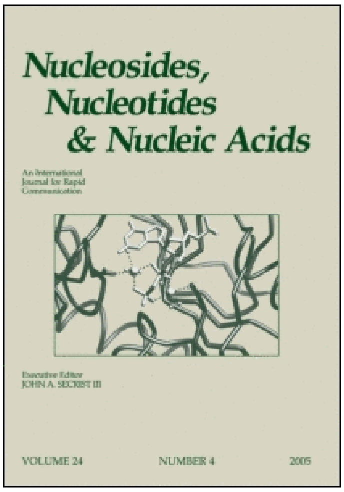

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α-DNA. Synthesis, Characterization and Base-Pairing Properties of Unnatural α-Oligodeoxyribonucleotides

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α-DNA. SYNTHESIS, CHARACTERIZATION AND BASE-PAIRING PROPERTIES OF UNNATURAL α-OLIGODEOXYRIBONUCLEOTIDES.

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Abstract : The novel hexadeoxyribonucleotides α-d(CpCpTpTpCpC) and α-d(CpApTpGpCpG), in which each glycosidic linkage exhibit the anomeric α-configuration, were synthesized by the phosphotriester method. ^{1}H-NMR and thermal denaturation studies provided evidence for these α-oligonucleotides to exhibit a secondary structure similar to that of the natural nucleic acids.

The aim of this work was to synthesize unnatural oligodeoxyribonucleotides consisting exclusively of α-nucleotide units, to test their substrate activities towards nucleases and to study their structure and conformation, as well as their ability to form duplexes with complementary β- or α-strands.

Starting from N-protected α-deoxy-2'-ribonucleosides, the corresponding fully-protected α-nucleotides were prepared by selective 5'-O-tritylation and 3'-O-phosphorylation. The α-hexadeoxyribonucleotides α-d(CpCpTpTpCpC) and α-d(CpApTpGpCpG) were synthesized[1] by the classical phosphotriester method, using MSNT as coupling agent.

Enzymatic studies indicated that both α-hexamers were completely resistant to calf spleen phosphodiesterase while they were degradated by *crotalus durrissus terrificus* snake venom phosphodiesterase and alkaline phosphatase, yielding the expected α-nucleoside ratio. However the rate of hydrolysis of these α-strands is considerably smaller than that of the analogous β-strands. The higher hypochromicity as determined for α-d(CpApTpGpCpG) (19.5%) compared to that of the analogous β - strand (14.2%) may reflect a higher degree of base stacking in the former strand.

^{1}H-NMR NOE examination of α-d(CpCpTpTpCpC) strand indicate that all the bases adopt the *anti* conformation ; the furanose ring of thymidine moieties probably adopt a $C_{3'}$-*endo* conformation and the cytidine furanose groups are close to $C_{2'}$-*endo* conformations. Both hyperchromicity in thermal melting and detection of base paired imino protons in ^{1}H-NMR studies provided evidence for annealing of α-d(CpCpTpTpCpC) and β-d(GpGpApApGpG).

In conclusion, unnatural oligodeoxyribonucleotides consisting exclusively of α-nucleotide units have been synthesized by the phosphotriester approach. Thermal denaturation, enzymatic and ^{1}H-NMR studies provided evidence for α-oligodeoxynucleotides to exhibit a secondary structure similar to that of the natural nucleic acids, featuring base stacking, base pairing and duplex formation with β-strands.

Work is in progress in order to determine the polarity of the strands in α,β- and α,α-duplexes as well as the thermal stability of these duplexes.

REFERENCES

1. F. Morvan, B. Rayner, J.-L. Imbach, D.-K. Chang and J.W. Lown, *Nucl. Acid Res., 14,* 5019 (1986).