Thermosensitive and pH-Sensitive Polymers Based on Maleic Anhydride Copolymers

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ABSTRACT: Amphiphilic copolymers with thermosensitive and pH-sensitive properties were prepared by grafting methoxy poly(ethylene glycol) (MPEG) of different molecular weights onto alternating copolymers of maleic anhydride with styrene and 4-*tert*-butylstyrene. Aqueous solutions of these graft copolymers exhibit lower critical solution temperatures (LCST). These LCST's are highly sensitive to changes in pH and salinity and to the presence of hydrophobic and hydrogen-bonding additives. The phase transitions are attributed to the cooperative effects of both hydrophobic interactions and intra/intermolecular hydrogen-bonding interactions.

Introduction

Recently, polymer systems that undergo phase transition in response to external stimuli such as changes in temperature and pH have attracted much attention.[1] Aqueous solutions of poly(*N*-isopropylacrylamide), pNIPAM, the most well-known temperature-responsive polymer, exhibit a lower critical solution temperature (LCST) around 32 °C. The reason for this phase transition lies in the balance of hydrophilic and hydrophobic interactions in the system. At low temperature, where water is a good solvent for the polymer, the polymer−solvent interactions are stronger than the polymer−polymer interactions, and the polymer chains are in the expanded "coil" conformation. The solvent quality decreases with increasing temperature, and the polymer−polymer interactions increase due to the hydrophobic interactions. At the Θ-temperature for the system, the polymer−polymer interactions are equal to the polymer−solvent interactions. Above this critical temperature, water becomes a poor solvent for the polymer, and the polymer chains collapse into compact "globules" and phase separation takes place.[2−5] Hence, any factor affecting the polymer−solvent, polymer−polymer, or solvent−solvent interactions will influence the phase transition temperature. For example, the LCST of NIPAM copolymers usually increases with copolymerization of hydrophilic monomers and decreases with incorporation of hydrophobic monomers.[6] However, Cho et al. found that the LCST of poly(*N*,*N*-(dimethylamino)ethyl methacrylate) copolymers decreased with increasing hydrophilic comonomer content, which was attributed to the enhanced intra/intermolecular hydrogen bonding.[7,8]

Amphiphilic graft copolymers have been extensively studied due to their wide applications in cosmetics, foods, coatings, and pharmaceuticals. They can be used to modify viscosity and interfacial structures and to encapsulate active compounds in controlled delivery systems. Polymers with hydrophobic backbones and with poly(ethylene oxide) grafts are among the most studied amphiphilic graft copolymers.[9,10] One of the questions in the area of amphiphilic graft copolymers has been the nature of the association of the polymer chains in aqueous solutions, which has been described as monomolecular as well as polymolecular micelles and also higher order aggregates.[11,12] Particular attention has been given to the solution properties of amphiphilic copolymers based on maleic anhydride copolymers, as these polymers are widely used as surfactants and materials for biomedical applications.[11−18]

In this study, we describe the temperature- and pH-responsive properties of poly(ethylene glycol) (PEG) grafted amphiphilic copolymers based on alternating copolymers of maleic anhydride with styrene and 4-*tert*-butylstyrene, respectively. The phase transitions of the resulting amphiphilic graft copolymers are attributed to the combination of hydrophobic interactions and intra/intermolecular hydrogen bonding. These copolymers have potential applications in developing new types of hydrogel and surfactants with pH/temperature-responsive properties.

Experimental Section

Materials. Styrene, 4-*tert*-butylstyrene, maleic anhydride, methoxy poly(ethylene glycol) of different molecular weights, and butyllithium (1.60 mol L^{-1} in hexane) were purchased from Aldrich. Maleic anhydride was recrystallized in chloroform before use; others were used as received. 2,2′-Azobis(isobutyronitrile) (AIBN) was obtained from American Polymer Standards Laboratories and recrystallized in methanol. The solvents, methyl ethyl ketone (MEK), tetrahydrofuran (THF), and anhydrous diethyl ether, were obtained from Caledon. The THF solvent was dried by refluxing with metallic sodium followed by distillation.

Preparation of Maleic Anhydride Copolymer. The styrene-*alt*-maleic anhydride copolymer (SMA) and the 4-*tert*-butylstyrene-*alt*-maleic anhydride copolymer (*t*BSMA) were prepared by solution copolymerization of styrene/maleic anhydride or 4-*tert*-butylstyrene/maleic anhydride.

4.91 g of maleic anhydride (0.05 mol) was dissolved in 100 mL of MEK in a 120 mL glass flask. 5.25 g of styrene (99%, 0.05 mol) was added. The solution was deoxygenated with nitrogen, and 0.055 g of AIBN (3.35×10^{-4} mol) was added. The polymerization was carried out at 70 °C for 7 h. The polymer product was precipitated in 500 mL of diethyl ether and dried in a vacuum. 6.25 g of product was obtained, in a yield of 62%. *t*-BSMA was prepared by the same procedure.

Preparation of Grafted Amphiphilic Copolymers. For a typical procedure, a solution of lithium alcoholate obtained by reacting 1.80 g (5.14×10^{-3} mol) of methoxy poly(ethylene glycol) (M_n: 350) with 3.2 mL of 1.6 mol L^{-1} butyllithium (5.12×10^{-3} mol) in 10 mL of THF was added dropwise to a solution of 1.0 g of SMA (4.95×10^{-3} mol) in 100 mL of THF. The reaction was carried out at room temperature under a nitrogen atmosphere for 24 h. The grafted copolymer was precipitated

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Table 1. Composition and LCST's of Graft Copolymers

graft polymer[a]	M_n of MPEG	MPEG/styrene units[b] (mol/mol)	LCST[c] (°C)
SMA-*g*-PEG160	164	0.96	not water-soluble[d]
SMA-*g*-PEG350	350	0.96	40.5
SMA-*g*-PEG550	550	0.98	65.8
SMA-*g*-PEG750	750	0.95	74.7
*t*BSMA-*g*-PEG350	350	0.98	33.7

[a] M_n(PDI) of SMA: 25 000 (2.1); M_n (PDI) of tBSMA: 63 000 (4.3). [b] Estimated from ^{1}H NMR. [c] LCST was measured at pH 3.00. [d] Below pH 4.50, even at 0 °C.

into 500 mL of diethyl ether and dried in a vacuum oven at 40 °C for 48 h. 2.60 g of grafted product was obtained (yield: 95%).

Characterization of Polymers. FT-IR spectra were measured on a Bio-RAD FTS-40 spectrometer using KBr pellets. ^{1}H NMR spectra were recorded on a Bruker AC 200 using D_2O as the solvent. The molecular weights of the maleic anhydride copolymers were determined using a size exclusion chromatograph consisting of a Waters 515 HPLC pump, three Ultrastyragel columns, and a Waters 2414 refractive index detector, using THF as solvent at a flow rate of 1 mL min^{-1}, and narrow disperse polystyrene as calibration standards.

The degree of ionization of the grafted copolymers at different pH's was determined from potentiometric titration curves. 20 mL of 1 wt % aqueous polymer solutions at pH 2.00 was titrated with 0.1 mol L^{-1} NaOH. The degree of ionization is defined as $\alpha = \alpha_N + [H^+]/C_p$, where α_N is the degree of neutralization, C_p is the equivalent concentration of polymer, and $[H^+]$ is the proton concentration and is deduced from the pH of the solution. The titration was performed on an automatic PC-Titrator (Mandel) at room temperature.

Measurement of LCST. The LCST's of amphiphilic grafted copolymer solutions were measured using the cloud point method. An automatic PC-Titrator (Mandel) equipped with a temperature probe and with a photometer incorporating a 1 cm path length fiber optics probe (GT-6LD, MITSUBISHI) was used to trace the phase transition by monitoring the transmittance of a white light beam. The turbidity of solution was recorded as photoinduced voltage, where a reading of about −220 mV corresponded to a transparent solution below the cloud point and a reading close to 0 mV for the system above the cloud point. The phase transition temperature was defined as the inflection point of the mV vs temperature curve, as determined by the maximum in the first derivative. The concentration of the polymer solutions was 1.0 wt %, and the heating rate was 1.0 °C min^{-1}.

Results and Discussion

Wesslén et al. have reported the preparation of MPEG grafted maleic anhydride copolymer by the direct reaction of MPEG with succinic anhydride groups.[10,11] In that reaction, the extent of MPEG esterification of anhydride units in SMA was limited to about 20% at most. In the present work, the grafting was carried out by reacting appropriate MPEG lithium alcoholates with maleic anhydride copolymers. Several amphiphilic copolymers with different styrenic units and different MPEG chain lengths were prepared, and their characteristics are summarized in Table 1.

Figure 1 shows typical IR spectra of both the starting and the grafted copolymers. It confirms that the grafting reaction is very efficient. The spectrum of the styrene−maleic anhydride (SMA) copolymer displays characteristic anhydride peaks at 1780 and 1850 cm^{-1}. In the spectrum of SMA-*g*-PEG350, the anhydride peaks have disappeared, and instead the spectrum shows characteristic absorptions of ester carbonyl at 1730 cm^{-1}, ether at 1106 cm^{-1}, and carboxylic acid at 1605 cm^{-1}.

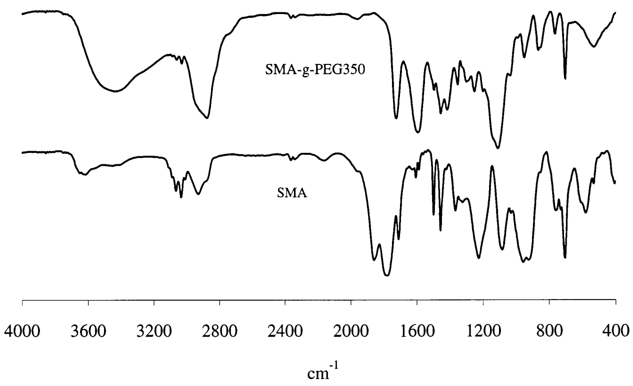

Figure 1. FT-IR spectra of SMA and SMA-*g*-PEG350.

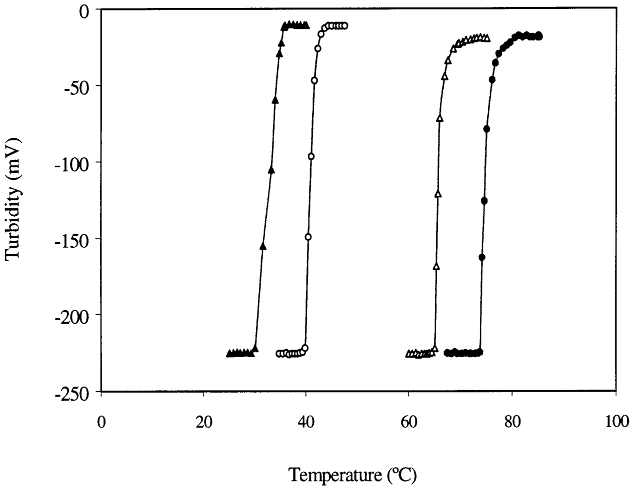

Figure 2. Phase transitions of grafted copolymer solutions at pH 3.00 (▲) *t*BSMA-*g*-PEG350, (○) SMA-*g*-PEG350, (△) SMA-*g*-PEG550, and (●) SMA-*g*-PEG750.

The amount of MPEG in the grafted copolymer is easily estimated from ^{1}H NMR spectra. ^{1}H NMR spectra (not shown) of the graft copolymers reveal a broad aromatic resonance at $\delta = 7.2$ ppm and peaks at $\delta = 3.56$ and 3.24 ppm, corresponding to the ethylene oxide and methoxy units of the PEG grafts, respectively. The extent of MPEG reaction with anhydride units in SMA can be estimated from the ratio of peak areas for methoxy protons (3H) vs phenyl protons (5 H for SMA and 4 H for *t*BSMA). The results are shown in Table 1. For each of the MPEGs studied, nearly complete esterification (>95%) of anhydride units is achieved. The estimated esterification extent is not 100% only because of the partial hydrolysis of SMA. Thus, there is one MPEG grafted chain in almost each repeating unit of the grafted copolymer.

The LCST's of the grafted copolymer solutions are dependent on the length of the grafted poly(ethylene glycol) chains (shown in Table 1 and Figure 2). SMA-*g*-PEG164 has grafted poly(ethylene glycol) chains with molecular weight of 164. This graft copolymer is not water-soluble below pH 4.50, even at 0 °C. Apparently, the hydrogen bonding between the acid groups and the short PEG side chains reduces the polymer−water interactions and prevents solvation of the polymer in acidic conditions.

With increasing length of poly(ethylene glycol), the grafted copolymers become water-soluble even under acidic conditions, and the solutions exhibit LCST's. The phase transition temperatures increase with the increasing PEG chain length (Figure 2), due to the

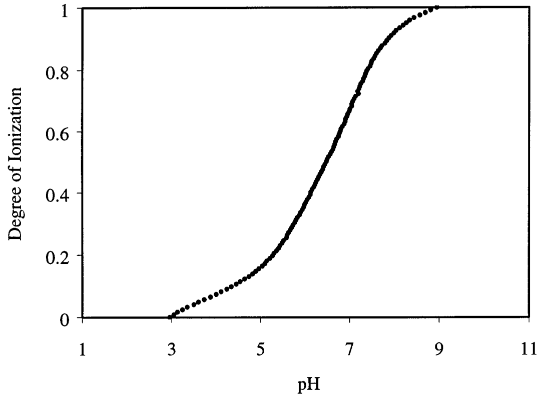

Figure 3. pH dependence of the degree of ionization of SMA-*g*-PEG350.

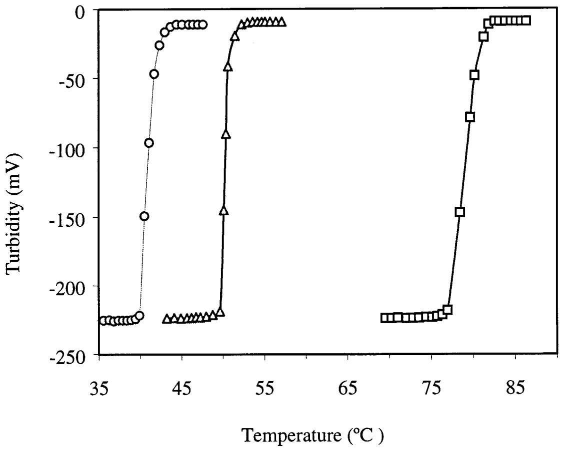

Figure 4. Dependence of the phase transition of SMA-*g*-PEG350 solution on pH: (○) pH 3.00; (△) pH 3.50; (□) pH 4.50.

increasing hydrophilicity of the polymer. Therefore, the poly(ethylene glycol) grafts have two opposing functions: up to the level of carboxylic acid available in the backbone, PEG ether units form intra/intermolecular hydrogen bonds with the acid groups, while any excess PEG is free to hydrogen bond with water. These two functions affect the LCST in opposite ways, depending on PEG/acid ratios.

*t*BSMA-*g*-PEG350 has 4-*tert*-butyl styrene units instead of styrene units. The LCST of *t*BSMA-*g*-PEG350 is 33.7 °C at acidic conditions, about 7 °C lower than that of SMA-*g*-PEG350 under identical conditions (see Figure 2). As expected, the LCST decreases with increasing hydrophobicity of the polymer.

Figure 3 describes the dependence of the degree of ionization on the pH of the solution for SMA-*g*-PEG350. The grafted amphiphilic copolymer is completely protonated at $\mathrm{pH} = 3.00$ and fully ionized at $\mathrm{pH} = 9.00$.

The dependence of the phase separation of SMA-*g*-PEG350 in aqueous solution on pH and degree of ionization is shown in Figures 4 and 5. At $\mathrm{pH} = 3.00$, the LCST is about 41 °C. The LCST increases rapidly with increasing pH of the solution: it is 51 °C at pH 3.50 (about 5% ionization) and 79 °C at pH 4.50 (about 10% ionization). The polymer solution does not exhibit an LCST at pH 5.50 (about 22% ionization). At high pH, the carboxylic acid is ionized, the intra/intermolecular hydrogen bonds are disrupted, and the polymer chains expand due to the electrostatic repulsion between charged sites along the polymer chains. As well, polymer–water interactions increase upon ionization. Together, these effects result in a steep increase of phase transition temperature with the degree of ionization. The solid line in Figure 5 is a second-order polynomial fit to the data points. The dashed line represents its extrapolation, suggesting a maximum degree of ionization that would still permit an LCST of about 12%.

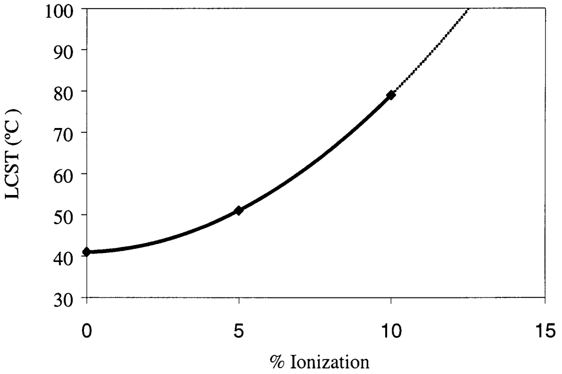

Figure 5. Dependence of the LCST of SMA-*g*-PEG350 on the degree of ionization.

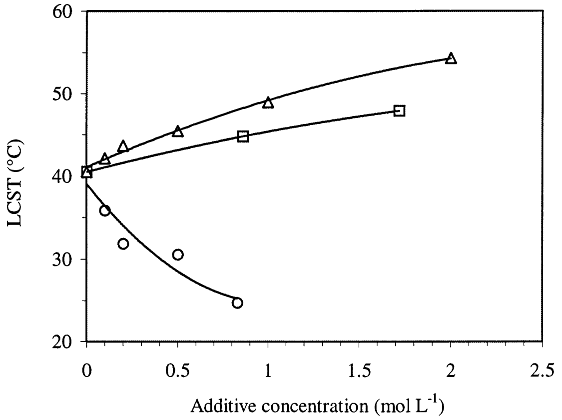

Figure 6. Effects of additives on the phase transition temperature of SMA-*g*-PEG350 in aqueous solution at pH 3.00. Trend lines are second-order polynomials. (○) NaCl; (□) EtOH; (△) urea.

Hoffman compared the phase transition behaviors of analogous random and graft copolymers, poly(acrylic acid-*co*-NIPAM) and poly(acrylic acid-*g*-NIPAM).[19] In the graft copolymer, the hydrophobic and hydrophilic units are separate and behave independently, such that the phase transition temperature of the NIPAM graft was not affected by the amount of hydrophilic acrylic acid units present. The analogous random copolymer, in contrast, showed a strong dependence of the cloud point on the acrylic acid comonomer fraction. For our alternating graft copolymers, the hydrophobic units and hydrophilic units are evenly distributed, such that the effects of incorporating hydrophilic units on the intra/intermolecular interactions should be even larger than that seen in random copolymers. Here, the ionization of the carboxylic groups should not only disrupt the intra/intermolecular hydrogen bonding but also suppress the hydrophobic–hydrophobic interaction between styrene units. This will be studied further in future work.

It is well-known that the effect of salts on the LCST is mainly due to the changes of the water structure by the added salts.[20] As shown in Figure 6, the LCST decreases with the addition of NaCl. NaCl is considered as a water-structure maker and hence shows a “salting-out” effect on the phase transition of grafted amphiphilic

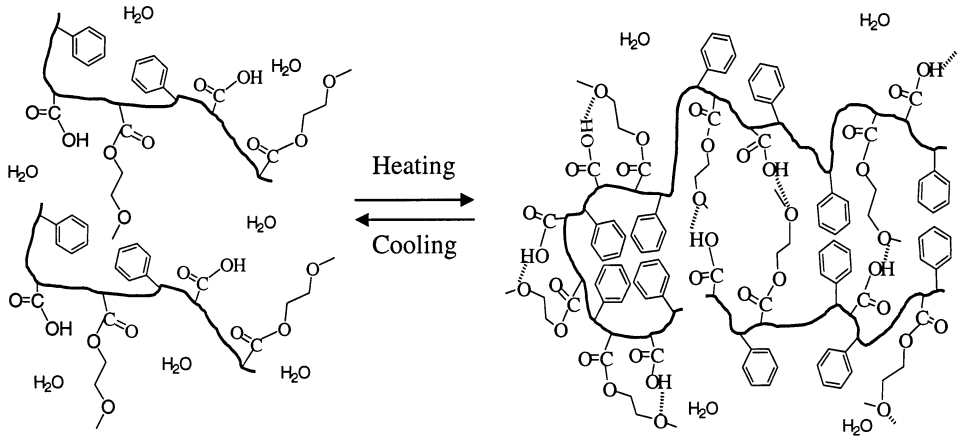

Figure 7. Schematic depiction of the dependence of the phase transition on temperature.

copolymers. With increasing NaCl concentration, the polymer–polymer interactions increase via the hydrophobic interactions of polymers.

Alcohols can disrupt the hydrophobic interactions in the aqueous polymer solutions.[21] With the addition of ethanol, the hydrophobic interactions are suppressed, polymer–water interactions increase, and the LCST shifts to higher temperature (shown in Figure 6).

Urea is known as a hydrogen-bond breaker.[22] With the increase of urea concentration in the solution, the LCST's of the grafted copolymer increase (Figure 6). Compared to the pNIPAM system, in which the urea and its concentration have less effect on the LCST than ethanol,[23,24] the effect of urea on the phase separation temperature of the studied grafted copolymer is obvious. This confirms that the intra/intermolecular hydrogen bonding plays an important role during the phase separation process.

Figure 7 schematically illustrates the phase transition process of the grafted amphiphilic copolymer solutions. When the temperature is below LCST, the polar groups of the polymer strongly interact with water. Although there are hydrophobic and hydrogen-bonding interactions between polymer sections, water is a good solvent for the polymer, and the polymer–water interactions are stronger than the polymer–polymer interactions. With increasing temperature, the polymer chains collapse due to the enhancements of the hydrophobic interactions and the intra/intermolecular hydrogen bonding, which are in turn caused by the increasing entropic penalty for binding to water. Moving above the LCST, the polymer–polymer interactions dominate over the polymer–water interactions, and phase transition takes place. The cooperative effects of hydrophobic interactions and the intra/intermolecular hydrogen bonding contribute to the phase transitions of the grafted amphiphilic copolymers. With the protection of hydrophobic interactions, the intra/intermolecular hydrogen bonding enhances the hydrophobic interactions.

Conclusion

Five thermosensitive and pH-sensitive amphiphilic graft copolymers based on maleic anhydride copolymers were prepared. Aqueous solutions of these grafted amphiphilic copolymers show LCST's covering a wide temperature range in response to pH, salinity, additives, and polymer compositions. The LCST's depend on the polymer–polymer and polymer–water interactions, which are related to the cooperative effects of intra/intermolecular hydrogen bonding and hydrophobic interactions of polymers. The grafted amphiphilic copolymers have potential applications as pH/temperature-responsive hydrogel and surfactants.

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