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Origin of DNA Helical Structure and Its Sequence Dependence†

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ABSTRACT: Conformational analysis of DNA shows that the origin of the B-form double helix can be attributed in large part to the atomic charge pattern in the base pairs. The charge patterns favor specific helical stacking of the base pairs. Base pairs alone—without backbones—have a strong tendency to form helix, indicating that the backbones play a rather passive role in determining the basic helical structure of DNA. It is mainly the electrostatic interactions determined by the charge pattern on base pairs that stabilize a particular helical conformation. The charge pattern in the base pairs appears to be responsible for much of the sequence dependence of DNA conformation, rather than steric clashes.

Double-helical DNA plays the essential role of storing genetic information in a stable form, and its stability affects the control of gene expression. The classical B-form DNA consists of a right-handed double helix with two polynucleotide strands twisted about each other. The successive base pairs stack on top of each other with a relative rotation near 36°. The double-stranded structure is stabilized by complementary hydrogen bonding, by stacking the flat surfaces of the base pairs, and by exposing the polar edges and phosphates to solvent. Although the structures of DNA have been studied in some detail (Arnott, 1976; Saenger, 1984; Dickerson et al., 1985; Shakked & Kennard, 1985), it is not well understood why DNA is stabilized in a particular helical conformation. Hydrogen bonding between bases leads to double-stranded forms but not to a specific type of helix. Within the major families, B, A, Z, etc., and depending upon the base sequence, DNA exhibits smaller scale local conformational variations (Dickerson et al., 1985; Shakked & Kennard, 1985), from small base pair orientational changes to DNA bending (Koo et al., 1986; Hagerman, 1986). Implications for biological function have recently been a focus of intensive research (Bossi & Smith, 1984; Ryder et al., 1986; Snyder et al., 1986; Zhan & Blattner, 1987). However, the physical reasons for this conformational polymorphism are not clearly understood, partly because interactions in such a macromolecule are very complex. To date, the most popular model of the sequence dependence of B-form variants was proposed by Calladine (1982), who stated that the steric clash between base pairs may be responsible for the conformational variation. In order to identify the important interactions responsible for the stabilization of particular conformations of a complex macromolecule like DNA, it is useful to first consider separate components, base pairs and backbones. In this paper, we analyze the interactions between base pairs to investigate the origin of DNA conformations and its sequence dependence in terms of chemical structure of base pairs and their interactions, and show that the DNA helix and its sequence-dependent variation are a direct consequence of the atomic charge pattern in the base pairs, and their interactions.

Method of Calculation

Our method is a combination of energy calculations and conformational statistics, developed especially for studying DNA conformations (Sarai et al., 1988). By generating large numbers of conformations, we estimate the conformational free energy. This method is particularly suitable for DNA, which exhibits unusually flat energy potentials with many minima, a problem that is not amenable to treatment with usual methods.

Consider the two base pairs shown in Figure 1. The coordinate system we have used to describe their geometry is as follows. The X axis connects atoms C8 and C6 in the base pair and is oriented as shown. The Y axis points along the helix direction from the center of the line between C8 and C6.

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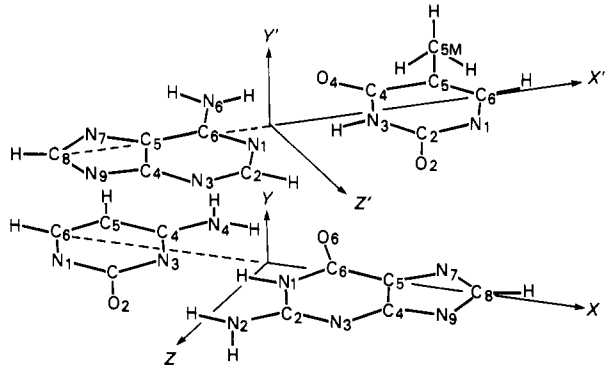

FIGURE 1: Coordinate system of two base pairs. Shown here are the C-G and A-T base pairs in a CA step.

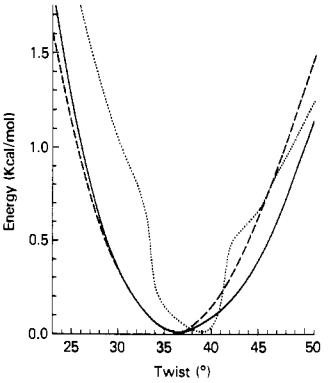

FIGURE 2: Energy dependence on twist angle for the AA (TT) step. The solid line is the free energy; the dashed line is the total energy; the dotted line is the electrostatic component of the total energy. Energies are shifted so that the energy minima are at 0. Calculations are for the quartet AAAA. The reason for a rather bumpy electrostatic curve is that we have averaged the total energy, rather than the electrostatic energy component.

Finally, the Z axis completes the right-handed orthogonal coordinate system, pointing toward the minor groove. If a base pair is considered as a rigid unit, the relative orientation of two adjacent base pairs is defined by three translations ("rise" along the Y axis and two "slides" along the X and Z axes) and by three rotations. The rotational orientation of the second base pair coordinate system (X', Y', Z') with respect to the first coordinates (X, Y, Z) can be uniquely specified in terms of nine direction cosines in the transformation matrix, $A = \{A_{ij}\}$, $j = X, Y, Z$, $i = X', Y', Z'$, between the two coordinate systems. Only three of the direction cosines are independent if orthonormality is preserved. In the calculations, the rotational transformation is performed with three Euler angles, ϕ, θ, ψ, as follows: The second base pair is rotated about the X axis by angle ϕ. Next, the rotated base pair is rotated about the new axis Y^* by the angle θ. Then, the rotated base is again rotated about the new axis X' by the angle ψ. The combined rotations represented in matrix A are the product of the three individual rotational matrices for these three rotations. Now, we rigorously define three rotational quantities, "twist", "roll", and "tilt", conventionally referred to in the literature, in terms of direction cosines as follows: twist $\equiv \cos^{-1} \tilde{A}_{X'X} = \theta$; roll $\equiv \sin^{-1} \tilde{A}_{Z'Y} = \sin^{-1} (\cos \psi \sin \phi + \sin \psi \cos \phi \cos \theta)$; tilt $\equiv \sin^{-1} \tilde{A}_{X'Y} = \sin^{-1} (-\sin \psi \sin \theta)$ where $\tilde{A}$ is the transpose of A. Twist is the angle between X' and X. Roll is defined as 90° – angle between Z' and Y. Thus, the sign of roll is defined as positive if the major groove is compressed. Tilt is similarly defined as 90° – angle between X' and Y. The advantage of the above definitions of twist, roll, and tilt is that they are uniquely determined from direction cosines, not as being associated with the rotational operations about particular Cartesian axes, so that the relative base pair orientation does not depend on the order of application of rotations. If twist, roll, and tilt were defined around the three axes Y, X, and Z, respectively, as has frequently been done in the literature, the relative base pair orientation would depend on the order of application of rotations (Srinivasan et al., 1987). We also consider the intra base pair degree of freedom, "propeller twist", in which matched bases rotate with respect to each other about the X axis.

The energy of base pairs is calculated as a sum of all atom pair contributions in the form of short-range repulsion, dispersion, and electrostatic terms. We use 6–12 Lennard–Jones potentials for the evaluation of the energy associated with the dispersion and repulsion, with coefficients derived by Zhurkin et al., (1981), except for the hydrogen bonds, for which we used 10–12 potentials with coefficients by Poltev and Shulypina (1986). The electrostatic energy is calculated with the equation $332 \sum_{ij} (1/\epsilon r_{ij}) C_i C_j \exp[-\alpha(r_{ij} - r_0)]$ (in kilocalories per mole), where α is the ionic screening parameter in units of Å^{-1} and ϵ is the effective dielectric constant. Although α and ϵ may have corresponding physical meanings, they should only be regarded as empirical parameters in the complex system like DNA. Previously, we evaluated these parameters by fitting the calculated structures against crystal structures (Sarai et al., 1988). Lavery (1988) used a similar electrostatic screening in his formulation of the dielectric constant. In the present calculation, we set (Sarai et al., 1988) $\alpha = 1.20$ and $\epsilon = 5.0$ unless otherwise stated. C_i and C_j are atomic charges, also taken from Zhurkin et al. (1981). r_0 is the contact distance between interacting charges, and it is qualitatively related to the sum of van der Waals radii. We take r_0 as equal to 3.0 Å, the closest distance between adjacent base pairs. The conformational states of base pairs and their energies can be described in the phase space spanned by the variables defined above [three translations, three rotations (ϕ, θ, and ψ), and propeller twist]. In the present calculation, we fix the slides at zero to restrict the conformation to B form. By assuming a canonical distribution of these variables, we calculate the Boltzmann averages of conformational properties. Conformational entropy and free energy are estimated from the partition function. For long chains of base pairs, the calculation is performed iteratively. One base pair is averaged at a time. That is, the average values of the conformational variables are calculated in succession. After the averages of these variables are computed, adding one base at each iteration step, the entire process is repeated, until a stationary steady-state solution is obtained. In order to take account of longer range interactions, because of cooperativity among base pairs, we have treated interactions among at least four base pairs.

Results and Discussion

Origin of Helix Conformation. Of the three rotations, twist is most directly related to the helicity of DNA. We calculate the energy potentials along the twist coordinate for all possible base sequence steps. At each twist angle, all the other degrees of freedom are varied to yield an adiabatic potential. The energy dependence on twist angle for the AA step is shown in Figure 2. Table I shows the Boltzmann average of twist angle and the twist angles corresponding to the minima in free energy, total energy, and electrostatic component of the total energy. It also shows the range of possible fluctuations about the average.

An interesting result is that most of these potential energies exhibit minima near the twist angles observed in B DNA, regardless of the base steps. In other words, the base pairs

Table I: Preferred Twist Angles and Fluctuations for All Base Steps[a]

base steps	average twist angle (deg)	twist angles (deg) at minima			fluctuation
		G	E_{total}	E_{el}	
AA (TT)	38	37	37	39	6.4
GG (CC)	40	40	40	42	5.4
AT	39		30	30	14.6
TA	24	18	37 (16)	40 (20)	8.3
GC	38	40	40	41	8.6
CG	23	24	25	25	6.3
CA (TG)	29	27	37 (21)	37 (21)	9.2
AC (GT)	40	41	40	40	11.0
CT (AG)	35	36	37	39	6.3
TC (GA)	38	38	41	48	6.9
mean	35	34	37	39	8.0

[a] G, free energy; E_{total}, total energy; E_{el}, electrostatic energy. Numbers in parentheses represent secondary minima. Averages and fluctuations are calculated at 300 K. Sequences in parentheses are the sequences of the matching strand. Although they represent the same structure, we calculate for both complementary sequences; the twist values are similar. The numbers given here for these sequences are averages of these two. The range of twist angles in the calculation is from 12° to 60°. Calculations are performed on the tetramer sequence NNMM by varying twist at the central base step. Although the twist angles are mainly determined by the nearest-neighbor interactions, the values are affected slightly by the flanking sequence. This can be rectified by averaging over all possible flanking sequences.

by themselves manifest strong tendencies to form helically stacked structures. It is evident from these results that the minima are principally due to the electrostatic interactions between the charges in neighboring base pairs. van der Waals interactions give a larger contribution to the stacking stability, but their twist angle dependence is smaller in this helical stacked configuration. A similar conclusion was reported by Polozov et al. (1975), who, with less complete calculations, found four energy minima, including the one near 36°, over the entire range of twist angles. In addition to the helix stacking tendency, the twist angle at the minima can vary to some extent, depending on the sequence. In general, pyrimidine (Y)–purine (R) steps tend to be undertwisted. This tendency agrees with experimental observations in the B-form DNA crystal (Dickerson & Drew, 1981) in which the CG step is undertwisted. The AT step has an extremely flat potential with no significant minimum and a correspondingly large fluctuation. Similarly, the minimum of the AC (or GT) step is significantly broader than the others. This is consistent with the experimental findings that the AT step is strongly deformed in the structure of *Eco*RI with DNA (McClarin et al., 1986). Since most of the preferred twist angles cluster near 36° regardless of base steps, it is unlikely that this result is only a manifestation of the particular choice of energy parameters. Nevertheless, we have also performed the same calculation with a different set of energy coefficients taken from Weiner et al. (1984), to confirm the generality of the conclusion. Although the individual values vary to some extent, we obtained qualitatively similar results. That indicates preferred twist angles clustered near the B-form 36°. The present result is also insensitive to the choice of values of the screening parameter α and dielectric constant ϵ. This consistency indicates the generality of the present result.

From energy calculations on the dodecamer d-(CGCGAATTCGCG), for which detailed X-ray structural analyses have been reported (Dickerson & Drew, 1981), we obtained a calculated structure, without backbone, that exhibits a helical conformation and agrees remarkably well with the crystal structure within a root mean square deviation of about 0.7 Å (Sarai et al., 1988). These results strongly suggest that

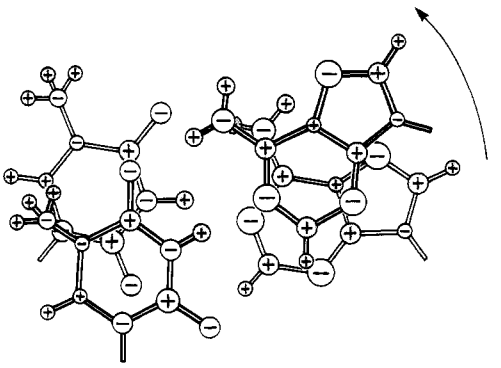

FIGURE 3: Partial atomic charges on the helical stacked base pairs in the two base pair AA step. Circles represent charges, their size taken to be approximately proportional to the magnitude of the charge. Positive charges are shaded, and negative charges are open circles.

the helical structure of DNA is mainly determined by the intrinsic interactions between base pairs. Backbone atoms probably tether atoms to limit the range of conformations, as well as providing additional overall stabilization to the base pairs, and may also influence their ionic environments. However, the present results strongly suggest that the backbone may play a substantially passive role in determining the basic helical structure of DNA. Other studies (Srinivasan et al., 1987) also indicated a rather small influence of backbone on the base pair morphologies.

This preference of helical structure for base pairs may be explained as follows. From looking at the partial charges on the base pairs, one of the interesting features is that the atomic charge pattern mostly alternates (see Figure 3). Nitrogens and oxygens, which are negatively charged, and carbons and hydrogens, which are mostly positively charged, are positioned in almost alternating sites in the base pairs. Therefore, the electrostatic potential will be approximately sinusoidal, upon rotation about the helix axis. That is, if one were to follow a circle with a fixed radius about the helix axis, the electrostatic potential would be oscillatory. The present calculations show that near 36° there are positions in this sinusoidal distribution for which the electrostatic distributions of neighboring base pairs are particularly favorably juxtaposed. For example, in the two base pair AA step shown in Figure 3, 36° of twist would bring N1(− charge) proximate to C6(+), C6(+) to N6(−), N6(−) to N6H(+), C2H(+) to N3(−), N3(−) to C5-(+), and C4(+) to N7(−) in A and O4(−) to C4(+) and C4(+) to N3(−) in T, all of which contribute to the stabilization of adjacent base pairs in terms of electrostatic interactions. What determines the specific twist angles would depend on the arrangement of atoms according to bond distances, bond angles, and distances from the center of the rotation axis. The importance of electrostatic interactions in stabilizing the stacking of base pairs in DNA has also been shown by quantum chemical calculations (Aida & Nagata, 1986). The success of the present approach in explaining the helix structure indicates that the electrostatic energy can be well approximated by the simple form presented in the method. It cannot be a coincidence that the twist angles of the DNA double helix and stable stacking configurations of most base pair neighbors occur at similar values. If base pairs were stabilized at quite different orientations, e.g., 0° instead of 36° twist angles, a stable double-helical DNA might not exist. It is more likely that A-T and G-C base pairs have special chemical structures and charge distributions selected through evolution to form stable helical structures.

In this study, we have not included water molecules, but their effect is partially included in the screening and dielectric

parameters. There is some experimental evidence implicating the importance of hydration around DNA in stabilizing particular conformations (Drew & Dickerson, 1981; Saenger et al., 1986). We have been studying the energetics of hydration for various conformations of DNA. Preliminary results indicate that the free energy of hydration shows small smooth changes upon conformational changes such as twist variation. Thus, the hydration may not be a dominant factor in determining the basic helical structure of DNA but may only perturb it.

Origin of Sequence-Dependent Conformation Change. Several structures of B and A DNA studied by X-ray crystallography reveal that DNA base pairs exhibit sequence-dependent conformational variation (Dickerson et al., 1985; Shakked & Kennard, 1985). Values of twist, roll, tilt, and propeller twist are distributed about the average in specific patterns according to the actual sequence. Calladine (1982) proposed that the local conformational variation is caused by steric clash between purines on opposite helix strands at adjacent base pairs. Most of the base pairs are positively propeller twisted (in screw direction) in order to improve the stacking interaction between adjacent base pairs. This brings the two purines in the YR step closer than van der Waals contact in the minor groove. Calladine (1982) suggested that such clashes would be relieved by flattening the propeller twist, by rolling the base pair into the major groove, by sliding the base pair, and by decreasing twist. The clash can also occur between purines in the RY step in the major groove, but the clash is not as severe as in the minor groove of the YR step. Dickerson (1983) quantified Calladine's model by introducing parameters according to the severity of the clash and was able to reproduce many features of the dodecamer X-ray structure. Although the Calladine–Dickerson model elegantly explains the experimental results, it does not prove that the steric clash caused by the propeller twist is solely responsible for the conformational variation. The observed DNA structure could be determined by a balance among many attractive and repulsive forces acting between base pairs. From looking at the structure, it is difficult to see whether the clash is the cause or the result of such a balance. Although that model has been extended to A-DNA structures with partial success (Dickerson, 1983), it does not distinguish between the two purines or between the two pyrimidines and fails to explain the DNA bending observed by gel electrophoresis (Koo et al., 1986; Hagerman, 1986) for various sequences containing A runs.

In order to test the importance of "propeller-twist induced steric clashes" in conformational variation, we performed energy calculations by artificially fixing propeller twist at zero. Then, there can be no significant steric clash between these parallel planar base pairs. Figure 4 shows the experimental and computed sequence dependences of twist and roll for the dodecamer d(CGCGAATTCGCG). Although the magnitude of the variation is slightly diminished in the absence of propeller twist, calculations both with and without propeller twist show the same features of sequence-dependent variation observed in the X-ray structure.

This result clearly demonstrates that the steric clash induced by propeller twist is not essential to qualitatively account for the sequence-dependent conformational variation of DNA. What is responsible for this conformational change? Again, electrostatic interactions between charges play an important role in the sequence-dependent change. Note in Table I that YR steps tend to be undertwisted. The CG step is undertwisted by more than 10° compared with a standard twist value of 36°. This is the same as in the dodecamer calculation,

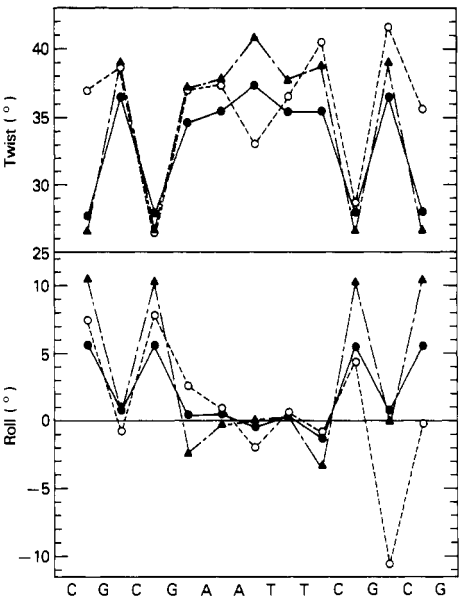

FIGURE 4: Sequence dependence of twist and roll in the dodecamer d(CGCGAATTCGCG). Closed circles are calculated for planar base pairs without propeller twist; closed triangles are claculations with variable propeller twists; open circles are experimental results. Since the definitions of twist, roll, and tilt are slightly different from Dickerson (1983), we reanalyzed the X-ray structure (1BNA in Brookhaven file) according to our definitions. For this reason, the values differ slightly from those in Dickerson et al. (1985). The apparent deviation in twist angles at the AT step may arise from its easy accessibility to a wide range of values due to its large flexibility.

where twist at the CG step is 26–27°. As noted, this tendency to undertwist is an intrinsic characteristic determined mainly by electrostatic interactions between base pairs, not by the steric clashes between base pairs. Electrostatic interactions also make important contributions to the variations of roll and tilt. In order to identify the atoms responsible for the conformational variations, we have decomposed the total energy into all possible combinations of atom–atom pairs between base pairs. In the case of the CG step, such inspection reveals that C2 and N2 of G have unfavorable interactions, both hard-core repulsive and electrostatic interactions, with atoms of the adjacent G in the minor groove. On the other hand, O6 of G and C4 of C have favorable electrostatic interactions on the major groove side. These interactions contribute to rolling the base pairs in the CG step into the major groove, as observed in the crystal structure.

These results suggest that electrostatic interactions among bases are a major driving force of the sequence-dependent conformational variation. Propeller twisting enhances this effect by positioning the relevant favored atom pairs closer and by introducing additional repulsive forces. Steric clash itself is not the largest force effecting conformational change and certainly not the only force. The propeller twists should improve the stacking of adjacent bases in the same strand, but they are unlikely to be strong enough to cause large changes of roll and tilt, which might weaken the stacking stability. The propeller twist is unlikely to be the cause of all the conformational variation, as proposed previously (Calladine, 1982; Dickerson, 1983), but rather it may play a passive role in affecting the sequence-dependent conformational variation, enhancing the electrostatic effect.

The present calculation also provides useful information about the sequence-dependent flexibility of DNA (see Table I). The apparent difference between calculated and experimental twist angles at the AT step is probably due to the very flat potential surface of this step. The calculated conforma-

tional fluctuation about twist at this step is 15° root mean square deviation from the mean angle. Thus, the difference is well within the range of thermal fluctuations. Such a large flexibility of the AT step is consistent with the structure reported for the complex between *Eco*RI and DNA containing the AATT segment (McClarin et al., 1986), in which the AT step is strongly undertwisted by about 25°.

Conclusions

We have shown that the basic double-helical structure of DNA and its local conformational variations result largely from the charge pattern in the base pairs and the electrostatic interactions between them. One of the most important conclusions is that the backbone plays a rather passive role and that the specific bases determine not only the sequence-dependent conformational variations but also the overall conformational structure. We confine our discussion to the classical B-DNA structure. However, this type of analysis can readily be extended to treat a broader range of conformational variation of DNA, such as A-form DNA. In fact, we have applied this method to study the B–A conformational transition, which includes sliding motion along the base plane. We found that the conformational preference is sequence dependent and it can be explained in the same way by the interactions between base pairs (Mazur et al., 1988). Another particularly direct and interesting application of these calculations would be to treat chemically modified bases to enable the introduction of particular changes into DNA conformation.

The present work represents an attempt to understand the origin of DNA structure and its conformational variation in terms of the chemical structures of base pairs and details of their interactions. We anticipate that such studies may ultimately provide significant insight into many relevant biological functions.

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Registry No. d(CGCGAATTCGCG), 77889-82-8; d(AA), 23339-45-9; d(GG), 15180-30-0; d(AT), 23339-47-1; d(TA), 19192-40-6; d(GC), 23405-83-6; d(CG), 15178-66-2; d(CA), 4624-07-1; d(AC), 23339-46-0; d(CT), 4829-64-5; d(TC), 5178-19-8; d(TT), 1969-54-6; d(CC), 26467-01-6; d(TG), 4251-20-1; d(GT), 23405-84-7; d(AG), 4336-87-2; d(GA), 4282-64-8.

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