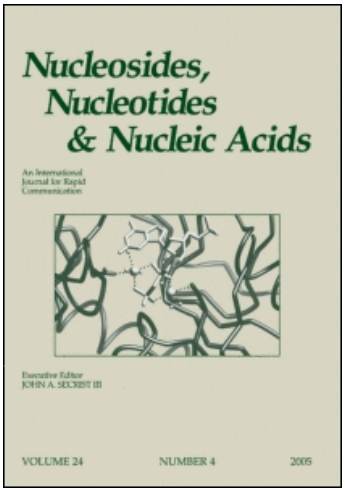

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Synthesis and Hybridization Properties of Oligonucleotide Analogues Containing Ornithine Backbone Modified with Nucleoalanines

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Key Words: Oligonucleotide analogues; Nucleopeptides; Nucleoalanines; Ornithine peptides.

The oligonucleotide analogues in which the entire phosphodiester backbone is replaced by a polyamide or peptide chain attract increasing attention as potential tools in molecular biology and as gene-targeted drugs. Among such analogues containing peptide chain, namely, oligonucleopeptides (ONPs), oligomers constructed on an β-amino alanine[1] and δ-ornithine[2] backbones demonstrated a good specific affinity to complementary nucleic acids. As a part of our studies on design and preparation of nucleopeptides[3,4] we report the synthesis and hybridization properties

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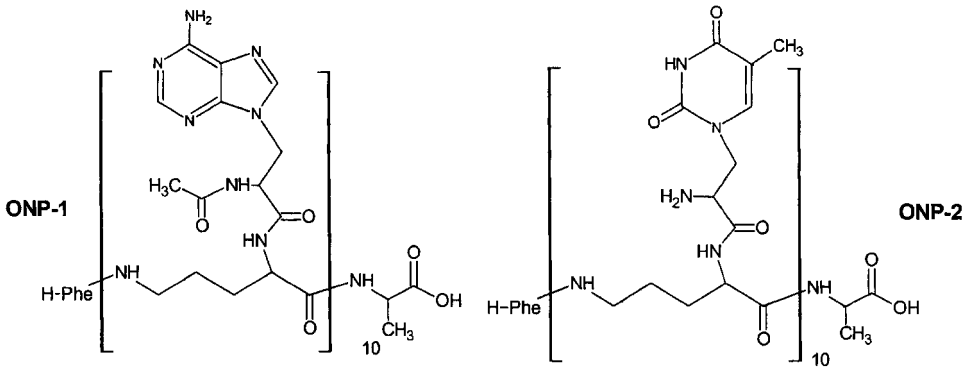

investigations of ONPs based on δ-ornithine decapeptides modified by nucleoalanines: D-3-(adeninyl-9)alanine (Aal) and L-3-(thyminyl-1) alanine (Tal).

Deca-δ-ornithine was synthesized by a solid phase procedure on a PAM resin modified with alanine, using HBTU as the coupling agent and Fmoc- and Boc-groups for protection of the α- and δ-ornithine amino functions, respectively. After Fmoc-deprotection of the peptidyl-polymer, α-amino groups of ornithine residues were acylated with Ac-D-Aal (ONP-1) or Boc-L-Tal (ONP-2). The mixture of trifluoromethanesulfonic acid and TFA effected a simultaneous release of the Boc-side chain protecting groups and the nucleopeptides from the resin.

Hybridization of ONP-1 and ONP-2 with complementary DNA and between themselves were examined by UV melting measurements. The solutions were prepared in a 50mM Tris-HCl buffer (pH 7.0) containing 100mM NaCl and 20mM $MgCl_2$, the concentration of each oligomer strand was 1.5×10^{-6} M; the complex formation was carried out by the slow fall of the solution temperature from ambient to 3°C during 6 h. Free energy values for the duplex dissociation were derived by computer-fitting the melting curves, using the two-state model.[5] These studies indicated that ONP-1 and ONP-2 have formed strong duplexes with complementary oligonucleotides and between themselves with T_m values comparable or higher than that for the natural DNA double strand (after a duplex system the Tm (K) and $-\Delta G^\circ_{298}$ (kJ mol^{-1}) values are indicated): ONP-1/dT_{12}, 289, −3,5; ONP-2/dA_{12}, 323, 23,9; ONP-1/ONP-2, 334, 16,5; dT_{10}/dA_{12}, 307, 32,2.

Our results show that the melting temperatures of an ONP/DNA and a DNA/DNA duplexes don't always yield a reliable estimate of the binding affinity of a ONP or a DNA to a complementary DNA sequence at ambient temperature, so, for ONP-2/dA_{12} duplex $-\Delta G^\circ_{298}$ is lower than for dT_{10}/dA_{12} duplex in spite of its high melting temperature. This discrepancy conforms to the slow kinetic ONP/DNA complex formation.

It should be noted that the synthesized ONP have the same geometric parameters of the monomer unit (the number of ordinary bonds between the nucleobases is six and the number of bonds between the backbone and a nucleobase is five) that the ONPs based on an β-amino alanine backbone which were the most effective peptide analogues of oligonucleotides for their ability to form complementary complexes with nucleic acids.[2]

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