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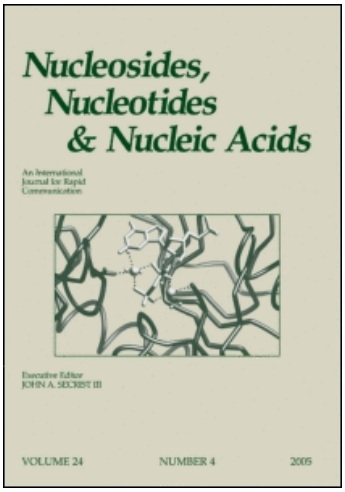

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COMPARISON OF THE MOLECULAR STRUCTURAL PARAMETERS IN THE SPERMINE-BOUND AND SPERMINE-FREE DNA OCTAMER d(GTGTACAC). THE CONFORMATIONAL PLASTICITY OF DNA.

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Abstract: The same DNA octamer sequence crystallizing in two different forms shows conformational differences that can be attributed to differences in the intermolecular contacts in the two crystal forms.

A question of great importance is: to what extent the macromolecular structure in the crystalline state is relevant to the structure in solution and biological state? This question arises because the crystalline forces may affect the molecular structure and conformation. The crystal structure apparently simulates the solution structure to a very large extent, since the macromolecular crystals are highly hydrated and contain a large amount of solvent (about 50% by volume). The x-ray structure thus provides the starting point for the study of the dynamical aspects of the molecule using spectroscopic methods such as NMR. Nevertheless, the crystalline state differs from the solution state in that close contacts between neighboring/symmetry-related molecules are always found, which can cause certain conformational distortions or perturbations of the structure. In contrast, during biological function, the interacting molecules do come into contact, and the crystal structure, therefore, bears some resemblance to it. Thus, the macromolecular strucure in the crystalline state has relevance to both the solution state and the

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biological state. The conformation seen in the crystal should shed important light on the functional state of the molecule.

The conformation of DNA is determined by its sequence. But because of its rod-like structure, the DNA molecule is inherently flexible, even though the individual nucleotide residues are confined to a few preferred conformations[1]. To test the effect of crystalline environment on DNA, we need to crystallize the same DNA sequence in more than one crystal form. We have succeeded in this with the octamer d(GTGTACAC), which has been crystallized in the tetragonal form with a bound spermine and in the hexagonal form without a bound spermine. The crystal structures have been determined at 2Å resolution and refined to agreement indices below 0.15[2,3]. The alternating Pu-Py sequence adopts the right-handed A-DNA structure in both forms. Here we discuss the conformational differences between them that are attributable to differences in the intermolecular contacts in the crystal. In this study, we have also carefully delineated the effects of spermine binding in the tetragonal structure.

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The crystal strucures reveal that the DNA duplexes in the two crystal forms have significant conformational differences (FIG. 1). An examination of the molecular packing of the two crystal forms indicates that, in the tetragonal structure, the diad-related neighbor impinges on the duplex at the third residue (G3) while a conformational distortion occurs at the backbone of the fifth residue (A5), two residues away, where interestingly, there are no direct intermolecular interactions. In the hexagonal form, the intermolecular contact is at residue A5, there is no distortion in the backbone at this central Py-Pu step, but the distortion occurs down the chain at residue A7. The sugar pucker of A7(A15) is C2'-*endo* rather than C3'-*endo* commonly found in A-DNA. The change in sugar pucker results in a concomittant glycosyl torsion angle, giving the C2'-*endo*/high-*chi* combination[1] found in B-DNA. It is interesting that the conformational distortions in both cases occur not at the place of closest intermolecular contacts, but away from it. In the hexagonal structure, the switch in the sugar pucker could be a result of steric compression resulting from intermolecular collision with another neighboring molecule. The spermine binds to the bases of the octamer in the tetragonal form in the deep groove with hydrogen bonds either directly or via water molecules[3]. Besides, there are extra Watson-Crick purine-purine, bifurcated, cross-strand hydrogen bonds. In the hexagonal form, there is no bound spermine eventhough

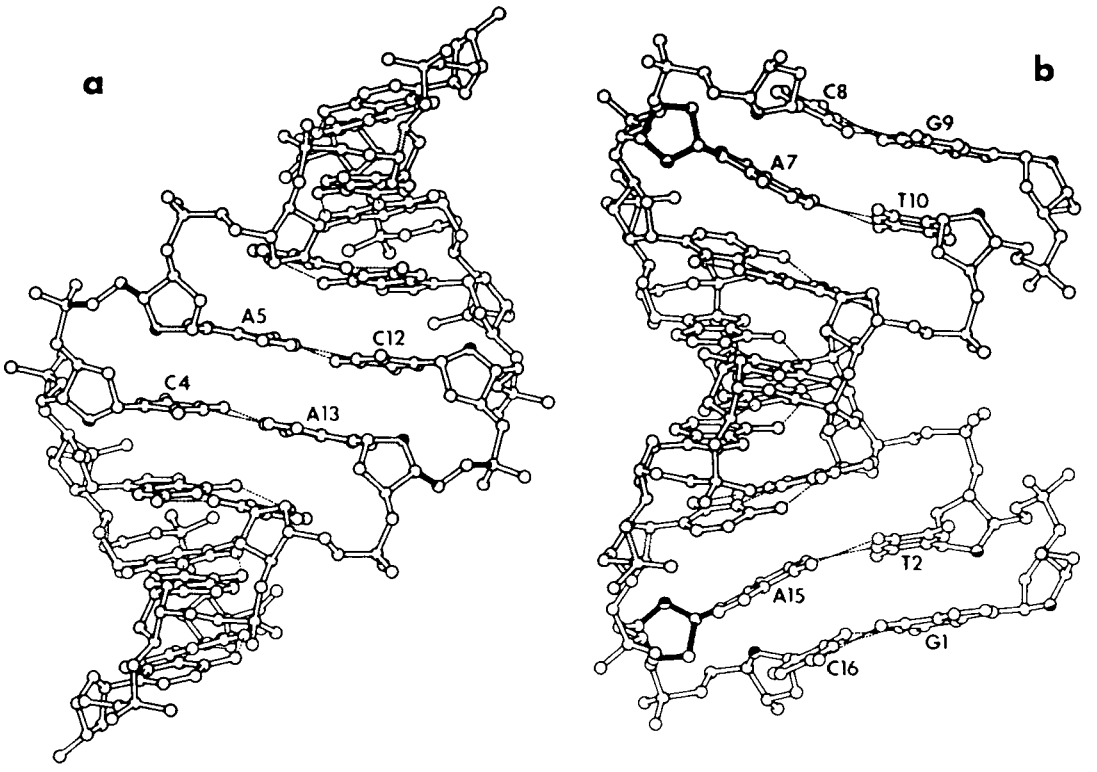

FIG. 1. The structure of the tetragonal form (left) and the hexagonal form (right) of the octamer duplex d(GTGTACAC). The regions in the two structures with conformational distortions are shown in dark bonds.

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it appears to be possible since the deep groove here is exposed and is found to be occupied with only water molecules. The extra Watson-Crick, cross-strand hydrogen bonds between purines here appear to be weaker than in the tetragonal structure. Several other octamers have been found to crystallize in the tetragonal form similar to ours and in all of these structures, including ours, the backbone of the fifth nucleotide residue is *trans*, *trans* around the O5'-P and C5'-C4' bonds respectively. This distortion in the backbone, then, is not spermine induced. Therefore, in our spermine-bound tetragonal structure of d(GTGTACAC), only small conformational changes may have been induced upon spermine binding.

Earlier two other octamers were found to crystallize in a hexagonal form ($P6_1$) but different from our hexagonal form ($P6_122$). In both octamers crystallizing

in $P6_1$, the central step was a Pu-Py sequence and did not exhibit any distortion in the backbone from the expected *gauche-*, *gauche+* conformation. So, it was thought that the distortion was induced by the base sequence difference in the central step from Pu-Py to Py-Pu. However, our hexagonal form has the same sequence as the tetragonal form, with a central Py-Pu step, but is not distorted. This then indicates that the conformational distortion in the central step is not generated by base sequence differences, but produced as a result of crystal packing.

The conformational distortions of the backbone of the two structures are further reflected in the differences in the helical and base-pair parameters. There are significant variations in the twist and roll angles between the tetragonal and hexagonal forms. The propeller twists have larger values for the G-C base pairs than for the A-T pairs in both crystal forms (average value of GC/AT: 12.4/9.1° for tetragonal and 15.4/10.8° for hexagonal), contrary to what is expected. Details of the comparisons will be published elsewhere[4].

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