On the Copolymerization of Epichlorohydrin and Glycidol

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ABSTRACT: The boron trifluoride-catalyzed cationic copolymerization of epichlorohydrin and glycidol is examined in some detail, with reference to the effect of various reaction variables such as temperature, water content, and stirring rate on the polymerization process and the copolymer product. The reaction temperature does not have a strong effect on the molecular weight of the copolymer, but the water content of the reaction mixture is inversely related to the molecular weight. The stirring rate strongly affects the exotherm associated with the initial stages of the reaction: improved stirring diminishes the exotherm. Based on the relative rates of monomer consumption and other observations, a reaction mechanism is proposed for the formation of the copolymer, in which glycidol polymerizes via what is known as the activated monomer (AM) mechanism rather than by the standard cationic ring-opening polymerization mechanism. © 1997 John Wiley & Sons, Inc. J Appl Polym Sci **65:** 1897–1904, 1997

Key words: cationic; copolymerization; epichlorohydrin; exotherm; glycidol

INTRODUCTION

Copolymers of epichlorohydrin and glycidol are a useful component of the coatings applied to microscopic porous crosslinked poly(styrene–divinylbenzene) beads used in chromatographic applications.[1] The crosslinked beads in their uncoated form are extremely hydrophobic and, therefore, have limited utility as chromatography media. When coated with this copolymer, the beads are rendered hydrophilic. Once coated, the beads—now rendered water-wettable—can be used to separate, purify, and analyze a wide range of important biological molecules, most of which are soluble in aqueous buffers. Besides being hydrophilic, the coating provides useful reactive groups on the bead surface such as the hydroxyl group from the glycidol, which can be further derivatized to create a variety of different chromatography media including ion exchangers, affinity supports, and resins for hydrophobic interaction chromatography. All these materials play a vitally important role in the separation, purification, and analysis of biomolecules.

The work described in this article has a dual focus on process and product. It explores the effects of some of the major factors influencing the polymerization process used in manufacturing the copolymer of epichlorohydrin and glycidol. It also investigates the effects of key variables on the copolymer product. Included herein is a proposed reaction mechanism for the formation of this copolymer under the conditions used in its manufacture.

EXPERIMENTAL

Materials

Epichlorohydrin, glycidol, and HPLC-grade dichloromethane were purchased from Aldrich Chemical and stored over 5A molecular sieves. Glycidol was stored under nitrogen in a refrigerator. Boron trifluoride diethyl etherate was pur-

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chased from Aldrich and stored under nitrogen in a bottle with a septum-sealed cap. HPLC-grade tetrahydrofuran (THF) was also purchased from Aldrich in 1- or 2-L bottles and used fresh each day; any unused THF remaining after 1 day was discarded. Narrow molecular weight poly(ethylene glycol) (PEG) standards were obtained from Waters Corp. All reagents were used without further treatment.

Methods

In a typical experiment, copolymers of epichlorohydrin and glycidol were prepared in the following manner: A clean, dry 5-L three-neck round-bottom flask, maintained at constant temperature with a water bath, was fitted with an addition funnel, a condenser operating at 5°C, and a mechanical stirrer having a glass shaft and a PTFE paddle. To this flask was added 1.5 L of dichloromethane, followed by 67 mL of glycidol and 134 mL of epichlorohydrin, and the mixture was stirred vigorously to ensure homogeneity. Using a syringe, 1 mL of BF₃ etherate was withdrawn through the septum seal of the bottle and added to the reaction mixture with continuous vigorous stirring. The above volume ratio of monomer, initiator, and solvent was kept constant in all cases. Within a couple of minutes, the reaction mixture turned cloudy and the dichloromethane started to reflux at the condenser. The solution stayed warm and cloudy for a few hours, while vigorous agitation continued. Reaction progress was monitored by tracking the monomer concentration using gas chromatography (GC). As the polymerization progressed overnight, the reaction mixture cooled to the bath temperature and turned clear. The polymerization was terminated in all cases after a maximum of 23 h of reaction time, measured from the addition of BF₃ etherate. The reaction was quenched by adding deionized water to the reaction mixture and continuous vigorous stirring for 1 h.

Reaction Monitoring

Reaction progress was monitored using a Hewlett-Packard Model 5890 series II gas chromatograph equipped with a thermal conductivity detector, a Model 7673 autosampler, and an HP-FFAP capillary column 10 m long × 0.53 mm diameter × 1.0 μm coating thickness. High-grade helium was used as the carrier gas. The GC was calibrated using different known concentrations of the two mono-

mers in dichloromethane. The GC was also calibrated to measure trace amounts of water in the reaction mixture by spiking dry dichloromethane with different small known concentrations of water, up to 0.1% by volume. At various intervals during the reaction, 1-mL aliquots of the reaction mixture were withdrawn from the flask and analyzed quantitatively for monomer content by GC, using the prior calibration data.

Characterization

Once the reaction was terminated, a small (approximately 5 mL) aliquot of the reaction mixture was taken out and evaporated under a vacuum at room temperature for 2 h to yield a few hundred milligrams of clear, colorless, viscous copolymer paste.

The copolymer was dissolved in HPLC-grade THF at a concentration of 8 mg/mL for the purpose of gel permeation chromatography (GPC) analysis. GPC measurement of the copolymer molecular weight was carried out using a Waters chromatography system consisting of a Model 600E system controller, 60F pump operating at 1 mL/min, 712 WISP autosampler, column heater with temperature control module operating at 30°C, R401 refractive index detector, SAT/IN analog-to-digital converter module, and computer workstation running Waters Millennium software for data reduction. The column set used was a pair of Waters Styragel HR 4E GPC columns, 300 mm long × 7.8 mm diameter, and the mobile phase was HPLC-grade THF. Every time a GPC analysis was performed, the instrument was calibrated using narrow molecular weight PEG standards of peak molecular weights M_p = 23,600, 4110, 1470, and 440 g/mol. A linear regression curve fit was used for the calibration plot of $\log(M_p)$ vs. retention time, consistently yielding a correlation coefficient $R \geq .999$.

Osmometric measurements of the copolymer number-average molecular weight M_n were performed on a UIC vapor-phase osmometer Model 070B using acetone as the solvent at 30°C. Selected samples were examined at four different concentrations, ranging from 5.00 to 20.00 mg/g.

Differential scanning calorimetry analysis was performed on a DuPont 2100 instrument from ambient temperature to 200°C, using a heating rate of 10°C/min. The analysis was done at ambient pressure and repeated with a fresh sample under a 900 psi helium atmosphere, to reduce evaporation during heating.

RESULTS AND DISCUSSION

Proem

A number of different factors were found to influence the progress of the reaction (process) and the nature of the copolymer formed (product). To evaluate the effect of each variable, the copolymer from each reaction was analyzed by a number of different chemical techniques, including mass spectrometry, IR, ^{1}H-NMR, UV-visible spectroscopy, and elemental analysis. These traditional tools of the chemist were unable to pry the secrets from this obdurate material: They could not discriminate between different batches of the copolymer. The method of choice for analyzing these copolymers was found to be molecular weight determination by GPC, which was sensitive to changes in the copolymer resulting from changes in the several reaction variables. The copolymer molecular weight was also found to correlate well with product performance in chromatographic coatings applications. Therefore, the effects of each variable on the product will be discussed below mainly in terms of how the molecular weight of the copolymer was affected. Since this copolymerization is an exothermic reaction, it was of great importance to control the rate of heat release for the sake of safety. Therefore, the effect of the various reaction variables on the copolymerization process will be discussed below mainly in terms of how the exotherm was affected.

Copolymerization Phenomena and Kinetics

In all cases, the very first observation made during this copolymerization process was the transformation of the clear, colorless solution of monomers into a cloudy, white, viscous liquid a couple of minutes after the addition of the BF_3 initiator. Within the next several minutes, a viscous, white polymer precipitate appeared on the flask walls and the solution started to reflux. The precipitation of this viscous polymer was the reason that a mechanical stirrer had to be used; magnetic stir bars simply got stuck in the polymer.

Volatile components of the reaction mixture were readily detected and resolved by GC. A representative GC trace of a sample containing both monomers is shown in Figure 1. Analysis of the reaction mixture by GC showed that most of the glycidol was consumed within the first few minutes after addition of BF_3, whereas the epichlorohydrin concentration remained unchanged during this time. Figure 2 shows the monomer consumption profiles for a typical reaction. The rapid disappearance of glycidol during the initial stages of the reaction indicates that the viscous precipitate formed during this phase is polyglycidol, which is insoluble in dichloromethane but readily soluble in water, due to the large number of polar hydroxyl groups present on the chain. The reflux associated with this stage of the reaction can be traced back to the energy released from the opening of the epoxide rings in glycidol during its polymerization.

The temperature profile of the reaction reflected the pattern of monomer consumption seen by GC; a representative temperature profile is shown in Figure 3. The initial rapid disappearance of glycidol was accompanied by a sharp rise in temperature during the first 0.5 h of the reaction. The reaction then segued smoothly to the rather slower polymerization of epichlorohydrin, which was accompanied, in turn, by a slow rise in temperature over the next couple of hours. Lastly, as the epichlorohydrin concentration decreased, the reaction slowed down and the temperature reverted slowly to ambient over a span of several hours.

During the early phase of the copolymerization, as the temperature and viscosity of the reaction mixture increased sharply, it was critically important to maintain vigorous stirring of the reaction mixture to prevent the exotherm from getting out of control. For example, in a 5-L round-bottom flask, a stirring rate of 330 rpm resulted in a mild reflux rate of a couple of drops per second at the condenser. When the reaction was carried out with a stirring rate of 260 rpm, the reflux rate was so violent that the bottom half of the condenser was flooded. Upon increasing the stirring rate to 330 rpm during this vigorous exotherm, the reflux reverted instantly back to its original mild rate of a couple of drops per second. Despite these differences in the process, it was interesting to note that the product generated in both these cases had essentially the same molecular weight, M_n = 1320 g/mol at 260 rpm and M_n = 1349 g/mol at 330 rpm.

These phenomena can be understood as follows: As the polyglycidol forms, it precipitates from the reaction mixture as a viscous gel and sticks to the wall of the reaction vessel. This precipitate, which contains most of the reactive ends of the growing polymer chains, also has trapped within it a substantial amount of monomer and solvent. Therefore, the local reaction rate in the
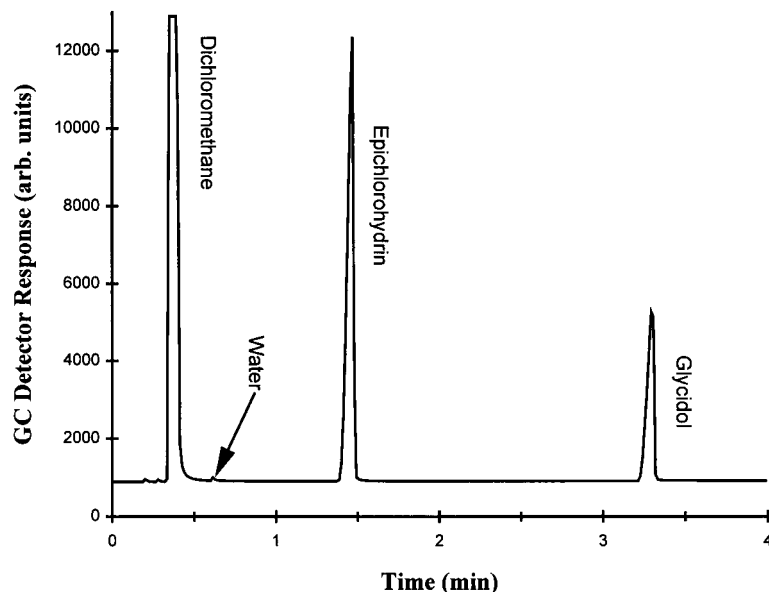
Figure 1   GC trace of a reaction mixture sample containing both monomers.

gel is much higher than in the bulk of the reaction mixture, where the reactive ends of the growing polymer chains are few. Due to the exothermic nature of the reaction, the solvent trapped in the gel is heated up tremendously, causing the violent reflux mentioned above. If the stirring rate is sufficiently high, however, the polyglycidol precipitate is broken up and distributed more or less uniformly throughout the reaction mixture. Consequently, the heat from the reaction is absorbed by the entire reaction mixture, instead of just the solvent trapped in the precipitate on the vessel walls, and the reaction mixture as a whole refluxes gently.

Once the glycidol is substantially converted to polymer, the reflux dies down. With the passage of time, the epichlorohydrin slowly reacts and is ultimately consumed over a period of several hours, forming the poly(glycidol–epichlorohydrin) copolymer. The epichlorohydrin adds slowly because most of the reactive ends of the growing polymer chains are trapped in the polyglycidol precipitate—this is a two-phase system during the early stages of the reaction. Therefore, the epichlorohydrin can only add to the polyglycidol at the interface of the precipitate and the solvent, lowering the reaction rate. As the copolymer forms, it becomes increasingly soluble in dichloromethane due to the addition of numerous nonpolar —CH_2Cl groups from epichlorohydrin to the
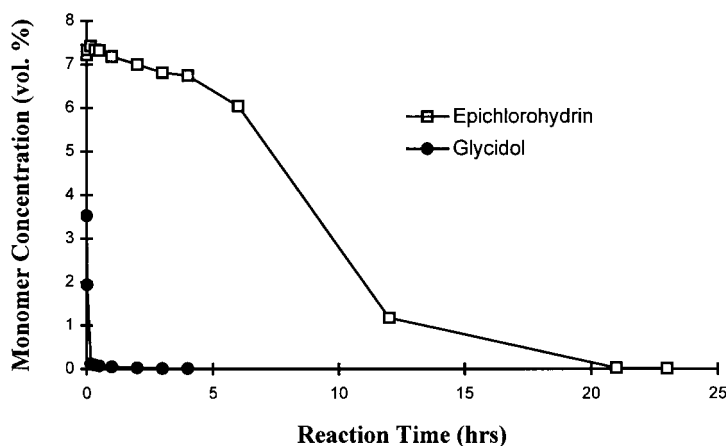
Figure 2   Monomer consumption curves for the copolymerization reaction.
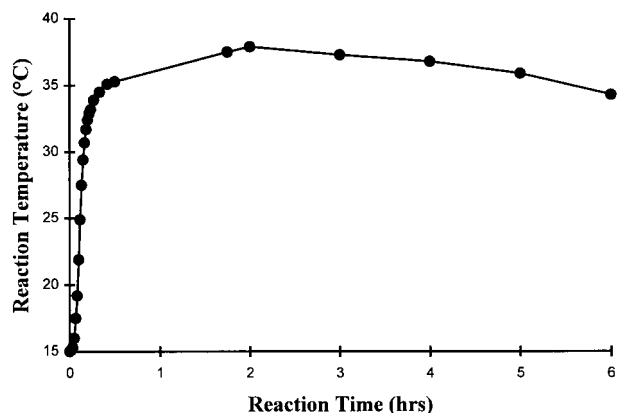
**Figure 3** Representative temperature profile of a copolymerization reaction.

Mechanism

Based on the above observations, a reaction mechanism can be propounded for this copolymerization. The mechanism, shown in Figure 4, is a modification of the standard cationic ring-opening polymerization mechanism for epoxides found in introductory polymer science texts.[2] The modification consists of taking into account the presence of a protic species, the hydroxyl group of glycidol. Normally, such cationic polymerizations are carried out with rigorous exclusion of protic species, which cause premature termination of the growing polymer chain ends. However, in the reaction under study, the hydroxyl group of glycidol actively participates in the copolymerization by engaging in acid-catalyzed cleavage of the epoxy ring, as described in introductory organic chemistry texts.[3] Detailed studies on the role of the hydroxyl group in the cationic polymerization of glycidol alone in dichloromethane have been reported elsewhere.[4,5]

From the fact that glycidol is consumed first, it can be deduced that it polymerizes chiefly via its hydroxyl group to form the white polyglycidol precipitate seen in the early stages of the reaction. Therefore, it can be concluded that a block or graft copolymer is formed rather than a random copolymer, with a poly(trimethylene oxide)-like backbone for the polyglycidol segments, which are formed first, and a poly(ethylene oxide)-like backbone for the polyepichlorohydrin segments, which are added later. In the cationic ring-open-

chain; when the epichlorohydrin is mostly consumed, the viscous precipitate seen at the beginning of the reaction disappears altogether.

ing polymerization of epoxides, there is a plethora of side reactions which can occur,[6] and this is further exacerbated in this instance by the presence of two different monomer species in the reaction mixture. Therefore, the mechanism set forth here should be taken to represent merely the most likely reaction pathway among a host of possibilities. The particular pathway for glycidol polymerization shown here has been called the activated monomer (AM) mechanism.[7,8]

Based on the proposed structure of polyglycidol shown in Figure 4, the heat of reaction for the polymerization of glycidol was calculated using the NIST Structures and Properties Database and Estimation Program v. 1.2. The calculation reached an asymptote assuming a degree of polymerization of only 4, with cyclic boundary conditions, i.e., formation of a cyclic tetramer. This yielded a value of 112.6 kJ/mol. The heat of reaction obtained in this manner is very close to the ring strain of 114 kJ/mol previously reported[9] for epoxy species, which supports the reaction mechanism presented here.
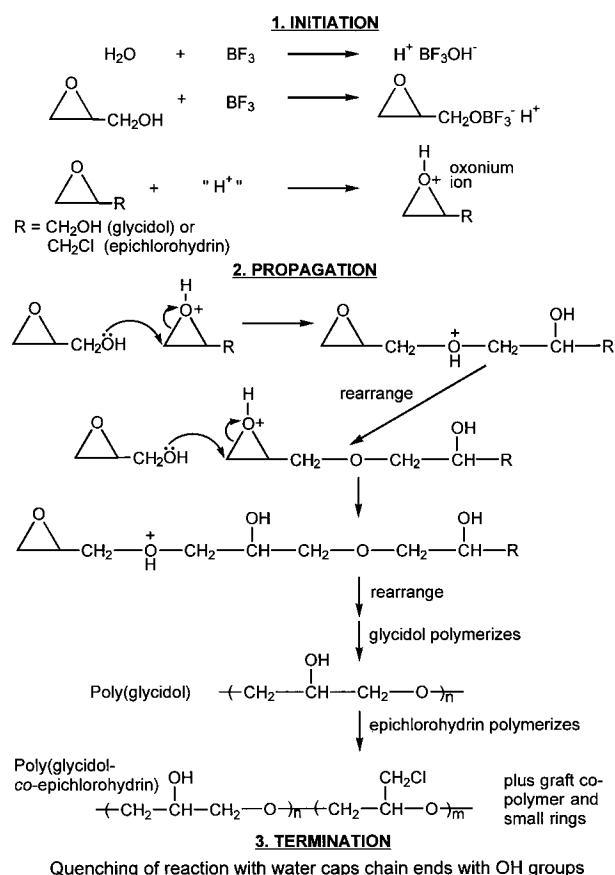
Figure 4 Proposed reaction mechanism for copolymer formation.

Process

The BF$_3$ initiator was added either undiluted or diluted 1 : 50 (v/v) in dichloromethane, all at once or dropwise over a period of time. Dilution did not affect either the process or the product, but the rate of addition of the diluted initiator was found to have a weak effect on the copolymerization process. When the diluted initiator was added in 6 min or less, a gentle reflux was observed and both monomers were consumed within the set maximum reaction time of 23 h. However, when the diluted initiator was added over 10 min, the induction time for the gentle reflux was slightly longer, about 5 min, and about 9% by volume of the epichlorohydrin still remained unpolymerized at the end of 23 h, although the glycidol was entirely consumed (no trace detectable by GC).

The amount of water added at the end of the reaction to terminate the polymerization was varied from 10 to 30 mL when the reaction was run in a 5-L flask, without any effect on the polymerization or the copolymer itself. In fact, since water is immiscible with dichloromethane (although miscible with glycidol), any volume of water greater than about 10 mL simply pooled on the surface of the reaction mixture. Also, because of this immiscibility, continuous vigorous stirring was required to disperse the water in the reaction mixture and effect the termination. The only physical effect observed during this quenching step was the appearance of a faint turbidity in the reaction mixture; no exotherm or endotherm was detected. Since the copolymer consists mostly of nonpolar epichlorohydrin repeat units, it is insoluble in water, and the turbidity observed on addition of water to the reaction mixture can be attributed to this insolubility.

The reaction could be scaled up safely and reproducibly to 500 gal of the reaction mixture in a 1000-gal glass-lined reactor. All reactors larger than 22 L had to be baffled and agitated at a high rate to promote good mixing, in order to keep the reflux rate reasonable. In vessels larger than 22 L, the entire diluted BF$_3$ initiator solution was added to the reactor within 5 min.

As the size of the reactor increased, the time needed for the initial exotherm to subside also increased. This was due to the lowering of the surface to volume ratio of the reactor as its size increased, causing the heat of the reaction to be dissipated more slowly than in a smaller reactor. The net result was that in reactors larger than about 50 L the reaction went to completion (no residual monomers detectable by GC) in about 12 h, well under the maximum of 23 h. To test this heat-dissipation hypothesis, a copolymerization was run in a well-insulated 5-L round-bottom flask, and the reaction was complete in 12 h, as expected.

At large scale (50 L or above), a faint pink tinge could be observed in the reaction mixture during the stage when the epichlorohydrin was being consumed. This same pink tinge appeared in a pronounced fashion in the copolymer itself after the solvent had been evaporated from the reaction mixture under a vacuum at 35°C. The intensity of this pink color was directly related to the temperature of the reaction mixture during evaporation and inversely related to the amount of water present in the reaction mixture. The pink color disappeared from the copolymer upon storage in the lab for several weeks, indicating that the chromophore was air-unstable. Polymerization of neat glycidol with BF$_3$ etherate yielded a colorless polymer, but polymerization of neat epichlorohydrin with BF$_3$ etherate yielded a pinkish polymer. This suggests that a colored complex of BF$_3$ and polyepichlorohydrin is responsible for the pink tinge observed in the reaction mixture, although the exact nature of the complex is still unknown.

Product

In three separate copolymerizations, the temperature of the reaction mixture was held constant at 25, 30, and 35°C after the subsidence of the initial exotherm, and the resultant copolymers were analyzed by GPC. Representative chromatograms of PEG standards and a copolymer sample are shown in Figure 5. Copolymer molecular weight was found to decrease slightly over this temperature range, as seen in Table I. This phenomenon can be attributed to the increased formation of small ring species instead of long-chain polymer at higher reaction temperatures.[6]

The water content of the reaction mixture was found to have a strong effect on the copolymer molecular weight, as displayed in Figure 6. The error bars represent the range of measured molecular weights for each sample. Despite the noise in the data, it is clear that the molecular weight depends inversely on the water content. Water serves to terminate growing polymer chain ends—it is used to quench the reaction, as mentioned in the methods section above—limiting the chain
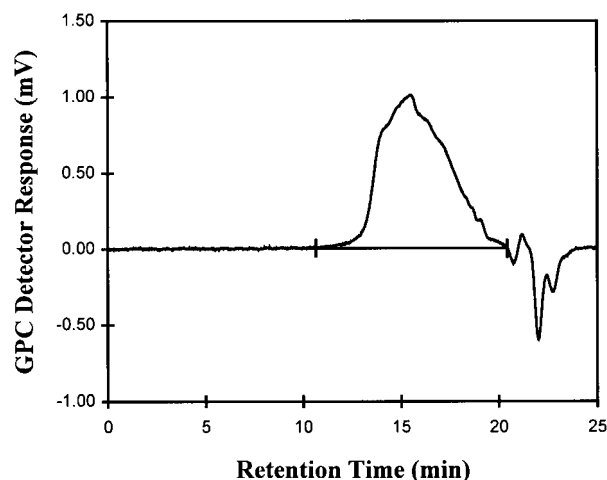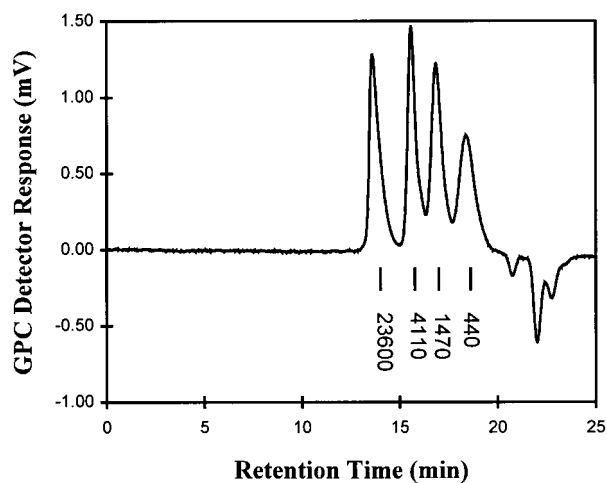
Figure 5 Sample GPC traces of (top) PEG standards and (bottom) copolymer.

length and, therefore, the molecular weight of the copolymer.

The monomer conversion percentage, obtained by GC analysis of the reaction mixture at the end of the reaction, is close to 100% for glycidol and about 95% or greater for epichlorohydrin, so, essentially, all the monomer is converted to polymer. The values of M_n obtained by GPC analysis of the copolymer were all well under 2000 g/mol,

Table I Variation of Copolymer Molecular Weight with Reaction Temperature

Reaction Temperature (°C)	M_n (g/mol)
25	1430
30	1310
35	1250
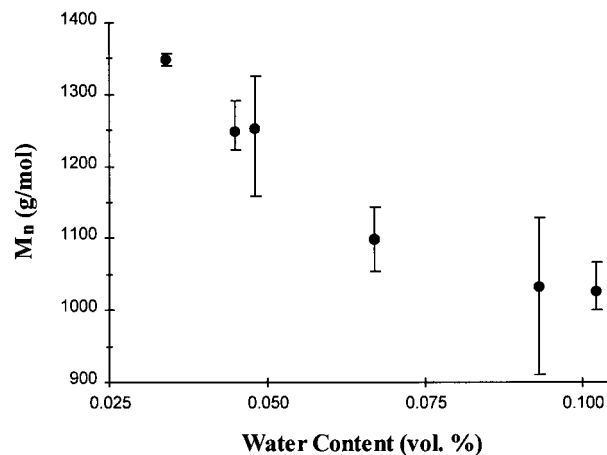
Figure 6 Dependence of copolymer molecular weight on reaction water content.

irrespective of variations in the reaction conditions discussed above. This is in keeping with the observation made by previous workers that considerable branching and ring formation can take place during the cationic polymerization of epoxy monomers in general[6] and glycidol in particular.[5] Both of these processes have the net effect of decreasing the molecular size: branching by decreasing the average end-to-end distance of the copolymer and ring formation by generating low molecular weight species. This, in turn, lowers the value of M_n obtained by GPC, which is a measurement of molecular size.

Vapor-phase osmometry (VPO) was performed on a selected few batches to corroborate the molecular weight data obtained from GPC. In general, the values for M_n obtained by these two vastly different methods correlated reasonably well with each other, as shown in Table II. The values obtained by GPC were always lower than those obtained by VPO, which is consistent with the expected diminution of molecular size as explained above.

Differential scanning calorimetry performed on

Table II Comparison of VPO and GPC Values for Molecular Weight

Sample No.	M_n from VPO (g/mol)	M_n from GPC (g/mol)
1	910	880
2	1430	1210
3	1610	1200
4	1670	1240

the copolymer yielded heat-flow curves completely devoid of any features. The copolymer, being a viscous liquid, is obviously above its melting point, and therefore no melting transitions can be expected in the temperature range examined here. Poly(alkylene oxides), in general, have glass transition temperatures well below room temperature,[10] so it comes as no surprise that these transitions were not observed either.

CONCLUSIONS

Copolymers of epichlorohydrin and glycidol, used as chromatographic coatings, have been produced by boron trifluoride-initiated polymerization in dichloromethane. The pattern of monomer consumption indicates the formation of a block or graft copolymer, with some branching and generation of small ring species. The proposed polymerization mechanism involves cationic oxonium ion intermediates, resulting in the formation of a poly(trimethylene oxide) backbone for the polyglycidol segment and a poly(ethylene oxide) backbone for the polyepichlorohydrin segment.

Molecular weight measured by GPC, which correlated well with molecular weight measured by VPO, was the only measure which was able to discriminate between different batches of polymer; IR, ^{1}H-NMR, mass spectrometry, UV-visible spectroscopy, and elemental analysis were all unable to distinguish between the various batches.

The stirring rate, while strongly affecting the reflux rate of the reaction, did not significantly affect the copolymer molecular weight. Increasing the temperature of the reaction mixture resulted in only a slight decrease in molecular weight. The one factor which strongly influenced the copolymer molecular weight, probably by premature termination of growing chain ends, was the amount of water present in the reaction mixture: The molecular weight varied inversely with the water content.

The viscous reaction mixture had to be stirred vigorously with a mechanical stirrer, especially in the initial stages of the reaction, to keep the exotherm under control. This was particularly important in reactors larger than 22 L, in which case the reactor had to be baffled to promote good mixing, in order to maintain a controlled reflux at the condenser. With efficient stirring, the reaction was scaled up to 500 gal in a 1000 gal reactor with the exotherm well under control, and the copolymer was synthesized safely.

APPENDIX: CAS REGISTRY NUMBERS

Boron trifluoride diethyl etherate, 109-63-7; dichloromethane, 75-09-2; epichlorohydrin, 106-89-8; glycidol, 556-52-5; poly(ethylene glycol), 25322-68-3; tetrahydrofuran, 109-99-9.

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