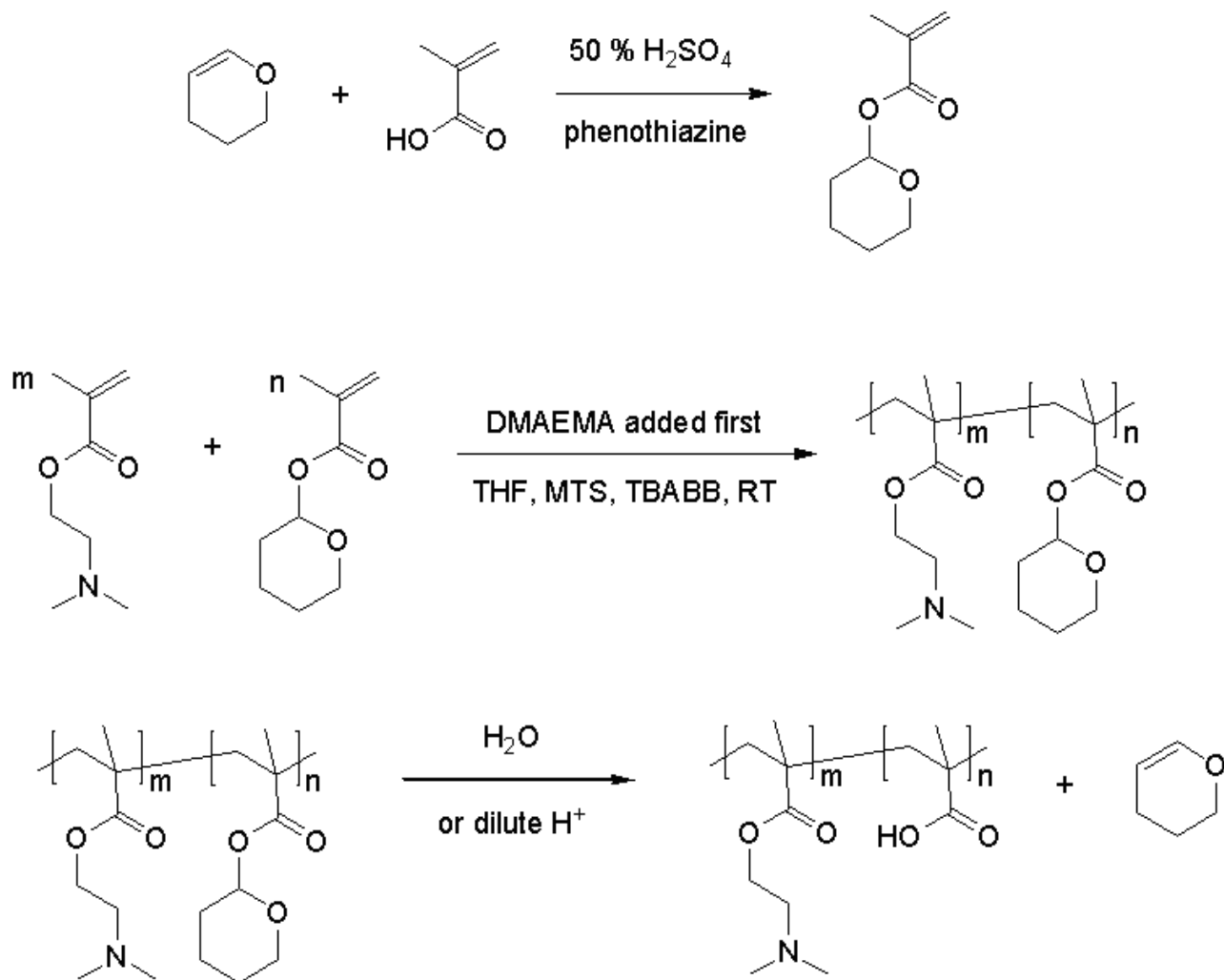


# Synthesis of AB Diblock Polyampholytes via GTP

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## 1. Procedure

### Materials:

Unless stated otherwise, all chemicals were purchased from Aldrich. 2-(Dimethylamino)-ethyl methacrylate (DMAEMA) was purified by passing through a column of basic alumina to remove the inhibitor, stored over CaH<sub>2</sub> 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 nitrogen atmosphere at below 0°C. The catalyst, tetra-*n*-butylammonium bibenzoate (TBABB), was prepared in-house according to the method of Dicker *et al.*<sup>2</sup>, and was stored as a solid under vacuum. The polymerization solvent, THF, was dried over sodium wire prior to reflux over potassium metal for three days. This THF was

collected under a dry nitrogen purge and stored over 4 Å molecular sieves under a nitrogen atmosphere.

*a. Synthesis of 2-tetrahydropyranyl methacrylate (THPMA)*

THPMA was prepared by the acid-catalyzed esterification of methacrylic acid (MAA) with 3,4-dihydro-2*H*-pyran using a modification of the method of Hertler.<sup>3</sup> To a 1 L, three-necked, round-bottomed flask equipped with a magnetic stir-bar, reflux condenser, inert gas inlet, and addition funnel was added 3,4-dihydro-2*H*-pyran (125 mL, 1.37 mol) and 10 drops of 50% sulfuric acid. This mixture was stirred at room temperature for approximately 20 min. A mixture of MAA (116 mL, 1.49 mol), 3,4-dihydro-2*H*-pyran (125 mL, 1.37 mol), and phenothiazine (1.0 g, 5.0 mmol) 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 (10.0 g, 0.119 mol) and anhydrous sodium sulfate (40.0 g, 0.282 mol) were added and the reaction mixture was left stirring overnight. The mixture was filtered and treated with CaH<sub>2</sub> (1.0 g, 23.8 mmol), phenothiazine (1.0 g, 5.0 mmol) and 2,2-diphenyl-1-picrylhydrazyl (DPPH, 0.2 g, 0.51 mmol). The excess 3,4-dihydro-2*H*-pyran was removed under reduced pressure. The remaining mixture was distilled at 70°C under reduced pressure, yielding approximately 100 mL of THPMA. THPMA was then further purified by passing over a column of basic alumina to remove residual traces of MAA. Two subsequent vacuum distillations, from CaH<sub>2</sub>/DPPH, yielded THPMA of sufficient purity for GTP.

*b. GTP synthesis of the DMAEMA-THPMA AB diblock copolymers*

All glassware was dried overnight at 150°C and assembled hot under a nitrogen 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 transfers. All liquid transfers were performed using double-tipped needles. Polymerizations were carried out at room temperature (~22°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 (~20.0 mg), was added as a solid through a sidearm of the polymerization flask. This was added to MTS (typically 0.20 mL, 1.62 mmol), and the reaction mixture was stirred for approximately 30 min. Subsequently, freshly distilled DMAEMA (10.0 mL, 59.3 mmol) 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

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exotherm monitored. Finally, once the reaction had cooled to room temperature, a small aliquot of the diblock copolymer was extracted for GPC analysis. The block copolymer was isolated by removing the THF under vacuum, followed by drying *in vacuo* overnight at room temperature.

### *c. 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 for ~24 h. Alternatively, for acid hydrolyses, the copolymer (~2.0 g) was stirred in 0.1 M HCl until dissolution, giving an optically transparent solution.<sup>4,5,6</sup> 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 form.

### *d. (Co)polymer characterization*

**Characterization in Organic Solvents by GPC.** Molecular weights and polydispersities of the precursor PDMAEMA homopolymers and the DMAEMA-*block*-THPMA copolymers were determined by gel permeation chromatography (GPC) 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<sup>-1</sup>. The GPC was calibrated with a series of four PMMA standards with molecular weights ranging from 2000 to 29,400.

**<sup>1</sup>H NMR Spectroscopy.** <sup>1</sup>H NMR spectra were recorded using a Bruker AC-P250 Fourier transform NMR spectrometer. Spectra were recorded in either CDCl<sub>3</sub> or DMSO-*d*<sub>6</sub> using residual nondeuterated solvent (CHCl<sub>3</sub> or DMSO) as an internal reference.

**Characterization in Water by 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<sup>3</sup> of 1.0 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<sup>-1</sup>.

The column temperature was maintained at 30°C. A series of poly(ethylene oxide) standards were used as calibrants.

## 2. Results

| sample ID | theor $M_n$ | obsd $M_n^a$ | theoretical composition | molar | observed composition <sup>b</sup> | molar | $M_w/M_n^a$ |
|-----------|-------------|--------------|-------------------------|-------|-----------------------------------|-------|-------------|
| 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        |

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

<sup>a</sup> As determined by GPC. <sup>b</sup> As determined by <sup>1</sup>H NMR spectroscopy.

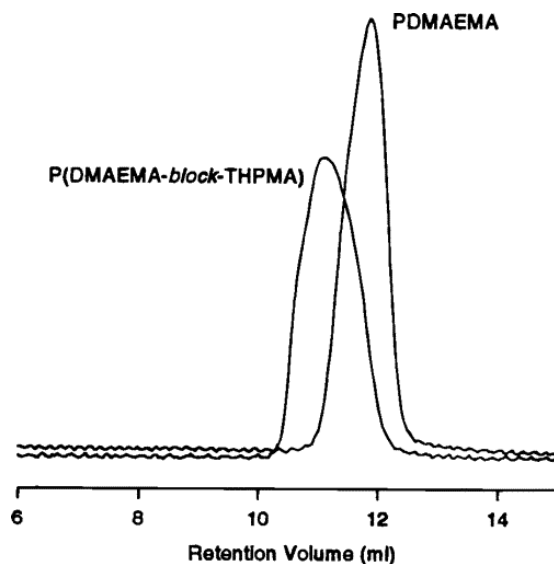


Figure 1. Typical GPC traces of a DMAEMA homopolymer and the corresponding DMAEMA-*block*-THPMA copolymer in THF.

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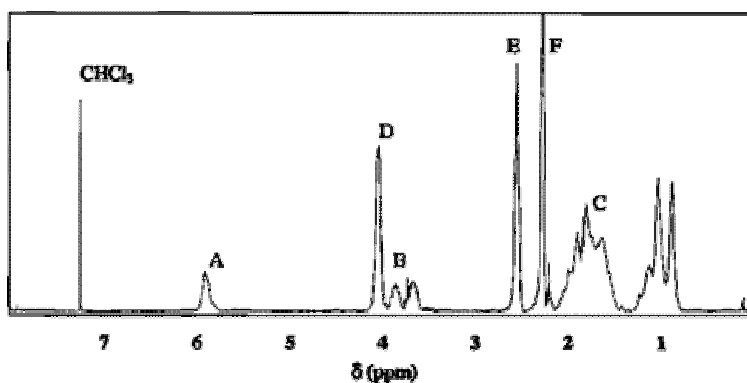
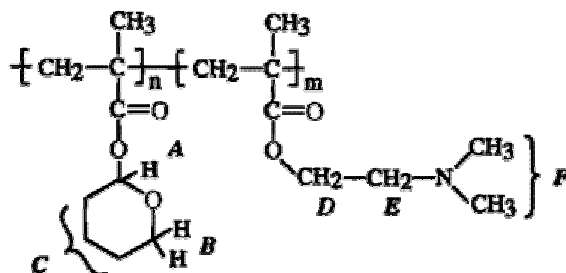


Figure 2.  $^1\text{H}$  NMR spectrum of a 64-36 DMAEMA-block-THPMA copolymer recorded in  $\text{CDCl}_3$

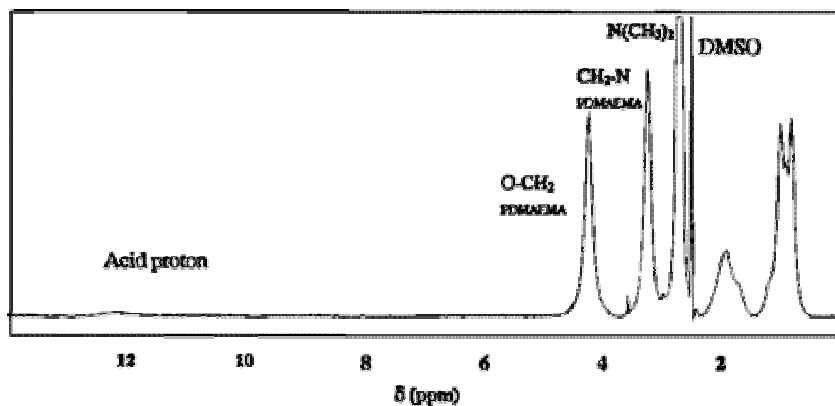


Figure 3.  $^1\text{H}$  NMR spectrum ( $\text{DMSO-d}_6$ ) of the 82-18 DMAEMA-block-MAA copolymer obtained from the acid hydrolysis of a DMAEMA-block-THPMA precursor copolymer (AB2)

| sample ID | block copolymer composition DMAEMA:MAA | calcd IEP | obsd IEP <sup>a</sup> |
|-----------|--|-----------|-----------------------|
| 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                  |

Table 1. Summary of the Calculated and Observed Isoelectric Points of the Zwitterionic DMAEAM-block-MAA Copolymers

<sup>a</sup> Taken as the midpoint of the precipitation range.

### 3. NOTES

1. Since THPMA is prepared using an excess of MAA, it is crucial that the THPMA be sufficiently pure since any residual MAA will 'kill' the polymerization.
2. While the THP protecting group may be removed by either thermolyses or acid hydrolysis, the hydrolysis route is the preferred method of choice. Thermolysis of PTHPMA homopolymer for an extended period (24 h) did indeed lead to the formation of PMAA, but also to the subsequent dehydration of the PMAA residues to form both inter- and intramolecular anhydride linkages.
3. The resulting DMAEMA-MAA, and precursor DMAEMA-THPMA block copolymers, exhibit interesting aqueous solution properties and also facilitate the preparation of zwitterionic shell-cross linked micelles.<sup>6,7</sup>

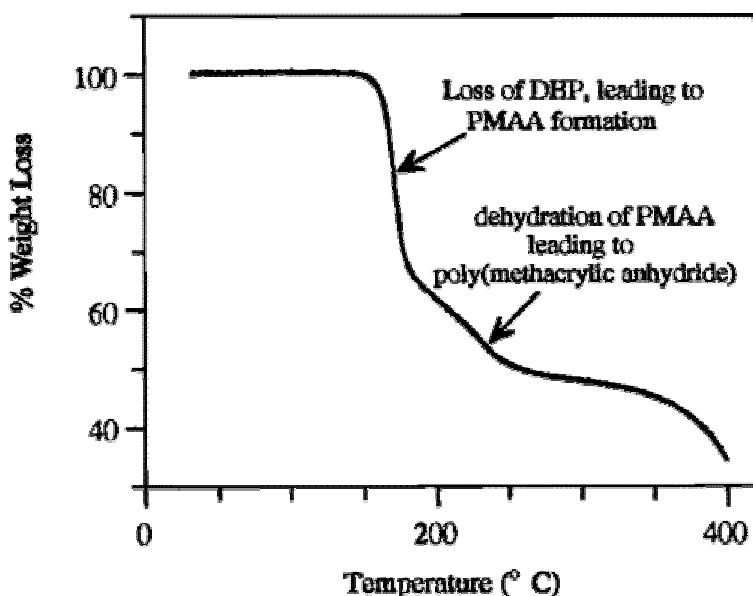


Figure 4. TGA trace of a THPMA homopolymer, showing the initial loss of the THP protecting group and the subsequent dehydration of the PMAA to poly(methacrylic anhydride)

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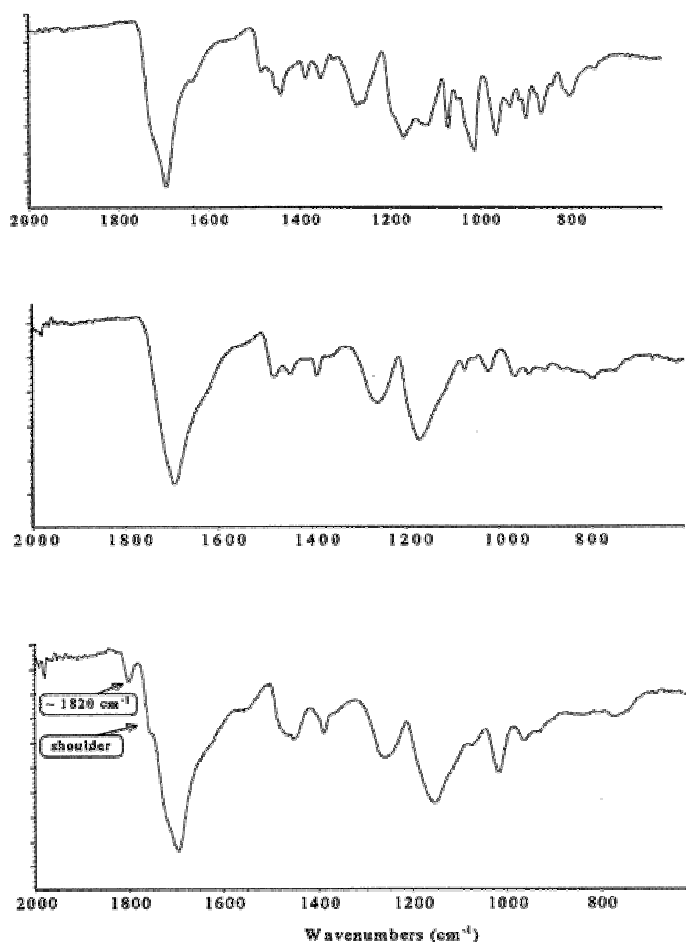


Figure 5. FTIR spectra of (a) THPMA homopolymer, (b) PMAA obtained from the thermolysis of THPMA homopolymer for 4 h, and (c) "PMAA" obtained from the thermolysis of THPMA homopolymer for 48 h. The additional band at 1820 cm<sup>-1</sup> indicates methacrylic anhydride formation

## 4. References

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