

**Effects of *N*-Substituents on Solution Behavior of Poly(sulfobetaine methacrylate)s in
Water: UCST and LCST**

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Abstract: A series of zwitterionic poly(sulfobetaine methacrylate)s (PSBMAs) with various *N*-substituents, including *n*-alkyl, cyclohexyl, 2-hydroxyethyl, and phenyl, was synthesized in order to elucidate the effects of *N*-substituents on solution behavior of PSBMAs in water. Upon increasing the lengths of two symmetric *N*-*n*-alkyl substituents simultaneously, PSBMAs exhibited an array of behavior in water, from UCST to soluble, to LCST, and insoluble, which presumably stemmed from the competition between the decrease in electrostatic zwitterionic interactions and the increase in hydrophobic effect with increasing alkyl length. Replacing *N*-*n*-hexyl with cyclohexyl while keeping the *N*-methyl substituent diminished the hydrophobic effect and made the LCST vanish. Introducing a 2-hydroxyethyl or a phenyl *N*-substituent enhanced the attractive interactions between zwitterionic groups, resulting in UCST behavior. The insight gained from this work can facilitate the design of UCST- and LCST-type thermoresponsive zwitterionic PSBMAs by varying *N*-substituents and will open up more opportunities for potential applications of already widely used zwitterionic materials (e.g., thermoresponsive zwitterionic polymer brushes and nanogels for use in bioseparation and drug delivery).

KEYWORDS: poly(sulfobetaine methacrylate), zwitterionic polymers, thermoresponsive, UCST, LCST, water-soluble, electrostatic zwitterionic interactions, hydrophobic effect

Introduction

Zwitterionic polymers are a special class of polyelectrolytes in which each repeat unit contains two oppositely charged moieties of equal magnitude that are most frequently both located on the pendant group.^{1,2} Although highly charged, zwitterionic polymers maintain charge neutrality globally and locally and exhibit many intriguing properties, including exceptional hydrophilicity (for common polyzwitterions),^{1,2} antipolyelectrolyte effect,^{3,4} and stimuli-responsive property.^{2,5-11} These unique characteristics have been exploited intensively for numerous applications, such as anti(bio)fouling,^{1,2,12-17} lubrication,^{18,19} anti-icing and anti-freezing,^{20,21} oil-water separation,²² cryopreservation,²³ etc. Among common zwitterionic homopolymers, poly(3-((2-methacryloyloxyethyl)dimethylammonio)propane-1-sulfonate) (P11 in Scheme 1), a representative of poly(sulfobetaine methacrylate)s (PSBMAs), and poly(3-(*N*-(3-methacrylamidopropyl)dimethylammonio)propane-1-sulfonate) (PMAMPS) are known to exhibit an upper critical solution temperature (UCST) in water.^{2,5,9,24,25} The UCST behavior is likely a result of the competition between electrostatic attractive interactions of zwitterionic groups and thermal energy; presumably, heating overcomes the electrostatic inter-locking of zwitterionic groups, causing the polymer to dissolve in water and thus exhibit a UCST.

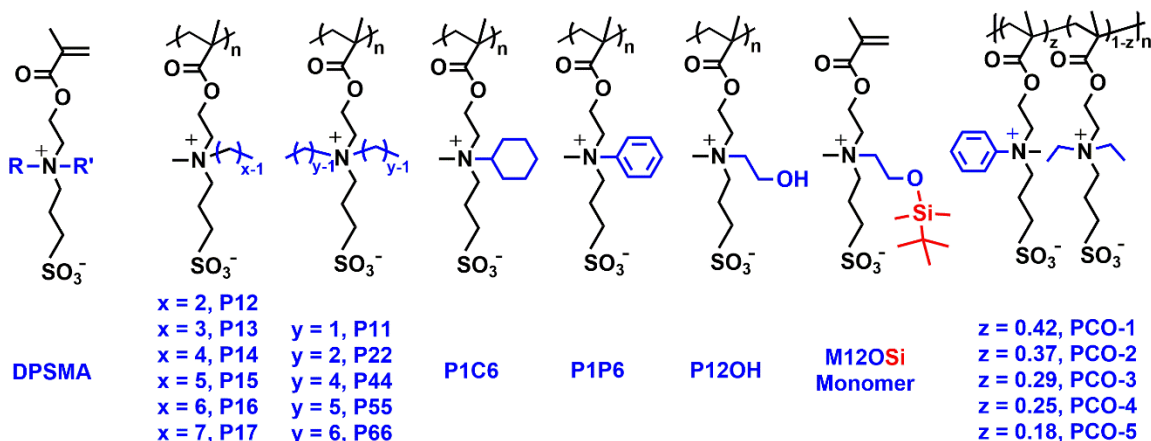
Despite the fact that zwitterionic polymers are structurally versatile,^{1-7,24-33} the vast majority of the systems reported in the literature for potential applications are built from the polymers of a small number of monomers.² Varying the structure of zwitterionic materials will change their solution behavior in water, and studies have shown that the effect is subtle, often counterintuitive, and hard to predict. For example, if a hydrophilic hydroxyl group is introduced onto the middle carbon atom in the spacer between the ammonium and the sulfonate group of PMAMPS, the cloud point (CP) of the resultant polymethacrylamide in water is found to be higher (i.e., the solubility

becomes poor).²⁴ When the dimethylammonio group in P11 is replaced with a six-membered piperidinio ring, the UCST disappears and the polymer becomes soluble in water in the temperature range of 0 – 100 °C, although the alkyl ring is larger and more hydrophobic than the two methyl groups.²⁵ The improved solubility of zwitterionic polymers in water with increasing alkyl size is attributed to the weakening of the electrostatic attractive forces between zwitterions caused by the steric hindrance from larger alkyl groups. On the other hand, larger hydrophobic groups introduce a larger hydrophobic effect, which is the origin of the lower critical solution temperature (LCST) transition of polymers in water.³³⁻³⁵ By keeping one methyl group on the nitrogen atom and systematically increasing the length of the other *N*-*n*-alkyl substituent, we prepared a series of PSBMA homopolymers (P11 – P17 in Scheme 1) from the corresponding zwitterionic DPSMA monomers (Scheme 1) and observed a range of solution behavior in water.³³ While P11 was a UCST thermoresponsive polymer as reported, P12, P13, and P14 were soluble in water in the temperature range of 0-100 °C likely due to the steric disruption of zwitterionic attractive interactions. Intriguingly, P15 and P16 exhibited LCST behavior with CPs at ~ 50 and 22 °C, respectively. On the other hand, P17 was found to be insoluble in water, apparently caused by the high hydrophobicity of the *N*-heptyl group.

To further understand the effects of *N*-substituents on solution behavior of DPSMA-based PSBMA (PDPSMA, with two CH₂ groups between the ester and the ammonium, three CH₂ groups between the ammonium and the sulfonate group, and two separate substituents, R and R', at the nitrogen atom) in water for facilitating the design of UCST- and LCST-type thermoresponsive zwitterionic polymers, we synthesized and investigated three subgroups of such PSBMA with various *N*-substituents (Scheme 1). (i) P11 – P66 are prepared for studying the effects of the number and length of *N*-*n*-alkyl substituents. (ii) A polar 2-hydroxyethyl group,

capable of hydrogen bonding and dipole-ion interactions, is introduced as an *N*-substituent to examine its effect on the solution behavior of P12OH in water in comparison to the corresponding P12, which is soluble in water. (iii) P16 with a *n*-hexyl, P1C6 with a cyclohexyl, and P1P6 with a phenyl substituent at the nitrogen atom are prepared for investigating the effects of molecular shape and aromaticity of *N*-substituents. Compared with the *n*-hexyl group, cyclohexyl is more compact and has a smaller contact area with water; the *N*-phenyl substituent can interact with cations and anions. The influences of these structural variations are revealed, and the results from this study not only improve our understanding of the structure-solution-behavior relationship of PDPSMAs in water but also provide an insight into the design of UCST- and LCST-type thermoresponsive as well as water-soluble zwitterionic PSBMAs.

Scheme 1. Molecular Structures of Zwitterionic Homopolymers of DPSMA Sulfobetaine Methacrylates with Various *N*-Substituents, Monomer M12OSi, and Copolymers of Two Monomers with Various Molar Contents.



Results and Discussion

Synthesis and Characterization of PDPSMAs. A total of seven PDPSMAs with various *N*-substituents, including symmetric di(*n*-alkyl) (P22, P44, P55, and P66), methyl and 2-hydroxyethyl (P12OH), methyl and cyclohexyl (P1C6), and methyl and phenyl (P1P6) on the nitrogen atom (Scheme 1), were synthesized by conventional free radical polymerization in 2,2,2-

trifluoroethanol (TFE) using 2,2'-azobis(2-methylpropionitrile) (AIBN) as initiator. We also made P11 for comparison with the PDPSMAs with symmetric *N,N*-di(*n*-alkyl) substituents and P16 for comparison with P1C6 and P1P6. All of the homopolymers were synthesized directly from the corresponding DPSMA sulfobetaine methacrylate monomers except P12OH, which was prepared by polymerization of M12OSi (Scheme 1) and subsequent removal of *tert*-butyldimethylsilyl protective groups under acidic conditions. In addition, three lower molecular weight P1P6 homopolymers were synthesized by reversible addition-fragmentation chain transfer (RAFT) polymerization.³⁶⁻³⁸ All of the polymer samples were purified by dialysis against Milli-Q water and freeze-dried. ¹H NMR analysis showed that the spectra agreed with the molecular structures of the zwitterionic polymers. The detailed synthesis and characterization data for the polymers, which are summarized in Table 1, and the corresponding monomers can be found in the Supporting Information.

The PDPSMAs shown in Table 1 represent a diverse set of zwitterionic materials with varying intra- and intermolecular interactions. We found that it was extremely challenging to characterize the molecular weights and dispersities of these samples by size exclusion chromatography (SEC) using one set of columns and one eluent (see Section S.1 of the Supporting Information). Therefore, we elected to measure the intrinsic viscosities of these zwitterionic polymers in TFE at 25.0 °C using a Ubbelohde viscometer. While conventional Huggins and Kraemer plots were attempted, we noticed that the curves often deviated significantly from linear relationships (see examples in Section S.3 of the Supporting Information). This pronounced non-linearity of η_{sp}/c (or $\ln\eta_{rel}/c$) versus *c* likely resulted from the complex electrostatic interactions between charged groups at dilute conditions as discussed by Wolf.³⁹ Therefore, we followed Wolf's method^{39,40} to determine the intrinsic viscosities of our zwitterionic polymers in TFE from the initial slope of the

dependence of $\ln\eta_{\text{rel}}$ on polymer concentration c (see Section S.3. of the Supporting Information) and the obtained $[\eta]$ values were in the range from 0.051 to 0.684 dL/g (Table 1). Note that the molecular weights and dispersities of lower molecular weight P1P6 samples made by RAFT polymerization (i.e., P1P6-2, -3, and -4) were measured by aqueous SEC analysis relative to PEO standards using a 0.2 M NaNO_3 aqueous solution as eluent (Table 1).

Table 1. Characterization Data and Solution Behavior in Water of Zwitterionic PDPSMA Homopolymers

PDPSMA Homopolymer	DPSMA Monomer	$[\eta]$ (dL/g) ^a	Solution Behavior in H ₂ O	Cloud Point ^c
P11	M11	0.284	UCST	47 °C
P22-1	M22	0.478	Soluble	N/A
P22-2	M22	0.684	Soluble	N/A
P44-1	M44	0.376	Soluble	N/A
P44-2	M44	0.309	Soluble	N/A
P55-1	M55	0.129	LCST	42 °C
P55-2	M55	0.288	LCST	40 °C
P66-1	M66	0.116	Insoluble	N/A
P66-2	M66	0.098	Insoluble	N/A
P16-1	M16	0.248	LCST	11 °C
P16-2	M16	0.227	LCST	12 °C
P1C6-1	M1C6	0.176	Soluble	N/A
P1C6-2	M1C6	0.520	Soluble	N/A
P1P6-1	M1P6	0.155	Insoluble	N/A
P1P6-2	M1P6	0.075; ^a ($M_{n,\text{SEC}} = 2.6$ kDa; $\bar{D} = 2.13$) ^b	Insoluble	N/A
P1P6-3	M1P6	0.056; ^a ($M_{n,\text{SEC}} = 2.3$ kDa; $\bar{D} = 2.04$) ^b	UCST	56 °C ^d
P1P6-4	M1P6	0.051; ^a ($M_{n,\text{SEC}} = 2.0$ kDa; $\bar{D} = 2.13$) ^b	UCST	37 °C ^d
P12OH-1	M12OSi	0.358	UCST	33 °C
P12OH-2	M12OSi	0.202	UCST	23 °C

^a $[\eta]$ values in 2,2,2-trifluoroethanol (TFE) at 25.0 °C were determined using the Wolf's method.^{39,40} ^b Number average molecular weight ($M_{n,\text{SEC}}$) and dispersity ($\bar{D}$) were measured by aqueous SEC analysis relative to PEO standards using a 0.2 M NaNO_3 solution as eluent. Note that P1P6-2, -3, and -4 are soluble in the 0.2 M NaNO_3 aqueous solution and also in D_2O with 0.5 M NaCl despite the observation that they are not soluble at room temperature in pure water. ^c Cloud points (CPs) were the temperatures at which a 50% transmittance change occurred. The CPs of UCST and LCST polymers were determined from cooling and heating curves, respectively, at 1.0 wt%. ^d The CPs are for 0.2 wt% polymer solutions. Note that the CP of P1P6-4 at 1.0 wt% was 66.5 °C.

Solution Behavior of PDPSMAs with Two Symmetric *N-n*-Alkyl Substituents in Water.

The solution behavior of P11, P22, P44, P55, and P66 in water at various temperatures was first

examined by visual inspection at a concentration of 1.0 wt% to study the effect of the lengths of two symmetric *N-n*-alkyl substituents. Those exhibiting thermoresponsive properties were further examined using a UV-vis spectrometer to record the transmittance at 500 nm as a function of temperature. As expected, P11 displayed a UCST transition in water; the polymer solution was clear at elevated temperatures but turned cloudy upon cooling as can be seen from the photos in Figure 1A. From the plot of transmittance versus temperature (Figure 2A), the CP of P11, which was determined as the temperature at which a 50% transmittance change occurred, was 47 °C. This value was higher than our previously reported CP (31 °C) of a P11 homopolymer synthesized by RAFT polymerization.³³ The CPs of UCST polymers in liquid media are known to be very sensitive to the molecular weight change, end group identity, and the presence of a small amount of structural defects,^{2,5,9,25,41-43} usually more than LCST-type thermosensitive polymers.^{5,34} For instance, Hildebrand et al. reported that the CP of P11 in H₂O increased from 41 to 71 °C with increasing the degree of polymerization from 85 to 585.²⁵ In contrast, P22 was completely soluble in water from 0 – 100 °C (Figure 1B), similar to the solution behavior of P12, P13, and P14.³³ Note that P22-2 has a $[\eta]$ value of 0.684 dL/g, much higher than that of P11 ($[\eta]$ = 0.284 dL/g). Interestingly, even with a total of 8 carbon atoms in the two *n*-alkyl substituents, P44 was completely soluble in water (Figure 1C), which is different from P17 that also has 8 carbon atoms in the two *N*-alkyl substituents but is insoluble in water.³³ This indicates that the effects of two alkyl substituents are not additive.

More interestingly, P55 with a total of 10 carbon atoms in the two substituents exhibited an LCST in water; the solution was clear at 10 °C but cloudy at 65 and 90 °C (Figure 1D). At a concentration of 1.0 wt% in Milli-Q water, the CPs of P55-1 ($[\eta]$ = 0.129 dL/g) and P55-2 ($[\eta]$ = 0.288 dL/g) were 42 °C (Figure 2B) and 40 °C (see Section S.5. of the Supporting Information),

respectively, consistent with the common observation that a higher molecular weight LCST polymer exhibits a lower CP.⁴⁵ The thermal hysteresis from heating and cooling processes was minimal for both samples (Figure 2B and Section S.5. of the Supporting Information). The CP increased with decreasing concentration of the polymer (Figure 2C), showing a

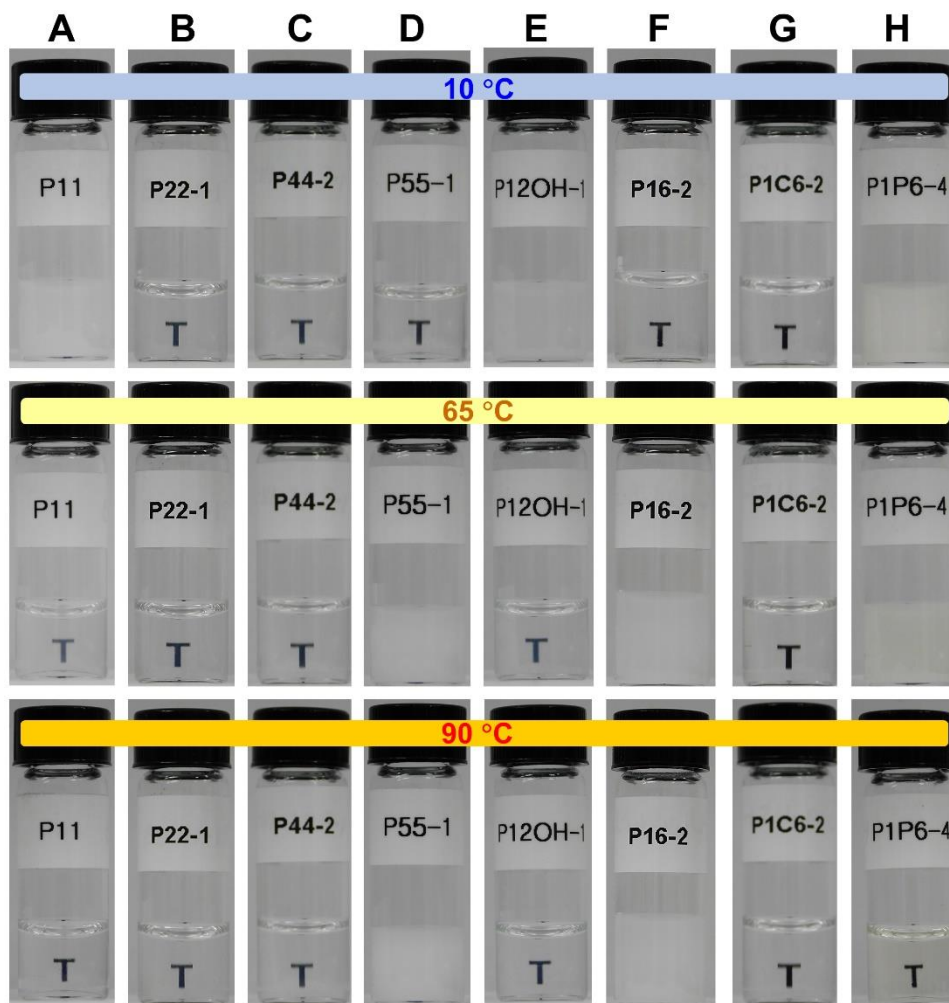


Figure 1. Optical photos of 1.0 wt% aqueous solutions of P11 (A), P22-1 (B), P44-2 (C), P55-1 (D), P12OH-1 (E), P16-2 (F), P1C6-2 (G), and P1P6-4 (H) at 10, 65, and 90 °C.

concave curve characteristic of LCST polymers (Figure 2D). The heating-induced LCST transition of P55-1 was further investigated by variable temperature ¹H NMR analysis at a concentration of 1 wt% in D₂O (Figure 3A); the peaks marked by the arrows decreased noticeably in intensity when

the temperature was raised from 40 °C to 43 °C and above, consistent with the CP of the same D₂O solution (39 °C) observed by visual inspection. Further increasing the lengths of two *n*-alkyl substituents by just one carbon atom resulted in a water-insoluble polymer, P66, despite the relatively low intrinsic viscosities (0.116 and 0.098 dL/g) of the two samples. We previously observed that the CPs of P15 and P16 in H₂O were ~ 50 and ~ 22 °C,³³ showing that adding one CH₂ unit into the longer alkyl while keeping the *N*-methyl constant decreases the CP substantially. The overall trend for both polymer series is qualitatively similar to the decrease of CP for LCST-type thermoresponsive poly(oligo(ethylene glycol) (meth)acrylate)s caused by the addition of one CH₂ group to the end of the side chain in each repeat unit.⁴⁶⁻⁴⁸

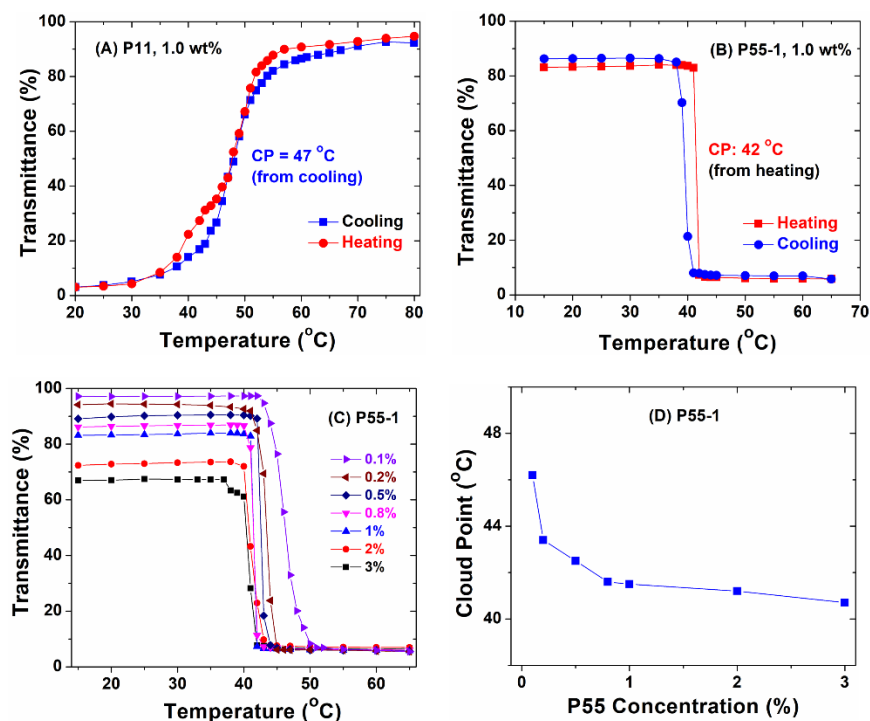


Figure 2. Plots of transmittance at the wavelength of 500 nm versus temperature for (A) 1.0 wt% P11 in Milli-Q water from a cooling-heating cycle and (B) 1.0 wt% P55-1 in Milli-Q water from a heating-cooling cycle. (C) Plots of transmittance versus temperature for aqueous solutions of P55-1 with various concentrations from the heating processes, and (D) plot of cloud point versus polymer concentration obtained from (C).

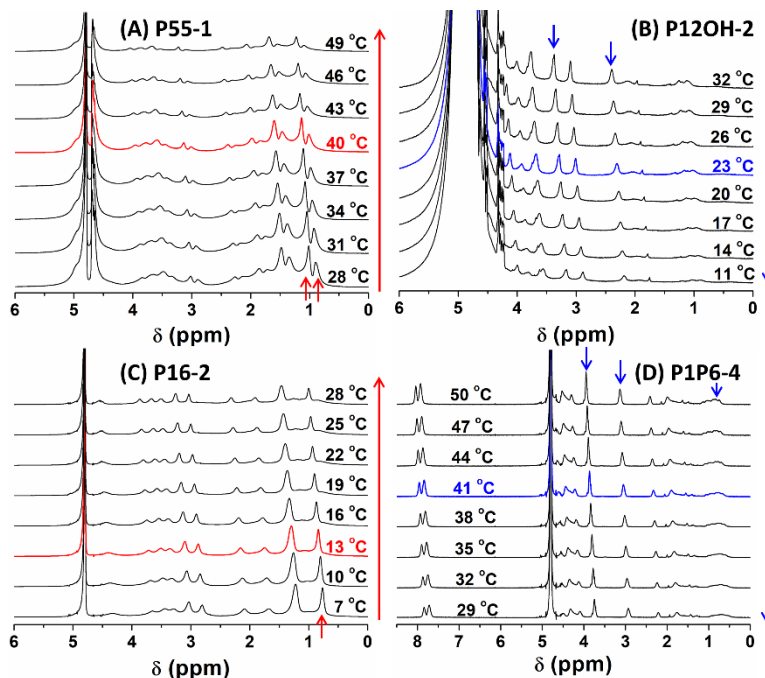
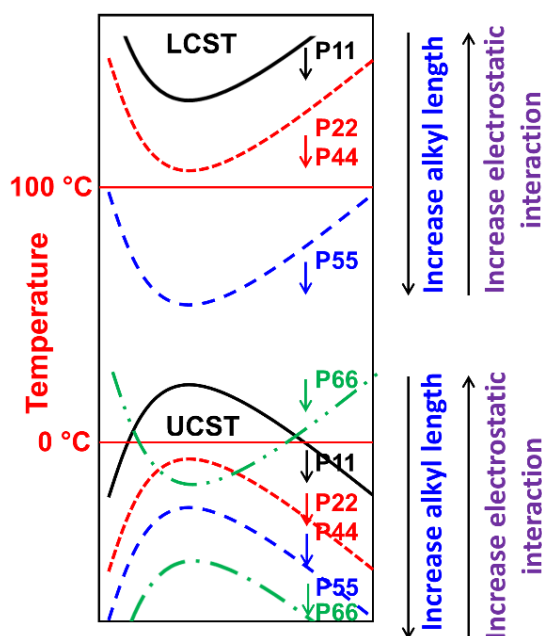


Figure 3. ^1H NMR spectra of thermoresponsive zwitterionic PDPSMA homopolymers with different N -substituents in D_2O at various temperatures: (A) 10 mg/g P55-1 (CP = 39 $^\circ\text{C}$ by visual inspection), (B) 4 mg/g P12OH-2 (CP = 23 $^\circ\text{C}$ by visual inspection), (C) 10 mg/g P16-2 (CP = 11 $^\circ\text{C}$ by visual inspection), and (D) 2 mg/g P1P6-4 (CP = 41 $^\circ\text{C}$ by visual inspection) at various temperatures from variable temperature ^1H NMR spectroscopy analysis studies. The HDO peak at 4.79 ppm was used to normalize all spectra for each polymer.

The observed evolution of solution behavior of PDPSMAs with two symmetric N - n -alkyl substituents in water from UCST to water-soluble, LCST and water-insoluble may be attributed to two competing effects that resulted from increasing alkyl length: steric weakening of electrostatic attractive interactions between zwitterionic groups and increase of the hydrophobic effect associated with n -alkyl groups. When the two N -substituents are as small as methyl, the electrostatic inter-locking of zwitterionic groups causes P11 to be insoluble in cold water. Upon heating, the thermal motions presumably overcome the electrostatic forces, resulting in the dissolution of P11 in water and a UCST transition (convex black curve in Scheme 2). Upon increasing the lengths of two symmetric N -substituents to 2 and 4 carbon atoms, the zwitterionic

interactions are likely sterically disrupted by two larger symmetric *N-n*-alkyl groups, making the polymers soluble in water and shifting the UCST curve below 0 °C (convex red dashed line in Scheme 2). Meanwhile, the entropic penalty from the *N-n*-alkyls is still small compared with the enthalpic gain from the hydration of zwitterionic groups and the LCST curve is still above 100 °C (concave red dashed line in Scheme 2). Consequently, the polymers are soluble from 0 – 100 °C. Note that the steric weakening of electrostatic zwitterionic interactions by larger *N*-alkyl groups would lead to a lower glass transition temperature in the bulk state. Köberle and Laschewsky reported that the glass transition temperature of a zwitterionic polymethacrylate with a molecular structure similar to P22 (the only difference is the spacer length between the ester and the ammonium moiety: eleven CH₂ groups vs. two CH₂ group in P22) was lower by more than 100 °C than that of the corresponding polymer with two *N*-methyl groups,⁴⁹ suggesting weaker interactions between zwitterionic groups for larger *N*-alkyls. Further increasing the lengths to 5 carbon atoms introduces a larger entropy penalty. While the polymer is soluble at lower temperatures, it is not at higher temperatures and hence exhibits an LCST in water (concave blue dashed line in Scheme 2). For P66, the entropic penalty is too high and the polymer becomes insoluble in water (concave green curve in Scheme 2). We emphasize here that our explanations are focused on PDPSMAs with a general molecular structure shown in Scheme 1 (i.e., two CH₂ groups between the ester and the ammonium, three CH₂ groups between the ammonium and sulfonate groups, and two separate substituents, R and R', at the nitrogen atom). It is not our intention in this work to extend our explanations to other zwitterionic polymers, e.g., with different spacers or spacer lengths between the ester or amide and the ammonium and between the ammonium and the sulfonate group.



Scheme 2. Hypothetical phase diagrams of zwitterionic PDPSMAs with various symmetric *N-n*-alkyl substituents in H₂O.

As mentioned earlier, P44 with a total 8 carbon atoms in the two *N*-substituents is soluble in water from 0 to 100 °C, while P15 and P16 with 6 and 7 carbon atoms, respectively, exhibit LCST transitions in water.³³ This difference is likely caused by the disruption of structured water on the portion of the hydrophobic alkyl groups adjacent to the positive charge center. The hydration of positively charged ammonium species occurs at the expense of nearby hydrophobic hydration⁵⁰ and thus diminishes the hydrophobic effect of two *n*-butyl substituents. Since the LCST is determined by the amount of water of hydrophobic hydration, the remaining hydrophobic hydration for the *n*-butyl groups is not sufficient for P44 to exhibit LCST behavior in water. On examining the behavior of P44 (soluble), P55 (LCST, CP = ~ 40 °C), P14 (soluble), P15 (LCST, CP = ~ 50 °C), and P16 (LCST, CP = ~ 22 °C) in water, it appears that a longer *n*-alkyl group is more important than the total number of carbon atoms in the two *N-n*-alkyl substituents for PDPSMAs to display an LCST in water. Moreover, since both P15 and P55 exhibit LCST behavior

and their CPs are quite close to each other (~ 50 and ~ 40 °C, respectively), P25 with one ethyl and one *n*-pentyl, P35 with one *n*-propyl and one *n*-pentyl, and P45 with one *n*-butyl and one *n*-pentyl substituent at the nitrogen atom would be expected to all exhibit LCST transitions in water likely with CPs in the range of 40 to 50 °C at similar molecular weights. Thus, increasing the lengths of two symmetric and asymmetric *N*-*n*-alkyl substituents of PDPSMAs presumably weakens the electrostatic attractive interactions between zwitterionic groups (Scheme 2), favoring the dissolution of the polymers in water, and simultaneously increases the hydrophobic effect. As a result, the behavior of zwitterionic PDPSMAs in water changes from UCST to soluble, LCST, and finally insoluble. We note here that for DPSMAs with two different *N*-substituents the nitrogen atom is a chiral center and we used racemic monomer mixtures in the polymerizations. It is unclear at this point how the chirality and the extent of symmetry affect the electrostatic interactions between zwitterionic groups and contribute to the solution behavior in water observed for the two polymer series, P11 – P17 and P11 – P66. This needs a further investigation probably through computer simulations.

Solution Behavior of P12OH with a Hydroxyethyl *N*-Substituent in Water. We previously reported that P12 with one methyl and one ethyl group at the nitrogen atom was soluble in water in the temperature range of 0 to 100 °C.³³ To study how the presence of a polar, hydrogen bonding-capable hydroxyl group at the end of the *N*-ethyl substituent affects the polymer's behavior in water, we prepared two P12OH samples (P12OH-1 with $[\eta] = 0.358$ dL/g and P12OH-2 with $[\eta] = 0.202$ dL/g) and found that both P12OH-1 and -2 exhibited UCST behavior in water. As shown in Figure 1E, a 1.0 wt% P12OH-1 solution was clear and homogeneous at 90 and 65 °C but cloudy at 10 °C. From the transmittance data (Figure 4A and B), the CPs of P12OH-1 and -2 at a concentration of 1.0 wt% from the cooling curves were 33 and 23 °C, respectively, with negligible

thermal hysteresis in the heating and cooling cycle. The CP of the high molecular weight P12OH sample is higher, as expected for UCST polymers.⁵ Contrary to LCST thermoresponsive P55, the CP of P12OH decreased with decreasing concentration (Figure 4C) and the plot of CP versus concentration showed a convex shape (Figure 4D), which is a characteristic of UCST thermoresponsive polymers. The UCST behavior of P12OH-2 was also studied by variable temperature ¹H NMR spectroscopy (Figure 3B). In contrast to LCST polymer P55, the peaks decreased in intensity with decreasing temperature from 32 to 11 °C. However, the transition was not as sharp as P55, likely because of the retention of a large amount of water by zwitterionic groups after the collapse.

Thus, replacing the *N*-ethyl substituent of P12 with a polar 2-hydroxyethyl group turned a water-soluble polymer into a UCST thermosensitive polymer. Instead of improving the polymer's solubility in water, the polar hydroxyl group enhanced the intra- and intermolecular attractions between zwitterionic groups, likely through the hydrogen bonding between each other and the dipole-ion interactions with zwitterionic groups, resulting in a poorer solubility in water. Note that the $[\eta]$ of P12OH-1 (0.358 dL/g) is higher than that of P11 (0.284 dL/g), but the CP (33 °C) was lower by 14 °C than P11, which means that everything else being equal the solubility of P12OH in water is better than P11. This is likely caused by the larger size of -CH₂CH₂OH, compared with the *N*-methyl of P11, which presents a higher steric hindrance than the methyl group and weakens to some degree the interactions between zwitterionic groups, as well as the hydrogen bonding between -CH₂CH₂OH and water. Based on this reasoning, it is possible that increasing the length of the *N*-(CH₂)_nOH substituent in a certain range while keeping the *N*-methyl substituent could result in the disappearance of the UCST transition in water without introducing LCST for corresponding PDPSMAs.

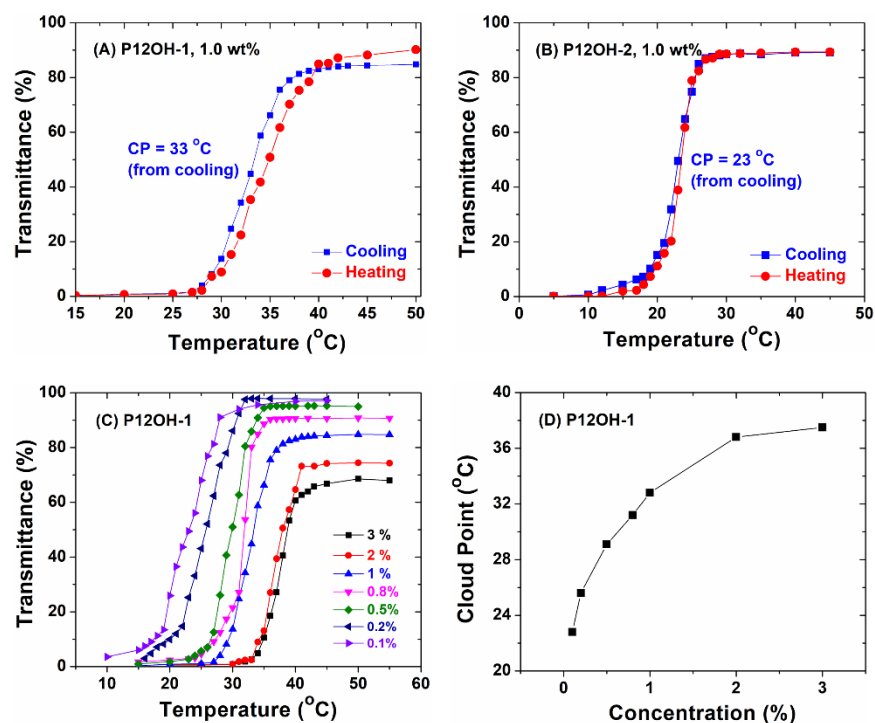


Figure 4. Plots of transmittance at the wavelength of 500 nm versus temperature for P12OH-1 (A) and P12OH-2 (B) in water at a concentration of 1.0 wt% from a cooling-heating cycle. (C) Plots of transmittance versus temperature for P12OH-1 in water at different concentrations from cooling processes and (D) plot of cloud point versus concentration for P12OH-1 determined from (C).

Solution Behavior of P1C6 and P1P6 in Water. Next, we investigated the effect of molecular shape of one *N*-alkyl substituent and the effect of aromaticity of one *N*-substituent, where the aromatic moiety does not comprise and is directly attached to the nitrogen atom as a substituent, on solution behavior of PDPSMAs in water. P16 with a *n*-hexyl and a methyl group at the nitrogen atom is a LCST-type thermoresponsive zwitterionic polymer with a CP of ~ 22 °C in water.³³ Compared with *n*-hexyl, cyclohexyl has a compact structure and a smaller surface area. Unlike saturated alkyls, aromatic *N*-substituents without containing the ammonium nitrogen can interact with charges. Therefore, to gain an understanding of the structure-solution-property relationship, it would be beneficial to examine how the molecular shape and the aromaticity of *N*-substituents of PDPSMAs affect the polymer's behavior in water. For comparison, two P16 samples were made

by conventional free radical polymerization in this work and as expected both exhibited a LCST transition in water (Figure 1F) with CPs of 11 °C (for P16-1 with $[\eta]$ of 0.248 dL/g) and 12 °C (for P16-2 with $[\eta]$ of 0.227 dL/g) from the heating process (Figures 5A and Section S.5 of the Supporting Information). These CPs were lower than that of the P16 we previously made by RAFT polymerization (~ 22 °C),³³ likely because the molecular weights of P16-1 and -2 are much higher. Similar to P55-1 in Figure 3A, variable temperature ^1H NMR spectroscopy analysis showed that the peaks of P16-2 decreased in intensity around the CP upon heating (Figure 3C). Replacing the linear *N*-hexyl substituent with cyclohexyl, we found, produced a soluble polymer (P1C6) with no LCST or UCST transition in water in the temperature range of 0 – 100 °C (Figure 1G). Note that P1C6-2 had a $[\eta]$ of 0.520 dL/g, much higher than those of P16-1 and -2. This could be attributed to three factors. (i) A compact, bulkier cyclohexyl group is likely more effective in sterically weakening the electrostatic attractive interactions between zwitterionic groups, making the polymer more soluble in water. (ii) Hydrophobic effect depends on the surface contact area of the hydrophobic moiety with water; a more compact molecular geometry of cyclohexyl means less structured water and thus less entropic penalty.^{51,52} Studies have shown that it costs 5.2 kJ mol⁻¹ to transfer cyclohexane into water from the vapor phase at 298 K, whereas it costs 10.7 kJ mol⁻¹ for hexane.⁵² (iii) A more compact molecular shape of the cyclohexyl group as an *N*-substituent means more carbon atoms closer to the positive charge center, resulting in more disruption of hydrophobic hydration and thus less water of hydrophobic hydration.⁵⁰

On the other hand, replacing the *N*-cyclohexyl with a phenyl ring gave a water-insoluble polymer by conventional free radical polymerization (P1P6-1 in Table 1). Suspecting that the molecular weight from the AIBN-initiated radical polymerization was too high, we made three lower molecular weight P1P6 samples by RAFT polymerization: P1P6-2 ($[\eta]$ = 0.075 dL/g; $M_{n,SEC}$

= 2.6 kDa), P1P6-3 ($[\eta] = 0.056$ dL/g; $M_{n,SEC} = 2.3$ kDa), and P1P6-4 ($[\eta] = 0.051$ dL/g; $M_{n,SEC} = 2.0$ kDa) (Table 1). Even with a $[\eta]$ value of 0.075 dL/g and a $M_{n,SEC}$ of 2.6 kDa, P1P6-2 was still insoluble in water; intriguingly, P1P6-3 and P1P6-4 displayed UCST behavior in pure water at low concentrations, and P1P6-4 with the lowest molecular weight had a better solubility. As can be seen from Figure 1H, the 1 wt% P1P6-4 in water is clear at 90 °C but cloudy at 65 and 10 °C. Figure 5B shows the plots of transmittance versus temperature for P1P6-4 at concentrations from 0.1 wt% to 1.0 wt%. Similar to P12OH-1 in Figures 4C and D, the CP decreased with decreasing concentration, a characteristic feature for UCST polymers (Figure 5C). The transmittance data for P1P6-3 in the concentration range of 0.04 wt% to 0.2 wt% can be found in the Supporting Information (Section S.5). (It was difficult to obtain homogeneous solutions at higher concentrations for P1P6-3.) At the concentration of 0.2 wt%, the CP of P1P6-3 was 56 °C, much higher than that of P1P6-4 (37 °C). Evidently, the solubility and the UCST transition of P1P6 in water are very sensitive to the molecular weight. Figure 3D shows the ^1H NMR spectra of 0.2 wt% P1P6-4 in D_2O at various temperatures; similar to P12OH-2 (Figure 3B), the peaks' intensities decreased with decreasing temperature across the CP, although no sharp transition was discerned. Our observation that high molecular weight P1P6 homopolymers are insoluble in water is consistent with many reports in the literature that incorporating aromatic rings, particularly N-containing heterocycles, into other zwitterionic polymers often produces polymers insoluble in pure water,^{3,6,26-28} although there also exist examples in the literature that the polymers are soluble in water.^{4,53-55} Vasantha et al. reported that imidazole-based zwitterionic polystyrenics were insoluble in pure water but exhibited UCST behavior in brine.⁶

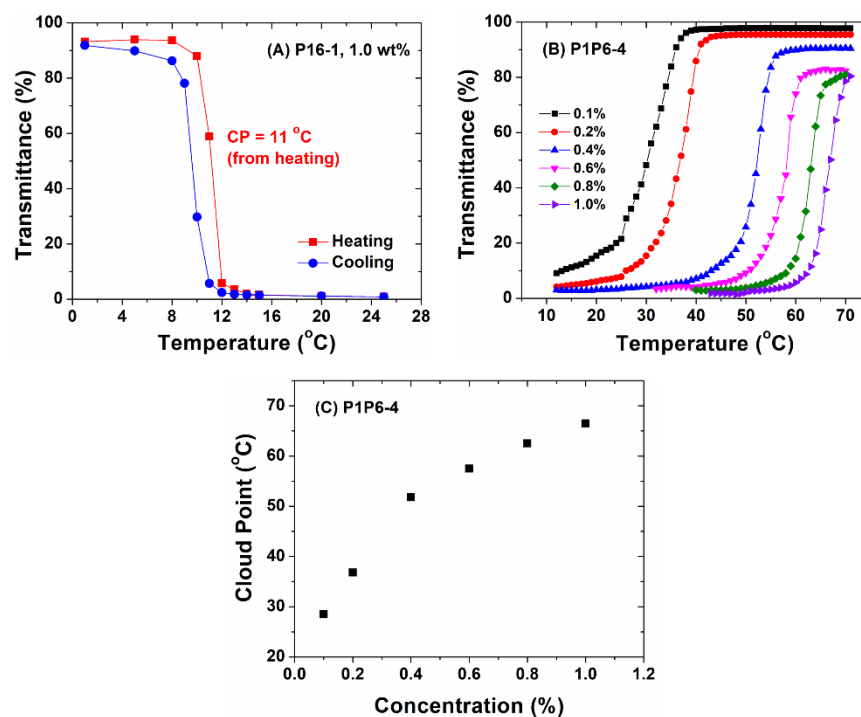


Figure 5. (A) Plot of transmittance at the wavelength of 500 nm versus temperature for 1.0 wt% P16-1 in Milli-Q water from a heating-cooling cycle. (B) Plot of transmittance versus temperature for P1P6-4 at various concentrations upon cooling, and (C) plot of cloud point versus polymer concentration for P1P6-4 from (B).

The results presented above showed that varying one *N*-substituent from *n*-hexyl to cyclohexyl and phenyl led to dramatic changes in the solution behavior and thermoresponsive properties of PDPSMAs in water. The introduction of an *N*-phenyl substituent significantly increased the attractive interactions between zwitterionic groups, making the polymer much less soluble in water. The enhanced overall intra- and intermolecular attractive forces between the pendant zwitterions likely resulted from the following effects and interactions. (i) The π - π interactions⁵⁶ between neighboring *N*-phenyl substituents will increase the attractive force between zwitterionic groups. (ii) There are strong intra- and interchain cation- π interactions between the positively charged ammonium cation and the electro-rich phenyl ring. The interaction between benzene and methylammonium in water could amount to 5.5 kcal/mol,⁵⁷ which is comparable to water-water

hydrogen bonding. (iii) There are also anion- π interactions⁵⁸ between sulfonate anions and phenyl rings, which could also contribute to the overall electrostatic interactions between zwitterionic groups. Note that for aromatic rings, the π system above and below the ring results in a quadrupole charge distribution in the ring, making it possible for aromatic rings to interact with both cations and anions. Despite the enhanced interactions, when the molecular weight of P1P6 is low, the electrostatic inter-locking can still be disrupted by thermal motions as shown above for P1P6-3 and -4, rendering a UCST transition to the polymers in water.

Tuning of UCST Transitions by Copolymerization of M1P6 and M22. Copolymerization of two or more monomers is widely used for tuning the LCST and UCST transitions of thermoresponsive polymers in water.⁵⁹⁻⁶² Because P1P6 is a UCST polymer only at rather low molecular weights and P22 is completely soluble in water from 0 to 100 °C, we copolymerized M1P6 and M22 with various molar ratios via AIBN-initiated radical polymerization in order to increase the solubility of the polymers in water and modify their UCST transition temperatures. Five copolymers with the molar contents of M1P6 units from 42.1 to 18.1% were synthesized and the characterization data are summarized in Table 2. All five copolymers were found to display a UCST transition in water. Figure 6A shows 1.0 wt% aqueous solutions of PCO-1, -2, -3, -4, and -5 at 10, 65, and 90 °C. The CPs of PCO-1 and -5 at a concentration of 1.0 wt% were 88 and 1 °C, respectively, determined by visual inspection using a thermostated oil bath and an Isotemp water bath, respectively. The CPs of the other three copolymers (PCO-2, -3 and -4) were measured from the plots of transmittance versus temperature presented in Figure 6B, and they were 46, 36, and 11 °C, respectively. Figure 6C shows the plot of CP versus molar content of M1P6 monomer units in the copolymer. Although there is a clear trend that the CP increased with increasing molar content of M1P6 monomer units, the correlation is not perfectly linear. This could be caused by the

different $[\eta]$ values of these copolymers, dispersities, distributions of two types of monomer units, etc. In particular, the CPs of UCST polymers are known to be heavily affected by molecular weight,^{5,25} as can also be seen from our P1P6 homopolymers. Nevertheless, this study showed that the CPs of the UCST zwitterionic copolymer of M1P6 and M22 can be tuned by varying the molar ratio of two zwitterionic monomer units.

Table 2. Synthesis and Characterization of Zwitterionic Copolymers of M1P6 and M22

Copolymer	Mole % of M1P6 in Feed ^a	Mole % of M1P6 in Copolymer ^b	$[\eta]$ (dL/g)	Cloud Point (°C)
PCO-1	50.0	42.1	0.299	88 °C
PCO-2	41.2	37.0	0.291	46 °C
PCO-3	33.3	29.3	0.415	36 °C
PCO-4	27.0	24.7	0.372	11 °C
PCO-5	16.7	18.1	0.439	1 °C

^a Molar content of M1P6 in the feed. ^b The molar content of M1P6 units in the copolymer was determined from the ¹H NMR spectrum using the integrals of the peaks in the range of 7.52 – 8.19 ppm, which corresponded to the five hydrogen atoms in the phenyl ring of M1P6 units, and the peaks from 2.72 – 3.19 ppm, which corresponded to -CH₂SO₃⁻ of M1P6 and M22 monomer units.

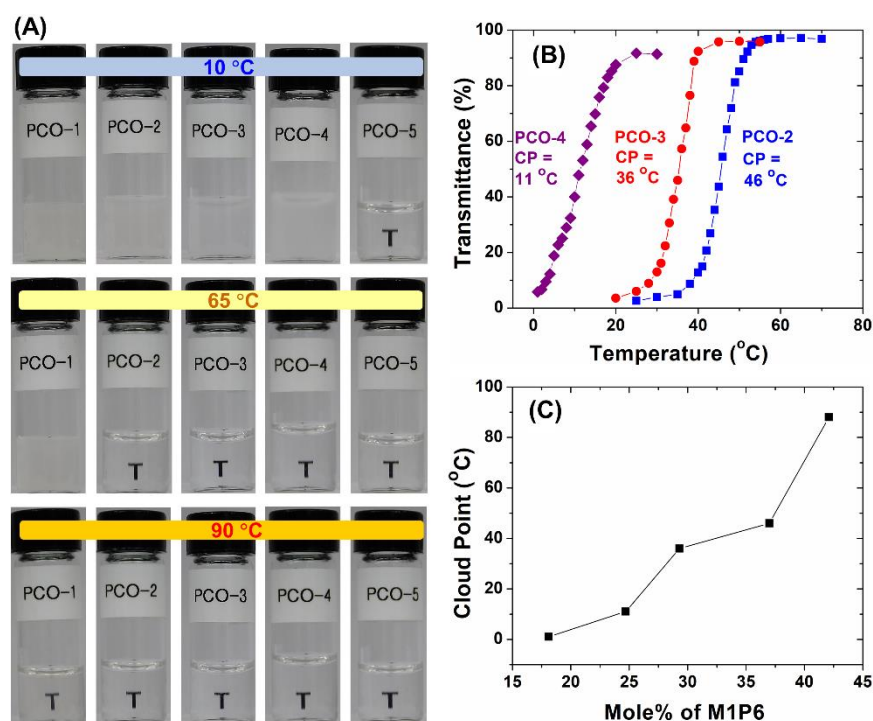


Figure 6. (A) Optical photos of five copolymers of M1P6 and M22 (PCO-1, -2, -3, -4, and -5) in Milli-Q water at a concentration of 1.0 wt% at 10, 65, and 90 °C. (B) Plot of transmittance at the wavelength of 500 nm versus temperature for a 1.0 wt% aqueous solution of PCO-2, PCO-3, and PCO-4 upon cooling, and (C) Plot of cloud point versus molar content of M1P6 in the copolymer.

Conclusions

In summary, we synthesized a series of DPSMA-based zwitterionic PSBMAs with various *N*-substituents, including two symmetric *n*-alkyls with varying lengths, one methyl and one *n*-hexyl, one methyl and one cyclohexyl, as well as one methyl and one phenyl group at the nitrogen atom, to elucidate the effects of *N*-substituents on solution behavior of these PDPSMAs in water. The main results are summarized below. (i) With increasing the lengths of two symmetric *N*-*n*-alkyl substituents simultaneously, the behavior of PDPSMAs in water changed from UCST to soluble, LCST, and insoluble, which likely is a result of the competition between the weakening of zwitterionic interactions and the increase of hydrophobic effect with increasing alkyl length. (ii) Installing a hydroxyl group at the end of the *N*-ethyl substituent of P12 enhanced the attractive interactions between zwitterion groups, turning a water-soluble polymer to a UCST polymer. (iii) Replacing the *N*-*n*-hexyl substituent of P16 with cyclohexyl changed the polymer from LCST-type thermoresponsive to water-soluble due to the decreased hydrophobic effect. Replacing the *N*-cyclohexyl group with a phenyl ring led to a water-insoluble polymer when the molecular weights were high, which was attributed to the increased zwitterionic inter-locking, while lower molecular weight species exhibited UCST behavior in water. In addition, we showed that the CP of the UCST thermoresponsive copolymers of M1P6 and M22 can be readily modified by varying the molar ratio of two monomer units.

This study provides an insight into the structure-solution-behavior relationship of zwitterionic PDPSMAs with a general molecular structure shown in Scheme 1 (i.e., two CH₂ groups between the ester and the ammonium, three CH₂ groups between the ammonium and the sulfonate group, and two separate substituents, R and R', at the nitrogen atom) in water, which may facilitate the design of UCST- and LCST-type thermoresponsive as well as water-soluble zwitterionic polymers

by varying *N*-substituents. (i) LCST-type thermoresponsive PDPSMAs may be produced by introducing *n*-alkyls of appropriate lengths (five or six carbon atoms) as *N*-substituents. (ii) UCST-type thermoresponsive PDPSMAs may be obtained by increasing zwitterionic interactions through the introduction of an aromatic or a small, hydroxyl-containing *N*-substituent. (iii) Water-soluble PDPSMAs may be obtained by using *n*-alkyls of intermediate lengths ($1 < \text{number of carbon atoms in each } N\text{-}n\text{-alkyl substituent} < 5$) or cycloalkyl or other compact (e.g., branched) structures as *N*-substituents. It is possible to achieve zwitterionic PDPSMAs that show UCST and LCST transitions in water in the temperature of $0 - 100\text{ }^{\circ}\text{C}$ ^{31,63} by using one substituent from (i) and another substituent from (ii). The knowledge generated from this study about PDPSMAs may be useful for understanding the structure-solution-behavior relationships of other types of zwitterionic polymers in water. Given the widespread use of zwitterionic materials, the insight gained from this work could open up new research opportunities for both fundamental studies and potential applications. Moreover, the zwitterionic polymers reported here could be used in the design of functional and responsive surfaces^{1,2,11-22} and in the synthesis of zwitterionic nanogels,⁹ zwitterionic schizophrenic block copolymer micelles,^{64,65} and shape-changing molecular bottlebrushes^{66,67} for possible applications such as drug delivery.

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Supporting Information. Experimental Section; ¹H NMR spectra of zwitterionic polymers; determination of intrinsic viscosities; SEC traces of P1P6-2, -3, and -4; plots of transmittance versus temperature for various thermoresponsive zwitterionic polymers; ¹H NMR spectra and

intrinsic viscosities of copolymers. The Supporting Information is available free of charge on the ACS Publications website at DOI: xxxxxxxxxxxxxx.

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Table of Contents Graphic:

