

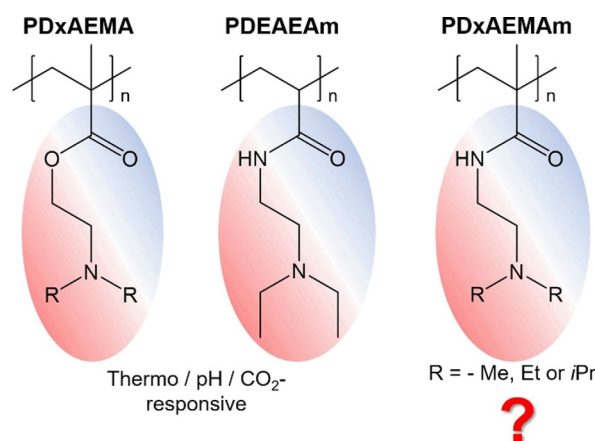
Multiresponsive Polymers

Converting Poly(Methyl Methacrylate) into a Triple-Responsive Polymer

 Christian Hils,^[a] Emma Fuchs,^[a] Franziska Eger,^[a] Judith Schöbel,^[b] and Holger Schmalz*^[a, c]

Abstract: Multiresponsive polymers that can respond to several external stimuli are promising materials for a manifold of applications. Herein, a facile method for the synthesis of triple-responsive (pH, temperature, CO₂) poly(*N,N*-diethylaminoethyl methacrylamide) by a post-polymerization amidation of poly(methyl methacrylate) (PMMA) is presented. Combined with trivalent counterions ([Fe(CN)₆]³⁻) both an upper and lower critical solution temperature (UCST/LCST)-type phase behavior can be realized at pH 8 and 9. PMMA and PMMA-based block copolymers are readily accessible by living anionic and controlled radical polymerization techniques, which opens access to various responsive polymer architectures based on the developed functionalization method. This method can also be applied on melt-processed bulk PMMA samples to introduce functional, responsive moieties at the PMMA surface.

Stimuli-responsive or “smart” polymers, which can change their physicochemical properties (e.g., solubility) upon applying an external stimulus (pH, temperature, light, magnetic fields, CO₂, etc.), are highly attractive and intensively studied materials due to the wide range of applications, such as responsive micelles and micro/nano-gels for biomedical applications, switchable membranes and coatings, smart actuators, or CO₂ sensing.^[1–3] The most prominent examples of multi-responsive polymers are based on methacrylate or acrylamide-type monomers with pendant *N,N*-dialkylamino groups (alkyl = methyl, ethyl, *iso*-



Scheme 1. Comparison of the chemical structure of known triple-responsive (pH, *T*, CO₂) polymers with poly(*N,N*-dialkylaminoethyl methacrylamide)s investigated in this study.

propyl; Scheme 1), which are commonly prepared by controlled radical polymerization techniques.^[2–9] In contrast, there are considerably less reports on living anionic polymerization, for example, of *N,N*-dimethylaminoethyl methacrylate (DMAEMA),^[10] despite the fact that anionic polymerization is still the best suited method to prepare well-defined, complex block copolymer architectures of high molecular weight on a large scale.^[11] Especially, when soft blocks based on polydienes (polybutadiene, polyisoprene) are required to allow a dynamic rearrangement of micellar nanostructures or a later fixation of the structures by cross-linking, anionic polymerization is the method of choice. However, the high requirements on monomer purity for anionic polymerization makes the purification of polar, high boiling monomers, such as DMAEMA, complex and time consuming. To overcome these limitations, we made use of an efficient post-polymerization modification to convert poly(methyl methacrylate) (PMMA), which is easily accessible by living anionic, as well as controlled radical polymerization techniques, into a triple-responsive polymer, being responsive to pH, temperature and CO₂. This was realized by amidation of PMMA with different preactivated *N,N*-dialkylethylenediamines to give the corresponding poly(*N,N*-dialkylaminoethyl methacrylamide)s (alkyl = methyl, ethyl, *iso*-propyl; PDxAEMAm), which were studied with respect to their responsive solution behavior. This concept was also applied for the surface functionalization of a bulk PMMA sample.

The amidation of PMMA with *N,N*-dialkylethylenediamines was conducted according to our previously published method

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<https://doi.org/10.1002/chem.202000485>.

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for the post-polymerization functionalization of polystyrene-*block*-polyethylene-*block*-poly(methyl methacrylate) triblock terpolymers (Figure 1A; details on used materials and synthesis protocols are given in the Supporting Information).^[12] Due to

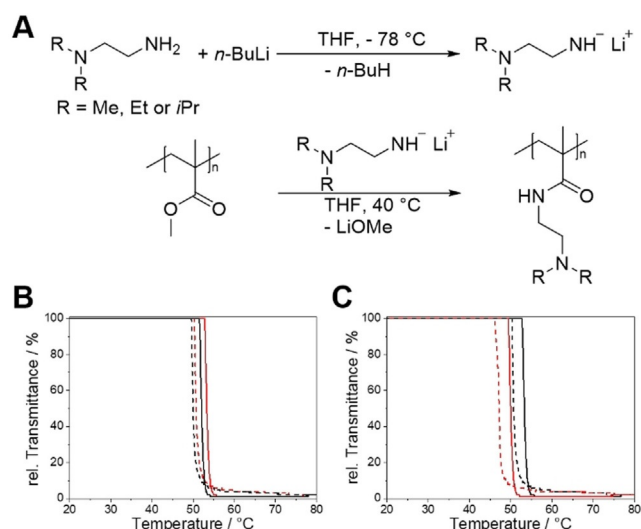


Figure 1. A) Reaction scheme for the amidation of PMMA with *N,N*-dialkylethylenediamines. B) Temperature-dependent transmittance of PDEAEMAm₂₁₀ ($M_n = 3.9 \times 10^4 \text{ g mol}^{-1}$, 1st cycle: red, 9th cycle: black) and C) comparison with PDEAEMAm₁₀₃₀ ($M_n = 1.9 \times 10^5 \text{ g mol}^{-1}$, red trace) in pH 9 buffer. Heating traces are depicted as solid and cooling traces as dashed lines, respectively ($c = 1 \text{ g L}^{-1}$).

the prior activation of the amines with *n*-butyllithium, quantitative functionalization can be reached in less than one hour, irrespective of the steric demand of the used amine (Figures S1, S2, and Table S1 in the Supporting Information), as was verified by ¹H NMR and FTIR studies. In addition, there are no signs of a broadening of the molecular weight distribution by size-exclusion chromatography (Figure S3), showing that amidation proceeds without significant side-reactions. A quantitative conversion of the methyl ester groups of PMMA is indispensable to avoid hydrolysis to methacrylic acid at elevated temperatures and high pH values, which will cause a significant shift of the cloud point to higher temperatures with time.^[8] This is manifested by the disappearance of the lower critical solution temperature (LCST)-type phase behavior of an intentionally prepared poly(methyl methacrylate-*co*-*N,N*-diethylaminoethyl methacrylamide) copolymer (P(MMA₃₁-*co*-DEAEMAm₁₇₉), subscripts correspond to the degree of polymerization) already after nine consecutive heating/cooling cycles in pH 10 buffer solution (Figure S4 in the Supporting Information).

The synthesized poly(*N,N*-dimethylaminoethyl methacrylamide) (PDMAEMAm₂₁₀) is neither responsive to pH nor to temperature, as was confirmed by turbidity measurements at varying pH (Figure S5A in the Supporting Information). In contrast, poly(*N,N*-diethylaminoethyl methacrylamide) (PDEAEMAm₂₁₀; Figure 1B) and poly(*N,N*-di-*iso*-propylaminoethyl methacrylamide) (PDiPAEMAm₂₁₀; Figure S5B) exhibit a LCST-type phase

behavior at pH 8. However, only PDEAEMAm₂₁₀ shows a narrow hysteresis ($\Delta T_{CP} \approx 3 \text{ K}$), whereas for PDiPAEMAm₂₁₀ the phase transitions upon heating and cooling are comparably broad with a large hysteresis ($\Delta T_{CP} \approx 24 \text{ K}$). The cloud point (T_{CP}) of PDEAEMAm₂₁₀ changes only marginally after nine consecutive heating/cooling cycles in pH 9 buffer solution (1st cycle: $T_{CP} = 53^\circ\text{C}$, 9th cycle: $T_{CP} = 52^\circ\text{C}$, Figure 1B), revealing the excellent hydrolytic stability of PDEAEMAm₂₁₀. There is a concentration dependence of the cloud point, which leads to a pronounced shift of T_{CP} by approximately 20°C to lower values with increasing T_{CP} concentration ($c = 0.05\text{--}2 \text{ g L}^{-1}$, Figure S5C in the Supporting Information). This is expected, because one moves along the binodal, which has a minimum in the LCST.

Figure 1C reveals an influence of the molecular weight on the cloud point, because the T_{CP} of PDEAEMAm₁₀₃₀ is about 5°C lower compared to that of PDEAEMAm₂₁₀. This indicates that PDEAEMAm acts as an LCST polymer of class I, that is, the cloud point decreases with increasing molecular weight.^[13]

Turbidity measurements were conducted in buffer solutions of different pH (Figure 2A and Table S2 in the Supporting Information) to further study the potential multiresponsivity of PDEAEMAm. PDEAEMAm is soluble over the entire temperature range for $\text{pH} \leq 7$, whereas for $8 < \text{pH} < 10$, the cloud point

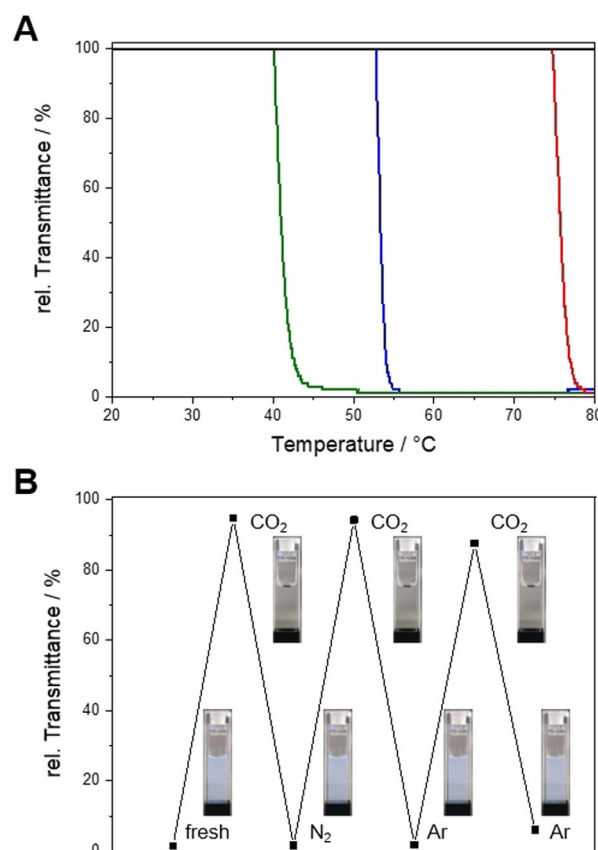


Figure 2. A) Temperature-dependent transmittance of PDEAEMAm₂₁₀ in buffer solutions of different pH ($c = 1 \text{ g L}^{-1}$, pH 7 black, pH 8 red, pH 9 blue and pH 10 green). B) Change in transmittance of PDEAEMAm₂₁₀ in pH 10 buffer at 55°C ($c = 1 \text{ g L}^{-1}$) upon bubbling CO_2 , N_2 or Ar through a cuvette.

shifts from $T_{CP}=72^{\circ}\text{C}$ at pH 8 to $T_{CP}=37^{\circ}\text{C}$ at pH 10. This matches well with the measured pK_a value of 7.1 (Figure S6 in the Supporting Information), that is, an LCST-type phase behavior is only observed for pH values at which less than 50% of the pendant tertiary amino groups are protonated. This is consistent with studies on the chemically similar poly(*N,N*-diethylaminoethyl methacrylate).^[4,9] The pH dependence of the cloud point can be harnessed for a reversible, CO_2 -induced phase transition (Figure 2B). Bubbling CO_2 through a turbid solution of PDEAEMAm₂₁₀ in pH 10 buffer at 55°C , that is, above the T_{CP} of 37°C at pH 10, results in a complete dissolution of the polymer. This is caused by a decrease in solution pH by the dissolved CO_2 (chemical equilibrium with carbonic acid) and consequently by the protonation of the pendant diethylamino groups as was proven by ^1H NMR analysis (Figure S7 in the Supporting Information). Subsequent bubbling of nitrogen or argon to remove the dissolved CO_2 gave again a turbid solution. This process can be repeated several times, proving the reversibility of the CO_2 -induced solubility switching.

In comparison to the respective methacrylate-based poly(*N,N*-dialkylaminoethyl methacrylate)s, the replacement of the ester linkage by an amide linkage in poly(*N,N*-dialkylaminoethyl methacrylamide)s leads to an increase in polarity and, thus, to an increased solubility. This is manifested by the fact that poly(*N,N*-dimethylaminoethyl methacrylate) (PDMAEMA) shows a pH-dependent LCST-type phase behavior for $\text{pH} \geq 7$,^[4,8] whereas PDMAEMAm is completely soluble irrespective of temperature and pH (Figure S5A; Tables S2 and S3 in the Supporting Information). A similar behavior is found for the diethyl derivatives. PDEAEMA shows an LCST-type phase behavior at pH 6–7 and is hardly soluble for $\text{pH} \geq 8$.^[9] In contrast, PDEAEMAm exhibits a temperature-dependent solubility for $\text{pH} \geq 8$. This is in line with the lower pK_a value observed for PDEAEMA ($pK_a=6.6$)^[9] with respect to that of PDEAEMAm ($pK_a=7.1$, Figure S6 in the Supporting Information). In analogy to poly(*N,N*-diethylaminoethyl acrylamide) (PDEAEAm) the synthesized PDEAEMAm also shows a triple-responsive behavior, being responsive to pH, temperature and CO_2 .^[5,7] However, introducing a methyl group in α -position leads to a slightly increased hydrophobicity and a resulting shift of the critical pH, at which an LCST-type phase behavior was observed, from pH 8.5 for PDEAEAm to pH 8 for PDEAEMAm, respectively (Table S2 in the Supporting Information).

In addition to the pH-dependent LCST-type phase behavior an upper critical solution temperature (UCST)-type phase behavior can be induced by the addition of small quantities of a trivalent counterion. This is realized by the addition of $\text{K}_3[\text{Fe}(\text{CN})_6]$ to the respective solutions of PDEAEMAm₁₀₃₀ ($c=1\text{ g L}^{-1}$) in buffers of pH 6–10 (Figure 3A and Figure S8 in the Supporting Information). For pH 8 and 9, both an UCST- and LCST-type phase behavior was observed, whereas for $\text{pH} < 8$ and $\text{pH} > 9$, only an UCST or LCST behavior can be detected, respectively. This can be explained by the lack of protonated (charged) repeating units for $\text{pH} > 9$, as electrostatic interactions between the positively charged polymer and the trivalent $[\text{Fe}(\text{CN})_6]^{3-}$ counterions are responsible for the UCST-type phase behavior.^[14] Consequently, at $\text{pH} < 8$ the polymer chain

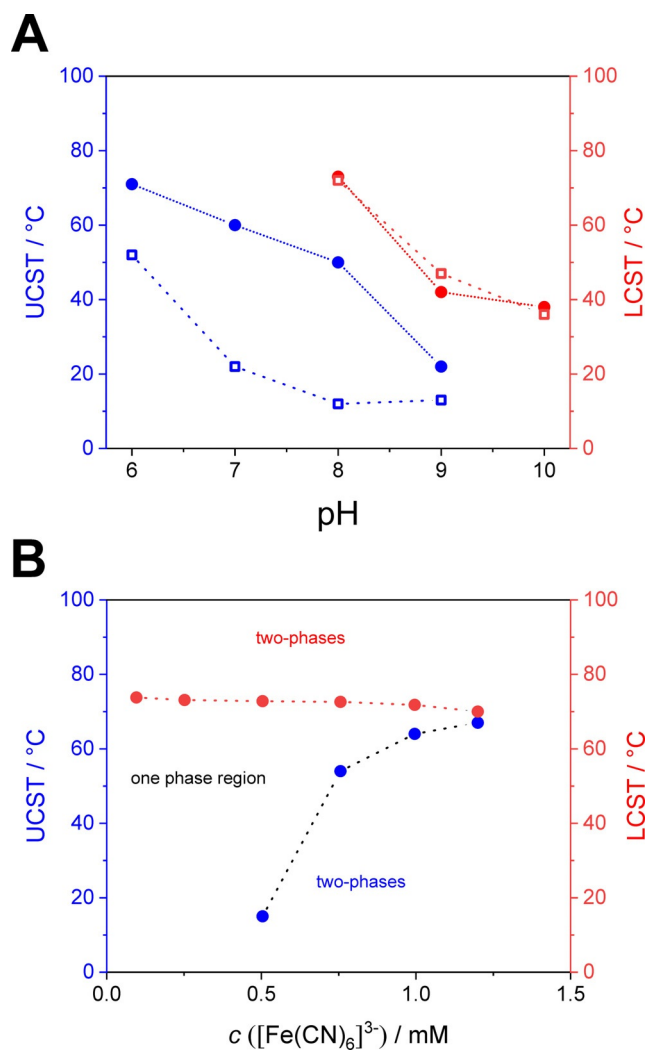


Figure 3. Tailoring the thermo-responsive solution behavior of PDEAEMAm₁₀₃₀ ($c=1\text{ g L}^{-1}$) in the presence of trivalent $[\text{Fe}(\text{CN})_6]^{3-}$ counterions. A) UCST- and LCST-type phase transitions in dependence of pH for two different $\text{K}_3[\text{Fe}(\text{CN})_6]$ concentrations ($c=0.5\text{ mM}$ (squares), $c=0.75\text{ mM}$ (circles)) and B) in dependence of $\text{K}_3[\text{Fe}(\text{CN})_6]$ concentration in pH 8 buffer solutions.

is highly charged ($pK_a=7.1$), which leads to a vanishing of the LCST. In analogy to studies on linear and star-shaped PDMAEMA, the UCST-type cloud point increases with the $[\text{Fe}(\text{CN})_6]^{3-}$ concentration, whereas the LCST-type cloud point is not affected (Figure 3B). However, the UCST-type phase transitions for PDEAEMAm₁₀₃₀ are more sensitive to the $[\text{Fe}(\text{CN})_6]^{3-}$ concentration and the UCST coincides with the LCST-type cloud point already at $c([\text{Fe}(\text{CN})_6]^{3-})=1.25\text{ mM}$.

The post-polymerization amidation of PMMA can even be conducted in bulk, allowing the direct heterogeneous amidation of melt-processed PMMA parts. The successful amidation of the surface of a PMMA disc with *N,N*-diethylethylenediamine was proven by FTIR spectroscopy, revealing the presence of the characteristic amide band at $\approx 1650\text{ cm}^{-1}$ (Figure S9 in the Supporting Information). Due to the increase in polarity the contact angle to water at 25°C decreases from $(93 \pm 2)^{\circ}$ to $(49 \pm 5)^{\circ}$ after amidation (Table S4 in the Supporting Information). The responsivity of the amidated PMMA surface can be

used for a temperature-induced switching of the contact angle. Employing a pH 10 buffer solution a shift of the contact angle from $(48 \pm 6)^\circ$ to $(77 \pm 1)^\circ$ can be induced by a temperature increase to 55°C , because under these conditions, the PDEAEMAm units become insoluble ($T_{\text{CP}}=37^\circ\text{C}$ at pH 10). Moreover, the diethylamino anchor groups at the PMMA surface can be utilized to bind preformed, citrate-stabilized gold nanoparticles (Au NPs, $D=9.5 \pm 2.4$ nm). After functionalization and loading with Au NPs the decoration of the PMMA surface with Au NPs is clearly visible in the digital photograph, as well as the scanning electron microscopy (SEM) image acquired with a back-scattered electron (BSE) detector (Figure 4).

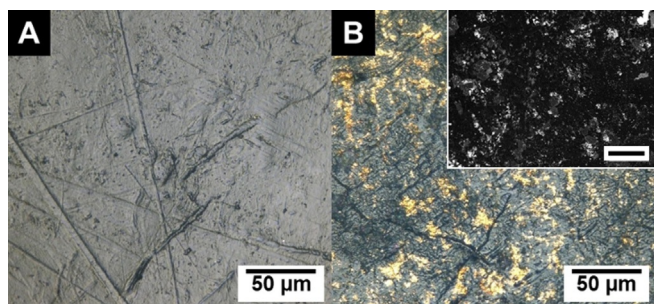


Figure 4. Digital photographs of the surface of the PMMA disc employed for heterogeneous amidation (A) and of the surface of the PMMA disc after amidation and successive loading with Au NPs (B). The inset shows the corresponding SEM image acquired with a BSE detector (Au NP rich regions appear bright, scale bar inset = 100 μm).

In conclusion, we have shown that PMMA can be converted to a triple-responsive (pH, temperature, CO_2) polymer by a fast and quantitative post-polymerization amidation with *N,N*-diethylethylenediamine. This opens access to a variety of responsive polymer architectures, such as defined (multi)block copolymers,^[12] because PMMA is easily accessible by controlled radical, as well as living anionic polymerization. The excellent efficiency of this functionalization reaction also allows a direct heterogeneous amidation of the surface of melt-processed PMMA parts, which can be harnessed for a temperature-induced switching of the surface hydrophilicity or the binding of metal nanoparticles, for example, for catalytic purposes. Hence, we believe that the herein established method will find broad application in the synthesis of responsive and/or functional materials that might find application in responsive gels, actuators, or catalysis.

Acknowledgements

This work was supported by the German Research Foundation (SFB 840, project A2). We acknowledge Prof. Andreas Greiner and Prof. Seema Agarwal for helpful discussions on heteroge-

neous amidation and thermo-responsive polymers, respectively. We thank Rika Schneider for SEC, Carmen Kunert for SEM and Lukas Weber for preparative work. C. Hils acknowledges support by the Graduate School of the University of Bayreuth.

Conflict of interest

The authors declare no conflict of interest.

Keywords: pH-responsive polymers · polymer analogous modification · switchable surface hydrophilicity · temperature-responsive polymers

- [1] a) M. A. C. Stuart, W. T. S. Huck, J. Genzer, M. Müller, C. Ober, M. Stamm, G. B. Sukhorukov, I. Szleifer, V. V. Tsukruk, M. Urban, F. Winnik, S. Zauscher, I. Luzinov, S. Minko, *Nat. Mater.* **2010**, *9*, 101; b) S. Guo, H. Zhang, X. Lu, H. Xiao, Y. Zhao, *J. Mater. Chem. C* **2019**, *7*, 4049; c) M. F. Cunningham, P. G. Jessop, *Macromolecules* **2019**, *52*, 6801; d) M. Wei, Y. Gao, X. Li, M. J. Serpe, *Polym. Chem.* **2017**, *8*, 127; e) L. Hu, Y. Wan, Q. Zhang, M. J. Serpe, *Adv. Funct. Mater.* **2019**, *6*, 1903471; f) H. Ko, A. Javey, *Acc. Chem. Res.* **2017**, *50*, 691; g) S.-J. Jeon, A. W. Hauser, R. C. Hayward, *Acc. Chem. Res.* **2017**, *50*, 161; h) X. Hu, Y. Zhang, Z. Xie, X. Jing, A. Bellotti, Z. Gu, *Biomacromolecules* **2017**, *18*, 649; i) Z.-Q. Cao, G.-J. Wang, *Chem. Rec.* **2016**, *16*, 1398.
- [2] P. Schattling, F. D. Jochum, P. Theato, *Polym. Chem.* **2014**, *5*, 25.
- [3] J. Madsen, S. P. Armes, *Soft Matter* **2012**, *8*, 592.
- [4] T. Thavanesan, C. Herbert, F. A. Plamper, *Langmuir* **2014**, *30*, 5609.
- [5] Z. Song, K. Wang, C. Gao, S. Wang, W. Zhang, *Macromolecules* **2016**, *49*, 162.
- [6] a) J. Lee, K. H. Ku, C. H. Park, Y. J. Lee, H. Yun, B. J. Kim, *ACS Nano* **2019**, *13*, 4230; b) G. Moad, *Polym. Chem.* **2017**, *8*, 177.
- [7] K. Wang, Z. Song, C. Liu, W. Zhang, *Polym. Chem.* **2016**, *7*, 3423.
- [8] F. A. Plamper, M. Ruppel, A. Schmalz, O. Borisov, M. Ballauff, A. H. E. Müller, *Macromolecules* **2007**, *40*, 8361.
- [9] A. Schmalz, M. Hanisch, H. Schmalz, A. H. E. Müller, *Polymer* **2010**, *51*, 1213.
- [10] a) I. Dewald, J. Gensel, E. Betthausen, O. V. Borisov, A. H. E. Müller, F. H. Schacher, A. Fery, *ACS Nano* **2016**, *10*, 5180; b) A. Hanisch, H. Schmalz, A. H. E. Müller, *Macromolecules* **2012**, *45*, 8300; c) F. Schacher, T. Rudolph, F. Wieberger, M. Ulbricht, A. H. E. Müller, *ACS Appl. Mater. Interfaces* **2009**, *1*, 1492; d) X. Wang, M. A. Winnik, I. Manners, *Macromolecules* **2005**, *38*, 1928; e) T. Lunkenbein, M. Kamperman, Z. Li, C. Bojer, M. Drechsler, S. Förster, U. Wiesner, A. H. E. Müller, J. Brey, *J. Am. Chem. Soc.* **2012**, *134*, 12685.
- [11] a) G. Polymeropoulos, G. Zapsas, K. Ntetsikas, P. Bilalis, Y. Gnanou, N. Hadjichristidis, *Macromolecules* **2017**, *50*, 1253; b) R. Bahrami, T. I. Löbbling, A. H. Gröschel, H. Schmalz, A. H. E. Müller, V. Altstädt, *ACS Nano* **2014**, *8*, 10048.
- [12] J. Schöbel, C. Hils, A. Weckwerth, M. Schlenk, C. Bojer, M. C. A. Stuart, J. Brey, S. Förster, A. Greiner, M. Karg, H. Schmalz, *Nanoscale* **2018**, *10*, 18257.
- [13] F. Meeussen, E. Nies, H. Berghmans, S. Verbrugghe, E. Goethals, F. Du Prez, *Polymer* **2000**, *41*, 8597.
- [14] F. A. Plamper, A. Schmalz, M. Ballauff, A. H. E. Müller, *J. Am. Chem. Soc.* **2007**, *129*, 14538.

Manuscript received: January 28, 2020

Revised manuscript received: February 14, 2020

Accepted manuscript online: February 17, 2020

Version of record online: April 24, 2020