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Abstract
Unique characteristics of a single polymer chain with the effects of stiffness and charge are discussed. It has been well established that a flexible polymer chain undergoes a continuous transition from an elongated coil to a compact globule, corresponding to the transition between disordered gas-like and disordered liquid-like states. Here, we will show that a semiflexible chain exhibits a discrete transition from coil to compact states, corresponding to a disorder–order transition to an ordered crystalline state. We will propose a novel strategy to obtain various kinds of nano-ordered structures from single chains connecting a pair of chains of different stiffness. We will also discuss the effect of charge, putting emphasis on intramolecular segregation in a single polyelectrolyte chain.

1. Introduction

Because of the recent developments in experimental techniques to study individual polymer chains, there is increasing interest in the intrinsic properties of single chains, especially in biopolymers. Among the rich variety of biopolymers, giant DNA molecules have been extensively studied because of their importance in life. From a physicochemical point of view, giant DNA molecules obtained from natural sources have the advantage of monodispersity.

In living cells, giant DNAs of several centimetres in length are confined in a narrow space of micrometre scale [4]. The compaction of DNA is known to be generated *in vitro* with the addition of various types of chemical agents, such as hydrophilic polymers, multivalent cations, and cationic surfactants [5, 6]. These *in vitro* experiments have indicated that DNA molecules are folded into a compact state as a thermodynamic equilibrium state. The drastic change of the density of DNA molecules is now termed as *DNA condensation* [6]. However, *DNA condensation* does not distinguish between an intramolecular folding transition and intermolecular aggregation.

Experiments of single DNA observation about a decade ago have clearly indicated that single DNA of over several kilo base pairs in size undergoes a large discrete transition

accompanied with a $\sim 10^4$ times change in the segment density [1, 2, 26], whereas the physicochemical properties of the ensemble of DNA molecules, such as viscosity and turbidity, exhibit a continuous nature owing to the presence of a rather wide parametric area on the coexistence of folded and coiled states [2].

Inspired by the experiments on single DNA molecules, physical properties in a single chain have recently been reexamined. In this context, including the effect of stiffness and charge is a naive and essential extension of the previous picture in polymer physics. A polymer chain having finite bending rigidity is referred to as a semiflexible polymer and is considered to reflect essential aspects of a double-stranded DNA molecule [11]. The electrostatic interaction also plays important roles in biological systems, for example, DNA–protein interactions. Physical importance is found in the field of like-charged attraction [17–19] and charge inversion [20], which cannot be explained by the well-known Poisson–Boltzmann treatment.

In the present paper, we will describe several interesting characteristics of a single polymer chain as a semiflexible polymer and a highly charged polyelectrolyte. We will focus on the unique nature of the transition, i.e., first-order phase transition on individual chains. First, we will discuss the change of the folding transition depending on the stiffness of a chain. Molecular chains are shown to display discrete transitions between disordered coil and ordered compact states, when the stiffness is above a certain strength. We will also discuss the new strategy to fabricate nano-ordered structures from a single polymer chain connecting flexible and semiflexible polymers. We will then explain the novel aspect of the folding transition in a highly charged polyelectrolyte.

2. First-order phase transition in a semiflexible chain

In polymer science, it has generally been regarded that a single polymer chain makes a transition from an elongated coil to a compact globule continuously through the tricritical point, which is often referred to as the Θ state [9, 8]. The mean field treatment can be justified near this state, and the interaction contribution in the free energy can be expanded with the virial expansion [10]. The free energy F as a function of the size of a single chain is given as the summation of elastic and interaction terms,

$$F[\alpha] = F_{\text{ela}} + F_{\text{int}} \sim \tfrac{3}{2}(\alpha^2 + \alpha^{-2}) + B\rho^2 V + C\rho^3 V + \mathcal{O}(\rho^4), \tag{1}$$

where $\alpha = R/R_0$ is a size of a chain normalized by that of a ideal chain $R_0 = N^{1/2}a$, and B and C are second and third virial coefficients, respectively. $\rho = N/V$ is the density of segments and $V \sim R^3$ is the volume occupied by the chain. The virial coefficients can be estimated to be

$$B \sim a^3\tau, \qquad C \sim a^6, \tag{2}$$

where a and τ are the width of a chain and the reduced temperature, $\tau = (T - T_\Theta)/T_\Theta$, respectively. By changing τ from positive to negative, we attain collapsed states. The third-order term in density is included to avoid unphysical divergence. The transition from an elongated coil to a compact globule induced by the increase in attractive interaction is accompanied by the gradual increase in the probability of contacts between segments. This is the coil–globule transition in a flexible polymer.

The free energy is largely modified in semiflexible polymer chains with persistence length l_{p}. Considering the orientational order, we can introduce the crossing angle between non-adjacent segments γ ($0 \leqslant \gamma \leqslant \pi/2$). We start from the free energy expansion (1) with $R_0 = N^{1/2}l_{\text{p}}$ and here the second virial coefficient strongly depends on γ. The virial coefficients can be evaluated as

$$B = B_0 + B_{\text{att}}(\gamma), \qquad C \sim a^3 l_{\text{p}}^3, \tag{3}$$

where $B_0 \sim l_p^2 a$ and B_{att} arise from steric and attractive interactions, respectively. Regarding the attractive pairwise interaction between the segments, the average attractive interaction ϵ should be maximized with parallel orientation and it decreases steeply with an increase in γ, thus

$$\epsilon \sim -\frac{a^2 \sigma}{\langle \sin \gamma \rangle + \lambda} \left(\frac{T_\Theta}{T} \right), \tag{4}$$

where σ is the characteristic length of the attractive potential. $\lambda = a/l_p$ is included to ensure $\lim_{\gamma \to 0} a/(\sin \gamma + \lambda) = l_p$.

On the other hand, we can estimate the volume of a chain to be

$$V \sim N a l_p^2 \langle \sin \gamma \rangle. \tag{5}$$

As a result, near $\tau \sim 0$, the second-order term becomes

$$B_{att} \sim a^3 l_p^2 \sigma \tau \rho, \tag{6}$$

and this term acts as a third-order term. It is now evident that with the increase of stiffness, the interaction term in free energy is represented as a higher-order term compared to the bare second virial coefficient.

From the above discussions, the free energy can be expressed using the effective third virial coefficient as

$$F[\alpha] \sim \frac{3}{2}(\alpha^2 + \alpha^{-2}) + C^* \alpha^{-6} - N \ln \left[1 - \frac{\lambda}{N^{1/2} \alpha^3} \right], \tag{7}$$

$$C^* \sim \lambda^3 (1 + \tilde{\sigma} \tau), \tag{8}$$

where $\tilde{\sigma} = \sigma/l_p$ in (7) is the reduced attractive interaction length. The last term shows the entropic decrease arising from the overlap of segments, which is introduced to avoid divergence. The equilibrium states can be obtained from

$$\alpha - \alpha^{-3} = 2C^* \alpha^{-7} + \frac{\lambda \alpha^{-4} N^{1/2}}{1 - \lambda N^{-1/2} \alpha^{-3}}. \tag{9}$$

Under the condition when N is sufficiently large, it is obvious that there exist two stable states in the free energy profile during the transition of a chain (figure 1). Folded compact states become more probable with a decrease in the third virial coefficient. It is also important to note that the barrier between the minima is quite large. This type of characteristic profile of the free energy indicates that the folding transition of a single semiflexible chain, for example, a long DNA, should undergo a large discrete transition. On the other hand, the absence of the interface between the semiflexible chains prevents coarsening on the ensemble of the chains. As a result, the transition appears to be continuous on the ensemble of the chains. In general, the coarsening in a transition contributes toward the minimization of the interfacial area. However, in the first-order phase transition of single chains, phase segregation between different polymers does not cause any penalty in the free energy in the ensemble of chains.

A detailed analysis of (9) indicates that the free energy always maintains the two stable states accompanied by a high barrier between the wells. Therefore, it becomes clear that a semiflexible chain undergoes a large discrete transition between a elongated coil and a compact globule even under the presence of the large fluctuation at the single chain level.

By means of computer simulations with multicanonical Monte Carlo methods, it has been confirmed that the intrinsic character of the folding transition of a polymer chain changes from a disorder–disorder continuous transition into a disorder–order discrete transition accompanied by an increase in the stiffness [21].

It can be expected that this nature of the folding transition in a semiflexible polymer implies the nucleation process at the early stage of the transition [7, 34]. In fact an individual DNA
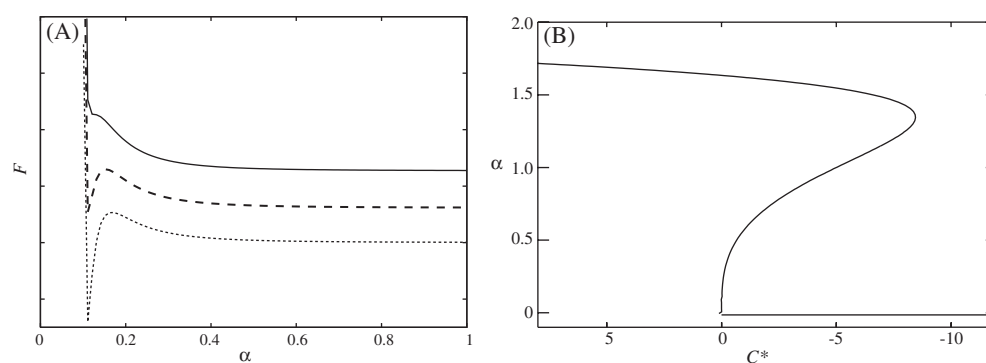
Figure 1. (A) Free energy landscape in a semiflexible polymer as a function of α, and (B) the fixed points for each C^*. The first-order phase transition between elongated and collapsed states occurs with the change in the solvent quality. The lines correspond to $C^* = -0.02$ (the solid curve), $C^* = -0.025$ (the dashed curve) and $C^* = -0.03$ (the dotted curve). The zero-point of each line in free energy is arbitrarily chosen.
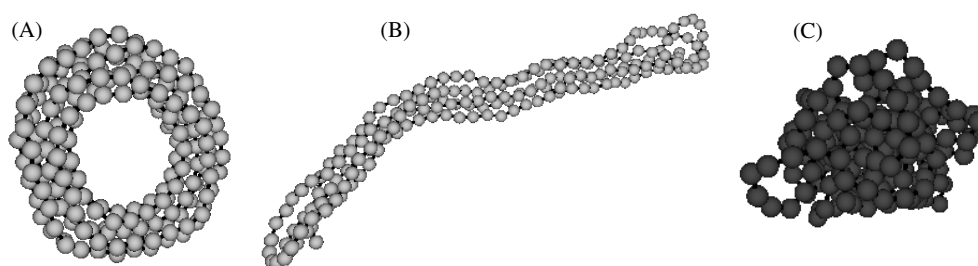

Figure 2. Various morphologies in the compact states of a single polymer. (A) Toroid and (B) rod states appear in a semiflexible polymer obtained under the same conditions of stiffness and temperature. (C) A spherical liquid-like globule state appears in a flexible polymer.

makes a transition by a process of nucleation and growth [26]. On the other hand, a flexible polymer exhibits very different transition kinetics, and spinodal decomposition occurs [33, 32].

3. Emergence of nano-ordered structures from a single chain

The transition of a single semiflexible polymer is characterized as a disorder–order transition, where the elongated coil is like a gas state and the compact state is close to an ordered crystal with a nanometre scale. It has been established that a single semiflexible chain forms a toroid, rod, or sphere as thermal equilibrium or metastable states (figure 2) [28]. In addition, the kinetics of the folding transition have a significant effect on determining the morphology of the compact state.

In this section, we will propose a new concept to construct nano-ordered compact states. It has already been mentioned that a polymer chain folds into an ordered structure, such as a toroid, through nucleation and growth. This implies that a rather long waiting time is necessary to obtain the nano-ordered crystal from a single chain. It is also noted that metastable morphologies are generated in the compaction process due to the kinetic effect.

Here, we will propose an alternative method to obtain ordered packing with high efficiency. Figure 3 exemplifies the result of Brownian dynamics simulations on the folding of a polymer
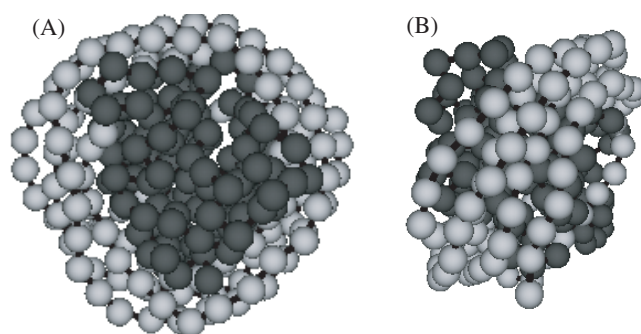
Figure 3. The *saturn-shaped* folding structure obtained from a single rod–coil copolymer from different viewpoints. Dark and light grey spheres show flexible and semiflexible parts, respectively. The semiflexible part wraps around the collapsed flexible polymer.
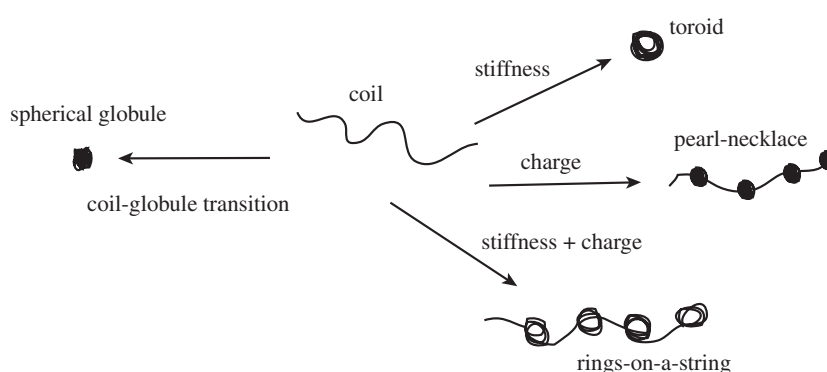

Figure 4. Various scenarios of the folding transition in a single polymer with the effects of stiffness and charge. A schematic picture of the classical coil–globule transition is also shown. By separately introducing the effects of stiffness and charge, toroidal ordered states and *pearl-necklace* structures can be obtained, respectively. The cooperative effects of stiffness and charge lead to *rings-on-a-string* structures.

in which flexible and semiflexible chains are connected to each other. With a lower solvent quality, i.e., with an increase in attraction between segments, *saturn-shaped* folding structures can be obtained. The flexible part collapses immediately into a liquid-like spherical globule. Subsequently the semiflexible part folds around the spherical globule and the entire chain finally forms a unique morphology. Such a scenario may be easily applicable to the design of various novel nanostructures derived form single chains. It should also be noted that many proteins contain both flexible and stiff parts in single molecules. It is expected that the difference in the kinetics of the folding between the flexible and stiff parts serves to find the optimal path to attain the native steric structures.

4. Nanoparticles and pearling on a single polyelectrolyte

The compact state of a single highly charged polyelectrolyte exhibits the property of a charged colloid. Accompanied with the compaction of a polyelectrolyte chain, counter-ions associate with the polyelectrolyte in the volume part to suppress the electronic repulsion by paying the penalty for the decrease in the translational entropy of counter-ions [13, 14]. As a result, the

electronic charge almost completely disappears in the volume part in tightly packed folded states [27], while it survives on the surface of the compact state, thus importing the property of charged colloids.

The colloidal stability of compact polyelectrolytes has been demonstrated with the single DNA measurements using optical tweezers [30]. Under a focused laser of infrared light with the wavelength of approximately 1000 nm, compact DNA molecules can be assembled onto the laser focus [31]. After the laser is switched off, they immediately disperse into individual particles, thus indicating the characteristic of charged colloids in the individual compact DNA molecules [22].

There is another interesting characteristic in relation to the folding transition of highly charged polyelectrolytes. Dubrinine *et al* proposed the possibility of the appearance of a *pearl-necklace* structure for a single polyelectrolyte chain in poor solvents [12]. They argued that the effect of long-range destabilization due to Coulomb interaction on the collapsed part should cause the charged globule to split into *pearls* that are interconnected by stretched, unfolded parts in a chain. The fundamental framework of their system considers a polyelectrolyte chain without any coexisting salt bathing in a poor solvent condition.

On the other hand, it has been reported that a single DNA molecule exhibits intrachain segregation with the experimental methods of single chain observation [23–25]. In the presence of salt as in these experiments, the negative charge of DNA is neutralized on tightly packed parts due to the association with counter-ions [27]. This originates from the competition between the decrease in the translational entropy of counter-ions and the increase of the electrostatic energy. Therefore, the scenario of the instability due to the long-range Coulomb interaction is not suitable in the presence of salt. Instead, the decrease in the translational entropy of counter-ions destabilizes the collapsed state at large length scale because the length scale of the translational entropy and the electrostatic energy becomes balanced due to the competition. As a result, *pearl-necklace* structures can be obtained under attractive interaction between segments in a polyelectrolyte (see figure 4). Details of the theoretical consideration of the change of the translational entropy of the counter-ions are described elsewhere [15].

The appearance of the effects of both stiffness and charge was demonstrated by the observation of DNA with cationic surfactants [29], wherein the interchain segregation is characterized as the coexistence of disordered and ordered states, referred to as a *rings-on-a-chain* conformation [16].

5. Summary

We have shown the appearance of the rich variety of exotic nanostructures that have been and will be generated from single semiflexible and/or polyelectrolyte chains. These simple concepts are expected to be applicable to further complex systems with suitable design for macromolecules.

We are currently at the stage of studying nonequilibrium states in a single polymer. Such studies, for example kinetics on the transition between the equilibrium states or a single polymer in external fields, will provide us with novel scenarios into soft matter physics.

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