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pH responsive self-healing hydrogels formed by boronate–catechol complexation†

Lihong He, Dominic E. Fullenkamp, José G. Rivera, and Phillip B. Messersmith

Biomedical Engineering Department, Chemistry of Life Processes Institute, and Institute for Bionanotechnology in Medicine, Northwestern University, Evanston, Illinois 60208, USA. Fax: 8474914928; Tel: 847-467-5273

Phillip B. Messersmith: philm@northwestern.edu

Abstract

Here we report the synthesis and characterization of pH-responsive, self-healing hydrogels based on boronate–catechol complexation.

Hydrogels are three-dimensional polymeric networks, which are hydrophilic and cross-linked *via* covalent or noncovalent interactions.^{1,2} There is great interest in biomedical applications of hydrogels, as they are homogenous soft materials with physical properties similar to soft tissues, and they have shown promise in a number of areas including sensors, separation systems, and biomaterials.³ Recently, significant efforts have focused on stimuli-responsive⁴ hydrogels due to their ability to respond to external triggers like pH,⁵ temperature,⁶ and light,⁷ making them a class of important biomaterials for applications in medicine and tissue engineering. Research on stimuli-responsive noncovalent hydrogels has mainly focused on supramolecular chemistry *via* host–guest interactions⁸ and hierarchical self-organization of associative block copolymers.⁹ However, physical (noncovalent) hydrogels are generally less stable and have poorer mechanical properties compared to covalent hydrogels.¹⁰ Therefore, integrating the stimuli-responsiveness of physical gels and the stability of chemical (covalent) gels into a single material is an important goal.

Complexation of certain diols and boronic acid is possible in aqueous solution *via* formation of a reversible boronate ester.¹¹ The stability of the boronate ester complex is significantly dependent on pH,¹² a feature that has been exploited for detection of sugars under specific conditions.¹³ Previous work demonstrated that complexation of diols with boronic acid occurs at pH values above the diol pK_a and is believed to be triggered by diol ionization.¹⁴ By incorporating phenylboronic acid into polymer chains, this reaction has been used to immobilize polymers on the cell surface through complexation of phenylboronic acid with glycosylated molecules.¹⁵ Recently, Kiser and coworkers reported the formation of hydrogels through boronate ester complexation based on using phenylboronic acid and salicylhydroxamic acid containing polymers.¹⁶

†Electronic supplementary information (ESI) available: 4-arm PEG catechol, MeO-PEG catechol synthesis and characterization; Additional images and Figures. See DOI: 10.1039/c1cc11928a

Correspondence to: Phillip B. Messersmith, philm@northwestern.edu.

Inspired by our previous studies of catechol containing polymer mimics of mussel adhesive proteins,¹⁷ we have prepared crosslinked polymeric hydrogels through complexation of a branched catechol derivatized poly(ethyleneglycol) (PEG) (Fig. S1, ESI[†]) with 1,3-benzenediboronic acid. The pH-responsiveness of the hydrogel has been characterized, demonstrating covalent gel behavior at alkaline pH and dissociation into a viscous liquid at neutral and acidic pH. To our knowledge, this is the first report of a PEG hydrogel based on the complexation of catechol with a difunctional boronic acid.

As shown in Scheme 1, under basic aqueous conditions 1,3-benzenediboronic acid (BDBA) forms a tetrahedral borate ester with catechol endgroups of 4-arm PEG catechol (cPEG), giving rise to a three dimensional polymeric network and gel formation. We chose cPEG as a simple model polymer to construct a hydrogel because of its branched architecture providing catechol multivalency, suitable molecular weight (11 200 g mol⁻¹) (Fig. S2, ESI[†]), and the recently demonstrated low tissue inflammatory response of cPEG gels.¹⁸ To form gels, solutions of cPEG and BDBA in PBS buffer were mixed at 20 °C and neutralized to alkaline pH. Hydrogels formed within 30 min of mixing at pH 9.0 ± 0.5 (Fig. 1). The pH of 9.0 for complexation was chosen because the pK_a of catechol and BDBA are 9.3 and 8.7, respectively, and the optimal pH for complexation is located between the two pK_a values as revealed in a previous report.^{14a}

Model UV-vis studies using linear monofunctional PEG-catechol (mPEG-cat; see ESI[†] for details) with BDBA revealed a large absorption peak at 490 nm resulting from covalent borate ester formation (Fig. 1A), which was distinct from the absorption correlated to catechol oxidation (330 nm peak, Fig. S3, ESI[†]).¹⁹ The 490 nm peak disappeared upon reduction of the solution pH to 3.0, indicating dissociation of the borate ester bond. Fig. 1B shows the hydrogel formed from cPEG and BDBA at alkaline pH, and in Fig. 1C its transition to a liquid after adjusting the pH to 3.0 using HCl. The gel to sol transition is accompanied by a colour change from red to yellow, attributed to dissociation of the borate-catechol complex. Using similar stoichiometry of borate and catechol, hydrogels were observed to form at polymer concentrations from 5 wt% to 15 wt%. Polymer hydrogels formed in this way are sticky to the touch, which is likely due to the viscoelastic nature of the gels and to the adhesive nature of the catechol.²⁰

Due to the stoichiometries of cPEG and BDBA, if the reaction shown in Scheme 1 proceeded to completion, a molar ratio of 1 : 2 cPEG :BDBA would lead to ideal network cross-linking upon complex formation. However, ideal network formation may not be observed, as the complexation between diols and boronic acid is dynamically reversible and critically depends on solution pH. A systematic study at pH 9.0 revealed that molar ratio affected hydrogel formation. As indicated in Table S1, when the polymer concentration was held at 15 wt%, red viscoelastic polymer hydrogels were formed in 30 min upon mixing of cPEG and BDBA at molar ratios of 1 : 6, 1 : 8, and 1 : 12 respectively. However, additional BDBA prevented gel formation, as presumably the catechol endgroups became saturated with mono-complexed BDBA, preventing network formation.

[†]Electronic supplementary information (ESI) available: 4-arm PEG catechol, MeO-PEG catechol synthesis and characterization; Additional images and Figures. See DOI: 10.1039/c1cc11928a

The complexation between boronate and catechol was further studied by ^{11}B and ^1H NMR using monofunctional mPEG-cat in order to avoid gelation of the solution. As shown in Fig. S4, the ^{11}B NMR spectrum of a 2:1 mixture of mPEG-cat and BDBA at pH 9.0 revealed a peak at 1.65 ppm correlating to uncomplexed 1,3-benzenediboronic acid as well as a peak with a chemical shift of 7.31 ppm that is consistent with the formation of the tetrahedral boronate–catechol structure.²¹ The peak corresponding to free BDBA decreased with time, suggesting that the complexation of BDBA with catechol occurs gradually, reaching about 80% in 48 h. It is interesting to note that even after 48 h at ideal stoichiometry (1 : 2), free uncomplexed BDBA can be detected in the mixture. This we attribute partially to the dynamic nature of the boronate–catechol complex, which fluctuates between the complexed and dissociated states and does not contribute to elastic network formation in the dissociated state. This dynamic behavior has implications for self-healing performance as discussed below.

^1H NMR studies confirmed mPEG-cat/complex formation (Fig. S5, ESI[†]). The three protons from BDBA which have chemical shifts of 7.0–7.6 decreased sharply during the first 30 min after mixing with mPEG-cat, indicating complexation between catechol and boronic acid. Here as well, the conversion of free to complexed BDBA occurred gradually over the first 48 h and was accompanied by a decrease in the chemical shift of boronic acid protons. Like those of the boronic acid, the chemical shifts of the catechol protons were observed to change upon complex formation. The aromatic protons of catechol (chemical shift 6.5–7.0 ppm in D_2O at pH 7) were broadened upon complex formation and narrowed again upon complex dissociation in acid. Proton signals from boronic acid were not straightforward to detect or interpret at pH 3.0 due to the limited solubility of BDBA under these conditions. However, acidification of the gel formed by cPEG and BDBA after 48 h at pH 9.0 and analysis by ^{11}B NMR revealed the disappearance of the 7.31 ppm peak associated with the boronate–catechol complex, and simultaneous reappearance of the 18.9 ppm peak attributed to free borate (Fig. S6, ESI[†]). This peak assignment was confirmed by ^{11}B NMR spectrum of borax/dopamine at pH 3.0 (Fig. S7, ESI[†]). Gels formed at pH 9.0 and then immersed in pH 7.4 buffer dissolved over a period of several hours (Fig. S8, ESI[†]).

Rheological studies of the cPEG/BDBA gels were consistent with covalently cross-linked hydrogels, exhibiting storage moduli greater than loss moduli across a wide frequency range and little change in storage modulus with frequency (Fig. 2). Storage modulus was concentration dependent within the range 5–15 wt% cPEG, with a maximum observed storage modulus of approximately 1500 Pa (15 wt%). The storage modulus at 37 °C was lower than at 20 °C (Fig. S9, ESI[†]).

Interestingly, hydrogels prepared in this way are sticky to the touch and possess self-healing ability. As depicted in Fig. 3, a cube of 15 wt% hydrogel was cut into two pieces and then brought back together at the fracture surfaces. The two pieces of fractured gel healed autonomously and rapidly by simply contacting the fractured surfaces together (Fig. 3b and c). No obvious border was seen between the connected gels after fusion, and the joint between the two parts of the healed gel was strong enough to be stretched without fracturing 30 s after fusion (Fig. 3d). This observation was repeatable and effective wherever the cut was made or the gels were fused. Fig. 4 demonstrates this self-healing property by

oscillatory rheology. In this experiment the gel was first strained up to 1000%, resulting in gel failure. Following this, the time- dependent recovery was monitored at 5% strain and 10 rads/s, revealing mechanical recovery of the storage modulus (G') on the minute time scale.

We believe the self-healing mechanism is mainly attributable to the dynamically reversible complexation between boronic acid and catechol.¹⁶ The ^{11}B NMR supports the availability of free 1,3-benzendioboronic acid under conditions where gel is formed, implying a dynamic equilibrium between free and complexed borate that could contribute to the self-healing mechanism. Upon return of fractured surfaces together, free BDBA and catechol functional groups should be capable of complexing with each other at the interface to reform the network.^{22,23} Covalent reactions may also contribute to healing the interface, as the catechol is known to undergo oxidative coupling under basic conditions.^{11a} However, we do not have any direct evidence for this effect at this time.

In conclusion, novel covalent hydrogels were produced by complexation of a multifunctional catechol polymer with a bifunctional borate compound. The dynamic nature of the boronate ester linkages gave rise to self-healing hydrogels exhibiting high stability at alkaline pH and low stability under acidic conditions. In the future it may be possible to employ this strategy for biomedical applications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Notes and references

1. Elisseff J. *Nat Mater.* 2008; 7:271. [PubMed: 18354410]
2. Peppas NA, Bures P, Leohandung W, Ichikawa H. *Eur J Pharm Biopharm.* 2000; 50:27. [PubMed: 10840191]
3. (a) Drury JL, Mooney DJ. *Biomaterials.* 2003; 24:4337. [PubMed: 12922147] (b) Peppas NA, Hilt JZ, Khademhosseini A, Langer R. *Adv Mater.* 2006; 18:1345.
4. Tsitsilianis C. *Soft Matter.* 2010; 6:2372.
5. (a) Iddou PD, Armes SP. *Eur Polym J.* 2007; 43:1234.(b) Sfika V, Tsitsilianis C. *Macromolecules.* 2003; 36:4983.
6. Li C, Tang Y, Armes SP, Morris CJ, Rose SF, Lloyd AW, Lewis AL. *Biomacromolecules.* 2005; 6:994. [PubMed: 15762670]
7. Tomatsu I, Hashidzume A, Harada A. *Macromolecules.* 2005; 38:5223.
8. (a) Deng W, Yamaguchi H, Takashima Y, Harada A. *Angew Chem, Int Ed.* 2007; 46:5144.(b) Ren L, He L, Sun T, Dong X, Chen Y, Huang J, Wang C. *Macromol Biosci.* 2009; 9:902. [PubMed: 19544291]
9. (a) Shen W, Kornfield JA, Tirell DA. *Macromolecules.* 2007; 40:689.(b) O'Lenick TG, Jiang XG, Zhao B. *Langmuir.* 2010; 26:8787. [PubMed: 20099880]
10. Gong JP. *Soft Matter.* 2010; 6:2583.

11. (a) Pizer R, Babcock L. *Inorg Chem.* 1977; 16:1677.(b) Fang H, Kaur G, Wang B. *J Fluoresc.* 2004; 14:481. [PubMed: 15617256]
12. (a) Paugam MF, Valencia LS, Boggess B, Smith BD. *J Am Chem Soc.* 1994; 116:11203.(b) Pizer R, Ricatto PJ. *Inorg Chem.* 1994; 33:2402.
13. (a) Asher SA, Alexeev VL, Goponenko AV, Sharma AC, Lednev IK, Wilcox CS, Finegold DN. *J Am Chem Soc.* 2003; 125:3322–3329. [PubMed: 12630888] (b) Dowlut M, Hall DG. *J Am Chem Soc.* 2006; 128:4226. [PubMed: 16568987]
14. (a) Yan J, Springsteen G, Deeter S, Wang BH. *Tetrahedron.* 2004; 60:11205–11209.(b) Springsteen G, Wang BH. *Tetrahedron.* 2002; 58:5291.
15. Winblade ND, Schmökel H, Baumann M, Hoffman AS, Hubbell JA. *J Biomed Mater Res.* 2001; 59:618. [PubMed: 11774323]
16. (a) Roberts MC, Hanson MC, Massey AP, Karren EA, Kiser PF. *Adv Mater.* 2007; 19:2503.(b) Roberts MC, Mahalingam A, Hanson MC, Kiser PF. *Macromolecules.* 2008; 41:8832. [PubMed: 23132956]
17. Lee B, Messersmith PB, Israelachvili JN, Waite JH. *Mussel-Inspired Adhesives and Coatings.* *Annual Reviews of Materials Research.* in press.
18. (a) Brubaker CE, Kissler H, Wang LJ, Kaufman DB, Messersmith PB. *Biomaterials.* 2010; 31:420–427. [PubMed: 19811819] (b) Bilic G, Brubaker CE, Messersmith PB, Mallik AS, Quinn T, Done E, Guccardo L, Zeisberger SM, Zimmermann R, Deprest J, Zisch AH. *Am J Obstet Gynecol.* 2010; 202:85, e1–9. [PubMed: 20096254]
19. Lee BP, Dalsin JL, Messersmith PB. *Biomacromolecules.* 2002; 3:1038. [PubMed: 12217051]
20. (a) Lee H, Scherer NF, Messersmith PB. *Proc Natl Acad Sci U S A.* 2006; 103:12999. [PubMed: 16920796] (b) Lee H, Dellatore S, Miller WM, Messersmith PB. *Science.* 2007; 318:426. [PubMed: 17947576]
21. (a) Shabbir SH, Joyce LA, Cruz GM, Lynch VM, Sorey S, Anslyn EV. *J Am Chem Soc.* 2009; 131:13125. [PubMed: 19691315] (b) Mancilla T, Contreras R. *J Organomet Chem.* 1987; 321:191.
22. Deng G, Tang C, Li F, Jiang H, Chem Y. *Macromolecules.* 2010; 43:1191.
23. Chen W, Leung V, Kroener H, Pelton R. *Langmuir.* 2009; 25:6863. [PubMed: 19354209]

Fig. 1.

(A) UV-vis spectra of mPEG-cat/BDBA at (a) pH 9.0, (b) pH 3.0 and (c) mPEG-cat at pH of 7.4. (B) Hydrogel formed from 7.5 wt% cPEG and BDBA at pH 9.0 and molar ratio of 1 : 8, and sol produced after the hydrogel shown in B was acidified to pH 3.0.

Fig. 2. Dynamic frequency sweep of hydrogels formed from BDBA and cPEG with polymer concentration of (a) 15 wt%, (b) 10 wt%, and (c) 5.0 wt%. The molar ratio of cPEG to BDBA was 1 : 8 for each concentration.

Fig. 3.

Self-healing properties of the covalent polymer gel formed from cPEG (15 wt%) and BDBA at pH 9.0. The gel was formed into a cube (a), cut into two pieces (b), fused together (c), and then stretched without fracture 30 s after fusion (d). The molar ratio of cPEG to BDBA was 1 : 8.

Fig. 4.

Time-dependent self-healing of gel after failure. The moduli of the gel before fracture are indicated by G'_0 and G''_0 . The gel was fractured under large strain (1000%, 10 rad s^{-1} ; 20°C) and then the recovery moduli G' and G'' were monitored at 5% strain. The molar ratio of cPEG to BDDBA was 1 : 8 and polymer concentration was 15 wt%.

Scheme 1.

Schematic illustration of pH-responsive hydrogel based on cPEG and 1,3-benzenediboronic acid in aqueous solution at 20 °C.