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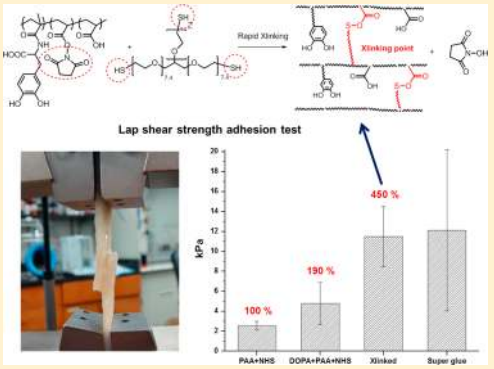
Rapidly Cross-Linkable DOPA Containing Terpolymer Adhesives and PEG-Based Cross-Linkers for Biomedical Applications

Hoyong Chung and Robert H. Grubbs*

Division of Chemistry and Chemical Engineering, California Institute of Technology, 1200 E. California Boulevard, Pasadena, California 91125, United States

Supporting Information

ABSTRACT: A new three-component bio-inspired adhesive was synthesized that is a terpolymer composed of a water-soluble segment, an interfacial adhesion segment, and a cross-linking segment. Strong wet adhesion properties are obtained utilizing a 3,4-dihydroxy-L-phenylalanine (DOPA) moiety. Poly(acrylic acid) provides high water solubility due to strong ionic interactions with water. An acrylic acid *N*-hydroxysuccinimide ester (NHS) was included in the adhesive polymer to allow rapid cross-linking with thiol-terminated, 3-armed poly(ethylene glycol) cross-linking agents. The thiol terminal poly(ethylene glycol) was designed to be bulky to avoid possible penetration of molecules to the cell and tissue. The NHS and thiol groups react within 30 s to form covalent bonds. This design allows for rapid optimization of properties for specific applications. Lap shear strength tests on wet porcine skin demonstrated a 190% increased value in adhesion strength for adhesives having the DOPA moiety. After cross-linking, adhesion was enhanced by 450% over poly(acrylic acid-*co*-acrylic acid NHS) and was 240% higher than un-cross-linked poly(acrylic acid-*co*-acrylic acid NHS-*co*-*N*-methacryloyl-3,4-dihydroxyl-L-phenylalanine). Rheology studies show adhesive viscosity drops significantly at high shear rates, demonstrating its potential to be injected via syringe. The cross-linked adhesive displayed much stronger mechanical properties and higher elastic and viscous moduli than an un-cross-linked adhesive model. Furthermore, the cross-linked adhesive has enhanced moduli near body temperature (38 °C) as compared to room temperature (23 °C), increasing the applications as a biomedical adhesive.



INTRODUCTION

Many medical polymer adhesives have been developed for a variety of purposes, such as closing wounds in tissue, preventing fluid leakage, and repairing damaged tissue.[1−5] There are a few examples of successful medical polymer adhesives including cyanoacrylates (Indermil, Dermabond),[1,6] glutaraldehyde-albumine reaction-based adhesives (BioGlue),[7−9] succinimidyl-thiol reaction-based adhesives (Coseal),[10,11] and fibrin-based adhesives (Tisseel, Crosseal, CoStasis, and Cryoseal).[12,13] These listed biomedical adhesives are commercially available and used in surgical applications. However, even with these successful results, various surgical conditions require new and better polymeric adhesives. A major challenge for improved biomedical adhesive is that the human body is composed of 60% of water and most of human body is wet except the outer skin.[14] Internal human organs are always wet with many types of liquids such as blood and mucus. Therefore, (1) strong wet adhesion capability is important for medical polymer adhesives. In addition to strong wet adhesion, a biomedical adhesive must be (2) nontoxic and without an immune response, (3) stable under physiological conditions, (4) rapidly cross-linkable without generation of heat, and (5) flexibility for use with soft organs and membranes. Additionally, more applications are possible if the adhesive can be delivered by syringe injection (6).[1−5] All six conditions should be satisfied in newly developed biomedical adhesives.

Recently, in order to improve polymer adhesive and tissue integration in wet condition, polymer adhesives using 3,4-dihydroxy-L-phenylalanine (DOPA) were proposed. DOPA is a specialized amino acid structure which is commonly found in many marine organisms such as mussels and sandcastle worms[15−19] where it is an essential point of strong wet adhesion property of these organisms. Because of the strong wet adhesion property of DOPA containing proteins, the DOPA functionality has been extensively studied to overcome current adhesives problems, poor wet adhesion. In general, water seriously inhibits the adhesion of synthetic adhesives for several reasons. First, water can plasticize adhesives and adherends. Second, adhesives, which are attached by physical interactions such as van der Waals forces, can be displaced by water when adherends have a high surface free energy. Finally, water can cause chemical degradation of adhesives and adherends.[20]

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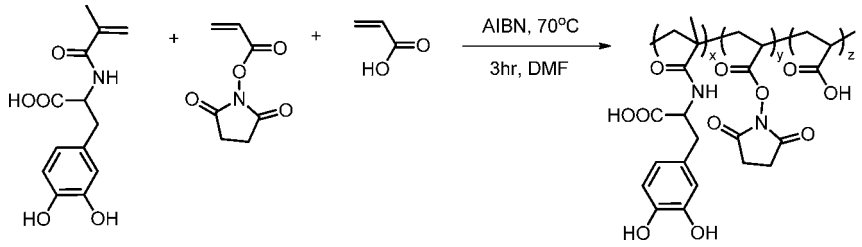
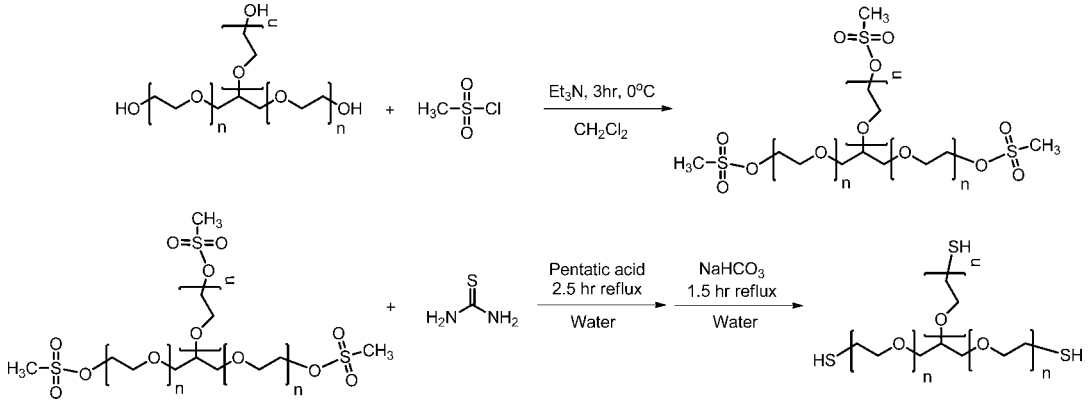
Scheme 1. Synthesis of Adhesives, Poly(AA-*co*-AANHS-*co*-MDOPA); x = 15, y = 15, and z = 70



Scheme 2. Synthesis of Cross-Linking Agent, Thiol PEG (n = 6−7)



The DOPA moiety has been widely applied to develop better materials and adhesives. For instance, Messersmith et al. developed DOPA poly(ethylene glycol) (PEG) and DOPA-protein bound antifouling materials.[21−24] These new materials protect various surfaces from foreign protein and microorganism adoption. In another example, the properties of carbon-nanotube-based fibers were enhanced by DOPA-functionalized polyethylenimine that strongly interconnect single fiber strings to form a fiber bundle with enhanced mechanical properties.[25] Also, simple polydopamine coatings are very useful in many surface modifications.[26−30] For example, the dopamine coating makes addition of macroscopic cells on non-bio-friendly surfaces possible.[26,29,30] DOPA-containing materials can also coat the surface of small size particles including nanoparticles[31−33] and even individual live cells.[28] Various types of synthetic/natural materials were integrated with a DOPA moiety to expend their adhesion applications; those materials includes PEG,[34−36] protein,[37−41] polysaccharide,[42−45] polycaprolactone,[46] polystyrene,[47] poly(methyl methacrylate),[47] and poly(methoxylethyl acrylate).[48−51]

Recently, it was reported that viscoelasticity tuning of a DOPA containing pressure-sensitive adhesive polymer can enhance the wet adhesion property by 185%.[51] The viscoelasticity of a DOPA containing polymer can be controlled by cross-linking. The most common cross-linking process in DOPA containing polymer is accomplished by reactions between the catechol moiety and metals such as Fe^{3+}, Ca^{2+}, Mg^{2+}, and Mn^{3+}.[52−57] pH variation of DOPA containing materials also can trigger cross-linking between catechol groups. The cross-linking yields viscoelastic property changes.[56,58] Oxidation of catechol groups using oxidants (e.g., $NaIO_4$) also can generate cross-linking between polymer chains.[59−61] Recently, the boronate−catechol complex is reported as a new cross-linking method.[58,62] Likewise, there have been various approaches to accomplish effective cross-linking in DOPA containing materials. Among them, introduction of cross-linking without sacrificing the DOPA moiety could be a new method to conserve the expensive key functionality, DOPA, for interfacial adhesion in adhesive materials.[51]

In this paper, we describe a newly designed DOPA containing terpolymer adhesives which were prepared by the polymerization of three vinyl monomers: acrylic acid (AA), acrylic acid *N*-hydroxysuccinimide ester (AANHS), and *N*-methacryloyl-3,4-dihydroxyl-L-phenylalanine (MDOPA). The adhesive uses rapid cross-linking reactions to form covalent bonds between polymer chains not via catechol groups at DOPA but via *N*-hydroxysuccinimide ester (NHS)−thiol condensation. Synthesis of terpolymer adhesives and cross-linker, thiol-terminated 3-armed poly(ethylene glycol) (thiol PEG), is presented in this report and along with in-vitro characterization to test adhesion and by rheology analysis.

EXPERIMENTAL SECTION

Materials. All chemicals were purchased from Aldrich. Vinyl group containing monomers were filtered through basic alumina-packed glass columns to remove inhibitors. All other chemicals were used as received. MDOPA[63] and AANHS[64−66] were synthesized and characterized as previously reported (Scheme S1). Porcine skins were purchased from a local grocery store.

Synthesis of Adhesives. Poly(AA-*co*-AANHS-*co*-MDOPA) was synthesized by azobis(isobutyronitrile) (AIBN)-initiated free radical polymerization of three monomers including AA, AANHS, and MDOPA as shown in Scheme 1. AA (2.624 g), AANHS (1.319 g), MDOPA (2 g), and AIBN (256.3 mg) were mixed in DMF (53 mL). The reaction mixture was degassed with dry argon gas bubbling for 15 min. The homogeneous reaction mixture was placed in a 70 °C oil bath and stirred for 3 h. After the reaction, the solution was added dropwise diethyl ether (800 mL). A white pulp-like solid precipitated and was recovered by vacuum filtration. The recovered solid was dried and dissolved in methanol (15 mL) and then precipitated once more into diethyl ether (200 mL). The final product was dried under vacuum overnight. The ^{1}H NMR spectrum of poly(AA-*co*-AANHS-*co*-MDOPA) is shown in Figure S1.

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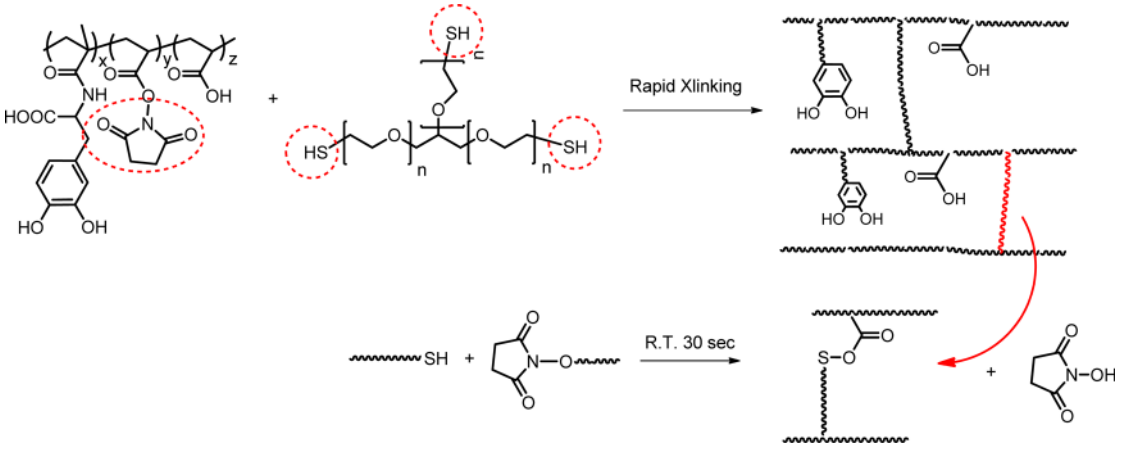
Scheme 3. Cross-Linking Scheme of Poly(AA-*co*-AANHS-*co*-MDOPA) and Thiol-Terminated 3-Armed Poly(ethylene glycol) Mixture[a]



[a]Adhesive and thiol PEG are covalently cross-linked by a rapid reaction between NHS and thiol group.

Synthesis of Cross-Linking Agents. Thiol PEG was synthesized and characterized according to a previously described process.[67] Briefly, thiol PEG was prepared by two steps: the first step is synthesis of mesylate terminated 3-armed PEG, and the second step is synthesis of thiol PEG. To prepare mesylate-terminated 3-armed PEG, glycerol ethoxylate (5 g) and triethylamine (3 g) were dissolved in methylene chloride (70 mL). In separate glassware, mesyl chloride (6.87 g) was dissolved in methylene chloride (30 mL). The two separated solutions were mixed slowly together while keeping the temperature at 0 °C in an ice bath. White fumes were observed during the mixing process. The reaction mixture was stirred for 3 h at 0 °C. After stirring, all solvents were removed by a rotary evaporator. The resulting viscous liquid was dissolved in water, and then $NaHCO_3$ was slowly added to neutralize the remaining mesyl chloride. Saturated $NaHCO_3$ also can be used instead of dry $NaHCO_3$ powder. The product was extracted with chloroform (60 mL × 3) and then dried over $MgSO_4$. The final product, mesylate-terminated 3-armed PEG, was obtained after removal of all chloroform by rotary evaporation.

Mesylate-terminated 3-armed PEG (7 g), diethylenetriaminepentaacetic acid (50 mg), and thiourea (3.2 g) were mixed in water (100 mL). The solution's pH was adjusted to 6.7 with KOH aqueous solution and refluxed for 2.5 h. After cooling the solution, 1.5 equiv of $NaHCO_3$ (2.65 g) was added to hydrolyze the isothiouronium salt. The solution was refluxed again for 1.5 h and cooled, and then aqueous sulfuric acid (1 M) was slowly added to the solution until the solution was neutralized. The final product was extracted with chloroform (50 mL × 3) and then dried over $MgSO_4$, and the solvent was removed using a rotary evaporator. The light brown and viscous final product was stored in the cold (−18 °C) and in the dark. The overall reaction scheme is presented in Scheme 2, and the thiol PEG's ^{1}H NMR spectrum is shown in Figure S1.

Adhesion Property Test (Lap Shear Strength Test). Adhesion properties were determined by lap shear strength tests. Porcine skin was selected due to its biological similarity to human dermis.[68−70] Approximately 3 mm thick porcine skins were cut and trimmed into 5 cm × 2.5 cm size. The prepared porcine skin was used as an adherend without further purification or modification in order to mimic real clinical condition. Adhesives were preweighed (100 mg) and swollen in a syringe (1 mL) with a water prior to use. Water was sprayed on porcine skin, and then water-swollen adhesives were aligned on wet porcine skin with three straight lines. Another porcine skin was overlaid on the adhesive applied part and quickly rubbed several times. The overlaid porcine skins with adhesives were compressed under 90 g of weight for 10 min. For cross-linked adhesive test, a cross-linker (100 μL) was applied between the adhesive lines on porcine skin so as not to mix adhesive and crossinker before the test. Exactly the same test sample preparation procedure was used for Super Glue (the original Super Glue, Rancho Cucamonga, CA) adhesion property tests. The porcine skin was thoroughly wet by water before addition of the adhesive (Figure 2.) Shear strength was measured at room temperature (23 °C) with an Instron testing machine (model E3000 and model 5569). Load was recorded as a function of displacement with a cross-head speed of 1 cm/min. The maximum load (force) was divided by the overlapping contact area of porcine skins to calculate adhesion strength. Tests were performed at least five times for each type of adhesive, and data points were averaged.

In order to test covalent bond formation between cross-linker and adhesive, three different amounts of cross-linker—50, 100, and 200 mg—were mixed with 100 mg of adhesives. The water-swollen adhesive was mixed with a designated amount of cross-linker and then frozen in dry ice. The frozen mixture was lyophilized for 24 h to remove water. The dry product was dissolved in DMSO-d_6 to quantify the reacted functional groups. In the ^{1}H NMR, peak integrations at 2.8 ppm were compared to calculate the consumed NHS group since the signal at 2.8 ppm indicates a $-CH_2CH_2-$ at AANHS segments in terpolymer. The ^{1}H NMR spectrum of adhesive and cross-linker mixture is shown in Figure S1.

Viscoelastic Property Analysis. Viscoelastic properties were characterized by a rheometer (TA Instruments, Model AR1000) equipped with 25 mm diameter stainless steel parallel plate geometry. Adhesive samples (200 mg) were swollen in water prior to testing. Steady state shear viscosity was recorded as a function of shear rate (s^{-1}) from 1000 to 0.1 s^{-1} at 23 and 38 °C. For dynamic mechanical analysis, frequency sweeps from 100 to 0.1 Hz were conducted to measure elastic modulus (G') and viscous modulus (G'') at 23 and 38 °C.

RESULTS AND DISCUSSION

Synthesis of Poly(AA-*co*-AANHS-*co*-MDOPA) and Thiol PEG. Poly(AA-*co*-AANHS-*co*-MDOPA) was synthesized by a thermally initiated free radical polymerization of AA, AANHS, and MDOPA as shown in Scheme 1. The prepared polymer was characterized by ^{1}H NMR to calculate ratios of each repeating unit in the final poly(AA-*co*-AANHS-*co*-MDOPA). ^{1}H NMR and chemical structure assignments are shown in Figure S1. After testing, samples which were prepared with various ratios of three repeating units, a terpolymer which has 70% of AA, 15% of AANHS, and 15% of MDOPA, demonstrated the most suitable properties for use as an adhesive. Therefore, this report focuses on an adhesive of this composition. According to ^{1}H NMR characterization, the final composition reflects the initial feeds of monomers.

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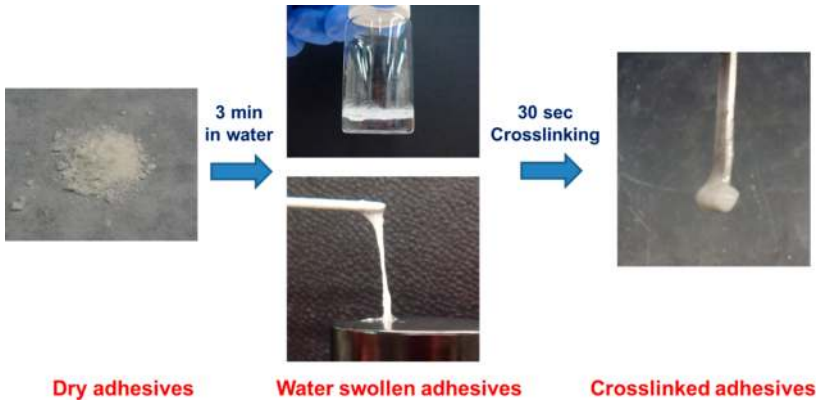

Figure 1. Property changes of adhesives in water and after cross-linking. Dry adhesive power is swollen in water and became viscous liquid in 3 min. The water-swollen adhesive liquid became a solid gel after cross-linking with thiol PEG.

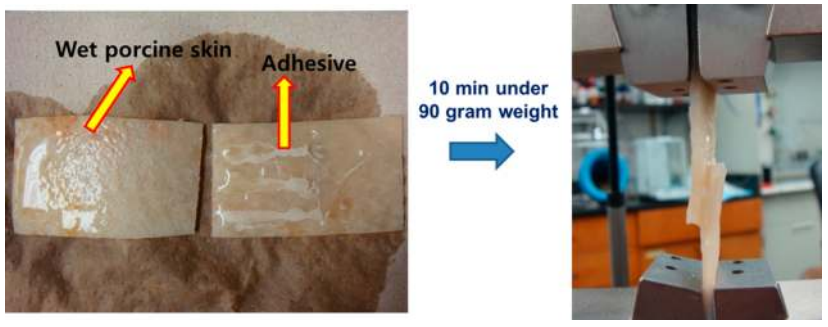

Figure 2. Images of lap shear strength test setup. Adhesive (white lines on porcine skin) was applied on wet porcine skin (adherend) prior to sandwiched and compressed under 90 g of weight for 10 min.

The polyAA functions as a water-soluble segment and is an FDA-approved nontoxic food additive. The ionic interaction of polyAA generates much stronger hydrophilicity than commonly used PEG–water interactions.[71−73] MDOPA functions as a strong interfacial adhesive. As already mentioned in the Introduction, there are many previous reports using a DOPA moiety in a synthetic adhesive that has strong wet adhesion.[15−19] AANHS segment forms covalent bonds to thiol groups at cross-linkers. The reaction is illustrated in Scheme 3. In this cross-linking chemistry, NHS reacts very rapidly with thiol groups and forms covalent bond at thio-ester groups with release of *N*-hydroxysuccinimide.[10,11]

Cross-linking agent, thiol PEG, was functionalized with glycerol ethoxylate which is a 3-armed poly(ethylene glycol). Poly(ethylene glycol) is commonly used in biomaterials due to its biocompatibility, hydrophilicity, and nontoxicity.[74,75] The starting material, glycerol ethoxylate, has an average M_n of 1000 g/mol, and the number of ethylene oxide repeating unit is 6−7 for each arm according to the manufacturer's information (Aldrich). The chemical structure was confirmed by ^{1}H NMR characterization. The viscosity of the selected glycerol ethoxylate was sufficiently low to allow effective mixing with the adhesives. The molecular weight of glycerol ethoxylate (M_n ≈ 1000 g/mol) can prevent or retard the possible absorption of surplus cross-linking agents in the cell/tissue after the reaction is complete. The multiple armed poly(ethylene glycol) architecture was selected to increase the reactivity for more effective cross-linking with adhesives. Thiol terminal functional groups were introduced in two steps as shown in Scheme 2. First, hydroxyl groups were converted to mesyl groups via substitution reactions with methanesulfonyl chloride. Second, a thiol group was introduced to PEG arm terminals after reaction of mesyl group and thiourea.[67]

Adhesion Property Characterization of Un-Cross-Linked and Cross-Linked Adhesives. The final state of the prepared adhesive is a white powder as shown in the first image of Figure 1. The dry powder is not an adhesive. But as soon as the powder was mixed with water, the adhesive became a very soft, viscous liquid as shown in the second image of Figure 1. The adhesive absorbed 2.5 times of its weight of water and did not dissolve in water homogeneously even after a long exposure time. Hydrogen bonding between the amide functionality at MDOPA and interaction between highly charged side chains contribute to strong aggregations and chain entanglement to limit solubility in water.

The water-swollen adhesive was mechanically mixed with thiol PEG to yield a cross-linked solid. The cross-linked adhesive was a flexible solid material as shown in the rightmost images of Figure 1. The mixture of adhesive and cross-linker was analyzed by ^{1}H NMR as shown in Figure S1. The 2.8 ppm signal from the $-CH_2CH_2-$ groups in the AANHS segments in the adhesive showed a significant decrease of integration compared to unreacted terpolymers. The NMR clearly demonstrates that a large amount of NHS was consumed after reaction with thiol groups of the cross-linker.

The adhesive utilize the DOPA moieties for interfacial adhesion not for cross-linking. Recently, slow Michael addition between thiol group and a catechol group was reported by Lee et al.[43,76] Unlike Lee et al.'s report, the presented cross-linking system occurred very rapidly within 30 s. In contrast to previously reported DOPA-thiol Michael addition which took at least 6 h at 37 °C until the completion of the reactions, the

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final rheological property results also support that there is no significant DOPA-thiol Michael reaction occurred during the testing time. According to the steady state shear viscosity test and dynamic mechanical analysis results (Figures 4 and 5), the cross-linked adhesives did not show significant viscosity change or moduli change during the test. More detailed rheological analysis will be discussed in the later part of this report.

Adhesion properties were evaluated by using lap shear strength test with an Instron (Model E3000 and model 5569). Porcine skin was used as an adherend to test the prepared adhesive's possible biomedical applications. Porcine skin is commonly used for various biomedical experiments due to its biological similarity to human dermis.[68−70] The porcine skin substrate was wet with purified deionized water (DI water) prior to adhesive application in order to test the wet adhesion property of adhesives. A typical adhesion test set up is demonstrated in Figure 2. The white lines on the porcine skin are adhesives in the left image of Figure 2. For the cross-linked adhesive test, adhesive and cross-linkers were aligned parallel and then the porcine skins were overlaid. The overlaid porcine skin was quickly rubbed several times prior to weight compression. All overlaid substrates were compressed by 90 g of weight for 10 min, which is a much shorter time than other previous DOPA containing biomedical adhesive researches.[46,57,59,77−79]

To confirmed the enhanced adhesion property with DOPA moiety in an adhesive chemical structure, poly(AA-*co*-AANHS) was prepared and tested. Poly(AA-*co*-AANHS) was synthesized by exactly the same method as poly(AA-*co*-AANHS-*co*-MDOPA), except for the MDOPA monomer. As shown in Figure 3, poly(AA-*co*-AANHS) demonstrated very low adhesion strength, 2.5 kPa on average. The terpolymer containing DOPA moiety, poly(AA-*co*-AANHS-*co*-MDOPA), presents much higher adhesion strength of 4.8 kPa, which is 190% over the value of adhesive without a DOPA moiety, poly(AA-*co*-AANHS). Cleary et al. reported a pH effect on polyAA's mucoadhesion property.[80] In his report, polyAA shows the highest adhesion at pH 5. As the pH was increased (pH 7 or higher), the adhesion property of the polyAA significantly deteriorated. Note that all adhesion tests were done in neutral DI water, which has a pH of 7. Considering Cleary et al.'s report, the main driving force of the enhanced adhesion property of poly(AA-*co*-AANHS-*co*-MDOPA) is the DOPA moiety in the polymer. The highest adhesion strength was obtained from a cross-linked adhesive mixture of poly(AA-*co*-AANHS-*co*-MDOPA) and thiol PEG. In Figure 3, this mixture of adhesive, poly(AA-*co*-AANHS-*co*-MDOPA), and cross-linker, thiol PEG, is demonstrated to be X-linked. The cross-linked adhesive showed a 450% increased adhesion strength compared to poly(AA-*co*-AANHS) under the given test conditions (cross-head speed of 10 mm/min). This adhesion strength was similar to commercially available Super Glue (cyanoacrylate). The standard deviation of Super Glue adhesion tests result was very large; in other words, Super Glue's adhesion property is undependable in wet condition on porcine skins. The force−displacement curve clearly shows differences of adhesive failure process before and after cross-linking (Figure S2) in terms of maximum force and failure pattern. Un-cross-linked adhesive shows a gradual decrease of load after it reaches the maximum strength and forms numerous adhesive fibers between adherends. Cross-linked adhesive demonstrates much higher maximum strength and sudden failure of adhesion without forming fibers between adherends. This phenomenon demonstrates that covalent cross-links were formed between adhesive polymer chains, and accordingly the cross-linking enhances the maximum adhesion strength by increasing cohesive strength in adhesive structures.

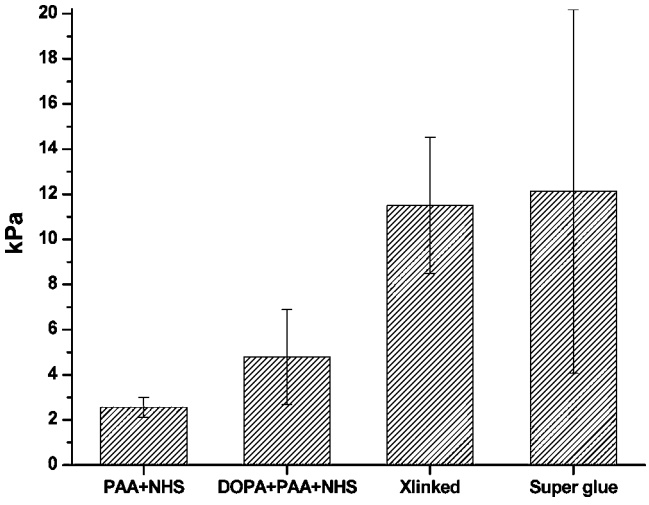

Figure 3. Adhesion properties of prepared adhesives and Super Glue. Lap shear strength of adhesives was obtained by dividing recorded maximum load (force) by overlapped porcine surface area. PAA + NHS: poly(AA-*co*-AANHS); DOPA + PAA + NHS: poly(AA-*co*-AANHS-*co*-MDOPA); X-linked: mixture of poly(AA-*co*-AANHS-*co*-MDOPA) and thiol PEG.

Viscoelastic Properties of Un-Cross-Linked and Cross-Linked Adhesives. Steady-state shear viscosity tests and dynamic mechanical analysis were carried out to characterize the viscoelastic properties of un-cross-linked (poly(AA-*co*-AANHS-*co*-MDOPA)) and cross-linked (mixture of poly(AA-*co*-AANHS-*co*-MDOPA) and the thiol PEG) adhesives. The viscoelastic properties were examined at room temperature (23 °C) and human body temperature (38 °C) to determine if the polymer could be a biomedical adhesive. Figure 4 shows steady-state shear viscosity as a function of shear rate (s^{-1}). Interestingly, un-cross-linked adhesive revealed a significant drop of viscosity near 100 s^{-1} (Figure 4a). This is a typical behavior of a shear thinning polymer because the entanglement density of polymer chains decreases with increasing shear rate.[81,82] This character is useful in biomedical adhesives which are delivered by syringe-needle injection due to significant increase of shear rate the adhesive polymers experience when it enters the narrow needle from a relatively large syringe body. The shear thinning effect could help easy injection of the adhesive material without severe back-pressure. A similar phenomenon was observed previously by Kaur et al.[79] At 38 °C in Figure 4a, un-cross-linked adhesive showed a sudden drop of viscosity at lower shear rate. At both 23 and 38 °C, un-cross-linked adhesive showed very stable viscosity before a shear rate of 100 s^{-1}. The cross-linked adhesive showed much higher viscosity over a range between 0.1 and 100 s^{-1} than the un-cross-linked adhesive at both 23 and 38 °C (Figure 4b). This viscosity result from the cross-linked adhesive test in Figure 4b shows that once the adhesive is fixed to the area of interest, it demonstrates stable and strong viscoelastic properties.

Both elastic and viscous moduli, G' and G'', are shown in log−log scale as a function of frequency (hertz) in Figure 5. All

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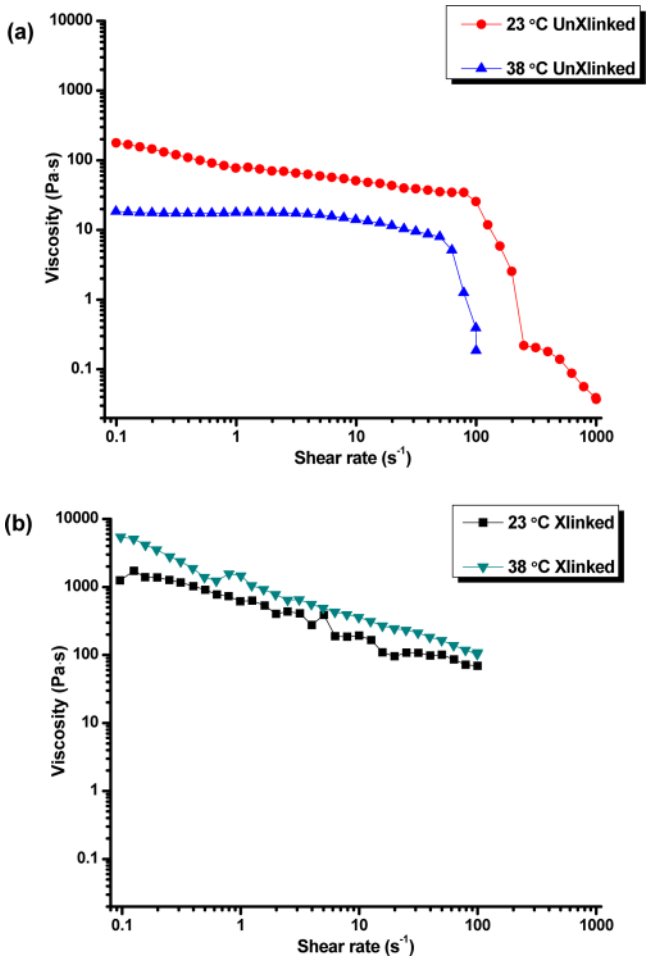

Figure 4. Viscosity measurement of (a) un-cross-linked, poly(AA-*co*-AANHS-*co*-MDOPA), and (b) cross-linked adhesives, mixture of poly(AA-*co*-AANHS-*co*-MDOPA) and the thiol PEG, as a function of shear rate at room temperature (23 °C) and human body temperature (38 °C); viscosity of un-cross-linked adhesives drops at high shear rate near 100 s^{-1} at both 23 and 38 °C. Cross-linked adhesives demonstrate stable viscosity over a wide range of shear rate with higher viscosity than un-cross-linked adhesive.

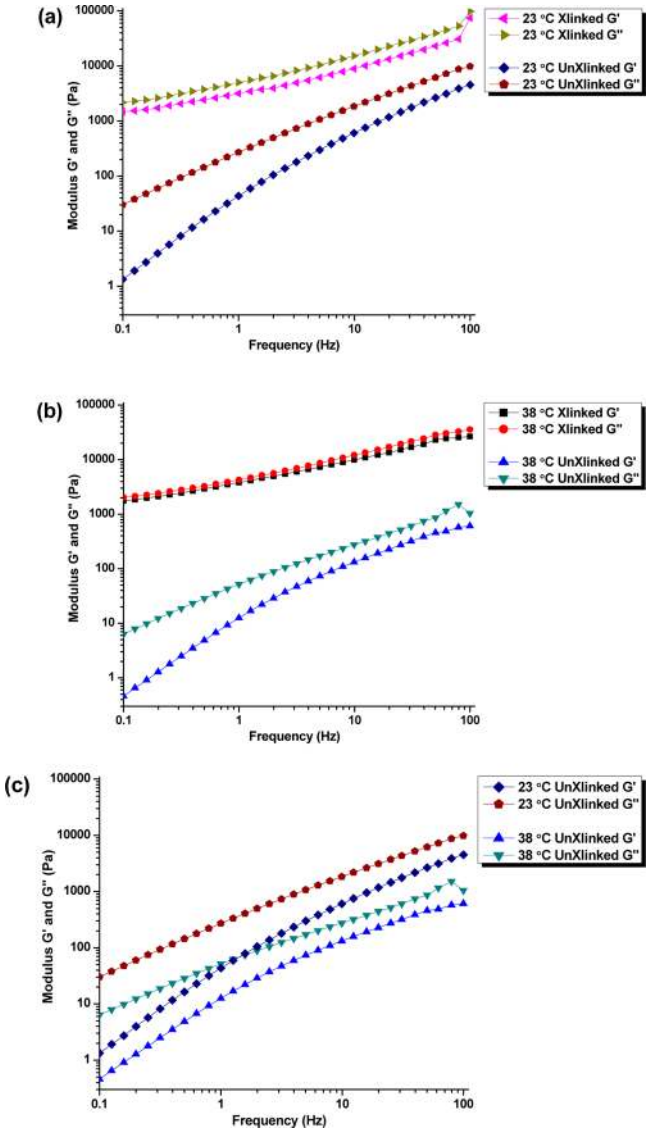

Figure 5. Elastic modulus (G') and viscous modulus (G'') as a function of frequency (hertz) for cross-linked and un-cross-linked adhesive. (a) 23 °C and (b) 38 °C (c) moduli of un-cross-linked adhesives for both 23 and 38 °C. The measurements were performed with constant strain of 5%.

cross-linked adhesives demonstrated a much higher moduli than un-cross-linked adhesives as shown in Figure 5a,b. Also, the elastic and viscous moduli of cross-linked adhesives were closer than un-cross-linked adhesives over all tested frequency range (Figure 5a,b). These results suggest that the un-cross-linked adhesive is more similar to a viscoelastic liquid, while cross-linked adhesive is closer to a viscoelastic solid.[83] No significant gel point was observed in both Figure 5a,b due to the adhesives' strong viscoelastic liquid behavior in all the tests. In other words, the cross-linked adhesive is not an absolute solid from a rheological point of view, but the cross-linked adhesive is closer to a solid than a liquid.[84] The shown rheology data are consistent with visual observation of the cross-linked adhesive material. While temperature effects on the cross-linked adhesives were not significant, un-cross-linked adhesives demonstrated a strong temperature effect on its viscoelastic behavior as shown in Figure 5c. At 38 °C, much lower moduli was observed for un-cross-linked adhesive, and moduli responded more significantly with changes of frequency. Overall, the prepared adhesive strengthens by cross-linking, and the cross-linked adhesive presents high stability under various temperatures while showing viscoelastic solid characters.

■ CONCLUSION

A novel designed bio-inspired adhesive composed of three monomers with different functions is described. 70 mol % of the total adhesive was polyAA which has the role of providing good water solubility by utilizing the strong ionic interaction between polyAA and water. 15 mol % each of MDOPA and AANHS was used to enhance wet interfacial adhesion and to provide a cross-linking. The cross-linking agent is a three-armed PEG with thiol end groups. The synthesized adhesive was water swellable and cross-linked rapidly and effectively. Adhesion property measurements, based on lap shear strength tests on a wet porcine skin, revealed that the cross-linked poly(AA-*co*-AANHS-*co*-MDOPA) demonstrated a 450% higher adhesion strength than un-cross-linked poly(AA-*co*-AANHS). The adhesive can be delivered by syringe and needle consistent

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with steady-state shear viscosity measurement. Also, dynamic mechanical analysis demonstrated that the cross-linked adhesive is a stable and strong material at human body temperature, 38 °C. This adhesive/cross-linker has the potential to be applied as a clinically useful biomedical adhesive.

■ ASSOCIATED CONTENT

Supporting Information

Scheme S1 and Figures S1 and S2. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rhg@caltech.edu.

Notes

The authors declare no competing financial interest.

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