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Boronic Acid-Based Hydrogels Undergo Self-Healing at Neutral and Acidic pH

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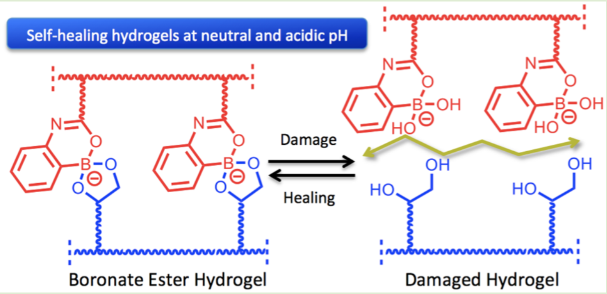
Supporting Information

ABSTRACT: This report describes the synthesis and characterization of boronate ester-cross-linked hydrogels capable of self-healing behavior at neutral and acidic pH. This atypically wide pH range over which healing behavior is observed was achieved through the use of an intramolecular coordinating boronic acid monomer, 2-acrylamidophenylboronic acid (2APBA), where the internal coordination helped to stabilize cross-links formed at acidic and neutral pH. Two different hydrogels were formed from a 2APBA copolymer cross-linked with either poly(vinyl alcohol) or a catechol-functionalized copolymer. The self-healing ability of these hydrogels was characterized through physical testing and rheological studies. Furthermore, the catechol cross-linked hydrogel was shown to be oxygen sensitive, demonstrating reduced self-healing and stress relaxation after partial oxidation. The synthesis of these hydrogels demonstrates a new strategy to produce boronic acid materials capable of self-healing at physiological pH.



Hydrogels consist of cross-linked networks of hydrophilic polymers swollen with an aqueous solution.[1] Hydrogels have been examined for a number of roles, with much of the current literature focused on applications in the field of biomedical engineering, including use in drug delivery, tissue engineering, and wound dressings.[2−6] Hydrogels are well-suited for biomedical applications due to their hydrophilic nature, porous structure, and adjustable stiffness.[7] Some hydrogels have been prepared with functional groups that permit reversible interactions or reversible cross-linking to allow for self-healing character.[8−13] The ability of a hydrogel to repair damage autonomously is tremendously useful in a variety of areas, including in many of the applications mentioned above.[14,15]

Reversibility in hydrogels can be accomplished by either relying on physical cross-links or employing reversible covalent bonds.[16] The advantage of the latter approach is that the gels can maintain both the robust integrity of covalently cross-linked materials and the intrinsic reversibility of physically cross-linked systems. One example of a reversible covalent bond that can be used for hydrogel cross-linking is the complexation between boronic acids and 1,2- or 1,3-diols.[17−20] The boronate ester bond has been employed to create self-healing networks, molecular sensors, and cancer cell sweepers.[21] The strength and reversibility of boronate ester cross-links in aqueous media is governed by an equilibrium that is heavily dependent on solution pH and the pK_a of the boronic acid component. At pH values above the pK_a of the boronic acid, boronate ester bond formation is favored, while below the pK_a the equilibrium favors the free boronic acid and diol.[22−24] As this system is in a dynamic equilibrium between diol/boronic acids and boronate esters, bond rearrangement can occur, which allows for self-healing behavior if the newly formed bonds span the damage interface between two boronate ester-cross-linked materials.

The pK_a of most aryl boronic acids lies in the range of 8−9. As mentioned above, the pK_a is important for self-healing applications of boronic acid−based materials, because exchange between boronic acid/diol and boronate esters is most effective when the pH is near the pK_a.[25] Employing boronic acids that can heal at lower pH would be advantageous, especially for biomedical applications.[26] One method to accomplish this is by using intramolecular coordination that can stabilize boronate ester formation at reduced pH.[27−30] In this work we employ a boronic acid-containing acrylamide monomer to prepare water-soluble polymers that can be cross-linked via boronate ester formation with diol-containing polymers. The monomer, 2-acrylamidophenylboronic acid (2APBA), allows for intramolecular coordination between the carbonyl oxygen of its acrylamido moiety and the boron of the boronic acid group (Figure S1, Scheme 1).[31] Compared to B−N coordination present in Wulff-type boronic acids, B−O bonds are stronger and should therefore be more capable of stabilizing the formed ester.[32,33] Given that ester formation between a boronic acid and diol is known to be favored by the boron existing in the tetrahedral form, polymers of 2APBA should be capable of forming strong boronate ester hydrogels when mixed with diol-containing polymers. More importantly, we reasoned that intramolecular B−O coordination in 2APBA would facilitate

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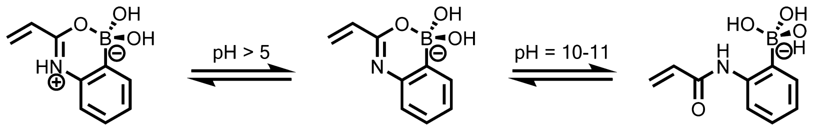
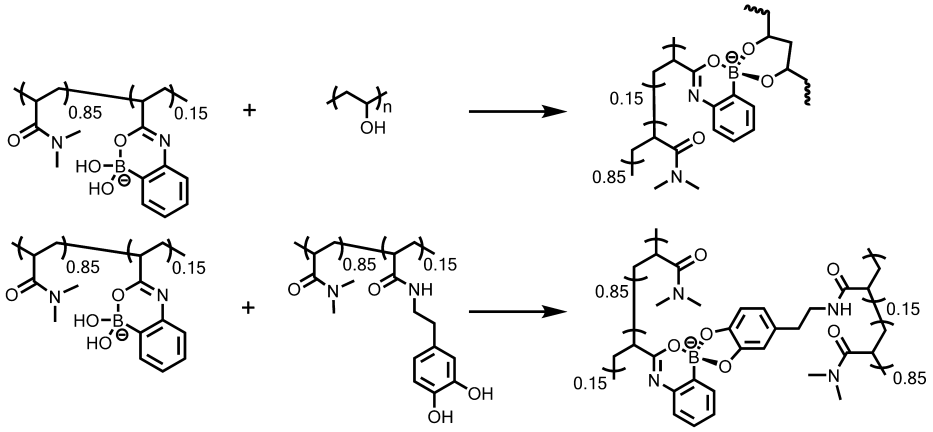
Scheme 1. Equilibrium of 2-Acrylamidophenylboronic Acid (2APBA) in Water[a]



[a]Intramolecular B−O bond formation leads to the tetrahedral geometry of the boron atom that promotes boronate ester formation.

Scheme 2. Hydrogel Formation between P(2APBA-*co*-DMA) (15 mol % 2APBA) with PVOH and P(DOPAAm-*co*-DMA) (15 mol % DOPAAm) at Neutral pH



boronic acid-diol complexation, even at neutral and acidic pH, while maintaining the dynamic exchange inherent to boronate esters in aqueous media. Therefore, hydrogels cross-linked via diol complexation with 2APBA units should demonstrate self-healing behavior at pH ranges that were previously considered too low for boronic acid-containing materials. Herein, we report the preparation and preliminary self-healing properties of boronate ester hydrogels based on 2APBA in neutral and acidic pH ranges that would typically be considered too low for most boronic acid−based polymers.

We set out to prepare separate boronic acid-containing copolymers and diol-containing (co)polymers that would form hydrogels on mixing. *N*,*N*-Dimethylacrylamide (DMA) was chosen as the comonomer for polymerization with the pinacol-protected ester of 2APBA (i.e., 2APBAE) because of its hydrophilicity and biocompatibility.[34] GPC analysis of the P(2APBAE-*co*-DMA) copolymers with 10 and 15 mol % 2APBA yielded M_n values of approximately 34,000 g/mol (Đ = 3.5) and 38,000 g/mol (Đ = 4.2), respectively (Figure S2). Two different diol-containing copolymers were considered (Scheme 2). A dopamine acrylamide (DOPAAm) copolymer, P(DOPAAm-*co*-DMA), was prepared, as catechol groups are known to bind strongly to boronic acids in aqueous media.[35,36] However, given that catechols are prone to oxidation at neutral pH when exposed to air,[37] which could potentially lead to loss of self-healing ability over time,[38] poly(vinyl alcohol) (PVOH) was also used as an alternative polymeric diol, due to the high density of 1,3-diol groups along its backbone.

The catechol polymers were synthesized via nucleophilic substitution of pentafluoroacrylate (PFPA)-DMA copolymers with dopamine.[39] Activated ester chemistry allowed for facile synthesis of the desired polymer, with the functionalization being readily monitored by ^{19}F NMR spectroscopy via the cleavage of the pentafluorophenolate group (Figure S3).[40] GPC analysis of the P(DOPAAm-*co*-DMA) copolymers with 10 and 15 mol % DOPAAm gave M_n values of approximately 90,000 g/mol (Đ = 2.9) and 111,000 g/mol (Đ = 3.0), respectively (Figure S4), though the insolubility of the polymer with 15 mol % DOPA prevented its subsequent use in hydrogels. The hydrogels of the P(2APBA-*co*-DMA) copolymers with P(DOPAAm-*co*-DMA) or PVOH were created in deionized water and in an acidic buffer at pH 4.0.

Hydrogel formation, qualitatively confirmed through a vial inversion test, occurred rapidly after mixing the two boronic acid- and diol-containing polymer solutions and gently stirring (Figure 1). The rapid onset of gelation is consistent with boronate ester formation under both acidic and neutral conditions. Interestingly, hydrogels created from P(DOPAAm-*co*-DMA) and P(2APBA-*co*-DMA) were initially

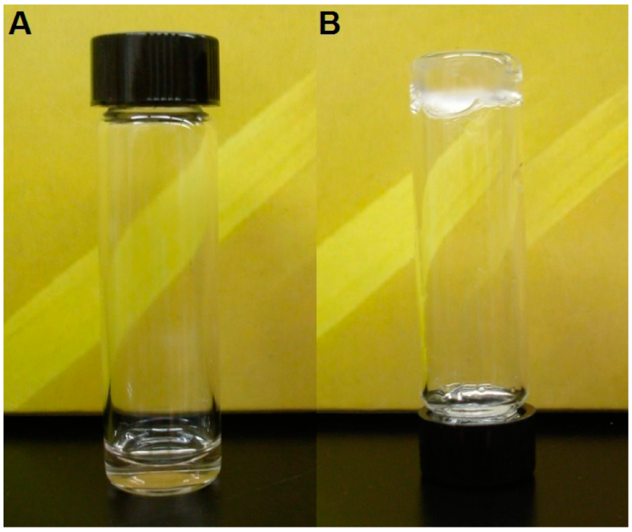


Figure 1. Solution (10 wt %) of P(2-APBA-*co*-DMA) (10 mol % 2APBA) at pH 7.0 (A) before and (B) after addition of a solution (10 wt %) of PVOH in deionized water.

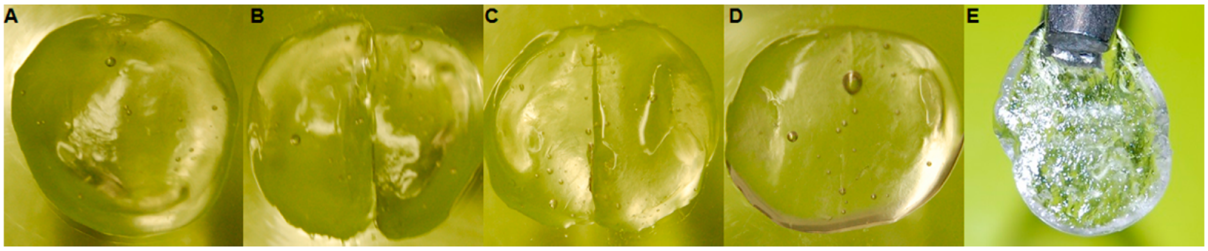


Figure 2. Healing of hydrogels formed by cross-linking P(2APBA-*co*-DMA) (10 mol % 2APBA) with PVOH. (A) Intact gel; (B) Cut gel; (C) Gel halves placed in contact immediately after cutting; (D) Healed gel after 60 min; (E) Healed gel suspended under its own weight. The concentration of both polymer solutions was 10 wt % prior to mixing.

colorless, but darkened over time due to catechol oxidation. This process was noticeable within 24 h in deionized water and over several days in acidic buffer. However, when these hydrogels were created in a reducing solution of sodium bisulfite, the hydrogel did not darken over time (Figure S5).

Given that all cross-links within the hydrogel were expected to be dynamic-covalent as a result of their rapid exchange due to boronate ester formation/hydrolysis, we decided to investigate the self-healing characteristics of the gels. As a qualitative assessment of self-healing ability, cut/heal tests were conducted on the hydrogels. Disks of each gel were created and subsequently sliced into two equal pieces. These halves were then placed in contact to induce healing. In all cases, the gels appeared to heal within 60 min, as evidenced by the gradual disappearance of the scar at the damage site and by the gels regaining their mechanical integrity (Figure 2). This behavior suggests that boronate ester formation across the damage interface allowed the gel to covalently heal. In aqueous media, boronate esters are under equilibrium with their boronic acid and diol constituents, which leads to a finite concentration of free boronic acid and diol groups available for covalent healing by esterification. The healed gels were sufficiently strong to support their own weight when suspended.

Rheometry was also employed to gain insight into the properties of the hydrogels and to quantify their self-healing nature. The stiffness of the gels demonstrated a slight dependence on copolymer composition for P(2APBA-*co*-DMA) copolymer, with increasing content of 2APBA leading to slightly higher storage moduli, presumably due to the higher degree of cross-linking. Most importantly, the rheological behavior of the gels was consistent with that expected for systems involving dynamic (i.e., reversible) cross-links. While permanently cross-linked gels demonstrate frequency-independent moduli with storage modulus (G') > loss modulus (G''), dynamically cross-linked gels are expected to demonstrate frequency-dependent moduli with $G' > G''$ at high frequencies. For these boronate ester hydrogels, G' was greater than G'' at all frequencies over 0.1 rad/s at pH 4.0 (Figure 3) and 7.0 (Figure S6A). These results indicate the time scale probed in these experiments is shorter than the lifetime of the reversible cross-links, which gives rise to predominantly elastic behavior because the network is not allowed time to restructure when perturbed.

The gels cross-linked with the DOPAAm copolymers and the PVOH homopolymers exhibited self-healing behavior in strain sweep experiments at acidic (Figure 4) and neutral pH (Figure S7). The hydrogels were subjected to increasing strain (10 rad/s) until the cross-links failed, as indicated by the crossover of G' and G''. At this critical point, the hydrogel begins to exhibit more fluid character than elastic character. After the strain was reduced to within the linear viscoelastic region, the cross-links recoupled rapidly, restoring the original hydrogel moduli values. The PVOH hydrogels had an overall higher equilibrium modulus (~1 kPa) than the DOPAAm hydrogels (~350 kPa), which can likely be attributed to the increased cross-link density expected in the presence of the PVOH hydrogels, as the concentration of diols that can participate in cross-linking in this homopolymer is considerably higher than for the P(DOPAAm-*co*-DMA) copolymer. Interestingly, there is little difference in the strength of each hydrogel between neutral and acidic pH, which is directly attributable to negligible difference in coordination strength at these pH values as a result of the intramolecular complexation within 2APBA.

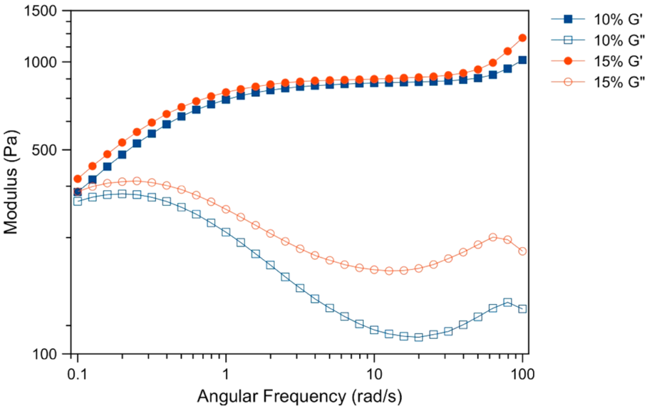


Figure 3. Frequency sweep of the hydrogels formed from P(2APBA-*co*-DMA) (10 mol % and 15 mol % 2APBA) with PVOH at pH 4.0. Original polymer solutions were 10 wt %. Strain was constant at 5%.

We were also interested in assessing the potential effect of catechol oxidation on the rheological and self-healing properties of the gels containing the random P(DOPAAm-*co*-DMA) copolymers. Rheometry was conducted on a gel formed from P(2APBA-*co*-DMA, 10 mol % 2APBA) and P(DOPAAm-*co*-DMA, 10% DOPAAm) that was left exposed to air for 24 h. Despite the apparent oxidation observed by the gradual change in color, the gel retained the same moduli values and self-healing abilities as a control gel that was kept in the absence of oxygen (Figure S8). However, there was a noticeable increase in gel stiffness upon prolonged oxidation, which resulted in increased difficulty of setting the gap used in previous rheological testing. A visual creep test was conducted on another P(DOPAAm-*co*-DMA) hydrogel that was left to oxidize for a week in a closed container. Although the unoxidized boronate ester hydrogels demonstrated noticeable creep over time, a behavior attributable to the equilibrium between dynamic-covalent cross-links, the oxidized gel did not creep and retained a definite shape (Figure S9). The same test

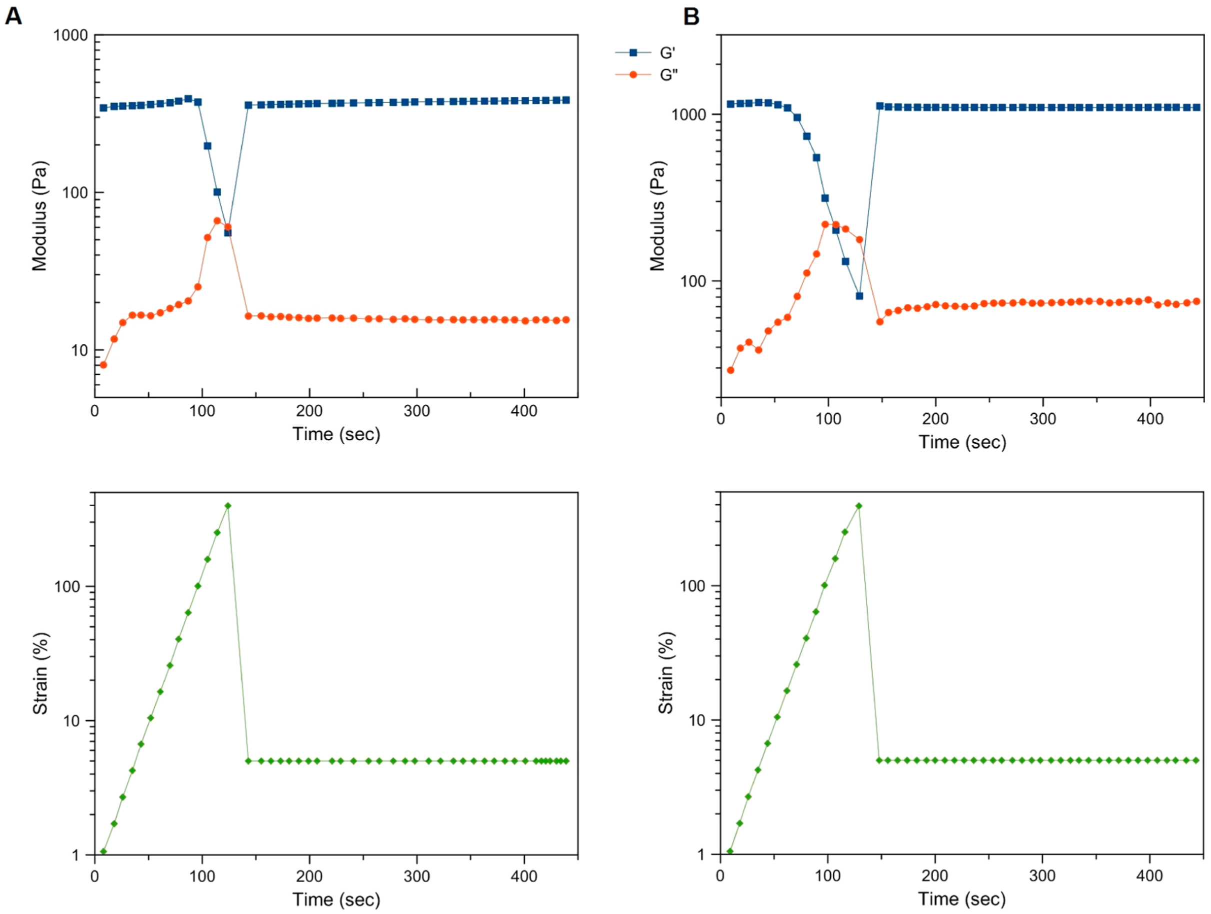


Figure 4. Self-healing of hydrogels after fracture. The top two plots demonstrate the change in modulus during the strain ramp described by the bottom plots. The hydrogels fractured during the strain ramp up to 400% and rapidly healed after the strain was reduced. (A) Hydrogels formed from P(2APBA-*co*-DMA) (10 mol % 2APBA) with P(DOPAAm-*co*-DMA) (10 mol % DOPAAm) at pH 4.0 and (B) hydrogels formed from P(2APBA-*co*-DMA) (10 mol % 2APBA) with PVOH at pH 4.0. Original polymer solutions were 10 wt %. Angular frequency was constant at 10 rad/s.

was conducted on a P(DOPAAm-*co*-DMA) hydrogel created and aged in a sodium bisulfite solution. This unoxidized hydrogel exhibited noticeable creep compared to the oxidized sample (Figure S10). The oxidized hydrogel also exhibited increased stiffness during rheometry. Unable to creep, the oxidized hydrogel transmitted more force on the rheometer at the same gap setting, exceeding the maximum allowed force of the instrument. Finally, the oxidized hydrogel was unable to self-heal, even after 48 h, when subjected to the same cut/heal test used previously. These findings are attributed to oxidation of the catechols into their quinone form, simultaneously removing boronate ester cross-linking potential in the hydrogel and causing permanent cross-links between quinone moieties.[41] As these covalent cross-links cannot rearrange like dynamic cross-links,[42] they reduce the creep and stress relaxation behaviors exhibited in the boronate ester cross-linked hydrogel.

In summary, we were able to create a boronic acid hydrogel that self-heals at acidic and neutral pH by exploiting a boronic acid-containing monomer capable of intramolecular coordination. This intramolecular coordination between the carbonyl oxygen and boron resulted in stabilized boronate ester cross-links, which in turn allowed for hydrogels to be formed at neutral and acidic pH. Rheometry demonstrated that there was little dependence of pH on the strength of the hydrogels and that PVOH-cross-linked materials exhibited greater strength than those cross-linked by P(DOPAAm-*co*-DMA) due to the higher cross-link density in the former. Additionally, we demonstrated that oxidation of the dopamine moieties in P(DOPAAm-*co*-DMA) may lead to gradual changes in hydrogel properties including a reduction in self-healing properties and minimalized creep. The broader pH range at which healing can occur increases the possible applications of boronate ester hydrogels as biological materials, with the additional stability at lower pH values potentially being of benefit in acidic environments like the gastrointestinal tract.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and supporting figures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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