Reversible Click Reactions with Boronic Acids to Build Supramolecular Architectures in Water

Matthias Arzt, Christiane Seidler, David Y. W. Ng, Prof. Dr. Tanja Weil

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Reversible click reactions with boronic acids to build supramolecular architectures in water

Matthias Arzt, Christiane Seidler, David. Y. W. Ng, and Tanja Weil*[a]

Abstract: The interaction of boronic acids with various bifunctional reagents offers great potential for the preparation of responsive supramolecular architectures. Boronic acids react with 1,2-diols yielding cyclic boronate esters that are stable at pH > 7.4 but can be hydrolyzed at pH < 5.0. The phenylboronic acid (PBA)-salicylhydroxamic acid (SHA)-system offers ultra-fast reaction kinetics and high binding affinities.This mini review summarizes the current advances in exploiting the bioorthogonal interaction of boronic acids to build pH-responsive supramolecular architectures in water.

Keywords: boronic acid • click-reaction • bioorthogonality • pH-reversibility

Introduction

In Nature, biomacromolecules like nucleic acids or proteins adopt their bioactive, three-dimensional architectures based on non-covalent bonds. These interactions are usually formed with fast reaction kinetics under physiological conditions at distinct positions and in the presence of multiple alternate functionalities without the necessity to apply protecting groups.[1, 2]

Chemical reactions that proceed very fast, with high efficiencies and regioselectivities, in high yields, under mild conditions and without the formation of side-products or the necessity for protection are often termed "click-reactions" and they have opened access to sophisticated heterocycles and combinatorial compound libraries.[3, 4] Prominent examples include the ring opening of epoxides, the Staudinger-ligation of azides with phosphines or the 1,3-dipolar cycloaddition of ethynyl groups with azides.[2, 3] However, there are also limitations: For instance, the 1,3-dipolar cycloaddition of azides and alkynes proceeds at high temperature and regioisomers are formed. Applying metal catalysts[5, 6] offers many advantages[4] such as regioselectivity and bioorthogonality but the presence of metal cations such as Cu(I) often limits biological applications due to cytotoxicity.[7, 8] Still, the robustness and irreversibility of "click reactions" allows building unique molecular architectures. Nowadays, there is an increasing interest in reversible click-reactions that facilitate the formation as well as the controlled desintegration of supramolecular architectures. In this aspect, a [4+2] Diels-Alder cycloaddition of a furanyl- and a maleimide-derivative occurs at around 65 °C, whereas the retro-Diels-Alder reaction happens at ca. 110 °C.[9] The group of Barner-Kowollik uses a similar approach installing polymers with cylopentadien- and electron-efficient dithioesters as endgroups, which undergo a Hetero-Diels-Alder-reaction. This reaction is accomplished within 5 minutes at room temperature and is described as one of the contemporary tools for ultrafast click conjugation.[10, 11] Reversible chemical bonds are receiving increasing attention with the advent of stimulus responsive assemblies, self-healing materials, hydrogels and nanotechnology. Therefore, a chemical conjugation strategy that offers "click" type reaction mechanics while simultaneously offering responsiveness would portray an attractive outlook for the future of click chemistry.

In the pursuit to integrate reaction efficiency and responsiveness, the evolution of boronic acids from synthetic intermediates for C-C cross coupling and protecting group chemistry into a unique class of "click chemistry" became significant in recent years. The discovery of boronic acids was made by Frankland and Duppa[12] in 1860, with their synthesis and rich conjugation chemistry, have stimulated many chemists and emerged as powerful reagents in organic synthesis[13-15], in transition metal catalyzed cross coupling reactions[16, 17] as well as chiral auxiliaries[18] or catalysts in Diels-Alder reactions[19].

Recently, their participation in reactions that occur in aqueous media has been explored in greater detail. Boronic acids undergo "click-reactions" with bifunctional alcohols[20], amines[21] or other nucleophiles[22] under physiological conditions reversibly in a pH-dependent fashion. Their pH responsiveness originates from their chemical structure: Two hydroxyl groups and one organic substituent arrange in a trigonal planar geometry surrounding a boron center. The empty p-orbital is orthogonal to the remaining sp^2-hybrid orbitals and can provide an avenue for Lewis bases to

[a] M. Arzt, C. Seidler, D.Y.W. Ng, Prof. Dr. T. Weil
Department of Organic Chemitry III
University of Ulm
Albert-Einstein-Allee 11
89081 Ulm (Germany)
Fax: (+49)7315022879
E-mail: tanja.weil@uni-ulm.de

coordinate to the electron deficient boron resulting in a tetrahedral structure. Hence, boronic acids act as Lewis acids and not as Brønsted acids even though two hydroxyl groups are present. The acidity of a boronic acid depends not only on the electrophilicity of the organic substituent but also on their steric requirements: The more nucleophilic and bulky the substituent on the boron atom is, the less acidic is the resultant boronic acid.[23] As mentioned, boronic acids display an unprecedented affinity towards various bifunctional molecules, facilitating the formation of stable cyclic boronate esters or tetrahedral boronate anions in aqueous environment. The repertoire of these ligands and their engineering capacity provide a strong foundation to develop these interactions as a platform for bioorthogonal click reactions in water. In this review, the pH-dependent and reversible interaction of boronic acid with α,β-diols and salicylhydroxamates will be discussed highlighting the extensive versatility and bioorthogonality of these reactions for building supramolecular architectures.

Abstract in German:

Die Wechselwirkung von Boronsäuren mit unterschiedlichen bifunktionellen Verbindungen bietet zahlreiche Möglichkeiten, um supramolekulare Architekturen aufzubauen. Boronsäuren können überhalb von pH 7.4 mit 1,2-Diolen zyklische Boronsäureester bilden, welche unter leicht sauren Bedingungen wieder hydrolisiert werden. Das Phenylboronsäure (PBA)-Salicylhydroxamsäure (SHA)-System bietet die Vorteile einer ultraschnellen Reaktionskinetik und einer hoher Bindungsaffinität. In diesem Review werden die gegenwärtigen Forschungs-fortschritte bezüglich der bioorthogonalen Wechselwirkung von Boronsäuren in Wasser zum Aufbau von supra-molekularen Architekturen zusammengefasst.

Matthias Arzt *studied chemistry at Ulm University from 2007-2012. He received his M.Sc. in 2012 in the group of Prof. Dr. Tanja Weil for studies on ultrafast click-reactions based on boronic acids for the building of supramolecular architectures. Currently he is a Ph.D. student in Prof. Weils group. His research interest is on the design of precise supramolecular biopolymers.*

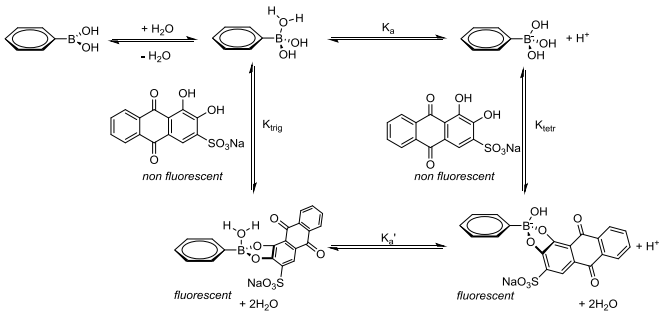
Christiane Seidler *is a Ph.D. student of Ulm University. She received her B.Sc and M.Sc degrees from Ulm University in 2011 and 2013. Her undergraduate work was performed in the group of Prof. Dr. Tanja Weil on the topic of supramolecular polymers based on boronic acid-salicylhydroxamate complexation. Following her research in the field of supramolecular polymers and biohybrids, she just started her Ph.D. under the supervision of Prof. Tanja Weil.*

David Y. W. Ng *studied chemistry and graduated from the National University of Singapore (B.Sc. Hons.) in 2009 and subsequently joined the Max Planck Institute for Polymer Research (2010-2013) including the IMPRS Program for 2011. He received his PhD from the University of Ulm in 2014 for tailoring functional dendritic protein hybrids as defined nanotransporters. Currently, he works as a group leader for precision polymer hybrid research in Prof. Weil's group.*

Tanja Weil *studied chemistry (1993-1998) at the TU Braunschweig, Germany, and the University of Bordeaux I, France, and completed her Ph.D. at the MPIP under the supervision of Prof. K. Müllen. From 2002 to 2008, she held several leadership positions at Merz Pharmaceuticals GmbH, Germany. In 2005, she was also appointed to the MPIP as a group leader and in 2008, as an Associate Professor at the NUS, Singapore. Since 2010 she has been Director of the Institute of Organic Chemistry III and Macromolecular Chemistry at Ulm University. Her current research interest includes dendrimer synthesis, site-directed peptide chemistry as well as designing innovative biopolymers and biomaterials for biomedical applications.*

Constructing responsive macromolecules and assemblies on boronic acid-diol interactions

In aqueous media, boronic acids form an equilibrium between trigonal planar complexes and tetrahedral boronate anions as depicted in Scheme 1. The structure of the boronate anion was first elucidated by Edwards and Lorand in 1959.[24] However, the complex formation of boronate esters is more complicated and not fully understood. Experimentally, the structural integrity of boronate esters depends on the solvent and the pH of the surrounding medium.[20] As such, comparative studies on the formation of these esters are often investigated using the chromophore Alizarin Red S (ARS), a chromophore that is non-fluorecent in its uncomplexed form. In the presence of phenylboronic acid, a fluorescent ARS-boronate anion complex is made with the equilibrium constant of K_{tetr} and the formation of the trigonal planar boronate ester proceeds with K_{trig}, whereas the difference between these two constants $K_{tetr}>K_{trig}$ can be up to ca. five orders in magnitude. The resulting complex is more acidic with an acidity constant K_a' for the complex as $pK_a>pK_a$'.[25]



Scheme 1. Acid-conjugate base equilibrium of phenylboronic acid and Alizarin Red S (ARS) in aqueous media.

This assay was used as a reference to assess the binding constants of different diol-containing compounds such as carbohydrates at various pH-values (Table 1).[20] The first equilibrium between the boronic acid and ARS can be directly measured by fluorescence spectroscopy, whereas the second equilibrium between the boronic acid and e.g. a carbohydrate perturbs the first equilibrium, resulting in an impact on the emission intensity of the boronic acid/ARS complexation. It is commonly accepted that the optimal pH for the interaction of a given diol and a boronic acid is above the pK_a of the boronic acid (e.g. phenylboronic acid has a pK_a of 8.70 in water at

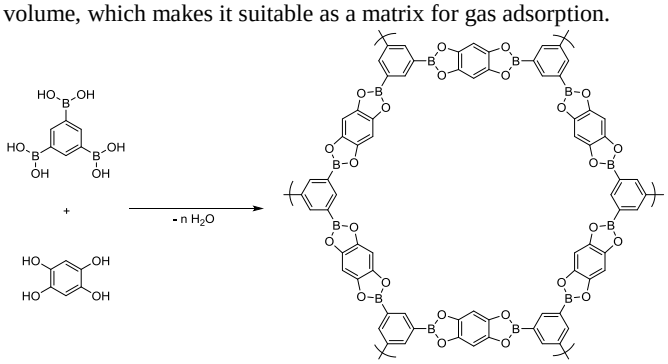
25 °C),[23, 26-28] demonstrated for the diols in Table 1. Nonetheless, the boronic acid/ARS-system represents an exception since optimal binding is found at pH 7.[20] Therefore, in order to facilitate complex formation, the pK_a values of both ligands need to be considered when incorporating boronate complexes for a designated application.[29, 30]

Table 1. Association constants K_{eq} of PBA-esters at different pH-values in 0.10 M phosphate buffer solution.

pH	K_{eq} (M^{-1}) of the complex with PBA						
	Fructose	Catechol	Glucose	Galactose	Sorbitol		ARS
4.6							190
5.8	4.6		31				990
6.5	29		150	0.84	2.1	47	1200
6.6	35		160				1500
7.0	92		500	2.0	8.4	160	1500
7.4	160		830	4.6		370	1300
7.5	210				17		1100
8.0	310		2900	7.2	38	840	670
8.5	560		3300	11	80	1000	450

In the past years boronic acid building blocks were tremendously investigated as tools for self-assembly, recognition or sensing.[22, 31]

Lavigne et al were one of the first groups to utilize this complexation reaction for the synthesis of delicate organic frameworks.[32] By mixing benzene-1,3,5-triboronic acid and 1,2,4,5-tetrahydroxybenzene, they obtained a highly ordered, microporous polyboronate network in high yields. This network showed enhanced stability, a high surface area and small micropore volume, which makes it suitable as a matrix for gas adsorption.



Scheme 2. Synthetic Scheme for the complexation of benzene-1,3,5-triboronic acid and1,2,4,5-tetrahydroxybenzene.[32]

Wang *et al.*[33] exploited the interaction of phenylboronic acids and catechols for the preparation of dual responsive, cross-linked micelles. A cross-linkable telodendrimer was achieved by combining two dendrimer branches, each one containing a pair of catechol and boronic acid groups (Figure 1a). In consideration of the long term stability and the critical micelle concentration, eight crosslinking points were chosen for building this architecture.[34] The resulting dendrimer micelles responded to changes in pH as well as towards mannitol while even exhibiting stability in human plasma. By reducing the pH from 7.4 to 5.0 or by adding an excess of mannitol (100 mM solution) to the micelle solution (Figure 1b), disintegration of the catechol-boronate ester occurred. In order to elucidate the capacity of such responsive micelles for drug delivery, paclitaxel (PTX) was used as a model drug to be encapsulated.

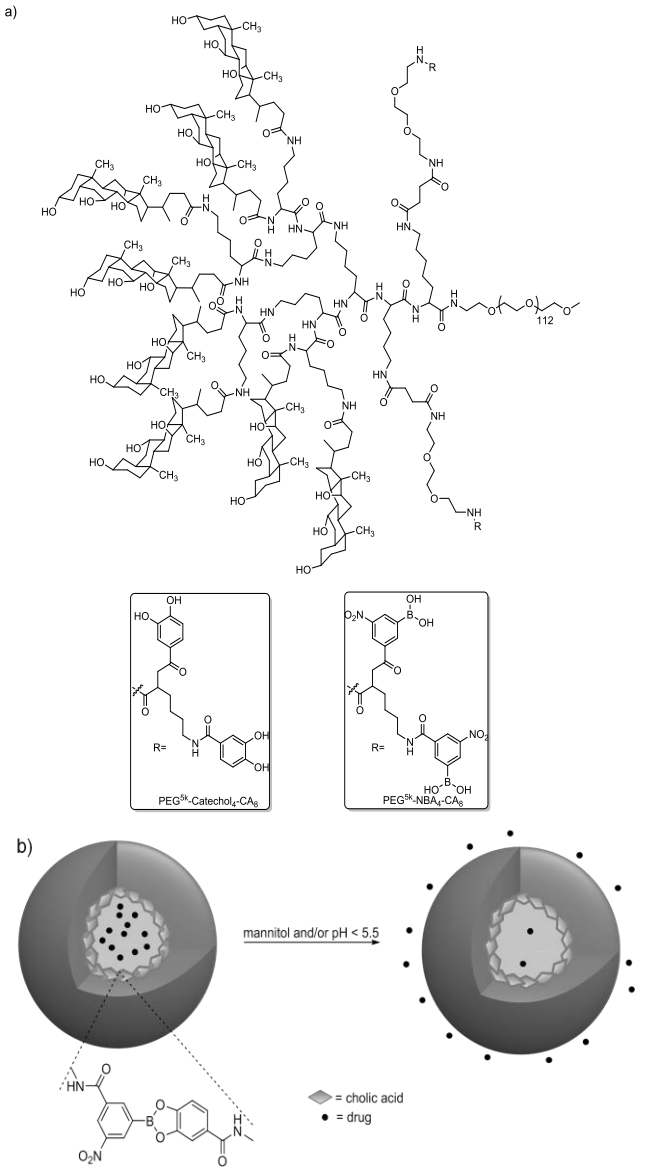


Figure 1. a) Telodendrimer pair consisting of catechol and boronic acid moieties described by Wang. b) Illustration of the boronate-catechol cross-linked micelles and stimulated drug release in response to mannitol or acidic pH.[33]

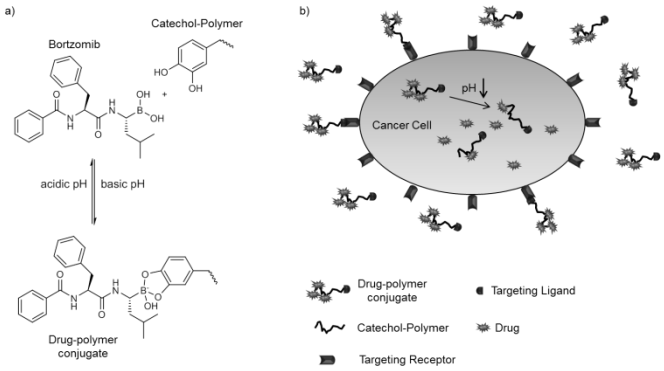


Figure 2. pH-responsive polymer-drug conjugates for delivering BTZ selectively into cancer cells. a) The catechol and the boronic acid structure in BTZ form a stable, covalently-bonded, inactive conjugate at neutral pH, but this structure dissociates in acidic environments to release the free active drug BTZ. b) The catechol polymer-BTZ conjugate can dissociate in response to a mildly acidic cancer tissue microenvironment

which liberates the free drug molecules. Alternatively, through the use of targeting ligands, the catechol polymer-BTZ conjugate was transported into cancer cells via receptor-mediated endocytosis, where it was proposed that the acidic environment in the endosome might induce intracellular drug release. [35]

PTX loaded micelles were stable under physiological conditions and drug release was accelerated at pH 5.0 or after addition of 100 mM mannitol solution. *In vitro* experiments with SKOV-3 ovarian cancer cells revealed two-fold increased cytotoxicity of the PTX loaded micelles compared with free PTX. [33]

In a similar context, Messersmith's group reported a catechol containing polymer for the targeted drug delivery of the anti-cancer drug Bortezomib (BTZ) into cancer cells.[35] It is known that the boron of BTZ binds to the catalytic site of the 26S proteasome with high affinity and specificity, which induces proteasome inhibition and thus degradation of pro-apoptotic factors.[36, 37] Stable polymer-drug complexes were formed at pH 7.4 due to the catechol-boronate interaction (Figure 2a). The complexes dissociated at pH 5.5 in the mildly acidic cancer tissue microenvironment and release of the cytotoxic drug molecules was observed (Figure 2b). Cell-type selectivity was achieved by the attachment of biotin to the polymer-BTZ conjugate since biotinylated polymers are well uptaken due to overexpression of biotin-receptors on cancer cells.[38] Cell studies with the non-biotinylated polymer-BTZ-conjugates revealed that BTZ was only moderately active and proteasome inhibition of BTZ was low. The biotinylated construct retained high proteasome-inhibiting activity as shown by cell viability tests over 48 h, supporting the attractive potential for integrating targeted delivery and controlled release strategies. [35]

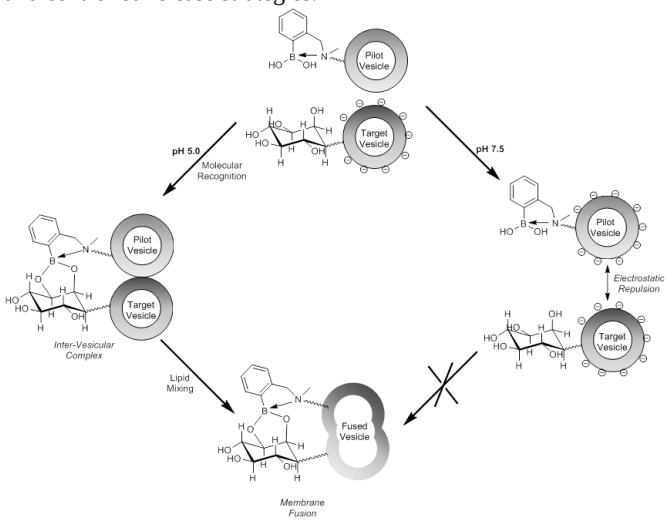


Figure 3. A schematic description of the pH-selective membrane fusion. [39]

The group of Matsuda has exploited the pH-dependent and bioorthogonal complex formation of boronic acids to produce a sophisticated, pH-responsive and target-selective vesicle fusion system.[39] It is well known that these fusion processes are observed in intercellular communications during fertilization[40], cellular membrane trafficking[41] and viral infection[42]. They have prepared a phenylboronic acid derivative containing a stearic acid anchor group that incorporates into the lipid bilayer of pilot vesicles. In close vicinity to the boronic acid, a tertiary amine group was positioned that stabilizes the boronic acid by forming a tetrahedral boronate anion (Figure 3). The boronic acid moiety of the pilot vesicle formed an intervesicular complex with the cis-diol function of the inositol-calix on the target vesicle, facilitating the hetero-fusion of the vesicles. The resulting vesicle fusion system was stable over a wide pH-range (from 5.0 to 10.5). Incorporation of responsive functions was achieved via the addition of 1,2-dipalmitoyl-sn-glycero-3-succinate to the pilot vesicle leading to a negatively charged surface at neutral and basic pH which resulted in the electrostatic repulsion of the two vesicles. The vesicle manipulation could be achieved at physiological pH (neutral to slightly acidic). This strategy could lead to engineered liposome-based applications such as drug/gene delivery systems and develop target specific non-viral vectors.

Sumerlin *et al.* built a watersoluble blockcopolymer consisting of 3-acrylamidophenylboronic acid and *N,N*-dimethylacrylamide. Upon addition of multifunctional diol-crosslinkers nanosized multiarm stars with boronic ester cores and PDMA coronas assembled. Those star-like architectures could be dissociated in the prescence of monofunctional diols, whereas the formation-dissociation process was repeatable over multiple cylces.[43]

The boronic acid-catechol system was used by the group of Stenzel to reversible bind folic acid groups for the targeted drug delivery of a polymeric micellular constract. Utilizing RAFT-polymerization they synthesized copolymer with covalently bound oxoplatin and a catechol endgroup. Due to the platinum micellular constructs of sizes 150 and 20 nm were formed in aqueous media. The catechols on the surface of the micelles were then functionalized with boronic acid conjugated folic acid to facilitate the target-selective cellular uptake.[44]

Instinctively, one could extrapolate boronic acid interactions with 1,2 diols to nucleic acids for constructing supramolecular hybrid architectures as DNA based smart materials and investigate the potential role in boron-DNA origami. Indeed, Smietana *et al*[45]. has presented a comprehensive review on these unique macromolecules and several preliminary applications towards therapeutic, diagnostic, and material aspects have proven to be very optimistic. [46-49] As such, one could envision that boronic acids may expeditiously develop into an impressive tool to define and tune self-organizational behaviour of macromolecules.

Boronic acid-salicylhydroxamate Complexation – A milestone towards ultrafast, stable and reversible "click chemistry"

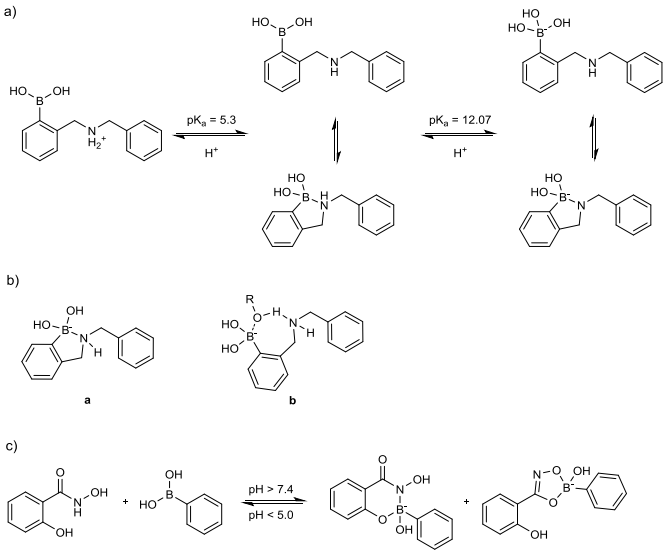


Figure 4. a) B-N interaction in *N*-methyl-*o*-(phenylboronic acid)-*N*-benzylamine at different pH. b) B-N interaction in (a) aprotic solvents and (b) protic solvents (solvent insertion). c) pH-dependency of the equilibrium of the PBA-SHA-complexation.

The development of ligands for the binary complexation was expanded to incorporate nitrogen donors in order to alleviate

limitations such as poor binding affinity (50 – 3000 M^{-1}) of oxygen based ligands. The interaction between boron and nitrogen was first reported in 1862 by E. Frankland in complexes of ammonia and trimethylborane.[50] This interaction was strongly dependent on the substituent: An increase in Lewis-acidity of boron was observed by electron withdrawing groups and the Lewis-basicity of the nitrogen was increased by electron donating substituents. Bulky substituents also influenced the B-N interaction by weakening the binding strength between boron and nitrogen.[23, 25] Due to the protonation state of the nitrogen center, amine based ligands interact in a highly pH dependent fashion, which is the main impetus for the design of reversible complexes. [51, 52] The reversible B-N interaction was elucidated in *N*-methyl-*o*-(phenylboronic acid)-*N*-benzyl amine, which showed a pH-dependent equilibrium with different structures being formed in three distinct pH regions (pH < 5.3, 5.3 < pH < 12.07, pH > 12.07, Figure 4a). [52, 53] In aprotic solvents, a B-N dative bond facilitates the formation of a five membered ring, whereas in protic solvents, a solvent molecule was found bridging between the oxophilic boron and amine nitrogen (Figure 4b). [52]

In an elegant interplay of nitrogen and oxygen donors, J.P. Wiley developed a salicylhydroxamate based ligand that offers both stability and reversibility within physiological pH fluctuations.[54] These stable boronate esters are formed readily at pH > 7.4 and were hydrolyzed at pH < 5.0 (Figure 4c). Investigations on the complexation of PBA-SHA using ^{11}B-NMR demonstrated that the hybridization of the boron center (trigonal or tetrahedral) is dependent on the pH.[54] In addition, it was shown that the formation of a six-membered boronate ester consisting of a reversible B-N- and B-O-bond was more favored in comparison to the five-membered counterpart. The association constants for this complexation reaction also varied depending on the pH, with 17,800 M^{-1} at pH 7.4 and 4 M^{-1} at pH 4.5.[55] Also the effect of common biological nucleophiles like cysteine, serine or D-glucose was tested against the PBA-SHA-interaction, and the ester formation was found to be robust due to the high complexation constant. The bioorthogonality of the reaction was ascertained when the complexation was performed in tissue culture media which contained small molecule cofactors, proteins and amino acids.[55] The kinetic rate constant of this bioorthogonal interaction was $k = (7.01 \pm 2.04) \cdot 10^6 M^{-2} s^{-1}$, as determined by UV spectrophotometry, suggesting very fast kinetics at pH 7.4 compared to other bioorthogonal reactions like the copper-free azide-alkyne cycloaddition $(k = 10^{-4} M^{-1} s^{-1})$.[2, 56, 57] Both parameters of the boronic acid/salicylhydroxamate complexation were exceptionally attractive, resulting in its induction into creating unique supramolecular architectures in aqueous medium. To develop this unique interaction further, Wiley et al. showed that the strong binding between PBA and SHA was able to immobilize proteins on surfaces facilitating the purification of PBA derivatized proteins under mild conditions. PBA-alkaline phosphatase and PBA-horseradish peroxidase conjugates were accomplished and their complexation was investigated by a SHA-Sepharose gel. The enzymatic activity of the functionalized horseradish peroxidase was quantitatively conserved but the activity of the functionalized alkaline phosphatase strongly depended on the amount of boronic acid moieties.[54] The PDBA-alkaline phosphatase-SHA -Sepharose conjugate showed superior performance for affinity chromatography over the covalent conjugated alkaline phosphatase with respect to immobilization of alkaline phosphatase, retention of alkaline phosphatase and recovery of anti-alkaline phosphatase at pH 11.0. [58] The strong established interaction between PDBA and SHA directly provided a platform for quantitative coupling of bioactive hetero-conjugates.[55, 59] Cristiano *et al.* developed a new polycation-based vector (polyethyleneimine – PEI/DNA) to which a specific peptide (CNGRC) was coupled via PBA-SHA complexation ensuring the structural integrity of the final vector. [59]

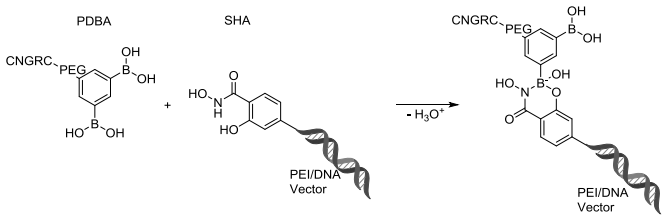


Figure 5. Complexation of the phenyldiboronic acid-PEG-linked peptide (CNGRC) and the salicylhydroxamate polyethylenimine/DNA-βgal vector. [59]

Furthermore, the PBA-SHA system was rapidly adopted as crosslinkers to induce changes in physical properties as a function of pH into bulk materials like hydrogels. Structurally, the hydrogel was composed of a water-soluble and biocompatible poly(hydroxylpropyl-methacrylamide) (pHPMAm) – backbone and pH-switchable crosslinks formed by PBA-SHA-groups. Due to the gelation behavior at different pH values, the material was used as a microbicide vehicle to prevent HIV-1 infection at the stage of transmission of HIV-1 from male (seminal fluid)-to-female (vaginal tract). The microstructural changes of the gel in response to a shift in pH acted as a barrier to HIV-1 diffusion and penetration. At pH 4 to 5 (precoital pH of the vaginal fluid), where the polymer mixture is a viscous fluid, the virions diffused most rapidly. However, when the virions enter the vaginal environment via the seminal fluid (slightly alkaline conditions), the polymer mixture crosslink density would increase, resulting in a reduction of the mesh size of the gel that inhibits viral transport.[60] Further research from the same group examined various properties of gels with unequal stoichiometry between the PBA and SHA ratios but with the same backbone. They showed that a 10:1 ratio of PBA: SHA in the polymer built a transient network[61] (dynamic self-healing network) across the entire pH range of interest (from pH 4.5 to pH 7.5). On the contrary, a hydrogel consisting 1:1 ratio of PBA: SHA could form transient networks only at pH 7.5, The control of the viscoelastic properties of the gel combined with the ability to withstand mechanical stress by self-healing makes this material particularly unique.[62] Similarly, P. F. Kiser *et al.* also tested the interactions between these crosslinked polymers with mucin and observed that the behavior of the new material in vaginal environment demonstrated mucoadhesive properties. The groups carried out safety evaluations of the material and indicated no significant loss in cell viability or irritation in either human ectocervical tissue or in a mouse model.[63]

The specificity of the PBA-SHA complexation is an appealing strategy for the synthesis of defined macromolecules, especially those involving sensitive proteins. In this aspect, our group utilized this mild strategy to construct a dendritic shell that exclusively encapsulates a single protein, simultaneously functioning as a macromolecular protecting group as well as a trans-membrane carrier. This approach alleviated several limitations of enzyme therapeutics which often involve poor cellular uptake, low stability due to rampant activity and degradation. The dendritic assembly was constructed by using SHA-core generation 2 poly(amido)amine dendrons and PBA functionalized enzymes (trypsin, papain, DNase I) at pH 7.4. The activity of the enzymes was shown to be dependent on the integrity of the dendritic shell; with little or no activity at pH 7.4 and was recovered at pH 5.0. Efficient cellular uptake and co-localization within acidic intracellular compartments were

demonstrated and the corresponding release of these proteolytic enzymes rapidly induced cell death. [64]

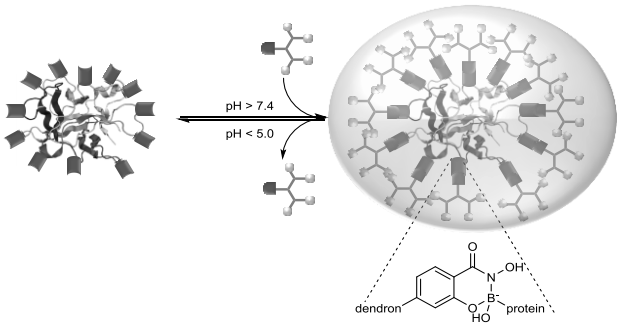


Figure 6. Synthesis and supramolecular dendritic assembly for the construction of hybrid zymogens.[64]

Collectively, each of these strategies have provided the first results in employing the PBA-SHA based complexation towards a very diverse class of bioconjugates, each showcasing the flexibility and robustness of the system.

Conclusion

In this focus review we reported the capability of boronic acids to undergo "click"-reactions in a bioorthogonal and pH-reversible manner. By changing the substituents on either the boronic acid or the ligand, the stability of the resulting boronates can be easily diversified to allow the construction of the aforementioned supramolecular architectures. One could envision changing the ligand to *N*-methyliminodiacetic acid (MIDA), which forms the so called MIDA-Boronates, firstly introduced by Martin D. Burke in 2007.[65] These boronates are even stable to very harsh acidic conditions, but can be hydrolyzed under alkaline environment within minutes, thus showing a contrast to the boronic acid-diol or –salicylhydroxamate systems.

Compared to other "click"-reactions, reactions involving boronic acids or boronates offer some distinct advantages since they occur under mild and physicological conditions and with high reaction kinetics. In addition, no cytotoxic metal catalyst has to be used to perform these complexations. These boronic acid based systems have displayed the potential to build up several different stimulus responsive materials and will be expected establish a strong foothold in reversible bioorthogonal click chemistry.

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Reversible click reactions with boronic acids to build supramolecular architectures in water

*Matthias Arzt, Christiane Seidler, David Y. W. Ng, Tanja Weil **

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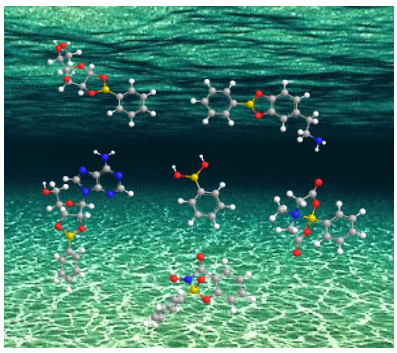
Reversible click reactions with boronic acids to build supra-molecular architectures in water



Boronic acids are able to undergo complexation with 1,2-diols or salicylhydroxamates in a pH-depenend manner. This allows building pH-reversible, supramolecular architectures in aqueous media.