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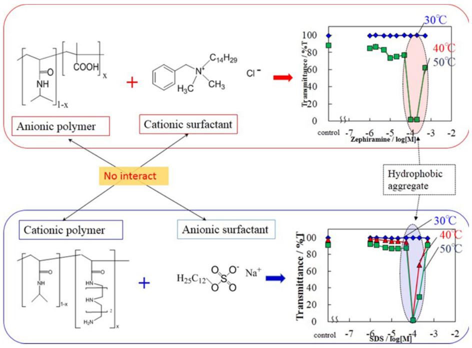
Specific formation of hydrophobic aggregates of ionic thermoresponsive polymers with oppositely charged ionic surfactants under extremely dilute conditions

Nobuo Uehara

Graduate School of Engineering, Utsunomiya University, 7-1-2 Yoto, Utsunomiya, Tochigi, 321-8585, Japan

GRAPHICAL ABSTRACT



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ABSTRACT

Cationic and anionic thermoresponsive polymers were synthesized and the formation of their hydrophobic aggregates with ionic surfactants was studied at extremely low polymer concentrations. Alongside the hydrophobic interactions, electrostatic interactions between the ionic groups of the polymers and surfactants played a major role in the formation of the hydrophobic aggregates. In the absence of an ionic surfactant, extremely dilute (i.e., 0.01 wt %) polymer solutions did not become turbid, even when they were heated above the phase-transition temperature. However, above the phase-transition temperature, the polymer solutions became turbid upon the addition of a specific concentration of an ionic surfactant with the opposite charge. In contrast, no increase in the turbidity was observed when an ionic surfactant with the same charge was added to the solution, regardless of the concentration of the ionic surfactant. Even below the phase-transition temperature, the application of a fluorescent probe that responded to the hydrophobicity of its environment revealed that the ionic thermoresponsive polymers formed a hydrophobic environment with oppositely charged surfactants owing to the electrostatic and hydrophobic interactions, even though hydrophobic precipitates were not observed. Thus, the electrostatic interactions between polymers and surfactants played crucial roles in the formation of hydrophobic aggregates under extremely low concentration of the polymers as well as the hydrophobic interactions did.

E-mail address: ueharan@cc.utsunomiya-u.ac.jp.

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1. Introduction

Thermoresponsive polymers are stimuli-responsive materials that undergo a reversible phase transition depending on the solution temperature. Poly(*N*-isopropylacrylamide) (p(NIPPAM)) is a typical thermoresponsive polymer with a phase-transition temperature of approximately 32 °C. As this phase-transition temperature is close to human body temperature, p(NIPPAM) and its analogues have been studied as potential materials for medical engineering applications [1–4]. In particular, cross-linked gels composed of thermoresponsive polymers have been investigated as potential materials for drug delivery systems because their size can be externally controlled using thermal stimuli owing to their phase-transition properties [5–7].

The phase transition of p(NIPPAM) is strongly influenced by the solution conditions such as the ionic strength and the concentrations of organic solvents and surfactants [8–20]. In particular, the interactions between surfactants and thermoresponsive polymers have attracted a great deal of engineering and scientific interest over the past decades owing to their potential for fabricating functional nanostructures. In the case of cross-linked gels, the phase-transition behavior was reported to be controlled by the surfactant concentration [9,11,21–26]. In the case of thermoresponsive linear polymers, the interaction of p(NIPPAM) with sodium dodecyl sulfate (SDS), a typical anionic surfactant, has been investigated extensively [27–38]. These studies revealed that p (NIPPAM) associates with SDS below the phase-transition temperature at SDS concentrations above 0.23 [37] or 0.37 mg/L [31], which is referred to as the critical association concentration (CAC) and is much lower than the critical micelle concentration (CMC) of SDS. The hydrophobic groups of *N*-isopropylacrylamide and SDS play an essential role in the association between the two components [43] It has been reported that aggregates of *N*-isopropylacrylamide and SDS can possess different structures depending on the concentrations of the two species [28,30,34–39]. For example, one typical aggregate is a necklace-type structure in which the SDS molecules are bound to hydrophobic domains in the polymer chain [30,36].

We previously reported that aggregation occurred upon mixing a low concentration (0.01 wt %) of p(NIPPAM) with 1×10^{-5} mol/L of SDS, which is much lower than the reported CAC [40]. Any research attention had not been paid such an extremely low concentration of SDS. We found that the resulting aggregates of p(NIPPAM) and SDS caused the solution to become turbid above the phase-transition temperature around this SDS concentration. The aggregates were only observed in this concentration region, and when the SDS concentration exceeded 1×10^{-5} mol/L, the aggregates became negatively charged and therefore water soluble owing to the association of excess SDS, resulting in the recovery of the transmittance of the solution. The use of a fluorescent probe that is sensitive to the hydrophobicity of its environment confirmed the existence of a hydrophobic environment in the solution even below the phase-transition temperature. The fluorescent probe also revealed that the formation of the hydrophobic environment as a result of hydrophobic interactions between p(NIPAAM) and SDS. However, the role of electrostatic interactions in aggregate formation at extremely low concentrations of thermoresponsive polymers remains unclear. The investigation of the interactions between surfactants and thermally responsive polymers containing ionic groups is expected to provide important insights for elucidating the interactions between SDS and water-soluble polymers such as proteins and oligonucleotides, because thermoresponsive polymers that change conformation upon exposure to external stimuli can be regarded as models for proteins.

In this study, we investigated the influence of electrostatic interactions between ionic surfactants and thermoresponsive polymers containing ionic functional groups on the formation of hydrophobic aggregates. For this purpose, thermoresponsive polymers containing cationic or anionic groups were synthesized from *N*-isopropylacrylamide and monomers containing amino or carboxyl groups, respectively. We synthesized the thermoresponsive polymers having amino groups [41,42] and carboxyl groups [43] for other research. We examined the formation of hydrophobic aggregates above and below the phase-transition temperature by measuring the solution transmittance and the fluorescence of a probe. Upon combining the ionic thermoresponsive polymers and ionic surfactants with opposite charges above the phase-transition temperature, an abrupt decrease in the transmittance occurred in a narrow range of surfactant concentrations. Furthermore, the hydrophobic aggregates of the polymers and surfactants appeared to bind the fluorescent probe even below the phase-transition temperature at the SDS concentration where the abrupt decrease in the transmittance occurred. These results would provide a deep understanding of the interaction between surfactants and biopolymers such as polypeptides and polynucleotides, which are intelligent stimuli-responsive polymers.

2. Experimental

2.1. Apparatus

The transmittance of the solutions was measured using a V-650 spectrophotometer (JASCO, Japan) with a 1 cm crystal cuvette. The fluorescence spectra of the solutions were recorded using an FP-6100 spectrofluorometer (JASCO) with a four-sided transparent crystal cuvette. The pH of the solutions was measured using an F-53 pH meter (Horiba, Japan). Pure water with a resistivity greater than 18 MΩ·cm^{-1} was prepared using an ELGA PURELAB system (ELGA LabWater, UK).

2.2. Reagents

N-Isopropylacrylamide, 2,2′-azobisisobutyronitrile (AIBN), acryloyl chloride, methacrylic acid, *N*-phenyl-1-naphthylamine (PN), triethylenetetramine, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED), 3-mercaptopropionic acid, potassium persulfate, and the sodium salts of alkyl sulfates were obtained from Wako Pure Chemicals (Tokyo, Japan) and used as received. Tetradecyldimethylbenzylammonium chloride (zephiramine) was purchased from Dojin Chemicals (Kumamoto, Japan). Other reagents and organic solvents were of analytical reagent grade. *N*-Isopropylacrylamide was recrystallized twice from hexane prior to polymerization. Methacrylic acid was purified by twice recrystallization through freeze and thaw. The chemical structures of SDS, zephiramine, and PN are depicted in Fig. 1(a), (b), and (c), respectively.

Stock solutions of the alkyl sulfate sodium salts and zephiramine were prepared by dissolving the purchased reagents in water to a concentration of 1.0×10^{-2} mol/L. These surfactant solutions were further diluted to the appropriate concentrations prior to use. A 1.0×10^{-3} mol/L stock solution of PN was prepared by dissolving the appropriate amount of PN in methanol. Subsequently, 1.0×10^{-5} mol/L solutions of PN were prepared by diluting the stock solution with 0.10 wt % solutions of the thermoresponsive polymers.

2.3. Synthesis of ionic thermoresponsive copolymers

Cationic thermoresponsive polymers, poly(*N*-isopropylacrylamide-*co*-*N*-acryloyl- triethylenetetramine) (p(NIP-TETA)), was prepared according to a previously reported method by changing feed rations of mononers [40,41]. Typically, a procedure of p(NIP$_{0.983}$-TETA$_{0.017}$) is described as follows. Prior to the radical copolymerization, a cationic precursor, *N*-acryloyl triethylenetetramine, was synthesized from acryloyl chloride and triethylenetetramine. Typically, 25 mL of a 1,4-dioxane solution containing 0.010 mol (0.91 g) of acryloyl chloride was added to 100 mL of a cooled 1,4-dioxane solution containing 0.10 mol (14.6 g) of triethylenetetramine. The resulting white precipitate was removed by filtration and then suspended in 100 mL of methanol containing 0.010 mol (0.59 g) of potassium hydroxide. After filtration of