s8a.m6.p5 **The structure of double helical Hexitol Nucleic Acids**. R. Declercq, L. Van Meervelt, *Biomolecular Architecture, Chemistry Departmen,t K.U. Leuven, Celestijnenlaan 200F, B-3001 Leuven, Belgium.*
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Antisense oligonucleotides are designed to hybridize to target mRNA sequences, and hence will inhibit the translation process. In order to overcome problems of low stability and cellular uptake of antisense drugs, modifications of the classical DNA backbone are necessary. Hexitol nucleic acids (HNA) are such modifications in which an extra methylene group is inserted between C1' and O4' of the β-D-2'-deoxyribose unit.

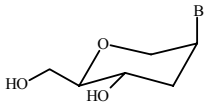

Figure 1: 1,5-anhydrohexitol building block for HNA

Crystals of h(GTGTACAC) were obtained by the hanging drop vapor-diffusion technique using a 24- matrix screen for nucleic acid fragments. Two distinctive forms were observed, hexagonal- and needle-shaped crystals.

The hexagonal-shaped crystals belong to space group $P6_222$ and diffract up to 2.21Å, while the space group $P3_212$ was found for the needle-shaped crystals diffracting up to 1.60Å. In both forms the octamer adopts an antiparallel right-handed double helix with normal base pairing and stacking, but high x-displacement. The hexitol rings adopt a chair conformation with the bases in the anti orientation. Analysis of torsion angles and helical parameters reveals a conformation as typically observed for A-type helices. The shallow minor groove is poorly hydrated which can be rationalized by the increased hydrophobicity of the HNA minor groove as compared to A-DNA.

The most significant difference between both crystal forms is observed when comparing inclination, twist and rise, resulting in a seriously underwound $P3_212$ form. End-to-end stacking of terminal base pairs gives rise to continuous helices throughout the crystal. The low twist and rather wide and deep major groove in the $P3_212$ structure permit the formation of a double helix of double helices in the crystal packing.

Both HNA conformations will be compared with their natural analogues and known HNA-RNA and HNA-DNA duplexes obtained by NMR techniques and molecular dynamics simulations.