

Temperature-Responsive Polymers in Mixed Solvents: Competitive Hydrogen Bonds Cause Cononsolvency

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If two good solvents become poor for a polymer when mixed, the solvent pair is called a cononsolvent pair. The sharp reentrant coil-to-globule-to-coil transition of a poly(*N*-isopropylacrylamide) chain observed in the mixed solvent of water and methanol is shown to be caused by the competitive hydrogen bonding by water and methanol molecules onto the polymer chain. On the basis of a new statistical-mechanical model for competitive hydrogen bonds, the mean square end-to-end distance is theoretically calculated and compared with experiment. The chain sharply collapses at the molar fraction $x_m \approx 0.2$ of methanol, stays collapsed up to $x_m \approx 0.4$, and finally recovers the swollen state at $x_m \approx 0.6$. Such a reentrant coil-globule transition takes place because the total number of hydrogen bonds along the chain exhibits a similar square-well-type depression as a result of the competition.

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The behavior of poly(*N*-isopropylacrylamide) (PNIPAM) in aqueous media has attracted the interest of many researchers ever since it was first reported by Heskins and Guillet [1]. The polymer exhibits a well-defined lower critical solution temperature (LCST) in water [1–6], and each individual chain shows a very sharp coil-to-globule transition [7,8] when heated to 34.5 °C. Crosslinked PNIPAM gels undergo analogous collapse transitions in aqueous solvents [9]. The flat LCST cloud-point line with accompanying sharp change in polymer conformation results from a balance between hydrogen bonding of water onto the chain (hydration) and hydrophobic aggregation of isopropyl groups [2].

A PNIPAM chain also exhibits peculiar conformational changes in water upon addition of a second water-miscible solvent such as methanol, tetrahydrofuran, or dioxane. Although the second solvent is a good solvent for the polymer, the polymer chain collapses in certain compositions of the mixed solvent, followed by the eventual re-swelling under the majority of the second solvent [10]. The tendency for phase separation is also strongly enhanced by the presence of the second solvent. For instance, the LCST of aqueous PNIPAM solutions shifts to lower temperature when methanol is added [11–13]. The temperature drop is the largest, from 31.5 °C down to –7 °C, for a specific molar fraction $x_m = 0.35$ of methanol. This enhanced phase separation in mixed good solvents is known as *cononsolvency* [11]. Crosslinked PNIPAM gels are also known to collapse sharply in water in the presence of methanol, at around $x_m = 0.3$, and gradually recover their swollen state with increasing methanol content [14,15]. There have been efforts to understand cononsolvency by the combination of three χ parameters [11], and also by the formation of stoichiometric compounds between the sol-

vent molecules [10]. Without considering direct hydrogen bonds between polymer and solvents, however, it is difficult to explain the sharp LCST behavior.

To elucidate the origin of the high temperature sensitivity and flat LCST of PNIPAM, we have introduced recently the concept of *cooperative hydration* and constructed a theoretical model on the basis of this mechanism [16]. The cooperativity in hydration is caused by the positive correlation between neighboring bound water molecules as a consequence of the existence of large hydrophobic isopropyl side groups. If a water molecule succeeds in forming a hydrogen bond with an amido group on a chain, a second water molecule can form a bond more easily than the first one because the first molecule causes some displacement of the isopropyl group, which creates more access space for the next molecule. As a result, consecutive sequences of bound water appear along the chain, which leads to a pearl-necklace type chain conformation (Fig. 1) [16,17]. When the chain is heated up, each sequence is dehydrated as a whole, resulting in the sharp collapse of the chain. In this report, we extend our model of cooperative hydration, and apply it to a PNIPAM chain in a mixed solvent of water and methanol. We show that cononsolvency results from the competition in forming PNIPAM-water (*p-w*) hydrogen bonds and PNIPAM-methanol (*p-m*) hydrogen bonds (competitive adsorption), and that the competition becomes stronger with the cooperativity. Small differences in the composition of the mixed solvent are greatly amplified by cooperativity, and as a result, the composition of the bound molecules along the chain deviates substantially from that in the bulk (nonlinear amplification). The total coverage θ of the chain by bound molecules is not a monotonic function but passes through a minimum at the composition where the competition is

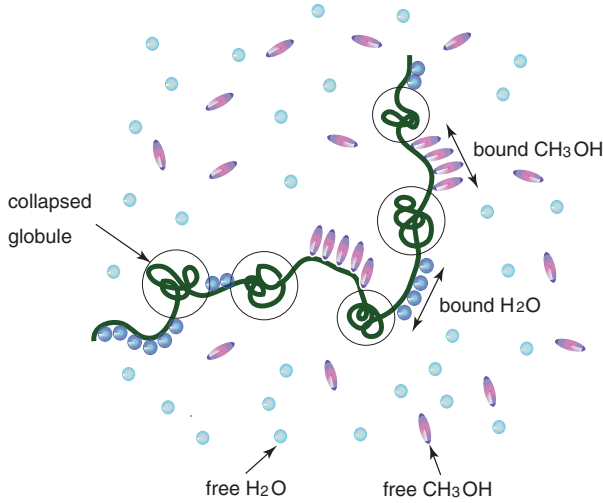


FIG. 1 (color). Competition between PNIPAM-water and PNIPAM-methanol hydrogen bonding. When there is strong cooperativity, continuous sequences of each species are exclusively formed along the chain. As a result, the chain takes a pearl-necklace conformation.

strongest. Occurrence of such a minimum coverage in competitive adsorption is well known in the case of adsorption of two species onto a flat surface. Because the monomers without hydrogen bonds (free monomers) tend to aggregate by hydrophobic interaction, the composition of minimum coverage corresponds to the minimum radius of gyration, or mean square end-to-end distance, of the chain.

Let us first consider a PNIPAM chain in pure water. At room temperature, the polymer chain is hydrated by p - w hydrogen bonds. If there is positive correlation between neighboring bound waters, contiguous sequences of bound waters are formed and distributed along the polymer chain [16]. Let $j_{\zeta}^{(w)}$ be the number of such hydrated sequences of length ζ (in terms of the number of water molecules) along the chain (see Fig. 1). These sequences are randomly selected from the finite total length, or degree of polymerization (DP) n of the chain. Let the binding free energy of the first bound water be $-\epsilon$. The second bound water and the following ones each gain the additional energy $-\Delta\epsilon$ when they are adsorbed at a position next to a bound water. The statistical weight of the sequence is then given by the form $\eta_{\zeta}^{(w)} = \sigma_w s_w(T)^{\zeta}$, where $\sigma_w \equiv \exp(-\Delta\epsilon/k_B T)$ appears from the boundary between a free monomer and a bound one, and $s_w(T) \equiv \exp[(\epsilon + \Delta\epsilon)/k_B T]$ is the association constant. This type of statistical weight was first introduced by Zimm and Bragg [18,19] (referred to as ZB) in the study of helix formation of biopolymers. The parameter σ is called *cooperativity parameter*.

We next consider addition of methanol. Methanol molecules are also hydrogen-bonded onto the chain by p - m bonds. The statistical weight of a sequence is similarly given by $\eta_{\zeta}^{(m)} = \sigma_m s_m(T)^{\zeta}$ by using cooperativity param-

eter and association constant for methanol. In order to take into consideration the difference in molecular size of the solvents, let p be the volume of methanol relative to that of water. It has a numerical value of 2–3. The number of different ways to choose such sequences from the finite total number n is then given by

$$\omega(\{j\}) = \frac{[n - \sum_{\zeta} \zeta j_{\zeta}^{(w)} + p \sum_{\zeta} \zeta j_{\zeta}^{(m)}]!}{\prod_{\zeta} (j_{\zeta}^{(w)}! j_{\zeta}^{(m)}!) [n - \sum_{\zeta} (\zeta + 1) j_{\zeta}^{(w)} - \sum_{\zeta} (p\zeta + 1) j_{\zeta}^{(m)}]!}. \quad (1)$$

We assume that the chain segments covered by bound water and methanol are swollen because both solvents are good, and the remaining free segments are collapsed by hydrophobic aggregation. By using this combinatorial factor in the sequence selection process, we find that the canonical partition function of a chain is given by

$$Z_n(n^{(w)}, n^{(m)}) = \sum_{\{j\}} \omega(\{j\}) \prod_{\zeta} [(\eta_{\zeta}^{(w)})^{j_{\zeta}^{(w)}} (\eta_{\zeta}^{(m)})^{j_{\zeta}^{(m)}}], \quad (2)$$

where $\eta_{\zeta}^{(\alpha)}$ is the statistical weight for a solvent α of length ζ , and $n^{(\alpha)} \equiv \sum_{\zeta \geq 1} \zeta j_{\zeta}^{(\alpha)}$ is the total number of adsorbed molecules of the solvent α . Such a combinatorial counting method in sequence selection process was introduced by Tanaka [20,21] to study helix formation of a polymer chain induced by hydrogen-bonding chiral molecules, and applied to their conformational change under tension. Since the solution is a particle reservoir, we introduce the activity λ_{α} of each type of solvent as independent variables (functions of the solvent composition), and move to the grand partition function

$$\Xi_n(\{\lambda\}) \equiv \sum_{n^{(w)}, n^{(m)}=0}^n \lambda_w^{n^{(w)}} \lambda_m^{n^{(m)}} Z_n(n^{(w)}, n^{(m)}). \quad (3)$$

The most probable distribution function of sequences that maximizes this grand partition function (equivalent to minimizing the free energy) is then found by variational calculation to be $j_{\zeta}^{(w)}/n = (1 - \theta) \eta_{\zeta}^{(w)} t (\lambda_w t)^{\zeta}$ for water, and $j_{\zeta}^{(m)}/n = (1 - \theta) \eta_{\zeta}^{(m)} t (\lambda_m t)^{\zeta}$ for methanol. Here, $\theta = \theta^{(w)} + p\theta^{(m)}$ is the total coverage (number of monomers covered by bound molecules relative to the total DP) with $\theta^{(\alpha)} \equiv \sum_{\zeta \geq 1} \zeta j_{\zeta}^{(\alpha)}/n$ being the coverage by each solvent. Similarly, $\nu = \nu^{(w)} + \nu^{(m)}$ is the total number of sequences (relative to the total DP) with $\nu^{(\alpha)} \equiv \sum_{\zeta \geq 1} j_{\zeta}^{(\alpha)}/n$ being the number of sequences of each solvent. The parameter t is defined by $t \equiv 1 - \nu/(1 - \theta)$, and has the physical meaning of the probability that an arbitrarily chosen monomer belongs to a free part. The grand partition function is given by $\Xi_n(\{\lambda\}) = t^{-n}$.

To find t as a function of the activities, we now substitute the equilibrium distribution $j_{\zeta}^{(w)}$ and $j_{\zeta}^{(m)}$ into the definitions of θ and ν , and find $\theta^{(w)} = (1 - \theta) t \nu_1^{(w)} (\lambda_w t)$, and

$\nu^{(w)} = (1 - \theta)tV_0^{(w)}(\lambda_w t)$ for water, and $\theta^{(m)} = (1 - \theta)tV_1^{(m)}(\lambda_m t^p)$, and $\nu^{(w)} = (1 - \theta)tV_0^{(w)}(\lambda_w t^p)$ for methanol. Here, the functions V_k are defined by $V_k^{(\alpha)}(x) \equiv \sum_{\zeta=1}^{n^*} \zeta^k \eta_{\zeta}^{(\alpha)} x^{\zeta}$. The upper limit of the sum is $n^* = n$ for water, and $n^* = [n/p]$ for methanol, where $[k]$ means the maximum integer smaller than, or equal to, k .

By the definition of t , we find that it should satisfy the condition

$$\frac{t}{1-t} \{V_0^{(w)}(\lambda_w t) + V_0^{(m)}(\lambda_m t^p)\} = 1. \quad (4)$$

This is basically the same as the equation found by ZB, but here it is properly extended to describe competition in p - w and p - m hydrogen bonding. Upon substitution of the solution for t into θ , we find that the total coverage θ is given by

$$\theta = 1 - 1/\{1 + t[V_1^{(w)}(\lambda_w t) + pV_1^{(m)}(\lambda_m t^p)]\}. \quad (5)$$

The mean square average end-to-end distance of a chain can be calculated by the equation [21]

$$\begin{aligned} \langle R^2 \rangle / \langle R^2 \rangle_c &= 1 + [n^{1-2\nu_G} \kappa_w^2 \zeta_w^{2\nu_F-1}(\lambda_w t) - 1] \theta_w(\lambda_w t) \\ &+ p[n^{1-2\nu_G} \kappa_m^2 \zeta_m^{2\nu_F-1}(\lambda_m t^p) - 1] \theta_m(\lambda_m t^p), \end{aligned} \quad (6)$$

where $\langle R^2 \rangle_c^{1/2} \equiv an^{\nu_G}$ is the end-to-end distance in the collapsed state, which is regarded as the reference state, $\zeta^{2\nu_F-1}(x) \equiv V_{2\nu_F}(x)/V_1(x)$ are the weight-average sequence lengths for each solvent, and κ are the ratios of the expansion factor of a bound monomer to that of a free monomer. The index ν_F is Flory's exponent for the mean end-to-end distance of a hydrogen-bonded segment of length ζ , and is assumed to take Flory's value $3/5$ for a chain swollen by excluded-volume effect. The index ν_G is the exponent for the mean end-to-end distance of a collapsed chain, and takes the value $\nu_G = 1/3$ for closely packed globules [21]

If we employ the ZB form for the statistical weight η_{ζ} , the arguments of the V functions become the combined variable $\lambda_w s_w t$ for water and $\lambda_m s_m t^p$ for methanol. We assume that the solvent-solvent interaction is weak, compared to the solvent-polymer interaction, and neglect it. The mixed solvent is regarded as an ideal mixture [22]. Then the activity is proportional to the molar fraction of each component. We can write $\lambda_w s_w = \tilde{\lambda}_w(T)(1 - x_m)$ and $\lambda_m s_m = \tilde{\lambda}_m(T)x_m$, where $\tilde{\lambda}$ s are functions of the temperature only. In the following study, we fix the temperature, and hence $\tilde{\lambda}$ s are constants depending upon the strength of the hydrogen bonds. Figure 2 shows the expansion factor for the end-to-end distance $\alpha_R \equiv [\langle R^2 \rangle / \langle R^2 \rangle_0]^{1/2}$ (solid lines) and the total coverage θ (broken lines) plotted against the molar fraction x_m of methanol. Here, $\langle R^2 \rangle_0$ is the value in pure water. The calculation was done by assuming that all parameters are symmetric and with $p =$

1. The cooperativity parameter σ varies from curve to curve. We can clearly see that the coverage takes a minimum value at $x_m = 0.5$ (stoichiometric concentration) as a result of the competition, so that the end-to-end distance also takes minimum at $x_m = 0.5$. As cooperativity becomes stronger, the depression of the end-to-end distance becomes narrower and deeper. In a real mixture, the association constant and cooperativity parameter are different for water and methanol, so that we expect asymmetric behavior with respect to the molar fraction.

We first examine the effect of the ratio p of the solvent molecular volumes. With increase in p , while keeping the other parameters fixed, the composition at the minimum expansion factor in Fig. 2 slightly shifts toward the methanol axis, and recovery of the expansion factor become less complete. This effect is caused by the wasted hydrogen-bonding sites; the longer the adsorbed molecule, the more vacant gaps remain between the sequences. The effect is named ‘‘car parking effect’’ [23,24]. Longer cars waste more space along the curb when they are randomly parked on the road.

We next examine the effect of the association constant $\tilde{\lambda}_m$ for the hydrogen bond of methanol. For the curve of the cooperativity $\sigma = 0.001$ in Fig. 2, we consider now the region $\tilde{\lambda}_m = 1.0$ – 3.0 with the other parameters fixed at the same value. With decreasing $\tilde{\lambda}_m$, the composition at the minimum shifts from 0.4 to 0.7, and the minimum becomes deeper with a flatter bottom. Below $\tilde{\lambda}_m = 1.5$, in particular, the curves show a sharp collapse with very flat bottoms. The flat bottom seen in α_R and θ indicates that the hydrogen bonding is highly competitive. Figure 3 shows

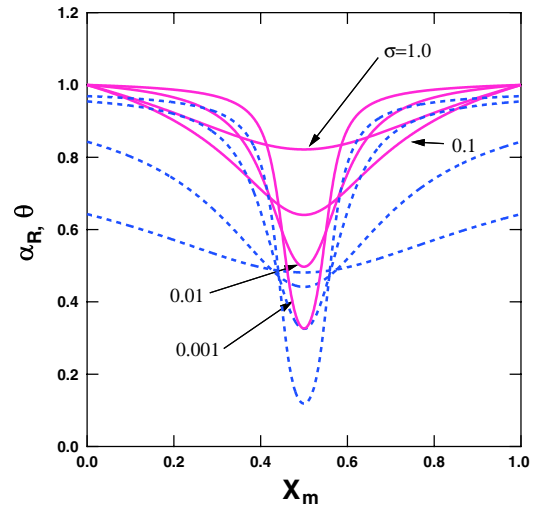


FIG. 2 (color online). The normalized end-to-end distance (solid lines) and the total coverage by bound molecules (broken lines) are plotted against the molar fraction of methanol. The DP of the polymer chain is fixed at $n = 100$. The volume ratio of the solvents is fixed at $p = 1$. The cooperativity parameter $\sigma_w = \sigma_m$ is varied from curve to curve. The association constants are fixed at $\tilde{\lambda}_w = \tilde{\lambda}_m = 1.8$. The monomer expansion factors are fixed at $\kappa_w = \kappa_m = 2.0$.

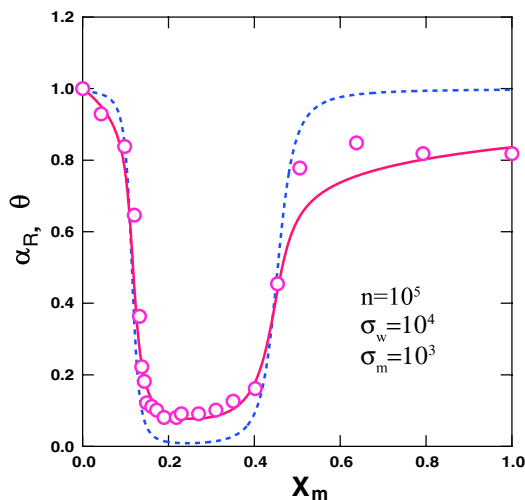


FIG. 3 (color online). Comparison between the present calculation (line) of the expansion factor for the mean square end-to-end distance for $n = 10^5$ and $p = 2$ and the experimental data of the radius of gyration by Zhang and Wu (circles) [10]. The total coverage is also plotted (broken line). The fitting parameters are $\tilde{\lambda}_w = 1.13$, $\tilde{\lambda}_m = 2.20$, $\kappa_w = 1.15$, $\kappa_m = 1.06$.

a comparison between the experimental mean radii of gyration (circles) obtained by laser light scattering measurements [10] and mean end-to-end distances obtained by theoretical calculations (solid line). Both are normalized by the reference value in pure water, so that they correspond to the expansion factor α_S for the radius of gyration and α_R for the end-to-end distance. They need not be identical, but are proportional to each other. Because the calculation of the radius of gyration of pearl-necklace conformation is not easy, we made such a comparison. The total coverage θ including bound water and bound methanol is also plotted (broken line). The molecular weight of the polymer used in the experiment is $M_w = 2.63 \times 10^7 \text{ g mol}^{-1}$, and hence we fixed $n = 10^5$. The volume ratio is set to be $p = 2$ from the molecular structure of methanol. For larger p , it turned out that the recovery of the expansion factor at high methanol composition was not sufficient. In order to have a sharp collapse at around $x_m \approx 0.17$ we had to fix the cooperativity as high as $\sigma_w = 10^{-4}$. Similarly, to produce the gradual recovery at around $x_m \approx 0.4$, we used $\sigma_m = 10^{-3}$.

In conclusion, we have successfully derived the detailed profile of the polymer expansion factor in the cononsolvent of mixed water and methanol as a function of the solvent composition on the basis of competitive hydrogen bonds. The existence of this p - w and p - m competition may be detectable experimentally by techniques such as Fourier-transformed infrared spectroscopy [25,26]. The concept of competitive hydrogen bonds can be directly applied to find the cloud-point curves of solutions, the volume change of cross-linked gels, etc., in the mixed solvents. Application to block copolymers with hydrogen bonding and nonbonding blocks will also lead to the development of new functional materials.

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