

New Boronate Monomers and Polymers

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Boronate ester technology is of great interest because esterification of boronic acid is spontaneous but is readily reversible and this is especially valuable when the alcohol is glucose because its boronate ester can function as a diabetic indicator of blood glucose or even as an insulin release mechanism. A recent excellent review goes into great detail concerning this interesting chemistry.

Brooks, William LA, and Brent S. Sumerlin. "Synthesis and applications of boronic acid-containing polymers: From materials to medicine." *Chemical reviews*, 116.3 (2015): 1375-1397.

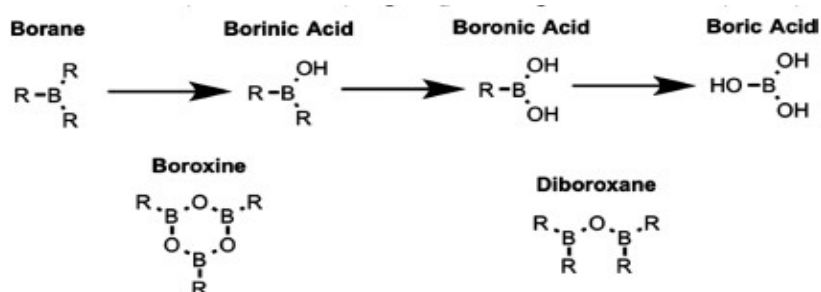
A simple search on Google Scholar returned thousands of boronate references, so it is no easy task to comprehend all of its chemistry; therefore, I limited my interest to polymeric boronate derivatives.

Vinyl boronate is the first monomer to come to mind, but even though it will polymerize, it is difficult to polymerize and never went commercial.

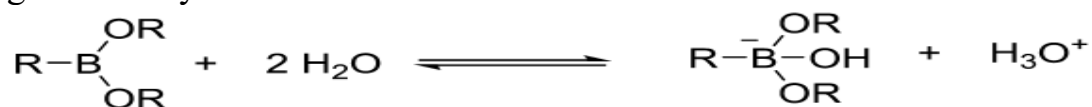
Mulvaney, J. E., R. A. Ottaviani, and J. J. Laverty. "Preparation of vinyl boronate copolymers and reactions." *Journal of Polymer Science Part A: Polymer Chemistry*, 20.7 (1982): 1949-1952.

A review of boronate chemistry will help explain my ideas.

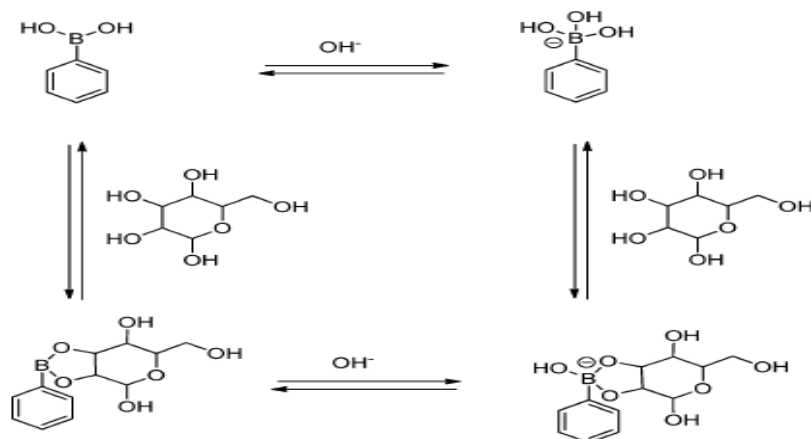
Hall, Dennis G. "Structure, properties, and preparation of boronic acid derivatives. Overview of their reactions and applications." *Boronic acids: preparation and applications in organic synthesis and medicine*, 1 (2006): 1-99 and 2011 2nd edition.



Scheme 1: Naming the oxidation derivatives of borane, while boroxine and diboroxane are analogous to anhydrides.



Because of the empty p-orbital on boron, the boronate esters will coordinate an hydroxide to fill that orbital releasing a proton.



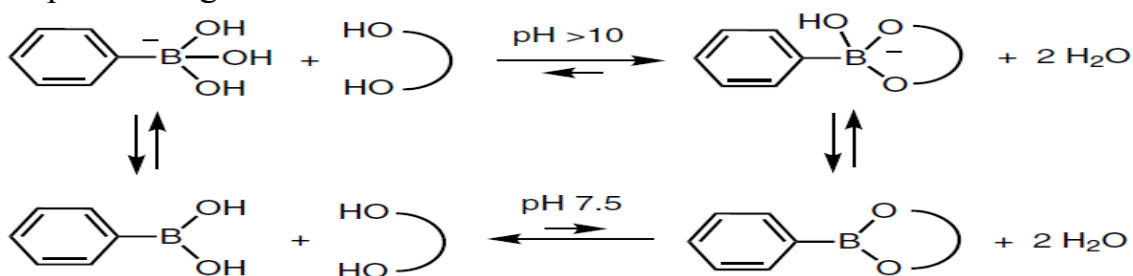
Scheme 2: (The reverse equilibrium arrow below the OH⁻ should have a H⁺ to reverse the equilibrium.)

As shown in scheme 2, this reaction is reversible and pH dependent. The reason is because boron has a free p orbital and acts as a Lewis acid in water.

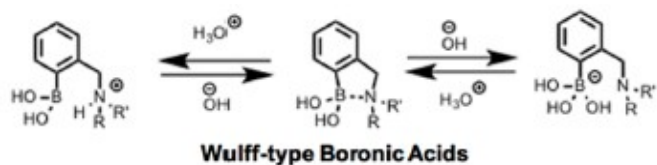
Li, Meng, et al. "Electrochemical sensing using boronic acids." *Chemical Communications*, 51.78 (2015): 14562-14573.

If you prepare a polymer with boronate esters in anhydrous solvents then add said polymers to aqueous containing solutions in which a sugar has also been added then because of the equilibria, a transfer of the more reactive diol will occur (pH also plays a roll here as acidic pH favors hydrolysis while higher pH favors ester formation). However, the point I'm making is that monomers and polymers containing boronate esters are stable enough when not in aqueous solution and their synthesis can be achieved in such anhydrous solvents without concern.

However, in water solution, boronic acids will form boronate esters at the pK_a of the boronic acid (alkaline). This is very unique because you can mix in aqueous media, polyboronic acids with polyalcohols to form supermolecular compounds! The reactions occur upon mixing even at RT.

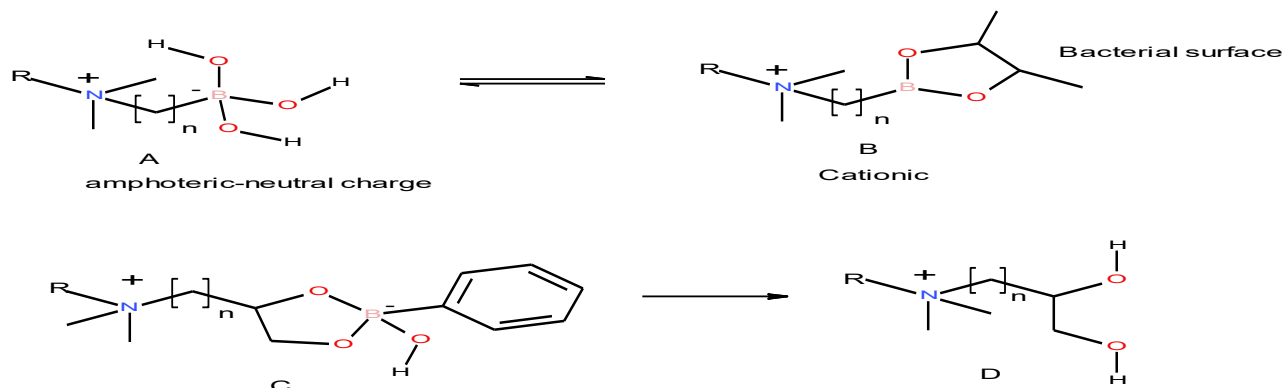


Scheme 3: Esterification at alkaline pH and negative charge on boron. Nitrogen containing molecules can replace one of the OH groups because it is more nucleophilic.



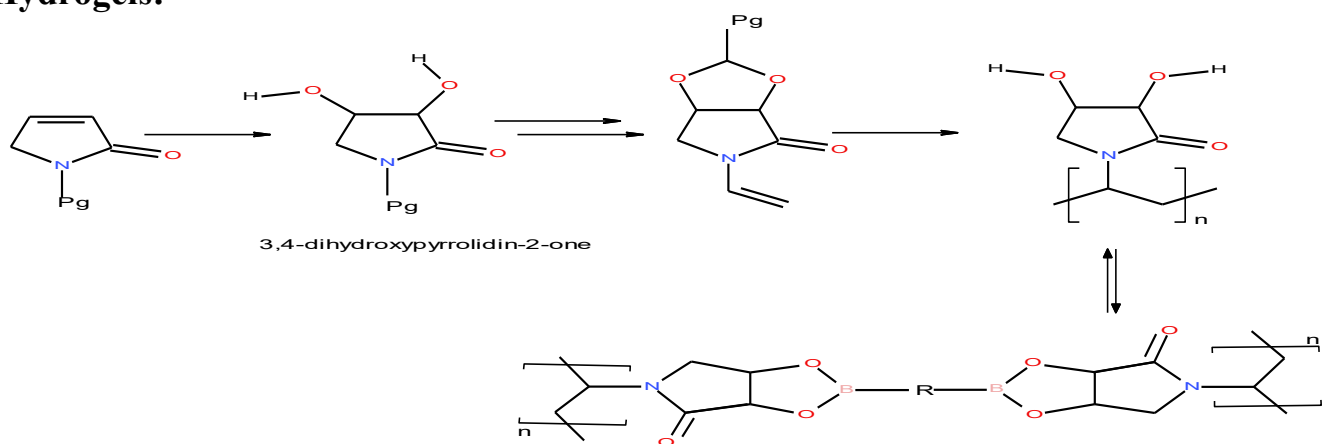
This is just an example as the nitrogen can be heterocyclic or on a separate compound etc.

Germicidal Boronates



Scheme 4: The general indicated quat stands for all types of quats; monomeric, polymeric or surfactants as long as they are capable of killing bacteria. The idea is that in water the cationic charge is balanced by the negative charge on boron rendering the amphoteric harmless. B is the idea that the bacteria have a polymeric sugar coat that will form a boronate ester, revealing the germicidal quat where it can do the most harm. D is the idea that the bacterial polymeric sugar coat will be more attractive and exchange the boronate ester, freeing the quat next to the bacterial coating where it can disrupt it.

Hydrogels:

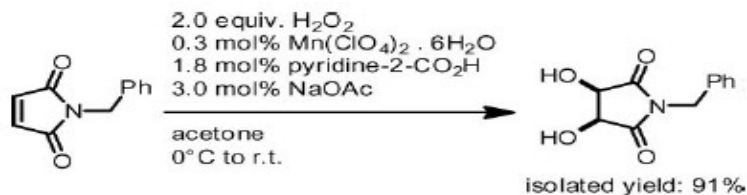


Scheme 5: Proposed dihydroxy NVP(OH groups must be cis) that can be cross linked in aqueous solution with diboronic acids upon mixing!

Synthesis of dihydroxy monomers:

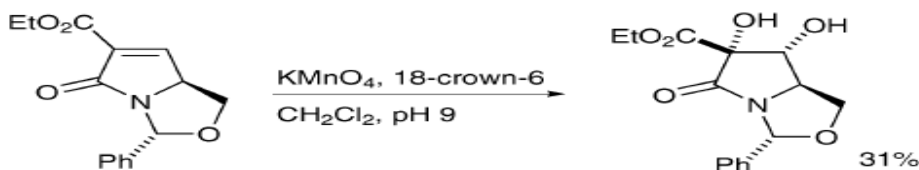
Ho, Chi-Ming, Wing-Yiu Yu, and Chi-Ming Che. "Ruthenium Nanoparticles Supported on Hydroxyapatite as an Efficient and Recyclable Catalyst for cis-Dihydroxylation and Oxidative Cleavage of Alkenes." *Angewandte Chemie*, 116.25 (2004): 3365-3369.

Brinksma, Jelle, et al. "Homogeneous cis-dihydroxylation and epoxidation of olefins with high H₂O₂ efficiency by mixed manganese/activated carbonyl catalyst system." *Tetrahedron letters*, 43.14 (2002): 2619-2622.



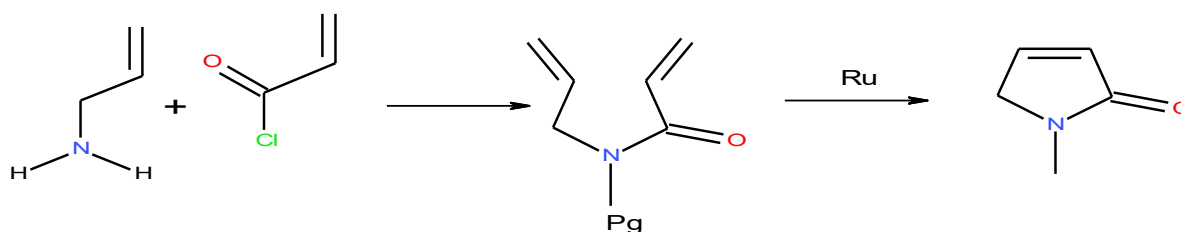
Scheme 1 *cis*-Dihydroxylation of 1-benzyl-1*H*-pyrrole-2,5-dione using the method described here.

Saisaha, Pattama, et al. "Manganese catalyzed cis-dihydroxylation of electron deficient alkenes with H₂O₂ DOI: 10.1039/c0ob00102c." *Organic & biomolecular chemistry*, 8.19 (2010): 4444-4450.



Scheme 27

Bataille, Carole JR, and Timothy J. Donohoe. "Osmium-free direct syn-dihydroxylation of alkenes." *Chemical Society Reviews*, 40.1 (2011): 114-128. (the low yield might be because of steric crowding)

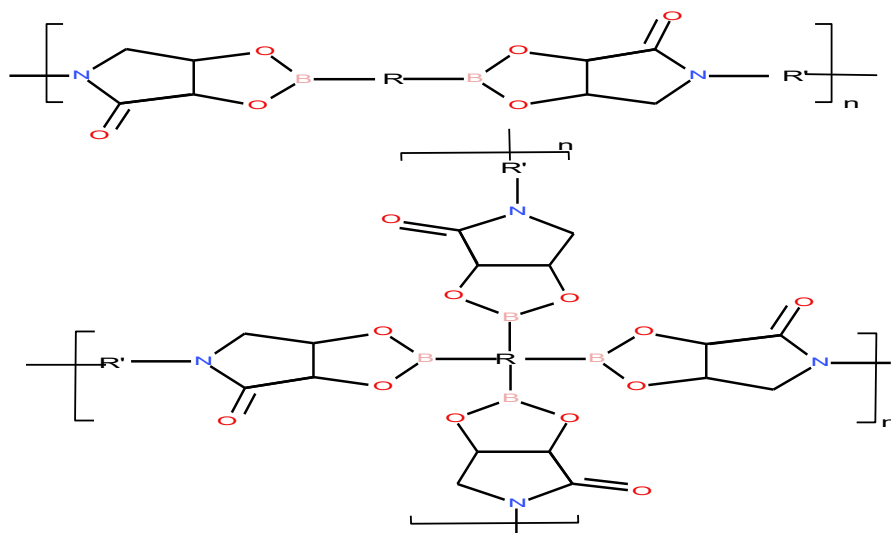


Scheme 6: Metathesis route to starting RM.

With NVP copolymers, the 3,4-dihydroxy comonomer would form water soluble copolymers that would form interesting and reversible gels with boronic crosslinkers suitable for delivering (poorly soluble) drugs, RNA and DNA or various proteins that had been mixed into the copolymer before crosslinking. Release of said drugs could be accomplished if for example a sugar happened to be present. It could even react through the diol with drugs derivatized with labile boronic acids as pro-drugs that would also be released when the pH was acidic.

Similar gels have found use as sugar indicators and insulin release systems because sugars will replace the crosslinks hence affording a method to detect them (gel swelling

or collapse). Insulin derivatized with releasable diols (the labile diol can be removed once outside the gel) that can be released by glucose. PVP based boronate copolymers would be safe vehicles for such chemistry because PVP has an excellent toxicity profile. Sun, Xiaolong, and Tony D. James. "Glucose sensing in supramolecular chemistry." *Chemical reviews*, 115.15 (2015): 8001-8037.

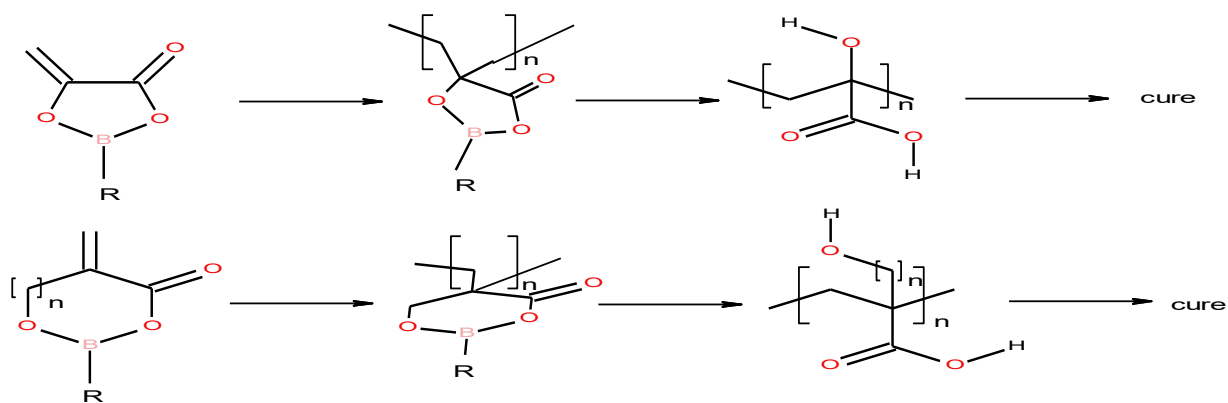


Scheme 7: Dimers of the 3,4 dihydroxy pyrrolidone can form linear and branched polymers examples of which are illustrated in scheme 5. These polymers will form spontaneously in water containing polyboronic acids at basic pH's (pka of the boronic acid). They are examples of COF chemistry (covalent organic frameworks).

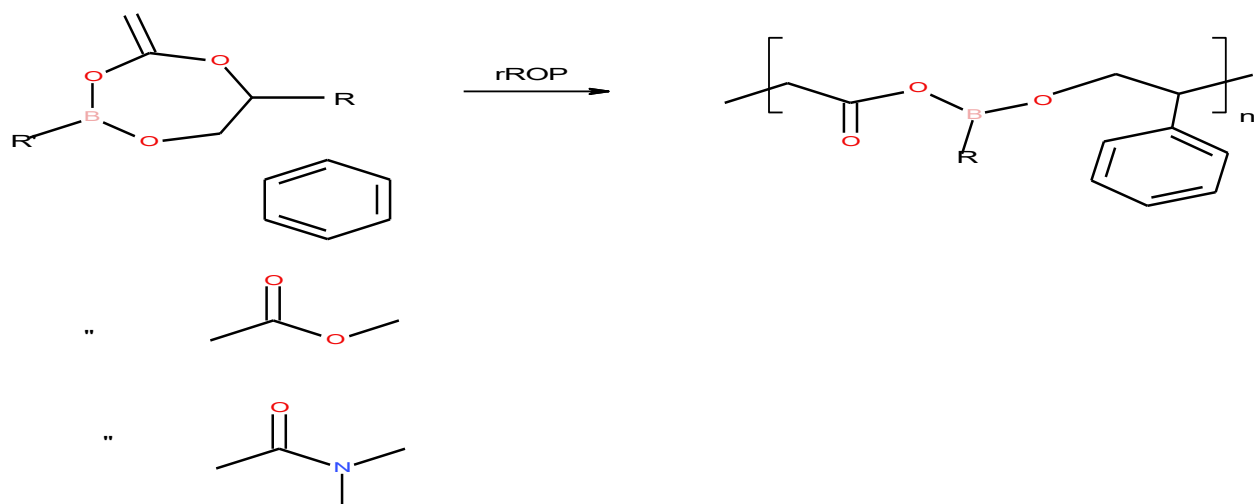
Rambo, Brett M., and John J. Lavigne. "Defining self-assembling linear oligo (dioxaborole) s." *Chemistry of materials*, 19.15 (2007): 3732-3739.

Kubo, Yuji, Ryuhei Nishiyabu, and Tony D. James. "Hierarchical supramolecules and organization using boronic acid building blocks." *Chemical Communications*, 51.11 (2015): 2005-2020.

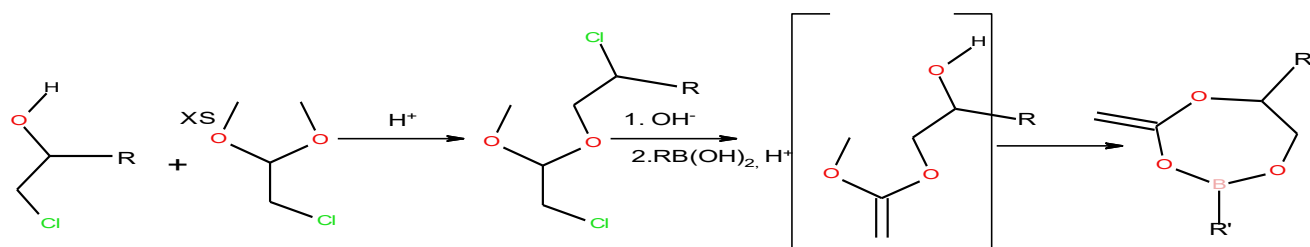
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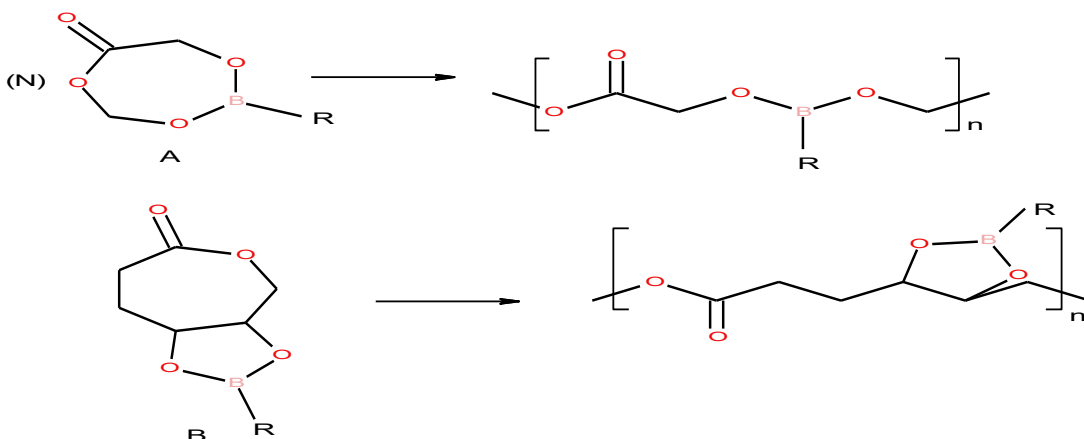
Scheme 8: Exocyclic acrylate type monomer idea. The five membered ring monomer would be easier to synthesize as it could be prepared from pyruvic acid and a boronic acid. The resulting polymer could be hydrolyzed in water under acidic conditions or by oxidation with hydrogen peroxide or with added reactive sugars. The resulting hydroxy carboxylic acid could cure (form polyesters) upon dry down.



Scheme 9: rROP boronate monomer possibilities.



Scheme 10: I'm betting that reaction with boronic acid is very fast and will grab the desired intermediate? I'm sure there are other synthetic routes, however?



Scheme 11: Polyester or polyamides are possible if the boronate esters would stand up to the catalysts and conditions required? Monomer A results in the boronate in the

polymer backbone where it would be very vulnerable to water hydrolysis even more so than the commercial polyanhydrides. B (..see cis-dihydroxylation references) would be more hydrolysis resistant but would easily exchange with more reactive diols(sugars) as a way to expose dihydroxy groups on the polymer backbone.

Obviously, boron chemistry is much more than boronic acid derivatives, even though they are extremely important for example in Suzuki coupling. The following book however shows how much more there is to this chemistry.

Hall, D. "Boronic Acids" Preparation and Applications in Organic Synthesis, Medicine and Materials Second Completely Revised Edition Preface." *Boronic Acids*, 2 (2011).

In conclusion, thank you for reading this proposal. I would welcome any comments or suggestions.

Thank you,
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