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journal or publication title	Physical Review E
volume	67
number	1
page range	011912-1-011912-6
year	2003-01-01
URL	http://hdl.handle.net/2297/1683

doi: <https://doi.org/10.1103/physreve.67.011912>

Glass transition in an off-lattice protein model studied by molecular dynamics simulationsA. Baumketner^{1,2,*} and J.-E. Shea¹*Department of Chemistry and Biochemistry, University of California at Santa Barbara, Santa Barbara, California 93106*

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(Received 6 September 2002; published 28 January 2003)

In this paper we report the results of a numerical investigation of the glass transition phenomenon in a minimalist protein model. The inherent structure theory of Stillinger and Weber was applied to an off-lattice protein model with a native state β -sheet motif. By using molecular dynamics simulations and the steepest descent method, sets of local potential energy minima were generated for the model over a range of temperatures. The mean potential energy of the inherent structures allowed to make rough estimates of the glass-transition temperature T_K . More accurately T_K was computed by direct evaluations of the total and vibrational entropies. It is found that for the present model the thermodynamic ratio of the folding and glass-transition temperatures is 1.7 which is in good agreement with experimental observations.

DOI: 10.1103/PhysRevE.67.011912

PACS number(s): 87.15.Aa, 64.70.Pf, 87.15.He

I. INTRODUCTION

According to the inherent structure (IS) theory [1], the partition function of a liquid can be represented as a sum of terms originating from averages taken over basins of attraction, or valleys, of the associated potential energy surface. As a result, all thermodynamic functions of the liquid state can be determined by knowing which basins of attraction are predominantly visited by the system at a given temperature. Since systems under study are typically of macroscopic dimensions, with an enormous number of valleys, a statistical description of the associated local minima becomes necessary. Configurational entropy $S_c(E)$ arises within the statistical approach as a measure of the number of local minima whose depth lies between E and $E + dE$. The configurational entropy plays a central role in the theory of the liquid-glass transition insofar as the transition temperature is concerned: the temperature at which $S_c(T)$ turns zero marks the ideal glass-transition, or Kauzmann, temperature T_K . The glass-transition follows the entropy crisis scenario in which systems under cooling gradually run out of thermally accessible states at T_K and remain in the neighborhood of a single basin of attraction at lower temperatures. A significant computational effort is required to simulate supercooled liquids and the IS formalism has only recently been applied to computer simulations of liquids. Algorithmic developments in the past few years have made it possible to use computer simulations to systematically explore the ways in which the glass-transition is approached in liquids, from both dynamical and structural points of view [2–4]. An important outcome of these simulations, the physical relevance of which extends well beyond the theory of the liquid state, is the accurate numerical prediction of T_K .

The glass-transition temperature T_K is just as important a

quantity in protein science as in the theory of liquids. The qualitative changes that occur to proteins upon glassification, such as the failure to carry out their biological functions, have attracted much experimental and theoretical interest to the glass-transition problem over the past few years [5–8]. The glass-transition temperature appears as a critical quantity in theoretical studies of protein folding. According to the landscape theory of protein folding [9] the ratio of folding to glass-transition temperatures T_f/T_K characterizes the amount of frustration present in a protein and controls many of its basic properties such as foldability or structural details of the transition state ensemble [10,11]. In light of the essential role of the glass-transition in the protein folding problem, it is of importance to be able to predict accurately the glass-transition temperature T_K through numerical simulations. To the best of our knowledge there have been only two papers [12,13] that addressed the issue of computing T_K in a continuous protein model—a situation highly indicative of the complexity of the problem. In one of them [12] an approximate formula derived from the random energy model was used. The other [13] tried to link glass-transition temperature with the fractional dimension of the underlying free energy surface. Due to either employed approximations or the lack of established conceptual formalism the final results of both papers cannot be considered rigorous.

At present, due to large numbers of degrees of freedom and long relaxation times involved in microscopic models of proteins, only proteins with reduced geometry representation are amenable to systematic numerical studies. These so-called minimalist models fall into two categories, depending on how the monomer configurations are dealt with, lattice or off lattice. Here we will focus on off-lattice protein models as they reproduce structure and kinetics of real proteins more faithfully. A large variety of these models have been presented recently and used to gain valuable insights into protein thermodynamics and kinetics [14,15]. In the present paper, we describe the results of an application of the IS theory to investigate the glass-transition in an off-lattice minimal protein comprised of a string of 16 spherical beads linked by

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virtual bonds of constant length and interacting via a number of potentials. These include bond angle, torsion, and hydrophobic potentials. The ground state, or native, conformation of the model is a β -sheet motif. By using molecular dynamics simulations and steepest descent energy minimization the mean depth $E_L(T)$ of the local potential energy minima was computed as a function of temperature. At sufficiently low T , $E_L(T)$ reaches a plateau with energy close to the ground state energy indicating that the majority of simulations at these temperatures sample conformations from the ground state basin. Consequently, it is predominantly into this basin of attraction that freezing takes place. By using simulations in the multicanonical ensemble we computed the mean potential energy of the model over a wide range of temperature that extends into the low- T region, where the harmonic approximation to the model's statistics applies. This allowed us to evaluate the total entropy of the system for temperatures ranging from freezing to above folding and collapse. Additionally the vibrational entropy associated with trapping in the native state basin was computed in a series of separate canonical simulations. From the point where the total and vibrational entropies match we were able to unambiguously determine the glass-transition temperature for the present model. It is also found that the vibrational motion of the molecule within the boundaries of the native state is highly nonharmonic. Employment of the harmonic approximation for the vibrational part of the entropy leads to a gross underestimation of T_K , erroneously by a factor of three compared to the correct value.

The paper is organized as follows. In Sec. II we briefly describe the foundations of the IS theory and its application to calculating the glass-transition temperature for a protein model. Section III concerns the main results of the present work and includes a detailed account of the method used to calculate T_K . The conclusions are presented in Sec. IV.

II. THEORETICAL BACKGROUND AND MODEL

Within the inherent structure theory [1,16] a basin of attraction of the potential energy surface (PES) is defined as a set of points of the configurational space that are connected to the same minimum via the steepest descent operation. The entire conformational space is divided into nonoverlapping regions and the canonical partition function of a condensed matter system can then be represented as a sum over these regions:

$$Z(\beta) = \frac{1}{\lambda^{3N}} \sum_a e^{-\beta U_a} \int_{\Gamma_a} e^{-\beta \Delta_a(\Gamma)} d\Gamma, \quad (1)$$

where λ is the thermal wavelength, N is the number of particles comprising the system, β is the inverse temperature, Γ refers to a single conformation in the $3N$ -dimensional configurational space, U_a is the minimal energy of attraction basin a , and $\Delta_a(\Gamma) = U(\Gamma) - U_a$. The integration in Eq. (1) is limited to the boundaries of basin a (indicated by the subscript a in the integral). When dealing with macroscopic numbers N , the number of local minima in the PES becomes macroscopic as well, with many minima being highly degen-

erate. In this case it makes sense to transform the summation in Eq. (1) over energy valleys into an integration over local potential energy minimum levels:

$$Z(\beta) = \int dE_L \Omega(E_L) e^{-\beta E_L - \beta f(\beta, E_L)}, \quad (2)$$

where $dE_L \Omega(E_L)$ denotes the number of local minima whose potential energy U_a lies between E_L and $E_L + dE_L$. $f(\beta, E_L)$ corresponds to the free energy of basin a and is defined as

$$-\beta f(\beta, E_L) = \ln \int_{\Gamma_a} e^{-\beta \Delta_a(\Gamma)} \frac{d\Gamma}{\lambda^{3N}}. \quad (3)$$

In the above equation, it is tacitly assumed that local minima with similar depth have similar shapes, and hence free energy. Vibrational properties related to individual valleys will henceforth be denoted by the subscript v . It can be shown [3] that at sufficiently low temperature the total entropy of the system is related to the configurational entropy $S_c(E) = k_b \ln \Omega(E)$ by the simple relationship:

$$S(E) = S_c(E) + S_v(E), \quad (4)$$

where $S_v(E)$ is the vibrational entropy of valleys with depth E . $S_v(E)$ can be evaluated from the free energy $f(\beta, E)$ of these valleys following standard thermodynamic relations. Equation (4) is central to the problem of identifying the glass-transition temperature. Its physical interpretation is that a liquid can be regarded as frozen glass whose atoms are permitted to vibrate around the positions of local minima. At points where the total and vibrational entropies match, i.e., when the relationship

$$S_c(T_K) = 0 \quad (5)$$

is satisfied, the system is said to undergo the ideal glass transition. From the definition of the configurational entropy it is clear that for $T \leq T_K$ the system is only allowed to remain in the neighborhood of a single minimum, while for $T > T_K$ multiple minima are accessible. In a nutshell this entropy crisis scenario of freezing can be explained as follows. The dynamics of a liquid are composed of vibrations within the basins of attraction as well as spontaneous jumps between the basins. As temperature decreases, it becomes more difficult for the system to change basins and jumps become infrequent. At $T = T_K$, the potential energy barriers separating valleys become too high, preventing jumps and locking the system into a single minimum. The specific minimum into which freezing takes place may not necessarily be the one with the lowest energy, and may not be unique. History of the cooling process strongly influences the final state into which the liquid freezes.

The above discussion pertained to liquids and their glass-transition, but made no mention of the specific characteristics of the liquid state. In principle, the IS formalism is applicable to other condensed matter systems which are characterized by potential energy surfaces with many local minima. This is the case for heteropolymers, in particular proteins

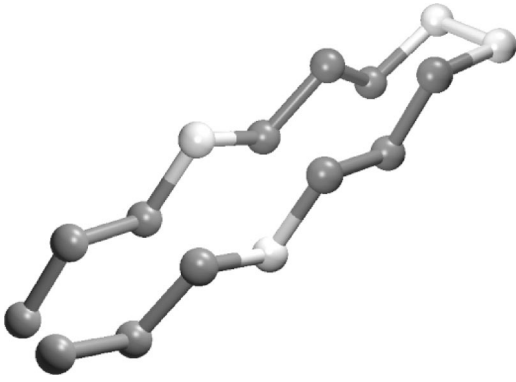


FIG. 1. Native state of the β -sheet model considered in the present study. Dark balls refer to the hydrophobic residues and the light denote the neutral residues.

(which will be the main subject of the present study), and the IS theory can be used to describe freezing phenomenon in these systems. In the case of proteins, freezing takes place from the globular state, which can consist of either folded or misfolded conformations. The main requirement is that the protein possesses sufficient conformational freedom in that state.

In order to determine in a detailed manner how the glass-transition is approached in proteins, we applied the inherent structure theory to an off-lattice protein model. The model is described in detail in our earlier work [17,18]. It consists of a string of 16 monomers connected by virtual bonds of fixed length. The monomers can be either of hydrophobic or neutral types depending on whether they attract each other or repel. There is a total of 12 hydrophobic and 4 neutral monomers. In addition to long-range hydrophobic forces, which are modeled by Lennard-Jones potentials, all monomers are also subject to harmonic bending and torsional potentials. The latter was carefully chosen so as to ensure the β -sheet conformation for the ground state of the model as shown in Fig. 1. For more details on the potential function parameters we refer the reader to our previous work [17,18].

According to Eq. (5), the evaluation of the glass-transition temperature T_K requires knowledge of both total and vibrational entropies. Entropy as a function of temperature can be calculated from the potential energy $U(T)$ obtained from computer simulations according to the well-known thermodynamic relation

$$S(T) = S(T_0) + \frac{U(T)}{T} - \frac{U(T_0)}{T_0} + \int_{T_0}^T \frac{U(s)}{s^2} ds. \quad (6)$$

Here T_0 denotes some reference temperature for which the entropy is assumed to be known. A simple choice of T_0 for the present system is some sufficiently low temperature such that the statistics of the system are well described by the harmonic approximation. If one approximates the real Hamiltonian $H(\Gamma)$ by a quadrature of independent degrees of freedom $H_h(\Gamma) = U_0 + \frac{1}{2} \sum_{i,j} H_{ij}^s x_i x_j$, where H_{ij}^s is the Hessian and x_i are generalized coordinates, all thermodynamic functions can be evaluated analytically. In particular, potential energy is given by

$$U_h(T) = U_0 + \frac{N_F}{2} k_b T \quad (7)$$

and the entropy

$$S_h(T) = \frac{N_F}{2} [1 - \ln(\beta)] - \frac{1}{2} \ln \frac{\lambda_1 \cdots \lambda_{N_F}}{2\pi} - (N-2) \ln \pi, \quad (8)$$

where $N_F = 2N - 5$ is the number of degrees of freedom that characterize the present model and U_0 is the energy of the local minimum around which the harmonic vibrations are considered. Equation (8) was obtained by choosing as independent degrees of freedom $\{x_i\}$ $N-2$ bond angles and $N-3$ torsion angles (which uniquely define conformational states of the model). The parameters $\lambda_1 \cdots \lambda_{N_F}$ are eigenvalues of the Hessian H^s . Since we consider here dynamics around local minima all λ 's are positive by definition.

III. RESULTS AND DISCUSSION

To investigate the glass-transition phenomenon in the context of the protein folding problem, we applied the IS theory and molecular dynamics to the off-lattice minimal protein described in the preceding section. Inherent structures were mapped from simulations organized according to the linear simulated annealing schedule $T_{n+1} = T_n + \Delta T$, carried out at varying parameter ΔT . Every τ time steps the current monomer configuration was used to initiate the steepest descent procedure and find a local potential energy minimum. A total number of 100 inherent structures were recorded at each T_n and stored into a file.

It has been observed in computer simulations of supercooled liquids [2], that as the temperature decreases, the system starts to explore all the deeper potential energy valleys. As a result, the mean energy $E_L(T)$ of the inherent structures rapidly drops with temperature and at sufficiently low T , $E_L(T)$ reaches a plateau and remains constant for lower temperatures. The exact value T_g where this plateau occurs can be interpreted as the temperature of glass-transition [16]. The specific low-energy valleys that are explored in computer simulations at low temperatures depend strongly on the system's relaxation times. The longer period τ a liquid is allowed to equilibrate, the deeper the potential energy valleys it visits. As a result, the glass-transition temperature T_g determined by computational means is context specific in that it is dependent on the details of the underlying cooling scheme. If one were able to run simulations on the laboratory time scales it would be possible to compute the thermodynamic (independent of the assumed time scale) glass-transition temperature T_K by using the computational methods described above. This is, however, not the case at present and the glass-transition temperature T_K in liquids is currently determined by extrapolations from molecular dynamics simulations performed at a higher temperature.

In proteins the situation is different from the above in two main aspects. First, according to the minimal frustration principle [19] the protein only occupies a limited number of conformations at low T . In fact the high "foldability" of

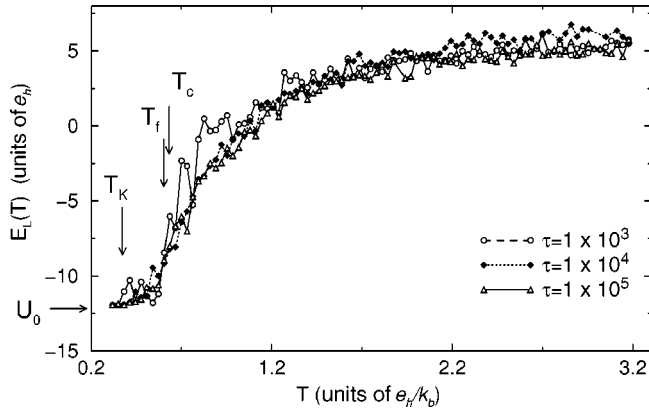


FIG. 2. Mean potential energy of inherent structures $E_L(T)$ computed for the present protein model in simulated annealing simulations at varying τ and $\Delta T=0.032$. $E_L(T)$ does not change significantly when τ is varied over an order of magnitude starting from equilibration times comparable to the folding time. In addition to the glass-transition temperature T_K also the temperatures of folding T_f and collapse T_c are indicated. Energy and temperature are measured in reduced units e_h and e_h/k_B , respectively [17,18].

proteins requires that their energy landscape have a funnel-like shape with unique native state at the bottom. Misfolded conformations with potential energy comparable to that of the native state may exist, but they are not numerous (certainly far less numerous than the equivalent local minima in supercooled liquids or random heteropolymers). Second, the relaxation time scale in proteins is set by the folding time τ_f . Events that occurs at times much longer than τ_f can be considered irrelevant to the problem. These two remarks should be kept in mind in the context of the mean potential energy of the inherent structures $E_L(T)$ calculated in the present work. $E_L(T)$, computed as a function of temperature by using simulated annealing runs with parameter $\Delta T=0.032$, is shown in Fig. 2. Energy and temperature in this figure, as well as in the rest of the paper, are shown in reduced units e_h and e_h/k_B , respectively [17,18], where e_h measures the strength of the hydrophobic interaction and k_B is the Boltzmann constant. The figure shows that $E_L(T)$ is clearly comprised of three consecutive parts: a first plateau extending from $T=0$ up to T_K and two additional regions at higher T . The main elements of $E_L(T)$ for our protein model are found in supercooled liquids [2]. What makes the present system differ is the behavior of $E_L(T)$ at low T with respect to the equilibration time τ . For τ shorter than folding time τ_f ($\tau_f \sim 2 \times 10^4$ time steps for the present model [18]), the mean energy of local minima is subject to considerable scattering. As τ grows, $E_L(T)$ smooths out and for equilibration times longer than 1×10^4 time steps remains almost constant even with variations in τ as great as an order of magnitude. This is the most important observation following from Fig. 2: as long as the equilibration time τ exceeds τ_f , it has very little influence on which potential energy valleys are visited by the molecule at low temperatures. The low- T plateau value of $E_L(T)$ is close to the energy of the native state and does not change with τ . As anticipated earlier, this is a direct consequence of the special funnel-like shape of the PES appropri-

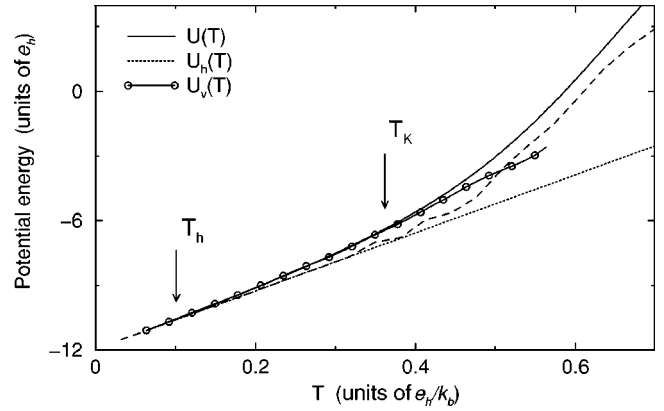


FIG. 3. Potential energy as function of temperature for the studied β -sheet motif. Solid line, total potential energy computed in multicanonical simulations, dotted line, harmonic approximation (7) for the ground state attraction basin, dashed line, harmonic approximation for attraction basins sampled during the simulated annealing runs performed at $\tau=1 \times 10^5$ and $\Delta T=0.032$; and symbols, vibrational energy of the ground state basin. The harmonic approximation becomes correct at $T_h=0.11$. The molecule begins its escapes from the ground state at $T_K=0.35$.

ate for optimized protein models. In order to further test the temperature behavior of the mean energy of inherent structures, we ran additional simulations at $\Delta T=0.016$ and $\Delta T=0.063$ and found no noticeable difference in the results compared to those shown in Fig. 2. This leads us to conclude that in optimized protein models with sufficiently smooth potential energy surfaces, freezing processes occurring on a time scale comparable to the folding time will take place predominantly into the attraction basin of the native state. Obviously, if the cooling schedule is chosen too fast, the glassification into other misfolded states cannot be ruled out. These situations may arise in special circumstances, for example when proteins are placed in media with extreme temperature gradients, and will not be considered here.

Judging from Fig. 2 and from previous numerical work on IS theory [16,2], we can make a first estimate of the glass transition temperature of the present model to be $T_K \sim 0.4$. A more accurate estimate of T_K , however, requires precise calculations of the vibrational and total entropies. As discussed in Sec. II, the total entropy can be calculated with the help of one reference temperature T_h at which the harmonic approximation is correct. This temperature can be determined from graphs of the total potential energy of the model and potential energy computed in the harmonic approximation (7) as shown in Fig. 3. The harmonic energy was computed both in the native state basin and, as is common practice in liquid simulations, in the basins of attraction sampled by the simulated annealing runs (performed at $\tau=1 \times 10^5$ and $\Delta T=0.032$). At a temperature in the vicinity of T_K , both curves start to deviate reflecting the fact that at this temperature, simulated annealing runs lead to minima other than the ground state. This information can also be inferred from Fig. 2. More interesting is to investigate the temperature at which the statistics of the molecule become harmonic, i.e., where $U(T)$ and $U_h(T)$ match. While the harmonic part of the

potential energy $U_h(T)$ is easy to compute by following formula (7) evaluation of the total potential energy $U(T)$ poses a serious difficulty. Due to long relaxation times near glass-transitions, proper equilibration of proteins (or liquids) at low temperatures is highly problematic. This limitation imposes a lower bound on temperatures for which $U(T)$ can be evaluated in simulations. In order to proceed to lower temperatures one needs to resort to extrapolations of potential energy, or entropy, as is commonly done in simulations of supercooled liquids with the help of known analytical formulas [3,4]. There are no analytical formulas available for potential energy as function of temperature in proteins and thus the situation becomes more complicated. The very definition of the glass-transition temperature implies that simulations performed at $T \sim T_K$ are destined to sample conformations from one attraction basin only. In this case $U(T)$ cannot be determined reliably. Fortunately the recent advent of the generalized-ensemble simulation techniques [20] provides an elegant solution to this difficulty. Simulations performed in a generalized ensemble are devoid of kinetic traps and sample configurations in a wide range of energy. When the simulation is carried out over a sufficiently long time the molecule can visit *all* the available attraction basins many times so that reasonable statistics can be collected. In this paper, we used the noniterative version of the multicanonical algorithm implemented in a deformed (due to the Tsallis statistical weight factor) potential energy landscape [21,22]. The simulation was performed for 8×10^8 time steps and we ensured sampling of the potential energy in an interval broad enough for the histogram reweighting method [23] to be applied. It is worth emphasizing that the ability of the generalized-ensemble simulation to overcome kinetic traps and gather information on all potential energy valleys at once is central to the success of the present work. In Fig. 3 the reweighted potential energy $U(T)$ is denoted by solid line. Comparison of this line with the dotted line of $U_h(T)$ reveals that the highest temperature at which the harmonic approximation holds true is $T_h = 0.11$. We will use this temperature to estimate the entropy of the present model later in the text.

In simulations of supercooled liquids [3,4] it is often assumed that basins of attraction are harmonic. This is clearly not the case for the present protein model since otherwise the glass-transition temperature T_K and the temperature T_h would coincide. An analysis of Figs. 2 and 3 shows that these two temperatures differ by about a factor of three and strong anharmonic effects exhibited by the present model at low temperatures hence are apparent. In order to compute the vibrational potential energy of the native state basin more accurately, (i.e., the potential energy the model would have if allowed to reside in the vicinity of the native state only), we performed a separate series of simulations. Starting from the initial ground state conformation, simulations were performed in the canonical ensemble for 2×10^7 time steps (10^3 times longer than the typical relaxation time) at temperatures ranging from 0.06 to 0.56. From each simulation an array of 2000 conformations were chosen at random and used to take statistical averages. The conformations were checked to see whether they belonged to the native state basin: if the steepest descent operation initiated from a given conformation led

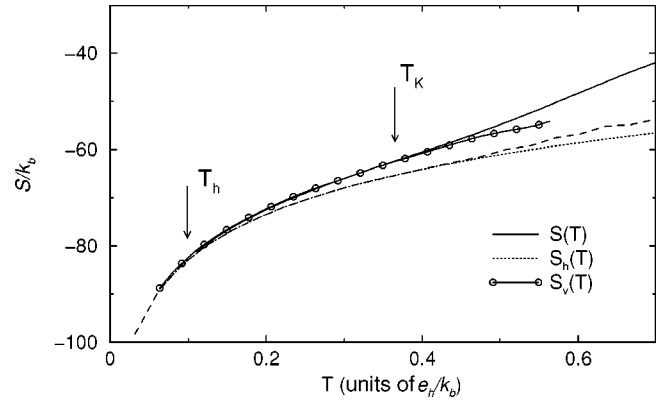


FIG. 4. Entropy (here we consider only excess entropy arising from interactions among particles and omit the trivial kinetic part) as function of temperature calculated in the present study for the β -sheet motif. Solid line, total entropy computed from $U(T)$ following formula (6); dotted line, harmonic approximation (8) for the ground state attraction basin; dashed line, harmonic approximation for attraction basins sampled during the simulated annealing runs; and symbols, vibrational entropy of the ground state basin. At $T > T_K$ availability of other attraction basins provides more entropy to the system than can be delivered by the native state basin alone.

to the native state, the conformation was retained in the averages (if not, the conformation was discarded). The resulting potential energy $U_v(T)$ is displayed in Fig. 3. Its statistical error is comparable to the size of the symbols shown in the figure. As expected, $U_v(T)$ strongly deviates from the energy obtained in the harmonic approximation $U_h(T)$ for $T > T_h$. For low temperatures up to T_K both functions for the total energy $U(T)$ and that for $U_v(T)$ merge into one curve. We recall that the former function was computed in simulations wherein the chain was allowed to visit all potential energy basins while the latter is essentially a single basin characteristics. Thus the most natural conclusion that follows from Fig. 3 is that at $T \leq T_K$ there remains only one basin of attraction, namely, the native state, that is thermally accessible to the molecule. This statement can be taken as a loose definition of the ideal glass-transition temperature. In order to make a more formal connection with the usual definition of the glass-transition temperature (5) the data shown in Fig. 3 can be inserted into Eq. (7). The total and vibrational entropies (including the harmonic part) computed from the reference point T_h by using analytical formula (8) are shown in Fig. 4. This figure convincingly confirms all our predictions made earlier on the basis of Figs. 2 and 3. The glass-transition occurs in the present model at $T_K = 0.35$, where $S(T)$ and $S_v(T)$ match. At lower temperatures all the total entropy of the system is delivered by the native state attraction basin. We note that the harmonic approximation to the Hamiltonian imposes too high-energy barriers on the molecule which lead to a reduction of entropy at $T_h < T < T_K$. At higher temperatures, constraining the molecule to the boundaries of the native state valley results in an underestimation of entropy at $T > T_K$. At this temperature the model starts to visit other energy minima and thus gains entropy.

IV. CONCLUSIONS

In this paper, we reported an application of the inherent structure theory coupled with molecular dynamics simulations to investigate the glass-transition phenomenon in an off-lattice protein model. Freezing was considered into the native state basin only as this was found to be the most likely cooling process on time scales comparable to the folding time of the model. At shorter relaxation times there could be chances that glassification would take place into another local minimum with sufficiently low energy. Although this scenario was not investigated here the present paper contains all conceptual and methodological tools necessary to carry out such an investigation. The only obstacle in this would be the increasingly high computational cost.

The glass-transition temperature T_K was computed in the following two manners. First, from the temperature depen-

dence of the potential energy of the inherent structures and second in a rigorous manner from entropy computations. Both methods produced quite consistent results making clear the remarkable success of the IS theory in predicting T_K when applied to the present protein model.

The thermodynamic ratio T_f/T_K characterizing the amount of frustration present in the protein, or its relative ruggedness, is about 1.7 for the present model. This value is in good agreement with other calculations of lattice protein models as well as experimental observations obtained for small single-domain proteins [9].

ACKNOWLEDGMENT

This work was supported in part by the NSF CAREER Grant No. 0133504.

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