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Articles

Synthesis of Zwitterionic Diblock Copolymers without Protecting Group Chemistry

Cong-Duan Vo* and Steven P. Armes*

Dainton Building, Department of Chemistry, The University of Sheffield, Sheffield, S3 7HF, United Kingdom

David P. Randall

School of Life Sciences, The University of Sussex, Brighton BN1 9QG, United Kingdom

Kenichi Sakai and Simon Biggs

Institute of Particle Science and Engineering (IPSE), University of Leeds, Leeds LS2 9JT, United Kingdom

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ABSTRACT: A two-step route was used to prepare a range of zwitterionic diblock copolymers in which both blocks are weak polyelectrolytes. In the first step, low polydispersity diblock copolymers of 2-hydroxypropyl methacrylate (HPMA) with either 2-(diethylamino)ethyl methacrylate (DEA) or 2-(diisopropylamino)ethyl methacrylate (DPA) were prepared by atom transfer radical polymerization in protic media under mild conditions in a convenient one-pot synthesis. Block copolymers with varying compositions were prepared by adjusting the comonomer/initiator molar ratio. In the second step, the hydroxyl groups of the diblock copolymers were esterified with excess succinic anhydride (SA) to produce the corresponding zwitterionic diblock copolymers, which exhibit complex pH-dependent behavior (isoelectric points and "schizophrenic"-type micellization) in aqueous solution. The electrostatic adsorption of "cationic corona" micelles onto near-monodisperse anionic silica particles was successful at pH 3.5, as evidenced by aqueous electrophoresis, FT-IR studies, thermogravimetric analysis, and scanning electron microscopy. The same "cationic corona" micelles were also adsorbed onto planar mica at pH 3.5. More surprisingly, inverted "anionic corona" micelles prepared from the same diblock copolymer could be adsorbed onto mica at pH 10. Presumably, this latter adsorption arises from relatively weak hydrophobic interactions due to the micelle cores, rather than strong electrostatic interactions due to the micelle corona. Both types of adsorbed micelles could be imaged by in situ atomic force microscopy.

Introduction

It is well-known that the spatial separation of charge in zwitterionic diblock copolymers gives rise to interesting aqueous solution properties such as isoelectric point (IEP) behavior[1] and micellization behavior.[2] Potential applications of such diblock copolymers include their use as "ubiquitous" pigment dispersants[3] and also in protein isolation/purification procedures.[4] The adsorption of zwitterionic diblock copolymer micelles onto either flat or spherical surfaces from aqueous solution has allowed the facile production of ultrathin stimuli-responsive films that can be potentially used as sensors or in controlled release applications.[5,6]

A number of synthetic routes have been explored over the past three decades. Typically classical anionic living polymerization[7−9] and group transfer radical polymerization[10,11] have been employed to produce zwitterionic diblock copolymers. These methods require protecting group chemistry and are therefore intrinsically atom-inefficient. Typically, protected esters such as *tert*-butyl methacrylate, 2-tetrahydropyranyl methacrylate, or benzyl methacrylate are block copolymerized with 2-vinylpyridine, 4-vinylpyridine, or tertiary amine methacrylates, followed by acid hydrolysis to produce the anionic blocks.[7−9] For example, Kamachi et al.[7] block copolymerized 2-vinylpyridine with either trimethylsilyl methacrylate or *tert*-butyl acrylate. The zwitterionic diblock copolymers were subsequently obtained via hydrolysis of the ester groups. On the other hand, Varoqui et al.[12] synthesized poly(2-vinylpyridine)-*block*-poly(sodium 4-styrenesulfonate) via selective sulfonation of a poly(2-vinylpyridine)-*block*-polystyrene precursor. Various tertiary amine methacrylate-based zwitterionic diblock copolymers have also been prepared using group transfer polymerization (GTP).[11] In this case ester deprotection must be achieved under mild conditions to avoid unwanted hydrolysis of the tertiary amine groups that constitute the cationic block. In this context, it is worth noting that incomplete hydrolysis of *tert*-butyl groups can affect the aqueous solution properties of polyacids.[13a]

The recent development of living radical polymerization provides further opportunities for the synthesis of zwitterionic diblock copolymers. Using nitroxide-mediated radical polym-

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* To whom correspondence should be addressed. E-mail: S.P.Armes@sheffield.ac.uk or C.Vo@sheffield.ac.uk.

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Table 1. Synthesis Parameters and Molecular Weight Data of Hydroxylated Diblock Copolymers Prepared via Atom Transfer Radical Polymerization[a]

		first block					second block			
entry no.	target composition (Dp)	reaction conditions	conv (%)	Dp	M_n (g mol^{-1})	M_w/M_n	reaction conditions	Dp	M_n (g mol^{-1})	M_w/M_n
1	$PHPMA_{50}-PDEA_{25}$	methanol, 9 h	98	49	8400	1.22	methanol, 15 h	15	10 500	1.24
2	$PHPMA_{50}-PDEA_{30}$	methanol, 9 h	100	49	8500	1.19	methanol, 15.5 h	26	11 900	1.21
3	$PHPMA_{50}-PDEA_{50}$	methanol, 9 h	100	50	8450	1.20	methanol, 24 h	42	13 800	1.21
4	$PHPMA_{50}-PDEA_{80}$	methanol, 9 h	100	50	8500	1.20	methanol, 36 h	72	17 700	1.32
5	$PHPMA_{50}-PDPA_{30}$	IPA/H_2O, 2.5 h	98	49	8400	1.23	IPA/H_2O, 10.5 h	29	13 000	1.23
6	$PHPMA_{50}-PDPA_{50}$	IPA/H_2O, 2.5 h	99	50	8500	1.23	IPA/H_2O, 23 h	47	15 800	1.23
7	$PHPMA_{50}-PDPA_{70}$	IPA/H_2O, 2.5 h	98	49	8400	1.29	IPA/H_2O, 49 h	65	20 800	1.22
8	$PHPMA_{50}-PDPA_{30}$	IPA/H_2O, 4.0 h	100	50	8300	1.24	IPA/H_2O, 15.5 h	30	13 800	1.22
9	$PHPMA_{50}-PDPA_{70}$	IPA/H_2O, 4.0 h	100	50	8500	1.26	IPA/H_2O, 49 h	70	21 300	1.24

[a] All reactions were carried out at 20 °C. ME-Br initiator was used for entries 1−7, whereas the ethyl 2-bromoisobutyrate initiator was used for entries 8 and 9.

erization, Gabaston et al.[14] block copolymerized sodium 4-styrenesulfonate with 4-(dimethylamino)methylstyrene. However, the second stage polymerization was substantially incomplete. In principle, reversible addition−fragmentation chain transfer (RAFT) polymerization should be a versatile technique for the synthesis of zwitterionic diblock copolymers in aqueous media without recourse to protecting group chemistry.[13] However, either hydrolysis of the RAFT agent-capped chain end or unwanted precipitation of the block copolymer at some intermediate pH (due to the isoelectric point effect) remains a potential problem. Atom transfer radical polymerization[15] (ATRP) can also be used to prepare zwitterionic diblock copolymers, but unfortunately protecting group chemistry is still required because the ATRP catalyst can complex with acidic monomers such as (meth)acrylic acid. Thus, the *direct* synthesis of zwitterionic diblock copolymers can be quite problematic even by living radical polymerization.

Bories-Azeau and co-workers recently reported a facile method to prepare zwitterionic diblock copolymers that did not require protecting chemistry.[16] A series of poly(2-(diethylamino)ethyl methacrylate)-*block*-poly(2-hydroxyethyl methacrylate) ($PDEA_{30}$-*b*-$PHEMA_n$, where *n* denotes the mean degree of polymerization (Dp) and is equal to 20, 30, or 50) were synthesized via “one-pot” ATRP using sequential monomer addition. Complete esterification of these hydroxylated diblock copolymer precursors with excess succinic anhydride in pyridine led to the final zwitterionic diblock copolymers.[16] However, because of incomplete monomer conversion (typically 80−95%) obtained during the first-stage bulk polymerization of DEA, the subsequent block was strictly a statistical copolymer, rather than purely comprising the second monomer. Obviously, 5−20% of DEA comonomer in the second block is undesirable and is likely to affect the aqueous solution properties of the zwitterionic copolymers.

In the present work we describe the optimization of our ATRP syntheses of various hydroxylated diblock copolymers with improved compositional purity. These diblock precursors were then esterified with succinic anhydride to produce well-defined zwitterionic diblock copolymers. The aqueous solution properties of the final zwitterionic diblock copolymers were characterized using ^{1}H NMR spectroscopy, dynamic light scattering, zeta potential measurements, and transmission electron microscopy (TEM). Preliminary investigations of the micellar adsorption of one of these zwitterionic diblock copolymers onto both near-monodisperse silica particles and also a planar mica surface are also described.

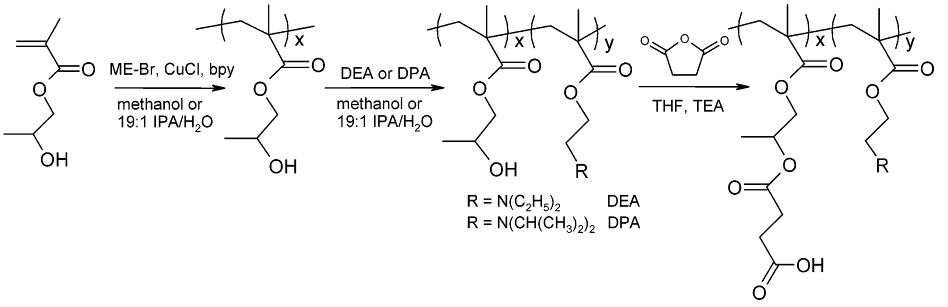
Experimental Section

Materials. 2-(Diethylamino)ethyl methacrylate (DEA; Aldrich) and 2-(diisopropylamino)ethyl methacrylate (DPA; Scientific Polymer Products) were passed through a basic alumina column (Aldrich) and a DHR-4 column (Scientific Polymer Products), respectively, to remove inhibitor and then stored in a refrigerator before use. 2-Hydroxypropyl methacrylate (HPMA) was kindly donated by Cognis Performance Chemicals (Hythe, UK) and was used as received. This monomer actually comprises an isomeric mixture of 75% HPMA and 25% 2-hydroxyisopropyl methacrylate,[17] but for clarity only the chemical structure of the major HPMA isomer is shown in this study. Silica gel 60 (0.063−0.2 mm particle diameter) was supplied by Merck (Darmstadt, Germany). Succinic anhydride (SA) and other reagents were supplied by Aldrich and were used as received. Deionized water with a resistivity greater than 1 MΩ cm (obtained from an Elgastat Option 3A water purification unit) was used for copolymer purification and preparation of aqueous copolymer solutions. Near-monodisperse Monospher 250 and 1000 nm silica particles (kindly supplied by E. Merck, Germany) were purified via three redispersion/centrifugation cycles with successive supernatants being replaced with 2-propanol, deionized water, and then 5 mM NaCl solution at pH 3.5.

Synthesis of 2-(4-Morpholino)ethyl 2-Bromoisobutyrate (ME-Br). The synthesis of the ME-Br initiator was carried out as reported previously.[18] A solution of 2-bromoisobutyryl bromide (53.30 g, 221.6 mmol) in 136 mL of dichloromethane was added dropwise to a solution of 4-(2-hydroxyethyl)morpholine (27.34 g, 206.4 mmol) and triethylamine (23.21 g, 221.6 mmol) in 300 mL of dichloromethane. This reaction mixture was stirred at 20 °C for 48 h, prior to being washed five times with 200 mL portions of deionized water. The organic layer was separated and then washed with 0.1 M aqueous solution of sodium carbonate until all the ammonium salts were removed. The combined organic phases were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The purified ME-Br (55.3 g, 95% yield) was stored in a freezer at −20 °C in the absence of light before use. ^{1}H NMR ($CDCl_3$, residual peak 7.27 ppm, 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 Diblock Copolymer Precursors via One-Pot ATRP. *Synthesis of PHPMA−PDEA Diblock Copolymers.* In a 100 mL two-neck round-bottomed flask, ME-Br initiator (299.5 mg, 1.07 mmol), HPMA monomer (7.71 g, 53.48 mmol, target degree of polymerization, Dp = 50), and 2,2′-bipyridine (bpy) (337 mg, 2.14 mmol) were mixed and degassed using a stream of nitrogen for 45 min. Then nitrogen-degassed methanol (7.7 mL) was added to the reaction mixture. The Cu(I)Cl catalyst (108 mg, 1.07 mmol) was then added quickly under a nitrogen blanket to start the polymerization. The reaction mixture turned dark brown and became viscous as the reaction progresses. After 9 h the polymerization was essentially complete (more than 98% conversion) as judged by ^{1}H NMR. Then a separately degassed of 50% w/v solution of DEA in methanol was added to the reaction solution via syringe. After a given time period (see Table 1) each polymerization was quenched by exposing the reaction mixture to air, followed by dilution with methanol (200 mL). The spent ATRP catalyst was removed by passing the blue solution through a silica gel column. The methanol was partially removed under vacuum, and the

Scheme 1. Synthesis of Zwitterionic Diblock Copolymers in Either Methanol or a 19:1 2-Propanol/Water Mixture at 20 °C[a]



[a] Only the major isomer of the HPMA monomer is shown for clarity.

copolymer was precipitated into 250 mL of deionized water. The recovered off-white copolymer was redissolved in methanol and precipitated into water to remove unreacted DEA monomer. The moist copolymer was dried under vacuum to obtain an off-white solid.

Synthesis of PHPMA−PDPA Diblock Copolymers. In a 100 mL round-bottomed flask, ME-Br initiator (299.5 mg, 1.07 mmol), HPMA monomer (7.71 g, 53.48 mmol, target Dp = 50), and bpy ligand (337 mg, 2.14 mmol) were mixed and degassed with nitrogen for 45 min. Then 7.7 mL of a degassed 2-propanol/water mixture (95:5 v/v 2-propanol/water) was added to the reaction mixture. The Cu(I)Cl catalyst (108 mg, 1.07 mmol) was then added quickly under nitrogen to start the polymerization. The dark brown reaction mixture became viscous as the reaction progressed. After 2.5 h, more than 98% monomer conversion had been achieved as determined from ^{1}H NMR analyses of extracted aliquots in CD_3-OD. A 50% w/v solution of DPA in degassed 2-propanol/water (95:5 v/v) was then added to the reaction solution via syringe. After the desired reaction time, the polymerization was quenched by exposing the dark brown solution to air, followed by dilution with THF (300 mL). The spent ATRP catalyst was removed by passing the copolymer solution through a silica gel column. The obtained solution was concentrated and poured into 500 mL of deionized water. The polymer was redissolved in THF and then precipitated into deionized water. The white solid copolymer was obtained after being dried under vacuum.

Esterification of Hydroxylated Diblock Copolymers with Succinic Anhydride. In a 100 mL round-bottomed flask, 2.0 g of diblock copolymer precursor was dissolved in 25 mL of anhydrous THF. Two molar equivalents of triethylamine (TEA) and succinic anhydride relative to the hydroxy groups of the hydroxylated block were then added under nitrogen. The esterification was allowed to proceed at 20 °C for 48 h, prior to termination by pouring the reaction mixture into excess deionized water (100 mL). THF was then removed under vacuum, and the crude zwitterionic diblock copolymer was purified by dialysis against water and saturated NaCl solution before freeze-drying from water overnight. The final esterified diblock copolymers were obtained as a white solid, and they were denoted either PSPMA−PDEA or PSPMA−PDPA (where “S” signifies the reacted succinic anhydride) in order to distinguish them from their PHPMA−PDEA or PHPMA−PDPA precursors (yields ranged from 82 to 97%).

Micelle Adsorption onto Near-Monodisperse Silica Particles. Acidic aqueous dispersions of purified Monospher 250 and 1000 nm silica sols were prepared at 10% w/v in 5 mM NaCl adjusted to pH 3.5 using HCl. A 0.50% w/v aqueous solution of $PSPMA_{50}$−$PDPA_{30}$ micelles was prepared at pH 3.5 with 5 mM NaCl background electrolyte using a 0.5 M HCl stock solution. This micelle solution was then added dropwise to the silica dispersions and stirred for 24 h at 20 °C to allow equilibrium adsorption. The nonadsorbed micelles were separated by centrifugation at 15 000 rpm, followed by redispersion using the same volume of acidified 5 mM NaCl solution to replace the supernatants. After a second centrifugation/redispersion cycle, the micelle-coated silica particles were characterized by aqueous electrophoresis and dynamic light scattering studies. The micelle-coated silica particles were also dried under vacuum at 20 °C for scanning electron microscopy studies and thermogravimetric analysis.

Polymer Characterization. *Nuclear Magnetic Resonance (NMR) Spectroscopy.* All ^{1}H NMR spectra were recorded in either D_2O, CD_3OD, $CDCl_3$, or d_5-pyridine using a Bruker AC-250 250 MHz spectrometer. Micellization of the zwitterionic diblock copolymers was studied in D_2O using either NaOD or DCl to adjust the solution pH.

Gel Permeation Chromatography (GPC). Molecular weights and molecular weight distributions of the homopolymer and copolymer precursors were determined using a GPC setup comprising Polymer Laboratories PL gel 5 μm MIXED-C columns. Calibration was carried out using a series of near-monodisperse poly(methyl methacrylate) [PMMA] standards. The GPC eluent was HLPC grade THF containing 2.0% v/v TEA, and the flow rate was 1.0 mL min^{-1}. The BHT stabilizer was used as an internal standard, and the column temperature was set at 30 °C.

Dynamic Light Scattering (DLS). DLS measurements were carried out at 20 °C using a Brookhaven BI-200SM goniometer equipped with a BI-9000AT digital correlator and a solid-state laser (125 mV, λ = 532 nm) at a fixed scattering angle of 90°. The intensity-average hydrodynamic diameter (*D*) and polydispersity index (μ_2/Γ^2) of micelles were evaluated from cumulants analysis of the experimental correlation function. Unless otherwise stated, 0.10% w/v aqueous copolymer solutions were used for all measurements, and the solution pH was adjusted using aqueous NaOH or HCl, where appropriate. The dilute copolymer solutions were ultrafiltered through 0.2 μm nylon filters (Fisher Scientific Ltd.) and allowed to stand overnight prior to DLS measurements.

Aqueous Electrophoresis Measurements. Electrophoresis measurements were carried out on 0.05% w/v copolymer solutions starting at either pH 10 or pH 3 using a Malvern Zetasizer NanoZS instrument equipped with an autotitrator (MPT-2 multipurpose titrator, Malvern Instruments). The zeta potential, ξ, was calculated from the electrophoretic mobility using the Henry equation and determined as a function of solution pH, which was adjusted using NaOH or HCl as required.

Scanning Electron Microscopy (SEM). SEM studies were performed on the Monospher 1000 silica particles before and after coating with the zwitterionic diblock copolymer micelles using a Stereoscan 420 instrument. The SEM samples were prepared by dropping 5 μL of the aqueous silica sol onto one end of a glass slide and then placing a second glass slide over the droplet. The suspension was drawn across the glass slide by surface tension. The second glass slide was then discarded, and the suspension was allowed to dry in air at 20 °C. Finally, all samples were sputter-coated with gold prior to examination to prevent sample charging problems.

Transmission Electron Microscopy (TEM). TEM samples were prepared by drying a drop of a dilute aqueous solution of copolymer micelles onto a carbon-coated copper grid. TEM images were obtained using a Phillips CM100 electron microscope operating at 100 kV.

Thermogravimetric Analyses (TGA). The extent of micelle adsorption onto the silica sols was determined using a Perkin-Elmer Pyris 1 TGA instrument. Dried samples were heated in air from 30 to 800 °C at a heating rate of 10 °C min^{-1}.

Atomic Force Microscopy (AFM). In-situ imaging of the adsorbed copolymer films on mica was performed with a Nanoscope IV AFM (Veeco, CA). Cantilevers with an integral silicon nitride tip (NanoProbe, Veeco, CA) were used for all AFM experiments and were cleaned using UV irradiation prior to use. A cleaved mica sheet was used as a substrate. Both the background electrolyte and copolymer solutions were passed through a syringe-mounted 0.20 μm GHP Acrodisk filter (Pall Gelman Science, MI) prior to injection into the AFM fluid cell. Images were collected using the soft-contact method.[19] This technique uses the minimum force necessary to obtain an image, thereby minimizing scanning-induced deformation of the adsorbed layer. All images presented are deflection images that have been zero-order flattened. At the beginning of each experiment, an aqueous solution of 5 mM NaCl adjusted either to pH 3.5 or pH 10 using HCl or NaCl was injected into the cell and left for ≈30 min to allow the substrate to reach equilibrium. After injection of the copolymer solution (0.50% w/v at pH 3.5 or pH 10 with 5 mM NaCl background electrolyte) into the AFM fluid cell, the system was equilibrated for the required time. All measurements were performed at room temperature (≈25 °C). Size analysis was conducted by measuring the lateral dimensions of 40−50 features (micelles) on a 1 × 1 μm image using a digital vernier calliper.

Results and Discussion

Synthesis of Hydroxylated Diblock Copolymers via One-Pot ATRP. Initially, we reexamined the conditions reported by Bories-Azeau and co-workers.[16] However, the ATRP of DEA in the bulk at 50 °C with a target Dp of 50 led to very viscous solutions at high conversion, which made it difficult to ensure full dissolution of the second monomer for the second-stage polymerization. Moreover, significant termination by combination was observed during the second-stage polymerization, as evidenced in the GPC traces of the crude diblock copolymers. In view of this problem, the ATRP of both DEA and HEMA was carried out in methanol at 20 °C. Under these conditions, more than 95% conversion was achieved for both monomers within 8−9 h. However, neither macroinitiator exhibited a high blocking efficiency for the second-stage polymerization. Indeed, extensive termination occurred as evidenced by high molecular weight shoulders in the GPC curves (see Figure S1 in Supporting Information). Similar problems were encountered by Weaver and co-workers when investigating the self-blocking efficiency of PHEMA using methanolic ATRP at 20 °C.[20] In this earlier study, high self-blocking efficiencies could only be obtained for the PHEMA macroinitiator if the HEMA conversion of the first-stage polymerization was lower than 70%. In view of these difficulties experienced with HEMA, we examined HPMA as an alternative hydroxylated monomer. HPMA had been previously polymerized via ATRP in protic media at room temperature in our laboratory by Save and co-workers, who used a Cu(I)Cl/2bpy catalyst.[17] The resulting homopolymer had a relatively low polydispersity ($M_w/M_n = 1.17$) at 98% conversion. Chain extension experiments using a second charge of HPMA suggested that good blocking efficiencies were possible even at high conversions.[20] We utilized a similar protocol to that reported by Save et al. (see Scheme 1).[17] Halogen exchange between the ME-Br initiator and the Cu(I)Cl catalyst is known to improve control in ATRP syntheses, as the rate of initiation is higher than the rate of propagation.[21] After 9−10 h, a HPMA conversion of more than 98% was achieved according to ^{1}H NMR analysis. (The integrated signal at δ 5.5 assigned to vinylic protons of the HPMA monomer was compared to that at δ 1.5−2.25 assigned to the vinyl methyl protons of HPMA monomer and the methylene backbone of the polymerized HPMA units.) The convenient one-pot synthesis of a range of diblock copolymer precursors was then performed by addition of a methanolic solution of DEA for various target degrees of polymerization. Table 1 summarizes the synthesis parameters and molecular weight data of several homopolymers and the corresponding diblock copolymers. Both homopolymers and diblock copolymers have relatively narrow molecular weight distributions, and the molecular weight of the diblock copolymers increased linearly with conversion. Figure 1a shows the typical evolution of the GPC chromatogram for PHPMA homopolymer and three PHPMA−PDEA diblock copolymers. Although the monomodal molecular weight distribution remains relatively narrow, a small degree of tailing was also evident, especially when the targeted Dp for the second block was 70. The high molecular weight shoulder suggests unwanted termination by combination. Thus, the second-stage polymerization of DEA at this Dp must be stopped at a conversion of around 90% or less to minimize molecular weight broadening due to termination.

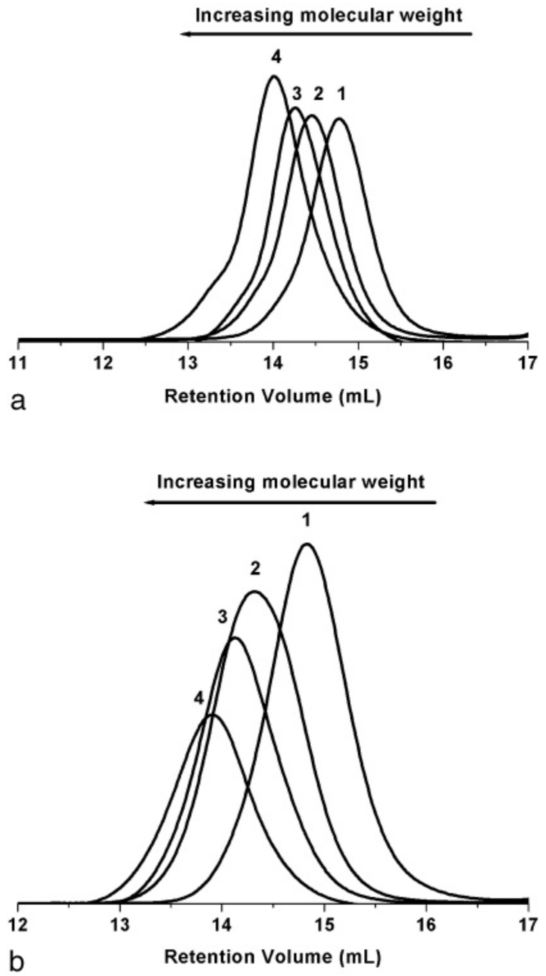


Figure 1. (a) GPC traces of (1) $PHPMA_{50}$, (2) $PHPMA_{49}-PDEA_{26}$, (3) $PHPMA_{50}-PDEA_{42}$, and (4) $PHPMA_{50}-PDEA_{72}$. (b) GPC traces of (1) $PHPMA_{50}$, (2) $PHPMA_{49}-PDPA_{29}$, (3) $PHPMA_{50}-PDPA_{47}$, and (4) $PHPMA_{49}-PDPA_{65}$. Each GPC chromatogram was recorded using a refractive index detector and THF eluent containing 2% v/v added TEA and 0.05% w/v BHT at 30 °C. A series of near-monodisperse poly(methyl methacrylate) standards were used for calibration.

We recently reported the unexpected transesterification of several tertiary amine methacrylates during methanolic ATRP at ambient temperature.[22a] This side reaction can be particularly

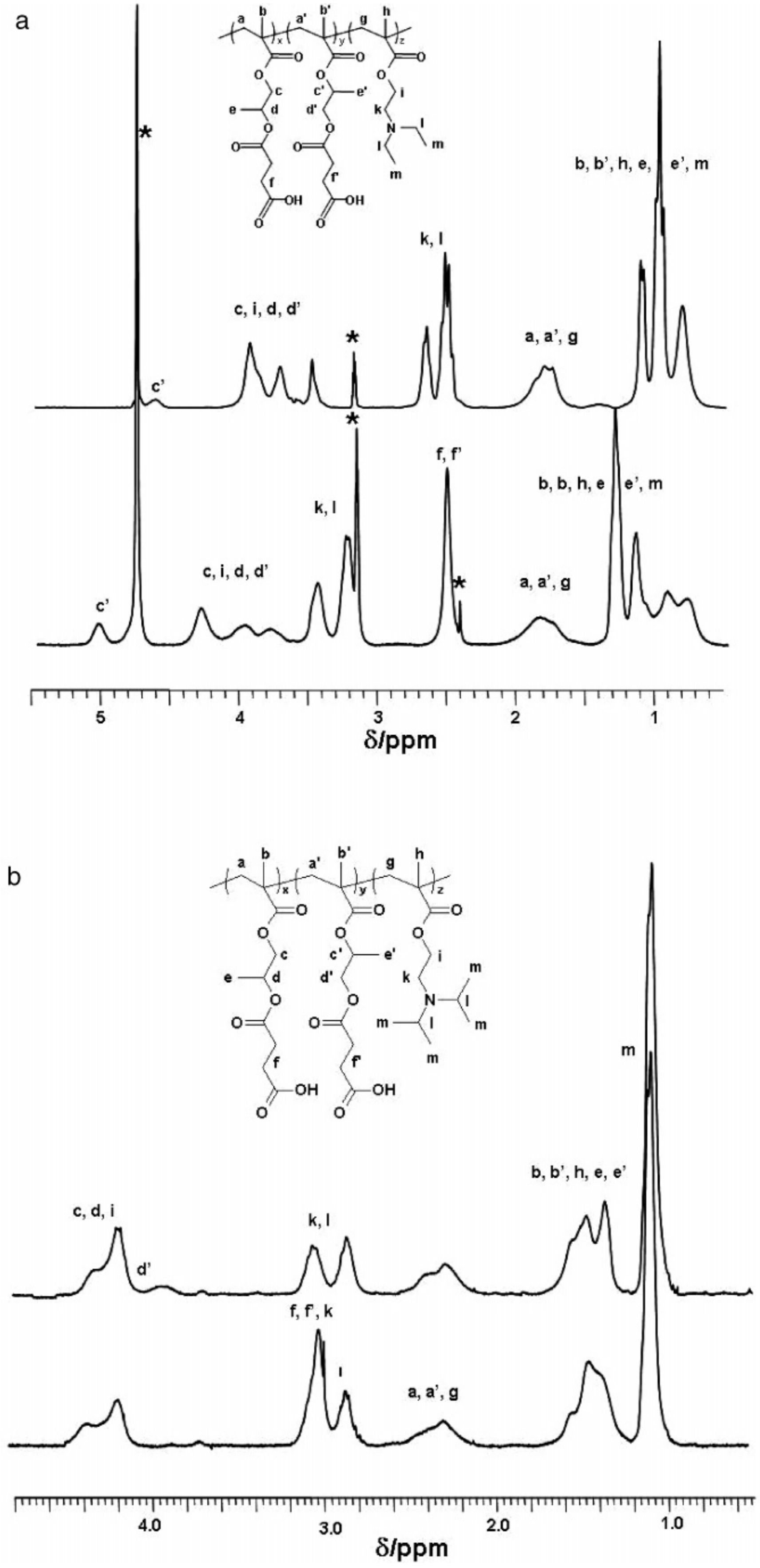


Figure 2. (a) ^{1}H NMR spectra recorded for PHPMA$_{50}$−PDEA$_{72}$ (top) and PSPMA$_{50}$−PDEA$_{72}$ (bottom) diblock copolymers in CD$_3$OD. **(**b**)** ^{1}H NMR spectra recorded for PHPMA$_{47}$−PDPA$_{65}$ (top) and PSPMA$_{47}$−PDPA$_{65}$ (bottom) diblock copolymers in d_5-pyridine.

problematic for DEA monomer, leading to undesirable statistical copolymers of DEA and MMA as judged by ^{1}H NMR spectroscopy (an additional weak signal appeared at δ 3.6−3.7 due to the methyl ester groups of the polymerized MMA units).

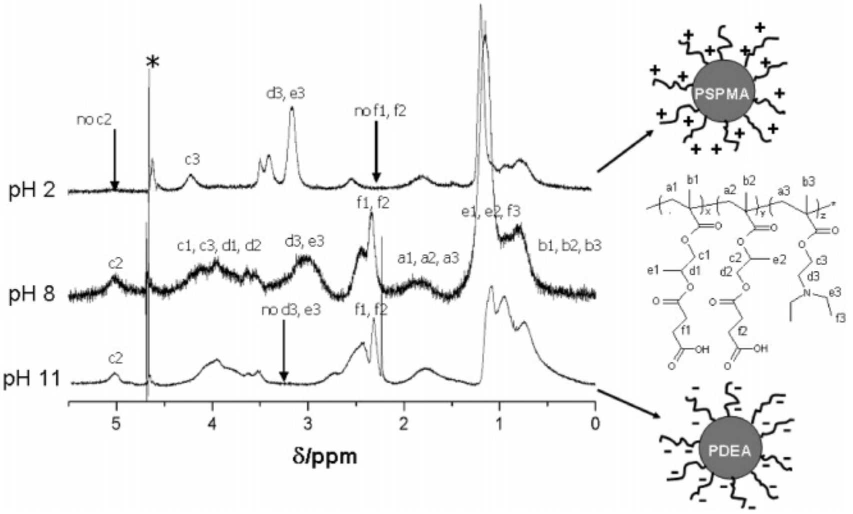


Figure 3. ^{1}H NMR spectra recorded for a PSPMA$_{50}$−PDEA$_{42}$ diblock copolymer in D$_2$O as a function of pH (adjusted using DCl and NaOD).

Unfortunately, overlapping HPMA and DEA peaks at δ 3.6−3.7 do not allow us to quantify the degree of transesterification in our present study. However, transesterification was reported to be negligible for the ATRP of DEA in methanol under similar reaction conditions by Cai and Armes.[22b] The reduced basicity of DPA monomer compared to DEA leads to negligible degrees of transesterification during the ATRP of the former monomer.[22a] Moreover, PDPA is appreciably more hydrophobic and less basic than PDEA (its approximate pK_a is 6.3 compared to around 7.3 for PDEA).[23] In our experience PDPA is also significantly more stable to oxidative and/or UV degradation than PDEA during long-term storage at ambient temperature.[20] Thus, using PDPA as a polybasic block in the synthesis of zwitterionic diblock copolymers may overcome some of the current limitations encountered with PDEA blocks.

PHPMA−PDPA diblock precursors were prepared using the same procedures as those outlined above for the PHPMA−PDEA diblocks, except that a mixture of 2-propanol and water was used as the reaction solvent. Using 2-propanol offers several advantages. First, it is a good solvent for both PHPMA and especially PDPA at higher Dp (50 or greater), whereas PDPA has only marginal solubility in methanol above a mean Dp of around 50. Second, using a secondary alcohol as a solvent essentially eliminates any possibility of transesterification occurring during the ATRP synthesis. Studies of the ATRP kinetics of HPMA in 2-propanol indicated that 97% conversion was attained within 4 h, and the resulting homopolymer had an M_n of 8100 g mol^{-1} and an M_w/M_n of 1.25. The reaction time was reduced significantly if a small amount of water was added to the reaction medium.[24] Indeed, more than 96% conversion was achieved within 2.5 h under the same reaction conditions if a 95:5 v/v mixture of 2-propanol and water was used instead of pure 2-propanol. Similar results have been reported in the literature for the ATRP of various methacrylate monomers in water/alcohol mixtures.[24] The synthesis parameters and molecular weight data are also summarized in Table 1. Good blocking efficiencies were obtained for the PHPMA macroinitiators when these were chain-extended using DPA monomer. Indeed, DPA conversions were high in all cases, and the resulting diblock copolymers each had relatively low polydispersities (see Table 1). The monomodal GPC traces indicate that the ATRP of DPA using the PHPMA macroinitiator was well-controlled. There is no evidence of significant termination, as shown in Figure 1b.

Esterification. We have recently shown that hydroxylated polymers such as PHEMA and PGMA can be fully esterified at 20 °C using SA in either anhydrous pyridine or in THF in the presence of added TEA within 48 h.[18] In the current study, similar conditions were employed to derivatize the diblock copolymer precursors. The PHPMA−PDEA or PHPMA−PDPA precursors were derivatized with 2 mol equiv of SA and TEA at ambient temperature. THF was chosen as the solvent as it is less malodorous than pyridine. After esterification, THF was removed under vacuum, and the resulting solid copolymer was

Table 2. DLS Studies of 0.10% w/v Aqueous Solutions of Selected Zwitterionic Diblock Copolymers in Either Acidic or Basic Aqueous Solutions[a]

zwitterionic diblock copolymer composition	DLS studies at pH 2 diam	DLS studies at pH 2 polydispersity	DLS studies at pH 10 diam	DLS studies at pH 10 polydispersity
PSPMA$_{49}$−PDEA$_{26}$	84	0.38	43	0.37
PSPMA$_{50}$−PDEA$_{42}$	35	0.28	137	0.44
PSPMA$_{50}$−PDEA$_{72}$	85	0.22	28	0.26
PSPMA$_{49}$−PDPA$_{29}$	33	0.53	130	0.16
PSPMA$_{50}$−PDPA$_{47}$	136	0.45	64	0.55
PSPMA$_{49}$−PDPA$_{65}$	31	0.48	45	0.40

[a] Copolymer solutions were adjusted to either pH 2 or pH 10 using either NaOH or HCl, then filtered through 0.2 μm nylon filters, and allowed to stand overnight prior to DLS measurements.

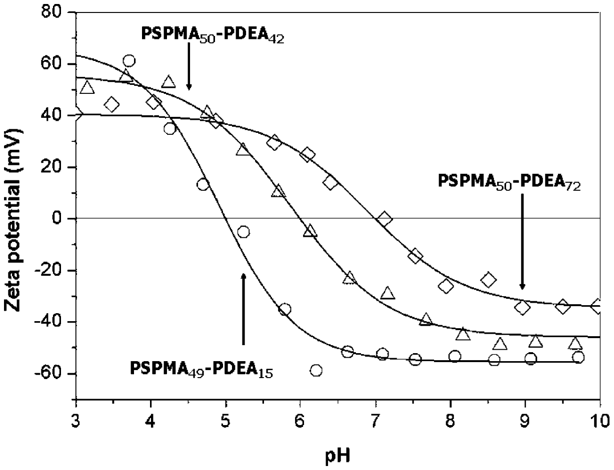


Figure 4. Zeta potential vs pH curves obtained for 0.10% w/v aqueous solutions of PSPMA$_x$−PDEA$_y$ zwitterionic copolymers in 5 mM NaCl solutions: (○) PSPMA$_{49}$−PDEA$_{15}$; (△) PSPMA$_{50}$−PDEA$_{42}$; (◇) PSPMA$_{50}$−PDEA$_{72}$.

Table 3. Calculated and Experimental IEP Values for 0.10% w/v Aqueous Solutions of Zwitterionic Diblock Copolymers in 5 mM NaCl[a]

			pK_a values of each homopolymer		isoelectric point (IEP)	
entry no.	zwitterionic diblock copolymer composition	R	PSPMA block	PDEA/PDPA block	theory	experiment
1	$PSPMA_{49}$–$PDEA_{15}$	3.26	5.5	7.3	5.14	5.10
2	$PSPMA_{50}$–$PDEA_{42}$	1.19	5.5	7.3	6.08	6.00
3	$PSPMA_{50}$–$PDEA_{72}$	0.69	5.5	7.3	6.99	7.11
4	$PSPMA_{49}$–$PDPA_{29}$	1.69	5.5	6.3	5.51	6.50
5	$PSPMA_{50}$–$PDPA_{47}$	1.06	5.5	6.3	5.85	6.51
6	$PSPMA_{47}$–$PDPA_{65}$	0.72	5.5	6.3	6.14	6.44
7	$PSPMA_{50}$–$PDPA_{30}$	1.67	5.5	6.3	5.52	6.17
8	$PSPMA_{50}$–$PDPA_{70}$	0.71	5.5	6.3	6.15	6.58

[a] ME-Br initiator was used for entries 1–6, whereas an ethyl 2-bromoisobutyrate initiator was used for entries 7 and 8.

Table 4. Calculated and Experimental IEP Values for a $PHPMA_{49}$–$PDEA_{15}$ Zwitterionic Diblock Copolymer Prepared at Various Partial Degrees of Esterification[a]

		pK_a values of homopolymers		IEP	
zwitterionic diblock copolymer composition	R	acid	base	theory	experiment
$PHPMA_{49}$:SA_9-*b*-$PDEA_{15}$	0.60	5.0–5.2[b]	7.3	7.13–7.14	7.48
$PHPMA_{49}$:SA_{24}-*b*-$PDEA_{15}$	1.60	5.2	7.3	5.41	5.71
$PHPMA_{49}$:SA_{35}-*b*-$PDEA_{15}$	2.33	5.3	7.3	5.17	5.06

[a] SA_9, SA_{24}, and SA_{35} denote the mean number of SA units that are incorporated into the $PHPMA_{49}$ block, as determined from ^1H NMR analysis in d_5-pyridine. [b] The pK_a of $PHPMA_{49}$:SA_9 could not be determined by titration due to this polymer's insolubility in water. However, the theoretical IEP of the analogous $PHPMA_{49}$:SA_9–$PDEA_{15}$ zwitterionic diblock copolymer does not change significantly if the pK_a of the $PHPMA_{49}$:SA_9 block is either 5.2 (IEP = 7.13) or 5.0 (IEP = 7.14).

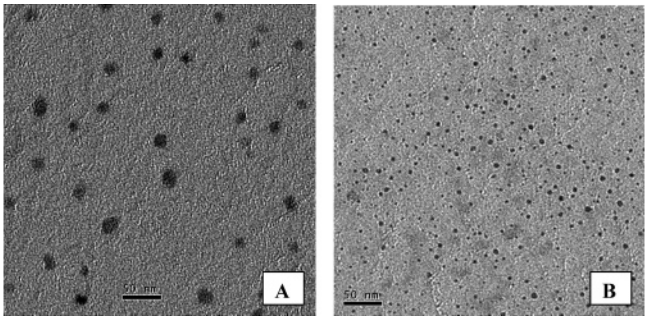


Figure 5. TEM images obtained for micelles prepared from aqueous solutions of $PSPMA_{50}$–$PDEA_{72}$ (A) and $PSPMA_{49}$–$PDPA_{29}$ (B) diblock copolymer micelles at pH 2. Under these conditions, the neutral (nonionized) PSPMA chains form the hydrophobic micelle cores, whereas the PDEA chains form the cationic micelle coronas.

dissolved in water and then purified using dialysis. It should be noted that dialysis against deionized water alone did not remove the TEA salt that was still present in the copolymer (clearly visible in the ^1H NMR spectra of the esterified copolymers). However, the unwanted TEA salt could be removed by dialysis in turn against first deionized water, followed by saturated NaCl solution in successive cycles, with a final dialysis against water to remove NaCl. At high NaCl concentration, the charge density on the copolymer chains is effectively screened, leading to little or no interaction between the TEA cations and the anionic polyacid block, thus allowing removal of the former contaminant.

The diblock compositions and the mean degrees of esterification of the hydroxylated block copolymers were determined from their ^1H NMR spectra in either CD_3OD (for the PDEA-based copolymer) or d_5-pyridine (for the PDPA-based copolymer), respectively. High degrees of esterification (typically at least 98%) were obtained in all cases. ^1H NMR spectra of selected zwitterionic diblock copolymers and their corresponding diblock precursors are shown in Figure 2a,b. On the basis of our earlier study, the narrow molecular weight distributions of the diblock precursors were expected to be preserved in the final zwitterionic diblock copolymers, since esterification was carried out under mild conditions.[18]

Aqueous Solution Behavior of the Zwitterionic Diblock Copolymers. The diblock precursors could not be dissolved directly in deionized water, whereas the zwitterionic diblock copolymers proved to be water-soluble (or water-dispersible) over a wide pH range. For example, the pH-induced reversible self-assembly of zwitterionic diblock copolymers such as $PSPMA_{50}$–$PDEA_{42}$ in D_2O could be monitored using ^1H NMR (Figure 3). At pH 8, the PSPMA and PDEA blocks are both weakly charged and hence water-soluble, so signals due to these two solvated blocks are visible in the ^1H NMR spectrum. Increasing the solution pH to 11 using NaOD led to the disappearance of the PDEA signals at δ 3.0–3.5 since the deprotonated PDEA block (pK_a 7.3) becomes hydrophobic at this pH. On the other hand, addition of DCl to the same PSPMA–PDEA solution led to the disappearance of the PSPMA signals at δ 2.2–2.6. These phenomena are in generally good agreement with those reported by Bories-Azeau for related, but structurally less well-defined, zwitterionic diblock copolymers.[16]

The aqueous properties of selected zwitterionic diblock copolymers were also assessed using DLS (see Table 2). Micelles ranging from 28 to 85 nm were formed, but the formation of larger aggregates of around 130 nm diameter was also observed. The reason(s) for the formation of these larger aggregates is not well understood, but similar nonmicellar aggregates have been reported by Jérôme and co-workers for closely related diblock copolymers.[9] Given the zwitterionic nature of these diblock copolymers, it is possible that electrostatic complexation promotes micelle aggregation when pH is changed from acid to base or vice versa. The effect of varying the solution pH on the structure of the micelles/aggregates can be monitored by aqueous electrophoresis. Figure 4 shows typical zeta potential vs pH curves obtained for aqueous solutions of three zwitterionic diblock copolymers (entries 1–3 in Table 3). At pH 2, the PDEA block is fully protonated, suggesting that the micelles/aggregates have cationic coronas under these conditions. As expected, zeta potentials of around +40 to +60 mV were observed at low pH for the micelles/aggregates formed by PSPMA–PDEA diblock copolymers. In contrast, zeta potentials of around −30 to −50 mV were obtained for the same copolymers in alkaline solution, suggesting the formation of micelles/aggregates with PDEA cores and PSPMA coronas. Table 3 summarizes the IEP data for the zwitterionic diblock copolymers. The experimental IEP values estimated from aqueous electrophoresis using the Nanosizer instrument are in reasonably good agreement with the theoretical IEP values

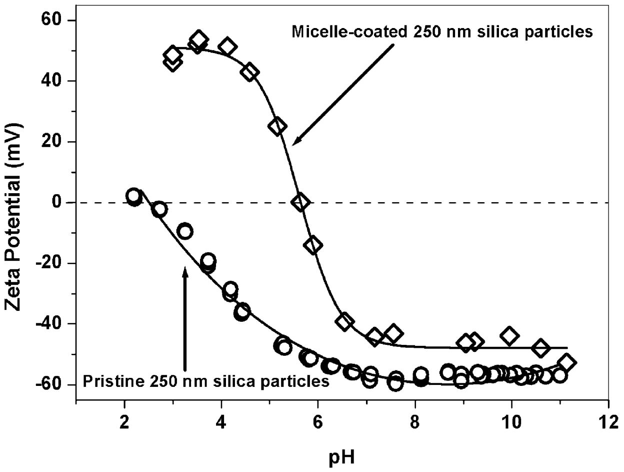


Figure 6. Zeta potential data obtained for (○) 250 nm near-monodisperse silica particles and (◇) $PSPMA_{50}-PDPA_{30}$ micelle-coated Monospher 250 silica particles using 5 mM NaCl as a background electrolyte in each case.

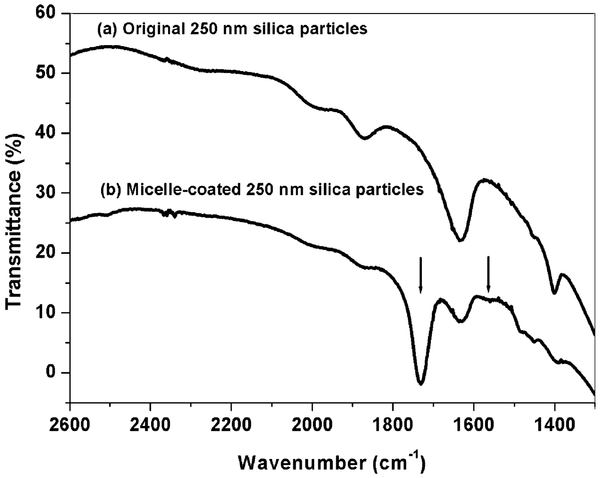


Figure 7. FT-IR spectra recorded for (a) pristine Monospher 250 silica particles and (b) $PSPMA_{50}-PDPA_{30}$ micelle-coated Monospher 250 silica particles.

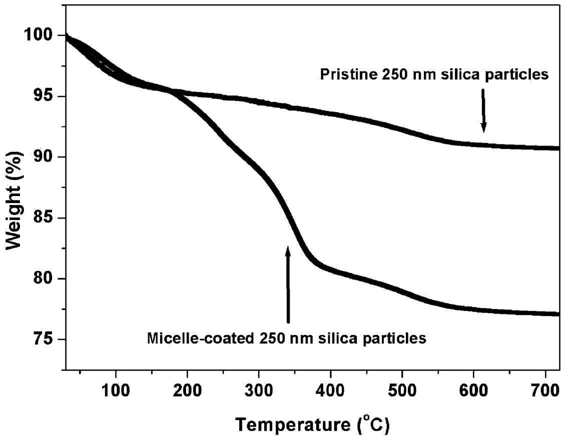


Figure 8. Mass loss curves obtained by thermogravimetric analyses of (a) Monospher 250 nm silica particles and (b) $PSPMA_{50}-PDPA_{30}$ micelle-coated Monospher 250 silica particles.

calculated using the following equation suggested by Patrickios and co-workers.[10,25]

$$\mathrm{IEP} = \mathrm{p}K_\mathrm{b} + \log\left\{\frac{1}{2}\left[\frac{1-R}{R} + \left(\left(\frac{1-R}{R}\right)^2 + \frac{4}{R}\,10^{\mathrm{p}K_\mathrm{a}-\mathrm{p}K_\mathrm{b}}\right)^{1/2}\right]\right\}$$

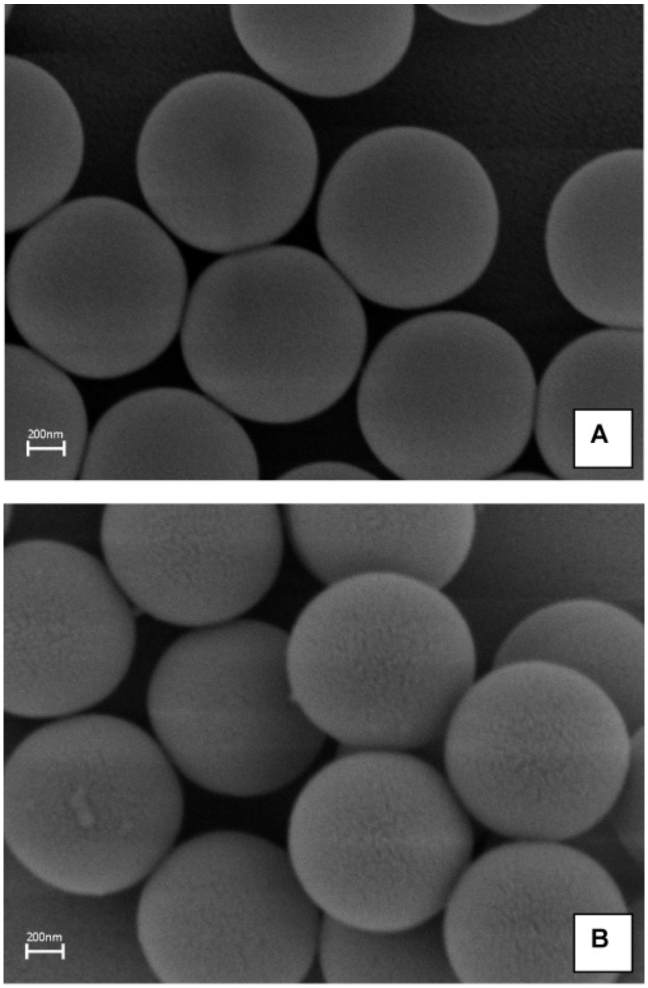


Figure 9. SEM images obtained for (a) uncoated Monospher 1000 silica particles and (b) Monospher 1000 silica particles coated with $PSPMA_{50}-PDPA_{30}$ micelles.

where R is the acid/base molar ratio and pK_a and pK_b are dissociation constants for the negative and positive charges, respectively. Increasing the PDEA block length (pK_a 7.3[23a]) at a fixed PSPMA block length (pK_a 5.5, determined by acid titration) allowed the IEP of the zwitterionic diblock copolymers to be shifted systematically from pH 5.10 to pH 7.11. Moreover, zwitterionic diblock copolymers with different IEP values were also obtained by simply adjusting the molar ratio of SA to hydroxy groups during esterification of the diblock copolymer precursors. Our acid titration studies also indicated that the pK_a of the carboxylic acid groups in PHPMA:SA statistical copolymers varies slightly according to the mean degree of esterification (see Figure S2, Supporting Information). Table 4 shows the dependence of the IEP of zwitterionic diblock copolymers on the mean degree of esterification. As expected, the IEP decreases at higher degrees of SA esterification of the diblock copolymers.

The experimental IEP values of the three PSPMA−PDPA diblock copolymers (entries 4−6 in Table 3) determined using the Nanosizer instrument are higher than predicted and are approximately constant, regardless of the PDPA block length. It is possible that the morpholine end groups (pK_a 8.4−8.8; derived from the ME-Br initiator)[26,27] in the copolymer chains may play a role in the unexpected difference between the experimental and calculated IEP values of these zwitterionic diblock copolymers. To test this hypothesis, an ethyl 2-bromoisobutyrate ATRP initiator was used instead of ME-Br to

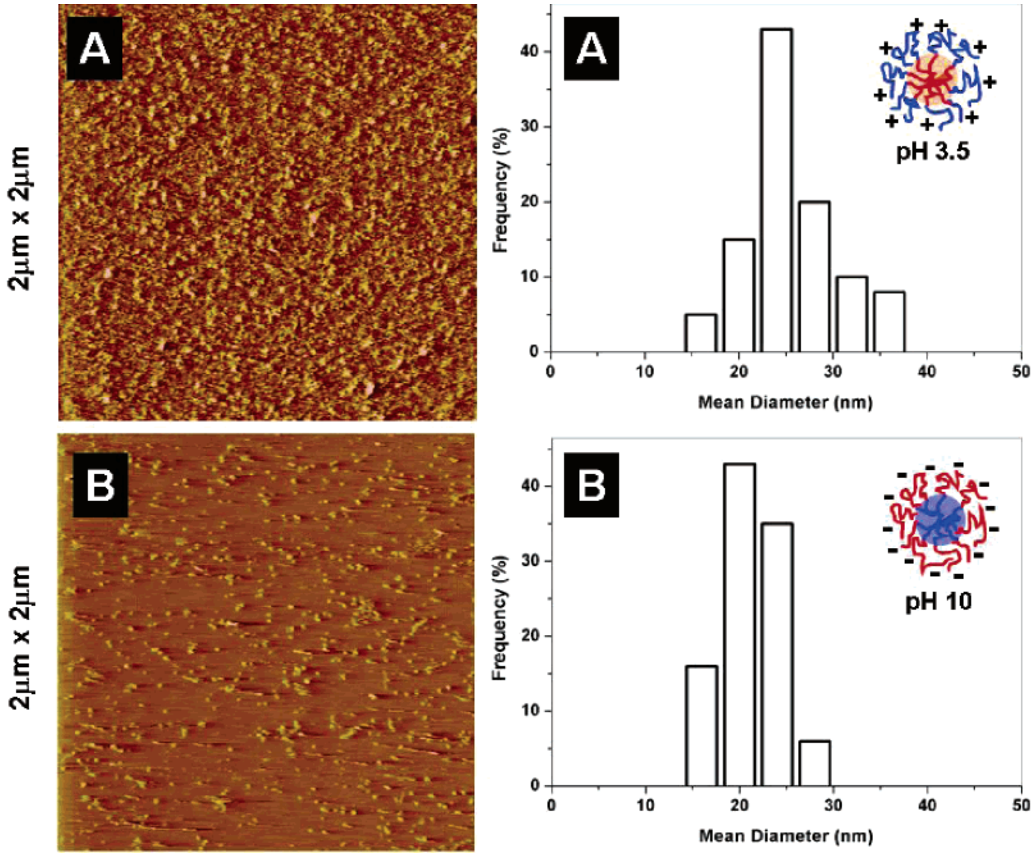


Figure 10. AFM images of PSPMA$_{50}$−PDPA$_{30}$ micelles adsorbed onto a planar mica surface at (A) pH 3.5 and (B) pH 10. Particle size distributions derived from analysis of the AFM images of these surface-adsorbed micelles.

synthesize PHPMA$_{50}$−PDPA$_{30}$ and PHPMA$_{50}$−PDPA$_{70}$ under similar polymerization conditions (entries 8 and 9, Table 1). The hydroxy groups of PHPMA block were then 100% esterified with SA before conducting aqueous electrophoresis studies. It is clear from Table 3 that the groups on the chain ends *do* appear to affect the IEP of the zwitterionic diblock copolymers. For example, the PSPMA$_{50}$−PDPA$_{30}$ and PSPMA$_{50}$−PDPA$_{70}$ diblock copolymers prepared using ethyl 2-bromoisobutyrate have IEP values of pH 6.17 and pH 6.58, respectively. However, both these isoelectric points are somewhat higher than those calculated using the equation reported by Patrickios and co-workers.[10,25] Thus, a satisfactory quantitative explanation for these IEP observations remains elusive. Micelles prepared from selected zwitterionic diblock copolymers were examined using TEM. Figure 5 shows the TEM images of micelles prepared from dilute aqueous solutions of either PSPMA$_{50}$−PDEA$_{72}$ or PSPMA$_{49}$−PDPA$_{29}$ copolymers at pH 2. The micelle diameters observed from TEM are smaller than those determined from DLS, as expected. For example, the intensity-average diameters of PSPMA$_{50}$−PDEA$_{72}$ and PSPMA$_{49}$−PDPA$_{29}$ micelles determined by DLS studies were 85 and 33 nm, respectively, whereas the corresponding number-average diameters determined from TEM were 18 and 5 nm, respectively. These discrepancies can be partly explained by the fact that TEM is only sensitive to the micelle cores, whereas DLS detects both the micelle cores and the micelle coronas.

Micelle Adsorption onto Near-Monodisperse Silica Particles and Planar Mica. Selected copolymer micelles were adsorbed onto two types of near-monodisperse silica particles (250 and 1000 nm diameter). The smaller silica sol was preferred for DLS studies, aqueous electrophoresis measurements, and thermogravimetric analyses, whereas the larger silica sol was better suited to SEM studies. Micelle adsorption was conducted at pH 3.5 as the silica particles still exhibit a relatively high negative zeta potential (−20 mV), and the zwitterionic diblock copolymers can form well-defined micelles with cationic coronas (zeta potential = +50 mV) at this pH (see Figure 6). The PSPMA$_{50}$−PDPA$_{30}$ diblock copolymer (entry 8, Table 1) formed well-defined micelles at 0.50% w/v in 5 mM NaCl at pH 3.5, with an intensity-average diameter of 45 nm. Micelle adsorption onto the silica particles was conducted for 24 h at 20 °C, and the nonadsorbed micelles were removed via two centrifugation/redispersion cycles. Aqueous electrophoresis studies confirmed that the zeta potential of the pristine 250 nm silica sol remained negative from pH 3 to pH 11. In contrast, the micelle-coated silica sols had an IEP at pH 5.7 (see Figure 6), which is only slightly lower than that of the corresponding zwitterionic diblock copolymer (for which the IEP is pH 6.17; see entry 7, Table 3). DLS studies on the micelle-coated silica sols in 5 mM NaCl solution at pH 3.5 indicated that there was an increase in the mean particle diameter of micelle-coated silica sols, as expected. For example, the nominal 250 nm uncoated silica sol, which is a little smaller than expected (see Figure S3 in the Supporting Information), had an initial intensity-average particle diameter of 190 nm, which increased to 245 nm for the micelle-coated silica sol. These data indicate an adsorbed micelle layer thickness of around 27 nm. Given that the original micelle diameter was 45 nm in bulk solution, this suggests significant flattening and spreading of the adsorbed micelles. FTIR studies confirmed the presence of an ester carbonyl band at 1730 cm^{-1} due to the PSPMA$_{50}$−PDPA$_{30}$ diblock copolymer that was absent in the pristine silica sol (Figure 7). In addition, a second very weak feature at 1560 cm^{-1} due to carboxylate anion was observed in the FTIR spectrum of the micelle-coated silica sol. This is reasonable as these PSPMA$_{50}$−DPA$_{30}$ micelles were adsorbed at pH 3.5; under these conditions relatively few carboxylic acid groups on the PSPMA block are actually ionized. The adsorbed micelle masses on the 250 and 1000 nm silica particles were approximately 9.5% and 3.5%, respectively, as determined by thermogravimetric analyses (see Figure 8). SEM studies of the micelle-coated silica particles indicate slightly rougher surfaces compared to the pristine Monospher 1000 silica sol, as expected (see Figure 9). Similar observations were reported by Pilon et al. for cationic shell cross-linked micelles adsorbed onto silica sols.[28]

Preliminary studies showed that "cationic corona" $PSPMA_{50}-PDPA_{30}$ micelles formed at pH 3.5 could be electrostatically adsorbed onto a planar mica surface immersed at the same pH, as expected. In situ AFM was used to image this adsorbed copolymer layer (see Figure 10a). As a control experiment, bare mica was also imaged under the same conditions and shown to be completely smooth and featureless (see Figure S4 in Supporting Information). The mean lateral diameter of the surface-adsorbed cationic micelles after 2 h adsorption was estimated to be around 25 nm by AFM analysis of 40 particles. Bearing in mind the mean DLS diameter for these micelles reported above, this suggests that a significant change in the micelle aggregation number occurs after micelle adsorption. Perhaps more surprisingly, the "anionic corona" $PSPMA_{50}-PDPA_{30}$ micelles (DLS studies indicated that this copolymer formed micelles of 97 nm diameter at 0.50% w/v in 5 mM NaCl at pH 10) were also adsorbed onto anionic mica at pH 10, despite the unfavorable electrostatic interactions. Significantly longer times (>16 h) were required under these conditions, perhaps because micelle adsorption is mediated by relatively weak hydrophobic interactions due to the micelle cores, rather than strong electrostatic interactions due to the micelle coronas. However, an alternative explanation could be that the $PSPMA_{50}-PDPA_{30}$ chains initially adsorb onto the mica as unimers, followed by the (slow) formation of surface micelles. In this scenario, the "anionic corona" copolymer micelles in bulk solution simply act as a reservoir for the unimers. In this context, it is noteworthy that the low T_g (ca. 16 °C) of the PDEA chains in the cores of these "anionic corona" micelles should enhance the rate of unimer–micelle exchange. Further studies are clearly required to elucidate the precise adsorption mechanism in this particular case. We emphasize that unimer adsorption is much less likely for the "cationic corona" micelles, since the favorable electrostatics should ensure rapid micelle adsorption. Figure 10b shows an AFM deflection image recorded for an adsorbed layer of "anionic corona" $PSPMA_{50}-PDPA_{30}$ micelles on mica after equilibration for 16 h. The mean lateral diameter of the surface-adsorbed anionic micelles was estimated to be around 21 nm (50 features counted). Moreover, the surface coverage is significantly lower for these hydrophobically adsorbed "anionic corona" micelles compared to the electrostatically adsorbed "cationic corona" micelles.

Conclusions

A two-step synthesis route to low polydispersity zwitterionic diblock copolymers via hydroxylated diblock precursors has been developed and optimized. Compared to an earlier report, improved control over the copolymer architecture was obtained by polymerizing 2-hydroxypropyl methacrylate first, followed by the tertiary amine methacrylate monomer. The former monomer enables significantly higher conversions to be attained and better blocking efficiencies to be achieved compared to 2-hydroxyethyl methacrylate. Very high degrees of esterification of the diblock precursors were obtained using excess succinic anhydride under mild conditions. The isoelectric points of the final zwitterionic diblock copolymers depend on the nature of the tertiary amine methacrylate monomer as well as the overall block composition (i.e., the relative molar ratio of acid to base groups) and the mean degree of esterification. These zwitterionic diblock copolymers can form two types of micelles in aqueous solution simply by adjusting the solution pH. Preliminary investigations confirm that it is possible to adsorb selected block copolymer micelles with cationic coronas onto anionic silica particles and also a planar mica surface at low pH. Moreover, adsorption of "anionic corona" $PSPMA_{50}-PDEA_{30}$ micelles onto mica also occurred at pH 10, presumably due to relatively weak hydrophobic interactions between the micelle cores and the mica surface, rather than strong electrostatic interactions. Our micelle adsorption observations indicate some potential for the preparation of "smart" stimulus-responsive surfaces and also suggest that such zwitterionic diblock copolymer micelles may be used for the elaboration of micelle multilayers by the layer-by-layer technique.[29]

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Supporting Information Available: DMF GPC traces of $PDEA_{50}$ homopolymer and $PDEA_{50}-HEMA_{70}$ diblock copolymers; acid titration curves for PHPMA:SA statistical copolymers of varying degrees of SA esterification; TEM images of nominal 250 nm silica particles and the corresponding 250 nm silica particles coated with $PSPMA_{50}-PDPA_{30}$ micelles; AFM image of a smooth planar mica surface prior to micelle adsorption. This information is available free of charge via the Internet at http://pubs.acs.org.

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