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Effect of Loop Entropy on the Helix–Coil Transition of α-Helical, Two-Chain, Coiled Coils. 3. Supermatrix Formulation of the Imperfect-Matching Model†

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ABSTRACT: The theory of the α-helix-to-random coil transition of two-chain, coiled coils (dimers) has been extended to include the possibility of mismatched association of the chains, viz., the loops-excluded, imperfect-matching model. Since loop entropy essentially restricts the number of interacting helical regions in the dimers to one, the only mismatched conformations consistent with this constraint are the out-of-register ones. Serial matrix product expressions for the internal partition function of the dimer, for the overall helix content, for the helix probability profiles, and for the ratio of the number of randomly coiled residues part of the random coil runs from the chain ends to the total number of random coils are derived. The loops-excluded, imperfect-matching model is applied to hypothetical homopolymeric coiled coils, and the qualitative effect of region specificity of the helix–helix interaction parameter on the character of the helix–coil transition is investigated. Comparison is also made between the present model and the loops-excluded, perfect-matching model developed previously, in which only in-register conformations are allowed.

I. Introduction

In a recent series of papers we have developed the theory of the α-helix-to-random coil transition of two-chain, coiled coils in the perfect-matching approximation.[1-4] That is, we a priori assumed that the portions of the two-chain, coiled coil (dimers) that are helical remain in-register throughout the course of the helix-to-random coil transition. Since it is presumably the interhelical interaction between chains that is responsible for the greatly enhanced helix content of the dimer relative to the isolated single chains, in the limit of 100% helix, the perfect-matching approximation is valid. However, as the helix content of the dimer decreases, the relative importance of out-of-register associations of the two chains, i.e., mismatch, increases: thus mismatched conformations would be expected to be important in the transition region of the thermal denaturation profile. To date, we have entirely ignored this effect. The purpose of the present paper is to extend the theory of the helix-to-coil transition in two-chain, coiled coils to include, via an extension of the supermatrix formulation developed previously,[4] the possibility of mismatched association of the chains. By way of illustration the theory will be applied to hypothetical dimers composed of identical, homopolymeric single chains but whose interhelical interactions may be region dependent.

At this juncture it is appropriate to review the fundamental assumptions of previous work that are applicable to two-chain, coiled coils with mismatch:[1,3]

(1) To account for the short-range interactions, the theory is formulated in terms of the Zimm–Bragg parameters σ and $s(T)$ characteristic of the individual amino acids in the isolated protein chains.[5] σ and $s(T)$ are assumed to depend only on the type of amino acid and are assumed to be independent of the type of nearest neighbor. Recent experimental verification of this assumption has been provided (at least for the isolated single chains in solution) by Kidera et al. for the case of single-chain, random copolymers of (hydroxypropyl)-L-glutamine, L-alanine, and glycine.[6] The practical realization of the theory for proteins such as tropomyosin requires the knowledge of the primary sequence of the molecule and the table of σ and $s(T)$ values for the various poly(amino acids) determined in a impressive experimental effort by Scheraga et al.;[7-20] these expressions have been summarized recently in a convenient algorithmic form.[21,22]

(2) To account for the long-range interactions believed responsible for the greatly augmented helix content of the

† This paper is dedicated to Professor Walter H. Stockmayer—a scientist and a gentleman in the very best sense of the words.

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dimer at low temperature relative to the calculated helix content of isolated single chains, we have introduced a parameter w;[1] $-RT \ln w$ is the free energy of a side-by-side pair of two interacting, α-helical turns relative to the translationally fixed, noninteracting α-helical blocks. In principle, $w(T)$ should be site dependent. Previously, in the case of tropomyosin, Tm, we have employed a uniform $w(T)$;[22,23] recent experimental evidence on Tm fragments indicates that w may be region dependent.[24-26]

A very important conclusion relevant to the present study emerges from the loops-excluded, perfect-matching model of two-chain, coiled coils.[3,4] Namely, for α-helical, two-chain, coiled coils of short to moderate length, the effect of loop entropy is so prohibitive as to completely eliminate interior random coil loops between interacting helical stretches in the dimer. Nevertheless, interior random coil sequences between noninteracting helical portions of the chains are permitted. (In these stretches there are no closed loops whatsoever.) The observation that there is a single interacting helical stretch in any given dimer in fact makes the treatment of mismatch straightforward as compared to the case of DNA. We remind the reader that there is a crucial difference between the helix in two-chain, coiled coils and the DNA-type helix: In the former, each individual chain can, in principle, form an α-helix; in the latter, it is the geometric arrangement of the double strands that constitutes the Watson–Crick double helix.[27] Considerable work on the mismatch problem in DNA helices has been done by Go[28] and Hijmans,[29] who considered the contribution to the partition function of all possible combinations of hairpins. Furthermore, Poland and Scheraga have considered helical stabilization brought about in single-stranded chains by interhelical contacts (such as the hairpin).[30] In all these cases, closed interior random coiled loops are formed and the effect of loop entropy[31-33] must be addressed.

Consider now the analogous problem in α-helical, two-chain, coiled coils of short to moderate length. The formation of a hairpin on one of the strands requires (at the very least) a minimum number of interior random coils between interacting helical regions. In the short to moderate length limit, these interior random coil sequences will have negligible statistical weight relative to an interacting helical sequence of the same length but without the loop. Thus, the single interacting helical stretch approximation pertains to the mismatched case also;[3,4] namely, the statistical weight of hairpin configurations is likely to be small—we a priori set them equal to zero. With the exclusion of hairpin-like conformations, the only mismatched conformations accessible to the two-chain, coiled coil are the out-of-register ones. Again consideration of the nature of loop entropy requires that there be just a single interacting helical stretch in the dimer. Otherwise stated, the incorporation of loop entropy into the theory has greatly simplified the treatment of mismatched in two-chain, coiled coils of short to moderate length; in a given molecule there is just a single interacting, and possibly out-of-register, helical stretch perhaps preceded and/or followed by noninteracting helical stretches punctuated by interior random coil sequences. The above features are embodied in the loops-excluded, imperfect–matching model developed below.

We would expect (and, as demonstrated below, find) that the introduction of out-of-register conformations in the loops-excluded, imperfect-matching model makes the helix–coil transition less cooperative relative to the case where only in-register, interacting helical sequences are permitted,[34] i.e., the loops-excluded, perfect-matching model developed previously.[3,4] At a given value of w, the loops-excluded, imperfect-matching model will have a larger (smaller) helix content at helix contents less than (greater than) about 50% relative to helix content obtained from the loops-excluded, perfect-matching model. Moreover, for the same interhelical interaction, due to the larger number of accessible conformations, the imperfect-matching model will always have a larger internal partition function than the perfect-matching model. Thus at a given w and overall protein concentration, the fraction of chains that exist as dimers rather than isolated single monomers is greater in the imperfect-matching model than in the perfect-matching model.

In the following we shall only treat non-cross-linked chains (in the absence of hairpin configurations, cross-linked chains such as α-tropomyosin cannot have interacting, out-of-register helical conformations[35]). Moreover, based on extant experimental data we shall assume that only the parallel configuration of the two chains is accessible.[36-41] At pH 7, one possible cause of the existence of only all-parallel states arises from the formation of salt bridges in the quasi-repeating heptet characteristic of the primary sequence of tropomyosin.[42-45] In the antiparallel configuration, like charges would be nearest neighbors; this would cause a repulsion between the e and g positions in the heptet rather than salt bridge formation, which would occur if the chains were parallel.[46] Whether the parallel configuration is also due to packing of the hydrophobic data side chains, in the a and d positions of the heptet,[42] at this time we cannot say. If in fact if turns out that under certain conditions the antiparallel arrangement of the two chains makes an appreciable contribution to the partition function, it is a straightforward matter to extend the theory to include them.

Since it is the interhelical interaction that is responsible for the greatly augmented helix content of the dimer relative to the isolated single chains, as mentioned above, in the limit of complete helix the imperfect-matching model must converge to the perfect-matching limit; i.e., the state with 100% helix is completely in-register. This conclusion is true regardless of whether w is uniform, region dependent, or site specific. However, the value of w necessary to achieve the perfect-matching, completely in-register limit will depend on the specificity of the interhelical interaction. If, for example, certain regions of the two chains have interactions that particularly favor the in-register configuration, the perfect-matching limit will be achieved at lower helix content. (The simplest illustration of this is a covalent cross-link between in-register residues.) Recent experimental work indicates that the N-terminal half of tropomyosin is more stable than the C-terminal half.[24-26] If the N-terminal half of the molecule is characterized by a helix–helix interaction parameter w_N and the C-terminal half by a parameter w_C, then if w_N is greater than w_C, at high helix content, those conformations closest to being in-register (perfect matching and one or two helical turns less the perfect matching) will be more highly populated than if w were uniform (the helix content is higher in the nonuniform model) and equal to w_C. The relative population of the significantly out-of-register conformations will depend on the out-of-register, helix–helix interaction parameter w_0. If w_0 is greater than w_C, then the out-of-register populations will be increased relative to the case where w_0 equaled w_C. Furthermore, for a given in-register, helix–helix interaction, the helix content will decrease (at high helix) as the interhelical interaction for very significantly out-of-register conformations increases. (Out-of-register conformations have a

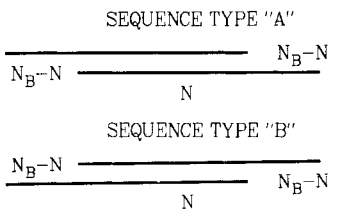

Figure 1. Schematic representative of the two types of $N_B - N$ out-of-register sequences. In sequence type "a", the left-most possible interacting block pair is composed of blocks "$N_B - N + 1$" in chain one and "1" in chain two. In sequence type "b", the left-most possible interacting block pair is composed of blocks "1" in chain one and "$N_B - N + 1$" in chain two.

smaller helix content.) Thus in the extreme case where a two-chain, coiled coil is cross-linked in an out-of-register conformation the dimer should have a lower helix content. We shall not, however, discuss the effect of cross-linking any further but refer the reader to the work of Mattice and Skolnick.[2]

In the following we shall flesh out and substantiate the qualitative picture of the helix–coil transition of two-chain, coiled coils developed above. The organization of the paper is as follows. In section II, the theory of the loops-excluded, imperfect-matching model is developed. Expressions applicable to a specific-sequence, two-chain, coiled coil for the calculation of the internal partition function of the dimer (Z_{sd}), the overall helix content of the dimer (f_{hd}), the helix probability profiles, and the fraction of random coils that unwind from the ends are given. Section III presents calculations on hypothetical, homopolymeric two-chain, coiled coils designed to illustrate the qualitative features of the helix–coil transition where the possibility of mismatch has been included. Comparison with the loops-excluded, perfect-matching model is given. Application is made to chains having a uniform as well as a region-dependent w. Finally, in section IV we highlight the conclusions of the present work and point out directions of future research.

II. Loops-Excluded, Imperfect-Matching Model

In the following we shall develop the loops-excluded, imperfect-matching model for a heteropolymeric, two-chain, coiled coil composed of parallel, identical chains. Extension of nonidentical chains is straightforward. Let each chain be composed of N_T residues, divided into N_B blocks, the ith block of which contains m_i residues. For a discussion of the physical basis of the coarse-graining approximation, we refer to previous work.[1,3,4] Suppose the maximum number of interacting blocks in a given conformation is N, where $1 \leq N \leq N_B$. Thus a chain with $N = N_B$ is in the perfect-matching limit developed previously. For all values of N less than N_B, two kinds of out-of-register states are accesible; these are depicted in Figure 1. In an "a"-type sequence, helical block "i" in chain one interacts with helical block "$i - (N_B - N)$" on chain two. Hence $i > N_B - N$. In a "b"-type sequence, helical block "i" in chain one interacts with helical block "$i + (N_B - N)$" on chain two. Hence $i \leq N$. In the former, case a, the left-most block in chain one that is capable of interacting with a block in chain two is block "$N_B - N + 1$"; in the latter, case b, the left-most block in chain one capable of interacting with a block in chain two is block "1". In a given conformation within the N-block sequence there is a single interacting helical stretch possibly preceded and followed by punctuated random coil and noninteracting helical sequences. Thus, the problem of mismatch differs from the perfect-matching model in that we must take appropriate account of the "end effects" of the $N_B - N$ noninteracting blocks on each of the chains in a given "a"- or "b"-type sequence.

It should be pointed out that in identical chains the contribution to the partition function of the "a"- and "b"-type sequences is the same. (They are related by a 180° flip about the axis between the interacting helical stretch.) Thus for the calculation of certain quantities such as the partition function and the overall helix content, we need only examine type-"a" sequences. The reader may find it helpful to review ref 4 on the perfect-matching limit of the loops-excluded model before continuing on to the rest of the paper. All equations referred to in ref 4 will have a prefix PM; e.g., eq II-2 of ref 4 is indicated by eq PM-II-2.

Statistical Weights of the Block Conformations. Let us begin with a review of the allowed conformations and their statistical weights required for the calculations presented below.[4] Define H (C) to represent a helical (random coil) block, i.e., a block consisting of m_i residues in the helical (random coil) conformation. Moreover, [H]C and [C]H represent random coil and helical blocks at the interface between a sequence of helical and coil blocks and coil and helical blocks, respectively. The statistical weights of the various conformations accessible to the ith block in a single chain poly(amino acid) are

conformation	statistical weight
[C]C	1
[C]H	$\tau_i = \sum_{j=1}^{m_i} \sigma_j \prod_{k=j}^{m_i} s_k$
[H]H	$SM_i = \prod_{j=1}^{m_i} s_j$
[H]C	$\mathcal{S}_i = 1 + \sum_{j=1}^{m_i-1} \prod_{k=1}^{j} s_k$

with σ_j and s_j the standard Zimm–Bragg helix initiation and propagation parameters for the jth amino acid.[5]

Calculation of the Internal Partition Function. As mentioned above for identical chains, the contribution of type-"a" and -"b" sequences to the partition function of the subpopulation containing a maximum of N interacting blocks is the same. Hence we need only focus on type-"a" sequences for the moment. The internal partition function of the dimer, Z_{sd}, can be represented by

$$Z_{sd} = 2Z_m - 1 + (2 - \delta_{N_B,N}) \sum_{N=1}^{N_B} Z(N) \qquad \text{(II-1)}$$

wherein Z_m is the partition function of an isolated single chain; the factor $2Z_m - 1$ accounts for the state in which one of two chains is completely randomly coiled. δ is the Kronecker delta. $Z(N)$ is the contribution to the partition function of the type-"a" sequences that contain a maximum of N interacting blocks. It is more convenient from a computational point of view to start the sum from the perfect-matching limit and continue down to the limit where there is a single interacting helical block pair, block "N_B" in chain one and block "1" in chain two. Now, if $1 < N \leq N_B$

$$Z(N) = \mathbf{J}^* \prod_{i=N_B-N+1}^{N_B} \mathbf{U}_{si}^a \mathbf{J} \qquad \text{(II-2a)}$$

where $\mathbf{J}^*$ is a row vector of one followed by eleven zeroes, $\mathbf{J}$ is a column vector of four zeros followed by eight ones, and $Z(1)$ is defined below in eq II-10.

In the above equation and all those that follow, a subscript labels the block number, and (for matrices) a superscript (either "a" or "b") labels the sequence type. Thus,

by way of illustration, $\mathbf{U}^{a}_{si}$ refers to the supermatrix associated with block "i" on chain one in a type-"a" sequence.

The presence of the noninteracting blocks "1" to "$N_B - N$" in chain one and blocks "$N + 1$" to "N_B" in chain two is accounted for by the statistical weight matrices $\mathbf{U}^{a}_{sN_B-N+1}$ and $\mathbf{U}^{a}_{sN_B}$, respectively; these matrices are defined in eq II-7 and II-9. Before considering these end matrices, which are somewhat more complicated, let us examine the expressions for $N_B - N + 1 < i < N_B$. The $\mathbf{U}^{a}_{si}$ are essentially identical with eq PM-II-7, but with the index of the statistical weights associated with blocks in chain two shifted by a factor $N_B - N \equiv \Delta$. That is, block "i" on chain one is associated with block $i - \Delta$ on chain two. Hence

$$\mathbf{U}^{a}_{si} = \begin{bmatrix} \mathbf{U}^{a}_{di} & \mathbf{U}^{a}_{CHi} & \bigcirc \\ \bigcirc & \mathbf{U}^{a}_{HHi} & \mathbf{U}^{a}_{HCi} \\ \bigcirc & \bigcirc & \mathbf{U}_{di} \end{bmatrix} \tag{II-2b}$$

$\mathbf{U}^{a}_{si}$ is a partitioned 12×12 matrix, with $\bigcirc$ at 4×4 null matrix and with the noninteracting block, statistical weight matrix given by

$$\mathbf{U}^{a}_{di} = \begin{bmatrix} 1 & \tau_{i-\Delta} & \tau_i & \tau_i\tau_{i-\Delta} \\ \mathcal{S}_{i-\Delta} & \mathbf{SM}_{i-\Delta} & \tau_i\mathcal{S}_{i-\Delta} & \tau_i\mathbf{SM}_{i-\Delta} \\ \mathcal{S}_i & \mathcal{S}_i\tau_{i-\Delta} & \mathbf{SM}_i & \mathbf{SM}_i\tau_{i-\Delta} \\ \mathcal{S}_i\tau_{i-\Delta} & \mathcal{S}_i\mathbf{SM}_{i-\Delta} & \mathbf{SM}_i\mathcal{S}_{i-\Delta} & \mathbf{SM}_i\mathbf{SM}_{i-\Delta} \end{bmatrix} \tag{II-3}$$

The initiation matrix of the interacting helix stretch is

$$\mathbf{U}^{a}_{CHi} = \begin{bmatrix} \bigcirc & \begin{matrix} 0 & \tau_i\tau_{i-\Delta}w_i \\ 0 & \tau_i\mathbf{SM}_{i-\Delta}w_i \end{matrix} \\ \bigcirc & \begin{matrix} 0 & \mathbf{SM}_i\tau_{i-\Delta}w_i \\ 0 & 0 \end{matrix} \end{bmatrix} \tag{II-4}$$

$\bigcirc$ is a 2×2 null matrix. Furthermore, the propagation matrix of the interacting helical stretch is

$$\mathbf{U}^{a}_{HHi} = \begin{bmatrix} \bigcirc & \bigcirc \\ \bigcirc & \begin{matrix} 0 & 0 \\ 0 & \mathbf{SM}_i\mathbf{SM}_{i-\Delta}w_i \end{matrix} \end{bmatrix} \tag{II-5a}$$

and the termination matrix of the interacting helical stretch is

$$\mathbf{U}^{a}_{HCi} = \begin{bmatrix} \bigcirc & \bigcirc \\ \begin{matrix} 0 & 0 \\ \mathcal{S}_i\mathcal{S}_{i-\Delta} & \mathcal{S}_i\mathbf{SM}_{i-\Delta} \end{matrix} & \begin{matrix} 0 & 0 \\ \mathcal{S}_{i-\Delta}\mathbf{SM}_i & 0 \end{matrix} \end{bmatrix} \tag{II-5b}$$

Observe that the statistical weight matrix characteristic of block i and $i + \Delta$ on chains one and two, respectively, in a type-"b" sequence is readily obtained from eq II-3 to II-5 by replacing the subcript $i - \Delta$ with $i + \Delta$.

Consider now the statistical weight matrix associated with block "$N_B - N + 1$". The probability of seeing a given conformation on block "$N_B - N + 1$" is the statistical weight of that conformation in the absence of the $N_B - N$ mismatched blocks times the statistical weights associated with all the possible conformations of the $N_B - N$ blocks in chain one. Now, if $N_B \neq N$, the statistical weight matrix associated with all accessible states on blocks "1" to "$N_B - N$" is merely a 4×4 matrix of the form

$$\mathbf{U}^{al} = \prod_{i=1}^{N_B-N} \mathbf{U}_{mi} \otimes \mathbf{E}_2 \tag{II-6a}$$

with $\mathbf{U}_{mi}$ the statistical weight matrix of noninteracting block i in the out-of-register, "dangling" left end of chain one (see eq PM-II-3b). $\mathbf{E}_2$ is the 2×2 identity matrix. The symbol $\otimes$ denotes the direct product and makes the matrix $\mathbf{U}^{al}$ conformable with 4×4 statistical weight matrices of the block pair composed of block "$N_B - N + 1$" in chain one and block "1" on chain two. Now, if $N_B = N$

$$\mathbf{U}^{al} = \mathbf{E}_4 \tag{II-6b}$$

and $\mathbf{E}_4$ is the 4×4 identity matrix. See supplementary material, Appendix A, for additional details. Hence

$$\mathbf{U}^{a}_{SN_B-N+1} = \begin{bmatrix} \mathbf{U}^{al}\mathbf{U}^{a}_{d} & \mathbf{U}^{al}\mathbf{U}^{a}_{CH} & \bigcirc \\ \bigcirc & \mathbf{U}^{al}\mathbf{U}^{a}_{HH} & \mathbf{U}^{al}\mathbf{U}^{a}_{HC} \\ \bigcirc & \bigcirc & \mathbf{U}^{al}\mathbf{U}^{a}_{d} \end{bmatrix} \tag{II-7}$$

Similarly, we define the direct-product, conformable statistical weight matrix associated with the sum over all accessible states of blocks "$N + 1$" to "N_B" in chain two if $N_B \neq N$ by

$$\mathbf{U}^{ar} = \mathbf{E}_2 \otimes \prod_{j=1}^{N_B-N} \mathbf{U}_{mN+j} \tag{II-8a}$$

and if $N_B = N$, by

$$\mathbf{U}^{ar} = \mathbf{E}_4 \tag{II-8b}$$

Thus

$$\mathbf{U}^{a}_{SN_B} = \begin{bmatrix} \mathbf{U}^{a}_{d}\mathbf{U}^{ar} & \mathbf{U}^{a}_{CH}\mathbf{U}^{ar} & \bigcirc \\ \bigcirc & \mathbf{U}^{a}_{HH}\mathbf{U}^{ar} & \mathbf{U}^{a}_{HC}\mathbf{U}^{ar} \\ \bigcirc & \bigcirc & \mathbf{U}^{a}_{d}\mathbf{U}^{ar} \end{bmatrix} \tag{II-9}$$

In the supplementary material, Appendix A, we derive recursion relations for $\mathbf{U}^{ar}$ and $\mathbf{U}^{al}$.

From the above, it is obvious that a molecule that is $N_B - 1$ blocks out-of-register can only be in a [C]H-type state, i.e., an initiating block pair of an interacting helical stretch. Hence, it follows from eq II-7 and II-9 that

$$Z(1) = \mathbf{J}_4{}^*\mathbf{U}^{al}(N{=}1)\mathbf{U}^{a}_{CHN_B}\mathbf{U}^{ar}(N{=}1)\mathbf{J}_4 \tag{II-10}$$

where $\mathbf{J}_4{}^*$ = Row (1, 0, 0, 0) and $\mathbf{J}_4$ = Col (1, 1, 1, 1).

In fact, antiparallel configurations exist and make an appreciable contribution to Z_{sd}; they can be included in eq II-1, with an appropriate Boltzmann factor in w_i accounting for the differences in stability between parallel and antiparallel chains.

Calculation of the Helix Content. In the calculation of the overall helix content, f_{hd}, we need only focus on the type-"a" sequence. Consider the contribution to f_{hd} of block pair "i" on chain one and "$i - (N_B - N)$" on chain two. The fraction of residues in block "$i - (N_B - N)$" in chain two that are helical in sequence type "a" is precisely the fraction of residues in block "$i - (N_B - N)$" in chain one that are helical in sequence type "b". Thus, by counting the total contribution to the helix content of block pair "i" and "$i - (N_B - N)$", we can obtain f_{hd} directly from consideration of type-"a" sequences alone. This particular formulation reduces the computer time necessary to cal-

culate the helix content by essentially a factor of 2. It should be used whenever the two strands of the two-chain, coiled coil are identical.

The overall helix content of the dimer is obtained from

$$f_{hd} = f_{hm}Z_m/Z_{sd} + N_T^{-1}Z_{sd}^{-1}\Big\{\mathbf{J}_s^*\prod_{i=1}^{N_B}\mathbf{A}_{si}\mathbf{J}_s + \sum_{N=2}^{N_B-1}[\mathbf{J}_s^*\mathbf{A}^a_{sN_B-N+1}\prod_{i=N_B-N+2}^{N_B-1}\mathbf{A}^a_{si}\mathbf{A}^a_{sN_B}\mathbf{J}_s + \mathbf{J}^*\mathbf{U}^{alp}_{sN_B-N+1}\prod_{i=N_B-N+2}^{N_B}\mathbf{U}^a_{si}\mathbf{J} + \mathbf{J}^*\prod_{i=N_B-N+1}^{N_B-1}\mathbf{U}^a_{si}\mathbf{U}^{arp}_{sN_B}\mathbf{J}] + \mathbf{J}_4^*\mathbf{U}^{alp}(N_B)\mathbf{U}^a_{CHN_B}\mathbf{U}^{ar}(N_B)\mathbf{J}_4 + \mathbf{J}_4^*\mathbf{U}^{al}(N_B)\mathbf{U}^a_{CHN_B}\mathbf{U}^{arp}(N_B)\mathbf{J}_4 + \mathbf{J}_4^*\mathbf{U}^{al}(N_B)\mathbf{U}'_{CHN_B}\mathbf{U}^{ar}(N_B)\mathbf{J}_4\Big\} \quad \text{(II-11)}$$

with f_{hm} the helix content of the monomer, $\mathbf{J}_s^*$ a row vector consisting of a one followed by twenty-three zeros, and $\mathbf{J}_s$ a column vector consisting of sixteen zeroes followed by eight ones. The first class of terms in the brackets sums over the contribution to f_{hd} of those chains that are completely in-register. The 24 × 24 partitioned matrices $\mathbf{A}_{si}$ are defined in eq PM-II-11. Expressions for the calculation of f_{hm} may be found in eq PM-II-12.

The first class of terms in eq II-11 contained within the sum over the out-of-register states calculates for a given value of N the contribution to f_{hd} of those residues in blocks that are capable of experiencing the interhelical interaction, i.e., those residues in blocks "$N_B - N + 1$" to "N_B" on chain one and "1" to "N" on chain two and not in a "dangling" end. More precisely, if $i = N_B - N + 1$

$$\mathbf{A}^a_{sN_B-N+1} = \begin{bmatrix} \mathbf{U}^a_{sN_B-N+1} & \mathbf{U}^{a'}_{spN_B-N+1} \\ \bigcirc & \mathbf{U}^a_{spN_B-N+1} \end{bmatrix} \quad \text{(II-12a)}$$

with $\mathbf{U}^a_{sN_B-N+1}$ defined in eq II-7, ◯ a 12 × 12 null matrix, and

$$\mathbf{U}^{a'}_{sN_B-N+1} = \begin{bmatrix} \mathbf{U}^{al}\mathbf{U}'_d & \mathbf{U}^{al}\mathbf{U}'_{CH} & \bigcirc \\ \bigcirc & \mathbf{U}^{al}\mathbf{U}'_{HH} & \mathbf{U}^{al}\mathbf{U}'_{HC} \\ \bigcirc & \bigcirc & \mathbf{U}^{al}\mathbf{U}'_d \end{bmatrix}_{N_B-N+1} \quad \text{(II-12b)}$$

with $\mathbf{U}^{al}$ defined in eq II-6a. Moreover

$$\mathbf{U}'_{di} = \begin{bmatrix} 0 & \tau'_{i-\Delta} & \tau'_i & \tau'_i\tau'_{i-\Delta}+\tau_i\tau'_{i-\Delta} \\ \mathcal{S}'_{i-\Delta} & m_{i-\Delta}\mathrm{SM}_{i-\Delta} & \tau'_i\mathcal{S}_{i-\Delta}+\tau_i\mathcal{S}'_{i-\Delta} & \mathrm{SM}_{i-\Delta}(\tau'_i+m_{i-\Delta}\tau_i) \\ \mathcal{S}'_i & \mathcal{S}'_i\tau_{i-\Delta}+\mathcal{S}_i\tau'_{i-\Delta} & m_i\mathrm{SM}_i & \mathrm{SM}_i(\tau'_{i-\Delta}+m_i\tau_{i-\Delta}) \\ \mathcal{S}'_i\mathcal{S}_{i-\Delta}+\mathcal{S}_i\mathcal{S}'_{i-\Delta} & \mathrm{SM}_{i-\Delta}(\mathcal{S}'_i+m_{i-\Delta}\mathcal{S}_i) & \mathrm{SM}_i(m_i\mathcal{S}_{i-\Delta}+\mathcal{S}'_{i-\Delta}) & (m_i+m_{i-\Delta})\mathrm{SM}_i\mathrm{SM}_{i-\Delta} \end{bmatrix} \quad \text{(II-12c)}$$

where τ'_i and $\mathcal{S}'_i$ have been defined in eq 31a and 31c of ref 1 and m_i is the number of residues in block "i". In addition

$$\mathbf{U}'_{CHi} = \begin{bmatrix} \bigcirc & \begin{matrix} 0 & (\tau'_i\tau'_{i-\Delta}+\tau_i\tau'_{i-\Delta})w_i \\ 0 & \mathrm{SM}_{i-\Delta}(\tau'_i+m_{i-\Delta}\tau_i)w_i \end{matrix} \\ \bigcirc & \begin{matrix} 0 & \mathrm{SM}_i(\tau'_{i-\Delta}+m_i\tau_{i-\Delta})w_i \\ 0 & 0 \end{matrix} \end{bmatrix} \quad \text{(II-12d)}$$

in which ◯ is a 2 × 2 null matrix. Furthermore, $\mathbf{U}'_{HH}$ in eq II-12b is given by

$$\mathbf{U}'_{HHi} = \begin{bmatrix} \bigcirc & \bigcirc \\ \bigcirc & \begin{matrix} 0 & 0 \\ 0 & \mathrm{SM}_i\mathrm{SM}_{i-\Delta}(m_i+m_{i-\Delta})w_i \end{matrix} \end{bmatrix} \quad \text{(II-12e)}$$

and

$$\mathbf{U}'_{HCi} = \begin{bmatrix} \bigcirc & \bigcirc \\ \begin{matrix} 0 & 0 \\ \mathcal{S}'_i\mathcal{S}_{i-\Delta}+\mathcal{S}_i\mathcal{S}'_{i-\Delta} & \mathrm{SM}_{i-\Delta}(\mathcal{S}'_i+m_{i-\Delta}\mathcal{S}_i) \end{matrix} & \begin{matrix} 0 & 0 \\ \mathrm{SM}_i(m_i\mathcal{S}_{i-\Delta}+\mathcal{S}'_{i-\Delta}) & 0 \end{matrix} \end{bmatrix} \quad \text{(II-12f)}$$

Now, if $N_B - N + 1 < i < N_B$

$$\mathbf{A}^a_{si} = \begin{bmatrix} \mathbf{U}^a_{si} & \mathbf{U}^{a'}_{si} \\ \bigcirc & \mathbf{U}^a_{si} \end{bmatrix} \quad \text{(II-13a)}$$

where $\mathbf{U}^a_{si}$ is given in eq II-2b and

$$\mathbf{U}^{a'}_{si} = \begin{bmatrix} \mathbf{U}'_{di} & \mathbf{U}'_{CHi} & \bigcirc \\ \bigcirc & \mathbf{U}'_{HHi} & \mathbf{U}'_{HCi} \\ \bigcirc & \bigcirc & \mathbf{U}'_{di} \end{bmatrix}_i \quad \text{(II-13b)}$$

with $\mathbf{U}'_d$, $\mathbf{U}'_{CH}$, $\mathbf{U}'_{HH}$, and $\mathbf{U}'_{HC}$ defined in eq II-12c–f, respectively. Finally, if $i = N_B$, we have

$$\mathbf{A}^a_{sN_B} = \begin{bmatrix} \mathbf{U}^a_{sN_B} & \mathbf{U}^{a'}_{sN_B} \\ \bigcirc & \mathbf{U}^a_{sN_B} \end{bmatrix} \quad \text{(II-14a)}$$

in which $\mathbf{U}^a_{sN_B}$ has been presented in eq II-9 and

$$\mathbf{U}^{a'}_{sN_B} = \begin{bmatrix} \mathbf{U}'_d\mathbf{U}^{ar} & \mathbf{U}'_{CH}\mathbf{U}^{ar} & \bigcirc \\ \bigcirc & \mathbf{U}'_{HH}\mathbf{U}^{ar} & \mathbf{U}'_{HC}\mathbf{U}^{ar} \\ \bigcirc & \bigcirc & \mathbf{U}'_d\mathbf{U}^{ar} \end{bmatrix} \quad \text{(II-14b)}$$

wherein $\mathbf{U}'_d$, $\mathbf{U}'_{CH}$, $\mathbf{U}'_{HH}$, and $\mathbf{U}'_{HC}$ have been defined in eq II-12c–f and $\mathbf{U}^{ar}$ has been given in eq II-8a.

The next two classes of terms in eq II-11 sum over the contribution to f_{hd} of these residues that are out-of-register and not contiguous to the other chain in the left and right ends in the type-"a" sequence, respectively. $\mathbf{J}^*$ and $\mathbf{J}$ are the row and column vectors defined below eq II-2a.

Now, we can write (for the second term in the bracket of eq II-11)

$$\mathbf{U}^{alp}_{sN_B-N+1} = \begin{bmatrix} \mathbf{U}^{alp}\mathbf{U}^a_d & \mathbf{U}^{alp}\mathbf{U}^a_{CH} & \bigcirc \\ \bigcirc & \mathbf{U}^{alp}\mathbf{U}^a_{HH} & \mathbf{U}^{alp}\mathbf{U}^a_{HC} \\ \bigcirc & \bigcirc & \mathbf{U}^{alp}\mathbf{U}^a_d \end{bmatrix} \quad \text{(II-15a)}$$

where $\mathbf{U}^{alp}$ sums the total contribution to the helix content of blocks "1" to "$N_B - N$" in chain one in a type-"a" se-

quence. An explicit prescription for the calculation of $\mathbf{U}^{alp}$ may be found in the supplementary material, Appendix A, eq A-11. Furthermore, the $\mathbf{U}^{a}_{si}$ for $i > N_B - N + 1$ have been given in eq II-2b and II-9, and their product provides the sum of the statistical weights of all blocks "$N_B - N + 2$" to "N_B" in chain one and blocks "2" to "N_B" in chain two.

In an analogous fashion the third term in the bracket of eq II-11 sums the total contribution to the helix content of blocks "$N + 1$" to "N_B" in chain one in a type-"b" sequence. The $\mathbf{U}_{si}$ for $i < N_B$ hve been defined above. We merely need examine

$$\mathbf{U}^{arp}_{sN_B} = \begin{bmatrix} \mathbf{U}^{a}_{d}\mathbf{U}^{arp} & \mathbf{U}^{a}_{CH}\mathbf{U}^{arp} & \mathbf{O} \\ \mathbf{O} & \mathbf{U}^{a}_{HH}\mathbf{U}^{arp} & \mathbf{U}^{a}_{HC}\mathbf{U}^{arp} \\ \mathbf{O} & \mathbf{O} & \mathbf{U}^{a}_{d}\mathbf{U}^{arp} \end{bmatrix} \quad \text{(II-15b)}$$

with $\mathbf{U}^{arp}$ the statistical weight matrix that sums the contribution to the helix content of blocks "$N + 1$" to "N_B" in chain one in the type-"b" sequence or equivalently the contribution to the total helix content of blocks "$N + 1$" to "N_B" of chain two in the type-"a" sequences. $\mathbf{U}^{arp}$ is defined explicitly in the supplementary material, Appendix A, eq A-12a,b.

The final three matrix products in eq II-11 include the contribution to f_{hd} of those molecules that are $N_B - 1$ blocks out-of-register. Presumably, at moderate to high helix content these terms are unimportant. The definition of $\mathbf{J}_4^*$ and $\mathbf{J}_4$ may be found below eq II-10. The term containing $\mathbf{U}^{alp}(N_B)$ evaluates the total helix content of blocks "1" to "$N_B - 1$" in chain one, sequence type "a". The term containing $\mathbf{U}^{arp}(N_B)$ evaluates the contribution to total helix content of blocks "2" to "N_B" in chain two, sequence type "a". Finally, the term containing $\mathbf{U}'_{CHN_B}$ (defined in eq II-12d) evaluates the contribution to the total helix content of the single possible interacting block pair, block "N_B" in chain one and block "1" in chain two in the $N_B - 1$ out-of-register conformation. Thus an expression for f_{hd} in the loops-excluded, imperfect-matching model has been developed.

Calculation of Helix Probability Profiles. The calculation of the fraction of residues in the jth block in chain one that are helical, $f_{hd}(j)$, is somewhat more complicated than the evaluation of f_{hd} in eq II-11. In the expression of eq II-11, we obtain at a given N, and for those blocks that are not dangling ends, the helix content of block "i" in chain one in sequence "a" and block "$i - (N_B - N)$" in chain one in sequence "b". When constructing the helix probability profile, we require $f_{hd}(j)$ alone. Consequently, even for identical chains, we are forced to evaluate the expressions for both "a" and "b"-type sequences. Hence we can write

$$f_{hd}(j) = f_{hm}(j)Z_m/Z_{sd} + m_j^{-1}Z_{sd}^{-1}\{\mathbf{J}^*\prod_{i=1}^{j-1}\mathbf{U}_{si}\mathbf{U}'_{sj}\prod_{i=j+1}^{N_B}\mathbf{U}_{si}\mathbf{J}\} + f(N_B - 1,j) + f(N_B,j) \quad \text{(II-16)}$$

In eq II-16, $f_{hm}(j)$ is the helix content of the jth block in the isolated single chain; an explicit expression for f_{hm} may be found in eq PM-II-14. The first class of terms in the braces evaluates the contribution to $f_{hd}(j)$ for the jth block in the completely in-register conformation; $\mathbf{U}_{si}$ and $\mathbf{U}'_{si}$ are defined in eq PM-II-7 and PM-II-11b, respectively.

$f(N_B - 1,j)$ is the contribution to the average helix content of block j in sequences that are out-of-register by 1 to $N_B - 2$ blocks. $f(N_B,j)$ evaluates the contribution to $f_{hd}(j)$ of the $N_B - 1$ out-of-register block sequence. More explicitly

$$f(N_B - 1,j) = m_j^{-1}Z_{sd}^{-1}\sum_{N=2}^{N_B-1}\{\mathbf{J}^*\mathbf{U}^{aj}_{sN_B-N+1}\prod_{i=N_B-N+2}^{N_B-1}\mathbf{U}^{a}_{si}\mathbf{U}^{aj}_{sN_B}\mathbf{J} + \mathbf{J}^*\mathbf{U}^{bj}_{s1}\prod_{i=2}^{N-1}\mathbf{U}^{bj}_{si}\mathbf{U}^{bj}_{sN}\mathbf{J}\} \quad \text{(II-17)}$$

wherein the first (second) class of terms deals with an "a" ("b")-type sequence. We examine the type-"a" sequence first.

Suppose $j \neq N_B - N + 1$; then

$$\mathbf{U}^{aj}_{sN_B-N+1} = \begin{bmatrix} \mathbf{U}^{alj}\mathbf{U}^{a}_{d} & \mathbf{U}^{alj}\mathbf{U}^{a}_{CH} & \mathbf{O} \\ \mathbf{O} & \mathbf{U}^{alj}\mathbf{U}^{a}_{HH} & \mathbf{U}^{alj}\mathbf{U}^{a}_{HC} \\ \mathbf{O} & \mathbf{O} & \mathbf{U}^{alj}\mathbf{U}^{a}_{d} \end{bmatrix} \quad \text{(II-18a)}$$

with

$$\mathbf{U}^{alj} = (\prod_{k=1}^{j-1}\mathbf{U}_{mk}\mathbf{U}'_{mj}\prod_{k=j+1}^{N}\mathbf{U}_{mk}) \otimes \mathbf{E}_2 \quad \text{(II-18b)}$$

if $j \leq N_B - N$ and in which

$$\mathbf{U}'_{mj} = \begin{bmatrix} 0 & \tau'_j \\ \mathcal{S}'_j & m_j\mathbf{SM}_j \end{bmatrix} \quad \text{(II-18c)}$$

and if $j > N_B - N$

$$\mathbf{U}^{alj} = \mathbf{U}^{al} \quad \text{(II-18d)}$$

where $\mathbf{U}^{al}$ has been defined in eq II-6a.

Suppose that $j = N_B - N + 1$; then we have

$$\mathbf{U}^{aj}_{N_B-N+1} = \begin{bmatrix} \mathbf{U}^{alj}\mathbf{U}'_{da} & \mathbf{U}^{alj}\mathbf{U}'_{CHa} & \mathbf{O} \\ \mathbf{O} & \mathbf{U}^{alj}\mathbf{U}'_{HHa} & \mathbf{U}^{alj}\mathbf{U}'_{HCa} \\ \mathbf{O} & \mathbf{O} & \mathbf{U}^{alj}\mathbf{U}'_{da} \end{bmatrix} \quad \text{(II-18e)}$$

The $\mathbf{U}'_{da}$, $\mathbf{U}'_{CHa}$, $\mathbf{U}'_{HHa}$, and $\mathbf{U}'_{HCa}$ differ from eq II-12c to II-12f, respectively, in that they only count the average number of residues in block "i", chain one, that are helical. The explicit forms of these statistical weight matrices are found in the supplementary material, Appendix B, eq B-1 to B-4, respectively.

Now, if $N_B - N + 1 < i < N_B - 1$, we have if $j \neq i$

$$\mathbf{U}^{aj}_{si} = \mathbf{U}^{a}_{si} \quad \text{(II-19a)}$$

with $\mathbf{U}^{a}_{si}$ defined in eq II-2b. If $j = i$

$$\mathbf{U}^{aj}_{si} = \begin{bmatrix} \mathbf{U}'_{da} & \mathbf{U}'_{CHa} & \mathbf{O} \\ \mathbf{O} & \mathbf{U}'_{HHa} & \mathbf{U}'_{HCa} \\ \mathbf{O} & \mathbf{O} & \mathbf{U}'_{da} \end{bmatrix} \quad \text{(II-19b)}$$

The nontrivial 4×4 statistical weight matrices may be found in the supplementary material, Appendix B.

Now, when $i = N_B$, we have if $j \neq N_B$

$$\mathbf{U}^{aj}_{sN_B} = \mathbf{U}^{a}_{sN_B} \quad \text{(II-20a)}$$

and if $j = N_B$

$$\mathbf{U}_{N_B}^{aj} = \begin{bmatrix} \mathbf{U}'_{da}\mathbf{U}^{ar} & \mathbf{U}'_{CHa}\mathbf{U}^{ar} & \mathbf{0} \\ \mathbf{0} & \mathbf{U}'_{HHa}\mathbf{U}^{ar} & \mathbf{U}'_{HCa}\mathbf{U}^{ar} \\ \mathbf{0} & \mathbf{0} & \mathbf{U}'_{da}\mathbf{U}^{ar} \end{bmatrix} \quad \text{(II-20b)}$$

in which $\mathbf{U}^{ar}$ has been presented in eq II-8a.

We next turn to the definition of the partitioned matrices in $f(N_B - 1,j)$ for a type-"b" sequence.

If $j \neq 1$, we have

$$\mathbf{U}_{s1}^{bj} = \begin{bmatrix} \mathbf{U}^{br}\mathbf{U}_{d}^{b} & \mathbf{U}^{br}\mathbf{U}_{CH}^{b} & \mathbf{0} \\ \mathbf{0} & \mathbf{U}^{br}\mathbf{U}_{HH}^{b} & \mathbf{U}^{br}\mathbf{U}_{HC}^{b} \\ \mathbf{0} & \mathbf{0} & \mathbf{U}^{br}\mathbf{U}_{d}^{b} \end{bmatrix}_1 = \mathbf{U}_{s1}^{b} \quad \text{(II-21a)}$$

for which

$$\mathbf{U}^{br} = \mathbf{E}_2 \otimes \prod_{i=1}^{N_B-N} \mathbf{U}_{mi} \quad \text{(II-21b)}$$

is the statistical weight matrix that sums all the accessible states of blocks "1" to "$N_B - N$" in chain two in a type-"b" out-of-register sequence. $\mathbf{U}_{di}^{b}$, $\mathbf{U}_{CHi}^{b}$, $\mathbf{U}_{HHi}^{b}$, and $\mathbf{U}_{HCi}^{b}$ may be obtained from eq II-3 to II-5b by replacing the index $i - \Delta$ with $i + \Delta$.

When $j = 1$, we have

$$\mathbf{U}_{s1}^{bj} = \begin{bmatrix} \mathbf{U}^{br}\mathbf{U}'_{db} & \mathbf{U}^{br}\mathbf{U}'_{CHb} & \mathbf{0} \\ \mathbf{0} & \mathbf{U}^{br}\mathbf{U}'_{HHb} & \mathbf{U}^{br}\mathbf{U}'_{HCb} \\ \mathbf{0} & \mathbf{0} & \mathbf{U}^{br}\mathbf{U}'_{db} \end{bmatrix} \quad \text{(II-21c)}$$

The procedure for constructing $\mathbf{U}'_{db}$, $\mathbf{U}'_{CHb}$, $\mathbf{U}'_{HHb}$, $\mathbf{U}'_{HCb}$ is outlined in the supplementary material, Appendix B. If $1 < i < N$ and if $j \neq i$

$$\mathbf{U}_{si}^{bj} = \begin{bmatrix} \mathbf{U}_{d}^{b} & \mathbf{U}_{CH}^{b} & \mathbf{0} \\ \mathbf{0} & \mathbf{U}_{HH}^{b} & \mathbf{U}_{HC}^{b} \\ \mathbf{0} & \mathbf{0} & \mathbf{U}_{d}^{b} \end{bmatrix} = \mathbf{U}_{si}^{b} \quad \text{(II-22a)}$$

and if $j = i$

$$\mathbf{U}_{si}^{bj} = \begin{bmatrix} \mathbf{U}'_{db} & \mathbf{U}'_{CHb} & \mathbf{0} \\ \mathbf{0} & \mathbf{U}'_{HHb} & \mathbf{U}'_{HCb} \\ \mathbf{0} & \mathbf{0} & \mathbf{U}'_{db} \end{bmatrix} \quad \text{(II-22b)}$$

Finally, if $i = N$ and $j < N$, we have

$$\mathbf{U}_{sN}^{bj} = \begin{bmatrix} \mathbf{U}_{d}^{b}\mathbf{U}^{bl} & \mathbf{U}_{CH}^{b}\mathbf{U}^{bl} & \mathbf{0} \\ \mathbf{0} & \mathbf{U}_{HH}^{b}\mathbf{U}^{bl} & \mathbf{U}_{HC}^{b}\mathbf{U}^{bl} \\ \mathbf{0} & \mathbf{0} & \mathbf{U}_{d}^{b}\mathbf{U}^{bl} \end{bmatrix} = \mathbf{U}_{sN}^{b} \quad \text{(II-23a)}$$

wherein

$$\mathbf{U}^{bl} = \prod_{i=N+1}^{N_B} \mathbf{U}_{mi} \otimes \mathbf{E}_2 \quad \text{(II-23b)}$$

If $j = N$, then

$$\mathbf{U}_{sN}^{bj} = \begin{bmatrix} \mathbf{U}'_{db}\mathbf{U}^{bl} & \mathbf{U}'_{CHb}\mathbf{U}^{bl} & \mathbf{0} \\ \mathbf{0} & \mathbf{U}'_{HHb}\mathbf{U}^{bl} & \mathbf{U}'_{HCb}\mathbf{U}^{bl} \\ \mathbf{0} & \mathbf{0} & \mathbf{U}'_{db}\mathbf{U}^{bl} \end{bmatrix} \quad \text{(II-23c)}$$

and if $j > N$, we have

$$\mathbf{U}_{sN}^{bj} = \begin{bmatrix} \mathbf{U}_{d}^{b}\mathbf{U}^{blj} & \mathbf{U}_{CH}^{b}\mathbf{U}^{blj} & \mathbf{0} \\ \mathbf{0} & \mathbf{U}_{HH}^{b}\mathbf{U}^{blj} & \mathbf{U}_{HC}^{b}\mathbf{U}^{blj} \\ \mathbf{0} & \mathbf{0} & \mathbf{U}_{d}^{b}\mathbf{U}^{blj} \end{bmatrix} \quad \text{(II-24a)}$$

in which we define if $j > N$

$$\mathbf{U}^{blj} = \left(\prod_{i=N+1}^{j-1} \mathbf{U}_{mi}\mathbf{U}'_{mj}\prod_{i=j+1}^{N_B} \mathbf{U}_{mi}\right) \otimes \mathbf{E}_2 \quad \text{(II-24b)}$$

and if $j \leq N$

$$\mathbf{U}^{blj} = \mathbf{U}^{bl} \quad \text{(II-24c)}$$

This completes the presentation of $f(N_B - 1,j)$.

In a similar fashion to $f(N_B - 1,j)$, we have for $f(N_B,j)$

$$f(N_B,j) = m_j^{-1}Z_{sd}^{-1}\{\mathbf{J}_4{}^*\mathbf{U}^{alj}(N_B)\mathbf{U}_{CHN_B}^{aj}\mathbf{U}^{ar}(N_B)\mathbf{J}_4 + \mathbf{J}_4{}^*\mathbf{U}^{br}(N_B)\mathbf{U}_{CH_1}^{aj}\mathbf{U}^{blj}(N_B)\mathbf{J}_4\} \quad \text{(II-25a)}$$

where $\mathbf{U}^{alj}(N_B)$ is defined in eq II-18b and II-18d.

If $j \neq N_B$

$$\mathbf{U}_{CHN_B}^{aj} = \mathbf{U}_{CHN_B}^{a} \quad \text{(II-25b)}$$

If $j = N_B$

$$\mathbf{U}_{CHN_B}^{aj} = \mathbf{U}'_{CHaN_B} \quad \text{(II-25c)}$$

and $\mathbf{U}^{ar}(N_B)$ is defined in eq II-8a. Moreover, $\mathbf{U}^{br}$ may be found in eq II-21b. If $j \neq 1$

$$\mathbf{U}_{CH_1}^{bj} = \mathbf{U}_{CH_1}^{b} \quad \text{(II-25d)}$$

If $j = 1$

$$\mathbf{U}_{CH_1}^{bj} = \mathbf{U}'_{CHbN_B} \quad \text{(II-25e)}$$

and $\mathbf{U}^{blj}$ has been presented in eq II-24b,c. This completes the formulation of $f_{hd}(j)$, the helix content of the jth block.

Fraction of Random Coils in Terminal Sequences. Defining N_{ERS} as the average number of randomly coiled blocks that are located in end random coil sequences, the fraction of blocks both that are randomly coiled and that propagate from an end is

$$f_{dce} = N_{ERS}/N_B \quad \text{(II-26)}$$

The objective of this section is to develop the expression of f_{dce} in the loops-excluded, imperfect-matching model. The general procedure followed is similar to that developed for the calculation of $f_{hd}(j)$. Namely, we must sum over all out-of-register sequences of both type-"a" and type-"b" sequences. More explicitly, f_{dce} may be obtained from

$$f_{dce} = \{Z_m(f_{mce} + 1) - 1\}Z_{sd}^{-1} + N_B^{-1}Z_{sd}^{-1}\{\mathbf{J}_s{}^*\prod_{i=1}^{N_B}\mathbf{A}_{fsi}\mathbf{J}_s + \mathbf{J}_s{}^*\prod_{i=1}^{N_B}\mathbf{A}_{bsi}\mathbf{J}_s\} + \{S_f^a(N_B - 1) + S_b^a(N_B - 1) + S_f^a(N_B) + S_f^b(N_B - 1) + S_b^b(N_B - 1) + S_f^b(N_B) + S_b^b(N_B)\} \quad \text{(II-27)}$$

In the above expression f_{mce} is the fraction of random coils in terminal sequences in an isolated single chain. An explicit expression for f_{mce} may be found in eq PM-II-20.

The class of terms in the first set of braces in eq II-27 evaluates the contribution to f_{dce} of the completely in-register conformation. The first (second) matrix product generates the contribution to f_{dce} in the perfect-matching conformation of these random coil sequences in chain one that unwind from the left (right) end of the molecule. The explicit forms of these matrices may be found in eq PM-II-16 to PM-II-19d. $\mathbf{J}_s^*$ and $\mathbf{J}_s$ are defined following eq II-11. The $S_f^\gamma(N_B - 1)$ ($S_b^\gamma(N_B - 1)$) generate the total contribution to f_{dce} of those sequences of type "γ" (either "a" or "b") in chain one that unwind from the left (right) end of the molecule and are 1 to $N_B - 2$ blocks out-of-register. $S_f^\gamma(N_B)$ ($S_b^\gamma(N_B)$) generates the contribution to f_{dce} of the sequence type "γ" that unwinds from the left (right) end of the molecule in chain one and is $N_B - 1$ blocks out-of-register. Observe that $S_b^a(N_B)$ is zero; for a type-"a" sequence in the single interacting helical sequence approximation, block "N_B" in chain one and block "1" in chain two in an $N_B - 1$ out-of-register block sequence are in a helix-initiating U_{CH}-type state, and thus there are no sequences in chain one that unwind from the right end of the molecule. In what follows we shall present the explicit expressions employed in the calculation of the above quantities.

Let us begin with the calculation of those states that unwind from the "left" end of the molecule; we examine type-"a" sequences first.

$$S_f^a(N_B - 1) = N_B^{-1} Z_{sd}^{-1} \sum_{N=2}^{N_B-1} \mathbf{J}_s^* \mathbf{A}^a_{fsN_B-N+1} \prod_{i=N_B-N+2}^{N_B-1} \mathbf{A}^a_{fsi} \mathbf{A}^a_{fsN_B} \mathbf{J}_s \quad \text{(II-28a)}$$

in which $\mathbf{A}_{fsN_B-N+1}$ includes these terminal coil random sequences that unwind from the left end in blocks "1" to "$N_B - N$".

$$\mathbf{A}^a_{fsN_B-N+1} = \begin{bmatrix} \mathbf{U}^a_{11f}\mathbf{U}^a_{fd} & \mathbf{U}^a_{11f}\mathbf{U}^a_{fCH} & \mathbf{O} & \mathbf{U}^a_{11f}\mathbf{U}^a_{fd} + \mathbf{U}^a_{12f}\mathbf{U}^a_{d} & \mathbf{U}^a_{11f}\mathbf{U}^a_{fCH} + \mathbf{U}^a_{12f}\mathbf{U}^a_{CH} & \mathbf{O} \\ \mathbf{O} & \mathbf{O} & \mathbf{O} & \mathbf{O} & \mathbf{O} & \mathbf{O} \\ \mathbf{O} & \mathbf{O} & \mathbf{O} & \mathbf{O} & \mathbf{O} & \mathbf{O} \\ \mathbf{O} & & & \mathbf{U}^a_{sN_B-N+1} & & \end{bmatrix}_{N_B-N+1} \quad \text{(II-28b)}$$

In the above 24 × 24 partitioned matrix, $\mathbf{U}^a_{11f}$ and $\mathbf{U}^a_{12f}$ account for the unwinding from the left end in chain one of blocks "1" to "$N_B - N$". The explicit forms for $\mathbf{U}^a_{11f}$ and $\mathbf{U}^a_{12f}$ may be found in the supplementary material, Appendix A. $\mathbf{U}^a_d$ and $\mathbf{U}^a_{CH}$ are defined in eq II-3 and II-4, respectively. Moreover, $\mathbf{U}^a_{N_B-N+1}$ may be found in eq II-7.

$$\mathbf{U}^a_{fdi} = \begin{bmatrix} 1 & \tau_p \\ 0 & 0 \end{bmatrix}_i \otimes \begin{bmatrix} 1 & \tau \\ \mathcal{S} & \mathrm{SM} \end{bmatrix}_{i-\Delta} \quad \text{(II-28c)}$$

wherein in τ_p is presented in eq PM-II-17d and

$$\mathbf{U}^a_{fCHi} = \begin{bmatrix} \mathbf{O} & \begin{matrix} 0 & \tau_{pi}\tau_{i-\Delta}w_i \\ 0 & \tau_{pi}\mathrm{SM}_{i-\Delta}w_i \end{matrix} \\ \mathbf{O} & \mathbf{O} \end{bmatrix} \quad \text{(II-28d)}$$

The analogous expressions for $\mathbf{U}^b_{fd}$ and $\mathbf{U}^b_{fCH}$ required below in consideration of type-"b" sequences are obtained by replacing the subscripts $i - \Delta$ by $i + \Delta$ in eq II-28c and II-28d, respectively.

For all $N_B - N + 1 < i < N_B$

$$\mathbf{A}^a_{fsi} = \begin{bmatrix} \mathbf{U}^a_{fsi} & \mathbf{U}^a_{fsi} \\ \mathbf{O} & \mathbf{U}^a_{si} \end{bmatrix} \quad \text{(II-28e)}$$

wherein

$$\mathbf{U}^a_{fsi} = \begin{bmatrix} \mathbf{U}^a_{fd} & \mathbf{U}^a_{fCH} & \mathbf{O} \\ \mathbf{O} & \mathbf{O} & \mathbf{O} \\ \mathbf{O} & \mathbf{O} & \mathbf{O} \end{bmatrix}_i \quad \text{(II-28f)}$$

and $\mathbf{U}^a_{si}$ is defined in eq II-2b.

Finally, when $i = N_B$

$$\mathbf{A}^a_{fsN_B} = \begin{bmatrix} \mathbf{U}^a_{fsN_B} & \mathbf{U}^a_{fsN_B} \\ \mathbf{O} & \mathbf{U}^a_{sN_B} \end{bmatrix} \quad \text{(II-28g)}$$

in which

$$\mathbf{U}^a_{fsN_B} = \begin{bmatrix} \mathbf{U}^a_{fdN_B}\mathbf{U}^{ar} & \mathbf{U}^a_{fCHN_B}\mathbf{U}^{ar} & \mathbf{O} \\ \mathbf{O} & \mathbf{O} & \mathbf{O} \\ \mathbf{O} & \mathbf{O} & \mathbf{O} \end{bmatrix} \quad \text{(II-28h)}$$

and $\mathbf{U}^a_{sN_B}$ is given in eq II-9.

$S_f^a(N_B)$ is immediately obtained from an examination of eq II-28b and II-28h to give

$$S_f^a(N_B) = N_B^{-1} Z_{sd}^{-1} \{\mathbf{J}_4^* \mathbf{U}^a_{11f}(N_B) \mathbf{U}^a_{fCHN_B} \mathbf{U}^{ar}(N_B) \mathbf{J}_4 + \mathbf{J}_4^* \mathbf{U}^a_{12f}(N_B) \mathbf{U}^a_{CHN_B} \mathbf{U}^{ar}(N_B) \mathbf{J}_4\} \quad \text{(II-29)}$$

with $\mathbf{U}^a_{11f}(N_B)$ and $\mathbf{U}^a_{12f}(N_B)$ defined in the supplementary material, Appendix A, eq A-14 to A-16. $\mathbf{U}^a_{fCHN_B}$ is defined in eq II-28d and $\mathbf{U}^a_{CHN_B}$ is defined in eq II-4.

We now turn to the evaluation of $S_b^a(N_B - 1)$, the average number of randomly coiled blocks that unwind from the right end of chain one in a type-"a" sequence.

$$S_b^a(N_B - 1) = N_B^{-1} Z_{sd}^{-1} \sum_{N=2}^{N_B-1} \mathbf{J}_s^* \mathbf{A}^a_{bsN_B-N+1} \prod_{i=N_B-N+2}^{N_B-1} \mathbf{A}_{bsi} \mathbf{A}^a_{bsN_B} \mathbf{J}_s \quad \text{(II-30a)}$$

Observe that in a type-"a" sequence at least one of the blocks "$N_B - N + 1$" to "N_B" in chain one must be helical. Thus, for a given N, there are no random coil states that unwind from the right end for blocks "1" to "$N_B - N$". Consequently

$$\mathbf{A}^a_{bsN_B-N+1} = \begin{bmatrix} \mathbf{U}^a_{sN_B-N+1} & \mathbf{O} \\ \mathbf{O} & \mathbf{O} \end{bmatrix} \quad \text{(II-30b)}$$

When $N_B - N + 1 < i < N_B$

$$\mathbf{A}^a_{bsi} = \begin{bmatrix} \mathbf{U}^a_{si} & \mathbf{U}^a_{bsi} \\ \mathbf{O} & \mathbf{U}^a_{bsi} \end{bmatrix} \quad \text{(II-30c)}$$

wherein $\mathbf{U}^{a}_{si}$ is defined in eq II-2b. $\mathbf{U}^{a}_{bsi}$ is a partitioned 12 × 12 matrix

$$\mathbf{U}^{a}_{bsi} = \begin{bmatrix} \mathbf{0} & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{U}^{a}_{bHC} \\ \mathbf{0} & \mathbf{0} & \mathbf{U}^{a}_{bd} \end{bmatrix}_{i} \tag{II-30d}$$

in which

$$\mathbf{U}^{a}_{bHCi} = \begin{bmatrix} \mathbf{0} & \mathbf{0} \\ 0 & 0 \\ \mathcal{S}_{pi}\mathcal{S}_{i-\Delta} & \mathcal{S}_{pi}\mathrm{SM}_{i-\Delta} \end{bmatrix} \tag{II-30e}$$

$\mathcal{S}_{pi}$ has been defined in eq PM-II-19c.

$$\mathbf{U}^{a}_{bd} = \begin{bmatrix} 1 & 0 \\ \mathcal{S}_{p} & 0 \end{bmatrix}_{i} \otimes \begin{bmatrix} 1 & \tau \\ \mathcal{S} & \mathrm{SM} \end{bmatrix}_{i-\Delta} \tag{II-30f}$$

$\mathbf{U}^{b}_{bHCi}$ and $\mathbf{U}^{b}_{bd}$ are obtained from eq II-30e and II-30f by replacing the subscript $i - \Delta$ with $i + \Delta$. Finally

$$\mathbf{A}^{a}_{bsN_B} = \begin{bmatrix} \mathbf{U}^{a}_{sN_B} & \mathbf{U}^{a}_{bsN_B} \\ \mathbf{0} & \mathbf{U}^{a}_{bsN_B} \end{bmatrix} \tag{II-30g}$$

where

$$\mathbf{U}^{a}_{bsN_B} = \begin{bmatrix} \mathbf{0} & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{U}^{a}_{bHC}\mathbf{U}^{ar} \\ \mathbf{0} & \mathbf{0} & \mathbf{U}^{a}_{bd}\mathbf{U}^{ar} \end{bmatrix} \tag{II-30h}$$

Thus, we are done with the presentation of sequence type "a" quantities.

We next focus our attention to the various quantities relevant to a type-"b" sequence.

$$S^{b}_{f}(N_B - 1) = N_B^{-1}Z_{sd}^{-1}\sum_{N=2}^{N_B-1}\mathbf{J}_s{}^{*}\mathbf{A}^{b}_{fs1}\prod_{i=2}^{N-1}\mathbf{A}^{b}_{fsi}\mathbf{A}^{b}_{fsN}\mathbf{J}_s \tag{II-31a}$$

evaluates the contribution to f_{dce} of these sequences that are 1 to $N_B - 2$ blocks out-of-register and that unwind from the left-hand end of chain one in a type-"b" sequence.

$$\mathbf{A}^{b}_{fs1} = \begin{bmatrix} \mathbf{U}^{b}_{fs1} & \mathbf{U}^{b}_{fs1} \\ \mathbf{0} & \mathbf{0} \end{bmatrix} \tag{II-31b}$$

with

$$\mathbf{U}^{b}_{fs1} = \begin{bmatrix} \mathbf{U}^{br}\mathbf{U}^{b}_{fd} & \mathbf{U}^{br}\mathbf{U}^{b}_{CH} & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{0} \end{bmatrix}_{1} \tag{II-31c}$$

$\mathbf{U}^{br}$ has been defined in eq II-21b. The prescription for the calculation of $\mathbf{U}^{b}_{fdi}$ and $\mathbf{U}^{b}_{fCH}$ follows eq II-28d. Furthermore, if $1 < i < N - 1$, we have

$$\mathbf{A}^{b}_{fsi} = \begin{bmatrix} \mathbf{U}^{b}_{fsi} & \mathbf{U}^{b}_{fsi} \\ \mathbf{0} & \mathbf{U}^{b}_{si} \end{bmatrix} \tag{II-31d}$$

Here

$$\mathbf{U}^{b}_{fsi} = \begin{bmatrix} \mathbf{U}^{b}_{fd} & \mathbf{U}^{b}_{fCH} & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{0} \end{bmatrix} \tag{II-31e}$$

and $\mathbf{U}^{b}_{si}$ is defined in eq II-22a.

Finally, if $i = N$

$$\mathbf{A}^{b}_{fsN} = \begin{bmatrix} \mathbf{U}^{b}_{fsN} & \mathbf{U}^{b}_{fsN} \\ \mathbf{0} & \mathbf{U}^{b}_{sN} \end{bmatrix} \tag{II-31f}$$

in which $\mathbf{U}^{b}_{sN}$ is given in eq II-23a and

$$\mathbf{U}^{b}_{fsN} = \begin{bmatrix} \mathbf{U}^{b}_{fd}\mathbf{U}^{bl} & \mathbf{U}^{b}_{fCH}\mathbf{U}^{bl} & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{0} \end{bmatrix} \tag{II-31g}$$

$\mathbf{U}^{bl}$ has been defined in eq II-23b. Thus, we have presented all the necessary partitioned matrices for the evaluation of $S^{b}_{f}(N_B - 1)$.

$S^{b}_{f}(N_B)$ can be readily constructed from the examination of eq II-31b and II-31f. The prefactor must account for the statistical weight of all possible sequences on chain two, blocks "1" to "$N_B - 1$". The postfactor must merely be $\mathbf{U}^{bl}$ (all blocks $i > 1$ have been preceded by the interacting helical block pair "1" in chain one and "N_B" in chain two). Hence

$$S^{b}_{f}(N_B) = N_B^{-1}Z_{sd}^{-1}\mathbf{J}_4{}^{*}\mathbf{U}^{br}(N_B)\mathbf{U}_{fCH1}\mathbf{U}^{bl}(N_B)\mathbf{J}_4 \tag{II-32}$$

with $\mathbf{J}_4{}^{*}$ and $\mathbf{J}_4$ defined following eq II-10.

We next construct $S^{b}_{b}(N_B - 1)$, given by

$$S^{b}_{b}(N_B - 1) = N_B^{-1}Z_{sd}^{-1}\sum_{N=2}^{N_B-1}\mathbf{J}_s{}^{*}\mathbf{A}^{b}_{bs1}\prod_{i=2}^{N-1}\mathbf{A}^{b}_{bsi}\mathbf{A}^{b}_{bsN}\mathbf{J}_s \tag{II-33a}$$

Now when $i = 1$

$$\mathbf{A}^{b}_{bs1} = \begin{bmatrix} \mathbf{U}^{b}_{s1} & \mathbf{0} \\ \mathbf{0} & \mathbf{0} \end{bmatrix} \tag{II-33b}$$

$\mathbf{U}^{b}_{s1}$ is defined in eq II-21a. There must be at least one helical block pair after or including the block pair "1", "$N_B - N + 1$". Thus the first block pair cannot have been in a random coil state unwinding from the right end of the chain.

If $1 < i \leq N - 1$, we have

$$\mathbf{A}^{b}_{bsi} = \begin{bmatrix} \mathbf{U}^{b}_{si} & \mathbf{U}^{b}_{bsi} \\ \mathbf{0} & \mathbf{U}^{b}_{bsi} \end{bmatrix} \tag{II-33c}$$

In the above $\mathbf{U}^{b}_{si}$ may be found in eq II-22a and

$$\mathbf{U}^{b}_{bsi} = \begin{bmatrix} \mathbf{O} & \mathbf{O} & \mathbf{O} \\ \mathbf{O} & \mathbf{O} & \mathbf{U}^{b}_{bHC} \\ \mathbf{O} & \mathbf{O} & \mathbf{U}^{b}_{bd} \end{bmatrix}_i \qquad \text{(II-33d)}$$

is a partitioned 12 × 12 matrix. The procedure for setting $\mathbf{U}^{b}_{bHC}$ and $\mathbf{U}^{b}_{bd}$ has been outlined in the section following eq II-30f.

Finally, when $i = N$

$$\mathbf{A}^{b}_{bsN} = \begin{bmatrix} \mathbf{U}^{b}_{sN} & \mathbf{U}^{b}_{12bsN} \\ \mathbf{O} & \mathbf{U}^{b}_{22bsN} \end{bmatrix} \qquad \text{(II-33e)}$$

In the above $\mathbf{U}^{b}_{sN}$ has been presented previously in eq II-23a and

$$\mathbf{U}^{b}_{12bsN} = \begin{bmatrix} \mathbf{U}^{b}_{dN}\mathbf{U}^{b}_{12b} & \mathbf{U}^{b}_{CHN}\mathbf{U}^{b}_{12b} & \mathbf{O} \\ \mathbf{O} & \mathbf{U}^{b}_{HHN}\mathbf{U}^{b}_{12b} & \mathbf{U}^{b}_{HCN}\mathbf{U}^{b}_{12b}+\mathbf{U}^{b}_{bHCN}\mathbf{U}^{b}_{22b} \\ \mathbf{O} & \mathbf{O} & \mathbf{U}^{b}_{dN}\mathbf{U}^{b}_{12b}+\mathbf{U}^{b}_{bdN}\mathbf{U}^{b}_{22b} \end{bmatrix} \qquad \text{(II-33f)}$$

$$\mathbf{U}^{b}_{22bsN} = \begin{bmatrix} \mathbf{O} & \mathbf{O} & \mathbf{O} \\ \mathbf{O} & \mathbf{O} & \mathbf{U}^{b}_{bHCN}\mathbf{U}^{b}_{22b} \\ \mathbf{O} & \mathbf{O} & \mathbf{U}^{b}_{bdN}\mathbf{U}_{22b} \end{bmatrix} \qquad \text{(II-33g)}$$

The $\mathbf{U}^{b}_{12b}$ and $\mathbf{U}^{b}_{22b}$ include the contribution to f_{dce} of out-of-register and noninteracting blocks, $N + 1$ to N_B that are in terminal, random coil stretches. The explicit formulas for $\mathbf{U}^{b}_{12b}$ and $\mathbf{U}^{b}_{22b}$ are found in the supplementary material, Appendix A, eq A-17 to A-19.

There merely remains the specification of $S^{b}_{b}(N_B)$, the contribution to f_{dce} of the $N_B - 1$, out-of-register, type-"b" sequence. On consideration of the analogous type of statistical weight matrices such as is found in eq II-33b and II-33e, we find

$$S^{b}_{b}(N_B) = N_B^{-1}Z_{sd}^{-1}\mathbf{J}_4{}^{*}\mathbf{U}^{br}(N_B)\mathbf{U}_{CH1}\mathbf{U}^{b}_{12b}(N_B)\mathbf{J}_4 \qquad \text{(II-34)}$$

The quantity of most interest in understanding the nature of the helix-to-random coil transition in the dimer is not f_{dce} itself but R_d, the ratio of the number of randomly coiled blocks that unwind from the ends to the total number of randomly coiled blocks, f_c (=1 − f_{bhd}).

$$R_d = f_{dce}/(1 - f_{bhd}) \qquad \text{(II-35)}$$

f_{hdc} may be obtained by setting the various m_i equal to unity in eq II-11, replacing N_T by N_B in eq II-11, and evaluating the modified equation. The relationship of 1 − f_c, the fraction of blocks that are helical, to f_{hd} is discussed previously and will not be discussed here.[4]

Thus expressions for the internal partition function of the dimer, the overall helix content of the dimer (f_{hd}), the helix probability profiles, and the ratio of the number of random coils that are in terminal-random sequences to the total number of random coils (R_d), have been derived for the loops-excluded, imperfect-matching model. The various algorithms are based on the fact that a given $N_B - N$ block out-of-register sequence can be treated as a nearest-neighbor interaction model. We then merely sum over all the populations of the various possible mismatched states.

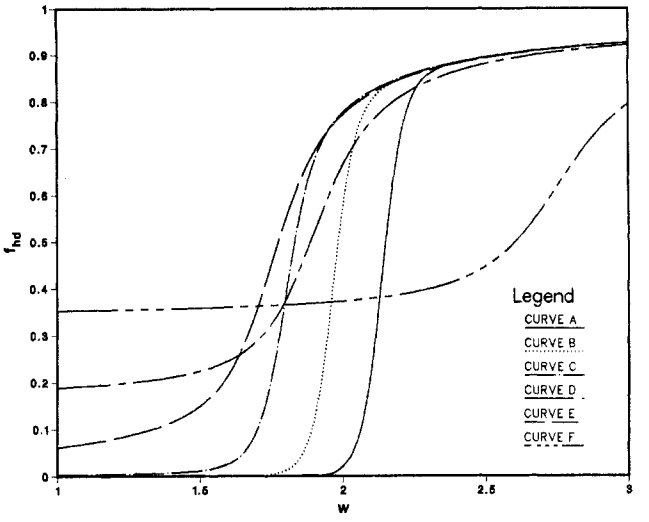

Figure 2. Plot of the fraction of helix in the dimer, f_{hd}, vs. the helix–helix interaction parameter w calculated by using eq II-11 for the loops-excluded, imperfect-matching model with $\sigma = 10^{-7}$, 10^{-6}, 10^{-5}, 10^{-4}, 10^{-3}, and 10^{-2}, in curves A–F, respectively, for a 284-residue, homopolymeric two-chain, coiled coil. In all cases $s = 0.94$, $N_B = 71$, $m = 4$, and w is assumed to be uniform.

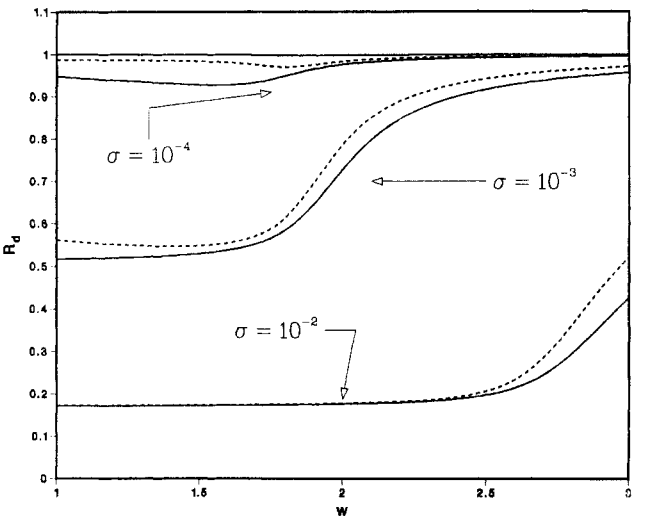

Figure 3. Plot of the ratio of the number of random coil blocks in the dimer that unwind from the ends to the total number of random coil blocks, R_d, vs. the helix–helix interaction parameter w. Solid lines, R_d vs. w, calculated by using eq II-27 for the loops excluded, imperfect-matching model for $\sigma = 10^{-5}$, 10^{-4}, 10^{-3} and 10^{-2}. Dashed lines, R_d vs. w, calculated by using eq PM-II-16 for the loops-excluded, perfect-matching model for $\sigma = 10^{-4}$, 10^{-3}, and 10^{-2}. The values of σ greater than 10^{-5} appropriate to the two sets of curves are indicated in the figure. When $\sigma = 10^{-5}$, R_d is essentially unity for both models. In all cases $s = 0.94$, $N_B = 71$, $m = 4$, and w is assumed to be uniform.

III. Application of the Loops-Excluded, Imperfect-Matching Model to Homopolymers

In this section we present the results of the calculations on a hypothetical homopolymeric two-chain, coiled coil containing the same number of residues, N_T, as the prototypical two-chain, coiled coil, tropomyosin, 284, and the same geometric mean value of $s = 0.94$.[22] In addition, we

set $N_B = 71$ and $m = 4$. We begin with the assumption of a site-independent, uniform w.

In Figure 2 we have plotted f_{hd}, calculated on the basis of eq II-11 with $\sigma = 10^{-7}$, 10^{-6}, 10^{-5}, 10^{-4}, 10^{-3}, and 10^{-2} in curves A–F, respectively. The qualitative behavior of these curves as a function of w is identical with that seen in the loops-excluded, perfect-matching model. To more clearly depict the nature of the transition, we refer to Figure 3, in which the solid lines present R_d vs. w plotted for the loops-excluded, imperfect-matching model with $\sigma = 10^{-5}$, 10^{-4}, 10^{-3}, and 10^{-2}. For values of σ less than 10^{-5}, R_d is essentially unity; moreover, the R_d vs. w curve for $\sigma = 10^{-4}$ lies very close to unity. The coil-to-helix transition for σ less than 10^{-4} is entirely due to the growth of the single interacting helical stretch in the dimer and is very much like the transition in the one-sequence model of single-chain poly(amino acids).[34] Hence in Figure 2 for the range of σ less than or equal to 10^{-4}, the f_{hd} vs. w curves are essentially parallel and reflect the fact that with increasing σ, the minimum value of w required to promote helix formation decreases.

As σ increased beyond 10^{-4}, the solid curves of Figure 3 indicate that R_d lies substantially below unity. In this range of σ, while there is a single interacting helical stretch per dimer, there are also noninteracting, helical regions on each chain that can contribute appreciably to the helix content. Hence the coil-to-α-helix transition shown in Figure 2 for σ less than 10^{-4} has become significantly broader and less cooperative. Nevertheless, the growth to complete helix involves the increase in mean length of the single interacting helical region in each dimer. This is reflected in the monotonic increase in R_d at moderate to high helix content as a function of w. We emphasize that the crossover from single helical stretch per dimer to multiple helical stretches is not an abrupt but rather a continuous function of σ.

In all of the curves plotted in Figure 2, at high helix the f_{hd} curves at larger σ approach the smaller σ curves from below. For example, although it is somewhat difficult to see on the scale of Figure 2 for the $\sigma < 10^{-3}$ curves, the crossover at high helix of the $\sigma = 10^{-7}$ curve occurs at smaller values of w for larger values of σ. We should point out that all of the behavior delineated above is also characteristic of single-chain homopolymers at finite values of N_T.[34]

We now turn to the question of the relationship of the loops-excluded, perfect-matching model and loops-excluded, imperfect-matching model. In Figure 4 we have plotted f_{hd} vs. w for $\sigma = 10^{-7}$ and $\sigma = 10^{-2}$ in the imperfect-matching model (solid lines) using eq II-11 and in the perfect-matching model (dashed lines) using eq PM-II-10. It is immediately obvious, especially for the $\sigma = 10^{-7}$ pair of curves, that the helix–coil transition in the perfect-matching model is more cooperative than in the imperfect-matching model. The helix content in the imperfect-matching model is greater (less) than the perfect-matching model at low (high) helix. While it is hard to differentiate the curves for the two models when w is near one and with $\sigma = 10^{-2}$, f_{hd} for the perfect-matching model is less than that for the imperfect-matching model (at $w = 1$, f_{hd} is 0.352 50 vs. 0.352 60 in the perfect- and imperfect-matching models, respectively).

The behavior of f_{hd} in Figure 4 may be rationalized as follows. In the limit of low helix, there are a greater number of small helical stretches in the imperfect-matching model than in the perfect-matching model. Thus, at low helix and at a given w, f_{hd} in the imperfect-matching model lies above f_{hd} in the perfect-matching

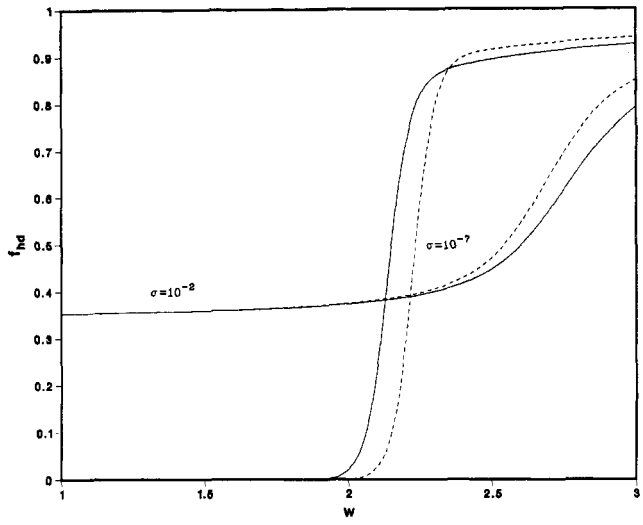

Figure 4. Comparison of the fraction of helix in the dimer, f_{hd}, vs. the helix–helix interaction parameter w for the loops-excluded, imperfect-matching model (solid line) and the loops-excluded, perfect-matching model (dashed line) with $\sigma = 10^{-7}$ and 10^{-2}. In all cases $s = 0.94$, $N_B = 71$, $m = 4$, and w is assumed to be uniform.

limit. As the helix content is increased, the mean length of the single interacting helix stretch grows. However, the maximum length a single interacting helical stretch can be for a given degree of mismatch is N. As the helix content increases, there will be a large number of conformations having a range of N values that contribute f_{hd}; thus at high helix, f_{hd}(perfect match) always exceeds f_{hd}(imperfect match). In the limit $w \to \infty$, the latter quantity approaches the former from below, and as the completely in-register conformation becomes the dominant term in the partition function, the two curves coalesce. To further compare the behavior of the two models we have also plotted in Figure 3 R_d vs. w (the dashed lines) with $\sigma = 10^{-4}$, 10^{-3}, and 10^{-2} in the loops-excluded, perfect matching model. In all cases at a given w, R_d(perfect match) > R_d(imperfect match). There are more noninteracting helical sequences in the imperfect-matching model than in the perfect-matching model. For $\sigma < 10^{-5}$, R_d in both models is essentially unity. Finally, we consider the behavior of the curves in Figure 4 as σ increases so that f_{hm}, the helix content of the monomer, attains an appreciable value; e.g., $\sigma = 10^{-2}$. In this limit, even for w near one, the noninteracting, out-of-register conformations are all somewhat helical, and the helix content in the imperfect-matching model is essentially but not exactly (see above) the same as in the perfect-matching limit. As w increases beyond unity, the two curves cross and the imperfect-matching model helix content curve lies below the perfect-matching model helix content curve.

In the limit of high helix, we might ask how the values of helix–helix interaction parameter for the perfect-matching and imperfect-matching models are related. As is the case when comparing a less cooperative with a more cooperative transition, at high (low) helix the value of w in the imperfect-matching model is greater than (less than) the value of w in the perfect-matching model necessary to produce the same mean helix content. Moreover, examination of Figures 3 and 4 reveals that curves at the same overall helix content have the same value of R_d. This is expected. Since the coil-to-helix transition arises from the growth of the single interacting helical stretch, molecules with the same R_d should have the same helix content. Finally, at a given ω due to the larger number of states accessible to the molecules having out-of-register sequences Z_{sd}(imperfect match) > Z_{sd}(perfect match); we shall ex-

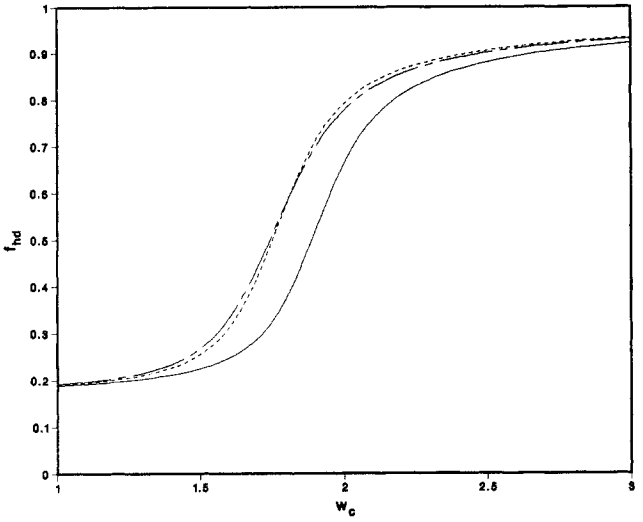

Figure 5. Fraction of helix in the dimer, f_{hd}, vs. the helix–helix interaction parameter characteristic of the C-terminal portion of the dimer, w_C, calculated with $\beta = 1$, $\gamma = 1$, (solid curve), $\beta = 1$, $\gamma = 1.184$ (dashed curve), and $\beta = \gamma^{1/2}$, $\gamma = 1.184$ (dot–dash curve) (see text, eq III-1c–d, for a definition of β and γ). In all cases $\sigma = 10^{-3}$, $s = 0.94$, $N_B = 71$, $m = 4$, and $N_D = 34$.

amine the relative populations of the various out-of-register conformations below.

Helix probability profiles were calculated by using eq II-16 for a homopolymer with $N_B = 71$, $\sigma = 10^{-3}$, and $s = 0.94$ and assuming a uniform w. As would be expected at a given f_{hd} the helix probability profiles are parabolic in form and are essentially identical with those calculated in the perfect-matching limit;[3] thus they are not displayed.

We now examine the qualitative effect of a nonuniform w on the α-helix-to-random coil transition in two-chain, coiled coils. Based on the T_1 and T_2 tropomyosin fragment data of Pato et al.[24] and by way of illustration, let us divide each chain into two pieces at block N_D and consider the interhelical interaction between block pair "i" on chain one and "j" on chain two. Then the helix–helix interaction parameter

$$w_{ij} = w_N \qquad \text{(III-1a)}$$

if both i and j are both less than N_D.

$$w_{ij} = w_C \qquad \text{(III-1b)}$$

if both i and j are greater than or equal to N_D. Finally

$$w_{ij} = \beta w_C \qquad \text{(III-1c)}$$

if i (j) is greater than or equal to N_D and j (i) is less than N_D. Hence w_C and w_N are the interhelical interaction parameters between blocks that are characteristic of the completely in-register molecule (in the perfect-matching limit). For convenience we shall write

$$w_N = \gamma w_C \qquad \text{(III-1d)}$$

At this point, the values of the β and γ parameters are unknown. In the following calculations, we shall set $\beta = 1$ and $\beta = (w_N/w_C)^{1/2}$. In the latter case, the interhelical interaction parameter between unlike regions is the geometric mean of the interhelical interaction parameter between like regions.

In Figure 5 we have calculated f_{hd} vs. w_C with $\beta = 1$, $\gamma = 1$ (solid curve); $\beta = 1$, $\gamma = 1.184$ (dashed curve); and $\beta = \gamma^{1/2}$, $\gamma = 1.184$ (dot–dash curve). Calculations were done on a two-chain, coiled coil with $N_B = 71$, with $\sigma = 10^{-3}$, $s = 0.94$, $N_B = 71$, and $m = 4$. By analogy to the fit of T_1 and T_2 using the neglect-loop-entropy model, we have chosen $\gamma = 1.184$, a value that roughly corresponds to the N-terminal half of the dimer being more stable than the C-terminal half by 100 cal (mol of block pairs)$^{-1}$.[47] Finally, we set $N_D = 34$. This corresponds to the approximate sizes of the T_1 and T_2 fragments.[24] As would be expected, the curves having a value of β and γ exceeding unity lie above the curve with $\gamma = \beta = 1$, i.e., the uniform-w approximation. Although it is somewhat difficult to see on the graph, the coil-to-helix transition for the $\beta = \gamma^{1/2}$ case is less cooperative than for the $\beta = 1$ case. Increasing the magnitude of the "out-of-register", helix–helix interaction parameter β increases the importance of the out-of-register conformations. We further take up this point below.

Table I
Fraction of Dimers Having a Maximum of N Interacting Helical Blocks, $P(N)$[a]

N	$P(N)$[b]	$P(N)$[c]	$P(N)$[d]	$P(N)$[e]
71	1.51 −1	1.90 −1	2.04 −1	1.73 −1
70	2.65 −1	3.14 −1	3.17 −1	2.91 −1
69	2.00 −1	2.11 −1	2.07 −1	2.07 −1
68	1.39 −1	1.28 −1	1.23 −1	1.34 −1
67	9.16 −2	7.25 −2	6.92 −2	8.19 −2
66	5.86 −2	3.97 −2	3.76 −2	4.84 −2
65	3.67 −2	2.12 −2	2.00 −2	2.80 −2
64	2.27 −2	1.11 −2	1.04 −2	1.59 −2
63	1.39 −2	5.77 −3	5.41 −3	8.98 −3
62	8.46 −3	2.97 −3	2.78 −3	5.03 −3
61	5.12 −3	1.52 −3	1.42 −3	2.80 −3
60	3.09 −3	7.77 −4	7.27 −4	1.56 −3
59	1.86 −3	3.96 −4	3.70 −4	8.61 −4
58	1.12 −3	2.01 −4	1.88 −4	4.77 −4
57	6.74 −4	1.02 −4	9.56 −5	2.63 −4
56	4.05 −4	5.19 −5	4.85 −5	1.45 −4
55	2.43 −4	2.63 −5	2.46 −5	8.02 −5
54	1.46 −4	1.33 −5	1.26 −5	4.42 −5
53	8.75 −5	6.76 −5	6.31 −6	2.44 −5
52	5.25 −5	3.42 −6	3.20 −6	1.34 −5
51	3.15 −5	1.73 −6	1.62 −6	7.41 −6
50	1.89 −5	8.78 −7	8.21 −7	4.08 −6
49	1.13 −5	4.45 −7	4.16 −7	2.25 −6
48	6.78 −6	2.52 −7	2.10 −7	1.24 −6
47	4.07 −6	1.14 −7	1.07 −7	6.84 −7
46	2.44 −6	5.78 −8	5.41 −8	3.77 −7

[a] We have used the notation $1.5 \times 10^{-3} \equiv 1.5 -3$. In all cases $\sigma = 10^{-3}$, $s = 0.94$, $N_B = 71$, $m = 4$, and $N_D = 34$. $N = 71$ corresponds to the completely in-register state. [b] $w_C = 3.0$, $\beta = \gamma = 1$, $Z_{sd} = 1.49 \times 10^{17}$, and $f_{hd} = 0.9211$. [c] $w_C = 3.552$, $\beta = \gamma = 1$ ($w_C = 3 \times 1.184$), $Z_{sd} = 8.31 \times 10^{21}$, and $f_{hd} = 0.9399$. [d] $w_C = 3.0$, $\beta = 1.0$, $\gamma = 1.184$, $Z_{sd} = 2.04 \times 10^{19}$, and $f_{hd} = 0.9331$. [e] $w_C = 3.0$, $\beta = \gamma^{1/2}$, $\gamma = 1.184$, $Z_{sd} = 2.41 \times 10^{19}$, $f_{hd} = 0.9308$.

To more fully appreciate the various effects, we now turn to the question of the relative populations of the various out-of-register sequences. Let $P(N)$ be the fraction of molecules possessing a maximum of N interacting helical blocks. That is

$$P(N) = Z(N)/Z_{sd} \qquad \text{(III-2)}$$

where $Z(N)$ is the partition formation function of a dimer having a maximum of N interacting helical blocks and is defined in eq II-2a and II-10. In Table I, we calculate $P(N)$ for $N = 71$ to 46, i.e., the fraction of molecules that are 0–25 blocks out of register. We have set $\beta = 1$, $\gamma = 1$; $\beta = 1$, $\gamma = 1.184$; and $\beta = \gamma^{1/2}$, $\gamma = 1.184$. The value of w_C chosen is indicated in the table caption. The following conclusions are readily apparent.

(1) Comparison of Table I, column 2, with Table I, column 3, reveals that even with a uniform w, in the limit of high helix, a concomitant condition of increasing the helix content is the increase in the relative populations of those sequences that are in-register or slightly out-of-register and the decrease in population of the more out-of-register sequences.

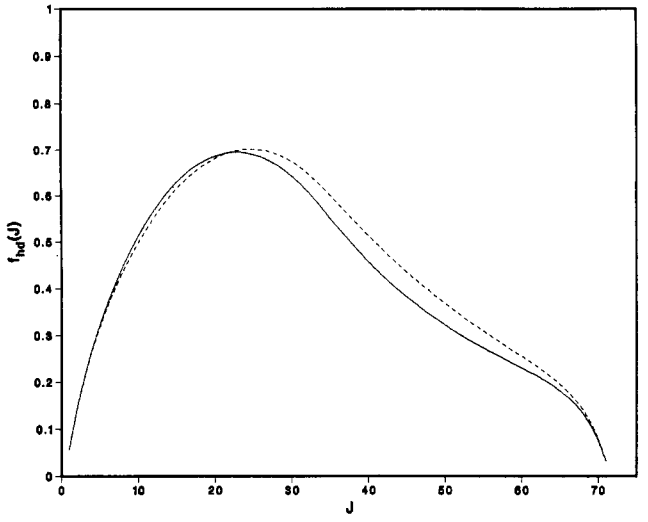

Figure 6. Helix probability profiles. In the solid curve, $\beta = 1.0$, $\gamma = 1.184$, and $f_{hd} = 0.4208$. In the dashed curve, $\beta = \gamma^{1/2}$, $\gamma = 1.184$, and $f_{hd} = 0.4409$. See text, eq III-1c–d, for the definition of β and γ. In both cases, $\sigma = 10^{-3}$, $s = 0.94$, $N_B = 71$, $m = 4$, $N_D = 34$, and $w_C = 1.7$.

(2) Comparison of either column 4 or column 5 with column 2 reveals that increasing γ increases the relative population of the in-register state. Moreover, comparison of the top of column 4 with the top of column 3 indicates that if helix–helix interaction in one end of the dimer is increased, and everything else remains the same, $P(N_B)$ increases even though the overall helix content is less (0.9331 vs. 0.9399). Hence as would be expected increasing the preference for the in-register regions of the two chains increases the relative population of those states more closely in-register, in particular, those states that are less than two heptets (actually octets in this case) out-of-register.

(3) Comparing the entries in Table I, column 4, with those in column 5, it is evident that increasing β from 1.0 to $\gamma^{1/2}$ has, as expected, increased the relative populations of the out-of-register sequences and also produces a concomitant lowering in f_{hd} from 0.9331 to 0.9308. In other words, by enhancing the stability of the out-of-register helical sequences, we have made mismatched states more important, and the coil–helix transition less cooperative.

Further evidence on the effect of increasing β from 1 to $\gamma^{1/2}$ in the helix–coil transition is seen in Figure 6. We have examined the helix probability profiles for two-chain, coiled coils with $\sigma = 10^{-3}$, $s = 0.94$, $w_C = 1.7$, $N_B = 71$, $m = 4$, and $N_D = 34$. In the solid curve, $\beta = 1$, $\gamma = 1.184$, and $f_{hd} = 0.4208$; in the dashed curve, $\beta = \gamma^{1/2}$, $\gamma = 1.184$, and $f_{hd} = 0.4409$. In both curves, the relative probability profiles are largest in that portion of the molecule having a greater w, i.e., blocks $i < 34$. Observe, however, that the profiles having $\beta = \gamma^{1/2}$ have a broader maximum than when $\beta = 1$ (indicative of the enhanced importance of out-of-register conformation in the former case as compared to the latter case; this is not just a reflection of the slightly differing total helix content).

We point out than when the helix content is 94% and a uniform w is assumed, about 84% of the dimers are less than two heptets out-of-regster. If f_{hd} is 94.9%, about 88% of the dimers are less than one and a half heptets out-of-register. Taking $\beta = 1$, $\gamma = 1.184$, when the helix content is 95.4%, 93.3% of the dimers are less than one and a half heptets out-of-register and 84.1% are less than one heptet out-of-register.

In summary, in this section we have applied the loops-excluded, imperfect-matching model to a hypothetical homopolymeric, two-chain, coiled coil. We have demonstrated that the inclusion of out-of-register sequences makes the helix–coil transition less cooperative–thereby modifying the apparent helix–helix interaction parameter that would be obtained if the possibility of mismatch were neglected. In all cases, since the helix–helix interaction between chains is the cause of the greatly increased dimer helix content vis-à-vis the isolated single chains, in the limit of high helix the imperfect-matching model converges to the perfect-matching limit. Namely, $\lim_{w\to\infty} P(N_B) = 1$. For finite and reasonable values of w, and at high helix, the hypothetical dimer population is dominated by species that are within one or two heptets out-of-register. For all populations, the effect of loop entropy is to restrict to one the number of interacting helical stretches in the dimer. Overall, it is seen that both loop entropy and mismatch exert important effects on qualitative features of the helix–coil transition in two-chain, coiled-coils. The former statistical effect makes the transition more cooperative and the latter effect makes it less cooperative.

IV. Conclusion

In this paper we have extended the theory of the α-helix-to-random coil transition in two-chain, coiled coils to include the effects of loop entropy and mismatch between chains; these effects are incorporated into the loops-excluded, imperfect-matching model. For chains of short to moderate length, loop entropy prohibits the introduction of random coil sequences between interacting pairs of helices in the two chains in the dimer. Thus in a given dimer, there is a single interacting helical region perhaps preceded and/or followed by noninteracting helical regions. The nature of loop entropy thereby reduces the problem of mismatched chain association to consideration of out-of-register sequences. Expressions have been derived for the partition function of the dimer, the helix content, the helix probability profiles, and the fraction of random coils that are in end random coil sequences. All these expressions basically sum over the N_B distinct out-of-register populations—within each population; i.e., for a given $N_B - N$ block out-of-register sequence, we have a nearest-neighbor model and the effect of mismatch is merely reduced to taking account of the two $N_B - N$ block out-of-register ends. We would expect mismatched conformations to be most important in the transition region of the thermal denaturation profiles.

Application has been made to hypothetical homopolymeric two-chain, coiled coils that may have differing regions of interhelical stability, and comparison was also made with the loops-excluded, perfect-matching model. We have investigated the dependence of the relative population of mismatched dimer, helix probability profiles, and helix content on the regiospecificity of w. On the basis of the present work we conclude that mere knowledge of an overall helix content is insufficient to completely characterize the helix–helix interaction parameter. For systems such as tropomyosin, in order to characterize the site specificity of w, additional investigations of fragment data are required.

The ability to essentially completely cross-link the sulfhydryl residues in cysteine-190 in α-helical tropomysin has been interpreted to indicate that tropomyosin is completely in-register.[39-41] Actually, these results merely imply that the time scale for exchange between out-of-register conformations is short relative to the total reaction time. (Actually about 90% of sulfhydryl groups are cross-linked.[41,48]) Using the homopolymeric relative populations of out-of-register sequences as a guide, it would not be surprising if 85–90% of all molecules are within one heptet

of perfect matching—and assuming fast exchange between these slightly out-of-register sequences relative to the reaction time, this could conceivably account for the experimental observations.

At this point, we have extended this avenue of development of the statistical mechanical theory of the α-helix-to-random-coil transition in two-chain, coiled coils about as far as it can profitably be pushed. The current approach is founded on the assumptions that the isolated chains have helix initiation and propagation parameters that depend only on amino acid type and not the nearest-neighbor environment and that we can account for the enhanced stability of the dimers by an additional interchain helix–helix interaction parameter w. In addition, the statistical effects of loop entropy and mismatch are also embodied in the loops-excluded, imperfect-matching model formulated here. In a forthcoming work, we shall apply the loops-excluded, imperfect-matching model to tropomyosin and tropomyosin fragments to test the theory as fully as is possible.

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Supplementary Material Available: Derivation of recursion relations for $\mathbf{U}^{al}$, $\mathbf{U}^{br}$, $\mathbf{U}^{ar}$, $\mathbf{U}^{bl}$, $\mathbf{U}^{alp}$, $\mathbf{U}^{arp}$, $\mathbf{U}^{a}_{11f}$, $\mathbf{U}^{a}_{12f}$, $\mathbf{U}^{b}_{12b}$, and $\mathbf{U}^{b}_{22}$ (Appendix A) and statistical weight matrices for helix probability profiles (6 pages). Ordering information is given on any current masthead page.

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