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Thermally Responsive 2-Hydroxyethyl Methacrylate Polymers: Soluble−Insoluble and Soluble−Insoluble−Soluble Transitions

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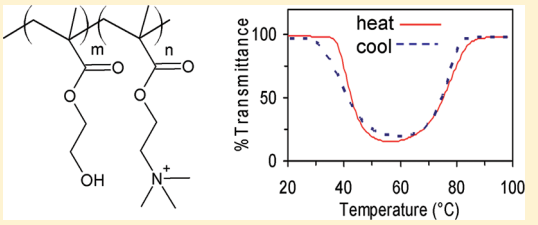
Supporting Information

ABSTRACT: 2-Hydroxyethyl methacrylate (HEMA)-based (co)polymers showed soluble to insoluble (S−I) thermoresponses, as measured by turbidimetry, when heated in aqueous solutions of appropriate ionic strength and/or pH. Surprisingly, many of the polymers showed a second insoluble to soluble (I−S) thermoresponse at higher temperatures, probably as a result of breaking of polymer−polymer H-bonding that allowed redissolution of the polymer chains. The thermoresponse of the charged copolymers was very sensitive to the polymer concentration, pH, and ionic strength likely due to the role of charge screening in the chain collapse and aggregation necessary to observe cloud points. Urea, a commonly used "H-bond breaker", raised the cloud point (and decreased the clearing point for systems that showed I−S transitions); however, subsequent cooling or heating runs in the presence of urea often showed dramatically different thermoresponses as a result of urea hydrolysis, leading to a pH change and/or polymer hydrolysis at high temperature. Marked hysteresis or changes from run to run were seen for some systems because of polymer precipitation or slow rehydration of phase-separated material or, in some cases, slow hydrolysis of HEMA units.



INTRODUCTION

Polymers such as poly(*N*-isopropylacrylamide) (PNIPAM),[1] poly(methyl vinyl ether) (PMVE),[2] poly(*N*,*N*-dimethylaminoethyl methacrylate) (PDMAEMA),[3] or poly(poly(ethylene glycol) methacrylate)[4,5] are among many whose aqueous solutions show a soluble to insoluble (S−I) transition, or lower critical solution temperature (LCST), when heated. These thermally responsive polymers are typically amphiphilic materials, and dissolution in water often requires H-bonding to hydrophilic groups along with solvation of the hydrophobic portions of the polymer chain. At higher temperatures the unfavorable entropy associated with this solvation overwhelms favorable interactions between water and the hydrophilic portions of the chain, and phase separation ensues.

Another class of responsive polymers shows an insoluble to soluble (I−S) transition, or upper critical solution temperature (UCST), when heated. This can occur because specific interactions such as H-bonds or ionic interactions are disrupted at higher temperatures, freeing hydrophilic functional groups. For example, polymers containing nucleic acids,[6] carboxylic acids, and/or amides[7] can show an I−S transition where the H-bonds between polymer-bound groups are broken upon heating. Poly(acrylic acid) (PAA) solutions are known to show an I−S transition in the presence of ≥400 mM NaCl.[8] Some zwitterionic polymers such as poly(sulfobetaines) show I−S transitions as heating breaks intra- and interchain ionic interactions.[9] Also, I−S transitions are seen for poly(oligo(ethylene glycol) methacrylates) in aliphatic alcohols including alcohol−water mixtures.[10]

There is also interest in thermally responsive polymer systems that show two or more phase transitions upon heating or cooling.[11] Many of these multiply responsive systems are block copolymers that exhibit two or more LCST-type transitions (S−I−I*) as different blocks undergo phase separation.[12] Systems that exhibit both LCST- and UCST-type transitions (i.e., S−I−S or I−S−I) are much rarer although this behavior has been examined theoretically for both organic and aqueous polymer solutions.[13] Polymer systems showing only a narrow range of (in)solubility in water may find novel roles as smart polymers and warrant further investigation. Typically, the polymers that show I−S−I or S−I−S transitions have, in addition to a suitable hydrophobic/hydrophilic balance, some specific interactions (H-bonding, electrostatic) that can be disrupted by heating to free the hydrophilic groups to interact with water. Systems that show I−S−I transitions include PMVE,[14] poly(vinyl alcohol),[15] PDMAEMA in the presence of Co^{3+} ions,[16] poly(NIPAM-*co*-*N*,*N*-dimethylacrylamide)-*b*-poly(4-vinylpyridine)) copolymer at low pH in the presence of a dianion (2,6-naphthalenedisulfonate),[17] a poly(glycidol)−poly(propylene oxide) block copolymer,[18] and several block copolymers that contain zwitterionic poly(sulfobetaine) blocks.[19]

Poly(ethylene oxide) exhibits S−I−S transitions as a feature of a closed-loop phase diagram; however, both transitions occur above 100 °C.[20] S−I−S behavior has also been observed for partially acetylated or butylated poly(vinyl alcohol).[21,22] Other examples include a NIPAM−AA copolymer,[23] an AA−vinylacetamide copolymer,[24] poly(riboadenylic acid),[25] poly(methyl 2-acetamidoacrylate),[26] a methacrylic acid (MAA)−diethylene glycol methacrylate copolymer,[27] a proline-based block copolymer,[28] and an oxazoline copolymer.[29] In most cases, these transitions are seen only for very

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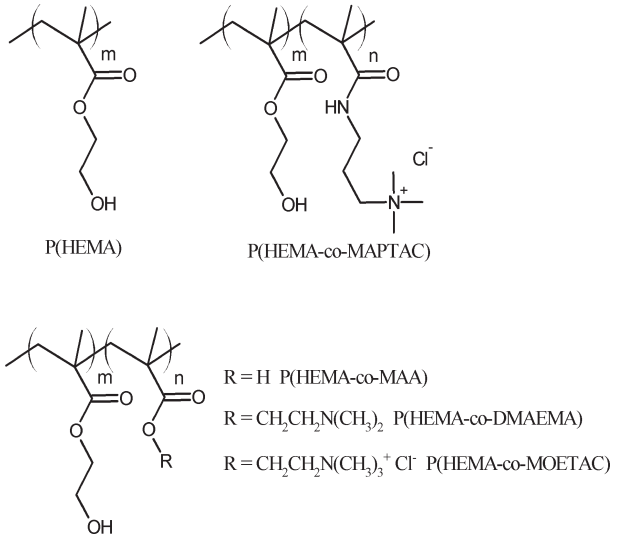
Scheme 1



narrow ranges of conditions (polymer composition, ionic strength, pH, or cosolvent), perhaps reflecting the delicate balance of factors necessary to observe this behavior. For example, S−I−S transitions were observed for the NIPAM−AA copolymer containing 17 mol % NIPAM, but only in solutions with ∼150−300 mM NaCl, while copolymers with 10 or 29 mol % NIPAM showed only I−S or S−I transitions, respectively.[23] The copolymer composed of 2-phenyl- and 2-ethyl-2-oxazoline showed S−I−S behavior only for the 50:50 copolymer and only in 60:40 water/ethanol mixtures.[29] With the poly(methyl 2-acetamidoacrylate) system, S−I−S transitions were seen in water for a polymer with a molecular weight of 23 kDa but not one of 15 kDa.[26] Matyjaszewski and co-workers examined the thermoresponse of several linear and brush copolymers composed of MAA and diethylene glycol methacrylate and found that only one linear copolymer with 9 mol % MAA showed S−I−S behavior and only at pH 9, not pH 7.[27]

Polymers based on 2-hydroxyethyl methacrylate (HEMA) or related hydroxy-containing monomers may be ideal candidates for investigation of doubly temperature responsive S−I−S behavior. PHEMA is a widely studied biocompatible polymer[30] that, while composed of a hydrophilic monomer, swells but does not dissolve in water. The insolubility is due, in part, to intra- and interchain H-bonding between polymeric hydroxy groups. Recently, Armes and co-workers[31] reported that PHEMA prepared by atom transfer radical polymerization (ATRP) was water-soluble if the samples had sufficiently low molecular weight (MW) and polydispersity. For example, those with degrees of polymerization (DP) < 20 were soluble at all temperatures while those with DP = 20−45 exhibited cloud points (S−I transitions). The short chains may H-bond less efficiently leaving a greater fraction of hydroxy groups to interact with water, or the H-bonding may simply not be sufficient to overcome the increased entropy of the short chains.

While there has been interest in thermally responsive polymers containing HEMA or related hydroxy-containing monomers,[31−38] there has been little focus on the possibility of redissolving these (co)polymers at higher temperatures (an I−S transition) through breaking of H-bonds. One possible exception involves a hydrogel composed of PMVE and PHEMA segments that exhibited an opaque to clear transition upon heating in water that may have been due to reswelling of the PHEMA segments at higher temperatures.[39]

In this paper HEMA-based polymers that exhibit S−I and in many cases S−I−S transitions are described. The polymers are made water-soluble by limiting the degree of polymerization or by adding hydrophilic comonomers such as MAA, DMAEMA, [2-(methacryloyloxy)ethyl]trimethylammonium chloride (MOETAC), or [3-(methacryloylamino)propyl]trimethylammonium chloride (MAPTAC), as shown in Scheme 1. The polymers were studied to see if, and under what conditions, they showed S−I transitions and then if at higher temperature it was possible to disrupt H-bonding and cause the polymers to redissolve (I−S). Systems with thermal responses over a broad range of solution conditions (ionic strength, pH) were obtained depending on the nature and amount of comonomer.

EXPERIMENTAL SECTION

Materials. HEMA (99+%), MAA (99%), DMAEMA (98%), MOETAC (75 wt % solution in water), MAPTAC (50 wt % solution in water), copper(I) chloride (99%), 2,2′-bipyridyl (bipy, 99+%), methyl 2-bromoisobutyrate (MeiBB, 99^{+}%), and isopropanol (HPLC, 99.5%) were purchased from Sigma-Aldrich (Oakville, ON) and used as received. 2,2′-Azobis(isobutyronitrile) (AIBN, 99.95%, Dupont, Mississauga, ON) and 2,2′-azobis(2,5-dimethylvaleronitrile) (Vazo-52, Polysciences, Warrington, PA) and ethanol (Commercial Alcohols, Brampton, ON) were used as received. Methanol (HPLC or Reagent), ethyl ether (anhydrous, Reagent), NaCl (Reagent), and urea (Reagent) from Caledon Laboratories, (Georgetown, ON) were used as received.

Conventional Polymerization. Copolymers of HEMA with MAA, DMAEMA, MOETAC, or MAPTAC were prepared by conventional free radical polymerization using AIBN or Vazo-52 as initiators. The preparation of P(HEMA-MOETAC)[95:5] in ethanol/water (90:10) and P(HEMA-MAA)[95:5] in ethanol are described below as examples.

P(HEMA-MOETAC)[95:5] was prepared by combining 9.225 g of HEMA (71.0 mmol), 0.775 g of MOETAC (1.003 g of 75% solution, 3.73 mmol), 0.186 g of Vazo-52 (0.75 mmol), 81 mL of ethanol, and 8.74 mL of water in a 125 mL HDPE bottle. The solution was bubbled with nitrogen for several minutes before the bottle was sealed. The bottle was placed in an oven and heated at 55 °C for 22 h while being slowly rotated (10 rpm) to provide mixing. The polymer was isolated and purified by dialysis (10−12 kDa MW cutoff) in water followed by freeze-drying. The purified polymer was then dried to a constant weight in a vacuum oven at 50 °C. Yield: 7.90 g (79%). Copolymers of HEMA with MOETAC or MAPTAC were prepared in this fashion.

P(HEMA-MAA)[95:5] was prepared by combining 9.663 g of HEMA (74.3 mmol), 0.336 g of MAA (3.90 mmol), 0.194 g of Vazo-52 (0.78 mmol), and 90 mL of ethanol in a 125 mL HDPE bottle. Polymerization was conducted as described above. The polymer was isolated and purified by precipitation in ethyl ether (1 L), washed with ether, and then dried to a constant weight in a vacuum oven at 50 °C. Yield: 9.09 g (91%). Copolymers of HEMA with MAA or DMAEMA were prepared in this fashion.

PHEMA by ATRP. Low-MW PHEMA was prepared by ATRP based on a method described in the literature.[31] CuCl (118.1 mg, 1.19 mmol) and bipy (465 mg, 2.98 mmol) were placed in a round-bottomed flask, which was sealed and flushed with nitrogen. HEMA (4.78 g, 36.7 mmol) and isopropanol (3.5 mL) were mixed, bubbled with nitrogen for 10 min, and then transferred via a double-tipped needle to the flask containing CuCl and bipy. The mixture was stirred for 10 min to allow catalyst formation. MeiBB (220.7 mg, 1.22 mmol) dissolved in isopropanol (0.5 mL) was bubbled with nitrogen for 5 min before being

Table 1. Properties of HEMA-Based Polymers

polymer	feed	% yield	composition[a]	M_n[b] (kg/mol)	PDI[b]
PHEMA-4K	30:1 (M:I)	43		3.65	1.34
	94% conv			(2.90[c])	
P(HEMA-MAA)	95:5	91	94:6	7.9	3.5
	90:10	92	91:9		
P(HEMA-DMAEMA)	95:5	90	96:4	12.2	3.1
	90:10	87	91:9	11.0	3.0
P(HEMA-MOETAC)	95:5	79	93:7	14.1	2.5
	90:10	51	92:8	13.9	4.0
	85:15	81	86:14		
P(HEMA-MAPTAC)	95:5	55	96:4	21.6	2.9
	90:10	90	93:7		
	90:10		91:9		

[a] Determined by ^{1}H NMR. [b] As measured by GPC in DMF (50 mM LiBr) calibrated with PEG standards. [c] Determined by ^{1}H NMR (end-group analysis).

transferred via a double-tipped needle to the reaction flask. After 85 min at room temperature (20 °C), the viscous, dark brown reaction mixture was exposed to air. A small sample was removed, dried under a stream of air, dissolved in methanol-d_4, and analyzed by ^{1}H NMR to determine monomer conversion (94%). Methanol was added to the remainder of the reaction mixture, which was then passed through a basic alumina column with methanol to remove the catalyst. The solution volume was reduced to ~10 mL, and the polymer was precipitated in ethyl ether (140 mL). The white solid was filtered, washed with ether, and dried to a constant weight in a vacuum oven at 50 °C. Yield: 2.15 g (43%).

Characterization. HEMA homopolymer and copolymers were characterized by ^{1}H nuclear magnetic resonance (NMR) spectroscopy using a Bruker AV 200 spectrometer for polymers dissolved in dimethyl-d_6 sulfoxide, methanol-d_4, or acetone-d_6. In addition, the composition of copolymers containing MAA or DMAEMA was determined by titration with a PC-Titrate automatic titrator (Man-Tech Associates). The polymers were dissolved in water with enough methanol to ensure the polymer remained in solution (typically ≤50 vol %), and then 0.1 M HCl was added to ensure complete protonation of the MAA or DMAEMA groups. The solution was titrated with 0.100 M NaOH, and the MAA or DMAEMA content was determined from the difference between the end points for titration of the excess HCl and the MAA or DMAEMA-H$^+$. Elemental analysis of copolymers made with 5 and 10 mol % MOETAC in the feed were performed by the Combustion Analysis and Optical Spectroscopy facility, Department of Chemistry, McMaster University.

Polymer molecular weights were determined by gel permeation chromatography (GPC) with a system consisting of a Waters 590 HPLC pump, three Waters Ultrastyragel Linear columns (30 cm × 7.8 mm (i.d.); <10 μm particles) at 40 °C, and a Waters 410 refractive index detector at 35 °C. The eluent was 50 mM LiBr in *N,N*-dimethylformamide (DMF), and the system was calibrated with narrow molecular weight PEG standards (Waters). (Note: warming (~60 °C/30 min) was needed to ensure dissolution of the PEG standards in DMF.)

Cloud Point Measurements. Cloud point measurements were performed with a Varian Cary 3E spectrophotometer fitted with a temperature-controlled 12-sample cell holder. The polymers were dissolved in deionized water containing the desired concentration of NaCl or urea and the polymer concentration was 1 wt % unless otherwise indicated. The temperature was ramped up or down at 1 °C/min, and the solution transmittance at 500 nm was measured at 0.5 °C intervals. Cloud points (soluble to insoluble transition) and clearing points (insoluble to soluble transition) were defined as the temperature at which the transmittance reached 50% during the heating run.

RESULTS AND DISCUSSION

Materials. HEMA was polymerized with several different hydrophilic comonomers as shown in Scheme 1. The polymer composition as determined by ^{1}H NMR was found to be similar to that used in the feed (Table 1), and comparable compositions were found for copolymers that were also characterized by titration or elemental analysis. For example, titration of copolymers prepared with 5 and 10 mol % MAA or DMAEMA gave 6 and 10.5% MAA and 5 and 11% DMAEMA. The carbon-to-nitrogen ratios as measured by elemental analysis for the copolymers made with 5 and 10 mol % MOETAC (52.89% C, 0.82% N and 53.08% C, 0.94% N, respectively) were consistent with 8.2 and 9.5% MOETAC, respectively, similar to the content determined by NMR.

GPC analysis of these amphiphilic copolymers was challenging since they are prone to hydrophobic or electrostatic interactions with the stationary phase. The use of 50 mM LiBr in DMF as the mobile phase and PEG standards for calibration allowed the MWs of most of the copolymers to be estimated by GPC (Table 1); however, copolymers with ≥10 mol % MAA, MOETAC, or MAPTAC could not be analyzed due to interactions with the column.

A low-MW HEMA homopolymer was prepared by ATRP based on the method of Armes and co-workers.[31] Initial attempts to prepare PHEMA in methanol with ethyl 2-bromoisobutyrate as initiator were frustrated by the occurrence of transesterification between methanol and HEMA monomer as had been seen previously for other methacrylates.[40] Following polymerization (83% conversion), the residual monomer consisted of a 75:25 mixture of HEMA and methyl methacrylate. The observation of transesterification in the initial polymerization attempts was likely due to the use of longer than necessary reaction times (20−24 h) and was probably largely restricted to the unreacted monomer. To avoid transesterification and possible incorporation of methyl methacrylate in the polymer, a shorter polymerization time was employed, and isopropanol was used as the polymerization solvent since methacrylate transesterification has been shown to be very slow in this solvent.[40] In addition, it had been difficult to detect the ethyl isobutyrate end-group in PHEMA by ^{1}H NMR so MeiBB was used as the initiator instead. Low-MW PHEMA was successfully prepared by ATRP in isopropanol using a 30:1 HEMA:MeiBB ratio. After 85 min, the polymerization had proceeded to 94% conversion corresponding to a DP of 28 (theoretical M_n = 3800 g/mol). End-group analysis by ^{1}H NMR (Supporting Information, Figure S1) indicated a DP of 21 (M_n = 2900 g/mol) while GPC in DMF containing 50 mM LiBr calibrated with PEG standards gave M_n = 3650 with a polydispersity of 1.34 (Supporting Information, Figure S2).

HEMA (Co)polymers in Water. The PHEMA-4K prepared in this work was not fully water-soluble at 1 wt % at room temperature but dissolved to give a clear solution when stored at lower temperature (~5 °C). The water solubility of this low-MW PHEMA is consistent with that observed for other low-MW samples (D P < 45) that have been prepared by controlled radical polymerization.[31,41] HEMA copolymers containing 7−14 mol % MOETAC or 4−9% MAPTAC were soluble in water at 20 °C while copolymers containing either MAA (6−9 mol %) or

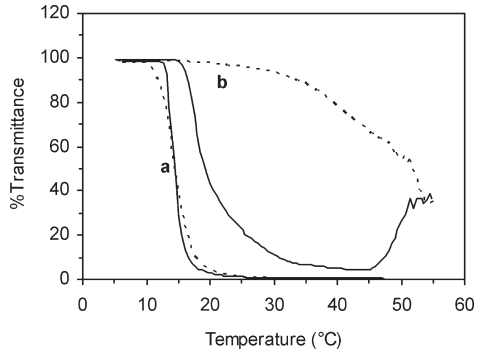


Figure 1. Heating (solid) and cooling (dashed) curves during the (a) first and (b) second runs on a 1% solution of PHEMA-4K in water. Heating/cooling rate: 1 °C/min.

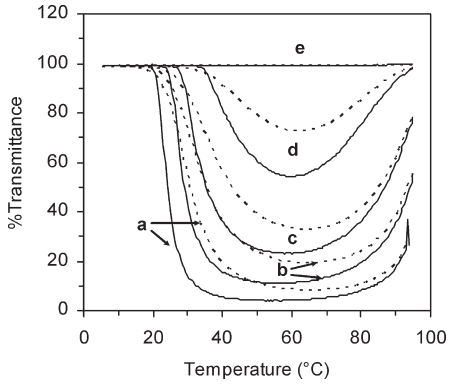


Figure 2. Heating (solid) and cooling (dashed) curves for solutions of PHEMA-4K at (a) 0.5%, (b) 0.4%, (c) 0.3%, (d) 0.2%, and (e) 0.1% in water. Heating/cooling rate: 1 °C/min.

DMAEMA (4−9%) were insoluble. The acid and amine functional groups of MAA and DMAEMA units will not be extensively ionized upon dissolution in water, and these groups may H-bond with the hydroxy groups of HEMA, further reducing their solubilizing ability. Similar effects have been used to explain the reduced solubility of a number of other copolymers containing H-bond acceptor and donor groups.[4,7,42,43] Once the MAA or DMAEMA groups were ionized by the addition of NaOH or HCl, respectively, the copolymers were water-soluble.

Thermoresponse: PHEMA. Consistent with the observations of Weaver et al.,[31] aqueous solutions of the low-MW PHEMA (DP ∼ 25; MW ∼ 4 kDa) prepared in this work exhibited a cloud point (CP) when heated from 5 to 50 °C, as shown in Figure S3 (Supporting Information). The CP of PHEMA-4K was found to be more sensitive to polymer concentration than is seen for most thermoresponsive systems increasing by nearly 10 °C (14.4−23.7 °C) when the concentration was lowered from 1 to 0.5%. High sensitivity to polymer concentration has been observed for some closely related polymers based on hydroxy monomers such as 2-hydroxypropyl acrylate (HPA),[33,37] 2-hydroxyethyl acrylate (HEA),[37] or hydroxyisopropylacrylamide.[44] In some cases, the phase-separated material formed by these hydroxy polymers has been described as being well-hydrated[33,35−37] or liquid.[32,44] Consistent with the behavior of these polymers, PHEMA-4K gave a liquid phase-separated material when a 1% solution was examined by optical microscopy at room temperature. The small droplets that were formed initially slowly aggregated and merged to give large droplets that deposited onto the glass slide. The observation of CPs by turbidimetry requires polymer aggregation and the sensitivity to polymer concentration of PHEMA and related systems may point to inefficient aggregation for these polymers. Individual PHEMA chains likely become insoluble at temperatures below the observed CPs but require additional time and/or higher temperature for the chains to form aggregates large enough or dense enough to effectively scatter light and allow detection by turbidity measurements. Future light scattering experiments may help to clarify the desolvation and aggregation processes responsible for the observed behavior.

The samples showed reversible behavior with cooling curves that matched the heating curves quite well although the transition during heating was always sharper. The 0.5% sample was run through four heating and cooling cycles, and the curves were reproducible with a CP of 23.7 ± 0.3 °C from the heating curves. This value is lower than the 39 °C determined by Weaver et al. for PHEMA with a similar DP but a different end-group (morpholino-ethyl vs methyl).[31] In contrast to the 0.5% solution, the 1% sample behaved more inconsistently with cooling curves that were sometimes quite different than the heating curves and with changes in the curves from run to run. For example, when the 1% sample was run through a second heating and cooling cycle, the heating curve was shallower and showed a higher CP (Figure 1). The solution began to clear as it was heated above 45 °C and continued to gradually clear as the sample was cooled. At the end of the second run, a gel or viscous liquid was visible at the bottom of the cuvette. The phase-separated material was not fully redissolved after sitting for 1 week at 5 °C but did dissolve immediately in methanol (following supernatant removal), indicating that it had not undergone cross-linking. Macroscopic aggregation and settling must have occurred during the second run, leaving a much lower (and steadily decreasing) polymer concentration in solution during cooling. A small degree of irreversible aggregation or settling during the first run may have caused the change in CP from the first to the second run of the 1% sample.

When the heating runs were extended to 95 °C, the PHEMA-4K solutions cleared or began to clear (I−S transition), as shown in Figure 2. The combined S−I−S thermoresponse was very sensitive to polymer concentration with the insoluble or cloudy region of the curves becoming deeper and wider as the concentration increased. Like many other examples of systems exhibiting UCSTs,[6,7,23,24,26−28] the high-temperature I−S transition is likely due to breaking of inter- and intrachain H-bonds between HEMA groups, which leads to redissolution of the polymer. That S−I−S transitions have been observed for functionalized PVA[21,22] too indicates that this might be a general phenomenon that could be observed for other hydroxy-containing polymers such as those based on HPA or HEA.

It is important to note that partial or full clearing of the solution could also be caused by aggregation leading to larger particles (less efficient scattering) or settling. If this were the case, the cooling curves might be expected to be dramatically different than the heating curves, and samples at higher concentrations should be most affected as seen for the 1% solution of PHEMA-4K (Figure 1). However, the transitions were reversible with cooling curves that resembled the heating curves in all cases except that they were shallower. The reduced turbidity during cooling may reflect the formation of more swollen particles when chain collapse and aggregation occurs at ∼70−80 °C during the cooling run compared to ∼30−40 °C during the heating run.

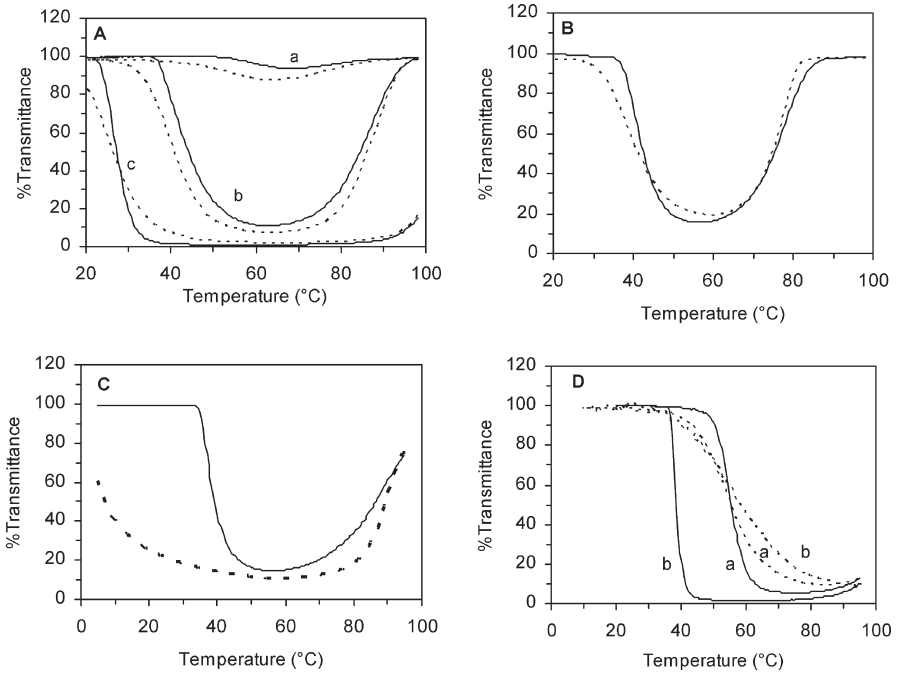


Figure 3. Heating (solid line) and cooling (dashed line) curves for (A) 1% P(HEMA-MOETAC) [93:7] in (a) 20, (b) 40, and (c) 60 mM NaCl; (B) 1% P(HEMA-MOETAC) [86:14] in 800 mM NaCl; (C) 0.5% P(HEMA-MAPTAC) [91:9] in 170 mM NaCl; and (D) 1% P(HEMA-MAANa) [94:6] in (a) 300 and (b) 400 mM NaCl. Heating/cooling rate = 1 °C/min.

Thermoresponse: HEMA Copolymers. The only copolymer that showed a thermoresponse (S−I) in the absence of added salt was P(HEMA-MAPTAC) [96:4], which had a CP of 52.1 °C for a 1% solution heated at 1 °C/min. All of the other copolymers required the addition of NaCl to the aqueous solutions before they exhibited a CP and the amount of NaCl required varied considerably between the different copolymers. For example, about 50 mM NaCl was necessary to observe a CP for P(HEMA-MOETAC) [93:7], while in excess of 1 M NaCl was needed for P(HEMA-MAANa) [91:9], as shown in Figure S4 (Supporting Information). In addition, the CP decreased for each polymer as the NaCl concentration was increased, as shown in Figure S5 (Supporting Information) for P(HEMA-MAANa) [94:6]. The addition of salts is often used to cause or modulate the thermoresponse of polymers, and both the nature and concentration of the added salts are known to influence the magnitude of the effect.[45−47] With the charged polymers studied here another important role may be the screening of electrostatic charges that would allow individual chains to collapse and facilitate chain−chain aggregation.[48,49]

When the heating runs were extended to temperatures close to 100 °C, many of the samples showed a clearing (or I−S) transition in addition to the S−I transition. Figure 3 shows the heating and cooling curves for several different HEMA copolymer solutions. The two MOETAC copolymers (Figure 3A,B) display obvious S−I−S transitions in both the heating and cooling curves with little difference between the heating and cooling runs. The DMAEMA copolymers (fully protonated) behaved similarly (see Figure S6, Supporting Information). The MAPTAC copolymer (Figure 3C) also showed S−I−S behavior in the heating curve but is very slow to clear during the cooling curve. This type of hysteresis is relatively common with thermally responsive polymers and can vary from fairly minor, where heating and cooling curves are separated by a few degrees, to examples where the phase transition is largely irreversible.[7d,27,28,33,36,48,50−54] The hysteresis is often ascribed to slow rehydration and chain disentanglement in the particles or aggregates that can become irreversible if the formation of strongly H-bonded networks or crystallization occurs in the phase-separated material. Macroscopic aggregation and settling was more pronounced if the MAPTAC copolymer solutions were stirred during the cloud point measurements presumably due to more collisions between the colloidally unstable particles. The gel that was present after the cooling run was slow to redissolve in the supernatant containing NaCl but dissolved quickly if it was replaced with water. The different behavior for copolymers made with the closely related MOETAC and MAPTAC may be due to the different nature of the aggregates formed after phase separation. There may be additional H-bonding within the aggregates involving the amide group of MAPTAC that slows redissolution as has been seen for PNIPAM.[47,55]

The final example (Figure 3D) shows only a slight increase in transmittance at high temperatures, and then when cooled, the sample with 300 mM NaCl (curve a) shows a roughly reversible cooling curve but the sample at higher salt concentration (curve b) displayed one shifted to higher temperature. In addition, there was a small amount of viscous liquid on the bottom of the cuvette at the end of the heating/cooling cycle. The early clearing of this sample during cooling was caused by aggregation and settling of the phase-separated polymer at high temperature that left the solution with a reduced polymer concentration and perhaps one that was enriched with the more soluble fractions of the sample (lower MW, higher MAANa content).

The effect of NaCl on the temperature response was investigated, and not surprisingly, all of the copolymers showed decreasing CPs as [NaCl] was increased. Figure 3A shows the effects for a 1% solution of P(HEMA-MOETAC) [93:7], which undergoes a dramatic change when the NaCl concentration is

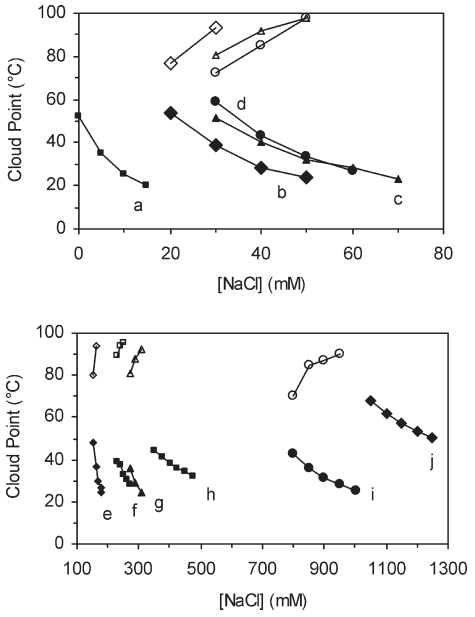


Figure 4. Cloud points (closed symbols) and clearing points (open symbols) as a function of NaCl concentration for 1% polymer solutions measured from the first heating curves. (a) P(HEMA-MAPTAC) [96:4], (b) P(HEMA-DMAEMA-HCl) [96:4], (c) P(HEMA-MOETAC) - [93:7], (d) P(HEMA-MOETAC) [92:8], (e) P(HEMA-MAPTAC) - [91:9], (f) P(HEMA-MAPTAC) [93:7], (g) P(HEMA-DMAEMA-HCl) [91:9], (h) P(HEMA-MAANa) [94:6], (i) P(HEMA-MOETAC) - [86:14], and (j) P(HEMA-MAANa) [91:9]. Heating rate = 1 °C/min.

varied. The CP dropped by more than 15 °C, and the region of insolubility grew as [NaCl] was changed from 40 to 60 mM.

In Figure 4, the effect of [NaCl] on the thermoresponse of the HEMA copolymers is summarized. The amount of salt needed to induce thermoresponsive behavior varied dramatically across the series of copolymers ranging from a few mM for P(HEMA-MAPTAC) [96:4] to more than 1 M for P(HEMA-*co*-MAANa) - [91:9]. In most instances, the greater the hydrophilic content, the greater the [NaCl] needed to cause the thermoresponse. The one exception is for the MAPTAC copolymers that contained 7 and 9 mol % MAPTAC after preparation. The discrepancy may be due to the uncertainty in determining the composition by NMR or to a change in polymer composition due to hydrolysis, which is discussed in more detail later. The need for higher [NaCl] for the MAANa copolymers compared to the MOETAC or MAPTAC ones of similar composition indicates that the anionic MAANa has a greater solubilizing ability than the cationic monomers, something that has been observed for other thermoresponsive systems.[49]

The CP curves are quite steep for the more sensitive systems (approximately −1000 °C/M) compared to −90 °C/M for more hydrophilic ones like P(HEMA-MAANa) [91:9]. All of the slopes in Figure 4 are steeper than are typically seen for uncharged systems such as alkylacrylamide polymers (approximately −10 °C/M).[45−47] However, high sensitivity of thermoresponse to [NaCl] has been seen for other charged systems[48] and points to the importance of charge screening in the chain collapse and aggregation necessary to observe the temperature response.

The clearing point data are more limited because some samples did not show signs of clearing or showed signs of clearing but had not reached 50% transmittance at temperatures attainable in the current experiments (e.g., Figure 2, curve a). Still other samples showed clearing that was due, at least partially, to aggregation and settling so they were not included in Figure 4. Although it may be a coincidence, distinct high-temperature I−S transitions were only observed with cationic copolymers. The cationic polymers may give initial aggregates that are less prone to settling or perhaps these aggregates are more highly swollen and, thus, more easily redissolved. It is possible that by employing lower polymer concentrations or other conditions that minimized aggregation and settling, some of the other copolymer solutions may have exhibited clearing at high temperature.

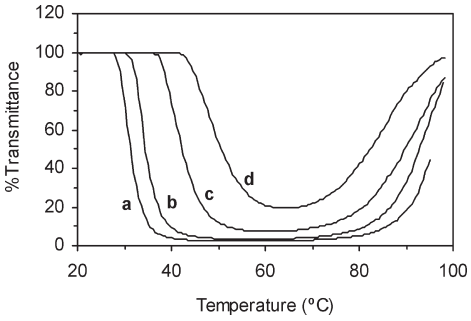


Figure 5. Effect of urea on the heating curves for aqueous solution of 1% P(HEMA-MOETAC) [93:7] with 70 mM NaCl. Urea concentration: (a) 0, (b) 200, (c) 400, and (d) 600 mM. Heating rate = 1 °C/min.

Urea. Strong inter- and intramolecular H-bonding is thought to contribute to the insolubility of PHEMA in water and, thus, additives that improve the H-bonding nature of the solvent may increase polymer solubility. Urea has been used to increase the solubility of a number of proteins or polymers where H-bonding is thought to play an important role.[4,6,7b,24,56] While this has often been attributed to the disruption of polymer−polymer H-bonds and improved interactions with solvent (urea and/or water), the mechanism of action is still the subject of debate.[57,58] Several studies have investigated the interactions of urea with HEMA-based polymers and gels and found that it improves the solubility of the polymers, but again there is uncertainty about the origin of this effect. Both disruption of H-bonds[59] and solubilization of hydrophobic polymer segments[60] have been proposed while urea induced ionization of MAA groups intentionally or accidentally incorporated into the polymers may also be important.[61]

The effect of urea on the thermoresponse of several HEMA-based polymers was investigated. P(HEMA-MOETAC) [93:7] (1%, 70 mM NaCl) showed increased solubility (i.e., a smaller phase-separated region) as urea was added to the solution (Figure 5). The CP increased by about 20 °C when the urea concentration was increased from 0 to 600 mM with the I−S transition decreasing by a comparable amount consistent with disruption of polymer−polymer H-bonding or hydrophobic interactions. Note that curve a in Figure 5 (70 mM NaCl, 0 mM urea) shows a CP (31 °C) that is a bit higher than seen for this same polymer in other experiments (Figure 3A; Figure 4, curve c). It is perhaps not surprising that there was change in the CP for experiments conducted several months apart since these systems are so sensitive to small variations of NaCl or polymer concentration as well as small changes in polymer composition due to hydrolysis (as described below).

A similar effect upon solubility was seen for P(HEMA-MAPTAC) - [96:4] (1%, 0 mM NaCl) in the presence of 0−600 mM urea on the first heating run, but this changed dramatically for the cooling run and

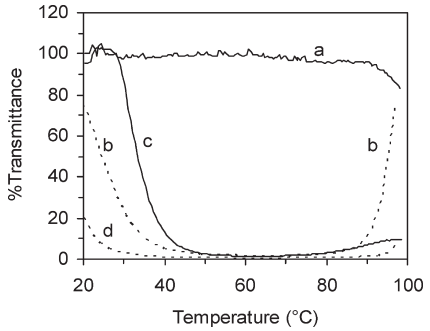


Figure 6. Heating (solid line) and cooling curves (dashed line) for 1% P(HEMA-MAPTAC) [96:4] in the presence of 600 mM urea: (a/b) first heat/cool cycle; (c/d) second heat/cool cycle. Heating/cooling rate: 1 °C/min.

subsequent heat/cool runs. While the sample with no urea showed only minor changes in the turbidity curves from run to run, the solution containing 600 mM urea exhibited greatly diminished polymer solubility after the first heating run (Figure 6). The decrease in solubility is first seen as a dip in the % transmittance near the end of the first heating run (Figure 6, curve a, T > 85 °C) but grows progressively worse.

Urea is known to hydrolyze when heated releasing ammonia that causes the pH to rise.[61] This could lead to the formation of anionic groups on the polymers either by ionization of trace polymer-bound acid impurities or by hydrolysis of HEMA groups to produce MAA groups. In the case of MAPTAC copolymers, this would reduce the net charge of the cationic polymer chains leading to reduced solubility as observed in Figure 6. When 3% solutions of P(HEMA-MAPTAC) in D_2O at pH 7 containing 0 or 500 mM urea were heated at 100 °C, hydrolysis of the HEMA units was detected by ^{1}H NMR, but hydrolysis was faster in the presence of urea. The urea-containing solution experienced ~3% hydrolysis after 1 h at 100 °C, about twice as much as had occurred in the absence of urea. Thus, it is likely that hydrolysis of the HEMA groups generating carboxylate anions and reducing the net charge per polymer chain is responsible for the dramatic changes in the thermoresponse observed for the MAPTAC copolymer in the presence of urea. Interestingly, the P(HEMA-MOETAC) [86:14] copolymer did not undergo appreciable hydrolysis in the presence of urea under similar conditions, perhaps showing that the amide group of the MAPTAC units plays a role in hydrolysis of neighboring HEMA groups.

The opposite effect, increased solubility after heating in the presence of urea, might be expected for polymers such as P(HEMA-MAA) or PHEMA where rising pH or HEMA hydrolysis would increase polymer hydrophilicity. These results demonstrate that caution must be employed when using urea to explore the role of H-bonding interactions in thermoresponsive systems.

pH. For HEMA copolymers containing acidic or basic groups, the solution pH will have dramatic effects on the thermoresponse by changing the degree of charge on the polymer chains. This will influence polymer solubility as well as the aggregation kinetics important for observation of the CP. The effect of pH was explored for P(HEMA-MAA) [91:9] and P(HEMA-DMAEMA) [91:9], as illustrated in Figure 7. When the MAA groups in the copolymer were fully deprotonated, NaCl concentrations in excess of 1 M were required to observe a cloud point (curve j, Figure 4). Lowering the pH to about 5.5 reduced the required NaCl concentration to less than 500 mM, and the thermoresponse around this pH was found to

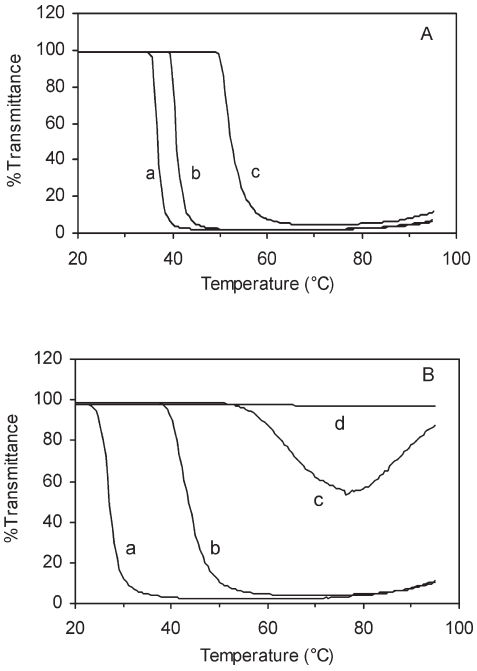


Figure 7. Effect of pH on the thermoresponse of (A) 0.5% P(HEMA-MAA) [91:9] solution containing 300 mM NaCl and 20 mM phosphate buffer at (a) pH 5.37, (b) pH 5.41, (c) pH 5.50 and (B) 0.5% P(HEMA-DMAEMA) [91:9] solution containing 121 mM NaCl at (a) pH 7.37, (b) pH 7.17, (c) pH 7.01, (d) pH 6.81. Heating rate: 1 °C/min.

be very sensitive to small changes of pH. Figure 7A shows the effect of changing the pH from 5.37 to 5.41 to 5.50, where the degree of ionization increased from about 81 to 85%, assuming that the pK_a of this copolymer is similar to that of acetic acid (4.74). The CP increased by 15 °C for this small change in pH and polymer ionization.

Similarly, the DMAEMA-containing copolymer was very sensitive to changing pH (Figure 7B). The thermoresponse changed from a CP of about 25 °C to a shallow S−I−S transition and finally to no discernible thermoresponse as the pH was decreased from 7.37 to 6.81. In this pH range, the % ionization increases from about 55 to 74% (based on the equivalents of HCl added). It is interesting to note that S−I−S behavior was seen for the fully protonated DMAEMA system (Supporting Information, Figure S6) and for the sample at pH 7.01 (% ionization ~74%) but not the ones at higher pH (Figure 7B, curves a and b) where the polymer charge was lower (% ionization ~55, 62%). Thus, it appears that a minimum charge density is needed for the DMAEMA system to exhibit the clearing portion of the S−I−S transitions perhaps because it prevents extensive aggregation that might slow redissolution or facilitates the rehydration of the phase separated material during clearing. However, the S−I−S transitions shown by the PHEMA homopolymer indicate that a minimum charge density is not a prerequisite for S−I−S behavior. In the case of the homopolymer, the low MW may facilitate rehydration. The pronounced pH sensitivity exhibited by the MAA- and DMAEMA-containing copolymers or related systems might prove useful for pH sensing or pH regulated processes (release or reaction control).

Hysteresis and Reproducibility. In the course of this work it became evident that many of the polymer solutions did not give entirely reproducible thermoresponsive behavior. As mentioned earlier, some of the polymer solutions cleared at significantly

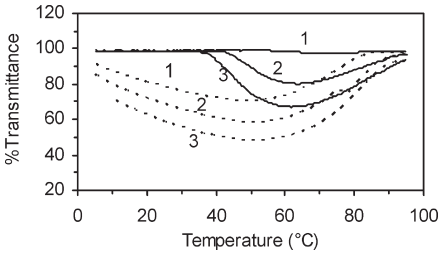


Figure 8. Percent transmittance during heating (solid lines) and cooling (dashed lines) for 0.1% P(HEMA-MAPTAC) [91:9] in 170 mM NaCl during the first, second, and third runs. Heating/cooling rate = 1 °C/min.

higher or lower temperatures during cooling than the CP observed in the heating curves. In addition, the thermoresponse changed during subsequent heat/cool cycles for a number of the samples. For example, the heating and cooling curves for a 0.1% solution of P(HEMA-MAPTAC) [91:9] in the presence of 170 mM NaCl, shown in Figure 8, reveal changes in the thermoresponse from heating to cooling and from run to run. Little or no phase separation occurs during the first heating run, yet it shows phase separation during the cooling run and subsequent heating runs. While aggregation, sedimentation, and slow rehydration of phase-separated material can explain the behavior of some systems, other factors are involved for the sample shown in Figure 8. The sample was maintained at ~5 °C for several days after each cooling run to facilitate redissolution of the polymer, yet increasing degrees of phase separation were detected in subsequent heating/cooling runs. If the phase-separated material had not fully redissolved, the solutions would have been less likely to show a thermoresponse because they would have lower polymer concentration and perhaps be enriched with the more soluble fractions of the sample (lower MW, higher MAPTAC content).

All of the MAPTAC samples showed a decreased CP when heating/cooling runs were repeated (Figure 9, curves a–c). The change in CP was quite dramatic for solutions that were heated to 95 °C in each run compared to those only heated to 60 °C. A 1% solution of P(HEMA-MAPTAC) [91:9] in 140 mM NaCl (curve a) went from having no CP to one of 40 °C after three runs while in the presence of 170 mM NaCl (curve c) the CP dropped 6.5 °C in the second run, after which the phase-separated material did not fully redissolve. However, a sample in 160 mM NaCl that was only heated to 60 °C in each run (curve b) showed a much smaller decrease, dropping only 1 °C over three runs. In contrast to the MAPTAC copolymers, a 1% solution of P(HEMA-MAANa) [94:6] that was heated to 95 °C over four runs showed a slight increase of CP (~4 °C in 300 mM NaCl and ~1 °C in 400 mM NaCl).

These observations are consistent with the occurrence of partial hydrolysis of the copolymers where some HEMA units are converted to MAA units. For the MAPTAC copolymers this can give less soluble materials because of H-bonding between MAA and HEMA groups at lower pH or because the chains bear both anionic (COO^-) and cationic ($-NMe_3^+$) groups leading to reduced net charge. Such changes may also have marked effects on the aggregation kinetics and, hence, the CP. For the MAANa copolymers, which are in a solution at higher pH, hydrolysis of HEMA groups would lead to more carboxylate anions per chain and improved solubility.

To check for hydrolysis, 3% solutions of HEMA-MAA, HEMA-MAPTAC, or HEMA-MOETAC copolymers in a 10 mM phosphate

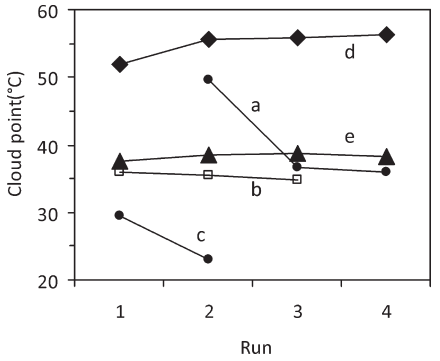


Figure 9. Cloud points taken from heating curves of successive runs on 1% P(HEMA-MAPTAC) [91:9] in (a) 140 mM NaCl, (b) 160 mM NaCl, and (c) 170 mM NaCl and on 1% P(HEMA-MAANa) [94:6] in (d) 300 mM NaCl and (e) 400 mM NaCl. The samples were heated to 95 °C in each run except for sample b, which was only heated to 60 °C in each run. Heating/cooling rate = 1 °C/min.

buffer in D_2O (p D = 7.0) were heated at 100 °C and then analyzed by ^1H NMR (Supporting Information, Figure S7). The P(HEMA-MAPTAC) [93:7] copolymer underwent about 3% hydrolysis after 2 h and 5% after 4 h as evidenced by the sharp signal for ethylene glycol at 3.6 ppm. There was little or no change detected for either P(HEMA-MAANa) [91:9] or P(HEMA-MOETAC) [86:14] after 2 h at 100 °C while after 4 h about 1% hydrolysis was detected. In the case of the MOETAC copolymer, hydrolysis of the MOETAC unit is possible but was not detected. When the P(HEMA-MAA) [91:9] was in its fully ionized form (pH ≥ 10), similar to the conditions used during the turbidity measurements, hydrolysis reached about 3% after 5 h at 100 °C, faster than at neutral pH but still much slower than for the MAPTAC copolymer at neutral pH. Thus, the MAPTAC system appears to be the most sensitive to hydrolysis, which might contribute to the pronounced hysteresis and changes in thermoresponse between runs seen for the MAPTAC copolymers. Indeed, the P(HEMA-MAPTAC) [93:7] sample showed ethylene glycol when first dissolved (Supporting Information, Figure S7), revealing that hydrolysis of HEMA units had occurred during storage of the solid polymer. Hydrolysis of HEMA units during storage was not detected for any of the other polymer types.

The occurrence of slow hydrolysis for these polymers at high temperatures means that they might not be useful in applications that required a repeatable thermoresponse over many cycles. However, this property might be useful in other applications where a change in thermoresponse or solubility over time would be desirable.[62]

CONCLUSIONS

Thermoresponsive HEMA-based polymers, including some that exhibit an uncommon soluble–insoluble–soluble double thermoresponse, were investigated. The polymers were made water-soluble by adding hydrophilic comonomers or by limiting the polymer MW in the case of the PHEMA homopolymer. All of the polymer solutions displayed LCST-type (S–I) transitions when heated under appropriate conditions (ionic strength, pH, polymer concentration), and many of these solutions showed a further clearing or UCST-type transition (I–S) at higher temperatures that has been attributed to the breaking of polymer–polymer H-bonds. The thermoresponse of the charged copolymers could be varied by changing the polymer composition, polymer concentration, ionic strength, and pH (in some cases) or by adding urea.

The high sensitivity to ionic strength and polymer concentration pointed to the importance of chain collapse and aggregation in the detection of phase separation by turbidimetry. Caution must be used when dealing with the effects of urea on these thermoresponsive polymers because urea hydrolysis may change the solution pH leading to a change in polymer ionization and/or cause polymer hydrolysis. Hysteresis (heating vs cooling) and changes in the thermoresponse from run-to-run were observed for some systems likely as a result of slow rehydration of the phase separated material, sedimentation leading to reduced polymer concentrations in solution, and/or hydrolysis leading to a change in polymer chemistry and solubility. These doubly temperature responsive systems (S−I−S) showing an easily controlled region of insolubility are fascinating materials and may find novel roles as smart polymers and certainly warrant further investigation. Future plans include light scattering experiments to clarify the desolvation, aggregation and rehydration processes responsible for the double thermoresponse, and an examination of other systems that might show this behavior.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H NMR spectrum and GPC chromatogram for PHEMA-4K; turbidity curves for PHEMA-4K as a function of polymer concentration; turbidity curves for P(HEMA-MOETAC)[93:7] in 50 mM NaCl and P(HEMA-MAANa)[91:9] in 1150 mM NaCl; turbidity curves for P(HEMA-MAANa)[94:6] as a function of NaCl concentration; cloud/clearing point data for P(HEMA-DMAEMA.HCl)[91:9]; ^{1}H NMR spectra of P(HEMA-MAPTAC)[93:7] before and after heating. This material is available free of charge via the Internet at http://pubs.acs.org.

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