The Synthesis of Polyethylene Glycol (PEG) with Different Functional Groups at Each End. II. Synthesis of a Series of Monosubstituted PEG via Polyvinyl Alcohol (PVA) as Support

JUNLIAN HUANG* and YOUQIAN HU

Institute of Material Science, Fudan University, Shanghai 200433, People's Republic of China

SYNOPSIS

Five monosubstituted PEGs with different mol wt were synthesized and isolated using PVA as support. They were PEG-N_3, —⬡—CHO, —⬡—NH_2 —⬡—CH=CH—CO—⬡ and —⬡—CH=CH—CO—CH=CH—⬡—N_3, respectively. The structure of these monosubstituted PEGs was characterized by IR, NMR, and element analysis. The effect of the reaction conditions on monosubstitution of PEGs was described. © 1993 John Wiley & Sons, Inc.

INTRODUCTION

The synthesis of macromolecules with different functional groups in two ends is a promising field of research. A lot of useful materials can be designed from the macromolecules. But, due to the difficulty of separation of the reacted mixture,[1] great achievements have not yet been made. Pozzo et al.[2] reported that some monofunctional derivatives of PEG could be prepared and separated by using excess PEG, but the mol wt of monosubstituted PEGs was no more than 1000. It is obvious that the higher the mol wt of starting PEG, the more difficult the isolation of monosubstituted PEG from the reacted mixture, because there was no sharp difference between monosubstituted, disubstituted, and raw PEGs in chemical and physical properties.

We have reported that the pure monotrityl substituted PEG, with mol wt in the range of 400–6000, was obtained by means of polymer matrix.[3] The yield of PEG with monotrityl group was strongly dependent on the feed molar ratio of raw PEG and trityl chloride and the reaction conditions.

In the present article, five monosubstituted PEGs were synthesized and isolated by using PVA as support and selecting the suitable reaction conditions. Two routes were used to prepare these: (1) changing functional end group of PEG, which was attached on PVA through chemical reaction, that is, all transfer of functional group proceeded on the one end of PEG, which was grafted on PVA; the final product could be obtained by hydrolysis of the grafter, and (2) PVA was only used as support for some monosubstitution of PEG, then the monofunctionized PEG was broken from PVA by hydrolysis. The variation of functional group was conducted between monosubstituted PEG and functional agent.

EXPERIMENTAL

Material

A diol type of polyethylene glycol, toluene-2,4-diisocyanate (TDI), was purchased from Fluka AG, Erling & Morten Lind, Norway. PEGs were dried by azeotropic distillation and TDI was dried and distilled before use; PVA ($\bar{M}n$ = 23,320) was obtained from Hoechst, Germany; sodium azide, 4-hydroxyl benzaldehyde, acetophenone and 4-aminoacetophenone were obtained from Kebo Lab AB, Norway. $HClO_4$, thymol blue, and methyl red were from Aldrich and were used without further purification.

* To whom correspondence should be addressed.

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All solvents were dried by a standard method before use.

Preparation of PVA Grafting PEG with Chloride (PVA-*g*-PEG-Cl)

Chlorinating of PEG

To PEG-3400 (6.8 g, 0.004 mol of OH), dried by azeotropic distillation of 300 mL dried toluene, 0.0025 mol of dried triethyl amine were added, under stirring, followed by dropwise addition of thionyl chloride (0.006–0.008 mol), which was freshly distilled from quinoline and then from linseed oil. The solution was refluxed for 5 h, cooled to room temperature, and filtered from triethyl amine hydrochloride salt. Filtrate was distilled by dryness, then dissolved in 100 mL dichloromethane and precipitated by ether, yield: 6.5 g.

I.R. (KBr) (cm^{-1}): 3410 (—OH), 1110 ($-CH_2OCH_2-$), 666 (—CCl).

Preparation of Isocyanate-Capped PEG

2.4 mL (0.02 mol) TDI was injected into 200 mL of dichloromethane containing 6.5 g of the abovementioned product. The system was stirred magnetically for 14 h in refluxing under N_2; the product was precipitated by ether and washed with *n*-hexane, then dried *in vacuo* to constant weight and stored in desiccator, yield: 6.46 g.

I.R. (nujol) (cm_{-1}): 3213 (—NH—), 2928 (aromatic $-CH_3$), 2253 (conjugated —NCO), 1678 (—CO—), 1495, 1466 (C=C ring), 1111 ($-CH_2OCH_2-$), 665 (—CCl).

Grafting of Isocyanate-Capped PEG on PVA

A solution of 100 mL DMSO, containing 8.23 g of the abovementioned product and 0.05 mL of dibutyltin dilaurate, was added dropwise to 400 mL DMSO, containing 2.42 g of PVA ($\bar{M}n$ = 23,320, 0.055 mol of OH, which was dried under vacuum at 50°C for 24 h). The reaction was conducted for 12 h at 70°C in dry N_2. The grafter was precipitated by dichloromethane with vigorous stirring. It could be purified by dissolving in DMSO and reprecipitating in methanol, yield: 9.2 g reacted mole fraction of hydroxyl group in PVA: 0.002.

I.R. (film) (cm^{-1}): 3415 (—OH), 3216 (—NH—), 2928 (aromatic $-CH_3$), 2856 ($-CH_2-$), 1681 (—CO—), 1490, 1465 (C=C ring), 1113 ($-CH_2OCH_2-$), 665 (—CCl), no —NCO absorption at 2253.

The dichloromethane filtrate was evaporated to about half its volume, then was slowly poured into ether with stirring; the precipitate, that is, dichlorosubstituted PEG, was purified by dissolving in dichloromethane and precipitating in ether again.

Characterization: I.R. (nujol) (cm^{-1}): 1112 ($-CH_2OCH_2-$), 664 (—CCl), no hydroxyl absorption at 3410; NMR (DMSO—d_6) (δ: ppm): 3.13–3.21 (*m*, 4H × 2, $-CH_2CH_2Cl$), 3.51–3.69 (*m*, 4 Hn, $(CH_2CH_2O)_n$), no peak for end group of OH at 4.51[4];

Element analysis:

calcd:	$C_{153.7}H_{307.5}Cl_2O_{75.9}$		
calcd:	C 53.62	H 8.94	Cl 2.06
found:	C 54.01	H 8.73	Cl 2.01
	53.88	8.80	1.97

The compound was confirmed that it has the formula:

$$Cl-(CH_2CH_2O)_n-CH_2CH_2Cl.$$

Preparation of PEG—N_3 [$HO-(CH_2CH_2O)_n-CH_2CH_2N_3$]

Azido-Reaction of PVA-Grafted PEG with Chloride End Group

7.6 g of the above mentioned grafter (PVA-*g*-PEG-Cl) [reacted mole fraction of hydroxyl group in PVA: 0.002, content of Cl: 0.062 g (0.001) mol)] was dissolved into 100 mL of DMF, 0.67 g sodium azide (0.01 mol) was added and the reaction was conducted at 110°C for 4 h with magnetic stirring. The solution was cooled to room temperature and was filtered; the filtrate was precipitated by dichloromethane, the precipitate was purified by dissolving in DMSO, and precipitating in dichloromethane again, yield: 7.1 g (93.3%).

I.R. (film) (cm^{-1}): 3418 (—OH), 3215 (—NH—), 2926 (aromatic $-CH_3$), 2855 ($-CH_2-$), 2112 ($-N_3$), 1679 (—CO—), no absorption for Cl at 664.

Hydrolysis of Grafter

7.1 g of the abovementioned grafter was hydrolized in 200 mL of distilled water containing 0.2 g of potassium carbonate under refluxing for 2 h, then was precipitated by methanol. After filtration, the filtrate was neutralized to PH 7 by 0.5 M HCl and evapo-

rated to dryness. The remainings were extracted by dichloromethane, the extracted solution was distilled to about half its volume, then it was poured into ether. The product could be purified by dissolution in dichloromethane and precipitation in ether again, yield: 2.06 g (66.3%).

Characterization: I.R. (nujol) (cm^{-1}): 3406 (— OH), 2109 (— N_3), 1110 (— CH_2OCH_2 —), no absorption for cl at 664; NMR (DMSO — d_6) (δ: ppm): 2.53–2.67 (m, 4 H, — $CH_2CH_2N_3$), 3.51–3.68 [m, 4 Hn, $(CH_2CH_2O)n$], 4.57 (t, 1 H, — OH);

Elemental analysis:

calcd:	$C_{153.8}H_{308.5}N_3O_{76.9}$		
calcd:	C 53.85	H 9.01	N 1.23
found:	C 54.17	H 8.77	N 1.06
	53.94	8.90	1.12

Mol wt: calcd: 3425

found: 3403, 3391, 3452

HPLC analysis showed no chain cleavage.

The compound was confirmed in that it had the formula:

$$HO — (CH_2CH_2O)_{75.9} — CH_2CH_2N_3$$

Preparation of PEG — CH_2CH_2 — NH_2 [HO — $(CH_2CH_2O)_n$ — $CH_2CH_2NH_2$][5]

2.1 g of HO — $(CH_2CH_2O)_{75.9}$ — $CH_2CH_2N_3$, which was dissolved in absolute ethanol, 10% Pd/C (0.08 g) added, and the mixture was hydrogenated in a Parr low pressure hydrogenation apparatus overnight. After filtration, the product was precipitated by ether; yield 1.95 g (93.7%).

Characterization: I.R. (nujol) (cm^{-1}) 3405 (— OH), 3357, 3304 (— NH_2), 1112 (— CH_2OCH_2 —), no absorption for N_3 at 2109. NMR (DMSO — d_6) (δ: ppm): 2.71–2.80 (m, 4 H, — CH_2CH_2 — NH_2), 3.04 (m, 2 H, — NH_2) 3.50–3.67 [m, 4 Hn, $CH_2CH_2O)_n$],

Element analysis:	$C_{153.8}H_{310.6}NO_{76.9}$		
calcd:	C 54.31	H 9.14	N 0.41
found:	C 54.12	H 9.02	N 0.53
	54.09	9.11	0.47

Mol wt: calcd: 3399

found: 3428, 3401, 3375

(Titration was conducted with 0.05N $HClO_4$/dioxane using thymol blue as indicator, and with 0.05N HCl using methyl red as indicator, respectively).

The product was confirmed in that it had the following structure:

$$HO — (CH_2CH_2O)_{75.9} — CH_2CH_2NH_2$$

Preparation of PEG — ⬡ — CHO [HO — $(CH_2CH_2O)_n$ — ⬡ — CHO]

Reaction between Grafter (PVA-g-PEG-Cl) and 4-hydroxyl Benzaldehyde

8.99 g of PVA grafting PEG (3400), with chloride end group (content of Cl: 0.071 g, 0.002 mol), was added to 250 ml of DMSO containing 2.44 g (0.02 mol) 4-hydroxyl benzaldehyde, and 0.46 g (0.02 mol) of sodium ethoxide. The reaction was carried out with stirring at 120°C under N_2. After 20 h, the solution was cooled and filtered. DMSO was evaporated to about half its volume; it was then poured into 300 mL of dichloromethane with stirring. The product was dissolved into DMSO, was precipitated in dichloromethane again, and was dried to constant weight, yield: 8.87 g (96.74%).

I.R. (film) (cm^{-1}): 3413 (— OH), 2928 (aromatic — CH_3), 2854 (— CH_2 —), 1674 (— CO —), 1488, 1463 (C=C ring), no Cl absorption at 665.

Protection of Benzaldehyde

4.57 g of the abovementioned grafter was dissolved in 125 mL of DMSO, 0.5 mL H_2SO_4 (98%), and 0.92 g absolute alcohol were added. The reaction was conducted at 55°C for 6 h, then was precipitated into 400 mL of dichloromethane. The precipitant was purified and dried with the same procedure as mentioned previously. Yield: 4.40 g (90.31%)

Hydrolysis of Grafter with Aldehyde Acetyl

9.01 g of grafter with protected benzaldehyde was hydrolyzed in K_2CO_3 water solution (0.2 g of potassium carbonate in 200 mL water). The procedure was outlined previously, yield: 3.83 g (93.4%).

Characterization: I.R. (nujol) (cm^{-1}), 3419 (— OH), 3016 (— CH_3), 2850 (— CH_2 —), 1587, 1485 (C=C ring), 1113 (— CH_2OCH_2 —) no absorption for carbonyl group at 1674 cm^{-1}.

Deprotection of Benzaldehyde Group

2.06 g monosubstituted PEG was dissolved in 50 mL absolute alcohol, then 0.5 mL H_2SO_4 (98%) was added with stirring for 4 h at 60°C under N_2, was cooled to the room temperature, and was filtered, then poured into 100 mL ether. The purified and dried procedure was used as described previously, yield: 1.76 g (87.56%).

Characterization: I.R. (KBr) (cm^{-1}): 3409 (—OH), 1697 (conjugated —CO—), 1591, 1483 (C=C ring), 1112 (—CH_2OCH_2—). NMR (DMSO—d_6) (δ: ppm): 3.50–3.68 [m, 4 Hn, $(CH_2CH_2O)_n$], 4.57 (t, 1 H, —OH), 6.38–6.49 (m, 4 H, —CH_2CH_2—O—⬡—), 7.25–7.34 (m, 4 H, —⬡—), 7.42 (s, 1 H, conjugated —CHO);

Element analysis:	calcd:	$C_{160.7}H_{313.5}O_{78.9}$
	calcd:	C 55.03 H 8.95
	found:	C 55.69 H 9.01
		55.87 8.94
Mol wt:	calcd:	3504
	found:	3486, 3467, 3451.

HPLC analysis showed no PEG chain cleavage.

This compound was confirmed to have the following structure:

$$HO—(CH_2CH_2O)_{75.9}—CH_2CH_2—O—⬡—CHO$$

Preparation of PEG—⬡—CH=CH—CO—⬡ [HO—$(CH_2CH_2O)_n$—⬡—CH=CH—CO—⬡]

Benzoin Condensation of PVA-Grafting PEG with Benzaldehyde End Group and Acetophenone

9.01 g of PVA grafting PEG with benzaldehyde end group (0.002 mol of benzaldehyde group) was dissolved into 200 mL DMSO, 1.2 g of acetophenone (0.01 mol); 10 mL alcohol was added, then NaOH–water solution (0.1 g NaOH was dissolved in 5 mL H_2O) was added dropwise with stirring at room temperature. Stirring continued for 4 h. The solution was neutralized to ph 7 with 6N HCl. After filtration, the filtrate was poured into 300 mL dichloromethane under stirring for precipitation. The product can be purified by dissolution in DMSO and precipitation with dichloromethane, yield: 8.49 g (89.1%).

I.R. (film) (cm^{-1}): 3412 (—OH), 1683 (conjugated —CO—) 1621 (conjugated —C=C), 1587, 1478 (C=C ring).

Hydrolysis of Grafter

8.4 g of the abovementioned grafter was hydrolyzed in K_2CO_3 water solution (0.2 g of potassium carbonate in 200 mL water). The procedure and the purification of the product were followed as shown previously, yield: 3.11 g (84.5%).

Characterization: I.R. (nujol) (cm^{-1}): 3410 (—OH), 1682 (conjugated —CO—), 1622 (conjugated —C=C—). NMR (DNSO—d_6) (δ: ppm): 3.50–3.69 [m, 4 Hn, $(CH_2CH_2O)_n$], 4.54 (t, 1 H, —OH), 6.98 (s, 2 H, —CH=C—), 7.31 (–7.40 (m, 9 H, —⬡—, —⬡).

Element analysis:	calcd:	$C_{168.7}H_{319.5}O_{78.9}$
	calcd:	C 56.14 H 8.86
	found:	C 55.90 H 8.72
		56.38 8.77
Mol wt:	calcd:	3606
	found:	3574, 3592, 3638

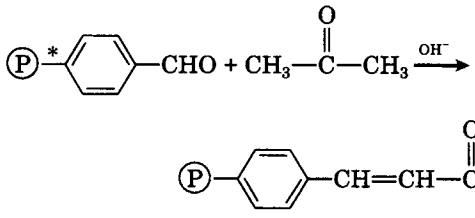
HPLC analysis confirmed no PEG chain cleavage

This compound was confirmed in that it had a structure as follows:

$$HO—(CH_2CH_2O)_{76.9}—⬡—CH=CH—CO—⬡$$

Preparation of PEG—⬡—CH=CH—CO—CH=CH—⬡—N_3 [HO—$(CH_2CH_2O)_n$—⬡—CH=CH—CO—CH=CH—⬡—N_3]

Benzoin Condensation between PVA Grafting PEG with Benzaldehyde and Acetone



(1)

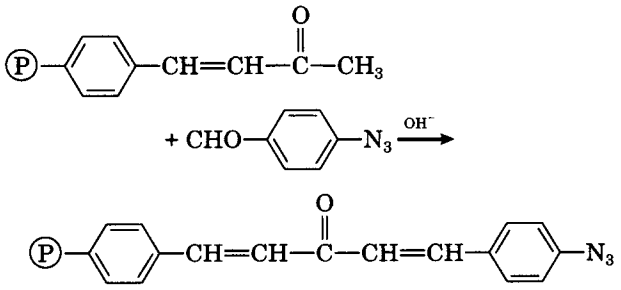
9.01 g of PVA grafting PEG with benzaldehyde end group (0.002 mol of benzaldehyde group) was dissolved into 200 mL of DMSO. 5.8 g acetone (0.1 mol) was added and the reaction procedure was car-

* Denoted PVA grafting PEG.

ried out as mentioned previously, yield: 8.23 g (80.5%).

I.R. (film) (cm^{-1}): 2898 ($-CH_3$), 1708 (ketone $-CO-$), 1624 (conjugated $-C=C-$).

Condensation between Abovementioned Product and 4-Azidobenzaldehyde



(2)

4-azidobenzaldehyde was synthesized as in Ref. 6. It is a dark red liquid.

Element analysis:

calcd:	C 57.14	H 3.40	N 28.57
found:	C 56.65	H 3.72	N 28.16
	56.43	3.46	28.29

3.02 g of 4-azidobenzaldehyde (0.02 mol) was dissolved in a NaOH–water solution (0.08 g NaOH was dissolved in 5 mL water), then was added dropwise to a solution of 100 mL of DMSO containing 8.23 g of the abovementioned compound. The reaction procedure and purification of product were conducted as described previously, yield: 8.02 g (93.6%).

I.R. (film) (cm^{-1}): 2113 ($-N_3$), 1708 (ketone, $-CO-$), 1620 (conjugated $-C=C-$), no absorption for $-CH_3$ at 2898.

Hydrolysis of Grafter

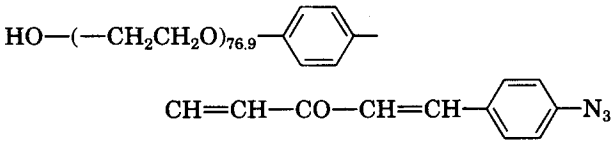
8.02 g of the abovementioned grafter was hydrolyzed in K_2CO_3 water solution, the reaction conditions, procedure, the purification, and dryness of the product were described previously, yield: 2.73 g (77.5%).

Characterization: I.R. (nujol) (cm^{-1}): 3413 ($-OH$), 2111 ($-N_3$), 1671 (conjugated $-CO-$), 1618 (conjugated $-C=C-$), 1502, 1453 (C=C ring); NMR (DMSO—d_6) (δ: ppm): 3.52–3.68 [*m*, 4 Hn, $(CH_2CH_2O)_n$], 4.53 (*t*, 1 H, $-OH$), 6.94 (*s*, 2 H × 2, $-CH=CH-$), 7.29–7.41 (*m*, 4 H × 2,);

Element analysis:

calcd:	$C_{170.7}H_{320.5}N_3O_{78.9}$		
calcd:	C 55.76	H 8.73	N 1.14
found:	C 55.14	H 8.93	N 0.94
	55.48	9.01	0.86
Mol wt:	calcd:	3673	
	found:	3716, 3689, 3654.	

This compound was confirmed in that it had following structures:



Whole condensation reactions should kept from light.

The synthesis of functionized PEG with another mol wt was conducted using the same procedure as described previously.

Measurements

IR spectra were recorded on a Perkin–Elmer 1310 IR Spectrophotometer; ^1H-NMR characterization of samples was conducted using Varian XL-300 NMR spectrometer, TMS as internal standard.

Shimadzu High Performance Liquid Chromatography (HPLC) (LC-4A) was used to check the mol wt of raw and reacted PEG. Column length: 1.2 m, filler: crosslinking polystyrene gel (1250 mesh), injection volume: 0.1 mL (concentration: 0.1%), solvent and eluant: THF, flow rate: 1.2 mL/min, pump pressure: 80 Kg/cm^2 (7.85×10^6 Pa), detecting wavelength: 254 nm.

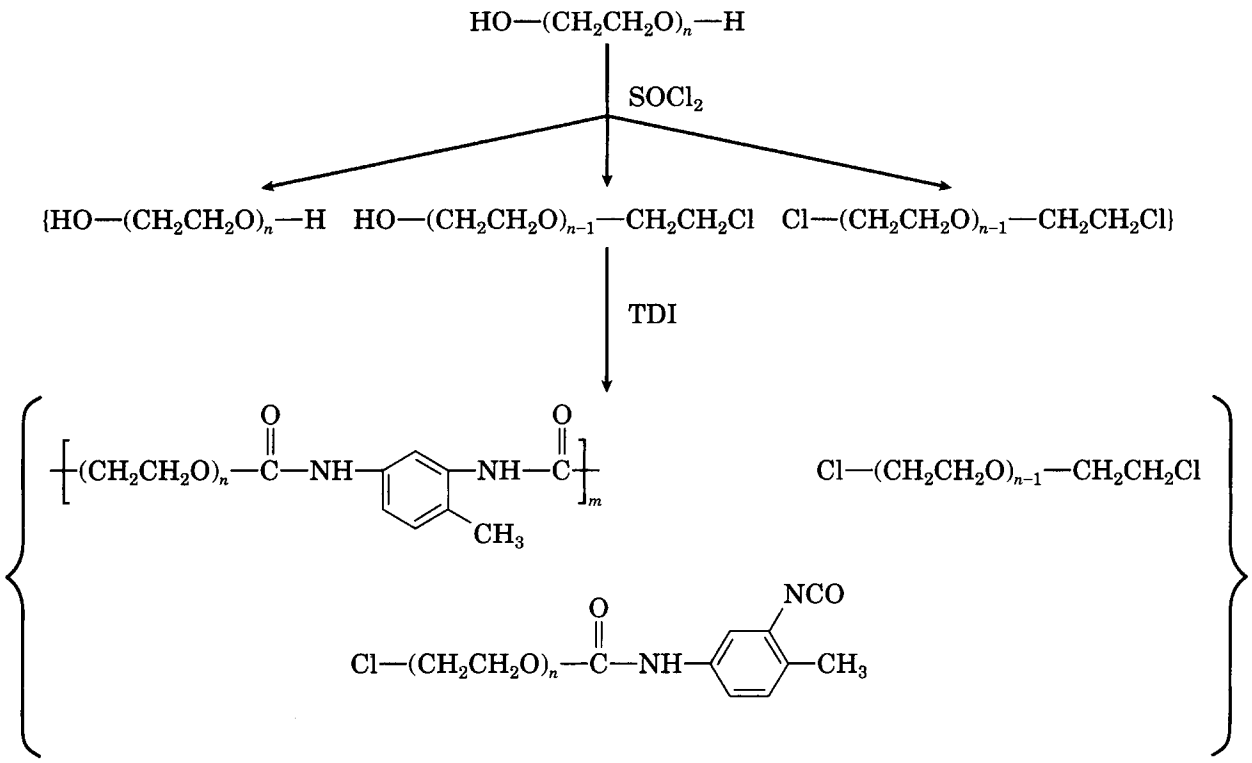
The mol wt of functionized PEGs with hydroxyl end group was measured by reaction with TDI first, then titrated —NCO group by butyl amine methol.[7]

RESULTS AND DISCUSSION

The effect of feed molar ratio of PEG vs. functional agent on the monosubstitution of PEGs

As reported, there is a suitable range of feed molar ratio of PEG vs. functional reagent, in which the higher yield of monosubstituted PEG could be achieved.[3] In the preparation of monobenzaldehyde substituted PEG via PVA-*g*-PEG-Cl as intermediate, it was found that in the range of 1 : 1.5–1 : 2.0 (mole number of PEG/mole number of thionyl chloride), satisfactory results, as Figure 1 shows, could be obtained.

But, if the ratio was more than 1 : 1.5, that is, the content of PEG in feed increased, for example 1 : 1, the results of GPC measurement of sample produced by reaction of TDI and chlorinated PEG revealed that a part of product with higher mol wt was formed as Figure 2 indicated. As is well known when the content of PEG in the feed ratio increased, the raw PEG may be left in the chlorinated product, the excess TDI might condense with PEG. In this case, the whole process may be expressed as follows:



According to the retention volume of standard sample, it was deduced that the mol wt of the condensation product between raw PEG (MW: 3400–6000) and TDI was about as high as two times of the raw PEG, which means that the condensation polymer was mainly composed of a dimer of PEG. The part with the higher mol wt was about $\frac{1}{3}$ of the total product, as Figure 2 shows, that is, when the feed molar ratio was 1 : 1, there was nearly $\frac{1}{3}$ of raw PEG left in the reacted product.

Figure 3 indicated that in the case of the feed, the molar ratio was 1 : 1, a series of peaks corresponding with the different polymerization degrees appeared in the GPC diagram when the raw PEG had lower mol wt (for example, 600).

The Stability of Isocyanate Capped-PEG

It was found that the isocyanate-capped PEG should be used immediately after being prepared. Their mol wt began to increase when it stood in air. Figure 4 shows the I.R. spectra of isocyanate-capped PEG (a) freshly prepared and (b) placed in air for about 5 min. There appeared to be absorption of ureas at 1660 cm^{-1} and primary amine at 3359, with 3305 in spectra (b). Some peaks that could be found in (a), for example, 2184 cm^{-1} for —NCO, decreased in (b).

Therefore, the reaction between isocyanate-capped PEG and moisture may be like this:

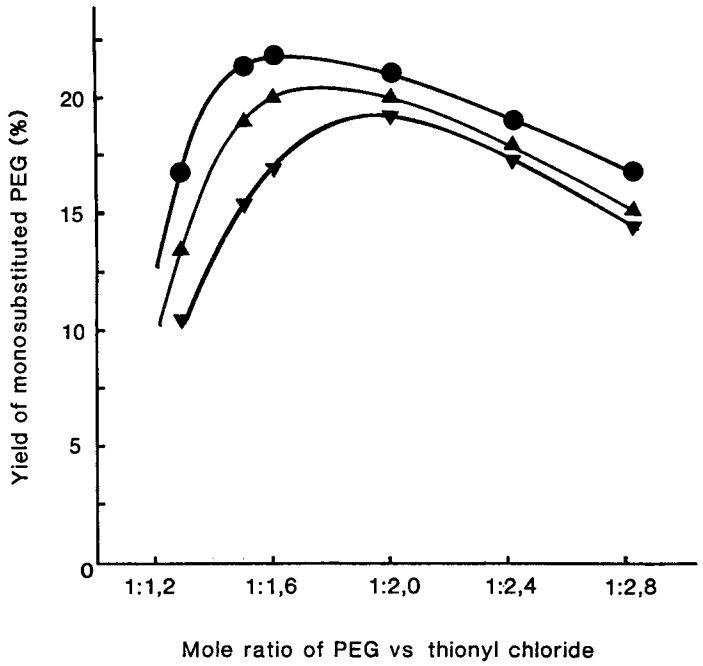


Figure 1 The effect of molar ratio of PEG vs. thionyl chloride on the yield of monosubstituted PEG. (Mol wt of PEG: (●) 600, (▲) 3400, (▼) 6000).

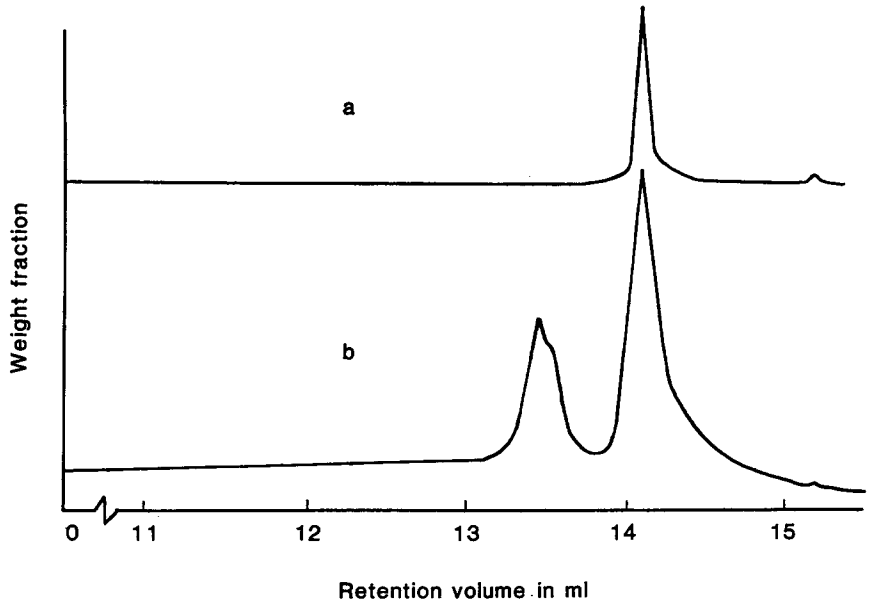


Figure 2 GPC diagram of reacted product between chlorinated PEG (3400) and TDI. (Molar ratio: (a) 1 : 1.5, (b) 1 : 1).

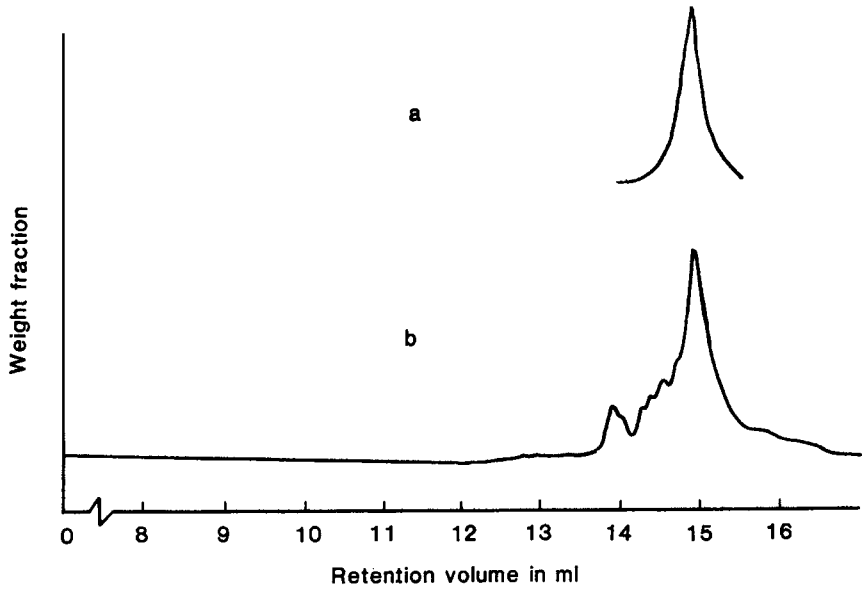


Figure 3 GPC diagram of reacted product between chlorinated PEG (600) and TDI. (Molar ratio: (a) 1 : 1.5, (b) 1 : 1).

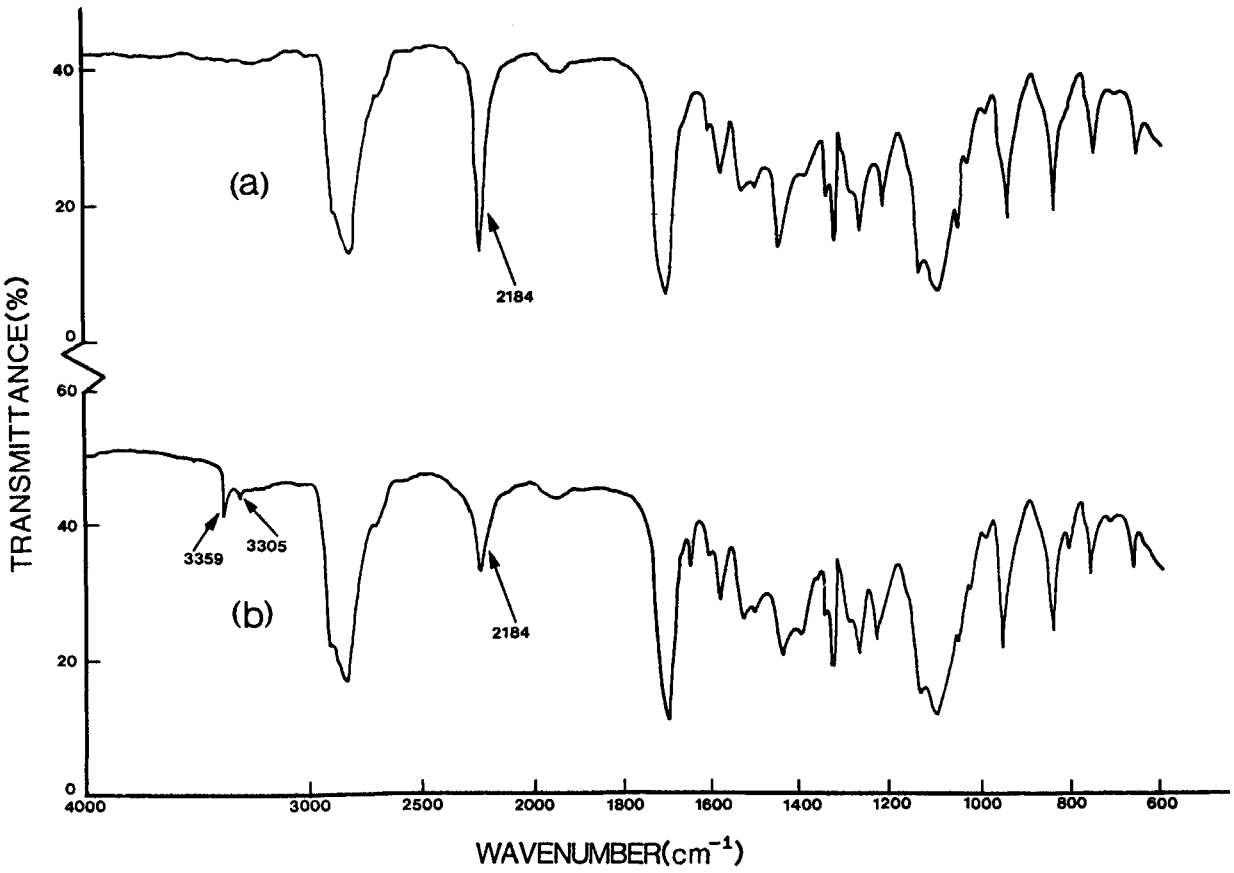


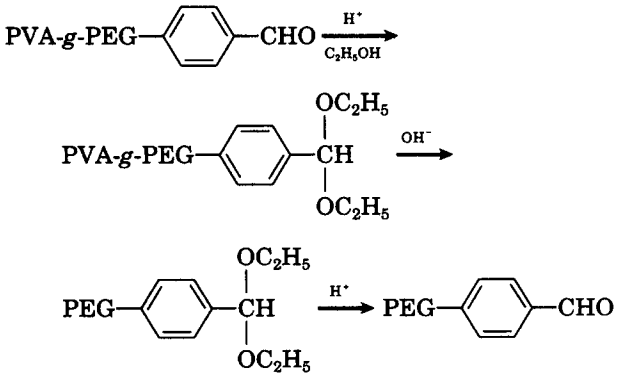
Figure 4 I.R. spectra of isocyanate capped-PEG. (a) freshly prepared, (b) placed in air for 5 min.

$$PEG—NCO + H_2O \rightarrow PEG—NH_2 + CO_2\uparrow \quad (4)$$

$$PEG—NH_2 + NCO—PEG \rightarrow PEG—NH—CO—NH—PEG \quad (5)$$

Preparation of PEG Having Terminal Benzaldehyde

In the preparation of monobenzaldehyde substituted PEG, aldehyde acetyl was used to protect the benzaldehyde group before hydrolysis of grafter; the product would be recovered in dilute acid after hydrolysis. The whole process could be expressed as follows:



If the benzaldehyde was not protected, the mol wt of the product after hydrolysis of grafter in base solution increased, the contents of benzaldehyde group decreased. The reason for this may be that the condensation between the benzaldehyde and hydroxyl groups of PEG macromolecules occurred in the base solution.

Benzoin Condensation

Benzoin condensation between PEG with benzaldehyde end group and acetone or acetophenone was carried out at room temperature. When the temperature rose to 60°C, the yield decreased.

Two routes were used to prepare condensation products. One is that condensation was conducted on the PVA grafting chain, the other is that monobenzaldehyde substituted PEG was used as reactant. However, some product with higher mol wt was formed in the latter case, as mentioned previously, so the former case is preferred.

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