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Communications to the Editor

Methanol–Water as a Co-nonsolvent System for Poly(*N*-isopropylacrylamide)

Cosolvency is a modestly rare phenomenon in which a mixture of two nonsolvents for a polymer forms a good solvent. For example, methanol and water are nonsolvents for poly(methyl methacrylate) (PMMA). There is, however, a range of mixtures of methanol and water that will dissolve PMMA.[1] Even fewer examples exist of the reverse situation, a polymer, very soluble in two pure solvents, which is insoluble in their mixture. We traced the first example to a 1923 publication by Mardles on cellulose acetate, which dissolved both in aniline and in glacial acetic acid but not in a mixture of the two solvents.[2] We happened upon a striking example of the phenomenon in the following way. We were puzzled by a procedure for the purification of poly(*N*-isopropylacrylamide) (PNIPAM) described by Schild and Tirrell.[3] They precipitated PNIPAM by pouring an aqueous solution of the polymer into an equal volume of methanol. This seemed very surprising, because PNIPAM is soluble in both pure solvents. We repeated the experiment, and, sure enough, the mixed solution turned turbid. The precipitated polymer could be redissolved by placing the sample in the freezer at −26 °C.

One of the special features of PNIPAM is its solubility in water as well as in a variety of polar organic liquids. In water, PNIPAM solutions are characterized by a lower critical solution temperature (LCST) at 32 °C: the polymer is soluble at room temperature, but the solution undergoes phase separation upon warming. The behavior described in the preceding paragraph suggested to us that the role of methanol addition to the aqueous solutions of PNIPAM is to lower the LCST. We report here the results of our investigation of this phenomenon.

Experimental Procedures. Water was deionized with a Millipore Milli-Q water purification system. Spectral grade methanol was used. PNIPAM ([η] 108 cm^3 g^{-1}, from THF solutions; M_v 1.7 × 10^6) was prepared by free-radical polymerization of *N*-isopropylacrylamide in *tert*-butyl alcohol.[4] Cloud points were determined by detection of the changes in turbidity of solutions heated at a constant rate (0.2 °C min^{-1}).[5] Turbidity was measured with a Hewlett-Packard 8480A diode array spectrometer. The temperature of the cell was controlled with a Hewlett-Packard 89100A temperature-control accessory consisting of a digitally controlled thermoelectrically heating and cooling cell holder with sample stirring and programmed temperature ramping capability. The temperature of the sample fluid was measured with a Teflon-coated probe immersed in the sample fluid. For measurements below 10 °C the cell holder was flushed with nitrogen to prevent moisture condensation on the cell. Solutions for cloud-point determinations were prepared by mixing solutions of PNIPAM (1.0 g L^{-1}) in water and in methanol. Volumes were measured with a micropipette, except in the case of the samples of 62.7, 63.6, and 64.4% v/v, for which the amounts were measured by weight, in order to ensure accuracy of the sample composition. Samples were stored below their LCST, either in a refrigerator (6 °C) or in a freezer (−26 °C) prior to measurements.

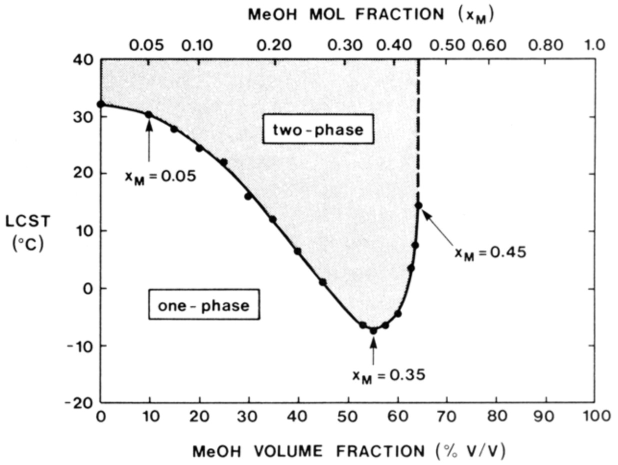

Figure 1. Phase diagram of poly(*N*-isopropylacrylamide) (1.0 g L^{-1}) as a function of solvent composition in methanol–water mixtures expressed in MeOH percent volume fraction (bottom axis) and in MeOH molar fraction (x_M, top axis).

Results and Discussion. The phase diagram of PNIPAM in water–methanol mixtures consists of four solvent composition ranges (Figure 1): (i) for methanol molar fractions (x_M) lower than 0.05, the LCST of PNIPAM is hardly affected; (ii) for $0.05 < x_M < 0.35$, the LCST decreases continuously from 31 °C to reach a minimum value of −7.5 °C; (iii) for $0.35 < x_M < 0.45$, the LCST increases sharply to reach a value of 14.5 °C;[6] (iv) for $x_M > 0.45$ (64.4% v/v), it is not possible anymore to detect a LCST. Solutions in this concentration range can be heated to 100 °C without showing any turbidity.

Methanol is a good solvent for PNIPAM. In this solvent the polymer behaves as a flexible coil, as indicated by a Mark–Houwink exponent of 0.64 (25 °C).[7] In pure water, on the other hand, the polymer is elongated and stiffer than in methanol.[8] Hydrogen bonding occurs between water molecules and the amide groups of the polymer, triggering the formation of a layer of highly organized water molecules around the polymer. Such polymer–water interactions contribute favorably to the free energy of mixing but unfavorably to the entropy of mixing. As the solution temperature is increased, polymer-bound water is released. The relative values of the thermodynamic functions change: the entropic term becomes dominant, resulting in a positive free energy of mixing; a two-phase system is favored.

The nature of solvent structure of methanol–water mixtures has been studied extensively over the past 50 years.[9] For solvent compositions of $x_M < 0.05$, the methanol molecules are kept apart from each other by the formation of hydration cages around each molecule.[10] Under these circumstances the polymer–solvent interactions are essentially undisturbed by the presence of methanol molecules. As the methanol mole fraction increases, there is no longer sufficient water to provide clathrate cavities for all the methanol molecules. These are now free to

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interact with polymer segments. Changes in LCST observed for $0.05 < x_M < 0.45$ reveal on a macroscopic scale the changes in the relative importance of the free energy of association in methanol–polymer, water–polymer, and methanol–water. In solutions of higher methanol content the methanol–polymer interactions become predominant.

The extreme sharpness of the change in LCST as a function of methanol content for $0.35 < x_M < 0.45$ is certainly surprising, and in the vicinity of $x_M = 0.45$ the LCST behavior simply vanishes. This is suggestive of a critical point in the phase diagram. This behavior, however, is consistent with reports by Amiya et al.[11] and by Hirotsu[12] on the behavior of cross-linked PNIPAM gels in mixed alcohol–water solvents. Such gels respond to changes in temperature or in solvent composition by reversible shrinking and swelling. For example, at 22 °C a PNIPAM gel containing 8 mM sodium acrylate is swollen for methanol compositions ranging from 0% to 30% v/v ($x_M = 0.16$).[11] At a methanol composition of 30% v/v the gel undergoes a discrete volume collapse by 10 times. The gel volume remains constant with further increase in methanol content up to 57% v/v ($x_M = 0.37$). At this concentration the gel "reswells discontinuously".[11] To account for the occurrence of the two transitions, Amiya et al. present a model that requires the free energy of the methanol–water interaction to become negative in a given methanol–water composition range. In the absence of polymer the interaction parameter between alcohol and water is always positive.[13] Addition of PNIPAM to water–methanol mixtures enhances the attractive interaction for water and methanol.

The decrease in LCST of aqueous PNIPAM solutions due to the addition of methanol is not limited to this solvent. It occurs also with ethanol, although the details of the phase diagrams are different for the two alcohols. The phenomena were also observed with derivatives of PNIPAM, such as those bearing fluorescent dyes and other hydrophobic groups. What is remarkable about this behavior is that it occurs in such dilute solution. It emphasizes, for example, that the behavior of PNIPAM gels arises from a molecular interaction of solvent and polymer and not from factors associated with cross-linking or the relatively high local concentration within the gel.

After submission of this paper, we were informed that the same phenomena have been studied independently by D. Tirrell and co-workers. Their work is the topic of a forthcoming publication.[14]

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