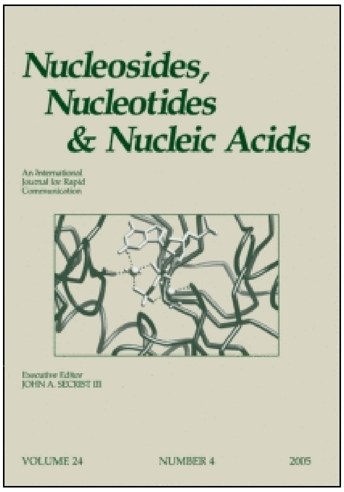

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To Wobble or Not to Wobble: Modified Bases Incorporated into DNA

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TO WOBBLE OR NOT TO WOBBLE: MODIFIED BASES INCORPORATED INTO DNA

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Abstract. The ambivalent base analogue P was incorporated in the d(CGCGPG) hexamer to investigate the G.P base pair geometry by X-ray diffraction. Both Watson-Crick and wobble geometries have been found for the crystallographic independent G.P base pairs.

Among base analogue mutagens, N^4-hydroxy- and N^4-methoxycytosine (mo^4C) have been much studied. The general explanation for their action is that since their tautomeric constants are in the region of 10-100 (in favor of the imino-form), the free energy difference between the two tautomers is small and that, in the latter case, Watson-Crick $mo^4C.A$ and $mo^4C.G$ base pairs should be of closely similar stabilities[1]. However, the preferred *syn* conformation of the methoxyl group with respect to N1 is destabilising, and in a crystallographic study of the Z-type duplex d(CGCGmo^4CG) the $mo^4C.G$ base pair is in the wobble conformation with the methoxyl group *syn*[2].

The related analogue P in which the N-O bond is *anti* gives much more stable duplexes when paired with both G and A. P is more T-like than C-like[3], and in an NMR study the A.P base pair was shown to be isostructural with A.T in a B-type octamer[4]. In the same duplex background, the G.P pair showed slow chemical

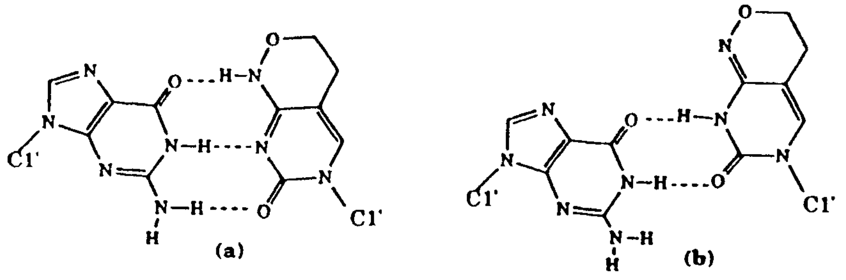

FIG. 1: Watson-Crick (a) and wobble type (b) conformation of G.P base-pairs in DNA

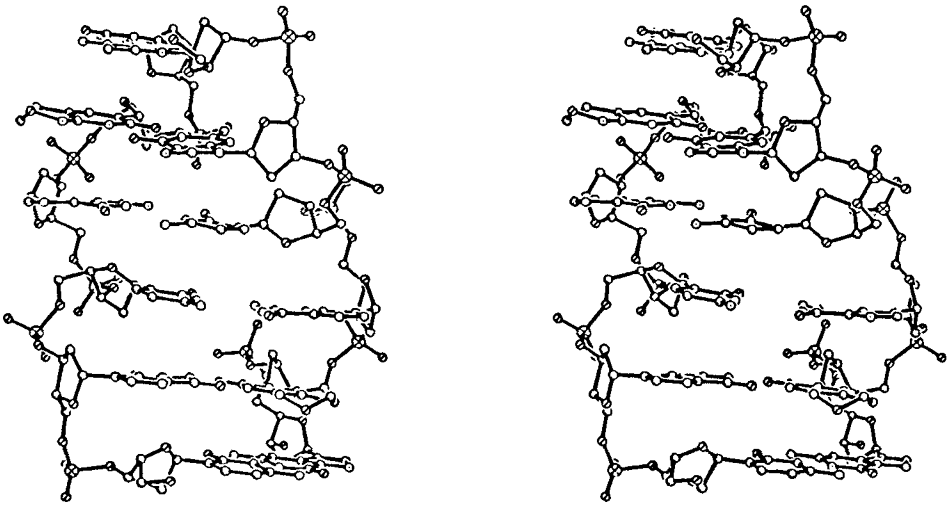

FIG. 2: Stereoscopic view of the hexamer d(CGCGPG) Z-DNA double helix

exchange[5] between Watson-Crick (FIG. 1a) and wobble conformations (FIG. 1b), and a related NMR study showed similar behavior of the mo^{4}C.G base pair[6].

To extend the crystallographic study, the structure of the duplex d(CGCGPG) has been determined by single crystal X-ray diffraction. The self-complementary d(CGCGPG) crystallizes as a left-handed Z-DNA double helix (FIG. 2). Refinement using 2798 reflections between 8 and 1.7Å converged to R=0.179 with the inclusion of 51 solvent molecules.

The most obvious and surprising result is that one of the P.G base pairs is of the Watson-Crick type (FIG. 1a), with the P base in the amino-form. The other, crystallographically independent, is of the wobble type (FIG. 1b), with the P base in the imino-form. The C4-N4 bond lengths, 1.44Å and 1.31Å respectively, are consistent with this.

In the NMR solution study, the G.P base pair interconversion must be accounted for by solvent catalysis, a situation that is not available in the crystal lattice where the two base pair conformations are frozen. The ordered crystal structure in which the molecular duplex twofold symmetry is broken must depend on intermolecular interactions. We are investigating this aspect of the structure further.

The present structural study confirms that in DNA, G.P, like the A.P base pair, can exist in a Watson-Crick conformation. In accord with this, it has recently been found that the P nucleoside is a powerful base analogue transition mutagen in *E. coli*[7].

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