

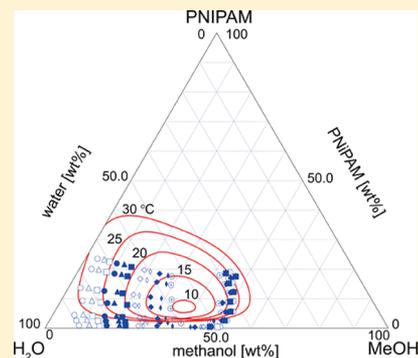
# Phase Behavior of Co-Nonsolvent Systems: Poly(*N*-isopropylacrylamide) in Mixed Solvents of Water and Methanol

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**ABSTRACT:** Cloud points of poly(*N*-isopropylacrylamide) in aqueous mixed solvents, with methanol as the cosolvent, are experimentally measured for polymer concentrations varied up to as high as the weight fraction 0.25. They are shown to form closed loops on the ternary phase plane in the temperature region between 5 and 30 °C, and hence co-nonsolvency is complete. Miscibility loops shrink by cooling, or equivalently, they exhibit lower critical solution temperature behavior. For a fixed polymer concentration, there is a composition of the mixed solvent at which the cloud-point temperature takes the lowest value. This minimum cloud-point temperature composition of the mixed solvent turned out to be almost independent of the polymer concentration, at least within the measured dilute region below the weight fraction 0.25. On the basis of the assumption that the phase separation is closely related to the preferential adsorption of the solvents by hydrogen bonding, we employ a model solution of Flory–Huggins type, augmented with direct and cooperative polymer–solvent hydrogen bonds, to construct the ternary phase diagrams. Theoretical calculation of the spinodal curves is performed, and the results are compared with the obtained experimental cloud-point data. The effect of molecular volume of the cosolvent is also studied within the same theoretical framework. Possibility for an upper critical solution temperature co-nonsolvency to appear for cosolvents with larger molecular volume is discussed.



## INTRODUCTION

Poly(*N*-isopropylacrylamide) (PNiPAM) chains in water has the  $\Theta$  temperature at 30.6 °C, where the second virial coefficient becomes zero, and a polymer chain shows the transition from coil conformation to globular one by heating.<sup>1</sup> There have been many reports studying PNiPAM solutions in various solvents, such as by scattering methods,<sup>1–5</sup> fluorescence,<sup>6</sup> electronic paramagnetic resonance,<sup>7</sup> IR spectroscopy,<sup>8–10</sup> calorimetry,<sup>11,12</sup> and dielectric relaxation spectroscopy.<sup>13,14</sup> A considerable amount of works on PNiPAM solutions is collected in the review.<sup>15</sup> For a nonequilibrium state, the solution properties of PNiPAM are also studied,<sup>16–19</sup> where thermal diffusion phenomena, also called Ludwig–Soret effect, have been studied by taking into account the coil–globule transition in the vicinity of the  $\Theta$  temperature.

Even in thermodynamic equilibrium and/or nonequilibrium states, the nature of solubility of PNiPAM in solvents is fundamentally important as the starting point of most of all PNiPAM studies on polymerization and chemical substitution for functioning aims, as well as on thermosensitive behaviors of single-chain or phase behavior, and on hydration–dehydration in molecular level. The phase behavior of PNiPAM has thus long been a focus of the study.

Quite recently, the phase behavior of PNiPAM in aqueous mixed solvents has been attracting interest of many researchers with relation to the phase separation<sup>20–31</sup> and the gelation<sup>32–35</sup> of temperature-sensitive water-soluble polymers. The combi-

nation of two good solvents which becomes poor when mixed, referred to as co-nonsolvency, is particularly interesting from the scientific view because of its mysterious nature, unknown molecular mechanism, and potential applications. Detailed molecular simulations have been carried out<sup>30,36–38</sup> for this interesting case.

Co-nonsolvency is roughly classified into two categories, that is, lower critical solution temperature (LCST)- and upper critical solution temperature (UCST) co-nonsolvency. The former is often observed in solutions with water as the primary solvent. However, the latter is also occasionally observed in aqueous solutions depending on the co-solvent.<sup>38–41</sup> In this study, we focus mainly on LCST case, but also suggest the possibility of the appearance of UCST.

To understand LCST of aqueous polymer solutions, conventional treatment by using van der Waals (vdW) interaction parameter ( $\chi$ -parameter in the Flory–Huggins theory) is not sufficient. The very flat LCST cloud-point curves observed on the temperature–concentration plane in aqueous solutions of PNiPAM was shown to appear as the result of abrupt hydration–dehydration transition of the polymer chains.<sup>42</sup> Such hydration is caused by the direct hydrogen bonding (HB) between amide groups on the side

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chain of the polymer and solvent water molecules. Hence, its strength influences the phase behavior. Also, the hydration process of PNIPAM is known to take place cooperatively, and as a result, the transition becomes extremely sharp, as revealed by very flat (concentration independent) cloud-point curves of the LCST type.

In this paper, we report the experimentally observed cloud points of PNIPAM/water/methanol on the ternary phase plane covering the polymer concentration region as high as the weight fraction 0.25, where the solution becomes highly viscous. Temperature is varied from 30 °C down to 5 °C. Methanol is a good solvent for PNIPAM in the temperature region. We also attempt to understand the obtained results by the concept of preferential adsorption of one solvent component by HB with the polymer chains.

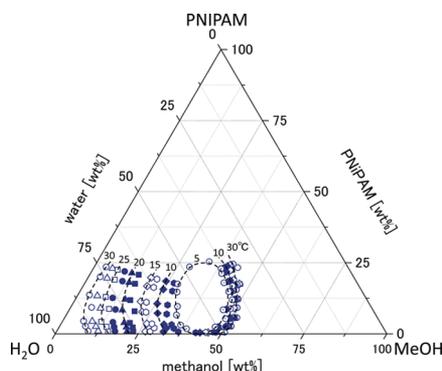
## EXPERIMENTAL SECTION

**Sample.** PNIPAM was polymerized and fractionated by a molecular weight fractionation method. Details are available elsewhere.<sup>1,40</sup> One fraction was used in this study which has the weight-averaged molecular weight  $M_w = 54.8 \text{ kg mol}^{-1}$  with a polydispersity index  $M_w/M_n$  of 1.2 obtained from gel permeation chromatography (Tosoh Co. Ltd.) system with methanol containing 10 mmol/L LiBr as an eluant. Methanol was purchased from Wako Pure Chemical Industries Ltd. with an analytical grade (at least 99.5% purity) and used as received.

**Cloud Point Curve Measurement.** Cloud-point curves were measured in the temperature range of  $5.0 < T/^\circ\text{C} < 30.0$  using a temperature-controlled water bath. A required amount of methanol or water was added to PNIPAM/water or PNIPAM/methanol to obtain ternary mixtures of PNIPAM/water/methanol. These solutions were settled in a temperature-controlled water bath with an uncertainty of temperature  $\pm 0.05 \text{ }^\circ\text{C}$  for the determination of the clouding temperature. To obtain cloud-point curves, the diminishing incident beam passing through the cloudy solution was observed for various ternary compositions and temperatures. The concentration of PNIPAM was restricted below 25 wt % because of the difficulty of solution handling due to very high viscosity.

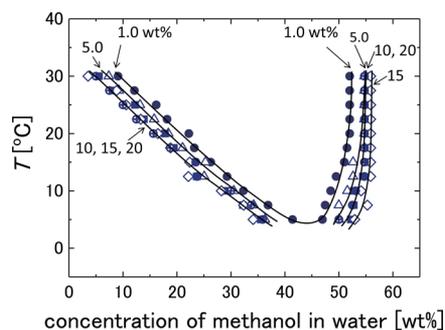
## RESULTS AND DISCUSSION

**Cloud-Point Curves on Ternary Phase Diagram.** Figure 1 shows the ternary phase diagram for PNIPAM in the mixed



**Figure 1.** Closed-loop ternary phase diagrams of PNIPAM/water/methanol mixtures. Cloud points are plotted for various ternary composition obtained by adding water (left side of the loops) or methanol (right side of the loops) to the prepared two-component (PNIPAM/methanol or PNIPAM/water) solutions. Temperature is changed from curve to curve. Dotted lines are drawn for guiding eyes. Although the data above 25 wt % of PNIPAM were impossible to obtain, the closed loops seem to be complete.

solvent of water/methanol, where the cloud-point temperatures are plotted for various compositions. Different symbols refer to the clouding temperatures plotted in 2.5 °C steps, and the dotted lines with the clouding temperatures are drawn for guiding eyes. The cloud-point curve at 5.0 °C exhibits a closed-loop shape, the inside of which is an immiscible region. In the water-rich side (left side of the loop), the cloud-point curve shifts toward the left with an increasing temperature, whereas in the methanol rich-side (right side of the loop), there is only a slight shift of the cloud-point curve to the right with a changing temperature from 5 to 10 °C and no shift of the cloud-point curves is observed at higher temperatures. A phase diagram of the temperature-mixed solvent composition plane is obtained by cross sections at fixed PNIPAM compositions, as shown in Figure 2.



**Figure 2.** Temperature–concentration cross section of the ternary mixtures PNIPAM/water/methanol. Cloud-point temperatures are plotted against the solvent composition of water/methanol for fixed PNIPAM concentrations as 1.0 (filled circle), 5.0 (triangle), 10 (filled square), 15 (diamond), and 20 wt % (circle-plus). The curves are drawn for guiding eyes. The temperature minimum occurs around 45 methanol wt % almost for all polymer concentrations covered here.

Different symbols indicate the concentrations of PNIPAM, as shown in Figure 2. The curves are drawn for guiding eyes. The system shows an LCST-type phase behavior, and the temperature minimum locates around 45 wt % ethanol in the mixed solvent ethanol/water for 1.0 wt % PNIPAM concentration. It is revealed that the immiscible region of the system expands with increasing PNIPAM concentration. Although for higher concentrations of PNIPAM, the minimum temperature is not accessible owing to the limit of experimental temperature range; the minimum temperatures of all PNIPAM concentrations seem to be located at the same methanol composition ( $45 \pm 5 \text{ wt } \%$ ).

**Theoretical Construction of the Ternary Phase Diagrams for Hydrogen Bonding-Mixed Solvents.** The molecular origin of LCST co-nonsolvency has been a focus of the recent studies of aqueous solutions of temperature-sensitive polymers. The molecular mechanisms of co-nonsolvency proposed so far can be roughly classified into three types.

First one is the formation of clusters of water and methanol by HBs. A pentagonal structure of water molecules and methanol molecules forms stoichiometric compounds. They behave as a poor solvent by expelling PNIPAM chains from the solvents.<sup>43</sup> This argument focuses on the formation of water/methanol clusters by neglecting polymer–solvent HBs. According to this hypothesis, the solvent composition at the minimum cloud-point temperature should not depend on the polymer molecular weight, which is opposite to the

observation. The experiments<sup>21,22,24</sup> revealed a systematic shift of the minimum toward higher composition of methanol. Also, it seems difficult to apply this idea to other cosolvents, such as ethanol, propanol, dioxane, and so forth, that do not form specific compounds with water but show co-nonsolvency.

The second one is the concentration fluctuation in the close vicinity of the critical point of the solvent phase separation, such as in the mixture of water and tetrahydrofuran (THF).<sup>44</sup> This concentration fluctuation of the solvents near the polymer chains induces attractive interaction between polymer chain segments, whose range is on the order of the correlation length, and can be comparable or larger than a polymer chain size near the critical regime. The attractive interaction leads to the conformation change of the polymer chains and induces their aggregation. This hypothesis may be important for partially miscible mixtures, such as water/THF mixtures, but it is difficult to apply to completely miscible mixtures of water and methanol.

The third one is the preferential adsorption caused as a result of the competition between polymer/water (p/w) HB and polymer/methanol (p/m) HB. The mixed solvent becomes poor by dehydration of polymer chains (dissociation of bound water molecules) because of preferential adsorption of methanol at higher composition of methanol.<sup>24,45,46</sup> If binding of water molecules is cooperative, this effect is enhanced, and takes place abruptly; continuous long trains of p/w HBs are entirely broken by the blocking of methanol molecules.

In what follows, we start from the third picture and theoretically construct ternary phase diagrams which show a complete co-nonsolvency with a closed-loop phase separation region and compare with the experimental data reported above. We first briefly review our model solution with competitive HBs employed previously for the study of co-nonsolvency.<sup>24</sup> It starts from a polymer solution of Flory–Huggins type but augmented by incorporating direct HBs among the constituent molecules. It therefore has, first of all, the conventional three Flory interaction parameters ( $\chi$ -parameters):  $\chi_{pw}(T)$  for polymer/water (p/w),  $\chi_{pm}(T)$  for polymer/methanol (p/m), and  $\chi_{wm}(T)$  for water/methanol (w/m). These parameters describe the strength of the vdW interaction among the monomers and solvents. They are assumed to include the so-called “hydrophobic interaction” between hydrophobic groups (isopropyl groups on the PNIPAM chains and methyl groups on the methanol molecules). They are weakened with increasing temperature so that the molecules are more miscible at higher temperature as in ordinary polymer solutions exhibiting UCST phase separation. Specifically, they are assumed to take the Shultz–Flory form<sup>47</sup>

$$n_\alpha \chi_\alpha(T) = 1/2 - \psi_\alpha(1 - \Theta_{\alpha,0}/T) \quad (1)$$

where  $\alpha = w$  and  $m$  for the combinations p/w and p/m. Because water and methanol is completely miscible in the temperature range of the measurement,  $\chi_{wm} = 0$  for w/m is assumed. The number  $n_\alpha$  is the molecular volume of the solvent  $\alpha$  measured in the unit of the Flory–Huggins lattice cell. We have taken the volume of a monomer (statistical repeat unit) as the reference volume. The volume of water is assumed to be the same as a monomer's ( $n_w = 1$ ), but  $n_m$  is allowed to vary to cope with cosolvents other than methanol within the same theoretical framework. In the calculation, we use the reduced temperature

$$\tau_\alpha = 1 - \Theta_{\alpha,0}/T \quad (2)$$

for each solvent, where  $\Theta_{\alpha,0}$  is the un-renormalized theta temperature, that is, the theta temperature of the solution without HBs (remark that because of the presence of HBs, they are different from the real theta temperature of the solution where the second virial coefficient vanishes). The Shultz–Flory form 1 is equivalent to the often used form  $n\chi(T) = A + B/T$  in the literature, where  $A, B (B > 0)$  are temperature-independent constants.

To derive the LCST behavior actually observed in aqueous PNIPAM solutions, however,  $\chi$ -parameters are not enough because they lead only to UCST. Therefore, we explicitly introduce HB interaction parameters into the Flory–Huggins solution model as in our previous work.<sup>24</sup> HBs give three association constants:  $\lambda_w(T)$  for p/w,  $\lambda_m(T)$  for p/m, and  $\lambda_{wm}(T)$  for w/m. They take the form

$$\lambda(T) = \lambda_0 \exp(-\epsilon/k_B T) \quad (3)$$

for each combination, where  $\epsilon (< 0)$  is the HB energy and  $\lambda_0$  is the temperature-independent constant because of the entropy change on forming a HB. We have also introduced cooperativity among the p/w HBs, that is, there is a preferable interaction  $\Delta\epsilon (< 0)$  between the bound water molecules located in the nearest neighboring position.<sup>42</sup> Therefore, we have  $\lambda_\zeta(T) = \sigma(T)\lambda(T)^\zeta$  for a continuous sequence of bound water molecules of the number  $\zeta$ , where  $\sigma(T) = \exp(\Delta\epsilon/k_B T)$  ( $\Delta\epsilon < 0$ ) is the conventionally called cooperativity parameter of the HB, and the association constant is renormalized to be  $\lambda(T) = \lambda_0 \exp[-(\epsilon + \Delta\epsilon)/k_B T]$ . Similarly, we introduce  $\sigma$  and  $\lambda$  for p/m, although binding and cooperativity have so far only been partially confirmed experimentally for methanol. For HBs with no cooperativity, such as random hydration, we have only to fix as  $\sigma = 1$ . Finally, we neglect HB between water and methanol because it plays only secondary role for co-nonsolvency as described above.

By imposing HB association equilibrium conditions on the chemical potentials derived in the model, we find the Gibbs matrix  $\hat{G}$  as a function of temperature, polymer volume fraction  $\phi$ , and the solvent composition  $u$ . The composition  $u$  is defined such that  $\phi_w = (1 - \phi)(1 - u)$  gives the volume fraction of water, and  $\phi_m = (1 - \phi)u$  gives that of methanol. The composition  $u$  of methanol introduced here is related to its mole fraction  $x$  in the mixed solvent through  $u = n_m x / [n_w(1 - x) + n_m x]$ , where  $n_w$  and  $n_m$  are their volumes measured relative to the monomer volume.

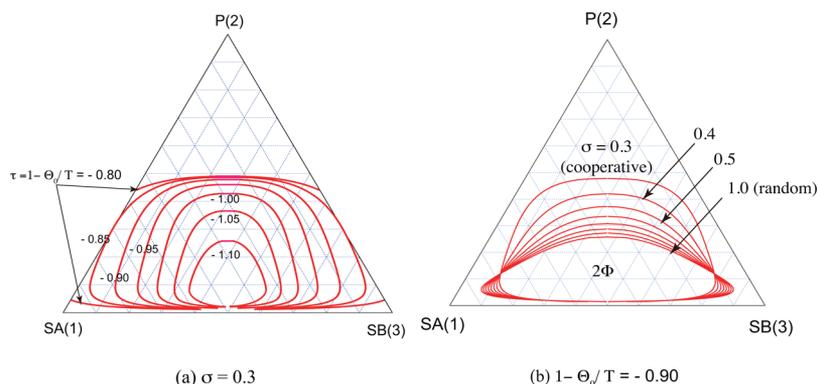
Some of the solvent molecules are bound to polymer chains and others remain free in the solution. Let  $y_A$  be the volume fraction of the free primary solvent (water), and let  $y_B$  be that of the cosolvent (methanol). They should satisfy the material conservation laws

$$y_A + n_A \phi \theta_A(y_A, y_B) = (1 - \phi)(1 - u) \quad (4a)$$

$$y_B + n_B \phi \theta_B(y_A, y_B) = (1 - \phi)u \quad (4b)$$

in terms of the average degree of binding  $\theta_A$  and  $\theta_B$  (the average number of bound solvent molecules per HB site on the polymer chains) as functions of the volume fractions of free A and B molecules. From these equations,  $y_A$  and  $y_B$  are found as functions of their concentrations  $\phi$  and  $u$  in the preparation stage.

To find the cloud-point curve on the ternary phase plane, we solve the spinodal condition  $|\hat{G}| = 0$  for the determinant of the Gibbs matrix  $\hat{G}$ . Theoretical details are described in our



**Figure 3.** Ternary phase diagrams showing cloud-point lines (spinodal lines) for a symmetric solvent mixture. (a) Effect of temperature for a fixed cooperative parameter  $\sigma$  ( $\equiv \sigma_A = \sigma_B$ ) = 0.3. The closed miscibility loop expands with temperature. (b) Effect of cooperativity parameter for a fixed temperature  $\tau = 1 - \Theta_0/T = 0.9$ . The loop expands as the cooperativity is increased (smaller values of  $\sigma$ ).

previous paper.<sup>24</sup> Here, we show only the final explicit form of the spinodal condition. It is

$$\begin{aligned} & -nn_A n_B \tilde{\chi} \phi \Phi - 2n_A n_B \chi_{AB} (\Phi + n\Psi) - 2n(\chi_A \Phi_A + \chi_B \Phi_B) \\ & + \Psi_A + \Psi_B + n(1 + n_A \theta_A + n_B \theta_B)^2 \phi = 0 \end{aligned} \quad (5)$$

where  $\Phi$  is defined by

$$\begin{aligned} \Phi(y_A, y_B) & \equiv y_A y_B + (\phi_A - y_A) y_B K_{A,A} + (\phi_B - y_B) y_A K_{B,B} \\ & + (\phi_A - y_A)(\phi_B - y_B) K \end{aligned} \quad (6)$$

The matrix  $K_{\alpha\beta}$  is defined by

$$K_{\alpha,\beta} \equiv \frac{\partial \ln \theta_\alpha}{\partial \ln y_\beta} \quad (7)$$

$K \equiv K_{A,A} K_{B,B} - K_{A,B} K_{B,A}$  is the determinant of the matrix  $\hat{K}$ . The rests are

$$\begin{aligned} \Psi & \equiv y_B \theta_A (\phi_A - y_A) + y_A \theta_B (\phi_B - y_B) \\ & + \frac{1}{2} \phi^2 (\theta_A K_{A,B} + \theta_B K_{B,A}) \\ & + (\phi_A - y_A)(\phi_B - y_B) [\theta_A (K_{B,B} - K_{A,B}) \\ & + \theta_B (K_{A,A} - K_{B,A})] \end{aligned} \quad (8)$$

and

$$\Psi_A \equiv n_A y_A + (\phi_A - y_A)(n_A K_{A,A} + n_B K_{A,B}) \quad (9a)$$

$$\Psi_B \equiv n_B y_B + (\phi_B - y_B)(n_B K_{B,B} + n_A K_{B,A}) \quad (9b)$$

$$\begin{aligned} \Phi_A & \equiv \Psi_A \phi + (\phi_A - y_A)(\phi_B - y_B) [n_A (K_{B,A} - K_{A,A}) \\ & - n_B (K_{A,B} - K_{B,B})] \end{aligned} \quad (9c)$$

$$\begin{aligned} \Phi_B & \equiv \Psi_B \phi + (\phi_A - y_A)(\phi_B - y_B) [n_B (K_{A,B} - K_{B,B}) \\ & - n_A (K_{B,A} - K_{A,A})] \end{aligned} \quad (9d)$$

The effective vdW interaction parameter  $\tilde{\chi}$  is defined by

$$\tilde{\chi} \equiv \chi_A^2 + \chi_B^2 + \chi_{AB}^2 - 2\chi_A \chi_B - 2\chi_A \chi_{AB} - 2\chi_B \chi_{AB} \quad (10)$$

For the practical calculation, we employ the form

$$\lambda_\alpha(T) = \lambda_{\alpha 0} \exp(l\epsilon_\alpha + \Delta\epsilon_\alpha/k_B T) = \lambda_{\alpha 0} \exp[\gamma_\alpha(1 - \tau_\alpha)] \quad (11)$$

for the association constants, where  $\gamma_\alpha \equiv l\epsilon_\alpha + \Delta\epsilon_\alpha/k_B \Theta_{\alpha,0}$  give the binding energy of a water molecule measured relative to the thermal energy at the reference theta temperature. The cooperativity parameters are given by  $\sigma_\alpha = \exp(-|\Delta\epsilon_\alpha|/k_B T)$ . In the following calculation, we assume  $\sigma_\alpha$  to be independent of the temperature in the measured region for the reason that cooperativity originates in the conformation entropy of the hydrophobic groups on the side chains.

We first test our theoretical calculation by treating a model symmetric solvent mixture for which all interaction parameters are assumed to be the same for both component A and B. We therefore need not indicate the subscripts A, B. This is an unrealistic artificial mixture but serves as an ideal case to understand the effect of temperature and cooperativity in HBs.

Figure 3 shows the isothermal cross-sectional view of the ternary phase diagram on which cloud-point curves (spinodals) are drawn. They show symmetric closed loops indicating the complete co-nonsolvency. In Figure 3a, the temperature is varied for a fixed interaction parameters, in particular, for a fixed cooperative parameter. Temperature is shown by the reduced nondimensional value  $\tau = 1 - \Theta_0/T$ . As temperature is raised, the miscibility loop expands because of the dissociation of the bound solvent molecules. Above a certain temperature ( $\tau = -0.88$  in this case), polymer in pure solvent (on the P-SA and P-SB side of the triangle) of both species shows phase separation, so that co-nonsolvency is changed to partial ones.

In Figure 3b, the cooperativity parameter  $\sigma$  is varied from curve to curve at a fixed temperature. Loops expand toward the polymer component, and polymers become gradually difficult to resolve. Therefore, cooperativity in HBs affect not only the sharpness of the transition but also the solubility of polymers at high concentrations.

**Comparison with the Experimental Data.** Let us proceed to the real ternary solutions. We first employ the known values of p/w  $\chi$ -parameter and p/w HB parameters from the experimental and theoretical studies of LCST phase separation of PNIPAM solutions in pure water<sup>24,42</sup> and volume phase transition of PNIPAM cross-linked gels in pure water.<sup>48–51</sup> They are summarized in Table 1. We then adjust p/m  $\chi$ -parameter and p/m HB parameters to fit the calculation to the experimental cloud-point curves. One set of the highly plausible candidates is summarized in Table 1. Because there are three adjustable parameters  $\sigma_m$ ,  $\lambda_{m0}$ , and  $\gamma_m$ , this set may not

Table 1. Summary of the Interaction Parameters

	p/w	p/m
<b>H-bonds</b>		
entropy part	$\lambda_{w0} = 0.002$	$\lambda_{m0} = 0.0042$
energy part	$\gamma_w = 3.5$	$\gamma_m = 3.0$
cooperativity	$\sigma_w = 0.27$	$\sigma_m = 0.4$
<b>van der Waals</b>		
volume	$n_w = 1$	$n_m = 2$
Shultz constant	$\psi_w = 1.0$	$\psi_m = 1.0$
theta temperature	$\Theta_{w0} = 565$	$\Theta_{m0} = 565$

be the optimum one, but it provides sufficient evidence for the co-nonsolvency to be caused by the blocking of hydration by p/m HBs in the region where two kinds of competing HBs balance. The effect of preferential adsorption is fundamentally important. If there is no cooperativity, the bound water molecules are replaced by methanol molecules one by one in proportion to the methanol composition, leading to a monotonic change of the cloud point with methanol composition. However, because of cooperativity, polymer chains can be covered by neither of the components because of the competition in the composition region where the strength of HB formation is comparable, and hence chain segments are directly in contact with the solvents without HB bonds, collapse, and aggregate by hydrophobic interaction (Figure 4).

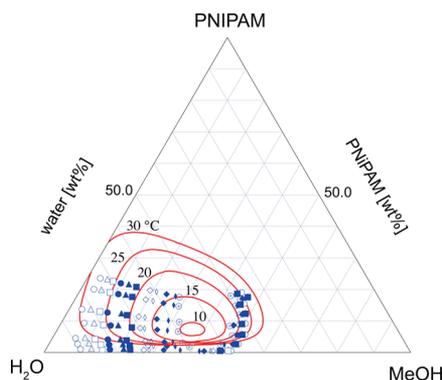


Figure 4. Comparison between the experimental data of the cloud points and theoretical calculation of the spinodal curves on the ternary phase plane. The temperature is changed from 30 °C down to 10 °C.

The fitting is not perfectly well in the following points: theoretical loops on the phase plane take flatter elliptic shape than the experimental data at low temperatures, and the right sides of the ellipses do not sufficiently overlap with each other compared to the observation (Figure 4). However, because it roughly captures all of the nature of the cloud points, the idea of cooperativity in competitive HBs provides a clue for understanding the molecular origin of the strange co-nonsolvent phase behavior.

Some lines of evidence were recently found in the molecular simulations<sup>36,37</sup> such that blocking of hydration (p/w HBs) is caused not by p/m HBs but by p/m vdW interaction. The spatial distribution of methanol near the polymer chains turns out to be denser than in the bulk in the methanol-dominant solvent composition region. Or in other words, co-nonsolvency is caused by the preferential absorption of methanol molecules by the polymer chains. We discuss briefly this important issue.

Throughout the paper, we have distinguished preferential adsorption from preferential absorption. In the former cite-binding case, solvent molecules are directly attached to the polymer chains in the bound state and move together with the chain (one center of mass for a complex chain), whereas in the latter space-binding case, solvent molecules surround the chains in their spatial vicinity but move independently (many centers of masses) with frequent exchange of their positions. They are not in the bound state. Thus, cite-binding and space-binding are fundamentally different. The mixing entropies of these two cases are different. The ordinary  $\chi$ -parameter for p/m vdW interaction only is difficult to explain the sharp re-entrance of the LCST recovery. In the simulation, therefore, it is necessary that not only the space distribution of the solvents but also their life time (frequency of exchange) is studied to distinguish.

**Effect of the Molecular Volume of Cosolvents.** Finally, we extend our discussion to other cosolvents and briefly discuss the effect of their molecular volume. The cloud points were recently measured for a series of alcohols (methanol, ethanol, 1-propanol, and 2-propanol) as cosolvents,<sup>38–41</sup> and the results were compared to each other. It turned out that not only LCST but also UCST appeared for the alcohol molecules whose molecular volume is larger than methanol. The phase-separated region between UCST and LCST becomes narrower with their volumes. The LCST curves seem to go down to minus infinity at a certain finite composition of the alcohol. Also, the cloud-point lines of 1- and 2-propanol turned out to fall almost on top of each other, and hence co-nonsolvency seems to depend on the molecular volume rather than on the molecular shape, in particular, the position of the  $-\text{OH}$  group on a molecule. (The strength of HBs is of course different.)

To understand the origin of UCST co-nonsolvency, we calculated the spinodal lines by changing  $n_B$  under the condition such that all other parameters, except  $\gamma_m(\gamma_B)$ , are kept the same as in 1. Because we have no information about the strength of  $\gamma_B$  as a function of  $n_B$ , we tried several possible forms for it. Result for a trial form  $\gamma_B = 2.50 + 0.55n_B$  is shown in Figure 5. (Of course, only the temperature region below 100

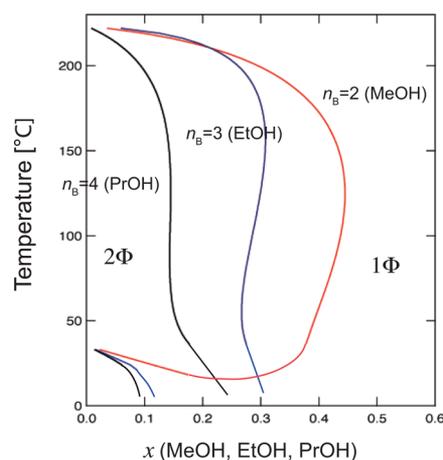


Figure 5. Cloud-point temperature plotted against the solvent composition (molar fraction  $x$ ) for methanol, ethanol, and propanol as cosolvents. Although only LCST co-nonsolvency is observed for methanol below 100 °C, the UCST cloud points can be seen at the intermediate temperature region for ethanol and propanol. The miscibility gaps for the latter therefore take the hourglass form, the bottom parts of which are merged with the lower UCST branches of the miscibility gap (called miscibility dome) at low-temperature region.

°C can be seen in the experiments.) The calculation properly describes the general tendency in the shape of UCST and LCST and their relative position. As seen in this figure, the phase separation region for all cosolvents takes a closed-loop shape. This is physically natural because any solution should be a homogeneous one if temperature is raised sufficiently high under the assumption that all components in the solution are not decomposed by heat. The difference lies only in the slope of the lines in the intermediate temperature region between 0 and 60 °C. For methanol, it is positive, whereas it is negative for others. The phase separation region is opened toward the lower temperature with increasing molecular volume of the cosolvent, and hence it takes an hourglass shape.

Such UCST–LCST co-nonsolvency was recently experimentally studied in detail.<sup>39,41</sup> In water/ethanol mixtures, the LCST seemingly diverges to minus infinity at some critical solvent composition, beyond which there is a narrow insoluble range followed by the UCST re-entrance of solubility at higher ethanol composition. This suggests a partitioning of the phase space in two different regimes: the low composition region where mixing entropy is irrelevant compared to the energetic contribution (HB), and the high composition region where the mixing entropy, leading to UCST as in ordinary polymer solutions, is important. The separation is, however, not complete: the coexistence of LCST and UCST at the same solvent composition should be observed when measured to sufficiently high temperatures because UCST curves must turn back toward the temperature axis. Any solution must be a homogeneous one at high temperature where the mixing entropy is dominant provided that all system components remain un-degraded by heat.

## CONCLUSIONS

We have reported our recent measurements on the isothermal cross section of the ternary phase diagram for PNIPAM in mixed solvents of water and methanol. The cloud-point curves are closed on the ternary phase plane for all temperatures between 5 and 30 °C, and hence co-nonsolvency turned out to be complete. In other words, PNIPAM dissolves in each solvent perfectly but becomes cloudy when the two solvents are mixed.

To explain the molecular origin of such closed-loop co-nonsolvency, we have assumed HB of the solvent molecules in competitively seeking for the HB sites on the polymer chain. If cooperativity in such hydrogen bond formation within the same species of the solvent is high, that is, the interaction energy, free energy, more precisely, between the neighboring bound solvent pair is strongly negative and the transition becomes sharper, showing steeper side of the miscibility loop.

We have also shown the cross section of the phase diagram at a constant polymer concentration with temperature as the vertical axis. The LCST curve takes a minimum value at a particular solvent composition, which locates at almost the same position irrespective of the polymer concentration. The solvent couple at this composition serves as an optimal mixed solvent for the structure formation in the solution, such as micellization, gelation, and interchain globule formation which are thermally driven by phase separation.

On the basis of these calculations, we extended our competitive hydrogen bonding model to cosolvents with larger molecular volumes. Larger molecules have stronger force for blocking the bound water sequences. As a result, the closed miscibility loop on the temperature–composition plane expands toward the low temperature, and opened into

hourglass shape, where the UCST cloud-point curve coexists with the LCST one. The cosolvent ethanol and propanol fall into this category. We hope more cosolvents of this type will be found for the experimental examination of new types of co-nonsolvency.

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### Notes

The authors declare no competing financial interest.

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