

Zwitterionic Poly(sulfobetaine methacrylate)s in Water: From Upper Critical Solution Temperature (UCST) to Lower Critical Solution Temperature (LCST) with Increasing Length of One Alkyl Substituent on the Nitrogen Atom

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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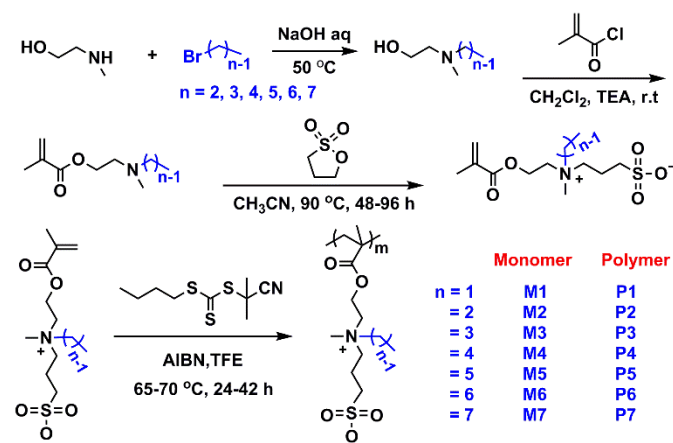
Ning Wang,^{a,b} Bryan T. Seymour,^a Evan M. Lewoczko,^a Ethan W. Kent,^a Ming-Li Chen,^{*b} Jian-Hua Wang,^b and Bin Zhao^{*a}

By gradually increasing the length of one linear alkyl substituent from one to seven carbon atoms on the nitrogen atom while keeping another substituent as a methyl group, poly(sulfobetaine methacrylate)s are found to exhibit a wide range of solution behavior in water, ranging from UCST, to totally soluble in water, to LCST, and then insoluble in water.

Zwitterionic polymers,^{1–13} which contain two ionic groups of opposite signs in each repeat unit, have received enormous attention because of their intriguing properties, such as superior hydrophilicity,^{1,2} antipolyelectrolyte effect,^{3,4} and stimuli-responsiveness,^{3–9} and their great potential in a wide variety of applications, including antifouling,^{1,2,10} lubrication,^{11,12} and cryopreservation.¹³ Poly(3-((2-methacryloyloxyethyl)dimethyl ammonio)propane-1-sulfonate) (PDMPS) and poly(3-(*N*-(3-methacrylamidopropyl)dimethylammonio)propane-1-sulfonate) are two well-known examples of zwitterionic polymers that exhibit a UCST in water.^{3–6,9} Their UCST transitions originate from the strong intra- and inter-molecular electrostatic interactions between zwitterionic groups;⁷ increasing temperature overcomes the electrostatic interlocking of polyzwitterions and dissolves the polymers in water.

Studies have been performed in order to elucidate the effects of structural variations of polysulfobetaines on thermoresponsive properties,^{3,14–18} and interestingly, the findings are often counterintuitive. For example, introducing a hydrophilic hydroxyl group between the ammonium and the sulfate group increases the cloud point (CP) of the polymer in water;¹⁴ replacing dimethylammonio with a six-membered piperidinio ring makes the polymer totally soluble in water in the temperature range of 0 – 100 °C, despite the fact that the alkyl ring substituent is larger and more hydrophobic.¹⁵ The

increased solubility of zwitterionic polymers in water with the increase of the alkyl size was believed to result from the decrease in electrostatic interactions between zwitterions caused by the steric hindrance of larger alkyl groups. Intrigued by these observations, we embarked on an effort to investigate the effect of substituents at the nitrogen atom in poly(sulfobetaine methacrylate). Apparently, the increase in the solubility of zwitterionic polymers in water with increasing length of alkyls at the nitrogen atom, compared with PDMAPS, has a limit. The water solubility of these polymers stems from the hydration of zwitterions, whereas the longer alkyl groups introduces a stronger hydrophobic effect, which is known to be the origin of the lower critical solution temperature (LCST) of polymers in water.^{19,20} Thus, it is possible that LCST-type thermoresponsive zwitterionic polymers could emerge. At even longer lengths, the polymers will likely be insoluble in water.



Scheme 1. Synthesis of Sulfobetaine Methacrylate Monomers with Different Alkyl Substituents at the Nitrogen Atom and Corresponding Polymers.

To study the effect of varying the alkyl length at the nitrogen atom in poly(sulfobetaine methacrylate) on polymer's solution behaviour in water, we synthesized a series of 3-((2-methacryloyloxyethyl)(methyl)(*n*-alkyl)ammonio)propane-1-sulfonate monomers (Scheme 1). For the two substituents at nitrogen, we kept one as methyl group and varied the length of

^a Department of Chemistry, University of Tennessee, Knoxville, Tennessee 37934, United States

^b Research Center for Analytical Sciences, Department of Chemistry, College of Sciences, Northeastern University, Shenyang, Liaoning 110819, China

* Emails: chenml@mail.neu.edu.cn (M.-L.C.), bzhao@utk.edu (B.Z.)

Electronic Supplementary Information (ESI) available: Experimental section and characterization data for monomers and polymers. See DOI: 10.1039/x0xx00000x

another substituent, linear alkyl $n\text{-C}_n\text{H}_{2n+1}$, systematically from $n = 1$ to 7. We maintained one methyl group because its small size would allow strong ion-dipole interactions between zwitterions and water molecules. Except monomer M1, all other monomers were made through a three-step procedure (Scheme 1), starting from the reaction between *N*-methylethanolamine and *n*-alkylbromide to produce a tertiary amine, followed by the reaction with methacryloyl chloride to form 2-(*N*-methyl-*N*-(*n*-alkyl)aminoethyl methacrylate).²¹ Sulfobetaine methacrylate monomers were then obtained by the reaction with 1,3-propanesultone.^{14–18} Interestingly, we found that at ambient conditions M1, M2, M6, and M7 are powders and M5 is a wax, whereas M3 and M4 are highly viscous liquids. We believe that the different appearances of these monomers reflect the differences in their intermolecular interactions. The characterization data are included in the ESI.

Zwitterionic polymers were synthesized from the corresponding methacrylate monomers by reversible addition-fragmentation chain transfer polymerization^{14,15,22,23} conducted in 2,2,2-trifluoroethanol using 2,2'-azobis(2-methylpropionitrile) as initiator and *n*-butyl (2-cyano-2-propyl) trithiocarbonate as chain transfer agent. The polymers were purified by dialysis using regenerated cellulose tubular membrane with nominal MWCO of 3500 against Milli-Q water and then freeze-dried. A total of 10 zwitterionic polymethacrylates were obtained. For polymers made from M1–M6, the molecular weights and dispersities were measured by using a size exclusion chromatography (SEC) system with a 0.2 M aqueous NaNO_3 solution as the eluent, relative to narrow disperse PEO standards. The polymer made from M7 was found to be insoluble in water; although it is soluble in 0.2 M aqueous NaNO_3 solution, no polymer was eluted out from the SEC system. The characterization data are summarized in Table 1. The somewhat large dispersity ($\bar{D}$) values indicated that the polymerizations were not controlled, for which the reason is unclear at this point.

Table 1. Molecular Characteristics and Solution Behaviour in Water of Poly(sulfobetaine methacrylate)s with Different Alkyl Substituents on the Nitrogen Atom

Sample	Monomer	$M_{n,SEC}$ (kDa) ^a	$\bar{D}$ ^a	Behaviour in Water ^b	Cloud Point ^c
P1	M1	9.1	1.80	UCST	31.4
P2-1	M2	9.6	1.91	Soluble	-
P2-2	M2	8.0	1.78	Soluble	-
P3-1	M3	10.2	1.79	Soluble	-
P3-2	M3	5.5	1.82	Soluble	-
P4-1	M4	4.4	2.41	Soluble	-
P4-2	M4	4.1	3.10	Soluble	-
P5-1	M5	2.6	3.00	LCST	50.8
P5-2	M5	19.7	2.17	LCST	48.9
P6	M6	14.1	3.09	LCST	22.3
P7	M7	NA	NA	Insoluble	-

^a Number average molecular weight ($M_{n,SEC}$) and dispersity ($\bar{D}$) were determined by aqueous size exclusion chromatography (SEC) using 0.2 M NaNO_3 aqueous solution as eluent, relative to narrow disperse poly(ethylene oxide) standards. ^b The solution

behaviour of each polymer in water was visually examined in the temperature range of 0 to 100 °C at a concentration of either 10 mg/g. ^c The cloud point in water was determined at a concentration of 10 mg/g by a UV-vis spectrometer.

To study the solution behaviour in water, a 1 wt% mixture in Milli-Q water was made for each of these zwitterionic polymers, and either a cold temperature (in an ice/water bath) or an elevated temperature was used to facilitate the dissolution of the polymers in water. Consistent with the literature report,⁵ P1 is soluble in water at elevated temperatures but precipitated out at lower temperatures, a characteristic of UCST-type thermoresponsive polymers.^{5–9} Despite longer alkyl substituents at the nitrogen atom compared with P1, P2-1, P2-2, P3-1, P3-2, P4-1, and P4-2 were found to be completely soluble in water, forming clear aqueous solutions that remained clear in the temperature range of 0 – 100 °C. Intriguingly, P5-1, P5-2, and P6 exhibited LCST-type thermoresponsive properties in water; at lower temperatures (e.g., in an ice/water bath) they were completely soluble in water, but the solutions turned cloudy upon heating. On the other hand, P7 is insoluble in water, regardless of the temperature. Figure 1 shows the optical photos of 1wt% solutions of P1, P3-2, P5-2, and P6 at 10, 65, and 90 °C, as well as a 1 wt% mixture of P7 in Milli-Q water.

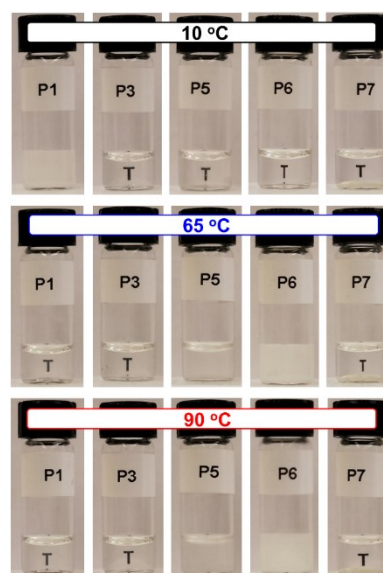


Figure 1. Optical photos of 1 wt% solutions of P1, P3-2, P5-2, and P6 in Milli-Q water as well as 1 wt% mixture of P7 in Milli-Q water at 10 °C (top row), 65 °C (middle row), and 90 °C (bottom). P7, which is insoluble in water, is on the bottom of the vial.

The CPs of P1, P5-1, P5-2, and P6 in water at various concentrations were determined by using a UV-vis spectrometer to record the transmittance of the solutions at 500 nm as a function of temperature. The samples were heated from a lower temperature or cooled from an elevated temperature gradually and at each selected temperature were equilibrated for 1 min prior to the transmittance measurement. Figure 2 shows the transmittance data for the four polymers, from which the CPs were determined to be the temperatures at which 50% of transmittance change occurred.²⁴ Evidently, P1 exhibited a UCST transition in water, with higher transmittances at higher temperatures and lower transmittances at lower

temperatures, whereas P5-1, P5-2, and P6 displayed LCST behaviours. Regardless of the type of transition, a common feature shown by all polymers is that the transition is sharper when the concentration is higher, which is reasonable because the aggregation occurred faster when more polymer molecules were present in the solutions. Note that during the revision of this paper we made a new 1 wt% aqueous solution for each of the four polymers and measured the transmittances in both heating and cooling processes (Figure S12). The differences between the transition temperatures from the heating and cooling curves for all of the polymers were small ($< 2\text{ }^{\circ}\text{C}$), similar to other types of thermoresponsive polymers.^{28,30}

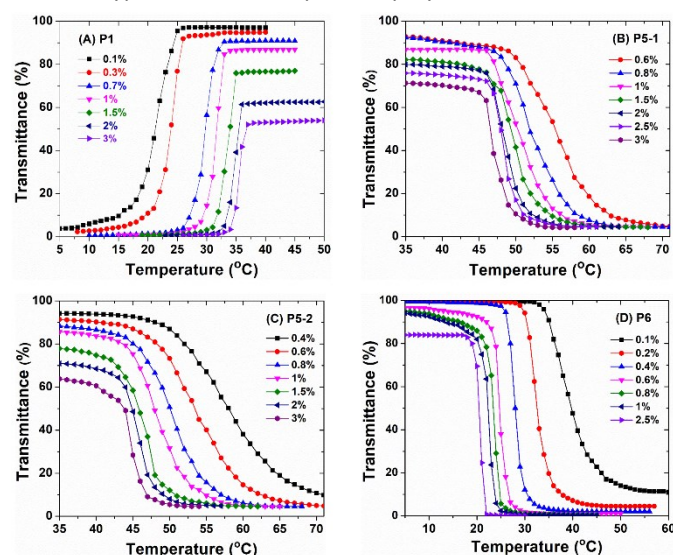


Figure 2. Plots of transmittance recorded at 500 nm using a UV-vis spectrometer versus temperature for solutions of (A) P1, (B) P5-1, (C) P5-2, and (D) P6 with various polymer concentrations in Milli-Q water. The data were obtained from cooling processes for P1 and heating processes for P5-1, P5-2, and P6.

The CPs of the four polymers in water at various concentrations determined from Figure 2 are summarized in Figure 3A, showing the effect of polymer concentration on CP. For P1, the CP increased with increasing concentration, from $21.3\text{ }^{\circ}\text{C}$ at 0.1 wt% to $35.3\text{ }^{\circ}\text{C}$ at 3 wt%, a characteristic of UCST-type thermoresponsive polymers in a liquid medium.^{5–8,25–28} In contrast, for P5-1, P5-2, and P6, the CP decreased with increasing concentration, a feature well known for LCST-type thermosensitive polymers.^{29,30} At 1 wt%, the cloud points of P5-1 and P5-2 were 50.8 and $48.9\text{ }^{\circ}\text{C}$, respectively, consistent with the expectation that a higher molecular weight would lead to a lower cloud point.^{29,31} The small difference between the CPs of P5-1 and P5-2 at the same concentration indicated that the molecular weight has a rather small effect on CP for this zwitterionic polymer. Increasing the length of one substituent from 5 carbon atoms in P5-1 and P5-2 to 6 carbon atoms in P6 was found to decrease the CP significantly; the CP of P6 at 1 wt% was $22.3\text{ }^{\circ}\text{C}$, which is about $27\text{ }^{\circ}\text{C}$ lower than that of P5-2 at the same concentration. Note that the molecular weights of P5-2 and P6 were similar, although the dispersity of P6 (3.09) was slightly higher than that of P5-2 (2.17). This is in line with the observation for the CPs of LCST-type thermosensitive poly(oligo(ethylene glycol) (meth)acrylate)s in water.^{29,32} In general, the CPs of UCST-type thermoresponsive polymers vary to a larger extent with concentration than LCST-type

polymers.^{5,26,28–31} Here, however, it appears that the UCST and LCST-type thermoresponsive zwitterionic polymers behaved similarly, as can be seen for P1 and P6 (Figure 3A).

Zwitterionic polymers are known to exhibit an antipolyelectrolyte effect; an increase in solution viscosity is observed with the addition of a low molar mass salt as a consequence of more extended conformations (i.e., the solubility increases with increasing salt concentration).^{3,5,33} On the other hand, the CP of a LCST-type thermoresponsive polymer in water usually decreases with increasing concentration of kosmotropic ions.^{30,34–36} Thus, it would be interesting to study how the concentration of a salt affects the CPs of P1, P5-1, P5-2, and P6 in water. Here we chose NaCl for a preliminary investigation in both heating and cooling processes (Figure S13), and the results from the cooling process for P1 and heating process for other three polymers are presented in Figure 3B. (As shown in Figure S13, the differences between the transition temperatures from heating and cooling are small for all of the four polymers ($< 2\text{ }^{\circ}\text{C}$).) For P1, the CP decreased with the increase of the concentration of NaCl, indicating that the solubility of the polymer is improved with the addition of NaCl, which is in agreement with the reports in the literature for P1.³³ Interestingly, there is a general trend that the CP for P5-1, P5-2, and P6 increased with increasing the salt concentration, although for P5-1 and P5-2 the CP decreased initially after the addition of NaCl followed by a smooth increase. The reason for the initial decrease is unclear; we repeated the experiment multiple times and observed the same phenomenon. The trend seen for P5-1, P5-2, and P6 is in stark contrast to the common observation for LCST-type thermoresponsive polymers in water,^{34–36} which reflects an anti-polyelectrolyte effect. Moreover, the effect on CP with the addition of NaCl varied among the four polymers, with the impact being the largest for P5-1 and P5-2. By increasing the NaCl concentration from about 5 to 20 mM, the CP for both polymers increased by $> 22\text{ }^{\circ}\text{C}$. In the similar salt concentration range, the CP for P6 increased by only about $6\text{ }^{\circ}\text{C}$. We speculate that this is related to the solubility of the polymer in water. For P5-1 and P5-2, the solubility in water is significantly better than P6, which can be seen from their higher CP in water. Addition of a small amount of NaCl could result in a large improvement in solubility.

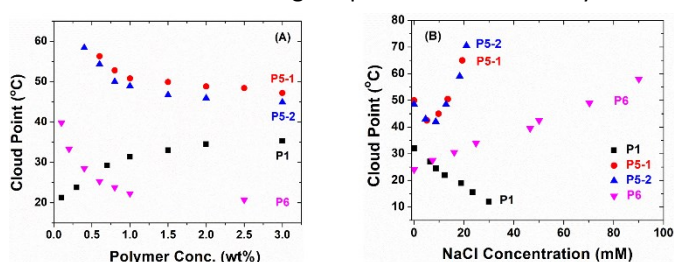


Figure 3. (A) Plots of cloud point (CP) versus polymer concentration in water for P1, P5-1, P5-2, and P6. (The CPs were determined from the data in Figure 2.) (B) Plots of CP for P1, P5-1, P5-2, and P6 at 1 wt% versus NaCl concentration.

The observed solution behaviour pattern for the studied poly(sulfobetaine methacrylate)s in water is believed to result from the two competing effects: the reduction of attractive electrostatic interactions between zwitterionic groups and the introduction of a stronger hydrophobic effect with increasing length of one alkyl substituent. When the two substituents are small methyl groups, the intra- and inter-molecular electrostatic

interactions between zwitterionic groups are stronger at lower temperatures, making the polymer insoluble in water. Upon heating, the attractive electrostatic forces between zwitterionic groups become weakened and the interactions between zwitterionic groups and water molecules are favoured, resulting in the dissolution of the polymer in water. With changing one substituent from methyl to ethyl, *n*-propyl, and *n*-butyl while keeping another methyl group in place, the longer hydrophobic alkyl groups sterically disrupt the electrostatic locking of zwitterions and decreases the electrostatic attractive forces between zwitterions, making the polymers totally soluble in water. On the other hand, a long alkyl substituent increases the entropic penalty due to the hydrophobic effect. However, the large enthalpic gain from the hydration of zwitterionic groups outweighs the entropic penalty from the hydrophobic effect, and the polymers are fully soluble in water in the entire temperature range of 0–100 °C. Further increasing the length of one substituent to *n*-pentyl and *n*-hexyl, however, results in a larger entropic penalty. Although a soluble state is still favoured at lower temperatures, it is not at higher temperatures. Consequently, the polymers exhibit LCST-type thermoresponsive properties. Note that these are the first zwitterionic sulfobetaine polymers that are reported to exhibit explicit LCST transitions in water. Further increasing the length to *n*-heptyl, the entropic penalty is too large for the polymer to be soluble in water.

Conclusions

In summary, we synthesized a series of zwitterionic poly(3-((2-methacryloyloxyethyl)(methyl)(*n*-alkyl)ammonio)propane-1-sulfonate)) homopolymers with the length of *n*-alkyl substituent gradually increasing from 1 to 7 carbon atoms and studied their solution properties in water in the temperature range of 0–100 °C. While P1 exhibited a UCST in water, P2, P3, and P4 are totally soluble in water. Intriguingly, P5 and P6 displayed LCST-type thermoresponsive properties in water; further increasing the alkyl length to *n*-heptyl resulted in a water-insoluble polymer. This interesting solution behaviour pattern is believed to be caused by the competition between the reduction of electrostatic attractive interactions between zwitterionic groups and the introduction of a stronger hydrophobic effect. The discovery of LCST-type thermoresponsive zwitterionic polymers could further expand the scope of zwitterionic polymers and their potential applications.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

N.W. thanks China Scholarship Council (CSC) for a scholarship to support her as a visiting scholar in the Department of Chemistry at the University of Tennessee, Knoxville. B.Z. thanks NSF for the partial support (DMR-1607076 and CHE-1709663).

ORCID

Bin Zhao: 0000-0001-5505-9390

Notes and references

- 1 S. Jiang and Z. Cao, *Adv. Mater.*, 2010, **22**, 920–932.
- 2 Q. Shao and S. Jiang, *Adv. Mater.*, 2015, **27**, 15–26.
- 3 A. Laschewsky, *Polymers*, 2014, **6**, 1544–1601.
- 4 A. Laschewsky and A. Rosenhahn, *Langmuir*, 2018, **34**, ASAP article. DOI: 10.1021/acs.langmuir.8b01789
- 5 J. Seuring and S. Agarwal, *Macromol. Rapid Commun.*, 2012, **33**, 1898–1920.
- 6 J. Niskanen and H. Tenhu, *Polym. Chem.*, 2017, **8**, 220–232.
- 7 V. A. Vasantha, S. Jana, A. Parthiban and J. G. Vancso, *Chem. Commun.*, 2014, **50**, 46–48.
- 8 Y. Biswas and T. K. Mandal, *Macromolecules*, 2017, **50**, 9807–9820.
- 9 W. Fu, C. Luo, E. A. Morin, W. He, Z. Li and B. Zhao, *ACS Macro Lett.*, 2017, **6**, 127–133.
- 10 P. Sae-ung, K. W. Kolewe, Y. Bai, E. W. Rice, J. D. Schiffman, T. Emrick and V. P. Hoven, *Langmuir*, 2017, **33**, 7028–7035.
- 11 X. Banquy, J. Burdyńska, D. W. Lee, K. Matyjaszewski and J. Israelachvili, *J. Am. Chem. Soc.*, 2014, **136**, 6199–6202.
- 12 M. Chen, W. H. Briscoe, S. P. Armes and J. Klein, *Science*, 2009, **323**, 1698–1701.
- 13 R. Rajan, F. Hayashi, T. Nagashima and K. Matsumura, *Biomacromolecules*, 2016, **17**, 1882–1893.
- 14 V. Hildebrand, A. Laschewsky and E. Wischerhoff, *Polym. Chem.* 2016, **7**, 731–740.
- 15 V. Hildebrand, A. Laschewsky, M. Päch, P. Müller-Buschbaum and C. M. Papadakis, *Polym. Chem.*, 2017, **8**, 310–322.
- 16 P. A. Woodfield, Y. Zhu, Y. Pan and P. J. Roth, *Macromolecules*, 2014, **47**, 750–762.
- 17 Y. Zhu, J.-M. Noy, A. B. Lowe, P. J. Roth, *Polym. Chem.*, 2015, **6**, 5705–5718.
- 18 R. A. Letteri, C. F. Chalarca, Y. Bai, R. C. Hayward and T. Emrick, *Adv. Mater.*, 2017, **29**, 1702921.
- 19 H. G. Schild, *Prog. Polym. Sci.*, 1992, **17**, 163–249.
- 20 N. X. Jin, J. W. Woodcock, C. M. Xue, T. G. O'Lenick, X. G. Jiang, S. Jin, M. D. Dadmun and B. Zhao, *Macromolecules*, 2011, **44**, 3556–3566.
- 21 D. M. Henn, R. A. E. Wright, J. W. Woodcock, B. Hu and B. Zhao, *Langmuir*, 2014, **30**, 2541–2550.
- 22 G. Moad, E. Rizzardo, S. H. Thang, *Acc. Chem. Res.*, 2008, **41**, 1133–1142.
- 23 B. Hu, W. Fu and B. Zhao, *Macromolecules*, 2016, **49**, 5502–5513.
- 24 X. Jiang and B. Zhao, *J. Polym. Sci. Part A: Polym. Chem.*, 2007, **45**, 3707–3721.
- 25 W. Fu and B. Zhao, *Polym. Chem.*, 2016, **7**, 6980–6991.
- 26 G. Zhang, Y. Wang, and G. Liu, *Polym. Chem.*, 2016, **7**, 6645–6654.
- 27 H. Zhang, S. Guo, W. Fan and Y. Zhao, *Macromolecules*, 2016, **49**, 1424–1433.
- 28 W. Fu, W. Bai, S. Jiang, B. T. Seymour and B. Zhao, *Macromolecules*, 2018, **51**, 1674–1680.
- 29 F. Hua, X. Jiang, D. Li and B. Zhao, *J. Polym. Sci. Part A: Polym. Chem.*, 2006, **44**, 2454–2467.
- 30 J.-F. Lutz, O. Akdemir and A. Hoth, *J. Am. Chem. Soc.*, 2006, **128**, 13046–13047.
- 31 S. Han, M. Hagiwara, T. Ishizone, *Macromolecules*, 2003, **36**, 8312–8319.
- 32 T. Ishizone, A. Seki, M. Hagiwara, S. Han, H. Yokoyama, A. Oyane, A. Deffieux and A. Carlotti, *Macromolecules*, 2008, **41**, 2963–2967.
- 33 D. N. Schulz, D. G. Peiffer, P. K. Agarwal, J. Larabee, J. J. Kaladas, L. Soni, B. Handwerker and R. T. Garner, *Polymer*, 1986, **27**, 1734–1742.
- 34 J. P. Magnusson, A. Khan, G. Pasparakis, A. O. Saeed, W. Wang and C. Alexander, *J. Am. Chem. Soc.*, 2008, **130**, 10852.
- 35 H. Du, R. Wickramasinghe and X. Qian, *J. Phys. Chem. B.*, 2010, **114**, 16594–16604.
- 36 M. M. Bloksma, D. J. Bakker, C. Weber, R. Hoogenboom and U. S. Schubert, *Macromol. Rapid Commun.*, 2010, **31**, 724.

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