

Synthesis of an epoxy-based adhesive hydrogel from asymmetrically protected ethylenediamine

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SUMMARY

Poly[aminoethylbutyl ether] (poly-AEBE), a new adhesive hydrogel film bearing primary amine pendants, was synthesized. The key synthetic step, in the synthesis of poly-AEBE, involved a novel use of asymmetrically and reversibly protected ethylenediamine (ED). Initially silylated oligomeric-AEBE was prepared from the reaction of 1,4-butanediol diglycidyl ether with *N,N*-bis(trimethylsilyl)-ethylenediamine. Oligomer crosslinking was initiated by deprotection of the primary amine pendants with excess ethanol, yielding poly-AEBE. When adhered to glass and skin, films of poly-AEBE gave peel forces of 16.90 ± 0.73 N and 1.05 ± 0.15 N, respectively. In addition, poly-AEBE had a high water uptake (1840%) and an equilibrium water content of 94%. The residual water extractables were 3.3%. These results strongly support the potential use of poly-AEBE for adhesive hydrogels and affinity chromatography supports.

INTRODUCTION

Epoxylation reactions of ethylenediamine(ED) can be partially controlled to produce mixtures of *N*; *N,N'*; *N,N*; and *N,N,N'* substituted products. However, only a trace of *N,N*-bis-substituted ethylenediamine is ever produced. A novel approach used by Zhong and Smith (1) has shown that the bis-substituted species could be synthesized as the sole product if ED was first asymmetrically and reversibly protected by *N,N*-bis-silylation. For example, treatment of *N,N*-bis(trimethylsilyl)-ethylenediamine [*N,N*-bis(TMS)ED] with propylene oxide produced *N',N'*-bis(2-hydroxypropyl)-*N,N*-bis(TMS)ED. Subsequent deprotection in ethanol produced *N,N*-bis(2-hydroxypropyl)ED. Based on this observation, we explored the potential use of this protected species in a polymerization reaction with bis-epoxide. Oligomers containing protected groups were initially formed from the reaction of bis-epoxide and selectively protected ED. Deprotection in ethanol generated the primary amine pendants, which crosslinked the polymer. This paper describes the synthesis and physical properties of poly-AEBE.

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MATERIALS

Ethylenediamine, n-butyl lithium, potassium fluoride, 18-Crown-6 ether, chlorotrimethylsilane, 1,4-butanediol diglycidyl ether, 1,1,1,3,3,3-hexamethyldisilazane, o-phthalaldehyde and mercaptoethanol were purchased from Aldrich Chemical Co. (Milwaukee, WI). Ethanol was purchased from Quantum Chemical Co. (Cincinnati, OH). Ethyl acetate and tetrahydrofuran were purchased from Fisher Chemical Co. (Itasca, IL). All reagents were fractionally distilled prior to use.

METHODS

NMR Experiments

All ^{13}C NMR spectra were taken on a Gemini 300 MHz instrument. Swelled poly-AEBE films in d-DMSO were used to obtain liquid state ^{13}C NMR. Solid state ^{13}C NMR experiments were done on a 4.7 Tesla home built spectrometer.

Synthesis of Poly-AEBE

A 250 mL round bottom flask, equipped with a magnetic stirring bar and a reflux condenser, was charged with N,N-bis(TMS)ED (4.57 g, 0.02 mol) and 1,4-butanediol diglycidyl ether (4.53 g, 0.02 mol). N,N-Bis(TMS)ED required for the synthesis was prepared following the methods of Zhong and Smith (1). The flask was maintained at 80°C for 3 hours. Approximately 8 mL THF was added to reduce the viscosity and the solution was maintained for an additional 2 hours. Excess ethanol (30 ml) was added to the solution and stirred for 24 hrs at room temperature, thus initiating the removal of the TMS protective groups and promoting the crosslinking of the oligomeric-AEBE. The solution was then concentrated in vacuo to give a highly viscous, clear and castable polymer. A crosslinked film, approximately one mil thick, was obtained by using a Gardner knife (Gardner Labs, Inc.) to draw out the viscous polymer on a Teflon-coated metal sheet. Poly-AEBE was oven cured at 60-70°C for 2-4 hours. Approximately 8 g of poly-AEBE was obtained. Solid State ^{13}C NMR: 0-5 ppm (6 C), 20-30 ppm (2 C), 43 ppm, 58 ppm, 60-90 ppm (8 C).

Equilibrium Water Content (EWC) and Water Uptake (WU)

The hydration of poly-AEBE can be defined in terms of equilibrium water content. EWC and WU are defined by the following equations:

$$\text{EWC} = \frac{\text{Wt of hydrated material} - \text{Wt of dry material}}{\text{Wt of hydrated material}} \times 100$$

Water uptake is defined as:

$$WU = \frac{\text{Wt of hydrated material} - \text{Wt of dry material}}{\text{Wt of dry material}} \times 100$$

EWC and WU for each polymer was determined by placing 0.4 g of oven dried polymer at 60-70°C in 100 ml water for 24 hours. Hydrated weights of the polymers were obtained after removal of excess water by vacuum filtration. Preliminary experiments in which poly-AEBE was hydrated for 48 and 72 hours showed no change in EWC and WU.

Peel Adhesion at 180° Peel Angle

Poly-AEBE films were immediately used after curing for evaluation of adhesion. No attempts were made to remove any residual TMS groups from the polymer, at this time. Following ASTM standard tests [2], peel adhesion data were obtained with a five kg load cell on an Instron model 1150. The crosshead rate was adjusted to 20 cm·min⁻¹. One mil thick test adhesive strips (1' x 5"), on polyurethane backing, were cut and then adhered to glass or human skin for 2 hours. Skin adhesion tests were approved by the University of Akron Animal Care and Human Welfare Committee. With the subject's consent, three adhesive strips were applied firmly to a shaved section of a forearm. Adhesive strips were peeled from glass or skin at a constant rate, and the peel force (N) was computed using the average of three consecutive samples.

Removal of TMS Protective Groups From Poly-AEBE

Solid state ¹³C NMR of poly-AEBE showed the presence of TMS groups remaining on the polymer. Three methods were attempted to remove the residual TMS protective groups from the polymer. In the first method, silylated oligomeric-AEBE was treated with KF (1 mmol) and 18-Crown-6 ether (2 mmol) in 30 mL ethanol at room temperature for 24 hours. The polymeric solution was filtered to remove KF and concentrated in vacuo to produce poly-AEBE films. In the second method, films of poly-AEBE were washed with a dilute solution of HCL (0.1 M) and then allowed to swell in 50% ethanol for 24 hours. All excess solvents were removed by vacuum filtration and dried at 60-70°C. In the third method, poly-AEBE films were allowed to swell in 0.1 M KOH solution which was vigorously stirred for 24 hours. The polymer was filtered, washed extensively with water and 95% ethanol, and oven dried at 60-70°C. Using solid state ¹³C NMR, all films were analyzed for the presence of TMS groups.

Titration Methods

Poly-AEBE was treated with 0.1 M KOH for 24 hours to ensure complete removal of the TMS protective groups. The poly-AEBE was then washed with ethanol and oven dried at 60-70°C. Primary amine groups in the polymer were selectively modified with o-phthalaldehyde to form a fluorescent

isoindole derivative (3), which was quantitatively measured by UV spectrophotometry. Polymer samples to be derivatized were prepared in a 1 ml cuvette, by adding 250 μL of *o*-phthalaldehyde, 500 μL of mercaptoethanol, 100 mg of finely dispersed poly-AEBE and 150 μL of boric acid buffer (pH 7.5). After one hour at 25°C, the absorbance of the derivatized amine group was determined, at $\lambda = 337 \text{ nm}$. An extinction coefficient of $7.66 \text{ M}^{-1} \cdot \text{cm}^{-1}$ was used in calculations.

RESULTS AND DISCUSSION

The stoichiometric addition of the monomers, 1,4-butanediol diglycidyl ether and *N,N*-bis(TMS)ED in THF at 80°C for five hours produced silylated oligomeric-AEBE (Figure 1, Step I). Ethanol initiated the removal of TMS groups from the oligomer, and subsequently catalyzed the crosslinking of the resulting reactive primary amines with residual epoxide groups (Figure 1, Step II). Crosslinking resulted in a highly viscous polymeric material which was easily castable. Films were cured at 60-70°C for two hours to remove excess solvents and ethoxy-trimethylsilane.

The physical properties of poly-AEBE films are presented in Table 1. The adhesion of poly-AEBE to both glass and skin was determined according to ASTM standards following the

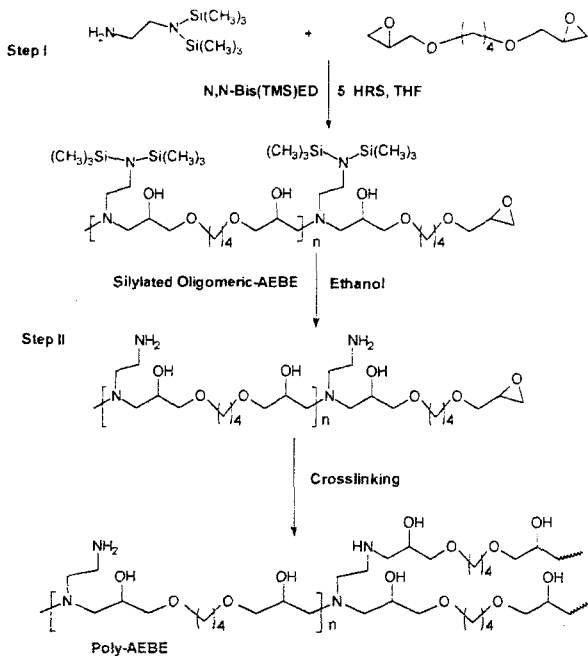


Figure 1. Synthesis of Poly-AEBE

procedure used in Mascarenhas, et al. [4]. Poly-AEBE had good adhesion to glass and skin with calculated peel forces of 16.90 ± 0.73 N and 1.05 ± 0.15 N, respectively. In comparison, peel adhesion forces of previously tested acrylate-based adhesives were lower for glass, ranging from 4.90 ± 0.58 N (Tegaderm[®]) to 11.56 ± 0.34 N (Semex[®]) and comparable for skin, ranging from 0.79 N (HyTape[®]) to 2.64 N (Semex[®]) (4).

Hydrophilic properties of the films were also investigated. When fully hydrated, poly-AEBE showed a WU of 1840% and EWC of 94%. Although a water absorption rate study was not performed, these poly-AEBE films were totally hydrated within six hours. Hydrated films completely lose their adhesive properties. When extracted with water for 24 hours, poly-AEBE films showed extremely low extractables, ranging from 3-3.5%. This suggests a very high efficiency of crosslinking, since the silylated oligomeric-AEBE was initially water soluble.

Peel Adhesion Peel Forces (N)		Equilibrium Water Content %	Water Uptake %	Water Extractables %	Primary Amine Titration
Skin	Glass				
1.05 ± 0.15	16.90 ± 0.73	94	1840	3.30	0.80

Table 1. Physical Properties of Poly-AEBE

Chemical derivatization methods and ¹³C NMR were used to determine the structure of poly-AEBE, in particular, the crosslinking density. The presence of a peak at 0-5 ppm from the spectroscopic analysis using solid state NMR of poly-AEBE suggests the presence of TMS groups (see figure 2A). Based on this spectroscopic evidence, approximately 43% of the TMS groups remained on poly-AEBE. Extensive swelling and washing of poly-AEBE with ethanol did not remove the TMS groups from the polymer. Therefore, various methods were attempted to completely remove the TMS groups from poly-AEBE. Treatment of silylated oligomeric-AEBE with an excess of KF in 18-Crown-6 ether or washing the polymeric film with a dilute hydrochloric acid solution in ethanol did not remove the TMS groups. However, KOH treatment of poly-AEBE films completely removed all traces of TMS groups (Figure 2B). The physical properties and the integrity of the polymeric film after KOH treatment could not be retained. Since the TMS groups are difficult to remove from the polymer, it is possible that these groups may have been transferred to the hydroxyl groups on the polymer backbone. Evidence for N to O trans-silylation was obtained using ¹³C liquid state NMR. Spectroscopic evidence from quantitative ¹³C showed

the presence of a doublet at 0-5 ppm with equal sized peaks, suggesting that half the TMS groups were transferred to hydroxyl groups on the polymer backbone.

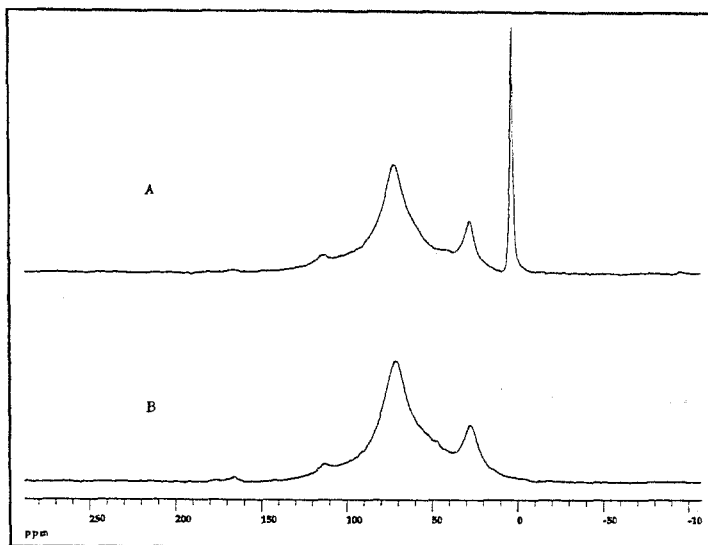


Figure 2. [A] Typical solid state ^{13}C NMR of poly-AEBE. [B] NMR spectra of base treated films

The percent crosslinking of the polymer was determined by measuring the density of the primary amine groups per repeating unit of the polymer. Selective modification of the primary amine groups to give an isoindole derivative was achieved using o-phthalaldehyde, and the concentration of the primary amine was determined. From the spectroscopic data, the calculated ratio of primary amine groups per repeating unit was 0.80, therefore the remaining 0.2 (e.g. 20%) of primary amine groups must have participated in crosslinking, resulting in a polymeric film.

CONCLUSION

Synthesis of poly-AEBE involved a novel asymmetrically protected ethylenediamine which upon deprotection generated repeating primary amine pendants. The attractive features of the newly synthesized polymer include high water absorbency, good adhesive properties and low water extractables. The available amines on the polymer backbone make it possible to derivatize poly-AEBE into a biospecific affinity support having almost any desired property. Furthermore, a variety of affinity supports using poly-AEBE could be developed by

taking advantage of biospecific, immunological, charge transfer, metal chelate and dye ligand interactions.

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