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Synthesis, Characterization, and Cross-Linking Strategy of a Quercetin-Based Epoxidized Monomer as a Naturally-Derived Replacement for BPA in Epoxy Resins

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The natural polyphenolic compound quercetin was functionalized and cross-linked to afford a robust epoxy network. Quercetin was selectively methylated and functionalized with glycidyl ether moieties using a microwave-assisted reaction on a gram scale to afford the desired monomer (Q). This quercetin-derived monomer was treated with nadic methyl anhydride (NMA) to obtain a cross-linked network (Q-NMA). The thermal and mechanical properties of this naturally derived network were compared to those of a conventional diglycidyl ether bisphenol A-derived counterpart (DGEBA-NMA). Q-NMA had similar thermal properties [i.e., glass transition (T_g) and decomposition (T_d) temperatures] and comparable mechanical properties (i.e., Young's Modulus, storage modulus) to that of DGEBA-NMA. However, it had a lower tensile strength and higher flexural modulus at elevated temperatures. The application of naturally derived, sustainable compounds for the replacement of commercially available petrochemical-based epoxies is of great interest to reduce the environmental impact of these materials. Q-NMA is an attractive candidate for the replacement of bisphenol A-based epoxies in various specialty engineering applications.

Introduction

Epoxy resins are one of the most widely used thermosetting systems across a vast number of industries including transportation (e.g., automobiles and airplanes), coatings, wind turbine blades and electronics.[1] It has been estimated that the epoxy industry was worth nearly 6 billion USD in 2013 and will grow to more than 9 billion USD by 2019.[2] This enormous industry is one of the many polymer/plastic markets that still largely rely on nonrenewable petrochemicals as starting materials.[3] Replacing these starting materials with sustainable and renewable resources would be beneficial for both environmental and financial reasons.[1] One common industrially used monomer for epoxy resins is the diglycidyl ether of bisphenol A (DGEBA), which provides excellent mechanical and thermal properties. Not only is this monomer derived from nonrenewable petrochemicals, but there have also been several health concerns associated with the precursor, bisphenol A (BPA), including its effect as an estrogen hormone disruptor.[4] A central area of research is devoted to finding a DGEBA replacement that is safe and sustainable without greatly sacrificing the mechanical integrity or thermal properties of the epoxy resin.

There are many ways to introduce sustainability into epoxy resins, such as the addition of natural toughening agents,[5] incorporation of natural cross-linkers or synthesis of naturally derived monomers through epoxidation or glycidyl ether functionalization.[1,3] A natural-product-based substitute can be selected depending on the petrochemical-based monomer that needs to be replaced, its properties and the intended application of the material. Currently, natural product derivatives such as itaconic acid, isosorbide and furan derivatives are platform chemicals for the synthesis of epoxy resins.[6] Although the use of natural toughening agents and cross-linkers reduces the petroleum-derived content of epoxy resins, in some systems, harmful BPA still remains as a building block in the DGEBA-based system. As plant-based substitutes of BPA, epoxidized natural products, derived from sources such as plant oils,[7–9] sugars,[10–12] lignin,[13,14] rosin acids[15–18] and many other naturally derived materials,[1,3] have been explored as epoxy monomers. Alternatively, functional groups inherent to the natural product, such as the hydroxyl groups on tannic acid,[19,20] have been used for ring opening of epoxides in cross-linked networks. Replacing a commercially available product such as a DGEBA-derived epoxy resin requires the new material to have the desired thermal, mechanical and other properties for the specific applications. It has been proposed that a class of natural polyphenolic compounds may be utilized as the starting materials for monomers in epoxy networks.[1]

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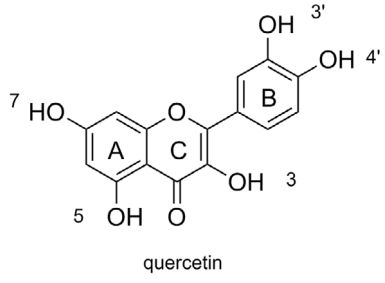
Quercetin is one such natural polyphenol that has the potential to be functionalized and act as a monomer in cross-linked epoxy networks. The first consideration is its wide availability in commonly ingested fruits and vegetables,[21] which has led to numerous studies investigating its health benefits including anti-inflammatory and antioxidant properties.[22,23] Methylated derivatives of quercetin have also been isolated in nature and studied for their biological properties.[24] Quercetin is not as cost efficient as petrochemical-based monomers at current market prices but extraction methods have been investigated as the demand for quercetin has increased over the past decade, in part owing to its numerous therapeutic applications.[25] Isolation methods from various fruits and vegetables have recently been reported.[26] A promising green method has been used to extract quercetin glycosides from onion waste using hot water extraction followed by enzymatic hydrolysis to afford quercetin.[27] Quercetin has been used as a cross-linker in epoxy chemistry in which the hydroxyl groups were reacted with sorbitol polyglycidyl ether and wood flour to form biocomposites.[28] To date, quercetin has not been explored as a replacement for DGEBA in epoxy resins, except as a co-monomer together with sorbitol,[28] or as a cross-linker in an epoxidized natural rubber/polycaprolactone, both in biocomposites.[29] The rigid tricyclic structure of quercetin is expected to impart desirable thermal and mechanical properties to the resulting epoxy resins. In addition, quercetin undergoes unique chemical reactivity with selective alkylation of the hydroxyl groups in the order 4′ > 7 > 3 > 3′ > 5 (Figure 1),[30,31] allowing for direct functionalization at positions 3′ and 5 with glycidyl ether groups, followed by reaction with a cross-linking agent to synthesize networks that have the potential to replace BPA-based epoxy resins.

This research entails the detailed evaluation of natural-product-based alternatives to DGEBA epoxy resins. The synthesis of a novel, quercetin-based monomer, 5,3′-diglycidyl ether-3,7,4′-trimethylquercetin (**2**), was explored using traditional and microwave synthesis conditions. This monomer was then cross-linked with nadic methyl anhydride (NMA) to form an epoxy resin (Q-NMA), which was characterized thermally and mechanically and compared to a DGEBA-based system prepared with the same cross-linker. The motivation for the synthesis of these quercetin-based materials was to investigate their potential as direct replacements for the BPA-based epoxy resins used in many applications.



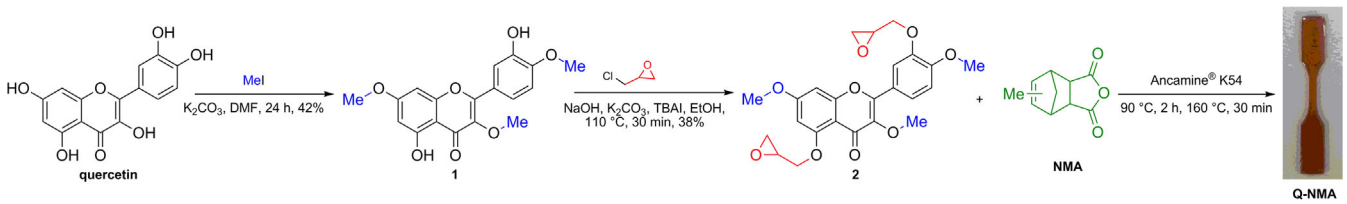
quercetin

Figure 1. The numbering of the hydroxy groups for the selective alkylation of quercetin.

Results and Discussion

Synthesis and characterization of epoxy monomer and cross-linked networks

The epoxy monomer was prepared by selective alkylation of the hydroxyl groups in two steps. The regioselectivity of quercetin has been thoroughly studied and has shown to allow good selectivity for alkylation of the 3, 7 and 4′ positions over the 5 and 3′ hydroxyl groups,[30,31] which provided a convenient route for the stepwise selective methylation and installation of the epoxide-containing glycidyl moieties to form the epoxy monomer (Scheme 1). Methylation using methods similar to those reported previously,[32] but on a larger scale, afforded 3,7,4′-trimethylquercetin (**1**). Briefly, quercetin was allowed to dissolve in *N,N*-dimethylformamide (DMF) at room temperature under an inert atmosphere, and was then treated with potassium carbonate followed by the addition of methyl iodide. The reaction was monitored by TLC and allowed to proceed for 24 h. The resultant mixture contained observable amounts of remaining starting material along with the di-, tri- and tetra-methylated quercetin products, which were separated by column chromatography and recrystallized to afford the desired tri-methylated product in 42% yield. The product was confirmed using ^{1}H NMR, ^{13}C NMR, IR and ESI-MS (Figure S1 and S2, Supporting Information). The regioselectivity was confirmed by single crystal X-ray analysis (Figure S6). The motivation for this specific selective protection was three-fold. Firstly, **1** has previously been extracted as the natural product, ayanin from *Croton schiedeanus*,[33] a plant found across Central and South America. The bioactivity of this natural product has been studied against several cell lines.[34–36] Secondly, the alkylation of the three hydroxyls leaves the two remaining hydroxyl sites on quercetin available for functionalization with glycidyl ether moieties, mimicking the two epoxide functionalities on DGEBA. Finally, limiting the number of free hydroxyl groups

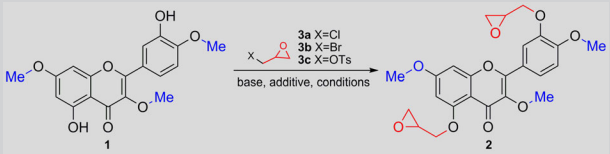


Scheme 1. Synthesis of the pre-monomer and monomer used for cross-linking Q-NMA networks.

present on the monomer would limits the number of reactive functionalities present during the cross-linking reaction and reduces the number of side reactions.

The second step, O-alkylation to synthesize the epoxy monomer (**2**), was first attempted using traditional synthesis conditions for the addition of an oxirane to a phenol[1] (Table 1, entries 1–2) utilizing a strong base (NaH) or an aqueous base solution (NaOH) with a phase transfer catalyst tetrabutylammonium bromide (TBAB); the reactions did not provide the desired product after 5 days, as monitored by TLC, even at elevated temperatures (80 °C). Subsequently, traditional conditions previously used to functionalize quercetin using K_2CO_3 as a solid base and the solvent, DMF[32,37] (Table 1, entries 3–5) delivered a 12% yield of the desired product using epibromohydrin (**3b**). However, when the reaction was scaled up to a gram scale, the only isolated product was the mono-reacted glycidyl ether, 3′-glycidyl ether-3,7,4′-trimethylquercetin (Table 1, entries 4–5). When tosylate (–OTs) was used as the leaving group of the oxirane starting material (**3c**), the large-scale reaction proceeded in five days with a poor yield (Table 1, entries 6–7). Additionally, this reaction required the extra step of converting glycidol to the (±)-oxiran-2-ylmethyl 4-methylbenzenesulfonate (**3c**) following a literature procedure,[38,39] which proceeded in excellent yield but increased the overall number of linear steps for the synthesis of **2**. A variety of different conventional heating methods for the addition of multiple glycidyl ether functionalities did not allow the reaction to be performed at a large scale to afford sufficient materials for cross-linking in the form of mechanical testing bars.

Table 1. Experimental conditions used for the attempted synthesis of the monomer, 3′,5-diglycidyl ether-3,7,4′-trimethylquercetin, (**2**).



Entries[a]	Reagent	Base + Additive	Solvent	T [°C]	t [h]	Yield [%]
1	**3a**	NaH	DMF	0–25	120	–
2	**3a**	NaOH + TBAB	H_2O	80	120	–
3	**3a**	K_2CO_3	DMF	80	120	–
4	**3b**	K_2CO_3	DMF	80	120	12
5[b]	**3b**	K_2CO_3	DMF	80	120	–
6	**3c**	K_2CO_3	DMF	80	120	34
7[b]	**3c**	K_2CO_3	DMF	80	120	25
8[c]	**3a**	NaOH + K_2CO_3 + TBAI	EtOH	110	0.5	49
9[b,c]	**3a**	NaOH + K_2CO_3 + TBAI	EtOH	110	0.5	38

[a] Standard conditions were performed on a 100 mg scale; [b] Performed on a gram scale; [c] Performed under microwave conditions; TBAB: tetrabutylammonium bromide, TBAI: tetrabutylammonium iodide.

Considering the two competing mechanisms that can take place to install the epoxide functionality using epichlorohydrin (**3a**), 1) the S_N2 reaction with the alkyl halide and 2) the S_N2' reaction, which involves opening of the epoxide followed by reformation of the epoxide to replace the halogen, alternative conditions were found to be effective at directing the reaction towards the desired product. In particular, limiting the opening of the epoxide or accelerating the closing of the ring to reform the epoxide could assist in promoting the forward reaction and increasing the yield. The Pchelka group has demonstrated that it is possible to activate ionic species in the analogous reactions for the preparation of 3-aryloxy-1,2-epoxypropane using microwave-assisted reaction conditions.[40] In conjunction with changing the heating method, potassium carbonate was used in addition to sodium hydroxide to further increase the yield. The conditions used in the studies of the 3-aryloxy-1,2-epoxypropanes were applied to the formation of the quercetin-based monomers.

Although the *O*-alkylation of simple phenols to afford 3-aryloxy-1,2-epoxypropanes has been studied extensively, the specific conditions for the alkylation of **1** required optimization owing to its unique characteristics. The most significant challenge was the limited reactivity of the 5-OH in quercetin and its analogs owing to hydrogen bonding with the ketone in the C ring (Figure 1), which was strongly suggested to be occurring, as shown in the crystal structure of **1** (Figure S6).[41] Additionally, the 3′-position of **1** is sterically affected by the *ortho*-methoxy substituent. By adapting the literature conditions[40] to the current reaction, **2** was prepared in reasonable yield in gram-scale quantities (Table 1, entry 9, 38%). The conditions were altered by extending the reaction time and increasing the number of equivalents of epichlorohydrin (**3a**). TBAB was also replaced with tetrabutylammonium iodide (TBAI). More importantly, this method significantly reduced the reaction time from 120 h to 0.5 h. To further confirm the regioselectivity of the di-substituted product was confirmed by ^1H and ^{13}C NMR spectroscopies and high-resolution mass spectrometry (NMR spectra are shown in Figure S3 and S4). To further confirm the regioselectivity of the final product structure, single crystal X-ray analysis of **2** was performed (Figure S7).[42]

Using the prepared monomer, cross-linked networks were synthesized by allowing the oxirane groups of **2** to undergo reaction with nadic methyl anhydride (NMA), a commercially available cross-linker. The catalyst chosen to accelerate the cross-linking reaction was ANCAMINE® K54 (2,4,6-tris(dimethylaminomethyl)phenol) (Figure S5) at a concentration of 3 phr (parts per hundred resin). This tertiary amine was used to promote alternating co-polymerization of NMA and an epoxy-based monomer through chain growth anionic polymerization.[43,44] Side reactions, such as homopolymerization of the oxirane ring and etherification, can occur to further induce cross-linking. Although the natural-based monomer was expected to undergo the same types of reactions as previously studied commercially available monomers, the physical properties of **2** led to a unique curing process.

There were several challenges in developing a curing protocol for Q-NMA, including the high melting point of the monomer (160 °C), evaporation of the cross-linker (>90 °C) (Figure S10) and rapid reaction (less than 1 min) of the starting materials in the presence of the catalyst at elevated temperatures. First, to determine an appropriate curing protocol for Q-NMA, the reaction kinetics were examined using non-isother-

mal heating at 10 °C min^{-1} from 40–200 °C using differential scanning calorimetry (DSC) (Figure 2) and ending at 200 °C to avoid degradation of the material. The DSC data indicated curing over a broad temperature (≈125–200 °C), with peak reactivity located at approximately 180 °C. As the quercetin-based epoxide monomer (**2**) was not soluble in NMA at room temperature, the first step in the protocol was the melting of **2** (160 °C) and mixing it with NMA in the absence of the catalyst for 3 min at 160 °C. Without the K54 catalyst, the mixture did not appear to visibly gel (observed up to 2 h at 160 °C). After mixing the two monomers at 160 °C for 3 min, the mass loss was 0.60 ± 0.07 % (Figure S11). Given the low expected conversion of a thermoset proceeding via chain growth polymerization without the presence of an initiator,[43] it is not anticipated that significant conversion of the monomer during the 3 min mixing time. The mixture was subsequently cooled to room temperature (25 °C) (during which it remained homogeneous), followed by addition of ANCAMINE® K54 and heating to the desired mixing/curing temperature. Mixing temperatures ranging from 30–90 °C were tested at 10 °C increments. At low temperatures the mixture was too viscous for stirring; therefore, the mixing could only proceed efficiently at 90 °C to ensure homogeneous distribution of the catalyst. After the addition of ANCAMINE® K54, the mixture was stirred for no longer than 3 min to avoid gelation of the materials in the vials. Following the mixing process, the mixture was cast into molds preheated at 90 °C to ensure a continuous cross-linking reaction. The networks were allowed to undergo reaction for 2 h at 90 °C. Thermogravimetric analysis (TGA) confirmed that NMA did not evaporate at this temperature (Figure S10). The curing time was determined by measuring the glass transition temperature (T_g) of the bar every 30 min during the curing at 90 °C until the T_g was constant. Subsequently, the resin was post-cured at a temperature higher than the network T_g and at the melting point of the monomer to help drive the reaction to completion. The post-curing time was also determined by monitoring the T_g as the resin was held at the post-curing temperature, until no noticeable changes occurred (Figure S8). The required post-curing time was 30 min at 160 °C. In summary, the final curing protocol chosen for Q-NMA included a heated mixing step followed by a two-stage curing that involved an initial curing step at 90 °C for 2 h and a post-curing at 160 °C for 30 min.

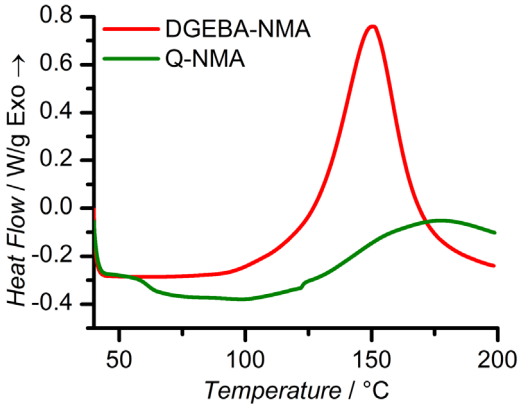


Figure 2. Assessment of the conditions used to cure **2** and NMA to produce Q-NMA, with evaluation of heat flow versus temperature by DSC.

The quercetin-network was characterized by IR spectroscopy (Figure 3). The IR spectrum of NMA (Figure 3b) shows peaks at 1852 cm^{-1} (asymmetrical C=O stretch) and at 1775 cm^{-1} (symmetrical C=O stretch), each of which disappeared upon formation of Q-NMA (Figure 3c), indicating the consumption of the

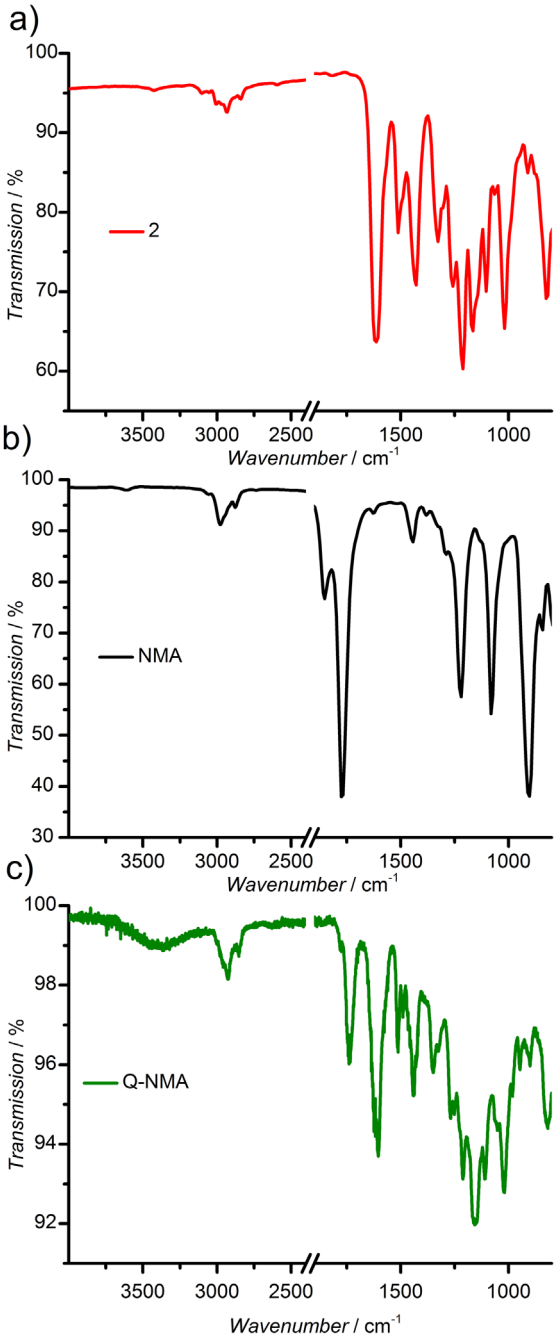


Figure 3. IR spectra of (a) monomer **2**, (b) cross-linker (NMA) and (c) cured network (Q-NMA).

anhydride functionality. The anhydride absorbances were replaced by a characteristic ester peak at 1736 cm^{-1} (C=O stretch) indicating the formation of the ring-opened product. The Q-NMA spectrum also contained a strong ester peak at 1157 cm^{-1} (C–O stretch) for the C–O stretching vibration and broad, albeit weak peak at 3675–3152 cm^{-1} (O–H stretch) indicating the presence of the –OH group of the unreacted chain ends. The combination of the IR peaks indicates that the reaction proceeded and cross-linking of the Q-NMA network occurred to afford the desired cross-linked materials.

To directly compare Q-NMA and DGEBA cross-linked with NMA (DGEBA-NMA), the DGEBA-NMA network was optimized by applying the same catalyst loading (3 phr) and curing temperatures. The reaction time was optimized for each monomer. Although the DGEBA-NMA curing kinetics have been previously reported,[45,46] the trace for the mixture curing is shown in Figure 2 for a comparison to the quercetin-based network (Scheme S1). The same process was applied to optimize the curing protocol times for the DGEBA-NMA network. In this case, the DGEBA monomer was a liquid at room temperature, therefore, there was no need for a complex mixing process. The DGEBA/NMA/K54 mixture was stirred at 90 °C for 5 min to ensure a homogeneous mixture before casting into the hot molds heated to 90 °C. The optimal conditions for the DGEBA-NMA reaction were determined to be curing for 1 h at 90 °C followed by 2 h at 160 °C, by monitoring the change in T_g during the second step. IR spectroscopy confirmed the presence of a cross-linked network, with the appearance of an ester peak at 1737 cm^{-1} (C=O stretch) and a strong ester peak at 1152 cm^{-1} (C–O stretch) as well as the disappearance of the anhydride peaks from NMA. The faint peak at 3645–3140 cm^{-1} (–O–H stretch) is indicative of the hydroxyl group of the ring-opened side reaction, similar to the one that appears in the Q-NMA system. The IR peaks of DGEBA-NMA were similar to those for Q-NMA, with the appearance of the hydroxyl and ester peaks and the disappearance of the anhydride peak (Figure S13). Following confirmation of the synthesis of the epoxy resins, the thermal and mechanical properties of the two systems were measured and compared.

Thermal properties of the Q-NMA and DGEBA-NMA networks

The two systems had similar thermal properties. The decomposition temperatures (T_d) of Q-NMA and DGEBA-NMA were 266 and 284 °C, respectively, measured at the 5% mass loss by TGA (Table 2). The glass transition temperatures, T_g, of Q-NMA and DGEBA-NMA measured by DSC were 134 °C and 137 °C, respectively, (Table 2). Using dynamic mechanical analysis (DMA) in tensile mode, the temperatures at which the maximum tan δ occurred (which are proportional to T_g), were determined to be 170 °C and 171 °C for Q-NMA and DGEBA-NMA, respectively. Given that the two epoxy resins have similar thermal properties, it is expected that replacement of DGEBA-NMA with Q-NMA could occur in applications covering a wide range of temperatures. High T_g values of the systems tend to correlate with high tensile strength and modulus, which was later explored.

Table 2. Thermal and mechanical properties of the cross-linked networks Q-NMA and DGEBA-NMA.

Property	Q-NMA	DGEBA-NMA
T_g[a] [°C]	134	137
$T_d^{5\%}$ [°C]	266	284
tensile strength[b] [MPa]	37 ± 8	66 ± 15
elongation at break[b] [%]	1.3 ± 0.4	2.8 ± 0.9
Young's modulus[b] [GPa]	3.5 ± 0.2	3.0 ± 0.2
storage modulus[b] [GPa]	1.72	1.75
flexural modulus[b] [GPa]	3.49	3.48
rubbery modulus, ε'[c] [MPa]	7.7	14.0
ν_c [mol cm^{-3}]	6.67×10^{-4}	1.21×10^{-3}

[a] Measured by DSC; [b] storage modulus, flexural modulus, tensile strength, % elongation at break and Young's Modulus were measured at 25 °C; [c] rubbery modulus was measured at 190 °C.

Mechanical properties of the Q-NMA and DGEBA-NMA networks

The dynamic moduli were measured for each system in tension and in three-point-bending mode using DMA (Figure 4A and 4B). The tensile storage modulus behavior with respect to temperature for the two systems was similar. Under tension, the temperature range at which the network is expected to behave as a glassy solid ($T < T_g$) and the temperature range at which the network is expected to behave as a rubbery solid ($T_g < T < T_d$) are equivalent for the two systems. Conversely, under flexural stress, DGEBA-NMA began to transition to its rubbery state at approximately 70 °C, a lower temperature than the Q-NMA transition (≈120 °C). From approximately 70–170 °C, Q-NMA exhibited a flexural modulus which was greater than that of DGEBA-NMA. At 130 °C Q-NMA exhibited a flexural modulus which was two orders of magnitude greater than that of DGEBA-NMA. Therefore, for elevated temperature applications (50–150 °C), Q-NMA is expected to be more resistant to bending (flexural stress/strain) compared to DGEBA-NMA. Using the theory of rubber elasticity, the cross-link density (ν_c), defined as the number of moles of elastically effective network chains per cubic centimeter of sample, can be calculated using the following equation:

$$\upsilon_c = \frac{\varepsilon'}{3RT} \quad (1)$$

where R is the gas constant, T is the temperature and ε' is the rubbery modulus at 190 °C measured using DMA in tension mode.[47] DGEBA-NMA has a higher cross-link density than that of the natural-product-based counterpart. Although there is a considerable difference in cross-link density between the different networks, the T_g, flexural modulus and storage modulus are similar, which is possibly owing to the rigidness of quercetin.

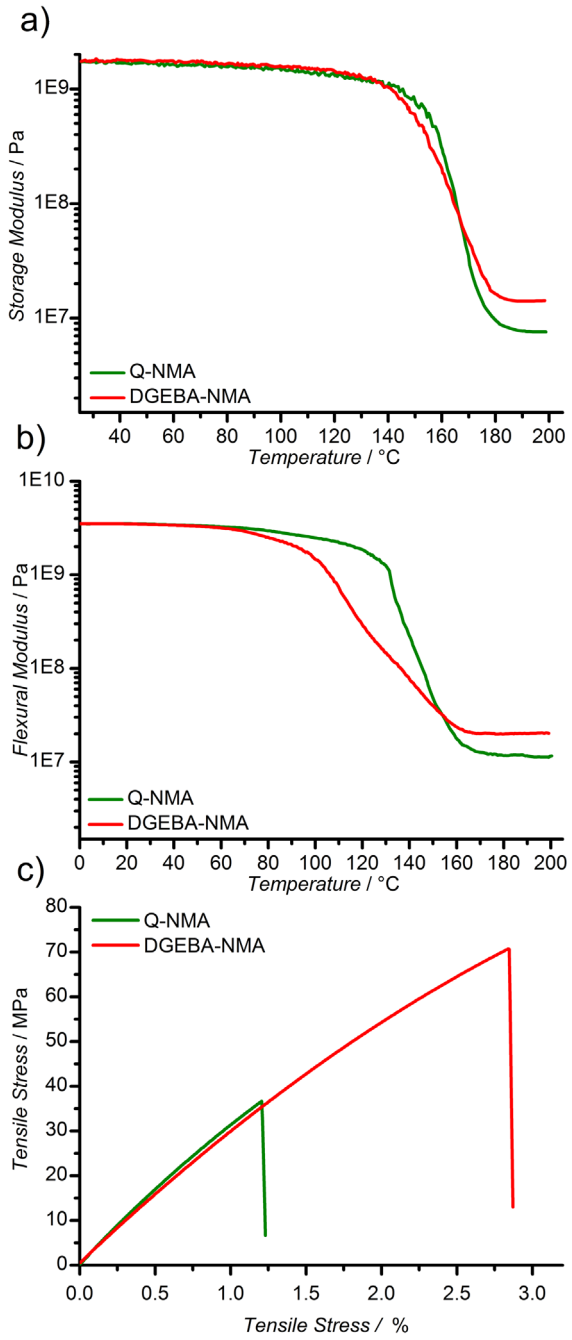


Figure 4. (a) Tensile storage modulus as a function of temperature. (b) Flexural modulus as a function of temperature. (c) Representative stress–strain behavior (n) = 5–6.

The tensile stress/strain behavior of the Q-NMA and DGEBA-NMA networks measured through tensile testing at 25 °C is shown in Figure 4c and relevant parameters are reported in Table 2. The average tensile strength, or maximum stress, was 37 ± 8 and 66 ± 15 MPa for Q-NMA and DGEBA-NMA, respectively. Both materials exhibited brittle fracture at less than 3% elongation. The Young's modulus, calculated from the linear portion of the stress–strain curve was 3.5 ± 0.2 and 3.0 ± 0.2 GPa for Q-NMA and DGEBA-NMA, respectively (Table 2, Figure 4C). Overall, the mechanical properties of Q-NMA, such as Young's Modulus, storage modulus and flexural modulus, are comparable to that of DGEBA-NMA, indicating the quercetin-based epoxy monomer is appropriate for the replacement of DGEBA in many epoxy resin applications.

Conclusions

A novel monomer from a natural polyphenolic starting material was synthesized in two steps. The monomer has the potential to replace the diglycidyl ether of bisphenol A (DGEBA) and, therefore, to eliminate the use of bisphenol A (BPA) in epoxy networks. The functionalization of the monomer with diglycidyl ether groups was performed using microwave synthesis conditions, which led to an increase in the yield and the scale, as well as a greatly reduced reaction time. The quercetin-based monomer was cross-linked with nadic methyl anhydride (NMA) to afford the cross-linked network (Q-NMA). The thermal and mechanical properties of Q-NMA were compared to that of DGEBA cross-linked with NMA (DGEBA-NMA), at optimized curing conditions. The two systems have similar decomposition and glass transition temperatures and many comparable mechanical properties including Young's modulus, flexural modulus and storage modulus at 25 °C. At elevated temperatures, Q-NMA exhibited a flexural modulus which was greater (by two orders of magnitude at 130 °C) than that of DGEBA-NMA. This naturally derived monomer shows tremendous potential to replace BPA in practical applications.

Experimental Section

Materials and methods

Quercetin was purchased from Cayman Chemicals. Epichlorohydrin and nadic methyl anhydride (NMA) were purchased from Sigma–Aldrich. Sodium hydroxide was purchased from EMD Millipore. Potassium carbonate and tetrabutylammonium iodide were purchased from Alfa Aesar. DER 331 (DGEBA) was received from Dow Chemical and ANCAMINE K54 (2,4,6-tris(dimethylaminomethyl)phenol) was received from Air Products & Chemicals. All chemicals were used as received without further purification. The monomer was synthesized in a CEM Intellivent Explorer microwave reactor and purified by medium pressure liquid chromatography (MPLC) using a CombiFlash R_f (Teledyne Isco).

Spectroscopic characterization

^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on a Varian 500 spectrometer interfaced to a UNIX computer using VnmrJ software. Chemical shifts were referenced to the residual proton resonance of the solvent (DMSO-d_6: 2.50 ppm or $CDCl_3$: 7.26 ppm). IR spectra were obtained on a Shimadzu IR Prestige attenuated total reflectance Fourier-transform infrared spectrometer (ATR-FTIR). Spectra were analyzed using IRsolution software package (Shimadzu) and were exported to Origin for analysis. The minimum number of scans was 32 with a minimum resolution of 16 and the apodization was set to SqrTriangle.

Thermal characterization

DSC studies were performed on a DSC822^e (Mettler-Toledo), with a heating rate of 10 °C min^{-1} to determine the melting point (m.p.) of the monomers, as the peak onset of the transition. The thermal degradation temperature was analyzed by TGA, using a TA Instruments Q500 analyzer. The sample was heated from 30–800 °C at a rate of 10 °C min^{-1} in an argon environment (the balance argon purge flow was 40 mL min^{-1} and the sample purge flow was 60 mL min^{-1}). The T_g and curing protocols were characterized by a TA Instruments Q2000 differential scanning calorimeter, calibrated with an indium standard, with a nitrogen flow rate of 50 mL min^{-1}. The sample was placed in the calorimeter (in a Tzero aluminum pan) and was heated from 40–200 °C, cooled back to 40 °C, and subsequently heated to 200 °C at a rate of 10 °C min^{-1}. The value of T_g was determined at the midpoint of the slope of the second heating using the TA Universal Analysis software.

Mechanical characterization

Strain-to-failure measurements were performed on an Instron 5966 tensile tester with a 2 kN load cell at a strain rate of 10 mm min^{-1} to obtain tensile strength and elongation at break of both Q-NMA and DGEBA-NMA at room temperature. Test specimens were dog-bone-shaped testing bars (following ASTM D638, bar type 5, thickness 2.0 mm). Pneumatic grips were used to affix the sample in the testing frame at a compressed air pressure of 50 psi. Each measurement was repeated with 5–6 test specimens.

DMA was performed on a Mettler Toledo TT-DMA system. Samples with dimensions of 3.32×2.03×5.10 mm for Q-NMA and 3.06×1.75×5.18 mm for DGEBA-NMA were tested in tension mode. Dynamic measurements were recorded at a frequency of 1 Hz, a dynamic force of 1 N and a static/dynamic force ratio of 1.5 from 25–200 °C at a rate of 3 °C min^{-1} with data sampling interval of 10 s. DMA data were obtained using Triton Laboratory software and exported to Origin Pro 9.0 for analysis. Three-point bending tests were performed on bars with dimensions of approximately 2.00×4.05×10 mm. The measurements were recorded at a frequency of 1 Hz, a dynamic force of 1 N and a static/dynamic force ratio of 1.5 from 0–200 °C at a rate of 3 °C min^{-1} with data sampling interval of 10 s.

Synthesis of 3,7,4′-trimethylquercetin (1)

The compound was prepared by a procedure adapted from Moalin et al.[32] A round bottom flask was charged with quercetin (20.0 g, 66.2 mmol), potassium carbonate (20.4 g, 148 mmol), methyl iodide (16.0 mL, 257 mmol) and DMF (500 mL) under nitrogen. The reaction was stirred at room temperature for 24 h and the DMF was then removed in vacuo, resulting in a brown solid product. The brown solid was purified using MPLC by eluting with 10% ethyl acetate in chloroform and recrystallized from chloroform to afford 3,7,4′-trimethylquercetin as a yellow solid (9.5 g, 42% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.65 (s, 1H, –OH), 9.44 (s, 1H, –OH), 7.59–7.55 (m, 2H, Ar), 7.11 (d, J = 8.4 Hz, 1H, Ar), 6.71 (d, J = 2.2 Hz, 1H, Ar), 6.37 (d, J = 2.2 Hz, 1H, Ar), 3.87 (s, 3H, –CH$_3$), 3.86 (s, 3H, –CH$_3$), 3.80 ppm (s, 3H, –CH$_3$); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 178.5, 165.5, 161.3, 156.7, 156.0, 150.7, 146.8, 138.6, 122.9, 120.8, 115.5, 112.2, 105.6, 98.2, 92.6, 60.2, 56.5, 56.1 ppm; FTIR (ATR): $\tilde{\nu}$ = 3579–3140, 3047–3000, 3000–2847, 1643, 1597, 1196, 918, 895, 818 cm^{-1}; HRMS (ESI+, m/z): $[M+H]^{+1}$ calculated for $[C_{18}H_{17}O_7]^+$, 345.0974, found 345.0970; m.p. 173 °C. Regiochemistry was confirmed by X-ray analysis (Figure S6).

Synthesis of 5,3′-diglycidyl ether-3,7,4′-trimethylquercetin (2)

3,7,4′-trimethylquercetin (2.00 g, 5.81 mmol), sodium hydroxide (460 mg, 11.5 mmol), potassium carbonate (6.40 g, 46.3 mmol), tetrabutylammonium iodide (420 mg, 1.14 mmol), epichlorohydrin (4.80 mL, 61.4 mmol) and ethanol (3.0 mL) were combined in an 80 mL microwave vessel including a magnetic stirring bar. The solution was heated to 110 °C for 30 min with stirring in a microwave reactor. The solution was filtered and the solid was washed with ethyl acetate (15 mL). The solvent was removed in vacuo. The crude product was purified using MPLC/flash column chromatograph (gradient of 0–100% hexanes/ethyl acetate). The solution was concentrated to a yellow solid and washed with tetrahydrofuran and dried in vacuo to afford 5,3′-diglycidyl ether-3,7,4′-trimethylquercetin as a white solid (1.02 g, 38%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.77–7.70 (m, 2H), 6.98 (app d, J = 8.5 Hz, 1H), 6.52 (app d, J = 2.2 Hz, 1H), 6.38 (app d, J = 2.1 Hz, 1H), 4.38 (dd, J = 11.3, 2.6 Hz, 1H), 4.34 (dd, J = 11.3, 3.4 Hz, 1H), 4.15 (dd, J = 11.3, 4.3 Hz, 1H), 4.09 (dd, J = 11.3, 5.6 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 3.84 (s, 3H), 3.46-3.41 (m, 2H), 3.19 (m, 1H), 2.94 (m, 2H), 2.80 ppm (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.7, 163.7, 159.6, 158.6, 152.5, 151.4, 147.6, 147.5, 141.2, 123.3, 122.7, 113.9, 111.3, 109.7, 97.6, 97.6, 93.3, 93.3, 70.4, 69.0, 59.99, 59.96, 55.99, 55.96, 55.8, 55.8, 50.2, 50.1, 45.1, 45.0 ppm; FTIR (ATR): $\tilde{\nu}$ = 3105-3009, 2931-2847, 1624, 1607, 1211, 1018, 822 cm^{-1}; HRMS (ESI+, m/z): calculated for $[M+H]^+$: $[C_{24}H_{25}O_9]^+$ 457.1499, found 457.1482; m.p. 156 °C. Regiochemistry was confirmed by X-ray analysis (Figure S7).

Synthesis of 5,3′-diglycidyl ether-3,7,4′-trimethyl quercetin-nadic methyl anhydride (Q-NMA)

5,3′-diglycidyl ether-3,7,4′-trimethylquercetin (**2**) (1.50 g, 3.25 mmol) and nadic methyl anhydride (1.17 g, 6.50 mmol) were combined in a glass vial, heated to 160 °C and stirred for 3 min. The mixture was allowed to cool to room temperature (25 °C) and ANCAMINE® K54 (45.0 mg) was added. The mixture was heated to 90 °C, stirred for 3 min and cast into molds preheated to the same temperature (90 °C). The bars were cured for 2 h at 90 °C then at 160 °C for 30 min to afford the Q-NMA networks. $T_d^{5\%}$ = 266 °C, $T_d^{10\%}$ = 297 °C, T_g = 134 °C; FTIR (ATR): $\tilde{\nu}$ = 3676–3152, 3047–3000, 3000–2808, 1780, 1736, 1623, 1436, 1429, 1349, 1325, 1157, 1108, 1020, 818 cm^{-1}.

Synthesis of diglycidyl ether of bisphenol A-nadic methyl anhydride (DGEBA-NMA)

DGEBA (10.0 g, 29.4 mmol), nadic methyl anhydride (10.5 g, 58.8) and ANCAMINE® K54 (300 mg) were combined in a round bottom flask, heated to 90 °C and stirred for 5 min. The mixture was cast into six molds preheated to 90 °C. The bars were cured for 1 h at 90 °C then at 160 °C for 2 h to afford the DGEBA-NMA network. $T_d^{5\%}$ = 284 °C, $T_d^{10\%}$ = 337 °C, T_g = 136 °C; FTIR (ATR): $\tilde{\nu}$ = 3645–3124, 3124–3022, 2917–2850, 1737, 1225, 1152, 1106, 1032, 827 cm^{-1}.

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[1] R. Auvergne, S. Caillol, G. David, B. Boutevin, J. P. Pascault, *Chem. Rev.* **2014**, *114*, 1082 – 1115.
[2] Epoxy Resin Market by Application (Paints & Coating, Wind Turbine, Composites, Construction, Electrical & Electronics, Adhesives) and Geography, Trends & forecasts to 2019 http://www.marketsandmarkets.com/Market-Reports/epoxy-resins-market-762.html **2014** (accessed February 2, 2016).
[3] C. Ding, A. S. Matharu, *ACS Sustainable Chem. Eng.* **2014**, *2*, 2217 – 2236.
[4] L. N. Vandenberg, M. V. Maffini, C. Sonnenschein, B. S. Rubin, A. M. Soto, *Endocr. Rev.* **2009**, *30*, 75 – 95.
[5] W. Liu, R. Zhou, H. L. S. Goh, S. Huang, X. Lu, *ACS Appl. Mater. Interfaces* **2014**, *6*, 5810 – 5817.
[6] S. Ma, T. Li, X. Liu, J. Zhu, *Polym. Int.* **2016**, *65*, 164 – 173.
[7] J. M. Pin, N. Guigo, L. Vincent, N. Sbirrazzuoli, A. Mija, *ChemSusChem* **2015**, *8*, 4149 – 4161.
[8] J. M. Pin, N. Sbirrazzuoli, A. Mija, *ChemSusChem* **2015**, *8*, 1232 – 1243.
[9] G. Yang, B. J. Rohde, M. L. Robertson, *Green Mater.* **2013**, *1*, 125 – 134.
[10] C. S. Kovash, Jr., E. Pavlacky, S. Selvakumar, M. P. Sibi, D. C. Webster, *ChemSusChem* **2014**, *7*, 2289 – 2294.
[11] Z. Rapi, B. Szolnoki, P. Bakó, P. Niedermann, A. Toldy, B. Bodzay, G. Keglevich, G. Marosi, *Eur. Polym. J.* **2015**, *67*, 375 – 382.
[12] J. Hong, D. Radojcic, M. Ionescu, Z. S. Petrovic, E. Eastwood, *Polym. Chem.* **2014**, *5*, 5360 – 5368.
[13] S. Zhao, M. M. Abu-Omar, *Biomacromolecules* **2015**, *16*, 2025 – 2031.
[14] A. Llevot, E. Grau, S. Carlotti, S. Grelier, H. Cramail, *Macromol. Rapid Commun.* **2016**, *37*, 9 – 28.
[15] C. Mantzaridis, A. L. Brocas, A. Llevot, G. Cendejas, R. Auvergne, S. Caillol, S. Carlotti, H. Cramail, *Green Chem.* **2013**, *15*, 3091 – 3098.
[16] A. L. Brocas, A. Llevot, C. Mantzaridis, G. Cendejas, R. Auvergne, S. Caillol, S. Carlotti, H. Cramail, *Des. Monomers Polym.* **2014**, *17*, 301 – 310.
[17] Q. Q. Ma, X. Q. Liu, R. Y. Zhang, J. Zhu, Y. H. Jiang, *Green Chem.* **2013**, *15*, 1300 – 1310.
[18] H. H. Wang, X. Q. Liu, B. Liu, J. W. Zhang, M. Xian, *Polym. Int.* **2009**, *58*, 1435 – 1441.
[19] M. Shibata, N. Teramoto, K. Makino, *J. Appl. Polym. Sci.* **2011**, *120*, 273 – 278.
[20] M. Shibata, K. Nakai, *J. Polym. Sci. Part B* **2010**, *48*, 425 – 433.
[21] K. H. Miean, S. Mohamed, *J. Agric. Food Chem.* **2001**, *49*, 3106 – 3112.
[22] J. V. Formica, W. Regelson, *Food Chem. Toxicol.* **1995**, *33*, 1061 – 1080.
[23] A. W. Boots, G. R. M. M. Haenen, A. Bast, *Eur. J. Pharmacol.* **2008**, *585*, 325 – 337.
[24] H. Matsuda, T. Morikawa, M. Yoshikawa, *Pure Appl. Chem.* **2002**, *74*, 1301 – 1308.
[25] G. D'Andrea, *Fitoterapia* **2015**, *106*, 256 – 271.
[26] S. G. Dmitrienko, V. A. Kudrinskaya, V. V. Apyari, *J. Anal. Chem.* **2012**, *67*, 299 – 311.
[27] C. Turner, P. Turner, G. Jacobson, K. Almgren, M. Waldebäck, P. Sjöberg, E. N. Karlsson, K. E. Markides, *Green Chem.* **2006**, *8*, 949 – 959.
[28] M. Shibata, S. Yoshihara, M. Yashiro, Y. Ohno, *J. Appl. Polym. Sci.* **2013**, *128*, 2753 – 2758.
[29] A. Masek, M. Zaborski, *C. R. Chim.* **2014**, *17*, 944 – 951.
[30] L. Jurd, *J. Am. Chem. Soc.* **1958**, *80*, 5531 – 5536.
[31] L. Jurd, *J. Org. Chem.* **1962**, *27*, 1294 – 1297.
[32] M. Moalin, G. P. F. van Strijdonck, M. Beckers, G. J. Hagemen, P. J. Borm, A. Bast, G. R. M. M. Haenen, *Molecules* **2011**, *16*, 9636 – 9650.
[33] P. Puebla, J. L. López, M. Guerrero, R. Carrón, M. L. Martìn, L. San Román, A. San Feliciano, *Phytochemistry* **2003**, *62*, 551 – 555.
[34] M. Kaulich, F. Streicher, R. Mayer, I. Müller, C. E. Müller, *Drug Dev. Res.* **2003**, *59*, 72 – 81.
[35] Z.-H. Shi, N.-G. Li, Y.-P. Tang, L. Wei, Y. Lian, J.-P. Yang, T. Hao, J.-A. Duan, *Eur. J. Med. Chem.* **2012**, *54*, 210 – 222.
[36] Y. Wang, M. Hamburger, J. Gueho, K. Hostettmann, *Phytochemistry* **1989**, *28*, 2323 – 2327.
[37] M. Bouktaib, S. Lebrun, A. Atmani, C. Rolando, *Tetrahedron* **2002**, *58*, 10001 – 10009.
[38] N. Toelle, H. Weinstabl, T. Gaich, J. Mulzer, *Angew. Chem. Int. Ed.* **2014**, *53*, 3859 – 3862; *Angew. Chem.* **2014**, *126*, 3940 – 3943.
[39] N. Toelle, H. Weinstabl, T. Gaich, J. Mulzer, *Angew. Chem.* **2014**, *126*, 3940 – 3943.
[40] B. K. Pchelka, A. Loupy, A. Petit, *Tetrahedron* **2006**, *62*, 10968 – 10979.
[41] CCDC 1451608 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
[42] CCDC 1451607 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
[43] Y. Tanaka, H. Kakiuchi, *J. Polym. Sci. Part A* **1964**, *2*, 3405 – 3430.
[44] J. Leukel, W. Burchard, R.-P. Krüger, H. Much, G. Schulz, *Macromol. Rapid Commun.* **1996**, *17*, 359 – 366.
[45] B. J. Rohde, M. L. Robertson, R. Krishnamoorti, *Polymer* **2015**, *69*, 204 – 214.
[46] M. K. Antoon, J. L. Koenig, *J. Polym. Sci. A* **1981**, *19*, 549 – 570.
[47] L. W. Hill, *Prog. Org. Coat.* **1997**, *31*, 235 – 243.

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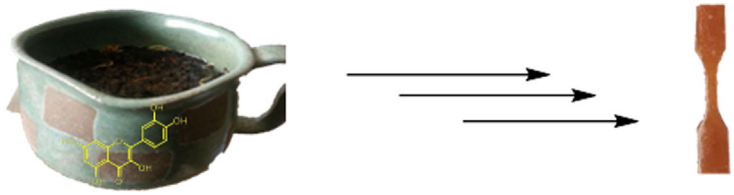

A natural solution: A diglycidyl monomer prepared in two steps using a natural polyphenolic starting material, quercetin, is reacted with nadic methyl anhydride to afford epoxy cross-linked networks. The thermal and mechanical properties of these networks are compared to similarly synthesized bisphenol A-based epoxy materials for potential replacement in advanced engineering applications.

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Synthesis, Characterization, and Cross-Linking Strategy of a Quercetin-Based Epoxidized Monomer as a Naturally-Derived Replacement for BPA in Epoxy Resins