Xanthate-Mediated Copolymerization of Vinyl Monomers for Amphiphilic and Double-Hydrophilic Block Copolymers with Poly(ethylene glycol)

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ABSTRACT: Two xanthate end-functional poly(ethylene glycol)s (PEGs) were tested as macromolecular chain-transfer agents (macroCTA) in the reversible addition−fragmentation transfer-mediated polymerization of vinyl acetate (VAc) and *N*-vinylpyrrolidone. The macroCTA leaving group played a determining role in the preparation of the block copolymers. PEG-*b*-PVAc and PEG-*b*-PVP diblock copolymers were obtained when the macroCTA had a propionyl ester leaving group, whereas under the same experimental conditions the macroCTA with a phenylacetyl ester leaving group inhibited the polymerization. In situ ^{1}H NMR spectroscopy polymerizations were performed with low molecular weight xanthate analogues to investigate the cause of inhibition. Block copolymers were prepared with the macroCTA which did not inhibit the polymerization and were characterized via size exclusion chromatography, high-performance liquid chromatography, and matrix-assisted laser desorption ionization time-of-flight mass spectrometry. The ability to produce narrowly distributed (PDI < 1.4) block copolymers end capped with a xanthate moiety with little to no homopolymer contaminant is presented.

Introduction

Poly(ethylene glycol) (PEG) is widely used in the pharmaceutical and biomedical fields. It is a nonionic polymer, soluble in water and most common organic solvents. The incorporation of a PEG segment in a macromolecule modulates its solution properties. Many synthetic pathways are available for the preparation of block copolymers comprising a PEG block. Each block can be prepared separately and connected by postpolymerization coupling of functional end groups.[1] Commercially available PEGs prepared via anionic polymerization can be found with one or two hydroxyl end functionalities, which enable almost unlimited chemical modification[2] and the preparation of di-, tri-, or multiblock copolymers. The main prerequisite for this approach is that the second polymeric block must be quantitatively end functionalized. Thus, this method has been used mostly to prepare biodegradable block copolymers of PEG with a second block obtained via polycondensation or ring opening polymerization.[3] Poly(*N*-vinylpyrrolidone) (PVP) and poly(vinyl acetate) (PVAc) are typical examples of widely used industrial polymers that can only be prepared via free-radical polymerization. Conventional free-radical polymerization does not normally provide end functionality because of transfer and termination reactions. By taking advantage of transfer reactions, however, Ranucci et al. synthesized a variety of low molecular weight PVPs bearing chain-end functionality.[4] Another synthetic approach consists of growing a second block from an end-functional PEG precursor. By selecting a macromolecular precursor bearing a functional group capable of controlling the polymerization of the second comonomer, it is possible to not only obtain block copolymers but also control the molecular weight distribution of the blocks. The recent development of living radical polymerization techniques has made it possible to match an appropriate control agent with almost any polymerizable monomer. Modified PEGs have been used as initiators for atom-transfer radical polymerization[5] and nitroxide-mediated polymerization[6] and as macromolecular chain-transfer agents (macroCTAs) for reversible addition−fragmentation transfer (RAFT)-mediated polymerization.[7,8] NVP and VAc present comparable polymerization characteristics; however, PVP is water soluble whereas PVAc is hydrophobic. As a result, block copolymers of PEG with NVP are all hydrophilic while PEG-*b*-PVAc copolymers are amphiphilic. To discover a common synthetic pathway for materials with dramatically different solution properties is an appealing concept. Successful control of VAc polymerization has only been reported using xanthates as mediating agents under a RAFT mechanism.[9] The first examples of block copolymers containing a PVP block prepared via living polymerization were reported recently, with the syntheses of polystyrene-*b*-poly(*N*-vinylpyrrolidone) and poly(methyl methacrylate)-*b*-poly(*N*-vinylpyrrolidone) via organostibine-mediated polymerization[10] and PVP-*b*-PVAc[11] via xanthate-mediated polymerization. While the introduction of organostibine functionality would require complicated chain-end modification reactions, modification of a commercially available PEG with a xanthate moiety is relatively straightforward and well documented.[8] The ability of xanthates to control the polymerization of both monomers led us to investigate the use of xanthate end-functional PEGs to prepare well-defined block copolymers with NVP and VAc. Some studies have been reported on the use of xanthates for the polymerization of NVP. The group of Kamigaito and Okamoto published the first paper on xanthate-mediated polymerization of NVP. They reported a living/controlled character with a phenyl ethyl leaving group despite long "inhibition".[12] A few leaving groups producing radicals centered on a primary carbon were investigated, i.e., cyanomethyl,[13] benzyl,[11,12] and phtalimidyl methyl.[14] Coote et

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al. recommend that the leaving group be chosen with comparable (slightly higher or slightly lower) radical stability with respect to that of the monomer-derived radical.[15] We showed that good control was achieved with a propionic acid leaving group although initialization was not completely selective.[16] On the basis of these results, we chose the leaving groups for the present study. We first looked at the efficiency of two PEG-based macroCTAs in reinitiating the polymerization of VAc and NVP and studied the initialization behavior of the polymerization with low molecular weight xanthate model compounds bearing similar reinitiating groups via ^{1}H NMR spectroscopy. We then identified a suitable macroCTA and carried out thorough characterization of the block copolymers via size exclusion chromatography (SEC), high-performance liquid chromatography (HPLC), and matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-ToF-MS).

Experimental Section

Chemicals. *N*-Vinylpyrrolidone (Aldrich, 99%) was dried over anhydrous magnesium sulfate and purified by distillation under reduced pressure. Vinyl acetate (Protea Chemicals, 99%) was distilled under reduced pressure, collected in a flask, and cooled in an ice bath. Tetrahydrofuran (THF) (KIMIX) was distilled from lithium aluminum hydride. Dichloromethane (KIMIX, CP-grade, 99.5%) and ethanol (SASOL, absolute, 99.5%) were stored over molecular sieves 3 Å. 2,2′-Azobis(isobutyronitrile) (AIBN) (Riedel de Haen) was recrystallized twice from methanol. Potassium *O*-ethyl dithiocarbonate (95%, Merck), 2-bromopropionyl bromide (97%, Fluka), ethyl-2-bromo propionate (98%, Fluka), α-chlorophenylacetyl chloride (90%, Aldrich), pyridine (SAARCHEM, CP-grade, 99.5%), and the deuterated solvent C_6D_6 (99.6%, Aldrich) were used without further purification. For column chromatography, silica gel (Fluka, particle size 0.063−0.2 mm, Brockmann 2-3) was used. Poly(ethylene glycol) monomethyl ether (EG_{75}−OH) (Pluriol A3010E, $M_{n,NMR}$ = 3300 g mol^{-1}, $M_{n,SEC}$ = 12100 g mol^{-1} (PMMA equivalents in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP)), PDI = 1.06) and the telechelic dihydroxyl poly(ethylene glycol) (HO−EG_{90}−OH) (Pluriol E4000, $M_{n,NMR}$ = 4000 g mol^{-1}, $M_{n,SEC}$ = 18300 g mol^{-1} (PMMA equivalents in HFIP), PDI = 1.08) were donated by BASF AG and used as received.

Synthesis of macroCTA EG_{75}−X1. *Synthesis of 2-Bromopropionic Acid [poly(Ethylene glycol) Methyl Ether] Ester (EG_{75}−Br)*. Poly(ethylene glycol) monomethyl ether (EG_{75}−OH, 32.0 g, 9.7 × 10^{-3} mol) was placed in a three-neck flask and stirred with pyridine (2.00 mL, 2.60 × 10^{-2} mol) in dichloromethane (80 mL). While the mixture was still cold, 2-bromopropionyl bromide (2.40 mL, 2.26 × 10^{-2} mol) was added slowly. The mixture was stirred for 16 h at room temperature. A white precipitate was filtered off. Dichloromethane (300 mL) was added. The solution was washed with saturated ammonium chloride (4 × 50 mL), saturated sodium hydrogen carbonate (4 × 50 mL), water (50 mL), and dried over anhydrous magnesium sulfate. The solvents were evaporated under vacuum. EG_{75}−Br was obtained (26.56 g, 83% recovery, >99% purity by ^{1}H NMR). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.36 (q, ^3J = 6.8 Hz, 1H, C*H*), 4.28, (m, 2H, CH_2OC(O)), 3.61 (s), 3.5−3.8 (m, CH_2CH_2O− of PEG backbone), 3.34 (s, 3H, CH_3O), 1.79 (d, ^3J = 6.8 Hz, 3H, CH_3).

Synthesis of EG_{75}−X1. EG_{75}−Br (3.30 g, 1.0 × 10^{-3} mol) was dissolved in dichloromethane (15 mL) in a three-neck flask and stirred with pyridine (4.20 mL, 5.3 × 10^{-2} mol). Potassium *O*-ethyl xanthate (0.48 g, 3.0 × 10^{-3} mol) was added portion wise. The mixture was stirred at room temperature for 16 h. Dichloromethane was added (140 mL). The solution was washed with concentrated ammonium chloride (4 × 40 mL), saturated sodium bicarbonate (4 × 50 mL), water (50 mL), and dried over anhydrous magnesium sulfate. The solvents were evaporated under vacuum, and the resulting powder was purified via Soxhlet extraction with diethylether. 2.80 g of EG_{75}−X1 was obtained (85% recovery). ^{1}H NMR indicated quantitative conversion of the end groups. ^{1}H NMR (600 MHz, $CDCl_3$, δ): 4.61 (q, ^3J = 7.2 Hz, 2H, SC(S)OCH_2CH$_3$), 4.39 (q, ^3J = 7.5 Hz, 1H, C*H*CH$_3$), 4.28 (m, 2H, CH_2OC(O)), 3.62 (s), 3.5−3.8 (m, −CH_2CH_2O−PEG backbone), 3.36 (s, 3H, CH_3O), 1.79 (d, ^3J = 7.5 Hz, 3H CHCH_3), 1.40 (t, ^3J = 7.2 Hz, 3H, SC(S)OCH$_2$CH_3). $M_{n,SEC}$ = 11900 g mol^{-1} (PMMA equivalents in HFIP), PDI=1.06.

In another experiment, the second step of the reaction was carried out for 10 h instead of 16 h. A 75% pure EG_{75}−X1, containing approximately 20% of unreacted EG_{75}−Br and less than 5% EG_{75}−OH (determined by ^{1}H NMR spectroscopy and HPLC), was obtained. This sample is used in the section dedicated to HPLC analysis in order to identify the various PEG derivatives according to their end groups. Note that this 75% pure product was not used for polymerizations.

Synthesis of the Difunctional macroCTA X1−EG_{90}−X1. The same synthetic procedure as for EG_{75}−X1 was applied; however, the molar equivalents of reagents were doubled so as to account for the difunctionality of the starting dihydroxyl telechelic PEG HO−EG_{90}−OH. X1−EG_{90}−X1 was obtained with 78% yield and >90% purity by ^{1}H NMR spectroscopy. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.61 (q, ^3J = 7.3 Hz, 4H, 2 × SC(S)OCH_2CH$_3$), 4.38 (q, ^3J = 7.5 Hz, 2H, 2 × C*H*CH$_3$), 4.26 (m, 4H, 2 × CH_2OC(O)), 3.61 (s), 3.4−3.8 (m, −CH_2CH_2O− of PEG backbone), 1.5, (d, ^3J = 7.5 Hz, 6H 2 × CHCH_3), 1.38, t, ^3J = 7.3 Hz, 6H, 2 × C(S)OCH$_2$CH_3). $M_{n,SEC}$ = 21 900 g mol^{-1} (PMMA equivalents in HFIP), PDI = 1.08.

Synthesis of macroCTA EG_{75}−X2. In the first step, chlorophenyl acetic acid [poly(ethylene glycol) methyl ether] ester (EG_{75}−Cl) was prepared from EG_{75}−OH and α-chlorophenylacetyl chloride according to the procedure reported in the literature.[7] Then, EG_{75}−Cl (4.40 g, 1.3 × 10^{-3} mol) was dissolved in dichloromethane (40 mL) in a three-neck flask fitted with a condenser and pyridine (1.70 mL, 2.15 × 10^{-2} mol) was added. Potassium *O*-ethyl xanthate (0.64 g, 3.9 × 10^{-3} mol) was added portion wise. The mixture was refluxed for 24 h. Dichloromethane (140 mL) was then added. The white precipitate was filtered off. The solution was washed with saturated ammonium chloride (4 × 40 mL), concentrated sodium bicarbonate (4 × 50 mL), water (50 mL) and dried over anhydrous magnesium sulfate. The polymer solution was concentrated under vacuum, and the polymer was recovered by precipitation from cold diethylether. EG_{75}−X2 was obtained (3.48 g, 79% recovery and >95% purity by ^{1}H NMR spectroscopy). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.25−7.45 (m, 5H, C_6H_5), 5.44 (s, 1H, C*H*C_6H_5), 4.59 (q, ^3J = 6.8 Hz, 2H, OCH_2CH$_3$), 4.27 (m, 2H, CH_2OC(O)), 3.61 (s), 3.5−3.8 (m, −CH_2CH_2O− of PEG backbone), 3.34 (s, 3H, CH_3O), 1.37 (t, ^3J = 6.8 Hz, 3H, OCH$_2$CH_3). $M_{n,SEC}$ = 11 700 g mol^{-1} (PMMA equivalents in HFIP), PDI=1.06.

Synthesis of (*S*)-2-(Ethyl propionate)-(*O*-ethyl xanthate) (X1′). Potassium *O*-ethyl xanthate (9.50 g, 5.80 × 10^{-2} mol) was added to a solution of ethyl-2-bromo propionate (9.48 g, 5.27 × 10^{-2} mol) in ethanol (30 mL) and stirred for 16 h at room temperature. The white precipitate was filtered off. The filtrate was diluted with 250 mL diethylether, washed with distilled water (4 × 50 mL), and dried over anhydrous magnesium sulfate. The product was purified by column chromatography using hexanes/ethyl acetate (95:5 v/v) as the eluent. A yellow oil (7.0 g) was obtained (60% yield, >99% purity by ^{1}H NMR spectroscopy). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.63 (q, 2H, ^3J = 7.2 Hz, C(S)OCH_2), 4.37 (q, 1H, ^3J = 7.4 Hz, C*H*), 4.20 (q, 2H, ^3J = 7.2 Hz, C(O)OCH_2), 1.56 (d, 3H, ^3J = 7.4 Hz, CH_3CH), 1.41 (t, 3H, ^3J = 7.2 Hz, C(S)OCH$_2$CH_3), 1.28 (t, 3H, ^3J = 7.2 Hz, C(O)OCH$_2$CH_3).

Synthesis of (*S*)-2-(Ethyl phenylacetate)-(*O*-ethyl xanthate) (X2′). α-Chlorophenylacetyl chloride (1.44 g, 7.6 × 10^{-3} mol) was added to 10.0 mL of absolute ethanol. The solution was stirred for 1 h at room temperature. Pyridine (1.85 mL, 2.34 × 10^{-2} mol) was added dropwise. Potassium *O*-ethyl xanthate (2.44 g, 1.52 × 10^{-2} mol) was then added. The mixture was stirred for 16 h at 50 °C. The solvents were evaporated under vacuum. Diethylether was added (160 mL). The white precipitate was removed by filtration. The filtrate was washed with hydrochloric acid (8 × 40 mL), saturated sodium bicarbonate (4 × 40 mL), water (2 × 30

mL) and dried over anhydrous magnesium sulfate. The solvents were evaporated under vacuum. The product, which contained 23% of unreacted α-chlorophenyl acetic acid ethyl ester, was purified by column chromatography using hexanes/ethyl acetate (95:5 v/v) as the eluent. A light yellow oil was recovered (50% yield, 93% pure by ^{1}H NMR spectroscopy). A short discussion regarding the effect of the presence of impurities in this CTA is included in the Supporting Information. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.30−7.44 (m, 5H, C_6H_5), 5.46 (s, 1H, CHC_6H_5), 4.62 (q, ^3J = 7.3 Hz, 2H, $SC(S)OCH_2CH_3$), 4.25 (m, 2H, $CH_3CH_2OC(O)$), 1.40 (t, ^3J = 7.3 Hz, 3H, $SC(S)OCH_2CH_3$), 1.25 (t, ^3J = 7.3 Hz, 3H, $CH_3CH_2OC(O)$). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 211.65 (C=S), 169.18 (C=O), 133.37 (C_{Ar}), 127.9−129.2 (CH_{Ar}), 70.18 ($C(S)OCH_2$), 62.09 ($C(O)OCH_2$), 56.97 (CH), 14.00, 13.58.

Polymerization Procedures. All polymerizations were carried out in a pear-shaped 50 mL Schlenk flask heated in an oil bath. The polymerization mixture was degassed with a minimum of four freeze−pump−thaw cycles followed by the introduction of ultrahigh purity argon. A typical polymerization was performed as follows.

Polymerization of N-Vinylpyrrolidone for Diblock Copolymer Synthesis. NVP (2.00 g, 1.80×10^{-2} mol), AIBN (0.100 g of a 0.032 g solution in 1.000 g of benzene, 1×10^{-5} mol), EG_{75}−X1 (0.140 g, 4.2×10^{-5} mol), and THF (2.14 g) were placed in a Schlenk flask and degassed via freeze−pump−thaw cycles. The flask was immersed in an oil bath preheated at 60 °C. After 15 h, poly(ethylene glycol)-*b*-poly(*N*-vinylpyrrolidone) ($EG_{75}-NVP_{347}$) was isolated by precipitation in diethylether (monomer conversion = 77%, $M_{n,SEC}$ = 52 300 g mol^{-1} (PMMA equivalents in HFIP), PDI = 1.35). Several $EG_{75}-NVP_n$ diblock copolymers were prepared with different average degrees of polymerization (*n*) for the PVP block with the same procedure by varying the initial concentration ratios of NVP to EG_{75}−X1 and conversion.

Polymerization of N-Vinylpyrrolidone for Triblock Copolymer Synthesis. NVP (2.00 g, 1.80×10^{-2} mol), AIBN (0.017 g, 1.0×10^{-4} mol), X1−EG_{90}−X1 (0.80 g, 2.0×10^{-4} mol), and THF (2.14 g) were placed in a Schlenk flask and degassed via freeze−pump−thaw cycles. The flask was immersed in an oil bath preheated at 60 °C. After 15 h, poly(*N*-vinylpyrrolidone)-*b*-poly(ethylene glycol)-*b*-poly(*N*-vinylpyrrolidone) ($NVP_{38}-EG_{75}-NVP_{38}$) was isolated by precipitation in diethylether (monomer conversion = 85%, $M_{n,SEC}$ = 37 700 g mol^{-1} (PMMA equivalents in HFIP), PDI = 1.10).

Polymerization of Vinyl Acetate for Diblock Copolymer Synthesis. VAc (1.60 g, 1.82×10^{-2} mol), AIBN (0.008 g, 5×10^{-5} mol), EG_{75}−X1 (0.665 g, 1.90×10^{-4} mol), and THF (2.3 g) were placed in a Schlenk flask and degassed via freeze−pump−thaw cycles. The flask was immersed in an oil bath preheated at 54 °C. After 14 h, poly(ethylene glycol)-*block*-poly(vinyl acetate) ($EG_{75}-VAc_{88}$) was isolated by evaporation of the solvent and the unreacted monomer (monomer conversion = 90%, $M_{n,NMR}$ = 6600 g mol^{-1}). Several $EG_{75}-VAc_n$ diblock copolymers were prepared with different *n* for the PVAc block with the same procedure by varying the initial concentration ratios of VAc to EG_{75}−X1 and conversion.

X1′-Mediated Polymerization of NVP in the Presence of EG_{75}−OH. NVP (1.00 g, 9.0×10^{-3} mol), AIBN (0.003 g, 2×10^{-5} mol), X1′ (0.023 g, 1.0×10^{-4} mol), EG_{75}−OH (0.231 g, 6.6×10^{-5} mol), and THF (1.23 g) were placed in a Schlenk flask and degassed via freeze−pump−thaw cycles. The flask was immersed in an oil bath preheated at 60 °C. After 17 h, a mixture of the starting poly(ethylene glycol) EG_{75}−OH and poly(*N*-vinylpyrrolidone) NVP_{77}−X1′ was isolated by precipitation in diethylether (monomer conversion = 86%, $M_{n,SEC}$ = 9600 g mol^{-1} (PMMA equivalents in HFIP), PDI = 1.33).

Conventional Free-Radical Polymerization of NVP in the Presence of EG_{75}-OH. NVP (1.00 g, 9.0×10^{-3} mol), AIBN (0.003 g, 2×10^{-5} mol), EG_{75}−OH (0.233 g, 6.7×10^{-5} mol), and THF (1.23 g) were placed in a Schlenk flask and degassed via freeze−pump−thaw cycles. The flask was immersed in an oil bath preheated at 60 °C. After 17 h, a mixture of the starting poly(ethylene glycol) EG_{75}−OH and poly(vinylpyrrolidone) (PVP) was isolated by precipitation in diethylether (monomer conversion > 99%, $M_{n,SEC}$ = 30 300 g mol^{-1} (PMMA equivalents in HFIP), PDI = 2.71, bimodal).

Hydrolysis of Poly(ethylene glycol)-b-poly(N-vinylpyrrolidone) Diblock Copolymer . A 0.050 g portion of diblock copolymer $EG_{75}-NVP_{347}$ ($M_{n,SEC}$ = 52300 g mol^{-1}, PDI = 1.35) was dissolved in 0.01 M potassium hydroxide (3 mL). The solution was stirred at room temperature for 16 h. The pH of the solution was adjusted to 7 by addition of hydrochloric acid (0.1 M) and dialyzed against distilled water for 8 h to remove the salts. Water was eliminated by freeze-drying and the sample analyzed via HPLC and SEC. The same procedure was applied to the diblock copolymer $EG_{75}-NVP_{46}$.

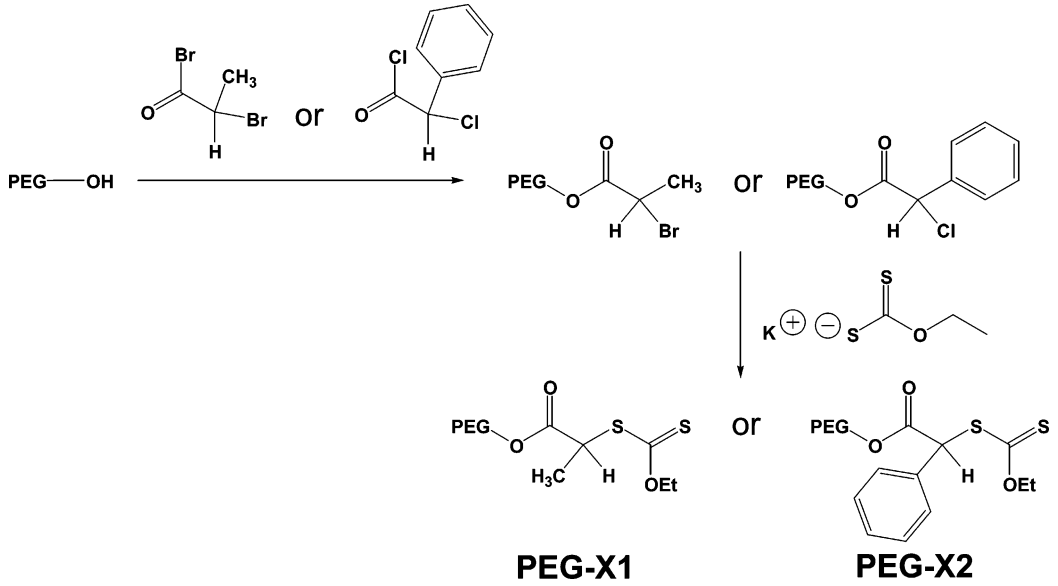
Initialization Experiments. In a typical in situ ^{1}H NMR spectroscopy initialization experiment, the desired amounts of monomer, CTA, and AIBN (molar ratio 5:1:0.1) and deuterated solvent C_6D_6 (0.25 g, 50 wt %) were weighed. The solutions were transferred to NMR tubes. The tubes were flushed with ultrahigh purity argon for 5 min. A sealed glass insert containing the integration reference standard (formic acid in C_6D_6) was inserted. In situ ^{1}H NMR experiments were carried out on a 600 MHz Varian UNITYINOVA spectrometer. A 5 mm inverse detection PFG probe was used for the experiments, and the probe temperature was calibrated using an ethylene glycol sample in the manner suggested by the manufacturer using the method of Van Geet.[17] ^{1}H spectra were acquired with a 3 μs (40°) pulse width and a 4 s acquisition time. For the ^{1}H kinetic experiments, samples were inserted into the magnet at 25 °C and the magnet was fully shimmed on the sample. A spectrum was collected at 25 °C to serve as a reference. The sample was then removed from the magnet, and the cavity of the magnet was raised to the required temperature (70 °C). Once the magnet cavity had stabilized at the required temperature, the sample was reinserted (time zero) and allowed to equilibrate for approximately 5 min. Additional shimming was then carried out to fully optimize the system, and the first spectra were recorded approximately 5 min after the sample was inserted into the magnet. ^{1}H NMR and ^{13}C NMR one-dimensional experiments, ^{13}C distorsionless enhancement by polarization effect, selective total correlation spectroscopy, and nuclear Overhauser effect spectrometry experiments and a series of two-dimensional experiments including homonuclear ^{1}H/^{1}H correlated spectroscopy as well as ^{1}H/^{13}C heteronuclear single quantum coherance and ^{1}H/^{13}C heteronuclear multiple-bond correlation NMR spectroscopy experiments on ex situ samples enabled the assignment of peaks for the various species involved in the xanthate-mediated polymerizations.

Characterization Techniques. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 or 600 MHz Varian UNITYINOVA spectrometer.

Size Exclusion Chromatography. The SEC setup consisted of an eluent degasser (Alltech Elite), a gradient pump (Shimadzu, LC-10AD), an injector (Spark Holland, MIDAS), a two-column set (PSS, PFG linear XL 7 μm, 8 mm × 300 mm, separation window 10^2-10^6 Da), a column oven (Spark Holland, Mistral) at 40 °C, and detectors in series: dual wavelength UV detector (Waters, 2487), light scattering (RALS/LALS) and viscometry (Viscotek 270), and differential refractive index detector (Waters 2414). The injection volume was 50 μL, and the flow rate was 0.8 mL min^{-1}. The eluent HFIP (Biosolve, AR-grade) with 0.02 M potassium trifluoroacetate added (3.0 g L^{-1}, Fluka 91702) was redistilled after use. A short silica column was placed after the pump to catch the free fluoride, possibly present in HFIP. A particle filter, 0.2 μm poly(tetrafluoroethylene) membrane, was placed between the columns and the UV detector to prevent small particles entering the light scattering detector. Data acquisition and processing were performed with Viscotec Omnisec 4.0 (all detectors) and Waters Empower 2.0 (UV and refractive index detectors). The calculated molecular weights were based on a calibration curve for poly(methyl methacrylate) (PMMA) standards (molecular weight range 650−1.5×10^4 g mol^{-1}) of narrow polydispersity (Polymer Laboratories) in HFIP.

High-Performance Liquid Chromatography. HPLC was performed using a dual pump setup comprising the following units: Waters 2690 separations module (Alliance), Agilent 1100 series

Scheme 1. Synthetic Schemes for the Modification of the Hydroxyl End-Functional Poly(ethylene glycol) Monomethyl Ether (PEG−OH) to Xanthate Derivatives PEG−X1 and PEG−X2 for Use as MacroCTAs



variable wavelength UV detector, and PL-ELS 1000 detector. Data was recorded and processed using PSS WinGPC unity (Build 2019) software. The conditions used for the separation of PEG-*b*-PVP samples were as follows. A C18-grafted silica column was used (Luna RP C18 3 μm 150 mm × 4.60 mm, Phenomenex) at 30 °C. The flow rate was 0.5 mL min^{-1}. In the following part of the discussion, a difference is made between HPLC under isocratic conditions and gradient HPLC. For clarity, the terms HPLC at critical conditions and gradient polymer elution chromatography (GPEC) will be used, which refer to isocratic and gradient conditions, respectively. The mobile phase composition for HPLC at critical conditions of PEG−OH was deionized water (with 0.1% formic acid)/acetonitrile (56:44 v/v). For GPEC analysis, the mobile phase was deionized water (with 0.1% formic acid)/acetonitrile and the composition ranged from 68:32 to 45:55 (v/v). Prior to HPLC and GPEC analyses, NVP-containing polymers were dialyzed for 24 h in distilled water using SnakeSkin pleated dialysis tubing (Pierce, 3.5K MWCO). Samples were prepared in the same solvent composition as the mobile phase at the beginning of each elugram (68:32 v/v)) at concentrations of 5 mg mL^{-1}. The injection volume was 10 μL. A PVP sample (NVP_{19}) prepared via xanthate-mediated polymerization was used as a reference to estimate the elution volume limit of PVP homopolymers under the size exclusion mode ($M_{n,SEC}$ = 2430 g mol^{-1} (PMMA equivalents in HFIP), PDI = 1.23). For GPEC analysis of PEG-*b*-PVAc copolymers, identical conditions were used except for the eluent composition, which was varied from 45:55 (v/v) water/acetonitrile to 100% acetonitrile.

Matrix-Assisted Laser Desorption Ionization Time-of-Flight Mass Spectrometry. MALDI-ToF-MS measurements were performed on a Voyager DE-STR instrument (Applied Biosystems, Framingham, MA) equipped with a 337 nm nitrogen laser. Positive-ion spectra were acquired in the reflector mode. *trans*-2-[3-(4-*tert*-Butylphenyl)-2-methyl-2-propenylidene]-malononitrile was used as the matrix. The matrix was dissolved in THF at a concentration of approximately 40 mg mL^{-1}. Potassium trifluoroacetate was used as the cationization agent and was added to THF at a concentration of 1 mg mL^{-1}. The polymer sample was dissolved in THF at a concentration of 2 mg mL^{-1}. In a typical measurement, the matrix, cationization agent, and sample solutions were premixed in a 10:1:5 ratio. Approximately 0.5 μL of the obtained mixture was handspotted on the target plate and left to dry. For each spectrum, 1000 laser shots were accumulated. Data Explorer software (Applied Biosystems) was used for data interpretation.

Results and Discussion

Comparison between the Two macroCTAs. Two xanthate end-functional PEGs were prepared (Scheme 1) in order to investigate the effect of the structure of the macromolecular leaving group on the ability to generate copolymers with poorly stabilized vinyl monomers. The two macroCTAs only differ in the nature of one of the substituents on the carbon adjacent to the xanthate, namely, a methyl substituent for EG_{75}−X1 versus a phenyl for EG_{75}−X2. The polymerization conditions and conversions are presented in Table 1. The macroCTA-mediated polymerization is expected to proceed as shown in Scheme 2, in accordance with the generally accepted mechanism of RAFT-mediated polymerization.

Block copolymers were obtained with the macroCTA EG_{75}−X1 and both NVP and VAc monomers (experiments 1a−d shown in Table 1). The incorporation of VAc units into the macroCTA was evidenced by ^{1}H NMR spectroscopy. Experiment 1b was stopped after 15% monomer conversion so as to obtain a short PVAc block for end group characterization (approximately six VAc units per chain). The areas of interest in the ^{1}H NMR spectrum of the starting macroCTA (EG_{75}−X1) and the resulting EG_{75}−VAc_6 (Figure 1) are indicated with arrows. The integration value for the xanthate end group signals (peaks a and g) did not decrease during the polymerization, but the peaks became broader due to the introduction of tacticity in the copolymer. The signal for the methine proton of the VAc unit in α-position from the xanthate was identified at 6.6 ppm (j′).[16] The reinitiating group signals b and f showed increased multiplicity and a shift to lower fields indicating their quantitative conversion to macromolecular species. Experiment 1b confirmed that the macromolecular xanthate was quantitatively converted to oligomeric VAc adducts even at low conversion. NVP cannot be easily removed by evaporation under vacuum as is the case of VAc. The polymer has to be precipitated many times to ensure successful removal of the monomer, whose signals otherwise overlap with some of the macroCTA signals. Another problem is that the characteristic C*H*−S signals are spread between 5.5 and 6.1 ppm in the case of NVP resulting in decreased resolution. As a result, the experiment was not repeated with NVP but instead the characterization of the block copolymers was performed, presented in the second part of the article, which is aimed at detecting the possible presence of the unmodified macroCTA.

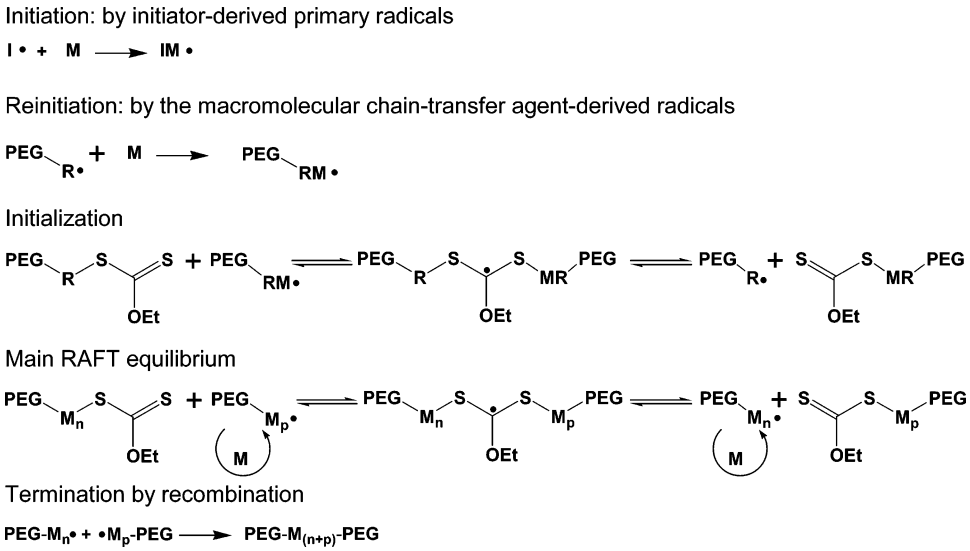
In Table 1, experimental molar masses from NMR are listed instead of those based on SEC. The main reason is that the

Table 1. Polymerization Conditions, Conversions, and Molecular Weight Data of the Diblock Copolymers for Comparison of the Two macroCTAs EG_{75}−X1 and EG_{75}−X2

ref	monomer	molar ratio of monomer: xanthate: initiator	macroCTA	time (h)	temp (°C)	conversion (%)	$M_{n,theo}$[c] (g mol^{-1})	$M_{n,NMR}$[d] (g mol^{-1})
1a	VAc	98:1:0.2	X1	14	54	90[a]	7600	6600
1b	VAc	47:1:0.2	EG_{75}−X1	12	54	15[a]	600	530
1c	NVP	98:1:0.2	EG_{75}−X1	15	60	98[b]	11 000	12 200
1d	NVP	70:1:0.2	EG_{75}−X1	15	60	65[b]	5100	5700
1e	VAc	98:1:0.2	EG_{75}−X2	15	54	<2[a]		
1f	VAc	47:1:0.2	EG_{75}−X2	14	54	<2[a]		
1g	NVP	70:1:0.2	EG_{75}−X2	15	60	<2[b]		
1h	NVP	98:1:0.2	EG_{75}−X2	15	60	<5[b]		

[a] Determined gravimetrically after evaporation of the solvent and monomer. [b] Determined gravimetrically after precipitation of the polymer from diethylether. [c] Number-average molecular weight (M_n) of the poly(vinyl monomer) block based on initial molar ratios of the polymerization mixture and conversion with the assumption that each chain contains one xanthate chain end and that the initial xanthate was quantitatively converted. [d] Determined as the ratio of the xanthate signals to monomer backbone signals via ^{1}H NMR spectroscopy analysis of the polymer after dialysis and freeze-drying.

Scheme 2. Reaction Scheme for the Block Copolymer Synthesis from Poly(ethylene glycol) (PEG)-Based MacroCTAs via Reversible Addition−Fragmentation Transfer-Mediated Polymerization



hydrodynamic volumes of PEG strongly deviate from those of PMMA (which was used as the calibration standard). SEC results of the block copolymers in this study are therefore likely to be a very poor reflection of the true molar mass. Below, it will be shown by HPLC that there was no significant homopolymer in the reaction mixture. Therefore, the values calculated from NMR most likely provide a good estimation of the average molar masses.

In the presence of the macroCTA EG_{75}−X2, no copolymer was obtained at all regardless of whether VAc or NVP was used (experiments 1e−h). At this point, it is important to report that the reproducibility of the experiments was poor in terms of conversion. In the preliminary work, two xanthate-mediated NVP polymerization experiments were conducted in parallel where the initial polymerization mixture was divided into two flasks. Both flasks were subjected to four freeze−pump−thaw cycles in parallel on the same Schlenk line and were heated in the same oil bath. The final yield was 44% in one flask and 69% in the other. Consequently, the yield cannot strictly be taken as an indication of the efficiency of the CTA (or initialization time). Nonetheless, the complete and systematic absence of polymerization when EG_{75}−X2 was used is remarkable. In a blank experiment, PVP was obtained via simple free-radical polymerization in the presence of EG_{75}−OH with quantitative conversion within 3.5 h. In another experiment, PVP was obtained via polymerization in the presence of EG_{75}−OH along with the low molecular weight CTA (*S*)-2-(ethyl propionate)-(*O*-ethyl xanthate) (X1′) in 86% yield in 17 h. These two experiments confirm that EG_{75}−OH does not inhibit the polymerization of NVP in the presence or absence of xanthate species. It was reported in the literature that impurities present in the CTA or traces of oxygen in the polymerization mixture may inhibit the xanthate-mediated polymerization of VAc.[18] In our case, it cannot be strictly excluded that impurities were not present at the origin of the inhibition, however the only end groups detected in the macroCTAs via 600 MHz ^{1}H NMR were the xanthate end groups. Moreover, the synthetic pathway for both macroCTAs being similar, it is unlikely that the impurities capable of fully inhibiting the polymerization were present in only one of the two macroCTAs.

In order to pinpoint the origin of the inhibition, we investigated the polymerization of NVP and VAc with low molecular weight xanthate analogues. We reported earlier that when NVP and VAc were polymerized in the presence of a xanthate the nature of the leaving group played a determining role in the mechanism of initialization and in turn in the level of control achieved.[16] A fine balance can be reached where the R group is a good enough leaving group so that R· radicals are formed preferentially upon fragmentation of CTA adduct radicals and where R· is reactive enough toward the monomer to enable fast reinitiation. This feature is crucial for the synthesis of well-defined block copolymers. If the macro-R group is not a good enough leaving group, new chains will be initiated late in the polymerization, resulting in increased polydispersity. If the

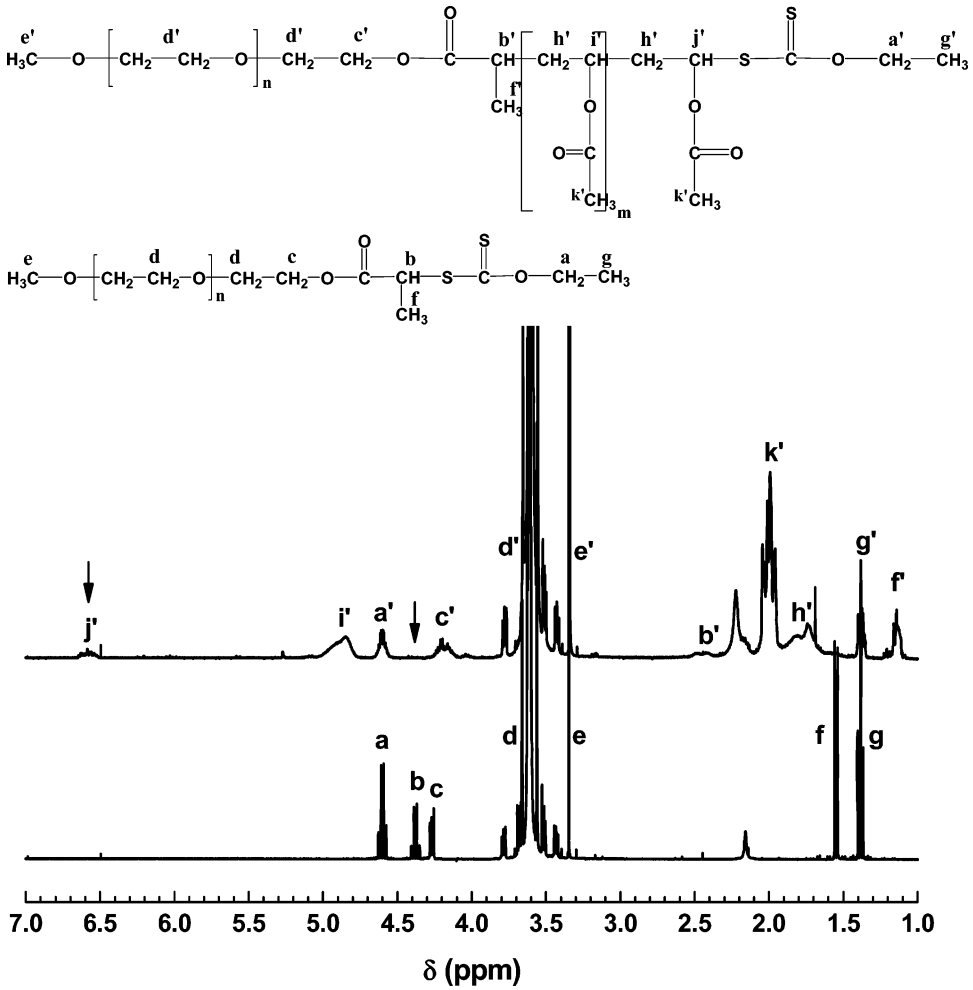
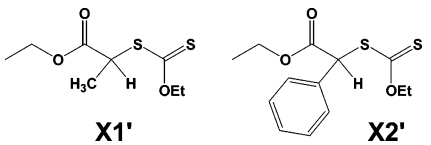


Figure 1. 600 MHz ^{1}H NMR spectra in $CDCl_3$ of the starting macroCTA EG_{75}−X1 (bottom) and the copolymer EG_{75}−VAc_6 (top), and their respective structures.



X1' **X2'**

Figure 2. Structures of the low molecular weight CTAs used in the initialization study via in situ ^{1}H NMR spectroscopy.

macro-R group is not able to efficiently reinitiate polymerization, termination and/or transfer of the macroCTA will occur, leading to heterogeneous homopolymer/copolymer mixtures or no polymerization at all. We extended our initialization studies via in situ ^{1}H NMR spectroscopy to NVP and VAc polymerizations with the CTAs (*S*)-2-(ethyl propionate)-(*O*-ethyl xanthate) (X1′) and (*S*)-2-(ethyl phenylacetate)-(*O*-ethyl xanthate) (X2′), which produce radicals with a similar chemical environment as EG_{75}−X1 and EG_{75}−X2, respectively (Figure 2).

We found that with X1′ initialization was highly selective and fast with VAc whereas loss of selectivity was observed with NVP (Figures S1 and S4 in the Supporting Information). The concentration of the single monomer adduct with NVP started decreasing while peaks corresponding to the higher adducts appeared before all of the starting X1′ was consumed. The lack of selectivity in the initialization step means that the monomer concentration decreases from the beginning of the reaction to form oligomeric or polymeric species despite the presence of the initial CTA. The consequence is that chains are formed later in the polymerization, which leads to an increase in the polydispersity index and could possibly result in the presence of initial CTA in the final polymer. When the macroCTA is used, the final mixture may even contain some starting homopolymer. Although initialization was not completely selective with NVP, less than 1.5 equiv of NVP was necessary for complete conversion of the CTA X1′. This is an indication that NVP and 2-propionic acid ethyl ester-derived radicals have comparable radical stability. The number of monomer units per chain at the end of initialization will depend on the initial stoichiometry. The lower the initial concentration in CTA, the higher the number of monomer additions prior to quantitative conversion of the CTA.

On the contrary, initialization was highly selective with X2′ for both monomers (Figures S2 and S5 in the Supporting Information). This means that the only reaction taking place was the conversion of one monomer unit with one X2′ equivalent to form single monomer adducts. This feature can be very interesting to ensure optimized control of the polymerization. The study on the initialization behavior suggested that X2′ could be a better CTA to control the polymerization of NVP than X1′. Nonetheless, the initialization time should also be taken into consideration. A time of 220 min was necessary for the initial CTA X2′ to be fully converted to its single monomer adduct with NVP, whereas the concentration of X1′ was halved within 10 min, and X1′ was fully converted within 90 min. With the monomer VAc, the initialization was extremely slow. After 18 h, 68% of the initial X2′ was still present. The leaving group in X2′ is expected to be more stable than that of X1′ because of the significantly stronger radical stabilizing effect of the

Table 2. Molecular Weight Data for PVP, PEG, and Their Block Copolymers

ref	expt description	[monomer]/[CTA]	conv (%)	$M_{n,theo}$[b] (g mol^{-1})	theor polymer composition	$M_{n,SEC}$[b,c] (g mol^{-1})	PDI
2a	starting material				$EG_{75}-OH$	12 100	1.06
2b	modified starting material				$EG_{75}-X1$	11 900	1.06
2c	$EG_{75}-X1$-mediated diblock copolymerization of NVP	70	65	5100	$EG_{75}-NVP_{46}$	17 000[c]	1.10
2d	$EG_{75}-X1$-mediated diblock copolymerization of NVP	450	77	38500	$EG_{75}-NVP_{347}$	52 300[c]	1.35
2e	conventional radical polymerization of NVP in the presence of $EG_{75}-OH$		>99		$EG_{75}-OH$ + PVP	30 300[d]	2.71
2f	X1′-mediated polymerization of NVP in the presence of $EG_{75}-OH$	89	86	9900	$EG_{75}-OH + NVP_{77}-X1'$	9600	1.33
2g	$X1-EG_{90}-X1$-mediated triblock copolymerization of NVP	88	75	4200 × 2	$NVP_{38}-EG_{90}-NVP_{38}$	37 700[c]	1.10
2h	hydrolysis of the diblock copolymer $EG_{75}-NVP_{46}$				$EG_{75}-OH + NVP_{46}$	8100[d]	1.42

[a] Polymerizations were carried out at 60 °C in 50 wt % solution in THF with a [xanthate]:[initiator] ratio of 1:0.2. In experiment 2e, where no CTA was used, the initiator concentration was the same as in experiment 2f ([monomer]:[initiator] = 445). Polymerizations were carried out for 15 h except for 2e, which was quantitative at 3.5 h, and 2f, which was conducted for 17 h. Hydrolysis was carried out by stirring the diblock copolymer in aqueous potassium hydroxide at pH = 12 at room temperature for 16 h. [b] Number-average molecular weight of the vinyl polymer block based on initial molar ratios of the polymerization mixture and conversion. [c] Presence of a low molecular weight peak excluded from the calculations. [d] Bimodal distribution resulting from the overlap of PEG and PVP homopolymer distributions.

phenyl substituent compared to that of the methyl substituent. Therefore, fragmentation of intermediate radicals toward the release of the R group should be favored in X2′ compared to that in X1′. As we observed that the rate of conversion of the CTA is lower in the case of X2′ than in X1′, the rate-limiting step must be the rate of addition of the leaving radicals onto the monomer, i.e., the reinitiation step. Although block copolymer synthesis involves higher monomer to CTA ratios, it is likely that the initialization remained selective with $EG_{75}-X2$. Thus, the apparent inhibition of the polymerization by $EG_{75}-X2$ can be attributed to the poorer efficiency of the macro-R group with a phenyl substituent to reinitiate the polymerization, at least in the case of VAc. This is supported by the ^{1}H NMR spectrum of the PEG recovered from the failed copolymerization with VAc. It indicated that the xanthate moieties were still present while approximately 40% of the leaving group had been modified. Signals similar to that of the low molecular weight adducts were detected in the region 6.3−6.9 ppm (see Supporting Information), which suggest that selective initialization may have occurred with the macroCTA $EG_{75}-X2$ and that the process was not complete when the experiment was stopped. Peak assignment of the PEG end groups was not achieved due to the high molecular weight of the CTA. However, these results indicate that the absence of polymerization was not due to degradation of the xanthate functionality. After the attempted polymerization with NVP for 15 h, a large proportion of the xanthate end groups was missing. Heating of the polymerization reaction was pursued for 48 h, and polymerization of NVP occurred on the longer time scale. A monomer conversion of 65% was achieved, but further characterization indicated that the sample was a mixture of homopolymers and possibly a fraction of block copolymer. Initialization is slower with X2′ than with X1′, but it may not be the only cause for the apparent inhibition with NVP in the polymerization mediated by X2′. For further comparison, NVP was polymerized in the presence of X2′ under the same conditions as those for the block copolymer synthesis. A yield of 19% was obtained within 15 h. NMR spectroscopic analysis revealed the presence of xanthate end groups and also a significant amount of other end groups, mostly unsaturated species in a molar ratio 60:40 (xanthate:unsaturated). The same ratio of end groups was obtained when the polymerization was carried out in bulk. In conclusion, the case of NVP is unclear and a combination of low reinitiation efficiency and the occurrence of side reactions affecting the xanthate moieties seem to be responsible for the failure to obtain PEG−PVP block copolymers from $EG_{75}-X2$.

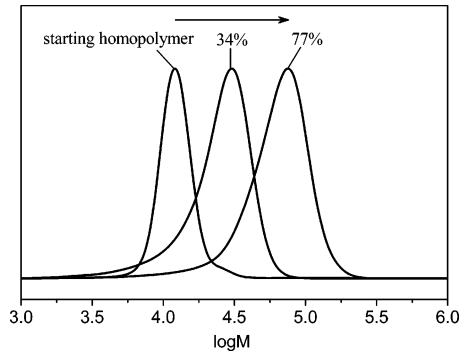


Figure 3. Evolution of the molecular weight distributions in the macromolecular xanthate $EG_{75}-X_1$-mediated polymerization of NVP as a function of conversion. From left to right: starting homopolymer $EG_{75}-X_1$ ($M_{n,SEC}$ = 12000 g mol^{-1}, PDI = 1.06); diblock copolymer $EG_{75}-PVP$ (reaction time = 6 h, conversion = 34%, $M_{n,SEC}$ = 19 200 g mol^{-1}, PDI = 1.43); $EG_{75}-PVP$ (reaction time = 15 h, conversion = 77%, $M_{n,SEC}$ = 52 300 g mol^{-1}, PDI = 1.35). The molar ratio of [NVP]:[$EG_{75}-X1$]:[AIBN] was 450:1:0.2. The reaction was carried out at 60 °C in a 50 wt % solution in THF.

Characterization of the Block Copolymers. The macroCTAs $EG_{75}-X1$ and $X1-EG_{90}-X1$ were used to mediate another set of polymerizations of NVP listed in Table 2. The copolymer homogeneity was characterized in terms of molecular weight distribution and copolymer composition. The molecular weight distributions (determined by SEC) were analyzed so as to estimate the level of control over the chain length. HPLC was used to investigate the presence of homopolymers.

SEC Analysis. The macroCTAs and copolymers with NVP were analyzed in HFIP. The livingness of NVP polymerization mediated by the macroCTA $EG_{75}-X1$ is illustrated in Figure 3. Two polymerizations were carried out in parallel at 60 °C with the same initial composition. The polymerizations were stopped at 6 and 15 h, respectively. The SEC chromatograms indicate a shift of the molecular weight distributions to higher M_n as conversion increased.

The number-average molecular weight (M_n) and the polydispersity index (PDI) calculations were based on PMMA calibration. While the values for M_n of the homo PVPs prepared

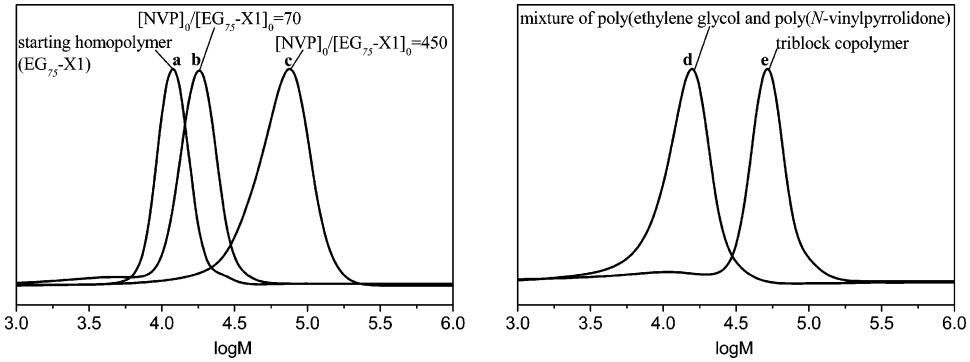


Figure 4. Size exclusion chromatograms measured in HFIP of (a) the macroCTA $EG_{75}-X1$, the diblock copolymers (b) poly(ethylene glycol)-*b*-poly(*N*-vinylpyrrolidone) $EG_{75}-NVP_{46}$ and (c) $EG_{75}-NVP_{347}$, (d) the mixture of poly(ethylene glycol) ($EG_{75}-OH$) and poly(*N*-vinylpyrrolidone) ($NVP_{77}-X1'$) homopolymers, and (e) the poly(*N*-vinylpyrrolidone)-*b*-poly(ethylene glycol)-*b*-poly(*N*-vinylpyrrolidone) triblock copolymer $NVP_{38}-EG_{90}-NVP_{38}$. $EG_{75}-NVP_{46}$ was obtained at 65% conversion with an initial concentration ratio of $[NVP]_0:[EG_{75}-X1]_0 = 70:1$, and $EG_{75}-NVP_{347}$ was obtained at 77% conversion with an initial concentration ratio of $[NVP]_0:[EG_{75}-X1]_0 = 450:1$.

via xanthate-mediated polymerization were generally close to those of the theoretical ones (see ref 2f, Table 2), the M_n values of the PEG-based copolymers were systematically significantly higher. The M_n of the PEG used as a CTA (ref 2b, Table 2) as determined by ^1H NMR was 3300 g mol^{-1} whereas the value obtained by SEC analysis was 11900 g mol^{-1}. Such a discrepancy is common in SEC chromatography, which separates the macromolecules according to their hydrodynamic volume and thus depends on the interactions between the polymer and the elution solvent. The fact that the M_n values obtained for the diblock copolymers (refs 2c and 2d, Table 2) match the sum of the M_n of the starting PEG and the theoretical M_n calculated for the PVP block may only be a coincidence. Nonetheless, the chromatograms presented in Figure 4 provide valuable information. The experimental M_n increased with the NVP content in the copolymer. As predicted by the RAFT mechanism, lower CTA concentrations resulted in increased M_n values. The low polydispersity of the PEG macroCTA was retained in the copolymers. These results indicate the ability of the PEG-based macroCTA $EG_{75}-X_1$ to control the polymerization of NVP. Further qualitative analysis of the chromatograms revealed, however, that a second low molecular weight distribution accounting for less than 10% of the total integration was present in most block-copolymer samples. Unfortunately, SEC provides little information on the homogeneity of the sample. For instance ref 2f (Table 2), which is a mixture of narrowly distributed PVP and PEG homopolymers ($NVP_{77}-X1 + EG_{75}-OH$), appears as a monomodal distribution (Figure 4d). The substantially higher elution volume for this sample compared with the elution volume for the triblock copolymer which has similar NVP content (Figure 4e) is an indication that the structures are different. The difference in elution volumes is consistent with the assumed structure of the polymers (i.e., homopolymer mixture versus triblock copolymer). Nonetheless, this example illustrates the need to complement SEC with other separation techniques. In the following section, we present the outcome of the HPLC analysis with an aim to determine the chemical homogeneity of the copolymers. Finally, let us remark that the SEC traces of the diblock copolymers do not display any detectable peak at the lower retention volume than the main distribution. This observation is relevant in the examination of bimolecular termination products. Recombination between propagating diblock copolymer radicals would result in PEG-*b*-PVP-*b*-PEG triblock copolymers (Scheme 2). The presence of two PEG segments in the recombination product would result in a significantly higher hydrodynamic volume than the diblock copolymers. The absence of signal corresponding to the higher hydrodynamic volume indicates that the bimolecular termination between propagating diblock copolymer radicals did not occur to a significant extent.

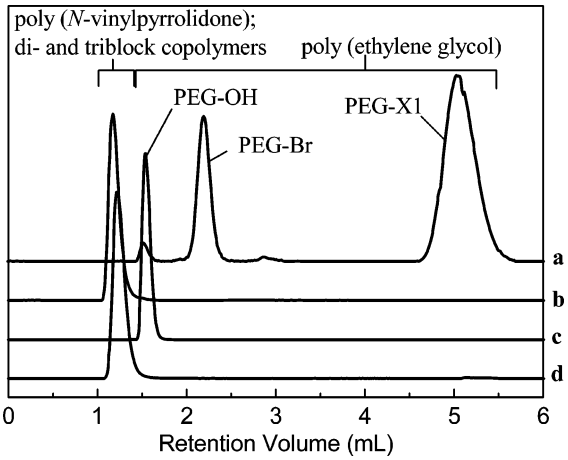


Figure 5. HPLC chromatograms at critical conditions for (a) poly(ethylene glycol) monomethyl ether of a 75% pure $EG_{75}-X1$ (PEG−X1), (b) poly(ethylene oxide) monomethyl ether $EG_{75}-OH$ (PEG−OH), (c) diblock copolymer $EG_{75}-NVP_{46}$, and (d) reference homopolymer NVP_{19}. The experimental details for the preparation of the diblock copolymer are in Table 2.

HPLC Analysis. Macko and Hunkeler[19] have compiled a variety of critical conditions reported in the literature, which enable the separation of PEGs according to the nature of the end groups via reversed-phase HPLC. We chose an eluent mixture composed of water and acetonitrile, which was able to dissolve all homo- and copolymer samples. We used dual detection, i.e., ELSD, to identify the macromolecular species and UV detection at a specific wavelength for the xanthate functionality (341 nm, results not shown) to help determine the chemical nature of the eluting species. Under these conditions, the chromatogram of the 75% pure $EG_{75}-X1$ macroCTA (Figure 5a) revealed the presence of four distinct chemical structures. The main peak at 4.6−5.7 mL showed a strong UV absorption and was attributed to the expected $EG_{75}-X1$ structure. Comparison with the chromatogram of the starting compound PEG monomethyl ether ($EG_{75}-OH$) and the fact that UV absorption was not present (results not shown) revealed that the first peak in the PEG−xanthate derivative (1.4−1.7 mL) corresponds to $EG_{75}-OH$. The second main peak was most likely unreacted $EG_{75}-Br$ (as confirmed by ^1H NMR spectroscopy). In the synthesis of the block copolymers, HPLC analysis was used to quantify the purity of the macroCTAs. Only $EG_{75}-X1$ samples which did not display any other signal than those

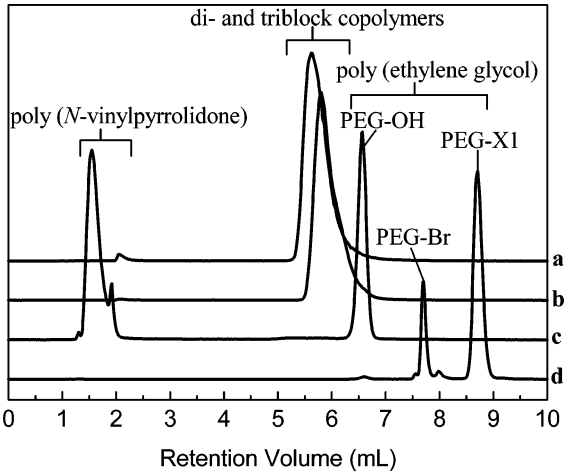


Figure 6. Gradient polymer elution chromatograms of PEG and PVP homopolymers and their block copolymers. (a) Triblock copolymer $NVP_{38}-EG_{90}-VP_{38}$, (b) before hydrolysis and (c) after hydrolysis of the diblock copolymer $EG_{75}-NVP_{46}$, and (d) comparison with 75% pure $EG_{75}-X1$. Hydrolysis was carried out by stirring the diblock copolymer in aqueous potassium hydroxide at pH = 12 at room temperature for 16 h. The 75% pure $EG_{75}-X1$ contained 20% of unreacted $EG_{75}-Br$ and less than 5% of $EG_{75}-OH$, as determined by ^1H NMR spectroscopy. Experimental details for the block copolymers are given in Table 2.

corresponding to $EG_{75}-X1$ and $EG_{75}-OH$ in low amounts were used. Both the diblock copolymer $EG_{75}-NVP_{46}$ and the homopolymer NVP_{19}, used as a reference, eluted at very low elution volumes (<1.5 mL) before all PEG derivatives. The dead volume of the column was measured at 1.5 mL, which indicates that under these conditions the PVP sample and block copolymers containing a PVP segment eluted under the size exclusion mode whereas PEGs with OH or hydrophobic end groups eluted under the adsorption mode. Both PVPs and PEGs are water-soluble polymers. This analysis showed that with the selected solvent composition PVP has a more hydrophilic behavior than PEG. To enable separation of the block copolymers from the PVP homopolymer, it is therefore required that the interaction between the PVP segments and the column be increased. The column being grafted with hydrophobic moieties, interactions with PVP are increased by decreasing the hydrophobicity of the eluent, i.e., increasing the water content.

In the following part, gradient HPLC was applied, also named gradient polymer elution chromatography (GPEC).[20] The initial composition of the eluent was chosen close to the critical conditions for PVP, and the final eluent composition was more hydrophobic than the critical composition for PEGs. This way, the separation of both PEG and PVP polymers is expected to occur in the adsorption mode. GPEC was preferred to isocratic HPLC at critical conditions for PVP so as to reduce the eluent volume and thus limit the time required to elute the more hydrophobic PEGs. As illustrated in Figure 6d, the PEG chromatogram still displayed efficient separation according to end groups, with the same number of well-resolved peaks as that under PEG critical conditions. The GPEC chromatogram of the diblock copolymer (Figure 6b) unambiguously confirmed the absence of starting $EG_{75}-X1$ macroCTA. The copolymer peaks present a shoulder at higher elution volumes, which indicates the presence of $EG_{75}-OH$. No PVP homopolymer was detected. At this point, it is particularly interesting to return to the interpretation of the SEC chromatogram of the same polymer (Figure 4b). It displayed a peak of lower intensity at a higher elution volume ($\log M \sim 3.5$) compared to the copolymer main peak and starting PEG peak. GPEC results indicate that the

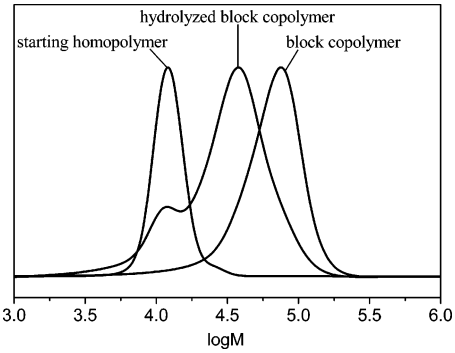


Figure 7. SEC traces of the starting homopolymer chain-transfer agent ($EG_{75}-X1$), the diblock copolymer $EG_{75}-NVP_{347}$, and the basic hydrolysis product of the diblock copolymer. Hydrolysis was carried out by stirring the diblock copolymer in aqueous potassium hydroxide at pH = 12 at room temperature for 16 h.

diblock copolymer sample does not contain homopolymers except for unmodified PEG. The signal observed in SEC may therefore be due to the presence of low molecular weight PVP formed upon hydrolysis of the ester linkage between the two blocks. This may have occurred during storage of the compound or during the SEC analysis, possibly via transesterification with the eluent HFIP. The GPEC chromatogram of the copolymer $NVP_{38}-EG_{90}-NVP_{38}$ (Figure 6a) confirmed that the main structure was a copolymer; however, it did not enable us to discern between the di- and triblock copolymer. A small amount of PVP homopolymer was detected (2.0−2.2 mL).

Additional experiments were carried out to test the efficiency of the RAFT process in synthesizing PEG-derived block copolymers and the ability of GPEC to detect the presence of homopolymer contaminants. The diblock copolymer $EG_{75}-NVP_{46}$ was hydrolyzed in basic aqueous solution (pH = 12). The chromatogram of the resulting mixture presented two distinct peaks corresponding to the homopolymers PVP and $EG_{75}-OH$ (Figure 6c). Quantitative hydrolysis of the ester linkage between the two blocks was assessed by the disappearance of the copolymer peak. This analysis demonstrated the usefulness of GPEC to identify the composition of polymer mixtures which were analyzed via SEC. It gave evidence for the origin of the bimodality of SEC chromatograms when related to the presence of the homopolymers.

Upon hydrolysis, the SEC chromatogram displayed a bimodal peak with a shoulder at higher elution volume than that of the starting $EG_{75}-NVP_{46}$ (results not shown). The hydrolysis experiment was repeated with the diblock copolymer $EG_{75}-NVP_{347}$. Figure 7 shows the SEC traces of the diblock copolymer $EG_{75}-NVP_{347}$ before and after hydrolysis and the starting macroCTA as a reference. The longer PVP segment enabled a better separation between the distributions via SEC. The results are fully in accordance with the observation from the GPEC experiments before and after hydrolysis. Let us remark that the hydrolysis was carried out at pH = 12. As indicated by GPEC and SEC analyses, basic hydrolysis resulted in cleavage of the ester linkage between the two blocks. It is well-known that xanthates, like other CTAs used for RAFT, also undergo degradation under basic conditions. In the preliminary work on PVP homopolymers, we observed that the SEC traces indicated an increase in M_n upon hydrolysis at pH = 12. This is most likely due to the formation of thiol end groups, which can undergo oxidation, resulting in the formation of disulfide bridges between two chains and subsequent doubling of M_n.[21] Most probably, this reaction at the chain ends also occurs in the case of diblock copolymers. It may account for the shoulder at high M_n values in the SEC chromatogram in Figure 7.

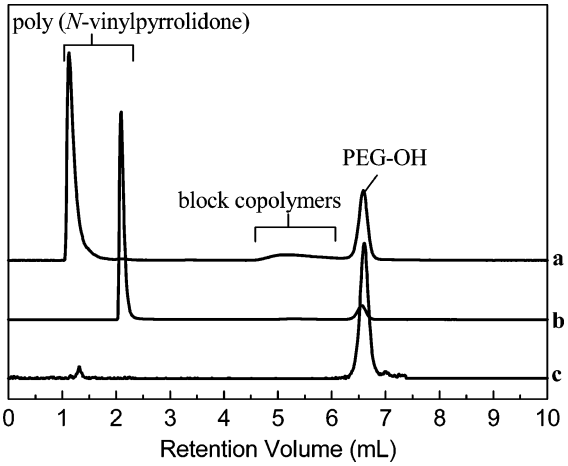


Figure 8. GPEC traces of (a) poly(ethylene glycol) monomethyl ether (PEG−OH) and its mixtures with PVP prepared via conventional free-radical polymerization in the presence of EG_{75}−OH (Table 2, ref 2e), (b) NVP_{77}−X1′ (Table 2, ref 2e) prepared via xanthate-mediated polymerization in the presence of EG_{75}−OH and the chain-transfer agent X1′, and (c) EG_{75}−OH.

As indicated previously, the only observable impurity in the macroCTAs used for polymerization was the unmodified PEG-OH. The following experiments were carried out to investigate the possible influence of PEG−OH on the polymerization of NVP and the possible formation of copolymers via a mechanism other than RAFT at the macroCTA chain end. NVP was polymerized in the presence of unmodified EG_{75}−OH (ref 2e, Table 2) and in the presence of both EG_{75}−OH and low molecular weight xanthate X1′ (ref 2f, Table 2). In the absence of RAFT agent, quantitative conversion of the monomer was reached within 3.5 h and the high viscosity disabled magnetic stirring, whereas in the other polymerization experiment, where a xanthate RAFT agent was used, the conversion did not exceed 86% in 17 h. The high rate of monomer conversion and the increase in viscosity, which could be related to the gel effect, are an indication of the uncontrolled character of the polymerization. The chromatograms of both products reveal the presence of homopolymers PEG-OH and PVP (Figure 8). PVPs did not elute at the same elution volume, which may be due to differences in the molecular weights and/or end groups. Traces of the copolymer were detected in the sample containing PVP prepared without a CTA in the presence of EG_{75}−OH (Figure 8a, peak at elution volume 4.5−6.3 mL). A possible cause for the copolymer formation is grafting via chain transfer to PEG and the subsequent growth of PVP branches.[22] Chain branching is less likely to occur to a significant extent in the presence of a CTA.[23] This translates experimentally to the absence of the copolymer signal (Figure 8b), where X1′ was added to the polymerization mixture. These experiments confirmed that the EG_{75}−OH mostly remained unmodified but did not inhibit either xanthate-mediated or conventional free-radical polymerization of NVP. They also confirmed that although transfer to PEG may occur it is not the origin for the formation of PEG-*b*-PVP copolymers in high yield as obtained with PEG−xanthate-mediated polymerization of NVP.

Separation of the PEG-*b*-PVAc polymers was not as challenging as PEG-*b*-PVP because of the significant difference in hydrophilicity of the two blocks. Gradient HPLC was performed with the initial conditions close to the critical conditions for PEG. When the hydrophobicity of the mobile phase was increased, the diblock copolymers were eluted first followed by the PVAc homopolymers (see Supporting Information). As expected, a longer PVAc block resulted in increased retention time. The chromatogram of EG_{75}−VAc_6 confirmed that even at low conversion the macroCTA was fully converted and that the product was a copolymer of PEG with VAc. The separation revealed the presence of PEG−OH in all samples. As PEG−OH was only present in trace amounts and since the peak area decreased relative to increased PVAc block length, its presence was probably due to incomplete conversion of the starting material rather than the blocks being hydrolyzed.

MALDI-ToF Mass Spectrometric Analysis. The nature of the block copolymer end groups was investigated via high-resolution MALDI-ToF-MS, which was performed on low molecular weight polymers, typically in the range of 1000−8000 g mol^{-1}. MALDI-ToF-MS spectra of copolymers are complex because a distribution of the copolymer composition is superimposed on the distribution of the degree of polymerization. Consequently, the observed complexity of the spectrum of the copolymer EG_{75}−VAc_6 compared to that of the homopolymer EG_{75}−X1 (Figure 9 a,b) was a first indication that copolymerization was successful. The increase in molecular weights resulting from the growth of a PVAc block from the PEG macroCTA was evidenced by a shift of the distribution to higher *m*/*z* values. Willemse et al.[24] have demonstrated the usefulness of high-resolution (reflector mode) MALDI-ToF-MS in copolymer analysis by reporting the complete structural analysis of polystyrene-*b*-polyisoprene samples. We applied their method

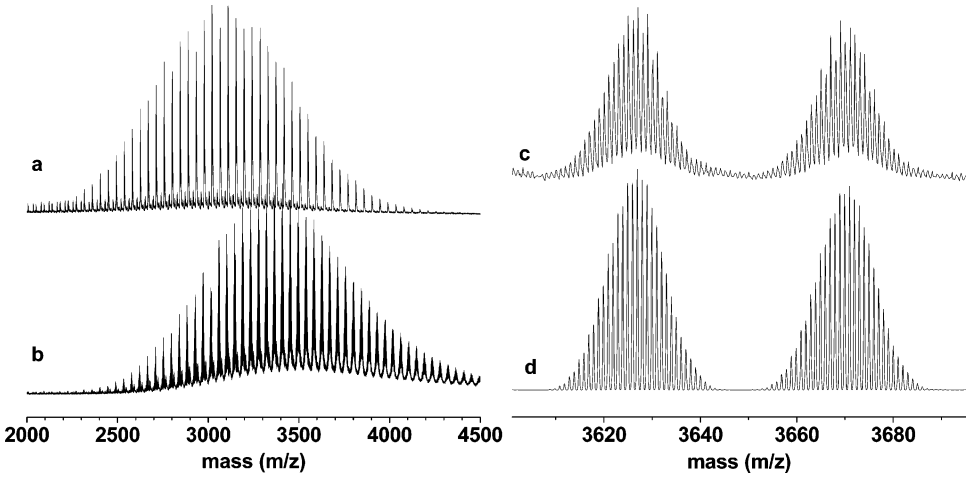


Figure 9. MALDI-ToF-MS spectra of (a) the macroCTA EG_{75}−X1 and (b) the block copolymer EG_{75}−VAc_6. Also shown are (c) the expansion of the experimental spectrum of EG_{75}−VAc_6 and the predicted isotopic pattern for CH_3O−$(CH_2CH_2O)_n$−C(O)$CH(CH_3)$−$(CH_2CH(O)COCH_3)_m$−$SC(S)OC_2H_5$, K^+ (d).

to identify the chemical composition of the end groups of PEG-*b*-PVAc samples. The type of comonomer sequence was already defined by the chemistry employed (only block copolymers or homopolymers could be obtained as opposed to random/statistical copolymers). Moreover, the average composition of the copolymers had been determined as a function of the conversion in VAc and confirmed via ^{1}H NMR spectroscopy, which greatly contributed to simplifying the calculations. The predictions for the expected structure of the diblock copolymer matched the experimental results (Figure 9c,d) with a correlation coefficient for the chemical composition of 0.955, confirming the presence of the xanthate end group and the low degree of polymerization of the PVAc block.

In the case of NVP-containing homo- and copolymers, we found significant fragmentation of the xanthate moiety even at low laser intensity and therefore we recommend other techniques, such as UV detection during SEC or HPLC analyses, to investigate the presence of the xanthate at the chain end.

Conclusions

The RAFT methodology was successfully applied to the synthesis of block copolymers of PEG with the poorly stabilized monomers VAc and NVP. Commercial mono- or dihydroxyl end-functional PEGs were modified into macroCTAs by introduction of a xanthate moiety. Of the two monofunctional macroCTAs prepared, the one which had a leaving group stabilized by a phenyl substituent did not provide block copolymers with the monomers tested. The cause of inhibition was identified as low reinitiation efficiency with VAc, while in the case of NVP it was more complex and the inhibition could have been caused by a combination of low reinitiation efficiency and side reactions. The leaving group with a methyl substituent produced copolymers, which were further analyzed by a combination of chromatographic and spectroscopic techniques. ^{1}H NMR spectroscopy confirmed the absence of any unmodified macroCTA in the final polymeric samples. MALDI-ToF-MS indicated the presence of the xanthate functionality on PEG-*b*-PVAc copolymers. Under the experimental conditions, only copolymers with a PVAc block could be successfully analyzed by MALDI-ToF-MS for end group determination because significant fragmentation occurred with the PVP-containing polymers. The control over the molecular weight distributions was estimated via SEC. Block copolymers with PEG-*b*-PVP and PVP-*b*-PEG-*b*-PVP where the PVP segments were short ($M_n \sim 5000$ g mol^{-1}) were obtained with a very low polydispersity index (PDI $\sim$ 1.1). With a longer PVP segment ($M_n \sim 39\,000$ g mol^{-1}), an increase in polydispersity was observed (PDI $\sim$ 1.4). The presence of homopolymers was investigated via gradient HPLC. A good separation between PEG and PVP or PEG and PVAc and their block copolymers was achieved. The samples generally contained traces of hydroxyl-functional PEG, which are most likely due to incomplete conversion during the synthesis of the macroCTA. Quantitative hydrolysis of a PEG-*b*-PVP sample was performed under basic conditions. Detection of PVP homopolymer and hydroxyl-functional PEG confirmed the presence and accessibility of the ester linkage between the blocks. The possible degradation of the block copolymers can be profitable in their use as biomaterials. While the molecular weight of the block copolymer can be sufficiently high to enable relatively long circulation time in the body, each of its fragments released upon hydrolysis might be short enough to enable renal clearance. This might be an interesting feature considering that both PEG and PVP have been used as drug carriers to improve the plasma half-life of drugs.[25]

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Supporting Information Available: Text and figures giving concentration profiles followed by in situ NMR spectroscopy during initialization studies, ^{1}H NMR spectra, and GPEC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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