PII: S0032-3861(96)00845-2

Effect of polymer complex formation on the cloud-point of poly(N-isopropyl acrylamide) (PNIPAAm) in the poly(NIPAAm-co-acrylic acid): polyelectrolyte complex between poly(acrylic acid) and poly(allylamine)

Mi Kyong Yoo and Yong Kiel Sung
Department of Chemistry, Dongguk University, Seoul 100-715, Korea

and Chong Su Cho*
Department of Polymer Engineering, Chonnam National University, Kwangju 500-757, Korea

and Young Moo Lee
Department of Industrial Chemistry, Hanyang University, Seoul 133-791, Korea

A series of pH/temperature-sensitive polymers which contain both temperature and pH-sensitive components were synthesized by copolymerizing N-isopropyl acrylamide (NIPAAm) and acrylic acid (AAc). The influence of poly(allylamine) (PAA) as the polyelectrolyte on the lower critical solution temperature (LCST) of pH/temperature-sensitive polymers was investigated in the pH range of 2–12. The LCSTs of PNIPAAm/water in P(NIPAAm-co-AAc) were determined by cloud-point measurements. The LCSTs of PNIPAAm/water in the copolymers were strongly affected by the pH, the presence of polyelectrolyte solute and AAc content in the P(NIPAAm-co-AAc). The polyelectrolyte complex between P(NIPAAm-co-AAc) and PAA was formed from the pK_a of PAAc to the pK_b of PAA. Also, the LCSTs of the PNIPAAm in the copolymers were dependent on the charge density of the PAAc and concentration of the PAA. © 1997 Elsevier Science Ltd.

INTRODUCTION

So called, intelligent polymers undergo reversible phase transition in response to external stimuli such as temperature[1-5], pH[6,7], electric current[8,9], ions[10], or chemical species[11]. Most of the intelligent polymers studied previously are responsive to only one kind of stimulus, but polymers which are responsive to more than one variable, in particular, temperature and pH, have recently been investigated[12,13]. The pH/temperature-sensitive polymers are hydrophilic ones which contain both pH- and temperature-sensitive components. The pH-sensitive polymers containing ionizable groups can lead to pH-dependent phase transition. The thermo-sensitive polymers exhibit a lower critical solution temperature (LCST) in water[3]. Interestingly, it was found that there was mutual influence between pH stimulus and temperature on the swelling, besides the individual influence of the pH and temperature on the swelling[14].

Poly(N-isopropyl acrylamide) (PNIPAAm) is the most popular polymer among the temperature sensitive polymers since it exhibits a sharp phase transition

close to 32°C[15,16]. The important and useful feature of PNIPAAm/water is the ability to tailor their LCST by incorporating comonomers[4,17] with hydrophilic or hydrophobic groups in the polymer or adding cosolvents[18-20], simple salts[21,22] or surfactants[23-25] to the polymer/water solution. Besides the effect of salts and surfactants, the effects of other solutes on the LCST of thermosensitive polymers has been little investigated[26]. The representative solute that affects the LCST of thermosensitive polymers is a polyelectrolyte[26]. A polyelectrolyte which contains ionizable groups is sensitive to environmental pH[27]. Poly(acrylic acid) (PAAc) is one of the pH-sensitive polymers which contains ionizable groups as the anionic polyelectrolyte. The pH of environment determines the degree of ionization of carboxylic acid groups of the PAAc. When a cationic polyelectrolyte which ionizes below the pK_b is mixed in an anionic polyelectrolyte solution, a polyelectrolyte complex is formed by electrostatic attraction between the two polyelectrolytes[28,29]. Therefore, it may be expected that the LCST of PNIPAAm incorporated with a pH-sensitive component will be affected by a polyelectrolyte complex according to the various pH values.

---

* To whom correspondence should be addressed

Table 1 Feed composition of poly(NIPAAm-*co*-AAc)

Code[a]	NIPAAm	AAc	AIBN[b] (g)	Dioxane[c] (ml)
NIPAAm	8.39×10^{-3} mol (1.00 g)	0.00	4.30×10^{-3}	2.90
NIP-*co*-AAc-10	7.95×10^{-3} mol (0.90 g)	8.84×10^{-4} mol (0.06 ml)	4.40×10^{-3}	2.80
NIP-*co*-AAc-20	7.07×10^{-3} mol (0.80 g)	1.77×10^{-3} mol (0.12 ml)	4.50×10^{-3}	2.70
NIP-*co*-AAc-30	6.19×10^{-3} mol (0.70 g)	2.65×10^{-3} mol (0.18 ml)	4.50×10^{-3}	2.58
NIP-*co*-AAc-40	5.30×10^{-3} mol (0.60 g)	3.54×10^{-3} mol (0.24 ml)	4.40×10^{-3}	2.47
NIP-*co*-AAc-50	4.42×10^{-3} mol (0.50 g)	4.42×10^{-3} mol (0.30 ml)	4.30×10^{-3}	2.37

[a] mole% of AAc against NIPAAm
[b] AIBN as an initiator: 0.3 mol% of monomers
[c] Dioxane as a solvent: 25 wt% of monomers

In this study, PAAc as the pH-sensitive component
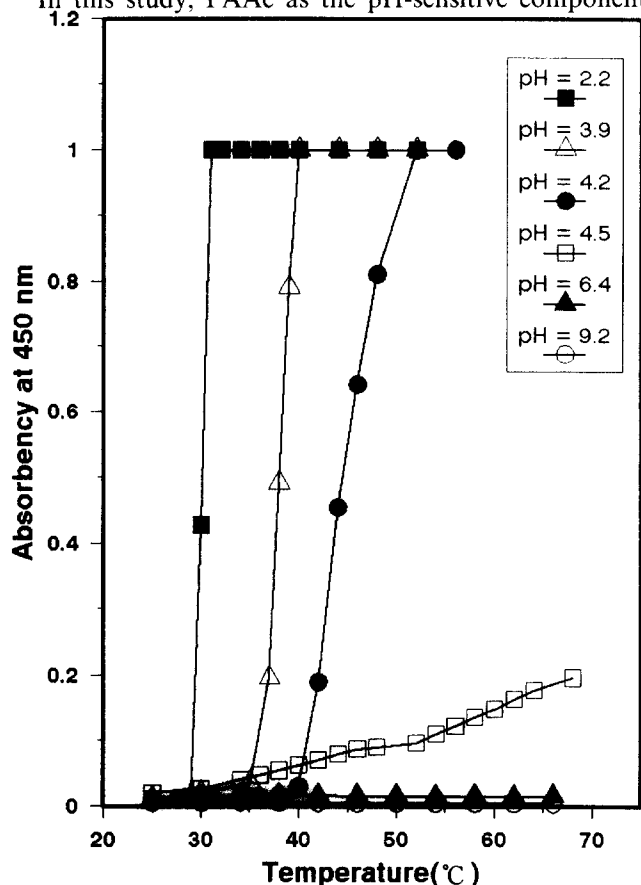
Figure 1 Absorbency at 450 nm of P(NIP-*co*-AAc-20) solution against temperature as a function of pH

was introduced in the temperature-sensitive PNIPAAm and the influence of polyelectrolyte solute on the LCST of pH/temperature-sensitive polymer according to the pH, the content of pH-sensitive component and the unit mole ratio of two polymers will be reported. Poly-(allylamine) (PAA) was used as cationic polyelectrolyte solute. The LCST of the pH/temperature-sensitive polymer will be affected by the polyelectrolyte complex formation. It is also our objective to clarify the mechanism of the mutual influence between pH and temperature stimulus on the structural and physical properties of the polyelectrolyte complex.

EXPERIMENTAL

Materials

N-isopropyl acrylamide (NIPAAm, Kasei, Tokyo) was recrystallized in *n*-hexane. Acrylic acid (AAc, Junsei Chem. Co., Tokyo) was purified by distillation at 40°C/26 mmHg. N,N'-azobisisobutyronitrile (AIBN, Kasida Co., Tokyo) was purified in methanol. 1,4-Dioxane (Duksan Co., Yongin) was purified by refluxing. Poly-(allylamine) (PAA, Aldrich, Milwaukee, WI), sodium hydroxide, and hydrochloric acid standard solution were used as received.

Synthesis of P(NIPAAm-co-AAc)

Synthesis of linear P(NIPAAm-*co*-AAc), containing 0, 10, 20, 30, 40, 50 mol% of AAc, was carried out in 1,4-dioxane (25 wt%) with AIBN as an initiator (0.3 mol% of monomers). Feed composition is listed in *Table 1*. Dried nitrogen was bubbled through the solution for 20 min prior to polymerization. After polymerization at 70°C for 5 h, the mixtures were dissolved in methanol and precipitated in diethyl ether. The precipitate was filtered and washed with acetone to remove the unreacted monomers and homopolymer.

Preparation of polyelectrolyte complex

A solution of P(NIPAAm-*co*-AAc), containing 0, 10, 20, 40, 50 mol% of AAc, was prepared by dissolving 0.2 g of copolymer in 5 ml of distilled water. A solution of PAA was prepared by dissolving 0.2 g of PAA in 5 ml of distilled water. Before mixing the two solutions, the pH of each solution was adjusted identically with HCl or NaOH standard solution. To each copolymer solution, PAA solution was added.

Cloud-point determination

The absorbency at 450 nm was measured against temperature using a u.v./VIS spectrophotometer. The temperature of the solutions was raised from 15°C to 70°C in 2°C increments every 10 min. The cloud-point was defined as the temperature at the inflection point in the normalized absorbance vs temperature curve and the cloud-point of solution which does not exhibit an inflection point was determined at 10% absorbance in the curve[30]. Turbidity of components can be caused by both demixing and gel formation. However, it is not our intention in this study to find out which governs the
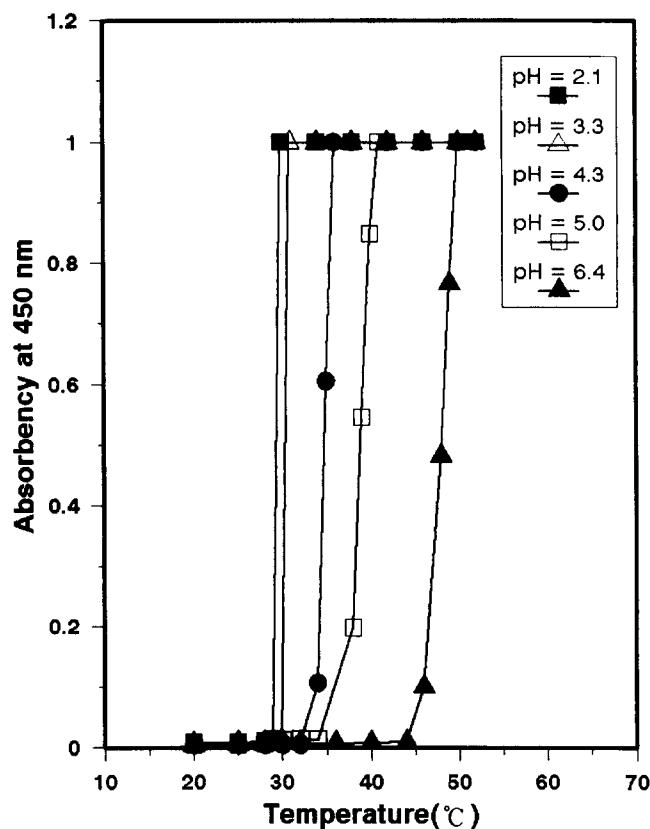
Figure 2 Absorbency at 450 nm of P(NIP-*co*-AAc-20) solution with 1.0 wt% of PAA solution against temperature as a function of pH

Figure 3 Cloud-point of 1.0 wt% of p(NIP-*co*-AAc-20) solution with 1.0 wt% PAA solution against pH

turbidity phenomena. In the P(NIPAAm) system, cloud-point is known to be little dependent on polymer concentration[31]. At the cloud-point of P(NIPAAm), simple and complex coacervations, which are general features of polymer/polymer interactions, do not occur.

RESULTS AND DISCUSSION

Absorbency at 450 nm of 1.0 wt% of P(NIPAAm-*co*-AAc-20) solution against temperature according to the various pH values is shown in *Figure 1*. The absorbency of the solution is dependent on the pH and the change of absorbency with temperature becomes smaller with an increase of pH. Particularly, a drastic change of absorbency of the solution with temperature is observed at around pH 4.2, which is related to the pK_a value of PAAc. Cloud-points of PNIPAAm in P(NIPAAm-*co*-AAc-20), defined as the transition point of absorbency against temperature, are 29.5, 36.0 and 41.0°C for the pH value of 2.2, 3.9 and 4.2, respectively. From these results, it is found that the cloud-point of PNIPAAm in the P(NIPAAm-*co*-AAc-20) solution decreases in the non-ionized state of PAAc whereas its cloud-point increases in the partially ionized state of PAAc in comparison with the cloud-point of PNIPAAm itself, 31–33°C[15,16]. It is thought that the cloud-point of PNIPAAm decreases through inter- or intramolecular hydrogen bonding between the amide group of PNIPAAm and the carboxylic acid group of PAAc. Above the pK_a value of PAAc, the cloud-point of PNIPAAm in the P(NIPAAm-*co*-AAc-20) solution is not observed below 70°C, since the carboxylic acid group in PAAc is completely ionized and results in electrostatic repulsion of ionized groups of PAAc.
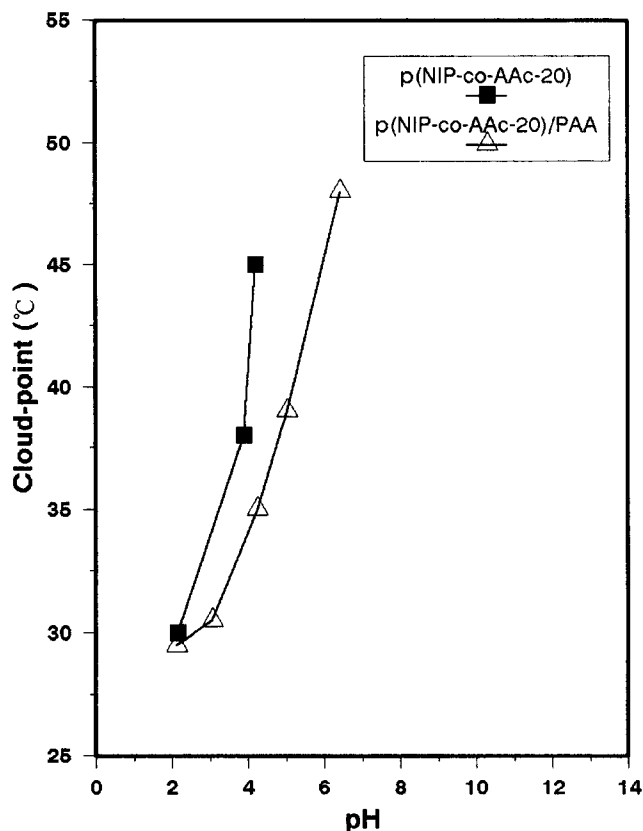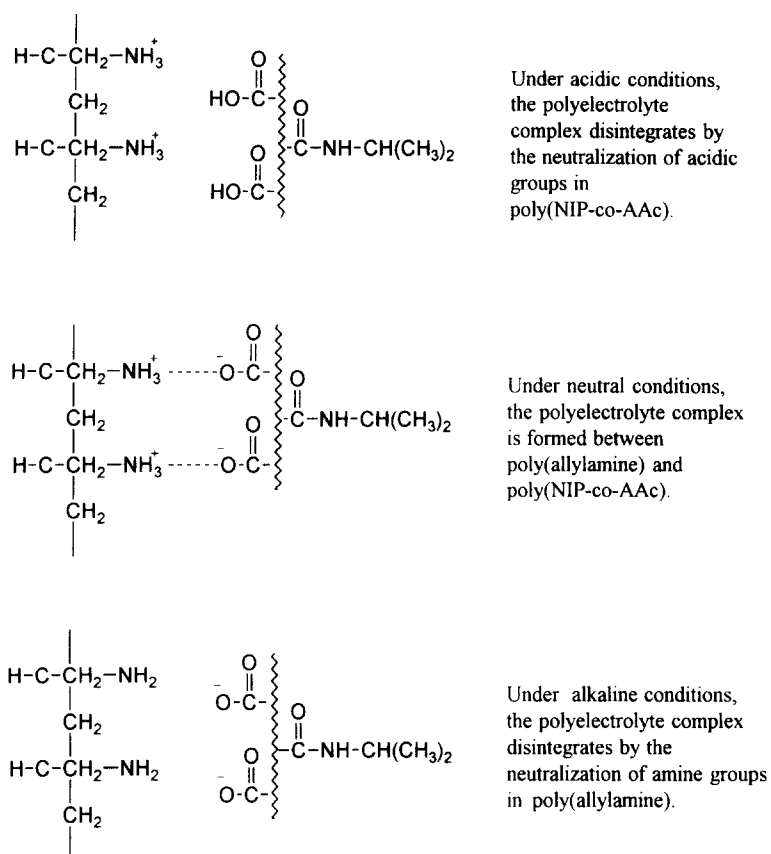
Absorbency at 450 nm of 1.0 wt% of P(NIPAAm-*co*-AAc-20) solution against temperature according to the various pH values in the presence of PAA as a polyelectrolyte solute is shown in *Figure 2*. The change of absorbency of the solution against temperature becomes larger with an increase of pH compared with P(NIPAAm-*co*-AAc-20) itself. Interestingly, a drastic change of absorbency of the solution against temperature is observed even above the pK_a value of PAAc in the presence of PAA. The cloud-points of PNIPAAm in P(NIPAAm-*co*-AAc-20) solution in the presence of PAA are 29.5, 30.5, 35.0, 39.0 and 48.0°C for the pH value of 2.1, 3.1, 4.3, 5.0 and 6.4, respectively. From these results, it is found that the cloud-point increases with pH value because the degree of ionization of carboxylic acid groups increases with pH value. Also, it was found that the cloud-point of PNIPAAm in the solution appears above the pK_a value of PAAc, which is not observed in the absence of PAA. The cloud-point of PNIPAAm in the solution in the presence of PAA decreases by polyelectrolyte complex formation between the carboxylic acid group of PAAc and the amine group of PAA, indicating that dehydration occurs around PNIPAAm. Around a pH value of 8.0, the cloud-point of PNIPAAm in the solution is not observed due to insoluble polyelectrolyte complex formation, indicating a compact form of the complex structure. Also, above the pK_b value of PAA, the cloud-points of PNIPAAm in the copolymer were not observed due to the free amine group of PAA, indicating non-association between the amine group of PAA and the carboxylic acid group of PAAc.

In *Figure 3*, the cloud-points of PNIPAAm of the copolymer in the solution are plotted against the pH

H-C-CH₂-NH₃⁺

CH₂

H-C-CH₂-NH₃⁺

CH₂

O
‖
HO-C-

O
‖
C-NH-CH(CH₃)₂

O
‖
HO-C-

Under acidic conditions,
the polyelectrolyte
complex disintegrates by
the neutralization of acidic
groups in
poly(NIP-co-AAc).

H-C-CH₂-NH₃⁺ ------O-C-

CH₂

H-C-CH₂-NH₃⁺ ------O-C-

CH₂

O
‖

O
‖
C-NH-CH(CH₃)₂

Under neutral conditions,
the polyelectrolyte complex
is formed between
poly(allylamine) and
poly(NIP-co-AAc).

H-C-CH₂-NH₂

CH₂

H-C-CH₂-NH₂

CH₂

O
‖
O-C-

O
‖
C-NH-CH(CH₃)₂

O
‖
O-C-

Under alkaline conditions,
the polyelectrolyte complex
disintegrates by the
neutralization of amine groups
in poly(allylamine).

Figure 4 Schematic illustration of the intermacromolecular interaction between poly(allylamine) and P(NIP-*co*-AAc) in acidic, neutral, and alkaline conditions
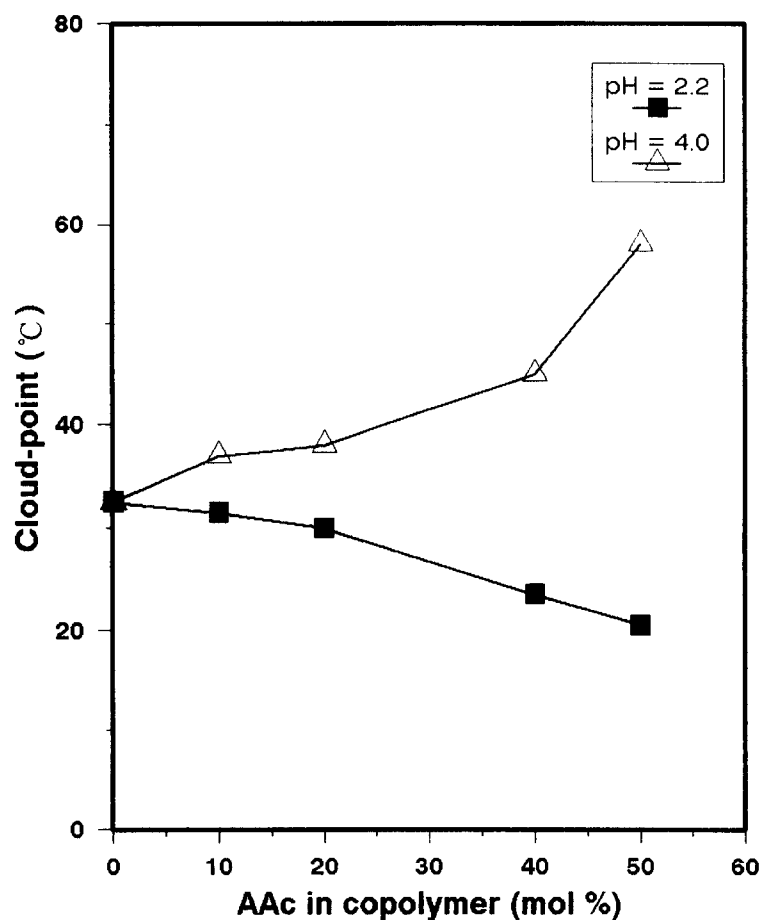
Figure 5 Plot of cloud-point of 1.0 wt% P(NIP-*co*-AAc) solutions against content of AAc as a function of pH
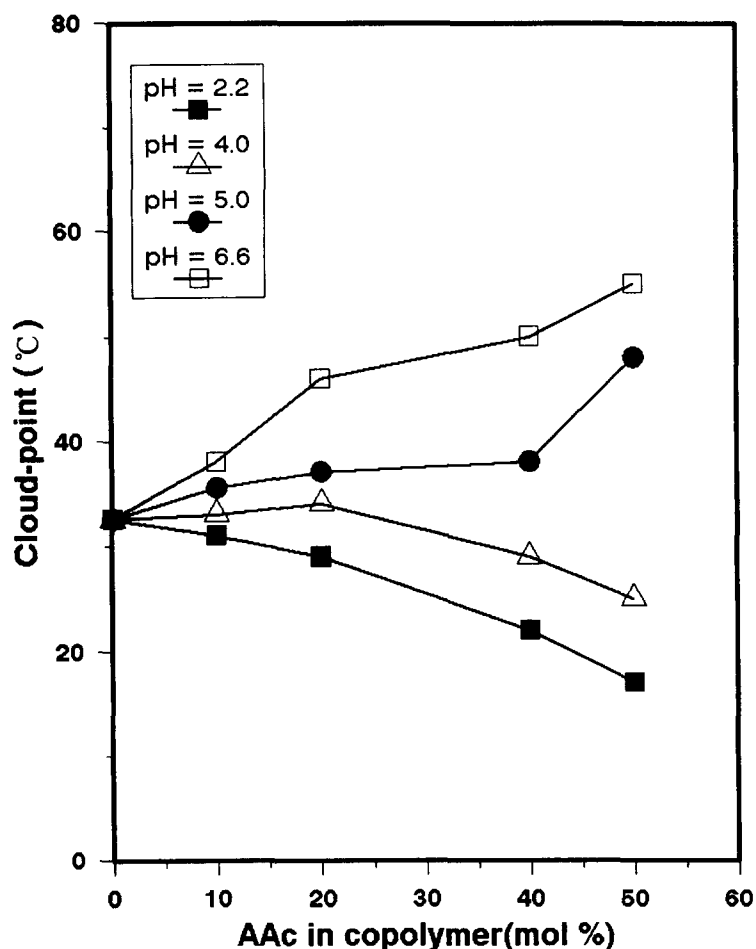
Figure 6 Plot of cloud-point of 1.0 wt% P(NIP-*co*-AAc) solutions with 1.0 wt% PAA solution against content of AAc as a function of pH

value in the presence of PAA. The cloud-points of PNIPAAm in the solution with PAA are lower than those of PNIPAAm without PAA. Also, it is found that the cloud-points of PNIPAAm in the solution appear above the pK_a value of PAAc in the presence of PAA.

Figure 4 illustrates intermolecular interaction between PAAc in the P(NIPAAm-*co*-AAc) and PAA in acidic, neutral and alkaline conditions[32]. There are reports on complex formation between PNIPAAm and PAAc, and between PAAc and PLL, respectively[33,34]. Since it is a well known phenomenon, spectroscopic measurements were not done in the study. In the pH region from pK_a of PAAc (partly or completely ionized) to pK_b of PAA (partly or completely protonated), the polyelectrolyte complex is formed due to Coulombic forces between opposite charges on both polymer chains. This may lead to a decreased cloud-point due to the reduced hydrophilic effect of the charged LCST polymer, the reduced accessibility and mobility of water surrounding the polymer and dehydration of LCST polymer chain by polyelectrolyte complex formation. In the pH region below the pK_a of PAAc, the cloud-point is affected by intra- or intermolecular hydrogen bonding between the amide groups of PNIPAAm and the carboxylic acid groups of PAAc. In the pH region above pK_b of PAA, the polyelectrolyte complex is not formed by the neutralization of amine groups in PAA.

Figure 5 exhibits the cloud-point of PNIPAAm against AAc mol% in the P(NIPAAm-*co*-AAc) copolymer solution according to the pH values. It is found that the cloud-points of PNIPAAm in the copolymer are

affected by pH and AAc content in the copolymer. The cloud-points of PNIPAAm in the solution decrease with an increase of AAc content in the copolymer around a pH value of 2.2 because more hydrogen bonding between the amide group of PNIPAAm and the carboxylic acid group of PAAc occur with an increase of the AAc content in the copolymer. On the other hand, the cloud-points of PNIPAAm in the solution increase with the AAc content in the copolymer around a pH value of 4.0 because of increased hydrophilicity with an increase of ionized PAAc.

In *Figure 6*, the cloud-points of PNIPAAm in the presence of PAA, according to the various pH values, are plotted against AAc mol% in the P(NIPAAm-*co*-AAc) copolymer solution. Not many differences in the cloud-points of PNIPAAm in the copolymer with and without PAA are found around a pH value of 2.2 due to the hydrogen bonding between PNIPAAm and PAAc. However, at around a pH value of 4.0, the cloud-points of PNIPAAm in the copolymer with PAA are much lower than those of it without PAA at the same content of PAAc because of polyelectrolyte complex formation between partially ionized PAAc and PAA. Also, in the pH region above the pK_a of PAAc, the cloud-points of PNIPAAm which have not been observed without PAA in the copolymer appear and increase with an increase of AAc content in the presence of PAA. Furthermore, it is found that the cloud-points of PNIPAAm in the copolymer increase with pH value at the same content of AAc since there are much more ionized carboxylic groups at a high pH value.
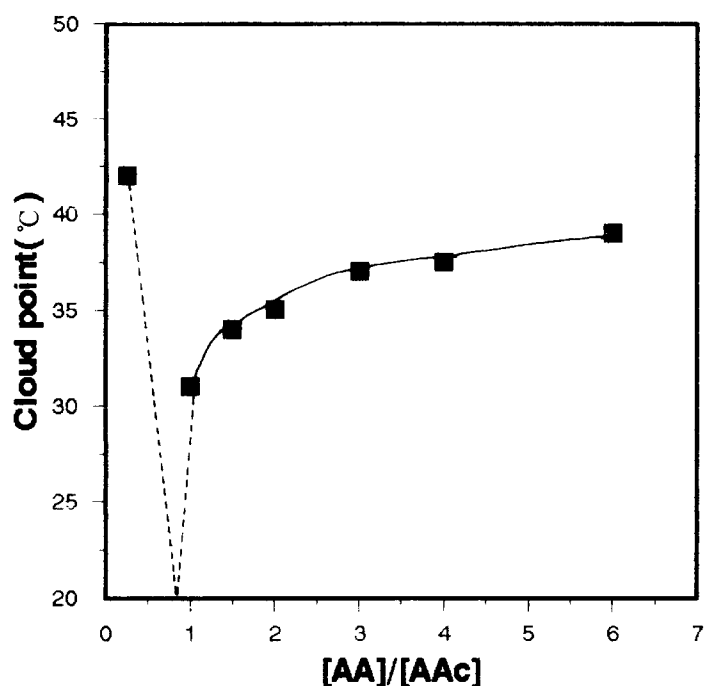
Figure 7 Plot of cloud-point of 1.0 wt% P(NIP-*co*-AAc) solutions with PAA solution against unit mole ratio for PAA/P(NIP-*co*-AAc-20) at pH = 5.0

Figure 7 shows the cloud-points of PNIPAAm in the P(NIPAAm-*co*-AAc-20)/PAA complex system against the ratio of [AA] to [AAc]. It is found that the cloud-point of PNIPAAm is not observed around [AA]/[AAc] = 1 due to precipitation, and increases at below or above [AA]/[AAc] = 1, because the charged groups not participating in polymer complex formation affect the cloud-points of PNIPAAm. A polyelectrolyte complex formed with equimolar proportions of each monomer component is neutral and the solubility of these complexes in water is very low because of mutual blocking of oppositely charged ionic groups that are responsible for water solubility and enhanced molecular weight by the formation of networks through secondary bonding. But when nonequimolar compositions are mixed, charges exist on the polymer complex and thus these charges can increase the solubility. Therefore, it can be said that the polyelectrolyte complex between PAAc and PAA is formed stoichiometrically.

The thermodynamics must have been changed by adding a third component to the copolymer/water system. As can be seen in *Figures 3, 6,* and *7,* the cloud-points have been changed with the variation of pH, AAc mole concentration and molar ratio of [AA]/ [AAc]. In this case, the miscibility gap must depend on the polymer concentrations and temperature. However, the miscibility gap was not measured and is outside the objective of the present study.

In conclusion, the cloud-points of PNIPAAm in P(NIPAAm-*co*-AAc) are strongly influenced by the pH and the presence and type of polyelectrolyte solute. A polyelectrolyte complex in the P(NIPAAm-*co*-AAc) system with PAA is formed from pK_a of PAAc to pK_b of PAA. Furthermore, the degree of change in cloud-point is dependent on the charge density of the polymer according to pH value and the ratio of [AA] to [AAc]. These results can be explained by intra- or intermolecular hydrogen bonding, the hydrophilicity of AAc and the polyelectrolyte complex between PAAc and PAA.

ACKNOWLEDGEMENT

REFERENCES

1. Hoffman, A. S., *J. Controlled Release*, 1986, **4**, 213.
2. Bae, Y. H., Okano, T. and Kim, S. W., *J. Controlled Release*, 1989, **9**, 271.
3. Bae, Y. H., Okano, T. and Kim, S. W., *J. Polym. Sci., Polym. Phys.*, 1990, **28**, 923.
4. Dong, L. C. and Hoffman, A. S., *J. Controlled Release*, 1986, **4**, 223.
5. Okano, T., Jacobs, Y. H. and Kim, S. W., *J. Controlled Release*, 1990, **11**, 225.
6. Kopecek, J., Vacik, J. and Lim, D., *J. Polym. Sci., Polym. Chem. Ed.*, 1971, **9**, 2801.
7. Alhaique, F., Marcheft, M., Riccier, F. M. and Santucci, E., *J. Pharmacol.*, 1981, **33**, 413.
8. Eisenberg, S. R. and Grodzinski, A. J., *J. Membrane Science*, 1984, **19**, 173.
9. Kwon, I. C., Bae, Y. H., Okano, T. and Kim, S. W., *J. Controlled Release*, 1991, **17**, 149.
10. Ricka, J. and Tanaka, T., *Macromolecules*, 1984, **17**, 2916.
11. Feil, H., Bae, Y. H., Feijen, J. and Kim, S. W., *Makromol. Chem., Rapid Commun.*, 1988, **14**, 243.
12. Beltran, S., Baker, J. P., Hooper, H. H., Blanch, H. W. and Prausnitz, J. M., *Macromolecules*, 1991, **24**, 549.
13. Dong, L. C. and Hoffman, A. S., *J. Controlled Release*, 1991, **15**, 141.
14. Feil, H., Bae, Y. H., Feijen, J. and Kim, S. W., *Macromolecules*, 1992, **25**, 5528.
15. Schild, H. G., *Progress in Polymer Science*, Vol. 17. Pergamon Press Ltd., 1992, p. 163.
16. Bae, Y. H., Okano, T., Sakurai, Y. and Kim, S. W., *Pharm. Res.*, 1991, **8**, 624.
17. Taylor, L. D. and Cereukowski, L. D., *J. Polym. Sci.*, 1975, **13**, 2551.
18. Winnik, F. M., Ottaviani, M. T. and Turro, N. J., *Macromolecules*, 1991, **25**, 6007.
19. Schild, H. G., Muthukumai, M. and Tirrell, D. A., *Macromolecules*, 1991, **24**, 948.
20. Amiya, T., Hirokawa, Y. and Hirose, Y., *J. Chim. Phys.*, 1987, **86**, 2375.

21. Louai, A., Sarazin, D. and Francois, J., *Polymer*, 1991, **32**, 713.
22. Schild, H. G. and Tirrell, D. A., *J. Phys. Chem.*, 1984, **88**, 207.
23. Schild, H. G. and Tirrell, D. A., *Langmuir*, 1990, **6**, 1676.
24. Bae, Y. H., Okano, T. and Kim, S. W., *J. Controlled Release* 1989, **9**, 271.
25. Cho, C. S., Jung, J. H., Sung, Y. K. and Lee, Y. M., *Makromol. Chem., Rapid Commun.*, 1994, **15**, 727.
26. Feil, H., Bae, Y. H., Feijen, J. and Kim, S. W., *Makromol. Chem., Rapid Commun.*, 1993, **14**, 465.
27. Oosawa, F., *Polyelectrolytes.* Marcel Dekker, Inc., New York, 1971.
28. Bekturov, E. A. and Bimendina, L. A., *Adv. Polym. Sci.*, 1981, **41**, 99.
29. Tsuchida, E. and Abe, K., *Adv. Polym. Sci.*, 1982, **45**, 1.
30. Chen, G. and Hoffman, A. S., *Nature*, 1995, **373**, 49.
31. Schild, H. G., *Prog. Polym. Sci.*, 1992, **17**, 163.
32. Kwon, I. C., PhD Thesis, Univ. of Utah, 1993, p. 139.
33. Hoffman, A. S., *Macromol. Chem. Phys.*, 1995, **196**, 1251.
34. Kabanov, V. A., *Vysokomol. Soed.*, 1972, **A14**, 772.