NOTE

Effects of Surfactants on Cloud Points in Aqueous Poly(N-isopropylacrylamide) Solutions

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RUNNING HEADS   Effects of Surfactants in Aqueous PNIPA Solutions

Introduction

Poly(N-isopropylacrylamide) (PNIPA) has long been attractive to polymer scientists because their aqueous solutions show lower-critical-solution-temperature miscibility behavior near the human body temperature, and also because it seems to have potential applications in drug delivery and smart materials. In recent years, it has been reported that the behavior of cloud-point curves for aqueous PNIPA solutions is considerably affected by the kind of chain-end group of the PNIPA sample used and also by the degree of branching of the sample.[1–5] It is also known that the phase behavior of aqueous PNIPA solutions is influenced by an addition of surfactants.[6–8] Because many biomolecules are showing surfactant behaviors, it is important to understand how surfactants affect the phase behavior of the aqueous PNIPA solutions, in order to fully utilize PNIPA as the drug delivery materials.

Schild and Tirrell[6] have studied phase behavior of aqueous mixtures of PNIPA and a series of sodium n-alkyl sulfates and shown that the cloud point in aqueous PNIPA solutions with an addition of sodium n-dodecyl sulfate (SDS) becomes higher than that in the aqueous PNIPA solution without SDS. They studied the phenomenon rather in detail using calorimetric and fluorescence probe methods, and suggested that the surfactant molecules bind to PNIPA chains in water in the form of adsorbed micelles and that electrostatic repulsion between the micelles results in the elevation of the cloud point.[6]

The surfactants used by Schild and Tirrell[6] were limited to the anionic ones. In addition, they used one PNIPA sample having a high molecular weight ($> 4 \times 10^5$), so that the effects of the chain-end group on the cloud points could not be detected. To inquire more deeply into the effects of surfactants on the cloud point, it is desirable to pursue an investigation using low-molecular-weight samples with cationic surfactant. Thus, in this study, we make a research into the cloud point in aqueous solutions of low-molecular-weight PNIPA samples with an addition of anionic SDS and cationic n-dodecyltrimethylammonium chloride (DTAC), to clarify whether or not the effect of the cationic surfactant on the cloud point in aqueous PNIPA solutions is the same as that of the anionic one. Further, we use two low-molecular-weight PNIPA samples with hydrophobic or hydrophilic chain-end group, in order to examine

the effect of chain-end group on the behavior of the cloud point.

EXPERIMENTAL PROCEDURE

Materials

The PNIPA sample M6 is the same as that used in the previous study[1] of the cloud points in aqueous solutions, that is, the fraction separated by fractional precipitation from a original sample synthesized by radical polymerization in methanol using azobis(isobutyronitrile) (AIBN) as an initiator. We note that almost all of the initiating and terminating chain ends of the sample M6 are considered to be the isobutyronitrile groups derived from AIBN.

A new PNIPA sample named R3 was prepared by aqueous redox polymerization using a redox catalyst consisting of ammonium persulfate $(NH_4)_2S_2O_8$ (Nacalai Tesque, Inc., Kyoto, Japan) as an oxidative part and sodium metabisulfite $Na_2S_2O_5$ (Nacalai Tesque, Inc.) as a reductive part, following the procedure reported by Wooten $et\ al.$[9] The detailed procedure for the polymerization and purification of the sample is the same as that described in the previous paper[5] except that the present sample was not fractionated. We note that almost all of the initiating chain ends of the sample R3 so obtained are considered to be the sulfonate group.[5] As for the terminating chain-end group of the sample R3, we don't have any detailed information. However, at least, it may be considered that the terminating chain-end group of the sample is not positively charged. For the sample R3, the ratio of the weight-average molecular weight M_w to the number-average molecular weight M_n was determined from analytical gel permeation chromatography (GPC) with two serially connected columns SB-805HQ and SB-804HQ (Showa Denko KK, Tokyo, Japan) connected to a solvent delivery pump L-7100 (Hitachi, Ltd, Tokyo, Japan) and a refractive index detector RI-930 (JASCO Corporation, Tokyo, Japan); N,N-dimethylformamide (DMF) containing 10 mM lithium bromide at 50 °C was used as an eluent and twelve standard polystyrene samples (Tosoh Corporation, Tokyo, Japan, $M_w = 550 - 5.46 \times 10^6$) as reference standards. The values of M_w determined from light-scattering (LS) measurements and M_w/M_n for the sample R3 are given in Table 1, along with those for the sample M6 determined previously.[1] The chemical structures of SDS and

DTAC, and those of the PNIPA samples M6 and R3 are shown in Figure 1. We note that both of the samples M6 and R3 are atactic.[1,5] We also note that both of the samples are considered to have small numbers of branch points.[1,5]

Table 1

Figure 1

The surfactants SDS (Wako Pure Chemical Industries, Ltd) and DTAC (Tokyo Chemical Industry Co., Ltd, Tokyo, Japan) added into aqueous PNIPA solutions in the measurements of the cloud point were of reagent grade.

Light Scattering

The LS measurement was carried out to determine M_w for the sample R3 in methanol at 25.0 °C. The apparatus system, experimental procedure, and method of data analysis are the same as those described in the previous papers.[1–5] For the refractive index increment $\partial n/\partial c$ for R3 in methanol at 25.0 °C at the wavelength of 436 nm, we used 0.186 cm^3/g.[5] As for the refractive index n_0 of methanol at 25.0 °C at the wavelength of 436 nm, we used the literature value 1.3337.[10]

Transmittance of Light

For both of the samples M6 and R3, the intensity of light passing through their aqueous solutions with an addition of SDS or DTAC was monitored. The PNIPA concentration c_p in all the measurements was chosen to be 10 mg/mL, and the surfactant concentration c_s was varied between 0 and 6.9 mM (=2.0 mg/mL) for SDS or between 0 and 38 mM (=10 mg/mL) for DTAC. All the measurements were carried out using the self-made apparatus with incident light of wavelength 650 nm from a laser diode module, constructed previously.[1,3–5]

In order to determine the cloud point in each solution, the temperature of the test solution was controlled to increase at the rate of *ca.* 1.5 °C/h. During continuous increase in temperature from 30 °C to 40 °C, the intensity of light passing through the test solution was

monitored by a photodiode. The output of the photodiode along with the solution temperature measured simultaneously was recorded on a personal computer. Then, the (relative) transmittance as defined as the ratio of the intensity of light through the test solution at a temperature to the intensity at a lower temperature at which the test solution is transparent was determined as a function of temperature.

RESULTS AND DISCUSSION

Figures 2a and 2b show plots of the (relative) transmittance against temperature for the aqueous solutions of the sample M6 with an addition of the surfactants SDS and DTAC, respectively, all at $c_p = 10$ mg/mL. We note that the shape of the transmittance curve for each solution is almost independent of the rate of increase in temperature if it is slower than 1.5 °C/h. In the figures, the heavy curves represent the values for the solution without surfactant, and the light curves represent those for the solutions with the surfactants at the indicated values of c_s. For the solutions of the sample M6 with SDS shown in Figure 2a, the transmittance curve shifts toward the high-temperature side as c_s is increased for $c_s \gtrsim 0.87$ mM. As for the solutions of the sample M6 with DTAC shown in Figure 2b, the transmittance curve is almost independent of c_s for $c_s \lesssim 27$ mM but shifts toward the high-temperature side with increasing c_s for $c_s \gtrsim 27$ mM. For all the solutions of M6, the transmittance decreases from 100 % to 0 % with increasing temperature and no macroscopic precipitate can be observed.

$$\boxed{\textbf{Figure 2}}$$

Figures 3a and 3b show plots of the (relative) transmittance against temperature for the aqueous solutions of the sample R3 with an addition of the surfactants SDS and DTAC, respectively, all at $c_p = 10$ mg/mL. As in Figures 2, the heavy curves represent the values for the solution without surfactant, and the light curves represent those for the solutions with the surfactants at the indicated values of c_s. For the solutions of the sample R3 with SDS shown in Figure 3a, the transmittance curve shifts toward the high-temperature side with increasing c_s as in the case of the sample M6 (Figure 2a), but the decrease in the transmittance for the solutions with SDS is much slower than that for the solution without SDS. In the previous

study,[4] we showed that the decrease in the transmittance in aqueous PNIPA solution arises from formation of aggregates of PNIPA in the solution. Therefore, the above result implies that the aggregation of PNIPA may be suppressed by an addition of SDS for the sample R3. On the other hand, for the solutions of the sample R3 with DTAC, it is seen from Figure 3b that the transmittance curve first shifts toward the low-temperature side with increasing c_{s} for $c_{\mathrm{s}} \lesssim 11$ mM and then shifts toward the high-temperature side for $c_{\mathrm{s}} \gtrsim 11$ mM. It is interesting to see that the transmittance for the aqueous solutions of R3 with DTAC for $c_{\mathrm{s}} \lesssim 11$ mM first decreases from 100 % with incresing temperature, then passes through a minimum, and finally becomes a finite value for higher temperature. It should be noted that macroscopic precipitates appear in the solutions of R3 with DTAC for $c_{\mathrm{s}} \lesssim 11$ mM above the temperature at which the transmittance takes the minimum value, although no macroscopic precipitate can be observed in the other solutions of the sample R3 as in the case of the sample M6.

<div style="text-align:center">

Figure 3

</div>

The cloud point in each solution was then determined as the temperature at which the transmittance becomes 90 %, as in the previous studies.[1,3,5] The cloud points so determined are plotted against c_{s} in Figure 4. In the figure, the symbols ○ and ● represent the values for the sample M6 with SDS and DTAC, respectively, and the symbols △ and ▲ represent those for the sample R3 with SDS and DTAC, respectively. The solid curves smoothly connect the respective data points. The cloud point in the aqueous solution of R3 without surfactant is higher than that of M6 because the hydrophilicity of the chain-end group is stronger for the former than for the latter, as pointed out in the previous study.[5] For comparison, the literature data for the aqueous PNIPA solutions with an addition of SDS reported by Schild and Tirrell[6] are also shown in the figure by the dotted curve. We note that the PNIPA sample used by Schild and Tirrell was prepared by radical polymerization in benzene with AIBN as an initiator and its molecular weight ($M_{\mathrm{w}} = 4.4 \times 10^5$, $M_{\mathrm{n}} = 1.6 \times 10^5$) is appreciably larger than our samples. We also note that they determined the cloud point by monitoring scattered light intensity from 0.40 mg/mL solutions of PNIPA at the scattering angle of 90°.

$$\boxed{\textbf{Figure 4}}$$

As expected from the results shown in Figures 2a and 3a, the cloud point in the solutions with an addition of SDS ($\bigcirc$ and $\triangle$) increases monotonically with increasing c_s as in the case of the literature data by Schild and Tirrell. As suggested by Schild and Tirrell,[6] the monotonic elevation of the cloud point in the solutions with SDS with increasing c_s results from electrostatic repulsion between negatively-charged PNIPA-SDS micelles formed by binding of the SDS molecules to the PNIPA chain in water, which suppresses the aggregation of the PNIPA chains. On the other hand, the cloud point in the solutions of M6 with DTAC ($\bullet$) is almost independent of c_s for $c_s \lesssim 27$ mM and then increases with increasing c_s for $c_s \gtrsim 27$ mM. It indicates that electrostatic repulsion between positively-charged PNIPA-DTAC micelles, which are formed by the binding of the DTAC molecules to the PNIPA chain, is not so strong as that between the above-mentioned PNIPA-SDS micelles.

As for the solutions of R3 with DTAC ($\blacktriangle$), the cloud point first decreases, then passes through a minimum value at $c_s \simeq 11$ mM, and finally increases for $c_s \gtrsim 11$ mM, with increasing c_s. The increase in the cloud point in the range of large c_s is due to the same reason as in the case of the solutions of M6 with DTAC, while the decrease in the cloud point for small c_s is characteristic of this case. Considering the fact that the sample R3 has the anionic sulfonate group at its chain end, the cationic DTAC molecules are expected to be adsorbed selectively onto the negatively-charged chain end if c_s is small. Then the hydrophobic alkyl chains of DTAC around the chain end diminish its hydrophilicity, and therefore the cloud point may be lowered. As c_s is further increased, the cloud point in the aqueous solutions turns to increase because of the electrostatic repulsion between the PNIPA-DTAC micelles, as mentioned above.

CONCLUDING REMARKS

For the two PNIPA samples, M6 having the hydrophobic chain-end group and R3 having the (negatively-charged) hydrophilic chain-end group, the cloud points were determined in their aqueous solutions with an addition of the surfactants, anionic SDS or cationic DTAC. The cloud point in the solutions of both of the samples with SDS increased monotonically and

rather steeply with increasing c_s, as in the case of the literature data reported by Schild and Tirrell.[6] On the other hand, the cloud point in the solutions of the sample M6 with DTAC was found to be almost independent of c_s for $c_s \lesssim 27$ mM and then increase with increasing c_s for $c_s \gtrsim 27$ mM. As for the solutions of the sample R3 with DTAC, it was found that the cloud point first decreases with increasing c_s, then passes through a minimum at $c_s \simeq 11$ mM, and finally increases for $c_s \gtrsim 11$ mM. The increase in the cloud point in all the solutions arises from the electrostatic repulsion between the charged PNIPA-surfactants micelles formed by binding of the surfactant molecules to the PNIPA chains. The decrease in the cloud point observed for the solutions of the sample R3 with DTAC for small c_s is considered to arise from the fact that the cationic DTAC molecule bound to the negatively-charged PNIPA chain end diminishes the hydrophilicity of the chain end.

Finally, we make a short remark on the structure of the PNIPA-surfactants micelles. The structural information on micelles formed from polymers and surfactants may be obtained by LS measurements.[11] An investigation of the PNIPA-surfactants micelles using LS techniques is one of the problems in the future.

REFERENCES

1. Kawaguchi, T., Kojima, Y., Osa, M. & Yoshizaki, T. Cloud points in aqueous poly(N-isopropylacrylamide) solutions. *Polym. J.* **40**, 455–459 (2008).

2. Kawaguchi, T., Kojima, Y., Osa, M. & Yoshizaki, T. Primary structure of poly(N-isopropylacrylamide) synthesized by radical polymerization. Effects of polymerization solvents. *Polym. J.* **40**, 528–533 (2008).

3. Kobayashi, K., Yamada, S., Nagaoka, K., Kawaguchi, T., Osa, M. & Yoshizaki, T. Characterization of linear poly(N-isopropylacrylamide) and cloud points in its aqueous solutions. *Polym. J.* **41**, 416–424 (2009).

4. Kawaguchi, T., Kobayashi, K., Osa, M. & Yoshizaki, T. Is a "cloud-point curve" in aqueous poly(N-isopropylacrylamide) solution binodal? *J. Phys. Chem. B* **113**, 5440–5447 (2009).

5. Ise, T., Nagaoka, K., Osa, M. & Yoshizaki, T. Cloud points in aqueous solutions of poly(N-isopropylacrylamide) synthesized by aqueous redox polymerization. *Polym. J.* **43**, 164–170 (2011).

6. Schild, H. G. & Tirrell, D. A. Interaction of poly(N-isopropylacrylamide) with sodium n-alkyl sulfates in aqueous solution. *Langmuir* **7**, 665–671 (1991).

7. Meewes, M., Ri*č*ka, J., de Silva, M., Nyffenegger, R. & Binkert, Th. Coil-globule transition of poly(N-isopropylacrylamide). A study of surfactant effects by light scattering. *Macromolecules* **24**, 5811–5816 (1991).

8. Walter, R., Ri*č*ka, J., Quellet, Ch., Nyffenegger, R. & Binkert, Th. Coil-globule transition of poly(N-isopropylacrylamide). A study of polymer-surfactant association. *Macromolecules* **29**, 4019–4028 (1996).

9. Wooten, W. C., Blanton, R. B. & Coover, H. W. Effect of pH on homopolymerization of N-isopropylacrylamide. *J. Polym. Sci.* **25**, 403–412 (1957).

10. Johnson, B. L. & Smith, J. in *Light Scattering from Polymer Solutions* (ed. Huglin, M. B.) Ch. 2 (Academic Press, London, 1972).

11. Uramoto, K., Shimomachi, T., Hashidzume, A. & Sato, T. Interaction of polymer and low molecular weight surfactant in water. *Polymer Preprints., Japan* **61**, 923 (2012).

Table 1.   Values of M_w and $M_\mathrm{w}/M_\mathrm{n}$ for Poly(N-isopropylacrylamide)

sample	M_w	$M_\mathrm{w}/M_\mathrm{n}$[a]
M6	6.45×10^4	1.19
R3	3.26×10^4	1.51

[a]The values of $M_\mathrm{w}/M_\mathrm{n}$ were determined by analytical GPC using standard PS samples as reference standards.

Figure Captions

Figure 1. Chemical structures of SDS and DTAC, and the PNIPA samples M6 and R3.

Figure 2. Temperature dependence of the (relative) transmittance of light passing through aqueous solutions of the PNIPA sample M6 (c_p = 10 mg/mL) with an addition of the surfactants SDS (a) or DTAC (b). The heavy curves represent the values for the solution without surfactant, and the light curves represent those for the solutions with SDS at c_s = 0.35, 0.87, 1.7, 3.5, and 6.9 mM or DTAC at c_s = 3.8, 27, 30, 34, and 38 mM.

Figure 3. Temperature dependence of the (relative) transmittance of light passing through aqueous solutions of the PNIPA sample R3 (c_p = 10 mg/mL) with an addition of the surfactants SDS (a) or DTAC (b). The heavy curves represent the values for the solution without surfactant, and the light curves represent those for the solutions with SDS at c_s = 0.35, 0.87, 1.7, 3.5, and 6.9 mM or DTAC at c_s = 0.95, 1.9, 3.8, 11, 30, 34, 38 mM.

Figure 4. Plots of the cloud point in aqueous PNIPA solutions against the concentration c_s of the added surfactants: ($\bigcirc$), the sample M6 with SDS; ($\bullet$), the sample M6 with DTAC; ($\triangle$), the sample R3 with SDS; ($\blacktriangle$), the sample R3 with DTAC. In all solutions, the concentration c_p of the PNIPA samples is 10 mg/mL. The solid curves connect smoothly the respective data points. The dotted curve represents the literature data for aqueous PNIPA solutions with SDS reported by Schild and Tirrell.[6]
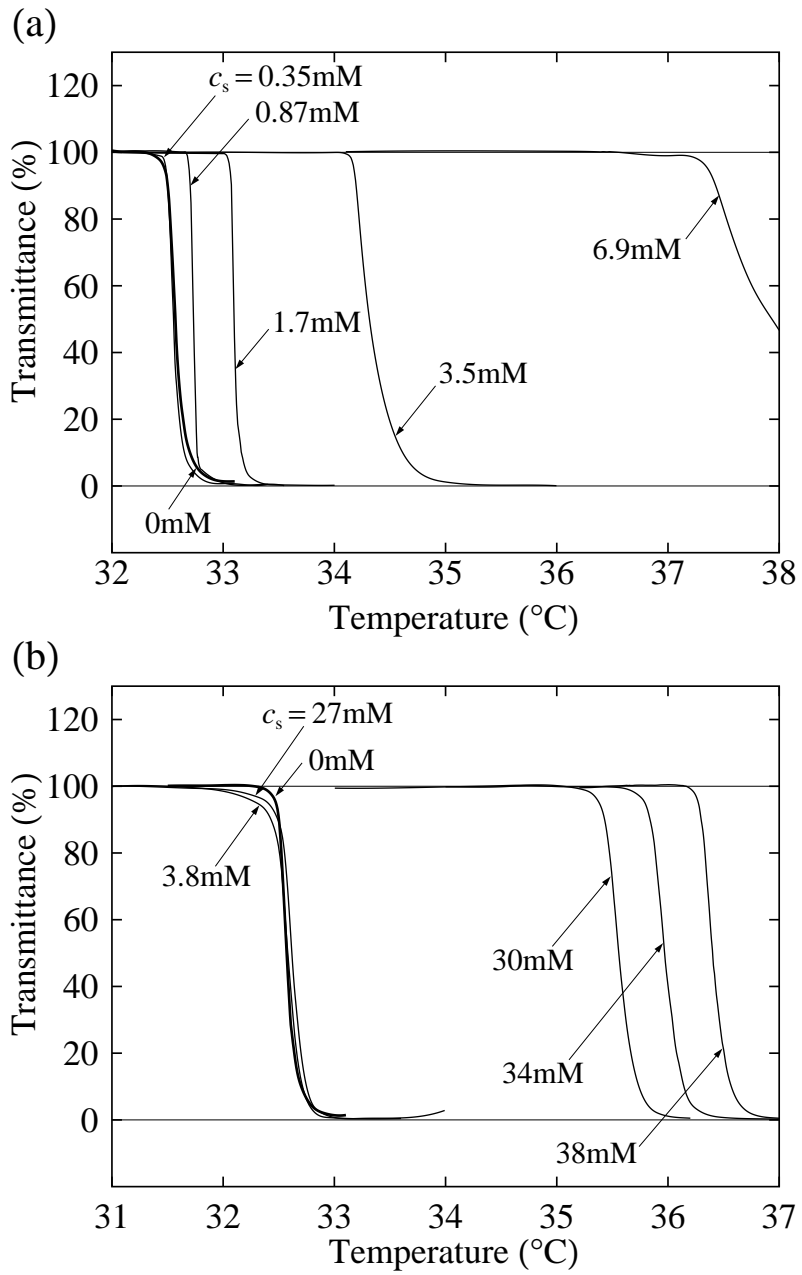
Table Caption

Table 1. Values of M_w and $M_\mathrm{w}/M_\mathrm{n}$ for Poly(N-isopropylacrylamide)

SDS

DTAC
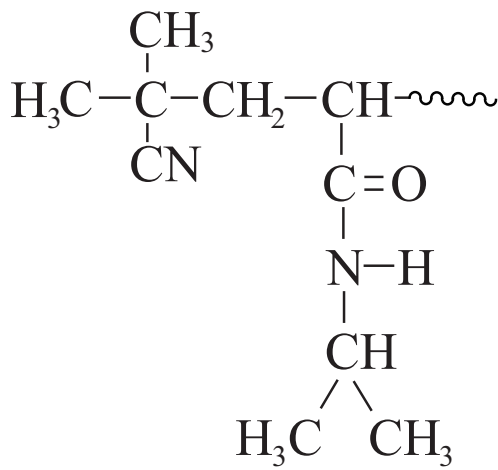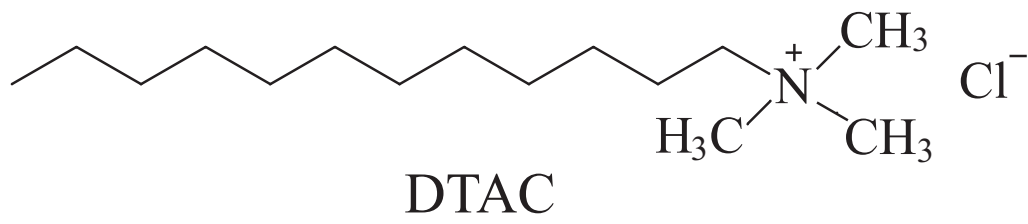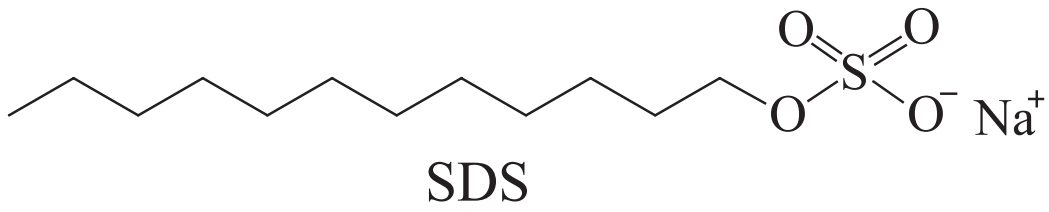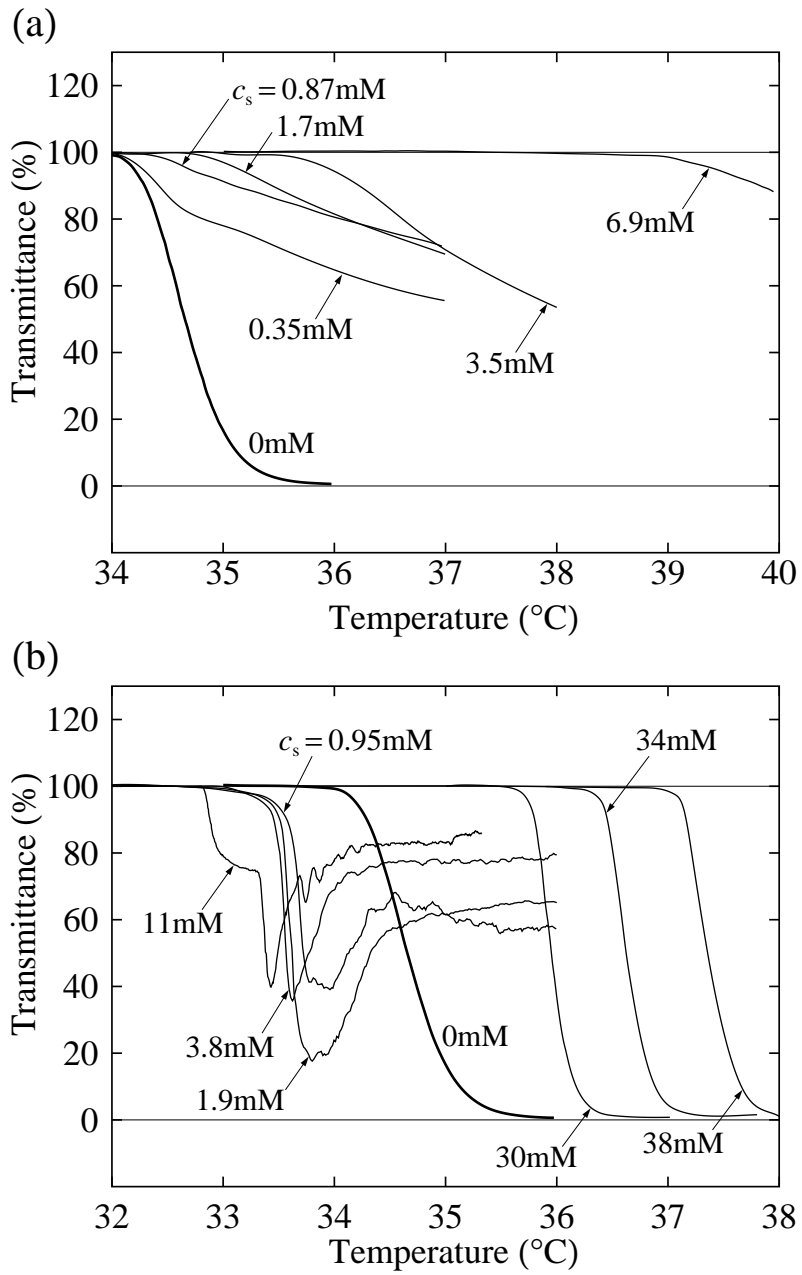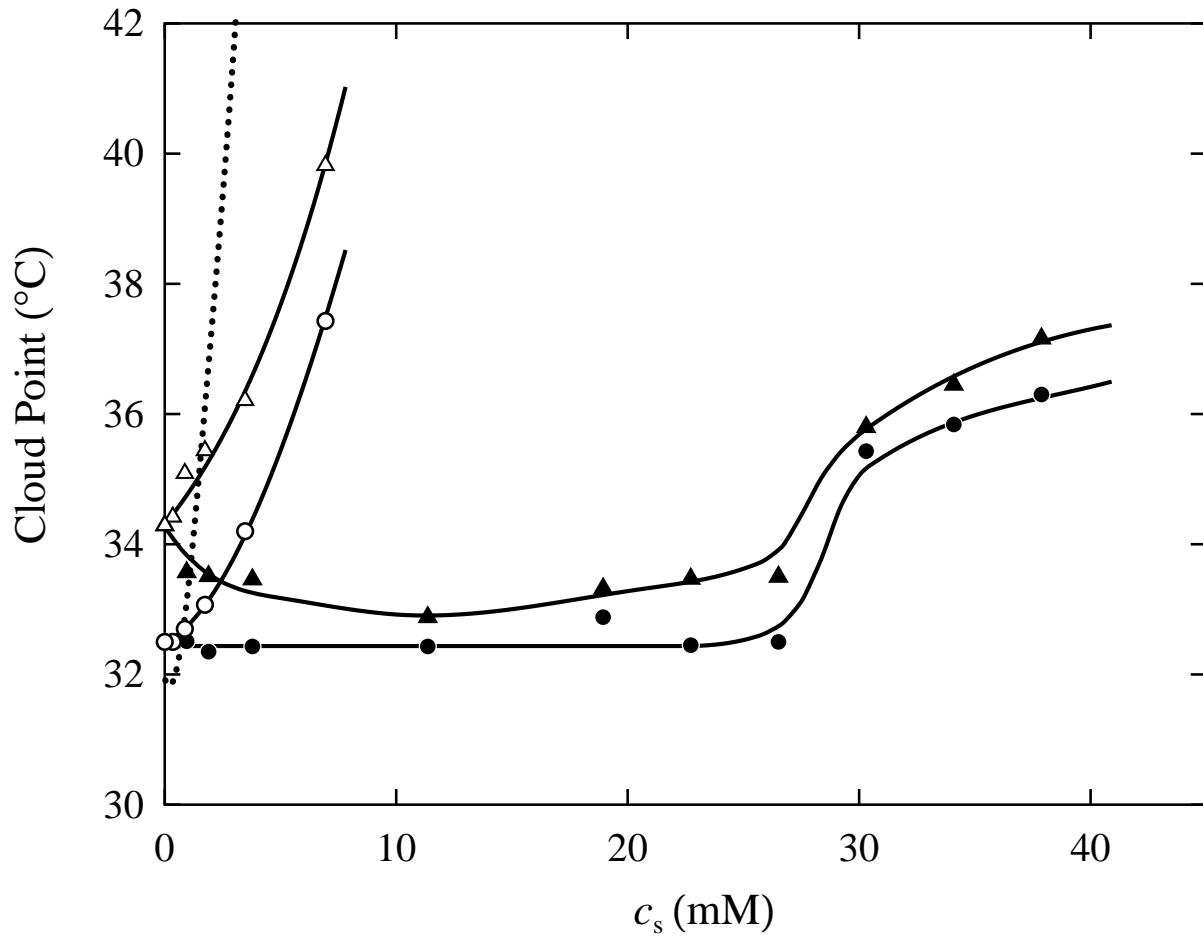
sample M6

sample R3

(a)

(b)

(a)

(b)
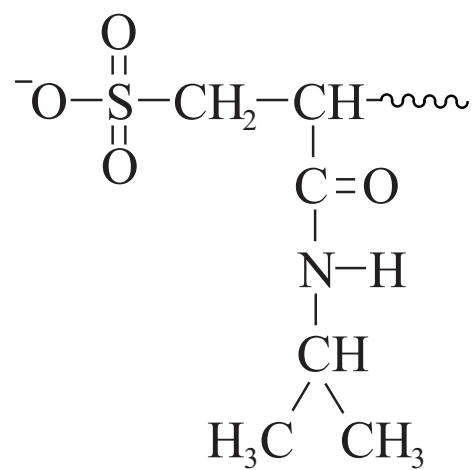
M. Osa *et al.*, Figure 3

M. Osa *et al.*, Figure 4

Graphical Abstract:

The cloud point was determined for aqueous solutions of two poly(N-isopropylacrylamide) samples, one having a hydrophobic nonionic chain-end group (M sample) and the other having a hydrophilic anionic chain-end group (R sample), with an addition of two kinds of surfactants, anionic sodium n-dodecyl sulfate (SDS) or cationic n-dodecyltrimethylammonium chloride (DTAC). It is found that behavior of the cloud point as a function of the concentration c_s of the surfactants largely depends on the kinds of chain-end group and surfactant.