The Unfolding Mechanism of Model Proteins under Shear Flow

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Introduction

Protein is a linear heteropolymer molecule consisting of 20 possible types of amino acid residues and fold to a unique native state under physiological conditions owing to its sequence of amino acids. To understand folding/unfolding mechanism of the protein, the energy landscape theory is developed and probed under various isotropic perturbation methods such as temperature-induced unfolding and denaturant-induced unfolding. Very recently, the anisotropic perturbation such as mechanical stretching has attracted special attention. From many experimental reports on these anisotropic stretching of proteins, there has been direct evidence for sequential unfolding of individual domains of the protein on stretching, which suggests that the structural motifs of single protein can be readily identified by apparatus such as atomic force microscopy.[1-3] While most of experiment and simulation works have focused on the mechanical stretching of proteins, the effect of shear flow on the protein and the shear-unfolding mechanism has been far less understood. In the present paper, we simulate a model protein subjected to simple shear flow using lattice model of folding and investigate the mechanism of shear-induced unfolding. In order to probe the pathway of shear-induced unfolding of the model protein, the free energy landscape is calculated by a Monte Carlo method.

Model and Simulation

The "20-letter" type of lattice protein consisting 27 monomers is designed by the sequence annealing proposed by Shakhnovich and Gutin.[4] The energy of the model protein is assumed to depend only on nearest neighbor interactions and has the form of

$$E = \sum_{i<j} B_{ij} \Delta(|\mathbf{r}_i - \mathbf{r}_j|), \tag{1}$$

where B_{ij} is the interaction energy between residues i and j located at positions $\mathbf{r}_i$ and $\mathbf{r}_j$, respectively, and $\Delta(r)$ is 1 if r is equal to a unit lattice spacing and is 0 otherwise. Fig. 1 presents the residue-residue interaction map for the protein sequence used in this study. The energy spectrum of the lowest 400 compact self-avoiding conformations for the model protein is shown in Fig. 2. In order to simulate folding or unfolding of the model protein, we utilize dynamic Monte Carlo method with Verdier-Stockmaier algorithm[5] and shear flow is introduced through a flow field potential, U_s,

$$U_s = -\zeta \dot{\gamma} x z \tag{2}$$

where ζ is the friction coefficient, $\dot{\gamma}$ is the shear rate, and x and z is the coordinates of the residue in shear direction and in the direction perpendicular to the shear plane. From the histogram recorded with respect to the energy (E) and the fraction of native contacts (Q), the free energy profiles as a function of Q are obtained from the conformational partition function of protein:

$$Z(Q,T) = \sum_{\{E\}} \frac{h(Q,E)}{h(Q=1, E=E_o)} \exp(-\frac{E_o}{k_B T}) \tag{3}$$

where $h(Q,E)$ is the histogram with respect to E and Q, and E_0 is the energy of the native state. All the simulation is started from the native state and shear-induced unfolding events is examined in terms of the reaction coordinate Q and E for 10^8 Monte Carlo steps.

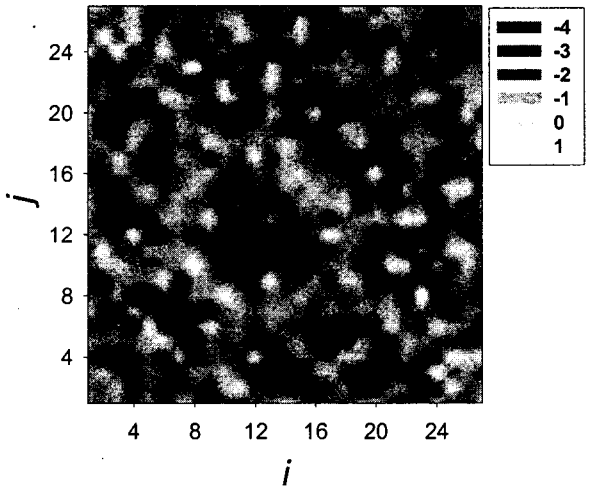

Fig. 1. The residue-residue interaction map for the model protein used in this study.

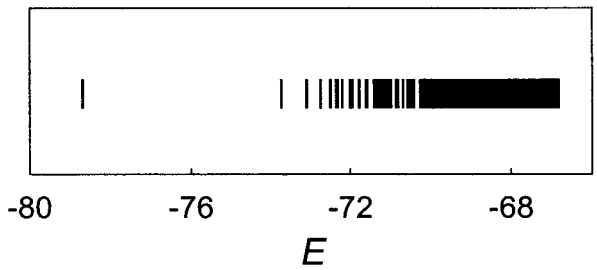

Fig. 2. The energy spectrum for the model protein. The energies of the lowest 400 compact conformations are used for the spectrum.

Results and Discussions

Fig. 3 presents the free energy profile plotted against the fraction of native contacts (Q) for the model protein at various shear rates. As the shear rate increases, the native state become destabilized and the fraction of native contacts in the unfolded state approaches to Q=0, i.e. there are no contacts in common with the native state. At the initial stage of unfolding, the shear force is exerted to overcome the free energy barrier and the unfolding is downhill after the barrier at $Q\cong0.6$. The detailed unfolding events under shear flow can be more clearly inspected by the free energy landscape. In Fig. 4a, we present the free energy of landscape in the Q-E space for the model protein subjected shear flow with $\dot{\gamma}$=0.1. Fig. 4a suggests that the shear-induced unfolding is two-stage process: At the initial stage, the compactness of the native structure is disrupted by the shear flow. At the next stage, the loosened conformation of the protein starts to be elongated to the shear direction. When compared to the isotropic

temperature-induced unfolding (Fig. 4b), shear-induced unfolding has much narrower pathway which lies within the pathway of temperature-induced unfolding.

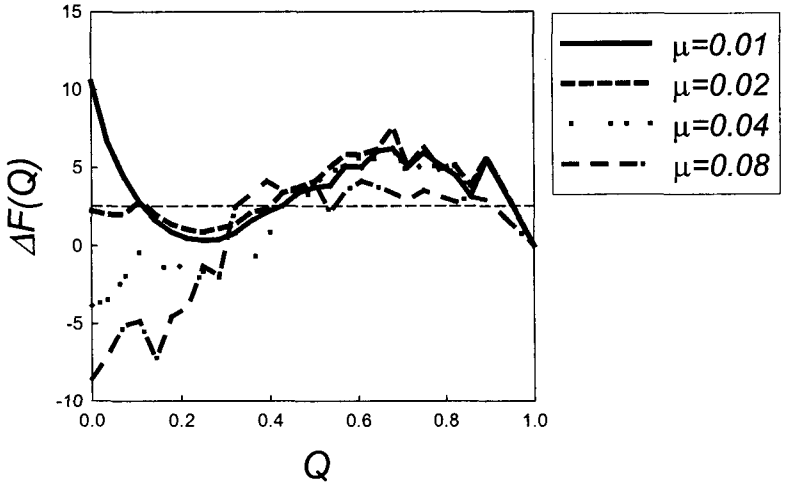

Fig. 3. The free energy profile as a function of the fraction of native state for various shear rate ($\mu = \zeta\dot{\gamma}$).

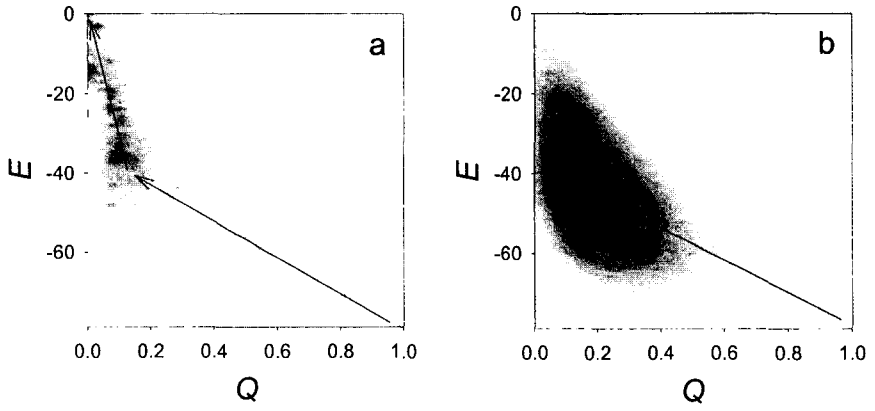

Fig. 4. The free energy landscape for (a) shear induced unfolding (μ=0.1, T=1.2) and (b) temperature-induced unfolding (T=2.0).

References

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