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Preparation of polystyrene–poly(ethylene glycol) diblock copolymer by 'living' free radical polymerisation

Xianyi Chen[a], Bo Gao[a], Jørgen Kops[a,*] and Walther Batsberg[b]
[a]*Department of Chemical Engineering, Technical University of Demark, DK 2800 Lyngby, Denmark*
[b]*Department of Solid State Physics, Risø National Laboratory, DK 4000 Roskilde, Denmark*
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Amphiphilic diblock copolymer containing segments of polystyrene and monomethoxypoly(ethylene glycol) (PS-b-PEG) was synthesised by a novel method. Initially, the adduct (BZ-TEMPO) obtained by reacting benzoyl peroxide, styrene, and 2,2,6,6-tetramethyl-piperidinyl-1-oxy (TEMPO) was isolated, characterised and hydrolysed. Conditions for the synthesis and hydrolysis of BZ-TEMPO were investigated and the hydrolysed product (HO-TEMPO) containing a primary hydroxyl group has been isolated in improved yield. The hydroxyl group of HO-TEMPO was coupled with tosylated PEG to yield the macroinitiator PEG terminated with a TEMPO unit (MPEG-TEMPO), which was further used to prepare the diblock copolymer PS-b-PEG by 'living' free radical polymerisation of styrene. The product was purified and identified by ^{1}H n.m.r. and GPC. However, large amounts of homopolystyrene was also formed by simultaneous thermal initiation and polymerisation. © 1997 Elsevier Science Ltd.

(Keywords: amphiphilic block copolymers; 'living' free radical polymerisation; poly (ethylene glycol)))

INTRODUCTION

Several publications have appeared in recent years concerning preparation of polystyrene–poly(ethylene glycol) block copolymers (PS-b-PEG) with well defined molecular structures[1–4]. The synthesis methods reported are mostly anionic polymerisation processes including coupling reaction and sequential polymerisation techniques. However, the synthesis has to be carried out under anhydrous conditions if sequential polymerisation is used, and extensive purification of monomers, solvents and initiators is also required. When the coupling technique is used, problems associated with producing pure end functional polymers and difficulties associated with conducting reactions between polymers may be encountered. It has been reported that PS-b-PEG may be synthesised by conventional free radical polymerisation, using a macroinitiator technique[5,6], but the copolymer obtained had a broad molecular weight distribution. Yang and coworkers synthesised polystyrene-*g*-poly(ethylene oxide) graft copolymers, using a macromonomer technique[7]. It was claimed that graft copolymers with long PEO side chains have better properties as biomaterials than block copolymers segmented with PEO chains[8]. Recently, studies have been made of the amphiphilic properties of polystyrene–poly(ethylene glycol) copolymers[9–11].

Very recently, 'living' free radical polymerisation has been used for preparing block copolymers of styrene with myrcene, vinylpyridine, acrylate, *p*-acetoxymethylstyrene, and butadiene[12–16]. Compared with ionic living polymerisation methods, an advantage of 'living' free radical polymerisation is that in the preparation of block copolymers, the terminal groups of the initial block segments, e.g. nitroxide groups, are stable in air at room temperature, and prepolymers can be isolated, stored and used as needed, and less stringent polymerisation conditions are required.

In the present study, 'living' free radical polymerisation has been investigated for synthesising PS-b-PEG amphiphilic block copolymers using the concept of M. K. Georges and coworkers[16] and the methodology developed by C. J. Hawker and J. L. Hedrick[17,18]. Thus, 1-benzoyl-2-phenyl-2-(2′,2′,6′,6′-tetramethyl-piperidinyl-1′-oxy)ethane (BZ-TEMPO) is synthesised and hydrolysed to the corresponding 1-hydroxyl derivative (HO-TEMPO). This functional nitroxyl compound is coupled with tosylated monomethoxypoly(ethylene glycol) (MPEG-OTs) according to *Scheme 1*. The resulting macroinitiator (MPEG-TEMPO) for 'living' free radical polymerisation is then heated in the presence of styrene (*Scheme 2*) for formation of the desired block copolymer.

EXPERIMENTAL

Materials and analysis

Monomethoxypoly(ethylene glycol) (MPEG) with molecular weight 2000 (Aldrich) was dried by azeotropic distillation with toluene before use. Styrene was obtained from Riedel-de Haen and made free of inhibitor by passing through a column ($\phi = 160\,\text{mm} \times 140\,\text{mm}$) filled with activated aluminium oxide (Aldrich, neutral, Brockmann 1, standard grade, ~150 mesh, 58 Å) at room temperature.

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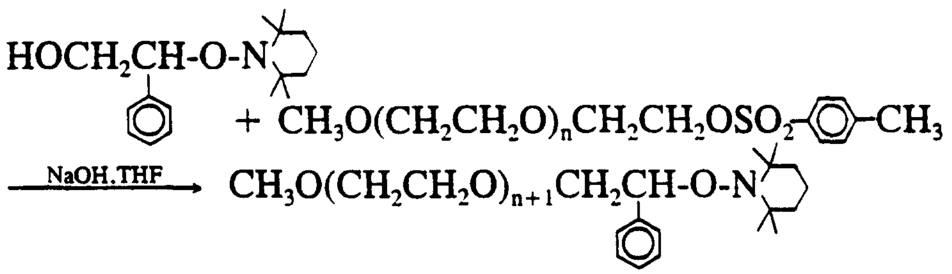
[*] To whom correspondence should be addressed



Scheme 1

Tetrahydrofuran (THF) was purified by fluxing and distillation from $LiAlH_4$ and then stored over CaH_2 and finally refluxed and distilled before use. Triethylamine (Et_3N) was purified by refluxing and distillation from acetic anhydride and stored over CaH_2. Before use, it was finally refluxed and distilled. Dichloromethane was mixed with sulfuric acid (96%) (100:10 v/v), refluxed for more than 4 h and then separated, washed with water, followed by washing with $NaHCO_3$ saturated solution and water again until neutrality. After drying over anhydrous $MgSO_4$, the dichloromethane was refluxed and distilled from CaH_2 before use. Benzoyl peroxide (BPO) (Aldrich, 97%), TEMPO (Aldrich, 98%), *p*-toluenesulfonyl chloride (Merck), and other chemicals were used as received.

The structure of reactants, intermediates and block copolymers was characterised by ^{1}H n.m.r. spectroscopy obtained using a 250 MHz Bruker spectrometer and CD_2Cl_2 or $CDCl_3$ as solvents. The molecular weight and molecular weight distribution of block copolymers were determined by gel permeation chromatographs (GPC) on a Viskotek, Knauer instrument with Nucleosil columns: 100 Å and 500 Å, using polystyrene standards as calibration, THF as eluent at room temperature with flow rate of 1 ml min^{-1}. Thin layer chromatography (TLC) analysis of intermediates with small molecular weight was carried out using silica gel aluminium sheets (25 DC-Alufolien 20 × 20 cm Kieselgel 60 F_{254}, Merck) containing a fluorescent indicator and by using a dichloromethane and methanol mixture as effluent.

Synthesis of 1-benzoyl-2-phenyl-2-(2′,2′,6′,6′-tetramethyl-piperidinyl-1′-oxy)ethane (BZ-TEMPO)

Synthesis and purification procedures of Hawker[15,17,18] and Georges[19] were modified. Thus, the synthesis of BZ-TEMPO was carried out in a 100 ml two-necked flask equipped with a condenser and immersed in an oil bath by adding a desired amount of TEMPO to a solution of benzoyl peroxide in purified styrene under nitrogen and stirring at controlled temperature for 20–24 h. After cooling, the reaction mixture was evaporated under vacuum at room temperature to remove the residual styrene, the desired BZ-TEMPO could be separated as a pale yellow oil by passing the reaction mixture through a column ($\phi = 25$ mm × 400 mm) packed with silica gel 60 (Merck) and eluting with a mixture of 1:100 (v/v) methanol/dichloromethane, gradually increasing to 2:100 (v/v) methanol/dichloromethane.

Synthesis of 1-hydroxy-2-phenyl-2-(2′,2′,6′,6′-tetramethyl-piperidinyl-1′-oxy)ethane (HO-TEMPO)

To purified BZ-TEMPO (0.5 g) was added 20 ml ethanol, 0.455 g potassium hydroxide and 2 ml H_2O. The solution was stirred and heated at reflux under nitrogen for 24 h. Then the solvent was evaporated by rotavap and 20 ml hexane and 10 ml H_2O were added. The organic layer was washed with H_2O until neutral, and the solvent hexane was evaporated. According to the separation conditions determined by TLC, the crude product was purified by passing through a silica gel column ($60F_{254}$, Merck) with 2:100 (v/v) methanol/dichloromethane as eluent to give HO-TEMPO as a pale yellow oil, yield: 85%. ^{1}H n.m.r. ($CDCl_3$): chemical shifts at 1.1–1.5 ppm (12 H, CH_3), 1.3–1.7 ppm (6H, CH_2), 3.7, and 4.2 ppm (1H, CH_2), 5.3 ppm (1H, CH), 5.9 ppm (OH), 7.2–7.5 ppm (5H, ArH).

Preparation of tosylated MPEG and reaction with HO-TEMPO to obtain macroinitiator MPEG-TEMPO

MPEG was tosylated[20] by the reaction with *p*-toluenesulfonyl chloride. Quantitative reaction was indicated by ^{1}H n.m.r.

The reaction conditions for the coupling of MPEG-OTs with HO-TEMPO were first established by reaction with the model compound 2-phenoxy ethanol. To a 250 ml three-necked flask was added 0.4 g (10 mmol) NaOH and a solution of 2-phenoxy ethanol (1.38 g, 10 mmol) in 30 ml THF. The solution was stirred and refluxed under nitrogen for 24 h. To this solution was added dropwise a MPEG-OTs (2 g, 1 mmol) solution in 40 ml tetrahydrofuran. Stirring and refluxing of the reaction mixture was continued for 48 h. After cooling, the precipitate was filtered and the solvent was removed by rotary evaporator, a small amount of CH_2Cl_2 was added and the product was precipitated twice in 500 ml ethanol from the CH_2Cl_2 at 4°C. The ^{1}H n.m.r. spectrum for the product was in accordance with the structure MPEG-$OCH_2CH_2OC_6H_5$.

The reaction of MPEG-OTs (0.6 g, 0.3 mmol) with HO-TEMPO (0.56 g, 2.04 mmol) was carried out in THF with 0.17 g (4.2 mmol) NaOH added where the reaction and purification procedure was the same as described for the model reaction. The product structure was 1-MPEG-2-phenyl-2-(2′,2′,6′,6′-tetramethyl-piperidinyl-1′-oxy)ethane (MPEG-TEMPO) according to ^{1}H n.m.r.

Synthesis and purification of diblock copolymer polystyrene–monomethoxypoly(ethylene glycol) (PS-b-PEG)

Diblock copolymer PS-b-PEG was synthesised by adding inhibitor-free styrene (12.24 g) to MPEG-TEMPO (0.302 g, 0.137 mmol). The solution was stirred and heated at 125°C for 14 h. During the reaction, the viscosity of the solution was observed to gradually increase until a clear solid was obtained. The solid was dissolved in 25 ml CH_2Cl_2, precipitated into 500 ml hexane for 24 h and reprecipitated from CH_2Cl_2 into 500 ml ethanol. The crude product was dried in a vacuum oven at room temperature for 48 h.

The separation of PS-b-PEG from PS and MPEG was carried out partly according to a procedure given by Xie *et al.*[1]. Thus, the crude product was extracted with cyclohexane at 30°C three times, in order to remove polystyrene. The residue was purified after drying by extraction with distilled water at room temperature two times in order to remove the unreacted MPEG. The purified product was dried in vacuum and weighted.

RESULTS AND DISCUSSION

BZ-TEMPO was synthesised to optimise the yield performed under a variety of conditions where the ratio of TEMPO to BPO was varied and also the reaction temperature. However, under all conditions, the yield was relatively low, no more than around 25%. The structure of the product was confirmed by the ^1H n.m.r. spectrum[15].

The hydrolysis of BZ-TEMPO gave a crude product from which the hydroxyl functional HO-TEMPO could be readily separated from unhydrolysed BZ-TEMPO. TLC gave two spots on the silica gel aluminium sheets corresponding to BZ-TEMPO and HO-TEMPO. Purification of the crude product was performed by flash chromatography using a

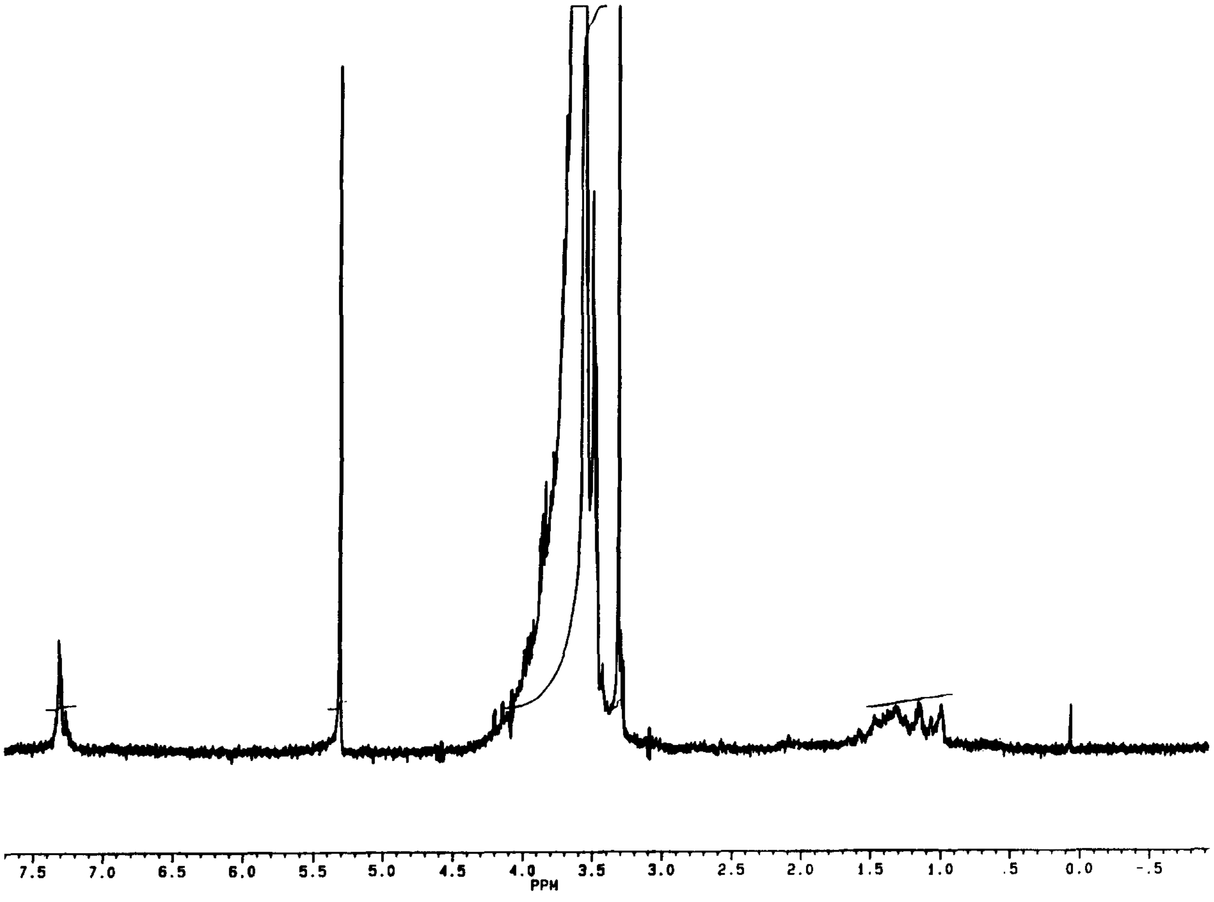
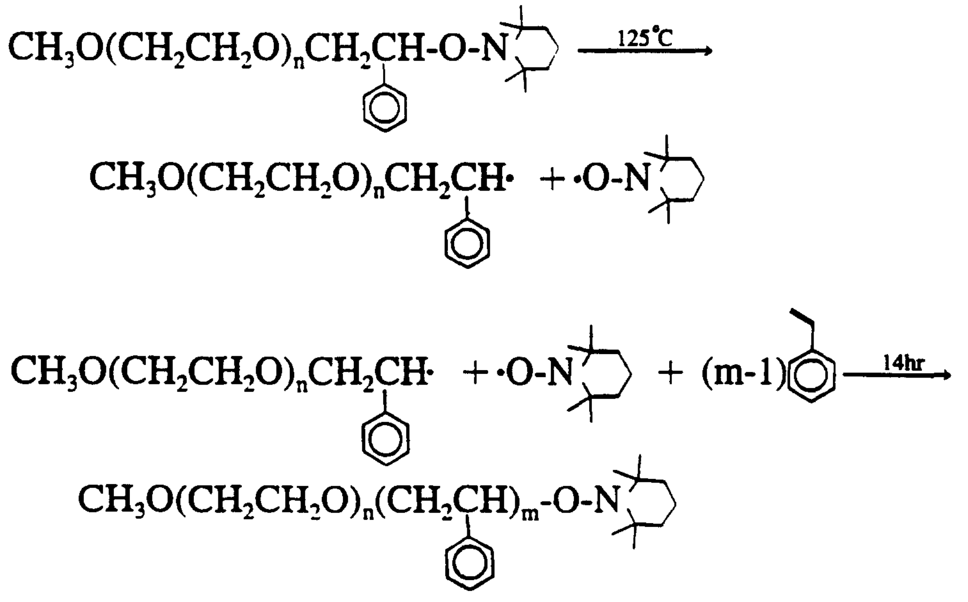


Figure 1 ^1H n.m.r. spectrum of macroinitiator MPEG-TEMPO



Scheme 2

silica gel column. The purified product was identified as HO-TEMPO by ^{1}H n.m.r.[17]. Only in a homogeneous alcohol/water medium with KOH as base could a high yield of the purified HO-TEMPO be obtained.

HO-TEMPO reacts with MPEG-OTs to give the macroinitiator MPEG-TEMPO according to *Scheme 1*. The reaction conditions were established after studying the coupling in the model reaction of tosylated MPEG with 2-phenoxy ethanol. The ^{1}H n.m.r. spectrum of the macroinitiator is shown in *Figure 1*. Comparision with the ^{1}H n.m.r. spectrum of MPEG-OTs indicates that in the reaction process, MPEG-OTs disappeared completely, and MPEG-TEMPO is being formed, since the signals representing the functional group *p*-toluene-sulfonyl at 2.43 ppm, 7.24–7.35 ppm and 7.74–7.83 ppm disappear, and instead, the functional group 2-phenyl-2-(2′,2′,6′,6′-tetramethyl-piperidinyl-1′-oxy)ethoxy appears with characteristic signals at 1.03–1.58 ppm and 7.20–7.40 ppm.

The thermal homolytic scission of the C–O bond of the aminoxy moiety of the MPEG-TEMPO took place at 125°C and caused the radical polymerisation of styrene to yield the amphiphilic block copolymer PS-b-PEG according to *Scheme 2*. The bond dissociation is considered to be reversible. The crude polymerisation product was purified as given in the experimental section. The yield of crude product corresponding to 72% was reduced to only 12% after purification. A large amount of homopolystyrene was produced which was isolated and identified by its ^{1}H n.m.r. spectrum.

^{1}H n.m.r. of the purified product (*Figure 2*) indicates the formation of block copolymer PS-b-PEG, since the chemical shifts at 6.3–6.7 ppm, 6.8–7.2 ppm represent the aromatic protons in polystyrene and those at 3.34–3.80 ppm the protons of the oxyethylene repeat unit.

Both the yields of purified PS-b-PEG and homopolystyrene and the ^{1}H n.m.r. spectra indicate that thermal polymerisation of styrene predominates the polymerisation process. Thermal polymerisation in connection with nitroxide free radical mediated polymerisation of styrene, and the factors affecting alkoxyamine homolysis rates have been reported[21,22]. In the TEMPO mediated polymerisation of styrene, it has been found that the polymerisation is driven by a constant supply of initiating radicals by thermal initiation to make up for the irreversible termination reactions while the adduct with TEMPO controls molecular weight and polydispersities by exchange reactions[23]. However, when the molecular weight of a dissociating radical as described[22] increases, that is, becomes that of the MPEG–styrene radical with a flexible chain, the reaction with styrene may be hindered. Therefore, the thermal polymerisation of styrene can play major role in the system. This phenomenon may be connected with the viscosity of the reaction mixture and in the present case perhaps also with a shielding effect by the hydrophilic PEG chain.

The low yield of purified block copolymer PS-b-PEG also indicates low initiator efficiency for MPEG-TEMPO. Indeed, in connection with the purification of the crude product, unreacted macroinitiator as well as water soluble PS-b-PEG with short polystyrene segments was identified in the reaction mixture. This observation is consistent with that reported by Georges *et al.*[16].

The purified PS-b-PEG consisted of a main product with $M_n = 170\,000$ and $M_w/M_n = 1.2$ as determined by GPC and a broad minor shoulder of low molecular fraction having $M_n = 6100$ and $M_w/M_n = 2.2$. The isolated homopolystyrene had $M_n = 105\,000$ and $M_w/M_n = 1.5$, narrower than was obtained by conventional thermal polymerisation. This is

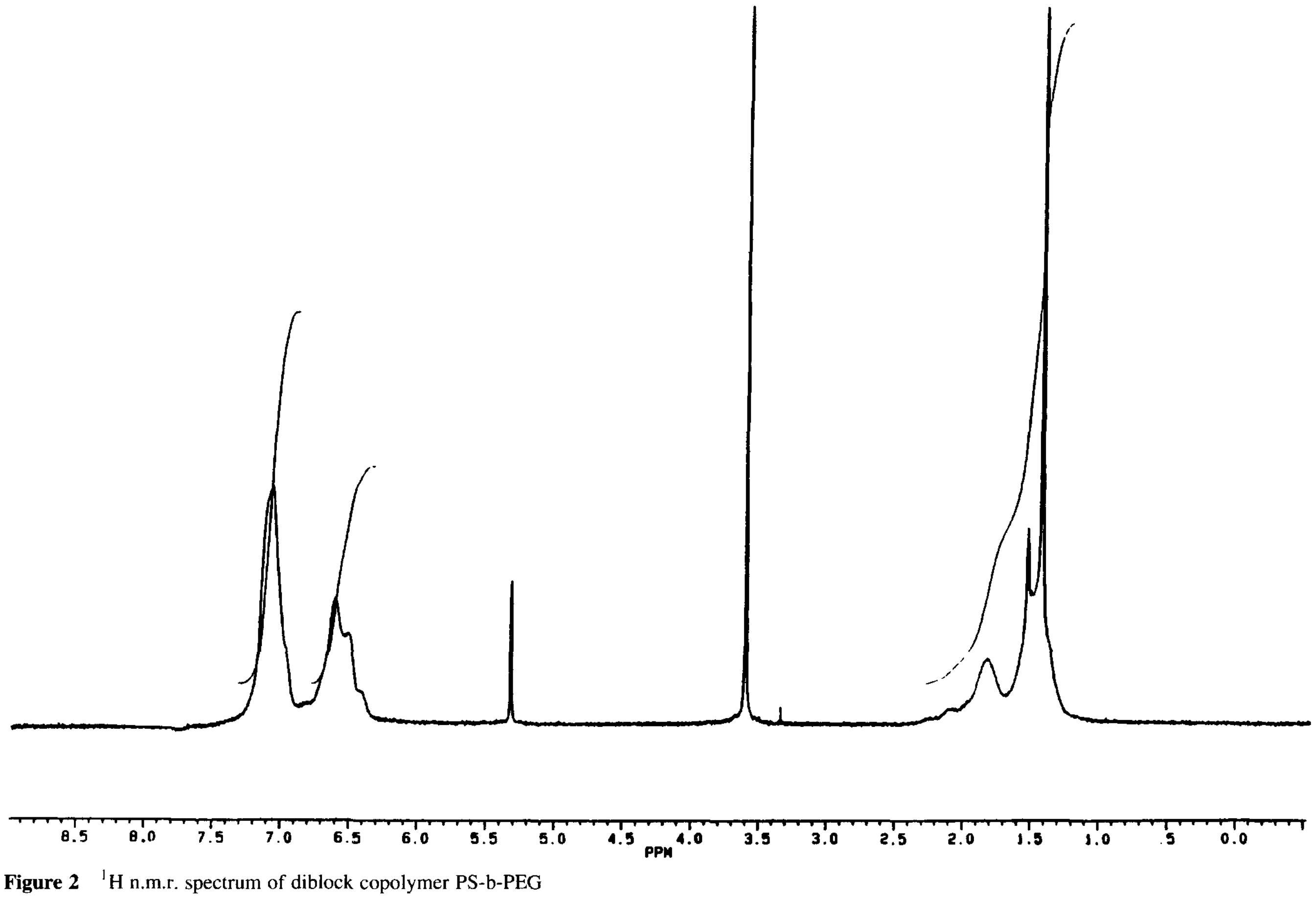


Figure 2 ^{1}H n.m.r. spectrum of diblock copolymer PS-b-PEG

because in the free-radical polymerisation of styrene at temperatures up to 80°C, the theoretical limiting polydispersity is 1.5 for low conversion, however, at temperatures above 80°C, termination occurs by a combination of coupling and disproportionation[24,25]. It can be proven that in this case, MWD has a theoretical limiting value larger than 1.5, and for high-conversion polymerisation, MWD becomes even broader[25].

The low yield of PS-b-PEG and a relatively narrow MWD of the homopolystyrene suggest that deactivation takes place during the 'living' free radical polymerisation of styrene initiated by macroinitiator MPEG-TEMPO and that polystyrene in the system after thermal initiation is probably partly formed by 'living' free radical polymerisation being mediated by transferred nitroxyl radicals[26,27]. At the same time, block copolymer formation is affected by deactivation by transfer and termination.

CONCLUSIONS

TEMPO-terminated poly(ethylene glycol) (MPEG-TEMPO) may be prepared by reacting tosylated monomethoxypoly(ethylene glycol) with HO-TEMPO. The macroinitiator MPEG-TEMPO initiates 'living' free radical polymerisation of styrene to yield amphiphilic diblock copolymer PS-b-PEG. However, only a small amount of this block copolymer could be obtained since transfer reaction occurs and, at the same time, large amounts of homopolystyrene with relative narrow MWD are generated by thermal initiated polymerisation in a process which becomes nitroxide mediated by transfer and exchange reactions.

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