Synthesis of a new internucleosidic linkage: the Borononucleotides

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ABSTRACT
The synthesis of a boronucleotide analogue of thymidine and its association with various nucleosides, nucleotides and saccharides is described.

INTRODUCTION
Boronic acids are versatile and valuable functional groups that are increasingly used in synthetic, biological and medicinal chemistry\(^1\). The broad interest in boronic acid-containing substrates results from various interesting features such as their relatively low mammalian toxicity, the electronic structure of boron and their ability to form reversible cyclic esters in the presence of cis-diols under physiological conditions. Whist a large number of chemically modified oligonucleotides have been introduced, the replacement of the phosphodiester linkage by a reversible covalent binding interaction would be an ideal building material for the programmed assembly of dynamic, highly ordered nanostructures. Here, we wish to report the synthesis of the first boronucleotide isostere of 5'-monophosphate thymidine (TMP) along with its affinity in water towards various nucleosides, nucleotides and saccharides.

RESULTS AND DISCUSSION
The boronic acid analogue of TMP was synthesized from 5’-O-dimethoxytritylthymidine (5’-O-DMTTr-T) in seven steps with 31% overall yield\(^2\) as shown in Scheme 1. Hence, 5’-O-DMTTr-T 1 was silylated to yield the 3’-O-tertbutyldimethylsilyl derivative 2 and the 5’-O-dimethoxytrityl group was next removed by means of acidic conditions to furnish the 3’-O-tertbutyldimethylsilyl protected thymidine 3. Compound 3 was then oxidized into the corresponding aldehyde derivative 4 by the general procedure of oxidation of primary alcohols with DMSO in the presence of dicyclohexylcarbodiimine (Moffat oxidation). Homologation of the aldehyde function using dimethyl-1-diazo-2-oxopropylphosphonate (Bestmann-Ohira reaction\(^3\)) gave alkyne 5 which was quantitatively reduced to the corresponding terminal alkene 6 by catalytic hydrogenation. Hydroboration of the latter was next achieved using disopinocampherylborane followed by oxidation with acetaldehyde to give 3’-O-TBDMS boronic acid 7. Desilylation under acidic conditions yielded boronucleotide analogue 8.

The reversible formation of the corresponding dinucleotide between the boronucleotide and various nucleosides or nucleotides (Figure 1) was next studied.

![Scheme 1. Synthesis of borononucleotide analogue of thymidine. Reagents and conditions: i. TBDMSCl, Imidazole, Pyridine, rt; ii. BSA 10%, CH\(_2\)Cl\(_2\)/MeOH; 7/3, -20°C, 76%; iii. (a) DCC, DMSO, dichloroacetic acid, rt; (b) oxalic acid, O°C, 78%; iv. Dimethyl-1-diazooxopropylphosphonate, K\(_2\)CO\(_3\), MeOH, rt, 76%; v. H\(_2\), Lindlar catalyst 15%, MeOH, rt, 99%; vi. (a) diisopinocampherylborane, THF, rt; (b) acetaldehyde, rt; (c) HCl 0.1M, 72%, vii. HCl 3M, rt, 98%.

Figure 1. Reversible formation of a dinucleotide modified by a boronate linkage between the borononucleotide analogue of thymidine and nucleotides or nucleosides.

The affinities of our analogue for carbohydrates were next analyzed in aqueous solution using Springsteen and Wang’s colorimetric assay based on the competitive release of Alizarin Red S (Figure 2).
confirmed the geometrical preferences of the resulting boronic esters.

Table 1. Calculated $K_d$ values towards various nucleosides and diols using the competitive ARS method.

Plus, as the binding of our analogue with saccharides are quite low, the complexes formations with ribonucleosides may also benefit entropically from internal stacking interactions.

CONCLUSION

A new type of internucleosidic linkage has been achieved through the synthesis of the borononucleotide analogue of thymidine. The formation of this novel reversible boronic ester backbone appeared to be dependent on the presence of a cis-diol system, a preorganized north-like sugar conformation of the diol moiety and stacking interactions. An extension of the borononucleotides family is currently under progress.

REFERENCES


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