Macromolecules

Making Hydrophilic Polymers Thermoresponsive: The Upper Critical Solution Temperature of Copolymers of Acrylamide and Acrylic Acid

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Temperature

random copolymers of acrylamide and acrylic acid of different compositions and molar masses have been synthesized. The thermoresponsive properties of the copolymers were studied to elucidate the effects of their composition, molar mass, and concentration by measuring their cloud point temperatures (T_{cp}) in acidic buffer solutions to keep the carboxylic acid groups in the protonated state. The effects of pH and added salts or urea were also studied.

INTRODUCTION

Thermoresponsive polymers with transition temperatures in aqueous solutions are an important category of "smart" materials, including polymers with a lower critical solution temperature (LCST) and with an upper critical solution temperature (UCST). Polymers with an LCST behavior in aqueous solutions have been widely studied due to their potential applications in the fields of drug delivery $^{1-3}$ and cell culture,^{4,5} or as enzyme carriers,⁶ actuators,⁷ and flocculants.^{8,9} UCST-type polymers are rarer than their LCST counterparts and therefore less explored, but they are advantageous in a variety of applications such as protein chilling capture and photothermal therapy.¹⁰ The molecular design of UCST polymers from common monomers is thus of great theoretical and practical interest.

exhibiting a UCST behavior. In this study, linear water-soluble

Generally, a UCST behavior arises from exothermic polymer-polymer interactions, such as the formation of ionic and hydrogen bonds.¹¹ In these cases, the polymer-polymer association is more favored than the interaction between a polymer and water, leading to their insolubility in water at a temperature lower than the critical temperature (T_c) . Zwitterionic polymers could exhibit the UCST behavior at pH values close to their isoelectronic points due to their strong interpolymer ionic interactions.^{12–14} Some polymers bearing both hydrogen-donor (H-donor) and hydrogen-acceptor (Hacceptor) in their repeating units may also have a UCST, including poly(N-acryloylglycinamide) (PNAGA),¹⁵ poly-(allylurea-co-allylamine),¹⁰ and poly(L-ornithine-co-L-citrulline).¹⁶ Poly(acrylamide) (PAM) and poly(acrylic acid) (PAA) also possess both H-donors and H-acceptors, but they are too hydrophilic to show a UCST in aqueous solutions. These two polymers can be turned into a UCST type by incorporating monomers with hydrophobic groups, such as acrylonitrile, cholic acid,^{18,19} and azobenzene,²⁰ in their structure.

Hydrogels of the PAA/PAM interpenetrating network (IPN) were reported to exhibit a UCST-type volume phase transition: the hydrogel swells upon heating but loses water upon cooling.^{21,22} The responsiveness was attributed to the strong "zipper-like" hydrogen bond (H-bond) arrays of the carboxylic acid and amide groups.²¹ A recent report mentioned that the UCST still exists even if the two monomers are copolymerized in a single network, indicating that the interpenetrating network (IPN) is not necessary for the appearance of UCST.²³ Besides the hydrogels, the mixture of the two homopolymers, PAA and PAM, has also demonstrated the UCST behavior in aqueous solutions if the molar masses of the two polymers are in a suitable range.²⁴ These observations indicate that a network structure is not an absolute requirement for the UCST and suggest that the carboxylic acid/amide H-bonds are strong

Received: April 29, 2021 **Revised:** August 19, 2021 Published: September 2, 2021





enough to yield a UCST transition.²⁵ All these previous findings seem to indicate that a series of copolymers may be synthesized to possess the UCST behavior in an aqueous environment. However, the UCST behavior of the linear poly(acrylic acid-coacrylamide)s [P(AA-co-AM)s] remains unexplored to date. It would be of theoretical and practical interest to prepare random copolymers made of these hydrophilic comonomers to systematically study the dependence of the UCST behavior on the physical characteristics of the polymers, particularly their chemical compositions and molar masses. In addition, these polymers are easy to make and would be useful in a variety of applications. In this work, we have prepared a series of random copolymers made of these hydrophilic monomers by reversibleaddition-fragmentation chain transfer (RAFT) living polymerization and studied the UCST behavior of the copolymers at various concentrations and pH levels and in the presence of additives, such as salts and urea.

EXPERIMENTAL SECTION

Materials. The RAFT agent 2-((butylthio)-carbonothioyl)thio-2methylpropanoic acid was synthesized as described elsewere.²⁶ All the following reagents were purchased from Sigma-Aldrich. AM (97%) was recrystallized before use. AA (99%) was purified through an alumina oxide column. 4,4'-Azobis(4-cyanovaleric acid) (ACVA), phosphoric acid (85 wt % in water), urea (99.0%), sodium iodide (99.0%), sodium chloride (99.0%), sodium sulfate (99.0%), and sodium thiocyanate (99.0%) were used without further purification.

Copolymerization of Acrylamide and Acrylic Acid. A series of P(AA-co-AM)s of various molar masses and AA/AM ratios were prepared by RAFT polymerization. AA and AM were dissolved in distilled water at 70 °C in the presence of the RAFT agent and freeradical initiator after being bubbled by nitrogen gas for 2 h minimum to initiate the polymerization. The total monomer concentration (10 M) was kept constant, while the concentrations of the RAFT agent and radical initiator were varied from 0.03 to 0.28 mM for the RAFT and 0.006 to 0.03 mM for ACVA to obtain the desired molar mass. The RAFT agent and ACVA were dissolved in a minimum of DMSO before the polymerization. For example, for Polymer 3 in Table 1, a mixture was prepared by dissolving 1.26 mL (20 mmol) of AA, 1.44 g (20 mmol) of AM, 33.7 mg (0.12 mmol) of the RAFT agent, and 6.2 mg (0.022 mmol) of ACVA, used as the free-radical initiator, in 4 mL of water in a reaction flask to prepare copolymers with various degrees of polymerization. The reaction mixture was diluted with 20 mL of water, transferred into a dialysis bag with a molecular weight cutoff of 3500, and finally immersed in a distilled water bath for 4 days with regular replacement of the media. The same reaction conditions were used for all RAFT polymerization procedures, and the conversion of the monomers averaged ca. 50%, ranging from 34 to 68% for the amount weighed after dialysis.

Copolymer Characterization. Size-exclusion chromatography (SEC) was performed on a 1260 HPLC system from Agilent equipped with a 1260 ALS autosampler, a 1260 quad pump, and a 1260 Infinity refractive index detector. The eluent H₂O containing 0.2 M NaNO₃ and 0.01 M NaH₂PO₄ was filtered through 0.20 μ m Nylon Millipore filters. The flow rate was set at 0.5 mL/min. The NMR spectra of the polymers in DMSO-d₆ and D₂O were recorded at 25 °C on a Bruker AV400 spectrometer operating at 400 MHz for ¹H (Figure S2 in the Supporting Information). Elementary analysis was conducted on an EAS 1108 spectrometer from Fison Instruments.

The transmittance of the polymer aqueous solutions was recorded as a function of temperature on a Cary 100 UV–vis spectrophotometer at 500 nm (Agilent) equipped with a temperature controller. The turbidity measurements were carried out by first cooling the solution to 10 °C below the cloud point ($T_{\rm cp}$) at a constant rate of 0.5 °C/min and then heating the solution back to the starting temperature at the same rate. The sample cells were equipped with a stirring bar and were stirred during the turbidity measurements. To dissolve the polymer completely, the samples were equilibrated at 60 °C for 15 min prior

Table 1. Characteristics of the Poly(acrylic acid-co-acrylamide) Used

	AM (mol %)				
polymer	in feed	in copolymer ^a	$M_{\rm n} \left({\rm g/mol}\right)^{b}$	\overline{D}^{b}	$T_{cp} (^{\circ}C)^{c}$
1	0.50	0.45	132,000	1.16	29.9 ± 0.3
2	0.50	0.45	21,500	1.22	16.8 ± 0.1
3	0.50	0.45	61,000	1.17	21.9 ± 0.2
4	0.50	0.44	152,500	1.18	31.4 ± 0.4
5	0.60	0.49	130,000	1.16	24.8 ± 0.4
6	0.70	0.58	170,000	1.14	12.9 ± 0.4
7	0.30	0.26	150,500	1.41	28.0 ± 0.7
8	0.20	0.17	100,500	1.22	20.0 ± 0.4
9	0.10	0.09	91,500	1.20	10.2 ± 0.5
10	0.00	0.00	173,000	1.19	<5
11	0.50	0.44	69,500	1.13	28.0 ± 0.4
12	0.50	0.40	12,000	1.32	20.6 ± 0.5
13	0.50	0.43	11,000	1.29	17.1 ± 0.5
14 ^d	0.50	0.44	840,000	1.50	37 ± 2
15 ^d	0.50	0.49	1,550,000	2.17	36.1 ± 0.8
16	0.40		148,000	1.08	36.0 ± 0.1

^{*a*}Determined by elementary analysis. ^{*b*}Number-averaged molar mass and dispersity index ($D = M_w/M_n$) measured by size-exclusion chromatography (SEC). ^{*c*}The mixing temperature (corresponding to the UCST behavior) was determined by turbidimetry at 4 wt % observed at 500 nm. ^{*d*}Prepared by conventional radical polymerization.

to scanning. The $T_{\rm cp}$ was set to be the temperature at the inflection point of the transmittance curve.

RESULTS AND DISCUSSION

Preparation of Copolymers. The copolymers P(AA-co-AM)s with varying AA/AM ratios were synthesized through RAFT polymerization, as shown schematically in Figure 1. The AM contents in the final polymers are slightly lower than the amount of AM added in the feed (Table 1), indicating a systematically lower reactivity than AA. We used the same reaction conditions for all the polymerization conditions. The polymers were synthesized in DMSO and were dialyzed in water for 4 days. The polymers were weighed after dialysis and the conversion of the monomers ranged from 34% (for Polymer 4) to 68% (for Polymer 7). The weight loss of the polymer samples in the dialysis bags may be a result of the relatively low apparent conversion since the polymer solutions were viscous and hard to transfer completely due to the high polymer concentrations in the bags, especially for the samples of higher molar masses. For this work, no effort was made to adjust the conversion of the monomers.

Effect of Polymer Composition. To study the effect the polymer composition (AA/AM ratio) on the cloud point (T_{cp}), a series of copolymers of similar molar masses (Polymers 4–10 and 16) were dissolved in a phosphate buffer solution (0.1 M, pH 2.0). Efforts were made to prepare copolymer samples of the same molar masses for a more direct comparison, but synthetic limitations made it impossible to obtain copolymers of identical molar masses. In this study, polymer samples with similar molar masses were selected, ranging from 9.2 × 10⁴ to 1.7 × 10⁵ g mol⁻¹, while the samples defining the peak region in Figure 2 had M_n values from 1.3 × 10⁵ to 1.5 × 10⁵ g mol⁻¹. The small variation of molar mass in the series should not cause large differences in the T_{cp} and the trend of the variation should be valid despite the discrepancy of the M_n values of the samples.

Figure 1. RAFT polymerization of poly(acrylic acid-*co*-acrylamide), where *x* and *n* represent the molar fraction of acrylamide and the degree of polymerization, respectively.



Figure 2. Influence of the AM molar ratio (X_{AM}) on the T_{cp} for the P(AA-*co*-AM) copolymers at 4.0 wt % in phosphoric acid buffer solution (pH 2.0, 100 mM). The dashed line serves as a visual guide. The M_n values of each of the samples are indicated next to the symbols in the graph.

The molar mass dispersity D values of these samples are typical of those prepared by RAFT polymerization, as shown in Table 1. They are relatively narrow and the small variation did not affect the T_{cp} values determined by UV-vis turbidity measurements (Figure 2) since the transitions are quite sharp for all the samples. As shown in Figure 2, at lower AM contents (i.e., from 0 to 44 mol %), increasing the AM ratio in the copolymers leads to an increased T_{cp} . At higher AM contents (from 44 to 58 mol %), the inverse trend can be observed: increasing the AM ratio in the polymers leads to a decreased $T_{\rm cp}$. A maximum transition temperature was observed to be ca. 37 °C at about 40 mol % of AM in the copolymer (Figure 2). This is similar to the phase transition behavior of the AA-AM homopolymer hydrogel network, which also showed the highest transition temperature for a mixture corresponding to approximately 40 mol % of AM.²³ These results indicate an unequal contribution of the two comonomers to the polymer-polymer H-bonding: a larger proportion of the AM comonomer is needed to achieve the maximum of the H-bonding strength.

The physical origin of the thermoresponsiveness of the P(AAco-AM) copolymers was then further investigated by comparing the strength of three types of H-bonds between the functional groups of AM-AM, AA-AA, and AA-AM. Both AA and AM are capable of forming an eight-membered ring structure containing two H-bonds (Figure 3), but neither of the corresponding

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Figure 3. Structures of the three types of H-bonds in the copolymers: (A) between AM and AM, (B) between AA and AA, and (C) between AA and AM. Arrows highlight the repulsive interactions between negatively charged carboxylate groups and between the positively charged protons.

homopolymers is thermoresponsive in water under ambient conditions. The carboxyl acid group is a better H-donor than the amide group. Therefore, the AA-AA H-bonds are more stable in water than the AM-AM H-bonds. This is evidenced by the fact that PAM possesses a hypothetical UCST of ca. -38 °C, but fully protonated PAA (in 0.2 M HCl) shows a UCST at ca. 14 °C.²⁷ To compare the strengths of the H-bonds of AA-AA and AA-AM, secondary electrostatic interactions, which refers to the repulsive interactions between the dipoles in a polarized Hbonded structure,^{28,29} must be taken into account. This effect has been successfully utilized to predict the strength of triple and quadruple H-bond arrays.²⁹ As for the AA-AA H-bonds, repulsive interactions exist between the negatively charged carboxylate groups and between the positively charged protons (arrows in Figure 3B), decreasing the strength of H-bonding. For the AA-AM H-bonds (Figure 3C), such repulsions do not exist since the N-H bond is less polarized. Therefore, AA-AM H-bonds are stronger than AA-AA H-bonds, leading to the UCST behavior of AA and AM. The asymmetry of the T_{cp} composition diagram in Figure 2B may also be related to the strength of H-bonds. Ideally, the most stable polymer-polymer complex would form when each AA unit matches an AM unit. However, due to the random distribution of the two monomers in the copolymer, there is always a mismatch of the monomers AA and AM even if their content is similar. An excess of AA may have suppressed the chances of AM-AM H-bonding, the weakest H-bond of the three, resulting in the highest T_{cp} at 40 mol % of AM in the copolymer.

Effect of Polymer Concentration (Partial Phase Diagrams). To evaluate the effects of molar mass and concentration of the copolymers on the T_{cp} , two copolymers with the same chemical composition (45 mol % AM, Polymers 1 and 2 in Table 1) but with different molar masses were diluted stepwise to vary the polymer concentration. The partial phase diagrams of the two polymers with different molar masses are shown in Figure 4. Both copolymers showed a similar trend with a stronger concentration dependence at lower polymer concentrations. The UCST polymers may be expected to present a bell-shaped curve with the UCST at the maximum of



Figure 4. Variation of T_{cp} as a function of the concentration of P(AA-*co*-AM) samples with similar chemical composition (45 mol % AM) and different molar masses in phosphate buffer solution (pH 2.0, 100 mM). Dashed lines are visual guides.

the binodal curve. Due to the dispersity in the molar mass of the polymers, a polymer solution is not exactly a binary mixture but a semi-binary mixture. The peak in the partial phase diagram may be stretched. The behavior shown in Figure 4 is similar to what was observed with other UCST polymers and corresponds to known in the literature in our understanding of this family of polymers.¹⁷

The T_{cp} increased from 7 to 17 °C when the polymer concentration increased from 0.2 to 6 wt % for P(AA-*co*-AM), reaching a plateau thereafter. Such a behavior was also observed in typical UCST polymers, such as PNAGA³⁰ and poly-(acrylamide-*co*-styrene),³¹ and was rationalized by more extensive intermolecular interactions at higher polymer concentrations. It seems that the copolymer of higher molar mass, P(AA-*co*-AM), reaches a plateau value at a lower polymer concentration. It also has a higher T_{cp} at all concentrations. This is consistent with the observations in the literature for other UCST polymers.¹⁷

Effect of Polymer Molar Mass. The molar mass of the polymer is known to have an impact on the $T_{\rm cp}$ of UCST polymers.^{17,18,30} To study this effect, we have synthesized copolymers of varying molar masses with a similar chemical composition of AM and AA (Figure 5). The $T_{\rm cp}$ value showed a strong dependence of the molar mass of the copolymer at the lower $M_{\rm n}$ end, gradually reaching a plateau at a higher $M_{\rm n}$ of ca. 3 × 10⁵ g/mol. The number of intermolecular H-bonds may be affected by the molar mass of the polymer and may lead to an increased enthalpy of the polymer and thus a higher $T_{\rm cp}$. This effect is especially pronounced for polymers of lower $M_{\rm n}$. A similar behavior can be observed for LCST polymers where a lower $T_{\rm cp}$ can be reached and maintained at higher molar masses.³²

Effect of the pH. The T_{cp} of a copolymer ($M_n = 21,500 \text{ g/mol}$ and 45 mol % of AM) was measured in a phosphate buffer solution with varying pH values to study the effect of pH on T_{cp} . The composition corresponding to 45 mol % of AM is close to the peak value of T_{cp} in Figure 2B with extensive H-bond formation. The T_{cp} was found to be lower at higher pH values (Figure 6). The p K_a for PAA was previously reported to be around 4.3,³³ showing a correspondence to our experimental data (Figure 6). At pH values lower than the p K_a , the carboxylic acid groups are protonated, facilitating the formation of H-bonds in the polymers; when the pH increases, the acid groups



Figure 5. Variation of the $T_{\rm cp}$ as a function of molar mass on the $T_{\rm cp}$ of P(AA-*co*-AM) (Polymers 1–4 and 11–15 in Table 1) at 4.2 wt % in phosphate buffer solutions (0.1 M, pH 2.0). The turbidity curves for the lower molecular weight polymers and their GPC scans are shown in Figures S1 and S3, respectively, in the Supporting Information.



Figure 6. pH effect on the T_{cp} of P(AA-*co*-AM) ($M_n = 21,500$ g/mol and 45 mol % of AM) in 0.8 wt % phosphate buffer solution (0.1 M, pH 1.5–3.0), showing the influence of the degree of protonation of carboxylic acid groups on the polymer.

are gradually deprotonated, disrupting the H-bonds and loading to a higher solubility of the polymer, therefore a lower T_{cp} .

Effect of Added Salts. To understand the effect of added salts on the $T_{\rm cp}$ of the polymer, two kosmotropic salts (Na_2SO_4 and NaCl) and two chaotropic salts (NaI and NaSCN) were selected. Na2SO4 and NaSCN are known to be weak bases and may affect the pH of the solutions at high salt concentrations. Therefore, a more concentrated phosphate buffer solution (2 M) was used for this study. The polymer solution showed an increased $T_{\rm cp}$ with added $\rm Na_2SO_4$ and NaCl and a decreased $T_{\rm cp}$ with added NaI and NaSCN. A linear change of the T_{cp} was observed as a function of the salt concentration in all cases. This linear behavior at relatively low salt concentrations (lower than 500 mM) was predicted by the Hoffmeister effect and was previously reported for other polymers.^{16,34,35} Kosmotropic salts, such as Na₂SO₄ and NaCl, showed a salting-out effect, leading to increased solubility of the polymer in water. They can facilitate the formation of H-bonded networks of water molecules around a polymer, thereby decreasing the entropy of mixing and increasing the $T_{\rm cp}$ of the polymer. Chaotropic salts, such as NaI and NaSCN, had a salting-in effect, leading to the opposite effects. Their behavior in water is less known than the kosmotropic salts but they lower the entropy of mixing to a lesser degree than the increased enthalpy of mixing by the added kosmotropic salts.^{34,36} Using the Hofmeister series, one can predict the behavior and its magnitude compared to other salts:

$$SO_4^{2-} < Cl^- < I^- < SCN^-$$

Salting-out anions are considered as "hard" charges that interact with water molecules to form a water shell surrounding the hydrophobic moieties. This would reduce the entropy gain and increase the $T_{\rm cp}$ since the polymer needs more energy to break from this shell. Salting-in salts are usually anions that are more polarizable so that they can interact with the polymer chain to induce a better solubility, thus decreasing the $T_{\rm cp}$.

Effect of Urea. Urea is known to disrupt H-bonds. When it was added to a copolymer solution, a clear impact on the T_{cp} was observed (Figure 6). Increasing the amount of urea reduces the T_{cp} of the copolymer, which is similar to a salting-in effect (Figure 7). This effect is also observed for other UCST



Figure 7. Dependence of the T_{cp} of P(AA-*co*-AM) on salt and urea concentrations in phosphate buffer solution (pH 2.0, 2 M)

polymers^{37–39} and P(AA-*co*-AM) gels.^{23,40} The disruption of interpolymer H-bonds leads to a higher hydrophilicity of the UCST polymer, which lowers the T_{cp} accordingly.

CONCLUSIONS

The homopolymers of either AM or AA are both water-soluble over a large ambient temperature range. The copolymerization of these monomers leads to a series of copolymers made of hydrophilic comonomers that can exhibit a tunable UCST behavior. The UCST behavior originates from the H-bonds formed between the carboxylic acid and the amide groups of the comonomers, which are stronger than the H-bonds between amide groups because of the higher acidity of carboxylic acid and also stronger than the H-bonds between the carboxylic acid groups due to the absence of the secondary electrostatic repulsion. The effect of H-bonding has a maximum at around 45 mol % of AM, corresponding to a peak value of $T_{\rm cp}$ for its UCST behavior. The polymers also show an increasing $T_{\rm cp}$ along with

the concentration of the copolymers, reaching a plateau at relatively low concentrations of less than 5 wt %. A similar trend is also observed for the molar mass effect of the copolymers, reaching a plateau of ca. 35 °C at an $M_{\rm p}$ value of ca. 3 × 10⁵ g/ mol. Higher pH leads to the deprotonation of the carboxylic acid group, increasing the solubility of the polymer and lowering its UCST. Adding salt and urea may also influence the solubility of the polymer, thus affecting their $T_{\rm cp}$. The strength of the Hbonds can be affected by the salting-in and out effects depending on the character of the added salts. The results presented here may help us understand why this copolymer is an excellent temperature-dependent flocculant.⁴¹ This study places emphasis on the effect of secondary electrostatic interactions in the Hbonded network of hydrophilic polymers possessing donors and acceptors for H-bonds. It points to the strategy in designing thermoresponsive UCST polymers as random copolymers made of monomers of hydrophilic characteristics in the absence of ionic interactions and without the use of hydrophobic monomers. The results shown here may lead to an enlarged repertoire of new thermoresponsive polymeric materials for practical applications.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.macromol.1c00952.

Turbidity scans, ¹H NMR spectra, and GPC chromatograms for selected copolymers (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by the Natural Sciences and Engineering Research Council (NSERC) of Canada (grant # RGPIN-2019-05469) and the Canada Research Chair program and through a stipend allocated to Guillaume Beaudoin via the NSERC-CREATE PrEEmiuM program. This work was also supported by the TransMedTech Institute (NanoBio Technology Platform) and its main funding partner, the Canada First Research Excellence Fund.

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