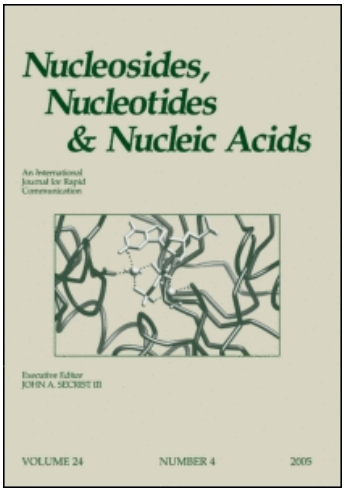

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Structural Characterization of LNA and α-L-LNA Hybridized to RNA

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Structural Characterization of LNA and α-L-LNA Hybridized to RNA

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ABSTRACT

LNA and α-L-LNA are promising candidates for the development of efficient oligonucleotide-based therapeutic agents. Here, we present a short overview of the structural results we have obtained for LNA:RNA and α-L-LNA:RNA hybrids. Specifically, we have shown that LNA acts as an A-type mimic, while α-L-LNA acts as a B-type mimic when built into oligonucleotides.

Key Words: LNA; α-LNA; NMR spectroscopy; Structure.

INTRODUCTION

LNA[1] (locked nucleic acid) and α-L-LNA[2] (α-L-*ribo* configured LNA) are diastereoisomeric oligonucleotide analogues, both of which display high-affinity recognition of RNA. Recently, the therapeutic potential of LNA has been described in various papers (reviewed in Ref.[3]).

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METHODS

NMR studies have been performed using standard 2D NOESY, DQF-COSY and E-COSY spectra. 2D NOE cross peaks have been converted to inter-proton distances using algorithms accounting for spin-diffusion, thus yielding accurate distance bounds for inclusion in simulated annealing protocols. Sugar puckers have been determined by simulation of COSY type spectra.

RESULTS

We have determined high-resolution NMR structures of various nonamer LNA:RNA and α-L-LNA:RNA hybrids and the main results of our studies are summarized below.[4]

i) LNA:RNA hybrids have A-type duplex geometries as gauged by for example wide minor grooves and *N*-type sugar puckers.
ii) LNA monomers perturb neighbouring sugars towards *N*-type sugar pucker.
iii) Three LNA monomers interspersed in a nonamer LNA:RNA hybrid shift the duplex geometry into an almost canonical A-type geometry. This is due to the locked *N*-type conformation of LNA and because LNA monomers, in addition, steer neighbouring sugars into *N*-type puckers.
iv) LNA monomers fit perfectly into an A-type geometry.
v) α-L-LNA:RNA hybrids possess a duplex geometry intermediate between A- and B-type duplex geometry, as do native DNA:RNA hybrids.
vi) α-L-LNA monomers do not perturb neighbouring sugars.
vii) In order to present the nucleobases in geometries suitable for Watson–Crick base pairing and stacking, the phosphate backbone is rearranged in α-L-LNA strands.

CONCLUSION

Our structural studies have shown that LNA fits seamlessly into an A-type duplex geometry, while α-L-LNA acts as a B-type mimic when built into oligonucleotides.

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