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THE RANDOM WALK DESCRIPTION FOR ISOTOPE EXCHANGE IN A POLYPEPTIDE

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Isotope exchange in a polypeptide is considered from the point of view in which the boundary point between helix and coil regions of a polypeptide behaves like a weakly asymmetric random walker. We assume that the boundary point is reflected completely at the ends of a polypeptide. The equilibrium fraction of helix region is obtained under this assumption, and this is also confirmed by computer simulation. The experimental results of isotope exchange can be explained in this situation. On the other hand, the rate constant of exchange of a residue given by experiments can also be explained by another assumption, as considered before (M. Fujiwara and N. Saitô, Polym. J. 9 (1977) 625.), in which the nucleations of coil states take place in the helix region. Which of the two is of major importance is left to further studies.

1. Introduction

Some polypeptide chains change their structures with change of pH in an aqueous solution. They form helical chains in a low-pH solution and become random coils in a high-pH solution, and thus undergo a helix–coil transition [1]. The experimental results [2,3] of isotope exchange in polypeptides show that the helical region of a polypeptide chain fluctuates from moment to moment. Hence, we regard the dynamic change of conformation of a polypeptide chain as movement of the boundary point between helix and coil regions like a random walker on a one-dimensional lattice. From this point of view we want to explain a steady helix fraction of a polypeptide chain and the amount of isotopes released from a polypeptide chain.

If the randomly walking boundary point is completely reflected at the ends of a chain, the probability of its position will be independent of its initial starting position after a sufficiently long time. Hence, we can obtain the stationary distribution of the helix fraction of a polypeptide chain. This fact means that the helix percentage is constant at constant pH of the solution.

If we color all the lattice points at the initial time and assume that the random walker decolors a lattice point with a probability η after crossing that point in the specified direction, then the number of decolored lattice points will become the number of exchanged isotopes. The number of decolored lattice points considered here is equal to the average number of distinct sites visited by the random walker, when η is equal to 1. This case has already been considered [4].

In section 2, we give the general formulation for obtaining the total amount of exchanged isotopes at time N. We consider the rate constant of exchange of an isotope by a residue of a polypeptide chain. Moreover, we give the helix fraction of a polypeptide chain at time N.

In section 3, we consider the case of a polypeptide chain in which every residue takes the coil state. In this case the number of remaining isotopes in a polypeptide decreases exponentially and the rate constant of exchange of each residue is equal.

In section 4, we consider a specific case of a randomly walking boundary point on a semi-in-

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finite lattice. In this section we obtain the equilibrium fraction of the helix region.

In section 5, we will discuss the case of major interest where the two boundary points between helix and coil regions walk randomly on a finite one-dimensional lattice with an asymmetric transition probability. Rigorous treatment of the mathematical formulation is very difficult so that we perform numerical calculation by computer simulation. The results obtained with the latter method are very similar to the results [2,3] obtained from experiments on isotope exchange in polypeptides.

In section 6, we discuss the dynamic picture of helix formation of a polypeptide from the microscopic motion of amino acid residues. We also consider the lifetime of a helix, which is given by the first passage time [5]. Furthermore, we reconsider the contribution to the isotope exchange from nucleation of the coil state, which takes place through a break of the helix chain, as considered by Fujiwara and Saitô [6].

2. General formulation of isotope exchange

We regard a polypeptide chain as a linear chain consisting of n lattice points. Each lattice point takes the helix or coil state at every discrete time or step. We assume that each site exchanges the hydrogen atom bonded to it with a hydrogen atom freely existing in a surrounding aqueous solution, with a probability η per unit time, only when the site takes the coil state. Hence a site, when it takes the coil state at time N, can release an isotope with the same probability η if we label all the sites with the isotopes at the initial time.

Now we introduce the probability $P_j^r(N)$ that a site j takes the rth time coil state at time N, in other words site j takes the coil state $r-1$ times up to time $N-1$, and takes the rth coil state at N. Then we can write the probability that the jth site has already released an isotope up to time N as

$$\sum_{N'=1}^{N}\sum_{r=1}^{N'}\eta(1-\eta)^{r-1}P_j^r(N'). \tag{1}$$

Therefore, the average number of released isotopes ($\langle D\rangle_N$) from a polypeptide chain is given by summing up the site numbers as follows:

$$\langle D\rangle_N=\sum_{j=1}^{n}\sum_{N'=1}^{N}\sum_{r=1}^{N'}\eta(1-\eta)^{r-1}P_j^r(N'). \tag{2}$$

The probability $P_j^r(N)$ depends upon the microscopic motion and the interactions of amino acid residues. We shall consider the case of the random coil conformation in section 3, and the case of major interest of the randomly walking boundary point in sections 4 and 5.

Moreover, we introduce the rate constant of exchange of a residue in order to discuss the number of remaining isotopes as a function of time N and to compare it with that obtained by experiment. The rate constant of exchange of the jth residue (K_j) is defined by the inverse value of the mean first releasing time $\overline{N}_j$ of an isotope at the jth residue, i.e.,

$$K_j=1/\overline{N}_j \tag{3}$$

where

$$\overline{N}_j=\sum_{N=1}^{\infty}N\sum_{r=1}^{N}\eta(1-\eta)^{r-1}P_j^r(N). \tag{4}$$

Eqs. 3 and 4 are obtained in a discrete time treatment similarly to the rate constant defined for continuous time treatment. In this connection a discussion will be given in Appendix A.

Finally, we define the fraction ($h(N)$) of the helix region of a polypeptide chain at time N as

$$h(N)=1-\frac{1}{n}\sum_{j=1}^{n}\sum_{r=1}^{N}P_j^r(N). \tag{5}$$

If the quantity $\sum_r P_j^r(N)$ reaches a stationary value for $N\to\infty$, then we can obtain a stationary fraction of the helix region in the sense of the ensemble average.

3. Random coil

We consider in this section the case in which every residue takes the coil state only. In this case the probability $P_j^r(N)$ is expressed as

$$P_j^r(N)=\delta_{r,N}. \tag{6}$$

where $\delta_{r,N}$ means Kronecker's delta, because each residue always takes the coil state. Hence, from eqs. 2–4 and 6, we obtain the quantities $\langle D\rangle_N$ and K_j as follows:

$$\langle D\rangle_N = n\left(1-(1-\eta)^N\right). \tag{7}$$

$$K_j = 1/\bar{N}_j = \eta. \tag{8}$$

Eq. 7 implies that the remaining isotopes in a polypeptide chain $(n-\langle D\rangle_N)$ decrease exponentially, and eq. 8 shows that the rate constant of release of isotopes is independent of the residue number. One can simulate this case on a computer using the Monte Carlo method. The average number of remaining isotopes in a polypeptide chain and the rate constant of release of isotope of each residue are shown in figs. 1 and 2, respectively, in agreement with eqs. 7 and 8.

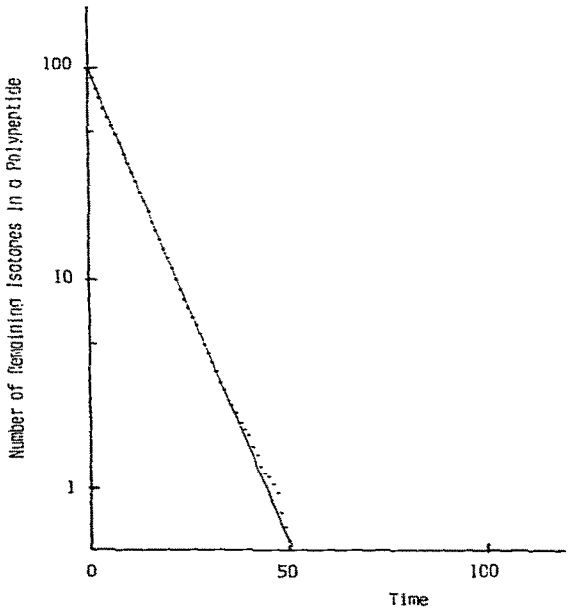

Fig. 1. The average number of remaining isotopes $(n-\langle D\rangle_N)$ in a polypeptide is plotted for the discrete time N. The result is obtained by the Monte Carlo method. The number of samples is 100. In this figure, a polypeptide takes a random coil conformation. $\eta = 0.1$ and $n = 100$.

Fig. 2. The rate constant of exchange for a residue is depicted in the case of a random-coiled polypeptide. The number of samples is 500. $\eta = 0.1$ and $n = 100$.

4. Random walk of one boundary point on a semi-infinite lattice

Now consider a particular case where only one boundary point walks on a semi-infinite lattice and a polypeptide consisting of n bonds lies on this lattice from site 1 to n. The origin is the reflecting barrier. The sites of the walker and of those to its left are in the coil state and those on the right are in the helix. The probability $P_j^r(N)$ can be written as

$$P_j^r(N) = \sum_{x=j}^{N} W_j^{r-1}(x,N) \tag{9}$$

where $W_j^{r-1}(x,N)$ is the probability that a walker lies on site x at time N when site j takes $r-1$ times the coil state up to time $N-1$. The expression of $W_j^{r-1}(x,N)$ is then

$$W_j^{r-1}(x,N) = \sum_{(\text{con.1})} P(z_N = x, z_{N-1}, \ldots, z_1, z_0) \tag{10}$$

where $P(z_N, z_{N-1}, \ldots, z_1, z_0)$ is the probability of a path drawn by a randomly walking boundary point and the summation is taken under the condition (con.1) that $r-1$ members of the set $(z_i, i = 1, \ldots, N-1)$ are on sites beyond site j and other members of this set are not. Moreover, the probability $W_j^{r-1}(x,N)$ satisfies the following master equations:

$$W_j^{r-1}(x,N) = w(x|x-1)W_j^{r-2}(x-1,N-1)$$

$$+ w(x|x+1)W_j^{r-2}(x+1,N-1) \quad \text{for } x \geq j$$

$$W_j^{r-1}(x,N) = w(x|x-1)W_j^{r-1}(x-1,N-1)$$
$$+ w(x|x+1)W_j^{r-1}(x+1,N-1) \quad \text{for } x < j. \tag{11}$$

Among many paths drawn by a walker from $(z_0, 0)$ to (x, N), only the paths where the jth site takes the coil state $r-1$ times contribute to the probability $W_j^{r-1}(x, N)$. Hence, we obtain the following relation:

$$\sum_{r=1}^{N} W_j^{r-1}(x,N) = P(x,N|z_0,0) \tag{12}$$

where $P(x, N|z_0, 0)$ is the probability that a walker is on site x at time N when it starts the random walks from the initial site z_0 at time 0. Noting the above discussion, we obtain the result of the fraction of the helix region at N, i.e.,

$$\begin{aligned} h(N) &= 1 - \frac{1}{n}\sum_{j=1}^{N}\sum_{r=1}^{N} P_j^r(N) \\ &= 1 - \frac{1}{n}\sum_{x=1}^{N}\sum_{j=1}^{x}\sum_{r=1}^{N} W_j^{r-1}(x,N) \\ &= 1 - \frac{1}{n}\sum_{x=1}^{N}\sum_{j=1}^{x} P(x,N|z_0,0) \\ &= 1 - \frac{1}{n}\sum_{x=1}^{N} xP(x,N|z_0,0) \\ &= 1 - \frac{1}{n}\langle x\rangle_N. \end{aligned} \tag{13}$$

From eq. 13, we see that the fraction of the helix region at time N is determined by the mean position of the random walker after N steps. If the random walker reflects at the origin completely, the distribution function $P(x, N|z_0, 0)$ becomes independent of its starting position z_0 at $N \to \infty$, as shown in ref. 7. The probability $P(x, N|z_0, 0)$ was given by eq. 41 in ref. 7 and has two terms. One of those terms remains finite but the second vanishes at $N \to \infty$, with the result

$$\lim_{N\to\infty} P(x,N|z_0,0) = \frac{p-q}{2pq}(q/p)^x_*,$$

where

$$(q/p)^x_* = \begin{cases} (q/p)^x & \text{if } x > 0 \\ 0 & \text{if } x = 0 \end{cases}$$

and p and q are the transition probabilities $w(x|x+1)$ and $w(x|x-1)$, respectively, i.e.,

$$p = w(x|x+1)$$
$$q = w(x|x-1).$$

Hence, the stationary fraction (h) of the helix region is given by

$$h = 1 - \frac{1}{n}\langle x\rangle_\infty = 1 - \frac{1}{2n(p-q)} \qquad (p \geq q). \tag{14}$$

The final expression of eq. 14 will be applicable only if the value of the mean position $\langle x\rangle_\infty$ is less than or equal to the degree of polymerization n. If the value of $\langle x\rangle_\infty$ is greater than n, we regard a polypeptide chain as forming a complete random coil. Moreover, we can obtain the following result from eq. 14:

If the degree of polymerization is infinite, only in the case $p = q$ does a polypeptide chain form the complete random coil, and in other cases $p > q$ a polypeptide has zero fraction of coil region compared with infinite chain length. In the cases $p < q$ the mean position of the walker goes to infinity. From the above reasons, the shape of the helix–coil transition becomes all-or-none type for a polypeptide with infinite chain length. This result is the same as that already obtained by assuming the presence of either complete helix or coil as discussed by Schellman (p.11 in ref. 1).

5. Two randomly walking boundary points between helix and coil regions on a finite chain

In this section we consider the case in which the boundary point between helix and coil regions moves like an asymmetric random walker on a polypeptide chain of finite length consisting of finite one-dimensional lattice points. The random walk model was considered by Kanô and Doi [8], who treated the movement of a helical region as a whole as a random walker by keeping its length constant. We do not, however, treat the case considered by them.

The boundary point takes a step to the helix region with transition probability q or to the coil region with $p = 1 - q$ per unit time. Since a polypeptide chain has two boundary points, we first introduce the probability of a path $P(z_N, z'_N,$

$z_{N-1}, z'_{N-1}, \ldots, z_0, z'_0$) which is drawn by two random walkers from initial sites (z_0, z'_0) to the specified sites (z_N, z'_N) at time N. This probability satisfies the following recurrence equation:

$$P(z_N, z'_N, z_{N-1}, z'_{N-1}, \ldots, z_0, z'_0) = w(z_N|z_{N-1})\hat{w}(z'_N|z'_{N-1}) \times P(z_{N-1}, z'_{N-1}, \ldots, z_0, z'_0) \quad (15)$$

where $w(z_N|z_{N-1})$ and $\hat{w}(z'_N|z'_{N-1})$ are transition probabilities,

$$w(z+1|z) = \hat{w}(z-1|z) = q$$
$$w(z-1|z) = \hat{w}(z+1|z) = p \text{ for } 2 \le z \le n-1$$
$$w(2|1) = \hat{w}(2|1) = 1$$
$$w(n-1|n) = \hat{w}(n-1|n) = 1$$

and all other $w(z_N|z_{N-1})$ and $\hat{w}(z'_N|z'_{N-1})$ are zero. If two random walkers happen to take the same site at the same time, we assume that a helix region never appears again after this occurrence. The probability of disappearance of the helix region at

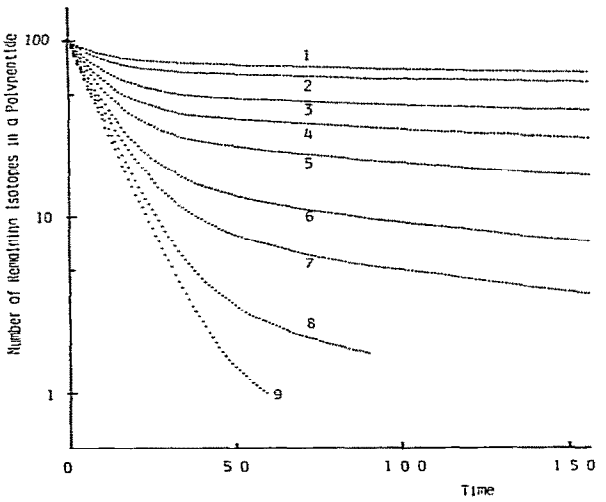

Fig. 3. The average number of remaining isotopes ($n - \langle D \rangle_N$) in a polypeptide is plotted for the case of two randomly walking boundary points. The numbers from 1 to 9 denote the following values of p: (1) 0.52, (2) 0.515, (3) 0.51, (4) 0.508, (5) 0.507, (6) 0.506, (7) 0.5055, (8) 0.5052, (9) 0.505. The number of samples is 1000. The initial site of each walker is given by the stationary mean position of a random walker on a semi-infinite lattice under the condition of a completely reflecting end. $\eta = 0.1$ and $n = 100$.

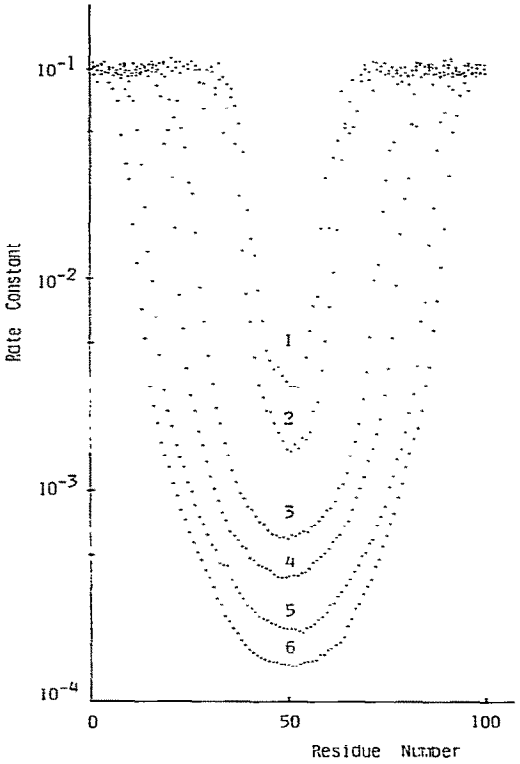

Fig. 4. The rate constants of exchange for a residue are depicted for various values of p. The numbers from 1 to 6 denote the following values of p: (1) 0.5055, (2) 0.506, (3) 0.508, (4) 0.51, (5) 0.515, (6) 0.52. The number of samples is 500. $\eta = 0.1$ and $n = 100$. It can be seen that the residues of a polypeptide are classified into three groups. The first group is the residues located in two coil regions. The second is the residues located near the random walking boundary points. The third is the residues located in the central part of a helix region. The residues in the third group make a so-called frozen region.

N after the jth site takes r times the coil state ($F_j^r(N)$) is given by using the probability of a path as follows:

$$F_j^r(N) = \sum_{z_N - 1}^{n} \sum_{\text{(con.2)}} P(z_N, z'_N = z_N, z_{N-1}, z'_{N-1}, \ldots, z_0, z'_0) \quad (16)$$

where (con.2) means the condition of summation stated as follows: l members of set ($z_i, i = 1, \ldots, N$)

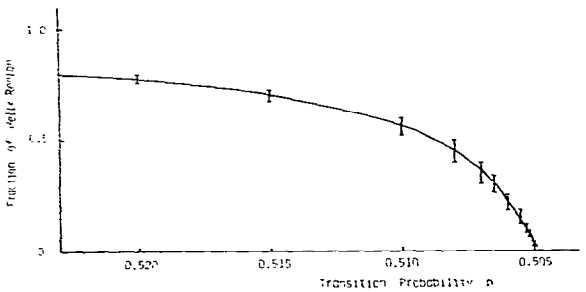

Fig. 5. The stationary fraction of helix region in a polypeptide is depicted for the weakly asymmetric transition probability p. The error bar represents the fluctuation region. The upper end of an error bar denotes the initial fraction.

are greater than or equal to j and other members of the set are less than j. $m = r - l$ members of set $(z_i', i = 1, \ldots, N)$ are less than or equal to j and other members of the set are greater than j. Furthermore, the two paths in i, z, z' space ($i = 0, 1, \ldots, N$; z, $z' = i, \ldots, n$) do not intersect except at N.

The above two probabilities yield the formal formulation of $P_j^r(N)$:

$$P_j^r(N) = \sum_{(\text{con.2})} P(z_N, z_N', z_{N-1}, z_{N-1}', \ldots, z_0, z_0') + \sum_{k=0}^{r-1} F_j^{r-k}(N-k). \tag{17}$$

It is hard to obtain a closed expression of eq. 17 as a function of p and q. Hence, we calculate eq. 17 using Monte Carlo simulation. The result is shown in fig. 3 for the number of remaining isotopes ($n - \langle D \rangle_N$) in a polypeptide chain. The rate constant of exchange for each residue is also calculated numerically, as shown in fig. 4. The fraction of the helix region is found to reach a stationary value after a long time, similarly to the finite chain on the semi-infinite lattice. Fig. 5 shows the results.

6. Discussion

The problem of isotope exchanges in a polypeptide has already been considered also by Ikegami et al. [9] from the point of view of Zimm-Bragg theory [10]. They showed that there exists a great difference between the nucleation probability of a coil state in the helix region obtained by the equilibrium helix percentage and the same probability given by isotope exchange. In our treatment we did not consider the nucleation of a coil state in a helix region to simplify the problem. This assumption holds in a helical chain sufficiently far from the transition point where the equilibrium state is represented by one helix region in the middle of the chain and two random coil regions near the ends. Thus, self-consistent results can be obtained without considering the nucleation of the coil state in a helix region. In our situation the magnitude of asymmetry of transition probability plays the role of pH in experiments. Furthermore, the ratio p/q calculated by the stationary fraction of helix region is close to the s value obtained in ref. 2.

We obtained the equilibrium fraction of the helix region under the condition that the boundary point is completely reflected at the ends of a polypeptide chain. Hence, one can see that the length of a coil region from the end of a polypeptide is independent of the degree of polymerization of a polypeptide. This fact is supported by experiment [3] for the equilibrium helix percentage when we reexamine the result as a function of the degree of polymerization. The equilibrium fraction of a helix region in the middle of a polypeptide chain obtained by the random walk model gives the same distribution for the length of a helix region as that obtained by Zimm-Bragg theory. We will discuss the details in Appendix B.

Now we consider how the asymmetry of the probability of forming and deforming the helix structure is interpreted by the microscopic molecular motions. Each amino acid residue always interacts with surrounding molecules of the solution. These interactions give rise to dynamic changes of the structure of a polypeptide. Amino acid residues in the helix region interact strongly with each other so that they are little affected by molecules of the solution. Amino acid residues in the coil region, however, are always influenced by molecules of the solution, in particular by OH^- in the case of poly(L-glutamic acid), for example. The

probability of forming the helix structure becomes small when the pH of the solution increases. Thus, the transition probabilities of forming or deforming an H-H bond by amino acid residues near the boundary between helix and coil regions have a weak asymmetry, and the experimental results of isotope exchange in a polypeptide can be explained as the embodiment of this asymmetry as given by $p - q < 0.04$.

Now we turn our attention to the lifetime of a helix state. The lifetime of the helix state of a residue is the first passage time for the boundary point to arrive at the specified residue of the helix region. This quantity plays an important role in the isotope exchange of a polypeptide shown in the previous sections. The lifetime of a helix state was considered by Jernigan et al. [5] and Miller [11] to explain the experimental results of nuclear magnetic resonance. Their treatments are similar to that considered here. They did not, however, mention the isotope exchange in a polypeptide. In our situation, the mean lifetime of a helix state is given by the summation of $NP_f^1(N)$ over N.

We reconsider the treatment of the problem considered here by Fujiwara and Saitô [6]. They regarded the nucleation of coil states in a helix region as the appearance of a break in the rod-like helix and considered that the isotope exchange in a polypeptide is caused predominantly by the nucleations of coil states in a helix region. Their model can also explain the experimental result of the rate constant of exchange for a residue. There exists, however, a great difference between the models. Therefore, we must consider which model is realized in real polypeptides and how to decide which model is true. In the treatment considered here when $\eta = 1$, there exist only three regions. One is the region in which all the residues are colored, i.e., the isotope atoms ^3H (or ^2H) in the residues are not exchanged for ^1H in the surrounding solution. The other two regions are those in which all the residues are already decolored. On the other hand, in the model of Fujiwara and Saitô [6], there exist colored residues and decolored residues mixed in the helix region. Hence, we can obtain a method of deciding which model is true when $\eta = 1$, i.e., if we cut a polypeptide chain into many parts, we will see that the distribution of frequency for the fraction of colored residues (or decolored residues) has clear double peaks (0 and 100%) in our present model but that they are broad in the Fujiwara and Saitô model. But when η is small, the distinction between the two will be difficult.

Finally, we summarize our results obtained in this article. The equilibrium fraction of the helix region is obtained under the assumption that the boundary point between helix and coil regions completely reflects at the end of a polypeptide chain. The results given by the experiments of isotope exchange in polypeptides can be explained from the point of view in which the boundary point behaves like a weakly asymmetric random walker under the same assumption. Jernigan et al. [5] also considered that the boundary point reflects at the end of polypeptide. Hence, we may say that one must make the assumption that the end of a polypeptide behaves as a reflecting barrier for the growth of the helix region whenever one would like to investigate problems involving the helix–coil transition. Further, we make mention of the rate constant of the helix–coil transition. It is well known in experimental results that there exist three kinds of rate constants corresponding to the methods of measurement. The most rapid rate constant of the helix–coil transition yields the unit time of random walks in our treatment. The next most rapid rate constant given by measurement of nuclear magnetic resonance is explained as the mean lifetime of a helix state from the point of view of the random walk model shown by Jernigan et al. [5] and Miller [11]. The slowest rate constant is that obtained by the presence of a finite rate of isotope exchange of a residue. We shall be able to explain all the rate constants concerned with the helix–coil transition exclusively from the point of view of randomly walking boundary points.

Acknowledgements

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Appendix A. On the rate constant of discrete time treatment

In section 2 we have given an expression for the rate constant $K_j = 1/\overline{N}_j$ in discrete time treatment without showing that this expression leads to a reasonable expression in the continuous limit. It is impossible to give proof for the case discussed there, because we do not have an analytical expression for $\overline{N}_j$. Consequently, we shall give in this appendix a simple example in which this expression is valid.

We consider a system consisting of n chemical species A and n chemical species B. Two chemical species A and B react and produce another chemical C, i.e.,

$$A + B \rightarrow C. \tag{A1}$$

We treat this chemical reaction as a discrete stochastic process. Let reaction A1 occur with a probability η within every specified unit time. Then we obtain the transition probability $E(z, N|k, N-1)$ that z products have been produced at time N when k products have been produced at time $N-1$, as follows:

$$E(z,N|k,N-1) = {}_{n-k}C_{z-k}\,\eta^{z-k}(1-\eta)^{n-z} \tag{A2}$$

Using this transition probability, the probability $U(z, N)$ that z products have been produced at time N satisfies the following recurrence equation:

$$U(z,N) = \sum_{k=0}^{z} E(z,N|k,N-1)U(k,N-1) \tag{A3}$$

After some tedious calculations under the initial condition $U(k,0) = \delta_{k,0}$, we obtain $U(z, N)$ as a function of η, i.e.,

$$U(z,N) = {}_nC_z\left(1-(1-\eta)^N\right)^z(1-\eta)^{N(n-z)}. \tag{A4}$$

Hence, we can see that the probability $U(z, N)$ satisfies the normalization:

$$\sum_{z=0}^{n} U(z,N) = 1. \tag{A5}$$

Furthermore, the expected amount of chemical C produced at time $N(\langle z\rangle_N)$ is given by

$$\langle z\rangle_N = n\left(1-(1-\eta)^N\right). \tag{A6}$$

From eq. A6 we see that the amount of product C tends to n when the time N tends to infinity.

Let Δ be the time difference in the discrete treatment, then $N = t/\Delta$ and $\eta = \eta_0\Delta$ provided Δ is small, where η_0 is the reaction probability in real unit time. In the limit $\Delta \rightarrow 0$ (in continuous treatment) we have

$$\langle z\rangle_N \rightarrow n(1-e^{-\eta_0 t}). \tag{A7}$$

Thus, the rate constant K is equal to η_0 in continuous treatment, and can be put $K = \eta$ in discrete treatment by putting $\Delta = 1$. Through the above consideration, we can define the rate constant K of this chemical reaction as

$$K = \eta. \tag{A8}$$

Now we consider the meaning of the value $1/\eta$. The probability $f(N)$ that a chemical A (or B) has firstly reacted with a chemical B (or A) at time N is given by

$$f(N) = \eta(1-\eta)^{N-1}. \tag{A9}$$

Hence, we can calculate the probability $U(z, N)$ that each z chemical has been reacted as

$$\begin{aligned} U(z,N) &= {}_nC_z\left(\sum_{N'=1}^{N} f(N')\right)^z\left(1-\sum_{N'=1}^{N} f(N')\right)^{n-z} \\ &= {}_nC_z\left(1-(1-\eta)^N\right)^z(1-\eta)^{N(n-z)}. \end{aligned} \tag{A10}$$

As shown in eq. A10, the probability $U(z, N)$ newly defined here is equivalent to the probability $U(z, N)$ given by eq. A4. Using the probability $f(N)$, we can calculate the mean first reacting time $\overline{N}$ of a reaction which occurs once, and obtain the result as

$$\overline{N} = \sum_{N=1}^{\infty} Nf(N) = 1/\eta. \tag{A11}$$

From the result, eq. A11, we can see that the rate constant defined in eq. A8 has the meaning that the rate constant of mutually independent chemical reactions is equivalent to the inverse value of the mean first reacting time, i.e.,

$$K = 1/\overline{N} = \eta. \tag{A12}$$

In conclusion, we can extend the concept of the rate constant as the inverse value of the mean first reacting time of a chemical reaction which occurs once.

Appendix B. Relationship between the equilibrium fraction of the helix region given by the random walk description and that of Zimm-Bragg theory

In this appendix, we consider the relation between the fraction of the helix region yielded by Zimm-Bragg theory and that given by the random walk description. It is well known in random walk theory that there exists a stationary distribution of the probability of the Walker's position when a walker reflects at the ends. Hence we obtain the equilibrium fraction of the helix region.

Now we consider the probability $P(l)$ that a polypeptide has a helical region l. We assume that a polypeptide has n H-H bonds. In the random walk model, $P(l)$ is described by the probability $P(i, j)$ that two walkers are on sites i and j of the finite one-dimensional lattice. To obtain the closed form of the probability $P(i, j)$, we further assume in this appendix that two walkers can go through each other with no interference. Hence, we define $P(0)$, in which all the residues take the coil state, by summing up the probability that the two walkers have crossed each other (see eq. B4), and $P(i, j)$ is assumed to be given by the product of the probabilities $P(i)$ and $P(j)$ that one walker is on a specified site i or j between two reflecting barriers, i.e.,

$$P(i,j) = P(i)P(j). \tag{B1}$$

The probabilities $P(i)$ and $P(j)$ have the well known form of the stationary value (see, for example, ref. 12), namely,

$$P(i) = \frac{1-q/p}{1-(q/p)^n}(q/p)^{i-1}$$

$$P(j) = \frac{1-q/p}{1-(q/p)^n}(q/p)^{n-j} \qquad 1 \le i, j \le n \tag{B2}$$

From eqs. B1 and B2, $P(i, j)$ becomes as follows:

$$P(i,j) = \left(\frac{1-q/p}{1-(q/p)^n}\right)^2 (q/p)^{i-1}(q/p)^{n-j} \qquad 1 \le i, j \le n \tag{B3}$$

Therefore, the final form of the probability $P(l)$ becomes as follows:

$$P(0) = \sum_{i \ge j} P(i,j) = \frac{(n+1-n(q/p))(q/p)^n - (q/p)^{2n}}{(1-(q/p)^n)^2} \tag{B4}$$

$$\begin{aligned} P(l) &= \sum_{i=1}^{n-l+1} P(i, i+l-1) \\ &= \left(\frac{1-q/p}{1-(q/p)^n}\right)^2 \sum_{i=1}^{2n-l+1} (q/p)^{i-1}(q/p)^{n-i-l+1} \\ &= \left(\frac{1-q/p}{1-(q/p)^n}\right)^2 (q/p)^n (n-l+1)(p/q)^l \end{aligned}$$

$$1 \le l \le n \tag{B5}$$

Now we turn our attention to the Zimm-Bragg theory of short polypeptide chains with at most one helix [1]. In this situation the probability $P(l)$ is given by

$$P(0) = 1/Z \tag{B6}$$

$$P(l) = \frac{\sigma}{Z}(n-l+1)s^l \qquad 1 \le l \le n, \tag{B7}$$

where

$$Z = 1 + \sigma \sum_{l=1}^{n} (n-l+1)s^l \tag{B8}$$

and s and σ are the statistical weight of the helix with and without hydrogen bond, respectively.

After comparing eqs. B4 and B5 with eqs. B6 and B7, we obtain the following relations:

$$s = p/q \tag{B9}$$

and

$$\begin{aligned} \sigma &= \left(\frac{1-q/p}{1-(q/p)^n}\right)^2 (q/p)^n / P(0) \\ &= (1-q/p)^2 / ((n(1-q/p)+1) - (q/p)^n) \\ &\simeq (1-q/p)/n = (s-1)/ns \qquad (p \ge q). \end{aligned} \tag{B10}$$

From eq. B10 the σ of our result depends upon the degree of polymerization n and statistical weight s.

To conclude this appendix, we summarize the results obtained here:

1. The probability $P(l)$ obtained by random walk theory can be written in the same form as Zimm-Bragg theory of one helix region lying in the middle of a polypeptide chain.

2. The values s and σ of random walk theory are not independent of each other.

Result 2 is different from Zimm-Bragg theory, in which s and σ are independent parameters, although the effect of a reflecting barrier leads to the Zimm-Bragg form of the probability $P(l)$. This

difference occurs from the assumption of two freely walking random walkers:

A polypeptide takes the random coil structure if two walkers walk through each other. In this calculation, we allow two walkers to move freely with no interactions. Hence, the nucleation of a helix region has to take place when two walkers walk through each other again. Therefore, the probability of nucleation of a helix core in a random-coiled polypeptide is written in terms of the transition probabilities of the walker and the degree of polymerization.

Finally, we can see that the distribution obtained by the random walk model for the length of a helix region in the middle of a polypeptide chain has the same shape as that obtained by Zimm-Bragg theory.

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