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Synthesis of Well-Defined Poly(2-ethylacrylic acid)

Jungsoo Kim and David A. Tirrell*

Department of Polymer Science and Engineering,
University of Massachusetts, Amherst, Massachusetts 01003

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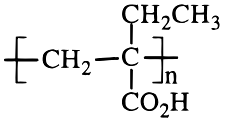
Introduction

The pH-dependent conformational transition of the hydrophobic polyelectrolyte poly(2-ethylacrylic acid) (PEAA, **1**) can be used to design lipid bilayer membranes that release their contents in response to changes in environmental parameters such as pH, temperature, light intensity, and solute (e.g., glucose) concentration.[1−4] Such responsive membrane systems are finding important applications in drug delivery, signal amplification in biochemical assays, and molecular recognition.



$$\left[CH_2-\underset{CO_2H}{\overset{CH_2CH_3}{C}}\right]_n$$

1

The use of macromolecules offers substantial advantages in membrane design. For example, one can adjust either the “critical” pH for the onset of membrane reorganization or the cooperativity of the structural transition by varying polymer architectural features such as molecular weight, stereochemistry, or copolymer composition.[2,5,6]

While PEAA is readily prepared by free radical methods, new polymerization routes are required in order to provide more precise control of the polymer structure. Living anionic polymerization, which proceeds without chain termination and transfer, provides a possible solution;[7−9] however, the carboxylic acid function of 2-ethylacrylic acid (EAA) must be protected in order to avoid termination via proton transfer. In our previous work, the methyl ester of EAA was polymerized by using *n*-butyllithium as initiator in toluene at −78 °C.[2] Although this method provided PEAA after hydrolysis of the side-chain ester, use of such a reactive initiator and a nonpolar solvent resulted in low yields and unpredictable molecular weights. It is also possible that the vigorous hydrolysis conditions required for removal of the methyl ester (reaction with concentrated sulfuric acid for several days) would cause problematic degradation of the polymer structure.

To overcome these problems we turned our attention to other ester derivatives of EAA. This paper reports a successful route to well-defined PEAA via anionic polymerization of benzyl 2-ethylacrylate.

Experimental Section

Materials. Triethylamine, benzyl alcohol, and trimethylsilyl iodide (TMSI) were purchased from Aldrich Chemical Co. and used without further purification. THF (Fisher, certified) was stirred over CaH_2, degassed, and distilled into a storage flask containing sodium/benzophenone. Fresh THF was obtained from this dark purple solution by distillation into the reaction flask. 2-Ethylacrylic acid was synthesized by the procedure reported by Ferritto and Tirrell.[10]

Synthesis of 2-Ethylacryloyl Chloride. Thionyl chloride (108 g, 0.9 mol) was placed in a 500 mL two-necked round-bottom flask equipped with a magnetic stirring bar, a reflux condenser, and a dropping funnel. The condenser and funnel were fitted with calcium chloride guard tubes.

As 2-ethylacrylic acid (75 g, 0.75 mol) was added dropwise, sulfur dioxide evolved and the liquid darkened considerably. When all of the 2-ethylacrylic acid had been added, the mixture was refluxed for 2 h. The apparatus was rearranged for distillation, and 2-ethylacryloyl chloride (bp 105−107 °C/760 mmHg) was collected (78 g, 88%). ^{1}H NMR ($CDCl_3$): δ 1.0 [t, J = 7.5 Hz, 3H, $-CH_2CH_3$], δ 2.3 [q, J = 7.5 Hz, 2H, $-CH_2$-CH_3], δ 6.0 and 6.5 [2H, CH_2=].

Synthesis of *tert*-Butyl 2-Ethylacrylate (*t*BEA). *tert*-Butyl alcohol (3.7 g, 0.05 mol) was dissolved in 75 mL of anhydrous THF in a three-necked, round-bottom flask equipped with a reflux condenser, a nitrogen inlet tube, and a thermometer. The contents were stirred with a magnetic stirring bar, and 1.6 M *n*-butyllithium in hexane (35.0 mL, 0.055 mol) was added over 10 min under nitrogen. After the addition was complete, the resulting lithium *tert*-butoxide was treated by dropwise addition (1 mL/min) of a THF solution of 2-ethylacryloyl chloride (6.49 g, 0.055 mol). The resulting solution was brought to reflux for 2 h, cooled by an ice bath, and then hydrolyzed by addition of 100 mL of water while the temperature was maintained below 5 °C. The product was extracted with three 50 mL portions of ethyl ether, and the combined ether extracts were washed once with 10% potassium carbonate and once with saturated sodium chloride and finally dried over anhydrous magnesium sulfate. The ether was removed by distillation, and the residue was fractionally distilled; bp 105−107 °C. The final yield was 5.9 g (75%). ^{1}H NMR ($CDCl_3$): δ 1.0 [t, J = 7.5 Hz, 3H, $-CH_2CH_3$], δ 1.5 [s, 9H, $-C(CH_3)_3$], δ 2.3 [q, J = 7.5 Hz, 2H, $-CH_2CH_3$], δ 5.4 and 6.0 [2H, CH_2=]. Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.11; H, 10.30.

Synthesis of Benzyl 2-Ethylacrylate (BzEA). A mixture of benzyl alcohol (27 g, 0.25 mol) and triethylamine (16 g, 0.16 mol) was placed in the three-necked, round-bottom flask equipped with a reflux condenser and a thermometer. The contents were stirred with a magnetic stirring bar, and the temperature was reduced to 0 °C. A solution of 2-ethylacryloyl chloride (8 g, 0.068 mol) in chloroform (20 mL) was added over 15 min. The reaction was strongly exothermic, and the rate of dropping was regulated so that temperature of the mixture did not exceed 30 °C. After the addition was complete, the mixture was heated under reflux for 4 h. After the reaction mixture cooled, 40 mL of ice-cold 6 N sulfuric acid was added with stirring, and the product was extracted with three 150 mL portions of hexane. The combined hexane extracts were washed once with 100 mL of 6 N sulfuric acid, twice with 100 mL of water, twice with 100 mL of 10% potassium carbonate, once with 200 mL of saturated sodium chloride, and twice with 100 mL of an ethanol/water (50/50 v/v) mixture and were finally dried over anhydrous magnesium sulfate. The hexane was evaporated, and the residue was fractionally distilled at reduced pressure (bp 66−68 °C/1 mmHg). The final yield was 11.3 g (90%). ^{1}H NMR ($CDCl_3$): δ 1.1 [t, J = 7.5 Hz, 3H, $-CH_2CH_3$], δ 2.4 [q, J = 7.5 Hz, 2H, $-CH_2CH_3$], δ 5.2 [s, 2H, $-CH_2-C_6H_5$], δ 5.6 and 6.2 [2H, CH_2=] and δ 7.3 [5H, $-C_6H_5$]. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.80; H, 7.39.

Initiator Preparation. An oven-dried 50 mL round-bottom flask with a glass stopcock on the sidearm was equipped with a magnetic stirring bar and capped with a rubber septum. The

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* To whom correspondence should be addressed at the Division of Chemistry and Chemical Engineering, California Institute of Technology, Mail Code 210-41, Pasadena, CA 91125.

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Table 1. Conditions and Results for Polymerization of *t*BEA

no.	solvent[a]	[tBEA] × 10^2, mol	[DPHLi][b] × 10^4, mol	time, h	yield,[c] %	M_n(calc),[d] g/mol	M_n(SEC),[e] g/mol	M_w/M_n[f]
1	THF	1.3	1.5	0.5	2	270	15 200	1.60
2	THF	3.3	5.0	68	10	1 000	27 400	1.78
3	toluene	3.3	5.0	68	5	500	35 900	1.80

[a] Solvent = 10−20 mL; polymerization temperature = −78 °C. [b] DPHLi = diphenylhexyllithium. [c] After precipitation from methanol. [d] Grams of *t*BEA polymerized/moles of DPHLi. [e] Calibration with poly(methyl methacrylate) standards. [f] Calculated from SEC.

Table 2. Conditions and Results for Polymerization of BzEA

no.	solvent[a]	[DPHLi][b] × 10^4, mol	[BzEA] × 10^2, mol	time, h	yield,[c] %	M_n(calc),[d] g/mol	M_n(SEC),[e] g/mol	M_w/M_n[f]
4	THF	6.8	1.1	15	99	2 400	3 100	1.16
5	THF	4.5	3.2	14	98	13 400	16 200	1.11
6	THF	3.0	3.2	14	99	20 200	24 600	1.07

[a] Solvent =10−20 mL; polymerization temperature = −78 °C. [b] DPHLi = diphenylhexyllithium. [c] After precipitation from methanol. [d] Grams of BzEA polymerized/moles of DPHLi. [e] Calibration with poly(methyl methacrylate) standards. [f] Calculated from SEC.

flask was purged three times with purified argon and evacuated each time. Finally, it was filled with argon and closed by the glass stopcock. THF (10 mL) and 1,1-diphenylethylene (0.53 mL, 3.0 mmol) were added to the flask by syringe and stirred for 10 min at room temperature. *n*-Butyllithium (1.5 mL, 3.0 mmol) was then introduced slowly by syringe. The solution turned dark red, indicating formation of 1,1-diphenylhexyllithium. The solution was stirred for 2 h before use in polymerization.

Polymerization. Polymerizations were carried out under argon using Schlenk-type glassware and gastight syringes. THF was first transferred into the glass reactor by syringe. After adding the desired amount of initiator, the solution was cooled to −78 °C, and the required amount of monomer was introduced by syringe. After the desired reaction time (cf. Tables 1 and 2), polymerization was stopped by addition of acidic methanol, and the polymer was recovered by precipitation into methanol or a methanol/water (50/50) mixture and dried under vacuum at 60 °C for 24 h.

Poly(*tert*-butyl 2-ethylacrylate): ^{1}H NMR ($CDCl_3$); δ 0.5−1.0 [$-CH_3$], δ 1.2−2.2 [$-C(CH_3)_3$, and $-CH_2-C(CH_2CH_3)(C{=}O)-$]. Anal. Calcd for $CH_3(CH_2)_3CH_2C(C_6H_5)_2\,[C_9H_{16}O_2]_nH$: C, 69.19; H, 10.32. Found: C, 70.88; H, 10.46. Poly(benzyl 2-ethylacrylate): ^{1}H NMR ($CDCl_3$); δ 0.4−0.9 [$-CH_3$], δ 1.3−2.2 [$-CH_2-C(CH_2CH_3)(C{=}O)-$], δ 4.5−5.1 [$-CH_2-C_6H_5$], δ 7.0−7.5 [$-C_6H_5$]. Anal. Calcd for $CH_3(CH_2)_3CH_2C(C_6H_5)_2$-$[C_{12}H_{14}O_2]_nH$: C, 75.76; H, 7.42. Found: C, 75.45; H, 7.41.

Deprotection of Poly(*tert*-butyl 2-ethylacrylate) (P*t*BEA). P*t*BEA was easily hydrolyzed under mild acidic conditions. P*t*BEA (0.5 g) was dissolved in a mixture of 5 mL of 1,4-dioxane and 1 mL of 10% hydrochloric acid and refluxed for 24 h. After the solvents were partially evaporated on a rotary evaporator, the product was diluted with 1−2 mL of methanol and poured into 100 mL of ether. The precipitated polymer was filtered and dried under vacuum at room temperature. ^{1}H NMR (DMSO-d_6, 25 °C): δ 0.4−0.9 [$-CH_3$], δ 1.4−2.2 [$-CH_2-C(CH_2CH_3)(C{=}O)-$], δ 12.2−12.4 [$-CO_2H$]. Anal. Calcd for $CH_3(CH_2)_3CH_2C(C_6H_5)_2\,[C_5H_8O_2]_nH$: C, 59.98; H, 8.05. Found: C, 58.86; H,8.16.

Deprotection of Poly(benzyl 2-ethylacrylate) (PBzEA). Debenzylation of PBzEA was carried out with trimethylsilyl iodide (TMSI). In a typical procedure, 2.8 g (14 mmol) of TMSI was added to a solution of 1 g (5.26 meq) of PBzEA in 30 mL of chloroform via syringe under argon. The reaction mixture was stirred for 48 h at room temperature and then warmed to 60 °C for 3 h. The dark red reaction mixture was cooled to room temperature, transferred to a separatory funnel, and washed with 50 mL of water several times and then with 50 mL of 5% aqueous sodium bisulfite to remove residual iodide. The polymer (located between the chloroform and water layers) was filtered and washed further with fresh water. The polymer was then treated with 10 mL of 1 N sodium hydroxide for 3 h at 80 °C to cleave the anhydride rings that form upon TMSI treatment; the bands at 1795 and 1750 cm^{-1} in the infrared spectrum of the intermediate polymer disappeared. Finally, the basic solution was slowly poured into dilute aqueous hydrochloric acid to reprecipitate the polymer. ^{1}H NMR (DMSO-d_6, 25 °C): δ 0.4−0.9 [$-CH_3$], δ 1.4−2.2 [$-CH_2-C(CH_2CH_3)(C{=}O)-$], δ 12.2−12.4 [$-CO_2H$]. Anal. Calcd for $CH_3(CH_2)_3CH_2C(C_6H_5)_2\,[C_5H_8O_2]_nH$: C, 59.98; H, 8.05. Found: C, 59.31; H, 8.22.

Measurements. ^{1}H NMR spectra were taken on a Bruker AC-200 instrument operated at 200 MHz. Infrared spectra were taken on a Perkin-Elmer 1600 series FT-IR instrument. Molecular weights and molecular weight distributions were determined by size exclusion chromatography (SEC) at a flow rate of 1 mL/min at 30 °C. For P*t*BEA and PBzEA, THF was used as eluent in a set of two Waters Styragel HR-4E columns which were calibrated with three poly(methyl methacrylate) standard samples. For poly(2-ethylacrylic acid), phosphate buffer solution (0.034 M, pH 8) was used as eluent with a set of two PL aquagel columns (PL aquagel-OH 30 and PL aquagel-OH 40). Calibration was done with three poly(ethylene oxide) (PEO) standard samples.

Results and Discussion

Our first attempts to prepare PEAA via anionic methods used *tert*-butyl 2-ethylacrylate (*t*BEA) because of the known susceptibility of the *tert*-butyl ester group toward facile hydrolysis. Hydrolysis of the *tert*-butyl ester has been widely used to prepare block copolymers containing blocks of methacrylic acid or alkali metal methacrylates from the corresponding methacrylate block copolymers.[11,12] Our results with *t*BEA are shown in Table 1.

Polymerizations were carried out at −78 °C in THF with diphenylhexyllithium (DPHLi) as initiator. Although addition of monomer to the initiator solution caused an immediate color change indicating generation of ester enolate anions, the rate of propagation was sufficiently slow that polymerization was incomplete even after several days (runs 2 and 3). Molecular weights obtained from size exclusion chromatography were different from those expected from the monomer: initiator ratio, and molecular weight distributions were broad ($M_w/M_n = 1.60-1.80$), indicating undesirable side reactions. This behavior was unexpected because *tert*-butyl methacrylate (*t*BMA) polymerized completely (>99%) under the same polymerization conditions (solvent = THF, [*t*BMA] = 1.3×10^{-2} mol, [DPHLi] = 1.5×10^{-4} mol, time = 0.5 h). It appears that approach of monomer to the propagating chain end is substantially hindered for *t*BEA. Although hydrolysis of the resulting poly(*tert*-butyl 2-ethylacrylate) efficiently produced (PEAA) (see Experimental Section), we did not explore this conversion thoroughly because of the ill-defined structure of the precursor polymer.

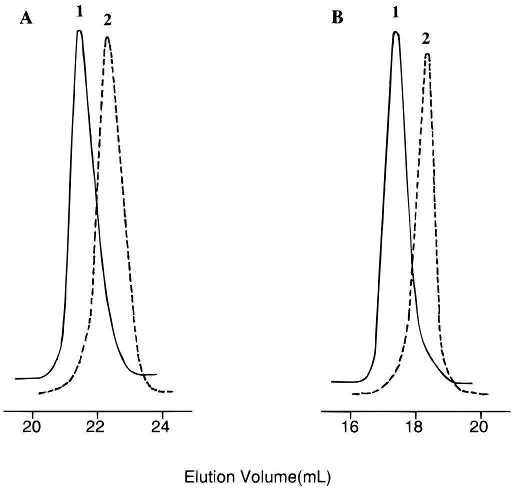

Figure 1. SEC-RI traces of (A) (1) PBzEA: $M_n = 24\ 600$, $M_w/M_n = 1.07$; (2) PMMA standard: $M_n = 15\ 300$, $M_w/M_n = 1.03$. (B) (1) PEAA: $M_n = 14\ 700$, $M_w/M_n = 1.16$; (2) PEO standard: $M_n = 5\ 900$, $M_w/M_n = 1.03$.

Benzyl 2-ethylacrylate (BzEA) proved to be a better choice of monomer. Table 2 summarizes results for BzEA. Although propagation was still slow (<10% yield in 0.5 h) polymerization was complete (>98%) in 15 h, and the observed molecular weights were comparable to those calculated from the initiator and monomer concentrations used. Because PBzEA standards are not available for SEC calibration, we do not know whether the small differences in the calculated and observed molecular weights listed in Table 2 are significant. Figure 1A shows a typical SEC chromatogram of a PBzEA sample (run 6 in Table 2) with a number-average molecular weight of 24 600 (SEC) and polydispersity 1.07.

PBzEA is readily converted to PEAA by treatment with trimethylsilyl iodide (TMSI). TMSI is known to cleave alkyl esters under ambient conditions to yield the corresponding acids,[13,14] and poly (*tert*-butyl methacrylate) has been converted to poly(methacrylic acid) at room temperature in 4 h by treatment with TMSI.[12] In our experiments with PBzEA, however, complete debenzylation took much longer; a minimum of 48 h was required for complete conversion at room temperature. Although reaction was fast at higher temperature (100% debenzylation at 80 °C in 12 h), we were concerned about chain degradation at elevated temperature.[15] The degree of debenzylation was calculated from the ^{1}H NMR spectrum. The benzylic and aromatic proton signals ((c) and (d) in Figure 2A) disappeared upon treatment with TMSI, and a new resonance from the carboxylic acid proton appeared at δ 5.3 ppm (in DMSO-d_6 at 100 °C; at room temperature this peak shifted to δ 12.2−12.4). Debenzylation was also confirmed by infrared spectroscopy (Figure 3); the ester carbonyl stretching band at 1724 cm^{-1} in PBzEA (Figure 3A) broadened and shifted to 1708 cm^{-1} upon conversion to PEAA (Figure 3B). A broad O−H stretching band also appears at higher frequency in the spectrum of the acid form of the polymer.

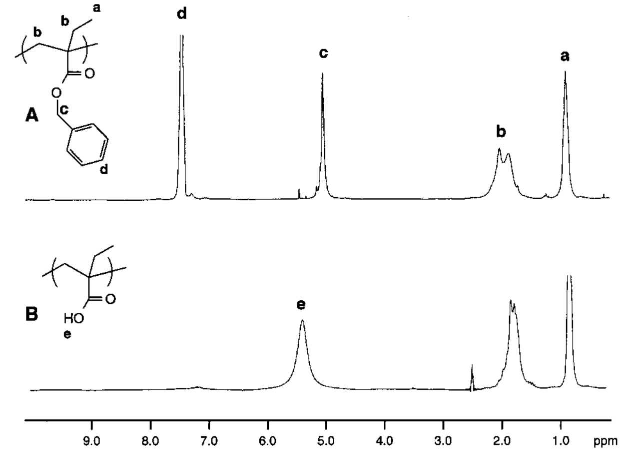

Figure 2. ^{1}H NMR spectra of (A) PBzEA (run 6 in Table 2) in CDCl$_3$ at 25 °C and (B) PEAA (run 9 in Table 3) in DMSO-d_6 at 100 °C. The signal at 2.5 ppm is due to the solvent.

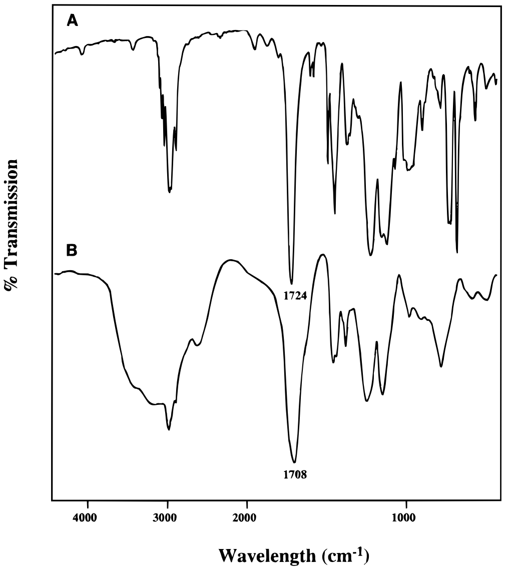

Figure 3. IR spectra of (A) PBzEA (run 6 in Table 2) and (B) PEAA (run 9 in Table 3); 10% KBr pellet.

Table 3. Debenzylation of PBzEA

no.	PBzEA precursor	M_n-(calc),[a] g/mol	M_n-(NMR),[b] g/mol	M_n-(SEC),[c] g/mol	M_w/M_n[d]	deg (%) of debenzylation[e]
7	4	1800	1900	2300	1.19	99
8	5	7300	6500	8300	1.15	100
9	6	10800	12100	14700	1.16	100

[a] [M_n(calc)] in Table 2 × 0.53. [b] Obtained from ratio of the integration area of the phenyl protons in initiator to that of methyl protons in α-ethyl group in ^{1}H NMR spectra. [c] Calibration with poly(ethylene oxide) standard samples. [d] Calculated from SEC. [e] Calculated from ^{1}H NMR spectra.

Table 3 summarizes the debenzylation results. The calculated molecular weights of the PEAA samples were obtained from the molecular weights of their precursors (Table 2) and were close to those obtained from ^{1}H NMR spectra. Molecular weights calculated from SEC were somewhat higher, probably owing to the use of poly(ethylene oxide) (PEO) standard samples for calibration. Polydispersities calculated from SEC were <1.20, indicating no significant chain degradation during the debenzylation step. Figure 1B shows a typical SEC trace of a PEAA sample obtained by treatment of PBzEA with TMSI (run 9 in Table 3).

In summary, well-defined PEAAs of various molecular weights were prepared by a two-step reaction sequence. Anionic polymerization of BzEA provided quantitative yields of PBzEAs of predetermined molecular weights and narrow molecular weight distributions. In the second step, TMSI efficiently removed the side-chain benzyl groups to produce PEAA without significant chain degradation. Similar methods should be useful for the preparation of well-defined polymers of other 2-substituted acrylic acids.

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