

Simulation of heteropolymer collapse with an explicit solvent in two dimensions

James M. Polson and Martin J. Zuckermann

Centre for the Physics of Materials, Department of Physics, McGill University, Rutherford Building, 3600 Rue Université, Montréal, PQ, Canada H3A 2T8

(Received 6 March 2000; accepted 21 April 2000)

Molecular dynamics simulations are used to study the equilibrium properties and collapse dynamics of a heteropolymer in the presence of an explicit solvent in two dimensions. The system consists of a single copolymer chain composed of hydrophobic (H) and hydrophilic (P) monomers, immersed in a Lennard-Jones solvent. We consider HP chains of varying hydrophobic number fraction n_H , defined as the ratio of the number of H monomers to the total number of monomers. We also consider homopolymer chains with a uniform variable degree of hydrophobicity λ , which describes the hydrophobic-solvent interaction, and which ranges from hydrophilic ($\lambda=0$) to hydrophobic ($\lambda=1$). We investigate the effects of varying n_H and λ , the HP sequencing, and the solvent density on the equilibrium and collapse properties of the chain. For sufficiently high n_H , we observe a collapse transition for random copolymers from a stretched coil to a liquidlike globule upon a decrease in temperature; the transition temperature decreases with increasing n_H . The transition can also be induced at a fixed (and sufficiently low) temperature by varying n_H for random copolymers or λ for homopolymers. We find that polymer size varies inversely with solvent density. The rate of polymer collapse is found to strongly vary inversely with increasing n_H and λ for copolymers and homopolymers, respectively. Further, the collapse rates for these two cases are very close for $n_H = \lambda$, except at lower values ($n_H = \lambda \approx 0.5$), where the homopolymers collapse more rapidly. At moderate densities ($\rho=0.5-0.7$, in LJ reduced units), we find that random copolymers collapse more rapidly at low density and that this difference tends to increase with decreasing n_H . At fixed solvent density and n_H we find the collapse rate differs little for random copolymers, and multi-block copolymers with equal n_H . Finally, the simulations suggest that copolymers tend to collapse by a uniform thickening rather than by first forming locally collapsed clusters which aggregate at longer time. The exception to this appears to be block-copolymers comprised of sufficiently long alternating H and P blocks. © 2000 American Institute of Physics. [S0021-9606(00)51027-7]

I. INTRODUCTION

The collapse of a single polymer chain from an extended coil in “good” solvent conditions to a dense globule in “poor” solvent conditions has been one of the most extensively studied topics in computational and theoretical polymer physics in recent years. One key reason for the interest in the coil-globule collapse transition is its close relationship to protein folding, one of the most important problems in molecular biology.¹⁻³ It is thought that in some cases protein folding proceeds first via a rapid collapse to a molten globule state, driven mainly by nonlocal hydrophobic interactions, after which native contacts are established through a slower process as the protein approaches its native structure. In addition to the relevance of the coil-globule collapse to protein folding, a direct comparison to standard polymer systems is now available, as recent advances in experimental methods have made possible the observation of the collapse transition of essentially isolated homopolymers in very dilute solution without the usual complication of chain aggregation.⁴⁻⁷

Numerous theoretical studies of the kinetics of polymer collapse have been reported. The problem was first discussed by de Gennes,⁸ who employed a phenomenological model to

construct a mean-field treatment for homopolymer collapse dynamics for slight departures from the θ -solvent conditions. In that study, it was proposed that the polymer initially collapses into a sausage shape, after which the effects of diffusion cause the sausage to thicken uniformly as the ends contract. Several studies employing a variety of related phenomenological homopolymer models were later reported.⁹⁻¹³ An alternative to the phenomenological model theories are Langevin-type theories, based on approximations of the Langevin equation.¹⁴⁻²² For example, Dawson and co-workers have developed the sophisticated analytical Gaussian Self-Consistent (GSC) theory to describe the collapse kinetics for both homopolymer¹⁷⁻¹⁹ and heteropolymer²⁰⁻²² chains. The latter studies point to a complicated heteropolymer collapse process, with the kinetics strongly dependent on the monomer sequence.

In addition to theoretical work on this topic, there have been extensive computer simulation studies of polymer collapse dynamics.²³⁻³⁰ Ostrovsky *et al.* have studied the collapse of homopolymers using Monte Carlo (MC) simulations in both two and three dimensions²³⁻²⁵ in conjunction with a model employing irreversible monomer aggregation, essen-

tially the far-from- θ -point condition. They observe a collapse process which is dominated by the diffusion of polymer ends, which effectively act as nucleation centers for the monomers. Dawson and co-workers have also employed both Langevin²⁷ and MC^{28,29} simulations to study the collapse of both homopolymer and heteropolymer systems. In these cases, monomer aggregation is not irreversible, and a different picture of the collapse emerges: Upon collapse, long chains form local clusters or “blobs” at random positions along the chain at short times, and which coalesce at longer time. This mechanism was also observed in Langevin simulations of the collapse of a random heteropolymer.³⁰

While the thermodynamics of the coil-globule transition is now fairly well understood, a clear picture of coil-globule collapse dynamics is not yet available, despite the considerable amount of theoretical and computational work in this field outlined above. One of the main goals of this study is to more fully account for the effects of hydrodynamics on the collapse dynamics by employing a model that includes an explicit solvent. By contrast, the models employed in the simulation studies discussed above typically consist of an isolated chain of linked monomers with repulsive cores and long-range attractive forces. This latter feature, which is essential for collapse to occur for isolated chains, must be thought of as an effective interaction mediated by the solvent, which therefore is incorporated in an implicit manner. A variation in the temperature, or, equivalently, the strength of the attractive component of the potential, drives the transition. While this model can be sufficient for describing the thermodynamic properties of the coil-globule transition, clearly the solvent will significantly affect the qualitative nature of the collapse dynamics. This fact arises from the complicated hydrodynamic interactions between monomers. This feature has been incorporated into the Rouse-Zimm theory equilibrium polymer dynamics,³¹ and has been shown to result in dynamic properties which scale with polymer size in a way which differs significantly from the case where the effects of hydrodynamics are omitted. These theoretical predictions have been validated by constant energy simulations of systems composed of a polymer in an explicit monomeric solvent.³²⁻³⁴ The importance of the effect of hydrodynamics on polymer collapse kinetics has been recognized and included in the GSC approach¹⁷⁻²² and in other theories.^{10,12,13}

That few comparable simulation studies of polymer collapse dynamics employing explicit-solvent models have been carried out is due to the high computational cost of studying a necessarily large system: One must employ a sufficiently large number of solvent particles to satisfy the two conditions that the solvent density is high (the realistic limit), and that the simulation cell side is large enough to exclude the possibility that the polymer can directly interact with periodic images of itself. Note that this constraint leads to minimum system sizes which increase rapidly with polymer length. We also note that it is significantly more difficult to attain the dilute limit in which the polymer does not interact with periodic images of itself via the long-range hydrodynamic forces, a point which has been noted by Dünweg and Kremer.³² In addition to system size constraints, many collapse runs must be performed and averaged in order to obtain

reliable collapse statistics. Despite the complications of simulating polymer collapse in an explicit solvent, it is clearly an interesting problem which should be studied. We anticipate that the collapse behavior for such models could differ qualitatively from that seen in simulation studies of isolated chain systems, or even from theories which include the effect of hydrodynamic interactions.

In the present work, we study the collapse dynamics for a system composed of a single polymer chain in a monomeric solvent. While most simulation studies of the coil-globule transition have employed homopolymer systems, we choose to study a heteropolymer system in order to provide a closer connection with the protein folding problem. We consider a simple heteropolymer model which is often used in theoretical studies of protein folding: an “HP” copolymer composed of “hydrophobic” (H) monomers and “hydrophilic” or polar (P) monomers. This model provides a simple picture to describe the structure of folded proteins in which hydrophobic amino acid monomers tend to be buried in the core and surrounded by a shell of hydrophilic monomers. Typically, such models employ monomer-monomer attractive interactions which are strongest for H-H interactions, and weakest (if they are included at all) for P-P interactions. Again, we note that the attractive interactions in these models are understood to be solvent-mediated, and not merely a component of the direct monomer-monomer pair interaction potential. Since we are primarily focused on the effects of the solvent on polymer collapse dynamics, we choose to differentiate H and P monomers in our explicit-solvent model solely on the basis of their interaction with the solvent. We study both the thermodynamics and collapse dynamics of the model system upon an abrupt change in the solvent conditions, and investigate the effects of varying a variety of properties, such as the ratio of the number of H to P monomers, HP sequencing, chain length and solvent density. We also make a detailed comparison between heteropolymer and homopolymer systems. As we are interested in the collapse properties of longer polymers, we choose first to study a two-dimensional system in order to circumvent some of the problems with system size discussed above. Clearly, the collapse properties will differ qualitatively from those of three dimensional systems; however, we view this as a very useful first step to guide our work in that direction.

II. MODEL AND METHODS

We consider a two-dimensional system composed of a single fully flexible polymer chain immersed in a Lennard-Jones solvent. The solvent is essentially a monomeric solvent in that the solvent particles have the same size and mass as the monomers on the polymer. Particle interactions are pairwise additive and depend on whether the particle is a hydrophobic (H) monomer, a hydrophilic (P) monomer, or a solvent (S) particle.

Solvent-solvent (SS), hydrophobic-hydrophobic (HH), hydrophilic-hydrophilic (PP), hydrophilic-hydrophobic (HP), and hydrophilic-solvent (PS) pair interactions are all identical and given by a truncated and shifted 6-12 Lennard-Jones potential:

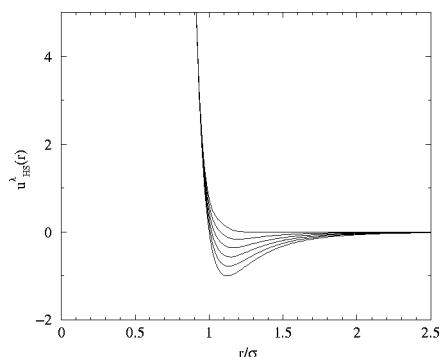


FIG. 1. Hydrophobic-solvent pair potential $u_{\text{HS}}^{\lambda}(r)$ vs r , for hydrophobic interaction degree values $\lambda = 1.0, 0.8, 0.6, 0.4, 0.2$ and 0.0 shown, respectively, from the top to the bottom.

$$u(r) = u_{\text{LJ}}(r) - u_{\text{LJ}}(r_C), \quad r \leq r_C$$

$$= 0, \quad r \geq r_C, \quad (1)$$

where

$$u_{\text{LJ}}(r) = 4\epsilon[(\sigma/r)^{12} - (\sigma/r)^6], \quad (2)$$

and where we have chosen a cutoff distance of $r_C = 2.5\sigma$. The hydrophobic-solvent pair interaction has been designed to have the same repulsive-core size as the standard LJ interaction, but differs from the former in that there is no attractive component to the potential, and therefore lacks a potential well. We define this interaction as the following:

$$u_{\text{HS}}(r) = \omega(r)u_{\text{LJ}}(r) + (1 - \omega(r))u_{\text{rep}}(r). \quad (3)$$

Here $u_{\text{rep}}(r)$ is a steeply repulsive interaction given by $u_{\text{rep}}(r) = 4\epsilon(r/\sigma)^n$, where we have chosen the value $n = 30$. The function $\omega(r)$ is a weighting function which has the effect of transforming $u_{\text{HS}}(r)$ from values close to $u_{\text{LJ}}(r)$ as low r to values close to $u_{\text{rep}}(r)$ at larger r in such a way as to avoid the presence of an attractive well. To this end we choose $\omega(r)$ to be a displaced error function:

$$\omega(r) = (1 + \text{erf}((a - r)/\sqrt{2}\gamma))/2, \quad (4)$$

where $a = 1.035$, and $\gamma = 0.040$. We also consider pair potential functions for HS interactions which lie intermediate to those given in Eqs. (1) and (2). We define this generalized function $u_{\text{HS}}^{\lambda}(r)$ as the following linear combination:

$$u_{\text{HS}}^{\lambda}(r) = \lambda u_{\text{HS}}(r) + (1 - \lambda)u_{\text{LJ}}(r), \quad (5)$$

where the hydrophobic interaction degree, λ , ranges from 0, in which case $u_{\text{HS}}^{\lambda}(r) = u_{\text{LJ}}(r)$, the hydrophilic limit, to 1, in which case $u_{\text{HS}}^{\lambda}(r) = u_{\text{HS}}(r)$, the hydrophobic limit. This potential has been designed to provide another measure of the degree of hydrophobicity suitable for homopolymers. The potential $u_{\text{HS}}^{\lambda}(r)$ is illustrated in Fig. 1 for several values of λ .

Finally, adjacent monomers on the chain are bonded by stiff springs which interact with a potential

$$u_b(r) = (k_b/2)(r - l_b)^2, \quad (6)$$

where we have chosen the spring constant of $k_b = 5000\epsilon\sigma^{-2}$ and a bond length of $l_b = \sigma$.

All quantities described below are in Lennard-Jones reduced units. Specifically, distances are expressed in terms of σ , energies in terms of ϵ , temperature in terms of k_B/ϵ , where k_B is Boltzmann's constant, and time in terms of $\sqrt{m\sigma^2/\epsilon}$, where m is the mass of each solvent particle and monomer. Further, the density of the system is defined to be the total particle density, $\rho = (N + N_s)\sigma^3/V$.

To permit an efficient calculation of the pair potentials described by Eqs. (3) and (5) and their corresponding pair forces, we employed a lookup table using 20 000 values of r for $0.5 \leq r \leq r_C$. Further, we employed the linked cell list method for the total calculation of all pair forces,³⁵ which for the large system sizes that we used was found to be considerably faster than the Verlet neighbor list method.

Simulations performed to monitor the equilibrium properties of the system employed the constant-temperature, constant-volume (NVT) ensemble with a Nosé-Hoover thermostat to regulate the temperature. The corresponding equations of motion were integrated using the reversible time-propagation integrators described by Martyna *et al.*³⁶ In most cases we used a time step of $\delta t = 0.005$, and a thermostat frequency of $\omega_p = 5.0$, from which the thermostat mass is given by $Q_p = N_f k_B T / \omega_p^2$, where N_f is the number of degrees of freedom of the system.³⁶ In addition, we employed the reference system propagator (RESPA) multiple time step (MTS) method to improve energy conservation.³⁶⁻³⁸ This enabled us to use a relatively large time step despite the presence of stiff spring bonds between adjacent monomers. Using the bonding force as the reference force, and employing a short time step of $\delta t_s = 0.001$ (i.e., $n_s \equiv \delta t / \delta t_s = 5$ reference force calculations per large time step) we observe satisfactory conservation of energy (strictly speaking, conservation of a quantity with units of energy) at $T = 1.0$, the temperature at which most of the simulations were performed. Higher temperature simulations employed shorter values of δt , but still used $n_s = 5$.

Most simulations employed polymers of length $N = 100$ monomers immersed in a bath of N_s solvent particles, such that the total number of particles was $N + N_s = 1225$. In a few cases, we considered smaller systems with $N = 40$ monomers and $N + N_s = 400$ particles, and larger systems with $N = 200$ monomers and $N + N_s = 4900$ particles. For any particular density, the particles of the system were initially placed on a square lattice. In the case of the polymer, the chain was initially straight with sharp bends at the edges of the simulation cell in order to occupy successive layers in the lattice. The system was next equilibrated for a considerable time, $\Delta t \geq 20\,000$, before any measurements were taken, as a result of the highly nonequilibrium (though easily constructed) initial chain configuration. The system coordinates were then used as initial coordinates for subsequent calculations. Upon variation of some system parameter (e.g., T , hydrophobic number fraction n_H , etc.) statistics would be accumulated for $\Delta t = 10\,000 - 50\,000$, depending on, e.g., the solvent density, after which the final configuration would be used as the initial configuration for a simulation with next value of the parameter, and so on. Prior to each accumulation of statistics, the system was further equilibrated for a period of at least $\Delta t = 2000$.

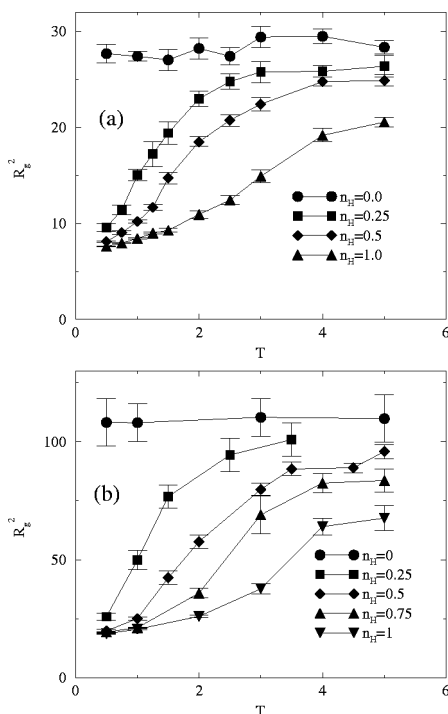


FIG. 2. Radius of gyration squared R_g^2 vs temperature T for a heteropolymer chain of length (a) $N=40$, and (b) $N=100$, for various values hydrophobic number fraction $n_H \equiv N_H/N$, where N_H is the number of hydrophobic monomers on the chain and N is the total number of monomers. The solvent density was fixed at $\rho=0.7$.

Many of the simulations in this study were performed to measure the collapse dynamics of the polymer upon abruptly changing the conditions of the system. Rather than quenching the system by changing the temperature, we chose instead the following approach. We choose equilibrium initial configurations for an all-P chain at $T=1.0$, at which point the polymer is in an extended coil state. Quenches are performed by changing the solvent-monomer interactions. For example, the sequence may be changed from an all-P chain to a random HP sequence chosen to be sufficiently hydrophobic that, at the same temperature and density, the equilibrium state of the chain configuration is the globular state. In addition to quenching with respect to n_H (see definition below) for copolymers, we have also quenched the system by changing λ [see Eq. (5)], which is another measure of the hydrophobicity of the chain, this time suitable for a homopolymer.

In order to obtain reliable statistics from the quenches, it was necessary to use a large number, typically 40–60, and in some cases, up to 120 initial configurations. The configurations were generated by conducting a very long simulation, and saving the coordinates after every time interval of at least $\Delta t=1000$. In the case of quenches employing random copolymers, we also carried out an additional average over three different random configurations. As the results for each individual random sequence did not differ significantly, we concluded that it was not necessary to average over more configurations. Each quench was carried out over a time of $\Delta t=2000$. During each quench, we employed the constant energy (NVE) simulation method to avoid the artificial dynamics associated with the Nosé–Hoover thermostat. Note

that when quenching with respect to n_H , for example, the initial configuration is representative of that of an all-P chain in a solvent. Consequently, in changing the nature of the interactions during the quench while keeping the energy fixed to that of the initial configuration, we expect that the temperature during the collapse will in general differ from that associated with the initial configuration. However, we find that at $T=1.0$ for the system sizes we investigated, the average temperature during the collapse is a negligible few per cent higher than its initial value.

HP copolymers are characterized by the hydrophobic fraction number, $n_H \equiv N_H/N$, where N_H and N are the number of hydrophobic monomers and the total number of monomers, respectively. Thus, n_H is a measure of the degree of hydrophobicity of the polymer which is controlled exclusively by the monomer-solvent interactions. Unless otherwise stated, HP copolymers of any n_H are assumed to have hydrophobic monomers characterized by $\lambda=1$, i.e., the case where $u_{HS}^\lambda(r)$ of Eq. (5) reduces to the form in Eq. (3), and which is shown as the top curve in Fig. 1. The case of arbitrary $\lambda \in [0,1]$ provides another measure of the degree of hydrophobicity of the polymer which is suitable measure for homopolymers. The two different measures provide a means to compare equilibrium and collapse properties of copolymers and homopolymers for comparable degrees of hydrophobicity.

In this study, two key quantities were measured and used as descriptors of the state of the polymer chain. The first is the radius of gyration, R_g , which is given by its standard definition:

$$R_g^2 = N^{-1} \left\langle \sum_{i=1}^N |\mathbf{R}_i - \mathbf{R}_{CM}|^2 \right\rangle, \quad (7)$$

where \mathbf{R}_i is the position of the i th monomer, \mathbf{R}_{CM} is the center of mass of the polymer chain, and where the average $\langle \dots \rangle$ denotes a time (or ensemble) average over all configurations of the chain. The second measure is n_{MM} , the average number of monomer–monomer contacts, where in this case a contact is defined as two monomers separated by a distance $r \leq 1.5\sigma$.

Finally, the rate of collapse was quantified by defining two separate collapse times t_{50} and t_{90} for monitoring both $R_g^2(t)$ and $n_{MM}(t)$. t_{50} is defined as the average time taken for either R_g^2 or n_{MM} to decay or grow from its initial value by 50% of the difference between the initial and final values. Likewise, t_{90} is defined as the average time taken for either R_g^2 or n_{MM} to decay or grow from its initial value by 90% of the difference between the initial and final values.

III. RESULTS AND DISCUSSION

A. Equilibrium properties

Figure 2 shows the temperature dependence of R_g^2 for random copolymers of varying hydrophobic number fraction n_H at fixed density $\rho=0.7$ for chains of length (a) $N=40$, and (b) $N=100$. Note that because of the time-consuming calculations required to measure R_g^2 accurately, each curve represents results for only a single random HP copolymer

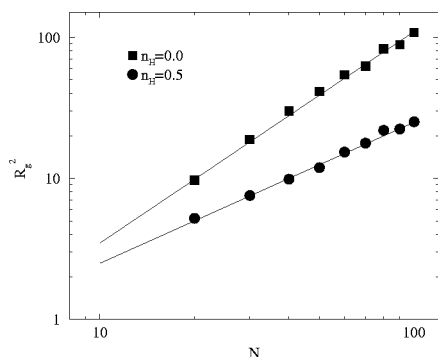


FIG. 3. Radius of gyration squared R_g^2 vs degree of polymerization N for random copolymers at $T=1.0$. The raw data shown are for the homopolymer case of $n_H=0$, and random copolymer case for $n_H=0.5$, each for $\lambda=0.0$. The superimposed lines are predictions in two dimensions from the scaling relation $R_g^2 \sim N^{2\nu}$ for the Flory coil, $\nu=0.75$ (upper line), and the compact globule, $\nu=1/3$ (lower line).

sequence; further averaging over HP sequencing is not expected to change the qualitative character of the results. Qualitatively, there is no difference between the results for the two chain lengths. In each case, one observes a substantial reduction in R_g^2 as T decreases. At higher T , R_g^2 levels off to a roughly constant value. At these temperatures the chains are in an extended or coil state—the “good” solvent conditions. After the abrupt decrease in R_g^2 with decreasing T , its value also begins to level off, though this is more apparent for the $N=100$ case with higher n_H . We find that the chain is in a liquidlike globule state in this regime, although for $T \leq 0.75$ the chain dynamics become very sluggish, and the chain is probably in a frozen or glassy state. Nevertheless, in each case there appears to be a distinct globule temperature regime, and, thus, the chain undergoes a clear thermally driven collapse transition from the extended coil state to a compact globule state. The transition region is generally smeared out over a wide range of T . The width of the transition is expected to decrease with increasing chain size, though it remains continuous (i.e., not first-order) as found in other studies of the polymer collapse transition for models without an explicit solvent. In this case, there is little evidence of the sharpening of the transition in going from $N=40$ to $N=100$: this would likely only be evident for much longer N . What is noticeable, however, is that the transition does become sharper and shifts to lower T with decreasing n_H . Eventually, in the limit $n_H=0$, the transition is completely suppressed, and the all-P chain retains a relatively constant R_g^2 and remains in the good solvent regime for all T .

We note that the calculations were performed for fixed ρ . As well, the range of T over the transition is generally quite broad. Consequently, the pressure P varies significantly over the transition—a feature that does not coincide with the standard experimental conditions of constant pressure. An alternative approach here would be to fix P and allow ρ to vary with T . We find that such conditions yield transition curves qualitatively similar to those in Fig. 2. In that case, however, we observed that ρ varies enormously over the transition temperature range. Ideally, we want to study the collapse kinetics of a polymer-solvent model system subject

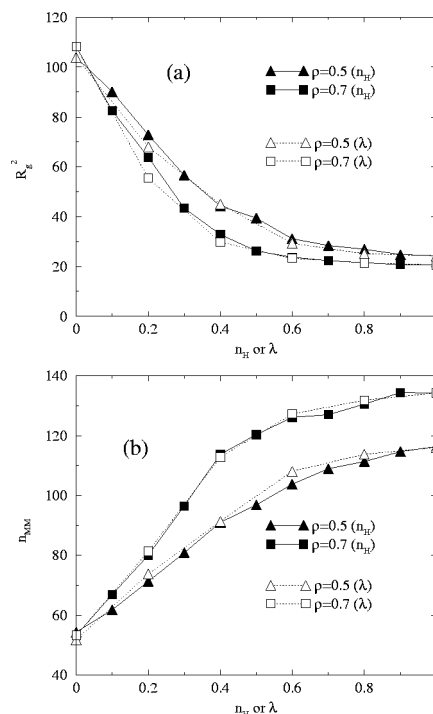


FIG. 4. Radius of gyration squared R_g^2 (top) and number of monomer-monomer contacts n_{MM} (bottom) vs hydrophobic number fraction n_H for random HP copolymers (closed symbols) or hydrophobic interaction degree λ for all-H homopolymers (open symbols) for a chain of length $N=100$ at $T=1.0$ at densities $\rho=0.5$ and 0.7 .

to standard experimental conditions of roughly constant solvent density and pressure, as an abrupt change in temperature would cause enormous changes either one of these two quantities and possibly lead to artifacts in the dynamics. Given this problem with the choice of studying polymer collapse dynamics by abruptly changing the temperature, we choose instead a different approach: changing n_H . As noted above, all-P polymers remain in the good solvent regime for all T , while, in general, other HP copolymers may be in the poor solvent (globule) regime at sufficiently low T . Consequently, we can observe a polymer collapse by starting with an extended coil configuration typical of all-P chain systems, and abruptly changing some P monomers to H monomers. This approach has the advantage that it can be done at constant temperature, and therefore at roughly constant pressure. It can be viewed as an abrupt nonthermal change in the solvent conditions of a real system, for example, a change in the pH of the solvent which will affect the solvent-monomer interactions.

We choose to fix $T=1.0$, a convenient temperature at which $N=100$ chains for $n_H \geq 0.5$ are definitely in the liquidlike globule state, and not in a frozen or glassy state. Figure 3 shows a plot of R_g^2 vs N on a log-log scale for two systems with $T=1.0$ and $\rho=0.7$: an all-P chain, and a random copolymer with $n_H=0.5$. The latter data were measured for a single random HP sequence (though with fixed n_H) for each N : a further average over HP sequencing would be useful, but not feasible. The lines drawn through the data sets are given by $R_g^2 \sim N^{2\nu}$, where $\nu=0.75$ for the all-P data and $\nu=1/3$ for the $n_H=0.5$ data. These exponents are the expected

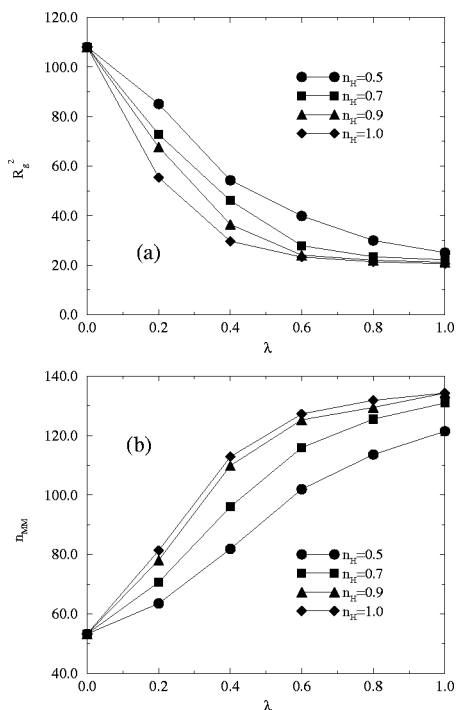


FIG. 5. Radius of gyration squared R_g^2 (top) and number of monomer-monomer contacts n_{MM} (bottom) versus hydrophobic interaction degree λ for a random HP copolymer chains of length $N=100$ for various hydrophobic number fractions $n_H \equiv N_H/N$, where N_H is the number of hydrophobic monomers on the chain and N is the total number of monomers. The simulations were carried out for at temperature $T=1.0$ and at fixed solvent density $\rho=0.7$.

values for good and poor solvent conditions in two dimensions. Thus, the collapse will involve a transition from an extended coil to a liquidlike globule state. We will consider only the case of quenching to $n_H \geq 0.5$, where the scaling relation illustrated for the copolymer in Fig. 3 is expected to remain valid.

Since we study the collapse kinetics by quenching with respect to n_H , it is useful to study equilibrium properties as a function of n_H . Figure 4 shows (a) R_g^2 , and (b) the number of monomer-monomer contacts n_{MM} , both as a function of n_H (closed symbols in the figures). As n_H increases, there is a reduction in the size of the chain as seen by the reduction in R_g^2 and the corresponding increase in n_{MM} . Note that for each point, only a single random HP copolymer sequence was used: sequence averaging is not expected to qualitatively change the results. The curves vary only slightly for $n_H > 0.5$, the regime corresponding to the globule state. Below $n_H=0.5$, the curves vary sharply. We expect that the observed transition would sharpen with increasing N , in analogy with typical results for thermally driven collapse transitions of model polymer systems.

Figure 4 also shows the effect of the variation of the solvent density on the equilibrium R_g^2 and n_{MM} : the chains in the $\rho=0.5$ solvent are consistently more expanded than those for the $\rho=0.7$ solvent as evidenced by the larger values of R_g^2 and lower values of n_{MM} . In the limit that $n_H=0$, the differences vanish to within the statistical accuracy of the measurements.

We also compare the effect of the variation of the hy-

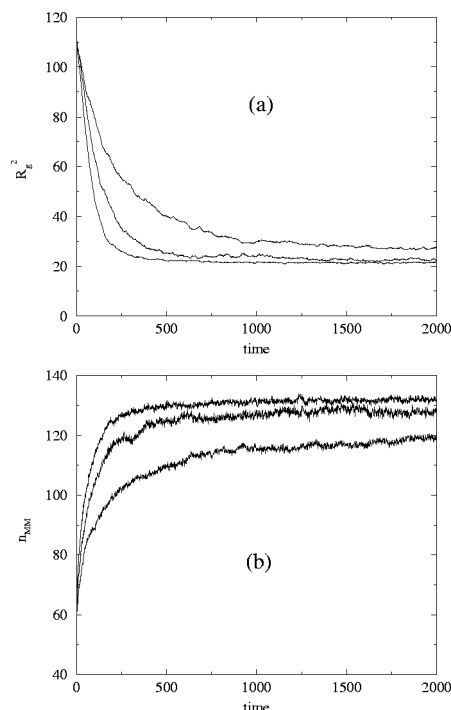


FIG. 6. Plots (a) radius of gyration squared R_g^2 vs time, and (b) number of monomer-monomer contacts n_{MM} vs time, for random HP copolymer collapse for chains of length $N=100$ monomers in a solvent with $N_{tot}=N+N_s=1225$, where N_{tot} , N and N_s are the total number of particles, the number of monomers and the number of solvent particles, respectively. The curves correspond to hydrophobic number fractions $n_H=0.5, 0.7$ and 0.9 from top to bottom for (a), and in reverse order for (b). Polymer collapse is induced by switching the hydrophobic interaction parameter from $\lambda=0.0$ to $\lambda=1.0$ at $T=1.0$.

drophobic interaction degree λ for all-H homopolymers on the same equilibrium properties with the effect of varying n_H for random HP copolymers. Figure 4 also shows R_g^2 and n_{MM} plotted as a function of λ (open symbols) superimposed on the previous data. For both densities, the curves overlap almost perfectly with the random copolymer curves. A slight difference is evident for R_g^2 at lower degrees of hydrophobicity ($n_H=\lambda \approx 0.2$), perhaps an indication that sequence specificity is important in copolymers at low n_H . However, in general, with respect to the static equilibrium properties, n_H and λ appear to be comparable measurements of hydrophobicity for copolymers and homopolymers, respectively, for this model.

For completeness, we consider the general case of the effect of the simultaneous variation of n_H and λ on random HP copolymers. Figure 5 shows results, again for equilibrium R_g^2 and n_{MM} , upon variation of λ for various hydrophobic number fractions n_H . Consistent with the particular case of $\lambda=1$ for HP copolymers in the data of Fig. 4, we see that the more general result is also true: as n_H increases for each fixed λ , the chains become more compact, with smaller R_g^2 and larger n_{MM} .

B. Collapse dynamics

We now consider the collapse properties of the polymer-solvent model system. Specifically, we consider collapse induced by an abrupt change in n_H , for the case of HP copoly-

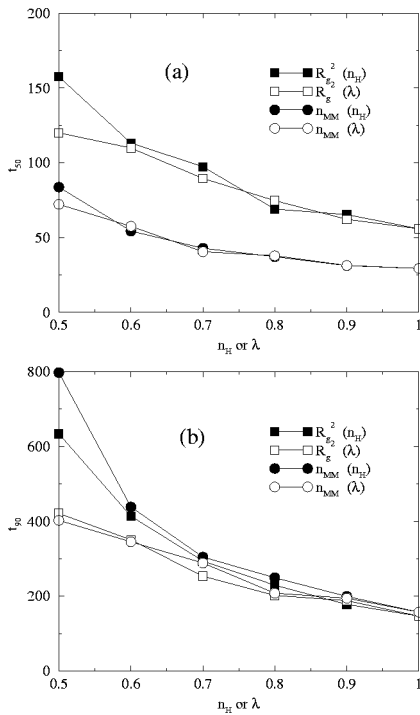


FIG. 7. Collapse times (a) t_{50} , and (b) t_{90} (see text for definition), vs hydrophobic number fraction n_H (for random HP copolymers) or λ (for all-H homopolymers) for chains of length $N=100$ monomers in a solvent with $N_{tot}=N+N_s=1225$, where N_{tot} , N and N_s are the total number of particles, the number of monomers and the number of solvent particles, respectively. Polymer collapse at $T=1.0$ is induced by switching the hydrophobic interaction parameter from $\lambda=0.0$ to either $\lambda=1.0$ for the random copolymers (times plotted vs n_H) or to other some other value of λ as labeled in the figure in the case of the homopolymers. The collapse times have been determined by monitoring the decay of the radius of gyration squared, R_g^2 , and the number of monomer-monomer contacts, n_{MM} .

mers, and by an abrupt change in λ , for the case of all-H homopolymers. As discussed in Sec. II, we consider the time-dependence of R_g^2 and n_{MM} during the quench, averaged over a large number of initial configurations representative of an all-P chain (i.e., $n_H=0$ for arbitrary λ), and, in the case of copolymers, over a few different random sequences, where appropriate, as well. The equilibrium results demonstrate that, under the system conditions considered ($T=1.0$, $\rho=0.5-0.7$) when the system parameters n_H or λ are abruptly changed from $n_H=\lambda=0$ to $n_H=\lambda \geq 0.5$, the system will undergo a conformational change from an extended coil to a liquidlike globule state.

Figure 6 shows averaged (a) $R_g^2(t)$, and (b) $n_{MM}(t)$, for random HP copolymers with different n_H . In all cases, the quantity relaxes from the initial value to its equilibrium final value over a time interval of $\Delta t < 2000$. The most notable point is that the decay is much more rapid for increasing hydrophobic number fraction n_H ; that is, increasing the number of hydrophobic monomers causes the chain to collapse more rapidly. Fitting to a stretched exponential function, we can obtain collapse times t_{50} and t_{90} , the 50% and 90% decay times defined in Sec. II. Figure 7 shows plots of (a) t_{50} , and (b) t_{90} vs n_H (closed symbols), for solvent density $\rho=0.7$, as determined by the decay of both R_g^2 and n_{MM} . The increase in the rate of collapse with n_H is very clear.

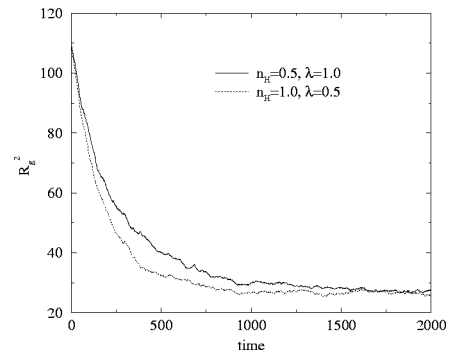


FIG. 8. Decay of radius of gyration squared vs time upon collapse for a random HP copolymer chain with hydrophobic number fraction $n_H=0.5$, and for an all-H homopolymer with $\lambda=0.5$.

As in the case of the equilibrium properties, we are interested in the differences in the collapse behavior between HP copolymers and all-H homopolymers upon variation of the hydrophobicity parameters n_H and λ , respectively. Results for the collapse times of homopolymers by quenching with respect to λ are also shown (open symbols) in Fig. 7. As in the case of the equilibrium average R_g^2 and n_{MM} , we find that the collapse times between the two systems are very close over a wide range of hydrophobicity, when n_H and λ are overlaid on the same scale. However, at lower values a difference begins to emerge: the homopolymer collapses more rapidly than the heteropolymer at $n_H=\lambda \approx 0.5$. This is made clear by the comparison of $R_g^2(t)$ of the collapses for the two different types of polymer shown in Fig. 8. We stress again that the equilibrium averages of the quantities are virtually identical at this value of n_H and λ , as seen in Fig. 4. Thus, it appears that a *uniform* increase in the hydrophobicity of a polymer chain results in more rapid collapse kinetics than a *heterogeneous* increase in hydrophobicity of the same magnitude. From Figs. 4 and 8, it is evident that the slower decay for the homopolymer case is manifest particularly in the longer time tail to the decay of R_g^2 and n_{MM} .

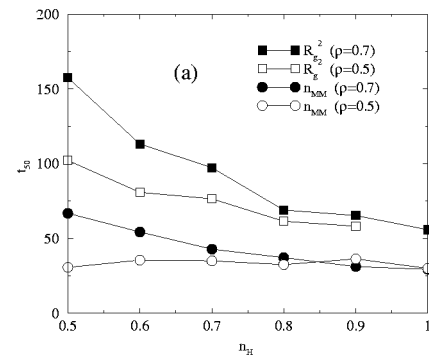


FIG. 9. Collapse times t_{50} vs degree of hydrophobicity n_H at densities $\rho=0.7$ and 0.5 for random copolymers of chain of length $N=100$ monomers in a solvent with $N_{tot}=N+N_s=1225$, where N_{tot} , N and N_s are the total number of particles, the number of monomers and the number of solvent particles, respectively. Polymer collapse at $T=1.0$ is induced by switching the hydrophobic interaction parameter from $\lambda=0.0$ to either $\lambda=1.0$ for the random copolymers. The collapse times have been determined by monitoring the decay of the radius of gyration squared, R_g^2 , and the number of monomer-monomer contacts, n_{MM} .

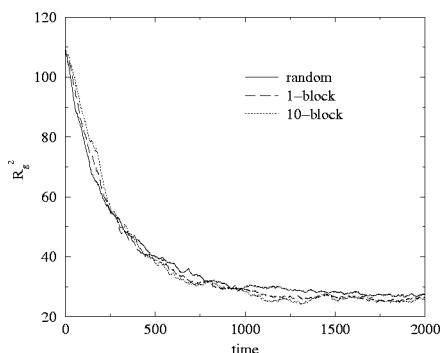


FIG. 10. Decay of radius of gyration squared versus time upon collapse for three HP copolymer chain sequences, all with hydrophobic number fraction $n_H=0.5$: random HP, alternating H and P monomers (1-block) and alternating 10-blocks of H and P monomers. $N_{\text{tot}}=N+N_s=1225$, where N_{tot} , N and N_s are the total number of particles, the number of monomers and the number of solvent particles, respectively.

We consider next the effect of solvent density on polymer collapse kinetics, this time, solely for random HP copolymers. Figure 9 shows t_{50} vs n_H for two densities, $\rho=0.5$ and 0.7 , as determined by measurement of $R_g^2(t)$ and $n_{\text{MM}}(t)$ during the collapse. Generally, the polymers in the lower density solvent collapse more rapidly than those in the higher density solvent. Although this difference appears to vanish in the $n_H=1$ limit, it increases monotonically with decreasing n_H . Thus, the rate of collapse of the more hydrophilic and more heterogeneous HP copolymers has a more sensitive dependence on the solvent density. It is worth noting again at this point that the polymer collapse occurs because it is energetically more favorable for the hydrophobic monomers to avoid contact as opposed to make contact with the solvent particles. Consequently, one might expect there to be a stronger driving force to collapse at higher solvent densities. On the other hand, the solvent can also be viewed as a sea of hard obstacles (neglecting the attractive component to the PS interaction) which tends to impede the collapse, as the solvent must flow out of the spaces between monomers. Clearly, the latter picture is more consistent with the observed density dependence of the collapse times.

The next case we consider is the effect of HP sequencing on the rate of collapse of HP copolymers. Due to the high computational cost of the calculations, we restrict the comparison to only three different sequences, all with $n_H=0.5$ at $T=1.0$ and $\rho=0.7$. The first case is just the random copolymer case, which we have discussed above. We also consider two HP sequences: a “one-block” composed of strictly alternating H and P monomers, and a “ten-block” composed of alternating blocks of ten H and P monomers. Figure 10 illustrates the basic result: in all three cases, the time-dependence of R_g^2 is virtually identical, as is also the case for the decay of n_{MM} . Thus, for the cases considered, sequence design has virtually no effect on the collapse dynamics of the copolymer.

This result is in marked contrast with many studies which have investigated the sequence dependence of heteropolymer systems, particularly so for those explicitly concerned with modeling protein folding. Generally, it is found that certain heteropolymer sequences can be designed to significantly increase the rate of collapse. A recent example is the study by Khokhlov and Khalatur,^{39,40} who have described a method for designing copolymer sequences that, relative to polymers composed of random sequences with the same number of hydrophobic monomers, have a sharper collapse transition at higher temperatures, and for which the collapse to the globule state proceeds more rapidly. Increasing the “blocky” character of the random sequences was also shown to have a similar, though less pronounced effect. Timoshenko *et al.*^{20,22} have also predicted a considerable sequence dependence of the collapse kinetics of heteropolymers using their GSC method.

More insight into the collapse dynamics of our polymer-solvent system may be obtained by inspection of a time-series of snapshots. Figure 11 shows a series of snapshots for a random heteropolymer chain with $n_H=0.9$. In this system, it appears that the chain collapses by a uniform thickening process. This appeared to be the general case for random copolymers independent of n_H . This is in marked contrast to results generally seen for a variety of homopolymer and heteropolymer systems, where typically the polymer collapses

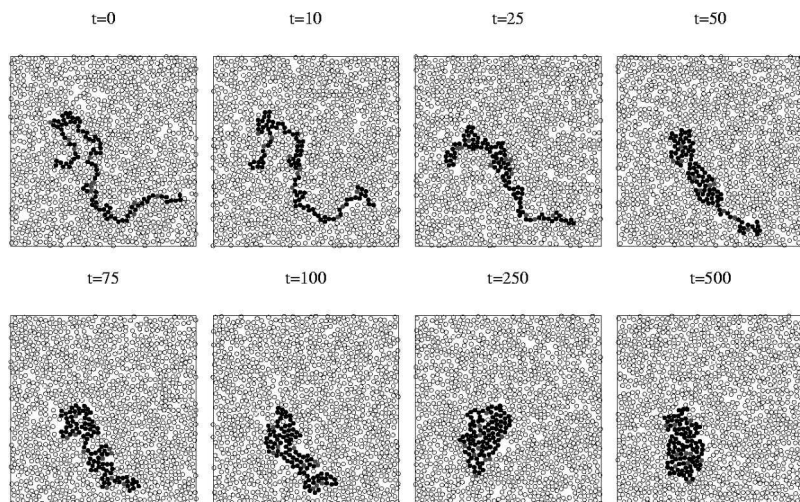


FIG. 11. Snapshots for random copolymer collapse at different times for chains of length $N=100$, and with $n_H=0.5$, for $N+N_s=1225$, $T=1.0$ and $\rho=0.7$. Open circles denote solvent particles, gray-filled circles denote P monomers, and black-filled circles represent H monomers.

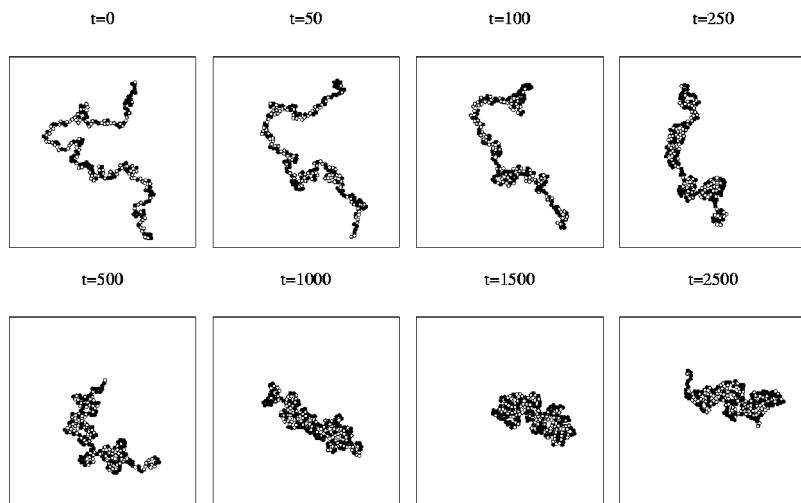


FIG. 12. Snapshots for random copolymer collapse at different times for chains of length $N=200$, and with $n_H=0.5$, at $T=1.0$ and $\rho=0.7$. Open circles represent H monomers and black-filled circles denote P monomers. The solvent has been omitted in the plots for convenience. Note that the simulation cell size is significantly larger than the boxes drawn around each chain snapshot.

into a number of local clusters over a short time which gradually coalesce over longer times. It is possible that the present observation is simply due to the fact that the $N=100$ chains are not long enough to display this effect in two dimensions. Consequently, we carried out several simulations for longer chains with $N=200$, with a total number of $N+N_s=4900$ particles. Figure 12 illustrates a collapse for a random copolymer with $n_H=0.5$. While we see some heterogeneity in the chain as it thickens upon collapse, there is still no clear formation of local clusters or “blobs.” Of course, it is possible that much longer chains are required to observe this effect, a case that is not feasible to pursue at present. Alternatively, it is possible that this is a general result in two dimensions where the effect of excluded volume is much more severe than in three dimensions.

The final case that we consider is a 10-block chain of $N=200$, whose collapse is illustrated in Fig. 13. In this case, we find that chain does indeed collapse with the cluster-forming mechanism. The clusters nucleate around the H-blocks, which cluster in order to minimize the number of contacts with the solvent. As the H-clusters form, the P-blocks move to the surface in order to “wet” the interface between the H clusters and the solvent particles. These clusters then appear to aggregate, and eventually form a globule

with a hydrophobic core, and a hydrophilic surface, reminiscent of the structure of a folded protein. A closer analogy is afforded with the designed copolymers of Khokhlov and Khalatur^{39,40} who observed a similar structure with their collapsed globules. Clearly, such a structure is energetically more favorable than a more random distribution of H and P monomers throughout the globule. However, the less blocky random HP copolymers are subject to a higher degree of “frustration,” and are unable to achieve this state. It is also interesting to compare the results for the 10-block collapse with the MC simulations of Kuznetsov *et al.*²⁸ who observed a local cluster formation upon collapse of random HP copolymers in which local blobs with hydrophobic cores and hydrophilic surfaces form, and then later coalesce. That they were able to see this effect for random copolymers while we did not is probably due to the fact that they used a 3-D model while ours is 2-D, where the frustration effects are likely to be more problematic. One other difference between the two studies is evident: Kuznetsov *et al.* note that the P-coated local clusters lead to very long coalescence times. By contrast, we find that this mechanism seen for the 10-block polymer, does not lead to any significant increase in the collapse times. Again, this was evident from the quantitative mea-

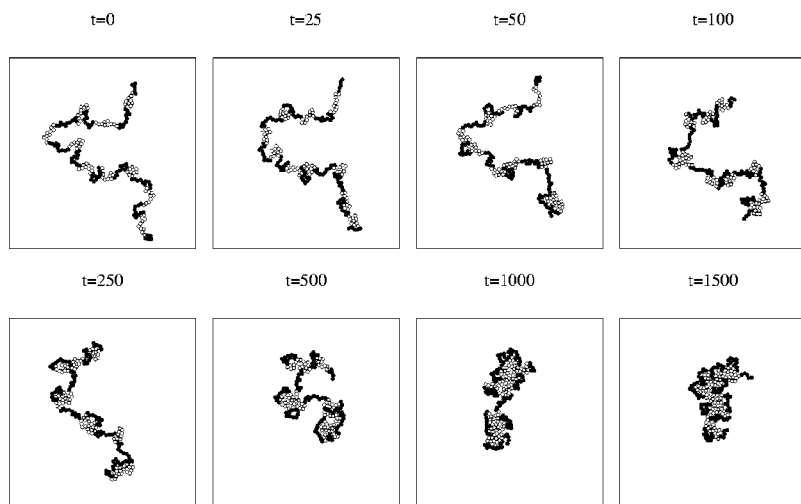


FIG. 13. Same as in Fig. 12, except for 10-block sequential copolymer.

surements illustrated in Fig. 10, as well as from a qualitative inspection of the snapshots of Figs. 12 and 13.

IV. CONCLUSIONS

In this paper, we have investigated the collapse transition properties of a simple two-dimensional system composed of a single flexible HP copolymer chain immersed in a Lennard-Jones solvent. The key feature of the model is the fact that H and P monomers are differentiated solely on the basis of their interaction with the solvent: HS interactions are purely repulsive while the PS pair potential have an attractive component as well. Chains with sufficiently high hydrophobic number fractions n_H were found to undergo a thermally driven transition from an extended coil in a "good" solvent to a liquidlike globule in a "poor" solvent. We noted that the transition for random copolymers occurred over a narrower temperature range and at lower temperatures with decreasing n_H . In addition, a comparable transition was observed at sufficiently low temperature upon variation of n_H . For comparison, we studied a similar collapse transition for a homopolymer system upon variation of λ , a parameter describing the degree of hydrophobicity of the hydrophobic-solvent interaction. The two parameters n_H and λ turned out to be quantitatively comparable measures of hydrophobicity for random copolymer and homopolymer chain systems, respectively, with respect to the measurement of equilibrium quantities, R_g^2 and n_{MM} .

For practical reasons we chose to study the collapse kinetics by making an abrupt change in n_H and λ , rather than temperature. In each case, we find that the collapse rates are sensitive to the final values of n_H and λ , and tend to increase upon decreasing each of these parameters. Thus, for example, copolymers with a greater number of hydrophobic monomers collapse more rapidly than those with fewer hydrophobic monomers. Unlike the case of the equilibrium properties of the transition, we find that the collapse rates between copolymers and hydrophobic homopolymers tend to differ as each n_H and λ are decreased. In particular, it appears that R_g^2 and n_{MM} for the copolymer chains have longer tails to their decays upon quenching than do those for the homopolymer chains of comparable hydrophobicity.

At moderate solvent densities, we find that the collapse rate for random copolymer chains increases with increasing chain density for all n_H . By contrast, we find no significant dependence of the collapse rates on the HP copolymer sequence, in contrast with results of other studies. A qualitative inspection of the system configurations upon collapse suggest that the chains collapse via a uniform thickening rather than the formation of local clusters, which is the case observed in other systems. This was the standard process observed for all random copolymers, independent of n_H . It is possible that this effect is a result of the two-dimensional character of the system, for which excluded volume effects may preclude such local structures, in general. One exception to this rule that we noted was the case of a polymer composed of sufficiently long alternating HP blocks. In this case, local clusters with H cores and P shells do first form, then coalesce at later times of the collapse.

To our knowledge, this is the first study of the coil-globule collapse dynamics using a model employing an explicit solvent. Clearly, more of such studies are required before a clear picture of collapse dynamics can emerge. While many of the existing theories of this process have attempted to account for the effects of hydrodynamics, simulation studies have thus far failed to do so in a satisfactory manner. Thus, inclusion of an explicit solvent in the simulation model represents a significant step in that direction. Of course, there are several important questions that this study raises. In particular, it is difficult to determine why some of the observed behavior in this system differs from that of other systems. As mentioned above, the two-dimensional nature of the system is expected to affect the collapse mechanism, in general. Of course, the explicit presence of the solvent is expected to play a significant role. Clearly, it would be of interest to conduct additional studies using a comparable model in three dimensions, as well as in the absence of an explicit solvent, in order to shed light on these matters. Such studies are currently underway.

ACKNOWLEDGMENTS

We would like to thank Andrew Torda and Christine Villeneuve for a critical reading of the manuscript. We would also like to thank Hong Guo, Christine Villeneuve, and Andrew Torda for very stimulating discussions. J.P. acknowledges the financial support of the National Sciences and Engineering Research Council of Canada (NSERC).

- ¹ *Protein Folding*, edited by T. E. Creighton (Freeman, New York, 1994).
- ² V. S. Pande, A. Y. Grosberg, T. Tanaka, and D. S. Rokhsar, *Curr. Opin. Struct. Biol.* **8**, 68 (1998).
- ³ E. I. Shakhovich, *Curr. Opin. Struct. Biol.* **7**, 29 (1997).
- ⁴ C. Wu and S. Zhou, *Phys. Rev. Lett.* **77**, 3053 (1996).
- ⁵ M. Nakata and T. Nakagawa, *Phys. Rev. E* **56**, 3338 (1997).
- ⁶ X. Wang, X. Qiu, and C. Wu, *Macromolecules* **31**, 2972 (1998).
- ⁷ X. Wang and C. Wu, *Macromolecules* **32**, 4299 (1999).
- ⁸ P. G. de Gennes, *J. Phys. (France) Lett.* **46**, L639 (1985).
- ⁹ A. Y. Grosberg, S. K. Nechaev, and E. I. Shakhovich, *J. Phys. (France) Lett.* **49**, 2095 (1988).
- ¹⁰ A. Buguin, F. Brochard-Wyart, and P. G. de Gennes, *C. R. Acad. Sci. Paris* **322**, 741 (1996).
- ¹¹ L. I. Klushin, *J. Chem. Phys.* **108**, 7917 (1998).
- ¹² E. Pittard, *Eur. Phys. J.: Appl. Phys.* **7**, 665 (1999).
- ¹³ A. Halperin and P. M. Goldbart, *Phys. Rev. E* **61**, 565 (2000).
- ¹⁴ F. Ganazzoli, R. L. Ferla, and G. Allegra, *Macromolecules* **28**, 5285 (1995).
- ¹⁵ T. Garel, H. Orland, and E. Pittard, in *Spin Glasses and Random Fields*, edited by A. P. Young (World Scientific, Singapore, 1998).
- ¹⁶ D. Thirumalai, *J. Phys. I* **5**, 1547 (1995).
- ¹⁷ E. G. Timoshenko, Y. A. Kuznetsov, and K. A. Dawson, *J. Chem. Phys.* **102**, 1816 (1995).
- ¹⁸ Y. A. Kuznetsov, E. G. Timoshenko, and K. A. Dawson, *J. Chem. Phys.* **104**, 3338 (1996).
- ¹⁹ Y. A. Kuznetsov, E. G. Timoshenko, and K. A. Dawson, *J. Chem. Phys.* **105**, 7116 (1996).
- ²⁰ E. G. Timoshenko, Y. A. Kuznetsov, and K. A. Dawson, *Phys. Rev. E* **54**, 4071 (1996).
- ²¹ E. G. Timoshenko, Y. A. Kuznetsov, and K. A. Dawson, *Physica A* **236**, 58 (1997).
- ²² E. G. Timoshenko, Y. A. Kuznetsov, and K. A. Dawson, *Phys. Rev. E* **57**, 6801 (1998).
- ²³ B. Ostrovsky and Y. Bar-Yam, *Europhys. Lett.* **25**, 409 (1994).
- ²⁴ B. Ostrovsky and Y. Bar-Yam, *Biophys. J.* **68**, 1694 (1995).
- ²⁵ G. E. Crooks, B. Ostrovsky, and Y. Bar-Yam, *Phys. Rev. E* **60**, 4559 (1999).

- ²⁶G. Tanaka and W. L. Mattice, *Macromolecules* **28**, 1049 (1995).
- ²⁷A. Byrne, P. Kierman, D. Green, and K. A. Dawson, *J. Chem. Phys.* **102**, 573 (1995).
- ²⁸Y. A. Kuznetsov, E. G. Timoshenko, and K. A. Dawson, *J. Chem. Phys.* **103**, 4807 (1995).
- ²⁹A. Byrne, E. G. Timoshenko, and K. A. Dawson, *Physica A* **243**, 14 (1997).
- ³⁰C. Villeneuve, H. Guo, and M. J. Zuckermann, *Macromolecules* **30**, 3066 (1997).
- ³¹M. Doi and S. F. Edwards, *The Theory of Polymer Dynamics* (Clarendon, Oxford, 1986).
- ³²B. Dünweg and K. Kremer, *Phys. Rev. Lett.* **66**, 2996 (1991).
- ³³C. Pierleoni and J. P. Ryckaert, *Phys. Rev. Lett.* **66**, 2992 (1991).
- ³⁴S. R. Shannon and T. C. Choy, *Phys. Rev. Lett.* **79**, 1455 (1997).
- ³⁵M. P. Allen and D. J. Tildesley, *Computer Simulation of Liquids* (Clarendon, Oxford, 1987), pp. 149–152.
- ³⁶G. J. Martyna, M. E. Tuckerman, D. J. Tobias, and M. L. Klein, *Mol. Phys.* **87**, 1117 (1996).
- ³⁷M. Tuckerman, G. J. Martyna, and B. J. Berne, *J. Chem. Phys.* **93**, 1287 (1990).
- ³⁸M. Tuckerman, B. J. Berne, and G. J. Martyna, *J. Chem. Phys.* **97**, 1990 (1992).
- ³⁹A. R. Khokhlov and P. G. Khalatur, *Physica A* **249**, 253 (1998).
- ⁴⁰A. R. Khokhlov and P. G. Khalatur, *Phys. Rev. Lett.* **82**, 3456 (1999).