Bending affects entropy of semiflexible polymers: Application to protein-DNA complexes

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We discuss a class of generalized wormlike chain models of polymers with spontaneous curvature and show that the density of states and consequently the entropy of such natively bent polymers are higher than that of straight ones. This effect changes the classical Langmuir binding isotherm by giving rise to enhanced binding of DNA-bending proteins.

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Nucleoid-associated proteins such as IHF, H-NS, HU, Fis, etc. play an important role in the organization and compaction of double-stranded DNA (dsDNA) in prokaryotic cells by introducing bends into DNA and/or changing its stiffness [1]. The effect of binding of such proteins on elastic properties of DNA was investigated using single-molecule experiments [2–6] and models [7–10]. In this paper, we focus on an important, hitherto unnoticed consequence of introducing large local bends into DNA, namely, that the presence of spontaneous curvature in the DNA-protein complex increases the torsional entropy of the bent polymer compared to that of bare DNA. Since our analysis is based on a particular generalization of the wormlike chain (WLC) model to large local deformations (the latter is based on the linear theory of elasticity and is strictly applicable only to small bending angles), we verify that our qualitative conclusions remain valid for several different generalizations of the WLC that go beyond linear theory of elasticity and, in particular, for the well-known freely rotating model of polymers [11]. Finally, we show that the bending-induced increase of torsional entropy leads to enhancement of the binding of DNA-bending proteins compared to the binding of proteins that do not affect the spontaneous curvature of the macromolecule.

A semiflexible polymer such as dsDNA whose cross section is much smaller than its persistence length can be modeled as an inextensible wormlike chain. In the WLC model, the bending energy penalty associated with a conformation [described by space curve $\vec{r}(s)$] of such a polymer is a quadratic functional of the local curvature $\kappa(s)=|d^2\vec{r}/ds^2|$ [11]

$$\frac{E}{k_BT}=\frac{l_p}{2}\int_0^L ds[\kappa(s)]^2. \tag{1}$$

Here, k_B and T are the Boltzmann constant and temperature, respectively, l_p is the persistence length, and L is the total contour length of the polymer. Inspection of Eq. (1) shows that the energetically favorable conformation is a straight line for which $\kappa(s)=0$. In the discrete form of WLC, the polymer is represented by a succession of N segments of length δs each, such that $L=N\delta s$. Scaling all lengths by δs and all energies by k_BT, the energy of a discrete WLC is given by

$$\tilde{E}=\frac{\tilde{l}_p}{2}\sum_n(\tilde{\kappa}_n)^2, \tag{2}$$

where we introduced the dimensionless quantities $\tilde{E}=E/(k_BT)$, $\tilde{l}_p=l_p/\delta s$, and $\tilde{\kappa}_n=\kappa\delta s$. The effective curvature of the discrete WLC can be related to the angle between the tangents of the nth $(\hat{t}_n)$ and $n+1$th $(\hat{t}_{n+1})$ segments, $\cos(\Delta\theta_n)=\hat{t}_n\cdot\hat{t}_{n+1}$. From the formal definition of curvature $\kappa=|d\hat{t}/ds|$, we obtain

$$\tilde{\kappa}_n=\sqrt{2(1-\cos\Delta\theta_n)}. \tag{3}$$

In the continuum limit, one usually considers only small local deformations for which the linear theory of elasticity applies ($\Delta\theta_n\to 0$ as $\delta s\to 0$) and, since expanding the above expression in $\Delta\theta_n$ yields $\tilde{\kappa}_n=\Delta\theta_n$, one recovers the familiar relationship $\kappa=d\theta/ds$.

While the assumption of small local bending deformations is adequate to describe most single-molecule mechanical studies of dsDNA, it breaks down in the presence of DNA-binding proteins that introduce sharp bends into DNA [12]. Indeed, experiments on HU-DNA complexes show that the binding of this nucleoid-associated bacterial protein introduces a bending angle from 65° [13,14] up to 140° [15,16] into DNA at the location of the bound protein. Within the framework of the linear theory of elasticity, the energy penalty for deviations from the bent reference state characterized by the preferred bending angle $\theta^{(0)}(s)$ is a quadratic functional of $\delta\kappa(s)=d\theta/ds-d\theta^{(0)}/ds$, where $d\theta^{(0)}/ds$ is the spontaneous curvature. This form holds only for small local deformations and its extension to large bending angles goes beyond linear elasticity and depends on microscopic details (e.g., [9,17]). In a recent paper [10], we generalized the discrete WLC by introducing the discrete spontaneous curvature $\tilde{\kappa}_n^{(0)}=\sqrt{2(1-\cos\Delta\theta_n^{(0)})}$. Assuming that the bending energy remains a quadratic functional of $\delta\tilde{\kappa}_n=\tilde{\kappa}_n-\tilde{\kappa}_n^{(0)}$, it can be written as $\tilde{E}=\Sigma_n\tilde{e}_n$, where

$$\tilde{e}_n=\frac{\tilde{l}_p}{2}(\delta\tilde{\kappa}_n)^2 \tag{4}$$

is the dimensionless energy per segment (see, e.g., [18]). Note that a given set of local curvatures $\{\tilde{\kappa}_n^{(0)}\}$ does not determine a unique spatial conformation of the polymer but rather represents a family of such conformations. This is a consequence of the fact that while any conformation of a discrete chain of segments is defined by the sets of bending $\{\Delta\theta_n\}$ and torsional $\{\Delta\varphi_n\}$ angles, in the absence of torsional rigidity (as is the case in the standard WLC model), there is no energy penalty for changing the latter angles and they can take any value in the interval $[-\pi,\pi]$ (see Fig. 1).

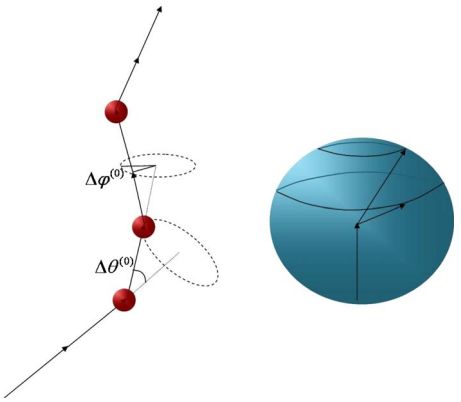

FIG. 1. (Color online) (Left) Schematic drawing of ground-state conformations of a protein-DNA complex. The ground state is degenerate since the binding of proteins determines the spontaneous angles $\{\Delta\theta_n^{(0)}\}$ but the torsional angles $\{\Delta\varphi_n^{(0)}\}$ are uniformly distributed in the interval $[-\pi,\pi]$. (Right) Since the measure contains a factor of $\sin\Delta\theta_n^{(0)}$, the number of states of a dimer for a particular $\Delta\theta_n^{(0)}$ is proportional to the circumference of the circle spanned by the rotation of the tangent on the unit sphere.

In the absence of excluded volume interactions, the partition function of the polymer can be written as the product of partition functions of overlapping dimers, each of which depends on the angle $\Delta\theta^{(0)}$ between two neighboring segments

$$\zeta_n = 2\pi\int_0^2 d\tilde{\kappa}_n\tilde{\kappa}_n e^{-\tilde{e}_n}, \tag{5}$$

where we integrated over the angle $\Delta\varphi$ and used the relation $\sin(\Delta\theta_n)d(\Delta\theta_n)=\tilde{\kappa}_n d\tilde{\kappa}_n$ (notice that $\tilde{\kappa}_n$ varies in the interval [0, 2]). In Fig. 2, we plot the dimensionless free energy $\tilde{f}=-\ln(\zeta_n)$, mean energy $\langle\tilde{e}_n\rangle=2\pi\int_0^2 d\tilde{\kappa}_n\tilde{\kappa}_n\tilde{e}_n\exp[-\tilde{e}_n]/\zeta_n$, and entropy $\tilde{s}=\langle\tilde{e}_n\rangle-\tilde{f}$ per segment against the spontaneous curvature $\tilde{\kappa}^{(0)}$, where the free energy and entropy are measured with respect to their values in the straight ($\tilde{\kappa}^{(0)}=0$) state

$$\Delta\tilde{f}=\tilde{f}(\tilde{\kappa}^{(0)})-\tilde{f}(0),$$

$$\Delta\tilde{s}=\tilde{s}(\tilde{\kappa}^{(0)})-\tilde{s}(0). \tag{6}$$

Inspection of Fig. 2(a) shows that (1) the free energy of a strongly bent chain ($\tilde{\kappa}^{(0)}\simeq 1$) is much lower than that of a chain with no spontaneous curvature, (2) this effect is mainly of entropic origin, and (3) the effect is nonmonotonic and the entropy first increases (for $\Delta\theta^{(0)}<\pi/2$) and then decreases (for $\Delta\theta^{(0)}>\pi/2$) with spontaneous angle. The variation of the entropy with spontaneous angle or curvature is a direct consequence of the three-dimensional geometry of the problem: if we take the z axis in the direction of the nth segment ($\hat{z}=\hat{t}_n$), the spherical angles $(\Delta\theta_n,\Delta\varphi_n)$ define the direction of the tangent to the $n+1$th segment. As $\Delta\theta_n^{(0)}$ increases from 0 to $\pi/2$ ($\tilde{\kappa}^{(0)}$ increases from 0 to $\sqrt{2}$), the circumference of the circle spanned by the rotation of the tangent on the unit sphere (as $\Delta\varphi_n$ varies between $-\pi$ to π) increases (see Fig. 1) and one concludes that there are more states available for the polymer in the vicinity of a higher spontaneous angle $\Delta\theta_n^{(0)}$ in the interval $[0,\pi/2]$ (density of states decreases with increasing $\Delta\theta_n^{(0)}$ in the interval $[\pi/2,\pi]$). The above argument becomes exact in the purely entropic, freely rotating chain (FRC) model in which the angle $\Delta\theta_n$ is constant (fixed at some value $\Delta\theta_n^{(0)}$) and the torsional angle $\Delta\varphi_n$ is distributed uniformly between $-\pi$ and π. The dimer partition function is

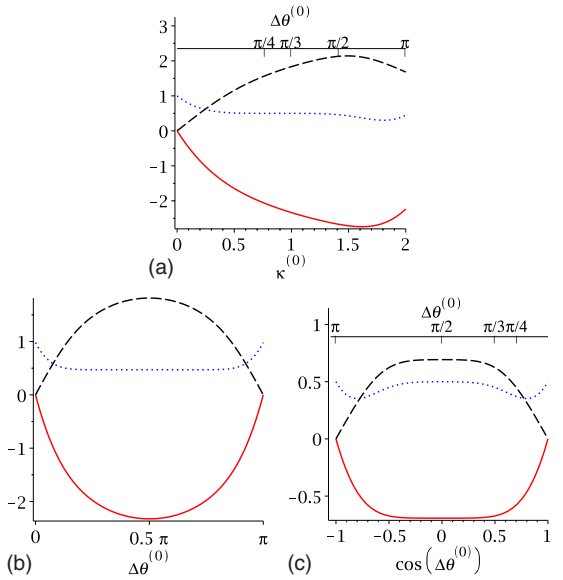

FIG. 2. (Color online) The dimensionless free energy (red solid line), entropy (black dashed line), and mean energy (blue dotted line) per segment of generalized WLC are plotted vs the spontaneous curvature for different models of semiflexible polymers described by (a) Eq. (4), (b) Eq. (9), and (c) Eq. (10). The dimensionless persistence length is taken to be $\tilde{l}_p=17$.

$$\zeta_{FRC}=2\pi\int_0^\pi d(\Delta\theta)\sin(\Delta\theta)\delta(\Delta\theta-\Delta\theta^{(0)})=2\pi\sin(\Delta\theta^{(0)}) \tag{7}$$

and, therefore, the torsional entropy

$$\tilde{s}_{FRC}\propto\ln[\sin(\Delta\theta^{(0)})] \tag{8}$$

is a symmetric function of $\Delta\theta^{(0)}$ in the interval $[0,\pi]$, with a maximum at $\pi/2$.

As mentioned earlier, the extension of the linear theory of elasticity to large local bending angles is nonunique and depends on the microscopic model of the polymer. In order to check whether the qualitative results of our extended WLC defined by Eq. (4) apply to other possible model choices, we calculated the thermodynamic potentials for some other energy functionals. The model defined by

$$\tilde{e}_n=\frac{\tilde{l}_p}{2}(\Delta\theta_n-\Delta\theta_n^{(0)})^2 \tag{9}$$

yields an entropy $\Delta\tilde{s}$ that is symmetric with to $\Delta\theta_n^{(0)}=\pi/2$ and behaves approximately like that of a FRC [see Fig. 2(b)]. For yet another choice of an energy functional,

$$\tilde{e}_n = \frac{\tilde{l}_p}{2}[\cos(\Delta\theta_n) - \cos(\Delta\theta_n^{(0)})]^2, \tag{10}$$

the partition function is

$$\zeta_n = 2\pi \int_{-1}^{1} d\eta e^{-(\tilde{l}_p/2)(\eta - \eta^{(0)})^2}, \tag{11}$$

where $\eta=\cos(\Delta\theta_n)$ and $\eta^{(0)}=\cos(\Delta\theta_n^{(0)})$. In this case, the entropy of a bent chain is larger than that of a straight one, but is nearly independent of the spontaneous curvature through most of the range [see Fig. 2(c)]. Notice that the results depend also on the choice of $\tilde{l}_p$ and, consistent with the relation between DNA persistence length $l_p \simeq 50$ nm and HU protein size $\delta s \simeq 3$ nm, we used $\tilde{l}_p=17$ for the plots in Fig. 2.

Based on the preceding discussion, we conclude that, independent of the precise microscopic model, the torsional entropy of a semiflexible polymer is an increasing function of its spontaneous curvature (for bending angles $<\pi/2$). The physical significance of this observation stems from the fact that while the spontaneous curvature of an isolated polymer is determined by its sequence and is fixed once and for all during the polymerization process, this curvature can be affected by binding of small molecules (e.g., proteins) that introduce sharp bends in the polymer. Since (for not too high bending angles) the free energy of a bent polymer-protein complex is lower than that of a bare (straight) polymer, more such proteins would bind to an elastic polymer than to a rigid rod. In order to demonstrate this effect, let us consider a discrete WLC model of DNA [the model of Eq. (4)] in solution of proteins characterized by a dimensionless chemical potential $\tilde{\mu}$ (which depends on the protein concentration in solution and on the DNA-protein binding energy). A dimer of the DNA chain can be either free (occupancy of node between the two segments $\phi=0$) and therefore straight or occupied by a protein (node occupancy $\phi=1$) and therefore bent at angle $\theta^{(0)}$ or, equivalently, having spontaneous curvature $\tilde{\kappa}^{(0)}$. The grand canonical partition function for the (open) DNA+bound proteins system is given by the product of the partition functions of the noninteracting dimers (neglecting cooperativity and excluded volume effects), each of which is of the form

$$\zeta_G = 2\pi \sum_{\phi=0}^{1} \int_0^2 d\tilde{\kappa}\tilde{\kappa} e^{-(\tilde{l}_p/2)(\tilde{\kappa} - \phi\tilde{\kappa}^{(0)})^2 + \phi\tilde{\mu}}. \tag{12}$$

Taking $\tilde{\kappa}^{(0)}=0$ in the above equation removes the coupling between protein binding and polymer elasticity and one recovers the standard Langmuir isotherm for the mean occupancy $\langle\phi\rangle$ vs chemical potential $\tilde{\mu}$. For $\tilde{\kappa}^{(0)}>0$, the isotherm is shifted to lower values of the chemical potential

$$\langle\phi\rangle = \frac{1}{1 + e^{\Delta\tilde{f} - \tilde{\mu}}}, \tag{13}$$

where $\Delta\tilde{f}<0$ [for not too high bending angles; see Fig. 2(a)] and we conclude that bending increases the effective binding affinity and promotes binding at low protein concentrations. This qualitative conclusion remains valid for other WLC-like models of polymer elasticity [Eqs. (9) and (10)] as well.

In summary, we have shown that spontaneous curvature increases the torsional entropy and therefore decreases the free energy of a wormlike polymer. As demonstrated by the freely rotating chain model, the origin of this effect is the three-dimensional geometry of space: the density of states of two connected segments increases with the angle between them. In order to illustrate the physical consequences of the torsional entropy increase, we calculated the resulting shift of the Langmuir adsorption isotherm and showed that it leads to enhanced binding of DNA-bending proteins. Finally, we would like to add a word of caution. In the literature, one often fails to make the distinction between torsion and twist; while curvature and torsion define the three-dimensional conformation of a line (through the Frenet equations of differential geometry), twist cannot be defined for a mathematical line and is the property of objects that have finite cross section (e.g., cylinders or ribbons [18]). The present paper deals only with polymers that can be described as wormlike chains, i.e., lines with bending but no twist rigidity. This captures the behavior of DNA molecules under extension but if one applies torque to DNA and changes its linking number, one can no longer neglect the twist degrees of freedom. Consideration of the effect of binding of proteins on the twist rigidity and intrinsic linking number of torsionally constrained dsDNA and through them on the balance between twist and writhe (reported in Ref. [19]) is beyond the scope of the present work.

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