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Doubly Dynamic Self-Healing Materials Based on Oxime Click Chemistry and Boronic Acids

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The dynamic covalent characteristics of oxime and boronate ester bonds have been explored. A small excess of a competing aldehyde under acidic conditions resulted in oxime-polymer degradation from high molecular weights (30 kDa) to low molecular weight oligomers (2.2 kDa). The dynamic nature of oxime bonds imparted oxime-crosslinked hydrogels with self-healing properties and the incorporation of phenyl boronic acid groups into the hydrogel network provided a platform for hydrogel functionalisation. The addition of a polyphenol (tannic acid) proved a facile means to incorporate a second, dynamic covalent crosslinking network through boronate ester formation which, owing to the increase in the degree of crosslinking, was found to nearly double the hydrogel strength (storage modulus increased from 4.6 to 8.5 kPa). Finally, the tannic-acid crosslinking network was selectively degraded returning the hydrogel storage modulus to its initial value and providing a means for the synthesis of materials with tunable mechanical properties.

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FIGURE FOR ToC_ABSTRACT

1. Introduction

Nature is reliant on complex dynamic chemistries, in particular, biology utilises dynamic covalent chemistry to control catalysis and to achieve self-assembly in DNA and proteins.^[1–3] Compared to non-covalent interactions (H-bonding, π -stacking etc.) dynamic covalent bonds exhibit higher strength and enable a greater degree of control over the reaction equilibrium.^[4,5] An impressive suite of synthetic materials have been prepared based on dynamic chemistries such as imine,^[6–13] hydrazone,^[14,15] Diels-Alder,^[16–18] disulphide,^[8,19–21] boronate ester^[22–26] and olefin metathesis^[27] which show potential for drug discovery,^[28] drug delivery,^[29,30] regenerative medicine,^[14,31] self-healing materials^[11–13,26,32–34] and shape-memory polymers.^[18,35]

The oxime bond, formed through the condensation between an aldehyde/ketone and a hydroxylamine, remains as one of the most unexplored dynamic covalent chemistries. Displaying favourable reaction conditions (high efficiency, chemoselectivity, formation in aqueous solvents and water as the only side-product) and bond properties (high hydrolytic stability)^[36] oxime chemistry has been used almost exclusively for bioconjugation.^[37] Owing to the demand for more versatile chemistry and more environmentally friendly means of synthesis the oxime ligation has recently seen an astonishing increase in materials science applications.^[38] Over the last few years oxime chemistry has been used in the development of bioadhesives,^[39,40] self-healing hydrogels,^[41] for step-growth polymer synthesis^[42] and for the creation of dynamic macromolecular assemblies.^[43]

Recently, materials possessing multiple orthogonal dynamic chemistries have been developed enabling the synthesis of intricate macromolecules which respond to multiple stimuli to achieve a desired response.^[44] Compared to a singly dynamic chemistry, the incorporation of multiple dynamic linkages allows for the fine-tuning of a material response to a particular stimuli or the incorporation of a dual-responsive nature which would be valuable for applications in drug delivery, sensing, surface patterning and materials science. The incorporation of multiple dynamic chemistries into a single material has been achieved with various orthogonal reactions: oxime and Diels-Alder,^[45] imine and ester^[6] and impressively, hydrazone, disulphide and boronate ester.^[46]

Herein, we present an investigation into the dynamic properties of oxime-based materials. High molecular weight step-growth polymers (30 kDa), synthesized via oxime click chemistry, can be degraded by careful control of the reaction equilibrium. We also demonstrate the versatility of oxime chemistry to develop self-healing hydrogels, again by controlled modulation of the oxime equilibrium. The hydrogel was shown to possess intrinsic self-healing prop-

erties confirmed through rheological characterisation. Finally, the oxime-based hydrogel was modified to incorporate a phenyl boronic acid moiety thereby creating a doubly dynamic material. The addition of a polyphenol, tannic acid, led to the formation of a boronate ester dynamic covalent crosslinking network within the oxime hydrogel which was found to increase the hydrogel strength. We also demonstrate the facile and orthogonal reversibility of the boronate ester network to recover the initial gel.

2. Experimental Section

Chemicals were purchased from Sigma Aldrich or Alfa Aesar and used without further purification. ¹H-NMR spectra were recorded using a Varian 400 MHz spectrometer. For differential refractive index (DRI) traces, DMF was used as an eluent and the size exclusion chromatography (SEC) analysis was conducted on a Shimadzu liquid chromatography system equipped with a Shimadzu RID-10 refractometer ($\lambda = 633$ nm) and Shimadzu SPD-20A UV-vis detector using two Phenomenex Phenogel columns (5 μ m bead size, 104 and 106 Å porosity) in series operating at 70°C. DMF with 0.05 mol L⁻¹ LiBr (>99%, Aldrich) was employed as the mobile phase at a flow rate of 1 mL min⁻¹. The system was calibrated using polystyrene standards. All samples were filtered through 0.45 μ m nylon filters prior to injection. Molecular weight distributions (PDIs) were calculated relative to linear polystyrene standards. Rheological properties of the gels were characterized by controlled strain rheometer with 40 mm parallel plate geometry (AR-G2, TA Instruments).

Tetraethylene glycol bishydroxylamine (M1): Synthesis of tetraethylene glycol bishydroxylamine (M1) was carried out according to a reported literature procedure.^[47] ¹H-NMR (400 MHz, CDCl₃): δ 4.24 (t, $J = 4$ Hz, 4H; CH₂), 3.82 (t, $J = 4$ Hz, 4H; CH₂), 3.71 (s, 8H; CH₂).

Dibenzaldehyde Tetraethylene Glycol (M2): Tetraethylene glycol (TEG) (5.00 g, 25.7 mmol), 4-formyl benzoic acid (7.92 g, 52.8 mmol) and dimethylaminopyridine (DMAP) (0.47g, 3.85 mmol) were dissolved in DCM (100 mL). N,N'-Dicyclohexylcarbodiimide (DCC) (10.88g, 52.7 mmol) in

DCM (20 mL) was added to the solution dropwise. The reaction was left to stir for 24 hours at room temperature. The crude reaction mixture was concentrated under reduced pressure then filtered. The filtrate was purified by column chromatography using hexane/ethyl acetate (80/20). The product was collected as a white solid (10.47g, 89%). ¹H-NMR (400 MHz, CDCl₃): δ 10.07 (s, 2H; HCO), 8.18 (d, J = 8 Hz, 4H; Ar), 7.91 (d, J = 8 Hz, 4H; Ar), 4.47 (t, J = 4 Hz, 4H; CH₂), 3.82 (t, J = 4 Hz, 4H; CH₂), 3.66 (m, J = 4 Hz, 8H; CH₂).

Glycerol Ethoxylate Tribenzaldehyde (M3): Glycerol ethoxylate (2.00 g, 2.00 mmol), 4-formyl benzoic acid (1.00 g, 6.66 mmol) and dimethylaminopyridine (DMAP) (0.04 g, 0.33 mmol) were dissolved in DCM (100 mL). N,N'-Dicyclohexylcarbodiimide (DCC) (1.37 g, 6.66 mmol) in DCM (50 mL) was added to the solution dropwise. The reaction was left to stir for 24 hours at room temperature. The crude reaction mixture was concentrated under reduced pressure then filtered. The filtrate was purified by column chromatography using DCM/Methanol (7% MeOH). The product was collected as a colorless oil (1.4 g, 50%). ¹H-NMR (400 MHz, CDCl₃): δ 10.08 (s, 3H; HCO), 8.19 (d, J = 8 Hz, 6H; Ar), 7.93 (d, J = 8 Hz, 6H; Ar), 4.48 (t, J = 4 Hz, 6H; CH₂), 3.82 (t, J = 4 Hz, 6H; CH₂), 3.60 (bs, 82H; CH₂).

Oxime Polymer Synthesis (P1): M2 in DMF (150 mmolL⁻¹) was added to solid M1 in equimolar amounts together with a desired volume of aniline (40 mol %). The polymerization was left to run for 3 hours at 60°C. Following polymerization, the product was repeatedly precipitated in hexane and distilled to afford the product as a tacky, amber solid. ¹H-NMR (400 MHz, CDCl₃): δ 8.12 (s, 2H; O=NCH), 8.03 (d, J = 8 Hz, 4H; Ar), 7.62 (d, J = 8 Hz, 4H; Ar), 4.46 (t, J = 4 Hz, 4H; CH₂), 4.35 (t, J = 4 Hz, 4H; CH₂), 3.80 (q, J = 4 Hz, 8H; CH₂), 3.67 (s, 16H; CH₂).

Oxime Hydrogel Synthesis (G1): M3 (0.661 g, 0.473 mmol) and M1 (0.210 g, 0.709 mmol) each dissolved in a minimum amount of MeOH were mixed together before aniline (51.7 μL, 0.567 mmol) was introduced. The reaction mixture was heated to 60°C and gelation was observed to occur within 5 minutes.

Boronic Acid Functional Hydrogel Synthesis (G_{Boron}): M3 (0.560 g, 0.400 mmol), M1 (0.196 g, 0.662 mmol) and 3,5-diformyl phenyl boronic acid (12.57 mg, 0.071 mmol) each dissolved in minimum amount of MeOH were mixed together before aniline (20 μL , 0.219 mmol) was introduced. The reaction mixture was heated to 60°C and gelation was observed to occur within 5 minutes.

Reversible Gel-Sol Transition (RG-1): TFA (2 mL, 26 mmol) and DCM (2 mL) were added to G1. After approximately 2 hours G1 had changed from a gel to a solution. Following the gel-sol transition, the solution was placed in the fume hood and the TFA allowed to evaporate affording gel re-formation (RG-1).

Doubly Dynamic Crosslinking through Boronate Ester Formation ($G_{\text{Boron-T}}$, $G_{\text{Boron-C}}$): Tannic acid (60 mg, 0.035 mmol) was dissolved in a pH 8.14 phosphate buffer (10 mL) before G_{Boron} was introduced to the solution. The sample was left to incubate overnight to allow sufficient tannic acid binding within the hydrogel ($G_{\text{Boron-T}}$). A similar procedure was undertaken for the synthesis of $G_{\text{Boron-C}}$. Catechol (777 mg, 7.06 mmol) was dissolved in a pH 8.14 phosphate buffer (10 mL) before G_{Boron} was introduced to the solution. The sample incubated three times with fresh catechol solutions, twice for two hour periods and once overnight to ensure sufficient tannic acid release and catechol binding within the hydrogel ($G_{\text{Boron-C}}$).

Rheological Characterization: Rheological properties of the gels were characterized by controlled stress rheometer with 40 mm parallel plate geometry (AR-G2, TA Instruments). The linear viscoelastic region of the gels was determined by dynamic strain sweeps performed at a frequency of 10 rad/s at 25°C. Mechanical properties of the gels were examined by dynamic frequency sweep at 25°C and 0.5% strain, which is within the linear viscoelastic region, as was previously determined by strain sweep experiments.

Self-Healing Analysis by Rheology: Self-healing of oxime-hydrogels was studied by a stress ramp up from 0.01 to 16,000 Pa performed at a frequency of 10 rad s⁻¹ at 25°C. The sample was placed between rheometer plates and deformed under stress until a rupture within the gel was observed as indicated by a sharp drop in the storage modulus. The stress was then removed and the sample al-

lowed to recover for 10 minutes. After recovery, the experiment was repeated to trace the changes in the gels dynamic moduli.

3. Results and Discussion

To synthesize difunctional A-A and B-B type molecules for step-growth polymerization ethylene glycol-based bis-hydroxylamine and dialdehyde monomers were prepared. Tetraethylene glycol bishydroxylamine, **M1**, was prepared utilising the Mitsunobu reaction followed by deprotection with hydrazine. Dibenzaldehyde tetraethylene glycol, **M2**, was prepared via a carbodi-imide coupling. The combination of monomers **M1** and **M2** with aniline (40 mol %) at 60°C yielded an oxime linked polymer (**P1**) which was analysed through ¹H-NMR and SEC (Figure 1A).

Figure 1. (A) Synthetic scheme for the synthesis of **P1** from monomers **M1** and **M2** and **P1** degradation resulting from the reaction with butyraldehyde under acidic conditions, and (B) corresponding SEC traces. Initial molecular weight was calculated to be 30 kDa (blue) which decreased to 22 kDa after 4 hours (red), to 15.5 kDa after 24 hrs (green), to 10.7 kDa after 48 hrs (purple) and to 8.7 kDa after 96 hrs (light blue) at 60°C.

The successful formation of the oxime polymer was confirmed through $^1\text{H-NMR}$, as a new singlet peak at 8.12 ppm appears which can be attributed to the new oxime proton, and SEC was utilised to calculate a molecular weight of 30 kDa (see Figure S1 for $^1\text{H-NMR}$ characterisation and Figure S2 for SEC).

The high M_w oxime polymers can be degraded by control of the oxime equilibrium via two distinct mechanisms: transoximation or hydrolysis. Degradation by transoximation can be achieved through the addition of butyraldehyde (BA), under acidic conditions at 60°C, forcing the reaction back towards the starting materials and successfully degrading P1 to low molecular weight oligomers within one week. Using 5 equivalents of trifluoroacetic acid (TFA) and BA, P1 reduced from 30.0 to 22.0 kDa after 4 hours, to 15.5 kDa after 24 hrs, to 10.7 kDa after 48 hrs and to 8.7 kDa after 96 hrs at 60°C (Figure 1b).

The degradation of P1 was also monitored by ^1H -NMR which showed a decrease in the intensity of the butyraldehyde aldehyde proton peak and a shifting of the TEG chain protons (Figure S3). The escape of TFA and BA was minimised through the use of a condenser. When no heating was applied the rate of polymer degradation reduced and a molecular weight of 21.2 kDa was calculated after 96 hrs. Polymer degradation was also achieved via hydrolysis through the manipulation of the equilibrium by the addition of a large excess of TFA (95 equivalents, reduction to 10.3 kDa after 96 hrs at 60°C, Figure S4) and through an alternative transoximation pathway through the addition of an excess of M1 under acidic conditions (5 equivalents, reduction to 2.2 kDa after 96hrs at 60°C, Figure S5) indicating the various methods to achieve oxime reversibility and hence polymer degradation.

In order to create a new oxime-linked hydrogel and investigate its self-healing/dynamic abilities a trifunctional aldehyde monomer was synthesized, **M3**. Again, simple carbo-dimide coupling between 4-formyl benzoic acid and glycerol ethoxylate was utilized to incorporate the aldehyde functionality which allowed for successful oxime-hydrogel synthesis, **G1**. Gelation occurred within 5 minutes at a **M1:M3** monomer ratio of 2:3 with 40 mol% aniline and heating to 60°C (Figure 2A).

Figure 2. (A) Synthetic scheme for the synthesis and reversibility of oxime-linked hydrogels, **G1** and **RG-1** through addition of TFA and removal by evaporation. RG-1 represents recycling of the gel G1 after evaporation of TFA. (B) Images of the reversible sol-gel transition stimulated by TFA addition and evaporation. (C) Rheological characterisation of **G1** (blue diamonds) and **RG-1** (red squares) showing a negligible decrease in the storage modulus during the TFA recycling procedure.

The dynamic nature of oxime bonds allows for the degradation of the polymer network affording a gel-sol transition. Recently, Sumerlin and co-workers reported that the addition of an excess of the monofunctional hydroxylamine, O-(4-tetrahydro-2H-pyran-2-yl)hydroxylamine, with TFA achieved a gel-sol transition of an oxime cross-linked hydrogel.^[41] We propose a reversible system for the degradation/re-formation of oxime hydrogels which exploits the volatility of TFA. Following gel degradation, TFA evaporation is expected to allow for the recovery of the polymer network. This was confirmed as, following

the addition of an excess of TFA yielding complete gel degradation after 2 hrs at room temperature, the gel successfully re-formed following acid evaporation (Figure 2B).

The storage modulus of the initial oxime hydrogel (**G1**) was examined by rheology and found to be 9.4 kPa (equilibrium modulus as indicated by the plateau region of the curve) which reduced slightly to 8.7 kPa (ca. 7.5 % decrease) during the recycling process (**RG-1**) (Figure 2C). This very small reduction in storage modulus during the recycling process indicates the potential for the re-use of oxime-based materials without significant loss in mechanical performance.

Oxime derived self-healing was first reported by Sumerlin and co-workers in the development of oxime-crosslinked acrylamide hydrogels.^[41] However, not all oxime-based materials have proven to be self-healing.^[14,48] The self-healing ability of **G1** and **RG-1** were investigated and analysed by both standard methods and rheometry. Gels were cut into two halves and physically pressed together which, after approximately 3 hours, successfully re-healed. Qualitatively, the re-healed gel was found to withstand significant force applied perpendicular to the original cut as well as to support itself under gravity (**Figure 3A-D**).

Figure 3. (A) The initial gel **G1**. (B) **G1** cut into two halves. (C) Healed gel. The two halves were placed back together, after approximately 3 hrs self-healing had occurred and the healed gel was

found to withstand significant force applied perpendicular to the original cut line. (D) The reformed gel was able to support itself under gravity. These images of **RG-1** demonstrate successful self-healing. (E) Rheological characterisation of **G1** self-healing. Stress on the gel was increased until failure was observed as indicated by a drop in storage modulus occurring at approximately 16 kPa. After gel failure stress was removed and the gel was left for 10 minutes to allow self-healing. Self-healing was confirmed by the return of the storage modulus to its initial value.

The self-healing ability of **G1** was confirmed by rheology. Stress on the gel was ramped up until structural failure was observed, as indicated by a drop in storage modulus. At approximately 16 kPa a sharp drop in the storage modulus is observed, and additionally the value for the loss modulus becomes higher than the storage modulus, indicating that the mechanical integrity of the gel is lost and the network is broken. Following this, the stress on the gel was removed to allow the gel to re-heal. After approximately 10 minutes the storage modulus was shown to recover back to the initial value indicating successful self-healing (Figure 3E).

Combining multiple dynamic chemistries into a single material has the potential to create next generation materials with tuneable properties. One pairing that holds promise is the combination of boronic acid and oxime bonds. It was recently reported that oxime formation is accelerated by proximal boronic acid groups,^[49,50] however the dynamic properties of the two has yet to be explored. The synthesis of various boronic acid functional polymers has recently been reviewed,^[25] here we present a new synthetic method to create boronic acid functional polymers using commercial starting materials and investigate the dynamic properties of boronic acid bonds within oxime-based hydrogels.

To synthesize a doubly dynamic oxime/boronic acid material we incorporated phenyl boronic acid groups into the oxime hydrogel. This enabled us to form a second dynamic plat-

form to allow a doubly crosslinked network to be formed and readily degraded thereby creating a material with tuneable mechanical properties. Through the incorporation of 10 mol% diformyl phenyl boronic acid (a commercially available dialdehyde) into the oxime hydrogel a doubly dynamic material was successfully synthesized ($\mathbf{G_{Boron}}$). Due to the change in reactant ratio caused by the addition of the dialdehyde functional boronic acid, $\mathbf{G_{Boron}}$ reduced in mechanical strength when compared to G1 ($G' = 4.6$ and 9.4 kPa respectively).

Double network hydrogels, traditionally prepared through the synthesis of two separate but interpenetrating networks, show potential for the synthesis of tough hydrogels.^[51,52] Through the use of dynamic boronate ester bonds we can prepare two covalently linked, yet reversible, crosslinking networks. The addition of the poly-phenol molecule tannic acid provided a means of crosslinking the boronic acid groups within the hydrogel.

Through the formation of this boronate ester network, a doubly dynamic, doubly cross-linked hydrogel was prepared ($\mathbf{G_{Boron-T}}$). The incorporation of the boronate ester-tannic acid network increased the degree of cross-linking and hence the storage modulus of $\mathbf{G_{Boron-T}}$ was found to be nearly double that of $\mathbf{G_{Boron}}$ ($G' = 8.5$ and 4.6 kPa respectively). We then demonstrated the reversible nature of boronate ester-tannic acid network by the addition of an excess of catechol, an aromatic diol not capable of crosslinking between boronic acid groups ($\mathbf{G_{Boron-C}}$). The addition of catechol was found to reduce the storage modulus of the $\mathbf{G_{Boron-C}}$ back to its original value thereby confirming the removal of the tannic acid and break down of the second crosslinking network (**Figure 4**).

Figure 4. (A) Rheological characterisation of the storage moduli of G_{Boron} (red squares), $G_{\text{Boron-T}}$ (blue diamonds) and $G_{\text{Boron-C}}$ (green triangles). (B) Images of G_{Boron} , $G_{\text{Boron-T}}$ and $G_{\text{Boron-C}}$. (C) Schematic representation of binding withing each hydrogel network. An initial storage modulus of 4.6 kPa is calculated for G_{Boron} which nearly doubles upon tannic acid crosslinking to yield $G_{\text{Boron-T}}$ with a storage modulus of 8.5 kPa. The addition of catechol removes the tannic acid and returns the storage modulus of the hydrogel back to its initial value.

4. Conclusion

In summary, we have demonstrated the dynamic properties of oxime-based materials. We explored the development of degradable polymers and recyclable hydrogels capable of self-healing. We show relatively stable oxime bonds and slow degradation profiles. This attractive property creates opportunities for oxime-based materials in biomedical application requiring longer residence times or slow, controlled release profiles.

By controlling the reaction equilibrium we also demonstrated the reversible nature of oxime-based hydrogels. These self-healing gels showed excellent recovery and successful recycling of the oxime-based materials.

Finally, the orthogonal nature of the oxime bond was demonstrated through the addition of a second dynamic covalent network using phenylboronic acid. The doubly dynamic gel was formed by reaction with a polyphenol, through boronate ester formation in the presence of stable oxime bonds, and the reverse process was demonstrated thus creating a doubly dynamic covalent network. The boronic acid platform allows for functionalisation with a wide range of molecules and exemplifies the versatile nature of the oxime bond and how this can be exploited for the synthesis of highly complex, stimuli-responsive materials.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author

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REFERENCES

- [1] A. C. Eliot, J. F. Kirsch, *Annu. Rev. Biochem.* **2004**, 73, 383.
- [2] C. Khosla, R. S. Gokhale, J. R. Jacobsen, D. E. Cane, *Annu. Rev. Biochem.* **1999**, 68, 219.
- [3] P. L. Hogg, *Trends Biochem. Sci.* **2003**, 28, 210.
- [4] S. J. Rowan, S. J. Cantrill, G. R. L. Cousins, J. K. M. Sanders, J. F. Stoddart, *Angew. Chemie Int. Ed.* **2002**, 41, 898.
- [5] Y. Jin, C. Yu, R. J. Denman, W. Zhang, *Chem. Soc. Rev.* **2013**, 42, 6634.

- [6] K. Fukuda, M. Shimoda, M. Sukegawa, T. Nobori, J.-M. Lehn, *Green Chem.* **2012**, *14*, 2907.
- [7] Y.-H. Ma, J. Yang, B. Li, Y.-W. Jiang, X. Lu, Z. Chen, *Polym. Chem.* **2016**, *7*, 2037.
- [8] D. A. Fulton, M. E. Bracchi, *Chem. Commun.* **2015**, *51*, 11052.
- [9] E. R. L. Brisson, Z. Xiao, L. Levin, G. V Franks, L. A. Connal, *Polym. Chem.* **2016**, *7*, 1945.
- [10] E. R. L. Brisson, Z. Xiao, L. A. Connal, *Aust. J. Chem.* **2016**, *69*, 705.
- [11] P. Taynton, K. Yu, R. K. Shoemaker, Y. Jin, H. J. Qi, W. Zhang, *Adv. Mater.* **2014**, *26*, 3938.
- [12] Z. Q. Lei, P. Xie, M. Z. Rong, M. Q. Zhang, *J. Mater. Chem. a* **2015**, *3*, 19662.
- [13] A. Chao, I. Negulescu, D. Zhang, *Macromolecules* **2016**, *49*, 6277.
- [14] N. Boehnke, C. Cam, E. Bat, T. Segura, H. D. Maynard, *Biomacromolecules* **2015**, *16*, 2101.
- [15] A. Dirksen, S. Dirksen, T. M. Hackeng, P. E. Dawson, *J. Am. Chem. Soc.* **2006**, *128*, 15602.
- [16] P. J. Boul, P. Reutenauer, J. M. Lehn, *Org. Lett.* **2005**, *7*, 15.
- [17] P. Reutenauer, E. Buhler, P. J. Boul, S. J. Candau, J. M. Lehn, *Chem. - A Eur. J.* **2009**, *15*, 1893.
- [18] M. Fan, J. Liu, X. Li, J. Zhang, J. Cheng, *Ind. Eng. Chem. Res.* **2014**, *53*, 16156.
- [19] Y. Nakai, A. Takahashi, R. Goseki, H. Otsuka, *Polym. Chem.* **2016**, *7*, 4661.
- [20] A. Rekondo, R. Martin, A. Ruiz de Luzuriaga, G. Cabañero, H. J. Grande, I. Odriozola, *Mater. Horizons* **2014**, *1*, 237.
- [21] E.-K. Bang, M. Lista, G. Sforazzini, N. Sakai, S. Matile, *Chem. Sci.* **2012**, *3*, 1752.
- [22] J. J. Cash, T. Kubo, A. P. Bapat, B. S. Sumerlin, *Macromolecules* **2015**, *48*, 2098.
- [23] A. R. Narkar, B. Barker, M. Clisch, J. Jiang, B. P. Lee, *Chem. Mater.* **2016**, *28*, 5432.
- [24] J.-C. Lai, J.-F. Mei, X.-Y. Jia, C.-H. Li, X.-Z. You, Z. Bao, *Adv. Mater.* **2016**, *28*, 8277.
- [25] G. Vancoillie, R. Hoogenboom, *Polym. Chem.* **2016**, DOI 10.1039/C6PY00775A.
- [26] C. C. Deng, W. L. A. Brooks, K. A. Abboud, B. S. Sumerlin, *ACS Macro Lett.* **2015**, *4*, 220.
- [27] M. Schuster, S. Blechert, *Angew. Chemie Int. Ed. English* **1997**, *36*, 2036.
- [28] O. Ramström, J.-M. Lehn, *Nat. Rev. Drug Discov.* **2002**, *1*, 26.
- [29] Y. Shao, W. Huang, C. Shi, S. T. Atkinson, J. Luo, *Ther. Deliv.* **2012**, *3*, 1409.
- [30] L. Qiu, C. Y. Hong, C. Y. Pan, *Int. J. Nanomedicine* **2015**, *10*, 3623.
- [31] H. Wang, S. C. Heilshorn, *Adv. Mater.* **2015**, *1*.
- [32] Y. Yang, M. W. Urban, *Chem. Soc. Rev.* **2013**, *42*, 7446.
- [33] J. M. Lehn, *Aust. J. Chem.* **2010**, *63*, 611.
- [34] D. L. Taylor, M. in het Panhuis, *Adv. Mater.* **2016**, DOI 10.1002/adma.201601613.
- [35] J. R. Kumpfer, S. J. Rowan, *J. Am. Chem. Soc.* **2011**, *133*, 12866.
- [36] J. Kalia, R. T. Raines, *Angew. Chemie - Int. Ed.* **2008**, *47*, 7523.
- [37] S. Ulrich, D. Boturyn, A. Marra, O. Renaudet, P. Dumy, *Chem. - A Eur. J.* **2014**, *20*, 34.
- [38] J. Collins, Z. Xiao, M. Müllner, L. A. Connal, *Polym. Chem.* **2016**, *7*, 3812.
- [39] G. N. Grover Garcia, J., Nguyen, M.M., Zanolli, M., Madani, M.M., Christman, K.L., *Adv. Healthc. Mater.* **2015**, *4*, 1327.
- [40] S. Ghosh, J. D. Cabral, L. R. Hanton, S. C. Moratti, *Acta Biomater.* **2016**, *29*, 206.
- [41] S. Mukherjee, M. R. Hill, B. S. Sumerlin, *Soft Matter* **2015**, *11*, 6152.
- [42] J. Collins, Z. Xiao, A. Espinosa-Gomez, B. P. Fors, L. A. Connal, *Polym. Chem.* **2016**, *7*, 2581.
- [43] S. Mukherjee, A. P. Bapat, M. R. Hill, B. S. Sumerlin, *Polym. Chem.* **2014**, *5*, 6923.
- [44] A. Wilson, G. Gasparini, S. Matile, *Chem. Soc. Rev.* **2014**, *43*, 1948.
- [45] S. Mukherjee, W. L. A. Brooks, Y. Dai, B. S. Sumerlin, *Polym. Chem.* **2016**, *7*, 1971.
- [46] S. Lascano, K.-D. Zhang, R. Wehlauch, K. Gademann, N. Sakai, S. Matile, *Chem. Sci.* **2016**,

- 7, 4720.
- [47] F. Taraballi, L. Russo, C. Battocchio, G. Polzonetti, F. Nicotra, L. Cipolla, *Org. Biomol. Chem.* **2014**, *12*, 4089.
- [48] N. Kuhl, M. Abend, S. Bode, U. S. Schubert, M. D. Hager, *J. Appl. Polym. Sci.* **2016**, *133*, 1.
- [49] D. Gillingham, *Org. Biomol. Chem.* **2016**, 7606.
- [50] P. Schmidt, C. Stress, D. Gillingham, *Chem. Sci.* **2015**, *6*, 3329.
- [51] H. J. Zhang, T. L. Sun, A. K. Zhang, Y. Ikura, T. Nakajima, T. Nonoyama, T. Kurokawa, O. Ito, H. Ishitobi, J. P. Gong, *Adv. Mater.* **2016**, 4884.
- [52] V. X. Truong, M. P. Ablett, S. M. Richardson, J. A. Hoyland, A. P. Dove, *J. Am. Chem. Soc.* **2015**, *137*, 1618.

The dynamic covalent characteristics of the oxime bond has been explored. Through equilibrium manipulation polymer degradation and hydrogel self-healing was achieved. By exploiting the orthogonal nature of the oxime ligation, doubly dynamic hydrogels incorporating a boronate ester-tannic acid crosslinking network were produced creating materials with tunable mechanical properties

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Doubly Dynamic Self-Healing Materials Based on Oxime Click Chemistry and Boronic Acids

Supporting Information

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Doubly Dynamic Self-Healing Materials Based on Oxime Click Chemistry and Boronic Acids

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Figure S1. Synthesis and ¹H-NMR characterisation of oxime-linked polymer **P1**. Two doublets at 8.03 and 7.62 ppm (b and c) are attributed to the aromatic benzyl protons, the two triplets at 4.46 and 4.35 ppm (d and e) are attributed to the terminal protons of the TEG chain adjacent to the carbonyl group while the quintet at 3.80 ppm (f) is attributed to the terminal protons of the TEG chain adjacent to the oxime bond. Finally, the singlet at 3.67 ppm (g) is attributed to the middle chain TEG protons.

Figure S2. SEC trace of **P1**. SEC was used to calculate a molecular weight of 30 kDa for **P1** (Figure S2) indicating the very high efficiency of oxime chemistry.

Figure S3. ¹H-NMR spectra of **P1** degradation with 5eq of butyraldehyde and TFA at 60°C. Spectra recorded after 4hrs (red), 24 hrs (green), 48 hrs (blue) and 96 hrs (purple). The reduction in the butyraldehyde aldehyde peak at 9.77 ppm and splitting of the TEG protons between 3.5 – 4.5 ppm confirms the degradation of **P1**.

Figure S4. SEC trace of **P1** before degradation, 30 kDa, (blue) and following degradation in the presence of 95 eq. of TFA, reduction to 10.3 kDa after 96 hrs (red).

Figure S5. SEC trace of **P1** before degradation, 30 kDa, (blue) and following degradation in the presence of 5 eq. of **M1**, reduction to 2.2 kDa after 96 hrs (red).

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