FACILE SYNTHESIS OF HYDROXYLATED DIMETHACRYLATES FOR USE IN BIOMEDICAL APPLICATIONS

Michael D. Weir, Chetan A. Khatri and Joseph M. Antonucci

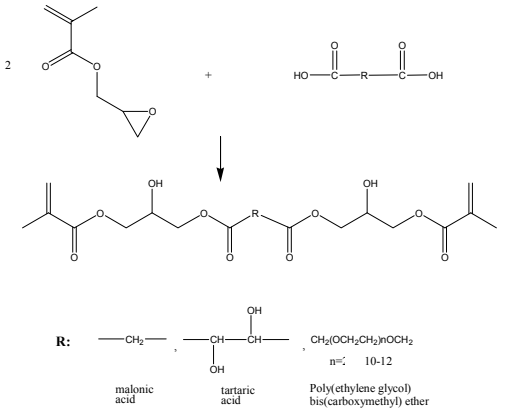
Polymers Division, National Institute of Standards and Technology, Gaithersburg, MD 20899.

Introduction

Biomedical applications for polymeric materials have historically found use in areas such as suture material, structural implants, drug-delivery systems, dental composites and bone cement to name only a few. Additionally, attention has recently turned to materials that can be transformed *in-situ* at the implantation site in the human body into polymer scaffolds for tissue engineering applications.[1-4] One of the key aspects of this type of tissue engineering is the design of biodegradable hydrogels that not only degrade at a controllable rate, but also degrade into benign products that can be safely eliminated from the body. For this application, the development of biocompatible and fast-curing crosslinking agents would be an asset. We have devised a facile synthetic route to tailor crosslinking monomers to specific uses. This approach is illustrated in Scheme A where, by reacting glycidyl methacrylate with a diacid, hydroxylated dimethacrylates can be formed in high yield. A benefit of this scheme is that by changing the spacer group, R, in the diacid, the physicochemical and mechanical properties of the crosslinked polymer network can be altered. For example, biodegradable crosslinkers of varied degrees of hydrophilicity and flexibility can be synthesized for use in applications such as scaffolds for guided bone regeneration and other areas of tissue engineering. For example, poly(propylene fumarate) is an unsaturated linear polyester that can be crosslinked. This polyester has been crosslinked through the fumarate double bond with monomers such as methyl methacrylate, N-vinyl pyrrolidone or poly(ethylene glycol)-dimethacrylate.[3] The method described here offers a versatile alternative to this approach. Moreover, hydrophobic crosslinkers of increased biostability also can be synthesized using hydrophobic diacids such as dimer acids. These types of dimethacrylates are designed for use in materials such as dental composites, where biostability, low shrinkage, low water sorption and high flexibility are important characteristics.[5]

Experimental

Synthesis of Hydroxylated Dimethacrylates. Combined in a 20 mL vial were 7.03 mmol glycidyl methacrylate (Aldrich Chemical), 3.52 mmol of poly(ethylene glycol)-bis(carboxymethyl) ether (M_n≈600, Hoechst Celanese), 15 mg Butylated hydroxytoluene (BHT) as an inhibitor and 0.15 g triethylamine (Aldrich Chemical) as a catalyst. Similarly, 7.03 mmol of glycidyl methacrylate was combined with 3.52 mmol of hydrogenated dimer acid (M_n≈570, Henkel Inc.), 15 mg BHT and 0.15 g triethylamine in a 20 mL vial and heated at 63 °C for 20 h. All chemicals were used as received. The products obtained were characterized using ^{1}H-NMR, NIR and FT-IR spectroscopies, with NIR being used to follow the course of the reactions.



Scheme A. Synthesis of hydroxylated dimethacrylates from glycidyl methacrylate and diacids.

Polymerization of Hydroxylated Dimethacrylates. The dimethacrylates derived from the PEG diacid and the dimer acid were each photopolymerized via activation with a modified bis-acyl phosphineoxide photoinitiator (1850, CIBA). The monomers, contained between 1 mm thick KBr discs, were exposed to visible light irradiation (470 nm; Triad 200 (Dentsply)) for 60 s per side at 23 °C and the conversion was assessed by mid-IR spectroscopy. Additionally, the dimer acid dimethacrylate (mass fraction, 48 %) was copolymerized in the same manner with 2,2′-bis[4(2-hydroxy-3-methacryloyloxypropyloxy)phenyl] propane (Bis-GMA; mass fraction, 51 %). Homopolymer and copolymer conversions were determined by mid-IR measurements collected prior to cure, immediately after irradiation and at 24 h at 23 °C. The absorption values of the spectra in Figures 1 through 4 contain a relative uncertainty of 0.5 % based on limitations of the instrumentation.

Results and Discussion

Synthesis of Hydroxylated Dimethacrylates. The reaction of glycidyl methacrylate with both diacids, PEG-bis(carboxymethyl) ether and dimer acid, proceeded via the typical nucleophilic substitution reaction where attack on the epoxide ring occurs at the less hindered epoxide carbon. The crude product formed was a clear, viscous liquid. This reaction can be conveniently monitored using NIR spectroscopy. It has been shown that the aliphatic stretching overtone of the epoxide ring occurs at 6070 cm^{-1} and the alkene C-H stretching overtone at 6164 cm^{-1} in the NIR spectrum.[6,7] Figure 1 highlights the important spectral characteristics of the glycidyl methacrylate, namely the aliphatic stretching overtone at 6070 cm^{-1}. The NIR spectra of the hydrophilic and hydrophobic diacids used are also shown in Figure 1 and illustrate the negligible overlap that occurs between the oxirane peak and the broad absorption bands of the diacids. Because of the lack of other absorption bands in this region of the spectrum, NIR can be an effective technique to monitor the synthesis reaction by the disappearance of the epoxide ring. This is illustrated in Figure 2. In Figure 2(a), the disappearance of the absorption band for the oxirane band upon reaction of glycidyl methacrylate with the PEG-bis(carboxymethyl) ether can be seen. A similar trend is seen in the reaction of glycidyl methacrylate with dimer acid (Figure 2(b)). It should be noted that the alkene C-H stretching overtone band at 6164 cm^{-1} remains constant throughout the reaction, indicating the stability of the double bond under these reaction conditions. Prolonged reaction at higher temperatures (T > 90 °C), however, caused gelation to occur in some cases. It should also be noted that the reactions between glycidyl methacrylate and these liquid diacids do not require solvents. However, when solid diacids such as tartaric acid or malonic acid are used, it is important to select a solvent that can dissolve the diacids and yet be easily removed from the product. Both diglyme and 1,3-dioxolane were effective in dissolving tartaric acid and malonic acid, but the relatively high boiling point of diglyme (T = 160 °C) makes its removal from the viscous crude product very difficult. Therefore, for these types of syntheses, more volatile polar solvents such as 1,3-dioxolane are preferred. Finally, although the synthetic scheme presented here describes the use of triethylamine as the catalyst, catalysts such as triphenylphosphine and *N,N*-dimethylbenzylamine can also be used effectively.

Polymerization of Hydroxylated Dimethacrylates. The homopolymerization of both dimethacrylates occurred readily. The extents of conversion were measured by mid-IR by following the disappearance of the vinyl absorption band at 1638 cm^{-1}. The extent of conversion of the dimer acid based dimethacrylate reached ≈ 98 % immediately after irradiation (approximately 1 min to 2 min) and remained constant after 24 h post cure. The extent of conversion of the poly(ethylene glycol)-based dimethacrylate reached ≈ 95 % immediately after irradiation and also remained constant after 24 h post cure. This is illustrated in Figures 3 and 4 respectively. Additionally, the dimer acid based dimethacrylate was copolymerized with Bis-GMA as an initial exploration of its viability for use in dental composites. The extent of conversion for the dimer acid-GMA/Bis-GMA copolymer was calculated after 1 min to be 73 % (relative standard uncertainty, 0.9 %) by mid-IR spectroscopy.

Conclusion

Representative reactions of glycidyl methacrylate with PEG-diacid and dimer acid showed the versatility of this synthetic technique to create hydroxylated dimethacrylates with hydrophilic and hydrophobic characteristics, respectively. NIR spectroscopy confirmed the disappearance

of the oxirane ring at 6070 cm^{-1} for each synthesis. The extent of reaction measured by mid-IR for both the homopolymerization and copolymerization were similar. These results suggest that dimethacrylates synthesized by this method have the potential for uses in many biomedical applications where control of the biodegradability and/or other properties is important.

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***Disclaimer.** Certain commercial materials and equipment are identified in this article to specify the experimental procedure. In no instance does such identification imply recommendation or endorsement by the National Institute of Standards and Technology or that the material or equipment identified is necessarily the best available for the purpose.

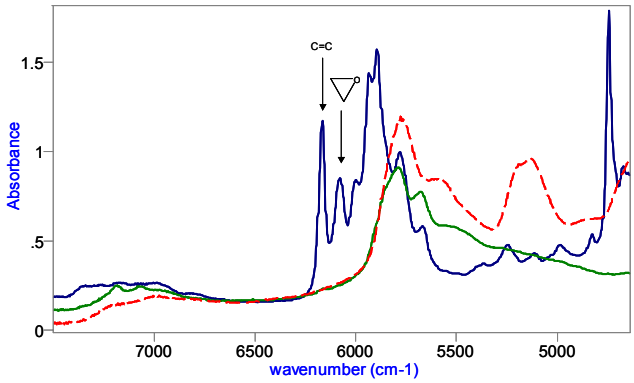

Figure 1. NIR spectra of glycidyl methacrylate, highlighting the H_2C=C and epoxide ring bands of glycidyl methacrylate. Also shown are NIR spectra of PEG-bis(carboxymethyl) ether (----) and dimer acid (——).

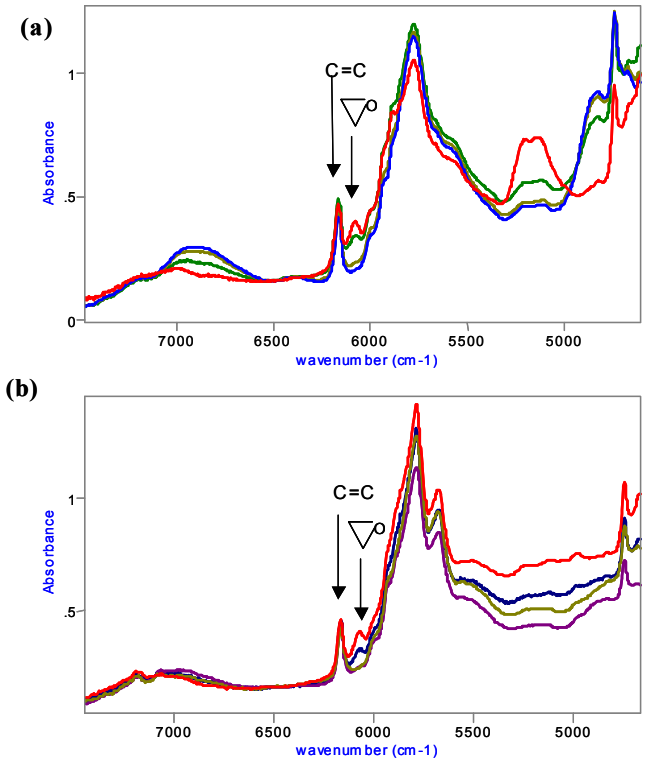

Figure 2. NIR spectra of reaction of glycidyl methacrylate with **(a)** PEG-bis(carboxymethyl) ether {t=(0, 5, 15, 20) h from top to bottom} and **(b)** dimer acid {t=(0, 7, 14, 20) h from top to bottom}.

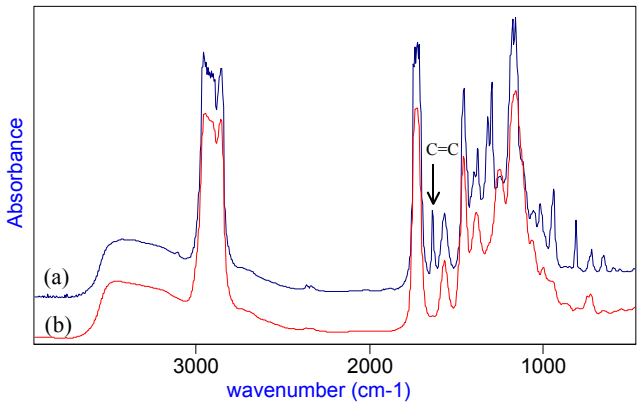

Figure 3. FT-IR of dimer acid based dimethacrylate (a) before cure and (b) post cure showing disappearance of vinyl absorption band.

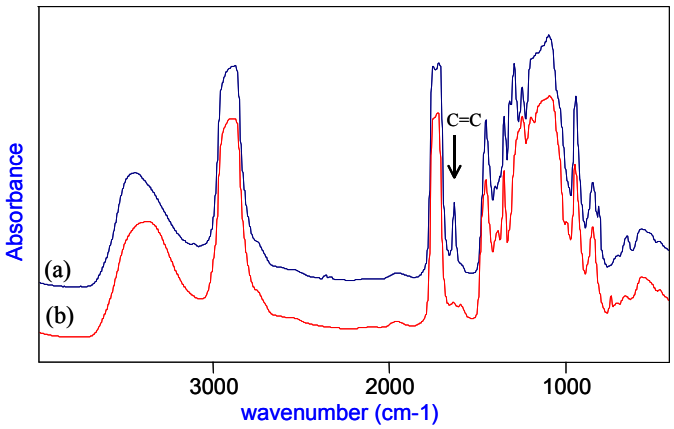

Figure 4. FT-IR of PEG-diacid based dimethacrylate (a) before cure and (b) post cure showing disappearance of vinyl absorption band.

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