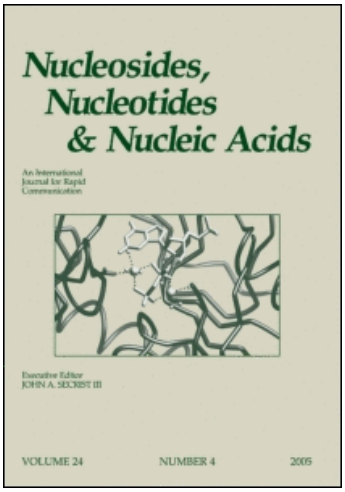

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Boranophosphate Nucleic Acids - A Versatile DNA Backbone

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BORANOPHOSPHATE NUCLEIC ACIDS - A VERSATILE DNA BACKBONE

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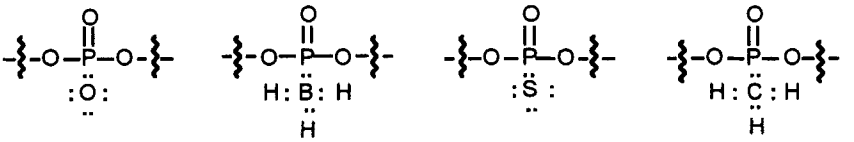
ABSTRACT: Important chemical and biochemical properties of boranophosphate DNA and RNA oligonucleotides are reviewed. Stereoregular boranophosphate oligomers can be synthesized enzymatically and form stable duplexes with DNA. Fully boronated, non-stereoregular oligothymidylates, synthesized chemically, form hybrids with poly(A) that have lower melting points than oligothymidylate:poly(A), yet they nevertheless can support the RNase H mediated cleavage of RNA.

INTRODUCTION: In boranophosphate oligodeoxyribonucleotides (BH_3–ODN) one of the phosphoryl oxygen atoms of a natural oligodeoxyribonucleotide (O–ODN) is replaced with a borane (BH_3) group.[1] Boranophosphates are isosteric with methylphosphonates and isoelectronic with normal phosphates, methylphosphonates, and phosphorothioates (Fig. 1).[1] BH_3-ODN carry a full negative charge and are water soluble, yet intermediate between normal phosphates and methylphosphonates in lipophilicity. The boronated TpT dimer is 18-fold more lipophilic and orders of magnitude more resistant to exo and endonucleases than natural TpT. The boranophosphate linkage is stable in acids or bases.

Fig. 1. Comparative structures of modified oligonucleotides



The single crystal X-ray structure and *ab initio* calculations of dimethyl-boranophosphate anion reveal some structural differences with the normal phosphate linkage. The 1.905 Å P–BH_3 bond is longer and less polar than the 1.51 Å P–O bond of the analogous normal phosphate diester.[2] Nonenzymatic hydrolysis of thymidine 5'-boranomonophosphate ($dTMP^B$) in both protic and aprotic solvents yields only thymidine

and not thymidine 5'-monophosphate, indicating that the P–BH_3 bond is more stable hydrolytically than the P–OR bond in $dTMP^B$.[3]

An effective chemical method of synthesis of non-stereoregular BH_3-ODN has been developed using an H-phosphonate chain elongation approach followed by silylation and boronation.[4] Stereoregular BH_3-ODN can be prepared by enzymatic incorporation of the deoxynucleoside 5'-(α-P-borano)triphosphates (dNTPαB)[5], which are excellent substrates for Klenow, Sequenase, and Vent DNA polymerases.[6,7] In experiments where dNTPαB were co-polymerized with natural dNTP in all combinations and proportions (0-100%), the yields of extended product with Sequenase 2 were the same (74-78%). Oligonucleotides prepared enzymatically with one or more boranophosphate linkages form stable duplexes with DNA[6,7] and can serve as templates for PCR.[7] Fully boronated, non-stereoregular oligothymidylates form hybrids with lower melting points than normal oligothymidylates[4b], yet they can nevertheless support the RNase H mediated cleavage of RNA, making them potentially useful antisense agents.[8] Boranophosphate RNA can be prepared with riboNTPαB using RNA polymerases.[9] The resistance of BH_3-ODN to nuclease hydrolysis relative to natural ODN forms the basis of a PCR-based method for DNA sequencing.[7] In summary, BH_3-ODN may provide an exceptionally useful addition to the repertoire of phosphate analogues, gene targeting, and gene sequencing agents.

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