Cononsolvency in Mixed Aqueous Solutions of Poly(N-isopropylacrylamide)

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ABSTRACT: The lower critical solution temperature (LCST) of poly(N-isopropylacrylamide) (PNIPAAM), prepared by an aqueous redox polymerization, was studied in the cononsolvent mixture of water and methanol by means of cloud-point and microcalorimetric measurements. The observed solution behavior was quite distinct from that of poly(vinyl methyl ether) in the same binary solvent. Other cononsolvents, including dioxane and tetrahydrofuran, yielded phase diagrams similar to those of PNIPAAM in water–methanol mixtures. Flory–Huggins ternary solution theory can explain the observed results only in terms of a change in the solvent–solvent interaction parameter (χ_{12}) in PNIPAAM solutions. We believe this to be physically implausible in the dilute (0.04%) solutions used in this work. Furthermore, we find in comparing our work with that of Hirotsu (Hirotsu, S. *J. Chem. Phys.* **1988**, *88*, 427) that the behavior of PNIPAAM in water–methanol mixtures is strikingly insensitive to a 200-fold variation in polymer concentration. We suggest that perturbation of χ_{12} is *not* the origin of cononsolvency or of the gel collapse transitions reported by Hirotsu and by Tanaka and co-workers (Amiya, T.; Hirokawa, Y.; Hirose, Y.; Li, Y.; Tanaka, T. *J. Chem. Phys.* **1987**, *86*, 2375).

Introduction

The behavior of poly(N-isopropylacrylamide) (PNIPAAM, **1**) in aqueous media is of interest from both theoretical and practical perspectives. The polymer

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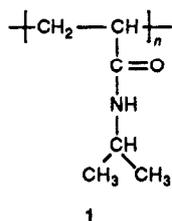
exhibits a well-defined lower critical solution temperature (LCST) in water,[1] and cross-linked PNIPAAM gels undergo analogous collapse transitions in aqueous solvents.[2,3] These transitions have been exploited in the development of novel temperature-sensitive methods for permeability control[4-8] and protein phase separation.[8]

The LCST, and the accompanying changes in polymer conformation, result from a balance between hydrogen-bonding[9] and hydrophobic[10] effects in aqueous solutions or water-swollen gels of PNIPAAM. Specific orientations of water that arise upon polymer dissolution lead to increasingly unfavorable entropic contributions to the free energy of mixing as the temperature is raised. Eventually, these overcome the favorable enthalpy changes associated with the formation of hydrogen bonds between polymer and solvent. Thus the LCST is expected to be a sensitive function of solvent composition, particularly with regard to cosolvents (or cosolutes) that modify water structure and hydrophobic interactions.

We examine here the dependence of the LCST on solvent composition in mixed aqueous solutions of PNIPAAM. We compare our results to the predictions of solution theory and to the solution behavior of poly(vinyl methyl ether) (PVME).[11] Quantitative agreement is demonstrated between our single-chain PNIPAAM results and previous investigations of cross-linked PNIPAAM gels[3] in similar solvent mixtures.

Experimental Section

Materials. N-Isopropylacrylamide was obtained from Eastman Kodak Co. and recrystallized (mp 64–66 °C) from a 65/35 mixture of hexane and benzene (Fisher Scientific Co.). Salts were obtained from Fisher except for magnesium sulfate (Mallinkrodt) and ammonium persulfate (J.T. Baker). Tetramethylethylenediamine (TEMED) was used as received from Kodak; chloroform, tetrahydrofuran (THF), and methanol were purchased from Aldrich Chemical Co. and were of HPLC grade. Wet cellulose dialysis tubing was no. 6, 1000 molecular weight cutoff, from Spectrum Medical Industries, Inc. Poly(vinyl methyl ether) (PVME) was purchased as a 50 wt % solution in toluene (Aldrich). The PVME solution (100 g) was diluted 6-fold with toluene and precipitated into 3–4 volumes of n-heptane (Fisher). The dried rubbery solid (35% yield) had an estimated $\bar{M}_w$ = 155 000 and $\bar{M}_n$ = 83 000 by gel permeation chromatography (GPC). Distilled water was analyzed (Barnstead Co., Newton, MA) to contain 0.66 ppm total ionized solids (as NaCl) and 0.17 ppm total organic carbon (as C).

Synthesis. The aqueous redox polymerization of PNIPAAM was adapted from a procedure reported by Hoffman and co-workers.[8] The solvent was a 15 mM phosphate buffer in normal saline (600 mL of distilled water, 0.6914 g of Na$_2$HPO$_4$, 0.9094 g of NaH$_2$PO$_4$, and 5.09 g of NaCl; titrated with ca. 50 mL of 0.1 N NaOH to pH 7.4). After 22.2 g of monomer, 2.3 g of ammonium persulfate in 5 mL of water, and 12 mL of TEMED were added, the reaction mixture was stirred for 15 h at room temperature under nitrogen. Precipitation was carried out by dropwise addition of the polymerization mixture to 800 mL of methanol. The resulting polymer was dissolved in 200 mL of distilled water and dialyzed against regularly freshened distilled water for 5 days. The polymer was then precipitated in an equal volume of methanol and vacuum-dried. The polymer was then dissolved in chloroform, the solution was dried (MgSO$_4$), and the polymer was precipitated in hexane. The 2.62-g sample of PNIPAAM obtained after vacuum-drying was designated R2A. Anal. Calcd for C$_6$H$_{11}$NO: C, 63.7; H, 9.8; N, 12.4. Found: C, 63.5; H, 9.9; N, 12.2. ^{1}H NMR (200 MHz, D$_2$O): δ 1.0 (CH$_3$, 6 H), 1.2–2.1 (–CH$_2$CH–, 3 H), 3.7 (CH, 1 H). No vinyl protons were detected. IR (CHCl$_3$, cast film): 3300, 2960, 2925, 2860, 1635, 1530, 1455, 1375, 1390, 1170, 1130, 750 cm^{-1}. Absent were the 1620 cm^{-1} (C=C), 1410 cm^{-1} (CH$_2$=), and C–H vinyl out-of-plane bending vibrations observed in the spectrum of the monomer. GPC: $\bar{M}_w$ = 160 000; $\bar{M}_n$ = 49 000; $\bar{M}_w/\bar{M}_n$ = 3.2. A second sample, designated R2B, was recovered from the filtrate by evaporation and then precipitated and dried as described above to provide 1.70 g of PNIPAAM of $\bar{M}_w$ = 76 000, $\bar{M}_n$ = 11 000, and $\bar{M}_w/\bar{M}_n$

≈ 6.9. All experiments using PNIPAAM were done with sample R2A.

Sample Preparation. Samples for cloud-point and micro-calorimetric measurements were prepared from 4.00 mg/mL stock solutions of PNIPAAM or PVME dissolved at room temperature in distilled water with 0.1% sodium azide as a bactericide. In each case, 0.2 mL of polymer stock solution was diluted to a total volume of 2.0 mL first with distilled water and then with methanol, keeping the order of addition consistent to avoid the hysteresis effects that have been reported in these systems.[12] If the polymer precipitated at room temperature, the sample was placed in the freezer until soluble. Samples were used the same day to avoid shifts in composition due to evaporation and were scanned only once to avoid ambiguities arising from slow redissolution.[13]

Measurements. Infrared spectra were obtained on films cast from chloroform on NaCl plates or as KBr pellets on a Perkin-Elmer 1320 infrared spectrophotometer. NMR spectra were obtained on a Varian XL-200 spectrometer. Gel permeation chromatography was performed with a Waters M45 solvent pump coupled to a R410 differential refractometer, four μstyragel columns (10⁶, 10⁵, 10⁴, and 10³ Å), and a Hewlett-Packard 3380A digital integrator. Degassed THF was eluted at 1.1 mL/min. Polystyrene standards (Polysciences) were used for calibration, and molecular weights are estimated as those of polystyrenes of equivalent elution volume. PNIPAAM samples were injected at 5 mg/mL and data analyzed with Basic programs on a Macintosh SE computer.

Optical density (OD) measurements were made at 500 nm on a Beckman DU-7 spectrophotometer with a water-jacketed cell holder coupled with a Lauda RM-6 circulating bath. Temperatures were manually ramped at rates of ca. 0.5 °C/min and monitored by a Fisher electronic thermometer. Cloud points were taken as the initial break points in the resulting optical density versus temperature curves and were independent of small fluctuations in the heating rate to within ±0.5 °C. Data points near and below 0 °C were obtained with a Lauda k-4/RD bath and an Omega 450-ATH thermistor thermometer.

Calorimetric (DSC) scans were obtained on a Microcal, Inc., MC-1 scanning microcalorimeter at a heating rate of 15 °C/h. Samples were degassed and transferred to the sample cell with a calibrated syringe. Polymer-free solutions of the same solvent composition were placed in the reference cell. Calibration was achieved by supplying a precisely known current to the reference cell of the calorimeter. Transition temperatures are accurate to within ±0.1 °C.

Phase diagrams were calculated on the UMASS Cyber 870 in Fortran V using the DI3000 plotting package.

Results and Discussion

Synthesis of PNIPAAM. The synthesis of PNIPAAM was accomplished in a buffered aqueous redox system initiated with ammonium persulfate and TEMED. A combination of dialysis and reprecipitation with chloroform–hexane was used to isolate a polymer sample (R2A) of reasonably high molecular weight ($\bar{M}_w$ = 160 000; $\bar{M}_n$ = 49 000; $\bar{M}_w/\bar{M}_n$ = 3.2). That partial fractionation occurred in this procedure is evident from the molecular weight and polydispersity of the polymer fraction (R2B) recovered from the filtrate; this fraction was characterized by $\bar{M}_w$ = 76 000, $\bar{M}_n$ = 11 000; $\bar{M}_w/\bar{M}_n$ = 6.9. This synthetic method is analogous to that used by Hirotsu to prepare PNIPAAM gels[3] and thus should serve to minimize any differences in chain microstructure between our work and theirs. Fraction R2A was used in all of the experiments described below. The importance of pH and ionic strength in aqueous redox polymerizations of PNIPAAM has been investigated;[14] we note here only that our attempt to synthesize PNIPAAM in an unbuffered medium led to very rapid polymerization and increased polydispersity.

Solution Properties of PVME and PNIPAAM. Cloud-Point Measurements. Several experimental techniques can be applied to the observation of critical solution temperatures.[15] Horne[11] demonstrated that cloud points
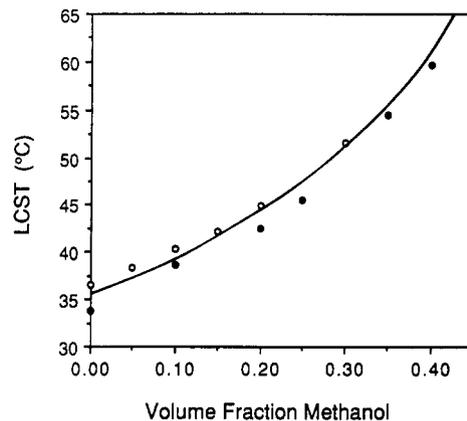
Figure 1. Phase diagram of PVME (0.40 mg/mL) in water–methanol mixtures. Filled symbols refer to cloud points and open symbols to calorimetric transition temperatures.
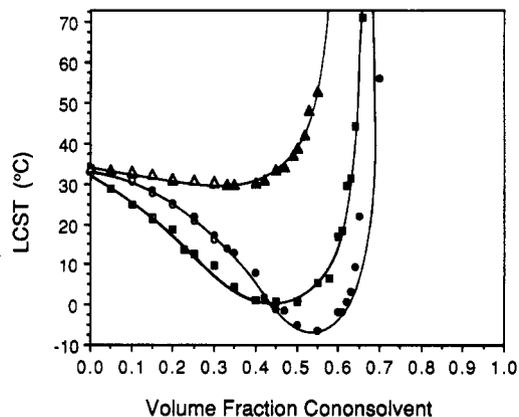
Figure 2. LCSTs of PNIPAAM (0.40 mg/mL) in water–cononsolvent mixtures. Filled symbols refer to cloud points and open symbols to calorimetric transition temperatures: (●, ○) methanol; (■, □) tetrahydrofuran; (▲, △) dioxane.

indicative of precipitation in PVME–water–methanol mixtures shifted to higher temperatures as the volume fraction of methanol increased. We have confirmed these results (Figure 1); both cloud-point and DSC measurements reveal a monotonic rise of ca. 25 °C in the LCST as the volume fraction of methanol is increased from 0 to 0.40. At higher methanol content the LCST exceeds the boiling point of the mixture.

One might expect a similar increase in the LCST of PNIPAAM in mixed aqueous solutions as methanol is substituted for water, since methanol is a better solvent for PNIPAAM based on light scattering,[16] viscometry,[17] and gel swelling experiments.[2] This is not observed, however (Figure 2); instead, there is an initial depression of the cloud point with the addition of methanol and then a sudden increase in solubility. Above a volume fraction of methanol of 0.66, the polymer does not precipitate below the boiling point of the mixture. These results are in excellent agreement with those reported by Winnik, Ringsdorf, and Venzmer.[18]

Thus, at room temperature, both methanol and water are solvents for PNIPAAM; yet the phase diagram shows that certain proportions result in immiscibility. This phenomenon has been termed "cononsolvency"[12,19,20] and is also observed, albeit in different degrees, in aqueous solutions of PNIPAAM with tetrahydrofuran (THF) or dioxane as the second solvent (Figure 2). Acetone has also been used as a cononsolvent to isolate PNIPAAM via precipitation from aqueous solutions,[1] and our preliminary studies identify dimethyl sulfoxide (DMSO) and ethanol as cononsolvents as well.
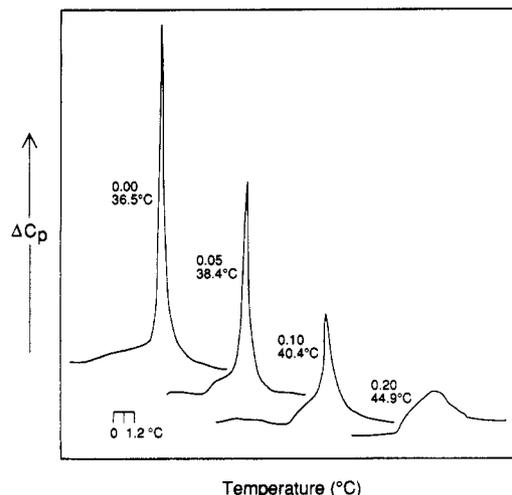
Figure 3. Microcalorimetric endotherms for aqueous PVME (0.40 mg/mL) solutions at various volume fractions of methanol. Figures adjacent to each endotherm give volume fraction of methanol (top) and temperature at maximum ΔC_p (bottom).
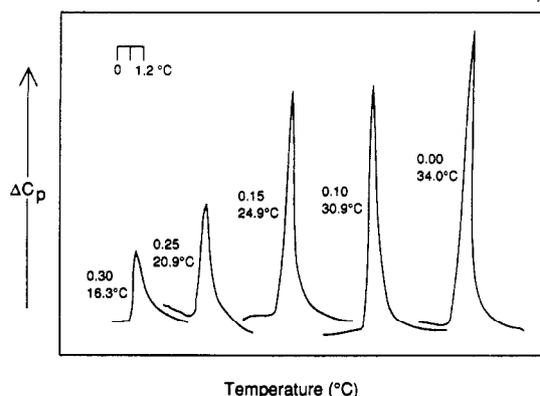
Figure 4. Microcalorimetric endotherms for aqueous PNIPAAM (0.40 mg/mL) solutions with added methanol. Figures adjacent to each endotherm give volume fraction of methanol (top) and temperature at maximum ΔC_p (bottom).
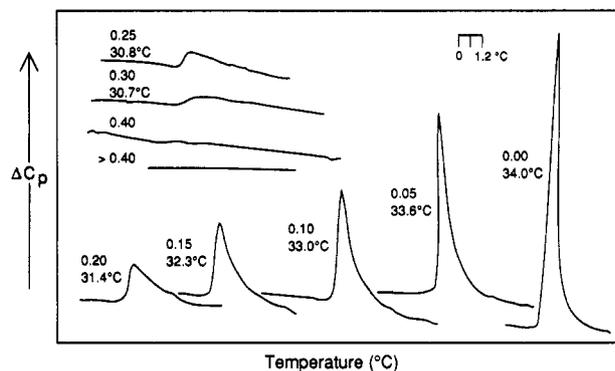
Figure 5. Microcalorimetric endotherms for aqueous PNIPAAM (0.40 mg/mL) solutions with added dioxane. Figures adjacent to each endotherm give volume fraction of dioxane (top) and temperature at maximum ΔC_p (bottom).

Microcalorimetry. Plotted in Figures 3–5 are the endothermic transitions observed upon heating aqueous PVME and PNIPAAM solutions in the differential scanning microcalorimeter. Transition temperatures determined calorimetrically agree quantitatively with the cloud-point temperatures. Interestingly, similar trends in peak shapes appear for PNIPAAM and PVME despite contrasting transition temperature trends. Heskins and Guillet[13] have attributed the PNIPAAM endotherm to the heat required to break polymer–water hydrogen bonds,

a view that is supported by the transition enthalpy measured in water (ca. 1.5 kcal/mol of repeating units).[21] Our results show that, as the volume fraction of the cononsolvent increases, the calorimetric enthalpy of the LCST endotherm decreases. This is shown most clearly in PNIPAAM–dioxane mixtures (Figure 5) where the range of measurement is not limited by the fact that the calorimeter is very difficult to equilibrate at temperatures below 15 °C. These results suggest that the nonaqueous solvent reduces either the number or the strength of polymer–water contacts. Preferential adsorption[22-24] of the nonaqueous solvent would result in a decrease transition enthalpy since the strength of hydrogen bonding of the polymer to the second solvent is likely to be lower than that to water.[25] Alternatively, water–alcohol complexation[23-24] might be expected to reduce the strength of favorable water–polymer interactions, even in the absence of preferential adsorption.

Ternary Solution Theory. The systems under study are ternary mixtures of two solvents (components 1 and 2) and a single polymer (component 3). Rather than reducing these systems to binary Flory–Humgins solutions by applying the single liquid approximation,[12,19,20] we adopt the approach of spinodal calculations on the extended ternary model[26,27] used successfully by Tompa,[28] Patterson,[29] and others.[30,31] The assumptions required to solve the complex binodal equations are avoided by exploiting the similarity of the binodal and spinodal curves. Solving the familiar expression for the free energy

$$\Delta G = RT(n_1 \ln v_1 + n_2 \ln v_2 + n_3 \ln v_3 + \chi_{12}n_1v_2 + \\ \chi_{13}n_1v_3 + \chi_{23}n_2v_3) \quad (1)$$

with the condition for the spinodal

$$(\delta\Delta G/\delta n_2\delta n_2)(\delta\Delta G/\delta n_3\delta n_3) = (\delta\Delta G/\delta n_2\delta n_3)^2 \quad (2)$$

the resulting equation can be plotted

$$v_1 + v_2 + m_1v_3 - 2(a + b)v_1v_2 - 2(b + c)m_1v_2v_3 - 2(a + \\ c)m_1v_1v_3 + 4(ab + ac + bc)m_1v_1v_2v_3 = 0 \quad (3)$$

where m_i is the degree of polymerization, n_i the mole fraction, and v_i the volume fraction of component i, and

$$2a = \chi_{12} + \chi_{13} - \chi_{23}$$

$$2b = \chi_{12} + \chi_{23} - \chi_{13}$$

$$2c = \chi_{13} + \chi_{23} - \chi_{12}$$

where χ_{rs} is the binary interaction parameter between components r and s. Let us denote water as component 1, methanol as component 2, and polymer as component 3. Why does cononsolvency occur with PNIPAAM and not with PVME? For both polymers, methanol is a good solvent at all temperatures below the boiling point since no binary critical solution temperatures are observed; thus, χ_{23} is always less than 0.50, the critical maximum value for polymer solubility. Since both polymers exhibit LCSTs in water, χ_{13} must be an increasing function of temperature, passing through 0.50 at the LCST. χ_{12} can be obtained from vapor–liquid equilibrium data;[32] calculated values vary from 1.10 to 1.70 depending upon composition and temperature. In the discussion that follows, we approximate χ_{12} as 1.60, averaging over its composition and temperature dependence; this approximation was not found to affect our conclusions. Thus we vary only χ_{13} with temperature for simplification. All of these χ's are composition dependent and probably perturbed from their
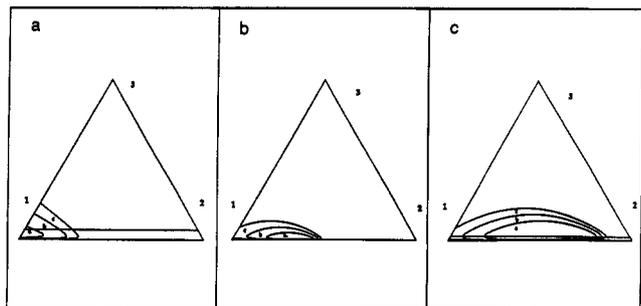
Figure 6. (a) Flory–Huggins ternary solution curves: m_1(water) = 1, m_2(methanol) = 1, m_3(PVME) = 1000. χ_{12} = 1.60; χ_{23} = 0.15; χ_{13} = 0.55 (a), 0.60 (b), 0.65 (c). χ_{13} > 0.50 is required for immiscibility. See equations in text for definition of terms. (b) Flory–Huggins ternary solution spinodal curves: m_1 = 1, m_2 = 1, m_3 = 1000. χ_{12} = 1.90; χ_{23} = 0.00; χ_{13} = 0.45 (a), 0.50 (b), 0.55 (c). Larger islands exist for increasing χ_{12} or χ_{13} and decreasing χ_{23}. (c) Flory–Huggins ternary solution spinodal curves: m_1(water) = 1, m_2(methanol) = 1, m_3(PNIPAAM) = 1000. χ_{12} = −0.50; χ_{23} = 0.45; χ_{13} = 0.45 (a), 0.50 (b), 0.55 (c). Larger islands exist for increasing χ_{13} or χ_{23} and decreasing χ_{12} (more negative).

values in binary solutions, but we apply these assumptions rather than incorporate additional parameters that would obscure the physical meaning of the treatment.[33-35]

Figure 6a illustrates the resulting phase diagrams calculated at constant temperatures for χ_{12} = 1.60. With this value of χ_{12} and χ_{23} <0.50, χ_{13} must be greater than 0.5 for immiscibility to be observed. Our experiments are a cross section at a constant and very low polymer concentration as shown by the horizontal line; thus, Figure 6a correctly reproduces the form of the phase diagram observed for PVME (Figure 1) since χ_{13} increases with increasing temperature.

By applying the Flory–Rehner equation to PNIPAAM gels, Hirotsu[2] has calculated χ_{23} (methanol as component 2, PNIPAAM as component 3) as a constant 0.45 and χ_{13} (water as component 1) as increasing from 0.45 to 0.55 as one heats to the temperature of the collapse transition (or, equivalently, the LCST, vide infra). As these are close to the values used to calculate the phase diagram in Figure 6a, it appears that peculiarities in χ_{12} cause cononsolvency in aqueous PNIPAAM mixtures. Wolf and Willms[12] conclude that cononsolvency occurs either when the two solvents are close to demixing (χ_{12} approaching +2) or when they complex between themselves (χ_{12} < 0).

Parts b and c of Figure 6 show that islands of immiscibility[12,15] characteristic of cononsolvency indeed appear when the absolute magnitude of χ_{12} is large. For positive χ_{12}, the islands grow (Figure 6b) upon increasing χ_{12} or χ_{13} or upon decreasing χ_{23}. One cannot create these islands with even higher positive values of χ_{12} if χ_{23} is fixed at the experimental value of 0.45 reported by Hirotsu[2] for PNIPAAM. On the other hand, with negative χ_{12} (Figure 6c), islands now increase in size with increasing χ_{23}, while still also increasing in size as the absolute magnitudes of the other two χ's increase. This then makes it possible to observe cononsolvency in PNIPAAM solutions with the known value[2] for χ_{23}. The resulting phase diagram lacks the critical-like point associated with the sudden increase in solubility, but the asymmetry observed in the experimental phase diagram is predicted.

Our calculations thus seem to support the suggestion by Tanaka[22] that the sign of the excess free energy between methanol and water must be negative in PNIPAAM solutions. One concludes from this treatment that the driving force for cononsolvency is the preference of water to complex with methanol rather than with PNIPAAM as reflected in the negative value of χ_{12} in PNIPAAM
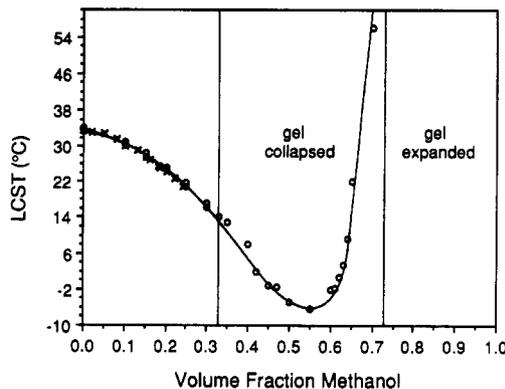
Figure 7. Phase diagram for PNIPAAM in water–methanol mixtures superimposed on Hirotsu's[3] gel collapse transitions. Composition ranges are shown where the gel is always collapsed or always expanded over the temperature range investigated: (O) cloud point; (●) DSC; (×) gel data.

solutions. We have grave reservations about this conclusion, as described below.[36]

Analogies with Gel Collapse Transitions. The phase diagram of PNIPAAM in aqueous methanol solutions is superimposed in Figure 7 on the data recently published by Hirotsu[3] for PNIPAAM gels. Hirotsu has reported collapse of PNIPAAM gels under conditions similar to those that induce precipitation of linear chains. The collapse temperaturs at low methanol concentrations extrapolated from his Figure 3 coincide with the LCSTs measured in this work, and the regions of gel collapse and expansion from his Figure 2 also are consistent with our observations; i.e., the linear polymer is always precipitated (volume fraction of methanol 0.33–0.72) or always in solution (volume fraction of methanol >0.72) within the temperature range investigated by Hirotsu. The reentrance of the gel is more gradual and occurs at a higher volume fraction of methanol than that of the single chain, in agreement with our finding that the critical volume fraction of methanol increases with molecular weight.[37] Gel collapse has also been obtained upon addition of DMSO to aqueous PNIPAAM gels;[38] as mentioned earlier, we find DMSO to be a cononsolvent for linear PNIPAAM chains in water. Thus the two experimental systems (gels and solutions) afford strikingly similar observations despite a 200-fold difference in polymer concentration (0.04% in the present work vs ca. 8% in the experiments of Tanaka[22] and Hirotsu[3]).

It is this difference in concentrations that prompts the reservations noted above. It is difficult to imagine a mechanism by which a polymer present at a concentration of 0.04% can change the sign of the solvent–solvent interaction parameter, since this requires that a single chain segment modulate the interactions of ca. 5000 solvent molecules. In the gels of Tanaka[22] and Hirotsu,[3] with the polymer present at a concentration of 8%, modulation of χ_{12} is plausible, but one would not then expect χ_{12} (and thus the phase diagram) to be insensitive to a 200-fold reduction in the PNIPAAM concentration. The observed similarity in the behavior of solutions and gels thus argues for a mechanism that involves local polymer–solvent interactions, both in dilute solutions and in gels. A mechanism of this kind would require, in the Flory–Huggins formalism described above, that one or both of the polymer–solvent interaction parameters vary in a composition-dependent manner. Such a variation would be consistent with the composition-dependent transition enthalpies reported herein.

Conclusions

PNIPAAM exhibits cononsolvency in mixed aqueous solutions while PVME exhibits more typical behavior (i.e., elevation of the LCST) upon addition of a better solvent. As methanol is substituted for water, the LCST of PNIPAAM is first depressed and then suddenly elevated. A wide variety of water-miscible polar solvents elicit qualitatively similar behavior. Calculations based on Flory–Huggins solution theory suggest that cononsolvency results from perturbation of χ_{12} and that water–methanol complexes are preferred to PNIPAAM–water hydrogen bonds. A similar proposal has been offered by Tanaka[20] as a basis for the collapse of PNIPAAM gels in aqueous methanol. These conclusions are cast into doubt by the strikingly similar behavior of PNIPAAM solutions and gels. The observation that the phase behavior of PNIPAAM in water–methanol mixtures is insensitive to a 200-fold variation in polymer concentration suggests that the relevant interactions must arise from local contacts between polymer and solvent.

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Registry No. 1, 25189-55-3; PVME, 9003-09-2; THF, 109-99-9; water, 7732-18-5; methanol, 67-56-1; dioxane, 123-91-1.