Reentrant Coil-to-Globule-to-Coil Transition of a Single Linear Homopolymer Chain in a Water/Methanol Mixture

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Both water and methanol are good solvents for poly(N-isopropylacrylamide) (PNIPAM) at room temperature, but strangely not a mixture of them. Using narrowly distributed linear PNIPAM chains ($M_w = 2.6 \times 10^7$ g/mol and $M_w/M_n < 1.1$), we have, for the first time, observed a coil-to-globule-to-coil transition of a single PNIPAM chain when methanol was gradually added into water. This novel reentrant transition leads to insight into the complexation between methanol and water. We also found that the chain was crumpled in its globule state and the globule still contained ~80% of solvent in its hydrodynamic volume.

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Poly(N-isopropylacrylamide) (PNIPAM) in solution and its related hydrogels are sensitive to environment [1], such as temperature, pH, ionic strength, and solvent composition. It has been shown that at room temperature PNIPAM hydrogels could undergo a swollen-shrunk-swollen process in water when dimethyl sulfoxide (DMSO) or methanol was added [2,3]. Linear PNIPAM chains have a similar soluble-precipitation-soluble property [4]. Note that both DMSO and methanol are good solvents for PNIPAM. Normally, a mixture of two poor solvents could result in a good one, but not the other way around. This strange behavior was qualitatively attributed to the perturbation of the solvent-solvent interaction parameter (χ_{12}) induced by PNIPAM [2,3] and a ternary complexation of water, methanol, and PNIPAM [4]. However, the results were far from conclusive because the inhomogeneity inside the gel and the interchain aggregation in the solution complicate the picture [5]. Therefore, it is necessary to study a single linear PNIPAM chain to simplify the problem.

It is known that a linear chain can exist in two distinct states: "coil" and "globule," respectively, in good and poor solvents. The transition between coil and globule has long been predicted [6–11] and investigated [12–16] because of its importance in many aspects [17–19], such as protein folding, DNA packing, and interchain complexation. In spite of numerous attempts, the observation of a thermodynamically stable single chain globule has been limited because the interchain association prior to the pure intrachain collapse often spoiled the experiment. Most of the past studies were conducted in a kinetic fashion (i.e., metastable) and the coil-to-globule transition was induced by temperature. Only a few studies touched the solvent-composition induced transition in a mixture of a good and a poor organic solvent [20].

On the basis of our previous studies of linear PNIPAM chains in pure water [21], we recently investigated the conformation change of a single ultralong PNIPAM chain with a contour length of ~60 μm in the mixture of water and methanol. The issues we intended to resolve were (1) whether a single linear polymer chain can collapse into a *stable* dense globule in a mixture of two good solvents, (2) what happens to the globule (if it could form) when more methanol is added into water, (3) how a long linear polymer chain is packed in the globule state, and (4) in which way methanol is complexed with water. The details are as follows.

The synthesis of PNIPAM was detailed before [21]. The resultant PNIPAM was fractionated by six successive dissolution/precipitation cycles at 25 °C in a mixture of extremely dried acetone and n-hexane. In each cycle, only the very first fraction was taken for the next cycle. The resultant PNIPAM sample had a weight average molar mass (M_w) of ~2×10^7 g/mol and contained a minor fraction ($M_w \sim 10^6$ g/mol). The sample was dissolved in water at 25 °C for ten days to ensure a complete dissolution. The solution was partially filtered through a 0.2 μm filter to remove the low molar mass fraction. The remaining solution was diluted to 5.0×10^{-7} g/ml which was further filtered through a 0.5 μm Milipore Millex-LCR filter to remove dust for laser light scattering (LLS) experiments. Such a combination of successive fractionation and filtration resulted in narrowly distributed high molar mass chains with $M_w = 2.6 \times 10^7$ g/mol and $M_w/M_n \sim 1.06$. The resistivity of deionized water used was 18.3 MΩ cm.

In static LLS [22], we were able to obtain both M_w and the z-average root-mean-square radius of gyration ($\langle R_g^2 \rangle^{1/2}$ or written as $\langle R_g \rangle$) of polymer chains in an extremely dilute solution from the angular dependence of the excess absolute scattering intensity, known as Rayleigh ratio $R_{vv}(q)$, where q is the scattering vector. In dynamic LLS [23], the cumulant analysis of the measured time correlation function $G^2(t)$ of nearly monodisperse PNIPAM chains resulted in an accurate average linewidth ($\langle \Gamma \rangle$) which can be converted to the average hydrodynamic radius $\langle R_h \rangle$. Our LLS instrumentation detailed before [21]

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has an exceptional small angle range down to 6°, which is vitally important for the study of the coil state of long linear polymer chains because a precise determination of M_w, $\langle R_g \rangle$, and $\langle R_h \rangle$ requires $q\langle R_g \rangle \ll 1$. The solution was so dilute that the extrapolation of $C \rightarrow 0$ was not necessary. The experimental temperature was 20.0 ± 0.1 °C.

Figure 1 shows the shrinking of the chains in the water/methanol mixture in terms of the slope (i.e., $\langle R_g \rangle$). The fact that the lines have the same intercept clearly indicates that M_w is independent of solvent, or, in other words, this is a true single chain process. We also found that for each given solvent composition, the scattering intensity was independent of the standing time; namely, the globules were stable, because the scattering intensity, which is proportional to the square of the molar mass, is very sensitive to the interchain aggregation.

Figure 2 clearly shows the collapse of the chain in the range of $x_{\text{methanol}} \sim 10\%-20\%$. Further addition of methanol in the range 20%–40% results in a slight swelling of the globule. The globule starts to melt (redissolve) at $x_{\text{methanol}} \sim 40\%$. Correspondingly, $\langle R_g \rangle$ first decreases more than 10 times from ~280 nm in pure water to ~26 nm in the mixture of $x_{\text{methanol}} \sim 17\%$ and then increases to ~230 nm when $x_{\text{methanol}} > 50\%$. Both $\langle R_g \rangle$ and $\langle R_h \rangle$ are independent of x_{methanol} in the range 50%–100%. It should be stated that no change of either $\langle R_g \rangle$ or $\langle R_h \rangle$ was observed even after the solution stood for a long time; namely, each point in Fig. 2 represents a thermodynamically stable value. Figure 2 also shows that during shrinking, $\langle R_h \rangle$ decreases slower than $\langle R_g \rangle$; while during melting, $\langle R_g \rangle$ increases much faster than $\langle R_h \rangle$. This is because $\langle R_g \rangle$ depends only on the chain density distribution in space, while $\langle R_h \rangle$, by its definition, is the hydrodynamic radius of a solid sphere that has the same translational diffusion coefficient as the polymer coil. For an extended polymer coil, R_h is much smaller than the physical dimension (R) in which the polymer coil reaches. As the polymer coil shrinks, more solvent molecules inside the coil move together with the coil so that the difference between R and R_h decreases because the decrease of R_h is slower than R.

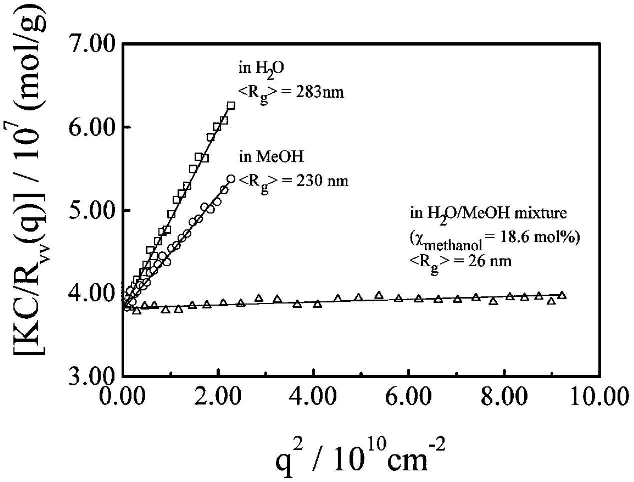

FIG. 1. Angular dependence of Rayleigh ratio $R_{vv}(q)$ for poly(N-isopropylacrylamide) in different solvents at 20.0 ± 0.1 °C, where K is a constant, $C = 5.0 \times 10^{-7}$ g/ml, and $q = (4\pi n/\lambda_0)\sin(\theta/2)$ with n, λ_0, and θ being the refractive index of the solvent, the laser wavelength in vacuum, and the scattering angle, respectively.

Figure 3 shows that $\langle \rho \rangle$ increases more than 100 times from 0.0016 g/cm^3 (coil) to 0.23 g/cm^3 (globule), indicating that each single PNIPAM chain globule, on average, still contains ~77% of solvent inside its hydrodynamic volume. The chain density of the globule is less than ~0.4 g/cm^3 predicted on the basis of a space-filling model [24], revealing that the chain is slightly swollen even in its globule state. On the other hand, we found that the "melting" or redissolving of the globule was extremely fast (less than 500 s) if x_{methanol} was suddenly increased from ~17% to ~50%. This implies that there exists no extensive chain knotting in the globule and the collapsed chain is in a crumpled state because it is known that it takes a few days to dissolve a solid PNIPAM sample (the chains are in the entanglement state) with a similar high molar mass.

Figure 4 shows a better view of this novel reentrant coil-to-globule-to-coil transition since $\langle R_g \rangle / \langle R_h \rangle$ directly reflects the chain conformation in solution. In pure water, $\langle R_g \rangle / \langle R_h \rangle \sim 1.5$, showing that the chain has a coil conformation. The decrease of $\langle R_g \rangle / \langle R_h \rangle$ from ~1.5 to ~0.7 clearly indicates the collapse of the chain because a uniform hard sphere has a value of $\langle R_g \rangle / \langle R_h \rangle = (3/5)^{1/2}$. It has been shown that before fully collapsing into a uniform dense globule, an extended coil chain first shrinks into a crumpled coil and then a molten globule characterized by a value of $\langle R_g \rangle / \langle R_h \rangle$ smaller than that of a uniform sphere [25]. The increase of $\langle R_g \rangle / \langle R_h \rangle$ from ~0.7 to ~1.35 in the range ~20%–50% clearly reveals the melting.

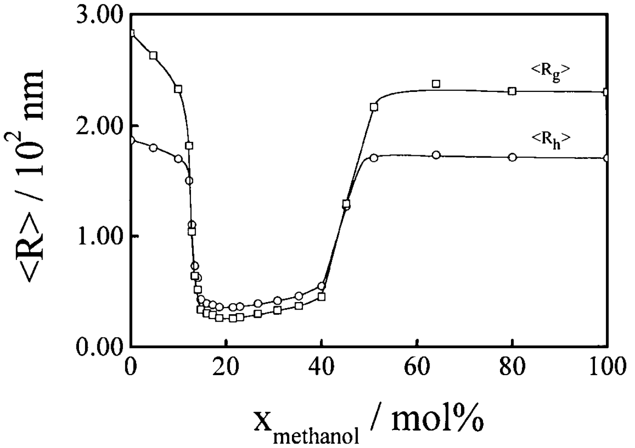

FIG. 2. Solvent-composition dependence of z-average root-mean-square radius of gyration ($\langle R_g \rangle$) and average hydrodynamic radius ($\langle R_h \rangle$) of poly(N-isopropylacrylamide) at 20.0 ± 0.1 °C.

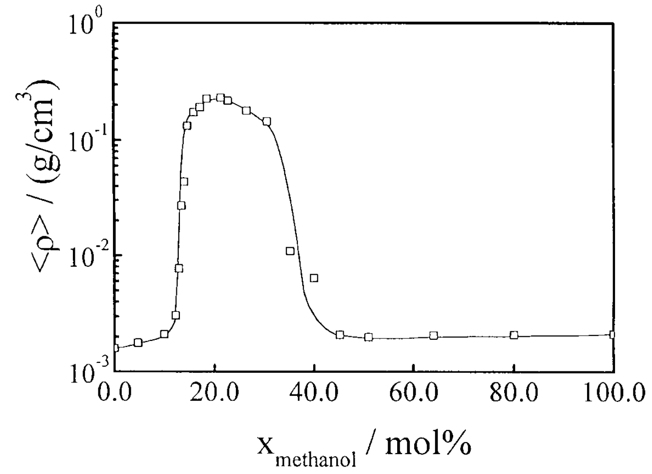

FIG. 3. Solvent-composition dependence of average chain density ($\langle\rho\rangle$) of a single poly(*N*-isopropylacrylamide) chain in its hydrodynamic volume at 20.0 ± 0.1 °C, where $\langle\rho\rangle$ is defined as $M_w/[(4/3)\pi\langle R_h\rangle^3]$.

We note that much attention has recently been paid to the complexation between water and methanol because they represent the pair of simplest molecules with hydrophobic and hydrophilic interaction and are completely miscible [26–32]. A number of possible compositions for the water/methanol complexes have been suggested. Recent evidence indicates that the complexes have two main compositions: $(CH_3OH)(H_2O)_5$ and $(CH_3OH)(H_2O)$, respectively, at low and high methanol content [33–35]. Note that in a dilute polymer solution, only a very small amount of solvent molecules are expected to directly interact with the polymer chain, while the rest just act as the "bulk" solvent.

Our result shows that when $x_{\text{methanol}} \sim 17\%$, i.e., $[CH_3OH]/[H_2O] \sim 5$, the chain collapses into a globule, suggesting that most of the water/methanol complexes do have a composition of $(CH_3OH)(H_2O)_5$. Further addition of methanol gradually changes the composition from $(CH_3OH)(H_2O)_5$ into $(CH_3OH)(H_2O)$ via different intermediate ones $(CH_3OH)(H_2O)_n$ with $1 < n < 5$. The collapse of the chain in the mixture of water and methanol indicates that the interaction between water and methanol is stronger than their interaction with PNIPAM. The water/methanol complexes have to be considered as new "compounds" and they are poor solvents for PNIPAM. This explains why there is nearly no change in $\langle R_g\rangle$ and $\langle R_h\rangle$ for the collapsed chain in the range ~20%–40%. At a higher methanol content, not all methanol molecules are able to complex with water so that free methanol molecules start to solvate the globule, leading to the increases of $\langle R_g\rangle$ and $\langle R_h\rangle$ in the range ~40%–50%. Note that $\langle R_g\rangle$ and $\langle R_h\rangle$ at $x_{\text{methanol}} \sim 50\%$ are similar to those in pure methanol, revealing that the chain is already fully swollen by methanol when x_{methanol} reaches ~50%. Methanol added in the range ~50%–100% simply stays in bulk.

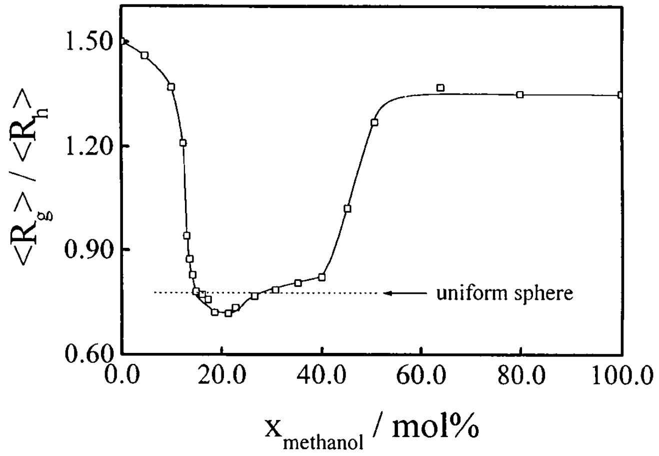

FIG. 4. Solvent-composition dependence of ratio of *z*-average root-mean-square radius of gyration ($\langle R_g\rangle$) to the average hydrodynamic radius ($\langle R_h\rangle$) of individual PNIPAM chains at 20.0 ± 0.1 °C.

In summary, this study clearly shows, for the first time, that a long flexible poly(*N*-isopropylacrylamide) homopolymer chain can collapse into a thermodynamically stable globule in a proper water/methanol mixture even pure water and pure methanol are good solvents for PNIPAM. The globule can redissolve or melt into coil if the methanol content is higher than ~50 mol %. In the globule state, the chain is crumpled and it still contains ~80% solvent in its hydrodynamic volume. This solvent-composition induced reentrant coil-to-globule-to-coil transition can be attributed to the formation of different water/methanol complexes which are poor solvents for PNIPAM. Our results indicate that as the methanol content increases, the composition of the complexes gradually changes from $(CH_3OH)(H_2O)_5$ to $(CH_3OH)(H_2O)$.

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