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Some implications of an alternative structure for DNA

(DNA structure/kinky helix/chromatin structure/DNA replication)

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ABSTRACT **We have constructed a space-filling (Corey–Pauling–Koltun) model of an alternative structure for DNA. This structure is not a double helix, but consists of a pair of polynucleotide strands lying side by side and held together by Watson–Crick base pairing. Each of the two strands has alternating right- and left-handed helical segments approximately five base pairs in length. Sugar residues in alternating segments along a strand point in opposite directions. A structure slightly different from the present one proposed earlier by ourselves and another group and in which sugars in a strand all point in the same direction is ruled out. The present structure yields natural solutions to the problems of supercoiling of DNA and of strand separation during DNA replication. This model is energetically more favorable than the double helix.**

The well-known structure for DNA as initially proposed by Watson and Crick (1) and subsequently refined by others (2–4) is a right-handed double helix. We have considered possible alternatives to this classical structure of DNA on the basis of energetically allowed conformations of the polynucleotide backbone and the puckering of the sugar moiety (5). The conclusion is that both right- and left-handed helices are equally likely; x-ray diffraction data are consistent with both types of helices, but do not permit discrimination between the two. This led us to propose a new structure for DNA (6) in which each of the two strands contains alternating right- and left-handed segments; the duplex is held together by Watson–Crick base pairing. Such a structure clearly avoids tangling of the two strands which is inherent in any double helix and which has always been a bothersome aspect of the classical structure for DNA. In this paper, we present a few interesting implications of this new structure. In particular, we will consider the bearing of this new structure on DNA profile, topology, and replication, and will also show that there is no need to invoke a kinky helix (7) in order to explain the supercoiling of DNA in chromatin.

New structure

We have shown that it is possible to build two types (types I and II) of nonintertwining structures for DNA (Figs. 1 and 2). Both structures involve alternating right- and left-handed helical segments. As a consequence, each strand has bends (folds) in it, resulting from the change in handedness occurring after about every five base pairs. In the type I structure all the sugars in a strand point in the same direction (Fig. 3*A*), whereas in type II the sugars in alternating segments point in opposite directions (Fig. 3*B*). From considerations of base stacking (unpublished data; see Tables 1 and 2), both these structures are energetically possible. It is interesting that, viewed from one particular angle, these structures appear very similar to the double helix (Figs. 1*A* and 2*A*). However, another view (Figs. 1*B* and 2*B*) reveals the essential difference between these structures and the double helix; the two strands are laterally separated, and not intertwined as in the double helix.

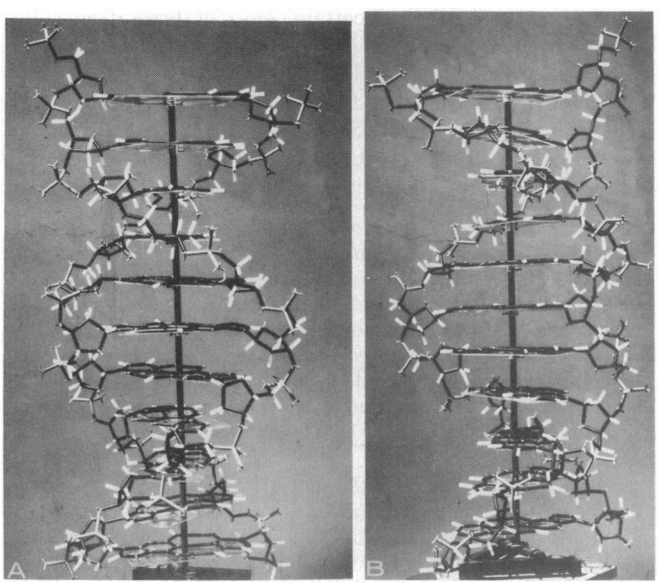

FIG. 1. (*A*) View of a model of the type I structure for DNA, in the B-form. (*B*) View of the type I structure taken at 90° from that in *A*.

On attempting to build space-filling (Corey–Pauling–Koltun) models, we have now found that this can be done only with the type II structure (Fig. 4) and not with type I due to short contacts between C8 of purines (or C6 of pyrimidines) and C2′ and C3′ of sugar in the left-handed segment. Thus, on the basis of base–sugar stereochemistry and energetics of base–base interactions (Tables 1 and 2) we rule out the possibility of type I structure. We, therefore, restrict our discussion to the type II structure. Our type I structure is very similar to a model for DNA recently proposed by Rodley *et al.* (8).

Profile and topology

As mentioned above, an important consequence of an alternating right- and left-handed arrangement of segments within each strand is that the complementary strands are no longer intertwined. Further, one has three degrees of freedom defining the relative orientations of two successive segments. We have made use of these degrees of freedom without breaking any hydrogen-bonded base pair. The resulting duplex requires no additional backbone strain or unfavorable base stacking.

The first degree of freedom involves a finite twist between the coiling of successive segments while maintaining the same helical axis. If we denote the resultant twist as θ for 10 base pairs (Fig. 5*A*), then θ is given by $0° \leq \theta \leq 30°–40°$. This leads to a major coiling of the duplex with a minimum number of 90–120 $[(360°/30°–40°) \times 10]$ base pairs in a repeat of the major coil.

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Abbreviation: SV40, simian virus 40.

Table 1. Base–base interactions for doublets in B-DNA

Sequence of base pairs I	II	Nature of stacking	Intrastrand interaction energy*	Interstrand interaction energy*			Total interaction energy*
				Interstrand stacking energy	In-place base-pairing interaction energy	Total interstrand interaction energy	
		Left	−13.1	+2.0	−46.0	−44.0	−57.1
C	G	Right	−28.1	+12.9	−46.0	−33.1	−61.2
G	C	Inverted	−1.8	−13.4	−46.0	−59.4	−61.2
		Left	+0.1	−9.2	−46.0	−55.2	−55.1
G	C	Right	+0.1	−9.2	−46.0	−55.2	−55.1
G	C	Inverted	−22.1	+9.5	−46.0	−36.5	−58.6
		Left	−8.7	−3.7	−31.1	−34.8	−43.5
C	G	Right	−8.8	−3.5	−31.1	−34.6	−43.4
A	T	Inverted	−13.9	+1.4	−31.1	−29.7	−43.6
		Left	−15.2	+3.2	−31.1	−27.9	−43.1
G	C	Right	−14.5	+3.0	−31.1	−28.1	−42.6
A	T	Inverted	−9.0	−2.1	−31.1	−33.2	−42.2
		Left	−9.4	−1.5	−16.2	−17.7	−27.1
T	A	Right	−9.4	−1.5	−16.2	−17.7	−27.1
T	A	Inverted	−14.0	+1.0	−16.2	−15.2	−29.2
		Left	−11.2	+1.5	−16.2	−14.7	−25.9
T	A	Right	−11.9	+1.4	−16.2	−14.8	−26.7
A	T	Inverted	−11.6	+0.1	−16.2	−16.1	−27.7

Doublets are two nearest-neighbor covalently linked base pairs. Nature of linkage is (3′-5′) phosphodiester bond from the base at the bottom to one at the top in strand I; in the antiparallel strand II, (3′-5′) phosphodiester linkage is from the base at the top to the one at the bottom. The base pairs are taken to be nearly perpendicular to the helix axis, which reduces the number of possible doublets since the doublet $\frac{G}{C}\frac{C}{G}$ in right stacking is same as $\frac{C}{G}\frac{G}{C}$ in left stacking, etc. Introduction of slight tilt and twist in the base pair does not alter the trend of the results. Note that the left, right, and inverted stacking are all energetically favorable. In some doublets, $\frac{G}{C}\frac{C}{G}$ inverted stacking is energetically more favorable than right or left stacking. This shows that bends in the type II model impart extra stability to the structure.

* kcal/4 mol of bases.

Table 2. Base–base interactions for triplets in B-DNA

Sequence of base pairs in triplet I	II	Nature of stacking: Bottom doublet	Nature of stacking: Upper doublet	Nature of bend	Energy of interaction (kcal/mol of triplet): Intrastrand interaction energy	Interstrand interaction energy	Total energy of interaction
		Left	Left	None	−41.4	−54.1	−95.5
G	C	Right	Right	None	−41.4	−54.1	−95.5
C	G	Left	Right	Type I	−26.2	−65.0	−91.2
G	C	Right	Left	Type I	−56.2	−43.2	−99.4
		Left	Right	Type II	−14.9	−80.4	−95.3
		Right	Left	Type II	−29.9	−69.5	−99.4
		Left	Left	None	−23.1	−21.3	−44.4
		Right	Right	None	−23.1	−21.3	−44.4
A	T	Left	Right	Type I	−22.4	−21.3	−43.7
T	A	Right	Left	Type I	−23.8	−21.5	−45.3
A	T	Left	Right	Type II	−22.8	−22.7	−45.5
		Right	Left	Type II	−23.5	−22.8	−46.3
		Left	Left	None	+0.2	−87.4	−87.2
		Right	Right	None	+0.2	−87.4	−87.2
G	C	Left	Right	Type I	+0.2	−87.4	−87.2
G	C	Right	Left	Type I	+0.2	−87.4	−87.2
G	C	Left	Right	Type II	−22.0	−68.8	−90.8
		Right	Left	Type II	−22.0	−68.8	−90.8
		Left	Left	None	−18.8	−27.3	−46.1
		Right	Right	None	−18.8	−27.3	−46.1
T	A	Left	Right	Type I	−18.8	−27.3	−46.1
T	A	Right	Left	Type I	−18.8	−27.3	−46.1
T	A	Left	Right	Type II	−23.4	−24.8	−48.2
		Right	Left	Type II	−23.4	−24.8	−48.2

In the alternative models, there are bends at regular intervals. At the bend regions, the continuity of a regular helix is lost. The base pair at the bend has the upper base pair stacked differently from the lower one. Therefore, in order to compare the interaction energy of the "double helix" and the alternative models, triplets would be a better description. A few triplet sequences are chosen as examples. Note that the type II model is energetically more favorable than the other two. The same trend of results follow for all other triple sequences. Details of our calculations will be published elsewhere.

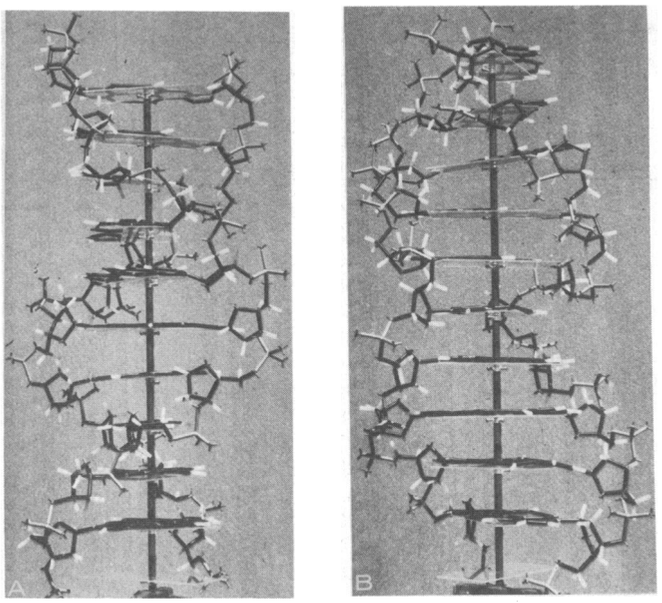

FIG. 2. (*A*) View of a model of the type II structure for DNA, in the B-form. (*B*) View of the type II structure taken at 90° from that in *A*.

The smaller the value of θ, the greater the number of base pairs in such a repeat.

The second degree of freedom involves a lateral displacement, d, of the axes of two consecutive segments. This shift maintains the base pair separation at 3.4 Å.

The final degree of freedom pertains to a relative tilt (α in Fig. 5*B*) of the axes of successive segments. This relative tilt permits the base-pair separation to vary from 3.4 to 4.5 Å.

Since our structure has considerable freedom to bend when compared with the double helix, it is of interest to see if it can contribute to a solution of the DNA-coiling puzzle. Needless to say, coiling of DNA will have to occur without an increase in the free energy of the structure. Consider simian virus 40 (SV40), a polyoma virus of 3×10^6 daltons. Its DNA has about 5000 base pairs and an overall length of 1.6 μm (9). An electron micrograph of SV40 DNA (9) shows that the structure can have loops in it, with circumferences ranging from 0.3 to 1.6 μm. To explain this on the basis of our model, suppose, for the sake of simplicity, that the axes of the segments are parallel (that is, $\alpha = 0°$) but displaced by a distance d between successive segments of opposite helical sense. Referring to Fig. 5*C*, let *AB* denote a stretch of five base pairs; the distance *AB* equals 5×3.4 Å or 17 Å. Call the angle of turn (d/AB) ω. For d ranging from 0 to 1 Å, ω varies from 0° to 3.3°. By giving relative displacement d (and hence ω) to successive segments in the same direction, a covalently closed, circular duplex can be generated. Thus, in order to get a covalently closed and a roughly circular

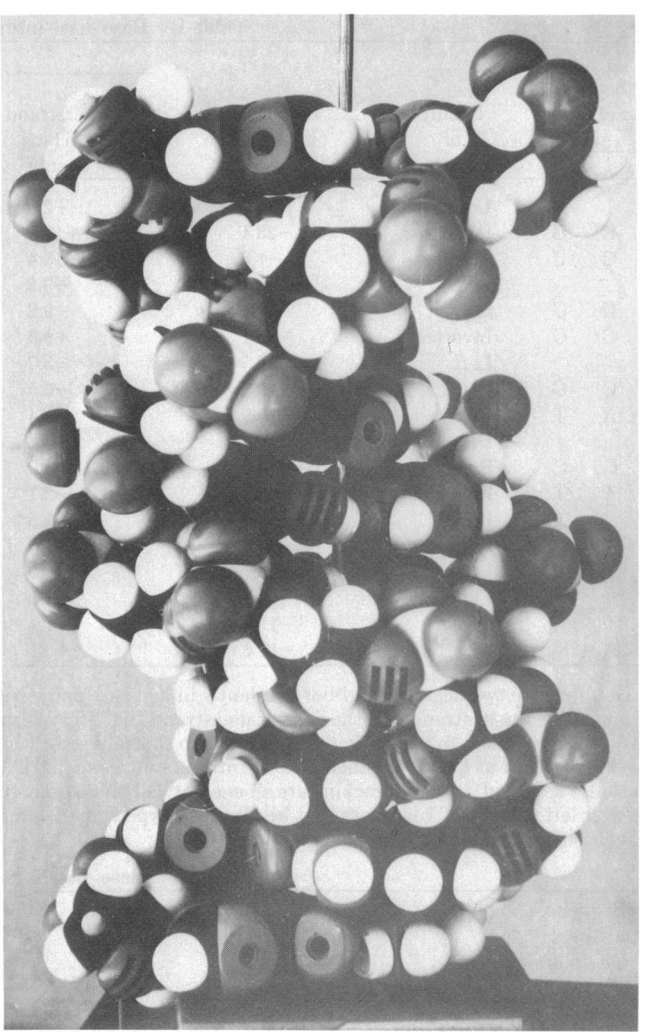

FIG. 4. Space-filling model of the type II structure. The corresponding model for the type I structure cannot be built.

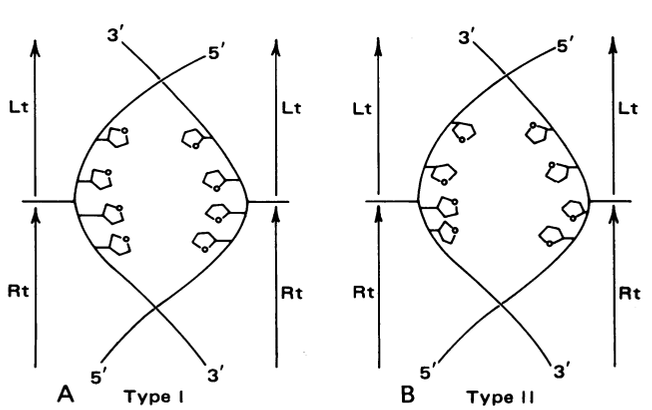

FIG. 3. The two structures differ in the orientations of the sugar moiety in alternating segments. (*A*) The type I structure; sugars point roughly in the same direction in alternating segments. (*B*) The type II structure; sugars in adjoining segments point in opposite directions.

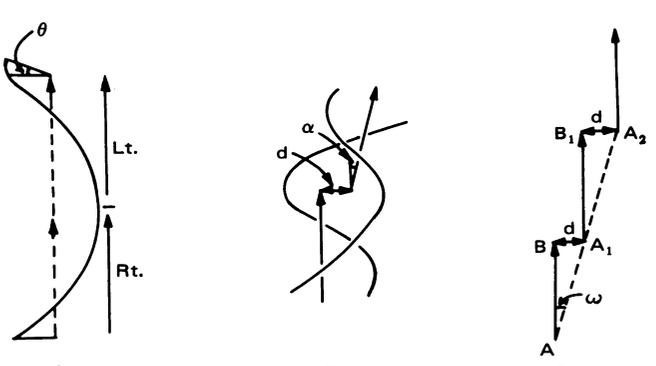

FIG. 5. (*A* and *B*) Degrees of freedom used in defining the relative orientation of the two consecutive segments. (*A*) Angle of twist, θ, for 10 base pairs. (*B*) Lateral displacement, d, and the angle of tilt, α, between the axes of two consecutive segments. (*C*) Formation of circular DNA by varying d only (with $\alpha = 0$). ω denotes the angle of turn in projection between two consecutive segments.

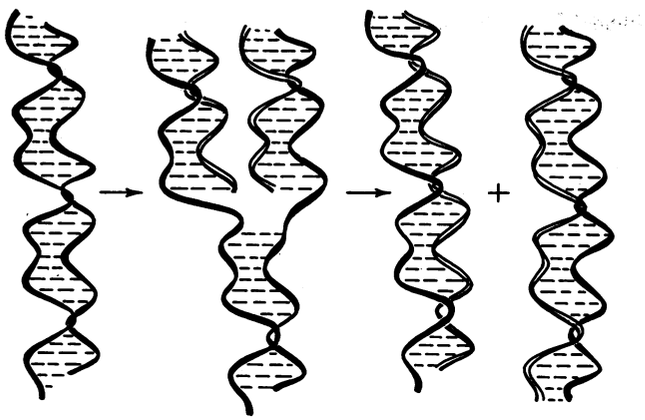

FIG. 6. Semiconservative mode of replication. Strand separation is achieved simply by breaking hydrogen bonds without an uncoiling motion.

loop one would need N base pairs, where $(\omega \times N/5) = 360°$ or $N = 1800/\omega$. For $0° \leqslant \omega \leqslant 3.3°$ one gets structures ranging from linear DNA to a circular loop consisting of about $N = 500$ base pairs (stretched length about 0.17 μm). For intermediate values of ω, we can expect looped structures of any circumference from 0.17 μm onwards. With reference to the SV40 DNA mentioned above, the 0.3-μm loop would correspond to about 1000 base pairs for $\omega = 1.65°$ ($d = 0.5$ Å) and the 1.6-μm loop would result from $\omega = 0.33°$ ($d = 0.1$ Å). The circumference of a DNA loop could of course be smaller than 0.17 μm with a nonzero angle of tilt α. The important point here is that this coiling of DNA does not occur at the expense of an increase in stacking or in backbone strain energy because the stacking interactions at the bend remain nearly the same, as given in Table 1 for a displacement $d < 1$ Å.

The introduction of the other two degrees of freedom, α and θ, can generate supercoiling in the circular duplex of SV40 DNA. Thus, supercoiling in a circular duplex can be achieved by exploiting d, α, and θ but still preserving the minor coiling in each connecting segment. On the basis of the present model, the action of ethidium bromide on the supercoiling of DNA can be interpreted as follows. It can intercalate at the bend region and release supercoiling through change of d, α, and θ or else it can intercalate in the helical segment and relieve supercoiling through alteration of the minor helix.

Replication

The essential advantage of our model over the double helix is that the energy expended in sliding and revolving of one strand with respect to the other is eliminated. Strand separation is achieved simply by the breaking of hydrogen bonds without an uncoiling motion (Fig. 6). Thus, DNA synthesis is initiated by the breakage of hydrogen bonds, leading to automatic strand separation, followed by copying of daughter strands on the parent template.

Structure of chromatin

Recent results strongly favor a periodic structure for the eukaryotic chromosome in which the histone-complexed DNA occurs in the form of tightly folded "beads" alternating with elongated stretches of "string" (10). These two regions have been called the nucleosome (or ν body) and spacer, respectively. A consequence of such a structure for chromatin is that the DNA molecule ought to be able to undergo considerable compression.

It is extremely difficult to bend double-helical DNA smoothly to give a radius of curvature of 30–50 Å, as estimated for ν bodies (11). As a means of getting over this problem, Crick and Klug (7) proposed that bending is achieved through kinks in between straight stretches of double-helical DNA. At kinks adjacent base pairs are completely unstacked, and are separated by a large distance (more than 7–8 Å), thus involving breaks in the continuity of the double helix.

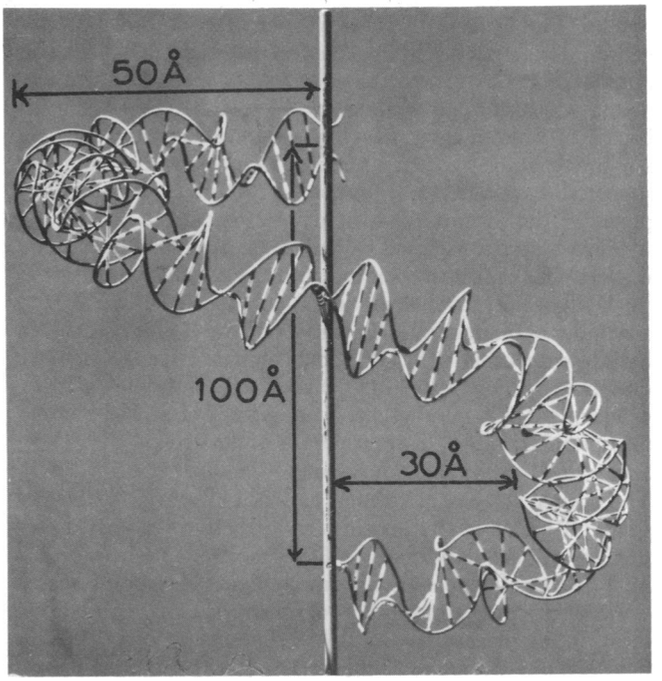

FIG. 7. Model for supercoiling of DNA in chromatin. A duplex of DNA of diameter 20 Å is bent to give a radius of curvature of 30–50 Å, wrapping tightly around a protein core of diameter 60 Å. The figure shows one turn of the supercoil with a pitch of 100 Å for 100 base pairs. This involves neither unfavorable base stacking nor breakage of hydrogen bonds.

On the other hand, our structure for DNA yields a more natural solution to this problem, since in this model the polynucleotide chains have an intrinsic tendency to trace a supercoil following energetically allowed folds at intervals. In fact, it is very easy to construct a model in which a DNA duplex of diameter of 20 Å is tightly wrapped around a core of diameter

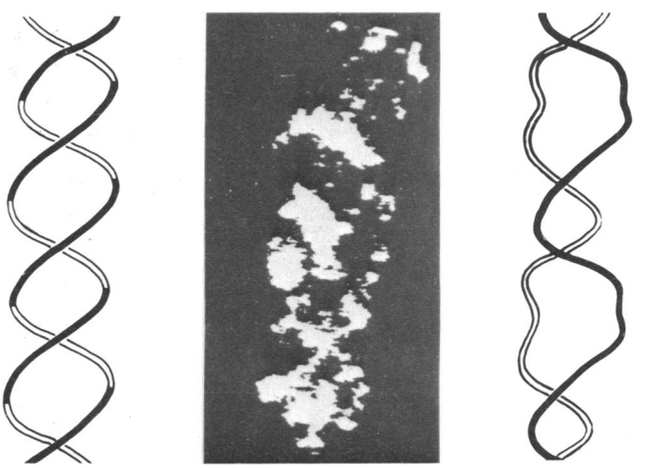

FIG. 8. High-resolution electron micrograph of viral DNA (14) and two schematic views of the double helix of Watson and Crick (*left*) and our alternative structure (*right*). (See text for discussion.) (The electron micrograph is reproduced with the permission of the *Journal of the American Medical Association;* Copyright 1971, American Medical Association.)

of 60 Å (Fig. 7). One turn of this supercoil comprises 100 base pairs and has a pitch of 100 Å. We feel that such a DNA–histone interaction in the nucleosome will enhance space optimization, that is, will further promote supercoiling of the DNA molecule. It must be stressed once again that neither unfavorable stacking nor breakage of hydrogen bonds is involved in building this supercoil. In addition, our proposed structure for the supercoil preserves the continuity of the DNA molecule.

H1 histones are assumed to bind to spacer regions in between nucleosomes (12). Such binding with the Watson–Crick model for DNA would involve winding a polypeptide chain around a cylinder of diamter 20 Å. In our model, the H1 histones do not have to wrap around the DNA, but can bind the duplex on one side since the two strands are not intertwined. A detailed study of histone–DNA interactions is necessary before the binding of protein and DNA in chromatin is understood.

Some additional considerations

The optical activity of circular as well as linear DNA is very small (13). Our model provides an attractive explanation for this low optical activity of the DNA molecule since there is a high degree of cancellation from segments of opposite sense.

Another interesting point concerns the high-resolution electron micrograph of viral DNA reported earlier (14). This has been interpreted as being consistent with a double-helical structure for DNA. Loops of different sizes are apparent in the electron micrograph (Fig. 8), whereas the double helix would predict loops of roughly the same size. This electron micrograph is in better agreement with our model for DNA, which demands loops of different sizes.

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