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Synthesis and Characterization of Zwitterionic Block Copolymers

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ABSTRACT: Zwitterionic poly(2-(dimethylamino)ethyl methacrylate-*block*-methacrylic acid) (PDMAEMA-*block*-PMAA) copolymers are synthesized by group transfer polymerization using 2-tetrahydropyranyl methacrylate (THPMA) as a protected monomer for the acid block. Subsequent thermolysis led to quantitative removal of the tetrahydropyranyl groups, but control experiments indicated significant broadening of the molecular weight distribution (MWD) of a PDMAEMA homopolymer under the same conditions. Hence this deprotection route was considered unsatisfactory. Acid hydrolysis of the block copolymers under mild conditions also led to quantitative removal of the THP groups, as judged by ^{1}H NMR spectroscopy. This deprotection chemistry was adopted as our preferred route, since it did not lead to MWD broadening of the same PDMAEMA homopolymer. A series of zwitterionic blocks were synthesized with good control over both molecular weight and copolymer composition. The aqueous solubility vs. pH behavior of these copolymers was determined by acid titration. Finally, the reversible micellization of these copolymers in aqueous media was examined using dynamic light scattering and variable temperature ^{1}H NMR spectroscopy.

Introduction

Zwitterionic polymers, or polyampholytes, possess both positive and negative charge and are therefore interesting synthetic analogues for proteins. There is considerable literature on the synthesis and aqueous solution properties of zwitterionic *statistical* copolymers.[1−3] These materials are typically made by the conventional free-radical copolymerization of acidic and basic comonomers and therefore inevitably have rather broad molecular weight distributions. In contrast, there have been very few reports of the synthesis of polyampholytes with *block copolymer* architectures. Such syntheses require sequential monomer addition under living polymerization conditions, usually with protected monomers. The first examples of zwitterionic block copolymers were reported by Kamachi et al.,[4] who copolymerized 2-vinylpyridine with either trimethylsilyl methacrylate or *tert*-butyl acrylate. These precursor blocks were then quantitatively deprotected via hydrolysis. Subsequently, Varoqui et al. reported the synthesis of poly(2-vinylpyridine-*block*-sodium 4-styrenesulfonate) copolymers via selective sulfonation of poly(2-vinylpyridine-*block*-styrene) precursors.[5] More recently, Morishima et al.[6] reported the synthesis of block copolymers of trimethylsilyl methacrylate with *p*-(*N*,*N*′-dimethylamino)styrene and Bekturov and co-workers[7,8] have described the synthesis and aqueous solution behavior of poly(1-methyl-4-vinylpyridinium chloride-*block*-methacrylic acid).

At Sussex we have used group transfer polymerization (GTP) as a means of synthesizing both hydrophilic−hydrophobic and hydrophilic−hydrophilic methacrylate (co)polymers. For example, basic monomers such as 2-(dimethylamino)ethyl methacrylate (DMAEMA) have been directly (co)polymerized by GTP to give near-monodisperse homopolymers and block (co)polymers.[9] Similarly, methacrylic acid homopolymers[10] and block copolymers[11] can be synthesized via GTP using benzyl methacrylate as a protected monomer. Quantitative debenzylation can be achieved via catalytic hydrogenolysis under mild conditions [Pd/C; H_2 (1 atm); 25 °C].

Recently we have examined various synthetic routes to zwitterionic block copolymers via GTP. Given our initial success with DMAEMA, we selected this monomer as the basic (cationic) block. We considered four protected monomers as candidates for the poly(methacrylic acid)-based anionic block: trimethylsilyl, *tert*-butyl, benzyl, and 2-tetrahydropyranyl methacrylates. Essential prerequisites for the protected monomer were good “livingness” under GTP conditions and selective deprotection under mild conditions. Earlier work in our laboratory had already established that there were considerable problems associated with the polymerization of both trimethylsilyl methacrylate and *tert*-butyl methacrylate under GTP conditions. The former monomer polymerized only very slowly and high molecular weight acid blocks were not possible with this monomer.[12] The “livingness” of the latter monomer was poor[13] and, in any case, subsequent control experiments on DMAEMA homopolymers suggested that the conditions required to remove the *tert*-butyl group (strong acids at elevated temperatures for extended times) were likely to cause significant degradative cross-linking and/or deprotection of the DMAEMA block.[14] Given our earlier success in synthesizing poly(methyl methacrylate-*block*-methacrylic acid) copolymers using benzyl methacrylate as a protected acid monomer, we elected to synthesize a series of DMAEMA−benzyl methacrylate block copolymers. This proved straightforward,[15] but unfortunately the benzyl groups could not be subsequently removed in the presence of the tertiary amine block via catalytic hydrogenolysis, probably due to poisoning of the Pd/C catalyst. Other hydrogenolysis catalysts were examined but without success. Acid hydrolysis using HBr in acetic acid proved to be nonselective: the benzyl groups were removed but significant cleavage of the DMAEMA ester groups also occurred.

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Finally, we examined 2-tetrahydropyranyl methacrylate (THPMA) as a protected monomer. Patrickios et al.[16] had reported using this monomer to synthesize two ABC triblock copolymers (A, DMAEMA; B, methyl methacrylate; C, methacrylic acid). Trimethylsilyl methacrylate was also used in the same study in the preparation of a series of similar ABC triblocks and, in addition, a single example of a relatively low molecular weight DMAEMA−methacrylic acid zwitterionic diblock copolymer. These workers discussed several disadvantages of this latter protected monomer (e.g., slow, incomplete polymerization) and stated that THPMA was preferred for the synthesis of higher molecular weight copolymers. Quantitative removal of the 2-tetrahydropyranyl protecting group was claimed via thermolysis at 140 °C under dynamic vacuum for 48 h. The polydispersities of the two protected DMAEMA−MMA−THPMA triblock copolymers reported by Patrickios et al. were not particularly narrow (the polydispersities were 1.27 and 1.33, respectively). In addition, and no doubt due to their poor solubility in organic media, no GPC analyses were attempted on the corresponding deprotected triblocks or, indeed, on the single example of the DMAEMA−methacrylic acid zwitterionic diblock copolymer.

The present work is concerned with the synthesis of a series of DMAEMA−THPMA diblock copolymers of varying copolymer composition and their subsequent deprotection to yield the desired zwitterionic block copolymers. It is demonstrated that there are problems with the thermolysis deprotection route favored by Patrickios et al. since, in control experiments, these conditions lead to significant changes in the GPC trace of a DMAEMA homopolymer. This suggests that DMAEMA−methacrylic acid diblocks are most likely partially cross-linked, rather than truly linear chains. In contrast, *acidic hydrolysis* under mild conditions (dilute acid at room temperature) leaves the GPC of DMAEMA homopolymer essentially unchanged. Thus we are confident that this latter deprotection route yields well-defined DMAEMA−methacrylic acid diblock copolymers. Having finally established a reliable synthetic route to zwitterionic diblock copolymers, preliminary studies of the aqueous solution properties of these complex and fascinating materials were carried out.

Experimental Section

Materials. Unless stated otherwise all chemicals were purchased from Aldrich. DMAEMA was purified by passing through a basic alumina column, to remove the inhibitor, stored over CaH_2 at below 0 °C, and distilled immediately prior to use. The initiator, 1-methoxy-1-(trimethylsiloxy)-2-methyl-1-propene (MTS) was distilled under high vacuum and stored in a graduated Schlenk flask under a dinitrogen atmosphere at below 0 °C. The catalyst, tetra-*n*-butylammonium bibenzoate (TBABB) was prepared in-house by the method of Dicker et al.[17] and stored as a solid under vacuum. The polymerization solvent, THF, was dried over sodium wire prior to reflux over potassium metal for 3 days. This THF was collected under a dry dinitrogen purge and stored over 4 Å molecular sieves under a dinitrogen atmosphere.

Synthesis of THPMA. THPMA was synthesized by the acid-catalyzed esterification of methacrylic acid (MAA) with 3,4-dihydro-2*H*-pyran using a modification of the method of Hertler.[18] To a 1 L, three-necked round-bottomed flask equipped with a magnetic stir bar, reflux condenser, dinitrogen inlet, and addition funnel was added 3,4-dihydro-2*H*-pyran (125 mL) and 10 drops of 50% sulfuric acid; this mixture was stirred at room temperature for approximately 20 min. A mixture of MAA (116 mL), 3,4-dihydro-2*H*-pyran (125 mL), and phenothiazine (1 g) was added via the addition funnel. The reaction mixture was then heated at 54 °C for 25 h. After cooling to room temperature, solid sodium hydrogen carbonate (10 g) and anhydrous sodium sulfate (40 g) were added and the reaction mixture was left stirring overnight. The mixture was filtered and treated with CaH_2 (1 g), phenothiazine (1 g), and DPPH (0.2 g). The excess 3,4-dihydro-2*H*-pyran was removed under reduced pressure. The remaining mixture was distilled at 70 °C under reduced pressure, giving approximately 100 mL of THPMA in 60% yield. THPMA was then further purified by passing through a basic alumina column to remove traces of residual MAA. Two vacuum distillations from CaH_2 yielded THPMA of sufficient purity for GTP.

Table 1. Summary of the Theoretical and Observed Number-Average Molecular Weights (M_n), the Theoretical and Observed Block Copolymer Compositions, and the Polydispersities of the DMAEMA-*block*-THPMA Precursor Copolymers

sample ID	theor M_n	obsd M_n[a]	theor molar composition	obsd molar composition[b]	M_w/M_n[a]
AB1	8 000	8 500	80:20	77:23	1.08
AB2	24 000	24 700	80:20	82:18	1.16
AB3	32 500	35 700	60:40	64:36	1.15
AB4	39 200	34 000	50:50	51:49	1.22
AB5	49 400	42 400	40:60	43:57	1.19

[a] As determined by GPC. [b] As determined by ^1H NMR spectroscopy.

Synthesis. All glassware was dried overnight at 150 °C and assembled hot under a dinitrogen purge and then flamed out under dynamic vacuum to remove any residual surface moisture. All polymerizations were performed in a 250 mL, three-necked round-bottomed flask equipped with a magnetic stir bar, and rubber septa for liquid transfer. Liquid transfers were performed using double-tipped needles. Polymerizations were carried out at room temperature (∼23 °C). Polymerization exotherms were monitored using a digital thermometer. A typical polymerization procedure for an AB diblock copolymer is detailed below.

To the polymerization flask was added THF (∼100 mL) via a double-tipped needle. The catalyst, TBABB (∼20 mg), was added as a solid through a sidearm of the polymerization flask. To this was added MTS (typically 0.20 mL), and the reaction mixture was stirred for approximately 30 min. Subsequently, freshly distilled DMAEMA (10 mL) was added dropwise to the reaction flask and the exotherm was monitored as stated above (DMAEMA was polymerized first in all cases). Once the exotherm had abated, a 1 mL sample was extracted via syringe for GPC analysis. Next, freshly distilled THPMA (6 mL for a theoretical molar composition of 60:40) was added dropwise to the living PDMAEMA solution and the reaction exotherm monitored. Finally, once the reaction had cooled to room temperature, a small aliquot of this diblock copolymer solution was extracted for GPC analysis. The block copolymer was isolated by removing the THF under vacuum, followed by drying in a vacuum oven overnight at room temperature.

Removal of the THP Protecting Group. The THP protecting group was removed by two different methods. For thermolyses, the solid copolymer was heated in a vacuum oven at 145 °C. Alternatively, for acid hydrolyses the copolymer (typically 2 g) was stirred in 0.1 M HCl until dissolution, giving an optically transparent solution.[19] Where possible, the resulting diblock polyampholyte was recovered via precipitation at the isoelectric point. This method of recovery inevitably led to the copolymers being isolated in their partially ionized, rather than neutral, form. In Table 2 the sample i.d.'s are AB1-D, AB2-D, etc. where the "D" denotes the deprotected zwitterionic copolymers derived from AB1, AB2, etc. (see Table 1).

Characterization in Organic Solvents. GPC. Molecular weights and polydispersities of the precursor PDMAEMA homopolymers and the DMAEMA-*block*-THPMA copolymers were determined by gel permeation chromatography (GPC)

Table 2. Summary of the Calculated and Observed Isoelectric Points of the Zwitterionic DMAEMA-*block*-MAA Copolymers

sample ID	block copolymer composition DMAEMA:MAA	calcd IEP	obsd IEP[a]
AB1-D	77:23	8.52	
AB2-D	82:18	8.65	8.56
AB3-D	64:36	7.89	7.40
AB4-D	51:49	6.86	6.74
AB5-D	43:57	5.83	5.62

[a] Taken as the midpoint of the precipitation range.

using a Polymer Labs mixed "D" column, connected to an RI detector, and a Knauer UV detector. The mobile phase was HPLC-grade THF stabilized with butylated hydroxytoluene, at a flow rate of 1 mL min^{-1}. The GPC was calibrated with a series of four PMMA standards with molecular weights ranging from 2000 to 29 400.

^{1}H NMR Spectroscopy. ^{1}H NMR spectra were recorded using a Bruker AC-P250 Fourier transform NMR spectrometer operating at 250 MHz. Spectra were recorded in either $CDCl_3$ or DMSO-d_6 using residual nondeuterated solvent ($CHCl_3$ or DMSO) as an internal reference.

Characterization in Water. Acid Titration. An acid-hydrolyzed, DMAEMA−MAA block (50 mg) was dispersed or dissolved in 5 g of doubly distilled deionized water. The dispersed copolymer was dissolved by the addition of 5−6 drops of 0.5 M HCl (resulting copolymer solution pH ~ 2). The copolymer solution was titrated with stirring using 0.5 M KOH solution (Aldrich); the solution pH was recorded using a HANNA Instruments 8521 pH meter calibrated with buffer solutions at pH 4 and pH 7.

Aqueous GPC. The molecular weights and molecular weight distributions of the polyampholytes were determined via aqueous gel permeation chromatography (GPC). The aqueous GPC system comprised a Pharmacia Biotech "Superdex" 200 HR 10/30 column connected to a ERC-7517A RI detector and a Polymer Labs LC 1200 UV/vis detector. The mobile phase consisted of a buffered solution of tris(hydroxymethyl)aminomethane (TRIZMA). TRIZMA·HCl, 2.21 g, and TRIZMA base, 4.36 g, were dissolved in 1 dm^3 of 1 M NaCl solution to give a 0.05 M solution of TRIZMA, at pH 8.5. The TRIZMA solution was vacuum-filtered and then sonicated and degassed for 30 min. This mobile phase was used at a flow rate of 1.50 mL min^{-1}. The column temperature was maintained at 30 °C. A series of poly(ethylene oxide) standards were used as calibrants.

Dynamic Light Scattering. Samples were prepared as 1 w/w % solutions in doubly distilled deionized water, with the pH adjusted by adding acid or base where appropriate prior to filtering through 0.20 μm Phenomenex syringe filters. Experiments were performed using a Malvern PCS 4700 spectrometer, equipped with a 75 mW argon-ion laser operating at 488 nm. Measurements were made at an angle of 90° in a temperature-controlled cell maintained via a thermostatically controlled waterbath. Both monomodal cumulants and CONTIN analyses were used to fit the data.

Results and Discussion

Precursor Block Copolymer Synthesis. GTP was utilized to synthesize a series of AB diblock polyampholytes, where the A block is DMAEMA and the B block is THPMA. Table 1 summarizes the theoretical and observed number-average molecular weights (M_n), theoretical and observed block copolymer compositions, and polydispersities of the resulting block copolymers. For AB1 the DMAEMA block length was ca. 6500. For AB2 to AB5, the molecular weight of the DMAEMA block was kept constant at ca. 19 000. DMAEMA was polymerized first in all cases since it was found that THPMA polymerized more readily as the second monomer.

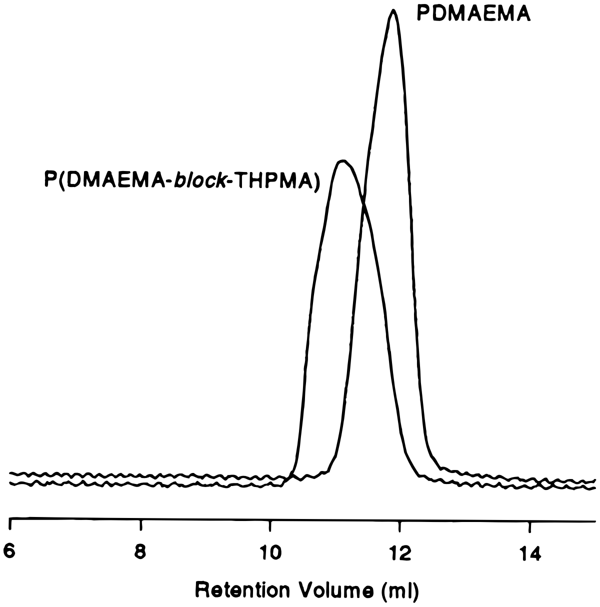


Figure 1. Typical GPC trace of a DMAEMA homopolymer and the corresponding DMAEMA-*block*-THPMA copolymer (AB3) in THF.

Quantitative yields were obtained in all copolymerizations, with good control being achieved over both molecular weight and block copolymer composition. The wide range of block copolymer compositions allows the isoelectric point of the zwitterionic blocks to be tuned. Polydispersity indices were in the range 1.08−1.22, which is typical of (co)polymers prepared via GTP. Figure 1 shows a GPC trace of a DMAEMA-*block*-THPMA copolymer (AB3; theoretical DMAEMA content of 60 mol %). The peak labeled PDMAEMA represents a homopolymer sample taken prior to the addition of the THPMA monomer. Given that the DMAEMA block represents the major component in this copolymer, and that this block was synthesized first, any homopolymer contamination that may be present cannot be easily resolved via GPC due to the relatively small difference in molecular weight between the block copolymer and the homopolymer.[20] The block copolymer composition was determined by ^{1}H NMR spectroscopy. Figure 2 depicts a ^{1}H NMR spectrum of AB3, recorded in $CDCl_3$, with $CHCl_3$ as an internal reference. The block copolymer composition is readily determined by comparing the signal labeled A (the hydrogen bound to the acetal carbon in the THPMA block) with the signal labeled either D or E (the methylene hydrogens bound to the ester group or nitrogen, respectively, in the DMAEMA block). The other key features are the signals labeled B and F. B represents the two methylene hydrogens adjacent to the oxygen atom in the THP residues, while F represents the six hydrogens of the dimethylamino groups in the DMAEMA block.

Conversion of Precursor Blocks to Zwitterionic Blocks. Given the need for a protected acid monomer, it is essential that this monomer is both readily (co)polymerizable and quantitatively cleaved under mild conditions so as to minimize side reactions such as chain scission or cross-linking. We have already mentioned some of the problems associated with alternative protected monomers for PMAA sequences. 2-Tetrahydropyranyl methacrylate is a convenient protected monomer for methacrylic acid and, in principle, can be cleaved by either thermolysis or acid hydrolysis, see

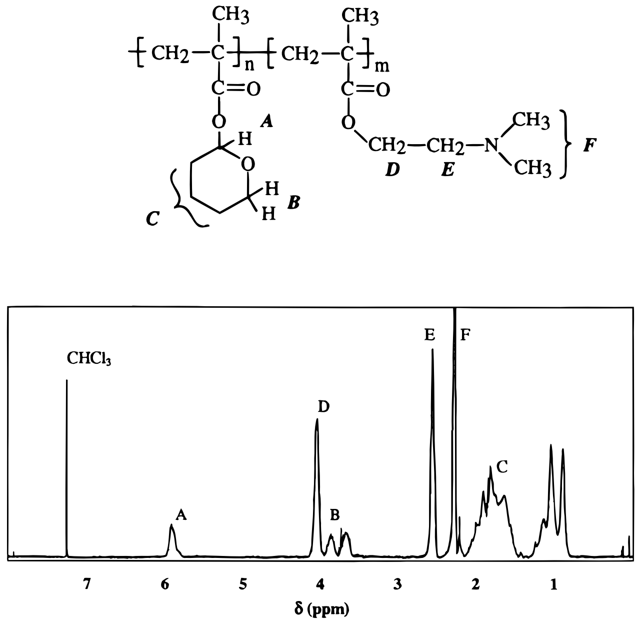
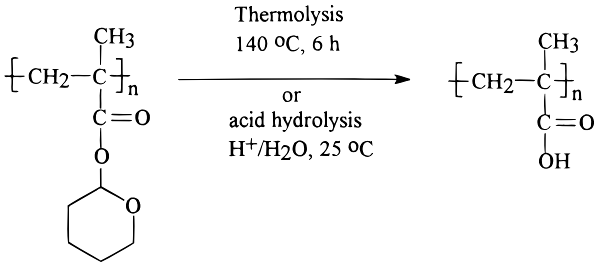


Figure 2. ^{1}H NMR spectrum of a 64−36 DMAEMA-*block*-THPMA copolymer recorded in $CDCl_3$.

Scheme 1. Conversion of PTHPMA to PMAA via Thermolysis and Acid Hydrolysis



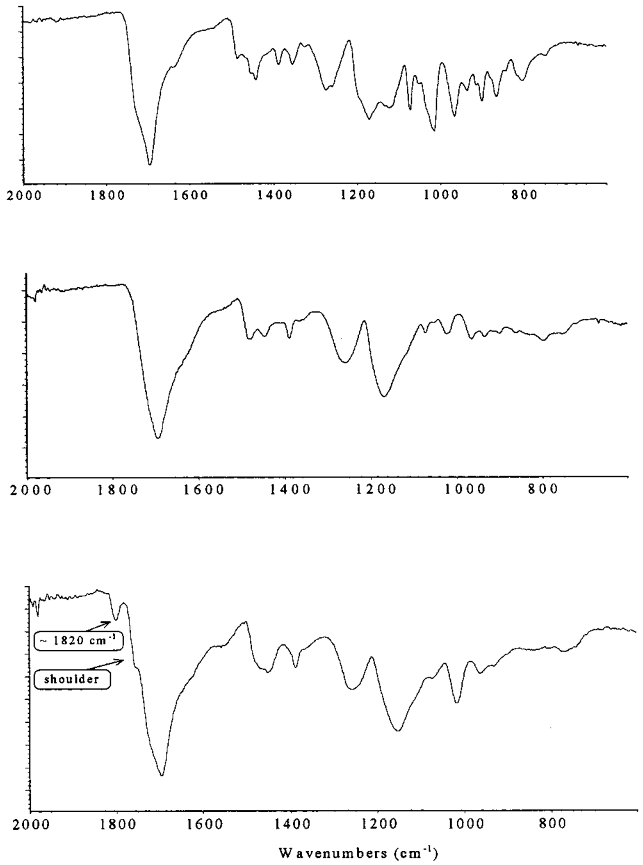


Figure 3. FTIR spectra of (a) THPMA homopolymer, (b) PMAA obtained from the thermolysis of THPMA homopolymer for 4 h, and (c) "PMAA" obtained from the thermolysis of THPMA homopolymer for 48 h. The additional band at 1820 cm^{-1} indicates methacrylic anhydride formation.

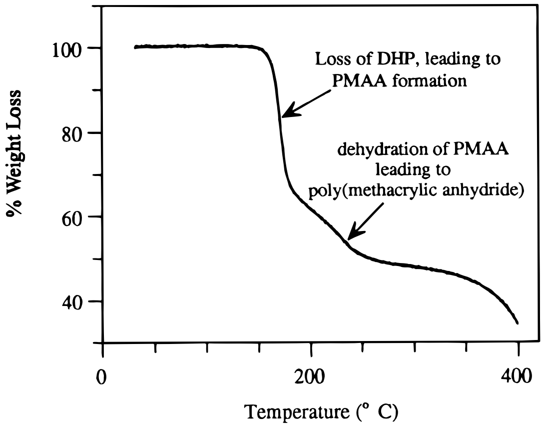


Figure 4. TGA trace of a THPMA homopolymer, showing the initial loss of the THP protecting group and the subsequent dehydration of the PMAA to poly(methacrylic anhydride).

Scheme 1. Initially, the thermolysis route was favored since this simply involved heating the bulk copolymer at 145 °C under vacuum, as outlined by Patrickios et al.[16] However, problems were encountered with this route. In preliminary experiments on THPMA homopolymer,[14] it was found that thermolysis under vacuum for 3−4 h (rather than 48 h, as reported by Patrickios et al.) at the required temperature was sufficient for complete conversion to PMAA, as determined via ^{1}H NMR spectroscopy. Subsequently, we found that prolonged heating under vacuum at this temperature, i.e., for 48 h, resulted in dehydration of the desired PMAA residues leading to random anhydride formation. This results in inter- and intrachain cross-linking and reduced solubility in aqueous solution. Qualitative evidence for anhydride formation was obtained from IR spectroscopy. Figure 3a shows an IR spectrum of THPMA homopolymer, and parts b and c of Figure 3 show PMAA's obtained from the thermolysis of this material for 4 and 48 h, respectively. The evidence for anhydride formation[21] is the appearance of a weak band at around 1820 cm^{-1} in Figure 3c. This feature is absent in Figure 3a,b. Similar observations were reported by Grand and Grassie, who investigated the thermal dehydration of PMAA.[22] More recently, Ito and Ueda studied the thermolysis of several polymethacrylates, including poly(α,α-dimethylbenzyl methacrylate). These workers used thermogravimetric analysis (TGA) and IR spectroscopy to show that thermal conversion to PMAA is usually followed by dehydration to poly(methacrylic anhydride).[23] In view of this latter work we carried out our own TGA study. Figure 4 shows the TGA curve obtained for a THPMA homopolymer. Up to ca. 150 °C, the TGA curve shows little or no weight loss. At ca. 150 °C a relatively large weight loss of approximately 45% is observed, which is attributed to the loss of dihydropyran, resulting in the formation of PMAA. At ca. 230 °C a second weight loss is observed, which is assigned to the dehydration of the MAA residues, leading to the formation of random inter- and intrachain anhydride linkages. This is in agreement with the work reported by Rannard et al.,[11] who

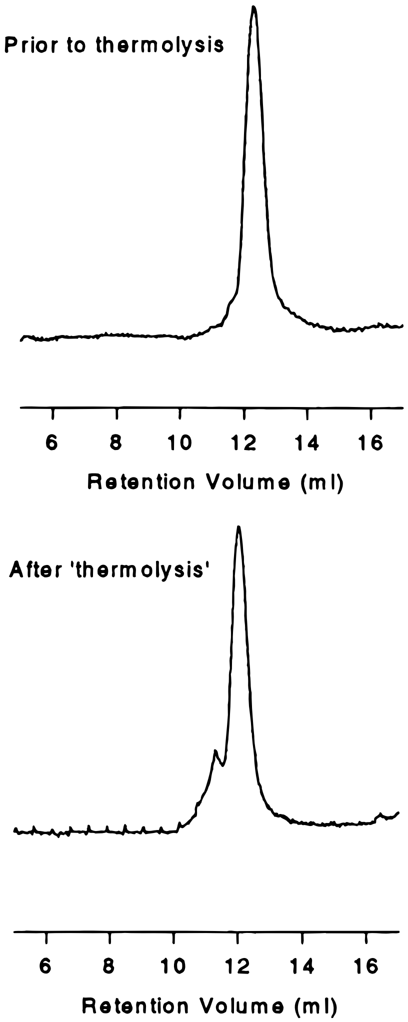


Figure 5. GPC traces of a DMAEMA homopolymer before (M_w = 43 900; M_w/M_n = 1.09) and after (M_w = 55 600; M_w/M_n = 1.29) thermolysis at 140 °C for 4 h.

observed a small weight loss at 240 °C in block copolymers of PMAA with poly(*n*-butyl methacrylate) and attributed it to the formation of poly(methacrylic anhydride).

Having established appropriate conditions for the quantitative thermolysis of PTHPMA to give PMAA, a control experiment was carried out on a DMAEMA homopolymer. Figure 5 shows a GPC trace of this DMAEMA homopolymer prior to and after the thermolysis conditions used for the deprotection of the THPMA residues. Prolonged heating under vacuum resulted in the appearance of a high molecular weight shoulder, resulting in significant broadening of the MWD and hence an increase in the polydispersity from 1.09 to 1.29. This suggests partial cross-linking of the PDMAEMA chains. Although we have no direct evidence, it is highly probable that this side reaction also occurs with the DMAEMA-*block*-THPMA copolymers.[24] Thus, we decided to explore the hydrolysis route.

As reported by Kearns et al.,[19] PTHPMA is readily converted to PMAA by hydrolysis under mild conditions. At neutral pH complete conversion is achieved within 24 h at 70 °C; in the presence of a small amount of mineral acid, the reaction time is reduced to several hours. In the present study 0.1 M HCl was used. For DMAEMA-*block*-THPMA copolymers that were initially insoluble, water-white solutions were usually obtained within 12 h at room temperature under these conditions. As with the thermolysis route, a control experiment was carried out using DMAEMA homopolymer to examine the possibility of side reactions (e.g., hydrolysis of DMAEMA ester residues) under these conditions. Not surprisingly, the DMAEMA homopolymer was unaffected. This observation is consistent with a recent paper by Hoogeveen et al., who found that DMAEMA homopolymer is relatively stable toward hydrolysis (unlike DMAEMA monomer, which was shown to hydrolyze rapidly in water at room temperature).[25] Figure 6 shows the ^{1}H NMR spectrum, recorded in DMSO-d_6, of the 82−18 DMAEMA−MAA zwitterionic copolymer obtained after acid hydrolysis of AB2. Peaks indicative of DMAEMA residues at δ ~4.3 ppm (oxymethylene hydrogens), 3.5 ppm (azamethylene hydrogens), and 2.7 ppm (dimethylamino hydrogens) are apparent, while the carboxylic acid hydrogen is just visible at δ ~12.0 ppm. The absence of any peak at δ ~6.0 ppm, which is associated with the acetal hydrogen of the THPMA ring, confirms that there are no residual THP protecting groups. It is perhaps worth noting that some caution should be taken in verifying the block copolymer composition from this ^{1}H NMR spectrum. It is quite likely that some degree of internal protonation of the tertiary amine groups by the acid groups may occur, which could reduce the relative intensity of the carboxylic acid signal.

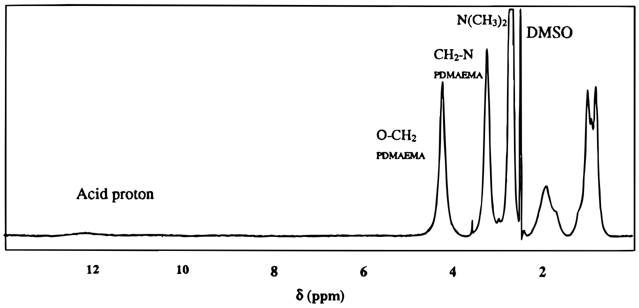


Figure 6. ^{1}H NMR spectrum (DMSO-d_6) of the 82−18 DMAEMA-*block*-MAA copolymer obtained from the acid hydrolysis of a DMAEMA-*block*-THPMA precursor copolymer (AB2).

Characterization in Aqueous Media. Acid Titrations and IEP Determination. A unique property of polyampholytes in solution is their so-called *isoelectric point* (IEP), which represents the pH at which the polyampholyte is electrically neutral and hence usually insoluble. The IEP's were determined by titrating a 1 w/w % solution of polyampholyte (initially adjusted to approximately pH 2 with dilute HCl) with 0.5 M KOH solution. The IEP was taken as the midpoint of the pH range of precipitation. Table 2 lists the experimental IEP's and also the IEP's calculated based on the method reported by Patrickios,[26] using the NMR block copolymer composition and the effective p*K*'s of methacrylic acid (pK_a = 5.35) and DMAEMA (pK_b = 8.00) as reported by Merle.[27] Given the experimental uncertainty in estimating the onset of precipitation, the observed IEP's are in good agreement with the calculated values. For an equimolar block copolymer, i.e. where the number of MAA residues is equal to the number of DMAEMA residues, the theoretical IEP is simply an arithmetic average of the two respective p*K* values. When the copolymer composition is shifted to either acid-rich or base-rich values, then the IEP also shifts toward that p*K*, e.g., for DMAEMA-rich blocks the

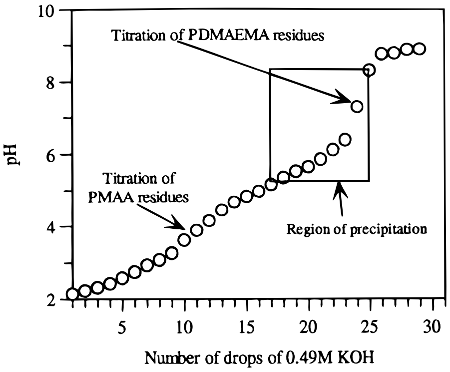


Figure 7. Acid titration curve obtained from the titration of the 51−49 DMAEMA-*block*-MAA zwitterionic copolymer obtained from the acid hydrolysis of AB4.

Table 3. Summary of the Observed Number-Average Molecular Weights and Polydispersities As Determined by Aqueous GPC for Selected DMAEMA-*block*-MAA Copolymers and Nonaqueous GPC for the Corresponding DMAEMA-*block*-THPMA Precursors

DMAEMA content (mol %)	obsd M_n of precursor via GPC (THF)	M_w/M_n of precursor block copolymers via GPC	obsd M_n via AGPC	M_w/M_n AGPC
82	24 700	1.16	10 400	1.18
64	34 000	1.22	13 900	1.21
43	42 400	1.19	16300	1.24

IEP will approach 8.00. Figure 7 shows a typical titration curve obtained for the 51−49 DMAEMA-*block*-MAA copolymer derived from the hydrolysis of AB4, with the precipitation region highlighted. The shape of the curve is typical for polyampholytes, with the lower region corresponding to the titration of the MAA residues and the upper region to the DMAEMA residues.

Aqueous GPC. To confirm that the block copolymers retained their narrow molecular weight distributions after hydrolysis, selected block copolymers were analyzed via aqueous GPC. The results are summarized in Table 3. It is evident that the narrow molecular weight distributions of the precursor DMAEMA-*block*-THPMA copolymers are retained in the resulting DMAEMA-*block*-MAA copolymers. Thus, the aqueous GPC data confirms that acid hydrolysis is the *preferred* route in the preparation of well-defined DMAEMA-MAA diblock polyampholytes via the THPMA precursor. The differences between the observed molecular weights, as determined by aqueous GPC and nonaqueous GPC (THF eluent), are most likely due to the large differences in hydrodynamic volumes of the zwitterionic blocks compared with the nonionic PEO calibration standards used in aqueous GPC (in contrast, the PMMA standards used in conjunction with the THF eluent are expected to be a reasonable approximation to the hydrodynamic volumes of the precursor DMAEMA−THPMA blocks). In addition, the hydrolyzed DMAEMA-*block*-MAA copolymers have significantly lower molecular weights than the DMAEMA-*block*-THPMA precursors due to the loss of the THP groups.

Dynamic Light Scattering (DLS). DLS experiments were carried out to assess the micellization behavior of the DMAEMA-*block*-MAA copolymers. Adjusting the pH of a 1.0 w/w % polyampholyte solution to either above the pK_a of DMAEMA or below the pK_a of MAA should result in the formation of a predominantly anionic or cationic block copolymer. Given that the DMAEMA block exhibits inverse temperature solubility in its nonionized form, it is, in principle, possible to form micelles simply by heating this copolymer solution beyond the cloud point of the DMAEMA block. The micelle cores should then comprise the DMAEMA blocks, with the still-solvated PMAA chains forming the micelle corona. Examination of a 1.0 w/w % solution of a 43−57 DMAEMA−MAA copolymer in 0.01 M NaCl at pH 9.5 by DLS confirmed very weak light scattering and unimer sizes at 25 °C. Heating this solution up to 50 °C produced much more intense light scattering. CONTIN analysis indicated the formation of near-monodisperse aggregates with an intensity-average hydrodynamic diameter of 390 nm, with a corresponding polydispersity of 0.057; see Figure 8. This temperature-induced aggregation is completely reversible. On cooling to room temperature, the intensity of the scattered light decreases dramatically and the block copolymer once again becomes molecularly dissolved. In the absence of salt much larger aggregates with hydrodynamic diameters of ca. 700 nm were formed.[28] The cloud point of a 1.0 w/v % DMAEMA homopolymer solution at pH 9.5 is in the range 32−46 °C depending on its molecular weight.[29] Thus it is likely that the cores of the aggregates formed at 50 °C comprise the now hydrophobic DMAEMA block, with the corona comprising the anionic solvated PMAA chains (see below).

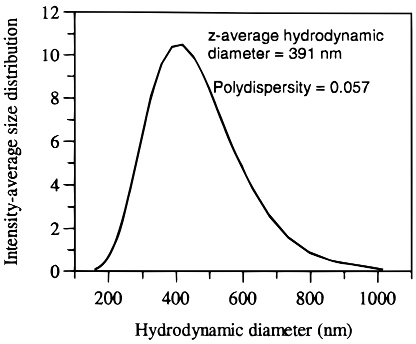


Figure 8. Intensity-average size distribution obtained for a 1.0 w/w % solution of a 43−57 DMAEMA-*block*-MAA zwitterionic copolymer at 50 °C in 0.01 M NaCl at pH 9.5.

Variable Temperature ^{1}H NMR Spectroscopy Studies. ^{1}H NMR spectroscopy was used to further examine the temperature-induced micellization of one of the DMAEMA−MAA zwitterionic copolymers. This technique is complementary to the DLS studies, since it should indicate which of the two blocks (PDMAEMA or PMAA) forms the nonsolvated micelle core at elevated temperature. ^{1}H NMR spectroscopy has been used previously by Forder et al.[30] to probe the micellization behavior of poly(methyl vinyl ether-*block*-methyl triethylene glycol vinyl ether) in aqueous media in the range 20−60 °C. Similarily, Bütün et al.[31] utilized ^{1}H NMR spectroscopy to study the pH-induced aggregation of tertiary amine methacrylate block copolymers at 25 °C. Figure 9 shows ^{1}H NMR spectra of a 1 w/v % solution of a 43−57 DMAEMA−MAA copolymer in 0.01 M NaCl/NaOD/D_2O (pH 9.5) recorded at 25, 40, and 60 °C. The upper spectrum represents the block copolymer at 25 °C. The key features are the peaks at $\delta \sim 2.25$ due to the six dimethylamino protons of the DMAEMA residues, and the peaks at $\delta \sim 2.60$ and $\delta \sim 4.10$ due to the azamethylene and oxymethylene protons of the DMAEMA residues, respectively). The broad peaks at $\delta \sim 0.7-1.7$ represent the methacrylate backbones of

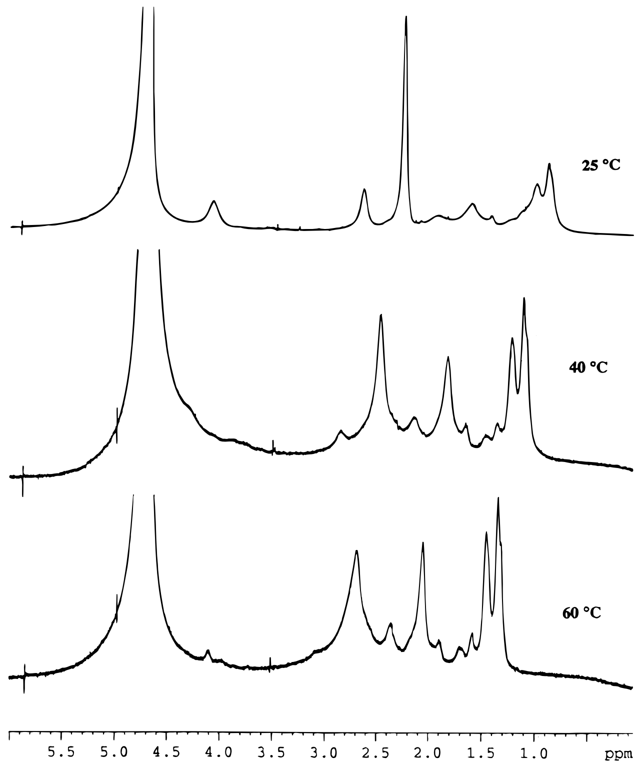


Figure 9. ^{1}H NMR spectra recorded for the 43−57 DMAEMA-*block*-MAA zwitterionic copolymer in 0.01 M NaCl/NaOD/D_2O at (a) 25 °C (upper spectrum), (b) 40 °C (middle spectrum), and (c) 60 °C (lower spectrum). Line broadening of the signals attributed to the DMAEMA residues confirms that these chains form the micellar core at elevated temperature.

both the PDMAEMA and the PMAA blocks. These latter peaks are the only signals that can be assigned to the PMAA block (the carboxylic acid proton is not observed due to rapid solvent exchange with the D_2O). As the temperature is raised to 40 °C all peaks, with the exception of the solvent peak, broaden and shift downfield. In addition, the intensities of the DMAEMA signals decrease relative to the methacrylate backbone signals. The NMR spectra confirm that the degree of solvation and the mobility of the DMAEMA residues decreases significantly with increasing temperature. This is consistent with the onset of micellization and indicates that the now hydrophobic DMAEMA block forms the micelle core, as expected. It is noteworthy that the most intense peak associated with the DMAEMA block (due to the six dimethylamino hydrogens, originally at $\delta \sim 2.25$) is still visible, even at 60 °C. This indicates that the DMAEMA block remains partially solvated, i.e., the micellar cores are still partially hydrated. On cooling this solution to 25 °C, the micelles dissociated into unimers and the original NMR spectrum was obtained. This confirms that the micellization is reversible. This is consistent with the work reported by Forder et al.[30] Block copolymers of methyl vinyl ether with methyl triethylene glycol vinyl ether exhibited similar temperature-dependent micellization, with the methyl vinyl ether block forming the micelle core. ^{1}H NMR spectroscopy studies clearly showed that water was still present in these micellar cores even at temperatures well beyond the cloud point of the methyl vinyl ether. On the other hand, Bütün et al.[31] have shown that tertiary amine methacrylate block copolymers form micelles with nonsolvated cores in aqueous solution, since NMR studies confirmed complete disappearance of all the proton signals associated with the less hydrophilic micellizing block.

Conclusions

A series of diblock copolymers of 2-(dimethylamino)ethyl methacrylate (DMAEMA) and 2-tetrahydropyranyl methacrylate (THPMA) have been synthesized via group transfer polymerization. Good control over molecular weight and copolymer composition was achieved. Subsequent quantitative deprotection of the THPMA residues results in well-defined zwitterionic DMAEMA−MAA block copolymers. It is shown that the preferred method of deprotection is acid hydrolysis; the alternative thermolysis route led to partial dehydration of the MAA residues under the conditions described by Patrickios et al. Furthermore, control experiments suggest the likelihood of side reactions associated with the DMAEMA residues. Aqueous GPC was utilized to confirm that the molecular weight distributions of the deprotected block copolymers remained narrow. This is not surprising considering the mild conditions employed. Dynamic light scattering indicated that the DMAEMA−MAA block copolymers formed micelles in alkaline solution at elevated temperatures. Smaller, more well-defined micelles are formed in the presence of 0.01 M NaCl. Variable temperature ^{1}H NMR studies confirm the formation of micelles and also indicates that it is the DMAEMA block that forms the micelle cores. Presumably, the MAA block forms the solvated corona. The micellar cores remain partially solvated even at 60 °C and, on cooling, the micelles dissociate to form molecularly dissolved copolymer chains. This temperature-induced micellization is also fully reversible.

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