Thermoresponsive Poly(2-Oxazoline) Molecular Brushes by Living Ionic Polymerization: Modulation of the Cloud Point by Random and Block Copolymer Pendant Chains

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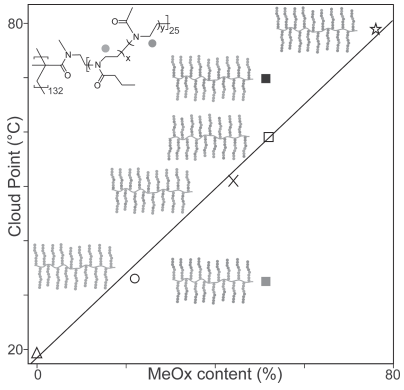
Molecular brushes (MBs) of poly(2-oxazoline)s were prepared by living anionic polymerization of 2-isopropenyl-2-oxazoline to form the backbone and living cationic ring-opening polymerization of 2-*n*-propyl-2-oxazoline and 2-methyl-2-oxazoline to form random and block copolymers. Their aqueous solutions displayed a distinct thermoresponsive behavior as a function of the side-chain composition and sequence. The cloud point (CP) of MBs with random copolymer side chains is a linear function of the hydrophilic monomer content and can be modulated in a wide range. For MBs with block copolymer side chains, it was found that the block sequence had a strong and surprising effect on the CP. While MBs with a distal hydrophobic block had a CP at 70 °C, MBs with hydrophilic outer blocks already precipitated at 32 °C.



1. Introduction

Recently, poly(2-oxazoline)s (POx) came into the focus of biomaterials research[1] as an alternative to the established poly(ethylene glycol) (PEG) systems.[1–5] Unlike PEG, the pseudo-polypeptide structure of POx and synthetic variability renders it as a suitable polymer to tailor biomaterials including polymer therapeutics,[6–19] coatings to control the bioadhesion,[20–26] and complex biomimetic systems such as artificial cell membranes.[20,27–37] The living cationic ring-opening polymerization (LCROP) of 2-substituted-2-oxazolines allows for the synthesis of defined macromolecules with a broad variety of architectures,[38–43] composition,[44,45] side and end functionalities,[46–56] able to cope with the various requirements for biomaterials development.[5,57,58] As the LCROP allows for defined random, gradient as well as block copolymerization and thus, that is, the amphiphilic contrast including the thermoresponsiveness of POx can be tuned in a wide range.[44,45,59–65]

POx comb copolymers or, for high side chain grafting densities so-called molecular brushes (MB), can be synthesized by the *grafting from*,[66–68] *grafting onto*,[22,23] or *grafting through*[69–72] approach. Recently, Schubert and co-workers[73,74] prepared comb copolymers of oligo(2-ethyl-2-oxazoline) on poly(methacrylic acid) backbones by *grafting onto* as well as *grafting through* using controlled radical polymerization to realize pH-dependent thermosensitive polymers. The grafting of hydrophilic poly(2-methyl-2-oxazoline)s onto poly(L-lysine) (PLL) was used by Textor and co-workers[22,23] to prepare tailored PLL–POx comb polymers for nonfouling surfaces and antimicrobial surface coatings that are immobilized by

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charge interactions. All methods have their advantages and limitations, however, analog to the surface-initiated polymerization to yield polymer brushes on solids, the *grafting from* approach results in maximum possible grafting density even for long backbones and thus into MBs. Using this strategy, we reported on the synthesis of MBs with poly(2-methyl-, 2-ethyl-, and 2-*iso*-propyl-2-oxazoline) (PMeOx, PEtOx, *i*PrOx) side chains grafted from poly(2-iso-propenyl-2-oxazoline) (PIPOx) macromonomers by LCROP.[39] The almost quantitative grafting/initiator efficiency and the side chain grafting polymerization kinetics that indicate the highly living nature of side-chain grafting by the LCROP[75] is in accordance with earlier observations of the formation of dense POx brushes on solids.[20,28,76] The thermoresponsive behavior of POx-based MBs could be modulated by the side-chain polymer as well as backbone and side chain length. However, a significant and much broader modulation of the MB cloud points (CPs) should be possible, as analog compositional variations of linear copolymers of POx result in a series of polymers with CPs from a few to almost 100 °C in aqueous solutions.[44,45,59–65] Moreover, the position of hydrophilic and hydrophobic monomer units along the pendant chains should play a significant role. Here, we report on the synthesis of defined POx-based MBs prepared by living ionic polymerization and the modulation of the thermoresponsive behavior of their aqueous solutions by the compositional and sequential variation of copolymer side chains.

2. Experimental Section

2.1. Materials and General Methods

Chemicals were purchased from Sigma–Aldrich (Steinheim, Germany) or Acros (Geel, Belgium) and were used as received unless otherwise stated. Methyl triflate (MeOTf), 2-isopropenyl-2-oxazoline (IPOx), 2-methyl-2-oxazoline (MeOx), 2-*n*-propyl-2-oxazoline (*n*PrOx), acetonitrile (ACN) used for polymer synthesis were dried by refluxing over CaH_2 under a dry nitrogen atmosphere and subsequent vacuum distillation prior to use. NMR spectra were recorded on a Bruker ARX 300 at 292 K. The spectra were calibrated using the solvent signals ($CDCl_3$ 7.26 ppm, CD_3CN 1.94 ppm). Gel permeation chromatography (GPC) was performed on a Waters system (pump mod. 510, RI-detector mod. 410) using Resi Pore Guard (50 × 7.5 mm) and 2× Resi Pore (300 × 7.5 mm) columns as the stationary and dimethyl acetamide (DMAc) (75 mmol L^{-1} LiBr, T = 80 °C, 1 mL min^{-1}) as the mobile phase. The calculation of the average molar mass was performed using a calibration with PMMA standards from PSS (Mainz, Germany). Prior to the measurements, the polymer samples were dissolved in DMAc and filtered through 0.2 μm PTFE filters. Gas chromatography was performed on a Varian CP 3380 equipped with a CombiPal robot arm and with a Nordion NB-54 column (25 m, 0.20 mm, 0.25 mm) and FID detector (helium carrier gas). For the kinetic measurements, the polymerization mixture was prepared and sealed in a glove box under an inert and dry atmosphere. The agitator was preheated to the indicated temperature. The CombiPal was programmed for 2 syringe wash cycles (ACN) prior and after sampling. The sealed reaction container was introduced to the agitator immediately (approx. 1 s) before the first sampling, to obtain a zero-time value. Per injection, 2 μL of the reaction mixture was taken. The monomer consumption was followed by the change of the ratio of the integrals of the monomer and the internal standard (chlorobenzene). Turbidity measurements were carried out on a Cary 3 UV–Vis spectrophotometer from Varian. The CP was determined by spectrophotometric detection of the changes in transmittance at λ = 500 nm of the aqueous polymer solutions (1.0 wt%). The heating/cooling rate was 1.0 °C min^{-1} followed by a 5 min period of constant temperature to ensure equilibration. Given values for the CP were determined as the temperature corresponding to a 10% decrease in optical transmittance.

2.2. Synthesis

2.2.1. 2-*n*-Propyl-2-oxazoline (*n*PrOx)

The monomer *n*PrOx was prepared according to a previously published procedure.[61,62]

2.3. Living Anionic Polymerization: Poly(2-isopropenyl-2-oxazoline)

Adapting our recent reports,[39,75] PIPOx was synthesized by living anionic polymerization of 2-isopropenyl-2-oxazoline using *n*-butyllithium as the initiator. Degree of polymerization n = 132, $\overline{M}_n$ = 14.6 kg mol^{-1}, $Đ = \overline{M}_w/\overline{M}_n$ = 1.20.

^{1}H NMR ($CDCl_3$): δ (ppm) = 4.16 (br, 2H, −O−CH_2−CH$_2$−N =), 3.76 (br, 2H, −O−CH$_2$−CH_2−N =), 1.86-1.75 (br, 2H, −C−CH_2−), 1.24-1.14 (br, 3H, −C−CH_3) and 0.85 (br, C_4H_9).

2.4. Macroinitiator Salt: Poly(2-isopropenyl-2-oxazolium triflate)

Under dry and inert conditions, PIPOx (222 mg, 1.0 equiv of oxazoline unit) and 394 mg (2.4 mmol, 1.2 equiv) of MeOTf were added to 5 mL dry acetonitrile at approximately –35 °C. After stirring for 5 h at 0–5 °C, the mixture was poured into cold and dry diethyl ether to precipitate the oxazolinium salt. The colorless precipitate was washed twice with cold ether to yield 529 mg (1.92 mmol, 96%). For details, please see main text and Table 1.

^{1}H NMR (CD_3CN): δ (ppm) 5.08 (br, 2H, −N−CH$_2$−CH_2−O−), 4.54 (br, 2H, −N−CH_2−CH$_2$−O−), 3.70 (s, 3H, CH_3−N), 2.49 (2H, −C−CH_2−), 1.36 (br, 3H, −C−CH_3).

2.5. General Procedure for the Preparation of Poly(2-Isopropenyl-2-oxazoline)-graft-poly(2-methyl-2-oxazoline)-*co*-poly(2-*n*-propyl-2-oxazoline); MB-1 to MB-8 (Random), MB-9 and MB-10 (Block)

At 0 °C, PIPOxOTf (44 mg, 0.16 mmol, 1.0 equiv) was dissolved in 4 mL of acetonitrile and 25 equiv. per initiator function of 2-oxa-

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Table 1. Analytical data of the PIPOx backbone and the respective molecular brushes with a variation of the side - chain composition comprising MeOx and *n*PrOx units along with the determined cloud points.

Entry	Monomer feed[a] (*n*PrOx:MeOx)	Composition (*n*PrOx:MeOx)[d]	$\overline{M}_n$ [kg mol^{-1}][b]	$Đ$ ($\overline{M}_w/\overline{M}_n$)[b]	CP [°C][c]
PIPOx	–	–	14.6	1.20	–
MB-1	25:0	25:0	84	1.20	19
MB-2	20:5	19:6	92	1.21	33
MB-3	15:10	14:11	95	1.20	51
MB-4	12.5:12.5	12:13	98	1.22	57
MB-5	11:14	9:16	99	1.28	79
MB-6	10:15	8:17	102	1.26	–
MB-7	5:20	5:20	113	1.40	–
MB-8	0:25	0:25	121	1.21	–
MB-9	12.5:12.5	12.5:12.5	121	1.20	70
MB-10	12.5:12.5	13:12	96	1.21	32

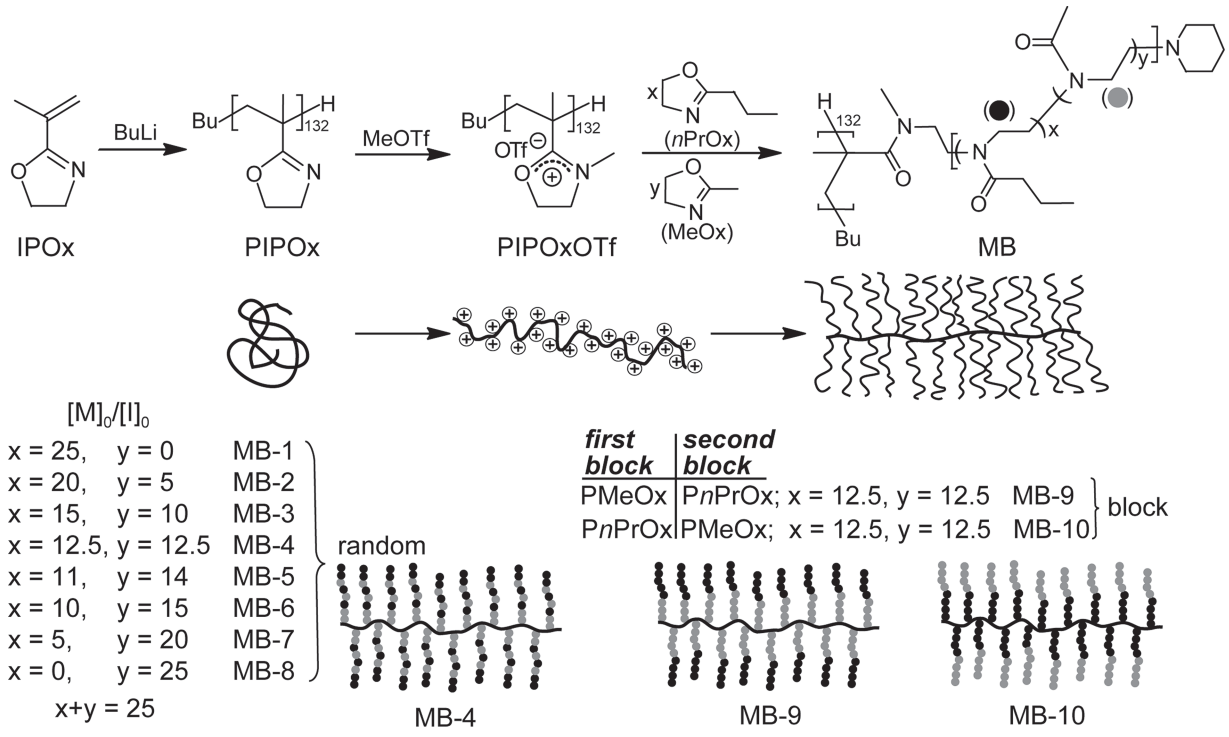
[a]Monomer feed ratio (mol) for random copolymer and relative feeds for block copolymer; [b]Dispersity index (Đ) determined by gel permeation chromatography (GPC); [c]Cloud point (CP) determined by turbidity measurements of a 1.0 wt% aqueous polymer solution at 90% transmittance upon heating; [d]End- group analysis based on ^{1}H NMR spectroscopy data.

zolines (MeOx and *n*PrOx for random copolymer or sequential monomer addition for block copolymer side chains) was added. The solution was heated by a prepared oil bath to 80 °C. The polymerization was stopped after approximately 20 h by adding 54.4 mg (0.64 mmol, 4 equiv.) of piperidine. After stirring the reaction mixture for 8 h at room temperature, an excess of finely grounded potassium carbonate (≈60 mg) was added and the mixture was allowed to stir overnight. The solvent was removed under reduced pressure and the residual dissolved in chloroform and then precipitated three times into dry diethyl ether. The product was freeze-dried (water) to yield a colorless powder. Additionally, the product was purified by column chromatography using Sephadex G100 (Sephadex G100 (bead size: 40–120 μm; cutoff value: 10 kDa) to quantitatively separate the product from minor portions of homopolymer side products. The MBs were characterized by GPC and ^{1}H NMR spectroscopy. For details, see Table 1 in the main text.

3. Results and Discussion

Molecular brushes of POx were synthesized as outlined in Scheme 1 following our previous reports.[39] Briefly, poly(2-isopropenyl-2-oxazoline) (PIPOx) was synthesized by anionic polymerization of 2-isopropenyl-2-oxazoline (IPOx) to give the MB backbone. For all experiments, the same PIPOx backbone with a degree of polymerization, n = 132, and a dispersity, $Đ$ = 1.20, was used. The macroinitiator, poly(2-isopropenyl-2-oxazolium triflate) (PIPOxOTf), for the successive *grafting from* reactions was obtained by conversion of PIPOx with methyl triflate (MeOTf). The conversion from PIPOx to the macroinitiator salt was at least 98.5% as determined by ^{1}H NMR spectroscopy. MBs were obtained by the subsequent LCROP of 2-oxazolines with PIPOxOTf. For the side chain formation via LCROP grafting, the initial monomer to initiator function ratio was fixed to $[M]_0/[I]_0$ = 25 for all experiments.

In order to achieve a wide modulation of the thermoresponsive properties (CPs) of MBs in aqueous solution, MeOx was chosen as it is the most hydrophilic monomer unit in the 2-alkyl-2-oxazoline series.[17,77] For the hydrophobic monomer unit, either 2-*iso*-(*i*PrOx) or *n*PrOx is suitable, as shown for linear copolymers.[44,45,59–65] Because of the additional contribution of hydrophobic interactions contributed by the PIPOx backbone, a combination of MeOx with more hydrophobic comonomers would result in water insoluble MBs even at low comonomer content. Moreover, the increasing difference of the copolymerization parameters of MeOx and comonomers with longer 2-alkyl-substituents would result in a significant gradient copolymerization instead of a desirable random copolymer. In order to find the most suitable comonomer pair, kinetic investigations of the polymerization of MeOx, *i*PrOx, and *n*PrOx using PIPOxOTf macroinitiator were performed. As shown in Figure 1, the conversion of the monomers MeOx and *n*PrOx reaches more than 95% within 10 h at 80 °C while *i*PrOx is significantly slower. In all cases, the LCROP grafting follows a pseudo-first-order kinetic and the apparent polymerization rates (k_p) per initiating group were calculated to be 2.12 and 2.95 mL S^{-1} mol^{-1} for *n*PrOx and MeOx but only 1.28 mL S^{-1} mol^{-1} for *i*PrOx. As reported earlier, the polymerization rate per initiator function of the macroinitiator salt is, within the experimental error, the same as for monofunctional initiators, that is, methyltriflate.[75]



Scheme 1. Synthesis of molecular brushes by anionic polymerization of 2-isopropenyl-2-oxazoline (IPOx) for the backbone, conversion to the PIPOxOTf macroinitiator, and grafting of side chains by living cationic ring-opening polymerization (LCROP) of MeOx and *n*PrOx.

The slight difference in the polymerization rate of MeOx and *n*PrOx will result in a nearly random copolymer with only a slight gradient character, whereas a copolymerization of MeOx with *i*PrOx would give a copolymer side chain with a significant gradual enrichment of *i*PrOx moieties toward the distal side chain ends. Based on these findings, the CP modulation of MBs was performed with MeOx and *n*PrOx. Starting with MB-1 with poly(*n*PrOx) side chains, the MeOx content was stepwise increased until for MB-8, the MB side chains are composed of poly(MeOx) homopolymers. In all cases, the final side-chain compositions are close to the initial monomer feed ratio as determined by ^{1}H NMR spectroscopy. As expected, the apparent molar mass measured by GPC was much lower than the theoretical values when the monomer conversion reaches 100%. This is in agreement with previous report as the GPC analysis using linear standards will strongly underestimate the molar mass of such compact brush molecules.[39,75,78,79] The analytical data are summarized in Table 1.

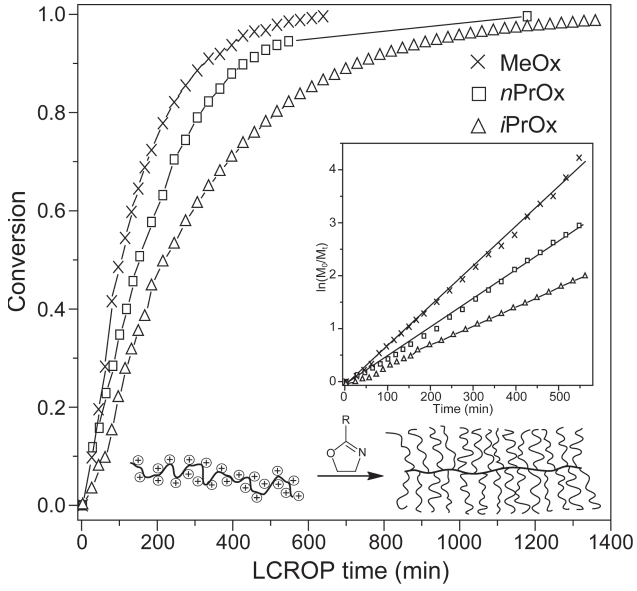


Figure 1. Monomer conversion plots for the polymerization of 2-methyl-, 2-*n*-propyl-2-, and 2-*iso*-2-oxazoline in the presence of the poly(oxazolinium) triflate macroinitiator (PIPOxOTf). Inset, first-order kinetic plots for the polymerizations ($[I]_0$ = 0.04 mol L^{-1}, which calculates to an initial monomer to initiator ratio of $[M]_0/[I]_0$ = 25).

For the series of MB-1 to MB-8, the CPs of their aqueous solutions (1.0 wt%) were determined and are also given in Table 1. For all compounds, the critical solution temperature were found to be very defined and upon heating, the MBs showed a very sharp and reproducible soluble–insoluble transition within 1–2 K with no significant hysteresis for heating and cooling cycles (Figure 2 inset). For MB-1 with poly(*n*PrOx)$_{25}$ homopolymer side chains, a CP of 19 °C was found, which is significantly different to the CP of a linear poly(*n*PrOx)$_{25}$ with a CP of 25 °C.[62] Beside the substantial difference of the molar mass (MB: 84 vs

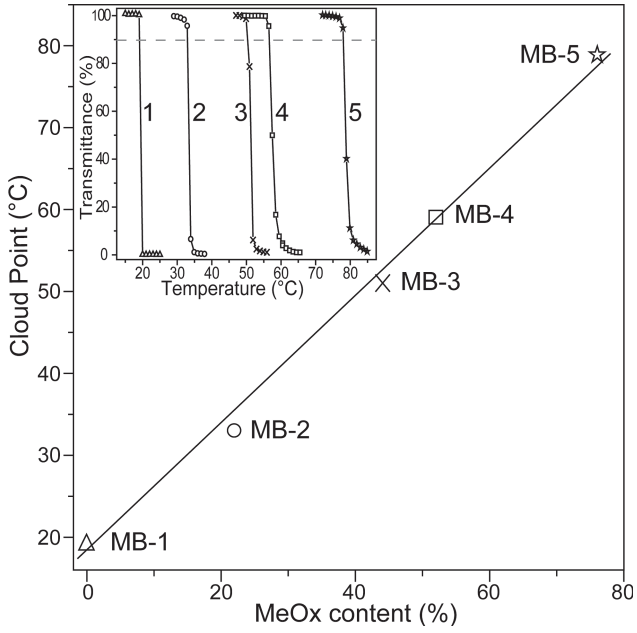


Figure 2. Cloud points (CP) of the molecular brushes MB-1 to MB-5 with random copolymer side chains as a function of the side-chain composition (MeOx molar content%). Inset: Cloud point measurements of a 1.0 wt.% aqueous solution of MB-1 to MB-5. CP values are given at 90% transmittance.

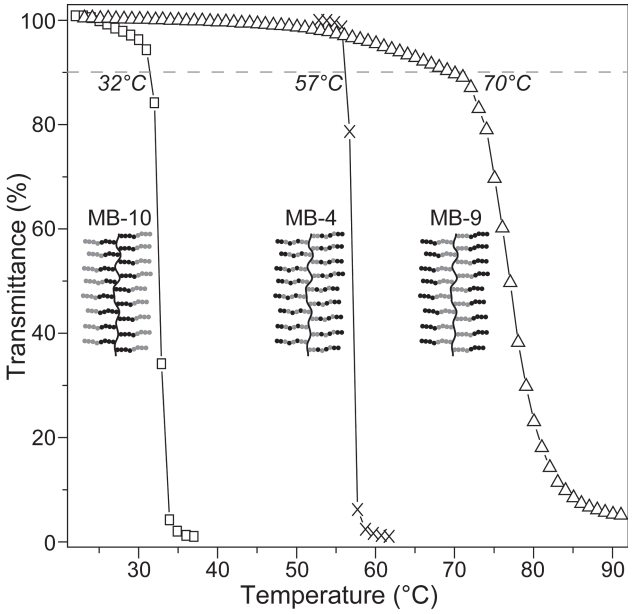


Figure 3. Determination of cloud points of the MBs with random and block copolymer side chains of identical side chain composition (MeOx:*n*PrOx = 12.5:12.5) along with a schematic representation of the distribution of the hydrophilic and hydrophobic monomer units.

3 kDa for the linear chain), the very different polymer architecture as well as the additional of hydrophobic moieties of the PIPOx backbone contributes to this difference in solubility. With increasing MeOx content within the random copolymer side chains, the CPs were found to linearly increase from 20 to 80 °C (MB-5; 70 mol% MeOx) as shown in Figure 2. At higher contents, the MBs remain soluble.

As reported for linear poly(2-oxazoline)s,[59,60,62,64,65,80] a systematic variation of the temperature sensitivity of POx-based MBs is possible by the combination of hydrophilic and hydrophobic 2-oxazoline monomer units in the pendant copolymer chains. The linear relationship between the CPs and the side chain composition allows a direct tuning of the thermosensitivity of MBs over a broad temperature interval.

Besides a random distribution of hydrophilic and hydrophobic moieties in the pendant chains, a block copolymer motive was realized by sequential monomer addition for the LCROP *grafting from* reaction to elucidate the impact of the monomer sequence upon the solubility. In order to relate the thermoresponsive behavior of the MBs featuring random side chains to the brushes with an amphiphilic copolymer corona, the same side chain length ($x + y = 25$) and the same monomer combination were used. Both sequences were realized, namely MBs with a hydrophilic proximal chain of MeOx units and a hydrophobic distal side chain of *n*PrOx (MB-9) and vice versa (MB-10) were synthesized. Both polymers had the same MeOx:*n*PrOx ratio as the MB with random copolymer side chains (MB-4). The respective analytical data are given in Table 1. Figure 3 displays the CP measurements of MB-9 and MB-10 along with MB-4 for comparison. As apparent, also MBs with block copolymer side chains display a defined thermoresponsive solubility behavior, analog to the MB-1 to MB-5 series with random side chains. While MB-4 with random side chains show a CP at 57 °C, the CP of MBs with block copolymer side chains can be found in between. However, the CP of MB-4 is nearer to the MB-9 compound with *n*PrOx units at the distal chain as the "random" copolymerization of MeOx and *n*PrOx gives a slightly gradual increase of *n*PrOx units toward the chain ends because of the higher reactivity of MeOx monomers (see Figure 1). The somewhat surprising finding is that MB-10 with a hydrophilic distal side chain precipitates already at 32 °C while MB-9 with a hydrophilic core and a hydrophobic shell stays soluble until a CP at 70 °C is observed.

Intuitively, one would expect the opposite result as upon collapse at a given temperature, MB-10 could form a monomolecular micelle or a micellar-like aggregate with a hydrophilic corona. In fact, this was observed by Matyjaszewski and co-workers[79] for MBs from oligo(ethylene oxide) methacylates. However, as the MBs described, there are of quite different chemical nature and chain architecture and of a significantly higher overall molar mass

with much longer backbone and side chains, both MB systems may collapse and aggregate differently. In a recent account, we investigated the temperature-dependent aggregation behavior of random or gradient as well as block copolymer POx of the same degree of polymerization as for side chains of MBs at the CP and found no formation of micelles of, that is, poly(*n*PrOx-*b*-*i*PrOx) block copolymers but a cooperative aggregation and precipitation with only one transition temperature. Only the introduction of strongly amphiphilic 2-oxazoline units such as 2-nonyl-2-oxazoline led to the formation of micelles and/or a local aggregation resulting into a network.[80] Hence, for POx-based MBs the formation of (unimolecular) micelles are probably only observable for a stronger amphiphilic contrast in the side chain composition using 2-oxazolines with aryl or longer alkyl substituents.[81–83]

4. Conclusion

In summary, a series of POx-based MBs with random as well as block copolymer side chains was prepared via sequential living anionic and living cationic polymerization of 2-oxazoline and the thermoresponsive behavior of their aqueous solutions investigated. The CPs depend strongly on the side-chain composition and increases linearly with increased content of the hydrophilic monomer. The solubility transition temperature could be varied from 20 to 80 °C. Moreover, MBs with block copolymer side chains were prepared and their CPs depend strongly on the block sequence. Surprisingly, MBs with hydrophilic proximal blocks showed the lowest CP as compared with MBs with random copolymer side chains or distal hydrophobic blocks.

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