Anisotropic flexibility of DNA and the nucleosomal structure

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ABSTRACT

Potential energy calculations of the DNA duplex dimeric subunit show that the double helix may be bent in the direction of minor and major grooves much more easily than in other directions. It is found that the total winding angle of DNA decreases upon such bending. A new model for DNA folding in the nucleosome is proposed on the basis of these findings according to which the DNA molecule is kinked each fifth base pair to the side of the minor and major grooves alternatively. The model explains the known contradiction between a C-like circular dichroism for the nucleosomal DNA and the nuclease digestion data, which testify to the B-form of DNA.

INTRODUCTION

Theoretical studies on the mechanism of DNA flexibility may be of interest for interpreting experimental data on DNA structure in solution as well as for the understanding of detailed DNA arrangement in chromatin.

The double-helical nature of DNA may imply that the DNA molecule bends to the side of the grooves, i.e. along the dyad axis, more easily than in a perpendicular direction. The question is to what extent this anisotropy is expressed.

Schellman (1) has considered the two extreme models for DNA flexibility: (I) in the "hinge model" the DNA helix can be folded into the minor (glycosidic) and major (non-glycosidic) grooves only; (II) in the isotropic model the DNA molecule bends in all directions equally likely.

The local DNA flexibility would determine the pattern of DNA folding in the nucleosome. According to the first model DNA may be described as a sequence of rigid segments, each consisting of N base pairs (N is multiple of 5), separated by "kinks"
(2,3). Note that Crick and Klug (2) suggested that N=20 and the DNA is kinked by an angle of 90° to the narrow groove side, whereas Sobell and coworkers (3) prefer the 40-degree kinks to the opposite direction; in their model N=10.

In the isotropic model DNA bends for one and the same angle in each interval between the pairs (4,5,6). For a nucleosome with 80 base pairs per superhelical turn and a pitch of 28 Å(7) the bending angle is equal to 4.5°.

The present work is aimed to reveal which of these two models is more realistic.

FORMALIZATION OF THE PROBLEM

Suppose that the helical axis in the curved DNA molecule is a space open polygon with the angles between the adjacent base pairs. Then description of a DNA loop reduces to description of the axis bends within successive duplex dimers. To define such a bend for two neighbouring pairs we use, besides the Arnott's parameters of the regular helix (8), two additional ones, Λ and β, which specify the direction and magnitude of bending. The Arnott's parameters are as follows: Ψ is the helical rotation angle, H is the distance between the adjacent bases along the helical axis, D is the distance of the base pairs from the axis, TL (tilt) is the angle of inclination of the base pairs, TW (twist) is the angle of propeller formed by the complementary bases in a pair. Conformation of the sugar-phosphate backbone is controlled by the dihedral angles \( \chi, \xi, \theta, \gamma, \varphi, \omega \), which can be calculated for the given bases' parameters using our previously published algorithm (9).

We shall now define the \( \alpha \) and \( \beta \) angles (Fig.1). Let \( A_1 \) and \( A_2 \) be the coordinate systems, related to adjacent base pairs. The X-axes in these systems are directed along the dyad axes to the side of the glycosidic bond; the Z-axes pass along the helix axis in the direction from 1 to 2; the vectors \( x, y, z \) form a right-handed reference system. Then the \( \beta \) angle is defined as that between \( z_1 \) and \( z_2 \), i.e. \( \beta = \angle A_2OA' \). Let OA be a dyad axis connecting base pairs prior to kinking; OB be a projection of OA onto the plane normal to \( A_1O \) and passing
through the point 0. Define the δ angle as that between OA and OB. Then, if $\overline{r}_2$ is a radius-vector of some point in the coordinate system $A_2$, then its position in the system $A_1$ will be given by the vector

$$\overline{r}_1 = Z(\tau/2 + \alpha) \cdot Y(\beta) \cdot (Z(\tau/2 - \alpha) \cdot \overline{r}_2 + \overline{h}/2) + \overline{h}/2$$

Here $Z(\gamma)$ and $Y(\gamma)$ are the matrices of rotation by γ angle around the corresponding axis, $\overline{h} = \begin{pmatrix} 0 \\ 0 \\ H \end{pmatrix}$.

Thus, a bending to the side of the narrow groove corresponds to $\alpha = 0^\circ$ and that to the side of the wide groove corresponds to $\alpha = 180^\circ$. Note that with these values of α the neighbouring pairs remain connected by a dyad axis (Fig.2).

We shall now consider how a possible anisotropy in local flexibility of DNA would affect its folding pattern in an "ordered" structure, such as that of nucleosome or of the covalently closed superhelix in solution. Suppose that the 80 b.p. duplex is closed in a ring so that the DNA axis is a plane polygon. (Note that this situation is close to that in the nucleosome since in the latter case the torsion of the DNA helix per base pair does not exceed 0.5° (7)). Then the conformation of
the duplex is described by the parameters \( \tau_1, D_1, H_1, TH_1, TW_1, \alpha_i, \beta_i \) (\( i = 1, 2, 3... 80 \)). Let \( \tau_i = \tau \) for all \( i \) values. In the case of planar loop the transition from the \( i \)-th pair to \((i+1)\)-th is accompanied by a change in the direction of bending by \( \tau \) angle: \( \alpha_{i+1} = \alpha_i - \tau \). For small values of \( \beta \) the bends in the adjacent tetranucleotides can be treated as independent of one another, and the energy of bending, \( \Delta E \), is proportional to \( \beta^2 \) (1): \( \Delta E(\alpha, \beta) = g(\alpha) \cdot \beta^2 \). Due to the constancy of all the \( \tau_i \) values the angles \( \alpha_i \) as well as the coefficients \( g_i = g(\alpha_i) \) are also constant. Therefore the equilibrium state of the duplex corresponds to the minimum of the sum \( \Sigma_i g_i \cdot \beta_i^2 \) provided that \( \Sigma_i \beta_i = 360^\circ \). It follows from the differentiation of the sum that this minimum is attained at \( \beta_i \) values proportional to \( 1/g_i \). One may expect that the pattern of the DNA folding would change only slightly after "unfreezing" the \( \tau_i \) angles.
Consequently, if the flexibility in the direction of grooves is much larger than that in other directions, then in a DNA planar loop kinks in the preferable directions will adjoin practically rod-like segments. So, if one neglects the long-range electrostatic repulsion between the phosphate groups, the DNA kink can be simulated by a bend of the duplex dimer (or complementary tetranucleotide, see Fig.2) with the fixed values of D, TL and TW, at least for small $\beta$ angles. It is evident that the $\tau$ and $H$ parameters may vary arbitrary.

On the other hand, if the dependence of energy of DNA bending, $\Delta E$, on $\alpha$ is nearly isotropic, then under an equilibrium state all the local bends are of comparable magnitude and all the bases' parameters as well as dihedral angles in the sugar-phosphate backbone vary smoothly from one pair to another. In order to find the precise dependence of $\Delta E$ on $\alpha$ in this case it is reasonable to consider the complementary tetranucleotide assuming that all the bases' parameters and the glycosidic angles, $\chi$, are unfrozen but equal to each other for the two base pairs ($\chi$ angles vary independently in both strands).

METHODS

The calculations were fulfilled in two steps: first, the tetranucleotide was bent in various directions with all the regular parameters unchanged; second, a minimization procedure (10) involving these parameters ($\tau$, D, H, TL, TW) was performed, assuming the $\alpha$ and $\beta$ angles to be constant. The $\alpha$ angle was varied from 0 to 360° with a 36° step; in addition $\alpha = \pm 18^\circ$ and $\alpha = 180^\circ \pm 18^\circ$ were considered as well; $\beta$ was equal to 1°, 2° and 4°. The conformation of the sugar-phosphate backbone (including H atoms) was found from the 7 parameters for bases using a modified version of algorithm for the regular helix published by us earlier (9). Forms of the B-family (the C2'endo standard sugar puckering (11) were considered; the valency angles and bond lengths had preset values (11, 12).

The potential energy of the tetranucleotide was calculated by the atom-atom potentials method as a sum of van der Waals (13,14,15), torsion (16,15) and electrostatic (17) terms. In or-
der to examine the effects due to thymine methyl group, both 
(dA-dA):(dT-dT) and (dA-dA):(dU-dU) tetranucleotides were con-
sidered.

It is noteworthy that according to our calculations (9) the 
DNA form of the lowest energy with completely neutralized phos-
phates is a C-like one with \( \tau \sim 40^\circ \); this is in agreement with 
the experimental data (18,19). Such an increase in the winding 
angle, \( \tau \), is accompanied by the diminution of the narrow (gly-
cosidic) groove size (9,18), which is unfavourable electrosta-

tically. Thus, the conformation of DNA in solution is a result 
of compromise between the tendency toward the increase in wind-
ing (the B \( \to \) C transition), preferable for non-electrostatic 
interactions, and the tendency to unwinding, which releases the 
repulsion between the phosphates of the opposite chains. There-
fore, we consider flexibility of the tetranucleotides both at 
the point of the minimum energy (\( \tau \sim 40^\circ \)) and at \( \tau = 36^\circ \) 
(Table 1).

RESULTS AND DISCUSSIONS

Dependence of \( \Delta E \) on \( \alpha \)

The indicatrixes for \( \tau \sim 40^\circ \) are shown in Fig.3. One may 
see that the flexibility at \( \alpha =0^\circ \) and \( 180^\circ \) greatly exceeds 
that found for other directions, and the indicatrixes look like

Table 1. Initial conformations of the tetranucleotides.

| Torsion angles | (dA-dA):(dT-dT) | (dA-dA):(dU-dU) | B-DNA* |
|---------------|-----------------|-----------------|-------|
| \( \tau^\circ \) | 40.0 3.15 0.1 0.9 -0.3 4.1 | 40.2 3.15 0.1 0.9 -0.3 4.1 | 36.0 3.35 -0.2 5.9 2.1 |
| \( \Delta E \) | 0.3 3.3 1.2 3.0 0.1 133 | 0.3 3.3 1.2 3.0 0.1 133 | 0.3 3.3 1.2 3.0 0.1 133 |
| \( \xi \) | 4.0 180 291 244 183 | 4.0 180 291 244 183 | 4.0 180 291 244 183 |
| \( \zeta \) | 0.0 0.0 0.0 0.0 0.0 0.0 | 0.0 0.0 0.0 0.0 0.0 0.0 | 0.0 0.0 0.0 0.0 0.0 0.0 |
| \( \gamma \) | 0.0 0.0 0.0 0.0 0.0 0.0 | 0.0 0.0 0.0 0.0 0.0 0.0 | 0.0 0.0 0.0 0.0 0.0 0.0 |
| \( \delta \) | 0.0 0.0 0.0 0.0 0.0 0.0 | 0.0 0.0 0.0 0.0 0.0 0.0 | 0.0 0.0 0.0 0.0 0.0 0.0 |

The bases' parameters have the same meaning as in ref.(8), but the TL and TW angles are measured in opposite 
direction (9). Torsion angles (degrees) are presented in Arnott's definition (8). The energy differences, \( \Delta E \), 
between the most favourable forms with \( \tau \sim 36^\circ \), and the total minimum forms (\( \tau \sim 40^\circ \)), is given in kcal/ 

mol of base pairs.

* The B-form with the C5' exo sugar puckering (17) is given for comparison.
Figure 3. Indicatrixes of flexibility of (a) (dA–dA):(dT–dT) and (b) (dA–dA):(dU–dU) tetranucleotides in their minimum energy conformations. Positive \( \alpha \) correspond to bends in the direction of adenines, negative \( \alpha \) are for bends to the thymine and uracil side. The energy scale is in kcal/mol. The dashed lines are for the constant regular parameters of the double helix \( (\tau, D, H, TL, TW) \); the solid lines show \( \Delta E \) after minimization in the space of these 5 parameters.

figure 8 rather than an ellipse. This is explained by the fact that one of the DNA chains is markedly stretched under bending in the unfavourable directions while the other is strongly com-
pressed. It was found that in the stretched chain the van der Waals interactions within the sugar–phosphate backbone are unfavourable, whereas the torsion term, base stacking (especially purine–purine) and a tight contact of 5′-sugar with 3′-base become unfavourable in the compressed chain. The latter contact of the furanose with the base from the neighbouring nucleotides explains the difference between the cases for thymine and for uracil.

The calculations with the frozen winding angle \( \varphi = 36^\circ \) reveal a smaller difference between T and U; the energy of bending, \( \Delta E \), however, increased 1.5–2 times for all directions in comparison with the case \( \varphi \sim 40^\circ \). So, at \( \alpha = \pm 90^\circ \) and \( \beta = 4^\circ \) the \( \Delta E \) value attains 12 kcal/mol of base pairs, whereas this magnitude should be equal to 0.26 kcal/mol to conform the experimental value of the DNA persistence length of 600 Å (20, 21), if the isotropic model were true (1). The independent variation of all the COP valency angles in both strands did not affect the general pattern of the \( \Delta E(\alpha) \) dependence.

**Torsion Angles**

We shall now consider how the dihedral angles depend on the direction of bending at \( \beta = 4^\circ \) (Fig.4). As mentioned above, the change of the \( \alpha \) angle by 36°–40° is equivalent to a transition to the neighbouring base pair in a DNA planar loop. Then the plot in Fig.4 may be visualized as the dependence of the torsion angles on the nucleotide number in the DNA loop. Note that the glycosidic angle, \( \chi \), changes less than by 5° per a step, thereby justifying our model (\( \chi_3 = \chi_5 \)). Smooth variations of the other angles resemble those obtained by other authors (4,5,6), where \( \beta \) was taken 3.9°, 3.8° and 4.4° respectively. But "unfreezing" \( \varphi \), \( \Theta, \delta \), etc. results in a marked deviation of the \( \chi, \Theta \) and \( \omega \) angles, especially with \( \alpha \) near \( \pm 90^\circ \); this is another evidence for the existence of some sterical hindrances upon bending the tetranucleotide in these directions.

In summary, calculations with tetranucleotide reveal the obvious advantage of the "hinge" model over the isotropic one.
Figure 4. The torsion angles in the (dA-dA):(dT-dT) tetranucleotide as functions of the direction of bending, $\alpha$, for the bending angle $\beta = 4^\circ$. The solid and dashed lines have the same meaning as in Figure 3.

Comparison with Published Calculations

It should be emphasized that among the authors who dealt with the uniform folding of DNA in nucleosome (4,5,6) only Levitt (6) has carried out energy calculations. His method considers both the valency angles and the bond lengths to be unfrozen. For superhelices with pitches equal to 55 Å and 28 Å he obtained $\Delta E$ values which exceed 2 and 4 times respectively the values, predicted by the isotropic model (1). These values of $\Delta E$ are possibly underestimated, since the pseudorotational barrier for the C2'-endo - C3'-endo transition in deoxyribose according to this method equals 0.5 kcal/mol (22), which is 4 times less than that obtained by other authors (23,24) and 8-10
times less than the experimental barrier for the intrafuranose conversion in adenosine (25).

As to the Levitt's conclusion about the increase of the equilibrium winding angle, \(\tau\), under the isotropic bending of DNA (6), this is confirmed by our data. According to our calculations the \(\tau\) mean value increases from 40° to 42° if the bending angle, \(\beta\), equals 4°; for \(\alpha = \pm 72°, \pm 108°\) \(\tau\) rises up to 44°, while for \(\alpha = 0, 180°\) \(\tau\) decreases to 39.6°. Such a uniform bending of the DNA molecule is, however, energetically unfavourable.

**The Hinge Model**

Let us consider in more detail the bending along the dyad axis of the tetranucleotide \((\alpha = 0\) and \(180°\)). As was said, the bends in these directions retain the symmetry of the two complementary pairs, and the tetranucleotide continues to be a part of regular helix. Only the parameters of this new helix, \(\tau', H', D', TL'\), are changed; evidently \(TW' = TW\) (see Fig. 5). It is therefore not surprising that consideration of the tetranucleotide flexibility separately from the whole helix leads to \(\Delta E = 0\) at \(\alpha = 0\) and \(180°\) with the unfrozen \(\tau\), \(H\), \(D\) and \(TL\) (Fig. 3). The real DNA helix probably falls into an intermediate situation between the complete freedom and full restriction of these parameters.

The results obtained for such an intermediate case are pre-

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**Figure 5.** Tetranucleotide, bent in direction of narrow groove \((\alpha = 0°)\). The dyad axes of the tetranucleotide before and after bending are shown together with the bent axis (solid line) and a "new" straight one (dashed line).
sented in Fig.6. Here D and TL have the same values as in the
equilibrium conformation, and \( \tau \) and H were allowed to change
free (see FORMALIZATION), deviation of \( TW \) and \( X \) from the minimum
energy form was small: \( \Delta TW \) did not exceed 5° and \( \Delta X \) was not
more than 10° for the bending angle \( \beta = 16° \). It is seen from
the plot that the dependence of \( \Delta E \) on \( \beta \) is close to the pa-
rabolic one and the energy of bending in the direction of both
grooves does not exceed the value predicted by the hinge model
(1) more than 1.5 times. This result is quite satisfactory if
one remembers, that in our model torsion angles are the only va-
riables.

Advantage of the hinge model of the DNA bending has an im-
portant consequence. As it follows from the above consideration
(see FORMALIZATION) the DNA molecule in a planar loop will be
bent every 5 base pairs \( (180°=36•5) \), and each bend \( \beta_i \) will be
5 times larger than that for the case of the isotropic model,
since \( \sum_i \beta_i \) should be the same. So, the sum \( \sum_i \beta_i^2 \) will
be 5 times larger for the hinge model. But the bending force con-
stant, \( g \) as estimated from the experimental value of persistence

\[
\begin{align*}
\Delta E &= 5 \\
\beta &= 16° \\
\alpha &= 180° \\
\end{align*}
\]

\[ \text{Figure 6. Energy of bending in the direction of narrow (} \alpha = 0° \text{) and wide (} \alpha = 180° \text{) grooves with the restricted variation of the regular helix parameters. The circles are for (} da-da\text{):(} dU-du\text{), the triangles are for (} da-da\text{):(}dT-dT\text{). The solid line presents} \Delta E(\beta) \text{ for the hinge model (1) provided that the persistence length of DNA is 600 Å.} \]

\[ = 180° \]

\[ = 0° \]
length, for the hinge model is 2 times less (1). Therefore, the bending energy, $\Delta E = \sum g \beta^2_i$ in our case will exceed the energy for the isotropic model 2.5 times. This fact should be taken into account when calculating the energy of the DNA bending in supercoils (26) and in nucleosome (27).

Interestingly, the winding angle of the helix, measured in the new reference system (see Fig. 5) increases after bending in both favourable directions: $\tau' > \tau$ (Fig. 7). This fact leads to a following effect: let the regular DNA helix have an equilibrium winding angle $\tau_o$ under some conditions and the helix is bent in one of the above directions. If one neglects the change in the interactions of the bent tetranucleotide with its neighbours (it is reasonable at low $\beta$ values), one may suggest that this favourable winding value is conserved, i.e. $\tau' = \tau_o$. Hence, $\tau < \tau_o$. In other words, in spite of the base-pairs' position as in a regular helix with $\tau = \tau_o$, the $\tau$ angle relating to the bent DNA axis becomes diminished. DNA bending is, thus, accompanied by a decrease in its total winding.

![Figure 7. Increase in the winding angle, $\Delta \tau = \tau' - \tau$, as a function of bending angle, $\beta$. The dependence of $\Delta \tau$ on $\beta$ is the same for $\alpha = 0^\circ$ and $\alpha = 180^\circ$.]
This decrease, though insignificant at low $\beta$ values, rises sharply with the increase in $\beta$ (Fig. 7).

Such unwinding of the double helix probably cannot be revealed by methods detecting the local conformation of DNA (e.g. circular dichroism), since in this case each tetranucleotide has practically the same geometry as in the regular helix with $\tau = \tau_0$.

The Model for DNA Packing in Nucleosome

The obtained results allow us to suggest the following model for DNA folding in the nucleosome. The DNA helix consists of rod-like segments, 5 basepairs in length, which are separated by the $15^\circ$-$20^\circ$-bends ("mini-kinks"); the mini-kinks occur in the directions of the major and minor grooves alternatively (Fig. 8). This differs our model from the previous ones, where DNA either is uniformly bent (4,5,6) or has the kinks in only one of the two bending directions (2,3).

Figure 8. Schematic representation of the model for the DNA packing in nucleosome by means of "mini-kinks" ($\beta = 22.5^\circ$). The smooth folding of DNA is shown for comparison ($\beta = 4.5^\circ$).
The DNA segments are present in a C-like conformation ($\tau = 38^\circ$ to $39^\circ$), which is found to be more favourable energetically than the B-form when the phosphates are neutralized (9). The DNA helix is unwound by about $10^\circ$ at the mini-kink sites for the reasons given above. (It is possible, that due to electrostatic repulsion of phosphates from the opposite chains the kink to the narrow groove side would be less favorable (3). This effect is not considered here.)

One important feature of the present model is that, while the helix as a whole decreases its winding, the bent tetranucleotides do not change the winding angle in the reference system of their regular continuation.

Hence, the C-like CD spectrum for the nucleosomal DNA (28, 29) becomes understandable. On the other hand, our model is in accord with the fact that nuclease digestion cuts the nucleosomal DNA into the 10 base pair segments (30,7), since due to the above decrease in winding at the kinks the average angle of helical rotation is close to $36^\circ$. (More specifically, in the case of left-handed superhelix with the pitch equal to 28 Å and 80 b.p. per turn, this angle measured relatively to bent DNA axis must be equal to $35.5^\circ$, in order to have 10 b.p. periodicity in DNA duplex.)

CONCLUSION

The Conformational analysis of complementary tetranucleotide has shown that the source of DNA double helix flexibility is primarily associated with its bends to the side of minor and major grooves. If one neglects the long-range (more than 10 Å) electrostatic repulsion between phosphates, bending in both directions is equally likely. These inferences seem to be valid for small bending angles up to $5^\circ$. As for larger kinks, where sliding of bases may play some role (3), a more complicated consideration of a larger segment of double helix should be performed. It is noteworthy that bending of DNA results in diminution of its total winding angle, this fact probably being important for the supercoiled duplexes. These findings allowed us to propose a new model for the DNA arrangement in nucleosome,
which explains why the CD spectrum of nucleosome resembles that of the C-form and at the same time the DNA has 10 b.p. periodicity according to the nuclease digestion data.

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