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The Influence of Hydrogen Bonds on the Globular Structure of HP-copolymers

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Summary: We present the results of computer modeling of coil-globule transition of HP-copolymer which can form hydrogen bonds between some specific monomer units (hydrogen bond units). Langevin dynamics approach is used for the simulation of coil-globule transition. We study the influence of the number and distribution of hydrogen bond units along primary sequence on the formation of globular conformations.

Keywords: computer modeling, copolymers, hydrogen bonds, primary sequence

Introduction

The properties of homopolymer globule formed by saturating bonds were studied theoretically in the paper.[1] The purpose of this work is to carry out computer experiments which simulate the dynamics of copolymers with saturating (hydrogen) bonds in order to understand the influence of copolymer character of the chain on the formation of a globule induced by hydrogen bonds. It is well-known that hydrogen bonds play very important role in conformational properties of biopolymers,[2-3] and that they have the property of saturation. In our model only specific pairs of units (hydrogen bond units, HBU) can form a hydrogen bond. In the previous paper[4] we have studied HP-copolymers with hydrophobic (H) and hydrophilic (P) monomer units. In particular, we have considered the so-called protein-like conformations with hydrophobic monomer units in the core of the globule and hydrophilic units in the envelope of this core. Such protein-like copolymers have various interesting physical and

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chemical properties,[5-12] in particular, special primary sequence obeying the so-called Levy-flight statistics.[11] In this paper the main emphasis is the general problem of hydrogen bonds influence on the stability of copolymer globular conformations, rather than the discussion of specific features of coil-globule transition for different primary sequences.

The Model of Hydrogen Bonds in Computer Experiment

To simulate model copolymers, we use Langevin dynamics.[13] The generalization of our previous simulations[4] is connected with the introduction of intramolecular potential taking into account hydrogen bonds.

We consider model freely-jointed chain, with fixed bond lengths l, consisting of N monomer units of the mass m. Let us define the vector $\boldsymbol{r}_n$ as the position of n-th monomer unit in the space and introduce the notation N_α ($\alpha = \mathrm{H,P}$) for the number of monomer units of the type α in the chain ($N_H + N_P = N$).

We will use a modified form of Lennard-Jones potential slightly different from that applied in the previous paper[4]

$$u(r) = \begin{cases} \varepsilon_0[(r/\sigma)^{-12} - 2(r/\sigma)^{-6}] + \varepsilon_0 - \varepsilon, & r \in (0,\sigma], \\ \varepsilon[(r/\sigma)^{-12} - 2(r/\sigma)^{-6}] & r \in (\sigma,+\infty), \end{cases} \tag{1}$$

where

$$r = |\boldsymbol{r}_n - \boldsymbol{r}_k|, \quad |n-k| > 1 \tag{2}$$

The potential (1) includes three parameters (σ, the characteristic size, ε, attractive energy parameter and, ε_0, excluded volume energy parameter).

The additional factor included in the mathematical model is connected with hydrogen bonds (HB). In our model HB is constituted of only two monomer units. Monomer units capable of forming of HB are called *hydrogen bond units*, HBU. HBU can take part only in one HB (saturation effect).

Here HB potential has the form

$$u_H(r)=\begin{cases}\varepsilon_{0H}[x^{-12}-2x^{-6}]+\varepsilon_{0H}-\varepsilon_H, & x\in(0,1],\\ \varepsilon_H[\mu^{-2}(x-1)^2-1], & x\in(1,1+\mu^2(\mu+\lambda)^{-1}],\\ -\varepsilon_H\lambda^{-1}(2\mu+\lambda)^{-1}(x-1-\mu-\lambda)^2, & x\in(1+\mu^2(\mu+\lambda)^{-1},1+\mu+\lambda],\\ 0, & x\in(1+\mu+\lambda,+\infty),\end{cases} \qquad (3)$$

where

$$x=r/\sigma_H, \qquad r=|\mathbf{r}_n-\mathbf{r}_k|, \qquad |n-k|>1. \qquad (4)$$

The parameters σ_H, ε_H and ε_{0H} have the similar meaning to the parameters σ, ε and ε_0 in equation (1). Dimensionless parameters μ and λ define the shape of potential curve. Only some monomer units (HBU) can be involved in HB. If two HBUs form HB, they can not participate in other HB. When two free HBUs are nearer than critical distance, i.e. $r<(1+\lambda+\mu)\sigma_H$, they form one HB. On the contrary if the distance between two units participating in HB becomes more than critical one (i.e. $r>(1+\lambda+\mu)\sigma_H$), the HB is destroyed (HB potential vanishes).

We use protein-like HP-copolymer[4] as suitable model for copolymer sequence and we consider the case of uniformly distributed HBU in the primary sequence. We consider three kinds of HBU distributions along the primary sequence: (a) distribution related to protein-like sequence, (b) random distribution, and (c) periodical distribution.

Let us describe the algorithm of the arrangement of hydrogen bonds related to protein-like sequence (see Fig. 1). First, we form dense globular protein-like "parent" conformation. Then we choose some points belonging to the body of parent globule and encircle them by spheres of radius *R*. In order to avoid the ambiguity, we put these points in the nodes of hexagonal grid with distance *d* between neighbors. Finally, within each sphere of radius *R* inside the body of the globule we find nearest pairs of monomer units and consider them as HB participants (HBUs).

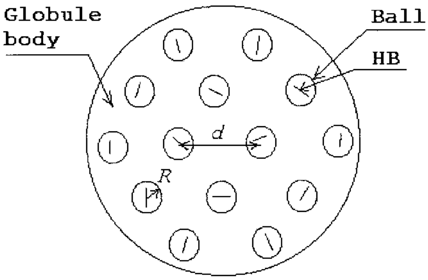

Fig. 1. The arrangement of hydrogen bonds related to protein-like sequence.

We obtain random arrangement of HBUs as a result of random choice of monomer units in the primary sequence.

In the case of periodical arrangement, the distance between two nearest HBUs along the chain is constant.

Freely-jointed chain has $2N+1$ degrees of freedom. Constraint dynamics of model polymer chain is described by the corresponding system of equations of motion.[14-17] Langevin forces are considered as linear combination of random noise and linear dissipation, taking into account heat action.[13] The numerical integration of equations of motion is carried out using the standard difference scheme.[18]

We use the same method of temperature estimation and the same cooling procedure as in our previous paper.[4]

The new way to estimate the temperature of coil-globule transition of HP-copolymer is proposed. Let us consider the finite chain of homopolymer. The temperature of coil-globule transition is usually defined as the inflection point of the dependence $R_g^2(T)$ of the square of gyration radius on temperature. This point corresponds to $\partial^2[R_g^2(T)]/\partial\tau^2=0$. From mathematical viewpoint the numerical differentiation is an ill-posed problem.[19] Thus we need higher accuracy of the values of $R_g^2(T)$ to estimate the temperature of coil-globule transition with necessary reliability. In order to achieve this level of accuracy we have to carry out longtime computations. When we consider copolymers the problem of evaluation becomes more complicated in comparison with homopolymers because different types of monomer units have their own temperature of coil-globule transition.

To overcome this difficulty, we use the dependence of the total energy $E(T)$

$$E(T) = < U_{LJ} > + < U_{HB} > + (2N-5)k_B T, \tag{5}$$

on temperature, where $< U_{LJ} >$ and $< U_{HB} >$ are time-averaged potential energies of van der Waals and hydrogen bonds interactions, respectively (the energy of covalent bonds between neighboring monomer units is excluded). The value of $(2N-5)$ in Eq. 5 is the number of internal degrees of freedom of freely-jointed chain. We consider $E(T)$ as an analogue of full mechanical energy. Negative values of full energy correspond to constrained motion of particles. Positive ones correspond to infinite motion. The curve $E(T)$ is characterized by monotonous growth. From mechanical viewpoint, the zero point of $E(T)$ is the boundary between constrained and infinite motion. We suppose that the zero point T_z of $E(T)$ is directly proportional to the temperature of coil-globule transition, T_{cg}, for a chain of the same length, *N*. In order to estimate the corresponding factor η_{cg}, we find the ratio T_{cg}/T_z for homopolymer and assume that $\eta_{cg} = T_{cg}/T_z$. Then we assume that the temperature of coil-globule transition of HP-copolymer can be obtained from the equation $T_{cg} = \eta_{cg} T_z$, where T_z is the zero point of $E(T)$ for HP-copolymer.

The purpose of our study is to understand how hydrogen bonds influence the structure of a globule. This question subdivides into the following items:

a) How does HBU arrangement in the primary sequence influence the protein-like structure (hydrophobic in the core, hydrophilic units in the envelope)?

b) How does the number of HBUs in the primary sequence influence the protein-like structure?

It is necessary to have a criterion for quantitative estimation of the quality of globular protein-like structure. We use the method of convex polyhedron described in our previous paper.[4] We consider time-averaged values of criterion function Λ[4] and study how they depend on temperature *T* at various arrangements and numbers of HBUs.

Results of Computer Simulations

In this study we assume that every monomer unit has unit mass ($m = 1$), and covalent bond between nearest neighbors has a fixed length ($l = 1$), while the number of monomer units in the chain is equal to $N = 256$.

Let us define other model parameters. The parameters of modified Lennard-Jones potential (1) are the following:

$$\varepsilon_0 = 1, \qquad \sigma = 1. \tag{6}$$

The energy parameters ε for HP-copolymer will be considered as a variable depending on the kind of interacting monomer units ($\varepsilon_{HH} = 2.0$, $\varepsilon_{PP} = 0.2$, $\varepsilon_{HP} = \sqrt{\varepsilon_{HH}\varepsilon_{PP}} = 0.6325$) The values of $\varepsilon_{\alpha\beta}$ $(\alpha, \beta = \mathrm{H}, \mathrm{P})$ correspond to optimum recovery of parent globule structure.[4] The primary sequence is protein-like. The parameters of HB potential have the following values:

$$\varepsilon_{0H} = 5, \qquad \varepsilon_H = 10, \qquad \sigma_H = 1, \qquad \lambda = 0.3, \qquad \mu = 0.2. \tag{7}$$

The parameters of HBU related to protein-like sequence (see Fig. 2) have the following values:

$$d = 2, \qquad R = 0.5. \tag{8}$$

As a first step, we define the coil-globule transition temperature for homopolymer chain composed of monomer units of H type ($\varepsilon = \varepsilon_{HH}$) without HB. Fig. 2 shows the temperature dependence of the mean square radius of gyration

$$R_g^2 = \frac{1}{N}\sum_{n=1}^{N} | \boldsymbol{r}_n - \boldsymbol{R}_c |^2, \tag{9}$$

where $\boldsymbol{R}_c$ is the center-of-mass position vector.

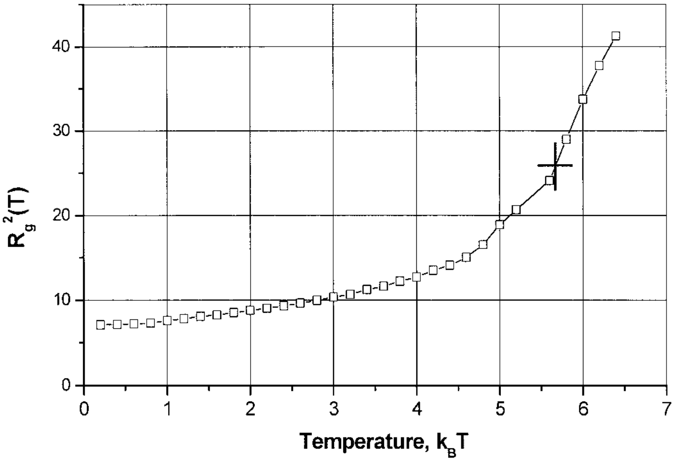

Fig. 2. The value of R_g^2 as a function of temperature for 256-unit homopolymer chain. The point of coil-globule transition is marked by the cross.

In Fig. 2, the inflection point corresponding to the temperature of coil-globule transition, T_{cg}, is marked by the cross ($\varepsilon = \varepsilon_{HH} = 2.0$). As we have mentioned above, it is more simple to find the zero point T_z of intramolecular energy (5) as a function of temperature T. Fig. 3 shows the dependence of intramolecular energy (per one degree of freedom) $e(T) = E(T)/(2N-5)$ on temperature T. Monotonous behavior of intramolecular energy gives unique root of the equation $e(T) = 0$.

We can see from Table 1 that the constancy of the factor $\eta_{cg} = T_{cg} / T_z$ for various types of polymer chains is observed with high accuracy (in the limits of confidence interval).

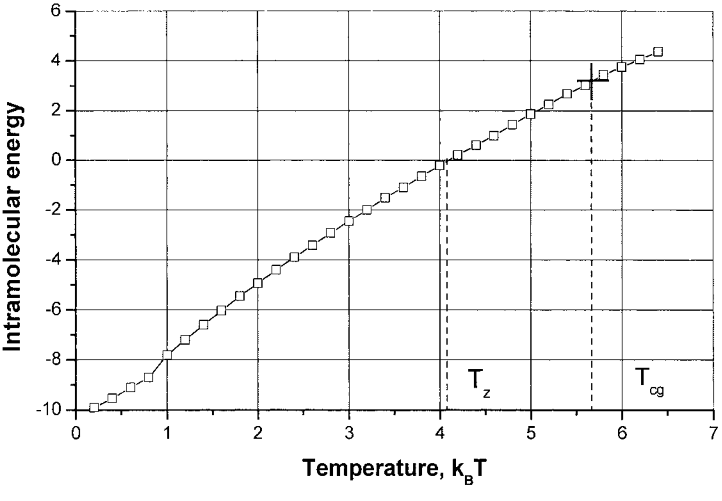

Fig. 3. The dependence of intramolecular energy $e(T) = E(T)/(2N-5)$ on temperature *T*. The temperature of coil-globule transition, T_{cg}, is marked by the cross (see also Fig. 2).

Table 1. The coefficient η_{cg} for different types of HP-copolymers ($N = 256$).

The type of HP-copolymer	η_{cg}	Error
Homopolymer	1.39	0.02
Protein-like HP-copolymer without HBU	1.38	0.02
Protein-like HP-copolymer with 20 HBU	1.37	0.03
Protein-like HP-copolymer with 256 HBU	1.44	0.05

In order to determine the temperature of coil-globule transition, T_{cg}, we define the factor $\eta_{cg} = T_{cg} / T_z$ and then use the equation

$$T_{cg} = \eta_{cg} T_z \qquad (10)$$

Thus, the equation (10) can be considered as a useful empiric rule.

The recovery of protein-like parent globular structure takes place within the temperature interval $[0, T_z]$. Monomer units of both types (H and P) are intermixed in the globule if the temperature $T > T_z$. We have found that the recovery of protein-like parent globular structure occurs in the presence of HB as well as in the absence of them. Let us first estimate the influence of an arrangement of HBU along the chain. We have considered three different distributions of 20 HBUs: (a) related to protein-like sequence, (b) random distribution, and (c) periodical distribution (see above). Three appropriate time-averaged curves of convex polyhedron criterion[4] $< \Lambda(T) >$ are shown in Fig. 4. As we can see, these three curves lie in the nearest vicinity to each other. Therefore the arrangement of HBUs along the chain have the secondary significance in comparison with the number of HBUs. Also, we can see another confirmation of the secondary significance of the arrangement of HBUs in the fact that the values of coil-globule transition temperature, $T_{cg} = 3.6 / k_B$, found for three types of arrangement (a)-(c) practically coincide.

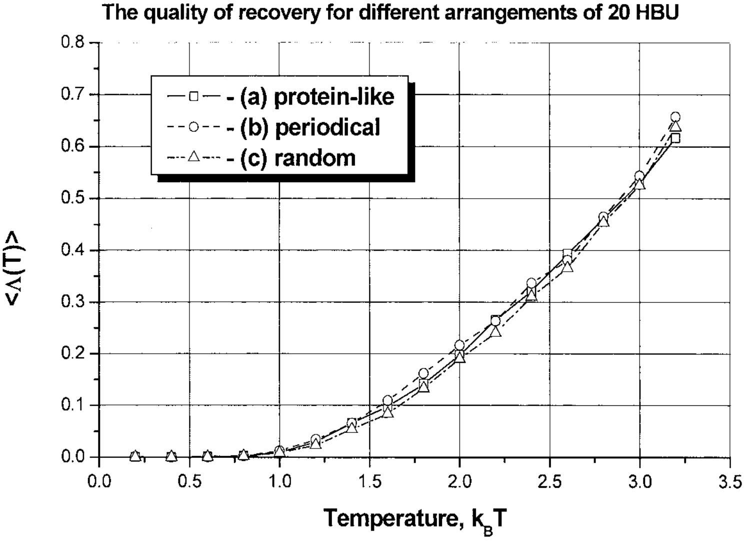

Fig. 4. Time-averaged convex polyhedron criterion $< \Lambda(T) >$ for the following arrangements of HBUs: (a) related to protein-like sequence, (b) random sequence, and (c) periodical sequence.

The conclusion that the HBU distribution has the secondary significance in the formation of parent globular structure allows us to consider only periodical HBU arrangement in the further investigation. It is interesting to study how the quality of the recovery depends on the number of HBU in the chain. The criterion functions $<\Lambda(T)>$ for different numbers of periodically arranged HBU in the chain are shown in Fig. 5.

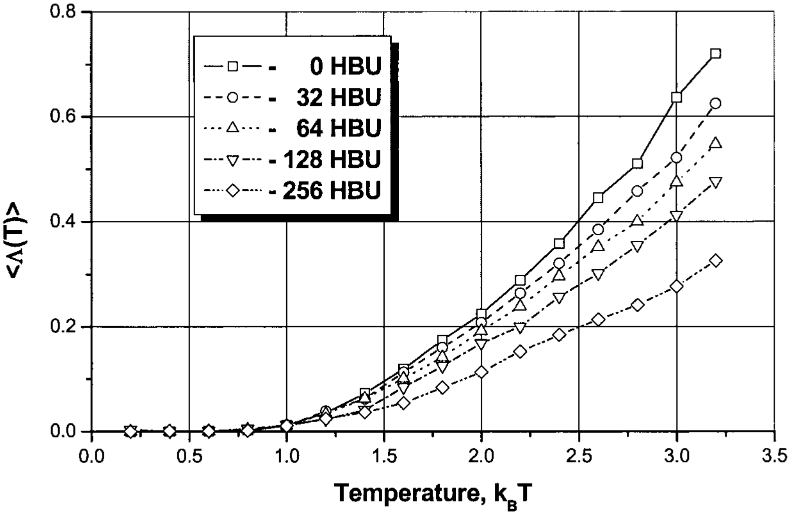

Fig. 5. Time-averaged criterion functions $<\Lambda(T)>$ for different numbers of periodically arranged HBU.

We have included minimum and maximum possible numbers of HBU, that is 0 and 256. The curves, corresponding to the numbers of HBU equal to 0 and 256, form the boundaries for the region in which other curves lay. The conclusion is evident: an increase in the number of HBU stabilizes protein-like parent globular structure.

It is interesting to consider the dependence of time-averaged quality of recovery on the number of HBU at a fixed temperature. The corresponding data are shown in Fig. 6 for three values of temperature *T*. These dependencies are monotonically decreasing functions. If the temperature is fixed, an increase in the number of HBU results in a decrease in the values of criterion function $<\Lambda(T)>$. In other words, the quality of recovery improves with increasing HBU.

We can see also that the dependence of the coil-globule transition temperature T_{cg} on the number of HBU is monotonically increasing and convex (see Fig. 7).

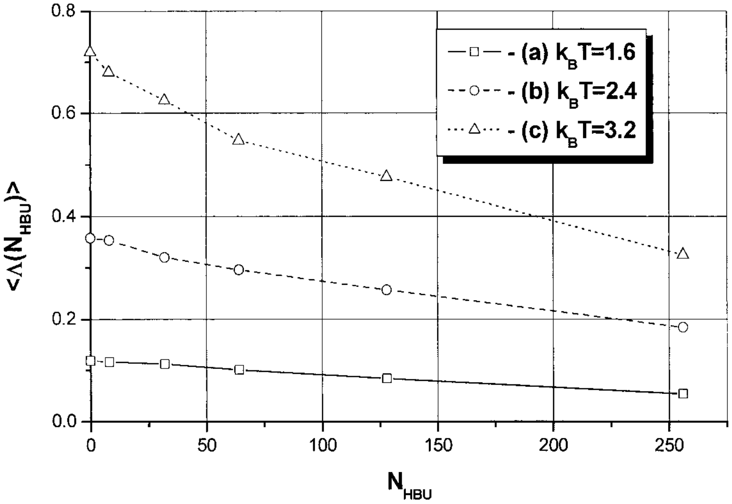

Fig. 6. The dependencies of time-averaged recovery quality $<\Lambda>$ on the number of HBU N_{HBU} for fixed temperatures T: (a) $T = 1.6/k_B$, (b) $T = 2.4/k_B$, and (c) $T = 3.2/k_B$.

It is also interesting to discuss the possibility of reconstruction of unique parent conformation. Our numerical experiments show that the parent globular conformation is never reproduced. To understand the role of HB in the possible conservation of unique parent conformation, the parent and recovered globular conformations were compared with the help of RMSD (root mean square distance)

$$RMSD = [\min_{W} \sum_{i=1}^{N} | \boldsymbol{W}(\boldsymbol{r}_i^{(2)} - \boldsymbol{R}_c^{(2)}) - \boldsymbol{r}_i^{(1)} + \boldsymbol{R}_c^{(1)} |^2]^{1/2}, \qquad (11)$$

where $\boldsymbol{W}$ is the matrix of rotations, $\boldsymbol{r}_i^{(k)}$ is the position of i-th monomer in the k-th chain ($k = 1,2$), and $\boldsymbol{R}_c^{(k)}$ denotes the center of mass of the k-th chain.

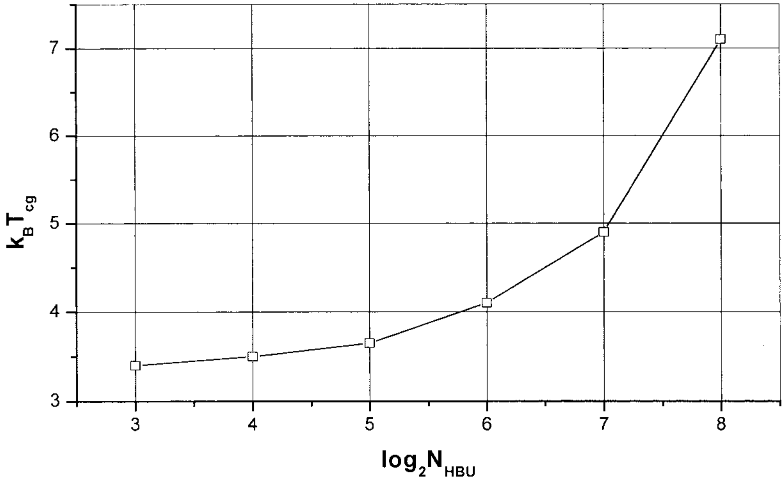

Fig. 7. The dependence of the temperature of coil-globule transition T_{cg} on the number of periodically arranged HBU N_{HBU}.

RMSD vanishes if two conformations of the same polymer chain coincide and it has the order of the size of the globule if they are different. In order to reveal how hydrogen bonds influence the process of reconstruction, we have considered three variants of HP-copolymer chain: (a) without HB, (b) with standard HB ($\varepsilon_H = 10$), and (c) with strong HB ($\varepsilon_H = 50$). In the cases (b) and (c), we used the HBU arrangement related to protein-like sequence.

The main feature of strong HBs is their inability to be destroyed in the temperature range $0 \le T \le T_{cg}^0 = 3.3 / k_B$, where $T_{cg}^0 = 3.3 / k_B$ is the temperature of coil-globule transition for HP-copolymer chain without HB. Standard HB may be destroyed within this temperature interval. We see that RMSD decreases as the intensity of HB increases. But the order of magnitude of RMSD is in all the cases of order of the globule size ($R_g \approx 2.6$). The conclusion is evident: HBs do not retain the information enabling the reconstruction of unique parent globular conformation.

Table 2. The RMS distances (in the units of σ from eq.(6)) between parent and recovered conformations for different types of HB.

The type of HP-copolymer	**Distance, σ**
With 20 strong HBU	2.45
With 20 standard HBU	3.13
Without HBU	3.51

Another point characterizing the uniqueness of the recovery of parent globule is the structure of HBs itself. We have carried out one hundred runs on "cooling" of protein-like HP-copolymer chain with 20 HBUs in order to discover the recovery of HBs related to protein-like sequence. It was found that the formation of HBs is completely random. The formation of HBs is more probable for nearest HBUs. An increase in distance between HBUs leads to a decrease in the probability of HB formation. We should stress that at the same time, the recovery of the parent globular structure takes place in all 100 cases with high quality (the values of criterion function are $\Lambda = 0$ in 95% of cases and $\Lambda < 10^{-3}$ in remaining 5% of cases for the temperature $T = 0.2/k_B$).

We can suppose that the distribution of monomer units in the globule and the structure of HBs are random, while the parent globular structure with H-units in the core and P-units on the surface is reproduced with high accuracy. This situation can be explained by the degeneracy of energetic levels corresponding to the conformations providing for parent protein-like globular structure. The degeneracy of energetic levels is the fundamental property of the chain consisting of monomer units interacting via central potential forces. For example, we can not distinguish right and left (mirror reflected) conformations from energetic point of view. We believe that only more complicated structure of monomer unit could enable the reconstruction of unique parent globular conformation.

We also consider the stability of HBs. Two main characteristics of the stability have been investigated: (a) average HB lifetime and (b) the number of breaks of HBs per time unit (i.e., the frequency of HB breaks). We have considered protein-like HP-copolymer with maximum number of HBUs ($N = 256$). HBs are stable for the temperatures in the range $0 < T \leq 1.0/k_B$ and the breaks of HBs are very rare. It is necessary to carry out the enormous volume of numerical calculations to get the statistical data on HBs in this temperature interval. We have performed appropriate computer experiments for the temperature $T = 3.1/k_B$. To determine relative average lifetime of HBs composed of two monomer units i and j ($|i-j|>1$), we used the ratio

$$\tau_{ij} = (\Delta t)^{-1} \sum_{n=1}^{L_{ij}} t_{ij}^{(n)}, \qquad (12)$$

where $t_{ij}^{(n)}$ is the lifetime of uninterrupted existence of a given HB before n-th break ($n = 1,\ldots, L_{ij}$) for time interval $\Delta t = 20000$ ($8 \cdot 10^6$ iterations).

In addition, we have determined the frequency of breaks of this HB

$$\nu_{ij} = (\Delta t)^{-1} L_{ij} \qquad (13)$$

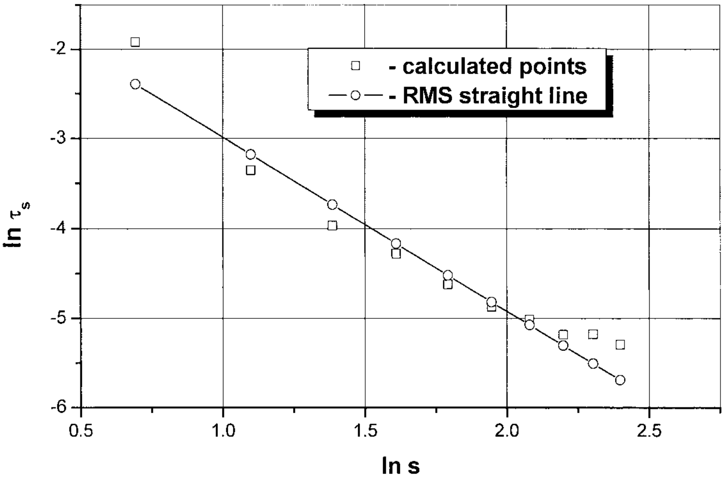

Fig. 8. The dependence of average relative lifetime of HBs τ_s and LSM straight line $\tau = a \ln s + b$ ($a = -1.93$, $b = -1.05$) on the logarithm of the chain distance s for maximum number of HBUs, $N_{HBU} = N = 256$.

As have been mentioned above, the formation of HB with given numbers i and j of monomer units is more or less random event. Therefore we need some parameter as an independent variable to describe statistical properties of relative lifetime and the frequency of HB breaks. To this end, we have chosen the distance $s=|i-j|$ between HBUs along the chain and defined average relative lifetime τ_s and average frequency of breaks ν_s

$$\tau_s = (N-s)^{-1} \sum_{|i-j|=s} \tau_{ij} , \qquad \nu_s = (N-s)^{-1} \sum_{|i-j|=s} \nu_{ij} , s = 2,\dots,N-1 . \tag{14}$$

These quantities are shown in Fig. 8 (τ_s) and Fig. 9 (ν_s) in double logarithmic scale as functions of chain distance s, at $s = 2,3,4,5$. Most of HB has the value of s in this region. Straight lines presented in Figs. 8 and 9 are calculated by LSM (least-squares method). We can suppose power laws for τ_s and ν_s and estimate the corresponding exponents (i.e., the parameter a in the equations $\tau = a\ln s + b$ and $\nu = a\ln s + b$). It is well known that the probability of the formation of loops in Gaussian chain scales as $\sim s^a$ with $a = -1.5$. The values of a found for the model under consideration are close to that observed for Gaussian chain. Weak distinctions can be explained by excluded volume effects.

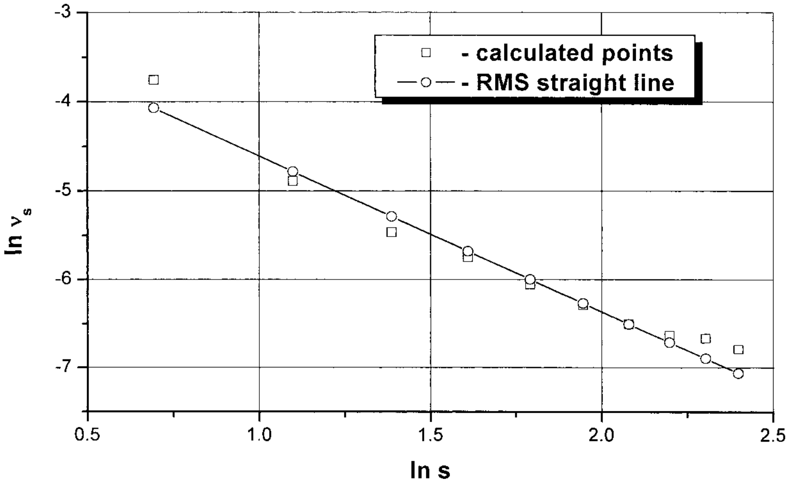

Fig. 9. The dependence of HB breaks frequency ν_s and LSM straight line $\nu = a\ln s + b$ ($a = -1.76$, $b = -2.85$) on the logarithm of the chain distance s for maximum number of HBUs, $N_{HBU} = N = 256$.

Conclusions

1) We proposed the model of HP-copolymer with hydrogen bonds (HB) for computer simulation of the formation of globular structure.

2) The new way for estimation of the temperature of coil-globule transition for HP-copolymers is proposed.

3) The primary structure of parent globule and the HB primary structure do not recover during slow "cooling"[4] of protein-like HP-copolymer.

4) HBs make protein-like globular structure more stable at higher temperatures. The more is the number of hydrogen bond units (HBUs) in the chain the more stable is the protein-like globular structure. The arrangement of HBUs along the chain has secondary significance.

5) The probability of the formation of HBs decreases with increasing the distance s between appropriate HBUs along the chain. We assume power dependence of this probability on s.

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