

Novel pH Responsive Amphiphilic Diblock Copolymers with Reversible Micellization Properties

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Abstract— Di-block copolymer of poly[methacrylic acid-*block-2*-(diethylamino)ethyl methacrylate] [P(MAA-*b*-DEA)] with narrow molecular weight distribution was synthesized using the atom transfer radical polymerization (ATRP) technique. The micellization behavior of the P(MAA-*b*-DEA) copolymer in aqueous solution at room temperature and different pH values were examined by potentiometric and conductivity titration, UV-Visible spectrophotometry, ¹H-NMR, static and dynamic laser light scattering. At low pH (< 4.2), core-shell micelles were formed with MAA core and protonated DEA shell. At moderate pH values, the polymer precipitated from water and formed a cloudy solution, where the polymer chains aggregated into larger particles resembling that of a hard sphere induced by electrostatic interactions. At high pH (> 9.5), core-shell like micelles consisting of hydrophobic DEA core and ionized MAA shell were re-established.

Index Terms— ATRP, laser light scattering, P(MAA-*b*-DEA), stimuli-responsive

I. INTRODUCTION

The stimuli-responsive water-soluble and amphiphilic polymers have attracted much interest since their micelles can be produced or destroyed by changing the temperature, pH, ionic strength, and solvent polarity.^{1,2} Recently, several research groups have reported on the reversible micellization behavior of block copolymers in solution.³⁻¹⁰ Laschewsky and Armes groups have successfully synthesized di-block copolymers of poly(N-

isopropylacrylamide-*block-3*-(N-(3-ethacrylamidopropyl)-N, N -dimethyl)ammonio propane sulfonate) (P(NIPAM-*b*-SPP)) and poly(2-(N-mor-pholino)ethyl methacrylate-*block-2*-(sulfobetaine-dimethylamino)ethyl methacrylate) (P(MEMA-*b*-SBMA)) by reversible addition fragmentation chain transfer (RAFT) and atom transfer radical polymerization (ATRP) respectively.^{3,4} By linking segments that possess lower critical solution temperature (LCST) and upper critical solution temperature (UCST) properties, temperature-responsive block copolymers could be produced. With increasing temperature, micelles containing SPP or SBMA hydrophobic core were converted to unimers, which then re-established their micellar structure consisting of NIPAM or MEMA core respectively. Armes and co-workers also reported studies on di-block copolymers with temperature- and pH-responsive reversible aggregation properties of the poly(2-(dimethylamino)ethyl methacrylate-*block*-methacrylic acid) (P(DMA-*b*-MAA)) synthesized using group transfer polymerization (GTP).^{6,7} Reversible aggregates containing DMA hydrophobic core and ionized MAA hydrophilic corona were produced at pH 9.5 and 50°C. The aggregates has a large hydrodynamic diameter of ~ 400 nm. Other research groups, such as Hatton's and Jerome's have also reported the pH- and temperature-responsive properties of P(DMA-*b*-MAA).^{11,12} Depending on the block composition, salt and pH, the copolymer is either soluble, insoluble or it forms large non-micellar aggregates. Another di-block copolymer with temperature and pH responsive reversible micellization property is the poly(propylene oxide-*block-2*-(diethylamino) ethyl methacrylate) (PPO-*b*-PDEA) synthesized by Armes and co-workers using ATRP.¹⁰ At high temperature (40°C) and low pH (5.5), the micelles with hydrophobic PPO core were formed in aqueous solution, while at low temperature (25°C) and high pH (8.5), micelles containing hydrophobic DEA core were produced. In addition, salt induced pH-responsive block copolymer of P(MEMA-*b*-DEA) was also synthesized by Armes and co-workers using the GTP method.^{8,9} At low pH value (< 6) and high salt

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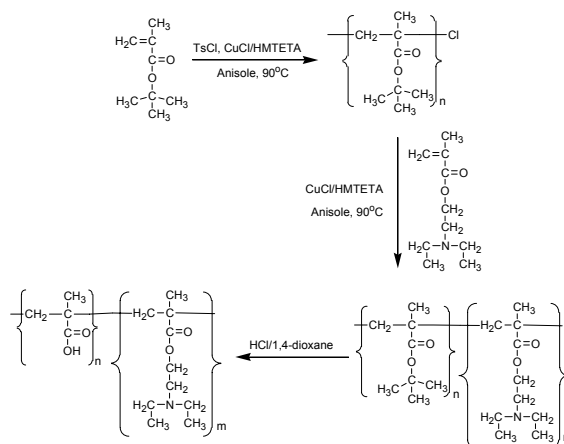
concentration (1 M K₂SO₄), micellar aggregates consisting of hydrophobic MEMA core and DEA corona shell were produced. Removal of salt by dialysis and adjusting the pH to greater than 8 produced reverse micelles containing hydrophobic DEA core and hydrophilic MEMA corona shell. Between the pH of 6 to 8, only unimers were found to exist. Until recently, there is no published report on the reversible micellization behavior induced only by pH changes. As we were finalizing this manuscript, we discovered a recent publication by Armes and co-workers⁵, where they reported the synthesis of poly(4-vinyl benzoic acid-*block*-2-(diethylamino) ethyl methacrylate) (P(VBA-*b*-DEA)) that exhibited pH reversible micellization property. Micelles with hydrophobic VBA core and hydrophilic DEA shell were produced at low pH, while DEA formed the hydrophobic core with VBA as the hydrophilic shell at high pH.

II. EXPERIMENTAL SECTION

We now report the synthesis and the solution behavior of a new pH induced reversible micellization of P(MAA-*b*-DEA). The biocompatibility of MAA and the higher hydrophobicity of DEA as compared to DMA at high pH make this an polymeric attractive system. As far as we are aware, this is the first reported study on P(MAA-*b*-DEA). This copolymer system is believed to have potential for drug delivery applications due to the biocompatibility of MAA and DEA. In this P(MAA-*b*-DEA) copolymer, one of the segments is a weak acid and the other a weak base (pK_a 7.3 for DEA and pK_a 5.4 for MAA).¹³ The DEA block could be protonated at low pH making this segment hydrophilic, while the MAA block could be ionized and becomes soluble at high pH. Since either block has different pK_a values and different chain lengths, the hydrophile-lipophile balance (HLB) of the block copolymer at high or low pH values are different.

The P(MAA-*b*-DEA) was synthesized by ATRP technique using protecting group chemistry, followed by hydrolysis in acid condition. The synthetic scheme is outlined in Scheme 1. For the first time, we have demonstrated the synthesis of a well-defined block copolymer using either poly(*tert*-butyl methacrylate) (PtBMA) or PDEA as the macroinitiators. In the first step, well-defined Cl-terminated PtBMA macroinitiator (M_n = 13000 Da & Mw/M_n = 1.11) was synthesised using *p*-toluene sulfonyl chloride as an a initiator and CuCl complexed with N,N,N',N',N'',N''-hexamethyltriethylenetetraamine (HMTETA) as a catalyst in 50 vol% anisole at 90°C. The resulting P(tBMA)-Cl was used as a macro-initiator to synthesize the block copolymer with DEA using the same reaction condition as in the homopolymer. The well-defined P(tBMA-*b*-DEA) had a M_n of 24800 Da and Mw/M_n of 1.22. P(MAA-*b*-DEA) was obtained by specific hydrolysis in acid condition (HCl/1,4-dioxane). Under this condition, DEA is insensitive towards hydrolysis.¹⁴ The complete hydrolysis of the P(tBMA-*b*-DEA) was confirmed by FTIR. The ¹H NMR spectrum (Figure 1) of the block copolymer

(unhydrolyzed) allows the degree of polymerization of the individual blocks to be determined from the relative intensity of the peaks at 1.45 ppm (-C(CH₃)₃ of the tBMA block) and 2.60-2.74 ppm (-N(CH₂)₃ of DEA block). Based on the GPC and NMR results, the composition of the block copolymer was obtained. The copolymer is represented by P(MAA₉₅-*b*-DEA₆₅).



Scheme 1. Synthetic outline for P(MAA-*b*-DEA)

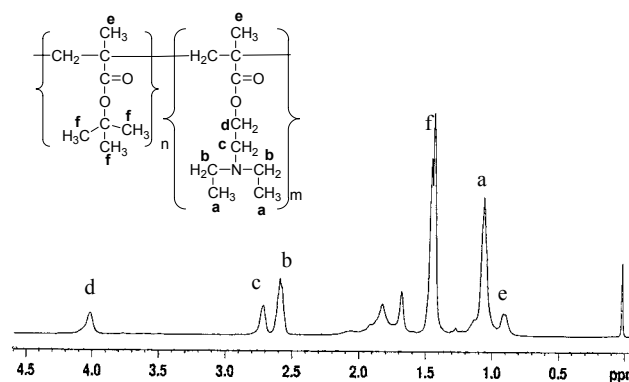


Figure 1. ¹H-NMR spectrum of P(tBMA-*b*-DEA) in CDCl₃

Figure 2 shows the potentiometric and conductivity titration curves of 0.04 wt% P(MAA-*b*-DEA) with NaOH at 25°C. Two transition points (pH ~ 4.2 and 9.8) indicated by “A” and “B” were evident in the conductivity curve. The first transition corresponds to the beginning of the neutralization of -COOH groups of MAA segment, while the second transition is related to the end of the deprotonation on the DEA block. During the titration, it was found that the transparent solution at low pH values becomes cloudy at moderate pH (between 6 to 9), but turned transparent again at high pH. The % transmittance at wavelength of 488 nm was used to monitor the turbidity associated with the phase behavior at different pH values (Figure 3). It is evident that the solution is transparent at the two extreme pH values, i.e. pH < 5.5 and pH > 9.2.

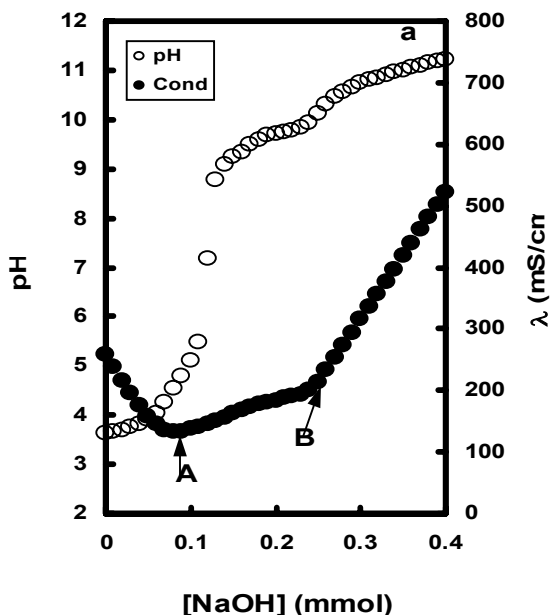


Figure 2. The potentiometric titration of 0.05 wt% P(MAA-*b*-DEA) by NaOH at 25°C.

Between pH range of 5.5 to 9.2, the solution becomes cloudy, with the maximum turbidity observed at pH 7.5. From the potentiometric and conductivity titration results, it is clear that the phase separation occurs after the neutralization of MAA segment and before the deprotonation of DEA segment.

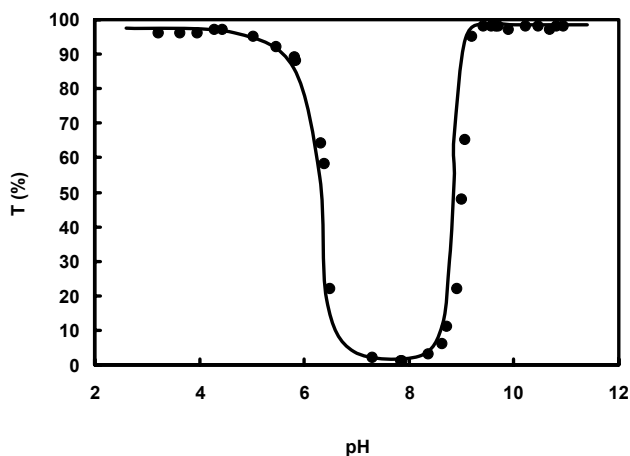


Figure 3. The UV-Vis transmittance of 0.05 wt% P(MAA-*b*-DEA) at different pHs.

Based on the chemical structure and the observed phenomena described above, pH-dependent reversible micelles are produced at low pH (Figure 2, below “A”) and high pH (Figure 2, above “B”) solutions. In the titration, the added NaOH first neutralizes the free HCl, followed by the neutralization of MAA segment (between 0 to 0.08 mmol of NaOH). At low pH (below point “A”), micelles of hydrophobic MAA core and protonated DEA

corona shell are formed. By increasing the pH beyond point “A”, the -COOH groups of MAA segment are progressively neutralized, thereby producing more hydrophilic -COO- groups. These -COO- groups interact with the protonated DEA segments through electrostatic attraction, which giving rise to the precipitation of the polymer in solution. As the pH increases beyond the IEP (iso-electric point)⁵, where the total negative charge equals to total positive charge (at electrically neutral condition), the DEA segment is progressively deprotonated, and the electrostatic balance is destroyed. The cloudy solution turns clear again due to the formation of reverse micelles containing deprotonated hydrophobic DEA core and neutralized hydrophilic MAA corona shell. Beyond point “B”, the DEA segment is completely deprotonated and only NaOH dilution is observed henceforth.

The ¹H NMR spectra of the P(MAA-*b*-DEA) at low and high pH are shown in Figure 4a. In the spectrum recorded at low pH, the signals at 1.29 (-CH₃), 3.29 (-N(CH₂CH₂)₂), and 3.62 ppm (-NCH₂CH₂-) correspond to the characteristic of DEA segments. These peaks are clearly detected in the ¹H-NMR spectrum indicating that the DEA block is solvated in the solvent (D₂O/DCI). At high pH value (adjusted using NaOD), all the DEA peaks have disappeared and only the -CH₃ protons of methacrylic acid at 0.76-0.89 ppm are observed. This confirms that reversible micelles are formed since the non-solvated DEA block is now in the core and the solvated methacrylic acid block forms the shell of the micelles.

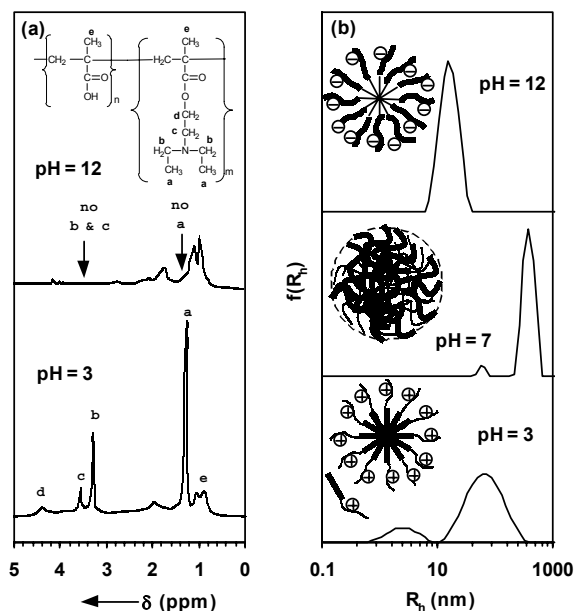


Figure 4. (a) ¹H NMR of P(MAA-*b*-DEA) at low pH and high pH values, and (b) The hydrodynamic radius distributions and the possible structures of P(MAA-*b*-DEA) at different pH values.

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The micellization behavior of the block copolymer at different pH was also studied by laser light scattering (Figure 4b). At low pH of 3, the dynamic light scattering (DLS) data revealed two translational diffusion modes in the decay time distribution functions. Based on the Stokes-Einstein relationship, the hydrodynamic radii of two species determined to be 2.7 nm and 70 nm, were for the unimers and micelles respectively. The composition of the unimers is estimated to be about 8 %wt. The radius of gyration R_g determined from static light scattering (SLS) was found to be 46 nm, giving rise to a R_g/R_h of 0.66, which is smaller than 0.774 for hard sphere. This suggests a thicker hydration layer within the core-shell micelle. Since the HLB value of P(MAA-*b*-DEA) at the prevailing pH value may not be low enough and the pKa of MAA is 5.4, a mixture of unimers and micelles was observed. By increasing the pH from 6 to 9, the solution became cloudy due to phase separation as indicated by the abrupt increase in the scattering intensity. The DLS data indicates the formation of large aggregates with an averaged size of 800 nm. At high pH (> 9), the solution became clear again and the scattering intensity decreased. It was observed the existence of only one narrow q^2 dependent peak in the decay time distribution function. The R_h and R_g were determined to be 17.5 and 12 nm respectively, giving rise to $R_g/R_h = 0.686$, which indicates again that the micelle possesses a core shell structure. Due to the high pKa value of the DEA (7.3) associated with the lower HLB values, the CMC is extremely small. The aggregation number measured using static light scattering technique was found to be ~ 50. The hydrodynamic radius distribution and the possible microstructure of the reversible pH-responsive micelles of P(MAA-*b*-DEA) in solution are shown in Figure 4b. To further clarify the pH dependent micellization properties, electrophoresis, steady fluorescence spectroscopy and time- resolved fluorescence quenching studies are currently in progress.

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