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Stimuli-Responsive Boronate Formation to Control Nucleic Acid-Based Functional Architectures

Michael Smietana*[a] and Sabine Müller*[b]

Boronate esters, formed by the reaction of an oligonucleotide bearing a 5′-boronic acid moiety with the 3′-terminal cis-diol of another oligonucleotide, support the assembly of functional nucleic acid architectures. Reversible formation of boronate esters occurs in templated fashion and has been shown to restore the activity of split DNA and RNA enzymes as well as a split fluorescent light-up aptamer. Apart from their suitability for the design and application of split nucleic acid enzymes and aptamers in the field of biosensing, boronate esters may have played an important role in early life as surrogates of the natural phosphodiester bond. Their formation is reversible and thus fulfills an important requirement for biological self-assembly. Here we discuss the general concept of stimuli-dependent boronate formation and its application in biomolecules with implications for future research.

1. Introduction

In the quest for developing chemosensors capable of detecting bioanalytes of importance, the use of dynamic covalent chemistry involving boronic acids has proven to be highly effective. Typically, the development of boronic acid sensors relies on the reversible covalent bond-forming interactions between boronic acids and diols in aqueous media.[1] Reported for the first time by Lorand and co-workers,[2] the reversible nature of the boronic acid/diol equilibrium has since become an intensive research area. Through this interaction, cyclic boronate esters with five- or six-membered rings are formed, but it's worth noting that this binding is less favorable under acidic conditions.

In contrast to unfavorable conditions at low pH, the addition of hydroxyl anions shifts the equilibrium towards the formation of a favored hydroxy boronate ester. This occurs through the complexation of the vacant p-orbital of the boron atom. As a consequence of this reaction, the angle strain around the boron atom is released, causing a change in the angles between oxygen atoms in the O–B–O and B–O–C bonds from 120° to 109°.[3] This results in the formation of a negatively charged tetravalent compound with a tetrahedral sp^3 geometry (Figure 1).[4] As a consequence, the rate of cyclic boronic ester formation from boronic acid anions is 10^3–10^4 times faster than that of neutral boronic acids.[5] These features have been frequently used for the development of sensors employed in the detection of saccharides, polysaccharides, or glycoproteins.[1,6] The stability of the resulting adduct also makes boronic acids an interesting asset in bioconjugation, smart materials, imaging and drug delivery.[3,7]

The presence of a cis-diol moiety in ribonucleic acid (RNA) also provides an opportunity to form boronate esters. In practice, boronic acids have been employed for a large variety of applications including separation and purification of RNA,[8] sensing,[9] and siRNA delivery.[10] In this context, our groups aimed at synergizing the unique characteristics of boronic acids with those of nucleic acids.[11]

2. DNA- and RNA-templated ligations

Our focus has been particularly on harnessing the diol functionality of ribonucleosides, which emerged as a prevailing recognition element. We began to view the boronate functionality as a substitute for internucleoside linkages and ultimately, leveraged these properties to control the formation of functional architectures.

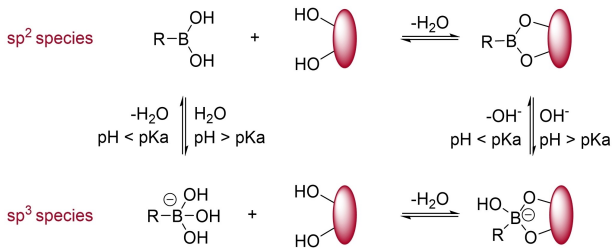

Figure 1. General scheme of boronate ester formation illustrating the pH-dependent reversible condensation of boronic acids and diols.

[a] *Prof. M. Smietana*
Institut des Biomolécules Max Mousseron
Université de Montpellier, CNRS, ENSCM
Pôle Chimie Balard
34095 Montpellier (France)
E-mail: michael.smietana@umontpellier.fr

[b] *Prof. S. Müller*
Institute of Biochemistry
University of Greifswald
Felix-Hausdorff-Straße 4
17489 Greifswald (Germany)
E-mail: sabine.mueller@uni-greifswald.de

These approaches relied on the synthesis of a new family of modified nucleosides carrying a 5′-boronic acid residue, accordingly named bononucleosides. These analogues of nucleosides were synthesized from commercially available 5′-*O*-dimethoxytrityl protected nucleosides both in DNA and RNA series and then transformed into their phosphoramidites in order to be incorporated at the 5′-end of DNA and RNA sequences (Figure 2).[12]

Our investigations began with the synthesis of a T_6T^{bn} sequence to promote the DNA-templated generation of a reversible boronate internucleoside linkage in the presence of a second strand carrying a ribonucleotide at its 3′-end. The capacity of the template to position the two functionalities in close proximity and promote the ligation was confirmed by UV thermal denaturation studies. Compared with their unmodified analogues, stabilizations ranging from 6.8 to 14.4 °C were observed by varying the pH from 7.5 to 9.5 (Figure 3A).[13]

The results obtained with DNA-templated ligations encouraged us to design dynamic systems capable of self-assembly by DNA-templated formation of multiple reversible boronate internucleoside bonds that can be switched on and off by pH variation. To this end bifunctional oligonucleotides containing a boronic acid at their 5′ end and ribonucleotide at their 3′ end have been prepared. This has been applied to the formation of duplexes with up to five boronate internucleoside linkages with templates carrying either repetitive or alternating sequences (Figure 3B).[14] Although we cannot totally rule out intramolecular cyclization reactions of these bifunctional probes, the formation of macrocycles joined by a boronate has never been identified. In fact, NMR studies carried out on monoribonucleosides containing a boronic acid have revealed the presence of a mixture of cyclic dimers and trimers, only in anhydrous organic solvents.[15] These results also underline the importance of the template for the formation of boronate junctions in aqueous media. After demonstrating the efficiency of DNA- and RNA-templated assembly of 5′-boronic acid-modified DNA oligomers, we envisaged applying the concept to RNA sequences modified at their 5′-extremities by a boronic acid. As expected the DNA- and RNA-templated ligation of U_6U^{bn} in the presence of a oligoribonucleotide partner showed a pH-dependent transition

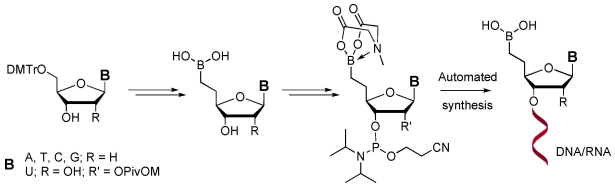

Figure 2. General structures of the bononucleoside and their attachment at the 5′-end of DNA and RNA sequences.

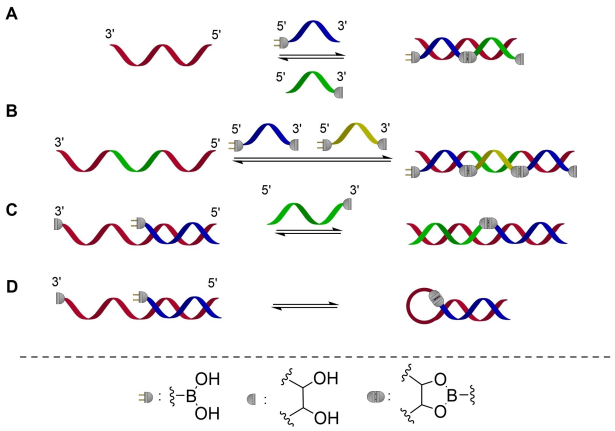

Figure 3. Dynamic DNA-templated formation of boronate internucleosidic linkages using A) a 5′-boronic acid-modified DNA sequence and B) bifunctional DNA probes. C) Dynamic RNA-templated formation of boronate internucleosidic linkages. D) Dynamic formation of a loop.

as a consequence of the formation of the boronate internucleoside linkage (Figure 3C).[12c]

Surprisingly, a thermal denaturation experiment performed with a RNA template and the U_6U^{bn} strand but without oligoribonucleotide partner gave a melting temperature 5.3 °C higher than the unmodified derivative, thus suggesting that the 5′-boronic acid was able to reach the 2′,3′-diol moiety at the 3′-end of the RNA template to form a loop having seven unpaired residues (Figure 3D). By contrast, thermal denaturation analysis in the presence of RNA templates containing at their 3′-end either a 2′-deoxy or a 2′-OMe residue revealed no differences

Prof. Michael Smietana was educated at the Ecole Normale Supérieure in Paris. He received his PhD in 2001 from the University of Strasbourg and then moved to Stanford University for two years as a Postdoctoral Fellow. In 2004, he was recruited as an Assistant Professor at the University of Montpellier and promoted to Full Professor in 2012. In 2018 he received the Jean-Marie Lehn award from the Organic Chemistry Division of the French Chemical Society. Since 2020 he leads the ChemBioNAC team at IBMM. His current research interests focus on molecular recognition, DNA-based asymmetric catalysis and nucleic acid bioconjugates.

Sabine Müller is a Full Professor of Biochemistry/Bioorganic Chemistry at the University of Greifswald in Germany. She received her Ph.D. from Humboldt University, Berlin in 1994, and did two years postdoctoral research at MRC, Cambridge, UK, before becoming a group leader at Humboldt University in 1996. In 2003 she moved to the Ruhr University Bochum, as Professor for Bioorganic Chemistry, before taking up her present appointment in 2006. Prof. Müller was awarded a Heisenberg fellowship by the Deutsche Forschungsgemeinschaft (DFG) and was elected to AcademiaNet in 2010. Her research focuses on the chemistry and biochemistry of nucleic acids, with an emphasis on functional RNAs and the Origin of Life.

between the modified and unmodified sequences thus confirming the necessity to have a cis-diol at the 3′-end to trigger the formation of the loop.[12c] The ability of RNA sequences modified by a boronic acid at their 5′-extremity to form loops with relatively distant diols opened new avenues to design larger and eventually functional architectures.

3. Split nucleic acid enzymes stabilized by boronate ester linkages

In recent years, split aptamers and ribozymes composed of multiple short nucleic acid strands that come together to form a functional structure have emerged as prospective tools in diagnostics and therapy.[16] However, their application is still rather limited, since the creation of a potent split system remains an ambitious task. An important challenge is the diminished stability of the split aptamer/ribozyme in comparison to its full-length counterpart. Stabilizing the split system can be accomplished through structural manipulation. This involves extending the individual fragments with additional nucleotides, which would assist in assembly and improve the stability of the split aptamer/ribozyme complex through complementary base pairing. Another approach is to decorate the fragments with reactive groups, allowing for covalent linkage during assembly and folding. Boronate ester linkage formation has proven to be an effective strategy for stabilizing split nucleic acid enzymes and aptamers,[17] among other chemistries such as Click ligation,[18] reaction between an amine and an aldehyde,[19] or *N*-methoxyoxazolidine formation.[20] In this context, we recently evaluated the activity of split 10–23 DNAzymes composed of two fragments for cleaving a suitable RNA substrate. (Figure 4A and B).[17a] All variants of the split DNAzymes exhibited a significant decrease in catalytic activity when assembled from non-modified fragments. Nonetheless, activity was restored for four out of the five split DNAzymes when the fragments were functionalized to permit boronate ester formation. Kinetic analysis of RNA cleavage by the borono-modified split DNAzymes demonstrated that the position of the split site has a major impact on DNAzyme conformation and, consequently, the restoration of activity. Furthermore, because of the interactions involved and the flexibility of the molecule, the choice of boronic acid is critical to the stability of the system. Split DNAzymes with 5′-boronothymidine, an analog of natural thymidine, showed the best activity. On the contrary, fragments with naphthylboronic acid or phenylboronic acid attached to the 5′-terminus performed poorly.[17a]

Moving from DNA to RNA, split hairpin ribozyme variants were designed and evaluated (Figure 4A and C).[17b] The hairpin ribozyme is a small, naturally occurring catalytic RNA that catalyzes the reversible cleavage of an appropriate substrate RNA at a specific position. Ribozyme variants were generated by assembly of two fragments, and functionality was evaluated by activity assays in which appropriate substrates were cleaved and/or ligated. Split hairpin ribozyme variants composed of

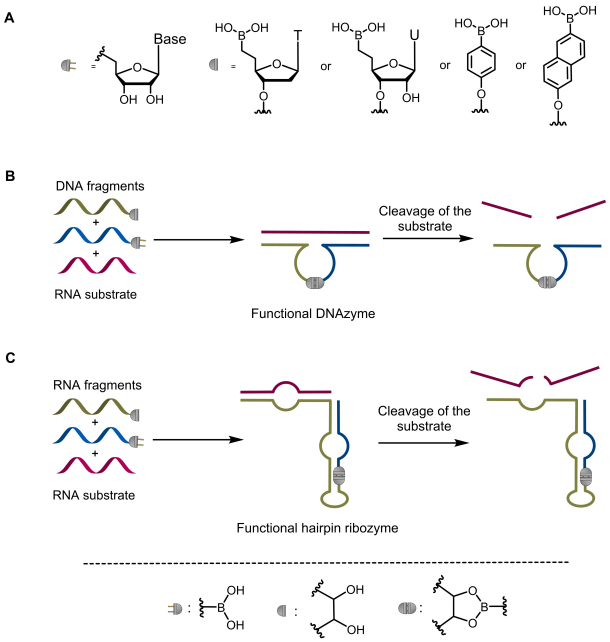

Figure 4. Split DNAzyme (B) and split hairpin ribozyme (C) stabilized by a boronate ester linkage between fragments functionalized as shown in (A).

unmodified fragments showed no detectable or significantly reduced activity. However, when decorated with 5′-boronic acid functionalities, some of the split variants showed restored cleavage activity.

Ligating proved to be more challenging. All ribozyme variants functioned well for ligation; however, the borono-modified variant exhibited reduced activity compared to the non-modified split variant. This is most likely due to a minor, yet significant structural distortion introduced by the non-natural boronate ester linkage, which impacts the stability of the folded catalytic complex. In the case of the hairpin ribozyme, stability is more critical for ligation than for cleavage.[21] Therefore, the beneficial effect of the boronate ester formation that was observed during the cleavage reaction did not translate into a successful ligation. 5′-boronouridine modified fragments were determined to be the most effective among the tested boronic acid derivatives for all of the modified split hairpin ribozyme variants. Following this, fragments carrying a 5′-boronothymidine exhibited intermediate performance. However, phenyl- or naphtylboronic acid derivatives performed not as well, which aligns with previous findings on DNAzymes. The hairpin ribozyme exhibited greater sensitivity to the substitution of the natural phosphodiester linkage with a boronate ester compared to the split DNAzymes. This may be attributed to the functional significance of some of the 2′-OH functionalities. Consequently, these findings provided new insights and validated prior results regarding the functional significance of specific 2′-OH groups in the hairpin ribozyme structure.

Taken together, it was demonstrated that the boronic acid ester linkage played an essential role in stabilizing the re-formed functional systems and enhancing the catalytic activity

of both split DNAzyme and hairpin ribozyme variants. The significance of the linkage was confirmed by competition experiments with the addition of catechol. Catechol competes with ribose to form a boronate ester, leading to a reversal of the observed activity restoration effect. This phenomenon was clearly observed for both the DNAzyme and hairpin ribozyme variants studied.[17]

4. A split light-up aptamer stabilized by a boronate ester linkage

In a subsequent study, the functionality of a split aptamer was achieved through the use of two fragments connected by a boronate ester (Figure 5).[17b] Fluorescent light-up aptamers (FLAPs) are RNA structures that bind fluorescent dyes and activate their fluorescence allowing imaging of FLAP-tagged RNAs of interest with low background fluorescence in living cells. Also split versions of FLAPs have potential for intracellular monitoring, imaging, and biomolecule sensing, however, often lack stability.[16] Split aptamers that use a boronate ester for stabilization can overcome this limitation and improve aptamer design and application.[17b]

The Mango light-up aptamer was developed through in vitro selection. It binds a specific thiazole orange derivative with an affinity of approximately 1 nM, leading to a fluorescence enhancement by a factor of >1500.[22] When split into two halves, the resulting Mango variant's function was almost entirely lost. However, when one of the two fragments was decorated with boronic acid at its 5′-end, the fluorescence was restored.[17b] Fragment assembly positions the borono moiety of one fragment and the 3′-cis-diol of the other in close proximity, enabling the formation of an internucleoside boronate ester linkage. It was demonstrated that napthylboronic acid is a viable substitute for 5′-borono nucleotides, and its fluorescence enhancement was nearly equivalent to the complete aptamer. This may be due to the large, stacked napthyl aromatic system, resulting in a stabilizing effect on the structure by interacting with Mango's typical quadruplex motif.

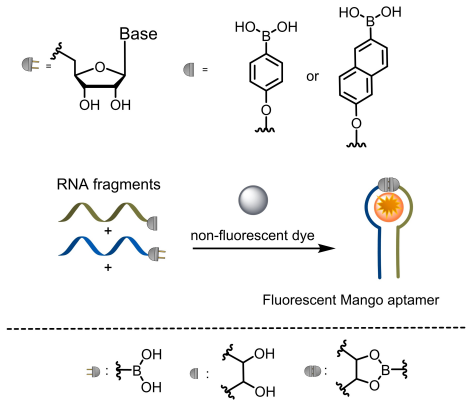

Figure 5. Split Mango aptamer stabilized by a boronate ester linkage between fragments functionalized as shown.

The reversal of the effect was achieved as described above for the DNAzyme and hairpin ribozyme studies, by adding catechol as a competitor in the formation of the boronate ester.[17b]

5. Boronate linkages in nucleic acid structures at the origin of life

In addition to their potential in developing novel biosensors, boronate ester linkages may have relevance to the RNA world hypothesis.[23] One unanswered question is how the first large RNAs necessary for complex functions emerged. A plausible scenario suggests that shorter sequences interacted to form functional assemblies. Since boronate esters may have appeared on the early Earth,[24] hypothesizing that the formation of internucleosidic boronate ester linkages assisted RNA assembly and increased the stability of the assembled structures is reasonable. This boronate-based ligation chemistry has some parallels with the earlier work of Eschenmoser and colleagues, who studied template-directed ligation of 2′,3′-cyclophosphates of short oligomers.[25] However, boronate esters between a 5′-bononucleoside and a 2′,3′-*cis*-diol of a ribonucleotide are formed much more rapidly (within seconds to minutes) than the corresponding phosphate linkages from 2′,3′-cyclic phosphates (within days to weeks) under similar conditions. In addition, the easily reversible formation of the boronate ester linkage is a particularly attractive feature. Reversible chemistry, allowing both chain forming and chain breaking steps, is an important prerequisite for biological self-organization, a feature that is realized by boronate ester chemistry. It is therefore plausible to hypothesize that boronate ester linkages, at least to some extent, may have preceded phosphate esters in nucleic acids.

6. Summary and Outlook

Stimuli-responsive boronate ester formation is an attractive concept with prospects in the fields of materials and diagnostics. It allows the controlled assembly of biomolecular architectures with potential applications in biosensing. We have shown that the activity of split DNAzymes and hairpin ribozymes, as well as the functionality of a FLAP, can be controlled by using two fragments, one modified with a boronic acid at the 5′-end and the other with a cis-diol at the 3′-end.[17] Fragment assembly orients the two moieties in close proximity to form an internucleoside boronate ester linkage. This results in stabilization of the ribozyme or aptamer structure and restores functionality. For the nucleic acid enzymes, 5′-boronothymidine or 5′-boronouridine modified fragments performed best, while in the case of the Mango aptamer naphthylboronic acid proved to be a suitable alternative. This is important, because it paves the way for the modification of a wide variety of molecules with a commercially available boronic acid residue without the need for the tedious and challenging synthetic preparation of a boronic acid-modified nucleoside. Split nucleic acid enzymes

and aptamers have great potential for intracellular monitoring, imaging and sensing of biomolecules.[16] As mentioned above, the overall concept involves splitting the parent full-length strand into a series of two or more independent and non-functional fragments that would assemble to form the functional entity. Thus, compared to full-length functional nucleic acids, split systems are easier to synthesize and, due to their smaller size, less prone to the formation of undesirable secondary structures that could provide false-positive or non-specific signals in the absence of the target. The issue of lower stability in split nucleic acids can be resolved by forming a covalent bond between their fragments during assembly, achieved through reversible boronate ester formation. Aptamers are crucial components for sensing small molecules or proteins, while nucleic acid enzymes are mainly utilized for detecting specific nucleic acid sequences or metal ions. Combining aptamers and nucleic acid enzymes into aptazymes is an attractive way to enhance signals. The enzyme amplifies the binding event of the target to the aptamer region, generating multiple reaction products that can be used for readout. In the long run, the reversible formation of boronate esters and the adjustable boronic acid ester-boronate equilibrium could potentially control functional nucleic acids and lead to the creation of valuable biosensing platforms. Nevertheless, despite its potential, the design and application of split aptamers and nucleic acid enzymes in biosensing applications is still in its infancy and challenging. Improving the stability of split nucleic acid target complexes to enhance sensitivity is a crucial objective. Additionally, quick and efficient methods utilizing colorimetry, fluorescence, chemiluminescence, or electrochemical detection should be implemented in split aptamer/nucleic acid enzyme assays to enhance their efficacy. Nevertheless, the functional assemblies derived from aptamers and ribozymes/DNAzymes reported to date demonstrate the proof of principle and pave the way for further implementations and new developments.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: boronate linkage · DNAzyme · Ribozyme · split structure · aptamer

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