

Photo-cross-linked Poly(thioether-co-carbonate) Networks Derived from the Natural Product Quinic Acid

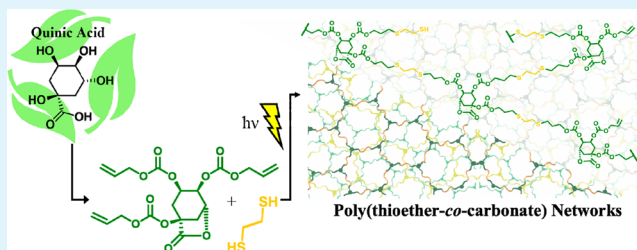
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S Supporting Information

ABSTRACT: Polycarbonate networks derived from the natural product quinic acid that can potentially return to their natural building blocks upon hydrolytic degradation are described herein. Solvent-free thiol–ene chemistry was utilized in the copolymerization of tris(alloc)quinic acid and a variety of multifunctional thiol monomers to obtain poly(thioether-co-carbonate) networks with a wide range of achievable thermomechanical properties including glass transition temperatures from -18 to $+65$ °C and rubbery moduli from 3.8 to 20 MPa. The network containing 1,2-ethanedithiol expressed an average toughness at 25 and 63 °C of 1.08 and 2.35 MJ/m³, respectively, and an order-of-magnitude increase in the average toughness at 37 °C of 15.56 MJ/m³.

KEYWORDS: quinic acid, polycarbonates, renewable polymers, thiol–ene chemistry, photo-cross-linking



Polymers derived from natural resources have attracted increased attention not only for their ability to form commodity plastics, which decrease dependence on petroleum processes, but also for their ability to form biocompatible materials with resorbable degradation products.^{1–3} Recently, polymers derived from naturally occurring precursors, such as nucleotides,⁴ carbohydrates,⁵ ferulic acid,⁶ and D-limonene^{7,8} have been reported as prospective degradable biomaterials. Common polyesters, including poly(lactic acid) and poly(glycolic acid), have shown to be useful in various tissue engineering applications including some orthopedic applications.^{9,10} They possess modulus values similar to those of cancellous bone (0.1–4.5 GPa) but still low compared to those of cortical bone (17–24 GPa), and orthopedic devices made from these materials may require challenging and costly fabrication and sterilization techniques.^{11,12} Materials for implant device applications demand polymer functionality at both the macromolecular and molecular levels to satisfy material design requirements and enable a desired physiological response. In the case of bioresorbable polymers for orthopedic devices, the design criteria include modulus and ultimate strength values similar to those of bone and a high degree of compatibility with surrounding tissue from initial implantation and throughout degradation.¹³ In the case of polyesters, inflammation and pain may arise if acidic degradation products are not cleared quickly.¹⁴

By utilizing the mechanical and degradation properties of polycarbonates, improvements in the limitations of conventional systems may be possible. When aliphatic carbonates undergo hydrolytic degradation, they are converted to alcohols

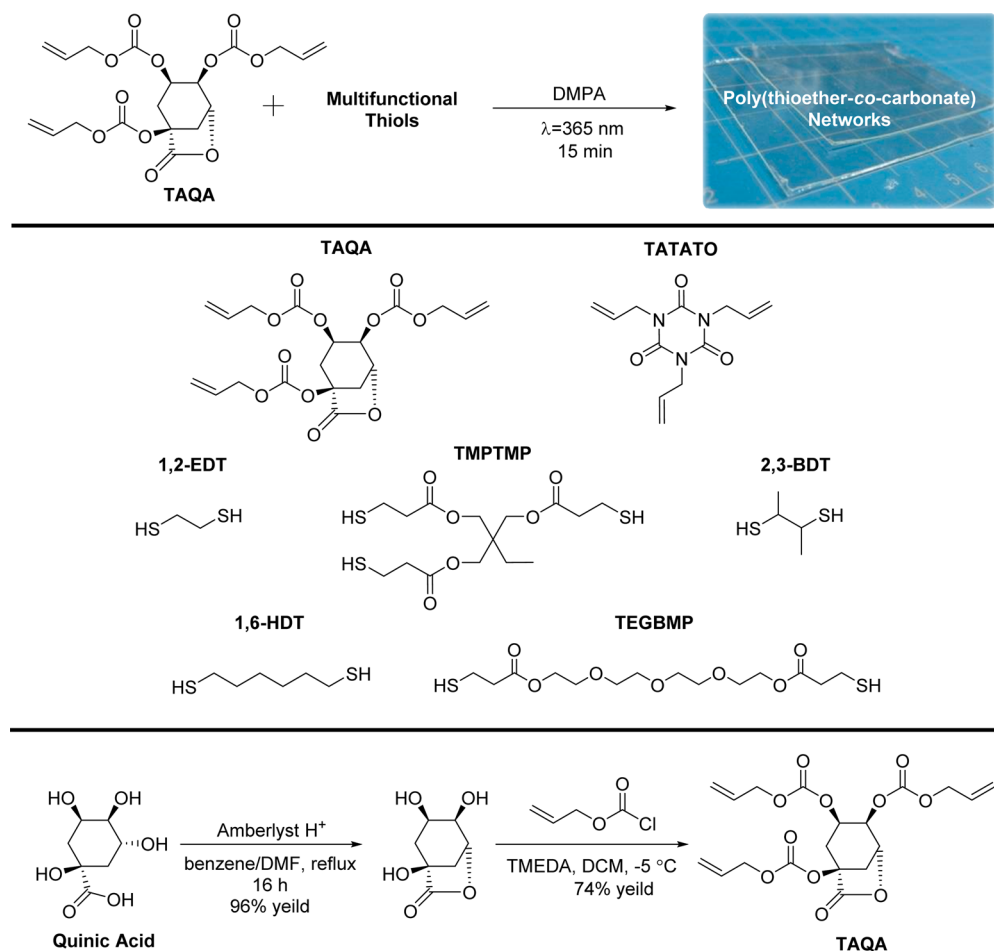
and carbon dioxide, which may decrease the risk of undesirable side effects and slow the rate of erosion, compared to the degradation products of polyesters.^{15–17} Furthermore, in the case of polycarbonates built from natural products, it is possible to design materials that produce bioactive products upon degradation. One such natural building block is quinic acid (QA), a polyhydroxyl compound found freely and in the form of esters with cinnamic acids, known as chlorogenic acids, in many agricultural products such as tree barks, tobacco, teas, coffee, and many fruits and vegetables.¹⁸ Free QA occurs naturally in green coffee beans, and upon roasting, hydrolysis of chlorogenic acids produces additional QA, making QA one of the dominant acids present in roasted coffee.¹⁹ QA can be isolated from natural sources or produced from glucose through environmentally friendly and cost-effective methods.²⁰ QA is metabolized by intestinal microflora to afford tryptophan and nicotinamide and promotes antioxidant activity and growth.^{21–23} Previously, the synthesis of poly(quinic acid carbonate)s was investigated by copolymerization of *tert*-butyldimethylsilyloxy-protected 1,4- and 1,5-diol monomers of QA and phosgene.²⁴ Although the polymers exhibited high glass transition temperatures [209 °C for poly(1,4-quinic acid carbonate) and 229 °C for poly(1,5-quinic acid carbonate)], they possessed only poor mechanical strength, which likely resulted from limited molecular weights and incomplete deprotection being achieved.

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Scheme 1. General Scheme for Photo-cross-linking of Poly(thioether-co-carbonate) Networks and an Example of Resulting Cured Films (Top), Monomer structures with Abbreviations (Middle), and Two-Step Synthesis of TAQA from QA (Bottom)



To introduce mechanically robust biobased polycarbonates, the synthesis and thermomechanical characterization of covalently cross-linked networks derived from QA are reported in this study. A quinic acid lactone was modified to produce the tris(alloc)quinic acid (TAQA) alkenyl monomer shown in Scheme 1. Three-dimensional networks were achieved by photocatalyzed thiol-ene chemistry upon polymerization with the multifunctional thiols also illustrated in Scheme 1. The thermomechanical properties of the poly(thioether-co-carbonate) networks were compared to those of networks containing the commercially available monomer triallyl-1,3,5-triazine-2,4,6-trione (TATATO). Thiol-ene chemistry^{25–27} is highly efficient and easily accessible, proceeds under mild conditions, is tolerant of many functional groups, and has been employed in various tissue engineering applications.^{28–30} Several material design criteria drove the monomer selection. Because one end goal is to synthesize amorphous polymers for use in orthopedic applications, it is important that the materials perform as a glassy solid at physiological temperature with a modulus close to that of bone. Thus, the optimal glass transition temperature (T_g) would be significantly above body temperature (37 °C). Many thiol-ene polymers undergo glass transitions below 37 °C because of the high flexibility of the thioether linkage, and increasing T_g has traditionally been a significant synthetic challenge.³¹ One method of increasing T_g in network polymers is to increase the cross-link density by increasing the monomer functionality; however, increasing the cross-link density to the

extent necessary to raise T_g above 37 °C in thiol-ene polymers has often resulted in significantly decreased toughness, which is undesirable.^{32,33} Therefore, an ideal material would have T_g well above 37 °C and a low, but sufficient, cross-link density. In this study, the bicyclic structure of TAQA is predicted to increase T_g by increasing the network rigidity in comparison with that of the commercially available triallyl monomer, TATATO. Concerning thiol monomer selection, the 1,2-ethanedithiol (1,2-EDT) monomer is predicted to form networks with high rigidity and toughness compared to other commercially available polythiols because the 1,2-EDT-co-TAQA polymer has the greatest TAQA weight fraction while also having a moderate cross-link density because of the difunctionality of 1,2-EDT.

The two-step synthesis of the TAQA monomer (Scheme 1, bottom) coupled with the solvent-free binary copolymerization enabled facile production of highly uniform cross-linked networks. The first step of the monomer synthesis was well-established lactonization of QA under acidic conditions.³⁴ QA and acidic Amberlyst resin were suspended in benzene and *N,N*-dimethylformamide and heated to reflux with azeotropic removal of water to afford the bicyclic triol quinic acid lactone in 96% yield. To install the three alloc functional groups, allyl chloroformate was added dropwise to quinic acid lactone suspended in *N,N,N',N'*-tetramethylethylenediamine and dichloromethane to give 74% yield of TAQA as a clear, viscous oil. The structure of TAQA was confirmed by Fourier

transform infrared (FTIR) and electrospray ionization mass spectrometry, as well as ^1H , ^{13}C , COSY, and HSQC NMR spectroscopies. Solvent-free cross-linking copolymerization by thiol-ene radical addition in the presence of 1 wt % 2,2-dimethoxy-2-phenylacetophenone photoinitiator was performed by mixing TAQA and multifunctional thiol monomers, based on equal molar functional groups, mold casting, and exposing to UV light ($\lambda = 365$ nm), to produce films with uniform thickness (0.4 mm). This was followed by postcuring at 120 °C for at least 4 h to vulcanize residual thiol groups. The samples were characterized by FTIR to verify consumption of alkene (1650 cm^{-1}) and thiol (2570 cm^{-1}) groups upon network formation. A variety of multifunctional thiols was investigated including 1,2-EDT, 2,3-butanedithiol (2,3-BDT), 1,6-hexanedithiol (1,6-HDT), trimethylolpropanyl tris(3-mercaptopropionate) (TMPTMP), and tetraethylene glycol bis(3-mercaptopropionate) (TEGBMP).

The dynamic mechanical analysis (DMA) results in Figure 1 show the relative thermomechanical behavior in tension of

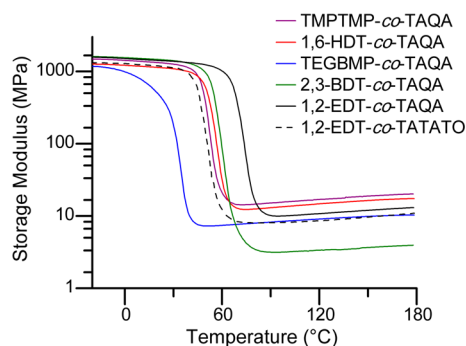


Figure 1. Storage modulus measurements by DMA of films (postcured for 24 h) as a function of the temperature.

cured samples synthesized from TAQA or TATATO and various thiol compounds. This behavior is characteristic of amorphous, covalently cross-linked polymers, which includes a glassy modulus plateau at temperatures below the glass transition, a transition region in which the modulus decreases with increasing temperature, and a rubbery plateau region in which the modulus remains constant or slightly increases with increasing temperature. The cross-link density of a thermosetting polymer is proportional to its rubbery modulus plateau in accordance with the relationship for an ideal rubber. Materials incorporating TMPTMP had the highest cross-link density because of its increased functionality compared to the other thiol monomers investigated. The relatively low cross-link density of the 2,3-BDT-*co*-TAQA networks, compared to the other materials, can be explained by ineffective cross-linking reactions due to steric hindrance by the bulky secondary thiols of 2,3-BDT. Table 1 lists the thermomechanical properties of the poly(thioether-*co*-carbonate) networks containing the various multifunctional thiols investigated. The T_g values, determined by differential scanning calorimetry (DSC), are consistent with the onset of the glass transition region in the storage modulus behavior shown in Figure 1. The 1,2-EDT-*co*-TAQA sample contained the greatest weight fraction of the rigid bicyclic TAQA monomer and the lowest weight fraction of flexible aliphatic spacer atoms and, thus, exhibited the highest T_g value (65 °C), comparable to that of poly(L-lactide) ($T_g = 60\text{--}65$ °C). In contrast, the TEGBMP-*co*-TAQA system's longer and more flexible TEGBMP-based spacer resulted in an

Table 1. Thermal Transitions and Moduli Exhibited by the Poly(thioether-*co*-carbonate) Networks Derived from TAQA in Comparison to Networks Derived from a Commercially Available Triallyl Monomer

sample	T_g [°C] ^a	T_d [°C] ^b	E' [MPa] ^c	E_r [MPa] ^d
TEGBMP- <i>co</i> -TAQA	-18	264	357	7.3
TMPTMP- <i>co</i> -TAQA	43	275	1290	14
1,6-HDT- <i>co</i> -TAQA	48	261	1110	12
2,3-BDT- <i>co</i> -TAQA	51	261	1440	3.1
1,2-EDT- <i>co</i> -TAQA	65	262	1400	10
1,2-EDT- <i>co</i> -TATATO	38	332	1170	7.2

^aDetermined by DSC. ^bOnset of thermal decomposition determined by thermogravimetric analysis. ^cStorage modulus at 25 °C determined by DMA. ^dRubbery modulus determined by DMA.

elastomeric material with T_g well below room temperature. The 1,2-EDT-*co*-TATATO network expressed T_g that was 27 °C lower than that of the 1,2-EDT-*co*-TAQA material. As predicted, the bicyclic TAQA monomer provided the 1,2-EDT-*co*-TAQA network with increased rigidity, which could not be achieved with the commercially available triallyl monomer TATATO in the 1,2-EDT-*co*-TATATO network. DMA experiments at multiple frequencies were used to determine the activation energy of the glass transition, E_a , of 1,2-EDT-*co*-TAQA, which was 374 ± 14 kJ/mol in accordance with the Arrhenius relationship.³⁵ In comparison with poly(lactic acid) ($E_a = 255$ kJ/mol),³⁶ 1,2-EDT-*co*-TAQA networks require more energy to impart segmental motion. Poly(bisphenol A carbonate), however, has a considerably higher E_a of 766 kJ/mol because of its rigidity and ability to dissipate energy effectively.³⁷

The temperature at which the onset of thermal decomposition began, T_d , was determined by thermogravimetric analysis. All of the poly(thioether-*co*-carbonate)s characterized had thermal decomposition temperatures greater than 260 °C (Table 1). To determine the postcure time necessary to drive the polymerization to completion, enable vaporization of residual small molecules, and allow for network relaxation, DSC experiments were run on samples subjected to various postcure times at 120 °C. As the postcure time increased from 0 to 4 h, T_g increased for each sample, and after 4 h, negligible changes in T_g were observed (Figure S5 in the Supporting Information, SI). Thermal analysis of the network materials synthesized in this study demonstrates that a significant variation in the thermomechanical properties is achievable by varying the thiol monomer chemistry. The diverse array of physiological environments within the body has given rise to the need for biomaterials that conform to a wide range of design criteria.

Each of the poly(thioether-*co*-carbonate) networks that met the requirement of being glassy at 37 °C, 1,2-EDT-*co*-TAQA, TMPTMP-*co*-TAQA, 2,3-BDT-*co*-TAQA, and 1,6-HDT-*co*-TAQA, was subjected to tensile-strain-to-failure measurements. The stress/strain behavior of each system at 25 °C is depicted in Figure 2a. Although all four of the samples performed similarly, the networks with lower T_g values, 1,6-HDT-*co*-TAQA and TMPTMP-*co*-TAQA, failed in a slightly more ductile manner, reaching a yield point at which the material exhibited an increase in strain at a constant or slightly decreasing stress, compared to the networks with higher T_g values, 1,2-EDT-*co*-TAQA and 2,3-BDT-*co*-TAQA. While 1,2-EDT-*co*-TAQA exhibited brittle behavior at 25 °C and failed at

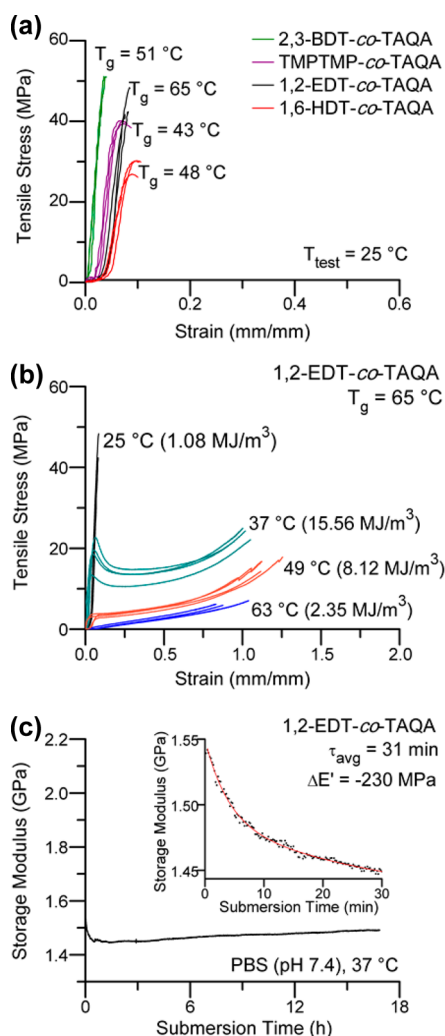


Figure 2. (a) Stress/strain behavior of poly(thioether-*co*-carbonate) networks that exhibit T_g values that are greater than physiological temperature. (b) Strain-to-failure of 1,2-EDT-*co*-TAQA at various temperatures. (c) Storage modulus as a function of time over 17 h obtained by submersion in PBS at 37 °C. Inset: In situ stress relaxation in response to solvent (first 30 min) fit to dual-exponential decay ($R^2 = 0.993$).

8% strain, it became more ductile at elevated temperatures, as shown in Figure 2b. At 63 °C, just below its T_g (65 °C), 1,2-EDT-*co*-TAQA underwent weak elastomeric failure at a stress of 6 MPa, but at 37 °C, 1,2-EDT-*co*-TAQA exhibited a more ductile behavior and failed at 100% strain while also exhibiting a failure stress greater than 23 MPa. While the average toughness values of 1,2-EDT-*co*-TAQA at 25 and 63 °C were 1.08 and 2.35 MJ/m³, respectively, the average toughness at 37 °C was 15.56 MJ/m³. This increase in toughness at physiological temperature is more than an order or magnitude difference from the toughness at room temperature. Along with increased toughness, it is also desirable that a material for orthopedic applications maintains rigidity and is resistant to plasticization upon implantation.

In order to measure solvent plasticization effects, 1,2-EDT-*co*-TAQA films were subjected to in situ matrix relaxation DMA experiments in physiologically relevant conditions, specifically, in a phosphate-buffered saline (PBS) solution (pH 7.4, 137 mM NaCl, 2.7 mM KCl, and 10 mM phosphate buffer) at 37 °C. Figure 2c shows the results of the first 17 h of submersion.

There was an initial thermal response upon submersion followed by a solvent plasticization response, after which the modulus begins to increase slightly over 15 h. The solvent response, after temperature effects, was a solvent-plasticized material with $\Delta E' = -230$ MPa (−15%) and a saturation lifetime of 31 min (Figure 2c, inset). Following the solvent plasticization response, a change, $\Delta E' = 80$ MPa, was observed in which the material stiffens. This may be an indication that, even when fully saturated, the system still requires time to reach its lowest-energy configuration. Therefore, the net response to submersion in a physiologically relevant environment over 17 h is $\Delta E' = -150$ MPa (−10%). The sample was allowed to recover for 24 h and was then subjected to the same experimental regimen (Figure S6 in the SI). The storage modulus behaved similarly in response to the initial solvent plasticization but did not increase over the following 15 h. This behavior indicates that the lower-energy configuration of the matrix was retained for at least 24 h after drying. Beyond 24 h, 1,2-EDT-*co*-TAQA may begin to undergo hydrolytic degradation, at which point there would be a reduction in the modulus. No significant differences in the surface roughness were observed by atomic force microscopy (AFM), indicating no significant film degradation during 15 h of submersion (Figure S7 in the SI).

We present a series of photo-cross-linked polymer networks derived from the natural product QA with controlled T_g values from −18 to +65 °C and rubbery modulus values from 3.8 to 20 MPa. The network containing the highest weight percent of rigid bicyclic monomer 1,2-EDT-*co*-TAQA exhibited T_g of 65 °C and a storage modulus of 1.4 GPa, properties comparable to those of common degradable polyesters used in orthopedic applications. At 37 °C, 1,2-EDT-*co*-TAQA exhibited an average toughness that was an order of magnitude higher than that at room temperature and was resistant to plasticization upon submersion in PBS for 17 h. The material maintained its modulus upon submersion in PBS at 37 °C, exhibiting only slight solvent plasticization within the first 30 min. Given the stability of the poly(thioether-*co*-carbonate) networks at 120 °C, for biomedical device applications, it may be possible to sterilize final devices by autoclaving or dry heating rather than by ethylene oxide or γ radiation, each of which has significant disadvantages.¹¹ These poly(thioether-*co*-carbonate)s have a wide range of achievable material properties, and potential applications include biomedical applications and expansion to nonpetroleum-based “green” engineering polymers for commodity plastic applications. We demonstrate the ability to form a polymer with carbonate linkages without using any harsh conditions or solvents, giving the resulting material a high degree of industrial and environmental relevance. In total, this system represents a thermosetting polycarbonate material that is expected to produce environmentally friendly and bioresorbable degradation products. Future investigations will focus on the degradation kinetics in vitro and in vivo of these materials, as well as on strategies for incorporating other chemistries and functional components.

■ ASSOCIATED CONTENT

Supporting Information

Further details of experimental and characterization methods, ¹H, ¹³C, COSY, and HSQC NMR spectroscopies of TAQA, the effects of postcure time on T_g of poly(thioether-*co*-carbonate) films, a repeat of the in situ relaxation measurement, and AFM images of the 1,2-EDT-*co*-TAQA film before and after solvent

immersion. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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