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How many base-pairs per turn does DNA have in solution and in chromatin? Some theoretical calculations

(DNA double helix/chromatin structure/energy calculations)

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ABSTRACT Calculations on a 20-base-pair segment of DNA double helix using empirical energy functions show that DNA can be bent smoothly and uniformly into a superhelix with a small enough radius (45 Å) to fit the dimensions of chromatin. The variation of energy with the twist of the base pairs about the helix axis shows the straight DNA free in solution is most stable with about 10½ base pairs per turn rather than 10 as observed in the solid state, whereas superhelical DNA in chromatin is most stable with about 10 base pairs per turn. This result, which has a simple physical interpretation, explains the pattern of nuclease cuts and the linkage number changes observed for DNA arranged in chromatin.

DNA in chromosomes is extensively folded; fully stretched out, the DNA double helix would be thousands of times longer than the chromosome itself. Such tight packaging of a long threadlike molecule in a way that can be easily undone presents serious problems of organization. The first step of this packaging process has received considerable attention in recent years, leading to a basic structure (1, 2) known as a "nucleosome" in which a stretch of DNA 200 base-pairs long is condensed around a protein core made of eight histone molecules (two each of the four main types).

There are two extreme models for the detailed arrangement of the DNA in nucleosomes: (*i*) the DNA is bent smoothly and isotropically, and (*ii*) the DNA consists of straight segments separated by sharp bends or kinks (3, 4). The isotropic bending modulus of DNA can be calculated from persistence length, A_m, of DNA random coils in solution. If the strain energy of a stretch of DNA l Å long bent to a radius of curvature r Å is given by $U = \alpha l/r^2$ kcal/mol, then $\alpha = A_m kT/4$ or $A_m kT/2$ Å·kcal/mol, depending on the model of smooth bending (see ref. 5). The measured DNA persistence length of 625 Å (6) gives $\alpha = 85$ or 170 Å·kcal/mol (714 Å·J/mol), so that 80 base pairs ($l = 80 \times 3.38 = 270$ Å) could be bent smoothly to a radius of 43 Å for a strain energy of $U = 85 \times 270/(43)^2 = 13$ kcal/mol or $U = 170 \times 270/(43)^2 = 25$ kcal/mol. The same length of DNA could also be bent into one turn of superhelix by means of four 90° kinks (3) or nine 40° kinks (4). Even if the increase of energy at each kink was only 3 kcal/mol, the total strain energy would be between 12 and 27 kcal/mol for a turn of kinked DNA. It is clear that both arrangements are energetically possible and that smooth bending must also be considered.

DNA is not an isotropic rod and the above equation relating strain energy to the radius of curvature cannot hold for very tight radii. At some point the atoms are forced together so tightly that the energy increases much more steeply than expected for smooth bending.

In this study, the arrangement of DNA in nucleosomes was investigated by using empirical energy calculations to give relaxed conformations of DNA double helices bent and twisted to different degrees. Results obtained with different sets of energy parameters show that, when DNA is bent tightly enough to fit into a nucleosome, the local conformation of each nucleotide is changed only slightly and the resulting increase in energy is small. The variation of the energy with the twist of the base pairs about the helix axis shows that straight DNA free in solution is most stable with about 10½ base pairs per turn rather than 10 as observed in the solid state (7). For superhelical DNA in chromatin, the structure is most stable with about 10 base pairs per turn. This result explains both the 10-base-pair repeat observed in partial nuclease digests of nucleosomes (8) and also the change in DNA linkage observed when nucleosomes are formed (9, 10).

METHODS

Energy Calculations and Relaxation. A 20-base-pair segment of double-stranded DNA was assumed for all the calculations. This fragment has random sequence but equal numbers of A·T, T·A, G·C, and C·G base pairs. The energy and deformations of this "molecule" were studied by using the same type of empirical energy calculations that have been used in the energy refinement of protein (11–14) and transfer RNA (15) coordinates, the study of enzyme reactions (16–18), the analysis of protein flexibility (19), and the simulation of protein dynamics (20). In general, the method changes the coordinates by about 0.2 Å to give a structure with good stereochemistry that still fits the x-ray data even at 2.0 Å or 1.5 Å resolution. With this approach, all of the 2460 Cartesian coordinates of the 820 nonhydrogen atoms of the DNA fragment are allowed to move in order to relax the structure and decrease the energy. The energy is expressed as a sum of many simple terms that allow for bond stretching, bond angle bending, bond twisting, van der Waals' interactions, and hydrogen bonds. The two main sets of energy parameters used here are presented elsewhere (16, 21).

Because we are interested in the properties of DNA helices much longer than 20 base pairs, the atomic positions of the top and bottom bases were constrained to remain at their initial positions (bases numbered 1, 20, 21, and 40). Because the segment studied contains approximately two full turns of DNA double helix, any systematic end effects due to the short length should be apparent.

The conformation was allowed to relax by energy minimization using the method of conjugate gradients (22). This

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Abbreviation: rms, root mean square.

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Table 1. Conformational parameters and energies of some straight, twisted, and superhelical DNA conformations

Conformation and conditions	Backbone torsion angles, deg.*							Orientation of bases,† deg.		Dyad,‡ deg.		RMS′,§ deg.	Energy, kcal/mol					RMS§ shift, Å
	ω	ϕ	ψ	ψ'	ϕ'	ω'	χ	κ	$\Delta\kappa$	ρ	δ		Total	Bond	Angle	Torsion	Nonbond	
1. Starting coords. (30)	313	214	36	156	155	265	82	6	4	4	0	32	1693	159	750	636	99	0
2. $n = 10$¶	295	170	65	108	178	275	47	18	12	28	5	0	353	12	192	475	−325	0.62
3. $n = 10$, $\theta^\circ_{COC} = 115°$	299	180	57	122	173	269	61	14	11	24	3	9	420	12	207	525	−325	0.48
4. $n = 10$ (set B)	299	188	52	129	168	271	56	12	13	10	8	13	−854	14	207	560	−1635	0.36
5. $n = 9$	287	172	71	127	179	261	55	16	12	25	5	10	484	23	231	540	−310	0.20
6. $n = 11$	304	169	56	100	177	278	49	17	11	29	5	6	336	11	196	449	−320	0.15
7. $n = 12$	310	170	48	97	174	280	54	17	10	28	5	9	401	15	241	454	−309	0.11
8. $n = 9.4$ (superhlx)	295	171	66	110	177	273	50	29†	14	30	8	5	372	12	203	472	−316	0.28
9. $n = 10$ (superhlx)	297	169	64	105	178	277	47	29†	14	31	7	5	348	11	201	449	−314	0.32
10. $n = 10.4$ (superhlx)	301	169	60	102	177	278	48	28†	13	30	6	5	354	10	198	449	−303	0.25

* The torsion angle notation (taken from ref. 25) reflects the symmetry of the backbone covalent structure. All angles are measured as positive by a clockwise rotation of the bond nearest to the eye with zero occurring for the *cis* conformation (the usual convention). The following atoms define each torsion angle: ω, O3′—P—O5′—C5′; ϕ, P—O5′—C5′—C4′; ψ, O5′—C5′—C4′—C3′; ψ', C5′—C4′—C3′—O3′; ϕ', C4′—C3′—O3′—P; ω', C3′—O3′—P—O5′; χ, O1′—C1′—N1—C6 (for pyrimidines) or O1′—C1′—N9—C8 (for purines).

† A vector normal to the plane of each base is used to calculate: κ, the tilt angle between the base normal and the z axis in the laboratory coordinate system (this parameter is not useful for superhelical structures); $\Delta\kappa$, the angle between base normal of adjacent nucleotides in one strand; ρ, the twist angle between the normals of paired bases.

‡ The dyad fit measures the rms deviation of torsion angles of three or four nucleotides that are dyad-related.

§ RMS′ measures the change in local geometry as the rms deviation of torsion angles from the reference values (line 2). The RMS shift measures the rms movement of atoms from the starting coordinate set. For lines 2–4, the starting set was line 1. For lines 5–10, it was a conformation like line 2 but after only 200 minimization cycles was then uniformly deformed to give the required number of base pairs per turn (lines 5–7) and the superhelix radius of 45 Å and pitch of 55 Å (lines 8–10). Each of lines 2–7 had a total of 300 cycles of minimization; lines 8–10 had a total of 400 cycles.

¶ n = number of base pairs per turn.

method is much better than the method of steepest descent used in the previous calculations referred to above: the energy decreases much more rapidly and the resulting changes in conformation can be much larger. Typically, 20 cycles of conjugate gradient minimization are equivalent to 100 cycles of steepest descent minimization. Here, conformations were allowed to relax for at least 100 cycles of conjugate gradient minimization. With so many degrees of freedom (2460), the energy never converged to a precise minimum: even after 300 cycles, the energy change per cycle (averaged over the last 20 cycles) was 0.044 kcal/mol and the root mean square (rms) Cartesian forces were 0.2 kcal/mol·Å. This lack of convergence makes comparison of final minimized energies problematic, but conformations, which converge much more rapidly, can be compared easily.

Smooth Deformations. Smooth deformations of the DNA double helix are particularly easy to study in the method used because all the Cartesian coordinates of the molecule are free to change. All one need do is apply a smooth and uniform coordinate transformation to the atomic positions of straight DNA and then energy-refine this structure to eliminate the many unacceptable bond lengths and bond angles. The deformations used here are characterized by three parameters: $\Delta\theta$, the twist per unit length (Å) about the DNA helix axis; r, the superhelix radius of curvature; and h, the superhelix pitch (closest separation of turns). The center of distortion (the region least distorted) was taken to be the centroid of the 20-base-pair fragment at $(x,y,z) = (0,0,z_o)$. The transformed coordinates were calculated in three steps.

1. Twist every atom i about the z axis (the DNA helix axis was always along z).

$$x_i' = x_i \cos(t_i) - y_i \sin(t_i);$$
$$y_i' = y_i \cos(t_i) + x_i \sin(t_i);$$
$$z_i' = z_i - z_o$$

in which the twist $t_i = \Delta\theta\,(z_i - z_o)$.

2. Rotate the double helix through the pitch angle $\alpha = \tan^{-1}(h/2\pi r)$ about the x' axis

$$x_i'' = x_i';$$
$$y_i'' = y_i' \cos(\alpha) - z_i' \sin(\alpha);$$
$$z_i'' = z_i' \cos(\alpha) + y_i' \sin(\alpha).$$

3. Bend the rotated double helix about a superhelix axis along the y'' axis and passing through the point $(-r,0,z_o)$

$$x_i''' = (x_i'' + r)\cos(\beta_i) - r;$$
$$y_i''' = y_i'';$$
$$z_i''' = (x_i'' + r)\sin(\beta_i) + z_o$$

in which the angle of arc is $\beta_i = z_i''/r$. Note that h and, therefore, α are negative for a left-handed superhelix. With these parameters, m base pairs will form N turns of superhelix, $N = (m \times 3.38)/[(2\pi r)^2 + h^2]^{1/2}$.

RESULTS AND DISCUSSION

Conformation of Straight B-DNA. Energy refinement of the x-ray conformation of B-DNA(7, 23, 24) moved the atomic positions by 0.62 Å rms and the seven single-bond torsion angles of each nucleotide by 32° rms (Table 1, lines 1 and 2). The mean values of ω, ϕ, ψ, and ϕ' all have moved closer to expected staggered conformations at 300°, 180°, 60°, and 180°, respectively. The mean value of χ (about the glycosidic bond) has dropped from the unusually high value of 82.1° to the more acceptable value of 47.3° (25, 26). The change of ψ' from 156.0° to 107.6° is at first sight unexpected because it indicates that the sugar ring pucker has changed from the "standard" C3′-*exo* pucker to a pucker between O1′-*endo* (ψ' = 96°) and C1′-*exo* (ψ' = 120°) that has only been observed in one crystal form.

Calculations on ring puckering in five-membered rings (27–29) do indicate, however, that the ring strain energy is almost constant as ψ' changes from 80° (C3′-*endo*) to 140° (C2′-*endo*). This ring strain is almost constant because a five-membered ring must always have some ring torsion angles close

to the unfavorable *cis* position (0°), which makes the initial ring closure difficult but then gives an energy that is equally unfavorable over a wide range of ring conformations. When the furanose ring was made unrealistically stiff (by changing the equilibrium value for the C1′—O1′—C4′ bond angle to 115°), the energy refined conformation obtained (line 3) was not as relaxed as before (line 2) and the ψ' value of 122.2° still tended toward a C1′-*exo* pucker.

The base orientation parameters (Table 1) show interesting changes on energy refinement. The base normals, which initially tilt 6.3° from the helix axis (measured by κ), now tilt 17.6°. The same large tilt value is obtained with the stiffer furanose ring and DNA smoothly twisted to have 9, 11, or 12 base pairs per turn (the base translation along the helix axis was always kept fixed at 3.38 Å). As a result of this tilt, the base normals of adjacent bases in the same strand are inclined at an angle of 11.9° rather than 3.9° (measured by $\Delta\kappa$). Because adjacent bases in the DNA helix cannot lie directly on top of one another, the base overlap is increased by this nonparallel arrangement of bases (compare Fig. 1 *a* and *b*). With more base pairs per turn, $\Delta\kappa$ decreases as the sideways separation of the base centers is decreased (compare the values for n = 9, 10, 11, and 12).

Another consequence of the increased tilt of the bases to the helix axis is the propeller-like twist of the base pair from the initial almost planar value of ρ = 4.1° to the pronounced twist of 28.1° (Fig. 1*b*). The hydrogen bonds between bases are weakened by this twist, although small out-of-plane movements of the hydrogen bonding groups (>C=O and $-NH_2$) compensate for the base-pair twist. When a different set of van der Waals' energy parameters were used (set B, ref. 21) together with a stronger hydrogen bond potential ($E_{HBOND} = \epsilon\{(r_o/r)^{12} - (r_o/r)^6\}$ with ϵ = 3 kcal/mol instead of 1.15 kcal/mol and r_o = 3 Å instead of 2.9 Å) the base pairs twisted less (ρ = 9.6°). The mean value of $\Delta\kappa$ = 12.9° was still much larger than in the x-ray B-DNA conformation (24). With the different nonbonded energy parameters (21) and the stiff furanose ring, the final bond angle and torsion angle strain energy are higher than before (compare lines 4 and 2 in Table 1).

The conformation of DNA obtained by energy refinement is not perfectly regular. The standard deviations of the torsion angles ω, ϕ, ψ, ϕ', and ω' are all less than 2° but ψ' (the ribose pucker) and χ (rotation about the glycosidic bond) show a larger variation due to the random sequence of the DNA fragment (3.6° and 6.2°, respectively). The angles between adjacent bases ($\Delta\kappa$) are also very variable, with a large value (~20°) followed by a small value (~5°) occurring between adjacent pyrimidines in the same strand.

Because energy refinement changed the coordinates of the x-ray structure of B-DNA by 0.6 Å, it was necessary to test the fit of this new structure to the x-ray data (24). The R factor ($\Sigma|Fo - Fc|/\Sigma|Fo|$) of the x-ray structure (line 1) was calculated to be 0.34 (it was not possible to get the value 0.31 given in ref. 24 because the precise atomic scattering curves used in that calculation were not available). The R factor of the energy-refined structure (line 2) was calculated to be 0.40. The corresponding value of R2 ($\Sigma|Fo - Fc|^2/\Sigma|Fo|^2$) were 0.153 and 0.165. In view of the uncertainty in the x-ray data, these R-factor differences are probably not significant.

When the same method (set A parameters, 300 cycles) was applied to the A form of DNA (23, 30), the atomic positions only moved 0.33 Å rms and the torsion angles, 14°. These movements are much smaller than for the B form, indicating that the large changes in B-DNA are a consequence of that structure and not of the energy parameters used here.

Conformation of Superhelical DNA. When the energy-refined conformation of straight 10-fold DNA was smoothly deformed into a superhelix of radius 45 Å and pitch 55 Å and then energy-refined for a further 200 cycles, the atoms moved only slightly from their initial positions (<0.32 Å rms). The mean backbone torsion angles of energy-refined superhelical DNA (Table 1) were very close to those of the refined straight DNA (<5.33° rms deviation), and the fluctuations of a given angle were only a little larger in the superhelical structure than in the straight structure. Fig. 2 shows how the torsion angles of the superhelical structure change with the position of the nucleotide along the chain. Only ω, ψ, and ϕ' show the periodic variation expected for smooth bending; the other torsion angles are either constant (ϕ and ω') or reflect the variation of the DNA sequence. The local dyads are preserved almost as well as in straight DNA (Table 1).

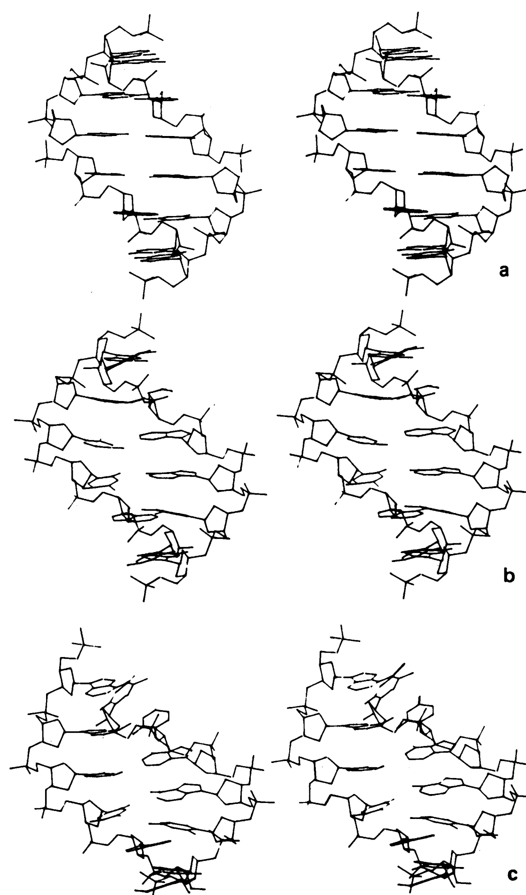

FIG. 1. Stereoscopic views of about one-half turn of DNA double helix. (*a*) Starting B-DNA x-ray coordinates (24, 30). (*b*) Energy-refined straight 10-fold DNA coordinates (line 2 of Table 1). (*c*) Energy-refined coordinates after bending into a superhelix of radius 45 Å and pitch 55 Å (line 10). (Nucleotides 5–10 and 31–36).

The propellor-like twist of the base pairs (ρ) of superhelical DNA is a little larger than for straight DNA. The inclination of adjacent base normals ($\Delta\kappa$) is also larger and shows the same decrease with increasing base overlap (more base pairs per turn).

Although the rms shift from the smoothly deformed starting coordinate is small (0.32 Å for n = 10), nucleotides on the inside of the curve shift more than those on the outside. Examination of the base tilt measured in the local coordinate system on the superhelix showed that these inside bases tilt more than the outside bases. This increased tilt enables the inside bases that are forced closer together by smooth bending to find low energy conformations and stack properly (Fig. 1*c*).

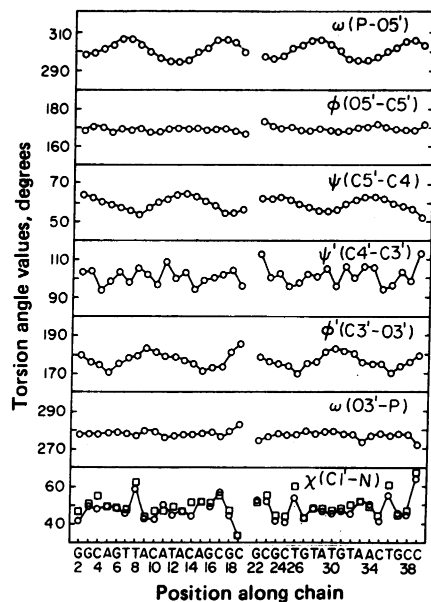

FIG. 2. Variation of the single-bond torsion angles with position along the chain in DNA bent into a superhelix of radius 45 Å and pitch 55 Å (line 9). Because the bonds about which ω and ψ operate are approximately collinear ($\phi \sim 180°$), changes in $(\omega - \psi)$ only affect the orientation of the O5′—C5′ bond; changes in $(\omega + \psi)$ affect the chain path. Here $\omega - \psi$ varies, but $\omega + \psi \sim 360°$ for all positions along the sequence. The fluctuations in χ are due to the random nucleotide sequence used: high χ values occur whenever T is preceded by T or C. Similar χ values (indicated by □) occur in the energy-refined structure of straight DNA.

Fig. 3 shows a large piece of smoothly deformed B-DNA that is formed by four repeats of the 20-base-pair fragment to give one full superhelix turn consisting of 80 base pairs. The pitch (28 Å) and radius (42.8 Å) used here were chosen to conform with the recent model proposed by Finch *et al.* (31). The energy of the 20-base-pair fragment (358 kcal/mol) was close to that obtained with the pitch (55 Å) and radius (45 Å) used in the rest of this work (348 kcal/mol).

Energetics of Twisting and Bending. The above results have concentrated on the conformations obtained by energy refinement. Consideration of the energy values themselves is beset by several problems. (*i*) The energy values depend on the number of cycles of minimization and the starting conformation. (*ii*) Changes in the energy parameters have a much greater effect on energy values than on conformations. (*iii*) The energy calculation neglects the interactions with the solvent so the calculated energy values cannot be compared with free energies in solution. Nevertheless, the energy values of straight DNA with different numbers of base pairs per turn (fixed 3.38 Å translation of bases along the helix axis) can be compared with one another because each conformation has had 100 cycles of energy refinement from the conformation in line 2 (Table 1), the same set of energy parameters have been used, and the interaction with solvent is likely to be very similar. Fig. 4 shows that straight DNA has the lowest energy for a base twist angle, θ, of 34° (10.6-fold). The three energy values obtained for superhelical DNA with different numbers of base pairs per turn [in the laboratory frame (33)] can also be compared with one another; the energy is lowest for $\theta = 35.5°$ (10.2-fold).

If these calculations reflect the energetic preferences of B-DNA in solution, the 10-fold repeat of DNA observed in fibers (7, 23, 24) must be a result of intermolecular packing forces. These forces will be most favorable when the number of base

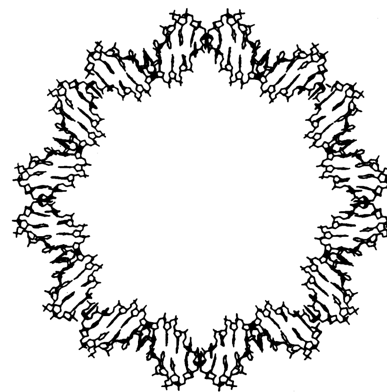

FIG. 3. Possible arrangement of smoothly bent DNA in the model of the nucleosome proposed by Finch *et al.* (31).

pairs per turn is integral because then the same stabilizing interaction can occur for each turn of the helix (32).

Comparison of straight and superhelical energies is more difficult: the straight structures have all been allowed to relax for 100 cycles after a relatively small twisting deformation from the conformation in line 3 (Table 1); the superhelical structures have all been allowed to relax for 200 cycles after a larger bending and twisting deformation. The actual energy difference between 10.6-fold straight DNA and 10-fold (in the local frame) superhelical DNA is 15 kcal/mol for the 20-base-pair fragment. This energy difference is a small fraction of the total strain energy (about 680 kcal/mol) and of the total van der Waals' energy (about −310 kcal/mol). The difference in energy between straight and superhelical DNA is about the same as between straight 10.6-fold DNA and straight 10-fold DNA (Fig. 4); superhelical 10-fold DNA actually has a lower energy than straight 10-fold DNA.

DISCUSSION

These results, obtained with the different sets of energy parameters, have shown that, if DNA is smoothly and uniformly bent to fit into a nucleosome (radius of curvature, ~45 Å), the local conformation of each nucleotide changes slightly (5°) and

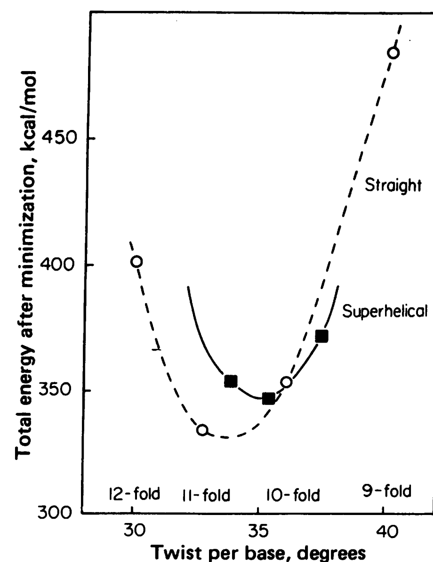

FIG. 4. Variation of the total energy after energy refinement with the twist per base pair, θ, about the helix axis for straight and superhelical DNA [in the laboratory coordinate frame (33)]. The value of θ in the local frame is about 0.8° larger than the value θ in the laboratory frame (n is 0.23 smaller) for a 55-Å pitch.

the energy increase is small (2%). Although the deviations from perfectly uniform bending are small (<0.35 Å), nucleotides on the inside of the curve deviate more than those on the outside. The main deviations from smooth bending are the increased relative tilts of these inside bases that can then come closer together along the smaller arc length.

The calculated preference of straight DNA for 10.6 base pairs per turn and of superhelical DNA for 10 base pairs per turn can also be explained by this increased base tilting in superhelical DNA. With fewer base pairs per turn, the sideways separation of bases (perpendicular to the helix axis) is larger and the bases overlap less. With less base overlap, the bases on the inside of the curve can tilt more to avoid the close base-base distances and so make favorable stacking interactions.

The flexibility of DNA is clearly influenced by the ability of the bases in each strand to tilt in an almost independent way. The tilting is possible in B-DNA because the bases overlap almost entirely with adjacent bases in the same strand (ref. 23; see Fig. 1). Preliminary calculations on the A-form of DNA, in which the bases in different strands also overlap (23, 30), showed that smooth bending was more difficult (the strain energy was 25 kcal/mol higher than for B-DNA, and the rms atomic deviation from uniform bending was 0.55 Å rather than 0.32 Å).

The number of base pairs per turn of straight DNA in solution (as opposed to DNA in fibers) cannot be measured directly. Low-angle x-ray scattering studies have suggested that the structure should be 11-fold with a 3.38-Å base translation (34). The number of base pairs per turn of superhelical B-DNA on nucleosomes has, however, been measured by the partial DNase I digestion patterns (8). The repeat is 10 ± 0.1 base pairs per turn (in the local coordinate system). This is in good agreement with the present result that superhelically bent 10-fold DNA has the lowest energy.

The relationship between the number of base pairs per turn of straight DNA in solution and DNA in nucleosomes has also been measured (9, 10). It was observed that the linkage number (33) (the number of times one DNA strand winds around the other) changes by about $-1\frac{1}{4}$ when a single nucleosome is formed. The linkage number of 200 base pairs of 10-fold DNA (in the local frame) wound into $2\frac{1}{2}$ turns of left-handed superhelix (80 base pairs per turn) would be $200/10 - 2\frac{1}{2} = 17\frac{1}{2}$. The linkage number of 200 base pairs of 10.6-fold straight DNA would be $200/10.6 = 18.9$, giving a linkage number change of $17.5 - 18.9 = -1.4$, in close agreement with experimental observations (9, 10).

Note Added in Proof. Independent calculations by Sussman and Trifanov (35) also show that DNA can be smoothly bent in chromatin.

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