

Globule-to-Coil Transition of a Single Homopolymer Chain in Solution

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Using a nearly monodisperse high molar mass poly(*N*-isopropylacrylamide) (PNIPAM) sample, we successfully made the conformation change of individual PNIPAM chains from a coil to a fully collapsed stable single chain globule in an extremely dilute aqueous solution, which enabled us to study for the first time the globule-to-coil transition of a single homopolymer chain in solution. A comparison to the coil-to-globule and the globule-to-coil transitions revealed a hysteresis in the globule-to-coil transition. Our results also confirmed the existence of two additional thermodynamically stable states between the coil and the globule states, namely, the crumpled coil and the molten globule. [S0031-9007(98)05965-1]

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“Coil” and “globule” are two distinct and defined (in theory) thermodynamically stable states for a linear flexible homopolymer chain in solution. The transition from a coil to a globule has long been predicted if the solvent quality changes from good to poor [1–6]. Experimentally, the coil-to-globule transition has been extensively studied in the last 20 years [7–11], because it is a fundamental problem related to many phenomena, such as the folding of a protein chain [12], the packing of DNA molecules [13], the collapse of a gel network [14], and the complexation between two polymer chains [15]. In contrast, the opposite process (the globule-to-coil transition) has never been studied because the demixing of the solution (interchain aggregation) always happens before individual polymer chains have a chance to reach the fully collapsed thermodynamically stable single chain globule state, or, in other words, the starting point of the globule-to-coil transition has never been established for a homopolymer chain in solution in spite of numerous tries in the past.

Three years ago, we studied the coil-to-globule transition of poly(*N*-isopropylacrylamide) (PNIPAM) in water with limited success; namely, we observed the kinetically stable single chain globules in solution, but failed to reach the fully collapsed thermodynamically stable single chain globule state [16]. On the basis of our own results and other unsuccessful studies in various laboratories, we came to a point to question whether the fully collapsed single chain globule state is thermodynamically stable in solution, what the chain density in the globule state will be, and how the globule-to-coil transition is if we reverse the coil-to-globule process. Recently, we studied an extremely dilute PNIPAM aqueous solution and answered the questions. The details are as follows.

The synthesis of PNIPAM has been detailed before [16]. The resultant PNIPAM was carefully fractionated by precipitation from an extremely dried acetone solution to *n* hexane at room temperature. A fraction with a

weight average molar mass (M_w) of $\sim 1 \times 10^7$ g/mol and a polydispersity index (M_w/M_n) of ~ 1.3 was obtained. Using this high molar mass fraction, we prepared a dilute aqueous solution (2.50×10^{-5} g/mL). The solution was kept at room temperature for more than one week to ensure a complete dissolution before further dilution and filtration. The solution was clarified by a $0.5 \mu\text{m}$ Millipore Millex-LCR filter prior to laser light scattering (LLS) experiments. The combination of fractionation and filtration led to an extremely dilute solution (6.7×10^{-7} g/mL) containing nearly monodisperse [$M_w/M_n \sim 1.02$ estimated from the relative width of the linewidth distribution $G(\Gamma)$ measured in dynamic light scattering] high molar mass (1.3×10^7 g/mol) PNIPAM chains. The resistivity of deionized water used was $18.3 \text{ M}\Omega \text{ cm}$.

In static LLS [17], we were able to obtain both the weight-average molecular mass (M_w) and the average radius of gyration ($\langle R_g \rangle$) 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 $q = (4\pi n/\lambda_0) \sin(\theta/2)$, with n , λ_0 , and θ being the solvent refractive index, the wavelength of the light in vacuum, and the scattering angle, respectively. In dynamic LLS [18], the cumulant analysis of the measured intensity-intensity time correlation function $G^2(t)$ of a nearly monodisperse PNIPAM sample was sufficient for an accurate determination of the average linewidth ($\langle \Gamma \rangle$) which can be related to the average transitional diffusion coefficient ($\langle D \rangle$) and the average hydrodynamic radius ($\langle R_h \rangle$) by $\langle D \rangle = (\langle \Gamma \rangle / q^2)_{q \rightarrow 0}$ and $\langle R_h \rangle = k_B T / (6\pi \eta \langle D \rangle)$, with k_B , η , and T being the Boltzmann constant, solvent viscosity, and the absolute temperature, respectively. The hydrodynamic radius distribution $f(R_h)$ of the PNIPAM chains was calculated from the Laplace inversion of $G^2(t)$ by using the CONTIN program. The LLS instrumentation has been detailed before [16]. It should be stated that our LLS spectrometer has an exceptional small angle range down to 6° , which is vitally important for the

study of the coil state of the long 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.

Figure 1 clearly shows the shrinking of the chains when the temperature increased from 20.0 to 35.9 °C. The inset shows that the extrapolation of $KC/R_{vv}(q)$ to $q \rightarrow 0$ leads to the same intercept, indicating that the coil and the globule have the same molar mass; i.e., each globule is made of a single PNIPAM chain. Our results also indicate that the scattering intensity of the solution at $q \rightarrow 0$ is independent on the standing time; namely, the globules are stable at 35.9 °C because the scattering intensity is proportional to the square of the molar mass and very sensitive to the interchain aggregation. Moreover, the time independence of the hydrodynamic radius distribution in the globule state (\circ , $t = 0$; and \triangle , $t = 33$ h) also demonstrates that the PNIPAM globules in the solution are stable.

Figure 2 shows that when (1) $T > 35$ °C, the PNIPAM chains are fully collapsed because both $\langle R_g \rangle$ and $\langle R_h \rangle$ are independent on the temperature; and (2) at a given temperature in the transition range, the PNIPAM chains in the cooling process are smaller. It should be stated that no change of either $\langle R_g \rangle$ or $\langle R_h \rangle$ was observed even after the solution was kept at each measurement temperature for 10 h, or, in other words, every data

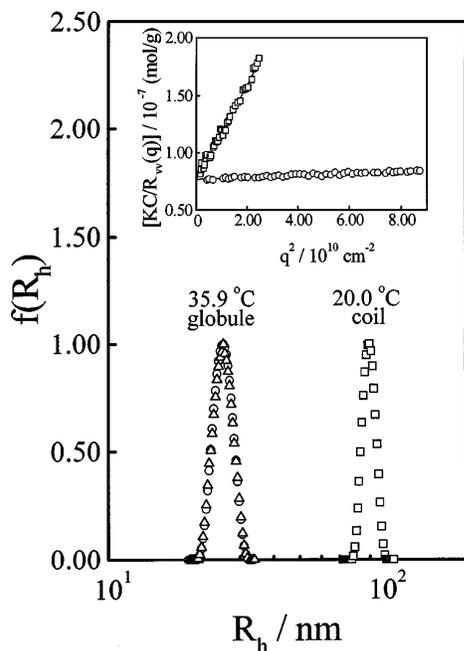


FIG. 1. Typical hydrodynamic radius distribution $f(R_h)$ of poly(*N*-isopropylacrylamide) chains in deionized water at two different temperatures, where polymer concentration is 6.7×10^{-7} g/mL. At 35.9 °C, \circ represents $f(R_h)$ just after the temperature reached equilibrium; and \triangle after ~ 33 h. The inset shows the angular dependence of the Rayleigh ratio $[R_{vv}(q)]$ of the polymer chains, respectively, in the coil (\square) and globule (\circ) states.

point in Fig. 2 represents a stable value. The hysteresis indicates that the coil-to-globule transition of individual PNIPAM chains involves the formation of intrachain structures in the globule state, presumably the intrachain hydrogen bonding, and these intrachain structures persist in the globule-to-coil transition.

The average chain density $\langle \rho \rangle$ estimated from $M_w/[N_A(\frac{4}{3})\pi\langle R_h \rangle^3]$ increases from 0.0025 g/cm³ (coil) to 0.34 g/cm³ (globule), close to ~ 0.4 g/cm³ predicted on the basis of a space-filling model [19]. Therefore, each PNIPAM globule, on average, still contains $\sim 66\%$ water inside its hydrodynamic volume. Another interesting point is that, in the heating process, $\langle R_h \rangle$ approaches a constant only when $T > \sim 37$ °C, while, in the cooling process, $\langle R_h \rangle$ remains a constant value until $T < \sim 34.0$ °C, indicating that, in the coil-to-globule transition, each coil gradually collapses into a uniform globule, while, in the globule-to-coil transition, the melting of the globule is hindered by the intrachain structures formed in the globule state. Figure 2 also shows that $\langle R_g \rangle$ decreases much faster than $\langle R_h \rangle$ in the temperature range 30.6–32.4 °C. Considering the definition of $\langle R_g \rangle$ and $\langle R_h \rangle$, we know that the collapse of the chain starts from the center because $\langle R_g \rangle$ is more sensitive to the chain density distribution.

The difference between the coil-to-globule and globule-to-coil transitions can be better viewed in terms of $\langle R_g \rangle/\langle R_h \rangle$ (the inset in Fig. 2), because it reflects the chain conformation. In the temperature range 20–30.6 °C (the Θ temperature), both $\langle R_g \rangle$ and $\langle R_h \rangle$ decrease, but $\langle R_g \rangle/\langle R_h \rangle$ is nearly a constant (~ 1.50), revealing that the chains keep the coil conformation as long as $T < \Theta$. In the temperature range 30.6–32.4 °C, $\langle R_g \rangle/\langle R_h \rangle$ decreases dramatically from ~ 1.50 to ~ 0.56 , clearly indicating the

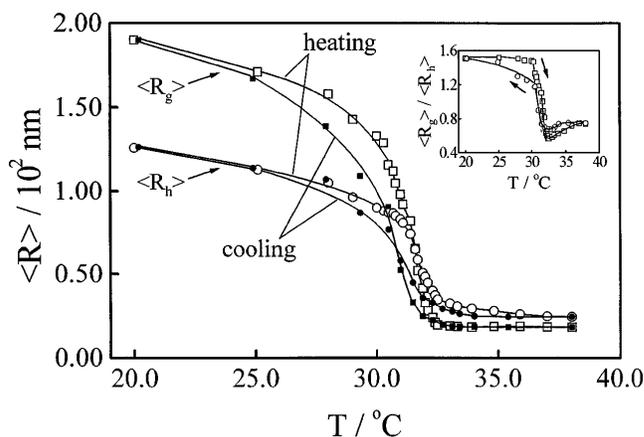


FIG. 2. Temperature dependence of the average radius of gyration $\langle R_g \rangle$ and the average hydrodynamic radius $\langle R_h \rangle$, respectively, in the coil-to-globule (heating) and the globule-to-coil (cooling) processes, where each point was obtained at least 2 h after the solution reached the thermal equilibrium to ensure that the polymer chains were thermodynamically stable. The inset shows the temperature dependence of $\langle R_g \rangle/\langle R_h \rangle$ in the heating and the cooling processes.

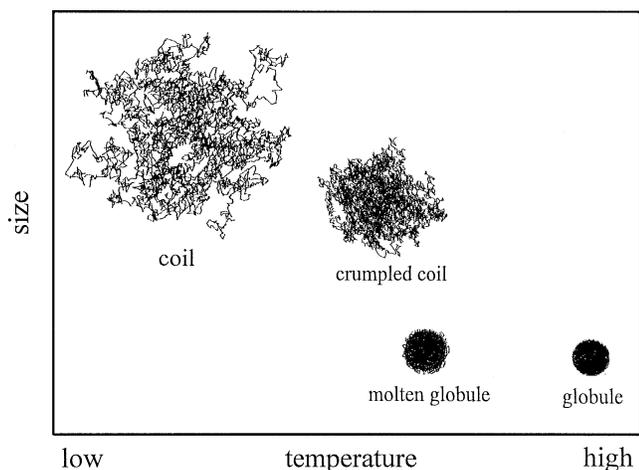


FIG. 3. Schematic of four thermodynamically stable states of a homopolymer chain in the coil-to-globule and the globule-to-coil transitions.

collapse of the PNIPAM chains. This temperature range can be roughly divided into the following two stages: One is from Θ to 31.6 °C at which $\langle R_g \rangle = \langle R_h \rangle$, and the other is from 31.6 to 32.4 °C at which $\langle R_g \rangle / \langle R_h \rangle$ reaches a minimum value of ~ 0.56 . The decrease of $\langle R_g \rangle / \langle R_h \rangle$ in the first stage reflects the conformation change from an extended random coil to a *crumpled* coil, while, in the second stage, the crumpled coil further collapses into a *molten* globule [20]. In the molten globule state, we speculate that each chain has already collapsed into a globule, but with a rough surface made of many small chain loops formed in the coil-to-globule transition. We can imagine that, on the one hand, these small loops are nondraining, which leads to a larger hydrodynamic size $\langle R_h \rangle$; and on the other hand, these small loops have a much less effect on $\langle R_g \rangle$. This is why $\langle R_g \rangle / \langle R_h \rangle$ could be smaller than $(\frac{3}{5})^{1/2}$ predicted for a uniform hard sphere. It can be imagined that stress is built up within these small loops when they become smaller and smaller, which slows down the shrinking of these small loops. This might explain why $\langle R_h \rangle$ decreases slightly, but there is no change in $\langle R_g \rangle$, when $T > 32.4$ °C.

Moreover, in the cooling process, $\langle R_g \rangle / \langle R_h \rangle$ reaches ~ 1.5 only after $T < 25$ °C, indicating that even water becomes a good solvent in the temperature range 25–30.6 °C, the globules are still not completely molten into the random coils, and the intrachain structures formed in the globule state persist in the globule-to-coil process until water becomes a very good solvent at lower temperatures. It can be seen that the decrease of $\langle R_g \rangle / \langle R_h \rangle$ at the left side of the minimum point is because $\langle R_g \rangle$ decreases faster than $\langle R_h \rangle$, while the increase of $\langle R_g \rangle / \langle R_h \rangle$ at the right side of the minimum point is due to the decrease of $\langle R_h \rangle$.

This study reveals that both the coil-to-globule and the globule-to-coil transitions of a single polymer chain involve four distinct thermodynamically stable states; namely, the *random coil*, the *crumpled coil*, the *molten*

globule, and the *fully collapsed globule*, schematically shown in Fig. 3. The first two states and the transition between them can be, respectively, described by the existing Flory and Birshtein-Pryamitsyn theories [21,22]. However, a quantitative description of the molten globule and the fully collapsed globule states still remains to be a challenge. We think that the deviation of the existing theories from the experimental results is, at least partially, because the molten globule and fully collapsed globule have different chain density distributions in comparison with the coils.

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