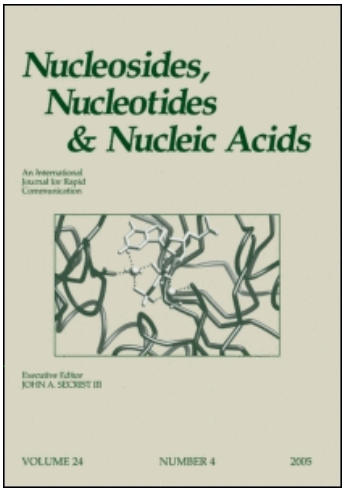

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Structural Studies on Nucleic Acids: From Nucleotides to the Double Helix

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STRUCTURAL STUDIES ON NUCLEIC ACIDS: FROM NUCLEOTIDES TO THE DOUBLE HELIX

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In the field of nucleic acids the nucleoside and nucleotide units represent the lowest level of structural sophistication. Since they play a role in a number of metablic processes as regulators and as coenzymes, their structural properties are as important as those of the polymeric nucleic acids which form single, double, triple and quadruple helices, depending on their nucleotide sequence and composition.

Concerning the nucleosides, there are two main structural parameters, the orientation of the base relative to the sugar which is described by the torsion angle χ about the glycosyl bond, syn or anti, and the sugar puckering mode which can be C2'-endo or C3'-endo or some modification thereof. If phosphate groups are attached at the O3' or O5' position, the orientation of the sugar-phosphate backbone is of importance which is described by the six torsion angles α(P-O5'), β(O5'--C5'), γ(C5'-C4'), δ(C4'-C3'; this torsion angle is determined by the sugar puckering), ε(C3'-O3'), ζ(O3'-P). In double

helical DNA with Watson-Crick base pairs, these torsion angles adopt well defined ranges with α and ζ at -gauche (-g), β at trans, γ at +g, δ at around 120° (C3'-endo sugar or near trans for C2'-endo sugar), and ε is close to 200°.

The RNA double helix occurs only in the A-form where the sugar moieties are in C3'-endo conformation and the base pairs are displaced from the helix axis and tilted by about 20°. DNA is more flexible. The A-DNA prevails under low humidity conditions (high salt) and adopts the same conformation as A-RNA. In contrast, "native" B-DNA which occurs in chromatin and under high humidity conditions, has C2'-endo (or the equivalent C3'-exo) sugar conformation and the base pairs are almost vertical to the helix axis which goes right through the base pairs. In contrast to the A- and B-DNA double helix which display a right handed helical screw sense, the Z-DNA is left handed with the helix axis shifted toward the minor groove of the Watson-Crick base pairs. It is formed by alternating purine/pyrimidine sequences like poly d(G-C) under high salt conditions, with guanosine in syn and cytidine in anti conformation.

In recent years, the advances in oligonucleotide synthesis have provided us with a number of crystal structure analyses which give information about the different DNA structures that were already known from fiber diffraction studies. Although these crystal structures are rather well determined with resolutions around 1.2 Å (for Z-DNA), 1.8 Å (for A-DNA) and 2.0 - 2.5 Å (for B-DNA), there is no information about the location of the counter ions which in most cases are magnesium and sodium. They are disordered in the crystal lattice and

therefore not "seen" in the electron density. In contrast, water molecules are rather well determined. They are hydrogen bonded to the O and N atoms of the bases and of the phosphate groups and their distribution is characteristic of the DNA conformation. In B-DNA, the phosphate groups are separated by about 7 Å and individually hydrated. In A-DNA and Z-DNA, the phosphate groups are closer together due to the different sugar puckering modes, and they are bridged by water molecules. Since the B-DNA conformation with individually hydrated phosphate groups prevails mainly under high humidity conditions (little or no salt) whereas under low humidity or high salt conditions the A-DNA and Z-DNA forms are favoured, the proposal was put forward that the economics of hydration of the phosphate groups is one of the factors that governs the different conformations of DNA. Besides this structure-dependent hydration of DNA, there are sequence-dependent hydration schemes such as the "spine of hydration' in the minor groove of A/T rich regions and water pentagons in the major groove of ATAT sequences of A-DNA.

DNA is not the linear, straight rod as it is usually believed to be. With the new gelelectrophoresis methods, it was found that DNA can have a systematic curvature, if tracts of about 5 adenines occur in phase, i.e. every ten nucleotides. The reason for the curvature is probably that the oligo A tracts are straight DNA with exactly ten base pairs per turn which is not only stabilized by Watson-Crick hydrogen bonding across the base-pairs but also by inter-base pair hydrogen bonds from N6-H of adenine to O4 of thymine in the Watson

Crick sense and in one base pair "up", i.e. the formation of a three-center or bifurcated hydrogen bond. Because the random-sequence DNA adjacent to this oligo A tract adopts the normal conformation with 10.5 base pairs per turn, there is a discontinuity at the junction which leads to the bending.

Another new finding is that DNA can form triple strands. These have previously been observed with synthetic polynucleotides of the form poly A·2polydT. Triple strand formation was also observed in natural DNAs which contain long stretches of alternating polypyrimidine and polypurine sequences such as $(dT\text{-}dC)_n \cdot (dA\text{-}dG)_n$. In the triple stranded H-DNA (hinged DNA), one stretch of the double helix remains and another part opens up and folds back such that the polypyrimidine strand hydrogen bonds in the Hoogsteen mode in the major groove of the Watson-Crick base pairs of the double strand to the polypurine strand to form the triple helix. As a consequence, the polypurine strand, which originally was Watson-Crick base paired to the polypyrimidine strand, is now "free", and not involved in any obvious secondary structure.

Certainly, the story of DNA structure is not yet at its end and it is necessary to study by crystallographic methods more and longer oligonucleotide sequences so that a more complete and systematic picture of local DNA structure as a function of DNA sequence is established. This of course must be embedded in studies on polymer nucleic acids, which have received great potential through the developments of genetic engineering.

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