

Formation of Helical States in Wormlike Polymer Chains

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We propose a potential for wormlike polymer chains which could be used to model the low-temperature polypeptide structures. We successfully reproduced helix ground states up to 6.5 helical loops, using the multicanonical Monte Carlo simulation method. We demonstrate that the coil-helix transition involves four distinct states: coil (gaslike), collapsed globular (liquidlike), and two helical states I and II (both solidlike). The helix I state is characterized by a helical ordering with dangling loose ends, and the helix II state corresponds to a near-perfect helical ordering in the entirely crystallized chain. [S0031-9007(98)07574-7]

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The structure of α helices is one of the most common conformations occurring in biological molecules such as proteins. It is this unique structure that acts as the building block for much more complicated tertiary structures [1]. In 1959, Zimm and Bragg proposed a mean-field model for the coil-helix transition that was based on the thermodynamics of a known sequence of pairing residues [2]. A tremendous number of theoretical works have been published since then, and the basic approaches are derivatives or alterations of the original Zimm-Bragg treatment [3,4]. Most recent numerical attempts to study the problem are based on more realistic potentials at the atomic level for helix-forming polypeptides, concentrating more on finding the ground-state structure [5] than on the thermodynamics at finite temperatures [6].

From a statistical-physics perspective, it is desirable to start from a simple theoretical model of general characteristics, in the same spirit as recent models for double stranded semiflexible polymers [7], for low-temperature lattice homopolymers [8], and for polymer chains containing dipolar segments [9]. In this Letter, we discuss alpha helices appearing in, for example, polypeptides due to hydrogen bonding. By ignoring the specifics of the amino acids, most proteins can be viewed as wormlike polymer chains. One can then ask simple questions such as, what are the minimum conditions required for a wormlike polymer chain to reproduce a helix ground state? What are the characteristics of the so-called coil-helix transition in comparison with the predictions of a Zimm-Bragg-type theory, and how different is it from the coil-collapsing transition in other polymeric molecules occurring near the theta temperature? From a polymer physics point of view, a related and inspiring question by itself is: What are the low-temperature structures of a wormlike chain, generally?

There are two basic characteristics common to all wormlike chains: the existence of a persistence length, which prevents the polymer from folding as a sharp hairpin loop at scales smaller than the persistence length, and an excluded volume interaction between the monomers, which prevents polymer chains from collapsing into a point at low temperatures. In addition, for helices with prototypical hydrogen bonds perpendicular to the local chain orientation, it is known that the attraction between segments is highly directional.

In the current approach we model wormlike polymers by fixing the bond angle θ between two adjacent polymer bonds of length a and allowing the azimuthal angle ϕ to rotate freely, as prescribed in the original freely rotating model [10]. Movement of monomers is realized by implementing a pivot algorithm [11], where a bond is chosen at random as a reference axis about which the entire polymer segment attached to this bond is rotated. The Metropolis method of sampling a canonical phase space is known to be ineffective for examining the possible conformational states at low temperatures, as a particular configuration could easily become trapped in a local energy minimum. To avoid this problem we have incorporated a multicanonical technique into the pivot algorithm, which involves reweighting the temperature as a function of energy, in order to produce a flat simulation histogram across the entire energy landscape [5,12]. This approach allows the polymer to potentially visit all possible energy states and to tunnel through local energy minima. For a more detailed explanation of the multicanonical technique the reader is referred to Refs. [6,12].

The interaction energy between the monomers labeled i and j having a center-to-center distance r_{ij} is proposed to be

$$V_{ij} = \begin{cases} 0 & \text{for } \sigma \leq r_{ij}, \\ -\epsilon[\hat{u}_i \cdot \hat{r}_{ij}]^m - \epsilon[\hat{u}_j \cdot \hat{r}_{ij}]^m & \text{for } d \leq r_{ij} \leq \sigma, \\ \infty & \text{for } 0 \leq r_{ij} \leq d, \end{cases} \quad (1)$$

where $\hat{u}_i = (\vec{r}_i - \vec{r}_{i-1}) \times (\vec{r}_{i+1} - \vec{r}_i) / \sin \theta$ and $\hat{r}_{ij} = (\vec{r}_i - \vec{r}_j) / |\vec{r}_i - \vec{r}_j|$. Here m represents the degree of directional bias in the potential, d is the excluded-volume diameter, and σ is the attractive-force range. The multicanonical technique is also an effective method to search for the ground states of a given potential. In an effort to answer the question of what type of potential is needed for the creation of a perfect helical ground state, the consequences of using various values of m were examined. We found that for an isotropic interaction ($m = 0$), the stable ground state structure is a disordered globular state with no particular relative directional ordering between the chain bonds. Thus, a directionalized interaction ($m \neq 0$) is obviously an essential condition for a helix-forming wormlike chain. We also found that weaker powers ($m = 2, 4$) would produce only a perfect helix ground state in short polymers; in longer polymers multiple bonds formed by spooling around a helix core might give rise to an even lower energy. In a perfect helical state, energy should be minimized when all monomers sit directly on top of each other. This requires a strongly directionalized attraction known to exist in helix-forming polypeptides [2,3], as effectively modeled by the $m = 6$ case, which will be reported here. Numerical data collected by using other powers of m will be reported elsewhere.

It is worth noting that our potential is not simply a function of the distance between the two involved monomers. The bonding preference also involves the directions of the bonds connected to these two monomers, similar to a prototypical hydrogen bond interaction in proteins. There are a number of other variables in the potential model. The diameter d and constant σ have been adjusted to have the values $3/2a$ and $\sqrt{45/8}a$, while the nearest neighbor interaction is ignored. The fixed bond angle θ is chosen to have a value of approximately $\pi/3$, corrected for the helical pitch to maintain six monomers per helix loop. These selections of values were based on the observation that under the current choice a stray end of the monomers cannot loop through an open core of a partially formed helical segment. We have also investigated the case of $\theta = \pi/5$ and found no major qualitative difference in the physical

properties to be examined below. This choice of potential, with the use of the multicanonical technique, was able to produce a perfect helical ground state relatively quickly [see Fig. 1(d)] for various polymer lengths $N = 13, 19, 26$, and 39, showing that the helix ground state can be constructed with the above mentioned three conditions of a helix-forming wormlike chain.

Therefore, a wormlike chain can have numerous types of ground states, which are dependent on the type of directional potential used. The construction of a potential which produces a singular ground state of a desired conformation is possible, although not a trivial exercise. The use of the multicanonical technique makes the search for these specific ground states simpler.

Knowing that our model has an attainable perfect helix ground state, we have calculated the multicanonical reweighting function for the temperature range discussed below, which enables us to conduct measurements of physical quantities in the subsequent production runs. As a most effective measure for exploring the phase transition signatures, the specific heat capacity of the polymer chain was calculated by measuring the energy fluctuations

$$C_v/k_B = [\langle E^2 \rangle - \langle E \rangle^2] / (k_B T)^2. \quad (2)$$

The mean square radius of gyration,

$$\langle R_g^2 \rangle = \left\langle \frac{1}{N} \sum_{i=1}^N (\vec{r}_i - \vec{r}_{\text{cm}})^2 \right\rangle, \quad (3)$$

where \vec{r}_{cm} is the center of mass vector, and the mean square end to end distance,

$$\langle R_{\text{end}}^2 \rangle = \langle (\vec{r}_1 - \vec{r}_N)^2 \rangle, \quad (4)$$

were also calculated to characterize the spatial dimension of the polymer chain. Finally we introduced three parameters to measure the degree of helicity within the chain. This is accessed in many references by examining the Ramachandran angles ϕ and ψ which are parameters not present in our current model. Equivalent to the same treatment, the first helicity parameter H_1 is based on an examination of the distance between the i th and $(i + 3)$ th monomers, which is calculated and evaluated as being in

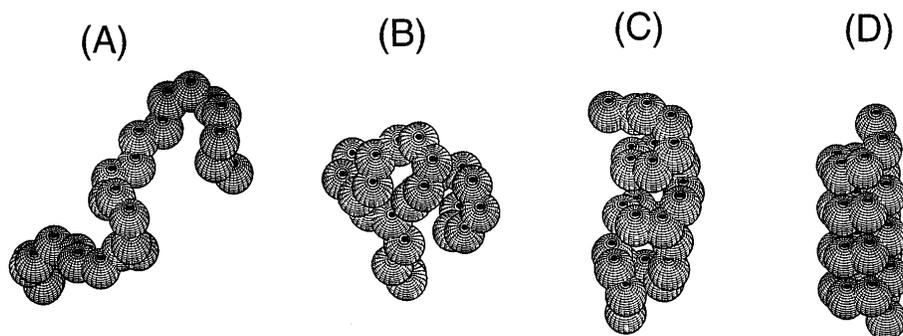


FIG. 1. Snapshots of the configurations of a 26mer at various temperatures: (a) $k_B T / \epsilon \approx 4$ (coil), (b) $k_B T / \epsilon \approx 1.3$ (globular), (c) $k_B T / \epsilon \approx 0.8$ (helix I), and (d) $k_B T / \epsilon \approx 0.1$ (helix II). The size of the beads represents the actual hard-core interaction between nonadjacent monomers, and the attraction force range is $\sqrt{45/8}a$, where a is the bond length. A highly directionalized potential with $m = 6$ [see Eq. (1)] is used.

a helical or nonhelical state, as the three connected bonds in the segment will be arranged in a very specific way when in the helix state. A window of allowed distances can then define a three-monomer segment as helical, and the average number of helical segments, H_1 , can be measured. A second method of characterizing the degree of local helicity within the polymer involves summing the dot products of the adjoining cross products of connected bond vectors:

$$H_2 = \frac{1}{N-2} \sum_{i=2}^{N-1} (\vec{u}_i \cdot \vec{u}_{i+1}). \quad (5)$$

A third measurement is the correlation function $G(i) \equiv \vec{u}_i \cdot \vec{u}_{\text{mid}}$, where \vec{u}_{mid} corresponds to the vector in Eq. (2) for the central monomer, characterizing the correlation of the helical ordering along the chain. Discussed below is the integrated correlation function,

$$H_3 = \frac{1}{N-2} \sum_{i=2}^{N-1} (\vec{u}_i \cdot \vec{u}_{\text{mid}}), \quad (6)$$

which represents the averaged correlation in the chain. These three parameters yield a global representation of the amount of helicity in the polymer.

Using the reweighting function from preliminary deterministic multicanonical runs, we performed a typical production run of 5×10^8 pivot rotations with measurement made every ten steps for rescaled temperatures $k_B T/\epsilon$ ranging from 0.1 to 5.0. Polymer chain lengths of 13, 19, 26, and 39 monomers were considered and the results are shown in Fig. 2.

Displayed in Fig. 2(a), the scaled heat capacity curves show a number of interesting features. The first and most obvious is the large peak near $kT/\epsilon \approx 1.2$ corresponding to the transition to a helix state. The words describing what is meant by a helix state must be chosen carefully for the reason that there are two distinct helix states observed in this study. Figures 1(b) and 1(c) are typical configurations just before and after the transition. Corresponding to a significant increase in the three helical parameters measured for $N = 19$ [Fig. 2(c)], a C_v anomaly occurs at this temperature, confirming that the polymer is making a transition from a disordered [Fig. 1(b)] state to the more ordered helical state [Fig. 1(c)]. The same sharp increase in C_v was also predicted in the Zimm-Bragg theory [1,2] and its variations and in recent Monte Carlo simulations by Okamoto and Hansmann [6]. Zimm and Bragg assumed *a priori* that a monomer will be coupled with the third one down the one dimensional chain and argued that this peak does not represent a phase transition consistent with the known conclusion regarding the impossibility of phase transitions in one dimensional systems. However, one can also argue that a helix polymer is not strictly a one dimensional system. Our peaks in the heat capacity curves continuously increase as N grows, which show a similar behavior as heat capacity curves in a prototypical second order phase transition and qualitatively agree with the observation in a more realistic polypeptide model [6]. It would be interesting to further examine a possible finite size scaling in the

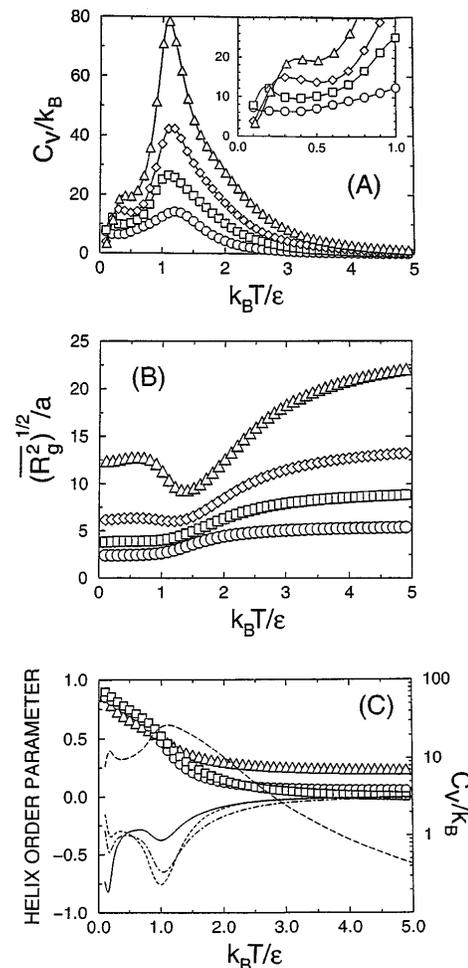


FIG. 2. Variation of physical quantities as a function of scaled temperature $\tilde{T} = k_B T/\epsilon$. Triangles, diamonds, squares, and circles in (a) and (b) correspond to 39mers, 26mers, 19mers, and 13mers, respectively. Only every tenth data point was plotted, and more data points are represented by the more smooth curves. The error bars of the C_v curve are almost twice the size of the plotted symbols and triple the size of the plotted symbols in the inset. Triangles, squares, and circles in (c) represent the helix parameters H_1 , H_2 , and H_3 for the case of 19mers, respectively. The solid, short-dashed, and dot-dashed curves represent $dH_1/d\tilde{T}$, $dH_2/d\tilde{T}$, and $dH_3/d\tilde{T}$, respectively. An overlay of the C_v curve (to the right scale) is also shown by the long-dashed curve for reference.

C_v peak values determined from our simulations. However, currently, the main obstacle to achieving this goal is the increasing computational time for larger N .

One of the most interesting features of Fig. 2(a) is the previously unknown second transition occurring in the neighborhood of a scaled temperature $k_B T/\epsilon \approx 0.3$. In a recent study of the phase transitions in isotropic homopolymers with specific ground states in a lattice model, Zhou *et al.* [8] have observed a similar transition and have suggested that this is a solid-solid transition accompanying the crystallization of their polymers into the ground state. In the present case, our wormlike chains have the specifically constructed ground state of a perfect helix, and we

believe that the second transition corresponds to the crystallization of the helix I state into a perfect helix II state. Above this transition we have observed that the chain is in a highly ordered helical structure only segmentally as demonstrated by Fig. 1(c). In particular, the end portion of the polymer may not necessarily be ordered. Even for the ordered segments, elongation motion and bending of the ordered segment as a whole would make the directional ordering weaker compared with the more tightly wound helix II. Thus, as the temperature continues to drop further, the few unbonded end segments arrange themselves into a perfect helical state (helix II), and in the mean time, the already existing helix segments crystallize to a near ground-state structure, as shown in Fig. 1(d). Such a crystallization transition has not been seriously modeled by previous theoretical studies, which usually treat the helix I to helix II transition as a smooth crossover with no sharp anomalies in the heat capacity [1–4]. The three lower curves in Fig. 2(c) are derivatives of the helical parameters, all showing a significant change in the slope corresponding to the low-temperature peak at the C_v curve. To further confirm this crystalline transition we have examined individual local helical parameters $\vec{u}_i \cdot \vec{u}_{i+1}$, which also show substantial changes before and after the helix I to helix II transition. Presently, we are unable to precisely determine the location and height of the second peak for large N polymers, due to large error bars associated with the low temperature behavior. Returning to Fig. 2(a), we would like to point out a third feature of interest, which is the emergence of a shoulder in the larger polymers near $k_B T/\epsilon \approx 2$, not easily detectable from Fig. 2(a). This shoulder corresponds to a θ temperature collapsing of the polymer chain from a gyrate coil (“gaslike”) to a randomly collapsed globular state (“liquidlike”). This collapsing is a direct cause of the directionally averaged attractive potential between the monomers, creating globular states which have little helical ordering. In Fig. 2(b), the radius of gyration curves shows a significant decrease near a transition temperature $k_B T/\epsilon \approx 2$, as the signature of a collapsing transition in polymers. At lower temperatures, as helix states start to form, there is an increase in both R_g and R_{end} (not shown). Such a turnover is actually a characterization of the helix formation, because in a large polymer, the ordered helix structure will be quite extended along the helix axis, forcing the monomers to have an average radius of gyration larger than that of a compact collapsed state. For shorter helices, the increase of polymer dimensions at low temperature does not exist, and the coil-globular and globular-helix I transitions merge to a single transition. Note that neither dimensional parameters show appreciable changes at the helix I–helix II transition, which is again consistent with our belief that the helix I to helix II transition merely involves the ordering of the end segments and tightening of the helix segments, with no significant structural rearrangement.

To summarize, we have described a simple model which can be used for examining the coil-helix transitions, for

helices formed solely from long range interactions in, for example, homopolypeptides. The coil-helix transition actually consists of three steps as the temperature is lowered. At high temperatures the polymer has a gaslike coil conformation which collapses into a liquidlike globular conformation while the relative bond directions still remain disordered. This state then makes a transition to a relatively well ordered solidlike helix I state, with a dramatic increase in bond direction correlation. Upon further cooling this conformation crystallizes to the very well ordered helix II state. It would be interesting to confirm that this transition indeed accompanies a C_v anomaly experimentally in short polypeptide chains which are known to exhibit perfect helical ground states. We hope the current model will shed some light on analyzing experimental data complimentary to a traditional Zimm-Bragg-type physical picture. We believe that the current treatment can be modified with little effort to produce a variety of ground states, important to modeling other interesting transitions in biological systems.

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