The Unexpected Transesterification between Glycidyl Methacrylate and 2-{[2(Dimethylamino)ethyl]methylamino}ethanol

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Introduction

In the course of some recent work involving novel metal chelating polymers,[1] we identified monomer **1** as an attractive target monomer in view of its likely hydrophilic character, the presence of a substantial flexible linkage between the diamino ligand functionality and the methacrylate residue, and the likely ease of synthesis from commercially available glycidyl methacrylate (GMA) and 2-{[2(dimethylamino)ethyl]methylamino}ethanol (DAEMAE) via Scheme 1. While evaluating likely reaction conditions, we had occasion to perform one reaction without NaH and to our surprise were able to synthesize a product similar to **1** but clearly lacking the glycidyl derived spacer group in **1**. Indeed, the analytical data suggested the product to be **2** (Figure 1), presumably arising from a transesterification reaction involving GMA and DAEMAE. Interestingly, we noted a similar reaction to this, between GMA and dextran, reported recently in this journal.[2] This paper reports our efforts to understand the basis of this reaction and to probe its generality.

Experimental Section

1. Materials. Glycidyl methacrylate (GMA), glycidyl acrylate (GA), 2-{[2-(dimethylamino)ethyl]methylamino}ethanol (DAEMAE), methyl methacrylate (MMA), and hydroquinone were purchased from the Aldrich Chemical Co. and used as supplied. Tetrahydrofuran (THF) was dried over sodium/benzophenone and distilled before use; methanol was dried over magnesium turnings and distilled before use.

2. Methods. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX250 or WM400 instrument; *J* values are given in hertz. JMOD spectra were acquired to show C and CH_2 signals in the positive phase (U) and CH and CH_3 signals in the negative phase (D). FTIR spectra were recorded on a Nicolet 400_D spectrometer. ES-MS spectra were recorded on a Fisons VG platform spectrometer.

Reaction of GMA with DAEMAE at Room Temperature. GMA (5 g, 35 mmol) was added to anhydrous THF (10 cm^3) and stirred under nitrogen at room temperature for 10 min. DAEMAE (5.2 g, 35 mmol) was added dropwise, as a solution in anhydrous THF (10 cm^3). The resulting solution was stirred at room temperature for a further 18 h. The solvent was removed under reduced pressure to yield a colorless oil. A portion of the crude product (3.0 g) was distilled under high vacuum (0.4 mmHg, 60 °C) in a Kugelröhr to yield a colorless oil (2.02 g, 67%) and a brown polymeric residue. Elemental microanalytical data for the oil: found (%) C, 60.7; H, 10.4; N, 13.5 (corresponding calculated (%) data for **1** and **2** are respectively C, 58.3; H, 9.8; N, 9.7; and C, 61.65; H, 10.35; N, 13.1). FTIR ν_{max}(liquid film)/cm^{-1}: 2950, 2816, 2775, 1719, 1638, 1453, 1302, 1163, 1025, 944, and 816.

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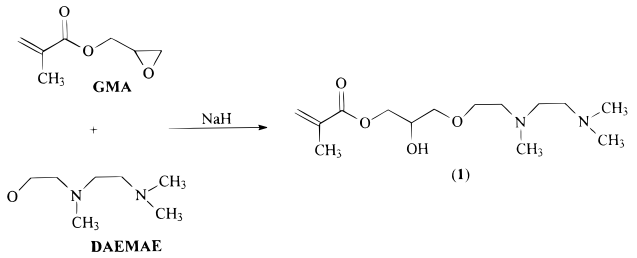
Scheme 1. Reaction of GMA with the Alkoxide Formed from DAEMAE and NaH Showing the Expected Pathway To Give Ring-Opened Product 1



^{1}H NMR (250 MHz; $CDCl_3$): δ 1.92 (3H, s, C^3−H), 2.22 (6H, s, $C^{10,11}$−H), 2.37 (3H, s, C^7−H), 2.40 (2H, t, J 6, C^9−H), 2.53 (2H, t, J 6, C^8−H), 2.71 (2H, t, J 6, C^6−H), 4.24 (2H, t, J 6, C^5−H), 5.54 (1H, s, C^1−H), and 6.09 (1H, s, C^1−H) (Figure 1).

^{13}C NMR (250 MHz; JMOD, $CDCl_3$): δ 18.21 (D, C^1), 42.39 (D, C^7), 45.37 (D, $C^{10,11}$), 55.67 (U, C^9), 55.89 (U, C^8), 57.21 (U, C^6), 62.47 (U, C^5), 125.29 (U, C^1), 136.04 (U, C^2) and 167.10 (U, C^4).

MS: Da 214.6 (M^+, 100%).

Reaction of GMA with DAEMAE with Heating. GMA (5.0 g, 35 mmol), DAEMAE (5.2 g, 35 mmol), and hydroquinone (10 mg) were added to anhydrous THF (10 cm^3). The solution was heated to reflux and stirred, under nitrogen, for 3 h. Following heating, the solution had darkened considerably and was left aside for 48 h. The supernatant was decanted off the polymer residue and the remaining solvent removed under reduced pressure to yield a colorless oil. The crude product was distilled under high vacuum (0.4 mmHg, 60 °C) in a Kugelröhr to yield **2** (4.7 g, 62%).

Reaction of GMA with DAEMAE during Distillation. GMA (1.0 g, 7 mmol) was added to DAEMAE (1.04 g, 7 mmol). The resulting solution was distilled under high vacuum (0.4 mmHg, 60 °C) in a Kugelröhr to give three fractions. The former two fractions proved to be unreacted starting materials while the latter was **2** (0.6 g, 39%).

Discussion

The facile nucleophilic ring-opening reaction of the epoxide group in GMA, and in polymer resins derived therefrom, using primary amines is a convenient and clean method for preparing ligand-modified monomers and polymers. We[3,4] and others[5,6] have used this route extensively in work on metal-chelating resins. To achieve a similar reaction with alcohols and phenols, it is usually necessary either to generate the anion of the alcohol or phenol[7] or to use a protic acid or Lewis acid catalyst.[8]

The synthesis described here shows unambiguously that the diamino alcohol, DAEMAE, undergoes a transesterification reaction directly with GMA with the elimination of the glycidoxy group. The final destiny of the eliminated glycidol (Scheme 3) has not been determined, but some reaction with amine seems likely. The transesterification itself reaction requires neither additional reactant nor catalyst and occurs readily while the reactants are heated under vacuum at 60 °C in the Kugelröhr still. To monitor the progress of the reaction by ^{1}H NMR spectroscopy, GMA and DAEMAE were dissolved in $CDCl_3$ in a standard NMR tube. Spectra recorded regularly over a 14 h period indicated that the reaction had not occurred (Figure 1). The NMR tube was then heated to 60 °C initially for 1 h and then for 18 h. The appearance of a small resonance at δ 4.21−4.23

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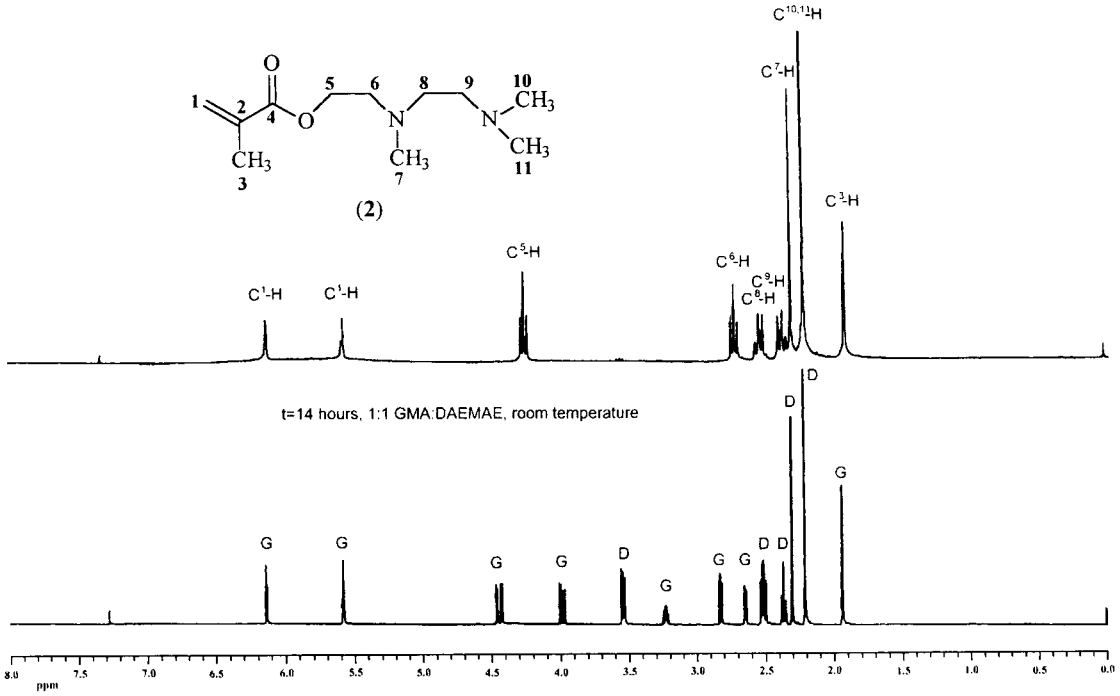
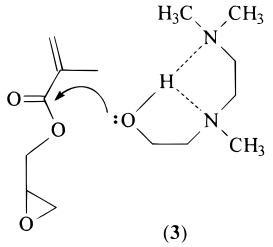


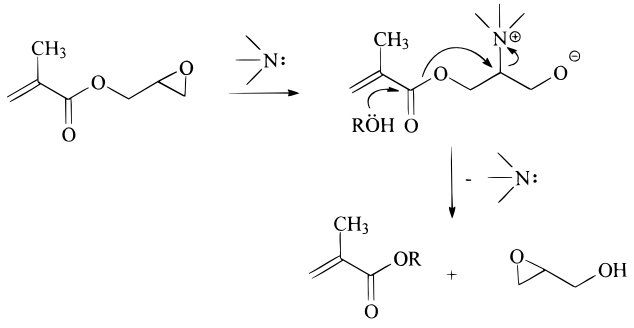
Figure 1. ^{1}H NMR spectra obtained during the NMR study showing the spectrum of monomer **2** with the spectrum of the 1:1 mixtures of GMA and DAEMAE below taken at $t = 14$ h at room temperature. G designates those peaks attributed to GMA, and D defines the peaks associated with DAEMAE.

Scheme 2. Possible Intramolecular Base-Catalyzed Nucleophilic Attack of the DAEMAE Hydroxyl Group on GMA



(3)

Scheme 3. Enhanced Leaving Group Character of the Glycidyl Unit via Nucleophilic Attack by a Tertiary Nitrogen Moiety of DAEMAE



(C^5−H) confirmed that the transesterification had occurred, but the conversion was only ∼14%. Clearly therefore while transesterification does occur slowly in solution at 60 °C, to achieve rapid conversion the bulk conditions arising in the Kugelröhr still are essential.

In an attempt to evaluate a possible mechanism for the transesterification, a number of model reactions were carried out using similar conditions. DAEMAE was reacted with methyl methacrylate to assess the role, if any, of the glycidyl ester moiety. No transesterification was detected. GMA was reacted with methanol, and again no transesterification was observed. Finally DAEMAE was reacted with glycidyl acrylate (GA), and again, somewhat surprisingly, no transesterification was apparent. (*Note*: The above conclusions are based on careful ^{1}H NMR spectral analysis of products from respective vacuum distillations. In all cases unreacted starting materials and polymeric residues were obtained.)

van Dijk-Wolthius et al.[2] have proposed that in the reaction of GMA with dextran the driving force may be the elimination of the glycidoxy anion which might be somewhat stabilized via delocalization of the negative charge over two oxygen atoms. Indeed, they were able to detect glycidol in their reaction supernatants using GC-MS analysis. Our results also confirm the importance of the presence of the glycidyl ester; a simple methyl ester will not undergo transesterification under our reaction conditions. The Dutch workers,[2] however, also showed that they could achieve a similar methacrylation, albeit less efficiently, using hydroxyethyl methacrylate instead of GMA. Rather more crucially they also used 4-(*N*,*N*-dimethylamino)pyridine as a strong base to achieve reaction at room temperature.

In our work it seems very likely therefore that DAEMAE has a very specific role in the reaction. It may act as a base catalyst to improve the nucleophilicity of the OH group, potentially via an intermolecular interaction (structure **3**, Scheme 2), with the glycidoxy anion functioning as a respectable leaving group. Alternatively, one or the other of the tertiary amino groups in DAEMAE may induce a nucleophilic ring opening of the glycidyl epoxy groups (Scheme 3), much improving the leaving group character of the ester and enhancing the reactivity toward transesterification. It would be nice if amine activation of the ester and transesterification could be modeled as an intramolecular process involving only one DAEMAE molecule with say a six-membered ring transition state; however, we have been unable to do this. In addition, a further weakness is that we have

shown the amine attack in Scheme 3 occurring at the more substituted carbon atom of the epoxide, so that the quaternary ammonium group formed can be subsequently displaced by the leaving alkoxide during transesterification with formation of the glycidoxy anion. Whatever the mechanism, however, DAEMAE plays a key role other than as a simple alcohol.

Why should GA not behave in the same way as GMA with DAEMAE with the same reaction conditions? This is very puzzling. The most likely explanation is stereochemical. The methacrylate group is significantly more bulky than the acrylate, with the latter having much freer rotation about the C−C bond connecting the C═C and the C═O. Usually this makes acrylate polymers more susceptible to hydrolysis than methacrylate ones. However, with the involvement of the amino group(s) of DAEMAE as well as the OH group in the transesterification, there may be some conformers of the (meth)acrylate more favored than others, and the population of these may be higher in the methacrylate ester.

Finally, it would of course be interesting to evaluate this reaction with linear polymers of glycidyl methacrylate and glycidyl acrylate.

Conclusions

We have shown that the transesterification reaction between DAEMAE and GMA occurs without other reagents or catalysts at 60 °C under vacuum distillation. The reaction is facile and is of positive synthetic utility. The ease of the reaction seems peculiar to the DAEMAE/GMA pair and almost certainly involves the glycidoxy anion as a respectable leaving group and the involvement of the amino group(s) in DAEMAE either as a base catalyst or an activating nucleophile. The absence of a similar facile reaction with GA is probably stereochemically based.

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