Relaxational Dynamics of a Random Heteropolymer

Christine Villeneuve, Hong Guo,* and Martin J. Zuckermann

Centre for the Physics of Materials and Department of Physics, McGill University, Rutherford Building, 3600 rue Université, Montréal, Québec, Canada H3A 2T8

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ABSTRACT: We have investigated the relaxational dynamics of a random heteropolymer after a temperature quench using extensive molecular dynamics simulation. The interaction between all monomers is taken to be a purely repulsive Lennard-Jones potential plus a random potential with a $1/r^6$ behavior. An equilibrium "phase diagram" is determined which allows us to find a characteristic temperature T_Θ which separates extended states from folded states of the heteropolymer. This temperature is an increasing function of the random interaction strength, and it permits us to determine appropriate initial and final temperatures for the quenches. Within the extended states the relaxation is found to be a pure exponential. It is a stretched exponential when quenching across the characteristic temperature. In particular, for long chains the relaxation is a two-stage process; both stages are of stretched form with different stretched exponents which we determine numerically for various system parameters. Our simulation clearly shows the nature of the relaxation process where a local folding takes place first followed by a global folding of the local blobs leading to the two folding stages. The results are discussed in relation to protein folding and to previous investigations.

I. Introduction

It is well-known that natural proteins fold into their native structures remarkably easily in spite of the enormous number of possible physical configurations.[1,2] It is believed[3−5] that protein sequences are "optimized" such that there is not only a stable unique structure for the ground state but also a funnel-like energy landscape which leads to efficient folding kinetics.[3,6] A principle of minimal frustration was proposed[7] to enforce a selection of the interactions between monomers such that as few energetic conflicts as possible occur and thus folding can take place efficiently. It has also been suggested that such folding takes place as a two-step process: a rapid folding to a "molten globule" intermediate configuration which is partially folded but more expanded than the compact native configuration and then a slow folding to the native configuration itself.[8] Among other research work in this field, considerable theoretical effort has been devoted to constructing proper models for protein folding and investigating various sequencings which lead to fast folding kinetics. Due to the immense complexity of the problem, much of our understanding and intuition have been obtained from various computer simulations based on lattice models.[9,10]

On the other hand, although heteropolymers with completely random monomer−monomer interactions usually do not fold on a reasonable time scale,[11] the heteropolymer models themselves are interesting in their own right as they may possess features similar to those of proteins. Indeed, much intuition concerning the equilibrium and kinetic properties of proteins has been obtained by investigating heteropolymers. Furthermore, from a polymer physics point of view, heteropolymers are interesting since they may behave completely different from homopolymers. Heteropolymers are also difficult to study due to the random interactions between the monomers, and thus relatively less is known about them.

In the following we present a numerical investigation of the folding kinetics of random heteropolymers. This is an important problem, and indeed several studies have appeared which examine various aspects of this topic. Recently, Iori et al.,[12,13] Struglia,[14] and Fukugita et al.[15] studied this problem as a model for protein folding kinetics using short random heteropolymers. They pointed out that, while homopolymers exhibit a coil and a collapsed or globule phase, random heteropolymers in analogy to proteins exhibit an additional frozen or folded phase. They identified the folded phase as a glassy state and found that its properties are completely different from the globule phase resulting from the homopolymer coil−globule transition. Iori et al.[12] further state that the globular phase of a *homopolymer* has no particular shape, whereas the frozen phase of a random *heteropolymer* has a definite frozen shape which is a "closed globule". Hence, in this sense the frozen phase is analogous to the unique native conformation of proteins in that the number of corresponding energy levels are few and have considerably lower energy than the globular states. On the kinetic studies, Iori et al. investigated the folding kinetics using Monte Carlo simulations of a heteropolymer model composed of 15 monomers with a large degree of quenched disorder. The internal energy of the system as a function of Monte Carlo time was monitored when the temperature is quenched from a high value to a lower one. It was found that the time course of the internal energy fits very well to a stretched exponential form for quenches to a final temperature which is not too low. The values of the stretched exponent, β, were found to be $\beta \simeq 0.54$ and 0.38, respectively, for two sets of the final temperature, with the smaller β corresponding to the lower of the two final temperatures. The same fitting procedure yielded a pure exponential kinetic behavior for the equivalent homopolymer, *i.e.*, $\beta = 1$ if there are no random interactions. Iori et al.[13] also made a Langevin analysis for the relaxation to the folded phase and again found a stretched exponential behavior for the relaxation to the folded phase on short time scales (compared to the experimental work on proteins of Frauenfelder et al.,[16] which predicts time scales on the order of seconds).

While the previous calculations have enabled us to obtain considerable intuition on the physics of the

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folding kinetics of heteropolymers, there are, nevertheless, many questions which remain unclear. First of all, we expect (and indeed find, see below) that the folding kinetics or relaxation of a heteropolymer with random interactions between monomers should depend on the final temperature which can be characterized in several regimes. For a general *homopolymer*, a particularly interesting temperature is the Θ point, which separates different scaling regimes. Below the Θ point the homopolymer is in a collapsed state. For a random heteropolymer, on the other hand, the existence of a Θ point is less clear, but a similar behavior is obviously expected; *i.e.*, below some characteristic temperature T_Θ the heteropolymer is folded in equilibrium. Thus, one can easily imagine that quenching the temperature from above T_Θ but remaining above, from above to below, and from below to below should lead to different forms of the relaxation. In our simulations we describe the homopolymer in the absence of a random interaction by a purely repulsive Lennard-Jones potential. Hence, the Θ point in this limit is zero and the occurrence of a characteristic temperature T_Θ plus the related folding for the random heteropolymer will therefore be entirely due to the random interaction. Second, from a statistical physics point of view, we believe that the useful approach to understanding the kinetics of protein or heteropolymer folding is based on the search for universal features in the folding process. Such universal properties which are generally related to the scaling regime do not depend on details of the chemical nature of the individual monomer groups.[17,18] Indeed, we have recently made a general study of such features as the dependence of the folding time on the energy level structure and the level spacing distributions for a simple protein folding model.[19] For the present problem, it is thus interesting to ask if the stretched exponential relaxation behavior discovered by Iori et al.[12] is generic and whether the exponent β is dependent on the parameters of the particular system studied or whether β is a universal number. Also what is its precise value? The purpose of this work is to answer these generic questions.

Since the problem of folding kinetics is extremely complicated and analytical results are difficult to obtain, we use a numerical simulation method for our investigation. The application of numerical simulation techniques to polymer science has led to a wealth of information regarding both the kinetics of formation and the equilibrium properties of synthetic and biological macromolecules. These techniques include the Metropolis Monte Carlo (MMC) simulations on self-avoiding walks using a variety of algorithms such as the crankshaft algorithm and the bond fluctuation algorithm; direct MMC simulations using physically motivated Hamiltonians such as the Edwards−de Gennes Hamiltonian;[20−22] and the Langevin dynamics and molecular dynamics (MD) methods.[23−25] The most interesting aspect for physicists is the use of simple models in conjunction with numerical methods for the understanding of the universal behavior of polymer systems in the limit of $N \rightarrow \infty$, where N is the number of effective monomers per polymer.

In the following we examine in detail the kinetics of formation of random heteropolymer conformations using MD simulations. We use a Hamiltonian similar to that of Iori et al.,[12,13] which consists of (i) a harmonic term between nearest-neighboring monomers of the heteropolymer, (ii) a purely repulsive Lennard-Jones potential between all monomers, and (iii) an additional $1/r^6$ potential whose coupling constant is chosen from a Gaussian distribution with width α, which represents the degree of quenched random interactions between the monomers. The description of the relaxation of random heteropolymers into the frozen or folded state via a stretched exponential is usually taken as an indication that the folded state behaves like a glassy phase. To investigate the folding kinetics after a temperature quench, we shall first make a systematic study of the "phase diagram" of these systems as a function of the temperature T and the degree of the random interaction strength α. Without this phase diagram, it is difficult to know where to make the temperature quench. The phase line between the extended state and the folded state would then be described in terms of a characteristic temperature, which will in this work be referred to as the "Θ point", T_Θ. Once the Θ point is located, we then perform systematic quenches in order to examine the relaxation properties of the random heteropolymer. The principal objectives of this paper are to examine the detailed relaxation behavior from the extended state to the folded state and to investigate the possible universality of this behavior as a function of α.

The paper is organized as follows. The model and the MD method are summarized in section II. The equilibrium results are presented in section III. This section contains a phase diagram for the collapsed versus the extended phase of the random heteropolymer over a broad range of temperature T and random interaction strength, α. The folding kinetics is studied in section IV which also gives details of the related conformations of the random heteropolymer. This section reports the results of quenches from the extended phase to the folded phase for which two time relaxation regimes were observed. Both relaxation processes were characterized by stretched exponentials, one of which was found to be generic. Section V contains a discussion and concludes the paper.

II. Model and Simulation Method

In our simulation, we use the model of Iori, Marinari, and Parisi,[12] for which the Hamiltonian can be written as follows:

$$H = H_{\mathrm{har}} + H_{\mathrm{lj}} + H_{\mathrm{dis}} \tag{1}$$

H_{har} is the Hamiltonian for the harmonic interaction between neighboring monomers on the heteropolymer chain and is given by

$$H_{\mathrm{har}} = \frac{k}{2}\sum_{i=1}^{N-1}(\vec{r}_i - \vec{r}_{i+1} - R_0)^2 \tag{2}$$

where R_0 is the length of the unstretched bond between monomers and $\vec{r}_i$ is the coordinate of the ith monomer ($i = 1, 2, ..., N$). H_{lj} is a Lennard−Jones (L−J) potential between all pairs (ij) of monomers. It is given by

$$\begin{aligned} H_{\mathrm{lj}} &= 4\epsilon \sum_{ij=1,i\neq j}^{N}\left[\left(\frac{\sigma}{r_{ij}}\right)^{12} - \left(\frac{\sigma}{r_{ij}}\right)^{6} + \left(\frac{\sigma}{r_c}\right)^{6} - \left(\frac{\sigma}{r_c}\right)^{12}\right]; \qquad r < r_c \\ &= 0; \qquad r \geq r_c \end{aligned} \tag{3}$$

where $r_{ij} = |\vec{r}_i - \vec{r}_j|$, ϵ is the coupling constant, and r_c is the position of the minimum in the L-J potential given by $r_c = 2^{1/6}\sigma$. r_c is also taken to be the cutoff for the L-J potential used in the simulations. The L-J potential is thus purely repulsive as is usually used for homopolymers in a good solvent.[25] The term $H_{\rm dis}$ represents a random interaction between each pair of monomers,

$$H_{\rm dis} = \frac{\epsilon}{2}\sum_{ij=1,i\neq j}^{N}\left(\frac{\eta_{ij}}{r_{ij}^{\;6}}\right) \tag{4}$$

where η_{ij} is a Gaussian random number with $\langle\eta_{ij}\rangle = 0$ and

$$\langle\eta_{ij}\eta_{kl}\rangle = \alpha\delta_{ik}\delta_{jl} \tag{5}$$

Hence, the "strength" of the random interaction is measured by the parameter α. Iori et al.[12] point out that, for application to protein folding, η_{ij} represents a series of complex biological interactions such as the interactions between different groups of amino acids and the interactions of these groups with the solvent (*e.g.*, an aqueous solution). Furthermore, Shakhnovich and Gutin in their paper on the relation between random heteropolymers and protein sequences[10] point out that, since there are 20 amino acids involved in protein sequences, there are 210 pairwise interactions, which gives a motivation for the use of a random distribution of mutual interactions between monomers. Finally the bonds between monomers should be regarded as a set of amino acids making up a single Kuhn length. The Kuhn length for the secondary sequences of proteins is on the order of 1.8 nm, which corresponds to 5−7 links.[26]

Both the equilibrium and relaxation data were obtained by implementing a molecular dynamics (MD) method described by Grest and Murat[25] in which each monomer is coupled to a heat bath via a friction coefficient. The equations of motion for the monomers which are assumed to have a mass m are basically Newton's equations plus a noise term, *i.e.*,

$$m\,\frac{{\rm d}^2\vec{r}_i}{{\rm d}t^2} = \vec{F}_i - m\Gamma\,\frac{{\rm d}\vec{r}_i}{{\rm d}t} + \vec{W}_i(t) \tag{6}$$

Here $W_i(t)$ is a white noise representing the random part of the coupling of the monomer to the heat bath and its satisfies the correlation:

$$\langle\vec{W}_i(t)\ \vec{W}_j(t)\rangle = 6k_{\rm B}Tm\Gamma\delta_{ij}\delta(t - t') \tag{7}$$

$\vec{F}_i$ is the force on the ith monomer and is obtained from the Hamiltonian of (1):

$$\vec{F}_i = -\vec{\nabla}_i H \tag{8}$$

The MD simulation proceeds by integrating eq 6 using a Verlet algorithm with an appropriate choice of the time step Δt.

In this work we have monitored the following physical quantities:

(a) The temperature, T, as calculated from the equipartition theorem.

(b) The average bond length between monomers.

(c) The average radius of gyration:

$$\langle R_{\rm gy}\rangle = \left\langle\left(\frac{1}{N}\sum_{i=1}^{N}(\vec{r}_i - \vec{r}_{\rm CM})^2\right)^{1/2}\right\rangle \tag{9}$$

where $\vec{r}_{\rm CM}$ is the coordinate of the center of mass of the polymer.

(d) The average end-to-end distance:

$$\langle R_{\rm E}\rangle = \langle|\vec{r}_N - \vec{R}_1|\rangle \tag{10}$$

(e) The average kinetic energy, $E_{\rm K}$.

(f) The average potential energy, $U_{\rm av}$, found from eqs 2−4, *i.e.*

$$U_{\rm av} = \langle H_{\rm lj} + H_{\rm dis} + H_{\rm har}\rangle \tag{11}$$

The total energy, $E_{\rm av}$, is the sum of $E_{\rm K}$ and $U_{\rm av}$.

III. Equilibrium Properties

In this section we present results obtained from equilibrium simulations for several values of α ranging from 0 to 6. In particular we need to find a characteristic temperature, called T_Θ, as a function of the random interaction strength α. Because we are primarily interested in the relaxational dynamics and the location of T_Θ is to give us an idea of where the temperature quenches take place, we have only attempted to compute a good enough T_Θ for our purposes. A precise determination of this quantity needs prohibitively large computer effort and is beyond this work. For a *homopolymer*, the Θ point can be located[25] by studying the scaling of the coil size as a function of the polymer length N: $R_{\rm gy} \sim N^\nu$. Above T_Θ, $\nu = {}^3/_5$; at T_Θ, $\nu = {}^1/_2$; while below T_Θ, $\nu = {}^1/_3$. For the random heteropolymer we use the same idea to locate a possible T_Θ.

Throughout the calculations we have fixed $\Delta t = 0.005\tau_0$ and checked that this value is compatible with the stability of the integration of the equations and with regard to rounding errors. Here $\tau_0 = \sigma(m/\epsilon)^{1/2}$. The value of Γ was fixed at $\Gamma = 0.5\tau_0^{\;-1}$, and the unstretched bond length was taken to be $R_0 = 1.5\sigma$. We used units for which $m = \sigma = 1$ and measured all energies in units of ϵ. In these units, the value of the coupling constant, k, for the harmonic interaction of eq 2 used in the simulations is $k = 30$. The number of monomers in a heteropolymer which we have used to study the equilibrium conformations in order to approximately determine a phase diagram and to locate T_Θ varied from $N = 30$ to $N = 200$ for values of α ranging from 0 to 6. We start from a self-avoiding random walk and add various interactions as shown in eq 1. The random heteropolymers were equilibrated using 3×10^6 time steps per monomer for $N \geq 100$ down to 10^6 time steps per monomer for $N = 30$. Several physical quantities were then collected at equal time intervals for time-averaging after the equilibration. Typically these quantities were saved every 3000 time steps per monomer up to a total of 1000 sets of data.

When $\alpha = 0$, the Hamiltonian of eq 1 reduces to the Hamiltonian for a homopolymer in a good solvent as described by a repulsive L-J interaction. The Θ point in this case is therefore zero. However, to verify that our simulation method gives the correct scaling in the homopolymer limit, we computed $\langle R_{\rm gy}\rangle$ for $N = 30$, 75, 100, 150, and 200 for $\alpha = 0$ and for two temperatures. We found that $\langle R_{\rm gy}\rangle \sim \alpha N^\nu$ with $\nu \approx 0.586$ for $T = 4$ and $\nu \approx 0.607$ for $T = 0.1$.

Since the Θ point is zero for $\alpha = 0$, the appearance of a "Θ-like" point for $\alpha \neq 0$ will be due entirely to the random interaction. Figure 1 shows $\langle R_{\rm gy}^{\;2}\rangle/N$ as a function of N for $\alpha = 3$ and for four different values of T. In this case values of $N = 50$, 75, 100, 125, 150, 175, and 200 were used. The figure shows that there should be a Θ point near $T \simeq 2$. Figure 2 shows the result for

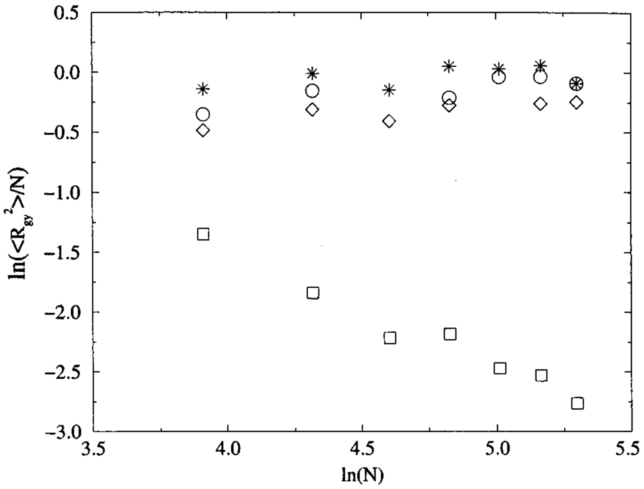

Figure 1. Average radius of gyration versus N for random heteropolymers with α = 3 for N = 50 to 200 and for temperatures T = 8 (*), 4 (○), 3 (◇), and 2 (□). T = 8, 4, and 3 are above T_Θ, where $\langle R_{gy}\rangle \sim N^\nu$ with $\nu \approx 0.59$. T = 2 is lower than T_Θ. The Θ point lies between T = 2 and 3.

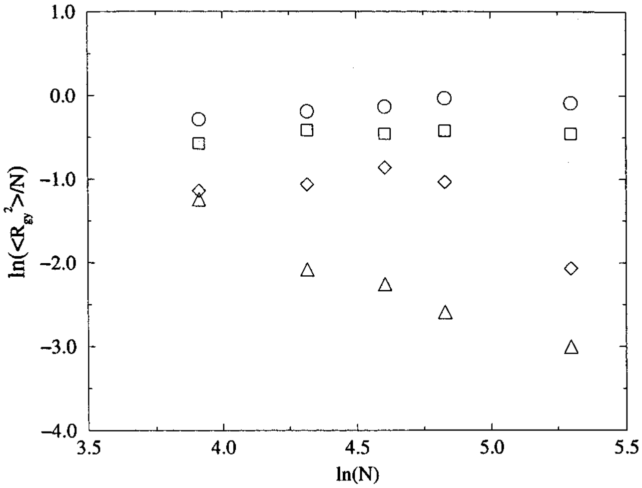

Figure 2. Average radius of gyration versus N for random heteropolymers with α = 6 for length N = 30−200 and for temperatures T = 10 (○), 8 (□), 7 (◇), and 6 (△). T = 10 is above T_Θ with $\langle R_{gy}\rangle \sim N^\nu$ where $\nu \approx 0.57$. T = 8 is close to T_Θ with $\nu \approx 0.50$. T = 7 and 6 are below T_Θ.

α = 6. For this (and other) larger value of α, it is very difficult to locate a precise value of T_Θ due to large fluctuations in the data, but from the figure it is reasonable to assume that it lies in the neighborhood of T = 8. For both α = 3 and 6 we found that $\langle R_{gy}\rangle \sim \alpha N^\nu$ with $\nu \simeq {}^3/_5$ for temperatures above the Θ point and that $\nu \simeq {}^1/_3$ for temperatures below it, provided that the temperature is not too low (for which case the simulation is hampered by metastable states). Near the Θ point, we roughly find that $\nu \simeq {}^1/_2$, as expected. The notion of a Θ point is also consistent with the behavior of $\langle R_{gy}\rangle$ as a function of temperature. We have confirmed that, near this temperature T_Θ, $\langle R_{gy}\rangle$ changes from a small value below it to a much larger value above it, indicating a conformation change of the heteropolymer from a compact structure to an extended one.

Although it is almost impossible to determine a precise value of T_Θ, it is clear that the effective value of T_Θ as determined by our simulation procedure increases considerably with increasing α. This is shown in the inset of Figure 3, where $\langle R_{gy}\rangle$ is plotted as a function of temperature for several values of α, fixing N = 100. From this plot we have operationally taken T_Θ as the temperature at which $\langle R_{gy}\rangle$ = 6.0, this being in the middle of its values. Although somewhat arbitrary, this procedure, nevertheless, gives a reasonable estimate of the Θ point. The values of T_Θ, as deduced this way from the inset of Figure 3, are exhibited in Figure 3, which effectively serves as a phase diagram for the heteropolymer model studied here. The nature of the equilibrium conformation can be directly examined by the final structures of the heteropolymer, and we have confirmed that these final structures are indeed consistent with the phase diagram obtained. Finally, in order to test the stability of our simulations, we calculated the average bond length of the polymer as a function of temperature, N and α. We found that the bond length increases with temperature in all cases but remains bounded to below 2.0σ up to T = 10. Hence, the average bond length stays reasonably close to its initially chosen value of 1.5σ and does not exhibit any unusual behavior throughout the entire simulation procedure.

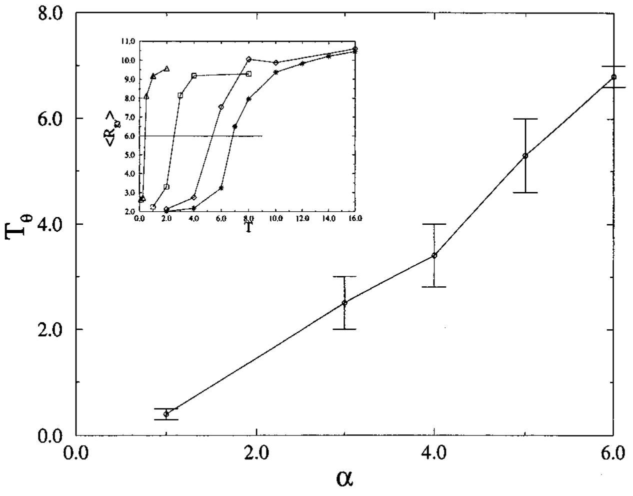

Figure 3. T_Θ versus α for N = 100. The values of T_Θ were measured at the points of inflection of the inset, and the error bars were estimated by using Figures 1 and 2 and related results for α = 1 and 5. This plot serves as an effective "phase diagram". The solid line is a guide to the eye. Inset: Average radius of gyration as a function of temperature for N = 100 and α = 1 (△), 3 (□), 5 (◇), and 6 (*). The horizontal line at $\langle R_{gy}\rangle$ = 6.0 corresponds to the point of inflection at which we measured T_Θ for different values of α. The solid lines are guides to the eye.

In the next section we study the relaxational dynamics of the heteropolymer after a quench of temperature in various regions of the phase diagram of Figure 3.

IV. Kinetics of Relaxation

The relaxational dynamics is investigated by quenching the temperature from an initial value T_I to a final one at T_F and monitoring the time evolution of the relevant physical quantities. Our phase diagram allowed us to examine the relaxation behavior by choosing the temperatures T_I and T_F for the related quenches systematically. The quenches were performed by first bringing the polymer to thermal equilibrium at T_I and then quenching to T_F. To study the relaxational dynamics after a temperature quench, for a given initial equilibrium conformation, 10^5 time steps per monomer were used and the relaxation process was monitored. The results were then averaged over 100−500 independent quench runs for the same initial condition. Finally, up to 16 impurity averages (different realizations of $\{\eta_{ij}\}$ for a given α) were performed for a given set of other system parameters.

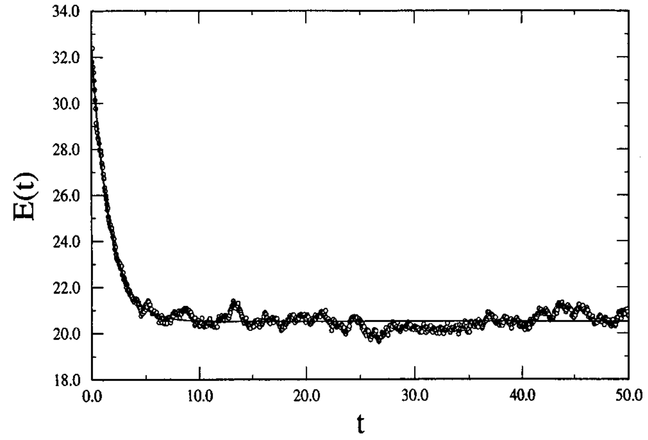

Figure 4. Energy versus time for a random heteropolymer after a temperature quench with parameters $\alpha = 6$, $N = 30$, $T_I = 16$, and $T_F = 10$. Both temperatures are above the Θ point. From the stretched exponential fit we find $\beta \approx 1.01$ and $\tau \approx 1.63$. Hence, this relaxation is a pure exponential. The solid line is the fit to eq 15.

In the homopolymer case where $\alpha = 0$, exponential relaxation behavior was always observed, as expected. For the random heteropolymer case $\alpha \neq 0$, we examined polymers of length $N = 30$ for $\alpha = 2, 3, 4, 5$, and 6 and $N = 100$ for $\alpha = 6$. As mentioned previously, 100–500 independent quench runs were averaged for a given $\{\eta_{ij}\}$ to reduce fluctuations in the data (the only difference between each quench run is the thermal noise). The total energy $E(t)$ of the polymer was calculated as a function of time t and was fitted to a stretched exponential form given by

$$E(t) = a_0 e^{-(t/\tau)^{\beta}} - a_1 \tag{12}$$

Here time t was measured in units of τ_0. One unit of time is thus equivalent to 200 MD steps. The parameters a_0, β, τ, and a_1 were obtained by using a χ^2 fit. Furthermore, these values must be impurity averaged.[27] For $N = 30$ we performed impurity averages over 8 different realizations of the random interactions $\{\eta_{ij}\}$ for a given α, whereas 16 such realizations were used for $N = 100$. We found that these impurity averages were vital in determining a reasonably accurate value for the relaxational exponent β.

Exponential relaxation behavior ($\beta = 1$) was always observed when both T_I and T_F were chosen to be in the extended phase, *i.e.*, above the Θ point. This is shown in Figure 4 for $N = 30$, $\alpha = 6$, $T_I = 16$, and $T_F = 10$. The values of β and τ are tabulated in Table 1, and for quenches above the Θ point β is consistently close to unity for all values of α used. We have confirmed that the data for $N = 100$ and $\alpha = 6$ were also well fitted to a pure exponential above the Θ point. This behavior is understandable since, above the Θ point, the heteropolymer in question is extended; thus, the random interactions $\{\eta_{ij}/r_{ij}^6\}$ play little role because it decays quickly for monomers far away in an extended conformation. In this case the whole system should indeed behave as that of a homopolymer indeed.

The quenches of interest for the problem of random heteropolymer folding are those effected *across* the Θ point, *i.e.*, from the extended to the folded states. For this case T_I was chosen to be well above T_Θ, while T_F was below. It turned out that, if T_F was chosen too low, the simulations were hampered by metastable states and the polymer could not relax to a well-folded equilibrium configuration. Hence, we have chosen the value of T_F to be not too far below the Θ point and always checked the final configurations to make sure that the system was not trapped in an extended metastable state.

We have examined the relaxation to equilibrium for quenches across the Θ point for long polymers in order to investigate the folding process in detail. In particular, we carefully considered the case of a random heteropolymer of length $N = 100$ for $\alpha = 6$, $T_I = 16$, and $T_F = 6$. Again the energy $E(t)$ was calculated as a function of t and fitted to eq 12. The results are summarized in Table 2. Out of the 16 realizations of $\{\eta_{ij}\}$, we found that 15 sets of data exhibited two relaxational time regimes: a fast relaxation from which partial “folding” resulted, followed by a crossover to a much slower regime in which the folding process was completed. The relaxation behavior in both regimes could be fitted to a stretched exponential of the form in eq 12. In the first time regime, as shown in Table 2, a stretched exponent $\beta \approx 0.7$ with time constant $\tau \sim 1.2$ was determined. These are completely consistent with the values found for $N = 30$ and $\alpha \neq 0$ to be reported below. In the second relaxation regime β was found to be approximately 0.2, a very small value indeed. Figure 5 gives relaxation data which shows the two regimes for one simulation together with the fits using eq 12.

Why are there two relaxational time regions? To answer this question, we plot typical conformations of the polymer during the relaxation process at various time intervals, as shown in Figure 6. At early times, from $t = 0$ to $t = 30$, where the stretched exponent $\beta \approx 0.7$, the conformations show that the folding is only *local*, where the overall conformation is still extended while locally the monomers fold into separate “blobs”. In fact, if we compute $\langle R_{gy}\rangle$ at $t = 30$, the value is still close to that of an extended polymer. By examining all 15 simulations where there were two relaxation regimes, we conclude that the first time regime was due to the local folding. After the first time regime, the folding process enters a crossover where the local blobs get together to form larger blobs, corresponding to $t = 75$ in Figure 6. At this stage the polymer has not completely folded but is certainly not extended, and from the point of view of protein folding, this could perhaps be regarded as a molten globule. Finally the folding enters the second time regime which roughly covers from $t = 100$ to the end of our simulation when the polymer is completely folded, with an exponent $\beta \approx 0.2$. We may now conclude that the second relaxation regime, with a small stretched exponent $\beta \approx 0.2$, is due to the folding of local blobs to the final folded equilibrium state. Clearly, because blobs are much more difficult to move around, the folding of local blobs should be much slower, which is reflected by the small β. Finally the only one among the 16 simulations which did not exhibit a second time regime seemed to be trapped in the crossover stage. This could happen for some special arrangements of the random interactions $\{\eta_{ij}\}$. However, largely speaking, our simulations show that the relaxation during a temperature quench from an extended to a folded state is a two-stage process, both characterized by a stretched exponent form.

How general is the value of the stretched exponent? We have examined this question by performing temperature quenches across the Θ point for a number of random interaction strengths $\alpha = 2-6$. As the simulations were very computationally intensive, we have used

Table 1. $\langle\beta\rangle$ and $\langle\tau\rangle$ Resulting from the Average over 8 Realizations of the Random Interaction $\{\eta_{ij}\}$ for $N = 30$[a]

across the "Θ point"	α = 2, $T_I = 4$, $T_F = 0.5$	α = 3, $T_I = 4$, $T_F = 1$	α = 4, $T_I = 6$, $T_F = 1$	α = 5, $T_I = 10$, $T_F = 4$	α = 6, $T_I = 16$, $T_F = 6$
$\langle\beta\rangle$	0.75 ± 0.03	0.70 ± 0.02	0.65 ± 0.04	0.68 ± 0.05	0.62 ± 0.06
$\langle\tau\rangle$	1.41 ± 0.04	1.54 ± 0.05	1.54 ± 0.04	1.43 ± 0.06	1.0 ± 0.2
within extended phase	α = 2, $T_I = 4$, $T_F = 2$	α = 3, $T_I = 10$, $T_F = 4$	α = 4, $T_I = 6$, $T_F = 4$	α = 5, $T_I = 10$, $T_F = 7$	α = 6, $T_I = 16$, $T_F = 10$
$\langle\beta\rangle$	0.97 ± 0.02	1.02 ± 0.02	0.88 ± 0.08	0.9 ± 0.2	1.01 ± 0.05
$\langle\tau\rangle$	1.42 ± 0.02	1.51 ± 0.02	1.6 ± 0.1	1.5 ± 0.1	1.59 ± 0.05
within the folded phase	α = 2, $T_I = 1$, $T_F = 0.5$			α = 5, $T_I = 4$, $T_F = 2$	α = 6, $T_I = 6$, $T_F = 4$
$\langle\beta\rangle$	0.38 ± 0.05			0.49 ± 0.07	0.32 ± 0.06
$\langle\tau\rangle$	3 ± 6			7 ± 1	4 ± 1

[a] The first row consists of results from relaxations across the Θ point. The second row presents the relaxations within the extended states. The third row results from quenches within the folded states. T_I and T_F are the initial and final temperature, respectively.

Table 2. $\langle\beta\rangle$ and $\langle\tau\rangle$ Resulting from the Average over Several Realizations of the Random Interaction $\{\eta_{ij}\}$ for $N = 100$[a]

across the "Θ point"	α = 6, $T_I = 16$, $T_F = 6$, $t = 0-30$	α = 6, $T_I = 16$, $T_F = 6$, $t = 100-500$
$\langle\beta\rangle$	0.69 ± 0.02	0.19 ± 0.02
$\langle\tau\rangle$	1.17 ± 0.04	25 ± 5

[a] All quenches were performed across the Θ point. Times $t = 0$ to $t = 30$ correspond to the first relaxation stage, and $t = 100$ to $t = 500$ correspond to the second stage. $\langle\beta\rangle$ and $\langle\tau\rangle$ were averaged over 16 realizations for the first relaxation stage and 15 realizations for the second stage.

shorter chains of $N = 30$. For these shorter heteropolymers we did not always observe two regimes and some relaxations took place in a single regime. Since the chains are quite short, some of the chains manage to avoid local folding by relaxing directly to their compact configurations. The results for these simulations are summarized in Table 1. Indeed, our results clearly confirm that $\beta \approx 0.7$ for all values of α studied for the first time regime. Typical relaxation data are shown in Figure 7 which gives $E(t)$ as a function of time for a single simulation and three values of α. The three sets of parameters were α = 2, $T_I = 4$, and $T_F = 0.5$; α = 4, $T_I = 6$, and $T_F = 1$; and α = 6, $T_I = 16$, and $T_F = 6$.

Another question of interest is whether the relaxation *form*, eq 12, and the stretched exponent β depend on the simulation parameter Γ^{-1} which gives the characteristic time for coupling to the heat bath in the simulation. Clearly this question is relevant for the first relaxation regime. To investigate this point, we examined the quenches using $N = 30$ and α = 6 for several values of Γ, *i.e.*, $\Gamma^{-1} = 0.8\tau_0$, $1.33\tau_0$, $1.0\tau_0$, and $4.0\tau_0$ in addition to $2.0\tau_0$. For all the simulations we found the stretched exponent $\beta \approx 0.7$, independent of Γ. Hence, the stretched exponential relaxation has a generic behavior as anticipated. On the other hand, we expected the time scale τ of the first relaxation regime to be affected by Γ: it was, in fact, found to be a linear function of Γ^{-1}. Finally we found no detectable Γ dependence for the results of the second relaxation regime.

We have also examined the second time regime seen in some of the relaxation curves for these short chains with α = 6 for the simulation shown in Figure 7. In this case we found that the relaxation could be characterized by an effective stretched exponent $\beta \approx 0.45$, in contrast to the case of $N = 100$ where $\beta \approx 0.2$. However, we do not expect to determine the stretched exponent, β, accurately for the second time regime for short chains, because the second relaxation regime is due to the folding of local blobs as discussed above, and for short chains there is a very small number of blobs to fold; hence, an effectively faster relaxation (larger β) is indeed expected. For long chains, however, it is possible that the exponent of the second time regime will be determined by the motion of the blobs in a random environment, thus leading to a generic value of β.

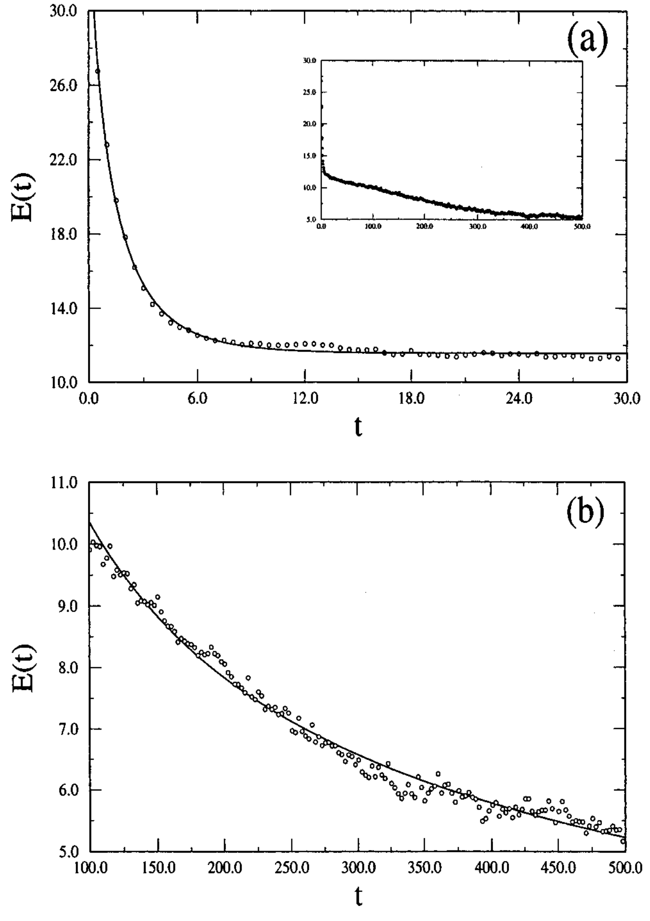

Figure 5. Energy as a function of time for a random heteropolymer after a temperature quench with parameters α = 6, $N = 100$, $T_I = 16$ (above the Θ point), and $T_F = 6$ (below the Θ point). Two relaxation regimes are found. (a) First time regime, from $t = 0$ to 30. The stretched exponential fit gives $\beta \approx 0.73$ and $\tau \approx 1.19$. The inset shows the complete relaxation curve from $t = 0$ to 500. (b) Second time regime, from $t = 100$ until the end of the simulation. Fitting to eq 15 gives $\beta \approx 0.25$ and $\tau \approx 8.71$ for this heteropolymer simulation in the second regime. Solid lines are the fit to eq 15.

Finally, we comment that, for even shorter chains such as $N = 15$, the second time regime is not revealed

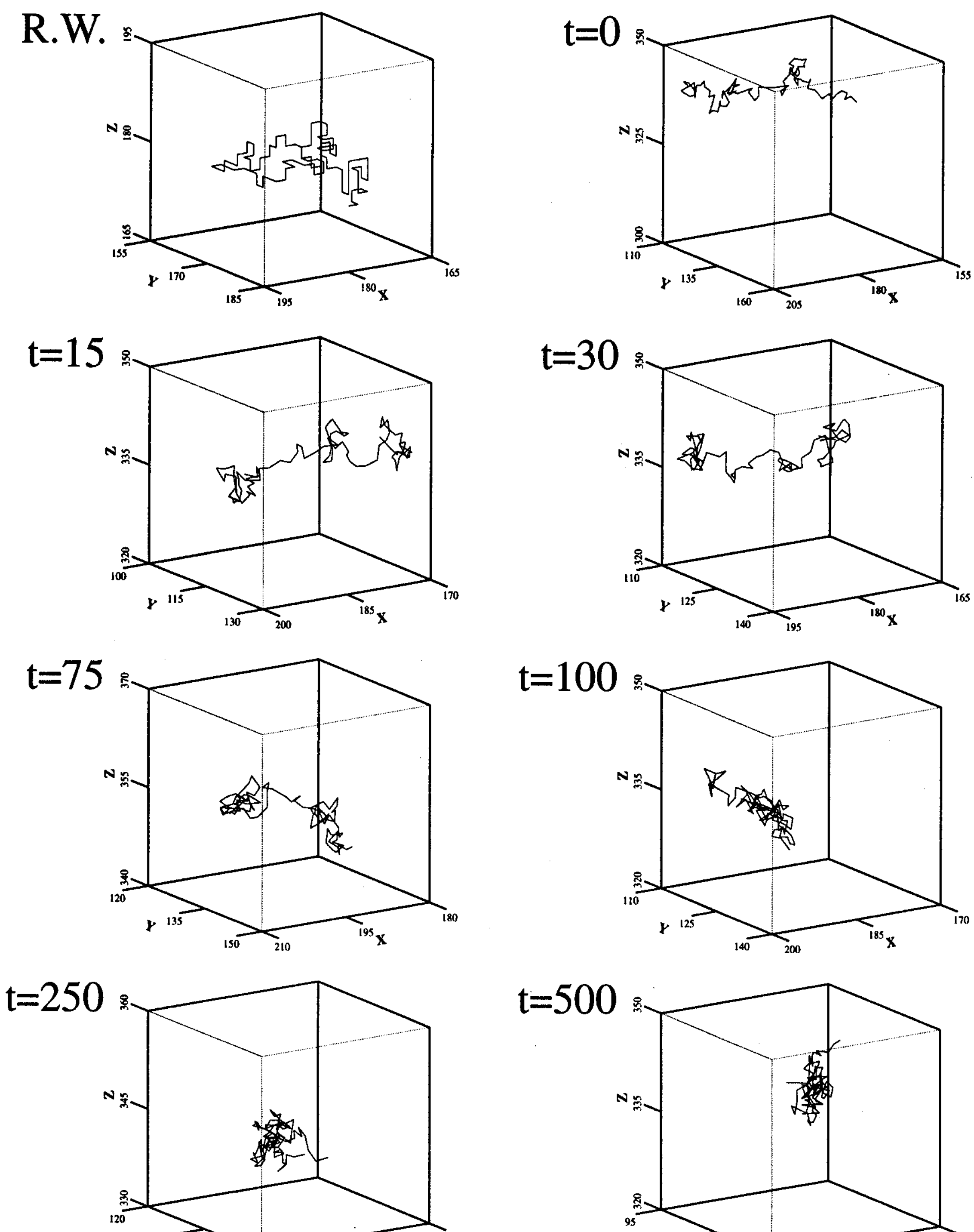

Figure 6. Configurations for a random heteropolymer (the same polymer as used in Figure 5) at various times after a temperature quench, with parameters $\alpha = 6$, $N = 1000$, $T_I = 16$, and $T_F = 6$. The first graph labeled R.W. represents the initial random walk used to arrive at the equilibrium configuration at $T_I = 16$, which serves as the $t = 0$ configuration just before the quench. Other graphs represent configurations at different times during the relaxation process. Local folding is clearly seen before $t = 75$. The polymer is essentially folded at $t = 500$.

as there is essentially no local folding and the entire chain simply folds with only one stretched exponent; this behavior was found in the work of Iori et al.[12] To check this point carefully, we performed MD simulations for random heteropolymers of length $N = 15$ corresponding to the case investigated in ref 12. Using $\alpha = 6$ and averaging 100 quench runs, the data of $E(t)$ was indeed fitted well with a single stretched exponential in agreement with the results of Iori et al. The value of the stretched exponent in this case was found to be consistent with the value reported above for the first time regime for $N = 30$, 100. Thus, as expected, the relaxation to equilibrium was rapid and occurred over 30 time units for these very short chains.

To examine the relaxational dynamics further, we performed temperature quenches entirely below the Θ point, *i.e.*, with T_I, $T_F < T_\Theta$, using heteropolymer chains with $N = 30$ and $\alpha = 2$, 5, 6. A typical relaxation behavior of the energy is shown in Figure 8, for parameters $N = 30$, $\alpha = 6$, $T_I = 6$, and $T_F = 4$. In this

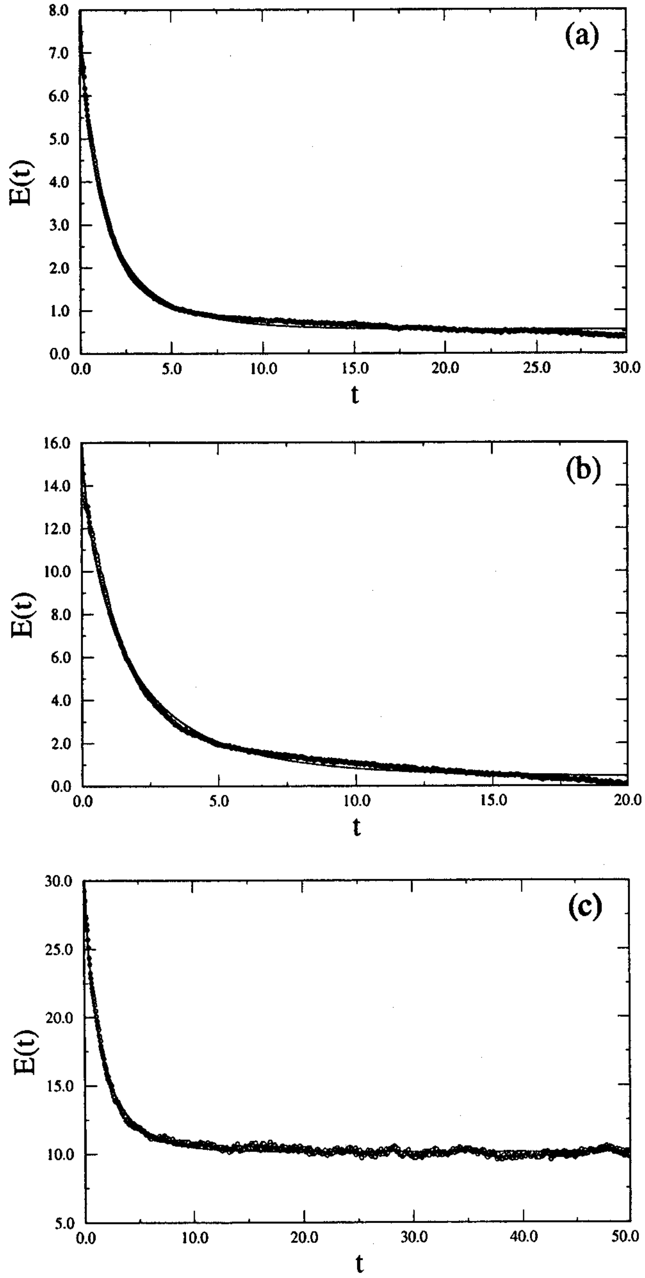

Figure 7. Relaxation curves for quenches across the Θ point fitted with stretched exponentials for $N = 30$. Only the first relaxation regime is shown. (a) For $\alpha = 2$, $T_I = 4$, and $T_F = 0.5$, we get $\beta \approx 0.69$ and $\tau \approx 1.26$. (b) For $\alpha = 4$, $T_I = 6$, and $T_F = 1$, we get $\beta \approx 0.70$ and $\tau \approx 1.53$. (c) For $\alpha = 6$, $T_I = 16$, and $T_F = 6$, we get $\beta \approx 0.72$ and $\tau \approx 1.41$. Each of these β and τ is only one of the values used to do the averages in Table 1. The solid lines are the fit to eq 15.

case there was only one relaxation regime, which is understandable since the chain was only changing from an already folded state to a more compactly folded state. Again the data can be well fitted with the stretched exponential form, and the results are summarized in Table 1. For these below-to-below quenches, our data gave $\beta \approx 0.4$ for all values of α used.

V. Discussion

In this work we first examined the phase diagram of a single random heteropolymer in detail. As has been clearly shown, a clear idea of the equilibrium is necessary for investigating the relaxational dynamics after a temperature quench since the dynamic behavior is different depending on the temperature ranges. Our model of the polymer is composed of N monomers connected by harmonic springs. The monomers mutually interact via a repulsive Lennard-Jones potential, and the random interactions between the monomers were included by means of a van der Waals interaction whose coupling constants are chosen from a Gaussian distribution of width α. The phase diagram was obtained from MD simulations. Two states were identified: a high-temperature extended state where the random heteropolymer is described in terms of a self-avoiding random walk, and a low-temperature folded state where the polymer takes up a closed compact configuration. The two states are separated by a Θ point whose temperature increases with increasing α.

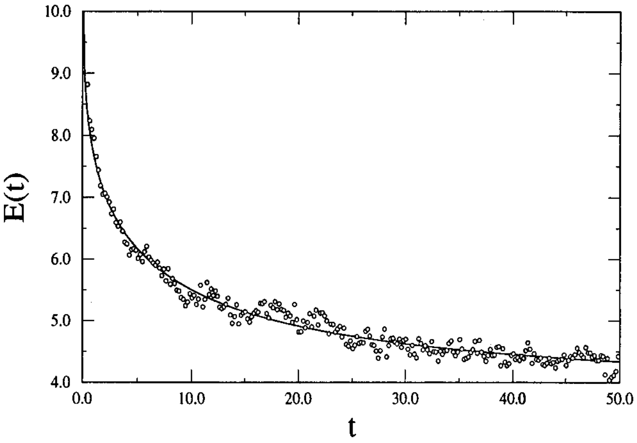

Figure 8. Energy versus time for a random heteropolymer after a temperature quench, with parameters $\alpha = 6$, $N = 30$, $T_I = 6$, and $T_F = 4$ (both below the Θ point). The stretched exponential fit gives $\beta \approx 0.40$ and $\tau \approx 4.02$ for this polymer.

Knowledge of the phase diagram allowed us to perform systematic studies of random heteropolymer relaxation processes. Relaxation to equilibrium for temperature quenches inside the extended "phase" showed a pure exponential behavior, whereas relaxation processes to the folded phase exhibited a stretched exponential behavior. We have discovered that the relaxation after a quench from above the Θ point to below can be characterized by a two-stage process. The first time stage is characterized by a faster stretched exponential relaxation process with exponent $\beta \approx 0.7$. This value does not depend on the values of α and is quite generic. In the first time stage, the chains locally fold into separate blobs but the entire chain is still rather extended. In the second time stage the local blobs fold together to the final compact structure, with another stretched exponential form and a smaller exponent β. For very short chains such as those examined in ref 12, the second time regime is absent as no local folding takes place. Finally for a quench from below the Θ point to still below, the relaxation is a one-stage process which is also well fitted with the stretched exponential form.

Relaxation to equilibrium for quenches from the extended to the folded phase is of most interest to us due to its relation to protein folding. Figure 6 shows that typical final polymer configurations for the first time regime (up to $t = 30$) are extended with a few compact blobs, particularly near the terminal monomers. This finding is in agreement with the work of Ostrovski and Bar-Yam.[28] These authors show by computer simulation based on cluster diffusion that the collapse of long homopolymers and certain heteropolymers is dominated by the nucleation and growth of large clusters at the ends of the polymer coupled with aggregation of smaller clusters inside the polymer. In our case the development of this growth and aggregation process occurs during the crossover, as can be seen from the configuration in Figure 6 near time $t = 75$. This configuration shows that the polymer is now more compact but with the blobs still connected by extended sections.

We believe that the relaxation data can be interpreted in terms of the molten globule concept; *i.e.*, we found a faster relaxation to an intermediate conformation in the first relaxation stage after an above-to-below temperature quench. This is the so-called "compact but extended" structure as discussed by Daggett and Levitt[29] for proteins. This relaxation stage is then followed by a slower relaxation to a folded equilibrium configuration.[8] The behavior is quite similar to that discussed in the literature for protein folding. Finally we note that the relaxation process studied here is quite different from that of the *homopolymer* collapse which proceeds via a single exponential.

There are many other questions of interests concerning the folding kinetics. A particularly useful study would be on the effects of solvents to the relaxation process for both random heteropolymers and heteropolymers with well-defined sequences mimicking proteins. Pande et al.[30] have recently shown that not all heteropolymers can be described in terms of the properties of random heteropolymers. Clearly, it would also be interesting to examine the kinetics of "unfolding", as protein denaturation is of great interest indeed.[29] We wish to report these investigations in the near future.

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