Synthesis of Near-Monodisperse Acidic Homopolymers and Block Copolymers from Hydroxylated Methacrylic Copolymers Using Succinic Anhydride under Mild Conditions

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ABSTRACT: A new convenient route to well-defined, low-polydispersity polyacids is reported that does not require protecting group chemistry. First, near-monodisperse hydroxylated polymers are synthesized via ATRP of either 2-hydroxyethyl methacrylate, 2-hydroxypropyl methacrylate, or glycerol monomethacrylate and then esterified using excess acid anhydride under mild conditions. For example, using a succinic anhydride/hydroxy group molar ratio of two in pyridine, essentially complete esterification of the hydroxy groups in poly(2-hydroxyethyl methacrylate) occurred within 48 h at 20 °C. Moreover, varying this molar ratio allows the final degree of esterification to be easily controlled. THF was examined as an alternative solvent, but a tertiary amine catalyst was required to achieve high degrees of esterification under these conditions. According to ^{1}H NMR studies, the succinate ester bonds were susceptible to hydrolysis at or above pH 12 but were relatively stable at pH 2. Finally, a new poly(ethylene oxide)-based diblock copolymer was synthesized that dissolves molecularly at neutral pH but undergoes micellar self-assembly at low pH.

Introduction

The synthesis of controlled-structure polyacids with narrow molecular weight distributions has traditionally involved living ionic polymerization combined with protecting group chemistry. For example, well-defined poly(methacrylic acid) can be prepared by group transfer polymerization of suitable methacrylic esters, such as trimethylsilyl methacrylate,[1,2] benzyl methacrylate,[3,4] or 2-tetrahydropyranyl methacrylate.[2,5−7] Similarly, poly(acrylic acid) is usually prepared by hydrolysis of poly(*tert*-butyl acrylate) that has been synthesized by either classical anionic polymerization[8] or atom transfer radical polymerization (ATRP).[9] Examples of near-monodisperse carboxylic acid-functionalized poly(vinyl ethers) synthesized via living cationic polymerization in conjunction with protecting group chemistry have also been reported.[10,11] Near-monodisperse polyacids are of interest as dispersants for calcium carbonate particles[12,13] and also for modifying the crystal habits of various inorganic materials[14,15] and as the anionic component of zwitterionic diblock copolymers, which have been used for both protein purification[2,16] and pigment dispersion applications[17,18] as well as the synthesis of shell cross-linked micelles.[19,20]

The development of living radical polymerization has led to a number of reports concerning the direct polymerization of various acidic monomers. For example, acrylic acid can be polymerized in its free acid form in nonaqueous media via either nitroxide-mediated polymerization[21] or radical addition−fragmentation transfer (RAFT) polymerization.[13,22] There is a growing number of reports of the controlled polymerization of various acidic monomers in (mixed) aqueous solution. For example, sodium 4-styrenesulfonate has been homopolymerized using nitroxide-mediated polymerization by Georges and co-workers, who achieved high conversions and relatively low polydispersities.[23] Our group has used ATRP in aqueous media to polymerize both sodium methacrylate[24] and sodium 4-vinylbenzoate,[25] but the former monomer suffered from incomplete conversions and poor living character, whereas the latter monomer is too expensive to be of commercial interest. More recently, we also investigated[26] the ATRP of sodium 4-styrenesulfonate in aqueous and mixed aqueous media, but we were unable to obtain the low polydispersities reported by Choi and Kim.[27] One of the more promising approaches appears to be the use of RAFT chemistry to polymerize various acidic monomers in their sodium salt forms,[28−30] but a recent study by McCormick and co-workers indicates that the RAFT agent is not hydrolytically stable under certain conditions.[31] Thus, it seems that the *direct* synthesis of controlled-structure polyacids by living radical polymerization is actually quite problematic.

Liu and co-workers[32] recently described the esterification of the hydroxy groups of a statistical terpolymer using succinic anhydride. The hydroxy content of this terpolymer was relatively low (13−18 mol %), and the extent of esterification was by no means complete. Nevertheless, given our recent success in the synthesis of a wide range of controlled-structure hydroxy-functional homopolymers and block copolymers,[33−36] we decided to examine whether the derivatization of hydroxy-functional precursors using acid anhydrides might

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be a viable route to controlled-structure polyacids. This atom-efficient route has allowed us to develop a new synthetic route to well-defined zwitterionic diblock copolymers,[37] and the esterification of surface-grafted hydroxy-functional polymer chains has also been demonstrated.[38,39] In the present work we describe in detail our optimization of the esterification of various near-monodisperse hydroxy-functional precursors using acid anhydrides.

Experimental Section

Materials. All reagents were high-purity grades and were used as received. Monomethoxy-capped poly(ethylene oxide) (PEO_{45}-OH, $M_w/M_n = 1.09$, $M_{n,NMR} = 2000$), 2-hydroxyethyl methacrylate (HEMA), and 2-hydroxypropyl methacrylate (HPMA) were kindly donated by Cognis Performance Chemicals (Hythe, UK), and glycerol monomethacrylate (GMA) was kindly donated by Röhm (Germany). Succinic anhydride (SA), 1,2-cyclohexanedicarboxylic acid anhydride (CDA), and 2,2′-bipyridine (bpy) were purchased from Acros, and silica gel 60 (0.063−0.200 mm) was purchased from Merck. D_2O, CD_3OD, and $CDCl_3$ were obtained from Goss Scientific (UK). Unless otherwise stated, all other reagents were purchased from Aldrich.

Synthesis of 2-(4-Morpholino)ethyl 2-Bromoisobutyrate (ME-Br). 2-Bromoisobutyryl bromide (19.50 g, 83.1 mmol, 1.1 equiv) was added dropwise to a dichloromethane solution (150 mL) containing 4-(2-hydroxyethyl)morpholine (10.00 g, 75.5 mmol) and triethylamine (TEA) (8.49 g, 83.1 mmol, 1.1 equiv) under nitrogen in 50 mL of dichloromethane. This reaction solution was stirred overnight at 20 °C and then poured into 200 mL of water. The organic layer was separated and washed three times with 0.1 M Na_2CO_3 aqueous solution until all the TEA hydrobromide salt was removed. The combined organic phases were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The final product was obtained as a reddish-brown liquid (10.34, yield 77%) and was stored in a freezer in the absence of light prior to use. ^{1}H NMR analysis in $CDCl_3$ (residual peak at δ 7.27, 300 MHz): $\delta = 4.25$ (t, 2H), 3.63 (t, 4H), 2.62 (t, 2H), 2.47 (t, 4H), 1.87 (s, 6H).

Synthesis of Monomethoxy-Capped Poly(ethylene oxide) 2-Bromoisobutyrate (PEO_{45}-Br). PEO_{45}-OH (30.00 g, 15.0 mmol, 1 equiv) was dissolved in toluene (300 mL) in a 500 mL three-necked flask at room temperature under nitrogen. After azeotropic distillation of toluene (30 mL) at reduced pressure to remove traces of water, TEA (2.30 g, 22.5 mmol, 1.5 equiv) was added, and the solution was cooled to 0 °C. 2-Bromoisobutyryl bromide (5.28 g, 22.5 mmol, 1.5 equiv) was added dropwise using a syringe over 1 h, and the reaction was stirred for 48 h. The reaction mixture was then treated with activated carbon, which was subsequently removed by filtration, and the solution was concentrated by evaporation of the toluene, prior to precipitation into a 10-fold excess of diethyl ether. The white precipitate was dried under vacuum to constant weight, and the polymer was obtained as a white solid (25.31 g, yield 78%). It was characterized by ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 4.30$ (t, 2H), 3.62 (s, 178H), 3.35 (s, 3H), 1.91 (s, 6H). Peak integration indicated an M_n of approximately 2200, and DMF aqueous GPC yielded an M_w/M_n of 1.10 against poly(ethylene oxide) standards.

Homopolymerization of Hydroxylated Monomers by 50% w/v Methanolic ATRP. HEMA, HPMA, and GMA were typically polymerized according to the following procedure: monomer (5.00 g, target $DP_n = 50$) and ME-Br initiator (0.62−0.79 mmol) were mixed and degassed by nitrogen bubbling for 30 min. Then degassed methanol (5.0 mL) was added via double-tipped needle to the monomer solution. Under nitrogen flow, the Cu(I)Cl/bpy catalyst (such that [bpy]:[Cu(I)Cl]:[ME-Br] = 2:1:1) was then quickly introduced, allowing the reaction to start. The polymerization was terminated by exposing the reaction vessel to air and adding methanol (50 mL). The spent catalyst was removed by passing the blue postreaction solution through a silica column, and methanol was evaporated under vacuum to yield an off-white solid. The same general protocol was used for the synthesis of the PEO_{45}-*b*-$HEMA_{30}$ copolymer, except that methanol was degassed along with the PEO_{45}-Br initiator and the HEMA monomer.

Esterification of Hydroxylated Polymers in Pyridine. The esterification protocol for derivatization of poly(2-hydroxyethyl methacrylate) (PHEMA) using 2 equiv of SA per HEMA residue is described. PHEMA (250 mg, 1.86 mmol OH residues) was dissolved in anhydrous pyridine (3.0 mL) at room temperature in a 10 mL round-bottomed flask. SA (372 mg, 3.72 mmol) was then added, and esterification was allowed to proceed at 20 °C for 48 h. Aliquots were regularly taken throughout the reaction, precipitated into excess diethyl ether, and dissolved in CD_3OD for ^{1}H NMR analysis. At the end of the reaction, the reaction mixture was precipitated into 50 mL of diethyl ether (for the esterified PEO_{45}-*b*-$HEMA_{30}$, *n*-pentane was preferred as a nonsolvent). The solid was redissolved in 5 mL of THF and precipitated into 50 mL of diethyl ether. This cleanup procedure was repeated until SA and pyridine were no longer detected by ^{1}H NMR. Finally, the off-white solid was dried for 48 h in a vacuum oven. The same general protocol was employed for various anhydride/OH residue molar ratios, a different acid anhydride (CDA), or other hydroxylated polymers. (For PGMA, 4 equiv of SA per GMA unit was used; i.e., the SA/OH molar ratio was 2.0.) TEA catalyst was sometimes added after dissolution of the polymer prior to the introduction of the acid anhydride to the solution.

Esterification of Hydroxylated Polymers in THF in the Absence of TEA. The esterification protocol for PHEMA with an SA/OH molar ratio of unity is described. In a 10 mL round-bottomed flask PHEMA (250 mg, 1.86 mmol OH residues) was dispersed in anhydrous THF (3.0 mL) at room temperature. SA (186 mg, 1.86 mmol) was added, and esterification was allowed to proceed at room temperature. At the end of the reaction, the reaction mixture was precipitated into 50 mL of diethyl ether. The solid was redissolved in 5 mL of methanol and reprecipitated into 50 mL of diethyl ether. This cleanup procedure was repeated until SA was no longer detected by ^{1}H NMR. Finally, the solid was dried for 48 h in a vacuum oven at ambient temperature. The same general protocol was employed for various SA/OH molar ratios and also for poly(2-hydroxypropyl methacrylate) (PHPMA), which unlike PHEMA is soluble in THF.

Esterification of Hydroxylated Polymers in THF with TEA. The esterification protocol for PHEMA with an SA/OH molar ratio of unity and a TEA/OH molar ratio of unity is described. PHEMA (250 mg, 1.86 mmol OH residues) was dispersed in anhydrous THF (3.0 mL) at room temperature in a 10 mL round-bottomed flask. SA (186 mg, 1.86 mmol) was added, and esterification was allowed to proceed at room temperature for 24 h. A precipitate appeared within 24 h and was dissolved in 5 mL of methanol, before being precipitated into 50 mL of diethyl ether. This cleanup procedure was repeated until SA was no longer detected by ^{1}H NMR. Finally, the solid was dried for 48 h in a vacuum oven at ambient temperature. The same general protocol was employed for other SA/OH molar ratios using the same PHEMA and also for PHPMA, which is soluble in THF.

Gel Permeation Chromatography (DMF Eluent). Molecular weights and molecular weight distributions for hydroxylated polymers were measured by DMF GPC. The GPC setup consisted of three Polymer Laboratories PL gel 5 μm mixed "B" columns and an RI detector. Calibration was carried out using PMMA standards. The GPC eluent was HPLC grade DMF with 0.01 M LiBr, and the flow rate was 1.0 mL min^{-1}. The GPC column temperature was set at 70 °C.

Gel Permeation Chromatography (Aqueous Eluent). Molecular weights and molecular weight distributions of esterified polymers were measured by aqueous GPC. The instrument was equipped with an RI detector and two PL Aquagel OH30/40 columns. Calibration was carried out using a series of near-monodisperse PEO calibration standards. The GPC eluent was based on that previously used to analyze PNaStS samples.[26] It comprised a 70:30 v/v water/methanol

mixture, where the aqueous solution was prepared with 0.20 M $NaNO_3$ and 0.01 M NaH_2PO_4 at pH 9.5 (adjusted with NaOH), at a flow rate of 1.0 mL min^{-1}. Polymers were solubilized in the eluent and agitated overnight to ensure complete solubilization.

Nuclear Magnetic Resonance (NMR). All ^1H NMR spectra were recorded in D_2O or CD_3OD using a Bruker Avance PDX 300 MHz spectrometer.

Acid Titrations. The pK_a's of PSEMA and PCEMA were determined by acid titration of a 2.5% w/v aqueous polymer solution (initially at pH 11) with 0.10 M HCl. The solution pH was monitored using a HANNA pH meter that had been previously calibrated using pH 4, 7, and 10 buffers.

Dynamic Light Scattering (DLS). DLS studies were performed with a Brookhaven Instrument Corp. BI-200SM goniometer equipped with a BI-9000AT digital correlator and a solid-state laser (125 mW, $\lambda = 532$ nm) at a fixed scattering angle of 90°. The intensity-average hydrodynamic diameters, $\langle D_h \rangle$, and polydispersities of the micelles were obtained by cumulants analysis of the experimental correlation function. Samples were prepared as 0.5% w/v solutions in doubly distilled deionized water, with the pH being adjusted by adding HCl or NaOH where appropriate. The solutions were stirred for 2−3 h, left unstirred overnight, and then ultrafiltered through a 0.20 μm nylon filter (Phenomenex) before being analyzed at 20 °C.

Results and Discussion

Syntheses in Pyridine. The esterification of an alcohol with an acid anhydride is well-known organic chemistry and has been extensively used in various syntheses.[40] However, polymer-analogous reactions are not necessarily straightforward and often require optimization (typically forcing conditions such as elevated temperature, excess reactants, etc.) to achieve the desired degree of modification. Moreover, these reactions are typically slower than small molecule reactions, and vigorous experimental conditions can sometimes cause chain scission or interchain cross-linking.[9] For example, Liu and co-workers[32] carried out the esterification of two PtBA-*b*-PHEMA copolymers in pyridine using 43 mol % SA per OH residue. The succinyl molar fractions in the two PHEMA blocks were found to be 13 and 18% after leaving the reaction overnight, which corresponds to 30 and 41% of the intended degree of esterification, respectively. In the present study, we investigated the esterification of PHEMA with two cyclic acid anhydrides, SA and CDA, leading to two different acidic homopolymers, poly(2-(succinyloxy)ethyl methacrylate) (PSEMA) and poly(2-(2-(carboxylic acid)cyclohexylcarboxy)ethyl methacrylate) (PCEMA), respectively (Scheme 1). Using the ME-Br initiator,[35] PHEMA was first synthesized by ATRP in methanol at 20 °C with good control ($M_w/M_n = 1.24$, $M_{n,NMR} = 6800$, which is in excellent agreement with $M_{n,theo} = 6800$). This PHEMA was then reacted with varying amounts of acid anhydride per OH residue (Table 1). Experiments were conducted at ambient temperature to avoid cross-linking between the new carboxylic acid functionality and the remaining unreacted hydroxy groups and also to ensure that chain scission would be unlikely to occur. When an equimolar ratio of SA was used (entry 3), 66% of OH residues were esterified. Varying this molar ratio resulted in different degrees of esterification being obtained (entries 1−5), with complete esterification being achieved for 2 equiv of SA per monomer unit (entry 5). Kinetic studies of the extent of esterification of PHEMA were carried out at various SA/OH residue molar ratios. When the reaction was carried out using 0.5 equiv of SA per OH, the conversion reached 30% within 24 h,

Scheme 1. Esterification of Poly(2-hydroxyethyl methacrylate) with Two Cyclic Anhydrides, Succinic Anhydride, and 1,2-Cyclohexanedicarboxylic Acid Anhydride, under Mild Conditions

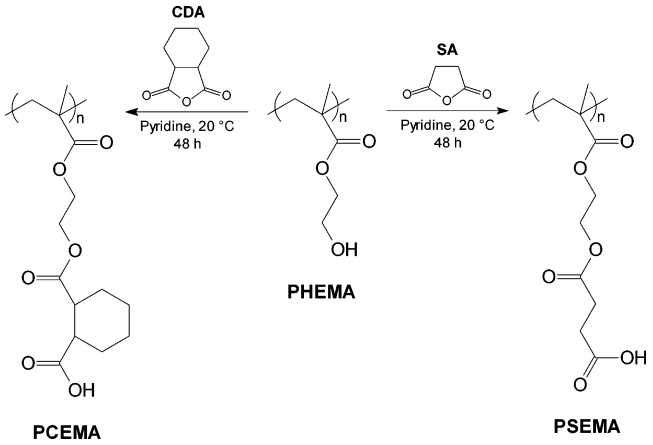

Table 1. Esterification of Hydroxylated Homopolymers Using Either Succinic Anhydride (SA) or 1,2-Cyclohexanedicarboxylic Acid Anhydride (CDA) in Pyridine at 20 °C[a]

entry	polymer precursor	anhydride type	anhydride/OH molar ratio	time (h)	conv (%)[b]
1	PHEMA	SA	0.5	24	30
2	PHEMA	SA	0.8	48	54
3	PHEMA	SA	1.0	48	66
4	PHEMA	SA	1.5	48	89
5	PHEMA	SA	2.0	48	99
6	PHEMA	CDA	1.0	48	64
7	PHEMA	CDA	2.0	48	98
8	PHPMA	SA	2.0	48	99
9	PGMA	SA	2.0	48	99

[a] Experimental conditions: 250 mg of hydroxy-functional polymer precursor in 3.0 mL of pyridine. [b] Determined by ^1H NMR.

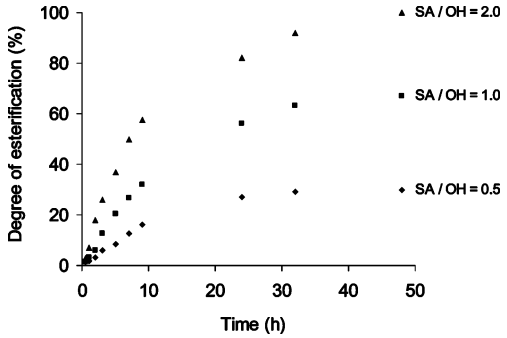

Figure 1. Evolution of degree of esterification of poly(2-hydroxyethyl methacrylate) with time for three SA/OH residue molar ratios: 0.5 (◆), 1.0 (■), and 2.0 (▲).

with no increase being observed thereafter (Figure 1). For esterifications using 1.0 and 2.0 equiv per OH, the maximum conversion was achieved within 48 h. Similar reactivities were observed with another cyclic anhydride, CDA (entries 6 and 7). Therefore, the structure of the anhydride does not appear to affect the efficiency of the esterification. This is presumably due to the relatively nucleophilic nature of the primary alcohol, which does not discriminate between these two acid anhydrides. Attachment of the succinic acid group to PHEMA led to the appearance of two new peaks at 4.2 and 4.4 ppm due to the shifts in the positions of the pendent oxyethylene protons (Figure 2). A new peak at 2.7 ppm was assigned to the methylene protons of the succinic group. Successive precipitations in diethyl ether

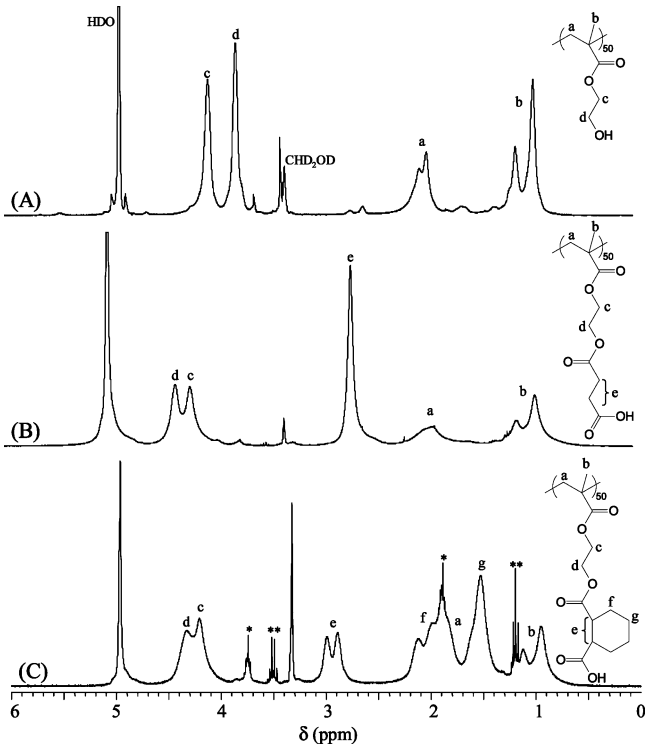

Figure 2. Representative ^{1}H NMR spectra (CD_3OD) of (a) PHEMA precursor, (b) PSEMA (entry 5), and (c) PCEMA (entry 7). Residual THF and diethyl ether signals are indicated by ∗ and ∗∗, respectively.

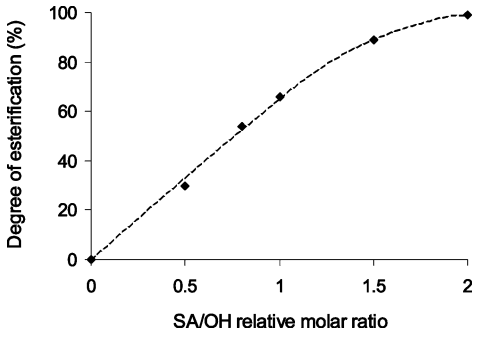

Figure 3. Relationship between the initial SA/OH molar ratio and the degree of esterification obtained for poly(2-hydroxyethyl methacrylate) (1.86 mmol of OH residues) in pyridine for 48 h at 20 °C.

ensured complete removal of the pyridine (disappearance of aromatic signals in the ^{1}H NMR spectra) as well as the excess anhydride (no signal found at 2.6 ppm). This simple purification procedure is much less time-consuming than dialysis and confirms that well-defined polyacids can be easily synthesized and purified. A ^{1}H NMR spectrum of PCEMA is also shown of Figure 2. The conversions in Table 1 indicate that the proportion of succinic groups could be readily controlled by simply adjusting the initial anhydride/OH residue relative molar ratio (Figure 3). Thus, this facile chemistry also allows the synthesis of well-defined statistical PHEMA-*stat*-PSEMA copolymers (Figure 4).

To examine whether this esterification was sensitive to the steric hindrance of the alcohol, the same reaction was carried out using two other hydroxylated polymers, PHPMA and PGMA (where PGMA stands for poly(glycerol monomethacrylate)). HPMA and GMA were also polymerized by methanolic ATRP at 20 °C,[34] using essentially the same protocol as that used for the HEMA

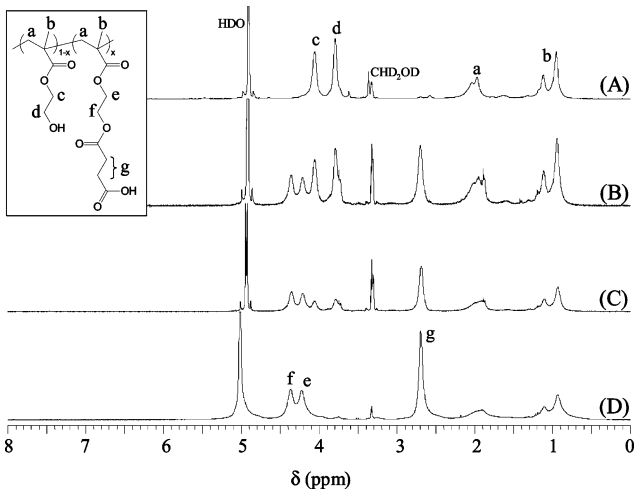

Figure 4. ^{1}H NMR spectra (CD_3OD) recorded for various statistical $PHEMA_{(1-x)}$-*stat*-$PSEMA_x$ copolymers: (a) $x = 0$, (b) $x = 0.30$ (Table 1, entry 1), (c) $x = 0.66$ (Table 1, entry 3), (d) $x = 0.99$ (Table 1, entry 5).

homopolymerization. Experimental conditions and characterization data for the resulting PHEMA, PHPMA, and PGMA homopolymers are summarized in Table 2.

It is noteworthy that the HPMA and GMA monomers are actually both mixtures of two closely related isomers. These isomeric impurities are produced during their industrial synthesis and have been discussed recently.[34] HPMA and GMA monomers contain 25 mol % 2-hydroxy-1-methylethyl methacrylate and 8 mol % 2-hydroxy-1-(hydroxymethyl)ethyl methacrylate, respectively, as isomeric impurities. Thus, both PHPMA and PGMA are actually statistical copolymers, rather than "genuine" homopolymers. However, since the chemical structures of these minor isomers are very similar to those of HPMA and GMA, these statistical copolymers will be described hereafter as homopolymers. Nevertheless, it is important to acknowledge these structural heterogeneities, since esterification might well be sensitive to the local environment of the hydroxy function(s). Both HPMA monomer and also the corresponding PHPMA "homopolymer" are actually a mixture of 75 mol % secondary alcohol and 25 mol % primary alcohol. Similarly, PGMA "homopolymer" actually contains 46 mol % secondary alcohol and 54 mol % primary alcohol, rather than 50 mol % of each alcohol, due to the presence of its minor isomer.

Both PHPMA and PGMA were reacted using 2 equiv of SA per OH (for the latter polymer this means an SA/GMA molar ratio of 4) in pyridine at 20 °C according to the optimized conditions indicated in Table 1. Degrees of esterification of 99% were obtained in both cases (entries 8 and 9), as judged by ^{1}H NMR spectroscopy (see Figures 5 and 6). The introduction of the succinyl groups in PHPMA and PGMA led to two "homopolymers", poly(2-(succinyloxy)propyl methacrylate) (PSPMA) and poly(2,3-bis(succinyloxy)propyl methacrylate) (PBSPMA), respectively. This demonstrates that essentially complete esterification of hydroxylated polymers can be achieved with SA in pyridine, at least for polymers containing primary and secondary alcohols. Furthermore, since 99% esterification for PHPMA and PGMA can be achieved within 48 h (i.e., on similar time scales to that used for PHEMA), the kinetics of esterification for PHPMA and PGMA are likely to be very similar to that of PHEMA. Hence, secondary alcohols

Table 2. Synthesis of Hydroxy-Functional Homopolymer Precursors by Methanolic ATRP at 20 °C[a]

entry	name	time (h)	conv (%)	$M_{n,theo}$[b]	$M_{n,NMR}$[c]	$M_{n,GPC}$[d]	M_w/M_n[d]
1	PHEMA	18	100	6800	6800	15 200	1.24
2	PHPMA	18	99	7500	8900	15 600	1.21
3	PGMA	3	100	8300	9400	16 500	1.17

[a] For all the experiments, the relative molar ratios $[monomer]_0:[ME\text{-}Br]_0:[CuCl]_0:[bpy]_0$ were 50:1:1:2. [b] $M_{n,theo} = \{(conversion \times [monomer]_0/[ME\text{-}Br]_0) \times M_{monomer}\} + M_{ME-Br}$. [c] Determined by ^1H NMR (CD_3OD) on the purified homopolymer. [d] Determined by DMF GPC, calibrated with PMMA standards.

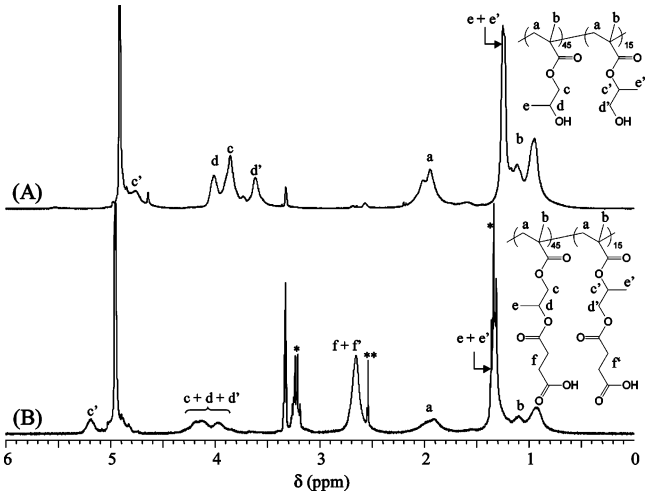

Figure 5. ^1H NMR spectra (CD_3OD) recorded for (a) the PHPMA precursor and (b) the SA-esterified polymer product, PSPMA. Residual diethyl ether and succinic acid (generated during the purification procedure) are indicated by ∗ and ∗∗, respectively.

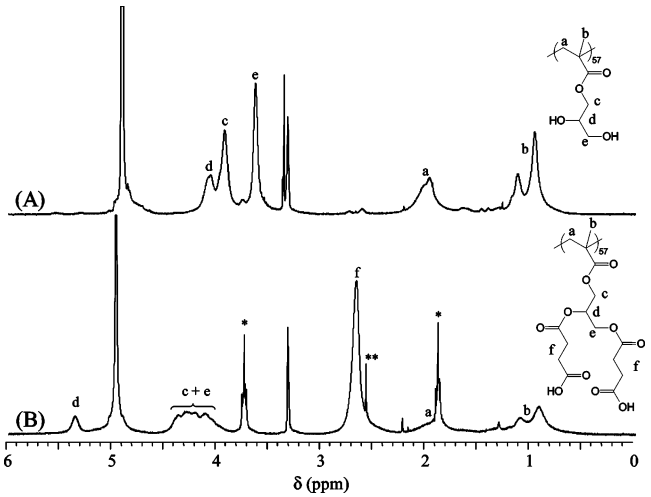

Figure 6. ^1H NMR spectra (CD_3OD) recorded for (a) the PGMA precursor and (b) PBSPMA. For clarity, and because GMA is the dominant isomer, only the "homopolymer" structure is shown. Residual THF and succinic acid (generated during the purification procedure) are indicated by ∗ and ∗∗, respectively.

appear to be as easily esterified as primary alcohols using SA under the stated conditions.

Syntheses in Tetrahydrofuran. The three hydroxy-functional polymers, as well as their esterified derivatives, are readily soluble in pyridine, and this basic solvent also catalyzes the esterification. However, pyridine is a toxic, malodorous solvent; hence, we investigated the use of THF as an alternative solvent. The derivatization of both PHEMA and PHPMA using SA was carried out in THF. PHPMA is soluble in THF but PHEMA is insoluble. Fortunately, the resulting esterified homopolymers are THF-soluble (or at least THF-dispersible: a THF solution of PSEMA or PSPMA appears homogeneous but has a slightly cloudy appearance). Therefore, the esterification of PHEMA was carried out under heterogeneous conditions, at least at the beginning of the reaction. On the other hand, PHPMA esterifications were conducted in homogeneous solution. As for the earlier reactions in pyridine, various SA/OH molar ratios were investigated, and in some cases either TEA or pyridine was used as a basic catalyst (Table 3). With 1 equiv of SA per OH residue (entry 1), 40% esterification was achieved within 24 h at ambient temperature, but no further conversion was observed by ^1H NMR spectroscopy for longer reaction times (up to 48 h). Interestingly, PHEMA undergoes esterification in THF, even though the initial reaction mixture is heterogeneous. At an SA/OH residue molar ratio of two, 58% esterification was achieved within 24 h (entry 2). When this relative molar ratio was increased to three, the reaction proceeded much more slowly, with only 4% esterification being achieved within 24 h, as judged by ^1H NMR. This may be due to the relatively high concentration of SA in THF (the same volume of THF was used for all experiments), which may have compromised solubilization of PHEMA. Nevertheless, 74% OH residues were esterified after 168 h (entry 3). When the reaction temperature was raised to 50 °C, the conversions surprisingly dropped to 22% and 38% within 24 h for 1 and 2 equiv of SA per OH residue, respectively (entries 4 and 5). TEA and pyridine were then examined as basic catalysts for the esterification. First, the reaction was carried out using an equimolar ratio of TEA with respect to both the hydroxy groups and SA. A slurry was formed after addition of all the reactants; the reaction proceeded, but no precipitation occurred initially. However, within 24 h a precipitate was formed, and unlike the reaction solution, the supernatant was now transparent. As judged by ^1H NMR in CD_3OD, no more polymer was detected in the THF phase, and the precipitate phase was shown by ^1H NMR to be a PHEMA-*stat*-PSEMA copolymer with 44 mol % SEMA

Table 3. Esterification of HEMA and HPMA Homopolymers Using Succinic Anhydride (SA) in THF at Either 20 or 50 °C[a]

entry	polymer	temp (°C)	SA/OH molar ratio	TEA/OH molar ratio	time (h)	conv (%)[b]
1	PHEMA	20	1.0	0.0	24	40
2	PHEMA	20	2.0	0.0	24	58
3	PHEMA	20	3.0	0.0	168	74
4	PHEMA	50	1.0	0.0	24	22
5	PHEMA	50	2.0	0.0	24	38
6	PHEMA	20	1.0	1.0	24	44
7	PHEMA	20	1.0	1.0[c]	48	66
8	PHPMA	20	1.0	0.0	96	3
9	PHPMA	20	1.0	1.0	24	86
10	PHPMA	20	2.0	1.0	24	99

[a] Experimental conditions: 250 mg polymer in 3.0 mL THF. [b] Determined by ^1H NMR. [c] Pyridine was used as the base.

Table 4. Summary of the Degrees of Esterification, Molecular Weights, and Polydispersities for the Hydroxylated Polymers and the Corresponding Esterified Polymers

	hydroxylated polymer precursor				derivatized polymer				
entry	name	$M_{n,NMR}$	$M_{n,GPC}$[a]	M_w/M_n[a]	name	deg of esterification	$M_{n,theo}$	$M_{n,GPC}$[b]	M_w/M_n[b]
1	PHEMA	6800	15 200	1.24	PSEMA	99	11 800	37 500	1.29
2	PHPMA	8900	15 600	1.21	PSPMA	99	14 800	49 300	1.23
3	PGMA	9400	16 500	1.17	PBSPMA	99[c]	16 500	58 200	1.39
4	PHEMA	6800	15 200	1.24	PCEMA	98	14 500	45 500	1.26

[a] Determined by GPC analysis in DMF eluent and calibrated with PMMA standards. [b] Determined by GPC analysis in 70:30 v/v water/methanol mixture (this mixed aqueous solution also contained 0.20 M $NaNO_3$ and 0.01 M NaH_2PO_4 at pH 9.5) and calibrated with PEO standards. [c] Conversion of each OH residue.

units (entry 6). Presumably, the carboxylic acid of the succinyl groups reacted with TEA to form a poly(ammonium salt) that was insoluble in THF. When pyridine was used as the catalyst, no precipitation occurred during the reaction. The conversion reached 56% within 24 h and 66% within 48 h, with no further esterification being observed thereafter (entry 7). Hence, pyridine seems to be a better catalyst for the esterification of PHEMA in THF. Because of its relatively low basicity ($pK_a = 5.14$ for pyridine[41] whereas $pK_a = 10.78$ for TEA[42]), pyridine does not lead to the formation of anionic carboxylate groups on the polymer chains and hence allows the PHEMA-*stat*-PSEMA copolymer to remain in solution.

The esterification of PHPMA was then assessed. This precursor is soluble in THF, yet when an SA/OH molar ratio of one was used, almost no esterification was observed (entry 8). As PHPMA comprises mainly secondary alcohols (75% according to the isomeric composition), this suggests that esterification under these conditions is very sensitive to steric hindrance effects. However, since PHPMA contains 25% primary alcohol, and under similar conditions 40% OH residues of a PHEMA precursor reacted with SA (entry 1), a degree of esterification of at least 10% was expected for the PHPMA precursor. A possible explanation could be the differing solubility in THF of PHPMA and the corresponding acidic polymer, PSPMA. PHPMA is more soluble in THF than PSPMA, and it is likely that the reduced solubility of the intermediate statistical copolymers reduces the overall conversion. Subsequently, TEA was used as a catalyst (equimolar quantities of TEA, SA, and OH residues), and the reaction yielded a precipitate corresponding to the ammonium salt of a statistical PHPMA-*stat*-PSPMA copolymer that contained 86 mol % SPMA units (entry 9). Using 2 equiv of SA with TEA, essentially complete esterification of the OH residues of PHPMA was achieved (entry 10). Thus, the presence of pyridine (either as a catalyst or as a solvent) is not essential to achieve high levels esterification of PHPMA.

Aqueous Solution Properties of the Polyacid Derivatives. As previously stated, the precursor polymers (PHEMA, PHPMA, and PGMA) were analyzed by ^{1}H NMR and DMF GPC. Each precursor had been synthesized by methanolic ATRP at 20 °C and hence had a relatively low polydispersity ($M_w/M_n \sim 1.2$). The discrepancy between the molecular weight calculated from the ^{1}H NMR spectrum of each homopolymer, and the GPC molecular weight is presumably due to the differences in hydrodynamic volumes between the hydroxylated polymers and the PMMA standards[35] (see Table 4). Aqueous GPC was used to examine whether the derivatized polymers had comparable polydispersities to those found for the homopolymer precursors. To avoid possible solubility problems, only acidic polymers with very high degrees of esterification were selected. The PHEMA, PHPMA, and PGMA precursors afforded PSEMA, PSPMA, and PBSPMA derivatives, respectively, after treatment with 2 equiv of SA. PHEMA was also reacted with 2 equiv of CDA to produce a PCEMA homopolymer. Large discrepancies were observed between the theoretical M_n values of the derivatized polymers and the GPC M_n data. However, this was expected given that nonionic PEO calibration standards are unlikely to be accurate calibration standards for anionic polyelectrolytes. Nevertheless, the molecular weight data followed the expected trend: M_n(PSEMA) < M_n(PSPMA) < M_n(PBSPMA), and M_n(PSEMA) < M_n(PCEMA). Moreover, the polydispersities were in generally good agreement with the polydispersities of the precursor polymers ($M_w/M_n = 1.2-1.3$). This confirmed that the mild conditions used for the esterification generally did not lead to cross-linking or chain scission problems. Only the esterified PGMA precursor (PBSPMA) had a somewhat higher polydispersity than expected ($M_w/M_n = 1.39$). This GPC trace was actually bimodal: a small tail to high molecular weight was observed. Thus, the aqueous GPC protocol might not be optimal for PBSPMA, which has two carboxylic acid groups per monomer unit. In addition, calibration with commercial anionic poly(sodium methacrylate) standards is likely to reduce the discrepancies between the calculated molecular weights and those observed by GPC. Nevertheless, these aqueous GPC data indicate that low-polydispersity polyacids can be synthesized via a two-step procedure. To the best of our knowledge, this is a rare example of the synthesis of such acidic copolymers without recourse to protecting group chemistry, which is inherently atom-inefficient.

Acid titration was carried out on PSEMA and PCEMA in order to determine the pK_a values of the two polyacids. Each homopolymer (2.5% w/v solution) was dissolved in turn at pH 11, and the solution pH was monitored as 0.1 M HCl was gradually added (Figure 7). Analysis of these titration curves gave pK_a values of 5.5 and 6.3 for PSEMA and PCEMA, respectively. The pK_a value of PSEMA is similar to that reported for poly(methacrylic acid) ($pK_a = 5.35$[44]). This suggests that PSEMA may behave similarly to a poly(methacrylic acid) block in terms of its aqueous solution properties. However, unlike poly(methacrylic acid), PSEMA is not soluble in acidic solution; protonation of the weak carboxylic acids below pH 4 leads to precipitation.[25] During these ^{1}H NMR studies the succinate half-ester linkage in the derivatized polymer was found to be susceptible to hydrolysis at or above pH 12. To investigate this further, ^{1}H NMR spectra of PSEMA were recorded in D_2O from pH 5 to pH 12 at various time intervals. No PHEMA peaks were observed at 3.7 and

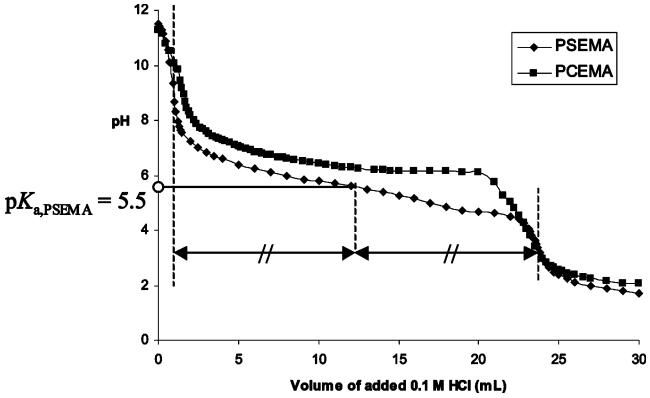

Figure 7. Typical acid titration curves obtained for PSEMA and PCEMA homopolymers (2.5% w/v solution) on addition of 0.10 M HCl. The pK_a values determined from these curves are 5.5 for PSEMA and 6.3 for PCEMA.

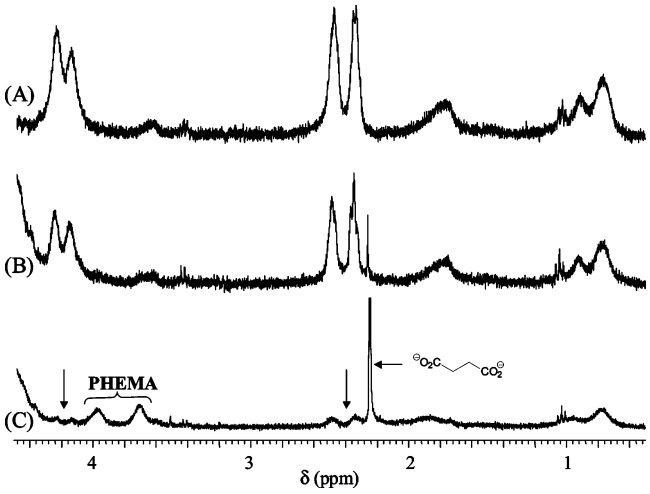

Figure 8. ^{1}H NMR (D_2O/NaOD) spectra recorded for a PSEMA homopolymer dissolved in alkaline solution and aged for various time periods: (a) after 0.5 h at pH 11; (b) after 0.5 h at pH 12; (c) after 16 h at pH 12.

4.0 ppm (or a succinic acid peak at 2.2−2.3 ppm) in ^{1}H NMR spectra recorded after 0.5 h at pH 5−11 (Figure 8A, where only the ^{1}H NMR spectrum of PSEMA at pH 11 is shown). These spectra were essentially unchanged after 5 days. However, after 0.5 h at pH 12, a new peak appeared at 2.25 ppm, corresponding to the conjugated base of succinic acid (see Figure 8B). After 16 h, PHEMA signals were detected in the same NMR sample, as well as a sharp increase in the intensity of the succinate peak (see Figure 8C). This confirmed that the succinate ester was cleaved rapidly at pH 12, whereas it is stable for at least 5 days at pH 11 or below. Similar observations were made for PCEMA, which was stable from pH 7 to pH 11 but hydrolyzed at pH 12. These esterified polymers are not soluble at low pH; hence, it is not possible to examine hydrolysis in homogeneous aqueous acidic solution. However, a PSEMA homopolymer was solubilized at pH 8, and the pH was adjusted to pH 2 using 0.1 M HCl. The polymer precipitated, as expected, and the heterogeneous solution was stirred for 24 h at pH 2, before adjusting the pH back to pH 8 using 0.1 M NaOH. A ^{1}H NMR spectrum of this solution was recorded in D_2O, and no additional signals were observed, suggesting that no significant hydrolysis had occurred. PSEMA was also solubilized in a 5:1 v/v CD_3OD/20% w/w DCl mixture, and its ^{1}H NMR spectrum

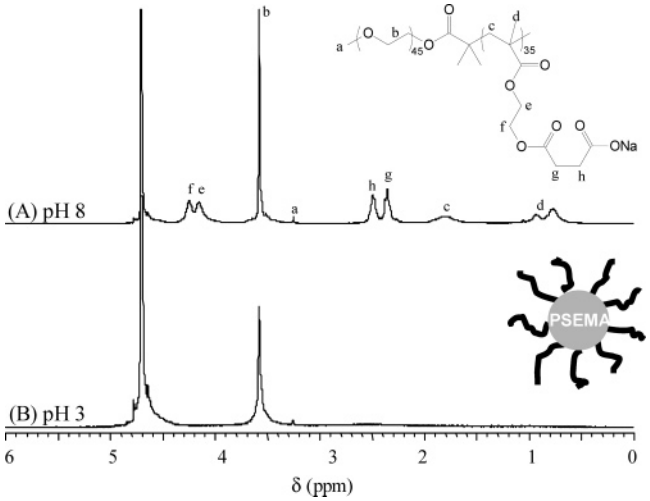

Figure 9. ^{1}H NMR (D_2O) spectra recorded for a PEO_{45}−$PSEMA_{35}$ diblock copolymer at (a) pH 8 and (b) pH 3 (after addition of DCl).

was recorded after 24 h in this solution. Again, essentially no hydrolysis was observed by ^{1}H NMR. These two experiments demonstrate that the esterified polymer is relatively stable at low pH.

Diblock Synthesis and Micellization Behavior. Having optimized the esterification chemistry for homopolymers, we then sought to exploit this chemistry for the synthesis of new acidic diblock copolymers. Accordingly, a PEO−PHEMA diblock copolymer (M_w/M_n = 1.14; $M_{n,NMR}$ = 6800; $M_{n,theo}$ = 6100) was synthesized via methanolic ATRP using a PEO_{45}-Br macroinitiator and a CuCl/2bpy catalyst. The resulting block copolymer was esterified with SA (2 equiv based on OH residues) in pyridine, and 99% esterification was achieved. Unexpectedly, the polymer did not precipitate readily in excess diethyl ether so *n*-pentane was used as a nonsolvent for its isolation and recovery. The polymer was isolated as a "glassy" solid, suggesting that this diblock copolymer had a high glass temperature (T_g).

Unlike PEO, which is permanently water-soluble, PSEMA is only soluble in water in its ionized form, i.e., above pH 5. Similar pH-responsive behavior has been reported for poly(4-vinylbenzoic acid) [PNaVBA]; NaVBA-based block copolymers exhibit reversible aggregation behavior, depending on the solution pH.[44,45] However, this is not the case for every polyacid: both poly(acrylic acid) and poly(methacrylic acid) are soluble in water at room temperature, regardless of the solution pH.[46] Therefore, the PEO−PSEMA diblock copolymer was expected to exhibit pH-responsive micellization in water. To investigate this behavior, this copolymer was molecularly dissolved in D_2O at pH 8. As the PSEMA block was anionic and highly hydrated at this pH, signals from both the PEO and PSEMA blocks were observed in the ^{1}H NMR spectrum (Figure 9A). Adjusting the solution pH to pH 3 with DCl led to the disappearance of the PSEMA signals at 4.1−4.3 and 2.5−2.3 ppm (Figure 9B). Dynamic light scattering studies indicated the formation of colloidal aggregates with a mean diameter of around 160 nm (polydispersity = 0.15). This size is too large to represent simple core−shell micelles: presumably, either compound micelles or vesicles are formed under these conditions.[47] Adjusting the solution pH back to pH 8 led to rapid dissolution of these colloidal aggregates, as expected.

Conclusions

The esterification of various hydroxylated polymers with two cyclic acid anhydrides has been investigated and optimized to enable the synthesis of low-polydispersity polyacids. Using an acid anhydride/OH residue molar ratio of two in pyridine, essentially complete esterification of the hydroxy groups was achieved within 48 h at 20 °C. Moreover, the incorporation of acidic moieties can be easily controlled by simply varying this molar ratio. THF was assessed as an alternative solvent, but a tertiary amine catalyst was necessary in order to achieve high degrees of esterification under these conditions. Using this protocol, a novel well-defined homopolymer with two carboxylic groups per monomer unit (PBSPMA) was obtained. Such polymers may find applications in wastewater treatment since efficient sequestration of divalent cations such as Ca^{2+} and Mg^{2+} is expected. According to ^1H NMR studies, the new succinate-based ester linkage was susceptible to hydrolysis at or above pH 12 but was relatively stable at pH 2. A new pH-responsive diblock copolymer, PEO-*b*-PSEMA, was also synthesized and was shown to undergo pH-modulated micellar self-assembly. In summary, it has been demonstrated that low-polydispersity acidic copolymers can be synthesized under mild conditions via a convenient, high yielding, and atom-efficient two-step procedure without recourse to protecting group chemistry.

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