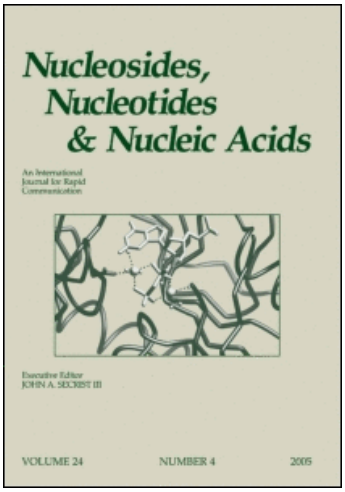

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

α-LNA (α-D-Configured Locked Nucleic Acid)

Nanna K. Christensen[a]; Michael Petersen[a]; Birte Vester[b]; Poul Nielsen[a]
[a] Nucleic Acid Center, Department of Chemistry, University of Southern Denmark, Odense M, Denmark [b] Nucleic Acid Center, Department of Biochemistry and Molecular Biology, University of Southern Denmark, Odense M, Denmark

Online publication date: 09 August 2003

To cite this Article Christensen, Nanna K. , Petersen, Michael , Vester, Birte and Nielsen, Poul(2003) 'α-LNA (α-D-Configured Locked Nucleic Acid)', Nucleosides, Nucleotides and Nucleic Acids, 22: 5, 1143 — 1145
To link to this Article: DOI: 10.1081/NCN-120022821
URL: http://dx.doi.org/10.1081/NCN-120022821

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 22, Nos. 5–8, pp. 1143–1145, 2003

α-LNA (α-D-Configured Locked Nucleic Acid)

Nanna K. Christensen,[1] Michael Petersen,[1] Birte Vester,[2] and Poul Nielsen[1,*]

[1]Nucleic Acid Center, Department of Chemistry, and
[2]Nucleic Acid Center, Department of Biochemistry and Molecular Biology,
University of Southern Denmark, Odense M, Denmark

ABSTRACT

Two pyrimidine α-LNA nucleoside monomers have been synthesised and incorporated into α-configured oligonucleotides. A fully modified mixed α-LNA sequence displays unprecedented parallel stranded hybridisation with complementary RNA and a remarkable selectivity for RNA over DNA. Modelling shows α-LNA : RNA to form an extended duplex with a very broad major groove.

Key Words: Locked nucleic acid; Parallel duplexes; Selective RNA-recognition.

LNA (Locked Nucleic Acid) is a nucleic acid analogue that displays unprecedented recognition of both single stranded DNA and RNA in all-modified LNA-oligomers as well as in LNA/DNA and LNA/RNA-mixmers.[1,2] The LNA monomers are bicyclo[2.2.1] nucleosides locked in an N-type conformation.[1,2] α-DNA, i.e., α-D-configured oligodeoxynucleotides, forms stable parallel stranded duplexes with complementary DNA and RNA.[3] Conformationally restricted analogues of

*Correspondence: Poul Nielsen, Nucleic Acid Center, Department of Chemistry, University of Southern Denmark, DK-5230 Odense M, Denmark; Fax: +45 66 15 87 80; E-mail: pon@chem.sdu.dk.

DOI: 10.1081/NCN-120022821
1525-7770 (Print); 1532-2335 (Online)

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Table 1. Buffer: Na_2HPO_4 (10 mM), NaCl (100 mM), EDTA (0,1 mM), pH 7.0; 1.5 μM of each strand. All detected T_M's were enhanced 3–6°C in a high salt buffer (NaCl, 750 mM). Boldface letters ~α-LNA.

T_m (ΔT_m per modification)/°C		Parallel DNA	ap DNA	Parallel RNA	ap RNA	Mismatch RNA (A to C)
α-DNA	5′-α-^{m}CT^{m}C^{m}CTT^{m}CTTT	43.0	< 10	32.0	< 10	
α-DNA/	5′-α-^{m}CT^{m}C^{m}CT**T**^{m}CTTT	30.5 (−12.5)	< 10	26.0 (−6.0)	< 10	
α-LNA	5′-α-^{m}C**T**^{m}C^{m}C**TT**^{m}C**TTT**	< 10	< 10	22.0 (−1.7)	< 10	
mixmers						
α-LNA	5′-α-**^{m}CT^{m}C^{m}CTT^{m}CTTT**	< 10	< 10	**61.5 (+2.9)**	< 10	47.0

α-DNA that contains bicyclic α-configured nucleosides have been introduced.[4,5] However, these have been restricted towards S-type conformations[4,5] which are also the conformations preferred by α-DNA. Subsequently, α-LNA is the first α-DNA analogue to be restricted in an N-type conformation due to the locked bicyclic carbohydrate skeleton.[6,7]

The successful synthesis of the α-LNA thymine monomer was accomplished from diacetone-α-D-allose through standard steps ending with a Vorbrüggen nucleobase coupling reaction, a ring-closing reaction and, subsequently, separation of the α- and (β-) LNA monomers.[6,7] The former was DMT-protected and converted by standard steps into two different phosphoramidites of either the thymine or the *N*-4-benzoyl-5-methylcytosine α-LNA monomers.[7] These as well as the two corresponding α-DNA phosphoramidites were used as building blocks for oligonucleotide sequences (Table 1).[7]

In α-DNA/α-LNA mixmers, the exchange of one or six α-DNA monomers with α-LNA monomers results in strongly decreased affinity against both DNA and RNA when compared to the unmodified α-DNA sequence. On the other hand, a fully modified mixed α-LNA sequence shows no recognition of DNA but a very strong recognition of RNA. This strong preference for RNA as well as for parallel over antiparallel duplex formation was confirmed by the use of a gel shift analysis. MD-simulations were performed assuming Watson-Crick base pairing (as no change in T_M was detected when lowering pH from 7 to 5) and suggested the α-LNA/RNA duplex to be an extended duplex with a major groove width of 20 Å and the nucleobases of the α-LNA monomers in *syn*-positions. Other duplex parameters were close to normal A- or B-type duplexes.

ACKNOWLEDGMENTS

The Nucleic Acid Center is funded by the Danish National Research Foundation for the studies on nucleic acid chemical biology.

REFERENCES

1. Koshkin, A.A.; Singh, S.K.; Nielsen, P.; Rajwanshi, V.K.; Kumar, R.; Meldgaard, M.; Olsen, C.E.; Wengel, J. Tetrahedron **1998**, *54*, 3607–3630.
2. Obika, S.; Nanbu, D.; Hari, Y.; Andoh, J.; Morio, K.; Doi, T.; Imanishi, T. Tetrahedron Lett. **1998**, *39*, 5401–5404.
3. Morvan, F.; Rayner, B.; Imbach, J.-L.; Chang, D.-K.; Lown, J. Nucleic Acids Research **1986**, *14*, 5019–5035.
4. Bolli, M.; Lubini, P.; Leumann, C. Helv. Chim. Acta **1995**, *78*, 2077–2096.
5. Keller, B.M.; Leumann, C. J. Synthesis **2002**, 789–796.
6. Nielsen, P.; Dalskov, J.K. Chem. Commun. **2000**, 1179–1180.
7. Nielsen, P.; Christensen, N.K.; Dalskov, J.K. Chem. Eur. J. **2002**, *3*, 712–722.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016