failure for small values $|i - j|$ of the assumption that the density distribution functions of r_{ij} follow a single Gaussian distribution for all i and j.

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Theory of Helix–Coil Transitions of α-Helical, Two-Chain, Coiled Coils. Analytic Treatment of the Homopolymeric, Neglect-Loop-Entropy Model

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ABSTRACT: Analytic expressions for the internal partition function and helix content in the limit of infinite molecular weight, f_{hd}^{∞}, are derived for homopolymeric, α-helical, two-chain, coiled coils (dimers) in which the effects of loop entropy and mismatch are neglected, i.e., the neglect-loop-entropy model. We examine the behavior of f_{hd}^{∞} as a function of the helix–helix interaction parameter, w, and as a function of the Zimm–Bragg helix initiation parameter, σ. Comparison is made between the helix–coil transition in infinite-length dimers and in an "analogous", isolated, single-chain, homopolypeptide. Furthermore, the dependence of the helix content of the dimer on chain length is investigated for various values of σ. On the basis of the present work, it is concluded that homopolypeptide dimers having the same degree of polymerization as the prototypical two-chain, coiled coil tropomyosin are in the short to moderate length limit, a necessary condition for the application of the theory that includes loop entropy and mismatch (*Macromolecules* **1984**, *17*, 645).

I. Introduction

In a series of papers, a statistical mechanical model of the helix–coil transition in two-chain, coiled coils (dimers) has been developed.[1-4] The theory ascribes to each individual amino acid two "short-range" interaction parameters, the standard Zimm–Bragg helix initiation parameter, σ, and helix propagation parameter s, that are assumed to depend only on amino acid types and not on amino acid sequence.[5] Furthermore, the theory accounts for the greatly increased helix content of the side-by-side, two-chain, coiled coil relative to the calculated helix content of isolated single chains by a "long-range" interaction parameter w; $-RT \ln w$ is the free energy of the positionally fixed interacting pair of helical turns in each of the two chains relative to the free energy of the positionally fixed pair of turns in the noninteracting chains. The theory has been extended to include the effects of loop entropy and mismatch on the helix–coil transition.[2-4] For a detailed account of the theory as well as a discussion of the relevant

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literature we refer the reader to previous work.[1-4]

In the present work, we return to the development of the original theory in which the effects of loop entropy and mismatch are neglected and focus explicitly on the properties of homopolymeric, two-chain, coiled coils. In section II, we derive analytic expressions for the eigenvectors and eigenvalues of the 4 × 4 statistical weight matrix of the neglect-loop-entropy model discussed previously.[1,3] We then present an analytic expression for the helix content of two-chain, coiled coils in the limit of infinite molecular weight, f_{hd}^{∞}. In section III, curves of f_{hd}^{∞} vs. w are calculated for various values of σ and a discussion of the properties of the infinite chain limit of the helix–coil transition in two-chain, coiled coils is given; comparison with the infinite chain limit of the helix-to-random coil transition in a single-chain, homopolymeric "analogue" is made. Furthermore, we present numerical results for the helix content of the dimer, f_{hd}, vs. w as a function of the degree of polymerization, N, of homopolymeric, two-chain, coiled coils. We show that homopolymeric chains possessing the same degree of polymerization as the prototypical, two-chain, coiled coil tropomyosin, where $N = 284$, are in the small to moderate length limit. This conclusion is consistent with the essential assumption of the theory which includes the effects of loop entropy and mismatch that the dimers are in a regime where end effects are important. In the limit of small σ (on the order of 10^{-4}) the theory which includes loop entropy (but without mismatch) is identical with the neglect-loop-entropy theory. Clearly then if the neglect-loop-entropy theory required homopolymeric dimers with $N = 284$ to be near the infinite chain limit, the theory which includes loop entropy would be suspect in its application to tropomyosin. This is, however, demonstrated not to be the case.

II. Analytic Treatment of Homopolymeric, Two-Chain, Coiled Coils: The Neglect-Loop-Entropy Model

Eigenvalues of the Statistical Weight Matrix. Consider a homopolymeric, two-chain, coiled coil containing N residues per chain and label the chains 1 and 2, respectively. In the following for simplicity, we shall employ the $m = 1$ approximation; i.e., coarse graining is ignored.[1] Extension to chains including coarse graining is straightforward.

The partition function of the dimer is given by

$$Z_{\mathrm{sd}} = \mathbf{J}^{*}\prod_{i=1}^{N}\mathbf{U}_{\mathrm{d}i}\mathbf{J} \qquad \text{(II-1)}$$

where $\mathbf{J}^{*}$ = row [1, 0, 0, 0] and $\mathbf{J}$ = col [1, 1, 1, 1]; row and col denote row and column vectors, respectively. Furthermore, the statistical weight matrix of the ith pair of residues is

$$\mathbf{U}_{\mathrm{d}i} = \begin{array}{c|cccc} & & & i & \\ i-1 & \mathrm{c}(1)\mathrm{c}(2) & \mathrm{c}(1)\mathrm{h}(2) & \mathrm{h}(1)\mathrm{c}(2) & \mathrm{h}(1)\mathrm{h}(2) \\ \hline \mathrm{c}(1)\mathrm{c}(2) & 1 & \sigma s & \sigma s & \sigma^2 s^2 w \\ \mathrm{c}(1)\mathrm{h}(2) & 1 & s & \sigma s & \sigma s^2 w \\ \mathrm{h}(1)\mathrm{c}(2) & 1 & \sigma s & s & \sigma s^2 w \\ \mathrm{h}(1)\mathrm{h}(2) & 1 & s & s & s^2 w \end{array} \qquad \text{(II-2)}$$

where c(j) (h(j)) denotes the coil (helix) state of the ith residue in chain j. σ and s are the standard Zimm–Bragg helix initiation and propagation parameters,[5] and w is the helix–helix interaction parameter for a pair of residues. Otherwise stated, $-RT \ln w$ is the free energy per pair of residues when the chains are side-by-side and interacting relative to the case where the pair of residues are noninteracting.

As has been pointed out previously[1]

$$\mathbf{U}_{\mathrm{d}} = \mathbf{U}_{\mathrm{m}} \otimes \mathbf{U}_{\mathrm{m}}\mathbf{E}_{w} \qquad \text{(II-3)}$$

where $\mathbf{U}_{\mathrm{m}}$ is the statistical weight matrix of a residue in a single chain

$$\mathrm{U}_{\mathrm{m}} = \begin{bmatrix} 1 & \sigma s \\ 1 & s \end{bmatrix} \qquad \text{(II-4a)}$$

and $\mathbf{E}_{w}$ is a diagonal matrix with unity along the diagonal except $\mathbf{E}_{w}(4,4) = w$. The eigenvalues of $\mathbf{U}_{\mathrm{m}}$ are

$$\lambda_{1,2} = \frac{1 + s \pm ((1 - s)^2 + 4\sigma s)^{1/2}}{2} \qquad \text{(II-4b)}$$

Equation II-3 implies that two of the eigenvalues of $\mathbf{U}_{\mathrm{d}}$ when $w = 1$ are

$$\lambda_{1,2}{}^{2} = \frac{1 + s^2 + 2\sigma s \pm ((1 - s)^2 + 4\sigma s(1 + s)^2)^{1/2}}{2} \qquad \text{(II-5a)}$$

where the subscript "1" refers to the plus root and the subscript "2" the minus root, respectively. There are also a pair of doubly degenerate eigenvalues

$$\lambda_1\lambda_2 = s(1 - \sigma) \qquad \text{(II-5b)}$$

Let us focus on the latter pair of eigenvalues given eq II-5b. First of all, we observe that $s(1 - \sigma)$ is an eigenvalue of eq II-2 *independent* of the value of w, with left eigenvector row [0, $-1/2^{1/2}$, $1/2^{1/2}$, 0] and right eigenvector col [0, $-1/2^{1/2}$, $1/2^{1/2}$, 0]. Thus, by performing a similarity transformation on eq II-2 it is possible to partially block diagonalize $\mathbf{U}_{\mathrm{d}}$ into a 3 × 3 and 1 × 1 matrix. The similarity transformation we choose will also simultaneously symmetrize $\mathbf{U}_{\mathrm{d}}$, thus demonstrating that all the eigenvalues of $\mathbf{U}_{\mathrm{d}}$ are real.

A suitable similarity transformation is

$$\mathrm{S}^{-1} = \frac{1}{2^{1/2}}\begin{bmatrix} 0 & -(\sigma s)^{1/2} & (\sigma s)^{1/2} & 0 \\ 0 & (\sigma s)^{1/2} & (\sigma s)^{1/2} & 0 \\ 1 & 0 & 0 & \sigma s w^{1/2} \\ 1 & 0 & 0 & -\sigma s w^{1/2} \end{bmatrix} \qquad \text{(II-6a)}$$

and

$$\mathrm{S} = \frac{1}{2^{1/2}}\begin{bmatrix} 0 & 0 & 1 & 1 \\ -\dfrac{1}{(\sigma s)^{1/2}} & \dfrac{1}{(\sigma s)^{1/2}} & 0 & 0 \\ \dfrac{1}{(\sigma s)^{1/2}} & \dfrac{1}{(\sigma s)^{1/2}} & 0 & 0 \\ 0 & 0 & \dfrac{1}{\sigma s w^{1/2}} & -\dfrac{1}{\sigma s w^{1/2}} \end{bmatrix} \qquad \text{(II-6b)}$$

Consequently, we find that

$$\mathrm{S}^{-1}\mathrm{U}_{\mathrm{d}}\mathrm{S} = \begin{bmatrix} s(1-\sigma) & 0 & 0 & 0 \\ 0 & s(1+\sigma) & (\sigma s)^{1/2}(1 + s w^{1/2}) & (\sigma s)^{1/2}(1 - s w^{1/2}) \\ 0 & (\sigma s)^{1/2}(1 + s w^{1/2}) & \dfrac{1 + s^2 w}{2} + \sigma s w^{1/2} & (1 - s^2 w)/2 \\ 0 & (\sigma s)^{1/2}(1 - s w^{1/2}) & \dfrac{1 - s^2 w}{2} & \dfrac{1 + s^2 w}{2} - \sigma s w^{1/2} \end{bmatrix} \qquad \text{(II-6c)}$$

The 3 × 3 matrix of eq II-6c gives rise to the secular equation

$$\lambda^3 + A_1\lambda^2 + A_2\lambda + A_3 = 0 \qquad \text{(II-7a)}$$

with

$$A_1 = -[s(1 + \sigma) + (1 + s^2 w)] \qquad \text{(II-7b)}$$

$$A_2 = s(1 - \sigma)(1 + s^2w) + (1 - \sigma^2)s^2w \qquad \text{(II-7c)}$$

$$A_3 = -s^3(1 - \sigma)^3w \qquad \text{(II-7d)}$$

The eigenvalues of the 3 × 3 matrix in eq II-6c are the three roots of eq II-7a, denoted by λ_+, λ_-, and λ_{12} respectively.

Now let us assume that λ_+, λ_-, and λ_{12} are of the form

$$\lambda_{+,-} = (a - \phi_0 \pm b^{1/2})/2 \qquad \text{(II-8a)}$$

$$\lambda_{12} = s(1 - \sigma) + \phi_0 \qquad \text{(II-8b)}$$

with a, b, and ϕ_0 functions of s, σ, and w to be determined. Observe that if $\phi_0 = 0$ when $w = 1$, eq II-8a,b are of the same form as eq II-5a,b.

We now determine a, using the well-known relation for the sum of the three roots of a cubic[6]

$$\lambda_+ + \lambda_- + \lambda_{12} = -A_1 \qquad \text{(II-9a)}$$

This immediately gives

$$a = 1 + s^2w + 2\sigma s \qquad \text{(II-9b)}$$

We next relate b to a and ϕ_0 using [6]

$$\lambda_+\lambda_-\lambda_{12} = -A_3 \qquad \text{(II-10a)}$$

which provides us with

$$b = (1 + \gamma)^{-1}\{(1 - s^2w)^2 + 4\sigma s(1 + 2sw + s^2w) + 4\sigma^2s^2(1 - w) + \gamma(a^2 - 2as(1 - \sigma)) + \gamma^2(s^2(1 - \sigma)^2 - 2as(1 - \sigma)) + \gamma^3s^2(1 - \sigma)^2\} \qquad \text{(II-10b)}$$

a is defined in eq II-9b and we have set

$$\phi_0 = s(1 - \sigma)\gamma \qquad \text{(II-10c)}$$

Hence our only problem is the determination of γ; the equation γ satisfies is provided by the relation between the sum of products of two of the roots of the cubic;[6] namely

$$(\lambda_+ + \lambda_-)\lambda_{12} + \lambda_+\lambda_- = A_2$$

where if we recognize that eq II-10a gives

$$\lambda_+\lambda_- = (1 + \gamma)^{-1}s^2w(1 - \sigma)^2 \qquad \text{(II-11)}$$

It follows after a bit of arithmetic that γ satisfies

$$-B_0\gamma^3 + B_1\gamma^2 + B_2\gamma + B_3 = 0 \qquad \text{(II-12a)}$$

for which

$$B_0 = s(1 - \sigma) \qquad \text{(II-12b)}$$

$$B_1 = a - 2s(1 - \sigma) \qquad \text{(II-12c)}$$

$$B_2 = a - s(1 + w) + \sigma s(3 - w) \qquad \text{(II-12d)}$$

$$B_3 = 2\sigma s(1 - w) \qquad \text{(II-12e)}$$

or dividing through eq II-12a by $-B_0$, we have

$$\gamma^3 + a_1\gamma^2 + a_2\gamma + a_3 = 0 \qquad \text{(II-13a)}$$

In eq II-13a

$$a_i = -B_i/B_0 \qquad \text{for } i = 1, 2, 3 \qquad \text{(II-13b)}$$

The solution we require to eq II-13a goes to zero when $w = 1$. This ensures the equivalency of eq II-8a with eq II-5a. Moreover, it is positive for all $w > 1$. Using the well-known relations for the analytic solution of a cubic equation,[6] it is straightforward to show that the desired root is

$$\gamma = S + T - a_1/3 \qquad \text{(II-14a)}$$

where

$$S = (R + (Q^3 + R^2)^{1/2})^{1/3} \qquad \text{(II-14b)}$$

$$T = (R - (Q^3 + R^2)^{1/2})^{1/3} \qquad \text{(II-14c)}$$

and in which

$$Q = (3a_2 - a_1^2)/9 \qquad \text{(II-14d)}$$

$$R = (9a_1a_2 - 27a_3 - 2a_1^3)/54 \qquad \text{(II-14e)}$$

In practice, it is in fact more convenient to solve eq II-13a numerically and then extract the smallest positive root. However, a simple analytical solution for λ in the limit of large w may be obtained by recognizing that the coefficient of λ^3 in eq II-12a, $-B_0$, is independent of w. Dividing eq II-12a by $1/w$ and letting $w \to \infty$, we see that II-12a becomes a quadratic equation:

$$\gamma^2s^2 + \gamma(s^2 - s - \sigma s) - 2\sigma s = 0 \qquad \text{(II-15a)}$$

the positive root of which is

$$\gamma = (2s)^{-1}\{-(s - 1 - \sigma) + [(s - 1 - \sigma)^2 + 8\sigma s]^{1/2}\} \qquad \text{(II-15b)}$$

Once γ is determined, inserting γ into eq II-10b gives b and thereby we have λ_+ and λ_- defined in eq II-8a as well as λ_{12} defined in eq II-8b.

It should be pointed out that λ_+ in eq II-8a reduces to the largest eigenvalue of the CC–HH model developed previously in the limit that $w \to \infty$ where terms of order σ and γ can be neglected.[1] Physically this reflects the fact that for finite w, c(1)h(2) (or equivalently h(1)c(2)) states make an appreciable contribution to the partition function. As $w \to \infty$, in both models, h(1)h(2) pairs make the dominant contribution to the partition function (the molecule is completely helical); hence the largest eigenvalue approaches s^2w.

Eigenvectors of the Statistical Weight Matrix. Since $\mathbf{U}_{di}$ defined in eq II-2 is a nonsymmetric matrix, the left and right eigenvectors are not in general the same. Clearly, on the basis of our previous discussion following eq II-5b for $\lambda_1 = s(1 - \sigma)$, a suitable set of left and right eigenvectors are row $[0, -1/2^{1/2}, 1/2^{1/2}, 0]$ and col $[0, -1/2^{1/2}, 1/2^{1/2}, 0]$.

Let us lebel the other three eigenvalues by $\lambda_i = \lambda_+, \lambda_-$, or λ_{12} if i = 2, 3, or 4, respectively. Furthermore, the ith normalized left eigenvector is represented by $\mathbf{y}_i$ = row $[y_{1i}/N_i, y_{2i}/N_i, y_{3i}/N_i, y_{4i}/N_i]$ and the ith normalized right eigenvector is represented by $\mathbf{x}_i$ = col $[x_{1i}/N_i, x_{2i}/N_i, x_{3i}/N_i, x_{4i}/N_i]$ wherein

$$N_i^2 = \sum_{j=1}^{4} x_{ji}y_{ji} \qquad \text{(II-16a)}$$

is the normalization factor.

After a bit of straightforward arithmetic, it can be shown that

$$y_{1i} = s(1 - \sigma) + \lambda_i \qquad \text{(II-16b)}$$

$$y_{2i} = y_{3i} = \sigma s + s(\lambda_i - 1) \qquad \text{(II-16c)}$$

$$y_{4i} = (\lambda_i - 1)[\lambda_i - s(1 + \sigma)] - 2\sigma s \qquad \text{(II-16d)}$$

Moreover

$$x_{1i} = y_{1i}\sigma^2s^2w \qquad \text{(II-17a)}$$

$$x_{2i} = x_{3i} = \sigma swy_{2i} \qquad \text{(II-17b)}$$

$$x_{4i} = y_{4i} \qquad \text{(II-17c)}$$

Having determined the left and right eigenvectors of $\mathbf{U}_d$, it is a straightforward matter to construct the matrices $\mathbf{T}^{-1}$ and $\mathbf{T}$ such that the similarity transformation diagonalizes $\mathbf{U}_d$; namely

$$\mathbf{T}^{-1}\mathbf{U}_d\mathbf{T} = \lambda \qquad \text{(II-18)}$$

produces the diagonal matrix λ, in which the ith element along the diagonal is λ_i. The ith row (column) of $\mathbf{T}^{-1}$ ($\mathbf{T}$) is $\mathbf{y}_i$ ($\mathbf{x}_i$). Moreover, it immediately follows from eq II-18 that the internal partition function of the dimer

$$Z_{\mathrm{sd}} = \sum_{j,l=1}^{4} T_{1j}\lambda_j^N T_{jl}^{-1} \qquad \text{(II-19)}$$

It should be noted that Z_{sd} reduces to the square of the internal partition function of the isolated single chain (monomer) when $w = 1$.

Helix Content of the Dimer in the Limit of Infinite Chain Length. For an arbitrary degree of polymerization of the helix content of the dimer, f_{hd} may be obtained from[1,7]

$$f_{\mathrm{hd}} = (2N)^{-1}\frac{\mathrm{d}\ln Z_{\mathrm{sd}}}{\mathrm{d}\ln s} \qquad \text{(II-20)}$$

While it is in principle possible to explicitly evaluate the derivative of Z_{sd} given in eq II-19 with respect to s, in practice it is more straightforward to use the serial matrix product representation developed previously.[1] In the limit of infinite chain length, however, we can approximate[7]

$$Z_{\mathrm{sd}} \sim \lambda_+^N \qquad \text{(II-21)}$$

with λ_+ the largest eigenvalue of the statistical weight matrix $\mathbf{U}_{\mathrm{d}}$. Thus eq II-20 becomes for an infinite chain

$$f_{\mathrm{hd}}^{\infty} = \frac{1}{2}\frac{\mathrm{d}\ln\lambda_+}{\mathrm{d}\ln s} \qquad \text{(II-22a)}$$

Explicitly differentiating $\ln\lambda_+$ with respect to $\ln s$ gives after considerable manipulation the compact result

$$f_{\mathrm{hd}}^{\infty} = (\lambda_+ - \lambda_-)^{-1}\left\{\frac{(\lambda_- - \lambda_{12})\gamma'/2 + \lambda_{12}(1+\gamma/2)}{1+\gamma} + \lambda_+ - (1+s)\right\} \qquad \text{(II-22b)}$$

in which

$$\gamma' = \frac{\mathrm{d}\gamma}{\mathrm{d}\ln s} = \frac{(\gamma+\gamma^2)(1-s^2w)}{-3\gamma^2B_0 + 2\gamma B_1 + B_2} \qquad \text{(II-22c)}$$

wherein B_0, B_1, and B_2 have been defined in eq II-12b–d, respectively. Observe that $\gamma' = 0$ when $w = 1$, and it is straightforward to show that when $w = 1$, f_{hd}^{∞} reduces to the infinite single-chain, homopolymeric limit[7]

$$f_{\mathrm{hd}}^{\infty} = f_{\mathrm{hm}}^{\infty} = (\lambda_1 - \lambda_2)^{-1}(\lambda_1 - 1); \quad w = 1 \qquad \text{(II-22d)}$$

with λ_1 and λ_2 given in eq II-4b.

III. Numerical Calculations

In this section, we present numerical results on the calculation of the helix content of a homopolymeric dimer in the neglect-loop-entropy approximation at various values of σ as a function of the helix–helix interaction parameter w and as a function of chain length. Comparison is also made in the infinite chain limit between the helix–coil transition in a homopolymeric, two-chain, coiled coil and in an "analogous" isolated, single-chain homopolypeptide constructed such that a pair of such noninteracting single chains has the same statistical weight for the h(1)h(2) state as in the interacting dimer.

Let us begin with the calculation of f_{hd} in the infinite chain limit. In Figure 1 we have plotted f_{hd}^{∞} vs. w calculated with eq II-22b for a homopolymeric dimer having $s = 0.94$ and $\sigma = 10^{-4}$ and 10^{-2} in curves A and C, respectively. Observe that for both cases when $sw^{1/2} = 1$, i.e., the statistical weight of a h(1)h(2) pair is unity, both curves have $f_{\mathrm{hd}}^{\infty} = 0.5$, independent of the value of σ. In curves B and D of Figure 1, we have plotted the helix content of the homopolymeric single chain, obtained from eq II-22d, vs. w, where the statistical weight of a noninterfacial helical residue, s_{m}, is assigned the statistical weight $0.94w^{1/2}$. Moreover, $\sigma = 10^{-4}$ and 10^{-2} in curves B and D, respectively. Note that when $0.94w^{1/2} = 1$, f_{hm}^{∞} equals 0.5 independent of the value of σ.

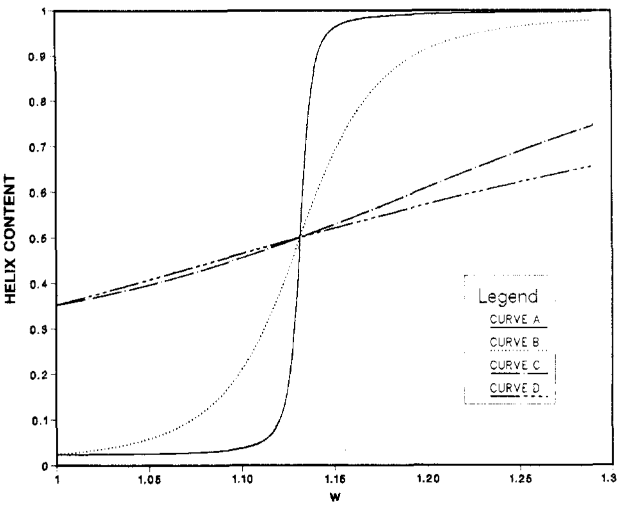

Figure 1. Plot of the fraction of helix in the infinite chain, homopolymeric, two-chain, coiled coil, f_{hd}, vs. the helix–helix interaction parameter, w, with $\sigma = 10^{-4}$ and $\sigma = 10^{-2}$ in curves A and C, respectively. f_{hd}^{∞} is calculated from eq II-22b with $s = 0.94$ and w taken to be uniform. Plot of the fraction of helix in the infinite chain monomer, f_{hm}^{∞}, vs. w with $\sigma = 10^{-4}$ and 10^{-2} in curves B and D, respectively. f_{hm}^{∞} is calculated from eq II-22d with the helix propagation parameter of a residue given by $0.94w^{1/2}$.

The fact that both f_{hd}^{∞} and $f_{\mathrm{hm}}^{\infty} = 0.5$ when $sw^{1/2} = 1$ may be rationalized as follows. Consider first the statistical weight of a noninterfacial c(1) or h(1) state in the monomer. For a single chain when the statistical weight of a coil residue equals that of a helical residue, in the limit of infinite chain length the only role of interfacial coil–helix states is to demark a boundary. One is just as likely to find a string of helical states as of coil states, each of length $1/\sigma^{1/2}$. If σ is smaller (larger), the mean length of a helical or coil state is longer (shorter), but there are equal numbers of such states. Thus $f_{\mathrm{hm}}^{\infty} = 0.5$ when $s_{\mathrm{m}} = sw^{1/2}$ equals unity, independent of σ (here s refers to the helix propagation parameter of a helical residue in the dimer when $w = 1$).

In the case of a two-chain, coiled coil, when $sw^{1/2} = 1$, the statistical weights of c(1)c(2) and noninterfacial h(1)h(2) pairs are unity. Hence, just as in the single-chain case, while σ determines the mean length of a run of helical h(1)h(2) or coiled c(1)c(2) pairs, there are equal numbers of such runs. However, there are also c(1)h(2) and h(1)c(2) states whose statistical weight is less than unity, but these states occur symmetrically on both chains and have the same statistical weight. The length of a string of h(1)c(2) or c(1)h(2) states is determined by the values of σ and s, but both types of states occur with the same frequency. Thus when $sw^{1/2} = 1$, in a infinite chain $f_{\mathrm{hd}}^{\infty} = 0.5$ independent of the value of σ.

In Figure 1, comparison of curve A with curve B, and curve C with curve D, clearly shows that at fixed σ, the helix–coil transition in the homopolymeric two-chain, coiled coil is more cooperative than that for an isolated single chain whose helix propagation parameter equals $sw^{1/2}$. That is at a given w, $f_{\mathrm{hd}}^{\infty} \le f_{\mathrm{hm}}^{\infty}$ when the helix content is less than 50% and $f_{\mathrm{hd}}^{\infty} > f_{\mathrm{hm}}^{\infty}$ when the helix

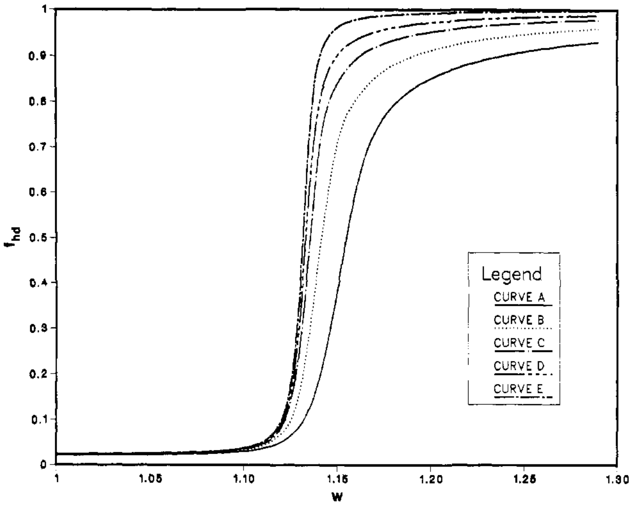

Figure 2. Plot of the fraction of helix in the dimer, f_{hd}, vs. the helix–helix interaction parameter, w, in a homopolymeric, two-chain, coiled coil, having 284, 500, 1000, 2000, and an infinite number of residues, N, per chain in curves A–E, respectively. In all cases $s = 0.94$, $\sigma = 10^{-4}$, and for finite N, f_{hd} is calculated by employing eq II-9 of ref 1. The infinite chain helix content, f_{hd}^{∞}, is calculated with eq II-22b.

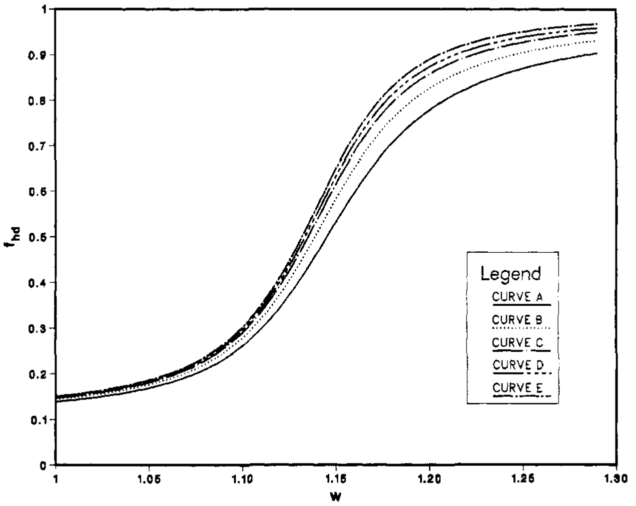

Figure 3. Plot of the fraction of helix in the dimer, f_{hd}, vs. the helix–helix interaction parameter, w in a homopolymeric, two-chain, coiled coil having 284, 500, 1000, 2000, and an infinite number of residues, N, per chain in curves A–E, respectively. In all cases, $s = 0.94$, $\sigma = 10^{-3}$, and for finite N, f_{hd} is calculated by employing eq II-9 of ref 1. The infinite chain helix content, f_{hd}^{∞}, is calculated with eq II-22b.

content is greater than 50%. The origin of the difference lies in the greater statistical weight of h(1)c(2) and c(1)h(2) pairs afforded in the "analogous" noninteracting single-chain model as compared to the dimer. Basically, the statistical weight matrix of two noninteracting single chains having a helix propagation parameter $sw^{1/2}$ is obtained from eq II-2 by multiplying each element of the second and third column of $\mathbf{U}_d$ in eq II-2 by $w^{1/2}$. Whereas in the interacting dimer only h(1)h(2) pairs experience an enhanced probability, in the monomers each individual helical state has a statistical weight enhanced by a factor $w^{1/2}$. Thus the single-chain coil-to-helix transition is broader than that seen in the dimeric, two-chain, coiled coil.

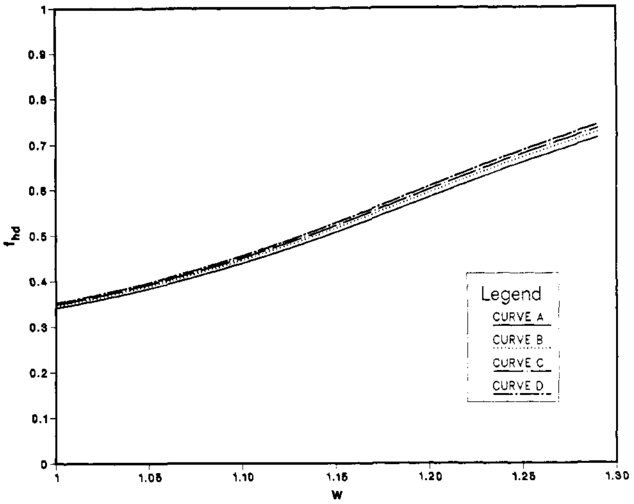

Figure 4. Plot of the fraction of helix in the dimer, f_{hd} vs. the helix–helix interaction parameter, w, in a homopolymeric, two-chain, coiled coil having 284, 500, 1000, and an infinite number of residues, N, per chain in curves A–D, respectively. In all cases $s = 0.94$, $\sigma = 10^{-2}$, and for finite N, f_{hd} is calculated by employing eq II-9 of ref 1. The infinite chain helix content, f_{hd}^{∞}, is calculated with eq II-22b.

In Figures 2–4, we have plotted f_{hd} vs. w for a homopolymeric, two-chain, coiled coil, where $w = 0.94$ and $\sigma = 10^{-4}$, 10^{-3}, and 10^{-2}, respectively. In Figures 2 and 3, $N = 284$, 500, 1000, 2000, and ∞ in curves A–E, respectively. In Figure 4, $N = 284$, 500, 1000, and ∞ in curves A–D, respectively. (On the scale of Figure 4, the curve with $n = 2000$ with $\sigma = 10^{-2}$ is essentially indistinguishable from the infinite chain limit.) The helix content of the dimer at finite N is obtained from eq 9 of ref 1. As is expected, at a given value of σ, the transition becomes sharper with increasing N. Furthermore, we point out that as σ is increased at fixed N, the curves lie closer to the $N = \infty$ limit, as is the case with single-chain homopolymers.[8] Basically when $N\sigma^{1/2} \gg 1$, that is, when the mean length of a helical or coil stretch is appreciably smaller than the overall length N of a chain, the dimer or monomer is in the infinite chain limit. Increasing σ decreases the mean length of a helical stretch and thereby at fixed N enhances the approach to the $N = \infty$ limit.

It is especially clear from curve A in Figures 2 and 3, where $N = 284$ and $\sigma = 10^{-4}$ and 10^{-3}, respectively, that a homopolymeric dimer having $N = 284$ is in the regime where end effects are important. This is in agreement with previous work on homopolymeric, two-chain, coiled coils, in which we concluded on the basis of the fraction of end coils in end-random-coil runs that a dimer with $N = 284$ is in the short to moderate chain limit.[2] Thus unwinding from the ends contributes substantially to the helix–coil transition, an assumption crucial to the development of the theories that include loop entropy with and without mismatch.[2-4] Thus the present work provides further support for the loops-excluded model (with or without mismatch) in which we assume the net effect of loop entropy is to produce a single interacting helical stretch possibly preceded and followed by noninteracting helical stretches punctuated by random coil sequences, a picture that is only applicable for chains where end effects are important.

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Theory of the Kinetics of the Helix–Coil Transition in Two-Chain, Coiled Coils. 1. Infinite-Chain Limit

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ABSTRACT: The kinetics of the α-helix-to-random coil transition in two-chain, coiled coils (dimers) is examined in the context of a kinetic Ising model. We consider the dynamics of the helix–coil transition (or vice versa) of parallel, in-register dimers in which the effects of loop entropy are ignored. Focusing explicitly on homopolymeric chains, we have formulated a master equation for the mean occupation number of the jth residue q_j (equal to +1 (−1) for a completely helical (randomly coiled) state). Analytic expressions for the time dependence and equilibrium values of q_j are derived for the limiting cases of an isolated single chain as well as a DNA-isomorphic model (in which the instantaneous occupation numbers of the jth residue in both chains are identical) for chains of arbitrary length where the final state corresponds to $s = 1$ and $s(w^0)^{1/2} = 1$, respectively. Here, s is the Zimm–Bragg helix propagation parameter of a single residue and w^0 is the helix–helix interaction parameter. For infinite single chains and dimers having arbitrary initial and final states, we introduce physically reasonable approximations to close the infinite hierarchy of coupled differential equations involving multiple-site correlation functions of the occupation numbers. We then solve the resulting coupled first-order linear equations including all orders of two-site correlation functions for the time dependence of the mean occupation number. In the case of single chains an analytic expression for the slowest rate is derived and an examination of the time dependence of the normalized helix content, $H(t)$, is undertaken. In the case of two-chain, coiled coils, numerical results are presented for the time dependence of $H(t)$. A comparison is made of the time scale of the helix–coil transition in single chains and in dimers. Moreover, the validity of approximating $H(t)$ by the slowest relaxing mode is examined for the case of small and large perturbations from an initial state. We conclude that in the context of this model, in dimers this approximation is excellent over a wide variety of initial states and helix contents.

I. Introduction

Over the past several years an equilibrium statistical mechanical theory of the helix-to-random coil transition of α-helical, two-chain, coiled coils (dimers) has been developed.[1–4] The theory seems capable of rationalizing the enhanced stability of the two-chain, coiled coil relative to the isolated single chain (monomers) through the use of a helix–helix interaction parameter w^0;[5,6] $-RT \ln w^0$ is the free energy of a positionally fixed, interacting pair of helical turns in the dimer relative to the free energy of the noninteracting, positionally fixed pair of helical turns in two isolated single chains. The equilibrium theory has been extended to include the effects of loop entropy[2,3] and mismatch on the helix–coil transition[4] and has been applied to the prototypical two-chain, coiled coil, the muscle protein tropomyosin, at near-neutral and at acidic pH.[5,6] Thus, it seems reasonable at this time to begin an investigation of the kinetics of the helix–coil transition in two-chain, coiled coils; the present paper addresses itself to the preliminary treatment of the kinetics of such transitions.

While there is a sizeable body of experimental work characterizing the thermodynamic stability of tropomyosin and a synthetic analogue as a function of temperature,[5–11] the experimental situation with regard to the kinetics of the denaturation is not so sanguine. Although temperature-jump studies of tropomyosin have not been made, Tsong, Himmelfarb, and Harrington have studied the melting kinetics of what they regard as structural domains in the myosin rod.[12] While our equilibrium picture is substantially different from theirs, nevertheless they extract relaxation times that experience a maxima as a function of temperature. The maximum occurs at the apparent midpoint of the transition, a situation reminiscent of that seen in the kinetics of the helix–coil transition in single-chain polypeptides.[13] This is a very important feature which we believe any even qualitatively successful theory of the helix–coil transition must be able to duplicate.

There is a substantial collection of literature on the kinetics of the helix–coil transition employing the kinetic version of the Zimm–Bragg[14] theory in single-chain polypeptides. Basically the approaches involve the solution of a master equation for a reduced probability distribution function or for a moment of the distribution function. In the former approach, one finds a coupled hierarchy of equations in which the $(n + 1)$th-order distribution function is needed to find the nth-order distribution function. Typically, closure relations which are exact at equilibrium are introduced to truncate the hierarchy. These equations have been solved by employing doublet,[15] triplet,[16–18] quadruplet,[19] and generalized closure schemes.[20–24] Schwarz,[13,23] Poland and Scheraga,[24] and Craig and Crothers[25] in particular have emphasized the importance of the initial slope as a well-defined rate constant for systems perturbed near as well as far from equilibrium. The initial rate treatment has been widely employed to interpret apparent approach to equilibrium measurements such as temperature jump,[25] ultrasonic

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