New Highly Functionalized Primary Allyl, Hydroxyl, and Tosyl Poly(propylene glycol)s (PPG) from Available PPG Derivatization

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ABSTRACT: The more stringent reaction conditions used to optimize the synthesis of α,ω-di-*O*-(4-toluenesulfonyl)poly(propylene glycol) from commercial poly(propylene glycol) (PPG) of 2000 g/mol molar mass, compared to those applied for allowing the same modification on PEG, showed that the secondary hydroxyl end groups were less reactive than the primary ones. Thus, chemical end group transformations were successfully done on this polymer by introducing various groups, such as oxopropyl, carboxymethyl, allyl, 3-hydroxy-*n*-propyl, and 3-(4-toluenesulfonate)-*n*-propyl, on its terminal monomer units in order to enhance their reactivity. These reactions were optimized by adjustment of the reaction conditions to obtain fully α,ω-functionalized poly(propylene glycol)s. Particularly, the more reactive primary diallyl, dihydroxyl, and ditosyl poly(propylene glycol)s were obtained with very high functionality within experimental accuracy in a range ±0.1.

Introduction

Poly(propylene glycol)s (PPG) are important in polymer chemistry since they are used in polyurethanes synthesis,[1] as hydraulic fluids, lubricants, and surface active and chemical intermediates.[2] They are obtained by base-catalyzed or nonbasic double-metal cyanide-catalyzed (such as zinc hexacyanocobalt) polymerization of propylene oxide (PO).[3] Propylene oxide and ethylene oxide (EO) can be copolymerized to obtain either random copolymers which are used as thermoseparating polymers for the partition of amino acids and peptides in aqueous two-phase system[4] or diblock and triblock copolymers which have also bioapplications. For example, the diblock copolymers (PPG-*b*-PEG) (Proxanols) and their derivatives can be grafted onto proteins providing new functions of modified proteins, such as the capability of translocation across biological membrane or the ability to form molecular assemblies due to interaction with various amphiphilic compounds.[5] About triblock copolymers based on PPG and PEG, there are various structures[6] owning different properties, especially the poly(ethylene glycol-*b*-propylene glycol-*b*-ethylene glycol)s (Pluronics) which have attracted significant attention for medical applications. More precisely, they can be used to prevent protein adsorption and platelet adhesion on surfaces owing to their amphiphilic character.[7] Furthermore, in solution, Pluronics form micelles which can be used to incorporate drug molecules into cells.[8] Recently, Pluronics were used in vivo for gene delivery into muscles and appeared to be valuable for this application.[9−11]

However, despite many applications described in the literature and except for the work of Luftmann,[3] little attention was provided to the chain end derivatization of PPG. The paper reports on the chemical modifications of poly(propylene glycol) end groups by various reactants, never previously employed for functionalization of this particular polymer. The transformation of secondary hydroxyl and allyl end groups into primary hydroxyls may be very helpful to those interested in the synthesis of amphiphilic compounds and block copolymers, in fields where high purity is required.

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Experimental Section

Chemicals. Methylene chloride (sds), DMF (sds), pentane (sds), triethylamine (Aldrich), and allyl bromide (Aldrich) were distilled over calcium hydride.

Poly(propylene glycol) (M_n = 2000 g/mol) (Aldrich), tosyl chloride (TsCl) (Aldrich), pyridine (Acros), H_2O_2 in water (35%) (Aldrich), chromium trioxide (Labosi), hydrochloric acid (12 M, Aldrich), iodine (Aldrich), trichloroacetyl isocyanate (Aldrich), methanol (sds), diethyl ether (sds), THF (sds), dioxane (sds), sodium hydroxide solution 30% (Aldrich), ethanol (sds), 9-borabicyclo[3.3.1]nonane (9-BBN) in THF (0.5 M, Aldrich), α-cyano-4-hydroxycinnamic acid (HCCA, Aldrich), NaH 60% dispersion in mineral oil (Aldrich), and potassium chloride (Prolabo) were used as received.

Polymer Characterization. Polymer analysis was performed by ^{1}H NMR spectroscopy (Bruker 300 MHz, scans: 128; solvents: $CDCl_3$ or DMSO-d_6); SEC (Waters system, columns: Styragel HR4E + HR1 (diameter 4.6 mm, *L* 30 cm), eluent: THF (0.3 mL/min), detector: RI (Waters 410), pump: Waters HPLC 515, software: Millenium 3.2, the calibration curve was obtained with PEG standards); FTIR (Bruker Tensor 27, method: ATR Ge, software: OPUS); mass spectrometry MALDI−TOF (MS experiments were performed using a Perseptive Biosystems Voyager-DE Pro STR MALDI−TOF mass spectrometer (Applied Biosystems/MDS SCIEX, Foster City), equipped with a nitrogen laser (λ = 337 nm). The mass spectrometer was operated in the positive ion reflectron mode with an accelerating potential of +20 kV. Mass spectra were recorded with the laser intensity set just above the ionization threshold (2800−3000 kW cm^{-2}) to avoid fragmentation and to maximize the resolution (pulse width 3 ns). For experiments, an equal volume (20 μL) of polymer (10^{-3} M in diethyl ether) was mixed with a solution of matrix HCCA (10^{-1} M in THF) before addition of 10 μL of 5×10^{-2} M potassium chloride salt solution in methanol and water (v/v: 1/1). About 1 μL of the resulting mixture was spotted onto the sample plate and allowed to air-dry at room temperature. Typically, five acquisitions corresponding to 30 shots each were summed for each deposit to obtain representative mass spectra).

Synthesis of α,ω-Di-*O*-(4-toluenesulfonyl)poly(propylene glycol) (PPG-diTs). Tosyl chloride (923 mg, 4.8 mmol) and triethylamine (2 mL, 14.3 mmol) were successively added

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to poly(propylene glycol) (2.16 g, 1.1 mmol). The reaction mixture was stirred at 55 °C for 161 h. The crude product was dissolved in methylene chloride, and the organic layer was washed with water to remove $N(Et)_3H^+/Cl^-$. Then, the organic layer was evaporated in vacuo, and pyridine (5 mL) was added to react with and remove the excess of tosyl chloride. Water and methylene chloride were added, and the organic layer was washed with acidic water to remove the excess of pyridine. The organic layer was evaporated and dried in vacuo. Yield was 2.25 g (90%). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.1 (d, $CH_2-CH(CH_3)-O$); 1.3 (d, $CH_2-CH(CH_3)-OTs$); 2.5 (s, CH_3-Ph); 3.4 and 3.6 (m, $CH_2-CH(CH_3)-O$); 4.7 (m, $CH_2-CH(CH_3)-OTs$); 7.3 and 7.8 (AA′BB′ system, H_{Ph}).

Synthesis of α,ω-Di-*O*-(2-oxopropyl)poly(propylene glycol) (PPG-diCH_2COCH_3). Pyridinium chlorochromate (PCC):[12] 3 g (0.03 mol) of CrO_3 was added rapidly on stirring to 5 mL of 6 M HCl (0.03 mol). After 5 min, the homogeneous solution was cooled to 0 °C, and 2.47 mL (0.03 mol) of pyridine was carefully added over 10 min. The orange solid obtained was filtered and dried in vacuo (yield 5.08 g, 78%).

To a solution of poly(propylene glycol) (0.80 g, 0.4 mmol) in methylene chloride (4 mL), PCC (0.61 g, 2.8 mmol) was added, and the mixture was heated at 55 °C for 15 h. After addition of diethyl ether and methylene chloride, the black solid was filtered. Yield was 696 mg (86%). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.1 (d, $CH_2-CH(CH_3)-O$); 2.2 (s, $CH_2-CO-CH_3$); 3.4 and 3.6 (m, $CH_2-CH(CH_3)-O$); 4.2 (s, $CH_2-CO-CH_3$). IR (cm^{-1}): 2971−2870 (ν Csp_3-H), 1725 (ν C=O ketone), 1452 (δ Csp_3-H), 1373 (δ Csp_3-H CH_3), 1103 (ν C−O).

Synthesis of α,ω-Di-*O*-(carboxymethyl)poly(propylene glycol) (PPG-diCH_2COO^-). PPG-diCH_2COCH_3 (696 mg, 0.3 mmol), I_2 (777 mg, 3 mmol), and NaOH in water (30%) (0.4 mL, 4 mmol) were dissolved in 5 mL of THF. The solution was stirred at 66 °C for 22 h. After evaporation of solvent in vacuo, the product was dissolved in methylene chloride, and then the organic layer was washed with a solution of sodium thiosulfate to remove the excess of I_2 and evaporated. To complete the reaction, the product was dissolved in dioxane (10 mL) before addition of I_2 (1.67 g, 6.6 mmol) and aqueous NaOH (30%) (1 mL, 10 mmol). The solution was then heated at 90 °C for 17 h more. After evaporation of solvents, the product was treated as described above. Yield was 317 mg (56%). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.1 (d, $CH_2-CH(CH_3)-O$); 3.4 and 3.6 (m, $CH_2-CH(CH_3)-O$). IR (cm^{-1}): 2970−2868 (ν Csp_3-H), 1613 (ν C=O carboxylate), 1456 (δ Csp_3-H), 1373 (δ Csp_3-H CH_3), 1103 (ν C−O).

Synthesis of α,ω-Di-*O*-allylpoly(propylene glycol) (PPG-diallyl). As a typical example, PPG (2.02 g, 1 mmol) was dissolved in 7 mL of dried DMF. NaH (2 g, 50 mmol) was washed with dried pentane. Then the solution of polymer was added to NaH, and the solution was stirred at room temperature under N_2. After 7 h, allyl bromide (5 mL, 57 mmol) and 3 mL of DMF were added. The mixture was heated at 80 °C for 62 h. Then, 3 mL of EtOH was added for the neutralization of NaH. Methylene chloride and water were added, the organic layer was washed with water to remove DMF. After evaporation, the product was dried in vacuo. Yield was 2.08 g (99%). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.1 (d, $CH_2-CH(CH_3)-O$); 3.4 and 3.6 (m, $CH_2-CH(CH_3)-O$); 4.1 (d, $CH_2-CH=CH_2$); 5.1 and 5.3 (d, $CH_2-CH=CH_2$); 5.9 (m, $CH_2-CH=CH_2$).

Synthesis of α,ω-Di-*O*-(3-hydroxy-*n*-propyl)poly(propylene glycol) (PPG-di$(CH_2)_3OH$). To α,ω-diallylpoly(propylene glycol) (3.52 g, 1.7 mmol), 9-BBN in THF (18.5 mL, 9.2 mmol) was added under N_2, and the solution was stirred at 65 °C for 23 h. Then, the mixture was cooled and NaOH in water (30%) (2 mL, 16 mmol) and H_2O_2 in water (17 mL, 194 mmol) were added before heating at 65 °C for 39 h. After addition of methylene chloride, the organic layer was washed with water and evaporated, and the modified polymer was dried in vacuo. Yield was 2.53 g (71%). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.0 (d, $CH_2-CH(CH_3)-O$); 1.6 (q, $CH_2-CH_2-CH_2-OH$); 3.3 and 3.4 (m, $CH_2-CH(CH_3)-O$); 4.3 (t, OH).

Synthesis of α,ω-Di-*O*-(3-(4-toluenesulfonate)-*n*-propyl)poly(propylene glycol) (PPG-di$(CH_2)_3OTs$). To a solution of primary PPGdiOH (PPG-di$(CH_2)_3OH$) (771 mg, 0.36 mmol) in methylene chloride (8 mL) were successively added tosyl chloride (362 mg, 1.9 mmol) and triethylamine (0.26 mL, 1.9 mmol). The solution was stirred at −20 °C for 64 h and then was processed as described above (cf. experimental part). Yield was 472 mg (53%). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.0 (d, $CH_2-CH(CH_3)-O$); 1.7 (q, $CH_2-CH_2-CH_2-OTs$); 2.4 (s, CH_3-Ph); 3.3 and 3.4 (m, $CH_2-CH(CH_3)-O$); 4.0 (t, $CH_2-CH_2-CH_2-OTs$), 7.5 and 7.8 (AA′BB′ system, H_{Ph}).

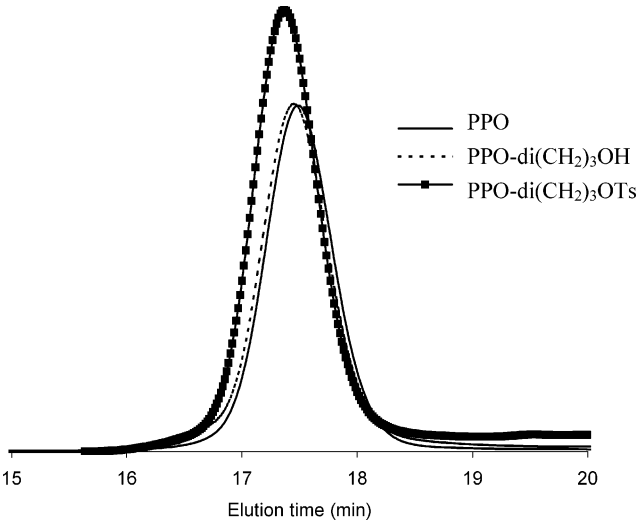


Figure 1. SEC traces in THF of (—) starting PPG (M_n = 2000 g/mol, I_p = 1.18), (- - -) PPG-di$(CH_2)_3OH$ (run 14, M_n = 2100 g/mol, I_p = 1.21), and (−■−) PPG-di$(CH_2)_3OTs$ (M_n = 2300 g/mol, I_p = 1.17).

Results and Discussion

Characterization of Hydroxy Telechelic Poly(propylene glycol) (PPG). It was important to know precisely the content of hydroxyl functions of poly(propylene glycol) (PPG) used as starting compound in this study, claimed for a number-average molar mass of 2000 g/mol and a functionality of 2 by the supplier. Thus, the study began by verifying the molecular weight of commercial polymer by two independent methods, since the knowledge of this parameter is an important clue for this work.

The number-average molecular weight obtained by SEC analysis in THF (M_n = 2000 g/mol, I_p = 1.18) was the same as the one pointed by the supplier (Figure 1). As stated by the supplier, this value was used to determine the hydroxyl functionality of polymer after end titration with KOH.

Furthermore, the mass spectrometry MALDI−TOF analysis of PPG was performed with an acidic matrix (HCCA) to which KCl was added to promote ion formation and using deisotoping process to reduce the complexity of the mass spectrum. The spectrum gives rise to an almost symmetrical main distribution of ions peaks centered around *m/z* 2030.4 (I_p = 1.04) and a minor series of peaks with a 16 Da difference lower in mass corresponding to a small amount of sodium adduct ions of compound (Figure 2A). This observed mass value agree within ±0.02% with the potassium adduct ion $[M + K]^+$ for a dihydroxypolypropylene glycol of polymerization degree 34, corresponding to that of determined from SEC with an experimental error about ±10%. Of note, the sharp distribution obtained confirms the narrow polydispersity index found by SEC as previously reported.[3] Thus, the above data allowed to estimate an average polymerization degree for available PPG equal

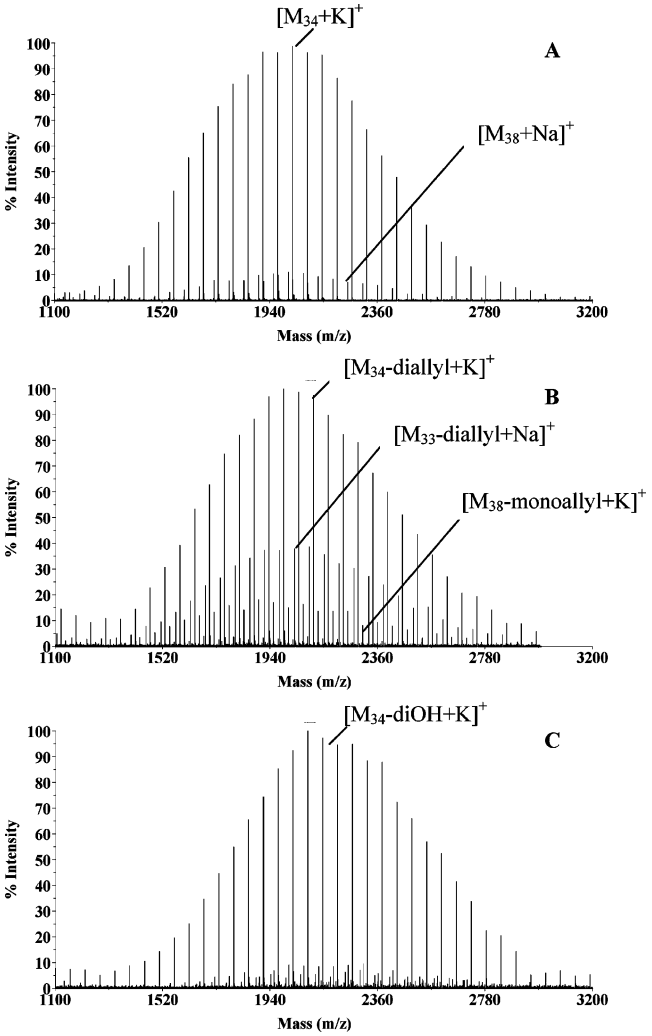


Figure 2. MALDI-TOF mass spectra (HCCA matrix) of (A) starting PPG 2000, (B) PPG-diallyl for run 10, and (C) PPG-di$(CH_2)_3$OH for run 14.

to 34 ± 4. Consequently, the hydroxy functionality given by purchaser was really found of 2 ± 0.2.

Then, the ^{1}H NMR spectrum of PPG in DMSO-d_6 showed, besides the protons of polymer chain at 1.0 ppm (−CH_2CH(CH_3)O−), 3.3 and 3.4 ppm (−CH_2CH-(CH_3)O−), a broad singlet characteristic of secondary hydroxyl groups at 4.4 ppm (Figure 3A). According to Boulares et al., the assignment of the alcohols class was confirmed by the ^{1}H-2D-NMR experiment performed on the sample after addition of trichloroacetylisocyanate (S1).[13] Beside the signals of polymer chain and hydroxy ends, the spectrum showed also the characteristic peaks of allyl group at 3.9, 5.1, 5.2, and 5.8 ppm (Figure 3A). This terminal double bond, arising from a side reaction during the base-catalyzed polymerization of propylene glycol, leads to an allyl alcoholate species which can also react with propylene oxide (PO) to give CH_2═CH−CH_2−(OCH_2CH(CH_3))$_n$−OH chains.[3,14,15] Of note, these mono-hydroxylated species were not detected in the MALDI spectrum at 18 Da below the main series, but only seen with a very low intensity level in the *m/z* range 1300−1600 as previously reported.[3]

From NMR intensities of allyl, hydroxyl, and polymer chain resonance protons, by assuming that all chains have either olefinic or alcohol end group, the polymerization degree of available PPG was calculated according to the following relation: $DP = 2h_{CH_3(PG)}/3(h_{all} + h_{OH})$, where $h_{CH_3(PG)}$, h_{all}, and h_{OH} are respectively the peaks integrations of β methyl (c), allyl (e), and hydroxyl (d) groups of polymer (Figure 3A). A DP = 37 ± 2 was found, that is to say with an accuracy of ±5%, allowing to estimate an hydroxyl functionality fct_{OH} of 1.9 ± 0.1. In the same way, the residual amount of allyl groups was found to about 7% of terminal functions, which correspond to an allyl functionality fct_{allyl} of 0.1 ± 0.1 for our starting PPG. At this point, it could be seen that evaluation of the polymerization degree by NMR has given a range value shorter and within the ones obtained from SEC and mass spectrum techniques. In addition, it is to be noted that both DP and fct_{OH} NMR values of PPG were in good agreement with the SEC ones determined above and more accurate. For these reasons, NMR quantitative determinations of modified poly(propylene glycol)s described in this work were made assuming DP = 37 for polymer chain, except when the modification permit us to distinguish the two end units from the others (using DP = 35 in this case).

Thus, the commercial PPG contained predominantly poor reactive secondary hydroxyl groups and made profit to be modified on their ends in order to obtain PPGs highly functionalized by telechelic moieties that are more reactive than secondary hydroxyl one.[1,3]

Synthesis of α,ω-Di-*O*-(4-toluenesulfonyl)poly-(propylene glycol) (PPG-diTs). The usefulness of ester-modified PPGs is interesting for synthesis of thermoplastic elastomers or amphiphilic copolymers such as polyalkyloxazoline-based copolymers. The experiments were carried out by reaction of PPG with excess tosyl chloride in methylene chloride at different temperatures and in the presence of triethylamine or not (Table 1).

On the ^{1}H NMR spectrum of tosylated PPG in $CDCl_3$, we observed the signals AA′BB′ spin system (7.3 and 7.8 ppm) and a singlet (2.5 ppm) both characteristics of tosyl ester end group, a doublet (1.3 ppm), and a peak (4.7 ppm) corresponding respectively to the β methyl and α methine protons of the terminal monomer units near the sulfonate functions (S2). The tosyl functionality was determined by ^{1}H NMR from peak intensities ratio of tosylate end groups (7.3 or 7.8 ppm) to that of backbone methyl protons (1.1 ppm), using in this case a DP_n = 35 for the polymer chain.

For the first experiment (run 1, Table 1), we have applied the same experimental conditions previously optimized in the laboratory for tosylation of poly-(ethylene glycol).[16] Contrarily to PEG for which the tosylation was complete, the PPG functionality obtained was only of 0.5 ± 0.1. This difference was assigned to the lower reactivity of secondary hydroxyl end group, compared to the primary one. Moreover, according to runs 6, 7, and 8 compared to run 5, triethylamine plays an important part, reacting with tosyle chloride to form an ionic active species. Also, as it can be seen for runs 2, 3, and 4, the functionality was unchanged whatever the temperature used but rises with increasing the reaction time (runs 4 and 6). The best result was obtained in bulk with an excess of triethylamine and the higher reaction time (run 8). In these conditions, according to the content of hydroxy group in the starting compound (see beginning of section), the tosylation of PPG was found to be complete (fct_{Ts} = 1.9 ± 0.1).

Further, the molar mass (2000 g/mol) and Ip (1.21) found for PPG-diTs by SEC analysis (data not shown) were very close to those of the starting polymer, allowing

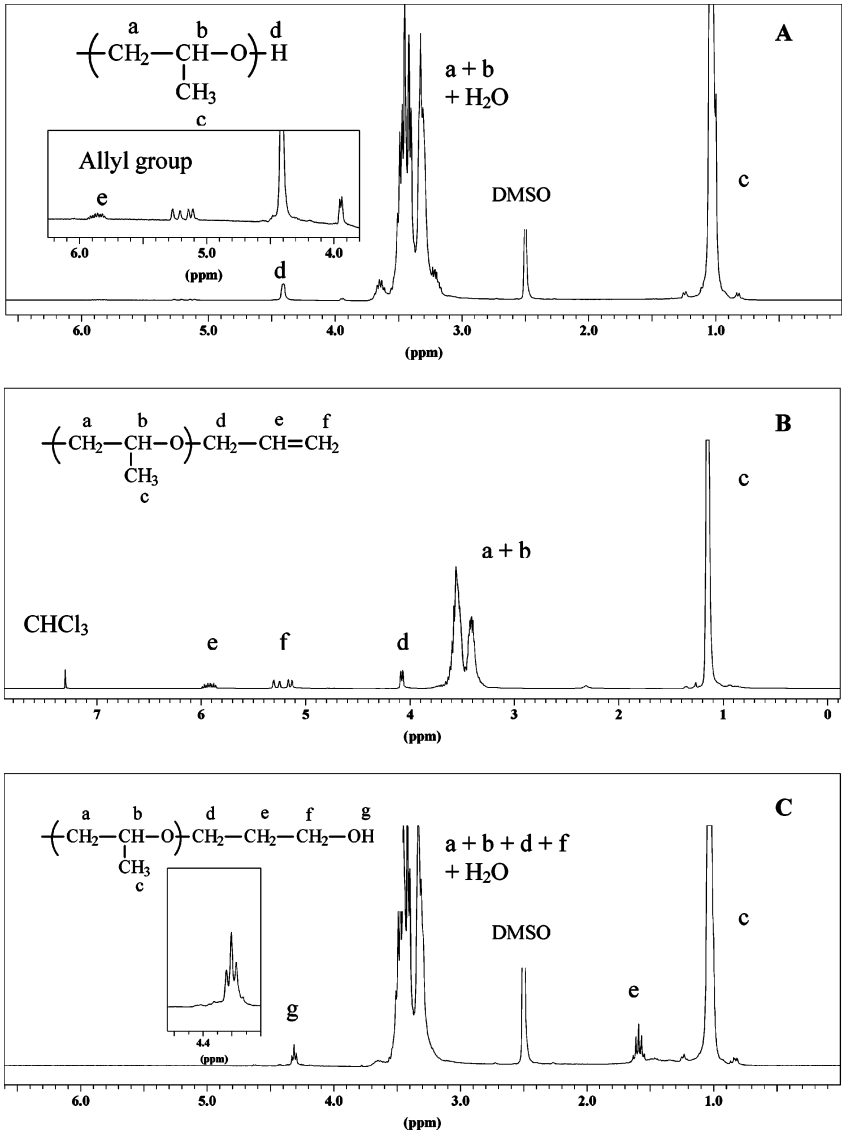
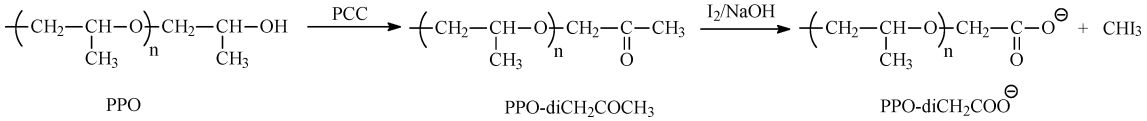


Figure 3. 300 MHz ^{1}H NMR spectra of (A) starting PPG 2000 in DMSO-d_6, (B) PPG-diallyl in $CDCl_3$ for run 10, and (C) PPG-di$(CH_2)_3$OH for run 14 in DMSO-d_6.

Scheme 1. Synthetic Route for PPG-diCH_2COCH_3 by Oxidation of PPG 2000 and for PPG-diCH_2COO^- by the Haloform Reaction on PPG-diCH_2COCH_3



to conclude that neither chain cleavage nor formation of duplication product occurred whatever the temperature used, contrarily to that previously observed during the tosylation of PEG.[16]

Synthesis of α,ω-Di-*O*-(2-oxopropyl)poly(propylene glycol) (PPG-diCH_2COCH_3). Oxidation is a characteristic reaction test to determine the alcohol class. Indeed, in mild oxidative conditions a primary alcohol gives an aldehyde while a secondary one leads to a ketone. This test can thus be used both to confirm the nature of terminal hydroxylic functions and to functionalize PPG (Scheme 1).

In a first time, an aqueous solution of ClO^- was used, but due to the insolubility of PPG in these conditions, the reaction medium was biphasic, and the resulting polymer was far from being quantitatively functionalized. Since the pyridinium chlorochromate (PCC) is a mild oxidizing agent when used in organic medium,[12]

Table 1. Tosylation of Commercial Poly(propylene glycol) ($[OH_{PPG}]$ = 0.1 mol/L) by TsCl ($[TsCl]/[OH_{PPG}]$ = 2.4) in CH_2Cl_2

run	$[N(Et)_3]/[TsCl]$	time (h)	temp (°C)	fct_{Ts}[a]
1	1	72	−21	0.5
2	1	24	0	0.2
3	1	24	RT	0.2
4	1	24	55	0.2
5	0	24	55	0
6	1	88	55	1.3
7[b]	2	89	55	1.6
8[b]	3	161	55	1.9

[a] Secondary tosyl ester functionality calculated from ^{1}H NMR using DP_n = 35 for PPG. [b] In bulk.

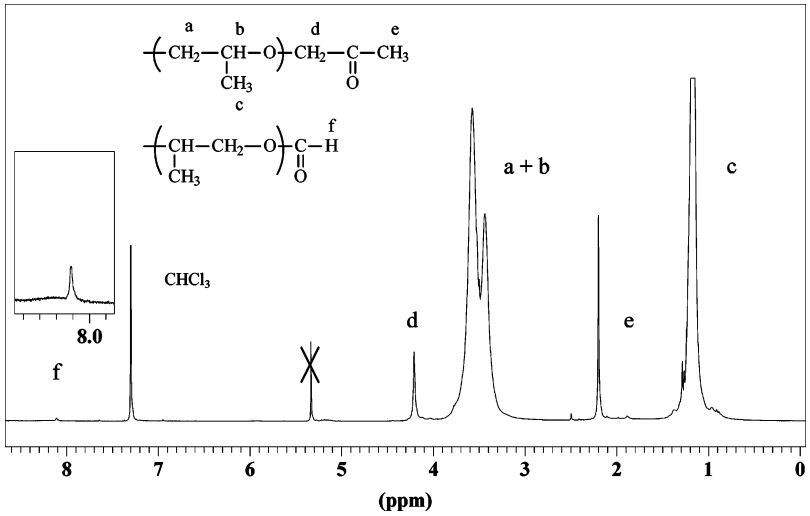


Figure 4. 300 MHz ^{1}H NMR spectrum of PPG-diCH_2COCH_3 in $CDCl_3$.

poly(propylene glycol) was then reacted with excess PCC in methylene chloride at 55°C for 15 h, to give α,ω-di-*O*-(2-oxopropyl)poly(propylene glycol) in high yield (86%).

On the ^{1}H NMR spectrum of the resulting polymer in $CDCl_3$, besides the peaks characteristics of main chain protons (1.1, 3.4, and 3.6 ppm), two singlets at δ = 4.2 and 2.2 ppm assigned to 2-oxopropyl end group ($-CH_2COCH_3$) appeared (Figure 4). The conversion of the hydroxy end groups into ketone functions was determined by ^{1}H NMR from the peak intensities ratio of terminal ketone function (4.2 ppm) to that of backbone methyl protons (1.1 ppm), assuming a $DP_n = 35$ for the polymer since the two terminal monomer units of PPG were now modified and therefore clearly distinguishable on the spectrum. It was found to be complete, since the measured functionality was 1.9 ± 0.1, in good agreement with the hydroxyl content of the initial PPG. The presence of carbonyl group in the polymer was also confirmed by FTIR spectroscopy of sample showing the band characteristic of ketone at 1725 cm^{-1}.

On the other hand, the characteristic peaks of allyl groups were absent while a singlet assigned to formyl−ester protons (PPG-OC*H*O) appeared at 8.1 ppm in a same amount as initial allyl group present in the starting PPG (fct_{OCHO} found 0.1 ± 0.1). At this point, Krompiec showed that isomerization of various allyl ethers to 1-propenyl derivatives is a known side reaction occurring ostensibly in moderate conditions when transition metal complex is used as catalyst with external addition of aromatic species (phosphine).[17] Moreover, it was also related that oxidative cleavage double bonds could arise and stopped at the aldehyde stage by using chromium-based reagents.[18] Thus, the formyl−ester units were possibly formed by oxidative cleavage of isomerized allylic double bond moiety, in the oxidative pyridinium chlorochromate medium.

Synthesis of α,ω-Di-*O*-(Carboxymethyl)poly(propylene glycol) (PPG-diCH_2COO^-). The haloform reaction on PPG-diCH_2COCH_3 was considered in order to introduce the more nucleophilic carboxylate group on chain ends by obtaining α,ω-di-*O*-(carboxymethyl)poly(propylene glycol) (Scheme 1). To achieve this goal, the PPG-diCH_2COCH_3 synthesized above was dissolved in a THF solution containing I_2 and NaOH before heating at 66 °C for 22 h. After the workup procedure (see Experimental Section), the polymer analyses were performed by both ^{1}H NMR and MALDI-TOF techniques.

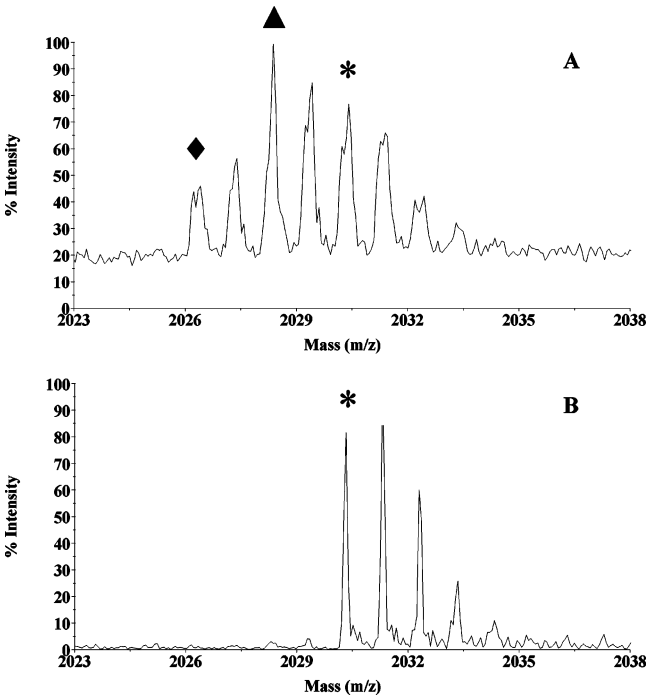


Figure 5. MALDI-TOF mass spectra (HCCA matrix) of (A) mixture of polymer (◆) PPG-diCH_2COCH_3/(▲) CH_3COCH_2−PPG-CH_2COOH/(∗) PPG-diCH_2COOH and (B) (∗) pure PPG-diCH_2COOH; observed isotope patterns for an individual polymer chain 32-mer containing the two modified ends, adduct K^+.

According to the ^{1}H NMR spectrum, the two singlets corresponding to methyl ketone function (2.2 and 4.2 ppm) remained present with a level of about 50%, indicating that the reaction was incomplete. The compound contained thus a mixture of polymers modified by either oxopropyl or carboxymethyl groups, which was confirmed in MALDI-TOF analysis by comparing the experimental and calculated isotope patterns for an individual polymer chain 32-mer containing the two modified ends (Figure 5A, S3). Indeed, the spectrum displayed both the potassium adduct ion peaks of the unreacted diketone polymer (PPG-diCH_2COCH_3) at *m/z*

Scheme 2. Synthetic Route for PPG-diallyl, PPG-di$(CH_2)_3$OH, and PPG-di$(CH_2)_3$OTs Polymers

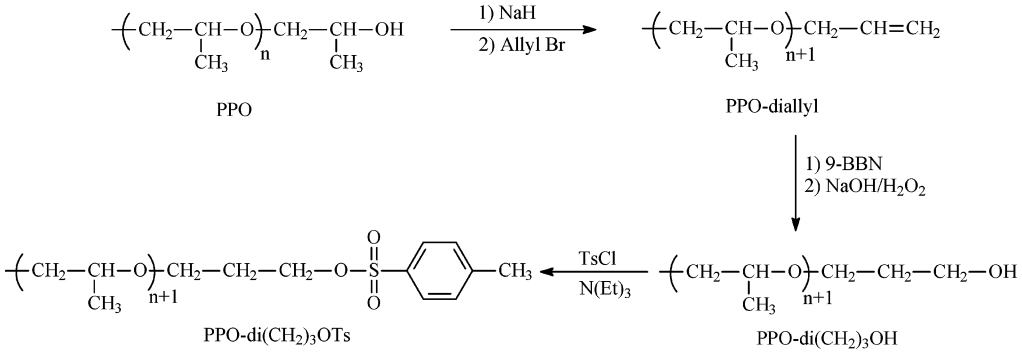


Table 2. Synthesis of α,ω-Di-*O*-Allylpoly(propylene glycol) from PPG with Allyl Br in Presence of NaH (Alcoholate Formation at RT Followed by Allylation Reaction at 80 °C) in DMF

run	[NaH]/[OH_{PPO}]	alcoholate formation time (h)	[allyl]/[OH_{PPO}]	allylation time (h)	fct_{allyl}[a]	yield (%)
9	6.7	6	15	16	1.4	95
10	25	7	28	63	2.0	97

[a] Allyl functionality calculated from ^{1}H NMR using $DP_n = 37$ for PPG.

2026.3 and those of the partially carboxylated one (CH_3-$COCH_2$-PPG-CH_2COOH) at *m/z* 2028.4.

To optimize the reaction, the mixture of polymers was reacted for 17 h more with a large excess of I_2 and NaOH at a higher temperature (90 °C). The NMR analysis of the polymer collected at that time showed the total disappearance of the characteristic peaks assigned to methyl ketone terminal functions and the appearance of a peak at 4.9 ppm corresponding to the protons of byproduct CHI_3 formed during the reaction (data not shown). Nevertheless, it did not show any characteristic peak of methylene near the carboxylate group. Because of oxidative conditions of haloform reaction, the residual formyl−ester ends were probably oxidized into carbonate groups (PPG-$OCOO^-$) since the corresponding peak at 8.1 ppm also disappeared, and no peak assignable to primary hydroxy end (coming from hydrolysis of this group) was observed in the spectrum.

However, FTIR spectroscopy confirmed the complete formation of the carboxylate function by showing at 1613 cm^{-1} the band corresponding to this function and the absence of ketone band at 1725 cm^{-1}. Also, the MALDI spectrum showed only the distribution of potassium adduct ion peaks characteristic of dicarboxylated-PPG centered around *m/z* 2030.3 (Figure 5B, S3). The carboxylate functionality obtained for PPG-diCH_2COO^- was thus claimed to be the same as the initial ketone content, that is to say, 1.9 ± 0.1.

Synthesis of α,ω-Di-*O*-allylpoly(propylene glycol) (PPG-diallyl). To obtain an olefinic group on PPG ends, which can be used to react for example with hydrogenopoly(dimethylsiloxane) to form block copolymers, allylation was considered. The synthesis of *O*-allylpoly(propylene glycol) was achieved in two steps: (i) PPG alcoholate formation by reaction with NaH followed by (ii) reaction with allyl bromide (Scheme 2), using different time−temperature conditions summarized in Table 2.

According to the results, it can be noticed that high quantities of NaH and allyl bromide as well as longer reaction time were required to optimize the conversion of secondary hydroxy groups into O-allyl ends, which tends to confirm once again their poor reactivity. The ^{1}H NMR spectrum of allylated PPG in $CDCl_3$ showed the resonance protons signals of introduced allylic groups, which allowed to determine their content by using the peak areas of olefinic group (5.9 ppm) and that of main chain (1.1 ppm) by assuming a $DP_n = 37$ for polymer (Figure 3B). The found values indicated a total conversion of terminal hydroxy group of PPG into allyl function for compound obtained on run 10 (Table 2). Nevertheless, because of solubility problems encountered with this polymer in DMSO probably because of the presence of a hydrophobic allyl group, it was not possible to verify the absence of a hydroxy group signal by NMR. Thus, a MALDI experiment was also done with this polymer.

As for the starting PPG (Figure 2A), the series belonging to potassium and sodium adduct ions of diallyl-PPG were clearly distinguished (Figure 2B). The peak height of the sodium series was higher in this case because of the use of NaCl salt during workup. A new shorter distribution also appeared with a 18 Da higher mass than the diallyl chains, which would correspond to potassium adduct series of monoallyl ones. However, at this point it is to be noted that the appraisal of these species content from the MS data can obviously be criticized, since it is strongly dependent on the experimental parameters used such as the nature of the matrix, the number of laser shots, and the quantity of added salt.[19] Particularly, Terrier et al. showed that desorption/ionization of the most hydrophobic chains (monoallylated Pluronics compared to diol ones in their case) was favored by using a hydrophobic matrix dithranol.[19] Applied to the more hydrophilic matrix HCCA used in the work, this result implies that the monoallyl chains have a better desorption than the diallyl ones in this case, and it could explain why in this MALDI experiment the monoallylated-PPG content seemed to be more significant than expected, according to the very high allyl content found by NMR for this polymer.

Synthesis of α,ω-Di-*O*-(3-hydroxy-*n*-propyl)poly(propylene glycol) (PPG-di$(CH_2)_3$OH). Previous work reported that the use of boron hydride reagents, such as 9-borabicyclo[3.3.1]nonane (9-BBN), allowed to convert allyl compounds to corresponding alkylboranes and then to primary alcohols as single regioisomers by oxidative hydrolysis with quantitative yield.[20]

To obtain selectively a primary hydroxyl end group, preliminary experiments were done according to the experimental conditions described by Kranz.[20] Thus, the diallyl-PPG synthesized above was treated with 9-BBN

Table 3. Synthesis of α,ω-Di(3-hydroxy-*n*-propyl)poly(propylene glycol) from Allylated-PPG (Coming from Run 10) by Hydroboration Followed by Oxidative Hydrolysis at 65 °C in THF

	first step[a] hydroboration		second step[b] oxidative hydrolysis		results	
run	[allyl] (mol/L)	time (h)	$[H_2O_2]/[9\text{-BBN}]$	time (h)	fct_{OH}[c]	yield (%)
11	0.1	19	21	22	1.4	91
12	0.2	20	11	3	1.5	52
13	0.2	65	21	23	1.6	76
14	0.2	23	21	39	2.0	71

[a] [9-BBN]/[allyl] = 2.6. [b] [NaOH]/[9-BBN] = 1.6. [c] Primary hydroxy functionality calculated from ^{1}H NMR using $DP_n = 37$ for PPG.

in THF at room temperature to form the corresponding alkylborane (first step), followed by oxidative workup with the mixture H_2O_2/NaOH (second step) (Scheme 2). The NMR analysis in DMSO of the polymer collected revealed an incomplete hydroboration since the allyl protons peaks were still present.

Other experiments using more stringent conditions were performed and described in Table 3. For the run 11, despite a higher temperature used compared to the preceding assay, the NMR spectrum still showed the presence of residual allyl functions (around 30%), indicating that the hydroboration process was yet not complete. Therefore, an optimization was carried out, concentrating the medium 2-fold in the two reaction steps. As we could see for runs 12−14 (Table 3), the hydroxy functionality increased with the increase of 9-BBN and H_2O_2 concentration as well as the reaction time. The primary hydroxyl functionality, estimated by ^{1}H NMR using peak intensities of methylene protons of terminal 3-hydroxy-*n*-propyl group (−$CH_2CH_2CH_2$−OH) (1.6 ppm) and that of main chain methyl protons (1.0 ppm, DP = 37), was found equal to 2.0 ± 0.1 for run 14 (Table 3, Figure 3C). However, we could also see a very weak peak at 4.4 ppm corresponding to about 5% of residual secondary hydroxyl end, in agreement with the low amount of monol species detected by mass spectrum in the former allylated polymer (Figure 2B). Moreover, the formation of primary alcohol was also confirmed by the upfield shift of the hydroxy groups peak at 4.3 ppm.

The SEC analysis showed that no side reaction occurred during the allylation, hydroboration, and hydrolysis steps since the molar masses and polydispersity indices of starting polymer (M_n = 2000 g/mol, I_p = 1.18) and PPG-di$(CH_2)_3$OH (M_n = 2100 g/mol, I_p = 1.21) were close to each other (Figure 1).

Finally, the MALDI mass spectrum of compound showed predominantly the distribution of potassium adduct ion peaks characteristic of α,ω-di-primary hydroxyl-PPG, centered around a peak at *m/z* 2146.4 corresponding to a polymer chain of 34-mer containing two 3-hydroxy-*n*-propyl ends (Figure 2C).

Synthesis of α,ω-Di-*O*-(3-(4-toluenesulfonate)-*n*-propyl)poly(propylene glycol) (PPG-di$(CH_2)_3$OTs). The last functionalization considered is the tosylation of PPG-di$(CH_2)_3$OH to obtain a primary tosyl ester end making profit of its increased reactivity in comparison with the secondary one of PPG-diTs synthesized above. The PPG-di$(CH_2)_3$OH was therefore reacted with tosyl chloride in the same conditions used for the tosylation of PEG (cf. run 1, Table 1).

After the workup procedure, the analysis of polymer by ^{1}H NMR in DMSO-d_6 showed the peaks of tosyl ester group (2.4, 7.5, and 7.8 ppm) and a quintuplet (1.7 ppm) assignable to the methylene protons in the β-position of the tosylate end (−$CH_2CH_2CH_2$-OTs) since it was weakly downfield shifted by this group compared to the same signal of the preceding compound (Figure 6). Also, a triplet at 4.0 ppm due to methylene protons at the α-position of function was observed, while the triplet ascribed to primary hydroxy protons of PPG-di$(CH_2)_3$-OH at 4.3 ppm disappeared. The conversion of hydroxy group into the tosyl ester function, determined from the peak intensities ratio of α methylene protons (4.0 ppm) to that of backbone methyl protons of modified PPG (1.0 ppm, DP = 37), was found to be very quantitative (fct_{Ts}: 1.9 ± 0.1). Again, the high tosyl functionality was confirmed by the negligible signal of the secondary alcohol remaining at 4.4 ppm (Figure 6). Of note, the MALDI experiment was not performed with this polymer since the tosyl moieties tend to be deleted in these conditions.

According to Figure 1 showing also the comparison between SEC analyses of PPG-di$(CH_2)_3$OH and PPG-di$(CH_2)_3$OTs, it could be seen again that the modification made on primary hydroxy-PPG occurred without any side reaction on polymer chain.

Finally, full tosylation obtained in this case in the same mild reaction conditions (i.e., in solution and at

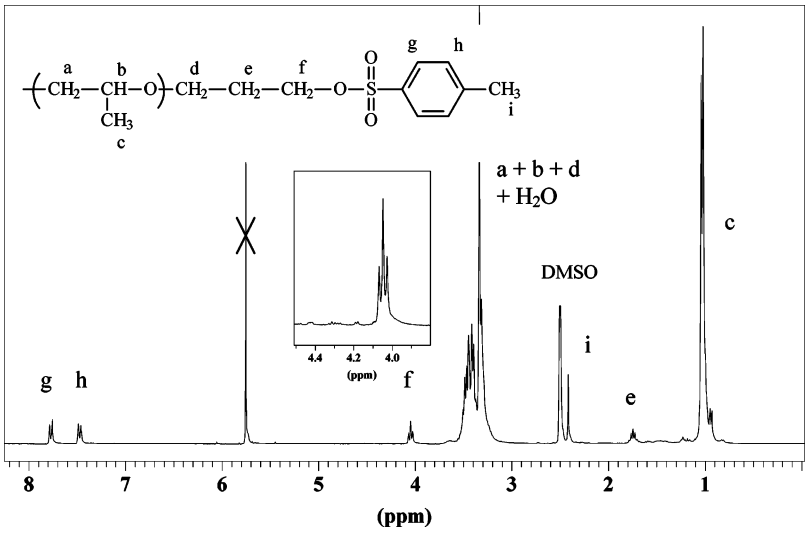


Figure 6. 300 MHz ^{1}H NMR spectrum of PPG-di$(CH_2)_3$OTs in DMSO-d_6.

lower temperature) as with PEG compared to that of commercial PPG confirmed the higher reactivity of terminal primary hydroxy group.

Conclusion

In this work, different functionalizations of commercially available poly(propylene glycol) have been studied in order to obtain various highly modified α,ω-poly(propylene glycol)s that will be able to react with other polymers or suitable for use as initiators of polymerization. Thus, the new 4-(toluenesulfonyl), oxopropyl, and allyl PPGs were obtained by direct modification of commercial PPG, with a functionality in a range 1.9 ± 0.1. The hydroboration reaction followed by oxidative hydrolysis carried out onto α,ω-diallyl PPG allowed to transform insaturated groups onto primary hydroxy ones on chain ends in very high content, according to the NMR and MALDI-TOF analyses. In addition, these chemical modifications occurred without side reaction on polymer backbone, since the molar mass and I_p obtained by SEC analysis for the primary PPG-diol were very close to those of the commercial polymer. Moreover, the full functionality of 1.9 ± 0.1 obtained for the primary tosyl poly(propylene glycol) synthesized from PPG-diol in mild reaction conditions confirmed both the high primary hydroxy content of the latter polymer and its higher reactivity compared to that of available PPG. These different functionalized poly(propylene glycol)s will be used to synthesize new triblock copolymers, and particularly the α,ω-ditelechelic toluenesulfonate poly(propylene glycol)s will be initiate the polymerization of suitable alkyloxazolines to lead to amphiphilic copolymers.

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