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Effect of solvent selectivity on crystallization-driven fibril growth kinetics of diblock copolymers

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ABSTRACT

We performed dynamic Monte Carlo simulations of diblock copolymers to investigate how the selective solvents on two blocks can suppress the crystallization-driven fibril self-assembly growth in dilute solutions. We found that either a lower hydrophilicity of the surrounding amorphous block or a lower hydrophobicity of the core crystallizable block can effectively reduce the fibril growth rates. Their mechanisms are different: the former is the shielding effect and the latter is the thermodynamic effect. We discussed the potential correlation of our results to the recent progress of drug discovery for the Alzheimer's disease that elongates the fibril structure of amyloid proteins as a consequence of crystallization of hydrophobic segments under nano-confinement of those hydrophilic segments. Our observations shed light onto the physicochemical background for the basic therapy strategy of protein-misfolding diseases.

1. Introduction

With the rapid development of medical technology on treating other fatal diseases, Alzheimer's disease nowadays becomes the top-ranking threat to the senior people, and the best way to prevent Alzheimer's disease is an early retardation of in vivo amyloid fibril growth for both oligomers and fibers [1]. Although the amyloid hypothesis [2] got challenged by the drug failure [3], there are still hopes [4]. Recently, the antibody Aducanumab has been found to bind selectively a hydrophilic group on the amyloid surface and hence reduce the amyloid plaques [5]. Its dose dependence implies a physicochemical mechanism on its effects and thus be worthy of a kinetic analysis via molecular modelling.

As a matter of the fact, the amyloid fiber contains a crystalline core of those residual groups holding mainly hydrophobic interactions, surrounded with the amorphous shell of those residual groups holding mainly hydrophilic interactions [6]. Thus, the fibril growth is presumably under nano-confinement of those amorphous segments, resulting in a fibril shape of the crystalline core rather than the conventional lamellar crystallites of polyamides. In this sense, a proper physicochemical model for amyloid fibril growth can be established by the nano-confined crystallization-driven fibril self-assembly of diblock copolymers in dilute solutions, as one amorphous block long enough to raise overcrowding on the interfaces and hence to make a nano-confinement to the crystal growth of the crystalline block [7]. The crystallization-driven self-assembly can be well controlled by the self-seeding technique to tailor the length of nano-rod structure [8], which appears as the prerequisite for a hierarchical construction of 3D nano-particles [9]. Theory and simulation study on the hierarchical self-assembly of block copolymers in solutions has been performed [10,11]. Even the silk-collagen-like triblocks can make crystallization-driven filament growth in solutions [12].

In the kinetic analysis of dose dependence, a nearly linear concentration dependence have been found for the linear growth rates of lamellar single crystals of polyethylene in dilute solutions, while the concentration dependence for small molecules is usually in a square relation [13]. The linear concentration dependence implies the single polymer dominating the lateral growth kinetics of lamellar polymer crystals, suggesting the intramolecular secondary crystal nucleation [14,15]. Indeed, such a linear concentration dependence has been confirmed by dynamic Monte Carlo simulations of a simple lattice polymer model performing lamellar crystal growth [16], by employing the parallel-packing interaction model as the molecular driving forces for polymer crystallization [17,18]. The simulations even revealed the kinetic competition between

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secondary nucleation and instant thickening at the lateral growth front, which determines the limit lamellar thickness of polymer crystals [19]. The linear concentration dependence of crystal growth rates was also been reproduced by the simulations of crystallization-driven fibril self-assembly of diblock copolymers, consistent with the basic crystal growth mechanism of polymers [20]. As a matter of fact, the molecular dynamics simulations of amyloid fiber growth have demonstrated two-step mechanism, i.e., reversible docking and irreversible locking, typical for secondary crystal nucleation [21]. In our previous simulations [20], the solvent was assumed to be athermal without any selective preferences for two blocks. How the separate solvent affinity of two blocks could reduce the fibril crystal growth rates is worthy of further investigation, which will shed light onto the physicochemical strategy on the suppression of amyloid fibril growth.

In this work, we separately changed the solvent affinity to two blocks, and performed dynamic Monte Carlo simulations of diblock copolymer solutions to investigate the solvent effect on the template-initiated quasi-1D crystal growth of the crystallizable blocks under the nano-confinement of the amorphous blocks.

2. Simulation techniques

The dynamic Monte Carlo simulations of the lattice polymer model has been used to investigate the broad issues on polymer crystallization [17,18]. Following our previous simulations in which various compositions have been investigated [20], we put 1200 chains, each containing 128 consecutive monomer sites with the monomer ratio of noncrystallizable to crystalline blocks as 112/16, into the lattice box of $128 \times 64 \times 64$ cubic cells. The rest single vacant sites were deemed to the solvent sites in the polymer solutions. Polymer chains performed trial micro-relaxation moves, with a random-selected monomer jumping into the random-selected solvent neighbor, incorporating partial sliding diffusion along the chain if necessary [17]. The unit time Monte Carlo (MC) cycle was defined by the amount of trial moves equal to the total amount of monomers. Periodic boundary conditions were applied to the simulation box, and double monomer occupation or bond crossing were forbidden in mimicking to the volume exclusion of polymers. In addition, we put one fixed polymer chain that occupied consecutive 64 lattice sites and folded into $1 \times 8 \times 8$ layer on the center of YZ plane at $X = 0$ (actually 128 according to periodic boundary conditions), and defined only its + X-side containing parallel-packing interactions as a crystal template to initiate the fibril growth along + X-axis.

The preset 128-mer chains were firstly relaxed under athermal solvent conditions over 1×10^6 MC cycles to achieve random coils. Then, the well-known Metropolis sampling algorithm was employed in each step of micro-relaxation, with the potential energy barrier as given by [17–20]

$$\begin{aligned} \Delta E/(\mathrm{k}T) &= \left(c \times E_c + p \times E_p + m \times B + f \times E_f\right) \Big/ (\mathrm{k}T) \\ &= \left(c + p \times E_p/E_c + m \times B/E_c + f \times E_f \Big/ E_c\right) \times E_c/(\mathrm{k}T) \end{aligned} \quad (1)$$

Here, c, p, m represent separately the net changes in the number of non-collinear connections between the consecutive bonds, in the number of non-parallel packing of neighboring bonds, and in the number of monomer-solvent pairs, and f sums over all the parallel-packed crystallizable bonds along the local sliding-diffusion path; E_c reflects the bending energy of the chain, $E_p/E_c = 1$ describes the reduced driving forces for polymer crystallization (five times larger along X-axis than other dimensions to secure the fibril growth [20]), B/E_c characterizes the mixing interactions between the solvent sites and the monomer sites, $E_f/E_c = 0.3$ makes a high frictional barrier to hinder any sliding motion of the bonds in the crystalline phase [17], and $\mathrm{k}T/E_c = 3.3$ (simplified as $T = 3.3$) represents the reduced system temperature (k is Boltzmann's constant, T the temperature). In practice, we assigned the reduced parameter *B01* to B/E_c for the mixing interactions between the solvent sites and the monomers on the non-crystallizable blocks, and the separate parameter *B02* on those crystallizable blocks.

3. Results and discussion

We started with an exploration of the proper parameter range of solvent affinity for the observation of steady fibril growth from the crystal template, without spontaneous primary crystal nucleation in the time window of our observations, as demonstrated for example in Fig. 1.

We defined the crystalline bond as the crystallizable monomer bond surrounded by 15 or above parallel neighbors of crystallizable bonds. We traced the time-evolution curves of the fibril growth front, while the growth front was recorded by the farthest X-axis distance of at least 3 crystalline bonds aligned in the parallel-oriented stem to the template. From the linear segment of the time-evolution curve, we obtained the slope as the linear crystal growth rate, averaged for five independent simulations, as for example demonstrated in Fig. 2. For maintaining the constant polymer concentration in the solution space during fibril crystal growth, we fed one more 128-mer chain into consecutive 128 vacancy sites at a randomly selected position, once a chain has joined into the crystal. So the fibril growth is set under almost stable thermodynamic conditions. The so-called feeding mode is relatively simple with constant thermodynamic parameters for the kinetic analysis, and the growth rates are relatively reproducible, in comparison to the depletion mode in which the concentration is shifting with the growth. Even in Fig. 2, the linear segment is not very broad because of the difficulty for the fed polymers to diffuse to the growth front at the later stage.

The averaged linear crystal growth rates with the corresponding error bars under various situations of solvent affinity of two blocks are summarized in Fig. 3. One can see that, with the reference to the athermal case as at the crossing of two dashed lines, a slightly decrease of *B02*, i.e. the slightly lower hydrophobicity of crystalline blocks, can effectively reduce the crystal growth rates (shifting down the curves); meanwhile, a slightly increase of *B01*, i.e. the slightly lower hydrophilicity of amorphous blocks (shifting to right), can make the same effects.

For the crystalline blocks at the same concentrations, their higher solvent affinity will suppress the equilibrium melting point [22]. The lower melting point gives a smaller supercooling or a weaker thermodynamic driving force for polymer crystal growth. Therefore, the linear growth rates are shifted down with the decrease of B02. In experiments, good solvent for the crystalline blocks will make longer nucleation period [23], which can also be assigned to this thermodynamic effect.

For the amorphous blocks, their lower solvent affinity will shrink the conformation of block coils on the surface of fibril crystals, making even stronger overcrowding at the front tip of the fibril crystal growth. Fig. 4a calculated the mean square radius of gyration of the amorphous blocks separately on the crystalline core and on the isolated coils in the solution. One can clearly see the decay of the coil sizes of amorphous blocks in both cases, and even relatively more on the crystalline core.

The shrinking of the amorphous blocks makes stronger overcrowding on the surface of the crystalline core, implying stronger nano-confinement to the crystallization of the other blocks. Under