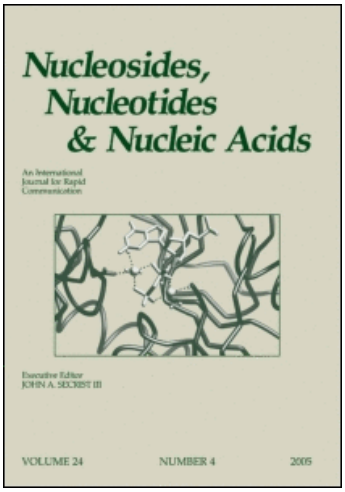

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Molecular and Crystal Structure of d(CGCGmo⁴CG): N⁴-Methoxy-cytosineguanine Base Pairs in Z-DNA

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MOLECULAR AND CRYSTAL STRUCTURE OF d(CGCGmo^{4}CG) : N^4-METHOXYCYTOSINE-GUANINE BASE PAIRS IN Z-DNA.

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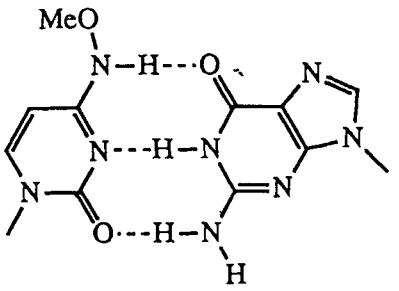
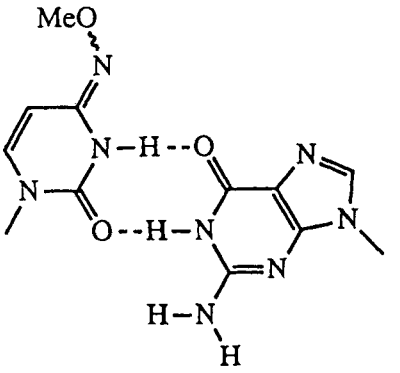
ABSTRACT. The base analogue N^4-methoxycytosine (mo^{4}C) is ambivalent in its hydrogen-bonding potential. In d(CGCGmo^{4}CG) it is in the imino form and so mimics thymine when wobble base pairing with guanine.

The design of oligonucleotide probes based on protein amino acid sequences is complicated by the genetic code redundancy. Mixed probes in which all codon assignments are taken into account are commonly used[1]. An alternative approach utilises base analogues which are degenerate in their hydrogen bonding potential. For example N^4-methoxycytosine has a K_T value[2,3] close to unity. Therefore it may Watson-Crick base pair with adenine or guanine, but a wobble structure may also exist. Melting studies and dot blot hybridisation experiments have shown that duplexes containing N^4-methoxycytosine base paired with adenine and guanine have comparable stability to those containing natural base pairs[4].

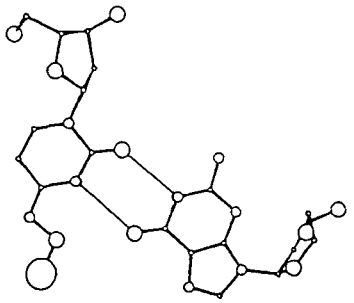


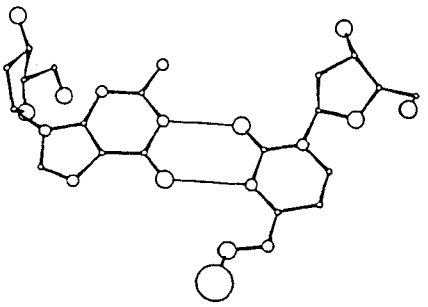
mo^{4}C-G Watson-Crick pair



mo^{4}C-G wobble pair

The hexamer d(CGCGmo^{4}CG) was synthesised by automated phosphoramidite methodology, purified by chromatography and crystallised in space group $P2_12_12_1$ with a=18.17, b=30.36, c=43.93Å. Intensities were collected on a Syntex $P2_1$ diffractometer at 4°C to 1.7Å resolution using an ω-scan mode with CuKα radiation. A semi-empirical absorption correction was applied. The structure was solved by molecular replacement (MERLOT) using the Z-DNA hexamer as a model, and refined by restrained least-squares (NUCLSQ). No hydrogen bond restraints were used to avoid any bias towards a particular mo^{4}C-G pairing. Because of the unknown stereochemistry of the methoxy group a cytosine moiety was used for the mo^{4}C base. Electron density maps, displayed on an E&S PS390 clearly indicated a wobble base pair geometry. During the refinement peaks in agreement with a syn stereochemistry were located in F_O-F_C maps. Refinement using 2559 reflections in the range 10-1.7Å converged with a final R=0.17 (Rw=0.13) including 79 solvent molecules. The mo^{4}C base mimics thymine when wobble base pairing with guanine, causing only a small distortion of the backbone in comparison with the parent sequence d(CGCGCG)[5].





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