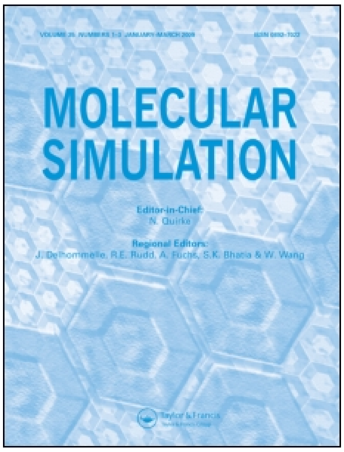

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Monte Carlo Simulation of the β-Sheet-Random Coil Transition of a Homopolypeptide. I. Equilibrium Study

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MONTE CARLO SIMULATION OF THE β-SHEET–RANDOM COIL TRANSITION OF A HOMOPOLYPEPTIDE. I. EQUILIBRIUM STUDY

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Monte Carlo simulation of the β-sheet – random coil conversion of a homopolypeptide chain was carried out on the basis of a model where successive two amino acid residues were assumed to change their states simultaneously and hence constituted a basic unit. Only three states were considered for each unit: extended, turn and coil. The conversion exhibited a transition between two states, random coil (C) and the β-sheet (B). In the transition region, two population maxima were always found, each corresponded to the local minimum of the free energy and there was an energy barrier between them. This behavior is characteristic of the all-or-none type transition. We have found that the nature of the first-order transition is retained in the case of a small system consisting of 100 units. The size of the cooperative unit was evaluated. According to the analytical theory of Kanô, a transition curve was obtained which was very close to the present one. This consistent result has suggested that equilibrium properties of the β-sheet-random coil transition are well evaluated with the mean field approximation. The matrix method of Mattice is also discussed.

KEY WORDS: β-sheet-random coil transition, β-sheet, equilibrium study, Monte Carlo simulation, homopolypeptide chain, first-order transition.

1 INTRODUCTION

β-sheets are one of the important secondary structures of polypeptides. In β-sheets interactions take place among residues that are from different strands and are distant in the primary structure or that are from different molecules, depending on whether the β-sheet is intra- or intermolecular [1]. An intramolecular β-sheet is not a completely regular structure because the segments of polypeptide chain connecting adjacent strands must adopt different conformations from that in the β-strands. In the case of homopolypeptides, it is not clear at all whether this chain reversal portions consist of short bends such as β-turn or of long random coils (interstrand loops). Experimental study on the intramolecular β-sheet using a homopolypeptide has been suffering from the aggregation of polypeptide chains. For the reason, little is known about the mechanism and the rate at which the β-sheet are formed [1,2].

Taking into account the difficulties encountered in the experimental approach to the problem, it is hoped that simulations on proper models provide useful information which facilitates our understanding the β-sheets. Because of shortage of experimental data, quantitative comparison of the result of the simulation with that from experiments is not attempted.

2 MODEL

We made several assumptions in constructing our model.

1. Adjacent polypeptide chains are in the antiparallel arrangement.
2. The chain reversal portion connecting two adjacent polypeptide chains consists of two residues. (β-turn)
3. To take into account the constraint of two-residue turn structure, we have chosen two residues as a fundamental structural unit of our model chain. A schematic representation of a chain is given in Figure 1.

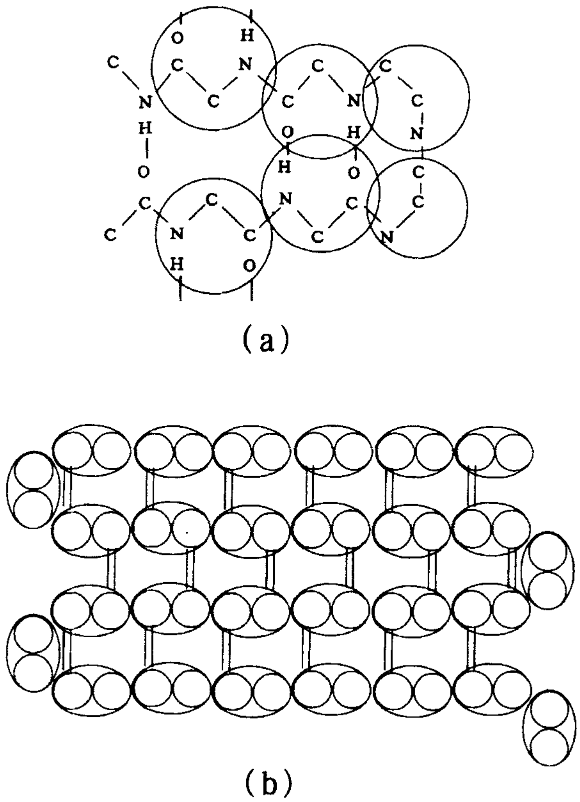


Figure 1 Schematic representation of the model chain consisting of *units*. Each unit represented with an ellipse in (b) consists of two residues represented with a circle in (a) and (b). Corresponding chemical structures is depicted in (a).

We consider three states that each residue can assume, random coil (c), β-conformation (s), and turn (t). Each state (i) is characterized with energy ε_i and area ω_i of the region in the two-dimensional conformational (dihedral angle) space. The free energy of one —CO··· HN— hydrogen bond is denoted as ε_h and corresponding enthalpy as h_h. Each unit has nine micro states corresponding to nine dyads of residues. We consider, however, only three states, coil (c), β(s), and turn(t) for a unit. Correspondence of the states between the residue and the unit is not unique. We have chosen tentatively the following correspondence. Out of nine dyads of the residue, the state tt corresponds to t state of a unit. Dyads st, ts, cs and sc are regarded as either s or c state of a unit with the probability of 1/2. Dyads ss and cc are taken as s and c of a unit, respectively. Energies and the areas of the region in the four dimensional conformation space for a unit (two rotation angles for each residue) are denoted as E_i and W_i, respectively. The unit in the interior of a β-sheet has two hydrogen bonds. According to this correspondence, parameters concerning unit are related to those of residues as follows.

$$\begin{aligned} W_t &= \omega_t^2 \\ W_s &= \omega_s^2 + \omega_s\omega_t + \omega_c\omega_s = \omega_s \\ W_c &= \omega_c^2 + \omega_s\omega_t + 2\omega_t\omega_c + \omega_c\omega_s \end{aligned} \tag{1}$$

$$\begin{aligned} E'_t &= 2\varepsilon_t \\ E'_s &= [2\varepsilon_s\omega_s^2 + (\varepsilon_s+\varepsilon_t)\omega_s\omega_t + (\varepsilon_c+\varepsilon_s)\omega_c\omega_s]/W_s \\ E'_c &= [2\varepsilon_c\omega_c^2 + (\varepsilon_s+\varepsilon_t)\omega_s\omega_t + 2(\varepsilon_t+\varepsilon_c)\omega_t\omega_c + (\varepsilon_c+\varepsilon_s)\omega_c\omega_s]/W_c \end{aligned} \tag{2}$$

Energies were measured from that of coil state of the unit.

$$E_i = E'_i - E'_c \tag{3}$$

All energies are expressed as dimensionless divided by an arbitrary constant ε_0 which was taken to be 0.6 kcal/mol. E_h represents the free energy of two hydrogen bonds

$$E_h = E'_h = 2\varepsilon_h \tag{4}$$

Most of the present simulation was carried out with the following values of parameters

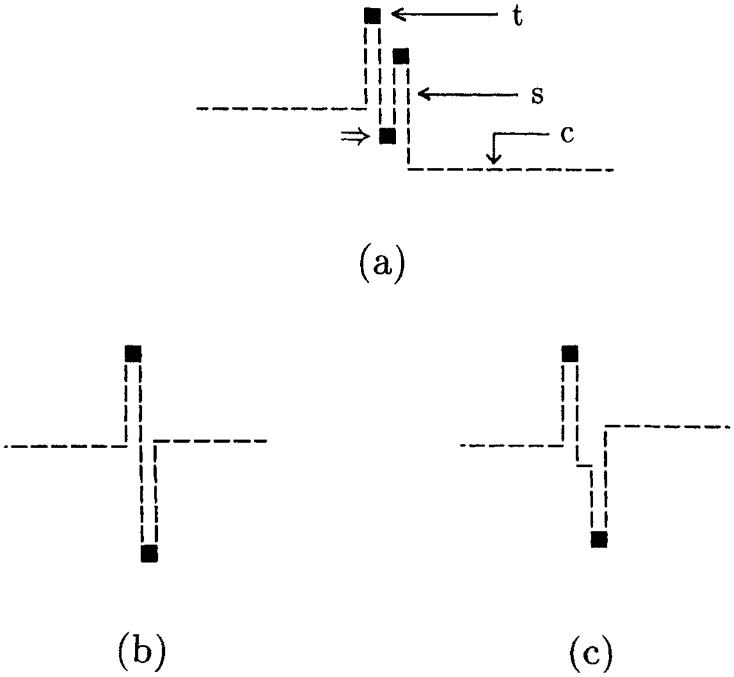
$$\begin{aligned} &E_c = 0, \quad E_t = -0.535, \quad E_s = -0.735, \quad E_h = -0.7, \\ &W_c = 0.809, \quad W_t = 0.033, \quad W_s = 0.158 \end{aligned} \tag{5}$$

In conformity with the reduced energies introduced above, the temperature T in the simulation is equivalent to RT_a/ε_0 where R is the Gas constant and T_a is the absolute temperature. Simulations with other sets of parameters were also carried out and qualitatively similar results were obtained.

Validity of assigned values for parameters concerning the residue is examined here. At first, we calculate the standard free energy difference per residue between the random coil and the β-sheet at a transition temperature described later, $\Delta\mu^*(\text{coil}\to\beta)$.

$$\begin{aligned}\Delta\mu^*(\text{coil}\to\beta) &= (\varepsilon_s+\varepsilon_h)\varepsilon_0 - RT_a\ln\frac{\omega_s}{\omega_c}\\ &= -0.20\ \text{kcal/mol} \qquad (6)\end{aligned}$$

Corresponding experimental values are -0.31 kcal/mol and -0.40 kcal/mol for poly (L-tyrosine) [3] and poly [S-carboxymethyl)-L-cysteine] (poly (Cys [CH_2COOH])) [4], respectively. As to the enthalpy change $\Delta H(\text{coil}\to\beta)$, we have $(\varepsilon_s+h_h)\varepsilon_0$. We expect h_h is more negative than ε_h(where $\varepsilon_h\varepsilon_0=-0.21$ kcal/mol), *i.e.*, $h_h\varepsilon_0=\varepsilon_h\varepsilon_0+\alpha$. Hence $\Delta H(\text{coil}\to\beta)=(-0.48-0.21+\alpha)$ kcal/mol $=(-0.69+\alpha)$ kcal/mol where α is negative. Experimental values are -1.3 kcal/mol and -1.5 kcal/mol for poly (L-tyrosine) [3] and poly (Cys [CH_2COOH]) [5], respectively. Comparison of these values between assigned and experimental values shows the validity of assigned values for parameters. As to the area in the conformational space, on the contrary, assigned values were rather arbitrary. In particular, values of ω_t was set to be a significantly large value. With small values of ω_t, we encountered difficulty to perform effective simulations: simulations showed few transitions between coil and β-sheet states. In Figure 2 we represent our model chain in a two-dimensional way. The units in c and s states are represented, respectively, with horizontal and vertical straight line segments. The units in t state are shown with



(a)

(b)

(c)

Figure 2 A two-dimensional way of representing the conformations of the model chain.

filled squares. Three examples of the conformational changes are also shown in Figure 2. The unit in t state, specified with an arrow in (a) will be in three states c, s, and t in the next step. When the unit takes s state, the corresponding conformation is shown in (b). When, on the other hand, it takes c state, then we have another conformation (c). The conversion between the two conformations (b) and (c) corresponds to a change between s and c state of unit.

3 SIMULATION

Our simulation procedure essentially follows that proposed by Metropolis *et al.* [6]. Consider our model polypeptide chain consisting of N units immersed in a bath of temperature T. In the present study N is taken as 100 in most cases. The conformation of the system was created as follows.

1. Set up i-th conformational state.
2. Choose a unit randomly at which the conformational change takes place.
3. Choose a type of conformational change of the unit.
4. Perform the conformational change. New conformation of the system is designated as j-th conformational state. The enthalpies of the i-th and j-th conformation of the system are denoted as H_i and H_j, respectively.
5. If $H_j \leqslant H_i$, this conformational change is accepted. In the case that $H_j > H_i$, the new state is accepted according to the probability, $\exp[-(H_j - H_i)/T]$. Temperature comes into the model through this probability. When these steps were completed, the time was increased by $\Delta t/N$. This process was repeated many times to ensure reasonable precision about observed properties [7, 8]. The average quantities and the time correlation functions were evaluated from the output data of sample at appropriate time intervals.

Observed quantities in the present simulations were coil fraction (θ_c), number of coil regions (n_c), number of turns (n_t), number of hydrogen bonds (n_h), enthalpy (H), radius of gyration (r_g) and end-to-end distance (r_e).

4 RESULTS

An example of temporal variation of the enthalpy H of the system is shown in Figure 3 at $T = 0.570$, which is characterized with two different states with an occasional transition between them. This kind of transition was rarely observed in the simulation due to the all-or-none nature of the transition. One of the states was characterized with low values of H ranging between about -120 to -100 while the other with less negative values of H ranging between about -70 to -40. Populations of various species characterized with a specified value of enthalpy H can be evaluated and are shown in Figure 4 for different temperatures. Populations with respect to any other property can be evaluated. Population distribution represented by $f(H)$ is bimodal over the entire transition temperature region. The system is well described in terms of the two-state model; one possesses high enthalpies and the other low enthalpies. No intermediate states are populated significantly. Changing

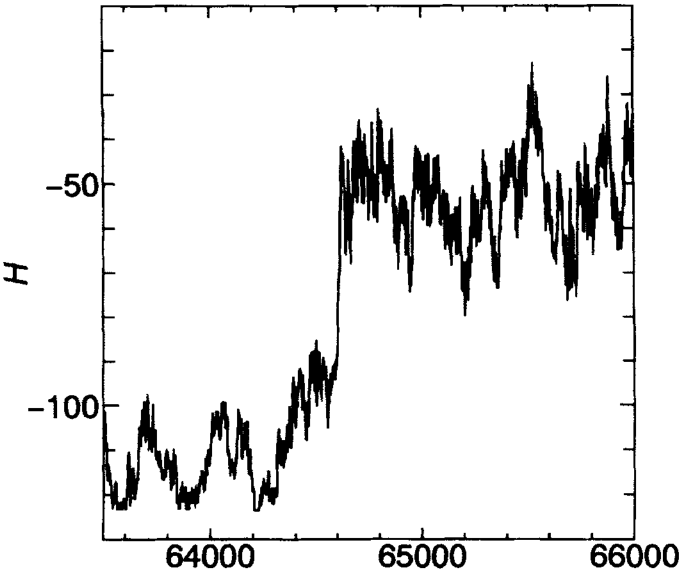


Figure 3 An example of temporal variation of the enthalpy *H* of the system at $T = 0.570$. Time *t* is given with the number of steps from a given initial state.

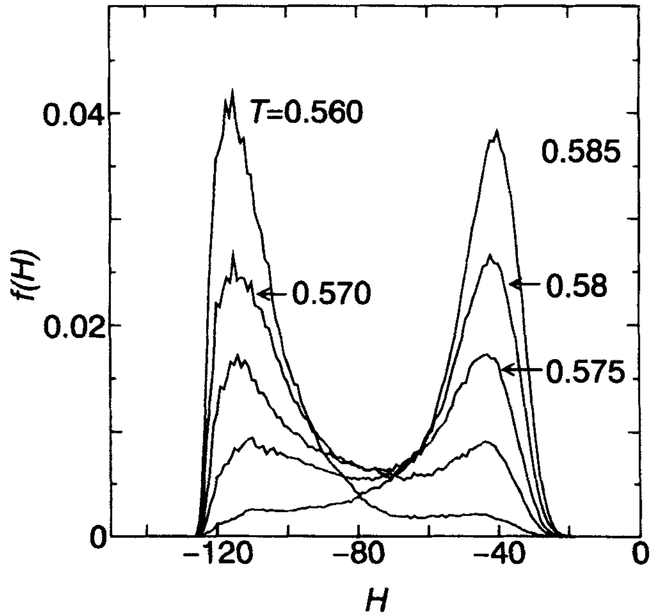


Figure 4 Relative populations $f(H)$ of various states characterized with the enthalpy *H*. Temperatures in the reduced unit are shown in the figure.

temperature causes a change of relative populations in the two states. Many other properties including θ_c, n_c and n_h exhibited the two-state behavior. On the other hand, those properties n_t, r_g and r_e did not show the behavior. As will be shown later, the two states correspond to random coil state (C) of high enthalpies and the β-sheet (B) of low enthalpies. The two-state character is one of the characteristics of the present system where interactions among units distant along the polypeptide chain are significant [9–12]. At the midpoint of the transition, fluctuation of the system is maximum. This is revealed by a sharp maximum of the specific heat shown in Figure 5, which was calculated according to the procedure proposed by Gō and Taketomi [13].

From the data shown in Figure 4, we calculated the average values of the enthalpy H for C and B state, H_c and H_B respectively, as well as for the entire system $\langle H \rangle$. In Figure 6 these three enthalpies are plotted against temperature T. By rough extrapolation, we could assign -35 and -120 to C-state at high T and to B-state at low T, respectively. The difference ΔH between the two states at a given T is rather constant in the transition region which is 70 ± 5 as evaluated from Figure 6. It is to be noted that although we take the coil state as a reference state of enthalpy ($E_c = 0$) in the level of *unit*, the average state assigned as the *random coil* (C) state for the whole polypeptide chain is characterized with negative enthalpies. Close inspection of conformations of *random coil* has revealed that one β-sheet of small size is found in most cases. The present result indicates that experimentally found values of ΔH don't necessarily represent the value expected for the difference between the complete β-sheet and the completely random coil state. In the present study *observed* ΔH

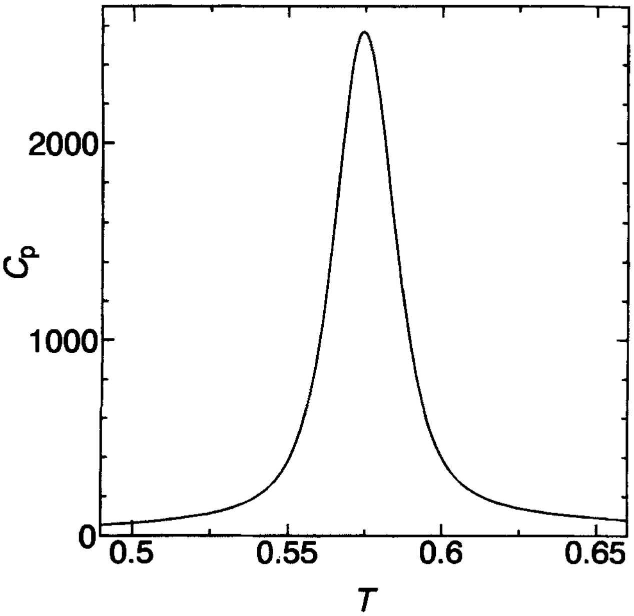


Figure 5 Specific heat C as a function of the temperature T. In the present simulation, C_p and C_v are identical.

value is about 70 while the expected value for the ideal case can be taken as 120: the expected value for the most stable B-state is suggested to be -120 from the result shown in Figure 4. The present result thus suggests a ratio of $70/120 = 0.6$ for the observed/ expected ratio. Although the Figure of 0.6 depends on the assigned values of the parameters of the model, it is certain that the ratio can be significantly smaller than unity. This indicates difficulty to assign reasonable values based on experimental values to parameters before carrying out simulations.

In Figure 6 the enthalpy of coil state H_C (T) or β-sheet $H_B(T)$ is shown in the temperature range where the other state is predominant. This implies that the two states, B and C, coexist over a significant range of T. This diffuse nature of the transition is believed to arise mainly from the *small system* nature of the present system. In the limit of large number of units, the system is predicted to exhibit the first order phase transition [9–11]. The branch represented with triangles corresponds to a supercooled C state in the limit $N \to \infty$. Similarly, the branch (open circles) to a superheated B state. In the limit $N \to \infty$, either of these metastable states can exist and transition exhibits a hysteresis. Even in the limit $N \to \infty$, the transition curve in Figure 6 would show some extent of diffuseness refrecting the fluctuation between B and C states.

From these three quantities shown in Figure 6 we can define a normalized order parameter $\xi_H(T)$ according to Equation (7).

$$\xi_H(T) \equiv \frac{H_C(T) - \langle H(T) \rangle}{H_C(T) - H_B(T)} \tag{7}$$

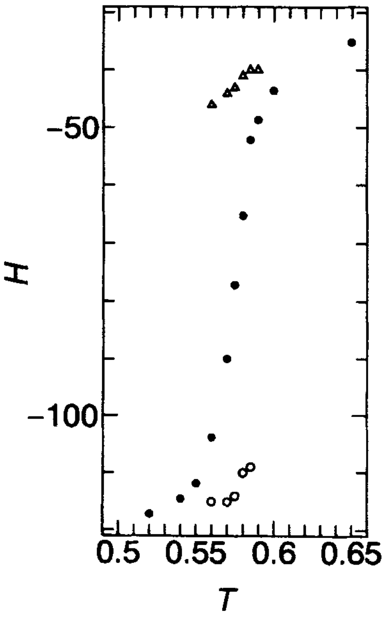


Figure 6 Temperature dependent conformational change. (●) The averaged enthalpy of the system, $\langle H \rangle$, (Δ) the enthalpy of the C-state, H_C, and (○) the enthalpy of the B-state, H_B.

Order parameters based on other properties exhibiting the two-state behavior were also calculated and they were essentially identical. In terms of ξ, the equilibrium constant K is defined as follows

$$K = \frac{1-\xi}{\xi} \tag{8}$$

which corresponds to an equilibrium

$$\mathrm{B} - \mathrm{state}(\beta - \mathrm{sheet}) \overset{K}{\rightleftharpoons} \mathrm{C} - \mathrm{state}(\mathrm{random\ coil}) \tag{9}$$

In Figure 7, values of ln K are plotted against T^{-1} with respect to the four properties θ_c, n_c n_h and H. Although the four constants from them scatter over a significant range, we regard them identical. From the slope of the straight line in Figure 7, we obtain van't Hoff enthalpy ΔH_{VH} and the corresponding entropy change ΔS^*.

$$\Delta H_{\mathrm{VH}} = -\frac{\partial \ln K}{\partial (1/T)} = 40.7 \tag{10}$$

$$\Delta S^* \equiv \frac{\Delta H_{\mathrm{VH}} - \Delta G^*}{T} = \frac{\Delta H_{\mathrm{VH}} + T \ln K}{T} = 71.0 \tag{11}$$

Transition temperature T_m is given as $T_m = \Delta H_{\mathrm{VH}}/\Delta S^* = 0.573$. According to the analytical theory [9] the transition temperature T_m for chains of infinite size (N is infinite) is 0.618 under given values of parameters, which is indicated in Figure 8.

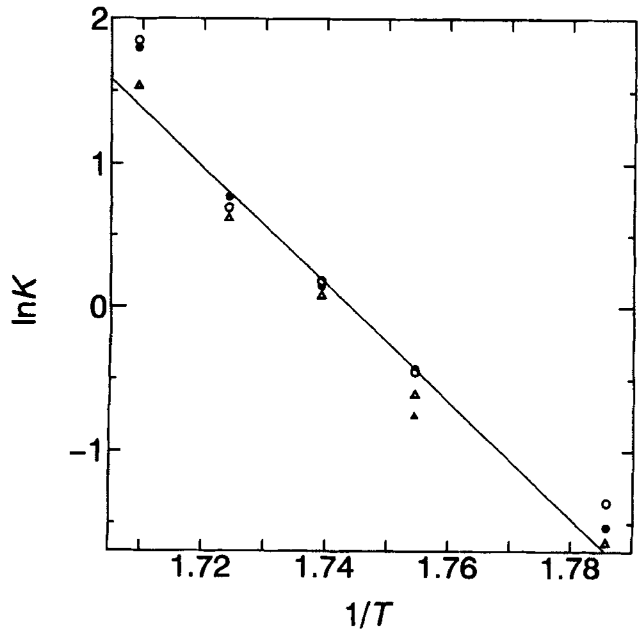


Figure 7 Van't Hoff plot. The equilibrium constants K were calculated according to Equation (8) in terms of the order parameters ξ obtained from four parameters: (●) θ_c, (○) n_c, (▲) n_h and (△) H.

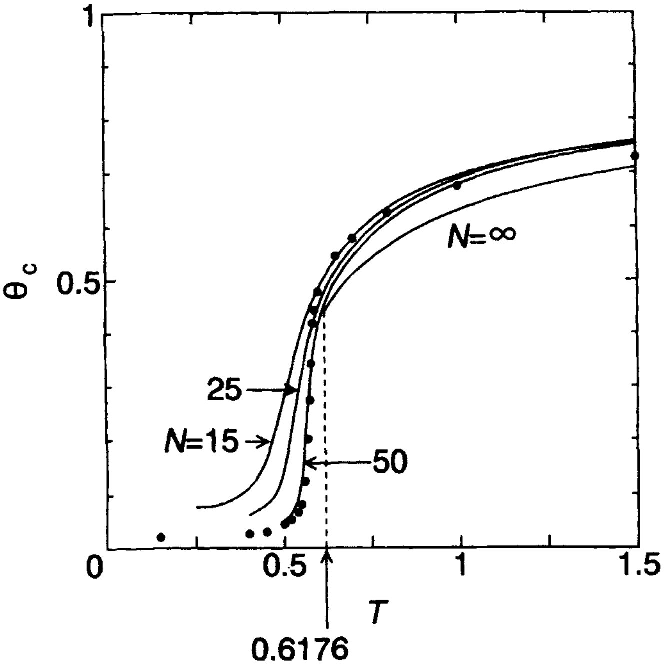


Figure 8 Comparison of the present result with those from the analytical theory of Kanô [9]. Solid lines: transition curves calculated according to Kanô theory for chains of different numbers of units N. $N = 15$, 25, 50 and ∞. The transition temperature for chains of infinite size is 0.6176. The results of the present simulation are shown with filled circles.

Since $\Delta H = 70$, the corresponding enthalpy change per unit amounts to 0.70. Number of the cooperative unit is thus estimated to be $\Delta H_{\mathrm{VH}}/0.70$, which is about 58. This is equivalent to 116 residues. In the present model, cooperativity is too much accentuated mainly from the following two reasons. One of them resides in the introduction of the unit instead of the residue: two successive residues have to change their state simultaneously. The other is that a folding pathway via various species with interstand loops is excluded in the present model (Assumption 2). Effect of interstrand loops was examined by Mattice [14]. When interstrand loops are allowed, the β-sheet content is enhanced in the early stage of the sheet formation but to complete the β-sheet becomes more difficult at the final stage. In this way, introduction of interstrand loops into the model makes the transition less cooperative. The cooperative unit of 58 should be taken as the maximum estimate.

5 DISCUSSION

Most theoretical study on the coil-β-sheet conversion including the present one has concluded that the conversion occurs as the first-order phase transition [9–11]. A possibility of the second-order transition was proposed under the condition that a fold or bend part was less stable than a residue in the peripheral strand of a β-sheet [9,10], although combinations of reasonable values of parameters did not lead to the case. On the other hand, the first-order transition has not been observed in the experimental study on the folding of homopolypeptides into the β-sheet. The coil-β-sheet conversion of several ionic polypeptides occurred essentially at a constant pH [15,16] which was manifestation of the first-order phase transition. However, this transition was found [16] to correspond to the formation of aggregates (intermolecular β-sheets) but not to the chain folding of single polypeptide chains. These aggregates behaved as they were forming a pseudo phase just like surfactant micelles. When polypeptide concentration was reduced the conversion did not take place at a constant pH any more [4,16].

Several theories are available to evaluate equilibrium properties of the random coil-β-sheet conversion of chains of finite lengths [9,11,12]. We have calculated the transition curves of chain consisting of different numbers of units according to the Kanô theory [9]. Parameters appearing in the theory are related to those in the present model as follows.

$$\begin{aligned} v &= /\varepsilon_s + \varepsilon_h - T\ln\frac{\omega_s}{\omega_c} = -1.15 + 1.43T \\ \rho &= \varepsilon_t - (\varepsilon_s + \varepsilon_h) - T\ln\frac{\omega_t}{\omega_s} = 0.75 - 0.14T \\ \eta &= -\varepsilon_h = 0.35 \end{aligned} \tag{12}$$

where v is the free energy of fully hydrogen-bonded residues and is taken as the reference state, and ρ and η are the free energies per residue of the bend region and two terminal strands, respectively. The results are compared with the result from the present simulation study in Figure 8. The transition becomes sharper as the number of units N increases. At a given temperature, the coil fraction θ_c is small for a large N. This suggests that the β-sheets of these short chain samples ($N = 50$) consist of the whole chain. This picture is consistent with the estimated cooperative unit of 58. It is interesting to note that the midpoint temperature $T_{1/2}$ does not coincide with the transition temperature T_m as N goes to infinity. The transition curve calculated by Kanô theory coincides with the present result approximately for the case of 50 units. This consistency suggests that β-sheet-random coil transition can be well described with the mean field theory as far as equilibrium properties are concerned. In Figure 9, probabilities $Q(s)$ for the β-sheet consisting of s units are given for a chain of $N = 50$ calculated according to Kanô theory [9,11]. Bimodal distributions of species are clearly seen at any temperature in the transition region.

We discuss next the result expected from the Mattice theory [12]. In Mattice's model a short bend consists of single unit and hence the basic unit of a polypeptide chain is identical to that in the present study: two amino acid residues in one unit. Also, interstrand loops are not allowed in both models. We evaluate the values of the parameters t, τ and δ appearing in the Mattice theory as follows.

$$t = \frac{W_s}{W_c}\exp\left(\frac{-(E_s + E_h) + E_c}{T}\right) = 0.20\exp\left(\frac{1.44}{T}\right) \tag{13}$$

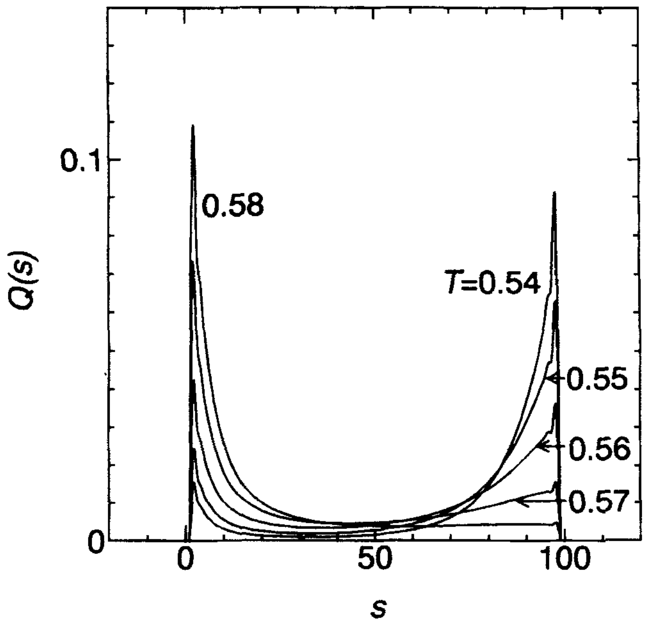


Figure 9 Bimodal distribution of various species for a chain of $N = 50$ in the transition region calculated according to the analytical theory [9,11].

Statistical weight for a unit in the strand located at the edge of a β-sheet is given as τt which in the present study is equal to $(W_s/W_c)\exp[(-E_s+E_c-E_h/2)/T]$. Hence

$$\tau = \exp\left(-\frac{E_h}{2T}\right) = \exp\left(-\frac{0.35}{T}\right) \tag{14}$$

Statistical weight for a bend is given as δt which corresponds to $(W_t/W_c)\ \exp[(-E_t+E_c)/T]$.

$$\delta = \frac{W_t}{W_s}\exp\left(\frac{-E_t+E_s+E_h}{T}\right) = 0.21\exp\left(-\frac{0.9}{T}\right) \tag{15}$$

In the present study, temperature range of interest is 0.54–0.60. In this temperature range, the values of the parameters are in the following range: $t(2.18-2.86)$, $\tau(0.56-0.52)$ and $\delta(0.05-0.04)$. As to other parameters in the Mattice theory $n = 100$, $I = n$ and $r = 1$ in the present study. According to the present result, the transition takes place at $t = 2.39$ and the width of the transition Δt is about 0.7. Examples of calculated results are given in ref. 12 for a variety of combinations of parameter values. A case with $\tau/\delta = 10$ (fifth case in ref. 12: $\delta = 0.1$, $\tau = r = 1$, $n = 300$) is found among them, which is best related to the present study ($\tau/\delta = 11-13$). It is interesting that this fifth case ($\tau/\delta = 10$) gave the least cooperative case among three cases: $\tau/\delta = 0.1$, 1 and 10. Transition widths Δt were about 0.4 for $\tau/\delta = 0.1$, about 2.0 for $\tau/\delta = 1$ and greater than 2.0 for $\tau/\delta = 10$. This peculiar behavior of the fifth case was ascribed to preferential occurrence of single strands (*rod*) because of difficulty to form bends connecting two *rods* [12]. The fifth case was declared as not producing β-sheets resembling those found in globular proteins [12]. It is interesting that in the present study, where t/δ is greater and chain length (100) is shorter than those in the fifth case, highly cooperative transition is observed. The origin of the inconsistency may reside in the values of τ. According to the 'phase diagram' of β-sheet, the condition $\delta \ll \tau < 1$ gives β-sheets while the condition $\tau \geqslant 1 \gg \delta$ gives straight rods (single β-strand) [2].

As found in the kinetic aspect of the present simulation given in the accompanying paper [17], the β-sheets at low temperatures are suggested to correspond to the conformations in the local free energy minima in the sense that each characterized with a given set of the locations of turns. Rearrangements including change of the locations of turns scarcely take place in the *time scale* of the present simulation. In the Kanô theory, on the other hand, properties in true equilibrium at infinite time are evaluated. It is unknown which situation prevails in the experiments. However, the difference does not show up in the equilibrium properties since the results from the two studies coincide with each other approximately.

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