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Monte Carlo simulations of protein-like heteropolymers[★][✪]

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Properties of a simple model of polypeptide chains were studied by the means of the Monte Carlo method. The chains were built on the (310) hybrid lattice. The residues interacted with long-range potential. There were two kinds of residues: hydrophobic and hydrophilic forming a typical helical pattern -HHPPHPP-. Short range potential was used to prefer helical conformations of the chain. It was found that at low temperatures the model chain formes dense and partially ordered structures (non-unique). The presence of the local potential led to an increase of helicity. The effect of the interplay between the two potentials was studied. After the collapse of the chain further annealing caused rearrangement of helical structures. Dynamic properties of the chain at low temperature depended strongly on the local chain ordering.

The phase transition of flexible polymeric chains from a random coil to a dense globule has been extensively investigated. For a homopolymeric chain the transition is continuous and the low-temperature structures do not exhibit any global ordering. In the case of natural proteins the transition from the random coil-like state to the dense globule is more complicated process [1–2].

In last 10 years simple lattice models were constructed in order to study the protein folding process [3–5]. These models were able to reproduce main features of the folding transition and gave unique structures at low temperatures. For the models of proteins containing helical motifs it has been found that a general pattern of hydrophobic and hydrophilic type residues was essential to obtain unique folded structures. The simulations demonstrated that a simple lattice models without any specific interactions could mimic the conformational transitions of globular proteins in both the topology and thermodynamics of the process as well as all-or-none character of the transition [3–4].

Recently, Kolinski & Madziar [6] have applied a simple heteropolymer chain as a model used in a simulation of polypeptide molecules on a very

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flexible lattice. Following this idea and treating the above model as a state of reference Romiszowski & Sikorski [7, 8] studied the interplay between long-range non-specific potential with local conformational stiffness.

In this work we present some preliminary results concerning structure properties of these models. We also determined the local (secondary) structure of the model polypeptide chain and its dynamic properties.

THE MODEL AND THE SIMULATION ALGORITHM

The residues in the polypeptide chain were represented by α-carbons only [9, 10]. The positions of residues were limited to a quasi-crystalline lattice. A very flexible hybrid (310) lattice with a high coordination number $z = 90$ was chosen. This lattice was based on vectors belonging of the type: (3,1,1), (3,1,0), (3,0,0), (2,1,1) and (2,2,0). Assuming the lattice unit equals 1.22 Å one can obtain the best fit to real polypeptide chain with the root-mean square (RMSD) of the order of 0.6–0.7 Å. The angles between consecutive virtual bond vectors were constrained to the range 72.5–154 degrees, as found in protein structures [11].

The residues forming the chain interacted by the long-range contact potential (the interaction concerns a pair of residues which are not adjacent along the chain contour). The potential has the form of a square well:

$$V_{ij} = \begin{cases} \varepsilon_{rep} \; for \; r_{ij} < 4 \\ \varepsilon_{ij} \; for \; 4 \le r_{ij} \le 6 \\ 0 \quad for \; r_{ij} > 6 \end{cases}$$

where $\varepsilon_{rep} = 5$ is the short-distance repulsive part, r_{ij} is the distance between the i^{th} and j^{th} residues. The value of ε_{ij} depends on the type of i^{th} and j^{th} residue; it can take the values ε_{HH}, ε_{PP} or ε_{HP}. The values of these three parameters (in dimensionless kT units) were chosen as described in the previous papers on this subject [6–8]: $\varepsilon_{HH} = -2$, $\varepsilon_{PP} = -1$, $\varepsilon_{HP} = 0$. In this paper we studied model chains consisting of the typical helical septets -HHPPHPP- repeated, where P denotes the hydrophilic (non-polar) and H is a hydrophilic (polar) residue. We focused our attention on this ideal helical pattern because in previous papers we already discussed the influence of the pattern type (e.g., random heteropolymer and homopolymer) on the structure of the collapsed chain [6–8].

The local potential was a simple preference of helical states. It was previously shown that the presence of a right-handed helical element of the chain can be found by the value of the following parameter [6]:

$$r^{*2}_{i-1,i+2} = (\mathrm{v}_{i-1} + \mathrm{v}_i + \mathrm{v}_{i-1})^2 \cdot$$
$$\cdot \, sign((\mathrm{v}_{i-1} \times \mathrm{v}_i) \cdot \mathrm{v}_{i+1})$$

where v_{i-1}, v_i and v_{i+1} are the three consecutive vectors of the model polypeptide chain. Right-handed helical states correspond to the values of the r^{*2} within the range 9–25. When the helical state appeared in the system its energy was lowered by ε_{hel}. Previously we found for simpler models (based on diamond lattice but the same in spirit) [3–5] that the formation of a helical structures needs the proper balance between the two kinds of potential. Thus, here we have the ratio $\varepsilon_{hh}/\varepsilon_{hel} = 0$, 2 and 4.

The classical Monte Carlo sampling algorithm was employed. The model chain undergoes a series of local micromodifications. For the hybrid (310) lattice the following set of local chain conformational changes was used [9–10]:

- i) 2-bond kink motion;
- ii) 3-bond motion;
- iii) chain ends motion.

During the Monte Carlo simulation run the temperature of the system was gradually lowered and at every temperature the model chain was equilibrated. The production run consisted of about 10^7 Monte Carlo steps and equlibration run of about 10^6 steps. Every Monte Carlo step (time unit) consisted of the following attempts of motion: $n - 2$ two-bond kinks, $n - 3$ three-bond kinks and 2 chain ends motion. The simulations started at $T = 4$ and were continued to $T = 1$ with the step $\Delta T = 0.2$. The simulation runs for every model studied were repeated at least 20 times and all were independent.

RESULTS AND DISCUSSION

The simulations were carried out for chains consisting of $n = 60$ residues for the local potential $\varepsilon_{hel} = 0$, -4 and -8. In Fig. 1 we present changes of the mean square radius of gyration of the model chain $< S^2 >$ with the temperature T for different values of ε_{hel}. The size of the system decreases gradually and smoothly with the decrease of T. All three curves in Fig. 1 are s-shaped but for the non-zero local potential ($\varepsilon_{hel} < 0$) a plateau region is observed at low temperatures. The stronger the local potential the longer plateau range. One can also observe that the transition to the collapsed state shifts towards the higher temperatures. The location of the temperature T_c in which the coil-to-globule transition takes place can be estimated from the location of the peak in the heat capacity plot (Fig. 2). The temperatures T_c shift toward higher values with increasing of the local potential.

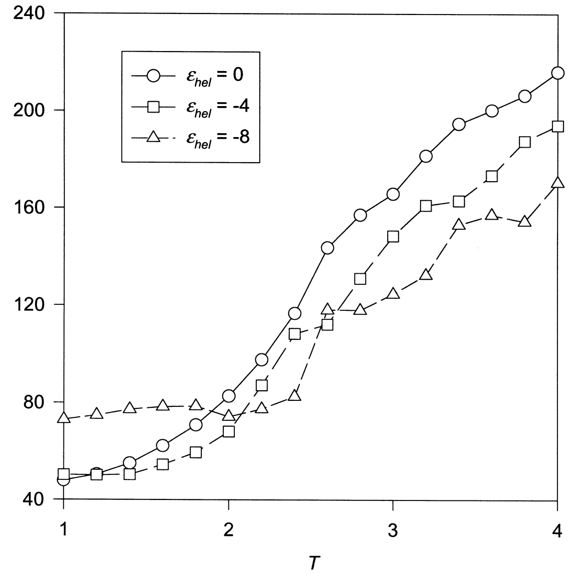

Figure 1. Mean radius of gyration $< S^2 >$ *versus* temperature *T* for different values of the local potential ε_{hel}.

The amount of secondary structure (helices) in the system can be expressed in terms of helicity, i.e. the percentage of residues forming helical structures. In Fig. 3 we present the helicity against temperature T for different values of ε_{hel}. In general the helicity grows with a decrease of temperature. For a chain with no helical potential the changes are rather small (from about 10% to about 20%). However, in the presence of the local potential, the changes become substantial: from 20% to 60% and from 30% to 80%, for $\varepsilon_{hel} = -4$ and -8, respectively. What is interesting, the steepest fragments of the curves are located well below the coil-to-globule transition temperature T_c. This suggests that after the collapsed globule is formed some kind of a rearrangement occurs where helical states are formed and hydrophobic contacts are broken. This rearrangement is caused by the fact that during the annealing of the system two concurrent processes take place — the forming a secondary structure and establishing of the binary contacts between the residues. An interesting consequence of this behavior can be observed in Fig. 3 for the strongest local potential ($\varepsilon_{hel} = -8$) where the helicity decreases at very low temperatures. The number of hydrophobic contacts increases while helices are broken into smaller pieces [8]. The representative structures of high-temperature and low temperature chains are given in Fig. 4. One can observe a relatively high number of helical states even at high temperatures for high local potential ($\varepsilon_{hel} = -8$). However, structure of the collapsed chain at low temperatures depends strongly on the value of local poten-

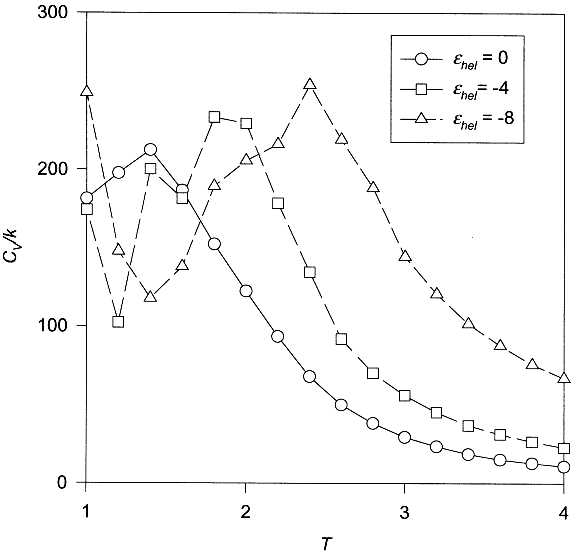

Figure 2. Heat capacity C_V/k *versus* temperature *T* for different values of the local potential ε_{hel}.

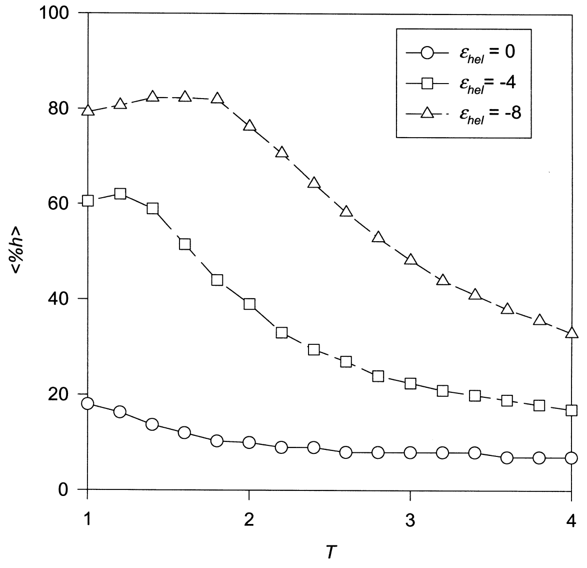

Figure 3. Mean helicity *versus* temperature *T* for different values of the local potential $\varepsilon_{\mathrm{hel}}$.

tial. For the case with no such potential the number of hydrophobic contacts increases significantly and a hydrophobic core is formed inside the collapsed chain. For strong local potential the chain conformation at low temperatures is rather open without a well-defined hydrophobic core but with long helical fragments.

In this work we also carried out simulations at a constant temperature in order to determine the dynamics properties of the polypeptide chains under considerations [7, 12]. In Fig. 5 we present the mean-square displacement of each residue g_i for different temperatures. At very high temperatures (T = 3.6) chain behave as a Rouse chain and the g_i function is parabolic (Fig. 5a). At low temperatures (T = 1.6) some fragments of the chain (ends and residues 38–49) exhibit greater mobility, all other residues move much slower and independently of their position along the chain (Fig. 5b). The residues, which move very slowly form apparently stable helical fragments and large number of contacts.

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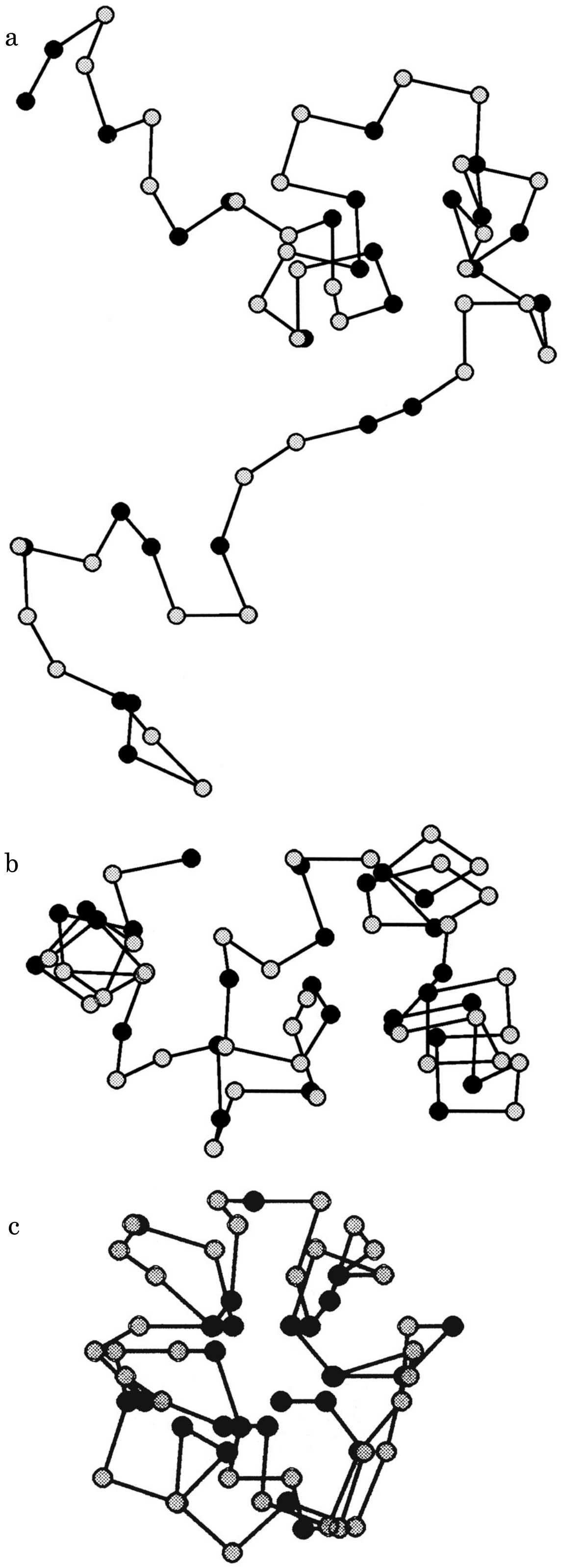

Figure 4. Snapshots of the chain configuration at the temperatures.

Black circles correspond to hydrophobic and gray circles to hydrophilic residues, respectively. The case of local potential ε_{hel} = –8 at T = 3.6 (a) and T = 1.6 (b), and ε_{hel} = 0 at T = 1.6 (c).

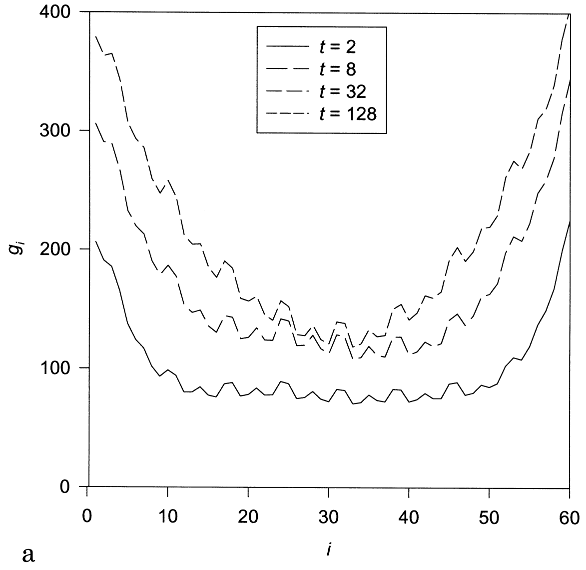

Figure 5a. Mean square displacement of the i^{th} residue of the chain at temperature $T = 3.6$.

The displacement was calculated for times shown in the inset.

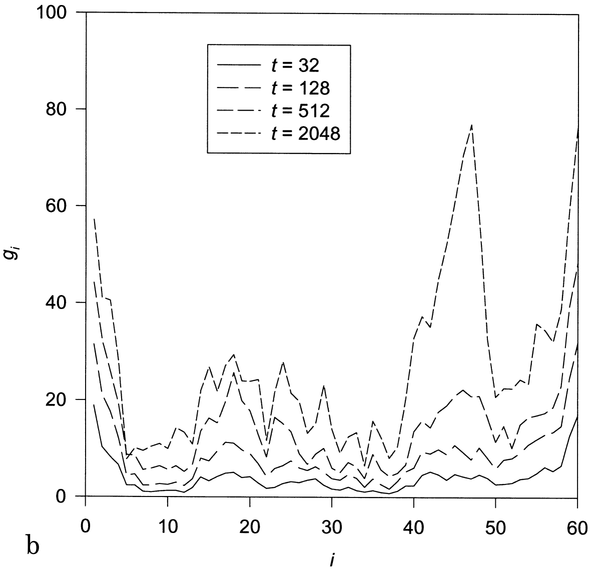

Figure 5b. Mean square displacement of the i^{th} residue of the chain at temperature $T = 1.6$.

The displacement was calculated for times shown in the inset.

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