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Improved Comonomer Reactivity Enhances Optical Clarity and Mechanical Properties of pH-Independent Synthetic and Mucin-Cross-Linked Boronic Acid Hydrogels

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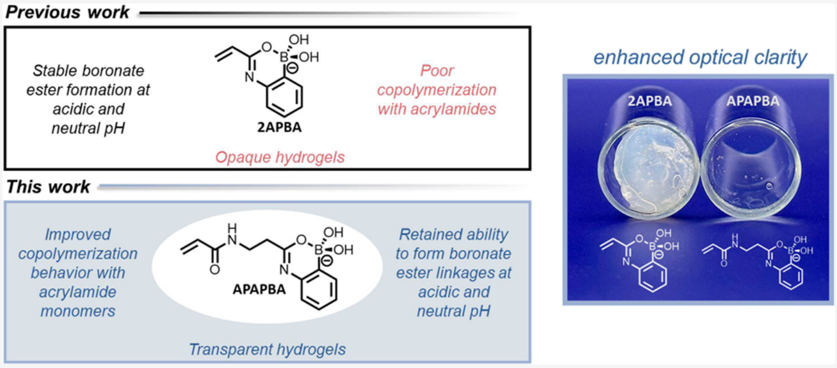

ABSTRACT: Boronate esters are formed from the complexation between boronic acids and *cis*-diols and are widely used as cross-links in self-healing hydrogels. Boronate esters are typically formed in a pH range of 8−9, although a variety of strategies allows for their formation at lower pH values. One such strategy is the use of an intramolecularly coordinating boronic acid monomer, 2-acrylamidophenylboronic acid (2APBA), where the internal coordination between the carbonyl oxygen and the boronic acid boron stabilizes cross-links formed at acidic and neutral pH. However, poly(vinyl alcohol) (PVA)/boronic acid hydrogels created from 2APBA become opaque over time, likely due to the development of regions of high cross-link density, which potentially precludes use in applications where optical transparency is needed. We attribute this phenomenon to the 2APBA copolymer precursors containing long runs of boronic acid units as a result of the disparate reactivity ratios with acrylamido comonomers. In this report, we synthesized a new boronic acid monomer, (2-(3-acrylamidopropanamido)phenyl) boronic acid (APAPBA), which exhibited improved reactivity with *N,N*−dimethylacrylamide and enables the synthesis of copolymers with more uniform distribution of boronic acids. The resulting hydrogels with PVA demonstrate higher moduli and optical transparency. Finally, these APAPBA-based copolymers were used to synthesize biohybrid hydrogels with natural mucin, highlighting the potential of this monomer for use in biological applications where optical clarity is important.

■ INTRODUCTION

Hydrogels are ubiquitous in diverse fields of research, notably in the area of biomedical engineering where they are used in drug delivery, tissue engineering, and as wound dressings.[1−5] While hydrogels are inherently well suited to these applications, more advanced functionalities can be incorporated to expand their utility. One such functionality is reversible cross-links. There has been a wide variety of reversible cross-links utilized in hydrogels, each with unique advantages and disadvantages.[6] The potential benefits of reversibly cross-linked hydrogels in biomedical applications are significant and include self-healing implants, improved mobility of cells in cell scaffolds, and injectable drug delivery.[7−10]

In the field of reversibly cross-linked hydrogels, our group has focused on dynamic covalent bonds. In one example, self-healing hydrogels were created from copolymers of *N,N*-dimethylacrylamide (DMA) and diacetone acrylamide.[11] Cross-linking was afforded via the formation of oximes with difunctional alkoxyamines. These hydrogels exhibited self-healing behavior in both cut-healing tests and rheometry.

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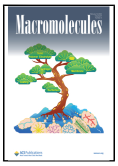
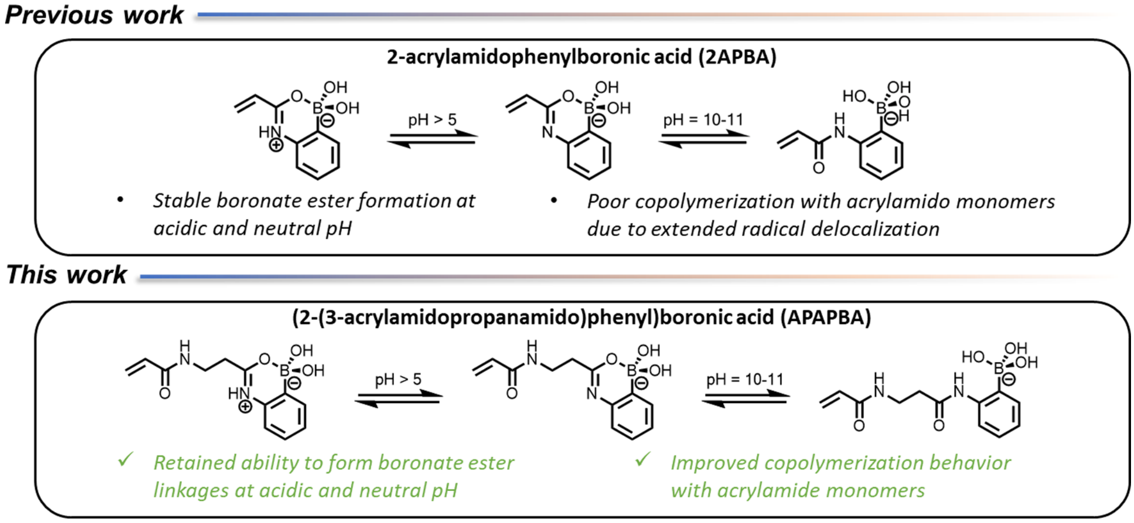


Scheme 1. Equilibrium of 2-Acrylamidiophenylboronic Acid (2APBA) and (2-(3-Acrylamidopropanamido)phenyl)boronic Acid (APAPBA) in Water



Another example is the use of boronate esters as hydrogel cross-links.[12,13] The formation of boronate esters occurs when boronic acids are complexed with *cis*-1,2- or 1,3-diols.[14−20] The lability of these boronate esters in aqueous media is governed by an equilibrium that is heavily dependent on both the solution pH and the pK_a of the boronic acid. 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.[21−24] The system being in equilibrium is important for self-healing, as the rearrangement allows for cross-linking moieties to break and reform to heal any defects.

The main challenge with using boronate esters as cross-links is that exchange between boronic acid/diol and boronate esters is most effective when the pH is above the boronic acid pK_a.[25] As the pK_a of most aryl boronic acids lies in the range of 8−9, materials containing boronic esters are generally not suited for applications at physiological pH. The ability to form boronate cross-linked hydrogels at neutral and acidic pH has been accomplished by exploiting intramolecular coordination that stabilizes boronate ester formation at reduced pH or by tuning the pK_a of aryl boronic acid moieties by substitution with electron-withdrawing groups.[26−30] Our group reported the use of 2-acrylamidophenylboronic acid (2APBA) to prepare water-soluble copolymers that were cross-linked via boronate ester formation with diol-containing polymers. The carbonyl oxygen of the acrylamido moiety in the 2APBA monomer coordinates with the boron of the boronic acid group (Scheme S1),[31] shifting the equilibrium toward the boronate ester. As this occurs at neutral and even acidic pH, hydrogels cross-linked with various diol polymers were able to be formed in pH ranges well below those typical for boronic acid hydrogels.[32] These hydrogels also demonstrated self-healing in neutral and acidic media through cut-healing tests and rheometry.

Despite successful gelation and demonstration of self-healing, 2APBA-based hydrogels become opaque over time, usually within minutes. This opacity potentially precludes their use in applications for which optical transparency is needed. For example, if the hydrogel is used as a cell scaffold, then cloudiness could complicate or prevent photometric assays. The source of this opacity is likely attributed to the distribution of the boronic acid monomer along the backbone of the copolymer. Specifically, if 2APBA preferentially polymerizes with itself over cross-propagation with less reactive comonomers, then copolymer drift would lead to copolymers with high incorporation and extended runs of 2APBA early in the polymerization. When these 2APBA-rich chains are cross-linked with poly(vinyl alcohol) (PVA), this disparate monomer incorporation would create a heterogeneous distribution of cross-link density, leading to enhanced scattering of light and unequal stress loading, producing weaker, opaque hydrogels.[33,34] This poor copolymerization behavior could be rationalized by the extended delocalization of the 2APBA propagating radical with the adjacent π system, thereby leading to poor cross-propagation with other acrylamido monomers. To enhance copolymerizability with traditional acrylamido monomers while retaining the intramolecular coordination of the boronic acid, we reasoned that an ethylene spacer could be installed between the acrylamido and the amidophenylboronic acid moiety (Scheme 1).

In this report, we quantify and compare the reactivity of 2-acrylamidophenylboronic acid pinacol ester (2APBAE) and (2-(3-acrylamidopropanamido)phenyl)boronic acid pinacol ester (APAPBAE) with DMA and discuss how this results in improved mechanical properties for self-healing hydrogels created from APAPBA copolymers. We also apply this discovery to synthesize biohybrid gels between boronic acid-containing copolymers and natural mucin that demonstrate improved optical clarity.

■ RESULTS AND DISCUSSION

Pinacol ester-protected APAPBA (APAPBAE) was synthesized via amide coupling of 3-acrylamidopropanoic acid and 2-aminophenylboronic acid pinacol ester and characterized by ^{1}H and ^{13}C NMR spectroscopy (Figures S1 and S2). Varying ratios of APAPBAE and DMA or 2APBAE and DMA were copolymerized by conventional radical polymerization (Table 1). Reactivity ratios were determined via copolymerization at different feed ratios of [DMA]:[boronic acid comonomer]. The reactivity ratio of DMA is denoted as r_1, where $r_1 = k_{11}/k_{12}$ (k_{11} is the rate constant of the propagating DMA radical reacting with the DMA monomer and k_{12} is the rate constant

Table 1. Copolymers of DMA and APAPBAE or 2APBAE Synthesized by Conventional Radical Polymerization

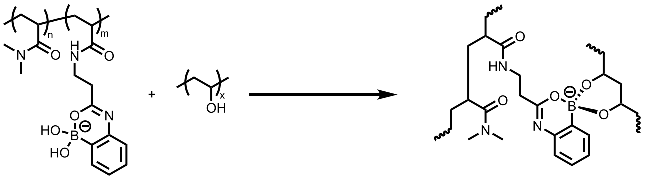
entry	boronic acid comonomer	mol % BA	$M_{n,SEC}$ (g/mol)	M_w/M_n
1	APAPBAE	5	80,000	1.60
2	APAPBAE	10	79,000	1.60
3	APAPBAE	15	55,000	2.40
4	APAPBAE	20	33,000	2.10
5	2APBAE	10	34,000	3.50
6	2APBAE	15	38,000	4.20

of the propagating DMA radical reacting with the boronic acid monomer). Similarly, r_2 is the reactivity ratio of the boronic acid where $r_2 = k_{22}/k_{21}$; k_{22} is the rate constant of the propagating boronic acid radical reacting with boronic acid monomer and k_{21} is the rate constant of the propagating boronic acid radical reacting with DMA monomer. Due to previous observations of 2APBA being consumed early in the polymerization, it was expected that its reactivity ratio would exceed unity. In other words, the rate of homopropagation of 2APBAE would be larger than cross-propagation with DMA. On the other hand, APAPBAE should demonstrate improved incorporation with DMA and have a reactivity ratio of less than unity. The extended Kelen-Tüdös (EKT) method was used with [DMA]:[boronic acid comonomer] ratios of 90:10, 70:30, 50:50, or 40:60, and 30:70 (Table S1). Conversions were limited to 15% or less in all copolymerizations. In the EKT plot, r_1 is given at $\xi = 1$, and $-r_2/\alpha$ is given at $\xi = 0$. The values obtained from the DMA:2APBAE plot (Figure S5) were $r_1 = 0.91$, $r_2 = 7.4$, and $r_1 \times r_2 = 6.7$. The reactivity ratio data suggest that 2APBAE favors homopropagation and that copolymerization with DMA would result in compositional drift and extended runs of 2APBAE units, consistent with our prediction. In contrast, APAPBAE was expected to cross-propagate with DMA to a greater degree. From the DMA:APAPBAE study, values of $r_1 = 0.80$, $r_2 = 0.009$, and $r_1 \times r_2$ of 0.007 were derived from the EKT plot (Figure S6). Interestingly, r_2 is very close to 0, indicating that APAPBAE vastly preferred cross-propagation to DMA, unlike 2APBAE. This, combined with the r_1 value of 0.80 suggests that poly(APAPBA-*co*-DMA) would have a more uniform distribution of APAPBA without blocky segments of boronic acid.

After evidence of improved monomer incorporation was obtained, we sought to explore its effect on optical and material properties. Aqueous solutions in 0.1 M acetate buffer of 10 wt % poly(APAPBA-*co*-DMA) and 10 wt % PVA were mixed at pH 3, 4, 5, 6, and 7, resulting in free-standing gels at all pH values (Scheme 2).

The optical clarity of the APAPBA hydrogel was then compared to that of the 2APBA hydrogel. Solutions of 10 wt % poly(APAPBA-*co*-DMA) or poly(2APBA-*co*-DMA) were mixed with 10 wt % solutions of PVA and allowed to rest for 24 h. The optical clarity of the resulting hydrogels was quantified via turbidity experiments, wherein the transmittance of light (λ = 490 nm) through the hydrogels was measured. As expected, this experiment showed a dramatic reduction in the percent transmittance of visible light through the 2APBA-containing gels (Figure 1A).

Scheme 2. General Cross-linking Mechanism between Poly(APAPBA-*co*-DMA) and PVA at Neutral pH



Oscillatory shear rheometry was used to characterize the viscoelastic properties and self-healing behavior of the APAPBA hydrogel. Rheometry was conducted on samples with 10 and 20 mol % APAPBA content. A dynamic strain sweep was used to determine the linear viscoelastic region of the hydrogel along with the storage modulus (G') and loss modulus (G'') (Figures S8 and S9). As the pH increased, G' increased, with a slight deviation at pH 7, as shown in Figure 2. The correlation of increased modulus with increasing pH is likely a result of the protonation state of the boronic acid amide. As the boronic acid amide transitions from protonated to deprotonated around pH = 5.0, the electron density is donated toward the boron center, increasing stability of the boronate ester.

The storage modulus of hydrogels containing 10 mol % APAPBA (ca. 2000 Pa) was higher than the values measured for those synthesized with 2APBA with a higher boronic acid loading of 15 mol % (ca. 1000 Pa) (Figure S7). The enhanced modulus of the APAPBA-containing gels could be due to the improvement in comonomer distribution, which would result in more homogeneous cross-linking and more equal allocation of stress throughout the chain. Additionally, the ethylene spacer may provide increased accessibility of the boronic acids for cross-linking. Interestingly, the hydrogels formed with poly(APAPBA-*co*-DMA) (10 mol % APAPBA) exhibited higher moduli values than hydrogels formed with poly(APAPBA-*co*-DMA) (20 mol % APAPBA) (Figures S6 and S7). This difference is likely due to the lower molecular weights of the poly(APAPBA-*co*-DMA) (20 mol % APAPBA) precursors since the 20 mol % polymer had less than half the molecular weight of the 10 mol % polymer, which would result in reduced entanglement within the hydrogel and a resulting reduction in modulus, a phenomenon observed in other boronic acid hydrogels.[29]

The self-healing ability of these hydrogels was investigated by conducting a ramping strain sweep. The increasing strain eventually resulted in the failure of the gel, which is shown by the crossover of G' and G'' in Figure 3. When the strain was then reduced to within the linear viscoelastic region immediately after the strain sweep, G' was again greater than G'', indicating that the cross-links had reformed.

Notably, the time required for modulus recovery was considerably shorter at an acidic pH (Figure S10). This difference is attributed to the dependence of relaxation time (τ) on pH. Since the hydrogels with lower τ are more labile and quicker to reform, there is less time required to recover the initial modulus. Frequency sweeps were conducted to test this hypothesis. For covalently cross-linked hydrogels, the modulus is typically frequency-independent, with $G' > G''$. In contrast, hydrogels with dynamic cross-links demonstrate frequency-dependent moduli values. At lower angular frequencies, the hydrogel cross-links have enough time to rearrange and allow for stress relaxation within the network. In this regime, $G'' > G'$ and the hydrogel can be considered to be in a more fluid-like state. At higher angular frequencies, the cross-links cannot rearrange quickly enough to dissipate stress, and this results in a crossover of G' and G'' at frequency ω_c. This point is then used to determine τ, where $\tau = 2\pi/\omega_c$. As the pH increased,

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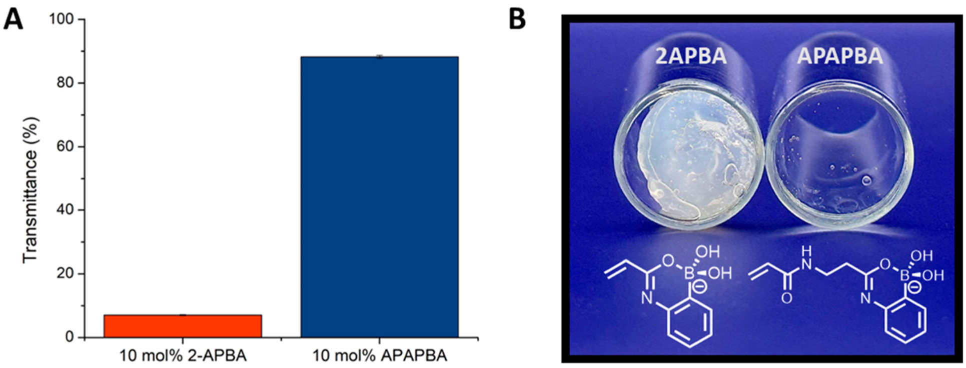

Figure 1. (A) Percent transmittance (% T) at 490 nm for mixtures of poly(2APBA-*co*-DMA) (10 wt %) or poly(APAPBA-*co*-DMA) (10 wt %) with PVA (10 wt %). (B) Comparison of two different boronic acid/PVA gels. 2APBA gels appear opaque, likely due to aggregation of PVA chains, while APAPBA gels appear transparent.

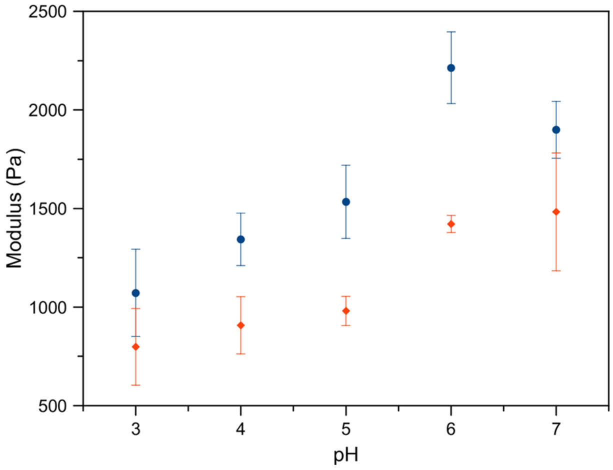

Figure 2. Storage modulus (G') values as determined from the linear viscoelastic region of strain sweeps conducted on hydrogels formed with poly(APAPBA-*co*-DMA) (blue: 10 mol % APAPBA; orange: 20 mol % APAPBA).

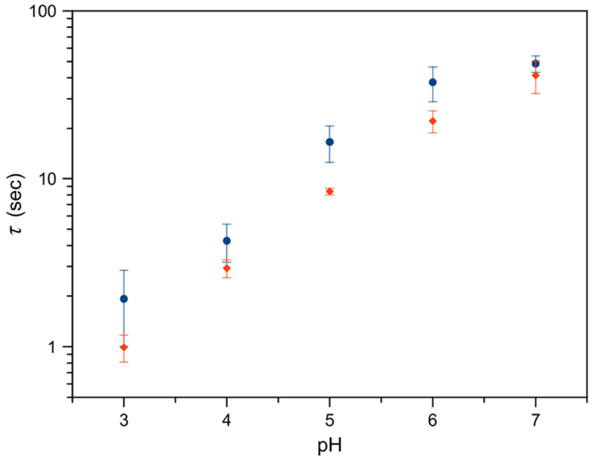

Figure 4. Characteristic relaxation times (τ) determined from frequency sweeps conducted on hydrogels formed with poly(APAPBA-*co*-DMA) (blue: 10 mol % APAPBA; orange: 20 mol % APAPBA). τ values increased with increasing pH.

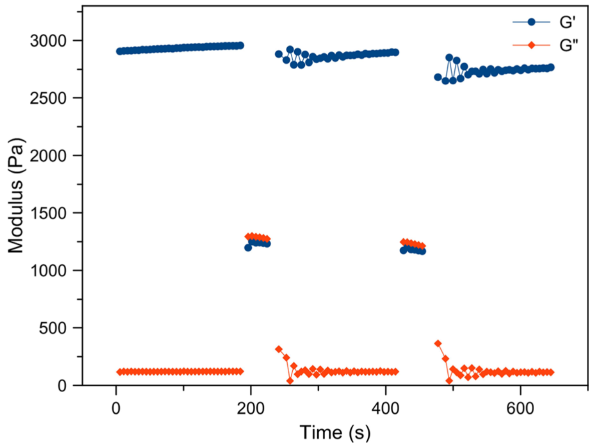

Figure 3. Strain sweep of poly(APAPBA-*co*-DMA) (10 mol % APAPBA) hydrogel in 0.01 M acetate buffer at pH 7. The initial strain was set at 1% (10 rad/s). When strain was increased to 300% (10 rad/s), a G'/G'' crossover occurred as cross-links were broken. When the strain was returned to 1%, moduli values recover toward their original values as cross-links reformed.

the G'/G'' crossover decreased, resulting in larger τ values (Figure 4). Once again, this trend can be attributed to the decreased electron donation at lower pH due to amide protonation. The difference in cross-link lability was also readily apparent during handling. At lower pH, the hydrogels flowed much more rapidly when perturbed, demonstrating spinnbarkeit behavior, whereas the hydrogels near neutral pH would retain their shape for long periods of time (Figure 5). Compared with the hydrogels prepared with 2APBA, the hydrogels with APAPBA universally had lower τ values, which is consistent with the faster healing times of the APAPBA hydrogel.

Due to the different binding characteristics and enhanced optical clarity compared to copolymers of 2APBA, we decided to explore potential applications of this new monomer and its resulting polymers. The functionality of boronic acid-containing copolymers can enable the synthesis of biohybrid materials through the binding of *cis*-diols on biomacromolecules like glycoproteins.[35,36] Mucins are a family of highly glycosylated proteins produced by epithelial cells that determine essential biochemical and biophysical properties of mucus and are present in all animals except sponges.[37] Mucins play an instrumental role in the barrier properties, hydration, lubrication, and bioactivity of mucus gels.[38,39] Furthermore, research suggests that aberrant mucins could be the underlying etiology of several illnesses such as Crohn's disease, cystic fibrosis, and dry eye disease.[40] Access to synthetic polymers

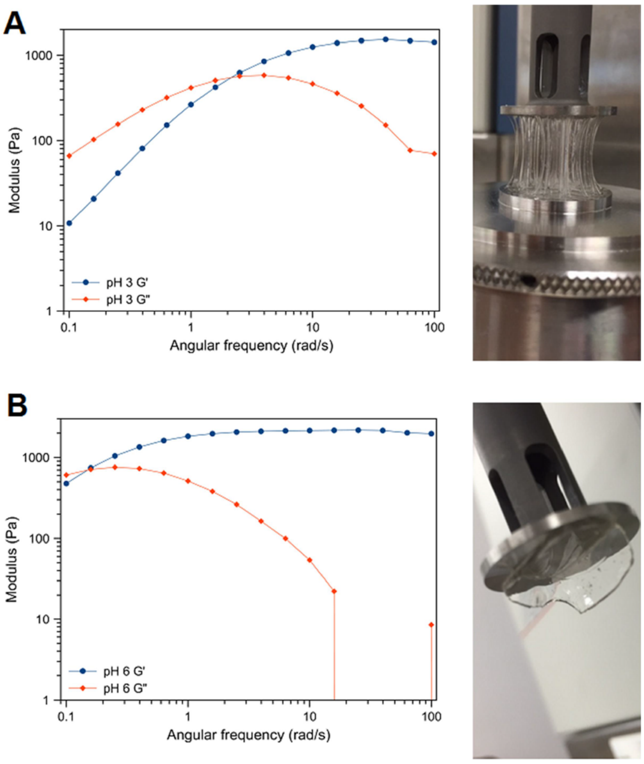

Figure 5. (A) Frequency sweep of the hydrogel formed with poly(APAPBA-*co*-DMA) (10 mol % APAPBA) in 0.1 M acetate buffer at (A) pH 3 and (B) pH 6 (1% strain for both).

capable of interaction and gelation with mucins could allow for the tuning of mucus gel properties, which are inextricably linked to their biological function. Accordingly, previous reports have utilized copolymers of 2APBA to synthesize biohybrid gels with purified porcine stomach mucin via boronic acid binding with diols present in mucin-bound sialic acid residues (Figure 6A).[35] We hypothesized that biohybrid gel formation with polymers containing APAPBA is also possible. Furthermore, these gels may show promise in applications where enhanced optical clarity is important.

Aqueous solutions (10 wt %) of poly(APAPBA-*co*-DMA) (15 mol % APAPBA) or poly(2APBA-*co*-DMA) (15 mol % 2APBA) and purified porcine gastric mucin (20 wt %) were mixed at pH 7.4 in 0.01 M phosphate-buffered saline (PBS). Rapid gelation was observed with mild mixing. It is important to note that hydrogels made with purified mucin are universally more opaque than those made with PVA as the purified gastric mucin solutions are inherently turbid, likely due to the amphiphilic nature of mucins. Nevertheless, turbidity experiments revealed that hydrogels formed from mucin and poly(APAPBA-*co*-DMA) had improved optical clarity relative to mucin alone (Figure S13). This improvement in optical clarity does not occur in gels prepared by mixing poly(2APBA-*co*-DMA) and mucin, where a slight decrease in transmittance was observed relative to mucin alone. We hypothesize that evenly dispersed APAPBA along the hydrophilic DMA backbone led to improved mucin binding and a resulting increase in solubility. On the other hand, the blocky structure of 2APBA copolymers that resulted from compositional drift during copolymerization likely leads to more highly aggregated mucin, similar to gels synthesized with PVA.

The rheological properties of these APAPBA-mucin gels revealed the formation of a dynamic network, demonstrating a frequency-dependent crossover of the storage and loss moduli (Figure 7). Notably, gels containing mucin showed a storage modulus around 100 Pa, which is on the order of native mucus gels.[41] These results indicate the successful mucin-binding ability of copolymers containing APAPBA. As reported by Sakai and co-workers, gels formed between 2APBA and mucin also show dynamic properties. However, compared to APAPBA, 2APBA-mucin gels have a slightly higher storage modulus and experience crossover at lower frequencies. We hypothesize that these differences could be due to the aggregation of high-molecular-weight mucin (e.g., MUC2 ∼ 550 kDa)[42] causing secondary network formation through entanglement, slightly increasing the modulus and greatly increasing relaxation time. These results show that changes in the monomer structure have measurable effects on the mechanical and optical properties of biohybrid boronic acid hydrogels. Furthermore, since APAPBA exhibits more favorable cross propagation during radical copolymerization with acrylamides compared to 2APBA, we foresee that this

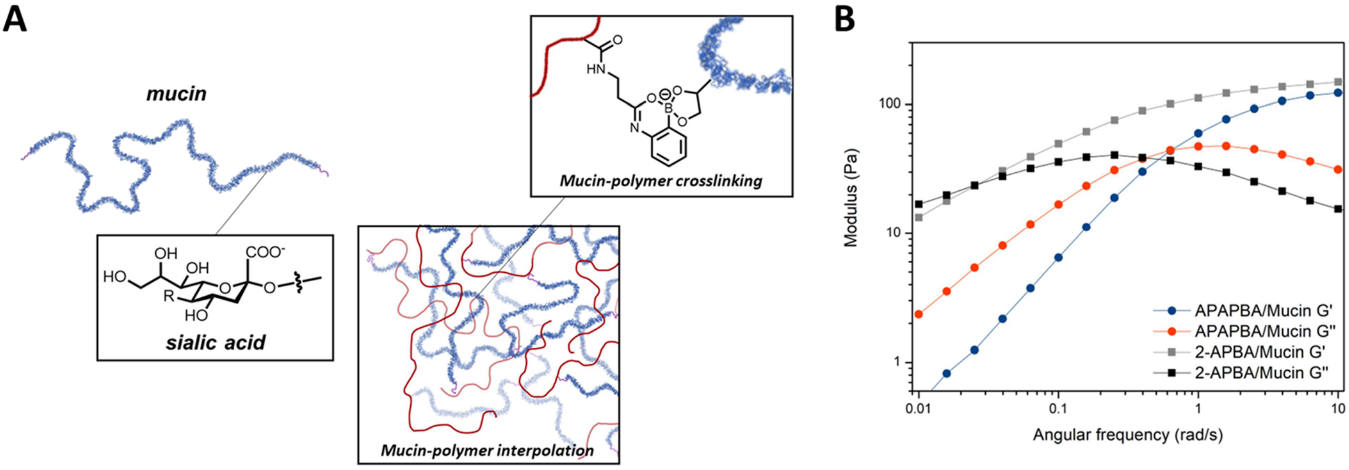

Figure 6. (A) Mucin-containing sialic acid residues capable of interpolating and complexing with synthetic polymers bearing boronic acid moieties to form biohybrid hydrogels. (B) Frequency sweeps of hydrogels formed with poly(APAPBA-*co*-DMA) (15 mol % APAPBA) (circles) and poly(2APBA-*co*-DMA) (15 mol %) (squares) with purified porcine gastric mucin at pH 7.4 in PBS (1% strain).

monomer provides promise in synthesizing mucoadhesive polymers via reversible-deactivation radical polymerization, unlocking the ability to explore key macromolecular properties such as molecular weight and polymer architecture and their effect on mucoadhesion, hydration, and lubricity.

■ CONCLUSIONS

In summary, we created hydrogels that exhibit a self-healing ability over a wide pH range and demonstrated improved optical clarity and mechanical properties over previously reported materials. An ethylene spacer used to separate the polymerizable vinyl group from the phenylboronic acid moiety in the monomer improved copolymerization behavior with DMA, leading to more homogeneous monomer incorporation. The homogeneous microstructure that results from the more similar monomer reactivity during copolymerization was hypothesized to be responsible for the reduced hydrogel cloudiness and increased modulus of gels prepared with APABA. The increased spacing of the boronic acid from the polymer backbone also seemed to facilitate cross-linking, resulting in faster hydrogel healing times. These hydrogels exhibited polyelectrolyte behavior as reduced buffer concentration resulted in increased moduli and stiffness. Finally, it was shown that copolymers of APAPBA and DMA successfully form gels with enhanced optical clarity and physiologically relevant moduli when mixed with porcine gastric mucin. These results demonstrated how a change in monomer structure can improve polymerization behavior and, in turn, control hydrogel mechanical and optical properties.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.macromol.3c01471.

Materials; experimental procedures; spectral data; and additional figures (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. C.L.G.D. and C.D. contributed equally.

Notes

The authors declare no competing financial interest.

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