Tuning the LCST of poly(2-oxazoline)s by varying composition and molecular weight: alternatives to poly(*N*-isopropylacrylamide)?†

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The cloud point of copolymers of 2-ethyl-2-oxazoline and 2-*n*-propyl-2-oxazoline could be tuned from 25 °C to 100 °C by varying molecular weight and composition; the reversibility and concentration dependence of the cloud points were evaluated to assess the potential of these copoly(2-oxazoline)s as alternatives to poly(*N*-isopropylacrylamide).

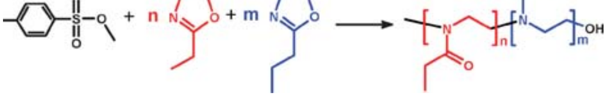
Thermoresponsive polymers that undergo a solubility transition upon changes in temperature are an interesting class of polymers for a variety of applications ranging from drug delivery[1,2] to bioengineering[3] and from responsive magnetic particles[4] to separation processes.[5] The most widely studied thermoresponsive polymer is poly(*N*-isopropylacrylamide) (PNIPAM) based on its lower critical solution temperature (LCST) of ~32 °C which is close to body temperature as well as the relatively small dependence of the LCST on changes in concentration, pH or ionic strength.[3,6,7] The LCST of PNIPAM can be tuned by controlling the molecular structure and composition as was demonstrated by varying, *e.g.*, the molecular weight, end-groups, architecture as well as branching.[3,6–13] However, the major disadvantage of PNIPAM is the strong hysteresis of the thermal solubility transition which is due to the formation of intramolecular hydrogen bonds in the collapsed state.[14–16] Therefore, continuous effort focuses on finding alternative polymers with LCSTs that are unaffected by environmental parameters combined with biocompatibility as well as a reversible transition without hysteresis, which is mostly met by PEGylated polymers.[17–20] However, PEG-based polymers might coordinate to metal ions in a similar way to crown-ethers indicating the necessity of developing novel amide based PNIPAM alternatives.

Poly(2-oxazoline)s can be prepared by a living cationic ring-opening polymerization of 2-oxazoline monomers (Scheme 1).[21–24] The resulting polymer properties strongly depend on the substituent on the 2-position of the monomer that forms the amidic side-chains of the resulting poly(2-oxazoline). Poly(2-oxazoline)s with ethyl, isopropyl and *n*-propyl side chains are known to exhibit LCST transitions at ~65 °C, ~36 °C and ~24 °C, respectively.[25–27] The thermal transition of poly(2-isopropyl-2-oxazoline) was found to be irreversible if the solution is kept longer above the transition temperature.[28,29] In general, the LCST of poly(2-oxazoline)s depends on the molecular weight[30–32] as well as the introduction of comonomers that influence the hydrophilic/hydrophobic balance of the copolymer.[27,33–35] Even though both the molecular weight and composition are known to affect the LCST of poly(2-oxazoline)s, the simultaneous evaluation of these factors has not been reported so far.

Here, we evaluate the LCST of statistical copolymers of 2-ethyl-2-oxazoline (EtOx) and 2-*n*-propyl-2-oxazoline (*n*PropOx; Scheme 1), whereby both the molecular weight and composition are systematically varied, as potential alternatives to PNIPAM with tuneable LCST. Previous reports already demonstrated that high-throughput experimentation methods are valuable tools for systematic studies on the LCST behavior of polymers.[36–40] Therefore, we have adapted an automated microwave synthesis protocol[41] while the cloud points were analyzed by automated parallel turbidity measurements (error within 1 °C).[34]

At first, the effect of chain length on the cloud point of PEtOx and P*n*PropOx homopolymers was investigated to define the parameter space that will be investigated in detail (Fig. 1). PEtOx with a degree of polymerization (DP) less than 100 does not exhibit a cloud point in between 0 °C and 100 °C. PEtOx with a DP larger than 100 shows a chain length dependent decrease in cloud point from 94 °C to 66 °C, whereby the steepest decrease was found from DP = 100 to DP = 200. In contrast, P*n*PropOx revealed the strongest decrease in cloud point from 43 °C to 30 °C in between DP = 10 and DP = 50. Since above DP = 150 only minor changes in cloud point were observed and below DP = 50 end-group effects might become dominant, the region in between DP = 50 and DP = 150 was chosen to evaluate the simultaneous effects of molecular weight and composition on the cloud points.

To assess the LCST behavior in this selected region, three series of statistical EtOx–*n*PropOx copolymers were prepared



Scheme 1 Schematic representation of the methyl tosylate initiated cationic ring-opening copolymerization of 2-ethyl-2-oxazolines and 2-*n*-propyl-2-oxazoline.

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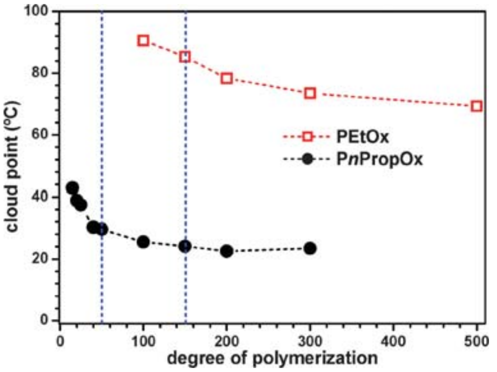


Fig. 1 Cloud point as function of chain length for PEtOx and P*n*PropOx homopolymers in water (5 mg mL^{-1}). The dotted lines indicate the region that is further investigated.

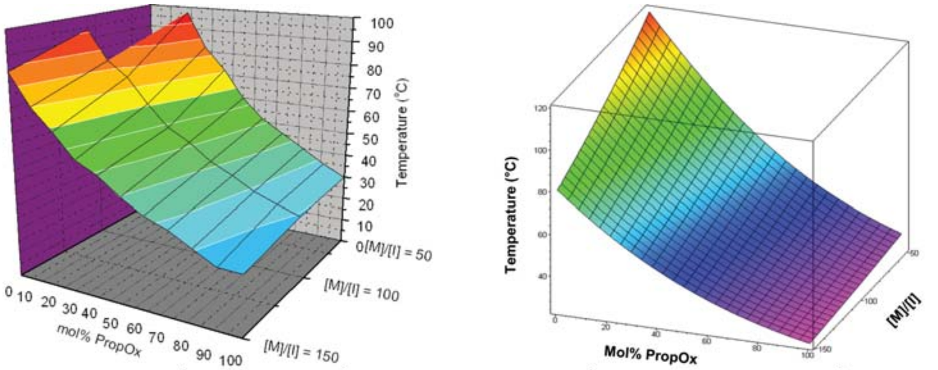
with a DP of 50, 100 and 150 using a microwave-assisted synthesis protocol.[42] The monomer composition was systematically varied from pure EtOx to pure *n*PropOx in steps of 10 mol%. Size exclusion chromatography and ^{1}H NMR spectroscopy revealed that all copolymers had the desired composition and reasonably well-defined structures with polydispersity indices mostly below 1.40 (see ESI†). Before evaluating the LCST behavior, the reactivity ratios for the statistical copolymerization of EtOx and *n*PropOx were determined to be $r_{\mathrm{EtOx}} = 0.94 \pm 0.07$ and $r_{n\mathrm{PropOx}} = 1.01 \pm 0.04$ demonstrating the formation of truly random copolymers (see ESI†). These reactivity ratios are slightly different from the previously reported $r_{\mathrm{EtOx}} = 1.04$ and $r_{n\mathrm{PropOx}} = 1.28$ for copolymerizations at 42 °C,[27] which might suggest that the reactivity ratios are temperature dependent.

The cloud points of the copolymer libraries were determined in water at 5 mg mL^{-1} in an automated parallel fashion allowing full evaluation of the 33 copolymers within 2 days. The resulting plot of cloud point *versus* both monomer composition and monomer to initiator ([M]/[I]) ratio (Fig. 2, left) demonstrates that the cloud points cover the entire range from 24 °C to 97 °C, whereby both incorporation of the more hydrophobic *n*PropOx as well as increasing the DP decreases the cloud point. Interestingly, the molecular weight dependence is stronger for the more hydrophilic polymers as indicated by the increasing slope of the contour lines when moving from the *n*PropOx-rich region to the EtOx-rich region (Fig. 2, left) indicating that shorter hydrophilic chains are better hydrated than longer hydrophilic chains while the hydration of relatively hydrophobic chains is not so much affected by the chain length. When following the contour lines, it is possible to tune the polymer properties, while keeping the cloud point constant. The possibility of this independent tuning of polymer properties is demonstrated for the polymers with a similar cloud point at ~34 °C, namely PEtOx$_5$-*stat*-P*n*PropOx$_{45}$, PEtOx$_{20}$-*stat*-P*n*PropOx$_{80}$ and PEtOx$_{45}$-*stat*-P*n*PropOx$_{105}$, which exhibit glass transitions at 29 °C, 42 °C and 45 °C, respectively.

Structure–property relationships were extracted for the cloud points by empirically fitting the data in Fig. 2, left. The resulting predictive model (Fig. 2, right and bottom) can be used to predict the cloud point of new polymers within the experimental range within 2 °C accuracy (see ESI for residuals†). In fact, this is the first example, to the best of our knowledge, of a model that predicts the cloud point of polymer solutions as function of both monomer composition and [M]/[I] ratio. The only related previous report provided a model for the LCST of poly(oligoethyleneglycolmethacrylates) over a limited range of monomer compositions.[43]

The potential of these poly(2-oxazoline)s as alternatives to PNIPAM was evaluated by investigating the reversibility and the concentration dependence of the phase transition. The transmittance *versus* temperature is shown for representative polymers in Fig. 3. Similar sharp transition curves were found for all reported (co)polymers having LCST behavior. The solubility transitions during both heating and cooling overlap within several degrees demonstrating the absence of hysteresis making these polymers superior to PNIPAM. In fact, P*n*PropOx is a structural isomer of PNIPAM in which the absence of the NH hydrogen bond donating group prevents the formation of intramolecular hydrogen bonds, which explains why hysteresis does not occur.

The effect of concentration on the cloud points was investigated for the PEtOx and P*n*PropOx homopolymers as well as for copolymers with a cloud point around 34 °C which are



$$\ln(\mathrm{LCST}) = a \cdot n\mathrm{PropOx}^3 + b \cdot n\mathrm{PropOx}^2 + c \cdot n\mathrm{PropOx} + d \cdot \mathrm{MI}^2 + e \cdot \mathrm{MI} + f \cdot n\mathrm{PropOx}^2 \cdot \mathrm{MI} + g$$

Fig. 2 Left: cloud points as function of both composition and molecular weight for EtOx-*n*PropOx statistical copolymers in water (5 mg mL^{-1}). Right: predictive model for the cloud points. Bottom: empirical formula that was used to model the cloud points. *n*PropOx = mol% *n*PropOx; MI = [M]/[I] ratio; $a = 0.247 \times 10^{-6}$; $b = -0.488 \times 10^{-4}$; $c = -0.120 \times 10^{-1}$; $d = 0.265 \times 10^{-5}$; $e = -0.452 \times 10^{-2}$; $f = 0.155 \times 10^{-6}$; $g = 5.00$.

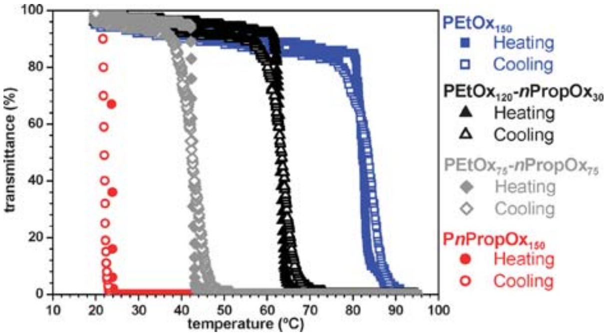


Fig. 3 Selected transmittance *versus* temperature plots for EtOx–*n*PropOx statistical copolymers at 5 mg mL^{-1} in water demonstrating the reversibility of the solubility transitions.

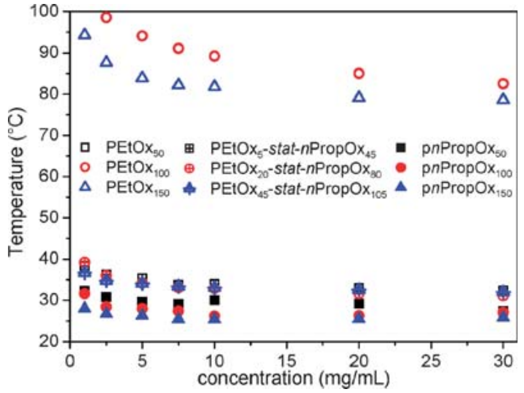


Fig. 4 Concentration dependence of the cloud points for PEtOx and P*n*PropOx homopolymers as well as selected EtOx–*n*PropOx copolymers.

potential alternatives to PNIPAM (Fig. 4). For the hydrophilic PEtOx, a strong decrease of 25 °C in cloud point is observed with increasing concentration while the cloud point of P*n*PropOx and the selected copolymers only decreases 5 °C, which is comparable to PNIPAM.[9,17] Apparently, the hydration of the hydrophilic PEtOx is not only strongly dependent on the molecular weight as discussed previously but also on the polymer concentration. The exact nature of the stronger dependence of polymer hydration on variations in chain length and concentration for the more hydrophilic poly(2-oxazoline)s is not yet understood and will be the focus of future work.

In conclusion, we have demonstrated the synthesis of a library of random EtOx–*n*PropOx copolymers ($r_{EtOx} = 0.94 \pm 0.07$ and $r_{nPropOx} = 1.01 \pm 0.04$) with systematic variations in composition and chain length. The cloud points of the copolymers decreased with increasing chain length as well as increasing *n*PropOx content. Furthermore, an empirical model was established to predict the cloud point of novel copolymers that are within the boundaries of the investigated library. Finally, the thermal transitions of copolymers with cloud points ~34 °C showed no hysteresis or concentration dependence, making them superior to PNIPAM.

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