# Facile Synthesis of Zwitterionic Diblock Copolymers without Protecting Group Chemistry

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ABSTRACT: A versatile new route to zwitterionic diblock copolymers that avoids protecting group chemistry is reported. Various tertiary amine methacrylates are block copolymerized with 2-hydroxyethyl methacrylate to produce hydroxy-functional diblock precursors via sequential monomer addition. These low-polydispersity precursors are then treated with succinic anhydride under mild conditions to produce a range of new near-monodisperse zwitterionic diblock copolymers in which both blocks are weak polyelectrolytes. Thus, the final copolymers exhibit complex aqueous solution behavior (isoelectric points, schizophrenic micellization behavior, etc.) depending on the solution pH.

## Introduction

Zwitterionic diblock copolymers are a fascinating class of materials: spatial separation of the ionic charge on the copolymer backbone leads to complex aqueous solution behavior.[1] Potential applications include use as "ubiquitous" pigment dispersants[2] and also for protein isolation and purification.[3] Indeed, zwitterionic diblock copolymers may be considered as simple synthetic analogues of proteins, since precipitation from aqueous solution occurs when the overall charge of the anionic block balances that of the cationic block (at the isoelectric point, or IEP).

A number of synthetic routes to zwitterionic diblock copolymers have been explored over the past three decades. For example, in 1979, Varoqui et al. reported the synthesis of poly(2-vinylpyridine)-*block*-poly(sodium 4-styrenesulfonate) via selective sulfonation of poly(2-vinylpyridine)-*block*-polystyrene precursors.[4] More typically, protecting group chemistry has been employed to produce the anionic block, with *tert*-butyl methacrylate (or other protected esters, such as 2-tetrahydropyranyl methacrylate) being block copolymerized with tertiary amine-based monomers or 4-vinylpyridine, followed by acid hydrolysis.[5−11] This approach is usually based on either classical anionic polymerization[5−9] or so-called group transfer polymerization[10,11] and is not atom efficient.

The first report of the synthesis of zwitterionic diblock copolymers via living radical polymerization was by Gabaston et al., who block copolymerized sodium 4-styrenesulfonate with 4-(dimethylamino)methylstyrene using nitroxide-mediated polymerization.[12] However, the second-stage polymerization was substantially incomplete. In principle, reversible addition−fragmentation chain transfer (RAFT) polymerization[13] can be used to prepare zwitterionic diblock copolymers directly in aqueous media. In practice, the RAFT agent-capped chain ends are prone to hydrolysis,[14] and unwanted precipitation may occur at intermediate pH if the IEP is reached at any stage during the copolymerization. Recently we reported the synthesis of two new classes of zwitterionic diblock copolymers[15,16] using atom transfer radical polymerization (ATRP).[17,18] However, protecting group chemistry was again required, overall copolymer yields were poor, and the anionic block was based on an expensive specialty monomer, 4-vinylbenzoic acid. Herein we report a facile new route to well-defined zwitterionic diblock copolymers that does not require protecting group chemistry.

## Experimental Section

**Materials.** 2-(Dimethylamino)ethyl methacrylate (DMA) and 2-(diethylamino)ethyl methacrylate (DEA) were purchased from Aldrich, 2-(diisopropylamino)ethyl methacrylate (DPA) was obtained from Scientific Polymer Products, and 2-*N*-(morpholino)ethyl methacrylate (MEMA) was purchased from Polysciences. Each of these monomers was passed through a basic alumina column to remove inhibitor and stored in a refrigerator before use. All other reagents were used as received. HEMA was kindly donated by Cognis Performance Chemicals (Hythe, UK). Silica gel 60 (0.063−0.200 mm) was purchased from Merck (Darmstadt, Germany). 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) of 4-(2-hydroxyethyl)morpholine (10.00 g, 75.5 mmol) and triethylamine (8.49 g, 83.1 mmol, 1.1 equiv) under nitrogen in 50 mL of dichloromethane, and this mixture was stirred overnight. At the end of the reaction, the reaction mixture was poured into water (200 mL). The organic layer was separated and washed three times with an aqueous solution of 0.1 M $Na_2CO_3$ until all the ammonium 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 red-brown liquid (10.34 g, yield 77%) and was stored in a freezer in the absence of light prior to use. $^1$H NMR ($CDCl_3$ (residual peak $\delta = 7.27$) 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 $DEA_{30}$−$HEMA_{30}$ Diblock Copolymer (Entry 1 in Table 1).** In a 100 mL round-bottomed flask, 1,1,4,7,10,10-hexamethyltriethylenetetramine (HMTETA) (254 mg, 1.07 mmol) and DEA (6.00 g, 32.06 mmol; target $DP_n = 30$) were mixed and degassed by nitrogen bubbling for 30 min. The Cu(I)Cl catalyst (108 mg, 1.07 mmol) was then quickly added under nitrogen. The ME-Br initiator (302 mg, 1.07 mmol) was introduced with a syringe, and the flask was immersed in a 50 °C oil bath. Aliquots were taken regularly for NMR and

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**Table 1. Synthesis Parameters, Molecular Weight Data, and Isoelectric Points for Six Zwitterionic Diblock Copolymers Prepared via ATRP**

| entry no. | target composition ($DP_n$ subscripts) | 1st block conv[a] (%) | 2nd block conv (%) | $M_{n,GPC}$[b] | $M_w/M_n$[b] | HEMA content of diblock (mol %) |  | degree of esterification[c] (%) | zwitterionic iblock |  |
|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  |  |  | (theory) | (expt) |  | IEP (theory) | IEP (expt) |
| 1 | $DEA_{30}-HEMA_{30}$ | 85 | 100 | 12 000 | 1.26 | 50 | 50 | 100 | 6.4 | 6.2 |
| 2 | $DEA_{30}-HEMA_{50}$ | 90 | 100 | 15 300 | 1.34 | 62 | 61 | 100 | 5.7 | 5.3 |
| 3 | $DEA_{30}-HEMA_{20}$ | 86 | 100 | 7 400 | 1.26 | 40 | 38 | 100 | 7.0 | 6.7 |
| 4 | $DEA_{30}-HEMA_{30}$ | 80 | 100 | 13 300 | 1.27 | 50 | 50 | 100 | 6.3 | 6.1 |
| 5 | $DPA_{30}-HEMA_{30}$ | 82 | 100 | 10 800 | 1.30 | 50 | 49 | 100 | 5.9 | 5.9 |
| 6 | $MEMA_{30}-HEMA_{30}$ | 95 | 98 | 12 800 | 1.26 | 50 | 50 | 100 | 5.2 | 5.1 |

[a] Conversion of the first block before addition of the second block. Actual $DP_n$ = conversion × target $DP_n$. [b] Determined by DMF GPC, calibrated with poly(methyl methacrylate) standards. [c] Degrees of esterification achieved using succinic anhydride as judged by $^1$H NMR to within ±2 mol %.

GPC analyses to assess the extent of polymerization. After 30 min, the reaction mixture became very viscous, and degassed methanol (4.2 mL) was added to dilute the viscous solution. Then HEMA (4.21 g, 32.01 mmol; target $DP_n = 30$), previously degassed by nitrogen bubbling for 30 min, was added to the reaction medium via a double-tipped needle. The polymerization was quenched by exposing the reaction vessel to air and adding methanol (50 mL). The catalyst was removed by passing this solution through a silica column, and methanol was evaporated under vacuum to provide an off-white solid. The same protocol was used for copolymerizations with the other tertiary amine methacrylates (DMA, DPA, MEMA), or for other target block compositions.

**Esterification of a $DEA_{30}-HEMA_{30}$ Diblock Copolymer.** In a 100 mL round-bottomed flask $DEA_{30}-HEMA_{30}$ (5.00 g, 15.2 mmol OH residues) was dissolved in anhydrous pyridine (30 mL) at room temperature under nitrogen. Under nitrogen flow, succinic anhydride (3.04 g, 30.4 mmol) was added, and the reaction was allowed to proceed at room temperature for 48 h. The reaction mixture was precipitated into 400 mL of methanol to remove the excess succinic anhydride. During precipitation some of the succinic anhydride was converted into monomethyl succinate, which was not removed (as judged by $^1$H NMR). Thus, the precipitate was redissolved in 10 mL of pyridine and precipitated into 400 mL of diethyl ether, which is a better solvent for the monomethyl succinate side product (n.b. using diethyl ether for the first precipitation was not successful). After removal of the solvents, deionized water (50 mL) was added, followed by small portions of $Na_2CO_3$ solution (with evolution of $CO_2$) until the precipitate was solubilized (pH ∼ 9). The solution was concentrated under vacuum until no pyridine was detectable by $^1$H NMR. Finally the solution was freeze-dried to yield a white powder. The same protocol was used for the other diblock precursors.

**Polymer Characterization. a. Gel Permeation Chromatography (DMF Eluent).** Molecular weights and molecular weight distributions of the diblock copolymer precursors were assessed using a GPC setup comprising three Polymer Laboratories PL gel 5 μm mixed "B" columns. Calibration was carried out using a series of near-monodisperse poly(methyl methacrylate) standards. The GPC eluent was HPLC grade DMF with 0.01 M LiBr, at a flow rate of 1.0 mL $min^{-1}$. The column temperature was set at 70 °C.

**b. Aqueous Electrophoresis.** Electrophoresis measurements were carried out using a Malvern ZetaMasterS instrument. Zeta potentials were calculated from mobilities using the Henry equation and determined as a function of solution pH, which was adjusted using HCl and NaOH.

**c. Dynamic Light Scattering.** DLS studies were performed at 20 °C using 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 solution pH being adjusted by adding HCl or NaOH where appropriate. The solutions were stirred for 2−3 h and then left unstirred overnight. They were then ultrafiltered through a 0.20 μm nylon filter (Phenomenex) before being analyzed.

**d. Nuclear Magnetic Resonance Spectroscopy.** All $^1$H NMR spectra were recorded in either $D_2O$, $CD_3OD$, or $CDCl_3$ using a Bruker Avance PDX 300 MHz spectrometer. Zwitterionic diblock copolymers were studied as 5.0% w/v copolymer solutions in $D_2O$; the solution pH was varied as required using DCl or NaOD.

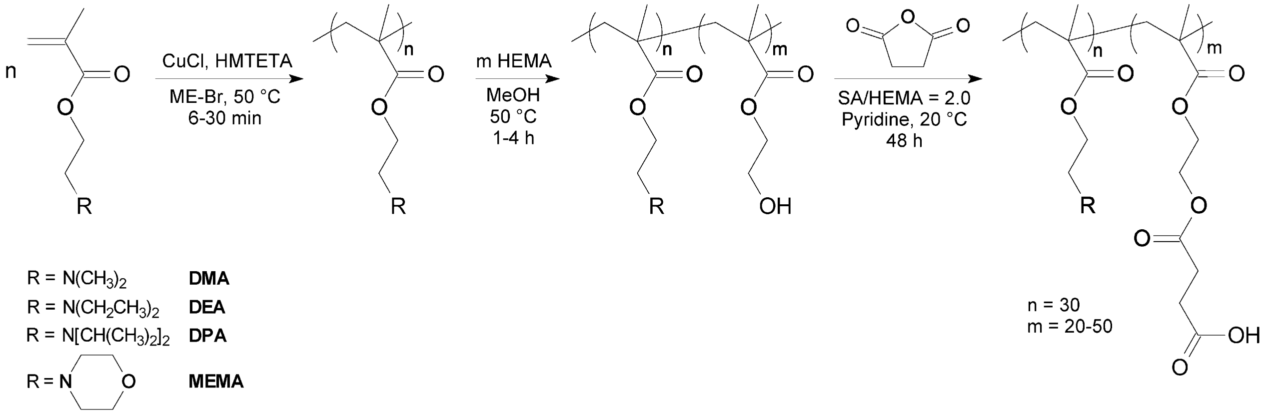
**e. Acid Titrations.** The IEP values for the zwitterionic copolymers were determined by titrating a 1.0% w/v copolymer solution at pH 11 using 0.1 M HCl solution. Solution pH was monitored using a HANNA pH sensor. Calibration was carried out using pH 4, 7, and 10 buffers. The $pK_a$ value of SEMA homopolymer was determined according to the same protocol using a 2.5% w/v homopolymer solution.

## Results and Discussion

The homopolymerization of DMA via ATRP at ambient temperature has been investigated in both organic solvents[19,20] and water.[21] However, ATRP of DMA in the bulk at elevated temperature has been shown to be controlled by several research groups using a wide range of initiators and linear tertiary amine ligands.[20,22,23] For example, DMA was successfully polymerized using a 2-vinyloxyethyl 2-bromoisobutyrate initiator and a CuBr/HMTETA catalyst at 60 °C.[23] At 80% conversion, the DMA homopolymer had a polydispersity of ca. 1.15. Using the same catalytic system but an allyl 2-bromoisobutyrate initiator, DMA was polymerized at 60 °C to high conversion (97%) with satisfactory control ($M_w/M_n = 1.27$).[20] Our protocol was similar to these conditions in that a 2-bromoisobutyrate-based initiator (ME-Br) was used with CuCl in conjunction with HMTETA for the first-stage polymerization (see Scheme 1). A convenient one-pot synthesis of the diblock precursor was achieved by bulk polymerization of the appropriate tertiary amine methacrylate [2-(dimethylamino)ethyl methacrylate (DMA), 2-(diethylamino)ethyl methacrylate (DEA), 2-(diisopropylamino)ethyl methacrylate (DPA), or 2-*N*-(morpholino)ethyl methacrylate (MEMA)] at 50 °C, followed by efficient chain extension with 2-hydroxyethyl methacrylate (HEMA) in methanol.[24] GPC studies confirmed little or no homopolymer contamination (see Figure 1). The purified diblock precursor was then derivatized[25] using succinic anhydride in pyridine at ambient temperature.[26] This two-step route is atom-efficient, leads to high monomer conversions (up to 95% for the first block, at least 98% for the second block) and fairly low polydispersities ($M_w/M_n = 1.26-1.34$), and allows access to a wide range of interesting new zwitterionic copolymers in which both blocks behave as weak polyelectrolytes, depending on the solution pH (Table 1).

$^1$H NMR studies allowed the block compositions of the copolymer precursors and the degrees of esterification

**Scheme 1. Synthesis of Zwitterionic Diblock Copolymers via Hydroxy-Functional Diblock Precursors**



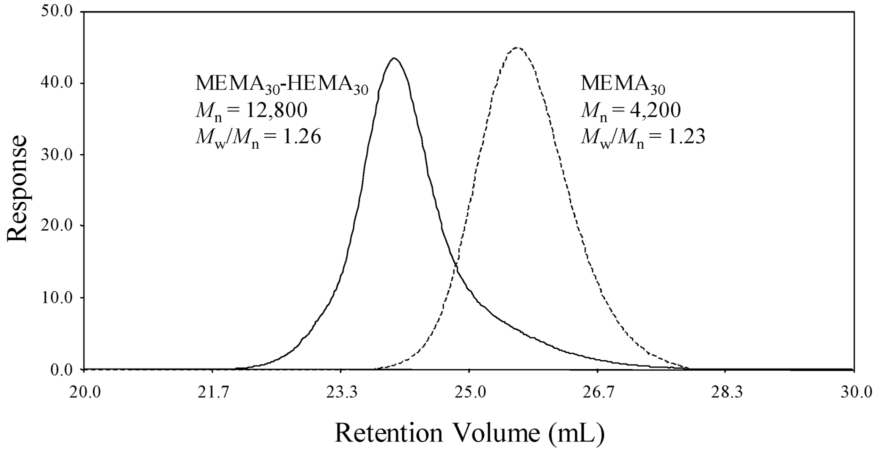


**Figure 1.** GPC traces for $MEMA_{30}$ homopolymer (dashed line) and $MEMA_{30}$-*b*-$HEMA_{30}$ block copolymer (plain line) (see entry 6 in Table 1).

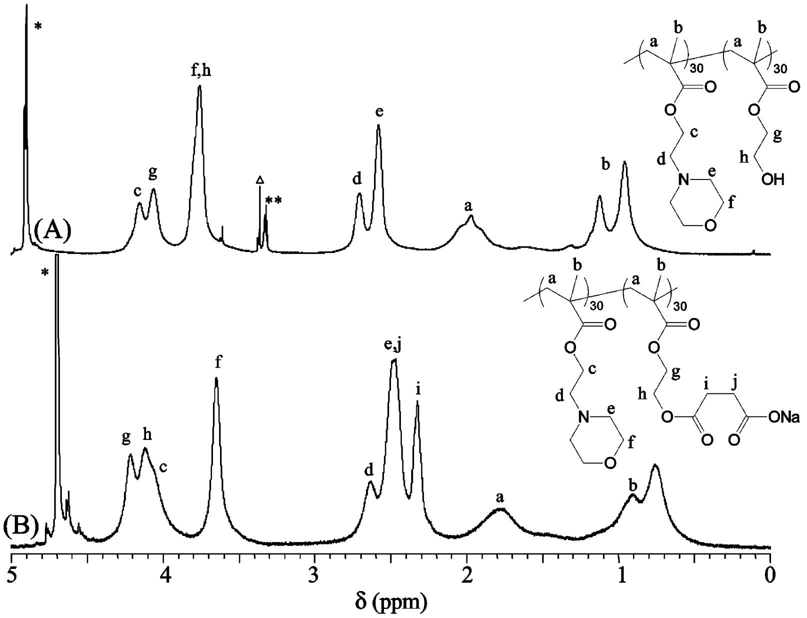


**Figure 2.** $^1H$ NMR spectra of (A) the $MEMA_{30}$-*b*-$HEMA_{30}$ diblock precursor in $CD_3OD$; * and ** indicate residual NMR solvent, and △ indicates residual methanol from the ATRP synthesis. (B) $MEMA_{30}$-*b*-$SEMA_{30}$ zwitterionic diblock copolymer in $D_2O$ (pH 8); * indicates residual water (entry 6 in Table 1).

of the hydroxylated blocks to be calculated (Figure 2). The degrees of esterification were very high in all cases. Moreover, since this reaction was carried out under mild conditions, the narrow molecular weight distributions of the diblock precursors should be retained in the final zwitterionic diblock copolymers.[26] $^1H$ NMR studies also allowed the pH-induced reversible self-assembly of the final zwitterionic diblock copolymers in aqueous solution to be monitored (Figure 3). The $DEA_{30}$-*b*-$SEMA_{30}$ diblock copolymer (SEMA is the succinate half-ester residues

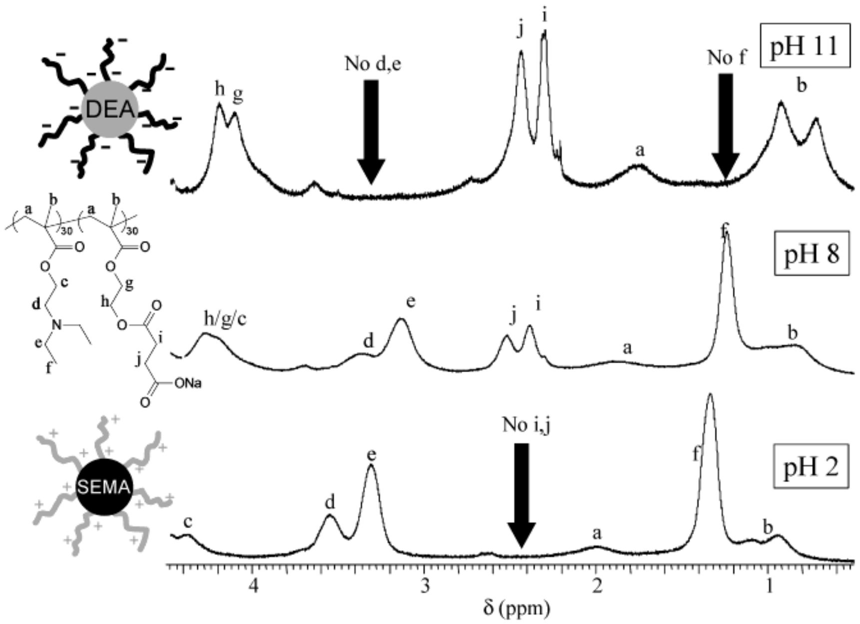


**Figure 3.** $^1H$ NMR spectra ($D_2O$, 20 °C) for the $DEA_{30}$-*b*-$SEMA_{30}$ zwitterionic diblock copolymer recorded at various pH using DCl and NaOD where appropriate.

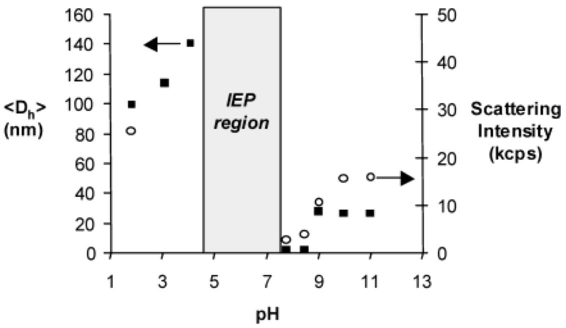


**Figure 4.** Variation of intensity-average hydrodynamic diameter $\langle D_h \rangle$ (■) and scattering intensity (○) as a function of pH for a 0.50% w/v aqueous solution of the $DEA_{30}$-*b*-$SEMA_{30}$ zwitterionic diblock copolymer at 20 °C. Scattering intensities of around 480 and 1400 were observed at pH 3 and 4, respectively.

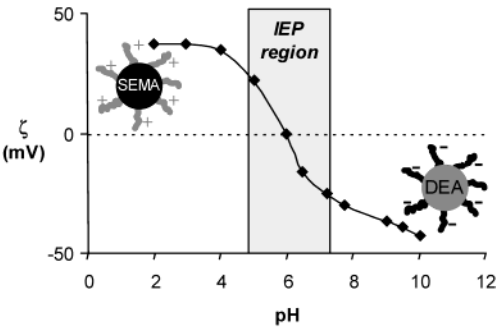


**Figure 5.** Variation of ζ potential with pH for a 0.50% w/v aqueous solution of the $DEA_{30}$-*b*-$SEMA_{30}$ zwitterionic diblock copolymer.

obtained from the reaction of succinic anhydride with the HEMA residues) was molecularly dissolved in water at pH 8, since signals due to both blocks are visible (see middle spectrum in Figure 3) and dynamic light scattering (DLS) studies indicated very low scattered light intensities (Figure 4). Adjusting the solution pH to pH 11 with NaOD led to the disappearance of the PDEA signals at $\delta$ 3.0−3.5 (upper spectrum in Figure 3), and DLS studies indicated the formation of micelles of 26 nm diameter (polydispersity = 0.16) with hydrophobic PDEA cores and anionic PSEMA coronas. This value is in good agreement with that reported by Liu and Armes,[16] who observed the formation of compact PDEA-core micelles with a mean diameter of 35 nm (polydispersity = 0.1−0.2) for a poly(sodium 4-vinylbenzoate)-*block*-PDEA zwitterionic diblock copolymer at pH 10. On the other hand, addition of DCl to the $DEA_{30}$-*b*-$SEMA_{30}$ copolymer micelles led to the disappearance of the PSEMA signals at $\delta$ 2.2−2.6 (lower spectrum in Figure 3), and DLS studies indicated the formation of aggregates of around 100 nm diameter (polydispersity = 0.22). This size is too large to represent simple core−shell micelles: it is possible that compound micelles are formed under these conditions.[27] It is likely that these latter DLS observations are related to the imperfect block architectures created by our sequential monomer addition approach. For example, the DEA block is a pure block (containing no SEMA residues) and hence forms well-defined micelles of 26 nm at high pH. On the other hand, the SEMA block contains a few randomly distributed DEA residues since the first-stage bulk polymerization of the DEA is incomplete. This is consistent with the formation of larger structures at low pH because the DEA “impurities” in the SEMA blocks will be protonated in acidic solution, and this cationic charge will tend to hinder the formation of compact hydrophobic micelle cores. This is in agreement with the observation of 100 nm aggregates by DLS at low pH.

The downfield shift in the PDEA signals at pH 2 confirms that this block becomes protonated in acidic solution, so these aggregates should have cationic coronas. This hypothesis is supported by aqueous electrophoresis data (see Figure 5). Zeta potentials of around +40 mV were obtained at low pH for micelles prepared from this $DEA_{30}$-*b*-$SEMA_{30}$ zwitterionic diblock copolymer. Addition of NaOH resulted in lower zeta potentials, and at around pH 6 the net charge on the particles was close to zero. This IEP is in relatively good agreement with the midpoint of the precipitation region (approximately pH 6.2) estimated from acid titration (see entry 1 in Table 1). At pH 10, zeta potentials of around −40 mV were observed, supporting the hypothesis of PDEA-core micelles with anionic PSEMA coronas. Surface tensiometry vs pH studies are consistent with the observation of micelles/aggregates in bulk solution (see Figure 1S in Supporting Information). At around the IEP the surface tension has its maximum value (62 mN $m^{-1}$), with lower surface tension values being obtained at both higher and lower pH. Moreover, surface tension values are lower in alkaline solution than in acid, which is consistent with the formation of well-defined micelles and larger colloidal aggregates, respectively, under these conditions.

The IEP's determined from the acid titration studies compared well with the theoretical IEP's calculated from the $pK_a$'s of the respective homopolymers and the known block compositions, using the equation reported by Patrickios et al.[10] Moreover, a range of IEP's may be obtained by adjusting either the relative block compositions and/or the respective $pK_a$'s of the two blocks. For example, if the cationic block length is held constant, the IEP increases with increasing anionic block length, as expected (see entries 1−3 in Table 1). The nature of the cationic block also affects the IEP. Acid titration studies by Bütün gave $pK_a$ values of 4.9, 6.3, 7.0, and 7.3 for MEMA, DPA, DMA, and DEA homopolymers, respectively.[28] Thus, if the overall diblock copolymer composition is held constant, the IEP increases with increasing basicity of the tertiary amine methacrylate block (compare entry 1 with entries 4−6 in Table 1). Our acid titration studies indicate that SEMA homopolymer has a $pK_a$ of around 5.5 (see Figure 2S in Supporting Information). In principle, using other acid anhydrides should allow the $pK_a$ of the acidic block to be adjusted.[26] Thus, the aqueous solution properties of these zwitterionic diblock copolymers are certainly complex, but they are both tunable and predictable. Finally, our preliminary studies indicate that the succinate half-ester linkage in the PSEMA block is susceptible to hydrolysis at or above pH 12 but has reasonably good long-term stability at pH 2.

## Conclusions

In summary, we report a new, convenient, and versatile route to zwitterionic diblock copolymers that does not require protecting group chemistry. This approach is atom-efficient and leads to low-polydispersity copolymers in high yields. Moreover, since both blocks are weak polyelectrolytes, "schizophrenic" behavior is observed: two types of colloidal aggregates are formed in aqueous solution on adjusting the solution pH.

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**Supporting Information Available:** Surface tension vs pH data at 20 °C for a $DEA_{30}-SEMA_{30}$ diblock copolymer and a representative titration curve for a 2.5% w/v aqueous solution of SEMA homopolymer. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) In unpublished work we have used aqueous GPC to establish that HEMA homopolymers derivatized with succinic anhydride have comparable polydispersities ($M_w/M_n = 1.2-1.3$) to those of the HEMA homopolymer precursors. Although we confine our discussion to HEMA in this paper, we have also shown that 2-hydroxypropyl methacrylate (HPMA) and glycerol monomethacrylate (GMA) homopolymers can be esterified efficiently using either succinic anhydride or 1,2-cyclohexanedicarboxylic anhydride (CDA) under mild conditions. The $pK_a$ of CDA-esterified HEMA homopolymer is 6.3.
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