Preparation of PEO with Amine and Sulfadiazine End Groups by Anion Ring-Opening Polymerization of Ethylene Oxide

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SYNOPSIS

Polyethylene oxides with amine and sulfadiazine end groups (PEO_{a-sf}) were prepared by alkoxy-anion ring-opening polymerization of ethylene oxide (EO); the potassium aminoethoxide with a protected amino group was used as initiator. The living polyethylene oxide anions was terminated by methanol first, then the separated polymer was continuously reacted to bromacetic acid in the presence of metal sodium. After that the purified intermediate was reacted sequentially with benzoyl chloride and sulfadiazine, then hydrolyzed with acetic acid. The final product PEO_{a-sf} and all intermediates are characterized in detail by IR, NMR, GPC, and chemical analysis; the effect of reaction conditions on the preparation of polyethylene oxides with various functional end groups are discussed. © 1996 John Wiley & Sons, Inc.

Keywords: polyethylene oxide • anionic polymerization • aminoethanol • amine • sulfadiazine

INTRODUCTION

Currently much attention has been focused on the attachment of drugs to polymers backbone because of the drug-release polymers increasing the duration of drug activity through slow release, or of target-directing function of polymer drugs in the body.[1-3] Polyethylene oxides (PEOs) were chosen as carrier polymer due to their unique properties; they are nontoxic,[4] nonantigenic, and biocompatible, soluble in water and organic solvents, and possess a solubilizing action and complexing ability with alkali metal ions.[5]

Various drugs have been attached to PEO such as procaine,[6] atropine,[7] various salicylates,[8] penicillin V, aspirin, amphetamine, and quinidine.[9] These kinds of polymer-drugs showed a longer duration of activity due to the slow release of the drug. Insulin as well as various enzymes have also been attached to PEG, leading to products which retain their biological and enzymatic activity.[10]

However, most of these PEOs are limited to homobifunctional polymers (e.g., PEO with primary amine at both ends) and polymers with only one reactive end group (e.g., PEO with hydroxyl or amine and methoxy end groups respectively). If it is possible to attach different functional end groups in PEO, many useful materials could be devised and prepared, however due to the difficulty of separation of the reacted mixture,[11] great achievements have not yet been made.

In previous work, we reported the preparation of PEG with different functional end groups using PVA as matrix,[12,13] but the process is complicated and time-consuming. The whole synthesis lasted about 3 weeks, and the yield was not high.

Recently, the anion ring-opening polymerization of EO was used for preparing the PEO containing antitumor drug structure on one end and sulfadiazine structure on another end. Comparing the method of polymer matrix,[12] the current synthesis procedure is simpler and more efficient. We intended to covalently fasten the antitumor drug and sulfa-

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Journal of Polymer Science: Part A: Polymer Chemistry, Vol. 34, 1933–1940 (1996)
 CCC 0887-624X/96/101933-08

diazine which has proven to be concentrated on the tumor cell[14] on different ends of PEO, and explored its biological behavior in the body.

This article reports the first part of our research, i.e., the preparation and characterization of PEO_{a-sf}. The attachment of antitumor drug to the amine end group of PEO_{a-sf}, and the pharmacological properties of this kind of drugs will be reported in the forthcoming studies.

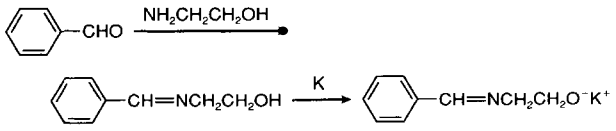
EXPERIMENTAL

Materials

Benzaldehyde (YiXing Auxiliary Reagent Factory, JianShu, China), aminoethanol (Shanghai Third Reagent Factory, China), and benzoyl chloride (Chemical Factory of Shanghai Chemical Reagent Station, China) were purified by distillation under reduced pressure, the fractions of 96°C/5 mm Hg for benzaldehyde, 90°C/10 mm Hg for aminoethanol, and 122°C/5 mm Hg for benzoyl chloride were collected, respectively. Ethylene oxide (Shanghai First Reagent Factory, China) and tetrafuran (THF) were dried by CaH_2, then distilled before use. Bromacetic acid (KunShan NianSha Auxiliary Factory, China) was recrystallized by petroleum ether, the melting point of purified sample is 50°C. Sulfadiazine (Shanghai Second Pharmaceutical Factory) was purified by a solvent mixture of dimethyl sulfoxide (DMSO) and alcohol (v/v: 9/1). The decomposition temperature of the purified sample was 250–253°C. All other solvents were purified by standard procedures.

Preparation of Initiator

The preparation of initiator of potassium *N*-benzylideneamino-ethoxide (BAE-k) was carried out following two steps:



NH_2-Protection of Aminoethanol

In a 1000 mL four-neck flask equipped with a thermometer, condenser, and dropping funnel, 106 g (1 mol) of benzaldehyde was introduced, then 61.1 g (1 mol) aminoethanol was added dropwise in 40 min with magnetic stirring under N_2. The reaction lasted about 12 h at room temperature. After the end of the reaction, 500 mL of benzene was added to extract the product. The upper was separated and dried with anhydrous sodium sulfate for 12 h. The transparent liquid product (*N*-benzylideneaminoethoxide) (BAE) with light yellow color was obtained by distillation under reduced pressure (162–166°C/20 mm Hg) with a yield of 65%.

ANAL. Calcd for $C_9H_{11}NO$: C, 72.48%; H, 7.38%; N, 9.40%. Found: C, 72.86%; H, 7.66%; N, 9.13%.

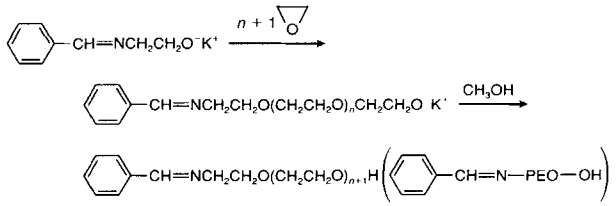
IR (cm^{-1}): 3351 (OH), 1641 (C=N), 1600 and 1578 (phenyl ring). ^{1}H-NMR ($CDCl_3$, ppm): 8.24 (—CH=N), 7.26–7.8 (phenyl ring), 3.1 (—OH).

Preparation of BAE-k

To a 100 mL ampoule containing 30 mL of dried toluene 11 g BAE (0.074 mol) was added, then 3 g (0.077 mol) metal potassium with fresh surface was introduced. After three cycles of freezing at 77 K and thawing under a vacuum system, the sealed ampoule was magnetically stirred for 24 h at room temperature. The solution color was changed from a light yellow in the beginning to dark red at the end, then stored in the refrigerator for use.

Polymerization of EO

The polymerization of EO was conducted on the following route:

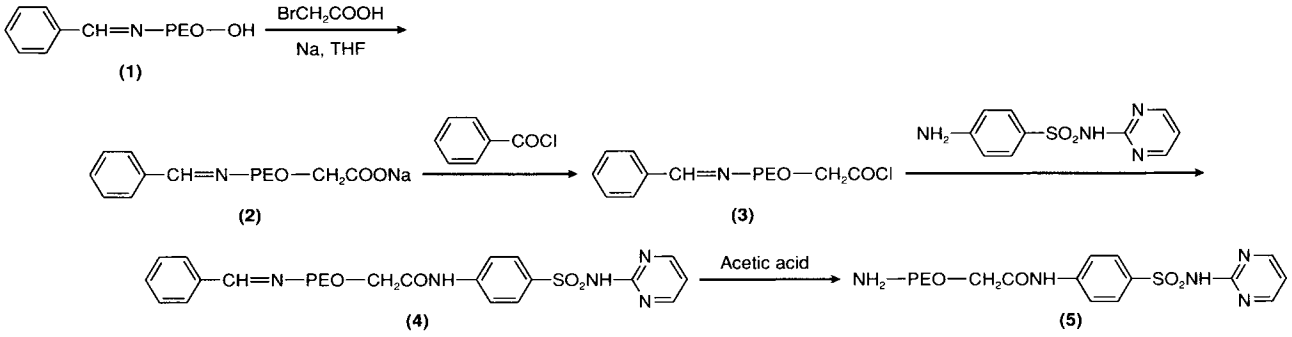


To a 100 mL ampoule which was demoistured, 1 mL of BAE-k toluene solution and 10 mL of EO were added by syringe. After sealing, the ampoule was placed in the room temperature for 10 h, and then put into a 40°C oil bath for 15 h. The viscosity of the polymerized system was so high that it was difficult to pour out the reaction product. The polymerization was terminated by the addition of 5 mL of methanol; 20 mL of chloroform was then added to dissolve the reaction product. The final product was obtained by precipitation in ether with a conversion of 97%. The PEO with end groups of Schiff's base (PEO_s) and hydroxyl could be purified by redissolving in dichloromethane and reprecipitation in ether with a yield of

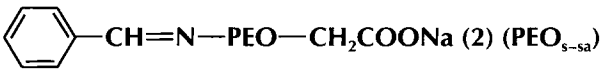
84%. The characterization of the product was as follows: IR (cm^{-1}): 1115 (C—O—C). UV (nm): 285 ($\pi \rightarrow \pi^*$ transition of phenyl ring). ^1H NMR (ppm): 3.64 ($-CH_2CH_2O-$), 7.24–7.36 (phenyl ring).

Preparation of PEO_{a-sf}

The object product of PEO_{a-sf} was synthesized according to the following reaction steps:

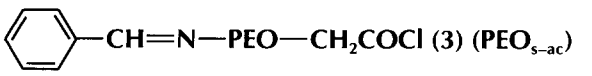


Preparation of



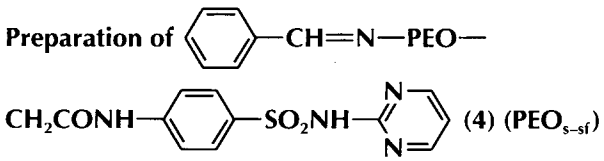
To a 500 mL four-neck flask equipped with mechanical stirrer, condenser, thermometer, and dropping funnel, 16 g (0.013 mol) of prepolymer PEO_s dissolved in 200 mL THF was added, then 0.8 g (0.015 mol) of metal sodium with a fresh surface was introduced. The contents were refluxed about 1 h, then cooled to 0°C in the ice bath. After that, 2.2 g (0.015 mol) of bromacetic acid in 20 mL THF was added dropwise to the flask in 50 min, then refluxed about 5 h. The reacted mixture was filtrated and the filtrate was concentrated to about 50 mL, then precipitated with ether. The product could be purified by dissolution in chloroform and reprecipitation in ether in a yield of 85%. IR (cm^{-1}): 1599 (—COONa). ^1H-NMR (ppm): 10.1 (—COOH) for acidized sample of **2** with 1*N* HCl to ph 7.5, and 2.03 (—OH) for **1** disappeared.

Preparation of



To a 250 mL flask with three necks fitted with a thermometer and condenser, 16 g **2** (0.0089 mol) and 30 mL (0.255 mol) of benzoyl chloride were added with magnetic stirring. The reaction lasted about 5 h at room temperature and 1 mL of the reacted product was withdrawn to precipitate with ether for characterization; excess benzoyl chloride distilled out under reduced pressure, the remaining were dissolved in 90 mL DMF for the next reaction. The intermediate product **3** did not separate from the reacted mixture due to its high reactivity.

Preparation of

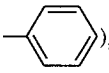


To a 250 mL flask with four necks fitted with a condenser, dropping funnel, and mechanical stirrer, 4 g (0.016 mol) of sulfadiazine dissolved in 30 mL DMF and 1.5 g (0.018 mol) of $NaHCO_3$ were added; then intermediate acid chloride **3** in 90 mL DMF was introduced dropwise with stirring for 45 min. The flask was placed into the bath at 60°C for 8 h under N_2. After that, the reacted product was poured into 500 mL chloroform slowly with stirring, then filtrated to remove the unreacted sulfadiazine and other by-products. The filtrate was concentrated to 50 mL, and precipitated with ether. The product could be purified by dissolution in chloroform and reprecipitation in ether with a yield of 73.5%. IR (cm^{-1}): 1720 (—CONH—), 1601, 1583 (1,4-bis-substituted phenyl ring). ^1H-NMR (ppm): 8.04–8.07 (pyrimidinyl ring), 7.2–7.5 (phenyl ring).

Deprotection of Amine End Group of PEO_{s-sf} and Formation of PEO_{a-sf} (5)

Twelve grams (0.01 mol) of PEO_{s-sf} was dissolved into 20 mL methanol, then 20 mL of acetic acid was added with stirring, the acidolysis was conducted at room temperature for 24 h, and the product (PEO_{a-sf})

Table I. Characterization of PEO_{s-ac}

Sample	UV (nm)	IR (cm^{-1})	^{1}H-NMR (ppm)
PEO_{s-ac}[a]	242	3351, 3270 (—NH_2), 1753 (—COOH), 1116 (—CH_2CH_2O—)	2.41 (s, —NH_2) 3.64 (m, —CH_2CH_2O—)
PEO_s	241	3442 (—OH), 3349, 3283 (—NH_2), 1119 (—CH_2CH_2O—)	2.03 (s, —OH), 2.40 (s, —NH_2), 3.64 (m, —CH_2CH_2O—)
PEO_{s-ac}[b]	285	1755 (—COOH), 1598, 1576 (— ), 1120 (—CH_2CH_2O—)	3.63 (m, —CH_2CH_2O—), 7.2–7.3 (m, — ),

[a] Sample formed by direct addition of bromacetic acid to polymerization system.
[b] Sample formed by two steps.

was precipitated with ether and purified with chloroform/ether in a yield of 58.9%.

Measurements

UV spectra were recorded on a Beckman DU-7 spectrometer. IR spectra were obtained on a Perkin-Elmer 983 G IR spectrometer. ^{1}H-NMR spectra were scanned on a Varian XL-300 NMR spectrometer with TMS as internal standard and $CDCl_3$ as solvent. The molecular weight and molecular weight distribution of the product and intermediates were measured by GPC which has been described in the previous paper.[15] The presence of hydroxyl[16] and amino end groups,[9] and the molecular weight of PEOs could also be checked by chemical titration.[9]

RESULTS AND DISCUSSION

Two-Step Reaction in the Preparation of PEO_{s-sa}

As is well known in the anionic polymerization, the functionalization of end group of the propagating species could be carried out by selecting the suitable terminating agent,[17] so it does not need to separate the polymer in advance, then functionized in a common procedure. However, in the preparation of PEO_{s-sa}, it was found that if the bromacetic acid was introduced directly to terminate the propagating oxoanionic species, some following by-reactions may occur:

1. Schiff's base-protected groups were broken, and amine groups were recovered. This could be confirmed by the variation of its UV, IR, and NMR spectra of functional groups before and after the reaction, as shown in Table I. Since the acidity of bromacetic acid is stronger than acetic acid, it is reasonable that the Schiff's base would be broken in the presence of bromacetic acid.
2. PEO was degradated, i.e. the PEO chain was cleaved since the molecular weight of PEO changed from original 1.2×10^3 [Fig. 1(A)] to 800 after the reaction, as shown in Figure 1(B). Therefore, it could be concluded that in the preparation of PEO_{s-sa}, the procedure of direct addition of bromacetic acid to terminate PEO macrospecies is unsuitable.

Thus, a two-step reaction via separating the PEO prepolymer from the polymerization system first, and then functionizing with bromacetic acid is preferable. Table I and Figure 1(C) showed that the capped Schiff's base group and the molecular weight of PEO are left intact in this procedure.

Acylchloration of PEO_{s-sa}

Thionyl chloride is a common acylchlorating agent, but when it was used in acylchloration of PEO_{s-sa}, no satisfied results could be obtained. It was also found the missing Schiff's base groups and the cleavage of PEO chains [Fig. 2(A)] as in the case of the preparation of PEO_{s-sa} by direct addition of bromacetic acid. Therefore benzoyl chloride was used to

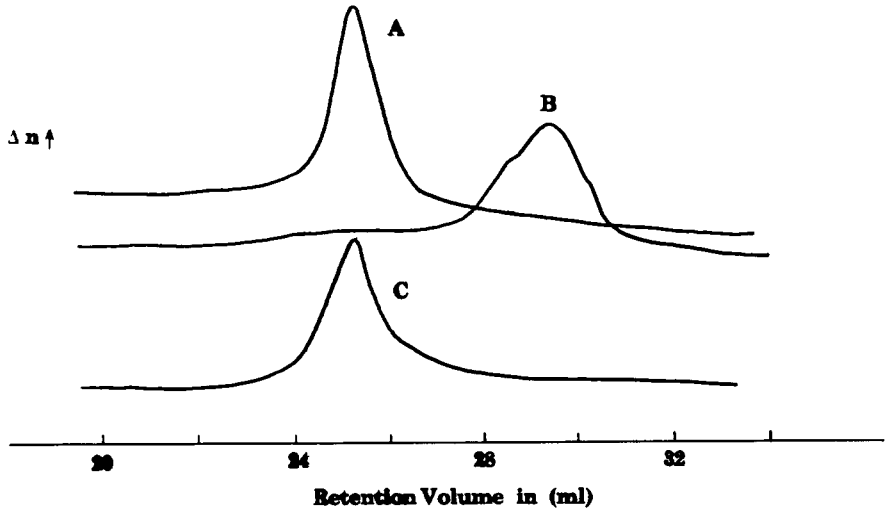


Figure 1. GPC measurement of molecular weight of PEO_{s-sa} (A) before and (B) after direct addition of bromacetic acid.

substitute the thionyl chloride. The IR spectra of (A) PEO_{s-sa} and acylchlorating product (B) (PEO_{s-ac}) are shown in Figure 3. The appearance of specific CO — Cl peak at 715 cm^{-1} for acylchlorating PEO_{s-sa} and 1603 and 1580 cm^{-1} attributed to phenyl ring confirmed the success of the reaction and the presence of Schiff's base end group. GPC data [Fig. 2(B)] also showed that no cleavage of PEO could be detected in the case of benzoyl chloride used as acylchlorating agent. PEO_{s-ac} was not purified further for the next reaction because: (1) PEO_{ac} is very reactive and very easy to hydrolyze, and (2) excess benzoyl chloride will not exert any effect on the following reaction. The by-product formed by the reaction of bynzoyl chloride and sulfadiazine could be removed in the purification of PEO_{s-sf} via the procedure of precipitation and dissolution.

Characterization of PEO_{s-sf}

The reaction between PEO_{s-ac} and sulfadiazine was carried out in DMF and in the condition of sulfadiazine in excess. The impurities including the unreacted sulfadiazine and by-product of above-mentioned reaction did not dissolve in chloroform. Thus, it is easy to remove them in the purification of PEO_{s-sf} by chloro-

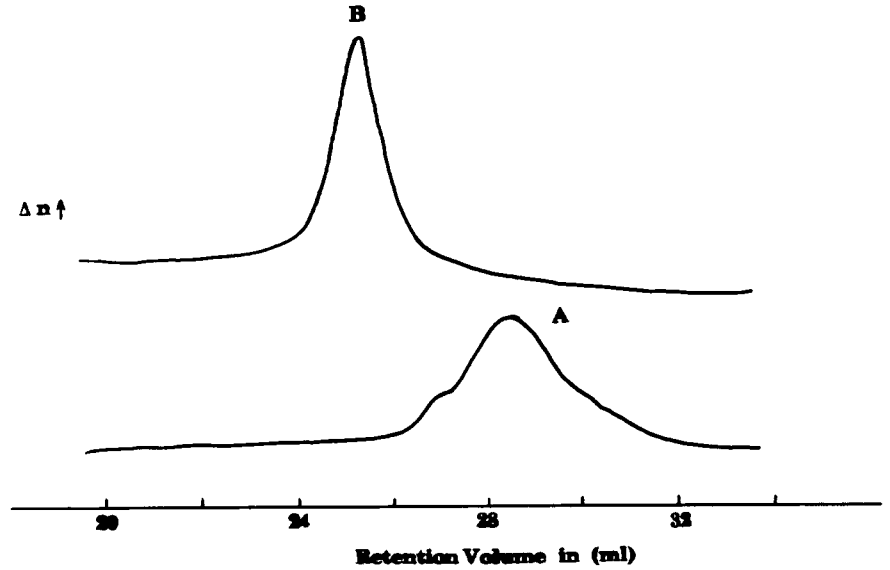


Figure 2. GPC measurement of molecular weight of acylchlorating PEO_{s-sa} with (A) thionyl chloride and (B) benzoyl chloride.

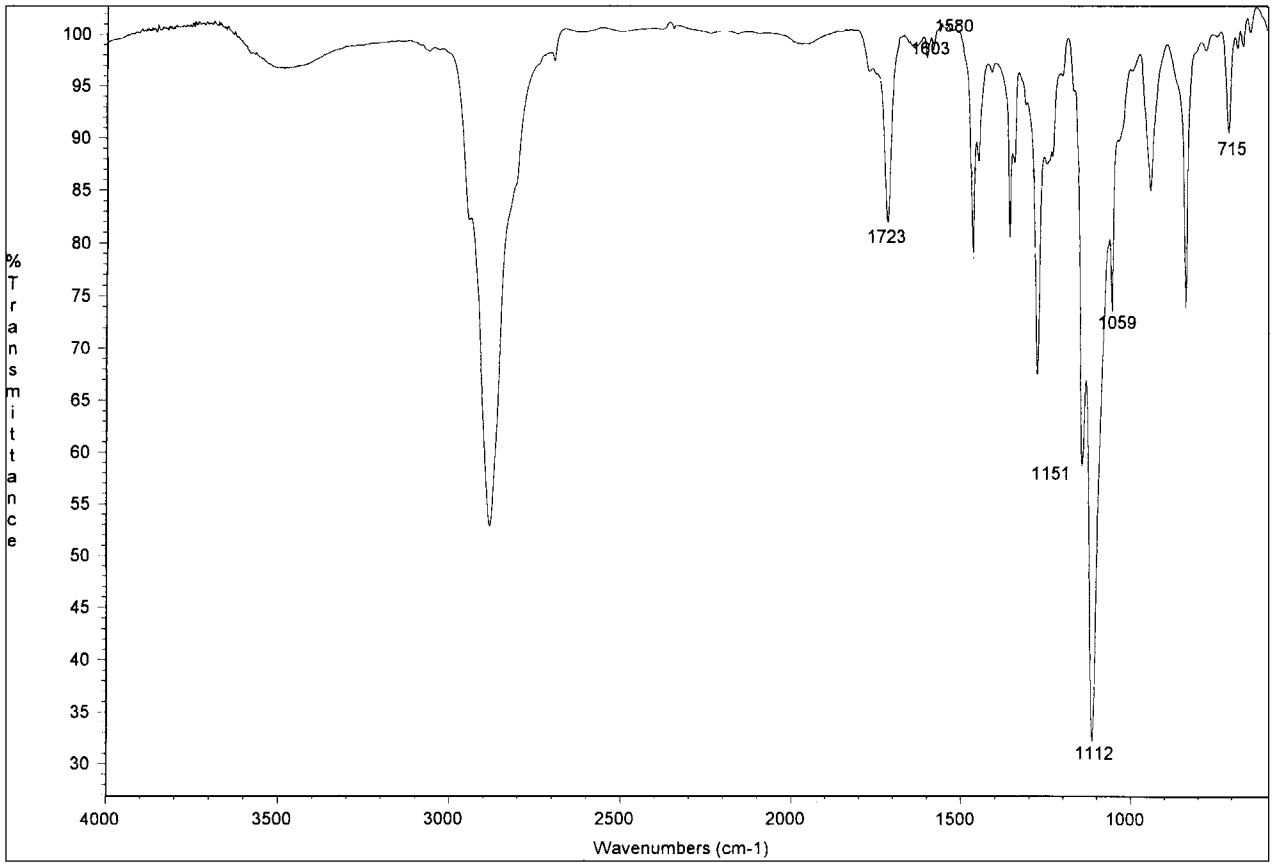


Figure 3. IR spectra of PEO_{s-ss} (A) before and (B) after acylchloration with benzoyl chloride.

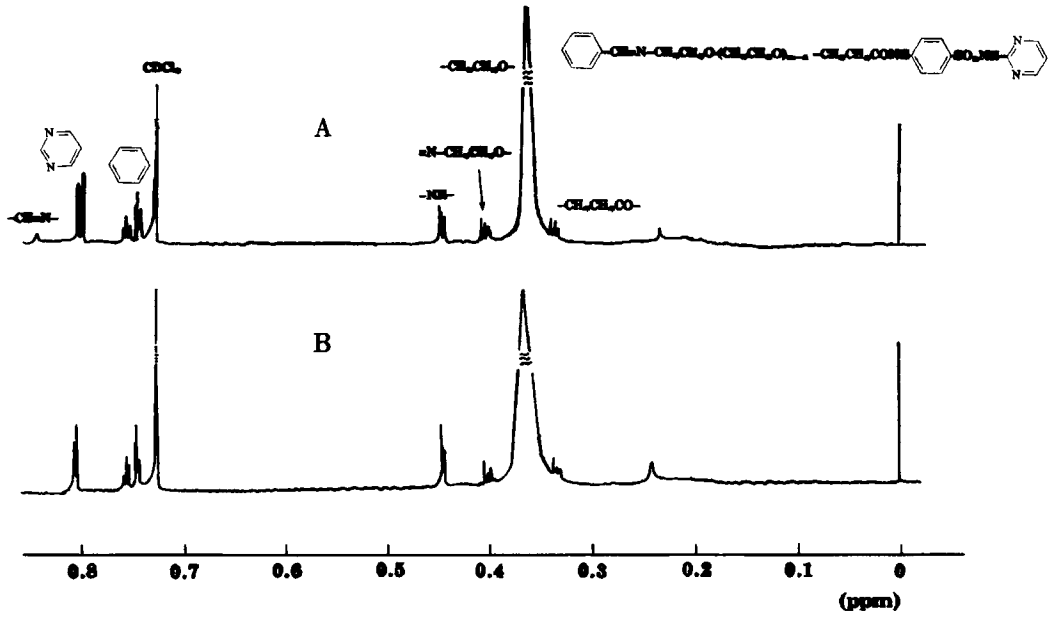


Figure 4. ^{1}H-NMR spectra of PEO_{s-sf} formed in DMF (A) before and (B) after acidolysis.

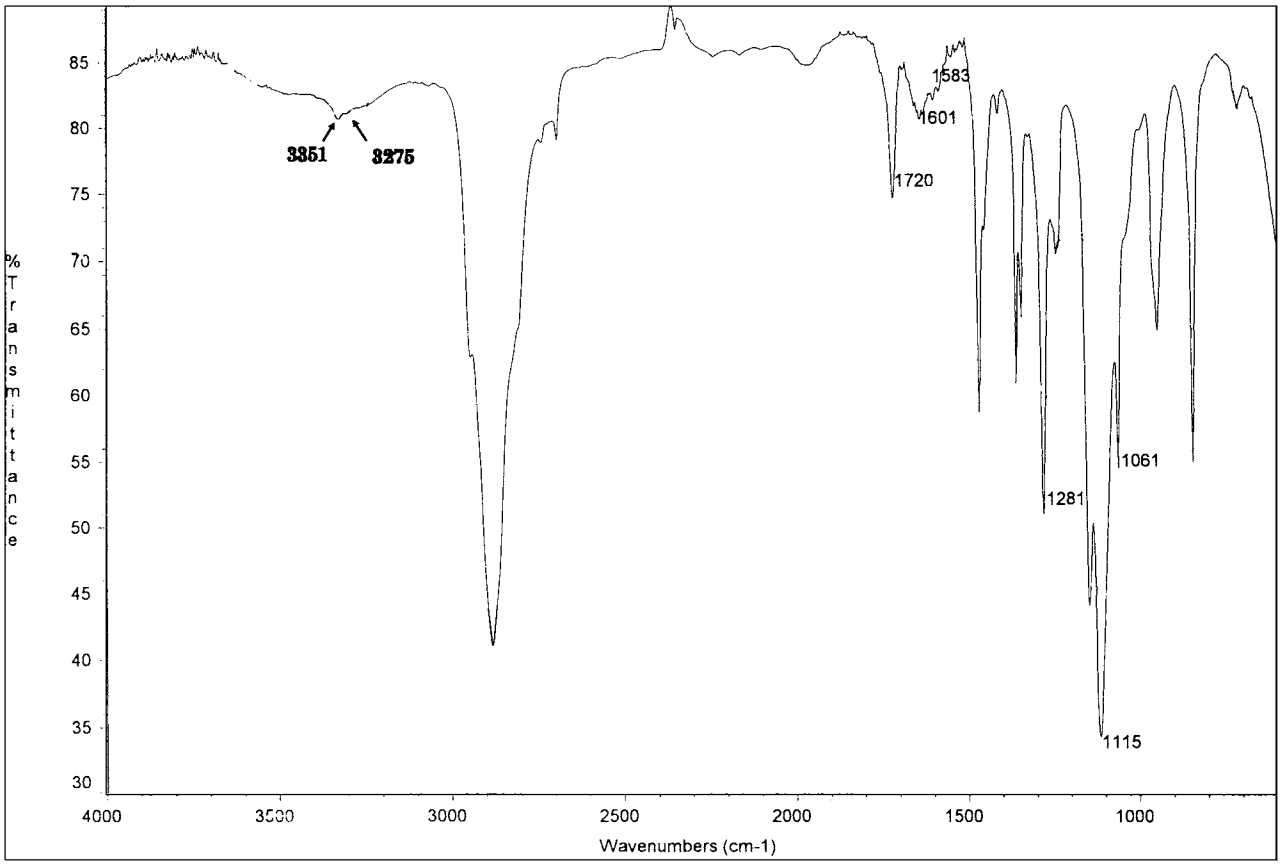


Figure 5. IR spectrum of PEO_{s-sf} formed in DMSO.

form/ether. Figure 4(A) indicated the ^{1}H-NMR of purified PEO_{s-sf} from which, except for the peak at 2.4 ppm, we could find all corresponding proton resonance signals of phenyl, pyrimidinyl, and $-CH_2CH_2O-$ that are identical with the structure of the expected object polymer PEO_{s-sf}. However, what are the specific groups corresponding to the chemical shift at 2.4 ppm, and which were subsequently identified? Comparing the NMR spectra [Fig. 4(B)] before and after acidolysis of PEO_{s-sf}, it was found that in the latter spectrum, the peak at 2.4 ppm appeared as well, where its integrated area is stronger than that of Figure 4(A). In addition, the peak at 8.24 ppm attributed to $-CH=N-$ for Schiff's base entirely disappeared after acidolysis. Thus, the peak at 2.4 ppm came from the amine groups formed by cleavage of Schiff's base group. In the reaction of PEO_{s-ac} with sulfadiazine, some hydrogen chlorides would also be produced, although a large part of it has been absorbed by DMF, but it is still possible for some unabsorbed hydrogen chlorides to induce Schiffs base to decompose. To confirm this hypothesis, DMSO, its basic capacity less than DMF, was used as solvent. Thus if our explanation for the appearance of the peak of 2.4 ppm in Figure 4(A) is correct, then when DMSO was used, the peak at 2.4 ppm would be much stronger than that in the case of DMF because of the thorough decomposition of Schiff's base end group. Figures 5 and 6 indicate the IR and ^{1}H-NMR spectra of the product formed by the reaction of PEO_{s-ac} and sulfadiazine in DMSO, the appearance of strong peak at 2.4 ppm and double peaks at 3351 and 3275 cm^{-1} in IR, and the disappearance of 8.24 ppm attributed to $-CH=N-$ for Schiff's base in NMR firmly confirmed our hypothesis by the existence of amine group. Thus, when DMSO and not DMF was used as solvent for the reaction between PEO_{s-ac} and sulfadiazine, the amine groups would also be produced. Therefore, the final product of PEO_{a-sf} could be obtained by a one-step reaction of PEO_{ac} and sulfadiazine in DMSO; further acidolysis for PEO_{s-sf} is unnecessary.

CONCLUSIONS

PEO with amine and sulfadiazine end groups at both ends are synthesized by anion ring-opening poly-

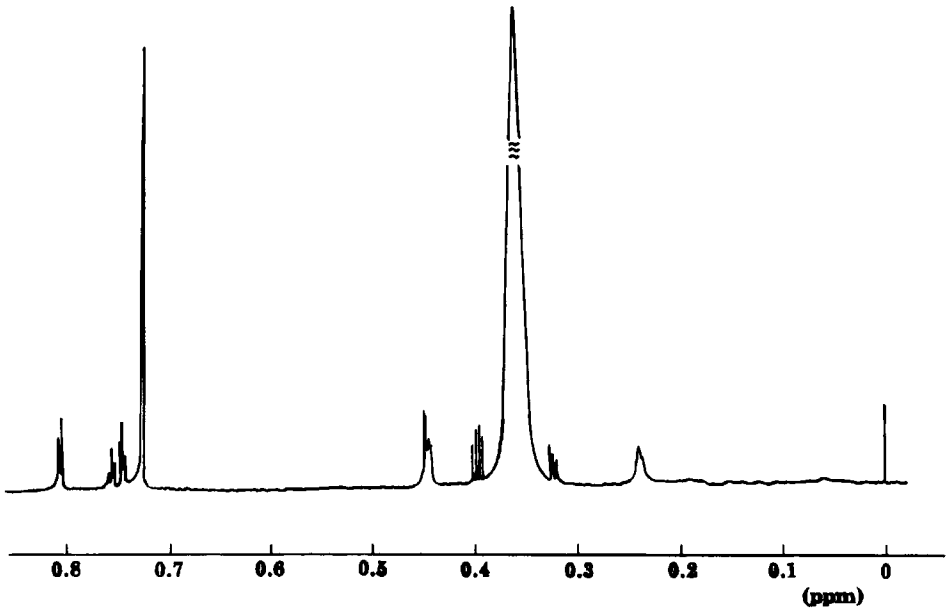


Figure 6. ^{1}H-NMR spectrum of PEO_{s-sf} formed in DMSO.

merization of ethylene oxide using protected potassium aminoethoxide as initiator and variation of end groups by functional agents. The functionization of end groups can not be carried out by the addition of functional agent to living polymerization system due to the instability of protected groups and cleavage of PEO chain in strong reaction conditions. The object product of PEO_{a-sf} could be obtained by sequential reaction of prepolymer PEO_s with bromacetic acid in the presence of metal sodium, benzoyl chloride, and sulfadiazine, and then acidolysis. If DMSO was used as solvent to replace DMF, the last two-step reactions was replaced by a single reaction.

This work was financially supported by the National Natural Science Foundation of China (Grant No. 29444003), Foundation of Doctor Training of State Education Committee of China, and Shanghai Local Natural Science Foundation, which is gratefully acknowledged.

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Received August 14, 1995
Accepted December 18, 1995