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INTRAMOLECULAR α-HELIX–β-STRUCTURE–RANDOM COIL TRANSITION IN POLYPEPTIDES

I. EQUILIBRIUM CASE

Hiromitsu WAKANA, Takao SHIGAKI and Nobuhiko SAITÔ

Department of Applied Physics, School of Science and Engineering, Waseda University, Okubo, Tokyo 160, Japan

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The present paper is devoted to the study of the conformational transition of polypeptides which are capable of forming α-helix, β-structure and random coil conformations with the finite homogeneous chain model. The experimental results on the surfactant-induced conformational change of poly(L-lysine) can be well described by the present model assuming cooperative binding of the surfactant ions to the polypeptide side groups.

1. Introduction

In this series of papers, we study the conformational change of polypeptides which are capable of forming the α-helix, the β-structure and the random coil (or the unordered) conformations from equilibrium statistical mechanics and from a dynamic approach as well. The experimental studies of protein folding show that a local structure absent in a certain region of a protein appears sometimes in the intermediate stage of folding and disappears finally [1]. Actually there exist some regions in globular proteins where the prediction of the secondary structure reveals a similar possibility for α-helix and β-sheet [2]. Some homopolymers like poly(L-lysine) are known to exist as α-helix, β-sheet and random coil, and the conformational transition occurs among these three structural states as a result of change in the pH, temperature and concentration of the solvent.

Adonts et al. [3] have developed a general equilibrium theory of the intramolecular helix-folded structure (β-structure)–random coil transition in an infinitely long chain model. In this and the following papers, we study the equilibrium as well as dynamic properties of the helix–β-structure–random coil transition in a finite chain model.

Satake et al. [4] have constructed the conformational phase diagram of poly(L-lysine) for the surfactant concentration vs. the temperature from circular dichroism, indicating the regions of α-helix, β-structure and random coil. We will discuss their experimental results by our present model.

2. Model

We consider the conformational transition of polypeptides which can form two types of the secondary structures, i.e., α-helix and β-structure. Their stabilities may be different from one another and they have several influences on the conformational transition.

Consider a one-dimensional array of N sites. Each site is assumed to take one of three states, i.e., α-helix, β-structure in antiparallel pleated sheet and random coil. The two ordered regions of the

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α-helix and β-structure are assumed not to be in direct contact with each other, a random coil region being located between them. Consider a state of the polypeptide chain defined by specifying the state of each residue as being in the helical region, the β-structure region or the random coil (or the unordered) region. The statistical weights of three types of secondary structures are defined as follows.

The statistical weight [5] of the helical region consisting of m sites is

$$\begin{array}{ll} v & \text{for } m = 1. \\ v^2 w^{m-2} & \text{for } m \geqq 2. \end{array} \tag{1}$$

A site at the interior of an uninterrupted sequence of more than two helical states contributes a factor w. The factor v is contributed by a site at the end of an uninterrupted sequence of helical states and is less than unity representing the difficulty involved in nucleation of the helical region.

The statistical weight of the β-structure region consisting of m sites assigned by Kanô [6] is adopted in the following form

$$\alpha\mu^{\sqrt{m}}\lambda^m. \tag{2}$$

which is obtained by the following considerations. Fig. 1 is a schematic drawing of a typical antiparallel pleated sheet. It is composed of five β-strands (A–E). The two terminal strands (A and E) are assumed to have half the length of the other strands (B–D). Half of the peptide groups consisting of the A- and E-strands and half parts of the B- and D-strands and the peptide groups at the bends between strands do not have intramolecular hydrogen bonds but are rather immobile. For simplicity it is assumed that at equilibrium the β-structure has the conformation whose free energy contributed by these residues is minimum for the fixed number m of residues consisting of the β-structure region. The free energy of a β-structure is then given by

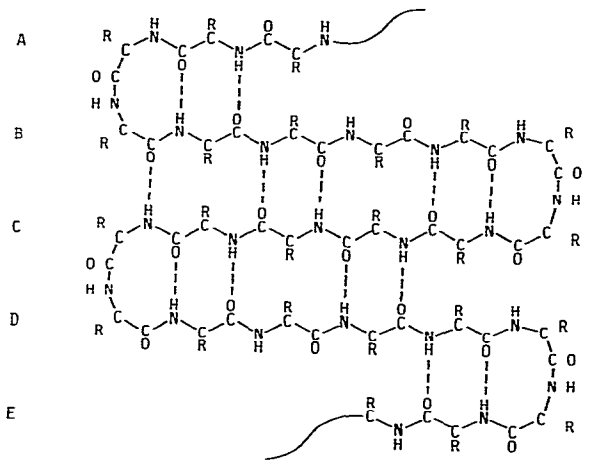

Fig. 1. Schematic drawing of a typical antiparallel β-sheet. It is composed of five β-strands (A–E).

$$F = n' \frac{m}{n+n'} \rho + n\eta + mv, \tag{3}$$

where ρ and $\eta/2$ are the free energies per residue of the bend region and two terminal strands, respectively. The free energy of fully hydrogen-bonded residues is assumed to be v/residue and is taken as the reference state. Then n and n' are the numbers of sites of an extended β-strand and the bending part between strands, respectively. If one site corresponds to one residue, two residues participate to form the bend conformation and have no hydrogen bond, i.e., $n' = 2$. The first term of F is the free energy contributed by the bend conformation, where $m/(n+n')$ is the number of the bends between strands. The second term comes from the end effect of a β-structure. From the condition of the minimum of the three energy:

$$\left(\frac{\partial F}{\partial n}\right)_m = 0. \tag{4}$$

We obtain $n = n^*$ which gives the minimum free energy F^*:

$$n^* = \sqrt{\frac{n'\rho m}{v}} - n'. \tag{5}$$

$$F^* = 2\sqrt{n'\rho\eta m} - n'\eta + mv. \tag{6}$$

The statistical weight becomes

$$\alpha\mu^{\sqrt{m}}\lambda^m, \tag{7}$$

where $\alpha = \exp(n'\eta/kT)$, $\mu = \exp(-2\sqrt{n'\rho\eta}/kT)$ and $\lambda = \exp(-v/kT)$. Here λ is the bulk term, and μ is concerned with the surface area and gives the system cooperativity. Eq. 7 is assumed to hold even for small m.

The statistical weight of a random coil region (or an unordered region) consisting of m sites is u^m, but we can take $u = 1$ without loss of generality. From these statistical weights of three states we can carry out calculations of the probability distributions and the average numbers of the ordered state.

The α-helix–β-structure–random coil transition in the case of the infinitely long chain limit can be treated by means of statistical mechanics. However, Adonts et al. [3] had already published details of the same kind of conformational transition. Thus, we describe the results obtained independently by us in Appendix A for the convenience of the present studies for short chains and partly because of the difference of the statistical weight for the β-structure which leads to a slightly different conclusion.

The conformational phase diagram obtained in this system is shown in fig. 2, where the first-order phase transition between the β-structure and the other two states is denoted by the dashed line, which is given by

$$w = \lambda - \frac{v^2}{\lambda^2 - \left(\sum_{m \geq 1} \alpha\mu^{\sqrt{m}} + 1\right)\lambda - v} \tag{8}$$

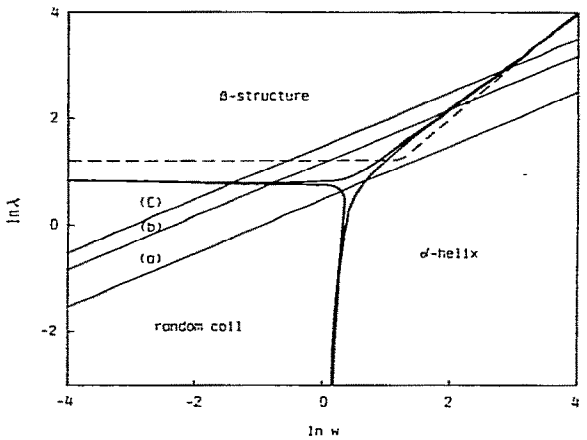

Fig. 2. Calculated conformational phase diagram of the present model in the cases of an infinitely long chain and a short chain ($N = 20$). All calculations are performed with $v = 0.1$, $\alpha = 1.5$ and $\mu = 0.05$. Straight lines represent eq. 29 with $n/m = 1/2$ and $(\ln K_\beta - (n/m)\ln K_\alpha)$: (a) 0.5, (b) 1.2, (c) 1.5.

The region above this line shows the phase in which all chains form completely β-structure. The full line shows the conformational phase diagram in the finite chain case (see below). The model studied by Adonts et al. [3] shows a first- and second-order phase transition between the β-structure and other states depending on the values of the parameters. In the present model the second-order phase transition cannot occur due to the different definition of the statistical weight of the β-structure.

In the case of the usually investigated helix–coil transition the first-order phase transition cannot occur even in the infinite system. The transition of such a system is not an all-or-none type transition. In the infinite case of the present model the occurrence of the first-order transition is caused by the long-range interaction in the β-structure, according to the analysis of Wako and Saitô [7]. We do not enter into any details about infinite lattice systems, but we will discuss the system of finite chain length by paying attention to the occurrence of the near all-or-none type transition in the finite system.

3. The finite chain system

We develop here a finite chain model suitable for computer formulation. The probability distribution of the ordered states in a chain consisting of N sites can be obtained by a recurrence formula. We take the numbers of sites in each ordered state, i.e., the α-helix and the β-structure, as macrovariables. Thus, let $P_N(j, m_\alpha, m_\beta)$ be the unnormalized probability distribution, used in the expression of the partition function, corresponding to the state consisting of m_α α-helical sites and m_β β-structure sites in the region from the jth to the Nth site. $P_N(j, m_\alpha, m_\beta)$ is described by $P_N(i, m'_\alpha, m'_\beta)$ for $i > j$, $m_\alpha \geqq m'_\alpha$ and $m\beta \geqq m'_\beta$ in the following recurrence formula:

$$P_N(j, m_\alpha, m_\beta) = \theta(m_\alpha) \sum_{k=1}^{m_\alpha} f_\alpha(j, j+k-1) f_c(j+k)$$

$$\times P_N(j+k+1, m_\alpha - k, m_\beta) + \theta(m_\beta) \sum_{k=1}^{m_\beta} f_\beta(j, j+k-1)$$

$$f_c(j+k)P_N(j+k+1,m_\alpha,m_\beta-k) + f_c(j)P_N(j+1,m_\alpha,m_\beta). \quad (9)$$

where $\theta(m)=0$ for $m=0$ and $\theta(m)=1$ for $m \geqq 1$, $f_\alpha(i,j)$ and $f_\beta(i,j)$ are the statistical weights when the region from the ith to the jth site forms the α-helix and the β-structure, respectively, and $f_c(j)$ is the statistical weight of the random coil state at the jth site. Here we put $P_N(j,0,0)=1$ for $N+1 \leqq j \leqq N+2$ and $f_c(N+1)=1$. Thus, we can carry out calculations of the probability distribution also in the case of the heterogeneous chain through the definitions of the statistical weight functions f_α, f_β and f_c. Consistency conditions exist which come from the restriction between the number of sites from the jth to the Nth and the sum of m_α and m_β:

$$(1)\ N-j \geqq m_\alpha+m_\beta \quad \text{for } m_\alpha \neq 0 \text{ and } m_\beta \neq 0, \quad (10)$$

$$(2)\ N-j+1 \geqq m_\alpha+m_\beta \quad \text{for } m_\alpha=0 \text{ and } m_\beta \neq 0, \text{ or } m_\alpha \neq 0 \text{ and } m_\beta=0. \quad (11)$$

Further, we have for $m_\alpha=m_\beta=0$,

$$P_N(j,0,0)=\prod_{k=j}^{N} f_c(k), \quad \text{for } 1 \leqq j \leqq N. \quad (12)$$

Condition 1 comes from the assumption that the ordered segments are not in direct contact with each other, a random coil region being located between them. We assume that the 1st and Nth sites are able to be in the α-helix, the β-structure or the random coil states. For given j of $P_N(j, m_\alpha, m_\beta)$, the set M_j of (m_α, m_β) is defined by the consistency conditions 1 and 2 and includes (0, 0).

Next, we define the probability distribution $P'_N(j, m_\alpha, m_\beta)$ with m_α helical sites and m_β β-structure sites between the 1st and jth sites. P'_N can be calculated easily from P_N by reversing the sequence, carrying out the calculation of $P_N(j, m_\alpha, m_\beta)$ and regarding $P_N(N+1-j, m_\alpha, m_\beta)$ as $P'_N(j, m_\alpha, m_\beta)$. The partition function $P_F(j, N)$ from the jth to the Nth site is defined as follows:

$$P_F(j,N)=\sum_{(m_\alpha,m_\beta)\in M_j} P_N(j,m_\alpha,m_\beta). \quad (13)$$

The partition function $P_R(1, j)$ from the 1st to the jth site is

$$P_R(1,j)=\sum_{(m_\alpha,m_\beta)\in M'_j} P'_N(j,m_\alpha,m_\beta), \quad (14)$$

where M'_j is the set M_{N+1-j} determined by the consistency condition for the reversed sequence mentioned above. Therefore, the partition function Z_N for all sites of this system is defined by,

$$Z_N=P_F(1,N)=P_R(1,N). \quad (15)$$

Some useful quantities can be obtained from these distribution functions and partition functions. The densities ϵ_α, ρ_β and ϵ_c of the α-helix, the β-structure and the random coil are given, respectively, by

$$\rho_\alpha=\sum_{(m_\alpha,m_\beta)\in M_1} m_\alpha P_N(1,m_\alpha,m_\beta)/Z_N \cdot N, \quad (16)$$

$$\rho_\beta=\sum_{(m_\alpha,m_\beta)\in M_1} m_\beta P_N(1,m_\alpha,m_\beta)/Z_N \cdot N, \quad (17)$$

$$\rho_c=1-\rho_\alpha-\rho_\beta. \quad (18)$$

The probability $P_j^\alpha(i)$ ($P_j^\beta(i)$) that the ith site is in a j-island α-helix (β-structure) is given as follows, where a j-island means the sequence of j consecutive ordered sites. Since several quantities of each ordered state, i.e., the α-helix and the β-structure, are defined by the same formulae, we use the symbol γ and use term γ-structure instead of distinguishing between the α-helix and the β-structure. Now we find,

$$P_j^\gamma(i)=\frac{1}{Z_N}\sum_{k=\max(i-j+1,1)}^{\min(i,N-j+1)} P_R(1,k-2)f_c(R-1) \times f_\gamma(k,k+j-1)f_c(k+j)P_F(k+j+1,N), \quad (19)$$

where $P_R(1,-1)=1$, $P_F(N+2, N)=1$, $f_c(0)=1$ and $f_c(N+1)=1$ are defined. The probability $P^\gamma(i)$ ($\gamma=\alpha$ or β) that the ith site is in the γ-structure is given by

$$P^\gamma(i)=\sum_{j=1}^{N} P_j^\gamma(i). \quad (20)$$

The average number $\bar{n}_j^\gamma$ of j-islands of γ-structure is given by

$$\bar{n}_j^\gamma=\frac{1}{Z_N}\sum_{k=1}^{N-j+1} P_R(1,k-2)f_c(k-1)f_\gamma(k,k+j-1) \times f_c(k+j)P_F(k+j+1,N). \quad (21)$$

The average number m^γ of islands, the probability f_j^γ that an island is a j-island of γ-structure, and the probability P_i^γ that a γ-structure site is in a

j-island are given, respectively, by

$$m^{\gamma} = \sum_{j=1}^{N} \bar{n}_j^{\gamma}, f_j^{\gamma} = \frac{\bar{n}_j^{\gamma}}{m^{\gamma}},$$

and

$$P_j^{\gamma} = \frac{jf_j^{\gamma}}{\Sigma jf_j^{\gamma}}. \tag{22}$$

In the case where the macrovariables are defined by the number of sites, i.e., m_α and m_β, and the number of islands, i.e., k_α and k_β, of α-helix and β-structure, respectively, the probability distribution $P_N(m_\alpha, m_\beta, k_\alpha, k_\beta)$ can be calculated as described in Appendix B.

4. Characters of this system

Now we consider the statistical mechanical properties of this system. In the present paper we restrict ourselves to the case of the homogeneous sequence, although we can treat also the heterogeneous case with the same formulation. Fig. 3 shows the β-structure–coil transition in the absence of α-helical structures in order to study the property of the statistical weight of the β-structure defined above. As shown in fig. 3, the transition property is rather insensitive to the values of the parameter α. We see also that the smaller the value of the parameter μ becomes, the sharper is the transition.

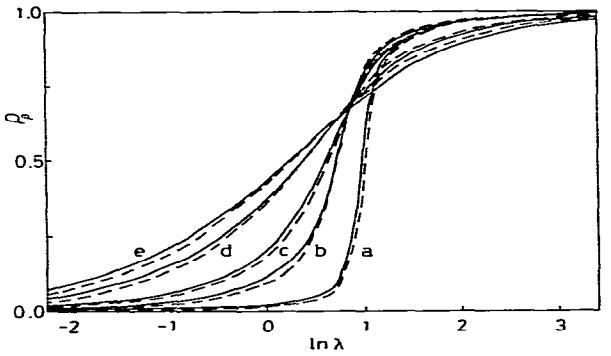

Fig. 3. Density of β-structure sites vs. λ in the case of the β-structure–random coil transition with $N = 20$: (a) $\mu = 0.01$, (b) $\mu = 0.05$, (c) $\mu = 0.1$, (d) $\mu = 0.3$, (e) $\mu = 0.5$; solid lines, $\alpha = 1.5$; dashed lines, $\alpha = 1.2$.

In this respect, the parameter μ has a similar property to parameter v in the helix–coil transition. Wako and Saitô [7] carried out the calculation of the probability P_j, defined in section 3, in order to see whether the transition of the system is an all-or-none type. In figs. 4 and 5 the probabilities P_j for the system of the helix–coil transition and the β-structure–coil transition are shown for several values of parameters w, μ and λ, respectively. The systems of the helix–coil transition and the β-structure–coil transition imply the systems in the absence of the β-structure state and the helical state, respectively. We can see that the P_j exhibit two peaks having different properties. In the helix–coil transition one of the two peaks moves gradually through the transition (a → b → c) and the other stays unmoved, showing the difficulty of the initial nucleation. On the other hand, in the β-structure–coil transition the two peaks scarcely move. This implies that one is thermodynamically stable while the other is metastable, and that through the transition the stable one becomes unstable and vice versa. This indicates that the

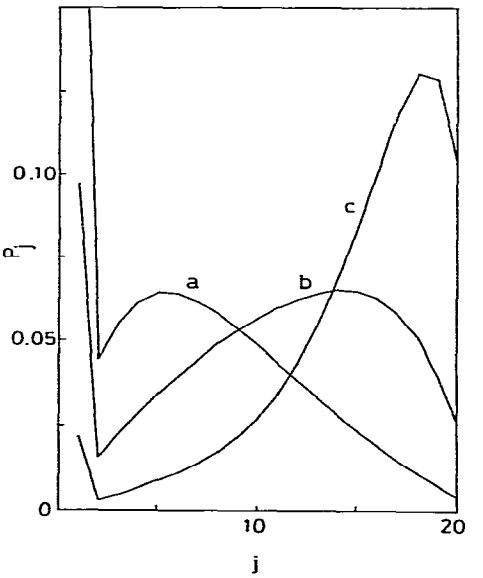

Fig. 4. Probability P_j in the helix–coil transition, calculated with $N = 20$ and $v = 0.1$: (a) $w = 1.0$, $\rho_\alpha = 0.23$; (b) $w = 1.2$, $\rho_\alpha = 0.43$; (c) $w = 1.5$, $\rho_\alpha = 0.74$.

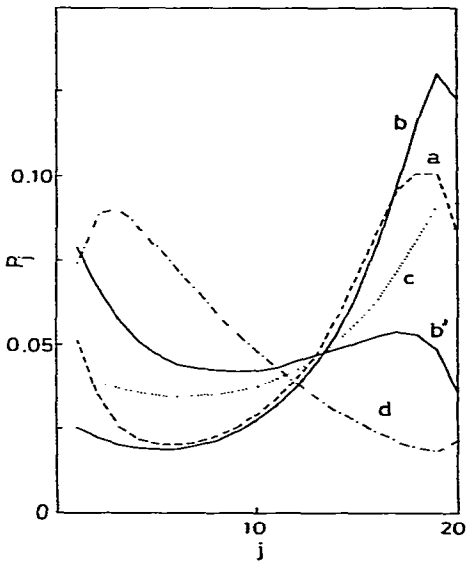

Fig. 5. Probability P_j in the β-structure–coil transition: $\alpha = 1.2$ and $N = 20$. (a) $\mu = 0.01$, $\lambda = 2.5$; (b) $\mu = 0.05$, $\lambda = 2.5$; (b') $\mu = 0.05$, $\lambda = 2.0$; (c) $\mu = 0.1$, $\lambda = 2.5$; (d) $\mu = 0.3$, $\lambda = 2.5$.

β-structure–coil transition has a typical all-or-none transition character.

5. Application of the present model to the surfactant-induced conformational transition

Through the experimental studies of optical rotatory dispersion and circular dichroism, poly(L-lysine) is known to exist as α-helix, β-sheet and random coil.

Satake et al. [4] have constructed the conformational phase diagram of poly(L-lysine) in aqueous 1-octanesulfonate solution from circular dichroism measurements at various temperatures and surfactant concentrations. They have detected the stepwise conformational changes from the random coil to the β-form and from the β-form to the helical structure with increase in surfactant concentration. They have suggested that the surfactant ions are bound electrostatically to the polypeptide side groups with opposite charges, and then the hydrophobic interaction between the bound surfactant ions plays a predominant role in the conformational changes. Moreover, they have adopted the Zimm-Bragg theory for the helix–coil transition to interpret the titration curves of poly(L-lysine) and poly(L-ornithine) in sodium dodecyl sulfate solution which undergo a coil-to-helix and coil-to-β transition, respectively [8].

Now we will apply the present model to the surfactant-induced conformational change of polypeptides using a similar consideration to that of the cooperative binding model by Satake et al. [8]. That is, we assume that the conformational changes are caused by the binding of surfactant ions onto the polypeptide side chains and by the formation of a micelle-like clustering of surfactant ions, and that the hydrophobic interaction between the bound surfactants gives rise to the cooperativity. Moreover, it is assumed that the surfactant ions are bound to the polypeptide in a different way between the β-structure and the helical structure. The differences in cooperativity caused by the surfactant are brought into consideration in the present model. To examine the effects of the surfactant on parameters λ and w, we consider the following association equilibrium between the surfactant ions and polypeptides:

$$\ldots caacc \ldots + mR^- \overset{K_a}{\rightleftarrows} \ldots caaac \ldots . \tag{23}$$

where K_a is the binding equilibrium constant of m surfactant molecules to a site which follows an α-helical island, R^- is the free surfactant molecule, a represents the site of a helix, and c is the site of a random coil. That is, it is assumed that the coil-to-helix transition of one site is caused by the electrostatic binding of one surfactant ion to the side group of an amino acid residue and clustering of $(m-1)$ surfactants by the hydrophobic interaction. From this scheme, w in the present model can be written as,

$$w = \frac{[caaac]}{[caacc]} = K_a[R^-]^m. \tag{24}$$

Then we have

$$\ln w = m\,23n[R^-] + \ln K_a. \tag{25}$$

where $[R^-]$ represents the concentration of free surfactant molecules.

Similarly, for the β-structure a similar association equilibrium holds,

$$\ldots c\beta\ldots\beta cc\ldots + nR^- \overset{K_\beta}{\rightleftharpoons} \ldots c\beta\ldots\beta\beta c\ldots, \quad (26)$$

where K_β is the binding constant of the surfactant to a site next to a β-structural island without rearrangement of the β-structure into a new one of free energy minimum. To investigate the relation between ln w and ln λ, we define λ as follows:

$$K_\beta[R^-]^n = \frac{[c\beta\ldots\beta\beta c]}{[c\beta\ldots\beta cc]} = \lambda. \quad (27)$$

$$\ln\lambda = n\ln[R^-] + \ln K_\beta. \quad (28)$$

From eqns. 25 and 28, we have

$$\ln\lambda = \frac{n}{m}\ln w + \left(\ln K_\beta - \frac{n}{m}\ln K_\alpha\right). \quad (29)$$

Yang et al. [9,10] proposed the following approach to determine the α-helix, β-sheet and unordered form in globular proteins in solution by circular dichroism data and optical rotatory dispersion data. They assumed additivity of the contributions from individual forms, and the following relation holds.

$$[\theta]_\lambda = \rho_\alpha[\theta_\alpha]_\lambda + \rho_\beta[\theta_\beta]_\lambda + \rho_c[\theta_c]_\lambda. \quad (30)$$

where the ρ values represent the fractions of the α-helix, β-sheet and unordered form, and the θ-values, the corresponding ellipticities. Tentatively, we put $[\theta_\alpha]_{222} = -29100$. $[\theta_\beta]_{222} = -6700$ and $[\theta_c]_{222} = +3400$ (deg cm^2 dmol^{-1}) which we read from the circular dichroism data at a temperature of 20°C and a wavelength of 222 nm (see Fig. 7).

In fig. 2, the calculated conformational phase diagram vs. ln w and ln λ with $N = 20$, $v = 0.1$, $\alpha = 1.5$ and $\mu = 0.05$ is shown. Each region indicates that the density ρ of the state corresponding to that phase is greater than half. As mentioned above, the dashed line shows the transition curve between the β-structure and the other states in the infinitely long chain limit. Straight lines indicate eq. 29 with $n/m = 1/2$ and several values of $(\ln K_\beta - (n/m)\ln K_\alpha)$. The choice of $n/m = 1/2$ gives rise to the transition in the order of coil, β and α, as can be seen in fig. 2. As shown below, the value $n/m = 1/2$ gives a good agreement with the experiments of Satake et al. [4]. On the other hand, the choice of higher values of n/m yields the transition in the order of coil, α and β. On the basis of eqn. 29, the calculated ellipticity $[\theta]_{222}^{calcd}$ is obtained as a function of ln w. As shown in fig. 6, $[\theta]_{222}^{calcd}$ indicates that the conformational change occurs from the coil to β-form and the β-form to helix with the increase in ln w and that the β-form area disappears with the decrease in $(\ln K_\beta - (n/m)\ln K_\alpha)$ in eq. 29. If $(\ln K_\beta - (n/m)\ln K_\alpha)$

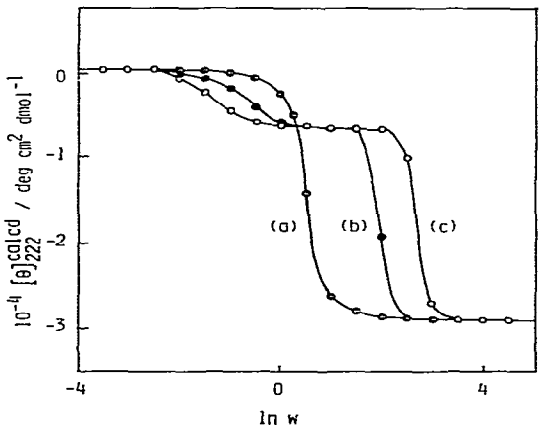

Fig. 6. Calculated ellipticity $[\theta]_{222}^{calcd}$ vs. ln w with $N = 20$, $v = 0.1$, $\alpha = 1.5$ and $\mu 0.05$. Letters a–c corresponds to straight lines a–c in fig. 2, respectively.

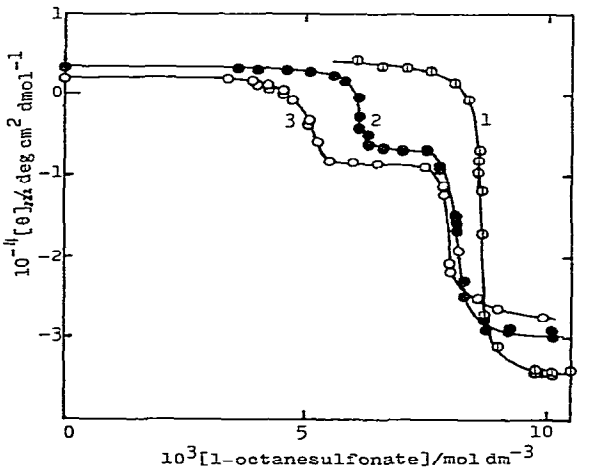

Fig. 7. The plots of $[\theta]_{222}$ vs. the concentration of 1-octanesulfonate. (1) 5°C, (2) 20°C, (3) 45°C. (From ref. 4.)

is a monotonically increasing function of temperature within the range of the temperature of the experiment, these results agree qualitatively with the experimental results given by Satake et al. [4] shown in fig. 7. That is, at temperatures 1 and 2 the transition from coil to helix occurs through a β-form within a quite narrow transition region but at a lower temperature (3) the β-form area disappears. Furthermore, as shown in fig. 7, the coil-to-β-form transition concentration increases successively with lowering temperature but the β-form-to-helix transition concentration shows similar but much less marked temperature dependence.

The relation between the parameter ln w and the free surfactant concentration, which, for simplicity, is supposed to be proportional to the total surfactant concentration, is given by eq. 25. Supposing that K_α also is an increasing function of temperature, the constant surfactant concentration corresponds to a larger value of ln w with increase in temperature. Accordingly, the β-form–helix transition concentration has less temperature dependence.

Thus, we found that the surfactant-induced conformational change of polypeptides can be well interpreted, at least qualitatively, in terms of the cooperative binding of surfactant ions to the polypeptide side groups, as pointed out by Satake et al. [4].

6. Discussion and conclusions

In the present paper, we studied the α-helix–β-structure–random coil transition from the viewpoint of equilibrium statistical mechanics, especially for homopolypeptides. In the case of the infinitely long chain limit, as stated in Appendix A, we found that the phase transition occurs between the β-structure and the other two states. This is the all-or-none type transition which seems to be characteristic of the folding of globular proteins.

In the case of finite chain length, we described the method of computer calculations of probability distributions and some useful quantities. By studying the P_j values, we found that properties of the all-or-none type transition into the β-structure are still retained even in the case of a short chain.

We applied the present model to interpret the surfactant-induced conformational transition of the polypeptides. Satake et al. [4] have observed that there occurs a stepwise conformational change from the coil to β-form and the β-form to helix with increase in surfactant concentration for poly(L-lysine). It is assumed that the conformational changes are caused by cooperative binding of the surfactant ions to the polypeptide side chains and that the β-structure-bound surfactants are different in cooperativity from the helix-bound ones. Supposing that the proper temperature dependence of the binding constant, in other words that K_α and (ln $K_\beta - (m/n)$ ln K_α) are increasing functions of temperature, we find that the calculated results can reproduce well the qualitative properties of the experimental results.

The available data on the conformational transition consisting of the three states are not plentiful. It should be emphasized that the values of the parameters used in this paper are tentative and are susceptible to change upon acquisition of more experimental data.

In the following paper, we will deal with the same α-helix–β-structure–random coil transition from the dynamic view point. The dynamic properties of the conformational transition are usually different from the equilibrium one, especially for large perturbation of environmental conditions. This will be discussed in the following paper [12] of this series of works.

Appendix A: The α-helix–β-structure–random coil transition in the case of an infinitely long chain

Following the treatment of ref. 11, we discuss the phase transition in the case of an infinitely long chain limit. In terms of the partition function Ξ_L, we define a limiting quantity p by

$$\beta p = \lim_{L \to \infty} (1/L) \ln \Xi_L . \tag{A1}$$

where L is the length of the polypeptide chain, i.e., the number of sites, and $\beta = 1/k_B T$, has its usual meaning. We introduce the generating function by

$$\psi(x) = \sum_{L=0}^{\infty} x^L \Xi_L . \tag{A2}$$

If x_0 is the radius of convergence of this series, we have

$$\beta p = -\ln x_0. \tag{A3}$$

To construct the generating function $\psi(x)$, we introduce several kinds of generating functions as follows. The generating function for a coil region between two islands is

$$V_c(x) = \sum_{n=1}^{\infty} x^n = \frac{x}{1-x}, \tag{A4}$$

the generating function for an α-helical island is

$$V_\alpha(x) = vx + \sum_{m=2}^{\infty} v^2 w^{m-2} x^m = vx + \frac{v^2 x^2}{1-wx}. \tag{A5}$$

and the generating function for a β-structure island is

$$V_\beta(x) = \sum_{m=1}^{\infty} \alpha \mu^{\sqrt{m}} (\lambda x)^m. \tag{A6}$$

On summing over all possible configurations we find

$$\psi(x) = (1-x)^{-1} + (1-x)^{-2} \sum_{\substack{m_1, m_2 \geqq 0 \\ m_1 + m_2 = 0}} \binom{m_1+m_2}{m_1} \times V_\alpha(x)^{m_1} V_\beta(x)^{m_2} V_c(x)^{m_1+m_2-1}$$
$$= (1-x)^{-1} + (1-x)^{-2} (V_\alpha(x) + V_\alpha(x)) / \left[1 - (V_\alpha(x) + V_\beta(x)) V_c(x)\right]. \tag{A7}$$

The radius of convergence x_0 is determined either by the exterior condition

$$\left[V_\alpha(x) + V_\beta(x)\right] V_c(x) = 1 \tag{A8}$$

or, from eqs. A5 and A6, by the interior condition

$$wx = 1 \tag{A9}$$

or

$$\lambda x = 1. \tag{A10}$$

For convenience, we reexpress eq. A8 as follows:

$$V_\beta(x) = Q(x), \tag{A11}$$

where

$$Q(x) = \frac{1}{V_c(x)} - V_\alpha(x) = \frac{1}{x} - 1 - vx - \frac{v^2 x^2}{1-wx}. \tag{A12}$$

The exterior condition means that x_0 is an intersecting point of $V_\beta(x)$ and $Q(x)$. From eqs. A6 and A12, $Q(x) \to +\infty$ as $x \to 0+$ and $Q(x) \to -\infty$ as $x \to 1/w-$, but $V_\beta(x)$ converges at $x = 1/\lambda$. Therefore, for a given w, x_0 exists such that

$$V_\beta(1/\lambda) < Q(x) \qquad \text{for } 0 < x < x_\sigma, \tag{A13}$$

then the radius of convergence x_0 is determined by the interior condition (eq. A10) in the stated x-interval. Then densities of the α-helix and the β-structure are given, respectively, by

$$\rho_\alpha = \beta \left(\frac{\partial p}{\partial \ln w}\right)_\beta = 0, \tag{A14}$$

and

$$\rho_\beta = \beta \left(\frac{\partial P}{\partial \ln \lambda}\right)_\beta = 1, \qquad \text{for } 0 \leqq x \leqq x_\sigma. \tag{A15}$$

From eq. A13, we have

$$\alpha \sum_{m=1}^{\infty} \mu^{\sqrt{m}} = \frac{1}{x_\sigma} - 1 - vx_\sigma - \frac{v^2 x_\sigma^2}{1-wxs} \tag{A16}$$

Evidently, the densities exhibit a discontinuity at $\lambda = 1/x_\sigma$, and eq. A16 yields, for $\lambda > w$,

$$w = \lambda - \frac{v^2}{\lambda^2 - \left(\alpha \sum_{m=1}^{\infty} \mu^{\sqrt{m}} + 1\right) \lambda - v}. \tag{A17}$$

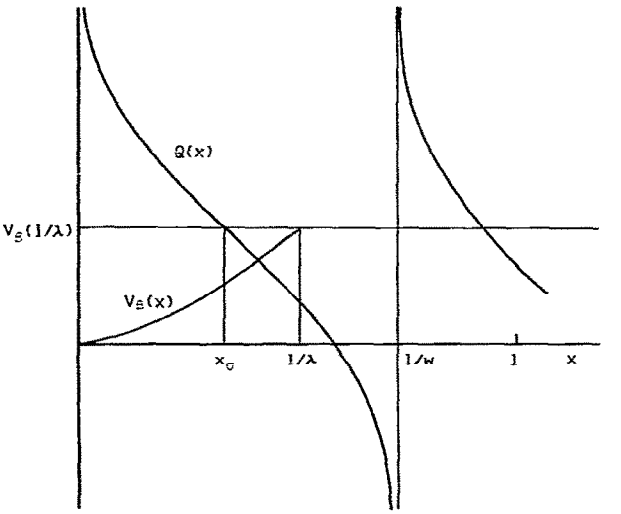

Fig. 8. $V_\beta(x)$ and $Q(x)$.

We now demonstrate the densities of the α-helix and the β-structure at the point of discontinuity. Differentiating eq. A11 by w and λ so as to calculate $\rho_\alpha = -w\partial \ln x/\partial w$ and $\rho_\beta = -\lambda \partial \ln x/\partial \lambda$, respectively, we finally have, for $x = x_\sigma = 1/\lambda$,

$$\frac{1}{\rho_\alpha} = \frac{(1-w')^2\left(K + \alpha\Sigma m\mu^{\sqrt{m}}\right)}{v'^2 w'}. \tag{A18}$$

and

$$\frac{1}{\rho\beta} = 1 + \frac{K}{\alpha\Sigma m\mu^{\sqrt{m}}} \tag{A19}$$

where

$$K = v' + \frac{v'^2(2-w')}{(1-w')^2} + \lambda, \qquad v' = v/\lambda.$$

and

$$w' = w/\lambda = 1 - \frac{v'^2}{\lambda - (\alpha\Sigma\mu^{\sqrt{m}} + 1 + v')}.$$

Here λ and w are the points of discontinuity and satisfy eq. A17.

Appendix B: The probability distribution $P_N(m_\alpha, m_\beta, k_\alpha, k_\beta)$

We will calculate the probability distribution $P_N(m_\alpha, m_\beta, k_\alpha, k_\beta)$ is the macrovariables m_α, m_β, k_α and k_β which are defined by the numbers of sites and numbers of islands of α-helix and β-structure. Similarly to the case of $P_N(m_\alpha, m_\beta)$, the probability distribution $P_N(j, m_\alpha, m_\beta, k_\alpha, k_\beta)$, not yet normalized, is defined for m_α α-helical sites, m_β β-structure sites, k_α α-helical islands and k_β β-structure islands existing in the region from the jth to the Nth site. This satisfies the following recurrence formula:

$$\begin{aligned}
P_N(j,m_\alpha,m_\beta,k_\alpha,k_\beta) &= P_N(j+1,m_\alpha,m_\beta,k_\alpha,k_\beta) f_c(j) \\
&+ \Theta(m_\alpha) \sum_{l=1}^{m_\alpha - k_\alpha + 1} f_\alpha(j,j+l-1) f_c(j+l) \\
&\quad \times P_N(j+l+1, m_\alpha - l, m_\beta, k_\alpha - 1, k_\beta) \\
&+ \Theta(m_\beta) \sum_{l=1}^{m_\beta - k_\beta + 1} f_\beta(j,j+l-1) f_c(j+l) \\
&\quad \times P_N(j+l+1, m_\alpha, m_\beta - l, k_\alpha, k_\beta - 1),
\end{aligned}$$

where we put $P_N(N+1,0,0,0,0) = P_N(N+2,0,0,0,0) = 1$, $f_c(N+1) = 1$, and $P_N(j, m_\alpha, m_\beta, k_\alpha, k_\beta) = 0$, for $(m_\alpha, m_\beta, k_\alpha, k_\beta) \in [0,N] \times [0,N] \times [0,N] \times [0,N] \setminus O_j$, the set O_j of $(m_\alpha, m_\beta, k_\alpha, k_\beta)$ for given j of $P_N(j, m_\alpha, m_\beta, k_\alpha, k_\beta)$ like the set M_j of available (m_α, m_β), is determined by the consistency conditions and is given by the sum of the following sets:

$$\begin{aligned}
&(1) \bigcup_{m_\alpha=1}^{N'-1} \bigcup_{m_\beta}^{N'-m_\alpha} \bigcup_{k_\alpha=1}^{m_\alpha} \bigcup_{k_\beta=1}^{m_\beta} \{(m_\alpha, m_\beta, k_\alpha, k_\beta)\} \\
&(2) \bigcup_{m_\alpha=1}^{N-j-1} \bigcup_{m_\beta=\max(N'+1-m_\alpha,1)}^{N-j-m_\alpha} \bigcup_{k_\alpha=1}^{\min(N-j+1-(m_\alpha+m_\beta),m_\alpha)} \\
&\qquad \bigcup_{k_\beta=1}^{\min(N-j+2-(m_\alpha+m_\beta+k_\alpha),m_\beta)} \{(m_\alpha, m_\beta, k_\alpha, k_\beta)\} \\
&(3) \bigcup_{m_\beta=1}^{N-j+1} \bigcup_{k_\beta=1}^{\min(m_\beta,N-j+2-m_\beta)} \{(0, m_\beta, 0, k_\beta)\} \\
&(4) \bigcup_{m_\alpha=1}^{N-j+1} \bigcup_{k_\alpha=1}^{\min(m_\alpha,M-j+2-m_\alpha)} \{(m_\alpha, 0, k_\alpha, 0)\} \\
&(5) \{(0,0,0,0)\}
\end{aligned}$$

where

$$N' = \left[\frac{N-j+2}{2}\right].$$

and

$$\left[\frac{n}{2}\right] = \begin{cases} \dfrac{n}{2}, & \text{for } n = \text{even}, \\ \dfrac{n-1}{2}, & \text{for } n = \text{odd}. \end{cases}$$

In terms of the probability distributions $P_N(j, m_\alpha, m_\beta, k_\alpha, k_\beta)$ and the sets O_j, we can obtain some useful quantities as mentioned in the case of (m_α, m_β).

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