Evidence for a new Z-type left-handed DNA helix: properties of Z(WC)-DNA

Allen T.Ansevin* and Amy H.Wang
Genetics Center, Graduate School of Biomedical Sciences, University of Texas Health Science Center, Houston, TX 77225, USA

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ABSTRACT

The structure of Z-DNA, currently accepted as a model for all left-handed DNAs, fails to provide convincing explanations for at least four well established properties of left-handed DNA polymers in solution. However, the major discrepancies between theory and experiment are resolved by the structure presently proposed for Z[WC]-DNA, a new left-handed, zig-zag double helix with Watson-Crick-type backbone directions. Structural features of Z[WC]-DNA include the presence of an additional H-bond between each guanine N2-amino group and an adjacent phosphate oxygen, the capacity to form four-stranded, base-matched complexes that should readily precipitate from solution, and backbone progressions that are the same as B-DNA (opposite to Z-DNA). However, since Z[WC]-DNA and Z-DNA have many parameters in common, they could be difficult to distinguish in a majority of existing experiments.

In view of the close relationship of the new helix to B-DNA, which allows a relatively unhindered right-to-left transition in handedness, Z[WC]-DNA is theorized to be the left-handed structure preferentially generated *in vivo* by the torque available in naturally occurring DNA supercoils.

INTRODUCTION

Background

The presence of even a small region of left-handed DNA within a strand of genomic nucleic acid creates a local structure that departs dramatically from that of the vast remainder of B-DNA. This unusual feature has been regarded as significant because presumptive left-handed sequences are often found in the control regions of both prokaryotic and eukaryotic DNAs (see reviews in refs. 1–7). Furthermore, it is known that the winding of such sequences can be modulated in response to the superhelical tension within the double helix (8–14), a parameter that, in turn, is regulated by specific cellular mechanisms (15–17).

Up to now, details of the structure of naturally-occurring, left-handed DNA have been assumed to conform to the cannonical helix of Z-DNA, first identified by Wang et al. (18) in crystals of the DNA oligomer $(dC\text{-}dG)_3$, and subsequently observed, with relatively minor variations, in crystals of other oligomers (19–27). However, a critical examination of experiments on left-handed polymeric DNA in solution discloses that a majority of the physical measurements bear on only two particular characteristics of the DNA structure: (a) the handedness of the helix, and (b) the dinucleotide repeat that generates an alternation of glycosidic angles, sugar puckers, and phosphate group environments. As it happens, most of the measurements presumed to substantiate the existence of a Z-type helix in polymeric DNA do not provide direct evidence about many of the subtle features of the structure nor about one of the more radical aspects of the Z-DNA model, namely, the reversed direction of the 5′-to-3′-OH progression in the backbone chains, relative to B-DNA (18).

At the same time, if more demanding standards are applied, a number of disagreements are revealed between observations and the theoretical expectations provided by the Z-DNA model. Specifically, the Z-DNA model: (1) fails to provide a clear understanding of why a purine-pyrimidine repeat with the sequence $(dA\text{-}dT)_n$ does not yield a left-handed helix under the conditions for Z-DNA formation while $(dA\text{-}dC)_n$ does (3–5, 28–31); or why $(dC\text{-}dG)_5$ readily forms a left-handed helix but $(dC\text{-}dG)_2\text{-}dT\text{-}dA\text{-}(dC\text{-}dG)_2$ does not (32); (2) it cannot explain why the hydrogen exchange displayed by amino groups in G:C base pairs is an order of magnitude slower in a left-handed helix than in a right-handed helix of the same sequence (33–35), (3) it fails to account for additional changes in the product of the B-to-Z transition or to supply insight into the molecular nature of the eventual, precipitated Z* state [reviewed by Jovin et al., (4)]; and (4) it fails to explain how the reversible B--Z transition could be facilitated when the transition path is blocked by bulky adducts situated in the major groove of B-DNA (see reviews: 3,4,28).

Alternative Left-Handed Helices

We have regarded this collection of apparent discrepancies as sufficient reason to examine whether or not a left-handed helix different from Z-DNA might be generated in solutions of polymers with an alternating purine-pyrimidine sequence or in susceptible genomic supercoils. This question, it should be noted, does not imply that there is an error in the structural solutions

* To whom correspondence should be addressed

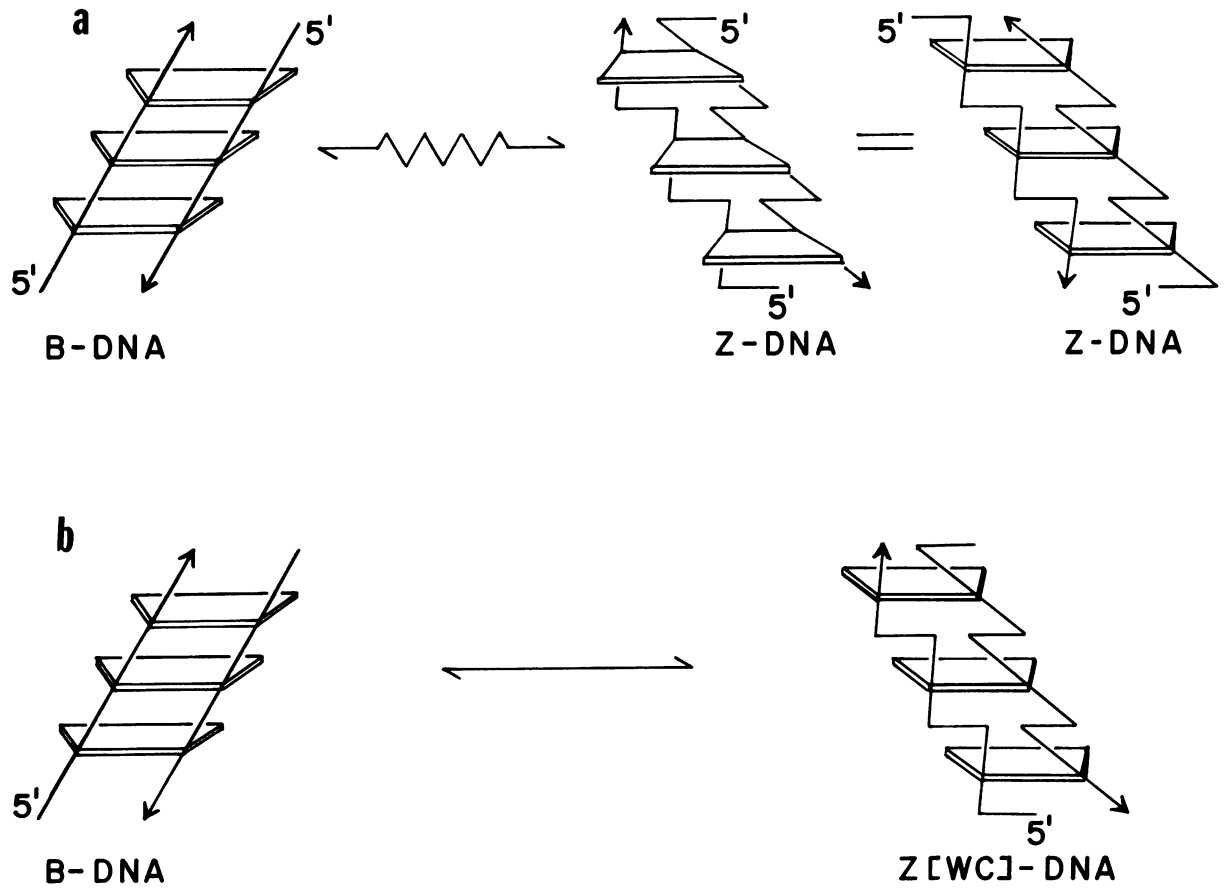

Fig. 1. a. Diagrammatic representation of reversible right–left transition between B-DNA and Z-DNA; right-handed B-DNA is shown on the left as viewed from the minor groove side with planes of base pairs (angular plates) projecting away from the observer; full arrow heads designate the 5′-to-3′OH progression of standard Watson-Crick backbone chains in B-DNA on the left, but counter-Watson-Crick directions in Z-DNA on the right. Steric hindrance during the transition to Z-DNA is indicated by the irregular portion of the transition arrow; the identity of the two structures on the right of the equilibrium is indicated by an equal sign, showing that a rotation of the base pair plane on the glycosidic bond is equivalent to a reversal of chain directions. DNA arrows on the right represent the zig-zag course of backbone chains in left-handed DNAs (planes for every other base pair have been deleted for simplicity). **b.** Diagram for the simpler right–left transition between B-DNA and Z[WC]-DNA; lack of steric hindrance from substituents located in the major groove of B-DNA is indicated by a straight transition arrow.

achieved for related DNA oligomers in the solid state.

Actually, quite a variety of left-handed helices have previously been suggested on the basis of limited experimental data or on purely theoretical grounds (36–42). However, none of these structures appears to agree with observations on left-handed DNAs better than does the Z-DNA model.

Consequently, we have concluded that serious and irremediable problems remain in assuming that any currently recognized structure serves as a fully adequate model for polymeric or naturally-occurring left-handed DNA.

The Steric Dilemma of the B--Z Transition

In our analysis, the most problematic feature of the Z-model is its reversed chain directions relative to B-DNA. However, the seriousness of the steric dilemma created by this geometry in the case of substituted bases has previously received scant attention. We suggest that a satisfactory resolution is crucial to the understanding of genomic left-handed segments, particularly in view of the expectation that local steric limitations should be compounded by the extreme length and relative crowding of biological molecules. As illustrated in Fig. 1a, the difficulty arises in the transition from B-DNA to Z-DNA because the Z-DNA model requires that the direction of the sugar-phosphate progression in the backbone chains be reversed. As pointed out earlier (18) this reversal, in practice, is the consequence of an apparent rotation of each base pair around its own 'horizontal' axis such that base pair edges originally adjacent to the major groove of B-DNA end up contacting the minor groove (the sole groove of Z-DNA).

A variety of speculations have been offered to illustrate how this base pair rotation and equivalent chain reversal might be accomplished. According to an initial suggestion of Wang et al. (18), the three hydrogen bonds of a G:C base pair in a poly(dG-dC):poly(dG-dC) sequence were considered to denature simultaneously, allowing a cytosine base with its attached sugar to rotate within one backbone while the guanine base of the other strand rotated on its glycosidic bond; this was presumed to be followed by further rearrangement and a final reannealing of the severed hydrogen bonds. These rotations, of course, would necessitate a prior, energy-requiring, local unstacking of base pairs. Finally, it was assumed that this sequence of events could be repeated unidirectionally along the length of a DNA polymer. This possibility, in which H-bonds between paired bases would be locally broken and reformed, has been probed by a number

of investigators, each time with negative findings (43–47). An alternative, full denaturation path can be envisioned for *oligomers*, only[1].

Several investigators, apparently concerned with the improbability of this denaturation-renaturation path, have suggested conceivable steps by which a B-helix might be converted into a Z-helix without severing the H-bonds of each G:C pair (43,47–49). Unfortunately, all of these hypothesized paths suffer from a common problem: namely, a tortuous and highly restricted course for accomplishing a 180° rotation of the base pair around an imaginary axis passing approximately through the two glycosidic bonds linking the bases to the backbones.

Because the steric tolerances for the rotation of a G:C base pair are already very close at critical intermediate steps, it is difficult to see how a significant increase in the width of the base pair could be accomodated in following any of the non-denaturing transition paths. Thus, a major anomaly lies in the finding that a series of substitutions at the C-5 position of cytosine not only fails to hinder the conversion, but apparently aids it, with the facilitation increasing as the size of the added substituent is made larger (reviewed by Jovin et al. 4,28).

A still more severe problem for the B--Z transition is encountered when 2-(acetylamino)fluorene (AAF) reacts with B-DNA at the C-8 position of guanine (50). The adducts formed are unusual in displaying physical effects that depend on the DNA sequence. The reaction of AAF with *random-sequence* DNA is found to induce interstrand crosslinking, helix denaturation, and helix bending at incorporation sites, and the fluorene ring structure is presumed to stack within the helix (51). In distinction, when the AAF-group is added to double-stranded poly(dG-dC) or to the corresponding 5-methylcytosine polymer, the AAF attaches covalently to C-8 of guanine without intercalation and does *not* denature the helix (52–54).

The 2-(acetylamino)fluorene group constitutes a giant appendage, with a volume approaching 500 Å^3. Remarkably, the AAF adduct on poly(dG-dC) facilitates, or even forces (at higher substitution ratios), the conversion of the B-helix to a left-handed helix (52–54). Our modeling with an alternating dG-dC sequence places the AAF group on the surface of the major groove of B-DNA and indicates that the acetyl group should project about 1.9 Å in one direction while the triple ring of the fluorene residue extends in the opposite direction about 7.8 Å, or well beyond the level of the preceding base pair. The physical effect of this arrangement can best be described as that of an anchor preventing any rotation of the guanine base to which it is attached. We have been unable to envision an acceptable path by which DNA substituted with the very bulky AAF group could be restructured to convert the Watson-Crick chain directions of B-DNA into the counter-Watson-Crick directions of Z-DNA without breaking covalent bonds or extensively denaturing the helix[2]. Because the conversion *is* readily achieved, we infer that the prevaling assumption about either the transition or the helix structure of *polymeric* left-handed DNA must be seriously in error.

Constant Chain Directions as a Solution

A simple answer to the steric dilemma above is found if the transition actually occurring in polymers proceeds as illustrated in Fig. 1b from B-DNA to a left-handed, Z-like helix that retains conventional Watson-Crick backbone directions (55). We shall call such a helix, Z[WC]-DNA, to indicate that the helix has a zig-zag backbone and chains that possess the standard orientation designated by Watson and Crick for B-DNA. In this connection, we have been particularly attracted by the earlier observation of Hopkins (56–58) that the right-left transition of a double helix is quite facile when no change occurs in the direction of the backbone progressions.

CHARACTERIZATION OF A NEW STRUCTURE

Structure Generation

A structural solution for the hypothetical Z[WC] helix was found to be possible. It was elaborated under the following constraints: the helix, (a) had to be left-handed, (b) have 12 base pairs per turn, (c) have a pitch of approximately 44 Å , (d) possess a dinucleotide repeat, and (e) have Watson-Crick chain directions. In the process of developing a new structure, a variety of modeling procedures were employed, including both physical and computer-based models. The CHEM-X molecular modeling program (Chemical Design, Ltd., Oxford, England; Apr. 1987) was found especially helpful for generating a base-paired unit from a simple dinucleotide sequence and extending this along the Z-axis to make a longer helix. The AMBER molecular modeling program [(59) Version 3.0 (60)] was employed to achieve an energy minimized structure over the repeating segment of a double-helix; this constrained minimization specifically included all hydrogen atoms. The resulting structure contained no improper bond lengths or unacceptable bond angles. A computer-resident model of ZII-DNA was assembled by base-pairing the dinucleotide unit given by Wang et al. (27) and repeating this larger unit along the z axis. An initial announcement of this structure was presented earlier (61) and full coordinates for a helix of 16 base pairs have been deposited with the Brookhaven Data Bank (62).

Structural Features of Z[WC]-DNA

The most significant observation about the Z[WC]-helix generated by the above procedure is that its structure provides straightforward solutions to each of the four major criticisms faced by the Z-DNA model (see Discussion). At the same time, the Z[WRC]-helix is remarkably similar in appearance to the Z-helix, as shown in Fig. 2 by stereo drawings of the two structures. Even though the chain directions of Z[WC]-DNA are opposite to those of Z-DNA, the new helix has an analogous zig-zag backbone. For both DNAs, a reorganization of the major groove of the B-DNA precurser has created a comparatively flat, 'major' face in the left-handed helix; this surface is accented in both by a single groove deeply indented between the two sugar-phosphate

[1] An alternative path might be suggested in double-stranded oligomers, especially at elevated temperatures; in this case, the extreme breadth of the melting transition for short DNA molecules might allow occasional, spontaneous, complete strand separation of a B-helical form followed by renaturation into a Z-helix. However, such an explanation is precluded for long polymers because of the high temperature and sharpness of their denaturation transitions.

[2] Although a 'facilitation' of the transition in some of the substituted polymers might be aided by a shift in the equilibirum, such as has been demonstrated for C-5 methyl derivatives by Behe and Felsenfeld (76), the B-to-Z kinetic path should be totally blocked for an AAF derivative. Thus, any ambiguity of interpretation concerning rate vs. equilibrium in the C-5 series is eliminated in this more extreme instance of steric hindrance at C-8 in guanine.

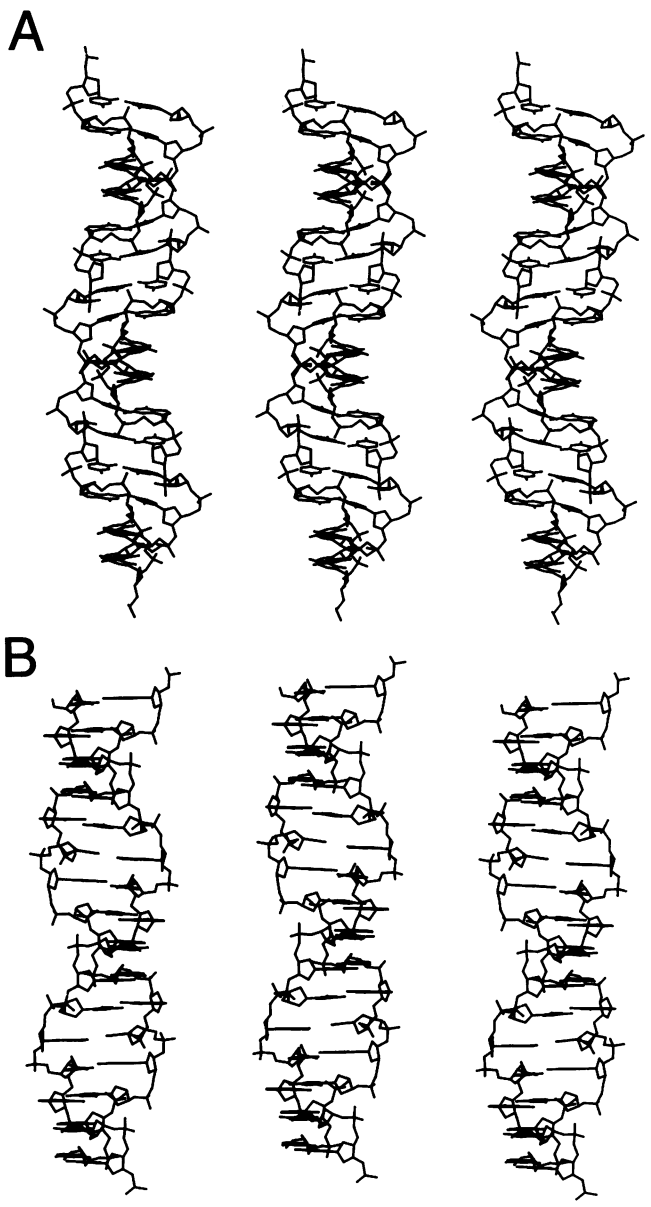

Fig. 2. Stereo 'Triptich'* (77) comparisons of two left-handed DNA models: (A) Z[WC]-DNA, (B) ZII-DNA of Wang et al. (27). In both models, a portion of the major face can be seen near the center of the 16-base pair helix while segments of the spiraling, single groove are exhibited at the bottom and the top. Chain directions may be distinguished by means of the dangling 3'- phosphate groups in each model; thus, it can be seen that the 5'-to-3' progression rises on the right side of the narrow groove in Z[WC]-DNA, but on the left side in ZII-DNA.

* Note: correct helical winding is registered only when observing the right two images of these triptich patterns by means of a stereo viewer, or the left two images by convergent (crossed eye) viewing; alternatively, the opposite side of the helix may be observed, but with incorrect winding, by reversing the viewing procedure; angular displacement of adjacent images is 5°.

backbones. Although the Z[WC]-type structure was elaborated with a dG-dC repeat, it can, in principle, be formed by double-stranded DNA sequences containing alternations of guanine with thymine or a randomly selected pyrimidine base.

Important parameters of the new Z[WC]-helix are compared to those of ZII-DNA, the left-handed model derived by Arnott et al. from fiber pattern data (36), and to right-handed B-DNA

Table I. Helix parameters

Parameter*	Z[WC]	ZII	B	Zf
Base Pairs per Turn	12	12	10	12
Pitch Height	44.6	44.6	34.0	43.5
Mean Rise per Base Pair	3.72	3.72	3.40	3.63
Helix Diameter (2×radius to outer P)	18.2	16.0	18.4	19.0
Rotation per Dinucleotide Unit	−60	−60	+72	−60
Phosphorous Radius: Inner	5.7	6.1	9.2	8.5
Outer	9.1	8.0	9.2	9.5
Mean Base Inclination **	15.0	2.3	8.1	5
Glycosidic Bond Orientation:				
Guanine	syn	syn	anti	syn
Cytosine	anti	anti	anti	anti
Aprox. Sugar Pucker:				
Guanine	C2'endo	C3'endo#	C2'endo	–
Cytosine	C3'endo	C2'endo#	C2'endo	–
P-P Distance Across Minor Groove:				
GpC to GpC (max width)	13.3	18.1		–
CpG to CpG (min width)	5.7	8.6		–
GpC to CpG (width)			11.8	

* Distances in Angstroms and angles in degrees.
ZII: Values derived from the idealized ZII-DNA coordinates of Wang et al. (27).
B: B-DNA values derived from revised fiber coordinates of S. Arnott and R. Chandrasekaran (private communication, 1987).
Zf: Fiber diffraction model of left handed DNA by Arnott et al. (36).
**: Inclination: angle (unsigned) between helix axis and best plane to ring atoms of base (calculated by CHEM-X for B-,Z-, and Z[WC]- DNAs).
#: Sugar pucker descriptions of Wang et al. (27) are quoted here, although others have suggested that alternative designations would be more precise (22).

in Table I. Full details were not published for the model of Arnott et al., but it obviously contains the characteristic zig-zag repeat of Z-DNA and has usually been assumed to belong to the Z-DNA family. Similarities among the three zig-zag helices of Table I may be observed in the syn conformation of guanine glycosidic bonds (in distinction to the all-anti conformations of B-DNA), the approximately 44 Å rise in one turn of the helix, and the six sets of the fundamental dinucleotide repeat per turn. It is also apparent that Z[WC]-DNA and ZII-DNA each posess a comparable alternation of sugar puckers along the backbones (between C2'endo and C3'endo domains), have approximately the same inner and outer radii of phosphorous atoms, and display a small but significant variation of phosphorous-phosphorous distances within the same strand (about 0.45 Å). Considering the many similarities in parameters for the Z[WC]-helix and the Z-family helices, we conclude that it would be extremely difficult to distinguish which helix type might actually be present in most experiments on left-handed DNA.

Distinctions Between Z[WC]-DNA and Z-DNA

Despite the close similarity in appearance between Z[WC]-DNA and Z-DNA, there are three major structural differences. First, the guanine-N2 amino group of Z[WC]-DNA forms an additional, strong hydrogen bond to a negatively charged oxygen of the 5'-adjacent phosphate group, thus reinforcing the left-handed helix. The unusually short length of this H-bond in the Z[WC] model (1.68 Å : N to O distance of 2.70 Å) is consistent with the type of strong interaction expected between an amino hydrogen and a charged oxygen atom (59,63). Second, the base stacking patterns are different. As shown in Fig. 3, the overlap between the bases of the Z[WC] primary stack is considerably greater than that of the corresponding stack in Z-DNA.

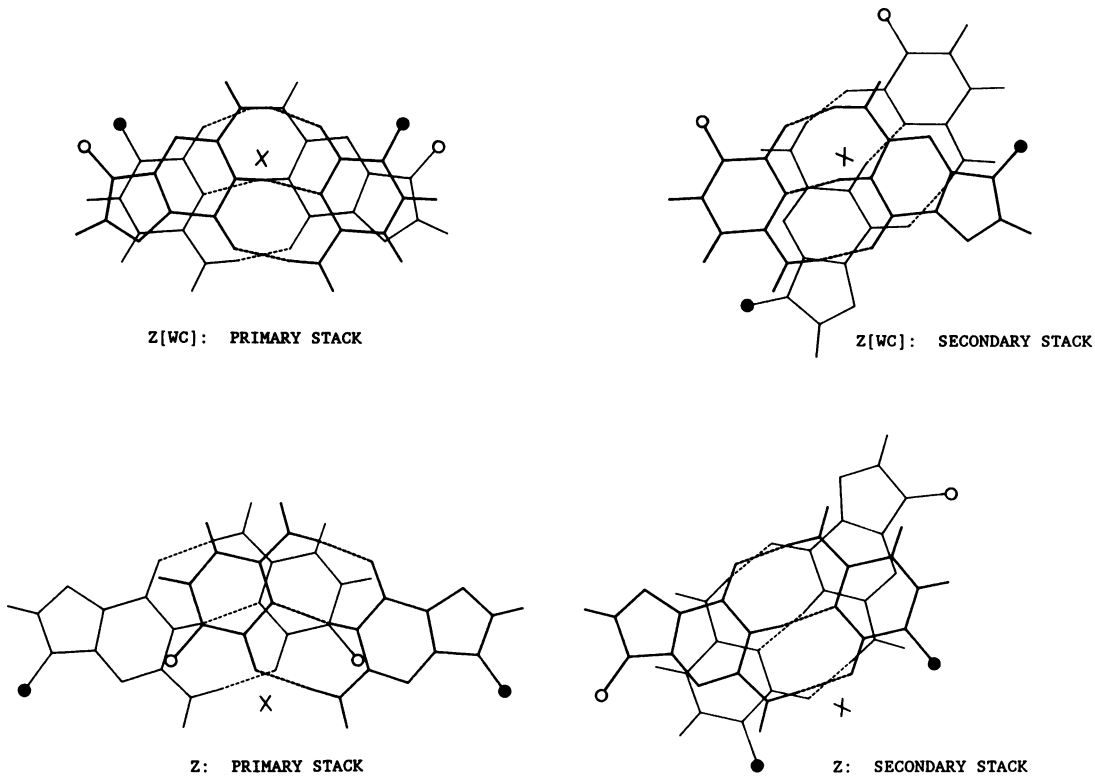

Fig. 3. Projection of three successive base pairs on a plane perpendicular to the helix axis, illustrating primary and secondary base stacking patterns. Z[WC]-DNA: primary stack = GpC; secondary stack = CpG. ZII-DNA: primary stack = CpG; secondary stack = GpC. Open circles: C 1′ atoms of 5′OH sugars; closed circles: C 1′ atoms of 3′OH sugars; - - -: hydrogen bonds; X: position of the helix axis. Heavy lines denote base pairs closest to viewer.

Third, and most fundamental, is the distinction in backbone chain directions. As illustrated in Fig. 1b, Z[WC]-DNA is related to B-DNA in having Watson-Crick-type backbone directions (55), while Z-DNA exhibits counter-Watson-Crick directions. Several differences of lesser significance will be discussed elsewhere.

DISCUSSION

New Solutions to Problems Befalling the Z-Model

As pointed out above, an examination of existing experimental data on polymeric left-handed DNA discloses that the Z-DNA helix suffers from at least four major defects as a model for the structural properties of left-handed polymers in solution. In distinction, the left-handed helix of Z[WC]-DNA is able to supply obvious structural explanations for each of these discrepancies.

To begin with, the Z[WC]-DNA model satisfies the first two criticisms reviewed in the Introduction (i.e., preference for G over A and slow hydrogen exchange) with the single structural feature of an additional hydrogen bond formed between guanine and oxygen in the solitary ('narrow') groove. This new H-bond is positioned so that it specifically reinforces the left-handed winding. Moreover, because this H-bond is made to a phosphate oxygen that carries a negative charge, it is both shorter and much stronger than a usual hydrogen bond (63). Its presence immediately makes clear why a left-handed helix with this structure should be more stable when it contains only guanine as the purine and why poly(dA-dT) does not form a left-handed helix under comparable conditions (64). The strength and position of this fourth H-bond of guanine also readily explains why one amino group per G:C base pair displays unusually slow hydrogen exchange only in left-handed helices (33–35). According to recent evidence quantitating the effect of A:T substitutions for G:C pairs in a sequence with left-handeded propensity, it appears that the stabilizing effect from guanine is sufficient to support a left-handed helix even when the purines on just one of the strands are guanine; thus, poly(dG-dT):poly(dA-dC) is observed to be stable in left-handed form. However, two successive adenine-containing base pairs, as in base-paired DNA with the sequence --dC-dG-dT-dA-dC-dG--, destabilize the formation of a potential left-handed segment (32,65).

We believe this explanation for guanine preference is quantitatively more realistic than existing suggestions that the formation of an unbroken 'spine of hydration' associated with guanine, but not adenine bases, in a left-handed helix provides essential stabilization for the Z-helix (3,23,25). For instance, it is apparent that a *complete* spine of hydration is not needed for left-handedness since the systematic alternation of G with A along the helix in $(dG\text{-}dT)_n$:$(dA\text{-}dC)_n$ does not block a left-handed helix. Furthermore, DNA in solution cannot be expected to duplicate the regularity of water molecules observed in crystals (23,25); indeed, the creation of ordered solvent in solution is entropically disfavored (66,67).

Nor does a purely theoretical approach to the expected first order hydration associated with Z-DNA geometry appear to explain guanine preference. Although a comprehensive consideration of hydration is clearly beyond the scope of this article, a first approximation to the energetics of hydration appears instructive. In this instance, hydration changes during the formation of a left-handed helix are restricted to the examination of only the most firmly bound water molecules. The requirements

can be further simplified by assuming that the critical difference between a Z-helix and a Z[WC]-helix lies in the distinction between a 'water bridge' formed between a phosphate oxygen and a guanine amino group in Z-DNA vs. a direct hydrogen bond made between the same two groups in Z[WC]-DNA. We are not aware of any indication that the free energy of H-bond formation between a water oxygen and an amino hydrogen in an open aqueous environment could be much greater than about −1 kcal. For instance, Fersht et al. (63) have found that the free energy contributed to complex formation by a hydrogen bond between uncharged donors and acceptors lay in a range between −0.5 and −1.5 kcal. Furthermore, they concluded that H-bond formation in aqueous solutions ordinarily is nearly isoenthalpic so that such associations are driven almost entirely by the entropy gained through the release of *two* water molecules; i.e., a water molecule initially hydrating the donor and another, the acceptor. In the present example of Z-DNA, only one water molecule gains entropy (by release from the guanine amino) when a water bridge is formed. Consequently, the free energy expected for H-bond formation in creating such a water bridge should be reduced to a level near or below thermal energy[3]. This conclusion is consistent with the discussion of Sundarlingam and Sekharudu (68), who inferred that a water bridge is formed as a temporary intermediate in the closely analogous case of the folding of a protein. Of course, such an intermediate in proteins is fleeting, and is driven further by a spontaneous elimination of the bridging water in regions with good potential for alpha helix formation. In the Z[WC]-helix (but not the Z-helix), the backbones are in a position to allow the two initially hydrated partners to come together to form a direct H-bond; here, the bond is expected to be considerably stronger than that stabilizing alpha helices (63). In conclusion, although a water bridge could easily exist in a nucleic acid crystal, it seems unlikely that it would contribute significantly to the maintenance of the macromolecular structure in solution.

It can be noted, incidentally, that the closer approach of phosphates in the geometry of thw Z[WC]-helix would be highly favored by the presence of divalent or multivalent cations, a solution parameter long recognized to aid left-handed DNA formation (3,4).

The third criticism listed for the Z-model is the failure to explain additional transitions that lead to the precipitaiton of an uncharacterized product from more concentrated solutions. According to the new model, this puzzling behavior can be attributed to a four-stranded complex formed between two Z[WC]-DNA strands with slightly modified helix parameters (Ansevin and Wang, in preparation). These complexes are Watson-Crick counterparts of the four-stranded structures described earlier by Hopkins (69). Thus, the generation of a precipitate in solutions of left-handed polymers on standing is interpreted as the consequence of a random interweaving of double helices between nodes of four-stranded interaction maintained by specific base pairing.

The fourth criticism of the Z-model simply does not apply to the Z[WC]-helix, by virtue of the condition initially imposed that the helix should have the same chain directions as B-DNA. Transitions to the new Z[WC]-helix remain unhindered for all mono-functional substitutions in the major groove of B-DNA. Indeed, a substituent such as AAF could be expected to *aid* the formation of left-handed DNA by virtue of its zig-zag distorting effect on a regular, right-handed helix (70), in agreement with experimental observations (52−54).

Significance of a New Helix

Since many of the differences between Z- and Z[WC]-DNA may appear small, it is appropriate to ask what significance should be attached to the new structure. First, Z[WC]-DNA appears to be a better candidate than Z-DNA for the left-handed DNA occurring in nature because it is much more consistent with experimental results. Second, in molecular terms, the difference in chain directions is substantial and assumes special importance because it affects the structural variability that is available to left-handed helices. For instance, it presently appears that the Z[WC]-type geometry described here represents the most constrained helix within a family of related, left-handed structures, some of which are expected to favor hydrogen-bonded associations within a four-stranded macro-helix. Comparable higher order associations are not predicted for the Z-family. In view of the possibility for sequence-specific matching in a Z[WC]-DNA complex, this type of self-association appears consistent with earlier suggestions that alternating purine-pyrimidine sequences could be sites of frequent genetic recombination (71−73). Furthermore, previous speculation has suggested that the aggregated Z* form might play a role in chromosome structure, condensation, or pairing (28).

A correct structure is important for understanding not only the above DNA-DNA interactions, but also specific protein-DNA associations of left-handed DNAs (3,28,74,75). An accurate description of the surface features of DNA, as well as anticipated modulations of its surface contours, is essential for analyzing the details of left-handed nucleoprotein complexes. In this context, we note that the Z[WC]-helix differs from the Z-helix in having better-defined hydrophobic patches and phosphate groups that are more closely spaced across the groove, two features that should favor specificity in protein-DNA interactions.

CONCLUSION

In this communication, we suggest that the helix of biological, left-handed DNA may be more closely related to B-DNA than is the Z-DNA helix. In fact, it appears that existing inconsistencies between theory and experiment are all satisfied by the backbone structure associated with the new Z[WC]-model. Although short purine-pyrimidine oligomers may well be more stable in a Z-type geometry under the equilibrium conditions that occur during crystal formation, we assume that dynamic factors should have great practical importance in the formation of left-handed segments within long molecules in solution.

We see special significance in Hopkins' earlier observation (56) about the ease with which a right-to-left transition can be accomplished if the DNA backbone directions remain unchanged. This is a finding that we have repeated with Z[WC]-DNA and B-DNA space-filling models, noting particularly that the switch to left-handedness is driven cooperatively by the type of torque present in an underwound superhelix. We suggest that in nature, where transitions of B-DNA to an alternate helical form are induced by negative superhelicity, the kinetic accessiblity of the new Z[WC]-DNA helix should strongly favor this structure as the left-handed DNA of genetic systems *in vivo*.

[3] It may be that a summation of small thermodynamic terms becomes effective in the solid state and thereby provides an explanation for differences in crystallization rates as a function of sequence (25); however, we presume that the additional degrees of freedom available to dissolved molecules render such solvent contributions noncooperative in solution and insignificant relative to thermal energies.

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