

LETTER TO THE EDITOR

Mechanics of Sequence-dependent Stacking of Bases in *B*-DNA

Dickerson and his colleagues have described the structure of the DNA dodecamer C-G-C-G-A-A-T-T-C-G-C-G in the *B* form at a level that shows clearly several aspects of some base sequence-dependent departures from the ideal, regular helical structure of *B*-DNA. I argue that the detailed conformation is a consequence of simple steric repulsive forces between purine bases in consecutive base-pairs but on opposite backbones. These repulsions are a consequence of the “propeller twist” of the base-pairs, together with the larger size of the purine bases, and they may occur in either the major or the minor groove. The argument is conducted in terms of the structural mechanics of a deformable elastic system. These repulsive forces between the base-pairs are resisted by stresses in the helical backbones, which may be studied quantitatively *via* the variation in torsion angles δ along the backbones, at the points where the sugar rings are connected. There is also a correlation between the cross-chain purine repulsions and the perturbations in helical twist angle between successive base-pairs. The work suggests some comments on the proposed “alternating *B*” form, the *Z* form and the *A* form of DNA.

It is now well-known that the helical configuration of *B*-DNA is not absolutely regular and indifferent to base sequence, as in the classical description (Watson & Crick, 1953; Stryer, 1975); instead, the molecule has geometric irregularities and non-uniformities, which somehow reflect the sequence of bases in a given stretch (Wells *et al.*, 1977; Jack, 1979). The most detailed description of the irregular configuration of *B*-DNA has come from Dickerson’s single-crystal X-ray analysis of a particular dodecamer d(CpGpCpGpApApTpTpCpGpCpG) (Drew *et al.*, 1981; Dickerson & Drew, 1981*a,b*; Drew & Dickerson, 1981).

In this letter I argue, in terms of the quantitative mechanics of an elastic system, that the detailed configuration of Dickerson’s dodecamer follows as a consequence of simple steric repulsive forces between purine bases in consecutive base-pairs but on opposite chains. These clashes are due to the larger size of purine bases, coupled with persistent “propeller twist” in the base-pairs, and they may occur in either the major or the minor groove.

It is easy to see that irregularities of base-packing in DNA can be accommodated by the flexibility of the helical sugar–phosphate backbones, since perturbations of the six degrees of freedom of one rigid base with respect to a neighbour up or down the same chain (three translational degrees, and three rotational) can be accommodated by small changes in the six torsion angles along the backbone between consecutive bases, in addition to the torsion angle about the glycosyl bond between the sugar ring and the base (Levitt, 1978). But it is not easy to predict exactly what irregularities of packing will be associated with a given sequence of bases.

It is now known that in *B*-DNA the typical hydrogen-bonded base-pair does not lie in a plane, but is assembled with propeller twist (Levitt, 1978; Hogan *et al.*, 1978; Jack, 1979). Thus, as viewed along the sugar-sugar "virtual bond", the far base is rotated counter-clockwise through an angle of the order of about 15° relative to the near base. Propeller twist is possible because of the directional flexibility of hydrogen bonds, and it is attributable partly to the improved stacking that it imparts to consecutive bases on the same strand. The base-pairs themselves would be more relaxed if there were no propeller twist; and it seems possible that the connection through the sugar ring between a base and its backbone is rather stiff against rotation of the kind that would reduce propeller twist, even though this connection may be relatively flexible in other respects. Anyhow, the propeller twist of base-pairs is a persistent feature of the assembly of *B*-DNA.

Now in both types of base-pair ($A \cdot T$, $G \cdot C$), a relatively large purine base (*A* or *G*) is joined to a relatively small pyrimidine base (*T* or *C*). Thus the hydrogen-bonded gap between the base does not lie midway along the sugar-sugar virtual bond, but somewhat towards the pyrimidine end; and indeed it is so far eccentric that the helix axis in ideal (uniform) *B*-DNA passes through the "space-filling" version of the purine base.

Figure 1(a) shows an axial view of the three guanine bases in a three-base-pair sequence ($C \cdot G \cdot C$), ($G \cdot C \cdot G$) of ideal, uniform *B*-DNA, which is shown schematically in Figure 1(b). In this view, the extremities of G2 overlap those of G4 and G6 in the major and minor grooves, respectively. This overlap would be of no consequence if all of the base-pairs lay in planes parallel to the diagram. However, as pointed out by Dickerson & Drew (1981a), the introduction of propeller twist to the base-pairs creates a problem, since the atoms involved in the overlaps will now come closer to each other. Thus the imposition of a propeller twist of 15° would reduce the

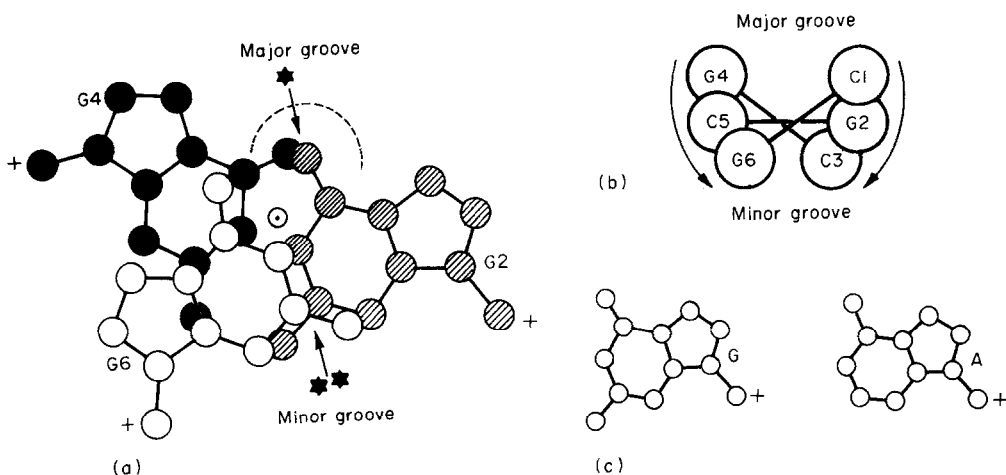


FIG. 1. (a) Axial view of 3 G bases in the ideal trimer shown in (b). Darker colour indicates greater distance from the observer. The C-1' atoms of the sugar ring are marked +, and major and minor-groove clashes are marked *, **, respectively. The van der Waals' radius is marked for 1 atom (Stryer, 1975, Table 6.4). (b) Schematic axial view of the trimer, showing location of all 6 bases. The arrows indicate the $5' \rightarrow 3'$ directions of the backbones, which are not shown. (c) Sketch of G and A bases.

separation of the edges of the bases from about 3.4 Å to about 2.8 Å; and this would constitute a strong steric clash. Figure 1(a) depicts the bases in the skeletal form for the sake of clarity, but the argument really applies to a space-filling model (Drew & Dickerson, 1981). The van der Waals' radius of the oxygen atom of G2 is indicated in Figure 1(a). The diagrams do not show hydrogen atoms, because these do not protrude at the upper and lower surface levels in a space-filling model. Table 3 of Dickerson & Drew (1981a) shows that the centres of the atoms involved in the overlaps do not approach closer than about 3.2 Å.

How can the bases re-adjust their position in order to avoid clashes of this sort? If we exclude the possibility of axial expansion of the gap between base-pairs, we find that four basic manoeuvres are available, as follows.

- (1) The propeller twist could be suppressed.
- (2) The base-pairs could rotate ("roll") as rigid units about their sugar-sugar virtual bonds.
- (3) Each base-pair could translate or *shift* sideways along the sugar-sugar virtual bond towards the purine end of the base-pair.
- (4) Each base-pair could rotate a little about the DNA axis. (For example, the minor-groove clash between G2 and G6 in Fig. 1(a) could be reduced by counter-clockwise and clockwise rotation of base-pairs G2·C5 and C1·G6, respectively, in the view of Fig. 1(b).)

Manoeuvres (1) and (2) involve rotation about the sugar-sugar virtual bond, while (3) and (4) involve motion only in planes normal to the axis.

Dickerson & Drew (1981a) pointed out that an overlap in projection between bases on opposite strands leads to a damping-down of propeller twist (manoeuvre (1)) in the dodecamer. But close examination of the stereoscopic views, diagrams and Tables given by Drew *et al.* (1981) and Dickerson & Drew (1981a,b) indicates that all of manoeuvres (1) to (4) are deployed, to greater or lesser degree, in the avoidance of steric clash. It is easy to see that the relative proportions of manoeuvres (1) to (4) may differ from base to base, since (2) and (4) are capable of relieving a clash for a given base either in the major groove or in the minor groove, but not in both, whereas manoeuvres (1) and (3) are able to relieve both single and double clashes.

The main point of this letter is to show that the incidence of manoeuvres (3) and (4) in the dodecamer may be analysed successfully by simple quantitative calculations within the framework of classical, elastic structural mechanics, and resting on the simple hypothesis that particular kinds of cross-chain purine clash exert specific "pushing apart" forces on the base-pairs. These result in sideways shift (manoeuvre (3)) in consequence of the *sum* of major and minor-groove repulsion, and perturbation of twist between base-pairs (manoeuvre (4)) in proportion to the *difference* between major and minor-groove repulsions.

Manoeuvre (3) is analogous to the way in which the tip of a blunt screwdriver tends to jump backwards out of the slot in the screw head when torque is applied to the screwdriver with insufficient thrust. Manoeuvre (4) is analogous to the way in which a heavy picture, hanging on the wall from a smooth peg, tends to rotate in the plane of the wall if one lower corner is pushed upwards.

(a) *A mechanical analysis*

Sideways shift of the base-pairs is revealed clearly in Figure 3 of Dickerson & Drew (1981*a*: an axial view of the dodecamer) when the mid-points of the sugar-sugar virtual bonds are marked. And indeed it may be associated with the strong *anti-correlation*, pointed out by Drew *et al.* (1981), between the backbone torsion angles δ at either end of the base-pairs: a high value of δ at one end of a base-pair goes with a low value at the other. Now δ is the backbone torsion angle for the links C-4'-C-3' that are common to both the backbone chains and the sugar rings that connect the bases to the backbones (Drew *et al.*, 1981; Dickerson & Drew, 1981*b*). Furthermore, these links are almost parallel to the axis of the helix in *B*-DNA. The essence of the changes in geometry that occur when values of δ change according to the principle of anti-correlation may thus be seen in the plane "ladder" shown in Figure 2. This consists of two reticulated backbones, which have elastic hinges at the points where the treads of the ladder are connected. The shift of a tread parallel to its own length is clearly associated with an increase of δ at one end and a decrease at the other. And indeed we can press this analogy between *B*-DNA and a plane ladder further, by proposing that the difference in δ values at the two ends of a base-pair is a measure of the *bending-moment* in the backbones at the point of attachment of the base-pair, as it would be if changes in torsion angle were resisted by a linear-elastic spring. Elementary analysis of the statical equilibrium of a beam subjected to equally spaced transverse forces of arbitrary magnitude shows that each transverse force is equal to the difference in shearing force in the two adjacent links; and that the shearing force in each link is proportional to the difference between the bending moments at its two ends (e.g. see Heyman, 1964). Thus the force applied at any joint is proportional to the (central) second difference along the chain of the bending moments at the joints. (This analysis does not depend on an assumed rigidity of the ladder components between the hinges; but it does introduce an element of approximation in the application of ordinary beam theory to a helix.)

A calculation along these lines is shown in Table 1. The first three columns label

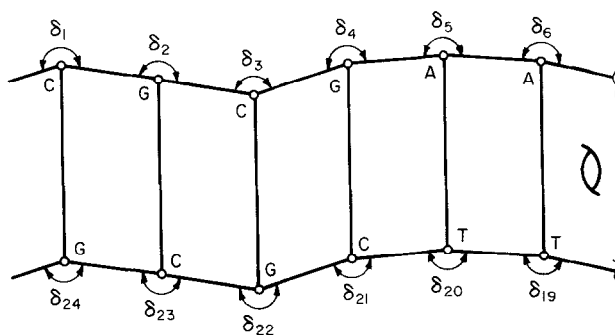


FIG. 2. Sketch of a plane reticulated ladder, which shows how the "principle of anti-correlation" of angles δ relates to the lateral shift of the base-pairs. Angles δ (Table 1, columns 2 and 3) are not to scale, but the *difference* in values of δ at either end of each base-pair (column 4) is correct. The numbering of bases is as shown in Table 1 (columns 8 and 10), and only half of the dodecamer is shown.

TABLE I
Calculations on repulsive forces and twist angles in the dodecamer

(1) Base- pair	(2) δ_{n1}	(3) δ_{n2}	(4) D	(5) ΔD	(6) $\Delta^2 D$	(7) $\Delta^2 D$ (approx.)	(8)	(9)	(10)	(11) Rotation (minor)	(12) Rotation (major)	(13) θ (net rotation)	(14) $\Delta\theta$	(15) \bar{t}_1	(16) Base step
							(3')		(5')						
1	147	95	52	-51			G24	--- C1		2a		2a	-3a	38	1
2	125	124	1	-55	-4	0	C23	--- G2		-2a	a	-a	2a	42	2
3	92	146	-54	80	135	3a	G22	--- C3		2a	-a	a	-3a	33	3
4	146	120	26	-9	-89	-2a	C21	--- G4		-2a		-2a	2a	39	4
5	133	116	17	4	13	0	T20	--- A5				0	a	37	5
6	125	104	21	-42	-46	-a	T19	--- A6			a	a	-2a	32	6
7	104	125	-21	4	46	a	A18	--- T7		-a	-a	-a	a	37	7
8	116	133	-17	-9	-13	0	A17	--- T8				0	2a	39	8
9	120	146	-26	80	89	2a	G16	--- C9		2a		2a	-3a	33	9
10	146	92	54	-55	-135	-3a	C15	--- G10		-2a	a	-a	2a	42	10
11	124	125	-1	-51	4	0	G14	--- C11		2a	-a	a	-3a	38	11
12	95	147	-52				C13	--- G12		-2a		-2a			
							(5')		(3')						

The base-pairing and labelling of bases is shown in columns 8 and 10, and the "diagonal" cross-chain repulsive forces are shown in column 9. The contents of columns 2 to 7, leading to a calculation of repulsive forces, and of columns 11 to 15, leading to a prediction of the variation $\Delta\theta$ in local twist angle, are explained in the text.

the base-pairs and give the corresponding δ values for the two strands: subscripts B1 and B2 refer to backbones 1 (column 10) and 2 (column 8), respectively. (These values of δ have been averaged end-to-end, in order to restore the 2-fold symmetry spoilt by crystal-induced bending: see Dickerson & Drew, 1981*a*.) Column 4 gives D , the difference between the values of δ at the two ends of a base-pair: $D = \delta_{B1} - \delta_{B2}$. $\Delta^2 D$ (column 6) is the second difference of D , calculated in the usual way: columns 5 and 6 give the (forward) first differences of the entries in columns 4 and 5, respectively.

Most of the numbers in column 6 are close to ± 135 , ± 90 or ± 45 , and in column 7 the numbers have been "rounded" and replaced by $\pm 3a$, $\pm 2a$, $\pm a$ and 0, where $a = 45$. This calculation immediately suggests a simple physical scheme, indicated in column 9, in which the forces exerted on the backbones by the base-pairs are assigned values of $2a$ and a units of repulsion between purines clashing in the minor and major grooves, respectively. Thus the repulsion of a units between A6 and A18 exerts forces to the left and right on base-pairs 18·7 and 19·6, respectively, and the quantities in column 7 represent the total forces exerted in this way on the base-pairs: the positive sense corresponds to a force acting towards the left. Minor-groove clashes are indicated by the double lines sloping down from left to right: they correspond directly to the clash between G2 and G6 in Figure 1(a). Major-groove clashes are shown as lines sloping in the opposite sense, and they correspond to the clash G2–G4 in Figure 1(a).

The scheme does not work perfectly at the two ends of the dodecamer; but complicating factors are obviously present in these regions (Drew *et al.*, 1981; Dickerson & Drew, 1981*a*).

According to this calculation, the G–G and A–A clashes in the major grooves are exactly equivalent. This corresponds to the fact that in a space-filling model, G and A are practically equivalent on the major-groove side, since the extra hydrogen atoms in the 6 position of the A do not contribute to the out-of-plane clashes involving the atom N-6. These bases only differ on the minor-groove side, where G has an extra "spur" (see Fig. 1(c)).

Encouraged by this correlation, let us proceed to investigate the changes in the twist angle between base-pairs (manoeuvre (4)) on account of purine clashes. It seems clear that an isolated major-groove clash such as that between A6 and A18 will cause the twist angle in the gap between base-pairs 19·6 and 18·7 to decrease. But beyond this, there seems to be a range of possibilities, lying somewhere between two extremes. *Either* (a) the decrease in twist angle at a base step comes about by means of local distortion of the backbones, with more or less rigid-body rotation of the remaining parts of the dodecamer, and involving in particular no change in the torsion angle in any other base-steps; *or* (b) the decrease in twist angle occurs by means of rotation of the two base-pairs, while all the other base-pairs remain fixed: in this case the backbones remain relatively rigid, and the flexibility comes mainly from the sugar rings, almost as if they were swinging gate-like from the backbone links C-4'–C-3'. This idea is shown schematically in Figure 3: the minor and major-groove repulsions, acting separately, tend to push base G2 upwards and downwards on the diagram, respectively, by virtue of this swing of the sugar ring.

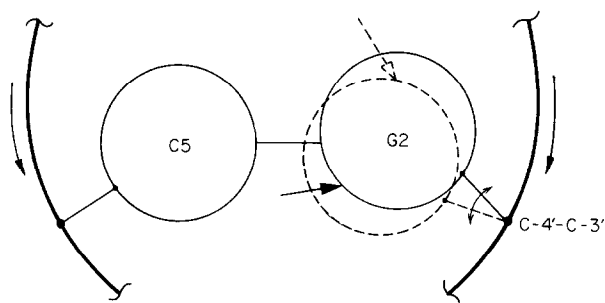


FIG. 3. Schematic view of the base-pair G2·C5 (Fig. 1(b)), showing the attachment of G2 to its more-or-less rigid backbone by a sugar ring, which swings gate-like from the backbone link C-4'-C-3' in response to minor and major-groove repulsive forces, which are also shown schematically. The associated movement of C5 is not shown.

It turns out that scheme (b) fits the observations much better than scheme (a). The appropriate calculations are set out in columns 11 to 14 of Table 1. For the sake of simplicity, it has been assumed that a given repulsive force of x force-units between purine bases in either the major or the minor groove imparts a rotation of $\pm x$ units of rotation to the base-pairs involved. Columns 11 and 12 show the separate rotation contributions from minor and major-groove repulsions, respectively, and these are summed in column 13 to give the net rotation θ . Clockwise rotations as seen from the C1·G24 end of the dodecamer are regarded as positive, and the net rotation of the base-pairs is thus proportional to the difference between the minor and major-groove repulsive forces acting on the purine bases.

Column 14 gives the perturbation $\Delta\theta$ to the twist angles in the base steps, found by taking first differences of the entries in column 13. Finally, the measured twist angles, from Drew *et al.* (1981) and Dickerson & Drew (1981*a*) (and averaged end-to-end) are given in column 15. Figure 4 shows plots of the data in columns 14 and 15, respectively. The shape of the two curves is remarkably similar, particularly if some allowance may be made for extraneous effects at the end of the dodecamer. Roughly, a "rotation units" are equivalent to 1.8° of rotation.

Thus we see that our simple hypothesis, that minor and major-groove clashes between purines in consecutive base-pairs exert repulsive forces of definite magnitude on the respective base-pairs, agrees well with the observed configuration of the dodecamer. The *sum* of these forces acting on a base-pair correlates with the second differences of the cross-chain differences of the backbone torsion angles δ , while the *difference* of these forces relates to the perturbations of rotation of the base-pairs about the DNA axis.

It is possible to discuss manoeuvres (1) and (2) in the dodecamer also in terms of structural mechanics. In contrast to (3) and (4), where there is a rough parity between major and minor-groove effects, it is clear from the available data that there is a fair correlation between flattening of propeller twist ((1)) and minor-groove clashes alone, while the rolling of base-pairs ((2)) correlates reasonably well with clashes in the major groove: see Dickerson & Drew (1981*a,b*). But there is

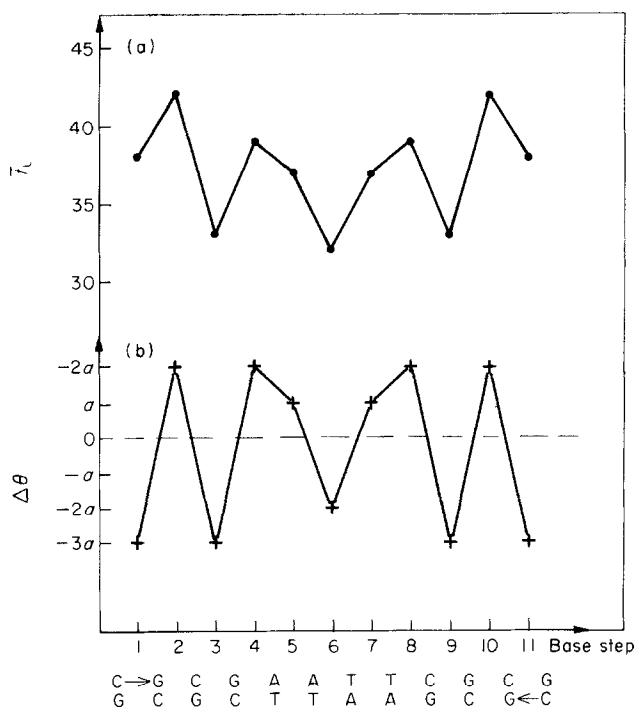


FIG. 4. Plots of (a) the measured local twist angle $\bar{\tau}_i$ and (b) calculated perturbations in twist angle $\Delta\theta$, in arbitrary units, both against base-step number. The arrangement of base-pairs is also indicated.

hardly enough information available to weigh the effects on (1) and (2) of clashes in the minor and major grooves. And indeed, it must be acknowledged that the preceding discussion of manoeuvres (3) and (4) rests on a small sample of data.

Drew *et al.* (1981) and Dickerson & Drew (1981b) attributed the low values of δ for pyrimidines to steric hindrance of the glycosyl torsion angle χ for the pyrimidine bases, together with a close mechanical coupling between χ and δ . In purely *kinematic* (i.e. geometrical) terms, there is no essential difference between their description and mine. The differences lie at the level of the *mechanics* of the problem; that is, in the interpretation of the geometric perturbations of the molecule in terms of forces. I attribute these perturbations primarily to cross-chain repulsive forces between purines, while they attribute them primarily to the steric hindrance noted above. In my scheme, the glycosyl torsion angles χ are determined mainly as a consequence of the cross-chain repulsive effects, and it turns out that potential steric hindrance in these regions is largely avoided. But it remains possible that the steric hindrance of angle χ for pyrimidines acts co-operatively with the cross-chain purine repulsions in predisposing the base-pairs to shift towards the purine ends, and thereby to avoid even stronger cross-chain purine clashes, which might otherwise occur on account of propeller twist.

Klug *et al.* (1979) have proposed a non-classical "alternating *B*" configuration for (A-T)_n, in which perturbations of the ideal form are brought about by the

differential overlap of successive bases along the same chain. In a step A-T of ideal, uniform *B*-DNA there is more overlap between bases A and T than in a step T-A; and Klug *et al.* argued that an enhancement of this difference, by a reduction in the twist angle at steps A-T and an increase at steps T-A, would stabilize the packing. An extension of this argument to purines and pyrimidines in general suggests that steps C-G and G-C will have relatively large and small twist angles, respectively; but, as Dickerson & Drew (1981*a*) note, this is exactly the opposite of what happens at the ends of their dodecamer, even though the central A-T step does fit the "base overlap" hypothesis. The present scheme would predict the sense of the perturbations of twist angles proposed by Klug *et al.* (1979) in a sequence (A-T)_{*n*}, provided the diagonal cross-chain A-A repulsions were stronger in the major groove than in the minor groove. Unfortunately, there are no minor-groove A-A clashes in Dickerson's dodecamer.

Oligomers (C-G-C-G-C-G)₂ and (C-G-C-G)₂ are known to form left-handed, zigzag, *Z*-DNA (Wang *et al.*, 1979; Arnott *et al.*, 1980; Drew *et al.*, 1980). It is clear from Figure 1 that diagonal cross-chain purine repulsions are strongest for (C-G)_{*n*} sequences; and it thus seems possible that they are somehow involved in *B* → *Z* transitions.

In the *A*-form of DNA, base sequence-dependent perturbations of the structure are not found (Shakkeed *et al.*, 1981; Conner *et al.*, 1982); or, if they are present, they are not nearly so strong as in *B*-DNA. The relationship between successive base-pairs is quite different in the *A*-form, mainly on account of the fact that the sugar-sugar virtual bonds lie much further from the axis of the helix (e.g. see Jack, 1979). Consequently, in a diagram like that in Figure 1(a) for *A*-DNA, the hexagonal parts of G2 and G6 would overlap considerably, while G4 would be well-separated from G2. In other words, diagonal cross-chain purine clashes do not occur in *A*-DNA.

Even though this work rests on a small sample of data, it suggests that classical structural mechanics may provide a useful tool for the elucidation of the sequence-dependent kinematical features of *B*-DNA; and hence also the way in which the base-sequence is "read" by intercalating drugs, repressors and other recognition proteins.

It is interesting to note that recently published data on base-step twist angles in the DNA octamer (G-G-C-C-G-G-C-C)₂ (Wang *et al.*, 1982) are predicted very well by the scheme of Table 1, columns 8 to 15, when a value of about 2° is assigned to the constant α . This is somewhat paradoxical, however, since the octamer is almost in an *A*-form, and its base-pairs appear to have relatively little propeller twist.

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Note added in proof: The assumption made by Kabsch *et al.* (Kabsch, W., Sander, C. & Trifonov, E. N. (1982). *Nucl. Acids Res.* **10**, 1097–1104), that the local helical twist angle in a base-step depends only on the composition of the two base-pairs which constitute the step, corresponds closely to scheme (a), described at the bottom of p. 348, and then rejected. According to my analysis (Table 1) the local helical twist angle in a given base-step depends on the composition of the *four* base-pairs closest to the step.

Edited by A. Klug.