Minireview

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Intrinsically Bent DNA

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Intrinsically bent or curved DNA molecules result when special base sequences or structural motifs are repeated in phase with the DNA helical repeat (≈10.5 bp[1]/turn). This places the recurrent elements along the same side of the double helix so that small bends associated with them add constructively to generate a large global curvature. Many base sequences can impart systematic curvature to DNA, but most such bends are small compared with the special effect produced by runs of homopolymeric dA·dT base pairs ("A-tracts"), each tract about half a helical turn long and repeated at 10–11-bp intervals.

Bent DNA was discovered by the laboratories of Englund and Crothers (1) during study of a minicircle DNA from the kinetoplast body of *Leishmania tarentolae*, in which appropriately phased A-tracts occur prominently (1, 2). The anomalous gel mobilities shown by bent DNA molecules have provided crucial experimental insight into the origin and nature of DNA bending. Application of early theories describing gel mobilities for molecules undergoing reptational migration (3, 4) leads one to expect slower motion for bent molecules because they have a shortened end-to-end distance. This criterion has proved to be a reliable guide to experimental properties, even though it ignores significant theoretical issues (5).

A critical experiment for diagnosing the presence and location of DNA bends has been comparison of the electrophoretic properties of circularly permuted DNA molecules, all of the same length but each having the bend at a different position. In the first application of this concept, Wu and Crothers (6) were able to identify a locus containing phased dA·dT tracts which provided the primary source of bending in *Leishmania* kinetoplast minicircle DNA. Since that time, phased dA·dT tracts have been identified in various gene regulatory regions (7–10), but the biological function of intrinsically bent DNA remains uncertain.

Theoretical Models for DNA Bending

Initial formulation of models for DNA bending was prompted by recognition that DNA must be bent for packaging into nucleosomes (11–13). Zhurkin *et al.* (14) concluded on the basis of conformational energy calculations that bending in nucleosomes should occur by roll every 5 bp, alternately toward both major and minor grooves, in preference to tilting toward one of the strands; this is now the generally accepted view for protein-induced DNA curvature. Trifonov and Sussman (15) developed the idea of a "wedge" contributed by independent dinucleotide steps in DNA and presented evidence for periodic repetition of particular dinucleotides (including AA) as facilitators of bending and hence nucleosome formation in eukaryotic DNA sequences. Both the Zhurkin *et al.* and Trifonov and Sussman models emphasize smooth deformation of DNA by a series of small independent roll or tilt components between adjacent base pair planes; we categorize these generally as "wedge models."

The model-building studies of Arnott, Wells, and collaborators (16) focused on an abrupt change in the DNA helix axis direction at the junction of A- and B-DNA helices. Because the base pairs in the two forms have different angular orientations relative to their respective helix axes, parallel stacking of the base pairs at the junction causes the two helix axes to be non-parallel. The locus at which the axes meet is called a "junction bend" in the model for curvature resulting from A-tracts (6, 17).

It should be emphasized that the wedge and junction models are not necessarily incompatible. For example, strong inclination[2] of the base pairs in an A-form DNA helix is necessarily accompanied by appreciable roll between them; consequently, curvature induced by placing a short A-form structure between two B-DNA helices can be viewed as arising either from the two junction bends or from the series of (roll) wedges between adjacent base pairs in the A-form segment. In the first case, one views the A-DNA segment as a whole, with a straight overall helix axis whose direction differs from that of the adjacent B-DNA segments. In the second case, the emphasis is on a local axis (defined as perpendicular to the base pair plane), which is deflected in a series of steps.

It is our view that the wedge model is the more general one, since any curving helix can be described by combining helical rotation with an appropriate series of wedge angles. However, the more restrictive and hence informative junction model is to be preferred where it actually applies. Specifically, the junction model is appropriate when evidence exists for a distinctive helical structure formed by the base sequence in question and when there are cooperative effects in nucleating this special structure within a segment of B-DNA; both of these tests are met for DNA bends that occur at dA·dT tracts. Cooperative induction of the special structure weakens the applicability of the wedge model because the dinucleotide-based wedge angles derived for B-DNA cannot be relied on to predict the properties of the altered structure and hence of the bend in a longer tract.

Models for the structure of poly(dA)·poly(dT) based on fiber diffraction (18, 19) share the common feature of negative roll between adjacent base pairs, which yields base pairs with negative inclination relative to the overall helix axis. In 1986, Koo *et al.* (21) pointed out that application of this characteristic predicts a bend oriented toward the minor groove at the center, or toward the 3′-strands at the ends, of the dA·dT tract (Fig. 1); both the direction and approximate magnitude of the bend as subsequently observed have been in general agreement with the model. However, uncertainty remains because crystallographic structures of oligonucleotides con-

[1] The abbreviation used is: bp, base pair(s).

[2] We use the definitions for base pair geometry prescribed by the EMBO workshop on DNA Curvature and Bending (20). Briefly, the terms *inclination* and *tip* describe the angular orientation of a base pair relative to a defined helix axis. *Inclination* reflects rotation of a base pair about its pseudodyad or short axis; the positive sign indicates a motion in which the ends of the long axis move in the 3′-direction along each strand. *Tip* results from rotation about the longer axis which is (roughly) perpendicular to both the pseudodyad and the (local) helix axis. The terms *roll* and *tilt* describe orientations between two adjacent base pairs; *roll* refers to rotations that compress the major (positive roll) or minor (negative roll) grooves, and *tilt* describes rotations which compress the long axes of the two base pairs together at one end. a uniform right-handed helix in which the base pairs show positive *inclination* and no *tip* will as a direct geometric consequence also have positive *roll* (and little or no *tilt*, depending on precise definitions) between adjacent base pairs; negative inclination also implies negative roll and vice versa.

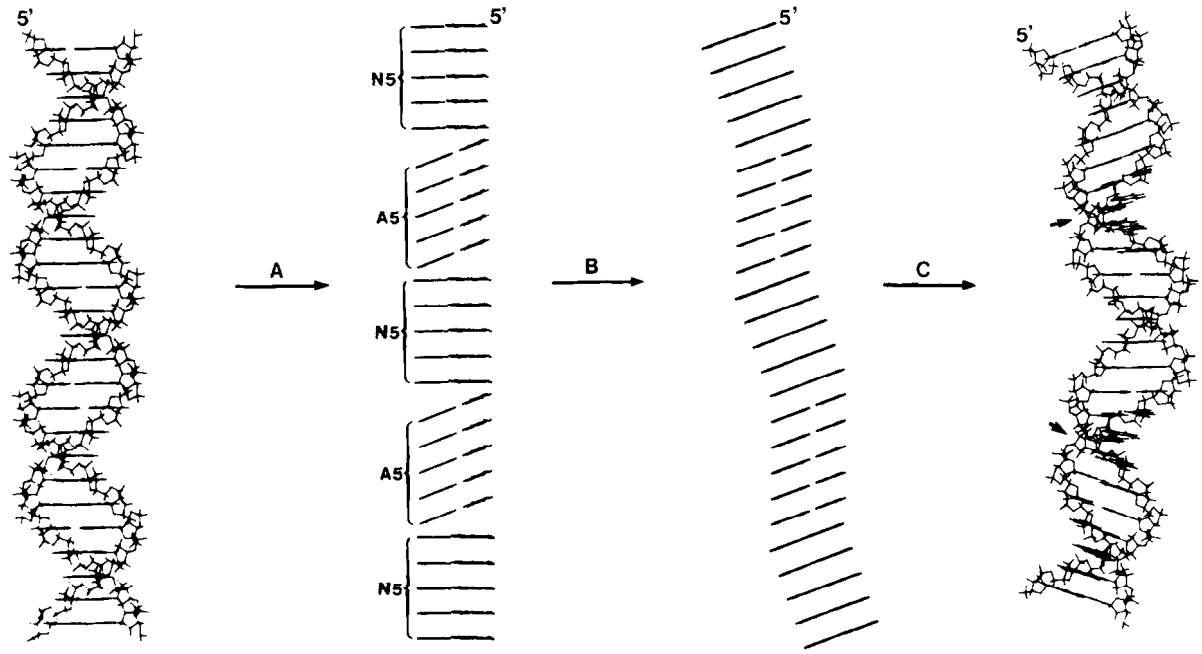

FIG. 1. **Schematic illustration of the A-tract induced bending of a DNA segment of sequence $N_5A_5N_5A_5N_5$.** In Step *A*, the B-form double helix on the left was unwound, its sugar-phosphate backbone removed (for purposes of clarity), and the base pairs within the A-tracts tilted or inclined relative to the helix axis in the direction characteristic of poly(dA)·poly(dT). (As drawn, the central figures represent views into the minor groove along the pseudo-dyad axis of each base pair. Had the backbones been shown, they would run lengthwise outside the base pairs, forming a ladder-like structure). In Step *B*, local helix axes reorient to facilitate base stacking at the junctions between the structurally dissimilar A5 and N5 regions; thus small bends in the helix axis arise from the inclination of the A·T pairs in combination with the requirement for favorable base stacking at the junctions. When these small local bends are positioned in phase with the helix repeat, large global curvature results. This can be seen in Step *C* where (i) the backbone was replaced, (ii) 36 ° twists were applied about the local helix axes between each set of adjacent base pairs, and (iii) the entire double helix was repositioned to put the overall bend in the plane of the page. Note that the direction of curvature produced by Steps *A–C* is geometrically equivalent to compression of the minor grooves at the centers of the A-tracts (shown by the *two small arrows*); this is in accord with the bend direction deduced from comparative electrophoretic mobility studies (21, 36, 37). In the figure on the *extreme right*, the bend magnitude is 20 ° per A-tract (10 °/junction), close to the value of 18 °/A-tract derived from the experiment (41); in the central two schematic figures, however, the bend magnitudes are twice those values for visual emphasis.

taining A tracts do not show the marked base pair inclination inferred from studies of the homopolymer. All workers would agree that DNA bending requires a *difference* in base step roll or tilt angles (or equivalently in base pair inclination or tip) between the A-tract and the intervening segments of B-DNA. It remains possible that DNA containing A-tracts is bent because of positive roll in the B-DNA segments, with zero roll in the A-tract regions. We do not favor this extreme view, partly because crystallographic structures of B-DNA do not provide support for the needed average base pair inclination (about 9 °, see below) relative to the overall helix axis.

Descriptive terminology has been controversial in this field because some workers, particularly Trifonov (22), have sought to restrict the use of the term "bent" DNA to cases in which a force, such as that due to protein binding, acts on the DNA; the term "curved" is recommended for the intrinsically bent form. We cannot accept this restriction, since a junction bend is discontinuous and cannot legitimately be called a curve. Instead, we prefer linguistic flexibility and emphasize the approximate interchangeability of "bend" and "curve" in their noun, adjective, and intransitive verb forms: rivers, roads, and DNA molecules bend. We add the terms "intrinsic" and "induced" when necessary to remove any ambiguity.

Extensive DNA Bending Requires Phased A-tracts and Depends on Conditions

The most direct evidence for the presence of a static bend, as opposed to a flexible hinge, at A-tracts comes from studies of ligated oligomers containing repeated $(dA \cdot dT)_{5/k}$tracts at various phasings. When the A-tracts recur at 10- or 11-bp intervals, or nearly in phase with the DNA helix screw, the ligated DNA molecules have anomalous electrophoretic mobilities, but the anomalies are much reduced if the $(dA \cdot dT)_n$ repeat is 9 or 12 (21, 23). In addition, it was found that the mobility is normal if the motif is repeated every 1.5 helical turns (21). The latter observation eliminates the possibility that the A-tract might provide a flexible hinge for bending in a plane, since planar bends without a preferred direction should reinforce equally well when phased by integral or half-integral numbers of helical turns.

Detailed analysis of the sequence requirements for bending, by means of comparative electrophoretic methods (21, 24), showed that an intact A-tract is crucial for the phenomenon. The following general picture emerges. (*a*) There must be at least 4 adjacent adenines in the tract for appreciable bending. (*b*) The maximum effect is observed when there are 6 residues in the tract, repeated with the helical screw. (*c*) Interrupting the sequence with another base, C, G, or T, greatly diminishes the effect; T is the least effective of the three. (*d*) The greatest degree of curvature is observed when the A-tract is flanked by C on the 5′-side and T on the 3′-side, but changes in the flanking nucleotides diminish the effect by less than 10–15% of the total value. (*e*) Substitution of unnatural nucleotides (25–27) reveals that the thymine methyl group is not responsible for the bending effect; of particular note, inosine can effectively replace adenine in the A-tract. Bending remains readily detectable in sequences such as AAIAA and AIAIA (25, 26) but diminishes substantially when further substitutions of I for A are incorporated. From these experiments it can be concluded that absence of the guanine 2-amino group from the minor groove is a critical factor for DNA bending. Finally, methylation can increase bending, as illustrated by the increase in curvature observed when the 6-amino group of the central A in AATT blocks is methylated (27).

The effect of elevated temperature is to reduce DNA bending (1, 28). By 60 °C the anomaly effectively disappears (28), presumably because the special structure of dA·dT tracts reverts to a more canonical B-DNA form. At lower tempera-

tures more complex dependences are observed (21, 28, 29), largely because the increased tendency to anomalous structure at low temperature may be compensated by the effect of temperature on the DNA helical screw (30), which can affect the phase match between A-tracts and the helix repeat.

Ionic conditions have an appreciable but not dramatic effect on apparent DNA curvature. Increasing NaCl concentration decreases the gel migration anomaly (2, 28), whereas the migration anomaly of most, but not all, sequences is increased by adding divalent ions (2, 28, 31–33). As with the case of temperature effects, it is not yet possible to deconvolute these effects fully into influence on actual bending, influences on the DNA helix screw, and possible effects on the calibration function between gel mobility and DNA curvature.

The Direction and Magnitude of Bending

In 1986 Koo *et al.* (21) showed that DNA bend direction is nearly unaffected by interchanging the T and A strands in a $(dA \cdot dT)_6$ tract. Hence the net bend has an approximate dyad axis that runs between the major and minor grooves at the center of the tract, and the bend must therefore be primarily directed toward the major or minor groove at the center. Addition of divalent ions has only a minor effect on bend direction, since the mobility anomalies measured by Diekmann (28) for mixed A and T tracts, compared with pure A tracts, imply only small differences in relative curvature over a wide range of Mg^{2+} concentration.

The remaining ambiguity in A-tract bend direction (*i.e.* major *versus* minor groove compression) was resolved in 1987 by Zinkel and Crothers (34), who measured the curvature direction relative to the bend induced when DNA wraps around CAP protein. They concluded that the A-tract bend direction is equivalent to *minor* groove compression at the center of the A-tract. Viewed from the global perspective of the overall bend, this is geometrically equivalent to (negative) tilt of the helix axis toward the sugar-phosphate backbone at the 3′-end of the A- and T-tracts (Fig. 1). This conclusion is consistent with comparative studies of the direction of the bend induced when the backbone tilts away from an extra or "bulged" base inserted on one strand (35).

Hagerman (36) explored the properties of adjoining $(dA \cdot dT)_n$ tracts and found that oligomers of the form $(A_4T_4N_2)_n$ exhibit extremely anomalous electrophoretic mobility, in sharp contrast to molecules of the form $(T_4A_4N_2)_n$ which show virtually normal mobility. Although these results were unpredicted, both the wedge and the junction models could subsequently be adjusted to account for them (37, 38).

Estimates of the extent of bending produced by phased A-tracts have varied by more than a factor of 2, from about 11 ° (39) to about 28 ° (31). The hydrodynamic experiments of Levene *et al.* (40) gave an estimate of 9 ° for each junction or about 18 ° total. This result is in agreement with the electron microscopic observations of Griffith *et al.* (41) and with recent computer simulation of cyclization kinetic experiments (42). Hence, with a total bend of 18 ° for $(dA \cdot dT)_6$, there must, in any model, be about a 9 ° *difference* in the average base pair inclination between the A-tract and adjacent B-DNA.

Cooperativity in A-tract Structure

The local structure of DNA can in principle be governed either by nearest neighbor effects in which the conformation of each base pair step is independent of that in adjacent steps or by longer range phenomena. Persuasive evidence now exists that as an A-tract is lengthened there is a cooperative switch from B-DNA structure to one more characteristic of poly(dA)·poly(dT). The properties of multimers of the series $T_nA_5N_{5-n}$ (n = 1–4) studied by Haran and Crothers (43) imply cooperative structural effects. Sequences with n = 1–3 migrate slowly in gel electrophoresis, whereas the T_4A_5N multimers migrate almost normally (due to offsetting bends associated with segments T_4 and A_5). Neither the wedge nor the junction model can account for the abrupt change in mobility observed in this series unless one assumes a cooperative structural transition in the T_n segment as n increases from 3 to 4.

NMR spectroscopy provides direct evidence for cooperative changes in helix structure as the length of the A-tract is increased. From measurements of imino proton exchange rates Leroy *et al.* (44) observed that A_n tracts with $n \geq 4$ show anomalously long lifetimes which increase further for n = 5, 6. Nadeau and Crothers (45) examined the NMR properties of a series of molecules containing A-tracts of different lengths (n = 2–9). Thymidine imino protons in short tracts (n = 3) tend to have chemical shifts like those characteristic of B-DNA, as do the imino protons near the 5′-end of an A-tract of any size. The 3′-end of the A-tract has much less tendency to hold the A-tract in the conformation characteristic of B-DNA.

Crystal Structures

Efforts to reveal the molecular details responsible for sequence-directed bending have led to structural determinations of several A-tract-containing duplexes by single crystal x-ray methods (46–49). The propeller twist of the A·T pairs in these structures is so pronounced that the C6 amino group of adenine, in addition to participating in the normal Watson-Crick pairing scheme, may form a second hydrogen bond with the O4 atom of the 3′-neighboring thymine. The resulting network of bifurcated H bonds connecting adjacent base pairs within the A-tract has been suggested (46, 47) as the basis for the apparent stiffness of poly(dA)·poly)dT) (50) and as a medium for the propagation of length-dependent changes in A-tract structure. However, the anomalous electrophoretic migration (25, 26) and long proton exchange rates (44) of inosine-containing A-tracts in solution suggest otherwise; since the number of potential bifurcated hydrogen bonds is reduced in these sequences, their contribution to A-tract structure and bending is dispensable.

Unfortunately, crystallographic structures also leave ambiguity concerning the source and direction of A-tract curvature of unconstrained molecules in solution. Duplexes in the crystalline lattice are bent in a direction roughly perpendicular to the overall curvature deduced from comparative electrophoretic mobility studies (21, 34). Moreover, DiGabriele *et al.* (48) have provided clear evidence that A-tract curvature in the crystal is due primarily to the intermolecular packing constraints of the crystal lattice. Models for DNA bending have nevertheless been proposed based on the assumption that the high propeller twist and straight local helix axis characteristic of crystalline A tracts persist in solution (39, 46, 51).

Solution Studies

Despite the absence of reliable three-dimensional structures of A-tracts in solution, certain revealing features have been established. Short A_n tracts ($n < 7$) lack regions of true poly(dA)·poly(dT)-like conformation and display non-uniform structure characterized in part by a progressive reduction in minor groove width in moving from the 5′- to the 3′-end of the A-strand (45, 52–54). In longer A_n tracts ($n \geq 7$), the minor groove narrows gradually over the first three base steps and then remains fairly constant over the remainder of the tract (45). In contrast, the GC-rich regions flanking the A-tracts feature a wider minor groove typical of canonical B-DNA; thus periodic alternation of A-tracts and GC-rich se-

quences leads to sinusoidal variation in minor groove width as detected by hydroxyl radical cleavage patterns (52). In the crystalline A-tract structures, the large propeller twist of the A·T pairs narrows the minor groove, in apparent qualitative agreement with solution results.

However, groove width is also governed by factors apart from propeller twist including base pair inclination and displacement of the base pairs from the local helix axis. These latter two quantities, both negligible in crystalline A-tracts, are substantial in models for poly(dA)·poly(dT) as derived from fiber diffraction (19), NMR studies (55, 56), and linear dichroism (57). Moreover, in long A_n tracts ($n \geq 7$) flanked by GC-rich segments, key interproton distances are more consistent with poly(dA)·poly(dT) models featuring substantial base pair inclination rather than high propeller twist (45). Thus it appears that A-tract structure in solution differs significantly from that observed in the crystal form.

A Unifying Model

As noted above and illustrated in Fig. 1, the direction and magnitude of bending are quite accurately predicted if one assumes that base pairs within A-tracts are inclined relative to the helix axis much as they are in models of poly(dA)·poly(dT), for which substantial experimental support exists. Energy calculations on poly(dA)·poly(dT) (58) indicate that the stacking energies for A·T pairs in this conformation are suboptimal but also that this seemingly unfavorable arrangement promotes formation of a network of hydration (59, 60) in the minor groove (linking Thy O2 and Ade N3 atoms on opposite strands) that more than compensates for the lost stacking energy. Removal of this water spine by increased temperature or organic solvents should reduce bending (61) by freeing the A·T pairs to adopt a more favorable base-stacking arrangement in which they are perpendicular to the helix axis (58). The hydration network cannot form in GC-rich sequences because the guanosine 2-amino group intrudes into the minor groove. According to the model, cooperativity effects should arise at least in part from the relative instability of the water spine in short (n = 2–3) A-tracts; once the A-tract has reached a length of 4 this nucleation effect is largely overcome. In addition, since minor groove hydration is thought to be disrupted by TpA but not ApT steps, a contiguous array of inclined A·T pairs may run across ApT but not TpA steps. Thus one expects the A_n and T_n tracts in sequences A_nT_n to act in concert as a single cooperative unit, whereas those in sequences T_nA_n should behave independently. NMR (44) and comparative gel mobility (38, 43) studies show this to be true.

We caution that Fig. 1 represents an idealized model for bending, wherein the conformation of all AA/TT base steps is identical and the bends are exclusively in the direction of tilt at the junctions.

All models that seek to explain DNA bending require a difference in base pair inclination between A-tract and B-DNA structures; we attribute the effect primarily to negative base pair inclination in the A-tract, which in turn is probably induced by strong minor groove hydration there. We expect, however, that significant net positive or negative inclination components can exist in the intervening B-DNA segments and that these will be found to cause modulation of DNA curvature in response to sequence alterations in the intervening B segments.

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