Surface-induced conformational changes in lattice model proteins by Monte Carlo simulation

Victoria Castells, Shaoxiong Yang, and Paul R. Van Tassel
Department of Chemical Engineering and Materials Science, Wayne State University, 5050 Anthony Wayne Drive, Detroit, Michigan 48202
(Received 26 December 2000; revised manuscript received 30 July 2001; published 5 March 2002)

We present Monte Carlo simulations of thermal, structural, and dynamic properties of a 27-segment lattice model protein adsorbed to a solid surface. The protein consists of a sequence of *A* and *B* segments whose order and topological contact energy values are chosen so that a unique ($3\times3\times3$ cubic) folded state occurs in the absence of an adsorbing surface [E. I. Shakhnovich and M. Gutin, Proc. Natl. Acad. Sci. USA **90**, 7195 (1993)]. The surface consists of a plane of sites that interact either (i) equally with all contacting protein segments (an equal affinity surface) or (ii) more strongly with type *A* contacting segments (an *A* affinity surface). For both surfaces, we find the conformational change of an initially folded protein to begin with a continuous transition to a structure where all segments contact the surface. This is followed by a partial refolding to a low energy state; this step is continuous and results in full surface contact for the equal affinity surface and is activated and results in significant loss of surface contact for the *A* affinity surface. We also observe a lesser (greater) degree of average surface contact in the equal (*A*) affinity surface with an increase in temperature.

DOI: 10.1103/PhysRevE.65.031912 PACS number(s): 87.15.Aa, 05.10.Ln

I. INTRODUCTION

The adsorption of proteins at a liquid-solid interface plays a major role in a wide range of biomedical and industrial applications. In certain cases—such as fouling of kidney dialysis membranes, processing equipment or contact lenses and the thrombosis arising from medical prostheses—adsorption leads to undesired events. In other cases, adsorption is exploited for technological gain. Examples of the latter are chromatographic separations, new delivery methods for protein drugs (e.g., insulin, human growth factor), and biosensing. Despite the practical importance of protein adsorption on solid surfaces, our fundamental understanding of many associated phenomena such as bond formation between proteins and surfaces, lateral diffusion, and conformational and/or orientational rearrangements of adsorbed proteins is still limited. Among these, the conformational rearrangements are particularly important as they affect protein adsorption kinetics, enzymatic activity, and ligand binding [1].

To understand the properties and functioning of an adsorbed protein, insight into conformational structure is essential. The influence of adsorption on protein conformation depends on the properties of the sorbent material, the solution, the structural characteristics of the protein, and the degree of surface filling. Considerable experimental evidence exists of surface-induced changes in conformation and orientation of adsorbed proteins. Spectroscopic methods based on fluorescence, circular dichroism, Fourier transform infrared (FT-IR), and absorbance spectra provide powerful tools for investigating the structural properties of proteins at interfaces [2–5]. Experimental studies of the activity and thermal stability of immobilized enzymes by physical adsorption have shown that the adsorption process induces conformational changes and decreases the activity of the protein molecules compared to those in solution [6]. Other methods like neutron reflection have been used to study the variation of the structure of adsorbed protein layers on solid surfaces with respect of bulk protein concentration and solution *p*H [7]. Surface-induced conformational changes in proteins have been studied as well using microfabricated cantilever sensors to measure the surface stress produced by protein adsorption onto metallic surfaces [8].

The presence of a post-adsorption change in conformation or orientation also affects the overall protein adsorption kinetics and has, therefore, been incorporated into coarse-grained models by several authors during the past few years. Van Tassel *et al.* [9] proposed a particle level model where the proteins were considered to be disks that adsorb sequentially, randomly, and without overlap onto the surface and once adsorbed, undergo one of two competing post-adsorption events: desorption or irreversible symmetric spreading to a larger diameter (representing a conformational change). Zhdanov and Kasemo have proposed a particle level model in which conformational changes may involve mutual penetrations between proteins [10]. These authors [11] as well as others [12,13] have also examined models that account for transport limitations.

Both our experimental understanding of post-adsorption conformational change and our ability to incorporate this event into mesoscopic model descriptions would be enhanced by a more detailed theoretical analysis aimed specifically at the conformational change. Toward this end, a lattice description, where a protein is modeled by a chain of linked beads, is both simple and instructive. Monte Carlo (MC) simulation studies employing coarse-grained lattice models have provided insight into kinetic and thermodynamic aspects of protein folding in the bulk (see, e.g., Dill *et al.* [14], Karplus and Sali [15], Shakhnovich [16], and Pande, Grosberg, and Tanaka [17]). Of particular importance are 27-segment model proteins whose units are either of type *A* or type *B*; these represent hydrophilic and hydrophobic portions of the protein. With appropriately chosen segment-segment interaction energies, this simple model protein is known to exhibit a folding transition by a rapid initial collapse to a coiled state followed by a slow, activated transition to a

unique, low energy ground (folded) state that is a $3\times3\times3$ cube [18,19].

Recently, similar lattice models have been adopted to simulate proteins adsorbed at interfaces. Anderson, Pande, and Radke have studied a single protein molecule adsorbed at the oil/water interface [20] and conclude that the protein unfolds into an extended structure and thereafter is essentially irreversibly attached to the interface. Zhdanov and Kasemo have studied the kinetics of denaturation of this model protein adsorbed to a solid surface. Their results show that trapping in metastable states can prevent the transition to a completely denatured state [21]. Refolding of the model protein has also been investigated by these authors: following a rapid denaturation, they observe a slow partial refolding [22]. Others have investigated somewhat shorter chains at interfaces, including short homopolymers [23] and more proteinlike heteropolymers [24]. In these systems, simulation is not needed since a complete enumeration of all possible conformations is possible.

In this paper, we present MC simulations of a 27 segment, *AB* cubic-lattice protein adsorbed to a solid surface. We investigate a range of structural, thermal, and dynamic properties and consider two different adsorbing surfaces: one a plane of sites interacting equally with all contacting protein segments (an equal affinity surface) and the other a plane of sites interacting more strongly with segments of type *A* (an *A* affinity surface).

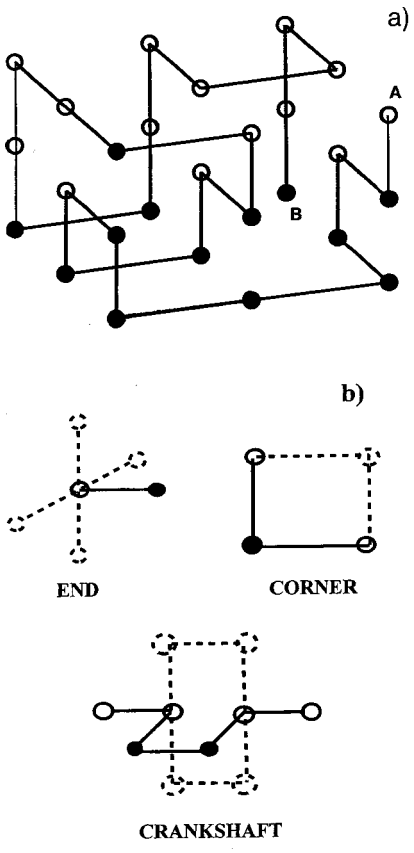

FIG. 1. (a) The $3\times3\times3$ cubic folded state (also the unique low energy state) for the model protein. All 28 topological contacts are native, i.e., between segments of the same type. The ends of the protein chain are marked with A (empty circles) and B (filled circles). The sequence is *ABABBBBBABBABABAAABBAAAAAAB* [25]. (b) The three types of possible MC moves used to generate the configurational space of the 27-segment lattice model protein. The current conformation is shown in thick lines. Possible new conformations are shown in dashed lines. The segments to be moved are shown in filled circles.

II. MODEL AND METHODS

A. The protein/surface model system

Our model protein is a linear, self-avoiding chain of 27 segments of two types (*A* and *B*) that are constrained to nearest neighbor positions on a cubic lattice. Contacts are formed between two segments that are not successive in sequence and are positioned at a unit distance from one another. The sequence, shown in Fig. 1(a), has an $A{:}B$ ratio of 14:13 [25]. A fully compact structure corresponds to a $3\times3\times3$ cubic arrangement containing 28 native (*AA* or *BB*) topological contacts and no non-native (*AB*) topological contacts.

The conformation of the protein is described by the coordinates r_i $(i=1,2,\ldots,N$; where $N=27)$. The conformational energy is assumed to depend only on the number of topological contacts and is taken to have the simple form

$$E_{\mathrm{conf}}=\sum_{i=1}^{N-3}\sum_{j=i+3}^{N}\epsilon_{\alpha_i\alpha_j}e(r_i,r_j), \tag{1}$$

where $\epsilon_{\alpha_i\alpha_j}$ is the contact energy between segments i and j located at positions r_i and r_j, respectively, α_i is the species of segment i ($\alpha_i=A$ or B), and $e(r_i-r_j)$ is 1 if segments i and j are in contact and is 0 otherwise. If the contacts are formed by segments of the same type, then the contact energy is $\epsilon_{AA}=\epsilon_{BB}=-3$ (in arbitrary energy units) and the contacts are called native. If the segments are of different type, the contact energy is $\epsilon_{AB}=-1$ and the contacts are called non-native. This model has a unique ground state with a conformation energy of $E_{\mathrm{conf}}=-84$ in which all topological contacts are formed by segments of the same type. The energy of solvation is implicit in this description.

The surface is simulated by a single layer of surface sites located at $z=-1$. Segments in the adsorbed protein with the coordinate $z_i=0$ are considered to be in contact with the surface. The adsorption energy is calculated according to

$$E_{ads}=\sum_{i=1}^{N}\epsilon_{\alpha_i S}e(z_i), \tag{2}$$

where $z_i\geqslant0$ is the coordinate perpendicular to the surface, $\epsilon_{\alpha_i S}$ is the adsorption energy between i (of type α_i) and a surface site, $e(0)=1$, and $e(z_i>0)=0$. In this paper, we consider two protein/surface interaction rules. In one case, both segments interact with the surface sites with an energy corresponding to a native contact, i.e., $\epsilon_{\mathrm{AS}}=\epsilon_{\mathrm{BS}}=-3$. We refer to this as an equal affinity surface. In the second case, the surface contains only type *A* sites; the corresponding ad-

sorption energies are $\epsilon_{AS}=-3$ and $\epsilon_{BS}=-1$. We call this system the *A* affinity surface. One could think of this surface as either strongly hydrophobic or strongly hydrophilic. The total energy for an adsorbed system is given by $E_{tot}=E_{conf}+E_{ads}$.

B. The Monte Carlo method

For clarity, we first describe the procedure for a bulk model protein. We begin with an extended random self-avoiding conformation. This is then iteratively updated by a large number of small discrete changes brought about by local moves that preserve nearest neighbor links and limit the lattice sites to single occupancy. We employ one-segment moves (end and corner) and two-segment moves (crankshaft) as shown in Fig. 1(b). This algorithm was first developed to study the chain dynamics of polymers [26–28] and has been extensively used in studies of the folding kinetics [18,19,29–31] and adsorption [20–22] of lattice model proteins.

Each MC step proceeds as follows. With equal probability, either a one-segment or a two-segment move is selected. In the former case, a segment is selected at random and either an end or a corner move is performed. In the latter case, a nearest neighbor pair is selected and a crankshaft move is performed. If the move violates the excluded volume constraint by moving a segment to an occupied site, it is rejected and the old conformation is recounted. When a move does not violate excluded volume, the energy of the new conformation is calculated and compared with the original value. The Metropolis criterion [32] is used to accept or reject the proposed move: if the total energy decreases, then the move is accepted unconditionally. If the total energy increases, then $\exp[-\beta(E_{tot}^{(new)}-E_{tot}^{(old)})]$ is compared with a random number uniformly distributed between 0 and 1. The move is accepted if the random number is smaller than the exponential. $E_{tot}^{(new)}$ and $E_{tot}^{(old)}$ are the total energies of the new and old conformations, respectively, and $\beta=1/k_BT$ where k_B is the Boltzmann constant and T is the absolute temperature (k_BT is expressed in the same energy units as the ϵ parameters). If the move is rejected, the previous conformation is reaccepted.

The conformational change of a single adsorbed protein is simulated by considering the molecule to initially be in its bulk native (folded) state with one of its sides (the side containing nine *B* segments) in contact with the surface. The energy of this state is $E_{tot}=-111$ on the equal affinity surface and $E_{tot}=-93$ on the *A* affinity surface. The set of moves as described above is used to generate the conformations of the adsorbed protein with the further spatial restrictions that no segment may penetrate the surface and that at least one segment must always remain in contact with the surface.

Each MC run consists of 10^5 equilibration steps followed by 3×10^8 production steps. We consider temperatures in the range of $1.3\leqslant k_BT\leqslant 2.0$. Four simulations are performed at each temperature for the protein in the bulk and for the protein adsorbed on the equal affinity and *A* affinity surface. We obtain, during the production stage, the mean values and histograms of thermal and structural properties. These include the total energy E_{tot}, the square of the radius of gyration R_g^2, the number of topological (native and non-native) contacts N_{top}, and the number of segments contacting the surface N_{surf}. We also calculate dynamic properties during the production stage. These include the first passage time—in MC step units—to a state of complete surface contact, (i.e., of all 27 segments), τ_{surf}; and the first passage time to the ground (minimum energy) state, τ_{gr}. To minimize statistical uncertainty, we include in the averages the results of reweighted histograms from simulations performed at nearby temperatures [33].

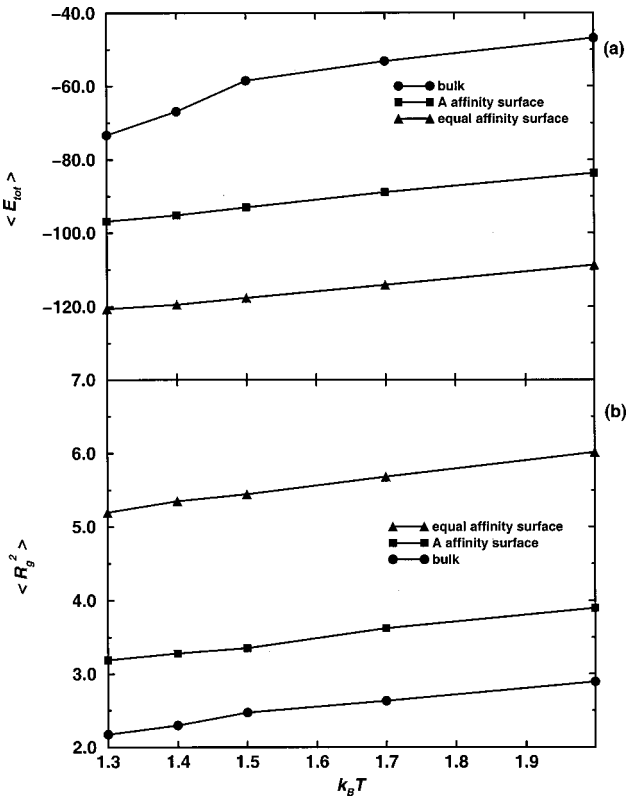

FIG. 2. Average values of the total energy (a) and radius of gyration (b) for a bulk protein and proteins adsorbed on equal and *A* affinity surfaces versus temperature. The units are as described in the text. The average statistical error in the results is smaller than the size of the data points.

III. RESULTS AND DISCUSSION

We begin our analysis by presenting results of the mean values of structural and thermal properties of the model protein in the bulk and adsorbed on equal affinity and A affinity surfaces. In Fig. 2(a), we show the mean value of the total energy E_{tot} as a function of the temperature. Proteins adsorbed on either surface possess a lower overall energy and exhibit a variation with temperature that is relatively smooth compared with the bulk protein. The structure of these systems can be evaluated by considering the mean square radius of gyration, defined as $\langle R_g^2\rangle=(1/N^2)\Sigma_{l=1}^{N-1}\Sigma_{j=l+1}^{N}|\vec{r}_i-\vec{r}_j|^2$ [34] ($N=27$), a structural property related to the elongation of the model protein. In Fig. 2(b), we show that $\langle R_g^2\rangle$ is greatest for a protein on the most strongly adsorbing surface

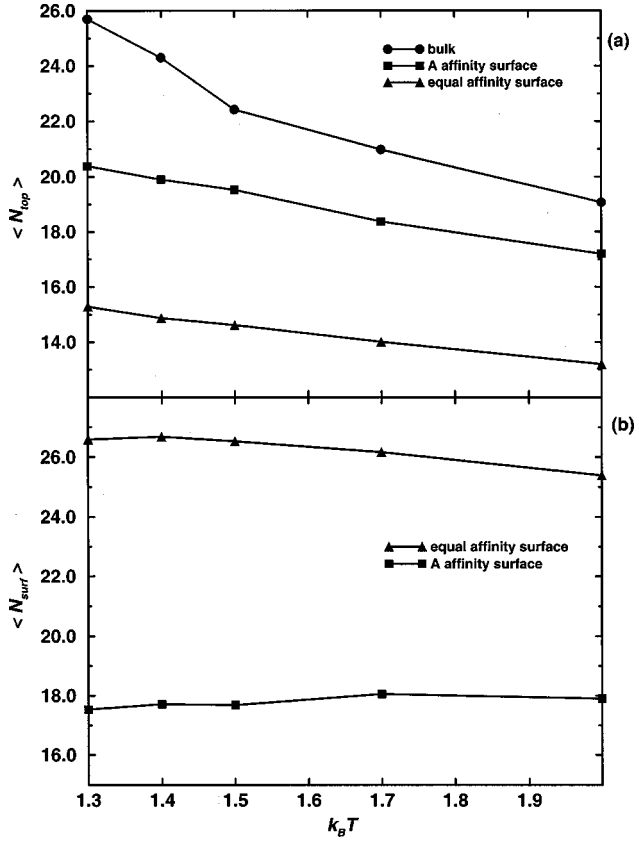

FIG. 3. Average values of the number of native and non-native topological contacts (a) and surface contacts (b) for a bulk protein and proteins adsorbed on equal and *A* affinity surfaces vs temperature. The units are as described in the text. The average statistical error in the results is smaller than the size of the data points.

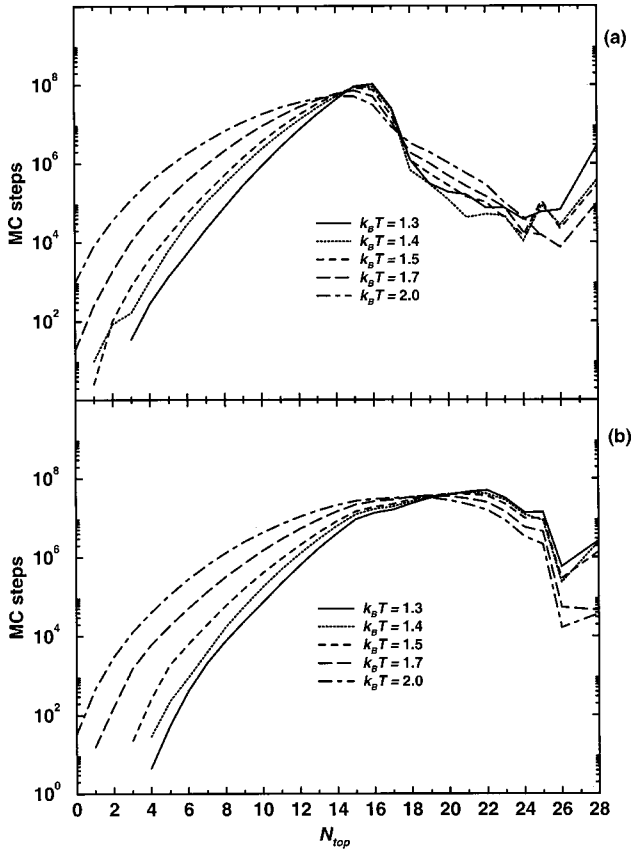

FIG. 4. The distribution—in Monte Carlo step units—of the number of topological contacts for the (a) equal affinity surface and (b) *A* affinity surface at temperatures equal to $k_BT=1.3$, 1.4, 1.5, 1.7, and 2.0.

and smallest for the bulk protein. This reflects a more elongated structure of the adsorbed protein. An increase in the radius of gyration of an adsorbed lattice protein has been previously reported in studies at the water-oil interface [20]. We see in all cases that $\langle R_g^2 \rangle$ increases with T, reflecting a reduced ability to form internal contacts.

Further information on the structure of the model protein is shown in Fig. 3, where we present the mean number of topological contacts within the protein $\langle N_{\mathrm{top}} \rangle$ and the mean number of segments contacting to the surface $\langle N_{\mathrm{surf}} \rangle$, as functions of the temperature. It is clear that the protein on the equal affinity surface undergoes a severe structural change due to a significant loss of internal contacts: on average, only 15 (at low temperature) to 13 (at high temperature) topological contacts are formed, compared to 28 in the fully folded structure. However, its degree of internal contact is less sensitive to temperature than that of the protein in the bulk or on the *A* affinity surface. In addition, most of the 27 segments contact the equal affinity surface (this only decreases slightly with temperature), indicating that most of the topological contacts in the protein are formed in the plane of the surface.

When the protein is adsorbed to the *A* affinity surface, the conformational changes are less drastic. We find that the protein retains an intermediate degree of internal contact after adsorption with $\langle N_{\mathrm{top}} \rangle \approx 20$ at low temperature and $\langle N_{\mathrm{top}} \rangle \approx 17$ at high temperature. There appears to be a balance between surface and internal interactions for a protein on the *A* affinity surface: relaxation occurs due to the strong interaction of the *A* segments, yet a significant degree of topological contact away from the surface is retained. In contrast to the observation for the equal affinity surface, here we see an increased degree of surface contact with increasing temperature. Interestingly, for both surfaces, N_{top} is a property more sensitive to variations in the temperature than N_{surf}. We note that although the variation of $\langle N_{\mathrm{top}} \rangle$ with temperature in the bulk protein is quite large, its degree of elongation is always less than that of the adsorbed proteins.

In Figs. 4(a) and 4(b), we show the distribution of N_{top} for proteins on the equal and *A* affinity surfaces at different temperatures. For both surfaces, we find local maxima at full internal contact ($N_{\mathrm{top}}=28$) and at partial internal contact ($N_{\mathrm{top}}<28$). The distribution for the *A* affinity surface is much broader, indicating a large conformational heterogeneity away from the folded state.

In Fig. 5, we present the probability distribution functions for the total energy. For the protein adsorbed on the equal affinity surface, the ground state probability remains quite low at all temperatures. A single sharp maximum occurs that shifts steadily to higher energy values with increasing temperature as would be expected for a continuous transition. The ground state of this system, with $E_{\mathrm{tot}}=-130$, is degen-

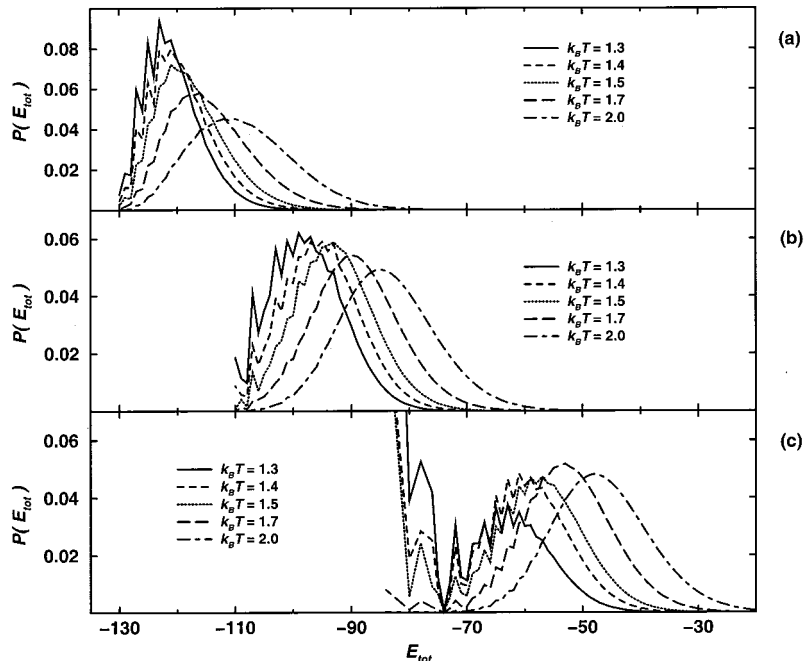

FIG. 5. The distribution of energies for a protein (a) on the equal affinity surface, (b) on the *A* affinity surface and, (c) in the bulk, at temperatures of $k_BT = 1.3$, 1.4, 1.5, 1.7, and 2.0.

erate and populated by conformations with 27 adsorbed segments and 17 topological contacts (of which 16 are native). This corresponds to compact structures in the plane of the surface [see, for example, Fig. 6(a)]. Complete surface contact ($N_{\rm surf}=27$) may also occur at energies above the ground state level for conformations possessing fewer topological contacts. This suggests that the protein may realize full surface contact and then, by internal rearrangements that lower the total energy, reach one of the ground state conformations.

For the *A* affinity surface, we find that at low and intermediate temperature ($k_BT=1.3$, 1.4, and 1.5), the ground state level corresponds to a secondary maximum. The principal maximum occurs at a higher energy and moves steadily outward as the temperature is increased. This indicates that upon adsorption, both continuous and activated transitions are possible. In particular, the level corresponding to $E_{\rm tot}=-108$ is a minimum at each of these temperatures. At high temperature, the histograms are clearly unimodal. The ground state of this system, with total energy $E_{\rm tot}=-110$, is not one of complete surface contact, but rather one with a considerable degree of self-contact [see, for example, Fig. 6(b)]. This state is highly degenerate with most conformations having 25 topological and 15 surface contacts. Since some higher energy states involve complete surface contact (with energies $-55\leqslant E_{\rm tot}\leqslant -104$), the protein may reach the ground energy by initially adsorbing at or near full contact and then forming topological contacts away from the surface while reducing its number of surface contacting segments.

In the case of the bulk protein, the low temperature plots display a multimodal distribution. As the temperature is increased, the relative heights of the peaks change; this indicates an activated (folding) transition. At higher temperature, a single peak moves steadily to higher energy values as would be expected for a continuous transition. These results are in complete agreement with previous calculations for this model [18]. Five energy levels, $E_{\rm conf}=-77$, -79, -81, -82, and -83, are not possible in this system, hence the gaps in the energy spectrum.

By considering each MC step as a unit of time, dynamic properties are discernible from the simulations. In Fig. 7, we plot the average time to reach complete surface contact (i.e., of all 27 segments), $\tau_{\rm surf}$, and the average time to reach the ground state energy, $\tau_{\rm gr}$, vs temperature. (These definitions have been previously used in MC studies of adsorbed lattice proteins [22].) As we mention above, complete surface contact may occur at energies above that of the ground state for both model surfaces. (In the case of the equal affinity surface, the ground state is also one of complete surface contact.) For both surfaces, we observe that the first time to a flat structure is always at least an order of magnitude smaller than the first time to the ground state energy. We also observe that complete contact and minimum energy are reached more quickly on the equal affinity surface and that the rates generally increase with temperature. An exception occurs at very high temperature on the *A* affinity surface where the time for complete contact begins to increase, indicating the entropic unfavorableness of the completely contacting state. In all of our runs, a completely contacting state is reached before a ground state. Thus, for both surfaces, the mechanism of conformational change involves an initial unfolding of the protein followed by a partial refolding. On the equal affinity surface, the refolding is continuous and results in a compact flat structure and on the *A* affinity surface, the refolding is activated and results in a three-dimensional structure with considerable internal contacts. Previous simulations of the reconfiguration of adsorbed proteins have also reported refolding [22]. Our results are consistent with experimental observations of adsorption-induced conformational changes [35] and with the observation that at high temperatures the rate of conformational changes is faster than at low temperatures [2]. Although the rates vary significantly, the thermodynamic average number of surface contacts, $\langle N_{\rm surf}\rangle$,

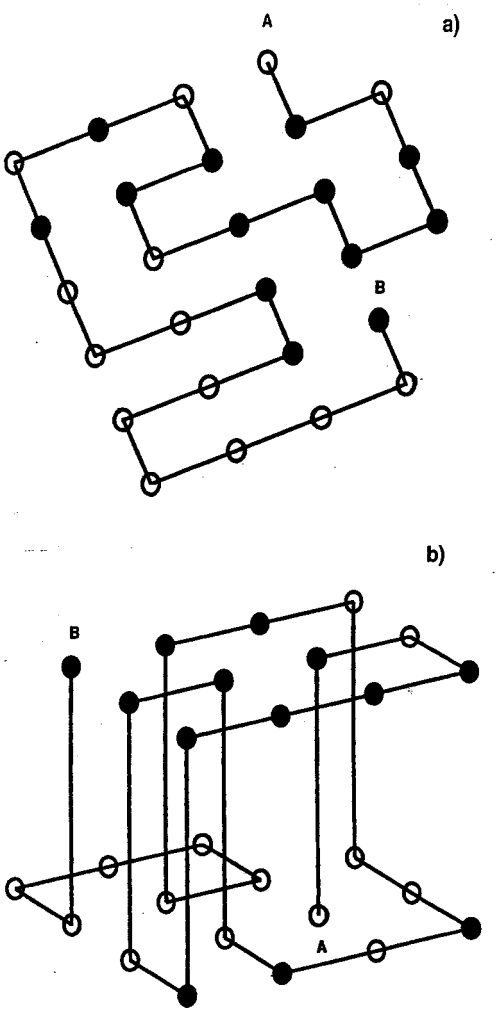

FIG. 6. An example of an adsorbed conformation in the ground state on (a) the equal affinity surface (with total energy $E_{\mathrm{tot}} = -130$) and (b) the *A* affinity surface (with total energy $E_{\mathrm{tot}} = -110$).

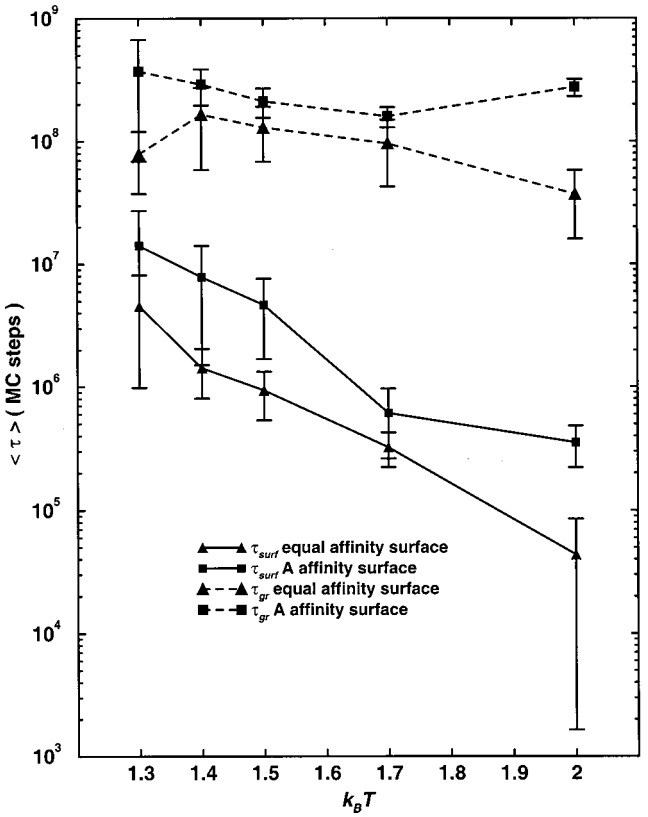

FIG. 7. The mean time of first passage—in MC step units—from an initially folded adsorbed state to a state of complete surface contact, τ_{surf}, (solid lines) and to a state of lowest energy, τ_{gr}, (dashed lines), on equal and *A* affinity surfaces, as functions of temperature.

changes little with temperature [(Fig. 3b)]. Examining the distribution of τ_{surf} for both surfaces in Fig. 8, we find that the variance in time is quite large, spanning about two orders of magnitude about the mean (these data were obtained from 100 MC runs). The variance in τ_{gr}, as seen in Fig. 9, is significantly smaller.

IV. DISCUSSION AND CONCLUSIONS

The changes occurring in the three-dimensional structure of a real protein when adsorbed to a solid surface are still not clearly identified despite the wide interest in and practical importance of this phenomenon. Internal rearrangements are caused by competing protein-surface and protein-protein interactions. Simple models allow one to investigate this competition. The 27 segment, *AB* lattice representation adopted in this paper is a coarse-grained description that makes a complete and detailed examination possible. We simulate the adsorption of a single model protein to isolate the effect of the surface on conformational changes in the adsorbed protein. Controlling the strength of the segment-segment interaction, the segment-surface interaction and the temperature, a wide range of conditions can be studied in great detail.

We find conformational behavior to depend strongly on surface type. For a surface that interacts equally with *A* and *B* segments, we find the model protein to undergo a continuous conformational change upon adsorption leading to a structure in complete contact with the surface with a low degree of internal contact. For a surface that interacts more strongly with the *A* segments, we find the model protein to undergo a continuous transition to a structure in complete contact with the surface, followed by an activated transition to a structure with a lower degree of surface contact but a higher degree of internal contact. For both surfaces, a fully contacting state is reached before the low energy state.

Although direct comparison to experiment is difficult, many of our findings appear to be in line with experimental observations and help provide clues to governing mechanisms. For example, differential scanning microcalorimetry experiments of globular proteins show the extent of conformational change (as measured by the enthalpy of denaturation) to be greatest on strongly adsorbing surfaces (as measured by the enthalpy of adsorption) [35]. This observation is fully consistent with our observed increase in radius of gyration on the more strongly adsorbing equal affinity surface. As another example, FTIR spectrometry shows the rate of

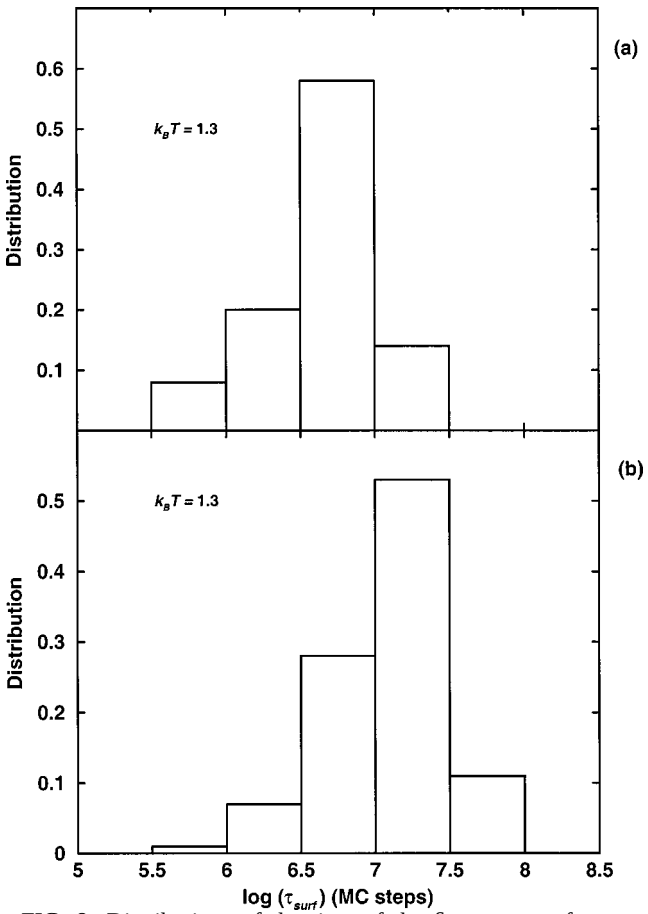

FIG. 8. Distributions of the time of the first passage from an initially folded adsorbed state to a state of complete surface contact for (a) the equal affinity surface and (b) the *A* affinity surface. The data for each curve were obtained from 100 MC runs.

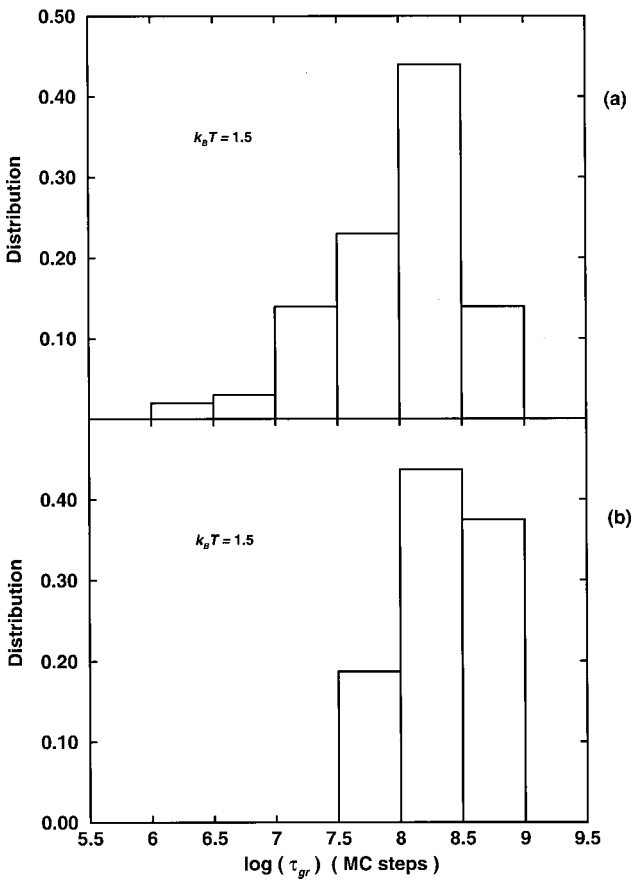

FIG. 9. Distributions of the time of the first passage from an initially folded adsorbed state to a state of lowest energy for (a) the equal affinity surface and (b) the *A* affinity surface.

conformational change to be greater on more strongly adsorbing hydrophobic surfaces [36]. We also observe a more rapid transition on the more strongly adsorbing of the two surfaces considered here. Finally, calorimetric experiments indicate that proteins adsorbed on silica (hydrophilic) surfaces exhibit a heat-induced transition while those adsorbed on teflon (hydrophobic) surfaces do not show a transition [3]. Our observations would suggest the former to be an activated transition (as we see in the *A* affinity surface system) and the latter to be a smooth transition (as we see in the equal affinity surface system). These and other results attest to the fact that adsorbed protein conformational behavior depends strongly on the nature of the surface [3–5,37]. Simple lattice models allow one to analyze—efficiently and in great structural detail—the conformational behavior as a function of certain energy parameters over a range of conditions.

ACKNOWLEDGMENTS

We acknowledge financial support from the National Science Foundation CAREER Program through Grant No. CTS-9733310 and the National Institutes of Health through R01-GM59487.

[1] W. Norde, Adv. Colloid Interface Sci. **25**, 267 (1986).
[2] M. C. L. Maste, W. Norde, and A. J. W. G. Visser, J. Colloid Interface Sci. **196**, 224 (1997); M. Tian, W.-K. Lee, M. K. Bothwell, and J. McGuire, *ibid.* **200**, 146 (1998); C. Yongli, Z. Xiufang, G. Yandao, Z. Nanming, Z. Tingying, and S. Xinqi, *ibid.* **214**, 38 (1999).
[3] T. Zoungrana, G. H. Findenegg, and W. Norde, J. Colloid Interface Sci. **190**, 437 (1997).
[4] S. Servagent-Noinville, M. Revault, H. Quiquampoix, and M.-H. Baron, J. Colloid Interface Sci. **221**, 273 (2000).
[5] A. W. P. Vermeer and W. Norde, J. Colloid Interface Sci. **225**, 394 (2000).
[6] T. Zoungrana and W. Norde, Colloids Surf., B **9**, 157 (1997).
[7] T. J. Su, J. R. Lu, R. K. Thomas, Z. F. Cui, and J. Penfold, J. Colloid Interface Sci. **203**, 419 (1998); J. R. Lu, T. J. Su, P. N. Thirtle, R. K. Thomas, A. R. Rennie, and R. Cubitt, *ibid.* **206**, 212 (1998).
[8] A. M. Moulin, S. J. O'Shea, R. A. Badley, P. Doyle, and M. E. Welland, Langmuir **15**, 8776 (1999).
[9] P. R. Van Tassel, P. Viot, G. Tarjus, and J. Talbot, J. Chem.

Phys. **101**, 7064 (1994); P. R. Van Tassel, J. Talbot, P. Viot, and G. Tarjus, Phys. Rev. E **53**, 785 (1996); P. R. Van Tassel, P. Viot, and G. Tarjus, J. Chem. Phys. **106**, 761 (1997); P. R. Van Tassel, L. Guemouri, J. J. Ramsden, G. Tarjus, P. Viot, and J. Talbot, J. Colloid Interface Sci. **207**, 317 (1998); M. A. Bursatori and P. R. Van Tassel, *ibid.* **219**, 333 (1999).

[10] V. P. Zhdanov and B. Kasemo, J. Chem. Phys. **109**, 6497 (1998).

[11] V. P. Zhdanov and B. Kasemo, Proteins: Struct., Funct., Genet. **30**, 177 (1998).

[12] V. Hlady, C.-H Ho, and D. W. Britt, in *Interfacial Dynamics*, edited by N. Kallay (Marcel Dekker, New York, 2000), p. 405, and references therein.

[13] C. Calonder and P. R. Van Tassel, Langmuir **17**, 4392 (2001).

[14] K. A. Dill, S. Bromberg, K. Yue, K. M. Fiebig, D. P. Yee, P. D. Thomas, and H. S. Chan, Protein Sci. **4**, 561 (1995).

[15] M. Karplus and A. Sali, Curr. Opin. Struct. Biol. **5**, 58 (1995).

[16] E. I. Shakhnovich, Curr. Opin. Struct. Biol. **7**, 29 (1997).

[17] V. S. Pande, A. Y. Grosberg, and T. Tanaka, Rev. Mod. Phys. **72**, 259 (2000).

[18] N. D. Socci and J. N. Onuchic, J. Chem. Phys. **101**, 1519 (1994); **103**, 4732 (1995); J. D. Bryngelson, J. N. Onuchic, N. D. Socci, and P. G. Wolynes, Proteins: Struct., Funct., Genet. **21**, 167 (1995).

[19] A. Sali, E. Shakhnovich, and M. Karplus, J. Mol. Biol. **235**, 1614 (1994); C. M. Dobson, A. Sali, and M. Karplus, Angew. Chem. Int. Ed. Engl. **37**, 868 (1998); A. R. Dinner, V. Abkevich, E. I. Shakhnovich, and M. Karplus, Proteins: Struct., Funct., Genet. **35**, 34 (1999); A. R. Dinner, A. Sali, L. J. Smith, C. M. Dobson, and M. Karplus, Trends Biochem. Sci. **25**, 331 (2000).

[20] R. Anderson, V. S. Pande, and C. J. Radke, J. Chem. Phys. **112**, 9167 (2000).

[21] V. P. Zhdanov and B. Kasemo, Phys. Rev. E **56**, 2306 (1997); Proteins: Struct., Funct., Genet. **30**, 168 (1998); Surf. Rev. Lett. **5**, 615 (1998).

[22] V. P. Zhdanov and B. Kasemo, Proteins: Struct., Funct., Genet. **42**, 481 (2001).

[23] M. R. Wattenbarger, H. S. Chan, D. F. Evans, V. A. Bloomfield, and K. A. Dill, J. Chem. Phys. **93**, 8343 (1990); H. S. Chan, M. R. Wattenbarger, D. F. Evans, V. A. Bloomfield, and K. A. Dill, *ibid.* **94**, 8542 (1991).

[24] R. Abdullah and I. Szleifer (unpublished).

[25] E. I. Shakhnovich and M. Gutin, Proc. Natl. Acad. Sci. U.S.A. **90**, 7195 (1993).

[26] P. H. Verdier and W. H. Stockmayer, J. Chem. Phys. **36**, 227 (1962).

[27] H. J. Hilhorst and J. M. Deutch, J. Chem. Phys. **63**, 5153 (1975).

[28] K. Kremer and K. Binder, Comput. Phys. Rep. **7**, 259 (1988).

[29] E. I. Shakhnovich, Phys. Rev. Lett. **72**, 3907 (1994).

[30] V. S. Pande and S. Rokhsar, Proc. Natl. Acad. Sci. **96**, 1273 (1999).

[31] R. Du, V. S. Pande, A. Y. Grosberg, T. Tanaka, and E. I. Shakhnovich, J. Chem. Phys. **111**, 10 375 (1999).

[32] N. Metropolis, A. W. Rosenbluth, M. N. Rosenbluth, A. N. Teller, and E. Teller, J. Chem. Phys. **21**, 1087 (1953).

[33] A. M. Ferrenberg and R. H. Swendson, Phys. Rev. Lett. **61**, 2635 (1988); **63**, 1195 (1989).

[34] A. Baumgärtner and K. Binder, J. Chem. Phys. **71**, 2541 (1979).

[35] C. A. Haynes and W. Norde, J. Colloid Interface Sci. **169**, 313 (1995).

[36] R. J. Green, I. Hopkinson, and R. A. L. Jones, Langmuir **15**, 5102 (1999).

[37] T. M. Price and M. L. Rudee, in *Proteins at Interfaces: Physicochemical and Biochemical Studies*, edited by J. L. Brash and T. A. Horbet (ACS Symposium Series, Washington, D.C., 1987), p. 48.