Theory of the Phase Transition between Helix and Random Coil in Polypeptide Chains

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The transition between the helical and randomly coiled forms of a polypeptide chain is discussed by reference to a simple model that allows bonding only between each group and the third preceding. Two principal parameters are introduced, a statistical parameter that is essentially an equilibrium constant for the bonding of segments to a portion of the chain that is already in helical form, and a special correction factor for the initiation of a helix. A third parameter which specifies the minimum number of segments in a random section between two helical portions has only a minor effect on the results. The partition function for this model is handled in two alternative ways, either as a summation suitable for short chains, or in terms of the eigenvalues and eigenvectors of a characteristic matrix; the latter is more suitable for long chains. A transition from the random to the helical form is encountered as either the bonding parameter or the chain length is increased. The critical value of the bonding parameter is unity for long chains, while the sharpness of the transition depends on the initiation parameter.

Depending on the values of the bonding parameter and the chain length, one of the following configurations dominates: random coils, single helices with occasional disorder at the ends, and for longer chains, helices occasionally broken by random sections. In rather narrow transition regions, mixtures of these forms may be found. A diagram is given that displays the relationships of these forms.

The theory is compared with published data on polybenzyl-glutamate with fair agreement.

I. INTRODUCTION

DOTY, Blout, and co-workers[1] have recently found that polypeptide chains in solution can be reversibly converted from the randomly coiled form to the α helix of Pauling *et al.*[2] The transformation is remarkably sharp. A change of a few degrees in temperature or a few percent in solvent composition is sufficient to complete it, and it seems fully to merit the term "phase transition" that has been applied to it.[1(b)]

The polypeptide chain consists of amide groups

$$
\begin{array}{c}
\text{O} \\
\|\| \\
-\text{N}-\text{C}- \\
| \\
\text{H}
\end{array}
$$
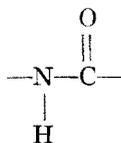
connected by intermediatry carbon atoms. In the α helix, the hydrogen atom of each amide group forms a hydrogen bond with the oxygen atom of the third preceding amide group. We shall refer to an amide group plus one adjacent carbon as a *segment* of the chain.

The amide group is a rigid planar structure. However, according to Pauling *et al.*[2] there is some freedom of rotation about the bonds to the adjacent carbon atoms. Therefore, if the hydrogen bonds are broken, the chain can assume the randomly coiled configurations usual to chain polymers.

Since there can be hardly any doubt that the transformation would occur in a single, isolated chain, we have the novelty of a rather sharp transition in a one-

dimensional system. Transformations in other such systems, such as the one-dimensional ferromagnet,[3,4] are quite diffuse. Furthermore, it has been shown[5] that different macroscopic phases cannot coexist in a one-dimensional system.

The transition is of obvious importance to the full understanding of the formation and stability of proteins. The construction of a theory should therefore be interesting from several points of view.

This paper presents a simple model of the chain that facilitates calculation of the dependence of the partition function on the hydrogen bonding. This model gives a rather sharp transition from the random to the helical form as the strength of the hydrogen bonds is increased beyond a critical value, in agreement with the experimental observations.

The sharpness of the transition is due to the following consequence of the model. The formation of the first turn of the helix is difficult because of a large reduction of entropy. Once formed, however, this turn acts as a nucleus to which further turns can add by hydrogen bonding. Thus this transformation has the property of nucleation characteristic of other sharp transitions.

Associated with the tendency to nucleate is a property that might be called a boundary tension. That is, such faults in the helical structure as exist tend to consist of a number of missing hydrogen bonds at adjacent segments, rather than of missing bonds distributed at random. Further, disorder is propagated inward from the ends of the helix, in a way similar to the inward propagation of disorder from the surface of a crystal lattice.

[1] (a) Doty, Holtzer, Bradbury, and Blout, J. Am. Chem. Soc. **76**, 4493 (1954); (b) P. Doty and J. T. Yang, *ibid.* **78**, 498 (1956); (c) Doty, Bradbury, and Holtzer, *ibid.* **78**, 947 (1956); (d) E. R. Blout and A. Asadourian, *ibid.* **78**, 955 (1956); (e) P. Doty and R. D. Lundberg, *ibid.* **78**, 4810 (1956); (f) P. Doty and K. Iso (private communication).

[2] Pauling, Corey, and Branson, Proc. Natl. Acad. Sci. U. S. **37**, 205, 241 (1951).

[3] E. Ising, Z. Physik **31**, 253 (1925).

[4] H. A. Kramers and G. H. Wannier, Phys. Rev. **60**, 252, 263 (1941).

[5] L. Landau and E. Lifshitz, *Statistical Physics* (Oxford University Press, New York, 1938), p. 232.

Schellman[6] has presented for this transformation a very simple theory, in which he considers special effects at the ends of the helix, equivalent to our nucleation, but ignores the possibility of alternation between helix and coil in the middle of the chain. Further, the transition appears in the theory as perfectly sharp, although dependent upon chain length. Our theory, described below, differs in that it gives a diffuse transition but confirms the dependence on chain length. In addition, it yields a convenient description of the alternation of helical and coiling regions which is important under some circumstances with long chains.

The treatment in this paper differs in another way from that of Schellman. The latter uses the heat and the entropy of adding a segment to the helix as his basic parameters. We prefer to employ two statistical parameters, one for the nucleation of the helix and one for its further growth. While both methods are equally correct, the expression of the results appears to be somewhat more direct in terms of the statistical parameters.

II. THE MODEL

This section presents a simple model of the chain that is intended to represent the significant physical features of the system, and at the same time is amenable to evaluation by simple means. Specifically, the model distinguishes between the contribution of a bonded segment and of an unbonded segment to the partition function, and additionally considers the influence of the state of neighboring segments on these contributions. To describe the model in detail, we first have to establish a notation for configurations of the chain.

It is convenient to base the description of the chain on the helical configuration. We assume that a given state of the chain can be completely described by the state of the oxygen atoms alone; i.e., by a statement as to whether or not each is bonded to the hydrogen of the third preceding segment. This amounts to assuming that bonding of a segment, if it occurs at all, is always to the third preceding segment. The state of a chain of n segments can then be described by a sequence of $n-3$ symbols, each of which can have one of two values. We establish the convention that the *first* three segments are always unbonded. This amounts to selecting as the "beginning" of the chain that end of the helix that has three unbonded oxygen atoms. If the digit 1 represents a bonded oxygen atom and 0 an unbonded atom, then a state of the chain is described by a sequence such as

$$000111000011\cdots.$$

Since our object is the writing down of a partition function, we must now make some specific assumptions about the statistical weights to be attached to particular states. Our concern lies primarily with the thermodynamics associated with the transition from random coil to helix; hence, it is not necessary to describe the quantum states or phase space of the individual segments in detail, as long as the relative weights of the random and helical forms are correctly represented. The following simple set of assumptions about the relative weights appears to be adequate.

The statistical weight* of a given state of the chain is assumed to be the product of the following factors:

(1) The quantity unity for every 0 that appears (unbonded segment).

(2) The quantity s for every 1 that follows a 1 (bonded segment).

(3) The quantity σs for every 1 that follows μ or more 0's (boundary between bonded and unbonded regions).

(4) The quantity 0 for every 1 that follows a number of 0's less than μ.

The effect of assumption (4) is that sequences of less than μ zeros do not appear. For the α helix, μ is usually considered to be about three.[6] The meaning of the first three weights is as follows. The factor unity is arbitrarily assigned as the statistical weight of a segment when it is not bonded into the helix. The factor s measures the contribution to the partition function of a bonded segment relative to that of an unbonded segment. This factor contains a decrease in statistical weight owing to restriction of freedom of motion, but is enhanced by the Boltzmann factor resulting from the bond energy. Finally, an abnormally large decrease in statistical weight is assumed to be caused by the first bond after μ or more unbonded segments since such a bond decreases the freedom of the segments intervening between the bonding oxygen and hydrogen, as well as restricting the freedom of the bonding segment itself. Since the same Boltzmann factor is involved, this contribution to the partition function is written σs, where σ is less than unity.

These assumptions constitute a highly simplified representation of the problem. The formalism is capable of dealing with more detailed assumptions without undue difficulty, but our present knowledge is too incomplete to justify a more refined model. For example, one might introduce a set of σ's, $\sigma(k)$, to give the decrease in statistical weight due to a bond following k unbonded segments. The plot of $\sigma(k)$ *versus* k would be expected to look like the curve shown in Fig. 1. The assumption of a single value of σ, and the ban on sequences of less than μ 0's, is the approximation shown by the dotted line.

There are two nonrigid bonds in each segment.[2] If the degree of restriction of the phase space of each on entering the helix is r, then we should have s proportional to r^2. Similarly, if the formation of a bond

[6] J. A. Schellman, Compt. rend. trav. lab. Carlsberg, Ser. chim. **29**, No. 15 (1955).

* By *statistical weight* we mean the factor that a segment contributes to the partition function, including, if appropriate, a Boltzmann factor; it is not just the number of quantum states, in contrast to one popular usage.
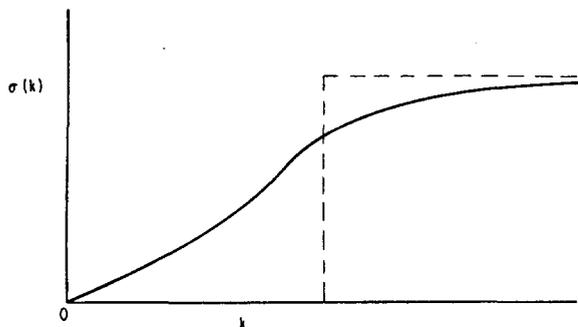
FIG. 1. The weighting factor $\sigma(k)$ for the initiation of a helix after k unbonded segments (schematic). The approximation used in this paper is represented by the dashed line.

restricts to the same degree the segments intervening between the oxygen and hydrogen atoms of the bond, we should have σs proportional to r^6 with the same constant, since there are six nonrigid bonds per turn. Then we have $\sigma = r^4$. Since r can hardly be greater than about $\frac{1}{3}$, σ must be of the order of 10^{-2} or less. The result is that the first turn of the helix can only be formed with difficulty.

We neglect several other possible effects that might have to be considered in a complete treatment. For example, one might introduce a correlation between the statistical weights for hydrogen bonding in one turn of the helix with the presence or absence of bonds in the preceding turn. This has been considered by Hill,[7] but without the correlation between successive bonds in the same turn of the helix on which we base the present paper. In our view the interactions between successive turns is likely to be of secondary importance compared to the interactions within a turn. We also neglect the possibility of hydrogen bonding to other than the segments characteristic of the alpha helix. This phenomenon would not be expected to occur except when the alpha helix was unstable, but under these conditions very few hydrogen bonds would form anyway; therefore we do not believe that the phenomenon is ever of major importance. Further, we assume that only helices of one sense, right- or left-handed, can form with a given chain; this seems to be in accord with experiment for all polypeptides bearing

side groups, where the side group interaction is apparently strong enough to establish a preference for one handedness over the other. Finally, we make no explicit reference to interactions between the side groups; to a considerable extent the effects of these interactions can be included in the parameter s.

III. MATHEMATICAL TREATMENT

Direct Derivation of the Partition Function and the Probability of Bonding

A formal representation of the partition function Q for a chain of n segments may be obtained from the above assumptions by direct enumeration of the number of ways of arranging a given number of zeros and ones in a chain always starting with three zeros. For example, with μ taken as unity, we have obtained the formula

$$Q = 1 + \sum_{l}^{(n-2)/2} \sigma^l \sum_{l}^{n-l-2} \frac{(k-1)!(n-k-2)!s^k}{l!(l-1)!(k-l)!(n-k-l-2)!}, \quad (1)$$

where $(n-2)/2$ is the largest integer less than $(n-2)/2$. Though this formula does not appear to be attractive for calculation in general, it is useful when the product of $n\sigma$ is small and s is appreciably greater than unity, since then only the first term of the summation over l is important. It will be shown that for rather short chains these are just the conditions under which the helix is formed. Physically, this corresponds to conditions under which only one helical section (unbroken sequence of 1's) would be expected.

It is easy to show that the expression $(d \ln Q/d \ln s)$ is the average number of hydrogen bonds formed in the chain at a given value of s, since the number of hydrogen bonds in any state is equal to the power of s in the corresponding term in the partition function. We define θ as the fraction of possible hydrogen bonds formed,

$$\theta = \frac{1}{(n-3)} \frac{d \ln Q}{d \ln s}. \quad (2)$$

Then, keeping only the first term of the summation over l, we get from Eq. (1),

$$\theta = \frac{\sum_{1}^{n-3} k(n-k-2)s^k}{(n-3)\left[1/\sigma + \sum_{1}^{n-3} k(n-k-2)s^k\right]}, \quad (3a)$$

$$= \frac{(n-3)(s-1)-2+[(n-3)(s-1)+2s]s^{-n+2}}{(n-3)(s-1)\{1+(s-1)^2s^{-n+1}/\sigma-[(n-3)(s-1)+s]s^{-n+2}\}}. \quad (3b)$$

These formulas are useful for calculation for small values of n. Since they are valid only when there is one unbroken helical sequence in the chain, they are inde-

pendent of the parameter μ which specifies the minimum possible number segments involved in a break in the helix. It appears, however, that any attempt to use all the terms of Eq. (1) would lead to very complicated expressions for large n. Fortunately, other

[7] T. L. Hill, J. Polymer Sci. 23, 549 (1957).

methods are available, and these will be discussed in the following section.

The Matrix Method

There are several well-known methods for evaluating complicated partition functions, e.g., the method of the maximum term and the method of steepest descents, but one method, the matrix method[4,7-9] is particularly well adapted to this chain problem, and to it we shall confine our attention. While the method as applied to infinite chains has been adequately described in the above references, we have found it desirable to extend its scope to include finite chains. For this reason we give a brief discussion of the method.

Formally the method is capable of taking into account interactions between distant segments as well as nearest neighbors. Our formal description will be given for the general case. Much of the later development is in terms of nearest neighbor interactions only ($\mu=1$), but a model which includes certain longer-range effects is also discussed ($\mu=3$).

If the physical situation requires the inclusion of effects between segments whose positions in the chain differ by the integer μ, the matrix method requires the state description of the chain to be in terms of the "joint configuration" of μ successive segments. Following Kramers and Wannier, we use an indexing of states based on binary numbers. To illustrate, let $\mu=3$. The various configurations of a group of three segments are described by sequences of 0's and 1's such as 110. The sequence can be interpreted as a binary number, and we define a single index for the configurations as the value of this binary number. Thus,

State	Index
000	0
001	1
010	2
011	3
$\cdots$	$\cdots$

and so on. There are 2^μ possible states for a group of μ segments.

The matrix method involves operations on a *statistical weight vector* $\mathbf{a}_i$. This column vector has 2^μ components, one for each joint configuration of the segments $i-\mu+1$, $i-\mu+2\cdots$, i. Each component, $\mathbf{a}_{i,l}$, is the statistical weight of the lth joint configuration of the segments $i-\mu+1$ through i, including the contributions to the statistical weight of all compatible configurations of the preceding $i-\mu$ segments. The partition function of the chain is just the sum of all the components of $\mathbf{a}_n$, where n is the number of segments in the entire chain.

[8] E. W. Montroll, J. Chem. Phys. **9**, 706 (1941); G. F. Newell and E. W. Montroll, Phys. Rev. **25**, 159 (1953).

[9] E. N. Lasettre and J. P. Howe, J. Chem. Phys. **9**, 747 (1941).

The vectors $\mathbf{a}_1$, $\mathbf{a}_2$, and $\mathbf{a}_3$ are taken to be

$$\mathbf{a}_1=\mathbf{a}_2=\mathbf{a}_3=(1,0,0,\cdots,0), \quad \mu<4, \quad (4)$$

since the first three segments cannot bond to preceding hydrogens. If μ is equal to or greater than four, further consideration may be necessary to establish $\mathbf{a}_4$, $\cdots$, $\mathbf{a}_\mu$. The succeeding discussion is for $\mu<4$, but the necessary modification for $\mu\geq4$ is formally a minor one.

As long as i is greater than the larger of 3 and μ, the vectors $\mathbf{a}_i$ can be generated by the use of a $2^\mu\times2^\mu$ matrix operator $\mathbf{M}$,

$$\mathbf{a}_i{}^\dagger=\mathbf{M}\mathbf{a}_{i-1}{}^\dagger, \quad (5)$$

where the symbol $\dagger$ indicates the transposed or column vector. The matrix embodies the physical assumptions of the problem. The element M_{kl} is the factor to be multiplied to the statistical weight upon adding the ith segment, if the segments i through $i-\mu+1$ form joint configuration k while the segments $i-1$ through $i-\mu$ are in joint configuration l. (For μ greater than 1, the matrix will have at most the fraction $2^{1-\mu}$ of its elements nonzero.)

The vector $\mathbf{a}_n$ is given by

$$\mathbf{a}_n{}^\dagger=\mathbf{M}^{n-3}\mathbf{a}_3{}^\dagger, \quad (6)$$

and the partition function is

$$Q=\omega\mathbf{M}^{n-3}\alpha^\dagger \quad (7a)$$

$$\alpha=(1,0,0,\cdots,0), \quad (7b)$$

$$\omega=(1,1,1,\cdots,1). \quad (7c)$$

Calculations based on Eqs. (7) are relatively easy. If the matrix $\mathbf{M}$ can be diagonalized,

$$\Lambda=\mathbf{T}^{-1}\mathbf{M}\mathbf{T}, \quad (8)$$

the diagonal matrix can be easily raised to the required power; the elements of the diagonal matrix Λ^k are the kth powers of the elements of Λ. When k is large the kth power of the largest element of Λ is so much greater than the others that it alone needs to be considered; this is the classical case discussed in the references.[4,8,9]

The diagonal elements of Λ are the eigenvalues of $\mathbf{M}$. Corresponding to each eigenvalue are two eigenvectors, a row vector and a column vector, since $\mathbf{M}$ is not symmetrical. The row vector is the eigenvector for $\mathbf{M}$ operating to the left and the column vector for $\mathbf{M}$ operating to the right. The column eigenvectors constitute the columns of $\mathbf{T}$ and the row vectors the rows of $\mathbf{T}^{-1}$.

The matrix $\mathbf{M}$ is unsymmetrical, and there are certain unsymmetrical matrices that cannot be diagonalized. The matrices encountered in our work can in general be diagonalized, although in the limiting case where σ is zero a matrix is formed that cannot be. This limiting case is that of a perfectly sharp transition. However, this limit can be evaluated after the entire computation has been done for finite σ.

Average States of Individual Segments

The model makes it easy to obtain approximations to the state of any given segment of the chain. The statistical weight to be attached to a given joint configuration of the segments $(i-\mu+1)$ through i is given by the sum of the statistical weights of all configurations of the entire chain consistent with the given joint configuration. Now the vector,

$$\mathbf{a}_i^\dagger = \mathbf{M}^{i-3}\alpha^\dagger, \tag{9}$$

has components which are the aggregate statistical weights of the possible joint configurations of segments $i-\mu+1$ through i, taking account also of the preceding part of the chain. In a similar way the row vector,

$$\mathbf{b}_i = \omega\mathbf{M}^{n-i}, \tag{10}$$

has components which are the aggregate statistical weights provided to each joint configuration by the states available to the remainder of the chain.

The definitions of $\mathbf{a}_i$ and $\mathbf{b}_i$ are such that

$$\mathbf{b}_i \cdot \mathbf{a}_i^\dagger = Q, \tag{11}$$

since Q is the sum of all statistical weights. The probability that segments i through $i-\mu+1$ are in joint configuration l is therefore

$$p_i(l) = (1/Q)b_{i,l}a_{i,l}. \tag{12}$$

Several special cases of Eq. (12) are of interest. First let us consider the state of a segment near the middle of a long chain. Then, by neglecting large powers of all eigenvalues of $\mathbf{M}$ relative to the same powers of the largest, λ_0, we may express $\mathbf{a}_i$ and $\mathbf{b}_i$ in terms of the principal eigenvectors only:

$$\mathbf{b}_i = \lambda_0^{n-i}\left(\sum_{k=0}^{\rho-1}T_{k0}\right)(T_{00}^{-1}, T_{01}^{-1}, T_{02}^{-1}, \cdots, T_{0\rho-1}^{-1}),$$

$$\mathbf{a}_i = \lambda_0^{i-3}T_{00}^{-1}(T_{00}, T_{10}, T_{20}, \cdots, T_{\rho-1,0}), \tag{13}$$

where $\rho=2^\mu$. Equation (12) then gives the simple expression,

$$p_i(l) = \frac{b_{i,l}a_{i,l}}{\sum_{l=0}^{\rho-1}{}'b_{i,l}a_{i,l}} = T_{0l}^{-1}T_{l0}. \tag{14}$$

If the segment of interest is near the end of a chain, the approximation involving the largest eigenvalue can be applied to the $\mathbf{a}$ vector but not the $\mathbf{b}$ vector. This leads to an expression

$$p_i(l) = \frac{b_{i,l}T_{l0}}{\sum_{l=0}^{\rho-1}{}'b_{i,l}T_{l0}}, \quad i \approx n, \tag{15}$$

for the probability that the joint configuration is state l. Simplifying the expression further depends on the form of the matrix $\mathbf{M}$; later an approximate form will be given.

It is also of interest to discuss the occurrence of breaks in the helix. Such a break (unbonded section) must be bounded by the configurations 10 and 01, i.e., it is described by a sequence such as $\cdots100001\cdots$. According to Eq. (14) the probability of the sequence 01 at the $(i-1)$th and ith positions near the middle of the chain, which is equal to the probability of the sequence 10, is

$$P_i(01) = \sum_{l=1}^{\rho-3}{}''p_i(l) = \sum_{l=1}^{\rho-3}{}''T_{0l}^{-1}T_{l0}, \tag{16}$$

where the double-primed sum includes only every fourth term, $l=1, 5, 9, \cdots \rho-3$. This formula applies when $\mu \geq 2$. The special case $\mu=1$ will be discussed at a later point.

The Form of the Operator M

The matrix $\mathbf{M}$ is of order $\rho \times \rho$, where $\rho=2^\mu$. Only certain elements can be nonzero. The assumptions listed above give a matrix of the form illustrated below for the case of $\mu=3$:

$$\mathbf{M} = \begin{bmatrix} 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ \sigma s & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & s & 0 & 0 & 0 & s & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & s & 0 & 0 & 0 & s \end{bmatrix}. \tag{17}$$

It can be shown that the characteristic equation of the matrix,

$$|M - I\lambda| = 0, \tag{18}$$

where $\mathbf{I}$ is the unit matrix, can be reduced in this case to

$$\lambda^{\mu-1}(1-\lambda)(s-\lambda) = \sigma s. \tag{19}$$

Furthermore, the trace is $1+s$, independent of μ.

Since σ is small, approximations to the roots of $\mathbf{M}$ are 1 and s with $\mu-1$ very small roots, provided $\sigma^{1/\mu}$ is less than unity. Therefore the nature of the partition function, which depends mainly on the large eigenvalues, will be to a large extent independent of μ. This being the case, we shall illustrate in most detail the case $\mu=1$. In a later section we shall give some of the results of the case $\mu=3$. In the case $\mu=1$ the steps described in the foregoing are especially simple.

The matrix $\mathbf{M}$, for $\mu=1$, is

$$\mathbf{M} = \begin{pmatrix} 1 & 1 \\ \sigma s & s \end{pmatrix}. \tag{20}$$

The characteristic equation is

$$(1-\lambda)(s-\lambda)=\sigma s, \qquad (21)$$

and the roots are

$$\lambda=\tfrac{1}{2}\{1+s\pm[(1-s)^2+4\sigma s]^{\frac{1}{2}}\}. \qquad (22)$$

We designate the larger of these by λ_0, the smaller by λ_1. The transformation that diagonalizes $\mathbf{M}$ is

$$\mathbf{T}=\begin{pmatrix} 1 & 1 \\ \lambda_0-1 & \lambda_1-1 \end{pmatrix}, \qquad (23)$$

$$\mathbf{T}^{-1}=\frac{1}{\lambda_1-\lambda_0}\begin{pmatrix} \lambda_1-1 & -1 \\ -\lambda_0+1 & 1 \end{pmatrix}. \qquad (24)$$

The expression for the partition function, Eq. (7a), is

$$Q=(1,1)\mathbf{M}^{n-3}(1,0)^\dagger=(1,1)\mathbf{T}\mathbf{\Lambda}^{n-3}\mathbf{T}^{-1}(1,0)^\dagger, \qquad (25)$$

which becomes, using Eq. (22) and the fact that $\lambda_0+\lambda_1=1+s$,

$$Q=\frac{\lambda_0^{n-2}(\lambda_0-s)+\lambda_1^{n-2}(s-\lambda_1)}{\lambda_0-\lambda_1}. \qquad (26)$$

According to Eq. (2), the average number of hydrogen bonds is

$$\theta=[s/(n-3)]\{[(n-2)\lambda_0'/\lambda_0+(\lambda_0'-1)/(\lambda_0-s)]\lambda_0^{n-2}(\lambda_0-s)$$

$$+[(n-2)\lambda_1'/\lambda_1+(1-\lambda_1')/(s-\lambda_1)]\lambda_1^{n-2}(s-\lambda_1)\}/[\lambda_0^{n-2}(\lambda_0-s)+\lambda_1^{n-2}(s-\lambda_1)]-\left(\frac{s}{n-3}\right)\left(\frac{\lambda_0'-\lambda_1'}{\lambda_0-\lambda_1}\right), \qquad (27)$$

where the prime denotes differentiation by s.

In order to discuss the state of a particular bond, say one in the middle or near an end of the chain, we need the vectors $\mathbf{a}_i$ and $\mathbf{b}_i$. From Eqs. (13), (23), and (24) these are

$$\mathbf{a}_i=[\lambda_0^{i-3}(\lambda_0-s)/(\lambda_0-\lambda_1)](1,\lambda_0-1), \qquad (28)$$

$$\mathbf{b}_i=[\lambda_0^{n-i+1}/(\lambda_0-\lambda_1)](\lambda_0-s,1) \qquad (29)$$

to the approximation involved in Eq. (13). Equation (14) gives directly the probability of the state l (0 or 1) at the ith segment near the center of the chain as

$$p_i(l)=T_{0l}^{-1}T_{l0}. \qquad (30)$$

The state of a segment near the end of a long chain is approximately given by Eq. (15). This can be simplified for large s in the present case by actually computing successive powers of the matrix (20). If a small number of these are calculated, and terms involving σ are dropped, it may be seen that the vector $\mathbf{b}_i$, Eq. (10), is approximately

$$\mathbf{b}_i=(1,1+s+s^2+\cdots+s^{n-i}). \qquad (31)$$

Then Eq. (15) yields

$$p_{n-i}(0)=T_{00}/[T_{00}+T_{10}(1+s+\cdots+s^{n-i})] \qquad (32a)$$

$$=1/[1+(\lambda_0-1)(1+s+\cdots+s^{n-i})]. \qquad (32b)$$

But for large s, $\lambda_0\approx s$, so that we have

$$p_{n-i}(0)=s^{-(n-i+1)}, \quad s>1. \qquad (33)$$

The end segment has the probability s^{-1} of being unbonded, the next segment the probability s^{-2}, and so on. The mean number of unbonded segments at one end, obtained by summing over the above probabilities, is $1/(s-1)$. These results are valid only for chains long enough so that the two ends do not influence each other. A formula for short chains is given in the next section.

The general formula for computing breaks in the chain, Eq. (16), cannot be used when $\mu=1$. However, it is easy to show in analogy to Eq. (14) that the probability of a sequence 01 near the middle of the chain, $P_i(01)$, is

$$P_i(01)=T_{00}^{-1}M_{01}T_{10}/\lambda_0, \quad \mu=1. \qquad (33a)$$

To illustrate these formulas, approximation may be made to the roots of Eq. (21). Since $\sigma\ll1$, we have the results shown in Table I. Then the probability of an unbonded segment, $p_i(0)$, near the center of the chain is, from Eq. (14),

$$1-\sigma s/(s-1)^2, \quad s<1,$$

$$\tfrac{1}{2}, \qquad\qquad\quad s=1,$$

$$\sigma s/(s-1)^2, \qquad s>1. \qquad (34)$$

From Eq. (33a) the probability of a change from bonded to unbonded region, $P_i(01)$, at any given segment near the middle is

$$\sigma s/(1-s), \quad s<1,$$

$$(\sigma)^{\frac{1}{2}}/2, \qquad s=1,$$

$$\sigma/(s-1), \qquad s>1. \qquad (35)$$

The probability that the last segment of a *short* chain is bonded is of interest in connection with the polymerization kinetics. We can find the formula from Eq. (10) with Eqs. (8), (23), and (24),

$$p_n(1)=\frac{(\lambda_0^{n-3}-\lambda_1^{n-3})(s-\lambda_1)(\lambda_0-s)}{\lambda_0^{n-2}(\lambda_0-s)+\lambda_1^{n-2}(s-\lambda_1)}. \qquad (36)$$

TABLE I.

	$s<1$	$s\approx1$	$s>1$
λ_0	$1+\sigma s/(1-s)$	$(1+s)/2+\sqrt{\sigma}$	$s+\sigma s/(s-1)$
λ_1	$s-\sigma s/(1-s)$	$(1+s)/2-\sqrt{\sigma}$	$1-\sigma s/(s-1)$

This reduces to a simple form if we use the above approximations to the eigenvalues and assume that ns^{-n} is much less than unity:

$$p_n(1) = \frac{\sigma s(s-1)(s^{n-3}-1)}{\sigma s^{n-1}+(s-1)^2}, \quad s>1. \quad (37)$$

When n is large this agrees with Eq. (33).

We note in passing that the above approximate eigenvalues substituted into Eq. (27) for θ yield Eq. (3b) if the first power only of σ is retained.

The Case of $\mu=3$

The case of $\mu=3$ is of special interest because it has been assumed[6] that this corresponds to real polypeptide chains. The right-hand and left-hand eigenvectors are respectively:

$$(1, \sigma s/\lambda, \sigma s/\lambda^2, \sigma s^2/\lambda^2, \lambda-1, 0, s(\lambda-1), s^2(\lambda-1))^{\dagger}, \quad (38a)$$

$$\frac{\lambda(\lambda-s)}{4\lambda^2-3\lambda s-3\lambda+2s}\left(1, \frac{\lambda-1}{\sigma s}, \frac{1}{\lambda^2}, \frac{\lambda-1}{\sigma s}, \frac{1}{\lambda}, \frac{\lambda-1}{\sigma s}, \frac{1}{\lambda^2}, \frac{\lambda-1}{\sigma s}\right). \quad (38b)$$

In these formulas the eigenvalue, λ_0 or λ_1, corresponding to the desired eigenvector is to be inserted for λ. These eigenvalues are the two largest roots of the secular equation, Eq. (19). For $s>1$ we have the approximations,

$$\lambda_0=s+\sigma/s(s-1), \quad (39a)$$

$$\lambda_1=1-\sigma s/(s-1). \quad (39b)$$

We omit other formulas for the eigenvalues since this case differs from that of $\mu=1$ only when s is large.

IV. RESULTS AND DISCUSSION

The discussion of this problem is somewhat complicated by the uncertainty regarding the value of μ, the parameter that represents the minimum number of hydrogen bonds that can be broken in one sequence. The formulas are generally simplest when μ is assumed to be unity, although some larger value, perhaps three, is more realistic. Fortunately, we find that many of the interesting results are practically independent of the value chosen. We shall therefore give the discussion in terms of μ equal to unity, except where we consider breaks in the sequence of hydrogen bonds in long helices.

The Transition

The first noteworthy result is the existence at large n of a transition which becomes sharper as σ is decreased. For very large n the partition function is dominated by the largest eigenvalue, λ_0, raised to the $(n-3)$ power. The fraction of hydrogen bonds is then given approximately by
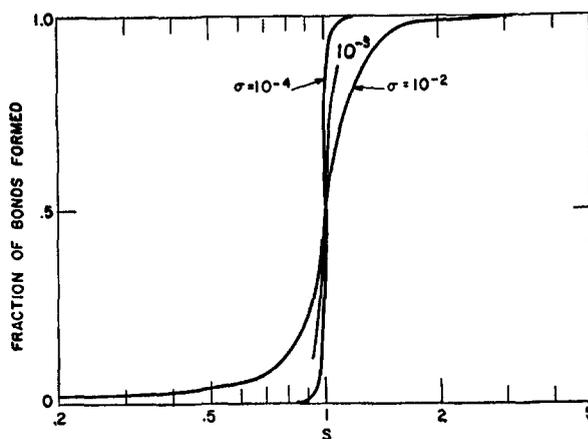
FIG. 2. Fraction of intersegment hydrogen bonds Θ as a function of the equilibrium constant s for various values of the initiation parameter σ.

$$\theta = d \ln\lambda_0/d \ln s. \quad (40)$$

The results from this formula are shown in Fig. 2 for the case of $\mu=1$ and various values of σ.

In this case when σ is unity there is no interaction between the states of successive segments, and s is just the equilibrium constant for the formation of the hydrogen bonds; the fraction of hydrogen bonds then shows a gradual rise with increasing s according to the formula

$$\theta = s/(1+s). \quad (41)$$

Quite different behavior appears at the other extreme when σ approaches zero; in this case there is an almost sharp transition at $s=1$ corresponding to the intersection of the two branches of λ_0, 1, and s. In view of the form of Eq. (21) and since λ is very nearly unity at the transition, the shape of the transition curve is not perceptibly dependent on the parameter μ which specifies the minimum number of hydrogen bonds that can be broken at one place. The value of unity is thus a critical value of s at which long chains go substantially into the helical form.

Critical Size

In a corresponding fashion there is also a critical value of the size n at which substantial helix formation appears for any given value of σ and for s greater than unity. From Eq. (3b), it appears that this value is approximately that at which

$$(s-1)^2 s^{-n+1} = \sigma. \quad (42)$$

The actual behavior of θ as a function of n is shown in Fig. 3 for several values of s and σ. These results were calculated from Eqs. (3a, b) as well as Eq. (27); a few values were also calculated by the corresponding formulas for the case of $\mu=2$, but the differences were insignificant. Thus the critical size effect is also independent of μ, at least at small n.
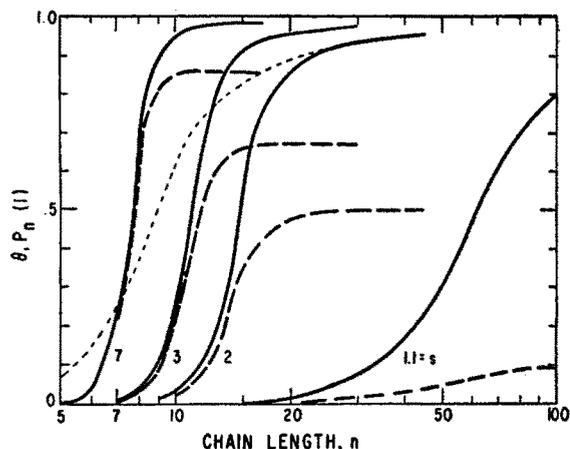
FIG. 3. Fraction of intersegment hydrogen bonds Θ and probability that the last segment be hydrogen-bonded, $p_n(1)$, Eq. (37), as functions of the number of segments n at various values of s and σ. While Eq. (37) specifically refers to the case where $\mu=1$, the results would not be significantly different for other values of μ. Solid lines, Θ at $\sigma=10^{-4}$ and the indicated values of s; thin dashed curve, Θ for $s=2$ and $\sigma=10^{-2}$; heavy dashed curves, $p_n(1)$ at $\sigma=10^{-4}$ and the indicated values of s.

The critical size effect offers the most definitive method of determining the two important parameters s and σ from experimental data on the fraction of hydrogen bonds. If a sequence of polymers of different chain lengths is available, the data may be compared to theoretical curves for different s and σ until the best fit is found.

Equilibrium Constants

Equilibrium constants can be defined for various processes involving the helix-coil transition. For example, a sort of an equilibrium constant is the ratio of the number of hydrogen-bonded segments to the number of unbonded segments, which is $\theta/(1-\theta)$. Another ratio accessible to direct measurement (by optical rotatory power) is the ratio of the number of segments in helical form to those in random form; this is $[(n-3)\theta+3]/(n-3)(1-\theta)$. The ratio of the number of molecules with any amount of helical content whatever to those without is another equilibrium constant, and is equal to $Q-1$.

Even the parameter s can be thought of as the equilibrium constant for a certain process, that of incorporating into a helical section the first adjoining segment from a long random section, since the ratio of the aggregate of the statistical weights of those states with a helical section of, say, $k+1$ segments in length to the aggregate of the weights of those states with a section of k segments is practically s, if the adjacent random section is sufficiently greater than the minimum length μ. By a familiar thermodynamic relation we then have

$$d \ln s/dT = \Delta H/RT^2, \qquad (43)$$

where T is the absolute temperature, and ΔH is the enthalpy change on converting one segment from the random to the helical form under the conditions described in the foregoing.

Temperature Dependence and the Heat of Helix Formation

Experimental data are available in some cases for the variation of θ with temperature, but the values of s and σ cannot be obtained from these curves unless data are available for different chain lengths. For example, data of Doty and Yang[1(b)] and Doty and Iso[1(f)] for polybenzyl-L-glutamate are shown in Fig. 4 together with the theoretical curves for two values of σ. In each case the relation between s and the temperature has been adjusted to give the best fit to the experimental curves. It is evident that a small change in $d \ln s/dT$ would be sufficient to make either value of σ satisfactory for either value of n alone, but with the two together the choice of $\sigma=2\times10^{-4}$ with $d \ln s/dT=0.00614$ is clearly preferable.

From Eq. (43) we immediately calculate that ΔH is $+990$ cal/mole. This heat, it should be remembered, includes the heat of desorption of solvent from the random-form segment when the latter is transformed to helix. The positive sign of ΔH, corresponding to heat adsorbed on helix formation, would be unintelligible otherwise.

In fitting the curves to the data we have assumed that σ does not depend on the temperature because of
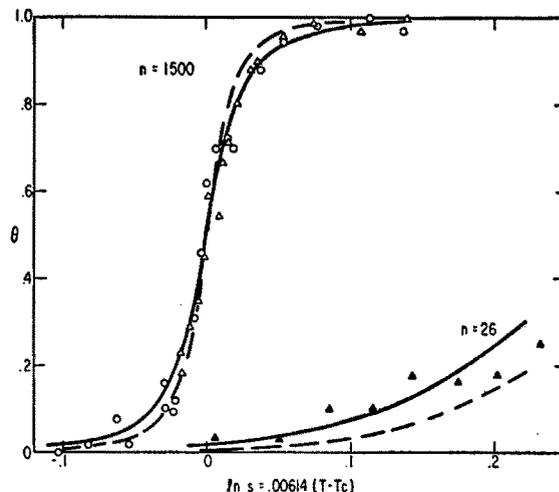
FIG. 4. Comparison of theoretical curves of fraction of segments intramolecularly hydrogen-bonded Θ with observations of Doty and Yang[1(b)] and Doty and Iso[1(f)] on poly-γ-benzyl-L-glutamate. The fraction intramolecularly bonded was assumed to be a linear function of the optical rotation and $\ln s$ was assumed to be linear in the temperature T; T_c is the temperature at which Θ is 0.5. Circles, Doty and Yang; triangles, Doty and Iso. Solid lines correspond to $\sigma=2\times10^{-4}$; dashed lines, $\sigma=1\times10^{-4}$. Doty and Yang's measurements on a sample of degree of polymerization, n, of 84 have been omitted because there is some doubt about the molecular-weight distribution of this sample (private communication from Professor Doty).
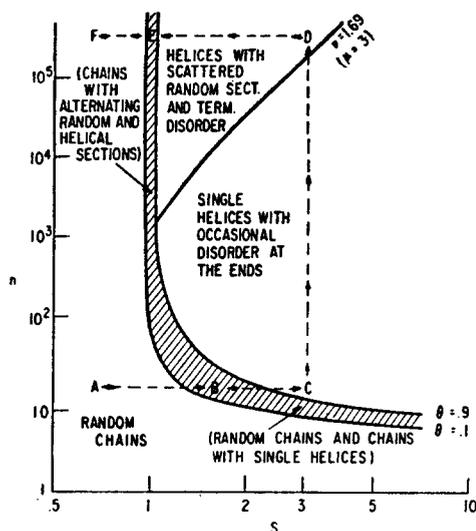
FIG. 5. The $n-s$ plane, calculated for $\sigma=10^{-4}$, and showing the characteristics of the chains in the various regions. The two contours of constant Θ are the (arbitrarily chosen) boundaries of the transition region. The line of constant ν corresponds to Eq. (45). The dotted line is the circuit described in the text.

the interpretation given earlier in terms of a ratio of available phase space; this ratio should not change much with temperature. We might hazard a guess that σ should be likewise independent of solvent, depending only on the constitution of the polymer. Data are not yet available to test this point.

The Dominant Configurations

We turn now to the description of the dominant configurations of the chains under various conditions. The situation is epitomized in Fig. 5. For small values of n or s the chains are in the random, unbonded configuration. At larger values of n and s the helical configurations dominate, but in different ways in the sectors of moderate n and large s or large n and moderate s; in the former sector each chain contains only one unbroken helical section, in the latter, several.

For the case of $\mu=1$ we have already seen how the probability of a break in the helix depends upon σ and s, Eq. (35). The case of $\mu=3$, corresponding to no less than three consecutive segments being unbonded at once, is more realistic, however, when both n and s are large. Let us define ν as the average number of unbroken helical sections per molecule; by analogy with Eq. (2) this is given by

$$\nu=(d\ln Q/d\ln\sigma). \tag{44}$$

With the eigenvalues and eigenfunctions of Eqs. (38) and (39) we can calculate easily the necessary terms of Q and obtain ν by differentiation. The result is

$$\nu=\sigma[n/s^2(s-1)+0(1)], \tag{45}$$

where $0(1)$ stands for terms of order unity. Likewise,

by the use of Eq. (15), the probability of finding a particular segment unbonded is

$$P(0)=\sigma(3s-2)/s^2(s-1)^2. \tag{46}$$

Since v is approximately the average number of sequences of unbonded segments, the ratio of $nP(0)$ to v is the average number of unbonded segments in one sequence; this is

$$(3s-2)/(s-1). \tag{47}$$

The average number of unbonded segments at a break in the helix is thus three or more, depending only on the value of s.

Returning to Fig. 5, we see that the two sectors of the region of helices are separated from each other by a line of constant v. The exact value of v is arbitrary; we have selected $v=1+\ln2$ for purposes of illustration, since along this line half the chains contain one unbroken helical section.

Let us proceed in sequence through the five distinct regions of the diagram to become acquainted with their characteristics, following the circuit indicated by the dotted line. We begin in the region of random chains at point A where n and s are small. If we maintain chain length n and increase the equilibrium constant s, we soon enter the transition region B, where chains containing helices start to appear in the ensemble. The critical value of s for a given n is the one that satisfies Eq. (42). Equation (42) implies that the aggregate statistical weights of the states containing helices are approximately equal to those of the random states. This has an interesting consequence; since θ is near one-half, about half of the chains of the ensemble must be nearly completely in the helical form while half are still in the random form. At any given time the individual chains "make a choice" between the two extreme forms; mixed forms are not favored at small n.

In the region beyond the transition C, most of the chains are in the helical form, except at the ends, where the sizable fraction of random configurations indicated by Eqs. (33) and (37) remain. The end effect depends only on s; therefore the fraction of bonds θ depends almost entirely on s alone in this region (compare curves for $s=2$, Fig. 3).

The end effect is still present in the same way in the next region of the diagram D at large n and large s, but disorder also appears in the middle of the chains as we increase n. This disorder takes the form of short sequences of broken bonds, as we have already seen.

When we decrease s the amount of disorder increases in all its manifestations: the length of the breaks, Eq. (47); the number of independent helical sections, Eq. (45); and the probability of segments unbonded at the ends, Eq. (33). Eventually we enter another branch of the transition region near $s=1$, point E, as shown in Fig. 5. A characteristic of this branch is the fact that single chains contain substantial sections in

both helical and random forms in contrast to the situation encountered in the lower branch of the transition region. The average combined length of a sequence of bonded segments followed by a sequence of unbonded segments is just the reciprocal of $P(01)$, which is given by Eq. (35) with sufficient accuracy when s is unity. At the midpoint of the transition the average length of a helical sequence is half of the reciprocal of $P(01)$, or $\sigma^{-\frac{1}{2}}$. The magnitude of this number is noteworthy. By comparison, if the bonds were arranged at random, the average length of a bonded sequence would be two. When we decrease s further the relative lengths of the random and helical sections disproportionate rapidly, until finally the chains become almost purely random in configuration, and we return to the region of random chains, point F.

Kinetics of Polymerization

The kinetics of polymerization have been found to show different rate constants when the polymer is in the helical or random forms. According to Doty and Lundeberg,[1(e)] the addition of monomer to the helical form occurs several times faster than the addition to the random form in dioxane solution. Presumably the rate depends upon the condition of the nth segment of the helix. For this reason we have plotted $p_n(1)$, Eq. (37), in Fig. 3. Here also the critical size is important, but the limiting value of $p_n(1)$ at large n is never quite as large as the limiting value of θ. Doty and Lundberg found that polybenzylglutamate in dioxane solution showed a rather sharp transition in rate of addition of monomer at about $n=8$; this would correspond to $s=5$ if σ is assumed to be 10^{-4} as is suggested by the apparent sharpness of the transition and in accordance with the results cited in the foregoing in the section on temperature dependence.

Relation to Other Work

Subsequent to Schellman's original publication[6] and more or less simultaneously with each other, a number of workers have been developing theories of the helix-random coil transition. Several preliminary accounts have already appeared[10–13] and others, in addition to the present paper, are now being published.[14–17] Insofar as we have been able to ascertain, there is substantial agreement about the results, although considerable divergence in the methodology and emphasis. Our justification for adding one more report on the topic is the fact that we alone seem to have made extensive use of the matrix method, which allows the simplest treatment on a unified basis of the various phenomena of interest for various modifications of the basic model.

It remains to clarify the relation of these results to the well known demonstration that a one-dimensional system cannot show a sharp phase transition in the usual sense. To be exact, the usual demonstration, as given for example by Landau and Lifshitz,[5] states that a sharp transition cannot occur unless the boundary tension between the two phases is infinite, since otherwise the two phases will always mix with each other to an appreciable extent. An infinite boundary tension corresponds in our treatment to σ equaling zero which is the only circumstance under which we find the transition to be sharp. Thus there is no contradiction. In fact, the prediction that the two phases will mix with each other when the boundary tension is finite is in complete accord with our result that a long chain near the transition point consists of alternating helical and random sections. It is this alternation of short sections of each phase that is characteristic of a one-dimensional system and that causes the transition to be diffuse.

V. ACKNOWLEDGMENT

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