An alternative pathway for the hydrolysis of epoxy ester compounds

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Abstract

The water-soluble polymer, poly(2,3-dihydroxypropyl methacrylate), also known as poly(glyceryl methacrylate), is known to isomerize and give a mixture of 2,3- and 1,3-isomers in both the monomeric and polymeric forms. The glyceryl methacrylate monomer was synthesized via acid-catalyzed hydrolysis of glycidyl methacrylate, which produced a mixture of 1,3- and 2,3-isomers in a ratio of 25% and 75%, respectively. This was surprising, as hydrolysis of epoxy compounds generally yields a 1,2-diol product. Furthermore, the level of 1,3-isomer at equilibrium is known to be 10% in both the glyceryl methacrylate monomer and polymer. An alternative hydrolysis pathway involving the ester and epoxy moieties was investigated for glycidyl methacrylate, and a mechanism was proposed.
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1. Introduction

Hydrophilic and water-soluble polymers have an extensive range of applications, including the use in optical lenses, dental materials and biomedical hydrogels [1−3]. They are also finding an increasing use in polymer therapeutics, which includes polymeric drugs, polymer–drug conjugates, polymer–protein conjugates, and polymeric micelles containing co-valently bound drug [4].

2,3-Dihydroxypropyl methacrylate (2,3-GM) (**1**) is a water-soluble monomer that readily undergoes free radical homo- and co-polymerization. These polymers have a range of important applications and are of particular interest for biological purposes. However, it is known that 2,3-GM and poly(2,3-GM) can isomerize to give their corresponding 1,3-dihydroxy isomers, such as 1,3-GM (**2**) as shown in Scheme 1. To pass through stringent regulatory conditions for therapeutic application, the processes that govern this isomerization must be understood.

Garcia et al. [5] have investigated the isomerization of poly(1,3-GM) and reported that the equilibrium level of 1,3-GM units in the polymer was 10%. van Dijk-Wolthuis

et al. [6] have also reported the level of 1,3-GM and 2,3-GM to be approximately 10% and 90%, respectively, in the monomer. The isomerization process involves migration of the ester group, which has been reported to occur in other mono and diglycerides [7−9].

The 2,3-GM monomer or poly(2,3-GM) are usually obtained by reacting a protected vicinal ketal form of glycerol with methacryloyl chloride, followed by acid hydrolysis of the ketal group of the protected glyceryl methacrylate monomer or polymer [10−14]. An alternative, more direct method for synthesizing glyceryl methacrylate and poly(glyceryl methacrylate) is achieved via the acid-catalyzed hydrolysis of glycidyl methacrylate (GMA) (**3**) and poly(glycidyl methacrylate). This pathway offers the advantage of being less expensive, due to the commercial availability of the GMA monomer, which is an important consideration for future commercial applications.

2,3-GM (**1**)   1,3-GM (**2**)
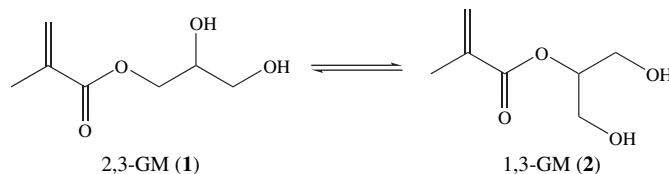
Scheme 1.

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Acid-catalyzed epoxy opening generally yields a 1,2-dihydroxy product. Therefore it would be expected that acid-catalyzed hydrolysis of GMA would produce 2,3-GM initially, which could then undergo isomerization reactions to give a mixture of approximately 90% 2,3-GM and 10% 1,3-GM at equilibrium. However, we have found that acid-catalyzed hydrolysis of GMA produces a significantly higher amount of the 1,3-GM isomer, at approximately 25%. Thus it appears that an alternative hydrolysis pathway has occurred in GMA to produce an elevated amount of the 1,3-isomer. This paper investigates how this alternative hydrolysis pathway has occurred, and a mechanism for the reaction is proposed.

2. Materials and methods

2.1. Materials

Glycidyl methacrylate (97%) and azoisobutyronitrile (AIBN) were purchased from Aldrich Fine Chemicals (Castle Hill, NSW, Australia). Glycidyl methacrylate was purified by distillation and AIBN was recrystallized from ethanol. All other reagents and solvents were of analytical grade and were used without further purification. Drying of solvents was achieved by distillation over CaH_2. Glacial acetic acid was purchased from Ajax Finechem. The 1,4-dioxaspiro[4,5]-decane-2-methyl methacrylate (DSDMA) monomer **4** was synthesized using a procedure described elsewhere [11].

2.2. Techniques

Nuclear magnetic resonance (NMR) spectra were obtained using a Varian Unity Plus 400 spectrometer operating at 400 MHz (^{1}H) and 100 MHz (^{13}C). The solvents used were deuterated chloroform and deuterated water. All ^{1}H and ^{13}C spectra were referenced to an internal standard, TMS at 0.00 ppm.

2.3. Hydrolysis of glycidyl methacrylate (GMA) (3)

GMA (19.9 g, 0.14 mol) was added to a solution of glacial acetic acid (70 ml) and water (190 ml) and the reaction mixture stirred at 80 °C for 1 h. The solution was cooled to room temperature and concentrated under reduced pressure to yield a mixture of 2,3- and 1,3-GM in a ratio of approximately 3:1 as a clear oil.

^{13}C NMR (D_2O): δ 20.27 (−CH$_3$), 63.03 (2× −CH$_2$OH), 65.28 (−CH$_2$OH), 68.35 (−O−CH$_2$−), 72.45 (−CHOH−), 78.32 (−O−CH−), 129.6 (H$_2$C=), 138.47 (−C=), 171.38 (−C=O).

2.4. Hydrolysis of 1,4-dioxaspiro[4,5]decane-2-methyl methacrylate (DSDMA) (4)

The DSDMA monomer (33.64 g, 0.14 mol) was added to a solution of glacial acetic acid (70 ml) and water (190 ml). The reaction mixture was stirred at 80 °C for 1 h. After cooling to room temperature, the aqueous layer was separated from

the reaction mixture and washed three times with toluene. The resulting solution was concentrated under reduced pressure to give 2,3-GM (**1**) as a yellow oil.

^{13}C NMR (D_2O): δ 20.17 (−CH$_3$), 65.16 (−CH$_2$OH), 68.24 (−O−CH$_2$−), 72.28 (−CHOH−), 129.58 (H$_2$C=), 138.21 (−C=), 171.29 (−C=O).

2.5. Hydrolysis of glycidyl isopropyl ether (GIE) (5)

Glycidyl isopropyl ether (2.91 g, 0.025 mol) was added to a solution of glacial acetic acid (12.5 ml) and water (37.5 ml) and the reaction mixture stirred at 80 °C for 1 h. The solution was cooled to room temperature and concentrated under reduced pressure to yield glycerol isopropyl ether.

^{13}C NMR (CDCl$_3$): δ 21.92 (−CH$_3$), 63.84 (−CH$_2$OH), 69.39 (−CH−), 71.21 (−O−CH$_2$), 72.50 (−CHOH−).

2.6. Polymerization of glycidyl methacrylate (GMA)

A mixture of GMA (14.92 ml, 0.105 mol) and AIBN (0.298 g, 2 wt.%) in 2-butanone (160 ml) was added to a Schlenk flask and degassed by three freeze−pump−thaw cycles. The flask was then back filled with argon and immersed in an oil bath at 60 °C for 16 h. The reaction mixture was concentrated under reduced pressure to one third of the original volume and precipitated into hexane. The precipitate was collected by vacuum filtration, to give poly(GMA) as a white solid.

^{13}C NMR (CDCl$_3$): δ 16.69, 18.75 (−CH$_3$), 44.60 (−CH$_2$−O−), 48.76 (−CH−O−), 54.12 (−C−), 65.86 (OC−O−CH$_2$−), 176.13, 176.93, 177.27 (C=O).

2.7. Hydrolysis of poly(glycidyl methacrylate) (poly(GMA))

Poly(GMA) (2 g) was added to a solution of THF (20 ml) and glacial acetic acid (30 ml). The reaction mixture was heated to reflux while stirring with the gradual addition of water (150 ml). The solution was evaporated and the polymer redissolved in a mixture of water/dioxane (1:1) and precipitated into hexane/ethanol (1:1) to give a glyceryl methacrylate co-polymer of approximately 77% 2,3-dihydroxy units and 23% 1,3-dihydroxy units.

^{13}C NMR (D_2O): δ 19.00, 20.97 (−CH$_3$), 47.17, 56.07 (−C−), 62.00 (−CH$_2$OH), 64.96 (−CH$_2$OH), 69.08 (−O−CH$_2$−), 71.7 (−CHOH−), 79.1 (−O−CH−), 180.96, 181.83 (C=O).

3. Results and discussion

The synthesis of glyceryl methacrylate was achieved via the acid-catalyzed hydrolysis of GMA. The hydrolysis of an epoxy ring usually gives a 1,2-diol product, which may then isomerize to give some 1,3-diol, depending on the structure. However, ^{13}C NMR analysis of the concentrated GMA hydrolysis mixture revealed a significant amount of the 1,3-GM isomer, as shown in Fig. 1. The relative amounts of each
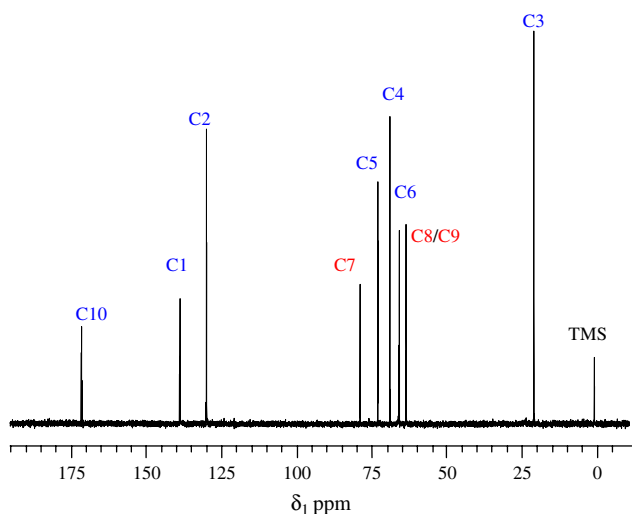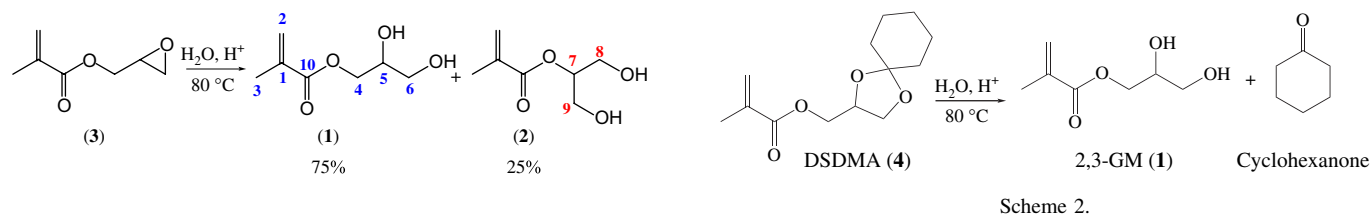
Scheme 2.

Fig. 1. ^{13}C NMR spectrum of the glycidyl methacrylate (GMA) (**3**) reaction mixture after hydrolysis in acetic acid/water for 1 h at 80 °C.

isomer were determined from integration of the signals corresponding to the CH groups of 1,3-GM and 2,3-GM in the ^{13}C NMR spectra, C7 and C5, respectively. The integration of decoupled carbon signals is not usually a reliable indication of the relative amounts of different compounds. However, if

two similar carbon types are integrated, such as the CH groups of 1,3-GM and 2,3-GM in this case, a reasonable approximation of the level of each compound can be obtained. Using this approach the proportion of 1,3-GM in the product mixture was calculated to be approximately 25%, which is significantly higher than the reported equilibrium level of 10%.

The formation of elevated amounts of the 1,3-GM isomer has also been reported by van Dijk-Wolthuis et al. [6], and was attributed to a higher extent of transesterification caused by basic reaction conditions. We therefore initially investigated the role of the hydrolysis conditions on isomerization. An exclusive precursor for the 2,3-GM isomer, 1,4-dioxaspiro[4,5]decane-2-methyl methacrylate (DSDMA) (**4**), was synthesized and subjected to acid hydrolysis under conditions identical to those used for GMA. ^{13}C NMR analysis of the concentrated reaction mixture demonstrated that initially only the 2,3-isomer was present in the reaction product (Scheme 2). The hydrolyzed DSDMA sample was then heated to 50 °C, and ^{13}C NMR spectra were recorded at specified intervals to study the isomerization reactions. The 1,3-GM isomer was first detectable in the hydrolyzed DSDMA sample after 192 h, and reached a constant level of approximately 10% after 360 h (Fig. 2a). When the hydrolyzed
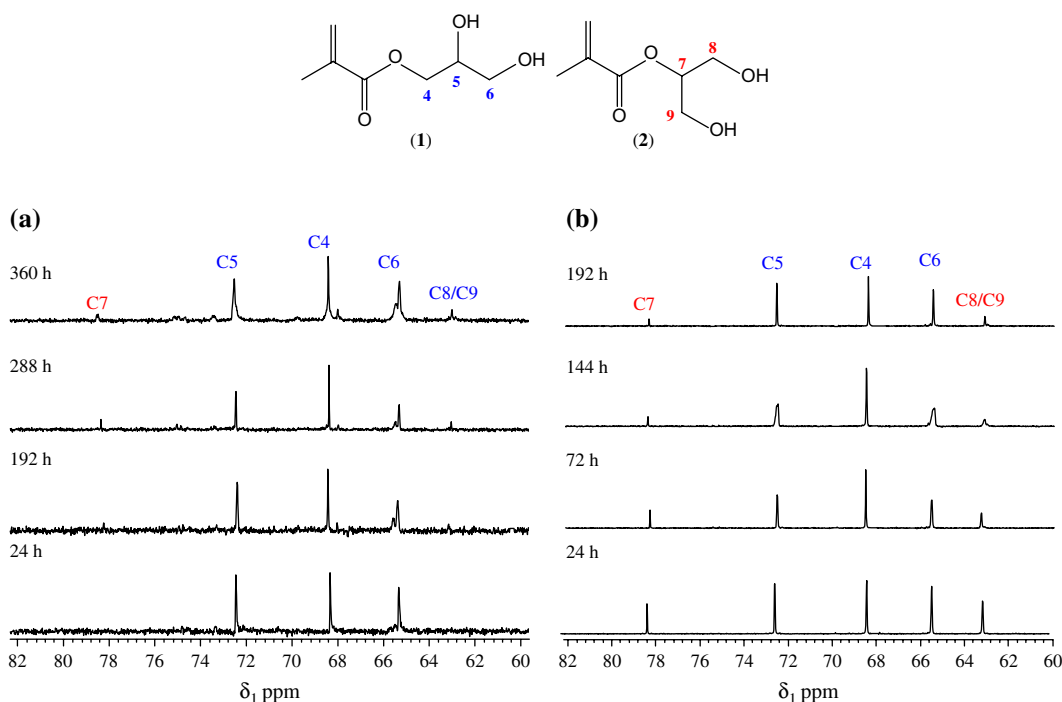

Fig. 2. ^{13}C NMR spectra of the isomerization process at 50 °C in the reaction mixture derived from (a) the hydrolysis of 1,4-dioxaspiro[4,5]decane-2-methyl methacrylate (DSDMA) (**4**) and (b) the hydrolyzed glycidyl methacrylate (GMA) (**3**).
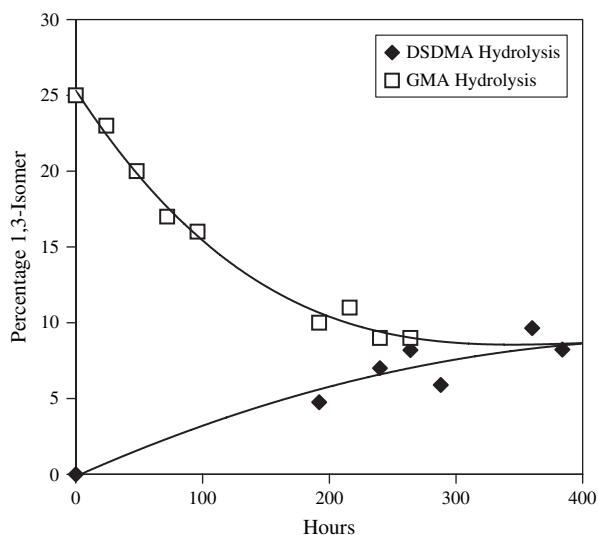
Fig. 3. Changes in 1,3-dihydroxypropyl methacrylate percentage over time in the isomerization of both the hydrolyzed DSDMA (4) and hydrolyzed GMA (3) at 50 °C.

Fig. 4. ^{13}C NMR spectra of hydrolyzed glycidyl isopropyl ether at 80 °C in acetic acid/water mixture for 1 h.

GMA sample was subjected to the same isomerization conditions, the amount of 1,3-GM decreased from the initial level of 25% to a constant level of approximately 10% after 192 h (Fig. 2b). Thus the level of 1,3-GM in both the hydrolyzed DSDMA and hydrolyzed GMA samples reached an equilibrium level of 10%, which is shown in the plot of the percentage of 1,3-isomer against isomerization time (Fig. 3). It was also found that distillation of hydrolyzed GMA could drive the mixture to equilibrium.

As 1,3-GM was formed in elevated amounts from acid hydrolysis of GMA but not DSDMA, it appears that the hydrolysis conditions are not driving the isomerization of 2,3-GM to produce 1,3-GM in high amounts. This suggests that the elevated levels of 1,3-GM are formed directly from an alternative epoxy ring opening pathway in GMA.
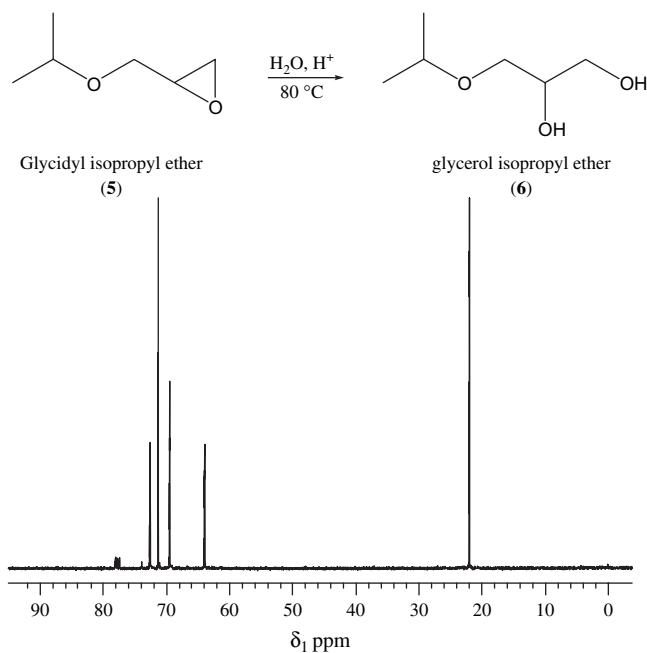
To investigate how this epoxy opening occurs, the required molecular structure linked to the epoxy group in GMA to facilitate such ring opening was investigated. Initially the influence of the methacrylate group was studied, via acid-catalyzed hydrolysis of the model compound glycidyl isopropyl ether (GIE) (5), which lacks a methacrylic moiety. The experiment shows that under identical hydrolysis conditions used for GMA hydrolysis, the epoxy opening of GIE produced a 2,3-diol, glycerol isopropyl ether (6), exclusively (Fig. 4). Therefore, the methacrylic moiety in GMA is necessary for the alternative epoxy opening mechanism to occur.

Acid-catalyzed hydrolysis of poly(GMA) was then performed to investigate whether the vinyl group of GMA is
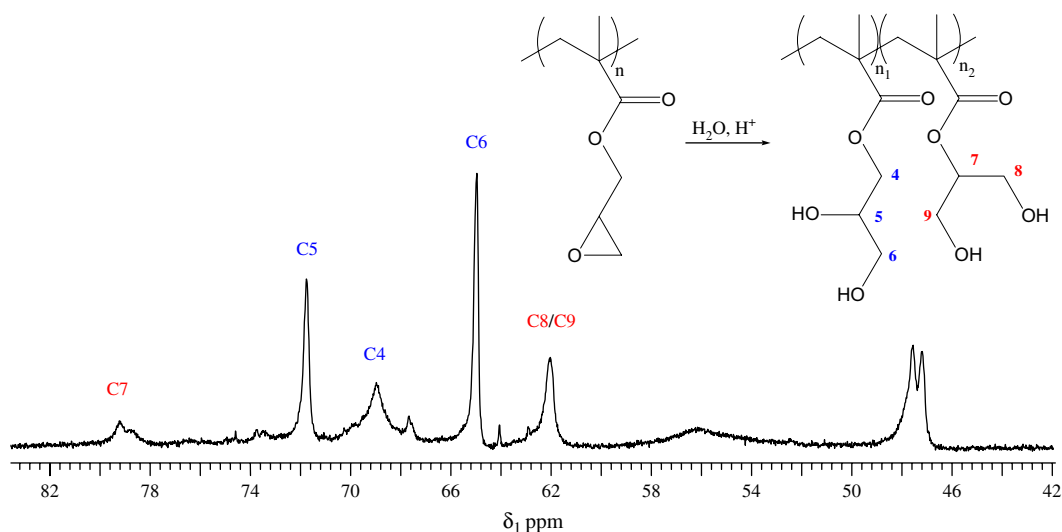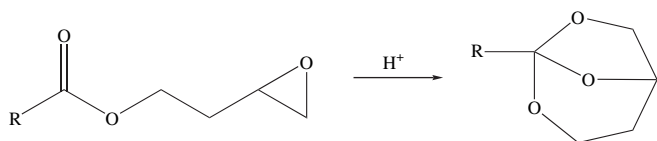

Fig. 5. ^{13}C NMR spectrum of the hydrolyzed poly(glycidyl methacrylate).
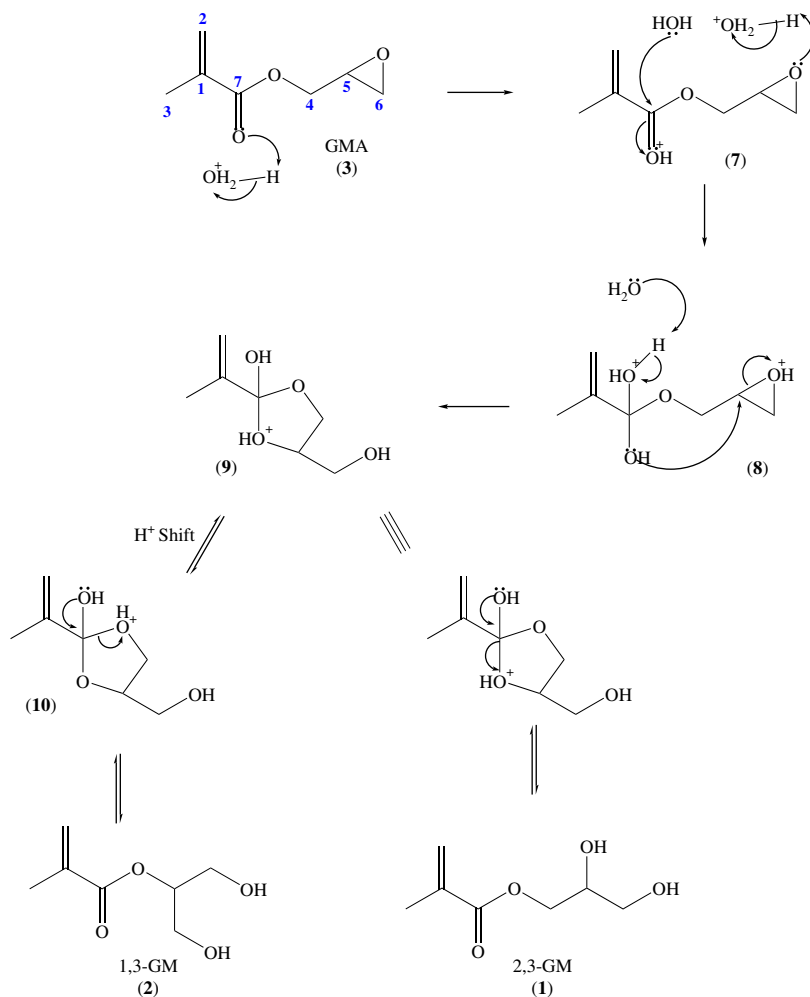
Scheme 3.

involved. ^{13}C NMR analysis revealed the proportion of 1,3-GM units in the hydrolyzed polymer to be approximately 23%, as shown in Fig. 5. This is similar to the hydrolysis of the GMA monomer, where approximately 25% of 1,3-GM isomer formed. As the equilibrium level of 1,3-GM units in the polymer is known to be approximately 10%, the hydrolysis of poly(GMA) also produced an elevated concentration of 1,3-GM units. Thus it appears that the alternative hydrolysis mechanism is also occurring in the GMA polymer. The ability for this pathway to occur in GMA and poly(GMA) but not in GIE suggests that while the ester group of the methacrylic residue is involved in the alternative epoxy hydrolysis, the vinyl group of GMA is not.

Intramolecular reactions between some epoxy and ester functionalities are known to occur, particularly in the formation of orthoesters [15–19]. Giner et al. [20] have reported

the synthesis of bicyclic orthoesters (Scheme 3), in a process that involves nucleophilic attack of the ester oxygen on the epoxy group, followed by attack of the epoxy oxygen on the carbocation. The hydrolysis of these orthoesters produced ester — dihydroxy compounds. It is possible that the 1,3-GM formation may occur through a similar bicyclic orthoester intermediate. To confirm this, a similar reaction was carried out in GMA. Glycidyl methacrylate in chloroform was treated with trifluoroacetic acid, according to the method described for orthoester formation by Giner et al. [20]. After 17 h, only unreacted glycidyl methacrylate could be detected in the ^{13}C NMR spectrum (data not shown). This experimental result indicate that GMA does not form a bicyclic orthoester. Therefore it is unlikely that the formation of 1,3-GM from glycidyl methacrylate is occurring via an orthoester intermediate.

We propose here that the alternative epoxy opening of GMA could involve a different interaction between the ester and epoxy moieties, which does not proceed via a bicyclic orthoester intermediate. The mechanism for this alternative hydrolysis pathway is given in Scheme 4. This process involves the protonation of the carbonyl group of the ester moiety of GMA to give 7, which is followed by nucleophilic attack of water to give 8. The newly formed hydroxyl group

Scheme 4.

can then attack the protonated epoxy at the C5 position, while the water group loses a proton to form **9**. The cyclic intermediate **9** can then undergo either direct ring opening to give 2,3-GM, or a proton shift to form **10**. The ring opening of **10** can then occur via nucleophilic attack of the hydroxyl group at C7, expelling the adjacent protonated hydroxyl group. The protonated carbonyl can then lose the proton to give 1,3-GM.

In the hydrolysis of GMA, the formation of the intermediate cyclic **9** is the key step. The formation of **10** by a proton shift is the reason for the direct formation of the 1,3-GM isomer. As the hydrolysis of GMA gave approximately 25% 1,3-GM and 75% 2,3-GM, the major hydrolysis pathway appears to be either the direct ring opening of **9**, or the conventional acid-catalyzed epoxy opening of GMA, both of which produce the 2,3-isomer.

4. Conclusion

The acid-catalyzed hydrolysis of GMA produced a mixture of 1,3-GM and 2,3-GM isomers in a ratio of 25% and 75%, respectively. This was unexpected, as hydrolysis of epoxy compounds generally yields a 2,3-dihydroxy product, and the equilibrium level of 1,3-GM is known to be 10%. Under identical reaction conditions, acid-catalyzed hydrolysis of DSDMA produced the 2,3-isomer exclusively. The isomerization reactions of the two reaction mixtures were analyzed, and it was found that both samples reached a level of 10% 1,3-GM and 90% 2,3-GM at equilibrium. A high proportion of 1,3-dihydroxy units were also formed in the acid-catalyzed hydrolysis of poly(GMA), however, hydrolysis of GIE generated only a 2,3-dihydroxy product. This suggests that an alternative epoxy opening pathway is occurring in GMA and poly(GMA) to form the 1,3-isomer, involving the ester group but not the vinyl unit of the methacrylic moiety. It was found that this pathway did not involve an orthoester intermediate, as has been reported to form in other intramolecular reactions between epoxy and ester moieties. An alternative mechanism involving the ester and epoxy functionalities suggested the formation of a cyclic intermediate for the 1,3-isomer from the acid-catalyzed hydrolysis of GMA.

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