Cooperative Chiral Order in the B-Z Transition in Random Sequences of DNA

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ABSTRACT We present a theory for cooperative chiral order in the transition between right-handed B-DNA and left-handed Z-DNA. This theory, based on the random-field Ising model, predicts the characteristic length scale of Z-DNA segments. This length scale depends on whether the DNA is a homopolymer or a random sequence: it is ~4000 nucleotides in a homopolymer but only ~25 nucleotides in a random sequence. These theoretical results are consistent with experiments on DNA homopolymers and random sequences.

INTRODUCTION

DNA can assume a variety of three-dimensional forms (Frank-Kamenetskii, 1990; Rich, 1993; Herbert and Rich, 1996). The most common form is the right-handed double helix called B-DNA, shown in Fig. 1 *A*. However, under some circumstances, DNA can form the left-handed double helix called Z-DNA, shown in Fig. 1 *B*. Z-DNA is not a mirror image of B-DNA, but it has the opposite sense of helicity. The transition between the B and Z conformations depends on several variables, including temperature, salt concentration in solution, and superhelical stress, a twisting force on the polymer due to topological constraints. It particularly depends on the sequence of nucleotides: Z-DNA is favored by sequences with alternating purines and pyrimidines, especially the alternation . . . CGCGCG. . . . A DNA polymer can have segments of the B and Z conformations, separated by helix reversals, if the nucleotide sequence favors B in some regions and Z in other regions. Thus, the three-dimensional structure of DNA, with alternating segments of B and Z, is a response to the fixed sequence of nucleotides. In this respect, DNA structure is analogous to protein structure, which is a far more complex response to a fixed sequence of amino acids.

The transition between B-DNA and Z-DNA has been extensively studied, both experimentally and theoretically. Most of these studies have investigated the conformation of short test sequences in closed circular plasmids under known superhelical stress (Peck and Wang, 1983; Frank-Kamenetskii and Vologodskii, 1984; Vologodskii and Frank-Kamenetskii, 1984; Ellison et al., 1985; Mirkin et al., 1987; Ho, 1994). These studies have established the key energetic parameters for the B-Z transition. In particular, they have determined the helix reversal energy and the energetic preference of various dinucleotides for the B or Z conformation. Based on these results, software has been developed that scans through known DNA sequences and identifies segments that are likely to form Z-DNA (Ho et al., 1986; Schroth et al., 1992). Recent experiments have indeed found that some of these segments form Z-DNA under the superhelical stress induced by the DNA transcription process (Wölfl et al., 1995; Müller et al., 1996).

In this paper, we consider a different theoretical issue in the B-Z transition. Rather than investigating the conformation of a *particular known sequence*, we investigate the statistics of cooperative order in *random sequences* of DNA. Using the energetic parameters derived by the earlier studies, we determine the characteristic length scale of cooperative order, i.e., the typical length of Z-DNA segments between helix reversals. Our results for random sequences show the typical length of Z-DNA segments that can be expected in biological sequences.

Our work is based on a theory of cooperative chiral order in random heteropolymers, which was originally developed to describe polyisocyanates. Polyisocyanates can be regarded as a simple analog of DNA. This polymer consists of a single chain with a random sequence of right-handed, left-handed, or achiral pendant groups, analogous to the sequence of nucleotides in DNA. In response to this sequence, the polymer adopts a conformation with segments of right- and left-handed helicity, analogous to segments of B-DNA and Z-DNA. The relative proportions of right- and left-handed segments can be determined by measuring the optical activity of the polymers in dilute solution. Recent experiments have found that the optical activity of polyisocyanates is extremely sensitive to slight chiral influences, such as a slight excess of right- over left-handed pendant groups (Green et al., 1995a, b). This sensitivity shows a high degree of cooperativity along the polymers.

To explain these results for polyisocyanates, Selinger and Selinger (1996, 1997) developed a theory based on the random-field Ising model. This theory shows that there are two cooperative length scales in polyisocyanates. First, there is a thermal domain size L_{th}, which gives the characteristic distance between helix reversals that are excited by thermal fluctuations. This length scale depends on temper-

Received for publication 18 February 1997 and in final form 8 May 1997.
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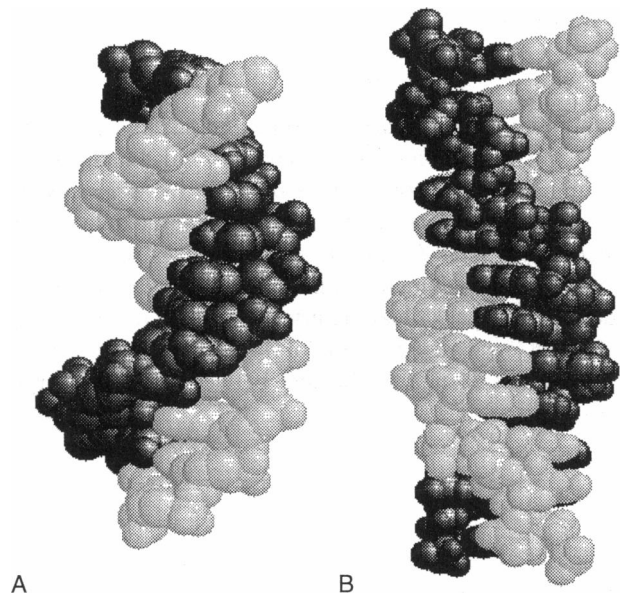

FIGURE 1 (*A*) Molecular structure of B-DNA (Drew et al., 1981, Brookhaven Protein Data Bank 1BNA). (*B*) Molecular structure of Z-DNA (Wang et al., 1981, Brookhaven Protein Data Bank 2ZNA). Both structures are visualized using RASMOL.

ature; it is ~800 monomers at room temperature. Second, there is a random-field domain size L_{rf}, which gives the characteristic distance between helix reversals that are induced by the competing chiral fields of right- and left-handed pendant groups. This length scale is ~100 monomers, independent of temperature. Using these characteristic length scales, the theory predicts the optical activity of polyisocyanates as a function of composition.

In this paper, we apply the same theoretical approach to the transition between B-DNA and Z-DNA. Our theory shows that DNA has the two cooperative length scales L_{th} and L_{rf}. In a DNA homopolymer with a simple repeating unit like . . . CGCGCG. . . , Z-DNA segments have the characteristic length L_{th}. By contrast, in a DNA heteropolymer with a random sequence of nucleotides, Z-DNA segments have the characteristic length L_{rf}. Both of these length scales can be estimated from the known energetic parameters for the B-Z transition: the thermal domain size is $L_{th} \approx$ 4000 nucleotides at room temperature, while the random-field domain size is only $L_{rf} \approx 25$ nucleotides. The length scale of 25 nucleotides is a characteristic length that should describe the typical size of Z-DNA segments in generic random sequences, and we would expect the same length scale to occur in biological sequences. The transcriptionally induced Z-DNA segments that have been found experimentally are all of this length scale. This consistency between theory and experiment suggests that our approach, based on the random-field Ising model, can indeed predict the extent of cooperative chiral order in DNA.

The plan of this paper is as follows. In the first section we review the theory of cooperative chiral order in random heteropolymers, based on the random-field Ising model. In the second section we show how this theory can be applied to the B-Z transition in DNA and predict the relevant length scales. Finally, in the third section, we compare these theoretical predictions with experiments on DNA and propose new experiments that can further test the theory.

THEORY OF COOPERATIVE CHIRAL ORDER

In this paper, we use a theory of cooperative chiral order in random heteropolymers that was originally developed for polyisocyanates. Polyisocyanates have the molecular structure shown in Fig. 2. The polymer has a single carbon—nitrogen backbone with a pendant group attached to each monomer. The backbone itself is achiral, while the pendant groups can be either chiral or achiral. Because of steric constraints, the polymer must form a helical conformation, which can be either right- or left-handed. If the pendant groups are achiral, the right- and left-handed helices have the same energy. A long polymer then consists of segments of right- and left-handed helicity, separated by occasional helix reversals. However, if the pendant groups are chiral, there is an energetic preference for one sense of helicity. This energetic preference leads to a difference in the proportions of right- and left-handed helices, which can be measured experimentally by measuring the optical activity of a dilute polymer solution.

In recent experiments, Green et al. (1995a, b) synthesized copolymers with a random sequence of right- and left-handed enantiomeric pendant groups, with concentrations p and $1 - p$, respectively. They measured the optical activity as a function of p. The results, shown in Fig. 2, have a surprisingly sharp dependence on p. A slight difference in the concentrations of the enantiomers has a very large effect on the optical activity of the system: a 56/44 mixture of enantiomers has almost the same optical activity as a pure

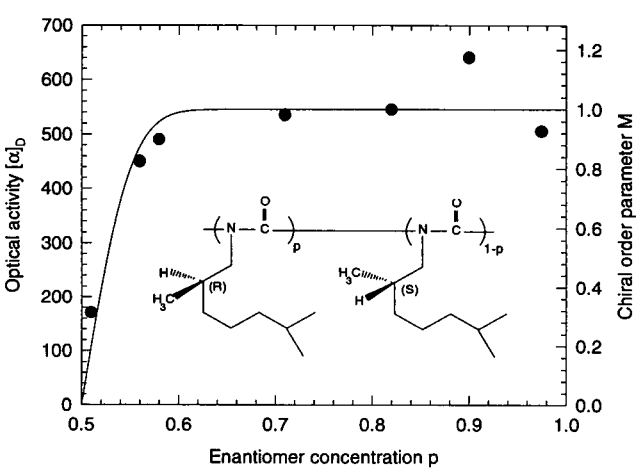

FIGURE 2 Cooperative chiral order in polyisocyanates. The symbols show the optical activity $[\alpha]_D$ at the sodium D line as a function of enantiomer concentration p (from Green et al., 1995a). The solid line shows the theoretical prediction for the chiral order parameter M (from Selinger and Selinger, 1996). The inset shows the molecular structure.

chiral homopolymer, and even a 51/49 mixture has about a third of that optical activity. This sharp response to a slight enantiomeric excess is the signature of a high degree of cooperativity along these polymers.

To explain these results, Selinger and Selinger (1996, 1997) developed a theory of cooperative chiral order in random heteropolymers. This theory maps the polymer onto the random-field Ising model, a standard model in the theory of random magnetic systems. In this mapping, the Ising spin σ_i corresponds to the local sense of the polymer helix at monomer i: $\sigma_i = +1$ represents a right-handed helix and $\sigma_i = -1$ a left-handed helix. The Hamiltonian for a polymer of length N can then be written as

$$H = -J \sum_{i=1}^{N-1} \sigma_i \sigma_{i+1} - \sum_{i=1}^{N} h_i \sigma_i. \quad (1)$$

The first term in the Hamiltonian gives the energy cost of a helix reversal. The parameter $2J \approx 4$ kcal/mol is known from fits of the optical activity of homopolymers as a function of temperature (Lifson et al., 1989). The second term in the Hamiltonian gives the local chiral bias, an effective field favoring one sense of the helix. If monomer i is right-handed (with probability p) then its chiral bias is $h_i = +h$, and if the monomer is left-handed (with probability $1 - p$) then $h_i = -h$. The field h_i is a quenched random variable; it is fixed by the polymerization of each chain and does not change in response to changes in σ_i. The parameter $2h \approx 0.4$ kcal/mol is known from molecular modeling (Lifson et al., 1992). The magnetization of the Ising model,

$$M = \left\langle \frac{1}{N} \sum_{i=1}^{N} \sigma_i \right\rangle, \quad (2)$$

corresponds to the chiral order parameter that is measured by the optical activity. To predict the optical activity as a function of enantiomer concentration, the theory must calculate M as a function of p.

To predict the chiral order parameter M, the theory uses the following approximate argument. Each polymer consists of segments of fixed helicity, separated by helix reversals. The theory assumes that these segments, or domains, have a characteristic length L. This characteristic length is determined by 1) the distance L_{th} between helix reversals that are induced by thermal fluctuations, 2) the distance L_{rf} between helix reversals that are induced by the random field h_i, and 3) the chain length N. Because each of these effects contributes to the density $1/L$ of domain boundaries, they combine to give

$$\frac{1}{L} \approx \frac{1}{L_{th}} + \frac{1}{L_{rf}} + \frac{1}{N}. \quad (3)$$

The thermal domain size is determined by the Boltzmann distribution of helix reversals, which gives the average value

$$L_{th} = e^{2J/k_B T}. \quad (4)$$

At room temperature $k_B T \approx 0.6$ kcal/mol, this length scale is $L_{th} \approx 800$ monomers. The random-field domain size is determined by the competition between the helix reversal energy, which favors large L_{rf}, and the chiral field energy, which favors small L_{rf}. For $p \approx 1/2$, the helix reversal energy is of order J per domain, while the chiral field energy is of order $h_{rms} L^{1/2}$ per domain (Imry and Ma, 1975). Here, h_{rms} is the root-mean-square value of h_i. Because $h_i = \pm h$, h_{rms} is just h itself. Hence, the balance between the two energies gives

$$L_{rf} \approx \left(\frac{J}{h_{rms}} \right)^2. \quad (5)$$

The known values of J and h imply that $L_{rf} \approx 100$ monomers. Finally, the chain length is $N \approx 350$-5800. Because L_{rf} is much less than L_{th} and N, the domain size L is limited by random-field effects. The chiral order parameter M can then be determined by integrating over the distribution of the total chiral field acting on a domain of size L. The result is

$$M \approx \mathrm{erf}\left[(2L)^{1/2} \left(p - \frac{1}{2} \right) \right]. \quad (6)$$

Although these predictions for L and M involve certain approximations, they have been confirmed by numerical simulations of the random-field Ising model (Selinger and Selinger, 1996, 1997).

The predictions of this theory are quite consistent with the experimental data of Green et al. (1995a). As shown in Fig. 2, the prediction for the chiral order parameter M agrees very well with the data for the optical activity. In particular, M saturates at a composition of 56/44, in agreement with the data. This saturation point is a direct measurement of $(2L)^{-1/2}$. Thus, the theory can predict the length scale of cooperative chiral order in polyisocyanates.

APPLICATION TO THE B-Z TRANSITION

In the previous section we outlined a theory of cooperative chiral order in random heteropolymers, based on the random-field Ising model. Many years ago a related theory, also based on the random-field Ising model, was applied to the helix-coil transition in DNA (Vedenov and Dykhne, 1969; Vedenov et al., 1972). Here, we apply the theory of the previous section to a different problem in DNA research: the transition between right-handed B-DNA and left-handed Z-DNA.

The basis of our theory of the B-Z transition is an analogy between DNA and polyisocyanates. The sense of the polymer helix in polyisocyanates corresponds to the B or Z conformation of DNA. The local conformation at nucleotide i can be described by the Ising spin variable σ_i, with $\sigma_i = +1$ representing B and $\sigma_i = -1$ representing Z. A helix

reversal in polyisocyanates then corresponds to a reversal between B and Z along a DNA polymer. The energy cost of such a helix reversal can be represented by the Ising parameter $2J$. The quenched sequence of right- and left-handed monomers in polyisocyanates corresponds to the quenched sequence of nucleotides in DNA. In polyisocyanates the quenched sequence of monomers is represented by the random field $h_i = \pm h$, with $h_i > 0$ for right-handed monomers and $h_i < 0$ for left-handed monomers. Similarly, in DNA the quenched sequence of nucleotides can be represented by a random field h_i, which gives the energetic preference of the local nucleotides for the B or Z conformation: $h_i > 0$ represents a preference for B and $h_i < 0$ a preference for Z.

The random field h_i is not necessarily associated with a *single* nucleotide at site i. Instead, because the alternation of purines and pyrimidines generally favors the Z conformation, it is more useful to consider the *dinucleotide*, i.e., the local sequence of two nucleotides along the DNA polymer, as the fundamental unit of the B or Z conformation (Ho et al., 1986; Schroth et al., 1992). Thus, $h_i > 0$ for typical dinucleotides, which favor B, while $h_i < 0$ for CG and most other alternating purines and pyrimidines, which favor Z.

We can make two remarks about the random-field h_i in DNA. First, in contrast to polyisocyanates, there is no mirror symmetry between the B and Z conformations of DNA. Hence, there is no symmetry between the positive h_i of dinucleotides that favor B and the negative h_i of dinucleotides that favor Z; they do not necessarily have the same magnitude. Second, the values of h_i depend on solution conditions such as salt concentration and temperature, and on the superhelical stress applied to a DNA polymer. Applying a superhelical stress, for example, adds a negative constant to all the h_i. Thus, changing the solution conditions or applying a superhelical stress can shift the average value of h_i from positive to negative. This shift drives the transition from B to Z.

The energetic parameters J and h_i are known, under conditions that approximate physiological conditions, from biochemical experiments that put short test sequences into closed circular plasmids under known superhelical stress (Peck and Wang, 1983; Frank-Kamenetskii and Vologodskii, 1984; Vologodskii and Frank-Kamenetskii, 1984; Ellison et al., 1985; Mirkin et al., 1987). The helix reversal energy is $2J \approx 5$ kcal/mol (per reversal). It is interesting that this energy is only slightly higher than the corresponding energy in polyisocyanates. The random field $2h_i$ depends on the local dinucleotide at site i; it ranges from 0.33 to 3.6 kcal/mol (per nucleotide). This value is substantially greater than the corresponding value in polyisocyanates. We can use $2h_{rms} = 1$ kcal/mol (per nucleotide) as an estimate of the root-mean-square value to characterize the variation in the chiral bias in a random sequence of nucleotides.

From the known energetic parameters, we can estimate the two length scales associated with chiral order in DNA. At the B-Z transition, any DNA homopolymer or random sequence has segments of each conformation. If the DNA is a homopolymer, with a single repeating unit, the characteristic segment length is the distance L_{th} between helix reversals that are induced by thermal fluctuations. From Eq. 4, this length scale is

$$L_{th} \approx \begin{cases} 4000 \text{ nucleotides at } T = 25°\text{C}. \\ 2600 \text{ nucleotides at } T = 45°\text{C}. \end{cases} \quad (7)$$

This length scale is large, and it is quite sensitive to temperature. By contrast, if the DNA is a random sequence, the characteristic segment length is the distance L_{rf} between helix reversals that are induced by the random field. From Eq. 5, this length scale is

$$L_{rf} \approx 25 \text{ nucleotides}. \quad (8)$$

This length scale is much smaller than L_{th}, and it is independent of temperature. Thus, in random sequences, the length scale of chiral order is dominated by quenched randomness in the sequence, rather than by thermal randomness.

Equations 7 and 8 predict the characteristic length of segments of each helical conformation at the B-Z transition. Away from that transition, the DNA polymer is dominated by one helical conformation, but it can still have segments of the other conformation. In other words, there can be segments of Z-DNA in polymers that are predominantly B-DNA, and vice versa. Equations 7 and 8 give an estimate of the length scale of segments of the minority conformation. In particular, Eq. 8 predicts that random sequences of B-DNA will contain segments of Z-DNA that are ~25 nucleotides long. This prediction should apply to generic random sequences, including biological sequences.

DISCUSSION

Our theoretical predictions for the length scales L_{th} and L_{rf} can be tested experimentally in two ways. First, one can pass through the B-Z transition by changing the salt concentration or the temperature, while measuring the circular dichroism (CD) at a wavelength that is sensitive to the B or Z conformation. For example, one can use a wavelength where the CD signal is negative for B-DNA and positive for Z-DNA. The CD signal as a function of salt concentration or temperature should then follow the curve shown schematically in Fig. 3. In the limit of low salt concentration or temperature, almost all the DNA is in the B conformation, and the CD signal is saturated at a negative value. In the opposite limit, almost all the DNA is in the Z conformation, and the CD signal is saturated at a positive value. Between those limits, the CD signal crosses over from negative to positive values as the fraction of Z-DNA goes from 0 to 1. The precise relationship between the CD signal and the fraction of Z-DNA may be quite complex, but the CD signal can at least show when the DNA is almost all B, almost all Z, or in a crossover regime. This experiment can be repeated for DNA homopolymers, such as ... CGCGCG... , of various lengths N. It can also be repeated for random

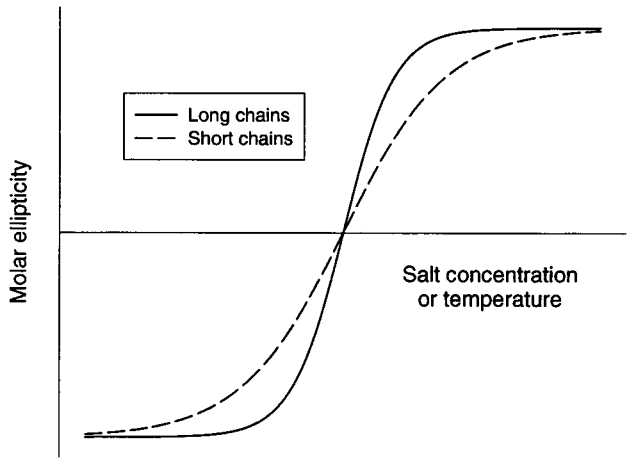

FIGURE 3 Schematic plot of the circular dichroism of DNA, at a wavelength sensitive to the B or Z conformation, measured while passing through the B-Z transition as a function of salt concentration or temperature. The width of the crossover regime will depend on the chain length N if N is less than the thermal domain size $L_{th} \approx 4000$ (for homopolymers) or the random-field domain size $L_{rf} \approx 25$ (for random sequences).

sequences—either synthetic random sequences with known statistics or biological sequences—of various lengths N.

The important quantity to determine in this experiment is the width of the crossover regime. This width gives an indirect measurement of the size of the cooperative domains of B-DNA and Z-DNA at the transition: a sharper crossover indicates larger domains and a broader crossover indicates smaller domains. Our theory makes several predictions for the width of this crossover regime. First, in the limit of long chains, homopolymers will have a sharper crossover and random sequences will have a much broader crossover, because homopolymers have the large domain size L_{th} while random sequences have the much smaller domain size L_{rf}. Second, the crossover width for long homopolymers will depend on temperature, because L_{th} is quite sensitive to temperature. By contrast, the crossover width for random sequences will not depend on temperature, because L_{rf} is limited by quenched randomness rather than thermal randomness. Most importantly, for shorter chains, the crossover width will depend on chain length N only for N less than L_{th} and L_{rf}. The crossover width will become narrower as N increases, until N grows to $L_{th} \approx 4000$ (for homopolymers) or $L_{rf} \approx 25$ (for random sequences), at which point the crossover width will saturate at a constant value. Thus, by measuring the crossover width as a function of N, with N in the range of 1000–10,000 (for homopolymers) or 10–100 (for random sequences) one can obtain a quantitative measurement of the domain size. This domain size can be compared directly with our theoretical predictions of Eq. 7 (for homopolymers) or Eq. 8 (for random sequences).

A preliminary version of this experiment has already been done for homopolymers (Szu and Charney, 1985). The length dependence of the crossover width is consistent with our theory. Further experiments will require more monodisperse chain lengths to give a more precise test of the theory. One can then gradually introduce randomness by constructing sequences of dinucleotides drawn from biased distributions. For example, one can make a random sequence that has 90% CG dinucleotides and 10% AT dinucleotides. That type of sequence should show a B-Z transition as a function of salt concentration or temperature. Even if a random sequence drawn from a uniform distribution of dinucleotides does not show a B-Z transition, this biased random sequence can be used to test our theoretical prediction for L_{rf}. Such a biased sequence might also be useful for technological applications of DNA, as discussed briefly below.

A second type of experimental test of our theory is to search for segments of Z-DNA in biological sequences, such as the human genome. As mentioned in the Introduction, software has been developed that scans through known DNA sequences and identifies segments that are likely to form Z-DNA (Ho et al., 1986; Schroth et al., 1992). These segments consist mainly of alternating purines and pyrimidines, because this alternation favors the formation of Z-DNA. However, these segments do not have *perfect* alternation of purines and pyrimidines; they can include some defects in the alternation. Z-DNA segments can extend over these defects to avoid the energy cost of extra helix reversals. Our theoretical result $L_{rf} \approx 25$ predicts the characteristic size of Z-DNA segments. Of course, the size of any particular Z-DNA segment depends on the specific sequence of nucleotides. However, the characteristic size $L_{rf} \approx 25$ *does not* depend on the details of the sequence. It *does* depend on the energy scales for a helix reversal and for the random field. If, for example, the helix reversal energy were 10 kcal/mol instead of 5 kcal/mol, then Z-DNA segments would extend over more defects in the purine-pyrimidine alternation in order to avoid helix reversals. For that reason, the characteristic size L_{rf} would be four times larger.

Recent experiments have searched for Z-DNA segments in regions suggested by the software in the human c-*myc* gene (Wölfl et al., 1995) and the human β-globin gene cluster (Müller et al., 1996). These experiments indeed found several segments of Z-DNA under conditions of superhelical stress induced by the transcription process. The first experiment found three Z-DNA segments of lengths 20–25, 35, and 20 nucleotides. The second found five Z-DNA segments with lengths ranging from 16 to 52 nucleotides. All of these segment lengths are of the order predicted by our theory. This consistency suggests that the theory can predict the length scale of cooperative chiral order in random sequences of DNA.

We can make two speculations about how our theoretical results can be used in future research. First, it has been suggested that the formation of Z-DNA segments plays a role in the DNA transcription process (Liu and Wang, 1987; Schroth et al., 1992). In this scenario, Z-DNA segments indicate where to begin transcription of a gene. If this scenario is correct, we would expect the transcription process to be particularly sensitive to Z-DNA segments ~25 nucleotides long, because that is the typical length in a disordered sequence. Second, it has also been suggested that

the material properties of DNA can be exploited in technological applications outside of biology. For example, Seeman et al. (1994) have proposed using DNA as a material for the construction of complex nanostructures, and using the B-Z transition to achieve mechanical motion within these nanostructures. Our theory predicts the typical spacing between helix reversals, which should be an important parameter for the design of such nanostructures. Both of these suggestions can be investigated in future research.

In conclusion, we have presented a theory for cooperative chiral order in the transition between the B and Z conformations of DNA. This theory, based on the random-field Ising model, predicts characteristic length scales for cooperative chiral order in DNA homopolymers and random sequences. These predictions are consistent with current experimental data, and they can be tested further by CD experiments on random sequences.

The authors thank M. Frank-Kamenetskii, A. Rich, and D. Voet for helpful discussions.

This work was supported by the Office of Naval Research.

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