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Adsorption of a hydrophobic-polar-model heteropolymer in an attractive nanotube

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The adsorption of an off-lattice hydrophobic-polar-model heteropolymer in an attractive hydrophobic nanotube is presented by means of a multicanonical Monte Carlo simulation. In the model, the Lennard-Jones potential is assumed as an interaction potential between the effective monomers and the nanotube wall. The global minimum-energy configurations and the values of radius of gyration and end-to-end distance of these configurations are compared for both pure hydrophobic and polar heteropolymer models and with interaction term included model. The low-energy conformations for heteropolymers are extended when they interact with the nanotube which the conformational extensions are detected with some structural parameters.

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I. INTRODUCTION

Adsorption of polymers on solid surfaces and geometries plays an important role in many applications including adhesion [1], chromatography, biomedical implant modification, and biosensors [2]. In many of these applications, it is desirable to have surface that selectively adsorbs specific monomer sequences along the adsorbing polymers. Recent theoretical studies of the adsorption of polymers or proteins suggest that polymers with a given sequence distribution recognize compatible patterns on the surface and adsorbs on them [3–7]. The conformation of polymers and especially proteins on a substrate is crucial for their activity [8]. The arrangements of the proteins across the substrate deserve particular attention since it provides mesoscale morphology for interactions with tissue [9] and also influences conformation [10]. If we understand the mechanisms by which polymers cluster together on the surface, we might hope to influence the growth of the polymer layers and hence engineer bioactive surfaces or other geometries with tailored properties.

In a biological context, the understanding of the binding and docking mechanisms of proteins at cell membranes is important for the reconstruction of biological cell processes. Similarly, specificity of peptides and binding affinity to selected substrates could be of great importance for future electronic nanoscale circuits and pattern recognition nanosensory devices [3]. In addition to flat substrates, DNA nanotubes have been made to form hollow tubes of 4–20 nm diameter. These are easily modified and connected to other structures to develop new technology [11]. The work considered in this paper could have practical implications for a broad variety of problems ranging from protein-ligand binding, designing smart sensors, to molecular pattern recognition and in discovery of new drugs that bind to specific receptors. A molecular level understanding of these self-assembly processes is lacking because the length and time scales of relevance largely fall outside of the scope of both experimental techniques and fully atomistic computer simulations. Therefore the theoretical treatment of the adsorption of macromolecules within the framework of minimalist effective protein models in statistical mechanics has been longstanding problem [12,13] that still gains a lot of interest [14–18]. In this study, a minimal theoretical model that captures some essential aspects of the physics of heteropolymer adsorption is presented. Coarse-grained models for biomolecules consist of two or more monomer types which represent at the lowest order the amino acids. These monomers can be classified either hydrophobic- (H) or polar- (P) type monomers which are known as hydrophobic-polar (HP) or *AB* models. The presence of an attractive substrate strongly affects the behavior of the polymer in the vicinity of the interface. The monomer-monomer attraction, being responsible for the collapse, and the surface-monomer attraction, resulting in the adsorption, compete with each other. In most theoretical and computational studies, the polymer is attached at the substrate with one of its ends which reduces the entropic freedom of the polymer. However, in many recent experiments of organic-inorganic interfaces, e.g., for peptide-metal [19,20] and peptide-semiconductor [21,22] interfaces, the setup is different and the polymer can move freely within the nanotube and the polymer can fold into conformations, where the ends have no contact with the surface. In this study, multicanonical Monte Carlo simulations are performed in order to analyze thermodynamic properties of the adsorption of heteropolymers in an unstructured, attractive nanotube and compare the results of pure *AB* heteropolymer model to get an insight what occurs when the heteropolymer is in an confined geometry. The thermodynamically stable global minimum-energy conformations of hydrophobic-polar off-lattice *AB* model inside a nanotube are presented. The presentation begins by replacing the explicit hydrophobic nanotube with an implicit potential, Lennard-Jones potential between the monomers and the nanotube. The objective of this work is to show that with a simple, minimal model, it is possible to capture some fundamental characteristics of the physics of heteropolymer adsorption.

The rest of the paper is organized as follows. In Sec. II, the hybrid heteropolymer-nanotube model and the multicanonical simulation method are described. In Sec. III, the results are presented and the paper is concluded in Sec. IV.

II. MODEL

The polymer chains are described by a coarse-grained hydrophobic-polar-model which also helped to understand

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protein folding channels from mesoscopic perspective [23]. A manifest off-lattice of the HP model [24] is the *AB* model [25], where the hydrophobic monomers are labeled by *A* and the polar or hydrophilic ones by *B*. As on the lattice, the adjacent monomers are connected by rigid covalent bonds. Thus, the distance is fixed and set to unity. The contact interaction is replaced by a distance-dependent Lennard-Jones type of potential accounting for short-range excluded volume repulsion and long-range interaction. An additional interaction accounts for the bending energy of any pair of successive bonds. This model was first applied in two dimensions [25] and generalized to three-dimensional *AB* proteins [26,27], partially with modifications taking implicitly into account additional torsional energy contributions of each bond.

The *AB* model as proposed in Ref. [26] with the energy function

$$E = -\kappa_1 \sum_{k=1}^{N-2} \mathbf{b}_k \cdot \mathbf{b}_{k+1} - \kappa_2 \sum_{k=1}^{N-3} \mathbf{b}_k \cdot \mathbf{b}_{k+2} + 4 \sum_{i=1}^{N-2} \sum_{j=i+2}^{N} C(\sigma_i,\sigma_j)\left(\frac{1}{r_{ij}^{12}} - \frac{1}{r_{ij}^{6}}\right), \qquad (1)$$

where $\mathbf{b}_k$ is the bond vector between the monomers k and $k+1$ with length unity. In Ref. [26], different values for the parameter set (κ_1, κ_2) were tested and finally set to $(-1,0.5)$ as this choice led to distributions for the angles between bond vectors $\mathbf{b}_k$ and $\mathbf{b}_{k+1}$ as well as the torsion angles between the surface vectors $\mathbf{b}_k \times \mathbf{b}_{k+1}$ and $\mathbf{b}_{k+1} \times \mathbf{b}_{k+2}$ that agreed best with distributions obtained for selected functional proteins. Since $\mathbf{b}_k \cdot \mathbf{b}_{k+1} = \cos \vartheta_k$, the choice $\kappa_1 = -1$ makes the coupling between successive bonds "antiferromagnetic" or "antibending." The second term in Eq. (1) takes torsional interactions into account without being an energy associated with the pure torsional barriers in the usual sense. The third term contains now a pure Lennard-Jones potential, where the $1/r_{ij}^6$ long-range interaction is attractive whatever types of monomers interact. The monomer-specific prefactor $C(\sigma_i,\sigma_j)$ only controls the depth of the Lennard-Jones valley:

$$C(\sigma_i,\sigma_j) = \begin{cases} +1, & \sigma_i,\sigma_j = A \\ +1/2, & \sigma_i,\sigma_j = B \ \text{ or } \ \sigma_i \neq \sigma_j. \end{cases} \qquad (2)$$

The energy function of the polymer chain is introduced above and the interaction of polymer chain monomers (m) and nanotube (n) is given with Lennard-Jones-type potential

$$E_{mn} = 4 \sum_{i=1}^{N_m} \sum_{j=1}^{N_n} C_{mn}(\sigma_i,\sigma_j)\left(\frac{1}{r_{ij}^{12}} - \frac{1}{r_{ij}^{6}}\right), \qquad (3)$$

where the N_m $(N_m=20)$ is the number of monomers in the polymer chain and N_n $(N_n=168)$ is the number of attraction sites in the nanotube taken as on the lattice. The C_{mn} parameter is settled from Eq. (2). The C_{mn} parameter is one for *AA* contacts and 0.5 for *AB* contacts which means that the nanotube is attractive for all but its attraction changes for monomer type. Then the total energy (E_T) of the system will contain pure *AB* model polymer chain energy and the polymer chain nanotube interaction energy $(E_T = E_{AB} + E_{mn})$. The initial configuration of the polymer chain is randomly generated where the ends have no contact with the nanotube surface. In some theoretical and computational studies, the polymer is attached at the surface with one of its end which reduces the entropic freedom of the system. However, in many recent experiments of the peptide-metal or peptide-semiconductor interfaces, the setup is considered by a freely moving polymer in a surface. This allows adsorbing conformations where none of the two polymer ends is in contact with the nanotube.

FIG. 1. (Color online) The starting configuration of the simulation. The polymer chain is a random start configuration and the nanotube is prepared by MATERIAL STUDIO visualization program.

The adsorption of a hydrophobic-polar polymer chains into a nanotube is simulated using off-lattice *AB* model with an implicit attractive interaction energy. It is considered a polymer chain confined in a nanotube. No special nanotube composition is taken into account. The nanotube is composed of purely hydrophobic-type sites and hydrophobic monomers in the polymer chain have more attractive interactions with the nanotube while the polar ones have less attractive interactions. As a result, an attractive nanotube is generated. A start configuration to the simulation is presented in Fig. 1. The nanotube position is fixed in the whole simulation. The atomistic detailed plot of the nanotube is only chosen for better visualization. I would like to point out that it is unstructured and contains no atomistic details. It is only generated as model hollow tube. The width and the length of the nanotube are 7.18 and 18.13, respectively. In the simulations, the lengths are unitless.

Simulations of this model were performed with multicanonical algorithm (MUCA) [28] in which the details are given below. The update mechanism for a polymer chain is spherical update which is described in Ref. [29] in details.

III. SIMULATION METHOD

The multicanonical ensemble is based on a probability function in which the different energies are equally probable.

TABLE I. The five *AB* sequences examined in this study.

Label	Sequence
SEQ1	*BAAAAAABAAAABAABAABB*
SEQ2	*AAAABAABABAABBAAABAA*
SEQ3	*AAAABBAAAABAABAAABBA*
20*A*	*AAAAAAAAAAAAAAAAAAAA*
20*B*	*BBBBBBBBBBBBBBBBBBBB*

However, implementation of the multicanonical algorithm (MUCA) is not straightforward because the density of states $n(E)$ is *a priori* unknown. In practice, one only needs to know the weights ω,

$$w(E) \sim 1/n(E) = \exp[(E - F_{T(E)})/k_B T(E)], \quad (4)$$

and these weights are calculated in the first stage of simulation process by an iterative procedure in which the temperatures $T(E)$ are built recursively together with the microcanonical free energies $F_{T(E)}/k_B T(E)$ up to an additive constant. The iterative procedure is followed by a long production run based on the fixed w's where equilibrium configurations are sampled. Reweighting techniques [30] enable one to obtain Boltzmann averages of various physical variables over a wide range of temperatures.

As pointed out above, the calculation of the *a priori* unknown MUCA weights is not trivial, requiring an experienced intervention. For lattice models, this problem was addressed in a sketchy way by Berg and Çelik [28] and later by Berg [31]. An alternative way is to establish an automatic process by incorporating the statistical errors within the recursion procedure.

IV. RESULTS AND DISCUSSIONS

For each polymer chain sequence, after calculating the multicanonical weights, 5×10^7 iteration was performed in production run. The sequences which are examined in this study are listed in Table I.

In literature, many recent papers [23,32–35] give only the minimum-energy values of these sequences, but no other aspects of physics are investigated for this effective protein model. In this study, conformational analysis of an off-lattice heteropolymer model in an attractive nanotube is investigated by multicanonical computer simulations. To characterize the hybrid-system behaviors, thermal fluctuations of energetic parameters, and specific heats, some structural quantities are analyzed and the stable lowest-energy conformations of heteropolymers are determined.

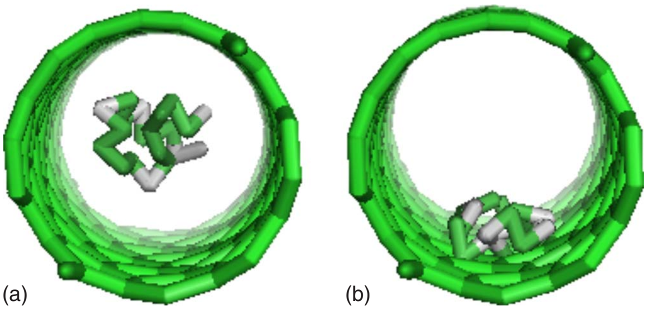

FIG. 2. (Color online) The minimum-energy conformations of SEQ1 within a nanotube modeled (a) with pure *AB* model and (b) when the interaction term is added.

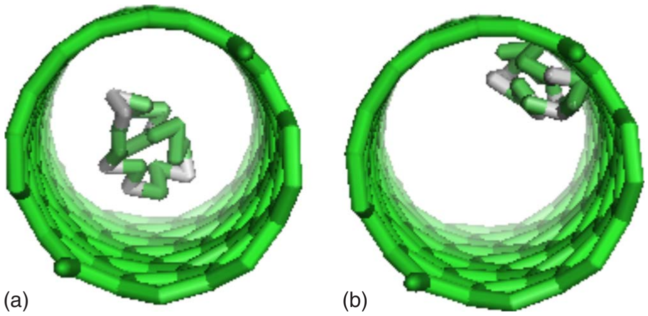

FIG. 3. (Color online) Same as Fig. 2 for SEQ2.

In Fig. 2, a the global minimum-energy configuration of the sequence SEQ1 is given in a nanotube which is compiled with pure *AB* model. There is no interaction term with the nanotube. As one expects, the polymer chain is in compact folded state. In Fig. 2(b), the polymer chain SEQ1 interacts with nanotube and adsorbs to the nanotube wall. Same is happening for the other sequences [Figs. 3(a) and 3(b) for SEQ2 and Figs. 4(a) and 4(b) for SEQ3]. When we undertake homopolymers, the purely hydrophobic polymer and also purely hydrophilic chain adsorb to the nanotube wall and then fold to compact structure because the nanotube wall is attractive for all types of monomers. On the other hand, for different parameter sets, for example, if we take the nanotube is only attractive for same type of monomers and neutral for the other type, then the purely polar chain has no contacts with the nanotube; this chain folds its native state (data not presented).

In order to get an insight about conformational transitions, the specific heats $C_V(T) = (\langle E^2 \rangle - \langle E \rangle^2)/k_B T^2$, with $\langle E^k \rangle = \Sigma_E g(E) E^k \exp(-E/k_B T)/\Sigma_E g(E) \exp(-E/k_B T)$, are calculated from the density of states $g(E)$. The density of states was found (up to an unimportant overall normalization constant) by reweighting the multicanonical energy distribution obtained with multicanonical sampling to the canonical distribution. Details are given in Ref. [29]. In Figs. 5(a)–5(c), the specific heats for both models for the three sequences (SEQ1, SEQ2, SEQ3) are given, respectively. A first obser-

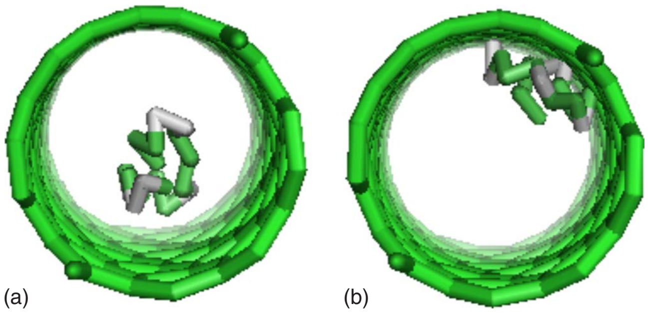

FIG. 4. (Color online) Same as Fig. 2 for SEQ3.

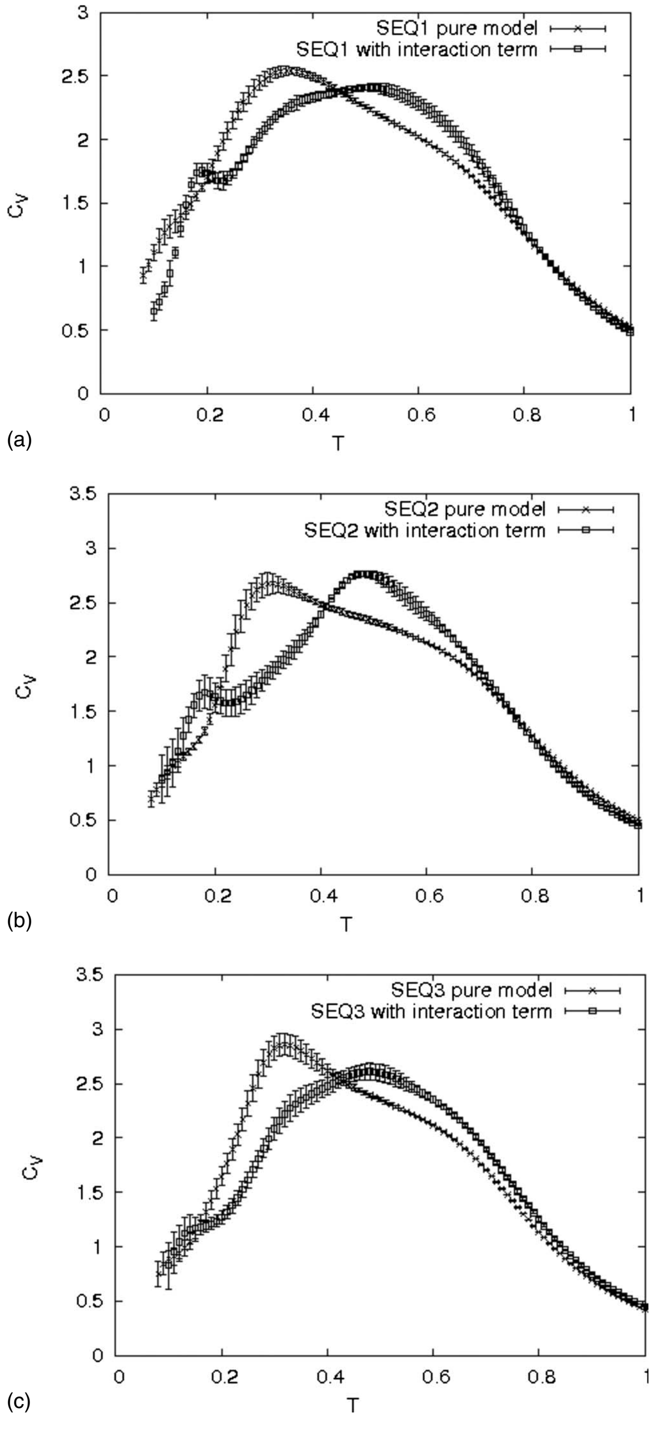

FIG. 5. The specific heat as a function of temperature for both models for (a) SEQ1, (b) SEQ2, and (c) SEQ3.

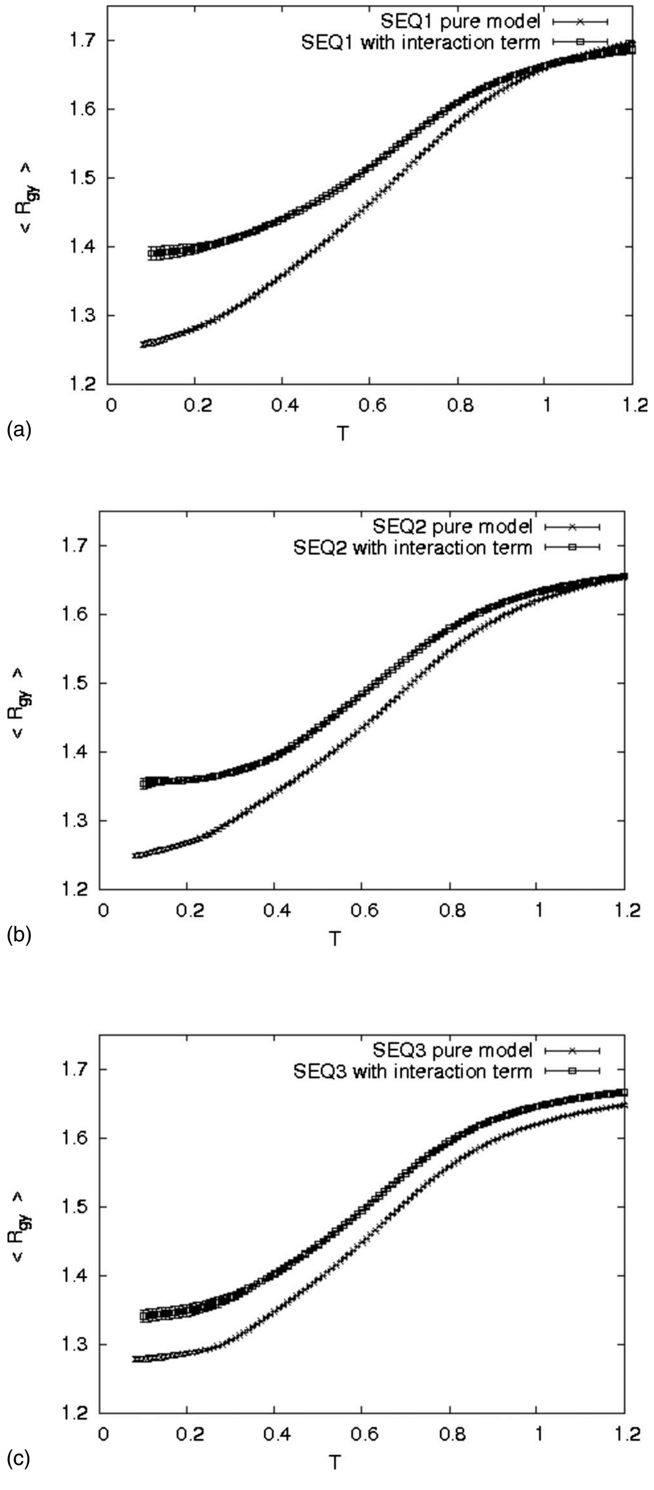

FIG. 6. The radius of gyration (R_{gy}) as a function of temperature for both models for (a) SEQ1, (b) SEQ2, and (c) SEQ3.

vation is that the specific heats obtained from simulations of pure *AB* model favor only one pronounced peak at T_C with a long-range high-temperature tail. The sequences considered here are short and the native fold contains a single hydrophobic core. Interpreting the curves for the specific heats in Fig. 5 in terms of conformational transitions, it can be concluded that the heteropolymers simulated with the pure *AB* model taken in this study present two phases. The conformations dominant for high temperatures $T > T_C$ are random coils, while for temperatures $T < T_C$, conformations with compact hydrophobic core are favored. It is widely believed and experimentally consolidated that realistic short single domain proteins are usually two-state folders [36]. This means that there is only one folding transition and the protein is either in the folded or an unfolded (or denatured) state. Therefore, the *AB* model used here could indeed serve as a simple effective model for two-state heteropolymers. The main difference from the other types of *AB* models [29] comes from containing an implicit torsional energy. This is in correspondence with more knowledge-based Go-like models with explicit torsional energy contributions for the study of small proteins with known typical two-state folding-unfolding kinetics [37]. Nonetheless, there are also examples of small peptides exhibiting two clear peaks in the specific heat. In Ref. [38], the artificial peptide $\mathrm{Ala}_{10}\mathrm{Gly}_{5}\mathrm{Ala}_{10}$ was studied in details and it turned out that two transitions separate the ground-state conformation and random-coil states. One is the alanine mediated helix-coil transition and second the formation of a glycine hairpin that leads to a more compact conformation which can be modeled with the other types of *AB* models [29]. Then returning to the model here, it can be then concluded that a conformational transition occurs from random-coil states to hydrophobic core in which the structures are compact conformations. In addition, the T_C values are in agreement with the previous study of this model [29].

TABLE II. The radius of gyration and its vertical and perpendicular components and the end-to-end distance parameters for the global minimum-energy conformations of five *AB* sequences for pure *AB* model and when the interaction term is added.

	Pure *AB* model				With adsorption potential			
Label	D_{ee}	R_{gy}	$R_{gy\parallel}$	$R_{gy\perp}$	D_{ee}	R_{gy}	$R_{gy\parallel}$	$R_{gy\perp}$
SEQ1	1.29	1.27	1.06	0.69	2.10	1.40	1.32	0.45
SEQ2	1.83	1.25	0.95	0.82	2.82	1.36	1.24	0.54
SEQ3	2.07	1.28	0.98	0.82	2.20	1.40	1.29	0.53
20*A*	1.21	1.22	1.04	0.64	1.90	1.47	1.34	0.60
20*B*	1.24	1.23	1.05	0.62	1.95	1.42	1.29	0.59

When we focus on the second situation, that is when the nanotube interactions are added to the model, the specific heat curves show one distinct peak and a minimal low-temperature shoulder for all the sequences. Two transitions can be identified. The first one is the adsorption separating desorbed and adsorbed conformations. Comparing to the pure model, the T_C values occur at higher temperatures which is also in agreement with the flat surface-polymer adsorption study [39]. The other transition is sort of a freezing transition at low temperatures. The low-temperature shoulder in the specific heat signalizes this freezing transition. It is concluded in Cecconi *et al.* [40] that low-temperature shoulder in specific heat is a signature of some type of transition which only partially structured conformations go by rearrangement into native state. Kriksin *et al.* [41] also showed that for polymer-flat substrate systems, the process comes into being as a two-step process. At the first step, the heteropolymer sticks to the substrate. At the second step, the adsorbed chain adjusts its equilibrium conformation. The freezing temperature seems to be rather constant. The lower parts of the curves suit each other. As a result, we can say that the heteropolymers first bind to the nanotube in one of its walls and then at low temperature, the sequence forms a compact structure.

In order to check the structural compactness of conformations or to identify the possible dispersion or extension of conformations because of adsorption, the radius of gyration and the end-to-end distance parameters are of interest. The radius of gyration is a measure for the extension of the polymer and defined by $R_{gy}^2=\Sigma_{i=1}^{N}\langle(\vec{r_i}-\vec{R_{cm}})^2\rangle/N=\Sigma_{i=1}^{N}\Sigma_{j=1}^{N}\langle(\vec{r_i}-\vec{r_j})^2\rangle/2N^2$, with $\vec{R_{cm}}=\Sigma_{i=1}^{N}\vec{r_i}/N$ being the center-of-mass of the polymer. Apart form the radius of gyration parameter itself, the behaviors of its component parallel and perpendicular to the *xy* plane are also investigated. The definitions are given as follows: $R_{gy\parallel}^2=\Sigma_{i=1}^{N}\Sigma_{j=1}^{N}\langle(\vec{x_i}-\vec{x_j})^2+(\vec{y_i}-\vec{y_j})^2\rangle/2N^2$ and $R_{gy\perp}^2=\Sigma_{i=1}^{N}\Sigma_{j=1}^{N}\langle(\vec{z_i}-\vec{z_j})^2\rangle/2N^2$, such that $R_{gy}^2=R_{gy\parallel}^2+R_{gy\perp}^2$. The radii of gyration as a function of temperature for the sequences are given in Fig. 6. It is obvious from the figures that the polymer-nanotube system has greater R_{gy} values contrary to pure polymer chain model. In other words, the interaction term causes to extension of the conformations at low temperatures. The radius of gyration, its components, and the end-to-end distance values for global minimum-energy conformations of three sequences for both situations of pure *AB* model and including the nanotube interaction term are calculated and given in Table II. For all the sequences, the end-to-end distances are increased for the second case (when the adsorption potential is added). Same is for radius of gyration. This means that the structures somewhat lose its compactness and stick to the nanotube. Much more clear evidences can be seen in components of the radius of gyration parameter: the parallel component increases in the second case for all sequences. On the other hand the

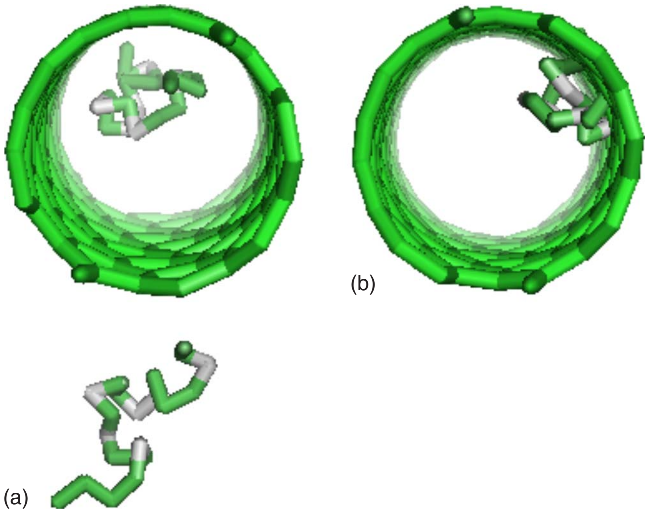

FIG. 7. (Color online) Typical conformations (a) above and (b) below the transition temperature for SEQ2.

perpendicular component decreases for the second case for all sequences. This indicates that the interaction of heteropolymers with the nanotube extends the conformations.

To support the identifications of the transitions deducted from specific heats, the typical conformations above and below the transition temperature T_C for one of the sequences (for SEQ2) are presented in Figs. 7(a) and 7(b), respectively. In Fig. 7(a), the conformation is desorbed and is not compact. The calculated end-to-end distance and the radius of gyration parameters for this conformation are 5.90 and 1.93, respectively. The inset picture from another sight which shows the random-coil structure more clearly and the values of end-to-end distance and the radius of gyration parameters support the conformation in random-coil structure. Figure 7(b) is an adsorbed conformation which is a typical conformation below the transition temperature. The end-to-end distance and the radius of gyration parameters for this adsorbed conformation are 2.98 and 1.50, respectively. Comparing to global minimum conformation of SEQ2 [Fig. 3(b)] with radius of gyration value 1.36, this conformation has greater radius of gyration, has more extended conformation, and is not in final compact form. From here, one can say that the binding process, as concluded also from specific-heat curves, is a two-step process. First, the heteropolymers stick to the nanotube and at the second step, the adsorbed chain finds its global minimum conformation by rearrangement. At the end, it should be noted that these sequences are studied recently within a different context [23,29,32–34] and therefore were not designed for this study.

V. CONCLUSION

In this paper, conformational analysis of an off-lattice heteropolymer model in an attractive nanotube is investigated by multicanonical computer simulations as the adsorption potential, Lennard-Jones-type potential, between the effective monomers and the nanotube wall is assumed. The global minimum-energy conformations and some structural parameters of the conformations, for both pure heteropolymer model and with the interaction term included model, are compared. It is found that the heteropolymer-nanotube binding can proceed as a two-step process. At the first step, the heteropolymer adsorbs to nanotube. At the second step, the adsorbed chain adjusts its equilibrium conformation. Kriksin *et al.* [41] also concluded that for flat surfaces, the process comes into being in same way. The low-energy conformations for heteropolymers are extended if they interact with the tube which the extensions are detected with some structural parameters. Despite the simplicity of the model, it allows a description of many features of real polymers (e.g., helped to understand folding channels, aggregation, etc.). In fact, this is one of the primary motivations for this study. Thus, the present work is a necessary intermediate step for further investigations addressing polymer adsorption. The work considered in this paper could have practical implications for a wide sort of problems ranging from protein-ligand binding to designing smart sensors.

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