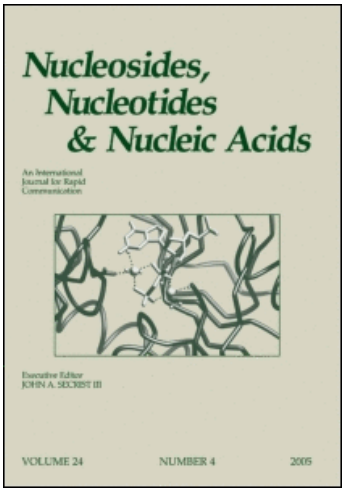


**Nucleosides, Nucleotides and Nucleic Acids**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

# A New Strategy for DNA Inhibition with Backbone Substituted DNA Analogues

H. M. Buck[a]
[a] Kasteel Twikkelerf, TW Tilburg, The Netherlands

**To cite this Article** Buck, H. M.(1999) 'A New Strategy for DNA Inhibition with Backbone Substituted DNA Analogues', Nucleosides, Nucleotides and Nucleic Acids, 18: 6, 1397 — 1398
**To link to this Article: DOI:** 10.1080/07328319908044729
**URL:** http://dx.doi.org/10.1080/07328319908044729

NUCLEOSIDES & NUCLEOTIDES, 18(6&7), 1397–1398 (1999)

# A NEW STRATEGY FOR DNA INHIBITION WITH BACKBONE SUBSTITUTED DNA ANALOGUES

H.M. Buck*
Kasteel Twikkelerf 94, 5037 TW Tilburg, The Netherlands

**ABSTRACT:** Methylphosphotriester DNA shows a number of unique (bio)chemical properties: formation of parallel right-handed, anti-parallel left- and right-handed duplexes, and a high sequence-specific affinity for natural DNA. The impact of (*pro*)chirality of phosphorus in natural and modified DNA is discussed.



Recently, we reviewed the (bio)chemical properties of methylphosphotriester DNA.[1,2] It is shown that this triester stores a number of unique properties compared to other uncharged modified DNA's. We mention the duplex formation of *right-handed parallel*-stranded oligonucleotides based on the formation of a T-T (U-U) and a C-C base pair with two equivalent hydrogen bonds and *antiparallel*-stranded *left-handed* duplexes (Z-DNA). The stereopreference for the $S_P$-chirality of phosphorus is demonstrated in parallel duplexes of C-C base pairs, in the Z-isomers, and in the methylphosphotriester DNA repair in *Escherichia coli* Ada.[3] The strong hybridization affinity of methylphosphotriester DNA with natural DNA in a *right-handed anti-parallel* duplex occurs for *short* fragments *without* the influence of phosphorus chirality. From the affinity studies for the complementary base ratio 1:1 in d($[C_P(O)OMe]_{n-1}C$). poly(dG) and d($[A_P(O)OMe]_{n-1}A$). poly(dT) a linear relationship between the melting temperature ($T_m$) and the number of bases (n = 2-5) is established (the ratio of the slopes approaches the expectation value of 1.5) with a maximum $T_m$-value of 90-100°C. With RNA as template a maximum in duplex stability is found for n = 2 (poly(rG) : $T_m$ = 28°C and poly U : $T_m$ = 13°C). The biological impact has been demonstrated : methylphosphotriester DNA exclusively reduces DNA synthesis whereas the protein synthesis is found to be essentially unaffected. Apparently, the constraints which methylphosphotriester DNA perceives in duplex formation with natural DNA (B-type) becomes more pronounced in a duplex with RNA (A-type).

The synthesis of *long* fragments methylphosphotriester DNA failed (except for C,T bases [4]): it must be noticed that sequence-specific inhibition which was found in a great variety of biological experiments must be ascribed to the presence of its complementary natural DNA under high (in)organic salt condition (increase of the $T_m$-value by anionic and/or hydrogen-bond shielding).[5-8]

We will focus the attention on two aspects. The role of short fragments of methylphosphotriester DNA having the correct geometry and correspondingly high affinity for natural DNA and the possible significance of parallel DNA under biological conditions.

Short fragments are a realistic alternative for modified DNA's which must be 16-30 nucleotides in length to show useful selectivity. The results for the short fragments point to the importance of a *cooperative* process which means that even short fragments of methylphosphotriester DNA in succession hybridized with natural DNA not only give rise to an increase in duplex stability, but that these short fragments should also be more sensitive for mismatches. Deviation from the geometry of natural DNA by backbone modification resulting in *specific* biological effects has been recently demonstrated and their application as *short* modified oligonucleotide for an effective binding with natural oligonucleotides has been suggested.[9]

The significance of parallel DNA under biological conditions is still an open question however T-T and C-C base pairing is possible for natural DNA in the presence of specifically defined cationic oligopeptides. With nucleotides as $dC_{10}$ , $d(C_6T_6)$ and $d(T_6C_2T_2)$ parallel duplex formation occurs in the presence of $Lys_{18}$ and not for $Orn_{18}$ whereas $dT_{10}$ forms a parallel duplex with both oligopeptides. Model studies show that in the case of $Orn_{18}$ complexation must occur with one of the non-bonded oxygens in the phosphate with the unfavourable $O_R$ - *pro*chirality thereby precluding C-C base pair formation. So there is a stereochemical analogy with the parallel duplexes of the corresponding methylphosphotriester DNA's. Via temporary fixation of the genetic information based on pairs of T-T and C-C it is possible then that the parallel DNA duplexes interfere with various levels of genetic processes resulting, for instance, in a mRNA with parts of GA deletion which is a characteristic of Alzheimer 's disease.[10]

Therefore it is of interest to mention recent results which show that synthetic polyamides containing *N*-methylimidazole and *N*-methylpyrrole amino acids have a sequence-specific affinity for natural antiparallel DNA duplexes.[11]



## REFERENCES

(1) Buck, H.M. *Proc.Kon.Ned.Akad. van Wetensch.*, **1996,** *99*, 145-153.
(2) Buck, H.M. *Proc.Kon.Ned.Akad. van Wetensch.*, **1997**, *100*, 1-9.
(3) Myers, L.C.; Terranova, M.P.; Ferentz, A.E.; Wagner, G.; Verdine, G.L. *Science, **1993,** 261*, 1164-1167.
(4) Koole, L.H.; van Genderen, M.H.P.; Buck, H.M. *J.Am.Chem.Soc., **1987**, 109*, 3916-3921.
(5) Moody, H.M.; Quaedflieg, P.J.L.M.; Koole, L.H.; van Genderen, M.H.P.; Buck, H.M.; Smit, L.; Jurriaans, S.; Geelen, J.L.M.C.; Goudsmit, J. *Science*, **1990**, *250*, 125.
(6) Moody, H.M.; van Genderen, M.H.P.; Koole, L.H.; Kocken, H.J.M.; Meijer, E.M.; Buck, H.M. *Nucleic Acids Res.*, **1989**, *17*, 4769-4782.
(7) Vanhommerig, S.A.M.; van Genderen, M.H.P.; Buck, H.M. *Proc.Kon.Ned.Akad. van Wetensch.*, **1990**, *93*, 197-202.
(8) Vanhommerig, S.A.M.; van Genderen, M.H.P.; Buck, H.M. *Biopolymers*, **1991**, *31*, 1087-1094.
(9) Blättler, M.O.; Wenz, C.; Pingoud, A.; Benner, S.A. *J.Am.Chem.Soc.*, **1998**, *120*, 2674-2675.
(10) Vogel, G. *Science*, **1998**, *279*, 174.
(11) Gottesfeld, J.M.; Neely, L.; Trauger, J.W.; Baird, E.E.; Dervan, P.B. *Nature*, **1997**, *387*, 202-205.