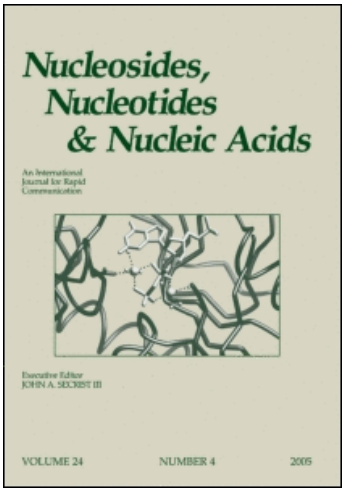

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Four-Stranded Intercalated Cytosine-Rich Molecules: Novel Insights into DNA Structure and Stability

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FOUR-STRANDED INTERCALATED CYTOSINE-RICH MOLECULES: NOVEL INSIGHTS INTO DNA STRUCTURE AND STABILITY

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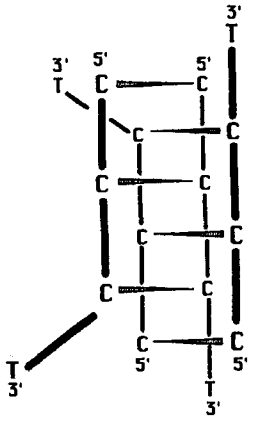
ABSTRACT: DNA fragments with stretches of cytosine residues can form four-stranded intercalated i-DNA molecules stabilized by hemiprotonated cytosine·cytosine$^+$ (C·C$^+$) base pairs. Intriguing features of this motif are the accomodation of base stacking that is unfavorable due to electrostatic repulsion and the close approach of phosphates in narrow grooves of the molecule. Unusual sources of stability in this structure involve sugar-base stacking and CH-O interribose short contacts between the backbones of adjacent strands.

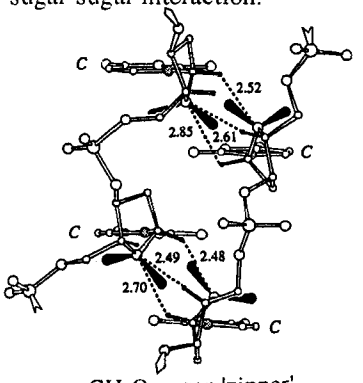
Nucleic acids show enormous conformational variability. An unusual, four-stranded structural motif, i-DNA, has been described in detail in our laboratory and others by high resolution studies of cytosine-rich oligonucleotide sequences.[1-4] In i-DNA, two parallel duplexes held together by hemiprotonated C·C$^+$ base pairs, intercalate into each other with opposite polarity to form a quadruplex. Characteristics of i-DNA are the existence of two broad and two narrow grooves, a stacking distance of 3.1Å, the absence of overlap between aromatic rings of adjacent bases, a slow right-handed helical twist ranging from 12-18°, and a fast proton transfer between the cytosines of hemiprotonated pairs.[1-4] DNA sequences with stretches of cytosine residues occur frequently in the genome of cells, in telomeric and centromeric DNA, as well as gene regulatory regions among others. Structural investigation of several of these sequences and the unusual physiological properties associated with them stimulated speculation about the involvement of i-DNA structures in biological processes.[5,6]



i-DNA quadruplex, d(C_3T)

We have crystallized and solved the three-dimensional structure of a number of cytosine-rich DNA oligonucleotide sequences.[2-5] The crystal structures reveal many details of this intercalated four-stranded DNA. From a chemical point of view, perhaps the most intriguing feature of i-DNA is the stacking of consecutive hemiprotonated base pairs, each carrying a positive charge. This should be associated with a large charge-charge repulsion as fully confirmed by quantum mechanical calculations.[7] Also, the structures show unusually close (5.9Å) interstrand phosphorus-phosphorus distances presumably resulting in further unfavorable electrostatic interactions.[8]

A unique feature of four-stranded intercalated i-DNA is the close contact between pairs of antiparallel sugarphosphate backbones from the two interdigitated duplexes as such close backbone-backbone contacts do not exist in any of the other two-, three- or four-stranded DNA structures. Consequently, in i-DNA, inter-strand phosphorus-phosphorus distances are created that are typically shorter than those between adjacent intra-strand phosphorus atoms in B-DNA.[8] Careful analysis of the geometry of the sugar rings in the narrow grooves of the molecule revealed the existence of CH-O short contacts involving CH1', CH4' hydrogens and O4' oxygen atoms of riboses of the two closely spaced backbones in the narrow grooves of the i-DNA quadruplex.[8,9] These interactions occur in a systematic fashion in the structure and suggest a stabilizing CH-O 'zipper' pairing the antiparallel strands via their riboses not unlike β-sheets in proteins, with a calculated yield of 2kcal/mol per sugar-sugar interaction.[8]



CH-O sugar 'zipper'

Other stabilizing factors in addition to these CH-O short contacts are dipole-dipole and ion-dipole interactions involving exocyclic keto and amino groups of the cytosine bases and stereoelectronic effects involving intra-cytidine C6H6-O4' hydrogen bonds. In addition, at certain base pair steps in i-DNA molecules where base-on ribose stacking occurs we found n-π* conjugations between the O4' lone electron pair and (partial) base double bonds .[8,9]

With the aim to improve our understanding of the sources of stability of i-DNA, we additionally carried out a set of unconstrained molecular dynamics simulations of fully solvated i-DNA molecules.[10] Interestingly, these simulations yielded stable trajectories on a nanosecond scale with exceptionally low rms deviations between the simulated structures and the crystal coordinates used as starting models.[10] This underscores the finding that DNA can

indeed adopt structures with unfavorable base stacking interactions and raises questions about the actual sources of stability of nucleic acids and the validity of current base stacking calculations in the rationalization of DNA structure.

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