# Ring-Opening Polymerization of Ethylene Oxide by Anion Initiation Using Sulfadiazine as Parents Compound

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SYNOPSIS

A new kind of anion initiator using sulfadiazine as the parent compound was prepared by the reaction of sulfadiazine with epoxy ethylene, and then the metal potassium. The structure of the intermediate was characterized in detail by NMR, MS, UV, IR, and DSC. Ring-opening polymerization of epoxy ethylene could be carried out by this initiation system. The molecular weight of the polymerized product, polyethylene oxide with a sulfadiazine end group ($PEO_{sf}$), is in the range of 3000–4000. © 1995 John Wiley & Sons, Inc.

## INTRODUCTION

Currently there is much interest in the attachment of medicines to polymers as a way to increase the duration of activity through slow release, or of target-directing medicine in the body. However, in the reaction of medicine with the polymer, that is, with the reactive functional groups of polymer, the yield is generally very low since the reactive groups were wrapped up due to the curling and entanglement of the polymer chain. In addition, it is not always possible for the polymer to supply a suitable functional group to react to the small molecules of the medicines and at the same time to maintain the biological activity of the medicine molecule. Therefore many methods were used, for example, selecting the good solvents as reaction medium to make the polymer chain extend fully and introducing highly reactive groups to increase the reaction activities between medicine and polymer. However, these procedures are complicated and overelaborate.

It has been noticed that many medicine molecules could be directly turned into initiators via their variation of reactive groups, with the premise of retaining pharmacological activity. For example, Rifampin[1] with a tertiary amino group is a kind of antibiotic. When it is mixed with benzoyl peroxide, a binary initiation system is constituted, which can successfully initiate hydroxyethyl methacrylate and *N*-vinyl pyrrolidone to polymerize. In the product, the Rifampin was covered with polymer and showed a longer duration of pharmacological activity. Another example is Perphemnazium, which is an antipsychotic. It can be turned into an anion by the reaction of its hydroxyethyl group with an alkali metal, then initiate such monomers as cyclic ether and lactone to polymerize.[2] The product also showed a slow release function.

Judging from this, if it is possible to find a method to turn medicine into an initiator and, simultaneously, to keep its pharmacological activity, the problem of low yield in the attachment of medicine molecules to polymer may be resolved. Moreover, by means of this method it would be a very easy procedure to control the contents of medicine in polymer and the release duration via the selection of the concentration of the initiator and polymerization conditions.

In this paper we report the synthesis and initiation properties of this kind of anion initiator using sulfadiazine as the parent compound, which has been proved to be concentrated selectively in the Walker carcinoma growing in rats.[3] Therefore polymeric sulfadiazine is not only a kind of slow release drug, but also a very good model compound for research in target-directing drugs.

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## EXPERIMENTAL

### Materials

Sulfadiazine was purchased from Shanghai Eleventh Pharmaceutical Factory, and recrystallized from the mixing solvents consisting of dimethyl sulfone and ethanol (v/v, 1 : 9). Ethylene oxide (EO) and tetrahydrofuran (THF) were dried with calcium hydride, then distilled under $N_2$ atmosphere before use. All other solvents were purified by standard procedure.

### Preparation of 4-Amino-*N*-hydroxyethyl-*N*-(2-pyrimidinyl)benzene Sulfonamide (AHPBS)

To a 100-mL ampoule containing 5 g (0.02 mol) of purified sulfadiazine, 20 mL of EO was added by a syringe. After sealing, the ampoule was placed in an oil bath at 60°C. The reaction lasted about 9 days. The product extracted with ether is a powder with a yellow color. The unreacted sulfadiazine could be removed by adding the dilute NaOH (0.5*N*) into the rude AHPBS; the NaOH will react with the amido group of sulfadiazine to form a water-soluble salt. The yield of purified AHPBS: 5.1 g (87.4%), mp: 225°C. Elemental analysis: found: C 48.14, H 4.03, N 18.84, S 10.22; calc.: C 48.98, H 4.76, N 19.05, S 10.88; molecular formula: $C_{12}H_{14}N_4SO_3$.

### Preparation of 4-Amino-*N*-ethoxypotassium-*N*-(2-pyrimidinyl)benzene Sulfonamide (AHPBS-k)

AHPBS (0.75 g, 0.026 mol) and THF (30 mL) were added to a specially designed 100-mL ampoule with a condenser, then potassium (0.3 g, 0.082 mol) with a fresh surface was added. The inlet was tightly slipped with a rubber tube (wall thickness 8 mm) and linked to the vacuum system for deaeration. After three cycles of freezing at 77 K and thawing, the rubber tube linked to the inlet of the ampoule was gripped with a pincer, then cut down. The reactor was magnetically stirred for 24 h at 60°C, then cooled to room temperature and stored in a refrigerator. The product is a brown suspending liquid.

### Anion Ring-Opening Polymerization of Ethylene Oxide

A 100-mL ampoule was deaerated in the vacuum system, then 1 mL of an AHPBS-k THF suspending solution and 20 mL of EO were added. After sealing, the ampoule was placed in an oil bath at a given temperature. At the beginning of the polymerization, AHPBS-k did not dissolve in EO, so it was in the bottom of the ampoule, but the solid AHPBS-k disappeared toward the end of the reaction, which means that $PEO_{sf}$ could be dissolved in THF and EO. The reaction was stopped by adding methanol (5 mL) after a suitable time, then precipitated with ether. The polymer could be purified by dissolution in chloroform and reprecipitation in ether. The purified product is a powder with a light yellow color; yield: 6.1 g (conversion 34%).

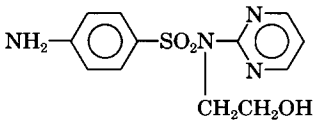
### Instruments

IR spectra were recorded on a Perkin-Elmer 983 G IR spectrometer; UV spectra were scanned on a Backman DU-7 spectrometer; $^1$H-NMR spectra were obtained on a Varian XL-300 NMR spectrometer with TMS as an internal standard and $CDCl_3$ and DMSO-$d_6$ as solvents; MS spectra were measured with DIP, 400 HP 5989 A mass spectrometer. Elemental analysis was carried out with a Yanaco-CHN MT3. The number-average molecular weight of the polymer was derived with a Shimadzu LC-3A gel permeation chromatograph (GPC) with a microcomputer; column length, 1.2 m; filler, crosslinked PS gel (1250 mesh, manufactured by Ji Lin University of China); injection volume, 0.1 mL (concentration, 0.1 g/mL); solvent and eluent, THF; flow rate, 1.2 mL/min; pump pressure, 60 kg/cm$^2$ ($7.85 \times 10^6$ Pa); detecting wavelength, 254 nm. The GPC was calibrated by standard poly(ethylene glycol) (Tokyo Kasei Kogyo Co., LTD.); DSC studies were conducted with SETARAM DSC 92 in a nitrogen atmosphere at a heating rate of 10°C/min.

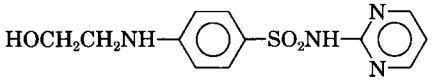
## RESULTS AND DISCUSSION

### Characterization of Reaction Product of Sulfadiazine with EO

Figures 1 and 2 show the IR and MS spectra of reaction product of sulfadiazine with EO. The appearance of molecular ion 294 confirmed the possibility of the presence of 4-amino-*N*-hydroxyethyl-*N*-(2-pyrimidinyl)benzene sulfonamide (AHPBS) (**A**) or 4-hydroxyethylamino-*N*-(2-pyrimidinyl)benzene sulfonamide (HAPBS) (**B**); their molecular formulas and the fragmentation processes of the molecular ion are shown as follows:



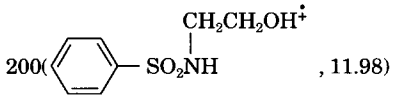
(A)

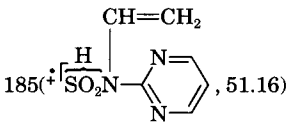


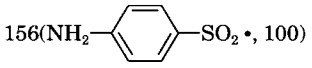
(B)

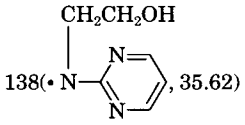
MS(m/e):

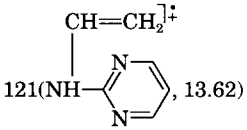
294($M^{\cdot+}$ 10.64)

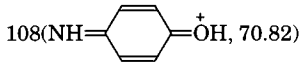


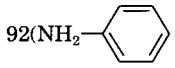



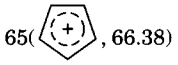




However, the appearance of the fragment radical ion with 156 and 138 mass which obviously came from the cleavage of the sulfonamine bond of AHPBS, and double peaks of aromatic amine at 3430

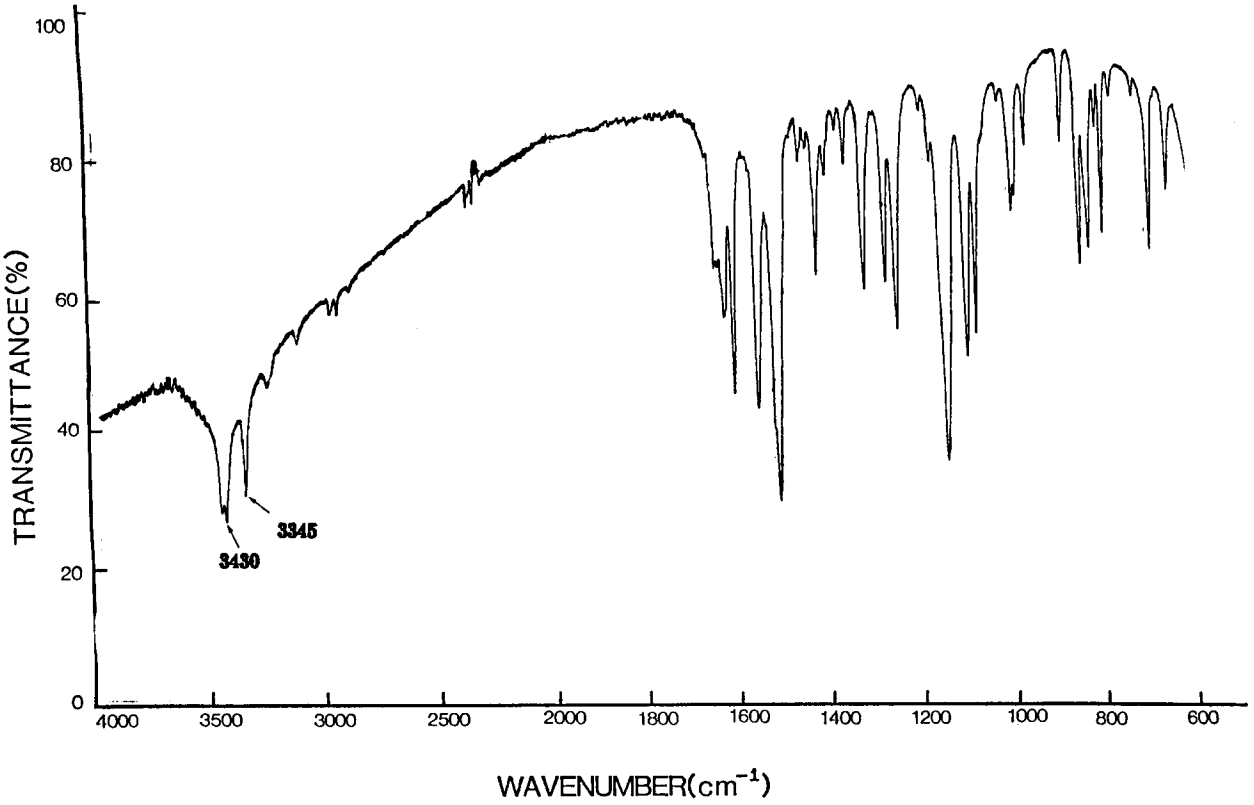



**Figure 1** IR spectrum of reaction product of sulfadiazine with EO (KBr).

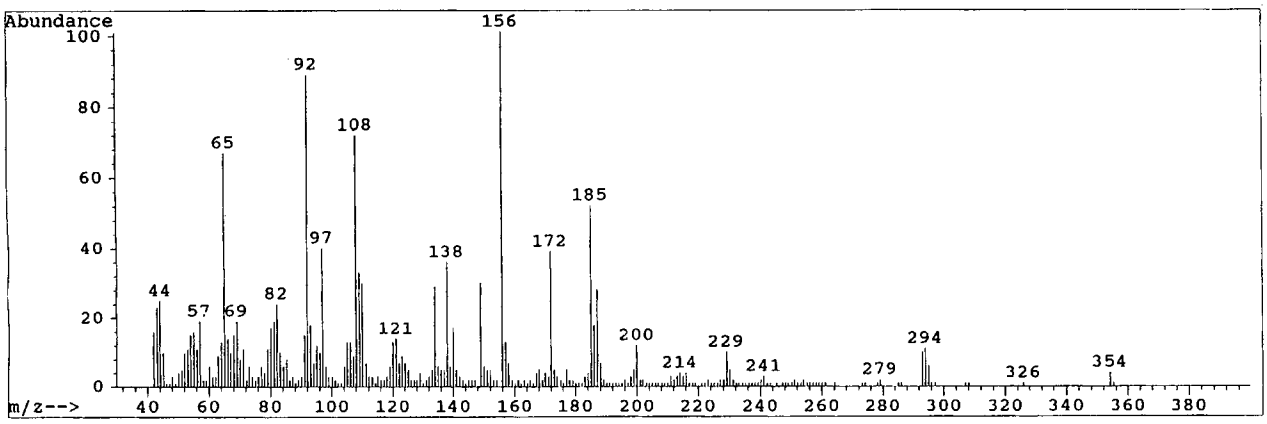
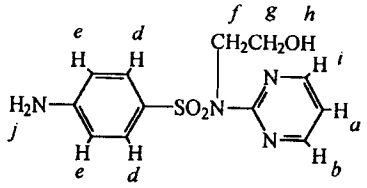



**Figure 2** MS spectrum of reaction product of sulfadiazine with EO.

and 3345 $cm^{-1}$ in Figure 1 indicated that AHPBS may be the correct choice.

Figure 3 is the $^1$H-NMR spectrum of the reaction product of sulfadiazine with EO, which evidenced resonance signals of phenyl, pyrimidinyl, —OH, $—CH_2O—$, $—CH_2—$, and $NH_2—$ protons of relative intensities corresponding to the number and type of protons. The peaks of 5.0 and 5.67 ppm are denoted by the chemical shifts of the protons of hydroxyl and aromatic amine in AHPBS. In the pyrazine ring the nonequivalence of the H atoms at b and i is attributed to the influence of sulfonamide with the hydroxyethyl substituted group on the chemical environment of H atoms at b and i.

The number-average molecular weight of polyethylene oxide which used AHPBS-k as initiator could be estimated by the retention volume in GPC measurement as indicated in Figure 4; its value is about $3.8 \times 10^3$. The molecular weight distribution ($\bar{M}_w/\bar{M}_n$) of the sample is about 1.14. The dual detection by RI and UV allowed a clear assignment of



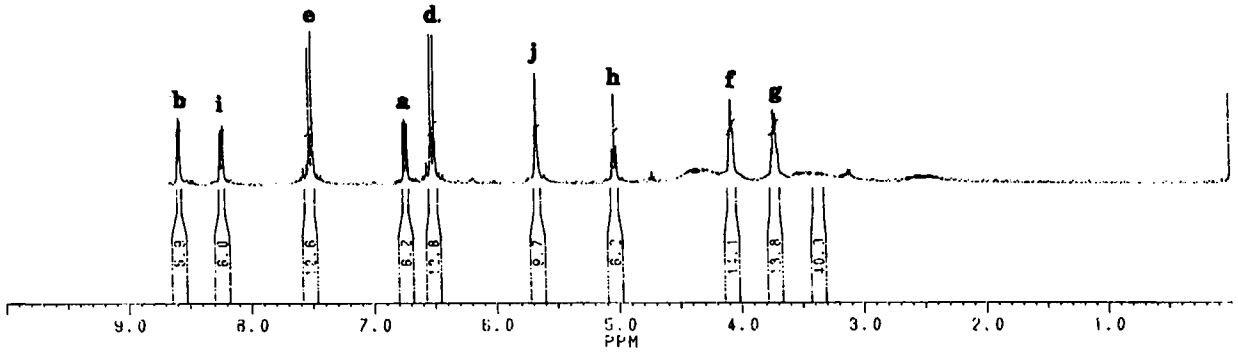




**Figure 3** $^1$H-NMR spectrum of reaction product of sulfadiazine with EO (TMS as internal standard, DMSO-$d_6$ as solvent).

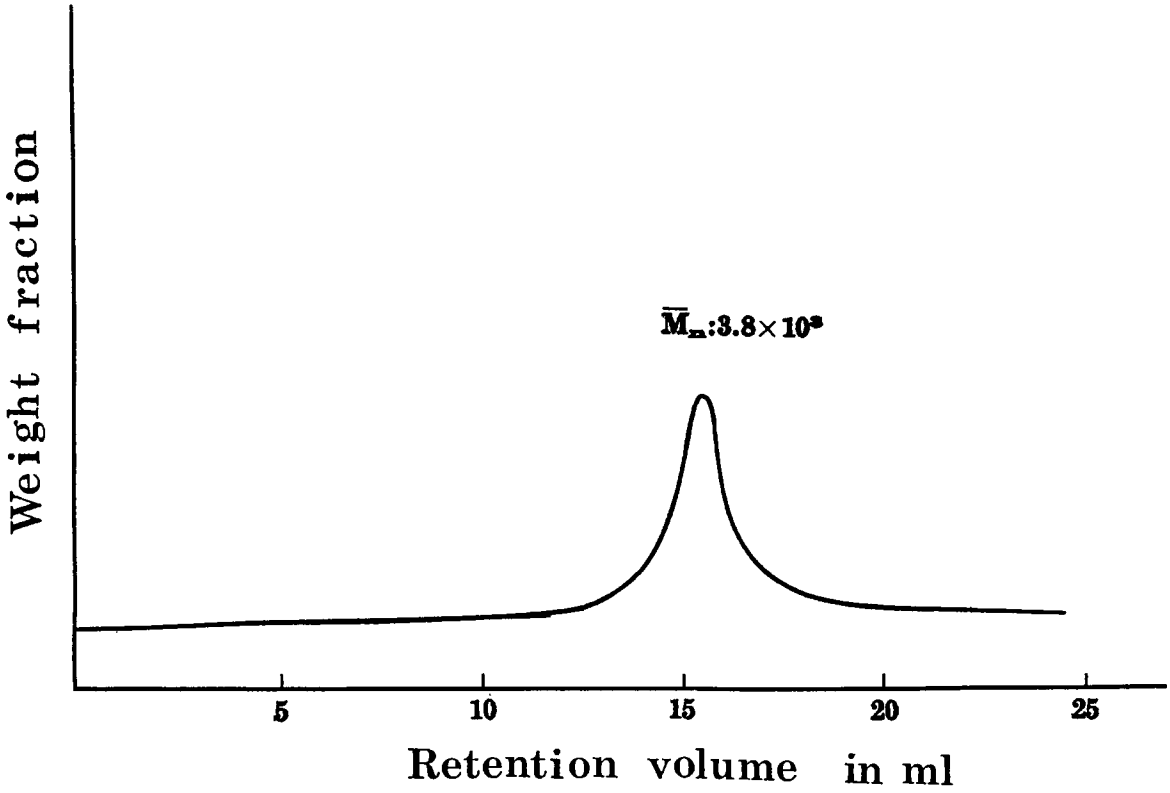
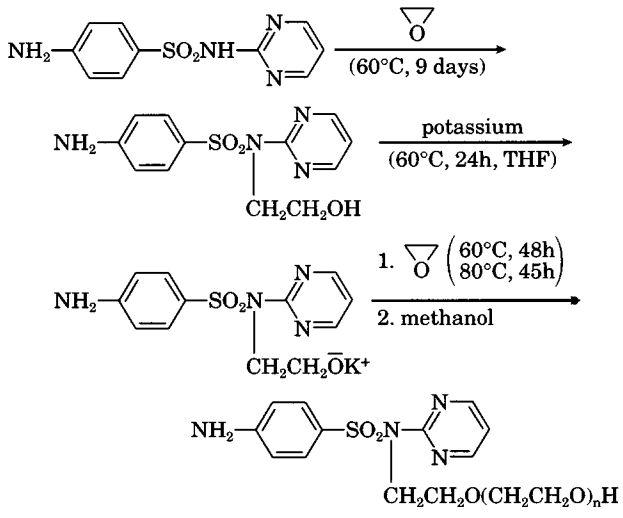



**Figure 4** GPC measurement of PEO initiated by AHPBS-k. Polymerization conditions: 1 mL of AHPBS-k THF solution; 20 mL of EO, 70°C for 48 h and then 80°C for 45 h.

this peak to $PEO_{sf}$ since pure PEO is transparent at 254 nm of the UV detector.

Thus the whole process of preparation of $PEO_{sf}$ could be summarized as follows:

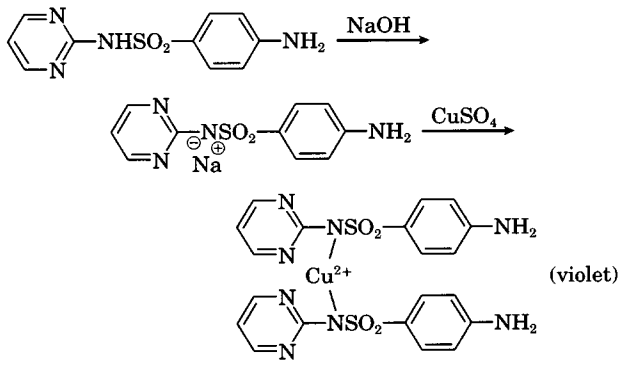



## Reaction Activity of Amino and Amido Groups in Sulfadiazine

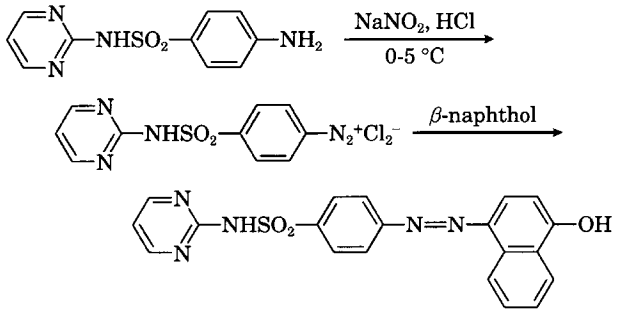
In sulfadiazine, there are two reactive sites which can react to EO: the amino group and the amido group. According to pharmacological analysis data, if the hydrogen atom of the sulfonamide or aniline group of sulfadiazine is substituted, the curative effect of sulfadiazine would decrease or disappear. So it is very important to determine which one would react with EO easily.

On the basis of the above-mentioned MS, IR and NMR measurements, we believe that for the sulfadiazine the amido group of sulfonamide should be more reactive than the amino group of aromatic amine, so the former should react with EO first. This conclusion could be further confirmed by chemical analysis[4] as shown in the following equations.

For the amino group:



For sulfonamide:




Therefore according to the experimental results, the sample could be diazotized and then coupled with β-naphthol to form an azo-compound with a blood red color, or could dissolve in sodium hydroxide solution and then complex with cupric ion to form the precipitate with a specific green to violet color; it could then be determined what kind of reactive groups of sulfadiazine have actually been reacted. From the data of Table I, it can see that in our reaction system, the proton of sulfonamide connected with the pyrimidine ring is more reactive than that of aromatic amine, so the aromatic amine, which was left unreacted, could have been diazotized and coupled with β-naphthol. Thus it can be concluded that the reaction product of sulfadiazine with EO is AHPBS.

## Evidences of EO Polymerization by Initiation of AHPBS-k

As we mentioned before, Figure 4 shows the molecular weight of the polymerized product, which is the direct evidence of EO polymerization initiated by AHPBS-k. Further evidence is given in Figure 5. In these UV spectra, the polymer sample used underwent purification by redissolution in chloroform, filtration to remove unreacted AHPBS, and then reprecipitation with ether. Comparing with the UV spectrum of small molecule sulfadiazine (A), the 270 nm absorbance peak attributed to $\pi \rightarrow \pi^*$ of the aromatic ring has moved to 274 nm for polymer sample (B). This phenomenon may be caused by the inter- and intramolecular hydrogen bonding action of $PEO_{sf}$. It was found that when the sample solution was diluted, for example, the concentration varied from 0.7 to 0.35 g/L, the maximum absorbance peak moved to 272 nm due to the reduction of the hydrogen bonding.

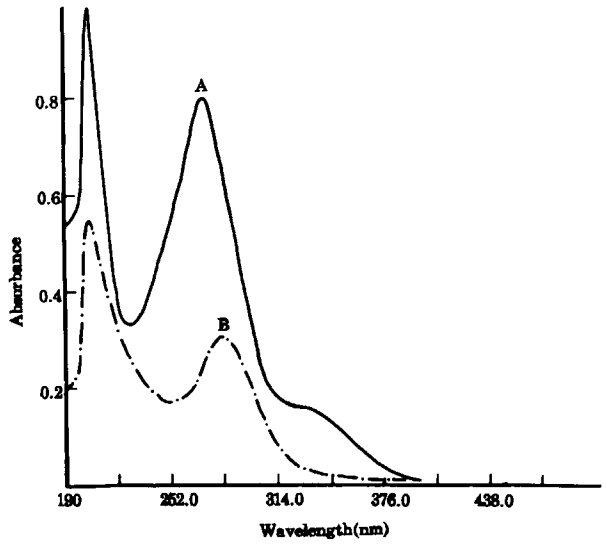



**Figure 5** UV spectra of sulfadiazine (A) and $PEO_{sf}$ (B). Solvent: alcohol, concentrations of A and B are 6.39 $\times 10^{-5}$ and 1.15 $\times 10^{-5}$ mol/L, respectively.

Curve (A) in Figure 6 is the DSC measurement of $PEO_{sf}$, its $T_g$ (−14°C) increased and crystal melting temperature $T_g$ (58°C) dropped compared with the common PEO [curve (B)] (MW: 4000, from Tokyo Kasei, Japan). The reason is very clear. When the sulfadiazine was introduced to the end group of the PEO, its chain rotation became more difficult

**Table I Chemical Analysis of AHPBS**

| | Amido | | Amino | |
|---|---|---|---|---|
| | | | Color | |
| Sample | Solubility (1*N* NaOH) | Color (1*N* $CuSO_4$) | Diazotization | Naphthol |
| Sulfadiazine | Great | Violet | Transparent | Blood red |
| AHPBS | Low[a] | Blue | Transparent | Blood red |

[a] If a large quantity of NaOH was added to AHPBS (pH > 12), the latter could also be dissolved due to the presence of the alcoholic hydroxyl group, but when the solution was brought to pH 8 with 1*N* HCl, the precipitate (AHPBS) appeared again.

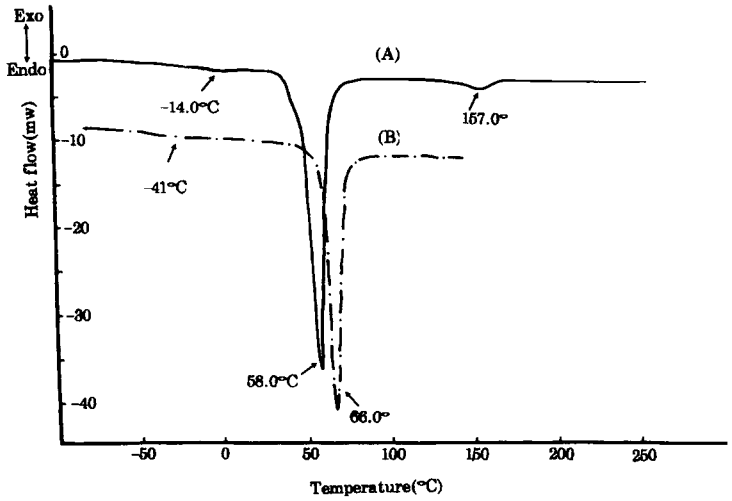



**Figure 6** DSC measurement of $PEO_{sf}$.

than before, so the $T_g$ increased. At the same time, the packing density of the PEO chain decreased due to the introduction of sulfadiazine, which led to the drop of $T_g$. This kind of influence could be weakened when the molecular weight of $PEO_{sf}$ increases, since the content of sulfadiazine in polymer decreased in this case. Therefore the DSC measurement result is further strong evidence for PEO formed by initiation of AHPBS-k. However, in the DSC diagram, there existed a very small endoenergic peak in the temperature range of 142.4 to 175°C, which is much lower than the decomposition temperature ($T_d$) of AHPBS (its $T_d$ is 225°C). We cannot explain this observation. Maybe the $T_d$ of sulfadiazine connected to the PEO would be varied, but we cannot provide strong evidence.

## Effect of Polymerization Conditions

Table II shows the experimental results obtained under the different polymerization conditions. The measurement of kinetic parameters in our system

**Table II Polymerization of EO Initiated by AHPBS-k under Different Conditions**

| | Polymerization | | | | | |
|---|---|---|---|---|---|---|
| | First stage | | Second stage | | | |
| Run | Temperature (°C) | Time (h) | Temperature (°C) | Time (h) | MW ($\times 10^{-3}$) | Conversion of EO (%) |
| 1 | 30 | 48 | | | — | 0 |
| 2 | | 240 | | | — | 0 |
| 3 | 50 | 240 | | | 0.2 | 1.3 |
| 4 | 30 | 120 | 50 | 24 | — | 0 |
| 5 | | | | 72 | — | 0 |
| 6 | 60 | 24 | | | 1.2 | 5.3 |
| 7 | | 72 | | | 2.8 | 9.7 |
| 8 | | 24 | 80 | 24 | 3.7 | 20.6 |
| 9 | | 48 | | 45 | 3.8 | 34.0 |
| 10 | | | | 60 | 3.9 | 38.7 |
| 11 | | | | 84 | 3.8 | 35.1 |
| 12 | 80 | 84 | | | 3.1 | 23.8 |
| 13 | 90[a] | 24 | | | 1.3 | 16.6 |

[a] A product with a deep yellow color was obtained.

was difficult due to the low solubility of AHPBS-k in THF. Although DMSO is a good solvent for sulfadiazine and AHPBS-k could be used to replace THF, the reaction that occurred between DMSO and potassium,[5] which will form another kind of anion to initiate polymerization of EO, made us abandon it. In spite of this, we still could derive some regularity from Table II: (1) The activity of AHPBS-k is very low; the low rate of polymerization may be attributed to the high electrostatic stability of the ion pair,[6] which is probably the main hindrance for an EO monomer to access the reactive center. (2) The molecular weight of $PEO_{sf}$ is always less than 4000 in the current polymerization system no matter how long the reaction time or how high the temperature. Arkhipovich et al.[7] reported that the stability of complexes of PEO with alkali metal ions increased with the molecular weight of PEO. From this viewpoint, when the molecular weight of a propagating chain of PEO reached a specific value, the interaction between PEO and alkali metal ion may be so strong that the activity of the propagating chain species is not enough to initiate the polymerization of EO, so the increase of molecular weight of PEO would be stopped. (3) Polymerization may be divided into two stages as indicated in Table II. If the polymerization was carried out directly at a temperature higher than 80°C, the yield was very low and a product with a deep yellow color was produced. It may be caused by the oxidization of the amino group due to the long reaction time under heating conditions. When the polymerization temperature is less than 30°C, little product was detected even if 10 days have passed. The high activation energy for epoxide polymerization may be the main cause for this phenomenon[6]; if the polymerization was carried out in the temperature range of 30–60°C, both the yield and the molecular weight of the product were very low. Satisfactory results could be obtained only by the polymerization of two stages, as shown in Table II.

Further studies of this kind of initiation system including the effect of synthesis condition on the activity and structure of AHPBS-k, side reactions in the polymerization, and the relationship between the polymerization conditions and the properties of slow release of sulfadiazine are now in progress. We will report them in the nearest future.

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## REFERENCES

1. Y. L. Li, D. Q. Liao, Q. R. Wu, and X. D. Feng, Preprints, IUPAC International Symposium on Olefin and Vinyl Polymerization and Functionalization, Hongzhou, China, 1991, p. 81.
2. J. L. Huang (unpublished data).
3. J. Calvert, T. A. Connors, and W. C. J. Ross, *Eur. J. Cancer,* **4,** 627 (1968).
4. J. H. Shun, *Pharmacochemistry,* RenMingWeiSheng Publishing House, 1990, p. 271.
5. H. Q. Xie, J. Liu, and H. Li, *J. Macromol. Sci. Chem.,* **A27**(6), 725 (1990).
6. K. S. Kazanskii, A. A. Solovyanov, and S. G. Entilis, *Eur. Polym. J.,* **7,** 1421 (1971).
7. G. N. Arkhipovich, S. A. Dubrovskii, K. S. Kazanskii, N. V. Ptitsina, and A. N. Shupik, *Eur. Polym. J.,* **18,** 569 (1982).

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