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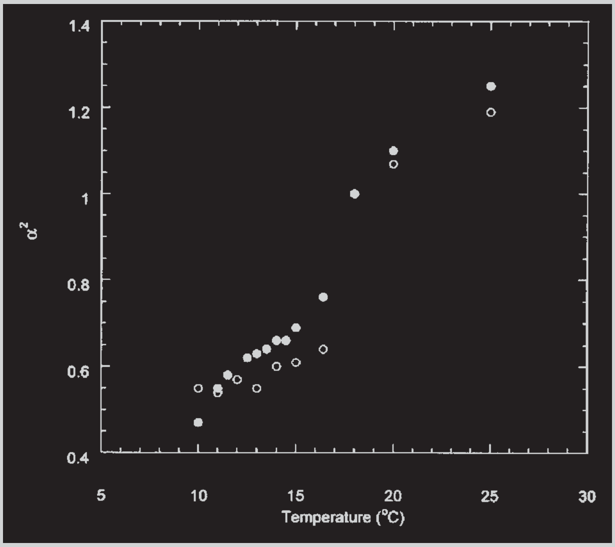
Macromolecular Theory and Simulations

Review: The transition of a solvated flexible macromolecular chain from random coil behavior in the θ-state to a globular compact form in the collapsed state has been the subject of extensive theoretical and experimental studies. Most of the coil-globule transition studies of macromolecules have concentrated on the prototypical polystyrene-cyclohexane system. However, chain contractions reported in this system have been around 75% of those in the unperturbed θ-state. This relatively small decrease in size does not satisfy the criterion for a densely packed, collapsed globule. Experimentally, the collapse from a coil to a true compact globular state has now been established for two flexible macromolecules: poly(*N*-isopropylacrylamide) in water and poly(methyl methacrylate) in various solvents. In this contribution, we review recent theoretical studies covering phenomenological and Langevin models as well as computer simulations. In addition, we outline recent experimental studies of the coil-globule transition of various flexible polymers, copolymers, and polyelectrolytes.



Expansion factor, α_h^2, versus temperature for NaPSS in 4.17 M aqueous NaCl solution. (●): NaPSS-1, (○): NaPSS-2.

Coil-Globule Collapse in Flexible Macromolecules

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Introduction

The transition of a flexible macromolecular chain from a random-coil conformation in the θ- state to a globular compact form in a collapsed state (before ultimate precipitation) has been the subject of extensive studies. This change in the state of a polymer chain from an open coil to a globular particle is called the coil-globule transition, and was first predicted by Stockmayer in 1960.[1] Williams et al.[2] summarized the contributions made by the end of 1970s; Fujita[3] and Des Cloizeaux and Jannink[4] presented further reviews on this subject in 1990.

The coil-globule transition of macromolecules provides a simple fundamental model for various phenomena. Besides its importance as a general and basic concept in polymer physics and solution dynamics, it has direct implications for many biological systems, such as protein folding, native DNA packing, and network collapse.

Theoretical Studies of Homopolymer Collapse

The thermodynamic and equilibrium properties of single chain collapse in a poor solvent have been studied in great detail. Mean-field self-consistent theories has been based on the classical equation proposed and developed by Flory.[5] Recently, the fundamental concepts and methods of statistical physics of macromolecular chains with volume interactions were formulated in detail by Grosberg and Khokhlov.[6] The statistical conformational properties of a single polymeric chain are discussed in this paper. In a poor solvent, a polymer chain is compressed and eventually forms a globule. It is predicted that the width of the

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coil-globule transition in an N-segment chain is proportional to $N^{-1/2}$ and tends to zero as $N \rightarrow \infty$; therefore, this transition can be treated as a phase transition.[6]

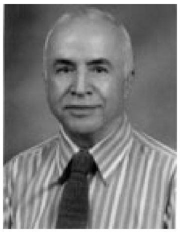
The character of the coil-globule transition essentially depends on the chain stiffness. For stiff chains, the transition is very sharp and close to a first-order phase transition; for flexible chains, it is rather smooth and resembles a second-order phase transition.[6,7]

The theory of the coil-globule transition in homopolymers has now been developed with quantitative accuracy. Theoretical studies have utilized a variety of approaches which focused on different aspects of the polymer collapse problem.[6,8]

Phenomenological Models

The kinetics of collapse were first considered by de Gennes in 1985.[9] The collapsing chain was viewed as a ''sausage'' of collapsed blobs. With further collapse, the diameter of the ''sausage'' increases and its length decreases. In this theory, the driving free energy is related to the interfacial free energy and the dissipation is attributed to hydrodynamic flow. A two-stage coil-to-globule transition is predicted: a rather fast crumpling of the unknotted polymer chain to a crumpled globule and a subsequent slow knotting or rearrangement of the thermal blobs of the collapsed polymer chain to a more compact globule. It was predicted that the characteristic collapse time (τ_c) should be proportional to N^2 (reminiscent of a Rouse relaxation time).[10] Furthermore, τ_c increases with ΔT, namely, larger quench depths yield a slower relaxation.

A somewhat mode free view was later proposed by Buguin, Brochard-Wyart, and de Gennes.[11] In this model, a polymer coil brought suddenly into poor solvent conditions by cooling should transform into a globular state in two steps: 1) the formation of ''pearls'' starting by the end of



Bahattin M. Baysal was born on December 8, 1922 in Kirsehir, Turkey. He studied Chemistry and Physics in the Faculty of Science at the University of Istanbul and received his B.Sc. degree in 1945. For his doctoral degree, Baysal went to Ankara and studied Physical Chemistry at the Faculty of Science under Professor Adolf G. Parts who had come to teach at the Ankara University from the University of Tartu, Estonia. Baysal received his D.Sc. in 1949. He became Dozent of University with his second thesis: Kinetics of Chain Reaction Polymerization (1952), which he prepared at the Polytechnic Institute of Brooklyn and Princeton University. Professor Baysal started his academic carrier at the Ankara University as an assistant in Physical Chemistry, and continued as Dozent from 1952 to 1960. He was appointed as Professor of Physical Chemistry at the Middle East Technical University (1960). For the next 15 years, he served as the Chairman of the Department of Chemistry and Dean of the Faculty of Sciences. In 1979, Baysal was appointed as professor at the Technical University of Istanbul and continued his work until his retirement, in 1990. In 1990, Baysal, moved to Bogazici University, Department of Chemical Engineering, a position he still holds. Baysal worked a considerable amount of years in various centers of USA: Polytechnic Institute of Brooklyn (1950–51), Princeton University (1951–52), (1970–71), Massachusetts Institute of Technology (1957–58), Brookhaven National Laboratory (1958–59), Dartmouth College (1965–66), (1986–87), University of Massachusetts (summer months, 1995–2002), and associated with the following prominent scientists: Prof. H. F. Mark, Prof. A. V. Tobolsky, Prof. C. D. Coryell, Prof. R. W. Dodson, W. H. Stockmayer, Prof. F. E. Karasz, Prof. M. Cvetkowska, Dr. D. Ballantine, Dr. G. Adler. Baysal has collaborated with about 200 scientists in Turkey, Europe and USA and in seven decades he published 250 scientific papers. 35 Ph.D. and 31 M.S. thesis were written under his supervision.

Karasz received his bachelor's degree in Chemistry from Imperial College, University of London, and his doctorate in Physical Chemistry from the University of Washington, Seattle. The University of London awarded him a D.Sc. in 1972. Professor Karasz has been at the University of Massachusetts since 1967, holding the rank of Distinguished University Professor since 1986 and Silvio 0. Conte Distinguished Professor of Polymer Science since 1992. He also served as Co-Director of the National Science Foundation-funded Materials Research Laboratory here from 1973 to 1985. Karasz has served on many committees, review and editorial boards, etc., and has received a number of international and national awards. These include the Mettler Award in Thermal Analysis (1972), the High Polymer Physics Prize (co-recipient) of the American Physical Society (1984), the Research Award of the Society of Plastics Engineers (1985) and the Herman F. Mark Medal of the Austrian Research Institute (2002). He was elected to the National Academy of Engineering in 1991 and is a member of three foreign engineering academies. Karasz has been active in many research areas in the physical chemistry of polymers and has received numerous research grants from government and private sources. He has authored or co-authored over five hundred and thirty scientific publications and several patents.

the chain and 2) a coalescence of the pearls. A tentative estimate for both times was proposed.

Recently, a phenomenological theory describing a self-similar, coarsening stage during the collapse of a long flexible homopolymer chain in dilute solution upon sudden quench has been presented by Klushin.[12] The approach is based on a ''necklace'' picture composed of clusters as demonstrated in computer simulations. In this model, the driving free energy is the transfer of free energy to the dense phase and dissipation is due to a Stokes drag force. The collapse is largely due to the decrease in randomly distributed chain segments.

The early stages of homopolymer collapse was studied by Halperin and Goldbart[8] using a phenomenological model for the kinetics following a quench from temperatures above to below the θ-temperature. As we have noted, the collapse of a flexible chain after an abrupt change in solvent quality displays certain features of a first-order phase transition. In this model, the onset of collapse first involves the formation of droplets of the dense ''phase''. Secondly, the collapse proceeds via intermediate states leading to a stretched, collapsed globule. The formation of droplets of the dense phase (pearls) is the faster process. The nascent droplets grow by accreting monomers from the bridges that connect them. Eventually, the droplets come into contact and coalesce into a single globule. The characteristic times of the ''pearling'', bridge-stretching, and the collapse of the pearl necklace are predicted to be proportional to $\sim N^0$, $\sim N^{1/5}$, and $\sim N^{6/5}$, respectively. The paper[8] also presented a detailed comparison of this treatment of the earlier phenomenological models.[9,11,12]

Langevin Models

Most theoretical studies have been based on calculations performed using the Langevin equation, which can provide a basic description of chain collapse in all stages of the process. A rigorous and complete solution of the relevant Langevin equation is difficult. Accordingly, all the Langevin-type theories introduce certain approximations to reach a mathematically tractable formalism. The treatments are mathematically demanding and often require numerical calculations. A detailed comparison with phenomenological theories is difficult because of the very different formulations.

The dynamics of equilibrium properties of polymers by means of a Gaussian self-consistent approximation have been studied by means of the Langevin equation.[13] The results of a simple power counting analysis of the equations yield exponent values, $v = 1/3$ for the Flory coil, $v = 1/2$ for the θ-point, and $v = 1/3$ for the collapsed globule phase. Timoshenko, Kuznetsov, and Dawson introduced approximations to the Langevin equation and studied the dynamics and kinetics at the collapse transition of homopolymers[14–16] and copolymers[16] in dilute solution.

Kuznetsov et al. have applied a Gaussian self-consistent method to the equilibrium and kinetic behavior of a stiff chain[17] and obtained an equilibrium phase diagram for stiff homopolymers. In this model, the collapse transition for a sufficiently flexible polymer is second-order. However, for higher stiffness chains it becomes first-order and leads to the formation of a toroidal globule. With the stronger two-body attraction, the torus can be transformed to a spherical globule via another first-order transition.[17] This treatment might be of importance as an intermediate stage in the development of more realistic statistical models for DNA and other stiff biopolymers. A number of limitations of this method have also been identified.[17] The same authors have extended the Gaussian self-consistent approach for multichain polymer systems and obtained information on the microstructure of the kinetic phenomena; they also predicted the existence of a long-lived, metastable state.[18]

The contraction kinetics of a moderately stiff chain after cooling below the θ-temperature was studied by Ganazzoli et al. using the appropriate Langevin equation. They predicted that the induction time scales as $\sim N^2$ and thus, may be very large for a high-molecular weight polymer.[19]

Recently, the kinetics of protein folding experiments have been analyzed using the idea that scaling laws can be formulated in analogy with the principles in polymer physics. The average activation barrier separating the low energy structures and the native state is predicted to scale as $N^{1/2}$, where N is the number of amino acid residues in the protein.[20]

Computer Simulations

In early computer simulations, polymethylene conformations were generated using fixed bond distances and bond angles, but allowing continuous variation of torsional angles.[21] The folding of this single isolated chains was examined with Monte Carlo simulated annealing. It was found that for long chains ($N > 64$), the random coil-globule transition is well-characterized in terms of a single-parameter mean field theory.[22] Lattice models lead to significant errors in the characterization of this system.[21]

Homopolymer collapse and earlier studies related to lattice simulations have been reviewed by Chan and Dill.[23] Major studies of the collapse of a chain leading to folding using molecular dynamic simulations have appeared during the last decade. In a molecular dynamic study of the crystallization of polyethylene, a two-stage collapse was observed: the chain first formed local collapsed domains, which then coalesced into a large lamella.[24]

Dawson et al.[25] studied the kinetics of homopolymer collapse by the Langevin equation simulation at infinite dilution for polymer chains of lengths up to $N = 1\,024$ units. The average cluster size and distribution, including radius of gyration, were used to characterize the collapse dynamics. It was shown that the overall collapse kinetics of the polymer have several underlying distinct mechanisms that result in different regimes. At the beginning of the conaction, a very rapid formation of small clusters occurs. This results in the straightening of sections of chain between the clusters. The second stage is cluster coarsening duringwhich time the average cluster size follows $\langle R_s \rangle = A \cdot t^z$, where $\langle R_s \rangle$ is the radius of gyration and z is a universal exponent, which is dependent on the third virial coefficient.[25]

Ma, Straub, and Shakhnovich studied the thermodynamic and kinetic properties of Lennard-Jones homopolymers and ring homopolymers by computer simulation of the polymeric chains at constant temperature, and during collapse following an abrupt temperature drop.[26] The homopolymer dynamics were simulated using both a Gaussian phase packet dynamic algorithm, which provides an approximate solution of the Liouville equation for the time-dependent classical density distribution, and conventional molecular dynamics. Simulation studies of the thermodynamic properties show the existence of a second-order, coil-globule phase transition.[26] It was predicted that the two-stage process and the structural properties of linear and ring homopolymers differ; the ring homopolymers exhibit only the features of a crumpled globule.[26]

Tanaka and Mattice performed an atomistic simulation of atactic poly(vinyl chloride) (PVC) chains in vacuum.[27] They found that an isolated PVC chain quickly folds into a compact, collapsed state for $N > 40$, but remains unperturbed for $\overline{DP} < 30$ (where N and $\overline{DP}$ represents the number of segments and degree of polymerization, respectively). During chain collapse, $\langle R_s \rangle$ and monomer clustering undergo two and three-stage processes, respectively. In the first stage, monomers nearest to each other stick together, and both the end-to-end distance and $\langle R_s \rangle$ sharply decrease. The shape of the chain changes from a thin wire to a ''sausage''. The second stage corresponds to the transformation from a sharp to a gradual decrease in $\langle R_s \rangle$. The third stage is characterized by the appearance of self-entanglement.[27]

Using a bond-fluctuation model, Wittkop, Kretmeier, and Göritz investigated the collapse transition of a single polymer chain in two and three dimensions.[28] In their Monte Carlo study, the obtained exponents, v, for the scaling law, $\langle R_s \rangle^2 \propto N^{2v}$, agree with values proposed in the literature cited above at and below the θ-temperature, T_θ ($v_\theta = 0.50 \pm 0.02$ in three dimensions).[29] The scaling function, $\alpha_s{}^3 \cdot \tau \cdot N^{1/2}$ versus $\tau \cdot N^{1/2}$, has a pronounced maximum before leveling off in the fully collapsed regime in accordance with the theory (Figure 1), where α_s and τ are defined as follows:

$$\alpha_s^2 = \langle R_s^2 \rangle / \langle R_s^2 \rangle_\theta \tag{1}$$

$$\tau = |(T - T_\theta)/T_\theta| \tag{2}$$

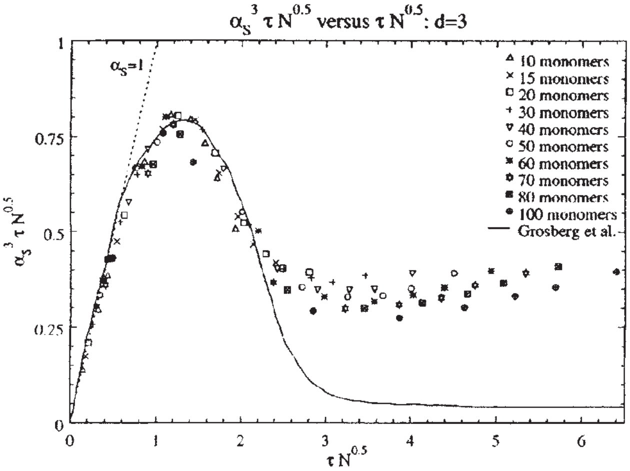


Figure 1. Plot of $\alpha_s^3 \cdot \tau \cdot N^{1/2}$ versus $\tau \cdot N^{1/2}$ (three dimension calculation) (ref.[28]), where α_s^2 were calculated by $\alpha_s^2 = \langle s_N^2 \rangle / \langle s_N^2 \rangle_\theta$. The points represent the simulated data and the solid line the theory of Grosberg end Kuznetsov (ref.[29]). The dotted line is given by $\alpha_s = 1$.

In this comprehensive investigation, the authors presented an exhaustive comparison of the behavior of several properties of the chains in two and three dimensions.[28] They also included a critical evaluation of earlier studies of polymer collapse, which are not retreated here.[28]

Other comprehensive simulations of θ-polymers in two and three dimensions have been published by Grassberger and Hegger[30,31] by using a new recursive sampling algorithm. These simulations extend far into regions of chain lengths and temperatures that have been inaccessible until now. It was found that collapse is very sudden for large N, but disagrees with the behavior at the θ-point with that predicted by field theory and observed in experiments.[31]

Ostrovsky and Bar-Yam reported polymer collapse under poor solvent conditions, so that monomers, which encounter each other, irreversibly adhere. The authors considered this adhesion to be the driving force for collapse.[32] They found that the polymer collapse in two and three dimensions appears to reduce to one dimension by driven diffusion of the polymer ends.[32]

Milchev and Binder studied time-dependent displacement of monomers and the center-of-gravity motion of a polymer chain below θ-temperatures by Monte Carlo simulations. The inner monomer displacements seem to diffuse according to a simple Rouse-like $t^{1/2}$ law,[10] but the center-of-gravity displacement shows anomalous diffusion.[33]

Gan and Eu studied solutions of the generalized Percus-Yevick integral equations for pair correlation functions in the case of a coiled, ideal, or collapsed state of the polymer.[34–36] The idea of universality of the power-law exponents for the expansion factors was tested by using hard-sphere, soft-sphere, and Lennard-Jones potential energy models. The necessity for more elaborate methods of solution for the integral equations, extending the chain length to a larger value to establish some of the limiting laws more firmly, are discussed.[36]

Computer simulations have been performed for a single polymer chain at different values of the chemical potential of the solvent, and a purely entropy-driven collapse in a lattice model of an athermal polymer in a hard-core solvent was obtained.[37] A phase diagram of the extended Potts model of the collapse of a two-dimensional, infinite branched polymer interacting with the solvent and with itself through contact interactions was studied.[38] The calculated results support the existence of a phase diagram with a single extended and a single compact phase.[38]

Liao and Jin recently carried out a molecular dynamic (MD) simulation and found segmental clusters during relaxation of a fully extended polyethylene chain at 300 K.[39] These simulations were performed in a study of the relaxation of fully extended polyethylene chains of 600–4 000 CH_2 units at room temperature up to 2 000 ps and provided a direct method to observe reentry-type chain folding. If a chain has more than 1 200 CH_2 units, the relaxation proceeds in three stages: subglobule formation, subglobule growth, and subglobule coalescence into one globule.[39] Because of a kinetic barrier, the number of subglobules is almost constant. This observation differs from the results based on Monte Carlo simulations of polymer collapse in dilute solution. The difference of lamella thickness between MD simulations and experiments was discussed.[39]

The phase transition behavior of a linear macromolecule treading through a membrane was studied, and an exact solution of an n-monomer was obtained for a three dimensional polymer problem, which displays a first-order thermodynamic phase transition, when $n \to \infty$.[40]

Models of polymer collapse in dilute solution have been explored since Flory[5] published his mean field theory of the θ-point in monodisperse solutions of a single polymer species. The θ-point was defined as the temperature below which the polymer is in a collapsed state. Configurations of polymers at high temperatures are dominated by excluded volume effects. The scaling of properties with the length of the polymer chain and the idea that the long length limit of polymers is a critical phenomenon was explored by de Gennes[41] and des Cloizeaux.[4]

A self-avoiding walk is a good model for a single macromolecule. As a subset of the self-avoiding walk concept, partially directed, self-avoiding walks (PDSAW) were introduced, and in the absence of monomer-monomer interactions, have been studied extensively and reviewed by Privman and Svrakic.[42] Later, an interacting PDSAWs (IPDSAV) model was introduced and studied by Owczarek, Prellberg, and Brak.[43–46] The existence of an analogue of the θ-point, at which the polymer collapses by undergoing a continuous transition, was shown. These authors extensively studied the mathematical properties and partition functions around the tricritical point in some models of polymer collapse.[43–46]

Owczarek and Prellberg conducted simulations of kinetic trails in four dimensions.[45–48] They proceeded from a kinetic growth model to a static model of self-interacting trials. They have shown the existence of a collapse temperature in four dimensions. The kinetic growth trails identified the collapse temperature correctly.[47] These authors also studied a canonical lattice model of polymer collapse by Monte Carlo simulations (ISAW) and indicated the collapse has many characteristics of a pseudo first-order transition.[48–50]

The behavior of a grafted polymer chain confined in a tube was studied by means of a scaling theory using biased Monte Carlo simulations. The results reinforce the ‘‘blob’’ picture. The collapse transition occurs within each blob independently. It was found that transition is a continuous phenomena, contrary to the case of a free, linear chain.[51]

Recently, a collapse transition of isolated Lennard-Jones (LJ) molecules was studied and exact results for a number of structural and thermodynamic equilibrium properties of flexible, short chains were reported.[52] The exact methods restrict this study to short chains ($N \le 5$); however, the results obtained are rigorous proof that a multi-stage collapse transition does occur for simple homopolymer systems. A bimodal, specific heat peak is found for certain chains of length $N = 5$, indicating a two-stage collapse process.[52]

In another simulation,[53] the internal structure of a polymer during collapse was studied. The collapse displays a process of fractal smoothing that first occurs at the shortest length scales. Along the contour, monomers have two bonds, their motion is more constrained, and aggregation is more difficult. Collapse is a one-dimensional process, where polymer ends accumulate mass by moving along the contour of the chain, while accreting monomers and small aggregates[53] as previously found in several models.

Polson and Zuckermann studied the equilibrium behavior and kinetics of a polymer collapse transition for a system composed of a short Lennard-Jones chain immersed in a LJ solvent for various solvent densities.[54] In these simulations, the relationship of the potential energy to the conformation size of the polymer chain depended on both the solvent density and the monomer solvent interaction parameter, λ. For a homopolymer of length $N = 20$, $\langle R_s^2 \rangle$ and the number of monomer-monomer contacts, n_{mm}, was plotted against the degree of hydrophobicity of λ at various solvent densities ($\rho = 0.6–0.9$). Calculations were carried out for flexible and semi-flexible chains. It was observed that a decrease in the size of homopolymer chain is observed with increasing λ, as evidenced by both the decrease in $\langle R_s^2 \rangle$ and the increase in n_{mm}. The contact number, n_{mm}, is noticeably different in flexible and semi-flexible chains. Increasing the density of solvent has a comparable degree of effect in decreasing R_s and increasing n_{mm} in the flexible and semi-flexible chain system.[54] The increase in the collapse times with increasing chain length is an expected result and is consistent with other simulation studies.[54]

Frisch and Verga presented a theoretical model for the unwinding of a globule under tension and compared it with numerical simulations. A very strong first-orderlike transition from a compact globule state to a stretched conformation was observed.[55]

Various experimental studies report a continuous transition from a coil to a globule for flexible polymer chains. A recent study carried out by Monte Carlo simulations of a semi-flexible chain showed that the ratio of the persistence length to the total chain length ($l_p \cdot N^{-1}$), is a key factor in predicting the coexistence of the coil and globule state.[56]

The collapse of a single, semi-flexible, or stiff polymer in solution was studied by a Brownian dynamics simulation in the presence of short range, attractive interactions. Contrary to the mechanism for flexible chains, it was shown that the collapse for semi-flexible chains occurs via a series of long-lived, metastable, dynamic intermediates.[57]

Recently, many experimental and theoretical studies have concentrated on the coil-globule transition of polymers in the presence of an amphiphile. Dawson et al.[58–60] in a detailed lattice-model Monte Carlo study of coil-globule and other conformational transitions of polymer amphiphiles and solvent, investigated the types of structures formed as a function of concentration, amphiphile strength, and the effect of solvent.

Experimental Studies on Homopolymer Collapse

Many coil-collapse experiments have been carried out using polystyrene solutions at extremely low concentrations. Various experimental methods, such as static and dynamic light scattering, small angle neutron scattering, and ultracentrifuge and viscometric measurements, have been used for the determination of polymer dimensions.

The temperature dependence of the expansion factor, α, can be obtained from the classical Flory equation for the excluded volume effect.[5] The contraction of the polymeric chain has been considered using both mean-field theories and newer approaches over a wide range of temperatures.[22,61,62] The applications of these theoretical equations to the expansion and contraction of a polystyrene chain have been discussed in several earlier publications.[63–67]

Birshtein and Pryamitsin postulated that the evaluation of the configurational entropy (and entropy force) of the coil-globule transition in earlier studies was based on an expression inapplicable to the chain contraction regime, but valid for the case of chain expansion.[68] Therefore, these authors carried out a rigorous calculation of the elastic entropy or the corresponding entropy force related to chain deformation. For the contracted coil ($\tau < 0$), they derived an equation for the expansion factor, α:

$$\alpha^3 - \alpha - C \cdot (\alpha^{-3} - 1) = B \cdot N^{1/2} \cdot \tau \tag{3}$$

where N represent the number of Kuhn segments in the chain, B and C are parameters that do not depend on molecular weight or the temperature, but rather on chain stiffness, $\tau = (T - \theta)/\theta$ is the reduced temperature; C is also related to by the third virial coefficient.[68] Equation (3) has a critical point below which the coil-globule transition becomes discontinuous.

For chain expansion ($\tau > 0$), a Flory type relation was obtained.[68]

$$\alpha^5 - \alpha^3 = (2/\pi^2)B \cdot N^{1/2} \cdot \tau \tag{4}$$

Two sets of contradictory experimental data for the contraction of polystyrene in cyclohexane have been reported in early studies:[64,65] one yielded a very sharp transition, whereas the other indicated a gradual contraction. Extensive static and dynamic light scattering studies carried out by Chu and co-workers have indicated that the previously observed, very sharp, coil-globule transition in polystyrene solutions can be ascribed to metastable states of the test solutions.[63–65] A typical example is the sharp, first-order contraction reported for a polystyrene ($MW = 27 \times 10^6$ Da) solution in cyclohexane at 34 °C by Tanaka et al.[61] A complete analysis of this work and the existence of metastable states in cyclohexane solution was given by Fujita.[69] The chain contraction reported for a polystyrene-cyclohexane system was only about 75% of that of the unperturbed θ-state.[63–67,69] Clearly, this small decrease in size does not satisfy the criterion for a densely packed, collapsed globule.

Because of the contradictory experimental data and limited contraction observed in the polystyrene-cyclohexane system, Baysal et al.[70] studied the collapse behavior of poly(*o*-chlorostyrene) and poly(*p*-chlorostyrene) in θ-solvents under poor solvent conditions by dynamic light scattering. Although values of contraction for these substituted polystyrene chains exceeded those reported for polystyrene in cyclohexane, they still do not give a satisfactory picture of single globule formation.

Phase Transition of Poly(N-isopropyl acrylamide) in Water Solutions

It has been shown by Tanaka and co-workers that polymer gels of poly(*N*-isopropyl acrylamide) (PNIPAM) exist in two states: a swollen and a collapsed phase.[71,72]

The single chain behavior of PNIPAM in aqueous solution has been studied by a number of authors. Fujishige and co-workers observed a decrease in the second virial coefficient with increasing temperature in aqueous solutions; this system exhibits lower critical solution temperature (LCST) behavior.[73] This is a characteristic property of non-ionic, water-soluble polymers arising from the combined effects of H-bonding and hydrophilic interactions.

Fujishige and co-workers[74,75] demonstrated, by means of dynamic and static light scattering, that on raising the temperature of very dilute PNIPAM aqueous solutions, an abrupt conformational change occurred, above the θ-point, around 32 °C, in which the conformation changed from a flexible and expanded coil at the lower temperature to a state of tightly packed globular particles at higher temperatures.

Wu and co-workers have studied the contraction of dilute aqueous solutions ($c \approx 5\ \mu g \cdot ml^{-1}$) of a narrow distribution, high molecular weight PNIPAM sample ($\overline{M}_w = 1.08 \times 10^7$ and $\overline{M}_w/\overline{M}_n < 1.06$) by using static and dynamic light scattering measurements over a temperature range ($20 < T < 33$ °C) around the θ-temperature (30.6 °C).[76–79] They observed a sharp contraction and globule formation at 32 °C. The average hydrodynamic radius, $\langle R_h \rangle$, was reduced to 54.1 nm at 31.82 °C from 112 nm at 19.90 °C. The reduced size of the globule appeared to be stable at 31.82 °C for a period of 3 d.[76] $\langle R_g \rangle$ values show a more dramatic decrease: when the temperature was varied from 20 to 33 °C; the PNIPAM chain dimension decreased eightfold from 160 to 20 nm.[77] A slow aggregation process was observed after the same PNIPAM solution was brought from 30.6 to 33.0 °C.[77,78]

Coil-Globule Transition Studies of Poly(methyl methacrylate) in Various Solvents

Nakata and co-workers observed that phase separation occurred very slowly for dilute solutions of poly(methyl methacrylate) (PMMA) in several solvents.[80–82] They studied the coil-globule transition of PMMA in a mixed solvent, water/*t*-butyl alcohol (*t*BA)[81] and in isoamyl acetate (IAA)[82] by static light scattering. The θ-temperatures of PMMA in water/*t*BA and in IAA were 41.5[81] and 61 °C,[82] respectively.

The coil-globule transition of PMMA was also studied in water/*t*BA and IAA by viscosity measurements[83] and dynamic light scattering.[84] Specification of the PMMA samples used in these coil-globule transition experiments is given in Table 1.

It is well-established that viscosity measurements performed on solutions under θ-conditions can yield information on the dimension of polymeric chains with the following relation:

$$[\eta] = [\eta]_\theta \cdot \alpha_\eta^3 \tag{5}$$

Table 1. PMMA samples used in coil-globule transition studies in various solvents.

Sample[a]	$[\eta]$[b] $dl \cdot g^{-1}$	$\overline{M}_w$ $g \cdot mol^{-1}$	$\overline{M}_w/\overline{M}_n$	Solvent[c]	ref.
PMMA-1		2.38×10^6	1.20	mixed	82
PMMA-2	6.12	2.57×10^6	1.35	mixed	83
PMMA-3	10.5	4.73×10^6	1.29	mixed	83
PMMA-4		4.44×10^6		IAA	82
PMMA-5		3.30×10^6	1.46	IAA	84
PMMA-6		6.47×10^6	1.40	IAA	143
PMMA-7		2.55×10^6	1.34	*n*-BC	87
PMMA-s[d]		1.18×10^6	1.36	*n*-BC	87

[a] PMMA: poly(methyl methacrylate).
[b] Intrinsic viscosity in chloroform at 25 °C.
[c] Mixed: *t*-butanol/water; IAA: isoamyl acetate; *n*-BC: *n*-butyl chloride.
[d] Syndiotactic PMMA.

where $[\eta]$ and $[\eta]_\theta$ represents the intrinsic viscosities in a good and in a θ-solvent, respectively. However, since the hydrodynamic radius of a polymer chain increases less rapidly than the statistical radius as the excluded volume increases, the expansion factors given in Equation (3)–(5) are not identical.[85] Several theoretical approaches exist to yield a relation between these expansion factors. For practical purposes, Baysal and Kayaman preferred to use the following exponential relation.[86]

$$\alpha_\eta^3 = \alpha^{2.43} \tag{6}$$

Figure 2 shows the experimental and theoretical values of the expansion factor α^2 for the coil-globule transition of PMMA in a mixed solvent.[83] Theoretical curves were calculated from Equation (3) for $T < \theta$ and Equation (4) for $T > \theta$. The α^2 values obtained from ref.[81] were included and are denoted by open diamond symbols. The crosses indicate coil-globule transition points. The transition studies of PMMA in this mixed solvent using three different experimental methods indicate that contraction of PMMA chains is a gradual, continuous process down to 15 °C.

A similar gradual contraction behavior using static[82] and dynamic[84] light scattering measurements was observed for PMMA in isoamyl acetate from the θ-temperature at 61 down to 0 °C (Figure 3).

Dynamic light scattering studies of atactic and syndiotactic PMMA in dilute *n*-butyl chloride (*n*BC) ($\theta = 38$ °C) solutions also indicated a continuous contraction up to the formation of single globule.[87]

To compare the observed behavior of the expansion factor, α, with the theoretical results (Equation (3)), the $(\alpha^3 - \alpha)/(1 - \alpha^{-3})$ values were plotted against $|\tau| \cdot N^{1/2}/(1 - \alpha^{-3})$ for $\alpha < 1$, see Figure 4.[84] The data points adequately fit the expected linear dependence. From the slope and the intercepts B and C values were evaluated for the PMMA-IAA system as well as the PMMA-*n*BC and PMMA-mixed solvent systems[81–84,87] and are given in Table 2. As noted, the parameters B and C, are independent of molecular weight, but dependent on the chain stiffness. As can be seen from Table 2, the C values are close to each other. On the

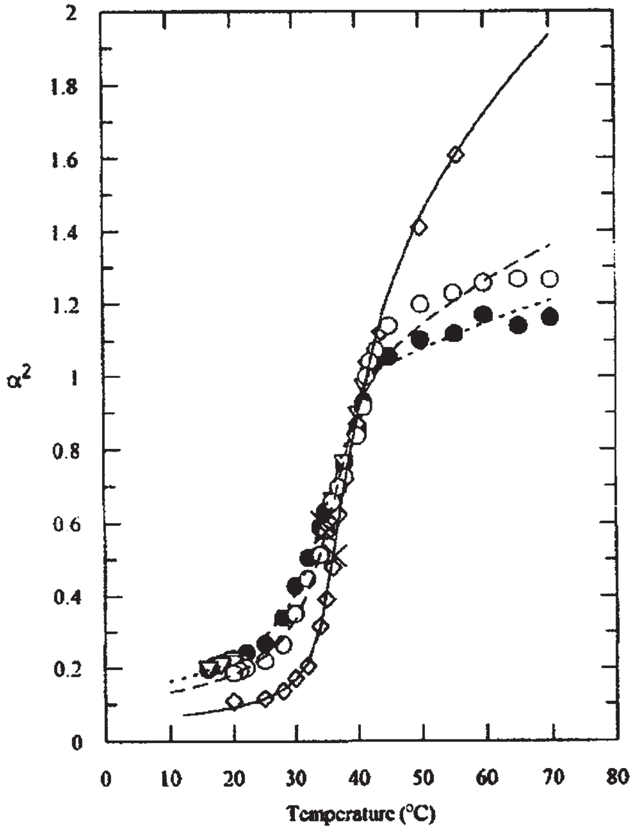


Figure 2. Plots of α^2 versus temperature for PMMA in *t*-butyl alcohol/water mixture, ref.[83]. Comparison of theoretical and experimental values of the expansion factor, α^2. Theoretical curves calculated from Equation (3) for $T < \theta$ and Equation (4) for $T > \theta$ denoted by broken lines. PMMA samples: (○): $\bar{M}_w = 4.73 \times 10^6$; (●): $\bar{M}_w = 2.55 \times 10^6$; (□): $\bar{M}_w = 2.55 \times 10^6$ "shock cooling experiments"; (△): $\bar{M}_w = 2.55 \times 10^6$ "repeat experiment with a new solution". For comparison, α^2 values from ref.[79] are included and denoted by open diamonds. For experimental points, the ordinate denotes $\alpha^2 = \alpha_\eta^{6/2.43}$ (see ref.[83]). The crosses indicate coil-globule transition points.

other hand, the values of *B* differ for the PMMA samples in different solvents. The observed differences are probably related to the effect of the finite size of solvent molecules on the second virial coefficient of the unit interaction in solution.[68]

The parameter *B* in Equation (4) was evaluated by plotting $(\alpha^5 - \alpha^3)$ against $N^{1/2} \cdot |\tau|$ for the expansion of PMMA chains ($\alpha > 1$) above the θ-temperature[83,84] The calculated *B* values are also shown in Table 2.

The temperature dependence of PMMA chain dimensions below the θ-temperatures shows similar behavior for the following three solvent systems: water/*t*BA,[81,83] *n*BC,[87] and IAA.[82,84] The transition in IAA occurs over a much wider temperature range. However, a gradual contraction of PMMA chains was observed and the chain size was reduced to about 40% of its θ-state dimensions.

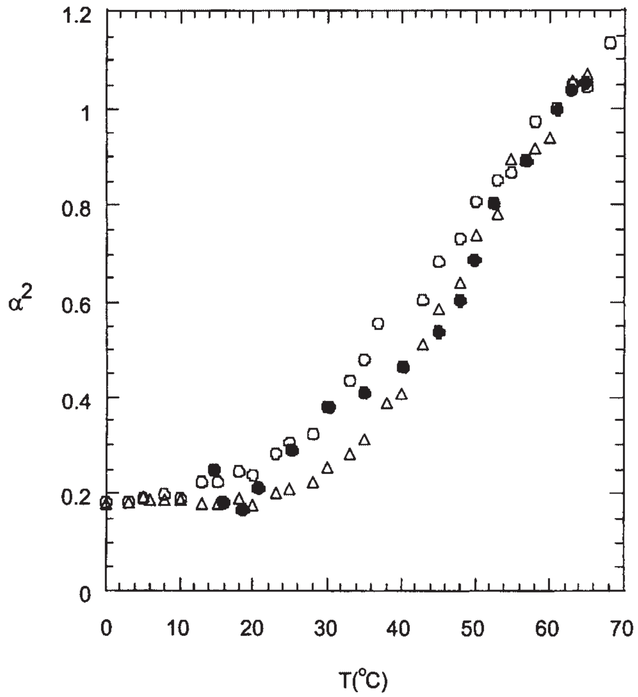


Figure 3. Plot of the expansion factor, α_h^2, versus temperature for PMMA in isoamyl acetate, ((●): $\bar{M}_w = 3.3 \times 10^6$ g · mol^{-1}), ref.[84]. For comparison, α_s^2 obtained from ref.[82] are included ((○): $\bar{M}_w = 2.35 \times 10^6$ g · mol^{-1}; (△): $\bar{M}_w = 4.4 \times 10^6$ g · mol^{-1}).

The segment volume fraction, Φ, in the globule is given by

$$\Phi = (\bar{M}_{w/\rho}) \cdot \left[(4\pi/3) \cdot \kappa \cdot \langle s^2 \rangle^{3/2} \cdot N_A\right] \qquad (7)$$

where ρ (= 1.2 g · ml^{-1}) is the density of PMMA in the liquid state, $\bar{M}_w$ is the molecular weight of PMMA, and N_A

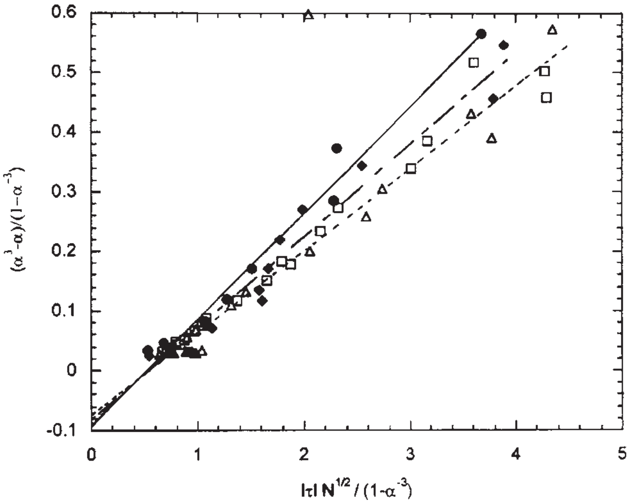


Figure 4. Plot of $(\alpha^3 - \alpha)/(1 - \alpha^{-3})$ versus $N^{1/2} \cdot |\tau|/(1 - \alpha^{-3})$ for the random coil – globule transition of PMMA, ref.[84]. ((◆): PMMA – isoamyl acetate, ref.[84]; (●): PMMA – *n*-butyl chloride, ref.[87]; (□, △): PMMA – isoamylacetate, ref.[82]

Table 2. *B* and *C* parameters in Equation (3) for PMMA obtained at $\tau < 0$.

System[a]	$\bar{M}_w \times 10^{-6}$ g · mol^{-1}	*B*	*C*
PMMA/IAA[b]	3.3	0.154	0.080
PMMA/*n*-BC[b]	3.3	0.177	0.085
PMMA/IAA[c]	2.35 and 4.4	0.130	0.073
PMMA/mixed	2.38[c]	0.506	0.044
	2.5[d]	0.377	0.110
	4.7[d]	0.295	0.085

[a] IAA: isoamyl acetate; *n*-BC: *n*-butyl chloride; mixed: *t*-butanol/water.

[b] DLS, ref.[84,87]

[c] SLS, ref.[81,82]

[d] Viscometry, ref.[83]

is Avogadro's number. (It should be noted that for a DLS value of radius R_h^3, $\kappa = 1$; for a radius of gyration $\langle s^2 \rangle^{3/2}$, $\kappa = (5/3)^{3/2} = 2.15$.[81–84]) The segment volume fraction (Φ) varies depending on the technique used, such as DLS, SLS, and viscometry; these are given in Table 3.[84] The segment volume fractions are estimated to be 0.56 and 0.63 for PMMA chains in isoamyl acetate by dynamic light scattering.[84,87] This indicates that the density in the polymer domain in the PMMA globules is not dilute.

Coil-Globule Transition of Copolymers

Interest in copolymer collapse arises from its relevance to the problem of protein folding in aqueous solutions.[21] However, as in the case of homopolymer collapse, there are many theoretical studies, but few experimental results.

Timoshenko, Kuznetsov, and Dawson developed the Gaussian self-consistent method to study the kinetics of random copolymer collapse as a prototype for protein folding.[88] The method was in good agreement with Monte Carlo simulations for the homopolymer kinetics performed on a lattice.[15] The system is described by time- and disorder-dependent effective potentials. The authors claim that this method permits the study of a complete phase diagram of the model and may provide information on the kinetics of protein folding.[88] They describe the phase structure of the system in terms of the following three globular phases: globule-like, glassy, and folded. The glassy phase probably corresponds to the molten globule; the folded structure has many similarities to the native state of proteins.[88] It was also emphasized that averaging over disorder is necessary if one is about to extract universal or generic laws. However, a Gaussian distribution seems too diffuse, and more realistic investigations must be directed at averaging over a more refined distribution, which is more appropriate for the protein folding problem.[88]

Timoshenko et al. proposed the above self-consistent method for the model of a Gaussian random, amphiphilic copolymer and applied it to the kinetics of the folding process.[88] In conclusion of this work, they studied the equilibrium diagram for different states of the model.[89] They observed that, in many respects the above method is satisfactory for dealing with this difficult problem. However, it has a deficiency in describing the freezing transition curve. Once more, it was noticed that a Gaussian sequence distribution is too broad to deal with average folding properties.[89]

These authors have extended the Gaussian self-consistent (GSC) method to study the equilibrium and kinetics of conformational transitions of heteropolymers with more complicated primary sequences.[90] Kinetic equations earlier derived were transformed to a form containing only the mean-squared distances between pairs of monomers. This revised GSC formalism creates important computational

Table 3. Polymer segment volume fractions (Φ of poly(methyl methacrylate) chains in the globule various solvents.

$\bar{M}_w$ g · mol^{-1}	θ-solvent[a]	T_θ °C	Lowest quench temp. °C	Φ	κ	Ref.
3.3×10^6	IAA[b]	61	18.4	0.56	–	84
4.4×10^6	IAA[c]	61	25	0.14	1	82
				0.07	$(5/3)^{3/2} = 2.15$	82
2.55×10^6	*n*-BC[b]	38	13.0	0.19	–	87
3.3×10^6	*n*-BC[b]	38	7.25	0.47	–	87
1.2×10^6	*n*-BC[b]	35	9.0	0.24	–	87
4.73×10^6	mixed[d]	41.5	20	0.06	–	83
$2,38 \times 10^6$	mixed[c]	41.5	25	0.36	1	81
				0.17	$(5/3)^{3/2} = 2.15$	81

[a] IAA: isoamyl acetate; *n*-BC: *n*-butyl chloride; mixed: *t*-butanol/water.

[b] DLS.

[c] SLS.

[d] Viscometry.

advantages.[90] They have applied the extended GSC method to specific heteropolymers, and they obtained equilibrium phase diagrams. In addition to the coil and two globular states, they postulated the possible existence of a large number of frustrated, partially misfolded, states.[90] In this comprehensive approach, the GSC method was applied to a single chain. Since the kinetic equations are covariant, it should, in principle, be easy to apply this method to solutions of many polymers.[90] However, the authors admit that a complete numerical solution of the GSC equations is computationally burdensome for systems with a few hundred monomers or more, and there are difficulties in obtaining correlation functions.[90] On the other hand, the strength of the modified GSC approach lies in its ability to describe a given heteropolymer sequence of finite length, rather than an infinite ensemble of sequences characterized in a certain probabilistic way. The authors believe that their method will be useful as a new mathematical tool for approaching the important problems of protein folding and other bioinformatics.[90]

Hu et al. has performed dynamic Monte Carlo simulations of a single homopolymer chain with 512 segments on a lattice to illustrate the special structure of the intermediate state.[91] This study shows that an equilibrium state containing a distinct core-shell structure can only occur after ensemble averaging, as a result of a microphase separation behavior in an isolated coil. The author claimed that this result may supply a new way of analyzing the thermodynamics of the molten globule state in protein folding.[91]

In recent years, studies of polyampholytes and biomolecules, such as proteins, have focused much attention on the conformational properties of inhomogeneous, polymeric chains: heteropolymers.

Ganazzoli proposed an analytical approach to the description of the coil-globule transition of random copolymers with a fixed sequence of units.[92] The theory is based on a self-consistent minimization of the intramolecular free energy, which includes two-body attractive interactions among connected units of a given type, two-and three-body repulsive interactions among all the units, and configurational entropy terms. Chain connectivity is accounted for. When considering copolymers containing 20–60% mutually attractive units, the theory always predicts a first-order, coil-globule transition.[92]

Recently, in a comprehensive article, Allegra and co-workers studied the globular collapse of short chains and the collapse of random AB copolymers.[93] Their mathematical approach consists of a self-consistent, free-energy minimization with the inclusion of intra and inter-molecular interactions, which specifies the chain conformation in detail. It is well-established that the transitions in a long flexible chain are smooth and continuous or second-order. They showed that no matter what the transition is, the collapsed chains form a ''random, Gaussian globule''. On the other hand, short chains may form ''compact, ordered states''.[93]

For the collapse transition and the globular state of random copolymers, Allegra and co-workers considered only copolymer chains with a random, but fixed sequence of two different types of beads, and they assumed that only beads of one kind are in a poor solvent and therefore, experience a mutually attractive two-body potential. Such a potential is not included for the interactions of at least one bead of the other kind, whereas all beads are equally subject to the repulsive interactions.[93] They showed two basic chain conformations related to the pattern described above: these were denoted as a ''compact globule'' and an ''open globule''.[93]

Monari and co-workers on the basis of exact enumeration and accurate Monte Carlo results showed that in two dimensions, a sufficient amount of sequence disorder and repulsive interactions can be relevant for the heteropolymer behavior in the whole range $T \leq T_\theta$, which determines, in particular, a universality class different from that of homopolymers for the θ-transition.[94]

Timoshenko and co-workers studied the conformational structure of amphiphilic copolymers in dilute solutions.[95] The Gaussian self-consistent (GSC) method has advantages in studying the fundamental kinetic laws of homopolymer collapse transition for a single chain and their extension to block and random copolymers. The authors extended the GSC method to any number of chains of any composition and with arbitrary topology. They showed that the folding of an open chain is slower than that of an equivalent ring.[95]

Random copolymers form an interesting topic in the general, statistical mechanics of random systems. Such systems are characterized by a Hamiltonian, which depends on a set of random parameters; in the case of random copolymers, these parameters are the identities of the individual monomers constituting the polymers.[96] If the free energy of such a system is equal to the quenched average free energy (for infinitely large systems), it may be regarded as thermodynamically self averaging. Orlandini and co-workers established a set of conditions for this purpose and showed that several lattice models of interacting copolymers satisfy them. They proved this result for a general potential which is linear in the number of contacts.[96]

The models employed in most of the simulation studies consist of an isolated chain of linked monomers with repulsive cores and long-range, attractive forces, which are essential for chain collapse. This model can be sufficient to establish the thermodynamic properties of the coil-globule transition, but does not satisfactorily provide a clear picture of coil-globule, collapse dynamics, due to the existence of solvent effects. Polson and Zuckermann studied the collapse dynamics for a system composed of a single heteropolymer chain in a monomeric solvent in two dimensions.[97] They considered a simple heteropolymer model similar to the one often used in theoretical protein folding studies: a copolymer chain composed of hydrophobic (H) and polar (P) segments and their interactions with the solvent (S). HS interactions are purely repulsive, whereas the PS pair potential has an attractive component. They found that chains with sufficiently high hydrophobic fractions undergo a thermally driven transition from an extended coil in a good solvent to a liquid-like globule in a poor solvent. The transition for random copolymers occurred over a narrower temperature range and at lower temperatures with decreasing hydrophobic fraction. The collapse rates were sensitive to the final values of hydrophobicity; copolymers with a greater number of hydrophobic segments collapsed more rapidly than those with fewer hydrophobic segments. The conformation of the chains upon collapse suggests that the chain collapses with uniform thickening rather than the formation of local clusters, which is also the case for other systems. This behavior may be attributed to the two-dimensional character of the system.[97]

A random copolymer model was introduced by Kantor and Kardar.[93] They considered two types (A, B) of monomers. The nearest-neighbor monomers interact with a potential, $+v_o$, if they are of the same type, and with $-v_o$, they are of the opposite type. For equal numbers of positive and negative charges ($N_A \approx N_B$) overall, the copolymer with $v_o > 0$ undergoes a transition from self-avoiding behavior to a compact state at T_θ. This collapse temperature, $\theta(x)$, decreases with the asymmetry $x = |N_A - N_B|/|N_A + N_B|$ and vanishes at $x \approx 0.6$. For $v_o < 0$, a θ-point is present at all x values.[98] The authors elaborated the above model to polyampholites, which are compact when completely neutral, but expand when highly charged.[99] They examined the transition between the two regimes by Monte Carlo simulations and by analogy to charged drops.[99] Using the random copolymer model, Grassberger and Hegger[100] presented simulation results indicating that, when $N_A \approx N_B$, a θ-transition close to that found by Kantor and Kardar[98] is present, but the θ-collapse disappears for smaller values of x than were found by the latter authors. The polymer first seems to collapse as $N = N_A + N_B$ increases, but this collapse stops for large N values. Therefore, Grassberger and Hegger suggested that long chains with $x \neq 0$ at low temperatures have a structure different from that proposed for copolymers with long-range interactions.[100]

The phase diagram relative to the conformational transitions of a diblock copolymer in two dimensions was studied by using the exact enumeration method and Monte Carlo simulations. A diblock copolymer with attractive interactions between monomers of different blocks and a triple contact interaction exhibits a first-order transition from a swollen chain to a compact spiral phase, if the triple contact interactions are negative. On the other hand, a sequence of a continuous so-called zipping transition and a collapse of the first-order type to a compact conformation at a lower temperature was obtained if the triple contacts are in the positive region.[101]

In the last few years, a large amount of work has focused attention on the conformational properties of heteropolymers. One of the questions is whether chain disorder could affect polymer behavior in the θ-state. Recent theoretical studies of randomly charged polymer-models in two and three dimensions has shown that disorder does not eliminate the universality of the θ-transition.[102] However, there are indications that a sufficient degree of chain disorder can modify the θ-behavior of heteropolymers compared to homopolymers.[94]

Recently, the coil-globule transition of A–B copolymer chains was studied by the following two methods: a lattice Monte Carlo (MC) simulations using a bond fluctuation model and a numerical self-consistent field (SCF) approach.[103] In this contribution, detailed information was provided for the motivation for using both of these methods. Co-polymeric chains of fixed length with A and B monomeric units with regular, random, and designated primary sequences are investigated.[103] The two computational techniques give qualitatively similar results for the coil-globule transition of AB copolymers.[103] In principle, the MC technique is more exact, but in practice, computational restrictions impede the theoretical advantages. This is particularly true when information is needed for a compact globule. On the other hand, the SCF computations, while not elaborate, are not capable of investigating individual conformations.[103] The authors found that the transition temperature is roughly an exponential function of the block length in a regular copolymer. The cooperativity of the transition is high for regular block copolymer molecules, but lower for the random and protein-like sequences because of the polydispersity of block length.[103] However, the globular state for protein-like sequences is more stable than that for statistical random copolymers. No comparison was made with experiments carried out on copolymers.[103]

Cook and Williams have examined the effect of chain sequence on the thermodynamics and kinetics of heteropolymer collapse using a Langevin dynamics simulation.[104] In this study, a bead-spring model was employed with two monomer types, one with a good solvent and the other with a poor one. The collapse of large blocks occurred over a wide temperature range. The kinetics of collapse was followed by measuring the number of clusters and the radius of gyration over time, starting from an instant temperature quench. In this study, the authors were able to track a chain of micelles. During collapse, small micellar-like clusters as intermediates and larger micelle structures as part of the final collapsed state were observed. They found that monomer sequence can have a strong effect on the kinetics and thermodynamics of polymer collapse as well as on the nature of the collapsed state.[104] The basic kinetics of collapse could be described as a rapid, initial formation of clusters followed by cluster aggregation or coalescence. Considerable variation of this basic idea is observed. Chains could be classified as "small", "intermediate", and "large" in terms of block sizes, and each of these classes is characterized by a distinct mechanism of collapse.[104]

We note that, whereas the number of theoretical contributions to dealing with homopolymer and copolymer collapse is increasing,[14,15,52,105,106] there is relatively little experimental work describing this process in copolymer chains. Some experimental studies have been reported on dilute, semi-dilute, and concentrated solutions of random and block copolymers.[107,108]

Coil-Globule Transitions of Random and Alternating Copolymers of Styrene and Methyl Methacrylate

Recently, Baysal and co-workers studied the coil-globule transitions of random (statistical) and alternating copolymers of styrene and methyl methacrylate in cyclohexanol and 2-ethoxyethanol.[109] Thermodynamic and solution properties of these two copolymers in the respective solvents were established earlier.[110–113] The characterization of copolymers used is given in Table 4.[109] The random copolymers of styrene and methyl methacrylate, P(St-*co*-MMA), were prepared by thermal bulk polymerization of the pure monomers of styrene and methyl methacrylate at room temperature. An alternating copolymer, P(St-*alt*-MMA), and a block copolymer, P(St-*block*-MMA), were obtained from Polymer Source Inc. (Dorval). In Figure 5, the contraction of the hydrodynamic radius (R_h) determined from the correlation function measurements by dynamic light scattering (DLS) is shown as a function of temperature for the dilute solutions ($c = 9 \times 10^{-5}$ g · ml^{-1}) of the random copolymer, P(St-*co*-MMA), in cyclohexanol ($\theta = 68.6$ °C) and in 2-ethoxyethanol ($\theta = 58.4$ °C).[109] The R_h values for the alternating copolymer, P(St-*alt*-MMA), in dilute cyclohexanol ($\theta = 60.8$ °C) solution is also included in Figure 5. It would also be interesting to study the contraction behavior of the block copolymer of these monomers, P(St-*block*-MMA); however the θ-temperature of this sample in cyclohexanol is too high (84 °C) to report any reliable DLS data.[109]

For the random and alternating copolymers, the temperature interval between the θ-state and that of the collapsed state is rather small compared to homopolymers (see Figure 2, 3, 5, and 6). Theoretical studies also predict that the transition for random copolymer should occur over a narrower temperature range.[97] These observations and predictions suggest that the early stage of collapse of a copolymer chains is more facile compared to that of homopolymers.

Figure 6 shows the squared linear expansion factor, α_h^2 [$\alpha_h = R_h(T)/R_h(\theta)$], as a function of $\tau \cdot \overline{M}_w^{1/2}$, where $\tau = l - (T/\theta)$ and $\overline{M}_w$ is given in g · mol^{-1} for the random and the alternating styrene-methyl methacrylate copolymers, together with PS[63] and PMMA.[84] It can be seen that the α^2 values for the copolymers decrease more rapidly than for the homopolymers with increasing $\tau \cdot \overline{M}_w^{1/2}$. At the lowest possible temperature, the expansion factor of random copolymer, P(St-*co*-MMA), in both solvents is very close to that for the PMMA homopolymer.[109]

The segment volume fraction, Φ, values were calculated using Equation (7). (The density of the copolymers in the amorphous state, $\rho = 1.1$ g · ml^{-1}, $\overline{M}_w$ is the weight average of copolymers, and $\kappa = 1$). These values are estimated to be $\Phi = 0.04$ and 0.03 for random copolymers in cyclohexanol and 2-ethoxyethanol, respectively, whereas for the alternating copolymer, a much more dense globule in cyclohexanol ($\Phi = 0.23$) was reported.[109]

Coil-Globule Transition of Polyelectrolytes

The extensive theoretical studies of heteropolymers have been motivated by their perceived relation to the protein

Table 4. Copolymer samples.

Sample[a]	Styrene[b]	$\overline{M}_w \times 10^{-5}$	$\overline{M}_w/\overline{M}_n$	η[c]
	mol-%	g · mol^{-1}		dl · g^{-1}
Random copolymers				
P(St-*co*-MMA)[d]	50	36.0	3.05	4.08
P(St-*co*-MMA)[e]		45.9	1.35	5.81
Alternating copolymer				
P(St-*alt*-MMA)	50	26.2	1.54	–
Block copolymer				
P(St-*block*-MMA)	11.5	1.34 (PSt blocks)	1.30	–

[a] See ref.[109]

[b] ^{1}H NMR (CD_3Cl, 500 MHz) and elemental analysis.

[c] In methyl ethyl ketone, 25 °C.

[d] Unfractionated.

[e] Fractionated.

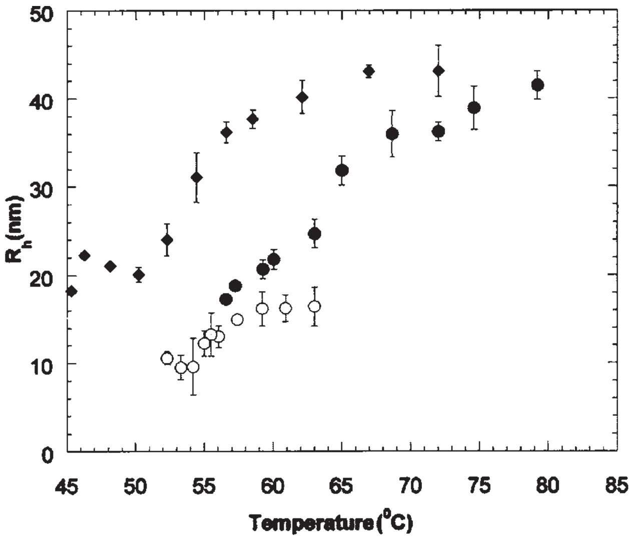


Figure 5. Hydrodynamic radius (R_h) versus temperature for P(St-*co*-MMA) in cyclohexane solution (●), P(St-*co*-MMA) in 2-ethoxyethanol (◆), and P(St-*alt*-MMA) in cyclohexanol (○), ref.[109]

folding problem. The logical next step in this field is, thus, the study of the coil-globule, collapse transition in polyelectrolytes.

One of the first relevant experiments was the study of dimensional changes of linear poly(*N*-isopropylacrylamide) ionomers in water.[114] Wu and co-workers studied coil-globule transition in poly(*N*-isopropylacrylamide-*co*-acrylic acid) with different ionic contents. At temperatures higher than the lower critical solution temperature (LCST), the ionic groups present in the chain can stabilize the collapsed hydrophobic PNIPAM chains to prevent interchain aggregation. The experimental results of the static and dynamic light scattering study in water showed that the collapse of PNIPAM ionomer chains involved two processes as the temperature increases above 32.5 °C: an intrachain, coil-globule transition and an interchain aggregation. A decrease in the ionomer concentration and an increase in the ionic content can suppress the interchain aggregation.[114] Tenhu and co-workers have prepared polyelectrolyte derivatives of PNIPAM by introducing 2-acrylamido-2-methylpropanesulfonic acid and 2-acetamidoacrylic acid as co-monomers in the chain.[115] The results of dynamic light scattering studies show that the relative amounts of the above co-monomers strongly affect the thermal properties and the conformation of terpolymers. The molecular weights of the polymer samples used were very low in the context of coil-collapse, transition studies.[115]

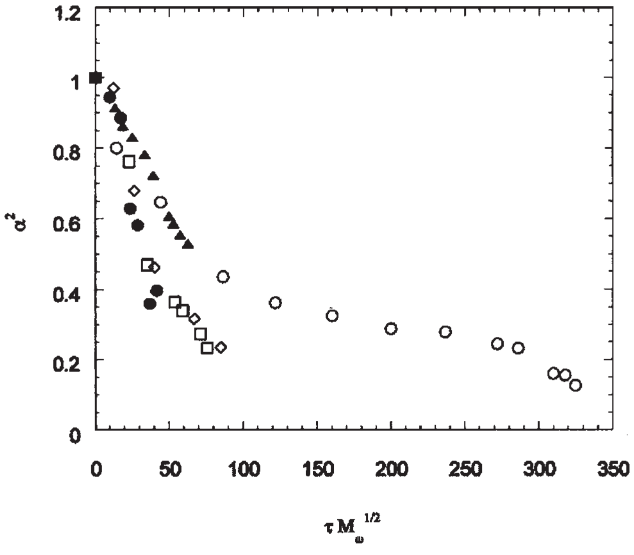


Figure 6. Expansion factor, α^2 versus $|\tau| \cdot \bar{M}_w^{1/2}$ with $\tau = 1 - (T/\theta)$ and molecular weight $\bar{M}_w$ ($g \cdot mol^{-1}$). (●): PMMA/cyclohexanol; (□): P(St-*co*-MMA)/cyclohexanol; (◇): P(St-*co*-MMA)/2-ethoxyethanol; (○): PMMA isoamylacetate; (▲): PSt cyclohexane, ref.[109]

Many biological macromolecules and synthetic polymers are highly charged. Cellular processes often take advantage of shape fluctuations of charged biomolecules performing biological functions.

The second virial coefficient of polyelectrolytes can be highly nonideal because of the electrostatic interaction between ionic charges as well as the polymeric character of the polyions. Most of the nonideal behavior of linear polyelectrolytes is compensated by the strong electrostatic interaction between charges, but the contribution of the polymeric character cannot be neglected.[116] There is a considerable amount of theoretical work on chain expansion and virial coefficients of charged homo and copolymers. A brief review of theories of polyelectrolyte conformation has recently been presented by Stigter and Dill.[117] They developed a theory for conformational changes in polyelectrolytes and for the interactions between two polyelectrolyte chains. Since most realistic polymer experiments and most biopolymer solutions involve added salt, this work concentrated on the effects of added salts. The authors presented a theory for the dependence of the radii of gyration and second virial coefficients of highly charged polyelectrolytes on molecular weight and ionic strength, and applied to this model to some biopolymers and poly(styrene sulfonate)s.[117] Using the experimental results of Takahashi et al.,[116] Borochov and Eisenberg[118] have found that an increase in salt concentration shields charge repulsion, leading to chains with smaller radii and reduced interchain repulsions.

Studies of the solution properties and chain expansion behavior of stiff DNA,[117–119] rigid rod,[120] and flexible polyelectrolytes has also been the subject of extensive research.[117,118,121] Dimensional studies have been performed using various polyelectrolytes, such as poly(styrene sulfonate)[117,118,121] and other ion-containing polymers.[120,122,123]

The collapse kinetics of strongly charged polyelectrolytes in poor solvents has been investigated by Langevin simulation and scaling arguments.[124] The role of the counterion, valency, solvent quality, and the shape of the counterions on the dynamics of collapse were studied in this contribution. Simulation results show that the rate of collapse, which is measured using the time-dependence of the radius of gyration of the chain, increases sharply as the counterion charge increases from 1 to 4. The structure of the globule is controlled by the counterion charge, and a general collapse mechanism emerges.[124] Other references relevant to polyelectrolytes can be found in this comprehensive study.[124]

Small-angle neutron scattering (SANS) experiments have been used to study fully charged poly(styrene sulfonate) (PSS) polyions. At low ionic strength, the conformation does not change and the chain remains wormlike. At high ionic strength in NaPSS solutions, progressive changes occur. With multivalent ions, the chain progressively deviates from the wormlike chain model. If multivalent ions are added, the chain appears ‘‘thicker’’, and it seems that ionic strength is not the only parameter that controls the conformation.[125]

SANS observations of the polycationic polyelectrolyte, poly(methacrylo ethyl trimethylammonium methyl sulfate), of high molecular weight in dilute solution in acetone-water mixtures displays a coil-globule transition above a certain threshold concentration of acetone. It was concluded that the collapsed state of this molecule consists of a short sequence of dense spheres with smooth surfaces, connected by regions of loose polymer.[126]

Coil-Globule Transition of Sodium Poly(styrene sulfate)

Recently, the coil-globule transition in sodium poly(styrene sulfate) (NaPSS) was studied by dynamic light scattering.[127] NaPSS has an extended chain conformation in pure aqueous solution due to the electrostatic repulsion between negative charges on the polyelectrolyte chain. If a salt is added to the dilute solution of NaPSS, counterion condensation causes the polyelectrolyte chain to contract. The conformation of NaPSS in aqueous solutions is strongly dependent on both the sulfur content of the macromolecules as well as the electrolyte concentration. Comments on the distinction between the dilute and semi-dilute concentration regimes, and on the ionic strength dependence of the dimensions of polyelectrolytes have been published recently.[128,129] Takahashi et al.[116] found that 4.17 M aqueous NaCl solution is a θ-solvent at 25 °C using phase separation experiments. However, Beer et al.[130] recently claimed that NaCl solutions of their NaPSS samples did not exhibit solubility or precipitation behavior consistent with the presence of a θ-state. In a comprehensive investigation Hirose et al.[121] analyzed samples of NaPSS with narrow molecular weight distribution by static light scattering, sedimentation equilibrium, and intrinsic viscosity in 0.5 M aqueous NaCl at 25 °C and in 4.17 M aqueous NaCl at 16.4 °C. They reported that the light scattering second virial coefficient vanished for high $\overline{M}_w$ samples in 4.17 M aqueous NaCl solution of NaPSS at 16.4 °C (the θ-point).

The chain dimensions of two polyelectrolyte samples (NaPSS-1, $\overline{M}_w = 1.01 \times 10^6$, $\overline{M}_w/\overline{M}_n = 1.17$; NaPSS-2, $\overline{M}_w = 7.96 \times 10^6$, $\overline{M}_w/\overline{M}_n = 1.16$) in 4.17 M aqueous NaCl solution have been studied by dynamic light scattering. Figure 7 shows the variations of α^2 as a function of temperature. In high ionic strength NaCl solution, the polyelectrolyte chains were already contracted due to the screening effect of the salt. However, further contraction of the polyelectrolyte was observed and globular forms were obtained at about 10 °C. The temperature interval from the θ-state to the globular state is rather small, 6–8 °C. Volume fractions of the globular state are estimated to be 0.58 (NaPSS-1) and 0.96 (NaPSS-2) for the two polyelectrolyte samples studied in this work.[127]

Kinetics of Polymer Collapse

The thermodynamic properties of polymers in dilute solutions have been extensively studied as described earlier in this review. The dynamics and kinetics of the collapse transition has not been investigated as comprehensively. Timoshenko and co-workers have handled this problem by using two approaches generally used for computer simulations of polymer systems.[14,15] Firstly, they introduced a

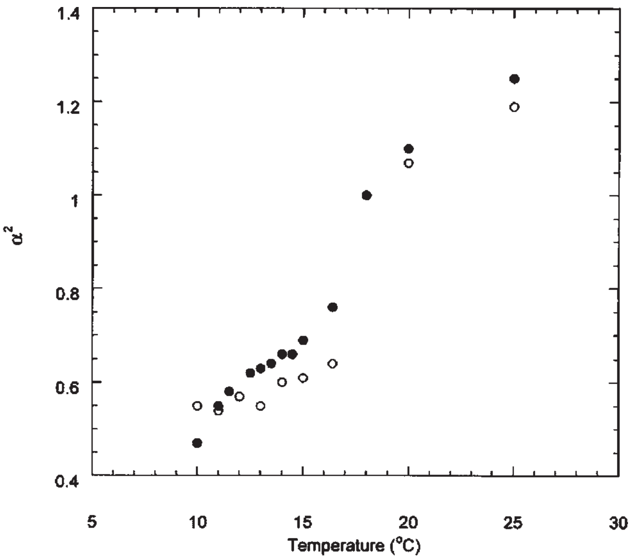


Figure 7. Expansion factor, α_h^2, versus temperature for NaPSS in 4.17 M aqueous NaCl solution. (●): NaPSS-1, (○): NaPSS-2. A reference temperature of 18.0 °C is assumed as $\alpha_h^2 = 1$ for both samples, ref.[127]

modification to the Langevin equation that can be used to study nonequilibrium dynamics and kinetics of conformational transitions in dilute solutions[14] and claimed the existence of a number of distinct stages in the overall process. They also presented results for the earliest and fast stage for the relaxation of a Flory coil to the collapsed state.

The second approach involved the application of Monte Carlo simulations. The same authors described the results of Monte Carlo simulations of the kinetics at the collapse transition of a homopolymer in a lattice model.[15] The kinetic laws found correspond to the three stages of the process. The early stage can be attributed to a rapid initial growth of the average number of clusters and average number of monomers in a cluster, which is consistent with the mechanism of globule formation. The mean-square radius of gyration decreases very rapidly during this earliest kinetic stage and can be approximated by[15]

$$R_{\mathrm{s}}^2(t) = R_0^2 - \mathrm{A} \cdot t^{\alpha};\ \alpha = 0.66 \pm 0.03 \tag{8}$$

The second or "coarsening" stage may be characterized by "blob" growth. In the simulations, it is clear that the growth of blobs proceeds mainly by the unification of smaller clusters. Polymer segments linking different clusters are quite tight and accretion of monomer units from such segments by the neighboring globules is a much less significant contribution.[15] The growth mechanism at quenches is not an end dominated process. At this stage, the cluster growth law can be described by a power law.

The next relaxation stage is the compaction of the internal structure of the collapsed globule and a rearrangement of the globule.[15]

Polymer collapse in dilute solution, equilibrium and dynamic aspects, and the kinetics of contraction of a stiff chain based on the kinetic equation and derived from the appropriate nonequilibrium Langevin equation were also studied by Allegra and co-workers in detail.[19,131] Recently, these authors have studied the properties of macromolecular clusters in poor solvents.[93,132,133] They found that, unlike long chains, the globular collapse of short chains may yield a compact, ordered state. The collapse takes place within an infinitely narrow temperature range, a feature associated with a first-order transition. For a long flexible chain, only a random Gaussian globule is allowed; the coil-globule transformation corresponds to a second-order transition.[93] Ordered structures may also arise in stiff, persistent chains and are predicted to assume a toroidal shape.[6,17,93]

During the last decade, three experimental groups published results on the kinetics of polymer collapse. Chu and co-workers reported a two-stage collapse of high molecular weight polystyrene chains in cyclohexane after quenching the solution from the θ-state into a two-phase, poor solvent region.[134–136] A theoretical, two-stage kinetic model of single chain collapse was proposed earlier.[9,137] The time dependence of the change in hydrodynamic size (R_{h}) of a single polystyrene chain in cyclohexane is quite different in refs.[134,136] for polystyrene samples with similar molecular weights ($\overline{M}_{\mathrm{w}} = 8 \times 10^6$). This discrepancy can not be explained by the difference of light scattering cells used in these measurements, which might cause differences of only a few minutes in thermal relaxation.

The validity of a two-stage collapse concept was challenged by Allegra and co-workers.[88,132] They considered the alternative possibility of chain clustering or aggregation during the second stage of collapse. They found that clusters of two to five polystyrene chains have a smaller radius than that of a single globular polystyrene chain. Therefore, Allegra and co-workers concluded that the much smaller objects observed in the second stage of collapse reported as "compact globules" emerging with time by Chu and co-workers[134–136] are actually macromolecular clusters resulting from the aggregation of a small number of polystyrene chains. Consequently, it was argued that the initial collapse stage with about 25% contraction corresponds to a final pseudo-equilibrium state for individual polystyrene macromolecules in cyclohexane.[88,132]

In the coil-globule transition process of polystyrene in various solvents, the phase separation stage is rather fast. This is the main reason for the known difficulties in studying the dimension of a polystyrene chain beyond about 25–30% initial contraction from the θ-state value.

Experimental Studies of the Kinetics of Polymer Collapse

Nakata and coworkers studied the kinetics of the coil-globule transition of poly(methyl methacrylate) in isoamyl acetate and in a mixed solvent, water / *t*-butyl alcohol, by static light scattering.[138,139] These authors also investigated the kinetics of chain aggregation of PMMA in the same solvents.[140–142] Since the dilute solutions of PMMA in these solvents indicate very slow phase separation, SLS measurements could be carried out for 30 min after quenching to low temperatures and the mean-square radius of gyration $\langle s^2 \rangle$ was determined from the θ-temperature to relatively low collapsing temperatures. Nakata and co-workers interpreted their coil-globule transition of chain collapse processes at various temperatures by plotting the square of the expansion factor values (α^2) as a logarithmic function of time ($\ln t$).[138,139]

Baysal and co-workers have studied the time dependence of coil-globule collapse of PMMA samples with various molecular weights in isoamyl acetate and in *n*-butyl chloride solvents by dynamic light scattering.[84,87,143] DLS measurements were conducted using thin-walled cylindrical Pyrex cells (0.35 mm wall thickness, 5 mm outer diameter, and 75 mm length). By measuring the temperature profile of a typical DLS cell quenched from 61

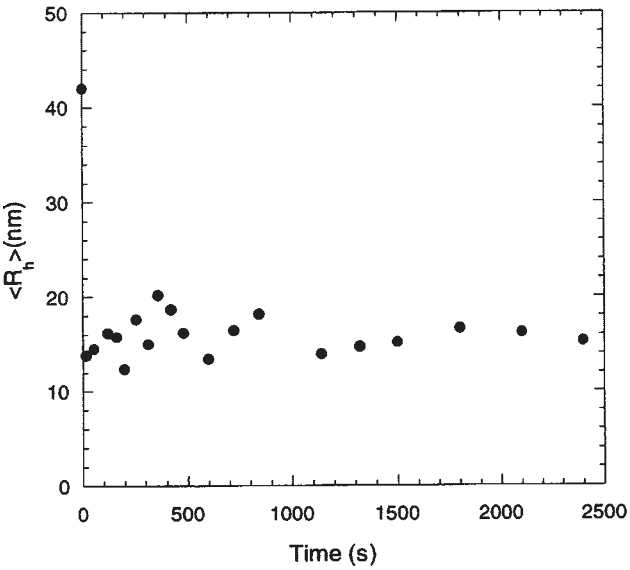


Figure 8. $\langle R_h \rangle$ versus time for PMMA-1 ($\bar{M}_w = 6.47 \times 10^6$ g · mol^{-1}) chain in isoamylacetate at 18.5 °C, procedure 1, ref.[143]

to 18.5 °C, it was found that the time for the contents to reach thermal equilibrium is about 20 s. Figure 8[143] shows the contraction of the hydrodynamic radius in DLS experiment from the θ-temperature (61 °C) to 18.5 °C as a function of time. The transition from the coil to globule in this cell was observed in about 30 s.[137] In this investigation, the effect of quench depth (ΔT) on the transition time of the coil-to-globule collapse of PMMA was studied. As the quench depth increases, the time required to reach the new equilibrium size decreases. In Table 5, the effect of the quench depth on time-dependence for thermal equilibrium is given. Larger quench depths yield a more rapid transition. The collapse of chains having high molecular weights is faster than that of the lower *MW* chains.[143]

An analysis of DLS experiments[84,87,143] together with the SLS studies of Nakata and co-workers[132,133] clearly shows that the collapse transition of PMMA is a two-stage process as measured in dilute solutions of three different solvents below their θ-temperatures. The validity of this conclusion considering typical experiments of the two research groups (SLS and DLS studies of PMMA) has been reported elsewhere.[144] The results of kinetic experiments of DLS and SLS measurements are summarized in Table 6. DLS experiments show that PMMA ($\bar{M}_w = 6.47 \times 10^6$ g · mol^{-1}) chains contracted by shock cooling or stepwise procedures in a period of about 30 s (Figure 8) which is close to the thermal equilibration times of solutions. (The details of these procedures are given in ref.[143]). For this sample, $\langle R_h \rangle$, which was 420 Å at 61.0 °C, was reduced by 52% to 200 Å by shock cooling to 19 °C (Figure 4(d) in ref.[143]). The shock cooling experiment yields a constant $\langle R_h \rangle$ value for about 20 min, but aggregation was observed after this period. In a stepwise cooling procedure, the radius of this sample was reduced by 64% to 150 Å at 18.5 °C (Figure 2 in ref.[143]). After these immediate contractions, the $\langle R_h \rangle$ value was constant for about 40 min. The scattering intensity in DLS experiments on samples shock cooled to 19 °C ($\Delta T = 42$ °C) increases with time, which indicates some interchain aggregation (Figure 5 in ref.[143]). When this sample was shock cooled to 30 °C, the $\langle R_h \rangle$ value was reduced from 420 to 250 Å (Figure 4(b) in ref.[143]), showing a 41% contraction, but there was no aggregation for the next 60 min.

Nakata and co-workers[138] have measured the time-dependence of the expansion factor, $\alpha^2 = \langle R_s^2 \rangle / \langle R_s^2 \rangle_\theta$ for the same polymer solvent system. For a PMMA sample with $\bar{M}_w = 8.4 \times 10^6$ g · mol^{-1}, the $\langle R_s \rangle_\theta$ value at the θ temperature (61.0 °C) was measured as 707 Å in isoamyl acetate. At 30 °C, $\langle R_s \rangle$ was reduced 50% to 342 Å in 30 min, and further reduced slowly after 1 500 min to 278 Å, which corresponds to a 19% reduction in the second slow stage.

Table 5. Equilibration times as a function of quench temperature: shock cooling, ref.[143]

ΔT a) / °C	t_e / s					
	PMMA-1				PMMA-2	
	iAA	$\langle R_h \rangle$ / nm	*n*-BC	$\langle R_h \rangle$ / nm	iAA	$\langle R_h \rangle$ / nm
21.0	200	(29 ± 2)				
24.2			150 (22 ± 2)			
31.0	170	(25 ± 2)				
41.0	35	(22 ± 3)			15b)	(15 ± 3)
42.0	35	(22 ± 2)				

a) Quench depth.
b) Close to thermal equilibrium time of pure solvent.

Table 6. Size reduction of PMMA chains below θ temperatures at different times of measurements.

$\bar{M}_w \times 10^6$ (Solvent)[a)]	Method	T	Time	$\langle R_h \rangle \langle R_s \rangle$	Size reduction	Φ	ref.
$g \cdot mol^{-1}$		°C	min	nm	%	%	
6.47 (IAA)	DLS	61.0 (θ)	0	42	–	–	143
		40.0	0.5	30	29	8.1	
		30.0	0.5	25	41	14	
		19.0	0.5	20	52	27	
		18.5	0.5	15	64	65	
8.4 (IAA)	SLS	61.0 (θ)	0	70.7	–	–	139
		30.0	30	34.2	50	3.2[b)]	
		30.0	1 500	27.8	19	6.0[b)]	
				overall	61		
12.3 (IAA)	SLS	61.0 (θ)	0	86.6	–	–	139
		30.0	30	42.1	54	2.5[b)]	
		30.0	3 980	32.1	23	5.6[b)]	
12.2 (mixed)	SLS	41.5 (θ)	0	90.5	–	–	140
		20.0	30	27.2	69	9.4[b)]	
		20.0	(months)	22.4	18	16.8[b)]	
4.0 (mixed)	SLS	41.5 (θ)	0	50.6	–	–	140
		20.0	30	16.1	68	8.9[b)]	
		20.0	300	16.1	68	8.9[b)]	
				overall	68		
4.73 (mixed)	VIS	41.5 (θ)	0	73.2	–	–	83
		20.0	30	29.5	60	6.1	

[a)] IAA: isoamyl acetate; mixed: t-butyl alcohol/2.5%H_2O.
[b)] Φ values are divided by $\kappa = (5/3)^{1/2}$.

The overall reduction was calculated to be 61%. During the last observation period (≈25 h), the apparent MW of the PMMA chains increased by about 10%.

It can be seen from Table 6 that the size reduction of contracting PMMA chains below θ-temperatures, particularly for the initial fast stage (30 s for DLS or 30 min for SLS) is rather large, about 50% or higher. Segment volume fraction (Φ) values calculated from Equation (7) are relatively low in the context of compact or knotted globules. Higher Φ values were obtained where ΔT (the shock cooling depths) were high. However, the slow rate of contraction observed by SLS measurements during the second stage of collapse, does not give any information about the shape or on the structure of the globule. Relatively high segment volume fractions were obtained only if the depth of shock cooling is very high (see Table 6) as in the case of DLS measurements of PMMA.

In conclusion, Baysal and Karasz have proposed that the fast contraction time (< 30 s) observed in DLS measurements[143,144] constitute the initial stage of collapse of PMMA in isoamyl acetate. This is a fast crumpling of polymer chain.[9,137] The unavoidable presence of a finite thermal equilibration time (~20 s) restricts the exact experimental determinations using the present light scattering methods. However, the relaxation time of the first stage of fast crumpling could be less than 30 s and might even approach the value of 10^{-3} s as predicted by theoretical calculations.[9] The slow contraction observed by SLS measurements[138–142] can be considered to be the second stage of globule formation. During the second stage of the collapse transition, an increase in molecular weight of PMMA chains (about 10%) indicates the presence of a certain degree of aggregation.[132–136] Total collapse can occur in the first stage if the depth of quenching is very deep, this can be seen in DLS measurements at 18.5 °C,[143] see Table 6. An end-dominated chain collapse process has been proposed at deep quenches.[145]

Conclusion

In this contribution, we reviewed representative studies of the transition of flexible macromolecular chains from an expended random-coil in the θ-state to a globular compact form in a collapsed state. The collapse transition from a coil to a compact globular state has been established experimentally for two flexible macromolecules: poly(N-isopropylacrylamide) in aqueous solutions and poly(methyl methacrylate) in several solvents. For both of these homopolymers, the compact globular state contains a large fraction of solvent molecules.[76–79,81–84,87,143] Therefore, the compact forms can be considered as ''molten globules'', a globule of polymer chain still containing a considerable fraction of solvent molecules.

The theory of homopolymer collapse has been developed with quantitative accuracy. Phenomenological and

Langevin models have been used to evaluate thermodynamic and dynamic properties of the coil-globule transition. Extensive studies using different approaches to the collapse of the chain leading to folding have been developed based on the molecular dynamic simulations.

There are only a few experimental studies of the coil-globule transition of copolymers. For random as well as alternating copolymers, the temperature interval between the θ-state and the collapsed state is rather small, when compared to homopolymers.[97,109]

The temperature interval is even narrower (6–8 °C) for contraction and collapse process of a polyelectrolyte, e.g., NaPSS. A rather dense form of molten-globules has observed with this polyelectrolyte.[127]

For the kinetics of coil-globule transition of poly(methyl methacrylate) detailed dynamic[84,87,143] and static[138,139] light scattering measurements have been carried out recently. The fast contraction time (<30 s) observed in DLS measurements show the initial stage of a fast crumpling of the polymer chain.[143,144] The slow contraction observed by SLS measurements[138–142] can be regarded as the second slow stage of globule formation.

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