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Conformational flexibility in DNA structure and its implications in understanding the organization of DNA in chromatin

By H. M. Sobell, C.-C. Tsai,† S. C. Jain and T. D. Sakore‡
Department of Chemistry, The University of Rochester, Rochester, New York 14627, *U.S.A.*
Department of Radiation Biology and Biophysics, The University of Rochester School of Medicine and Dentistry, Rochester, New York 14620, *U.S.A.*

X-ray crystallographic studies of drug–nucleic acid crystalline complexes have suggested that DNA first bends or 'kinks' before accepting an intercalative drug or dye. This flexibility in DNA structure is made possible by altering the normal C2′ *endo* deoxyribose sugar puckering in B DNA to a mixed sugar puckering pattern of the type C3′ *endo* (3′–5′) C2′ *endo* and partially unstacking base pairs. A kinking scheme such as this would require minimal stereochemical rearrangement and would also involve small energies. This has prompted us to ask more generally if a conformational change such as this could be used by proteins in their interactions with DNA. Here we describe an interesting superhelical DNA structure formed by kinking DNA every ten base pairs. This structure may be used in the organization of DNA within the nucleosome structure in chromatin.

Crick & Klug (1975) have recently suggested that DNA may 'kink' rather than continuously bend to form a left-handed toroidal superhelix in chromatin. Their kink is accomplished by unstacking base pairs and altering the sugar-phosphate backbone from its normal *gauche–gauche* conformation (along the C4′–C5′ bond direction) to a *gauche–trans* conformation. This results in a rather abrupt kink (helical sections of DNA above and below the kink form an angle of 98°) that would have to be introduced every 20 base pairs in order to fit the parameters in chromatin.

This paper calls attention to a more subtle conformational flexibility in DNA structure that is made possible by altering the normal C2′ *endo* deoxyribose sugar ring puckering in B DNA to a mixed sugar-puckering pattern of the type C3′ *endo* (3′–5′) C2′ *endo*, with the concomitant partial unstacking of base pairs. Such a kink, when introduced into B DNA every 10 base pairs, results in a more continuous left-handed superhelical structure that may be involved in the organization of DNA within the nucleosome structure in chromatin.

Conformational flexibility in DNA structure

The conformational flexibility in DNA structure can be explored most easily with the Corey–Pauling–Koltun (C.P.K.) space-filling molecular models of DNA. Using these models, it is apparent that DNA flexibility is highly directional; DNA has natural flexibility down its dyad axis (i.e. the dyad axis that falls *between* adjacent base pairs). This flexibility reflects the ability of neighbouring base pairs to 'roll' upon each other's van der Waals surfaces, and small but systematic departures of bond angles and distances from their equilibrium values in both sugar-phosphate chains.

† Present address: Department of Chemistry, Kent State University, Kent, Ohio, U.S.A.
‡ Permanent address: Department of Chemistry, Indian Institute of Technology, Bombay, India.

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Conceptually, it is possible to bend DNA in one of two directions. If we bend DNA into the narrow groove, negatively charged phosphate groups on opposite chains approach each other and this introduces a repulsive term in the total free energy. Furthermore, strain energy in both sugar-phosphate chains appears to be evenly distributed over three or so nucleotide base pairs; there is no tendency for DNA to kink so as to relieve this strain energy. If we bend DNA into the wide groove, however, negatively charged phosphate groups do not approach each other significantly even after bending DNA 20–30°. Moreover, the strain energy in both sugar-phosphate chains remains highly localized to the central nucleotide base-paired region.

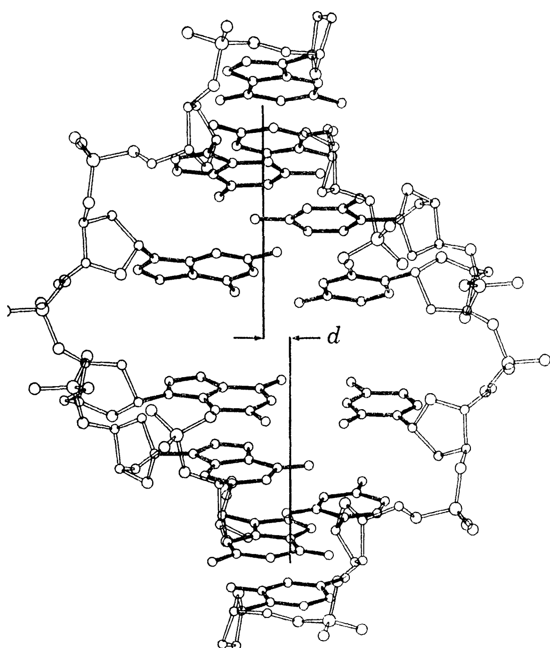

FIGURE 1

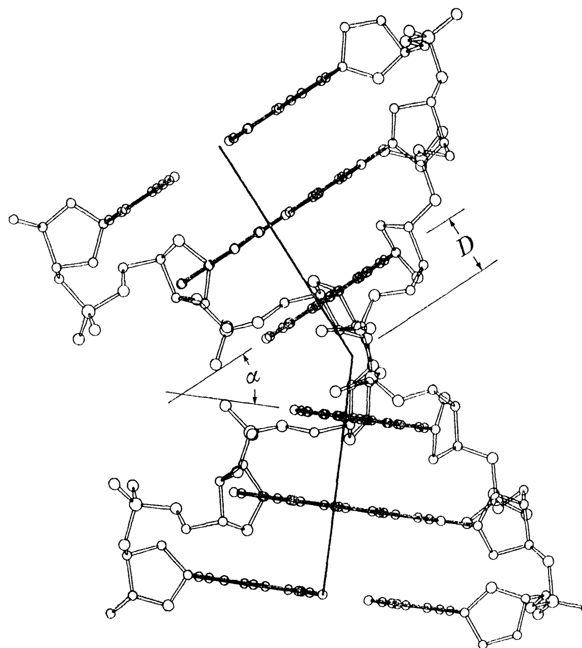

FIGURE 2

FIGURE 1. View of the kink down its dyad axis. Helix axes of B DNA above and below the kink are displaced -0.1 nm (i.e. $d = -0.1$ nm). See text for further discussion.

FIGURE 2. View of the kink from a sidewise direction. Base pairs are tilted approximately 40° to each other (i.e. $\alpha = 40°$). Another parameter describes the separation between base pairs ($D = 0.23$ nm), and has been shown in this figure. See text for discussion.

This strain energy can be relieved rather dramatically by simultaneously altering the puckering of deoxyribose sugar residues related across the dyad axis to give a C3′ *endo* (3′–5′) C2′ *endo* sugar puckering pattern. This results in a kinked DNA structure in which base pairs are partially unstacked (base pairs form an angle of about 40° to one another) and helical axes for B DNA above and below the kink are displaced by about -0.1 nm. Kinking DNA causes it to unwind. We estimate that adjacent base pairs at the kink are twisted by about 26° (this has been calculated using projectional geometry and is described in detail by Sobell, Tsai, Jain & Gilbert 1977); this gives rise to an effective unwinding of DNA by about $-10°$ and is an important additional parameter in describing this conformational flexibility in DNA.

Details of the kink are shown in figures 1 and 2. The stereochemistry of the kink appears to be primarily determined by the sugar-phosphate geometry; however, back contacts between van der Waals surfaces of adjacent base pairs at the kink may play an important additional

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rôle in determining the precise geometry of the kink. It is possible that different nucleotide sequences can give rise to small variations in the kink parameters.

A DNA conformational change such as this would require minimal stereochemical rearrangement and would probably involve small energies. We have speculated that DNA may kink spontaneously at thermal energies *in vitro*, and that drug intercalation is preceded by such a conformational change (Sobell *et al.* 1976). Although the energies associated with DNA kinking have been difficult for us to predict with any confidence, it is of interest that if we assume a free energy change of between 3.5 and 4.0 kcal/mol (between about 14.5 and 17 kJ/mol), then, at 37 °C, this would result in a kink appearing every 280–630 base pairs in DNA on the average; this corresponds to current estimates of the rod-like persistence length in DNA (see, for example, Bloomfield, Crothers & Tinoco 1974). A conformational fluctuation such as this could explain the enhanced rate of tritium exchange observed by Teitelbaum & Englander (1975*a*, *b*), and may also explain the reactivity of double-stranded DNA to formaldehyde (McGhee & von Hippel 1975*a*, *b*), and could correspond to 'breathing' of DNA. We will discuss these points in detail elsewhere.

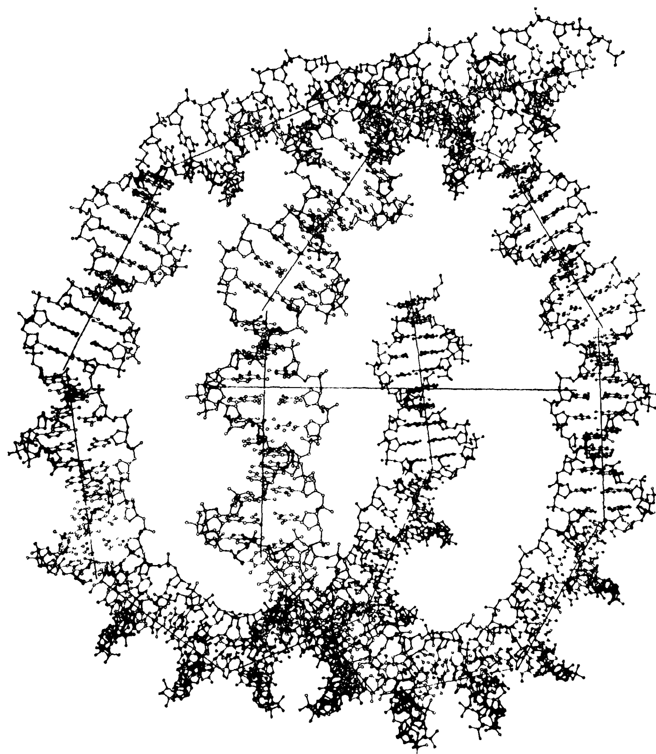

FIGURE 3. An oblique view of the κ kinked B DNA structure shown in perspective. Long central line indicates superhelix axis. See text for discussion.

KINKING OF DNA IN CHROMATIN–κ KINKED B DNA

A particularly interesting superhelical DNA structure possibly involved in the organization of DNA in chromatin can be obtained by introducing our kink every 10 base pairs into B DNA, a structure we have called κ kinked B DNA (Sobell *et al.* 1976). This structure (shown in figure 3) is a left-handed (kinked) toroidal helix with a diameter (estimated from the radius of the point in the middle of each kink) of about 10 nm. Each residue of the helix contains

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10 base pairs. The helix is generated from this residue by a twist of $-41.1°$ and a translation along the helix axis of 0.526 nm. 140 base pairs in this superhelix would contain about $1\frac{1}{2}$ turns and have an axial length of about 8 nm. This axial length is rather sensitively determined by the magnitude of angular unwinding at the kink (i.e. estimated to be about 10°), and could be in error by ± 0.5 nm or so.

An important property of this superhelical DNA structure is its twofold rotational symmetry. This reflects the twofold symmetry relating sugar-phosphate chains at the kink, and the orthogonality of this symmetry axis to the superhelix axis in the κ kinked B DNA structure. Twofold symmetry will almost certainly prove to be an important element governing the organization of the histone–DNA complex within the nucleosome. This feature of chromatin organization, implicit in the Kornberg (1974) model, has been discussed more explicitly in recent models of chromatin and in discussions of protein–nucleic acid interactions in recent years (Weintraub, Worcel & Alberts 1976; Sobell 1976).

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