

Effect of the Coil–Globule Transition on the Free-Energy Barrier for Intrachain Crystal Nucleation[†]

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The rate of crystal nucleation of colloids and globular proteins can be enhanced by critical density fluctuations. It has been argued that a closely related phenomenon influences the rate of intramolecular “crystallization” of single-chain polymers. We report Monte Carlo simulations of the free-energy barrier that separates the crystalline state of a homopolymer chain from the disordered state. The simulations show that the barrier for nucleation of the ordered state is drastically lowered as the disordered state changes from a coil to a globule. We discuss the relation of the present findings to intramolecular nucleation of heteropolymers, such as proteins.

I. Introduction

The facility with which a new phase nucleates from a metastable parent phase depends strongly on the free-energy density of the interface separating the old and new phases.¹ Any physical condition that affects the surface free energy is therefore likely to have a pronounced effect on the nucleation process. A case in point is the nucleation from a solution of crystals of colloids or globular proteins.^{2–4} If the range of attraction between the particles is sufficiently short, fluid–fluid demixing occurs in a temperature region where the fluid phase itself is metastable with respect to the crystalline phase.⁵ In that case, a crystal nucleus may be wetted by a layer of the dense fluid phase. Near a liquid–liquid critical point, there is a strong decrease in the free-energy density of the interface between the dense fluid in the wetting layer and the low-density fluid outside. This effect results in a significant decrease of the surface free energy of the crystal nucleus, and hence an increase in the probability that such nuclei form by thermal fluctuations.

A single polymer chain is, of course, different from a bulk phase. However, the “phase behavior” of single chains is reminiscent of that of a simple liquid: at high temperatures, the polymer is in the low-density coil state (analogous to the vapor phase of a simple molecular system). Upon cooling, this coil may collapse to form a dense globule (the equivalent of the liquid state), and at still lower temperatures, this globule may transform into its native state: a single-chain crystallite—the equivalent of the crystalline solid (for an early discussion, see, e.g., ref 6). In the past decade, numerical evidence supporting this three-state model has come from a number of studies^{7–11}. The analogy of the “phase diagram” of a single chain with that of simple atomic or colloidal systems suggests that the order in which the freezing and coil–globule transitions occur should depend on the nature of the interaction between the chain units. If the coil–native transition is dominated by an intramolecular nucleation event, we should expect that the ease of folding into the native state is strongly affected by the vicinity of the metastable coil–globule transition. For protein

models, there is much evidence that the folding rate increases strongly as the coil–globule transition approaches the folding transition. For instance, Klimov and Thirumalai¹² showed that the folding rates of short “lattice proteins” correlate very well with the distance between the folding temperature and the coil–globule collapse temperature: the folding rate was found to increase steeply as the collapse temperature approached the folding temperature. This evidence suggests the existence of a nucleation barrier for folding that is sensitive to the vicinity of a coil–globule transition. However, the model proteins studied in ref 12 were very short (15–27 monomers), in which case it is not meaningful to distinguish between “surface” and “bulk” regions. Hence, we should not expect a macroscopic picture, such as classical nucleation theory,¹ to apply directly to this situation. There is, however, evidence from simulations on longer ($N = 100$) semiflexible homopolymer chains¹¹ that show clear evidence for the existence of a free-energy barrier separating the molten-globule state and the crystalline state. However, the simulations of ref 11 were limited to cases where the barrier was so low that it could be probed by conventional Metropolis sampling. This limited the study to barriers that were less than $5 k_B T$ in height. However, as we show below, intramolecular nucleation barriers for moderately long chains ($N = 512$) may easily be at least 1 order of magnitude higher than that. To study the effect of the coil–globule transition on the rate of formation of a single-chain crystal (a “native state” in the protein language), it is clearly important to correlate the behavior of the intramolecular crystal-nucleation barrier at many different points in the single-chain phase diagram, including points where the probability of spontaneous barrier crossing on the time scale of a simulation is negligible.

II. Simulations

In a recent paper, we use techniques that have been developed in the numerical study of crystal nucleation¹³ to study the intramolecular nucleation barrier that separates the disordered (coil or globule) state from the ordered single-chain crystalline state. To this end, we consider a simple lattice model for homopolymers. It should be noted that the simplest, Flory-style lattice models for homopolymers do not exhibit a freezing transition. The reason is that the entropy loss associated with

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freezing is not compensated by a corresponding energy gain. To achieve that, it is necessary to have a system where energetic gain can only be achieved at the expense of ordering. This is certainly the case for most protein models, in particular for the Gō model²¹ where only contacts that are nearest neighbors in the native state result in an energy gain. Semiflexible chains provide another example of models where energy gain requires (local) ordering, as the attractive interaction between neighboring segments is maximal when the segments are perfectly aligned. In the present study, we use a simple model that mimics a semiflexible homopolymer chain.¹⁴ In this model, bonds may be oriented either along the lattice axes or along the (body or plane) diagonals. Hence, the coordination number of each lattice site is $6 + 12 + 8 = 26$. This implies that there are 13 distinct orientations possible for every bond. This model¹⁴ has sufficient flexibility to allow the chain to form a coil, a liquidlike globule, and a single-chain crystal. More importantly, changing the nature of the interaction between chain units allows us to control whether the chain undergoes a direct coil–crystal (“vapor–crystal”) transition or if a coil–globule (“vapor–liquid”) transition occurs first. In the model of ref 14, no two monomers can occupy the same lattice position, and bonds cannot cross. The monomers have both an isotropic nearest-neighbor attraction (strength B) and an attractive interaction between nonbonded parallel bonds (strength E_p). In the present calculations, we assume that the polymers are fully flexible; that is, there is no energy penalty for introducing a kink in the polymer chain. The ratio B/E_p controls the relative location of the coil–globule and coil–native transition curves.

Earlier simulations on the present model have established that it is a good candidate to study the interplay between the coil–globule and coil–crystal transitions, as there is a clear free-energy barrier separating the coil state from the crystalline state.¹⁵ In the present study, we investigate how this barrier is changed as the chain-freezing transition crosses the coil–globule transition. Of course, such a comparison is only meaningful if, in all cases, the driving force for crystallization is the same. We therefore considered the case where the free-energy minima in the crystalline state and the coil state are the same. In the thermodynamic limit, this condition is equivalent to the statement that the system is equally as likely to be found in a crystalline state or a disordered state. For the relatively long but finite chains that we use, the equality of free-energy minima is a convenient approximation of the coexistence point. In a bulk system, the nucleation barrier diverges at coexistence,¹ but in a finite system, such as a single-chain system, the barrier is finite.

We performed dynamic Monte Carlo (MC) simulations on a single lattice polymer chain, containing 512 monomeric units. We employed periodic boundary conditions (thus obviating the need to constrain the center of mass of the polymer), but the size of the simulation box (128^3 lattice sites) was large enough to eliminate virtually all spurious self-contacts of a chain with its periodic images. In the MC algorithm,¹⁶ we allow for local moves of the chain units, provided that they do not disrupt the chain connectivity. In addition, we allow for local sliding moves that facilitate the diffusion of kinks along the chain. These moves include reptation moves as a limiting case. We started the simulations by cooling a single chain down from the high-temperature “coil” state. During cooling, we monitored the onset of both the chain collapse transition and chain crystallization. This information allowed us to construct an approximate phase diagram of the single-chain system (see Figure 1). This figure shows the tentative single-chain phase diagrams as obtained

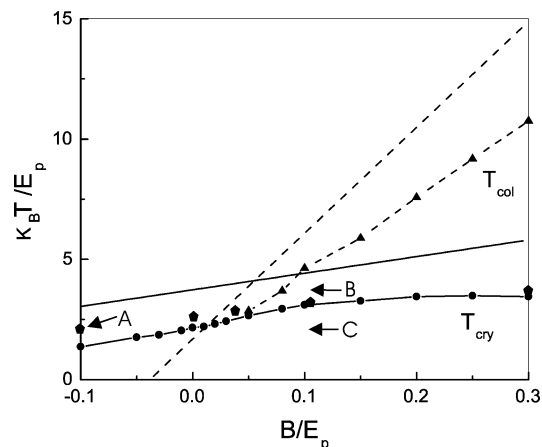


Figure 1. Tentative phase diagrams of a single-chain polymer as obtained from dynamic MC simulations. The different points correspond to cooling runs performed at different B/E_p values. The cooling procedure involved a stepwise increase in the value of $E_p/(k_B T)$, starting from the infinite temperature limit. During cooling, the step size in $E_p/(k_B T)$ was chosen to be equal to 0.01. After every step, the chains were equilibrated during one million Monte Carlo cycles (one cycle corresponds to one trial move per chain unit). A chain contains 512 units. In the figure, the filled circles denote the onset of crystallization while the filled triangles denote the onset of the collapse transition. The estimates of the freezing transition based on free-energy calculations are indicated by filled pentagons. The dashed curve denotes the mean-field prediction¹⁷ for the critical temperature for bulk liquid–liquid demixing, and the solid curve refers to the mean-field prediction for bulk freezing at the critical demixing concentration. The arrows next to the letters A, B, and C indicate the state points of the snapshots in Figures 5–7.

from cooling runs in our kinetic MC simulations. In our simulations, chain collapse was detected by monitoring the fraction of solvent particles surrounding the monomeric units of the polymer chain. For a fully extended chain, this fraction is 1; for a fully collapsed chain, this number is small but nonzero, as monomers on the surface are always in contact with solvent particles. Crystallization was detected by monitoring the average fraction of parallel chain segments that are in contact with (but not directly bonded to) the segments of the polymer chain. In a coil, this number is close to zero, and in a perfectly crystalline chain, it is large but, due to surface effects, not equal to 1. The freezing curves thus estimated by detecting the point where crystallization occurs spontaneously agree rather well with the results of the free-energy calculations (filled pentagons). There is clear evidence for supercooling in the regime where the transition is directly from coil to crystal. This is not surprising because, as can be seen from Figure 3, this is precisely the regime where the nucleation barrier is highest. In Figure 1, we also indicate the mean-field predictions¹⁷ for the critical temperatures for bulk liquid–liquid demixing and the equilibrium freezing temperatures of a bulk polymer crystal at the critical demixing concentration plotted as a function of B/E_p . The locations of the freezing and demixing transitions predicted by mean-field theory for a bulk solution of polymer chains are in qualitative agreement with the observed coil–globule and coil–crystal transition curves. From these phase diagrams, we can see that, upon cooling a polymer in a relatively good solvent ($B/E_p < 0.05$), the coil state transforms directly into a single-chain crystallite. However, in poor solvents, the polymer undergoes a coil–globule transition before freezing.

Using free-energy calculations, we subsequently determined the temperature where the free-energy minimum of the coil (or globule) state is equal to that of the crystalline state. We traced the progress of melting by counting the number of disordered

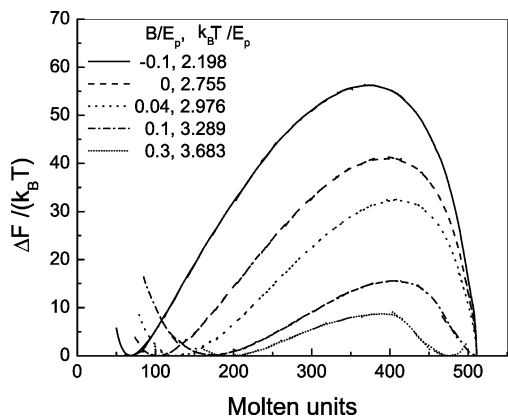


Figure 2. Height of the free-energy barrier (ΔF) that separates the stable ordered state and the disordered state. The free energy (ΔF) has been expressed in units of the thermal energy ($k_B T$). The barriers have been computed at the temperatures where the free-energy difference between the minima that correspond to the ordered and disordered states vanishes. In the thermodynamic limit, this corresponds to the melting temperature. The B/E_p values corresponding to the different barriers are indicated in the figure.

(“molten”) units, defined here as polymer bonds having less than five parallel neighbors (out of a maximum of 24 nonbonded neighbors). We computed the free energy of the chain as a function of the number of molten units, using the fluctuation expression $\Delta F/(k_B T) = -\ln P(n)$, where $P(n)$ is the probability to find n molten units in the single-chain system. To be able to probe free-energy barriers that are much higher than $k_B T$, we used multihistogram umbrella sampling.^{18,19} To speed up equilibration, we combined the multihistogram method with parallel tempering.

Figure 2 shows the intrachain crystal-nucleation barriers for a range of B/E_p values. For temperatures above approximately $3E_p/k_B$ (and $B/E_p > 0.05$), the barrier separates the crystalline state from the molten-globule state. However, below that temperature, the system transforms directly from the coil state to the crystalline state. This indicates that the coil–crystal coexistence curve intersects the globule–crystal curve around $T = 3E_p/k_B$. The transition from coil to molten globule is continuous, and there is no free-energy barrier associated with this transition. Figure 3 shows that the height of the crystal-nucleation barriers decreases very strongly as the temperature approaches the coil–globule–native “triple point” from below. This suggests that, already well before the point where the globule state is thermodynamically stable, fluctuations associated with the vicinity of this phase assist the transformation from the coil to the crystalline state. However, the nucleation barriers are not at a minimum at the point where the coil–globule transition coincides with the coil–crystal transition. Rather, we find that the barrier for crystallization continues to decrease as the range of stability of the molten-globule state expands. This suggests that the behavior of the homopolymer system studied here may, at least in some respect, be different from the protein model studied by Klimov and Thirumalai.¹² However, as mentioned above, the study of ref 12 focused on the folding rate of very short “protein” chains, while we computed the nucleation barrier for long homopolymers where a nucleation picture may be more appropriate. In view of this difference in approach, we cannot conclude to what extent the observed differences between the present results and those reported in ref 12 reflect real differences in the behavior of semiflexible homopolymers and protein-like heteropolymers or could be simply attributed to size effects.

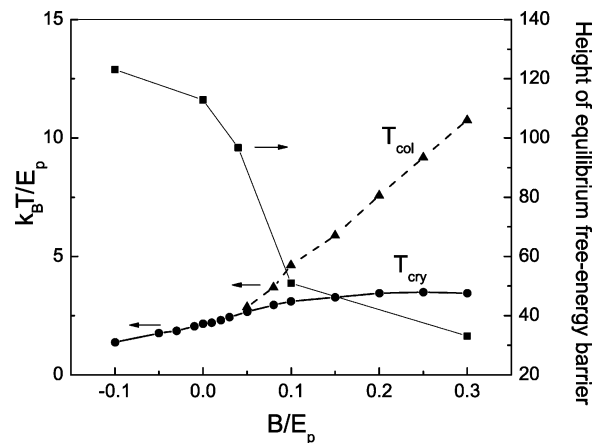


Figure 3. This figure shows the dependence of the barrier for intramolecular crystallization on the parameter B/E_p that controls the nature of the single-chain phase diagram. In the same figure, this phase diagram is also shown. As can be seen from the figure, the barrier for nucleation drops sharply upon approach to the point where the molten globule intervenes between the coil state and the crystalline state.

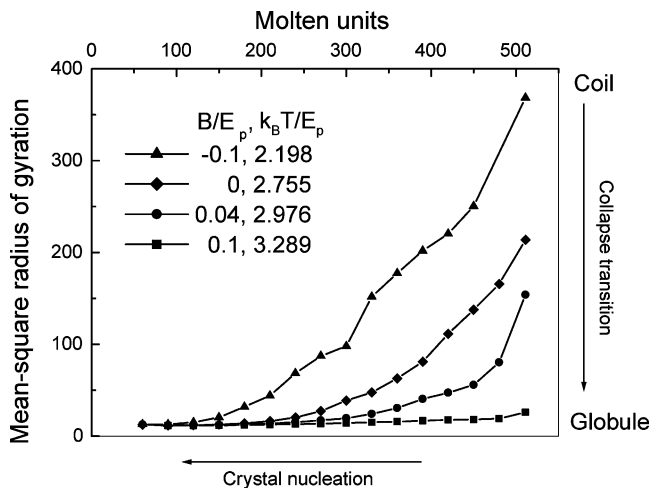


Figure 4. Relation between mean-square radius of gyration and number of molten units for a single-chain polymer for various B/E_p values. The arrows indicate the directions of the collapse transition and of crystal nucleation, respectively.

Figures 2 and 3 do not provide direct information about the qualitative difference between the freezing transitions in good and poor solvents. To make this difference clear, Figure 4 shows the mean-square radius of gyration of a single chain as a function of the number of molten (i.e., noncrystalline) units, at the temperature where the single-chain crystal coexists with the disordered state. As can be seen from this figure, single-chain freezing in a good solvent implies chain collapse. In contrast, freezing in a poor solvent is simply a transition from one compact state (the globule) to another (the crystallite). The transition barely affects the spatial extent of the polymer. Figures 5–7 show typical structures of the coil, globule, and crystal states of a single lattice polymer.

III. Discussion

To place these results in a broader context, it is instructive to consider the role of the interaction parameters B and E_p . The parameter B describes a nonspecific interaction that favors a dense (but still disordered) state of the polymer over the dilute coil state. In contrast, the parameter E_p specifically favors a highly ordered, dense state. As was mentioned in the Introduction, there are many other models for chain molecules where

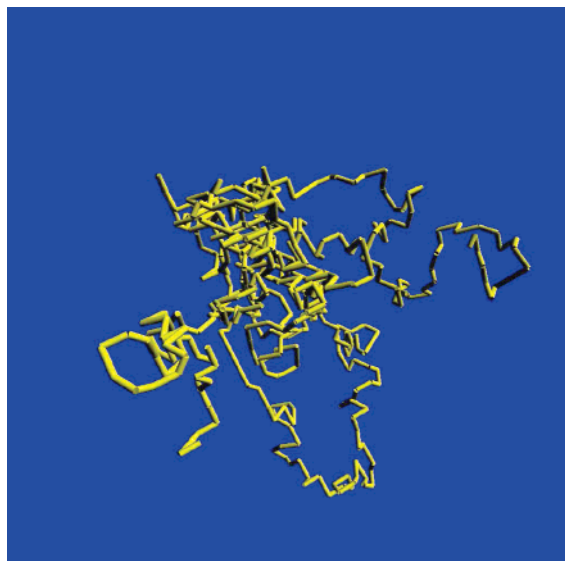


Figure 5. Snapshot showing the coil state of a 512-segment semiflexible lattice polymer at $B/E_p = -0.1$ and $k_B T/E_p = 2.174$ (symbol A in Figure 1).

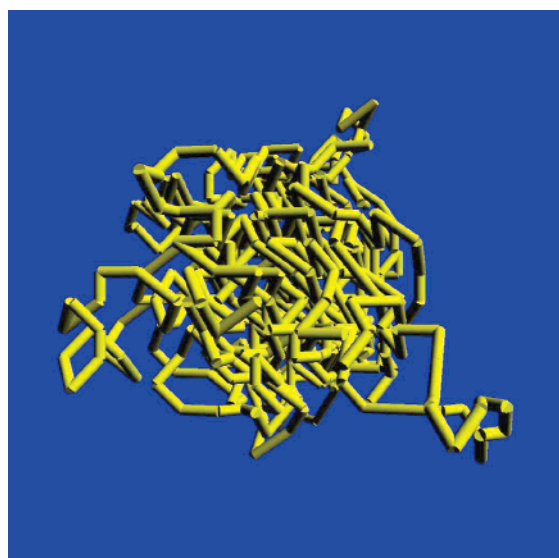


Figure 6. Snapshot showing the molten-globule state of a 512-segment semiflexible lattice polymer at $B/E_p = 0.1$ and $k_B T/E_p = 3.289$ (symbol B in Figure 1).

interaction parameters similar to E_p appear (for an overview of lattice models in the context of protein folding, see ref 20). For instance, in the $G\bar{o}$ model for proteins,²¹ the interactions between monomers (“amino acids”) are designed to uniquely favor one particular native state (or, to be more precise, a small number of, usually symmetry-related, lowest-energy states). Hence, the nearest-neighbor interaction in the $G\bar{o}$ model is similar to E_p : it favors an ordered structure, but because the interaction is so specific, there is little driving force for the formation of a disordered dense globule. By analogy with the present results, we should expect that the $G\bar{o}$ model therefore behaves as a system where B/E_p is small, that is, in the range where there is a high free-energy barrier separating the coil and native states.

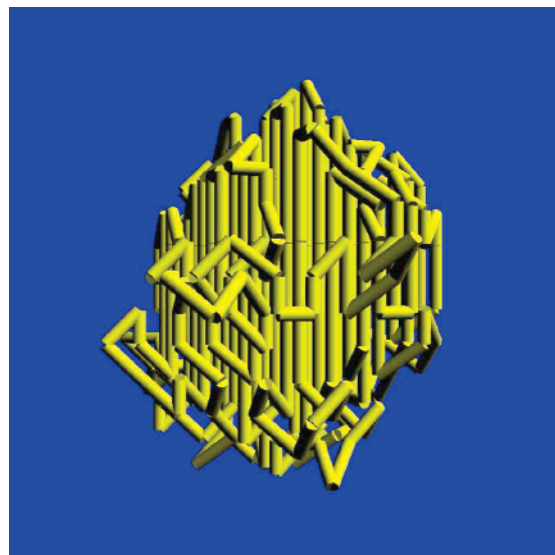


Figure 7. Snapshot showing the crystalline state of a 512-segment semiflexible lattice polymer at $B/E_p = 0.1$ and $k_B T/E_p = 2.289$ (symbol C in Figure 1).

In fact, it is well-known that the $G\bar{o}$ model does, indeed, yield strong, first-order-like, coil-to-native transitions.^{20,22} The present study suggests that adding a nonspecific attraction to the $G\bar{o}$ model should facilitate the transition from the coil to the native state by lowering the nucleation barrier.

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