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Kinetic Study of Coil-to-Globule Transition

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The transition of a polymer chain from an extended coil to a collapsed compact state is of particular interest not only because of its direct applications in biological functions, such as, native DNA packing and protein folding, but also because of its fundamental role in our understanding on polymer segment–segment and segment–solvent interactions. The subject has been extensively studied both theoretically and experimentally.[1,2] In this laboratory, we have worked on this interesting problem since the late 1970s. A linear uncharged long homopolymer chain in a poor solvent, i.e., polystyrene (PS) in cyclohexane (CY), has been selected as the basic model system by many researchers and is the system of our choice. Measurements of both the radius of gyration (R_G) and the hydrodynamic radius (R_H) of a single polystyrene chain in cyclohexane have been performed by using laser light scattering.[1] The contraction of a PS chain has been observed at temperatures below the Θ temperature, and the behavior of the collapse was in good agreement with scaling theories. However, the *amount* of contraction, which could be represented by an expansion factor α ($=R(T)/R(\Theta)$ with $R(T)$ and $R(\Theta)$ being the polymer chain sizes at temperatures T and Θ, respectively), was only ≥ 0.7 under the best experimental conditions and was far from that of a totally collapsed state of a densely packed coil. So although we have reached a "globule" state based on scaling, we have certainly not reached an expansion factor sufficiently low to convince ourselves that we have truly achieved the *collapsed* state in the usual sense. For example, the packing of DNA molecules in bacteriophage heads demonstrates the accessibility of a highly compact state, which has been observed experimentally.[3] For the polystyrene/cyclohexane system, it appears that if we could not reach a value of α much less than 0.7 even with very narrow molecular weight distribution PS having a M_w of $\sim 50 \times 10^6$ g/mol and at a concentration of ~ 30 ng/mL under equilibrium conditions, we may perhaps observe the contraction under *kinetic* conditions.

The theoretical work on the kinetics of collapse of a polymer chain[4,5] proposed a two-stage contraction process, i.e., crumpled globule and spherical globule, after an abrupt decrease of temperature. However, to our knowledge, the two-stage collapse process has not yet been observed. Here, we present the first experimental observations on the kinetic behavior of collapse of a polymer chain.

Highly dilute solutions of polystyrene/cyclohexane (PS/CY) were used in the present study. The size change of a polymer chain was probed by means of dynamic light scattering (DLS) in terms of the hydrodynamic radius. Abrupt temperature changes were employed instead of very slow temperature decreases in the previous experiments; i.e., the polymer solution was quenched to a designated temperature from a temperature slightly higher than the Θ temperature. The time for the polymer solution to reach the new designated temperature was about 15–20 min in the light scattering spectrometer without stirring the polymer solution. With $\tau = 1 - T/\Theta$ the plateau regime in the master curve of $\alpha^3 \tau M_w^{1/2}$ vs $\tau M_w^{1/2}$ was first reached at the designated temperature T. Aggregation limits the range of observation of collapse of a single polymer chain. However, it is very interesting that a two-stage process has been observed at temperatures slightly lower than those temperatures at which the polymer solution is thermodynamically stable. After ~ 20 min for thermal equilibration of the entire polymer solution at the new designated temperature, the polymer chain reached a collapsed state whose behavior could be fitted to the master curve. Within a certain time period which was temperature and concentration dependent, the solution was stable and the contracted polymer chain size (essentially in the absence of polymer aggregates) remained the same. After that certain time period, polymer aggregation/contraction started. An interesting phenomenon was that, in addition to the observation of big aggregated particles, a smaller particle size had also been observed. The size of the smaller particles decreased with increasing time and then approached a relatively stable value for another time period while the size of the big aggregates continued to increase. Eventually, the scattered intensity of the polymer aggregates dominated the phenomenon. The expansion factor of the small particles in this time period approached the value of a completely collapsed dense coil in the presence of polymer aggregates. The following is a brief description of our experimental observation.

A high molecular weight, narrow molecular weight distribution polystyrene sample ($M_w = 8.60 \times 10^6$ and $M_w/M_n = 1.26$, characterized by ref 1) employed in the previous study was used here. In studying the coil-to-globule transition, it is well-known that polydispersity could prevent the polymer solution from reaching the globule state because of fractional precipitation. The solvent cyclohexane was distilled freshly. The solution preparation for DLS measurements was the same as that described previously.[1]

Figure 1 shows the hydrodynamic size distribution of polystyrene in cyclohexane at Θ temperature (35.0 °C) with $R_H \approx 61.0$ nm. A very small variance of 0.02 confirmed the small polydispersity of the polymer solution. The current characterization yielded $M_z/M_w = 1.08$ which was smaller than the previous characterization of 1.26. This discrepancy might be due to the difference in the details of sample preparation procedures since sample clarification could be a very important factor in DLS measurements.

Figure 2 shows a master curve of the scaled expansion factor of hydrodynamic size $\alpha_H^3 \tau M_w^{1/2}$ vs $\tau M_w^{1/2}$ where $\alpha_H = R_H(T)/R_H(\Theta)$. Hollow circles denote the results from ref 1, and filled symbols denote the current results. Temperatures are for when the polymer solution was thermodynamically stable, e.g., 31.0 and 29.5 °C, for a PS concentration of 9.60×10^{-6} g/mL. The hydrodynamic sizes were obtained after the sample was quenched to those temperatures after a 20-min waiting period. The sizes had no further time dependence for days (represented by filled squares). The filled triangle and the star denote the values from the kinetics of a two-stage collapse process.

For the polymer solution at $C = 9.60 \times 10^{-6}$ g/mL, the kinetics of collapse has been observed. Table I lists the time dependence of R_H when the polymer solution was quenched from 35.0 to 29.0 °C. Within a 1-h period after the polymer solution had reached thermal equilibrium, the polymer chain "collapsed" and the behavior could be described by scaling theories as indicated in Figure 2 where the scaled expansion factor followed the master curve. The polymer coil was stable in the contracted state for a time period of about 1 h! However, with a further increase

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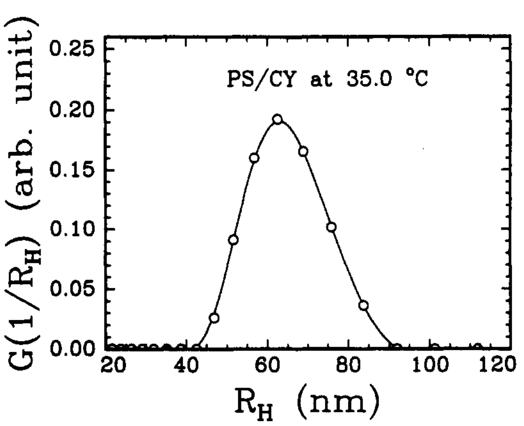

Figure 1. Typical hydrodynamic size distribution of polystyrene (M_w = 8.60 × 10^6 g/mol) in cyclohexane at a Θ temperature of 35.0 °C and a scattering angle of 33.0° from the CONTIN analysis. The concentration of the polymer solution was 9.60 × 10^{-6} g/mL.

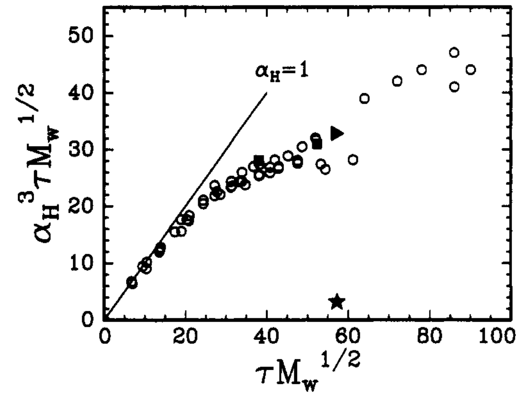

Figure 2. Plot of the master curve of $\alpha_H^3 \tau M_w^{1/2}$ vs $\tau M_w^{1/2}$. Hollow circles denote the results in ref 1. Filled symbols denote the present results. Filled squares are obtained from the thermodynamically stable solution. The filled triangle and star represent the results from the first and second stage of collapse, respectively, from kinetic studies at a quenched temperature of 29.0 °C.

Table I
Time Dependence of the Hydrodynamic Size of Polystyrene in Cyclohexane

time,[a] min	R_H,[b] nm	A[c]
56	50.2	1
65	50.8	1
75	51.1	1
85	52.6	1
110	52.4	0.83
150	38.8	0.25
160	32.9	0.16
185	32.0	0.14
195	18.0	0.10
200	28.9	0.11
230	19.1	0.17
235	27.1	0.11
260	21.0	0.17
270	25.3	0.11

[a] Time represents the time period starting from the time when the polymer solution at 35.0 °C was inserted to the thermostat at 29.0 °C. It takes about 20 min for the polymer solution in the light scattering cell to reach thermal equilibrium. [b] R_H represents the hydrodynamic radius from the CONTIN analysis of the intensity–intensity time correlation function. In the presence of aggregation, R_H was the size of the smaller particle in the bimodal distribution. $R_H \equiv \langle R_H \rangle_{sp}$. [c] A represents the area (intensity) ratio of single polymer chains to polymer aggregates in the normalized characteristic line-width distribution $G(1/R_H)$.

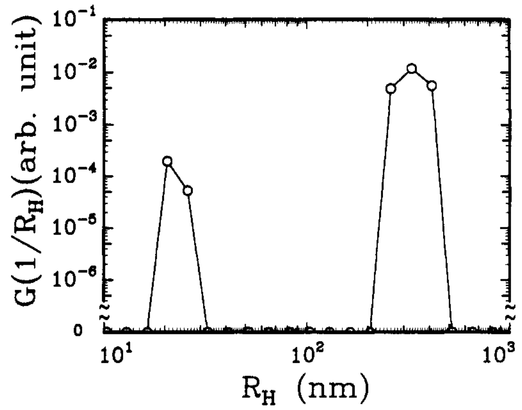

Figure 3. Typical hydrodynamic size distribution of polystyrene in cyclohexane during the second stage of collapse. The temperature was 29.0 °C, the concentration was 9.60 × 10^{-6} g/mL, and scattering angle was 33.0°. The measurement was performed after the sample had been brought to 29.0 °C for about 260 min.

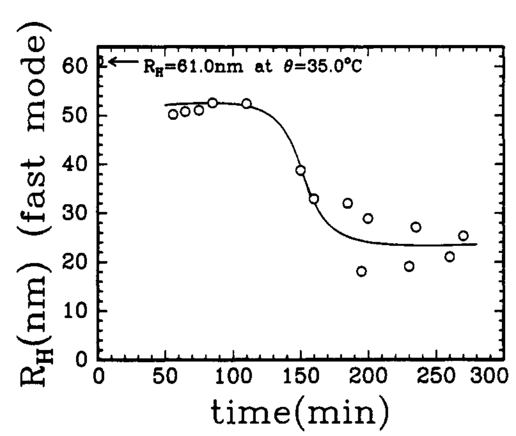

Figure 4. Time dependence of the hydrodynamic size of a single polystyrene chain in cyclohexane. The sample was quenched from 35.0 to 29.0 °C at C = 9.60 × 10^{-6} g/mL and scattering angle = 33.0°. The line is only for guiding the eyes.

in time, the aggregation effect among the higher molecular weight fractions of the polymer chains due to intermolecular interactions began to become observable. The intensity time correlation function was no longer near single exponential. Line-width distribution analysis of the intensity time correlation data from DLS by the CONTIN method[6] yielded a bimodal distribution at this stage. A typical particle hydrodynamic size distribution obtained from CONTIN is shown in Figure 3. After some more time, the intensity contribution from the larger particles became dominant (see the area ratio listed in Table I). While the larger size particles could be attributed easily to the aggregation of polymer chains, the fast motion might come from the internal motions of those aggregates where KR_g (aggregates) would exceed 1, with K being the scattering vector. To exclude the possibility of internal motion contributions, measurements at different K values were performed during the aggregation process. Similar bimodal *sizes* could be deduced using DLS measurements at different scattering angles. Thus the fast motion must come from the diffusion process of smaller particles. The size of the smaller particles (sp) decreased with time and reached a relatively stable value at time ~200 min. The size of the smaller particles remained basically constant over a time period from 200 to 270 min, i.e., $\langle R_H \rangle_{sp}$ = 23.2 ± 4.5 nm with an area ratio of about 13 ± 3%. The time dependence of the hydrodynamic size of the smaller particles is shown in Figure 4. The fluctuations in size were mainly due to the effect of a dominant intensity contribution from the aggregates in the data analysis. The expansion factors showed two plateau regimes in Figure 4 with 0.83 for the first stage, at which the single polymer chains contracted and obeyed the scaling concept, and 0.38 for the second stage, at which the single polymer chain collapsed further in the presence of aggregations. It should be noted that the reduced expansion factor at the first stage could be fitted to the master curve (see filled triangle in Figure 2) in this quenching experiment, but the polymer solution was not in the stable region.

A metastable collapsed regime has been observed in the previous study[1] for fairly broad high molecular weight polystyrene samples with polydispersity indices of M_w/M_n = 1.7–2.1. Considering the polydispersity and the fractional separation, the drop in the expansion factor from the master curve was speculated as due to the precipitation of high molecular weight polymer fractions, leaving only the lower molecular weight PS fractions in solution with a lower R_H. In the present study, the fractionation effect should also be considered. By examining the absolute excess scattered intensity, the ratio of the scattered intensity (I) of the polymer solution due to aggregates and single chains, we could estimate the amount of polymer fractions belonging to the original distribution at a time period of 4 h after thermal equilibrium. I(with aggregation) $\approx 4.3I$(stable single polymer chain). From the area ratio of the smaller particles to the large particles in the hydrodynamic size distribution, i.e., I(small) $\approx$ 13% I(with aggregation), the ratio of the intensity of the smaller particles to that of the original polymer chains was about 56%, i.e., I(small) = 13% × 4.3I(stable single chain) = 56% I(stable single chain). With about 56% single polymer chains left over in the presence of aggregation, M_w could not be much smaller than the original M_w. Therefore, some fractionation effect must be present due to aggregation, i.e., higher molecular weight polymers formed aggregates while lower molecular weight polymers were still in their single chain states. However, the fractionation effect could not be excessively large since 56% of the original fractions remained in the single polymer chain state. The estimated R_H from the smaller size particles at the second stage of collapse is displayed in Figure 2 (see filled star), which falls off remarkably from the master curve.

To summarize, the present *kinetic* observation of the collapse process suggests that the previously obtained collapsed state might be only the first stage of the collapse process. Further collapse was observed although at present it could be accomplished only in the presence of aggregation. The expansion factor from the further collapsed state dropped off sharply from the master curve. The two-stage collapse process was very *similar* to the kinetic theory of collapse of a polymer chain proposed by de Gennes and Grosberg et al.[4,5] However, we observed a clear transition time at around 150 min as shown in Figure 4. The sharp transition time was surprising. Its behavior could be expected to be more complex than the kinetic theories[4,5] could predict, because our experiments tried to strike a delicate balance between coil collapse at infinite dilution and phase separation at finite concentrations. Some of the time effects, especially those related to phase separation, could depend on polymer concentration, polydispersity, and the degree of quenching (i.e., the temperature distance from the coexistence curve into the metastable region). For example, Figure 4 shows that the hydrodynamic size of the small (unaggregated) particles (denoted by subscript sp) remained relatively constant between 200 and 270 min after quenching. This time period was arbitrary because of limitations of DLS measurements and of the CONTIN method of time correlation function data analysis. It should be emphasized that according to theory, after the crumpled globule is shrank to a spherical globule, the spherical polymer coil (at infinite dilution) remains stable in the one-phase region, while our experiments deal with the contraction of partially collapsed coils to highly condensed coils in the presence of polymer aggregates in the metastable region. Although the partially collapsed size was comparable to that under equilibrium conditions, the polystyrene/cyclohexane system already crossed the coexistence curve in our quenching experiment (denoted by a solid triangle and a solid star in Figure 2) and underwent a phase-separation process in the presence of coil collapse. Therefore, our kinetic times are more complex than $\tau_c \simeq \tau_R \Delta T/\Theta$,[4] with ΔT and τ_R being a temperature shift from Θ condition and the Rouse time of the Θ chain, respectively, and $\tau_s \ll \tau_c$, with τ_s being the relaxation time in the second stage. The estimated τ_s values[4] in the absence of phase separation were much faster than what we observed in the presence of phase separation for a nonmonodisperse sample at a finite concentration. We did not measure a corresponding τ_c because of the long temperature equilibration time of our experiments. Detailed experiments and comparison with theoretical predictions are under way. In particular, we hope to examine whether the first stage takes a very fast time $\sim N^2$ and leads to a crumpled globule[5] or "sausage",[4] with N being the chain links, while the second stage takes a slower and experimentally accessible time $\sim N^3$ and leads to a compact globule which is the completely collapsed state.

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