

Synthesis of tri-block copolymer based on polyisobutylene and poly(ethylene glycol)

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Summary

A block copolymer having polyisobutylene (PIB) as hydrophobic segment and poly(ethylene glycol) (PEG) as hydrophilic segments has been synthesized by a two-step process. Polyisobutylene was functionalized with phenol at both ends using $\text{BF}_3 \cdot \text{OEt}_2$ as catalyst, and then coupled with tosylated monomethoxy PEG. The reaction conditions were established by model studies. The characterization of the reaction product by NMR and GPC verified the formation of block copolymer by the coupling reaction.

Introduction

Amphiphilic polymers, which contain hydrophobic and hydrophilic segments in the same molecules, are of great interest for a variety of applications in the pharmaceutical, detergent, coating, agricultural and biotechnical industries since they show affinity towards polar as well as nonpolar phases. For example, the block copolymers PEG-PPO-PEG⁽¹⁻³⁾ have been used for drug delivery and for concentrating hydrophobic trace contamination in polluted water. The graft polymer PS-g-PEG has been given much attention for use as compatibilizer for polymer blends⁽⁴⁾. Various PIB-based amphiphilic networks have been prepared⁽⁵⁻¹¹⁾ and tested for example for drug release properties. By sequential polymerization the block copolymer poly(isobutylene-*b*-methyl vinyl ether) has been prepared⁽¹²⁾, which exhibits amphiphilic character, and from PIB's carrying *p*-toluene sulfonic acid ester end groups amphiphilic poly(ethyleneimine-*b*-isobutylene) block copolymers were obtained⁽¹³⁾.

We wish to report how amphiphilic polymers, PEG-PIB-PEG of controlled structure

and properties may be prepared. Kennedy et al.⁽¹⁴⁻¹⁷⁾ have previously prepared PIB/PEG di- or tri- block copolymers by converting PIBs carrying hydroxyl termini into isocyanate termini and subsequently couple these with PEG blocks. However, separation of the block copolymers from homopolymer constituents was necessary. We have carried out the block copolymer synthesis by functionalizing first PIB with phenol and then coupling with mPEG-OTs. This way a block copolymer controlled structure and properties may be obtained.

The model compound, 2,4,4-trimethyl-1-pentene (TMP), or PIB ($M_w < 4000$) can readily react with phenol by using $\text{BF}_3 \cdot \text{OEt}_2$ as a catalyst in hexane solution when phenol was used in a very high excess. A nearly 100% conversion could be reached^(18,19). However, if the molecular weight of the PIB was over 7000, elimination at the tert-chloride end group of the PIB was found to take place rather than alkylation of phenol and the terminal phenolic group could only be obtained when phenol is used in an extreme excess.

Experimental

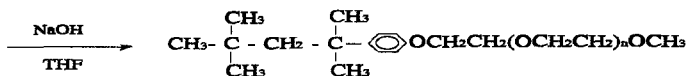
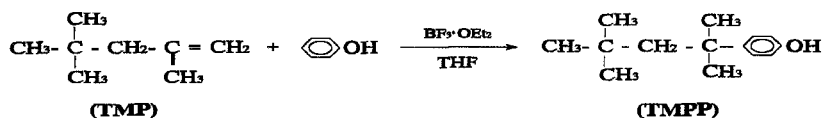
Materials and instruments

Phenol was purified and dried by azeotropic distillation with toluene using a Dean Stark trap, topped with a reflux condenser, then recrystallized from dry hexane at 4°C. n-Hexane (Merck, 96%) was mixed with sulfuric acid(96%), refluxed for 6 hours and then washed with water. This was followed by washing with NaHCO_3 solution and water again until neutrality. After drying over anhydrous MgSO_4 , the n-hexane was distilled over calcium hydride before use. Tetrahydrofuran (THF) was purified by distillation from LiAlH_4 , then stored over CaH_2 , and finally distilled before used. 2,4,4-trimethyl-1-pentene (TMP)(Fluka) was distilled over CaH_2 before use. Boron trifluoride etherate ($\text{BF}_3 \cdot \text{OEt}_2$)(Fluka) and p-toluenesulfonyl chloride (Merck) were used as received. PIB was prepared as previously described⁽²⁰⁾ with dicumyl methyl ether as initiator. The polymer with tert-chlorine end groups had a number average molecular weight of 7,700 and $\overline{M}_w/\overline{M}_n = 1.25$. The monomethoxy polyethylene glycol(m-PEG) with molecular weight 2000 was obtained from Aldrich and dried by azeotropic distillation with toluene before use.

The structure of the block copolymers were characterized by $^1\text{H-NMR}$ spectra recorded on a 250 MHz Bruker spectrometer in CDCl_3 or CD_2Cl_2 solution. The molecular weights of polymer samples were determined by GPC (Waters Model 200) in THF solvent.

Model Reaction

1). Phenolation of 2,4,4-trimethyl-1-pentene (TMP)



Scheme 1

The phenolation of TMP was based on a procedure described by Kennedy et al.^(18,19). Thus, in a 250 ml flask, equipped with a condenser, gas inlet-outlet and a dropping funnel, was placed 5.65 g (60 mmol) phenol and 0.528 ml (4.2 mmol) $\text{BF}_3 \cdot \text{OEt}_2$ in 90 ml dry hexane. Then a solution of 0.67 g (6 mmol) TMP in 15 ml hexane was added dropwise at 40–45°C. After 26 hours stirring the reactor was cooled to room temperature and 50 ml water was added. The mixture was transferred to a 500 ml separatory funnel. The organic phase was washed with water sixteen times until no more phenol was present as checked by UV, and then dried over MgSO_4 overnight. Finally the solvent was evaporated and dried in vacuum oven.

Conversion: >99%, Yield: 1.43 g (80%)

2). Tosylation of $m\text{PEG}_{2000}$

5.72 g (30 mmol) of p-toluenesulfonyl chloride in 20 ml dry methylene chloride was mixed at 0°C with 1.82 g (18 mmol) triethylamine and 1.47 g (12 mmol) 4-dimethylaminopyridine dissolved in 15 ml methylene chloride. To this solution, 12 g (6 mmol) of mPEG in 50 ml CH_2Cl_2 was added dropwise during 1 hour under dry nitrogen, then the temperature was increased to room temperature. The reaction was continued with stirring for 45 hours and two thirds of the solvent was removed by rotary evaporator. The product was precipitated from ethanol at 4°C, then dissolved in small amount of CH_2Cl_2 and reprecipitated from ethanol (4°C), which was repeated three times. The amount of unreacted mPEG was calculated on the basis of the $^1\text{H-NMR}$ spectrum after addition of trichloroacetyl isocyanate which yields a characteristic chemical shift at $\delta = 4.43$ ppm.

Conversion: >96%, Yield: 9.4 g (78%)

3). The reaction of $m\text{PEG}_{2000}\text{-OTs}$ with TMPP

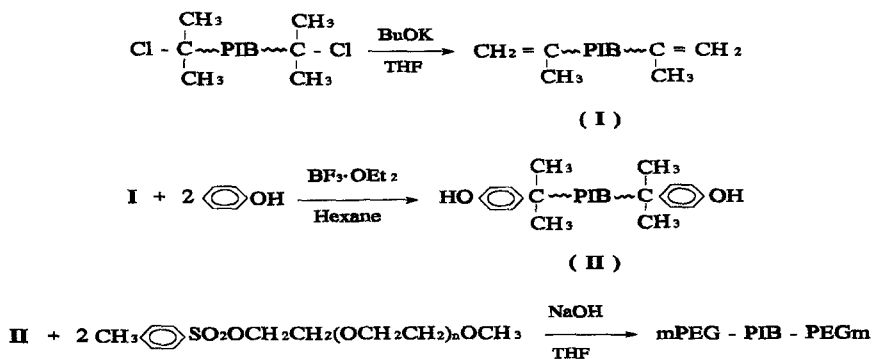
To powdered sodium hydroxide (0.12 g, 3 mmol) was added a solution of TMPP (0.618 g, 3 mmol) in 20 ml dry THF under nitrogen. The solution was heated under reflux with stirring for 24 hours, then cooled down. A solution of 6.25 g (3 mmol) of $m\text{PEG}_{2000}\text{-OTs}$ in 20 ml THF was added completely, and heated again under reflux for 48 hours. A

white solid was formed and separated by centrifugation. The product was obtained by reprecipitation from ethanol (4°C) three times as described in subsection 2), and dried under vacuum.

Conversion: 92%, Yield: 4.2 g (63%)

Preparation of tri-block copolymer PEG-PIB-PEG

The tri-block copolymer PEG-PIB-PEG was prepared by the procedure shown in scheme 2.



Scheme 2

1). Dehydrochlorination of PIB

The dehydrochlorination of PIB was carried out as previously described⁽²¹⁾. To a refluxing solution of PIB (Mn=7700) in THF (4.4 g/100 ml), a solution of t-BuOK in THF (0.8 g / 40 ml) was added dropwise over a period of 10 minutes, stirred for 25 hours and then cooled to room temperature. Subsequently, 90 ml hexane was added, stirred for 5 minutes, followed by addition of 200 ml distilled water and stirred for 10 minutes. The organic layer was washed with 200 ml distilled water till neutral, separated and dried over anhydrous MgSO₄. The product was filtered, the solvent removed by rotary evaporator and dried in vacuum oven at room temperature.

Conversion: ~ 100%, Yield: 3.0 g (69%)

2). Phenolation

The boron trifluoride etherate (14 mmol) was transferred to a solution of phenol, 200 mmol in 200 ml hexane and stirred at 40-45°C in a three-necked flask. It was observed that BF₃ · OEt₂ could not be dissolved completely. The solution of I in hexane (0.2 mmol / 20 ml) was then added dropwise over 20 minutes. The temperature was raised to 50-55°C and stirring was continued for 41 hours. After the reactor was cooled at room

temperature, 200 ml water was slowly added. The organic layer was washed 10 times with water, and then concentrated. Subsequently, the product was precipitated from methanol, then dissolved in small amount of hexane and reprecipitated from methanol four times until it was free of phenol as checked by UV. Finally, the product was dissolved in 50 ml hexane and dried over anhydrous MgSO_4 . The solvent was removed by rotary evaporation and the product was dried in vacuum oven. The conversion of reaction was determined from the $^1\text{H-NMR}$ spectrum by comparing integrated signal from phenol groups to signals from aromatic protons in the center of PIB.

Conversion: 91%, Yield: 0.87 g (75%)

3). Preparation of PEG-PIB-PEG

The block copolymer was synthesized by mixing an excess of sodium hydroxide powder 0.27 g (6.72 mmol) with a solution of **II** 0.4308 g (0.056 mmol) in 60 ml THF, and allowing the mixture to reflux for 24 hours. Then the mixture was cooled, and a solution of mPEG-OTs 6.72 g (3.36 mmol) in 40 ml THF was added. The reaction was allowed to take place for 69 hours under reflux. A white solid was formed, and separated by centrifugation. After the mixture had been neutralized with 0.5N HCl, all THF was removed by rotary evaporator. The pure block copolymer was obtained by partition chromatography on methanol treated cellulose⁽²²⁾, eluted by ethyl acetate.

Yield: 0.4 g (75%)

Results and Discussion

The synthesis of tri-block copolymers PEG-PIB-PEG was based on a procedure deduced from the results of the model experiments shown in scheme 1. It was a two-step process in which TMP was converted to a reactive TMPP in the first step, a Friedel-Crafts alkylation of phenol. This reaction easily proceeds to high conversion in the presence of $\text{BF}_3 \cdot \text{OEt}_2$. In the second step, since tosylate is a good leaving group TMPP readily reacted with mPEG-OTs in the strong basic solution.

In the $^1\text{H-NMR}$ spectrum of TMPP, resonances at 4.75, 6.75 and 7.25 ppm are associated with the protons of the -OH group (1 proton), and of the ortho and meta aromatic protons (each 2 protons) and confirming phenolation when compared with the protons signals from two different types of methyl groups at 0.7 ppm and 1.3 ppm. After reaction with the tosylated m-PEG the $^1\text{H-NMR}$ spectrum of mPEG-TMPP showed characteristic signals related to a coupled product. In addition to the above signals for the TMPP, aside from the phenolic proton which has disappeared, the signals from the poly(ethylene oxide) repeat structure is found at 3.5-4.0 ppm while the methoxy end group appear at 3.4 ppm, and a characteristic signal is found at 4.1-4.2 ppm for the phenoxy methylene group, which is a good indicator for the coupling reaction.

In accordance with the model reactions, phenol was then alkylated by PIB with molecular weight 7700. However, the progress of the reaction was quite different

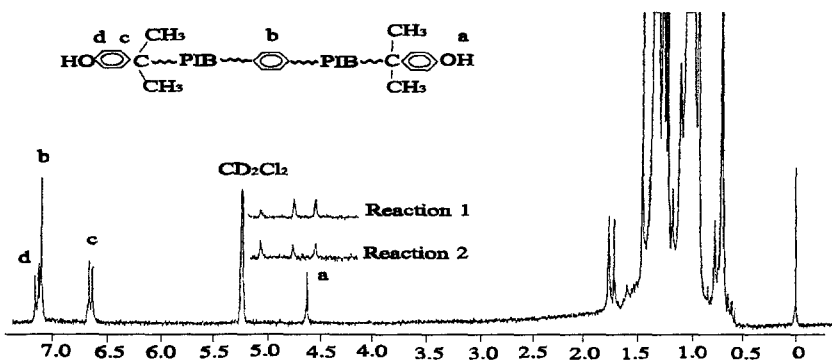


Fig.1 ^1H -NMR spectrum of a phenolated PIB with assignments compared to that of the model reaction. The reaction became more difficult with the increased molecular weight of the PIB. In order to obtain the desired product a large excess of phenol had to be used. Three reactions were carried out using different amounts of phenol as shown in Fig.1. In the first reaction, a 10 times excess of phenol was added. The NMR shows that elimination has taken place instead of alkylation of the phenol. The two resonances at 4.6 and 4.78 ppm indicate the presence of $-\text{C}(\text{CH}_3)=\underline{\text{C}}\text{H}_2$, and the small resonance at 5.1 ppm is related to $-\underline{\text{C}}\text{H}=\text{C}(\text{CH}_3)_2$ proton. When increasing the amount of phenol addition to 70 times excess in a further second reaction of the product obtained from the first reaction, phenol was still not connected to the PIB. However, in a third repeated reaction, when an extreme excess of phenol was used (actually one thousand times), the NMR spectrum indicates that bis(p-phenol)-polyisobutylene was obtained. This is in accordance with reports by Nemes et al.⁽¹⁸⁾ who also found it necessary to use a very high excess of phenol. The key singlet at 4.6 ppm proves the presence of the protons of the phenolic $-\text{OH}$ groups. The two resonances at 6.75 and 7.2 ppm are due to the aromatic

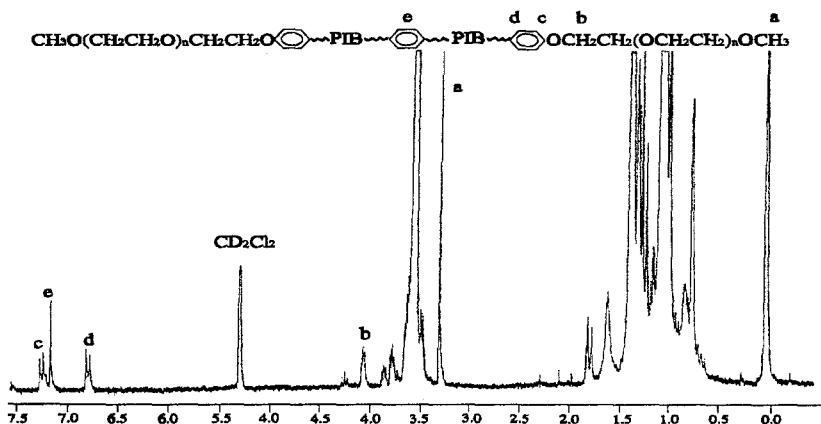


Fig. 2 ^1H -NMR spectrum of the block copolymer mPEG-PIB-PEGm

protons in the phenolic groups, and the resonance at 7.1 ppm is due to four protons of the central aromatic ring.

The structure of block copolymer mPEG-PIB-PEGm was characterized by $^1\text{H-NMR}$ shown in Fig.2. The region from 1.0 to 1.6 ppm contains protons related to the methyl and methylene groups in PIB segments. The region from 3.3 to 4.2 ppm are due to the mPEG segments. The important peak at 4.1 ppm proves the presence of the phenoxy methylene group $\text{C}_6\text{H}_4\text{-OCH}_2\text{-}$ and shows that the PIB has been coupled with mPEG. The resonance at 7.18 ppm represents four aromatic protons in the center of PIB. While the resonances at 6.8 and 7.25 ppm represent aromatic protons between PIB and mPEG.

The GPC traces are shown in Fig.3. The dotted lines represent the starting materials PIB₇₇₀₀ and mPEG₂₀₀₀ which appear at the higher elution counts. The solid line is the trace of block copolymer PEG-PIB-PEG which shows a shift to lowest elution count confirming the coupling of PIB with PEG.

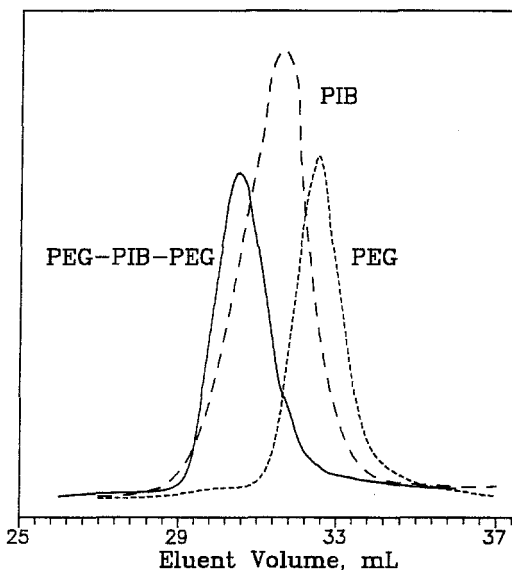


Fig.3. GPC chromatograms of the block copolymer and starting materials.

Conclusions

The present investigation has shown that amphiphilic block copolymers mPEG-PIB-PEGm can be prepared by a two steps process. In the first step, polyisobutylene (PIB) is activated by a Friedel-Crafts alkylation of phenol using $\text{BF}_3 \cdot \text{OEt}_2$ as a catalyst. In the second step, phenol ended PIB is coupled with mPEG-OTs in basic solution. If molecular weight of PIB is over 7000, the terminal phenolic hydroxyl PIB may only be obtained when the amount of phenol is used in an extreme excess.

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