Helix–coil transition of polypeptides on the basis of correlated walks[a)]

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The helix-coil transition of polypeptides is treated on the basis of the correlated walk model which incorporates both the physical shape (helix or coil) and the hydrogen bonding. The statistical mechanical calculations reproduce the essential features of the classic theory established by Zimm and Bragg. Moreover, the nucleation parameter σ, which represents the degree of difficulty for forming a first helical turn, is related to the probability γ' of the model polymer making the correct turn: $\sigma = \gamma'^3$. In the model in which the hydrogen bonding is attained only after three successive correct turns, the numerical value for the probability γ' obtained after comparison with the optical rotation study of the poly-γ-benzyl-*l*-glutamate by Doty and Yang is found to be 0.010. This value is compatible with the detailed molecular calculations by Scherag and his collaborators, but it is about one-sixth of the value which results from $\gamma' = \sqrt[3]{\sigma}$ with $\sigma \approx 2 \times 10^{-4}$ obtained in the truncated Z–B model. This difference arises from the more detailed representation of the phase-volume restriction for generating part of a helix and thus acquiring the hydrogen bonding in the present work.

I. INTRODUCTION

In the mid-fifties Doty and his associates and others,[1] demonstrated experimentally that a single polypeptide in solution undergoes a helix-coil transition. Many important theories[2,3] followed this fascinating discovery. In 1959, Zimm and Bragg (Z–B) published a classic paper[4] on the helix–coil transition in terms of the solutions of a modified Ising chain. This theory describes the qualitative features of the phase transition very well. In particular, the narrow temperature range usually observed for the transition is accounted for by the smallness of the nucleation parameter σ. In the Z–B model the hydrogen bonding states are accounted for directly but the associated physical shape (helix or coil) is only implied. Lifson and Roig[5] introduced the internal rotation angles (ϕ, ψ) within each peptide unit, and calculated the partition function. In a series of papers, Scheraga and his associates[6] reported very extensive conformational analyses of polypeptides by using realistic potential functions for the internal rotations, arising from various sources including dipole–dipole interactions between amide groups and hydrogen bonding.

Recently we proposed a theory of the conformation of a simple polymer based on the correlated walk model.[7] Extending this model with inclusion of the hydrogen bonding, we propose a new model of a polymer (polypeptide) capable of helix–coil transition. This generalized model contains the Z–B model as a special case if we look only at the hydrogen bonding states of α-amino acid residue -NH-CHR-CO- but it incorporates the physical shape as well.

The solution of the model appropriate in the vicinity of the helix–coil transition is obtained in terms of the solutions of modified linear Ising model. The main features of our results are as follows:

(a) General results are qualitatively similar to those of the Z–B theory.

(b) The nucleation parameter σ can simply be related to the turn probability γ, which represents the bending property arising from the internal rotation within the residues: $\sigma = \gamma'^3$.

(c) The γ' obtained after comparison with the optical rotation study of the poly-γ-benzyl-L-by Doty and Yang,[1] has the numerical value 0.010. This value is compatible with the detailed molecular calculations by Scheraga and his collaborators,[6] but it is about one-sixth of the value which results from $\gamma' = \sqrt[3]{\sigma}$ with $\sigma = 2 \times 10^{-4}$ obtained in the truncated Z–B model.[4]

In Sec. II a model of a polymer capable of helix–coil transition is presented. This model is reduced further in Sec. III, and the solution of the reduced model is obtained and discussed. In Sec. IV a refined treatment of the helix–coil transition is given in terms of the solutions of the Ising chain with up-to-third nearest-neighbor interactions. Section V concludes with discussions and remarks.

II. THE MODEL

Let us consider a polypeptide, H-(NH-CHR-CO)$_n$-OH, where n is the number of amino acid residues. Let us

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choose each residue as unit segment. From the nature of the residues, any neighboring segments may be bent at right angles but may not be pointed in antiparallel directions. The global conformation of the polymer in solution will now be represented by a model polymer stretched over on a simple cubic lattice with the following rules: A segment follows the direction of the preceding segment with probability α or turns at right angles (four possibilities) with probability γ but does not reverse. The probabilities are normalized such that $\alpha + 4\gamma = 1$. The lattice constant a_0 will be chosen to equal the average linear size of the unit amide residue.

In a coil state, the average configuration of the polymer will be characterized in terms of the parameters (α, γ) and a_0. In particular, the mean square end-to-end distance for the model polymer was calculated in Ref. 7, and is given by

$$\frac{\langle R^2\rangle}{a_0^2} = \frac{1+\alpha}{1-\alpha}\, n - \frac{2(1-\alpha^n)}{(1-\alpha)^2} \quad . \tag{2.1}$$

This expression has the following limit behavior:

$$\langle R^2\rangle \to \tfrac{3}{2} n a_0^2 \,, \quad \text{for } \alpha = \gamma = \tfrac{1}{5} \,, \tag{2.2}$$

and

$$\langle R^2\rangle \to n^2 a_0^2 \,, \quad \text{for } \alpha = 1 \;. \tag{2.3}$$

The case in which $\alpha = \gamma$ corresponds to the *state of random coil*. The result (2.2) for this case is in agreement with the result on the basis of the restricted random walks with prohibition of the immediate reversal. In the other extreme case in which $\alpha = 1$, the model polymer stretches out like a solid bar, which yields Eq. (2.3).

The expression (2.1) was derived with no self-avoiding restriction[8] except for the immediate reversal. In particular, closed loops such as the loop with four successive segments as shown in Fig. 1(b) are allowed in the statistical average. The averaging done in this manner should correspond to the reality better[7]; it should represent a result more reasonable than the result which would be obtained with prohibition of any and all closed loops as prescribed in the self-avoiding walk models.

Let us now consider a helical state of the polypeptide. In the Pauling–Corey alpha-helix structure,[9] each amide (CONH) is hydrogen-bonded to the carbonyl oxygen of the third following amide group, and approximately four residues make up a helix unit. See Fig. 1(a). Such a helix by construction is represented by the closed square formed by four segments as shown in Fig. 1(b). We will postulate that the hydrogen bonding is attained only when a segment completes a new square with the preceding three segments. Thus for example, in Fig. 1, the fifth to eighth segments attain the bonding.

If the hydrogen-bonding state of the model polymer in Fig. 1 is looked at from one end, it will be represented by the sequence 000011110..., where the digit 1 represents a bonded segment and the digit 0 an unbonded segment. In general, the first three segments are always unbounded and no sequence of less than three 0's should appear by construction. This is in complete agreement with the original Z–B model.

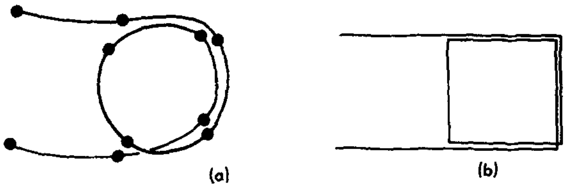

FIG. 1. A polymer backbone forming helices (a) is represented by a model polymer stretched over on the orthogonal lattice (b). By assumption, the hydrogen bonding is attained when a segment completes a new square with the preceding three segments.

In our model, the complete helical state (ground state) corresponds to the polymer being wound around a single square repeatedly. This representation neglects the obvious three-dimensional form of the polypeptide, and therefore is far from the reality. The representation however, should be reasonable in the region of helix–coil transition where the main emphasis of our study is directed.

III. THE HELIX–COIL TRANSITION—THE SIMPLIFIED MODEL

Our model clearly contains two extreme states: random coil and helical states. Let us now look at the transition between the two. The analysis of the original model is far too complicated as it stands. We will now reduce it to a manageable model.

Let us take a model polymer with several repeated squares representing helical loops. We divide it in units of three segments. Each unit together with the last segment of its preceding unit may or may not form a square. The state of jth unit will be represented by

$$\mu_j = \begin{cases} 1\,, & \text{for closed square (loop)}\,, \\ -1\,, & \text{for open figure}\;. \end{cases} \tag{3.1}$$

The statistical weight of a given state $\{\mu_j\}$ of the chain of units is now assumed to be the product of the following factors:

(1) the loop (square) formation factor p if $\mu_j = 1$,

(2) the factor $q \equiv 1 - p$, if $\mu_j = -1$,

(3) the Boltzmann factor $\exp(\beta K)$ if a loop follows another loop and unity otherwise; the energy K represents the bond energy between the units.

The loop formation factor p is prescribed to account for the fact that the segments in the unit proceed in a well-defined orientation to close a square. This factor therefore may be chosen as

$$p = (\gamma/4)^3 \quad , \tag{3.2}$$

since only one of the four possible turns is correct to generate a square.

The total bond energy can be expressed by the Hamiltonian

$$H = -K \sum_j f(\mu_{j-1}\,,\ \mu_j)\ , \tag{3.3}$$

where

$$f(\mu_1,\ \mu_2) = \tfrac{1}{4}(1+\mu_1)(1+\mu_2) = \begin{cases} 1\ , & \text{if } \mu_1 = \mu_2 = 1\ , \\ 0\ , & \text{otherwise}\ . \end{cases} \tag{3.4}$$

The above assumption about the statistical factors represents a very crude approximation. In particular, a partially formed square followed by a complete closed square can get no benefit of bonding in this simplified model. A theory improved upon this point will be presented in the following section.

The partition function Z for the simplified model can be obtained simply, using the standard languages[3] for the linear Ising chain with nearest neighbor interaction. The transfer matrix $\mathbf{T}$ is given by[10]

$$\mathbf{T} = \begin{pmatrix} q & q \\ p & pe^{\beta K} \end{pmatrix}\ . \tag{3.5}$$

If we introduce

$$t \equiv p/q\ ; \quad s \equiv te^{\beta K}\ , \tag{3.6}$$

the matrix $\mathbf{T}$ can be written as

$$\mathbf{T} = q \begin{pmatrix} 1 & 1 \\ t & s \end{pmatrix} \equiv q\hat{\mathbf{T}}\ . \tag{3.7}$$

The largest root of the characteristic equation

$$|\hat{\mathbf{T}} - \lambda| = 0 \tag{3.8}$$

is given by

$$\lambda_0 = \tfrac{1}{2}\{1 + s + [(1-s)^2 + 4t]^{1/2}\}\ . \tag{3.9}$$

We note that $s \equiv t\exp(\beta K)$ represents the ratio of the helix contribution to the partition function to the coil contribution.

In the limit of large n, the free energy ψ per unit is given by

$$\psi = -k_B T \ln \lambda_0\ . \tag{3.10}$$

The average degree of helicity, that is, the ratio of the number of helical loops to the total number of units, is

$$\langle f \rangle = \frac{\partial \ln \lambda_0}{\partial(\beta K)} = \frac{s}{\lambda_0} \frac{\lambda_0 - 1}{2\lambda_0 - s - 1} \tag{3.11}$$

This quantity against s for selected values of t is shown in Fig. 2.

For smaller values of the loop formation factor p (or t), the transition, which occurs around $s = 1$, becomes more and more abrupt. A reasonable fit with the experimental observations of Doty and Yang on poly-γ-benzyl-L-glutamate,[1] which are indicated by dots, can be obtained for $t = 2\times 10^{-4}$.

The results obtained have great similarities to those explicitly worked out by Zimm and Bragg. In fact, the transfer matrix in this theory[4] is

$$\mathbf{T}_{\text{Z-B}} = \begin{pmatrix} 1 & 1 \\ \sigma s & s \end{pmatrix}\ . \tag{3.12}$$

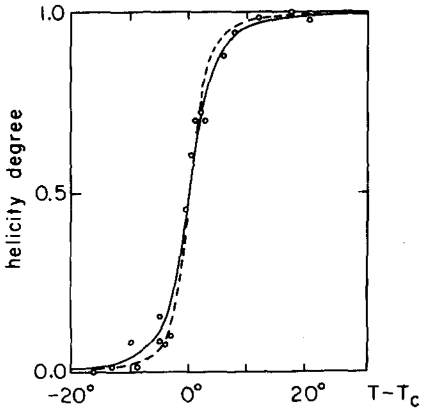

FIG. 2. Theoretical curves of the helicity degree calculated from (3.11) for two t values: the solid line for $t = 2\times 10^{-4}$ and the broken line for $t = 1\times 10^{-4}$. The circles represent experimental data of optical rotation of poly-γ-benzul-L-glutamate observed by Doty and Yang.[1]

If the nucleation factor σs is replaced by the factor t, the matrix $\mathbf{T}_{\text{Z-B}}$ is identical to our matrix T within the overall multiplicative factor q. (This last factor q does not affect the physical results.) While s and σ were the parameters in the Z–B theory, s and t are in the present theory. In spite of this difference it is found that the two theories give mutually indistinguishable results for the average degree of helicity when both $t = p/q$ and σ take the same values, 10^{-2} or less. This means that the parameter p, just as the nucleation parameter σ, characterizes the difficulty of forming an initial loop. Since our model contains the physical shape (helix or coil) explicitly a clearer picture of the nucleation emerges. The nucleation factor p is related to the turn factor γ as in (3.2). We will further discuss this point in the following sections.

IV. REFINED TREATMENT OF THE HELIX-COIL TRANSITION

Scheraga and his associates demonstrated, on the basis of molecular calculations in terms of the potential between the bond–bond ($C^\alpha - C'$, $N - C^\alpha$) angles within an amide group, that each amide residue should follow the next in a well-defined manner in order to form a helical conformation.[6] Such fine feature was partially lost in our crude model described in the last section. In this section we present a refined model for the helix-coil transition. For this purpose, we take each segment representing a single amide residue as one unit, and will postulate the following rules:

(1) If a segment follows the preceding segment in the correct direction, the statistical factor p' is given; otherwise the factor $q' \equiv 1 - p'$ is assigned.

(2) The Boltzmann factor $\exp(\beta K')$ is given if a segment makes a third correct turn following the two correct turns; otherwise unity is assigned.

The statistical factor p' represents the probability that the amide residue takes a suitable conformation for a right-hand or left-hand helix. This factor will be small compared with unity because the unsuitable conformation corresponds to much greater phase-space volume. The factors p' or q', can be related to the bond–bond angles within the amide residue, and this connection will further be discussed in the following section. A succession of three correct turns clearly generates a closed square. Therefore, the rule (2) for the attainment of the hydrogen bonding has the same content as the original postulate laid out in Sec. II.

In the vicinity of helix–coil transition, the tendency of forming helices to gain the bonding competes head-on against the accompanying decrease in the conformational entropy. The contribution of the conformational entropy to the partition function is given in terms of the probabilities (p', q') and that of the hydrogen bonding in terms of the Boltzmann factor $e^{\beta K'}$. The factor p' obviously is connected with the turn probability γ in the model introduced in Sec. III. But they are distinct from each other. First, the factor p' is defined with the restriction that the successive segments should conform in such a way to generate part of a helix. Because of this restriction, the factor p' in general will be smaller than the probability which is free from such restriction. Secondly, the factors p' and q' represent the polymer conformation only partially. In fact, a given sequence of p' and q', does not generate the overall conformation of the model polymer except for extreme cases of complete helix and random coil. As far as the general feature of the helix–coil transition is concerned, the above two rules should describe the states of the model polymer in a semiquantitative manner.

The partition function for the model polymer may be calculated by use of the Ising languages as follows. We assign +1 or −1 to the state (μ_j) of each segment. The statistical weight of a state (μ_j), of the chain of n segments is given by the product of the following factors:

(1) the turn factor p', if $\mu_j = -\mu_{j-1}$,

(2) the factor $q' \equiv 1 - p'$, if $\mu_j = \mu_{j-1}$, and

(3) the Boltzmann factor $\exp(\beta K')$, if $\mu_j = -\mu_{j-1} = \mu_{j-2} = -\mu_{j-3}$, and unity otherwise; the energy K' represents the bond energy between the jth and $(j-3)$th segments.

The total bond energy may be expressed by the Hamiltonian

$$H = -K' \sum_j f(\mu_j,\ \mu_{j-1},\ \mu_{j-2},\ \mu_{j-3}) , \tag{4.1}$$

where

$$f(\mu_1,\ \mu_2,\ \mu_3,\ \mu_4) = \tfrac{1}{8} \left| (\mu_1 - \mu_2)(\mu_2 - \mu_3)(\mu_3 - \mu_4) \right| .$$

$$= \begin{cases} 1 , & \text{if } \mu_1 = -\mu_2 = \mu_3 = -\mu_4 , \\ 0 , & \text{otherwise} . \end{cases} \tag{4.2}$$

We note that this Hamiltonian corresponds to that of the Ising chain with first to third nearest neighbor interactions.

The partition function for this model can be obtained simply, using the correlated-walk-Ising languages.[10,11] The transfer matrix $\mathbf{T}$ is given by

$$\mathbf{T} = \begin{pmatrix} q' & p' & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & p' & q' & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & q' & p'e^{\beta K'} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & p' & q' \\ q' & p' & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & p'e^{\beta K'} & q' & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & q' & p' & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & p' & q' \end{pmatrix} = q'\hat{\mathbf{T}} . \tag{4.3}$$

The characteristic equation

$$0 = |\hat{\mathbf{T}} - \lambda| \equiv \lambda^2 D_1 D_2 , \tag{4.4}$$

where

$$\begin{aligned} D_1 &= \lambda^3 + (s' - 1)\lambda^2 - (s' - t')\lambda + t'(s' - t') , \\ D_2 &= \lambda^3 - (1 + s')\lambda^2 + (s' - t')\lambda + t'(s' - t') , \end{aligned} \tag{4.5}$$

$$s' \equiv t' \exp(\beta K') , \quad t' \equiv p'/q' , \tag{4.6}$$

has all real roots. The maximum root is found to come from

$$D_2(\lambda) = 0 , \tag{4.7}$$

and is given by

$$\lambda_0 = 2(-a/3)^{1/2} \cos(\phi/3) - P/3 , \tag{4.8}$$

where

$$a \equiv Q - \tfrac{1}{3}P^2 , \quad \phi \equiv \cos^{-1}[-b/2(-a^3/27)^{1/2}] , \tag{4.8}$$

$$b \equiv (2P^3 - 9PQ + 27R)/27 , \tag{4.9}$$

$$P \equiv -1 - s' , \quad Q \equiv s' - t' , \quad R \equiv t'(s' - t') . \tag{4.10}$$

The quantities s' and t' defined in (4.6) refer to the *segment* rather than the unit of three segments. Except

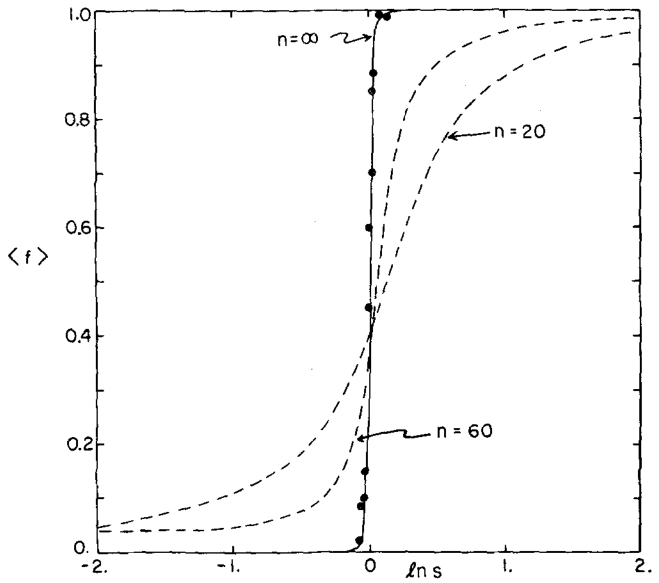

FIG. 3. The average helicity degree $\langle f \rangle$ calculated from (4.12) with $t'=0.010$, shown in solid line, is in good agreement with experimental data by Doty and Yang.[1] The broken lines correspond to the calculations from the partition function Z_n in (A3) with $n=20$ and 60, and $t'=0.010$.

for this, they may be interpreted in the same manner as s and t defined in the last section.

The partition function Z_n for a model polymer of n segments can be obtained in terms of the roots of Eq. (4.4), and is given in the Appendix. In the limit of large n, the free energy per segment, ψ, is given by

$$\psi \equiv k_B T \lim_{n\to\infty}(1/n) \ln Z_n = -k_B T \ln \lambda_0 \ . \tag{4.11}$$

The average degree of helicity is given by

$$\langle f \rangle = \frac{\partial \ln \lambda_0}{\partial(\beta K')} \ . \tag{4.12}$$

This quantity as a function of s' is plotted in Fig. 3, where a good fit with the same experimental data of Doty and Yang,[1] is obtained for $t'=0.010$.

V. DISCUSSIONS

In the last two sections we have seen that both approximate models yield good fits with the same experimental data. The values used for the "nucleation" parameters are $t=2\times10^{-4}$ and $t'=0.010$. If we apply (3.2) to the former, we obtain

$$\tfrac{1}{4}\gamma = t^{1/3} = 0.059 \tag{5.1}$$

for the correct-turn probability. On the other hand, $t' \cong p'$ in the second model can be identified with the probability for the "correct" turn. We have, therefore,

$$\gamma' \cong t' = 0.010, \tag{5.2}$$

which is considerably smaller than 0.059. This means that first, the qualitative behavior of the degree of helicity can be fit without tight control as long as two primary parameters characterizing the bonding and nucleation are introduced. We note that this general feature has been observed in most of the previous theories dealing with the helix-coil transition.[3-5] Secondly, the way of representing the phase-volume restriction for generating part of a helix and thus acquiring the hydrogen bonding, affects the value of the probability significantly. In our seond and more refined model, this restriction is represented in terms of the first to third nearest-neighbor interactions, see Eqs. (4.1) and (4.2).

The obtained value $\gamma' \cong t' \cong 0.010$ is quite consistent with the molecular calculations of Scheraga *et al.* In their analysis, equipotential contours in the rotation angle pair plane (ψ, ϕ) were calculated by using semiempirical potential functions arising from various sources including the hydrogen bonding between backbone NH and Co groups. The fraction of the area enclosed by the contour at some appropriate thermal energy corresponding to a helical conformation against the total area $(2\pi)\times(2\pi)$ in the (ψ, ϕ) plane, may roughly be regarded as the fraction of the favorable phase-space volume. For almost all cases, the contour calculated for a variety of polymers extends over several degrees in both ψ and ϕ, and the area within makes up about 1% of the total area. This is in agreement with the obtained value $\gamma'=0.010$ for the correct turn, but far from the value $\frac{1}{4}\gamma=0.059$ obtained by use of the simplified model.

The average degree of helicity should actually depend on the molecular weight. For relatively small number of the amide residues, the partition function Z_n should characterize the thermodynamic behavior. The partition function for the second model Z_n is given by (A3) in the Appendix. The average helicity degree calculated from $Z_n(s, t, n)$ for $n=20$, 60, and ∞, are shown in Fig. 3. For smaller n, the transition near $s'=1$ is milder, which is a general feature of the phase transition.

It is known that a purely one-dimensional system cannot undergo a sharp phase transition.[12] In our simplified model, the smallness of the loop formation factor p generates a smooth but sharp transition between helix and coil. This factor p was expressed in terms of the correct-turn probability γ' as $p=(\gamma/4)^3 \equiv \gamma'^3$. If a hypothetical loop contained a large number k of segments, $p=\gamma'^k$ would have followed. Since γ' is considerably smaller than unity, the factor p would rapidly approach zero for a large k. In the limit of large k *and* large n, we would have had an extremely sharp transition. There is no contradiction, however. The hypothetical system can be represented by a Hamiltonian of some Ising chain with up to $(k-1)$th nearest-neighbor interaction like Eq. (4.1). With the large k limit, the system corresponds to an Ising chain with infinite range of interaction, which is known to undergo an infinitely sharp phase transition (in the thermodynamic limit).[13]

The models and calculations presented here may be applied with a slight modification to the DNA. Since the bases forming the unit of the double helix are bigger and more numerous, the loop formation factor $p=\gamma'^k$ with a large k, will be very much smaller. This yields a more abrupt phase transition around $s=1$, which is in agreement with the experimental observation; the melting curves for DNA show a transition within a few degrees in temperature while the corresponding temperature range for the α helix typically extends five degrees or more.[14] Since the nucleation parameter $\sigma \sim p$ should roughly be regarded independent of temperature and base species, the melting temperature T_m, determined from

$$s = p \exp(-K/k_B T_m) = 1 , \tag{5.3}$$

should be proportional to the bond energy per unit double helix, K:

$$T_m \propto K . \tag{5.4}$$

The average bond energy can be varied in a controlled manner with the content of G–C base pairs. If the usual linear relationship is assumed here, then the melting temperature T_m should vary linearly with the content of G–C base pairs.

This feature also is in good agreement with experimental data.[14]

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APPENDIX: THE PARTITION FUNCTION Z_n

The characteristic Eq. (4.4) has the following roots:

$$\lambda_j = 2(-a/3)^{1/2} \cos\left(\frac{\phi}{3} + \frac{2\pi}{3} j\right) - \frac{P}{3} , \quad j = 0, 1, 2 ,$$

$$\lambda_k = 2(-a_1/3)^{1/2} \cos\left(\frac{\phi_1}{3} + \frac{2\pi}{3} k\right) - \frac{P_1}{3} , \quad k = 3, 4, 5 , \tag{A1}$$

where

$$a_1 \equiv Q_1 - \tfrac{1}{2} P_1^2 , \quad b_1 \equiv (2P_1^3 - 9P_1 Q_1 + 27R_1)/27 ,$$

$$\phi_1 \equiv \cos^{-1}\left(-\frac{b_1}{2(-a_1^3/27)^{1/2}}\right) ,$$

$$P_1 \equiv -1 + s' , \quad Q_1 \equiv t' - s' , \quad R_1 \equiv t'(s'' - t') . \tag{A2}$$

In terms of these roots, the partition function Z_n is given by

$$\frac{1}{n} \ln Z_n = \ln q' + \ln \lambda_0 + \frac{1}{n} \ln\left[\sum_{\rho=1}^{5} A_\rho \left(\frac{\lambda_\rho}{\lambda_0^2}\right)^n \times (\lambda_\rho^6 + \alpha_4 \lambda_\rho^4 + \alpha_3 \lambda_\rho^3 + \alpha_2 \lambda_\rho^2 + \alpha_1 \lambda_\rho + \alpha_0)\right] , \tag{A3}$$

where

$$A_\rho \equiv \left[\prod_{\sigma \neq \rho} (\lambda_\rho - \lambda_\sigma)\right]^{-1} , \tag{A4}$$

$$\alpha_0 \equiv t'(t'-1)(s'-t')^2 , \quad \alpha_1 = (s'^2 - t'^2) ,$$

$$\alpha_2 \equiv (1-t')(t'-s') , \quad \alpha_3 \equiv 3t' - 2t'^2 - 2 + s' ,$$

$$\alpha_4 \equiv 1 - s'^2 . \tag{A5}$$

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