

Free Energy Trajectory for Escape of a Single Chain from a Diblock Copolymer Micelle

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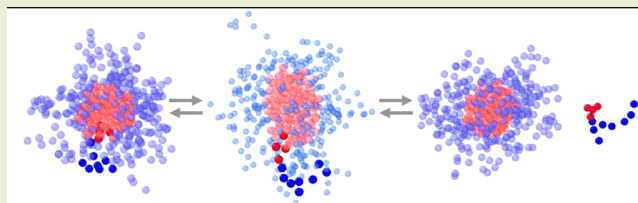


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ABSTRACT: We use umbrella sampling to compute the free energy trajectory of a single chain undergoing expulsion from an isolated diblock copolymer micelle. This approach elucidates the experimentally unobservable transition state, identifies the spatial position of the maximum free energy, and reveals the chain conformation of a single chain as it undergoes expulsion. Combining umbrella sampling with dissipative particle dynamics simulations of A_4B_8 micelles reveals that the core block (A) of the expelled chain remains partially stretched at the transition state, in contrast with the collapsed state assumed in some previous models. The free energy barrier increases linearly with the Flory–Huggins interaction parameter χ up to large interaction energies, where the structure of the otherwise spherical core apparently deforms near the transition state.



The self-assembly of block copolymers into micelles is essential for a variety of applications, including viscosity modification of oils,^{1,2} the formation of complex block polymer phases,³ and controlled drug release.^{4–6} Many of these applications require micelles to maintain a dynamic equilibrium. Importantly, chain exchange is a fundamental process of micelle relaxation which has been shown theoretically to be the dominant mechanism close to equilibrium.^{7,8} However, despite substantial experimental progress, an understanding of the molecular level details of the process remains incomplete.

Experimentally, chain exchange has been studied with fluorescence spectroscopy,^{9,10} stopped-flow techniques,^{11–13} and more recently time-resolved small-angle neutron scattering (SANS).^{14–26} All of these methods provide information about the kinetics of chain exchange for the system ensemble and cannot directly probe the transition state. In the case of SANS, the free energy barrier to chain expulsion, assumed to be the rate-limiting step for chain exchange,⁸ can be obtained from the measured time constant for exchange, τ_{ex} either by examining the temperature dependence of τ_{ex} or by fitting to a model. The position of the transition state along the “reaction coordinate” should provide insight into the conformation of the block copolymer chain as it undergoes expulsion from the micelle; however, the full free energy profile for chain exchange has only been computed for small-molecule surfactant systems.²⁷ Most exchange experiments have been interpreted in the context of the theory of Halperin and Alexander,⁸ which describes the process of chain expulsion for block copolymer micelles by assuming that the core block collapses into a globule upon entering the corona. In this theory, their model for the transition state that leads to a free energy barrier scales as $\gamma N_A^{2/3}$, where γ is the interfacial energy between the core block and the solvent and N_A is the core block degree of

polymerization. Recent studies have found the barrier to scale linearly with N_A ,^{14,15,17,34} casting doubt on the postulated transition state by Halperin and Alexander. The same linear dependence was also reported in the barrier from measurements of chain diffusion in ordered block copolymer melts.^{28–30} These results raise the possibility that a core block is not significantly collapsed upon entering the unfavorable domain. As the resolution of experimental techniques is not yet sufficient to yield information about the conformation of single chains undergoing expulsion, there remains a need to develop simulation techniques to access the core block conformation at the transition state for chain exchange.

In this work, we introduce a simulation framework to evaluate the nature of the transition state to chain exchange and thus the foundations of the Halperin and Alexander model. Here, we employ an umbrella sampling method to compute the free energy landscape for a chain undergoing expulsion from a spherical micelle. We utilize a model dissipative particle dynamics^{31,32} (DPD) system of coarse-grained A_4B_8 block polymers in dilute solution, a system originally studied by Li and Dormidontova and others.^{33–35} Notably, we expect this model to provide information about chain exchange despite lacking molecular-level details because the experimental results^{14,15,17} are independent of the polymer system. DPD

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uses soft potentials for bead–bead repulsion, which do not capture in detail steric interactions but provide fast equilibration that is desirable for our work. We do not expect the approximations in DPD to impact the key results. Our micelles have amorphous, roughly spherical cores, so the impact of steric interactions on the structure of the micelle core will not play a role here. The most likely impact of the soft DPD potential is to allow chain crossing, which produces dynamics that are faster than expected in an experiment with an entangled micelle core. Since we examine the thermodynamics rather than kinetics, this does not impact our results. Moreover, experiments of interest¹⁷ use molar masses that are low enough that the core blocks are not entangled, rendering the chain crossing a minor issue. Finally, although this level of coarse graining cannot resolve the globule hypothesis due to limitations in excluded volume and chain length, it provides a necessary first step toward understanding the behavior of single chains undergoing expulsion.

In this model, monomer beads of mass m are linked by a harmonic bond with equilibrium distance $r_0 = d_p$ and force constant $k = 100k_B T/d_p^2$; $k_B T$ and d_p are units for energy and distance, respectively. The solvent (S) is modeled by single B-type monomer beads. Characteristic of the DPD model, the interaction force between beads is the pairwise sum of a conservative force, f_C , a random force describing thermal fluctuations, f_R , and a dissipative or frictional force, f_D , which acts as a thermostat to conserve the system energy.

The functional forms of these forces are described elsewhere;^{31,32} they are short-ranged with a cutoff distance $r_c = d_p$. Similar to previous work,^{33,34} a frictional force with magnitude $\xi = 3.0k_B T/d_p^2$ and a time step $\Delta t = 0.04$ ($md_p^2/k_B T$)^{1/2} were used. In these simulations, 81 000 beads were placed randomly in a cubic box of side $30d_p$ with a polymer volume fraction $\phi = 0.05$. Periodic boundary conditions were implemented, and the repulsive interaction parameter for like particles, $a_{AA} = a_{BB} = a_{BS}$, was set to $25k_B T/d_p^2$.³² In the following, we omit the units of $k_B T/d_p^2$ for conciseness. The system was equilibrated for a value of excess interaction energy for contacts between A and B beads ($\Delta a = a_{AB} - a_{AA}$) of 15 by slowly increasing Δa and monitoring the system until the aggregation numbers were stable ($t \approx 10^6$, or 2.5×10^7 steps). The system was then placed in the strong segregation regime, where the excess interaction energy was then set to larger values from 22.5 to 40 to halt chain exchange during the umbrella sampling procedure, essentially freezing the distribution of aggregation numbers Q . Importantly, we use larger values of Δa than past simulations of chain exchange kinetics,^{33,34} which were limited to lower interaction energies to allow micelles to equilibrate within a reasonable simulation time. Our work is intended to mimic experimental systems, in which micelles often cannot fully equilibrate as the necessary relaxation processes are too slow.^{18,21,36,37}

A single aggregate was selected for umbrella sampling from the frozen micellar system at the designated interaction energy. First, a cluster analysis using a cutoff distance between core beads of 1.8 was performed to find the distribution of aggregation numbers Q .³³ A locally equilibrated micelle was then chosen with $Q = 36$, which was always within 10% of the weight-average aggregation number of the frozen Q distribution, and all other micelles in the system were replaced by solvent beads. Notably, $Q = 36$ would likely be below the global equilibrium aggregation number Q_{eq} for the system. It is possible to determine Q_{eq} by computing the escape free energy

as a function of micelle size;⁴⁵ however, it is not necessary for our micelle to be at equilibrium as we are interested in the single-chain behavior rather than the system ensemble. Following Halperin and Alexander,⁸ the reaction coordinate r was defined as the distance between the center-of-mass of the micelle core and the position of the A–B chain junction. As shown in Figure 1, a harmonic force with $k = 12.0$ was exerted

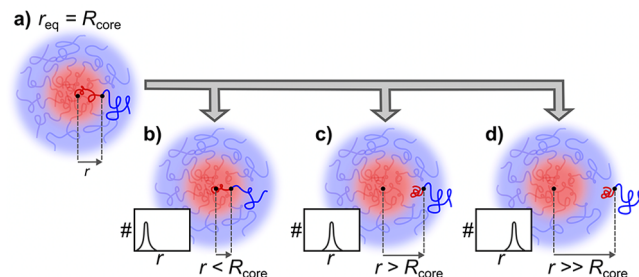


Figure 1. Schematic of the umbrella sampling procedure. (a) The equilibrium state of a micelle and the beginning point of the umbrella sample. (b–d) Separated simulations with biasing potentials added to hold the junction of the chain (b) closer to the micelle center-of-mass than is likely at equilibrium, (c) slightly further away than the equilibrium state, and (d) at a much larger distance than the equilibrium state. Insets in (b–d): Schematic of the number of points in the simulation that have approximately a distance r between the micelle center-of-mass and the biased chain center-of-mass.

via the *colvars* module³⁸ in LAMMPS³⁹ to bias the system such that a randomly chosen chain was held at a selected distance away from the micelle center-of-mass. If another chain exchange event occurred during the course of the umbrella sampling window, the data were discarded due to an incorrect center-of-mass calculation, and the simulation was repeated. The value of the reaction coordinate r was calculated every 10^3 time steps, and distances for subsequent umbrella windows were chosen such that the resulting histograms overlapped and the simulations yielded information for all observable distances of r , as illustrated in Figure 2. These histograms were shown to be self-consistent, as determined by a procedure derived from the Kolmogorov–Smirnov test (Figure S1),⁴⁰ indicating that

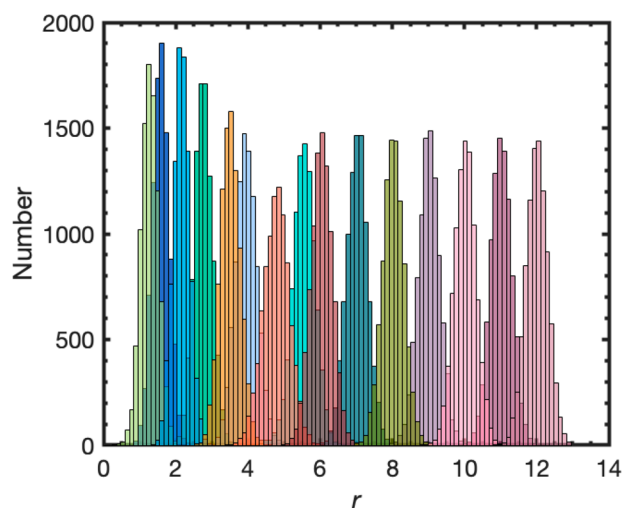


Figure 2. Histograms of observed values of the reaction coordinate r over the course of the simulation for $\Delta a = 25$. Each color represents a different umbrella window.

our sampling was sufficient. The potential of mean force was extracted from the observed histograms through the weighted histogram analysis method (WHAM),^{41,42} similar to what has been done in hydration studies of proteins.⁴³ The results were shown to be insensitive to the number of histograms (Figure S2), and error analysis was performed via bootstrapping. The simulation trajectories were confirmed to be reversible by a reverse pulling simulation (Figure S3) as performed for past simulations of surfactant micelles.^{44,45}

Figure 3 shows that there is a sharp increase in free energy as the chain junction departs from the core–corona interface at r

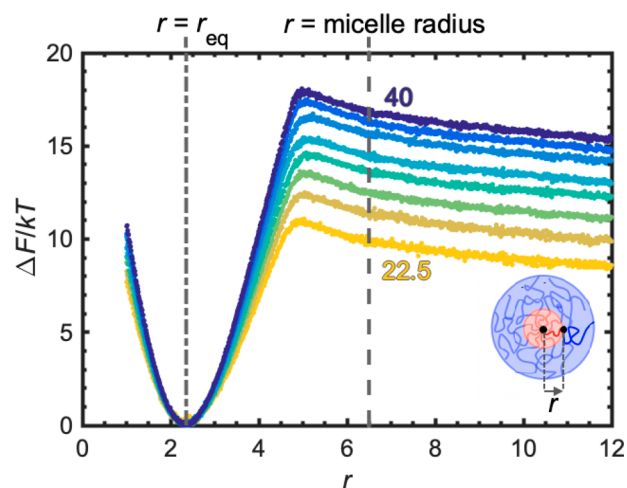


Figure 3. Free energy profiles of chain expulsion from a micelle with $Q = 36$ as a function of the distance between the center-of-mass of the micelle and the junction of the chain being expelled (r). From bottom to top: Δa ranges from 22.5 to 40 in increments of 2.5. The dash-dot line designates the average distance around equilibrium, and the dashed line is the approximate outer radius of the micelle, i.e., the extent of the micelle corona.

≈ 2.35 (the zero-free-energy or reference state). Below the equilibrium value of r , the corona block is pulled into the core along with the chain junction, and the unfavorable contacts between the core and corona beads result in an increase in internal energy of the system. Similarly, as the distance between the chain junction and micelle center-of-mass increases, the interaction between the core beads and the solvated corona beads adds an internal energy penalty. In this case, however, corona crowding adds an additional entropic penalty. The point of highest free energy, designated the transition state, occurs near a value $r^* \approx 5.0$ in all cases, recalling that all micelles have the same aggregation number and therefore the same core radius.

To compare the results in Figure 3 to experiment, we applied Kramers' rate theory to the computed free energy profiles. Here, we converted from DPD to real units using $R_{\text{core}} \sim 90 \text{ \AA}$ and $D \sim 10^{-11} \text{ cm}^2/\text{s}$ as calculated from the Rouse model, taking experiments by Choi et al. as a model system.⁴⁶ We found a time scale of chain exchange on the order of minutes to days for varying Δa (Figure S4). This is similar to the observed experimental chain exchange times, an encouraging result given that this analysis is far from a rigorous comparison.

To analyze the core chain conformation at the transition state, we calculated the radius of gyration, R_g , for the perturbed core chain as a function of r . Here, we isolate the data for $\Delta a =$

25; however, the same trend holds for all interaction energies studied (see the Supporting Information for other values of Δa). As seen in Figure 4, the radius of gyration initially

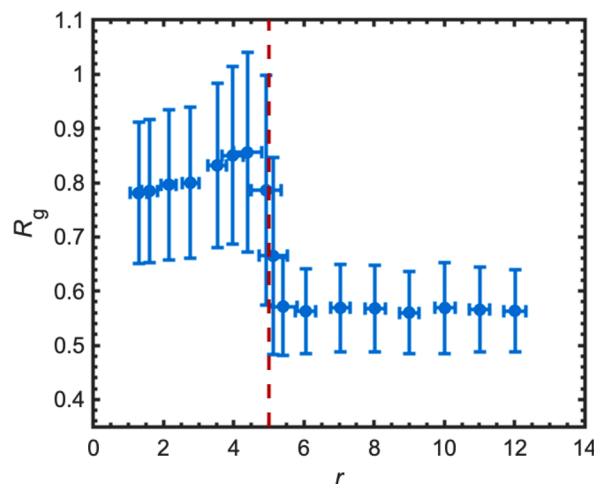


Figure 4. Radius of gyration of the core block along the reaction coordinate for chain expulsion, the distance between the center-of-mass of the micelle, and the junction of the chain being expelled. Each point represents one umbrella window. Error bars are the standard deviation for observations over the course of the umbrella sample.

increases as the chain is being expelled, likely due to chain stretching as part of the chain remains in the core to minimize the internal energy penalty of exposure to corona. The radius of gyration begins to rapidly decrease as r is increased beyond the transition state. Notably, however, the core chain is still partially expanded at the transition state, but the radius of gyration decreases to its minimum while the chain junction is within the micelle corona, which extends to $r \approx 6.5$. This system with $N_A = 4$ is too small to collapse completely to form a globule, however, consistent with prior DPD work.⁴⁷ This is a limitation of this model system and indicates that we cannot really assess the validity of the postulated globular transition state.⁸ The observed transition state, where the perturbed core block stretches to remain partially shielded in the spherical core, does not necessarily reflect what occurs in solutions of longer chains that fully collapse in a bad solvent. In the future, we plan to use this technique to examine micelles with longer chains to address this important point.

It is evident that both the free energy increase upon chain expulsion and the height of the barrier are strongly dependent on the excess interaction energy Δa , as a higher interfacial energy leads to a larger enthalpic penalty for exposure of core beads to solvent. Figure 5a shows that the height of the free energy barrier in Figure 3 increases approximately linearly with Δa , with a slope of 0.43. Here, we can conclude that an increase in Δa or χ will yield a monotonic increase in the free energy barrier. Notably, there is a slight deviation from the linear trend at high interaction energies ($\Delta a \geq 40$). It is possible that this difference is due to the deformation of the micelle core at the transition state seen in the inset of Figure 5a. Although the unperturbed micelle remains spherical at $\Delta a = 40$, the micelle core distorts near the transition state to accommodate the displacement of the core block. This reduces the energetic penalty of exposure of core beads to the micelle core even as it extends toward the transition state.

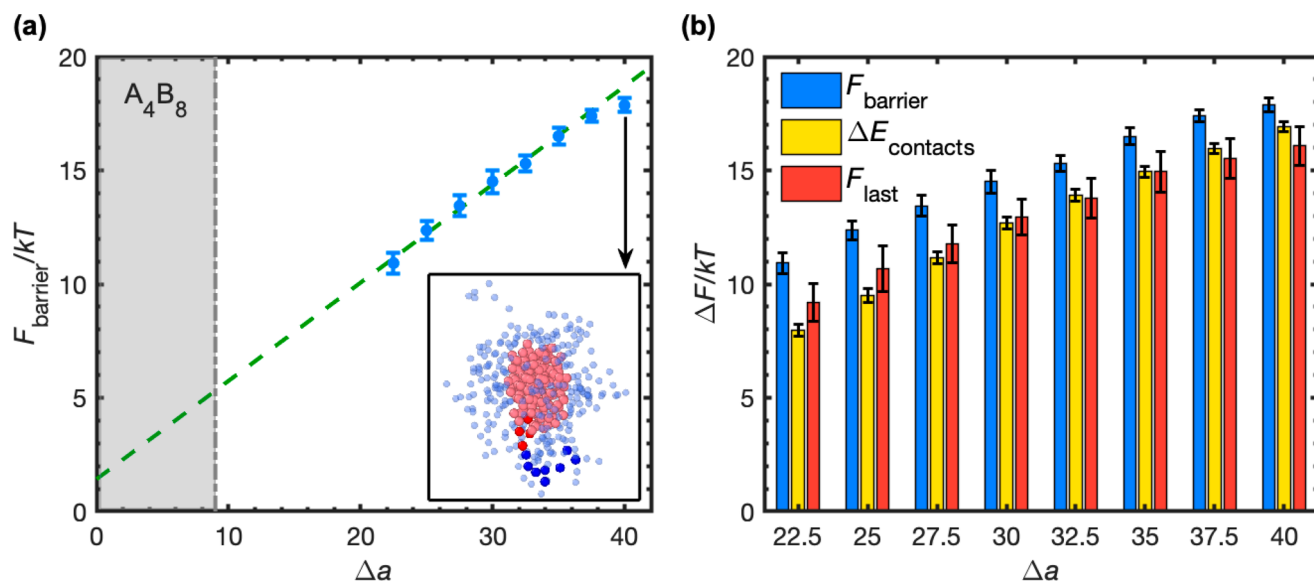


Figure 5. Effect of interaction energy on free energy contributions to chain expulsion. (a) Blue points designate the free energy barrier for chain exchange, with the dashed line indicating a linear fit to the first 6 points. The gray dashed line marks the approximate boundary beyond which micelles do not form. Inset: Configuration of a micelle close to the transition state for the largest interaction energy case ($\Delta a = 40$), rendered by VMD (solvent beads are omitted). Core beads are shown in red and corona beads in blue. Transparency is decreased for the chain being expelled. (b) Yellow bars represent the increase in energy due solely to contacts of the core block with solvent upon expulsion, and red indicates the change in free energy once the chain is fully expelled from the micelle compared to the minimum free energy state.

A second point is that the extrapolated barrier for Δa or $\chi = 0$ from the data in Figure 5a is positive, where we would expect the barrier to be zero if there were no excess interaction energy for A–B contacts. In fact, Ma and Lodge,¹⁵ and later Wang et al.,²⁰ discussed a possible offset from a zero free energy barrier at $\chi = 0$, as no micelles should form for a block polymer where the core block is at, or above, the theta point ($\chi \geq 0.5$). Thus, there is reason to expect that the barrier might not remain linear in Δa as the demicellization transition is approached. Note also that the extrapolation is substantial, as the umbrella sampling method can only be implemented at large Δa values where chain exchange is rare. Additionally, the simulations are intended to mimic the experimental situation for many block copolymer micelles, which tend not to be in equilibrium. In a system with larger excess free energy, the equilibrium aggregation number is expected to increase, but the current system is frozen at lower Q .

The free energy barrier to chain exchange ranges from 11 to 18 kT with increasing interaction energy. To resolve the contribution that is due to an increase in energy, we examined the increase in energy due to contacts of the core block upon expulsion into the solvent. Here, the energy due to pairwise contacts in each case (as a free chain and within the micelle) is calculated as

$$E_{\text{core}} = \sum_{i=1}^{N_A} \sum_{j=1}^N E_{ij} \quad (1)$$

where

$$E_{ij} = \begin{cases} \frac{a_{ij}}{2} (1 - r_{ij})^2 & r_{ij} < 1 \\ 0 & r_{ij} \geq 1 \end{cases} \quad (2)$$

where N is the number of beads and r_{ij} is the distance between beads i and j . The excess energy due to contacts, $\Delta E_{\text{contacts}}$ or

$E_{\text{core,micelle}} - E_{\text{core,free}}$ is displayed in Figure 5b. For comparison, the increase in free energy at large values of r (designated F_{last} in Figure 5b), where the chain is fully expelled, is also shown. This increase in free energy, compared to the reference state where the chain junction lies at the core–corona interface, reflects the combined effects of a relief of corona stretching and the energetic penalty of the free chain in solution as well as a change in free energy per chain for the micelle as Q is decreased.

From Figure 5b, it is clear that $\Delta E_{\text{contacts}}$ accounts for the large majority of the free energy barrier to chain expulsion. This contribution increases with interaction energy, from 73% for $\Delta a = 22.5$ to 94% for $\Delta a = 40$. This is likely because the other main contribution to the free energy barrier is due to chain stretching at the transition state, which should not be strongly dependent on interaction energy for micelle cores that remain spherical at the transition state. Moreover, we find that $\Delta E_{\text{contacts}}$ is not significantly different from F_{last} , supporting the conclusion that an increase in entropy due the relief of corona chain stretching is a relatively minor contribution to the total change in free energy. We do note that the chosen aggregation number of $Q = 36$ is likely to be below the optimal aggregation number for this system and for most experimental systems, and one should therefore expect an additional increase in free energy per chain of the micelle upon expulsion because the ensemble is moving further away from equilibrium.

In summary, this work demonstrates that umbrella sampling can be used to compute the free energy profile for chain expulsion in a block copolymer micelle. As the chain is expelled through the corona, the core block initially stretches until it begins to shrink at the transition state due to internal energy considerations. The free energy barrier to chain exchange was found to increase linearly with the Flory–Huggins interaction parameter χ , validating past experimental and theoretical results; however, at large interaction penalties, the transition state may involve a deformation of the micelle core, causing a

296 deviation from this linear trend. This work provides insight
297 into the behavior of single chains during expulsion from block
298 polymer micelles and a pathway for future studies evaluating
299 discrepancies surrounding the process of single-chain exchange
300 and the proposed transition state.

301 ■ ASSOCIATED CONTENT

302 ■ Supporting Information

303 The Supporting Information is available free of charge at
304 <https://pubs.acs.org/doi/10.1021/acsmacrolett.1c00508>.

305 Test of histogram sampling, reverse pulling simulations
306 confirming the reversibility of umbrella sampling
307 trajectories, histogram consistency test, and details on
308 the core chain radius of gyration as a function of the
309 reaction coordinate at other interaction energies (PDF)

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330 Notes

331 The authors declare no competing financial interest.

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