnPMAm and α-CD was determined by the method of continuous variations (Job's method).[43] For our system, the cloud point of the solution is related to the concentration of the inclusion complexes. We found that when the molar concentration fraction of α-CD was equal to 0.5, the concentration of the complex was at a maximum (see the Supporting Information). This result indicates that the stoichiometry of the inclusion complex of α-CD and the repeating unit is 1.

3.3. Relationship between the Cloud Point and the Inclusion Complexation. We measured the cloud point of a

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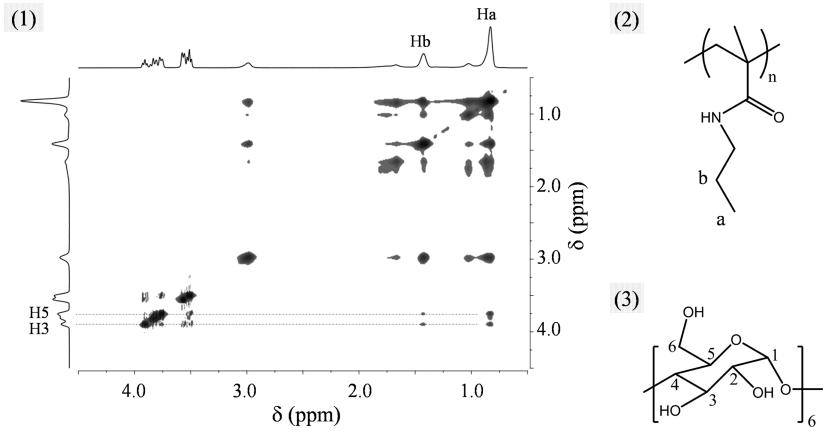

Figure 2. (1) ^{1}H−^{1}H NOESY NMR spectrum of PnPMAm (24 mmol/L) and α-CD (24 mmol/L) in 10% D_2O at 298 K. The positions of protons (Ha, Hb, H3, and H5) were defined in the chemical structures of PnPMAm (2) and α-CD (3).

series of 3.9 mmol/L PnPMAm solutions that contained different molar concentrations of α-CD, as shown in Figure 3.

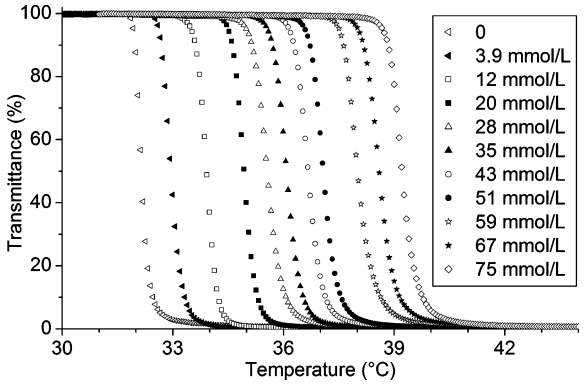

Figure 3. Transmittance−temperature curves of the 3.9 mmol/L PnPMAm solutions containing different molar concentration of α-CD during heating.

The cloud point of the 3.9 mmol/L PnPMAm solution was found to be 31.9 °C but the cloud point of the 3.9 mmol/L PnPMAm solution that contained 75 mmol/L α-CD was found to be 38.6 °C. The cause of the increase in the cloud point could be that the complexation of α-CD and PnPMAm made the polymer more hydrophilic. Apart from affecting the hydrophilicity, the inclusion complexation between α-CD and the polymer side group could hinder the intra- and interchain hydrophobic interactions of PnPMAm, leading to an increase in the cloud point.

We then plotted the cloud point as a function of the molar concentration of α-CD. As shown in Figure 4, the cloud point increases nonlinearly with an increase in the molar concentration of α-CD. We used eq 5 from a previous paper.[41] We replaced nC_0 with D_0 and obtained eq 1.

$$T_c = \frac{(T_{c0} - T_0)K_{eq}D_0}{(1 + K_{eq}D_0)} + T_0 \quad (1)$$

T_0 is the cloud point of PnPMAm in the absence of α-CD. T_{c0} is the cloud point of PnPMAm when all the repeat units of PnPMAm are complexed with α-CD (it is an imaginary state). T_c is the actual cloud point of the PnPMAm solution containing different amounts of α-CD. D_0 is the initial concentration of α-CD. K_{eq} is the inclusion complexation constant. The solid line in Figure 4 is the curve that was fitted using eq 1. The obtained fitting parameters are K_{eq} = 6.1 ± 1.1 L/mol and T_{c0} = 52.9 ± 2.6 °C. The coefficient of determination (R^2) is 0.998. This equation reveals the relationship between the cloud point and the inclusion complexation from a thermodynamic viewpoint. In addition, an inclusion complexation constant of 7.4 ± 3.2 L/mol was obtained by an NMR titration at 298 K (see the Supporting Information).

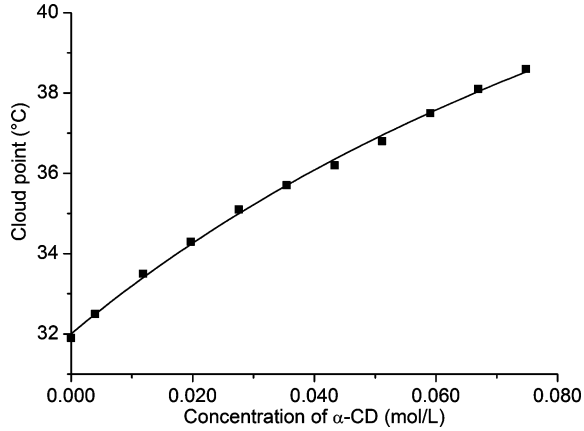

Figure 4. Increase in the cloud point with an increase in the molar concentration of α-CD and curve fitting using eq 1 (solid line).

3.4. Effect of Cyclodextrins on the Cloud Points of the Four Polymers with Similar Structures. Since other research groups have reported that the cloud point of PiPAAm is hardly affected by β-CD,[40,42] we compared the influence of CDs on the cloud points of four polymers with similar structures. As shown in Figure 5, when β-CD or γ-CD was added to solutions of PnPMAm, PnPAAm, PiPMAm, or PiPAAm, the change in the cloud point was found to be less than 1 °C. When α-CD was added to a PiPAAm solution and a PiPMAm solution, the change in the cloud point was less than 1 °C. In contrast, when α-CD was added to a PnPAAm solution and a PnPMAm solution, the cloud point increased significantly, especially for solutions containing high concentration of α-CD. The formation of inclusion complex of α-CD and n-propyl of PnPAAm was confirmed by NOESY NMR spectrum (see the Supporting Information). Isopropyl is wider and shorter than n-propyl. The change in cloud point suggests that PiPAAm did not form an inclusion complex with the three

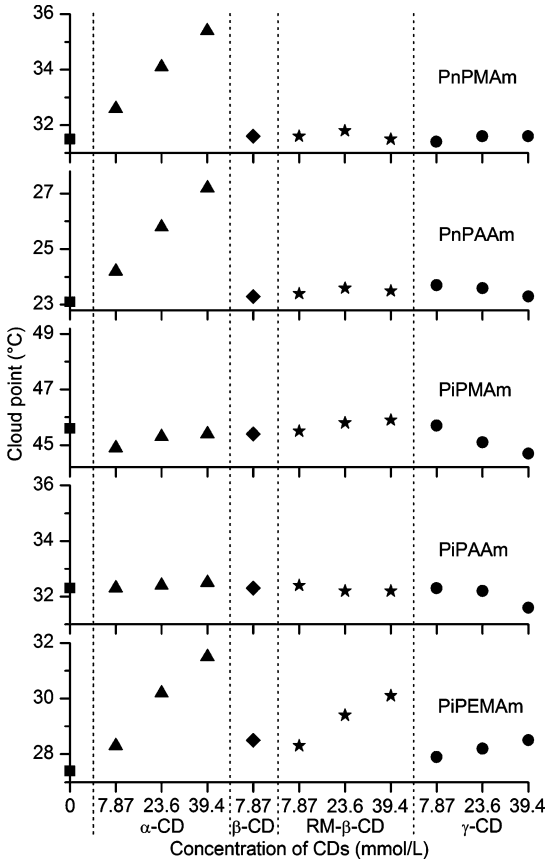

Figure 5. Cloud points (°C) of polymer solutions and polymer solutions containing different molar concentration of CDs. (Molar concentration for the five polymers is 7.87 mmol/L.).

differently sized CDs, and neither did PiPMAm. Figure 5 also shows that the addition of α-CD increased the cloud point of poly(*N*-(2-isopropoxyethyl)methacrylamide) (PiPEMAm), and correlation signals in NOESY NMR spectrum indicate the inclusion complexation between α-CD and isopropyl of PiPEMAm (see the Supporting Information). On the basis of this phenomenon and the diameter of the cavity of α-CD (0.47−0.53 nm), the isopropyl group fits the hole of α-CD. The maximum distance between the methyl of the side group and the main chain of PnPAAm is about 0.56 nm, whereas that of PiPAAm is about 0.42 nm, which were measured with ChemBio3D software. On the basis of the height of α-CD (0.79 nm), we infer that steric hindrance of the main chain of PiPAAm and PiPMAm might prevent the formation of inclusion complexes when a bulky CD attempts to encircle a short isopropyl group.

4. CONCLUSIONS

The cloud point of a PnPMAm solution increased gradually with an increase in the concentration of α-CD. In contrast, neither α-CD nor β-CD affected the cloud point of PiPAAm. On the basis of the influence of different-sized CDs on the cloud point of five polymers and the corresponding NOESY NMR data, we inferred that the steric hindrance of main chain of PiPAAm might be responsible for the bulky CD being unable to form a complex with the short isopropyl group. In addition, we found that the addition of α-CD resulted in an increase in the cloud points of poly(*N*-acryloyl-*N*′-propylpiperazine)[17] and poly(*N*-(3-ethoxypropyl)acrylamide). Therefore, we infer that some of other thermosensitive homopolymers can also form inclusion complexes with CDs. Inclusion complexation between CDs and thermosensitive polymers might be used in switching the surface wettability of a polymer-modified substrate,[44] separating polymers with similar structures, and tuning the micellization temperature of block copolymers.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR data of the monomers and polymers, Job's plot for inclusion complexation of PnPMAm and α-CD, inclusion complexation constant of PnPMAm and α-CD determined with NMR titration, determination of inclusion complexation constants by analyzing effect of CDs on cloud points of PnPAAm and PiPEMAm, inclusion complexation between CDs and PnPAAm and PiPEMAm studied by NOESY NMR. This material is available free of charge via the Internet at http://pubs.acs.org/.

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